



Effective Health Care Program

Comparative Effectiveness Review
Number 69

Screening for Hepatitis C Virus Infection in Adults



Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

Comparative Effectiveness Review

Number 69

Screening for Hepatitis C Virus Infection in Adults

Prepared for:

Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-2007-10057-I

Prepared by:

Oregon Evidence-based Practice Center
Portland, OR

Investigators:

Roger Chou, M.D.
Erika K. Barth Cottrell, Ph.D., M.P.P.
Ngoc Wasson, M.P.H.
Basmah Rahman, M.P.H.
Jeanne-Marie Guise, M.D., M.P.H.

This report is based on research conducted by the Oregon Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2007-10057-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

This document is in the public domain and may be used and reprinted without special permission. Citation of the source is appreciated.

Persons using assistive technology may not be able to fully access information in this report. For assistance contact EffectiveHealthCare@ahrq.hhs.gov.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Suggested citation: Chou R, Cottrell EB, Wasson N, Rahman B, Guise J-M. Screening for Hepatitis C Virus Infection in Adults. Comparative Effectiveness Review No. 69. (Prepared by the Oregon Evidence-based Practice Center under Contract No. 290-2007-10057-I.) AHRQ Publication No. 12(13)-EHC090-EF. Rockville, MD: Agency for Healthcare Research and Quality. November 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director
Evidence-based Practice Program
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Christine Chang M.D., M.P.H.
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Acknowledgments

We thank our colleagues at the Oregon Evidence-based Practice Center, Robin Paynter, M.L.I.S., and Rose Campbell, M.L.I.S., for conducting the literature searches, and Leah Williams, B.S., Ed Reid, M.A., Alexander Ginsburg, M.A., M.C.R.P., Maya Rowland, M.P.H., and Elaine Graham, M.L.S. for editorial support. We also acknowledge Christina Bougatsos, M.P.H., Ian Blazina, M.P.H., Tracy Dana, M.L.S., and Jessica Griffin, M.S., for assistance with data extraction and evidence table editing. We appreciate and acknowledge the contributions of AHRQ Task Order Officer Christine Chang, M.D., M.P.H., and USPSTF Medical Officer Iris Mabry-Hernandez, M.D., M.P.H. We also thank the Key Informants, members of the Technical Expert Panel, and Peer Reviewers.

Key Informants

Miriam Alter, Ph.D., M.P.H.
Professor, Infectious Disease Epidemiology
Department of Internal Medicine
Division of Infectious Disease
University of Texas
Austin, TX

Michael Ninburg, M.P.A.
Executive Director
Hepatitis Education Project
Seattle, WA

Janet Patin, M.D.
Oregon Rural Practice-based Research
Network (ORPRN)
Dunes Family Clinic
Reedsport, Oregon

John Ward, M.D., M.P.H.
Director, Viral Hepatitis Division
Centers for Disease Control and Prevention
Atlanta, GA

Barbara Yawn, M.D., M.Sc., F.A.A.C.P.
Director of Research, Olmstead Medical
Center
University of Minnesota
Minneapolis, MN

Technical Expert Panel

Miriam Alter, Ph.D., M.P.H.
Professor, Infectious Disease Epidemiology
Department of Internal Medicine
Division of Infectious Disease
University of Texas
Austin, TX

Kirsten Bibbins-Domingo, Ph.D., M.D.,
M.A.S.
U.S. Preventive Services Task Force
Associate Professor
Department of Medicine and Epidemiology
& Biostatistics
University of California, San Francisco
San Francisco, CA

Adelita G. Cantu, Ph.D., R.N.
Assistant Professor
Family and Community Health Systems
University of Texas Health Science Center
at San Antonio
San Antonio, TX

Brian Edlin, M.D., F.I.D.S.A.
Division of Infectious Disease
SUNY Downstate Medical Center
Brooklyn, NY

W. Ray Kim, M.D.
Division of Gastroenterology and
Hepatology
Mayo Medical School
Rochester, MN

Steven Pearson, M.D., M.Sc., F.R.C.P.
Director
Institute for Clinical & Economic Review
Department of Population Medicine
Harvard Medical School
Boston, MA

Bruce A. Runyon, M.D.
Loma Linda University Medical Center
Division of Gastroenterology and
Hepatology
Loma Linda, CA

Thomas Shehab, M.D.
Huron Gastroenterology
Center for Digestive Care
St. Joseph Mercy Hospital
Ann Arbor, MI

Bryce Smith, Ph.D.
Centers for Disease Control and Prevention
Division of Viral Hepatitis
Atlanta, GA

Donna E. Sweet, M.D.
Director of Internal Medicine Education-St.
Francis Campus
University of Kansas Medical School
Wichita, KS

John Ward, M.D., M.P.H.
Director, Viral Hepatitis Division
Centers for Disease Control and Prevention
Atlanta, GA

Kimberly Workowski, M.D.
Associate Professor of Medicine
The Emory Clinic
Emory University
Atlanta, GA

Peer Reviewers

Adelita G. Cantu, Ph.D., R.N.
Assistant Professor
Family and Community Health Systems
University of Texas Health Science Center
at San Antonio
San Antonio, TX

Brian Edlin, M.D., F.I.D.S.A.
Division of Infectious Disease
SUNY Downstate Medical Center
Brooklyn, NY

Linda Kinsinger, M.D., M.P.H.
Chief Consultant for Preventive Medicine
Department of Veterans Affairs, Center for
Health Promotion/Disease Prevention
San Diego, CA

David Ross, M.D., Ph.D.
Director
Department of Veterans Affairs, Office of
Clinical Public Health Programs
Washington DC

Bruce A. Runyon, M.D.
Loma Linda University Medical Center
Division of Gastroenterology and
Hepatology
Loma Linda, CA

Stephen Stewart, Ph.D.
Consultant Hepatologist
Mater Misericordiae University Hospital
Centre for Liver Disease
Dublin, Ireland

Donna E. Sweet, M.D.
Director of Internal Medicine Education-St.
Francis Campus
University of Kansas Medical School
Wichita, KS

Screening for Hepatitis C Virus Infection in Adults

Structured Abstract

Objectives. Many patients with chronic hepatitis C virus (HCV) infection are unaware of their status. Screening could identify patients at earlier stages of disease, when interventions might be effective in improving clinical outcomes or reducing transmission risk. The purpose of this report is to systematically review the evidence on screening for HCV infection in asymptomatic adults without known liver enzyme abnormalities, including pregnant women. This review focuses on research gaps identified in the 2004 United States Preventive Services Task Force (USPSTF) review and new studies published since that review, and it reviews evidence on prenatal HCV screening not included in the 2004 USPSTF review. This report examines both direct evidence on the effects of screening for HCV infection compared to no screening on clinical outcomes, as well as the indirect chain of evidence (diagnosis, workup, and treatment) needed to understand effects of screening on clinical outcomes. Treatments evaluated included immunizations, counseling, and interventions to potentially reduce risk of mother-to-child transmission. To complement this review of screening for HCV, the Agency for Healthcare Research and Quality (AHRQ) commissioned a separate review on effectiveness of antiviral treatments.

Data sources. Articles were identified from searches (from 1947 to May 2012) of the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, EBM Reviews, and Ovid MEDLINE[®]. The searches were supplemented by reviewing reference lists and searching clinical trial registries.

Review methods. We used predefined criteria to determine study eligibility. We selected randomized trials and observational studies that evaluated effects of screening, counseling interventions, and immunizations on clinical and intermediate outcomes. We also selected studies that evaluated effects of labor and delivery practices and breastfeeding on mother-to-child transmission of HCV infection. We selected studies that evaluated the diagnostic accuracy of noninvasive tests compared to liver biopsy for diagnosing fibrosis or cirrhosis in patients with chronic HCV infection. The quality of included studies was assessed, data were extracted, and results were summarized.

Results. Of the 10,786 citations identified at the title and abstract level, we screened and reviewed 808 full-length articles. A total of 182 studies were included. There was no direct evidence on clinical benefits associated with screening compared with no screening (or comparing different screening approaches) in nonpregnant or pregnant adults. Retrospective studies found that screening strategies targeting multiple risk factors were associated with sensitivities of over 90 percent and numbers needed to screen to identify one case of HCV infection of less than 20. Narrowly targeted screening strategies based on history of intravenous drug use were associated with numbers needed to screen of less than two, but missed up to two-thirds of infected people. Data on harms of screening (such as labeling and anxiety) were sparse. Compared with liver biopsy, a number of indices based on panels of blood tests were associated with a median area under the receiver operating characteristic curve (AUROC) of 0.75 to 0.86 for diagnosing fibrosis and a median AUROC of 0.80 to 0.91 for diagnosing cirrhosis, but there was insufficient evidence to determine clinical outcomes associated with strategies incorporating

noninvasive tests for evaluating patients with HCV infection. Limited evidence suggested that knowledge of HCV status and counseling interventions may reduce alcohol use and risky injection drug use behaviors, but more evidence is needed to demonstrate long-term sustainability and to understand effects on clinical outcomes and transmission risk. In pregnant women, cohort studies found no clear association between mode of delivery and risk of vertical transmission of HCV infection and consistently found no association between breastfeeding and transmission risk. Evidence on the association between other labor and delivery management practices and risk of vertical transmission of HCV infection was sparse, but suggested that prolonged rupture of membranes is associated with increased risk.

Conclusions. Although screening tests can accurately identify adults with chronic HCV infection, targeted screening strategies based on the presence of risk factors miss some patients with HCV infection. As a result, more research is needed to understand the effects of different screening strategies on clinical outcomes. Evidence on effects of knowledge of HCV status and counseling and immunizations on clinical and intermediate outcomes in patients diagnosed with HCV infection remains sparse and more research is needed to understand effective interventions for preventing vertical transmission. A complete assessment of benefits and harms of screening requires consideration of the effectiveness of antiviral regimens, which are the subject of a complementary review.

Contents

Executive Summary	ES-1
Introduction	1
Scope and Key Questions	6
Methods	10
Topic Development.....	10
Search Strategy	10
Study Selection	10
Population and Conditions of Interest.....	10
Interventions and Comparators	11
Outcomes	12
Timing.....	12
Setting	12
Types of Studies.....	12
Data Extraction	12
Quality Assessment of Individual Studies	13
Assessing Research Applicability.....	14
Evidence Synthesis and Rating the Body of Evidence	14
Peer Review	15
Results	16
Key Question 1a. Does screening for HCV infection in asymptomatic nonpregnant adults reduce mortality and morbidity due to HCV, affect quality of life, or reduce transmission of HCV?	18
Key Question 1b. Does screening for HCV infection during pregnancy reduce vertical transmission of HCV or improve mortality or morbidity for the mother or child?	18
Key Question 2a. What is the effectiveness of different risk- or prevalence-based methods for screening for HCV infection on clinical outcomes?.....	18
Key Question 2b. What is the sensitivity and number needed to screen to identify one case of HCV infection of different risk- or prevalence-based methods for screening for HCV infection?	19
Key Question 3. What are the harms associated with screening for HCV infection, including adverse effects such as anxiety, labeling, and impact on relationships?	24
Key Question 4a. What is the comparative effectiveness and comparative diagnostic accuracy of various tests and strategies for the workup to guide treatment decisions in patients who are HCV positive?	25
Effectiveness	25
Diagnostic Accuracy.....	25
Key Question 4b. What proportion of patients with screen-detected HCV infection receives treatment?.....	42
Key Question 5. What are the harms associated with the workup for guiding treatment decisions?.....	44
Key Question 6a. How effective is counseling or immunization of patients with HCV infection at improving health outcomes or reducing the spread of HCV?	45

Key Question 6b. Does becoming aware of positive HCV infection status decrease high-risk behaviors?.....	45
Key Question 6c. How effective is counseling and immunization of patients with HCV infection at improving intermediate outcomes, including change in high-risk behaviors?.....	46
Key Question 7. Do any interventions decrease or increase the vertical transmission of HCV during delivery or in the perinatal period?.....	47
Mode of Delivery	48
Labor Management	50
Breastfeeding	51
Discussion	53
Findings in Relationship to What Is Already Known.....	54
Applicability	55
Implications for Clinical and Policy Decisionmaking	56
Limitations of the Comparative Effectiveness Review Process	60
Limitations of the Evidence Base	61
Research Gaps.....	61
Conclusions.....	62
Supplemental Tables	63
References	146
Abbreviations and Acronyms	162

Tables

Table A. Summary of Evidence on Comparative Benefits and Harms of Screening for Hepatitis C Virus Infection	ES-11
Table 1. Current Hepatitis C Virus Infection Screening Recommendations	3
Table 2. Screening Strategies: Studies of Alternative Screening Strategies (Key Question 2b)..	20
Table 3. Screening Strategies: Effects of Applying Alternative Screening Criteria on Sensitivity and Number Needed To Screen To Identify One Case of HCV Infection (Key Question 2b).....	21
Table 4. Diagnostic Accuracy Summary Table	27
Table 5. Aspartate Aminotransferase-Platelet Ratio Index Compared With Fibrotest.....	35
Table 6. Aspartate Aminotransferase/Alanine Aminotransferase Ratio Compared With Other Indices	37
Table 7. Platelet Count Compared With Multicomponent Indices.....	40
Table 8. Blood Tests Compared With Imaging	42
Table 9. Proportion of Screened Patients Who Were Treated	43
Table 10. Hepatitis C Virus Transmission by Mode of Delivery: Elective Cesarean Compared With Emergent Cesarean or Vaginal Delivery.....	48
Table 11. Hepatitis C Virus Transmission by Mode of Delivery: Cesarean (Elective or Emergent) Compared With Vaginal Delivery.....	50
Table 12. Labor Management: Transmission by Duration of Membrane Rupture.....	51
Table 13. Labor Management: Transmission by Fetal Monitoring	51
Table 14. Transmission by Type of Infant Feeding.....	52
Table 15. Summary of Evidence on Comparative Benefits and Harms of Screening for Hepatitis C Virus Infection	56

Supplemental Tables

Supplemental Table 1. Key Question 4a: Diagnostic Accuracy Individual Tests	63
Supplemental Table 2. Key Question 4a: Diagnostic Accuracy Indices	80
Supplemental Table 3. Key Question 4a: Diagnostic Accuracy Direct Comparisons (based on areas under the receiver operating characteristic curve)	133

Figures

Figure A. Analytic Framework: Screening for Hepatitis C Virus Infection in Adults	ES-6
Figure 1. Analytic Framework: Screening for Hepatitis C Virus Infection in Adults	7
Figure 2. Study Flow Diagram: Screening for Hepatitis C Virus Infection in Asymptomatic Adults and Pregnant Women.....	17

Appendixes

Appendix A. Exact Search Strategy	
Appendix B. Hepatitis C Screening: Inclusion Criteria by Key Question	
Appendix C. Included Studies	
Appendix D. Excluded Studies	
Appendix E. Quality Assessment Methods	
Appendix F. Overall Strength of Evidence: Summary of Grading Domains	
Appendix G. Evidence Tables and Overall Quality Ratings	

Executive Summary

Background

Hepatitis C virus (HCV) is a single-stranded, positive-sense RNA virus of the family Flaviviridae. HCV is the most common chronic bloodborne pathogen in the United States. The prevalence of anti-HCV antibody in the United States is estimated at 1.6 percent.¹ Approximately 78 percent of those who test positive for anti-HCV antibody have the HCV detectable in the blood (viremia), indicating chronic infection;¹ those with anti-HCV antibody but no viremia are considered to have cleared the infection. About two-thirds of patients with HCV infection were born between 1945 and 1964, with the highest prevalence (4.3 percent) in people 40 to 49 years of age in 1999–2002.¹ The prevalence of chronic HCV infection is thought to have peaked in 2001 at 3.6 million people.² The yearly incidence of HCV infection averaged more than 200,000 cases per year in the 1980s, but by 2001 had declined to around 25,000 cases per year.³ The Centers for Disease Control and Prevention (CDC) estimated 16,000 new cases of HCV infection in 2009.⁴

HCV infection is a leading cause of complications from chronic liver disease and was associated with an estimated 15,000 deaths in the United States in 2007.⁵ One study estimated that the total number of patients with cirrhosis will peak at 1.0 million in 2020, though rates of hepatic decompensation and liver cancer are expected to continue to rise for another 10 to 13 years given the long lag time between infection and development of cirrhosis and other complications.² HCV-related end-stage liver disease is the most common indication for liver transplantation among American adults, accounting for more than 30 percent of cases, with a fivefold increase in the number of patients with HCV who underwent liver transplantation between 1990 and 2000.^{6,7} Studies suggest that about half of the recently observed threefold increase in incidence of hepatocellular carcinoma is related to acquisition of HCV infection two to four decades earlier.^{8,9} HCV without cirrhosis is associated with worse quality of life measures and symptoms (primarily fatigue) compared with the general population.¹⁰⁻¹⁴

HCV is primarily acquired via percutaneous exposures to infected blood. The strongest risk factor for HCV infection is injection drug use. The prevalence of HCV infection in injection drug users varies widely depending on age, duration of injection drug use, and other factors (such as availability and use of needle exchange programs).¹⁵ Prevalences range from less than 50 percent in more recent studies of younger injection drug users to more than 90 percent in older studies of older injection drug users.¹⁶⁻²² About 60 percent of new infections occur in individuals who report injecting drugs within the last 6 months.³ Although large population-based studies^{16, 17, 23} report independent associations between HCV infection and some high-risk sexual behaviors (multiple sexual partners, unprotected sex, and/or sex with a person infected with HCV infection or using injection drugs), the efficiency of transmission via sexual contact appears to be low, and high-risk sexual behaviors may be a marker for unacknowledged drug use or other risk factors. Transfusions prior to 1992 are a risk factor for HCV infection but transfusions after 1992 are not an important source of infection due to the implementation of effective screening programs for donated blood.^{24, 25}

The natural course of chronic HCV infection varies. Many patients with chronic HCV infection have only mild liver disease even after decades of infection or never develop histologic evidence of liver disease.²⁶ In other patients, inflammation and fibrosis of the liver may progress to cirrhosis, which can lead to end-stage liver disease or hepatocellular carcinoma. Once cirrhosis develops, patients have a much higher risk of death, and some may benefit from liver

transplantation. Well-established predictors of advanced fibrosis in those with chronic HCV infection include older age at infection, longer duration of infection, male sex, concomitant HIV or hepatitis B virus (HBV) infection, and greater alcohol use.²⁶⁻²⁸ Other factors that may be associated with increased risk of fibrosis include insulin resistance, hepatic steatosis, higher viral load, and the presence of certain HLA class II polymorphisms.

Estimating the proportion of patients in the general population with HCV infection who progress to cirrhosis is difficult because the time of acquisition is often unclear and important endpoints often do not occur until after decades of infection.²⁹ For example, six retrospective cohort studies of HCV-infected adults with known time of infection (based on an identified exposure, often to contaminated blood products during young adulthood) reported cirrhosis in 0 to 10 percent of patients after at least 10 years of followup.^{14,30-35} Overall, studies of community cohorts estimate cirrhosis in an average of 7 percent of people after 20 years of HCV infection, with rates about twice as high in clinical and referral cohorts.^{28,36} Studies with longer followup suggest that progression to cirrhosis may accelerate after 20 years of chronic infection.³³

Screening for HCV infection in asymptomatic adults who have no history of liver disease or known liver enzyme abnormalities may identify infected patients at earlier stages of disease, before they develop serious or irreversible liver damage. A high proportion of people with chronic HCV infection are thought to be unaware of their status. One study of young injection drug users in the United States found that 72 percent were unaware of their HCV-positive status.³⁷ Patients with chronic HCV infection may be eligible for antiviral treatments, which have become increasingly effective at long-term eradication of HCV in the blood. In addition, identification of HCV infection might help prevent transmission by decreasing high-risk injection drug use and other risky behaviors, or identify those who might benefit from hepatitis A or B vaccinations, alcohol cessation counseling, or other interventions.

Screening for HCV infection in asymptomatic individuals without known liver enzyme abnormalities might identify patients who could benefit from such interventions. Recommendations on HCV screening vary. In 2004, the United States Preventive Services Task Force (USPSTF) recommended against screening for HCV infection in adults not at increased risk (D recommendation) and found insufficient evidence to recommend for or against screening in adults at high-risk (I recommendation).³⁸ The 2004 evidence review commissioned by the USPSTF to inform its recommendations found that screening is accurate in identifying people with HCV infection and that antiviral treatments improved intermediate outcomes such as viremia.³⁹ The D recommendation in low-risk individuals was based on evidence indicating a relatively low prevalence of HCV infection, natural history studies showing that most patients with chronic HCV infection do not develop major long-term negative health outcomes (such as death, cirrhosis, or need for liver transplantation), lack of direct evidence showing that screening or antiviral treatments improves important health outcomes, and potential harms of screening including those related to unnecessary treatments and labeling. Although the USPSTF concluded that screening high-risk populations would be a more efficient strategy than screening average-risk populations, it found insufficient evidence on the effects of screening or antiviral treatments on health outcomes and on the association between improved intermediate and clinical outcomes to determine the balance of benefits and harms with screening.³⁸

Unlike the USPSTF, other groups (including the American Association for the Study of Liver Disease, the Infectious Diseases Society of America, and the American College of Gastroenterology) recommend screening in higher-risk patients.⁴⁰⁻⁴² These recommendations are based on the higher prevalence of HCV infection in higher-risk populations, acceptance of the

link between improved intermediate outcomes following antiviral treatments and improved clinical outcomes, and presumed public health benefits related to the potential for reduced risky behaviors and transmission. The CDC recently recommended the screening of high-risk patients as well as age-cohort based HCV screening of all people born between 1945 and 1965.⁴³

Mother-to-child (vertical) transmission is believed to be the main route of HCV infection acquisition in children.⁴⁴ Estimates of vertical transmission range from 3 to 10 percent.⁴⁴⁻⁴⁸ The risk of transmission is highest among women with a high viral load at the time of delivery⁴⁴⁻⁴⁸ and among women coinfecting with HIV.^{47, 49} Routine prenatal screening for HCV infection is not currently recommended; the CDC⁵⁰ and the 2007 American College of Obstetricians and Gynecologists recommend offering HCV screening to at-risk pregnant women⁵¹ and the 2004 USPSTF recommendations did not address screening for HCV during pregnancy. While antiviral therapies are contraindicated in pregnancy due to teratogenic risks, identification of HCV infection during pregnancy could facilitate decisionmaking around the management and use of interventions during labor and delivery or in the perinatal period that might reduce risk of mother-to-child transmission.⁵²

The purpose of this report is to review the evidence screening for chronic HCV infection in asymptomatic adults without known liver enzyme abnormalities. The Agency for Healthcare Research and Quality (AHRQ), which commissioned this review, also commissioned a separate but complementary review on effectiveness of antiviral treatments.⁵³ Together, these reviews will be used by the USPSTF to update its recommendations on HCV screening. This review focuses on research gaps identified in the 2004 USPSTF review and new studies published since that review. In addition, it evaluates evidence on screening for both pregnant and nonpregnant adults.

Objectives

The following Key Questions are the focus of our report:

Key Question 1

- a. Does screening for HCV infection in nonpregnant adults without known abnormal liver enzymes reduce mortality and morbidity due to HCV infection, affect quality of life, or reduce incidence of HCV infection?
- b. Does screening for HCV infection during pregnancy reduce vertical transmission of HCV or improve mortality or morbidity for the mother or child?

Key Question 2

- a. What is the effectiveness of different risk- or prevalence-based methods for screening for HCV infection on clinical outcomes?
- b. What is the sensitivity and number needed to screen to identify one case of HCV infection of different risk- or prevalence-based methods for screening for HCV infection?

Key Question 3

What are the harms associated with screening for HCV infection, including adverse effects such as anxiety, labeling, and impact on relationships?

Key Question 4

- a. What is the comparative effectiveness and comparative diagnostic accuracy of various tests and strategies for the workup to guide treatment decisions in patients who are HCV positive?
- b. What proportion of patients with screen-detected HCV infection receives treatment?

Key Question 5

What are the harms associated with the workup for guiding treatment decisions?

Key Question 6

- a. How effective is counseling or immunizations of patients with HCV infection at improving health outcomes or reducing the spread of HCV?
- b. Does becoming aware of positive HCV infection status decrease high-risk behaviors?
- c. How effective is counseling or immunization of patients with HCV infection at improving intermediate outcomes, including change in high-risk behaviors?

Key Question 7

Do any interventions decrease or increase the vertical transmission of HCV during delivery or in the perinatal period?

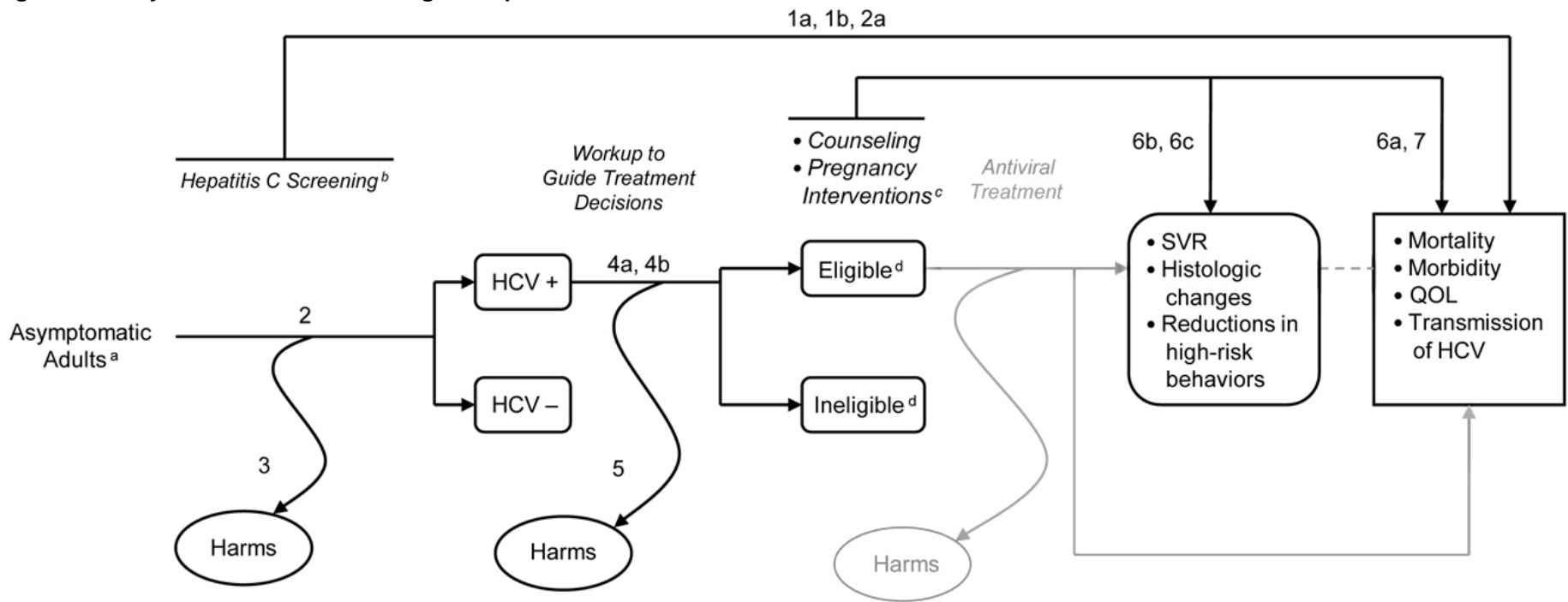
Analytic Framework

The analytic framework (Figure A) depicts the Key Questions in the framework of the population, interventions, and outcomes considered in the review. The figure is a modified version of a larger framework depicting the effect of both screening and treatment for HCV in adults. This report focuses on the screening portion of the framework. The overarching Key Questions (1a and 1b) in the analytic framework address direct evidence that screening for HCV infection improves important health outcomes compared with not screening. When such direct evidence is sparse or unavailable, indirect evidence can be used to assess the effects of screening on health outcomes. Therefore, the remainder of the analytic framework evaluates the chain of indirect evidence needed to link screening for HCV infection with improvements in important health outcomes. Links in the chain of indirect evidence include the performance of the screening test or testing strategy for identifying individuals with HCV infection, the clinical utility and diagnostic accuracy of the workup used to guide treatment decisions, and the effectiveness of treatments in those identified as infected with HCV infection, as well as any harms from the screening test and subsequent diagnostic tests and treatments. We did not re-review the accuracy of HCV antibody testing, which the prior USPSTF review found to be highly accurate. The proportion of patients with HCV infection who receive antiviral treatment is important for understanding potential benefits of screening, as not all patients will receive (and potentially benefit from) treatment. Critical gaps in any of the links of the indirect chain of evidence can make it impossible to reliably estimate benefits and harms of screening.

The target population was adults (including pregnant women) without signs or symptoms of liver disease or known liver enzyme abnormalities. We excluded post-transplant patients, HIV patients, hemodialysis patients, and patients with occupational exposures. The interventions include screening for HCV infection risk factors, screening for HCV antibody, diagnostic tests for workup of treatable disease, interventions to prevent mother-to-child transmission of HCV infection, counseling against risky behaviors, and immunization for other hepatitis infections. In

people with chronic HCV infection, becoming infected with hepatitis A or hepatitis B virus may result in fulminant hepatitis or more rapid progression of liver disease. Clinical outcomes were mortality, morbidity, quality of life, and HCV transmission, as well as harms of screening and/or workup; intermediate outcomes were risky behaviors (virologic and histologic intermediate outcomes were evaluated in a complementary review on antiviral treatments).

Figure A. Analytic framework: Screening for hepatitis C virus infection in adults



HCV = hepatitis C virus; QOL = quality of life; SVR = sustained virologic response

Note: Portions in gray refer to Key Questions addressed in a separate review on antiviral treatments.⁵³

^a Nonpregnant and pregnant adults without abnormal lab values. Excluding people with HIV, transplant recipients, and patients with renal failure.

^b HCV antibody testing with confirmatory HCV RNA testing as indicated.

^c Interventions that may affect vertical transmission of HCV, such as cesarean section, amniocentesis, fetal monitoring, or others.

^d Refers to eligibility for antiviral treatment based on viral and host factors.

Methods

Input From Stakeholders

The topic of HCV screening was nominated for a comparative effectiveness review (CER) in a public process. The Key Questions were proposed in the public nomination process and developed by investigators from the Evidence-based Practice Center with input from expert Key Informants, who helped to refine Key Questions, identify important methodological and clinical issues, and define parameters for the review of evidence. The revised Key Questions were then posted to a public Web site for comment. AHRQ agreed upon the final Key Questions after reviewing the public comments and receiving additional input from a Technical Expert Panel (TEP) convened for this report. Prior to participation in this report, the TEP members disclosed all financial or other conflicts of interest. The AHRQ Task Order Officer and the authors reviewed all of these disclosures and determined the panel members had no significant conflicts of interest that precluded participation.

Data Sources and Selection

To identify articles relevant to each Key Question, a research librarian searched Ovid® MEDLINE, Embase, Scopus, and PsycINFO from 1947 to May 2012. Gray literature was identified by searching clinical trial registries (Ovid® EBM Reviews: Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, Current Controlled Trials, Clinical Trial Results, and WHO Trial Registries) and grants databases (NIHRePORTER, HSRProj, and AHRQ GOLD). We supplemented the electronic searches by reviewing the reference lists of retrieved articles. We updated searches prior to finalization of the report to identify new publications.

We developed criteria for inclusion and exclusion of studies based on the Key Questions and the populations, interventions, comparators, outcomes, timing, and setting (PICOTS) approach. Papers were selected for full review if they were about chronic HCV infection, were relevant to Key Questions in the analytic framework, and met the predefined inclusion criteria.

We restricted inclusion to English language articles and excluded studies only published as abstracts. Studies of nonhuman subjects were excluded, as were studies that did not include original data.

Abstracts and full-text articles were dual reviewed for inclusion or exclusion for each Key Question. Full-text articles were obtained for all studies that either investigator identified as potentially meeting inclusion criteria. Two investigators independently reviewed all full-text articles for final inclusion or exclusion. Discrepancies were resolved through discussion and consensus, and a third investigator was included in the discussion if necessary.

We included randomized trials, cohort studies, and case-control studies pertinent to all Key Questions. We also included studies that reported the diagnostic accuracy of noninvasive tests for evaluating fibrosis or cirrhosis in patients with chronic HCV infection compared with liver biopsy.

Data Extraction and Quality Assessment

We extracted the following data from included trials: study design, setting, population characteristics (including sex, age, ethnicity/race, and diagnosis), eligibility and exclusion criteria, hepatitis C intervention and comparisons, the method of outcome ascertainment if

available, and results for each outcome. Evidence tables with included studies are presented for all Key Questions unless there was only very weak evidence (i.e., because of major methodological shortcomings or studies designed without comparison groups).

For studies reporting the diagnostic yield of different screening strategies, we computed the number needed to screen to identify one case of HCV infection by dividing the number of screening tests performed by the number of HCV cases identified. The proportion screened was the number of patients screened upon application of a particular screening strategy, divided by the total number of patients assessed.

For studies of diagnostic accuracy, we created 2x2 tables from information provided (usually sample size, prevalence, sensitivity, and specificity) and compared calculated measures of diagnostic accuracy based on the 2x2 tables with reported results. Although we abstracted data for severe fibrosis (defined as biopsy showing METAVIR F3-F4, Ishak 4-6, or equivalent), we summarized results for fibrosis (defined as biopsy showing METAVIR F2-F4, Ishak 3-6, or equivalent) and cirrhosis (defined as biopsy showing METAVIR F4, Ishak 5-6, or equivalent), unless there was insufficient evidence for fibrosis. We also abstracted reported area under the receiver operating characteristic curve (AUROC).^{54,55} The AUROC, which is based on sensitivities and specificities across a range of test results, is a measure of discrimination, or the ability of a test to distinguish people with a condition from people without. An AUROC of 1.0 indicates perfect discrimination and an AUROC of 0.5 indicates complete lack of discrimination. Interpretation of AUROC values between 0.5 and 1.0 is somewhat arbitrary, but a value of 0.90 to <1.0 may be classified as excellent, 0.80 to <0.90 good, 0.70 to <0.80 fair, and <0.70 poor. Data abstraction for each study was completed by two investigators: the first abstracted the data, and the second reviewed the abstracted data for accuracy and completeness.

We assessed the quality of each study based on predefined criteria. We adapted criteria from methods proposed by Downs and Black (observational studies),⁵⁶ USPSTF,⁵⁷ and the Quality Assessment of Diagnostic Accuracy Studies-2 Group.⁵⁸ The criteria used are consistent with the approach recommended by AHRQ in the Methods Guide for Comparative Effectiveness Reviews.⁵⁹ We used the term “quality” rather than the alternate term “risk of bias”; both refer to internal validity.

We rated the quality of each randomized trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to followup; the use of intent-to-treat analysis; and ascertainment of outcomes.⁵⁷

We rated the quality of each cohort study based on whether it used nonbiased selection methods to create an inception cohort; whether it evaluated comparable groups; whether rates of loss to followup were reported and acceptable; whether it used accurate methods for ascertaining exposures, potential confounders, and outcomes; and whether it performed appropriate statistical analyses of potential confounders.⁵⁷ For assessing the quality of case-control studies, we evaluated whether similar inclusion and exclusion criteria were applied to select cases and controls; whether they used accurate methods to identify cases; whether they used accurate methods for ascertaining exposures and potential confounders; and whether they performed appropriate statistical analyses of potential confounders.⁵⁷

We rated the quality of each diagnostic accuracy study based on whether it evaluated a representative spectrum of patients; whether it enrolled a random or consecutive sample of patients meeting predefined criteria; whether it used a credible reference standard; whether the

same reference standard was applied to all patients; whether the reference standard was interpreted independently from the test under evaluation; and whether test cutoff thresholds were predefined.^{57, 58}

Following assessment of individual quality criteria, individual studies were rated as “good,” “fair,” or “poor” quality, as defined below.⁵⁹

Good-quality studies are considered likely to be valid. Good-quality studies clearly describe the population, setting, interventions, and comparison groups; use a valid method for allocation of patients to interventions; clearly report dropouts and have low dropout rates; use appropriate methods for preventing bias; and appropriately measure outcomes and fully report results.

Fair-quality studies have some methodological deficiencies, but no flaw or combination of flaws judged likely to cause major bias. The study may be missing information, making it difficult to assess its methods or assess limitations and potential problems. The fair-quality category is broad, and studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are likely to be valid, while others are only probably valid.

Poor-quality studies have significant flaws that may invalidate the results. They have a serious or “fatal” flaw in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting. The results of these studies are judged to be at least as likely to reflect flaws in the study design as true effects of the interventions under investigation. We did not exclude studies rated poor quality a priori, but they were considered to be the least reliable studies when synthesizing the evidence, particularly when discrepancies between studies were present.

We recorded factors important for understanding the applicability of studies, such as whether the publication adequately described the study population, how similar patients were to populations likely to be targeted by screening, whether differences in outcomes were clinically (as well as statistically) significant, and whether the interventions and tests evaluated were reasonably representative of standard practice.⁶⁰ We also recorded the funding source and role of the sponsor. We did not assign a rating of applicability (such as “high” or “low”) because applicability may differ based on the user of this report.

We did not attempt to pool studies of screening or treatments quantitatively due to small numbers of studies, lack of randomized trials, and substantial clinical diversity with respect to the populations, settings, and comparisons evaluated. We also did not quantitatively pool results on diagnostic accuracy (such as creating a summary receiver operating characteristic curve) due to differences across studies in populations evaluated, differences in how fibrosis or cirrhosis were defined, and methodological limitations in the studies. Instead, we created descriptive statistics with the median sensitivity and specificity at specific cutoffs and reported AUROCs, along with associated ranges. The total range, rather than the interquartile range, was chosen because certain outcomes were only reported by a few studies and the summary range highlighted the greater variability (and uncertainty) in the estimates.

We rated the strength of evidence for each Key Question using the four categories recommended in the AHRQ Methods Guide.⁵⁹ We synthesized the overall quality of each body of evidence, based on the type and quality of studies (graded good, fair, or poor); the precision of the estimate of effect, based on the number and size of studies and confidence intervals for the estimates (graded high, moderate, or low); the consistency of results between studies (graded high, moderate, or low); and the directness of the evidence linking the intervention and health outcomes (graded direct or indirect). We were not able to assess for publication bias in studies of interventions using graphical or statistical methods due to small number of studies,

methodological shortcomings, differences across studies in designs, measured outcomes, and other factors. Rather, we searched clinical trial registries and grants databases in order to identify relevant unpublished studies and qualitatively assess their potential effects on conclusions. We rated the strength of evidence for each comparison and outcome using the four categories recommended in the AHRQ guide.⁵⁹ A “high” grade indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effect. A “moderate” grade indicates moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of effect and may change the estimate. A “low” grade indicates low confidence that the evidence reflects the true effect and further research is likely to change the confidence in the estimate of effect and is likely to change the estimate. An “insufficient” grade indicates evidence either is unavailable or too limited to permit a conclusion.

Peer Review

Experts in gastroenterology, hepatology, and infectious disease fields and individuals representing stakeholder and user communities were invited to provide external peer review of this CER; AHRQ and an associate editor also provided comments. The draft report was posted on the AHRQ Web site for 4 weeks to elicit public comment. We addressed all reviewer comments, revising the text as appropriate, and documented comments and responses in a disposition report that will be made available 3 months after AHRQ posts the final CER on its Web site.

Results

The strength of the evidence and key findings of this review are summarized in Table A. Of the 10,786 citations identified at the title and abstract level, we screened and reviewed 808 full-length articles. A total of 182 studies were included. We identified no relevant unpublished studies from searches on clinical trials registries and grants databases. There was no direct evidence on clinical benefits associated with screening compared with no screening (or of different screening approaches) in nonpregnant or pregnant adults. Retrospective studies found that screening strategies targeting multiple risk factors were associated with sensitivities of over 90 percent and numbers needed to screen to identify one case of HCV infection of less than 20.^{64,65,67,68} More narrowly targeted alternative screening strategies (such as only screening persons with a history of injection drug use) were associated with numbers needed to screen of less than two, but missed up to two-thirds of infected patients. Data on harms of screening (such as labeling and anxiety) were sparse. A number of indices based on panels of blood tests were associated with an AUROC of 0.75 to 0.86 for diagnosing fibrosis and an AUROC of 0.80 to 0.91 for diagnosing cirrhosis compared with liver biopsy, but there was insufficient evidence to determine clinical outcomes associated with different strategies for evaluating patients with HCV infection. Limited evidence suggested that knowledge of HCV status and counseling interventions may reduce alcohol use and risky injection drug use behaviors, but more evidence is needed to demonstrate long-term sustainability and effects on clinical outcomes and transmission risk. In pregnant women, cohort studies found no clear association between mode of delivery and risk of vertical transmission of HCV infection and consistently found no association between breastfeeding and transmission risk. Evidence on the association between other labor and delivery management practices and risk of vertical transmission of HCV

infection was sparse, but suggested that prolonged rupture of membranes is associated with increased risk.

Although screening tests can accurately identify adults with chronic HCV infection, targeted screening strategies based on presence of risk factors misses a substantial proportion of patients with HCV infection. As a result, more research is needed to understand the effects of different screening strategies on clinical outcomes. Evidence on effects of knowledge of HCV status and counseling and immunizations in patients diagnosed with HCV infection remains sparse. The assessments of benefits and harms of screening are likely to be contingent on the effectiveness of antiviral regimens, which are the subject of a complementary review.

Table A. Summary of evidence on comparative benefits and harms of screening for hepatitis C virus infection

Key Question	Strength of Evidence	Summary
Key Question 1a. Does screening for HCV infection in nonpregnant adults without known abnormal liver enzymes reduce mortality and morbidity due to HCV infection, affect quality of life, or reduce incidence of HCV infection?	Insufficient	No studies
Key Question 1b. Does screening for HCV infection during pregnancy reduce vertical transmission of HCV or improve mortality or morbidity for the mother or child?	Insufficient	No studies
Key Question 2a. What is the effectiveness of different risk- or prevalence-based methods for screening for HCV infection on clinical outcomes?	Insufficient	No studies
Key Question 2b. What is the sensitivity and number needed to screen to identify one case of HCV infection of different risk- or prevalence-based methods for screening for HCV infection?	Low	Five studies found that screening strategies targeting multiple risk factors were associated with sensitivities of over 90% and numbers needed to screen to identify one case of HCV infection of less than 20. More narrowly targeted screening strategies were associated with numbers needed to screen of less than two, but with the trade-off of missing up to two-thirds of infected patients. All studies were retrospective and had methodological shortcomings.
Key Question 3. What are the harms associated with screening for HCV infection, including adverse effects such as anxiety, labeling, and impact on relationships?	Insufficient	Five studies of patients diagnosed with HCV infection suggested potential negative psychological and social effects, but are difficult to interpret due to small sample sizes and methodological shortcomings, including no unscreened comparison group.

Table A. Summary of evidence on comparative benefits and harms of screening for hepatitis C virus infection (continued)

Key Question	Strength of Evidence	Summary
Key Question 4a. <i>What is the Comparative Effectiveness and Comparative Diagnostic Accuracy of Various Tests and Strategies for the Workup to Guide Treatment Decisions in Patients who are HCV Positive?</i>		
Clinical Outcomes	Insufficient	One retrospective cohort study (n=156) of patients who received interferon plus ribavirin therapy found no difference in rates of sustained virologic rates between patients who did not undergo biopsy prior to treatment compared with matched patients who did undergo biopsy.
Diagnostic accuracy: Platelet counts vs. liver biopsy	Low	For fibrosis (defined as METAVIR F2-F4, Ishak 3-6, or equivalent), the median AUROC was 0.71 (range 0.38 to 0.94) in 5 studies. For cirrhosis (defined as METAVIR F4, Ishak 5-6, or equivalent), the AUROC was 0.89 (range 0.64 to 0.99) in five studies.
Diagnostic accuracy: Age-platelet index vs. liver biopsy	Moderate	For fibrosis, the median AUROC was 0.69 (range 0.64 to 0.77) in four studies. For cirrhosis, the median AUROC was 0.89 (range 0.67 to 0.91) in four studies.
Diagnostic accuracy: Aspartate aminotransferase-platelet ratio index (APRI) vs. liver biopsy	High	For fibrosis, the median AUROC was 0.76 (range 0.58 to 0.95) in 44 samples reported in 42 studies. For cirrhosis, the median AUROC was 0.85 (range 0.61 to 0.92) in 32 studies.
Diagnostic accuracy: Aspartate aminotransferase-alanine aminotransferase ratio (AST/ALT ratio, or AAR) vs. liver biopsy	High	For fibrosis, the median AUROC was 0.59 (range 0.50 to 0.82) in nine studies. For cirrhosis, the median AUROC was 0.66 (range 0.52 to 0.91) in eleven studies.
Diagnostic accuracy: Cirrhosis Discriminant Score (CDS, also Bonacini Index) vs. liver biopsy	Moderate	For cirrhosis, the median AUROC was 0.77 (range 0.70 to 0.91) in six studies. Although the CDS was developed to identify cirrhosis, three studies reported a median AUROC of 0.67 (range of 0.64 to 0.71) for fibrosis.
Diagnostic accuracy: Enhanced Liver Fibrosis Index (ELF) or Simplified Enhanced Liver Fibrosis Index (Simplified ELF) vs. liver biopsy	Moderate	For fibrosis, the median AUROC was 0.81 (range 0.72 to 0.87) in seven samples reported in five studies. For cirrhosis, the median AUROC was 0.88 (range 0.78 to 0.91) in six samples reported in three studies.
Diagnostic accuracy: FIB-4 vs. liver biopsy	Moderate	For severe fibrosis (defined as METAVIR F3-F4, Ishak 4-6, or equivalent), the median AUROC was 0.86 (range 0.73 to 0.90) in four studies. For cirrhosis, the median AUROC was 0.87 (range 0.83 to 0.92) in six studies.
Diagnostic accuracy: FibroIndex vs. liver biopsy	Moderate	For fibrosis, the median AUROC was 0.71 (range 0.58 to 0.86) in five samples reported in four studies. For cirrhosis, the AUROCs were 0.86 and 0.92 in two studies.
Diagnostic accuracy: Fibrometer vs. liver biopsy	Moderate	For fibrosis, the median AUROC was 0.82 (range 0.78 to 0.85) in eight samples reported in seven studies. For cirrhosis, the median AUROC was 0.91 (range 0.89 to 0.94) in five studies.
Diagnostic accuracy: FibroSpect II vs. liver biopsy	Low	For fibrosis, the median AUROC was 0.86 (range 0.82 to 0.90) in four studies. No study evaluated the diagnostic accuracy of FibroSpect II for cirrhosis.

Table A. Summary of evidence on comparative benefits and harms of screening for hepatitis C virus infection (continued)

Key Question	Strength of Evidence	Summary
Key Question 4a. <i>What is the Comparative Effectiveness and Comparative Diagnostic Accuracy of Various Tests and Strategies for the Workup to Guide Treatment Decisions in Patients who are HCV Positive? (continued)</i>		
Diagnostic accuracy: Fibrotest vs. liver biopsy	High	For fibrosis, the median AUROC for was 0.79 (range 0.70 to 0.89) in 21 samples reported in twenty studies. For cirrhosis, the median AUROC was 0.86 (range 0.71 to 0.92) in eleven studies.
Diagnostic accuracy: Forns' Index vs. liver biopsy	High	For fibrosis, the median AUROC was 0.75 (range 0.60 to 0.86) in sixteen samples reported in fifteen studies. For cirrhosis, the median AUROC was 0.88 (range 0.85 to 0.91) in six studies.
Diagnostic accuracy: Hepascore vs. liver biopsy	High	For fibrosis, the median AUROC was 0.79 (range 0.69 to 0.82) in nine studies. For cirrhosis, the median AUROC was 0.89 (range 0.88 to 0.94) in eight samples reported in seven studies.
Key Question 4a. <i>What is the Comparative Effectiveness and Comparative Diagnostic Accuracy of Various Tests and Strategies for the Workup to Guide Treatment Decisions in Patients who are HCV Positive? (continued)</i>		
Diagnostic accuracy: Lok Index vs. liver biopsy	Moderate	For cirrhosis, the median AUROC was 0.80 (range 0.61 to 0.91) in eight samples reported in six studies. One study reported an AUROC of 0.69 (95% CI 0.69 to 0.74). No study reported the AUROC for the Lok Index for fibrosis.
Diagnostic accuracy: Pohl Index vs. liver biopsy	Low	For severe fibrosis (METAVIR F3-F4, Ishak 3-6, or equivalent), one study reported an AUROC of 0.53 (95% CI 0.51 to 0.56). For cirrhosis, the AUROC was 0.64 and 0.66 in two studies.
APRI vs. Fibrotest	Moderate	Sixteen studies (some of which evaluated overlapping populations) consistently found no differences between the APRI and Fibrotest based on the AUROC.
AST/ALT ratio vs. other indices	Moderate	Twelve of fourteen studies found the AST/ALT ratio associated with a lower AUROC compared with various other indices.
Key Question 4b. What proportion of patients with screen-detected HCV infection receives treatment?	Moderate	Three longitudinal studies reported that 15% to 33% of patients with screen-detected chronic HCV infection received treatment.
Key Question 5. What are the harms associated with the workup for guiding treatment decisions?	Moderate	One study (n=2740) of patients with chronic HCV infection and compensated cirrhosis with an Ishak fibrosis score of ≥ 3 reported serious adverse events in 1.1% of patients, including 0.6% serious bleeds and 0.3% severe pain, with no deaths. Five large (n=1,398 to 61,184) interventions series published since 2004 of patients undergoing percutaneous liver biopsy for a variety of reasons reported peri-procedural mortality in <0.2% and serious complications in 0.3% to 1.0%.

Table A. Summary of evidence on comparative benefits and harms of screening for hepatitis C virus infection (continued)

Key Question	Strength of Evidence	Summary
Key Question 6a. <i>How Effective is Counseling or Immunization of Patients With HCV infection at Improving Health Outcomes or Reducing the Spread of HCV?</i>		
Clinical outcomes or spread of disease: counseling	Insufficient	One randomized trial found a self-management program associated with slight improvements in SF-36 vitality scores compared with provision of educational materials after 6 weeks, but there were no effects on other measures of generic or HCV-related quality of life.
Clinical outcomes: Immunization	Insufficient	No studies.
Key Question 6b. Does becoming aware of positive HCV infection status decrease high-risk behaviors?	Low	Three retrospective studies reported substantial reductions in alcohol use following diagnosis of HCV infection, but two prospective studies found no evidence of sustained reductions in high-risk behaviors (alcohol use or injection drug use behaviors) following diagnosis. Results from two cross-sectional studies were mixed.
Key Question 6c. <i>How Effective is Counseling or Immunization of Patients with HCV Infection at Improving Intermediate Outcomes, Including Change in High Risk Behaviors?</i>		
High-risk behaviors: counseling	Insufficient	Two randomized trials reported somewhat mixed results regarding effects of counseling interventions based on behavioral principles compared with simple educational interventions, though one trial that trained patients to serve as peer mentors reported sustained absolute decreases of about 15% in the proportion engaging in risky injection drug behaviors. Two before-after studies of HCV-infected heavy drinkers following found 36% to 44% reported abstinence 6 to 22 months after a counseling intervention.
Intermediate outcomes: immunization	Insufficient	No studies.
Key Question 7. <i>Do any Interventions Decrease or Increase the Vertical Transmission of HCV During Delivery or in the Perinatal Period?</i>		
Vertical transmission: Elective cesarean vs. vaginal delivery	Low	Two good-quality studies found no statistically significant difference in risk of vertical transmission of HCV infection between elective cesarean and vaginal delivery, but trends were in opposite directions.
Vertical transmission: Any cesarean vs. vaginal delivery	Moderate	Ten of 11 observational studies (one good quality) found no statistically significant difference in risk of vertical transmission of HCV infection following vaginal compared with cesarean (not specified if elective or emergent) delivery.
Vertical transmission: Internal fetal monitoring vs. no internal fetal monitoring	Insufficient	Three observational studies (two good quality) found inconsistent evidence on the association between internal fetal monitoring and the risk of vertical transmission of HCV infection (no association in 2 studies) and OR 6.7 (95% CI 1.1 to 36) in the third study.

Table A. Summary of evidence on comparative benefits and harms of screening for hepatitis C virus infection (continued)

Key Question	Strength of Evidence	Summary
Key Question 7. Do any Interventions Decrease or Increase the Vertical Transmission of HCV During Delivery or in the Perinatal Period? (continued)		
Vertical transmission: Prolonged rupture of membranes vs. less prolonged rupture of membranes	Low	Two studies (one good quality) found an association between prolonged labor after membrane rupture and risk of vertical transmission of HCV infection. In the good-quality study, membrane rupture >6 hours was associated with an adjusted OR of 9.3 (95% CI 1.5 to 180) for vertical transmission.
Vertical transmission: Breastfeeding vs. no breastfeeding	Moderate	Fourteen studies consistently found no significant association between breastfeeding and risk of transmission.

AAR = aspartate aminotransferase-alanine aminotransferase ratio; APRI = aspartate aminotransferase platelet ratio index; AUROC = area under the receiver operating characteristic curve; CI = confidence interval; CDS = Cirrhosis Discriminant Score; ELF = Enhanced Liver Fibrosis Index; HCV = hepatitis C virus; OR = odds ratio

Discussion

Key Findings and Strength of Evidence

Table A summarizes the findings of this review, including strength of evidence grades. Details about factors assessed to determine the overall strength of evidence for each body of evidence are shown in Appendix F. As in the 2004 USPSTF review,³⁹ we found no direct evidence on benefits of screening for HCV infection compared with no screening in asymptomatic adults without liver enzyme abnormalities. Although direct harms of screening appear minimal (since it is a simple blood test), other harms such as labeling, anxiety, and stigmatization remain poorly studied, though reported in some qualitative and other studies.⁶¹⁻⁶³

Retrospective studies found that screening strategies targeting multiple risk factors were associated with sensitivities of over 90 percent and numbers needed to screen to identify one case of HCV infection of less than 20.^{64,65,67,68} More narrowly targeted alternative screening strategies were associated with numbers needed to screen of less than two, but missed up to two-thirds of infected patients. No study prospectively compared different screening strategies or assessed effects of alternative screening strategies on outcomes. Epidemiologic data indicates that about two-thirds of people with chronic HCV infection were born between 1945 and 1965, suggesting that testing of all people in this birth-cohort could be an efficient strategy. However, the only published report on birth-cohort screening is a cost-effectiveness modeling study which did not meet inclusion criteria because it did not assess clinical data.²²

In the absence of direct evidence on screening, understanding the accuracy of the screening test as well as benefits and harms of subsequent workup and treatments in patients found to be HCV-positive can provide an indirect chain of evidence regarding potential benefits of screening. HCV antibody testing with subsequent polymerase chain reaction testing for circulating virus was found to be accurate for identifying patients with HCV infection in a previous systematic review³⁹ and diagnostic accuracy was not re-reviewed for this report. Regarding the workup in patients found to be HCV-positive, a number of blood indices were associated with an AUROC of 0.75 to 0.86 to 0.82 for fibrosis (METAVIR F2-F4, Ishak 3-6, or

equivalent) and 0.80 to 0.91 for cirrhosis (METAVIR F4, Ishak 5-6, or equivalent), generally considered “good” to “very good” diagnostic accuracy.^{54,55} Only one study⁶⁹ evaluated the clinical impact of no biopsy prior to antiviral treatment, showing no differences compared with patients who underwent biopsy prior to treatment. Harms of biopsy appeared to be small, with a risk of death of <0.2 percent and serious complications (primarily bleeding and severe pain) in about 1 percent.⁷⁰⁻⁷⁵ However, estimating harms of screening associated with liver biopsy is a challenge. Although clinical practice has evolved toward less routine use of biopsy prior to antiviral therapy, we found no studies reporting current estimates of the proportion of patients who undergo biopsy prior to treatment.

Some evidence published since the 2004 review suggests that patients who become aware of being HCV positive may reduce risky behaviors,^{37,76-79} but prospective studies suggest that such behavior changes may not be sustained.^{79,80} Evidence on effective methods of counseling to reduce risky behaviors remains sparse, though one randomized trial showed an intervention based on behavioral principles was effective at reducing risky injection drug use behaviors.⁸¹ We did not review evidence on the general effectiveness of counseling and risk prevention interventions in non-HCV infected people. Whether such evidence can be extrapolated to patients with HCV infection requires assumptions regarding applicability. No study has evaluated effects of immunizations for hepatitis A virus (HAV) or hepatitis B virus (HBV) infection on clinical outcomes or effects of counseling or awareness of HCV status on transmission risk.

Many of the benefits from screening are likely to occur as a result of antiviral treatments, which have become increasingly effective at achieving a sustained virologic response (SVR) (a strong predictor of long-term virologic response).⁸² Antiviral treatments, including recently approved new regimens, and the association between SVR and improvement in clinical outcomes (a key evidence gap in the 2004 USPSTF review)³⁹ will be addressed in a separate review. In screened populations, benefits of antiviral treatments will depend in part on the proportion of patients who actually receive treatment. Two studies of screen-detected patients found that 15 to 33 percent of screen-detected patients with chronic HCV infection received antiviral treatment.⁸³⁻⁸⁵ However, interpreting these findings is a challenge, as the proportion of patients who receive treatment is likely to vary depending on the population studied and criteria used to determine treatment eligibility, which continue to evolve and differ across settings.

No study compared effects of screening with not screening pregnant women. Cohort studies report conflicting information regarding intrapartum management including effects of mode of delivery on transmission risk. Two studies^{47,86} that looked at rupture of membranes, which is most commonly experienced by women intending vaginal delivery, reported increased risk of HCV transmission with more prolonged duration of ruptured membranes. Based on those findings, it would be expected that elective cesarean delivery, in which women undergo planned cesarean (intended to be prior to labor or rupture of membranes) should be associated with decreased risk of vertical transmission; however, studies reported conflicting information, with the largest single study⁸⁷ reporting a nonstatistically significant higher trend towards increased transmission following elective cesarean compared with vaginal delivery. Possible explanations include threshold effects (in terms of duration of prolonged rupture of membranes), influence of viral load, or other potential modifying factors in women with ruptured membranes. Studies consistently found no association between breastfeeding and transmission risk.

Findings in Relationship to What Is Already Known

Like an earlier evidence review on HCV screening conducted for the USPSTF,³⁹ we found no direct evidence on clinical benefits associated with screening compared with no screening. As in that review, we found that screening strategies targeted at people with a history of intravenous drug use are associated with small numbers needed to screen to identify one case of HCV infection, but miss a significant proportion of people screened.

The USPSTF review found HCV screening tests to be accurate and we did not re-review diagnostic accuracy. Consistent with other reviews,⁸⁸⁻⁹³ we found that noninvasive tests have fair to good accuracy for diagnosing fibrosis and good to excellent accuracy for diagnosing cirrhosis compared to liver biopsy. Estimates of serious harms associated with liver biopsy are also consistent with estimates from the prior USPSTF review.

Evidence showing that knowledge of HCV status or interventions in people with HCV infection is effective at reducing transmission or high-risk behaviors for transmission remains limited. Studies reporting rates of antiviral treatment in screen-detected patients with HCV infection were all published after the USPSTF review,³⁹ which included studies of referral populations, rather than cohorts of patients identified through screening. The studies of referral populations reported somewhat higher rates of treatment (30-40 percent) compared to the studies of screen-detected patients (15–33 percent) in our review.

The prior USPSTF evidence review did not address prenatal screening for HCV screening. However, our findings were similar to a guideline from the American Congress of Obstetricians and Gynecologists (ACOG), which concluded that there are no known effective preventive measures for reducing the risk of mother-to-child transmission of HCV infection.⁵¹ Like our review, ACOG found limited evidence suggesting a possible association between prolonged rupture of membrane after labor and use of internal fetal monitoring and increased risk of vertical transmission.

Applicability

Several issues may limit applicability of our findings to screening settings likely to be encountered in clinical practice. Most of the studies⁶⁴⁻⁶⁸ evaluating the sensitivity and yield of different screening strategies (Key Question 2b) were conducted in higher prevalence settings, potentially limiting applicability to average- or low-risk populations.

Few studies evaluating harms of liver biopsy were conducted specifically in populations of patients with HCV infection, and none specifically evaluated a screen-identified cohort. The applicability of estimates of serious harms such as bleeding from such studies to a screen-detected population would depend on the presence and severity of liver disease and other comorbidities in the people who underwent biopsy. For example, patients with end-stage liver disease or undergoing biopsy for hepatocellular carcinoma are likely to be at increased risk for bleeding following liver biopsy compared to asymptomatic patients identified through screening.

Studies reporting rates of antiviral treatment in cohorts of patients with screen-detected HCV infection are also difficult to interpret, as the proportion of patients who receive treatment is likely to vary depending on the population studied and criteria used to determine treatment eligibility, which continue to evolve and differ across settings. In addition, two of the studies were conducted in Veterans Affairs (VA) settings^{83, 85} and the third⁸⁴ in people with a history of intravenous drug use (IVDU), and may not accurately reflect treatment patterns in other settings.

Although none of the studies assessing diagnostic accuracy of noninvasive tests compared to liver biopsy were conducted in screen-detected patients, studies generally enrolled a broad spectrum of patients who varied in severity of fibrosis and other markers of HCV infection severity. Therefore, estimates of diagnostic accuracy are likely to be applicable to patients identified by screening.

We did not include evidence on the general effectiveness of interventions to reduce alcohol use or risky injection drug use behaviors, as the applicability of such studies to patients specifically with HCV infection is uncertain. Our findings are not applicable to patients with HIV infection, end-stage renal disease, or following transplant, as these populations were excluded from the review.

Similarly, our findings on the association between labor and delivery management practices and breastfeeding on risk of vertical transmission are not applicable to women with concomitant HIV infection. Risk of mother-to-child transmission of HCV appears to be higher in women with concomitant HIV infection compared to those without HIV infection. Specific interventions already recommended to prevent vertical transmission of HIV infection include antiretroviral therapy, avoidance of breastfeeding, and elective cesarean in selected patients.⁹⁴

Implications for Clinical and Policy Decisionmaking

Our review has some important potential implications for clinical and policy decisionmaking. Because of the lack of direct evidence showing clinical benefits associated with HCV screening, decisions regarding screening must necessarily be made on the basis of the indirect chain of evidence. Evidence clearly supports that HCV antibody tests are accurate for identifying HCV infection, but that strategies targeted at clinical risk factors miss a substantial proportion of infected patients, in part due to undisclosed or unknown risks. Regardless of the screening strategy applied, for screening to be effective, identification of people with HCV infection must lead to subsequent interventions that improve clinical outcomes. Given the lack of evidence showing beneficial effects of screening and subsequent interventions on transmission risk or on intermediate outcomes such as risky behaviors, screening decisions are likely to be critically dependent on the effectiveness of antiviral treatments, which is covered in a separate review.⁵³ Therefore, we recommend that decisions about screening should only be made after also considering the evidence on screening and treatment in totality.

In the prenatal setting, no intervention has been clearly demonstrated to reduce the risk of vertical transmission of HCV infection. Nonetheless, until more evidence is available, if a woman with HCV attempts vaginal delivery, clinicians may consider limiting the duration of ruptured membranes to less than 6 hours given some evidence of an association between prolonged rupture of membranes and increased risk of vertical transmission.⁹⁴

Clinicians and policymakers may consider modeling studies to help estimate potential benefits and harms of screening. We did not include such studies, whose usefulness will depend on the veracity of the model and the reliability of various input parameters.

Limitations of the Comparative Effectiveness Review Process

We excluded non-English language articles, which could result in language bias, though we identified no non-English language studies that would have met inclusion criteria. We included cohort studies on the association between labor and delivery practices or breastfeeding and vertical transmission. Such studies are more susceptible to bias and confounding than well-conducted randomized trials. We therefore focused on results from studies that performed

adjustment and were otherwise assessed as being at lower risk of bias. For Key Questions related to effects of knowledge of HCV status or counseling on risky behaviors, we included weaker study designs such as before-after studies and cross-sectional studies due to lack of evidence from studies with stronger designs. We were unable to formally assess for publication bias due to small numbers of studies, methodological shortcomings, and differences across studies in designs, measured outcomes, and other factors. We did not attempt to pool results for any Key Questions due to differences across studies in populations, interventions, and outcomes assessed. Finally, we did not evaluate evidence on potential barriers to screening and how they might affect estimates of benefits and harms.

Limitations of the Evidence Base

The evidence base on HCV screening had a number of important limitations. No direct evidence comparing clinical outcomes in patients screened with those not screened, or clinical outcomes associated with different HCV screening strategies, is available. Studies on the sensitivity and yield of different screening strategies were primarily conducted in higher-prevalence populations.^{64, 65, 67, 68} Only one small observational study evaluated clinical outcomes in people who underwent liver biopsy compared to no liver biopsy prior to antiviral treatment.⁶⁹ The only studies reporting rates of antiviral treatment in cohorts of patients with screen-identified HCV infection were conducted in VA settings or in a population of IVUDs and may be of limited applicability in other settings.⁸³⁻⁸⁵ Few studies evaluated the effectiveness of interventions for reducing alcohol use or risky injection drug use behaviors in people specifically with HCV infection. In pregnant women, although studies have evaluated the association between prolonged rupture of membranes and internal fetal monitoring and risk of vertical transmission, no study has evaluated whether interventions to reduce their occurrence are associated with decreased risk.

Research Gaps

Significant research gaps continue to limit full understanding of the benefits and harms of screening for HCV infection. Studies that compare clinical outcomes in patients screened and not screened for HCV infection would provide the most direct evidence, but would require large sample sizes and long duration of followup. However, such studies would not necessarily need to be prospective, as well-conducted retrospective studies could also be informative. In addition, in lieu of direct evidence on effects of screening on clinical outcomes, studies that prospectively evaluate the accuracy and efficiency of alternative screening strategies (such as the CDC birth-cohort approach of screening all adults born between 1945 and 1965)⁴³ would help fill important research gaps and provide some evidence to help guide strategies for targeted screening. No studies have adequately assessed the harmful impacts due to anxiety, labeling, or relationships with family and sexual partners that may result from screening for HCV infection in these patients and whether these harmful impacts can be minimized by appropriate counseling.

Another important research gap is that although many studies have assessed the diagnostic accuracy of noninvasive tests compared to liver biopsy, there is insufficient evidence to determine effects of foregoing liver biopsy on clinical outcomes. Although liver biopsy is still regarded as the most accurate method for assessing the histologic stage of HCV infection, it is an invasive test with some risk for serious harms, making workup strategies that make use of noninvasive tests with high diagnostic accuracy a potential alternative. Studies that evaluate the

outcomes of patients who receive treatment without liver biopsies would be helpful in determining whether all or selected patients should undergo pretreatment biopsy.

Another important research gap is that even though screening for chronic HCV infection may have importance not only in terms of individual clinical outcomes, but also as a public health measure, there is insufficient evidence to determine effects of screening on risk of transmission. In addition, screening might also help identify patients who would benefit from counseling about alcohol use or hepatitis A and B vaccinations, but there is insufficient evidence to determine effects of these interventions. Studies demonstrating important individual or public health benefits from counseling, immunizations, and following a diagnosis of HCV in asymptomatic patients would help strengthen the case for screening

In pregnant women, although limited evidence suggests an association between prolonged rupture of membranes and vertical transmission of HCV infection, more studies are needed to understand the strength of the association and whether interventions targeted at avoiding prolonged rupture of membranes are effective at reducing risk of transmission.

Conclusions

Although screening can accurately identify adults with chronic HCV infection, more research is needed to understand the effects of different screening strategies on clinical outcomes. Evidence on effects of knowledge of HCV status and counseling and immunizations in patients diagnosed with HCV infection remains sparse, and more research is needed to understand effective interventions for preventing vertical transmission. A complete assessment of benefits and harms of screening requires consideration of the effectiveness of antiviral regimens, which are the subject of a complementary review.

References

1. Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med.* 2006;144(10):705-14. PMID: 16702586.
2. Davis GL, Alter MJ, El-Serag H, et al. Aging of hepatitis C virus (HCV)-infected persons in the United States: A multiple cohort model of HCV prevalence and disease progression. *Gastroenterology.* 2010;138(2):513-21.e6. PMID: 19861128.
3. Wasley A, Grytdal S, Gallagher K, et al. Surveillance for acute viral hepatitis--United States, 2006. *MMWR Surveill Summ.* 2008;57(2):1-24. PMID: 18354374.
4. National Center for HIV/AIDS, STD & TB Prevention. Disease Burden from Viral Hepatitis A, B, and C in the United States [pdf]. Center for Disease Control; 2011. www.cdc.gov/hepatitis/Statistics/2009Surveillance/PDFs/2009HepSurveillanceRpt.pdf. Accessed May 31, 2012.
5. Ly KN, Xing J, Klevens RM, et al. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. *Ann Intern Med.* 2012;156(4):271-8. PMID: 22351712.
6. Busch MP. Insights into the epidemiology, natural history and pathogenesis of hepatitis C virus infection from studies of infected donors and blood product recipients. *Transfusion Clinique et Biologique.* 2001;8(3):200-6. PMID: 11499958.
7. Kim WR. The burden of hepatitis C in the United States. *Hepatology.* 2002;36(5 Suppl 1):S30-S4. PMID: 12407574.
8. El-Serag HB. Hepatocellular carcinoma: recent trends in the United States. *Gastroenterology.* 2004;127(5 Suppl 1):S27-S34. PMID: 15508094.
9. El-Serag HB. Hepatocellular carcinoma. *CORD Conference Proceedings.* 2011;365(12):1118-27. PMID: 21992124
10. Foster G, Goldin R, Thomas H. Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis. *Hepatology.* 1998;27:209 - 12. PMID: 9425939.
11. Rowan PJ, Al-Jurdi R, Tavakoli-Tabasi S, et al. Physical and psychosocial contributors to quality of life in veterans with hepatitis C not on antiviral therapy. *J Clin Gastroenterol.* 2005;39(8):731-6. PMID: 16082286.
12. Koff RS. Impaired health-related quality of life in chronic hepatitis C: the how, but not the why. *Hepatology.* 1999;29(1):277-9. PMID: 9862878.
13. Rodger AJ, Jolley D, Thompson SC, et al. The impact of diagnosis of hepatitis C virus on quality of life. *Hepatology.* 1999 Nov;30(5):1299-301. PMID: 10534353.
14. Kenny-Walsh E. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. *Irish Hepatology Research Group. N Engl J Med.* 1999;340(16):1228-33. PMID: 10210705.
15. Hagan H, Pouget ER, Des Jarlais DC, et al. Meta-regression of hepatitis C virus infection in relation to time since onset of illicit drug injection: the influence of time and place. *CORD Conference Proceedings.* 2008;168(10):1099-109. PMID: 18849303.
16. Alter H. Discovery of non-A, non-B hepatitis and identification of its etiology. *Am J Med.* 1999;107(6B):16S-20S. PMID: 10653450.
17. Kaur S, Rybicki L, Bacon BR, et al. Performance characteristics and results of a large-scale screening program for viral hepatitis and risk factors associated with exposure to viral hepatitis B and C: results of the National Hepatitis Screening Survey. *National Hepatitis Surveillance Group. Hepatology.* 1996 Nov;24(5):979-86. PMID: 8903363.
18. Yawn BP, Gazzuola L, Wollan PC, et al. Development and maintenance of a community-based hepatitis C registry. *Am J Manage Care.* 2002 Mar;8(3):253-61. PMID: 11915975.
19. Austin GE, Jensen B, Leete J, et al. Prevalence of hepatitis C virus seropositivity among hospitalized US veterans. *Am J Med Sci.* 2000;319(6):353-9. PMID: 10875289.

20. Cheung R. Epidemiology of hepatitis C virus infection in American veterans. *Am J Gastroenterol.* 2000;95(3):740-7. PMID: 10710068.
21. Garfein RS, Vlahov D, Galai N, et al. Viral Infections in short-term injection drug users: The prevalence of the hepatitis C, hepatitis B, human immunodeficiency, and human T-lymphotropic viruses. *Am J Public Health.* 1996;86(5):655-61. PMID: 8629715.
22. Rein DB, Smith BD, Wittenborn JS, Lesesne SB, Wagner LD, Roblin DW, et al. The cost-effectiveness of birth-cohort screening for hepatitis C antibody in U.S. primary care settings. *Ann Intern Med.* 2012; 156(4):263-70. PMID: 22056542
23. Bellentani S, Pozzato G, Saccoccio G, et al. Clinical course and risk factors of hepatitis C virus related liver disease in the general population: report from the Dionysos study. *Gut.* 1999;44(6):874-80. PMID: 10323892.
24. Alter MJ. Epidemiology of hepatitis C. *Hepatology.* 1997;26(3 Suppl 1):62S-5S. PMID: 8781897.
25. Schreiber GB, Busch MP, Kleinman SH, et al. The risk of transfusion-transmitted viral infections. The Retrovirus Epidemiology Donor Study. *N Engl J Med.* 1996;334(26):1685-90. PMID: 8637512.
26. Bialek SR, Terrault NA. The changing epidemiology and natural history of hepatitis C virus infection. *Clin Liver Dis.* 2006;10(4):697-715. PMID: 17164113.
27. McCaughan GW, George J. Fibrosis progression in chronic hepatitis C virus infection. *Gut.* 2004;53(3):318-21. PMID: 14960506.
28. Freeman AJ, Dore GJ, Law MG, et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. *Hepatology.* 2001;34(4 Pt 1):809-16. PMID: 11584380.
29. Seeff LB. Natural history of chronic hepatitis C. *Hepatology.* 2002;36(5 Suppl 1):S35-S46. PMID: 12407575.
30. Barrett S, Goh J, Coughlan B, et al. The natural course of hepatitis C virus infection after 22 years in a unique homogenous cohort: spontaneous viral clearance and chronic HCV infection. *Gut.* 2001;49(3):423-30. PMID: 11511566.
31. Wiese M, Berr F, Portst H, et al. Low frequency of cirrhosis in a large hepatitis C outbreak after 20 years. *J Hepatol.* 2000;32(Suppl 2):101. PMID: 10869294.
32. Seeff LB, Miller RN, Rabkin CS, et al. 45-year follow-up of hepatitis C virus infection in healthy young adults. *Ann Intern Med.* 2000;132(2):105-11. PMID: 10644270.
33. Wiese M, Grüngreiff K, Güthoff W, et al. Outcome in a hepatitis C (genotype 1b) single source outbreak in Germany—a 25-year multicenter study. *J Hepatol.* 2005;43(4):590-8. PMID: 16237783.
34. Harris HE, Ramsay ME, Andrews N, et al. Clinical course of hepatitis C virus during the first decade of infection: cohort study. *BMJ.* 2002;324(7335):450-3. PMID: 11859045.
35. Thomas DL. Hepatitis C epidemiology: injecting new tools in the field. *Hepatology.* 2000 Mar;31(3):790-1. PMID: 10706576.
36. Thein HH, Yi Q, Dore GJ, et al. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. *Hepatology.* 2008;48(2):418-31. PMID: 18563841.
37. Hagan H, Campbell J, Thiede H, et al. Self-reported hepatitis C virus antibody status and risk behavior in young injectors. *Public Health Rep.* 2006;121(6):710-9. PMID: 17278406.
38. Anonymous. Screening for hepatitis C virus infection in adults: recommendation statement. *Ann Intern Med.* 2004;140(6):462-4. PMID: 15023712.
39. Chou R, Clark EC, Helfand M. Screening for hepatitis C virus infection: A review of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med.* 2004;140(6):465-79+I62. PMID: 15023713.
40. Ghany MG, Strader DB, Thomas DL, et al. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology.* 2009;49:1335-74.
41. Dienstag JL, McHutchison JG. American Gastroenterological Association medical position statement on the management of hepatitis C. *Gastroenterology.* 2006;130(1):225-30. PMID: 16401485.

42. AAP. Hepatitis C virus infection. American Academy of Pediatrics. Committee on Infectious Diseases. *Pediatrics*. 1998;101(3):481-5. PMID: 9499195.
43. Smith BD, Morgan RL, Beckett GA, Falck-Ytter Y, Holtzman D, Ward JW. Hepatitis C virus testing of persons born during 1945 to 1965: Recommendations from the Centers for Disease Control and Prevention. *Ann Intern Med*. 2012 Aug 16. PMID: 22910836.
44. European Paediatric Hepatitis CVN. Three broad modalities in the natural history of vertically acquired hepatitis C virus infection. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2005;41:45-51. PMID: 15937762.
45. England K, Thorne C, Newell ML. Vertically acquired paediatric coinfection with HIV and hepatitis C virus. *Lancet Infect Dis*. 2006;6(2):83-90. PMID: 16439328.
46. Ceci O, Margiotta M, Mareello F, et al. High rate of spontaneous viral clearance in a cohort of vertically infected hepatitis C virus infants: What lies behind? *J Hepatol*. 2001;35(5):687-8. PMID: 11690723.
47. Mast EE, Hwang LY, Seto DSY, et al. Risk factors for perinatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy. *J Infect Dis*. 2005;192(11):1880-9. PMID: 16267758.
48. Pembrey L, Newell ML, Tovo PA. The management of HCV infected pregnant women and their children European paediatric HCV network. *J Hepatol*. 2005 Sep;43(3):515-25. PMID: 16144064.
49. Yeung LTF, King SM, Roberts EA. Mother-to-infant transmission of hepatitis C virus. *Hepatology*. 2001;34(2):223-9.
50. Centers for Disease Control and Prevention. Hepatocellular carcinoma—United States, 2001-2006. *MMWR - Morbidity & Mortality Weekly Report*. 2010 May 7;59(17):517-20. PMID: 20448528.
51. American College of Obstetricians and Gynecologists (ACOG). *Viral hepatitis in pregnancy*. 86 ed. ACOG practice bulletin: Washington DC; 2007.
52. Boaz K, Fiore AE, Schrag SJ, et al. Screening and counseling practices reported by obstetrician-gynecologists for patients with hepatitis C virus infection. *Infect Dis Obstet Gynecol*. 2003;11(1):39-44. PMID: 12839631.
53. Chou RC, Hartung D, Rahman B, et al. Comparative Effectiveness of Treatment for Hepatitis C Virus Infection in Adults. Comparative Effectiveness Review. (Prepared by Oregon Evidence-based Practice Center under Contract No. 290-2007-10057-I.). Forthcoming 2012
54. Altman DG, Bland JM. Diagnostic tests 3: receiver operating characteristic plots. *BMJ*. 1994;309(6948):188. PMID: 8044101.
55. Zweig MH, Campbell G. Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. *Clin Chem*. 1993;39(4):561-77. PMID: 8472349.
56. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health*. 1998;52(6):377-84. PMID: 9764259.
57. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med*. 2001;20(3 Suppl):21-35. PMID: 11306229.
58. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: A revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011;155(8):529-36. PMID: 22007046.
59. *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*. AHRQ Publication No. 10(12)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality; April 2012. Chapters available at: http://www.effectivehealthcare.ahrq.gov/ehc/products/60/318/MethodsGuide_Prepublication-Draft_20120523.pdf Accessed June 19, 2012.
60. Atkins D, Chang S, Gartlehner G, et al. Assessing applicability when comparing medical interventions: Agency for Healthcare Research and Quality and the Effective Health Care Program. *Journal of clinical epidemiology*. 2011;64(11):1198-207. PMID: 21463926.

61. Stewart BJ, Mikocka-Walus AA, Harley H, et al. Help-seeking and coping with the psychosocial burden of chronic hepatitis C: A qualitative study of patient, hepatologist, and counsellor perspectives. *Int J Nurs Stud*. 2011 May;49(5):560-9. PMID: 22154094.
62. Zickmund S, Ho EY, Masuda M, et al. "They treated me like a leper". Stigmatization and the quality of life of patients with hepatitis C. *J Gen Intern Med*. 2003;18(10):835-44. PMID: 14521647.
63. Conrad SGL, Cooksley WGE, Dunne MP, Macdonald GA. Living with chronic hepatitis C infection means 'you just haven't got a normal life any more'. *Chronic Illn*. 2006;2(2):121-31. PMID: 17175655.
64. Gunn RA, Murray PJ, Brennan CH, et al. Evaluation of screening criteria to identify persons with hepatitis C virus infection among sexually transmitted disease clinic clients: results from the San Diego Viral Hepatitis Integration Project. *Sex Transm Dis*. 2003 Apr;30(4):340-4. PMID: 12671556.
65. McGinn T, O'Connor-Moore N, Alfandre D, et al. Validation of a hepatitis C screening tool in primary care. *Arch Intern Med*. 2008 Oct 13;168(18):2009-13. PMID: 18852403.
66. Nguyen MT, Herrine SK, Laine CA, et al. Description of a new hepatitis C risk assessment tool. *Arch Intern Med*. 2005 Sep 26;165(17):2013-8. PMID: 16186472.
67. Zuniga IA, Chen JJ, Lane DS, et al. Analysis of a hepatitis C screening programme for US veterans. *Epidemiol Infect*. 2006 Apr;134(2):249-57. PMID: 16490127.
68. Zuure F, Davidovich U, Kok G, et al. Evaluation of a risk assessment questionnaire to assist hepatitis C screening in the general population. *Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin*. 2010 Apr 15;15(15):19539. PMID: 20429995.
69. Andriulli A, Persico M, Iacobellis A, et al. Treatment of patients with HCV infection with or without liver biopsy. *J Viral Hepat*. 2004;11(6):536-42. PMID: 15500554.
70. Atwell TD, Smith RL, Hesley GK, et al. Incidence of bleeding after 15,181 percutaneous biopsies and the role of aspirin. *AJR Am J Roentgenol*. 2010;194(3):784-9. PMID: 20173160.
71. Huang JF, Hsieh MY, Dai CY, et al. The incidence and risks of liver biopsy in non-cirrhotic patients: An evaluation of 3806 biopsies. *Gut*. 2007;56(5):736-7. PMID: 17440193.
72. Myers RP, Fong A, Shaheen AA. Utilization rates, complications and costs of percutaneous liver biopsy: a population-based study including 4275 biopsies. *Liver Int*. 2008;28(5):705-12. PMID: 18433397.
73. Seeff LB, Everson GT, Morgan TR, et al. Complication rate of percutaneous liver biopsies among persons with advanced chronic liver disease in the HALT-C Trial. *Clin Gastroenterol Hepatol*. 2010;8(10):877-83. PMID: 20362695.
74. van der Poorten D, Kwok A, Lam T, et al. Twenty-year audit of percutaneous liver biopsy in a major Australian teaching hospital. *Intern Med J*. 2006;36(11):692-9. PMID: 17040353.
75. West J, Card TR. Reduced mortality rates following elective, percutaneous liver biopsies. *Gastroenterology*. 2010 2010;139(4):1230-7. PMID: 20547160.
76. Kwiatkowski CF, Fortuin Corsi K, Booth RE. The association between knowledge of hepatitis C virus status and risk behaviors in injection drug users. *Addiction*. 2002;97(10):1289-94. PMID: 12359033.
77. Scognamiglio P, Galati V, Navarra A, et al. Impact of hepatitis C virus infection on lifestyle. *World J Gastroenterol*. 2007;13(19):2722-6. PMID: 17569142.
78. Trepka MJ, Zhang G, Leguen F, et al. Benefits and adverse effects of hepatitis C screening: early results of a screening program. *J Public Health Manag Pract*. 2007 May-Jun;13(3):263-9. PMID: 17435493.
79. Tsui JI, Vittinghoff E, Hahn JA, et al. Risk behaviors after hepatitis C virus seroconversion in young injection drug users in San Francisco. *Drug Alcohol Depend*. 2009;105(1-2):160-3. PMID: 19647375.

80. Ompad DC, Fuller CM, Vlahov D, et al. Lack of behavior change after disclosure of hepatitis C virus infection among young injection drug users in Baltimore, Maryland. *Clin Infect Dis*. 2002 Oct 1;35(7):783-8. PMID: 12228813.
81. Latka MH, Hagan H, Kapadia F, et al. A randomized intervention trial to reduce the lending of used injection equipment among injection drug users infected with hepatitis C. *Am J Public Health*. 2008;98:853-61. PMID: 18382005.
82. Brok J, Gluud LL, Gluud C. Ribavirin plus interferon versus interferon for chronic hepatitis C. *Cochrane Database Syst Rev*. 2010;20(1):CD005445-CD. PMID: 20091577.
83. Groom H, Dieperink E, Nelson DB, et al. Outcomes of a hepatitis C screening program at a large urban VA medical center. *J Clin Gastroenterol*. 2008 Jan;42(1):97-106. PMID: 18097298.
84. Lindenburg CEA, Lambers FAE, Urbanus AT, et al. Hepatitis C testing and treatment among active drug users in Amsterdam: Results from the DUTCH-C project. *Eur J Gastroenterol Hepatol*. 2011;23(1):23-31. PMID: 21042221.
85. Mallette C, Flynn MA, Promrat K. Outcome of screening for hepatitis C virus infection based on risk factors. *Am J Gast*. 2008 Jan;103(1):131-7. PMID: 17894850.
86. Spencer JD, Latt N, Beeby PJ, et al. Transmission of hepatitis C virus to infants of human immunodeficiency virus-negative intravenous drug-using mothers: rate of infection and assessment of risk factors for transmission. *J Vir Hep*. 1997;4(6):395-409. PMID: 9430360.
87. European Paediatric Hepatitis C Virus Network. A significant sex--but not elective cesarean section--effect on mother-to-child transmission of hepatitis C virus infection. *J Infect Dis*. 2005;192(11):1872-9. PMID: 16267757.
88. Poynard T, Morra R, Halfon P, et al. Meta-analyses of FibroTest diagnostic value in chronic liver disease. *BMC Gastroenterol*. 2007;7(1):40. PMID: 17937811.
89. Lin Z-H, Xin Y-N, Dong Q-J, et al. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: An updated meta-analysis. *Hepatology*. 2011;53(3):726-36. PMID: 21319189.
90. Smith JO, Sterling RK. Systematic review: non-invasive methods of fibrosis analysis in chronic hepatitis C. *Aliment Pharmacol Ther*. 2009;30(6):557-76. PMID: 19519733.
91. Parkes J, Guha IN, Roderick P, et al. Performance of serum marker panels for liver fibrosis in chronic hepatitis C. *J Hepatol*. 2006;44(3):462-74. PMID: 16427156.
92. Halfon P, Munteanu M, Poynard T. FibroTest-ActiTest as a non-invasive marker of liver fibrosis. *Gastroenterologie Clinique et Biologique*. 2008;32(6, Supplement 1):22-39.
93. Shaheen AAM, Wan AF, Myers RP. FibroTest and FibroScan for the prediction of hepatitis C-related fibrosis: a systematic review of diagnostic test accuracy. *Am J Gastroenterol*. 2007;102(11):2589-600. PMID: 17850410.
94. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States.; 2011. p. 1-207. <http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf>. Accessed on June 20, 2011.

Introduction

Hepatitis C virus (HCV) is a single-stranded, positive-sense RNA virus of the family Flaviviridae. HCV is the most common chronic blood borne pathogen in the United States. The prevalence of anti-HCV antibody in the United States is estimated at 1.6 percent.¹ Approximately 78 percent of those who test positive for anti-HCV antibody have the HCV detectable in the blood (viremia), indicating chronic infection;¹ those with anti-HCV antibody but no viremia are considered to have cleared the infection. About two-thirds of patients with HCV infection were born between 1945 and 1964, with the highest prevalence (4.3 percent) in people 40 to 49 years of age in 1999-2002.¹ The prevalence of chronic HCV infection is thought to have peaked in 2001 at 3.6 million people.² The yearly incidence of HCV infection averaged more than 200,000 cases per year in the 1980s, but by 2001 had declined to around 25,000 cases per year.³ The Centers for Disease Control and Prevention (CDC) estimated 16,000 new cases of HCV infection in 2009.⁴

HCV infection is a leading cause of complications from chronic liver disease and was associated with an estimated 15,000 deaths in the United States in 2007.⁵ One study estimated that the total number of patients with cirrhosis will peak at 1.0 million in 2020, though rates of hepatic decompensation and liver cancer are expected to continue to rise for another 10 to 13 years, given the long lag time between infection and development of cirrhosis and other complications.² HCV-related end-stage liver disease is the most common indication for liver transplantation among American adults, accounting for more than 30 percent of cases, with a 5-fold increase in the number of patients with HCV who underwent liver transplantation between 1990 and 2000.^{6,7} Studies suggest that about half of the recently observed increase in incidence of hepatocellular carcinoma is related to acquisition of HCV infection 2-4 decades earlier.⁸ HCV infection without cirrhosis may be associated with symptoms such as fatigue and worse quality of life compared with the general population.⁹⁻¹³

HCV is primarily acquired via percutaneous exposures to infected blood. The strongest risk factor for HCV infection is injection drug use. The prevalence of HCV infection in injection drug users varies widely depending on age, duration of injection drug use, and other factors (such as availability and use of needle exchange programs).¹⁴ Prevalences range from less than 50 percent in more recent studies of younger injection drug users to over 90 percent in past studies of older injection drug users.¹⁵⁻²¹ About 60 percent of new infections occur in individuals who report injecting drugs within the last 6 months.³ Although large population-based studies^{15, 16, 22} report independent associations between HCV infection and some high-risk sexual behaviors (multiple sexual partners, unprotected sex, and/or sex with a person infected with HCV infection or using injection drugs), the efficiency of transmission via sexual contact appears to be low, and high-risk sexual behaviors may be a marker for undisclosed drug use or other risk factors. Transfusions prior to 1990 are a risk factor for HCV infection but are no longer an important source of infection due to the implementation of effective screening programs for donated blood.^{23, 24} Evidence on tattoos as a risk factor for HCV infection is mixed.²⁵⁻³⁰ Data on other percutaneous exposures and their association with HCV infection risk are limited, and their relative importance may vary depending on geographic locale and other factors.

The natural course of chronic HCV infection varies. Many patients with chronic HCV infection have only mild liver disease even after decades of infection or never develop histologic evidence of liver disease.³¹ In other patients, inflammation and fibrosis of the liver may progress to cirrhosis, which can lead to end-stage liver disease or hepatocellular carcinoma. Once cirrhosis develops, patients have a much higher risk of death and some may benefit from liver transplantation. Well-established predictors of advanced fibrosis in those with chronic HCV

infection include older age at infection, longer duration of infection, male sex, concomitant HIV or hepatitis B virus (HBV) infection, and greater alcohol use.³¹⁻³³ Other factors that may be associated with increased risk of fibrosis include insulin resistance, hepatic steatosis, higher viral load, and the presence of certain HLA class II polymorphisms.

Estimating the proportion of patients in the general population with HCV infection who progress to cirrhosis is difficult because the time of acquisition is often unclear and important endpoints often do not occur until after decades of infection.³⁴ For example, six retrospective cohort studies of HCV-infected adults with known time of infection (based on a known exposure, often to contaminated blood products during young adulthood) reported cirrhosis in 0³⁵ to 10 percent³⁶ of patients after at least 10 years of followup.^{13, 35-40} Overall, studies of community cohorts estimate cirrhosis in an average of 7 percent of people after 20 years of HCV infection, with rates averaging about twice as high in clinical and referral cohorts.^{33, 41} Studies with longer followup suggest that progression to cirrhosis may accelerate after 20 years of chronic infection.³⁹

Screening for HCV infection in asymptomatic adults who have no history of liver disease or known liver function test abnormalities may identify infected patients at earlier stages of disease before they develop serious or irreversible liver damage. A high proportion of people with chronic HCV infection are thought to be unaware of their status. One study of young injection drug users in the United States found that 72 percent were unaware of their HCV-positive status.⁴² Patients with chronic HCV infection may be eligible for antiviral treatments, which have become increasingly effective in achieving long-term eradication of HCV from the blood. In addition, knowledge of or counseling regarding HCV infection might help prevent transmission by decreasing high-risk injection drug use and other risky behaviors or identify those who might benefit from hepatitis A or B vaccinations, alcohol cessation counseling, or other interventions.

Recommendations on HCV screening vary (Table 1). In 2004, the United States Preventive Services Task Force (USPSTF) recommended against screening for HCV infection in adults not at increased risk of infection (D recommendation) and found insufficient evidence to recommend for or against screening in adults at high-risk of infection (I recommendation).⁴³ The 2004 evidence review commissioned by the USPSTF to inform its recommendations found that screening is accurate in identifying people with HCV infection and that antiviral treatments improved intermediate outcomes such as viremia.⁴⁴ The D recommendation in low-risk individuals was based on evidence indicating a relatively low prevalence of HCV infection, natural history studies showing that most patients with chronic HCV infection do not develop major long-term negative health outcomes (such as death, cirrhosis, or need for liver transplantation), lack of direct evidence showing that screening or antiviral treatments improves important health outcomes, and potential harms of screening including those related to unnecessary treatments and labeling. Although the USPSTF concluded that screening high-risk populations would be a more efficient strategy than screening average-risk populations and would lead to improvements in intermediate outcomes (based on sustained virologic response rates), it found insufficient evidence on the effects of screening or antiviral treatments on health outcomes to determine the balance of benefits and harms to screening.⁴³

Table 1. Current hepatitis C virus infection screening recommendations

Organization	Recommended	Uncertain Need	Not Recommended
<p>American Academy of Pediatrics</p> <p>Hepatitis C Infection, Committee on Infectious Diseases (1998)</p>	<p>Children with risk factors</p> <p>Children born to HCV infected mothers</p>	<p>Not stated</p>	<p>Routine testing of pregnant women</p>
<p>American Association for the Study of Liver Diseases</p> <p>American Association for the Study of Liver Diseases Practice Guidelines (2009)</p>	<p>History of any IV drug use</p> <p>People with conditions associated with a high prevalence of HCV infection including:</p> <ul style="list-style-type: none"> • HIV infection • Hemophilia who received clotting factor concentrates prior to 1987 • History of having been on hemodialysis • Unexplained abnormal aminotransferase levels • Prior recipients of transfusions or organ transplants prior to July 1992 including: <ul style="list-style-type: none"> ○ recipients of blood from a donor who later tested positive for HCV infection ○ recipients of transfusion of blood or blood products ○ recipients of an organ transplant • Children born to HCV-infected mothers • Health care, emergency medical and public safety workers after a needle stick injury or mucosal exposure to HCV-positive blood • Current sexual partners of HCV-infected people <p>A liver biopsy should be considered in patients with chronic hepatitis C infection if the patient and health care provider wish information regarding fibrosis stage for prognostic purposes or to make a decision regarding treatment (Class IIa, Level B)</p>	<p>Liver biopsy may be unnecessary in infected people with Genotypes 2 and 3 due to high rates of SVR with treatment</p> <p>Uncertain need for liver biopsy in Genotype 1:</p> <ul style="list-style-type: none"> • 50% response to treatment in Caucasians • 30% response in African Americans <p>Uncertain need for liver biopsy in Genotypes 4–6 due to low prevalence</p>	<p>Routine testing for anti-HCV at birth of children born to HCV-infected mothers due to high rate of positive antibody via passive transfer from the mother. Testing for anti-HCV may be performed at 18 months of age or older</p>
<p>American College of Obstetricians and Gynecologists</p> <p>American College of Obstetricians and Gynecologists practice bulletin; no. 86 (2007)</p>	<p>Screening of at-risk pregnant women for HCV infection</p> <p>Considerations for amniocentesis, route of delivery and breastfeeding in women infected with hepatitis</p>	<p>Not stated</p>	<p>Routine screening considered but not recommended</p>

Table 1. Current hepatitis C virus infection screening recommendations (continued)

Organization	Recommended	Uncertain Need	Not Recommended
<p>American College of Preventive Medicine</p> <p>Practice policy statement (2005)</p>	<ul style="list-style-type: none"> • Current and former IV drug users or sex with an IV drug user • Transfusion or organ transplant recipients prior to 1992 • Clotting factor recipient prior to 1987 • Hemodialysis patients • Individuals with signs and symptoms of liver disease 	<p>Insufficient evidence for or against universal screening</p>	<p>Not stated</p>
<p>American Gastroenterological Association</p> <p>Statement on the Management of Hepatitis C (2006)</p>	<ul style="list-style-type: none"> • Current and former IV drug users • Clotting factor recipient prior to 1987 • Individuals with signs and symptoms of liver disease • Frequent percutaneous exposures • Immigrants from countries with a high prevalence of HCV infections 	<p>Not stated</p>	<p>Routine screening of all asymptomatic adults, who have a low prior probability of HCV infection</p>
<p>Centers for Disease Control and Prevention</p> <p>Recommendations for prevention and control of HCV infection and HCV related chronic disease (1998)</p> <p>Hepatitis C virus testing of persons born during 1945 to 1965 (2012)</p>	<ul style="list-style-type: none"> • Transfusion or organ transplant recipients prior to 1992 • Occupational exposure to HCV positive blood • Health care professionals exposed to HCV infected blood • Signs or symptoms of liver disease • Children born to HCV infected mothers • Persons born during 1945 to 1965 	<p>Recipients of transplanted tissue</p> <p>Intranasal cocaine and other noninjection drug users</p> <p>People with a history of tattooing or body piercing</p> <p>People with a history of multiple sex partners or sexually transmitted diseases</p> <p>Long-term steady sex partners of HCV positive people</p>	<p>Healthcare and public safety workers</p> <p>Pregnant women</p> <p>Household (nonsexual) contacts of HCV positive people</p> <p>General population</p>
<p>United States Preventive Services Task Force</p> <p>Recommendation Statement (2004)</p>	<p>None</p>	<p>Patients with specific risk factors</p>	<p>Patients with no specific risk factors for HCV infection and no symptoms of liver disease</p>

Table 1. Current hepatitis C virus infection screening recommendations (continued)

Organization	Recommended	Uncertain Need	Not Recommended
<p>Veterans Affairs Hepatitis C Resource Center Program</p> <p>Topic Review: Screening Veterans for Hepatitis C Infection (Accessed 2011)</p>	<p>Individuals who request screening</p> <p>Individuals with one or more of the following risk factors:</p> <ul style="list-style-type: none"> • Current and former IV drug users • Transfusion or organ transplant recipients prior to 1992 • Hemodialysis patients • Vietnam-era Veteran, defined by dates of service from 1964 through 1975 • Health care professionals exposed to HCV infected blood • Tattoos or body-piercings obtained in nonregulated settings • Intranasal drug users who have shared paraphernalia • Sex partner of an HCV carrier • 10 or more lifetime sexual partners • HIV infected individuals • History of hemophilia and/ or clotting factor recipient prior to 1987 • Individuals with signs and symptoms of liver disease • Alcoholic hepatitis • Diagnosis (DSM-IV) of alcohol abuse or dependence • Children born to HCV-infected mothers 	<p>Not stated</p>	<p>Not stated</p>

HCV = hepatitis C virus; IV = intravenous

Unlike the USPSTF, other groups (including the American Association for the Study of Liver Disease, the Infectious Diseases Society of America, and the American College of Gastroenterology) recommend screening in higher risk patients.⁴⁵⁻⁴⁷ These recommendations are based on the higher prevalence of HCV infection in higher-risk populations, acceptance of the link between improved intermediate outcomes following antiviral treatments and improved clinical outcomes, and presumed public health benefits related to the potential for reduced risky behaviors and transmission. The CDC recently recommended the screening of high-risk patients as well as age-cohort based HCV screening of all people born between 1945 and 1965⁴⁸

Mother-to-child (vertical) transmission is believed to be the main route of HCV infection acquisition in children.⁴⁹ Estimates of vertical transmission range from 3 to 10 percent.⁴⁹⁻⁵³ The risk of transmission is highest among women with a high viral load at the time of delivery⁴⁹⁻⁵³ and among women coinfecting with HIV.^{52, 54} Routine prenatal screening for HCV infection is not currently recommended by the CDC.⁵⁵ In 2007, the American College of Obstetricians and Gynecologists (ACOG) recommended offering HCV screening to at-risk pregnant women.⁵⁶ The 2004 USPSTF recommendations did not address screening for HCV during pregnancy. While antiviral therapies are contraindicated in pregnancy due to teratogenic risks, identification of HCV infection during pregnancy could facilitate decisionmaking around the use of interventions during labor and delivery or in the perinatal period to prevent mother-to-child transmission.⁵⁷

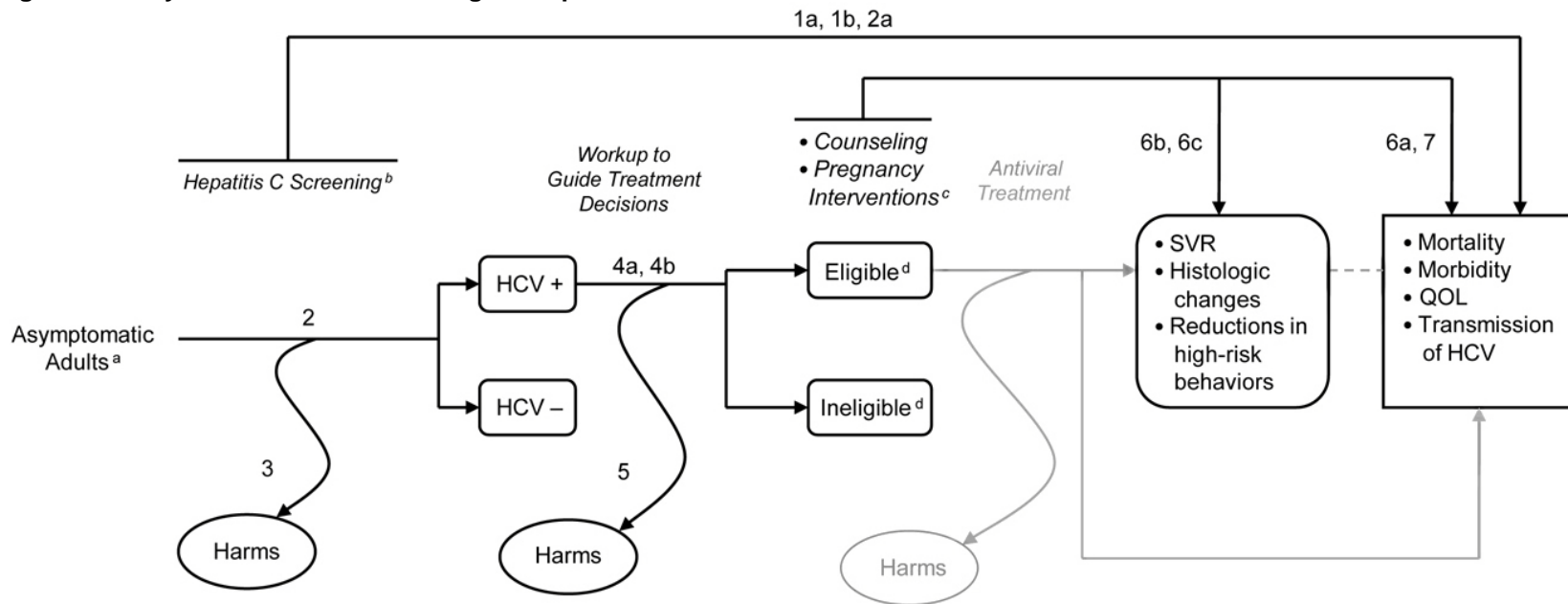
The purpose of this report is to review the evidence on screening for chronic HCV infection in asymptomatic adults without known liver enzyme abnormalities. The Agency for Healthcare Research and Quality (AHRQ), which commissioned this review, also commissioned a separate

but complementary review on effectiveness of antiviral treatments, including newer regimens, which is critical for fully understanding benefits and harms of screening.⁵⁸ Together, these reviews will be used by the USPSTF to update its recommendations on HCV screening. This review focuses on research gaps identified in the 2004 USPSTF review and new studies published since that review. In addition, unlike the 2004 USPSTF review, which focused on nonpregnant adults, it also evaluates evidence on prenatal HCV screening.

Scope and Key Questions

The analytic framework and Key Questions used to guide this report are shown below (Figure 1). The analytic framework shows the target populations, interventions, and intermediate and health outcome measures we examined. We defined universal screening to mean that everyone was tested, regardless of symptoms or risk factors. We defined targeted screening to mean only those who met specific criteria were tested.

Figure 1. Analytic framework: Screening for hepatitis C virus infection in adults



HCV = hepatitis C virus; QOL = quality of life; SVR = sustained virologic response

Note: Portions in grey refer to Key Questions addressed in a separate review on antiviral treatments.⁵⁸

^a Nonpregnant and pregnant adults without abnormal lab values. Excluding people with HIV, transplant recipients, and patients with renal failure.

^b HCV antibody testing with confirmatory HCV RNA testing as indicated.

^c Interventions that may affect vertical transmission of HCV, such as cesarean section, amniocentesis, fetal monitoring, or others.

^d Refers to eligibility for antiviral treatment based on viral and host factors.

Key Question 1

- a. Does screening for HCV infection in nonpregnant adults without known abnormal liver enzymes reduce mortality and morbidity due to HCV infection, affect quality of life, or reduce incidence of HCV infection?
- b. Does screening for HCV infection during pregnancy reduce vertical transmission of HCV or improve mortality or morbidity for the mother or child?

Key Question 2

- a. What is the effectiveness of different risk- or prevalence-based methods for screening for HCV infection on clinical outcomes?
- b. What is the sensitivity and number needed to screen to identify one case of HCV infection of different risk- or prevalence-based methods for screening for HCV infection?

Key Question 3

What are the harms associated with screening for HCV infection, including adverse effects such as anxiety, labeling, and impact on relationships?

Key Question 4

- a. What are the comparative effectiveness and comparative diagnostic accuracy of various tests and strategies for the workup to guide treatment decisions in patients who are HCV positive?
- b. What proportion of patients with screen-detected HCV infection receives treatment?

Key Question 5

What are the harms associated with the workup for guiding treatment decisions?

Key Question 6

- a. How effective is counseling or immunization of patients with HCV infection at improving health outcomes or reducing the spread of HCV?
- b. Does becoming aware of positive HCV infection status decrease high-risk behaviors?
- c. How effective is counseling or immunization of patients with HCV infection at improving intermediate outcomes, including change in high-risk behaviors?

Key Question 7

Do any interventions decrease or increase the risk of vertical transmission of HCV during delivery or in the perinatal period?

The overarching Key Questions (1a and 1b) in the analytic framework focus on direct evidence that screening for HCV infection improves important health outcomes compared with not screening. When such direct evidence is sparse or unavailable, indirect evidence can be used to assess the effects of screening on health outcomes. Therefore, the remainder of the analytic framework evaluates the chain of indirect evidence needed to link screening for HCV infection with improvements in important health outcomes. Links in the chain of indirect evidence include the performance of the screening test or testing strategy for identifying individuals with HCV infection, the clinical utility and diagnostic accuracy of the workup used to guide treatment decisions, and the effectiveness of treatments in those identified as infected with HCV infection, as well as any harms from the screening test and subsequent diagnostic tests and treatments. We

did not re-review the accuracy of HCV antibody testing, which the prior USPSTF review found to be highly accurate. The proportion of patients with HCV infection that receives antiviral treatment is important for understanding potential benefits of screening, as not all patients will receive (and potentially benefit from) treatment. Critical gaps in any of the links of the indirect chain of evidence can make it impossible to reliably estimate benefits and harms of screening.

Methods

Topic Development

The topic of HCV screening was nominated for a comparative effectiveness review (CER) in a public process. The Key Questions were proposed in the public nomination process and developed by investigators from the Evidence-based Practice Center (EPC) with input from expert Key Informants, who helped to refine Key Questions, identify important methodological and clinical issues, and define parameters for the review of evidence. The revised Key Questions were then posted to a public Web site for comment. The Agency for Healthcare Research and Quality (AHRQ) and the EPC agreed upon the final Key Questions after reviewing the public comments and receiving additional input from a Technical Expert Panel (TEP) convened for this report.

Search Strategy

To identify articles relevant to each Key Question, a research librarian searched Ovid® MEDLINE (see Appendix A. Exact Search Strategy), EMBASE, Scopus, and PsycINFO from 1947 to May 2012. Gray literature was identified by searching clinical trial registries (Ovid® EBM Reviews: Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, Current Controlled Trials, Clinical Trial Results, and WHO Trial Registries) and grants databases (NIHRePORTER, HSRProj, and AHRQ GOLD). We supplemented the electronic searches by reviewing the reference lists of retrieved articles.

We updated searches prior to finalization of the report to identify new publications.

Study Selection

We developed criteria for inclusion and exclusion of studies based on the Key Questions and the populations, interventions, comparators, outcomes, timing, and setting (PICOTS) approach. Inclusion and exclusion criteria, summarized below, are described in more detail by Key Question in Appendix B. Papers were selected for full review if they were about chronic HCV infection, were relevant to Key Questions in the analytic framework, and met the predefined inclusion criteria. We restricted inclusion to English language articles since translation of foreign language articles was not feasible due to resource limitations and excluded studies only published as abstracts. Studies of nonhuman subjects were also excluded, and studies had to include original data.

Abstracts and full-text articles were dual reviewed for inclusion or exclusion for each Key Question. Full-text articles were obtained for all studies that either investigator identified as potentially meeting inclusion criteria. Two investigators independently reviewed all full-text articles for final inclusion or exclusion (Appendix C. Included studies list). A list of excluded studies can be found in Appendix D. Discrepancies were resolved through discussion and consensus, and a third investigator was included in the discussion if necessary.

Population and Conditions of Interest

The target population was adults without signs or symptoms of liver disease or known liver function test abnormalities. Specific Key Questions (1b and 7) addressed screening in pregnant

women. We excluded children because of the low prevalence of anti-HCV antibodies (0.2-0.4 percent in 6-19 years old)¹⁵ and because of limited data on benefits and harms of antiviral treatments in children. We excluded specific populations such as post-transplant patients, HIV patients, and hemodialysis patients, because screening test characteristics, natural history of HCV infection, and treatment considerations may differ from what is observed in the general population.⁵⁹⁻⁶³ In addition, evaluation of such patients for chronic HCV infection may be indicated for other reasons such as for informing use of antiretroviral therapies in individuals with HIV infection or assessing prognosis. Patients with occupational exposures were excluded because of consensus regarding screening after percutaneous exposures.⁶⁴ See Appendix B for detailed inclusion and exclusion criteria.

Interventions and Comparators

Our review assumed screening with a later-generation HCV enzyme-linked immunoassay (ELISA) as the initial test, with confirmatory recombinant immunoblot assay (RIBA) or nucleic acid testing for HCV infection for positive ELISA.⁴⁴ We considered patients to have chronic HCV infection if they had hepatitis C viremia based on reverse transcriptase polymerase chain reaction (PCR) or nucleic acid testing. Diagnostic accuracy of HCV antibody testing was reviewed for an earlier report and was not re-reviewed, given the high accuracy of later-generation ELISA testing for HCV antibody with confirmatory RIBA (sensitivity of third-generation ELISA 94 percent or higher and specificity 97 percent or higher; positive predictive value 73 to 86 percent), followed by PCR testing to detect viremia in those with positive tests.⁴⁴ Rather, this report focused on the effects of different screening strategies on clinical outcomes (Key Question 2a) and their yield (sensitivity) and efficiency (number needed to screen to identify one HCV infection) (Key Question 2b). A rapid HCV test was approved by the US Food and Drug Administration (FDA) in 2011 for point-of-care testing, with diagnostic accuracy comparable to standard HCV testing, but is not yet in widespread use.⁶⁵⁻⁶⁷

In most patients with chronic HCV infection, liver biopsy is still recommended as a standard part of the workup for guiding decisions regarding eligibility for antiviral treatments.⁴⁵ The absence of bridging fibrosis (METAVIR F0-F2, Ishak stage 0–3, or equivalent) on liver biopsy is associated with a low likelihood for liver-related complications over the next 10 to 20 years and is an important consideration when making individualized treatment decisions.⁶⁸ However, liver biopsy is invasive and associated with potential complications, is subject to sampling errors, and requires expertise and judgment to interpret. Therefore, a number of tests (including blood tests and imaging studies) have been proposed as potential noninvasive alternatives to biopsy. We evaluated the diagnostic accuracy of noninvasive tests for identifying fibrosis or cirrhosis in patients with HCV infection compared with liver biopsy as the reference standard. We excluded the 13c methacetin breath test⁶⁹ and ultrasonographic transient elastography,⁷⁰ as these are not approved by the FDA and are not in widespread use in the United States.

For treatment of chronic HCV infection, we focused on evidence regarding effects of interventions for reducing risky behaviors associated with transmission of HCV infection, counseling regarding alcohol use, and immunizations for hepatitis A and hepatitis B virus infections. Alcohol use is associated with accelerated liver disease in people with HCV infection and becoming infected with hepatitis A or hepatitis B virus infection may result in fulminant hepatitis or more rapid progression. We also evaluated how knowledge of HCV-positive status affects risky behaviors and alcohol use. Antiviral treatments for HCV infection will be reviewed in a separate report.⁵⁸

For interventions in pregnant women, we focused on evidence regarding effects of labor and delivery and postnatal interventions and practices on risk of vertical transmission. These include mode of delivery (cesarean vs. vaginal delivery), breastfeeding, use of internal fetal monitoring, and management of premature rupture of membranes. Antiviral therapy is contraindicated in pregnant women due to potential teratogenic effects. Management of HCV infection in children was outside the scope of this review.

Outcomes

Clinical outcomes assessed were mortality, end-stage liver disease, cirrhosis, hepatocellular cancer, need for transplantation, quality of life, and HCV transmission. Intermediate outcomes were sustained virological response, histological changes, and reductions in high-risk behaviors (such as alcohol use or intravenous drug use behaviors). Harms of screening included labeling and anxiety. We also reviewed adverse outcomes from screening and treatment including effects of diagnosing chronic HCV infection on quality of life, psychological outcomes, and social and family relationships. We also reviewed adverse outcomes associated with percutaneous liver biopsy such as bleeding, gut perforation, pain, and other complications.

For diagnostic accuracy of noninvasive blood tests for evaluating patients with chronic HCV infection, we evaluated sensitivity and specificity against liver biopsy (considered the reference standard). Because sensitivity and specificity varies depending on the cutoff evaluated, we also evaluated the area under the receiver operating characteristic curve (AUROC), a measure of discrimination that incorporates diagnostic information at multiple cutoffs. An AUROC of >0.90 is often interpreted as indicating excellent discrimination, >0.80 to 0.90 good discrimination, >0.70 to 0.80 fair discrimination, and ≤ 0.70 poor, though cutoffs are somewhat arbitrary. We did not focus on predictive values because they vary depending on the prevalence of the population being evaluated. All of the studies of diagnostic accuracy evaluated referral populations with substantially higher prevalence of fibrosis and cirrhosis than would be expected in screen-detected patients.

Timing

We did not apply a minimum threshold for duration of studies.

Setting

Studies conducted in primary care and specialty settings were included.

Types of Studies

We included randomized trials, cohort studies, and case-control studies pertinent to all Key Questions. If such studies were not available, we included cross-sectional studies and intervention series. We also included studies that reported the diagnostic accuracy of noninvasive tests for evaluating fibrosis or cirrhosis in patients with chronic HCV infection compared with liver biopsy. See appendix B for detailed inclusion and exclusion criteria.

Data Extraction

We extracted the following data from included trials: study design, setting, population characteristics (including sex, age, ethnicity/race, and diagnosis), eligibility and exclusion

criteria, HCV infection intervention and comparisons, the method of outcome ascertainment if available, and results for each outcome. Evidence tables with included studies are presented for all Key Questions unless there was only very weak evidence (e.g., because of major methodological shortcomings or study designed without (comparison groups)).

For studies reporting the diagnostic yield of different screening strategies, we computed the number needed to screen to identify one case of HCV infection by dividing the number of screening tests performed by the number of HCV cases identified. The proportion screened was the number of patients screened upon application of a particular screening strategy, divided by the total number of patients assessed.

For studies of diagnostic accuracy, we attempted to create 2x2 tables from information provided (usually sample size, prevalence, sensitivity, and specificity) and compared calculated measures of diagnostic accuracy based on the 2x2 tables with reported results. Although we abstracted data for severe fibrosis (defined as biopsy showing METAVIR F3-F4, Ishak 4-6, or equivalent), we summarized results for fibrosis (defined as biopsy showing METAVIR F2-F4, Ishak 3-6, or equivalent) and cirrhosis (defined as biopsy showing METAVIR F4, Ishak 5-6, or equivalent), unless there was insufficient evidence for fibrosis. We also abstracted reported area under the receiver operating characteristic curve (AUROC).^{71,72} The AUROC, which is based on sensitivities and specificities across a range of test results, is a measure of discrimination, or the ability of a test to distinguish people with a condition from people without. An AUROC of 1.0 indicates perfect discrimination, and an AUROC of 0.5 indicates complete lack of discrimination. Interpretation of AUROC values between 0.5 and 1.0 is somewhat arbitrary, but a value of 0.90 to <1.0 may be classified as excellent, 0.80 to <0.90 good, 0.70 to <0.80 fair, and <0.70 poor. Data abstraction for each study was completed by two investigators: the first abstracted the data, and the second reviewed the abstracted data for accuracy and completeness. See Appendix G for evidence tables of extracted data.

Quality Assessment of Individual Studies

We assessed the quality of each study based on predefined criteria. We adapted criteria from methods proposed by Downs and Black (observational studies),⁷³ the USPSTF,⁷⁴ and the Quality Assessment of Diagnostic Accuracy Studies-2 Group.⁷⁵ The criteria used are consistent with the approach recommended by AHRQ in the Methods Guide for Comparative Effectiveness Reviews.⁷⁶ We used the term “quality” rather than the alternate term “risk of bias”; both refer to internal validity.

We rated the quality of each randomized trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to followup; the use of intent-to-treat analysis; and ascertainment of outcomes.⁷⁴

We rated the quality of each cohort study based on whether it used nonbiased selection methods to create an inception cohort; whether it evaluated comparable groups; whether rates of loss to followup were reported and acceptable; whether it used accurate methods for ascertaining exposures, potential confounders, and outcomes; and whether it performed appropriate statistical analyses of potential confounders.⁷⁴ For assessing quality of each case-control study, we evaluated whether similar inclusion and exclusion criteria were applied to select cases and controls, whether it used accurate methods to identify cases, whether it used accurate methods

for ascertaining exposures and potential confounders, and whether it performed appropriate statistical analyses of potential confounders.⁷⁴

We rated the quality of each diagnostic accuracy study based on whether it evaluated a representative spectrum of patients, whether it enrolled a random or consecutive sample of patients meeting predefined criteria, whether it used a credible reference standard, whether the same reference standard was applied to all patients, whether the reference standard was interpreted independently from the test under evaluation, and whether thresholds were predefined.^{74, 75}

Following assessment of individual quality criteria, individual studies were rated as “good,” “fair,” or “poor” quality, as defined below.⁷⁶

Good-quality studies are considered likely to be valid. Good-quality studies clearly describe the population, setting, interventions, and comparison groups; use a valid method for allocation of patients to interventions; clearly report dropouts and have low dropout rates; use appropriate methods for preventing bias; and appropriately measure outcomes and fully report results.

Fair-quality studies have some methodological deficiencies, but no flaw or combination of flaws judged likely to cause major bias. The study may be missing information, making it difficult to assess its methods or assess limitations and potential problems. The fair-quality category is broad, and studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are likely to be valid, while others are only probably valid.

Poor-quality studies have significant flaws that may invalidate the results. They have a serious or “fatal” flaw in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting. The results of these studies are judged to be at least as likely to reflect flaws in the study design as true effects of the interventions under investigation. We did not exclude studies rated poor quality a priori, but they were considered to be the least reliable studies when synthesizing the evidence, particularly when discrepancies between studies were present. For detailed quality assessment methods see Appendix E.

Assessing Research Applicability

We recorded factors important for understanding the applicability of studies, such as whether the publication adequately described the study population, how similar patients were to populations likely to be targeted by screening, whether differences in outcomes were clinically (as well as statistically) significant, and whether the interventions and tests evaluated were reasonably representative of standard practice.⁷⁷ We also recorded the funding source and role of the sponsor. We did not assign a rating of applicability (such as “high” or “low”) because applicability may differ based on the user of this report.

Evidence Synthesis and Rating the Body of Evidence

We did not attempt to pool studies of screening or treatments quantitatively due to small numbers of studies, lack of randomized trials, and substantial clinical diversity with respect to the populations, settings, and comparisons evaluated. We also did not quantitatively pool results on diagnostic accuracy (such as creating summary receiver operating characteristic curves) due to differences across those studies in populations evaluated, differences in how fibrosis or cirrhosis were defined, and methodological limitations in the studies. Instead, we created descriptive statistics with the median sensitivity and specificity at specific cutoffs and reported AUROCs, along with associated ranges. The total range, rather than the interquartile range, was

chosen because certain outcomes were only reported by a few studies and the summary range highlighted the greater variability (and uncertainty) in the estimates.

We assessed the overall strength of evidence for each body of evidence in accordance with the AHRQ Methods Guide for Comparative Effectiveness Reviews.⁷⁶ We synthesized the quality of the studies; the consistency of results within and between study designs; the directness of the evidence linking the intervention and health outcomes; the precision of the estimate of effect (based on the number and size of studies and confidence intervals for the estimates); and strength of association (magnitude of effect). We were not able to formally assess for publication bias in studies of interventions due to small number of studies, methodological shortcomings, or differences across studies in designs, measured outcomes, and other factors. We rated the strength of evidence for each Key Question using the four categories recommended in the AHRQ Methods Guide:⁷⁶ A “high” grade indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effect. A “moderate” grade indicates moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of effect and may change the estimate. A “low” grade indicates low confidence that the evidence reflects the true effect and further research is likely to change the confidence in the estimate of effect and is likely to change the estimate. An “insufficient” grade indicates evidence either is unavailable or does not permit a conclusion. See Appendix F for strength of evidence tables.

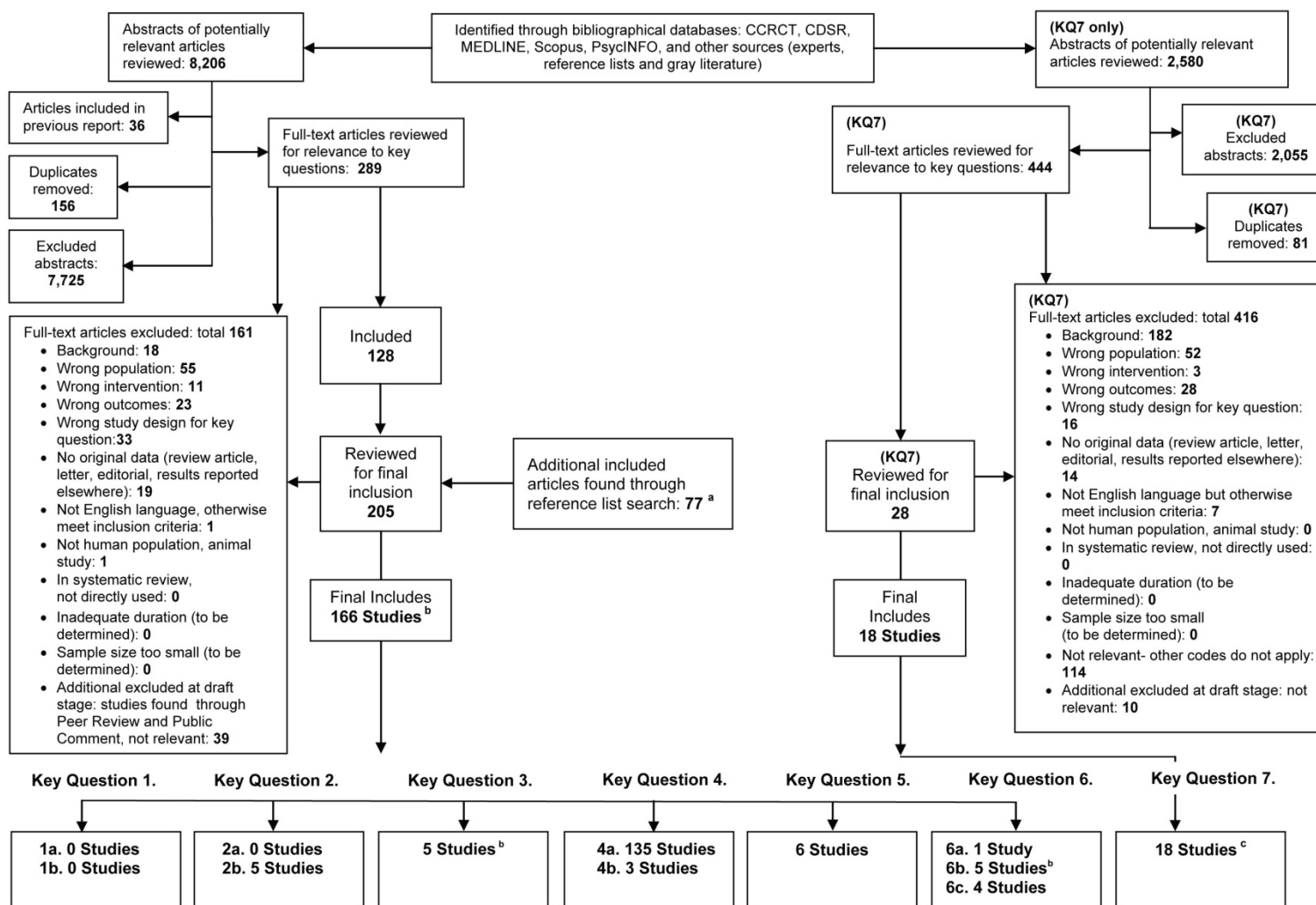
Peer Review

Experts in gastroenterology, hepatology, and infectious disease fields and individuals representing stakeholder and user communities were invited to provide external peer review of this CER; AHRQ and an associate editor also provided comments. The draft report was posted on the AHRQ Web site for 4 weeks to elicit public comment. We addressed all reviewer comments, revising the text as appropriate, and documented everything in a disposition of comments report that will be made available 3 months after the Agency posts the final CER on the AHRQ Web site.

Results

The search and selection of articles are summarized in the study flow diagram (Figure 2). Database searches resulted in 8,206 potentially relevant articles related to screening for hepatitis C virus (HCV) infection in asymptomatic nonpregnant adults and 2,580 potentially relevant articles related to screening for HCV infection in pregnant women. After dual review of abstracts and titles, 289 articles related to screening for HCV infection in asymptomatic adults were selected for full-text review, and 106 were determined by dual review at the full-text level to meet inclusion criteria. In addition, 116 studies were found by reviewing reference lists of published studies and through peer review and public comments. After dual review of abstracts and titles, 444 studies related to screening for HCV infection in pregnant women were selected for full-text review, and 17 were determined by dual review at the full-text level to be relevant. A total of 182 studies were included in this review. We identified no relevant unpublished studies from searches on clinical trials registries and grants databases.

Figure 2. Study flow diagram: Screening for hepatitis C virus infection in asymptomatic adults and pregnant women



^a Includes studies found through Peer Review and Public Comment.

^b One study used for two Key Questions.

^c One study resulting in two publications.

Key Question 1a. Does screening for HCV infection in asymptomatic nonpregnant adults reduce mortality and morbidity due to HCV, affect quality of life, or reduce transmission of HCV?

- No randomized trials or observational studies compared clinical outcomes between individuals screened and not screened for HCV infection (strength of evidence: insufficient).

No randomized trials or observational studies compared clinical outcomes between individuals (either in the general adult population or in higher-risk populations) screened and not screened for HCV infection. Two studies evaluated a screening intervention compared with no screening but did not meet inclusion criteria. One, a cluster randomized trial of methadone patients (n=196) in general practitioner offices in Ireland did not meet inclusion criteria because it evaluated a complex intervention that included provider education on screening for HCV as well as components related to evaluation, referral, and treatments for those found to be hepatitis C positive and was not designed or powered to evaluate clinical outcomes.⁷⁸ It reported no deaths at 6 months, and did not report other clinical outcomes such as morbidity due to HCV, quality of life, and incidence or transmission of HCV infection. The second—a nonrandomized study comparing a screening intervention (targeted at patients aged 30–54 years in an area of Scotland with high HCV and injection drug use prevalence) with no intervention—also did not evaluate clinical outcomes.⁷⁹ In the practice that implemented the intervention, 72 percent (421/584) of those in the target age group were offered HCV screening. Of these, 117 (of 421) were tested, 15 of those tested were HCV antibody positive, two received antiviral therapy, and one achieved a sustained virologic response. No patients in the target age group underwent HCV screening in the comparison practice.

Key Question 1b. Does screening for HCV infection during pregnancy reduce vertical transmission of HCV or improve mortality or morbidity for the mother or child?

- No randomized trials or observational studies evaluated vertical transmission rates of HCV infection in women screened for HCV infection during pregnancy compared with those not screened (strength of evidence: insufficient).
- No randomized trials or observational studies evaluated clinical outcomes in women screened for HCV during pregnancy compared with those not screened, or in infants of women screened compared with those not screened (strength of evidence: insufficient).

Key Question 2a. What is the effectiveness of different risk- or prevalence-based methods for screening for HCV infection on clinical outcomes?

- No randomized trials or observational studies compared clinical outcomes associated with different risk- or prevalence-based strategies for targeted HCV screening (strength of evidence: insufficient).

Key Question 2b. What is the sensitivity and number needed to screen to identify one case of HCV infection of different risk- or prevalence-based methods for screening for HCV infection?

- Five studies found that screening strategies targeting multiple risk factors were associated with sensitivities of over 90 percent and numbers needed to screen to identify one case of HCV infection of less than 20. More narrowly targeted screening strategies were associated with numbers needed to screen of less than two, but with the trade-off of missing up to two-thirds of infected patients. All studies were retrospective and had methodological shortcomings. (strength of evidence: low).

Four cross-sectional studies (samples sizes 985 to 3,367) provided data to calculate effects of applying alternative screening criteria on diagnostic accuracy and yield (Table 2, Table 3, Evidence Table 1, Appendix G).⁸⁰⁻⁸³ Three of the studies were published after the 2004 USPSTF review.⁴⁴ Two studies evaluated patients attending sexually transmitted disease clinics^{80, 83} and two evaluated patients attending urban primary care clinics.^{81, 82} Three studies evaluated higher-prevalence populations (HCV prevalence 4.6 to 8.3 percent)⁸⁰⁻⁸² and one evaluated a lower-prevalence population (HCV prevalence 1.0 percent).⁸³ One smaller study (n=429) in primary care and gastroenterology clinics (n=429) also evaluated alternative screening criteria, but used a case-control design.⁸⁴ All of the studies applied and evaluated alternative screening criteria retrospectively. Other limitations of the studies were that high proportions of potentially eligible patients were not included in analyses because of unknown HCV status, or the study did not report the proportion with unknown HCV status (Evidence Table 2, Appendix G). Although the studies used different criteria for targeted screening, several factors (a personal history of injection drug use, sexual intercourse with an injection drug user, and pre-1992 blood transfusion) were consistently used across studies to identify higher-risk individuals

Table 2. Studies of alternative screening strategies (Key Question 2b)

Author, Year Country	Study Design	Sample Size	Setting Population Characteristics	HCV Screening Strategies	Quality
Gunn, 2003 USA ⁸⁰	Cross-sectional	n=3,367	STD clinic Age ≥30 years: 4.6% Female: Not reported Self-reported intravenous drug use: 5.7%	A: Screen all B: Ever injected drugs (self-report) C: Ever injected drugs or blood transfusions before 1992 (self-report) D: Same as C, or sex partner used injection drugs (self-report) E: Same as D (self-report or identified by clinic staff) F: Same as E, plus bacterial sexually transmitted disease in last 5 years G: Same as F, plus age ≥30 years	Fair
McGinn, 2008 USA ⁸¹	Cross-sectional	n=1,000	Urban primary care clinic Age: Mean 50 years Female: 73% Non-white: 90%	A: Screen all B: Positive findings in ≥1 of 3 domains C: Positive findings in ≥2 domains D: Positive findings in 3 domains	Fair
Nguyen, 2005 USA ⁸⁴	Case-control	n=429 (225 HCV-positive, 204 HCV-negative)	Gastroenterology and primary care clinics Born 1940-1949: 20% Born 1950-1959: 38% Born 1960-1969: 18% Female: 58% Non-white: 37% Reports seeing use of injecting drugs: 34%	A: Screen all B: At least 1 risk factor, based on 7-item instrument (self-report history of sex with a prostitute, history of exposure to potentially infected blood during transfusion, rejection as a blood donor, refused life insurance, witnessing use of injecting drugs, sexual intercourse with an injecting drug user, self-report of HBV infection) C: At least 2 risk factors D: At least 3 risk factors E: Four or more risk factors	Poor
Zuniga, 2006 USA ⁸²	Cross-sectional	n=2,263	Urban primary care clinics Age 40-54 years: 31% White: 78% Female: 3.9% Vietnam era veteran: 50% Blood transfusion prior to 1992: 17% Any intravenous drug use: 4.5% Abnormal liver function tests: 9.1%	A: Any of 11 risk factors (Vietnam era veteran, multiple sexual contacts, tattoo/body piercing, intemperate alcohol use, blood transfusion prior to 1992, intranasal cocaine use, blood exposure (mucous membranes), abnormal liver enzymes, injection drug use (past or present), unexplained liver disease, hemodialysis) B: Any of 5 risk factors (Vietnam era veteran, tattoo/body piercing, blood transfusion prior to 1992, abnormal liver enzymes, injection drug use) C: Self-reported injection drug use (past or present)	Fair
Zuure, 2010 Netherlands ⁸³	Cross-sectional	n=985	STD clinics Population characteristics not reported	A: Screen all B: At least 1 risk factor, based on 20-item questionnaire	Fair

HBV = hepatitis B virus; HCV = hepatitis C virus; STD = sexually transmitted disease

Table 3. Screening strategies: Effects of applying alternative screening criteria on sensitivity and number needed to screen to identify one case of HCV infection (Key Question 2b)

Author, Year Country	HCV Prevalence	Screening Strategy	Proportion Screened	Sensitivity	Specificity	Number Needed To Screen To Identify One Case of HCV Infection
Gunn, 2003 USA ⁸⁰	4.9% (165/3,367)	A: Screened all B: IVDU (self-report) C: IVDU or blood transfusions (self-report) D: IVDU, blood transfusions, or sex partner was an IVDU (self-report) E: Same as D (self-report or identified by clinic staff) F: Same as E, plus bacterial sexually transmitted disease in last 5 years G: Same as F, plus age ≥30 years	A: 100% (3,356/3,356) B: 5.8% (193/3,356) C: 7.5% (253/3,356) D: 10% (347/3,356) E: 12% (413/3,356) F: 34% (1,145/3,356) G: 63% (2,127/3,356)	A: 100% (165/165) B: 60% (99/165) C: 64% (105/165) D: 67% (110/165) E: 70% (116/165) F: 81% (134/165) G: 97% (160/165)	A: 0% (0/3191) B: 97% (3097/3191) C: 95% (3043/3191) D: 93% (2954/3191) E: 91% (2894/3191) F: 68% (2180/3191) G: 38% (1224/3191)	A: 20 (3,356/165) B: 1.9 (193/99) C: 2.4 (253/105) D: 3.2 (347/110) E: 3.6 (413/116) F: 8.5 (1,145/134) G: 13 (2,127/160)
McGinn, 2008 USA ⁸¹	8.3% (83/1,000)	A: Screen all B: Positive findings in ≥1 of 3 domains C: Positive findings in ≥2 domains D: Positive findings in 3 domains	A: 100% (1,000/1,000) B: 71% (709/1,000) C: 23% (228/1,000) D: 5.6% (56/1,000)	A: 100% (83/83) B: 92% (76/83) C: 65% (54/83) D: 34% (28/83)	A: 0% (0/917) B: 31% (284/917) C: 81% (743/917) D: 97% (889/917)	A: 12 (1,000/83) B: 9.3 (709/76) C: 4.2 (228/54) D: 2.0 (56/28)
Nguyen, 2005 USA ⁸⁴	Case-control design: 225 HCV-positive, 204 HCV-negative	A: Screen all B: At least 1 risk factor, based on 7-item instrument C: At least 2 risk factors D: At least 3 risk factors E: Four or more risk factors	A: 100% (429/429) B: 78% (335/429) C: 48% (207/429) D: 28% (118/429) E: 13% (56/429)	A: 100% (225/225) B: 94% (212/225) C: 79% (178/225) D: 51% (115/225) E: 24% (55/225)	A: 0% (0/204) B: 35% (81/204) C: 86% (175/204) D: 99% (201/204) E: 100% (203/204)	Not applicable (case control design)

Table 3. Screening strategies: Effects of applying alternative screening criteria on sensitivity and number needed to screen to identify one case of HCV infection (Key Question 2b) (continued)

Author, Year Country	HCV Prevalence	Screening Strategy	Proportion Screened	Sensitivity	Specificity	Number Needed To Screen To Identify One Case of HCV Infection
Zuniga, 2006 USA ⁸²	4.6% (103/2,263)	A: Any of 11 risk factors B: Any of 5 risk factors C: Self-reported injection drug use (past or present)	A: 100% (2,263/2,263) B: 78% (1,776/2,263) C: 3.0% (68/2,263)*	A: 100% (103/103) B: 97% (100/103) C: 41% (42/103)	A: 0% (0/2160) B: 22% (484/2160) C: 99% (2134/2160)	A: 22 (2,263/103) B: 18 (1,776/100) C: 1.6 (68/42)
Zuure, 2010 ⁸³ Netherlands	1.0% (98/985)	A: Screen all B: At least 1 risk factor, based on 20-item questionnaire	A: 100% (985/985) B: 21% (207/985)	A: 100% (98/98) B: 90% (88/98)	A: 0% (0/887) B: 87% (768/887)	A: 10 (985/98) B: 2.4 (207/88)

HCV = hepatitis C virus; IVDU = intravenous drug user; STD = sexually transmitted disease

One cross-sectional study evaluated a lower-prevalence population (n=985, HCV seroprevalence 1 percent).⁸³ It found that targeted screening for HCV infection in a Dutch sexually transmitted diseases clinic based on presence of one or more positive items on a 20-item questionnaire was associated with a sensitivity of 90 percent for identifying persons with HCV infection, and a number needed to screen to identify one case of HCV infection of 2.4.

Three cross-sectional studies in higher-prevalence populations found that screening strategies targeting multiple risk factors were associated with sensitivities of over 90 percent and numbers needed to screen of 9.3 to 18.⁸⁰⁻⁸² One cross-sectional study in a sexually transmitted disease clinic (n=3,367, HCV seroprevalence 4.9 percent) found that screening patients with one of five risk factors (injection drug user, sex partners of injection drug user, received a pre-1992 blood transfusion, bacterial sexually transmitted disease in last 5 years, or age ≥ 30 years) would have resulted in testing 63 percent of clinic attendees, with a sensitivity of 97 percent for identifying HCV infection and a number needed to screen of 13.⁸⁰ One study of patients in an inner city primary care clinic (n=1,000; HCV seroprevalence 8.3 percent) found that screening patients with positive findings in at least one of three domains (medical history, exposure history, or social history) would have resulted in screening 71 percent of the population, with a sensitivity of 92 percent for identifying HCV infection and a number needed to screen of 9.3 to identify one case of HCV infection.⁸¹ A study of U.S. veterans (n=2,263, HCV seroprevalence 4.6 percent) found that screening patients based on presence of one or more of five risk factors (Vietnam era veteran, tattoo/body piercing, blood transfusion prior to 1992, abnormal liver enzymes, past or present injection drug use) would have resulted in screening 78 percent of the population compared to screening based on presence of these or six additional risk factors (multiple sexual contacts, intemperate alcohol use, intranasal cocaine use, blood exposure (mucous membranes), unexplained liver disease, hemodialysis), with a sensitivity of 97 percent and number needed to screen of 18.⁸²

More narrowly targeted screening strategies evaluated in these studies were associated with specificities of over 95 percent and numbers needed to screen of less than two, but missed up to two-thirds of infected patients.⁸⁰⁻⁸² Two studies found that screening injection drug users would have resulted in testing 3.0 percent and 5.8 percent of the population, respectively, with sensitivities of 41 percent and 60 percent, and numbers needed to screen of 1.6 and 1.9.^{80, 82} One study found that screening patients with positive findings in three different domains (medical, exposure, or social history) would have resulted in testing 5.6 percent of the population, with a sensitivity of 34 percent and number needed to screen of 2.0.⁸¹

A case-control study (222 cases) found that screening based on presence of four or more of seven risk factors (self-reported history of sex with a prostitute, history of exposure to potentially infected blood transfusion, rejections as a blood donor, refused life insurance, witnessed use of injecting drugs, sexual intercourse with an injection drug user, or self-reported hepatitis B virus [HBV] infection) would have identified 24 percent of HCV-infected persons, with a specificity of nearly 100 percent (203/204).⁸⁴ Screening patients with one or more risk factors would have identified 94 percent of infected persons, with a specificity of 35 percent.

The 2004 USPSTF review⁴⁴ included a post-hoc analysis of data from the National Hepatitis Screening Survey that found that screening patients using one of three different risk factor models would have identified between 53 to 69 percent of patients with chronic HCV infection.⁸⁵

A large study based on a French national survey (n=14,416, HCV seroprevalence 0.8 percent) compared different screening strategies but did not meet inclusion criteria because it did not report the proportion screened, the sensitivity, or the number needed to screen to identify one

case of HCV infection with each strategy.⁸⁶ It found screening based on a model that included 11 variables (age, sex, pre-1992 blood transfusion, intravenous drug use, receipt of medical welfare, previous surgeries, illicit nasal drug use, previous HCV screening, tattoo, raised alanine aminotransferase level, and birth in a country with higher HCV prevalence) performed better than screening based on a model with six of these variables (intravenous drug use, elevated alanine aminotransferase level, pre-1992 blood transfusion, tattoo, acupuncture, high HCV prevalence birth region) for discriminating seropositive from seronegative individuals (c-statistic 0.87 [95% confidence interval (CI) 0.86 to 0.87] vs. 0.82 [95% CI 0.81 to 0.82]). The strongest predictors of HCV seropositivity other than intravenous drug use (odds ratio [OR] 36) or history of elevated alanine aminotransferase level (OR 11) was being 40 to 80 years old (the study was based on data collected in 2004), with ORs ranging from 11-36 depending on the 10-year age cohort. The Centers for Disease Control and Prevention (CDC) recently initiated a study to evaluate a screening strategy targeted at the highest-prevalence birth cohort (those born between 1945 and 1965), which is in progress.⁴⁸

Key Question 3. What are the harms associated with screening for HCV infection, including adverse effects such as anxiety, labeling, and impact on relationships?

- Five studies of patients diagnosed with HCV infection suggested potential negative psychological and social effects, but are difficult to interpret due to small sample sizes and methodological shortcomings, including no unscreened comparison group (strength of evidence: insufficient).

Few studies evaluated harms associated with screening for HCV infection. A small, fair-quality cross-sectional study (n=34) of intravenous drug users with chronic HCV infection found those aware of their HCV status reported worse quality of life compared with those who were not aware of their status.¹² A retrospective, before-after study of patients with HCV infection (n=161) found that 44 percent reported a negative impact on psychological status (not otherwise defined); the proportion was similar regardless of time since diagnosis (≤ 1 , >1 to ≤ 5 , or >5 years).⁸⁷ The proportion reporting a negative psychological impact was also similar in the subgroup of patients who reported receiving counseling (not characterized further) from a general practitioner. A study that evaluated a series of 15 newly diagnosed patients with HCV infection found that four binged on alcohol and two thought they were positive for a different virus within 2 weeks of receiving their result.⁷⁹ A survey of 44 patients who were diagnosed with HCV infection through a screening program found that 33 percent reported strain on their relationship with their spouse or significant other and that 40 percent reported difficulty obtaining health insurance.⁸⁸ However, 86 percent reported satisfaction with the decision to be tested and none reported discrimination at work—though in about half of the patients no one at work was aware of the patient's positive HCV status or the patient did not work.

The 2004 USPSTF report⁴⁴ included a small (n=34) controlled trial, published only in abstract form, that found that a brief counseling program helped improve sense of well-being in women diagnosed with HCV.⁸⁹

Key Question 4a. What is the comparative effectiveness and comparative diagnostic accuracy of various tests and strategies for the workup to guide treatment decisions in patients who are HCV positive?

- One retrospective cohort study (n=156) of patients who received interferon plus ribavirin therapy found no difference in sustained virologic rates between patients who did not undergo biopsy prior to treatment compared with matched patients who did undergo biopsy. The study was not designed or powered to evaluate longer-term clinical outcomes (strength of evidence: insufficient).
- 135 studies (thirteen good quality) evaluated various noninvasive tests against liver biopsy for diagnosing fibrosis or cirrhosis in patients with HCV infection. Sensitivity and specificity varied depending on the cutoff used to define a positive test.
- For fibrosis (METAVIR F2-F4, Ishak 3-6, or equivalent), the median AUROC was 0.75 to 0.86 for the aspartate transaminase platelet ratio index (APRI), the Enhanced Liver Fibrosis Index (ELF), FIB-4, the Fibrometer, the FibroSpect II, the Fibrotest, Forns' Index, and Hepascore (strength of evidence: moderate to high, depending on test).
- For cirrhosis (METAVIR F4, Ishak 5-6, or equivalent), the median AUROC ranged from 0.80 to 0.91 for platelet count, the age-platelet index, the APRI, the Enhanced Liver Fibrosis Index, FIB-4, Fibrometer, Fibrotest, Hepascore, and the Lok Index (strength of evidence: moderate to high, depending on test).
- 47 studies evaluated multiple indices against liver biopsy for diagnosing fibrosis or cirrhosis, allowing for direct comparisons of diagnostic accuracy.
 - Sixteen studies (some of which evaluated overlapping populations) consistently found no differences between the APRI and Fibrotest based on the AUROC (strength of evidence: moderate).
 - Twelve of 14 studies found the AST/ALT ratio associated with a lower AUROC compared with various other indices (strength of evidence: moderate).

Effectiveness

One study evaluated clinical outcomes associated with different workup strategies in patients with HCV infection (Evidence Table 3 and Evidence Table 4, Appendix G).⁹⁰ A retrospective cohort study of 156 HCV-positive patients who received interferon plus ribavirin therapy found no difference in sustained virologic response rates between patients who did not undergo biopsy prior to treatment compared with matched patients who did undergo biopsy (41 vs. 44 percent, p=0.87). About three-quarters of the patients who did not undergo biopsy refused it and about one-quarter had contraindications. The study was not designed or powered to evaluate longer-term clinical outcomes and did not report harms associated with biopsy.

Diagnostic Accuracy

One hundred thirty-five studies evaluated the diagnostic accuracy of noninvasive tests for fibrosis or cirrhosis in patients with HCV infection (Evidence Table 5, Appendix G).⁹¹⁻²²³ We also reviewed four subsequent reports²²⁴⁻²²⁷ of diagnostic accuracy from three included studies.^{149, 156, 177}

All studies compared the accuracy of noninvasive tests against liver biopsy as the reference standard. Thirteen studies were rated good quality,^{91, 112, 113, 118, 131, 155, 173-175, 178, 200, 214, 223} four

poor quality,^{100, 125, 128, 194} and the remainder fair quality (Evidence Table 6, Appendix G). Fifty-nine did not describe interpretation of liver biopsies blinded to results of the test being evaluated, 72 studies did not describe enrollment of a consecutive or random sample of patients meeting pre-defined inclusion criteria, and 78 did not evaluate clearly predefined test cutoff values. The studies were primarily conducted in the United States, Europe, and Asia, in referral populations. No study specifically evaluated a screen-detected population of patients with chronic HCV infection. Studies varied with respect to inclusion criteria, including presence of elevated aminotransferases, antiviral therapy status, alcohol use status, and other factors.

Platelet Counts

Fifteen studies evaluated platelet counts (Supplemental Table 1).^{93, 98, 112, 117, 134, 136, 147, 148, 151, 156, 164, 169, 188, 200, 204} For fibrosis (defined as METAVIR F2-F4, Ishak 3-6, or equivalent), the median AUROC was 0.71 (range 0.38 to 0.94, 5 studies) (Table 4).^{93, 98, 117, 156, 204} At a cutoff of <140,000 to <163,000, median sensitivity was 0.51 (range 0.28 to 0.70) and median specificity 0.92 (range 0.71 to 1.0) in seven studies.^{93, 117, 136, 147, 156, 169, 188}

For cirrhosis (defined as METAVIR F4, Ishak 5-6, or equivalent), the median AUROC was 0.89 (range 0.64 to 0.99) in five studies.^{93, 112, 156, 200, 204} At a cutoff of <140,000 to <155,000, median sensitivity was 0.82 (range 0.41 to 0.93) and median specificity 0.88 (range 0.84 to 0.99) in seven studies.^{112, 148, 156, 164, 188, 200, 204}

Other Individual Blood Tests and Indices

Other individual blood tests evaluated for diagnostic accuracy in a number of studies included serum ALT,^{100, 168, 186, 215-217, 219, 220} AST,^{100, 127, 219} bilirubin,^{93, 138, 191} gamma-glutamyl transferase (GGT),^{100, 138, 176, 191, 203} hyaluronic acid,^{100, 140, 141, 143, 159, 166, 168, 176, 182, 184, 194, 220, 223} matrix metalloproteinase-2 (MMP-2),^{100, 126, 168, 217} procollagen-III-peptide,^{133, 140, 141, 159, 161, 168, 194, 212, 215} tissue inhibitor of metalloproteinase-1 and -2 (TIMP-1 and -2),^{100, 126, 168, 217} and type IV collagen (Supplemental Table 1).^{168, 169, 194, 212, 216} For these tests, different cutoffs or assays were evaluated across studies, precluding summary estimates of sensitivity and specificity. In addition, few studies reported the AUROC, which incorporates data across different cutoffs. For ALT, three studies that appeared to evaluate the same or overlapping populations reported AUROCs that ranged from 0.51 to 0.59.²¹⁵⁻²¹⁷ A fourth study reported an AUROC of 0.82.¹⁸⁶ For hyaluronic acid, the median AUROC was 0.75 (range 0.65 to 0.88; seven samples in six studies^{143, 159, 176, 184, 194, 223}) for fibrosis and 0.91 (range 0.85 to 0.97; five samples in four studies^{140, 143, 176, 194}) for cirrhosis.

Individual blood tests evaluated in one or two studies included albumin,^{93, 100} alkaline phosphatase,^{93, 100} apolipoprotein A1,^{138, 191} a-glutathione-S-transferase,²²⁰ haptoglobin,^{138, 191} laminin P1,^{133, 216} alpha-2 macroglobulin,^{138, 191} prothrombin index,¹¹² soluble inter-cellular adhesion molecule-1,¹⁶¹ soluble vascular cell adhesion molecule-1,¹⁶¹ and YKL-40 (Supplemental Table 1).¹⁹⁴ One study evaluated body mass index.²⁰⁹

Table 4. Diagnostic accuracy summary table

	Fibrosis (METAVIR F2-F4, Ishak 3-6, or Equivalent) ^a				Cirrhosis (METAVIR F4, Ishak 3-6, or Equivalent)			
	Cutoff (for Sensitivity and Specificity)	Sensitivity: Median (Range); n Samples	Specificity: Median (Range); n Samples	AUROC: Median (Range); n Samples	Cutoff (for Sensitivity and Specificity)	Sensitivity: Median (Range); n Samples	Specificity: Median (Range); n Samples	AUROC: Median (Range); n Samples
Platelet count	<140,000 to <163,000	0.51 (0.28-0.70); 7	0.92 (0.71-1.0); 7	0.71 (0.38-0.94); 5	<140,000- <155,000	0.82 (0.41-0.93); 7	0.88 (0.84-0.99); 7	0.89 (0.64-0.99); 5
Age-platelet index	>3.5 or >4.0	0.70 and 0.50; 2	0.74 and 0.77; 2	0.69 (0.64-0.77); 4	>5.0 or ≥6.0	0.72 (0.67-0.80); 3	0.89 (0.87-0.93); 3	0.89 (0.67-0.91); 4
	>6.0	0.51 and 0.19; 2	0.93 and 0.86; 2					
Aspartate aminotransferase-platelet ratio index	≥0.5 to >0.55	0.82 (0.29-0.98); 25	0.55 (0.13-0.94); 25	0.76 (0.58-0.95); 44	>1.0 or ≥1.0	0.77 (0.33-1.0); 17	0.75 (0.30-0.87); 17	0.85 (0.61-0.92); 32
	>1.5 or ≥1.5	0.41 (0-0.72); 21	0.95 (0.58-1.0); 21		>2.0 or ≥2.0	0.49 (0.30-0.76); 17	0.94 (0.65-0.97); 17	
Aspartate aminotransferase-alanine aminotransferase ratio	>1.0	0.35 (0.10-0.45); 5	0.77 (0.62-1.0); 5	0.59 (0.50-0.82); 9	>1.0	0.36 (0.12-0.78); 16	0.92 (0.68-1.0); 16	0.66 (0.52-0.91); 11
Cirrhosis Discriminant Score	Only AUROC reported	Not reported	Not reported	0.67 (0.64-0.71); 3	>2.0 or >3.0	0.85 and 1.0; 2	0.22 and 0.58; 2	0.77 (0.70-0.91); 6
					>7.0	0.15 and 0.17; 2	1.0 and 1.0; 2	
Enhanced Liver Fibrosis Index or Simplified Enhanced Liver Fibrosis Index	Varied	Not calculated	Not calculated	0.81 (0.72-0.87); 7	Varied	Not calculated	Not calculated	0.88 (0.78-0.91); 6
FIB-4	>1.45 or ≥1.45	0.74 (0.72-0.92); 5	0.67 (0.51-0.80); 5	0.86 (0.73-0.90); 4	>1.45	0.90; 1	0.55; 1	0.87 (0.83-0.92); 6
	>3.25	0.38 (0.28-0.59); 5	0.98 (0.82-1.0); 5		>3.25	0.55; 1	0.92; 1	
FibroIndex	>1.25	0.94 (0.62-0.97); 3	0.40 (0.40-0.48); 3	0.71 (0.58-0.86); 5	>1.6	0.90; 1	0.74; 1	0.86 and 0.92; 2
	>2.25 or ≥2.25	0.30 (0.17-0.36); 3	0.97 (0.87-1.0); 3					
Fibrometer	>0.419 to >0.59	0.69 (0.64-0.80); 3	0.81 (0.76-0.81); 3	0.82 (0.78-0.85); 8	Varied	Not calculated	Not calculated	0.91 (0.89-0.94); 5
FibroSpect II	Varied	Not calculated	Not calculated	0.86 (0.82-0.90); 4	No studies	No studies	No studies	No studies

Table 4. Diagnostic accuracy summary table (continued)

	Fibrosis (METAVIR F2-F4, Ishak 3-6, or Equivalent) ^a				Cirrhosis (METAVIR F4, Ishak 3-6, or Equivalent)			
	Cutoff (for Sensitivity and Specificity)	Sensitivity: Median (Range); n Samples	Specificity: Median (Range); n Samples	AUROC: Median (Range); n Samples	Cutoff (for Sensitivity and Specificity)	Sensitivity: Median (Range); n Samples	Specificity: Median (Range); n Samples	AUROC: Median (Range); n Samples
Fibrotest	>0.10 to >0.22	0.92 (0.88-0.97); 5	0.46 (0.27-0.56); 5	0.79 (0.70-0.89); 21	>0.56 or >0.66	0.85 and 0.82; 2	0.74 and 0.77; 2	0.86 (0.71-0.92); 11
	>0.70 or >0.80	0.30 (0.20-0.50); 4	0.96 (0.95-0.98); 4		≥0.73, ≥0.75 or >0.862	0.56 (0.30-1.0); 7	0.81 (0.24-0.96); 7	
Forns' Index	>4.2 or ≥4.2	0.88 (0.57-0.94); 12	0.52 (0.20-0.58); 12	0.75 (0.60-0.86); 16	>4.2	0.98; 1	0.27; 1	0.88 (0.85-0.91); 6
	>6.9	0.42 (0.18-0.61); 9	0.94 (0.66-0.99); 9		>6.9	0.67; 1	0.91; 1	
Hepascore	>0.46 to ≥0.55	0.66 (0.54-0.82); 5	0.79 (0.65-0.86); 5	0.79 (0.69-0.82); 9	>0.801 or ≥0.84	0.71 (0.71-0.80); 5	0.84 (0.81-0.89); 5	0.89 (0.88-0.94); 8
Lok Index	No studies	No studies	No studies	No studies	≥0.2	0.90 (0.67-1.0); 6	0.56 (0.30-0.82); 6	0.80 (0.61-0.91); 8
					≥0.5 or >0.6	0.52 (0.40-0.79); 6	0.91 (0.60-0.95); 6	
Pohl Index	Positive	0.20 (0.09-0.86); 5	0.98 (0.84-0.98); 5	0.53; 1	Positive	0.27 (0.26-0.34); 3	0.99 (0.98-0.99); 3	0.64 and 0.66; 2

AUROC = area under the receiver operating characteristic curve

Note: Some studies reported results for more than one population sample.

Note: Medians not calculated for <3 studies (results from individual studies provided).

^aFibrosis results for FIB-4 and Pohl Index are for severe fibrosis (METAVIR F3-F4, Ishak 4-6, or equivalent).

Age-Platelet Index

Six studies evaluated the age-platelet index (Supplemental Table 2).^{102, 124, 125, 129, 156, 160} For fibrosis, the median AUROC was 0.69 (range 0.64 to 0.77) in four studies (Table 4).^{124, 129, 156, 160} At a cutoff of >3.5 or >4.0, sensitivity was 0.70 and 0.50 and specificity 0.74 and 0.77 in two studies.^{124, 160} At a cutoff of >6.0, sensitivity was 0.51 and 0.19 and specificity 0.93 and 0.86 in two studies.^{156, 160}

For cirrhosis, the median AUROC was 0.89 (range 0.67 to 0.91) in four studies.^{102, 124, 125, 129} At a cutoff of >5.0 or ≥ 6.0 , median sensitivity was 0.72 (range 0.67 to 0.80) and median specificity was 0.89 (range 0.87 to 0.93) in three studies.^{102, 124, 125}

Aspartate Aminotransferase-Platelet Ratio Index (APRI)

Fifty-eight studies evaluated the aspartate aminotransferase-platelet (APRI) index (Supplemental Table 2).^{92, 93, 96, 98, 99, 102, 103, 105, 106, 109, 110, 112, 114-119, 122, 124, 125, 127, 129, 130, 135, 137, 142, 145, 146, 148, 151, 153, 156-158, 160, 162, 165, 175, 176, 178, 180, 189, 196-201, 204-206, 209, 213, 214, 219, 221, 223} For fibrosis, the median AUROC was 0.76 (range 0.58 to 0.95; 44 samples in 42 studies) (Table 4).^{92, 93, 98, 105, 109, 110, 114-117, 119, 122, 123, 129, 135, 137, 142, 145, 146, 151, 156-158, 160, 162, 165, 176, 178, 189, 196-198, 200, 201, 205, 206, 209, 213, 214, 219, 221, 223} At a cutoff of >0.5, ≥ 0.5 , ≥ 0.53 , or >0.55, the median sensitivity was 0.82 (range 0.29 to 0.98) and median specificity was 0.55 (range 0.13 to 0.94) in 25 samples reported in 24 studies.^{93, 99, 105, 110, 118, 123, 137, 142, 146, 153, 156, 158, 160, 165, 180, 189, 197, 198, 200, 201, 204, 205, 214, 219} At a cutoff of >1.5 or ≥ 1.5 , median sensitivity was 0.41 (range 0.0 to 0.72) and median specificity was 0.95 (range 0.58 to 1.0) in 21 samples reported in 20 studies.^{93, 99, 105, 118, 137, 142, 146, 153, 156, 158, 160, 165, 180, 197, 198, 200, 201, 205, 214, 219} Excluding an outlier study¹⁶⁰ with unusually poor sensitivity and high specificity narrowed the ranges but had no effect on median values.

For cirrhosis, the median AUROC was 0.85 (range 0.61 to 0.92) in 32 studies.^{92, 102, 103, 105, 106, 109, 112, 116, 119, 124, 125, 129, 130, 135, 137, 142, 145, 146, 151, 156, 157, 162, 165, 176, 196, 197, 199-201, 204, 214, 223} At a cutoff of ≥ 1.0 or >1.0, median sensitivity was 0.77 (range 0.33 to 1.0) and median specificity was 0.75 (range 0.30 to 0.87) in 17 studies.^{99, 102, 105, 109, 112, 118, 137, 142, 146, 151, 156, 165, 196, 197, 200, 201, 214} At a cutoff of ≥ 2.0 or >2.0, the median sensitivity was 0.49 (range 0.30 to 0.76) and median specificity was 0.94 (0.65 to 0.97) in 17 studies.^{99, 102, 105, 112, 118, 137, 142, 146, 148, 156, 165, 197, 199-201, 205, 214}

Aspartate Aminotransferase to Alanine Aminotransferase Ratio (AST/ALT Ratio, or AAR)

Twenty-seven studies evaluated the AST/ALT ratio (Supplemental Table 2).^{93, 95, 98, 101, 102, 112, 117, 125, 127, 129, 134-136, 146, 148, 150, 156, 160, 164, 176, 177, 183, 187, 198, 200, 202, 218} For fibrosis, the median AUROC was 0.59 (range 0.50 to 0.82) in nine studies (Table 4).^{98, 117, 129, 135, 146, 156, 160, 176, 198} At a cutoff of >1.0, the median sensitivity was 0.35 (range 0.10 to 0.45) and median specificity was 0.77 (range 0.62 to 1.0) in five studies.^{117, 146, 160, 183, 198}

For cirrhosis, the median AUROC was 0.66 (range 0.52 to 0.91) in 11 studies.^{93, 102, 112, 125, 129, 135, 146, 156, 176, 177, 200} At a cutoff of >1.0, the median sensitivity was 0.36 (range 0.12 to 0.78) and the median specificity was 0.92 (0.68 to 1.0) in 16 studies.^{93, 95, 102, 112, 134, 146, 148, 150, 156, 164, 176, 177, 187, 200, 202, 218}

Cirrhosis Discriminant Score (CDS)

The cirrhosis discriminant score (CDS) or Bonacini index (based on the platelet count, AST/ALT ratio, prothrombin index, presence of ascites, and presence of spider angiomas) was evaluated in eight studies (Table 4).^{101, 102, 121, 124, 129, 130, 156, 192} For cirrhosis, the median AUROC was 0.77 (range 0.70 to 0.91) in six studies (Table 4).^{102, 124, 129, 130, 156, 192} At a cutoff of >2.0 or >3.0, two studies reported sensitivities of 0.85 and 1.0 and specificities of 0.22 and 0.58.^{102, 192} At a cutoff of >7.0, the same studies reported sensitivities of 0.15 and 0.17, and both reported a specificity of 1.0. Although the CDS was developed to identify cirrhosis, three studies reported a median AUROC of 0.67 (range of 0.64 to 0.71) for fibrosis.^{124, 129, 156}

European Liver Fibrosis Index (ELF) and Enhanced Liver Fibrosis Index (simplified ELF)

Seven studies evaluated the European liver fibrosis index (ELF) index (based on age, hyaluronic acid, amino-terminal propeptide of type III collagen, and TIMP-1) or the enhanced liver fibrosis (simplified ELF) index (a subsequent version, without age) (Supplemental Table 2).^{115, 119, 132, 165, 179, 190, 223} For fibrosis, the median AUROC was 0.81 (range 0.72 to 0.87) in seven samples reported in five studies (Table 4).^{115, 119, 165, 179, 223} For cirrhosis, the median AUROC was 0.88 (range 0.78 to 0.91) in six population samples reported in four studies.^{119, 165, 179, 223} AUROC estimates were similar when studies were stratified according to whether they evaluated the ELF or simplified ELF. Cutoffs varied across studies and differed for the ELF and simplified ELF, precluding summary estimates of sensitivity or specificity.

FIB-4 Index

The FIB-4 index (based on age, AST, ALT, and platelet count) was evaluated in fifteen studies (Supplemental Table 2).^{92, 93, 96, 110, 115, 122, 124, 142, 165, 180, 200, 204, 207, 211, 223} The FIB-4 has primarily been evaluated for identification of severe (METAVIR F3-F4, Ishak 3-6, or equivalent) fibrosis. In four studies, the median AUROC for severe fibrosis was 0.86 (range 0.73 to 0.90) (Table 4).^{92, 93, 165, 211} The AUROC was similar for cirrhosis in six studies (median 0.87, range 0.83 to 0.92).^{92, 124, 142, 165, 204, 223} At a cutoff of >1.45 or ≥ 1.45 , the median sensitivity for severe fibrosis was 0.74 (range 0.72 to 0.92) and median specificity was 0.67 (range 0.51 to 0.80) in five studies.^{93, 96, 165, 207, 211} At a cutoff of >3.25, the median sensitivity for severe fibrosis was 0.38 (range 0.28 to 0.59) and median specificity was 0.98 (range 0.82 to 1.0) in the same five studies.

FibroIndex

The FibroIndex (based on platelet count, AST, and gamma globulin) was evaluated in four studies (Supplemental Table 2).^{92, 129, 155, 198} For fibrosis, the median AUROC was 0.71 (range 0.58 to 0.86) in five samples reported in four studies (Table 4).^{92, 129, 155, 198} At a cutoff of >1.25, median sensitivity was 0.94 (range 0.62 to 0.97) and median specificity 0.40 (range 0.40 to 0.48) in three samples reported in two studies.^{155, 198} At a cutoff of >2.25 or ≥ 2.25 , median sensitivity was 0.30 (range 0.17 to 0.36) and median specificity 0.97 (range 0.87 to 1.0) in the same three samples.

For cirrhosis, two studies reported AUROCs of 0.86 and 0.92.^{92, 129} Only one study reported sensitivity or specificity (Table 4).¹²⁹

Fibrometer

The Fibrometer (based on age, sex, alpha-2-macroglobulin, prothrombin time, platelet count, AST, urea, GGT, and ALT) was evaluated in eight studies (Supplemental Table 2).^{106, 107, 110, 111, 122, 145, 157, 223} For fibrosis, the median AUROC was 0.82 (range 0.78 to 0.85) in eight samples reported in seven studies (Table 4).^{107, 110, 111, 122, 145, 157, 223} At a cutoff of >0.419 to >0.59, median sensitivity was 0.69 (range 0.64 to 0.80) and median specificity was 0.81 (range 0.76 to 0.81) in three studies.^{110, 122, 145} For cirrhosis, the median AUROC was 0.91 (range 0.89 to 0.94) in five studies.^{106, 111, 145, 157, 223} Cutoffs varied across studies, precluding summary estimates of sensitivity and specificity.

FibroSpect II

The FibroSpect II (based on TIMP-1, alpha-2 macroglobulin, and hyaluronic acid) was evaluated in four studies (Supplemental Table 2).^{180, 181, 206, 222} For fibrosis, the median AUROC was 0.86 (range 0.82 to 0.90) in the four studies (Table 4).^{180, 181, 206, 222} Cutoffs varied across studies, precluding summary estimates of sensitivity and specificity. No study evaluated the diagnostic accuracy of FibroSpect II for cirrhosis.

Fibrotest (Fibrosure)

Twenty-eight studies evaluated the Fibrotest (marketed as Fibrosure in the United States) (Supplemental Table 2).^{92, 104, 106, 110, 112, 114, 120, 122, 132, 138, 144, 145, 149, 157, 158, 170, 180, 184, 185, 191, 193, 198-201, 207, 219, 223} The original derivation study for the Fibrotest evaluated a six-marker version based on alpha-2-macroglobulin, haptoglobin, gamma-globulin, apolipoprotein A1, GGT, and total bilirubin.¹⁴⁹ Subsequently, the Fibrotest was modified to a five-marker version without gamma-globulin.

For fibrosis, the median AUROC for was 0.79 (range 0.70 to 0.89) in 21 samples reported in 20 studies (Table 4).^{92, 110, 114, 122, 138, 144, 145, 149, 157, 158, 170, 180, 184, 185, 191, 193, 200, 201, 219, 223} In one study, the AUROC was slightly worse in the subgroup with normal ALT (0.70, 95% CI 0.59 to 0.81) compared with those with elevated ALT (0.79, 95% CI 0.74 to 0.84), but confidence intervals overlapped.¹⁹⁸ At a cutoff of >0.10 to >0.22, median sensitivity was 0.92 (range 0.88 to 0.97) and median specificity 0.46 (range 0.27 to 0.56) in five studies.^{144, 149, 158, 170, 191, 193} At a cutoff of >0.70 or >0.80, median sensitivity was 0.30 (range 0.20 to 0.50) and median specificity 0.96 (range 0.95 to 0.98) in four studies.^{144, 149, 170, 191} At a cutoff of >0.435 to >0.50, median sensitivity was 0.68 (range 0.56 to 1.0) and median specificity 0.79 (range 0.61 to 0.82) in seven studies.^{110, 138, 145, 180, 193, 200, 201} Excluding studies that evaluated earlier versions of the Fibrotest did not affect median estimates or ranges.

For cirrhosis, the median AUROC was 0.86 (range 0.71 to 0.92) in 11 studies.^{92, 104, 106, 112, 145, 157, 193, 199-201, 223} In two studies that evaluated cutoffs of >0.56 and >0.66, sensitivities were 0.85 and 0.82 and specificities were 0.74 and 0.77.^{106, 145} In seven studies that evaluated cutoffs of >0.73, \geq 0.75 or >0.862, median sensitivity was 0.56 (range 0.30 to 1.0) and median specificity 0.81 (range 0.24 to 0.96).^{106, 112, 132, 193, 200, 201, 207}

Forns' Index

Eighteen studies evaluated the Forns' Index (based on age, GGT, cholesterol, and platelet count) (Supplemental Table 2).^{92, 103, 105, 115, 122, 129, 131, 142, 148, 158, 165, 180, 189, 198, 200, 201, 204, 223} For fibrosis, the median AUROC was 0.75 (range 0.60 to 0.86) in sixteen samples reported in fifteen studies (Table 4).^{92, 103, 105, 115, 122, 129, 131, 142, 158, 165, 189, 200, 201, 204, 223} At a cutoff of >4.2 to >4.57,

median sensitivity was 0.88 (range 0.57 to 0.94) and median specificity was 0.52 (range 0.20 to 0.58) in twelve samples reported in eleven studies.^{105, 122, 131, 158, 165, 180, 189, 198, 200, 201, 204} At a cutoff of >6.9, median sensitivity was 0.42 (range 0.18 to 0.61) and median specificity was 0.94 (range 0.66 to 0.99) in nine samples reported in eight studies.^{105, 131, 142, 158, 165, 198, 200, 201}

For cirrhosis, six studies reported a median AUROC of 0.88 (range 0.85 to 0.91).^{92, 103, 129, 142, 165, 204} Only one study reported sensitivity or specificity (Table 4).¹⁴²

Hepascore

Eleven studies evaluated the Hepascore (based on α_2 -macroglobulin, hyaluronic acid, gamma GGT, total bilirubin, age, and sex) (Supplemental Table 2).^{91, 96, 104, 106, 110, 122, 139, 145, 157, 158, 223}

For fibrosis, the median AUROC was 0.79 (range 0.69 to 0.82) in nine studies (Table 4).^{96, 104, 110, 122, 139, 145, 157, 158, 223} At a cutoff of >0.46 to ≥ 0.55 , the median sensitivity was 0.66 (range 0.54 to 0.82) and median specificity 0.79 (range 0.65 to 0.86) in five studies.^{96, 104, 110, 139, 158}

For cirrhosis, the median AUROC was 0.89 (range 0.88 to 0.94) in eight samples reported in seven studies.^{91, 104, 106, 139, 145, 157, 223} At a cutoff of >0.801 to >0.84, the median sensitivity was 0.71 (range 0.71 to 0.80) and median specificity was 0.84 (range 0.81 to 0.89) in five samples reported in four studies.^{91, 104, 106, 139}

Lok Index

Eight studies evaluated the Lok Index (based on platelet count, AST/ALT ratio, and INR (Supplemental Table 2)).^{112, 117, 125, 130, 156, 163, 200, 204} For cirrhosis, the median AUROC was 0.80 (range 0.61 to 0.91) in eight samples reported in six studies (Table 4).^{112, 125, 130, 163, 200, 204} At a cutoff of ≥ 0.2 , median sensitivity was 0.90 (range 0.67 to 1.0) and median specificity 0.56 (range 0.30 to 0.82) in six samples reported in four studies.^{112, 156, 163, 200, 204} At a cutoff of ≥ 0.5 or >0.6, median sensitivity was 0.52 (range 0.40 to 0.79) and median specificity was 0.91 (range 0.60 to 0.95) in six samples reported in five studies.^{112, 125, 156, 163, 200} For fibrosis, one study reported an AUROC Of 0.70 (95% CI 0.62 to 0.77)²⁰⁴ and for severe fibrosis, one study reported an AUROC of 0.69 (95% CI 0.69 to 0.74).¹¹⁷ No study evaluated diagnostic accuracy of the Lok Index for fibrosis.

Pohl Index

Ten studies evaluated the Pohl Index (positive result defined as AST/ALT ratio >1 and platelet count <150,000)^{102, 117, 124, 125, 148, 154, 156, 164, 183} or variants with slightly lower platelet count cutoffs (<140,000 or <130,000) (Supplemental Table 2).^{134, 164} The Pohl Index has primarily been evaluated for identification of more advanced fibrosis. For severe fibrosis (METAVIR F3-F4, Ishak 3-6, or equivalent), one study reported an AUROC of 0.53 (95% CI 0.51 to 0.56) (Table 4).¹¹⁷ The median sensitivity was 0.20 (range 0.09 to 0.86) and median specificity was 0.98 (range 0.84 to 0.99) in five studies.^{117, 148, 154, 156, 183}

For cirrhosis, the AUROC was 0.64 and 0.66 in two studies that evaluated the standard Pohl Index.^{124, 125} With the standard Pohl Index or using a platelet count cutoff of <140,000, median sensitivity was 0.27 (range 0.26 to 0.34) and median specificity was 0.99 (range 0.98 to 0.99) in three studies.^{102, 125, 164} In one study that used a platelet count cutoff of <130,000, sensitivity was higher (0.72) and specificity was similar (0.99).¹³⁴

Sensitivity Analyses

Only one study rated as poor quality evaluated the indices described above.¹²⁵ Its exclusion had no effect on medians or ranges for diagnostic accuracy. Excluding studies that reported results from samples used to derive the various indices also had little effect on findings.^{91, 101, 124, 131, 149, 163, 183, 214} Excluding multiple studies reporting results from similar or overlapping populations also had little effect on findings.

Restriction of analyses to studies that reported a median biopsy length of >15 mm and >5 portal tracts also had little effect on estimates of diagnostic accuracy, though many studies did not report biopsy quality. In addition, there was no consistent association between shorter biopsy length and lower AUROCs or other markers of diagnostic accuracy in studies that stratified results based on biopsy specimen length.^{123, 158, 163, 180, 197} Excluding studies that restricted enrollment to patients with normal serum aminotransferase levels generally had little effect on medians. For diagnosing fibrosis with the APRI at a cutoff of >0.5, one study that restricted enrollment to patients with normal aminotransferases appeared to be an outlier,¹⁶⁰ with a much lower sensitivity (0.29) than the other studies (range 0.67 to 0.97). However, there were relatively few cases (n=21) and the AUROC (0.67) was within the range reported from other studies (0.62-0.92). Studies that stratified patients according to whether they had normal or elevated aminotransferases found no clear effect on the AUROC.^{155, 198, 199}

Other Indices and Combined or Algorithmic Approaches

A number of other indices were evaluated in three or fewer studies, including the Fibro- α Score,¹⁷⁴ Fibrosis Index,^{93, 173} Fibrosis-Cirrhosis Index,⁹³ Fibrosis Probability Index (also known as the Sud Index),^{189, 208} the Fibrosis-protein Index,¹¹⁶ the FibroQ Index,¹⁴⁶ the Goteburg University Cirrhosis Index,^{125, 151} the Globulin/albumin ratio,^{148, 164} the HALT-C model,¹³⁰ the King's Score,^{103, 123, 124} the MP3 score,^{158, 159} the Sabadell NIHCED index,^{97, 172} the Significant Fibrosis Index,¹¹⁵ the Zeng Index,¹¹⁵ and others (Supplemental Table 2). Due to the small numbers of studies, there was insufficient evidence to draw firm conclusions about diagnostic accuracy, though AUROCs when reported generally appeared comparable to other, better-studied indices.

Nine studies evaluated combinations of indices (Supplemental Table 2).^{102, 108, 113, 122, 148, 164, 197, 201, 206} The Sequential Algorithm for Fibrosis Evaluation (SAFE) was evaluated in four studies.^{108, 113, 197, 201} For fibrosis, SAFE (based on the sequential application of the APRI and Fibrotest based on an algorithm) was associated with an AUROC of 0.90 and 0.94 in two studies.^{113, 197} Median sensitivity was 1.0 (range 1.0 to 1.0) and median specificity 0.82 (range 0.77 to 0.88) in four studies.^{108, 113, 197, 201} For cirrhosis, SAFE was associated with a median AUROC of 0.87 (range 0.87 to 0.92) in three studies.^{113, 197, 201} Median sensitivity was 0.84 (range 0.62 to 0.90) and median specificity 0.92 (range 0.90 to 0.93) in four studies.^{108, 113, 197, 201} In single studies, the Leroy and Fibropaca algorithms and various combinations of APRI, FibroSpect II, Fibrotest, FIB-4, and Fibrometer were also associated with diagnostic accuracy somewhat higher than observed with single indices.^{122, 201, 206}

Imaging Findings

Eight studies evaluated the diagnostic accuracy of various imaging findings for fibrosis or cirrhosis on liver biopsy, including hepatic transit time, spleen size, portal vein diameter, presence of liver nodularity, splenic artery pulsatility index, and assessments of portal or hepatic

venous flow (Supplemental Table 1).^{119, 121, 147, 160, 175, 195, 196, 209} Few studies reported AUROCs, making it difficult to draw firm conclusions about diagnostic accuracy. In one study, the AUROC for hepatic transit time was 0.71 (95% CI 0.59 to 0.84) for fibrosis and 0.83 (95% CI 0.69 to 0.97) for cirrhosis.¹¹⁹ Other studies reported AUROCs for fibrosis of 0.86 (95% CI 0.78 to 0.95) for the splenic artery pulsatility index¹⁶⁰ and 0.74 (95% CI 0.63 to 0.84) for the platelet-spleen diameter ratio²⁰⁹ and an AUROC for cirrhosis of 0.80 (CI not reported) for portal venous flow.¹⁹⁵ Two studies found presence of liver surface nodularity associated with sensitivities of 0.60 and 0.16 for fibrosis, and specificities of 0.92 and 0.97.^{121, 147}

Direct Comparisons

Forty-seven studies reported the AUROC for multiple indices for diagnosing fibrosis or cirrhosis against liver biopsy, allowing for direct comparisons of diagnostic accuracy (Supplemental Table 3).^{91-93, 98, 102-106, 110-112, 114-117, 119, 122, 124, 125, 127, 129, 130, 134, 142, 145, 151, 155-158, 160, 165, 170, 171, 176, 178, 180, 189, 198-201, 204, 206, 219, 223} Nine of these studies also compared different indices with platelet counts alone.^{93, 98, 112, 117, 124, 156, 170, 200, 204}

The most frequent direct comparison was of the APRI with the Fibrotest, which was evaluated in 16 studies, though several evaluated overlapping populations (Table 5).^{92, 105, 106, 110, 112, 114, 122, 145, 157, 158, 198-201, 219, 223} There was no clear pattern suggesting differences between the APRI and the Fibrotest, with most tests reporting similar AUROC estimates. Twelve^{93, 98, 102, 112, 117, 125, 129, 156, 160, 176, 198, 200} of fourteen^{127, 134} studies found the AST/ALT ratio associated with lower AUROCs compared with various other indices (Table 6). Seven^{93, 112, 117, 124, 156, 200, 204} of nine^{98, 170} studies found no clear difference in AUROCs for platelet counts compared with various multicomponent indices (Table 7).

Three studies found no clear differences between blood tests compared with imaging findings based on the AUROC (Table 8).^{119, 196, 209}

Table 5. Aspartate aminotransferase-platelet ratio index compared with Fibrotest

Study, Year	Country	N	Diagnosis	APRI: AUROC (95% CI)	Fibrotest: AUROC (95% CI)
Adler, 2008 ⁹²	Belgium	152	A: Fibrosis (METAVIR F2-F4) B: Severe fibrosis (METAVIR F3-F4) C: Cirrhosis (METAVIR F4)	A: 0.74 (CI not reported) B: 0.89 (CI not reported) C: 0.92 (CI not reported)	A: 0.79 (CI not reported) B: 0.90 (CI not reported) C: 0.92 (CI not reported)
Bourliere, 2006 ^{a105}	France	235	Fibrosis (METAVIR F2-F4)	0.71 (0.67 to 0.79)	0.81 (0.76 to 0.86)
Boursier, 2009 ^{b106}	France	1,056	A: Severe fibrosis (METAVIR F3-F4) B: Cirrhosis (METAVIR F4)	A: 0.82 (0.79 to 0.85) B: 0.84 (0.80 to 0.88)	A: 0.84 (0.81 to 0.86) B: 0.88 (0.86 to 0.91)
Cales, 2008 ^{b110}	France	1,056	Fibrosis (METAVIR F2-F4)	0.79 (CI not reported)	0.81 (CI not reported)
Castera, 2009 ^{d228}	France	298	Cirrhosis (METAVIR F4)	0.80 (0.74 to 0.86)	0.82 (0.73 to 0.86)
Castera, 2005 ¹¹⁴	France	193	A: Fibrosis (METAVIR F2-F4) B: Severe fibrosis (METAVIR F3-F4)	A: 0.78 (0.70 to 0.85) B: 0.84 (0.78 to 0.89)	A: 0.85 (0.78 to 0.90) B: 0.90 (0.85 to 0.94)
Crisan, 2012 ¹²²	Romania	446	A: Fibrosis (METAVIR F2-F4) B: Severe fibrosis (METAVIR F3-F4)	A: 0.73 (CI not reported) B: 0.74 (CI not reported)	A: 0.78 (CI not reported) B: 0.78 (CI not reported)
Halfon, 2007 ^{a,c145}	France	356	A: Fibrosis (METAVIR F2-F4) B: Severe fibrosis (METAVIR F3-F4) C: Cirrhosis (METAVIR F4)	A: 0.76 (0.72 to 0.81) B: 0.81 (0.76 to 0.85) C: 0.92 (0.88 to 0.94)	A: 0.79 (0.75 to 0.83) B: 0.81 (0.77 to 0.85) C: 0.86 (0.82 to 0.89)
Leroy, 2008 ¹⁵⁷	France	825	A: Fibrosis (METAVIR F2-F4) B: Severe fibrosis (METAVIR F3-F4) C: Cirrhosis (METAVIR F4)	A: 0.79 (0.76 to 0.82) B: 0.84 (0.80 to 0.87) C: 0.86 (0.82 to 0.90)	A: 0.80 (0.77 to 0.83) B: 0.85 (0.82 to 0.88) C: 0.89 (0.86 to 0.92)
Leroy, 2007 ^{c158}	France	180	A: Fibrosis (METAVIR F2-F4) B: Severe fibrosis (METAVIR F3-F4)	A: 0.81 (0.74 to 0.88) B: 0.82 (0.74 to 0.90)	A: 0.84 (0.79 to 0.90) B: 0.87 (0.81 to 0.93)
Sebastiani, 2008 ^{e198}	Italy	244 (80 normal ALT, 164 elevated ALT)	Fibrosis (METAVIR F2-F4)	Normal ALT: 0.69 (0.54 to 0.85) Elevated ALT: 0.75 (0.65 to 0.85)	Normal ALT: 0.70 (0.59 to 0.81) Elevated ALT: 0.79 (0.74 to 0.84)
Sebastiani, 2006 ^{e199}	Italy	190	A: Fibrosis (METAVIR F2-F4) B: Cirrhosis (METAVIR F4)	A: 0.69 (0.54 to 0.85) (elevated ALT) and 0.77 (0.63 to 0.91) (normal ALT) B: 0.61 (0.49 to 0.73) (whole sample)	A: 0.81 (0.72 to 0.91) (elevated ALT) and 0.71 (0.49 to 0.92) (normal ALT) B: 0.71 (0.60 to 0.82) (whole sample)

Table 5. Aspartate aminotransferase-platelet ratio index compared with Fibrotest (continued)

Study, Year	Country	N	Diagnosis	APRI: AUROC (95% CI)	Fibrotest: AUROC (95% CI)
Sebastiani, 2011 ²⁰⁰	Europe	1,810	A: Fibrosis (METAVIR F2-F4) B: Cirrhosis (METAVIR F4)	A: 0.70 (0.65 to 0.75) (whole sample) and 0.63 (0.57 to 0.71) (normal ALT) B: 0.76 (0.71 to 0.81) (whole sample) and 0.65 (0.60 to 0.70) (normal ALT)	A: 0.70 (0.65 to 0.75) (whole sample) and 0.65 (0.60 to 0.70) (normal ALT) B: 0.72 (0.67 to 0.77) (whole sample) and 0.65 (0.60 to 0.70) (normal ALT)
Sebastiani, 2012 ²⁰¹	Europe	1,013	A: Fibrosis (METAVIR F2-F4) B: Cirrhosis (METAVIR F4)	A: 0.70 (0.64 to 0.76) B: 0.77 (0.71 to 0.83)	A: 0.71 (0.64 to 0.78) B: 0.72 (0.67 to 0.77)
Wilson, 2006 ²¹⁹	USA	119	Ishak 3-4 fibrosis	0.70 (CI not reported)	0.74 (CI not reported)
Zarski, 2012 ²²³	France	436	A: Fibrosis (METAVIR F2-F4) B: Cirrhosis (METAVIR F4)	A: 0.76 (0.72 to 0.81) B: 0.86 (0.81 to 0.91)	A: 0.80 (0.75 to 0.84) B: 0.86 (0.83 to 0.90)

ALT = alanine aminotransferase; APRI = aspartate aminotransferase (AST) to platelets ratio; AUROC = area under the receiver operating characteristic curve; CI = confidence interval

^a Evaluated overlapping populations from the FIBROPACA study.

^b Evaluated the same population.

^c Population included in Cales 2008.

^d Incorporated population evaluated in Castera 2005.

^e Populations overlap.

Table 6. Aspartate aminotransferase/alanine aminotransferase ratio compared with other indices

Study, Year	Country	N	Diagnosis	AST/ALT Ratio: AUROC (95% CI)	Other Predictive Index: AUROC (95% CI)
Ahmad, 2011 ^{a93}	Pakistan	157	Cirrhosis (METAVIR F4)	0.61 (0.48 to 0.74) for cutoff >1, 0.47 (0.38 to 0.56) for cutoff <1	Platelet count: 0.99 (0.98 to 1.0) Fibrosis to cirrhosis index: 1.0 (0.99 to 1.0) Fibrosis Index: 0.99 (0.98 to 1.0)
Borroni, 2006 ¹⁰²	Italy	228	Cirrhosis (Knodell F4)	0.76 (0.68 to 0.84)	Age-platelet index: 0.88 (0.82 to 0.94) APRI: 0.86 (0.79 to 0.93) Cirrhosis Discriminant Score: 0.83 (0.75 to 0.92)
Castera, 2009 ^{b112}	France	298	Cirrhosis (METAVIR F4)	0.61 (0.53 to 0.70)	APRI: 0.80 (0.74 to 0.86) Fibrotest: 0.82 (0.73 to 0.86) Lok Index: 0.80 (0.73 to 0.86)
Cheung, 2008 ¹¹⁷	USA	490	A: Fibrosis (Batts-Ludwig F2-F4) B: Severe fibrosis (Batts-Ludwig F3-F4)	A: 0.54 (0.48 to 0.59) B: 0.52 (0.47 to 0.58)	APRI A: 0.69 (0.64 to 0.74); B: 0.76 (0.71 to 0.81) Pohl Index A: 0.52 (0.51 to 0.54); B: 0.53 (0.51 to 0.56)
Cross, 2009 ¹²⁴	United Kingdom	602 (derivation sample) 105 (validation sample)	A: Fibrosis (Ishak ≥ 3) B: Cirrhosis (Ishak 5-6)	A: 0.58 (0.51 to 0.64) B: 0.68 (0.60 to 0.75)	Age-platelet index A: 0.77 (0.73 to 0.81); B: 0.90 (0.86 to 0.93) APRI A: 0.76 (0.72 to 0.80); B: 0.88 (0.85 to 0.92) Cirrhosis Discriminant Score A: 0.67 (0.62 to 0.72); B: 0.74 (0.68 to 0.81) FIB-4 A: 0.76 (0.68 to 0.83); B: 0.91 (0.89 to 0.94) King's Score A: 0.79 (0.75 to 0.83)*; B: 0.91 (0.89 to 0.94)* Pohl Index A: 0.53 (0.46 to 0.59); B: 0.64 (0.55 to 0.73)
Ehsan, 2008 ¹²⁵	Egypt	116	Cirrhosis (Ishak 5-6)	0.65 (CI not reported)	Age-platelet index: 0.91 (CI not reported) APRI: 0.86 (CI not reported) Lok Index: 0.88 (CI not reported) Cirrhosis discriminate score: 0.87 (CI not reported) Goteborg University Cirrhosis Index: 0.86 (CI not reported) Pohl Index: 0.66 (CI not reported)
El-Sayed, 2011 ¹²⁷	Egypt	37	Severe fibrosis (METAVIR F3-F4)	0.76 (CI not reported)	APRI: 0.63 (CI not reported)

Table 6. Aspartate aminotransferase/alanine aminotransferase ratio compared with other indices (continued)

Study, Year	Country	N	Diagnosis	AST/ALT Ratio: AUROC (95% CI)	Other Predictive Index: AUROC (95% CI)
Fabris, 2008 ¹²⁹	Italy	167	A: Fibrosis (METAVIR F2-F4) B: Cirrhosis (METAVIR F4)	A: 0.59 (0.51 to 0.66) B: 0.66 (0.58 to 0.73)	Age-platelet index A: 0.64 (0.56 to 0.72); B: 0.67 (0.59 to 0.74) APRI A: 0.72 (0.64 to 0.79); B: 0.86 (0.79 to 0.90) Cirrhosis Discriminant Score A: 0.64 (0.56 to 0.71); B: 0.71 (0.64 to 0.78) Fibroindex A: 0.71 (0.63 to 0.77); B: 0.86 (0.80 to 0.91) Forns' Index A: 0.70 (0.62 to 0.76); B: 0.86 (0.80 to 0.91)
Giannini, 2003b ¹³⁵	Italy	239	Fibrosis (criteria not reported)	A: 0.82 (CI not reported) B: 0.91 (CI not reported)	APRI A: 0.77 (CI not reported) B: 0.81 (CI not reported)
Ben Jazia, 2009 ⁹⁸	Tunisia	35	Fibrosis (METAVIR F2-F4)	0.68 (CI not reported)	APRI: 0.91 (CI not reported)
Lackner, 2005 ¹⁵⁶ and Lackner, 2006 ²²⁴	Austria	194	A: Fibrosis (Ishak ≥ 3) B: Cirrhosis (Ishak 5-6)	A: 0.57 (0.48 to 0.65) B: 0.73 (0.63 to 0.83)	Age-platelet index A: 0.74 (0.67 to 0.81); B: 0.91 (0.87 to 0.96) APRI A: 0.80 (0.73 to 0.86); B: 0.90 (0.85 to 0.95) Cirrhosis Discriminant Score A: 0.71 (0.63 to 0.79); B: 0.91 (0.85 to 0.96)
Liu, 2006 ¹⁶⁰	Taiwan	79	Fibrosis (METAVIR F2-F4)	A: 0.50 (0.35 to 0.66)	Age-platelet index: 0.64 (0.51 to 0.77) APRI: 0.67 (0.54 to 0.81)
Parise, 2006 ¹⁷⁶	Brazil	206	A: Fibrosis (Batts-Ludwig F2-F4) B: Cirrhosis (Batts-Ludwig F4)	A: 0.59 (0.51 to 0.67) B: 0.65 (0.56 to 0.75)	APRI A: 0.82 (0.77 to 0.88) B: 0.84 (0.77 to 0.90)
Sebastiani, 2008 ^{c198}	Italy	244 (80 normal ALT, 164 elevated ALT)	Fibrosis (METAVIR F2-F4)	Normal ALT: 0.51 (0.40 to 0.62) Elevated ALT: 0.54 (0.48 to 0.60)	Normal ALT and elevated ALT, respectively APRI 0.69 (0.54 to 0.85); 0.75 (0.65 to 0.85) Fibrotest 0.70 (0.59 to 0.81); 0.79 (0.74 to 0.84) Forns' Index 0.60 (0.50 to 0.71); 0.76 (0.71 to 0.81) Fibroindex 0.58 (0.43 to 0.73); 0.74 (0.63 to 0.85)

Table 6. Aspartate aminotransferase/alanine aminotransferase ratio compared with other indices (continued)

Study, Year	Country	N	Diagnosis	AST/ALT Ratio: AUROC (95% CI)	Other Predictive Index: AUROC (95% CI)
Sebastiani, 2011 ²⁰⁰	Europe	1,810 (595 normal ALT)	Cirrhosis (METAVIR F4)	Normal ALT: 0.52 (0.46 to 0.58)	Normal ALT APRI: 0.65 (0.60 to 0.70) Fibrotest: 0.65 (0.60 to 0.70) Lok Index: 0.61 (0.57 to 0.69) Platelet count: 0.64 (0.58 to 0.70)

ALT = alanine aminotransferase; APRI = aspartate aminotransferase (AST) to platelets ratio; CI = confidence interval

^a Study reported different AUROCs for the same test and diagnosis.

^b Incorporated population evaluated in Castera 2005.

^c Populations substantially overlap.

Table 7. Platelet count compared with multicomponent indices

Study, Year	Country	N	Diagnosis	Platelet Count	Other Predictive Index
Ahmad, 2011 ^{a93}	Egypt	157	A: Fibrosis (METAVIR F2-F4) B: Cirrhosis (F4)	A: 0.94 (0.90 to 0.97) B: 0.99 (0.98 to 1.0)	Fibrosis-cirrhosis index A: 0.93 (0.90 to 0.97) B: 1.0 (0.99 to 1.0) APRI A: 0.88 (0.78 to 0.97) for cutoff >1.5, 0.72 (0.64 to 0.780) for cutoff <0.5 Fibrosis Index A: 0.94 (0.90 to 0.97) B: 0.99 (0.98 to 1.0) AST/ALT ratio B: 0.61 (0.48 to 0.74) for cutoff >1, 0.47 (0.38 to 0.56) for cutoff <1
Castera, 2009 ^{b228}	France	298	Cirrhosis (METAVIR F4)	0.79 (0.72 to 0.85)	APRI: 0.80 (0.74 to 0.86) AST/ALT ratio: 0.61 (0.53 to 0.70) Fibrotest: 0.82 (0.73 to 0.86) Lok Index: 0.80 (0.73 to 0.86)
Cheung, 2008 ¹¹⁷	USA	490	A: Fibrosis (Batts-Ludwig F2-F4) B: Severe fibrosis (Batts-Ludwig F3-F4)	A: 0.60 (0.56 to 0.63) for <150; 0.52 (0.51 to 0.53) for <100 [^] B: 0.64 (0.60 to 0.68) for <150; 0.53 (0.52 to 0.55) for <100 [^]	APRI A: 0.69 (0.64 to 0.74); B: 0.76 (0.71 to 0.81) AST/ALT ratio A: 0.54 (0.48 to 0.59); B: 0.52 (0.47 to 0.58) Pohl Index A: 0.52 (0.51 to 0.54); B: 0.53 (0.51 to 0.56)
Cross, 2009 ¹²⁴	United Kingdom	602 (derivation sample) 105 (validation sample)	A: Fibrosis (Ishak ≥3) B: Cirrhosis (Ishak 5-6)	A: 0.66 (0.60 to 0.72) B: 0.88 (0.85 to 0.91)	Age-platelet index A: 0.77 (0.73 to 0.81); B: 0.90 (0.86 to 0.93) APRI A: 0.76 (0.72 to 0.80); B: 0.88 (0.85 to 0.92) AST/ALT ratio A: 0.58 (0.51 to 0.64); B: 0.68 (0.60 to 0.75) Cirrhosis Discriminant Score A: 0.67 (0.62 to 0.72); B: 0.74 (0.68 to 0.81) FIB-4 A: 0.76 (0.68 to 0.83); B: 0.91 (0.89 to 0.94) King's Score A: 0.79 (0.75 to 0.83)*; B: 0.91 (0.89 to 0.94)* Pohl Index A: 0.53 (0.46 to 0.59); B: 0.64 (0.55 to 0.73)
Ben Jazia, 2009 ⁹⁸	Tunisia	35	Fibrosis (METAVIR F2-F4)	0.38 (CI not reported)	APRI: 0.91 (CI not reported) AST/ALT ratio: 0.68 (CI not reported)

Table 7. Platelet count compared with multicomponent indices (continued)

Study, Year	Country	N	Diagnosis	Platelet Count	Other Predictive Index
Lackner, 2005 ¹⁵⁶ and Lackner, 2006 ²²⁴	Austria	194	A: Fibrosis (Ishak ≥ 3) B: Cirrhosis (Ishak 5-6)	A: 0.71 (0.64 to 0.79) B: 0.89 (0.83 to 0.94)	Age-platelet index A: 0.74 (0.67 to 0.81); B: 0.91 (0.87 to 0.96) APRI A: 0.80 (0.73 to 0.86); B: 0.90 (0.85 to 0.95) AST/ALT ratio A: 0.57 (0.48 to 0.65); B: 0.73 (0.63 to 0.83) Cirrhosis Discriminant Score A: 0.71 (0.63 to 0.79); B: 0.91 (0.85 to 0.96)
Myers, 2003 ^{c170}	France	323	A: Fibrosis (METAVIR F2-F4) B: Severe fibrosis (METAVIR F3-F4)	A: 0.67 (0.64 to 0.70) B: 0.74 (0.70 to 0.78)	Age-platelet index A: 0.72 (0.69 to 0.75); B: 0.81 (0.78 to 0.84) Fibrotest A: 0.84 (0.82 to 0.86); B: 0.92 (0.90 to 0.94)
Sebastiani, 2011 ²⁰⁰	Europe	1,810 (595 normal ALT)	Cirrhosis (METAVIR F4)	Normal ALT subgroup: 0.64 (0.58 to 0.70)	Normal ALT subgroup APRI: 0.65 (0.60 to 0.70) Fibrotest: 0.65 (0.60 to 0.70) AST/ALT ratio: 0.52 (0.46 to 0.58) Lok Index: 0.61 (0.57 to 0.69)
Sirli, 2010 ²⁰⁴	Romania	150	A: Fibrosis (METAVIR F2-F4) B: Cirrhosis (METAVIR F4)	A: 0.73 (0.65 to 0.80) B: 0.90 (0.84 to 0.94)	APRI A: 0.77 (0.69 to 0.83) B: 0.91 (0.85 to 0.95) Forns' Index A: 0.75 (0.67 to 0.82) B: 0.91 (0.85 to 0.95) Lok Index A: 0.70 (0.62 to 0.77) B: 0.87 (0.81 to 0.92) FIB-4 A: 0.69 (0.60 to 0.76) B: 0.84 (0.77 to 0.90)

APRI = aspartate aminotransferase (AST) to platelets ratio; AST/ALT = aspartate aminotransferase–alanine aminotransferase;
CI = confidence interval

^a Study reported different AUROCs for the same test and diagnosis.

^b Incorporated population evaluated in Castera 2005.

^c Evaluated same population.

Table 8. Blood tests compared with imaging

Study, Year	Country	N	Proportion with Fibrosis or Cirrhosis	Population Characteristics	Diagnosis	APRI: AUROC (95% CI)	Imaging Findings: AUROC (95% CI)
Cobbold, 2009 ²²⁹	UK	67	Fibrosis (Ishak ≥ 3): 55% Cirrhosis (Ishak 5 or 6): 21%	Age: 50 years Female: 34% Genotype 1: Not reported No current antiviral treatment Excluded if >20 g alcohol/day	A: Fibrosis (Ishak ≥ 3) B: Cirrhosis (Ishak 5-6)	APRI A: 0.83 (0.73 to 0.93) B: 0.86 (0.75 to 0.97) ELF Index A: 0.82 (0.73 to 0.92) B: 0.91 (0.82 to 1.0)	Hepatic transit time A: 0.71 (0.59 to 0.84) B: 0.83 (0.69 to 0.97)
Schneider, 2006 ¹⁹⁶	Germany	83	Fibrosis (Ishak ≥ 3): 57% Cirrhosis (Ishak 5 or 6): 23%	Age: 48 years Female: 51% Genotype 1: 84%	Cirrhosis (Ishak 5-6)	APRI: 0.71 (CI not reported)	Portal venous flow: 0.80 (CI not reported)
Testa, 2006 ²⁰⁹	Italy	75	Fibrosis (Ishak ≥ 3): 49% Cirrhosis (Ishak 5 or 6): 12%	Age: 50 years Female: 32% Genotype 1b: 43% All elevated aminotransferases No alcohol abuse	Fibrosis (Ishak ≥ 3)	Fibrosis (Ishak ≥ 3) APRI: 0.72 (0.60 to 0.82)	Platelet-spleen diameter ratio: 0.74 (0.63 to 0.84) Fibrosis model 1: 0.80 (0.69 to 0.88) ^a

APRI = aspartate aminotransferase (AST) to platelets ratio; AUROC = area under the receiver operating characteristic curve; CI = confidence interval

^a Based on sample used to derive the risk prediction instrument.

Key Question 4b. What proportion of patients with screen-detected HCV infection receives treatment?

- Three intervention series reported that 15 to 33 percent of patients with screen-detected chronic HCV infection received treatment (strength of evidence: moderate).

Three longitudinal intervention series (n=449, 5,646, and 12,485) evaluated the proportion of screen-detected patients with HCV infection who received treatment (Table 9, Evidence Table 7, Appendix G).²³⁰⁻²³² Two studies were conducted in (different) Veterans Affairs (VA) centers^{230, 232} and one evaluated a non-VA population of active and former drug users.²³¹ The proportions of HCV-antibody-positive patients who were viremic ranged from 58 to 76 percent, and the proportions of viremic patients who received treatment ranged from 15 to 33 percent. One factor that could confound estimates of treatment rates is differences in how patients were assessed as eligible for treatment. For example, one of the studies classified patients with genotype 1 or 4 HCV infection and less than moderate fibrosis as ineligible for treatment,²³¹ but another²³² did not describe genotype as a treatment eligibility consideration. In addition, although both studies reported general medical or psychiatric contraindications as reasons for ineligibility, specific contraindications were not well described. In the two studies, the proportion of viremic patients categorized as eligible for treatment were 57 and 71 percent. The third study did not report reasons for treatment ineligibility.²³⁰ Other challenges in interpreting these studies included failure to report liver biopsy protocols and use of poorly defined and standardized eligibility criteria (which were applied retrospectively in one study²³²).

Table 9. Proportion of screened patients who were treated

Author, Year Country	Study Population Number Screened Study Design	Number HCV Antibody Positive	Proportion HCV Antibody Positive who were Viremic	Proportion Viremic who Received Treatment	Proportion Viremic Classified as Eligible for Treatment	Reasons for Ineligibility: Percent (n)	Proportion Classified as Eligible for Treatment who Received Treatment
Groom, 2008 ²³⁰ USA	Veterans Affairs patients who tested positive for anti-HCV antibody by risk-based screening n=12,385 Retrospective intervention series	681	76% (520/681)	24% (124/520)	Not reported	Not reported	Not reported
Lindenburg, 2011 ²³¹ The Netherlands	Active and former drug users who tested positive for anti-HCV antibody n=449 Prospective intervention series	267	64% (134/208, HIV-negative); 84/134 completed further screening	33% (44/134)	71% (60/84)	Medical, social, or psychiatric contraindication: 33% (8) Genotype 1 or 4 with less than moderate fibrosis on liver biopsy (treatment postponed): 67% (16)	73% (44/60)
Malette, 2008 ²³² USA	Veterans Affairs patients who tested positive for anti-HCV antibody by risk-based screening n=5,646 Retrospective intervention series	260 (newly diagnosed)	58% (122/211)	15% (18/122)	57% (70/122)	Ongoing substance or alcohol abuse: 24% (29) Major medical contraindication: 7.4% (9) Severe psychiatric disease: 6.6% (8) Refused further evaluation: 4.9% (6)	26% (18/70)

HCV = hepatitis C virus

Key Question 5. What are the harms associated with the workup for guiding treatment decisions?

- One study (n=2,740) of patients with chronic HCV infection and compensated cirrhosis with an Ishak fibrosis score of ≥ 3 reported serious adverse events in 1.1 percent of patients, including 0.6 percent serious bleeds and 0.3 percent severe pain, with no deaths. Five large (n=1,398 to 61,184) interventions series published since 2004 of patients undergoing percutaneous liver biopsy for a variety of reasons reported peri-procedural mortality in <0.2 percent and serious complications in 0.3 to 1.0 percent (strength of evidence: moderate).

Few studies evaluated harms associated with liver biopsy specifically in HCV-infected patients. One study of 2,740 percutaneous liver biopsies in HCV-infected patients with compensated cirrhosis and an Ishak fibrosis score of 3 or greater reported 29 serious adverse events (defined as complications requiring hospitalization, additional costly investigations, blood transfusion, or complications that led to perforation of an organ, surgery, or death), for a rate of 1.1 percent.²³³ The most common serious adverse event was bleeding (16 cases), followed by severe pain (seven cases). No deaths occurred. Predictors of bleeding were platelet count <60,000/mm³ and INR >1.3. Patients with platelet counts <60,000/mm³ accounted for 25 percent (4 of 16) cases, but only 2 percent of biopsies. Most biopsies (80 percent) were performed with bedside ultrasound guidance. There was no clear association between use of ultrasound guidance, operator experience, or type of needle used and risk of complications. Two other small studies (n=126 and 166) included in the 2004 USPSTF review reported no episodes of bleeding, perforation, or death following percutaneous liver biopsy in patients with HCV infection, including those with known or suspected cirrhosis.^{192, 234} No study of percutaneous liver biopsies specifically examined asymptomatic patients with chronic HCV who may be at lower risk for complications.

In patients undergoing liver biopsy for a variety of reasons, large series (n=1,398 to 61,184) published since 2004 reported peri-procedural mortality rates of 0 to 0.2 percent.²³⁵⁻²³⁹ Major complications (primarily bleeding) occurred after 0.3 to 1.0 percent of biopsies. The largest study (n=61,184) reported substantially higher mortality risk in patients with cancer as the indication for biopsy (1.2 percent) compared with those undergoing biopsy for other indications (≤ 0.01 percent).²³⁹ It also found use of image guidance associated with slightly increased risk of complications, perhaps due to tendency towards increased use in more complicated patients. One study reported minor complications following 14 percent of biopsies.²³⁸ Another study reported that 30 percent of patients who underwent liver biopsy experienced pain requiring strong analgesic medications.²⁴⁰

The newer studies were consistent with earlier studies that reported mortality rates of <0.1 percent and major complications in 0 to 3.7 percent of patients undergoing liver biopsy for a variety of reasons.²⁴¹⁻²⁴⁷ Older studies comparing blind with ultrasound-guided biopsy have generally reported higher risk for complications with the blind technique.²⁴⁸

Key Question 6a. How effective is counseling or immunization of patients with HCV infection at improving health outcomes or reducing the spread of HCV?

- One randomized trial found a self-management program associated with slight improvements in SF-36 vitality scores compared with provision of educational materials after 6 weeks, but there were no effects on other measures of generic or HCV-related quality of life (strength of evidence: insufficient).
- No study evaluated effects of immunizations of patients with HCV infection on health outcomes (strength of evidence: insufficient).

One randomized trial of HCV-infected VA patients (n=137) found a self-management program based on cognitive-behavioral principles that included information dissemination, problem solving, and development and re-evaluation of action plans (six weekly sessions, 2 to 2.5 hours each) associated with slightly greater improvements in SF-36 vitality scores after 6 weeks (mean change -2.1 vs. 4.6, $p=0.040$) compared with provision of educational materials (Evidence Table 8, Appendix G).²⁴⁹ There were no differences in other SF-36 scores or measures of depression, global health status, or HCV-specific quality of life. The trial was rated fair quality due to failure to describe allocation concealment and failure to blind outcome assessors/data analysts (Evidence Table 9, Appendix G).

No study evaluated the effect of counseling regarding alcohol consumption or the effect of formal alcohol treatment programs after diagnosis of HCV on subsequent clinical outcomes such as cirrhosis and related complications. No study evaluated effects of counseling regarding risky behaviors on transmission rates from patients with HCV infection or estimated rates of transmission from patients with HCV infection aware of their status compared with those not aware of their status.

No study evaluated the effect of immunization for hepatitis A virus (HAV) or HBV infection after diagnosis of HCV on subsequent clinical outcomes or estimated risk of serious HAV or HBV infection in patients with HCV infection aware of their serostatus compared with those unaware of their status. Although evidence described in the 2004 USPSTF review showed high rates of protective seroconversion following HAV and HBV vaccination in patients with HCV infection, they were not designed to assess subsequent clinical outcomes.²⁵⁰

Key Question 6b. Does becoming aware of positive HCV infection status decrease high-risk behaviors?

- Three retrospective studies reported substantial reductions in alcohol use following diagnosis of HCV infection, but two prospective studies found no evidence of sustained reductions in high-risk behaviors (alcohol use or injection drug use behaviors) following diagnosis. Results from two cross-sectional studies were mixed (strength of evidence: low).

Five studies compared self-reported behaviors in patients before and after becoming aware of their positive HCV status.^{88, 251-254} Two cross-sectional studies compared self-reported behaviors in HCV-positive infected patients aware and unaware of their status.^{42, 255} All of the studies relied on patient self-report to assess behaviors.

Two prospective before-after studies found no evidence of sustained reductions in high-risk behaviors following diagnosis of HCV infection.^{252, 254} A study of young (<30 years old), HCV-negative injection drug users (n=112) who underwent quarterly testing reported decreased

likelihood of self-reported alcohol use (OR 0.51, 95% CI 0.27 to 0.97) immediately after becoming aware of seroconversion compared with before becoming aware of their status, but effects were not sustained after 6 or 12 months (OR 0.84, 95% CI 0.42 to 1.6).²⁵⁴ There was no significant effect on likelihood of injection drug use, lending or sharing of injecting equipment, or unprotected intercourse at any time. Another prospective study, included in the 2004 review,⁴⁴ found no significant reduction in high-risk behaviors (such as backloading or sharing needles, syringes, or other injection paraphernalia) in young (age 15 to 30 years) injection drug users (n=46) 6 months after notification of positive HCV infection status compared with behaviors prior to testing.²⁵² For example, 17 percent of patients reported no change in needle sharing, 17 percent reported an increase, and 11 reported percent a decrease. There was also no change in reported alcohol consumption.

Three retrospective before-after studies reported substantial reductions in risky behaviors following diagnosis of HCV infection.^{88, 251, 253} Due to their retrospective design, such studies may be more susceptible to recall bias. One study of 275 HCV-positive patients found that of the 153 subjects reporting alcohol use at the time of diagnosis, 58 percent reported giving up alcohol and another 16 percent reported reducing alcohol use a median of 5 years following diagnosis.²⁵³ Another study of patients who were surveyed 1 to 3 years after diagnosis with chronic HCV infection found that 85 percent (28/33) who drank at the time of screening reported decreased alcohol use, with 64 percent (21/33) reporting abstinence.⁸⁸ Of the seven injection drug users at the time of diagnosis, four reported no injection drug use. A French observational study included in the 2003 review found that out of 25 patients who reported “excessive” alcohol consumption prior to HCV diagnosis, 9/25 reported that they had become completely abstinent and 14/25 reported cutting back to “moderate” intake.²⁵¹

Two cross-sectional studies that compared risky behaviors of HCV-positive patients aware of their status compared with HCV-positive patients unaware of their status reported inconsistent results.^{42, 255} One study found HCV-positive injection drug users unaware of their positive status (n=97) more likely than those aware (n=39) to use a previously used needle (59 vs. 28 percent, p<0.001), share drug paraphernalia (70 vs. 53 percent, p<0.05), and report not always injecting safely (63 vs. 44 percent, p<0.05).²⁵⁵ However, another study of young (15-30 years of age) injection drug users found no significant difference in the number of injection partners or reported alcohol use between those aware of their HCV-positive status (n=288), those who thought they were negative (n=414), and those who did not know their status (n=331).⁴²

Key Question 6c. How effective is counseling and immunization of patients with HCV infection at improving intermediate outcomes, including change in high-risk behaviors?

- Two randomized trials reported somewhat mixed results regarding effects of counseling interventions based on behavioral principles compared with simple educational interventions, though one trial that trained patients to serve as peer mentors reported sustained absolute decreases of about 15 percent in the proportion engaging in risky injection drug behaviors. Two before-after studies of HCV-infected heavy drinkers following found 36 to 44 percent reported abstinence 6 to 22 months after a counseling intervention. No study evaluated intermediate outcomes associated with immunizations in patients with HCV infection (strength of evidence: insufficient).

Two randomized trials^{256, 257} and one before-after study²⁵⁸ evaluated effects of counseling interventions in patients with HCV infection (Evidence Table 8, Appendix G). Both trials were rated fair quality (Evidence Table 9, Appendix G). Shortcomings included failure to describe adequate allocation concealment methods,^{256, 257} baseline differences between randomized groups,²⁵⁷ and high loss to followup.^{256, 257} Due to the nature of the interventions, patients and care providers could not be blinded. Neither trial blinded outcome assessors.

One trial of HCV-infected injection drug users (n=418) evaluated effects of a behavioral intervention that trained drug users to be peer mentors regarding safer injecting practices compared with participation in a video discussion control group.²⁵⁶ The trial was based on the hypothesis that training to be a peer mentor would positively impact injection drug behaviors in the mentors through education, discussion, and self-modeling of safer behaviors, and reinforce such behavior by providing a more positive social identity. It found the behavioral intervention associated with decreased risk of self-reported distributed risk behaviors (lending used syringes, sharing drug preparation equipment, or dividing drugs with syringe used by oneself) at 3 months (44 vs. 59 percent, adjusted OR 0.46, 95% CI 0.27 to 0.79) and 6 months (37 vs. 53 percent, adjusted OR 0.51, 95% CI 0.31 to 0.83), with the difference mainly attributable to a decrease in frequency of sharing drug preparation equipment (41 vs. 55 percent at 3 months and 35 vs. 47 percent at 6 months). The intervention was also associated with increased likelihood of refraining from injection drug use (24 vs. 10 percent at 3 months, adjusted OR 3.6, 95% CI 1.6 to 7.8 and 34 vs. 23 percent at 6 months, adjusted OR 1.6, 95% CI 0.96 to 2.7).

A trial of 851 injection drug users, about half of whom had HCV infection, found that a motivational intervention (based on motivational interviewing techniques) was associated with an overall lower likelihood of alcohol use at 6-month followup compared with an educational intervention (OR 0.67, 95% CI 0.46 to 0.97), but there was no effect in the subgroup of HCV-positive patients (OR 0.94, 95% CI 0.64 to 1.4).²⁵⁷ There was also no effect on safer injecting practices or condom use.

A small (n=47) before–after study of heavy drinkers with HCV infection found that 62 percent reported alcohol intake reduced by greater than 50 percent compared to baseline at 8- to 22-month followup after receiving brief outpatient clinic alcohol counseling intervention followed by psychiatric nurse followup, including 36 percent who reported abstinence.²⁵⁸ Another small (n=53) before-after study of heavy drinkers reported alcohol abstinence in 44 percent at the end of a 6-month individualized alcohol counseling intervention.²⁵⁹

Key Question 7. Do any interventions decrease or increase the vertical transmission of HCV during delivery or in the perinatal period?

- Four observational studies (two good quality) totaling 2,080 mother-infant pairs specifically compared rates of transmission among women who delivered by elective cesarean compared with vaginal or emergent cesarean delivery. The two good-quality studies found no statistically significant difference in risk of vertical transmission of HCV infection (strength of evidence: low).
- Ten of 11 observational studies (one good quality) found no statistically significant difference in risk of vertical transmission of HCV infection following vaginal compared with cesarean (not specified if elective or emergent) delivery (strength of evidence: moderate).

- Three observational studies (two good quality) found inconsistent evidence on the association between internal fetal monitoring and the risk of vertical transmission of HCV infection (strength of evidence: insufficient).
- Two studies (one good quality) found an association between prolonged labor after membrane rupture and risk of vertical transmission of HCV infection. The good-quality study reported membrane rupture >6 hours associated with an adjusted OR of 9.3 for vertical transmission (95% CI 1.5 to 180) (strength of evidence: low).
- Fourteen observational studies (two good quality) consistently found no association between breastfeeding and risk of vertical transmission of HCV infection (strength of evidence: moderate).

Mode of Delivery

Fourteen observational studies (reported in 16 publications) with a range of 56 to 1034 mother-infant pairs evaluated the association between mode of delivery and vertical transmission of HCV (Tables 10 and 11, Evidence Table 10, Appendix G).^{51, 52, 260-273} Two reports from the European Pediatric Hepatitis C Network evaluated overlapping patient populations^{260, 261} and two studies evaluated nonoverlapping (different time periods of enrollment) patient populations in Dublin, Ireland.^{264, 266} Nine studies were conducted in Europe,^{51, 260, 261 262, 264-266, 268, 270, 272, 273} two in Australia,^{263, 269} two in Japan,^{267, 271} and one in the United States⁵². Two studies were good quality^{52, 260, 261}, four studies were fair quality^{51, 264, 266, 268}, and the remainder were poor quality (Evidence Table 11, Appendix G). Only four studies performed statistical analysis on potential confounders,^{51, 52, 260, 261, 264} no study reported baseline characteristics according to mode of delivery or matched women on key potential confounders.

Table 10. Hepatitis C virus transmission by mode of delivery: Elective cesarean compared with emergent cesarean or vaginal delivery

Author, Year Quality	N	Elective Cesarean	Vaginal/Emergent Cesarean	Comments/Results ^d (95% CI)
Gibb, 2000 Fair ²⁶⁴	424 ^b	0/31 (0%)	29/393 (7.4%)	OR 0 (0 to 0.87), p=0.04, adjusted for HIV status and breastfeeding
Mast, 2005 ⁵² Good	181 ^a	0/12 (0%)	7/169 (4.1%)	RR 0.87 (0.05 to 14)
McMenamin, 2008 ²⁶⁶ Fair	441 ^c	1/33 (3.0%)	17/408 (4.2%)	RR 0.73 (0.09 to 5.30)
EPHN (Tovo), 2005 ²⁶⁰ Good	1,034 ^a	NR	NR	OR 1.57 (0.88 to 2.83), p=0.13, unadjusted OR 1.59 (0.88 to 2.86), p=0.13 adjusted for sex, mode of delivery, prematurity, and breastfeeding
Total	2,080			

OR = odds ratio; RR = relative risk

^a 0% HIV coinfecting.

^b 5% HIV coinfecting.

^c 5.9% HIV coinfecting.

^d Unadjusted unless otherwise indicated.

Four studies,^{52, 260, 264, 266} totaling 2,080 mother-infant pairs (two good quality^{52, 260}) compared the risk of transmission following elective cesarean delivery prior to the onset of labor with risk of transmission in women who went into labor and delivered vaginally or by emergency cesarean (Table 10). Three studies^{52, 264, 266} reported trends towards higher transmission following vaginal or emergent cesarean delivery, but the difference was only statistically significant in one fair-

quality study.²⁶⁴ It reported no cases of transmission following elective cesarean, compared with 7.4 percent following vaginal or emergency cesarean delivery (adjusted OR 0, 95% CI 0 to 0.87).²⁶⁴ One good quality-study reported a rate of vertical transmission of 4.1 percent (7/169) following vaginal or emergent cesarean, compared with no cases following 12 elective cesarean births (RR 0.87, 95% CI 0.05 to 14).⁵² The other good-quality study, which also evaluated the largest sample (1,034 HCV-positive, HIV-negative mother-infant pairs, or larger than the other three added together), reported the opposite trend, towards increased risk of vertical transmission following elective cesarean compared with vaginal or emergency cesarean (adjusted OR 1.6, 95% CI 0.88 to 2.9).²⁶⁰

Eleven studies totaling 2,308 mother-infant pairs compared the risk of vertical transmission following vaginal with cesarean deliveries, without specifying whether the cesarean delivery was elective or emergent (Table 11).^{51, 261-264, 266, 268-273} Ten of the 11 studies (one good quality²⁶¹) found no association between mode of delivery and risk of HCV transmission.^{51, 261-263, 265, 268-273} The exception was one small (n=59) Japanese prospective cohort study (poor quality) in which there was a trend towards increased risk of vertical transmission following vaginal compared with cesarean delivery (17 vs. 0 percent, p=0.09), with a statistically significant difference in the subgroup of mothers with a high viral load ($\geq 2.5 \times 10^6$ copies/mL).²⁶⁷

Table 11. Hepatitis C virus transmission by mode of delivery: Cesarean (elective or emergent) compared with vaginal delivery

Author, Year Quality	N	Cesarean	Vaginal	Comments/Results ^d (95% CI)
Ceci, 2001 ⁵¹ Fair	78 ^a	No association (data NR)	No association (data NR)	NR
Conte, 2000 ²⁶² Poor	365 ^b	1/106 (0.9%)	7/259 (2.7%)	RR 0.35 (0.04 to 2.80)
Garland, 1998 ²⁶³ Poor	83 ^a	0/22 (0%)	3/61 (4.9%)	RR not calculated
La Torre, 1998 ²⁶⁵ Poor	80 ^a	1/14 (7%)	1/66 (1.5%)	RR 4.71 (0.31 to 70.94)
Okamoto, 1999 ²⁶⁷ Poor	59 ^a	0/18 (0%), 0/10 (0%) in women with high viral load	7/41 (17%), 7/16 (44%) in women with high viral load	RR not calculated, p=0.089, p=0.023 in women with high viral load
EPHN (Pembrey), 2001 ²⁶¹ Good	884 ^a	15/218 (6.9%)	39/666 (5.9%)	OR 1.17 (0.59 to 2.31), adjusted for breastfeeding, maternal age at delivery, center category
Resti, 1998 ²⁶⁸ Fair	275 ^a	4/62 (6.5%)	9/213 (4.2%)	RR 1.53 (0.48 to 4.79)
Spencer, 1997 ²⁶⁹ Poor	63 ^a	1/7 (14%)	5/55 (9.1%)	RR 1.57 (0.21 to 11.6)
Syriopoulou, 2005 ²⁷⁰ Poor	56 ^c	0/17 (0%)	2/39 (5.1%)	RR, not calculated, p=0.34
Tajiri, 2001 ²⁷¹ Poor	114 ^a	1/24 (4.2%)	8/90 (8.8%)	RR 0.46 (0.61 to 3.53)
Zanetti, 1998 ²⁷³ and 1999 ²⁷² Poor	251 ^a	1/58 (1.7%)	7/193 (3.6%)	RR 0.48 (0.06 to 3.79)
Total	2,308			

NR = not reported; OR = odds ratio; RR = relative risk

^a 0% HIV coinfecting.

^b 4% HIV coinfecting.

^c 2% HIV coinfecting.

^d Unadjusted unless otherwise indicated.

Labor Management

Rupture of Membranes

One good-quality study⁵² and one fair-quality study,²⁶⁹ (total 245 mother-infant pairs) found more prolonged rupture of membranes associated with higher risk of transmission (Table 12). The good-quality study reported greater risk of vertical transmission in women with membrane rupture longer than 6 hours (OR 9.3, 95% CI 1.5 to 180).⁵² The poor-quality study reported longer average duration of membrane rupture in women who transmitted the virus to the infant compared with those who didn't (28 vs. 16 hours, p=0.03).²⁶⁹

Table 12. Labor management: Transmission by duration of membrane rupture

Author, Year Quality	N	Duration of Membrane Rupture	Comments/Results (95% CI)
Mast, 2005 ⁵² Good	182 ^a	<1 vs. 1-5 vs. 6-12 vs. ≥13: 0/53 vs. 1/59 (1.7%) vs. 4/40 (10%) vs. 2/30 (6.7%), p=0.02	Membrane rupture >6 hours OR, 9.3 (1.5 to 179.7), adjusted for maternal demographic characteristics, HCV RNA level, fetal monitoring, history of IVDU, and cigarette smoking during pregnancy.
Spencer, 1997 ²⁶⁹ Poor	63 ^a	Mean hours (± SD), transmitted vs. not transmitted: 28±10 vs. 16±4, p=0.03	All mothers were viremic.
Total	245		

CI = confidence interval; IVDU = intravenous drug use; HCV = hepatitis C virus; OR = odds ratio

^a0% HIV coinfectd.

Fetal Monitoring

Three studies (two good quality^{52, 261} and one poor quality²⁶⁶) reported conflicting findings regarding the association between use of fetal monitoring and risk of vertical transmission (Table 13). One of the good-quality studies (n=181)⁵² found a greater risk of vertical transmission associated with internal fetal monitoring (adjusted OR 6.7, 95% CI 1.1 to 36) but the other (n=724)²⁶¹ found no association. The study²⁶⁶ rated poor quality also found no association between fetal monitoring and risk of vertical transmission, but only tested 11 of 23 infants who had scalp electrodes during delivery, none of whom were found to be HCV-positive.

Table 13. Labor management: Transmission by fetal monitoring

Author, Year Quality	N	Fetal Monitoring During Delivery	Comments/ Results ^c (95% CI)
Mast, 2005 ⁵² Good	181 ^a	Internal vs. external: 3/16 (18.8%) vs. 4/165 (2.4%),	RR 7.7 (1.9 to 31.6), p=0.02, unadjusted Internal fetal monitoring, OR 6.7 (1.1 to 35.9), adjusted for maternal demographic characteristics, HCV RNA level, history of IVDU, and cigarette smoking during pregnancy.
McMenamin, 2008 ²⁶⁶ Fair	23 ^b	Infant HCV RNA+: 0/11 (0%) Infant not tested for HCV: 12	RR not calculated
European Paediatric Hepatitis C Virus Network (Pembrey), 2001 ²⁶¹ Good	724 ^a	Yes vs. no: 11/93 (11.8%) vs. 58/631 (9.2%)	RR 1.24 (95% CI 0.70 to 2.20)
Total	928		

CI = confidence interval; IVDU = intravenous drug use; HCV = hepatitis C virus; OR = odds ratio; RR = relative risk

^a0% HIV coinfectd.

^b5.9% HIV coinfectd in overall sample of 441.

^cUnadjusted unless otherwise indicated.

Breastfeeding

Fourteen cohort studies totaling 2,971 mother-infant pairs found no association between breastfeeding and increased risk of HCV infection in infants of HCV-infected mothers (Table 14, Evidence Table 10, Appendix G).^{52, 260-265, 268-279} The majority of studies followed HCV-positive mothers and their infants prospectively and observed the infants for at least 1 year. Sample sizes

ranged from fewer than 50^{275, 276, 278} to more than 1,000 mother-infant pairs²⁶⁰. Two of the studies were rated good quality,^{52, 260} two were fair quality,^{264, 268} and 10 were poor quality.^{262, 265, 269-273, 275, 276, 278, 279}

Methodological shortcomings in the poor-quality studies included failure to perform statistical adjustment on potential confounders and insufficient information to determine comparability of groups at baseline stratified by breastfeeding status.

The finding of no significant association between breastfeeding and risk of transmission was consistent across studies, regardless of sample size, adjustment for confounders, or overall quality.

Table 14. Transmission by type of infant feeding

Author, Year Quality	N	Breast Fed	Formula Fed	Comments/Results ^e (95% CI)
Conte, 2000 ²⁶² Poor	370 ^b	2/90 (2.2%)	6/280 (2.1%)	RR 1.02 (.305 to 3.45)
Gibb, 2000 ²⁶⁴ Fair	414 ^c	7.7% (2.2 to 17.8)	6.7% (3.7 to 10.6)	OR 1.52 (0.35 to 5.12), adjusted for HIV status and mode of delivery
La Torre, 1998 ²⁶⁵ Poor	80 ^a	0/10 (0%)	2/46 (4.3%)	RR not calculated.
Lin, 1995 ²⁷⁵ Poor	15 ^a	0/11 (0%)	0/4 (0%)	RR not calculated
Mast, 2005 ⁵² Good	182 ^a	2/62 (3.2%)	5/120 (4.2%)	RR 0.8 (0.2 to 3.9)
Moriya, 1995 ²⁷⁹ Poor	74 ^a	Not applicable (case control design)	Not applicable (case control design)	5/6 infected (83%) vs. 54/68 uninfected (79%) were breast fed; OR 1.3 (0.14 to 12.0)
Pipan, 1996 ²⁷⁶ Poor	25 ^a	0/6 (0%)	0/19 (0%)	RR not calculated
Resti, 1998 ²⁶⁸ Fair	275 ^a	6/87(6.9%)	7/188(3.7%)	RR 1.85 (0.64 to 5.35), p=0.36
Spencer, 1997 ²⁶⁹ Poor	63 ^a	2/33 (6.0%)	4/30 (13%)	RR 0.45 (0.09 to 2.31) Viral RNA detected in breast milk: 0/38 (0%)
Syriopoulou, 2005 ²⁷⁰ Poor	56 ^d	0/15 (0%)	2/41 (4.9%)	RR not calculated, p=0.38
Tajiri, 2001 ²⁷¹ Poor	114 ^a	9/98 (9.2%)	0/16 (0%)	RR not calculated, p=0.24
Tanzi, 1997 ²⁷⁸ Poor	18 ^a	0%	0%	RR undefined
EPHN (Tovo), 2005 ²⁶⁰ Good	1034 ^a	Not reported	Not reported	OR 0.88 (0.48 to 1.61), unadjusted OR 0.92 (0.50 to 1.70), adjusted for sex, prematurity, and mode of delivery
Zanetti, 1998 ²⁷³ and 1999 ²⁷² Poor	251 ^a	3/127 (2.4%)	5/124 (4.0%)	RR 0.59 (0.14 to 2.40)
Total	2,971			

HCV = hepatitis C virus; OR = odds ratio; RR = relative risk

^a 0% HIV coinfectd.

^b 4% HIV coinfectd.

^c 5% HIV coinfectd.

^d 2% HIV coinfectd.

^eUnadjusted unless otherwise indicated.

Discussion

Key Findings and Strength of Evidence Table 15 summarize the findings of this review, including strength of evidence grades. Details about factors assessed to determine the overall strength of evidence for each body of evidence are shown in Appendix F. As in the 2004 USPSTF review,⁴⁴ we found no direct evidence on benefits of screening for hepatitis C virus (HCV) infection compared with no screening in asymptomatic adults with no liver enzyme abnormalities. Although direct harms of screening appear minimal (since it is a simple blood test), other harms such as labeling, anxiety, and stigmatization remain poorly studied, though reported in some qualitative and other studies.²⁸⁰⁻²⁸²

Retrospective studies found that screening strategies targeting multiple risk factors were associated with sensitivities of over 90 percent and numbers needed to screen to identify one case of HCV infection of less than 20.⁸⁰⁻⁸³ More narrowly targeted alternative screening strategies were associated with numbers needed to screen of less than two, but missed up to two-thirds of infected patients. No study prospectively compared different screening strategies or assessed effects of alternative screening strategies on outcomes. Epidemiologic data indicates that about two-thirds of people with chronic HCV infection were born between 1945 and 1965, suggesting that testing of all people in this birth-cohort could be an efficient strategy. However, the only published report on birth cohort screening is a cost-effectiveness modeling study which did not meet inclusion criteria because it did not assess clinical data.²¹

In the absence of direct evidence on screening, understanding the accuracy of the screening test as well as benefits and harms of subsequent workup and treatments in patients found to be HCV-positive can provide an indirect chain of evidence regarding potential benefits of screening. HCV antibody testing with subsequent polymerase chain reaction (PCR) testing for circulating virus was found to be accurate for identifying patients with HCV infection in a previous systematic review⁴⁴ and diagnostic accuracy was not re-reviewed for this report. Regarding the workup in patients found to be HCV-positive, a number of blood indices were associated with an area under the receiver operating characteristic curve (AUROC) of 0.75 to 0.86 for fibrosis (METAVIR F2-F4, Ishak 3-6, or equivalent) and 0.80 to 0.91 for cirrhosis (METAVIR F4, Ishak 5-6, or equivalent) (generally considered “good” to “very good” diagnostic accuracy).^{71, 72} Only one study⁹⁰ evaluated the clinical impact of no biopsy prior to antiviral treatment, showing no differences compared with patients who underwent biopsy prior to treatment. Harms of biopsy appeared to be small, with a risk of death of <0.2 percent and serious complications (primarily bleeding and severe pain) in about 1 percent.^{233, 235-239} However, estimating harms of screening associated with liver biopsy is a challenge. Although clinical practice has evolved toward less routine use of biopsy prior to antiviral therapy, we found no studies reporting current estimates of the proportion of patients who undergo biopsy prior to treatment.

Some evidence published since the 2004 review suggests that patients who become aware of being HCV positive may reduce risky behaviors,^{42, 88, 253-255} but prospective studies suggest that such behavior changes may not be sustained.^{252, 254} Evidence on effective methods of counseling to reduce risky behaviors remains sparse, though one randomized trial showed an intervention based on behavioral principles was effective at reducing risky injection drug use behaviors.²⁵⁶ We did not review evidence on the general effectiveness of counseling and risk prevention interventions in non-HCV infected people. Whether such evidence can be extrapolated to patients with HCV infection requires assumptions regarding applicability. No study evaluated

effects of immunizations for hepatitis A virus (HAV) or hepatitis B virus (HBV) infection on clinical outcomes or effects of counseling or awareness of HCV status on transmission risk.

Much of the benefits from screening are likely to occur as a result of antiviral treatments, which have become increasingly effective at achieving a sustained virologic response (SVR) (a strong predictor of long-term virologic response).²⁸³ Antiviral treatments, including recently approved new regimens, and the association between SVR and improvement in clinical outcomes (a key evidence gap in the 2004 USPSTF review)⁴⁴ will be addressed in a separate review. In screened populations, benefits of antiviral treatments will depend in part on the proportion of patients who actually receive treatment. Three studies of screen-detected patients found that 15 to 33 percent of screen-detected patients with chronic HCV infection received antiviral treatment.²³⁰⁻²³² However, interpreting these findings is a challenge, as the proportion of patients who receive treatment is likely to vary depending on the population studied and criteria used to determine treatment eligibility, which continue to evolve and differ across settings.

No study compared effects of screening with not screening pregnant women. Cohort studies report conflicting information regarding intrapartum management including effects of mode of delivery on transmission risk. Two studies^{52, 269} that looked at rupture of membranes, which is most commonly experienced by women intending vaginal delivery, reported increased risk of HCV transmission with more prolonged duration of ruptured membranes. Based on those findings, it might be expected that elective cesarean delivery, in which women undergo planned cesarean (typically prior to labor or rupture of membranes) should be associated with decreased risk of vertical transmission; however, studies reported conflicting information, with the largest single study²⁶⁰ reporting a nonstatistically significant higher trend towards increased transmission following elective cesarean compared with vaginal delivery. Possible explanations include threshold effects (in terms of duration of prolonged rupture of membranes) or influence of viral load or other potential modifying factors in women with ruptured membranes. Studies consistently found no association between breastfeeding and transmission risk.

Findings in Relationship to What Is Already Known

Like an earlier evidence review on HCV screening conducted for the USPSTF,²⁸⁴ we found no direct evidence on clinical benefits associated with screening compared with no screening. As in that review, we found that screening strategies targeted at people with a history of intravenous drug use are associated with small numbers needed to screen to identify one case of HCV infection, but miss a significant proportion of people screened.

The USPSTF review found HCV screening tests to be accurate and we did not re-review diagnostic accuracy. Consistent with other reviews,²⁸⁵⁻²⁹⁰ we found that noninvasive tests have fair to good accuracy for diagnosing fibrosis and good to excellent accuracy for diagnosing cirrhosis compared to liver biopsy. Estimates of serious harms associated with liver biopsy are also consistent with estimates from the prior USPSTF review.

Evidence showing that knowledge of HCV status or interventions in people with HCV infection is effective at reducing transmission or high-risk behaviors for transmission remains limited. Studies reporting rates of antiviral treatment in screen-detected patients with HCV infection were all been published after the USPSTF review,²⁸⁴ which included studies of referral populations, rather than cohorts of patients identified through screening. The studies of referral populations reported somewhat higher rates of treatment (30–40 percent) compared to the studies of screen-detected patients (15–33 percent) in our review.

The prior USPSTF evidence review did not address prenatal screening for HCV screening. However, our findings were similar to a guideline from the American Congress of Obstetricians and Gynecologists, which concluded that there are no known effective preventive measures for reducing the risk of mother-to-child transmission of HCV infection.⁵⁶ Like our review, ACOG found limited evidence suggesting a possible association between prolonged rupture of membrane after labor and use of internal fetal monitoring and increased risk of vertical transmission.

Applicability

Several issues may limit applicability of our findings to screening settings likely to be encountered in clinical practice. Most of the studies⁸⁰⁻⁸⁴ evaluating the sensitivity and yield of different screening strategies (Key Question 2b) were conducted in higher prevalence settings, potentially limiting applicability to average- or low-risk populations.

Few studies evaluating harms of liver biopsy were conducted specifically in populations of patients with HCV infection, and none specifically evaluated a screen-identified cohort. The applicability of estimates of serious harms such as bleeding from such studies to a screen-detected population would depend on the presence and severity of liver disease and other comorbidities in the people who underwent biopsy. For example, patients with end-stage liver disease or undergoing biopsy for hepatocellular carcinoma are likely to be at increased risk for bleeding following liver biopsy compared to asymptomatic patient identified through screening.

Studies reporting rates of antiviral treatment in cohorts of patients with screen-detected HCV infection are also difficult to interpret, as the proportion of patients who receive treatment is likely to vary depending on the population studied and criteria used to determine treatment eligibility, which continue to evolve and differ across settings. In addition, two of the studies were conducted in Veterans Affairs (VA) settings^{230, 232} and the third²³¹ in people with a history of intravenous drug use (IVDU), and may not accurately reflect treatment patterns in other settings.

Although none of the studies assessing diagnostic accuracy of noninvasive tests compared to liver biopsy were conducted in screen-detected patients, studies generally enrolled a broad spectrum of patients who varied in severity of fibrosis and other markers of HCV infection severity. Therefore, estimates of diagnostic accuracy are likely to be applicable to patients identified by screening.

We did not include evidence on the general effectiveness of interventions to reduce alcohol use or risky injection drug use behaviors, as the applicability of such studies to patients specifically with HCV infection is uncertain. Our findings are not applicable to patients with HIV infection, end-stage renal disease, or following transplant, as these populations were excluded from the review.

Similarly, our findings on the association between labor and delivery management practices and breastfeeding on risk of vertical transmission are not applicable to women with concomitant HIV infection. Risk of mother-to-child transmission of HCV appears to be higher in women with concomitant HIV infection compared to those without HIV infection. Specific interventions already recommended to prevent vertical transmission of HIV infection include antiretroviral therapy, avoidance of breastfeeding, and elective cesarean in selected patients.²⁹¹

Implications for Clinical and Policy Decisionmaking

Our review has some important potential implications for clinical and policy decisionmaking. Because of the lack of direct evidence showing clinical benefits associated with HCV screening, decisions regarding screening must necessarily be made on the basis of the indirect chain of evidence. Evidence clearly supports that HCV antibody tests are accurate for identifying HCV infection, but that strategies targeted at clinical risk factors misses a substantial proportion of infected patients, in part due to undisclosed or unknown risks. Regardless of the screening strategy applied, for screening to be effective, identification of people with HCV infection must lead to subsequent interventions that improve clinical outcomes. Given the lack of evidence showing beneficial effects of screening and subsequent interventions on transmission risk or on intermediate outcomes such as risky behaviors, screening decisions are likely to be critically dependent on the effectiveness of antiviral treatments, which is covered in a separate review.⁵⁸ Therefore, we recommend that decisions about screening should only be made after also considering such the evidence on screening and treatment in totality.

In the prenatal setting, no intervention has been clearly demonstrated to reduce the risk of vertical transmission of HCV infection. Nonetheless, until more evidence is available, if a woman with HCV attempts vaginal delivery, clinicians may consider limiting the duration of ruptured membranes to less than 6 hours given some evidence of an association between prolonged rupture of membranes and increased risk of vertical transmission.²⁹¹

Clinicians and policymakers may consider modeling studies to help estimate potential benefits and harms of screening. We did not include such studies, whose usefulness will depend on the veracity of the model and the reliability of various input parameters.

Table 15. Summary of evidence on comparative benefits and harms of screening for hepatitis C virus infection

Key Question	Strength of Evidence	Summary
Key Question 1a. <i>Does screening for HCV infection in nonpregnant adults without known abnormal liver enzymes reduce mortality and morbidity due to HCV infection, affect quality of life, or reduce incidence of HCV infection?</i>	Insufficient	No studies.
Key Question 1b. <i>Does screening for HCV infection during pregnancy reduce vertical transmission of HCV or improve mortality or morbidity for the mother or child?</i>	Insufficient	No studies.
Key Question 2a. <i>What is the effectiveness of different risk- or prevalence-based methods for screening for HCV infection on clinical outcomes?</i>	Insufficient	No studies.

Table 15. Summary of evidence on comparative benefits and harms of screening for hepatitis C virus infection (continued)

Key Question	Strength of Evidence	Summary
Key Question 2b. <i>What is the sensitivity and number needed to screen to identify one case of HCV infection of different risk- or prevalence-based methods for screening for HCV infection?</i>	Low	Five studies found that screening strategies targeting multiple risk factors were associated with sensitivities of over 90% and numbers needed to screen to identify one case of HCV infection of less than 20. More narrowly targeted screening strategies were associated with numbers needed to screen of less than two, but with the trade-off of missing up to two-thirds of infected patients. All studies were retrospective and had methodological shortcomings.
Key Question 3. <i>What are the harms associated with screening for HCV infection, including adverse effects such as anxiety, labeling, and impact on relationships?</i>	Insufficient	Five studies of patients diagnosed with HCV infection suggested potential negative psychological and social effects, but are difficult to interpret due to small sample sizes and methodological shortcomings, including no unscreened comparison group.
Key Question 4a. <i>What is the Comparative Effectiveness and Comparative Diagnostic Accuracy of Various Tests and Strategies for the Workup to Guide Treatment Decisions in Patients who are HCV Positive?</i>		
Clinical Outcomes	Insufficient	One retrospective cohort study (n=156) of patients who received interferon plus ribavirin therapy found no difference in rates of sustained virologic rates between patients who did not undergo biopsy prior to treatment compared with matched patients who did undergo biopsy.
Diagnostic accuracy: Platelet counts vs. liver biopsy	Low	For fibrosis (defined as METAVIR F2-F4, Ishak 3-6, or equivalent), the median AUROC was 0.71 (range 0.38 to 0.94) in 5 studies. For cirrhosis (defined as METAVIR F4, Ishak 5-6, or equivalent), the AUROC was 0.89 (range 0.64 to 0.99) in five studies.
Diagnostic accuracy: Age-platelet index vs. liver biopsy	Moderate	For fibrosis, the median AUROC was 0.69 (range 0.64 to 0.77) in four studies. For cirrhosis, the median AUROC was 0.89 (range 0.67 to 0.91) in four studies.
Diagnostic accuracy: Aspartate aminotransferase-platelet ratio index (APRI) vs. liver biopsy	High	For fibrosis, the median AUROC was 0.76 (range 0.58 to 0.95) in 44 samples reported in 42 studies. For cirrhosis, the median AUROC was 0.85 (range 0.61 to 0.92) in 32 studies.
Diagnostic accuracy: Aspartate aminotransferase-alanine aminotransferase ratio (AST/ALT ratio, or AAR) vs. liver biopsy	High	For fibrosis, the median AUROC was 0.59 (range 0.50 to 0.82) in nine studies. For cirrhosis, the median AUROC was 0.66 (range 0.52 to 0.91) in eleven studies.
Diagnostic accuracy: Cirrhosis Discriminant Score (CDS, also Bonacini Index) vs. liver biopsy	Moderate	For cirrhosis, the median AUROC was 0.77 (range 0.70 to 0.91) in six studies. Although the CDS was developed to identify cirrhosis, three studies reported a median AUROC of 0.67 (range of 0.64 to 0.71) for fibrosis.
Diagnostic accuracy: Enhanced Liver Fibrosis Index (ELF) or Simplified Enhanced Liver Fibrosis Index (Simplified ELF) vs. liver biopsy	Moderate	For fibrosis, the median AUROC was 0.81 (range 0.72 to 0.87) in seven samples reported in five studies. For cirrhosis, the median AUROC was 0.88 (range 0.78 to 0.91) in six samples reported in three studies.

Table 15. Summary of evidence on comparative benefits and harms of screening for hepatitis C virus infection (continued)

Key Question	Strength of Evidence	Summary
Key Question 4a. <i>What is the Comparative Effectiveness and Comparative Diagnostic Accuracy of Various Tests and Strategies for the Workup to Guide Treatment Decisions in Patients who are HCV Positive? (continued)</i>		
Diagnostic accuracy: FIB-4 vs. liver biopsy	Moderate	For severe fibrosis (defined as METAVIR F3-F4, Ishak 4-6, or equivalent), the median AUROC was 0.86 (range 0.73 to 0.90) in four studies. For cirrhosis, the median AUROC was 0.87 (range 0.83 to 0.92) in six studies.
Diagnostic accuracy: FibroIndex vs. liver biopsy	Moderate	For fibrosis, the median AUROC was 0.71 (range 0.58 to 0.86) in five samples reported in four studies. For cirrhosis, the AUROCs were 0.86 and 0.92 in two studies.
Diagnostic accuracy: Fibrometer vs. liver biopsy	Moderate	For fibrosis, the median AUROC was 0.82 (range 0.78 to 0.85) in eight samples reported in seven studies. For cirrhosis, the median AUROC was 0.91 (range 0.89 to 0.94) in five studies.
Diagnostic accuracy: FibroSpect II vs. liver biopsy	Low	For fibrosis, the median AUROC was 0.86 (range 0.82 to 0.90) in four studies. No study evaluated the diagnostic accuracy of FibroSpect II for cirrhosis.
Diagnostic accuracy: Fibrotest vs. liver biopsy	High	For fibrosis, the median AUROC for was 0.79 (range 0.70 to 0.89) in 21 samples reported in twenty studies. For cirrhosis, the median AUROC was 0.86 (range 0.71 to 0.92) in eleven studies.
Diagnostic accuracy: Forns' Index vs. liver biopsy	High	For fibrosis, the median AUROC was 0.75 (range 0.60 to 0.86) in sixteen samples reported in fifteen studies. For cirrhosis, the median AUROC was 0.88 (range 0.85 to 0.91) in six studies.
Diagnostic accuracy: Hepascore vs. liver biopsy	High	For fibrosis, the median AUROC was 0.79 (range 0.69 to 0.82) in nine studies. For cirrhosis, the median AUROC was 0.89 (range 0.88 to 0.94) in eight samples reported in seven studies.
Diagnostic accuracy: Lok Index vs. liver biopsy	Moderate	For cirrhosis, the median AUROC was 0.80 (range 0.61 to 0.91) in eight samples reported in six studies. One study reported an AUROC of 0.69 (95% CI 0.69 to 0.74). No study reported the AUROC for the Lok Index for fibrosis.
Diagnostic accuracy: Pohl Index vs. liver biopsy	Low	For severe fibrosis (METAVIR F3-F4, Ishak 3-6, or equivalent), one study reported an AUROC of 0.53 (95% CI 0.51 to 0.56). For cirrhosis, the AUROC was 0.64 and 0.66 in two studies.
APRI vs. Fibrotest	Moderate	Sixteen studies (some of which evaluated overlapping populations) consistently found no differences between the APRI and Fibrotest based on the AUROC.
AST/ALT ratio vs. other indices	Moderate	Twelve of fourteen studies found the AST/ALT ratio associated with a lower AUROC compared with various other indices.
Key Question 4b. <i>What proportion of patients with screen-detected HCV infection receives treatment?</i>	Moderate	Three longitudinal studies reported that 15% to 33% of patients with screen-detected chronic HCV infection received treatment.

Table 15. Summary of evidence on comparative benefits and harms of screening for hepatitis C virus infection (continued)

Key Question	Strength of Evidence	Summary
<p>Key Question 5. <i>What are the harms associated with the workup for guiding treatment decisions?</i></p>	Moderate	<p>One study (n=2,740) of patients with chronic HCV infection and compensated cirrhosis with an Ishak fibrosis score of ≥ 3 reported serious adverse events in 1.1% of patients, including 0.6% serious bleeds and 0.3% severe pain, with no deaths. Five large (n=1,398 to 61,184) interventions series published since 2004 of patients undergoing percutaneous liver biopsy for a variety of reasons reported peri-procedural mortality in <0.2% and serious complications in 0.3% to 1.0%.</p>
<p>Key Question 6a. <i>How Effective is Counseling or Immunization of Patients With HCV Infection at Improving Health Outcomes or Reducing the Spread of HCV?</i></p>		
Clinical outcomes or spread of disease: counseling	Insufficient	<p>One randomized trial found a self-management program associated with slight improvements in SF-36 vitality scores compared with provision of educational materials after 6 weeks, but there were no effects on other measures of generic or HCV-related quality of life.</p>
Clinical outcomes: Immunization	Insufficient	No studies.
<p>Key Question 6b. Does becoming aware of positive HCV infection status decrease high-risk behaviors?</p>	Low	<p>Three retrospective studies reported substantial reductions in alcohol use following diagnosis of HCV infection, but two prospective studies found no evidence of sustained reductions in high-risk behaviors (alcohol use or injection drug use behaviors) following diagnosis. Results from two cross-sectional studies were mixed.</p>
<p>Key Question 6c. <i>How Effective is Counseling or Immunization of Patients With HCV Infection at Improving Intermediate Outcomes, Including Change in High Risk Behaviors?</i></p>		
High-risk behaviors: counseling	Insufficient	<p>Two randomized trials reported somewhat mixed results regarding effects of counseling interventions based on behavioral principles compared with simple educational interventions, though one trial that trained patients to serve as peer mentors reported sustained absolute decreases of about 15% in the proportion engaging in risky injection drug behaviors. Two before-after studies of HCV-infected heavy drinkers following found 36% to 44% reported abstinence 6 to 22 months after a counseling intervention.</p>
Intermediate outcomes: immunization	Insufficient	No studies.

Table 15. Summary of evidence on comparative benefits and harms of screening for hepatitis C virus infection (continued)

Key Question	Strength of Evidence	Summary
Key Question 7. Do Any Interventions Decrease or Increase the Vertical Transmission of HCV During Delivery or in the Perinatal Period?		
Vertical transmission: Elective cesarean vs. vaginal delivery	Low	Two good-quality studies found no statistically significant difference in risk of vertical transmission of HCV infection between elective cesarean and vaginal delivery, but trends were in opposite directions.
Vertical transmission: Any cesarean vs. vaginal delivery	Moderate	Ten of 11 observational studies (one good quality) found no statistically significant difference in risk of vertical transmission of HCV infection following vaginal compared with cesarean (not specified if elective or emergent) delivery.
Vertical transmission: Internal fetal monitoring vs. no internal fetal monitoring	Insufficient	Three observational studies (two good quality) found inconsistent evidence on the association between internal fetal monitoring and the risk of vertical transmission of HCV infection (no association in 2 studies) and OR 6.7 (95% CI 1.1 to 36) in the third study.
Vertical transmission: Prolonged rupture of membranes vs. less prolonged rupture of membranes	Low	Two studies (one good quality) found an association between prolonged labor after membrane rupture and risk of vertical transmission of HCV infection. In the good-quality study, membrane rupture >6 hours was associated with an adjusted OR of 9.3 (95% CI 1.5 to 180) for vertical transmission.
Vertical transmission: Breastfeeding vs. no breastfeeding	Moderate	Fourteen studies consistently found no significant association between breastfeeding and risk of transmission.

AAR = aspartate aminotransferase-alanine aminotransferase ratio; APRI = aspartate aminotransferase platelet ratio index; AUROC = area under the receiver operating characteristic curve; CI = confidence interval; CDS = Cirrhosis Discriminant Score; ELF = Enhanced Liver Fibrosis Index; HCV = hepatitis C virus; OR = odds ratio

Limitations of the Comparative Effectiveness Review Process

We excluded non-English language articles, which could result in language bias, though we identified no non-English language studies that would have met inclusion criteria. We included cohort studies on the association between labor and delivery practices or breastfeeding and vertical transmission. Such studies are more susceptible to bias and confounding than well-conducted randomized trials. We therefore focused on results from studies that performed adjustment and were otherwise assessed as being at lower risk of bias. For Key Questions related to effects of knowledge of HCV status or counseling on risky behaviors, we included weaker study designs such as before-after studies and cross-sectional studies, due to lack of evidence from studies with stronger designs. We were unable to formally assess for publication bias due to small numbers of studies, methodological shortcomings, and differences across studies in designs, measured outcomes, and other factors. We did not attempt to pool results for any Key Questions due to differences across studies in populations, interventions, and outcomes assessed.

Finally, we did not evaluate evidence on potential barriers to screening and how they might affect estimates of benefits and harms.

Limitations of the Evidence Base

The evidence base on HCV screening had a number of important limitations. No direct evidence comparing clinical outcomes in patients screened with those not screened, or clinical outcomes associated with different HCV screening strategies, is available. Studies on the sensitivity and yield of different screening strategies were primarily conducted in higher-prevalence populations.⁸⁰⁻⁸³ Only one small observational study evaluated clinical outcomes in people who underwent liver biopsy compared to no liver biopsy prior to antiviral treatment.⁹⁰ The only studies reporting rates of antiviral treatment in cohorts of patients with screen-identified HCV infection were conducted in VA settings or in a population of IVUDs and may be of limited applicability in other settings.²³⁰⁻²³² Few studies evaluated the effectiveness of interventions for reducing alcohol use or risky injection drug use behaviors in people specifically with HCV infection. In pregnant women, although studies have evaluated the association between prolonged rupture of membranes and internal fetal monitoring and risk of vertical transmission, no study has evaluated whether interventions to reduce their occurrence are associated with decreased risk.

Research Gaps

Significant research gaps continue to limit full understanding of the benefits and harms of screening for HCV infection. Studies that compare clinical outcomes in patients screened and not screened for HCV infection would provide the most direct evidence, but would require large sample sizes and long duration of followup. However, studies would not necessarily need to be prospective, as well-conducted retrospective studies could also be informative. In addition, in lieu of direct evidence on effects of screening on clinical outcomes, studies that prospectively evaluate the accuracy and efficiency of alternative screening strategies (such as the CDC birth-cohort approach of screening all adults born between 1945 and 1965)⁴⁸ would help fill important research gaps and provide some evidence to help guide strategies for targeted screening. No studies have adequately assessed the harmful impacts due to anxiety, labeling, or relationships with family and sexual partners that may result from screening for HCV infection in these patients and whether these harmful impacts can be minimized by appropriate counseling. If screening is effective, research on methods for addressing potential barriers to screening (such as use of rapid point-of-care tests) will be needed to help define optimal screening strategies.

Another important research gap is that although many studies have assessed the diagnostic accuracy of noninvasive tests compared to liver biopsy, there is insufficient evidence to determine effects of foregoing liver biopsy on clinical outcomes. Although liver biopsy is still regarded as the most accurate method for assessing the histologic stage of HCV infection, it is an invasive test with some risk for serious harms, making workup strategies that make use of noninvasive tests with high diagnostic accuracy a potential alternative. Studies that evaluate the outcomes of patients who receive treatment without liver biopsies would be helpful in determining whether all or selected patients should undergo pretreatment biopsy.

Another important research gap is that even though screening for chronic HCV infection may have importance not only in terms of individual clinical outcomes, but also as a public health measure, there is insufficient evidence to determine effects of screening on risk of transmission. In addition, screening might also help identify patients who would benefit from counseling about

alcohol use or hepatitis A and B vaccinations, but there is insufficient evidence to determine effects of these interventions. Studies demonstrating important individual or public health benefits from counseling, immunizations, and following a diagnosis of HCV in asymptomatic patients would help strengthen the case for screening

In pregnant women, although limited evidence suggests an association between prolonged rupture of membranes and vertical transmission of HCV infection, more studies are needed to understand the strength of the association and whether interventions targeted at avoiding prolonged rupture of membranes are effective at reducing risk of transmission.

Conclusions

Although screening can accurately identify adults with chronic HCV infection, more research is needed to understand the effects of different screening strategies on clinical outcomes. Evidence on effects of knowledge of HCV status and counseling and immunizations in patients diagnosed with HCV infection remains sparse, and more research is needed to understand effective interventions for preventing vertical transmission. A complete assessment of benefits and harms of screening requires consideration of the effectiveness of antiviral regimens, which are the subject of a complementary review.

Supplemental Tables

Supplemental Table 1. Key Question 4a: Diagnostic accuracy individual tests

Study, Year	Biopsy Quality	Test and Cutoff	Diagnosis	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value ^a	Area Under the Receiver Operating Curve
Alanine Aminotransferase (ALT)								
Fibrosis								
Boeker, 2002 ¹⁰⁰	Not reported	ALT >22 U/l	Ishak, grades not reported	0.96 (26/27)	0.16 (5/32)	0.49 (26/53)	0.83 (5/6)	Not reported
Murawaki, 2001b ¹⁶⁸	Not reported	ALT >80 IU/l	F2 or F3 fibrosis (Desmet)	0.60 (49/81)	0.66 (58/88)	0.62 (49/79)	0.64 (58/90) [0.65]	Not reported
Pradat, 2002 ¹⁸⁶	Not reported	ALT >upper limit of normal	METAVIR F2-F4	0.99 (603/612)	0.23 (57/252)	0.76 (603/798)	0.86 (57/66)	Not reported
Pradat, 2002 ¹⁸⁶	Not reported	ALT >2.25 upper limit of normal	>METAVIR A1F1	0.72	0.74	NR	NR	0.82 (CI not reported)
Walsh, 2000 ²¹⁶	Not reported	ALT (no cutoff, only AUROC reported)	Ishak ≥3 and HAI ≥6	Not reported	Not reported	Not reported	Not reported	0.54 (0.34-0.74)
Walsh, 1999a ²¹⁵	Not reported	ALT >55 IU/l	Ishak ≥3 and HAI ≥6	0.71	0.44	Not reported	Not reported	0.51 (0.39-0.63)
Walsh, 1999b ²¹⁷	Not reported	ALT >60 IU/l	Ishak ≥3 and HAI ≥6	0.67	0.52	Not reported	Not reported	0.59 (0.41-0.77)
Wilson, 2006 ²¹⁹	Not reported	ALT >upper limit of normal	Ishak 3-4 fibrosis	0.73 (8/11)	0.73 (79/108)	0.22 (8/37)	0.96 (79/82)	Not reported
Severe Fibrosis								
Pradat, 2002 ¹⁸⁶	Not reported	ALT >upper limit of normal	METAVIR F3-F4	1.0 (200/201)	0.10 (65/663)	0.25 (200/798)	0.98 (65/66)	Not reported
Wong, 1998 ²²⁰	Not reported	ALT (cutoff not described)	Modified Ishak 4-5 (max 5)	0.76 (16/21)	0.48 (52/109)	0.22 (16/73)	0.91 (52/57)	Not reported
Cirrhosis								
Boeker, 2002 ¹⁰⁰	Not reported	ALT >22 U/l	Ishak, grades not reported	0.89 (17/19) [0.88]	0.10 (6/59) [0.11]	0.24 (17/70)	0.75 (6/8)	Not reported
Pradat, 2002 ¹⁸⁶	Not reported	ALT >upper limit of normal	METAVIR F4	0.98 (64/65)	0.08 (65/799)	0.08 (64/798)	0.98 (65/66)	Not reported
Aspartate Aminotransferase (AST)								
Fibrosis								
Boeker, 2002 ¹⁰⁰	Not reported	AST >18 U/l	Ishak, grades not reported	0.78 (21/27)	0.41 (13/32) [0.40]	0.52 (21/40)	0.68 (13/19)	Not reported
Wilson, 2006 ²¹⁹	Not reported	AST >upper limit of normal	Ishak 3-4 fibrosis	0.82 (9/11)	0.64 (69/108)	0.19 (9/48)	0.97 (69/71)	Not reported

Supplemental Table 1. Key Question 4a: Diagnostic accuracy individual tests (continued)

Study, Year	Biopsy Quality	Test and Cutoff	Diagnosis	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value ^a	Area Under the Receiver Operating Curve
Aspartate Aminotrans-Ferase (AST) (continued)								
Severe Fibrosis								
El-Sayed, 2011 ¹²⁷	AST, cutoff not reported	All ≥10 and ≥5 portal tracts	METAVIR F3-F4	Not reported	Not reported	Not reported	Not reported	0.59 (CI not reported)
Cirrhosis								
Boeker, 2002 ¹⁰⁰	Not reported	AST >18 U/l	Ishak, grades not reported	0.79 (15/19) [0.81]	0.59 (35/59) [0.60]	0.38 (15/39)	0.90 (35/39)	Not reported
Albumin								
Fibrosis								
Ahmad, 2011 ⁹³	Not reported	Albumin <4.1 g/dl	METAVIR F2-F4	0.67 (60/89)	1.0 (68/68)	1.0 (60/60)	0.70 (68/97)	0.81 (0.74-0.89)
Boeker, 2002 ¹⁰⁰	Not reported	Albumin <37 g/l	Ishak, grades not reported	0.26 (7/27) [0.27]	0.91 (29/32) [0.90]	0.70 (7/10)	0.59 (29/49)	Not reported
Cirrhosis								
Ahmad, 2011 ⁹³	Not reported	Albumin <3.85 g/dl	METAVIR F4	0.71 (15/21)	0.93 (126/136)	0.60 (15/25)	0.95 (126/132)	0.88 (0.80-0.96)
Boeker, 2002 ¹⁰⁰	Not reported	Albumin <37 g/l	Ishak, grades not reported	0.74 (14/19) [0.73]	0.86 (51/59)	0.64 (14/22)	0.91 (51/56)	Not reported
Alkaline Phosphatase								
Fibrosis								
Ahmad, 2011 ⁹³	Not reported	Alkaline phosphatase >120 U/l	METAVIR F2-F4	0.70 (62/89)	0.85 (58/68)	0.86 (62/72)	0.68 (58/85)	0.83 (0.76-0.90)
Boeker, 2002 ¹⁰⁰	Not reported	Alkaline phosphatase >190 U/l	Ishak, grades not reported	0.22 (6/27)	0.84 (27/32)	0.55 (6/11)	0.56 (27/48)	Not reported
Cirrhosis								
Ahmad, 2011 ⁹³	Not reported	Alkaline phosphatase >240 U/l	METAVIR F4	0.81 (17/21)	0.92 (125/136)	0.61 (17/28)	0.97 (125/129)	0.93 (0.88-0.98)
Boeker, 2002 ¹⁰⁰	Not reported	Alkaline phosphatase >190 U/l	Ishak, grades not reported	0.47 (9/19)	0.85 (50/59)	0.50 (9/18)	0.83 (50/60)	Not reported
Apolipo-Protein A1								
Fibrosis								
Grigorescu, 2007 ¹³⁸	Not reported	Apolipoprotein A1 >1.41 g/L	METAVIR F2-F4	0.74 (97/130)	0.43 (33/76)	0.69 (97/140)	0.50 (33/66)	0.60 (CI not reported)
Rossi, 2003 ¹⁷⁸	Not reported	Apolipoprotein A1 >1.41 g/L	METAVIR F2-F4	0.26 (12/48)	0.50 (38/77)	0.24 (12/51)	0.51 (38/74)	Not reported

Supplemental Table 1. Key Question 4a: Diagnostic accuracy individual tests (continued)

Study, Year	Biopsy Quality	Test and Cutoff	Diagnosis	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value ^a	Area Under the Receiver Operating Curve
Bilirubin								
Fibrosis								
Ahmad, 2011 ⁹³	Not reported	Bilirubin >0.95 mg/dL	METAVIR F2-F4	0.68 (61/89)	0.85 (58/68)	0.86 (61/71)	0.67 (58/86)	0.73 (0.64-0.82)
Grigorescu, 2007 ¹³⁸	Not reported	Bilirubin >12.65 micromol/L	METAVIR F2-F4	0.46 (60/130)	0.80 (61/76)	0.80 (60/75)	0.47 (61/131)	0.67 (CI not reported)
Rossi, 2003 ¹⁷⁸	Not reported	Bilirubin >10 mmol/L	METAVIR F2-F4	0.61 (29/48)	0.53 (41/77)	0.45 (29/65)	0.68 (41/60)	Not reported
Cirrhosis								
Ahmad, 2011 ⁹³	Not reported	Bilirubin >1.5 mg/dL	METAVIR F4	0.67 (14/21)	0.96 (130/136)	0.70 (14/20)	0.95 (130/137)	0.89 (0.80-0.96)
Gamma-Glutamyl Transferase (GGT)								
Fibrosis								
Boeker, 2002 ¹⁰⁰	Not reported	GGT >28 U/l	Ishak, grades not reported	0.67 (18/27) [0.65]	0.53 (17/32)	0.55 (18/33)	0.65 (17/26)	Not reported
Grigorescu, 2007 ¹³⁸	Not reported	GGT >47 IU/L	METAVIR F2-F4	0.71 (93/130)	0.64 (49/76)	0.78 (93/120)	0.57 (49/86)	0.70 (CI not reported)
Parise, 2006 ¹⁷⁶	Not reported	GGT ≥1.5xULN	Batts-Ludwig F2-F4	0.77 (66/86) [0.76]	0.55 (66/120)	0.55 (66/120)	0.77 (66/86)	0.70 (0.63-0.78)
Rossi, 2003 ¹⁹¹	Not reported	GGT >45 U/L	METAVIR F2-F4	0.57 (27/48)	0.55 (42/77)	0.39 (27/62)	0.67 (42/63)	Not reported
Severe Fibrosis								
Silva, 2004 ²⁰³	Not reported	GGT >1x upper limit of normal	Desmet 3 or 4	0.63 (40/63)	0.59 (82/138)	0.42 (40/96)	0.78 (82/105)	Not reported
Cirrhosis								
Boeker, 2002 ¹⁰⁰	Not reported	GGT >28 U/l	Ishak, grades not reported	0.74 (14/19) [0.73]	0.47 (28/59)	0.31 (14/45)	0.85 (28/33)	Not reported
Parise, 2006 ¹⁷⁶	Not reported	GGT ≥2xULN	Batts-Ludwig F4	0.61 (27/44)	0.58 (94/162)	0.28 (27/95)	0.85 (94/111)	0.67 (0.59-0.75)
α-Glutathione-S Transferase (GST)								
Severe Fibrosis								
Wong, 1998 ²²⁰	Not reported	α-glutathione-S transferase (GST) cutoff not described	Modified Ishak 4-5 [max 5]	0.48 (10/21)	0.39 (43/109)	0.13 (10/76)	0.80 (43/54)	Not reported
Haptoglobin								
Fibrosis								
Grigorescu, 2007 ¹³⁸	Not reported	Haptoglobin >0.81 g/L	METAVIR F2-F4	0.50 (66/130)	0.68 (52/76)	0.73 (66/90)	0.45 (52/116) [0.44]	0.63 (CI not reported)
Rossi, 2003 ¹⁹¹	Not reported	Haptoglobin >0.56 g/L	METAVIR F2-F4	0.21 (10/48)	0.79 (61/77)	0.38 (10/26)	0.62 (61/99)	0.74 (0.64-0.84)

Supplemental Table 1. Key Question 4a: Diagnostic accuracy individual tests (continued)

Study, Year	Biopsy Quality	Test and Cutoff	Diagnosis	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value ^a	Area Under the Receiver Operating Curve
<i>Hyaluronic Acid</i>								
<i>Fibrosis</i>								
Boeker, 2002 ¹⁰⁰	Not reported	Hyaluronic acid >30 mcg/l	Ishak, grades not reported	0.48 (13/27)	0.84 (27/32)	0.72 (13/18)	0.66 (27/41)	Not reported
Halfon, 2005 ¹⁴³	Biopsy ≥25 mm	Hyaluronic acid ≥16 mcg/l	METAVIR F2-F4	<u>Derivation sample:</u> 0.96 (69/72)	<u>Derivation sample:</u> 0.19 (15/79)	<u>Derivation sample:</u> 0.52 (69/133)	<u>Derivation sample:</u> 0.83 (15/18)	<u>Derivation sample:</u> 0.75 (0.72-0.78)
				<u>Validation sample:</u> 0.91 (107/118)	<u>Validation sample:</u> 0.36 (49/136)	<u>Validation sample:</u> 0.55 (107/194)	<u>Validation sample:</u> 0.82 (49/60)	<u>Validation sample:</u> 0.73 (0.70-0.76)
Halfon, 2005 ¹⁴³	Biopsy ≥25 mm	Hyaluronic acid >121 mcg/l	METAVIR F2-F4	<u>Derivation sample:</u> 0.18 (13/72)	<u>Derivation sample:</u> 0.97 (77/79)	<u>Derivation sample:</u> 0.87 (13/15)	<u>Derivation sample:</u> 0.57 (77/136)	<u>Derivation sample:</u> 0.75 (0.72-0.78)
				<u>Validation sample:</u> 0.14 (16/118)	<u>Validation sample:</u> 0.99 (135/136)	<u>Validation sample:</u> 0.94 (16/17)	<u>Validation sample:</u> 0.57 (135/237)	<u>Validation sample:</u> 0.73 (0.70-0.76)
Leroy, 2004 ¹⁵⁹	Not reported	Hyaluronic acid >8 g/ml	METAVIR F2-F4	0.43 (36/84)	0.90 (94/104)	0.78 (36/46)	0.66 (94/142)	0.74 (CI not reported)
Murawaki, 2001b ¹⁶⁸	Not reported	Hyaluronic acid >50 ng/ml	Desmet F2 or F3	>50 ng/ml: 0.75 (61/81)	>50 ng/ml: 0.80 (70/88)	>50 ng/ml: 0.77 (61/79)	>50 ng/ml: 0.78 (70/90)	Not reported
Parise, 2006 ¹⁷⁶	Not reported	Hyaluronic acid ≥34.2	Batts-Ludwig F2-F4	0.85 (73/86)	0.71 (85/120)	0.68 (73/108)	0.87 (85/98)	0.88 (0.83-0.93)
Poynard, 2002 ¹⁸⁴	Not reported	Hyaluronic acid, cutoff not described	Knodell F3	Not reported	Not reported	Not reported	Not reported	0.65 (0.62-0.68)
Saitou, 2005 ¹⁹⁴	Not reported	Hyaluronic acid >75.7	METAVIR F2-F4	0.75 (58/77)	0.81 (26/32)	0.91 (58/64) [0.79]	0.58 (26/45) [0.76]	0.80 (CI not reported)
Zarski, 2012 ²²³	All ≥20 mm or ≥15 mm and ≥11 portal tracts	Hyaluronic acid, cutoff not reported	METAVIR F2-F4	Not reported	Not reported	Not reported	Not reported	0.75 (0.70-0.80)

Supplemental Table 1. Key Question 4a: Diagnostic accuracy individual tests (continued)

Study, Year	Biopsy Quality	Test and Cutoff	Diagnosis	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value ^a	Area Under the Receiver Operating Curve
<i>Hyaluronic Acid (continued)</i>								
<i>Severe Fibrosis</i>								
Guechot, 1996 ¹⁴⁰	Not reported	Hyaluronic acid >85 mcg/l	Knodell F3-F4	0.65 (71/110) [0.64]	0.91 (197/216)	0.79 (71/90)	0.83 (197/236)	0.86 (CI not reported)
Guechot, 1994 ¹⁴¹	Not reported	Hyaluronic acid >85 mg/l	Knodell F2 or F3	0.55 (11/20)	0.92 (35/38)	0.79 (11/14)	0.80 (35/44)	Not reported
Halfon, 2005 ¹⁴³	Biopsy ≥25 mm	Hyaluronic acid >25 mcg/l	METAVIR F3-F4	<u>Derivation sample:</u> 0.92 (36/39) <u>Validation sample:</u> 0.78 (47/60)	<u>Derivation sample:</u> 0.54 (61/112) <u>Validation sample:</u> 0.53 (103/194)	<u>Derivation sample:</u> 0.41 (36/87) <u>Validation sample:</u> 0.34 (47/138)	<u>Derivation sample:</u> 0.95 (61/64) <u>Validation sample:</u> 0.89 (103/116)	<u>Derivation sample:</u> 0.82 (0.80-0.84) <u>Validation sample:</u> 0.77 (0.73-0.81)
Halfon, 2005 ¹⁴³	Biopsy ≥25 mm	Hyaluronic acid >160 mcg/l	METAVIR F3-F4	<u>Derivation sample:</u> 0.26 (10/39) <u>Validation sample:</u> 0.22 (13/60)	<u>Derivation sample:</u> 0.99 (111/112) <u>Validation sample:</u> 1.0 (194/194)	<u>Derivation sample:</u> 0.91 (10/11) <u>Validation sample:</u> 1.0 (13/13)	<u>Derivation sample:</u> 0.79 (111/140) <u>Validation sample:</u> 0.80 (194/241)	<u>Derivation sample:</u> 0.82 (0.80-0.84) <u>Validation sample:</u> 0.77 (0.73-0.81)
Leroy, 2004 ¹⁵⁹	Not reported	Hyaluronic acid >8 g/ml	METAVIR F3-F4	0.86 (31/36)	0.70 (106/152)	0.40 (31/77)	0.95 (106/111)	0.82 (CI not reported)
McHutchison, 2000 ¹⁶⁶	≥1 cm and at least 3 portal tracts	Hyaluronic acid >60 mcg/l	Knodell 3 or 4	0.88 (123/139)	0.59 (206/347)	0.47 (123/264)	0.93 (206/222)	Not reported
McHutchison, 2000 ¹⁶⁶	≥1 cm and at least 3 portal tracts	Hyaluronic acid >80 mcg/l	Knodell 3 or 4	0.83 (115/139)	0.72 (250/347)	0.54 (115/212)	0.91 (250/274)	Not reported
McHutchison, 2000 ¹⁶⁶	≥1 cm and at least 3 portal tracts	Hyaluronic acid >100mcg/l	Knodell 3 or 4	0.76 (105/139)	0.82 (284/347)	0.63 (105/168)	0.89 (284/318)	Not reported
McHutchison, 2000 ¹⁶⁶	≥1 cm and at least 3 portal tracts	Hyaluronic acid >110 mcg/l	Knodell 3 or 4	0.73 (101/139)	0.83 (288/347)	0.63 (101/160)	0.88 (288/326)	Not reported
Murawaki, 2001b ¹⁶⁸	Not reported	Hyaluronic acid >70 ng/ml	Desmet F3	>70 ng/ml: 0.50 (20/40)	>70 ng/ml: 0.79 (102/129)	>70 ng/ml: 0.43 (20/47) [0.42]	>70 ng/ml: 0.84 (102/122)	Not reported
Wong, 1998 ²²⁰	Not reported	Hyaluronic acid, cutoff not described	Ishak 4-5 [max 5]	0.86 (18/21)	0.88 (96/109)	0.58 (18/31)	0.97 (96/99)	Not reported

Supplemental Table 1. Key Question 4a: Diagnostic accuracy individual tests (continued)

Study, Year	Biopsy Quality	Test and Cutoff	Diagnosis	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value ^a	Area Under the Receiver Operating Curve
<i>Hyaluronic Acid (continued)</i>								
Cirrhosis								
Boeker, 2002 ¹⁰⁰	Not reported	Hyaluronic acid >30 mcg/l	Ishak, grades not reported	0.89 (17/19) [0.90]	0.73 (43/59)	0.52 (17/33)	0.96 (43/45)	Not reported
Guechot, 1996 ¹⁴⁰	Not reported	Hyaluronic acid >110 mcg/l	Knodell F4	0.79 (42/53)	0.89 (244/273)	0.59 (42/71)	0.96 (244/255)	0.92 (CI not reported)
Halfon, 2005 ¹⁴³	Biopsy ≥25 mm	Hyaluronic acid >25 mcg/l	METAVIR F4	<u>Derivation sample:</u> 0.92 (11/12)	<u>Derivation sample:</u> 0.72 (100/139)	<u>Derivation sample:</u> 0.22 (11/50)	<u>Derivation sample:</u> 0.99 (100/101)	<u>Derivation sample:</u> 0.89 (0.86-0.92)
				<u>Validation sample:</u> 1.0 (13/13)	<u>Validation sample:</u> 0.79 (190/241)	<u>Validation sample:</u> 0.20 (13/64)	<u>Validation sample:</u> 1.0 (190/190)	<u>Validation sample:</u> 0.97 (0.93-1.0)
Halfon, 2005 ¹⁴³	Biopsy ≥25 mm	Hyaluronic acid >237 mcg/l	METAVIR F4	<u>Derivation sample:</u> Not reported	<u>Derivation sample:</u> Not reported	<u>Derivation sample:</u> 0.71 (n/N not reported)	<u>Derivation sample:</u> Not reported	<u>Derivation sample:</u> 0.89 (0.86-0.92)
				<u>Validation sample:</u> 0.31 (4/13)	<u>Validation sample:</u> 0.99 (239/241)	<u>Validation sample:</u> 0.67 (4/6)	<u>Validation sample:</u> 0.96 (239/248)	<u>Validation sample:</u> 0.97 (0.93-1.0)
McHutchison, 2000 ¹⁶⁶	≥1 cm and at least 3 portal tracts	Hyaluronic acid >60 mcg/l	Knodell 3 or 4	0.98 (78/80)	0.54 (220/406)	0.30 (78/264)	0.99 (220/222)	Not reported
McHutchison, 2000 ¹⁶⁶	≥1 cm and at least 3 portal tracts	Hyaluronic acid >80 mcg/l	Knodell 3 or 4	0.93 (74/80)	0.66 (268/406)	0.35 (74/212)	0.98 (268/274)	Not reported
McHutchison, 2000 ¹⁶⁶	≥1 cm and at least 3 portal tracts	Hyaluronic acid >100 mcg/l	Knodell 3 or 4	0.89 (71/80)	0.76 (309/406)	0.42 (71/168)	0.97 (309/318)	Not reported
McHutchison, 2000 ¹⁶⁶	≥1 cm and at least 3 portal tracts	Hyaluronic acid >110 mcg/l	Knodell 3 or 4	0.88 (70/80)	0.78 (316/406)	0.44 (70/160)	0.97 (316/326)	Not reported
Parise, 2006 ¹⁷⁶	Not reported	Hyaluronic acid ≥78.6	Batts-Ludwig F4	0.91 (40/44)	0.81 (132/162) [0.82]	0.57 (40/70)	0.97 (132/136)	0.91 (0.87-0.95)

Supplemental Table 1. Key Question 4a: Diagnostic accuracy individual tests (continued)

Study, Year	Biopsy Quality	Test and Cutoff	Diagnosis	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value ^a	Area Under the Receiver Operating Curve
<i>Hyaluronic Acid (continued)</i>								
<i>Cirrhosis (continued)</i>								
Plevris, 2000 ¹⁸²	Not reported	Hyaluronic acid >100 mcg/l	Knodell F4	0.73 (11/15) [0.72]	0.93 (50/54)	0.73 (11/15)	0.93 (50/54)	Not reported
Plevris, 2000 ¹⁸²	Not reported	Hyaluronic acid >200 mcg/l	Knodell F4	Not reported	0.98 (53/54)	Not reported	Not reported	Not reported
Plevris, 2000 ¹⁸²	Not reported	Hyaluronic acid >300 mcg/l	Knodell F4	Not reported	1.0 (54/54)	Not reported	Not reported	Not reported
Saitou, 2005 ¹⁹⁴	Not reported	Hyaluronic acid >183.5	METAVIR F4	0.80 (24/30)	0.80 (63/79)	0.60 (24/40) [0.80]	0.91 (63/69) [0.80]	0.85 (CI not reported)
<i>Laminin P1</i>								
<i>Severe Fibrosis</i>								
Gabrielli, 1997 ¹³³	≥5 portal tracts and ≥5 terminal hepatic veins	Laminin P1 >1.4	Scheuer F3-F4	0.79	0.40	0.35	0.82	Not reported
Gabrielli, 1997 ¹³³	≥5 portal tracts and ≥5 terminal hepatic veins	Laminin P1 >2.0	Scheuer F3-F4	0.48	0.88	0.63	0.81	Not reported
Gabrielli, 1997 ¹³³	≥5 portal tracts and ≥5 terminal hepatic veins	Laminin P1 >2.4	Scheuer F3-F4	0.31	0.96	0.88	0.77	Not reported
<i>Severe Fibrosis or Cirrhosis (Advanced Liver Disease)</i>								
Walsh, 2000 ²¹⁶	Not reported	Serum laminin >1.26 U/ml	Ishak ≥3 and HAI ≥6	0.80	0.83	Not reported	Not reported	0.82 (0.66-0.98)

Supplemental Table 1. Key Question 4a: Diagnostic accuracy individual tests (continued)

Study, Year	Biopsy Quality	Test and Cutoff	Diagnosis	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value ^a	Area Under the Receiver Operating Curve
a-2 Macro-Globulin								
Fibrosis								
Grigorescu, 2007 ¹³⁸	Not reported	a-2 macroglobulin >3.01 g/L	METAVIR F2-F4	0.74 (96/130)	0.58 (44/76)	0.75 (96/128)	0.56 (44/78)	0.73 (CI not reported)
Rossi, 2003 ¹⁹¹	Not reported	a-2 macroglobulin >2.52 g/L	METAVIR F2-F4	0.75 (36/48)	0.67 (52/77)	0.43 (36/61)	0.81 (52/64)	Not reported
Matrix Metalloproteinase-2 (MMP-2)								
Fibrosis								
Boeker, 2002 ¹⁰⁰	Not reported	MMP-2 (Biotrak) >1500 mcg/l	Ishak, grades not reported	0.07 (2/27)	1.0 (32/32)	1.0 (2/2)	0.56 (32/57)	Not reported
Boeker, 2002 ¹⁰⁰	Not reported	MMP-2 (Quantikine) >320 mcg/l	Ishak, grades not reported	0.07 (2/27)	0.97 (31/32)	0.67 (2/3)	0.55 (31/56)	Not reported
El-Gindy, 2003 ¹²⁶	Not reported	MMP-2 >400 ng/ml	Ishak 1-4 vs. Ishak 0	0.07 (1/15)	0.92 (11/12) [0.97]	0.50 (1/2)	0.44 (11/25)	0.57 (0.49-0.65)
Murawaki, 2001b ¹⁶⁸	Not reported	MMP-2 >550 ng/ml	Desmet F2 or F3	0.75 (61/81)	0.70 (62/88)	0.70 (61/87) [0.72]	0.76 (62/82) [0.73]	Not reported
Murawaki, 2001b ¹⁶⁸	Not reported	MMP-2 >575 ng/ml	Desmet F3	0.68 (27/40)	0.69 (89/129)	0.40 (27/67) [0.44]	0.87 (89/102) [0.85]	Not reported
Severe Fibrosis or Cirrhosis (Advanced Liver Disease)								
Walsh, 1999b ²¹⁷	Not reported	MMP-2 >860 ng/ml	Ishak ≥3 and HAI ≥6	0.69	0.59	Not reported	Not reported	0.67 (0.47-0.87)
Cirrhosis								
Boeker, 2002 ¹⁰⁰	Not reported	MMP-2 (Biotrak) >1,500 mcg/l	Ishak, grades not reported	0.74 (14/19)	1.0 (59/59)	1.0 (14/14)	0.92 (59/64)	Not reported
Boeker, 2002 ¹⁰⁰	Not reported	MMP-2 (Quantikine) >320 mcg/l	Ishak, grades not reported	0.84 (16/19) [0.84]	0.97 (57/59) [0.96]	0.89 (16/18)	0.95 (57/60)	Not reported
El-Gindy, 2003 ¹²⁶	Not reported	MMP-2 >400 ng/ml	Ishak 5-6	0.86 (12/14) [0.83]	0.96 (26/27)	0.92 (12/13)	0.93 (26/28)	0.97 (0.95-0.99)

Supplemental Table 1. Key Question 4a: Diagnostic accuracy individual tests (continued)

Study, Year	Biopsy Quality	Test and Cutoff	Diagnosis	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value ^a	Area Under the Receiver Operating Curve
-------------	----------------	-----------------	-----------	-------------	-------------	---------------------------	--	---

Supplemental Table 1. Key Question 4a: Diagnostic accuracy individual tests (continued)

Study, Year	Biopsy Quality	Test and Cutoff	Diagnosis	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value ^a	Area Under the Receiver Operating Curve
Platelet Count								
Fibrosis								
Ahmad, 2011 ⁹³	Not reported	Platelet count <150,000	METAVIR F2-F4	0.70 (62/89)	0.98 (67/68)	0.98 (62/63)	0.71 (67/94)	0.94 (0.90-0.97)
Cheung, 2008 ¹¹⁷	Not reported	Platelet count <100,000	Batts-Ludwig 2-4	0.05 (15/323)	0.99 (166/167)	0.94 (15/16)	0.35 (166/474)	0.52 (0.51-0.53)
Cheung, 2008 ¹¹⁷	Not reported	Platelet count <150,000	Batts-Ludwig 2-4	0.28 (89/323)	0.92 (153/167)	0.86 (89/103)	0.40 (153/387)	0.60 (0.56-0.63)
Giannini, 2006 ¹³⁶	Not reported	Platelet count <163,000	Ishak 3-6 or METAVIR F2-F4	0.62 (108/175)	0.81 (189/234)	0.71 (108/153)	0.74 (189/256)	Not reported
Iacobellis, 2005a ¹⁴⁷	All ≥5 portal tracts	Platelet count <140,000	Scheuer F2-F4	0.51 (330/648)	0.90 (446/495)	0.87 (330/379)[0.96]	0.58 (446/764) [0.29]	Not reported
Ben Jazia, 2009 ⁹⁸	Not reported	Platelet count	METAVIR F2-F4	Not reported	Not reported	Not reported	Not reported	0.38 (CI not reported)
Lackner, 2005 ¹⁵⁶ and Lackner, 2006 ²²⁴	All ≥6 portal tracts	Platelet count <130,000	Ishak 3-6	0.30 (29/97)	1.0 (97/97)	1.0 (29/29)	0.59 (97/165)	0.71 (0.64-0.79)
Lackner, 2005 ¹⁵⁶ and Lackner, 2006 ²²⁴	All ≥6 portal tracts	Platelet count <150,000	Ishak 3-6	0.42 (41/97)	0.97 (94/97)	0.93 (41/44)	0.63 (94/150)	0.71 (0.64-0.79)
Murawaki, 2001a ¹⁶⁹	Not reported	Platelet count <140,000	Desmet F2 or F3	Not reported	Not reported	Not reported	0.89 (94/106)	Not reported
Murawaki, 2001a ¹⁶⁹	Not reported	Platelet count <160,000	Desmet F2 or F3	0.68 (53/78)	0.71 (62/87)	0.68 (53/78)	0.71 (62/87)	Not reported
Renou, 2001 ¹⁸⁸	Not reported	Platelet count <140,000	METAVIR F2-F4	0.30 (14/33)	1.0 (57/57)	1.0 (14/14)	1.0 (57/57)	Not reported
Sirli, 2010 ²⁰⁴	All ≥20 mm and ≥8 portal tracts	Platelet count <176,000	METAVIR F2-F4	0.37 (50/134)	1.0 (16/16)	1.0 (50/50)	0.16 (16/100)	0.73 (0.65-0.80)

Supplemental Table 1. Key Question 4a: Diagnostic accuracy individual tests (continued)

Study, Year	Biopsy Quality	Test and Cutoff	Diagnosis	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value ^a	Area Under the Receiver Operating Curve
Platelet Count (continued)								
Severe Fibrosis								
Cheung, 2008 ¹¹⁷	Not reported	Platelet count <100,000	Batts-Ludwig 3 or 4	0.08 (14/187)	0.99 (301/303)	0.88 (14/16)	0.64 (301/474)	0.53 (0.52-0.55)
Cheung, 2008 ¹¹⁷	Not reported	Platelet count <150,000	Batts-Ludwig 3 or 4	0.39 (72/187) [0.38]	0.90 (272/303)	0.70 (72/103)	0.70 (272/387)	0.64 (0.60-0.68)
Iacobellis, 2005b ¹⁴⁸	All ≥5 portal tracts	Platelet count <140,000	Scheuer F3 or F4	0.71 (172/243)	0.86 (873/1,009)	0.56 (172/308) [0.77]	0.92 (873/944) [0.93]	Not reported
Murawaki, 2001a ¹⁶⁹	Not reported	Platelet count <140,000	Desmet F3	0.68 (26/38)	0.74 (94/127)	0.44 (26/59)	0.89 (94/106)	Not reported
Murawaki, 2001a ¹⁶⁹	Not reported	Platelet count <160,000	Desmet F2 or F3	Not reported	Not reported	0.68 (53/78)	0.71 (62/87)	Not reported
Renou, 2001 ¹⁸⁸	Not reported	Platelet count <140,000	METAVIR F3-F4	0.47 (14/30)	1.0 (74/74)	1.0 (14/14)	1.0 (74/74)	Not reported
Cirrhosis								
Ahmad, 2011 ⁹³	Not reported	Platelet count <100,000	METAVIR F4	0.81 (17/21)	0.98 (134/136)	0.89 (17/19)	0.97 (134/138)	0.99 (0.98-1.0)
Castera, 2009 ¹¹²	All ≥10 mm and ≥6 portal tracts; mean 20 mm and 15 portal tracts	Platelet count <150,000	METAVIR F4	0.41 (29/70)	0.94 (214/228)	0.67 (29/43)	0.84 (214/255)	0.79 (0.72-0.85)
Giannini, 2003a ¹³⁴	Not reported	Platelet count <130,000	Scheuer F4 or clinical signs of portal hypertension	0.91 (82/90)	0.88 (143/162)	0.81 (82/101)	0.95 (143/151)	Not reported
Iacobellis, 2005a ¹⁴⁷	All ≥5 portal tracts	Platelet count <140,000	Scheuer F4	0.82 (67/82)	0.87 (923/1,061)	0.33 (67/205) [0.32]	0.98 (923/938)	Not reported
Iacobellis, 2005b ¹⁴⁸	All ≥5 portal tracts	Platelet count <140,000	Scheuer F4	0.86 (67/78)	0.87 (1,018/1,174)	0.30 (67/223) [0.29]	0.99 (1,018/1,029) [0.87]	Not reported
Islam, 2005 ¹⁵¹	≥10 mm and ≥4 portal tracts	Platelet count <190,000	Ishak 5 or 6	0.80 (16/20)	0.77 (122/159)	0.30 (16/53)	0.97 (122/126)	Not reported

Supplemental Table 1. Key Question 4a: Diagnostic accuracy individual tests (continued)

Study, Year	Biopsy Quality	Test and Cutoff	Diagnosis	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value ^a	Area Under the Receiver Operating Curve
Platelet Count (continued)								
Cirrhosis (continued)								
Lackner, 2005 ¹⁵⁶ and Lackner, 2006 ²²⁴	All ≥6 portal tracts	Platelet count <130,000	Ishak 5-6	0.53 (17/32)	0.93 (151/162)	0.61 (17/28) [0.59]	0.91 (151/166)	0.89 (0.83-0.94)
Lackner, 2005 ¹⁵⁶ and Lackner, 2006 ²²⁴	All ≥6 portal tracts	Platelet count <150,000	Ishak 5-6	0.78 (25/32) [0.77]	0.88 (143/162)	0.57 (25/44) [0.56]	0.95 (143/150)	0.89 (0.83-0.94)
Luo, 2002 ¹⁶⁴	All >5 portal tracts	Platelet count ≤140,000	Scheuer F4	0.83 (19/23)	0.85 (75/88)	0.59 (19/32)	0.95 (75/79)	Not reported
Renou, 2001 ¹⁸⁸	Not reported	Platelet count <140,000	METAVIR F4	0.93 (13/14)	0.99 (89/90)	0.93 (13/14)	0.99 (89/90)	Not reported
Sebastiani, 2011 ²⁰⁰	Mean 18 mm and 11 portal tracts; 43% >20 mm	Platelet count <150,000	METAVIR F4	Whole sample: Not reported Normal ALT: 0.44 (8/19)	Whole sample: Not reported Normal ALT: 0.90 (519/576)	Whole sample: Not reported Normal ALT: 0.12 (8/65) [0.34]	Whole sample: Not reported Normal ALT: 0.98 (519/530) [0.94]	Whole sample: Not reported Normal ALT: 0.64 (0.58-0.70)
Sirli, 2010 ²⁰⁴	All ≥20 mm and ≥8 portal tracts	Platelet count <155,000	METAVIR F4	0.87 (13/15)	0.84 (113/135)	0.37 (13/35)	0.98 (113/115)	0.90 (0.84-0.94)
Procollagen-III-Peptide (PIIIP)								
Fibrosis								
Leroy, 2004 ¹⁵⁹	Not reported	PIIIP >6 ng/ml	METAVIR F2-F4	0.47 (39/84)	0.93 (95/104)	0.85 (39/46)	0.68 (95/140)	0.77 (CI not reported)
Murawaki, 2001b ¹⁶⁸	Not reported	PIIIP >0.80	Desmet F2 or F3	0.74 (60/81)	0.52 (46/88)	0.59 (60/102) [0.60]	0.69 (46/67) [0.68]	Not reported
Saitou, 2005 ¹⁹⁴	Not reported	PIIIP >0.835	METAVIR F2-F4	0.78 (60/77)	0.75 (24/32)	0.88 (60/68) [0.76]	0.59 (24/41) [0.77]	0.75 (CI not reported)

Supplemental Table 1. Key Question 4a: Diagnostic accuracy individual tests (continued)

Study, Year	Biopsy Quality	Test and Cutoff	Diagnosis	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value ^a	Area Under the Receiver Operating Curve
Procollagen-III-Peptide (PIIIP) (continued)								
Severe Fibrosis								
Gabrielli, 1997 ¹³³	≥5 portal tracts and ≥5 terminal hepatic veins	PIIIP >0.6	Scheuer F3-F4	0.93	0.13	0.30	0.82	Not reported
Gabrielli, 1997 ¹³³	≥5 portal tracts and ≥5 terminal hepatic veins	PIIIP >1.0	Scheuer F3-F4	0.34	>0.94	0.71	0.78	Not reported
Gabrielli, 1997 ¹³³	≥5 portal tracts and ≥5 terminal hepatic veins	PIIIP >1.6	Scheuer F3-F4	0.03	0.98	0.47	0.71	Not reported
Guechot, 1996 ¹⁴⁰	Not reported	PIIIP >0.80 U/ml	Knodell F3-F4	0.70 (77/110)	0.63 (137/216)	0.49 (77/156)	0.81 (137/170)	0.69 (CI not reported)
Guechot, 1994 ¹⁴¹	Not reported	PIIIP >0.80 U/ml	Knodell F2 or F3	0.40 (8/20)	0.66 (25/38)	0.38 (8/21)	0.68 (25/37)	Not reported
Leroy, 2004 ¹⁵⁹	Not reported	PIIIP >5 ng/ml	METAVIR F3-F4	0.92 (33/36)	0.76 (116/152)	0.48 (33/69)	0.97 (116/119)	0.88 (CI not reported)
Lo Iacono, 1998 ¹⁶¹	Not reported	PIIIP >10.57 mcg/ml	Scheuer F3 or F4	0.89	0.52	NR	NR	0.73 (CI not reported)
Murawaki, 2001b ¹⁶⁸	Not reported	PIIIP >0.90	Desmet F3	0.65 (26/40) [0.64]	0.59 (76/129)	0.33 (26/79)	0.84 (76/90)	Not reported
Severe Fibrosis or Cirrhosis (Advanced Liver Disease)								
Walsh, 1999a ²¹⁵	Not reported	PIIIP (Col 1-3 and Col 1 assay) >0.8 U/ml	Ishak ≥3 and HAI ≥6	0.50	0.88	Not reported	Not reported	0.76 (0.58-0.94)
Walsh, 1999a ²¹⁵	Not reported	PIIIP (Col 1-3 assay) >4.2 mg/l	Ishak ≥3 and HAI ≥6	0.85	0.38	Not reported	Not reported	0.67 (0.57-0.87)

Supplemental Table 1. Key Question 4a: Diagnostic accuracy individual tests (continued)

Study, Year	Biopsy Quality	Test and Cutoff	Diagnosis	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value ^a	Area Under the Receiver Operating Curve
<i>Procollagen-III-Peptide (PIIP) (continued)</i>								
<i>Cirrhosis</i>								
Guechot, 1996 ¹⁴⁰	Not reported	PIIP >1.00 U/ml	Knodell F4	0.60 (32/53)	0.74 (202/273)	0.31 (32/103)	0.91 (202/223)	0.73 (CI not reported)
Saitou, 2005 ¹⁹⁴	Not reported	PIIP >0.995	METAVIR F4	0.77 (23/30)	0.66 (52/79)	0.46 (23/50) [0.69]	0.88 (52/59) [0.67]	0.79 (CI not reported)
Verbaan, 1997 ²¹²	Not reported	PIIP >1.11 U/ml	Scheuer F4	0.82 (9/11) [0.78]	0.56 (49/87)	0.19 (9/47)	0.96 (49/51)	Not reported
<i>Prothrombin Index</i>								
<i>Cirrhosis</i>								
Castera, 2009 ¹¹²	All ≥10 mm and ≥6 portal tracts; mean 20 mm and 15 portal tracts	Prothrombin index ≤85%	METAVIR F4	0.36 (25/70)	0.90 (205/228)	0.52 (25/48)	0.52 (25/48)	0.73 (0.66-0.80)
<i>Soluble Inter-Cellular Adhesion Molecule-1 (sICAM-1)</i>								
<i>Severe Fibrosis</i>								
Lo Iacono, 1998 ¹⁶¹	Not reported	Soluble ICAM-1 >520 ng/ml	Scheuer F3 or F4	0.64	0.56	NR	NR	0.75 (CI not reported)
<i>Soluble Vascular Cell Adhesion Molecule-1 (sVCAM-1)</i>								
<i>Severe Fibrosis</i>								
Lo Iacono, 1998 ¹⁶¹	Not reported	Soluble VCAM-1 >1208 ng/ml	Scheuer F3 or F4	1.00	0.85	NR	NR	0.96 (CI not reported)
<i>Tissue Inhibitor of Metalloproteinase-1 (TIMP-1)</i>								
<i>Fibrosis</i>								
Boeker, 2002 ¹⁰⁰	Not reported	TIMP-1 (Biotrak) >950 mcg/l	Ishak, grades not reported	0.52 (14/27)	0.88 (28/32)	0.78 (14/18)	0.68 (28/41)	Not reported
Boeker, 2002 ¹⁰⁰	Not reported	TIMP-1 (Quantikine) >85 mcg/l	Ishak, grades not reported	0.67 (18/27)	0.69 (22/32) [0.68]	0.64 (18/28)	0.71 (22/31)	Not reported
El-Gindy, 2003 ¹²⁶	Not reported	TIMP-1 >195 ng/ml	Ishak 1-4 vs. Ishak 0	0.67 (10/15)	0.67 (8/12) [0.69]	0.71 (10/14)	0.62 (8/13)	0.71 (0.64-0.78)
Murawaki, 2001b ¹⁶⁸	Not reported	TIMP-1 >160 ng/ml	Desmet F2 or F3	0.79 (64/81)	0.56 (49/88)	0.62 (64/103) [0.63]	0.74 (49/66) [0.73]	Not reported

Supplemental Table 1. Key Question 4a: Diagnostic accuracy individual tests (continued)

Study, Year	Biopsy Quality	Test and Cutoff	Diagnosis	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value ^a	Area Under the Receiver Operating Curve
Tissue Inhibitor of Metalloproteinase-1 (TIMP-1) (continued)								
Severe Fibrosis or Cirrhosis (Advanced Liver Disease)								
Murawaki, 2001b ¹⁶⁸	Not reported	TIMP-1 >170 ng/ml	Desmet F3	0.82 (33/40) [0.83]	0.54 (70/129)	0.36 (33/92) [0.34]	0.91 (70/77)	Not reported
Walsh, 1999b Walsh, 1999b ²¹⁷	Not reported	TIMP-1 >500 ng/ml	Ishak ≥3 and HAI ≥6	0.94	0.57	Not reported	Not reported	0.73 (0.57-0.89)
Cirrhosis								
Boeker, 2002 ¹⁰⁰	Not reported	TIMP-1 (Biotrak) >950 mcg/l TIMP-1 (Quantikine) >85 mcg/l	Ishak, grades not reported	Biotrak >950 mcg/l: 1.0 (19/19) Quantikine >85 mcg/l: 1.0 (19/19)	Biotrak >950 mcg/l: 0.88 (28/32) Quantikine >85 mcg/l: 0.69 (22/32) [0.68]	Biotrak >950 mcg/l: 0.78 (14/18) Quantikine >85 mcg/l: 0.64 (18/28)	Biotrak >950 mcg/l: 0.68 (28/41) Quantikine >85 mcg/l: 0.71 (22/31)	Not reported
El-Gindy, 2003 ¹²⁶	Not reported	TIMP-1 >195 ng/ml	Ishak 5-6	1.0 (14/14)	0.74 (20/27) [0.75]	0.67 (14/21)	1.0 (20/20)	0.89 (0.85-0.93)
Tissue Inhibitor of Metalloproteinase-2 (TIMP-2)								
Severe Fibrosis or Cirrhosis (Advanced Liver Disease)								
Walsh, 1999b ²¹⁷	Not reported	TIMP-2 >102 ng/ml	Ishak ≥3 and HAI ≥6	0.85	0.57	Not reported	Not reported	0.73 (0.57-0.89)
Type-IV Collagen (PIVNP)								
Fibrosis								
Murawaki, 2001a ¹⁶⁹	Not reported	Type-IV collagen >110	Desmet F2 or F3	0.77 (60/78)	0.74 (64/87) [0.73]	0.72 (60/83)	0.74 (64/82)	Not reported
Murawaki, 2001b ¹⁶⁸	Not reported	Type-IV collagen (PIVNP) >6.0	Desmet F2 or F3	0.70 (57/81)	0.73 (64/88)	0.70 (57/81) [0.71]	0.73 (64/88) [0.72]	Not reported
Saitou, 2005 ¹⁹⁴	Not reported	Type IV collagen >5.75	METAVIR F2-F4	0.65 (50/77)	0.69 (22/32)	0.83 (50/60) [0.67]	0.45 (22/49) [0.66]	0.74 (CI not reported)

Supplemental Table 1. Key Question 4a: Diagnostic accuracy individual tests (continued)

Study, Year	Biopsy Quality	Test and Cutoff	Diagnosis	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value ^a	Area Under the Receiver Operating Curve
Type-IV Collagen (PIVNP) (continued)								
Severe Fibrosis or Cirrhosis (Advanced Liver Disease)								
Murawaki, 2001a ¹⁶⁹	Not reported	Type-IV collagen >110	Desmet F3	0.66 (25/38)	0.75 (95/127)	0.44 (25/57)	0.88 (95/108)	Not reported
Murawaki, 2001b ¹⁶⁸	Not reported	Type-IV collagen (PIVNP) >6.5	Desmet F3	0.63 (25/40)	0.73 (94/129)	0.42 (25/60) [0.41]	0.86 (94/109) [0.87]	Not reported
Walsh, 2000 ²¹⁶	Not reported	Type IV collagen >148 ng/ml	Ishak ≥3 and HAI ≥6	0.73	0.85	Not reported	Not reported	0.83 (0.69-0.97)
Cirrhosis								
Saitou, 2005 ¹⁹⁴	Not reported	Type IV collagen >6.55	METAVIR F4	0.60 (18/30)	0.61 (48/79)	0.37 (18/49) [0.61]	0.80 (48/60) [0.60]	0.60 (CI not reported)
Verbaan, 1997 ²¹²	Not reported	Type-IV collagen >250 ng/ml	Scheuer F4	0.91 (10/11) [0.87]	0.75 (65/87)	0.31 (10/32)	0.98 (65/66)	Not reported
YKL-40 (Human Cartilage-Glyco-Protein 39 or Chitinase 3-like 1)								
Fibrosis								
Saitou, 2005 ¹⁹⁴	Not reported	YKL-40 >186.4	METAVIR F2-F4	0.78 (60/77)	0.81 (26/32)	0.91 (60/66) [0.80]	0.60 (26/43) [0.79]	0.81 (CI not reported)
Cirrhosis								
Saitou, 2005 ¹⁹⁴	Not reported	YKL-40 >284.8	METAVIR F4	0.80 (24/30)	0.71 (56/79)	0.51 (24/47) [0.73]	0.90 (56/62) [0.78]	0.80 (CI not reported)
Body Mass Index (BMI)								
Fibrosis								
Testa, 2006 ²⁰⁹	All ≥15 mm; mean 24 mm	BMI >25	Ishak ≥3	0.62 (23/37)	0.84 (32/38)	0.79 (23/29)	0.70 (32/46)	0.73 (0.61-0.82)

Supplemental Table 1. Key Question 4a: Diagnostic accuracy individual tests (continued)

Study, Year	Biopsy Quality	Test and Cutoff	Diagnosis	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value ^a	Area Under the Receiver Operating Curve
Imaging Findings								
Fibrosis								
Cobbold, 2009 ²²⁹	All ≥10 mm, mean 24 mm	Hepatic transit time >8.0	Ishak 3-6	0.53 (20/37) [0.54]	0.73 (22/30)	0.71 (20/28) [0.62]	0.56 (22/39) [0.66]	0.71 (0.59-0.84)
Colli, 2005 ¹²¹	Mean 41 mm	Nodular liver present	METAVIR F3-F4	0.60 (40/67)	0.92 (100/109)	0.82 (40/49)	0.79 (100/127)	Not reported
Iacobellis, 2005a ¹⁴⁷	All ≥5 portal tracts	Spleen length >120 mm	Scheuer F2-F4	0.16 (104/648)	0.96 (475/495)	0.84 (104/124) [0.85]	0.47 (475/1,019)	Not reported
Iacobellis, 2005a ¹⁴⁷	All ≥5 portal tracts	Nodular liver present	Scheuer F2-F4	0.16 (104/648)	0.97 (480/495)	0.87 (104/119)	0.47 (480/1,024)	Not reported
Iacobellis, 2005a ¹⁴⁷	All ≥5 portal tracts	Portal vein diameter >12 mm	Scheuer F2-F4	0.07 (45/648)	1.0 (494/495)	0.98 (45/46)	0.45 (494/1,097)	Not reported
Liu, 2006 ¹⁶⁰	Mean 19 mm length and 1.4 mm diameter	Splenic artery pulsatility index >0.85	METAVIR F2-F4	0.98 (20/21)	0.39 (23/58)	0.36 (20/55) [0.37]	0.96 (23/24) [0.98]	0.86 (0.78-0.95)
Liu, 2006 ¹⁶⁰	Mean 19 mm length and 1.4 mm diameter	Splenic artery pulsatility index >1.05	METAVIR F2-F4	0.67 (14/21)	0.90 (52/58)	0.70 (14/20)	0.88 (52/59)	0.86 (0.78-0.95)
Testa, 2006 ²⁰⁹	All ≥15 mm; mean 24 mm	Platelet-spleen diameter ratio <1750	Ishak ≥3	0.78 (29/37)	0.79 (30/38)	0.78 (29/37)	0.79 (30/38)	0.74 (0.63-0.84)
Severe Fibrosis								
Paggi, 2008 ¹⁷⁵	Median 4.1 cm	Liver surface nodularity	METAVIR F3-F4	0.72 (116/160) [0.73]	0.90 (243/270)	0.81 (116/143)	0.85 (243/287)	Not reported

Supplemental Table 1. Key Question 4a: Diagnostic accuracy individual tests (continued)

Study, Year	Biopsy Quality	Test and Cutoff	Diagnosis	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value ^a	Area Under the Receiver Operating Curve
Imaging Findings (continued)								
Cirrhosis								
Cobbold, 2009 ²²⁹	All ≥10 mm, mean 24 mm	Hepatic transit time >8.0	Ishak 3-6	Hepatic transit time: 0.71 (10/14)	Hepatic transit time: 0.91 (48/53)	Hepatic transit time: 0.67 (10/15)	Hepatic transit time: 0.92 (48/52)	Hepatic transit time: 0.83 (0.69-0.97)
Iacobellis, 2005a ¹⁴⁷	All ≥5 portal tracts	Spleen length >120 mm	Scheuer F4	0.40 (33/82)	0.91 (966/1,061)	0.26 (33/128)	0.95 (966/1,015)	Not reported
Iacobellis, 2005a ¹⁴⁷	All ≥5 portal tracts	Nodular liver	Scheuer F4	0.46 (38/82)	0.93 (987/1,061)	0.34 (38/112) [0.33]	0.96 (987/1,031)	Not reported
Iacobellis, 2005a ¹⁴⁷	All ≥5 portal tracts	Portal vein diameter >12 mm	Scheuer F4	0.19 (15/82)	0.97 (1,029/1,061)	0.32 (15/47) [0.35]	0.94 (1,029/1,096)	Not reported
Schneider, 2006 ¹⁹⁶	Not reported	Portal venous flow <12.5 cm/s	Ishak 5-6	0.89 (17/19) [0.88]	0.66 (42/64) [0.65]	0.44 (17/39)	0.95 (42/44)	0.80 (CI not reported)
Schneider, 2005 ¹⁹⁵	Not reported	Portal venous flow <14.5 cm/s	Ishak 5-6	0.74 (13/17)	0.53 (54/102)	0.21 (13/61)	0.93 (54/58)	Not reported
Schneider, 2005 ¹⁹⁵	Not reported	Portal venous undulations reduced	Ishak 5-6	0.76 (13/17)	1.0 (102/102)	1.0 (13/13)	0.96 (102/106)	Not reported
Schneider, 2005 ¹⁹⁵	Not reported	Hepatic venous flow pattern mono- or biphasic	Ishak 5-6	0.31 (5/17)	0.47 (48/102)	0.08 (5/59)	0.80 (48/60)	Not reported
Schneider, 2005 ¹⁹⁵	Not reported	Longitudinal spleen size (cutoff not reported)	Ishak 5-6	0.78 (13/17)	0.53 (54/102)	0.21 (13/61)	0.93 (54/58)	Not reported
Schneider, 2005 ¹⁹⁵	Not reported	Transverse spleen size >5 cm	Ishak 5-6	0.86 (15/17)	0.35 (36/102)	0.19 (15/81)	0.95 (36/38)	Not reported

^a Reported value differs from value calculated from 2 x 2 table: values in brackets are reported predictive values when they differed from values calculated from sample size, prevalence, sensitivity, and specificity.

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
Age-Platelet Index						
Fibrosis						
Cross, 2009 ¹²⁴	Age-platelet index >3.5	All >10 mm and >10 portal tracts	Ishak ≥3	0.70 (190/271)	0.74 (245/331)	0.77 (0.73-0.81)
Fabris, 2008 ¹²⁹	Age-platelet index, only AUROC reported	Average 19 mm and median 7 portal tracts	METAVIR F2-F4	Not reported	Not reported	0.64 (0.56-0.72)
Lackner, 2005 ¹⁵⁶ and Lackner, 2006 ²²⁴	Age-platelet index ≥6.0	All ≥6 portal tracts	Ishak 3-6	0.51 (49/97)	0.93 (90/97)	0.74 (0.67-0.81)
Liu, 2006 ¹⁶⁰	Age-platelet index: >4.0	Mean 19 mm length and 1.4 mm diameter	METAVIR F2-F4	0.52 (11/21)	0.77 (45/58)	0.64 (0.51-0.77)
Liu, 2006 ¹⁶⁰	Age-platelet index: >6.0	Mean 19 mm length and 1.4 mm diameter	METAVIR F2-F4	0.19 (4/21)	0.86 (50/58)	0.64 (0.51-0.77)
Cirrhosis						
Borroni, 2006 ¹⁰²	Age-platelet index ≥6.0	All ≥6 portal fields	Knodell 4	0.67 (20/30)	0.87 (172/198)	0.88 (0.82-0.94)
Cross, 2009 ¹²⁴	Age-platelet index >5.0	All >10 mm and >10 portal tracts	Ishak 5 or 6	0.80 (106/132)	0.89 (418/470)	0.90 (0.86-0.93)
Ehsan, 2008 ¹²⁵	Age-platelet index >5.0	Mean 12 mm	Ishak 5-6	0.72 (25/35)	0.93 (75/81)	0.91 (CI not reported)
Fabris, 2008 ¹²⁹	Age-platelet index, only AUROC reported	Average 19 mm and median 7 portal tracts	METAVIR F4	Not reported	Not reported	0.67 (0.59-0.74)
Aspartate Aminotransferase-Platelet Ratio Index (APRI)						
Fibrosis						
Adler, 2008 ⁹²	APRI (cutoff not reported)	Not reported	METAVIR F2-F4	Not reported	Not reported	0.74 (CI not reported)
Ahmad, 2011 ⁹³	APRI >0.5	Not reported	METAVIR F2-F4	0.98 (87/89)	0.19 (13/68)	0.72 (0.64-0.80)
Ahmad, 2011 ⁹³	APRI >1.5	Not reported	METAVIR F2-F4	0.35 (31/89)	0.68 (46/68)	0.88 (0.78-0.97)
Ben Jazia, 2009 ⁹⁸	APRI >0.72	Not reported	METAVIR F2-F4	0.93 (25/27)	0.58 (5/8)	0.91 (CI not reported)
Berg, 2004 ⁹⁹	APRI >0.5	Not reported	Scheuer F2-F4	0.82 (207/253)	0.53 (122/231)	Not reported
Berg, 2004 ⁹⁹	APRI >1.5	Not reported	Scheuer F2-F4	0.37 (93/253)	0.93 (215/231)	Not reported
Bota, 2011 ¹⁰³	APRI (cutoff not reported)	All ≥8 portal tracts, mean 34 mm	METAVIR F2-F4	Not reported	Not reported	0.69 (CI not reported)
Bourliere, 2006 ¹⁰⁵	APRI >0.5	Mean 20 mm and median 9 portal tracts; 59% ≥15 mm and ≥5 portal tracts	METAVIR F2-F4	0.70 (69/99)	0.55 (75/136)	0.71 (0.67-0.79)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
<i>Aspartate Aminotransferase-Platelet Ratio Index (APRI) (continued)</i>						
<i>Fibrosis (continued)</i>						
Bourliere, 2006 ¹⁰⁵	APRI ≥1.5	Mean 20 mm and median 9 portal tracts; 59% ≥15 mm and ≥5 portal tracts	METAVIR F2-F4	0.22 (22/99)	0.95 (129/136)	0.71 (0.67-0.79)
Burton, 2011 ¹⁰⁹	APRI >0.6	Not reported	Batts-Ludwig 2-4	Whole sample: 0.70 (92/131) Black subjects: 0.65 (38/58), White subjects: 0.75 (52/69)	Whole sample: 0.72 (99/137), Black subjects: 0.75 (63/84) White subjects: 0.68 (33/48)	Whole sample: Not reported Black subjects: 0.70 (0.60-0.80) White subjects: 0.76 (0.66-0.76)
Cales, 2008 ¹¹⁰	APRI >0.55	Not reported	METAVIR F2-F4	0.62 (343/549)	0.84 (423/507)	0.79 (CI not reported)
Castera, 2005 ¹¹⁴	APRI (cutoff not reported)	Median 17 mm, median 2 fragments	METAVIR F2-F4	Not reported	Not reported	0.78 (0.70-0.85)
Cheong, 2011 ¹¹⁵	APRI (cutoff not reported)	Mean 12.6 mm and mean 13.2 portal tracts; 71% had ≥11 portal tracts	METAVIR F2-F4	Not reported for HCV subgroup	Not reported for HCV subgroup	0.82 (0.72-0.92)
Cheung, 2008 ¹¹⁷	APRI (cutoff not reported)	Not reported	Batts-Ludwig 2-4	Not reported	Not reported	0.69 (0.64-0.74)
Cheung, 2011 ¹¹⁶	APRI >0.5	Median 1.6-2.0 cm and >8 portal tracts	METAVIR F2-F4	Not reported	Not reported	Validation sample only 0.72 (0.60-0.85)
Chrysanthos, 2006 ¹¹⁸	APRI >0.5	All >1.5 cm	Ishak ≥3	0.79 (115/146)	0.46 (64/138)	Not reported for HCV subgroup
Chrysanthos, 2006 ¹¹⁸	APRI >1.5	All >1.5 cm	Ishak ≥3	0.30 (44/146)	0.88 (122/138)	Not reported for HCV subgroup
Cobbold, 2009 ²²⁹	APRI >0.66	All ≥10 mm, mean 24 mm	Ishak 3-6	0.83 (31/37) [0.84]	0.78 (23/30) [0.77]	0.83 (0.73-0.93)
Crisan, 2012 ¹²²	APRI >0.44	All >5 portal tracts; median 11 mm and mean 14 portal tracts	METAVIR F2-F4	0.72 (203/282)	0.67 (109/163)	0.73 (CI not reported)
Cross, 2009 ¹²⁴	APRI >0.53	All >10 mm and >10 portal tracts	Ishak ≥3	Derivation sample only 0.69 (187/271)	Derivation sample only 0.77 (255/331)	Derivation sample only 0.76 (0.72-0.80)
Fabris, 2008 ¹²⁹	APRI (cutoff not reported)	Average 19 mm and median 7 portal tracts	METAVIR F2-F4	Not reported	Not reported	0.72 (0.64-0.79)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
Aspartate Aminotransferase-Platelet Ratio Index (APRI) (continued)						
Fibrosis (continued)						
Giannini, 2003b ¹³⁵	APRI (cutoff not reported)	Not reported	Not reported	Not reported	Not reported	0.77 (CI not reported)
Gomes da Silva, 2008 ¹³⁷	APRI >0.5	Not reported	METAVIR F2-F4	0.93 (26/28)	0.45 (10/22)	0.92 (0.83-1.0)
Gomes da Silva, 2008 ¹³⁷	APRI >0.93	Not reported	METAVIR F2-F4	0.93 (26/28)	0.96 (21/22)	0.92 (0.83-1.0)
Gomes da Silva, 2008 ¹³⁷	APRI >1.5	Not reported	METAVIR F2-F4	0.50 (14/28) [0.46]	1.0 (22/22)	0.92 (0.83-1.0)
Güzelbulut, 2011 ¹⁴²	APRI >0.5	Not reported	METAVIR F2-F4	0.84 (70/83)	0.45 (30/67)	0.77 (0.73-0.86)
Güzelbulut, 2011 ¹⁴²	APRI >1.5	Not reported	METAVIR F2-F4	0.43 (36/83)	0.91 (61/67)	0.77 (0.73-0.86)
Halfon, 2007 ¹⁴⁵	APRI >0.39	All >15 mm	METAVIR F2-F4	0.77 (112/146)	0.66 (139/210)	0.76 (0.72-0.81)
Hsieh, 2009 ¹⁴⁶	APRI >0.5	Not reported	METAVIR F2-F4	0.97 (113/116)	0.13 (3/24)	0.63 (0.52-0.74)
Hsieh, 2009 ¹⁴⁶	APRI >1.2	Not reported	METAVIR F2-F4	0.66 (77/116)	0.50 (12/24)	0.63 (0.52-0.74)
Hsieh, 2009 ¹⁴⁶	APRI >1.5	Not reported	METAVIR F2-F4	0.54 (63/116)	0.58 (14/24)	0.63 (0.52-0.74)
Islam, 2005 ¹⁵¹	APRI (cutoff not reported)	≥10 mm and ≥4 portal tracts	Ishak 5-6	Not reported	Not reported	0.71 (CI not reported)
Khan, 2008 ¹⁵³	APRI >0.5	Not reported	METAVIR F2-F4	0.83 (53/64)	0.57 (32/56)	Not reported
Khan, 2008 ¹⁵³	APRI >1.5	Not reported	METAVIR F2-F4	0.41 (26/64)	0.95 (53/56)	Not reported
Lackner, 2005 ¹⁵⁶ and Lackner, 2006 ²²⁴	APRI ≥0.5	All ≥6 portal tracts	Ishak 3-6	0.88 (85/97)	0.44 (43/97)	0.80 (0.73-0.86)
Lackner, 2005 ¹⁵⁶ and Lackner, 2006 ²²⁴	APRI ≥1.5	All ≥6 portal tracts	Ishak 3-6	0.44 (43/97)	0.96 (93/97)	0.80 (0.73-0.86)
Leroy, 2007 ¹⁵⁸	APRI >0.5	Median 23 mm and median 17 portal tracts; 89% >15 mm and 45% >25 mm	METAVIR F2-F4	0.92 (83/91)	0.27 (24/89)	Whole sample and excluding patients with biopsy <15 mm or <7 portal tracts (n=161) 0.81 (0.74-0.88) and 0.80 (CI not reported)
Leroy, 2007 ¹⁵⁸	APRI >1.0	Median 23 mm and median 17 portal tracts; 89% >15 mm and 45% >25 mm	METAVIR F2-F4	0.80 (72/91)	0.63 (56/89)	Whole sample and excluding patients with biopsy <15 mm or <7 portal tracts (n=161) APRI: 0.81 (0.74-0.88) and 0.80 (CI not reported)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
<i>Aspartate Aminotransferase-Platelet Ratio Index (APRI) (continued)</i>						
<i>Fibrosis (continued)</i>						
Leroy, 2007 ¹⁵⁸	APRI >1.5	Median 23 mm and median 17 portal tracts; 89% >15 mm and 45% >25 mm	METAVIR F2-F4	0.72 (66/91)	0.88 (78/89)	Whole sample and excluding patients with biopsy <15 mm or <7 portal tracts (n=161) 0.81 (0.74-0.88) and 0.80 (CI not reported)
Leroy, 2007 ¹⁵⁸	APRI >2.0	Median 23 mm and median 17 portal tracts; 89% >15 mm and 45% >25 mm	METAVIR F2-F4	0.58 (53/91)	0.94 (84/89)	Whole sample and excluding patients with biopsy <15 mm or <7 portal tracts (n=161) 0.81 (0.74-0.88) and 0.80 (CI not reported)
Leroy, 2008 ¹⁵⁷	APRI (cutoff not reported)	55% >20 mm; 84% >15 mm	METAVIR F2-F4	0.39 (155/400)	0.95 (404/425)	0.79 (0.76-0.82)
Liu, 2006 ¹⁶⁰	APRI >0.4	Mean 19 mm length and 1.4 mm diameter	METAVIR F2-F4	0.48 (10/21)	0.75 (44/58)	0.67 (0.54-0.81)
Liu, 2006 ¹⁶⁰	APRI >0.5	Mean 19 mm length and 1.4 mm diameter	METAVIR F2-F4	0.29 (6/21)	0.94 (55/58)	0.67 (0.54-0.81)
Liu, 2006 ¹⁶⁰	APRI >1.5	Mean 19 mm length and 1.4 mm diameter	METAVIR F2-F4	0.0 (0/21)	1.0 (58/58)	0.67 (0.54-0.81)
Loeza-del-Castillo, 2008 ¹⁶²	APRI >0.64	Not reported	METAVIR F2-F4	0.75 (62/83)	0.68 (55/81)	0.78 (0.70-0.85)
Martinez, 2011 ¹⁶⁵	APRI >0.5	Mean 15 mm, 72% >15 mm	METAVIR F2-F4	0.91 (209/229)	0.50 (56/111) 0.51]	0.83 (0.79-0.88)
Martinez, 2011 ¹⁶⁵	APRI >1.5	Mean 15 mm, 72% >15 mm	METAVIR F2-F4	0.47 (107/220)	0.93 (103/111)	0.83 (0.79-0.88)
Parise, 2006 ¹⁷⁶	APRI ≥0.7	Not reported	Batts-Ludwig F2-F4	0.85 (73/86)	0.66 (79/120)	0.82 (0.77-0.88)
Park, 2011 ¹⁷⁸	APRI (cutoff not reported)	Not reported	METAVIR F2-F4	Not reported	Not reported	0.79 (0.69-0.89)
Patel, 2009 ¹⁸⁰	APRI >0.5	Mean 18 mm	METAVIR F2-F4	0.95 (21/22)	0.64 (46/72)	Not reported
Patel, 2009 ¹⁸⁰	APRI ≥1.5	Mean 18 mm	METAVIR F2-F4	0.41 (9/22)	0.99 (71/72)	Not reported
Romera, 2006 ¹⁸⁹	APRI ≥0.5	Mean 10 portal tracts	Scheuer F2-F4	0.81 (50/62)	0.36 (25/69)	0.70 (CI not reported)
Schneider, 2006 ¹⁹⁶	APRI >0.7	Not reported	Ishak 3-6	0.81 (38/47)	0.65 (23/36)	0.75 (CI not reported)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
<i>Aspartate Aminotransferase-Platelet Ratio Index (APRI) (continued)</i>						
<i>Fibrosis (continued)</i>						
Sebastiani, 2006 ²⁹²	APRI >0.5	All ≥1.5 cm and ≥7 portal tracts	METAVIR F2-F4	Elevated ALT and normal ALT subgroups, respectively [n/N not reported] 0.84 and 0.79	Elevated ALT and normal ALT subgroups, respectively [n/N not reported] 0.77 and 0.95	Elevated ALT and normal ALT subgroups, respectively [n/N not reported] 0.69 (0.54-0.85) and 0.77 (0.63-0.91)
Sebastiani, 2006 ²⁹²	APRI >1.5	All ≥1.5 cm and ≥7 portal tracts	METAVIR F2-F4	Elevated ALT and normal ALT subgroups, respectively 0.30 and 0.27	Elevated ALT and normal ALT subgroups, respectively [n/N not reported] 0.94 and 1.0	Elevated ALT and normal ALT subgroups, respectively [n/N not reported] 0.69 (0.54-0.85) and 0.77 (0.63-0.91)
Sebastiani, 2008 ¹⁹⁸	APRI >0.5	All ≥15 mm and ≥7 portal tracts	METAVIR F2-F4	Whole sample, normal ALT, and elevated ALT, respectively 0.70 (103/147), 0.36 (12/32), 0.79 (91/115)	Whole sample, normal ALT, and elevated ALT, respectively 0.74 (72/97), 0.91 (44/48), 0.57 (28/49)	Normal ALT and elevated ALT, respectively (AUROC not reported for whole sample) 0.69 (0.54-0.85) and 0.75 (0.65-0.85)
Sebastiani, 2008 ¹⁹⁸	APRI >1.5	All ≥15 mm and ≥7 portal tracts	METAVIR F2-F4	Whole sample, normal ALT, and elevated ALT, respectively 0.24 (35/147), 0.14 (4/32), 0.27 (31/115)	Whole sample, normal ALT, and elevated ALT, respectively 1.0 (97/97), 1.0 (48/48), 1.0 (49/49)	Normal ALT and elevated ALT, respectively (AUROC not reported for whole sample) 0.69 (0.54-0.85) and 0.75 (0.65-0.85)
Sebastiani, 2009 ¹⁹⁷	APRI >0.5	Mean 18 mm and mean 10.6 portal tracts	METAVIR F2-F4	0.67 (625/931)	0.73 (810/1,104)	0.70 (0.65-0.75)
Sebastiani, 2009 ¹⁹⁷	APRI >1.5	Mean 18 mm and mean 10.6 portal tracts	METAVIR F2-F4	0.27 (255/931)	0.96 (1,064/1,104)	0.62 (0.59-0.65)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
<i>Aspartate Aminotransferase-Platelet Ratio Index (APRI) (continued)</i>						
<i>Fibrosis (continued)</i>						
Sebastiani, 2011 ²⁰⁰	APRI >0.5	Mean 18 mm and 11 portal tracts; 43% >20 mm	METAVIR F2-F4	Whole sample: Not reported Normal ALT: 0.43 (76/176)	Whole sample: Not reported Normal ALT: 0.82 (346/419)	Whole sample: 0.70 (0.65-0.75) Normal ALT: 0.63 (0.57-0.71)
Sebastiani, 2011 ²⁰⁰	APRI >1.5	Mean 18 mm and 11 portal tracts; 43% >20 mm	METAVIR F2-F4	Whole sample: 0.46 (374/820) Normal ALT: 0.27 (48/176)	Whole sample: 0.95 (941/990) Normal ALT: 0.89 (372/419)	Whole sample: 0.70 (0.65-0.75) Normal ALT: 0.63 (0.57-0.71)
Sebastiani, 2012 ²⁰¹	APRI >0.5	Mean 20 mm and 11 portal tracts; 45% >20 mm	METAVIR F2-F4	0.70 (381/552)	0.73 (338/461)	0.70 (0.64-0.76)
Sebastiani, 2012 ²⁰¹	APRI >1.5	Mean 20 mm and 11 portal tracts; 45% >20 mm	METAVIR F2-F4	0.29 (160/552)	0.95 (440/461)	0.70 (0.64-0.76)
Sirli, 2010 ²⁰⁴	APRI >0.52	All >20 mm and ≥8 portal tracts	METAVIR F2-F4	0.70 (94/134)	0.81 (13/16)	0.77 (0.69-0.83)
Snyder, 2006 ²⁰⁵	APRI >0.5	Not reported	Batts-Ludwig F2-F4	Retro-spective and prospective samples, respectively : 0.84 (147/176) [0.83] and 0.87 (68/78)	Retro-spective and prospective samples, respectively : 0.55 (95/174) [0.54] and 0.62 (45/72)	Retrospective and prospective samples, respectively: 0.79 (0.74-0.83) and 0.89 (0.82-0.93)
Snyder, 2006 ²⁰⁵	APRI ≥1.0	Not reported	Batts-Ludwig F2-F4	Retro-spective and prospective samples, respectively : Not reported and 0.65 (51/78)	Retro-spective and prospective samples, respectively : Not reported and 0.92 (66/72)	Retrospective and prospective samples, respectively: 0.79 (0.74-0.83) and 0.89 (0.82-0.93)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
Aspirate Aminotransferase-Platelet Ratio Index (APRI) (continued)						
Fibrosis (continued)						
Snyder, 2006 ²⁰⁵	APRI ≥1.2	Not reported	Batts-Ludwig F2-F4	Retro-spective and prospective samples, respectively : 0.39 (69/107) [0.41] and not reported	Retro-spective and prospective samples, respectively : 0.90 (157/174) and not reported	Retrospective and prospective samples, respectively: 0.79 (0.74-0.83) and 0.89 (0.82-0.93)
Snyder, 2006 ²⁰⁵	APRI ≥1.5	Not reported	Batts-Ludwig F2-F4	Retro-spective and prospective samples, respectively : 0.30 (52/176) [0.31] and 0.45 (35/78) [0.44]	Retro-spective and prospective samples, respectively : 0.97 (168/174) [0.96] and 0.94 (68/72)	Retrospective and prospective samples, respectively: 0.79 (0.74-0.83) and 0.89 (0.82-0.93)
Snyder, 2007 ²⁰⁶	APRI >0.42	Mean 25 mm	Batts-Ludwig F2-F4	0.98 (49/50)	0.44 (19/43)	0.89 (0.81-0.92)
Snyder, 2007 ²⁰⁶	APRI >1.20	Mean 25 mm	Batts-Ludwig F2-F4	0.62 (31/50)	0.95 (41/43)	0.89 (0.81-0.92)
Testa, 2006 ²⁰⁹	APRI >0.864	All ≥15 mm; mean 24 mm	Ishak ≥3	0.70 (11/37)	0.79 (30/38)	0.72 (0.60-0.82)
Viana, 2009 ²¹³	APRI ≥0.75	All >10 portal tracts	METAVIR F2-F4	Sample 1 and sample 2, respectively : 0.82 (98/120) and 0.83 (105/126)	Sample 1 and sample 2, respectively : 0.95 (76/80) and 0.82 (61/74)	Sample 1 and sample 2, respectively: 0.95 (0.91-0.97) and 0.92 (0.87-0.95)
Wai, 2003 ²¹⁴	APRI >0.50	Not reported	Ishak 3-6	0.91 (83/91)	0.47 (47/101)	0.83 (0.78-0.88)
Wai, 2003 ²¹⁴	APRI >1.5	Not reported	Ishak 3-6	0.41 (37/91)	0.95 (96/101)	0.83 (0.78-0.88)
Wilson, 2006 ²¹⁹	APRI ≥0.5	Not reported	Ishak 3-4	0.73 (8/11)	0.59 (63/108) [0.58]	0.70 (CI not reported)
Wilson, 2006 ²¹⁹	APRI >1.5	Not reported	Ishak 3-4	0.18 (2/11)	0.94 (102/108)	0.70 (CI not reported)
Yilmaz, 2011 ²²¹	APRI >0.44	Not reported	METAVIR F1-F4	0.73 (CI not reported)	0.62 (CI not reported)	0.58 (0.52-0.70)
Zarski, 2012 ²²³	APRI (cutoff not reported)	All ≥20 mm or ≥15 mm and ≥11 portal tracts	METAVIR F2-F4	Not reported	Not reported	0.76 (0.72-0.81)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
<i>Aspirate Aminotransferase-Platelet Ratio Index (APRI) (continued)</i>						
<i>Severe Fibrosis</i>						
Adler, 2008 ⁹²	APRI (cutoff not reported)	Not reported	METAVIR F3-F4	Not reported	Not reported	0.89 (CI not reported)
Becker, 2009 ⁹⁶	APRI >0.5	All ≥10 mm or ≥8 portal tracts; median 16 mm, 11% <10 mm	METAVIR F3-F4	0.77 (107/139)	0.60 (152/252)	Not reported
Becker, 2009 ⁹⁶	APRI >1.5	All ≥10 mm or ≥8 portal tracts; median 16 mm, 11% <10 mm	METAVIR F3-F4	0.27 (38/139)	0.97 (245/252)	Not reported
Bota, 2011 ¹⁰³	APRI (cutoff not reported)	All ≥8 portal tracts, mean 34 mm	METAVIR F3-F4	Not reported	Not reported	0.82 (CI not reported)
Boursier, 2009 ¹⁰⁶	APRI >0.581	Not reported	METAVIR F3-F4	0.78 (205/264)	0.75 (591/792)	0.82 (0.79-0.85)
Boursier, 2009 ¹⁰⁶	APRI >1.159	Not reported	METAVIR F3-F4	0.51 (134/264)	0.92 (726/792)	0.82 (0.79-0.85)
Burton, 2011 ¹⁰⁹	APRI >0.99	Not reported	Batts-Ludwig 3-4	Whole sample: 0.65 (47/72) Black subjects: 0.62 (18/29) White subjects: 0.70 (29/41)	Whole sample: 0.82 (161/196) Black subjects: 0.86 (97/113) White subjects: 0.75 (57/76)	Whole sample: Not reported Black subjects: 0.77 (0.65-0.89) White subjects: 0.76 (0.66-0.86)
Castera, 2005 ¹¹⁴	APRI (cutoff not reported)	Median 17 mm, median 2 fragments	METAVIR F3-F4	Not reported	Not reported	0.84 (0.78-0.89)
Cheung, 2008 ¹¹⁷	APRI (cutoff not reported)	Not reported	Batts-Ludwig 3 or 4	Not reported	Not reported	0.76 (0.71-0.81)
Cheung, 2011 ¹¹⁶	APRI (cutoff not reported)	Median 1.6-2.0 cm and >8 portal tracts	METAVIR F3-F4	Not reported	Not reported	0.87 (0.75-0.98)
Crisan, 2012 ¹²²	APRI >1.69	All >5 portal tracts; median 11 mm and mean 14 portal tracts	METAVIR F3-F4	0.61 (75/122)	0.77 (251/324)	0.74 (CI not reported)
El-Sayed, 2011 ¹²⁷	APRI (cutoff not reported)	All ≥10 mm and ≥5 portal tracts	METAVIR F3-F4	Not reported	Not reported	0.63 (CI not reported)
Halfon, 2007 ¹⁴⁵	APRI >0.58	All >15 mm	METAVIR F3-F4	0.75 (38/51)	0.76 (232/305)	0.81 (0.76-0.85)
Iacobellis, 2005b ¹⁴⁸	APRI >1.5	All ≥5 portal tracts	Scheuer F3 or F4	0.60 (145/243)	0.88 (891/1009)	Not reported

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
<i>Aspartate Aminotransferase-Platelet Ratio Index (APRI) (continued)</i>						
<i>Severe Fibrosis (continued)</i>						
Khan, 2008 ¹⁵³	APRI >0.9	Not reported	METAVIR F3-F4	0.87 (26/30)[0.90]	0.70 (63/90)	0.87 (0.79-0.94)
Khan, 2008 ¹⁵³	APRI >1.75	Not reported	METAVIR F3-F4	0.57 (17/30) [0.56]	0.94 (85/90)	0.87 (0.79-0.94)
Leroy, 2007 ¹⁵⁸	APRI >0.5	Median 23 mm and median 17 portal tracts; 89% >15 mm and 45% >25 mm	METAVIR F3-F4	0.94 (48/51)	0.22 (28/129)	Whole sample and excluding patients with biopsy <15 mm or <7 portal tracts (n=161) 0.82 (0.74-0.90) and 0.81 (CI not reported)
Leroy, 2007 ¹⁵⁸	APRI >1.0	Median 23 mm and median 17 portal tracts; 89% >15 mm and 45% >25 mm	METAVIR F3-F4	0.89 (45/51)	0.54 (69/129)	Whole sample and excluding patients with biopsy <15 mm or <7 portal tracts (n=161) 0.82 (0.74-0.90) and 0.81 (CI not reported)
Leroy, 2007 ¹⁵⁸	APRI >1.5	Median 23 mm and median 17 portal tracts; 89% >15 mm and 45% >25 mm	METAVIR F3-F4	0.87 (44/51)	0.75 (96/129)	Whole sample and excluding patients with biopsy <15 mm or <7 portal tracts (n=161) 0.82 (0.74-0.90) and 0.81 (CI not reported)
Leroy, 2007 ¹⁵⁸	APRI >2.0	Median 23 mm and median 17 portal tracts; 89% >15 mm and 45% >25 mm	METAVIR F3-F4	0.74 (38/51)	0.84 (108/129)	Whole sample and excluding patients with biopsy <15 mm or <7 portal tracts (n=161) 0.82 (0.74-0.90) and 0.81 (CI not reported)
Leroy, 2008 ¹⁵⁷	APRI (cutoff not reported)	55% >20 mm; 84% >15 mm	METAVIR F3-F4	Not reported	Not reported	0.84 (0.80-0.87)
Loeza-del-Castillo, 2008 ¹⁶²	APRI >0.7532	Not reported	METAVIR F3-F4	0.78 (52/67)	0.75 (73/97)	0.80 (0.74-0.87)
Martinez, 2011 ¹⁶⁵	APRI >2.0	Mean 15 mm, 72% >15 mm	METAVIR F3-F4	Not reported	Not reported	0.86 (0.82-0.90)
Paggi, 2008 ¹⁷⁵	APRI >1.0	Median 4.1 cm	METAVIR F3-F4	0.79 (127/160)	0.70 (189/270)	Not reported
Paggi, 2008 ¹⁷⁵	APRI >2.0	Median 4.1 cm	METAVIR F3-F4	0.36 (58/160)	0.92 (249/270)	Not reported

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
Aspartate Aminotransferase-Platelet Ratio Index (APRI) (continued)						
Severe Fibrosis (continued)						
Snyder, 2006 ^{c205}	APRI >0.50	Not reported	Batts-Ludwig F3-F4	Retro-spective and prospective samples, respectively : 0.94 (62/66) and 0.96 (47/49)	Retro-spective and prospective samples, respectively : 0.43 (117/273) and 0.48 (49/102);	Not reported
Snyder, 2006 ²⁰⁵	APRI >0.70	Not reported	Batts-Ludwig F3-F4	Retro-spective and prospective samples, respectively : 0.79 (52/66) and 0.88 (43/49)	Retro-spective and prospective samples, respectively : 0.62 (169/273) and 0.64 (65/102) [0.63]	Not reported
Snyder, 2006 ²⁰⁵	APRI ≥1.20	Not reported	Batts-Ludwig F3-F4	Retro-spective and prospective samples, respectively : 0.50 (33/66) and 0.71 (35/49) [0.73]	Retro-spective and prospective samples, respectively : 0.81 (220/273) and 0.82 (84/102)	Not reported
Viana, 2009 ²¹³	APRI ≥1.051	All >10 portal tracts	METAVIR F3-F4	Sample 1 and sample 2, respectively : 0.88 (70/80) and 0.86 (73/85)	Sample 1 and sample 2, respectively : 0.95 (114/120) and 0.90 (104/115)	Sample 1 and sample 2, respectively: 0.96 (0.93-0.98) and 0.93 (0.88-0.96)
Cirrhosis						
Adler, 2008 ⁹²	APRI (cutoff not reported)	Not reported	METAVIR F4	Not reported	Not reported	0.92 (CI not reported)
Berg, 2004 ⁹⁹	APRI >1.0	Not reported	Scheuer F4	0.76 (47/62)	0.74 (310/422)	Not reported
Berg, 2004 ⁹⁹	APRI >2.0	Not reported	Scheuer F4	0.76 (47/62)	0.89 (377/422)	Not reported
Borroni, 2006 ¹⁰²	APRI >1.0	All ≥6 portal fields	Knodell 4	0.77 (23/30)	0.83 (164/198)	0.86 (0.79-0.93)
Borroni, 2006 ¹⁰²	APRI ≥2.0	All ≥6 portal fields	Knodell 4	0.43 (13/30)	0.94 (186/198)	0.86 (0.79-0.93)
Bota, 2011 ¹⁰³	APRI (cutoff not reported)	All ≥8 portal tracts, mean 34 mm	METAVIR F4	Not reported	Not reported	0.88 (CI not reported)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
<i>Aspartate Aminotransferase-Platelet Ratio Index (APRI) (continued)</i>						
<i>Cirrhosis (continued)</i>						
Bourliere, 2006 ¹⁰⁵	APRI >1.0	Mean 20 mm and median 9 portal tracts; 59% ≥15 mm and ≥5 portal tracts	METAVIR F4	0.69 (11/16)	0.82 (180/219)	0.81 (0.76-0.86)
Bourliere, 2006 ¹⁰⁵	APRI >2.0	Mean 20 mm and median 9 portal tracts; 59% ≥15 mm and ≥5 portal tracts	METAVIR F4	0.38 (6/16)	0.96 (210/219)	0.81 (0.76-0.86)
Boursier, 2009 ¹⁰⁶	APRI >0.652	Not reported	METAVIR F4	0.85 (98/116)	0.72 (672/940)	0.84 (0.80-0.88)
Boursier, 2009 ¹⁰⁶	APRI >2.532	Not reported	METAVIR F4	0.27 (32/116)	0.98 (918/940)	0.84 (0.80-0.88)
Burton, 2011 ¹⁰⁹	APRI >1.0	Not reported	Batts-Ludwig 4	Whole sample: 0.74 (33/44) Black subjects: 0.60 (9/15) White subjects: 0.85 (24/28)	Whole sample: 0.78 (175/224) Black subjects: 0.81 (103/127) White subjects: 0.73 (65/89)	Whole sample: Not reported Black subjects: 0.75 (0.59-0.91) White subjects: 0.82 (0.74-0.90)
Castera, 2009 ¹¹²	APRI ≥1.0	All ≥10 mm and ≥6 portal tracts; mean 20 mm and 15 portal tracts	METAVIR F4	0.64 (45/70)	0.82 (186/228) [0.81]	0.80 (0.74-0.86)
Castera, 2009 ¹¹²	APRI ≥2.0	All ≥10 mm and ≥6 portal tracts; mean 20 mm and 15 portal tracts	METAVIR F4	0.30 (21/70)	0.94 (215/228)	0.80 (0.74-0.86)
Cheung, 2011 ¹¹⁶	APRI >1.0	Median 1.6-2.0 cm and >8 portal tracts	METAVIR F4	Not reported	Not reported	0.92 (0.84-1.0)
Chrysanthos, 2006 ¹¹⁸	APRI >1.0	All >1.5 cm	Ishak 5 or 6	0.60 (35/58)	0.72 (162/226)	Not reported for HCV subgroup
Chrysanthos, 2006 ¹¹⁸	APRI >2.0	All >1.5 cm	Ishak 5 or 6	0.38 (22/58)	0.91 (206/226)	Not reported for HCV subgroup
Cobbold, 2009 ²²⁹	APRI >0.92	All ≥10 mm, mean 24 mm	Ishak 5-6	0.86 (12/14)	0.77 (41/53)	0.86 (0.75-0.97)
Cross, 2009 ¹²⁴	APRI >0.75	All >10 mm and >10 portal tracts	Ishak 5 or 6	0.84 (111/132)	0.78 (367/470)	0.88 (0.85-0.92)
Ehsan, 2008 ¹²⁵	APRI >1.5	Mean 12 mm	Ishak 5-6	0.66 (23/35)	0.94 (76/81)	0.86 (CI not reported)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
<i>Aspirate Aminotransferase-Platelet Ratio Index (APRI) (continued)</i>						
<i>Cirrhosis (continued)</i>						
Fabris, 2008 ¹²⁹	APRI (cutoff not reported)	Average 19 mm and median 7 portal tracts	METAVIR F4	Not reported	Not reported	0.86 (0.79-0.90)
Fontana, 2008 ¹³⁰	APRI (cutoff not reported)	Mean 1.84 cm	Ishak 5-6	Not reported	Not reported	0.73 (0.69-0.78)
Giannini, 2003b ¹³⁵	APRI (cutoff not reported)	Not reported	Not reported	Not reported	Not reported	0.81 (CI not reported)
Gomes da Silva, 2008 ¹³⁷	APRI >1.0	Not reported	METAVIR F4	0.92 (12/13)	0.70 (26/37) [0.73]	0.92 (0.85-1.0)
Gomes da Silva, 2008 ¹³⁷	APRI >1.73	Not reported	METAVIR F4	0.77 (10/13)	0.97 (36/37)	0.92 (0.85-1.0)
Gomes da Silva, 2008 ¹³⁷	APRI >2.0	Not reported	METAVIR F4	0.54 (7/13) [0.46]	0.97 (36/37)	0.92 (0.85-1.0)
Güzelbulut, 2011 ¹⁴²	APRI >1.0	Not reported	METAVIR F4	0.73 (37/51)	0.81 (80/99)	0.84 (0.77-0.91)
Güzelbulut, 2011 ¹⁴²	APRI >2.0	Not reported	METAVIR F4	0.43 (22/51)	0.95 (94/99)	0.84 (0.77-0.91)
Halfon, 2007 ¹⁴⁵	APRI >0.39	All >15 mm	METAVIR F4	1.0 (13/13)	0.83 (285/343)	0.92 (0.88-0.94)
Hsieh, 2009 ¹⁴⁶	APRI >1.0	Not reported	METAVIR F4	1.0 (6/6)	0.30 (40/134)	0.63 (0.51-0.76)
Hsieh, 2009 ¹⁴⁶	APRI >1.5	Not reported	METAVIR F4	0.83 (5/6)	0.50 (67/134)	0.63 (0.51-0.76)
Hsieh, 2009 ¹⁴⁶	APRI >2.0	Not reported	METAVIR F4	0.50 (3/6)	0.65 (87/134)	0.63 (0.51-0.76)
Iacobellis, 2005b ¹⁴⁸	APRI >2.0	All ≥5 portal tracts	Scheuer F4	0.66 (51/78)	0.90 (1,054/1,174)	Not reported
Islam, 2005 ¹⁵¹	APRI >1.0	≥10 mm and ≥4 portal tracts	Ishak 5 or 6	0.78 (16/20)	0.75 (119/159)	0.83 (CI not reported)
Lackner, 2005 ¹⁵⁶ and Lackner, 2006 ²²⁴	APRI ≥1.0	All ≥6 portal tracts	Ishak 5-6	0.93 (30/32)	0.70 (113/162)	0.90 (0.85-0.95)
Lackner, 2005 ¹⁵⁶ and Lackner, 2006 ²²⁴	APRI ≥2.0	All ≥6 portal tracts	Ishak 5-6	0.55 (18/32)	0.93 (151/162)	0.90 (0.85-0.95)
Leroy, 2008 ¹⁵⁷	APRI (cutoff not reported)	55% >20 mm; 84% >15 mm	METAVIR F4	Not reported	Not reported	0.86 (0.82-0.90)
Loeza-del-Castillo, 2008 ¹⁶²	APRI >0.7532	Not reported	METAVIR F4	0.89 (42/47)	0.71 (83/117)	0.83 (0.76-0.90)
Martinez, 2011 ¹⁶⁵	APRI >1.0	Mean 15 mm, 72% >15 mm	METAVIR F4	0.82 (102/124)	0.74 (159/216)	0.86 (0.82-0.90)
Martinez, 2011 ¹⁶⁵	APRI >2.0	Mean 15 mm, 72% >15 mm	METAVIR F4	0.49 (61/124)	0.91 (196/216)	0.86 (0.82-0.90)
Parise, 2006 ¹⁷⁶	APRI >1.5	Not reported	Batts-Ludwig F4	0.73 (32/44)	0.81 (131/162)	0.84 (0.77-0.90)
Schneider, 2006 ¹⁹⁶	APRI >1.0	Not reported	Ishak 5-6	0.79 (15/19) [0.77]	0.63 (40/64)	0.71 (CI not reported)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
<i>Aspartate Aminotransferase-Platelet Ratio Index (APRI) (continued)</i>						
<i>Cirrhosis (continued)</i>						
Sebastiani, 2006 ¹⁹⁹	APRI >2.0	All ≥1.5 cm and ≥7 portal tracts	METAVIR F4	0.38 (11/29)	0.87 (140/161)	0.61 (0.49-0.73)
Sebastiani, 2009 ¹⁹⁷	APRI >1.0	Mean 18 mm and mean 10.6 portal tracts	METAVIR F4	0.78 (149/191)	0.84 (1,542/1,844)	0.80 (0.77-0.83)
Sebastiani, 2009 ¹⁹⁷	APRI >2.0	Mean 18 mm and mean 10.6 portal tracts	METAVIR F2-F4	0.47 (90/191)	0.94 (1,743/1,844)	0.71 (0.69-0.73)
Sebastiani, 2011 ²⁰⁰	APRI >1.0	Mean 18 mm and 11 portal tracts; 43% >20 mm	METAVIR F4	Whole sample: Not reported Normal ALT: 0.33 (6/19)	Whole sample: Not reported Normal ALT: 0.87 (501/576)	Whole sample: 0.76 (0.71-0.81) Normal ALT: 0.65 (0.60-0.70)
Sebastiani, 2011 ²⁰⁰	APRI >2.0	Mean 18 mm and 11 portal tracts; 43% >20 mm	METAVIR F4	Whole sample: 0.67 (110/164) Normal ALT: 0.26 (5/19)	Whole sample: 0.94 (1543/1647) Normal ALT: 0.89 (516/576)	Whole sample: 0.76 (0.71-0.81) Normal ALT: 0.65 (0.60-0.70)
Sebastiani, 2012 ²⁰¹	APRI >1.0	Mean 20 mm and 11 portal tracts; 45% >20 mm	METAVIR F4	0.75 (84/113)	0.79 (715/900)	0.77 (0.71-0.83)
Sebastiani, 2012 ²⁰¹	APRI >2.0	Mean 20 mm and 11 portal tracts; 45% >20 mm	METAVIR F4	0.41 (47/113)	0.94 (842/900)	0.77 (0.71-0.83)
Sirli, 2010 ²⁰⁴	APRI >1.38	All >20 mm and ≥8 portal tracts	METAVIR F4	0.93 (14/15)	0.83 (112/135)	0.91 (0.85-0.95)
Snyder, 2006 ²⁰⁵	APRI ≥2.0	Not reported	Batts-Ludwig F4	0.50 (13/26)	0.94 (118/125)	Not reported
Wai, 2003 ²¹⁴	APRI >1.0	Not reported	Ishak 5 or 6	0.89 (25/28)	0.75 (41/164)	0.90 (0.86-0.94)
Wai, 2003 ²¹⁴	APRI >2.0	Not reported	Ishak 5 or 6	0.57 (16/28)	0.93 (152/164)	0.90 (0.86-0.94)
Zarski, 2012 ²²³	APRI (cutoff not reported)	All ≥20 mm or ≥15 mm and ≥11 portal tracts	METAVIR F4	Not reported	Not reported	0.86 (0.81-0.91)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
AST/ALT Ratio						
Fibrosis						
Ben Jazia, 2009 ⁹⁸	AST/ALT ratio, cutoff not reported	Not reported	METAVIR F2-F4	Not reported	Not reported	0.68 (CI not reported)
Cheung, 2008 ¹¹⁷	AST/ALT ratio ≥ 1.0	Not reported	Batts-Ludwig 2-4	0.20 (65/323)	0.82 (137/167)	0.54 (0.48-0.59)
Fabris, 2008 ¹²⁹	AST/ALT ratio, cutoff not reported	Average 19 mm and median 7 portal tracts	METAVIR F2-F4	Not reported	Not reported	0.59 (0.51-0.66)
Giannini, 2003b ¹³⁵	AST/ALT ratio ≥ 1.0	Not reported	Not reported	Not reported	Not reported	0.82 (CI not reported)
Giannini, 2006 ¹³⁶	AST/ALT ratio >0.66	Not reported	Ishak 3-6 or METAVIR F2-F4	0.74 (129/175)	0.65 (152/234)	Not reported
Hsieh, 2009 ¹⁴⁶	AST/ALT ratio >0.54	Not reported	METAVIR F2-F4	0.77 (89/116)	0.63 (15/24)	0.73 (0.62-0.85)
Hsieh, 2009 ¹⁴⁶	AST/ALT ratio >1.0	Not reported	METAVIR F2-F4	0.10 (12/116)	1.0 (24/24)	0.73 (0.62-0.85)
Lackner, 2005 ¹⁵⁶ and Lackner, 2006 ²²⁴	AST/ALT ratio, cutoff not reported	All ≥ 6 portal tracts	Ishak 3-6	Not reported	Not reported	0.57 (0.48-0.65)
Liu, 2006 ¹⁶⁰	AST/ALT ratio >0.6	Mean 19 mm length and 1.4 mm diameter	METAVIR F2-F4	0.86 (18/21)	0.05 (3/58)	0.50 (0.35-0.66)
Liu, 2006 ¹⁶⁰	AST/ALT ratio >1.0	Mean 19 mm length and 1.4 mm diameter	METAVIR F2-F4	0.45 (10/21)	0.62 (36/58)	0.50 (0.35-0.66)
Parise, 2006 ¹⁷⁶	AST/ALT ratio ≥ 0.8	Not reported	Batts-Ludwig F2-F4	0.52 (45/86)	0.61 (73/120)	0.59 (0.51-0.67)
Pohl, 2001 ¹⁸³	AST/ALT ratio ≥ 1.0	Not reported	METAVIR F2-F4	0.35 (19/54)	0.77 (76/99)	Not reported
Sebastiani, 2008 ¹⁹⁸	AST/ALT ratio >1.0	All ≥ 15 mm and ≥ 7 portal tracts	METAVIR F2-F4	Whole sample, normal ALT, and elevated ALT, respectively : 0.37 (54/147), 0.13 (4/32) [0.12], 0.43 (50/115)	Whole sample, normal ALT, and elevated ALT, respectively : 0.73 (71/97), 0.88 (42/48), 0.59 (29/49) [0.58]	Normal ALT and elevated ALT, respectively (AUROC not reported for whole sample): 0.51 (0.40-0.62) and 0.54 (0.48-0.60)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
AST/ALT Ratio (continued)						
Severe Fibrosis						
Bonacini, 1997 ¹⁰¹	AST/ALT ratio >1.0	Not reported	Knodell 3 or 4	0.83 (23/28)	0.75 (38/51)	Not reported
Cheung, 2008 ¹¹⁷	AST/ALT ratio ≥1.0	Not reported	Batts-Ludwig 3 or 4	0.19 (40/210) [0.21]	0.97 (248/255) [0.82]	0.52 (0.47-0.58)
El-Sayed, 2011 ¹²⁷	AST/ALT, cutoff not reported	All ≥10 and ≥5 portal tracts	METAVIR F3-F4	Not reported	Not reported	0.76 (CI not reported)
Iacobellis, 2005b ¹⁴⁸	AST/ALT ratio ≥1.0	All ≥5 portal tracts	Scheuer F3 or F4	0.26 (63/243)	0.88 (883/1,009)	Not reported
Pohl, 2001 ¹⁸³	AST/ALT ratio ≥1.0	Not reported	METAVIR F3-F4	0.47 (17/36)	0.81 (95/117) [0.82]	Not reported
Cirrhosis						
Ahmad, 2011 ^{93a}	AST/ALT ratio >1.0	Not reported	METAVIR F4	0.43 (9/21)	0.68 (92/136)	0.61 (0.48-0.74) for >1; 0.47 (0.38-0.56) for <1
Anderson, 2000 ⁹⁵	AST/ALT ratio ≥1.0	Not reported	Not reported	0.31 (19/61)	0.99 (71/72)	Not reported
Borroni, 2006 ¹⁰²	AST/ALT ratio ≥1.0	All ≥6 portal fields	Knodell 4	0.30 (9/30)	0.97 (192/198)	0.76 (0.68-0.84)
Castera, 2009 ¹¹²	AST/ALT ratio ≥1.0	All ≥10 mm and ≥6 portal tracts; mean 20 mm and 15 portal tracts	METAVIR F4	0.31 (22/70)	0.89 (203/228)	0.61 (0.53-0.70)
Ehsan, 2008 ¹²⁵	AST/ALT ratio >1.5	Mean 12 mm	Ishak 5-6	0.44 (15/35)	0.91 (74/81)	0.65 (CI not reported)
Fabris, 2008 ¹²⁹	AST/ALT ratio, cutoff not reported	Average 19 mm and median 7 portal tracts	METAVIR F4	Not reported	Not reported	0.66 (0.58-0.73)
Giannini, 2003a ¹³⁴	AST/ALT ratio ≥1.0	Not reported	Scheuer F4 or clinical signs of portal hypertension	0.78 (70/90)	0.97 (157/162)	Not reported
Giannini, 2003b ¹³⁵	AST/ALT ratio, cutoff not reported	Not reported	Not reported	Not reported	Not reported	0.91 (CI not reported)
Hsieh, 2009 ¹⁴⁶	AST/ALT ratio >0.75	Not reported	METAVIR F4	0.83 (5/6)	0.67 (90/134)	0.78 (0.60-0.97)
Hsieh, 2009 ¹⁴⁶	AST/ALT ratio >1.0	Not reported	METAVIR F4	0.33 (2/6)	0.92 (123/134)	0.78 (0.60-0.97)
Iacobellis, 2005b ¹⁴⁸	AST/ALT ratio ≥1.0	All ≥5 portal tracts	Scheuer F4	0.32 (25/78)	0.87 (1,020/1,174)	Not reported

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
<i>AST/ALT Ratio (continued)</i>						
<i>Cirrhosis (continued)</i>						
Imperiale, 2000 ¹⁵⁰	AST/ALT ratio ≥ 1.0	Not reported	Hytiroglou 4	Whole sample, excluding patients with normal AST and ALT, and excluding patients with heavy alcohol use, respectively : 0.56 (23/41), 0.56 (23/41) and 0.52 (15/29)	Whole sample, excluding patients with normal AST and ALT, and excluding patients with heavy alcohol use, respectively : 0.90 (123/136), 0.94 (117/124) and 0.91 (116/128)	Not reported
Lackner, 2005 ¹⁵⁶ and Lackner, 2006 ²²⁴	AST/ALT ratio ≥ 1.0	All ≥ 6 portal tracts	Ishak 5-6	0.36 (12/32)	0.90 (146/162)	0.73 (0.63-0.83)
Luo, 2002 ¹⁶⁴	AST/ALT ratio ≥ 1.0	All >5 portal tracts	Scheuer F4	0.39 (9/23)	0.92 (81/88)	Not reported
Parise, 2006 ¹⁷⁶	AST/ALT ratio >1.0	Not reported	Batts-Ludwig F4	0.36 (16/44)	0.82 (133/162)	0.65 (0.56-0.75)
Park, 2000 ¹⁷⁷ and 2005	AST/ALT ratio ≥ 1.0	Not reported	Scheuer F4	0.47 (14/30)	0.96 (118/123)	0.85 (0.77-0.93)
Reedy, 1998 ¹⁸⁷	AST/ALT ratio ≥ 1.0	Not reported	Knodell F4	0.43 (10/23) [0.44]	0.94 (45/48)	Not reported
Sebastiani, 2011 ²⁰⁰	AST/ALT ratio >1.0	Mean 18 mm and 11 portal tracts; 43% >20 mm	METAVIR F4	Whole sample: Not reported Normal ALT: 0.12 (2/19)	Whole sample: Not reported Normal ALT: 0.88 (504/576)	Whole sample: Not reported Normal ALT: 0.52 (0.46-0.58)
Sheth, 1998 ²⁰²	AST/ALT ratio ≥ 1.0	Not reported	Hytiroglou F4	0.53 (25/47)	1.0 (92/92)	Not reported
Williams, 1988 ²¹⁸	AST/ALT ratio >1.0	Not reported	Hoofnagle criteria	0.27 (3/11)	0.94 (31/33)	Not reported

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
<i>Cirrhosis Discriminant Score</i>						
<i>Fibrosis</i>						
Cross, 2009 ¹²⁴	Cirrhosis Discriminant Score, cutoff not reported	All >10 mm and >10 portal tracts	Ishak ≥3	Not reported	Not reported	Derivation sample: 0.67 (0.62-0.72)
Fabris, 2008 ¹²⁹	Cirrhosis Discriminant Score, cutoff not reported	Average 19 mm and median 7 portal tracts	METAVIR F2-F4	Not reported	Not reported	0.64 (0.56-0.71)
Lackner, 2005 ¹⁵⁶ and Lackner, 2006 ²²⁴	Cirrhosis Discriminant Score, cutoff not reported	All ≥6 portal tracts	Ishak 3-6	Not reported	Not reported	0.71 (0.63-0.79)
<i>Severe Fibrosis</i>						
Bonacini, 1997 ¹⁰¹	Cirrhosis discriminant score ≥7.0	Not reported	Knodell 3 or 4	0.86 (24/28)	0.84 (43/51)	Not reported
Bonacini, 1997 ¹⁰¹	Cirrhosis discriminant score ≥8.0	Not reported	Knodell 3 or 4	0.46 (13/28)	0.98 (50/51)	Not reported
Colli, 2005 ¹²¹	Cirrhosis discriminant score >3.0	Mean 41 mm	METAVIR F3-F4	0.93 (62/67)	0.54 (59/109)	Not reported
Colli, 2005 ¹²¹	Cirrhosis discriminant score >7.0	Mean 41 mm	METAVIR F3-F4	0.06 (4/67)	0.96 (105/109)	Not reported
Lackner, 2005 ¹⁵⁶ and Lackner, 2006 ²²⁴	Cirrhosis Discriminant Score ≥8.0	All ≥6 portal tracts	Ishak 4-6	0.10 (5/50)	1.0 (144/144)	Not reported
<i>Cirrhosis</i>						
Borroni, 2006 ¹⁰²	Cirrhosis Discriminant Score >2.0	All ≥6 portal fields	Knodell 4	1.0 (30/30)	0.22 (43/198)	0.83 (0.75-0.92)
Borroni, 2006 ¹⁰²	Cirrhosis Discriminant Score >7.0	All ≥6 portal fields	Knodell 4	0.17 (5/30)	1.0 (198/198)	0.83 (0.75-0.92)
Cross, 2009 ¹²⁴	Cirrhosis Discriminant Score, cutoff not reported	All >10 mm and >10 portal tracts	Ishak 5 or 6	Not reported	Not reported	0.74 (0.68-0.81)
Fabris, 2008 ¹²⁹	Cirrhosis Discriminant Score, cutoff not reported	Average 19 mm and median 7 portal tracts	METAVIR F4	Not reported	Not reported	0.71 (0.64-0.78)
Fontana, 2008 ¹³⁰	Cirrhosis Discriminant Score, cutoff not reported	Mean 1.84 cm	Ishak 5-6	Not reported	Not reported	0.70 (0.66-0.75)
Lackner, 2005 ¹⁵⁶ and Lackner, 2006 ²²⁴	Cirrhosis Discriminant Score, cutoff not reported	All ≥6 portal tracts	Ishak 5-6	Not reported	Not reported	0.91 (0.85-0.96)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
<i>Cirrhosis Discriminant Score (continued)</i>						
<i>Cirrhosis (continued)</i>						
Saadeh, 2001 ¹⁹²	Cirrhosis Discriminant Score >3.0	Not reported	Knodell F4	0.85 (29/34)	0.58 (45/77)	0.80 (CI not reported)
Saadeh, 2001 ¹⁹²	Cirrhosis Discriminant Score >7.0	Not reported	Knodell F4	0.15 (5/34)	1.0 (77/77)	0.80 (CI not reported)
<i>Enhanced Liver Fibrosis Index (ELF Index) and Simplified Enhanced Liver Fibrosis Index (Simplified ELF)</i>						
<i>Fibrosis</i>						
Cheong, 2011 ¹¹⁵	ELF index, cutoff not reported	Mean 12.6 mm and mean 13.2 portal tracts; 71% had ≥11 portal tracts	METAVIR F2-F4	Not reported	Not reported	0.72 (0.60-0.84)
Cobbold, 2009 ²²⁹	ELF Index >8.75	All ≥10 mm, mean 24 mm	Ishak 3-6	0.84 (31/37)	0.70 (21/30)	0.82 (0.73-0.92)
Friedrich-Rust, 2010 ¹³²	Simplified ELF Index >9.78	All >10 mm and ≥6 portal tracts; mean 22 mm, median 20 mm	METAVIR F2-F4	0.85	0.80	Not reported
Martinez, 2011 ¹⁶⁵	Simplified ELF index ≥0.45	Mean 15 mm, 72% >15 mm	METAVIR F2-F4	0.90 (207/229)	0.52 (58/111)	0.81 (0.76-0.86)
Martinez, 2011 ¹⁶⁵	Simplified ELF index >1.07	Mean 15 mm, 72% >15 mm	METAVIR F2-F4	0.47 (108/229)	0.90 (100/111)	0.81 (0.76-0.86)
Parkes, 2011 ¹⁷⁹	Simplified ELF index, cutoff not reported	Not reported	METAVIR F2-F4 or Ishak 3-6	Not reported	Not reported	Reported separately for 3 validation cohorts: 0.74 (0.63-0.84), 0.83 (0.76-0.89), 0.87 (0.80-0.95)
Zarski, 2012 ²²³	ELF index, cutoff not reported	All ≥20 mm or ≥15 mm and ≥11 portal tracts	METAVIR F2-F4	Not reported	Not reported	0.78 (0.74-0.83)
<i>Severe Fibrosis</i>						
Friedrich-Rust, 2010 ¹³²	Simplified ELF Index >10.22	All >10 mm and ≥6 portal tracts; mean 22 mm, median 20 mm	METAVIR F3-F4	0.82	0.74	Not reported
Martinez, 2011 ¹⁶⁵	Simplified ELF index ≥0.45	Mean 15 mm, 72% >15 mm	METAVIR F3-F4	Not reported	Not reported	0.83 (0.79-0.87)
Parkes, 2011 ¹⁷⁹	Simplified ELF index >9.39	Not reported	METAVIR F3-F4 or Ishak 4-6	0.90 (100/111)	0.55 (130/236)	Reported separately for 3 validation cohorts 0.84 (0.74-0.94), 0.86 (0.80-0.92), 0.89 (0.83-0.96)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
Enhanced Liver Fibrosis Index (ELF Index) and Simplified Enhanced Liver Fibrosis Index (Simplified ELF)						
(continued)						
Severe Fibrosis (continued)						
Parkes, 2011 ¹⁷⁹	Simplified ELF index >10.22	Not reported	METAVIR F3-F4 or Ishak 4-6	0.70 (78/111)	0.85 (201/236)	Reported separately for 3 validation cohorts 0.84 (0.74-0.94), 0.86 (0.80-0.92), 0.89 (0.83-0.96)
Parkes, 2011 ¹⁷⁹	Simplified ELF index >10.90	Not reported	METAVIR F3-F4 or Ishak 4-6	0.54 (60/111)	0.95 (224/236)	Reported separately for 3 validation cohorts 0.84 (0.74-0.94), 0.86 (0.80-0.92), 0.89 (0.83-0.96)
Rosenberg, 2004 ¹⁹⁰	ELF Index >0.063	>12 mm and >5 portal tracts	Scheuer F3-F4	0.95	0.29	0.77 (0.70-0.85)
Rosenberg, 2004 ¹⁹⁰	ELF Index >0.190	>12 mm and >5 portal tracts	Scheuer F3-F4	0.63	0.8	0.77 (0.70-0.85)
Rosenberg, 2004 ¹⁹⁰	ELF Index >0.564	>12 mm and >5 portal tracts	Scheuer F3-F4	0.30	0.99	0.77 (0.70-0.85)
Cirrhosis						
Cobbald, 2009 ²²⁹	ELF Index >8.75	All ≥10 mm, mean 24 mm	Ishak 5-6	0.93 (13/14)	0.79 (42/53)	0.91 (0.82-1.0)
Friedrich-Rust, 2010 ¹³²	Simplified ELF Index >10.31	All >10 mm and ≥6 portal tracts; mean 22 mm, median 20 mm	METAVIR F4	0.89	0.63	Not reported
Martinez, 2011 ¹⁶⁵	Simplified ELF index >0.06	Mean 15 mm, 72% >15 mm	METAVIR F4	0.90 (111/124)	0.53 (114/216)	0.82 (0.78-0.87)
Martinez, 2011 ¹⁶⁵	Simplified ELF index >1.73	Mean 15 mm, 72% >15 mm	METAVIR F4	0.52 (65/124)	0.90 (195/216)	0.82 (0.78-0.87)
Parkes, 2011 ¹⁷⁹	Simplified ELF index, cutoff not reported	Not reported	METAVIR F2-F4 or Ishak 3-6	Not reported	Not reported	Reported separately for 3 validation cohorts: 0.90 (0.81-0.98), 0.87 (0.81-0.93), 0.89 (0.82-0.96)
Zarski, 2012 ²²³	ELF index, cutoff not reported	All ≥20 mm or ≥15 mm and ≥11 portal tracts	METAVIR F2-F4	Not reported	Not reported	0.78 (0.74-0.83)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
FIB-4						
Fibrosis						
Adler, 2008 ⁹²	Cutoff not reported	Not reported	METAVIR F2-F4	Not reported	Not reported	0.79 (CI not reported)
Cales, 2008 ¹¹⁰	FIB-4 >1.116	Not reported	METAVIR F2-F4	0.74 (406/549)	0.72 (365/507)	0.80 (CI not reported)
Cheong, 2011 ¹¹⁵	FIB-4, cutoff not reported	Mean 12.6 mm and mean 13.2 portal tracts; 71% had ≥11 portal tracts	METAVIR F2-F4	Not reported	Not reported	0.80 (0.70-0.90)
Crisan, 2012 ¹²²	FIB-4 >1.26	All >5 portal tracts; median 11 mm and mean 14 portal tracts	METAVIR F2-F4	0.64 (182/283)	0.75 (123/163)	0.71 (CI not reported)
Güzelbulut, 2011 ¹⁴²	FIB-4 >0.6	Not reported	METAVIR F2-F4	1.0 (83/83)	0.10 (7/67)	0.76 (0.69-0.84)
Güzelbulut, 2011 ¹⁴²	FIB-4 ≥1	Not reported	METAVIR F2-F4	0.92 (76/83)	0.30 (20/67)	0.76 (0.69-0.84)
Patel, 2009 ¹⁸⁰	FIB-4 >1.45	Mean 18 mm	METAVIR F2-F4	0.86 (12/14)	0.68 (54/80)	Not reported
Patel, 2009 ¹⁸⁰	FIB-4 >3.25	Mean 18 mm	METAVIR F2-F4	0.43 (6/14)	0.96 (77/80)	Not reported
Sebastiani, 2011 ²⁰⁰	FIB-4 >1.45	Mean 18 mm and 11 portal tracts; 43% >20 mm	METAVIR F2-F4	Whole sample: Not reported Normal ALT: 0.64 (114/176)	Whole sample: Not reported Normal ALT: 0.72 (303/419)	Whole sample: Not reported Normal ALT: 0.61 (0.56-0.66)
Sebastiani, 2011 ²⁰⁰	FIB-4 >3.25	Mean 18 mm and 11 portal tracts; 43% >20 mm	METAVIR F2-F4	Whole sample: Not reported Normal ALT: 0.53 (93/176)	Whole sample: Not reported Normal ALT: 0.59 (246/419)	Whole sample: Not reported Normal ALT: 0.61 (0.56-0.66)
Sirli, 2010 ²⁰⁴	FIB-4 >2.14	All ≥20 mm and ≥8 portal tracts	METAVIR F2-F4	0.36 (48/134)	1.0 (16/16)	0.69 (0.60-0.76)
Zarski, 2012 ²²³	FIB-4, cutoff not reported	All ≥20 mm or ≥15 mm and ≥11 portal tracts	METAVIR F2-F4	Not reported	Not reported	0.76 (0.71-0.80)
Severe Fibrosis						
Adler, 2008 ⁹²	Cutoff not reported	Not reported	METAVIR F3-F4	Not reported	Not reported	0.90 (CI not reported)
Ahmad, 2011 ⁹³	FIB-4 >1.45	Not reported	METAVIR F3-F4	0.85 (47/55)	0.51 (52/102)	0.73 (0.66-0.81)
Ahmad, 2011 ⁹³	FIB-4 >3.25	Not reported	METAVIR F3-F4	0.59 (33/55)	0.82 (84/102)	0.54 (0.46-0.64)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
FIB-4 (continued)						
Severe Fibrosis (continued)						
Becker, 2009 ⁹⁶	FIB-4 ≥1.45	All ≥10 mm or ≥8 portal tracts; median 16 mm, 11% <10 mm	METAVIR F3-F4	0.73 (101/139)	0.67 (169/252)	Not reported
Becker, 2009 ⁹⁶	FIB-4 >3.25	All ≥10 mm or ≥8 portal tracts; median 16 mm, 11% <10 mm	METAVIR F3-F4	0.30 (42/139)	0.98 (248/252)	Not reported
Crisan, 2012 ¹²²	FIB-4 >3.74	All >5 portal tracts; median 11 mm and mean 14 portal tracts	METAVIR F3-F4	0.63 (77/122)	0.81 (262/324)	0.77 (CI not reported)
Martinez, 2011 ¹⁶⁵	FIB-4 >1.45	Mean 15 mm, 72% >15 mm	METAVIR F3-F4	0.92 (142/155)	0.64 (118/185)	0.87 (0.83-0.91)
Martinez, 2011 ¹⁶⁵	FIB-4 >3.25	Mean 15 mm, 72% >15 mm	METAVIR F3-F4	0.54 (83/155)	0.91 (168/185)	0.87 (0.83-0.91)
Stibbe, 2011 ²⁰⁷	FIB-4 >1.45	All ≥20 mm	METAVIR F4	0.72 (13/18)	0.70 (16/23)	Not reported
Stibbe, 2011 ²⁰⁷	FIB-4 >3.25	All ≥20 mm	METAVIR F4	0.28 (5/18)	1.0 (23/23)	Not reported
Vallet-Pichard, 2007 ²¹¹	FIB-4 ≥1.45	Not reported	METAVIR F3-F4	0.74 (108/146)	0.80 (562/701)	0.85 (0.82-0.89)
Vallet-Pichard, 2007 ²¹¹	FIB-4 >3.25	Not reported	METAVIR F3-F4	0.38 (55/146)	0.98 (688/701)	0.85 (0.82-0.89)
Cirrhosis						
Adler, 2008 ⁹²	Cutoff not reported	Not reported	METAVIR F4	Not reported	Not reported	0.92 (CI not reported)
Cross, 2009 ¹²⁴	FIB-4 >0.41	All >10 mm and >10 portal tracts	Ishak 5 or 6	Derivation sample: 0.83 (110/132)	Derivation sample: 0.78 (367/470)	Derivation sample: 0.87 (0.82-0.91)
Güzelbulut, 2011 ¹⁴²	FIB-4 >1.45	Not reported	METAVIR F4	0.90 (46/51)	0.58 (57/99)	0.87 (0.82-0.93)
Güzelbulut, 2011 ¹⁴²	FIB-4 ≥3.25	Not reported	METAVIR F4	0.55 (28/51)	0.92 (91/99)	0.87 (0.82-0.93)
Martinez, 2011 ¹⁶⁵	FIB-4, cutoff not reported	Mean 15 mm, 72% >15 mm	METAVIR F4	Not reported	Not reported	0.89 (0.85-0.92)
Sirli, 2010 ²⁰⁴	FIB-4 >2.31	All ≥20 mm and ≥8 portal tracts	METAVIR F4	0.80 (12/15)	0.78 (105/1,135)	0.84 (0.77-.90)
Zarski, 2012 ²²³	FIB-4, cutoff not reported	All ≥20 mm or ≥15 mm and ≥11 portal tracts	METAVIR F4	Not reported	Not reported	0.83 (0.76-0.89)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
Fibro-α Score						
Fibrosis						
Oman, 2011 ¹⁷⁴	Fibro- α score >1.28	All \geq 15 mm and/or >5 portal tracts	METAVIR F2-F4	Derivation sample: 0.70 (45/64) Validation sample: 0.70 (40/57)	Derivation sample: 0.60 (81/135) Validation sample: 0.54 (42/78)	Derivation sample: 0.74 (CI not reported) Validation sample: 0.72 (CI not reported)
Severe Fibrosis						
Oman, 2011 ¹⁷⁴	Fibro- α score >1.30	All \geq 15 mm and/or >5 portal tracts	METAVIR F3-F4	Derivation sample: 0.88 (26/30) Validation sample: 0.88 (CI not reported)	Derivation sample: 0.60 (101/169) Validation sample: 0.60 (CI not reported)	Derivation sample: 0.82 (CI not reported) Validation sample: 0.82 (CI not reported)
Cirrhosis						
Oman, 2011 ¹⁷⁴	Fibro- α score >1.35	All \geq 15 mm and/or >5 portal tracts	METAVIR F4	Derivation sample: 0.90 (14/15) Validation sample: 0.73 (40/57)	Derivation sample: 0.57 (105/184) Validation sample: 0.70 (CI not reported)	Derivation sample: 0.80 (CI not reported) Validation sample: 0.76 (CI not reported)
FibroIndex						
Fibrosis						
Adler, 2008 ⁹²	Cutoff not reported	Not reported	METAVIR F2-F4	Not reported	Not reported	0.69 (CI not reported)
Fabris, 2008 ¹²⁹	FibroIndex >1.6	Average 19 mm and median 7 portal tracts	METAVIR F2-F4	0.54 (37/69)	0.82 (80/98)	0.71 (0.63-0.77)
Koda, 2007 ¹⁵⁵	FibroIndex >1.25	Mean 18 mm, all \geq 10 mm	METAVIR F2-F3 of F2-F4	Derivation vs. validation samples, respectively : 0.94 (116/123) and 0.97 (58/60)	Derivation vs. validation samples, respectively : 0.40 (70/117) and 0.40 (24/60);	Derivation sample, normal ALT only (n=73): 0.77 (0.65-0.89) Validation sample (excluding F4): 0.83 (0.75-0.90) Validation sample (with F4): 0.86 (0.81-0.92) Validation sample, normal ALT only (n=39): 0.86 (0.74-0.98)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
<i>FibroIndex (continued)</i>						
<i>Fibrosis (continued)</i>						
Koda, 2007 ¹⁵⁵	FibroIndex ≥ 2.25	Mean 18 mm, all ≥ 10 mm	METAVIR F2-F3 of F2-F4	Derivation vs. validation samples, respectively : 0.36 (44/123) and 0.30 (18/60)	Derivation vs. validation samples, respectively : 0.97 (114/117) and 0.97 (58/60)	Derivation sample: 0.83 (0.78-0.88) Derivation sample, normal ALT only (n=73): 0.77 (0.65-0.89) Validation sample (excluding F4): 0.83 (0.75-0.90) Validation sample (with F4): 0.86 (0.81-0.92) Validation sample, normal ALT only (n=39): 0.86 (0.74-0.98)
Sebastiani, 2008 ¹⁹⁸	FibroIndex > 1.25	All ≥ 15 mm and ≥ 7 portal tracts	METAVIR F2-F4	Whole sample, normal ALT, and elevated ALT, respectively : 0.62 (91/147), 0.41 (13/32), 0.68 (78/115);	Whole sample, normal ALT, and elevated ALT, respectively : 0.48 (46/97), 0.77 (37/48), 0.18 (9/49) [0.19]	Normal ALT and elevated ALT, respectively (AUROC not reported for whole sample): 0.58 (0.43-0.73) and 0.74 (0.63-0.85)
Sebastiani, 2008 ¹⁹⁸	FibroIndex > 2.25	All ≥ 15 mm and ≥ 7 portal tracts	METAVIR F2-F4	Whole sample, normal ALT, and elevated ALT, respectively : 0.17 (25/147), 0.09 (3/32) [0.10], 0.19 (22/115)	Whole sample, normal ALT, and elevated ALT, respectively : 1.0 (97/97), 1.0 (48/48), 1.0 (49/49)	Normal ALT and elevated ALT, respectively (AUROC not reported for whole sample): 0.58 (0.43-0.73) and 0.74 (0.63-0.85)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
<i>FibroIndex (continued)</i>						
<i>Severe Fibrosis</i>						
Adler, 2008 ⁹²	Cutoff not reported	Not reported	METAVIR F3-F4	Not reported	Not reported	0.87 (CI not reported)
Koda, 2007 ¹⁵⁵	FibroIndex >1.25	Mean 18 mm, all ≥10 mm	METAVIR F3 or F3-F4	Not reported	Not reported	Derivation sample: 0.81 (0.76-0.87) Derivation sample, normal ALT only (n=73): 0.76 (0.58-0.95) Validation sample (excluding F4): 0.81 (0.73-0.89) Validation sample (with F4): 0.85 (0.79-0.91) Validation sample, normal ALT only (n=39): 0.93 (0.85-1.0)
Koda, 2007 ¹⁵⁵	FibroIndex ≥2.25	Mean 18 mm, all ≥10 mm	METAVIR F3 or F3-F4	Not reported	Not reported	Derivation sample: 0.81 (0.76-0.87) Derivation sample, normal ALT only (n=73): 0.76 (0.58-0.95) Validation sample (excluding F4): 0.81 (0.73-0.89) Validation sample (with F4): 0.85 (0.79-0.91) Validation sample, normal ALT only (n=39): 0.93 (0.85-1.0)
<i>Cirrhosis</i>						
Adler, 2008 ⁹²	Cutoff not reported	Not reported	METAVIR F4	Not reported	Not reported	0.92 (CI not reported)
Fabris, 2008 ¹²⁹	FibroIndex >1.6	Average 19 mm and median 7 portal tracts	METAVIR F4	0.90 (17/19)	0.74 (110/148)	0.86 (0.80-0.91)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
Fibrometer						
Fibrosis						
Boursier, 2011 ¹⁰⁷	FibroMeter, cutoff not reported	94% ≥15 mm and ≥8 portal tracts	METAVIR F2-F4	Not reported	Not reported	Derivation sample: 0.81 (0.78-0.83) Validation sample: 0.84 (0.82-0.86)
Cales, 2008 ¹¹⁰	FibroMeter >0.419	Not reported	METAVIR F2-F4	0.80 (439/549)	0.76 (385/507)	0.85
Cales, 2010 ¹¹¹	FibroMeter 3 rd generation (hyaluronic acid replaced with GGT) >0.440	Not reported	METAVIR F2-F4	Derivation sample: 0.81 (446/549)	Derivation sample: 0.74 (376/507)	Derivation sample: 0.84 (0.83-0.87) Validation sample: 0.81 (CI not reported)
Crisan, 2012 ¹²²	Fibrometer >0.59	All >5 portal tracts; median 11 mm and mean 14 portal tracts	METAVIR F2-F4	0.69 (195/283)	0.81 (132/163)	0.80 (CI not reported)
Halfon, 2007 ¹⁴⁵	Fibrometer >0.57	All >15 mm	METAVIR F2-F4	0.64 (93/146)	0.81 (170/210)	0.78 (0.73-0.82)
Leroy, 2008 ¹⁵⁷	FibroMeter, cutoff not reported	55% >20 mm; 84% >15 mm	METAVIR F2-F4	0.75 (301/400)	0.78 (332/425)	0.84 (0.81-0.87)
Zarski, 2012 ²²³	FibroMeter, cutoff not reported	All ≥20 mm or ≥15 mm and ≥11 portal tracts	METAVIR F2-F4	Not reported	Not reported	0.82 (0.78-0.86)
Severe Fibrosis						
Boursier, 2009 ¹⁰⁶	FibroMeter >0.628	Not reported	METAVIR F3-F4	0.84 (221/264)	0.79 (629/792)	0.88 (0.86-0.91)
Boursier, 2009 ¹⁰⁶	FibroMeter >0.83	Not reported	METAVIR F3-F4	0.60 (158/264)	0.91 (722/792)	0.88 (0.86-0.91)
Crisan, 2012 ¹²²	Fibrometer >0.76	All >5 portal tracts; median 11 mm and mean 14 portal tracts	METAVIR F3-F4	0.80 (98/122)	0.72 (235/324)	0.81 (CI not reported)
Halfon, 2007 ¹⁴⁵	Fibrometer >0.57	All >15 mm	METAVIR F3-F4	0.64 (93/146)	0.81 (170/210)	0.78 (0.73-0.82)
Leroy, 2008 ¹⁵⁷	FibroMeter, cutoff not reported	55% >20 mm; 84% >15 mm	METAVIR F3-F4	Not reported	Not reported	0.89 (0.87-0.92)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
Fibrometer (continued)						
Cirrhosis						
Boursier, 2009 ¹⁰⁶	FibroMeter >0.628	Not reported	METAVIR F4	0.96 (111/116); >0.979: 0.36 (41/116)	0.71 (668/940)	0.91 (0.88-0.93)
Boursier, 2009 ¹⁰⁶	FibroMeter >0.979	Not reported	METAVIR F4	0.36 (41/116)	0.98 (921/940)	0.91 (0.88-0.93)
Cales, 2010 ¹¹¹	FibroMeter 3 rd generation (hyaluronic acid replaced with GGT), cutoff not reported	Not reported	METAVIR F4	Not reported	Not reported	0.89 (0.87-0.92) optimized for fibrosis, 0.91 (0.88-0.94) optimized for cirrhosis
Halfon, 2007 ¹⁴⁵	Fibrometer >0.88	All >15 mm	METAVIR F4	0.92 (12/13)	0.87 (298/343)	0.94 (0.91-0.96)
Leroy, 2008 ¹⁵⁷	FibroMeter, cutoff not reported	55% >20 mm; 84% >15 mm	METAVIR F4	Not reported	Not reported	0.93 (0.90-0.95)
Zarski, 2012 ²²³	FibroMeter, cutoff not reported	All ≥20 mm or ≥15 mm and ≥11 portal tracts	METAVIR F4	Not reported	Not reported	0.89 (0.86-0.93)
Fibrosis Index						
Fibrosis						
Ahmad, 2011 ⁹³	Fibrosis Index >2.1	Not reported	METAVIR F2-F4	0.58 (52/89)	1.0 (68/68)	0.94 (0.90-0.97)
Ohta, 2006 ¹⁷³	Fibrosis Index ≥2.1	Not reported	Desmet F2-F4	Derivation and validation samples, respectively : 0.82 (151/184) and 0.77 (121/157)	Derivation and validation samples, respectively : 0.67 (123/184) and 0.68 (63/92)	Derivation and validation samples, respectively: 0.85 (CI not reported) and not reported
Cirrhosis						
Ahmad, 2011 ⁹³	Fibrosis Index >3.3	Not reported	METAVIR F2-F4	0.38 (8/21)	1.0 (136/136)	0.99 (0.98-1.0)
Ohta, 2006 ¹⁷³	Fibrosis Index ≥3.3	Not reported	Desmet F4	Derivation and validation samples, respectively : 0.68 (21/31) and 0.71 (17/24)	Derivation and validation samples, respectively : 0.98 (330/337) and 0.78 (221/225)	Derivation and validation samples, respectively: 0.98 (CI not reported) and not reported

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
Fibrosis-Cirrhosis Index						
Fibrosis						
Ahmad, 2011 ⁹³	Fibrosis-cirrhosis index >0.130	Not reported	METAVIR F2-F4	0.86 (77/89)	0.81 (55/68)	0.93 (0.90-0.97)
Cirrhosis						
Ahmad, 2011 ⁹³	Fibrosis-cirrhosis index >1.25	Not reported	METAVIR F4	0.86 (18/21)	1.0 (136/136)	1.0 (0.99-1.0)
Fibrosis-Probability Index (Sud Index)						
Fibrosis						
Romera, 2006 ¹⁸⁹	Fibrosis Probability Index ≥ 0.2	Mean 10 portal tracts	Scheuer F2-F4	0.77 (48/62)	0.58 (40/69)	0.80 (CI not reported)
Sud, 2004 ²⁰⁸	Fibrosis Probability Index ≥ 0.2	Not reported	Scheuer F2-F4	Derivation sample: 0.96 (80/83) Validation sample: 0.85 (63/74)	Derivation sample: 0.44 (38/87) Validation sample: 0.48 (25/52)	Derivation sample: 0.84 Validation sample: 0.77
Sud, 2004 ²⁰⁸	Fibrosis Probability Index ≥ 0.8	Not reported	Scheuer F2-F4	Derivation sample: 0.45 (37/83) Validation sample: 0.42 (31/74)	Derivation sample: 0.94 (82/87) Validation sample: 0.98 (51/52)	Derivation sample: 0.84 Validation sample: 0.77
Fibrosis-Protein Index						
Fibrosis						
Cheung, 2011 ¹¹⁶	Fibrosis-protein Index (a-2 macroglobulin and hemopexin) >3.53	Median 1.6-2.0 cm and >8 portal tracts	METAVIR F2-F4	0.81 (75/93) [0.80-0.83]	0.71 (30/42) [0.62-0.79]	0.82 (0.73-0.92)
Severe Fibrosis						
Cheung, 2011 ¹¹⁶	Fibrosis-protein Index (a-2 macroglobulin and hemopexin) >4.78	Median 1.6-2.0 cm and >8 portal tracts	METAVIR F3-F4	0.79 (33/42) [0.74-0.89]	0.78 (73/93) [0.71-0.87]	0.92 (0.86-0.99)
Cirrhosis						
Cheung, 2011 ¹¹⁶	Fibrosis-protein Index (a-2 macroglobulin and hemopexin) >5.31	Median 1.6-2.0 cm and >8 portal tracts	METAVIR F4	0.75 (21/28) [0.80-0.81]	0.81 (84/104) [0.73-0.94]	0.88 (0.77-0.98)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
FibroQ						
Fibrosis						
Hsieh, 2009 ¹⁴⁶	FibroQ (age, AST, PT, platelets, ALT) >1.6	Not reported	METAVIR F2-F4	0.79 (92/116)	0.71 (17/24)	0.78 (0.69-0.88)
Cirrhosis						
Hsieh, 2009 ¹⁴⁶	FibroQ (age, AST, PT, platelets, ALT) >2.6	Not reported	METAVIR F4	1.0 (6/6)	0.65 (87/134)	0.79 (0.68-0.90)
FibroSpect II						
Fibrosis						
Patel, 2004 ¹⁸¹	FibroSpect II (TIMP-1, alpha-2-macroglobulin, hyaluronic acid) >0.36	Biopsy ≥10 mm and at least 5 portal tracts	METAVIR F2-F4	Derivation sample: 0.83 (123/149) Validation sample: 0.77 (160/208)	Derivation sample: 0.66 (96/145) Validation sample: 0.73 (144/194)	0.82 (confidence interval not reported)
Patel, 2009 ¹⁸⁰	FibroSpect II (TIMP-1, alpha-2-macroglobulin, hyaluronic acid) >0.36	Mean 18 mm	METAVIR F2-F4	Whole sample: 0.95 (21/22) Excluding biopsies <15 mm: 1.0 (15/15)	Whole sample: 0.66 (48/73) Excluding biopsies <15 mm: 0.73 (27/37)	Whole sample: 0.90 (0.84-0.96) Excluding biopsies <15 mm: 0.94 (0.88-1.0)
Snyder, 2007 ²⁰⁶	FibroSpect II >25	Mean 25 mm	Batts-Ludwig F2-F4	1.0 (50/50)	0.42 (18/43)	0.88 (0.79-0.94)
Snyder, 2007 ²⁰⁶	FibroSpect II ≥55	Mean 25 mm	Batts-Ludwig F2-F4	0.82 (41/50)	0.77 (33/43)	0.88 (0.79-0.94)
Snyder, 2007 ²⁰⁶	FibroSpect II ≥85	Mean 25 mm	Batts-Ludwig F2-F4	0.52 (26/50)	1.0 (43/43)	0.88 (0.79-0.94)
Zaman, 2007 ²²²	FibroSpect II (TIMP-1, alpha-2-macroglobulin, hyaluronic acid) ≥42	All >15 mm and >5 portal tracts	METAVIR F2-F4	0.72 (28/39)	0.74 (51/69)	0.83 (CI not reported)
Severe Fibrosis						
Zaman, 2007 ²²²	FibroSpect II (TIMP-1, alpha-2-macroglobulin, hyaluronic acid) ≥42	All >15 mm and >5 portal tracts	METAVIR F3-F4	0.82 (11/14)	0.63 (59/94)	Not reported

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
Fibrotest						
Fibrosis						
Adler, 2008 ⁹²	Cutoff not reported	Not reported	METAVIR F2-F4	Not reported	Not reported	0.79 (CI not reported)
Cales, 2008 ¹¹⁰	Fibrotest >0.435	Not reported	METAVIR F2-F4	0.68 (372/549)	0.82 (415/507)	0.81 (0.78-0.84)
Castera, 2005 ¹¹⁴	Fibrotest, cutoff not reported	Median 17 mm, median 2 fragments	METAVIR F2-F4	Not reported	Not reported	0.85 (0.78-0.90)
Crisan, 2012 ¹²²	Fibrotest >0.34	All >5 portal tracts; median 11 mm and mean 14 portal tracts	METAVIR F2-F4	0.65 (184/283)	0.80 (125/163)	0.78 (CI not reported)
Colletta, 2005 ¹²⁰	Fibrotest ≥0.31	Mean 20 mm and median 7 portal tracts	METAVIR F2-F4	0.64 (9/14)	0.31 (8/26)	Not reported
Friedrich-Rust, 2010 ¹³²	Fibrotest >0.32	All >10 mm and ≥6 portal tracts; mean 22 mm, median 20 mm	METAVIR F2-F4	0.81 (CI not reported)	0.60 (CI not reported)	Not reported
Grigorescu, 2007 ¹³⁸	Fibrotest >0.47	Not reported	METAVIR F2-F4	0.80 (104/130)	0.63 (48/76)	0.78 (FI not reported)
Halfon, 2006 ¹⁴⁴	Fibrotest >0.10	Median 15 mm and 9 portal tracts; 55% ≥15 mm and ≥5 portal tracts	METAVIR F2-F4	0.97 (223/230)	0.27 (74/274);	0.79 (0.75-0.82)
Halfon, 2006 ¹⁴⁴	Fibrotest >0.36	Median 15 mm and 9 portal tracts; 55% ≥15 mm and ≥5 portal tracts	METAVIR F2-F4	0.73 (168/230)	0.72 (197/274)	0.79 (0.75-0.82)
Halfon, 2006 ¹⁴⁴	Fibrotest >0.80	Median 15 mm and 9 portal tracts; 55% ≥15 mm and ≥5 portal tracts	METAVIR F2-F4	0.20 (46/230)	0.98 (269/274)	0.79 (0.75-0.82)
Halfon, 2007 ¹⁴⁵	Fibrotest >0.44	All >15 mm	METAVIR F2-F4	0.67 (98/146)	0.80 (168/210)	0.79 (0.75-0.83)
Imbert-Bismut, 2001 ¹⁴⁹ ; Thabut, 2003 ²²⁷ ; Le Calvez, 2004 ²²⁵	Fibrotest (6-marker) >0.20	All ≥10 mm	METAVIR F2-F4	Validation sample: 0.92 (55/60)	Validation sample: 0.46 (34/74)	Derivation sample: 0.84 (SD 0.43) and Validation sample: 0.87 (SD 0.34)
Imbert-Bismut, 2001 ¹⁴⁹ ; Thabut, 2003 ²²⁷ ; Le Calvez, 2004 ²²⁵	Fibrotest (6-marker) >0.50	All ≥10 mm	METAVIR F2-F4	Validation sample: 0.75 (45/60)	Validation sample: 0.85 (63/74)	Derivation sample: 0.84 (SD 0.43) and Validation sample: 0.87 (SD 0.34)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
<i>Fibrotest (continued)</i>						
<i>Fibrosis (continued)</i>						
Imbert-Bismut, 2001 ¹⁴⁹ ; Thabut, 2003 ²²⁷ ; Le Calvez, 2004 ²²⁵	Fibrotest (6-marker) >0.80	All ≥10 mm	METAVIR F2-F4	Validation sample: 0.38 (23/60)	Validation sample: 0.97 (72/74)	Derivation sample: 0.84 (SD 0.43) and Validation sample: 0.87 (SD 0.34)
Imbert-Bismut, 2001 ¹⁴⁹ ; Thabut, 2003 ²²⁷ ; Le Calvez, 2004 ²²⁵	Fibrotest (5 marker), cutoff not reported	All ≥10 mm	METAVIR F2-F4	Not reported	Not reported	Derivation sample: 0.83 (SD 0.43) and Validation sample: 0.85 (SD 0.34)
Leroy, 2007 ¹⁵⁸	Fibrotest >0.22	Median 23 mm and median 17 portal tracts; 89% >15 mm and 45% >25 mm	METAVIR F2-F4	0.89 (81/91)	0.53 (47/89)	Whole sample: 0.84 (0.79-0.90) Excluding patients with biopsy <15 mm or <7 portal tracts (n=161): 0.83 (CI not reported)
Leroy, 2008 ¹⁵⁷	Fibrotest, cutoff not reported	55% >20 mm; 84% >15 mm	METAVIR F2-F4	0.58 (231/400)	0.85 (363/425)	0.80 (0.77-0.83)
Myers, 2003 ¹⁷⁰	Fibrotest 7-item index (Fibrotest items plus PT and platelet count) >0.20	All ≥10 mm	METAVIR F2-F4	0.88 (115/131)	0.56 (107/192)	0.84 (0.82-0.86)
Myers, 2003 ¹⁷⁰	Fibrotest 7-item index (Fibrotest items plus PT and platelet count) >0.80	All ≥10 mm	METAVIR F2-F4	0.50 (66/131)	0.95 (183/192)	0.84 (0.82-0.86)
Patel, 2009 ¹⁸⁰	Fibrosure ≥0.48	Mean 18 mm	METAVIR F2-F4	Whole sample: 1.0 (18/18) Excluding biopsies <15 mm: 1.0 (12/12)	Whole sample: 0.61 (40/66) Excluding biopsies <15 mm: 0.66 (21/32)	Whole sample: 0.89 (0.81-0.97) Excluding biopsies <15 mm: 0.89 (0.79-0.99)
Poynard, 2002 ¹⁸⁴	Fibrotest, cutoff not reported	Not reported	Knodell F3	Not reported	Not reported	0.74 (0.71-0.77)
Poynard, 2003 ¹⁸⁵	Fibrotest, cutoff not reported	Not reported	METAVIR F2-F4	Not reported	Not reported	0.73 (0.70-0.76)
Rossi, 2003 ¹⁹¹	Fibrotest >0.10	Not reported	METAVIR F2-F4	0.92 (44/48)	0.29 (22/77)	0.74 (0.64-0.84)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
<i>Fibrotest (continued)</i>						
<i>Fibrosis (continued)</i>						
Rossi, 2003 ¹⁹¹	Fibrotest >0.30	Not reported	METAVIR F2-F4	0.75 (36/48)	0.61 (47/77)	0.74 (0.64-0.84)
Rossi, 2003 ¹⁹¹	Fibrotest >0.60	Not reported	METAVIR F2-F4	0.42 (20/48)	0.94 (72/77)	0.74 (0.64-0.84)
Rossi, 2003 ¹⁹¹	Fibrotest >0.80	Not reported	METAVIR F2-F4	0.22 (11/48)	0.96 (74/77)	0.74 (0.64-0.84)
Said, 2010 ¹⁹³	Fibrotest >0.5	Mean 17.7 mm, 10.5 portal tracts; 88% >15 mm	METAVIR F2-F4	0.85 (40/47)	0.72 (13/18)	0.87 (0.78-0.96)
Sebastiani, 2006 ¹⁹⁹	Fibrotest, cutoff not reported	All ≥1.5 cm and ≥7 portal tracts	METAVIR F2-F4	Normal ALT, F2 cutoff: 0.58 Elevated ALT, F2 cutoff: 0.65	Normal ALT, F2 cutoff: 0.91 Elevated ALT, F2 cutoff: 0.81	Normal ALT, F2 cutoff: 0.71 (0.49-0.92) Elevated ALT, F2 cutoff: 0.81 (0.72-0.91)
Sebastiani, 2008 ¹⁹⁸	Fibrotest >0.49	All ≥15 mm and ≥7 portal tracts	METAVIR F2-F4	Whole sample: 0.78 (115/147) Normal ALT: 0.66 (21/32) [0.67] Elevated ALT: 0.82 (94/115)	Whole sample: 0.78 (76/97) Normal ALT: 0.85 (41/48) Elevated ALT: 0.71 (35/49) [0.72]	Normal ALT: 0.70 (0.59-0.81) Elevated ALT: 0.79 (0.74-0.84)
Sebastiani, 2011 ²⁰⁰	Fibrotest >0.49	Mean 18 mm and 11 portal tracts; 43% >20 mm	METAVIR F2-F4	Whole sample: 0.56 (461/820) Normal ALT: 0.35 (62/176)	Whole sample: 0.79 (781/990) Normal ALT: 0.88 (371/419)	Whole sample: 0.70 (0.65-0.75) Normal ALT: 0.62 (0.58-0.66)
Sebastiani, 2012 ²⁰¹	Fibrotest >0.49	Mean 20 mm and 11 portal tracts; 45% >20 mm	METAVIR F2-F4	0.62 (341/552)	0.81 (375/461)	0.71 (0.64-0.78)
Stibbe, 2011 ²⁰⁷	Fibrotest >0.31	All ≥20 mm	METAVIR F2-F4	0.74 (16/22)	0.76 (14/18)	Not reported
Wilson, 2006 ²¹⁹	Fibrosure ≥0.31	Not reported	Ishak 3-4	0.89 (n/N unclear)	0.49 (n/N unclear)	0.74 (CI not reported)
Wilson, 2006 ²¹⁹	Fibrosure ≥0.48	Not reported	Ishak 3-4	0.56 (n/N unclear)	0.65 (n/N unclear)	0.74 (CI not reported)
Zarski, 2012 ²²³	Fibrotest, cutoff not reported	All ≥20 mm or ≥15 mm and ≥11 portal tracts	METAVIR F2-F4	Not reported	Not reported	0.80 (0.75-0.84)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
<i>Fibrotest (continued)</i>						
<i>Severe Fibrosis</i>						
Adler, 2008 ⁹²	Cutoff not reported	Not reported	METAVIR F3-F4	Not reported	Not reported	0.90 (CI not reported)
Bourliere, 2008 ¹⁰⁴	Fibrotest, cutoff not reported	Mean 20 mm and median 9 portal tracts; 59% ≥15 mm and ≥5 portal tracts	METAVIR F3-F4	0.69 (90/130)	0.86 (290/337)	0.84 (0.80-0.87)
Boursier, 2009 ^{106c}	Fibrotest >0.448	Not reported	METAVIR F3-F4	0.84 (223/264)	0.71 (563/792)	0.84 (0.81-0.86)
Boursier, 2009 ¹⁰⁶	Fibrotest >0.631	Not reported	METAVIR F3-F4	0.67 (176/264)	0.84 (664/792)	0.84 (0.81-0.86)
Castera, 2005 ¹¹⁴	Fibrotest, cutoff not reported	Median 17 mm, median 2 fragments	METAVIR F3-F4	Not reported	Not reported	0.90 (0.85-0.94)
Crisan, 2012 ¹²²	Fibrotest >0.54	All >5 portal tracts; median 11 mm and mean 14 portal tracts	METAVIR F3-F4	0.83 (101/122)	0.63 (206/324)	0.78 (CI not reported)
Friedrich-Rust, 2010 ¹³²	Fibrotest >0.59	All >10 mm and ≥6 portal tracts; mean 22 mm, median 20 mm	METAVIR F3-F4	0.65 (CI not reported)	0.79 (CI not reported)	Not reported
Halfon, 2006 ¹⁴⁴	Fibrotest >0.10	Median 15 mm and 9 portal tracts; 55% ≥15 mm and ≥5 portal tracts	METAVIR F3 or F4	0.99 (119/120)	0.21 (81/384)	0.80 (0.76-0.83)
Halfon, 2006 ¹⁴⁵	Fibrotest >0.44	Median 15 mm and 9 portal tracts; 55% ≥15 mm and ≥5 portal tracts	METAVIR F3 or F4	0.76 (91/120)	0.70 (269/384)	0.80 (0.76-0.83)
Halfon, 2006 ¹⁴⁵	Fibrotest >0.80	Median 15 mm and 9 portal tracts; 55% ≥15 mm and ≥5 portal tracts	METAVIR F3 or F4	0.29 (35/120)	0.97 (372/384)	0.80 (0.76-0.83)
Halfon, 2007 ¹⁴⁵	Fibrotest >0.45	All >15 mm	METAVIR F3-F4	0.84 (43/51)	0.69 (210/305)	0.81 (0.77-0.85)
Leroy, 2007 ¹⁵⁸	Fibrotest >0.22	Median 23 mm and median 17 portal tracts; 89% >15 mm and 45% >25 mm	METAVIR F3-F4	0.94 (48/51)	0.42 (54/129)	Whole sample: 0.87 (0.81-0.93) Excluding patients with biopsy <15 mm or <7 portal tracts (n=161): 0.86 (CI not reported)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
<i>Fibrotest (continued)</i>						
<i>Severe Fibrosis (continued)</i>						
Leroy, 2007 ¹⁵⁸	Fibrotest >0.32	Median 23 mm and median 17 portal tracts; 89% >15 mm and 45% >25 mm	METAVIR F3-F4	0.90 (46/51)	0.64 (83/129)	Whole sample: 0.87 (0.81-0.93) Excluding patients with biopsy <15 mm or <7 portal tracts (n=161): 0.86 (CI not reported)
Leroy, 2007 ¹⁵⁸	Fibrotest >0.59	Median 23 mm and median 17 portal tracts; 89% >15 mm and 45% >25 mm	METAVIR F3-F4	0.67 (34/51)	0.88 (114/129)	Whole sample: 0.87 (0.81-0.93) Excluding patients with biopsy <15 mm or <7 portal tracts (n=161): 0.86 (CI not reported)
Leroy, 2008 ¹⁵⁷	Fibrotest, cutoff not reported	55% >20 mm; 84% >15 mm	METAVIR F3-F4	Not reported	Not reported	0.85 (0.82-0.88)
Myers, 2003 ¹⁷⁰	Fibrotest 7-item index (Fibrotest items plus PT and platelet count) >0.70	All ≥10 mm	METAVIR F4	Not reported	Not reported	0.92 (0.90-0.94)
Myers, 2003 ¹⁷⁰	Fibrotest 7-item index (Fibrotest items plus PT and platelet count) >0.80	All ≥10 mm	METAVIR F4	Not reported	Not reported	0.92 (0.90-0.94)
Poynard, 2003 ¹⁸⁵	Fibrotest, cutoff not reported	Not reported	METAVIR F3-F4	Not reported	Not reported	0.73 (0.69-0.77)
Said, 2010 ¹⁹³	Fibrotest >0.52	Mean 17.7 mm, 10.5 portal tracts; 88% >15 mm	METAVIR F3-F4	0.92 (24/26)	0.54 (21/39)	0.76 (0.64-0.88)
Stibbe, 2011 ²⁰⁷	Fibrotest >0.58	All ≥20 mm	METAVIR F3-F4	0.91 (16/18)	0.41 (13/22)	Not reported
<i>Cirrhosis</i>						
Adler, 2008 ⁹²	Cutoff not reported	Not reported	METAVIR F4	Not reported	Not reported	0.92 (CI not reported)
Bourliere, 2008 ¹⁰⁴	Fibrotest, cutoff not reported	Mean 20 mm and median 9 portal tracts; 59% ≥15 mm and ≥5 portal tracts	METAVIR F4	0.91 (32/35)	0.75 (324/432)	0.89 (0.86-0.93)
Boursier, 2009 ¹⁰⁶	Fibrotest >0.660	Not reported	METAVIR F4	0.82 (96/116)	0.77 (726/940)	0.88 (0.86-0.91)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
<i>Fibrotest (continued)</i>						
<i>Cirrhosis (continued)</i>						
Boursier, 2009 ¹⁰⁶	Fibrotest >0.862	Not reported	METAVIR F4	0.42 (49/116)	0.96 (898/940)	0.88 (0.86-0.91)
Castera, 2009 ¹¹²	Fibrotest ≥0.75	All ≥10 mm and ≥6 portal tracts; mean 20 mm and 15 portal tracts	METAVIR F4	0.56 (39/70)	0.55 (197/228)	0.82 (0.73-0.86)
Friedrich-Rust, 2010 ¹³²	Fibrotest >0.73	All >10 mm and ≥6 portal tracts; mean 22 mm, median 20 mm	METAVIR F4	0.67	0.81	Not reported
Halfon, 2007 ¹⁴⁵	Fibrotest >0.56	All >15 mm	METAVIR F4	0.85 (11/13)	0.74 (254/343)	0.86 (0.82-0.89)
Leroy, 2008 ¹⁵⁷	Fibrotest, cutoff unclear	55% >20 mm; 84% >15 mm	METAVIR F4	Not reported	Not reported	0.89 (0.86-0.92)
Said, 2010 ¹⁹³	Fibrotest >0.75	Mean 17.7 mm, 10.5 portal tracts; 88% >15 mm	METAVIR F4	0.86 (6/7)	0.71 (41/58)	0.85 (0.72-0.97)
Sebastiani, 2006 ¹⁹⁹	Fibrotest, cutoff not reported	All ≥1.5 cm and ≥7 portal tracts	METAVIR F4	0.48 (14/29) [0.50]	0.93 (150/161)	0.71 (0.60-0.82)
Sebastiani, 2011 ²⁰⁰	Fibrotest >0.75	Mean 18 mm and 11 portal tracts; 43% >20 mm	METAVIR F4	Whole sample: 0.54 (88/163) Normal ALT: 0.33 (6/19)	Whole sample: 0.90 (1,484/1,647) Normal ALT: 0.94 (541/576)	Whole sample: 0.72 (0.67-0.77) Normal ALT: 0.65 (0.60-0.70)
Sebastiani, 2012 ²⁰¹	Fibrotest >0.75	Mean 20 mm and 11 portal tracts; 45% >20 mm	METAVIR F4	0.30 (34/113)	0.89 (800/900)	0.72 (0.67-0.77)
Stibbe, 2011 ²⁰⁷	Fibrotest >0.75	All ≥20 mm	METAVIR F4	1.0 (11/11)	0.24 (22/29)	Not reported
Zarski, 2012 ²²³	Fibrotest, cutoff not reported	All ≥20 mm or ≥15 mm and ≥11 portal tracts	METAVIR F2-F4	Not reported	Not reported	0.86 (0.83-0.90)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
Forns' Index						
Fibrosis						
Adler, 2008 ⁹²	Cutoff not reported	Not reported	METAVIR F2-F4	Not reported	Not reported	0.75 (CI not reported)
Bota, 2011 ¹⁰³	Forns' Index (cutoff not reported)	All ≥8 portal tracts, mean 34 mm	METAVIR F2-F4	Not reported	Not reported	0.74 (CI not reported)
Bourliere, 2006 ¹⁰⁵	Forns' Index ≥4.21	Mean 20 mm and median 9 portal tracts; 59% ≥15 mm and ≥5 portal tracts	METAVIR F2-F4	0.90 (79/99)	0.54 (73/136)	0.76 (0.70-0.82)
Bourliere, 2006 ¹⁰⁵	Forns' Index >6.9	Mean 20 mm and median 9 portal tracts; 59% ≥15 mm and ≥5 portal tracts	METAVIR F2-F4	0.30 (30/99)	0.96 (130/136)	0.76 (0.70-0.82)
Cheong, 2011 ¹¹⁵	Forns' Index, cutoff not reported	Mean 12.6 mm and mean 13.2 portal tracts; 71% had ≥11 portal tracts	METAVIR F2-F4	Not reported	Not reported	0.80 (0.70-0.90)
Crisan, 2012 ¹²²	Forns' Index >4.47	All >5 portal tracts; median 11 mm and mean 14 portal tracts	METAVIR F2-F4	0.80 (226/283)	0.49 (81/163)	0.68 (CI not reported)
Fabris, 2008 ¹²⁹	Forns' Index, cutoff not reported	Average 19 mm and median 7 portal tracts	METAVIR F2-F4	Not reported	Not reported	0.70 (0.62-0.76)
Forns, 2002 ¹³¹	Forns' Index >4.2	All ≥6 portal tracts	Scheuer F2-F4	Derivation sample: 0.94 (80/85) Validation sample: 0.94 (31/33)	Derivation sample: 0.45 (120/266) Validation sample: 0.51 (47/92)	Derivation sample: 0.86 (CI not reported) Validation sample: 0.81 (CI not reported)
Forns, 2002 ¹³¹	Forns' Index >6.9	All ≥6 portal tracts	Scheuer F2-F4	Derivation sample: 0.44 (37/85) Validation sample: 0.30 (10/33)	Derivation sample: 0.96 (256/266) Validation sample: 0.95 (87/92)	Derivation sample: 0.86 (CI not reported) Validation sample: 0.81 (CI not reported)
Güzelbulut, 2011 ¹⁴²	Forns' Index >6.9	Not reported	METAVIR F2-F4	0.47 (39/83)	0.94 (63/67)	0.80 (0.73-0.86)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
<i>Forns' Index (continued)</i>						
<i>Fibrosis (continued)</i>						
Leroy, 2007 ¹⁵⁸	Forns' Index >4.2	Median 23 mm and median 17 portal tracts; 89% >15 mm and 45% >25 mm	METAVIR F2-F4	0.88 (80/91)	0.42 (38/89)	Whole sample: 0.78 (0.71-0.85) Excluding patients with biopsy <15 mm or <7 portal tracts (n=161): 0.78 (CI not reported)
Leroy, 2007 Leroy, 2007 ¹⁵⁸	Forns' Index >6.9	Median 23 mm and median 17 portal tracts; 89% >15 mm and 45% >25 mm	METAVIR F2-F4	0.42 (38/91)	0.93 (83/89)	Whole sample: 0.78 (0.71-0.85) Excluding patients with biopsy <15 mm or <7 portal tracts (n=161): 0.78 (CI not reported)
Martinez, 2011 ¹⁶⁵	Forns' Index >4.2	Mean 15 mm, 72% >15 mm	METAVIR F2-F4	0.89 (204/229)	0.58 (64/111)	0.83 (0.78-0.87)
Martinez, 2011 ¹⁶⁵	Forns' Index >6.9	Mean 15 mm, 72% >15 mm	METAVIR F2-F4	0.44 (101/229)	0.93 (103/111)	0.83 (0.78-0.87)
Patel, 2009 ¹⁸⁰	Forns' Index >4.21	Mean 18 mm	METAVIR F2-F4	Whole sample: 0.91 (20/22) Excluding biopsies <15 mm: 0.50 (11/22)	Whole sample: 0.53 (38/72) Excluding biopsies <15 mm: 0.93 (61/72)	Not reported
Romera, 2006 ¹⁸⁹	Forns' Index ≥4.2	Mean 10 portal tracts	Scheuer F2-F4	0.79 (49/62)	0.48 (33/69)	0.71 (CI not reported)
Sebastiani, 2008 ¹⁹⁸	Forns' Index >4.2	All ≥15 mm and ≥7 portal tracts	METAVIR F2-F4	Whole sample: 0.79 (116/147) Normal ALT: 0.56 (18/32) [0.57] Elevated ALT: 0.85 (98/115)	Whole sample: 0.58 (56/97) Normal ALT: 0.67 (32/48) Elevated ALT: 0.49 (24/49)	Normal ALT: 0.60 (0.50-0.71) Elevated ALT: 0.76 (0.71-0.81)
Sebastiani, 2008 ¹⁹⁸	Forns' Index >6.9	All ≥15 mm and ≥7 portal tracts	METAVIR F2-F4	Whole sample: 0.18 (27/147) Normal ALT: 0.06 (2/32) [0.05] Elevated ALT: 0.22 (25/115) [0.21]	Whole sample: 0.99 (96/97) Normal ALT: 1.0 (48/48) Elevated ALT: 1.0 (49/49)	Normal ALT: 0.60 (0.50-0.71) Elevated ALT: 0.76 (0.71-0.81)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
Forns' Index (continued)						
Fibrosis (continued)						
Sebastiani, 2011 ²⁰⁰	Forns' Index >4.2	Mean 18 mm and 11 portal tracts; 43% >20 mm	METAVIR F2-F4	Whole sample: Not reported Normal ALT: 0.57 (100/176)	Whole sample: Not reported Normal ALT: 0.67 (279/419)	Whole sample: Not reported Normal ALT: 0.60 (0.55-0.65)
Sebastiani, 2011 ²⁰⁰	Forns' Index >6.9	Mean 18 mm and 11 portal tracts; 43% >20 mm	METAVIR F2-F4	Whole sample: Not reported Normal ALT: 0.18 (31/176)	Whole sample: Not reported Normal ALT: 0.89 (373/419)	Whole sample: Not reported Normal ALT: 0.60 (0.55-0.65)
Sebastiani, 2012 ²⁰¹	Forns' Index >4.2	Mean 20 mm and 11 portal tracts; 45% >20 mm	METAVIR F2-F4	0.94 (521/552)	0.20 (90/461)	0.64 (0.58-0.70)
Sebastiani, 2012 ²⁰¹	Forns' Index >6.9	Mean 20 mm and 11 portal tracts; 45% >20 mm	METAVIR F2-F4	0.61 (336/552)	0.66 (304/461)	0.64 (0.58-0.70)
Sirli, 2010 ²⁰⁴	Forns' Index >4.57	All >20 mm and ≥8 portal tracts	METAVIR F2-F4	0.72 (96/138)	0.68 (11/16)	0.75 (0.67-0.82)
Zarski, 2012 ²²³	Forns' Index, cutoff not reported	All ≥20 mm or ≥15 mm and ≥11 portal tracts	METAVIR F2-F4	Not reported	Not reported	0.75 (0.71-0.80)
Severe Fibrosis						
Adler, 2008 ⁹²	Cutoff not reported	Not reported	METAVIR F3-F4	Not reported	Not reported	0.90 (CI not reported)
Bota, 2011 ¹⁰³	Forns' Index (cutoff not reported)	All ≥8 portal tracts, mean 34 mm	METAVIR F3-F4	Not reported	Not reported	0.80 (CI not reported)
Crisan, 2012 ¹²²	Forns' Index >7.3	All >5 portal tracts; median 11 mm and mean 14 portal tracts	METAVIR F3-F4	0.86 (105/122)	0.49 (157/324)	0.74 (CI not reported)
Iacobellis, 2005b ¹⁴⁸	Forns' Index >6.9	All ≥5 portal tracts	Scheuer F3 or F4	0.79 (193/243)	0.86 (871/1,009)	Not reported
Leroy, 2007 ¹⁵⁸	Forns' Index >4.2	Median 23 mm and median 17 portal tracts; 89% >15 mm and 45% >25 mm	METAVIR F3-F4	0.92 (47/51)	0.34 (44/129)	Whole sample: 0.78 (0.71-0.87) Excluding patients with biopsy <15 mm or <7 portal tracts (n=161): 0.80 (CI not reported)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
<i>Forns' Index (continued)</i>						
<i>Severe Fibrosis (continued)</i>						
Leroy, 2007 ¹⁵⁸	Forns' Index >6.9	Median 23 mm and median 17 portal tracts; 89% >15 mm and 45% >25 mm	METAVIR F3-F4	0.54 (28/51)	0.87 (112/129)	Whole sample: 0.78 (0.71-0.87) Excluding patients with biopsy <15 mm or <7 portal tracts (n=161): 0.80 (CI not reported)
Martinez, 2011 ¹⁶⁵	Forns' Index, cutoff not reported	Mean 15 mm, 72% >15 mm	METAVIR F3-F4	Not reported	Not reported	0.85 (0.81-0.89)
<i>Cirrhosis</i>						
Adler, 2008 ⁹²	Cutoff not reported	Not reported	METAVIR F4	Not reported	Not reported	0.89 (CI not reported)
Bota, 2011 ¹⁰³	Forns' Index (cutoff not reported)	All ≥8 portal tracts, mean 34 mm	METAVIR F4	Not reported	Not reported	0.85 (CI not reported)
Fabris, 2008 ¹²⁹	Forns' Index, cutoff not reported	Average 19 mm and median 7 portal tracts	METAVIR F4	Not reported	Not reported	0.86 (0.80-0.91)
Güzelbulut, 2011 ¹⁴²	Forns' Index >4.2	Not reported	METAVIR F4	0.98 (50/51)	0.27 (27/99)	0.88 (0.82-0.94)
Güzelbulut, 2011 ¹⁴²	Forns' Index >6.9	Not reported	METAVIR F4	0.67 (34/51)	0.91 (90/99)	0.88 (0.82-0.94)
Martinez, 2011 ¹⁶⁵	Forns' Index, cutoff not reported	Mean 15 mm, 72% >15 mm	METAVIR F4	Not reported	Not reported	0.87 (0.83-0.91)
Sirli, 2010 ²⁰⁴	Forns' Index >5.93	All >20 mm and ≥8 portal tracts	METAVIR F4	1.0 (15/15)	0.74 (100/135)	0.91 (0.85-0.95)
<i>Globulin/Albumin Ratio</i>						
<i>Significant Fibrosis</i>						
Iacobellis, 2005b ¹⁴⁸	Globulin/albumin ratio >1.0	All ≥5 portal tracts	Scheuer F3 or F4	0.31 (74/243)	0.85 (858/1,009)	Not reported
<i>Cirrhosis</i>						
Iacobellis, 2005b ¹⁴⁸	Globulin/albumin ratio >1.0	All ≥5 portal tracts	Scheuer F4	0.38 (30/78)	0.96 (1,125/1,174)	Not reported
Luo, 2002 ¹⁶⁴	Globulin/albumin ratio ≥1.0	All >5 portal tracts	Scheuer F4	0.43 (10/23)	0.98 (86/88)	Not reported

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
Goteborg University Cirrhosis Index						
Fibrosis						
Islam, 2005 ¹⁵¹	Goteborg University Cirrhosis Index (GUCI), cutoff not reported	≥10 mm and ≥4 portal tracts	Ishak ≥3	Not reported	Not reported	0.72 (CI not reported)
Cirrhosis						
Ehsan, 2008 ¹²⁵	Goteborg University Cirrhosis Index >1.5	Mean 12 mm	Ishak 5-6	0.74 (26/35)	0.89 (72/81)	0.86 (CI not reported)
Islam, 2005 ¹⁵¹	Goteborg University Cirrhosis Index >1.0	≥10 mm and ≥4 portal tracts	Ishak 5 or 6	0.80 (16/20)	0.78 (124/159)	0.85 (CI not reported)
HALT-C Model						
Cirrhosis						
Fontana, 2008 ¹³⁰	HALT-C model (platelet count, TIMP-1, hyaluronic acid) ≥0.2	Mean 1.84 cm	Ishak 5-6	0.88 (156/177)	0.45 (132/294)	0.81 (0.77-0.85)
Fontana, 2008 ¹³⁰	HALT-C model (platelet count, TIMP-1, hyaluronic acid) ≥0.5	Mean 1.84 cm	Ishak 5-6	0.47 (84/177)	0.92 (270/294)	0.81 (0.77-0.85)
Hepascore						
Fibrosis						
Becker, 2009 ⁹⁶	Hepascore ≥0.55	All ≥10 mm or ≥8 portal tracts; median 16 mm, 11% <10 mm	METAVIR F2-F4	0.82 (161/196)	0.65 (127/195)	0.81 (CI not reported)
Bourliere, 2008 ¹⁰⁴	Hepascore ≥0.5	Mean 20 mm and median 9 portal tracts; 59% ≥15 mm and ≥5 portal tracts	METAVIR F2-F4	0.63 (146/231)	0.86 (203/236)	0.82 (0.79-0.86)
Cales, 2008 ¹¹⁰	Hepascore >0.46	Not reported	METAVIR F2-F4	0.66 (363/549)	0.79 (401/507)	0.78
Crisan, 2012 ¹²²	Hepascore >0.34	All >5 portal tracts; median 11 mm and mean 14 portal tracts	METAVIR F2-F4	0.57 (182/283)	0.72 (118/163)	0.69 (CI not reported)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
Hepascore (continued)						
Fibrosis (continued)						
Guechot, 2010 ¹³⁹	Hepascore (with automated hyaluronic acid assay) >0.25	Mean 25 mm, >25 mm in 49%	METAVIR F2-F4	0.47 (117/247)	0.95 (252/265)	0.81 (0.78-0.85)
Guechot, 2010 ¹³⁹	Hepascore (with automated hyaluronic acid assay) >0.5	Mean 25 mm, >25 mm in 49%	METAVIR F2-F4	0.77 (190/247)	0.70 (186/265)	0.81 (0.78-0.85)
Halfon, 2007 ¹⁴⁵	Hepascore >0.32	All >15 mm	METAVIR F2-F4	0.77 (112/146)	0.63 (132/210)	0.76 (0.71-0.80)
Leroy, 2007 ¹⁵⁸	Hepascore >0.5	Median 23 mm and median 17 portal tracts; 89% >15 mm and 45% >25 mm	METAVIR F2-F4	0.54 (49/91)	0.84 (75/89)	Whole sample: 0.79 (0.72-0.85) Excluding patients with biopsy <15 mm or <7 portal tracts (n=161): 0.78 (CI not reported)
Leroy, 2008 ¹⁵⁷	Hepascore, cutoff unclear	55% >20 mm; 84% >15 mm	METAVIR F2-F4	0.64 (254/400)	0.80 (341/425)	0.78 (0.75-0.81)
Zarski, 2012 ²²³	Hepascore, cutoff not reported	All ≥20 mm or ≥15 mm and ≥11 portal tracts	METAVIR F2-F4	Not reported	Not reported	0.82 (0.78-0.85)
Severe Fibrosis						
Adams, 2005 ⁹¹	Hepascore ≥0.5	All ≥5 portal tracts; median 9 portal tracts and 13 mm	METAVIR F3-F4	Derivation sample: 0.95 (21/22) Validation sample: 0.88 (21/214)	Derivation sample: 0.81 (77/95) Validation sample: 0.74 (59/80)	Derivation sample: 0.96 (0.92-1.0) Validation sample: 0.90 (0.84-0.97)
Becker, 2009 ⁹⁶	Hepascore >0.2	All ≥10 mm or ≥8 portal tracts; median 16 mm, 11% <10 mm	METAVIR F3-F4	0.99 (138/139)	0.23 (58/252)	0.83 (CI not reported)
Bourliere, 2008 ¹⁰⁴	Hepascore, cutoff not reported	Mean 20 mm and median 9 portal tracts; 59% ≥15 mm and ≥5 portal tracts	METAVIR F3-F4	0.69 (90/130)	0.87 (293/337)	0.84 (0.80-0.87)
Boursier, 2009 ¹⁰⁶	Hepascore >0.497	Not reported	METAVIR F3-F4	0.82 (217/264)	0.71 (560/792)	0.83 (0.81-0.86)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
Hepascore (continued)						
Severe Fibrosis (continued)						
Crisan, 2012 ¹²²	Hepascore >0.61	All >5 portal tracts; median 11 mm and mean 14 portal tracts	METAVIR F3-F4	0.61 (74/122)	0.73 (237/324)	0.70 (CI not reported)
Guechot, 2010 ¹³⁹	Hepascore (with automated hyaluronic acid assay) >0.6	Mean 25 mm, >25 mm in 49%	METAVIR F3-F4	0.80 (124/155)	0.70 (250/357)	0.92 (0.78-0.86)
Halfon, 2007 ¹⁴⁵	Hepascore >0.53	All >15 mm	METAVIR F3-F4	0.78 (40/51)	0.72 (220/305)	0.81 (0.76-0.85)
Leroy, 2007 ¹⁵⁸	Hepascore >0.5	Median 23 mm and median 17 portal tracts; 89% >15 mm and 45% >25 mm	METAVIR F3-F4	0.76 (39/51)	0.90 (116/129)	Whole sample: 0.85 (0.80-0.92) Excluding patients with biopsy <15 mm or <7 portal tracts (n=161): 0.85 (CI not reported)
Leroy, 2008 ¹⁵⁷	Hepascore, cutoff unclear	55% >20 mm; 84% >15 mm	METAVIR F2-F4	0.64 (254/400)	0.80 (341/425)	0.84 (0.81-0.87)
Cirrhosis						
Adams, 2005 ⁹¹	Hepascore ≥0.84	All ≥5 portal tracts; median 9 portal tracts and 13 mm	METAVIR F4	Derivation sample: 0.71 (5/7) Validation sample: 0.71 (12/17)	Derivation sample: 0.84 (92/110) Validation sample: 0.89 (77/87)	Derivation sample: 0.94 (0.92-1.0) Validation sample: 0.89 (0.80-0.98)
Bourliere, 2008 ¹⁰⁴	Hepascore ≥0.84	Mean 20 mm and median 9 portal tracts; 59% ≥15 mm and ≥5 portal tracts	METAVIR F4	0.71 (25/35)	0.88 (380/432)	0.90 (0.87-0.93)
Boursier, 2009 ¹⁰⁶	Hepascore >0.801	Not reported	METAVIR F4	0.80 (93/116)	0.82 (776/940)	0.90 (0.87-0.92)
Guechot, 2010 ¹³⁹	Hepascore (with automated hyaluronic acid assay) >0.75	Mean 25 mm, >25 mm in 49%	METAVIR F4	0.86 (65/76)	0.74 (323/436)	0.88 (0.84-0.91)
Guechot, 2010 ¹³⁹	Hepascore (with automated hyaluronic acid assay) >0.84	Mean 25 mm, >25 mm in 49%	METAVIR F4	0.72 (55/76) [0.73]	0.81 (353/436)	0.88 (0.84-0.91)
Halfon, 2007 ^{145b}	Hepascore >0.61	All >15 mm	METAVIR F4	0.92 (12/13)	0.72 (247/343)	0.89 (0.86-0.92)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
Hepascore (continued)						
Cirrhosis (continued)						
Leroy, 2008 ¹⁵⁷	Hepascore, cutoff not reported	55% >20 mm; 84% >15 mm	METAVIR F4	Not reported	Not reported	0.89 (0.86-0.93)
Zarski, 2012 ²²³	Hepascore, cutoff not reported	All ≥20 mm or ≥15 mm and ≥11 portal tracts	METAVIR F4	Not reported	Not reported	0.89 (0.86-0.93)
King's Score						
Fibrosis						
Bota, 2011 ¹⁰³	King's Score (cutoff not reported)	All ≥8 portal tracts, mean 34 mm	METAVIR F2-F4	Not reported	Not reported	0.76 (CI not reported)
Cross, 2010 ¹²³	King's Score >9.87	All ≥10 mm or >10 portal tracts; mean 15 mm	Ishak ≥3	0.84 (75/89)	0.70 (69/98)	Whole sample: 0.89 (CI not reported) Normal AST: 0.83 (0.68-0.99) Elevated AST: 0.79 (0.69-0.89), Liver biopsy <15 mm: 0.84 (0.70-0.98) Liver biopsy >15 mm: 0.83 (0.72-0.93)
Cross, 2009 ¹²⁴	King's Score ≥12.3	All >10 mm and >10 portal tracts	Ishak ≥3	Derivation sample: 0.70 (190/271)	Derivation sample: 0.85 (281/331)	Derivation sample: 0.79 (0.75-0.83) Validation sample: 0.89 (0.81-0.96)
Severe Fibrosis						
Bota, 2011 ¹⁰³	King's Score (cutoff not reported)	All ≥8 portal tracts, mean 34 mm	METAVIR F3-F4	Not reported	Not reported	0.82 (CI not reported)
Cirrhosis						
Bota, 2011 ¹⁰³	King's Score (cutoff not reported)	All ≥8 portal tracts, mean 34 mm	METAVIR F4	Not reported	Not reported	0.89 (CI not reported)
Cross, 2009 ¹²⁴	King's Score ≥16.7	All >10 mm and >10 portal tracts	Ishak 5 or 6	Derivation sample: 0.86 (114/132)	Derivation sample: 0.80 (376/470)	Derivation sample: 0.91 (0.89-0.94) Validation sample: 0.94 (0.87-1.0)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
King's Score (continued)						
Cirrhosis (continued)						
Cross, 2010 ¹²³	King's Score >24.3	All ≥10 mm or >10 portal tracts; mean 15 mm	Ishak 5 or 6	0.74 (37/50)	0.90 (123/137)	Whole sample: 0.88 (0.82-0.94) Normal AST: 0.96 (0.91-1.0) Elevated AST: 0.78 (0.67-0.88) Liver biopsy <15 mm: 0.94 (0.87-1.0) Liver biopsy >15 mm: 0.82 (0.71-0.90)
Lok Index						
Fibrosis						
Sirli, 2010 ²⁰⁴	Lok Index >0.17	All ≥20 mm and ≥8 portal tracts	METAVIR F2-F4	0.58 (77/134)	0.81 (13/16)	0.70 (0.62-0.77)
Severe Fibrosis						
Cheung, 2008 ¹¹⁷	Lok Index ≥0.2	Not reported	Batts-Ludwig 3 or 4	0.93 (174/187)	0.31 (94/303)	0.69 (0.64-0.74)
Cheung, 2008 ¹¹⁷	Lok Index >0.5	Not reported	Batts-Ludwig 3 or 4	0.51 (95/187)	0.83 (252/303)	0.69 (0.64-0.74)
Cirrhosis						
Castera, 2009 ¹¹²	Lok Index ≥0.2	All ≥10 mm and ≥6 portal tracts; mean 20 mm and 15 portal tracts	METAVIR F4	0.86 (60/70)	0.46 (105/228)	0.80 (0.73-0.86)
Castera, 2009 ¹¹²	Lok Index ≥0.5	All ≥10 mm and ≥6 portal tracts; mean 20 mm and 15 portal tracts	METAVIR F4	0.40 (28/70)	0.94 (215/228)	0.80 (0.73-0.86)
Ehsan, 2008 ¹²⁵	Lok Index >0.6	Mean 12 mm	Ishak 5-6	0.79 (28/35)	0.88 (71/81)	0.88 (CI not reported)
Fontana, 2008 ¹³⁰	Lok Index, cutoff not reported	Mean 1.84 cm	Ishak 5-6	Not reported	Not reported	0.79 (0.74-0.83)
Lackner, 2005 ¹⁵⁶ and Lackner, 2006 ²²⁴	Lok Index ≥0.2	All ≥6 portal tracts	Ishak 5-6	1.0 (32/32)	0.58 (94/162)	Not reported
Lackner, 2005 ¹⁵⁶ and Lackner, 2006 ²²⁴	Lok Index ≥0.5	All ≥6 portal tracts	Ishak 5-6	0.44 (14/32)	0.94 (152/162)	Not reported

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
<i>Lok Index (continued)</i>						
<i>Cirrhosis (continued)</i>						
Lok, 2005 ¹⁶³	Lok Index ≥ 0.2	65% ≥ 1.5 cm, 14% >2.5 cm	Ishak 5-6	Derivation sample: 0.92 (284/309) External validation sample: 0.98 (39/40)	Derivation sample: 0.30 (142/474) External validation sample: 0.53 (119/225)	Derivation sample: 0.78 (0.74-0.81) Internal validation sample: 0.81 (0.75-0.86) External validation sample: 0.91 (0.84-0.97) Fragmented biopsies: 0.72 (0.66-0.78) Nonfragmented biopsies: 0.80 (0.76-0.83) Biopsy <1.5 cm: 0.77 (0.72-0.82) Biopsy 1.5-2.5 cm: 0.80 (0.76-0.84) Biopsy >2.5 cm: 0.79 (0.70-0.88)
Lok, 2005 ¹⁶³	Lok Index ≥ 0.5	65% ≥ 1.5 cm, 14% >2.5 cm	Ishak 5-6	Derivation sample: 0.54 (167/309) External validation sample: 0.53 (21/40)	Derivation sample: 0.85 (403/474) External validation sample: 0.95 (213/225)	Derivation sample: 0.78 (0.74-0.81) Internal validation sample: 0.81 (0.75-0.86) External validation sample: 0.91 (0.84-0.97) Fragmented biopsies: 0.72 (0.66-0.78) Nonfragmented biopsies: 0.80 (0.76-0.83) Biopsy <1.5 cm: 0.77 (0.72-0.82) Biopsy 1.5-2.5 cm: 0.80 (0.76-0.84) Biopsy >2.5 cm: 0.79 (0.70-0.88)
Sebastiani, 2011 ²⁰⁰	Lok Index >0.2	Mean 18 mm and 11 portal tracts; 43% >20 mm	METAVIR F4	Whole sample: Not reported Normal ALT: 0.67 (13/19)	Whole sample: Not reported Normal ALT: 0.35 (202/576)	Whole sample: Not reported Normal ALT: 0.61 (0.57-0.69)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
Lok Index (continued)						
Cirrhosis (continued)						
Sebastiani, 2011 ²⁰⁰	Lok Index >0.5	Mean 18 mm and 11 portal tracts; 43% >20 mm	METAVIR F4	Whole sample: Not reported Normal ALT: 0.52 (10/19)	Whole sample: Not reported Normal ALT: 0.60 (348/576)	Whole sample: Not reported Normal ALT: 0.61 (0.57-0.69)
Sirli, 2010 ²⁰⁴	Lok Index >0.26	All ≥20 mm and ≥8 portal tracts	METAVIR F4	0.87 (13/15)	0.82 (111/135)	0.87 (0.81-0.92)
MP3 Score						
Fibrosis						
Leroy, 2004 ¹⁵⁹	MP3 score >0.20	Not reported	METAVIR F2-F4	0.91 (76/84)	0.35 (36/104)	0.82 (CIs not reported)
Leroy, 2004 ¹⁵⁹	MP3 score >0.30	Not reported	METAVIR F2-F4	0.65 (55/84)	0.85 (88/104)	0.82 (CIs not reported)
Leroy, 2004 ¹⁵⁹	MP3 score >0.40	Not reported	METAVIR F2-F4	0.35 (29/84)	0.96 (100/104)	0.82 (CIs not reported)
Leroy, 2004 ¹⁵⁹	MP3 score >0.50	Not reported	METAVIR F2-F4	0.17 (14/84)	0.99 (103/104)	0.82 (CIs not reported)
Leroy, 2007 ¹⁵⁸	MP3 score >0.20	Median 23 mm and median 17 portal tracts; 89% >15 mm and 45% >25 mm	METAVIR F2-F4	0.96 (87/91)	0.24 (21/89)	Whole sample: 0.84 (0.78-0.90) Excluding patients with biopsy <15 mm or <7 portal tracts (n=161): 0.83 (CI not reported)
Leroy, 2007 ¹⁵⁸	MP3 score >0.30	Median 23 mm and median 17 portal tracts; 89% >15 mm and 45% >25 mm	METAVIR F2-F4	0.82 (75/91)	0.73 (65/89)	Whole sample: 0.84 (0.78-0.90) Excluding patients with biopsy <15 mm or <7 portal tracts (n=161): 0.83 (CI not reported)
Leroy, 2007 ¹⁵⁸	MP3 score >0.40	Median 23 mm and median 17 portal tracts; 89% >15 mm and 45% >25 mm	METAVIR F2-F4	0.44 (40/91)	0.96 (85/89)	Whole sample: 0.84 (0.78-0.90) Excluding patients with biopsy <15 mm or <7 portal tracts (n=161): 0.83 (CI not reported)
Leroy, 2007 ¹⁵⁸	MP3 score >0.50	Median 23 mm and median 17 portal tracts; 89% >15 mm and 45% >25 mm	METAVIR F2-F4	0.44 (40/91)	0.96 (85/89)	Whole sample: 0.84 (0.78-0.90) Excluding patients with biopsy <15 mm or <7 portal tracts (n=161): 0.83 (CI not reported)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
MP3 Score (continued)						
Fibrosis (continued)						
Zarski, 2012 ²²³	MP3 score, cutoff not reported	All ≥20 mm or ≥15 mm and ≥11 portal tracts	METAVIR F2-F4	Not reported	Not reported	0.76 (0.71-0.80)
Severe Fibrosis						
Leroy, 2004 ¹⁵⁹	MP3 score >0.20	Not reported	METAVIR F3-F4	0.94 (34/36)	0.28 (43/152)	0.88 (CIs not reported)
Leroy, 2004 ¹⁵⁹	MP3 score >0.30	Not reported	METAVIR F3-F4	0.85 (31/36)	0.74 (112/152)	0.88 (CIs not reported)
Leroy, 2004 ¹⁵⁹	MP3 score >0.40	Not reported	METAVIR F3-F4	0.58 (21/36)	0.92 (140/152)	0.88 (CIs not reported)
Leroy, 2004 ¹⁵⁹	MP3 score >0.50	Not reported	METAVIR F3-F4	0.26 (9/36)	0.97 (147/152)	0.88 (CIs not reported)
Leroy, 2007 ¹⁵⁸	MP3 score >0.20	Median 23 mm and median 17 portal tracts; 89% >15 mm and 45% >25 mm	METAVIR F3-F4	1.0 (51/51)	0.20 (26/129)	Whole sample: 0.88 (0.82-0.93) Excluding patients with biopsy <15 mm or <7 portal tracts (n=161): 0.89 (CI not reported)
Leroy, 2007 ¹⁵⁸	MP3 score >0.30	Median 23 mm and median 17 portal tracts; 89% >15 mm and 45% >25 mm	METAVIR F3-F4	0.92 (47/51)	0.59 (76/129)	Whole sample: 0.88 (0.82-0.93) Excluding patients with biopsy <15 mm or <7 portal tracts (n=161): 0.89 (CI not reported)
Leroy, 2007 ¹⁵⁸	MP3 score >0.40	Median 23 mm and median 17 portal tracts; 89% >15 mm and 45% >25 mm	METAVIR F3-F4	0.61 (31/51)	0.90 (116/129)	Whole sample: 0.88 (0.82-0.93) Excluding patients with biopsy <15 mm or <7 portal tracts (n=161): 0.89 (CI not reported)
Leroy, 2007 ¹⁵⁸	MP3 score >0.50	Median 23 mm and median 17 portal tracts; 89% >15 mm and 45% >25 mm	METAVIR F3-F4	0.31 (16/51)	0.98 (127/129)	Whole sample: 0.88 (0.82-0.93) Excluding patients with biopsy <15 mm or <7 portal tracts (n=161): 0.89 (CI not reported)
Multibiomarker Score						
Fibrosis						
Park, 2011 ¹⁷⁸	Multibio-marker score, cutoff not reported	Not reported	METAVIR F2-F4	Not reported	Not reported	0.78 (0.68-0.89)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
Pohl Index						
Fibrosis						
Cheung, 2008 ¹¹⁷	Pohl Index positive	Not reported	Batts-Ludwig 2-4	0.07 (21/323)	0.98 (164/167)	0.52 (0.51-0.54)
Cross, 2009 ¹²⁴	Pohl Index positive	All >10 mm and >10 portal tracts	Ishak ≥3	Not reported	Not reported	Derivation sample: 0.53 (0.46-0.59) Validation sample: NR
Pohl, 2001 ¹⁸³	Pohl Index positive	Not reported	METAVIR F2-F4	0.60 (32/54)	0.76 (74/99) [0.75]	Not reported
Severe Fibrosis						
Cheung, 2008 ¹¹⁷	Pohl Index positive	Not reported	Batts-Ludwig 3 or 4	0.09 (17/187)	0.98 (296/303)	0.53 (0.51-0.56)
Iacobellis, 2005b ¹⁴⁸	Pohl Index positive	All ≥5 portal tracts	Scheuer F3 or F4	0.20 (48/243)	0.84 (845/1,009)	Not reported
Iacobellis, 2005b ¹⁴⁸	AST/ALT >1 + platelets <140,000	All ≥5 portal tracts	Scheuer F3 or F4	0.19 (47/243)	0.84 (845/1,009)	Not reported
Khokhar, 2003 ¹⁵⁴	Pohl Index positive	Not reported	METAVIR F3-F4	0.86 (134/157)	0.90 (98/109)	Not reported
Lackner, 2005 ¹⁵⁶ and Lackner, 2006 ²²⁴	Pohl Index positive	All ≥6 portal tracts	Ishak 4-6	0.18 (9/50)	0.98 (141/144)	Not reported
Pohl, 2001 ¹⁸³	Pohl Index positive	Not reported	METAVIR F2-F4	0.42 (15/36) [0.41]	0.99 (116/117)	Not reported
Cirrhosis						
Borroni, 2006 ¹⁰²	Pohl Index positive	All ≥6 portal fields	Knodell 4	0.27 (8/30)	0.99 (196/198)	Not reported
Cross, 2009 ¹²⁴	Pohl Index positive	All >10 mm and >10 portal tracts	Ishak 5 or 6	Not reported	Not reported	Derivation sample: 0.64 (0.55-0.73) Validation sample: NR
Ehsan, 2008 ¹²⁵	Pohl Index positive	Mean 12 mm	Ishak 5 or 6	0.34 (12/35)	0.99 (80/81)	0.66 (CI not reported)
Giannini, 2003a ¹³⁴	AST/ALT ratio ≥1 and platelet count <130,000	Not reported	Scheuer F4 or clinical signs of portal hypertension	0.72 (65/90)	0.99 (160/162)	Not reported
Luo 2002 ¹⁶⁴	AST/ALT ratio ≥1 + platelet count <140,000	All >5 portal tracts	Scheuer F4	0.26 (6/23)	0.98 (86/88)	Not reported

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
Sabadell NIHCED Index						
Severe Fibrosis						
Bejarano, 2009 ⁹⁷	Sabadell NIHCED index >6	Mean 11.6 mm and 12.2 portal tracts	Knodell 3-4	0.72 (137/190)	0.75 (98/131)	(0.74-0.84)
Cirrhosis						
Obrador, 2006 ¹⁷²	Sabadell NIHCED index ≥22	Mean 11.6 mm, 12.2 portal tracts	Knodell F4	Derivation sample: 0.89 (42/47) Validation sample: 0.80 (16/20)	Derivation sample: 0.83 (102/123) Validation sample: 0.96 (136/142)	Derivation sample: 0.91 (0.86-0.96) Validation sample: Not reported
Significant Fibrosis Index						
Fibrosis						
Cheong, 2011 ¹¹⁵	Significant Fibrosis Index, cutoff not reported	Mean 12.6 mm and mean 13.2 portal tracts; 71% had ≥11 portal tracts	METAVIR F2-F4	Not reported	Not reported	0.80 (0.70-0.90)
Zeng Index						
Fibrosis						
Cheong, 2011 ¹¹⁵	Zeng Index, cutoff not reported	Mean 12.6 mm and mean 13.2 portal tracts; 71% had ≥11 portal tracts	METAVIR F2-F4	Not reported	Not reported	0.80 (0.70-0.90)
Other and Unnamed Predictive Indices						
Fibrosis						
Alsatie, 2007 ⁹⁴	5-item predictive index (DM, platelet count, INR, bilirubin, AST) ≥1	All ≥15 mm	METAVIR F2-F4	Derivation sample: 0.88 (53/60) Validation sample: 0.85 (22/26)	Derivation sample: 0.53 (69/130) Validation sample: 0.49 (33/68)	Derivation sample: 0.79 (CI not reported) Validation sample: 0.75 (CI not reported)
Alsatie, 2007 ⁹⁴	5-item predictive index (DM, platelet count, INR, bilirubin, AST) ≥4	All ≥15 mm	METAVIR F2-F4	Derivation sample: 0.38 (23/60) Validation sample: 0.56 (9/26)	Derivation sample: 0.98 (128/130) Validation sample: 0.99 (67/68)	Derivation sample: 0.79 (CI not reported) Validation sample: 0.75 (CI not reported)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
Other and Unnamed Predictive Indices (continued)						
Fibrosis (continued)						
El-Shorbagy, 2004 ¹²⁸	7-item predictive index (platelet count, MMP-9, portal vein diameter, spleen diameter, ALT, AST, viral load) >3	Not reported	G2S2 or G3S3	0.80 (70/87)	0.82 (18/22)	Not reported
Myers, 2002 ¹⁷¹	Historical index (age at infection and biopsy, sex, and alcohol consumption) >0.20	All ≥10 mm	METAVIR F2-F4	0.94 (79/84)	0.21 (27/127)	0.71 (0.67-0.75)
Myers, 2002 ¹⁷¹	Historical index (age at infection and biopsy, sex, and alcohol consumption) >0.60	All ≥10 mm	METAVIR F2-F4	0.24 (20/84)	0.91 (116/127)	0.71 (0.67-0.75)
Testa, 2006 ²⁰⁹	Fibrosis model 1 (BMI, APRI, PLT/SPD) >0.801	All ≥15 mm; mean 24 mm	Ishak ≥3	0.81 (30/37)	0.71 (27/38)	0.80 (0.69-0.88)
Severe Fibrosis						
Metwally, 2007 ¹⁶⁷	3-item predictive index (platelet count, AST, albumin) ≥2	Not reported	METAVIR F3-F4	0.88 (28/32) [0.87]	0.69 (72/105)	0.88 (CI not reported)
Metwally, 2007 ¹⁶⁷	3-item predictive index (platelet count, AST, albumin) ≥4	Not reported	METAVIR F3-F4	0.47 (15/32)	0.99 (104/105)	0.88 (CI not reported)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
<i>Other and Unnamed Predictive Indices (continued)</i>						
<i>Cirrhosis</i>						
El-Shorbagy, 2004 ¹²⁸	7-item predictive index (platelet count, MMP-9, portal vein diameter, spleen diameter, ALT, AST, viral load) >6	Not reported	G3S3	0.80 (16/20)	0.97 (86/89)	Not reported
Kaul, 2002 ¹⁵²	4-item predictive model (male sex, AST, platelet count, spider nevi)	Not reported	Scheuer F4	Not reported	Not reported	Derivation sample: 0.94 (0.91-0.97) Validation sample: 0.93 (CI not reported)
<i>Combined or Sequential Predictive Indices</i>						
<i>Fibrosis</i>						
Boursier, 2012 ¹⁰⁸	SAFE fibrosis algorithm	79% ≥15 mm	METAVIR F2-F4	1.0 (976/976)	0.88 (714/809)	Not reported
Castera, 2010 ¹¹³ (same population as Castera, 2009)	SAFE algorithm (based on APRI and Fibrotest)	All ≥10 mm and ≥6 portal tracts; mean 20 mm and 15 portal tracts	METAVIR F2-F4	1.0 (230/230)	0.87 (63/72)	0.94 (0.90-0.98)
Sebastiani, 2009 ¹⁹⁷	SAFE fibrosis algorithm	Mean 18 mm and mean 10.6 portal tracts	METAVIR F2-F4	Whole sample: 1.0 (931/931) Excluding F4 patients: 1.0 (740/740) Biopsy ≤15 mm: 1.0 (n/N not reported) Biopsy >15 mm: 1.0 (n/N not reported)	Whole sample: 0.77 (850/1104) Excluding F4 patients: 0.82 (905/1104) Biopsy ≤15 mm: 0.80 (n/N not reported) Biopsy >15 mm: 0.79 (n/N not reported)	Whole sample: 0.90 (0.87-0.93) Excluding F4 patients: 1.0 (905/905) Biopsy ≤15 mm: 0.90 (0.88-0.93) Biopsy >15 mm: 0.89 (0.87-0.92)
Sebastiani, 2012 ²⁰¹	SAFE fibrosis algorithm	Mean 20 mm and 11 portal tracts; 45% >20 mm	METAVIR F2-F4	1.0 (552/552)	0.78 (361/461)	0.90 (0.85-0.95)
Sebastiani, 2012 ²⁰¹	Fibropaca algorithm	Mean 20 mm and 11 portal tracts; 45% >20 mm	METAVIR F2-F4	0.86 (472/552)	0.90 (414/461)	0.88 (0.82-0.94)

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
Combined or Sequential Predictive Indices (continued)						
Fibrosis (continued)						
Sebastiani, 2012 ²⁰¹	Leroy algorithm	Mean 20 mm and 11 portal tracts; 45% >20 mm	METAVIR F2-F4	0.90 (495/552)	0.98 (451/461)	0.94 (0.89-0.99)
Snyder, 2007 ²⁰⁶	APRI + FibroSpect II	Mean 25 mm	Batts-Ludwig F2-F4	Not reported	Not reported	0.93 (0.86-0.97)
Severe Fibrosis						
Iacobellis, 2005b ¹⁴⁸	Platelet count <140,000 + globulin/albumin (G/A) ratio >1	All ≥5 portal tracts	Scheuer F3 or F4	0.29 (70/243)	0.84 (850/1,009)	Not reported
Iacobellis, 2005b ¹⁴⁸	globulin/albumin (G/A) ratio >1 + AST/ALT ratio ≥1	All ≥5 portal tracts	Scheuer F3 or F4	0.11 (27/243)	0.82 (829/1,009)	Not reported
Iacobellis, 2005b ¹⁴⁸	Platelet count <140,000 + globulin/albumin (G/A) ratio >1 + AST/ALT ratio ≥1	All ≥5 portal tracts	Scheuer F3 or F4	0.09 (22/243)	0.82 (827/1,009)	Not reported
Cirrhosis						
Borroni, 2006 ¹⁰²	APRI and age-platelet index, cutoff not reported (Combination A)	All ≥6 portal fields	Knodell 4	0.37 (11/30)	0.98 (194/198)	Not reported
Borroni, 2006 ¹⁰²	APRI and age-platelet index, cutoff not reported (Combination B)	All ≥6 portal fields	Knodell 4	0.73 (22/30)	0.83 (164/198)	Not reported
Boursier, 2012 ¹⁰⁸	SAFE fibrosis algorithm	79% ≥15 mm	METAVIR F4	0.62 (140/227)	0.93 (1,455/1,558)	Not reported
Castera, 2010 ¹¹³ (same population as Castera, 2009)	SAFE algorithm (based on APRI and Fibrotest)	All ≥10 mm and ≥6 portal tracts; mean 20 mm and 15 portal tracts	METAVIR F4	0.86 (64/74)	0.90 (205/228)	0.87 (0.84-0.90)
Crisan, 2012 ¹²²	APRI + FibroMeter	All >5 portal tracts; median 11 mm and mean 14 portal tracts	METAVIR F2-F4	0.79 (224/283)	0.88 (144/163)	Not reported

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
Combined or Sequential Predictive Indices (continued)						
Cirrhosis (continued)						
Crisan, 2012 ¹²²	APRI + FibroMeter	All >5 portal tracts; median 11 mm and mean 14 portal tracts	METAVIR F3-F4	0.78 (95/122)	0.84 (273/324)	Not reported
Crisan, 2012 ¹²²	APRI + Fibrotest	All >5 portal tracts; median 11 mm and mean 14 portal tracts	METAVIR F2-F4	0.79 (224/283)	0.88 (144/163)	Not reported
Crisan, 2012 ¹²²	APRI + Fibrotest	All >5 portal tracts; median 11 mm and mean 14 portal tracts	METAVIR F3-F4	0.90 (109/122)	0.78 (252/324)	Not reported
Crisan, 2012 ¹²²	FIB-4 + FibroMeter	All >5 portal tracts; median 11 mm and mean 14 portal tracts	METAVIR F2-F4	0.76 (214/283)	0.92 (150/163)	Not reported
Crisan, 2012 ¹²²	FIB-4 + FibroMeter	All >5 portal tracts; median 11 mm and mean 14 portal tracts	METAVIR F3-F4	0.84 (103/122)	0.90 (293/324)	Not reported
Crisan, 2012 ¹²²	FIB-4 + Fibrotest	All >5 portal tracts; median 11 mm and mean 14 portal tracts	METAVIR F2-F4	0.76 (214/283)	0.84 (137/163)	Not reported
Crisan, 2012 ¹²²	FIB-4 + Fibrotest	All >5 portal tracts; median 11 mm and mean 14 portal tracts	METAVIR F3-F4	0.89 (109/122)	0.82 (264/324)	Not reported
Crisan, 2012 ¹²²	APRI + FIB-4 + Fibrometer	All >5 portal tracts; median 11 mm and mean 14 portal tracts	METAVIR F2-F4	0.80 (226/283)	0.95 (155/163)	Not reported
Crisan, 2012 ¹²²	APRI + FIB-4 + Fibrometer	All >5 portal tracts; median 11 mm and mean 14 portal tracts	METAVIR F3-F4	0.84 (103/122)	0.91 (295/324)	Not reported
Crisan, 2012 ¹²²	APRI + FIB-4 + Fibrotest	All >5 portal tracts; median 11 mm and mean 14 portal tracts	METAVIR F2-F4	0.74 (209/283)	0.95 (155/163)	Not reported
Crisan, 2012 ¹²²	APRI + FIB-4 + Fibrotest	All >5 portal tracts; median 11 mm and mean 14 portal tracts	METAVIR F3-F4	0.88 (108/122)	0.83 (270/324)	Not reported

Supplemental Table 2. Key Question 4a: Diagnostic accuracy indices (continued)

Study, Year	Test and Cutoff	Biopsy Quality	Diagnosis	Sensitivity	Specificity	Area Under the Receiver Operating Curve
<i>Combined or Sequential Predictive Indices (continued)</i>						
<i>Cirrhosis (continued)</i>						
Luo, 2002 ¹⁶⁴	AST/ALT ratio ≥ 1 + globulin/albumin ratio ≥ 1	All >5 portal tracts	Scheuer F4	0.39 (9/23)	1.0 (88/88)	Not reported
Luo, 2002 ¹⁶⁴	Globulin/albumin ratio ≥ 1 + platelet count <140,000	All >5 portal tracts	Scheuer F4	0.39 (9/23)	1.0 (88/88)	Not reported
Sebastiani, 2009 ¹⁹⁷	SAFE cirrhosis algorithm	Mean 18 mm and mean 10.6 portal tracts	METAVIR F4	Whole sample: 0.90 (173/191) Excluding F0 and F1 patients: 0.53 (100/191) Biopsy ≤ 15 mm: 0.84 (n/N not reported) Biopsy >15 mm: 0.96 (n/N not reported)	Whole sample: 0.93 (1709/1844) Excluding F0 and F1 patients: 0.92 (683/740) Biopsy ≤ 15 mm: 0.91 (n/N not reported) Biopsy >15 mm: 0.92 (n/N not reported)	Whole sample: 0.92 (0.89-0.94) Excluding F0 and F1 patients: 0.77 (0.73-0.81) Biopsy ≤ 15 mm: 0.88 (0.83-0.93) Biopsy >15 mm: 0.94 (0.91-0.97)
Sebastiani, 2012 ²⁰¹	SAFE cirrhosis algorithm	Mean 20 mm and 11 portal tracts; 45% >20 mm	METAVIR F4	0.82 (92/113)	0.92 (832/900)	0.87 (0.81-0.93)
Sebastiani, 2012 ²⁰¹	Fibropaca algorithm	Mean 20 mm and 11 portal tracts; 45% >20 mm	METAVIR F4	0.73 (82/113)	0.97 (870/900)	0.85 (0.79-0.91)

^a Study reports different AUROCs for the same index and diagnosis.

Supplemental Table 3. Key Question 4a: Diagnostic accuracy direct comparisons (based on areas under the receiver operating characteristic curve)

Study, Year	Country	N	Diagnosis	Age-Platelet Index	APRI	AST/ALT Ratio	FibroMeter	Fibrotest	Forns' Index	Hepascore	Platelet Count	Other Predictive Index
Adams, 2005 ⁹¹	Australia	117 (derivation sample)	A: Fibrosis (METAVIR F2-F4) B: Severe fibrosis (METAVIR F3-F4) C: Cirrhosis (METAVIR F4)	—	—	—	—	A: 0.79 (0.71-0.88) B: 0.91 (0.83-0.98) C: 0.97 (0.92-1.0)	—	A: 0.85 (0.78-0.93) B: 0.96 (0.92-1.0) C: 0.94 (0.92-1.0)	—	—
Adler, 2008 ⁹²	Belgium	152	A: Fibrosis (METAVIR F2-F4) B: Severe fibrosis (METAVIR F3-F4) C: Cirrhosis (METAVIR F4)	—	A: 0.74 B: 0.89 C: 0.92	—	—	A: 0.79 B: 0.90 C: 0.92	A: 0.75 B: 0.90 C: 0.89	—	—	Fibroindex A: 0.69 B: 0.87 C: 0.92 FIB-4 A: 0.79 B: 0.90 C: 0.92
Ahmad, 2011 ^{a 93}	Pakistan	157	A: Fibrosis (METAVIR F2-F4) B: Cirrhosis: METAVIR F4)	—	A: 0.88	B: 0.61 (0.48-0.74) for cutoff >1, 0.47 (0.38-0.56) for cutoff <1	—	—	—	—	A: 0.94 (0.90-0.97) B: 0.99 (0.98-1.0)	Fibrosis Index A: 0.94 (0.90-0.97) B: 0.99 0.98-1.0) Fibrosis-cirrhosis index A: 0.93 (0.90-0.97) B: 1.0 (0.99-1.0)
Borroni, 2006 ¹⁰²	Italy	228	Cirrhosis (Knodell F4)	0.88 (0.82-0.94)	0.86 (0.79-0.93)	0.76 (0.68-0.84)	—	—	—	—	—	Cirrhosis Discriminant Score: 0.83 (0.75-0.92)

Supplemental Table 3. Key Question 4a: Diagnostic accuracy direct comparisons (based on areas under the receiver operating characteristic curve) (continued)

Study, Year	Country	N	Diagnosis	Age-Platelet Index	APRI	AST/ALT Ratio	FibroMeter	Fibrotest	Forns' Index	Hepascore	Platelet Count	Other Predictive Index
Bota, 2011 ¹⁰³	Romania	212	A: Fibrosis (METAVIR F2-F4) B: Severe fibrosis (METAVIR F3-F4) C: Cirrhosis (METAVIR F4)	—	A: 0.69 B: 0.82 C: 0.88	—	—	—	A: 0.74 B: 0.80 C: 0.85	—	—	King's Score A: 0.76 B: 0.82 C: 0.89
Bourliere, 2008 ¹⁰⁴	France	467	A: Fibrosis (METAVIR F2-F4) B: Severe fibrosis (METAVIR F3-F4) C: Cirrhosis (METAVIR F4)	—	—	—	—	A: 0.83 (0.79-0.86) B: 0.84 (0.80-0.87) C: 0.89 (0.86-0.93)	—	A: 0.82 (0.79-0.86) B: 0.84 (0.80-0.87) C: 0.90 (0.87-0.93)	—	—
Bourliere, 2006 ¹⁰⁵	France	235	Fibrosis (METAVIR F2-F4)	—	0.71 (0.67-0.79)	—	—	0.81 (0.76-0.86)	0.76 (0.70-0.82)	—	—	—
Boursier, 2009 ¹⁰⁶	France	1,056	A: Severe fibrosis (METAVIR F3-F4) B: Cirrhosis (METAVIR F4)	—	A: 0.82 (0.79-0.85) B: 0.84 (0.80-0.88)	—	Fibrometer A: 0.88 (0.86-0.91) B: 0.91 (0.88-0.93) Modified Fibrometer A: Not reported B: 0.92 (CI not reported)	A: 0.84 (0.81-0.86) B: 0.88 (0.86-0.91)	—	A: 0.83 (0.81-0.86) B: 0.90 (0.87-0.92)	—	—
Cales, 2008 ¹¹⁰	France	1,056	Fibrosis (METAVIR F2-F4)	—	0.79 (CI not reported)	—	0.85 (CI not reported)	0.81 (CI not reported)	—	0.78 (CI not reported)	—	FIB-4: 0.80 (CI not reported)

Supplemental Table 3. Key Question 4a: Diagnostic accuracy direct comparisons (based on areas under the receiver operating characteristic curve) (continued)

Study, Year	Country	N	Diagnosis	Age-Platelet Index	APRI	AST/ALT Ratio	FibroMeter	Fibrotest	Forns' Index	Hepascore	Platelet Count	Other Predictive Index
Cales, 2010 ¹¹¹	France	1,056	Cirrhosis (METAVIR F4)	—	—	—	Fibrometer: 0.91 (0.88-0.93) Fibrometer 3G: 0.89 (0.87-0.92)	0.88 (0.86-0.91)	—	0.89 (0.86-0.92)	—	—
Castera, 2009 ^{e293}	France	298	Cirrhosis (METAVIR F4)	—	0.80 (0.74-0.86)	0.61 (0.53-0.70)	—	0.82 (0.73-0.86)	—	—	0.79 (0.72-0.85)	Lok Index: 0.80 (0.73-0.86)
Castera, 2005 ¹¹⁴	France	193	A: Fibrosis (METAVIR F2-F4) B: Severe fibrosis (METAVIR F3-F4)	—	A: 0.78 (0.70-0.85) B: 0.84 (0.78-0.89)	—	—	A: 0.85 (0.78-0.90) B: 0.90 (0.85-0.94)	—	—	—	—
Cheong, 2011 ¹¹⁵	Korea	79 (derivation sample)	Fibrosis (METAVIR F2-F4)	—	0.82 (0.72-0.92)	—	—	—	0.80 (0.70-0.90)	—	—	Significant Fibrosis Index: 0.80 (0.70-0.90) ELF index: 0.72 (0.60-0.84) FIB-4: 0.80 (0.80-0.90) Zeng Index: 0.80 (0.70-0.90)
Cheung, 2011 ¹¹⁶	Belgium	73 (validation sample)	A: Fibrosis (METAVIR F2-F4) B: Severe fibrosis (METAVIR F3-F4) C: Cirrhosis (METAVIR F4)	—	A: 0.72 (0.60-0.85) B: 0.87 (0.75-0.98) C: 0.92 (0.84-1.0)	—	—	—	—	—	—	Fibrosis-protein index A: 0.82 (0.73-0.92) B: 0.92 (0.86-0.99) C: 0.88 (0.77-0.98)

Supplemental Table 3. Key Question 4a: Diagnostic accuracy direct comparisons (based on areas under the receiver operating characteristic curve) (continued)

Study, Year	Country	N	Diagnosis	Age-Platelet Index	APRI	AST/ALT Ratio	FibroMeter	Fibrotest	Forns' Index	Hepascore	Platelet Count	Other Predictive Index
Cheung, 2008 ¹¹⁷	USA	490	A: Fibrosis (Batts-Ludwig F2-F4) B: Severe fibrosis (Batts-Ludwig F3-F4)	—	A: 0.69 (0.64-0.74) B: 0.76 (0.71-0.81)	A: 0.54 (0.48-0.59) B: 0.52 (0.47-0.58)	—	—	—	—	A: 0.60 (0.56-0.63) for <150; 0.52 (0.51-0.53) for <100 B: 0.64 (0.60-0.68) for <150; 0.53 (0.52-0.55) for <100	Pohl Index A: 0.52 (0.51-0.54) B: 0.53 (0.51-0.56)
Cobbold, 2009 ²²⁹	UK	67	A: Fibrosis (Ishak ≥3) B: Cirrhosis (Ishak 5-6)	—	A: 0.83 (0.73-0.93) B: 0.86 (0.75-0.97)	—	—	—	—	—	—	ELF Index A: 0.82 (0.73-0.92) B: 0.91 (0.82-1.0)
Crisan, 2012 ¹²²	Romania	446	A: Fibrosis (METAVIR F2-F4) B: Severe fibrosis (METAVIR F3-F4)	—	A: 0.73 B: 0.74	—	A: 0.80 B: 0.81	A: 0.78 B: 0.78	A: 0.68 B: 0.74	A: 0.69 B: 0.70	—	FIB-4 A: 0.71 B: 0.77

Supplemental Table 3. Key Question 4a: Diagnostic accuracy direct comparisons (based on areas under the receiver operating characteristic curve) (continued)

Study, Year	Country	N	Diagnosis	Age-Platelet Index	APRI	AST/ALT Ratio	FibroMeter	Fibrotest	Forns' Index	Hepascore	Platelet Count	Other Predictive Index
Cross, 2009 ¹²⁴	UK	602 (derivation sample) 105 (validation sample)	A: Fibrosis (Ishak ≥3) B: Cirrhosis (Ishak 5-6)	A: 0.77 (0.73-0.81) B: 0.90 (0.86-0.93)	AL 0.76 (0.72-0.80) B: 0.88 (0.85-0.92)	A: 0.58 (0.51-0.64) B: 0.68 (0.60-0.75)	—	—	—	—	A: 0.66 (0.60-0.72) B: 0.88 (0.85-0.91)	Cirrhosis Discriminant Score A: 0.67 (0.62-0.72) B: 0.74 (0.68-0.81) FIB-4 A: 0.76 (0.68-0.83) B: 0.91 (0.89-0.94) King's Score A: 0.79 (0.75-0.83) B: 0.91 (0.89-0.94) Pohl Index A: 0.53 (0.46-0.59) B: 0.64 (0.55-0.73)

Supplemental Table 3. Key Question 4a: Diagnostic accuracy direct comparisons (based on areas under the receiver operating characteristic curve) (continued)

Study, Year	Country	N	Diagnosis	Age-Platelet Index	APRI	AST/ALT Ratio	FibroMeter	Fibrotest	Forns' Index	Hepascore	Platelet Count	Other Predictive Index
Ehsan, 2008 ¹²⁵	Egypt	116	Cirrhosis (Ishak 5-6)	0.91 (CI not reported)	0.86 (CI not reported)	0.65 (CI not reported)	—	—	—	—	—	Lok Index: 0.88 (CI not reported) Cirrhosis discriminate score: 0.87 (CI not reported) Goteborg University Cirrhosis Index: 0.86 (CI not reported) Pohl Index: 0.66 (CI not reported)
El-Sayed, 2011 ¹²⁷	Egypt	37	Severe fibrosis (METAVIR F3-F4)	—	0.63	0.76	—	—	—	—	—	—
Fabris, 2008 ¹²⁹	Italy	167	A: Fibrosis (METAVIR F2-F4) B: Cirrhosis (METAVIR F4)	A: 0.64 (0.56-0.72) B: 0.67 (0.59-0.74)	A: 0.72 (0.64-0.79) B: 0.86 (0.79-0.90)	A: 0.59 (0.51-0.66) B: 0.66 (0.58-0.73)	—	—	A: 0.70 (0.62-0.76) B: 0.86 (0.80-0.91)	—	—	Cirrhosis Discriminant Score A: 0.64 (0.56-0.71) B: 0.71 (0.64-0.78) Fibroindex A: 0.71 (0.63-0.77) B: 0.86 (0.80-0.91)

Supplemental Table 3. Key Question 4a: Diagnostic accuracy direct comparisons (based on areas under the receiver operating characteristic curve) (continued)

Study, Year	Country	N	Diagnosis	Age-Platelet Index	APRI	AST/ALT Ratio	FibroMeter	Fibrotest	Forns' Index	Hepascore	Platelet Count	Other Predictive Index
Fontana, 2008 ¹³⁰	USA	513	Cirrhosis (Ishak 5-6)	—	0.73 (0.69-0.78)	—	—	—	—	—	—	Cirrhosis Discriminant Score 0.70 (0.66-0.75) HALT-C model: 0.81 (0.77-0.85) Lok Index: 0.79 (0.74-0.83)
Giannini, 2003b ¹³⁵	Italy	239	Fibrosis (criteria not reported)	—	A: 0.77 (CI not reported) B: 0.81 (CI not reported)	A: 0.82 (CI not reported) B: 0.91 (CI not reported)	—	—	—	—	—	—
Güzelbulut, 2011 ¹⁴²	Turkey	150	A: Fibrosis (METAVIR F2-F4) B: Cirrhosis (METAVIR F4)	—	A: 0.77 (0.73-0.86) B: 0.84 (0.77-0.91)	—	—	—	A: 0.80 (0.73-0.86) B: 0.88 (0.82-0.90)	—	—	FIB-4 A: 0.76 (0.69-0.84) B: 0.87 (0.82-0.93)
Halfon, 2007 ^{b,d145}	France	356	A: Fibrosis (METAVIR F2-F4) B: Severe fibrosis (METAVIR F3-F4) C: Cirrhosis (METAVIR F4)	—	A: 0.76 (0.72-0.81) B: 0.81 (0.76-0.85) C: 0.92 (0.88-0.94)	—	A: 0.78 (0.73-0.82) B: 0.84 (0.80-0.88) C: 0.94 (0.91-0.96)	A: 0.79 (0.75-0.83) B: 0.81 (0.77-0.85) C: 0.86 (0.82-0.89)	—	A: 0.76 (0.71-0.80) B: 0.81 (0.76-0.85) C: 0.89 (0.86-0.92)	—	—

Supplemental Table 3. Key Question 4a: Diagnostic accuracy direct comparisons (based on areas under the receiver operating characteristic curve) (continued)

Study, Year	Country	N	Diagnosis	Age-Platelet Index	APRI	AST/ALT Ratio	FibroMeter	Fibrotest	Forns' Index	Hepascore	Platelet Count	Other Predictive Index
Islam, 2005 ¹⁵¹	Sweden	179	A: Fibrosis (Ishak ≥3) B: Cirrhosis (Ishak 5-6)	—	A: 0.71 (CI not reported) B: 0.83 (CI not reported)	—	—	—	—	—	—	Goteborg University Fibrosis Index A: 0.72 (CI not reported) B: 0.85 (CI not reported)
Ben Jazia, 2009 ⁹⁸	Tunisia	35	Fibrosis (METAVIR F2-F4)	—	0.91 (CI not reported)	0.68 (CI not reported)	—	—	—	—	0.38 (CI not reported)	—
Koda, 2007 ¹⁵⁵	Japan	240 (derivation sample) 162 (validation sample)	A: Fibrosis (METAVIR F2-F4) B: Severe fibrosis (METAVIR F3-F4)	—	A: 0.79 (0.74-0.85) B: 0.80 (0.74-0.86)	—	—	—	A: 0.79 (0.73-0.84) B: 0.77 (0.70-0.83)	—	—	Fibroindex A: 0.83 (0.78-0.88) B: 0.81 (0.76-0.87)
Koda, 2007 ¹⁵⁵	Japan	162 (validation sample)	A: Fibrosis (METAVIR F2-F4) B: Severe fibrosis (METAVIR F3-F4)	—	A: 0.82 (0.76-0.88) B: 0.81 (0.74-0.88)	—	—	—	A: 0.84 (0.77-0.90) B: 0.83 (0.77-0.89)	—	—	Fibroindex A: 0.86 (0.81-0.92) B: 0.85 (0.79-0.91)
Lackner, 2005 ¹⁵⁶ and Lackner, 2006 ²²⁴	Austria	194	A: Fibrosis (Ishak ≥3) B: Cirrhosis (Ishak 5-6)	A: 0.74 (0.67-0.81) B: 0.91 (0.87-0.96)	A: 0.80 (0.73-0.86) B: 0.90 (0.85-0.95)	A: 0.57 (0.48-0.65) B: 0.73 (0.63-0.83)	—	—	—	—	A: 0.71 (0.64-0.79) B: 0.89 (0.83-0.94)	Cirrhosis Discriminant Score A: 0.71 (0.63-0.79) B: 0.91 (0.85-0.96)

Supplemental Table 3. Key Question 4a: Diagnostic accuracy direct comparisons (based on areas under the receiver operating characteristic curve) (continued)

Study, Year	Country	N	Diagnosis	Age-Platelet Index	APRI	AST/ALT Ratio	FibroMeter	Fibrotest	Forns' Index	Hepascore	Platelet Count	Other Predictive Index
Leroy, 2008 ¹⁵⁷	France	825	A: Fibrosis (METAVIR F2-F4) B: Severe fibrosis (METAVIR F3-F4) C: Cirrhosis (METAVIR F4)	—	A: 0.79 (0.76-0.82) B: 0.84 (0.80-0.87) C: 0.86 (0.82-0.90)	—	A: 0.84 (0.81-0.87) B: 0.89 (0.87-0.92) C: 0.93 (0.90-0.95)	A: 0.80 (0.77-0.83) B: 0.85 (0.82-0.88) C: 0.89 (0.86-0.92)	—	A: 0.78 (0.75-0.81) B: 0.84 (0.81-0.87) C: 0.89 (0.86-0.93)	—	—
Leroy, 2007 ^{d158}	France	180	A: Fibrosis (METAVIR F2-F4) B: Severe fibrosis (METAVIR F3-F4)	—	A: 0.81 (0.74-0.88) B: 0.82 (0.74-0.90)	—	A: 0.86 (0.80-0.91) B: 0.91 (0.86-0.96)	A: 0.84 (0.79-0.90) B: 0.87 (0.81-0.93)	A: 0.78 (0.71-0.85) B: 0.78 (0.71-0.87)	A: 0.79 (0.72-0.85) B: 0.85 (0.80-0.92)	—	MP3 score A: 0.84 (0.78-0.90) B: 0.88 (0.82-0.93)
Liu, 2006 ¹⁶⁰	Taiwan	79	Fibrosis (METAVIR F2-F4)	A: 0.64 (0.51-0.77)	A: 0.67 (0.54-0.81)	A: 0.50 (0.35-0.66)	—	—	—	—	—	—
Martinez, 2011 ¹⁶⁵	Spain	340	A: Fibrosis (METAVIR F2-F4) B: Severe fibrosis (METAVIR F3-F4) C: Cirrhosis (METAVIR F4)	—	A: 0.83 (0.79-0.88) B: 0.86 (0.82-0.90) C: 0.86 (0.82-0.90)	—	—	—	A: 0.83 (0.78-0.87) B: 0.85 (0.81-0.89) C: 0.87 (0.83-0.91)	—	—	Simplified ELF index A: 0.81 (0.76-0.86) B: 0.83 (0.79-0.87) C: 0.82 (0.78-0.87) FIB-4 A: 0.85 (0.81-0.89) B: 0.87 (0.83-0.91) C: 0.89 (0.85-0.92)

Supplemental Table 3. Key Question 4a: Diagnostic accuracy direct comparisons (based on areas under the receiver operating characteristic curve) (continued)

Study, Year	Country	N	Diagnosis	Age-Platelet Index	APRI	AST/ALT Ratio	FibroMeter	Fibrotest	Forns' Index	Hepascore	Platelet Count	Other Predictive Index
Myers, 2003 ¹⁷⁰	France	323	A: Fibrosis (METAVIR F2-F4) B: Severe fibrosis (METAVIR F3-F4)	A: 0.72 (0.69-0.75) B: 0.81 (0.78-0.84)	—	—	—	A: 0.84 (0.82-0.86) B: 0.92 (0.90-0.94)	—	—	A: 0.67 (0.64-0.70) B: 0.74 (0.70-0.78)	—
Myers, 2002 ¹⁷¹	France	211	A: Fibrosis (METAVIR F2-F4) B: Severe fibrosis (METAVIR F3-F4)	—	—	—	—	A: 0.80 (0.76-0.83) B: 0.92 (0.89-0.95)	—	—	—	Historical index A: 0.71 (0.67-0.75) B: 0.76 (0.71-0.81)
Parise, 2006 ¹⁷⁶	Brazil	206	A: Fibrosis (Batts-Ludwig F2-F4) B: Cirrhosis (Batts-Ludwig F4)	—	A: 0.82 (0.77-0.88) B: 0.84 (0.77-0.90)	A: 0.59 (0.51-0.67) B: 0.65 (0.56-0.75)	—	—	—	—	—	—
Park, 2011 ¹⁷⁸	Korea	91	Fibrosis (METAVIR F2-F4)	—	0.79 (0.69-0.89)	—	—	—	—	—	—	Multi-biomarker score: 0.78 (0.68-0.89)
Patel, 2009 ¹⁸⁰	France, Germany, Canada	95	Fibrosis (METAVIR F2-F4)	—	—	—	—	0.89 (0.81-0.97)	—	—	—	FibroSpect II: 0.90 (0.84-0.96)
Romera, 2006 ¹⁸⁹	Spain	131	Fibrosis (Scheuer F2-F4)	—	0.70 (CI not reported)	—	—	—	0.71 (CI not reported)	—	—	Fibrosis Probability Index: 0.80 (CI not reported)

Supplemental Table 3. Key Question 4a: Diagnostic accuracy direct comparisons (based on areas under the receiver operating characteristic curve) (continued)

Study, Year	Country	N	Diagnosis	Age-Platelet Index	APRI	AST/ALT Ratio	FibroMeter	Fibrotest	Forns' Index	Hepascore	Platelet Count	Other Predictive Index
Sebastiani, 2008 ^{g198}	Italy	244 (80 normal ALT, 164 elevated ALT)	Fibrosis (METAVIR F2-F4)	—	Normal ALT: 0.69 (0.54-0.85) Elevated ALT: 0.75 (0.65-0.85)	Normal ALT: 0.51 (0.40-0.62) Elevated ALT: 0.54 (0.48-0.60)	—	Normal ALT: 0.70 (0.59-0.81) Elevated ALT: 0.79 (0.74-0.84)	Normal ALT: 0.60 (0.50-0.71) Elevated ALT: 0.76 (0.71-0.81)	—	—	Fibroindex Normal ALT: 0.58 (0.43-0.73) Elevated ALT: 0.74 (0.63-0.85)
Sebastiani, 2006 ^{g199}	Italy	190	A: Fibrosis (METAVIR F2-F4) B: Cirrhosis (METAVIR F4)	—	A: 0.69 (0.54-0.85) (elevated ALT) and 0.77 (0.63-0.91) (normal ALT) B: 0.61 (0.49-0.73) (whole sample)	—	—	A: 0.81 (0.72-0.91) (elevated ALT) and 0.71 (0.49-0.92) (normal ALT) B: 0.71 (0.60-0.82) (whole sample)	A: 0.79 (0.68-0.90) (elevated ALT) and 0.58 (0.43-0.73) (normal ALT) B: Not reported	—	—	—

Supplemental Table 3. Key Question 4a: Diagnostic accuracy direct comparisons (based on areas under the receiver operating characteristic curve) (continued)

Study, Year	Country	N	Diagnosis	Age-Platelet Index	APRI	AST/ALT Ratio	FibroMeter	Fibrotest	Forns' Index	Hepascore	Platelet Count	Other Predictive Index
Sebastiani, 2011 ²⁰⁰	Europe	1,810	A: Fibrosis (METAVIR F2-F4) B: Cirrhosis (METAVIR F4)	—	A: 0.70 (0.65-0.75) (whole sample) and 0.63 (0.57-0.71) (normal ALT) B: 0.76 (0.71-0.81) (whole sample) and 0.65 (0.60-0.70) (normal ALT)	B: 0.53 (0.46-0.58) (normal ALT)	—	A: 0.70 (0.65-0.75) (whole sample) and 0.62 (0.58-0.66) (normal ALT) B: 0.72 (0.67-0.77) (whole sample) and 0.65 (0.60-0.70) (normal ALT)	A: 0.60 (0.55-0.65) (normal ALT)	—	B: 0.64 (0.58-0.70) (normal ALT)	FIB-4 A: 0.61 (0.56-0.66) (normal ALT) Lok Index B: 0.61 (0.57-0.69) (normal ALT)
Sebastiani, 2012 ²⁰¹	Europe	1,013	A: Fibrosis (METAVIR F2-F4) B: Cirrhosis (METAVIR F4)	—	A: 0.70 (0.64-0.76) B: 0.77 (0.71-0.83)	—	—	A: 0.71 (0.64-0.78) B: 0.72 (0.67-0.77)	A: 0.64 (0.58-0.70)	—	—	—
Sirli, 2010 ²⁰⁴	Romania	150	A: Fibrosis (METAVIR F2-F4) B: Cirrhosis (METAVIR F4)	—	A: 0.77 (0.69-0.83) B: 0.91 (0.85-0.95)	—	—	—	A: 0.75 (0.67-0.82) B: 0.91 (0.85-0.95)	—	A: 0.73 (0.65-0.80) B: 0.90 (0.84-0.94)	FIB-4 A: 0.69 (0.60-0.76) B: 0.84 (0.77-0.90) Lok Index A: 0.70 (0.62-0.77) B: 0.87 (0.81-0.92)

Supplemental Table 3. Key Question 4a: Diagnostic accuracy direct comparisons (based on areas under the receiver operating characteristic curve) (continued)

Study, Year	Country	N	Diagnosis	Age-Platelet Index	APRI	AST/ALT Ratio	FibroMeter	Fibrotest	Forns' Index	Hepascore	Platelet Count	Other Predictive Index
Snyder, 2007 ²⁰⁶	USA	93	Fibrosis (Batts-Ludwig F2-F4)	—	0.89 (0.81-0.92)	—	—	—	—	—	—	FIBROSpect II: 0.88 (0.79-0.94)
Wilson, 2006 ²¹⁹	USA	119	Ishak 3-4 fibrosis	—	0.70 (CI not reported)	—	—	0.74 (CI not reported)	—	—	—	—
Zarski, 2012 ²²³	France	436	A: Fibrosis (METAVIR F2-F4) B: Cirrhosis (METAVIR F4)	—	A: 0.76 (0.72-0.81) B: 0.86 (0.81-0.91)	—	A: 0.82 (0.78-0.86) B: 0.89 (0.86-0.93)	A: 0.80 (0.75-0.84) B: 0.86 (0.83-0.90)	A: 0.75 (0.71-0.80)	A: 0.82 (0.78-0.85) B: 0.89 (0.86-0.93)	—	MP3 A: 0.76 (0.71-0.80) ELF A: 0.78 (0.74-0.83) B: 0.88 (0.83-0.92) FIB-4 B: 0.83 (0.76-0.89)

^a Study reports different AUROCs for the same index and diagnosis.

^b Evaluated overlapping populations from the FIBROPACA study.

^c Evaluated the same population.

^d Population included in Cales 2008.

^e Incorporated population evaluated in Castera 2005.

^f Evaluated same population.

^g Populations substantially overlap.

References

1. Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med.* 2006;144(10):705-14. PMID: 16702586.
2. Davis GL, Alter MJ, El-Serag H, et al. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology.* 2010;138(2):513-21.e6. PMID: 19861128.
3. Wasley A, Grytdal S, Gallagher K, et al. Surveillance for acute viral hepatitis--United States, 2006. *MMWR Surveill Summ.* 2008;57(2):1-24. PMID: 18354374.
4. National Center for HIV/AIDS VH, STD & TB Prevention,. Disease Burden from Viral Hepatitis A, B, and C in the United States [pdf]. Center for Disease Control; 2011. www.cdc.gov/hepatitis/Statistics/2009Surveillance/PDFs/2009HepSurveillanceRpt.pdf. Accessed on May 31, 2012.
5. Ly KN, Xing J, Klevens RM, et al. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. *Ann Intern Med.* 2012;156(4):271-8. PMID: 22351712.
6. Busch MP. Insights into the epidemiology, natural history and pathogenesis of hepatitis C virus infection from studies of infected donors and blood product recipients. *Transfusion Clinique et Biologique.* 2001;8(3):200-6. PMID: 11499958.
7. Kim WR. The burden of hepatitis C in the United States. *Hepatology.* 2002;36(5 Suppl 1):S30-S4. PMID: 12407574.
8. El-Serag HB. Hepatocellular carcinoma: recent trends in the United States. *Gastroenterology.* 2004;127(5 Suppl 1):S27-S34. PMID: 15508094.
9. Foster G, Goldin R, Thomas H. Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis. *Hepatology.* 1998;27:209 - 12. PMID: 9425939.
10. Rowan PJ, Al-Jurdi R, Tavakoli-Tabasi S, et al. Physical and psychosocial contributors to quality of life in veterans with hepatitis C not on antiviral therapy. *J Clin Gastroenterol.* 2005;39(8):731-6. PMID: 16082286.
11. Koff RS. Impaired health-related quality of life in chronic hepatitis C: the how, but not the why. *Hepatology.* 1999;29(1):277-9. PMID: 9862878.
12. Rodger AJ, Jolley D, Thompson SC, et al. The impact of diagnosis of hepatitis C virus on quality of life. *Hepatology.* 1999 Nov;30(5):1299-301. PMID: 10534353.
13. Kenny-Walsh E. Clinical outcomes after hepatitis C infection from contaminated anti-D immune globulin. *Irish Hepatology Research Group. N Engl J Med.* 1999;340(16):1228-33. PMID: 10210705.
14. Hagan H, Pouget ER, Des Jarlais DC, et al. Meta-regression of hepatitis C virus infection in relation to time since onset of illicit drug injection: the influence of time and place. *CORD Conference Proceedings.* 2008;168(10):1099-109. PMID: 18849303.
15. Alter H. Discovery of non-A, non-B hepatitis and identification of its etiology. *Am J Med.* 1999;107(6B):16S-20S. PMID: 10653450.
16. Kaur S, Rybicki L, Bacon BR, et al. Performance characteristics and results of a large-scale screening program for viral hepatitis and risk factors associated with exposure to viral hepatitis B and C: results of the National Hepatitis Screening Survey. *National Hepatitis Surveillance Group. Hepatology.* 1996 Nov;24(5):979-86. PMID: 8903363.
17. Yawn BP, Gazzuola L, Wollan PC, et al. Development and maintenance of a community-based hepatitis C registry. *Am J Manage Care.* 2002 Mar;8(3):253-61. PMID: 11915975.
18. Austin GE, Jensen B, Leete J, et al. Prevalence of hepatitis C virus seropositivity among hospitalized US veterans. *Am J Med Sci.* 2000;319(6):353-9. PMID: 10875289.

19. Cheung R. Epidemiology of hepatitis C virus infection in American veterans. *Am J Gastroenterol.* 2000;95(3):740-7. PMID: 10710068.
20. Garfein RS, Vlahov D, Galai N, et al. Viral Infections in short-term injection drug users: The prevalence of the hepatitis C, hepatitis B, human immunodeficiency, and human T-lymphotropic viruses. *Am J Public Health.* 1996;86(5):655-61. PMID: 8629715.
21. Rein DB, Smith BD, Wittenborn JS, Lesesne SB, Wagner LD, Roblin DW, et al. The cost-effectiveness of birth-cohort screening for hepatitis C antibody in U.S. primary care settings. *Ann Intern Med.* 2012; 156(4):263-70. PMID: 22056542
22. Bellentani S, Pozzato G, Saccoccio G, et al. Clinical course and risk factors of hepatitis C virus related liver disease in the general population: report from the Dionysos study. *Gut.* 1999;44(6):874-80. PMID: 10323892.
23. Alter MJ. Epidemiology of hepatitis C. *Hepatology.* 1997;26(3 Suppl 1):62S-5S. PMID: 8781897.
24. Schreiber GB, Busch MP, Kleinman SH, et al. The risk of transfusion-transmitted viral infections. The Retrovirus Epidemiology Donor Study. *N Engl J Med.* 1996;334(26):1685-90. PMID: 8637512.
25. Alter MJ. Prevention of spread of hepatitis C. *Hepatology.* 2002;36:S93-S8. PMID: 12407581.
26. Haley RW, Fischer RP. The tattooing paradox: Are studies of acute hepatitis adequate to identify routes of transmission of subclinical hepatitis C infection? *Arch Intern Med.* 2003;163(9):1095-8.
27. Balasekaran R, Bulterys M, Jamal MM, et al. A case-control study of risk factors for sporadic hepatitis C virus infection in the southwestern United States. *Am J Gastroenterol.* 1999 May;94(5):1341-6. PMID: 10235216.
28. Murphy EL, Bryzman S, Williams AE, et al. Demographic determinants of hepatitis C virus seroprevalence among blood donors. *JAMA.* 1996;275(13):995-1000. PMID: 8596257.
29. Silverman AL, Sekhon JS, Saginaw SJ, et al. Tattoo application is not associated with an increased risk for chronic viral hepatitis. *Am J Gastroenterol.* 2000;95(5):1312-5. PMID: 10811345.
30. Conry-Cantilena C, VanRaden M, Gible J, et al. Routes of infection, viremia, and liver disease in blood donors found to have hepatitis C virus infection. *N Engl J Med.* 1996;334(26):1691-6. PMID: 8637513.
31. Bialek SR, Terrault NA. The changing epidemiology and natural history of hepatitis C virus infection. *Clin Liver Dis.* 2006;10(4):697-715. PMID: 17164113.
32. McCaughan GW, George J. Fibrosis progression in chronic hepatitis C virus infection. *Gut.* 2004;53(3):318-21. PMID: 14960506.
33. Freeman AJ, Dore GJ, Law MG, et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. *Hepatology.* 2001;34(4 Pt 1):809-16. PMID: 11584380.
34. Seeff LB. Natural history of chronic hepatitis C. *Hepatology.* 2002;36(5 Suppl 1):S35-S46. PMID: 12407575.
35. Barrett S, Goh J, Coughlan B, et al. The natural course of hepatitis C virus infection after 22 years in a unique homogenous cohort: spontaneous viral clearance and chronic HCV infection. *Gut.* 2001;49(3):423-30. PMID: 11511566.
36. Harris HE, Ramsay ME, Andrews N, et al. Clinical course of hepatitis C virus during the first decade of infection: cohort study. *BMJ.* 2002;324(7335):450-3. PMID: 11859045.
37. Wiese M, Berr F, Portst H, et al. Low frequency of cirrhosis in a large hepatitis C outbreak after 20 years. *J Hepatol.* 2000;32(Suppl 2):101. PMID: 10869294.
38. Seeff LB, Miller RN, Rabkin CS, et al. 45-year follow-up of hepatitis C virus infection in healthy young adults. *Ann Intern Med.* 2000;132(2):105-11. PMID: 10644270.
39. Wiese M, Grüngreiff K, Güthoff W, et al. Outcome in a hepatitis C (genotype 1b) single source outbreak in Germany—a 25-year multicenter study. *J Hepatol.* 2005;43(4):590-8. PMID: 16237783.

40. Thomas DL. Hepatitis C epidemiology: injecting new tools in the field. *Hepatology*. 2000 Mar;31(3):790-1. PMID: 10706576.
41. Thein HH, Yi Q, Dore GJ, et al. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. *Hepatology*. 2008;48(2):418-31. PMID: 18563841.
42. Hagan H, Campbell J, Thiede H, et al. Self-reported hepatitis C virus antibody status and risk behavior in young injectors. *Public Health Rep*. 2006;121(6):710-9. PMID: 17278406.
43. Anonymous. Screening for hepatitis C virus infection in adults: recommendation statement. *Ann Intern Med*. 2004;140(6):462-4. PMID: 15023712.
44. Chou R, Clark E, Helfand M. Screening for Hepatitis C Virus Infection. Systematic Evidence Review N01 24. (Prepared by Oregon Evidence-based Practice Center under Contract No. 290-97-0018). March, 2004. www.effectivehealthcare.ahrq.gov/reports/financial.cfm. www.ahrq.gov/downloads/pub/prevent/pdfser/hepcser.pdf
45. Ghany MG, Strader DB, Thomas DL, et al. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology*. 2009;49:1335-74.
46. Dienstag JL, McHutchison JG. American Gastroenterological Association medical position statement on the management of hepatitis C. *Gastroenterology*. 2006;130(1):225-30. PMID: 16401485.
47. AAP. Hepatitis C virus infection. American Academy of Pediatrics. Committee on Infectious Diseases. *Pediatrics*. 1998;101(3):481-5. PMID: 9499195.
48. Smith BD, Morgan RL, Beckett GA, Falck-Ytter Y, Holtzman D, Ward JW. Hepatitis C virus testing of persons born during 1945 to 1965: Recommendations from the Centers for Disease Control and Prevention. *Ann Intern Med*. 2012 Aug 16. PMID: 22910836
49. European Paediatric Hepatitis CVN. Three broad modalities in the natural history of vertically acquired hepatitis C virus infection. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2005;41:45-51. PMID: 15937762.
50. England K, Thorne C, Newell ML. Vertically acquired paediatric coinfection with HIV and hepatitis C virus. *Lancet Infect Dis*. 2006;6(2):83-90. PMID: 16439328.
51. Ceci O, Margiotta M, Mareello F, et al. High rate of spontaneous viral clearance in a cohort of vertically infected hepatitis C virus infants: What lies behind? *J Hepatol*. 2001;35(5):687-8. PMID: 11690723.
52. Mast EE, Hwang LY, Seto DSY, et al. Risk factors for perinatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy. *J Infect Dis*. 2005;192(11):1880-9. PMID: 16267758.
53. Pembrey L, Newell ML, Tovo PA. The management of HCV infected pregnant women and their children European paediatric HCV network. *J Hepatol*. 2005 Sep;43(3):515-25. PMID: 16144064.
54. Yeung LTF, King SM, Roberts EA. Mother-to-infant transmission of hepatitis C virus. *Hepatology*. 2001;34(2):223-9.
55. Centers for Disease Control and Prevention. Hepatocellular carcinoma—United States, 2001-2006. *MMWR - Morbidity & Mortality Weekly Report*. 2010 May 7;59(17):517-20. PMID: 20448528.
56. American College of Obstetricians and Gynecologists (ACOG). Viral hepatitis in pregnancy. 86 ed. ACOG practice bulletin: Washington DC; 2007.
57. Boaz K, Fiore AE, Schrag SJ, et al. Screening and counseling practices reported by obstetrician-gynecologists for patients with hepatitis C virus infection. *Infect Dis Obstet Gynecol*. 2003;11(1):39-44. PMID: 12839631.
58. Chou RC, Hartung D, Rahman B, et al. Comparative Effectiveness of Treatment for Hepatitis C Virus Infection in Adults. Comparative Effectiveness Review. (Prepared by Oregon Evidence-based Practice Center under Contract No. 290-2007-10057-I.). Forthcoming 2012

59. Soto B, Sanchez-Quijano A, Rodrigo L, et al. Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. *J Hepatol.* 1997;26(1):1-5. PMID: 9147999.
60. Sanchez-Quijano A, Andreu J, Gavilan F, et al. Influence of human immunodeficiency virus type 1 infection on the natural course of chronic parenterally acquired hepatitis C. *Eur J Clin Microbiol Infect Dis.* 1995;14(11):949-53. PMID: 8654444.
61. Furusyo N, Hayashi J, Kanamoto-Tanaka Y, et al. Liver damage in hemodialysis patients with hepatitis C virus viremia: a prospective 10-year study. *Dig Dis Sci.* 2000;45(11):2221-8. PMID: 11215743.
62. Rostaing L, Rumeau JL, Cisterne JM, et al. Liver histology in renal transplant patients after more than 10 years of hepatitis C virus infection. *Transplant Proc.* 1996;28(5):2836-7. PMID: 8908089.
63. Kliem V, van den Hoff U, Brunkhorst R, et al. The long-term course of hepatitis C after kidney transplantation. *Transplantation.* 1996;62(10):1417-21. PMID: 8958266.
64. Anonymous. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. Centers for Disease Control and Prevention. *MMWR - Morbidity & Mortality Weekly Report.* 1998;47(RR-19):1-39. PMID: 9790221.
65. Smith B, Jan JD, Amy AJ, et al. Evaluation of three rapid screening assays for detection of antibodies to hepatitis C virus. *CORD Conference Proceedings.* 2011;204(6):825-31. PMID: 21849279.
66. Lee SR, Yearwood GD, Guillon GB, et al. Evaluation of a rapid, point-of-care test device for the diagnosis of hepatitis C infection. *CORD Conference Proceedings.* 2010;48(1):15-7. PMID: 20362493.
67. Lee SR, Kardos KW, Schiff E, et al. Evaluation of a New; Rapid Test for Detecting HCV Infection; Suitable for Use with Blood or Oral Fluid. *J Virol Methods.* 2010PMID: 21182871.
68. Thomas DL, Seeff LB. Natural history of hepatitis C. *Clin Liver Dis.* 2005 Aug;9(3):383-98, vi. PMID: 16023972.
69. Ilan Y. Review article: the assessment of liver function using breath tests. *Aliment Pharmacol Ther.* 2007;26(10):1293-302. PMID: 17868431.
70. Cardoso AC, Carvalho-Filho RJ, Marcellin P. Transient elastography in chronic viral hepatitis: a critical appraisal. *Gut.* 2011PMID: 21450696.
71. Altman DG, Bland JM. Diagnostic tests 3: receiver operating characteristic plots. *BMJ.* 1994;309(6948):188-. PMID: 8044101.
72. Zweig MH, Campbell G. Receiver-operating characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine. *Clin Chem.* 1993;39(4):561-77. PMID: 8472349.
73. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* 1998;52(6):377-84. PMID: 9764259.
74. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med.* 2001;20(3 Suppl):21-35. PMID: 11306229.
75. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: A revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med.* 2011;155(8):529-36. PMID: 22007046.
76. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(12)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality; April 2012. Chapters available at: http://www.effectivehealthcare.ahrq.gov/ehc/products/60/318/MethodsGuide_Prepublication-Draft_20120523.pdf June 19, 2012.
77. Atkins D, Chang S, Gartlehner G, et al. Assessing applicability when comparing medical interventions: Agency for Healthcare Research and Quality and the Effective Health Care Program. *Journal of clinical epidemiology.* 2011;64(11):1198-207. PMID: 21463926.

78. Cullen W, Stanley J, Langton D, et al. Hepatitis C infection among injecting drug users in general practice: A cluster randomised controlled trial of clinical guidelines' implementation. *Br J Gen Pract.* 2006;56(532):848-56. PMID: 17132352.
79. Anderson EM, Mandeville RP, Hutchinson SJ, et al. Evaluation of a general practice based hepatitis C virus screening intervention. *Scott Med J.* 2009 Aug;54(3):3-7. PMID: 19728405.
80. Gunn RA, Murray PJ, Brennan CH, et al. Evaluation of screening criteria to identify persons with hepatitis C virus infection among sexually transmitted disease clinic clients: results from the San Diego Viral Hepatitis Integration Project. *Sex Transm Dis.* 2003 Apr;30(4):340-4. PMID: 12671556.
81. McGinn T, O'Connor-Moore N, Alfandre D, et al. Validation of a hepatitis C screening tool in primary care. *Arch Intern Med.* 2008 Oct 13;168(18):2009-13. PMID: 18852403.
82. Zuniga IA, Chen JJ, Lane DS, et al. Analysis of a hepatitis C screening programme for US veterans. *Epidemiol Infect.* 2006 Apr;134(2):249-57. PMID: 16490127.
83. Zuure F, Davidovich U, Kok G, et al. Evaluation of a risk assessment questionnaire to assist hepatitis C screening in the general population. *Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin.* 2010 Apr 15;15(15):19539. PMID: 20429995.
84. Nguyen MT, Herrine SK, Laine CA, et al. Description of a new hepatitis C risk assessment tool. *Arch Intern Med.* 2005 Sep 26;165(17):2013-8. PMID: 16186472.
85. Lapane KL, Jakiche AF, Sugano D, et al. Hepatitis C infection risk analysis: who should be screened? Comparison of multiple screening strategies based on the National Hepatitis Surveillance Program. *Am J Gastroenterol.* 1998;93(4):591-6.
86. King LA, Le Strat Y, Meffre C, et al. Assessment and proposal of a new combination of screening criteria for hepatitis C in France. *Eur J Public Health.* 2009 Oct;19(5):527-33. PMID: 19667051.
87. Fabris P, Tositti G, Giordani MT, et al. Assessing patients' understanding of hepatitis C virus infection and its impact on their lifestyle. *Aliment Pharmacol Ther.* 2006;23(8):1161-70. PMID: 16611277.
88. Trepka MJ, Zhang G, Leguen F, et al. Benefits and adverse effects of hepatitis C screening: early results of a screening program. *J Public Health Manag Pract.* 2007 May-Jun;13(3):263-9. PMID: 17435493.
89. Coughlan B, Sheehan J, Carr A, et al. Evaluation of a brief group based psychological/educational treatment programme for women with an iatrogenic chronic hepatitis C virus infection. *J Clin Psychol Med Settings.* 2004;11(4):303-14.
90. Andriulli A, Persico M, Iacobellis A, et al. Treatment of patients with HCV infection with or without liver biopsy. *J Viral Hepat.* 2004;11(6):536-42. PMID: 15500554.
91. Adams LA, Bulsara M, Rossi E, et al. Hepascore: An Accurate Validated Predictor of Liver Fibrosis in Chronic Hepatitis C Infection. *Clin Chem.* 2005 October 1;51(10):1867-73. PMID: 16055434.
92. Adler M, Gulbis B, Moreno C, et al. The predictive value of FIB-4 versus FibroTest, APRI, FibroIndex and Forns index to noninvasively estimate fibrosis in hepatitis C and nonhepatitis C liver diseases. *Hepatology.* 2008;47(2):762-3. PMID: 18220307.
93. Ahmad W, Ijaz B, Javed FT, et al. A comparison of four fibrosis indexes in chronic HCV: development of new fibrosis-cirrhosis index (FCI). *BMC Gastroenterology.* 2011;11:44. PMID: 21507271.
94. Alsatie M, Kwo PY, Gingerich JR, et al. A multivariable model of clinical variables predicts advanced fibrosis in chronic hepatitis C. *J Clin Gastroenterol.* 2007;41(4):416-21. PMID: 17413613.
95. Anderson FH, Zeng L, Rock NR, et al. An assessment of the clinical utility of serum ALT and AST in chronic hepatitis C. *Hepatology Res.* 2000;18(1):63-71. PMID: 10838037.

96. Becker L, Salameh W, Sferruzza A, et al. Validation of hepascore, compared with simple indices of fibrosis, in patients with chronic hepatitis C virus infection in United States. *Clin Gastroenterol Hepatol*. 2009;7(6):696-701. PMID: 19514117.
97. Bejarano G. Prospective evaluation of liver fibrosis in chronic viral hepatitis C infection using the Sabadell NIHCED (Non-Invasive Hepatitis-C-Related Cirrhosis Early Detection) index.; 2009. <http://hepatop.biopredictive.com/publication/19527078/prospective-evaluation-of-liver-fibrosis-in-chronic-viral-hepatitis-c-infection-using-the-sabadell-nihced-non-invasive-hepatitis-c-related-cirrhosis-early-detection-index/>. Accessed on June 20, 2011.
98. Ben Jazia E, Kaabia N, Benabdelkader A, et al. Noninvasive fibrosis markers for the prediction of significant fibrosis in patients with chronic hepatitis C virus infection in Tunisia. *Infect Dis Clin Pract (Baltim Md)*. 2009;17(6):385-.
99. Berg T, Sarrazin C, Hinrichsen H, et al. Does noninvasive staging of fibrosis challenge liver biopsy as a gold standard in chronic hepatitis C? *Hepatology*. 2004;39(5):1456-7. PMID: 15122779.
100. Boeker KH, Haberkorn CI, Michels D, et al. Diagnostic potential of circulating TIMP-1 and MMP-2 as markers of liver fibrosis in patients with chronic hepatitis C. *Clin Chim Acta*. 2002;316(1-2):71-81. PMID: 11750276.
101. Bonacini M, Hadi G, Govindarajan S, et al. Utility of a discriminant score for diagnosing advanced fibrosis or cirrhosis in patients with chronic hepatitis C virus infection. *Am J Gastroenterol*. 1997;92(8):1302-4. PMID: 9260794.
102. Borroni G, Ceriani R, Cazzaniga M, et al. Comparison of simple tests for the non-invasive diagnosis of clinically silent cirrhosis in chronic hepatitis C. *Aliment Pharmacol Ther*. 2006;24(5):797-804. PMID: 16918883.
103. Bota S, Sirlir R, Sporea I, et al. A new scoring system for prediction of fibrosis in chronic hepatitis C. *Hepat Mon*. 2011;11(7):548-55. PMID: 22087193.
104. Bourliere M, Penaranda G, Ouzan D, et al. Optimized stepwise combination algorithms of non-invasive liver fibrosis scores including Hepascore in hepatitis C virus patients. *Aliment Pharmacol Ther*. 2008;28(4):458-67. PMID: 18498446.
105. Bourliere M, Penaranda G, Renou C, et al. Validation and comparison of indexes for fibrosis and cirrhosis prediction in chronic hepatitis C patients: proposal for a pragmatic approach classification without liver biopsies. *J Viral Hepat*. 2006;13(10):659-70. PMID: 16970597.
106. Boursier J, Bacq Y, Halfon P, et al. Improved diagnostic accuracy of blood tests for severe fibrosis and cirrhosis in chronic hepatitis C. *Eur J Gastroenterol Hepatol*. 2009;21(1):28-38. PMID: 19060630.
107. Boursier J, de Ledinghen V, Zarski J-P, et al. A new combination of blood test and fibroscan for accurate non-invasive diagnosis of liver fibrosis stages in chronic hepatitis C. *Am J Gastroenterol*. 2011;106(7):1255-63. PMID: 21468012.
108. Boursier J, de Ledinghen V, Zarski JP, et al. Comparison of eight diagnostic algorithms for liver fibrosis in hepatitis C: new algorithms are more precise and entirely noninvasive. *Hepatology*. 2012;55(1):58-67. PMID: 21898504.
109. Burton MJ, Sunesara I, Penman A, et al. Comparing the aspartate aminotransferase (AST) to platelet ratio index (APRI) between African American and white veterans with chronic hepatitis C. *South Med J*. 2011;104(5):309-14. PMID: 21606706.
110. Calès P, De Ledinghen V, Halfon P, et al. Evaluating the accuracy and increasing the reliable diagnosis rate of blood tests for liver fibrosis in chronic hepatitis C. *Liver Int*. 2008;28(10):1352-62. PMID: 18492022.
111. Calès P, Boursier J, Bertrais S, et al. Optimization and robustness of blood tests for liver fibrosis and cirrhosis. *Clin Biochem*. 2010;43(16-17):1315-22. PMID: 20713037.
112. Castera L. Transient elastography and other noninvasive tests to assess hepatic fibrosis in patients with viral hepatitis. *J Vir Hep*. 2009;16(5):300-14. PMID: 19254351.

113. Castéra L, Sebastiani G, Le Bail B, et al. Prospective comparison of two algorithms combining non-invasive methods for staging liver fibrosis in chronic hepatitis C. *J Hepatol.* 2010;52(2):191-8. PMID: 20006397.
114. Castéra L, Vergniol J, Foucher J, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology.* 2005;128(2):343-50. PMID: 15685546.
115. Cheong JY, Um SH, Seo YS, et al. Non-invasive index for predicting significant liver fibrosis: comparison of diagnostic performances in patients with chronic hepatitis B and C. *Dig Dis Sci.* 2011;56:555-63. PMID: 20585981.
116. Cheung KJ, Tilleman K, Deforce D, et al. Usefulness of a novel serum proteome-derived index FI-PRO (fibrosis-protein) in the prediction of fibrosis in chronic hepatitis C. *Eur J Gastroenterol Hepatol.* 2011;23(8):701-10. PMID: 21623191.
117. Cheung RC, Currie S, Shen H, et al. Can we predict the degree of fibrosis in chronic hepatitis C patients using routine blood tests in our daily practice? *J Clin Gastroenterol.* 2008;42(7):827-34. PMID: 18285716.
118. Chrysanthos NV, Papatheodoridis GV, Savvas S, et al. Aspartate aminotransferase to platelet ratio index for fibrosis evaluation in chronic viral hepatitis. *Eur J Gastroenterol Hepatol.* 2006;18(4):389-96. PMID: 16538110.
119. Cobbold JF, Crossey MM, Colman P, et al. Optimal combinations of ultrasound-based and serum markers of disease severity in patients with chronic hepatitis C. *J Viral Hepat.* 2009;17(8):537-. PMID: 19804501.
120. Colletta C, Smirne C, Fabris C, et al. Value of two noninvasive methods to detect progression of fibrosis among HCV carriers with normal aminotransferases. *Hepatology.* 2005;42(4):838-45. PMID: 16121354.
121. Colli A, Colucci A, Paggi S, et al. Accuracy of a predictive model for severe hepatic fibrosis or cirrhosis in chronic hepatitis C. *World J Gastroenterol.* 2005;11(46):7318-22. PMID: 16437635
122. Crisan D, Radu C, Lupsor M, et al. Two or more synchronous combination of noninvasive tests to increase accuracy of liver fibrosis assesment in chronic Hepatitis C; results from a cohort of 446 patients. *Hepat Mon.* 2012;12(3):177-84. PMID: 22550525.
123. Cross TJ, Calvaruso V, Maimone S, et al. Prospective comparison of Fibroscan, King's score and liver biopsy for the assessment of cirrhosis in chronic hepatitis C infection. *J Viral Hepat.* 2010;17(8):546-. PMID: 19874477.
124. Cross TJS, Rizzi P, Berry PA, et al. King's Score: an accurate marker of cirrhosis in chronic hepatitis C. *Eur J Gastroenterol Hepatol.* 2009;21(7):730-8. PMID: 19430302.
125. Ehsan N, Badr M, Raouf A, et al. Correlation between liver biopsy findings and different serum biochemical tests in staging fibrosis in Egyptian patients with chronic hepatitis C virus infection. *Arab J Gastroenterol* 2008;9(1):7-12.
126. El-Gindy I, El Rahman AT, El-Alim MA, et al. Diagnostic potential of serum matrix metalloproteinase-2 and tissue inhibitor of metalloproteinase-1 as non-invasive markers of hepatic fibrosis in patients with HCV related chronic liver disease. *Egypt J Immunol.* 2003;10(1):27-35. PMID: 15719620.
127. El-Sayed R, Fahmy M, El Koofy N, et al. Can aspartate aminotransferase to platelet ratio index replace liver biopsy in chronic hepatitis C? *Trop Gastroenterol.* 2011;32(4):267-72. PMID: 22696906.
128. el-Shorbagy E, Afefy AF, Ibrahim IA, et al. Non-invasive markers and predictors of severity of hepatic fibrosis in HCV patients at Sharkia Governorate, Egypt. *J Egypt Soc Parasitol.* 2004;34(1):459-78. PMID: 15124753.
129. Fabris C, Smirne C, Toniutto P, et al. Usefulness of six non-proprietary indirect markers of liver fibrosis in patients with chronic hepatitis C. *Clin Chem Lab Med.* 2008;46(2):253-9. PMID: 18324909.

130. Fontana RJ, Goodman ZD, Dienstag JL, et al. Relationship of serum fibrosis markers with liver fibrosis stage and collagen content in patients with advanced chronic hepatitis C. *Hepatology*. 2008;47(3):789-98. PMID: 18175357.
131. Forns X, Ampurdanès S, Llovet JM, et al. Identification of chronic hepatitis C patients without hepatic fibrosis by a simple predictive model. *Hepatology*. 2002;36(4):986-92. PMID: 12297848.
132. Friedrich-Rust M, Rosenberg W, Parkes J, et al. Comparison of ELF, FibroTest and FibroScan for the non-invasive assessment of liver fibrosis. *BMC Gastroenterology*. 2010;10(1):103. PMID: 20828377.
133. Gabrielli GB, Capra F, Casaril M, et al. Serum laminin and type III procollagen in chronic hepatitis C. Diagnostic value in the assessment of disease activity and fibrosis. *Clin Chim Acta*. 1997;265(1):21-31. PMID: 9352126.
134. Giannini (a) E, Risso D, Botta F, et al. Validity and clinical utility of the aspartate aminotransferase-alanine aminotransferase ratio in assessing disease severity and prognosis in patients with hepatitis C virus-related chronic liver disease. *Arch Intern Med*. 2003 January 27;163(2):218-24. PMID: 12546613.
135. Giannini (b) E, Testa R. Noninvasive diagnosis of fibrosis: The truth is rarely pure and never simple. *Hepatology*. 2003;38(5):1312-3. PMID: 14578874.
136. Giannini EG, Zaman A, Ceppa P, et al. A simple approach to noninvasively identifying significant fibrosis in chronic hepatitis C patients in clinical practice. *J Clin Gastroenterol*. 2006;40(6):521-7. PMID: 16825935.
137. Gomes da Silva. Aspartate aminotransferase-to-platelet ratio index for fibrosis and cirrhosis prediction in chronic hepatitis C patients. *Braz J Infect Dis*. 2008;12(1)PMID: 18553008.
138. Grigorescu M, Rusu M, Neculoiu D, et al. The FibroTest value in discriminating between insignificant and significant fibrosis in chronic hepatitis C patients. The Romanian experience. *J Gastrointest Liver Dis*. 2007;16(1):31-7. PMID: 17410286.
139. Guéchet J, Lasnier E, Sturm N, et al. Automation of the Hepascore and validation as a biochemical index of liver fibrosis in patients with chronic hepatitis C from the ANRS HC EP 23 Fibrostar cohort. *Clin Chim Acta*. 2010;411(1-2):86-91. PMID: 19850017.
140. Guéchet J, Laudat A, Loria A, et al. Diagnostic accuracy of hyaluronan and type III procollagen amino-terminal peptide serum assays as markers of liver fibrosis in chronic viral hepatitis C evaluated by ROC curve analysis. *Clin Chem*. 1996;42(4):558-63. PMID: 8605673.
141. Guéchet J, Poupon RE, Giral P, et al. Relationship between procollagen III aminoterminal propeptide and hyaluronan serum levels and histological fibrosis in primary biliary cirrhosis and chronic viral hepatitis C. *J Hepatol*. 1994;20(3):388-93. PMID: 8014451.
142. Güzelbulut. AST-platelet ratio index, Forns index and FIB-4 in the prediction of significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Turk J Gastroenterol*. 2011;22(3):279-85. PMID: 21805418.
143. Halfon P. Accuracy of hyaluronic acid level for predicting liver fibrosis stages in patients with hepatitis C virus. *Comp Hepatol*. 2005;4(1)PMID: 16008833.
144. Halfon P. Independent prospective multicenter validation of biochemical markers (fibrotest-actitest) for the prediction of liver fibrosis and activity in patients with chronic hepatitis C: the fibropaca study. *Am J Gastroenterol*. 2006;101(3):547-55. PMID: 16542291.
145. Halfon P, Bacq Y, De Muret A, et al. Comparison of test performance profile for blood tests of liver fibrosis in chronic hepatitis C. *J Hepatol*. 2007;46(3):395-402. PMID: 17156890.
146. Hsieh YY, Tung SY, Lee IL, et al. FibroQ: an easy and useful noninvasive test for predicting liver fibrosis in patients with chronic viral hepatitis. *Chang Gung Med J*. 2009;32(6):614-22. PMID: 20035640.

147. Iacobellis (a) A, Fusilli S, Mangia A, et al. Ultrasonographic and biochemical parameters in the non-invasive evaluation of liver fibrosis in hepatitis C virus chronic hepatitis. *Aliment Pharmacol Ther.* 2005;22(9):769-74. PMID: 16225484
148. Iacobellis (b) A, Mangia A, Leandro G, et al. External validation of biochemical indices for noninvasive evaluation of liver fibrosis in HCV chronic hepatitis. *Am J Gastroenterol.* 2005;100(4):868-73. PMID: 15784034
149. Imbert-Bismut F, Ratziu V, Pieroni L, et al. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. *The Lancet.* 2001;357(9262):1069-75. PMID: 11297957.
150. Imperiale TF, Said AT, Cummings OW, et al. Need for validation of clinical decision aids: use of the AST/ALT ratio in predicting cirrhosis in chronic hepatitis C. *Am J Gastroenterol.* 2000;95(9):2328-32. PMID: 11007237.
151. Islam S, Antonsson L, Westin J, et al. Cirrhosis in hepatitis C virus-infected patients can be excluded using an index of standard biochemical serum markers. *Scand J Gastroenterol.* 2005;40(7):867-72. PMID: 16109665.
152. Kaul V, Friedenberg FK, Braitman LE, et al. Development and validation of a model to diagnose cirrhosis in patients with hepatitis C. *Am J Gastroenterol.* 2002;97(10):2623-8. PMID: 12385450.
153. Khan. Evaluation of diagnostic accuracy of APRI for prediction of fibrosis in hepatitis C patients. *J Ayub Med Coll Abbottabad.* 2008;20(4):122-6. PMID: 19999223.
154. N K. Serum aminotransferase levels and platelet count as predictive factor of fibrosis and cirrhosis in patients with chronic hepatitis C infection. *J Pak Med Assoc.* 2003;53(3):101-4. PMID: 12779023.
155. Koda M, Matunaga Y, Kawakami M, et al. Fibroindex, a practical index for predicting significant fibrosis in patients with chronic hepatitis C. *Hepatology.* 2007;45(2):297-306. PMID: 17256741.
156. Lackner C, Struber G, Liegl B, et al. Comparison and validation of simple noninvasive tests for prediction of fibrosis in chronic hepatitis C. *Hepatology.* 2005;41(6):1376-82. PMID: 15915455.
157. Leroy V, Halfon P, Bacq Y, et al. Diagnostic accuracy, reproducibility and robustness of fibrosis blood tests in chronic hepatitis C: A meta-analysis with individual data. *Clin Biochem.* 2008;41(16-17):1368-76. PMID: 18655779.
158. Leroy V, Hilleret M-N, Sturm N, et al. Prospective comparison of six non-invasive scores for the diagnosis of liver fibrosis in chronic hepatitis C. *J Hepatol.* 2007;46(5):775-82. PMID: 17321634.
159. Leroy V, Monier F, Bottari S, et al. Circulating matrix metalloproteinases 1, 2, 9 and their inhibitors TIMP-1 and TIMP-2 as serum markers of liver fibrosis in patients with chronic hepatitis C: comparison with PIIINP and hyaluronic acid. *Am J Gast.* 2004;99(2):271-9. PMID: 15046217.
160. Liu CH, Lin JW, Tsai FC, et al. Noninvasive tests for the prediction of significant hepatic fibrosis in hepatitis C virus carriers with persistently normal alanine aminotransferases. *Liver Int.* 2006;26(9):1087-94. PMID: 17032409.
161. Lo Iacono O, García-Monzón C, Almasio P, et al. Soluble adhesion molecules correlate with liver inflammation and fibrosis in chronic hepatitis C treated with interferon-alpha. *Aliment Pharmacol Ther.* 1998;12(11):1091-9. PMID: 9845398.
162. Loeza-del-Castillo A, Paz-Pineda F, Oviedo-Cárdenas E, et al. AST to platelet ratio index (APRI) for the noninvasive evaluation of liver fibrosis. *Ann Hepatol.* 2008;7(4):350-7. PMID: 19034235.
163. Lok ASF, Ghany MG, Goodman ZD, et al. Predicting cirrhosis in patients with hepatitis C based on standard laboratory tests: Results of the HALT-C cohort. *Hepatology.* 2005;42(2):282-92. PMID: 15986415.
164. Luo J, Hwang S, Chang F, et al. Simple blood tests can predict compensated liver cirrhosis in patients with chronic hepatitis C. *Hepatogastroenterology.* 2002;49(44):478-81. PMID: 11995477.

165. Martinez SM, Fernández-Varo G, González P, et al. Assessment of liver fibrosis before and after antiviral therapy by different serum marker panels in patients with chronic hepatitis C. *Aliment Pharmacol Ther.* 2011;33(1):138-48. PMID: 21083589.
166. McHutchison JG, Blatt LM, de Medina M, et al. Measurement of serum hyaluronic acid in patients with chronic hepatitis C and its relationship to liver histology. Consensus Interferon Study Group. *J Gastroenterol Hepatol.* 2000;15(8):945-51. PMID: 11022838.
167. Metwally MA, Zein CO, Zein NN. Predictors and noninvasive identification of severe liver fibrosis in patients with chronic hepatitis C. *Dig Dis Sci.* 2007;52(2):582-8. PMID: 17211710.
168. Murawaki (b) Y, Ikuta Y, Okamoto K, et al. Diagnostic value of serum markers of connective tissue turnover for predicting histological staging and grading in patients with chronic hepatitis C. *J Gastroenterol.* 2001;36(6):399-406. PMID: 11428586.
169. Murawaki (a) Y, Koda M, Okamoto K, et al. Diagnostic value of serum type IV collagen test in comparison with platelet count for predicting the fibrotic stage in patients with chronic hepatitis C. *J Gastroenterol Hepatol.* 2001;16(7):777-81. PMID: 11446886.
170. Myers RP, de Torres M, Imbert-Bismut F, et al. Biochemical markers of fibrosis in patients with chronic hepatitis C: A comparison with prothrombin time, platelet count, and age-platelet index. *Dig Dis Sci.* 2003;48(1):146-53. PMID: 12645802.
171. Myers RP, Ratziu V, Imbert-Bismut F, et al. Biochemical markers of liver fibrosis: a comparison with historical features in patients with chronic hepatitis C. *Am J Gastroenterol.* 2002;97(9):2419-25. PMID: 12358267.
172. Obrador BD, Prades MG, Gómez MV, et al. A predictive index for the diagnosis of cirrhosis in hepatitis C based on clinical, laboratory, and ultrasound findings. *Eur J Gastroenterol Hepatol.* 2006;18(1):57-62. PMID: 16357620.
173. Ohta T, Sakaguchi K, Fujiwara A, et al. Simple surrogate index of the fibrosis stage in chronic hepatitis C patients using platelet count and serum albumin level. *Acta Med Okayama.* 2006;60(2):77-84. PMID: 16680183
174. Omran MM, Farid K, Emran TM, et al. Fibro-(alpha) score as a simple and useful non-invasive test for predicting significant liver fibrosis in chronic hepatitis C patients. *Arab J Gastroenterol.* 2011;12(2):74-9. PMID: 21684477.
175. Paggi S, Colli A, Fraquelli M, et al. A non-invasive algorithm accurately predicts advanced fibrosis in hepatitis C: A comparison using histology with internal-external validation. *J Hepatol.* 2008;49(4):564-71. PMID: 18706734.
176. Parise ER, Oliveira AC, Figueiredo-Mendes C, et al. Noninvasive serum markers in the diagnosis of structural liver damage in chronic hepatitis C virus infection. *Liver Int.* 2006;26(9):1095-9. PMID: 17032410.
177. Park GJH, Lin BP, Ngu MC, et al. Aspartate aminotransferase : alanine aminotransferase ratio in chronic hepatitis C infection: Is it a useful predictor of cirrhosis? *J Gastroenterol Hepatol.* 2000;15(4):386-90. PMID: 10824882.
178. Park SH, Kim CH, Kim DJ, et al. Diagnostic value of multiple biomarker panel for prediction of significant fibrosis in chronic hepatitis C. *Clin Biochem.* 2011;44(17-18):1396-9. PMID: 21971609.
179. Parkes J, Guha IN, Roderick P, et al. Enhanced Liver Fibrosis (ELF) test accurately identifies liver fibrosis in patients with chronic hepatitis C. *J Viral Hepat.* 2011 Jan;18(1):23-31. PMID: 20196799.
180. Patel K, Benhamou Y, Yoshida EM, et al. An independent and prospective comparison of two commercial fibrosis marker panels (HCV FibroSURE and FIBROSpect II) during albinterferon alfa-2b combination therapy for chronic hepatitis C. *J Vir Hep.* 2009;16(3):178-86. PMID: 19175870.
181. Patel K, Gordon SC, Jacobson I, et al. Evaluation of a panel of non-invasive serum markers to differentiate mild from moderate-to-advanced liver fibrosis in chronic hepatitis C patients. *J Hepatol.* 2004;41(6):935-42. PMID: 15582126.

182. Plevris JN, Haydon GH, Simpson KJ, et al. Serum hyaluronan--a non-invasive test for diagnosing liver cirrhosis. *Eur J Gastroenterol Hepatol.* 2000;12(10):1121-7. PMID: 11057458.
183. Pohl A, Behling C, Oliver D, et al. Serum aminotransferase levels and platelet counts as predictors of degree of fibrosis in chronic hepatitis C virus infection. *Am J Gastroenterol.* 2001;96(11):3142-6. PMID: 11721762.
184. Poynard T, Imbert-Bismut F, Ratziu V, et al. Biochemical markers of liver fibrosis in patients infected by hepatitis C virus: longitudinal validation in a randomized trial. *J Vir Hep.* 2002;9(2):128-33. PMID: 11876795.
185. Poynard T, McHutchison J, Manns M, et al. Biochemical surrogate markers of liver fibrosis and activity in a randomized trial of peginterferon alfa-2b and ribavirin. *Hepatology.* 2003;38(2):481-92. PMID: 12883493.
186. Pradat P, Alberti A, Poynard T, et al. Predictive value of ALT levels for histologic findings in chronic hepatitis C: a European collaborative study. *Hepatology.* 2002;36(4 Pt 1):973-7. PMID: 12297846.
187. Reedy DW, Loo AT, Levine RA. AST/ALT ratio \geq 1 is not diagnostic of cirrhosis in patients with chronic hepatitis C. *Dig Dis Sci.* 1998;43(9):2156-9. PMID: 9753286.
188. Renou C, Muller P, Jouve E, et al. Relevance of moderate isolated thrombopenia as a strong predictive marker of cirrhosis in patients with chronic hepatitis C virus. *Am J Gastroenterol.* 2001;96(5):1657-9. PMID: 11374731.
189. Romera M, Corpas R, Romero Gómez M. Insulin resistance as a non-invasive method for the assessment of fibrosis in patients with hepatitis C: a comparative study of biochemical methods. *Rev Esp Enferm Dig.* 2006;98(3):161-9. PMID: 16737415.
190. Rosenberg WM, Voelker M, Thiel R, et al. Serum markers detect the presence of liver fibrosis: a cohort study. *Gastroenterology.* 2004;127(6):1704-13. PMID: 15578508.
191. Rossi E, Adams L, Prins A, et al. Validation of the FibroTest Biochemical Markers Score in assessing liver fibrosis in hepatitis C patients. *Clin Chem.* 2003 March 1;49(3):450-4. PMID: 12600957.
192. Saadeh S, Cammell G, Carey WD, et al. The role of liver biopsy in chronic hepatitis C. *Hepatology.* 2001;33(1):196-200. PMID: 11124836.
193. Said Y, Bouzaidi S, Debbeche R, et al. Correlation entre la biopsie hépatique et le Fibrotest dans l'évaluation de la fibrose hépatique chez les patients atteints d'hépatite chronique C. *La Tunisie Medicale.* 2010;88(8):573-83.
194. Saitou Y, Shiraki K, Yamanaka Y, et al. Noninvasive estimation of liver fibrosis and response to interferon therapy by a serum fibrogenesis marker, YKL-40, in patients with HCV-associated liver disease. *World J Gastroenterol.* 2005;11(4):476-81. PMID: 15641129.
195. Schneider AR, Teuber G, Kriener S, et al. Noninvasive assessment of liver steatosis, fibrosis and inflammation in chronic hepatitis C virus infection. *Liver Int.* 2005;25(6):1150-5. PMID: 16343065.
196. Schneider AR, Teuber G, Paul K, et al. Patient age is a strong independent predictor of 13C-aminopyrine breath test results: a comparative study with histology, duplex-Doppler and a laboratory index in patients with chronic hepatitis C virus infection. *Clin Exp Pharmacol Physiol.* 2006;33(4):300-4. PMID: 1662029.
197. Sebastiani G, Halfon P, Castera L, et al. SAFE biopsy: A validated method for large-scale staging of liver fibrosis in chronic hepatitis C. *Hepatology.* 2009;49(6):1821-7. PMID: 19291784.
198. Sebastiani G, Vario A, Guido M, et al. Performance of noninvasive markers for liver fibrosis is reduced in chronic hepatitis C with normal transaminases. *J Vir Hep.* 2008;15(3):212-8. PMID: 18179453.
199. Sebastiani G, Vario A, Guido M, et al. Stepwise combination algorithms of non-invasive markers to diagnose significant fibrosis in chronic hepatitis C. *J Hepatol.* 2006;44(4):686-93. PMID: 16490278.

200. Sebastiani G, Castera L, Halfon P, et al. The impact of liver disease aetiology and the stages of hepatic fibrosis on the performance of non-invasive fibrosis biomarkers: an international study of 2411 cases. *Aliment Pharmacol Ther.* 2011;34(10):1202-16. PMID: 21981787.
201. Sebastiani G, Halfon P, Castera L, et al. Comparison of three algorithms of non-invasive markers of fibrosis in chronic hepatitis C. *Aliment Pharmacol Ther.* 2012;35(1):92-104. PMID: 22035045.
202. Sheth SG, Flamm SL, Gordon FD, et al. AST/ALT ratio predicts cirrhosis in patients with chronic hepatitis C virus infection. *Am J Gast.* 1998;93(1):44-8. PMID: 9448172.
203. Silva IS, Ferraz MLC, Perez RM, et al. Role of γ -glutamyl transferase activity in patients with chronic hepatitis C virus infection. *J Gastroenterol Hepatol.* 2004;19(3):314-8. PMID: 14748879.
204. Sirli R, Sporea I, Bota S, et al. A comparative study of non-invasive methods for fibrosis assessment in chronic HCV infection. *Hepat Mon.* 2010;10(2):88-94. PMID: 22312379.
205. Snyder N, Gajula L, Xiao S-Y, et al. APRI: An easy and validated predictor of hepatic fibrosis in chronic hepatitis C. *J Clin Gastroenterol.* 2006;40(6):535-42. PMID: 16825937.
206. Snyder N, Nguyen A, Gajula L, et al. The APRI may be enhanced by the use of the FIBROSpect II in the estimation of fibrosis in chronic hepatitis C. *Clinica Chimica Acta.* 2007;381(2):119-23. PMID: 17442291.
207. Stibbe KJM, Verveer C, Francke J, et al. Comparison of non-invasive assessment to diagnose liver fibrosis in chronic hepatitis B and C patients. *Scand J Gastroenterol.* 2011 Jul;46(7-8):962-72. PMID: 21623677.
208. Sud A, Hui JM, Farrell GC, et al. Improved prediction of fibrosis in chronic hepatitis C using measures of insulin resistance in a probability index. *Hepatology.* 2004;39(5):1239-47. PMID: 15122752.
209. Testa R, Testa E, Giannini E, et al. Noninvasive ratio indexes to evaluate fibrosis staging in chronic hepatitis C: role of platelet count/spleen diameter ratio index. *J Int Med.* 2006;260(2):142-50. PMID: 16882278.
210. Trocme C, Leroy V, Sturm N, et al. Longitudinal evaluation of a fibrosis index combining MMP-1 and PIIINP compared with MMP-9, TIMP-1 and hyaluronic acid in patients with chronic hepatitis C treated by interferon-alpha and ribavirin. *J Vir Hep.* 2006;13(10):643-51. PMID: 16970595.
211. Vallet-Pichard A, Mallet V, Nalpas B, et al. FIB-4: An inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. *Hepatology.* 2007;46(1):32-6. PMID: 17567829.
212. Verbaan H, Bondeson L, Eriksson S. Non-Invasive Assessment of Inflammatory Activity and Fibrosis (Grade and Stage) in Chronic Hepatitis C Infection. *Scand J Gastroenterol.* 1997;32(5):494-9. PMID: 9175214
213. Viana MSVB. Use of AST platelet ratio index (APRI Score) as an alternative to liver biopsy for treatment indication in chronic hepatitis C. *Ann Hepatol.* 2009;8(1) PMID: 19221530.
214. Wai C-T, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology.* 2003;38(2):518-26. PMID: 12883497.
215. Walsh (a) KM, Fletcher A, MacSween RN, et al. Comparison of assays for N-amino terminal propeptide of type III procollagen in chronic hepatitis C by using receiver operating characteristic analysis. *Eur J Gastroenterol Hepatol.* 1999;11(8):827-31. PMID: 10514112.
216. Walsh KM, Fletcher A, MacSween RN, et al. Basement membrane peptides as markers of liver disease in chronic hepatitis C. *J Hepatol.* 2000;32(2):325-30. PMID: 10707874.
217. Walsh (b) KM, Timms P, Campbell S, et al. Plasma levels of matrix metalloproteinase-2 (MMP-2) and tissue inhibitors of metalloproteinases -1 and -2 (TIMP-1 and TIMP-2) as noninvasive markers of liver disease in chronic hepatitis C: comparison using ROC analysis. *Dig Dis Sci.* 1999;44(3):624-30. PMID: 10080160.
218. Williams AL, Hoofnagle JH. Ratio of serum aspartate to alanine aminotransferase in chronic hepatitis. Relationship to cirrhosis. *Gastroenterology.* 1988;95(3):734-9. PMID: 3135226.

219. Wilson LE, Torbenson M, Astemborski J, et al. Progression of liver fibrosis among injection drug users with chronic hepatitis C. *Hepatology*. 2006;43(4):788-95. PMID: 16557548.
220. Wong VS, Hughes V, Trull A, et al. Serum hyaluronic acid is a useful marker of liver fibrosis in chronic hepatitis C virus infection. *J Viral Hepat*. 1998;5(3):187-92. PMID: 9658372.
221. Yilmaz Y, Yonal O, Kurt R, et al. Noninvasive assessment of liver fibrosis with the aspartate transaminase to platelet ratio index (APRI): usefulness in patients with chronic liver disease. *Hepat Mon*. 2011;11(2):103-7. PMID: 22087126.
222. Zaman A, Rosen HR, Ingram K, et al. Assessment of FIBROSpect II to detect hepatic fibrosis in chronic hepatitis C patients. *Am J Med*. 2007;120(3):280-14. PMID: 17349453.
223. Zarski J-P, Sturm N, Guechot J, et al. Comparison of nine blood tests and transient elastography for liver fibrosis in chronic hepatitis C: the ANRS HCEP-23 study. *J Hepatol*. 2012 Jan;56(1):55-62. PMID: 21781944.
224. Lackner C, Struber G, Bankuti C, et al. Noninvasive diagnosis of cirrhosis in chronic hepatitis C based on standard laboratory tests. *Hepatology*. 2006;42(2):378-9. PMID: 16440344.
225. Le Calvez S, Thabut D, Messous D, et al. The predictive value of Fibrotest vs. APRI for the diagnosis of fibrosis in chronic hepatitis C. *Hepatology*. 2004;39(3):862-3. PMID: 14999708.
226. Park G, Jones DB, Katelaris P. Value of AST/ALT ratio as fibrotic predictor in chronic hepatitis C. *Am J Gastroenterol*. 2005;100(7):1623-4. PMID: 15984996.
227. Thabut D, Simon M, Myers RP, et al. Noninvasive prediction of fibrosis in patients with chronic hepatitis C. *Hepatology*. 2003;37(5):1220-1. PMID: 12717403.
228. Castera L, Le Bail B, Roudot-Thoraval F, et al. Early detection in routine clinical practice of cirrhosis and oesophageal varices in chronic hepatitis C: comparison of transient elastography (FibroScan) with standard laboratory tests and non-invasive scores. *J Hepatol*. 2009;50(1):59-68. PMID: 19013661.
229. Cobbold J, Crossey M, Colman P, et al. Optimal combinations of ultrasound-based and serum markers of disease severity in patients with chronic hepatitis C. *J Viral Hepat*. 2010;17(8):537-45. PMID: 19804501.
230. Groom H, Dieperink E, Nelson DB, et al. Outcomes of a hepatitis C screening program at a large urban VA medical center. *J Clin Gastroenterol*. 2008 Jan;42(1):97-106. PMID: 18097298.
231. Lindenburg CEA, Lambers FAE, Urbanus AT, et al. Hepatitis C testing and treatment among active drug users in Amsterdam: Results from the DUTCH-C project. *Eur J Gastroenterol Hepatol*. 2011;23(1):23-31. PMID: 21042221.
232. Mallette C, Flynn MA, Promrat K. Outcome of screening for hepatitis C virus infection based on risk factors. *Am J Gast*. 2008 Jan;103(1):131-7. PMID: 17894850.
233. Seeff LB, Everson GT, Morgan TR, et al. Complication rate of percutaneous liver biopsies among persons with advanced chronic liver disease in the HALT-C Trial. *Clin Gastroenterol Hepatol*. 2010;8(10):877-83. PMID: 20362695.
234. Farrell RJ, Smiddy PF, Pilkington RM, et al. Guided versus blind liver biopsy for chronic hepatitis C: clinical benefits and costs. *J Hepatol*. 1999;30(4):580-7. PMID: 10207798.
235. Atwell TD, Smith RL, Hesley GK, et al. Incidence of bleeding after 15,181 percutaneous biopsies and the role of aspirin. *AJR Am J Roentgenol*. 2010;194(3):784-9. PMID: 20173160.
236. Huang JF, Hsieh MY, Dai CY, et al. The incidence and risks of liver biopsy in non-cirrhotic patients: An evaluation of 3806 biopsies. *Gut*. 2007;56(5):736-7. PMID: 17440193.

237. Myers RP, Fong A, Shaheen AA. Utilization rates, complications and costs of percutaneous liver biopsy: a population-based study including 4275 biopsies. *Liver Int.* 2008;28(5):705-12. PMID: 18433397.
238. van der Poorten D, Kwok A, Lam T, et al. Twenty-year audit of percutaneous liver biopsy in a major Australian teaching hospital. *Intern Med J.* 2006;36(11):692-9. PMID: 17040353.
239. West J, Card TR. Reduced mortality rates following elective, percutaneous liver biopsies. *Gastroenterology.* 2010;139(4):1230-7. PMID: 20547160.
240. Bravo AA, Sheth SG, Chopra S. Liver Biopsy. *N Engl J Med.* 2001;344(7):495-500. PMID: 11172192.
241. Cadranel JF, Rufat P, Degos F. Practices of liver biopsy in France: results of a prospective nationwide survey. For the Group of Epidemiology of the French Association for the Study of the Liver (AFEF). *Hepatology.* 2000;32(3):477-81. PMID: 10960438.
242. Froehlich F, Lamy O, Fried M, et al. Practice and complications of liver biopsy. Results of a nationwide survey in Switzerland. *Dig Dis Sci.* 1993;38(8):1480-4. PMID: 8344104.
243. Garcia-Tsao G, Boyer JL. Outpatient liver biopsy: how safe is it? *Ann Intern Med.* 1993;118(2):150-3. PMID: 8416312
244. Gilmore IT, Burroughs A, Murray-Lyon IM, et al. Indications, methods, and outcomes of percutaneous liver biopsy in England and Wales: an audit by the British Society of Gastroenterology and the Royal College of Physicians of London. *Gut.* 1995 March 1, 1995;36(3):437-41. PMID: 7698705.
245. Janes CH, Lindor KD. Outcome of patients hospitalized for complications after outpatient liver biopsy. *Ann Intern Med.* 1993;118(2):96-8. PMID: 8416324.
246. McGill D, Rakela J, Zinsmeister A, et al. A 21-year experience with major hemorrhage after percutaneous liver biopsy. *Gastroenterology.* 1990;99(5):1396-400. PMID: 2101588.
247. Vautier G, Scott B, Jenkins D. Liver biopsy: blind or guided? *BMJ.* 1994;309(6967):1455-6. PMID: 7804036
248. Al Knawy B, Shiffman M. Percutaneous liver biopsy in clinical practice. *Liver Int.* 2007;27(9):1166-73. PMID: 17919227.
249. Groessl EJ, Weingart KR, Stepnowsky CJ, et al. The hepatitis C self-management programme: a randomized controlled trial. *J Viral Hepat.* 2011;18:358-68. PMID: 20529203.
250. Keeffe EB, Iwarson S, McMahon BJ, et al. Safety and immunogenicity of hepatitis A vaccine in patients with chronic liver disease. *Hepatology.* 1998;27(3):881-6.
251. Nalpas B, Martin S, Fontaine H, et al. Impact of medical recommendations on alcohol consumption in HCV positive patients. *J Hepatol.* 2001;35(2):312-3. PMID: 11580161.
252. Ompad DC, Fuller CM, Vlahov D, et al. Lack of behavior change after disclosure of hepatitis C virus infection among young injection drug users in Baltimore, Maryland. *Clin Infect Dis.* 2002 Oct 1;35(7):783-8. PMID: 12228813.
253. Scognamiglio P, Galati V, Navarra A, et al. Impact of hepatitis C virus infection on lifestyle. *World J Gastroenterol.* 2007;13(19):2722-6. PMID: 17569142.
254. Tsui JI, Vittinghoff E, Hahn JA, et al. Risk behaviors after hepatitis C virus seroconversion in young injection drug users in San Francisco. *Drug Alcohol Depend.* 2009;105(1-2):160-3. PMID: 19647375.
255. Kwiatkowski CF, Fortuin Corsi K, Booth RE. The association between knowledge of hepatitis C virus status and risk behaviors in injection drug users. *Addiction.* 2002;97(10):1289-94. PMID: 12359033.
256. Latka MH, Hagan H, Kapadia F, et al. A randomized intervention trial to reduce the lending of used injection equipment among injection drug users infected with hepatitis C. *Am J Public Health.* 2008;98:853-61. PMID: 18382005.
257. Zule WA, Costenbader EC, Coomes CM, et al. Effects of a Hepatitis C virus educational intervention or a motivational intervention on alcohol use, injection drug use, and sexual risk behaviors among injection drug users. *Am J Public Health.* 2009;99(Supp.):S180-S6. PMID: 19218179.

258. Dieperink E, Ho SB, Heit S, et al. Significant reductions in drinking following brief alcohol treatment provided in a hepatitis C clinic. *Psychosomatics*. 2010;51(2):149-56. PMID: 20332290.
259. Proeschold-Bell RJ, Patkar AA, Naggie S, et al. An integrated alcohol abuse and medical treatment model for patients with hepatitis C. *Dig Dis Sci*. 2011; PMID: 22134784.
260. European Paediatric Hepatitis C Virus Network. A significant sex--but not elective cesarean section--effect on mother-to-child transmission of hepatitis C virus infection. *J Infect Dis*. 2005;192(11):1872-9. PMID: 16267757.
261. European Paediatric Hepatitis C Virus Network. Effects of mode of delivery and infant feeding on the risk of mother-to-child transmission of hepatitis C virus. *European Paediatric Hepatitis C Virus Network. BJOG*. 2001;108(4):371-7. PMID: 11305543.
262. Conte D, Fraquelli M, Prati D, et al. Prevalence and clinical course of chronic hepatitis C virus (HCV) infection and rate of HCV vertical transmission in a cohort of 15,250 pregnant women. 3 ed. UNITED STATES: Cattedra di Gastroenterologia, IRCCS Ospedale Maggiore, Milan, Italy. Dario.Conte@unimi.it; 2000. p. 751-5.
263. Garland SM, Tabrizi S, Robinson P, et al. Hepatitis C--role of perinatal transmission. 4 ed. AUSTRALIA: Microbiology Department, The Royal Women's Hospital, Melbourne, Victoria, Australia.; 1998. p. 424-7.
264. Gibb DM, Goodall RL, Dunn DT, et al. Mother-to-child transmission of hepatitis C virus: evidence for preventable peripartum transmission. *Lancet*. 2000;356(9233):904-7. PMID: 11036896.
265. La Torre A, Biadaoli R, Capobianco T, et al. Vertical transmission of HCV. *Acta Obstetrica et Gynecologica Scandinavica*. 1998;77(9):889-92. PMID: 9808375.
266. McMenamin MB, Jackson AD, Lambert J, et al. Obstetric management of hepatitis C-positive mothers: analysis of vertical transmission in 559 mother-infant pairs. *Am J Obstet Gynecol*. 2008;199(3):315.e1-5. PMID: 18771997.
267. Okamoto M, Nagata I, Murakami J, et al. Shift in the buoyant density of hepatitis C virus particles in infants infected by mother-to-infant transmission. *Pediatr Int*. 1999;41(4):369-73. PMID: 10453185.
268. Resti M, Azzari C, Mannelli F, et al. Mother to child transmission of hepatitis C virus: Prospective study of risk factors and timing of infection in children born to women seronegative for HIV-1. *BMJ*. 1998;317(7156):437-40. PMID: 9703524.
269. Spencer JD, Latt N, Beeby PJ, et al. Transmission of hepatitis C virus to infants of human immunodeficiency virus-negative intravenous drug-using mothers: rate of infection and assessment of risk factors for transmission. *J Vir Hep*. 1997;4(6):395-409. PMID: 9430360.
270. Syriopoulou V, Nikolopoulou G, Daikos GL, et al. Mother to child transmission of hepatitis C virus: Rate of infection and risk factors. *Scand J Infect Dis*. 2005;37(5):350-3. PMID: 16051571.
271. Tajiri H, Miyoshi Y, Funada S, et al. Prospective study of mother-to-infant transmission of hepatitis C virus. *Pediatr Infect Dis J*. 2001 Jan;20(1):10-4. PMID: 11176560.
272. Zanetti AR, Tanzi E, Newell ML. Mother-to-infant transmission of hepatitis C virus. *J Hepatol, Supplement*. 1999;31(1):96-100. PMID: 10622569.
273. Zanetti AR, Tanzi E, Romano L, et al. A prospective study on mother-to-infant transmission of hepatitis C virus. *Intervirology*. 1998;41(4-5):208-12. PMID: 10213898.
274. Polywka S, Feucht H, Zollner B, et al. Hepatitis C virus infection in pregnancy and the risk of mother-to-child transmission. 2 ed. GERMANY: Institute for Medical Microbiology and Immunology, University Hospital Eppendorf, Hamburg, Germany.; 1997. p. 121-4.
275. Lin HH, Kao JH, Hsu HY, et al. Absence of infection in breast-fed infants born to hepatitis C virus-infected mothers. *J Pediatr*. 1995;126(4):589-91. PMID: 7535353.

276. Pipan C, Amici S, Astori G, et al. Vertical transmission of hepatitis C virus in low-risk pregnant women. *Eur J Clin Microbiol Infect Dis*. 1996 Feb;15(2):116-20. PMID: 8801082.
277. Polywka S, Schröter M, Feucht HH, et al. Low risk of vertical transmission of hepatitis C virus by breast milk. *Clin Infect Dis*. 1999;29(5):1327-9. PMID: 10524987.
278. Tanzi M, Bellelli E, Benaglia G, et al. The prevalence of HCV infection in a cohort of pregnant women, the related risk factors and the possibility of vertical transmission. *Eur J Epidemiol*. 1997;13(5):517-21. PMID: 9258562.
279. Moriya T, Sasaki F, Mizui M, et al. Transmission of hepatitis C virus from mothers to infants: its frequency and risk factors revisited. *Biomed Pharmacother*. 1995;49(2):59-64.
280. Stewart BJ, Mikocka-Walus AA, Harley H, et al. Help-seeking and coping with the psychosocial burden of chronic hepatitis C: A qualitative study of patient, hepatologist, and counsellor perspectives. *Int J Nurs Stud*. 2011 May;49(5):560-9. PMID: 22154094.
281. Zickmund S, Ho EY, Masuda M, et al. "They treated me like a leper". Stigmatization and the quality of life of patients with hepatitis C. *J Gen Intern Med*. 2003;18(10):835-44. PMID: 14521647.
282. Conrad SGL, Cooksley WGE, Dunne MP, Macdonald GA. Living with chronic hepatitis C infection means 'you just haven't got a normal life any more'. *Chronic Illn*. 2006;2(2):121-31. PMID: 17175655.
283. Brok J, Gluud LL, Gluud C. Ribavirin plus interferon versus interferon for chronic hepatitis C. *Cochrane Database Syst Rev*. 2010;20(1):CD005445-CD. PMID: 20091577.
284. Chou R, Clark EC, Helfand M. Screening for hepatitis C virus infection: A review of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2004;140(6):465-79+I62. PMID: 15023713.
285. Poynard T, Morra R, Halfon P, et al. Meta-analyses of FibroTest diagnostic value in chronic liver disease. *BMC Gastroenterol*. 2007;7(1):40. PMID: 17937811.
286. Lin Z-H, Xin Y-N, Dong Q-J, et al. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: An updated meta-analysis. *Hepatology*. 2011;53(3):726-36. PMID: 21319189.
287. Smith JO, Sterling RK. Systematic review: non-invasive methods of fibrosis analysis in chronic hepatitis C. *Aliment Pharmacol Ther*. 2009;30(6):557-76. PMID: 19519733.
288. Parkes J, Guha IN, Roderick P, et al. Performance of serum marker panels for liver fibrosis in chronic hepatitis C. *J Hepatol*. 2006;44(3):462-74. PMID: 16427156.
289. Halfon P, Munteanu M, Poynard T. FibroTest-ActiTest as a non-invasive marker of liver fibrosis. *Gastroenterologie Clinique et Biologique*. 2008;32(6, Supplement 1):22-39.
290. Shaheen AAM, Wan AF, Myers RP. FibroTest and FibroScan for the prediction of hepatitis C-related fibrosis: a systematic review of diagnostic test accuracy. *Am J Gastroenterol*. 2007;102(11):2589-600. PMID: 17850410.
291. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States.; 2011. p. 1-207. <http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf>. Accessed on June 20, 2011.
292. Sebastiani G, Alberti A. Non invasive fibrosis biomarkers reduce but not substitute the need for liver biopsy. *World J Gastroenterol*. 2006;12:3682 - 94. PMID: 16773685.
2934. Castera L, Sebastiani G, Le Bail B, et al. Prospective comparison of two algorithms combining non-invasive methods for staging liver fibrosis in chronic hepatitis C. *J Hepatol*. 2010;52(2):191-8. PMID: 20006397.

Abbreviations and Acronyms

ACOG	American College of Obstetricians and Gynecologists
AHRQ	Agency for Healthcare Research and Quality
ALT	Alanine aminotransferase
APRI	Aspirate Aminotransferase-Platelet Ratio Index
AST	Aspirate aminotransferase
AUROC	Area under the receiver operating characteristic curve
CDC	Centers for Disease Control and Prevention
CDS	Cirrhosis Discriminant Score
CER	Comparative effectiveness review
CHIP	Children's Health Insurance Program
CI	Confidence interval
ELF	European Liver Fibrosis Index
ELISA	Enzyme-linked immunoassay
EPC	Evidence-based Practice Center
GGT	Gamma-glutamyl transferase
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
IVDU	Intravenous drug use
PCR	Polymerase chain reaction
PICOTS	Populations, Interventions, Comparators, Outcomes, Timing and Setting
RIBA	Recombinant immunoblot assay
Simplified ELF	Enhanced Liver Fibrosis Index
SVR	Sustained virologic response
TEP	Technical Expert Panel
TIMP	Tissue inhibitor of metalloproteinase
USPSTF	United States Preventive Services Task Force

Appendix A. Exact Search Strategy

The following databases have been searched for relevant information and an updated search was conducted in May 2012:

Database Searches: Hepatitis C: Screening/Diagnosis, Treatment, and Pregnancy

Name	Date Limits	Platform Provider
Medline	2002 to May Week 3 2012	OvidSP
Embase	2002-2012	Embase (Elsevier)
Cochrane Library: CDSR, DARE, CCRCT	2002-2012	Cochrane Library
Clinical Trials.gov	2002-2012	
Drugs@FDA	2002-2012	
Health Canada Drug Products Database	2002-2012	
European Public Assessment Reports (European Medicine Agency)	2002-2012	
Scopus	2002-2012	Scopus
PsycINFO	2002 to May Week 4 2012	OvidSP

Hand Search of Journals & Supplements - Topic-Specific Search Terms

Concept	Controlled Vocabulary	Keywords
Hepatitis C	Hepatitis C/ Hepatitis C, Chronic/ Hepacivirus/ OR	hcv.mp hepacivirus\$.mp
Screening	Exp Mass screening/ Population surveillance/ Sentinel Surveillance/ Seroepidemiologic Studies/	((public\$ or communit\$ or universal\$ or widespread or open\$ or unrestricted or group\$ or adult\$) adj3 (screen\$ OR test\$ or surveillance)) (antibod\$ ADJ3 (test\$ or screen\$ or surveillance))

Concept	Controlled Vocabulary	Keywords
Diagnosis	Hepatitis C/di, pa, ra, us Immunoenzyme Techniques/ Enzyme-Linked Immunosorbent Assay/ Immunoblotting/ Polymerase Chain Reaction/ Reverse Transcriptase Polymerase Chain Reaction/ Liver function tests/ (liver/ AND biopsy/) Breath Tests/ Diagnostic Imaging/ Magnetic Resonance Imaging/ EXP Tomography, X-ray Computed/ Alanine Transaminase/ "sensitivity and specificity"/ Limit of Detection/ ROC Curve/ Diagnostic errors/ False Negative Reactions/ False Positive Reactions/ Hepatitis C Antibodies/ Antibodies, viral/	ELISA EIA recombinant immunoblot assay RIBA PCR RT-PCR transcription-mediated amplification TMA Branched-chain DNA bDNA radioimmunoblot assay HCV-RNA (liver\$ ADJ3 biops\$) Fibrosis non-invasive blood test\$ blood marker\$ breath\$ test\$ transient elastography Fibrometer FibroTest Hepascore MRI alanine aminotransferase ALT misdiagnos\$ CT-scan Ultrasound HCV Antibodies anti hcv anti-hcv
Treatment	Antiviral agents/ Interferons/ Interferon-alpha/ Interferon Alfa-2a/ Interferon Alpha-2b/ Exp Polyethylene Glycols/ Ribavirin/ Exp Protease Inhibitors/	Interferon\$ interferon alpha-2a interferon alpha-2b IFNalpha2a IFNalpha2b interferon alpha 2a interferon alpha 2b pegasys Peg-intron peginterferon alpha-2a peginterferon alpha-2b peginterferon alpha 2a peginterferon alpha 2b pegylated interferon\$ IFN\$ PEG IFN\$ Ribavirin RBV protease inhibitor\$ polymerase inhibit\$ HCV protease\$ Telaprevir boceprevir

Concept	Controlled Vocabulary	Keywords
Harms - treatment	AE.fs MO.fs PO.fs TO.fs CT.fs AE=adverse effects CT=contraindications MO=mortality PO=poisoning TO=toxicity	Unsafe Safety harm\$ complication\$ poison\$ risk\$ side-effect\$ side effect\$ (undesirable ADJ1 effect\$) (treatment ADJ1 emergent) tolerab\$ toxic\$ adrs (adverse ADJ2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)) (undesirable ADJ1 effect\$) (treatment ADJ1 emergent) tolerab\$ toxic\$ adrs (adverse ADJ2 (effect or effects or reaction or reactions or event or events or outcome or outcomes))
Harms - screening	AE.fs CT.fs AE=adverse effects CT=contraindications	Unsafe Safety Harm Harm complication\$ risk\$ side-effect\$ (undesirable ADJ1 effect\$) (treatment ADJ1 emergent) tolerab\$ adrs (adverse ADJ2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)) Anxiety anxious\$ label\$ impact\$
Pregnancy	Pregnancy/ Pregnancy Complications, Infectious/ Pregnancy Complications/ Exp Delivery, Obstetric/ Maternal Exposure/ Fetus/ Infant, Newborn/ Infant/ Prenatal Diagnosis/ Neonatal Screening/ Prenatal Care/ Infectious Disease Transmission, Vertical/ Milk, Human/ Breast Feeding/ Postpartum Period/	gravid\$ pregnan\$ prenatal perinatal antenatal parturiency partuition gestat\$ childbirth child birth reproduct\$ birth\$ childbearing child-bearing

Concept	Controlled Vocabulary	Keywords
High Risk Groups	Substance-abuse, Intravenous/ Needle Sharing/ Opioid-Related Disorders/ Unsafe Sex/ Sexual Behavior/ HIV/ HIV Infections/	high risk high-risk drug\$ abuse\$
Counseling Immunizations	Counseling/ Sex Counseling/ Health Education/ Patient Education as Topic/ Psychotherapy/ Behavior Therapy/ Cognitive Therapy/ Immunization/ Immunotherapy/ Psychotherapy, Brief/ Socioenvironmental Therapy/	

Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1947 to June Week 2 2011,

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations June 17, 2011

Date Searched: 06/20/2011

1	Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/ or Hepatitis C.mp. or hepacivirus\$.mp. or HCV.mp.	54983
2	Mass Screening/ or Population Surveillance/ or Sentinel Surveillance/ or Seroepidemiologic Studies/ or Prenatal Diagnosis/ or Neonatal Screening/ or Infectious Disease Transmission, Vertical/ or Disease Transmission, Infectious/ or tm.fs. or transmi\$.ti,ab. or ((public\$ or communit\$ or universal\$ or widespread or open\$ or unrestricted or group\$ or adult\$ or adolescen\$ or antibod\$) adj3 (screen\$ or test\$ or surveillance)).ti,ab.	555260
3	Pregnancy/ or Pregnancy Complications, Infectious/ or Pregnancy Complications/ or exp Delivery, Obstetric/ or Maternal-Fetal Exchange/ or Fetal Monitoring/ or Labor, Induced/ or Fetus/ or Infant, Newborn/ or Infant/ or Prenatal Care/ or Milk, Human/ or Breast Feeding/ or Postpartum Period/ or exp cesarean section/ or exp obstetric labor/ or amniocentesis/ or chorionic villi/	1401109
4	1 and 2 and 3	1247
5	remove duplicates from 4	1234

Medline Update Search

Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to October Week 3 2011,

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations October 31, 2011

Date Searched: 05/31/2012

1	Hepatitis C/ or Hepatitis C, Chronic/ or Hepacivirus/ or Hepatitis C.mp. or hepacivirus\$.mp. or HCV.mp.	58120
2	Mass Screening/ or Population Surveillance/ or Sentinel Surveillance/ or Seroepidemiologic Studies/ or Prenatal Diagnosis/ or Neonatal Screening/ or Infectious Disease Transmission, Vertical/ or Disease Transmission, Infectious/ or tm.fs. or transmi\$.ti,ab. or ((public\$ or communit\$ or universal\$ or widespread or open\$ or unrestricted or group\$ or adult\$ or adolescen\$ or antibod\$) adj3 (screen\$ or test\$ or surveillance)).ti,ab.	576254
3	Pregnancy/ or Pregnancy Complications, Infectious/ or Pregnancy Complications/ or exp Delivery, Obstetric/ or Maternal-Fetal Exchange/ or Fetal Monitoring/ or Labor, Induced/ or Fetus/ or Infant, Newborn/ or Infant/ or Prenatal Care/ or Milk, Human/ or Breast Feeding/ or Postpartum Period/ or exp cesarean section/ or exp obstetric labor/ or amniocentesis/ or chorionic villi/	1436320
4	1 and 2 and 3	1291
5	remove duplicates from 4	1250

Appendix B. Hepatitis C Screening: Inclusion Criteria by Key Question

All Key Questions	Inclusion Criteria
Populations	Asymptomatic adults and pregnant women without known liver function test abnormalities
Settings	For screening studies, primary care, or other settings generalizable to primary care (e.g., family planning clinics, school-based health clinics), other settings in which screening is commonly performed (e.g., emergency room or urgent care). Focus on studies conducted in the U.S. and other developed countries.
Study designs	Randomized controlled trials and cohort studies (all KQ's), studies of diagnostic accuracy (KQ 2b, 4a), before-after studies (KQ's 3, 4b, 5, 6a, 6b, 6c, and 7), and cross sectional studies (KQ's 2a, 2b, 6b)
Screening	<p>KQ 1a. Does screening for hepatitis C virus (HCV) infection in non pregnant adults without known abnormal liver function tests reduce mortality and morbidity due to HCV infection, affect quality of life, or reduce incidence of HCV infection?</p> <p>KQ 1b. Does screening for HCV infection during pregnancy reduce vertical transmission of HCV or improve mortality or morbidity for the mother or child?</p> <p>KQ 2a. What is the effectiveness of different risk- or prevalence-based methods for screening for HCV infection on clinical outcomes?</p> <p>KQ 2b. What is the sensitivity and number needed to screen to identify one case of HCV infection of different risk- or prevalence-based methods for screening for HCV infection?</p> <p>KQ 3. What are the harms associated with screening for HCV infection, including adverse effects such as anxiety, labeling, and impact on relationships?</p>
Interventions	HCV antibody testing
Outcomes	<p>KQs 1a, 1b, and 2: Intermediate outcomes: sustained virological response rates, histological improvements, behavioral changes to improve health outcomes, and reduce HCV transmission. Clinical outcomes: mortality due to HCV infection, morbidity due to HCV infection including hepatic cirrhosis, hepato-cellular carcinoma, rate of liver transplantation, and quality of life.</p> <p>KQ 1b: Mother-to-child transmission rates of HC.</p> <p>KQ 3: Anxiety; labeling; partner discord, abuse, or violence.</p>
Comparisons	<p>KQs 1a, 1b, and 3: HCV screening vs. no screening.</p> <p>KQ 2: Comparisons of different screening strategies.</p>
Workup	<p>KQ 4a. What is the comparative effectiveness and comparative diagnostic accuracy of various tests and strategies for the workup to guide treatment decisions in patients who are HCV positive?</p> <p>KQ 4b. What proportion of patients with screen-detected HCV infection receives treatment?</p> <p>KQ 5. What are the harms associated with the workup for guiding treatment decisions?</p>
Populations	KQ 4b and 5: Persons with screen-detected HCV infection.
Interventions	KQ 4a and 5: Liver biopsy, laboratory tests, imaging tests.
Comparisons	KQ 4a and 5: Comparisons of different workup strategies and different tests to diagnose fibrosis or cirrhosis.
Outcomes	<p>KQ 4a: Diagnostic accuracy, clinical outcomes (see KQs 1a, 1b, and 2).</p> <p>KQ 4b: Proportion who receives treatment.</p> <p>KQ 5: Bleeding, infection, other complications</p>

All Key Questions	Inclusion Criteria
Interventions	KQ 6a. How effective is counseling or immunizations of patients with HCV infection at improving health outcomes or reducing the spread of HCV? KQ 6b. Does becoming aware of positive HCV infection status decrease high risk behaviors? KQ 6c. How effective is counseling or immunizations of patients with HCV infection at improving intermediate outcomes, including change in high risk behaviors? KQ 7. Do any interventions decrease or increase the vertical transmission of HCV during delivery or in the perinatal period?
Populations	KQ 6a, 6b, 7: Persons with chronic HCV infection
Interventions	KQ 6a and 6b: Counseling on risky behaviors or alcohol use and immunizations for HAV and HBV infection. KQ 7: Labor management or delivery practices and breast feeding.
Comparisons	KQ 6a and 6b: Counseling or immunizations vs. no intervention. KQ 7: Comparisons of different labor and delivery practices; breast feeding vs. no breast feeding.
Outcomes	KQ 6a, 6b: See KQs 1a, 1b, and 2. KQ 7: See KQ 1b.

Appendix C. Included Studies

- Adams LA, Bulsara M, Rossi E, et al. Hepascore: an accurate validated predictor of liver fibrosis in chronic hepatitis C infection. *Clin Chem*. 2005 October 1, 2005;51(10):1867-73. PMID: 16055434.
- Adler M, Gulbis B, Moreno C, et al. The predictive value of FIB-4 versus FibroTest, APRI, FibroIndex and Forns index to noninvasively estimate fibrosis in hepatitis C and nonhepatitis C liver diseases. *Hepatology*. 2008;47(2):762-3. PMID: 18220307.
- Ahmad W, Ijaz B, Javed FT, et al. A comparison of four fibrosis indexes in chronic HCV: Development of new fibrosis-cirrhosis index (FCI). *BMC Gastroenterol*. 2011;11(1):44-. PMID: 21507271.
- Alsatie M, Kwo PY, Gingerich JR, et al. A multivariable model of clinical variables predicts advanced fibrosis in chronic hepatitis C. *J Clin Gastroenterol*. 2007;41(4):416-21. PMID: 17413613.
- Anderson EM, Mandeville RP, Hutchinson SJ, et al. Evaluation of a general practice based hepatitis C virus screening intervention. *Scott Med J*. 2009 Aug;54(3):3-7. PMID: 19728405.
- Anderson FH, Zeng L, Rock NR, et al. An assessment of the clinical utility of serum ALT and AST in chronic hepatitis C. *Hepatol Res*. 2000;18(1):63-71. PMID: 10838037.
- Andriulli A, Persico M, Iacobellis A, et al. Treatment of patients with HCV infection with or without liver biopsy. *J Viral Hepat*. 2004;11(6):536-42. PMID: 15500554.
- Atwell TD, Smith RL, Hesley GK, et al. Incidence of bleeding after 15,181 percutaneous biopsies and the role of aspirin. *Am J Roentgenol*. 2010;194(3):784-9. PMID: 20173160.
- Becker L, Salameh W, Sferruzza A, et al. Validation of hepascore, compared with simple indices of fibrosis, in patients with chronic hepatitis C virus infection in United States. *Clin Gastroenterol Hepatol*. 2009;7(6):696-701. PMID: 19514117.
- Bejarano G. Prospective evaluation of liver fibrosis in chronic viral hepatitis C infection using the Sabadell NIHCED (Non-Invasive Hepatitis-C-Related Cirrhosis Early Detection) index.; 2009. <http://hepatop.biopredictive.com/publication/19527078/prospective-evaluation-of-liver-fibrosis-in-chronic-viral-hepatitis-c-infection-using-the-sabadell-nihced-non-invasive-hepatitis-c-related-cirrhosis-early-detection-index/>.
- Ben Jazia E, Kaabia N, Benabdelkader A, et al. Noninvasive Fibrosis Markers for the Prediction of Significant Fibrosis in Patients With Chronic Hepatitis C Virus Infection in Tunisia. *Infect Dis Clin Pract (Baltim Md)*. 2009;17(6):385.
- Berg T, Sarrazin C, Hinrichsen H, et al. Does noninvasive staging of fibrosis challenge liver biopsy as a gold standard in chronic hepatitis C? *Hepatology*. 2004;39(5):1456-7. PMID: 15122779.
- Boeker KH, Haberkorn CI, Michels D, et al. Diagnostic potential of circulating TIMP-1 and MMP-2 as markers of liver fibrosis in patients with chronic hepatitis C. *Clin Chim Acta*. 2002;316(1-2):71-81. PMID: 11750276.
- Bonacini M, Hadi G, Govindarajan S, et al. Utility of a discriminant score for diagnosing advanced fibrosis or cirrhosis in patients with chronic hepatitis C virus infection. *Am J Gastroenterol*. 1997;92(8):1302-4. PMID: 9260794.
- Borroni G, Ceriani R, Cazzaniga M, et al. Comparison of simple tests for the non-invasive diagnosis of clinically silent cirrhosis in chronic hepatitis C. *Aliment Pharmacol Ther*. 2006;24(5):797-804. PMID: 16918883.
- Borsoi Viana MS, Takei K, Collarile Yamaguti DC, et al. Use of AST platelet ratio index (APRI Score) as an alternative to liver biopsy for treatment indication in chronic hepatitis C. *Ann Hepatol*. 2009;8(1):26-31. PMID: 19221530.
- Bota S, Sirli R, Sporea I, et al. A new scoring system for prediction of fibrosis in chronic hepatitis C. *CORD Conference Proceedings*. 2011;11(7):548-55. PMID: 22087193.

Bourliere M, Penaranda G, Ouzan D, et al. Optimized stepwise combination algorithms of non-invasive liver fibrosis scores including Hepascore in hepatitis C virus patients. *Aliment Pharmacol Ther.* 2008;28(4):458-67. PMID: 18498446.

Bourliere M, Penaranda G, Renou C, et al. Validation and comparison of indexes for fibrosis and cirrhosis prediction in chronic hepatitis C patients: proposal for a pragmatic approach classification without liver biopsies. *J Viral Hepat.* 2006;13(10):659-70. PMID: 16970597.

Boursier J, Bacq Y, Halfon P, et al. Improved diagnostic accuracy of blood tests for severe fibrosis and cirrhosis in chronic hepatitis C. *Eur J Gastroenterol Hepatol.* 2009;21(1):28-38. PMID: 19060630.

Boursier J, de Ledinghen V, Zarski J-P, et al. A new combination of blood test and fibroscan for accurate non-invasive diagnosis of liver fibrosis stages in chronic hepatitis C. *Am J Gastroenterol.* 2011;106(7):1255-63. PMID: 21468012.

Boursier J, de Ledinghen V, Zarski JP, et al. Comparison of eight diagnostic algorithms for liver fibrosis in hepatitis C: new algorithms are more precise and entirely noninvasive. *Hepatology.* 2012;55(1):58-67. PMID: 21898504.

Burton MJ, Sunesara I, Penman A, et al. Comparing the aspartate aminotransferase (AST) to platelet ratio index (APRI) between african american and white veterans with chronic hepatitis C. *South Med J.* 2011;104(5):309-14. PMID: 21606706.

Calès P, De Ledinghen V, Halfon P, et al. Evaluating the accuracy and increasing the reliable diagnosis rate of blood tests for liver fibrosis in chronic hepatitis C. *Liver Int.* 2008;28(10):1352-62. PMID: 18492022.

Calès P, Boursier J, Bertrais S, et al. Optimization and robustness of blood tests for liver fibrosis and cirrhosis. *Clin Biochem.* 2010;43(16-17):1315-22. PMID: 20713037.

Castéra L, Sebastiani G, Le Bail B, et al. Prospective comparison of two algorithms combining non-invasive methods for staging liver fibrosis in chronic hepatitis C. *J Hepatol.* 2010;52(2):191-8. PMID: 20006397.

Castéra L, Vergniol J, Foucher J, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology.* 2005;128(2):343-50. PMID: 15685546.

Castera L. Transient elastography and other noninvasive tests to assess hepatic fibrosis in patients with viral hepatitis. *J Vir Hep.* 2009;16(5):300-14. PMID: 19254351.

Ceci O, Margiotta M, Marello F, et al. High rate of spontaneous viral clearance in a cohort of vertically infected hepatitis C virus infants: What lies behind? [4]. *Journal of Hepatology.* 2001;35(5):687-8. PMID: 11690723.

Cheong JY, Um SH, Seo YS, et al. Non-invasive index for predicting significant liver fibrosis: comparison of diagnostic performances in patients with chronic hepatitis B and C. *Dig Dis Sci.* 2011;56:555-63. PMID: 20585981.

Cheung KJ, Tilleman K, Deforce D, et al. Usefulness of a novel serum proteome-derived index FI-PRO (fibrosis-protein) in the prediction of fibrosis in chronic hepatitis C. *Eur J Gastroenterol Hepatol.* 2011;23(8):701-10. PMID: 21623191.

Cheung RC, Currie S, Shen H, et al. Can we predict the degree of fibrosis in chronic hepatitis C patients using routine blood tests in our daily practice? *J Clin Gastroenterol.* 2008;42(7):827-34. PMID: 18285716.

Chrysanthos NV, Papatheodoridis GV, Savvas S, et al. Aspartate aminotransferase to platelet ratio index for fibrosis evaluation in chronic viral hepatitis. *Eur J Gastroenterol Hepatol.* 2006;18(4):389-96. PMID: 16538110.

Cobbold JF, Crossey MM, Colman P, et al. Optimal combinations of ultrasound-based and serum markers of disease severity in patients with chronic hepatitis C. *J Viral Hepat.* 2009;17(8):537. PMID: 19804501.

Colletta C, Smirne C, Fabris C, et al. Value of two noninvasive methods to detect progression of fibrosis among HCV carriers with normal aminotransferases. *Hepatology*. 2005;42(4):838-45. PMID: 16121354.

Colli A, Colucci A, Paggi S, Fraquelli M, Massironi S, Andreoletti M, Michela V, Conte D. Accuracy of a predictive model for severe hepatic fibrosis or cirrhosis in chronic hepatitis C. *World J Gastroenterol* 2005; 11(46):7318-7322

Conte D, Fraquelli M, Prati D, et al. Prevalence and clinical course of chronic hepatitis C virus (HCV) infection and rate of HCV vertical transmission in a cohort of 15,250 pregnant women. *Hepatology*. 2000;31(3):751-5. PMID: 10706568.

Coughlan B, Sheehan J, Carr A, et al. Evaluation of a Brief Group Based Psychological/Educational Treatment Programme for Women with an Iatrogenic Chronic Hepatitis C Virus Infection. *J Clin Psychol Med Settings*. 2004;11(4):303-14.

Crisan D, Radu C, Lupsor M, et al. Two or more synchronous combination of noninvasive tests to increase accuracy of liver fibrosis assessment in chronic hepatitis C; results from a cohort of 446 patients. *CORD Conference Proceedings*. 2012;12(3):177-84. PMID: 22550525.

Cross TJ, Calvaruso V, Maimone S, et al. Prospective comparison of Fibroscan, King's score and liver biopsy for the assessment of cirrhosis in chronic hepatitis C infection. *J Viral Hepat*. 2010;17(8):546-. PMID: 19874477.

Cross TJS, Rizzi P, Berry PA, et al. King's Score: an accurate marker of cirrhosis in chronic hepatitis C. *Eur J Gastroenterol Hepatol*. 2009;21(7):730-8 PMID: 19430302.

Dieperink E, Ho SB, Heit S, et al. Significant reductions in drinking following brief alcohol treatment provided in a hepatitis C clinic. *Psychosomatics*. 2010;51(2):149-56. PMID: 20332290.

Ehsan N, Badr M, Raouf A, et al. Correlation between liver biopsy findings and different serum biochemical tests in staging fibrosis in Egyptian patients with chronic hepatitis C virus infection. *Arab J Gastroenterol*. 2008;9(1):7-12.

El-Gindy I, El Rahman AT, El-Alim MA, et al. Diagnostic potential of serum matrix metalloproteinase-2 and tissue inhibitor of metalloproteinase-1 as non-invasive markers of hepatic fibrosis in patients with HCV related chronic liver disease. *Egypt J Immunol*. 2003;10(1):27-35. PMID: 15719620.

El-Shorbagy E, Afefy AF, Ibrahim IA, et al. Non-invasive markers and predictors of severity of hepatic fibrosis in HCV patients at Sharkia Governorate, Egypt. *J Egypt Soc Parasitol*. 2004;34(1):459-78. PMID: 15124753.

El-Sayed R, Fahmy M, El Koofy N, et al. Can aspartate aminotransferase to platelet ratio index replace liver biopsy in chronic hepatitis C? *Tropical Gastroenterology*, 2011;32(4):267.272.

European Paediatric Hepatitis C Virus Network. A significant sex--but not elective cesarean section--effect on mother-to-child transmission of hepatitis C virus infection. *J Infect Dis*. 2005 Dec 1;192(11):1872-9. PMID: 16267757.

European Paediatric Hepatitis C Virus Network. Effects of mode of delivery and infant feeding on the risk of mother-to-child transmission of hepatitis C virus. *European Paediatric Hepatitis C Virus Network. BJOG*. 2001;108:371-7. PMID: 11305543.

Fabris C, Smirne C, Toniutto P, et al. Usefulness of six non-proprietary indirect markers of liver fibrosis in patients with chronic hepatitis C. *Clin Chem Lab Med*. 2008;46(2):253-9. PMID: 18324909.

Fabris P, Tositti G, Giordani MT, et al. Assessing patients' understanding of hepatitis C virus infection and its impact on their lifestyle. *Ailment Pharmacol Ther*. 2006;23(8):1161-70. PMID: 16611277.

Fontana RJ, Goodman ZD, Dienstag JL, et al. Relationship of serum fibrosis markers with liver fibrosis stage and collagen content in patients with advanced chronic hepatitis C. *Hepatology*. 2008;47(3):789-98. PMID: 18175357.

Forns X, Ampurdanès S, Llovet JM, et al. Identification of chronic hepatitis C patients without hepatic fibrosis by a simple predictive model. *Hepatology*. 2002;36(4):986-92. PMID: 12297848.

Friedrich-Rust M, Rosenberg W, Parkes J, et al. Comparison of ELF, FibroTest and FibroScan for the non-invasive assessment of liver fibrosis. *BMC Gastroenterology*. 2010;10(1):103. PMID: 20828377.

Gabrielli GB, Capra F, Casaril M, et al. Serum laminin and type III procollagen in chronic hepatitis C. Diagnostic value in the assessment of disease activity and fibrosis. *Clin Chim Acta*. 1997;265(1):21-31. PMID: 9352126.

Garland SM, Tabrizi S, Robinson P, et al. Hepatitis C--role of perinatal transmission. *Aust N Z J Obstet Gynaecol*. 1998 Nov;38(4):424-7. PMID: 9890224.

Giannini (a) E, Risso D, Botta F, et al. Validity and clinical utility of the aspartate aminotransferase-alanine aminotransferase ratio in assessing disease severity and prognosis in patients with hepatitis C virus-related chronic liver disease. *Arch Intern Med*. 2003 January 27, 2003;163(2):218-24. PMID: 12546613.

Giannini (b) E, Testa R. Noninvasive diagnosis of fibrosis: The truth is rarely pure and never simple. *Hepatology*. 2003;38(5):1312-3. PMID: 14578874.

Giannini EG, Zaman A, Ceppa P, et al. A simple approach to noninvasively identifying significant fibrosis in chronic hepatitis C patients in clinical practice. *J Clin Gastroenterol*. 2006;40(6):521-7. PMID: 16825935.

Gibb DM, Goodall RL, Dunn DT, et al. Mother-to-child transmission of hepatitis C virus: evidence for preventable peripartum transmission. 2000;356(9233):904-7. PMID: 11036896.

Gomes da Silva. Aspartate aminotransferase-to-platelet ratio index for fibrosis and cirrhosis prediction in chronic hepatitis C patients. *Braz J Infect Dis*. 2008;12(1):15-9. PMID: 18553008.

Grigorescu M, Rusu M, Neculoiu D, et al. The FibroTest value in discriminating between insignificant and significant fibrosis in chronic hepatitis C patients. The Romanian experience. *J Gastrointestin Liver Dis*. 2007;16(1):31-7. PMID: 17410286.

Groessl EJ, Weingart KR, Stepnowsky CJ, et al. The hepatitis C self-management programme: a randomized controlled trial. *J Viral Hepat*. 2011;18:358-68. PMID: 20529203.

Groom H, Dieperink E, Nelson DB, et al. Outcomes of a hepatitis C screening program at a large urban VA medical center. *J Clin Gastroenterol*. 2008 Jan;42(1):97-106. PMID: 18097298.

Guéchet J, Lasnier E, Sturm N, et al. Automation of the Hepascore and validation as a biochemical index of liver fibrosis in patients with chronic hepatitis C from the ANRS HC EP 23 Fibrostar cohort. *Clin Chim Acta*. 2010;411(1-2):86-91. PMID: 19850017.

Guéchet J, Laudat A, Loria A, et al. Diagnostic accuracy of hyaluronan and type III procollagen amino-terminal peptide serum assays as markers of liver fibrosis in chronic viral hepatitis C evaluated by ROC curve analysis. *Clin Chem*. 1996;42(4):558-63. PMID: 8605673.

Guéchet J, Poupon RE, Giral P, et al. Relationship between procollagen III aminoterminal propeptide and hyaluronan serum levels and histological fibrosis in primary biliary cirrhosis and chronic viral hepatitis C. *J Hepatol*. 1994;20(3):388-93. PMID: 8014451.

Güzelbulut. AST-platelet ratio index, Forns index and FIB-4 in the prediction of significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Turk J Gastroenterol*. 2011;22(3):279-85. PMID: 21805418.

Gunn RA, Murray PJ, Brennan CH, et al. Evaluation of screening criteria to identify persons with hepatitis C virus infection among sexually transmitted disease clinic clients: results from the San Diego Viral Hepatitis Integration Project. *Sex Transm Dis*. 2003 Apr;30(4):340-4. PMID: 12671556.

Halfon P, Bacq Y, De Muret A, et al. Comparison of test performance profile for blood tests of liver fibrosis in chronic hepatitis C. *J Hepatol*. 2007;46(3):395-402. PMID: 17156890.

- Halfon P, Bourliere M, Deydier R, et al. Independent prospective multicenter validation of biochemical markers (fibrotest-actitest) for the prediction of liver fibrosis and activity in patients with chronic hepatitis C: the fibropaca study. *Am J Gastroenterol.* 2006 Mar;101(3):547-55. PMID: 16542291.
- Halfon P. Accuracy of hyaluronic acid level for predicting liver fibrosis stages in patients with hepatitis C virus. *Comp Hepatol.* 2005;4(1):6. PMID: 16008833.
- Hsieh YY, Tung SY, Lee IL, et al. FibroQ: an easy and useful noninvasive test for predicting liver fibrosis in patients with chronic viral hepatitis. *Chang Gung Med J.* 2009;32(6):614-22. PMID: 20035640.
- Huang JF, Hsieh MY, Dai CY, et al. The incidence and risks of liver biopsy in non-cirrhotic patients: An evaluation of 3806 biopsies. *Gut.* 2007;56(5):736-7. PMID: 17440193.
- Iacobellis (a) A, Fusilli S, Mangia A, et al. Ultrasonographic and biochemical parameters in the non-invasive evaluation of liver fibrosis in hepatitis C virus chronic hepatitis. *Ailment Pharmacol Ther.* 2005;22(9):769-74. PMID: 16225484
- Iacobellis (b) A, Mangia A, Leandro G, et al. External validation of biochemical indices for noninvasive evaluation of liver fibrosis in HCV chronic hepatitis. *Am J Gastroenterol.* 2005;100(4):868-73. PMID: 15784034
- Imbert-Bismut F, Ratziu V, Pieroni L, et al. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. *Lancet.* 2001;357(9262):1069-75. PMID: 11297957.
- Imperiale TF, Said AT, Cummings OW, et al. Need for validation of clinical decision aids: use of the AST/ALT ratio in predicting cirrhosis in chronic hepatitis C. *Am J Gastroenterol.* 2000;95(9):2328-32. PMID: 11007237.
- Islam S, Antonsson L, Westin J, et al. Cirrhosis in hepatitis C virus-infected patients can be excluded using an index of standard biochemical serum markers. *Scand J Gastroenterol.* 2005;40(7):867-72. PMID: 16109665.
- Kaul V, Friedenberg FK, Braitman LE, et al. Development and validation of a model to diagnose cirrhosis in patients with hepatitis C. *Am J Gastroenterol.* 2002;97(10):2623-8. PMID: 12385450.
- Khan. Evaluation of diagnostic accuracy of APRI for prediction of fibrosis in hepatitis C patients. *J Ayub Med Coll Abbottabad.* 2008;20(4):122-6. PMID: 19999223.
- Khokhar. Serum aminotransferase levels and platelet count as predictive factor of fibrosis and cirrhosis in patients with chronic hepatitis C infection. *J Pak Med Assoc.* 2003;53(3):101-4. PMID: 12779023.
- Koda M, Matunaga Y, Kawakami M, et al. Fibroindex, a practical index for predicting significant fibrosis in patients with chronic hepatitis C. *Hepatology.* 2007;45(2):297-306. PMID: 17256741.
- La Torre A, Biadaioli R, Capobianco T, et al. Vertical transmission of HCV. *Acta Obstetrica et Gynecologica Scandinavica.* 1998;77(9):889-92. PMID: 9808375.
- Lackner C, Struber G, Liegl B, et al. Comparison and validation of simple noninvasive tests for prediction of fibrosis in chronic hepatitis C. *Hepatology.* 2005;41(6):1376-82. PMID: 15915455.
- Latka MH, Hagan H, Kapadia F, et al. A randomized intervention trial to reduce the lending of used injection equipment among injection drug users infected with hepatitis C. *Am J Public Health.* 2008;98:853-61. PMID: 18382005.
- Leroy V, Halfon P, Bacq Y, et al. Diagnostic accuracy, reproducibility and robustness of fibrosis blood tests in chronic hepatitis C: A meta-analysis with individual data. *Clin Biochem.* 2008;41(16-17):1368-76. PMID: 18655779.
- Leroy V, Hilleret M-N, Sturm N, et al. Prospective comparison of six non-invasive scores for the diagnosis of liver fibrosis in chronic hepatitis C. *J Hepatol.* 2007;46(5):775-82. PMID: 17321634.

- Leroy V, Monier F, Bottari S, et al. Circulating matrix metalloproteinases 1, 2, 9 and their inhibitors TIMP-1 and TIMP-2 as serum markers of liver fibrosis in patients with chronic hepatitis C: comparison with PIIINP and hyaluronic acid. *The American journal of gastroenterology*. 2004;99(2):271-9. PMID: 15046217.
- Lin HH, Kao JH, Hsu HY, et al. Absence of infection in breast-fed infants born to hepatitis C virus-infected mothers. *J Pediatr*. 1995;126(4):589-91. PMID: 7535353.
- Lindenburg CE, Lambers FA, Urbanus AT, et al. Hepatitis C testing and treatment among active drug users in Amsterdam: Results from the DUTCH-C project. *Eur J Gastroenterol Hepatol*. 2011;23(1):23-31. PMID: 21042221.
- Liu CH, Lin JW, Tsai FC, et al. Noninvasive tests for the prediction of significant hepatic fibrosis in hepatitis C virus carriers with persistently normal alanine aminotransferases. *Liver Int*. 2006;26(9):1087-94. PMID: 17032409.
- Loeza-del-Castillo A, Paz-Pineda F, Oviedo-Cárdenas E, et al. AST to platelet ratio index (APRI) for the noninvasive evaluation of liver fibrosis. *Ann Hepatol*. 2008;7(4):350-7. PMID: 19034235.
- Lo Iacono O, García-Monzón C, Almasio P, et al. Soluble adhesion molecules correlate with liver inflammation and fibrosis in chronic hepatitis C treated with interferon-alpha. *Aliment Pharmacol Ther*. 1998;12(11):1091-9. PMID: 9845398.
- Lok ASF, Ghany MG, Goodman ZD, et al. Predicting cirrhosis in patients with hepatitis C based on standard laboratory tests: Results of the HALT-C cohort. *Hepatology*. 2005;42(2):282-92. PMID: 15986415.
- Luo. Simple blood tests can predict compensated liver cirrhosis in patients with chronic hepatitis C. *Hepatogastroenterology*. 2002;49(44):478-81. PMID: 11995477.
- Mallette C, Flynn MA, Promrat K. Outcome of screening for hepatitis C virus infection based on risk factors. *Am J Gastroenterol*. 2008 Jan;103(1):131-7. PMID: 17894850.
- Martinez SM, Fernández-Varo G, González P, et al. Assessment of liver fibrosis before and after antiviral therapy by different serum marker panels in patients with chronic hepatitis C. *Ailment Pharmacol Ther*. 2011;33(1):138-48. PMID: 21083589.
- Mast EE, Hwang LY, Seto DSY, et al. Risk factors for perinatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy. *J Infect Dis*. 2005;192(11):1880-9. PMID: 16267758.
- McGinn T, O'Connor-Moore N, Alfandre D, et al. Validation of a hepatitis C screening tool in primary care. *Arch Intern Med*. 2008 Oct 13;168(18):2009-13. PMID: 18852403.
- McHutchison JG, Blatt LM, de Medina M, et al. Measurement of serum hyaluronic acid in patients with chronic hepatitis C and its relationship to liver histology. Consensus Interferon Study Group. *J Gastroenterol Hepatol*. 2000;15(8):945-51. PMID: 11022838.
- McMenamin MB, Jackson AD, Lambert J, et al. Obstetric management of hepatitis C-positive mothers: analysis of vertical transmission in 559 mother-infant pairs. *Am J Obstet Gynecol*. 2008;199(3):315. PMID: 18771997.
- Metwally MA, Zein CO, Zein NN. Predictors and noninvasive identification of severe liver fibrosis in patients with chronic hepatitis C. *Dig Dis Sci*. 2007;52(2):582-8. PMID: 17211710.
- Moriya T, Sasaki F, Mizui M, et al. Transmission of hepatitis C virus from mothers to infants: its frequency and risk factors revisited. *Biomed Pharmacother*. 1995;49(2):59-64.
- Murawaki (a) Y, Koda M, Okamoto K, et al. Diagnostic value of serum type IV collagen test in comparison with platelet count for predicting the fibrotic stage in patients with chronic hepatitis C. *J Gastroenterol Hepatol*. 2001;16(7):777-81. PMID: 11446886.
- Murawaki (b) Y, Ikuta Y, Okamoto K, et al. Diagnostic value of serum markers of connective tissue turnover for predicting histological staging and grading in patients with chronic hepatitis C. *J Gastroenterol*. 2001;36(6):399-406. PMID: 11428586.

Myers RP, de Torres M, Imbert-Bismut F, et al. Biochemical markers of fibrosis in patients with chronic hepatitis C: A comparison with prothrombin time, platelet count, and age-platelet index. *Dig Dis Sci*. 2003;48(1):146-53. PMID: 12645802.

Myers RP, Fong A, Shaheen AA. Utilization rates, complications and costs of percutaneous liver biopsy: a population-based study including 4275 biopsies. *Liver Int*. 2008;28(5):705-12. PMID: 18433397.

Myers RP, Ratziu V, Imbert-Bismut F, et al. Biochemical markers of liver fibrosis: a comparison with historical features in patients with chronic hepatitis C. *Am J Gastroenterol*. 2002;97(9):2419-25. PMID: 12358267.

Nalpas B, Martin S, Fontaine H, et al. Impact of medical recommendations on alcohol consumption in HCV positive patients. *J Hepatol*. 2001;35(2):312-3. PMID: 11580161.

Nguyen MT, Herrine SK, Laine CA, et al. Description of a new hepatitis C risk assessment tool. *Arch Intern Med*. 2005 Sep 26;165(17):2013-8. PMID: 16186472.

Ohta T, Sakaguchi K, Fujiwara A, et al. Simple surrogate index of the fibrosis stage in chronic hepatitis C patients using platelet count and serum albumin level. *Acta Med Okayama*. 2006;60(2):77-84. PMID: 16680183.

Obrador BD, Prades MG, Gómez MV, et al. A predictive index for the diagnosis of cirrhosis in hepatitis C based on clinical, laboratory, and ultrasound findings. *Eur J Gastroenterol Hepatol*. 2006;18(1):57-62. PMID: 16357620.

Okamoto M, Nagata I, Murakami J, et al. Shift in the buoyant density of hepatitis C virus particles in infants infected by mother-to-infant transmission. *Pediatr Int*. 1999;41(4):369-73. PMID: 10453185.

Ompad DC, Fuller CM, Vlahov D, et al. Lack of behavior change after disclosure of hepatitis C virus infection among young injection drug users in Baltimore, Maryland. *Clin Infect Dis*. 2002 Oct 1;35(7):783-8. PMID: 12228813.

Omran MM, Farid K, Emran TM, et al. Fibro- α score as a simple and useful non-invasive test for predicting significant liver fibrosis in chronic hepatitis C patients. *Arab J Gastroenterol*. 2011;12(2):74-9. PMID: 21684477.

Paggi S, Colli A, Fraquelli M, et al. A non-invasive algorithm accurately predicts advanced fibrosis in hepatitis C: A comparison using histology with internal-external validation. *J Hepatol*. 2008;49(4):564-71. PMID: 18706734.

Parise ER, Oliveira AC, Figueiredo-Mendes C, et al. Noninvasive serum markers in the diagnosis of structural liver damage in chronic hepatitis C virus infection. *Liver Int*. 2006;26(9):1095-9.

Park GJH, Lin BP, Ngu MC, et al. Aspartate aminotransferase : alanine aminotransferase ratio in chronic hepatitis C infection: Is it a useful predictor of cirrhosis? *J Gastroenterol Hepatol*. 2000;15(4):386-90. PMID: 10824882.

Park SH, Kim CH, Kim DJ, et al. Diagnostic value of multiple biomarker panel for prediction of significant fibrosis in chronic hepatitis C. *Clin Biochem*. 2011 PMID: 21971609

Parkes J, Guha IN, Roderick P, et al. Enhanced Liver Fibrosis (ELF) test accurately identifies liver fibrosis in patients with chronic hepatitis C. *Journal of Viral Hepatitis*. 2011;18(1):23-31. PMID: 20196799.

Patel K, Benhamou Y, Yoshida EM, et al. An independent and prospective comparison of two commercial fibrosis marker panels (HCV FibroSURE and FIBROSpect II) during albinterferon alfa-2b combination therapy for chronic hepatitis C. *J Vir Hep*. 2009;16(3):178-86. PMID: 19175870.

Patel K, Gordon SC, Jacobson I, et al. Evaluation of a panel of non-invasive serum markers to differentiate mild from moderate-to-advanced liver fibrosis in chronic hepatitis C patients. *J Hepatol*. 2004;41(6):935-42. PMID: 15582126.

Pipan C, Amici S, Astori G, et al. Vertical transmission of hepatitis C virus in low-risk pregnant women. *Eur J Clin Microbiol Infect Dis*. 1996 Feb;15(2):116-20. PMID: 8801082.

- Plevris JN, Haydon GH, Simpson KJ, et al. Serum hyaluronan--a non-invasive test for diagnosing liver cirrhosis. *Eur J Gastroenterol Hepatol.* 2000;12(10):1121-7. PMID: 11057458.
- Pohl A, Behling C, Oliver D, et al. Serum aminotransferase levels and platelet counts as predictors of degree of fibrosis in chronic hepatitis C virus infection. *Am J Gastroenterol.* 2001;96(11):3142-6. PMID: 11721762.
- Poynard T, Imbert-Bismut F, Ratziu V, et al. Biochemical markers of liver fibrosis in patients infected by hepatitis C virus: longitudinal validation in a randomized trial. *J Vir Hep.* 2002;9(2):128-33. PMID: 11876795.
- Poynard T, McHutchison J, Manns M, et al. Biochemical surrogate markers of liver fibrosis and activity in a randomized trial of peginterferon alfa-2b and ribavirin. *Hepatology.* 2003;38(2):481-92. PMID: 12883493.
- Pradat P, Alberti A, Poynard T, et al. Predictive value of ALT levels for histologic findings in chronic hepatitis C: a European collaborative study. *Hepatology.* 2002;36(4 Pt 1):973-7. PMID: 12297846.
- Proeschold-Bell RJ, Patkar AA, Naggie S, et al. An integrated alcohol abuse and medical treatment model for patients with hepatitis C. *Dig Dis Sci.* 2011 PMID: 22134784.
- Reedy DW, Loo AT, Levine RA. AST/ALT ratio > or = 1 is not diagnostic of cirrhosis in patients with chronic hepatitis C. *Dig Dis Sci.* 1998;43(9):2156-9. PMID: 9753286.
- Renou C, Muller P, Jouve E, et al. Relevance of moderate isolated thrombopenia as a strong predictive marker of cirrhosis in patients with chronic hepatitis C virus. *Am J Gastroenterol.* 2001;96(5):1657-9. PMID: 11374731.
- Resti M, Azzari C, Mannelli F, et al. Mother to child transmission of hepatitis C virus: Prospective study of risk factors and timing of infection in children born to women seronegative for HIV-1. Tuscany Study Group on Hepatitis C Virus Infection. *BMJ.* 1998;317(7156):437-41. PMID: 9703524.
- Rodger AJ, Jolley D, Thompson SC, et al. The impact of diagnosis of hepatitis C virus on quality of life. *Hepatology.* 1999 Nov;30(5):1299-301. PMID: 10534353.
- Romera M, Corpas R, Romero Gómez M. Insulin resistance as a non-invasive method for the assessment of fibrosis in patients with hepatitis C: a comparative study of biochemical methods. *Rev Esp Enferm Dig.* 2006;98(3):161-9. PMID: 16737415.
- Rosenberg WM, Voelker M, Thiel R, et al. Serum markers detect the presence of liver fibrosis: a cohort study. *Gastroenterology.* 2004;127(6):1704-13. PMID: 15578508.
- Rossi E, Adams L, Prins A, et al. Validation of the FibroTest Biochemical Markers Score in Assessing Liver Fibrosis in Hepatitis C Patients. *Clin Chem.* 2003 March 1, 2003;49(3):450-4. PMID: 12600957.
- Saadeh S, Cammell G, Carey WD, et al. The role of liver biopsy in chronic hepatitis C. *Hepatology.* 2001;33(1):196-200. PMID: 11124836.
- Said Y, Bouzaidi S, Debbeche R, et al. Correlation entre la biopsie hépatique et le Fibrotest dans l'évaluation de la fibrose hépatique chez les patients atteints d'hépatite chronique C. *La Tunisie Médicale.* 2010; 88(8):573-578.
- Saitou Y, Shiraki K, Yamanaka Y, et al. Noninvasive estimation of liver fibrosis and response to interferon therapy by a serum fibrogenesis marker, YKL-40, in patients with HCV-associated liver disease. *World J Gastroenterol.* 2005;11(4):476-81. PMID: 15641129.
- Schneider AR, Teuber G, Kriener S, et al. Noninvasive assessment of liver steatosis, fibrosis and inflammation in chronic hepatitis C virus infection. *Liver Int.* 2005;25(6):1150-5. PMID: 16343065.
- Schneider AR, Teuber G, Paul K, et al. Patient age is a strong independent predictor of 13C-aminopyrine breath test results: a comparative study with histology, duplex-Doppler and a laboratory index in patients with chronic hepatitis C virus infection. *Clin Exp Pharmacol Physiol.* 2006;33(4):300-4. PMID: 1662029.
- Scognamiglio P, Galati V, Navarra A, et al. Impact of hepatitis C virus infection on lifestyle. *World J Gastroenterol.* 2007 May 21;13(19):2722-6. PMID: 17569142.

Sebastiani G, Vario A, Guido M, et al. Stepwise combination algorithms of non-invasive markers to diagnose significant fibrosis in chronic hepatitis C. *J Hepatol.* 2006;44(4):686-93. PMID: 16490278.

Sebastiani G, Vario A, Guido M, et al. Performance of noninvasive markers for liver fibrosis is reduced in chronic hepatitis C with normal transaminases. *Journal of Viral Hepatitis.* 2008;15(3):212-8. PMID: 18179453.

Sebastiani G, Halfon P, Castera L, et al. SAFE biopsy: A validated method for large-scale staging of liver fibrosis in chronic hepatitis C. *Hepatology.* 2009;49(6):1821-7. PMID: 19291784.

Sebastiani G, Castera L, Halfon P, et al. The impact of liver disease aetiology and the stages of hepatic fibrosis on the performance of non-invasive fibrosis biomarkers: an international study of 2411 cases. *CORD Conference Proceedings.* 2011;34(10):1202-16. PMID: 21981787.

Sebastiani G, Halfon P, Castera L, et al. Comparison of three algorithms of non-invasive markers of fibrosis in chronic hepatitis C. *Aliment Pharmacol Ther.* 2012;35(1):92-104. PMID: 22035045.

Seeff LB, Everson GT, Morgan TR, et al. Complication rate of percutaneous liver biopsies among persons with advanced chronic liver disease in the HALT-C trial. *Clin Gastroenterol Hepatol.* 2010;8(10):877-83. PMID: 20362695.

Sheth SG, Flamm SL, Gordon FD, et al. AST/ALT ratio predicts cirrhosis in patients with chronic hepatitis C virus infection. *Am J Gastroenterol.* 1998;93(1):44-8. PMID: 9448172.

Silva IS, Ferraz MLC, Perez RM, et al. Role of γ -glutamyl transferase activity in patients with chronic hepatitis C virus infection. *J Gastroenterol Hepatol.* 2004;19(3):314-8. PMID: 14748879.

Sirli R, Sporea I, Bota S, et al. A comparative study of non-invasive methods for fibrosis assessment in chronic HCV infection. *CORD Conference Proceedings.* 2010;10(2):88-94. PMID: 22312379.

Snyder N, Gajula L, Xiao S-Y, et al. APRI: An easy and validated predictor of hepatic fibrosis in chronic hepatitis C. *J Clin Gastroenterol.* 2006;40(6):535-42. PMID: 16825937.

Snyder N, Nguyen A, Gajula L, et al. The APRI may be enhanced by the use of the FIBROSpect II in the estimation of fibrosis in chronic hepatitis C. *Clin Chim Acta.* 2007;381(2):119-23. PMID: 17442291.

Spencer JD, Latt N, Beeby PJ, et al. Transmission of hepatitis C virus to infants of human immunodeficiency virus-negative intravenous drug-using mothers: rate of infection and assessment of risk factors for transmission. *J Vir Hep.* 1997;4(6):395-409. PMID: 9430360.

Stibbe KJ, Verveer C, Francke J, et al. Comparison of non-invasive assessment to diagnose liver fibrosis in chronic hepatitis B and C patients. *Scand J Gastroenterol.* 2011:1-11. PMID: 21623677.

Sud A, Hui JM, Farrell GC, et al. Improved prediction of fibrosis in chronic hepatitis C using measures of insulin resistance in a probability index. *Hepatology.* 2004;39(5):1239-47. PMID: 15122752.

Syriopoulou V, Nikolopoulou G, Daikos GL, et al. Mother to child transmission of hepatitis C virus: Rate of infection and risk factors. *Scand J Infect Dis.* 2005;37(5):350-3. PMID: 16051571.

Tajiri H, Miyoshi Y, Funada S, et al. Prospective study of mother-to-infant transmission of hepatitis C virus. *Pediatr Infect Dis J.* 2001 Jan;20(1):10-4. PMID: 11176560.

Tanzi M, Bellelli E, Benaglia G, et al. The prevalence of HCV infection in a cohort of pregnant women, the related risk factors and the possibility of vertical transmission. *Eur J Epidemiol.* 1997;13(5):517-21. PMID: 9258562.

Testa R, Testa E, Giannini E, et al. Noninvasive ratio indexes to evaluate fibrosis staging in chronic hepatitis C: role of platelet count/spleen diameter ratio index. *J Intern Med.* 2006;260(2):142-50. PMID: 16882278.

Trepka MJ, Zhang G, Leguen F, et al. Benefits and adverse effects of hepatitis C screening: early results of a screening program. *J Public Health Manag Pract.* 2007 May-Jun;13(3):263-9. PMID: 17435493.

Trocme C, Leroy V, Sturm N, et al. Longitudinal evaluation of a fibrosis index combining MMP-1 and PIIINP compared with MMP-9, TIMP-1 and hyaluronic acid in patients with chronic hepatitis C treated by interferon-alpha and ribavirin. *J Vir Hep.* 2006;13(10):643-51. PMID: 16970595.

Tsui JI, Vittinghoff E, Hahn JA, et al. Risk behaviors after hepatitis C virus seroconversion in young injection drug users in San Francisco. *Drug Alcohol Depend.* 2009;105(1-2):160-3. PMID: 19647375.

Vallet-Pichard A, Mallet V, Nalpas B, et al. FIB-4: An inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. *Hepatology.* 2007;46(1):32-6. PMID: 17567829.

van der Poorten D, Kwok A, Lam T, et al. Twenty-year audit of percutaneous liver biopsy in a major Australian teaching hospital. *Intern Med J.* 2006;36(11):692-9. PMID: 17040353.

Varaut A, Fontaine H, Serpaggi J, et al. Diagnostic Accuracy of the Fibrotest in Hemodialysis and Renal Transplant Patients with Chronic Hepatitis C Virus. *Transplantation.* 2005;80(11):1550-5
10.097/01.tp.0000183399.85804.02. PMID: 16371924.

Verbaan H, Bondeson L, Eriksson S. Non-Invasive Assessment of Inflammatory Activity and Fibrosis (Grade and Stage) in Chronic Hepatitis C Infection. *Scand J Gastroenterol.* 1997;32(5):494-9. PMID: 9175214

Wai C-T, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology.* 2003;38(2):518-26. PMID: 12883497.

Walsh (a) KM, Fletcher A, MacSween RN, et al. Comparison of assays for N-amino terminal propeptide of type III procollagen in chronic hepatitis C by using receiver operating characteristic analysis. *Eur J Gastroenterol Hepatol.* 1999;11(8):827-31. PMID: 10514112.

Walsh (b) KM, Timms P, Campbell S, et al. Plasma levels of matrix metalloproteinase-2 (MMP-2) and tissue inhibitors of metalloproteinases -1 and -2 (TIMP-1 and TIMP-2) as noninvasive markers of liver disease in chronic hepatitis C: comparison using ROC analysis. *Dig Dis Sci.* 1999;44(3):624-30. PMID: 10080160.

Walsh KM, Fletcher A, MacSween RN, et al. Basement membrane peptides as markers of liver disease in chronic hepatitis C. *J Hepatol.* 2000;32(2):325-30. PMID: 10707874.

West J, Card TR. Reduced mortality rates following elective, percutaneous liver biopsies. *Gastroenterology.* 2010 2010;139(4):1230-7. PMID: 20547160.

Williams AL, Hoofnagle JH. Ratio of serum aspartate to alanine aminotransferase in chronic hepatitis. Relationship to cirrhosis. *Gastroenterology.* 1988;95(3):734-9. PMID: 3135226.

Wilson LE, Torbenson M, Astemborski J, et al. Progression of liver fibrosis among injection drug users with chronic hepatitis C. *Hepatology.* 2006;43(4):788-95. PMID: 16557548.

Wong VS, Hughes V, Trull A, et al. Serum hyaluronic acid is a useful marker of liver fibrosis in chronic hepatitis C virus infection. *J Viral Hepat.* 1998;5(3):187-92. PMID: 9658372.

Yilmaz Y, Yonal O, Kurt R, et al. Noninvasive assessment of liver fibrosis with the aspartate transaminase to platelet ratio index (APRI): Usefulness in patients with chronic liver disease: APRI in chronic liver disease. *CORD Conference Proceedings.* 2011;11(2):103-6. PMID: 22087126.

Zaman A, Rosen HR, Ingram K, et al. Assessment of FIBROSpect II to detect hepatic fibrosis in chronic hepatitis C patients. *Am J Med.* 2007;120(3):280-14. PMID: 17349453.

Zanetti AR, Tanzi E, Newell ML. Mother-to-infant transmission of hepatitis C virus. *J Hepatol.* 1999;31 Suppl(1):96-100. PMID: 10622569.

Zanetti AR, Tanzi E, Romano L, et al. A prospective study on mother-to-infant transmission of hepatitis C virus. *Intervirology.* 1998;41(4-5):208-12. PMID: 10213898.

Zarski JP, Sturm N, Guechot J, et al. Comparison of nine blood tests and transient elastography for liver fibrosis in chronic hepatitis C: the ANRS HCEP-23 study. *J Hepatol.* 2012;56(1):55-62. PMID: 21781944.

Zule WA, Costenbader EC, Coomes CM, et al. Effects of a Hepatitis C virus educational intervention or a motivational intervention on alcohol use, injection drug use, and sexual risk behaviors among injection drug users. *A J Public Health.* 2009;99(Supp.):S180-S6. PMID: 19218179.

Zuniga IA, Chen JJ, Lane DS, et al. Analysis of a hepatitis C screening programme for US veterans. *Epidemiol Infect.* 2006 Apr;134(2):249-57. PMID: 16490127.

Zuure F, Davidovich U, Kok G, et al. Evaluation of a risk assessment questionnaire to assist hepatitis C screening in the general population. *Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin.* 2010 Apr 15;15(15):19539. PMID: 20429995.

Appendix D. Excluded Studies

Afdhal and Nunes. Evaluation of liver fibrosis: a concise review. *Am J Gastro*. 2004;99(6):1160-1174. PMID: 15180741. **Exclusion reason** - no original data

Aitken, et al. Does information about IDUs' injecting networks predict exposure to the hepatitis C virus? *Hepatitis Monthly*. 2009;9(1):17-23. PMID: n/a. **Exclusion reason** - not relevant

Al-Faleh, et al. Treatment of chronic hepatitis C genotype IV with interferon-ribavirin combination in Saudi Arabia: a multicentre study. *Journal of Viral Hepatitis*. 2000;7(4):287-91. PMID: n/a. **Exclusion reason** - wrong outcomes

Alice Unah. When liver stiffness is not so straight forward and Fibroscan not so simple. *J Gastroenterol Hepatol*. 2009;24(6):934-936. PMID: 19638074. **Exclusion reason** - no original data

Al Knawy B, Shiffman M. Percutaneous liver biopsy in clinical practice. *Liver Int*. 2007;27(9):1166-73. PMID: 17919227. **Exclusion reason** - not relevant

Anderson, et al. Evaluation of a general practice based hepatitis C virus screening intervention. *Scott Med J*. 2009 Aug;54(3):3-7. PMID: 19728405. **Exclusion reason** - wrong outcomes

Atwell TD, Smith RL, Hesley GK, et al. Incidence of bleeding after 15,181 percutaneous biopsies and the role of aspirin. *Am J Roentgenol*. 2010;194(3):784-9. PMID: 20173160. **Exclusion reason** - not relevant

Barbaro, et al. Hepatic glutathione deficiency in chronic hepatitis C: quantitative evaluation in patients who are HIV positive and HIV negative and correlations with plasmatic and lymphocytic concentrations and with the activity of the liver disease. *American Journal of Gastroenterology*. 1996;91(12):2569-73. PMID: 8946988. **Exclusion reason** - wrong population

Bedossa and Carrat. Liver biopsy: the best, not the gold standard. *Journal of Hepatology*. 2009 50(1):1-3. PMID: 19017551. **Exclusion reason** - no original data

Bialek SR, Terrault NA. The changing epidemiology and natural history of hepatitis C virus infection. *Clin Liver Dis*. 2006;10(4):697-715. PMID: 17164113. **Exclusion reason** - not relevant

Bini, et al. Prospective multicenter study of eligibility for antiviral therapy among 4,084 U.S. veterans with chronic hepatitis C virus infection. *Am J Gastroenterol*. 2005;100(8):1772-1779. PMID: 16086714. **Exclusion reason** - wrong population

Borsoi Viana MS, Takei K, Collarile Yamaguti DC, et al. Use of AST platelet ratio index (APRI Score) as an alternative to liver biopsy for treatment indication in chronic hepatitis C. *Ann Hepatol*. 2009;8(1):26-31. PMID: 19221530. **Exclusion reason** - not relevant

Brener and Treloar. Alcohol and other drug treatment experiences of hepatitis C-positive and negative clients: implications for hepatitis C treatment. *Australian Health Review*. 2009;33(1):100-106. PMID: 19203339. **Exclusion reason** - wrong study design

Bruggmann, et al. Treatment outcome in relation to alcohol consumption during hepatitis C therapy: An analysis of the Swiss Hepatitis C Cohort Study. *Drug and Alcohol Dependence*. 2010;110(1-2):167-171. PMID: 20334985. **Exclusion reason** - wrong population

Burt, et al. Serosorting for hepatitis C status in the sharing of injection equipment among Seattle area injection drug users. *Drug and Alcohol Dependence*. 2009;105(3):215-220. PMID: 19720473. **Exclusion reason** - wrong population

Butt, et al. Reasons for non-treatment of hepatitis C in veterans in care. *Journal of Viral Hepatitis*. 2005;12(1):81-85. PMID: 15655052. **Exclusion reason** - not relevant

Caldwell S, Northup PG. Bleeding Complication with Liver Biopsy: Is it Predictable? *Clin Gastroenterol Hepatol*. 2010;8(10):826-9. PMID: 20601136. **Exclusion reason** - not relevant

Calès, et al. Evaluation and improvement of a reliable diagnosis of cirrhosis by blood tests. *Gastroenterologie Clinique et Biologique*. 2008;32(12):1050-1060. PMID: 19019606. **Exclusion reason** - no original data

Cales, et al. A novel panel of blood markers to assess the degree of liver fibrosis. *Hepatology*. 2005;42(6):1373 - 1381. PMID: 16317693. **Exclusion reason** - wrong population

Cardoso AC, Carvalho-Filho RJ, Marcellin P. Transient elastography in chronic viral hepatitis: a critical appraisal. *Gut*. 2011 Jun;60(6):759-64. PMID: 21450696. **Exclusion reason** - not relevant

Carey E, Carey WD. Noninvasive tests for liver disease, fibrosis, and cirrhosis: Is liver biopsy obsolete? *Cleve Clin J Med*. 2010;77(8):519-27. PMID: 20682514. **Exclusion reason** - not relevant

Castera, et al. Non-invasive evaluation of liver fibrosis using transient elastography. *J Hepatol*. 2008;48(5):835-847. PMID: 18334275. **Exclusion reason** - wrong intervention

Chan, et al. Changing paradigm in the management of hepatocellular carcinoma improves the survival benefit of early detection by screening. *Annals of Surgery*. 2008;247(4):666-673. PMID: 18362630. **Exclusion reason** - wrong population

Cheung, et al. Galectin-3-binding protein: a serological and histological assessment in accordance with hepatitis C-related liver fibrosis. *European Journal of Gastroenterology & Hepatology*. 2010;22(9):1066-1073. 10.1097/MEG.0b013e328337d602. PMID: 20186066. **Exclusion reason** - wrong outcomes

Cheung, et al. Effectiveness of a screening program for hepatitis C. *Digestive Diseases & Sciences*. 2006 May;51(5):976-81. PMID: 16642419. **Exclusion reason** - wrong outcomes

Conrad SGL, Cooksley WGE, Dunne MP, Macdonald GA. Living with chronic hepatitis C infection means 'you just haven't got a normal life any more'. *Chronic Illn*. 2006;2(2):121-31. PMID: 17175655. **Exclusion reason** - not relevant

Cox, et al. Access to sterile injecting equipment is more important than awareness of HCV status for injection risk behaviors among drug users. *Substance Use and Misuse*. 2009;44(4):548-568. PMID: 19242863. **Exclusion reason** - wrong study design

Crofts, et al. Epidemiology of hepatitis C virus infection among injecting drug users in Australia. *Journal of Epidemiology and Community Health*. 1997 December 1, 1997;51(6):692-697. PMID: 9519134. **Exclusion reason** - wrong outcomes

Croquet, et al. Prothrombin index is an indirect marker of severe liver fibrosis. *European Journal of Gastroenterology & Hepatology*. 2002;14(10):1133-1141. PMID: 12362105. **Exclusion reason** - wrong population

Cullen, et al. Management of hepatitis C among drug users attending general practice in Ireland: Baseline data from the dublin area Hepatitis C in general practice initiative. *European Journal of General Practice*. 2007;13(1):5-12. PMID: 17366287. **Exclusion reason** - wrong study design

Cullen, et al. Hepatitis C infection among injecting drug users in general practice: A cluster randomised controlled trial of clinical guidelines' implementation. *Br J Gen Pract*. 2006;56(532):848-856. PMID: 17132352. **Exclusion reason** - wrong outcomes

Dal Molin G, D'Agaro P, Ansaldo F, et al. Mother-to-infant transmission of hepatitis C virus: rate of infection and assessment of viral load and IgM anti-HCV as risk factors. *Journal of medical virology*. 2002;67(i9n, 7705876):137-42. PMID: 11992574. **Exclusion reason** - not relevant

De Lédighen, et al. Diagnosis of hepatic fibrosis and cirrhosis by transient elastography in HIV/hepatitis C virus-coinfected patients. *J Acquir Immune Defic Syndr*. 2006;41(2):175-179. PMID: 16394849. **Exclusion reason** - wrong intervention

De Lédighen, et al. Liver Stiffness Measurement in Children Using FibroScan: Feasibility Study and Comparison With Fibrotest, Aspartate Transaminase to Platelets Ratio Index, and Liver Biopsy. *Journal of Pediatric Gastroenterology and Nutrition*. 2007;45(4):443-450. 10.1097/MPG.0b013e31812e56ff. PMID: 18030211. **Exclusion reason** - wrong population

Defossez, et al. Evaluation of the French national plan to promote screening and early management of viral hepatitis C, between 1997 and 2003: a comparative cross-sectional study in Poitou-Charentes region. *European Journal of Gastroenterology & Hepatology*. 2008 May;20(5):367-72. PMID: 18403936. **Exclusion reason** - wrong population

Delarocque-Astagneau, et al. The impact of the prevention programme of hepatitis C over more than a decade: the French experience. *Journal of Viral Hepatitis*. 2010 Jun;17(6):435-43. PMID: 19780936. **Exclusion reason** - wrong study design

Deuffic-Burban, et al. Impact of pegylated interferon and ribavirin on morbidity and mortality in patients with chronic hepatitis C and normal aminotransferases in France. *Hepatology*. 2009;50(5):1351-1359. PMID: 19676130. **Exclusion reason** - not relevant

Dieperink E, Ho SB, Heit S, et al. Significant reductions in drinking following brief alcohol treatment provided in a hepatitis C clinic. *Psychosomatics*. 2010;51(2):149-56. PMID: 20332290 **Exclusion reason** - not relevant

Doehring, et al. Screening for IL28B gene variants identifies predictors of hepatitis C therapy success. *Antiviral Therapy*. 2010;15(8):1099-1106. PMID: 21149916. **Exclusion reason** - not relevant

Drainoni M. Effectiveness of a Risk Screener in Identifying Hepatitis C Virus in Primary Care. **Exclusion reason** - unable to find

El-Serag. Hepatocellular carcinoma. *CORD Conference Proceedings*. 2011;365(12):1118-27. PMID: 21992124. **Exclusion reason** - not relevant

El-Serag HB. Hepatocellular carcinoma: recent trends in the United States. *Gastroenterology*. 2004;127(5 Suppl 1):S27-S34. PMID: 15508094. **Exclusion reason** - not relevant

England K, Pembrey L, Tovo PA, et al. Excluding hepatitis C virus (HCV) infection by serology in young infants of HCV-infected mothers. *Acta Paediatrica, International Journal of Paediatrics*. 2005;94(4):444-50. PMID: 16092459. **Exclusion reason** - not relevant

England K, Thorne C, Newell ML. Vertically acquired paediatric coinfection with HIV and hepatitis C virus. *Lancet Infect Dis.* 2006;6(2):83-90. PMID: 16439328. **Exclusion reason** - not relevant

Fabris P, Tositti G, Giordani MT, et al. Assessing patients' understanding of hepatitis C virus infection and its impact on their lifestyle. *Ailment Pharmacol Ther.* 2006;23(8):1161-70. PMID: 16611277. **Exclusion reason** - not relevant

Follett, et al. HCV confirmatory testing of blood donors. *Lancet.* 1991;338(8773):1024. PMID: 1681334. **Exclusion reason** - wrong intervention

Foucher, et al. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. *Gut.* 2006;55(3):403-8. PMID: 16020491. **Exclusion reason** - wrong intervention

Fried. Pegylated interferon in combination with ribavirin: efficacy and safety results from a phase III randomized actively controlled multicenter study [abstract]. *Gastroenterology.* 2001;120(Suppl):A-55. PMID: n/a. **Exclusion reason** - not relevant

Fukuhara, et al. Variants in IL28B in liver recipients and donors correlate with response to peg-interferon and ribavirin therapy for recurrent hepatitis C. *Gastroenterology.* 2010;139(5):1577-1585.e3. PMID: 20708617. **Exclusion reason** - not relevant

Ganne-Carrié, et al. Accuracy of liver stiffness measurement for the diagnosis of cirrhosis in patients with chronic liver diseases. *Hepatology.* 2006;44(6):1511-1517. PMID: 17133503. **Exclusion reason** - wrong intervention

Garfein, et al. A peer-education intervention to reduce injection risk behaviors for HIV and hepatitis C virus infection in young injection drug users. *AIDS.* 2007 Sep 12;21(14):1923-32. PMID: 17721100. **Exclusion reason** - wrong population

Gebo, et al. Role of liver biopsy in management of chronic hepatitis C: A systematic review. *Hepatology.* 2002;36:S161 - S172. PMID: doi:10.1002/hep.1840360721. **Exclusion reason** - wrong study design

Giacchino R, Tasso L, Timitilli A, et al. Vertical transmission of hepatitis C virus infection: usefulness of viremia detection in HIV-seronegative hepatitis C virus-seropositive mothers. *The Journal of pediatrics.* 1998;132(jl, 0375410):167-9. PMID: 9470023. **Exclusion reason** - not relevant

Gidding. Predictors of deferral of treatment for hepatitis C infection in Australian clinics. *Medical Journal of Australia.* 2011;194(8):398-402. PMID: 21495939. **Exclusion reason** - wrong outcomes

Goldberg and Seth. Hepatitis C services and individuals with serious mental illness. *Community Mental Health Journal.* 2008;44(5):381-384. PMID: 18465227. **Exclusion reason** - not relevant

Goldstein, et al. Serum alpha-fetoprotein levels in patients with chronic hepatitis C. Relationships with serum alanine aminotransferase values, histologic activity index, and hepatocyte MIB-1 scores. *A J Clin Pathol.* 1999;111(6):811-6. PMID: 10361518. **Exclusion reason** - wrong population

Granovsky MO, Minkoff HL, Tess BH, et al. Hepatitis C virus infection in the mothers and infants cohort study. *Pediatrics.* 1998;102(oxv, 0376422):355-9. PMID: 9685438. **Exclusion reason** - not relevant

Grebely, et al. Factors associated with uptake of treatment for recent hepatitis C virus infection in a predominantly injecting drug user cohort: The ATAHc study. *Drug and Alcohol Dependence.* 2010;107(2-3):244-249. PMID: 19926405. **Exclusion reason** - not relevant

Groessl, et al. Development of the Hepatitis C Self-Management Program. *Patient Education and Counseling.* 2011;83(2):252-255. PMID: 20638216. **Exclusion reason** - not relevant

Hagan, et al. Reduced risk of hepatitis B and hepatitis C among injection drug users in the Tacoma syringe exchange program. *Am J Public Health.* 1995 November 1, 1995;85(11):1531-1537. PMID: 7485666. **Exclusion reason** - not relevant

Hahn, et al. Hepatitis C virus risk behaviors within the partnerships of young injecting drug users. *Addiction.* 2010;105(7):1254-1264. PMID: 20491725. **Exclusion reason** - not relevant

Hahn, et al. Potential impact of vaccination on the hepatitis C virus epidemic in injection drug users. *Epidemics.* 2009;1(1):47-57. PMID: 20491725. **Exclusion reason** - wrong study design

Hagan H, Campbell J, Thiede H, et al. Self-reported hepatitis C virus antibody status and risk behavior in young injectors. *Public Health Rep.* 2006;121(6):710-9. PMID: 17278406. **Exclusion reason** - not relevant

Hagan H, Pouget ER, Des Jarlais DC, et al. Meta-regression of hepatitis C virus infection in relation to time since onset of illicit drug injection: the influence of time and place. *CORD Conference Proceedings.* 2008;168(10):1099-109. PMID: 18849303. **Exclusion reason** - not relevant

Hare, et al. Comparison of characteristics of treated and non-treated patients with Hepatitis C infection. *Pharmacoepidemiology and Drug Safety.* 2006;15(2):71-76. PMID: 16136612. **Exclusion reason** - wrong outcomes

Harris. Pleasure and Guilt: Alcohol Use and Hepatitis C. *Qualitative Health Research.* 2010 April 19, 2010 PMID: 20404360. **Exclusion reason** - wrong study design

Hepburn, et al. The accuracy of the report of hepatic steatosis on ultrasonography in patients infected with hepatitis C in a clinical setting: A retrospective observational study. *BMC Gastroenterology*. 2005;5:14. PMID: 15829009. **Exclusion reason** - not relevant

Hoffmann, et al. Sarcoidosis associated with interferon-alpha therapy for chronic hepatitis C. *Journal of Hepatology*. 1998;28(6):1058-63. PMID: n/a. **Exclusion reason** - wrong outcomes

Holmberg S, Ly KN, Xing J, et al. The growing burden of mortality associated with viral hepatitis in the United States, 1999-2007 [abstract #243]. *Hepatology*. 2011;54(4 suppl):483A. PMID: 21483021. **Exclusion reason** - not relevant

Huang JF, Hsieh MY, Dai CY, et al. The incidence and risks of liver biopsy in non-cirrhotic patients: An evaluation of 3806 biopsies. *Gut*. 2007;56(5):736-7. PMID: 17440193. **Exclusion reason** - not relevant

Hung, et al. Long-term effect of interferon alpha-2b plus ribavirin therapy on incidence of hepatocellular carcinoma in patients with hepatitis C virus-related cirrhosis. *Journal of Viral Hepatitis*. 2006;13(6):409-414. PMID: 16842444. **Exclusion reason** - not relevant

Hwang, et al. Hepatitis B and hepatitis C prevalence and treatment referral among Asian Americans undergoing community-based hepatitis screening. *American Journal of Public Health*. 2010 Apr 1;100 Suppl 1:S118-24. PMID: 20147697. **Exclusion reason** - not relevant

Ilan Y. Review article: the assessment of liver function using breath tests. *Aliment Pharmacol Ther*. 2007;26(10):1293-302. PMID: 17868431. **Exclusion reason** - not relevant

Kalambokis G, Manousou P, Vibhakorn S, et al. Transjugular liver biopsy--indications, adequacy, quality of specimens, and complications--a systematic review. *J Hepatol*. 2007;47(2):284-94. PMID: 17561303. **Exclusion reason** - not relevant

Kamal, et al. Peginterferon alfa-2b therapy in acute hepatitis C: Impact of onset of therapy on sustained virologic response. *Gastroenterology*. 2006;130(3):632-638. PMID: 16530503. **Exclusion reason** - wrong population

Kapadia, et al. Design and feasibility of a randomized behavioral intervention to reduce distributive injection risk and improve health-care access among hepatitis C virus positive injection drug users: The Study to Reduce Intravenous Exposures (STRIVE). *Journal of Urban Health*. 2007;84(1):99-115. PMID: 17200799. **Exclusion reason** - not relevant

Kilbourne, et al. Guideline-concordant hepatitis C virus testing and notification among patients with and without mental disorders. *General Hospital Psychiatry*. 2008 Nov-Dec;30(6):495-500. PMID: 19061674. **Exclusion reason** - wrong intervention

Kim, et al. Blood cell, liver function, and response changes by PEG-interferon-(alpha)2b plus ribavirin with polaprezinc therapy in patients with chronic hepatitis C. *Hepatology International*. 2008;2(1):111-115. PMID: 19669286. **Exclusion reason** - not relevant

King, et al. Assessment and proposal of a new combination of screening criteria for hepatitis C in France. *Eur J Public Health*. 2009 Oct;19(5):527-33. PMID: 19667051. **Exclusion reason** - wrong outcomes

Kramer, et al. Importance of Patient, Provider, and Facility Predictors of Hepatitis C Virus Treatment in Veterans: A National Study. *Am J Gastroenterol*. 2011;106(3) PMID: 21063393. **Exclusion reason** - wrong population

Kraus, et al. Psychiatric side effects of pegylated interferon alfa-2b as compared to conventional interferon alfa-2b in patients with chronic hepatitis C. *World Journal of Gastroenterology*. 2005;11(12):1769-1774. PMID: 15793861. **Exclusion reason** - not relevant

Kumar, et al. Influence of quasispecies on virological responses and disease severity in patients with chronic hepatitis C. *World Journal of Gastroenterology*. 2008;14(5):701-708. PMID: 18205258. **Exclusion reason** - not relevant

Kwiatkowski CF, Fortuin Corsi K, Booth RE. The association between knowledge of hepatitis C virus status and risk behaviors in injection drug users. *Addiction*. 2002;97(10):1289-94. PMID: 12359033. **Exclusion reason** - not relevant

Lebray, et al. Liver stiffness is an unreliable marker of liver fibrosis in patients with cardiac insufficiency. *Hepatology*. 2008;48(6):2089. PMID: 19003902. **Exclusion reason** - not relevant

Lee SR, Kardos KW, Schiff E, et al. Evaluation of a new, rapid test for detecting HCV infection, suitable for use with blood or oral fluid. *J Virol Methods*. 2010;172(1-2):27-31. PMID: 21182871. **Exclusion reason** - not relevant

Lee SR, Yearwood GD, Guillon GB, et al. Evaluation of a rapid, point-of-care test device for the diagnosis of hepatitis C infection. *CORD Conference Proceedings*. 2010;48(1):15-7. PMID: 20362493. **Exclusion reason** - not relevant

Leroy. Other non-invasive markers of liver fibrosis. *Clin Res Hepatol Gastroenterol*. 2008;32(6 Suppl 1):52-57. PMID: 18973846. **Exclusion reason** - no original data

- Lin, et al. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: An updated meta-analysis. *Hepatology*. 2011;53(3):726-736. PMID: 21319189. **Exclusion reason** - wrong study design
- Lindenburg, et al. Hepatitis C testing and treatment among active drug users in Amsterdam: Results from the DUTCH-C project. *Eur J Gastroenterol Hepatol*. 2011;23(1):23-31. PMID: 21042221. **Exclusion reason** - not relevant
- Lorenzo-Zúñiga, et al. Serum Concentrations of Insulin-Like Growth Factor-I (IGF-I) as a Marker of Liver Fibrosis in Patients With Chronic Hepatitis C. *Digestive Diseases and Sciences*. 2007;52(11):3245-3250. PMID: 17410466. **Exclusion reason** - wrong outcomes
- Lucidarme, et al. Factors of accuracy of transient elastography (fibroscan) for the diagnosis of liver fibrosis in chronic hepatitis C. *Hepatology*. 2009;49(4):1083-1089. PMID: 19140221. **Exclusion reason** - wrong intervention
- Lurie, et al. Medex Test, a Novel Modality for Liver Disease Diagnosis: A Pilot Study. *Journal of Clinical Gastroenterology*. 2007;41(7):700-705. 10.1097/01.mcg.0000225641.83275.6a. PMID: 17667055. **Exclusion reason** - wrong population
- Maclean and Fox. Universal hepatitis C screening in genitourinary medicine. *International Journal of STD & AIDS*. 2010 Jul;21(7):504-5. PMID: 20852201. **Exclusion reason** - wrong study design
- Malik, et al. A prospective study of change in visual function in patients treated with pegylated interferon alpha for hepatitis C in the UK. *British Journal of Ophthalmology*. 2008;92(2):256-258. PMID: 17962387. **Exclusion reason** - not relevant
- Manolakopoulos S, Triantos C, Bethanis S, et al. Ultrasound-guided liver biopsy in real life: comparison of same-day prebiopsy versus real-time ultrasound approach. *J Gastroenterol Hepatol*. 2007;22(9):1490-3. PMID: 17573828. **Exclusion reason** - not relevant
- Maor, et al. Improving estimation of liver fibrosis using combination and newer noninvasive biomarker scoring systems in hepatitis C-infected haemophilia patients. *Haemophilia*. 2007;13(6):722-729. PMID: 17973848. **Exclusion reason** - wrong population
- Mapagu, et al. Screening for hepatitis C in sexual health clinic attendees. *Sexual Health*. 2008 Mar;5(1):73-6. PMID: 18361858. **Exclusion reason** - wrong study design
- Martin, et al. Optimal Control of Hepatitis C Antiviral Treatment Programme Delivery for Prevention amongst a Population of Injecting Drug Users. *PLoS ONE*. 2011;6(8):e22309. PMID: 21853030. **Exclusion reason** - not relevant
- Martin, et al. Can antiviral therapy for hepatitis C reduce the prevalence of HCV among injecting drug user populations? A modeling analysis of its prevention utility. *J Hepatol*. 2011;54(6):1137-1144. PMID: 21145810. **Exclusion reason** - not relevant
- Martin, et al. The cost-effectiveness of HCV antiviral treatment for injecting drug user populations. *Hepatology*. 2011;55(1) PMID: 21898506. **Exclusion reason** - not relevant
- Martinez, et al. Noninvasive assessment of liver fibrosis. *Hepatology*. 2011;53(1):325-35. PMID: 21254180. **Exclusion reason** - wrong study design
- Matser, et al. The effect of hepatitis C treatment and HIV coinfection on the disease burden of hepatitis C among injecting drug users in Amsterdam. *Addiction*. 2011;no-no. PMID: 21919987. **Exclusion reason** - not relevant
- Meffre, et al. Prevalence of hepatitis B and hepatitis C virus infections in france in 2004: Social factors are important predictors after adjusting for known risk factors. *Journal of Medical Virology*. 2010;82(4):546-555. PMID: 20166185. **Exclusion reason** - not relevant
- Mehta, et al. Exceeding the limits of liver histology markers. *Journal of Hepatology*. 2009;50(1):36-41. PMID: 19012989. **Exclusion reason** - wrong outcomes
- Melia, et al. Analysis of reasons for treatment ineligibility in the IDEAL study: African Americans (AA) vs non-African Americans (non-AA). *Hepatology*. 2009;50:702A-703A. PMID: n/a. **Exclusion reason** - not relevant
- MMWR. Prevalence of Selected Risk Behaviors and Chronic Diseases --- Behavioral Risk Factor Surveillance System (BRFSS), 39 Steps Communities, United States, 2005. *Surveillance Summaries: Morbidity and Mortality Weekly Report (MMWR)*; 2008. p. 1-20. **Exclusion reason** - not relevant
- Monnet, et al. Targeted hepatitis C screening: How to reach high risk populations? Lesson learnt from a campaign in a rural area [5]. *Gastroenterologie Clinique et Biologique*. 2004;28(8-9):817-819. PMID: 15646548. **Exclusion reason** - not relevant
- Morisco, et al. Retrospective, observational, multicentre study on an Italian population affected by chronic hepatitis C who failed to clear HCV-RNA after the combined therapy (PEG-IFN and ribavirin): NADIR study. *Journal of Viral Hepatitis*. 2010;17(6):427-434. PMID: 19780939. **Exclusion reason** - not relevant
- Myers, et al. Serum biochemical markers accurately predict liver fibrosis in HIV and hepatitis C virus-coinfected patients. *AIDS*. 2003;17:1 - 5. PMID: doi:10.1097/00002030-200303280-00010. **Exclusion reason** - wrong population

- Myers RP, Fong A, Shaheen AA. Utilization rates, complications and costs of percutaneous liver biopsy: a population-based study including 4275 biopsies. *Liver Int.* 2008;28(5):705-12. PMID: 18433397. **Exclusion reason** - not relevant
- Nalpas, et al. Hepatitis C viremia and anti-HCV antibodies in alcoholics. *Journal of Hepatology.* 1992;14(2-3):381-384. PMID: 1380027. **Exclusion reason** - wrong outcomes
- Narasimhan, et al. Treatment rates in patients with chronic hepatitis C after liver biopsy. *Journal of Viral Hepatitis.* 2006;13(11):783-786. PMID: 17052279. **Exclusion reason** - wrong population
- Nash, et al. Hepatocellular carcinoma in patients with chronic hepatitis C virus infection without cirrhosis. *World Journal of Gastroenterology.* 2010;16(32):4061-4065. PMID: n/a. **Exclusion reason** - wrong study design
- Nalpas B, Martin S, Fontaine H, et al. Impact of medical recommendations on alcohol consumption in HCV positive patients. *J Hepatol.* 2001;35(2):312-3. PMID: 11580161. **Exclusion reason** - not relevant
- National Center for HIV/AIDS VH, STD & TB Prevention. Disease Burden from Viral Hepatitis A, B, and C in the United States [pdf]. Center for Disease Control; 2011. http://www.cdc.gov/hepatitis/pdfs/disease_burden.pdf. Accessed on October 27 2011. **Exclusion reason** - not relevant
- National Guideline C. Viral hepatitis in pregnancy. Rockville MD: Agency for Healthcare Research and Quality (AHRQ); 2011. <http://www.guideline.gov>. Accessed on 10/28/2011. **Exclusion reason** - not relevant
- Ndako, et al. Occurrence of antibodies against hepatitis C virus (HCV) among alcoholics. *African Journal of Biotechnology.* 2010;9(52):8908-8912. PMID: n/a. **Exclusion reason** - wrong study design
- Neumeister, et al. Hepatitis-C prevalence in an urban native-American clinic: a prospective screening study. *Journal of the National Medical Association.* 2007 Apr;99(4):389-92. PMID: 17444428. **Exclusion reason** - wrong study design
- Nguyen and Talwalkar. Noninvasive assessment of liver fibrosis. *Hepatology.* 2011;53(6):2107-2110. PMID: 21547935. **Exclusion reason** - no original data
- Nguyen, et al. Role of ethnicity in risk for hepatocellular carcinoma in patients with chronic hepatitis C and cirrhosis. *Clinical Gastroenterology and Hepatology.* 2004;2(9):820-824. PMID: 15354283. **Exclusion reason** - wrong population
- Nguyen, et al. Risk factors, genotype 6 prevalence, and clinical characteristics of chronic hepatitis C in Southeast Asian Americans. *Hepatology International.* 2010;4(2):523-529. PMID: 20827411. **Exclusion reason** - not relevant
- Nguyen, et al. Recruitment and follow-up of injecting drug users in the setting of early hepatitis C treatment: Insights from the ATAHC study. *International Journal of Drug Policy.* 2007;18(5):447-451. PMID: 17854736. **Exclusion reason** - not relevant
- Norden, et al. Knowledge of status and assessment of personal health consequences with hepatitis C are not enough to change risk behaviour among injecting drug users in Stockholm County, Sweden. *Scandinavian Journal of Infectious Diseases.* 2009;41(10):727-734. PMID: 19688640. **Exclusion reason** - wrong population
- Ompad DC, Fuller CM, Vlahov D, et al. Lack of behavior change after disclosure of hepatitis C virus infection among young injection drug users in Baltimore, Maryland. *Clin Infect Dis.* 2002 Oct 1;35(7):783-8. PMID: 12228813. **Exclusion reason** - not relevant
- Page, et al. Acute hepatitis C virus infection in young adult injection drug users: a prospective study of incident infection, resolution, and reinfection. *Journal of Infectious Diseases.* 2009;200(8):1216-1226. PMID: 19764883. **Exclusion reason** - not relevant
- Page-Shafer, et al. Testing strategy to identify cases of acute hepatitis C virus (HCV) infection and to project HCV incidence rates. *Journal of Clinical Microbiology.* 2008;46(2):499-506. PMID: 18032621. **Exclusion reason** - not relevant
- Page-Shafer, et al. Hepatitis C virus infection in young, low-income women: The role of sexually transmitted infection as a potential cofactor for HCV infection. *American Journal of Public Health.* 2002;92(4):670-676. PMID: 11919070. **Exclusion reason** - not relevant
- Paradisi, et al. Safety of etanercept in patients with psoriasis and hepatitis C virus assessed by liver histopathology: Preliminary data. *Journal of the American Academy of Dermatology.* 2010;62(6):1067-1069.e2. PMID: 20466184. **Exclusion reason** - not relevant
- Parkes, et al. Performance of serum marker panels for liver fibrosis in chronic hepatitis C. *Journal of Hepatology.* 2006;44(3):462-474. PMID: 16427156. **Exclusion reason** - wrong study design
- Parvez and Anwar. Diagnostic value of alpha-fetoprotein in liver cancer. *Medical Forum Monthly.* 2002;13(1):19-21. PMID: n/a. **Exclusion reason** - not relevant

Paternoster, et al. [Pregnancy in women infected with the hepatitis C virus]. *Acta Biomed Ateneo Parmense*. 2000;71 Suppl 1:553-7. PMID: 11424805. **Exclusion reason** - not relevant

Paul, et al. Incidence of hepatocellular carcinoma among Indian patients with cirrhosis of liver: An experience from a tertiary care center in northern India. *Indian Journal of Gastroenterology*. 2007;26(6):274-278. PMID: 18431010. **Exclusion reason** - not relevant

Paul V. Strategies for prevention of viral hepatitis in the United States. *International Hepatology Communications*. 1996;5(1):3-9. PMID: n/a. **Exclusion reason** - no original data

Paydas, et al. Anti-HCV and HCV-RNA prevalence and clinical correlations in cases with non-Hodgkin's lymphoma. *American Journal of Hematology*. 2003;74(2):89-93. PMID: 14508793. **Exclusion reason** - not relevant

Peixoto, et al. Executive functions in chronic hepatitis C virus-infected patients. *Advances in Clinical and Experimental Medicine*. 2008;17(1):53-60. PMID: n/a. **Exclusion reason** - not relevant

Peixoto, et al. Vertical transmission of hepatitis C virus in a hospital in Southern Brazil. *Arquivos de Gastroenterologia*. 2004;41(2):84-87. PMID: 15543379. **Exclusion reason** - wrong population

Pekow, et al. Hepatic steatosis is associated with increased frequency of hepatocellular carcinoma in patients with hepatitis C-related cirrhosis. *Cancer*. 2007;109(12):2490-2496. PMID: 17487861. **Exclusion reason** - not relevant

Pellicano, et al. Interferon (beta)-1a alone or in combination with ribavirin: A randomized trial to compare efficacy and safety in chronic hepatitis C. *World Journal of Gastroenterology*. 2005;11(29):4484-4489. PMID: 16052676. **Exclusion reason** - not relevant

Pennesi, et al. Sero-placental viremia and mother-to-infant transmission of the hepatitis C virus. *Giornale Italiano di Ostetricia e Ginecologia*. 2005;27(3):73-76. PMID: n/a. **Exclusion reason** - not relevant

Pérez, et al. The prevalence of antibodies against hepatitis B and C virus in odontology students. Prevalencia de anticuerpos contra los virus de hepatitis B y C en estudiantes de odontología. 2002;32(1):21-23. PMID: 12136687. **Exclusion reason** - not relevant

Pergam, et al. Pregnancy complications associated with hepatitis C: data from a 2003-2005 Washington state birth cohort. *American Journal of Obstetrics and Gynecology*. 2008;199(1) PMID: 18486089. **Exclusion reason** - not relevant

Peters and Rockstroh. Biomarkers of fibrosis and impaired liver function in chronic hepatitis C: how well do they predict clinical outcomes? *Current Opinion in HIV and AIDS*. 2010;5(6):517-523. PMID: 20978395. **Exclusion reason** - wrong outcomes

Peterson, et al. Effect of tumour necrosis factor (alpha) antagonists on serum transaminases and viraemia in patients with rheumatoid arthritis and chronic hepatitis C infection. *Annals of the Rheumatic Diseases*. 2003;62(11):1078-1082. PMID: 14583571. **Exclusion reason** - not relevant

Petre, et al. Increased prevalence of reduced estimated glomerular filtration rate in chronic Hepatitis C patients. *Digestive Diseases and Sciences*. 2010;55(5):1450-1457. PMID: 20300844. **Exclusion reason** - not relevant

Phukan, et al. Magnitude of hepatitis C virus infection in upper Assam [3]. *Indian Journal of Gastroenterology*. 2003;22(1):34. PMID: 12617459. **Exclusion reason** - not relevant

Pirillo, et al. Seroprevalence of hepatitis B and C viruses among HIV-infected pregnant women in Uganda and Rwanda. *Journal of Medical Virology*. 2007 Dec;79(12):1797-801. PMID: 17935164. **Exclusion reason** - wrong study design

Polesel, et al. The impact of obesity and diabetes mellitus on the risk of hepatocellular carcinoma. *Annals of Oncology*. 2009;20(2):353-357. PMID: 18723550. **Exclusion reason** - not relevant

Polis, et al. Impact of maternal HIV coinfection on the vertical transmission of hepatitis C virus: a meta-analysis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2007;44(a4j, 9203213):1123-31. PMID: 17366462. **Exclusion reason** - not relevant

Polymerou, et al. Evaluation of three immunoassays for hepatitis C virus antibody detection. *Clinical Microbiology and Infection*. 2010;16:S697. PMID: n/a. **Exclusion reason** - not relevant

Polywka, et al. Accuracy of HCV-RNA PCR tests for diagnosis or exclusion of vertically acquired HCV infection. *Journal of Medical Virology*. 2006;78(2):305-310. PMID: 16372293. **Exclusion reason** - wrong population

Polywka, et al. The vertical transmission of the hepatitis C virus - Low risk of HCV transmission by breast feeding. *Medizinische Welt*. 2000;51(11):337-340. PMID: n/a. **Exclusion reason** - not relevant

Polywka, et al. Low risk of vertical transmission of hepatitis C virus by breast milk. *Clin Infect Dis*. 1999;29(5):1327-1329. PMID: 10524987. **Exclusion reason** - not relevant

- Polywka S, Feucht H, Zollner B, et al. Hepatitis C virus infection in pregnancy and the risk of mother-to-child transmission. *Eur J Clin Microbiol Infect Dis*. 1997 Feb;16(2):121-4. PMID: 9105838. **Exclusion reason** - not relevant
- Portolani, et al. Intrahepatic cholangiocarcinoma and combined hepatocellular- cholangiocarcinoma: A Western experience. *Annals of Surgical Oncology*. 2008;15(7):1880-1890. PMID: 18443881. **Exclusion reason** - not relevant
- Poujol-Robert, et al. Association between ABO blood group and fibrosis severity in chronic hepatitis C infection. *Digestive Diseases and Sciences*. 2006;51(9):1633-1636. PMID: 16927132. **Exclusion reason** - not relevant
- Poynard, et al. Overview of the diagnostic value of biochemical markers of liver fibrosis (FibroTest, HCV-Fibrosure) and necrosis (ActiTest) in patients with chronic hepatitis C. *Comp Hepatol*. 2004;3:8. PMID: doi:10.1186/1476-5926-3-8. **Exclusion reason** - wrong study design
- Poynard, et al. A comparison of fibrosis progression in chronic liver diseases. *Journal of Hepatology*. 2003;38(3):257-265. PMID: 12586290. **Exclusion reason** - not relevant
- Poynard, et al. Meta-analyses of FibroTest diagnostic value in chronic liver disease. *BMC Gastroenterology*. 2007;7(1):40. PMID: doi:10.1186/1471-230X-7-40. **Exclusion reason** - wrong study design
- Poynard, et al. Prospective Analysis of Discordant Results between Biochemical Markers and Biopsy in Patients with Chronic Hepatitis C. *Clin Chem*. 2004 August 1, 2004;50(8):1344-1355. PMID: 15192028. **Exclusion reason** - wrong outcomes
- Proeschold-Bell, et al. An integrated alcohol abuse and medical treatment model for patients with hepatitis C. *Dig Dis Sci*. 2011 PMID: 22134784. **Exclusion reason** - not relevant
- Proude. Alcohol Reduction for People with Hepatitis C Discipline of Addiction Medicine. 2009:1-16. PMID: n/a. **Exclusion reason** - no original data
- Quaglio, et al. Prevalence and risk factors for viral hepatitis in the Kosovarian population: Implications for health policy. *Journal of Medical Virology*. 2008;80(5):833-840. PMID: 18360897. **Exclusion reason** - not relevant
- Quinti, et al. European surveillance of immunoglobulin safety - Results of initial survey of 1243 patients with primary immunodeficiencies in 16 countries. *Clinical Immunology*. 2002;104(3):231-236. PMID: 12217332. **Exclusion reason** - not relevant
- Quiroga, et al. Identification of serologically silent occult hepatitis C virus infection by detecting immunoglobulin G antibody to a dominant HCV core peptide epitope. *Journal of Hepatology*. 2009;50(2):256-263. PMID: 19070391. **Exclusion reason** - not relevant
- Randhawa and Cashman. Screening for hepatitis C in adults. *American Family Physician*. 2005;71(5):955-956. PMID: 15768624. **Exclusion reason** - not relevant
- Ransy, et al. Maternal immunity and mother-to-child transmission of HCV and HIV-1: Challenges and recent advances. *Medecine/Sciences*. 2007;23(11):991-996. PMID: 18021713. **Exclusion reason** - not relevant
- Reesink, et al. Mother-to-infant transmission and hepatitis C virus. *Lancet*. 1990;335(8699):1216-1217. PMID: 1971054. **Exclusion reason** - not relevant
- Rhodes, et al. Hepatitis C and its risk management among drug injectors in London: renewing harm reduction in the context of uncertainty. *Addiction*. 2004 May;99(5):621-33. PMID: 15078237. **Exclusion reason** - wrong study design
- Rich, et al. A Syringe Prescription Program to Prevent Infectious Disease and Improve Health of Injection Drug Users. *Journal of Urban Health*. 2004;81(1):122-134. PMID: 15047791. **Exclusion reason** - not relevant
- Rifai, et al. Hepatitis C screening and treatment outcomes in patients with substance use/dependence disorders. *Psychosomatics*. 2006 Mar-Apr;47(2):112-21. PMID: 16508022. **Exclusion reason** - wrong population
- Roberts and Yeung. Maternal-infant transmission of hepatitis C virus infection. *Hepatology*. 2002;36(5 I):S106-S113. PMID: 12407583. **Exclusion reason** - not relevant
- Roblin D, Bryce DBDS, Cindy MCMW, et al. HCV screening practices and prevalence in an MCO, 2000-2007. *CORD Conference Proceedings*. 011;17(8):548-55. **Exclusion reason** - not relevant
- Rockey and Bissell. Noninvasive measures of liver fibrosis. *Hepatol*. 2006;43(2 Suppl 1):S113-S120. PMID: 16447288. **Exclusion reason** - no original data
- Rodger AJ, Jolley D, Thompson SC, et al. The impact of diagnosis of hepatitis C virus on quality of life. *Hepatology*. 1999 Nov;30(5):1299-301. PMID: 10534353.
- Rogers, et al. Hepatitis c as a risk factor for renal cell carcinoma. *Journal of Urology*. 2009;181(4):112-113. PMID: n/a. **Exclusion reason** - not relevant

- Romero Requejo, et al. Perinatal transmission of hepatitis C virus. *Journal of Maternal-Fetal and Neonatal Medicine*. 2010;23:392. PMID: n/a. **Exclusion reason** - not relevant
- Rosenberg. Other non-invasive markers of liver fibrosis. *Clin Res Hepatol Gastroenterol*. 2008;32(6 Suppl 1):52-57. PMID: n/a. **Exclusion reason** - no original data
- Rosenberg, et al. Serum markers detect the presence of liver fibrosis: A cohort study. *Gastroenterology*. 2004;127(6):1704-1713. PMID: 15578508. **Exclusion reason** - wrong population
- Rouse. A significant sex - But not elective Cesarean section - Effect on mother-to-child transmission of hepatitis C virus infection: Commentary. *Obstetrical and Gynecological Survey*. 2006;61(4):218-219. PMID: n/a. **Exclusion reason** - not relevant
- Rowan, et al. Physical and psychosocial contributors to quality of life in veterans with hepatitis C not on antiviral therapy. *J Clin Gastroenterol*. 2005;39(8):731-736. PMID: 16082286. **Exclusion reason** - not relevant
- Roy, et al. Hepatitis C virus incidence among young street-involved IDUs in relation to injection experience. *Drug & Alcohol Dependence*. 2009 Jun 1;102(1-3):158-61. PMID: 19251382. **Exclusion reason** - wrong population
- Rubio Quevedo, et al. [Vertical transmission of hepatitis C virus]. *Anales Espanoles de Pediatria*. 2001 Jan;54(1):27-31. PMID: 11181191. **Exclusion reason** - not relevant
- Ruiz Estremera, et al. Study of genetic variation in IL28B and vertical transmission of hepatitis C virus and spontaneous clearance of childhood HCV infection. *Journal of Hepatology*. 2011;54:S530. PMID: n/a. **Exclusion reason** - not relevant
- Ruiz-Extremera, et al. Follow-up of transmission of hepatitis C to babies of human immunodeficiency virus-negative women: The role of breast-feeding in transmission. *Pediatric Infectious Disease Journal*. 2000;19(6):511-516. PMID: 10877164. **Exclusion reason** - not relevant
- Rumi, et al. Hepatitis C reactivation in patients with chronic infection with genotypes 1b and 2c: A retrospective cohort study of 206 untreated patients. *Gut*. 2005;54(3):402-406. PMID: 15710990. **Exclusion reason** - not relevant
- Sabatino. Vertical transmission of hepatitis C virus: An epidemiological study on 2,980 pregnant women in Italy. *European Journal of Epidemiology*. 1996;12(5):443-447. PMID: 8905303. **Exclusion reason** - wrong outcomes
- Saez, et al. Diagnostic and prognostic value of virologic test in vertical transmission of hepatitis C virus infection: Results of a large prospective study in pregnant women. *Hepato-Gastroenterology*. 2004;51(58):1104-1108. PMID: 15239255. **Exclusion reason** - not relevant
- Safir, et al. Maternal hepatitis B virus or hepatitis C virus carrier status as an independent risk factor for adverse perinatal outcome. *Liver International*. 2010;30(5):765-770. PMID: 20214739. **Exclusion reason** - wrong outcomes
- Sagnelli and Pasquale. Vertical and intrafamilial transmission of HCV. *Journal of Preventive Medicine and Hygiene*. 1993;34(1-2):97-100. PMID: n/a. **Exclusion reason** - not relevant
- Saito H and H. Efficacy of non-invasive elastometry on staging of hepatic fibrosis. *Hepato Res*. 2004;29(2):97-103. PMID: 15163431. **Exclusion reason** - wrong intervention
- Salomon, et al. Cost-effectiveness of Treatment for Chronic Hepatitis C Infection in an Evolving Patient Population. *Journal of the American Medical Association*. 2003;290(2):228-237. PMID: 12851278. **Exclusion reason** - not relevant
- Sandrin, et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. *Ultrasound Med Biol*. 2003;29(12):1705-1713. PMID: 14698338. **Exclusion reason** - no original data
- Sanvisens, et al. Hyaluronic acid, transforming growth factor-beta1 and hepatic fibrosis in patients with chronic hepatitis C virus and human immunodeficiency virus co-infection. *J Viral Hepat*. 2009;16(7):513-518. PMID: 19200132. **Exclusion reason** - wrong population
- Schackman, et al. The cost-effectiveness of elective Cesarean delivery to prevent hepatitis C transmission in HIV-coinfected women. *AIDS* 2004;18(aid, 8710219):1827-34. PMID: 15316344. **Exclusion reason** - not relevant
- Schöniger-Hekele and Müller. The Combined Elevation of Tumor Markers CA 19-9 and CA 125 in Liver Disease Patients Is Highly Specific for Severe Liver Fibrosis. *Digestive Diseases and Sciences*. 2006;51(2):338-345. PMID: 16534678. **Exclusion reason** - wrong population
- Schwimmer and Balistreri. Transmission, natural history, and treatment of hepatitis C virus infection in the pediatric population. *Seminars in Liver Disease*. 2000;20(1):37-46. PMID: 10895430. **Exclusion reason** - wrong intervention
- Seeff LB, Everson GT, Morgan TR, et al. Complication rate of percutaneous liver biopsies among persons with advanced chronic liver disease in the HALT-C trial. *Clin Gastroenterol Hepatol*. 2010;8(10):877-83. PMID: 20362695. **Exclusion reason** - not relevant

- Seme, et al. Twenty-four mini-pool HCV RNA screening outside a blood transfusion setting: results of a 2-year prospective study. *Journal of Virological Methods*. 2007 Mar;140(1-2):218-21. PMID: 17157928. **Exclusion reason** - wrong study design
- Sène, et al. Biological markers of liver fibrosis and activity as non-invasive alternatives to liver biopsy in patients with chronic hepatitis C and associated mixed cryoglobulinemia vasculitis. *Clinical Biochemistry*. 2006;39(7):715-721. PMID: 16765932. **Exclusion reason** - wrong population
- Shaheen, et al. FibroTest and FibroScan for the Prediction of Hepatitis C-Related Fibrosis: A Systematic Review of Diagnostic Test Accuracy. *Am J Gastroenterol*. 2007;102(11):2589-2600. PMID: 17850410. **Exclusion reason** - wrong study design
- Sharma and Spearman. The Impact of Cesarean Delivery on Transmission of Infectious Agents to the Neonate. *Clinics in Perinatology*. 2008;35(2):407-420. PMID: 18456077. **Exclusion reason** - no original data
- Shebl, et al. Prospective cohort study of mother-to-infant infection and clearance of hepatitis C in rural Egyptian villages. *Journal of Medical Virology*. 2009;81(6):1024-1031. PMID: 19382251. **Exclusion reason** - wrong outcomes
- Shehab, et al. Identification and management of hepatitis C patients in primary care clinics. *American Journal of Gastroenterology*. 2003;98(3):639-644. PMID: 12650800. **Exclusion reason** - not relevant
- Shiah, et al. Phase I and pharmacokinetic study of oral thalidomide in patients with advanced hepatocellular carcinoma. *Cancer Chemotherapy and Pharmacology*. 2006;58(5):654-664. PMID: 16520988. **Exclusion reason** - not relevant
- Shiraki, et al. [Maternal-fetal transmission of non-A, non-B viral hepatitis]. *Nippon rinsho. Japanese journal of clinical medicine*. 1988;46(kim, 0420546):2735-43. PMID: 3149347. **Exclusion reason** - not relevant
- Shiraki, et al. [Non-A, non-B hepatitis in infants and possibilities of maternal infection]. *Nippon rinsho. Japanese journal of clinical medicine*. 1981;39(kim, 0420546):3289-96. PMID: 6803028. **Exclusion reason** - not relevant
- Silverman, et al. Detection of hepatitis C virus antibodies and specific hepatitis C virus ribonucleic acid sequences in cord bloods from a heterogeneous prenatal population. *American Journal of Obstetrics and Gynecology*. 1995;173(5):1396-1400. PMID: 7503175 **Exclusion reason** - not relevant
- Simon and Gurakan. Vertical transmission of hepatitis C virus [1]. *New England Journal of Medicine*. 1994;331(6):399-400. PMID: 8028624. **Exclusion reason** - not relevant
- Singal, et al. Use of the AST to platelet ratio index in HCV/HIV co-infected patients. *Aliment Pharmacol Ther*. 2011; 33: 566-577 PMID: 21205257. **Exclusion reason** - wrong population
- Smith. Comparison of Hepatitis C Virus Infection Screening Strategies: Elevated Alanine Aminotransferase Levels Versus Birth Cohort. . AASLD Hepatitis Single Topic Conference. **Exclusion reason** - unable to find
- Smith, et al. Performance of premarket rapid hepatitis C virus antibody assays in 4 national human immunodeficiency virus behavioral surveillance system sites. *Clin Infect Dis*. 2011;53(8):780-786. PMID: 21921221. **Exclusion reason** - not relevant
- Smith and Sterling. Systematic review: non-invasive methods of fibrosis analysis in chronic hepatitis C. *Alimentary Pharmacology & Therapeutics*. 2009;30(6):557-576. PMID: 19519733. **Exclusion reason** - wrong study design
- Smith B, Jan JD, Amy AJ, et al. Evaluation of three rapid screening assays for detection of antibodies to hepatitis C virus. *CORD Conference Proceedings*. 2011;204(6):825-31. PMID: 21849279. **Exclusion reason** - not relevant
- Snyder, et al. The APRI may be enhanced by the use of the FIBROSpect II in the estimation of fibrosis in chronic hepatitis C. *Clinica Chimica Acta*. 2007;381(2):119-123. PMID: 17442291. **Exclusion reason** - not relevant
- Somsouk, et al. A cost-identification analysis of screening and surveillance of hepatitis C infection in a prospective cohort of dialysis patients. *Digestive Diseases and Sciences*. 2008;53(4):1093-1099. PMID: 17934829. **Exclusion reason** - not relevant
- Søreide. Seroprevalence of bloodborne viruses in Scandinavian trauma victims. *Scandinavian Journal of Surgery*. 2007;96(1):88. PMID: 17461320. **Exclusion reason** - not relevant
- Southern WN, Drainoni ML, Smith BD, et al. Hepatitis C testing practices and prevalence in a high-risk urban ambulatory care setting. *J Viral Hepat*. 2010. **Exclusion reason** - no original data
- Soulie. [Rationale for a trial of prevention of perinatal transmission of hepatitis C via specific immunoglobulins]. *Bases decisionnelles d'un essai de prophylaxie de la transmission perinatale de l'hepatite C par immunoglobulines spécifiques*. 1997;4(bx0, 9423846):213-9. PMID: 9162427. **Exclusion reason** - not relevant
- Soza and Lopez-Lastra. [Hepatitis C in Chile: burden of the disease]. *Revista Medica de Chile*. 2006 Jun;134(6):777-88. PMID: 17130955. **Exclusion reason** - wrong study design

Stark, et al. Prevalence and determinants of anti-HCV seropositivity and of HCV genotype among intravenous drug users in Berlin. *Scandinavian Journal of Infectious Diseases*. 1995;27(4):331-7. PMID: 8658065. **Exclusion reason** - wrong outcomes

Stein, et al. Hepatitis C disease among injection drug users: knowledge, perceived risk and willingness to receive treatment. *Drug and Alcohol Dependence*. 2001;61(3):211-215. PMID: 11164684. **Exclusion reason** - not relevant

Stein, et al. Organic or psychosomatic? Facilitating inquiry with children and parents. *Journal of Developmental and Behavioral Pediatrics*. 2003;24(5):359-363. PMID: 14578697. **Exclusion reason** - not relevant

Steininger C, Kundi M, Jatzko G, et al. Increased risk of mother-to-infant transmission of hepatitis C virus by intrapartum infantile exposure to maternal blood. *The Journal of infectious diseases*. 2003;187(ih3, 0413675):345-51. PMID: 12552417.

Stewart BJ, Mikocka-Walus AA, Harley H, et al. Help-seeking and coping with the psychosocial burden of chronic hepatitis C: A qualitative study of patient, hepatologist, and counsellor perspectives. *Int J Nurs Stud*. 2011 Dec 6 PMID: 22154094. **Exclusion reason** - not relevant

Stine JG, Liss G, Lewis JH. The Safety of Same-Day Endoscopy and Percutaneous Liver Biopsy. *Dig Dis Sci*. 2010;56(4):1201-6 PMID: 20857198. **Exclusion reason** - not relevant

Stoszek, et al. Prevalence of and risk factors for hepatitis C in rural pregnant Egyptian women. *Transactions of the Royal Society of Tropical Medicine & Hygiene*. 2006 Feb;100(2):102-7. PMID: 16289168. **Exclusion reason** - wrong outcomes

Suárez, et al. Vertical transmission of HCV infection by HIV-negative mothers [1]. *Transmisión vertical de la infección por VHC de madres VIH-negativas*. 2004;22(9):555-556. PMID: 15511398. **Exclusion reason** - not relevant

Sulkowski, et al. Peginterferon-alpha-2a (40kD) and ribavirin in patients with chronic hepatitis C: a phase II open-label study. *Biodrugs*. 2002 9/7/02;16(2):105-9. PMID: 11985484. **Exclusion reason** - wrong outcomes

Talwalkar. Elastography for Detecting Hepatic Fibrosis: Options and Considerations. *Gastroenterology*. 2008;135(1):299-302. PMID: 18555023 **Exclusion reason** - no original data

Talwalkar, et al. Ultrasound-Based Transient Elastography for the Detection of Hepatic Fibrosis: Systematic Review and Meta-analysis. *Clinical Gastroenterology and Hepatology*. 2007;5(10):1214-1220. PMID: 17916549. **Exclusion reason** - wrong study design

Talwalkar, et al. Magnetic resonance imaging of hepatic fibrosis: Emerging clinical applications. *Hepatology*. 2008;47(1):332-342. PMID: 18161879. **Exclusion reason** - no original data

Tanaka, et al. Epidemiology of hepatitis C virus and hepatocellular carcinoma in Japan. *Nippon rinsho. Japanese journal of clinical medicine*. 2004;62 Suppl 7(Pt 1):611-614. PMID: 15359870. **Exclusion reason** - not relevant

Taseer, et al. Frequency of anti-HCV, HBsAg and related risk factors in pregnant women at Nishtar Hospital, Multan. *Journal of Ayub Medical College, Abbottabad : JAMC*. 2010;22(8910750):13-6. PMID: 21409894. **Exclusion reason** - wrong study design

Thomas, et al. Correlates of Hepatitis C Virus Infections among Injection Drug Users. *Medicine*. 1995;74(4):212-220. PMID: 7623656. **Exclusion reason** - wrong outcomes

Thorpe, et al. Hepatitis C Virus Infection: Prevalence, Risk Factors, and Prevention Opportunities among Young Injection Drug Users in Chicago, 1997–1999. *Journal of Infectious Diseases*. 2000 December 1, 2000;182(6):1588-1594. PMID: 11069228. **Exclusion reason** - not relevant

Tibbs. Methods of transmission of hepatitis C. *Journal of Viral Hepatitis*. 1995;2(3) PMID: 7493305. **Exclusion reason** - no original data

Tovo, et al. Increased risk of maternal-infant hepatitis C virus transmission for women coinfecting with human immunodeficiency virus type 1. *Clinical Infectious Diseases*. 1997;25(5):1121-1124. PMID: 9402369. **Exclusion reason** - not relevant

Tovo, et al. A significant sex - But not elective cesarean section - Effect on mother-to-child transmission of hepatitis C virus infection. *Journal of Infectious Diseases*. 2005;192(11):1872-1879. PMID: n/a. **Exclusion reason** - not relevant

Trepka MJ, Zhang G, Leguen F, et al. Benefits and adverse effects of hepatitis C screening: early results of a screening program. *J Public Health Manag Pract*. 2007 May-Jun;13(3):263-9. PMID: 17435493. **Exclusion reason** - not relevant

Tsiveriotis, et al. Prevalence of HBV, HCV and HIV infections among obstetrics/gynaecology patients. *Clinical Microbiology and Infection*. 2009;15:S585. PMID: n/a. **Exclusion reason** - not relevant

Tsui, et al. Treatment eligibility and outcomes in elderly patients with chronic hepatitis C: Results from the VA HCV-001 study. *Digestive Diseases and Sciences*. 2008;53(3):809-814. PMID: 17823868. **Exclusion reason** - not relevant

Tsui JI, Vittinghoff E, Hahn JA, et al. Risk behaviors after hepatitis C virus seroconversion in young injection drug users in San Francisco. *Drug Alcohol Depend*. 2009;105(1-2):160-3. PMID: 19647375. **Exclusion reason** - not relevant

Tyler. Knowledge about hepatitis C virus infection and health care utilization for hepatitis C infection among homeless adults. Vita. Thesis (Ph.D.)--UCLA, 2009. Includes bibliographical references (leaves 113-118). 2009(xii, 118 leaves):xii, 118 leaves. PMID: n/a. **Exclusion reason** - not relevant

Uehara, et al. The incidence of vertical transmission of hepatitis C virus. The Tohoku journal of experimental medicine. 1993;171(vtf, 0417355):195-202. PMID: 7512756. **Exclusion reason** - not relevant

Van Den Berg, et al. Never injected, but hepatitis C virus-infected: A study among self-declared never-injecting drug users from the Amsterdam Cohort Studies. Journal of Viral Hepatitis. 2009;16(8):568-577. PMID: 19243497. **Exclusion reason** - not relevant

van der Poorten D, Kwok A, Lam T, et al. Twenty-year audit of percutaneous liver biopsy in a major Australian teaching hospital. Intern Med J. 2006;36(11):692-9. PMID: 17040353.

Varaut, et al. Diagnostic Accuracy of the Fibrotest in Hemodialysis and Renal Transplant Patients with Chronic Hepatitis C Virus. Transplantation. 2005;80(11):1550-1555
10.1097/01.tp.0000183399.85804.02. PMID: 16371924. **Exclusion reason** - wrong population

Vergniol, et al. Noninvasive tests for fibrosis and liver stiffness predict 5-year outcomes of patients with chronic hepatitis C. Gastroenterology. 2011;140(7):1970-9, 1979.e1-3. PMID: 21376047. **Exclusion reason** - wrong outcomes

Vicari, et al. Study of mother-to-child transmission of hepatitis C (HCV) and G(GBV- C/HGV) virus infection by polymerase chain reaction (PCR). Trasfusione del Sangue. 1999;44(5):246-253. PMID: n/a. **Exclusion reason** - not relevant

Vidal-Trecan, et al. HCV status knowledge and risk behaviours amongst intravenous drug users. European Journal of Epidemiology. 2000 May;16(5):439-45. PMID: 10997831. **Exclusion reason** - wrong population

Vizzutti, et al. Liver stiffness measurement predicts severe portal hypertension in patients with HCV-related cirrhosis. Hepatology. 2007;45(5):1290-1297. PMID: 17464971. **Exclusion reason** - not relevant

Wahl, et al. Prevalence of antibodies against hepatitis B and C virus among pregnant women and female blood donors in Sweden. Serodiagnosis and Immunotherapy in Infectious Disease. 1994;6(3):127-129. PMID: n/a. **Exclusion reason** - not relevant

West J, Card TR. Reduced mortality rates following elective, percutaneous liver biopsies. Gastroenterology. 2010 2010;139(4):1230-7. PMID: 20547160. **Exclusion reason** - not relevant

Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies. Ann Intern Med. 2011;155(8):529-36. PMID: 22007046. **Exclusion reason** - not relevant

Wiese M, Grüngreiff K, Güthoff W, et al. Outcome in a hepatitis C (genotype 1b) single source outbreak in Germany--a 25-year multicenter study. J Hepatol. 2005;43(4):590-8. PMID: 16237783. **Exclusion reason** - not relevant

Wiessing, et al. European monitoring of notifications of hepatitis C virus infection in the general population and among injecting drug users (IDUs) - the need to improve quality and comparability. Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin. 2008;13(21):22. PMID: 18761969. **Exclusion reason** - wrong study design

Williams, et al. Incidence and transmission patterns of acute hepatitis C in the United States, 1982-2006. Archives of Internal Medicine. 2011;171(3):242-248. PMID: 21325115. **Exclusion reason** - not relevant

Wnuk, et al. Prevention of vertical transmission of human immunodeficiency virus (HIV-1) in own material. HIV and AIDS Review. 2006;5(1):30-35. PMID: n/a. **Exclusion reason** - wrong population

Yaari, et al. Detection of HCV salivary antibodies by a simple and rapid test. Journal of Virological Methods. 2006 Apr;133(1):1-5. PMID: 16360219. **Exclusion reason** - wrong population

Yakaryilmaz, et al. Prevalence of occult hepatitis B and hepatitis C virus infections in Turkish hemodialysis patients. Renal Failure. 2006;28(8):729-735. PMID: 17162434. **Exclusion reason** - wrong population

Yamaguchi, et al. HTLV-I, HIV-I, and hepatitis B and C viruses in Western Province, Papua New Guinea: a serological survey. Japanese Journal of Cancer Research. 1993 Jul;84(7):715-9. PMID: 7690354. **Exclusion reason** - wrong population

Yamamoto, et al. Hepatobiliary and pancreatic: Cholangiocellular cancer and hepatitis C. Journal of Gastroenterology and Hepatology. 2003;18(11):1317. PMID: 14535991. **Exclusion reason** - wrong study design

Yanaga, et al. Hepatitis C virus infection among Japanese general surgical patients. World Journal of Surgery. 1995 Sep-Oct;19(5):694-6; discussion 697. PMID: 7571665. **Exclusion reason** - wrong study design

Yanai, et al. Surveillance of infection control procedures in dialysis units in Japan: A preliminary study. Therapeutic Apheresis and Dialysis. 2006;10(1):78-86. PMID: 16556141. **Exclusion reason** - wrong study design

- Yanase, et al. The prevalence of HIV, HBV and HCV among Filipino blood donors and overseas work visa applicants. *Bulletin of the World Health Organization*. 2007 Feb;85(2):131-7. PMID: 17308734. **Exclusion reason** - wrong population
- Yang, et al. HIV, syphilis, hepatitis C and risk behaviours among commercial sex male clients in Sichuan province, China. *Sexually Transmitted Infections*. 2010;86(7):559-564. PMID: 20826867. **Exclusion reason** - not relevant
- Yang, et al. Viral hepatitis infections in southern Taiwan: A multicenter community-based study. *Kaohsiung Journal of Medical Sciences*. 2010;26(9):461-469. PMID: 20837342. **Exclusion reason** - wrong population
- Yang, et al. Prevalence and clinical significance of HGV/GBV-C infection in patients with chronic hepatitis B or C. *Japanese Journal of Infectious Diseases*. 2006 Feb;59(1):25-30. PMID: 16495630. **Exclusion reason** - wrong population
- Yang, et al. HCV positivity rate in the seronegative blood donors in China. *Biomedicine and Pharmacotherapy*. 2009;63(4):319-320. PMID: 19246175. **Exclusion reason** - wrong population
- Yano, et al. Clinical features of hepatocellular carcinoma seronegative for both HBsAG and anti-HCV antibody but positive for anti-HBC antibody in Japan. *American Journal of Gastroenterology*. 2002;97(1):156-161. PMID: 11808941. **Exclusion reason** - wrong population
- Yarom, et al. Association between hepatitis C virus infection and oral lichen planus in Israeli patients. *Israel Medical Association Journal: Imaj*. 2007 May;9(5):370-2. PMID: 17591375. **Exclusion reason** - wrong population
- Yawn, et al. Development and maintenance of a community-based hepatitis C registry. *Am J Manage Care*. 2002 Mar;8(3):253-61. PMID: 11915975. **Exclusion reason** - not relevant
- Yazdanpanah, et al. Risk factors for hepatitis C virus transmission to health care workers after occupational exposure: A European case-control study. *Revue d'Epidemiologie et de Sante Publique*. 2006;54(HS1):1S23-1S31. PMID: 17073127. **Exclusion reason** - not relevant
- Yazdanpanah, et al. Risk factors for hepatitis C virus transmission to health care workers after occupational exposure: A European case-control study. *Clinical Infectious Diseases*. 2005;41(10):1423-1430. PMID: 16231252. **Exclusion reason** - not relevant
- Yeung LTF, King SM, Roberts EA. Mother-to-infant transmission of hepatitis C virus. *Hepatology*. 2001;34(2):223-9. PMID: 11481604. **Exclusion reason** - not relevant
- Yildirim, et al. Seroprevalence of hepatitis B and C viruses in the province of Tokat in the Black Sea region of Turkey: A population-based study. *Turkish Journal of Gastroenterology*. 2009 Mar;20(1):27-30. PMID: 19330732. **Exclusion reason** - wrong population
- Yin, et al. Abdominal magnetic resonance elastography. *Top Magn Reson Imaging*. 2009;20(2):79-87. PMID: 20010062. **Exclusion reason** - no original data
- Yoshida, et al. Prevalence of seropositivity for hepatitis C virus in cataract patients and the general population. *Journal of Cataract & Refractive Surgery*. 2002 Oct;28(10):1789-92. PMID: 12388029. **Exclusion reason** - wrong population
- Zakizad, et al. Seroprevalence of hepatitis C infection and associated risk factors among addicted prisoners in Sari-Iran. *Pakistan Journal of Biological Sciences*. 2009 Jul 15;12(14):1012-8. PMID: 19947179. **Exclusion reason** - wrong population
- Zaller, et al. Risk factors for Hepatitis C virus infection among blood donors in Georgia. *European Journal of Epidemiology*. 2004;19(6):547-553. PMID: 15330127. **Exclusion reason** - wrong population
- Zamani, et al. Prevalence and correlates of hepatitis C virus infection among injecting drug users in Tehran. *International Journal of Drug Policy*. 2007 Oct;18(5):359-63. PMID: 17854723. **Exclusion reason** - wrong population
- Zamani, et al. Prevalence of HIV/HCV/HBV infections and drug-related risk behaviours amongst IDUs recruited through peer-driven sampling in Iran. *International Journal of Drug Policy*. 2010;21(6):493-500. PMID: 20483578. **Exclusion reason** - wrong population
- Zanetti AR, Tanzi E, Newell ML. Mother-to-infant transmission of hepatitis C virus. *J Hepatol*. 1999;31 Suppl(1):96-100. PMID: 10622569. **Exclusion reason** - not relevant
- Zein. Vertical transmission of hepatitis C: To screen or not to screen. *Journal of Pediatrics*. 1997;130(6):859-861. PMID: 9202605. **Exclusion reason** - not relevant
- Zeldis, et al. Seroepidemiology of viral infections among intravenous drug users in northern California. *Western Journal of Medicine*. 1992 Jan;156(1):30-5. PMID: 1310362. **Exclusion reason** - not relevant
- Zeuzem, et al. Risk factors for the transmission of hepatitis C. *Journal of Hepatology*. 1996;24(2 Suppl):3-10. PMID: 8836883. **Exclusion reason** - not relevant
- Zhang, et al. Hepatitis C virus infection, Linxian, China. *Emerging Infectious Diseases*. 2005 Jan;11(1):17-21. PMID: 15705317. **Exclusion reason** - wrong population

Zhao, et al. Analysis of true voluntary blood donors with anti-HCV prevalence and implications for donor management in Chongqing, China [4]. *Transfusion Medicine*. 2007;17(3):210-211. PMID: 17561867.

Exclusion reason - wrong population

Zheng, et al. Liver fibrosis in chronic viral hepatitis: An ultrasonographic study. *World Journal of Gastroenterology*. 2003;9(11):2484-2489. PMID: 14606081. **Exclusion reason** - not relevant

Zickmund S, Ho EY, Masuda M, et al. "They treated me like a leper". Stigmatization and the quality of life of patients with hepatitis C. *J Gen Intern Med*. 2003;18(10):835-44. PMID: 14521647.

Zumrutdal, et al. Effect of anti-HCV positivity on markers of malnutrition and inflammation in hemodialysis patients. *Renal Failure*. 2007;29(1):85-90. PMID: 17365915. **Exclusion reason** - wrong population

Zuure, et al. Using mass media and the internet as tools to diagnose hepatitis C infections in the general population. *American Journal of Preventive Medicine*. 2011;40(3):345-352. PMID: 21335268. **Exclusion reason** - not relevant

Appendix E. Quality Assessment Methods

Individual studies were rated as “good,” “fair” or “poor” as defined below:

For Controlled Trials:

Each criterion was give an assessment of yes, no, or unclear.

1. Was the assignment to the treatment groups really random?
 - Adequate approaches to sequence generation:
 - Computer-generated random numbers
 - Random numbers tables
 - Inferior approaches to sequence generation:
 - Use of alternation, case record numbers, birth dates or week days
 - Randomization reported, but method not stated
 - Not clear or not reported
 - Not randomized
2. Was the treatment allocation concealed?
 - Adequate approaches to concealment of randomization:
 - Centralized or pharmacy-controlled randomization (randomization performed without knowledge of patient characteristics).
 - Serially-numbered identical containers
 - On-site computer based system with a randomization sequence that is not readable until allocation
 - Sealed opaque envelopes
 - Inferior approaches to concealment of randomization:
 - Use of alternation, case record numbers, birth dates or week days
 - Open random numbers lists
 - Serially numbered non- opaque envelopes
 - Not clear or not reported
3. Were the groups similar at baseline in terms of prognostic factors?
4. Were the eligibility criteria specified?
5. Were outcome assessors and/or data analysts blinded to the treatment allocation?
6. Was the care provider blinded?
7. Was the patient kept unaware of the treatment received?
8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?
9. Did the study maintain comparable groups?
10. Did the article report attrition, crossovers, adherence, and contamination?
11. Is there important differential loss to followup or overall high loss to followup?

For Cohort Studies:

Each criterion was give an assessment of yes, no, or unclear.

1. Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?

2. Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?
3. Did the study use accurate methods for ascertaining exposures, potential confounders, and outcomes?
4. Were outcome assessors and/or data analysts blinded to treatment?
5. Did the article report attrition?
6. Did the study perform appropriate statistical analyses on potential confounders?
7. Is there important differential loss to followup or overall high loss to followup?
8. Were outcomes pre-specified and defined, and ascertained using accurate methods?

For Case-control Studies

Each criterion was given an assessment of yes, no, or unclear.

1. Did the study attempt to enroll all (or a random sample of) cases using pre-defined criteria?
2. Were the controls derived from the same population as the cases, and would they have been selected as cases if the outcome was present?
3. Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?
4. Did the study report the proportion of cases and controls who met inclusion criteria that were analyzed?
5. Did the study use accurate methods for identifying outcomes?
6. Did the study use accurate methods for ascertaining exposures and potential confounders?
7. Did the study perform appropriate statistical analyses on potential confounders?

For Studies of Diagnostic Accuracy

Each criterion was given an assessment of yes, no, or unclear.

1. Did the study evaluate a representative spectrum of patients?
2. Did the study enroll a random or consecutive sample of patients meeting pre-defined criteria?
3. Did the study evaluate a credible reference standard?
4. Did the study apply the reference standard to all patients, or to a random sample?
5. Did the study apply the same reference standard to all patients?
6. Was the reference standard interpreted independently from the test under evaluation?
7. If a threshold was used, was it pre-specified?

Appendix E References

Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. *Am J Prev Med* 2001;20:21-35.

Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health*. 1998;52(6):377-84.

Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies. *Ann Intern Med*. 2011;155(8):529-36.

Appendix F. Overall Strength of Evidence: Summary of Grading Domains

Key Question	Number of Studies	Quality (Good, Fair, Poor)	Consistency (High, Moderate, Low)	Directness (Direct or indirect)	Precision (High, Moderate, Low)	Number of Subjects	Strength of Evidence
1a. Does screening for HCV infection in non pregnant adults without known abnormal liver function tests reduce mortality and morbidity due to HCV infection, affect quality of life, or reduce incidence of HCV infection?	No studies	No studies	No studies	No studies	No studies	No studies	Insufficient
1b. Does screening for HCV infection during pregnancy reduce vertical transmission of HCV or improve mortality or morbidity for the mother or child?	No studies	No studies	No studies	No studies	No studies	No studies	Insufficient
2a. What is the effectiveness of different risk- or prevalence-based methods for screening for HCV infection on clinical outcomes?	No studies	No studies	No studies	No studies	No studies	No studies	Insufficient
2b. What is the sensitivity and number needed to screen to identify one case of HCV infection of different risk- or prevalence-based methods for screening for HCV infection?	5 studies (4 cross-sectional, one case-control)	Poor	High	Direct	High	8,044	Low
3. What are the harms associated with screening for HCV infection, including adverse effects such as anxiety, labeling, and impact on relationships?	5 (1 cross-sectional, 3 intervention series and 1 Controlled Trial)	Poor	Unable to assess (assessed different outcomes)	Direct	Low	288	Insufficient

Key Question	Number of Studies	Quality (Good, Fair, Poor)	Consistency (High, Moderate, Low)	Directness (Direct or indirect)	Precision (High, Moderate, Low)	Number of Subjects	Strength of Evidence
4a. What is the comparative effectiveness and comparative diagnostic accuracy of various tests and strategies for the work-up to guide treatment decisions in patients who are HCV positive?^a							
Clinical outcomes	1 cohort study	Fair	Unable to assess (one study)	Direct	Low	156	Insufficient
Diagnostic accuracy: Platelet counts vs. liver biopsy	15 studies of diagnostic accuracy	Fair	Moderate	Direct	Low	2,836 (AUROC for fibrosis) and 2,311 (AUROC for cirrhosis)	Low
Diagnostic accuracy: Age-platelet index vs. liver biopsy	6 studies of diagnostic accuracy	Fair	High	Direct	Moderate	1,121 (AUROC for fibrosis) and 1,113 (AUROC for cirrhosis)	Moderate
Diagnostic accuracy: APRI vs. liver biopsy	58 studies of diagnostic accuracy	Fair	High	Direct	High	13,999 (AUROC for fibrosis) and 13,077 (AUROC for cirrhosis)	High
Diagnostic accuracy: AAR vs. liver biopsy	27 studies of diagnostic accuracy	Fair	High	Direct	High	3,798 (AUROC for fibrosis) and 3,708 (AUROC for cirrhosis)	High
Diagnostic accuracy: CDS (also Bonacini Index) vs. liver biopsy	8 studies of diagnostic accuracy	Fair	High	Direct	Moderate	1,139 (AUROC for fibrosis) and 1,991 (AUROC for cirrhosis)	Moderate
Diagnostic accuracy: ELF or Simplified ELF vs. liver biopsy	7 studies of diagnostic accuracy	Fair	High	Direct	Moderate	1,217 (AUROC for fibrosis) and 754 (AUROC for cirrhosis)	Moderate
Diagnostic accuracy: FIB-4 vs. liver biopsy	15 studies of diagnostic accuracy	Fair	High (two studies)	Direct	Moderate	4,227 (AUROC for severe fibrosis)	Moderate

Key Question	Number of Studies	Quality (Good, Fair, Poor)	Consistency (High, Moderate, Low)	Directness (Direct or indirect)	Precision (High, Moderate, Low)	Number of Subjects	Strength of Evidence
Diagnostic accuracy: FibroIndex vs. liver biopsy	4 studies of diagnostic accuracy	Fair	High	Direct	Low	803 (AUROC for fibrosis) and 803 (AUROC for cirrhosis)	Moderate
Diagnostic accuracy: Fibrometer vs. liver biopsy	8 studies of diagnostic accuracy	Fair	High	Direct	Moderate	2,667 (AUROC for fibrosis) and 3,729 (AUROC for cirrhosis)	Moderate
Diagnostic accuracy: FibroSpect II vs. liver biopsy	4 studies of diagnostic accuracy	Fair	High	Direct	Low	590 (AUROC for fibrosis) and 108 (AUROC for cirrhosis)	Low
Diagnostic accuracy: Fibrotest vs. liver biopsy	28 studies of diagnostic accuracy	Fair	High	Direct	High	8,272 (AUROC for fibrosis) and 6,516 (AUROC for cirrhosis)	High
Diagnostic accuracy: Forn's Index vs. liver biopsy	16 studies of diagnostic accuracy	Fair	High	Direct	High	5,867 (AUROC for fibrosis) and 4,128 (AUROC for cirrhosis)	High
Diagnostic accuracy: Hepascore vs. liver biopsy	11 studies of diagnostic accuracy	Fair	High	Direct	High	3,787 (AUROC for fibrosis) and 3,437 (AUROC for cirrhosis)	High
Diagnostic accuracy: Lok Index vs. liver biopsy	8 studies of diagnostic accuracy	Fair	High	Direct	Moderate	3,215 (AUROC for cirrhosis)	Moderate
Diagnostic accuracy: Pohl Index vs. liver biopsy	10 studies of diagnostic accuracy	Fair	High (two studies)	Direct	Low	490 (AUROC for fibrosis) and 718 (AUROC for fibrosis)	Low
APRI vs. Fibrotest	16 studies of diagnostic accuracy	Fair	High	Direct	Moderate	6,399(excluding overlapping populations)	Moderate
AST/ALT ratio vs. other indices	14 studies of diagnostic accuracy	Fair	High	Direct	Moderate	3,991	Moderate

Key Question	Number of Studies	Quality (Good, Fair, Poor)	Consistency (High, Moderate, Low)	Directness (Direct or indirect)	Precision (High, Moderate, Low)	Number of Subjects	Strength of Evidence
4b. What proportion of patients with screen-detected HCV infection receives treatment?	3 intervention series	Fair	High	Direct	Moderate	18,580	Moderate
5. What are the harms associated with the work-up for guiding treatment decisions?	6 intervention series (1 of patients specifically undergoing liver biopsy for evaluation of HCV infection)	Fair	High	Direct	High	88,587	Moderate
6a. How effective is counseling or immunizations of patients with HCV infection at improving health outcomes or reducing the spread of HCV?	1 randomized controlled trial	Fair	Unable to assess (one study)	Direct	Low	137	Insufficient
6b. Does becoming aware of positive HCV infection status decrease high risk behaviors?	5 (2 prospective before-after studies, 3 retrospective post-intervention series)	Fair	Moderate	Direct	Moderate	1,660	Low
6c. How effective is counseling or immunizations of patients with HCV infection at improving intermediate outcomes, including change in high risk behaviors?	4 (2 RCTs, 2 before-after studies)	Fair	High	Direct	Low	1,369	Insufficient

Key Question	Number of Studies	Quality (Good, Fair, Poor)	Consistency (High, Moderate, Low)	Directness (Direct or indirect)	Precision (High, Moderate, Low)	Number of Subjects	Strength of Evidence
7. Do any interventions decrease or increase the vertical transmission of HCV during delivery or in the perinatal period?							
Elective cesarean vs. vaginal delivery	4 cohort studies	Fair	Moderate	Direct	Low	2,080	Low
Any cesarean vs. vaginal delivery	11 cohort studies	Fair	High	Direct	Low	2,308	Moderate
Internal fetal monitoring vs. no internal fetal monitoring	3 cohort studies	Fair	Moderate	Direct	Low	928	Insufficient
Prolonged rupture of membranes vs. less prolonged rupture of membranes	2 cohort studies	Fair	High	Direct	Low	245	Low
Breastfeeding vs. no breastfeeding	14 cohort studies	Fair	High	Direct	High	2,971	Moderate

Abbreviations: APRI, aspartate transaminase-platelet ratio index; AAR, aspartate transaminase-alanine transaminase ratio; CDS, Cirrhosis Discriminant Score; ELF, Enhanced Liver Fibrosis Index; HCV, hepatitis C virus.

^a Not all studies of diagnostic accuracy reported the area under the receiver operating curve (AUROC). Sensitivity and specificity at different cutoffs are summarized in the Results.

Appendix G. Evidence Tables and Overall Quality Ratings

Evidence Table 1: Key Question 2b. Screening Strategies

Author, year Country Overall Quality	Eligibility	Sample size	Baseline characteristics	Screening strategy	HCV prevalence	Results	Funding source	Comments
Gunn, 2003 ¹ USA Overall Quality: Fair	STD clinic attendees in San Diego offered HCV screening as part of routine care	3,367	Age ≥30 years: 4.6% Female: Not reported Self-reported intravenous drug use: 5.7%	A: All screened for HCV infection B: HCV screening only those who self-reported ever injecting drugs C: HCV screening only those who self-reported ever injecting drugs or had blood transfusions before 1992 D: HCV screening only those who self-reported ever injecting drugs, blood transfusion before 1992, or sex partner was an injection drug user E: HCV screening only those who self-reported or were identified by clinic staff as ever injecting drugs, blood transfusion before 1992, or sex partner was an injection drug user F: HCV screening only those who self-reported or were identified by clinic staff as ever injecting drugs, blood transfusion before 1992, sex partner was an injection drug user, or bacterial sexually transmitted disease G: HCV screening only those who self-reported or were identified by clinic staff as ever injecting drugs, blood transfusion before 1992, sex partner was an injection drug user, bacterial sexually transmitted disease, or age ≥30 years	4.9%	A vs. B vs. C vs. D vs. E vs. F vs. G Proportion screened: 100% (3356/3356) vs. 5.8% (193/3356) vs. 7.5% (253/3356) vs. 10% (347/3356) vs. 12% (413/3356) vs. 34% (1145/3356) vs. 63% (2127/3356) Sensitivity: 100% (165/165) vs. vs. 60% (99/165) vs. 64% (105/165) vs. 67% (110/165) vs. 70% (116/165) vs. 81% (134/165) vs. 97% (160/165) Number needed to screen to identify one case of HCV infection: 20 vs. 1.9 vs. 2.4 vs. 3.2 vs. 3.6 vs. 8.5 vs. 13	Centers for Disease Control and Prevention	Proportion screened, and number needed to screen calculated from prevalence and sensitivity/specificity provided in the article.
McGinn, 2008 ² USA Fair	Patients attending an adult primary care clinic in New York for a scheduled visit with their primary care provider or for an unscheduled visit for an urgent problem, age >18 years, language English or Spanish	1,000	Age: Mean 50 years Female: 73% Non-white: 90%	A: Screen all B: Positive findings in ≥1 of 3 domains C: Positive findings in ≥2 domains D: Positive findings in 3 domains	8.3% (2.5% newly diagnosed)	A vs. B vs. C vs. D Proportion screened: 100% (1000/1000) vs. 71% (709/1000) vs. 23% (228/1000) vs. 0.5% (56/1000) Sensitivity: 100% (83/83) vs. 91% (76/83) vs. 65% (54/83) vs. 34% (28/83) Number needed to screen to identify one case of HCV infection: 12 vs. 9.3 vs. 4.2 vs. 2.0	None reported	Proportion screened, and number needed to screen calculated from prevalence and sensitivity/specificity provided in the article.

Author, year Country Overall Quality	Eligibility	Sample size	Baseline characteristics	Screening strategy	HCV prevalence	Results	Funding source	Comments
Nguyen, 2005 ³ USA Poor	Age 18 to 60; able to complete English-language survey; patients with known HCV infection receiving care in gastroenterology clinic and patients receiving care in general internal medicine clinic with no apparent clinical liver disease, no history of previous HCV testing	429 (225 HCV-positive, 204 HCV-negative)	Born 1940-1949: 20% Born 1950-1959: 38% Born 1960-1969: 18% Female: 58% Non-white: 37% Reports seeing use of injecting drugs: 34%	A: Screen all B: At least 1 risk factor, based on 7-item instrument (self-report history of sex with a prostitute, history of exposure to potentially infected blood during transfusion, rejection as a blood donor, refused life insurance, witnessing use of injecting drugs, sexual intercourse with an injecting drug user, self-report of HBV infection) C: At least 2 risk factors D: At least 3 risk factors E: Four or more risk factors	Not applicable (case-control design)	A vs. B vs. C vs. D vs. E Proportion screened: 100% (429/429) vs. 78% (335/429) vs. 48% (207/429) vs. 28% (118/429) vs. 13% (56/429) Sensitivity: 100% (225/225) vs. 94% (212/225) vs. 79% (178/225) vs. 51% (115/225) vs. 24% (55/225) Number needed to screen to identify one case of HCV infection: Not applicable (case-control design)	Schering-Plough Corp	Estimated positive predictive value for 1.0% HCV prevalence population ≥0 risk factors: 1.0% ≥1 risk factor: 1.6% ≥2 risk factors: 5.3% ≥3 risk factors: 25% ≥4 risk factors: 33%
Zuniga, 2006 ⁴ USA Fair	Patients with one or more risk factors for HCV infection in primary care outpatient departments in New York	2,263	Age 40-54 years: 31% White: 78% Female: 3.9% Vietnam era veteran: 50% Blood transfusion prior to 1992: 17% Any intravenous drug use: 4.5% Unexplained liver disease: 3.2% Abnormal liver function tests: 9.1%	A: HCV screening for any of 11 positive risk factors (Vietnam era veteran, multiple sexual contacts, tattoo/body piercing, intemperate alcohol use, blood transfusion prior to 1992, intranasal cocaine use, blood exposure (mucous membranes), abnormal liver function tests, injection drug use (past or present), unexplained liver disease, hemodialysis) B: HCV screening for any of 5 positive risk factors (Vietnam era veteran, tattoo/body piercing, blood transfusion prior to 1992, abnormal liver function tests, injection drug use) C: HCV screening only those with self-reported injection drug use (past or present)	4.6%	A vs. B vs. C Proportion screened: 100% (2263/2263) vs. 78% (1776/2263) vs. 3.0% (68/2263) Sensitivity: 100% (103/103) vs. 97% (100/103) vs. 41% (42/103) Number needed to screen to identify one case of HCV infection: 22 vs. 18 vs. 1.6	Funding source not stated, declared no conflicts of interest	*Study reports 3% of subjects screened if screening targeted only to injection drug users, but elsewhere in article reports 4.5% prevalence of injection drug use

Author, year Country Overall Quality	Eligibility	Sample size	Baseline characteristics	Screening strategy	HCV prevalence	Results	Funding source	Comments
Zuure, 2010 ⁷ Netherlands Fair	Patients screened for HCV in a sexually transmitted disease clinics in the Netherlands	985	Not reported	A: Screen all B: HCV screening for at least 1 risk factor, based on 20-item questionnaire (injection drug use, born in HCV-endemic country, blood transfusion prior to 1992, HCV-infected bother, mother is/was injection drug user, living with HCV-infected individual, living with injection drug user, needle exposure to high-risk person, needle exposure in HCV-endemic country, hemophilia patient, hemodialysis patient, organ recipient, received blood products in medium/high risk country, exposure of healthcare workers to blood/tissue in medium/high risk country, surgical/dental procedure in medium/high risk country, ritual intervention (circumcision, scarification) in medium/high risk country, tattoo in medium/high risk country, body-piercing in medium/high risk country, HIV-positive status, non-injection drug use ≥ 3 times/week for ≥ 3 months)	1%	A vs. B Proportion screened: 100% (985/985) vs. 14% (140/985) Sensitivity: 100% (98/98) vs. 90% (88/98) Number needed to screen to identify one case of HCV infection: 10 vs. 2.4	Netherlands organization for health research and development	Questionnaire developed in a population with high prevalence of previously diagnosed self-reported HCV infection (48%), remainder self-reported as negative or unknown HCV status (results not reported here)

Abbreviations: AUROC, area under the receiver operating characteristic; HBV, hepatitis B virus; HCV, hepatitis C virus; PCR, polymerase chain reaction; STD, sexually transmitted disease.

Evidence Table 2: Key Question 2b. Screening Strategies Overall Quality Rating

Study, year	(1) Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	(2) Did the study evaluate a representative spectrum?	(3) Did the study report the proportion of eligible patients who met inclusion criteria who underwent screening?	(4) Was there a high rate of non-screening among eligible patients?	(5) Did the study describe methods for ascertaining risk factors?	(6) Did the study prospectively compare different pre-defined screening strategies?	Overall Quality
Gunn, 2003 ¹	Yes	Yes	No	Unclear	Yes (questionnaire)	No	Fair
McGinn, 2008 ²	Yes	Yes	Yes	Yes (67%)	Yes (risk factor assessment questionnaire)	No	Fair
Nguyen, 2005 ³	Unclear	No (case-control design)	No	Yes (76%)	Yes (questionnaire)	No	Poor
Zuniga, 2006 ⁴	Yes	Yes	Yes	Yes (58%)	Yes (screening questionnaire)	No	Fair
Zuure,, 2010 ⁵	Unclear	Yes	No	Unclear	Yes (screening questionnaire)	No	Fair

Evidence Table 3: Key Question 4a. Biopsy Outcomes

Author, year Country	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Baseline characteristics	Intervention	Duration of followup	Results	Funding source	Overall Quality
Andriulli, 2004 ⁶ Italy	Patients referred for evaluation for elevated liver enzymes and markers of HCV infection, scheduled for treatment with interferon and ribavirin but refused pretreatment liver biopsy; matched controls who underwent biopsy prior to treatment	Previously treated with antiviral therapies, hepatitis B surface antigen positive, required biopsy for suspicion of malignancy, decompensated cirrhosis, referred for transplant evaluation	Number screened and eligible not reported 78 cases and 78 matched controls	Reports no differences across groups, results reported for whole sample Age: 49 years Female: 41% Genotype 1: 53% No liver biopsy vs. liver biopsy Cirrhosis: 24% vs. 17%	A: No liver biopsy prior to interferon + ribavirin B: Liver biopsy prior to interferon + ribavirin	72 weeks (48 weeks treatment and 24 weeks followup for SVR)	A vs. B End-of-treatment response: 53% (41/78) vs. 58% (45/78) (p=0.63) SVR: 41% (32/78) vs. 44% (34/78) (p=0.87) Withdrawal due to adverse events: 10% (8/78) vs. 6.4% (5/78)	Not reported	Fair

Abbreviations: HCV, hepatitis C virus; SVR, sustained virologic response.

Evidence Table 4: Key Question 4a. Biopsy Overall Quality Rating

Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study use accurate methods for ascertaining exposures, potential confounders, and outcomes?	Were outcome assessors and/or data analysts blinded to treatment?	Did the article report attrition?	Did the study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to followup or overall high loss to followup?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Overall Quality
Andriulli, 2004 ⁶	Yes	Yes	Yes	Unclear	Yes	No	No	Yes	Fair

Evidence Table 5: Key Question 4a. Diagnostic Accuracy

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive test	Cutoffs predefined	Biopsy Overall Quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Adams, 2005 ⁷	Hepascore (bilirubin, g-glutamyltransferase, hyaluronic acid, a-2 macroglobulin, age, and sex) Fibrotest	Prospective	Derivation and validation samples reported separately	Australia	117 (derivation sample) 104 (validation sample)	Fibrosis (METAVIR F2-F4): 44% (derivation sample) and 57% (validation sample) Cirrhosis (METAVIR F4): 6% and 16%	Hepascore: Cutoff ≥ 0.5 (range 0.0-1.0) for fibrosis; ≥ 0.84 for cirrhosis	No for derivation sample, yes for validation sample	All ≥ 5 portal tracts; median 9 portal tracts and 13 mm	Derivation vs. validation sample Age: 40 vs. 41 years Female: 32% vs. 27% Genotype 1: 61% vs. 48% All treatment-naïve	Not stated	Predictive values not reported
Ahmad, 2011 ⁸	Fibrosis-cirrhosis index (alkaline phosphatase, bilirubin, albumin, platelet count) AST/ALT ratio APRI FIB-4 Fibrosis Index Alkaline phosphatase Bilirubin Albumin Platelet count	Retrospective	Yes (for fibrosis-cirrhosis index)	Pakistan	157	Fibrosis (METAVIR F2-F4): 57% Cirrhosis (METAVIR F4): 13%	Fibrosis-cirrhosis index > 0.130 or > 1.25 AST/ALT ratio > 1 APRI > 0.5 or > 1.5 FIB-4 > 1.45 or > 3.25 Fibrosis Index > 2.1 or > 3.3 Alkaline phosphatase > 120 or > 240 IU/l Bilirubin > 0.95 or > 1.5 mg/dl Albumin < 3.85 or < 4.1 g/dl Platelet count $< 100,000$ or $< 150,000$	No for fibrosis-cirrhosis index, otherwise yes	Not stated	Age: 38 years Female: 27% Genotype 1: 14% All treatment-naïve	Not stated	Yes
Alsatie, 2007 ⁹	5-item predictive index (DM, platelet count, INR, bilirubin, AST)	Retrospective	Derivation and validation samples reported separately	USA	190 (derivation sample) 94 (validation sample)	Fibrosis (METAVIR F2-F4): 41% Cirrhosis (METAVIR F4): 17%	5-item predictive index: Cutoffs ranged from 0 to 4	No for derivation sample, yes for validation sample	All ≥ 15 mm	Reported for derivation and validation samples together Age: 45 years Female: 40% Genotype 1: 50% All treatment-naïve	Not stated	Yes
Adler, 2008 ¹⁰	Fibrotest FIB-4 Forns' Index APRI Fibroindex	Unclear	No	Belgium	152	Fibrosis (METAVIR F2-F4): 73% Cirrhosis (METAVIR F4): 12%	Only AUROC reported	Only AUROC reported	Not stated	Not reported	Not stated	Only AUROC reported

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive test	Cutoffs predefined	Biopsy Overall Quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Anderson, 2000 ¹¹	AST/ALT ratio	Retrospective	No	Canada	133	Fibrosis or cirrhosis (method unclear): 82% Cirrhosis (method unclear): 46%	AST/ALT ratio ≥ 1	Yes	Not reported	Age: 46 years Female: 30% Genotype 1: Not reported All had elevated ALT 18% on treatment	6/139 excluded for unavailable liver biopsy	Yes
Becker, 2009 ¹²	Hepascore/APRI/FIB-4	Unclear	No	USA	391	Fibrosis (METAVIR F2-F4): 50% Cirrhosis (METAVIR F4): 19%	Hepascore > 0.2 , > 0.55 , or ≥ 0.8 APRI > 0.5 or > 1.5 FIB-4 ≥ 1.45 or $> 3.2.5$	Yes for APRI and FIB-4, no for Hepascore	All ≥ 10 mm or ≥ 8 portal tracts; median 16 mm, 11% < 10 mm	Age: 50 years Female: 30% Genotype 1: 75% None treated at time of biopsy	Not stated	Yes
Bejarano, 2009 ³	Sabadell NIHCED index	Prospective	No	Spain	321	Severe fibrosis (Knodell 3-4): 59% (no patients had Knodell 2) Cirrhosis (Knodell 4): 20%	Sabadell NIHCED index > 6	No	Mean 11.6 mm and 12.2 portal tracts	Age: 48 years Female: 44% Genotype 1: Not reported	Not stated	Yes
Berg, 2004 ¹⁴	APRI	Retrospective	No	Germany	484	Fibrosis (Scheuer F2-F4): 52% Cirrhosis (Scheuer F4): 13%	APRI: Cutoffs ranged from > 0.50 to > 2.0	Yes	Not reported	Age: 46 years Female: 44% Genotype 1: Not reported All treatment-naïve	Not stated	Yes
Ben Jazia, 2009 ⁵	AST/ALT ratio APRI Platelet count	Retrospective	No	Tunisia	35	Fibrosis (METAVIR F2-F4): 77% Cirrhosis (METAVIR F4): Not reported	APRI > 0.72 AST/ALT ratio and platelet count: Cutoffs not reported	No	Not reported	Age: 49 years Female: 69% Genotype 1: 46% All treatment-naïve	Not reported	No
Boeker, 2002 ¹⁶	TIMP-1/MMP-2 Hyaluronic acid AST/ALT Alkaline phosphatase GGT Albumin	Unclear	No	Germany	78	Fibrosis (Ishak, grades not reported): 46% (27/59, excluding patient with cirrhosis) Cirrhosis (Ishak, grades not reported): 24% (19/78)	TIMP-1 (Biotrak) > 950 mcg/l TIMP-1 (Quantikine) > 85 mcg/l MMP-2 (Biotrak) > 1500 mcg/l MMP-2 (Quantikine) > 320 mcg/l Hyaluronic acid > 30 mcg/l AST > 18 U/l ALT > 22 U/l Alkaline phosphatase > 190 U/l GGT > 28 U/l Albumin < 37 g/l	Unclear	Not reported	Age: Not reported Female: Not reported Genotype 1: Not reported	Not stated	Predictive values not reported

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive test	Cutoffs predefined	Biopsy Overall Quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Bonacini, 1997 ¹⁷	Cirrhosis discriminant score (platelet count, AST/ALT ratio, prothrombin index, ascites, spider angiomas)AST/ALT ratio	Retrospective	Yes	USA	79	Fibrosis: Not reported Severe fibrosis (Knodel F3-F4): 35% Cirrhosis: Not reported	Cirrhosis discriminant score ≥ 7 or ≥ 8 AST/ALT ratio	No (for cirrhosis discriminant score)	Not reported	Age: Not reported Female: Not reported Genotype 1: Not reported No histologic evidence of alcoholic liver disease	Not stated	Predictive values not reported
Borroni, 2006 ¹⁸	AST/ALT ratio Cirrhosis Discriminant Score APRI Pohl's Index Age-platelet index	Retrospective	No	Italy	228	Severe fibrosis (Knodel F3-F4): 49% Cirrhosis (Knodel F4): 13%	AST/ALT ratio ≥ 1 Cirrhosis Discriminant Score > 2 or > 7 APRI ≥ 2 Pohl's Index positive Age-platelet index ≥ 6 Combinations of APRI and age-platelet index: cutoffs not reported	No	All ≥ 6 portal fields	Age: 42 years Female: 27% Genotype 1: 47% All elevated transaminases All treatment-naïve	4 with < 6 portal tracts excluded from analysis	Yes
Bota, 2011 ¹⁹	King's score Forn's Index APRI	Retrospective	No	Romania	212	Fibrosis (METAVIR F2-F4): 91% Severe fibrosis (METAVIR F3-F4): 45% Cirrhosis (METAVIR F4)	Only AUROC reported	Only AUROC reported	All ≥ 8 portal tracts; mean 34 mm	Age: 50 years Female: 67% Genotype 1: Not reported	Not stated	Only AUROC reported
Bourliere, 2008 ²⁰	Hepascore Fibrotest	Prospective	No	France	467	Fibrosis (METAVIR F2-F4): 49% Cirrhosis (METAVIR F4): 7.5%	Hepascore ≥ 0.5 and ≥ 0.84 or not reported Fibrotest: Not reported	Unclear	Mean 20 mm and median 9 portal tracts; 59% ≥ 15 mm and ≥ 5 portal tracts	Age: 47 years Female: 41% Genotype 1: Not reported	Not stated	Yes
Bourliere, 2006 ²¹	Fibrotest APRI Forn's Index	Unclear	No	France	235	Fibrosis (METAVIR F2-F4): 42% Cirrhosis (METAVIR F4): 6.8%	Fibrotest > 0.1 or ≥ 0.6 APRI > 0.5 to > 2 Forn's index: ≥ 4.21 or > 6.9	Yes	Mean 20 mm and median 9 portal tracts; 59% ≥ 15 mm and ≥ 5 portal tracts	Age: 46 years Female: 45% Genotype 1: Not reported	Not stated	Yes

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive test	Cutoffs predefined	Biopsy Overall Quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Boursier, 2012 ²²	SAFE algorithm (based on APRI and Fibrotest)	Retrospective	No	France	1785	Fibrosis (METAVIR F2-F4): 55% Cirrhosis (METAVIR F4): 13%	SAFE fibrosis algorithm positive SAFE cirrhosis algorithm positive	Yes	>=15 mm in 79%	Mean age: 48 years Female: 40% Genotype 1: Not reported Excluded for alcohol >30 g/day (men) or >20 g/day (women)	Not stated	Yes
Boursier, 2011 ²³	FibroMeter	Unclear	No	France	349 (derivation sample) 380 (validation sample)	Derivation vs. validation sample Fibrosis (METAVIR F2-F4): 68% vs. 49% Cirrhosis (METAVIR F4): 12% vs. 18%	Not reported	No	94% ≥15 mm and ≥8 portal tracts	Derivation vs. validation sample Age: 52 vs. 51 years Female: 40% vs. 38% Genotype 1: Not reported	Not stated	Predictive values not reported
Boursier, 2009 ²⁴	FibroMeterFibrotestHepascoreAPRIModified Fibrotest	Retrospective	No, except for modified Fibrotest	France	1056	Fibrosis (METAVIR F2-F4): 52% Cirrhosis (METAVIR F4): 11%	FibroMeter >0.628, >0.830, or >0.979 Fibrotest >0.448, >0.631, >0.660, or >0.862 Hepascore >0.497, >0.801, >0.904, or >0.999 APRI >0.581, >0.652, >1.159, or >2.532 Modified Fibrometer >0.089 or >0.442	No	Not reported	Mean age: 46 years Female: 40% Genotype 1: Not reported	Not stated	Yes
Burton, 2011 ²⁵	APRI	Retrospective	No	USA	268 (142 black, 117 white)	Fibrosis (Batt-Ludwig 2-4): 49% Cirrhosis (Batt-Ludwig 4): 16%	APRI: Cutoffs ranged from >0.50 to >1.0	No	Not reported	Age: 52 years Female: 4.5% Genotype 1: 81% All treatment-naïve	Not stated	Yes

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive test	Cutoffs predefined	Biopsy Overall Quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Cales, 2010 ²⁶	FibroMeter FibroMeter 3G (hyaluronic acid replaced with GGT) FibroTest Hepascore	Retrospective	Yes (for FibroMeter 3G)	France	1056 (derivation sample) 458 (validation sample)	Fibrosis (METAVIR F2-F4): 52% and 48% Cirrhosis (METAVIR F4): 11% and 15%	FibroMeter >0.419 FibroMeter 3G >0.440	Unclear	Not reported	Only reported for derivation sample Mean age: 46 years Female: 40% Genotype 1: Not reported No antiviral treatment in last 6 months	Not stated	Only AUROC reported
Cales, 2008 ²⁷	FibroMeter Fibrotest Hepascore APRI FIB-4	Retrospective	No	France	1056	Fibrosis (METAVIR F2-F4): 52% Cirrhosis (METAVIR F4): 11%	FibroMeter >0.419 Fibrotest >0.435 Hepascore >0.465 APRI >0.548 FIB-4 >1.116	No	Not reported	Mean age: 46 years Female: 40% Genotype 1: Not reported No antiviral treatment in last 6 months	Not stated	Yes
Castera, 2010 ²⁸	SAFE algorithm (based on APRI and Fibrotest)	Prospective	No (for SAFE algorithm)	France	302	Fibrosis (METAVIR F2-F4): 76% Cirrhosis (METAVIR F4): 25%	APRI: Algorithm based on scores ≤0.5, 0.5-1.5, or >1.5 Fibrotest (for patients with APRI 0.5-1.5): >0.48	Yes	All ≥10 mm and ≥6 portal tracts; mean 20 mm and 15 portal tracts	Age: 52 years Female: 43% Genotype 1: Not reported All elevated ALT	12 insufficient liver tissue	Yes
Castera, 2009 ²⁹	AST/ALT ratio APRI Prothrombin index Platelet count Fibrotest Lok Index	Prospective	No	France	298	Fibrosis (METAVIR F2-F4): 74% Cirrhosis (METAVIR F4): 23%	Platelet count: <150 Fibrotest: ≥0.75 Prothrombin index: ≤85% AST/ALT ratio: ≥1 APRI: ≥1.0 or 2.0 Lok Index: ≥0.2 or ≥0.5	Yes	All ≥10 mm and ≥6 portal tracts; mean 20 mm and 15 portal tracts	Age: 52 years Female: 43% Genotype 1: Not reported	Not reported	Yes
Castera, 2005 ³⁰	APRI Fibrotest	Prospective	No	France	193	Fibrosis (METAVIR F2-F4): 74% Cirrhosis (METAVIR F4): 25%	Only AUROC reported	Only AUROC reported	Median 17 mm, median 2 fragments	Age: 51 years Female: 43% Genotype 1: Not reported	Not reported	Unable to construct 2 x 2 table

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive test	Cutoffs predefined	Biopsy Overall Quality	Population characteristics	Proportion unexamined by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Cheong, 2011 ³¹	Significant Fibrosis Index (haptoglobin, a2MG, TIMP1, MMP2, GGT) Zeng Index APRI Forn's Index FIB-4 ELF index	Prospective	Yes (for Significant Fibrosis Index)	Korea	HCV infected: 79 (derivation sample) and 27 (validation sample)	Derivation and validation samples, respectively (includes persons with HCV and HBV infection) Fibrosis (METAVIR F2-F4): 79% and 77% Cirrhosis (METAVIR F4): 13% and 28%	Significant Fibrosis Index >2.2 or >3.3	No (for Significant Fibrosis Index)	Mean 12.6 mm and mean 13.2 portal tracts; 71% had ≥11 portal tracts	Derivation vs. validation samples (includes persons with HCV and HBV infection) Age: 42 vs. 42 years Female: 31% vs. 35% Genotype 1: Not reported No antiviral treatment in last 6 months	Not reported	Sensitivity, specificity, and predictive values not reported for HCV subgroup
Cheong, 2011 ³²	Fibrosis-protein Index (a-2 macroglobulin and hemopexin)APRI	Unclear	Yes (for Fibrosis-protein Index)	Belgium	62 (derivation sample) 73 (validation sample)	Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4): 50% and 71% Cirrhosis (METAVIR F4): 26% and 14%	Fibrosis-protein Index: >3.53 and >4.78 APRI: >0.5 or >1.0	No (for Fibrosis-protein Index), yes for APRI	Median 1.6-2.0 cm and >8 portal tracts	Derivation vs. validation samples Age: 50 vs. 50 years Female: 48% vs/ 53% Genotype 1 or 4: 69% vs. 71% All treatment-naïve	Not reported	Yes for Fibrosis-protein Index, not reported for APRI
Cheong, 2008 ³³	Platelet count Normalized AST/ALT ratio Pohl score APRI Lok Index	Prospective	No	USA	490	Fibrosis (Batt-Ludwig 2-4): 66% Cirrhosis (Batt-Ludwig 4): 14%	Platelet count: <100 or <150 Normalized AST/ALT ratio: ≥1 Pohl score: Positive (platelet count <150 and AST/ALT ratio ≥1) APRI: ≥0.5, ≥1.0, ≥1.5, or ≥2.0 Lok Index: >0.2 or >0.5	Yes	Not reported	Age: 49 years Female: 2% Genotype 1: Not reported	Not reported	Yes, except for AST/ALT ratio for severe fibrosis
Chrysanthos, 2006 ³⁴	APRI	Unclear	No	Greece	284	Fibrosis (Ishak score ≥3): 51% Cirrhosis (Ishak score 5 or 6): 20%	APRI: >0.50 or >1.50 for fibrosis, >1.00 or >2.00 for cirrhosis	Yes	All >1.5 cm	Age: 49 years Female: 49% Genotype 1: Not reported No antiviral treatment last 6 months	14 patients out of entire (HCV + HCV) sample of 489 patients had inadequate biopsy specimen	Yes

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive test	Cutoffs predefined	Biopsy Overall Quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Cobbold, 2010 ³⁵	APRI ELF Index Hepatic transit time	Prospective	No	UK	67	Fibrosis (Ishak ≥3): 55% Cirrhosis (Ishak 5 or 6): 21%	APRI >0.66 or >0.92 ELF Index >8.75 or >9.4 Hepatic Transit Time >8.0 or >10.25	No	All ≥10 mm, mean 24 mm	Age: 50 years Female: 34% Genotype 1: Not reported No current antiviral treatment Excluded if >20 g alcohol/day	3 had inadequate biopsy specimen	Some inconsistency
Colletta, 2005 ³⁶	Fibrotest	Unclear	No	Italy	40	Fibrosis (METAVIR F2-F4): 35% Cirrhosis (METAVIR F4): 0%	Fibrotest: ≥0.31	Yes	Mean 20 mm, 7 portal tracts	Age: 44 years Female: 45% Genotype 1: 30% All had ALT ≤1.2 times the upper limit of the reference range and Ishak score ≤2 All treatment-naïve	Not stated	Yes
Colli, 2005 ³⁷	Cirrhosis discriminant score Liver surface nodularity	Prospective	No	Italy	176	Severe fibrosis (METAVIR F3-F4): 38%	Liver surface nodularity present	Yes	Mean 41 mm	Age: 54 years Female: 45% Genotype 1: Not reported All had ALT ≥1.5 times upper limit of normal	3/179	Predictive values not reported
Crisan, 2012 ³⁸	APRI Forn's Index FIB-4 Hepascore Fibrometer Fibrotest Combinations of APRI, Fibrometer, and Fibrotest	Prospective	No	Romania	446	Fibrosis (METAVIR F2-F4): 63% Severe fibrosis (METAVIR F3-F4): 27%	APRI >0.44 or >1.69 Forn's Index >4.47 or >7.3 FIB-4 >1.26 or >3.74 Hepascore >0.34 or >0.61 Fibrometer >0.59 or >0.76 Fibrotest >0.34 or >0.54	No	Median 11 mm, mean 14 portal tracts, all >5 portal tracts	Age: 49 years Female: 62% Genotype 1: Not reported All treatment-naïve Excluded if alcohol >30 g/day (men) or >20 g/day (women)	Not reported	Some inconsistency

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive test	Cutoffs predefined	Biopsy Overall Quality	Population characteristics	Proportion unexamined by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Cross, 2010 ³⁹	King's Score	Unclear	No	UK	187	Fibrosis (Ishak ≥ 3): 48% Cirrhosis (Ishak 5 or 6): 27%	King's Score: >9.87 or >24.3	No	All ≥ 10 mm or >10 portal tracts; mean 15 mm	Age: 49 years Female: 41% Genotype 1: 42% Patients with high alcohol consumption excluded All treatment-naïve	Not reported	Yes
Cross, 2009 ⁴⁰	King's Score (age, AST, INR, platelets), AST/ALT ratio AST APRI Age-platelet index Cirrhosis Discriminant Score FIB-4 index Pohl index (AAR ≥ 1 and platelets <150)	Retrospective	Yes, measures of diagnostic accuracy similar for derivation and validation samples, diagnostic accuracy reported for derivation sample	UK	602 (derivation sample) 105 (validation sample)	Derivation vs. validations samples, respectively Fibrosis (Ishak ≥ 3): 45% vs. 48% Cirrhosis (Ishak 5 or 6): 22% vs. 14%	King's Score: >12.3 or 16.7 AST: >62 or >64.5 Age-platelet index: >3.5 or >5 APRI: >0.53 or >0.75 Platelets: <187 or <149 FIB-4: >0.34 or 0.41	No	All >10 mm and >10 portal tracts	Derivation vs. validation samples Age: median 43 vs. 43 years Female: 35% vs. 30% Genotype 1: 55% vs. not reported Heavy alcohol excluded (>60 g/day men, >40 g/day women) All treatment-naïve	12 insufficient liver tissue	Yes
Ehsan, 2008 ⁴¹	Age-platelet index Lok Index Cirrhosis discriminant score Goteborg University Cirrhosis Index APRI Pohl Index AST/ALT ratio	Unclear	No	Egypt	116	Fibrosis: Not reported Cirrhosis (Ishak 5-6): 30%	Age-platelet index >5 Lok Index >0.6 Cirrhosis discriminant score >7 Goteborg University Cirrhosis Index >1.5 APRI >1.5 Pohl Index positive AST/ALT ratio >1.5	No	Mean 12 mm	Age: 39 years Female: 16% Genotype 1: Not reported No alcohol Schistosomiasis: 46% All treatment-naïve	Not reported	No
El-Gindy, 2003 ⁴²	MMP-2 TIMP-1	Unclear	No	Egypt	41	Fibrosis (Ishak 1-6): 71% Cirrhosis (Ishak 5-6): 34%	MMP-2 >400 ng/ml TIMP-1 >195 ng/ml AST >34 IU/L ALT >44 IU/L Albumin <3.5 g/100 ml	No	Not reported	Age: 48 years Female: 41% Genotype 1: Not reported No habitual alcohol All treatment-naïve	Not reported	Predictive values not reported; some sensitivities and specificities don't match reported data

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive test	Cutoffs predefined	Biopsy Overall Quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
El-Sayed, 2011 ⁴³	APRI AST/ALT ratio AST	Unclear	No	Egypt	37	Severe fibrosis (METAVIR F3-F4): 68%	Only AUROC reported	Only AUROC reported	All ≥10 mm and ≥5 portal tracts	Age: 41 years Female: 14% Genotype 1: Not reported	Not reported	Only AUROC reported
El-Shorbagy, 2004 ⁴⁴	7-item predictive index (platelet count, MMP-9, portal vein diameter, spleen diameter, ALT, AST, viral load)	Unclear	Yes	Egypt	109	Fibrosis (G2S2 or G3S3): 80% Cirrhosis (G3S3): 18%	7-item predictive index >3 or ≥6	No	Not reported	Age: 46 years Female: 29% Genotype 1: Not reported	Not reported	Yes
Fabris, 2008 ⁴⁵	APRI/AST/ALT ratio Age-platelet index Cirrhosis Discriminant Score Forn's Index Fibro Index	Retrospective	No	Italy	167	Fibrosis (METAVIR F2-F4): 41% Cirrhosis (METAVIR F4): 11%	Fibroindex >1.6 Not reported for other tests	Unclear	Average 19 mm and median 7 portal tracts	Age: 49 years Female: 50% Genotype 1 + 4: 50% 1/4 reported significant alcohol use All treatment-naïve	Unclear	Yes for Fibro Index (Sensitivity, specificity, and predictive values not reported for other tests)
Fontana, 2008 ⁴⁶	HALT-C model (platelet count, TIMP-1, hyaluronic acid) Lok Index APRI Cirrhosis Discriminant Score	Unclear	Yes (for HALT-C model)	USA	513	Fibrosis (Ishak score ≥3): 93% Cirrhosis (Ishak 5 or 6): 38% (study excluded patients with Ishak 0 or 1)	HALT-C model at cutoffs from <0.1 to >0.9	No	Mean 1.84 cm	Age: 49 years Female: 29% Genotype 1: Not reported All previously failed treatment, all had Ishak 3 fibrosis within the last year	2/515	Yes
Forns, 2002 ^{47c}	Forns Index (age, GGT, cholesterol, platelet count)	Unclear	Derivation and validation samples reported separately	Spain	351 (derivation sample) 125 (validation sample)	Derivation vs. validation samples Fibrosis (Scheuer F2-F4): 24% vs. 26% Cirrhosis (Scheuer F4): 6.0% vs. 3.2%	Forns Index <4.21 and >6.9	Yes (for validation sample)	All ≥6 portal tracts	Derivation vs. validation samples Age: 39 vs. 38 years Female: 36% vs. 36% Genotype 1: 86% vs. 84% All had elevated ALT Excluded regular alcohol >30 g/day All treatment-naïve	Unclear	Yes

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive test	Cutoffs predefined	Biopsy Overall Quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Friedrich-Rust, 2010 ⁴⁸	Simplified ELF index Fibrotest	Retrospective	No	Germany	36	Fibrosis (METAVIR F2-F4): 66% (whole sample) Cirrhosis (METAVIR F4): 15%	Simplified ELF index cutoffs >9.78, >10.22, or >10.31 Fibrotest cutoffs >0.32, >0.59, or >0.73	Unclear	All >10 mm and ≥6 portal tracts; mean 22 mm, median 20 mm	Whole sample Age: 50 years Female: 57% Genotype 1: Not reported	Unclear	Unable to construct 2 x 2 table
Gabrielli, 1997 ⁴⁹	Laminin P1 PIIIP	Unclear	No	Italy	99	Fibrosis (Scheuer F2-F4): Not reported Cirrhosis (Scheuer F4): 16%	Laminin P1 range from 1.4 to 2.4 U/ml PIIIP range from 0.6 to 1.6 U/ml	No	≥5 portal tracts and ≥5 terminal hepatic veins	Age: 50 years Female: 36% Genotype 1: Not reported All had histologically proven chronic hepatitis	Unclear	Unable to construct 2 x 2 table
Giannini, 2006 ⁵⁰	AST/ALT ratio Platelet count	Retrospective	No	Italy and USA	409	Fibrosis (Ishak ≥3 in Italian sample, METAVIR F2-F4 in US sample): 43%	AST/ALT >0.66 Platelet count <163,000	No	Not reported	Age: 47 (Italy) and 43 (USA) years Female: 27% and 36% Genotype 1: Not reported Excludes >40 g alcohol/day All treatment-naïve	Unclear	Yes
Giannini, 2003a ⁵¹	AST/ALT ratio Platelet count AST/ALT ratio and platelet count (Pohl Index variant)	Retrospective	Yes (for platelet count and combination of AST/ALT ratio and platelet)	Italy	252	Fibrosis (Scheuer F2-F4 or clinical signs of portal hypertension): 55% Cirrhosis (Scheuer F4 or clinical signs of portal hypertension): 36%	AST/ALT ratio ≥1 Platelet count <130,000	Yes for AST/ALT ratio, no for platelet count	Not reported	Age: 48 years Female: 26% Genotype 1: 57%	Unclear	Yes
Giannini, 2003b ⁵²	AST/ALT ratio APRI	Retrospective	No	Italy	239	Fibrosis (criteria not reported): 54% Cirrhosis (criteria not reported): 27%	AST/ALT ratio ≥1 APRI cutoffs not reported	Yes for AST/ALT ratio, unclear for APRI	Not reported	Age: 47 years Female: 28% Genotype 1: Not reported	Unclear	Predictive values not reported

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive test	Cutoffs predefined	Biopsy Overall Quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Gomes da Silva, 2008 ⁵³	APRI	Retrospective	No	Brazil	50	Fibrosis (METAVIR F2-F4): 56% Cirrhosis (METAVIR F4): 26%	APRI >0.50 to >2.00	Yes (reported best cutoffs and pre-defined cutoffs)	Not reported	Age: 50 years Female: 32% Genotype 1: 54% All treatment-naïve	Not stated	Yes (slight discrepancies)
Grigorescu, 2007 ⁵⁴	Fibrotest alpha-2 macroglobulin Haptoglobin Apolipoprotein-A1 Total bilirubin GGT	Retrospective	No	Romania	116	Fibrosis (METAVIR F2-F4): 63%	Fibrotest >0.47 alpha-2 macroglobulin >3.01 g/L Haptoglobin >0.81 g/L Apolipoprotein-A1 >1.41 g/L Total bilirubin >12.65 micromol/L GGT >47 IU/L	No	Not reported	Age: 47 years Female: 63% Genotype 1: Not reported Excluded if alcohol >30 g/day (men) or >20 g/day (women)	Not stated	Yes
Guechot, 2010 ⁵⁵	Hepascore (with automated hyaluronic acid assay)	Prospective	No	France	512	Fibrosis (METAVIR F2-F4): 48% Cirrhosis (METAVIR F4): 15%	Hepascore ≥0.25, >0.5, >0.6, >0.75, or >0.84	No	Mean 25 mm, >25 mm in 49%	Age: Median 50 years Female: 40% Genotype 1: Not reported All treatment-naïve	42 excluded due to insufficient liver tissue	Yes
Guechot, 1996 ⁵⁶	PIIIP Hyaluronic acid	Unclear	No	France	326	Severe fibrosis (Knodell F3-F4): 34% Cirrhosis (Knodell F4): 16%	PIIIP >0.80 or >1.00 U/ml Hyaluronic acid >85 or >100 mcg/l	No	Not reported	Age: 44 years Female: 45% Genotype 1: Not reported All elevated ALT All treatment-naïve	Unclear	Predictive values not reported
Guechot, 1994 ⁵⁷	PIIIP Hyaluronic acid	Unclear	No	France	58	Fibrosis (Knodell F1-3): 76% Cirrhosis (Knodell F3): 17%	PIIIP >0.80 U/ml Hyaluronic acid >90 mg/l	No	Not reported	Age: Mean not reported (range 25-68 years) Female: 29% Genotype 1: Not reported	Unclear	Yes

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive test	Cutoffs predefined	Biopsy Overall Quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Guzelbulut, 2011 ⁵⁸	APRI FIB-4 Forns' Index	Retrospective	No	Turkey	150	Fibrosis (METAVIR F2-F4): 55% Cirrhosis (METAVIR F4): 34%	APRI >0.5->2.0 FIB-4 >0.6 to >3.25 Forns' Index >4.2 or >6.9	Yes	Not reported	Age: 52 years Female: 48% Genotype 1: Not reported Antiretroviral-naïve No alcohol abuse for >6 months	Unclear	Yes
Halfon, 2007 ⁵⁹	Fibrotest APRI Fibrometer Hepascore	Retrospective	No	France	356	Fibrosis (METAVIR F2-F4): 41% Cirrhosis (METAVIR F4): 4%	FibroMeter >0.57 or >0.88 Fibrotest >0.44 or >0.56 Hepascore >0.32 or >0.61 APRI >0.39 or >0.83	Unclear	All >15 mm	Age: 45 years Female: 47% Genotype 1: Not reported No antiviral treatment in last 6 months	Not reported	Yes
Halfon, 2006 ⁶⁰	Fibrotest	Prospective	No	France	504	Fibrosis (METAVIR F2-F4): 46% Cirrhosis (METAVIR F4): 5.8%	Fibrotest cutoffs ranged from 0.10 to 0.80	No	Median 15 mm and 9 portal tracts; 55% ≥15 mm and ≥5 portal tracts	Age: 45 years Female: 46% Genotype 1: Not reported	15	Yes
Halfon, 2005 ⁶¹	Hyaluronic acid	Prospective	Derivation and validation samples reported separately	France	151 (derivation sample) 254 (validation sample)	Derivation vs. validation samples Fibrosis (METAVIR F2-F4): 48% vs. 46% Cirrhosis (METAVIR F4): 7% vs. 5%	Hyaluronic acid ≥16 to >237	Yes (for validation sample)	Biopsy ≥25 mm	Derivation vs. validation samples: 51 vs. 47 years Female: 54% vs. 52% Genotype 1: Not reported	Not reported	Yes
Hsieh, 2009 ⁶²	FibroQ (age, AST, PT, platelets, ALT) AAR APRI	Retrospective	Yes (for FibroQ)	Taiwan	140 (113 HCV, 9 HCV/HBV, 18 HBV)	Fibrosis (METAVIR F2-F4): 83% Cirrhosis (METAVIR F4): 4.3%	FibroQ >1.6 or >2.6 APRI >0.54 to >1 AAR >0.5 to >2.0	No for FibroQ and for some analyses of AAR and APRI	Not reported	Age: 53 years Female: 35% Genotype 1: Not reported No alcohol >20 g/day 6% HBV/HCV coinfectd and 13% HBV infected without HCV infection All treatment-naïve	Not stated	Yes

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive test	Cutoffs predefined	Biopsy Overall Quality	Population characteristics	Proportion unexamined by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Iacobellis, 2005a ⁶³	Platelet count, ultrasonographic parameters	Retrospective	Yes, for combined findings	Italy	1143	Fibrosis (Scheuer F2-F4): 57% Cirrhosis (Scheuer F4): 7.2%	Platelet count <140 Spleen >120 mm Nodular liver present Portal vein >12 mm	Yes	All ≥5 portal tracts	Age: 53 years Female: 43% Genotype 1: Not reported All elevated aminotransferases All treatment-naïve	109 (lacking ultrasound parameters)	No, for platelet count <140
Iacobellis, 2005b ⁶⁴	AST/ALT ratio Platelet count Globulin/albumin ratio Combinations of the above APRI Forns' Index	Retrospective	Yes, for combined tests	Italy	1252	Fibrosis (Scheuer F3 or F4): 19% Cirrhosis (Scheuer F4): 6.2%	AST/ALT ratio ≥1 Platelet count <140,000 or <150,000 Globulin/albumin ratio >1 Combinations of the above APRI >1.5 or >2 Forns' Index >6.9	Yes	All ≥5 portal tracts	Age: 54 years Female: 43% Genotype 1: Not reported All elevated aminotransferases All treatment-naïve	Unclear	No
Imbert-Bismut, 2001 ⁶⁵ ; Thabut, 2003 ⁶⁶ ; Le Calvez, 2004 ⁶⁷	Fibrotest (original 6-marker version) APRI	Prospective	Derivation and validation samples reported separately	France	205 (derivation sample) 134 (validation sample)	Derivation vs. validation sample Fibrosis (METAVIR F2-F4): 38% vs. 45% Cirrhosis (METAVIR F4): 10% vs. 16%	Fibrotest cutoffs ranged from 0.10 to 0.90	No	All ≥10 mm	Derivation vs. validation sample Age: 47 vs. 48 years Female: 47% vs. 34% Genotype 1: Not reported	38/377 (10%) of derivation + validation samples did not have stageable fibrosis (30) or had missing biomarkers (8)	Yes
Imperiale, 2000 ⁶⁸	AST/ALT ratio	Retrospective	No	USA	177	Fibrosis: Not reported Cirrhosis (Hytioglou 4): 23%	AST/ALT ratio ≥1	Yes	Not reported	Age: 42 years Female: 37% Genotype 1: Not reported	Not stated	Yes
Islam, 2005 ⁶⁹	Normalized AST Platelet count APRI Goteborg University Cirrhosis Index (GUCI) (AST x PT-INR x 100/platelet count)	Retrospective	Yes (for GUCI)	Sweden	179	Fibrosis (Ishak ≥3): 41% Cirrhosis (Ishak 5 or 6): 11%	Normalized AST/ALT ratio >2.0 Platelet count <190 APRI >1.0 GUCI >1.0	No	≥10 mm and ≥4 portal tracts	Age: 44 years Female: 44% Genotype 1: Not reported	Not reported	Yes

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive test	Cutoffs predefined	Biopsy Overall Quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Kaul, 2002 ⁴⁰	4-item predictive model (seg, AST, platelet count, spider nevi)	Retrospective	Derivation and validation samples reported separately	USA	264 (derivation sample) 102 (validation sample)	Fibrosis (Scheuer F2-F4): Not reported Cirrhosis (Scheuer F4): 33% (derivation sample) vs. 16% (validation sample)	Not reported (reports only AUROC)	4-item predictive model: Only AUROC reported	Not reported	Derivation vs. validation samples Age: 45 vs. not reported Female: 39% vs. not reported Genotype 1: Not reported All in derivation sample had elevated AST or ALT	Not reported	Measures of diagnostic accuracy not reported
Khan, 2008 ⁷¹	APRI	Unclear	No	Pakistan	120	Fibrosis (METAVIR F2-F4): 54% Cirrhosis (METAVIR F4): 8%	APRI >0.5 to >1.75	No	Not reported	Age: 37 years Female: 30% Genotype 1: Not reported All treatment-naïve	Unclear	Yes
Khokhar, 2003 ⁷²	Pohl Index	Retrospective	Yes	Pakistan	266	Fibrosis (METAVIR F2-F4): 80% Cirrhosis (METAVIR F4): 56%	Pohl Index positive	No	Not reported	Age: 45 years Female: 44% Genotype 1: Not reported No alcohol use	Unclear	Yes
Koda, 2007 ⁷³	Fibro Index (platelet count, AST, GGT) Forn's Index APRI	Unclear	Derivation and validation samples reported separately	Japan	240 (derivation sample) 162 (validation sample)	Derivation vs. validation sample Fibrosis (METAVIR F2-F3): 51% vs. 50% (excluding F4) Cirrhosis (F4): 0% vs. 0% (excluded from primary analyses; 26% in secondary analysis of validation sample)	Fibro Index >1.25 or ≥2.25 APRI >0.36 or ≥0.85 Forns Index >4.5 or ≥8.7	Yes (for validation sample)	Mean 18 mm, all ≥10 mm	Age: 54 years Female: 40% Genotype 1: Not reported No alcohol >10 g/day All treatment-naïve	Unclear	Yes
Lackner, 2005 ⁷⁴ and Lackner, 2006 ⁷⁵	AST/ALT ratio Cirrhosis Discriminant Score Age-platelet Index Pohl Index APRI Platelet count Lok Index	Unclear	No	Austria	194	Fibrosis (Ishak score ≥3): 50% Cirrhosis (Ishak score 5 or 6): 16%	AST/ALT ratio ≥1.0 Cirrhosis Discriminant Score ≥8 Age-platelet index ≥6 Pohl Index positive APRI ≥0.5 to ≥2.0 Platelet count <130,000 or <150,000 Lok Index ≥0.20	Yes	All ≥6 portal tracts	Age: 48 years Female: 43% Genotype 1: 84% No alcohol >20 g/day All treatment-naïve	17	Yes

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive test	Cutoffs predefined	Biopsy Overall Quality	Population characteristics	Proportion unexamined by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Leroy, 2008 ⁷⁶	FibroMeterFibrotestHepascoreAPRI	Retrospective	No	France	825	Fibrosis (METAVIR F2-F4): 48% Cirrhosis (METAVIR F4): 11%	Not reported	Unclear	55% >20 mm; 84% >15 mm	Age: 44 years Female: 40% Genotype 1: Not reported No alcohol >30 g/day No antiviral treatment in last 6 months	441/1266 excluded due to missing data	Yes
Leroy, 2007 ⁷⁷	MP3 FibroMeter Fibrotest Hepascore Forn's Index APRI	Unclear	No	France	180	Fibrosis (METAVIR F2-F4): 51% Cirrhosis (METAVIR F4): 14%	MP3: ranged from >0.20 to >0.50 FibroMeter: No cutoff assessed (only estimated AUROC) Fibrotest: ranged from >0.22 to >0.59 Hepascore: >0.50 or >0.84 Forn's Index: >4.20 or >6.90 APRI: ranged from >0.50 to >2.0	Yes	Median 23 mm and median 17 portal tracts; 89% >15 mm and 45% >25 mm	Age: 44 years Female: 38% Genotype 1: 61% No alcohol >30 g/day All treatment-naïve	Not reported	Yes
Leroy, 2004 ⁷⁸	Hyaluronic acid PIIIP MP3 score (MMP-1 and PIIIP)	Unclear	Yes	France	188	Fibrosis (METAVIR F2-F4): 45% Cirrhosis (METAVIR F4): 7.4%	MP3 cutoffs ranged from >0.20 to >0.50 PIIIP >5 or >6 ng/ml Hyaluronic acid >35 ng/ml or >80 g/ml TIMP-1 >1300 ng/ml	No	Not reported	Age: 43 years Female: 36% Genotype 1: 51% All treatment-naïve	Stage of fibrosis not determined in 6 patients	No
Liu, 2006 ⁷⁹	APRI Age-platelet index AST/ALT ratio Splenic artery pulsatility index	Unclear	No	Taiwan	79	Fibrosis (METAVIR F2-F4): 27% Cirrhosis (METAVIR F4): 0%	APRI >0.40, >0.50, or >1.50 Age-platelet index >4.00 or >6.00 AST/ALT ratio >0.60 or >1.00 Splenic artery pulsatility index >0.85 or >1.05	Unclear	Mean 19 mm length and 1.4 mm diameter	Age: 43 years Female: 65% Genotype 1: 61% All had normal ALT All treatment-naïve	Not stated	Yes
Loeza-del-Castillo, 2008 ⁸⁰	APRI	Retrospective	No	Mexico	164	Fibrosis (METAVIR F2-F4): 51% Severe fibrosis (METAVIR F3-F4): 41% Cirrhosis (METAVIR F4): 10%	APRI >0.64 or >0.7532	No	Not reported	Age: 49 years Female: 64% Genotype 1: 73%	Not reported	Yes

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive test	Cutoffs predefined	Biopsy Overall Quality	Population characteristics	Proportion unexamined by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Lo Iacono, 1998 ⁸¹	Soluble ICAM-1 Soluble VCAM-1 PIIIP	Unclear	No	Italy	52	Fibrosis (Scheuer F2-F4): Not reported Cirrhosis (Scheuer F4): 21%	sICAM-1 >520 ng/ml sVCAM-1 >1208 ng/ml PIIIP >10.57 mcg/ml	No	Not reported	Age: 41 years Female: 37% Genotype 1: 73%	Not reported	Predictive values not reported
Lok, 2005 ⁸²	Lok Index (platelet count, AST/ALT ratio, and INR)	Prospective	Derivation and validation samples reported separately	USA	783 (derivation sample) 358 (internal validation sample) 265 (external validation sample)	Derivation vs. internal validation vs. external validation samples Fibrosis (Ishak score ≥3): 100% vs. 100% vs. 48% Cirrhosis (Ishak score 5 or 6): 39% vs. 34% vs. 15%	Lok Index: Ranged from 0.10 to 0.90 Platelet count ≤150,000 INR >1 AST/ALT ratio >1	Yes (for validation sample)	65% ≥ 1.5 cm, 14% >2.5 cm	Derivation vs. internal validation vs. external validation samples Age: 50 vs. 50 vs. 47 years Female: 28% vs. 27% vs. 36% Genotype 1: 90% vs. 87% vs. 74% All patients in derivation and internal validation samples had failed interferon plus ribavirin therapy All Ishak ≥3	4 subjects excluded from derivation and internal validation samples due to biopsies too small; 5 subjects excluded from validation sample for missing INR	Yes
Luo, 2002 ⁸³	AST/ALT ratio Globulin/albumin ratio Platelet count AST/ALT ratio + globulin/albumin ratio AST/ALT ratio + platelet count Globulin/albumin ratio + platelet count	Unclear	Yes (for combined tests)	Taiwan	103	Fibrosis (Scheuer F2-F4): 48% Cirrhosis (Scheuer F4): 21%	AST/ALT ratio ≥1 Globulin/albumin ratio ≥1 Platelet count ≤140,000 AST/ALT ratio ≥1 + globulin/albumin ratio ≥1 AST/ALT ratio ≥1 + platelet count <140,000 Globulin/albumin ratio ≥1 + platelet count ≤140,000	Unclear	All >5 portal tracts	Age: 52 years Female: 31% Genotype 1: Not reported All elevated ALT No alcohol >60 g/day	Not reported (8 excluded for incomplete data)	Yes
Martinez, 2011 ⁸⁴	Forn's Index APRI Simplified ELF index (PIIIP, HA, and TIMP-1, without age) FIB-4	Unclear	Yes (for modified ELF)	Spain	340	Fibrosis (METAVIR F2-F4): 67% Cirrhosis (METAVIR F4): 36%	Forn's Index >4.2 or >6.9 APRI >0.5, >1, >1.5, or >2 Simplified ELF index >-0.45, >0.06, >1.07, or >1.73 FIB-4 >1.45 or >3.25	Yes, except for modified ELF	Mean 15 mm, 72% >15 mm	Age: 48 years Female: 36% Genotype 1: 74%	Not reported	Yes

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive test	Cutoffs predefined	Biopsy Overall Quality	Population characteristics	Proportion unexamined by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
McHutchison, 2000 ⁸⁵	Hyaluronic acid	Prospective	No	USA	486	Fibrosis (Knodell 1-3): 76% Cirrhosis (Knodell 3): 17%	Hyaluronic acid range from >60 to >100 mcg/l	No	≥1 cm and at least 3 portal tracts	Age: Median 41 years Female: 27% Genotype 1: not reported Excluded those with history of alcoholism	486/821 enrollees had adequate liver biopsy	Yes
Metwally, 2007 ⁸⁶	3-item predictive index (platelet count, AST, albumin)	Prospective	No (diagnostic accuracy only reported for validation sample)	USA	137 (validation sample)	Severe fibrosis (METAVIR F3-F4): 23% Cirrhosis (METAVIR F4): Not reported	3-item predictive index: Cutoffs ranged from 1 to 7	No	Not reported	Demographics not reported for validation sample All treatment-naïve	Not reported	Yes
Murawaki, 2001a ⁸⁷	Type-IV collagen Platelet count	Unclear	No	Japan	165	Fibrosis (Desmet F2-F3): 47% Cirrhosis (Desmet F4): 0% (excluded)	Type-IV collagen >110 or >130 ng/ml Platelet count: <140,000 or <160,000	No	Not reported	Age: 53 years Female: 33% Genotype 1: Not reported All had elevated ALT All treatment-naïve	Not reported	Yes
Murawaki, 2001b ⁸⁸	7S fragment of type IV collagen (PIVNP) PIIIP Hyaluronic acid MMP-2 TIMP-1 ALT	Unclear	No	Japan	169	Fibrosis (Desmet F2-F3): 48% Cirrhosis (Desmet F4): 0% (excluded)	PIVNP >6.0 or >6.5 ng/ml PIIIP >0.80 or >0.90 ng/ml Hyaluronic acid >50 or >70 ng/ml MMP-2 >550 or >575 ng/ml TIMP1 >160 or >170 ng/ml ALT >80 IU/l	No	Not reported	Age: 53 years Female: 34% Genotype 1: Not reported All had elevated ALT All treatment-naïve	Not reported	Yes
Myers, 2003 ⁸⁹	Fibrotest 7-item index (Fibrotest items plus PT and platelet count)	Unclear	No	France	323	Fibrosis (METAVIR F2-F4): 41% Cirrhosis (METAVIR F4): 13%	Fibrotest: >0.20 and >0.70 Platelet count: <150,000 Prothrombin time: <80% and 100% Age-platelet Index: >2.0 and >7.0	No	All ≥10 mm	Age: 47 years Female: 42% Genotype 1: Not reported All treatment-naïve	Fibrosis not stage able in 30/422; biochemical markers missing in 24/422	Yes
Myers, 2002 ⁹⁰	Fibrotest Historical index (age at infection and biopsy, sex, and alcohol consumption)	Unclear	Yes (for historical index and revised historical index)	France	211	Fibrosis (METAVIR F2-F4): 40% Cirrhosis (METAVIR F4): 9%	Fibrotest: >0.20 and >0.80 Historical index: >0.20 and >0.60	No	All ≥10 mm	Age: Median 42 years Female: 44% Genotype 1: Not reported All treatment-naïve	Fibrosis not stage able in 30/422; biochemical markers missing in 24/422	Yes

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive test	Cutoffs predefined	Biopsy Overall Quality	Population characteristics	Proportion unexamined by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Obrador, 2006 ⁹¹	Sabadell NIHCED (non-invasive hepatitis C related cirrhosis early detection) index (age ≥60 years, platelet count ≤100, AST/ALT index ≥1, PT ≥1.1, right hepatic lobe atrophy, splenomegaly, caudate lobe hypertrophy)	Unclear	Derivation and validation samples reported separately	Spain	170 (derivation sample)162 (validation sample)	Derivation vs. validation sample Fibrosis: Not reported Cirrhosis (Knodell F4): 28% and 12%	Sabadell NIHCED index ≥22	No for derivation sample, yes for validation sample	Mean 11.6 mm, 12.2 portal tracts	Derivation vs. validation samples Mean age: 52 vs. 45 years Female: 44% vs. 44% Genotype 1: Not reported All elevated liver enzymes	Not reported	Yes
Ohta, 2006 ⁹²	Fibrosis Index (albumin, platelet count)	Retrospective	Derivation and validation samples reported separately	Japan	368 (derivation sample) 249 (validation sample)	Derivation vs. validation sample Fibrosis (Desmet F2-F4): 50% and 63% Cirrhosis (Desmet F4): 8.4% and 9.6%	Fibrosis Index >=2.1 or >=3.3	No for derivation sample, yes for validation sample	Not reported	Reported for derivation sample only Mean age: 44 years Female: 39% Genotype 1: Not reported All elevated liver enzymes	Not reported	Yes
Omran, 2011 ⁹³	Fibro-α (alpha-fetoprotein, AST, ALT, platelet count)	Unclear	Derivation and validation samples reported separately	Egypt	199 (derivation sample) 135 (validation sample)	Derivation vs. validation sample Fibrosis (METAVIR F2-F4): 32%and 42% Severe fibrosis (METAVIR F3-F4): 15% and not reported Cirrhosis (METAVIR F4): 7.5% and not reported	Fibro-a score >1.28, >1.30, or >1.35	No for derivation sample, yes for validation sample	All >=15 mm and/or >5 portal tracts	Derivation vs. validation samples Mean age: 44 years vs. not reported Female: 30% vs. 33% Genotype 1: Not reported	Not reported	Yes for derivation sample for fibrosis, otherwise unable to construct 2 x 2 table or predictive values not reported
Paggi, 2008 ⁹⁴	APRI Liver surface nodularity	Unclear	No	Italy	430	Fibrosis (METAVIR F2-F4): 70% Cirrhosis (METAVIR F4): 37%	APRI >1 or >2 Liver surface nodularity present	Yes	Median 4.1 cm	Age: Median 43 years Female: 45% Genotype 1 or 4: 55% All elevated liver enzymes	Not reported	Predictive values not reported

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive test	Cutoffs predefined	Biopsy Overall Quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Parise, 2006 ⁹⁵	Hyaluronic acid APRI GGT AST/ALT ratio	Prospective	No	Brazil	206	Fibrosis (Batt-Ludwig F2-F4): 42% Cirrhosis (Batt-Ludwig F4): 21%	Hyaluronic acid ≥ 34.2 or ≥ 78.6 APRI ≥ 0.70 or > 1.5 GGT $\geq 1.5 \times \text{ULN}$ or $\geq 2 \times \text{ULN}$ AST/ALT ≥ 0.8 or > 1	No	Not reported	Age: 47 years Female: 44% Genotype 1: 61% Excluded men with > 40 g/day and women with > 20 g/day alcohol	Not reported	Predictive values not reported
Park, 2011 ⁹⁶	APRI Multibiomarker score (alpha-2 macroglobulin, hyaluronic acid)	Prospective	Yes (for multi-biomarker score)	Korea	91	Fibrosis (METAVIR F2-F4): 67%	Only AUROC reported	Only AUROC reported	Not reported	Age: 50 years Female: 42% Genotype 1: 47% Excluded for alcohol ≥ 50 g/day All treatment-naïve	Not reported	Only AUROC reported
Park, 2000 and 2005 ^{97, 98}	AST/ALT ratio	Retrospective	No	Australia	153	Fibrosis: Not reported Cirrhosis (Scheuer F4): 20%	AST/ALT ratio ≥ 1	Yes	Not reported	Age: 47 years Female: 36% Genotype 1: Not reported All treatment-naïve	Not reported	Yes
Parkes, 2011 ⁹⁹	Simplified Enhanced Liver Fibrosis index (ELF) (TIMP-1, hyaluronic acid, PIIIP)	Retrospective and prospective (3 cohorts)	Results for HCV patients only reported for validation sample	UK	347	Fibrosis (METAVIR F2-F4 or Ishak ≥ 3): 51% Cirrhosis (F4 or Ishak 5-6): 14%	Simplified ELF: > 9.13 to > 10.90	No	Not reported	Age: Median 42 to 45 years (3 cohorts) Female: Not reported Genotype 1: Not reported All treatment-naïve	Not stated	Yes
Patel, 2009 ¹⁰⁰	Fibrotest (Fibrosure) FibroSpect II APRI Forn's Index FIB-4	Unclear	No	France, Germany, Canada	95	Fibrosis (METAVIR F2-F4): 95% Cirrhosis: Not reported	Fibrotest ≥ 0.48 FibroSpect II > 0.36 APRI > 0.5 or ≥ 1.5 Forn's Index > 4.21 or > 6.9 FIB-4 > 1.45 or > 3.25	Yes	Mean 18 mm	Age: 46 years Female: 40% Genotype 1: Not reported All treatment-naïve	Not stated	Yes

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive test	Cutoffs predefined	Biopsy Overall Quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Patel, 2004 ¹⁰¹	FibroSpect II (TIMP-1, alpha-2-macroglobulin, hyaluronic acid)	Retrospective	Derivation and validation samples reported separately	USA and France	294 (derivation sample)402 (validation sample)	Fibrosis (METAVIR F2-F4): 0.52 (both samples)Cirrhosis (METAVIR F4): 18% (derivation sample) and 16% (validation sample)	FibroSpect II: >0.36	No for derivation sample, yes for validation sample	Biopsy ≥10 mm and at least 5 portal tracts	Derivation vs. validation samples Age: 45 vs. 46 years Female: 31% vs. 35% Genotype 1: Not reported All alcohol <10 g/day	Not stated	Yes
Plevris, 2000 ¹⁰²	Hyaluronic acid	Prospective	No	UK	69 (hepatitis C subgroup)	Fibrosis: Not reported Cirrhosis (Knodell F4): 22%	Hyaluronic acid >100 to >300 mcg/l	No	Not reported	Age: Not reported Female: Not reported Genotype 1: Not reported All treatment-naïve	Not stated	Predictive values not reported
Pohl, 2001 ¹⁰³	AST/ALT ratio Pohl Index (AST/ALT ratio and platelet count)	Retrospective	Yes	USA	153 (excludes patients with history of alcohol abuse)	Fibrosis (METAVIR F2-F4): 35% Cirrhosis (METAVIR F4): 13%	AST/ALT ratio ≥1 Pohl Index positive (AST/ALT ratio ≥1 and platelet count <150,000)	No (for Pohl Index)	Not reported	Age: 46 years Female: 48% Genotype 1: 49% No history of alcohol abuse	Not stated	Some inconsistency
Poynard, 2003 ¹⁰⁴	Fibrotest	Retrospective	No	Europe, Canada, Argentina, and USA	352	Fibrosis (METAVIR F2-F4): 38% Cirrhosis (METAVIR F4): 8.5%	Fibrotest: No cutoffs reported, only AUROC reported	No	Not reported	Age: 45 years Female: 36% Genotype 2 or 3: 27% All patients had elevated ALT All treatment-naïve	Not stated, 352/1530 randomized patients included	Predictive values not reported
Poynard, 2002 ¹⁰⁵	Fibrotest Hyaluronic acid	Retrospective	No	France	165	F3 fibrosis (Knodell F3): 33% Cirrhosis (Knodell F4): 0%	Fibrotest: No cutoffs reported, only AUROC reported	No	Not reported	Age: 41 years Female: 40% Genotype 1: Not reported All patients had ALT >1.5 x upper limit of normal No chronic alcohol use All treatment-naïve	Not stated, 165/244 randomized patients included	Predictive values not reported

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive test	Cutoffs predefined	Biopsy Overall Quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Pradat, 2002 ¹⁰⁶	ALT	Unclear	No	Europe	864	Fibrosis (METAVIR F2-F4): 71% Cirrhosis (METAVIR F4): 7.5%	ALT > upper limit of normal or > 2.25 upper limit of normal	Yes (for upper limit of normal), no for >2.25 upper limit of normal	Not reported	Age: Not reported Female: Not reported Genotype: Not reported	Not stated	Yes
Reedy, 1998 ¹⁰⁷	AST/ALT ratio	Retrospective	No	USA	71	Fibrosis: Not reported Cirrhosis (Knodell F4): 32%	AST/ALT ratio \geq 1	Yes	Not reported	Age: 44 years Female: 31% Genotype 1: Not reported No history of significant alcohol	Not stated	Yes
Renou, 2001 ¹⁰⁸	Platelet count	Unclear	No	France	104	Fibrosis (METAVIR F2-F4): 45% Cirrhosis (F4): 13%	Platelet count <140,000	No	Not reported	Age: Not reported Female: Not reported Genotype 1: Not reported All had elevated ALT All treatment-naïve	Not stated	Predictive values not reported
Romera, 2006 ¹⁰⁹	Forn's Index APRI Fibrosis Probability Index (Sud or Sydney Index)	Retrospective	No	Spain	131	Fibrosis (Scheuer F2-F4): 47% Cirrhosis (Scheuer F4): 17%	Forn's Index \geq 4.2 APRI \geq 0.5 Fibrosis Probability Index \geq 0.2	Yes	Mean 10 portal tracts	Age: 40 years Female: 40% Genotype 1: 43% All treatment-naïve	Not stated	Sensitivity and specificity not provided, calculated from predictive values
Rosenberg, 2004 ¹¹⁰	European Liver Fibrosis test (age, hyaluronic acid, amino-terminal propeptide of type III collagen, and TIMP-1)	Prospective	No (diagnostic accuracy for HCV subgroup only reported on validation sample)	Europe	Number of HCV patients in validation sample (n=521) not reported	Not reported	ELF cutoffs ranged from >0.063 to >0.564	No	>12 mm and >5 portal tracts	Age: Not reported Female: Not reported Genotype 1: Not reported All abnormal liver function tests for >6 months	Not reported	Unable to construct 2 x 2 table
Rossi, 2003 ¹¹¹	Fibrotest-2 macroglobulin Apolipoprotein A1 Bilirubin GGT Haptoglobin	Unclear	No	Australia	125	Fibrosis (METAVIR F2-F4): 38% Cirrhosis (METAVIR F4): 7.2%	Cutoffs ranged from <0.1 to >0.6	Yes for Fibrotest; unclear for individual tests	Not reported	Age: 40 years Female: 34% Genotype 1: Not reported	Not reported	Yes for Fibrotest (predictive values not reported for individual tests)

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive test	Cutoffs predefined	Biopsy Overall Quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Saadeh, 2001 ¹¹²	Cirrhosis discriminant score	Retrospective	No	USA	111	Fibrosis: Not reported Cirrhosis (Knodell F4): 31%	Cirrhosis discriminant score >3 or >7	No	Not reported	Age: 44 years Female: 25% Genotype 1: Not reported All had elevated ALT	Not reported; results reported for 111/126	Predictive values not reported
Said, 2010 ¹¹³	Fibrotest	Prospective	No	Tunisia	65	Fibrosis (METAVIR F2-F4): 71% Severe fibrosis: (METAVIR F3-F4): 39% Cirrhosis (METAVIR F4): 10%	Fibrotest >0.50, >0.52, or >0.75	No	Mean 17.7 mm, 10.5 portal spaces; 88% >15 mm	Age: 50 years Female: 57% Genotype 1: 92% Antiviral-naïve	Not reported	Yes
Saitou, 2005 ¹¹⁴	Type IV collagen PIIIP Hyaluronic acid YKL-40	Unclear	No	Japan	109	Fibrosis (METAVIR F2-F4): 71% Cirrhosis (METAVIR F4): 28%	Type IV collagen >5.75 or >6.55 ng/ml PIIIP >0.835 or >0.995 U/ml Hyaluronic acid >75.7 or >183.5 ng/ml YKL-40 >186.4 or >284.8 ng/ml	No	Not reported	Age: 54 years Female: 43% Genotype 1: Not reported	Not reported	No
Schneider, 2006 ¹¹⁵	APRI Portal venous flow	Prospective	No	Germany	83	Fibrosis (Ishak 3-6): 57% Cirrhosis (Ishak 5 or 6): 23%	APRI >0.7 or >1.0 Portal venous flow <12.5 cm/s	No	Not reported	Age: 48 years Female: 51% Genotype 1: 84%	Not reported	Predictive values not reported
Schneider, 2005 ¹¹⁶	Portal venous flow Portal venous undulations Hepatic venous flow pattern Longitudinal spleen size Transverse spleen size	Prospective	No	Germany	119	Fibrosis: Not reported Cirrhosis (Ishak 5 or 6): 14%	Portal venous flow: <14.5 cm/s Portal venous undulations: Reduced Hepatic venous flow pattern: Mono- or biphasic Longitudinal spleen size: Not reported Transverse spleen size: >5 cm	No for spleen size and portal venous flow	Not reported	Age: median 45 years Female: 45% Genotype 1: 77%	Not reported	Yes for portal venous undulations, predictive values not reported for other tests

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive test	Cutoffs predefined	Biopsy Overall Quality	Population characteristics	Proportion unexamined by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Sebastiani, 2012 ¹¹⁷	Fibrotest APRI Forn's Index SAFE algorithm Fibropaca algorithm Leroy algorithm	Retrospective	No	Europe	1013	Fibrosis (METAVIR F2-F4): 54% Cirrhosis (METAVIR F4): 11%	Fibrotest >0.49 or >0.75 APRI>0.5, >1.0, >1.5, or >2.0 Forn's Index >4.2 or >6.9 SAFE algorithm positive Fibropaca algorithm positive Leroy algorithm positive	Yes	Mean 20 mm and 11 portal tracts, 45% >20 mm	Age: 48 years Female: 43% Genotype 1: 65% Excluded for alcohol >20 g/day All treatment-naïve	Not reported	Some inconsistency
Sebastiani, 2011 ¹¹⁸	APRI Fibrotest FIB-4 AST/ALT ratio Forn's Index Lok Index	Retrospective	No	Europe	1810	Fibrosis (METAVIR F2-F4): 45% Cirrhosis (METAVIR F4): 9.0%	APRI >0.5, >1.0, >1.5, or >2.0 Fibrotest >0.49 or >0.75 FIB-4: >1.45 or >3.25 AST/ALT ratio >1 Forn's Index >4.2 or >6.9 Lok Index >0.2 or >0.5	Yes	Mean 18 mm and 11 portal tracts, 43% >20 mm	Age: 47 years Female: 44% Genotype 1: Not reported All treatment-naïve	Not reported	No
Sebastiani, 2009 ¹¹⁹	APRI SAFE fibrosis algorithm SAFE cirrhosis algorithm	Retrospective	No	Europe	2035	Fibrosis (METAVIR F2-F4): 46% Cirrhosis (METAVIR F4): 9.4%	APRI >0.5, >1.0, >1.5, or >2.0 SAFE fibrosis algorithm positive SAFE cirrhosis algorithm positive	Yes	Mean 18 mm and mean 10.6 portal tracts	Age: 47 years Female: 44% Genotype 1: 68% All treatment-naïve	Not reported	Yes
Sebastiani, 2008 ¹²⁰	Fibrotest AST/ALT ratio Forn's Index Fibroindex APRI	Unclear	No	Italy	244 (80 normal ALT, 164 elevated ALT)	Fibrosis: (METAVIR F2-F4): 60% Cirrhosis (METAVIR F4): 9.8%	Fibrotest >0.49 AST/ALT ratio >1 Forn's Index >4.2 or >6.9 Fibroindex >1.25 or >2.25 APRI >0.5 or >1.5	Yes	All ≥15 mm and ≥7 portal tracts	Age: 48 years Female: 45% Genotype 1: 57%	Not reported	No
Sebastiani, 2006 ¹²¹	FibrotestAPRI	Unclear	No	Italy	190	Fibrosis (METAVIR F2-F4): 59% Cirrhosis (F4): 15%	Fibrotest: F2 and F4 cutoff APRI >2.0	Yes for APRI, unclear for Fibrotest	All ≥1.5 cm and ≥7 portal tracts	Age: 49 Female: 44% Genotype 1: 63% No alcohol >20 g/day	Not reported	Some inconsistency
Sheth, 1998 ¹²²	AST/ALT ratio	Retrospective	No	USA	139	Fibrosis: Not reported Cirrhosis (Hytioglou F4): 34%	AST/ALT ratio ≥1	Yes	Not reported	Age: 44 years Female: 33% Genotype 1: Not reported All had elevated ALT	Not reported	Yes

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive test	Cutoffs predefined	Biopsy Overall Quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Silva, 2004 ¹²³	GGT	Retrospective	No	Brazil	201	Severe fibrosis (Desmet 3 or 4): 28% Cirrhosis (Desmet 4): 16%	GGT >1x upper limit of normal	Yes	Not reported	Age: 40 years Female: 29% Genotype 1: Not reported No alcohol >20 g/day All treatment-naïve	Not reported	Predictive values not reported
Sirli, 2010 ¹²⁴	APRI Forns' Index Lok Index FIB-4 Platelet count	Retrospective	No	Romania	150	Fibrosis (METAVIR F2-F4): 89% Cirrhosis (METAVIR F4): 10%	APRI >0.52 or >1.38 Forns' Index >4.57 or >5.93 Lok Index >0.17 or >0.26 FIB-4 >2.14 or >2.31 Platelet count <155 or <176	No	All >=20 mm and >=8 portal tracts	Age: 50 years Female: 68% Genotype 1: Not reported Excluded for chronic alcohol abuse	Not reported	Yes
Snyder, 2007 ¹²⁵	APRI FIBROSpect II APRI + FIBROSpect II	Prospective	No	USA	93	Fibrosis (Batts-Ludwig F2-F4): 54%	APRI >0.42 or >=1.20 FIBROSpect II >25, >=55, or >=85	Yes for APRI, unclear for FIBROSpect II	Mean 25 mm	Age: 47 years Female: 30% Genotype 1: 69% Antiviral-naïve Excluded if >15 g alcohol/day	Not reported	Yes for reported predictive values (not all predictive values reported)
Snyder, 2006 ¹²⁶	APRI	Retrospective and prospective	No	USA	339 (retrospective sample)151 (prospective sample)174+176	Fibrosis (Batt-Ludwig F2-F4): 49% (retrospective sample) and 52% (prospective sample) Cirrhosis (Batt-Ludwig F4): 1.8% and 17%	APRI: Cutoffs ranged from ≥0.30 to ≥1.50	No	Not reported	Retrospective vs. prospective samples Age: 44 vs. 48 years Female: 28% vs. 30% Genotype 1: 76% vs. 74% No antiviral treatment within 1 year	60 patients in retrospective sample didn't have screening test labs, 5 patients in prospective sample unable to obtain biopsy sample	Yes
Stibbe, 2011 ¹²⁷	Fibrotest FIB-4	Prospective	No	The Netherlands	41	Fibrosis (METAVIR F2-F4): 54% Severe fibrosis (METAVIR F3-F4): 44% Severe fibrosis (METAVIR F4): 27%	Fibrotest >0.31, >0.58, or >0.75 FIB-4 >1.45 or >3.25	Unclear	All >=20 mm	Age: 47 years Female: 66% Genotype 1: Not reported Excluded for alcohol intake >20 g/day	Not reported	No for Fibrotest

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive test	Cutoffs predefined	Biopsy Overall Quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Sud, 2004 ¹²⁸	Fibrosis probability index	Prospective	Derivation and validation samples reported separately	Australia	170 (derivation sample) 126 (validation sample)	Fibrosis (Scheuer F2-F4): 49% (derivation sample) and 59% (validation sample) Cirrhosis (Scheuer F4): 6% and 13%	Cutoffs ranged from ≥ 0.2 to ≥ 0.8	No for derivation sample, yes for validation sample	Not reported	Data reported for derivation sample only Age: 41 years Female: 35% Genotype 1: Not reported	Not reported	Yes
Testa, 2006 ¹²⁹	Body mass index Platelet-spleen diameter ratio APRI Fibrosis model 1 (BMI, APRI, PLT/SPD)	Unclear	Yes (for fibrosis models)	Italy	75	Fibrosis (Ishak ≥ 3): 49% Cirrhosis (Ishak 5 or 6): 12%	ABT > 8.1 BMI > 25 Platelet-spleen diameter ratio < 1750 APRI > 0.864 Fibrosis model 1 > 1.589	No	All ≥ 15 mm; mean 24 mm	Age: 50 years Female: 32% Genotype 1b: 43% All elevated transaminases No alcohol abuse	5/80 had inadequate sample size on liver biopsy	Predictive values not reported
Trocme, 2006 ¹³⁰	PIIIP/MMP-1 index	Retrospective	No	France	79	Fibrosis (METAVIR F2-F4): 66% Cirrhosis (METAVIR F4): 8.9%	PIIIP/MMP-1 index ≥ 0.20 or > 0.50	Unclear	Not reported	Age: 46 years Female: 43% Genotype 1: 62% All elevated ALT All treatment-naïve	Not stated	Diagnostic accuracy not reported
Vallet-Pichard, 2007 ¹³¹	FIB-4	Retrospective	No	France	847	Fibrosis (METAVIR F2-F4): 36% Cirrhosis (METAVIR F4): 7.2%	FIB-4 ≥ 1.45 or > 3.25	Yes	Not reported	Age: 44 years Female: 46% Genotype 1: Not reported	Not stated	Yes
Verbaan, 1997 ¹³²	Procollagen III propeptide (PIIIP) Type-IV collagen	Retrospective	No	Sweden	98	Fibrosis: Not reported Cirrhosis (Scheuer F4): 11%	PIIIP > 1.11 U/ml Type-IV collagen > 250 ng/ml	No	Not reported	Age: 46 years Female: 34% Genotype 1: Not reported All treatment-naïve	Not stated	Predictive values not reported
Viana, 2009 ⁵⁸	APRI	Prospective	No	Brazil	200 (sample 1) 200 (sample 2)	Fibrosis (METAVIR F2-F4): 60% (sample 1) vs. 63% (sample 2) Cirrhosis (METAVIR F4): 20% vs. not reported	APRI ≥ 0.75 or ≥ 1.05	No	All > 10 portal tracts	Sample 1 vs. sample 2 Age: 51 vs. 50 years Female: 46% vs. 61% Genotype 1b: 54% vs. not reported No alcohol > 40 g/day for men or > 20 g/day for women	Not stated	Yes

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive test	Cutoffs predefined	Biopsy Overall Quality	Population characteristics	Proportion unexamined by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Wai, 2003 ¹³³	Aspartate aminotransferase to platelet ratio index (APRI)	Retrospective	Yes, measures of diagnostic accuracy similar for derivation and validation samples, diagnostic accuracy reported for combined sample	USA	270 (derivation + validation sample)	Fibrosis (Ishak ≥ 3): 48% Cirrhosis (Ishak 5 or 6): 15%	Cutoffs ranged from >0.50 to >2.00	No (derivation sample)	Not reported	Age: 48 years Female: 36% Genotype 1: 74% All treatment-naïve	20 (4 insufficient liver tissue, 16 incomplete data on CBC and/or liver panel)	Yes
Walsh, 2000 ¹³⁴	Type-IV collagen Serum laminin ALT	Unclear	No	UK	37	Advanced liver disease (Ishak score ≥ 3 and HAI ≥ 6): Not reported	Type IV collagen >148 ng/ml Serum laminin >1.26 U/ml ALT cutoff not reported	Unclear	Not reported	Age: Not reported Female: 32% Genotype 1: Not reported Excludes excess alcohol intake	Not stated	Predictive values not reported
Walsh, 1999a ¹³⁵	PIIPALT	Unclear	No	UK	30	Advanced liver disease (Ishak score ≥ 3 and HAI ≥ 6): Not reported	PIIP (Col 1-3 and Col 1 peptide assay) >0.8 U/ml PIIP (Col 1-3 peptide) >4.2 mg/IALT >55 IU/l	Unclear	Not reported	Age: Not reported Female: 36% Genotype 1: Not reported	Not stated	Predictive values not reported
Walsh, 1999b ¹³⁶	TIMP-1 TIMP-2 MMP-2 ALT	Unclear	No	UK	43 (TIMP-1 and ALT) 30 (TIMP-2 and MMP-2)	Advanced liver disease (Ishak score ≥ 3 and HAI ≥ 6): Not reported	TIMP-1 >500 ng/ml TIMP-2 >102 ng/ml MMP-2 >860 ng/ml ALT >60 IU/l	Unclear	Not reported	Age: Not reported Female: 33% Genotype 1: Not reported	4/43 biopsies insufficient tissue	Predictive values not reported
Williams, 1988 ¹³⁷	AST/ALT ratio	Unclear	No	USA	44 (non-A, non-B hepatitis subgroup)	Fibrosis: Not reported Cirrhosis (Hoofnagle criteria): 25%	AST/ALT ratio >1.0	Yes	Not reported	Age: 51 years Female: Not reported Genotype 1: Not reported All elevated aminotransferases All treatment-naïve	Not stated	Predictive values not reported
Wilson, 2006 ¹³⁸	Fibrotest (Fibrosure) APRI ALT AST	Prospective	No	USA	119	Ishak 3-4 fibrosis: 9.2% Cirrhosis (Ishak 5-6): 0% (excluded)	Fibrotest ≥ 0.31 or >0.48 APRI ≥ 0.5 or >1.5 ALT >upper limit of normal AST >upper limit of normal	Unclear	Not reported	Age: 42 years Female: 18% Genotype 1: 97%	Not stated	Yes

Study, Year	Test	Method of data collection	Derivation study	Country	N	Proportion with fibrosis or cirrhosis	Definition of a positive test	Cutoffs predefined	Biopsy Overall Quality	Population characteristics	Proportion unexaminable by screening test or reference standard	Reported predictive values consistent with calculated values based on reported prevalence, sensitivity, and specificity
Wong, 1998 ¹³⁹	Hyaluronic acid ALTα-glutathione-S transferase (GST)	Unclear	No	UK	130	Fibrosis (modified Ishak 3-5 [max 5]): 34% Cirrhosis (modified Ishak 5): 8.5%	Hyaluronic acid: cutoff not reported ALT: cutoff not reported GST: cutoff not reported	Unclear	Not reported	Age: median 37 years Female: 28% Genotype 1: not reported Excludes excess alcohol use All treatment-naïve	Not stated	Predictive values not reported
Yilmaz, 2011 ¹⁴⁰	APRI	Unclear	No	Turkey	108	Not reported	APRI >0.44	No	Not reported	Age: 53 years Female: 75% Genotype 1: Not reported Excluded for alcohol >30 g/day (men) or >20 g/day (women)	Not stated	Predictive values not reported
Zaman, 2007 ¹⁴¹	FibroSpect II	Prospective	No	USA	108	Fibrosis (METAVIR F2-F4): 36% Cirrhosis (METAVIR F4): 2%	FibroSpect II ≥42	Yes	All >15 mm and >5 portal tracts	Age: 44 years Female: 35% Genotype 1: Not reported Alcohol-associated liver disease: 15%	Not stated	Yes
Zarski, 2012 ¹⁴²	FibroTest FibroMeter Forn's Index APRI MP3 ELF Hepascore FIB-4 Hyaluronic acid	Prospective	No	France	436	Fibrosis (METAVIR F2-F4): 46% Cirrhosis (METAVIR F4): 14%	Only AUROC reported	Only AUROC reported	All ≥20 mm or ≥15 mm and ≥11 portal tracts	Age: 51 years Female: 38% Genotype 1: Not reported All treatment-naïve	Not stated	Only AUROC reported

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Adams, 2005 ⁷	<p>Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) Hepascore ≥ 0.5: 0.67 (34/51) and 0.63 (37/59)</p> <p>Advanced fibrosis (METAVIR F3-F4) Hepascore ≥ 0.5: 0.95 (21/22) and 0.88 (21/214)</p> <p>Cirrhosis (METAVIR F4) Hepascore ≥ 0.84: 0.71 (5/7) and 0.71 (12/17)</p>	<p>Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) Hepascore ≥ 0.5: 0.92 (61/66) and 0.89 (40/45)</p> <p>Advanced fibrosis (METAVIR F3-F4) Hepascore ≥ 0.5: 0.81 (77/95) and 0.74 (59/80)</p> <p>Cirrhosis (METAVIR F4) Hepascore ≥ 0.84: 0.84 (92/110) and 0.89 (77/87)</p>	<p>Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) Hepascore ≥ 0.5: 0.87 (34/39) and 0.88 (37/42)</p> <p>Advanced fibrosis (METAVIR F3-F4) Hepascore ≥ 0.5: 0.54 (21/39) and 0.50 (21/42)</p> <p>Cirrhosis (METAVIR F4) Hepascore ≥ 0.84: 0.22 (5/23) and 0.55 (12/22)</p>	<p>Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) Hepascore ≥ 0.5: 0.78 (61/78) and 0.65 (40/62)</p> <p>Advanced fibrosis (METAVIR F3-F4) Hepascore ≥ 0.5: 0.99 (77/78) and 0.95 (59/62)</p> <p>Cirrhosis (METAVIR F4) Hepascore ≥ 0.84: 0.98 (92/94) and 0.94 (77/82)</p>	<p>Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) Hepascore: 0.85 (0.78-0.93) and 0.82 (0.74-0.90) Fibrotest: 0.79 (0.71-0.88) and not reported</p> <p>Advanced fibrosis (METAVIR F3-F4) Hepascore: 0.96 (0.92-1.0) and 0.90 (0.84-0.97) Fibrotest: 0.91 (0.83-0.98) and not reported</p> <p>Cirrhosis (METAVIR F4) Hepascore: 0.94 (0.92-1.0) and 0.89 (0.80-0.98) Fibrotest: 0.97 (0.92-1.0) and not reported</p>	Sir Charles Gairdner Hospital Research Fund	Fair	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Ahmad, 2011 ⁸	<p>Fibrosis (METAVIR F2-F4) Fibrosis-cirrhosis index >0.130: 0.86 (77/89) APRI >0.5: 0.98 (87/89); >1.5: 0.35 (31/89) Fibrosis Index >2.1: 0.58 (52/89) Alkaline phosphatase >120: 0.70 (62/89) Bilirubin >0.95: 0.68 (61/89) Albumin <4.1: 0.67 (60/89) Platelet count <150: 0.70 (62/89)</p> <p>Severe fibrosis (METAVIR F3-F4) FIB-4 >1.45: 0.85 (47/55); >3.25: 0.59 (33/55)</p> <p>Cirrhosis (METAVIR F4) Fibrosis-cirrhosis index >1.25: 0.86 (18/21) AST/ALT ratio >1: 0.43 (9/21) Fibrosis Index >3.3: 0.38 (8/21) Alkaline phosphatase >240: 0.81 (17/21) Bilirubin >1.5: 0.67 (14/21) Albumin <3.85: 0.71 (15/21) Platelet count <100: 0.81 (17/21)</p>	<p>Fibrosis (METAVIR F2-F4) Fibrosis-cirrhosis index >0.130: 0.81 (55/68) APRI >0.5: 0.19 (13/68); >1.5: 0.68 (46/68) Fibrosis Index >2.1: 1.0 (68/68) Alkaline phosphatase >120: 0.85 (58/68) Bilirubin >0.95: 0.85 (58/68) Albumin <4.1: 1.0 (68/68) Platelet count <150: 0.98 (67/68)</p> <p>Severe fibrosis (METAVIR F3-F4) FIB-4 >1.45: 0.51 (52/102); >3.25: 0.82 (84/102)</p> <p>Cirrhosis (METAVIR F4) Fibrosis-cirrhosis index >1.25: 1.0 (136/136) AST/ALT ratio >1: 0.68 (92/136) Fibrosis Index >3.3: 1.0 (136/136) Alkaline phosphatase >240: 0.92 (125/136) Bilirubin >1.5: 0.96 (130/136) Albumin <3.85: 0.93 (126/136) Platelet count <100: 0.98 (134/136)</p>	<p>Fibrosis (METAVIR F2-F4) Fibrosis-cirrhosis index >0.130: 0.86 (77/90) APRI >0.5: 0.61 (87/142); >1.5: 0.58 (31/53) Fibrosis Index >2.1: 1.0 (52/52) Alkaline phosphatase >120: 0.86 (62/72) Bilirubin >0.95: 0.86 (61/71) Albumin <4.1: 1.0 (60/60) Platelet count <150: 0.98 (62/63)</p> <p>Severe fibrosis (METAVIR F3-F4) FIB-4 >1.45: 0.48 (47/97); >3.25: 0.65 (33/51) [0.64*]</p> <p>Cirrhosis (METAVIR F4) Fibrosis-cirrhosis index >1.25: 1.0 (18/18) AST/ALT ratio >1: 0.17 (9/53) Fibrosis Index >3.3: 1.0 (8/8) Alkaline phosphatase >240: 0.61 (17/28) Bilirubin >1.5: 0.70 (14/20) Albumin <3.85: 0.60 (15/25) Platelet count <100: 0.89 (17/19)</p>	<p>Fibrosis (METAVIR F2-F4) Fibrosis-cirrhosis index >0.130: 0.82 (55/67) APRI >0.5: 0.87 (13/15); >1.5: 0.44 (46/104) Fibrosis Index >2.1: 0.65 (68/105) Alkaline phosphatase >120: 0.68 (58/85) Bilirubin >0.95: 0.67 (58/86) Albumin <4.1: 0.70 (68/97) Platelet count <150: 0.71 (67/94)</p> <p>Severe fibrosis (METAVIR F3-F4) FIB-4 >1.45: 0.87 (52/60); >3.25: 0.79 (84/106)</p> <p>Cirrhosis (METAVIR F4) Fibrosis-cirrhosis index >1.25: 0.98 (136/139) AST/ALT ratio >1: 0.88 (92/104) Fibrosis Index >3.3: 0.91 (136/149) Alkaline phosphatase >240: 0.97 (125/129) Bilirubin >1.5: 0.95 (130/137) Albumin <3.85: 0.95 (126/132) Platelet count <100: 0.97 (134/138)</p>	<p>Fibrosis (METAVIR F2-F4) Fibrosis-cirrhosis index: 0.93 (0.90-0.97) APRI: 0.88 (0.78-0.97) for >1.5, 0.72 (0.64-0.80) for <0.5 Fibrosis Index: 0.94 (0.90-0.97) Alkaline phosphatase: 0.83 (0.76-0.90) Bilirubin: 0.73 (0.64-0.82) Albumin: 0.81 (0.74-0.89) Platelet count: 0.94 (0.90-0.97)</p> <p>Severe fibrosis (METAVIR F3-F4) FIB-4: 0.73 (0.66-0.81) for <1.45, 0.54 (0.46-0.64) for >3.25</p> <p>Cirrhosis (METAVIR F4) Fibrosis-cirrhosis index: 1.0 (0.99-1.0) AST/ALT ratio: 0.61 (0.48-0.74) for >1, 0.47 (0.38-0.56) for <1 Fibrosis Index: 0.99 (0.98-1.0) Alkaline phosphatase: 0.93 (0.88-0.98) Bilirubin: 0.89 (0.82-0.96) Albumin: 0.88 (0.80-0.96) Platelet count: 0.99 (0.98-1.0)</p>	Not reported, authors report no conflicts of interest to declare	Fair	Study reports different AUROCs for the same diagnosis/diagnostic test at different cutoffs; higher AUROC abstracted here
Alsatie, 2007 ⁹	Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) 5-item predictive index score ≥ 1 : 0.88 (53/60) and 0.85 (22/26); ≥ 4 : 0.38 (23/60) and 0.56 (9/26)	Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) 5-item predictive index score ≥ 1 : 0.53 (69/130) and 0.49 (33/68); ≥ 4 : 0.98 (128/130) and 0.99 (67/68)	Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) 5-item predictive index score ≥ 1 : 0.46 (53/114) and 0.39 (22/57); ≥ 4 : 0.92 (23/25) and 0.90 (9/10)	Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) 5-item predictive index score ≥ 1 : 0.91 (69/76) and 0.89 (33/37); ≥ 4 : 0.78 (128/165) and 0.80 (67/84)	Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) 5-item predictive index: 0.79 and 0.75 (CI's not reported)	National Institutes of Health K24 Grant	Fair	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Adler, 2008 ¹⁰	Not reported	Not reported	Not reported	Not reported	Fibrosis (METAVIR F2-F4) Fibrotest: 0.79 FIB-4: 0.79 Forns' Index: 0.75 APRI: 0.74 Fibroindex: 0.69 Severe fibrosis (METAVIR F3-F4) Fibrotest: 0.90 FIB-4: 0.90 Forns' Index: 0.90 APRI: 0.89 Fibroindex: 0.87 Cirrhosis (METAVIR F4) Fibrotest: 0.92 FIB-4: 0.92 Forns' Index: 0.89 APRI: 0.92 Fibroindex: 0.92	Not reported	Fair	
Anderson, 2000 ¹¹	Cirrhosis (method unclear) AST/ALT ratio \geq 1: 0.31 (19/61)	Cirrhosis (method unclear) AST/ALT ratio \geq 1: 0.99 (71/72)	Cirrhosis (method unclear) AST/ALT ratio \geq 1: 0.95 (19/20)	Cirrhosis (method unclear) AST/ALT ratio \geq 1: 0.67 (71/113)	Not reported	Not reported	Fair	
Becker, 2009 ¹²	Fibrosis (METAVIR F2-F4) Hepascore \geq 0.55: 0.82 (161/196) Severe fibrosis (METAVIR F3-F4) Hepascore $>$ 0.2: 0.99 (138/139); \geq 0.8: 0.67 (93/139) APRI $>$ 0.5: 0.77 (107/139); $>$ 1.5: 0.27 (38/139) FIB-4 \geq 1.45: 0.73 (101/139); $>$ 3.25: 0.30 (42/139)	Fibrosis (METAVIR F2-F4) Hepascore \geq 0.55: 0.65 (127/195) Severe fibrosis (METAVIR F3-F4) Hepascore $>$ 0.2: 0.23 (58/252); \geq 0.8: 0.77 (194/252) APRI $>$ 0.5: 0.60 (152/252); $>$ 1.5: 0.97 (245/252) FIB-4 \geq 1.45: 0.67 (169/252); $>$ 3.25: 0.98 (248/252)	Fibrosis (METAVIR F2-F4) Hepascore \geq 0.55: 0.70 (161/229) Severe fibrosis (METAVIR F3-F4) Hepascore $>$ 0.2: 0.42 (138/332); \geq 0.8: 0.62 (93/151) APRI $>$ 0.5: 0.52 (107/207); $>$ 1.5: 0.84 (38/45) FIB-4 \geq 1.45: 0.55 (101/184); $>$ 3.25: 0.91 (42/46)	Fibrosis (METAVIR F2-F4) Hepascore \geq 0.55: 0.78 (127/162) Severe fibrosis (METAVIR F3-F4) Hepascore $>$ 0.2: 0.98 (58/59); \geq 0.8: 0.81 (194/240) APRI $>$ 0.5: 0.83 (152/184); $>$ 1.5: 0.71 (245/346) FIB-4 \geq 1.45: 0.82 (169/207); $>$ 3.25: 0.72 (248/345)	Fibrosis (METAVIR F2-F4) Hepascore: 0.81 (CI not reported) Severe fibrosis (METAVIR F3-F4) Hepascore: 0.83 (CI not reported) APRI: Not reported FIB-4: Not reported Cirrhosis (METAVIR F4) Hepascore: 0.88 (CI not reported)	Quest Diagnostics	Fair	AUROC for Hepascore and fibrosis similar when biopsies $<$ 10 mm included (0.81) and excluded (0.82). Excluding patients with single hepascore component elevation resulted in better diagnostic accuracy. PPV for fibrosis increased from 0.62 for hepascore \geq 0.8 alone to 0.91 with hepascore \geq 0.8 followed by FIB $>$ 3.25 and to 0.82 for hepascore \geq 0.8 followed by APRI $>$ 1.5
Bejarano, 2009 ¹³	Severe fibrosis (Knodell 3-4) Sabadell NIHCED index $>$ 6: 0.72 (137/190)	Severe fibrosis (Knodell 3-4) Sabadell NIHCED index $>$ 6: 0.75 (98/131)	Severe fibrosis (Knodell 3-4) Sabadell NIHCED index $>$ 6: 0.81 (137/170)	Severe fibrosis (Knodell 3-4) Sabadell NIHCED index $>$ 6: 0.64 (98/151)	Severe fibrosis (Knodell 3-4) Sabadell NIHCED index: 0.79 (0.74-0.84)	Corporacio Parc Tauli, Instituto de Salud Carlos III	Fair	Same population as Obrador, 2006

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Berg, 2004 ¹⁴³	Fibrosis (Scheuer F2-F4) APRI >0.50: 0.82 (207/253) APRI >1.50: 0.37 (93/253) Cirrhosis (Scheuer F4) APRI >1.0: 0.76 (47/62) APRI >2.0: 0.48 (30/62)	Fibrosis (Scheuer F2-F4) APRI >0.50: 0.53 (122/231) APRI >1.50: 0.93 (215/231) Cirrhosis (Scheuer F4) APRI >1.0: 0.74 (310/422) APRI >2.0: 0.89 (377/422)	Fibrosis (Scheuer F2-F4) APRI >0.50: 0.66 (207/316) APRI >1.50: 0.85 (93/109) Cirrhosis (Scheuer F4) APRI >1.0: 0.30 (47/159) APRI >2.0: 0.40 (30/75)	Fibrosis (Scheuer F2-F4) APRI >0.50: 0.73 (122/168) APRI >1.50: 0.57 (215/375) Cirrhosis (Scheuer F4) APRI >1.0: 0.95 (310/325) APRI >2.0: 0.92 (377/409)	Not reported	German BMBF Network of Competence for Viral Hepatitis (Hep Net)	Fair	
Ben Jazia, 2009 ¹⁵	Fibrosis (METAVIR F2-F4) APRI >0.72: 0.93 (25/27) AST/ALT ratio: Not reported Platelet count: Not reported	Fibrosis (METAVIR F2-F4) APRI >0.72: 0.58 (5/8) AST/ALT ratio: Not reported Platelet count: Not reported	Fibrosis (METAVIR F2-F4) APRI >0.72: 0.83 (25/28) [0.87*] AST/ALT ratio: Not reported Platelet count: Not reported	Fibrosis (METAVIR F2-F4) APRI >0.72: 0.71 (5/7) [0.60*] AST/ALT ratio: Not reported Platelet count: Not reported	Fibrosis (METAVIR F2-F4) APRI: 0.91 (CI not reported) AST/ALT ratio: 0.68 (CI not reported) Platelet count: 0.38 (CI not reported)	Not stated	Fair	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Boeker, 2002 ¹⁶	Fibrosis (Ishak, grades not reported) TIMP-1 (Biotrak) >950 mcg/l: 0.52 (14/27) TIMP-1 (Quantikine) >85 mcg/l: 0.67 (18/27) MMP-2 (Biotrak) >1500 mcg/l: 0.07 (2/27) MMP-2 (Quantikine) >320 mcg/l: 0.07 (2/27) Hyaluronic acid >30 mcg/l: 0.48 (13/27)AST >18 U/l: 0.78 (21/27)ALT >22 U/l: 0.96 (26/27) Alkaline phosphatase >190 U/l: 0.22 (6/27) GGT >28 U/l: 0.67 (18/27) [0.65*] Albumin <37 g/l: 0.26 (7/27) [0.27*] Cirrhosis (Ishak, grades not reported) TIMP-1 (Biotrak) >950 mcg/l: 1.0 (19/19) TIMP-1 (Quantikine) >85 mcg/l: 1.0 (19/19) MMP-2 (Biotrak) >1500 mcg/l: 0.74 (14/19) MMP-2 (Quantikine) >320 mcg/l: 0.84 (16/19) [0.84*] Hyaluronic acid >30 mcg/l: 0.89 (17/19) [0.90*]AST >18 U/l: 0.79 (15/19) [0.81*] ALT >22 U/l: 0.89 (17/19) [0.88*] Alkaline phosphatase >190 U/l: 0.47 (9/19)GGT >28 U/l: 0.74 (14/19) [0.73*] Albumin <37 g/l: 0.74 (14/19) [0.73*]	Fibrosis (Ishak, grades not reported) TIMP-1 (Biotrak) >950 mcg/l: 0.88 (28/32) TIMP-1 (Quantikine) >85 mcg/l: 0.69 (22/32) [0.68*] MMP-2 (Biotrak) >1500 mcg/l: 1.0 (32/32) MMP-2 (Quantikine) >320 mcg/l: 0.97 (31/32) Hyaluronic acid >30 mcg/l: 0.84 (27/32)AST >18 U/l: 0.41 (13/32) [0.40*] ALT >22 U/l: 0.16 (5/32) Alkaline phosphatase >190 U/l: 0.84 (27/32) GGT >28 U/l: 0.53 (17/32) Albumin <37 g/l: 0.91 (29/32) [0.90*] Cirrhosis (Ishak, grades not reported) TIMP-1 (Biotrak) >950 mcg/l: 0.75 (44/59) TIMP-1 (Quantikine) >85 mcg/l: 0.56 (33/59) MMP-2 (Biotrak) >1500 mcg/l: 1.0 (59/59)MMP-2 (Quantikine) >320 mcg/l: 0.97 (57/59) [0.96*] Hyaluronic acid >30 mcg/l: 0.73 (43/59) AST >18 U/l: 0.59 (35/59) [0.60*] ALT >22 U/l: 0.10 (6/59) [0.11*] Alkaline phosphatase >190 U/l: 0.85 (50/59) [0.85*] GGT >28 U/l: 0.47 (28/59) Albumin <37 g/l: 0.86 (51/59)	Fibrosis (Ishak, grades not reported) TIMP-1 (Biotrak) >950 mcg/l: 0.78 (14/18) TIMP-1 (Quantikine) >85 mcg/l: 0.64 (18/28) MMP-2 (Biotrak) >1500 mcg/l: 1.0 (2/2) MMP-2 (Quantikine) >320 mcg/l: 0.67 (2/3) Hyaluronic acid >30 mcg/l: 0.72 (13/18)AST >18 U/l: 0.52 (21/40) ALT >22 U/l: 0.49 (26/53) Alkaline phosphatase >190 U/l: 0.55 (6/11) GGT >28 U/l: 0.55 (18/33) Albumin <37 g/l: 0.70 (7/10) Cirrhosis (Ishak, grades not reported) TIMP-1 (Biotrak) >950 mcg/l: 0.56 (19/34) TIMP-1 (Quantikine) >85 mcg/l: 0.42 (19/45) MMP-2 (Biotrak) >1500 mcg/l: 1.0 (14/14) MMP-2 (Quantikine) >320 mcg/l: 0.89 (16/18) Hyaluronic acid >30 mcg/l: 0.52 (17/33) AST >18 U/l: 0.38 (15/39) ALT >22 U/l: 0.24 (17/70) Alkaline phosphatase >190 U/l: 0.50 (9/18) GGT >28 U/l: 0.31 (14/45) Albumin <37 g/l: 0.64 (14/22)	Fibrosis (Ishak, grades not reported) TIMP-1 (Biotrak) >950 mcg/l: 0.68 (28/41) TIMP-1 (Quantikine) >85 mcg/l: 0.71 (22/31) MMP-2 (Biotrak) >1500 mcg/l: 0.56 (32/57) MMP-2 (Quantikine) >320 mcg/l: 0.55 (31/56) Hyaluronic acid >30 mcg/l: 0.66 (27/41) AST >18 U/l: 0.68 (13/19) ALT >22 U/l: 0.83 (5/6) Alkaline phosphatase >190 U/l: 0.56 (27/48) GGT >28 U/l: 0.65 (17/26) Albumin <37 g/l: 0.59 (29/49) Cirrhosis (Ishak, grades not reported) TIMP-1 (Biotrak) >950 mcg/l: 1.0 (44/44) TIMP-1 (Quantikine) >85 mcg/l: 1.0 (33/33) MMP-2 (Biotrak) >1500 mcg/l: 0.92 (59/64) MMP-2 (Quantikine) >320 mcg/l: 0.95 (57/60) Hyaluronic acid >30 mcg/l: 0.96 (43/45) AST >18 U/l: 0.90 (35/39) ALT >22 U/l: 0.75 (6/8) Alkaline phosphatase >190 U/l: 0.83 (50/60) GGT >28 U/l: 0.85 (28/33) Albumin <37 g/l: 0.91 (51/56)	Not reported	Gessellschaft der Freunde der MHH	Poor	Excluded patients with cirrhosis from fibrosis analyses; appeared to use case-control design for cirrhosis analysis
Bonacini, 1997 ¹⁷	(Knodell F3-F4) Cirrhosis discriminant score ≥ 7 : 0.86 (24/28); ≥ 8 : 0.46 (13/28) AST/ALT ratio >1: 0.83 (23/28)	(Knodell F3-F4) Cirrhosis discriminant score ≥ 7 : 0.84 (43/51); ≥ 8 : 0.98 (50/51) AST/ALT ratio >1: 0.75 (38/51)	(Knodell F3-F4) Cirrhosis discriminant score ≥ 7 : 0.75 (24/32); ≥ 8 : 0.93 (13/14) AST/ALT ratio >1: 0.64 (23/36)	(Knodell F3-F4) Cirrhosis discriminant score ≥ 7 : 0.91 (43/47); ≥ 8 : 0.77 (50/65) AST/ALT ratio >1: 0.88 (38/43)	Not reported	Not stated	Fair	Study reports 77 enrolled but diagnostic results presented for 79; 22% HIV-positive

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Borroni, 2006 ¹⁸	<p>Cirrhosis (Knodell F4) AST/ALT ratio ≥ 1: 0.30 (9/30) Cirrhosis Discriminant Score >2: 1.0 (30/30); >7: 0.17 (5/30) APRI >1: 0.77 (23/30); ≥ 2: 0.43 (13/30) Pohl's Index positive: 0.27 (8/30) Age-platelet index ≥ 6: 0.67 (20/30) Combination A (APRI and age-platelet index) (cutoff not reported): 0.37 (11/30) Combination B (APRI and age-platelet index) (cutoff not reported): 0.73 (22/30)</p>	<p>Cirrhosis (Knodell F4) AST/ALT ratio ≥ 1: 0.97 (192/198) Cirrhosis Discriminant Score >2: 0.22 (43/198); >7: 1.0 (198/198) APRI >1: 0.83 (164/198); ≥ 2: 0.94 (186/198) Pohl's Index positive: 0.99 (196/198) Age-platelet index ≥ 6: 0.87 (172/198) Combination A (APRI and age-platelet index) (cutoff not reported): 0.98 (194/198) Combination B (APRI and age-platelet index) (cutoff not reported): 0.83 (164/198)</p>	<p>Cirrhosis (Knodell F4) AST/ALT ratio ≥ 1: 0.60 (9/15) [0.57*] Cirrhosis Discriminant Score >2: 0.16 (30/185); >7: 1.0 (5/5) APRI >1: 0.40 (23/57); ≥ 2: 0.52 (13/25) [0.54*] Pohl's Index positive: 0.80 (8/10) Age-platelet index ≥ 6: 0.43 (20/46) [0.46*] Combination A (APRI and age-platelet index) (cutoff not reported): 0.73 (11/15) [0.79*] Combination B (APRI and age-platelet index) (cutoff not reported): 0.39 (22/56)</p>	<p>Cirrhosis (Knodell F4) AST/ALT ratio ≥ 1: 0.90 (192/213) Cirrhosis Discriminant Score >2: 1.0 (43/43); >7: 0.89 (198/223) APRI >1: 0.96 (164/171); ≥ 2: 0.92 (186/203) Pohl's Index positive: 0.90 (196/218) Age-platelet index ≥ 6: 0.95 (172/182) Combination A (APRI and age-platelet index) (cutoff not reported): 0.91 (194/213) Combination B (APRI and age-platelet index) (cutoff not reported): 0.95 (164/172)</p>	<p>Cirrhosis (Knodell F4) AST/ALT ratio: 0.76 (0.68-0.84) Cirrhosis Discriminant Score : 0.83 (0.75-0.92) APRI: 0.86 (0.79-0.93) Pohl's Index: Not reported Age-platelet index: 0.88 (0.82-0.94) Combinations A and B (APRI and age-platelet index): Not reported</p>	No external funding	Fair	
Bota, 2011 ¹⁹	Not reported	Not reported	Not reported	Not reported	<p>Fibrosis (METAVIR F2-F4) King's score: 0.76 Forns' Index: 0.74 APRI: 0.69</p> <p>Severe fibrosis (METAVIR F3-F4) King's score: 0.82 Forns' Index: 0.80 APRI: 0.82</p> <p>Cirrhosis (METAVIR F4) King's score: 0.89 Forns' Index: 0.85 APRI: 0.88</p>	No funding	Fair	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Bourliere, 2008 ²⁰	Cutoffs unclear except as noted Fibrosis (METAVIR F2-F4) Hepascore: 0.55 (134/231); ≥0.5: 0.63 (146/231) Fibrotest: 0.62 (143/231) Severe fibrosis (METAVIR F3-F4) Hepascore: 0.69 (90/130) Fibrotest: 0.69 (90/130) Cirrhosis (METAVIR F4) Hepascore: 0.86 (30/35); ≥0.84: 0.71 (25/35) Fibrotest: 0.91 (32/35)	Cutoffs unclear except as noted Fibrosis (METAVIR F2-F4) Hepascore: 0.86 (203/236); ≥0.5: 0.86 (203/236) Fibrotest: 0.86 (203/236) Severe fibrosis (METAVIR F3-F4) Hepascore: 0.87 (293/337) Fibrotest: 0.86 (290/337) Cirrhosis (METAVIR F4) Hepascore: 0.83 (359/432); ≥0.84: 0.88 (380/432) Fibrotest: 0.75 (324/432)	Cutoffs unclear except as noted Fibrosis (METAVIR F2-F4) Hepascore: 0.80 (134/167) [0.82*]; ≥0.5: 0.82 (146/179) Fibrotest: 0.81 (143/176) Severe fibrosis (METAVIR F3-F4) Hepascore: 0.67 (90/134) Fibrotest: 0.66 (90/137) [0.65*] Cirrhosis (METAVIR F4) Hepascore: 0.29 (30/103); ≥0.84: 0.32 (25/77) [0.33*] Fibrotest: 0.23 (32/140)	Cutoffs unclear except as noted Fibrosis (METAVIR F2-F4) Hepascore: 0.68 (203/300) [0.69*]; ≥0.5: 0.70 (203/288) Fibrotest: 0.70 (203/291) [0.67*] Severe fibrosis (METAVIR F3-F4) Hepascore: 0.88 (293/333) Fibrotest: 0.88 (290/330) Cirrhosis (METAVIR F4) Hepascore: 0.99 (359/364); ≥0.84: 0.97 (380/390) Fibrotest: 0.99 (324/327)	Fibrosis (METAVIR F2-F4) Hepascore: 0.82 (0.79-0.86) Fibrotest: 0.83 (0.79-0.86) Severe fibrosis (METAVIR F3-F4) Hepascore: 0.84 (0.80-0.87) Fibrotest: 0.84 (0.80-0.87) Cirrhosis (METAVIR F4) Hepascore: 0.90 (0.87-0.93) Fibrotest: 0.89 (0.86-0.93)	Reports no financial support or competing interests	Fair	Population overlaps with Halfon 2006 and Halfon 2007 and Bourliere 2006. Diagnostic accuracy of Hepascore at defined cutoffs doesn't match tables comparing Hepascore and Fibrotest (with undefined cutoffs). Study evaluated a number of algorithms but didn't report diagnostic accuracy of them.
Bourliere, 2006 ²¹	Fibrosis (METAVIR F2-F4) Fibrotest >0.1: 0.97 (96/99); ≥0.6: 0.55 (54/99) APRI >0.5: 0.70 (69/99); ≥1.5: 0.22 (22/99) Forn's Index ≥4.21: 0.90 (79/99); >6.9: 0.30 (30/99) Cirrhosis (METAVIR F4) APRI >1.0: 0.69 (11/16); >2: 0.38 (6/16)	Fibrosis (METAVIR F2-F4) Fibrotest >0.1: 0.20 (27/136); ≥0.6: 0.90 (122/136) APRI >0.5: 0.55 (75/136); ≥1.5: 0.95 (129/136) Forn's Index ≥4.21: 0.54 (73/136); >6.9: 0.96 (130/136) Cirrhosis (METAVIR F4) APRI >1.0: 0.82 (180/219); >2: 0.96 (210/219)	Fibrosis (METAVIR F2-F4) Fibrotest >0.1: 0.45 (96/215) [0.47*]; ≥0.6: 0.79 (54/68) APRI >0.5: 0.53 (69/130); ≥1.5: 0.76 (22/29) Forn's Index ≥4.21: 0.56 (79/142); >6.9: 0.83 (30/36) Cirrhosis (METAVIR F4) APRI >1.0: 0.22 (11/50); >2: 0.40 (6/15)	Fibrosis (METAVIR F2-F4) Fibrotest >0.1: 0.590(27/30); ≥0.6: 0.73 (122/167) APRI >0.5: 0.71 (75/105); ≥1.5: 0.63 (129/206) Forn's Index ≥4.21: 0.78 (73/93) [0.79*]; >6.9: 0.65 (130/199) Cirrhosis (METAVIR F4) APRI >1.0: 0.97 (180/185); >2: 0.95 (210/220) [0.96*]	Fibrosis (METAVIR F2-F4) Fibrotest: 0.81 (0.76-0.86) APRI: 0.71 (0.67-0.79) Forn's Index: 0.76 (0.70-0.82) Cirrhosis (METAVIR F4) APRI: 0.81 (0.76-0.86)	Not stated	Fair	Population (Fibropaca) overlaps with Halfon 2006 and Halfon 2007 and Bourliere 2008. Study evaluated an algorithm but didn't report diagnostic accuracy.
Boursier, 2012 ²²	Fibrosis (METAVIR F2-F4) SAFE algorithm: 1.0 (976/976) Cirrhosis (METAVIR F4) SAFE algorithm: 0.62 (140/227)	Fibrosis (METAVIR F2-F4) SAFE algorithm: 0.88 (714/809) Cirrhosis (METAVIR F4) SAFE algorithm: 0.93 (1455/1558)	Fibrosis (METAVIR F2-F4) SAFE algorithm: 0.91 (976/1071) Cirrhosis (METAVIR F4) SAFE algorithm: 0.58 (140/243) [0.56*]	Fibrosis (METAVIR F2-F4) SAFE algorithm: 1.0 (714/714) Cirrhosis (METAVIR F4) SAFE algorithm: 0.94 (1455/1542) [0.95*]	Not reported	French Department of Health	Fair	Same or overlapping populations as Boursier, 2009 and 2011, Cales, 2008 and 2011, Zarski 2012
Boursier, 2011 ²³	Not reported	Not reported	Not reported	Not reported	Fibrosis (derivation and validation samples, respectively) FibroMeter: 0.81 (0.78-0.83) and 0.84 (0.82-0.86)	French National Agency for Research on AIDS and Viral Hepatitis	Fair	FIBROSTAR study database

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Boursier, 2009 ²⁴	Severe Fibrosis (METAVIR F3-F4) Fibrometer >0.628: 0.84 (221/264); >0.830: 0.60 (158/264) Fibrotest >0.448: 0.84 (223/264); >0.631: 0.67 (176/264) Hepascore >0.497: 0.82 (217/264); >0.904: 0.48 (127/264) APRI >0.581: 0.78 (205/264); >1.159: 0.51 (134/264) Cirrhosis (METAVIR F4) Fibrometer >0.628: 0.96 (111/116); >0.979: 0.36 (41/116) Fibrotest >0.660: 0.82 (96/116); >0.862: 0.42 (49/116) Hepascore >0.801: 0.80 (93/116); >0.999: 0.38 (45/116) APRI >0.652: 0.85 (98/116); >2.532: 0.27 (32/116) Modified Fibrometer >0.089: 0.87 (101/116); >0.442: 0.55 (64/116)	Severe Fibrosis (METAVIR F3-F4) Fibrometer >0.628: 0.79 (629/792); >0.830: 0.91 (722/792) Fibrotest >0.448: 0.71 (563/792); >0.631: 0.84 (664/792) Hepascore >0.497: 0.71 (560/792); >0.904: 0.93 (737/792) APRI >0.581: 0.75 (591/792); >1.159: 0.92 (726/792) Cirrhosis (METAVIR F4) Fibrometer >0.628: 0.71 (668/940); >0.979: 0.98 (921/940) Fibrotest >0.660: 0.77 (726/940); >0.862: 0.96 (898/940) Hepascore >0.801: 0.82 (776/940); >0.999: 0.98 (926/940) APRI >0.652: 0.72 (672/940); >2.532: 0.98 (918/940) Modified Fibrometer >0.089: 0.81 (761/940); >0.442: 0.98 (920/940)	Severe Fibrosis (METAVIR F3-F4) Fibrometer >0.628: 0.58 (221/384); >0.830: 0.69 (158/228) [0.70*] Fibrotest >0.448: 0.49 (223/452); >0.631: 0.58 (176/304) [0.57*] Hepascore >0.497: 0.48 (217/449); >0.904: 0.70 (127/182) APRI >0.581: 0.50 (205/406); >1.159: 0.67 (134/200) Cirrhosis (METAVIR F4) Fibrometer >0.628: 0.29 (111/383) [0.30*]; >0.979: 0.68 (41/60) [0.70*] Fibrotest >0.660: 0.31 (96/310) [0.29*]; >0.862: 0.54 (49/91) [0.52*] Hepascore >0.801: 0.36 (93/257) [0.37*]; >0.999: 0.76 (45/59) APRI >0.652: 0.27 (98/366); >2.532: 0.59 (32/54) [0.62*] Modified Fibrometer >0.089: 0.36 (101/280) [0.37*]; >0.442: 0.76 (64/84) [0.77*]	Severe Fibrosis (METAVIR F3-F4) Fibrometer >0.628: 0.94 (629/672 [0.93*]); >0.830: 0.87 (722/828) Fibrotest >0.448: 0.93 (563/604) [0.94*]; >0.631: 0.88 (664/752) [0.89*] Hepascore >0.497: 0.92 (560/607); >0.904: 0.84 (737/874) APRI >0.581: 0.91 (591/650); >1.159: 0.85 (726/856) Cirrhosis (METAVIR F4) Fibrometer >0.628: 0.99 (668/673); >0.979: 0.92 (921/996) Fibrotest >0.660: 0.97 (726/746) [0.98*]; >0.862: 0.93 (898/965) [0.94*] Hepascore >0.801: 0.97 (776/799); >0.999: 0.93 (926/997) APRI >0.652: 0.97 (672/690); >2.532: 0.92 (918/1002) Modified Fibrometer >0.089: 0.98 (761/776); >0.442: 0.95 (920/972) [0.94*]	Severe Fibrosis (METAVIR F3-F4) Fibrometer: 0.88 (0.86-0.91) Fibrotest: 0.84 (0.81-0.86) Hepascore: 0.83 (0.81-0.86)APRI: 0.82 (0.79-0.85) Cirrhosis (METAVIR F4) Fibrometer: 0.91 (0.88-0.93) Fibrotest: 0.88 (0.86-0.91) Hepascore: 0.90 (0.87-0.92)APRI: 0.84 (0.80-0.88) Modified Fibrometer: 0.92 (CI not reported)	French Department of Health	Fair	Same population as Cales, 2008 (which included Cales 2005 (excluded b/c it evaluated patients with HBV and HCV infection), Halfon 2007, and Leroy 2007)
Burton, 2011 ²⁵	Whole sample, black subjects, and white subjects, respectively Fibrosis (Batt-Ludwig 2-4)APRI >0.60: 0.70 (92/131), 0.65 (38/58), 0.75 (52/69) Severe fibrosis (Batt-Ludwig 3-4) APRI >0.99: 0.65 (47/72), 0.62 (18/29), 0.70 (29/41) Cirrhosis (Batt-Ludwig 4)APRI >1.0: 0.74 (33/44), 0.60 (9/15), 0.85 (24/28)	Whole sample, black subjects, and white subjects, respectively Fibrosis (Batt-Ludwig 2-4)APRI >0.60: 0.72 (99/137), 0.75 (63/84), 0.68 (33/48) Severe fibrosis (Batt-Ludwig 3-4) APRI >0.99: 0.82 (161/196), 0.86 (97/113), 0.75 (57/76) Cirrhosis (Batt-Ludwig 4)APRI >1.0: 0.78 (175/224), 0.81 (103/127), 0.73 (65/89)	Whole sample, black subjects, and white subjects, respectively Fibrosis (Batt-Ludwig 2-4)APRI >0.60: 0.71 (92/130) [0.72*], 0.67 (38/57) [0.68*], 0.78 (52/67) Severe fibrosis (Batt-Ludwig 3-4) APRI >0.99: 0.57 (47/82), 0.53 (18/34) [0.55*], 0.60 (29/48) [0.61*] Cirrhosis (Batt-Ludwig 4)APRI >1.0: 0.40 (33/82), 0.27 (9/33), 0.50 (24/48)	Whole sample, black subjects, and white subjects, respectively Fibrosis (Batt-Ludwig 2-4)APRI >0.60: 0.72 (99/138) [0.73*], 0.76 (63/83 [0.77*], 0.66 (33/50) Severe fibrosis (Batt-Ludwig 3-4) APRI >0.99: 0.87 (161/186), 0.90 (97/108), 0.83 (57/69) Cirrhosis (Batt-Ludwig 4)APRI >1.0: 0.94 (175/186), 0.94 (103/109) [0.95*], 0.94 (65/69)	Black and white samples, respectively (not reported for whole sample)Fibrosis (Batt-Ludwig 2-4)APRI: 0.70 (0.60-0.80) and 0.76 (0.66-0.76) Severe fibrosis (Batt-Ludwig 3-4)APRI: 0.77 (0.65-0.89) and 0.76 (0.66-0.86) Cirrhosis (Batt-Ludwig 4)APRI: 0.75 (0.59-0.91) and 0.82 (0.74-0.90)	South Central VA Healthcare Network	Fair	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Cales, 2010 ²⁶	Fibrosis (METAVIR F2-F4), derivation sample only FibroMeter >0.419: 0.80 (439/549) FibroMeter 3G >0.440: 0.81 (446/549)	Fibrosis (METAVIR F2-F4), derivation sample only FibroMeter >0.419: 0.76 (385/507) FibroMeter 3G >0.440: 0.74 (376/507)	Fibrosis (METAVIR F2-F4), derivation sample only FibroMeter >0.419: 0.78 (439/561) FibroMeter 3G >0.440: 0.77 (446/577) [0.78*]	Fibrosis (METAVIR F2-F4), derivation sample only FibroMeter >0.419: 0.78 (385/495) FibroMeter 3G >0.440: 0.78 (376/479)	Fibrosis (METAVIR F2-F4), derivation and validation samples FibroMeter: 0.85 (0.83-0.88) and 0.82 (CI not reported) FibroMeter 3G: 0.84 (0.83-0.87) and 0.81 (CI not reported) FibroTest: 0.81 (0.78-0.84) Hepascore: 0.79 (0.76-0.82) Cirrhosis (METAVIR F4), derivation sample only FibroMeter: 0.91 (0.88-0.93) FibroMeter optimized for cirrhosis: 0.92 (0.89-0.94) FibroMeter 3G: 0.89 (0.87-0.92) FibroMeter 3G optimized for cirrhosis: 0.91 (0.88-0.94) FibroTest: 0.88 (0.86-0.91) Hepascore: 0.89 (0.86-0.92)	French Department of Health	Fair	Same population as Cales 2008 and overlaps with Zarski 2012 and Boursier 2009
Cales, 2008 ¹⁴⁴	Fibrosis (METAVIR F2-F4) FibroMeter >0.419: 0.80 (439/549) Fibrotest >0.435: 0.68 (372/549) Hepascore >0.46: 0.66 (363/549) APRI >0.55: 0.62 (343/549) FIB-4 >1.116: 0.74 (406/549)	Fibrosis (METAVIR F2-F4) FibroMeter >0.419: 0.76 (385/507) Fibrotest >0.435: 0.82 (415/507) Hepascore >0.46: 0.79 (401/507) APRI >0.55: 0.84 (423/507) FIB-4 >1.116: 0.72 (365/507)	Fibrosis (METAVIR F2-F4) FibroMeter >0.419: 0.78 (439/561) Fibrotest >0.435: 0.80 (372/464) Hepascore >0.46: 0.77 (363/469) [0.78*] APRI >0.55: 0.80 (343/427) FIB-4 >1.116: 0.74 (406/548)	Fibrosis (METAVIR F2-F4) FibroMeter >0.419: 0.78 (385/495) Fibrotest >0.435: 0.70 (415/592) Hepascore >0.46: 0.68 (401/587) APRI >0.55: 0.67 (423/629) FIB-4 >1.116: 0.72 (365/508)	Fibrosis (METAVIR F2-F4) FibroMeter: 0.85 (0.83-0.88) Fibrotest: 0.81 (0.78-0.84) Hepascore: 0.78 (0.76-0.82) APRI: 0.79 (0.76-0.82) FIB-4: 0.80 (0.78-0.84)	French Department of Health	Fair	Same population as Boursier, 2009 (which included Cales 2005 (excluded b/c it evaluated patients with HBV and HCV infection), Halfon 2007, and Leroy 2007)
Castera, 2010 ²⁸	Fibrosis (METAVIR F2-F4) SAFE algorithm: 1.0 (230/230) Cirrhosis (METAVIR F4) SAFE algorithm: 0.86 (64/74)	Fibrosis (METAVIR F2-F4) SAFE algorithm: 0.87 (63/72) Cirrhosis (METAVIR F4) SAFE algorithm: 0.90 (205/228)	Fibrosis (METAVIR F2-F4) SAFE algorithm: 0.96 (230/239) Cirrhosis (METAVIR F4) SAFE algorithm: 0.74 (64/87) [0.78*]	Fibrosis (METAVIR F2-F4) SAFE algorithm: 1.0 (63/63) Cirrhosis (METAVIR F4) SAFE algorithm: 0.95 (205/215) [0.94*]	Fibrosis (METAVIR F2-F4) SAFE algorithm: 0.94 (0.90-0.98) Cirrhosis (METAVIR F4) SAFE algorithm: 0.87 (0.84-0.90)	Authors report no funding from industry or conflicts of interests	Fair	Same population as Castera 2009 and incorporates population from Castera 2005

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Castera, 2009 ²⁹	Cirrhosis (METAVIR F4) Platelet count <150: 0.41 (29/70) Fibrotest \geq 0.75: 0.56 (39/70) Prothrombin index \leq 85%: 0.36 (25/70) AST/ALT ratio \geq 1: 0.31 (22/70) APRI \geq 1.0: 0.64 (45/70); \geq 2.0: 0.30 (21/70) Lok Index \geq 0.2: 0.86 (60/70); \geq 0.5: 0.40 (28/70)	Cirrhosis (METAVIR F4) Platelet count <150: 0.94 (214/228) Fibrotest \geq 0.86: 0.55 (197/228) Prothrombin index \leq 85%: 0.90 (205/228) AST/ALT ratio \geq 1: 0.89 (203/228) APRI \geq 1.0: 0.82 (186/228) [0.81*]; \geq 2.0: 0.94 (215/228) Lok Index \geq 0.2: 0.46 (105/228); \geq 0.5: 0.94 (215/228)	Cirrhosis (METAVIR F4) Platelet count <150: 0.67 (29/43) Fibrotest \geq 0.75: 0.56 (39/70) [0.55*] Prothrombin index \leq 85%: 0.52 (25/48) AST/ALT ratio \geq 1: 0.47 (22/47) APRI \geq 1.0: 0.52 (45/87); \geq 2.0: 0.62 (21/34) Lok Index \geq 0.2: 0.33 (60/183) [0.32*]; \geq 0.5: 0.68 (28/41)	Cirrhosis (METAVIR F4) Platelet count <150: 0.84 (214/255) Fibrotest \geq 0.86: 0.86 (197/228) Prothrombin index \leq 85%: 0.82 (205/250) AST/ALT ratio \geq 1: 0.81 (203/251) APRI \geq 1.0: 0.88 (186/211); \geq 2.0: 0.81 (215/264) Lok Index \geq 0.2: 0.91 (105/115); \geq 0.5: 0.84 (215/257)	Cirrhosis (METAVIR F4) Platelet count: 0.79 (0.72-0.85) Fibrotest: 0.82 (0.73-0.86) Prothrombin index: 0.73 (0.66-0.80) AST/ALT ratio: 0.61 (0.53-0.70) APRI: 0.80 (0.74-0.86) Lok Index: 0.80 (0.73-0.86)	No funding from manufacturers of tests evaluated in study	Good	Same population as Castera 2010 and incorporates population from Castera 2005
Castera, 2005 ³⁰	Not reported	Not reported	Not reported	Not reported	Fibrosis (METAVIR F2-F4) APRI: 0.78 (0.70-0.85) Fibrotest: 0.85 (0.78-0.90) Severe fibrosis (METAVIR F3-F4) APRI: 0.84 (0.78-0.89) Fibrotest: 0.90 (0.85-0.94)	Not stated	Good	Same population incorporated in Castera 2009 and 2010
Cheong, 2011 ³¹	Not reported for HCV subgroup	Not reported for HCV subgroup	Not reported for HCV subgroup	Not reported for HCV subgroup	Validation sample only Fibrosis (METAVIR F2-F4) Significant Fibrosis Index: 0.80 (0.70-0.90) Zeng Index: 0.80 (0.70-0.90) APRI: 0.82 (0.72-0.92) Forn's Index: 0.80 (0.70-0.90) FIB-4: 0.80 (0.70-0.90) ELF index: 0.72 (0.60-0.84)	Ministry for Health, Welfare and Family Affairs, Republic of Korea	Fair	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Cheung, 2011 ³²	Fibrosis (METAVIR F2-F4) Fibrosis-protein index >3.53: 0.81 (75/93) [0.80-0.83*] APRI >0.5: Not reported Severe fibrosis (METAVIR F3-F4) Fibrosis-protein Index >4.78: 0.79 (33/42) [0.74-0.89*] APRI: Not reported Cirrhosis (METAVIR F4) Fibrosis-protein index >5.31: 0.75 (21/28) [0.80-0.81*] APRI >1.0: Not reported	Reported only as ranges Fibrosis (METAVIR F2-F4) Fibrosis-protein Index >3.53: 0.71 (30/42) [0.62-0.79*] APRI >0.5: Not reported Severe fibrosis (METAVIR F3-F4) Fibrosis-protein Index >4.78: 0.78 (73/93) [0.71-0.87*] APRI: Not reported Cirrhosis (METAVIR F4) Fibrosis-protein Index >5.31: 0.81 (84/104) [0.73-0.94*] APRI >1.0: Not reported	Reported for derivation and validation samples combined Fibrosis (METAVIR F2-F4) Fibrosis-protein Index >3.53: 0.86 (75/87) APRI >0.5: 0.89 Severe fibrosis (METAVIR F3-F4) Fibrosis-protein Index >4.78: 0.62 (33/53) [0.51-0.61*] APRI: Not reported Cirrhosis (METAVIR F4) Fibrosis-protein Index >5.31: 0.51 (21/41) [0.51-0.61*] APRI >1.0: 0.62	Reported for derivation and validation samples combined Fibrosis (METAVIR F2-F4) Fibrosis-protein Index >3.53: 0.62 (30/48) APRI >0.5: 0.50 Severe fibrosis (METAVIR F3-F4) Fibrosis-protein Index >4.78: 0.89 (73/82) [0.90-0.95*] Cirrhosis (METAVIR F4) Fibrosis-protein Index >5.31: 0.92 (84/91) [0.90-0.95*] APRI >1.0: 0.94	Validation sample only Fibrosis (METAVIR F2-F4) Fibrosis-protein Index: 0.82 (0.73-0.92) APRI: 0.72 (0.60-0.85) Severe fibrosis (METAVIR F3-F4) Fibrosis-protein Index: 0.92 (0.86-0.99) APRI: 0.87 (0.75-0.98) Cirrhosis (METAVIR F4) Fibrosis-protein Index: 0.88 (0.77-0.98) APRI: 0.92 (0.84-1.0)	Declared no financial disclosures or conflicts of interest	Fair	Reported PPV's and NPV's unclear for Fibrosis-protein Index and severe fibrosis or cirrhosis and inconsistent with data from 2 x 2 table constructed from Figure 4; also total sample size went down from 135 to 132 based on Figure 4.
Cheung, 2008 ³³	Fibrosis (Batt-Ludwig 2-4) Platelet count <100: 0.05 (15/323), <150: 0.28 (89/323) AST/ALT ratio ≥1.0: 0.20 (65/323) Pohl score positive: 0.07 (21/323) APRI Severe fibrosis (Batt-Ludwig 3 or 4) Platelet count <100: 0.08 (14/187); <150: 0.39 (72/187) [0.38*] AST/ALT ratio ≥1.0: 0.19 (40/210) [0.21*] Pohl score positive: 0.09 (17/187) APRI Lok Index ≥0.2: 0.93 (174/187); >0.5: 0.51 (95/187)	Fibrosis (Batt-Ludwig 2-4) Platelet count <100: 0.99 (166/167), <150: 0.92 (153/167) AST/ALT ratio ≥1.0: 0.82 (137/167) Pohl score positive: 0.98 (164/167) APRI Severe fibrosis (Batt-Ludwig 3 or 4) Platelet count <100: 0.99 (301/303); <150: 0.90 (272/303) AST/ALT ratio ≥1.0: 0.97 (248/255) [0.82*] Pohl score positive: 0.98 (296/303) APRI Lok Index ≥0.2: 0.31 (94/303); >0.5: 0.83 (252/303)	Fibrosis (Batt-Ludwig 2-4) Platelet count <100: 0.94 (15/16), <150: 0.86 (89/103) AST/ALT ratio ≥1.0: 0.68 (65/95) Pohl score positive: 0.88 (21/24) APRI Severe fibrosis (Batt-Ludwig 3 or 4) Platelet count <100: 0.88 (14/16); <150: 0.70 (72/103) AST/ALT ratio ≥1.0: 0.85 (40/47) [0.42*] Pohl score positive: 0.71 (17/24) APRI Lok Index ≥0.2: 0.45 (174/383); >0.5: 0.65 (95/146)	Fibrosis (Batt-Ludwig 2-4) Platelet count <100: 0.35 (166/474), <150: 0.40 (153/387) AST/ALT ratio ≥1.0: 0.35 (137/395) Pohl score positive: 0.35 (164/466) APRI Severe fibrosis (Batt-Ludwig 3 or 4) Platelet count <100: 0.64 (301/474); <150: 0.70 (272/387) AST/ALT ratio ≥1.0: 0.59 (248/418) [0.63*] Pohl score positive: 0.64 (296/466) APRI Lok Index ≥0.2: 0.88 (94/107); >0.5: 0.73 (252/344)	Fibrosis (Batt-Ludwig 2-4) Platelet count: 0.60 (0.56-0.63) for <150; 0.52 (0.51-0.53) for <100 AST/ALT ratio: 0.54 (0.48-0.59) Pohl score: 0.52 (0.51-0.54) APRI: 0.69 (0.64-0.74) Severe fibrosis (Batt-Ludwig 3 or 4) Platelet count: 0.64 (0.60-0.68) for <150; 0.53 (0.52-0.55) for <100 AST/ALT ratio: 0.52 (0.47-0.58) Pohl score: 0.53 (0.51-0.56) APRI: 0.76 (0.71-0.81) Lok Index: 0.69 (0.64-0.74)	Schering Plough Corporation and VA National Hepatitis C Program	Fair	Sensitivities/specificities for increasing APRI values inconsistent with expected trends.
Chrysanthos, 2006 ³⁴	Fibrosis (Ishak ≥3) APRI >0.50: 0.79 (115/146); >1.50: 0.30 (44/146) Cirrhosis (Ishak 5 or 6) APRI >1.00: 0.60 (35/58); >2.00: 0.38 (22/58)	Fibrosis (Ishak ≥3) APRI >0.50: 0.46 (64/138); >1.50: 0.88 (122/138) Cirrhosis (Ishak 5 or 6) APRI >1.00: 0.72 (162/226); >2.00: 0.91 (206/226)	Fibrosis (Ishak ≥3)APRI >0.50: 0.61 (115/189); >1.50: 0.73 (44/60) Cirrhosis (Ishak 5 or 6) APRI >1.00: 0.35 (35/99); >2.00: 0.52 (22/42)	Fibrosis (Ishak ≥3) APRI >0.50: 0.67 (64/95); >1.50: 0.54 (122/224) Cirrhosis (Ishak 5 or 6) APRI >1.00: 0.88 (162/185); >2.00: 0.85 (206/242)	Not reported for HCV subgroup	Funding source not reported, no conflicts of interest declared	Good	AUROC's for APRI entire sample (HBV + HCV): 0.65 for fibrosis and 0.70 for cirrhosis (CI's not reported)

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Cobbold, 2009 ¹⁴⁵	<p>Fibrosis (Ishak 3-6) APRI >0.66: 0.83 (31/37) [0.84*] ELF Index >8.75: 0.84 (31/37) Hepatic transit time >8.0: 0.53 (20/37) [0.54*]</p> <p>Cirrhosis (Ishak 5-6) APRI >0.92: 0.86 (12/14) ELF Index >8.75: 0.93 (13/14) Hepatic transit time >8.0: 0.71 (10/14)</p>	<p>Fibrosis (Ishak 3-6) APRI >0.66: 0.78 (23/30) [0.77*] ELF Index >8.75: 0.70 (21/30) Hepatic transit time >8.0: 0.73 (22/30)</p> <p>Cirrhosis (Ishak 5-6) APRI >0.92: 0.77 (41/53) ELF Index >8.75: 0.79 (42/53) Hepatic transit time >8.0: 0.91 (48/53)</p>	<p>Fibrosis (Ishak 3-6) APRI >0.66: 0.82 (31/38) [0.76*] ELF Index >8.75: 0.78 (31/40) Hepatic transit time >8.0: 0.71 (20/28) [0.62*]</p> <p>Cirrhosis (Ishak 5-6) APRI >0.92: 0.50 (12/24) ELF Index >8.75: 0.54 (13/24) Hepatic transit time >8.0: 0.67 (10/15)</p>	<p>Fibrosis (Ishak 3-6) APRI >0.66: 0.79 (23/29) [0.85*] ELF Index >8.75: 0.78 (21/27) Hepatic transit time >8.0: 0.56 (22/39) [0.66*]</p> <p>Cirrhosis (Ishak 5-6) APRI >0.92: 0.95 (41/43) ELF Index >8.75: 0.98 (42/43) Hepatic transit time >8.0: 0.92 (48/52)</p>	<p>Fibrosis (Ishak 3-6) APRI: 0.83 (0.73-0.93) ELF Index: 0.82 (0.73-0.92) Hepatic transit time: 0.71 (0.59-0.84)</p> <p>Cirrhosis (Ishak 5-6) APRI: 0.86 (0.75-0.97) ELF Index: 0.91 (0.82-1.0) Hepatic transit time: 0.83 (0.69-0.97)</p>	Pfizer UK Ltd., Sandwich, United Kingdom National Institute of Health Research, British Medical Research Council	Fair	
Colletta, 2005 ³⁶	<p>Fibrosis (METAVIR F2-F4) Fibrotest ≥0.31: 0.64 (9/14)</p>	<p>Fibrosis (METAVIR F2-F4) Fibrotest ≥0.31: 0.31 (8/26)</p>	<p>Fibrosis (METAVIR F2-F4) Fibrotest ≥0.31: 0.33 (9/27)</p>	<p>Fibrosis (METAVIR F2-F4) Fibrotest ≥0.31: 0.62 (8/13)</p>	Not reported	University of Eastern Piedmont and MIUR	Fair	
Colli, 2005 ³⁷	<p>Severe fibrosis (METAVIR F3-F4) Cirrhosis discriminant score >3: 0.93 (62/67); >7: 0.06 (4/67) Liver surface nodularity present: 0.60 (40/67)</p>	<p>Severe fibrosis (METAVIR F3-F4) Cirrhosis discriminant score >3: 0.54 (59/109); >7: 0.96 (105/109) Liver surface nodularity present: 0.92 (100/109)</p>	<p>Severe fibrosis (METAVIR F3-F4) Cirrhosis discriminant score >3: 0.55 (62/112); >7: 0.50 (4/8) Liver surface nodularity present: 0.82 (40/49)</p>	<p>Severe fibrosis (METAVIR F3-F4) Cirrhosis discriminant score >3: 0.92 (59/64); >7: 0.62 (105/168) Liver surface nodularity present: 0.79 (100/127)</p>	Not reported	Not reported	Fair	Severe fibrosis (METAVIR F3-F4) Cirrhosis discriminant score >3: 0.93 (62/67); >7: 0.06 (4/67) Liver surface nodularity present: 0.60 (40/67)

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Crisan, 2012 ³⁸	<p>Fibrosis (METAVIR F2-F4) APRI >0.44: 0.72 (203/283) Forn's Index >4.47: 0.80 (226/283) FIB-4 >1.26: 0.64 (182/283) Hepascore >0.34: 0.57 (182/283) Fibrometer >0.59: 0.69 (195/283) Fibrotest >0.34: 0.65 (184/283) APRI + Fibrometer: 0.79 (224/283) APRI + Fibrotest: 0.79 (224/283) FIB-4 + Fibrometer: 0.76 (214/283) FIB-4 + Fibrotest: 0.76 (214/283) APRI + FIB-4 + Fibrometer: 0.80 (226/283) APRI + FIB-4 + Fibrotest: 0.74 (209/283)</p> <p>Severe fibrosis (METAVIR F3-F4) APRI >1.69: 0.61 (75/122) Forn's Index >7.3: 0.86 (105/122) FIB-4 >3.74: 0.63 (77/122) Hepascore >0.61: 0.61 (74/122) Fibrometer >0.76: 0.80 (98/122) Fibrotest >0.54: 0.83 (101/122) APRI + Fibrometer: 0.78 (95/122) APRI + Fibrotest: 0.90 (109/122) FIB-4 + Fibrometer: 0.84 (103/122) FIB-4 + Fibrotest: 0.89 (109/122) APRI + FIB-4 + Fibrometer: 0.84 (103/122) APRI + FIB-4 + Fibrotest: 0.88 (108/122)</p>	<p>Fibrosis (METAVIR F2-F4) APRI >0.44: 0.67 (109/163) Forn's Index >4.47: 0.49 (81/163) FIB-4 >1.26: 0.75 (123/163) Hepascore >0.34: 0.72 (118/163) Fibrometer >0.59: 0.81 (132/163) Fibrotest >0.34: 0.80 (125/163) APRI + Fibrometer: 0.88 (144/163) APRI + Fibrotest: 0.88 (144/163) FIB-4 + Fibrometer: 0.92 (150/163) FIB-4 + Fibrotest: 0.84 (137/163) APRI + FIB-4 + Fibrometer: 0.95 (155/163) APRI + FIB-4 + Fibrotest: 0.87 (141/163)</p> <p>Severe fibrosis (METAVIR F3-F4) APRI >1.69: 0.77 (251/324) Forn's Index >7.3: 0.49 (157/324) FIB-4 >3.74: 0.81 (262/324) Hepascore >0.61: 0.73 (237/324) Fibrometer >0.76: 0.72 (206/324) APRI + Fibrometer: 0.84 (273/324) APRI + Fibrotest: 0.78 (252/324) FIB-4 + Fibrometer: 0.90 (293/324) FIB-4 + Fibrotest: 0.82 (264/324) APRI + FIB-4 + Fibrometer: 0.91 (295/324) APRI + FIB-4 + Fibrotest: 0.83 (270/324)</p>	<p>Fibrosis (METAVIR F2-F4) APRI >0.44: 0.79 (203/257) [0.77*] Forn's Index >4.47: 0.73 (226/308) [0.41*] FIB-4 >1.26: 0.82 (182/222) [0.80*] Hepascore >0.34: 0.80 (182/227) [0.82*] Fibrometer >0.59: 0.86 (195/226) [0.88*] Fibrotest >0.34: 0.83 (184/222) [0.87*] APRI + Fibrometer: 0.92 (224/243) [0.93*] APRI + Fibrotest: 0.92 (224/243) [0.91*] FIB-4 + Fibrometer: 0.94 (214/227) [0.95*] FIB-4 + Fibrotest: 0.89 (214/240) [0.91*] APRI + FIB-4 + Fibrometer: 0.97 (226/234) APRI + FIB-4 + Fibrotest: 0.90 (209/231) [0.94*]</p> <p>Severe fibrosis (METAVIR F3-F4) APRI >1.69: 0.51 (75/148) [0.46*] Forn's Index >7.3: 0.39 (105/272) [0.34*] FIB-4 >3.74: 0.55 (77/139) [0.51*] Hepascore >0.61: 0.46 (74/161) [0.50*] Fibrometer >0.76: 0.52 (98/187) [0.54*] Fibrotest >0.54: 0.46 (101/219) [0.49*] APRI + Fibrometer: 0.65 (95/146) [0.64*] APRI + Fibrotest: 0.60 (109/181) [0.62*] FIB-4 + Fibrometer: 0.77 (103/134) [0.73*] FIB-4 + Fibrotest: 0.64 (109/169) APRI + FIB-4 + Fibrometer: 0.78 (103/132) [0.76*] APRI + FIB-4 + Fibrotest: 0.67 (108/162) [0.68*]</p>	<p>Fibrosis (METAVIR F2-F4) APRI >0.44: 0.58 (109/189) [0.60*] Forn's Index >4.47: 0.69 (81/138) [0.61*] FIB-4 >1.26: 0.55 (123/224) [0.57*] Hepascore >0.34: 0.54 (118/219) [0.43*] Fibrometer >0.59: 0.60 (132/220) [0.56*] Fibrotest >0.34: 0.56 (125/224) [0.52*] APRI + Fibrometer: 0.71 (144/203) [0.68*] APRI + Fibrotest: 0.71 (144/203) [0.64*] FIB-4 + Fibrometer: 0.68 (150/219) [0.67*] FIB-4 + Fibrotest: 0.67 (137/206) [0.68*] APRI + FIB-4 + Fibrometer: 0.73 (155/212) [0.68*] APRI + FIB-4 + Fibrotest: 0.66 (141/215)</p> <p>Severe fibrosis (METAVIR F3-F4) APRI >1.69: 0.84 (251/298) [0.86*] Forn's Index >7.3: 0.90 (157/174) [0.92*] FIB-4 >3.74: 0.85 (262/307) [0.88*] Hepascore >0.61: 0.83 (237/285) [0.81*] Fibrometer >0.76: 0.91 (235/259) [0.90*] Fibrotest >0.54: 0.91 (206/227) [0.90*] APRI + Fibrometer: 0.91 (273/300) [0.92*] APRI + Fibrotest: 0.95 (252/265) FIB-4 + Fibrometer: 0.94 (293/312) [0.95*] FIB-4 + Fibrotest: 0.95 (264/277) APRI + FIB-4 + Fibrometer: 0.94 (295/314) APRI + FIB-4 + Fibrotest: 0.95 (270/284)</p>	<p>Fibrosis (METAVIR F2-F4) APRI: 0.73 Forn's Index: 0.68 FIB-4: 0.71 Hepascore: 0.69 Fibrometer: 0.80 Fibrotest: 0.78</p> <p>Severe fibrosis (METAVIR F3-F4) APRI: 0.74 Forn's Index: 0.74 FIB-4: 0.77 Hepascore: 0.70 Fibrometer: 0.81 Fibrotest: 0.78</p>	None	Fair	<p>Fibrosis (METAVIR F2-F4) APRI >0.44: 0.72 (203/283) Forn's Index >4.47: 0.80 (226/283) FIB-4 >1.26: 0.64 (182/283) Hepascore >0.34: 0.57 (182/283) Fibrometer >0.59: 0.69 (195/283) Fibrotest >0.34: 0.65 (184/283) APRI + Fibrometer: 0.79 (224/283) APRI + Fibrotest: 0.79 (224/283) FIB-4 + Fibrometer: 0.76 (214/283) FIB-4 + Fibrotest: 0.76 (214/283) APRI + FIB-4 + Fibrometer: 0.80 (226/283) APRI + FIB-4 + Fibrotest: 0.74 (209/283)</p> <p>Severe fibrosis (METAVIR F3-F4) APRI >1.69: 0.61 (75/122) Forn's Index >7.3: 0.86 (105/122) FIB-4 >3.74: 0.63 (77/122) Hepascore >0.61: 0.61 (74/122) Fibrometer >0.76: 0.80 (98/122) Fibrotest >0.54: 0.83 (101/122) APRI + Fibrometer: 0.78 (95/122) APRI + Fibrotest: 0.90 (109/122) FIB-4 + Fibrometer: 0.84 (103/122) FIB-4 + Fibrotest: 0.89 (109/122) APRI + FIB-4 + Fibrometer: 0.84 (103/122) APRI + FIB-4 + Fibrotest: 0.88 (108/122)</p>

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Cross, 2010 ³⁹	Fibrosis (Ishak \geq 3)King's Score >9.87: 0.84 (75/89)Cirrhosis (Ishak 5 or 6)King's Score >24.3: 0.74 (37/50)	Fibrosis (Ishak \geq 3)King's Score >9.87: 0.70 (69/98)Cirrhosis (Ishak 5 or 6)King's Score >24.3: 0.90 (123/137)	Fibrosis (Ishak \geq 3)King's Score >9.87: 0.72 (75/104) [0.74*]Cirrhosis (Ishak 5 or 6)King's Score >24.3: 0.73 (37/51) [0.70*]	Fibrosis (Ishak \geq 3)King's Score >9.87: 0.83 (69/83) [0.80*]Cirrhosis (Ishak 5 or 6)King's Score >24.3: 0.90 (123/136) [0.91*]	Whole sample, normal AST, elevated AST, liver biopsy <15 mm, liver biopsy >15 mm, respectivelyFibrosis (Ishak \geq 3)King's Score: 0.89 (CI not reported), 0.83 (0.68-0.99), 0.79 (0.69-0.89), 0.84 (0.70-0.98), 0.83 (0.72-0.93)Cirrhosis (Ishak 5 or 6)King's Score: 0.88 (0.82-0.94), 0.96 (0.91-1.0), 0.78 (0.67-0.88), 0.94 (0.87-1.0), 0.82 (0.71-0.90)	Not reported	Fair	Different population from Cross, 2009

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Cross, 2009 ⁴⁰	<p>Derivation sample only Fibrosis (Ishak ≥ 3) King's Score ≥ 12.3: 0.70 (190/271) FIB-4 score >0.34: 0.62 (168/271) Age-platelet index >3.5: 0.70 (190/271) APRI >0.53: 0.69 (187/271) Platelets <187: 0.64 (173/271) AST >62: 0.60 (163/271)</p> <p>Cirrhosis (Ishak 5 or 6) King's Score ≥ 16.7: 0.86 (114/132) FIB-4 score >0.41: 0.83 (110/132) Age-platelet index >5: 0.80 (106/132) APRI >0.75: 0.84 (111/132) Platelets <149: 0.72 (95/132) AST >64.5: 0.77 (102/132)</p>	<p>Derivation sample only Fibrosis (Ishak ≥ 3) King's Score ≥ 12.3: 0.85 (281/331) FIB-4 score >0.34: 0.79 (261/331) Age-platelet index >3.5: 0.74 (245/331) APRI >0.53: 0.77 (255/331) Platelets <187: 0.74 (245/331) AST >62: 0.81 (268/331)</p> <p>Cirrhosis (Ishak 5 or 6) King's Score ≥ 16.7: 0.80 (376/470) FIB-4 score >0.41: 0.78 (367/470) Age-platelet index >5: 0.89 (418/470) APRI >0.75: 0.78 (367/470) Platelets <149: 0.91 (428/470) AST >64.5: 0.75 (352/470)</p>	<p>Derivation sample only Fibrosis (Ishak ≥ 3) King's Score ≥ 12.3: 0.79 (190/240) [0.81*] FIB-4 score >0.34: 0.71 (168/238) Age-platelet index >3.5: 0.69 (190/276) [0.70*] APRI >0.53: 0.71 (187/263) [0.75*] Platelets <187: 0.67 (173/259) [0.68*] AST >62: 0.72 (163/226) [0.73*]</p> <p>Cirrhosis (Ishak 5 or 6) King's Score ≥ 16.7: 0.55 (114/208) [0.56*] FIB-4 score >0.41: 0.52 (110/213) [0.41*] Age-platelet index >5: 0.67 (106/158) APRI >0.75: 0.52 (111/214) [0.53*] Platelets <149: 0.69 (95/137) AST >64.5: 0.46 (102/220) [0.47*]</p>	<p>Derivation sample only Fibrosis (Ishak ≥ 3) King's Score ≥ 12.3: 0.78 (281/362) [0.77*] FIB-4 score >0.34: 0.72 (261/364) Age-platelet index >3.5: 0.75 (245/326) [0.74*] APRI >0.53: 0.75 (255/339) Platelets <187: 0.71 (245/343) AST >62: 0.71 (268/376)</p> <p>Cirrhosis (Ishak 5 or 6) King's Score ≥ 16.7: 0.95 (376/394) [0.96*] FIB-4 score >0.41: 0.94 (367/389) [0.96*] Age-platelet index >5: 0.94 (418/444) APRI >0.75: 0.95 (367/388) [0.94*] Platelets <149: 0.92 (428/465) AST >64.5: 0.92 (352/382)</p>	<p>Derivation and validation samples, respectively Fibrosis (Ishak ≥ 3) King's Score: 0.79 (0.75-0.83) and 0.89 (0.81-0.96) FIB-4: 0.76 (0.68-0.83) and NR AST: 0.68 (0.62-0.74) and NR 1/platelets: 0.66 (0.60-0.72) and NR AST/ALT ratio: 0.58 (0.51-0.64) and NR Age-platelet index: 0.77 (0.73-0.81) and NR Cirrhosis Discriminant Score: 0.67 (0.62-0.72) and NR APRI: 0.76 (0.72-0.80) and NR Pohl Index: 0.53 (0.46-0.59) and NR</p> <p>Cirrhosis (Ishak 5 or 6) King's Score: 0.91 (0.89-0.94) and 0.94 (0.87-1.0) FIB-4: 0.87 (0.82-0.91) and NR AST: 0.79 (0.74-0.83) and NR 1/platelets: 0.88 (0.85-0.91) and NR AST/ALT ratio: 0.68 (0.60-0.75) and NR Age-platelet index: 0.90 (0.86-0.93) and NR Cirrhosis Discriminant Score: 0.74 (0.68-0.81) and NR APRI: 0.88 (0.85-0.92) and NR Pohl Index: 0.64 (0.55-0.73) and NR</p>	Funding source not reported, no conflicts of interest declared	Fair	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Ehsan, 2008 ⁴¹	Cirrhosis (Ishak 5-6) Age-platelet index >5: 0.72 (25/35) Lok Index >0.6: 0.79 (28/35) Cirrhosis discriminant score >7: 0.48 (17/35) Goteborg University Cirrhosis Index >1.5: 0.74 (26/35) APRI >1.5: 0.66 (23/35) Pohl Index positive: 0.34 (12/35) AST/ALT ratio >1.5: 0.44 (15/35)	Cirrhosis (Ishak 5-6) Age-platelet index >5: 0.93 (75/81) Lok Index >0.6: 0.88 (71/81) Cirrhosis discriminant score >7: 0.99 (80/81) Goteborg University Cirrhosis Index >1.5: 0.89 (72/81) APRI >1.5: 0.94 (76/81) Pohl Index positive: 0.99 (80/81) AST/ALT ratio >1.5: 0.91 (74/81)	Cirrhosis (Ishak 5-6) Age-platelet index >5: 0.81 (25/31) [0.91*] Lok Index >0.6: 0.74 (28/38) [0.87*] Cirrhosis discriminant score >7: 0.94 (17/18) [0.98*] Goteborg University Cirrhosis Index >1.5: 0.74 (26/35) [0.87*] APRI >1.5: 0.82 (23/28) [0.92*] Pohl Index positive: 0.92 (12/13) AST/ALT ratio >1.5: 0.68 (15/22) [0.83*]	Cirrhosis (Ishak 5-6) Age-platelet index >5: 0.88 (75/85) [0.77*] Lok Index >0.6: 0.91 (71/78) [0.80*] Cirrhosis discriminant score >7: 0.82 (80/98) [0.66*] Goteborg University Cirrhosis Index >1.5: 0.89 (72/81) [0.77*] APRI >1.5: 0.86 (76/88) [0.74*] Pohl Index positive: 0.78 (80/103) [0.60*] AST/ALT ratio >1.5: 0.79 (74/94) [0.72*]	Cirrhosis (Ishak 5-6) Age-platelet index: 0.91 (CI not reported) Lok Index: 0.88 (CI not reported) Cirrhosis discriminant score: 0.87 (CI not reported) Goteborg University Cirrhosis Index: 0.86 (CI not reported) APRI: 0.86 (CI not reported) Pohl Index: 0.66 (CI not reported) AST/ALT ratio: 0.65 (CI not reported)	Not stated, reported no competing interests	Poor	
El-Gindy, 2003 ⁴²	Fibrosis (Ishak 1-4 vs. Ishak 0) MMP-2 >400 ng/ml: 0.07 (1/15) TIMP-1 >195 ng/ml: 0.67 (10/15) AST >34 IU/L: 0.80 (12/15) [0.78*] ALT >44 IU/L: 0.93 (14/15) [0.96*] Albumin <3.5 g/100 ml: 0.27 (4/13) Cirrhosis (Ishak 5-6) MMP-2 >400 ng/ml: 0.86 (12/14) [0.83*] TIMP-1 >195 ng/ml: 1.0 (14/14) AST >34 IU/L: 0.79 (11/14) [0.81*] ALT >44 IU/L: 0.86 (12/14) [0.88*] Albumin <3.5 g/100 ml: 0.71 (10/14) [0.73*]	Fibrosis (Ishak 1-4 vs. Ishak 0) MMP-2 >400 ng/ml: 0.92 (11/12) [0.97*] TIMP-1 >195 ng/ml: 0.67 (8/12) [0.69*] AST >34 IU/L: 0.42 (5/12) [0.40*] ALT >44 IU/L: 0.17 (2/12) [0.16*] Albumin <3.5 g/100 ml: 0.92 (11/12) [0.90*] Cirrhosis (Ishak 5-6) MMP-2 >400 ng/ml: 0.96 (26/27) TIMP-1 >195 ng/ml: 0.74 (20/27) [0.75*] AST >34 IU/L: 0.59 (16/27) [0.60*] ALT >44 IU/L: 0.11 (3/27) Albumin <3.5 g/100 ml: 0.85 (23/27) [0.86*]	Fibrosis (Ishak 1-4 vs. Ishak 0) MMP-2 >400 ng/ml: 0.50 (1/2) TIMP-1 >195 ng/ml: 0.71 (10/14) AST >34 IU/L: 0.63 (12/19) ALT >44 IU/L: 0.58 (14/24) Albumin <3.5 g/100 ml: 0.80 (4/5) Cirrhosis (Ishak 5-6) MMP-2 >400 ng/ml: 0.92 (12/13) TIMP-1 >195 ng/ml: 0.67 (14/21) AST >34 IU/L: 0.50 (11/22) ALT >44 IU/L: 0.33 (12/36) Albumin <3.5 g/100 ml: 0.71 (10/14)	Fibrosis (Ishak 1-4 vs. Ishak 0) MMP-2 >400 ng/ml: 0.44 (11/25) TIMP-1 >195 ng/ml: 0.62 (8/13) AST >34 IU/L: 0.62 (5/8) ALT >44 IU/L: 0.67 (2/3) Albumin <3.5 g/100 ml: 0.55 (11/20) Cirrhosis (Ishak 5-6) MMP-2 >400 ng/ml: 0.93 (26/28) TIMP-1 >195 ng/ml: 1.0 (20/20) AST >34 IU/L: 0.84 (16/19) ALT >44 IU/L: 0.60 (3/5) Albumin <3.5 g/100 ml: 0.85 (23/27)	Fibrosis (Ishak 1-4 vs. Ishak 0) MMP-2: 0.57 (0.49-0.65) TIMP-1 >195 ng/ml: 0.71 (0.64-0.78) AST: NR ALT: NR Albumin: NR Cirrhosis (Ishak 5-6) MMP-2 >400 ng/ml: 0.97 (0.95-0.99) TIMP-1 >195 ng/ml: 0.89 (0.85-0.93) AST: NR ALT: NR Albumin: NR	Not stated	Fair	
El-Sayed, 2011 ⁴³	Not reported	Not reported	Not reported	Not reported	Severe fibrosis (METAVIR F3-F4) (Cis not reported) APRI: 0.63 AST/ALT ratio: 0.76 AST: 0.59	Not stated	Fair	
El-Shorbagy, 2004 ⁴⁴	Fibrosis (G2S2 or G3S3) 7-item predictive index >3: 0.80 (70/87) Cirrhosis (G3S3) 7-item predictive index ≥6: 0.80 (16/20)	Fibrosis (G2S2 or G3S3) 7-item predictive index >3: 0.82 (18/22) Cirrhosis (G3S3) 7-item predictive index ≥6: 0.97 (86/89)	Fibrosis (G2S2 or G3S3) 7-item predictive index >3: 0.95 (70/74) Cirrhosis (G3S3) 7-item predictive index ≥6: 0.84 (16/19)	Fibrosis (G2S2 or G3S3) 7-item predictive index >3: 0.51 (18/35) Cirrhosis (G3S3) 7-item predictive index ≥6: 0.96 (86/90)	Not reported	Not stated	Poor	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Fabris, 2008 ⁴⁵	Fibrosis (METAVIR F2-F4) Fibro Index >1.6: 0.54 (37/69) Cirrhosis (METAVIR F4) Fibro Index >1.6: 0.90 (17/19)	Fibrosis (METAVIR F2-F4) Fibro Index >1.6: 0.82 (80/98) Cirrhosis (METAVIR F4) Fibro Index >1.6: 0.74 (110/148)	Fibrosis (METAVIR F2-F4) Fibro Index >1.6: 0.67 (37/55) Cirrhosis (METAVIR F4) Fibro Index >1.6: 0.31 (17/55)	Fibrosis (METAVIR F2-F4) Fibro Index >1.6: 0.71 (80/112) Cirrhosis (METAVIR F4) Fibro Index >1.6: 0.98 (110/112)	Fibrosis (METAVIR F2-F4) Fibro Index: 0.71 (0.63-0.77) Age-platelet index: 0.64 (0.56-0.72) AST/ALT ratio: 0.59 (0.51-0.66) APRI: 0.72 (0.64-0.79) Cirrhosis Discriminant Score: 0.64 (0.56-0.71) Forn's Index: 0.70 (0.62-0.76) Cirrhosis (METAVIR F4) Fibro Index: 0.86 (0.80-0.91) Age-platelet index: 0.67 (0.59-0.74) AST/ALT ratio: 0.66 (0.58-0.73) APRI: 0.86 (0.79-0.90) Cirrhosis Discriminant Score: 0.71 (0.64-0.78) Forn's Index: 0.86 (0.80-0.91)	Not stated	Fair	
Fontana, 2008 ⁴⁶	Cirrhosis (Ishak 5-6) HALT-C model ≥ 0.2 : 0.88 (156/177); ≥ 0.5 : 0.47 (84/177)	Cirrhosis (Ishak 5-6) HALT-C model ≥ 0.2 : 0.45 (132/294); ≥ 0.5 : 0.92 (270/294)	Cirrhosis (Ishak 5-6) HALT-C model ≥ 0.2 : 0.49 (156/318); ≥ 0.5 : 0.78 (84/108)	Cirrhosis (Ishak 5-6) HALT-C model ≥ 0.2 : 0.86 (132/153); ≥ 0.5 : 0.74 (270/363)	Cirrhosis (Ishak 5 or 6) HALT-C model: 0.81 (0.77-0.85) Lok Index: 0.79 (0.74-0.83) APRI: 0.73 (0.69-0.78) Cirrhosis Discriminant Score: 0.70 (0.66-0.75)	NIDDKD, NIAID, NCI, NIH, Hoffman-La Roche Inc	Fair	HALT-C cohort also evaluated in Lok, 2005
Forns, 2002 ⁴⁷	Derivation and validation samples, respectively Fibrosis (Scheuer F2-F4) Forns Index >4.2: 0.94 (80/85) and 0.94 (31/33); >6.9: 0.44 (37/85) and 0.30 (10/33)	Derivation and validation samples, respectively Fibrosis (Scheuer F2-F4) Forns Index >4.2: 0.45 (120/266) and 0.51 (47/92); >6.9: 0.96 (256/266) and 0.95 (87/92)	Derivation and validation samples, respectively Fibrosis (Scheuer F2-F4) Forns Index >4.2: 0.35 (80/226) and 0.41 (31/76); >6.9: 0.79 (37/47) and 0.67 (10/15)	Derivation and validation samples, respectively Fibrosis (Scheuer F2-F4) Forns Index >4.2: 0.96 (120/135) and 0.96 (47/49); >6.9: 0.84 (256/304) and 0.79 (87/11)	Derivation and validation samples, respectively Fibrosis (Scheuer F2-F4) Forns Index: 0.86 and 0.81 (CI's not reported)	Not stated	Good	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Friedrich-Rust, 2010 ⁴⁸	Fibrosis (METAVIR F2-F4) Simplified ELF index >9.78: 0.85 Fibrotest >0.32: 0.81 Severe fibrosis (METAVIR F3-F4) Simplified ELF index >10.22: 0.82 Fibrotest >0.59: 0.65 Cirrhosis (METAVIR F4) Simplified ELF index >10.31: 0.89 Fibrotest >0.73: 0.67	Fibrosis (METAVIR F2-F4) Simplified ELF index >9.78: 0.80 Fibrotest >0.32: 0.60 Severe fibrosis (METAVIR F3-F4) Simplified ELF index >10.22: 0.74 Fibrotest >0.59: 0.79 Cirrhosis (METAVIR F4) Simplified ELF index >10.31: 0.63 Fibrotest >0.73: 0.81	Fibrosis (METAVIR F2-F4) Simplified ELF index >9.78: 0.92 Fibrotest >0.32: 0.84 Severe fibrosis (METAVIR F3-F4) Simplified ELF index >10.22: 0.74 Fibrotest >0.59: 0.73 Cirrhosis (METAVIR F4) Simplified ELF index >10.31: 0.44 Fibrotest >0.73: 0.54	Fibrosis (METAVIR F2-F4) Simplified ELF index >9.78: 0.67 Fibrotest >0.32: 0.55 Severe fibrosis (METAVIR F3-F4) Simplified ELF index >10.22: 0.82 Fibrotest >0.59: 0.71 Cirrhosis (METAVIR F4) Simplified ELF index >10.31: 0.94 Fibrotest >0.73: 0.88	Not reported	None	Fair	
Gabrielli, 1997 ⁴⁹	Severe fibrosis (Scheuer F3-F4) Laminin P1 >1.4: 0.79, >2.0: 0.48; >2.4: 0.31 PIIIP >0.6: 0.93, >1.0: 0.34, >1.6: 0.03	Severe fibrosis (Scheuer F3-F4) Laminin P1 >1.4: 0.40; >2.0: 0.88; >2.4: 0.96 PIIIP >0.6: 0.13, >1.0: 0.94; >1.6: 0.98	Severe fibrosis (Scheuer F3-F4) Laminin P1 >1.4: 0.35, >2.0: 0.63; >2.4: 0.88 PIIIP >0.6: 0.30, >1.0: 0.71, >1.6: 0.47	Severe fibrosis (Scheuer F3-F4) Laminin P1 >1.4: 0.82; >2.0: 0.81; >2.4: 0.77 PIIIP >0.6: 0.82, >1.0: 0.78; >1.6: 0.71	Not reported	Ministero dell'Universita e della Ricerca Scientifica, Italy	Fair	
Giannini, 2006 ⁵⁰	Fibrosis (Ishak 3-6 or METAVIR F2-F4) AST/ALT >0.66: 0.74 (129/175) Platelet count <163: 0.62 (108/175)	Fibrosis (Ishak 3-6 or METAVIR F2-F4) AST/ALT >0.66: 0.65 (152/234) Platelet count <163: 0.81 (189/234)	Fibrosis (Ishak 3-6 or METAVIR F2-F4) AST/ALT >0.66: 0.61 (129/211) Platelet count <163: 0.71 (108/153)	Fibrosis (Ishak 3-6 or METAVIR F2-F4) AST/ALT >0.66: 0.77 (152/198) Platelet count <163: 0.74 (189/256)	Not reported	Not stated	Fair	
Giannini, 2003a ⁵¹	Cirrhosis (Scheuer F4 or clinical signs of portal hypertension) AST/ALT ratio \geq 1: 0.78 (70/90) Platelet count <130,000: 0.91 (82/90) AST/ALT ratio \geq 1 or platelet count <130,000: 0.97 (87/90) AST/ALT ratio \geq 1 and platelet count <130,000: 0.72 (65/90)	Cirrhosis (Scheuer F4 or clinical signs of portal hypertension) AST/ALT ratio \geq 1: 0.97 (157/162) Platelet count <130,000: 0.88 (143/162) AST/ALT ratio \geq 1 or platelet count <130,000: 0.86 (140/162) AST/ALT ratio \geq 1 and platelet count <130,000: 0.99 (160/162)	Cirrhosis (Scheuer F4 or clinical signs of portal hypertension) AST/ALT ratio \geq 1: 0.93 (70/75) Platelet count <130,000: 0.81 (82/101) AST/ALT ratio \geq 1 or platelet count <130,000: 0.80 (87/109) AST/ALT ratio \geq 1 and platelet count <130,000: 0.97 (65/67)	Cirrhosis (Scheuer F4 or clinical signs of portal hypertension) AST/ALT ratio \geq 1: 0.89 (157/177) Platelet count <130,000: 0.95 (143/151) AST/ALT ratio \geq 1 or platelet count <130,000: 0.98 (140/143) AST/ALT ratio \geq 1 and platelet count <130,000: 0.86 (160/185)	Not reported	Not stated	Fair	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Giannini, 2003b ⁵²	Not reported	Not reported	Fibrosis (criteria not reported) AST/ALT ratio ≥ 1 : 0.89 (n/N not reported) APRI: Not reported	Not reported	Fibrosis (criteria not reported) AST/ALT ratio: 0.82 (CI not reported) APRI: 0.77 (CI not reported) Cirrhosis (criteria not reported) AST/ALT ratio: 0.91 (CI not reported) APRI: 0.81 (CI not reported)	Not stated	Fair	Substantial overlap with population evaluated in Giannini 2003a (199 of 239 subjects were included in Giannini 2003a)
Gomes da Silva, 2008 ⁵³	Fibrosis (METAVIR F2-F4) APRI >0.50: 0.93 (26/28); >0.93: 0.93 (26/28); >1.50: 0.50 (14/28) [0.46*] Cirrhosis (METAVIR F4) APRI >1.00: 0.92 (12/13); >1.73: 0.77 (10/13); >2.00: 0.54 (7/13) [0.46*]	Fibrosis (METAVIR F2-F4) APRI >0.50: 0.45 (10/22); >0.93: 0.96 (21/22); >1.50: 1.0 (22/22) Cirrhosis (METAVIR F4) APRI >1.00: 0.70 (26/37) [0.73*]; >1.73: 0.97 (36/37); >2.00: 0.97 (36/37)	Fibrosis (METAVIR F2-F4) APRI >0.50: 0.68 (26/38) [0.70*]; >0.93: 0.96 (26/27); >1.50: 1.0 (14/14) Cirrhosis (METAVIR F4) APRI >1.00: 0.52 (12/23) [0.54*]; >1.73: 0.91 (10/11); >2.00: 0.88 (7/8) [0.86*]	Fibrosis (METAVIR F2-F4) APRI >0.50: 0.83 (10/12) [0.85*]; >0.93: 0.91 (21/23); >1.50: 0.61 (22/36) [0.60*] Cirrhosis (METAVIR F4) APRI >1.00: 0.96 (26/27); >1.73: 0.92 (36/39); >2.00: 0.86 (36/42) [0.84*]	Fibrosis (METAVIR F2-F4) APRI: 0.92 (0.83-1.0) Cirrhosis (METAVIR F4) APRI: 0.92 (0.85-1.0)	Not stated	Fair	
Grigorescu, 2007 ⁵⁴	Fibrosis (METAVIR F2-F4) Fibrotest >0.47: 0.80 (104/130) alpha-2 macroglobulin >3.01 g/L: 0.74 (96/130) Haptoglobin >0.81 g/L: 0.50 (66/130) Apolipoprotein-A1 >1.41 g/L: 0.74 (97/130) Total bilirubin >12.65 micromol/L: 0.46 (60/130) GGT >47 IU/L: 0.71 (93/130)	Fibrosis (METAVIR F2-F4) Fibrotest >0.47: 0.63 (48/76) alpha-2 macroglobulin >3.01 g/L: 0.58 (44/76) Haptoglobin >0.81 g/L: 0.68 (52/76) Apolipoprotein-A1 >1.41 g/L: 0.43 (33/76) Total bilirubin >12.65 micromol/L: 0.80 (61/76) GGT >47 IU/L: 0.64 (49/76)	Fibrosis (METAVIR F2-F4) Fibrotest >0.47: 0.79 (104/132) alpha-2 macroglobulin >3.01 g/L: 0.75 (96/128) Haptoglobin >0.81 g/L: 0.73 (66/90) Apolipoprotein-A1 >1.41 g/L: 0.69 (97/140) Total bilirubin >12.65 micromol/L: 0.80 (60/75) GGT >47 IU/L: 0.78 (93/120)	Fibrosis (METAVIR F2-F4) Fibrotest >0.47: 0.65 (48/74) [0.66*] alpha-2 macroglobulin >3.01 g/L: 0.56 (44/78) Haptoglobin >0.81 g/L: 0.45 (52/116) [0.44*] Apolipoprotein-A1 >1.41 g/L: 0.50 (33/66) Total bilirubin >12.65 micromol/L: 0.47 (61/131) GGT >47 IU/L: 0.57 (49/86)	Fibrosis (METAVIR F2-F4) Fibrotest: 0.78 alpha-2 macroglobulin: 0.73 Haptoglobin: 0.63 Apolipoprotein-A1: 0.60 Total bilirubin: 0.67 GGT: 0.70	Not stated	Fair	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Guechot, 2010 ⁵⁵	Fibrosis (METAVIR F2-F4) Hepascore ≥ 0.25 : 0.47 (117/247); >0.5 : 0.77 (190/247) Severe fibrosis (METAVIR F3-F4) Hepascore >0.6 : 0.80 (124/155) Cirrhosis (METAVIR F4) Hepascore >0.75 : 0.86 (65/76); >0.84 : 0.72 (55/76) [0.73*]	Fibrosis (METAVIR F2-F4) Hepascore ≥ 0.25 : 0.95 (252/265); >0.5 : 0.70 (186/265) Severe fibrosis (METAVIR F3-F4) Hepascore >0.6 : 0.70 (250/357) Cirrhosis (METAVIR F4) Hepascore >0.75 : 0.74 (323/436); >0.84 : 0.81 (353/436)	Fibrosis (METAVIR F2-F4) Hepascore ≥ 0.25 : 0.90 (117/130); >0.5 : 0.71 (190/269) Severe fibrosis (METAVIR F3-F4) Hepascore >0.6 : 0.54 (124/231) Cirrhosis (METAVIR F4) Hepascore >0.75 : 0.37 (65/178); >0.84 : 0.40 (55/138) [0.41*]	Fibrosis (METAVIR F2-F4) Hepascore ≥ 0.25 : 0.66 (252/382); >0.5 : 0.77 (186/243) Severe fibrosis (METAVIR F3-F4) Hepascore >0.6 : 0.90 (250/281) Cirrhosis (METAVIR F4) Hepascore >0.75 : 0.97 (323/334); >0.84 : 0.94 (353/374)	Fibrosis (F2-F4) Hepascore: 0.81 (0.78-0.85) Severe fibrosis (F3-F4) Hepascore: 0.92 (0.78-0.86) Cirrhosis (F4) Hepascore: 0.88 (0.84-0.91)	French de National Agency for Research on AIDS and Viral Hepatitis (ANRS), Societe Francaise de Biologie Clinique, Association pour l'Etude du Foie	Fair	
Guechot, 1996 ⁵⁶	Severe fibrosis (Knodell F3-F4) PIIIP >0.80 U/ml: 0.70 (77/110) Hyaluronic acid >85 mcg/l: 0.65 (71/110) [0.64*] Cirrhosis (Knodell F4) PIIIP >1.00 U/ml: 0.60 (32/53) Hyaluronic acid >110 mcg/l: 0.79 (42/53)	Severe fibrosis (Knodell F3-F4) PIIIP >0.80 U/ml: 0.63 (137/216) Hyaluronic acid >85 mcg/l: 0.91 (197/216) Cirrhosis (Knodell F4) PIIIP >1.00 U/ml: 0.74 (202/273) Hyaluronic acid >110 mcg/l: 0.89 (244/273)	Severe fibrosis (Knodell F3-F4) PIIIP >0.80 U/ml: 0.49 (77/156) Hyaluronic acid >85 mcg/l: 0.79 (71/90) Cirrhosis (Knodell F4) PIIIP >1.00 U/ml: 0.31 (32/103) Hyaluronic acid >110 mcg/l: 0.59 (42/71)	Severe fibrosis (Knodell F3-F4) PIIIP >0.80 U/ml: 0.81 (137/170) Hyaluronic acid >85 mcg/l: 0.83 (197/236) Cirrhosis (Knodell F4) PIIIP >1.00 U/ml: 0.91 (202/223) Hyaluronic acid >110 mcg/l: 0.96 (244/255)	Severe fibrosis (Knodell F3-F4) PIIIP: 0.69 (CI not reported) Hyaluronic acid: 0.86 Cirrhosis (Knodell F4) PIIIP: 0.73 (CI not reported) Hyaluronic acid: 0.92 (CI not reported)	Not stated	Fair	Degree of overlap with Guechot 1994 unclear.
Guechot, 1994 ⁵⁷	Severe fibrosis (Knodell F2 or F3) PIIIP >0.80 U/ml: 0.40 (8/20) Hyaluronic acid >85 mg/l: 0.55 (11/20)	Severe fibrosis (Knodell F2 or F3) PIIIP >0.80 U/ml: 0.66 (25/38) Hyaluronic acid >85 mg/l: 0.92 (35/38)	Severe fibrosis (Knodell F2 or F3) PIIIP >0.80 U/ml: 0.38 (8/21) Hyaluronic acid >85 mg/l: 0.79 (11/14)	Severe fibrosis (Knodell F2 or F3) PIIIP >0.80 U/ml: 0.68 (25/37) Hyaluronic acid >85 mg/l: 0.80 (35/44)	Not reported	Not stated	Fair	Degree of overlap with Guechot 1996 unclear. Cirrhosis defined as Knodell F3 (?old system).
Guzelbulut, 2011 ⁵⁸	Fibrosis (METAVIR F2-F4) APRI >0.5 : 0.84 (70/83); >1.5 : 0.43 (36/83) FIB-4 >0.6 : 1.0 (83/83); ≥ 1 : 0.92 (76/83) Forns' Index >4.2 : 0.94 (78/83); >6.9 : 0.47 (39/83) Cirrhosis (METAVIR F4) APRI >1 : 0.73 (37/51); >2 : 0.43 (22/51) FIB-4 >1.45 : 0.90 (46/51); ≥ 3.25 : 0.55 (28/51) Forns' Index >4.2 : 0.98 (50/51); >6.9 : 0.67 (34/51)	Fibrosis (METAVIR F2-F4) APRI >0.5 : 0.45 (30/67); >1.5 : 0.91 (61/67) FIB-4 >0.6 : 0.10 (7/67); ≥ 1 : 0.30 (20/67) Forns' Index >4.2 : 0.34 (23/67); >6.9 : 0.94 (63/67) Cirrhosis (METAVIR F4) APRI >1 : 0.81 (80/99); >2 : 0.95 (94/99) FIB-4 >1.45 : 0.58 (57/99); ≥ 3.25 : 0.92 (91/99) Forns' Index >4.2 : 0.27 (27/99); >6.9 : 0.91 (90/99)	Fibrosis (METAVIR F2-F4) APRI >0.5 : 0.65 (70/107); >1.5 : 0.86 (36/42) FIB-4 >0.6 : 0.58 (83/143); ≥ 1 : 0.62 (76/123) Forns' Index >4.2 : 0.64 (78/122); >6.9 : 0.91 (39/43) Cirrhosis (METAVIR F4) APRI >1 : 0.66 (37/56); >2 : 0.81 (22/27) FIB-4 >1.45 : 0.52 (46/88); ≥ 3.25 : 0.78 (28/36) Forns' Index >4.2 : 0.41 (50/122); >6.9 : 0.79 (34/43)	Fibrosis (METAVIR F2-F4) APRI >0.5 : 0.70 (30/43); >1.5 : 0.56 (61/108) FIB-4 >0.6 : 1.0 (7/7); ≥ 1 : 0.74 (20/27) Forns' Index >4.2 : 0.82 (23/28); >6.9 : 0.59 (63/107) Cirrhosis (METAVIR F4) APRI >1 : 0.85 (80/94); >2 : 0.76 (94/123) FIB-4 >1.45 : 0.92 (57/62); ≥ 3.25 : 0.80 (91/114) Forns' Index >4.2 : 0.96 (27/28); >6.9 : 0.84 (90/107)	Fibrosis (METAVIR F2-F4) APRI: 0.77 (0.73-0.86) FIB-4: 0.76 (0.69-0.84) Forns' Index: 0.80 (0.73-0.86) Cirrhosis (METAVIR F4) APRI: 0.84 (0.77-0.91) FIB-4: 0.87 (0.82-0.93) Forns' Index: 0.88 (0.82-0.94)	Not stated	Fair	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Halfon, 2007 ⁵⁹	<p>Fibrosis (METAVIR F2-F4) FibroMeter >0.57: 0.64 (93/146) Fibrotest >0.44: 0.67 (98/146) Hepascore >0.32: 0.77 (112/146) APRI >0.39: 0.77 (112/146)</p> <p>Severe fibrosis (METAVIR F3-F4) FibroMeter >0.67: 0.82 (42/51) Fibrotest >0.45: 0.84 (43/51) Hepascore >0.53: 0.78 (40/51) APRI >0.58: 0.75 (38/51)</p> <p>Cirrhosis (METAVIR F4) FibroMeter >0.88: 0.92 (12/13) Fibrotest >0.56: 0.85 (11/13) Hepascore >0.61 : 0.92 (12/13) APRI >0.39: 1.0 (13/13)</p>	<p>Fibrosis (METAVIR F2-F4) FibroMeter >0.57: 0.81 (170/210) Fibrotest >0.44: 0.80 (168/210) Hepascore >0.32: 0.63 (132/210) APRI >0.39: 0.66 (139/210)</p> <p>Severe fibrosis (METAVIR F3-F4) FibroMeter >0.67: 0.76 (232/305) Fibrotest >0.45: 0.69 (210/305) Hepascore >0.53: 0.72 (220/305) APRI >0.58: 0.76 (232/305)</p> <p>Cirrhosis (METAVIR F4) FibroMeter >0.88: 0.87 (298/343) Fibrotest >0.56: 0.74 (254/343) Hepascore >0.61 : 0.72 (247/343) APRI >0.39: 0.83 (285/343)</p>	<p>Fibrosis (METAVIR F2-F4) FibroMeter >0.57: 0.70 (93/133) Fibrotest >0.44: 0.70 (98/140) Hepascore >0.32: 0.59 (112/190) APRI >0.39: 0.61 (112/183)</p> <p>Severe fibrosis (METAVIR F3-F4) FibroMeter >0.67: 0.37 (42/115) Fibrotest >0.45: 0.31 (43/138) Hepascore >0.53: 0.32 (40/125) APRI >0.58: 0.34 (38/111)</p> <p>Cirrhosis (METAVIR F4) FibroMeter >0.88: 0.21 (12/57) Fibrotest >0.56: 0.11 (11/100) Hepascore >0.61 : 0.11 (12/108) APRI >0.39: 0.18 (13/71)</p>	<p>Fibrosis (METAVIR F2-F4) FibroMeter >0.57: 0.76 (170/233) [0.77*] Fibrotest >0.44: 0.78 (98/140) Hepascore >0.32: 0.80 (132/166) APRI >0.39: 0.80 (139/173)</p> <p>Severe fibrosis (METAVIR F3-F4) FibroMeter >0.67: 0.96 (232/241) Fibrotest >0.45: 0.96 (210/218) Hepascore >0.53: 0.95 (220/231) APRI >0.58: 0.95 (232/245)</p> <p>Cirrhosis (METAVIR F4) FibroMeter >0.88: 1.0 (298/299) Fibrotest >0.56: 0.99 (254/256) Hepascore >0.61 : 1.0 (247/248) APRI >0.39: 1.0 (285/285)</p>	<p>Fibrosis (METAVIR F2-F4) FibroMeter: 0.78 (0.73-0.82) Fibrotest: 0.79 (0.75-0.83) Hepascore: 0.76 (0.71-0.80) APRI: 0.76 (0.72-0.81)</p> <p>Severe fibrosis (METAVIR F3-F4) FibroMeter: 0.84 (0.80-0.88) Fibrotest: 0.81 (0.77-0.85) Hepascore: 0.81 (0.76-0.85) APRI: 0.81 (0.76-0.85)</p> <p>Cirrhosis (METAVIR F4) FibroMeter: 0.94 (0.91-0.96) Fibrotest: 0.86 (0.82-0.89) Hepascore: 0.89 (0.86-0.92) APRI: 0.92 (0.88-0.94)</p>	Not stated	Fair	Some overlap in patient populations between Halfon 2006 and Halfon 2007
Halfon, 2006 ⁶⁰	<p>Fibrosis (METAVIR F2-F4) Fibrotest >0.10: 0.97 (223/230); >0.36: 0.73 (168/230); >0.80: 0.20 (46/230)</p> <p>Severe fibrosis (METAVIR F3 or F4) Fibrotest >0.10: 0.99 (119/120); >0.44: 0.76 (91/120); >0.80: 0.29 (35/120)</p>	<p>Fibrosis (METAVIR F2-F4) Fibrotest >0.10: 0.27 (74/274); >0.36: 0.72 (197/274); >0.80: 0.98 (269/274)</p> <p>Severe fibrosis (METAVIR F3 or F4) Fibrotest >0.10: 0.21 (81/384); >0.44: 0.70 (269/384); >0.80: 0.97 (372/384)</p>	<p>Fibrosis (METAVIR F2-F4) Fibrotest >0.10: 0.53 (223/423); >0.36: 0.69 (168/245); >0.80: 0.90 (46/51)</p> <p>Severe fibrosis (METAVIR F3-F4) Fibrotest >0.10: 0.28 (119/422); >0.44: 0.44 (91/206); >0.80: 0.73 (35/47) [0.74*]</p>	<p>Fibrosis (METAVIR F2-F4) Fibrotest >0.10: 0.91 (74/81); >0.36: 0.76 (197/259); >0.80: 0.59 (269/453)</p> <p>Severe fibrosis (METAVIR F3-F4) Fibrotest >0.10: 0.99 (81/82); >0.44: 0.90 (269/298); >0.80: 0.81 (372/457)</p>	<p>Fibrosis (METAVIR F2-F4) Fibrotest: 0.79 (0.75-0.82)</p> <p>Severe fibrosis (METAVIR F3-F4) Fibrotest: 0.80 (0.76-0.83)</p>	Not stated	Fair	Some overlap in patient populations between Halfon 2006 and Halfon 2007

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Halfon, 2005 ⁶¹	<p>Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) Hyaluronic acid ≥ 16 mcg/l: 0.96 (69/72) and 0.91 (107/118); >121 mcg/l: 0.18 (13/72) and 0.14 (16/118) Advanced fibrosis (METAVIR F3-F4) Hyaluronic acid >25 mcg/l: 0.92 (36/39) and 0.78 (47/60); >160 mcg/l: 0.26 (10/39) and 0.22 (13/60)</p> <p>Cirrhosis (METAVIR F4) Hyaluronic acid >50 mcg/l: 0.92 (11/12) and 1.0 (13/13); >237 mcg/l: Not reported and 0.31 (4/13)</p>	<p>Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) Hyaluronic acid ≥ 16 mcg/l: 0.19 (15/79) and 0.36 (49/136); >121 mcg/l: 0.97 (77/79) and 0.99 (135/136) Advanced fibrosis (METAVIR F3-F4) Hyaluronic acid >25 mcg/l: 0.54 (61/112) and 0.53 (103/194); >160 mcg/l: 0.99 (111/112) and 1.0 (194/194)</p> <p>Cirrhosis (METAVIR F4) Hyaluronic acid >50 mcg/l: 0.72 (100/139) and 0.79 (190/241); >237 mcg/l: Not reported and 0.99 (239/241)</p>	<p>Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) Hyaluronic acid ≥ 16 mcg/l: 0.52 (69/133) and 0.55 (107/194); >121 mcg/l: 0.87 (13/15) and 0.94 (16/17) Advanced fibrosis (METAVIR F3-F4) Hyaluronic acid >25 mcg/l: 0.41 (36/87) and 0.34 (47/138); >160 mcg/l: 0.91 (10/11) and 1.0 (13/13)</p> <p>Cirrhosis (METAVIR F4) Hyaluronic acid >50 mcg/l: 0.22 (11/50) and 0.20 (13/64); >237 mcg/l: 0.71 (n/N not reported) and 0.67 (4/6)</p>	<p>Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) Hyaluronic acid ≥ 16 mcg/l: 0.83 (15/18) and 0.82 (49/60); >121 mcg/l: 0.57 (77/136) and 0.57 (135/237) Advanced fibrosis (METAVIR F3-F4) Hyaluronic acid >25 mcg/l: 0.95 (61/64) and 0.89 (103/116); >160 mcg/l: 0.79 (111/140) and 0.80 (194/241)</p> <p>Cirrhosis (METAVIR F4) Hyaluronic acid >50 mcg/l: 0.99 (100/101) and 1.0 (190/190); >237 mcg/l: Not reported and 0.96 (239/248)</p>	<p>Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) Hyaluronic acid: 0.75 (0.72-0.78) and 0.73 (0.70-0.76) Advanced fibrosis (METAVIR F3-F4) Hyaluronic acid: 0.82 (0.80-0.84) and 0.77 (0.73-0.81)</p> <p>Cirrhosis (METAVIR F4) Hyaluronic acid: 0.89 (0.86-0.92) and 0.97 (0.93-1.0)</p>	Not stated	Fair	Overlap with Halfon 2006 and 2007?
Hsieh, 2009 ⁶²	<p>Fibrosis (METAVIR F2-F4) FibroQ >1.6: 0.79 (92/116) AAR >0.54: 0.77 (89/116); >1: 0.10 (12/116) APRI >0.5: 0.97 (113/116); >1.2: 0.66 (77/116); >1.5: 0.54 (63/116)</p> <p>Cirrhosis (METAVIR F4) FibroQ >2.6: 1.0 (6/6) AAR >0.75: 0.83 (5/6); >1.0: 0.33 (2/6) APRI >1.0: 1.0 (6/6); >1.5: 0.83 (5/6); >2.0: 0.50 (3/6)</p>	<p>Fibrosis (METAVIR F2-F4) FibroQ >1.6: 0.71 (17/24) AAR >0.54: 0.63 (15/24); >1: 1.0 (24/24) APRI >0.5: 0.13 (3/24); >1.2: 0.50 (12/24); >1.5: 0.58 (14/24)</p> <p>Cirrhosis (METAVIR F4) FibroQ >2.6: 0.65 (87/134) AAR >0.75: 0.67 (90/134); >1.0: 0.92 (123/134) APRI >1.0: 0.30 (40/134); >1.5: 0.50 (67/134); >2.0: 0.65 (87/134)</p>	<p>Fibrosis (METAVIR F2-F4) FibroQ >1.6: 0.93 (92/99) AAR >0.54: 0.91 (89/98); >1: 1.0 (12/12) APRI >0.5: 0.84 (113/134); >1.2: 0.87 (77/89); >1.5: 0.86 (63/73)</p> <p>Cirrhosis (METAVIR F4) FibroQ >2.6: 0.12 (6/51) AAR >0.75: 0.10 (5/49); >1.0: 0.15 (2/13) APRI >1.0: 0.06 (6/100); >1.5: 0.07 (5/72); >2.0: 0.06 (3/50)</p>	<p>Fibrosis (METAVIR F2-F4) FibroQ >1.6: 0.41 (17/41) AAR >0.54: 0.36 (15/42); >1: 0.19 (24/128) APRI >0.5: 0.50 (3/6); >1.2: 0.24 (12/51); >1.5: 0.21 (14/67)</p> <p>Cirrhosis (METAVIR F4) FibroQ >2.6: 1.0 (87/87) AAR >0.75: 0.99 (90/91); >1.0: 0.97 (123/127) APRI >1.0: 1.0 (40/40); >1.5: 0.99 (67/68); >2.0: 0.97 (87/90)</p>	<p>Fibrosis (METAVIR F2-F4) FibroQ: 0.78 (0.69-0.88) AAR: 0.73 (0.62-0.85) APRI: 0.63 (0.52-0.74)</p> <p>Cirrhosis (METAVIR F4) FibroQ: 0.79 (0.68-0.90) AAR: 0.78 (0.60-0.97) APRI: 0.63 (0.51-0.76)</p>	Not stated	Fair	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Iacobellis, 2005a ⁶³	<p>Fibrosis (Scheuer F2-F4) Platelet count <140: 0.51 (330/648) Spleen >120 mm: 0.16 (104/648) Nodular liver present: 0.16 (104/648) Portal vein >12 mm: 0.07 (45/648) Spleen >120 mm or platelets <140: 0.33 (214/648) Nodular liver or platelets <140: 0.33 (214/648) Portal vein >12 mm or platelets <140: 0.31 (201/648) Cirrhosis (Scheuer F4) Platelet count <140: 0.82 (67/82) Spleen >120 mm: 0.40 (33/82) Nodular liver present: 0.46 (38/82) Portal vein >12 mm: 0.19 (15/82) Spleen >120 mm or platelets <140: 0.85 (70/82) Nodular liver or platelets <140: 0.90 (74/82) Portal vein >12 mm or platelets <140: 0.83 (68/82)</p>	<p>Fibrosis (Scheuer F2-F4) Platelet count <140: 0.90 (446/495) Spleen >120 mm: 0.96 (475/495) Nodular liver present: 0.97 (480/495) Portal vein >12 mm: 1.0 (494/495) Spleen >120 mm or platelets <140: 0.92 (455/495) Nodular liver or platelets <140: 0.93 (460/495) Portal vein >12 mm or platelets <140: 0.95 (470/495) Cirrhosis (Scheuer F4) Platelet count <140: 0.87 (923/1061) Spleen >120 mm: 0.91 (966/1061) Nodular liver present: 0.93 (987/1061) Portal vein >12 mm: 0.97 (1029/1061) Spleen >120 mm or platelets <140: 0.82 (870/1061) Nodular liver or platelets <140: 0.83 (881/1061) Portal vein >12 mm or platelets <140: 0.85 (902/1061)</p>	<p>Fibrosis (Scheuer F2-F4) Platelet count <140: 0.87 (330/379) [0.96*] Spleen >120 mm: 0.84 (104/124) [0.85*] Nodular liver present: 0.87 (104/119) Portal vein >12 mm: 0.98 (45/46) Spleen >120 mm or platelets <140: 0.84 (214/254) [0.85*] Nodular liver or platelets <140: 0.86 (214/249) Portal vein >12 mm or platelets <140: 0.89 (201/226) [0.90*] Cirrhosis (Scheuer F4) Platelet count <140: 0.33 (67/205) [0.32*] Spleen >120 mm: 0.26 (33/128) Nodular liver present: 0.34 (38/112) [0.33*] Portal vein >12 mm: 0.32 (15/47) [0.35*] Spleen >120 mm or platelets <140: 0.27 (70/261) Nodular liver or platelets <140: 0.33 (74/254) [0.30*] Portal vein >12 mm or platelets <140: 0.30 (68/227) [0.31*]</p>	<p>Fibrosis (Scheuer F2-F4) Platelet count <140: 0.58 (446/764) [0.29*] Spleen >120 mm: 0.47 (475/1019) Nodular liver present: 0.47 (480/1024) Portal vein >12 mm: 0.45 (494/1097) Spleen >120 mm or platelets <140: 0.51 (460/894) [0.52*] Nodular liver or platelets <140: 0.51 (460/894) Portal vein >12 mm or platelets <140: 0.51 (470/917) Cirrhosis (Scheuer F4) Platelet count <140: 0.98 (923/938) Spleen >120 mm: 0.95 (966/1015) Nodular liver present: 0.96 (987/1031) Portal vein >12 mm: 0.94 (1029/1096) Spleen >120 mm or platelets <140: 0.99 (870/882) [0.98*] Nodular liver or platelets <140: 0.99 (881/889) Portal vein >12 mm or platelets <140: 0.98 (902/916)</p>	Not reported	States no external funding	Fair	Same population as Iacobellis 2005b. Unclear if positive combinations of tests based on both tests positive or either test positive

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Iacobellis, 2005b ⁶⁴	<p>Significant fibrosis (Scheuer F3 or F4)AST/ALT ratio \geq1: 0.26 (63/243)</p> <p>Platelet count <140,000: 0.71 (172/243)</p> <p>Globulin/albumin ratio >1: 0.31 (74/243)</p> <p>Platelets and G/A: 0.29 (70/243)</p> <p>Platelets and AST/ALT: 0.19 (47/243)</p> <p>G/A and AST/ALT: 0.11 (27/243)</p> <p>Platelets and G/A and AST/ALT: 0.09 (22/243)</p> <p>AST/ALT and platelets: 0.20 (48/243)</p> <p>APRI >1.5: 0.60 (145/243)</p> <p>Forns' Index >6.9: 0.79 (193/243)</p> <p>Cirrhosis (Scheuer F4) AST/ALT ratio \geq1: 0.32 (25/78)</p> <p>Platelet count <140,000: 0.86 (67/78)</p> <p>Globulin/albumin ratio >1: 0.38 (30/78)</p> <p>Platelets and G/A: 0.34 (27/78)</p> <p>Platelets and AST/ALT: 0.29 (23/78)</p> <p>G/A and AST/ALT: 0.20 (15/78)</p> <p>Platelets and G/A and AST/ALT: 0.17 (13/78)</p> <p>AST/ALT and platelets: 0.03 (2/78)</p> <p>APRI >2: 0.66 (51/78)</p>	<p>Significant fibrosis (Scheuer F3 or F4)</p> <p>AST/ALT ratio \geq1: 0.88 (883/1009)</p> <p>Platelet count <140,000: 0.86 (873/1009)</p> <p>Globulin/albumin ratio >1: 0.85 (858/1009)</p> <p>Platelets and G/A: 0.84 (850/1009)</p> <p>Platelets and AST/ALT: 0.84 (845/1009)</p> <p>G/A and AST/ALT: 0.82 (829/1009)</p> <p>Platelets and G/A and AST/ALT: 0.82 (827/1009)</p> <p>AST/ALT and platelets: 0.84 (845/1009)</p> <p>APRI >1.5: 0.88 (891/1009)</p> <p>Forns' Index >6.9: 0.86 (871/1009)</p> <p>Cirrhosis (Scheuer F4) AST/ALT ratio \geq1: 0.87 (1020/1174)</p> <p>Platelet count <140,000: 0.87 (1018/1174)</p> <p>Globulin/albumin ratio >1: 0.96 (1125/1174)</p> <p>Platelets and G/A: 0.96 (1125/1174)</p> <p>Platelets and AST/ALT: 0.95 (1120/1174)</p> <p>G/A and AST/ALT: 0.95 (1114/1174)</p> <p>Platelets and G/A and AST/ALT: 0.95 (1113/1174)</p> <p>AST/ALT and platelets: 0.96 (1129/1174)</p> <p>APRI >2: 0.90 (1054/1174)</p>	<p>Significant fibrosis (Scheuer F3 or F4)</p> <p>AST/ALT ratio \geq1: 0.33 (63/189)</p> <p>Platelet count <140,000: 0.56 (172/308) [0.77*]</p> <p>Globulin/albumin ratio >1: 0.33 (74/225) [0.58]</p> <p>Platelets and G/A: 0.31 (70/229) [0.91*]</p> <p>Platelets and AST/ALT: 0.22 (47/211) [0.82*]</p> <p>G/A and AST/ALT: 0.13 (27/207) [0.64*]</p> <p>Platelets and G/A and AST/ALT: 0.11 (22/204) [0.88*]</p> <p>AST/ALT and platelets: 0.23 (48/212) [0.74*]</p> <p>APRI >1.5: 0.55 (145/263)</p> <p>Forns' Index >6.9: 0.58 (193/331)</p> <p>Cirrhosis (Scheuer F4) AST/ALT ratio \geq1: 0.14 (25/179)</p> <p>Platelet count <140,000: 0.30 (67/223) [0.29*]</p> <p>Globulin/albumin ratio >1: 0.38 (30/79) [0.23*]</p> <p>Platelets and G/A: 0.36 (27/76) [0.44*]</p> <p>Platelets and AST/ALT: 0.30 (23/77) [0.39*]</p> <p>G/A and AST/ALT: 0.20 (15/75) [0.36*]</p> <p>Platelets and G/A and AST/ALT: 0.18 (13/74) [0.50*]</p> <p>AST/ALT and platelets: 0.04 (2/47) [0.34*]</p> <p>APRI >2: 0.30 (51/171)</p>	<p>Significant fibrosis (Scheuer F3 or F4)AST/ALT ratio \geq1: 0.83 (883/1065)</p> <p>Platelet count <140,000: 0.92 (873/944) [0.93*]</p> <p>Globulin/albumin ratio >1: 0.83 (858/1028) [0.95*]</p> <p>Platelets and G/A: 0.83 (850/1023) [0.995*]</p> <p>Platelets and AST/ALT: 0.81 (845/1041) [0.99*]</p> <p>G/A and AST/ALT: 0.79 (829/1045) [0.98*]</p> <p>Platelets and G/A and AST/ALT: 0.79 (827/1048) [0.997*]</p> <p>AST/ALT and platelets: 0.81 (845/1040) [0.98*]</p> <p>APRI >1.5: 0.90 (891/989)</p> <p>Forns' Index >6.9: 0.95 (871/921)</p> <p>Cirrhosis (Scheuer F4) AST/ALT ratio \geq1: 0.95 (1020/1073)</p> <p>Platelet count <140,000: 0.99 (1018/1029) [0.87*]</p> <p>Globulin/albumin ratio >1: 0.96 (1125/1173) [0.91*]</p> <p>Platelets and G/A: 0.96 (1125/1176) [0.97*]</p> <p>Platelets and AST/ALT: 0.95 (1120/1175) [0.97*]</p> <p>G/A and AST/ALT: 0.95 (1114/1177) [0.98*]</p> <p>Platelets and G/A and AST/ALT: 0.94 (1113/1178) [0.99*]</p> <p>AST/ALT and platelets: 0.94 (1129/1205) [0.96*]</p> <p>APRI >2: 0.98 (1054/1081) [0.98*]</p>	Not reported	Not reported	Fair	Same population as Iacobellis 2005a

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Imbert-Bismut, 2001 ⁶⁵ ; Thabut, 2003 ⁶⁶ ; Le Calvez, 2004 ⁶⁷	Fibrosis (METAVIR F2-F4) (validation sample only) Fibrotest (original 6-marker version) >0.20: 0.92 (55/60); >0.50: 0.75 (45/60); >0.80: 0.38 (23/60)	Fibrosis (METAVIR F2-F4) (validation sample only) Fibrotest (original 6-marker version) >0.20: 0.46 (34/74); >0.50: 0.85 (63/74); >0.80: 0.97 (72/74)	Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) Fibrotest (original 6-marker version) >0.20: 0.89 (106/119) [0.90*] and 0.58 (55/95); >0.50: NR and 0.80 (45/56); >0.80: NR and 0.92 (23/25)	Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) Fibrotest (original 6-marker version) >0.20: NR and 0.87 (34/39); >0.50: NR and 0.81 (63/78) [0.80*]; >0.80: 0.90 (45/50) and 0.66 (72/109) [0.62*]	Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) Fibrotest (original 6-marker version): 0.84 (SD 0.43) and 0.87 (SD 0.34) Fibrotest (original 5-marker version): 0.83 (SD 0.43) and 0.85 (SD 0.34)	Association pour la Recherche sur le Cancer	Fair	Original study deriving the Fibrotest; included 6 (rather than 5) markers (alpha-2 globulin removed for the 5-item Fibrotest). Le Calvez 2004 reported an AUROC of 0.74 for APRI vs. 0.83 for Fibrotest in a sample of 323 patients from this population; sensitivities/specificities not reported. Thabut 2003 reported an AUROC of 0.78 (0.75-0.81) for Forn's Index and 0.84 (0.82-0.86) for Fibrotest for F2-F4 fibrosis/
Imperiale, 2000 ⁶⁸	Whole sample, excluding patients with normal AST and ALT, and excluding patients with heavy alcohol use, respectively Cirrhosis (Hytiroglou 4) AAR ≥1: 0.56 (23/41), 0.56 (23/41) and 0.52 (15/29)	Whole sample, excluding patients with normal AST and ALT, and excluding patients with heavy alcohol use, respectively Cirrhosis (Hytiroglou 4) AAR ≥1: 0.90 (123/136), 0.94 (117/124) and 0.91 (116/128)	Whole sample, excluding patients with normal AST and ALT, and excluding patients with heavy alcohol use, respectively Cirrhosis (Hytiroglou 4) AAR ≥1: 0.64 (23/36), 0.77 (23/30) [0.74*] and 0.56 (15/27)	Whole sample, excluding patients with normal AST and ALT, and excluding patients with heavy alcohol use, respectively Cirrhosis (Hytiroglou 4) AAR ≥1: 0.87 (123/141), 0.87 (117/135) and 0.89 (116/130)	Not reported	Not stated	Fair	
Islam, 2005 ⁶⁹	Cirrhosis (Ishak 5 or 6) Normalized AST/ALT ratio >2.0: 0.67 (13/20) Platelet count <190,000: 0.80 (16/20) APRI >1.0: 0.78 (16/20) GUCI >1.0: 0.80 (16/20)	Cirrhosis (Ishak 5 or 6) Normalized AST/ALT ratio >2.0: 0.80 (127/159) Platelet count <190,000: 0.77 (122/159) APRI >1.0: 0.75 (119/159) GUCI >1.0: 0.78 (124/159)	Cirrhosis (Ishak 5 or 6) Normalized AST >2.0: 0.29 (13/45) [0.30*] Platelet count <190,000: 0.30 (16/53) APRI >1.0: 0.29 (16/56) [0.30*] GUCI >1.0: 0.31 (16/51)	Cirrhosis (Ishak 5 or 6) Normalized AST/ALT ratio >2.0: 0.95 (127/134) Platelet count <190,000: 0.97 (122/126) APRI >1.0: 0.97 (119/123) [0.96*] GUCI >1.0: 0.97 (124/128)	Fibrosis (Ishak ≥3) Normalized AST/ALT ratio: Not reported Platelet count: Not reported APRI: 0.71 (CI not reported) GUCI: 0.72 (CI not reported) Cirrhosis (Ishak 5 or 6) Normalized AST/ALT ratio: Not reported Platelet count: Not reported APRI: 0.83 (CI not reported) GUCI: 0.85 (CI not reported)	Not stated	Fair	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Kaul, 2002 ⁷⁰	Not reported	Not reported	Not reported	Not reported	Derivation and validation samples, respectively Cirrhosis (Scheuer F4) 4-item predictive model: 0.94 (0.91-0.97) and 0.93 (CI not reported)	Not stated	Fair	
Khan, 2008 ⁷¹	Fibrosis (METAVIR F2-F4) APRI >0.5: 0.83 (53/64); >1.5: 0.41 (26/64) Severe fibrosis (METAVIR F3-F4) APRI >0.90: 0.87 (26/30) [0.90*]; >1.75: 0.57 (17/30) [0.56*]	Fibrosis (METAVIR F2-F4) APRI >0.5: 0.57 (32/56); >1.5: 0.95 (53/56) Severe fibrosis (METAVIR F3-F4) APRI >0.90: 0.70 (63/90); >1.75: 0.94 (85/90)	Fibrosis (METAVIR F2-F4) APRI >0.5: 0.69 (53/77) [0.72*]; >1.5: 0.90 (26/29) Severe fibrosis (METAVIR F3-F4) APRI >0.90: 0.49 (26/53); >1.75: 0.77 (17/22) [0.78*]	Fibrosis (METAVIR F2-F4) APRI >0.5: 0.74 (32/43) [0.78*]; >1.5: 0.58 (53/91) Severe fibrosis (METAVIR F3-F4) APRI >0.90: 0.94 (63/67) [0.95*]; >1.75: 0.87 (85/98) [0.86*]	Fibrosis (METAVIR F2-F4) APRI: Not reported Cirrhosis (METAVIR F3-F4) APRI: 0.87 (0.79-0.94)	Not stated	Fair	
Khokhar, 2003 ⁷²	Severe fibrosis (METAVIR F3-F4) AST/ALT ratio >1 and platelet count <150,000: 0.86 (134/157)	Severe fibrosis (METAVIR F3-F4) AST/ALT ratio >1 and platelet count <150,000: 0.90 (98/109)	Severe fibrosis (METAVIR F3-F4) AST/ALT ratio >1 and platelet count <150,000: 0.92 (134/145)	Severe fibrosis (METAVIR F3-F4) AST/ALT ratio >1 and platelet count <150,000: 0.81 (98/121)	Not reported	Not stated	Fair	Reports different diagnostic test accuracy for diagnosis of F0-F2 compared to diagnosis of F3-F4 though they should be evaluating the same thing.

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Koda, 2007 ⁷³	Derivation vs. validation samples, respectively F2 or F3 fibrosis (METAVIR) Fibro Index >1.25: 0.94 (116/123) and 0.97 (58/60); ≥2.25: 0.36 (44/123) and 0.30 (18/60) Forn's Index >4.5: 0.98 (120/123) and 0.93 (56/60); ≥8.7: 0.24 (30/123) and 0.22 (13/60) APRI >0.36: 0.95 (117/123) and 0.98 (59/60); ≥1.85: 0.34 (42/123) and 0.32 (19/60)	Derivation vs. validation samples, respectively F2 or F3 fibrosis (METAVIR) Fibro Index >1.25: 0.40 (70/117) and 0.40 (24/60); ≥2.25: 0.97 (114/117) and 0.97 (58/60) Forn's Index >4.5: 0.26 (30/117) and 0.25 (15/60); ≥8.7: 0.97 (113/117) and 0.98 (59/60) APRI >0.36: 0.26 (31/117) and 0.32 (19/60); ≥0.85: 0.96 (112/117) and 0.92 (55/60)	Derivation vs. validation samples, respectively F2 or F3 fibrosis (METAVIR) Fibro Index >1.25: 0.62 (116/186) and 0.62 (58/94); ≥2.25: 0.94 (44/47) and 0.90 (18/20) Forn's Index >4.5: 0.58 (120/207) and 0.55 (56/101); ≥8.7: 0.88 (30/34) and 0.93 (13/14) APRI >0.36: 0.58 (117/203) and 0.59 (59/100); ≥1.85: 0.89 (42/47) and 0.79 (19/24)	Derivation vs. validation samples, respectively F2 or F3 fibrosis (METAVIR) Fibro Index >1.25: 0.87 (47/54) and 0.92 (24/26); ≥2.25: 0.59 (114/193) and 0.58 (58/100) Forn's Index >4.5: 0.91 (30/33) and 0.79 (15/19); ≥8.7: 0.55 (113/206) and 0.56 (59/106) APRI >0.36: 0.84 (31/37) and 0.95 (19/20); ≥1.85: 0.58 (112/193) and 0.57 (55/96)	Derivation sample, derivation sample (normal ALT only, n=73), validation sample (excluding F4), validation sample (with F4), and validation sample (normal ALT only, n=39), respectively F2-3 or F2-4 fibrosis (METAVIR) Fibro Index: 0.83 (0.78-0.88), 0.77 (0.65-0.89), 0.83 (0.75-0.90), 0.86 (0.81-0.92), and 0.86 (0.74-0.98) Forns Index: 0.79 (0.73-0.84), 0.74 (0.62-0.86), 0.78 (0.70-0.86), 0.84 (0.77-0.90), and 0.81 (0.67-0.96) APRI: 0.79 (0.74-0.85), 0.72 (0.60-0.84), 0.78 (0.69-0.86), 0.82 (0.76-0.88), and 0.88 (0.76-1.0) F3 or F3-4 fibrosis (METAVIR) Fibroindex: 0.81 (0.76-0.87), 0.76 (0.58-0.95), 0.81 (0.73-0.89), 0.85 (0.79-0.91) and 0.93 (0.85-1.0) Forn's Index: 0.77 (0.70-0.83), 0.74 (0.55-0.92), 0.76 (0.68-0.85), 0.83 (0.77-0.89), and 0.90 (0.79-1.0) APRI: 0.80 (0.74-0.86), 0.64 (0.44-0.84), 0.77 (0.69-0.86), 0.81 (0.74-0.88), and 0.92 (0.82-1.0)	Not stated	Fair	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Lackner, 2005 ⁷⁴ and Lackner, 2006 ⁷⁵	Fibrosis (Ishak 3-6) Platelet count <130,000: 0.30 (29/97); <150,000: 0.42 (41/97) APRI ≥0.5: 0.88 (85/97); ≥1.5: 0.44 (43/97) Age-platelet index ≥6: 0.51 (49/97) Severe fibrosis (Ishak 4-6) Cirrhosis Discriminant Score ≥8: 0.10 (5/50) Pohl Index positive: 0.18 (9/50) Cirrhosis (Ishak 5-6) Platelet count <130,000: 0.53 (17/32); <150,000: 0.78 (25/32) [0.77*] APRI ≥1.0: 0.93 (30/32); ≥2.0: 0.55 (18/32) AST/ALT ratio ≥1: 0.36 (12/32) Lok Index ≥0.20: 1.0 (32/32); ≥0.50: 0.44 (14/32)	Fibrosis (Ishak 3-6) Platelet count <130,000: 1.0 (97/97); <150,000: 0.97 (94/97) APRI ≥0.5: 0.44 (43/97); ≥1.5: 0.96 (93/97) Age-platelet index ≥6: 0.93 (90/97) Severe fibrosis (Ishak 4-6) Cirrhosis Discriminant Score ≥8: 1.0 (144/144) Pohl Index positive: 0.98 (141/144) Cirrhosis (Ishak 5-6) Platelet count <130,000: 0.93 (151/162); <150,000: 0.88 (143/162) APRI ≥1.0: 0.70 (113/162); ≥2.0: 0.93 (151/162) AST/ALT ratio ≥1: 0.90 (146/162) Lok Index ≥0.20: 0.58 (94/162); ≥0.50: 0.94 (152/162)	Fibrosis (Ishak 3-6) Platelet count <130,000: 1.0 (29/29); <150,000: 0.93 (41/44) APRI ≥0.5: 0.61 (85/139) [0.60*]; ≥1.5: 0.91 (43/47) Age-platelet index ≥6: 0.88 (49/56) Severe fibrosis (Ishak 4-6) Cirrhosis Discriminant Score ≥8: 1.0 (5/5) Pohl Index positive: 0.75 (9/12) [0.73*] Cirrhosis (Ishak 5-6) Platelet count <130,000: 0.61 (17/28) [0.59*]; <150,000: 0.57 (25/44) [0.56*] APRI ≥1.0: 0.38 (30/79); ≥2.0: 0.62 (18/29) AST/ALT ratio ≥1: 0.43 (12/28) [0.41*] Lok Index ≥0.20: 0.32 (32/100) [0.30*]; ≥0.50: 0.58 (14/24)	Fibrosis (Ishak 3-6) Platelet count <130,000: 0.59 (97/165); <150,000: 0.63 (94/150) APRI ≥0.5: 0.78 (43/55) [0.80*]; ≥1.5: 0.63 (93/147) [0.64*] Age-platelet index ≥6: 0.64 (90/140) [0.66*] Severe fibrosis (Ishak 4-6) Cirrhosis Discriminant Score ≥8: 0.76 (144/189) [0.77*] Pohl Index positive: 0.77 (141/182) Cirrhosis (Ishak 5-6) Platelet count <130,000: 0.91 (151/166); <150,000: 0.95 (143/150) APRI ≥1.0: 0.98 (113/115); ≥2.0: 0.92 (151/165) AST/ALT ratio ≥1: 0.88 (146/166) [0.87*] Lok Index ≥0.20: 1.0 (94/94); ≥0.50: 0.89 (152/170) [0.90*]	Fibrosis (Ishak 3-6) Platelet count: 0.71 (0.64-0.79) APRI: 0.80 (0.73-0.86) Age-platelet index: 0.74 (0.67-0.81) AST/ALT ratio: 0.57 (0.48-0.65) Cirrhosis Discriminant Score: 0.71 (0.63-0.79) Cirrhosis (Ishak 5-6) Platelet count: 0.89 (0.83-0.94) APRI: 0.90 (0.85-0.95) Age-platelet index: 0.91 (0.87-0.96) AST/ALT ratio: 0.73 (0.63-0.83) Cirrhosis Discriminant Score: 0.91 (0.85-0.96)	Not stated, though reports no conflicts of interest to report	Fair	
Leroy, 2008 ⁷⁶	Fibrosis (METAVIR F2-F4) FibroMeter (unclear cutoff): 0.75 (301/400) Fibrotest (unclear cutoff): 0.58 (231/400) Hepascore (unclear cutoff): 0.64 (254/400) APRI (unclear cutoff): 0.39 (155/400)	Fibrosis (METAVIR F2-F4) FibroMeter (unclear cutoff): 0.78 (332/425) Fibrotest (unclear cutoff): 0.85 (363/425) Hepascore (unclear cutoff): 0.80 (341/425) APRI (unclear cutoff): 0.95 (404/425)	Fibrosis (METAVIR F2-F4) FibroMeter (unclear cutoff): 0.76 (301/394) Fibrotest (unclear cutoff): 0.79 (231/293) Hepascore (unclear cutoff): 0.75 (254/338) APRI (unclear cutoff): 0.88 (155/176)	Fibrosis (METAVIR F2-F4) FibroMeter (unclear cutoff): 0.77 (332/431) Fibrotest (unclear cutoff): 0.68 (363/532) Hepascore (unclear cutoff): 0.70 (341/487) APRI (unclear cutoff): 0.62 (404/649)	Fibrosis (METAVIR F2-F4) FibroMeter: 0.84 (0.81-0.87) Fibrotest: 0.80 (0.77-0.83) Hepascore: 0.78 (0.75-0.81) APRI: 0.79 (0.76-0.82) Severe fibrosis (METAVIR F3-F4) FibroMeter: 0.89 (0.87-0.92) Fibrotest: 0.85 (0.82-0.88) Hepascore: 0.84 (0.81-0.87) APRI: 0.84 (0.80-0.87) Cirrhosis (METAVIR F4) FibroMeter: 0.93 (0.90-0.95) Fibrotest: 0.89 (0.86-0.92) Hepascore: 0.89 (0.86-0.93) APRI: 0.86 (0.82-0.90)	French Department of Health	Fair	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Leroy, 2007 ⁷⁷	<p>Fibrosis (METAVIR F2-F4) MP3 >0.20: 0.96 (87/91); >0.30: 0.82 (75/91); >0.40: 0.44 (40/91); >0.50: 0.19 (17/91) APRI >0.50: 0.92 (83/91); >1.0: 0.80 (72/91); >1.5: 0.72 (66/91); >2.0: 0.58 (53/91) Forn's Index >4.2: 0.88 (80/91); >6.9: 0.42 (38/91) Fibrotest >0.22: 0.89 (81/91); >0.32: 0.76 (69/91); >0.59: 0.45 (41/91) Hepascore >0.50: 0.54 (49/91); >0.84: 0.33 (30/91) Severe fibrosis (METAVIR F3-F4) MP3 >0.20: 1.0 (51/51); >0.30: 0.92 (47/51); >0.40: 0.61 (31/51); >0.50: 0.31 (16/51) APRI >0.50: 0.94 (48/51); >1.00: 0.89 (45/51); >1.50: 0.87 (44/51); >2.00: 0.74 (38/51) Forn's Index >4.2: 0.92 (47/51); >6.9: 0.54 (28/51) Fibrotest >0.22: 0.94 (48/51); >0.32: 0.90 (46/51); >0.59: 0.67 (34/51) Hepascore >0.50: 0.76 (39/51); >0.84: 0.47 (24/51)</p>	<p>Fibrosis (METAVIR F2-F4) MP3 >0.20: 0.24 (21/89); >0.30: 0.73 (65/89); >0.40: 0.96 (85/89); >0.50: 0.99 (88/89) APRI >0.50: 0.27 (24/89); >1.0: 0.63 (56/89); >1.5: 0.88 (78/89); >2.0: 0.94 (84/89) Forn's Index >4.2: 0.42 (38/89); >6.9: 0.93 (83/89) Fibrotest >0.22: 0.53 (47/89); >0.32: 0.74 (66/89); >0.59: 0.90 (80/89) Hepascore >0.50: 0.84 (75/89); >0.84: 0.92 (82/89) Severe fibrosis (METAVIR F3-F4) MP3 >0.20: .20 (26/129); >0.30: 0.59 (76/129); >0.40: 0.90 (116/129); >0.50: 0.98 (127/129) APRI >0.50: 0.22 (28/129); >1.00: 0.54 (69/129); >1.50: 0.75 (96/129); >2.00: 0.84 (108/129) Forn's Index >4.2: 0.34 (44/129); >6.9: 0.87 (112/129) Fibrotest >0.22: 0.42 (54/129); >0.32: 0.64 (83/129); >0.59: 0.88 (114/129) Hepascore >0.50: 0.81 (105/129); >0.84: 0.90 (116/129)</p>	<p>Fibrosis (METAVIR F2-F4) MP3 >0.20: 0.56 (87/155); >0.30: 0.76 (75/99); >0.40: 0.91 (40/44); >0.50: 0.94 (17/18) APRI >0.50: 0.56 (83/148); >1.0: 0.69 (72/105); >1.5: 0.86 (66/77); >2.0: 0.91 (53/58) Forn's Index >4.2: 0.61 (80/131); >6.9: 0.86 (38/44) Fibrotest >0.22: 0.66 (81/123); >0.32: 0.75 (69/92); >0.59: 0.82 (41/50) Hepascore >0.50: 0.78 (49/63); >0.84: 0.81 (30/37) Severe fibrosis (METAVIR F3-F4)MP3 >0.20: 0.33 (51/154); >0.30: 0.47 (47/100) [0.48*]; >0.40: 0.70 (31/44); >0.50: 0.89 (16/18) APRI >0.50: 0.32 (48/149); >1.00: 0.43 (45/105); >1.50: 0.57 (44/77); >2.00: 0.64 (38/59) Forn's Index >4.2: 0.36 (47/132) [0.35*]; >6.9: 0.62 (28/45) Fibrotest >0.22: 0.39 (48/123); >0.32: 0.50 (46/92); >0.59: 0.69 (34/49) [0.68*] Hepascore >0.50: 0.62 (39/63); >0.84: 0.65 (24/37)</p>	<p>Fibrosis (METAVIR F2-F4) MP3 >0.20: 0.84 (21/25); >0.30: 0.80 (65/81); >0.40: 0.62 (85/136); >0.50: 0.54 (88/162) APRI >0.50: 0.75 (24/32); >1.0: 0.75 (56/75); >1.5: 0.76 (78/103); >2.0: 0.69 (84/122) Forn's Index >4.2: 0.78 (38/49); >6.9: 0.61 (83/136) Fibrotest >0.22: 0.82 (47/57); >0.32: 0.75 (66/88); >0.59: 0.62 (80/130) Hepascore >0.50: 0.64 (75/117); >0.84: 0.57 (82/143) Severe fibrosis (METAVIR F3-F4) MP3 >0.20: 1.0 (26/26); >0.30: 0.95 (76/80); >0.40: 0.85 (116/136); >0.50: 0.78 (127/162) APRI >0.50: 0.90 (28/31); >1.00: 0.92 (69/75) [0.93*]; >1.50: 0.93 (96/103) [0.94*]; >2.00: 0.89 (108/121) [0.92*] Forn's Index >4.2: 0.92 (44/48) [0.91*]; >6.9: 0.83 (112/135) Fibrotest >0.22: 0.95 (54/57); >0.32: 0.94 (83/88); >0.59: 0.87 (114/131) Hepascore >0.50: 0.90 (105/117); >0.84: 0.81 (116/143)</p>	<p>Whole sample and excluding patients with biopsy <15 mm or <7 portal tracts (n=161) Fibrosis (METAVIR F2-F4) MP3: 0.84 (0.78-0.90) and 0.83 (CI not reported) APRI: 0.81 (0.74-0.88) and 0.80 (CI not reported) Forn's Index: 0.78 (0.71-0.85) and 0.78 (CI not reported) Fibrotest: 0.84 (0.79-0.90) and 0.83 (CI not reported) Hepascore: 0.79 (0.72-0.85) and 0.78 (CI not reported) Fibrometer: 0.86 (0.80-0.91) and 0.85 (CI not reported) Severe fibrosis (METAVIR F3-F4) MP3: 0.88 (0.82-0.93) and 0.89 (CI not reported) APRI: 0.82 (0.74-0.90) and 0.81 (CI not reported)Forn's Index: 0.78 (0.71-0.87) and 0.80 (CI not reported) Fibrotest: 0.87 (0.81-0.93) and 0.86 (CI not reported) Hepascore: 0.85 (0.80-0.92) and 0.85 (CI not reported) Fibrometer: 0.91 (0.86-0.96) and 0.90 (CI not reported)</p>	Direction de la Recherche Clinique, CHU de Grenoble, France	Fair	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Leroy, 2004 ⁷⁸	Fibrosis (METAVIR F2-F4) MP3 score >0.20: 0.91 (76/84); >0.30: 0.65 (55/84); >0.40: 0.35 (29/84); >0.50: 0.17 (14/84) PIIIP >6 ng/ml: 0.47 (39/84) Hyaluronic acid >8 g/ml: 0.43 (36/84) TIMP-1: Not reported Severe fibrosis (METAVIR F3-F4) MP3 score >0.20: 0.94 (34/36); >0.30: 0.85 (31/36); >0.40: 0.58 (21/36); >0.50: 0.26 (9/36) PIIIP >5 ng/ml: 0.92 (33/36) Hyaluronic acid >36 ng/ml: 0.86 (31/36) TIMP-1 >1300 ng/ml: 0.75 (27/36)	Fibrosis (METAVIR F2-F4) MP3 score >0.20: 0.35 (36/104); >0.30: 0.85 (88/104); >0.40: 0.96 (100/104); >0.50: 0.99 (103/104) PIIIP >6 ng/ml: 0.93 (95/104) Hyaluronic acid >8 g/ml: 0.90 (94/104) TIMP-1: Not reported Severe fibrosis (METAVIR F3-F4) MP3 score >0.20: 0.28 (43/152); >0.30: 0.74 (112/152); >0.40: 0.92 (140/152); >0.50: 0.97 (147/152) PIIIP >5 ng/ml: 0.76 (116/152) Hyaluronic acid >36 ng/ml: 0.70 (106/152) TIMP-1 >1300 ng/ml: 0.70 (106/152)	Fibrosis (METAVIR F2-F4) MP3 score >0.20: 0.53 (76/144); >0.30: 0.77 (55/71) [0.76*]; >0.40: 0.88 (29/33) [0.91*]; >0.50: 0.93 (14/15) [1.0*] PIIIP >6 ng/ml: 0.85 (39/46) Hyaluronic acid >8 g/ml: 0.78 (36/46) TIMP-1: Not reported Severe fibrosis (METAVIR F3-F4) MP3 score >0.20: 0.24 (34/143); >0.30: 0.44 (31/71) [0.43*]; >0.40: 0.64 (21/33) [0.66*]; >0.50: 0.64 (9/14) [0.77*] PIIIP >5 ng/ml: 0.48 (33/69) Hyaluronic acid >36 ng/ml: 0.40 (31/77) TIMP-1 >1300 ng/ml: 0.37 (27/73)	Fibrosis (METAVIR F2-F4) MP3 score >0.20: 0.82 (36/44) [0.88*]; >0.30: 0.75 (88/117); >0.40: 0.65 (100/155); >0.50: 0.60 (103/173) PIIIP >6 ng/ml: 0.68 (95/140) Hyaluronic acid >8 g/ml: 0.66 (94/142) TIMP-1: Not reported Severe fibrosis (METAVIR F3-F4) MP3 score >0.20: 0.96 (43/45) [0.95*]; >0.30: 0.96 (112/117) [0.95*]; >0.40: 0.90 (140/155) [0.91*]; >0.50: 0.85 (147/173) PIIIP >5 ng/ml: 0.97 (116/119) Hyaluronic acid >36 ng/ml: 0.95 (106/111) TIMP-1 >1300 ng/ml: 0.92 (106/115)	Fibrosis (METAVIR F2-F4) MP3 score: 0.82 (CI's not provided) PIIIP: 0.77 (CI's not provided) Hyaluronic acid: 0.74 (CI's not provided) Severe fibrosis (METAVIR F3-F4) MP3 score: 0.88 (CI's not provided) PIIIP: 0.88 (CI's not provided) Hyaluronic acid: 0.82 (CI's not provided)	DRRC, CHU de Grenoble	Fair	
Liu, 2006 ⁷⁹	Fibrosis (METAVIR F2-F4) APRI >0.40: 0.48 (10/21); >0.50: 0.29 (6/21); >1.5: 0.0 (0/21) Age-platelet index: >4.00: 0.52 (11/21); >6.00: 0.19 (4/21) AST/ALT ratio >0.60: 0.86 (18/21); >1.00: 0.45 (10/21) Splenic artery pulsatility index >0.85: 0.98 (20/21); >1.05: 0.67 (14/21)	Fibrosis (METAVIR F2-F4) APRI >0.40: 0.75 (44/58); >0.50: 0.94 (55/58); >1.5: 1.0 (58/58) Age-platelet index: >4.00: 0.77 (45/58); >6.00: 0.86 (50/58) AST/ALT ratio >0.60: 0.05 (3/58); >1.00: 0.62 (36/58) Splenic artery pulsatility index >0.85: 0.39 (23/58); >1.05: 0.90 (52/58)	Fibrosis (METAVIR F2-F4) APRI >0.40: 0.41 (10/24); >0.50: 0.67 (6/9) [0.63*]; >1.5: 0.0 (0/0) Age-platelet index: >4.00: 0.46 (11/24) [0.45*]; >6.00: 0.33 (4/12) [0.34*] AST/ALT ratio >0.60: 0.25 (18/73); >1.00: 0.31 (10/32) [0.30*] Splenic artery pulsatility index >0.85: 0.36 (20/55) [0.37*]; >1.05: 0.70 (14/20)	Fibrosis (METAVIR F2-F4) APRI >0.40: 0.80 (44/55); >0.50: 0.79 (55/70) [0.78*]; >1.5: 0.73 (58/79) [1.0*] Age-platelet index: >4.00: 0.82 (45/55); >6.00: 0.75 (50/67) AST/ALT ratio >0.60: 0.50 (3/6); >1.00: 0.77 (36/47) [0.76*] Splenic artery pulsatility index >0.85: 0.96 (23/24) [0.98*]; >1.05: 0.88 (52/59)	Fibrosis (METAVIR F2-F4) APRI: 0.67 (0.54-0.81) Age-platelet index: 0.64 (0.51-0.77) AST/ALT ratio: 0.50 (0.35-0.66) Splenic artery pulsatility index: 0.86 (0.78-0.95)	National Taiwan University Hospital, National Science Council, Department of Health, Executive Yuan, Taiwan	Fair	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Loaeza-del-Castillo, 2008 ⁸⁰	Fibrosis (METAVIR F2-F4) APRI >0.64: 0.75 (62/83) Severe fibrosis (METAVIR F3-F4) APRI >0.7532: 0.78 (52/67) Cirrhosis (METAVIR F4) APRI >0.7532: 0.89 (42/47)	Fibrosis (METAVIR F2-F4) APRI >0.64: 0.68 (55/81) Severe fibrosis (METAVIR F3-F4) APRI >0.7532: 0.75 (73/97) Cirrhosis (METAVIR F4) APRI >0.7532: 0.71 (83/117)	Fibrosis (METAVIR F2-F4) APRI >0.64: 0.70 (62/88) Severe fibrosis (METAVIR F3-F4) APRI >0.7532: 0.68 (52/76) Cirrhosis (METAVIR F4) APRI >0.7532: 0.55 (42/76)	Fibrosis (METAVIR F2-F4) APRI >0.64: 0.72 (55/76) Severe fibrosis (METAVIR F3-F4) APRI >0.7532: 0.83 (73/88) Cirrhosis (METAVIR F4) APRI >0.7532: 0.94 (83/88)	Fibrosis (METAVIR F2-F4) APRI: 0.78 (0.70-0.85) Severe fibrosis (METAVIR F3-F4) APRI: 0.80 (0.74-0.87) Cirrhosis (METAVIR F4) APRI: 0.83 (0.76-0.90)	Not stated	Fair	
Lo Iacono, 1998 ⁸¹	Severe fibrosis (Scheuer F3 or F4) sICAM-1 >520 ng/ml: 0.64 sVCAM-1 >1208 ng/ml: 1.00 PIIIP >10.57 mcg/ml: 0.89	Severe fibrosis (Scheuer F3 or F4) sICAM-1 >520 ng/ml: 0.56 sVCAM-1 >1208 ng/ml: 0.85 PIIIP >10.57 mcg/ml: 0.52	Not Reported	Not Reported	Severe fibrosis (Scheuer F3 or F4) sICAM-1: 0.75 (CI not reported) sVCAM-1 >1208 ng/ml: 0.96 (CI not reported) PIIIP >10.57 mcg/ml: 0.73 (CI not reported)	INSALUD and Comunidad Autonoma de Madrid	Fair	Unable to generate 2x2 table

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Lok, 2005 ⁸²	Derivation and external validation samples, respectively Cirrhosis (Ishak 5-6)Lok Index ≥ 0.2 : 0.92 (284/309) and 0.98 (39/40); ≥ 0.5 : 0.54 (167/309) and 0.53 (21/40) Sample (n=403) Platelet count <150,000: 0.76 (146/191) AST/ALT ratio >1: 0.41 (79/191) INR >1: 0.79 (150/191)	Derivation and external validation samples, respectively Cirrhosis (Ishak 5-6)Lok Index ≥ 0.2 : 0.30 (142/474) and 0.53 (119/225); ≥ 0.5 : 0.85 (403/474) and 0.95 (213/225) Sample (n=403) Platelet count <150,000: 0.71 (150/212)AST/ALT ratio >1: 0.80 (169/212) INR >1: 0.74 (157/212)	Derivation and external validation samples, respectively Cirrhosis (Ishak 5-6) Lok Index ≥ 0.2 : 0.46 (284/616) and 0.27 (39/145); ≥ 0.5 : 0.70 (167/238) and 0.64 (21/33) Sample (n=403) Platelet count <150,000: 0.70 (146/208) AST/ALT ratio >1: 0.65 (79/122) INR >1: 0.73 (150/205)	Derivation and external validation samples, respectively Cirrhosis (Ishak 5-6) Lok Index ≥ 0.2 : 0.85 (142/167) [0.86*] and 0.99 (119/120); ≥ 0.5 : 0.74 (403/545) and 0.92 (213/232) Sample (n=403)Platelet count <150,000: 0.77 (150/195) AST/ALT ratio >1: 0.60 (169/281) INR >1: 0.79 (157/198)	Derivation, internal validation, external validation, fragmented biopsies, nonfragmented biopsies, biopsy <1.5 cm, biopsy 1.5-2.5 cm, and biopsy >2.5 cm (biopsy subgroups from derivation + internal validation samples), respectivelyCirrhosis (Ishak 5-6)Lok Index: 0.78 (0.74-0.81), 0.81 (0.75-0.86), and 0.91 (0.84-0.97), 0.72 (0.66-0.78), 0.80 (0.76-0.83), 0.77 (0.72-0.82), 0.80 (0.76-0.84), and 0.79 (0.70-0.88)Platelet count: 0.73 (0.69-0.77), 0.78 (0.72-0.84), not reported, 0.68 (0.61-0.74), 0.75 (0.71-0.79), 0.74 (0.68-0.79), 0.75 (0.70-0.79), and 0.76 (0.66-0.84)AST/ALT ratio: 0.66 (0.62-0.70), 0.64 (0.57-0.71), not reported, 0.60 (0.53-0.66), 0.67 (0.63-0.71), 0.64 (0.58-0.70), 0.66 (0.61-0.71), and 0.64 (0.54-0.76)APRI: 0.70 (0.66-0.75), 0.79 (0.74-0.85), not reported, 0.70 (0.64-0.76), 0.73 (0.69-0.77), 0.74 (0.68-0.79), 0.74 (0.70-0.79), and 0.67 (0.57-0.78)	National Institute of Diabetes and Digestive and Kidney Diseases, and other federal agencies	Fair	HALT-C cohort also evaluated in Fontana, 2008. External validation sample is the same population evaluated in Wai, 2003.

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Luo, 2002 ⁸³	Cirrhosis (Scheuer F4) AST/ALT ratio ≥ 1 : 0.39 (9/23) Globulin/albumin ratio ≥ 1 : 0.43 (10/23) Platelet count $\leq 140,000$: 0.83 (19/23) AST/ALT ratio ≥ 1 + globulin/albumin ratio ≥ 1 : 0.39 (9/23) AST/ALT ratio ≥ 1 + platelet count $< 140,000$: 0.26 (6/23) Globulin/albumin ratio ≥ 1 + platelet count $\leq 140,000$: 0.39 (9/23)	Cirrhosis (Scheuer F4)AST/ALT ratio ≥ 1 : 0.92 (81/88) Globulin/albumin ratio ≥ 1 : 0.98 (86/88) Platelet count $\leq 140,000$: 0.85 (75/88) AST/ALT ratio ≥ 1 + globulin/albumin ratio ≥ 1 : 1.0 (88/88) AST/ALT ratio ≥ 1 + platelet count $< 140,000$: 0.98 (86/88) Globulin/albumin ratio ≥ 1 + platelet count $\leq 140,000$: 1.0 (88/88)	Cirrhosis (Scheuer F4) AST/ALT ratio ≥ 1 : 0.56 (9/16) Globulin/albumin ratio ≥ 1 : 0.83 (10/12) Platelet count $\leq 140,000$: 0.59 (19/32) AST/ALT ratio ≥ 1 + globulin/albumin ratio ≥ 1 : 1.0 (9/9) AST/ALT ratio ≥ 1 + platelet count $< 140,000$: 0.75 (6/8) Globulin/albumin ratio ≥ 1 + platelet count $\leq 140,000$: 1.0 (9/9)	Cirrhosis (Scheuer F4) AST/ALT ratio ≥ 1 : 0.85 (81/95) Globulin/albumin ratio ≥ 1 : 0.87 (86/99) Platelet count $\leq 140,000$: 0.95 (75/79)AST/ALT ratio ≥ 1 + globulin/albumin ratio ≥ 1 : 0.86 (88/102) AST/ALT ratio ≥ 1 + platelet count $< 140,000$: 0.83 (86/103) Globulin/albumin ratio ≥ 1 + platelet count $\leq 140,000$: 0.86 (88/102)	Not reported	Taipei Veterans General Hospital	Fair	
Martinez, 2011 ⁸⁴	Fibrosis (METAVIR F2-F4) Forn's Index > 4.2 : 0.89 (204/229); > 6.9 : 0.44 (101/229) APRI > 0.5 : 0.91 (209/229); > 1.5 : 0.47 (107/220) Simplified ELF index > -0.45 : 0.90 (207/229); > 1.07 : 0.47 (108/229) Severe fibrosis (METAVIR F3-F4) FIB-4 > 1.45 : 0.92 (142/155); > 3.25 : 0.54 (83/155) Cirrhosis (METAVIR F4) APRI > 1 : 0.82 (102/124); > 2 : 0.49 (61/124) Simplified ELF index > 0.06 : 0.90 (111/124); > 1.73 : 0.52 (65/124)	Fibrosis (METAVIR F2-F4) Forn's Index > 4.2 : 0.58 (64/111); > 6.9 : 0.93 (103/111) APRI > 0.5 : 0.50 (56/111) [0.51*]; > 1.5 : 0.93 (103/111) Simplified ELF index > -0.45 : 0.52 (58/111); > 1.07 : 0.90 (100/111) Severe fibrosis (METAVIR F3-F4) FIB-4 > 1.45 : 0.64 (118/185); > 3.25 : 0.91 (168/185) Cirrhosis (METAVIR F4) APRI > 1 : 0.74 (159/216); > 2 : 0.91 (196/216) Simplified ELF index > 0.06 : 0.53 (114/216); > 1.73 : 0.90 (195/216)	Fibrosis (METAVIR F2-F4) Forn's Index > 4.2 : 0.81 (204/251); > 6.9 : 0.93 (101/109) APRI > 0.5 : 0.79 (209/264); > 1.5 : 0.93 (107/115) Simplified ELF index > -0.45 : 0.80 (207/260); > 1.07 : 0.91 (108/119) Severe fibrosis (METAVIR F3-F4) FIB-4 > 1.45 : 0.68 (142/209) [0.74*]; > 3.25 : 0.83 (83/100) Cirrhosis (METAVIR F4) APRI > 1 : 0.64 (102/159); > 2 : 0.75 (61/81) Simplified ELF index > 0.06 : 0.52 (111/213); > 1.73 : 0.76 (65/86)	Fibrosis (METAVIR F2-F4) Forn's Index > 4.2 : 0.72 (64/89); > 6.9 : 0.45 (103/231) APRI > 0.5 : 0.74 (56/76); > 1.5 : 0.46 (103/225) Simplified ELF index > -0.45 : 0.73 (58/80); > 1.07 : 0.45 (100/221) Severe fibrosis (METAVIR F3-F4) FIB-4 > 1.45 : 0.90 (118/131); > 3.25 : 0.70 (168/240) [0.77*] Cirrhosis (METAVIR F4) APRI > 1 : 0.88 (159/181); > 2 : 0.76 (196/259) Simplified ELF index > 0.06 : 0.90 (114/127); > 1.73 : 0.77 (195/254)	Fibrosis (METAVIR F2-F4) Forn's Index: 0.83 (0.78-0.87) APRI: 0.83 (0.79-0.88) FIB-4: 0.85 (0.81-0.89) Simplified ELF index : 0.81 (0.76-0.86) Severe fibrosis (METAVIR F3-F4) Forn's Index: 0.85 (0.81-0.89) APRI: 0.86 (0.82-0.90) FIB-4: 0.87 (0.83-0.91) Simplified ELF index : 0.83 (0.79-0.87) Cirrhosis (METAVIR F4) Forn's Index: 0.87 (0.83-0.91) APRI: 0.86 (0.82-0.90) FIB-4: 0.89 (0.85-0.92) Simplified ELF index: 0.82 (0.78-0.87)	Instituto de Salud Carlos III, Direccion General de Investigacion Cientifica y Tecnica	Fair	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
McHutchison, 2000 ⁸⁵	Severe fibrosis (Knodell 3 or 4) Hyaluronic acid >60 mcg/l: 0.88 (123/139); >80 mcg/l: 0.83 (115/139); >100 mcg/l: 0.76 (105/139); >110 mcg/l: 0.73 (101/139) Cirrhosis (Knodell 4) Hyaluronic acid >60 mcg/l: 0.98 (78/80); >80 mcg/l: 0.89 (74/80); >100 mcg/l: 0.89 (71/80); >110 mcg/l: 0.88 (70/80)	Severe fibrosis (Knodell 3 or 4) Hyaluronic acid >60 mcg/l: 0.59 (206/347); >80 mcg/l: 0.72 (250/347); >100 mcg/l: 0.82 (284/347); >110 mcg/l: 0.83 (288/347) Cirrhosis (Knodell 4) Hyaluronic acid >60 mcg/l: 0.54 (220/406); >80 mcg/l: 0.66 (268/406); >100 mcg/l: 0.76 (309/406); >110 mcg/l: 0.78 (316/406)	Severe fibrosis (Knodell 3 or 4) Hyaluronic acid >60 mcg/l: 0.47 (123/264); >80 mcg/l: 0.54 (115/212); >100 mcg/l: 0.63 (105/168); >110 mcg/l: 0.63 (101/160) Cirrhosis (Knodell 4) Hyaluronic acid >60 mcg/l: 0.30 (78/264); >80 mcg/l: 0.35 (74/212); >100 mcg/l: 0.42 (71/168); >110 mcg/l: 0.44 (70/160)	Severe fibrosis (Knodell 3 or 4) Hyaluronic acid >60 mcg/l: 0.93 (206/222); >80 mcg/l: 0.91 (250/274); >100 mcg/l: 0.89 (284/318); >110 mcg/l: 0.88 (288/326) Cirrhosis (Knodell 4) Hyaluronic acid >60 mcg/l: 0.99 (220/222); >80 mcg/l: 0.98 (268/274); >100 mcg/l: 0.97 (309/318); >110 mcg/l: 0.97 (316/326)	Not reported	Not reported	Fair	
Metwally, 2007 ⁸⁶	Severe fibrosis (METAVIR F3-F4) 3-item predictive index ≥2: 0.88 (28/32) [0.87*]; ≥4: 0.47 (15/32)	Severe fibrosis (METAVIR F3-F4) 3-item predictive index ≥2: 0.69 (72/105); ≥4: 0.99 (104/105)	Severe fibrosis (METAVIR F3-F4) 3-item predictive index ≥2: 0.46 (28/61); ≥4: 0.94 (15/16)	Severe fibrosis (METAVIR F3-F4) 3-item predictive index ≥2: 0.95 (72/76); ≥4: 0.86 (104/121)	Severe fibrosis (METAVIR F3-F4) 3-item predictive index: 0.88 (CI not reported)	Not reported	Fair	
Murawaki, 2001a ⁸⁸	F2 or F3 fibrosis (Desmet) Type-IV collagen >110: 0.77 (60/78) Platelet count <160,000: 0.68 (53/78) Type-IV collagen >110 and platelet count <160,000: 0.53 (41/78) Type IV collagen >110 or platelet count <160,000: 0.91 (71/78) F3 fibrosis (Desmet) Type-IV collagen >130: 0.66 (25/38) Platelet count <140,000: 0.68 (26/38) Type-IV collagen >130 and platelet count <140,000: 0.47 (18/38) Type-IV collagen >130 or platelet count <140,000: 0.87 (33/38)	F2 or F3 fibrosis (Desmet) Type-IV collagen >110: 0.74 (64/87) [0.73*] Platelet count <160,000: 0.71 (62/87) Type-IV collagen >110 and platelet count <160,000: 0.93 (81/87) Type IV collagen >110 or platelet count <160,000: 0.52 (45/87) F3 fibrosis (Desmet) Type-IV collagen >130: 0.75 (95/127) Platelet count <140,000: 0.74 (94/127) Type-IV collagen >130 and platelet count <140,000: 0.89 (113/127) Type-IV collagen >130 or platelet count <140,000: 0.49 (62/127)	F2 or F3 fibrosis (Desmet) Type-IV collagen >110: 0.72 (60/83) Platelet count <160,000: 0.68 (53/78) Type-IV collagen >110 and platelet count <160,000: 0.87 (41/47) Type IV collagen >110 or platelet count <160,000: 0.63 (71/113) F3 fibrosis (Desmet) Type-IV collagen >130: 0.44 (25/57) Platelet count <140,000: 0.44 (26/59) Type-IV collagen >130 and platelet count <140,000: 0.56 (18/32) Type-IV collagen >130 or platelet count <140,000: 0.34 (33/98) [0.40*]	F2 or F3 fibrosis (Desmet) Type-IV collagen >110: 0.78 (64/82) Platelet count <160,000: 0.71 (62/87) Type-IV collagen >110 and platelet count <160,000: 0.69 (81/118) Type IV collagen >110 or platelet count <160,000: 0.87 (45/52) [0.86*] F3 fibrosis (Desmet) Type-IV collagen >130: 0.88 (95/108) Platelet count <140,000: 0.89 (94/106) Type-IV collagen >130 and platelet count <140,000: 0.85 (113/133) Type-IV collagen >130 or platelet count <140,000: 0.93 (62/67) [0.94*]	Not reported	Viral Hepatitis Research Foundation of Japan	Fair	Excluded patients with cirrhosis. Sample appears to overlap with Murawaki 2001b.

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Murawaki, 2001b ⁵⁷	F2 or F3 fibrosis (Desmet) PIVNP >6.0: 0.70 (57/81) PIIIP >0.80: 0.74 (60/81) Hyaluronic acid >50 ng/ml: 0.75 (61/81) MMP-2 >550 ng/ml: 0.75 (61/81) TIMP-1 >160 ng/ml: 0.79 (64/81) ALT >80 IU/l: 0.60 (49/81) Hyaluronic acid >50 ng/ml and MMP-2 >550 ng/ml: 0.60 (49/81) [0.61*] Hyaluronic acid >50 ng/ml or MMP-2 >550 ng/ml: 0.86 (70/81) F3 fibrosis (Desmet) PIVNP >6.5: 0.63 (25/40) PIIIP >0.90: 0.65 (26/40) [0.64*] Hyaluronic acid >70 ng/ml: 0.50 (20/40) MMP-2 >575 ng/ml: 0.68 (27/40) TIMP-1 >170 ng/ml: 0.82 (33/40) [0.83*]	F2 or F3 fibrosis (Desmet) PIVNP >6.0: 0.73 (64/88) PIIIP >0.80: 0.52 (46/88) Hyaluronic acid >50 ng/ml: 0.80 (70/88) MMP-2 >550 ng/ml: 0.70 (62/88) TIMP-1 >160 ng/ml: 0.56 (49/88) ALT >80 IU/l: 0.66 (58/88) Hyaluronic acid >50 ng/ml and MMP-2 >550 ng/ml: 0.84 (74/88) Hyaluronic acid >50 ng/ml or MMP-2 >550 ng/ml: 0.60 (53/88) F3 fibrosis (Desmet) PIVNP >6.5: 0.73 (94/129) PIIIP >0.90: 0.59 (76/129) Hyaluronic acid >70 ng/ml: 0.79 (102/129) MMP-2 >575 ng/ml: 0.69 (89/129) TIMP-1 >170 ng/ml: 0.54 (70/129)	F2 or F3 fibrosis (Desmet) PIVNP >6.0: 0.70 (57/81) [0.71*] PIIIP >0.80: 0.59 (60/102) [0.60*] Hyaluronic acid >50 ng/ml: 0.77 (61/79) MMP-2 >550 ng/ml: 0.70 (61/87) [0.72*] TIMP-1 >160 ng/ml: 0.62 (64/103) [0.63*] ALT >80 IU/l: 0.62 (49/79) Hyaluronic acid >50 ng/ml and MMP-2 >550 ng/ml: 0.78 (49/63) [0.80*] Hyaluronic acid >50 ng/ml or MMP-2 >550 ng/ml: 0.67 (70/105) [0.69*] F3 fibrosis (Desmet) PIVNP >6.5: 0.42 (25/60) [0.41*] PIIIP >0.90: 0.33 (26/79) Hyaluronic acid >70 ng/ml: 0.43 (20/47) [0.42*] MMP-2 >575 ng/ml: 0.40 (27/67) [0.44*] TIMP-1 >170 ng/ml: 0.36 (33/92) [0.34*]	F2 or F3 fibrosis (Desmet) PIVNP >6.0: 0.73 (64/88) [0.72*] PIIIP >0.80: 0.69 (46/67) [0.68*] Hyaluronic acid >50 ng/ml: 0.78 (70/90) MMP-2 >550 ng/ml: 0.76 (62/82) [0.73*] TIMP-1 >160 ng/ml: 0.74 (49/66) [0.73*] ALT >80 IU/l: 0.64 (58/90) [0.65*] Hyaluronic acid >50 ng/ml and MMP-2 >550 ng/ml: 0.70 (74/106) [0.68*] Hyaluronic acid >50 ng/ml or MMP-2 >550 ng/ml: 0.83 (53/64) [0.81*] F3 fibrosis (Desmet) PIVNP >6.5: 0.86 (94/109) [0.87*] PIIIP >0.90: 0.84 (76/90) Hyaluronic acid >70 ng/ml: 0.84 (102/122) MMP-2 >575 ng/ml: 0.87 (89/102) [0.85*] TIMP-1 >170 ng/ml: 0.91 (70/77)	Not reported	Ministry of Education, Science, and Culture of Japan and Viral Hepatitis Research Foundation of Japan	Fair	Excluded patients with cirrhosis. Sample appears to overlap with Murawaki 2001a.
Myers, 2003 ⁸⁹	Fibrosis (METAVIR F2-F4) Fibrotest >0.20: 0.88 (115/131); >0.70: 0.50 (66/131) Platelet count <150,000: 0.34 (45/131) Prothrombin time <80% predicted: 0.15 (20/131); 100% predicted: Not reported Age-platelet index >2.0 or >7.0: Not reported Severe fibrosis (METAVIR F4) Fibrotest >0.70: Not reported; >0.80: Not reported	Fibrosis (METAVIR F2-F4) Fibrotest >0.20: 0.56 (107/192); >0.70: 0.95 (183/192) Platelet count <150,000: 0.89 (170/192) Prothrombin time <80% predicted: 0.96 (185/192); 100% predicted: Not reported Age-platelet index >2.0 or >7.0: Not reported Severe fibrosis (METAVIR F3-F4) Fibrotest >0.70: Not reported; >0.80: Not reported	Fibrosis (METAVIR F2-F4) Fibrotest >0.20: 0.58 (115/200); >0.70: 0.88 (66/75) Platelet count <150,000: 0.67 (45/67) Prothrombin time <80% predicted: 0.74 (20/27); 100% predicted: Not reported Age-platelet index >2.0: Not reported; >7.0: 0.69 (n/N not available) Severe fibrosis (METAVIR F3-F4) Fibrotest >0.70: Not reported; >0.80: 0.73 (n/N not available)	Fibrosis (METAVIR F2-F4) Fibrotest >0.20: 0.87 (107/123); >0.70: 0.74 (183/248) Platelet count <150,000: 0.66 (170/256) Prothrombin time <80% predicted: 0.62 (185/296); 100% predicted: 0.71 (n/N not available) Age-platelet index >2.0: 0.69; >7.0: 0.86 (n/N's not available) Severe fibrosis (METAVIR F3-F4) Fibrotest >0.70: 0.93 (n/N not available); >0.80: Not reported	Fibrosis (METAVIR F2-F4) Fibrotest: 0.84 (0.82-0.86) 7-item index: 0.84 (0.82-0.86) Platelet count: 0.67 (0.64-0.70) Prothrombin time: 0.66 (0.63-0.69) Age-platelet index: 0.72 (0.69-0.75) Severe fibrosis (METAVIR F3-F4) Fibrotest: 0.92 (0.90-0.94) 7-item index: 0.94 (0.92-0.96) Platelet count: 0.74 (0.70-0.78) Prothrombin time: 0.76 (0.72-0.80) Age-platelet index: 0.81 (0.78-0.84)	Canadian Association for the Study of the Liver, Schering Canada, Royal College of Physicians and Surgeons of Canada, and Association Pour la Recherche sur les Maladies Hepatiques Viroles	Fair	Same population as Myers, 2002

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Myers, 2002 ⁹⁰	Fibrosis (METAVIR F2-F4) Fibrotest >0.20: 0.88 (74/84); >0.80: 0.25 (21/84) Historical index >0.20: 0.94 (79/84); >0.60: 0.24 (20/84)	Fibrosis (METAVIR F2-F4) Fibrotest >0.20: 0.53 (67/127); >0.80: 0.93 (118/127) Historical index >0.20: 0.21 (27/127); >0.60: 0.91 (116/127)	Fibrosis (METAVIR F2-F4) Fibrotest >0.20: 0.55 (74/134); >0.80: 0.70 (21/30) Historical index >0.20: 0.44 (79/179); >0.60: 0.65 (20/31)	Fibrosis (METAVIR F2-F4) Fibrotest >0.20: 0.87 (67/77); >0.80: 0.65 (118/181) Historical index >0.20: 0.84 (27/32); >0.60: 0.64 (116/180)	Fibrosis (METAVIR F2-F4) Fibrotest: 0.80 (0.76- 0.83) Historical index: 0.71 (0.67-0.75) Severe fibrosis (METAVIR F3-F4) Fibrotest: 0.92 (0.89- 0.95) Historical index: 0.76 (0.71-0.81)	Canadian association for the Study of the Liver, Schering Canada, Royal College of Physicians and Surgeons of Canada, and Association Pour la Recherche sur les Maladies Hepatiques Viroles	Fair	Same population as Myers, 2003
Obrador, 2006 ⁹¹	Derivation and validation samples, respectively Cirrhosis (Knodell F4)Sabadell NIHCED index ≥22: 0.89 (42/47) and 0.80 (16/20)	Derivation and validation samples, respectively Cirrhosis (Knodell F4)Sabadell NIHCED index ≥22: 0.83 (102/123) and 0.96 (136/142)	Derivation and validation samples, respectively Cirrhosis (Knodell F4)Sabadell NIHCED index ≥22: 0.67 (42/63) and 0.73 (16/22)	Derivation and validation samples, respectively Cirrhosis (Knodell F4)Sabadell NIHCED index ≥22: 0.95 (102/107) and 0.97 (136/140)	Derivation and validation samples, respectively Cirrhosis (Knodell F4)Sabadell NIHCED index: 0.91 (0.86-0.96) and not reported	Funding sources not stated, no conflicts of interest declared	Fair	Same population as Bejarano, 2009.
Ohta, 2006 ⁹²	Derivation and validation samples, respectively Fibrosis (Desmet F2-F4) Fibrosis Index ≥2.1: 0.82 (151/184) and 0.77 (121/157) Cirrhosis (Desmet F4) Fibrosis Index ≥3.3: 0.68 (21/31) and 0.71 (17/24)	Derivation and validation samples, respectively Fibrosis (Desmet F2-F4) Fibrosis Index ≥2.1: 0.67 (123/184) and 0.68 (63/92) Cirrhosis (Desmet F4) Fibrosis Index ≥3.3: 0.98 (330/337) and 0.78 (221/225)	Derivation and validation samples, respectively Fibrosis (Desmet F2- F4) Fibrosis Index ≥2.1: 0.71 (151/212) and 0.81 (121/150) Cirrhosis (Desmet F4) Fibrosis Index ≥3.3: 0.75 (21/28) and 0.81 (17/21)	Derivation and validation samples, respectively Fibrosis (Desmet F2-F4) Fibrosis Index ≥2.1: 0.79 (123/156) and 0.64 (63/99) Cirrhosis (Desmet F4) Fibrosis Index ≥3.3: 0.97 (330/340) and 0.97 (221/228)	Derivation and validation samples, respectively Fibrosis (Desmet F2- F4) Fibrosis Index: 0.85 and not reported Cirrhosis (Desmet F4) Fibrosis Index: 0.98 and not reported	Not reported	Good	
Omran, 2011 ⁹³	Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) Fibro-a score >1.28: 0.70 (45/64) and 0.70 (40/57) Severe fibrosis (METAVIR F3-F4) Fibro-a score >1.30: 0.88 (26/30) and 0.88 Cirrhosis (METAVIR F4) Fibro-a score >1.35: 0.90 (14/15) and 0.73	Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) Fibro-a score >1.28: 0.60 (81/135) and 0.54 (42/78) Severe fibrosis (METAVIR F3-F4) Fibro-a score >1.30: 0.60 (101/169) and 0.60 Cirrhosis (METAVIR F4) Fibro-a score >1.35: 0.57 (105/184) and 0.70	Derivation and validation samples, respectively Fibrosis (METAVIR F2- F4) Fibro-a score >1.28: 0.45 (45/99) and 0.70 (40/76) Severe fibrosis (METAVIR F3-F4) Fibro-a score >1.30: 0.28 (26/94) and not reported Cirrhosis (METAVIR F4) Fibro-a score >1.35: 0.15 (14/79) and not reported	Derivation and validation samples, respectively Fibrosis (METAVIR F2- F4) Fibro-a score >1.28: 0.81 (81/100) and 0.71 (42/59) Severe fibrosis (METAVIR F3-F4) Fibro-a score >1.30: 0.96 (101/105) and not reported Cirrhosis (METAVIR F4) Fibro-a score >1.35: 0.99 (105/106) and not reported	Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) Fibro-a score: 0.74 and 0.72 (CIs not reported) Severe fibrosis (METAVIR F3-F4) Fibro-a score: 0.82 and 0.82 (CIs not reported) Cirrhosis (METAVIR F4) Fibro-a score: 0.80 and 0.76 (CIs not reported)	Not stated, reported no conflict of interest	Good	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Paggi, 2008 ⁹⁴	Severe fibrosis (METAVIR F3-F4) APRI >1: 0.79 (127/160); >2: 0.36 (58/160) Liver surface nodularity present: 0.72 (116/160) [0.73*]	Severe fibrosis (METAVIR F3-F4) APRI >1: 0.70 (189/270); >2: 0.92 (249/270) Liver surface nodularity present: 0.90 (243/270)	Severe fibrosis (METAVIR F3-F4) APRI >1: 0.61 (127/208); >2: 0.73 (58/79) Liver surface nodularity present: 0.81 (116/143)	Severe fibrosis (METAVIR F3-F4) APRI >1: 0.85 (189/222); >2: 0.71 (249/351) Liver surface nodularity present: 0.85 (243/287)	Severe fibrosis (METAVIR F3-F4) APRI: Not reported Liver surface nodularity: Not reported Sequential APRI and liver surface nodularity: 0.81 (0.76-0.85) Sequential FIB-4 and liver surface nodularity: 0.83 (0.79-0.87)	Declared no financial disclosures or conflicts of interest	Fair	
Parise, 2006 ⁹⁵	Fibrosis (Batt-Ludwig F2-F4) Hyaluronic acid \geq 34.2: 0.85 (73/86) APRI \geq 0.70: 0.85 (73/86) GGT \geq 1.5xULN: 0.77 (66/86) [0.76*] AST/ALT ratio \geq 0.8: 0.52 (45/86) Cirrhosis (Batt-Ludwig F4) Hyaluronic acid \geq 78.6: 0.91 (40/44) APRI >1.5: 0.73 (32/44) GGT \geq 2xULN: 0.61 (27/44) AST/ALT ratio >1: 0.36 (16/44)	Fibrosis (Batt-Ludwig F2-F4) Hyaluronic acid \geq 34.2: 0.71 (85/120) APRI \geq 0.70: 0.66 (79/120) GGT \geq 1.5xULN: 0.55 (66/120) AST/ALT ratio \geq 0.8: 0.61 (73/120) Cirrhosis (Batt-Ludwig F4) Hyaluronic acid \geq 78.6: 0.81 (132/162) [0.82*] APRI >1.5: 0.81 (131/162) GGT \geq 2xULN: 0.58 (94/162) AST/ALT ratio >1: 0.82 (133/162)	Fibrosis (Batt-Ludwig F2-F4) Hyaluronic acid \geq 34.2: 0.68 (73/108) APRI \geq 0.70: 0.64 (73/114) GGT \geq 1.5xULN: 0.55 (66/120) AST/ALT ratio \geq 0.8: 0.49 (45/92) Cirrhosis (Batt-Ludwig F4) Hyaluronic acid \geq 78.6: 0.57 (40/70) APRI >1.5: 0.51 (32/63) GGT \geq 2xULN: 0.28 (27/95) AST/ALT ratio >1: 0.36 (16/45)	Fibrosis (Batt-Ludwig F2-F4) Hyaluronic acid \geq 34.2: 0.87 (85/98) APRI \geq 0.70: 0.86 (79/92) GGT \geq 1.5xULN: 0.77 (66/86) AST/ALT ratio \geq 0.8: 0.64 (73/114) Cirrhosis (Batt-Ludwig F4) Hyaluronic acid \geq 78.6: 0.97 (132/136) APRI >1.5: 0.92 (131/143) GGT \geq 2xULN: 0.85 (94/111) AST/ALT ratio >1: 0.83 (133/161)	Fibrosis (Batt-Ludwig F2-F4) Hyaluronic acid: 0.88 (0.83-0.93) APRI: 0.82 (0.77-0.88) GGT: 0.70 (0.63-0.78) AST/ALT ratio: 0.59 (0.51-0.67) Cirrhosis (Batt-Ludwig F4) Hyaluronic acid: 0.91 (0.87-0.95) APRI: 0.84 (0.77-0.90) GGT: 0.67 (0.59-0.75) AST/ALT ratio: 0.65 (0.56-0.75)	FAPESP	Fair	
Park, 2011 ⁹⁶	Not reported	Not reported	Not reported	Not reported	Fibrosis (METAVIR F2-F4) APRI: 0.79 (0.69-0.89) Multibiomarker score: 0.78 (0.68-0.89)	Korea Ministry of Health	Good	
Park, 2000 ⁹⁷ and 2005 ⁹⁸	Cirrhosis (Scheuer F4)AST/ALT ratio \geq 1: 0.47 (14/30)	Cirrhosis (Scheuer F4)AST/ALT ratio \geq 1: 0.96 (118/123)	Cirrhosis (Scheuer F4)AST/ALT ratio \geq 1: 0.74 (14/19)	Cirrhosis (Scheuer F4)AST/ALT ratio \geq 1: 0.88 (118/134)	Fibrosis (Scheuer F2-F4)AST/ALT ratio: 0.71 (0.62-0.79)Cirrhosis (Scheuer F4)AST/ALT ratio: 0.85 (0.77-0.93)	Not stated	Fair	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Parkes, 2011 ⁹⁹	Severe fibrosis (METAVIR F3-F4 or Ishak 4-6) Simplified ELF >9.39: 0.90 (100/111); >10.22: 0.70 (78/111); >10.90: 0.54 (60/111)	Severe fibrosis (METAVIR F3-F4 or Ishak 4-6) Simplified ELF >9.39: 0.55 (130/236); >10.22: 0.85 (201/236); >10.90: 0.95 (224/236)	Severe fibrosis (METAVIR F3-F4 or Ishak 4-6) Simplified ELF >9.39: 0.49 (100/206) [0.48*]; >10.22: 0.69 (78/113) [0.68*]; >10.90: 0.83 (60/72) [0.82*]	Severe fibrosis (METAVIR F3-F4 or Ishak 4-6) Simplified ELF >9.39: 0.92 (130/141); >10.22: 0.86 (201/234); >10.90: 0.81 (224/275)	Reported separately for 3 validation cohorts Fibrosis (METAVIR F2-F4 or Ishak 3-6) Simplified ELF: 0.74 (0.63-0.84), 0.83 (0.76-0.89), 0.87 (0.80-0.95) Severe fibrosis (METAVIR F3-F4 of Ishak 4-6) Simplified ELF: 0.84 (0.74-0.94), 0.86 (0.80-0.92), 0.89 (0.83-0.96) Cirrhosis (METAVIR F4 or Ishak 5-6) Simplified ELF: 0.90 (0.81-0.98), 0.87 (0.81-0.93), 0.89 (0.82-0.96)	Funding sources not stated, some authors disclosed interests and stocks in companies that conduct ELF assays	Fair	Simplified version of original ELF evaluated in Rosenberg 2004.
Patel, 2009 ¹⁰⁰	Whole sample and excluding biopsies <15 mm, respectively (subgroup analysis only reported for Fibrosure and FibroSpect II) Fibrosis (METAVIR F2-F4) Fibrotest ≥0.48: 1.0 (18/18) and 1.0 (12/12) FibroSpect II >0.36: 0.95 (21/22) and 1.0 (15/15) APRI >0.5: 0.95 (21/22); ≥1.5: 0.41 (9/22) Forn's Index >4.21: 0.91 (20/22); 0.50 (11/22) FIB-4 >1.45: 0.86 (12/14); >3.25: 0.43 (6/14)	Whole sample and excluding biopsies <15 mm, respectively (subgroup analysis only reported for Fibrosure and FibroSpect II) Fibrosis (METAVIR F2-F4) Fibrotest ≥0.48: 0.61 (40/66) and 0.66 (21/32) FibroSpect II >0.36: 0.66 (48/73) and 0.73 (27/37) APRI >0.5: 0.64 (46/72); ≥1.5: 0.99 (71/72) Forn's Index >4.21: 0.53 (38/72); 0.93 (67/72) FIB-4 >1.45: 0.68 (54/80); >3.25: 0.96 (77/80)	Whole sample and excluding biopsies <15 mm, respectively (subgroup analysis only reported for Fibrosure and FibroSpect II) Fibrosis (METAVIR F2-F4) Fibrotest ≥0.48: 0.41 (18/44) and 0.52 (12/23) FibroSpect II >0.36: 0.46 (21/46) and 0.60 (15/25) APRI >0.5: 0.45 (21/47); ≥1.5: 0.90 (9/10) Forn's Index >4.21: 0.37 (20/54); 0.69 (11/16) FIB-4 >1.45: 0.32 (12/38); >3.25: 0.67 (6/9)	Whole sample and excluding biopsies <15 mm, respectively (subgroup analysis only reported for Fibrosure and FibroSpect II) Fibrosis (METAVIR F2-F4) Fibrotest ≥0.48: 1.0 (40/40) and 1.0 (21/21) FibroSpect II >0.36: 0.98 (48/49) and 1.0 (27/27) APRI >0.5: 0.98 (46/47); ≥1.5: 0.85 (71/84) Forn's Index >4.21: 0.95 (38/40); 0.86 (67/78) FIB-4 >1.45: 0.96 (54/56) [0.95*]; >3.25: 0.91 (77/85)	Whole sample and excluding biopsies <15 mm, respectively Fibrosis (METAVIR F2-F4) Fibrotest: 0.89 (0.81-0.97) and 0.89 (0.79-0.99) FibroSpect II: 0.90 (0.84-0.96) and 0.94 (0.88-1.0) APRI: Not reported Forn's Index: Not reported FIB-4: Not reported	Human Genome Sciences and Novartis	Fair	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Patel, 2004 ¹⁰¹	Fibrosis (derivation and validation samples, respectively) FibroSpect II >0.36: 0.83 (123/149) and 0.77 (160/208)	Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) FibroSpect II >0.36: 0.66 (96/145) and 0.73 (144/194)	Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) FibroSpect II >0.36: 0.72 (123/172) and 0.76 (160/210)	Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) FibroSpect II >0.36: 0.79 (96/122) and 0.75 (144/192)	Derivation and validation samples, respectively Fibrosis (METAVIR F2-F4) FibroSpect II: and 0.82 (confidence interval not reported) (For the following markers, AUROC evaluated for sample of 194 patients) Hyaluronic acid: 0.82 (0.76-0.78) TIMP-1: 0.77 (0.71-0.85) Laminin: 0.52 (0.44-0.61) PIIIP: 0.78 (0.72-0.84) Type IV-7S collagen: 0.73 (0.66-0.80) YKL-40: 0.70 (0.62-0.77) Alpha2-macroglobulin: 0.72 (0.65-0.79)	Scripps Clinic	Fair	
Plevris, 2000 ¹⁰²	Cirrhosis (Knodell F4) Hyaluronic acid >100 mcg/l: 0.73 (11/15) [0.72*]; >200 and >300 mcg/l: not reported	Cirrhosis (Knodell F4) Hyaluronic acid >100 mcg/l: 0.93 (50/54); >200: 0.98 (53/54); >300 mcg/l: 1.0 (54/54)	Cirrhosis (Knodell F4) Hyaluronic acid >100 mcg/l: 0.73 (11/15); >200 and >300 mcg/l: not reported	Cirrhosis (Knodell F4) Hyaluronic acid >100 mcg/l: 0.93 (50/54); >200 and >300 mcg/l: not reported	Not reported	Not reported	Fair	
Pohl, 2001 ¹⁰³	Fibrosis (METAVIR F2-F4) AST/ALT \geq 1: 0.35 (19/54) Pohl Index positive: 0.60 (32/54) Severe fibrosis (METAVIR F4) AST/ALT \geq 1: 0.47 (17/36) Pohl Index positive: 0.42 (15/36) [0.41*]	Fibrosis (METAVIR F2-F4) AST/ALT \geq 1: 0.77 (76/99) Pohl Index positive: 0.76 (74/99) [0.75*] Severe fibrosis (METAVIR F3 or F4) AST/ALT \geq 1: 0.81 (95/117) [0.82*] Pohl Index positive: 0.99 (116/117)	Fibrosis (METAVIR F2-F4) AST/ALT \geq 1: 0.45 (19/42) Pohl Index positive: 0.56 (32/57) [0.60*] Severe fibrosis (METAVIR F3 or F4) AST/ALT \geq 1: 0.44 (17/39) [0.43*] Pohl Index positive: 0.94 (15/16) [0.93*]	Fibrosis (METAVIR F2-F4) AST/ALT \geq 1: 0.68 (76/111) Pohl Index positive: 0.78 (74/95) [0.67*] Severe fibrosis (METAVIR F3 or F4) AST/ALT \geq 1: 0.83 (95/114) [0.84*] Pohl Index positive: 0.85 (116/137)	Not reported	Not reported	Fair	Analyses excluded 54 patients with history of alcohol abuse due to no correlation between AST/ALT ratio and fibrosis stage
Poynard, 2003 ¹⁰⁴	Not reported	Not reported	Not reported	Not reported	Fibrosis (METAVIR F2-F4) Fibrotest: 0.73 (0.70-0.76) Severe fibrosis (METAVIR F3-F4) Fibrotest: 0.73 (0.69-0.77)	Schering Plough Research Institute and Associatiogn pour la Recherche sur les Maladies Hepatiques Virales	Fair	Evaluated patients enrolled in a randomized trial of antiviral therapy

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Poynard, 2002 ¹⁰⁵	Not reported	Not reported	Not reported	Not reported	F3 fibrosis (Knodel) Fibrotest: 0.74 (0.71-0.77) Hyaluronic acid: 0.65 (0.62-0.68)	Direction Regionale de la Recherche Clinique and Association pour la Recherche sur le Cancer	Fair	Evaluated patients enrolled in a randomized trial of antiviral therapy
Pradat, 2002 ¹⁰⁶	Fibrosis (METAVIR F2-F4) ALT >ULN: 0.99 (603/612) Greater than METAVIR A1F1 ALT >2.25 ULN: 0.72 Severe fibrosis (METAVIR F3-F4) ALT >ULN: 1.0 (200/201) Cirrhosis (METAVIR F4) ALT >ULN: 0.98 (64/65)	Fibrosis (METAVIR F2-F4) ALT >ULN: 0.23 (57/252) Greater than METAVIR A1F1 ALT >2.25 ULN: 0.74 Severe fibrosis (METAVIR F3-F4) ALT >ULN: 0.10 (65/663) Cirrhosis (METAVIR F4) ALT >ULN: 0.08 (65/799)	Fibrosis (METAVIR F2-F4) ALT >ULN: 0.76 (603/798) Greater than METAVIR A1F1 ALT >2.25 ULN: NR Severe fibrosis (METAVIR F3-F4) ALT >ULN: 0.25 (200/798) Cirrhosis (METAVIR F4) ALT >ULN: 0.08 (64/798)	Fibrosis (METAVIR F2-F4) ALT >ULN: 0.86 (57/66) Greater than METAVIR A1F1 ALT >2.25 ULN: NR Severe fibrosis (METAVIR F3-F4) ALT >ULN: 0.98 (65/66) Cirrhosis (METAVIR F4) ALT >ULN: 0.98 (65/66)	Greater than METAVIR A1F1 ALT: 0.82 (CI not reported)	Schering-Plough International	Fair	
Reedy, 1998 ¹⁰⁷	Cirrhosis (Knodel F4)AST/ALT ratio \geq 1: 0.43 (10/23) [0.44*]	Cirrhosis (Knodel F4)AST/ALT ratio \geq 1: 0.94 (45/48)	Cirrhosis (Knodel F4)AST/ALT ratio \geq 1: 0.77 (10/13)	Cirrhosis (Knodel F4)AST/ALT ratio \geq 1: 0.78 (45/58)	Not reported	Hoffman LaRoche, Inc. and Schering-Plough Corporation	Fair	Study reports 77 patients evaluated but diagnostic data only presented for 71
Renou, 2001 ¹⁰⁸	Fibrosis (METAVIR F2-F4) Platelet count <140,000: 0.30 (14/33) Severe fibrosis (METAVIR F3-F4) Platelet count <140,000: 0.47 (14/30) Cirrhosis (METAVIR F4) Platelet count <140,000: 0.93 (13/14)	Fibrosis (METAVIR F2-F4) Platelet count <140,000: 1.0 (57/57) Severe fibrosis (METAVIR F3-F4) Platelet count <140,000: 1.0 (74/74) Cirrhosis (METAVIR F4) Platelet count <140,000: 0.99 (89/90)	Fibrosis (METAVIR F2-F4) Platelet count <140,000: 1.0 (14/14) Severe fibrosis (METAVIR F3-F4) Platelet count <140,000: 1.0 (14/14) Cirrhosis (METAVIR F4) Platelet count <140,000: 0.93 (13/14)	Fibrosis (METAVIR F2-F4) Platelet count <140,000: 1.0 (57/57) Severe fibrosis (METAVIR F3-F4) Platelet count <140,000: 1.0 (74/74) Cirrhosis (METAVIR F4) Platelet count <140,000: 0.99 (89/90)	Not reported	Not reported	Fair	?Overlap with Halfon?
Romera, 2006 ¹⁰⁹	Fibrosis (Scheuer F2-F4) Forn's Index \geq 4.2: 0.79 (49/62) APRI \geq 0.5: 0.81 (50/62) Fibrosis Probability Index \geq 0.2: 0.77 (48/62)	Fibrosis (Scheuer F2-F4) Forn's Index \geq 4.2: 0.48 (33/69) APRI \geq 0.5: 0.36 (25/69) Fibrosis Probability Index \geq 0.2: 0.58 (40/69)	Fibrosis (Scheuer F2-F4) Forn's Index \geq 4.2: 0.58 (49/85) APRI \geq 0.5: 0.53 (50/94) Fibrosis Probability Index \geq 0.2: 0.62 (48/77)	Fibrosis (Scheuer F2-F4) Forn's Index \geq 4.2: 0.72 (33/46) APRI \geq 0.5: 0.68 (25/37) Fibrosis Probability Index \geq 0.2: 0.74 (40/54)	Fibrosis (Scheuer F2-F4) Forn's Index: 0.71 (CI not reported) APRI: 0.70 (CI not reported) Fibrosis Probability Index: 0.80 (CI not reported)	Consejeria de Innovacion, Junta de Analucia, Spain	Fair	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Rosenberg, 2004 ¹¹⁰	Severe fibrosis (Scheuer F3-F4) ELF >0.063: 0.95; >0.190: 0.63; >0.564: 0.30	Severe fibrosis (Scheuer F3-F4) ELF >0.063: 0.29; >0.190: 0.80; >0.564: 0.99	Severe fibrosis (Scheuer F3-F4) ELF >0.063: 0.28; >0.190: 0.48; >0.564: 0.90	Severe fibrosis (Scheuer F3-F4) ELF >0.063: 0.95; >0.190: 0.88; >0.564: 0.83	Severe fibrosis (Scheuer F3-F4) ELF: 0.77 (0.70-0.85)	Not stated	Fair	
Rossi, 2003 ¹¹¹	Fibrosis (METAVIR F2-F4) Fibrotest >0.10: 0.92 (44/48); >0.30: 0.75 (36/48); >0.60: 0.42 (20/48); >0.80: 0.22 (11/48) a-2 macroglobulin >2.52 g/L: 0.75 (36/48) Apolipoprotein A1 >1.41 g/L: 0.26 (12/48) Bilirubin >10 mmol/L: 0.61 (29/48)GGT >45 U/L: 0.57 (27/48) Haptoglobin >0.56 g/L: 0.21 (10/48)	Fibrosis (METAVIR F2-F4) Fibrotest >0.10: 0.29 (22/77); >0.30: 0.61 (47/77); >0.60: 0.94 (72/77); >0.80: 0.96 (74/77)a-2 macroglobulin >2.52 g/L: 0.67 (52/77) Apolipoprotein A1 >1.41 g/L: 0.50 (38/77) Bilirubin >10 mmol/L: 0.53 (41/77)GGT >45 U/L: 0.55 (42/77) Haptoglobin >0.56 g/L: 0.79 (61/77)	Fibrosis (METAVIR F2-F4) Fibrotest >0.10: 0.44 (44/99) [0.45*]; >0.30: 0.55 (36/66) [0.54*]; >0.60: 0.80 (20/25) [0.78*]; >0.80: 0.79 (11/14) a-2 macroglobulin >2.52 g/L: 0.43 (36/61) Apolipoprotein A1 >1.41 g/L: 0.24 (12/51) Bilirubin >10 mmol/L: 0.45 (29/65)GGT >45 U/L: 0.39 (27/62) Haptoglobin >0.56 g/L: 0.38 (10/26)	Fibrosis (METAVIR F2-F4) Fibrotest >0.10: 0.85 (22/26); >0.30: 0.80 (47/59); >0.60: 0.72 (72/100); >0.80: 0.67 (74/111) [0.66*] a-2 macroglobulin >2.52 g/L: 0.81 (52/64) Apolipoprotein A1 >1.41 g/L: 0.51 (38/74) Bilirubin >10 mmol/L: 0.68 (41/60)GGT >45 U/L: 0.67 (42/63) Haptoglobin >0.56 g/L: 0.62 (61/99)	Fibrosis (METAVIR F2-F4) Fibrotest: 0.74 (0.64-0.84)	Sir Charles Gairdner Hospital Research Fund	Fair	
Saadeh, 2001 ¹¹²	Cirrhosis (Knodell F4) Cirrhosis discriminant score >3: 0.85 (29/34); >7: 0.15 (5/34)	Cirrhosis (Knodell F4) Cirrhosis discriminant score >3: 0.58 (45/77); >7: 1.0 (77/77)	Cirrhosis (Knodell F4) Cirrhosis discriminant score >3: 0.48 (29/61); >7: 1.0 (5/5)	Cirrhosis (Knodell F4) Cirrhosis discriminant score >3: 0.90 (45/50); >7: 0.73 (77/106)	Cirrhosis (Knodell F4) Cirrhosis discriminant score: 0.80	Not stated	Fair	
Said, 2010 ¹¹³	Fibrosis (METAVIR F2-F4) Fibrotest >0.5: 0.85 (40/47) Severe fibrosis (METAVIR F3-F4) Fibrotest >0.52: 0.92 (24/26) Cirrhosis (METAVIR F4) Fibrotest >0.75: 0.86 (6/7)	Fibrosis (METAVIR F2-F4) Fibrotest >0.5: 0.72 (13/18) Severe fibrosis (METAVIR F3-F4) Fibrotest >0.52: 0.54 (21/39) Cirrhosis (METAVIR F4) Fibrotest >0.75: 0.71 (41/58)	Fibrosis (METAVIR F2-F4) Fibrotest >0.5: 0.89 (40/45) Severe fibrosis (METAVIR F3-F4) Fibrotest >0.52: 0.57 (24/42) Cirrhosis (METAVIR F4) Fibrotest >0.75: 0.26 (6/23)	Fibrosis (METAVIR F2-F4) Fibrotest >0.5: 0.65 (13/20) Severe fibrosis (METAVIR F3-F4) Fibrotest >0.52: 0.91 (21/23) Cirrhosis (METAVIR F4) Fibrotest >0.75: 0.98 (41/42)	Fibrosis (METAVIR F2-F4) Fibrotest: 0.87 (0.78-0.96) Severe fibrosis (METAVIR F3-F4) Fibrotest: 0.76 (0.64-0.88) Cirrhosis (METAVIR F4) Fibrotest: 0.85 (0.72-0.97)	Not stated	Fair	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Saitou, 2005 ¹⁴	<p>Fibrosis (METAVIR F2-F4) Type IV collagen >5.75: 0.65 (50/77) PIIIP >0.835: 0.78 (60/77) Hyaluronic acid >75.7: 0.75 (58/77) YKL-40 >186.4: 0.78 (60/77)</p> <p>Cirrhosis (METAVIR F4) Type IV collagen >6.55: 0.60 (18/30) PIIIP >0.995: 0.77 (23/30) Hyaluronic acid >183.5: 0.80 (24/30) YKL-40 >284.8: 0.80 (24/30)</p>	<p>Fibrosis (METAVIR F2-F4) Type IV collagen >5.75: 0.69 (22/32) PIIIP >0.835: 0.75 (24/32) Hyaluronic acid >75.7: 0.81 (26/32) YKL-40 >186.4: 0.81 (26/32)</p> <p>Cirrhosis (METAVIR F4) Type IV collagen >6.55: 0.61 (48/79) PIIIP >0.995: 0.66 (52/79) Hyaluronic acid >183.5: 0.80 (63/79) YKL-40 >284.8: 0.71 (56/79)</p>	<p>Fibrosis (METAVIR F2-F4) Type IV collagen >5.75: 0.83 (50/60) [0.67*] PIIIP >0.835: 0.88 (60/68) [0.76*] Hyaluronic acid >75.7: 0.91 (58/64) [0.79*] YKL-40 >186.4: 0.91 (60/66) [0.80*]</p> <p>Cirrhosis (METAVIR F4) Type IV collagen >6.55: 0.91 (18/49) [0.61*] PIIIP >0.995: 0.46 (23/50) [0.69*] Hyaluronic acid >183.5: 0.60 (24/40) [0.80*] YKL-40 >284.8: 0.51 (24/47) [0.73*]</p>	<p>Fibrosis (METAVIR F2-F4) Type IV collagen >5.75: 0.45 (22/49) [0.66*] PIIIP >0.835: 0.59 (24/41) [0.77*] Hyaluronic acid >75.7: 0.58 (26/45) [0.76*] YKL-40 >186.4: 0.60 (26/43) [0.79*]</p> <p>Cirrhosis (METAVIR F4) Type IV collagen >6.55: 0.80 (48/60) [0.60*] PIIIP >0.995: 0.88 (52/59) [0.67*] Hyaluronic acid >183.5: 0.91 (63/69) [0.80*] YKL-40 >284.8: 0.90 (56/62) [0.78*]</p>	<p>Fibrosis (F2-F4) Type IV collagen: 0.74 (CI not reported) PIIIP: 0.75 (CI not reported) Hyaluronic acid: 0.80 (CI not reported) YKL-40: 0.81 (CI not reported)</p> <p>Cirrhosis (F4) Type IV collagen: 0.60 (CI not reported) PIIIP: 0.79 (CI not reported) Hyaluronic acid: 0.85 (CI not reported) YKL-40: 0.80 (CI not reported)</p>	Not stated	Poor	
Schneider, 2006 ¹⁵	<p>Fibrosis (Ishak 3-6)APRI >0.7: 0.81 (38/47) Cirrhosis (Ishak 5-6)APRI >1.0: 0.79 (15/19) [0.77*] Portal venous flow <12.5 cm/s: 0.89 (17/19) [0.88*]</p>	<p>Fibrosis (Ishak 3-6)APRI >0.7: 0.65 (23/36) Cirrhosis (Ishak 5-6)APRI >1.0: 0.63 (40/64) Portal venous flow <12.5 cm/s: 0.66 (42/64) [0.65*]</p>	<p>Fibrosis (Ishak 3-6)APRI >0.7: 0.75 (38/51) Cirrhosis (Ishak 5-6)APRI >1.0: 0.38 (15/39) Portal venous flow <12.5 cm/s: 0.44 (17/39)</p>	<p>Fibrosis (Ishak 3-6)APRI >0.7: 0.72 (23/32) Cirrhosis (Ishak 5-6)APRI >1.0: 0.91 (40/44) Portal venous flow <12.5 cm/s: 0.95 (42/44)</p>	<p>Fibrosis (Ishak 3-6)APRI: 0.75 (CI not reported) Portal venous flow: Not reported Cirrhosis (Ishak 5-6)APRI: 0.71 (CI not reported) Portal venous flow: 0.80 (CI not reported)</p>	Not stated	Fair	Degree of population overlap with Schneider 2005 unclear
Schneider, 2005 ¹⁶	<p>Cirrhosis (Ishak 5-6) Portal venous flow <14.5 cm/s: 0.74 (13/17) Portal venous undulations reduced: 0.76 (13/17) Hepatic venous flow pattern mono- or biphasic: 0.31 (5/17) Longitudinal spleen size (cutoff not reported): 0.78 (13/17) Transverse spleen size >5 cm: 0.86 (15/17)</p>	<p>Cirrhosis (Ishak 5-6) Portal venous flow <14.5 cm/s: 0.53 (54/102) Portal venous undulations reduced: 1.0 (102/102) Hepatic venous flow pattern mono- or biphasic: 0.47 (48/102) Longitudinal spleen size (cutoff not reported): 0.53 (54/102) Transverse spleen size >5 cm: 0.35 (36/102)</p>	<p>Cirrhosis (Ishak 5-6) Portal venous flow <14.5 cm/s: 0.21 (13/61) Portal venous undulations reduced: 1.0 (13/13) Hepatic venous flow pattern mono- or biphasic: 0.08 (5/59) Longitudinal spleen size (cutoff not reported): 0.21 (13/61) Transverse spleen size >5 cm: 0.19 (15/81)</p>	<p>Cirrhosis (Ishak 5-6) Portal venous flow <14.5 cm/s: 0.93 (54/58) Portal venous undulations reduced: 0.96 (102/106) Hepatic venous flow pattern mono- or biphasic: 0.80 (48/60) Longitudinal spleen size (cutoff not reported): 0.93 (54/58) Transverse spleen size >5 cm: 0.95 (36/38)</p>	Not reported	Not stated	Fair	Degree of population overlap with Schneider 2006 unclear

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Sebastiani, 2012 ¹⁷	<p>Fibrosis (METAVIR F2-F4) Fibrotest >0.49: 0.62 (341/552) APRI >0.5: 0.69 (381/552); >1.5: 0.29 (160/552) Forn's Index >4.2: 0.94 (521/552); >6.9: 0.61 (336/552) SAFE algorithm positive: 1.0 (552/552) Fibropaca algorithm positive: 0.86 (472/552) Leroy algorithm positive: 0.90 (495/552)</p> <p>Cirrhosis (METAVIR F4) Fibrotest >0.75: 0.30 (34/113) APRI >1.0: 0.75 (84/113); >2.0: 0.41 (47/113) SAFE algorithm positive: 0.82 (92/113) Fibropaca algorithm positive: 0.73 (82/113)</p>	<p>Fibrosis (METAVIR F2-F4) Fibrotest >0.49: 0.81 (375/461) APRI >0.5: 0.73 (338/461); >1.5: 0.95 (440/461) Forn's Index >4.2: 0.20 (90/461); >6.9: 0.66 (304/461) SAFE algorithm positive: 0.78 (361/461) Fibropaca algorithm positive: 0.90 (414/461) Leroy algorithm positive: 0.98 (451/461)</p> <p>Cirrhosis (METAVIR F4) Fibrotest >0.75: 0.89 (800/900) APRI >1.0: 0.79 (715/900); >2.0: 0.94 (842/900) SAFE algorithm positive: 0.92 (832/900) Fibropaca algorithm positive: 0.97 (870/900)</p>	<p>Fibrosis (METAVIR F2-F4) Fibrotest >0.49: 0.80 (341/427) [0.86*] APRI >0.5: 0.76 (381/504) [0.70*]; >1.5: 0.88 (160/181) [0.90*] Forn's Index >4.2: 0.58 (521/892) [0.59*]; >6.9: 0.68 (336/493) [0.69*] SAFE algorithm positive: 0.85 (552/652) [0.84*] Fibropaca algorithm positive: 0.91 (472/519) [0.90*] Leroy algorithm positive: 0.98 (495/505) [0.90*]</p> <p>Cirrhosis (METAVIR F4) Fibrotest >0.75: 0.25 (34/134) [0.74*] APRI >1.0: 0.31 (84/269) [0.68*]; >2.0: 0.45 (47/105) [0.55*] SAFE algorithm positive: 0.58 (92/160) [0.57*] Fibropaca algorithm positive: 0.73 (82/112)</p>	<p>Fibrosis (METAVIR F2-F4) Fibrotest >0.49: 0.64 (375/586) [0.61*] APRI >0.5: 0.66 (338/509) [0.77*]; >1.5: 0.53 (440/832) [0.39*] Forn's Index >4.2: 0.74 (90/121); >6.9: 0.58 (304/520) SAFE algorithm positive: 1.0 (361/361) Fibropaca algorithm positive: 0.84 (414/494) [0.85*] Leroy algorithm positive: 0.89 (451/508) [0.98*]</p> <p>Cirrhosis (METAVIR F4) Fibrotest >0.75: 0.91 (800/879) APRI >1.0: 0.96 (715/744); >2.0: 0.93 (842/908) SAFE algorithm positive: 0.98 (832/853) Fibropaca algorithm positive: 0.97 (870/901) [0.96*]</p>	<p>Fibrosis (METAVIR F2-F4) Fibrotest: 0.71 (0.64-0.78) APRI: 0.70 (0.64-0.76) Forn's Index: 0.64 (0.58-0.70) SAFE algorithm positive: 0.90 (0.85-0.95) Fibropaca algorithm positive: 0.88 (0.82-0.94) Leroy algorithm positive: 0.94 (0.89-0.99)</p> <p>Cirrhosis (METAVIR F4) Fibrotest: 0.72 (0.67-0.77) APRI: 0.77 (0.71-0.83) SAFE algorithm positive: 0.87 (0.81-0.93) Fibropaca algorithm positive: 0.85 (0.79-0.91)</p>	No funding	Fair	Major inconsistencies between reported and calculated diagnostic accuracy

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Sebastiani, 2011 ¹⁸	595 nom	<p>Whole sample and normal ALT subgroup, respectively Fibrosis (METAVIR F2-F4) APRI >0.5: Not reported and 0.82 (346/419); >1.5: 0.95 (941/990) and 0.89 (372/419) FibroTest >0.49: 0.79 (781/990) and 0.88 (371/419) FIB-4 >1.45: Not reported and 0.72 (303/419); not reported and >3.25: 0.59 (246/419) Forn's Index >4.2: Not reported and 0.67 (279/419); >6.9: Not reported and 0.89 (373/419)</p> <p>Cirrhosis (METAVIR F4) APRI >1.0: Not reported and 0.87 (501/576); >2.0: 0.94 (1543/1647) and 0.89 (516/576) FibroTest >0.75: 0.90 (1484/1647) and 0.94 (541/576) AST/ALT ratio >1.0: Not reported and 0.88 (504/576) Lok Index >0.2: Not reported and 0.35 (202/576); >0.5: Not reported and 0.60 (348/576) Platelets <150: Not reported and 0.90 (519/576)</p>	<p>Whole sample and normal ALT subgroup, respectively Fibrosis (METAVIR F2-F4) APRI >0.5: Not reported and 0.51 (76/149) [0.51*]; >1.5: 0.88 (374/423) [0.86*] and 0.51 (48/95) [0.71*] FibroTest >0.49: 0.69 (461/670) [0.84*] and 0.56 (62/110) [0.57*] FIB-4 >1.45: Not reported and 0.50 (114/230); not reported and >3.25: 0.35 (93/266) [0.70*] Forn's Index >4.2: Not reported and 0.42 (100/240) [0.75*]; >6.9: Not reported and 0.40 (31/77) [0.90*]</p> <p>Cirrhosis (METAVIR F4) APRI >1.0: Not reported and 0.07 (6/81) [0.26*]; >2.0: 0.46 (110/214) and 0.08 (5/65) [0.40*] FibroTest >0.75: 0.35 (88/251) [0.53*] and 0.15 (6/41) [0.27*] AST/ALT ratio >1.0: Not reported and 0.03 (2/74) [0.70*] Lok Index >0.2: Not reported and 0.03 (13/387) [0.40*]; >0.5: Not reported and 0.04 (10/238) [0.65*] Platelets <150: Not reported and 0.12 (8/65) [0.34*]</p>	<p>Whole sample and normal ALT subgroup, respectively Fibrosis (METAVIR F2-F4) APRI >0.5: Not reported and 0.78 (346/446) [0.77*]; >1.5: 0.68 (941/1387) [0.73*] and 0.74 (372/500) [0.61*] FibroTest >0.49: 0.69 (781/1140) [0.68*] and 0.76 (371/485) FIB-4 >1.45: Not reported and 0.83 (303/365) [0.78*]; not reported and >3.25: 0.75 (246/329) [0.41*] Forn's Index >4.2: Not reported and 0.79 (279/355) [0.47*]; >6.9: Not reported and 0.72 (373/595) [0.34*]</p> <p>Cirrhosis (METAVIR F4) APRI >1.0: Not reported and 0.97 (501/514) [0.94*]; >2.0: 0.97 (1543/1596) [0.97*] and 0.97 (516/530) [0.96*] FibroTest >0.75: 0.95 (1484/1559) and 0.98 (541/554) [0.94*] AST/ALT ratio >1.0: Not reported and 0.97 (504/521) [0.30*] Lok Index >0.2: Not reported and 0.97 (202/208) [0.84*]; >0.5: Not reported and 0.97 (348/357) [0.45*] Platelets <150: Not reported and 0.98 (519/530) [0.94*]</p>	<p>Whole sample and normal ALT subgroup, respectively Fibrosis (METAVIR F2-F4) APRI: 0.70 (0.65-0.75) and 0.63 (0.57-0.71) FibroTest: 0.70 (0.65-0.75) and 0.62 (0.58-0.66) FIB-4: Not reported and 0.61 (0.56-0.66) Forn's Index: Not reported and 0.60 (0.55-0.65)</p> <p>Cirrhosis (METAVIR F4) APRI: 0.76 (0.71-0.81) and 0.65 (0.60-0.70) FibroTest: 0.72 (0.67-0.77) and 0.65 (0.60-0.70) AST/ALT ratio: Not reported and 0.52 (0.46-0.58) Lok Index: Not reported and 0.61 (0.57-0.69) Platelets: Not reported and 0.64 (0.58-0.70)</p>	Not reported	Good	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Sebastiani, 2009 ¹⁹	Fibrosis (METAVIR F2-F4) APRI >0.5: 0.67 (625/931); >1.5: 0.27 (255/931) SAFE fibrosis algorithm positive (whole sample, excluding F4 patients, biopsy ≤15 mm, and biopsy >15 mm, respectively [n/N not reported for biopsy length subgroups]): 1.0 (931/931), 1.0 (740/740), 1.0, and 1.0 Cirrhosis (METAVIR F4) APRI >1.0: 0.78 (149/191); >2.0: 0.47 (90/191) SAFE cirrhosis algorithm positive (whole sample, excluding F0 and F1 patients, biopsy ≤15 mm, and biopsy >15 mm, respectively [n/N not reported for biopsy length subgroups]): 0.90 (173/191), 0.53 (100/191), 0.84, and 0.96	Fibrosis (METAVIR F2-F4) APRI >0.5: 0.73 (810/1104); >1.5: 0.96 (1064/1104) SAFE fibrosis algorithm positive (whole sample, excluding F4 patients, biopsy ≤15 mm, and biopsy >15 mm, respectively [n/N not reported for biopsy length subgroups]): 0.77 (850/1104), 0.82 (905/1104), 0.80, and 0.79 Cirrhosis (METAVIR F4) APRI >1.0: 0.84 (1542/1844); >2.0: 0.94 (1743/1844) SAFE cirrhosis algorithm positive (whole sample, excluding F0 and F1 patients, biopsy ≤15 mm, and biopsy >15 mm, respectively [n/N not reported for biopsy length subgroups]): 0.93 (1709/1844), 0.92 (683/740), 0.91, and 0.92	Fibrosis (METAVIR F2-F4) APRI >0.5: 0.68 (625/919); >1.5: 0.86 (255/295) SAFE fibrosis algorithm positive (whole sample, excluding F4 patients, biopsy ≤15 mm, and biopsy >15 mm, respectively [n/N not reported for biopsy length subgroups]): 0.79 (740/939) [0.84*], 1.0 (905/905), 0.83, and 0.85 Cirrhosis (METAVIR F4) APRI >1.0: 0.33 (149/451); >2.0: 0.47 (90/191) SAFE cirrhosis algorithm positive (whole sample, excluding F0 and F1 patients, biopsy ≤15 mm, and biopsy >15 mm, respectively [n/N not reported for biopsy length subgroups]): 0.56 (173/308), 0.64 (100/157) [0.60*], 0.53, and 0.56	Fibrosis (METAVIR F2-F4) APRI >0.5: 0.73 (810/1116); >1.5: 0.61 (1064/1740) [0.38*] SAFE fibrosis algorithm positive (whole sample, excluding F4 patients, biopsy ≤15 mm, and biopsy >15 mm, respectively [n/N not reported for biopsy length subgroups]): 1.0 (850/850), 1.0 (905/905), 1.0, and 1.0 Cirrhosis (METAVIR F4) APRI >1.0: 0.97 (1542/1584); >2.0: 0.95 (1743/1844) SAFE cirrhosis algorithm positive (whole sample, excluding F0 and F1 patients, biopsy ≤15 mm, and biopsy >15 mm, respectively [n/N not reported for biopsy length subgroups]): 0.99 (1709/1727), 0.88 (683/774) [0.90*], 0.98, and 1.0	Fibrosis (METAVIR F2-F4) APRI >0.5: 0.70 (0.65-0.75); >1.5: 0.62 (0.59-0.65) SAFE fibrosis algorithm positive (whole sample, excluding F4 patients, biopsy ≤15 mm, and biopsy >15 mm, respectively): 0.89 (0.87-0.90), 0.90 (0.87-0.93), 0.90 (0.88-0.93), 0.89 (0.87-0.92) Cirrhosis (METAVIR F4) APRI >1.0: 0.80 (0.77-0.83); >2.0: 0.71 (0.69-0.73) SAFE cirrhosis algorithm positive (whole sample, excluding F0 and F1 patients, biopsy ≤15 mm, and biopsy >15 mm, respectively): 0.92 (0.89-0.94), 0.77 (0.73-0.81), 0.88 (0.83-0.93), 0.94 (0.91-0.97)	Not stated, though reports no conflicts of interest to report	Fair	Population overlaps with Sebastiani 2008 and 2006 and appears to overlap with Halfon, Castera. Not clear how positive and negative results with SAFE algorithms defined and samples used to estimate diagnostic accuracy; unclear why different AUROC's reported for APRI based on cutoff values; unclear why specificity changes when excluding F4 patients from the SAFE fibrosis algorithm analysis

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Sebastiani, 2008 ¹²⁰	Whole sample, normal ALT, and elevated ALT, respectively Fibrosis (METAVIR F2-F4) Fibroindex >1.25: 0.62 (91/147), 0.41 (13/32), 0.68 (78/115); >2.25: 0.17 (25/147), 0.09 (3/32) [0.10*], 0.19 (22/115) APRI >0.5: 0.70 (103/147), 0.36 (12/32), 0.79 (91/115); >1.5: 0.24 (35/147), 0.14 (4/32), 0.27 (31/115) Fibrotest >0.49: 0.78 (115/147), 0.66 (21/32) [0.67*], 0.82 (94/115) AAR >1: 0.37 (54/147), 0.13 (4/32) [0.12*], 0.43 (50/115) Forns' Index >4.2: 0.79 (116/147), 0.56 (18/32) [0.57*], 0.85 (98/115); >6.9: 0.18 (27/147), 0.06 (2/32) [0.05*], 0.22 (25/115) [0.21*]	Whole sample, normal ALT, and elevated ALT, respectively Fibrosis (METAVIR F2-F4) Fibroindex >1.25: 0.48 (46/97), 0.77 (37/48), 0.18 (9/49) [0.19*]; >2.25: 1.0 (97/97), 1.0 (48/48), 1.0 (49/49) APRI >0.5: 0.74 (72/97), 0.91 (44/48), 0.57 (28/49); >1.5: 1.0 (97/97), 1.0 (48/48), 1.0 (49/49) Fibrotest >0.49: 0.78 (76/97), 0.85 (41/48), 0.71 (35/49) [0.72*] AAR >1: 0.73 (71/97), 0.88 (42/48), 0.59 (29/49) [0.58*], Forns' Index >4.2: 0.58 (56/97), 0.67 (32/48), 0.49 (24/49); >6.9: 0.99 (96/97), 0.98 (48/49), 1.0 (48/48)	Whole sample, normal ALT, and elevated ALT, respectively Fibrosis (METAVIR F2-F4) Fibroindex >1.25: 0.65 (91/140), 0.54 (13/24) [0.75*], 0.66 (78/118) [0.84*]; >2.25: 1.0 (25/25), 1.0 (3/3), 1.0 (22/22) APRI >0.5: 0.80 (103/128), 0.75 (12/16) [0.90*], 0.81 (91/112); >1.5: 1.0 (35/35), 1.0 (4/4), 1.0 (31/31) Fibrotest >0.49: 0.85 (115/136), 0.75 (21/28) [0.88*], 0.87 (94/108) AAR >1: 0.68 (54/80), 0.40 (4/10) [0.70*], 0.71 (50/70) [0.67*] Forns' Index >4.2: 0.74 (116/157), 0.53 (18/34) [0.75*], 0.80 (98/123) [0.79*]; >6.9: 0.96 (27/28), 1.0 (2/2), 0.96 (25/26)	Whole sample, normal ALT, and elevated ALT, respectively Fibrosis (METAVIR F2-F4) Fibroindex >1.25: 0.45 (46/102), 0.66 (37/56) [0.43*], 0.20 (9/46) [0.47*]; >2.25: 0.44 (97/219), 0.62 (48/77) [0.39*], 0.35 (49/142) [0.33*] APRI >0.5: 0.62 (72/116), 0.69 (44/64) [0.42*], 0.54 (28/52); >1.5: 0.46 (97/209), 0.63 (48/76) [0.57*], 0.37 (49/133) [0.36*] Fibrotest >0.49: 0.70 (76/108), 0.79 (41/52) [0.61*], 0.63 (35/56) [0.64*] AAR >1: 0.43 (71/164), 0.60 (42/70) [0.30*]; 0.31 (29/94) [0.35*] Forns' Index >4.2: 0.64 (56/87), 0.70 (32/46) [0.47*], 0.59 (24/41) [0.58*]; >6.9: 0.44 (96/216), 0.62 (48/78) [0.38*], 0.35 (48/138)	Normal ALT and elevated ALT, respectively (AUROC not reported for whole sample) Fibrosis (METAVIR F2-F4) Fibroindex: 0.58 (0.43-0.73) and 0.74 (0.63-0.85) APRI: 0.69 (0.54-0.85) and 0.75 (0.65-0.85) Fibrotest: 0.70 (0.59-0.81) and 0.79 (0.74-0.84) AAR: 0.51 (0.40-0.62) and 0.54 (0.48-0.60) Forns' Index: 0.60 (0.50-0.71) and 0.76 (0.71-0.81)	Not stated	Fair	Population substantially overlaps with Sebastiani 2006
Sebastiani, 2006 ¹²¹	Elevated ALT and normal ALT subgroups, respectively [n/N not reported] Fibrosis (METAVIR F2-F4) Fibrotest F2 cutoff: 0.65 and 0.58 Forn's Index >4.2: 0.80 and 0.79; >6.9: 0.24 and 0.12 APRI >0.5: 0.84 and 0.79; >1.5: 0.30 and 0.27 Cirrhosis (METAVIR F4) (whole sample) APRI >2.0: 0.38 (11/29) Fibrotest (cutoff not reported): 0.48 (14/29) [0.50*]	Elevated ALT and normal ALT subgroups, respectively [n/N not reported] Fibrosis (METAVIR F2-F4) Fibrotest F2 cutoff: 0.81 and 0.91 Forn's Index >4.2: 0.61 and 0.82; >6.9: 0.77 and 1.0 APRI >0.5: 0.77 and 0.95; >1.5: 0.94 and 1.0 Cirrhosis (METAVIR F4) (whole sample) APRI >2.0: 0.87 (140/161) Fibrotest (cutoff not reported): 0.93 (150/161)	Elevated ALT and normal ALT subgroups, respectively [n/N not reported] Fibrosis (METAVIR F2-F4) Fibrotest F2 cutoff: 0.80 and 0.78 Forn's Index >4.2: 0.78 and 0.85; >6.9: 0.95 and 1.0 APRI >0.5: 0.87 and 0.96; >1.5: 0.96 and 1.0 Cirrhosis (METAVIR F4) (whole sample) APRI >2.0: 0.34 (11/32) Fibrotest (cutoff not reported): 0.56 (14/25)	Elevated ALT and normal ALT subgroups, respectively [n/N not reported] Fibrosis (METAVIR F2-F4) Fibrotest F2 cutoff: 0.67 and 0.81 Forn's Index >4.2: 0.64 and 0.75; >6.9: 0.51 and 0.52 APRI >0.5: 0.72 and 0.72; >1.5: 0.53 and 0.57 Cirrhosis (METAVIR F4) (whole sample) APRI >2.0: 0.89 (140/158) Fibrotest (cutoff not reported): 0.91 (150/165)	Elevated ALT and normal ALT subgroups, respectively [n/N not reported] Fibrosis (METAVIR F2-F4) Fibrotest F2 cutoff: 0.81 (0.72-0.91) and 0.71 (0.49-0.92) Forn's Index: 0.79 (0.68-0.90) and 0.58 (0.43-0.73) APRI: 0.69 (0.54-0.85) and 0.77 (0.63-0.91) Cirrhosis (METAVIR F4) (whole sample) APRI: 0.61 (0.49-0.73) Fibrotest: 0.71 (0.60-0.82)	Not stated	Fair	Population substantially overlaps with Sebastiani 2008
Sheth, 1998 ¹²²	Cirrhosis (Hytiroglou F4) AST/ALT ratio \geq 1: 0.53 (25/47)	Cirrhosis (Hytiroglou F4) AST/ALT ratio \geq 1: 1.0 (92/92)	Cirrhosis (Hytiroglou F4) AST/ALT ratio \geq 1: 1.0 (25/25)	Cirrhosis (Hytiroglou F4) AST/ALT ratio \geq 1: 0.81 (92/114)	Not reported	Not stated	Fair	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Silva, 2004 ¹²³	Severe fibrosis (Desmet 3 or 4) GGT >1x upper limit of normal: 0.63 (40/63)	Severe fibrosis (Desmet 3 or 4) GGT >1x upper limit of normal: 0.59 (82/138)	Severe fibrosis (Desmet 3 or 4) GGT >1x upper limit of normal: 0.42 (40/96)	Severe fibrosis (Desmet 3 or 4) GGT >1x upper limit of normal: 0.78 (82/105)	Not reported	Not stated	Fair	
Sirli, 2010 ¹²⁴	Fibrosis (METAVIR F2-F4) APRI >0.52: 0.70 (94/134) Forns' Index >4.57: 0.72 (96/138) Lok Index >0.17: 0.58 (77/134) FIB-4 >2.14: 0.36 (48/134) Platelet count <176: 0.37 (50/134) Cirrhosis (METAVIR F4) APRI >1.38: 0.93 (14/15) Forns' Index >5.93: 1.0 (15/15) Lok Index >0.26: 0.87 (13/15) FIB-4 >2.31: 0.80 (12/15) Platelet count <155: 0.87 (13/15)	Fibrosis (METAVIR F2-F4) APRI >0.52: 0.81 (13/16) Forns' Index >4.57: 0.68 (11/16) Lok Index >0.17: 0.81 (13/16) FIB-4 >2.14: 1.0 (16/16) Platelet count <176: 1.0 (16/16) Cirrhosis (METAVIR F4) APRI >1.38: 0.83 (112/135) Forns' Index >5.93: 0.74 (100/135) Lok Index >0.26: 0.82 (111/135) FIB-4 >2.31: 0.78 (105/135) Platelet count <155: 0.84 (113/135)	Fibrosis (METAVIR F2-F4) APRI >0.52: 0.97 (94/97) Forns' Index >4.57: 0.95 (96/101) Lok Index >0.17: 0.96 (77/80) FIB-4 >2.14: 1.0 (48/48) Platelet count <176: 1.0 (50/50) Cirrhosis (METAVIR F4) APRI >1.38: 0.38 (14/37) Forns' Index >5.93: 0.30 (15/50) Lok Index >0.26: 0.35 (13/37) FIB-4 >2.31: 0.29 (12/42) Platelet count <155: 0.37 (13/35)	Fibrosis (METAVIR F2-F4) APRI >0.52: 0.27 (13/49) [0.24*] Forns' Index >4.57: 0.22 (11/16) [0.24*] Lok Index >0.17: 0.19 (13/70) FIB-4 >2.14: 0.16 (16/102) Platelet count <176: 0.16 (16/100) Cirrhosis (METAVIR F4) APRI >1.38: 0.99 (112/113) Forns' Index >5.93: 1.0 (100/100) Lok Index >0.26: 0.98 (111/113) FIB-4 >2.31: 0.97 (105/108) Platelet count <155: 0.98 (113/115)	Fibrosis (METAVIR F2-F4) APRI: 0.77 (0.69-0.83) Forns' Index: 0.75 (0.67-0.82) Lok Index: 0.70 (0.62-0.77) FIB-4: 0.69 (0.60-0.76) Platelet count: 0.73 (0.65-0.80) Cirrhosis (METAVIR F4) APRI: 0.91 (0.85-0.95) Forns' Index: 0.91 (0.85-0.95) Lok Index: 0.87 (0.81-0.92) FIB-4: 0.84 (0.77-0.90) Platelet count: 0.90 (0.84-0.94)	Not stated	Fair	
Snyder, 2007 ¹²⁵	Fibrosis (Batts-Ludwig F2-F4) APRI >0.42: 0.98 (49/50); >=1.20: 0.62 (31/50) FIBROSpect II >25: 1.0 (50/50); >=55: 0.82 (41/50); >=85: 0.52 (26/50)	Fibrosis (Batts-Ludwig F2-F4) APRI >0.42: 0.44 (19/43); >=1.20: 0.95 (41/43) FIBROSpect II >25: 0.42 (18/43); >=55: 0.77 (33/43); >=85: 1.0 (43/43)	Fibrosis (Batts-Ludwig F2-F4) APRI >0.42: 0.63 (49/73); >=1.20: 0.94 (31/33) FIBROSpect II >25: 0.67 (50/75); >=55: 0.80 (41/51); >=85: 1.0 (26/26)	Fibrosis (Batts-Ludwig F2-F4) APRI >0.42: 0.95 (19/20); >=1.20: 0.68 (41/60) FIBROSpect II >25: 1.0 (18/18); >=55: 0.79 (33/42); >=85: 0.64 (43/67)	Fibrosis (Batts-Ludwig F2-F4) APRI: 0.89 (0.81-0.92) FIBROSpect II: 0.88 (0.79-0.94) APRI + FIBROSpect II: 0.93 (0.86-0.97)	National Institutes of Health	Fair	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Snyder, 2006 ¹²⁶	<p>Fibrosis (Batt-Ludwig F2-F4) (retrospective and prospective samples, respectively) APRI >0.50: 0.84 (147/176) [0.83*] and 0.87 (68/78); ≥1.0: Not reported and 0.65 (51/78); ≥1.2: 0.39 (69/107) [0.41*] and not reported; ≥1.5: 0.30 (52/176) [0.31*] and 0.45 (35/78) [0.44*]</p> <p>Severe fibrosis (Batt-Ludwig F3-F4) (retrospective and prospective samples, respectively) APRI >0.50: 0.94 (62/66) and 0.96 (47/49); >0.70: 0.79 (52/66) and 0.88 (43/49); ≥1.20: 0.50 (33/66) and 0.71 (35/49) [0.73*]</p> <p>Cirrhosis (Batt-Ludwig F4) (prospective sample)APRI ≥2.0: 0.50 (13/26)AST/ALT ≥1.0: 0.42 (11/26)</p>	<p>Fibrosis (Batt-Ludwig F2-F4) (retrospective and prospective samples, respectively) APRI >0.50: 0.55 (95/174) [0.54*] and 0.62 (45/72); ≥1.0: Not reported and 0.92 (66/72); ≥1.2: 0.90 (157/174) and not reported; ≥1.5: 0.97 (168/174) [0.96*] and 0.94 (68/72)</p> <p>Severe fibrosis (Batt-Ludwig F3-F4) (retrospective and prospective samples, respectively) APRI >0.50: 0.43 (117/273) and 0.48 (49/102); >0.70: 0.62 (169/273) and 0.64 (65/102) [0.63*]; ≥1.20: 0.81 (220/273) and 0.82 (84/102)</p> <p>Cirrhosis (Batt-Ludwig F4) (prospective sample) APRI ≥2.0: 0.94 (118/125) AST/ALT ≥1.0: 0.87 (109/125)</p>	<p>Fibrosis (Batt-Ludwig F2-F4) (retrospective and prospective samples, respectively) APRI >0.50: 0.65 (147/226) and 0.72 (68/95); ≥1.0: Not reported and 0.89 (51/57) [0.90*]; ≥1.2: 0.80 (69/86) [0.78*] and not reported; ≥1.5: 0.90 (52/58) and 0.90 (35/39)</p> <p>Severe fibrosis (Batt-Ludwig F3-F4) (retrospective and prospective samples, respectively) APRI >0.50: 0.28 (62/218) and 0.47 (47/100); >0.70: 0.33 (52/104) and 0.54 (43/80); ≥1.20: 0.38 (33/86) and 0.66 (35/53)</p> <p>Cirrhosis (Batt-Ludwig F3-F4) (prospective sample) APRI ≥2.0: 0.65 (13/20) AST/ALT ≥1.0: 0.41 (11/27)</p>	<p>Fibrosis (Batt-Ludwig F2-F4) (retrospective and prospective samples, respectively) APRI >0.50: 0.77 (95/124) and 0.82 (45/55); ≥1.0: Not reported and 0.71 (66/93); ≥1.2: 0.59 (157/264) and not reported; ≥1.5: 0.58 (168/292) and 0.61 (68/111)</p> <p>Severe fibrosis (Batt-Ludwig F3-F4) (retrospective and prospective samples, respectively) APRI >0.50: 0.97 (117/121) and 0.96 (49/51); >0.70: 0.92 (169/183) and 0.92 (65/71); ≥1.20: 0.87 (220/253) and 0.86 (84/98)</p> <p>Cirrhosis (Batt-Ludwig F4) (prospective sample) APRI ≥2.0: 0.90 (118/131) AST/ALT ≥1.0: 0.88 (109/124)</p>	Fibrosis (retrospective and prospective samples, respectively) APRI: 0.79 (0.74-0.83) and 0.89 (0.82-0.93) AST/ALT: 0.52 (0.47-0.57) and 0.62 (0.54-0.69) Severe fibrosis and cirrhosis: Not reported	National Institutes of Health	Fair	Data presented for 350 patients in retrospective sample, but only 339 reported as enrolled
Stibbe, 2011 ¹²⁷	<p>Fibrosis (METAVIR F2-F4) FibroTest >0.31: 0.74 (16/22)</p> <p>Severe fibrosis (METAVIR F3-F4) FibroTest >0.58: 0.91 (16/18) FIB-4 >1.45: 0.72 (13/18); >3.25: 0.28 (5/18)</p> <p>Cirrhosis (METAVIR F4) FibroTest >0.75: 1.0 (11/11)</p>	<p>Fibrosis (METAVIR F2-F4) FibroTest >0.31: 0.76 (14/18)</p> <p>Severe fibrosis (METAVIR F3-F4) FibroTest >0.58: 0.41 (13/22) FIB-4 >1.45: 0.70 (16/23); >3.25: 1.0 (23/23)</p> <p>Cirrhosis (METAVIR F4) FibroTest >0.75: 0.24 (22/29)</p>	<p>Fibrosis (METAVIR F2-F4) FibroTest >0.31: 0.80 (16/20) [0.74*]</p> <p>Severe fibrosis (METAVIR F3-F4) FibroTest >0.58: 0.55 (16/29) [0.68*] FIB-4 >1.45: 0.65 (13/20); >3.25: 1.0 (5/5)</p> <p>Cirrhosis (METAVIR F4) FibroTest >0.75: 0.33 (11/33) [0.64*]</p>	<p>Fibrosis (METAVIR F2-F4) FibroTest >0.31: 0.70 (14/20) [0.76*]</p> <p>Severe fibrosis (METAVIR F3-F4) FibroTest >0.58: 0.82 (9/11) [0.78*] FIB-4 >1.45: 0.76 (16/21); >3.25: 0.64 (23/36)</p> <p>Cirrhosis (METAVIR F4) FibroTest >0.75: 1.0 (7/7)</p>	Not reported for HCV subgroup	Not reported	Fair	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Sud, 2004 ¹²⁸	Derivation and validation samples, respectively Fibrosis (Scheuer F2-F4) Fibrosis probability index ≥ 0.2 : 0.96 (80/83) and 0.85 (63/74); ≥ 0.8 : 0.45 (37/83) and 0.42 (31/74)	Derivation and validation samples, respectively Fibrosis (Scheuer F2-F4) Fibrosis probability index ≥ 0.2 : 0.44 (38/87) and 0.48 (25/52); ≥ 0.8 : 0.94 (82/87) and 0.98 (51/52)	Derivation and validation samples, respectively Fibrosis (Scheuer F2-F4) Fibrosis probability index ≥ 0.2 : 0.62 (80/129) and 0.70 (63/90); ≥ 0.8 : 0.88 (37/42) and 0.97 (31/32)	Derivation and validation samples, respectively Fibrosis (Scheuer F2-F4) Fibrosis probability index ≥ 0.2 : 0.93 (38/41) and 0.69 (25/36); ≥ 0.8 : 0.64 (82/128) and 0.54 (51/94)	Derivation and validation samples, respectively Fibrosis (Scheuer F2-F4) Fibrosis probability index: 0.84 and 0.77 (confidence intervals not reported)	National Institutes of Health, the Centre for Clinical Research Excellence award, the Australian National Health and Medical Research Council, and the Robert W. Storr Bequest	Fair	
Testa, 2006 ¹²⁹	Fibrosis (Ishak ≥ 3) BMI >25 : 0.62 (23/37) Platelet-spleen diameter ratio <1750 : 0.78 (29/37) APRI >0.864 : 0.70 (11/37) Fibrosis model 1 >0.801 : 0.81 (30/37)	Fibrosis (Ishak ≥ 3) BMI >25 : 0.84 (32/38) Platelet-spleen diameter ratio <1750 : 0.79 (30/38) APRI >0.864 : 0.79 (30/38) Fibrosis model 1 >0.801 : 0.71 (27/38)	Fibrosis (Ishak ≥ 3) BMI >25 : 0.79 (23/29) Platelet-spleen diameter ratio <1750 : 0.78 (29/37) APRI >0.864 : 0.58 (11/19) Fibrosis model 1 >0.801 : 0.73 (30/41)	Fibrosis (Ishak ≥ 3) BMI >25 : 0.70 (32/46) Platelet-spleen diameter ratio <1750 : 0.79 (30/38) APRI >0.864 : 0.54 (30/56) Fibrosis model 1 >0.801 : 0.79 (27/34)	Fibrosis (Ishak ≥ 3) BMI: 0.73 (0.61-0.82) Platelet-spleen diameter ratio: 0.74 (0.63-0.84) APRI: 0.72 (0.60-0.82) Fibrosis model 1: 0.80 (0.69-0.88)	Funded in part by Ministero dell'universita e della Ricerca Scientifica e Tecnologica and by Fondazione Aurelia Castagnino ONLUSS	Fair	
Trocme, 2006 ¹³⁰	Fibrosis Not reported	Fibrosis Not reported	Fibrosis Not reported	Fibrosis Not reported	Fibrosis PIIIP/MMP-1 index: 0.77 (CI not reported)	DRRC, CHU de Grenoble	Fair	
Vallet-Pichard, 2007 ¹³¹	Severe fibrosis (METAVIR F3-F4)FIB-4 ≥ 1.45 : 0.74 (108/146); >3.25 : 0.38 (55/146)	Severe fibrosis (METAVIR F3-F4)FIB-4 ≥ 1.45 : 0.80 (562/701); >3.25 : 0.98 (688/701)	Severe fibrosis (METAVIR F3-F4)FIB-4 ≥ 1.45 : 0.44 (108/247); >3.25 : 0.81 (55/68) [0.82*]	Severe fibrosis (METAVIR F3-F4)FIB-4 ≥ 1.45 : 0.94 (562/600) [0.95*]; >3.25 : 0.88 (688/779)	Severe fibrosis (METAVIR F3-F4)FIB-4: 0.85 (0.82-0.89)	Not stated	Fair	
Verbaan, 1997 ¹³²	Cirrhosis (Scheuer F4) PIIIP >1.11 U/ml: 0.82 (9/11) [0.78*] Type-IV collagen >250 ng/ml: 0.91 (10/11) [0.87*]	Cirrhosis (Scheuer F4) PIIIP >1.11 U/ml: 0.56 (49/87) Type-IV collagen >250 ng/ml: 0.75 (65/87)	Cirrhosis (Scheuer F4) PIIIP >1.11 U/ml: 0.19 (9/47) Type-IV collagen >250 ng/ml: 0.31 (10/32)	Cirrhosis (Scheuer F4) PIIIP >1.11 U/ml: 0.96 (49/51) Type-IV collagen >250 ng/ml: 0.98 (65/66)	Not reported	Not stated	Fair	Unable to construct 2 x 2 table
Viana, 2009 ⁵⁸	Fibrosis (METAVIR F2-F4), sample 1 and sample 2, respectively APRI ≥ 0.75 : 0.82 (98/120) and 0.83 (105/126) Cirrhosis (METAVIR F4), sample 1 and sample 2, respectively APRI ≥ 1.05 : 0.88 (70/80) and 0.86 (73/85)	Fibrosis (METAVIR F2-F4), sample 1 and sample 2, respectively APRI ≥ 0.75 : 0.95 (76/80) and 0.82 (61/74) Cirrhosis (METAVIR F4), sample 1 and sample 2, respectively APRI ≥ 1.05 : 0.95 (114/120) and 0.90 (104/115)	Fibrosis (METAVIR F2-F4), sample 1 and sample 2, respectively APRI ≥ 0.75 : 0.96 (98/102) and 0.89 (105/118) Cirrhosis (METAVIR F4), sample 1 and sample 2, respectively APRI ≥ 1.05 : 0.92 (70/76) and 0.87 (73/84)	Fibrosis (METAVIR F2-F4), sample 1 and sample 2, respectively APRI ≥ 0.75 : 0.78 (76/98) and 0.74 (61/82) Cirrhosis (METAVIR F4), sample 1 and sample 2, respectively APRI ≥ 1.05 : 0.92 (114/124) and 0.90 (104/116)	Fibrosis (METAVIR F2-F4), sample 1 and sample 2, respectively APRI ≥ 0.75 : 0.95 (0.91-0.97) and 0.92 (0.87-0.95) Cirrhosis (METAVIR F4), sample 1 and sample 2, respectively APRI ≥ 1.05 : 0.96 (0.93-0.98) and 0.93 (0.88-0.96)	Not stated	Fair	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Wai, 2003 ¹³³	Fibrosis (Ishak 3-6) APRI >0.50: 0.91 (83/91); >1.50: 0.41 (37/91) Cirrhosis (Ishak 5 or 6) APRI >1.00: 0.89 (25/28); >2.00: 0.57 (16/28)	Fibrosis (Ishak 3-6) APRI >0.50: 0.47 (47/101); >1.50: 0.95 (96/101) Cirrhosis (Ishak 5 or 6) APRI >1.00: 0.75 (41/164); >2.00: 0.93 (152/164)	Fibrosis (Ishak 3-6) APRI >0.50: 0.61 (83/137); >1.50: 0.88 (37/42) Cirrhosis (Ishak 5 or 6) APRI >1.00: 0.38 (25/66); >2.00: 0.57 (16/28)	Fibrosis (Ishak 3-6) APRI >0.50: 0.86 (47/55); >1.50: 0.64 (96/150) Cirrhosis (Ishak 5 or 6) APRI >1.00: 0.98 (123/126); >2.00: 0.93 (152/164)	Fibrosis (Ishak 3-6) APRI: 0.83 (0.78- 0.88) Cirrhosis (Ishak 5 or 6) APRI: 0.90 (0.86- 0.94)	Singapore HMDP Fellowship and National Institutes of Health	Good	Derivation and validation sets, results not reported separately but estimates were similar between groups.
Walsh, 2000 ¹³⁴	Advanced liver disease (Ishak ≥ 3 and HAI ≥ 6) Type IV collagen >148 ng/ml: 0.73 Serum laminin >1.26 U/ml: 0.80	Advanced liver disease (Ishak ≥ 3 and HAI ≥ 6) Type IV collagen >148 ng/ml: 0.85 Serum laminin >1.26 U/ml: 0.83	Not reported	Not reported	Advanced liver disease (Ishak ≥ 3 and HAI ≥ 6) Type IV collagen: 0.83 (0.69-0.97) Serum laminin: 0.82 (0.66-0.98) ALT: 0.54 (0.34-0.74)	Sanofi Winthrop Foundation and Peel Medical Research Trust	Fair	Can't create 2 x 2 table (no prevalence of advanced liver disease given). May be same population as Walsh 1999a and 1999b.
Walsh, 1999a ¹³⁵	Advanced liver disease (Ishak ≥ 3 and HAI ≥ 6) PIIIP (Col 1-3 and Col 1 assay) >0.8 U/ml: 0.50 PIIIP (Col 1-3 assay) >4.2 mg/l: 0.85 ALT >55 IU/l: 0.71	Advanced liver disease (Ishak ≥ 3 and HAI ≥ 6) PIIIP (Col 1-3 and Col 1 assay) >0.8 U/ml: 0.88 PIIIP (Col 1-3 assay) >4.2 mg/l: 0.38 ALT >55 IU/l: 0.44	Not reported	Not reported	Advanced liver disease (Ishak ≥ 3 and HAI ≥ 6) PIIIP (Col 1-3 and Col 1 assay): 0.76 (0.58-0.94) PIIIP (Col 1-3 assay): 0.67 (0.57-0.87) ALT: 0.51 (0.39-0.63)	Sanofi Winthrop Foundation and Peel Medical Research Trust	Fair	Can't create 2 x 2 table (no prevalence of advanced liver disease given). Appears to be same population as Walsh 1999b, and may be same population as Walsh 2001.
Walsh, 1999b ¹³⁶	Advanced liver disease (Ishak ≥ 3 and HAI ≥ 6) TIMP-1 >500 ng/ml: 0.94 TIMP-2 >102 ng/ml: 0.85 MMP-2 >860 ng/ml: 0.69 ALT >60 IU/l: 0.67	Advanced liver disease (Ishak ≥ 3 and HAI ≥ 6) TIMP-1 >500 ng/ml: 0.57 TIMP-2 >102 ng/ml: 0.47 MMP-2 >860 ng/ml: 0.59 ALT >60 IU/l: 0.52	Not reported	Not reported	Advanced liver disease (Ishak ≥ 3 and HAI ≥ 6) TIMP-1: 0.73 (0.57-0.89) TIMP-2: 0.73 (0.55-0.91) MMP-2: 0.67 (0.47-0.87) ALT: 0.59 (0.41-0.77)	Sanofi Winthrop Foundation and Peel Medical Research Trust	Fair	Can't create 2 x 2 table (no prevalence of advanced liver disease given). Appears to be same population as Walsh 1999a, and may be same population as Walsh 2001.
Williams, 1988 ¹³⁷	Cirrhosis (Hoofnagle criteria) AST/ALT ratio >1.0: 0.27 (3/11)	Cirrhosis (Hoofnagle criteria) AST/ALT ratio >1.0: 0.94 (31/33)	Cirrhosis (Hoofnagle criteria) AST/ALT ratio >1.0: 0.60 (3/5)	Cirrhosis (Hoofnagle criteria) AST/ALT ratio >1.0: 0.79 (31/39)	Not reported	Not stated	Fair	Non-A, non-B hepatitis based on history of parenteral drug abuse or exposure to blood products, elevation in serum aminotransferases for at least 6 months, absence of hepatitis B surface antigen, absence of other known cause for liver disease, and compatible hepatic histology

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Wilson, 2006 ¹³⁸	Ishak 3-4 fibrosis Fibrotest ≥ 0.31 : 0.89; >0.48 : 0.56 (n/N unclear) APRI ≥ 0.5 : 0.73 (8/11); >1.5 : 0.18 (2/11) ALT $>$ upper limit of normal: 0.73 (8/11) AST $>$ upper limit of normal: 0.82 (9/11)	Ishak 3-4 fibrosis Fibrotest ≥ 0.31 : 0.49; >0.48 : 0.65 (n/N unclear) APRI ≥ 0.5 : 0.59 (63/108) [0.58*]; >1.5 : 0.94 (102/108) ALT $>$ upper limit of normal: 0.73 (79/108) AST $>$ upper limit of normal: 0.64 (69/108)	Ishak 3-4 fibrosis Fibrotest ≥ 0.31 : 0.13 (n/N unclear); >0.48 : 0.14 (5/37) [0.12*] APRI ≥ 0.5 : 0.15 (8/53); >1.5 : 0.25 (2/8) ALT $>$ upper limit of normal: 0.22 (8/37) AST $>$ upper limit of normal: 0.19 (9/48)	Ishak 3-4 fibrosis Fibrotest ≥ 0.31 : 0.98 (52/53); >0.48 : 0.94 APRI ≥ 0.5 : 0.95 (63/66); >1.5 : 0.92 (102/111) ALT $>$ upper limit of normal: 0.96 (79/82) AST $>$ upper limit of normal: 0.97 (69/71)	Fibrosis (Ishak 3-4) Fibrotest: 0.74 (CI not reported) APRI: 0.70 (CI not reported) ALT $>$ upper limit of normal: Not reported AST $>$ upper limit of normal: Not reported	US Public Health Service	Fair	Excludes patients with Ishak 5-6 fibrosis; all injection drug users
Wong, 1998 ¹³⁹	Severe fibrosis (modified Ishak 4-5 [max 5]) Hyaluronic acid (cutoff not described): 0.86 (18/21) ALT (cutoff not described): 0.76 (16/21) GST (cutoff not described): 0.48 (10/21)	Severe fibrosis (modified Ishak 4-5 [max 5]) Hyaluronic acid (cutoff not described): 0.88 (96/109) ALT (cutoff not described): 0.48 (52/109) GST (cutoff not described): 0.39 (43/109)	Severe fibrosis (modified Ishak 4-5 [max 5]) Hyaluronic acid (cutoff not described): 0.58 (18/31) ALT (cutoff not described): 0.22 (16/73) GST (cutoff not described): 0.13 (10/76)	Severe fibrosis (modified Ishak 4-5 [max 5]) Hyaluronic acid (cutoff not described): 0.97 (96/99) ALT (cutoff not described): 0.91 (52/57) GST (cutoff not described): 0.80 (43/54)	Not reported	Not stated	Fair	
Yilmaz, 2011 ¹⁴⁰	Mild fibrosis (METAVIR F1-F4) APRI >0.44 : 0.73	Mild fibrosis (METAVIR F1-F4) APRI >0.44 : 0.62	Not reported	Not reported	Mild fibrosis (METAVIR F1-F4) APRI: 0.58 (0.52-0.70)	Not stated	Fair	
Zaman, 2007 ¹⁴¹	Fibrosis (METAVIR F2-F4) FibroSpect II ≥ 42 : 0.72 (28/39) Severe fibrosis (METAVIR F3-F4) FibroSpect II ≥ 42 : 0.82 (11/14)	Fibrosis (METAVIR F2-F4) FibroSpect II ≥ 42 : 0.74 (51/69) Severe fibrosis (METAVIR F3-F4) FibroSpect II ≥ 42 : 0.63 (59/94)	Fibrosis (METAVIR F2-F4) FibroSpect II ≥ 42 : 0.61 (28/46) Severe fibrosis (METAVIR F3-F4) FibroSpect II ≥ 42 : 0.24 (11/46) [0.20*]	Fibrosis (METAVIR F2-F4) FibroSpect II ≥ 42 : 0.82 (51/62) Severe fibrosis (METAVIR F3-F4) FibroSpect II ≥ 42 : 0.95 (59/62) [0.97*]	Fibrosis (METAVIR F2-F4) FibroSpect II: 0.83 (CI not reported) Severe fibrosis (METAVIR F3-F4) FibroSpect II: Not reported	Not stated	Fair	

Study, Year	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area under the receiver operating curve	Funding source	Overall Quality	Notes
Zarski, 2012 ¹⁴²	Not reported	Not reported	Not reported	Not reported	<p>Fibrosis (METAVIR F2-F4) FibroTest: 0.80 (0.75-0.84) FibroMeter: 0.82 (0.78-0.86) Forn's Index: 0.75 (0.71-0.80) APRI: 0.76 (0.72-0.81) MP3: 0.76 (0.71-0.80) ELF: 0.78 (0.74-0.83) Hepascore: 0.82 (0.78-0.85) FIB-4: 0.76 (0.71-0.80) Hyaluronic acid: 0.75 (0.70-0.80)</p> <p>Cirrhosis (METAVIR F4) FibroTest: 0.86 (0.83-0.90) FibroMeter: 0.89 (0.86-0.93) APRI: 0.86 (0.81-0.91) ELF: 0.88 (0.83-0.92) Hepascore: 0.89 (0.86-0.93) FIB-4: 0.83 (0.76-0.89)</p>	French Agency for Research on AIDS and Viral Hepatitis	Good	ANRS HCEP 23 Fibrostar

Abbreviations: HCV, hepatitis C virus; SVR, sustained virologic response.

Evidence Table 6: Key Question 4a. Overall Quality Rating

Study, year	Representative spectrum	Random or consecutive sample	Test cutoffs predefined	Credible reference standard	Attempted to apply reference standard to all patients, or a random subset	Same reference standard applied to all patients	Reference standard interpreted independently from test under evaluation	Overall Quality
Adams, 2005 b ⁷	Yes	Unclear	Yes (for validation sample)	Yes	Yes	Yes	Yes	Good
Ahmad, 2011 ⁸	Yes	Unclear	Not relevant (AUROC only)	Yes	Yes	Yes	Yes	Fair
Alder, 2008 ¹⁰	Yes	Unclear	Not relevant (AUROC only)	Yes	Yes	Yes	Yes	Fair
Alsatie, 2007 ⁹	Yes	Unclear	Yes (for validation sample)	Yes	Yes	Yes	Unclear	Fair
Anderson, 2000 ¹¹	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Fair
Becker, 2009 ¹²	Yes	Unclear	Unclear (for Hepascore)	Yes	Yes	Yes	Yes	Fair
Bejarano, 2009 ¹³	No (no grade 2 fibrosis)	Yes	No	Yes	Yes	Yes	Yes	Fair
Ben Jazia, 2009 ¹⁵	Yes	Unclear	No	Yes	Yes	Yes	Unclear	Fair
Berg, 2004 ¹⁴³	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	Fair
Boeker, 2002 ¹⁶	No (case-control design)	Unclear	Unclear	Yes	Yes	Yes	Unclear	Poor
Bonacini, 1997 ¹⁷	Yes	Unclear	No (for Cirrhosis Discriminant Score)	Yes	Yes	Yes	Yes	Fair
Borroni, 2006 ¹⁸	Yes	Yes	No	Yes	Yes	Yes	Yes	Fair
Bota, 2011 ¹⁹	No	Unclear	Not relevant (AUROC only)	Yes	Yes	Yes	Yes	Fair
Bourliere, 2008 ²⁰	Yes	Yes	No	Yes	Yes	Yes	Unclear	Fair
Bourliere, 2006 ²¹	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Fair
Boursier, 2012 ²²	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Fair
Boursier, 2011 ²³	Yes	Unclear	No	Yes	Yes	Yes	Unclear	Fair
Boursier, 2009 ²⁴	Yes	Unclear	No	Yes	Yes	Yes	Yes	Fair
Burton, 2011 ²⁵	Yes	Unclear	No	Yes	Yes	Yes	Unclear	Fair

Study, year	Representative spectrum	Random or consecutive sample	Test cutoffs predefined	Credible reference standard	Attempted to apply reference standard to all patients, or a random subset	Same reference standard applied to all patients	Reference standard interpreted independently from test under evaluation	Overall Quality
Cales, 2010 ²⁶	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Fair
Cales, 2008 ¹⁴⁴	Yes	Unclear	No	Yes	Yes	Yes	Yes	Fair
Castera, 2010 ²⁸	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Castera, 2009 ²⁹	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Castera, 2005 ³⁰	Yes	Yes	Not relevant (AUROC only)	Yes	Yes	Yes	Yes	Fair
Cheong, 2011 ³¹	Yes	Yes	No (for Significant Fibrosis Index)	Yes	Yes	Yes	Yes	Fair
Cheung, 2008 ³³	Yes	No	Yes	Yes	Yes	Yes	Unclear	Fair
Cheung, 2011 ³²	Yes	Unclear	No (for Fibrosis-protein Index)	Yes	Yes	Yes	Unclear	Fair
Chrysanthos, 2006 ³⁴	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Cobbold, 2009 ¹⁴⁵	Yes	Unclear	No	Yes	Yes	Yes	Yes	Fair
Colletta, 2005 ³⁶	Yes	Yes	Yes (for Fibrotest)	Yes	Yes	Yes	Yes	Fair
Colli, 2005 ³⁷	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Fair
Crisan, 2012 ³⁸	Yes	Yes	No	Yes	Yes	Yes	Unclear	Fair
Cross, 2010 ³⁹	Yes	Yes	No	Yes	Yes	Yes	Yes	Fair
Cross, 2009 ⁴⁰	Yes	Yes	No	Yes	Yes	Yes	Yes	Fair
Ehsan, 2008 ⁴¹	Yes	Unclear	No	Yes	Yes	Yes	Unclear	Poor
El-Gindy, 2003 ⁴²	Yes	Unclear	No	Yes	Yes	Yes	Unclear	Fair
El-Sayed, 2011 ⁴³	No	Unclear	Not relevant (AUROC only)	Yes	Yes	Yes	Yes	Fair
El-Shorbagy, 2004 ⁴⁴	Yes	Unclear	No	Unclear	Yes	Yes	Unclear	Poor
Fabris, 2008 ⁴⁵	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Fair
Fontana, 2008 ⁴⁶	Yes	Yes	No	Yes	Yes	Yes	Unclear	Fair
Forns, 2002 ⁴⁷	Yes	Yes	Yes (for validation sample)	Yes	Yes	Yes	Yes	Good
Friedrich-Rust, 2010 ⁴⁸	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Fair

Study, year	Representative spectrum	Random or consecutive sample	Test cutoffs predefined	Credible reference standard	Attempted to apply reference standard to all patients, or a random subset	Same reference standard applied to all patients	Reference standard interpreted independently from test under evaluation	Overall Quality
Gabrielli, 1997 ⁴⁹	Yes	Unclear	No	Yes	Yes	Yes	Unclear	Fair
Giannini, 2006 ⁵⁰	Yes	Unclear	No	Yes	Yes	Yes	Yes	Fair
Giannini, 2003a ⁵¹	Yes	Unclear	Yes (for AST/ALT ratio)	Yes	Yes	Yes	Yes	Fair
Giannini, 2003b ⁵²	Yes	Unclear	Yes (for AST/ALT ratio)	Yes	Yes	Yes	Unclear	Fair
Gomes da Silva, 2008 ⁵³	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Fair
Grigorescu, 2007 ⁵⁴	Yes	Unclear	No	Yes	Yes	Yes	Yes	Fair
Guechot, 2010 ⁵⁵	Yes	Unclear	No	Yes	Yes	Yes	Yes	Fair
Guechot, 1996 ⁵⁶	Yes	Unclear	No	Yes	Yes	Yes	Unclear	Fair
Guechot, 1994 ⁵⁷	Yes	Unclear	No	Yes	Yes	Yes	Unclear	Fair
Guzelbulut, 2011 ⁵⁸	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Fair
Halfon, 2007 ⁵⁹	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Fair
Halfon, 2006 ⁶⁰	Yes	Yes	No	Yes	Yes	Yes	Unclear	Fair
Halfon, 2005 ⁶¹	Yes	Unclear	Yes (for validation sample)	Yes	Yes	Yes	Unclear	Fair
Hsieh, 2009 ⁶²	Yes	Yes	No	Yes	Yes	Yes	Unclear	Fair
Iacobellis, 2005a ⁶³	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	Fair
Iacobellis, 2005b ⁶⁴	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	Fair
Imbert-Bismut, 2001 ⁶⁵	Yes	Yes	No	Yes	Yes	Yes	Yes	Fair
Imperiale, 2000 ⁶⁸	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Fair
Islam, 2005 ⁶⁹	Yes	Unclear	No	Yes	Yes	Yes	Yes	Fair
Kaul, 2002 ⁷⁰	Yes	Unclear (for validation sample)	Not relevant (AUROC only)	Yes	Yes	Yes	Yes	Fair
Khan, 2008 ⁷¹	Yes	Unclear	No	Yes	Yes	Yes	Yes	Fair
Khokhar, 2003 ⁷²	Yes	Unclear	No	Yes	Yes	Yes	Yes	Fair
Koda, 2007 ⁷³	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Lackner, 2005 ⁷⁴ and 2006 ⁷⁵	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Fair

Study, year	Representative spectrum	Random or consecutive sample	Test cutoffs predefined	Credible reference standard	Attempted to apply reference standard to all patients, or a random subset	Same reference standard applied to all patients	Reference standard interpreted independently from test under evaluation	Overall Quality
Leroy, 2008 ⁷⁶	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Fair
Leroy, 2007 ⁷⁷	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Fair
Leroy, 2004 ⁷⁸	Yes	Yes	No	Yes	Yes	Yes	Yes	Fair
Liu, 2006 ⁷⁹	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Fair
Lo Iacono, 1998 ⁸¹	Yes	Yes	No	Yes	Yes	Yes	Unclear	Fair
Loeza-del-Castillo, 2008 ⁸⁰	Yes	Yes	No	Yes	Yes	Yes	Unclear	Fair
Lok, 2005 ⁸²	No	Yes	Yes	Yes	Yes	Yes	Unclear	Fair
Luo, 2002 ⁸³	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Fair
Martinez, 2011 ⁸⁴	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Fair
McHutchison, 2000 ⁸⁵	No (no grade 2 fibrosis)	Unclear	Yes	Yes	Yes	Yes	Yes	Fair
Metwally, 2007 ⁸⁶	Yes	Yes	No	Yes	Yes	Yes	Yes	Fair
Murawaki, 2001a ⁸⁸	Yes (except no F4)	Unclear	No	Yes	Yes	Yes	Yes	Fair
Murawaki, 2001b ⁸⁷	Yes (except no F4)	Unclear	No	Yes	Yes	Yes	Unclear	Fair
Myers, 2003 ¹⁴⁶	Yes	Unclear	No	Yes	Yes	Yes	Unclear	Fair
Myers, 2003 ⁸⁹	Yes	Yes	No	Yes	Yes	Yes	Yes	Fair
Myers, 2002 ⁹⁰	Yes	Yes	No	Yes	Yes	Yes	Yes	Fair
Obrador, 2006 ⁹¹	Yes	Yes	Yes (for derivation sample)	Yes	Yes	Yes	Yes	Fair
Ohta, 2006 ⁹²	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Omran, 2011 ⁹³	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Paggi, 2008 ⁹⁴	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Parise, 2006 ⁹⁵	Yes	Yes	No	Yes	Yes	Yes	Yes	Fair
Park, 2000 ⁹⁷	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Fair
Park, 2011 ⁹⁶	Yes	Yes	Not Relevant (AUROC only)	Yes	Yes	Yes	Yes	Good
Parkes, 2011 ¹⁴⁷	Yes	Unclear	No	Yes	Yes	Yes	Unclear	Fair

Study, year	Representative spectrum	Random or consecutive sample	Test cutoffs predefined	Credible reference standard	Attempted to apply reference standard to all patients, or a random subset	Same reference standard applied to all patients	Reference standard interpreted independently from test under evaluation	Overall Quality
Patel, 2009 ¹⁰⁰	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Fair
Patel, 2004 ¹⁰¹	Yes	No	Yes (for validation sample)	Yes	Yes	Yes	Yes	Fair
Plevris, 2000 ¹⁰²	Yes	Unclear	No	Yes	Yes	Yes	Yes	Fair
Pohl, 2001 ¹⁰³	Yes	Yes	No (for Pohl Index)	Yes	Yes	Yes	Yes	Fair
Poynard, 2003 ¹⁰⁴	Yes	No	No	Yes	Yes	Yes	Unclear	Fair
Poynard, 2002 ¹⁰⁵	Yes	No	No	Yes	Yes	Yes	Unclear	Fair
Pradat, 2002 ¹⁰⁶	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	Fair
Reedy, 1998 ¹⁰⁷	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Fair
Renou, 2001 ¹⁰⁸	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Fair
Romera, 2006 ¹⁰⁹	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	Fair
Rosenberg, 2004? ¹¹⁰	Yes	Unclear	No	Yes	Yes	Yes	Unclear	Fair
Rossi, 2003 ¹¹¹	Yes	Yes	Yes (for Fibrotest)	Yes	Yes	Yes	Yes	Fair
Saadeh, 2001 ¹¹²	Yes	Yes	No	Yes	Yes	Yes	Unclear	Fair
Said, 2010 ¹¹³	Yes	Yes	No	Yes	Yes	Yes	Yes	Fair
Saitou, 2005 ¹¹⁴	Yes	Unclear	No	Yes	No	No	Unclear	Poor
Schneider, 2006 ¹¹⁵	Yes	Unclear	No	Yes	Yes	Yes	Unclear	Fair
Schneider, 2005 ¹¹⁶	Yes	Yes	No (for portal venous flow and spleen size)	Yes	Yes	Yes	Unclear	Fair
Sebastiani, 2012 ¹¹⁷	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Fair
Sebastiani, 2011 ¹¹⁸	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Sebastiani, 2009 ¹¹⁹	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Fair
Sebastiani, 2008 ¹²⁰	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair
Sebastiani, 2006 ¹²¹	Yes	Yes	Unclear (for Fibrotest)	Yes	Yes	Yes	Yes	Fair
Sene, 2006 ¹⁴⁸	Yes	Yes	No	Yes	Yes	Yes	Unclear	Fair

Study, year	Representative spectrum	Random or consecutive sample	Test cutoffs predefined	Credible reference standard	Attempted to apply reference standard to all patients, or a random subset	Same reference standard applied to all patients	Reference standard interpreted independently from test under evaluation	Overall Quality
Sheth, 1998 ¹²²	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Fair
Silva, 2004 ¹²³	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Fair
Sirli, 2010 ¹²⁴	Yes	Unclear	No	Yes	Yes	Yes	Unclear	Fair
Snyder, 2007 ¹²⁵	Yes	Yes	No	Yes	Yes	Yes	Yes	Fair
Snyder, 2006 ¹²⁶	Yes	Unclear	No	Yes	Yes	Yes	Unclear (for retrospective sample)	Fair
Stibbe, 2011 ¹²⁷	Yes	Unclear	Unclear	Yes	Yes	Yes	Unclear	Fair
Sud, 2004 ¹²⁸	Yes	Yes	Yes (for validation sample)	Yes	Yes	Yes	Unclear	Fair
Testa, 2006 ¹²⁹	Yes	Unclear	No	Yes	Yes	Yes	Yes	Fair
Trocme, 2006 ¹³⁰	Yes (except no F0)	No	Unclear	Yes	Yes	Yes	Yes	Fair
Vallet-Pichard, 2007 ¹³¹	Yes	No	Yes	Yes	Yes	Yes	Unclear	Fair
Varaut, 2005 ¹⁴⁹	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Fair
Viana, 2009 ⁵⁸	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Fair
Wai, 2003	Yes	Yes	Yes (for validation sample)	Yes	Yes	Yes	Unclear	Good
Walsh, 2000 ¹³⁴	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Fair
Walsh, 1999a ¹³⁵	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Fair
Walsh, 1999b ¹³⁶	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Fair
Williams, 1988 ¹³⁷	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Fair
Wilson, 2006 ¹³⁸	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Fair
Wong, 1998 ¹³⁹	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Fair
Yilmaz, 2011 ¹⁴⁰	Unclear	Unclear	No	Yes	Yes	Yes	Yes	Fair
Zaman, 2007 ¹⁴¹	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Fair
Zarski, 2012 ¹⁴²	Yes	Yes	Not relevant (AUROC only)	Yes	Yes	Yes	Yes	Good

Abbreviations: APRI, aspartate aminotransferase (AST) to platelets ratio; AST/ALT, aspartate aminotransferase–alanine aminotransferase; AUROC, area under the receiver operating characteristic.

Evidence Table 7: Key Question 4b. Proportion of Screened Patients who were Treated

Author, year Country	Study Type	Study population Timeframe	Criteria for antiviral treatment eligibility	Liver biopsy	Number screened	Number HCV antibody positive	Proportion HCV antibody positive who were viremic	Proportion viremic who received treatment	Proportion viremic classified as eligible for treatment	Reasons for ineligibility: % (n)	Proportion classified as eligible for treatment who received treatment
Groom, 2008 ¹⁵⁰ USA	Retrospective intervention series	Veterans affairs patients who tested positive for anti-HCV antibody by risk-based screening from January 2000 to December 2001 (Minneapolis)	Based on VA hepatitis C treatment guidelines and 1997 NIH consensus document	61% of 382 viremic patients evaluated in hepatitis clinic had liver biopsy performed	12485	681	76% (520/681)	24% (124/520)	Not reported	Not reported	Not reported
Lindenburg, 2011 ¹⁵¹ The Netherlands	Prospective intervention series	Active and former drug users who tested positive for anti-HCV antibody from January 2005 to April 2007	Decompensated liver cirrhosis Cardiac failure Autoimmune disease No stable housing (Psychiatric illness, active drug and alcohol use not considered exclusion criteria if they did not interfere with scheduled visits and considered stable by managing physician)	Yes, for patients with genotype 1 or 4, however could refuse (not part of protocol for other genotypes)	449	267	64% (134/208, HIV- negative) 63% (84/134) completed further screening	33% (44/134)	71% (60/84)	Medical, social, or psychiatric contraindication: 33% (n=8) Genotype 1 or 4 with less than Fair fibrosis on liver biopsy (treatment postponed): 67% (n=16)	73% (44/60)

Author, year Country	Study Type	Study population Timeframe	Criteria for antiviral treatment eligibility	Liver biopsy	Number screened	Number HCV antibody positive	Proportion HCV antibody positive who were viremic	Proportion viremic who received treatment	Proportion viremic classified as eligible for treatment	Reasons for ineligibility: % (n)	Proportion classified as eligible for treatment who received treatment
Mallette, 2008 ¹⁵² USA	Retrospective intervention series	Veterans Affairs patients who tested positive for anti-HCV antibody by risk-based screening from July 2000 to June 2001 (Providence)	Not described	Not specified, however biopsy results reported for 32% (39/122)	5646	260 newly diagnosed	58% (122/211)	15% (18/122)	57% (70/122)	Ongoing substance or alcohol abuse: 24% (n=29) Major medical contraindication: 7.4% (n=9) Severe psychiatric disease: 6.6% (n=8) Refused further evaluation: 4.9% (n=6)	26% (18/70)

Abbreviations: HCV, hepatitis C virus

Evidence Table 8: Key Questions 6a and 6c. Counseling Randomized Trials

Author, year Country Study name Overall Quality	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Baseline characteristics	Intervention program	Duration of followup	Results	Funding source
Groessl, 2011 ¹⁵³ USA (VA San Diego Healthcare System) Fair	US military veterans \geq 18 years of age with a confirmed diagnosis of chronic HCV, receiving care at VA Sand Diego Health Care system and willing to participate in a 6 weekly sessions of 2.5 hours in length.	Ongoing or scheduled to receive antiviral therapy, outside of geographic region, fatal co-morbid condition (life expectancy < 6 months), or receiving treatment for another life-threatening illness.	NR/327/137/132 (ITT)	Mean age: 54.6 years [Groups (A vs. B) significantly different in age 56.4 vs. 53.0 years; $p=0.003$] 5% Female 59% Non-Hispanic white 24% African American 10% Hispanics Marital status: 79% divorced, separated or never married	A: Information only: Educational booklet and handouts B: Self-management program (SMP): 6 weekly workshops based on self-management and cognitive-behavioral principles, each 2-2.5 hours	6 weeks (end of program)	Information only vs. self-management program (p-value): 1) HCV knowledge change: 1.3 vs. 3.4 ($p<0.0001$) 2) HCV self-efficacy change: -0.09 vs. 0.75 ($p= 0.01$) 3) Energy change: 0.15 vs. 0.05 ($p=0.46$) 4) CES-D change: 1.0 vs. -0.7 ($p=0.93$) 5) Health distress change: 1.0 vs. -0.07 ($p=0.06$) 6) QWB change: 0.01 vs. 0.04 ($p=0.26$) 7) Global health status change (VAS 0-100): -0.4 vs. 5.5 (0.11) 8) SF-36 results (change in scores): a) Physical function: -3.6 vs. 3.3 ($p=0.06$) b) General health: 1.8 vs. 1.1 ($p=0.2$) c) Body pain: 7.8 vs. 0.9 ($p=0.07$) d) PCS: 0.5 vs. 1.7 ($p=0.4$) e) MCS: -0.5 vs. 0.6 ($p=0.6$) 9) HQLQ results (change in scores) a) Health distress (covariate=age): -3.3 vs. 3.6 ($p=0.1$) b) Positive well-being: 1.3 vs. 0.5 ($p=0.8$) c) HCV-specific limitations: 2.0 vs. -0.2 ($p=0.6$) d) HCV-specific health distress (covariate=age): -2.7 vs. 0.3 ($p=0.5$)	VA HSR&D Grant

Author, year Country Study name Overall Quality	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Baseline characteristics	Intervention program	Duration of followup	Results	Funding source
Latka, 2008 ⁵⁴ USA The Study to Reduce Intravenous Exposures (STRIVE) Fair	Aged 18 to 35 years, used injection drugs within 6 months, plans to live in area for 12 months, documented HCV-antibody positive and HIV-antibody negative serostatus, able to provide sample for liver function and HCV RNA testing, able to complete assessments and group sessions in English (recruited from a larger study of HIV- and HCV-negative injection drug users)	Not stated	640/Not reported/418 (222 to behavioral intervention, 196 to control)/261 at 3 months	Age: 27 vs. 26 years Female: 24% vs. 24% Non-white: 43% vs. 43% Aware of positive HCV status >6 months: 55% vs. 46% Injecting at least once daily: 70% vs. 68%	A: Peer mentoring intervention: 6 sessions x hours, twice weekly, trained participants to be peer mentors for safer injection practices (hypothesized to reduce risky behaviors in the participants as well); content delivered via various methods including demonstrations, games, discussions, and videos B: Video discussion: 6 sessions x 2 hours, twice weekly	6 months	Peer mentoring intervention vs. video discussion Combined distributive risk (how often lent used syringe, shared drug preparation equipment, divided drugs with syringe used by oneself): 44% vs. 59% at 3 months, p=0.02, AOR 0.46 (95% CI 0.27 to 0.79); 37% vs. 53% at 6 months, p=0.007, AOR 0.51 (95% CI 0.31-0.83) Frequency of lending used syringe to other: No differences at 3 months or 6 months (unadjusted) Frequency of preparing drugs with a syringe previously used by oneself: No differences at 3 months or 6 months (unadjusted) Frequency of sharing drug preparation equipment with or before someone else: 41% vs. 55%, at 3 months, p=0.03, AOR 0.47 (95% CI 0.27-0.82); 35% vs. 23% at 6 months, p=0.03, AOR 0.55 (95% CI 0.33- 0.92) Refrained from injection drug use: 24% vs. 9.6% at 3 months, p=0.002, AOR 3.6 (95% CI 1.6-7.8); 34% vs. 23% at 6 months, p=0.03, AOR 1.6 (95% CI 0.96- 2.7) Refrained from lending syringe because of HCV- positive status: 69% vs. 69% at 3 months, p=0.98, AOR 1.3 (95% CI 0.65-2.7); 67% vs. 60% at 6 months, p=0.39, AOR 1.5 (95% CI 0.74-3.0)	National Institute on Drug Abuse (NIDA)

Author, year Country Study name Overall Quality	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Baseline characteristics	Intervention program	Duration of followup	Results	Funding source
Zule, 2009 ¹⁵³ USA Fair	At least 18 years of age, self-reported IDU in previous 30 days, visible tracks or positive urine specimen for heroin, cocaine, or methamphetamine, no formal substance abuse treatment in previous 30 days and current residence in area of study.	Not stated	861/855/847/625 Note: 1286 (of 1786) met preliminary eligibility criteria	Mean age: 41.2 years, 9.3 SD 66% African American 27% Non-Hispanic white 7% Other 27% Female 55% HCV positive Risk Behaviors (in past 30 days):70% used alcohol 17% shared syringe 23% shared cooker, cotton or rinse water 27% > 1 sexual partner 57% unprotected at last sexual intercourse	A. Motivational intervention: 6 sessions including 2 cue-card sessions presented by PowerPoint. First session included 20 slides adapted from NIDA; 2nd session included 24 slides (number depended on test results) and additional sessions focused increasing motivation to change, eloping a plan for change, reviewing progress and reaffirming commitments to change.B. Educational intervention: 6 sessions with first 2 session based on cue cards from the NIDA and followed up with 4 additional sessions with videos of 1 hour in length. Topics included hepatitis A, B, C; indirect screening practices; and addiction.Note: participants screened for HCV and given results during the study.	12 months	Motivational intervention vs. educational education, HCV positive participants: OR (95% CI) Alcohol use (in past 30 days): 1) 6 months followup: 0.65 (0.44, 0.94) 2) 12 months followup: 0.94 (0.64-1.38) Other results not stratified by those HCV positive	NIDA and NIH

Evidence Table 9: Key Questions 6a and 6c. Counseling Randomized Trials Overall Quality Rating

Author, Year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Attrition and withdrawals reported?	Loss to followup: differential/high?	Intention-to-treat (ITT) analysis	Overall Quality
Groessl, 2011 ¹⁵³	Yes	Unclear	No (age, % homeless)	Yes	No	No	No	Yes	No	Yes	Fair
Latka, 2008 ¹⁵⁴	No (mixed method depending on group size)	Unclear	Yes	Yes	No	No	No	No	Yes	No	Fair
Zule, 2009 ¹⁵⁵	Unclear	Unclear	No (alcohol use)	Yes	No	No	No	Yes	Yes	No	Fair

Evidence Table 10: Key Question 7. Pregnancy Intervention Observational Studies

Author, year Country Study Name Overall Quality	Study Type	Definition of mother-to-child transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population	HCV genotype HCV viral load HIV infection IV drug use	Overall transmission	Transmission by labor mgmt: Intra-uterine pressure catheter (IUPC)
Ceci, 2001 ¹⁵⁶ Italy Fair	Prospective cohort study	Presence of anti- HCV antibodies beyond 18 months or HCV- positive on two separate tests	HCV maternal risk factors (exposure to blood products and IVDU), HCV viral load, HCV genotype, gestational age, mode of delivery, birth weight	24 months	HCV-positive, HIV-negative women	HIV-positive	2447/ 78/ 78/ 78	Maternal age (n=78) Median (range): 30 (21-42) *Characteristics of HCV-RNA positive mothers (n=60) HCV risk factors Absent: 25 (42%) Blood transfusion: 14 (23%) IVDU: 20 (33%) Blood transfusion and IVDU: 1 (2%) Mode of delivery Vaginal: 43 (72%) Cesarean: 17 (28%) Gestational age <36 weeks: 9 (15%) >=36 weeks: 51 (85%) Birth weight <2500g: 14 (23%) >=2500g: 46 (77%)	Maternal HCV- RNA status (n=78) Positive: 60 (77%) Negative: 18 (23%) *Characteristics of HCV-RNA positive mothers (n=60) genotype 1a: 9 (15%) 1b: 25 (42%) 2a: 20 (33%) 3: 6 (10%) Viral load <0.2X10 ⁶ : 9 (15%) >0.2X10 ⁶ : 51 (85%)	Overall transmission (n=78) 2 consecutive positive tests: 8 (10%) 24 month followup: 2 (3%) *not adjusted	Not reported

Author, year Country Study Name Overall Quality	Study Type	Definition of mother-to-child transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population	HCV genotype HCV viral load HIV infection IV drug use	Overall transmission	Transmission by labor mgmt: Intra-uterine pressure catheter (IUPC)
Conte, 2000 ¹⁵⁷ Italy Poor	Prospective cohort study	Newborns of anti-HCV positive mothers were tested at birth (on cord blood samples) and infants underwent determination of AST, ALT, anti- HCV and HCV/RNA after 4, 8, 12, and 18 months	Not Reported	First month of pregnancy through 18 months after birth	Anti-HCV positive pregnant women between 1/95 and 12/98 attending Ob/Gyn unit of local Ospedale Maggiore (living in area of about 20 km around Bergamo in northern Italy)	Not Reported	15,250/370/370/370	Maternal age (n=370) mean (SD): 30.9 (± 5.2) Mode of delivery (n=370) Vaginal: 259 (71%) Cesarean: 106 (29%)	Maternal HCV/RNA status (n=370) Positive: 266 (72%) Negative: 104 (28%) Maternal genotype (n=370): 1a: 51 (19%) 1b: 82 (31%) 2: 64 (24%) 3a: 53 (20%) 4: 5 (2%) Indeterminate: 11 (4%) Maternal HIV infection (n=370) Yes: 15 (4%) No: 355 (96%) Past or current IVDU (heroin only) (n=370) 118 (32%) Past blood transfusions (n=370) 68 (18.4%)	HCV/RNA+ at birth (n=366): 18 (4.9%) 4 months (n=167): 8 (4.8%) 8 months (n=161): 8 (5%) 12 months (n=155): 8 (5.1%)	Not Reported

Author, year Country Study Name Overall Quality	Study Type	Definition of mother-to-child transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population	HCV genotype HCV viral load HIV infection IV drug use	Overall transmission	Transmission by labor mgmt: Intra-uterine pressure catheter (IUPC)
European Pediatric Hepatitis C Virus Network, 2001 ¹⁵⁸ (Pembrey) Italy, Spain, Germany, Ireland, Scotland, Belgium, Sweden Good	Multicenter prospective cohort study	Infected: antibody positive beyond 18 months and/or had at least two positive PCR tests (on 2 separate occasions) Indeterminate: born more than 18 months before data collection, antibody positive before 18 months of age, and either 1) no PCR performed, 2) no positive PCR result, or 3) only a single PCR result	Mode of delivery, breastfeeding, HIV status, maternal age at delivery	At least until 18 months of age	Mother HCV positive at or before delivery or baby identified as HCV positive within 1 month of delivery & maternal infection confirmed Children born on or after Jan 1 1992 (when 2nd generation tests widely used) and at least 18 months at last laboratory assessment (or born more than 18 months before data collection and no longer in followup)	Children with a history of blood transfusion	1655 mother-child pairs/1474 children/1474/1474 (916 HIV-)	Maternal age (n=1311) <20: 219 (17%) 20-25: 563 (43%) 30-39: 495 (38%) >=40: 34 (3%) Gestational age (n=1248) <36 weeks: 105 (8%) >=36 weeks: 1143 (92%) Low birth weight (<2500g) (n=1362) Yes: 523 (38%) No: 839 (62%) Fetal scalp monitors (n=724) Yes: 93 (13%) No: 631 (87%) Mode of delivery (n=1400) Cesarean: 382 (27%) Vaginal: 1018 (73%) Breastfeeding (n=1424) Breastfed: 351 (25%) Not breastfed: 1073 (75%) Other infections in pregnancy (n=996) Yes: 90 (9%) No: 906 (91%)	Maternal HIV infection (n=1419) Yes: 503 (35%) No: 916 (65%) Maternal IV drug use (n=1384) During this pregnancy: 362 (26%) Yes, but not during pregnancy: 455 (33%) Never: 567 (41%) Maternal history of hepatitis (n=1038) Yes: 421 (41%) No: 617 (59%)	Overall transmission (n=1474) 136 (9.2%) *not adjusted	Not Reported

Author, year Country Study Name Overall Quality	Study Type	Definition of mother-to-child transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population	HCV genotype HCV viral load HIV infection IV drug use	Overall transmission	Transmission by labor mgmt: Intra-uterine pressure catheter (IUPC)
European Pediatric Hep C Virus Network, 2005 ¹⁵⁹ (Tovo) Italy, Spain, Germany, Ireland, UK, Norway, Sweden Good	Multicenter prospective cohort study	Children considered infected if they had ≥ 2 positive HCV RNA PCR test results and/or were anti- HCV antibody positive after 18 months. Children considered uninfected if they had < 2 positive HCV RNA PCR test results and ≤ 2 negative HCV RNA PCR rest results and/or were anti- HCV antibody negative after 18 months.	To account for differences between centers in the HCV RNA PCR assays used to determine infection, and to allow for center- associated unobserved differences in background characteristics, the authors incorporated a random effect in the multivariable models at the center level	Children received clinical examinations at birth, 6 weeks, and 3, 6, 9, 12, 18, and 24 months; and thereafter every 6 months if infected or every year if uninfected	HCV infected mothers and their singleton infants or first- born infants from multiple pregnancies with confirmed HCV infection status.	Second-born twins and second- and third-born triplets were excluded. Mother-infant pairs with infants of indeterminate infection status were excluded.	1787/ 1479/ 1479/ 1220 (1034 HIV-)	Maternal age (n=1205) Mean (SD): 31.7 (5.17) Median (range): 32 (17.1-45.1) Mode of delivery (n=1455) Vaginal: 764 (52.5%) Emergency CS: 160 (11%) Elective CS: 480 (33%) CS (unspecified): 51 (3.5%) Infant feeding type (n=1357) Breast-fed: 452 (32.7%) Formula fed: 930 (67.3%) Sex of child (n=1470) Male: 802 (54.6%) Female: 668 (45.4%) Gestational age (n=1382) ≤ 34 weeks: 97 (7%) 35-36 weeks: 122 (8.8%) ≥ 37 weeks: 1163 (84.2%)	Maternal HIV infection (n=1391) Yes: 208 (15%) No: 1183 (85%) Child HIV infection (n=1435) Yes: 10 (0.7%) No: 1397 (97.4%) Indeterminate: 28 (1.9%) Maternal IV drug use (n=1162) History: 448 (38.6%) No history: 714 (61.4%)		

Author, year Country Study Name Overall Quality	Study Type	Definition of mother-to-child transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population	HCV genotype HCV viral load HIV infection IV drug use	Overall transmission	Transmission by labor mgmt: Intra-uterine pressure catheter (IUPC)
Garland, 1998 ¹⁶⁰ Australia Poor	Prospective cohort study	Infants tested at 3, 6 and 12 months for HCV antibodies. Testing included detection of antibody to HCV, and genotyping for presence of 1a, 2a, 2b, 3 a, 4 & 6 HCV genotypes.	NR/Unclear: Collected data on age, parity, type of delivery, time of rupture, drug use, scalp electrodes and breastfeeding but did not indicate if adjustment for confounding was analyzed.	Three years; followup included seropositive women, their newborns & siblings of the newborns.	Women with a history of illicit IV drug use, seen in the Chemical Dependency Unit (CDU) of the Royal Women's Hospital and subject to routine screening for HCV. Women with positive anti- HCV test results.	Not Reported	Not Reported/ 84/ 83/ 83 women, 91 newborns & 16 siblings of newborns	Mode of delivery (n=83) Vaginal: 61 (74%)	Maternal HIV infection (n=83) Yes: 0 (100%) Maternal IV drug use (n=83) Yes: 83(100%)	3/91 (3%)	Not Reported
Gibb, 2000 ¹⁶¹ Ireland, UK Fair	Prospective cohort study	Positive result for HCV antibody within 90 days of birth	adjusted for HIV status, breastfeeding, and mode of delivery	24 months	Mother known to be HCV infected during pregnancy or if child had positive result for HCV antibody within 90 days of birth	UK children born before 1996	499/ 441/ 441/ 441	Maternal age (n=441) Mean (SD): 27 (6) Race (n=441) White: 413 (94%) Non-white: 28 (6%) Breastfeeding (n=414) Yes: 59 (14%) No: 355 (86%) Mode of delivery (n=424) Vaginal: 339 (80%) Emergency cesarean: 54 (13%) Elective cesarean: 31 (7%)	Maternal HIV infection (n=441) Yes: 22 (5%) No: 328 (74%) Unknown: 91 (21%) Maternal IV drug use (n=441) History: 343 (78%) No history: 98 (22%)	Overall (n=441) 6.7% (4.1-10.2) unadjusted	Not Reported

Author, year Country Study Name Overall Quality	Study Type	Definition of mother-to-child transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population	HCV genotype HCV viral load HIV infection IV drug use	Overall transmission	Transmission by labor mgmt: Intra-uterine pressure catheter (IUPC)
LaTorre, 1998 ¹⁶² Italy Poor	Prospective cohort study	Babies were tested for ALT levels, anti-HCV antibodies by ELISA III and RIBA II and HCV-RNA by RT-PCR. Babies who retained anti-HCV antibodies through 12 months were considered infected	none	Blood test and clinical evaluation of infants within days after birth and then every 4 months for 2 years	Mothers who tested anti-HCV positive before delivery and were HIV negative	Mothers who tested negative for HCV or positive for HIV	5025/ 5000/ 80/ 80	Mode of delivery (n=80) Vaginal: 66 (82.5%) *52/66 were HCV-RNA positive cesarean: 14 (17.5%) Breastfeeding (n=80) yes: 24 (30%) *Including 10 HCV-RNA positive and 14 HCV-RNA negative women	Maternal HCV-RNA status (n=80) Positive: 56 (70%) Negative: 24 (30%) HCV viral load (n=19) ALT increase>40 U/L: 18 (32.5%) Maternal IV drug use (n=80) Yes: 34 (43%) Blood transfusion (n=80) 10 (12%)	Overall transmission (n=80) 2/80 (2.5%)	Not Reported
Lin, 1995 ¹⁶³ Republic of China Poor	Prospective cohort study	Detection of HCV antibodies (serum); detection of HCV RNA in infants tested at 1, 3, 6, 9 or 12 months of age	Not Reported	Up to 12 months	HCV infected mothers	NR	Not Reported/ 40/ 15/+3 healthy controls 15	Not Reported	HCV viral load (n=15) RNA titers 10 ² to 2.5 x 10 ⁶ copies/mL HIV infection None	0/15 (0%)	Not Reported

Author, year Country Study Name Overall Quality	Study Type	Definition of mother-to-child transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population	HCV genotype HCV viral load HIV infection IV drug use	Overall transmission	Transmission by labor mgmt: Intra-uterine pressure catheter (IUPC)
Mast, 2005 ¹⁶⁴ US (Houston & Honolulu) Good	Prospective cohort study	Infant serum collected at birth and 8 well-child visits. Testing included detection of antibody to HCV, detection of HCV RNA (qualitative and quantitative), and genotyping.	Variables with p<.1 from the univariate analysis and maternal demographic characteristics included in multivariate analysis	Infants born to HCV+ mothers followed from birth to >=12 months, HCV- infected infants followed annually until age 5	Women presenting for prenatal care (and in Houston, those who didn't receive prenatal care who presented for delivery at 2 county hospitals) were offered testing. Women with positive anti- HCV test results were invited to enroll (those with indeterminate status were invited to enroll until HCV status was confirmed).	Mothers with serum testing as RIBA indeterminate and HCV RNA negative were excluded from the analysis.	75,909/ 567/ 332/ 242 women & 244 infants	Age (n=242) <20: 7 (2.9%) 20-29: 103 (42.6%) 30-39: 120 (49.6%) >=40: 12 (4.9%) Race (n=242) White: 79 (32.6%) Black: 77 (31.8%) Hispanic: 49 (20.3%)	Mother HCV RNA+ (n=242) At enrollment or delivery: 194 (79.5%) Both: 179 (77.2%) Delivery: 5 (2.2%) Enrollment: 4 (1.7%) Maternal HIV infection (n=242): Yes: 11 (4.5%) HIV and HCV RNA+ (n=242) 7 (2.9%) Maternal IVDU (n=242) 126 (52.3%) Geometric mean HCV RNA level at delivery (n=194) HIV-: 2.38*10 ⁶ Maternal HCV genotype (n=116) Genotype 1a: 76 (66%) Genotype 1b: 16 (14%) Genotype 2b: 10 (9%) Genotype 3a: 13 (11%) Genotype 4a: 1 (.01%)	9/244(3.7%)	Not Reported

Author, year Country Study Name Overall Quality	Study Type	Definition of mother-to-child transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population	HCV genotype HCV viral load HIV infection IV drug use	Overall transmission	Transmission by labor mgmt: Intra-uterine pressure catheter (IUPC)
McMenamin, 2008 ¹⁶⁵ Ireland Fair	Retrospective cohort study	Positive neonatal results for HCV antibody after 1 month of age	None	Infant HCV RNA samples tested at median of 6 weeks after delivery, mean 12.5 weeks (range 4-166 weeks)	Mothers who tested positive for HCV antibody antenatally and delivered a liveborn infant, HCV positive mothers identified through the National Virus Reference Laboratory	Mothers who tested negative for HCV antenatally or mothers who tested positive for HCV antenatally and miscarried or had a stillbirth	26,390/559/559/441	Maternal age (n=559) Median (range): 26 (16-44) Mode of delivery (n=559) Vaginal delivery: 443 (79%) Emergency cesarean: 72 (13%) Planned pre labor cesarean: 44 (8%) Gestation (n=559) Median (range): 39 (28-42) Intrapartum procedures (n=559) Intrapartum fetal blood sample: 1 (.002%) Fetal scalp electrode: 23 (4%)	Maternal HIV infection (n=559) Yes: 18 (3%) Maternal HBV status (n=559) Positive: 3 (0.5%) Maternal HCV RNA status (n=559) Positive: 295 (53%) Negative: 166 (30%) Missing: 98 (17%)	Overall transmission (n=441) 18/441 (4.1%)	Not Reported
Moriya, 1995 ¹⁶⁶ Japan Poor	2 prospective cohort studies, additional pediatric chart review	Infants testing positive for antibody to HCV	Not Reported	12 months, up to 24 months	Infants born to mothers who were HCV RNA positive	Not Reported	16714/ 163/ 100 mothers/ 84 mothers, 87 infants	Not Reported	Maternal HIV infection (n=84) None (n=84) Maternal genotype (n=4) Type 111/2a: n=2 Type 11/1b: n=2	2/87 (2.3%) ("during followup period")	Not Reported

Author, year Country Study Name Overall Quality	Study Type	Definition of mother-to-child transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population	HCV genotype HCV viral load HIV infection IV drug use	Overall transmission	Transmission by labor mgmt: Intra-uterine pressure catheter (IUPC)
Okamoto et al, 2000 ¹⁶⁷ Japan (Tottori University & Medical Center) Poor	Prospective cohort study	Positive test for HCV RNA by RT-PCR analysis with high titers of HCV RNA within 3 months of age. Serum samples of the children born to Ab1 mothers were tested for anti- HCV antibody, HCV RNA, and liver function approximately every 3 months during the first year and biannually thereafter.	Not Reported	Minimum followup period was 6 months	Pregnant women were screened for anti-HCV antibody in Tottori Prefecture, Japan. None of the mothers had risk factors for HIV infection	Not Reported	21791/NR Eligible/NR Enrolled/ 59	Mode of delivery (n=84) Vaginal: 56 (66%) Cesarean: 28 (33%)	Maternal HCV/RNA status (n=84) Positive: 50 (60%) Maternal viral load (n=84) high ($\geq 2.5 \times$ 106 copies/mL): 21 (25%)	7/84 (8%)	Not Reported
Pipan, 1996 ¹⁶⁸ Italy Poor	Prospective cohort	HCV/RNA detection in children over a period of 12 months	none	Every three months for one year	Anti-HCV positive pregnant women, no history of Hepatitis B, no apparent source of HCV exposure	History of Hepatitis B, apparent source of HCV exposure	1338/36/25/25	Maternal age (n=25) Median (range) 26.4 (19-35)	Maternal HCV/RNA+ (n=25) Positive:18 (72%)	Infant HCV/RNA+ at birth (n=25) None Infant HCV/RNA+ at 12 months (n=25) 0	Not Reported

Author, year Country Study Name Overall Quality	Study Type	Definition of mother-to-child transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population	HCV genotype HCV viral load HIV infection IV drug use	Overall transmission	Transmission by labor mgmt: Intra-uterine pressure catheter (IUPC)
Resti, 1998 ¹⁶⁹ Italy Fair	Prospective cohort study	Children were considered infected when hepatitis C virus RNA was detected or when antibodies to the virus persisted beyond age 2 years or reappeared after having disappeared. Alanine aminotransferase concentrations were defined as raised if they were higher than twice the upper limit of normal	Study data suggests that there may be a higher risk of vertical transmission in mothers with a higher viral titre, but the results were not significant. IV drug users were not excluded from analysis, but authors suggest inclusion of these mothers did not significantly impact findings	Median followup in the 403 children who completed the study was 28 (24-38) months	19 centres participated in the study Women (and their babies) with confirmed hepatitis C antibodies but negative for HIV1	History of blood product transfusions or IV drug use was carefully investigated by face to face interviews with experienced pediatricians using standardized questionnaires, but these individuals were not excluded	NR/442/403/ 403 & 403 infants (275 RNA+ mothers)	RNA+/HIV- mothers (n=275) Mode of delivery Vaginal: 213 (77%) Caesarean: 62 (23%) Breastfeeding Yes: 87 (32%) No: 188 (68%)	Maternal IVDU (n=275) 111 (80%)	13/275 (4.7%)	Not Reported

Author, year Country Study Name Overall Quality	Study Type	Definition of mother-to-child transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population	HCV genotype HCV viral load HIV infection IV drug use	Overall transmission	Transmission by labor mgmt: Intra-uterine pressure catheter (IUPC)
Spencer, 1997 ¹⁷⁰ Australia Poor	prospective cohort study	Presence of HCV RNA in serum collected from infant anytime during followup.	Potential maternal risk factors assessed: duration/type of drug use, alcohol, smoking, past HBV infection, age	At least 6 months, up to 6 years when possible	HCV positive and HCV negative pregnant women, IVDU on methadone maintenance program and their infants	Not Reported	Not Reported/ Not Reported/ 131/ 125 anti-HCV+, 63 HCV RNA+	Maternal age mean: 30	Maternal HCV RNA status (n=125) Positive: 63 (62.4%) Maternal genotype transmitting mothers Type 1a: 5 (83.3%) Type 3a: 1 (16.7%) Non- transmitting mothers Type 1: 1 (1.6%) Type 1a: 36 (57.1%) Type 1b: 4 (6.3%) Type 2a: 1 (1.6%) Type 2b: 2 (3.2%) Type 3a: 18 (28.6%) Untypeable: 1 (1.6%) HIV infection None IVDU 131 (100%)	6/63 (9.5%) (at 18 months)	Not Reported

Author, year Country Study Name Overall Quality	Study Type	Definition of mother-to-child transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population	HCV genotype HCV viral load HIV infection IV drug use	Overall transmission	Transmission by labor mgmt: Intra-uterine pressure catheter (IUPC)
Syriopoulou, 2005 ¹⁷¹ Greece Poor	Prospective cohort study	HCV/RNA+ more than 2 times after 3 months and/or anti-HCV+ after 18 months	Univariate analysis of IVDU, mother's age, mode of delivery, genotype, type of feeding (but no multivariate analysis)	Every three months until 1 year of age, then every 6 months	Anti-HCV positive pregnant women	Not Reported	NR/86/86/86 mother-child pairs	Mean age at delivery (SD): 29.6 (+/- 3 yrs) Mode of delivery (n=86) Vaginal: 53 (62%) Cesarean: 33 (38%)	Maternal HCV genotype (n=54) 3a: 23 (42%) 1a: 10 (19%) 1b: 7 (13%) 1a/1b: 6 (11%) 2a/2c: 6 (11%) 4c/4d: 2 (4%) Maternal HCV/RNA status (n=86) Positive: 56 (65%) Maternal HIV infection (n=86) Yes: 1 (1%) IVDU (n=86) during pregnancy: 2 (2%) before pregnancy: 6 (7%)	Overall transmission (n=86): 2 (2.3%)	Not Reported
Tajiri, 2001 ¹⁷² Japan (seven hospitals in the Osaka metropolitan area) Poor	Prospective cohort study	Babies were tested for serum alanine aminotransferase (ALT) activity, anti-HCV antibodies and HCV RNA at 0, 3, 6, 9, 12 months and every year thereafter. Babies with repeated positive HCV RNA tests were considered infected.	Not Reported	All infants were followed 9 to 61 months	Pregnant women who tested positive for anti-HCV antibodies	Not Reported	16800/154/141/114	Route of transmission (n=141) Mother-to-child: 9/141 (6%) Blood transfusion: 31/141 (22%) Accidental needle stick injury: 3/141 (2%) HCV carriers in their families: 11/141 (8%) Other/unidentified: 87/141 (62%) Mode of delivery (n=114) Vaginal: 90 (21%) Cesarean: 24 (79%)	Maternal IVDU None Maternal HIV infection (n=73) Positive: 0 Negative: 73 Not tested: 68 (68 not tested because HIV infection is not endemic in Japan including the areas studied (adult rate of infection, 0.01%) Maternal HCV viral load High: 46 (63%) Low: 27 (37%)	9/114 (7.8%)	Not Reported

Author, year Country Study Name Overall Quality	Study Type	Definition of mother-to-child transmission	Confounders assessed in analysis	Duration of followup	Eligibility	Exclusion	Number screened/ eligible/ enrolled/ analyzed	Demographic characteristics of study population	HCV genotype HCV viral load HIV infection IV drug use	Overall transmission	Transmission by labor mgmt: Intra-uterine pressure catheter (IUPC)
Tanzi, 1997 ¹⁷³ Italy Poor	Prospective cohort study	presence of antibodies for one or more HCV antigens at birth, 3, 6, 10, and 18 months	None	18 months	Women admitted to the Maternity Clinic of University of Parma from January to December 1993, those who tested positive for antibodies were invited to submit their children for period checks	Not Reported	1347/1347/1347/1347	NR	Maternal anti- HCV+ (n=1347) 31 (2.3%) Maternal HCV- RNA+ (n=1347) 18 (1.3%) Maternal HIV infection (n=1347) 4 (.27%)	Overall transmission (n=32) Infant HCV/RNA+ at birth: 2 (6%) at 3, 6, 10, 18 months: 0 (0%) Infant anti- HCV+ at birth: 32 (100%) at 18 months: 0 (0%)	Not Reported
Zanetti, 1998 ¹⁷⁴ (Intervirolgy) Italy A prospective Study on Mother-to- Infant Transmission of Hepatitis C virus Zanetti, 1999 ¹⁷⁵ (Journal of Hepatology) Italy Mother-to- infant transmission of hepatitis C virus Poor	Prospective cohort study	Detection of HCV-RNA, persistence of anti-HCV beyond 18 months of age or ex novo production of antibody were assumed to represent evidence of infection	Not Reported	For babies born to HCV seropositive mothers, peripheral blood sampling, laboratory and clinical evaluations were scheduled at birth, about every 3 months during the 1st year of life and then every 6 months.	Infants born to HCV- infected mothers, including mothers with history of IV drug use who were screened for HIV antibodies.	Not Reported	40000+/482/291/291 & 291 infants	Not Reported	Maternal HIV infection (n=291) Yes: 40 (14%) Maternal HCV/RNA status (n=291) Positive: 251 (86%) Maternal genotype (n=17) 3a: 6/17 1a: 4/17 2a: 3/17 1b: 2/17 4a: 1/17 4c/4d: 1/17	HCV+: 17/291 (5.8%) HCV+/HIV+: 3/17 (17.6%)	Not Reported

Author, year Country Study Name Overall Quality	Transmission by labor mgmt: Fetal monitoring	Transmission by mgmt: Rupture of membranes	Transmission by route of delivery	Transmission by type of infant feeding	Transmission by other risk factors (maternal)	Transmission by other risk factors (child)	Sub-group analyses	Adverse events	Funding source	(Cont'd) Transmission rate by other risk factors (maternal)	(Cont'd) Transmission rate by other risk factors (maternal)
Ceci, 2001 ¹⁵⁶ Italy Fair	Not Reported	Not Reported	No association (data NR)	Not Reported	Transmission from women with no known risk of infection was significantly lower (RR=0.17%, 0.04-0.73%; p=0.0063)	Not Reported	Not Reported	Not Reported	Not Reported	By maternal blood transfusion (n=38) 2+ positive tests vs. 0 positive tests 3/8 (37.5%) vs. 2/30 (6.7%), p<0.05 By maternal viremia (n=38) 2+ positive tests vs. 0 positive tests 6.90 +/- 5.87 x 10 ⁶ vs. 3.93 +/- 2.94 x 10 ⁶	
Conte, 2000 ¹⁵⁷ Italy Poor	Not Reported	Not Reported	Cesarean vs. vaginal (n=365) 1/106 (1%) vs. 7/259 (2.7%) *RR: .245 (.275- 49.463)	Breast vs. formula (n=370) 2/90 (2%) vs. 6/280 (2%) *RR: 1.02 (.305-3.45)	Not Reported	Not Reported	Not Reported	Not Reported	Not Reported		

Author, year Country Study Name Overall Quality	Transmission by labor mgmt: Fetal monitoring	Transmission by mgmt: Rupture of membranes	Transmission by route of delivery	Transmission by type of infant feeding	Transmission by other risk factors (maternal)	Transmission by other risk factors (child)	Sub-group analyses	Adverse events	Funding source	(Cont'd) Transmission rate by other risk factors (maternal)	(Cont'd) Transmission rate by other risk factors (maternal)
European Pediatric Hepatitis C Virus Network, 2001 (Pembrey) ¹⁵⁸ Italy, Spain, Germany, Ireland, Scotland, Belgium, Sweden Good	Fetal scalp monitoring during delivery (yes vs. no) (n=724) 11/93 (11.8%) vs. 58/631 (9.2%) OR=1.33 (95% CI 0.63-2.74) *not adjusted	Not Reported	Cesarean vs. Vaginal (n=1400) 28/382 (7.3%) vs. 101/1018 (9.9%) OR: .739 (.467- 1.163) *type of cesarean (CS) or vaginal delivery elective CS: 20/192 (10.4%) Emergency CS: 7/115 (6.1%) Unspecified CS: 1/75 (1.3%) Vaginal, spontaneous: 81/825 (9.8%) Vaginal, instrumented: 12/79 (15.2%) Vaginal, unspecified: 8/114 (7%) HIV- mothers (n=884) Cesarean vs. vaginal 15/218 (6.9%) vs. 39/666 (5.9%) OR 1.17 (0.59-2.31, p=.66) *Adjusted for breastfeeding status, maternal age at delivery, and center category *info on type of CS or vaginal delivery NR for HIV-	Breast vs. formula (n=1424) 29/351 (8.3%) vs. 102/1073 (9.5%) HIV- mothers Breast vs. formula (n=887) 21/319 (6.6%) vs. 36/568 (6.3%) OR 1.07 (0.57- 2.02, p=0.83) *Adjusted for mode of delivery, maternal age at delivery HIV+ mothers breast vs. Formula (n=497) 5/13 (38.5%) vs. 64/484 (13.2%) OR 6.41 (1.25- 32.94), p=0.03 *Adjusted for mode of delivery, maternal age at delivery	Mother HIV positive vs. negative (n=1419) 70/503 (13.9%) vs. 60/916 (6.6%), OR 2.31 (1.58- 3.37) No maternal drug use ever vs. not during pregnancy vs. during pregnancy (n=1384) 43/567 (7.6%) vs. 49/455 (10.8%) vs. 33/362 (9.1%), OR=0.82 (.50- 1.35) vs. OR=1.20 (.74- 1.97) Maternal history of hepatitis (yes vs. no) (n=1038) 50/421 (11.9%) vs. 55/617 (8.9%), OR=1.38 (0.90-2.10) Other infections during pregnancy (yes vs. no) (n=996) 7/90 (7.8%) vs. 84/906 (9.3%), OR=0.83 (0.38-1.81) *Not adjusted	<36 weeks gestational age vs. >36 weeks (n=1248) 7/105 (6.7%) vs. 109/1143 (9.5%), OR 0.68 (0.26- 1.50) Birth weight <2500g vs. >2500 g (n=1362) 49/523 (9.4%) vs. 109/1143 (9.5%), OR 1.05 (0.71- 1.56)	Not Reported	Not Reported	European Commission DG XII Biomed2 Programme		

Author, year Country Study Name Overall Quality	Transmission by labor mgmt: Fetal monitoring	Transmission by mgmt: Rupture of membranes	Transmission by route of delivery	Transmission by type of infant feeding	Transmission by other risk factors (maternal)	Transmission by other risk factors (child)	Sub-group analyses	Adverse events	Funding source	(Cont'd) Transmission rate by other risk factors (maternal)	(Cont'd) Transmission rate by other risk factors (maternal)
European Pediatric Hep C Virus Network, 2005 (Tovo) ¹⁷⁶ Italy, Spain, Germany, Ireland, UK, Norway, Sweden Good			<p>Elective cesarean vs. emergency cesarean or vaginal delivery (n=1220) OR 1.66 (1.00-2.74) unadjusted, p=.05 OR 1.46 (0.86-2.48) adjusted, p=.16</p> <p>HIV- mothers elective vs. emergency cesarean or vaginal delivery (n=1034) 1.57 (0.88-2.83) unadjusted, p=0.13 1.59 (0.88-2.86) adjusted, p=0.13</p> <p>*adjusted for sex, mode of delivery, prematurity, and infant feeding type</p>	<p>Breast vs. formula (n=1220) OR 0.74 (0.42-1.31) unadjusted, p=.30 OR .88 (0.48-1.61) adjusted, p=.68</p> <p>HIV- mothers breast vs. formula (n=1034) OR 0.88 (0.48-1.61) unadjusted, p=.68 OR 0.92 (0.50-1.70) adjusted, p=.60</p>	<p>Mother HIV positive vs. negative (n=1220) OR 1.89 (1.05-3.40) unadjusted, p=.03 OR 1.82 (0.94-3.52) adjusted, p=.06</p>	<p>Female vs. male (n=1220) OR 2.12 (1.27-3.56) unadjusted, p=.004 OR 2.07 (1.23-3.48) adjusted, p=.006</p> <p>Premature vs. term (n=1220) OR 0.54 (0.23-1.26) unadjusted, p=.15 OR 0.45 (0.19-1.08) adjusted, p=.07</p> <p>HIV- mothers female vs. male (n=1034) OR 1.79 (1.00-3.22) unadjusted, p=.05 OR 1.80 (1.00-3.24) adjusted, p=.07</p> <p>HIV- mothers premature vs. term (n=1034) OR 0.83 (0.32-2.13) unadjusted, p=.69 0.83 (0.32-2.15) adjusted, p=.80</p>	Not Reported	Not Reported	European Commission Regione Piemonte, Italy; UK Medical Research Council		

Author, year Country Study Name Overall Quality	Transmission by labor mgmt: Fetal monitoring	Transmission by mgmt: Rupture of membranes	Transmission by route of delivery	Transmission by type of infant feeding	Transmission by other risk factors (maternal)	Transmission by other risk factors (child)	Sub-group analyses	Adverse events	Funding source	(Cont'd) Transmission rate by other risk factors (maternal)	(Cont'd) Transmission rate by other risk factors (maternal)
Gibb, 2000 ¹⁶¹ Ireland, UK Fair	Not Reported	Not Reported	Elective cesarean vs. emergency cesarean vs. vaginal (n=424) 0% (0-7.4) vs. 5.9% (1.0-17.8) vs. 7.7% (4.5-11.9) OR elective cesarean 0 (95% CI 0-0.86) vs. OR emergency cesarean 0.84 (95% CI 0.12-3.63) vs. *Adjusted for HIV status and breastfeeding Elective cesarean vs. vaginal/emergency cesarean (n=424) 0% (0-7.4) vs. 7.4% (4.5-11.3) OR 0 (0-0.87) *Adjusted for HIV status and breastfeeding	Breast vs. formula (n=414) 7.7% (2.2-17.8) vs. 6.7% (3.7-10.6) OR 1.52 (0.35-5.12) *Adjusted for HIV status and mode of delivery	HIV positive vs. negative (n=441) 18.6% (5.8-38.6) vs. 6.4% (3.5-10.3) OR= 3.8 (0.92-13.2) *Adjusted for breastfeeding and HIV status	Not Reported	Not Reported	Not Reported	UK Department of Health	Not Reported	
Garland, 1998 ¹⁶⁰ Australia Poor	Not Reported	Not Reported	Vaginal vs. cesarean (n=83) 3/61 (4.9%) vs. 0/22 (0%)	Viral RNA detected in breast milk: 0/18 (0%)	Not Reported	Not Reported	Sibling HCV RNA+: 1/16 (6%)	Not Reported	Not Reported		
LaTorre, 1998 ¹⁶² Italy Poor	Not Reported	Not Reported	Vaginal vs. cesarean (n=80) 1/66 (1.5%) vs. 1/14 (7%)	Breastfed vs. formula fed (n=80) 0/24 (0%) vs. 2/56 (3.6%) *none of the HCV-RNA positive mothers breastfed	By maternal HCV RNA status (n=80) mother positive: 2/56 (3.6%) mother negative: 0/24 (0%) *not adjusted	Not Reported	Not Reported	Not Reported	Not specified, research and testing took place at Careggi Hospital, University of Florence		
Lin, 1995 ¹⁶³ Republic of China Poor	Not Reported	Not Reported	Not Reported	Breast feeding transmission rate: (n=11 breast fed) None (0%)	IVDU during pregnancy: 1/12 (8.3%) infants HCV+	Not Reported	Not Reported	Not Reported	National Science Council, Yuan, China		

Author, year Country Study Name Overall Quality	Transmission by labor mgmt: Fetal monitoring	Transmission by mgmt: Rupture of membranes	Transmission by route of delivery	Transmission by type of infant feeding	Transmission by other risk factors (maternal)	Transmission by other risk factors (child)	Sub-group analyses	Adverse events	Funding source	(Cont'd) Transmission rate by other risk factors (maternal)	(Cont'd) Transmission rate by other risk factors (maternal)
Mast, 2005 ¹⁶⁴ US (Houston and Honolulu) Good	<p>* Results are for HCV RNA+/HIV-mothers (n=181)</p> <p>Internal vs. external 3/16 (18.8%) vs. 4/165 (2.4%), RR 7.7 (1.9-31.6), p=.02</p> <p>Internal fetal monitoring *Adjusted OR, 6.7 (1.1-35.9)</p>	<p>* Results are for HCV RNA+/HIV-mothers (n=182)</p> <p>Rupture of membranes before onset of labor yes vs. no 4/45 (8.9%) vs. 3/137 (2.2%), RR 4.1 (0.9-17.5), p=.06</p> <p>Duration of membrane rupture <1 vs. 1-5 vs. 6-12 vs. >=13 0/53 vs. 1/59 (1.7%) vs. 4/40 (10%) vs. 2/30 (6.7%), p=.02</p> <p>Membrane rupture >6 hrs OR, 9.3 (1.5-179.7) *adjusted</p>	<p>* Results are for HCV RNA+/HIV-mothers (n=181)</p> <p>Elective cesarean vs. emergency cesarean vs. vaginal delivery 0/12 (0%) vs. 1/18 (5.5%) vs. 6/151 (4%), elective cesarean RR undefined, emergency cesarean RR 1.4 (0.2-1.1), p=.55</p> <p>Elective cesarean vs. emergency cesarean/vaginal 0/12 vs. 7/169 (4%), RR 0.87 (0.05 to 14)</p>	<p>* Results are for HCV RNA+/HIV-mothers (n=182)</p> <p>Breast vs. formula 2/62 (3.2%) vs. 5/120 (4.2%), RR 0.8 (0.2-3.9), p=1.0</p>	<p>Maternal HCV/RNA status at delivery positive vs. negative 9/190 (4.6%) vs. 0/54, RR undefined</p> <p>*Remaining results are for HCV/RNA+ mothers (n=190)</p> <p>maternal HIV status positive vs. negative 2/8 (25%) vs. 7/182 (3.8%), RR 6.5 (1.6-26.4)</p> <p>Maternal HCV RNA level, genome copies/mL <=10⁶ vs. >10⁶, <10⁷ vs. >10⁷, 1/61 (1.6%) vs. 2/87 (2.3%) vs. 4/34 (11.8%), p=.03</p> <p>Maternal age at delivery, years >=30 vs. <30 5/100(5) vs. 2/81(2.5), RR 2.0(0.4-10.2), p=0.46 (results continued in last 2 columns)</p>	<p>*Results for infants born to HCV/RNA+ mothers (n=190)</p> <p>Sex Male vs. female 2/85 (2.3%) vs. 5/96 (5.2%), RR 0.45 (0.09-2.27), p=.45</p> <p>Gestational age <37 vs. >=37 0/27 vs. 7/155 (4.5%), RR undefined, p=.6</p> <p>Birth weight <2500g vs. >=2500g 1/22 (4.6%) vs. 6/160 (3.8%), RR 1.2 (0.2-9.6), p=1</p> <p>Apgar score at 5 min <=8 vs. >8 0/21 vs. 7/161 (4.4%), RR undefined, p=1</p>	Not Reported	Not Reported	Centers for Disease Control	<p>Prior pregnancies >4 vs. <=4 2/73 vs. 5/109, RR 0.6(0.1-3.0)</p> <p>ALT level at delivery, U/L >35 vs. <=35 3/45(6.7) vs. 4/137, RR 2.3(0.5-9.8)</p> <p>Duration of membrane rupture <1 vs. 1-5 vs. 6-12 vs. >=13 0/53(0) vs. 1/59(1.7) vs. 4/40(10) vs. 2/30(6.7), (p=.02) adjusted OR for membrane rupture >6h, 9.3(1.5-179.7)</p> <p>Duration of labor, h <=6 vs. 7-12 vs. >=13 2/84(2.4) vs. 4/48(8.3) vs. 1/44(2.3), (p=.78)</p>	<p>Cigarette smoking during pregnancy yes vs. no 1/99(1) vs. 6/83(7.23), RR 0.14(0.02-1.1)</p> <p>Alcohol intake during pregnancy yes vs. no 1/42(2.4) vs. 6/140(4.3), RR 0.6(0.1-4.5)</p> <p>History of IVDU yes vs. no 1/94(1.1) vs. 6/88(6.8), RR 0.2 (0.02-1.27)</p> <p>Amniotic fluid clear (ref) vs. meconium vs. bloody 2/129(1.6) vs. 4/40(10) vs. 1/10(10), RR 6.5(1.2-33.9) RR 6.5 (0.6-65.2)</p>

Author, year Country Study Name Overall Quality	Transmission by labor mgmt: Fetal monitoring	Transmission by mgmt: Rupture of membranes	Transmission by route of delivery	Transmission by type of infant feeding	Transmission by other risk factors (maternal)	Transmission by other risk factors (child)	Sub-group analyses	Adverse events	Funding source	(Cont'd) Transmission rate by other risk factors (maternal)	(Cont'd) Transmission rate by other risk factors (maternal)
McMenamin, 2008 ¹⁶⁵ Ireland Fair	Fetal scalp electrode (n=23) Infant HCV RNA+: 0/11 (0%) infant not tested: 12	Not Reported	Elective cesarean vs. emergency cesarean or vaginal delivery (n=441): 1/33 (3%, 95% CI 0% - 8%) vs. 17/408 (4.2%, 95% CI 2.3%-6.2%) p=NS *Not adjusted*same results if limited to HIV- mothers Elective cesarean vs. emergency cesarean or vaginal delivery HCV-RNA+ women (n=295) 5.3% vs. 7.2% p=NS *Not adjusted *Authors didn't provide raw numbers	Not Reported	HCV RNA positive vs. negative vs. unknown (n=441) Positive vs. negative vs. unknown: 18/255 (7.1%, 95% CI 6.3%- 7.9%, p<.05) vs. 0/17 (0%, p<.05) vs. 0/69 (0%)*not adjusted HIV positive vs. negative (n=441) 1/17 (5.9%, 95% CI 0%- 17.2%, p=NS)vs. 17/418 (4.1%, 95% CI 2.2%- 6.0%, p=NS) Mother status unknown: 0/6 (0%)	Not Reported	Not Reported	Not Reported	Not specified, retrospective review of data from National Maternity Hospital and Rotunda Hospital		
Moriya, 1995 ¹⁶⁶ Japan Poor	Not Reported	Not Reported	Not Reported	Breast feeding transmission rate (n=74): 5/6 infected received breast milk (83% %) vs. 54/68 uninfected (79%) OR 1.3 (0.14 to 12.0)	Not Reported	Not Reported	Not Reported	Not Reported	Ministry of Health & Welfare, Japan		

Author, year Country Study Name Overall Quality	Transmission by labor mgmt: Fetal monitoring	Transmission by mgmt: Rupture of membranes	Transmission by route of delivery	Transmission by type of infant feeding	Transmission by other risk factors (maternal)	Transmission by other risk factors (child)	Sub-group analyses	Adverse events	Funding source	(Cont'd) Transmission rate by other risk factors (maternal)	(Cont'd) Transmission rate by other risk factors (maternal)
Okamoto , 2000 ¹⁶⁷ Japan (Tottori University & Medical Center) Poor	Not Reported	Not Reported	Vaginal vs. cesarean 7/41 (17%) vs. 0/18 (0%), p=089 High Viral Load mothers (>2.5x10 ⁶ copies/mL): 7/16 (44%) vs. 0/10 (0%), p=.023	The sample size was too small to test the effect of breast-feeding.	History of blood transfusion, history of clinical hepatitis NS, data NR	HCV-RNA+ titers of vaginally delivered infants born to RNA+ mothers: Mothers (Geometric average, 95% CI): Infected: 5, (7.0, 2.4–20.0) vs. Noninfectious: 31, (1.5, 0.9– 2.3), p<.001 Children (Geometric average, 95% CI): Infected: 7, (8.0, 3.8–16.7) vs. Uninfected: 34, (1.4 0.9– 2.2), p<.001	Not Reported	Research on Children and Families of the Ministry of Welfare of Japan	Not Reported		
Pipan, 1996 ¹⁶⁸ Italy Poor	Not Reported	Not Reported	Not Reported	Breast vs. formula (n=25) 0/6 (0%) vs. 0/19 (0%)	Not Reported	Not Reported	Not Reported	Not Reported	MURST grant and the FVG Branch of Italian League against Virus Disease		

Author, year Country Study Name Overall Quality	Transmission by labor mgmt: Fetal monitoring	Transmission by mgmt: Rupture of membranes	Transmission by route of delivery	Transmission by type of infant feeding	Transmission by other risk factors (maternal)	Transmission by other risk factors (child)	Sub-group analyses	Adverse events	Funding source	(Cont'd) Transmission rate by other risk factors (maternal)	(Cont'd) Transmission rate by other risk factors (maternal)
Resti , 1998 ⁶⁹ Italy Fair	Not Reported	Not Reported	Vaginal vs. cesarean (n=275) 9/213 (4%) vs. 4/62 (6%), RR 0.65 (0.21-2.05), p=0.498	Breast vs. formula (n=275) 6/87(7%) vs. 7/188(4%), RR = 1.85 (0.64 to 5.35), p=0.358. 3/6 infected breast fed children had hepatitis C virus RNA detected on the day of birth	Transmission from women with no known risk of infection was significantly lower (RR=0.17%, 0.04-0.73%; P=0.0063) IVDU during pregnancy 1/12 (8.3%) infants HCV+ HCV viral load No significant difference (z=0.380; P=0.704) in RNA load between mothers who transmitted the virus and those who did not (3.8 (0.02 to 56)×10 ⁵ RNA copies/ml v 2.4 (0.01 to 92.7)×10 ⁵ RNA copies/ml)	6 babies had hepatitis C virus RNA immediately after birth. The transmission rate was higher in 20 recipients of blood transfusions (RR=10%, 95% CI 3-17%)	Not Reported	Not Reported	Partially supported by grant 394/A from Regione Toscana, III Programma Ricerca Sanitaria and by a grant from Ministero della Ricerca Scientifica	Not Reported	

Author, year Country Study Name Overall Quality	Transmission by labor mgmt: Fetal monitoring	Transmission by mgmt: Rupture of membranes	Transmission by route of delivery	Transmission by type of infant feeding	Transmission by other risk factors (maternal)	Transmission by other risk factors (child)	Sub-group analyses	Adverse events	Funding source	(Cont'd) Transmission rate by other risk factors (maternal)	(Cont'd) Transmission rate by other risk factors (maternal)
Spencer, 1997 ¹⁷⁰ Australia Poor	Not Reported	Viremic mothers (mean hours ± SD) (n=63) Transmitted vs. not transmitted: 28±10 vs. 16±4, p=.03	Viremic mothers, cesarean (n=63) transmitted vs. not transmitted 1/6 (14%) vs. 6/56 (9%), p=.5 Cesarean vs. vaginal 1/7 (14%) vs. 5/55 (9%)	Viremic mothers breastfeeding (n=63) transmitted vs. not transmitted 2/6 (33%) vs. 31/57 (54%) p=0.4 Breast fed vs. formula fed 2/33 (6%) vs. 4/30 (13%) Viral RNA detected in breast milk: (n= 38) 0%	Viremic mothers transmitting vs. non- transmitting Viral load at delivery 8.9x10 ⁵ vs. 3.9x10 ⁵ , p=0.04 Drug use, mean years 8.8±1.4 vs. 10±0.8, p=0.7 Past HBV infection 4/6 (66%) vs. 34/55 (62%), p<0.9 Heroin use during pregnancy 2/2 (100%) vs. 38/45 (84%), p<0.9	Birth weight (mean g) 2698 (transmitted n=6) vs. 3020 (no transmission n=57) p= 0.4 Gestational Age transmitting vs. non- transmitting: 37±0.9 weeks vs. 39±0.3 weeks, p=0.3	Not Reported	Not Reported	Not Reported		

Author, year Country Study Name Overall Quality	Transmission by labor mgmt: Fetal monitoring	Transmission by mgmt: Rupture of membranes	Transmission by route of delivery	Transmission by type of infant feeding	Transmission by other risk factors (maternal)	Transmission by other risk factors (child)	Sub-group analyses	Adverse events	Funding source	(Cont'd) Transmission rate by other risk factors (maternal)	(Cont'd) Transmission rate by other risk factors (maternal)
Syriopoulou, 2005 ¹⁷¹ Greece Poor	Not Reported	Not Reported	Vaginal vs. cesarean (n=56) 2/39 (5%) vs. 0/17 (0%), p=0.34	Breast vs. formula (n=56) 0/15 (0%) vs. 2/41 (5%), p=0.38	HCV/RNA+ vs. HCV/RNA- (n=86) 2/56 (3.6%) vs. 0/30 (0%) HIV+ vs. HIV- (n=56) 1/2 (50%) vs. 1/54 (2%) (p<.001) IVDU use during pregnancy, yes vs. no (n=56) 2/3 (67%) *1 mother was HIV+ vs. 0/54 (0%) (p<.001) IVDU ever, yes vs. no (n=56) 2/8 (25%) vs. 0/48 (0%) (p<.001)	Not Reported	Not Reported	Not Reported	Not Reported		
Tajiri , 2001 ¹⁷² Japan (seven hospitals in the Osaka metropolitan area) Poor	Not Reported	Not Reported	Vaginal vs. cesarean (n=114) 8/90 (8.8%) vs. 1/24 (4.2%), p = 0.396 *RR: 2.04 (.284 - 43.42)	Breast vs. formula (n=114) 9/98 (9.2%) vs. 0/16, p=0.243	Maternal HCV Viremia: positive: 9/81 vs. negative: 0/33, p=.040 Maternal viral load: High: 8/46 vs. Low: 0/27, p=0.019	Not Reported	Not Reported	Not Reported	Not Reported		
Tanzi, 1997 ¹⁷³ Italy Poor	Not Reported	Not Reported	Not Reported	HCV RNA+ mothers (n=18) 12/18 HCV/RNA+ mothers breastfed, none infected at 3 month followup	Not Reported	Not Reported	Not Reported	Not Reported	Not Reported		

Author, year Country Study Name Overall Quality	Transmission by labor mgmt: Fetal monitoring	Transmission by mgmt: Rupture of membranes	Transmission by route of delivery	Transmission by type of infant feeding	Transmission by other risk factors (maternal)	Transmission by other risk factors (child)	Sub-group analyses	Adverse events	Funding source	(Cont'd) Transmission rate by other risk factors (maternal)	(Cont'd) Transmission rate by other risk factors (maternal)
Zanetti , 1998 ¹⁷⁴ (Intervirolology) Italy A prospective Study on Mother-to-Infant Transmission of Hepatitis C virus Zanetti et al, 1999 ¹⁷⁵ (Journal of Hepatology) Italy Mother-to-infant transmission of hepatitis C virus Poor	Not Reported	Not Reported	Vaginal vs. cesarean (HCV+) 7/193 (3.6%) vs. 1/58 (1.7%), p = 0.7 (HCV+/HIV+) 0/4(0%) vs. 9/36(25%), p = 0.5	HIV- mothers breast vs. formula (n=251) 3/127 (2.4%) vs. 5/124 (4.0%), p = 0.5 HIV+ mothers breast vs. formula (n= 40) 0 vs. 9/40 (22.5%)	Transmission by History of IVDU: HCV+: Yes: 3/67 (4.5%) vs. No: 5/184 (2.7%), p=0.4 HCV+/HIV+: Yes: 9/40 (22.5%) vs. No: 0 Transmission by History of Chronic Liver Disease or elevated ALT: HCV+: Yes: 3/85 (3.5%) vs. No: 5/166 (3%), p=1 HCV+/HIV+: Yes: 4/10 (40%) vs. No: 5/30 (16.7%), p=0.2	Not Reported	Not Reported	Not Reported			

Abbreviations: HCV, hepatitis C virus; SVR, sustained virologic response.

Evidence Table 11: Key Question 7. Pregnancy Intervention Observational Studies Overall Quality Rating

Author, Year	(1) Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	(2) Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	(3) Did the study maintain comparable groups through the study period?	(4) Did the study use accurate methods for ascertaining exposures and potential confounders?	(5) Were outcome assessors and/or data analysts blinded to the exposure being studied?	(6) Did the article report attrition?	(7) Is there important differential loss to followup or overall high loss to followup?	(8) Did the study perform appropriate statistical analyses on potential confounders?	(9) Were outcomes pre-specified and defined, and ascertained using accurate methods?	Overall Quality
Ceci, 2001 ¹⁵⁶	Yes	Unclear	Unclear	Yes	No	Yes	Unclear	Yes	Yes	Fair
Conte, 2000 ¹⁵⁷	Unclear	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Yes	Poor
European Paediatric Hepatitis C Virus Network, 2001 (Pembrey) ¹⁵⁸	Yes	Unclear	Unclear	Yes	Unclear	No	No	Yes	Yes	Good
European Paediatric Hepatitis C Virus Network, 2005 (Tovo) ¹⁷⁷	Yes	Unclear	Unclear	Yes	Unclear	No	No	Yes	Yes	Good
Garland, 1998 ¹⁶⁰	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes	No	Yes	Poor
Gibb, 2000 ¹⁶¹	Unclear	Unclear	Unclear	Yes	No	No	No	Yes	Yes	Fair
LaTorre, 1998 ¹⁶²	Yes	Unclear	Unclear	Yes	Unclear	No	Unclear	No	Unclear	Poor
Lin, 1995 ¹⁶³	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Unclear	No	Yes	Poor
Mast, 2005 ¹⁶⁴	Yes	Unclear	Unclear	Yes	No	Yes	No	Yes	Yes	Good
McMenamin, 2008 ¹⁶⁵	Yes	Unclear	Unclear	Yes	Unclear	Yes	Yes	No	No	Fair
Moriya, 1995 ¹⁶⁶	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	No	No	Yes	Poor

Author, Year	(1) Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	(2) Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	(3) Did the study maintain comparable groups through the study period?	(4) Did the study use accurate methods for ascertaining exposures and potential confounders?	(5) Were outcome assessors and/or data analysts blinded to the exposure being studied?	(6) Did the article report attrition?	(7) Is there important differential loss to followup or overall high loss to followup?	(8) Did the study perform appropriate statistical analyses on potential confounders?	(9) Were outcomes pre-specified and defined, and ascertained using accurate methods?	Overall Quality
Okamoto, 1999 ¹⁶⁷	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	No	Unclear	Poor
Pipan, 1996 ¹⁶⁸	Yes	Unclear	Unclear	Yes	Yes	No	No	No	Yes	Poor
Resti et al, 1998 ¹⁶⁹	Yes	Unclear	Unclear	Unclear	Unclear	Yes	No	No	Yes	Fair
Spencer, 1997 ¹⁷⁰	Unclear	Unclear	Unclear	No	Unclear	Yes	Yes	No	Yes	Poor
Syriopoulou, 1998 ¹⁷¹	Unclear	Unclear	Unclear	No	Unclear	No	No	No	Yes	Poor
Tajiri, 2001 ¹⁷²	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	No	Unclear	Poor
Tanzi, 1997 ¹⁷³	Yes	Unclear	Unclear	Yes	Unclear	No	Unclear	No	Yes	Poor
Zanetti et al, 1998 ¹⁷⁴ , Zanetti et al, 1999 ¹⁷⁵	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	No	Yes	Poor

Appendix G References

1. Gunn RA, Murray PJ, Brennan CH, et al. Evaluation of screening criteria to identify persons with hepatitis C virus infection among sexually transmitted disease clinic clients: results from the San Diego Viral Hepatitis Integration Project. *Sex Transm Dis.* 2003 Apr;30(4):340-4. PMID: 12671556.
2. McGinn T, O'Connor-Moore N, Alfandre D, et al. Validation of a hepatitis C screening tool in primary care. *Arch Intern Med.* 2008 Oct 13;168(18):2009-13. PMID: 18852403.
3. Nguyen MT, Herrine SK, Laine CA, et al. Description of a new hepatitis C risk assessment tool. *Arch Intern Med.* 2005 Sep 26;165(17):2013-8. PMID: 16186472.
4. Zuniga IA, Chen JJ, Lane DS, et al. Analysis of a hepatitis C screening programme for US veterans. *Epidemiol Infect.* 2006 Apr;134(2):249-57. PMID: 16490127.
5. Zuure F, Davidovich U, Kok G, et al. Evaluation of a risk assessment questionnaire to assist hepatitis C screening in the general population. *Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin.* 2010 Apr 15;15(15):19539. PMID: 20429995.
6. Andriulli A, Persico M, Iacobellis A, et al. Treatment of patients with HCV infection with or without liver biopsy. *J Viral Hepat.* 2004;11(6):536-42. PMID: 15500554.
7. Adams LA, Bulsara M, Rossi E, et al. Hepascore: An Accurate Validated Predictor of Liver Fibrosis in Chronic Hepatitis C Infection. *Clin Chem.* 2005 October 1;51(10):1867-73. PMID: 16055434.
8. Ahmad W, Ijaz B, Javed FT, et al. A comparison of four fibrosis indexes in chronic HCV: development of new fibrosis-cirrhosis index (FCI). *BMC Gastroenterology.* 2011;11:44. PMID: 21507271.
9. Alsatie M, Kwo PY, Gingerich JR, et al. A multivariable model of clinical variables predicts advanced fibrosis in chronic hepatitis C. *J Clin Gastroenterol.* 2007;41(4):416-21. PMID: 17413613.
10. Adler M, Gulbis B, Moreno C, et al. The predictive value of FIB-4 versus FibroTest, APRI, FibroIndex and Forns index to noninvasively estimate fibrosis in hepatitis C and nonhepatitis C liver diseases. *Hepatology.* 2008;47(2):762-3. PMID: 18220307.
11. Anderson FH, Zeng L, Rock NR, et al. An assessment of the clinical utility of serum ALT and AST in chronic hepatitis C. *Hepato Res.* 2000;18(1):63-71. PMID: 10838037.
12. Becker L, Salameh W, Sferruzza A, et al. Validation of hepascore, compared with simple indices of fibrosis, in patients with chronic hepatitis C virus infection in United States. *Clin Gastroenterol Hepatol.* 2009;7(6):696-701. PMID: 19514117.
13. Bejarano G. Prospective evaluation of liver fibrosis in chronic viral hepatitis C infection using the Sabadell NIHCED (Non-Invasive Hepatitis-C-Related Cirrhosis Early Detection) index.; 2009. <http://hepatop.biopredictive.com/publication/19527078/prospective-evaluation-of-liver-fibrosis-in-chronic-viral-hepatitis-c-infection-using-the-sabadell-nihced-non-invasive-hepatitis-c-related-cirrhosis-early-detection-index/>. Accessed on June 20, 2011.
14. Berg T, Hoffmann RM, Teuber G, et al. Efficacy of short-term induction therapy with ribavirin plus interferon alfa in previously untreated patients with chronic hepatitis C. *Journal of Hepatology.* 1999;30(Suppl. 1):70.
15. Ben Jazia E, Kaabia N, Benabdelkader A, et al. Noninvasive fibrosis markers for the prediction of significant fibrosis in patients with chronic hepatitis C virus infection in Tunisia. *Infect Dis Clin Pract (Baltim Md).* 2009;17(6):385-.
16. Boeker KH, Haberkorn CI, Michels D, et al. Diagnostic potential of circulating TIMP-1 and MMP-2 as markers of liver fibrosis in patients with chronic hepatitis C. *Clin Chim Acta.* 2002;316(1-2):71-81. PMID: 11750276.
17. Bonacini M, Hadi G, Govindarajan S, et al. Utility of a discriminant score for diagnosing advanced fibrosis or cirrhosis in patients with chronic hepatitis C virus infection. *Am J Gastroenterol.* 1997;92(8):1302-4. PMID: 9260794.
18. Borroni G, Ceriani R, Cazzaniga M, et al. Comparison of simple tests for the non-invasive diagnosis of clinically silent cirrhosis in chronic hepatitis C. *Aliment Pharmacol Ther.* 2006;24(5):797-804. PMID: 16918883.
19. Bota S, Sirli R, Sporea I, et al. A new scoring system for prediction of fibrosis in chronic hepatitis C. *Hepat Mon.* 2011;11(7):548-55. PMID: 22087193.

20. Bourliere M, Penaranda G, Ouzan D, et al. Optimized stepwise combination algorithms of non-invasive liver fibrosis scores including Hepascore in hepatitis C virus patients. *Aliment Pharmacol Ther.* 2008;28(4):458-67. PMID: 18498446.
21. Bourliere M, Penaranda G, Renou C, et al. Validation and comparison of indexes for fibrosis and cirrhosis prediction in chronic hepatitis C patients: proposal for a pragmatic approach classification without liver biopsies. *J Viral Hepat.* 2006;13(10):659-70. PMID: 16970597.
22. Boursier J, de Ledinghen V, Zarski JP, et al. Comparison of eight diagnostic algorithms for liver fibrosis in hepatitis C: new algorithms are more precise and entirely noninvasive. *Hepatology.* 2012;55(1):58-67. PMID: 21898504.
23. Boursier J, de Ledinghen V, Zarski J-P, et al. A new combination of blood test and fibroscan for accurate non-invasive diagnosis of liver fibrosis stages in chronic hepatitis C. *Am J Gastroenterol.* 2011;106(7):1255-63. PMID: 21468012.
24. Boursier J, Bacq Y, Halfon P, et al. Improved diagnostic accuracy of blood tests for severe fibrosis and cirrhosis in chronic hepatitis C. *Eur J Gastroenterol Hepatol.* 2009;21(1):28-38. PMID: 19060630.
25. Burton MJ, Sunesara I, Penman A, et al. Comparing the aspartate aminotransferase (AST) to platelet ratio index (APRI) between African American and white veterans with chronic hepatitis C. *South Med J.* 2011;104(5):309-14. PMID: 21606706.
26. Calès P, Boursier J, Bertrais S, et al. Optimization and robustness of blood tests for liver fibrosis and cirrhosis. *Clin Biochem.* 2010;43(16-17):1315-22. PMID: 20713037.
27. Calès P, Boursier J, de Lédighen V, et al. Evaluation and improvement of a reliable diagnosis of cirrhosis by blood tests. *Gastroenterologie Clinique et Biologique.* 2008;32(12):1050-60. PMID: 19019606.
28. Castéra L, Sebastiani G, Le Bail B, et al. Prospective comparison of two algorithms combining non-invasive methods for staging liver fibrosis in chronic hepatitis C. *J Hepatol.* 2010;52(2):191-8. PMID: 20006397.
29. Castera L, Le Bail B, Roudot-Thoraval F, et al. Early detection in routine clinical practice of cirrhosis and oesophageal varices in chronic hepatitis C: comparison of transient elastography (FibroScan) with standard laboratory tests and non-invasive scores. *J Hepatol.* 2009;50(1):59-68. PMID: 19013661.
30. Castéra L, Vergniol J, Foucher J, et al. Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology.* 2005;128(2):343-50. PMID: 15685546.
31. Cheong JY, Um SH, Seo YS, et al. Non-invasive index for predicting significant liver fibrosis: comparison of diagnostic performances in patients with chronic hepatitis B and C. *Dig Dis Sci.* 2011;56:555-63. PMID: 20585981.
32. Cheung KJ, Tilleman K, Deforce D, et al. Usefulness of a novel serum proteome-derived index FI-PRO (fibrosis-protein) in the prediction of fibrosis in chronic hepatitis C. *Eur J Gastroenterol Hepatol.* 2011;23(8):701-10. PMID: 21623191.
33. Cheung RC, Currie S, Shen H, et al. Can we predict the degree of fibrosis in chronic hepatitis C patients using routine blood tests in our daily practice? *J Clin Gastroenterol.* 2008;42(7):827-34. PMID: 18285716.
34. Chrysanthos NV, Papatheodoridis GV, Savvas S, et al. Aspartate aminotransferase to platelet ratio index for fibrosis evaluation in chronic viral hepatitis. *Eur J Gastroenterol Hepatol.* 2006;18(4):389-96. PMID: 16538110.
35. Cobbold J, Crossey M, Colman P, et al. Optimal combinations of ultrasound-based and serum markers of disease severity in patients with chronic hepatitis C. *J Viral Hepat.* 2010;17(8):537-45. PMID: 19804501.
36. Colletta C, Smirne C, Fabris C, et al. Value of two noninvasive methods to detect progression of fibrosis among HCV carriers with normal aminotransferases. *Hepatology.* 2005;42(4):838-45. PMID: 16121354.
37. Colli A, Colucci A, Paggi S, et al. Accuracy of a predictive model for severe hepatic fibrosis or cirrhosis in chronic hepatitis C. *World J Gastroenterol.* 2005;11(46):7318-22. PMID: 16437635
38. Crisan D, Radu C, Lupsor M, et al. Two or more synchronous combination of noninvasive tests to increase accuracy of liver fibrosis assesment in chronic Hepatitis C; results from a cohort of 446 patients. *Hepat Mon.* 2012;12(3):177-84. PMID: 22550525.
39. Cross TJ, Calvaruso V, Maimone S, et al. Prospective comparison of Fibroscan, King's score and liver biopsy for the assessment of cirrhosis in chronic hepatitis C infection. *J Viral Hepat.* 2010;17(8):546-. PMID: 19874477.

40. Cross TJS, Rizzi P, Berry PA, et al. King's Score: an accurate marker of cirrhosis in chronic hepatitis C. *Eur J Gastroenterol Hepatol.* 2009;21(7):730-8. PMID: 19430302.
41. Ehsan N, Badr M, Raouf A, et al. Correlation between liver biopsy findings and different serum biochemical tests in staging fibrosis in Egyptian patients with chronic hepatitis C virus infection. *Arab J Gastroenterol* 2008;9(1):7-12.
42. El-Gindy I, El Rahman AT, El-Alim MA, et al. Diagnostic potential of serum matrix metalloproteinase-2 and tissue inhibitor of metalloproteinase-1 as non-invasive markers of hepatic fibrosis in patients with HCV related chronic liver disease. *Egypt J Immunol.* 2003;10(1):27-35. PMID: 15719620.
43. El-Sayed R, Fahmy M, El Koofy N, et al. Can aspartate aminotransferase to platelet ratio index replace liver biopsy in chronic hepatitis C? *Trop Gastroenterol.* 2011;32(4):267-72. PMID: 22696906.
44. el-Shorbagy E, Afefy AF, Ibrahim IA, et al. Non-invasive markers and predictors of severity of hepatic fibrosis in HCV patients at Sharkia Governorate, Egypt. *J Egypt Soc Parasitol.* 2004;34(1):459-78. PMID: 15124753.
45. Fabris C, Smirne C, Toniutto P, et al. Usefulness of six non-proprietary indirect markers of liver fibrosis in patients with chronic hepatitis C. *Clin Chem Lab Med.* 2008;46(2):253-9. PMID: 18324909.
46. Fontana RJ, Goodman ZD, Dienstag JL, et al. Relationship of serum fibrosis markers with liver fibrosis stage and collagen content in patients with advanced chronic hepatitis C. *Hepatology.* 2008;47(3):789-98. PMID: 18175357.
47. Forns X, Ampurdanès S, Llovet JM, et al. Identification of chronic hepatitis C patients without hepatic fibrosis by a simple predictive model. *Hepatology.* 2002;36(4):986-92. PMID: 12297848.
48. Friedrich-Rust M, Rosenberg W, Parkes J, et al. Comparison of ELF, FibroTest and FibroScan for the non-invasive assessment of liver fibrosis. *BMC Gastroenterology.* 2010;10(1):103. PMID: 20828377.
49. Gabrielli GB, Capra F, Casaril M, et al. Serum laminin and type III procollagen in chronic hepatitis C. Diagnostic value in the assessment of disease activity and fibrosis. *Clin Chim Acta.* 1997;265(1):21-31. PMID: 9352126.
50. Giannini EG, Zaman A, Ceppa P, et al. A simple approach to noninvasively identifying significant fibrosis in chronic hepatitis C patients in clinical practice. *J Clin Gastroenterol.* 2006;40(6):521-7. PMID: 16825935.
51. Giannini (a) E, Risso D, Botta F, et al. Validity and clinical utility of the aspartate aminotransferase-alanine aminotransferase ratio in assessing disease severity and prognosis in patients with hepatitis C virus-related chronic liver disease. *Arch Intern Med.* 2003 January 27;163(2):218-24. PMID: 12546613.
52. Giannini (b) E, Testa R. Noninvasive diagnosis of fibrosis: The truth is rarely pure and never simple. *Hepatology.* 2003;38(5):1312-3. PMID: 14578874.
53. Gomes da Silva. Aspartate aminotransferase-to-platelet ratio index for fibrosis and cirrhosis prediction in chronic hepatitis C patients. *Braz J Infect Dis.* 2008;12(1) PMID: 18553008.
54. Grigorescu M, Rusu M, Neculoiu D, et al. The FibroTest value in discriminating between insignificant and significant fibrosis in chronic hepatitis C patients. The Romanian experience. *J Gastrointest Liver Dis.* 2007;16(1):31-7. PMID: 17410286.
55. Guéchet J, Lasnier E, Sturm N, et al. Automation of the Hepascore and validation as a biochemical index of liver fibrosis in patients with chronic hepatitis C from the ANRS HC EP 23 Fibrostar cohort. *Clin Chim Acta.* 2010;411(1-2):86-91. PMID: 19850017.
56. Guéchet J, Laudat A, Loria A, et al. Diagnostic accuracy of hyaluronan and type III procollagen amino-terminal peptide serum assays as markers of liver fibrosis in chronic viral hepatitis C evaluated by ROC curve analysis. *Clin Chem.* 1996;42(4):558-63. PMID: 8605673.
57. Guéchet J, Poupon RE, Giral P, et al. Relationship between procollagen III aminoterminal propeptide and hyaluronan serum levels and histological fibrosis in primary biliary cirrhosis and chronic viral hepatitis C. *J Hepatol.* 1994;20(3):388-93. PMID: 8014451.
58. Güzelbulut. AST-platelet ratio index, Forns index and FIB-4 in the prediction of significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Turk J Gastroenterol.* 2011;22(3):279-85. PMID: 21805418.
59. Halfon P, Bacq Y, De Muret A, et al. Comparison of test performance profile for blood tests of liver fibrosis in chronic hepatitis C. *J Hepatol.* 2007;46(3):395-402. PMID: 17156890.

60. Halfon P. Independent prospective multicenter validation of biochemical markers (fibrotest-actitest) for the prediction of liver fibrosis and activity in patients with chronic hepatitis C: the fibropaca study. *Am J Gastroenterol.* 2006;101(3):547-55. PMID: 16542291.
61. Halfon P. Accuracy of hyaluronic acid level for predicting liver fibrosis stages in patients with hepatitis C virus. *Comp Hepatol.* 2005;4(1)PMID: 16008833.
62. Hsieh YY, Tung SY, Lee IL, et al. FibroQ: an easy and useful noninvasive test for predicting liver fibrosis in patients with chronic viral hepatitis. *Chang Gung Med J.* 2009;32(6):614-22. PMID: 20035640.
63. Iacobellis (a) A, Fusilli S, Mangia A, et al. Ultrasonographic and biochemical parameters in the non-invasive evaluation of liver fibrosis in hepatitis C virus chronic hepatitis. *Aliment Pharmacol Ther.* 2005;22(9):769-74. PMID: 16225484
64. Iacobellis (b) A, Mangia A, Leandro G, et al. External validation of biochemical indices for noninvasive evaluation of liver fibrosis in HCV chronic hepatitis. *Am J Gastroenterol.* 2005;100(4):868-73. PMID: 15784034
65. Imbert-Bismut F, Ratziu V, Pieroni L, et al. Biochemical markers of liver fibrosis in patients with hepatitis C virus infection: a prospective study. *The Lancet.* 2001;357(9262):1069-75. PMID: 11297957.
66. Thabut D, Simon M, Myers RP, et al. Noninvasive prediction of fibrosis in patients with chronic hepatitis C. *Hepatology.* 2003;37(5):1220-1. PMID: 12717403.
67. Le Calvez S, Thabut D, Messous D, et al. The predictive value of Fibrotest vs. APRI for the diagnosis of fibrosis in chronic hepatitis C. *Hepatology.* 2004;39(3):862-3. PMID: 14999708.
68. Imperiale TF, Said AT, Cummings OW, et al. Need for validation of clinical decision aids: use of the AST/ALT ratio in predicting cirrhosis in chronic hepatitis C. *Am J Gastroenterol.* 2000;95(9):2328-32. PMID: 11007237.
69. Islam S, Antonsson L, Westin J, et al. Cirrhosis in hepatitis C virus-infected patients can be excluded using an index of standard biochemical serum markers. *Scand J Gastroenterol.* 2005;40(7):867-72. PMID: 16109665.
70. Kaul V, Friedenberg FK, Braitman LE, et al. Development and validation of a model to diagnose cirrhosis in patients with hepatitis C. *Am J Gastroenterol.* 2002;97(10):2623-8. PMID: 12385450.
71. Khan. Evaluation of diagnostic accuracy of APRI for prediction of fibrosis in hepatitis C patients. *J Ayub Med Coll Abbottabad.* 2008;20(4):122-6. PMID: 19999223.
72. N K. Serum aminotransferase levels and platelet count as predictive factor of fibrosis and cirrhosis in patients with chronic hepatitis C infection. *J Pak Med Assoc.* 2003;53(3):101-4. PMID: 12779023.
73. Koda M, Matunaga Y, Kawakami M, et al. Fibroindex, a practical index for predicting significant fibrosis in patients with chronic hepatitis C. *Hepatology.* 2007;45(2):297-306. PMID: 17256741.
74. Lackner C, Struber G, Liegl B, et al. Comparison and validation of simple noninvasive tests for prediction of fibrosis in chronic hepatitis C. *Hepatology.* 2005;41(6):1376-82. PMID: 15915455.
75. Lackner C, Struber G, Bankuti C, et al. Noninvasive diagnosis of cirrhosis in chronic hepatitis C based on standard laboratory tests. *Hepatology.* 2006;42(2):378-9. PMID: 16440344.
76. Leroy V, Halfon P, Bacq Y, et al. Diagnostic accuracy, reproducibility and robustness of fibrosis blood tests in chronic hepatitis C: A meta-analysis with individual data. *Clin Biochem.* 2008;41(16-17):1368-76. PMID: 18655779.
77. Leroy V, Hilleret M-N, Sturm N, et al. Prospective comparison of six non-invasive scores for the diagnosis of liver fibrosis in chronic hepatitis C. *J Hepatol.* 2007;46(5):775-82. PMID: 17321634.
78. Leroy V, Monier F, Bottari S, et al. Circulating matrix metalloproteinases 1, 2, 9 and their inhibitors TIMP-1 and TIMP-2 as serum markers of liver fibrosis in patients with chronic hepatitis C: comparison with PIIINP and hyaluronic acid. *Am J Gast.* 2004;99(2):271-9. PMID: 15046217.
79. Liu CH, Lin JW, Tsai FC, et al. Noninvasive tests for the prediction of significant hepatic fibrosis in hepatitis C virus carriers with persistently normal alanine aminotransferases. *Liver Int.* 2006;26(9):1087-94. PMID: 17032409.
80. Loaeza-del-Castillo A, Paz-Pineda F, Oviedo-Cárdenas E, et al. AST to platelet ratio index (APRI) for the noninvasive evaluation of liver fibrosis. *Ann Hepatol.* 2008;7(4):350-7. PMID: 19034235.

81. Lo Iacono O, García-Monzón C, Almasio P, et al. Soluble adhesion molecules correlate with liver inflammation and fibrosis in chronic hepatitis C treated with interferon-alpha. *Aliment Pharmacol Ther.* 1998;12(11):1091-9. PMID: 9845398.
82. Lok ASF, Ghany MG, Goodman ZD, et al. Predicting cirrhosis in patients with hepatitis C based on standard laboratory tests: Results of the HALT-C cohort. *Hepatology.* 2005;42(2):282-92. PMID: 15986415.
83. Luo J, Hwang S, Chang F, et al. Simple blood tests can predict compensated liver cirrhosis in patients with chronic hepatitis C. *Hepatogastroenterology.* 2002;49(44):478-81. PMID: 11995477.
84. Martinez SM, Fernández-Varo G, González P, et al. Assessment of liver fibrosis before and after antiviral therapy by different serum marker panels in patients with chronic hepatitis C. *Aliment Pharmacol Ther.* 2011;33(1):138-48. PMID: 21083589.
85. McHutchison JG, Blatt LM, de Medina M, et al. Measurement of serum hyaluronic acid in patients with chronic hepatitis C and its relationship to liver histology. Consensus Interferon Study Group. *J Gastroenterol Hepatol.* 2000;15(8):945-51. PMID: 11022838.
86. Metwally MA, Zein CO, Zein NN. Predictors and noninvasive identification of severe liver fibrosis in patients with chronic hepatitis C. *Dig Dis Sci.* 2007;52(2):582-8. PMID: 17211710.
87. Murawaki (b) Y, Ikuta Y, Okamoto K, et al. Diagnostic value of serum markers of connective tissue turnover for predicting histological staging and grading in patients with chronic hepatitis C. *J Gastroenterol.* 2001;36(6):399-406. PMID: 11428586.
88. Murawaki (a) Y, Koda M, Okamoto K, et al. Diagnostic value of serum type IV collagen test in comparison with platelet count for predicting the fibrotic stage in patients with chronic hepatitis C. *J Gastroenterol Hepatol.* 2001;16(7):777-81. PMID: 11446886.
89. Myers RP, de Torres M, Imbert-Bismut F, et al. Biochemical markers of fibrosis in patients with chronic hepatitis C: A comparison with prothrombin time, platelet count, and age-platelet index. *Dig Dis Sci.* 2003;48(1):146-53. PMID: 12645802.
90. Myers RP, Ratziu V, Imbert-Bismut F, et al. Biochemical markers of liver fibrosis: a comparison with historical features in patients with chronic hepatitis C. *Am J Gastroenterol.* 2002;97(9):2419-25. PMID: 12358267.
91. Obrador BD, Prades MG, Gómez MV, et al. A predictive index for the diagnosis of cirrhosis in hepatitis C based on clinical, laboratory, and ultrasound findings. *Eur J Gastroenterol Hepatol.* 2006;18(1):57-62. PMID: 16357620.
92. Ohta T, Sakaguchi K, Fujiwara A, et al. Simple surrogate index of the fibrosis stage in chronic hepatitis C patients using platelet count and serum albumin level. *Acta Med Okayama.* 2006;60(2):77-84. PMID: 16680183.
93. Omran MM, Farid K, Emran TM, et al. Fibro-(alpha) score as a simple and useful non-invasive test for predicting significant liver fibrosis in chronic hepatitis C patients. *Arab J Gastroenterol.* 2011;12(2):74-9. PMID: 21684477.
94. Paggi S, Colli A, Fraquelli M, et al. A non-invasive algorithm accurately predicts advanced fibrosis in hepatitis C: A comparison using histology with internal-external validation. *J Hepatol.* 2008;49(4):564-71. PMID: 18706734.
95. Parise ER, Oliveira AC, Figueiredo-Mendes C, et al. Noninvasive serum markers in the diagnosis of structural liver damage in chronic hepatitis C virus infection. *Liver Int.* 2006;26(9):1095-9. PMID: 17032410.
96. Park SH, Kim CH, Kim DJ, et al. Diagnostic value of multiple biomarker panel for prediction of significant fibrosis in chronic hepatitis C. *Clin Biochem.* 2011;44(17-18):1396-9. PMID: 21971609.
97. Park GJH, Lin BP, Ngu MC, et al. Aspartate aminotransferase : alanine aminotransferase ratio in chronic hepatitis C infection: Is it a useful predictor of cirrhosis? *J Gastroenterol Hepatol.* 2000;15(4):386-90. PMID: 10824882.
98. Park J-W. [Hepatocellular carcinoma in Korea: introduction and overview]. *Korean Journal of Gastroenterology/Taehan Sohwagi Hakhoe Chi.* 2005 Apr;45(4):217-26. PMID: 15843747.
99. Parkes J, Guha IN, Roderick P, et al. Enhanced Liver Fibrosis (ELF) test accurately identifies liver fibrosis in patients with chronic hepatitis C. *J Viral Hepat.* 2011 Jan;18(1):23-31. PMID: 20196799.

100. Patel K, Benhamou Y, Yoshida EM, et al. An independent and prospective comparison of two commercial fibrosis marker panels (HCV FibroSURE and FIBROSpect II) during albinferon alfa-2b combination therapy for chronic hepatitis C. *J Vir Hep.* 2009;16(3):178-86. PMID: 19175870.
101. Patel K, Gordon SC, Jacobson I, et al. Evaluation of a panel of non-invasive serum markers to differentiate mild from moderate-to-advanced liver fibrosis in chronic hepatitis C patients. *J Hepatol.* 2004;41(6):935-42. PMID: 15582126.
102. Plevris JN, Haydon GH, Simpson KJ, et al. Serum hyaluronan--a non-invasive test for diagnosing liver cirrhosis. *Eur J Gastroenterol Hepatol.* 2000;12(10):1121-7. PMID: 11057458.
103. Pohl A, Behling C, Oliver D, et al. Serum aminotransferase levels and platelet counts as predictors of degree of fibrosis in chronic hepatitis C virus infection. *Am J Gastroenterol.* 2001;96(11):3142-6. PMID: 11721762.
104. Poynard T, McHutchison J, Manns M, et al. Biochemical surrogate markers of liver fibrosis and activity in a randomized trial of peginterferon alfa-2b and ribavirin. *Hepatology.* 2003;38(2):481-92. PMID: 12883493.
105. Poynard T, Imbert-Bismut F, Ratzu V, et al. Biochemical markers of liver fibrosis in patients infected by hepatitis C virus: longitudinal validation in a randomized trial. *J Vir Hep.* 2002;9(2):128-33. PMID: 11876795.
106. Pradat P, Alberti A, Poynard T, et al. Predictive value of ALT levels for histologic findings in chronic hepatitis C: a European collaborative study. *Hepatology.* 2002;36(4 Pt 1):973-7. PMID: 12297846.
107. Reedy DW, Loo AT, Levine RA. AST/ALT ratio > or = 1 is not diagnostic of cirrhosis in patients with chronic hepatitis C. *Dig Dis Sci.* 1998;43(9):2156-9. PMID: 9753286.
108. Renou C, Muller P, Jouve E, et al. Relevance of moderate isolated thrombopenia as a strong predictive marker of cirrhosis in patients with chronic hepatitis C virus. *Am J Gastroenterol.* 2001;96(5):1657-9. PMID: 11374731.
109. Romera M, Corpas R, Romero Gómez M. Insulin resistance as a non-invasive method for the assessment of fibrosis in patients with hepatitis C: a comparative study of biochemical methods. *Rev Esp Enferm Dig.* 2006;98(3):161-9. PMID: 16737415.
110. Rosenberg WM, Voelker M, Thiel R, et al. Serum markers detect the presence of liver fibrosis: a cohort study. *Gastroenterology.* 2004;127(6):1704-13. PMID: 15578508.
111. Rossi E, Adams L, Prins A, et al. Validation of the FibroTest Biochemical Markers Score in assessing liver fibrosis in hepatitis C patients. *Clin Chem.* 2003 March 1;49(3):450-4. PMID: 12600957.
112. Saadeh S, Cammell G, Carey WD, et al. The role of liver biopsy in chronic hepatitis C. *Hepatology.* 2001;33(1):196-200. PMID: 11124836.
113. Said Y, Bouzaidi S, Debbeche R, et al. Correlation entre la biopsie hépatique et le Fibrotest dans l'évaluation de la fibrose hépatique chez les patients atteints d'hépatite chronique C. *La Tunisie Medicale.* 2010;88(8):573-83.
114. Saitou Y, Shiraki K, Yamanaka Y, et al. Noninvasive estimation of liver fibrosis and response to interferon therapy by a serum fibrogenesis marker, YKL-40, in patients with HCV-associated liver disease. *World J Gastroenterol.* 2005;11(4):476-81. PMID: 15641129.
115. Schneider AR, Teuber G, Paul K, et al. Patient age is a strong independent predictor of 13C-aminopyrine breath test results: a comparative study with histology, duplex-Doppler and a laboratory index in patients with chronic hepatitis C virus infection. *Clin Exp Pharmacol Physiol.* 2006;33(4):300-4. PMID: 1662029.
116. Schneider AR, Teuber G, Kriener S, et al. Noninvasive assessment of liver steatosis, fibrosis and inflammation in chronic hepatitis C virus infection. *Liver Int.* 2005;25(6):1150-5. PMID: 16343065.
117. Sebastiani G, Halfon P, Castera L, et al. Comparison of three algorithms of non-invasive markers of fibrosis in chronic hepatitis C. *Aliment Pharmacol Ther.* 2012;35(1):92-104. PMID: 22035045.
118. Sebastiani G, Castera L, Halfon P, et al. The impact of liver disease aetiology and the stages of hepatic fibrosis on the performance of non-invasive fibrosis biomarkers: an international study of 2411 cases. *Aliment Pharmacol Ther.* 2011;34(10):1202-16. PMID: 21981787.
119. Sebastiani G, Halfon P, Castera L, et al. SAFE biopsy: A validated method for large-scale staging of liver fibrosis in chronic hepatitis C. *Hepatology.* 2009;49(6):1821-7. PMID: 19291784.

120. Sebastiani G, Vario A, Guido M, et al. Performance of noninvasive markers for liver fibrosis is reduced in chronic hepatitis C with normal transaminases. *J Vir Hep.* 2008;15(3):212-8. PMID: 18179453.
121. Sebastiani G, Vario A, Guido M, et al. Stepwise combination algorithms of non-invasive markers to diagnose significant fibrosis in chronic hepatitis C. *J Hepatol.* 2006;44(4):686-93. PMID: 16490278.
122. Sheth SG, Flamm SL, Gordon FD, et al. AST/ALT ratio predicts cirrhosis in patients with chronic hepatitis C virus infection. *Am J Gast.* 1998;93(1):44-8. PMID: 9448172.
123. Silva IS, Ferraz MLC, Perez RM, et al. Role of γ -glutamyl transferase activity in patients with chronic hepatitis C virus infection. *J Gastroenterol Hepatol.* 2004;19(3):314-8. PMID: 14748879.
124. Sirli R, Sporea I, Bota S, et al. A comparative study of non-invasive methods for fibrosis assessment in chronic HCV infection. *Hepat Mon.* 2010;10(2):88-94. PMID: 22312379.
125. Snyder N, Nguyen A, Gajula L, et al. The APRI may be enhanced by the use of the FIBROSpect II in the estimation of fibrosis in chronic hepatitis C. *Clinica Chimica Acta.* 2007;381(2):119-23. PMID: 17442291.
126. Snyder N, Gajula L, Xiao S-Y, et al. APRI: An easy and validated predictor of hepatic fibrosis in chronic hepatitis C. *J Clin Gastroenterol.* 2006;40(6):535-42. PMID: 16825937.
127. Stibbe KJM, Verveer C, Francke J, et al. Comparison of non-invasive assessment to diagnose liver fibrosis in chronic hepatitis B and C patients. *Scand J Gastroenterol.* 2011 Jul;46(7-8):962-72. PMID: 21623677.
128. Sud A, Hui JM, Farrell GC, et al. Improved prediction of fibrosis in chronic hepatitis C using measures of insulin resistance in a probability index. *Hepatology.* 2004;39(5):1239-47. PMID: 15122752.
129. Testa R, Testa E, Giannini E, et al. Noninvasive ratio indexes to evaluate fibrosis staging in chronic hepatitis C: role of platelet count/spleen diameter ratio index. *J Int Med.* 2006;260(2):142-50. PMID: 16882278.
130. Trocme C, Leroy V, Sturm N, et al. Longitudinal evaluation of a fibrosis index combining MMP-1 and PIIINP compared with MMP-9, TIMP-1 and hyaluronic acid in patients with chronic hepatitis C treated by interferon-alpha and ribavirin. *J Vir Hep.* 2006;13(10):643-51. PMID: 16970595.
131. Vallet-Pichard A, Mallet V, Nalpas B, et al. FIB-4: An inexpensive and accurate marker of fibrosis in HCV infection. comparison with liver biopsy and fibrotest. *Hepatology.* 2007;46(1):32-6. PMID: 17567829.
132. Verbaan H, Bondeson L, Eriksson S. Non-invasive assessment of inflammatory activity and fibrosis (grade and stage) in chronic hepatitis C infection. *Scand J Gastroenterol.* 1997;32(5):494-9. PMID: 9175214
133. Wai C-T, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology.* 2003;38(2):518-26. PMID: 12883497.
134. Walsh KM, Fletcher A, MacSween RN, et al. Basement membrane peptides as markers of liver disease in chronic hepatitis C. *J Hepatol.* 2000;32(2):325-30. PMID: 10707874.
135. Walsh (a) KM, Fletcher A, MacSween RN, et al. Comparison of assays for N-amino terminal propeptide of type III procollagen in chronic hepatitis C by using receiver operating characteristic analysis. *Eur J Gastroenterol Hepatol.* 1999;11(8):827-31. PMID: 10514112.
136. Walsh (b) KM, Timms P, Campbell S, et al. Plasma levels of matrix metalloproteinase-2 (MMP-2) and tissue inhibitors of metalloproteinases -1 and -2 (TIMP-1 and TIMP-2) as noninvasive markers of liver disease in chronic hepatitis C: comparison using ROC analysis. *Dig Dis Sci.* 1999;44(3):624-30. PMID: 10080160.
137. Williams AL, Hoofnagle JH. Ratio of serum aspartate to alanine aminotransferase in chronic hepatitis. Relationship to cirrhosis. *Gastroenterology.* 1988;95(3):734-9. PMID: 3135226.
138. Wilson LE, Torbenson M, Astemborski J, et al. Progression of liver fibrosis among injection drug users with chronic hepatitis C. *Hepatology.* 2006;43(4):788-95. PMID: 16557548.
139. Wong VS, Hughes V, Trull A, et al. Serum hyaluronic acid is a useful marker of liver fibrosis in chronic hepatitis C virus infection. *J Viral Hepat.* 1998;5(3):187-92. PMID: 9658372.

140. Yilmaz Y, Yonal O, Kurt R, et al. Noninvasive assessment of liver fibrosis with the aspartate transaminase to platelet ratio index (APRI): usefulness in patients with chronic liver disease. *Hepat Mon.* 2011;11(2):103-7. PMID: 22087126.
141. Zaman A, Rosen HR, Ingram K, et al. Assessment of FIBROSpect II to detect hepatic fibrosis in chronic hepatitis C patients. *Am J Med.* 2007;120(3):280-14. PMID: 17349453.
142. Zarski J-P, Sturm N, Guechot J, et al. Comparison of nine blood tests and transient elastography for liver fibrosis in chronic hepatitis C: the ANRS HCEP-23 study. *J Hepatol.* 2012 Jan;56(1):55-62. PMID: 21781944.
143. Berg T, Sarrazin C, Hinrichsen H, et al. Does noninvasive staging of fibrosis challenge liver biopsy as a gold standard in chronic hepatitis C? *Hepatology.* 2004;39(5):1456-7. PMID: 15122779.
144. Calès P, De Ledinghen V, Halfon P, et al. Evaluating the accuracy and increasing the reliable diagnosis rate of blood tests for liver fibrosis in chronic hepatitis C. *Liver Int.* 2008;28(10):1352-62. PMID: 18492022.
145. Cobbold JF, Crossey MM, Colman P, et al. Optimal combinations of ultrasound-based and serum markers of disease severity in patients with chronic hepatitis C. *J Viral Hepat.* 2009;17(8):537-. PMID: 19804501.
146. Myers R, Tainturier M, Ratzu V, et al. Prediction of liver histological lesions with biochemical markers in patients with chronic hepatitis B. *J Hepatol.* 2003;39:222 - 30. PMID: 12873819.
147. Parkes J, Guha IN, Roderick P, et al. Enhanced Liver Fibrosis (ELF) test accurately identifies liver fibrosis in patients with chronic hepatitis C. *Journal of Viral Hepatitis.* 2011;18(1):23-31. PMID: 20196799.
148. Sène D, Limal N, Messous D, et al. Biological markers of liver fibrosis and activity as non-invasive alternatives to liver biopsy in patients with chronic hepatitis C and associated mixed cryoglobulinemia vasculitis. *Clinical Biochemistry.* 2006;39(7):715-21. PMID: 16765932.
149. Varaut A, Fontaine H, Serpaggi J, et al. Diagnostic accuracy of the Fibrotest in hemodialysis and renal transplant patients with chronic hepatitis C virus. *Transplantation.* 2005;80(11):1550-5. PMID: 16371924.
150. Groom H, Dieperink E, Nelson DB, et al. Outcomes of a hepatitis C screening program at a large urban VA medical center. *J Clin Gastroenterol.* 2008 Jan;42(1):97-106. PMID: 18097298.
151. Lindenburg CEA, Lambers FAE, Urbanus AT, et al. Hepatitis C testing and treatment among active drug users in Amsterdam: Results from the DUTCH-C project. *Eur J Gastroenterol Hepatol.* 2011;23(1):23-31. PMID: 21042221.
152. Mallette C, Flynn MA, Promrat K. Outcome of screening for hepatitis C virus infection based on risk factors. *Am J Gast.* 2008 Jan;103(1):131-7. PMID: 17894850.
153. Groessl EJ, Weingart KR, Gifford AL, et al. Development of the Hepatitis C Self-Management Program. *Patient Education and Counseling.* 2011;83(2):252-5. PMID: 20638216.
154. Latka MH, Hagan H, Kapadia F, et al. A randomized intervention trial to reduce the lending of used injection equipment among injection drug users infected with hepatitis C. *Am J Public Health.* 2008;98:853-61. PMID: 18382005.
155. Zule WA, Costenbader EC, Coomes CM, et al. Effects of a Hepatitis C virus educational intervention or a motivational intervention on alcohol use, injection drug use, and sexual risk behaviors among injection drug users. *Am J Public Health.* 2009;99(Suppl.):S180-S6. PMID: 19218179.
156. Ceci O, Margiotta M, Mareello F, et al. High rate of spontaneous viral clearance in a cohort of vertically infected hepatitis C virus infants: What lies behind? *J Hepatol.* 2001;35(5):687-8. PMID: 11690723.
157. Conte D, Fraquelli M, Prati D, et al. Prevalence and clinical course of chronic hepatitis C virus (HCV) infection and rate of HCV vertical transmission in a cohort of 15,250 pregnant women. 3 ed. UNITED STATES: Cattedra di Gastroenterologia, IRCCS Ospedale Maggiore, Milan, Italy. Dario.Conte@unimi.it; 2000. p. 751-5.
158. European Paediatric Hepatitis C Virus Network. Effects of mode of delivery and infant feeding on the risk of mother-to-child transmission of hepatitis C virus. *European Paediatric Hepatitis C Virus Network. BJOG.* 2001;108(4):371-7. PMID: 11305543.
159. European Paediatric Hepatitis CVN. Three broad modalities in the natural history of vertically acquired hepatitis C virus infection. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2005;41:45-51. PMID: 15937762.

160. Garland SM, Tabrizi S, Robinson P, et al. Hepatitis C--role of perinatal transmission. 4 ed. AUSTRALIA: Microbiology Department, The Royal Women's Hospital, Melbourne, Victoria, Australia.; 1998. p. 424-7.
161. Gibb DM, Goodall RL, Dunn DT, et al. Mother-to-child transmission of hepatitis C virus: evidence for preventable peripartum transmission. *Lancet*. 2000;356(9233):904-7. PMID: 11036896.
162. La Torre A, Biadaioli R, Capobianco T, et al. Vertical transmission of HCV. *Acta Obstetricia et Gynecologica Scandinavica*. 1998;77(9):889-92. PMID: 9808375.
163. Lin HH, Kao JH, Hsu HY, et al. Absence of infection in breast-fed infants born to hepatitis C virus-infected mothers. *J Pediatr*. 1995;126(4):589-91. PMID: 7535353.
164. Mast EE, Hwang LY, Seto DSY, et al. Risk factors for perinatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy. *J Infect Dis*. 2005;192(11):1880-9. PMID: 16267758.
165. McMenamin MB, Jackson AD, Lambert J, et al. Obstetric management of hepatitis C-positive mothers: analysis of vertical transmission in 559 mother-infant pairs. *Am J Obstet Gynecol*. 2008;199(3):315.e1-5. PMID: 18771997.
166. Moriya T, Sasaki F, Mizui M, et al. Transmission of hepatitis C virus from mothers to infants: its frequency and risk factors revisited. *Biomed Pharmacother*. 1995;49(2):59-64.
167. Okamoto M, Nagata I, Murakami J, et al. Shift in the buoyant density of hepatitis C virus particles in infants infected by mother-to-infant transmission. *Pediatr Int*. 1999;41(4):369-73. PMID: 10453185.
168. Pipan C, Amici S, Astori G, et al. Vertical transmission of hepatitis C virus in low-risk pregnant women. *Eur J Clin Microbiol Infect Dis*. 1996 Feb;15(2):116-20. PMID: 8801082.
169. Resti M, Azzari C, Mannelli F, et al. Mother to child transmission of hepatitis C virus: Prospective study of risk factors and timing of infection in children born to women seronegative for HIV-1. *BMJ*. 1998;317(7156):437-40. PMID: 9703524.
170. Spencer JD, Latt N, Beeby PJ, et al. Transmission of hepatitis C virus to infants of human immunodeficiency virus-negative intravenous drug-using mothers: rate of infection and assessment of risk factors for transmission. *J Vir Hep*. 1997;4(6):395-409. PMID: 9430360.
171. Syriopoulou V, Nikolopoulou G, Daikos GL, et al. Mother to child transmission of hepatitis C virus: Rate of infection and risk factors. *Scand J Infect Dis*. 2005;37(5):350-3. PMID: 16051571.
172. Tajiri H, Miyoshi Y, Funada S, et al. Prospective study of mother-to-infant transmission of hepatitis C virus. *Pediatr Infect Dis J*. 2001 Jan;20(1):10-4. PMID: 11176560.
173. Tanzi M, Bellelli E, Benaglia G, et al. The prevalence of HCV infection in a cohort of pregnant women, the related risk factors and the possibility of vertical transmission. *Eur J Epidemiol*. 1997;13(5):517-21. PMID: 9258562.
174. Zanetti AR, Tanzi E, Romano L, et al. A prospective study on mother-to-infant transmission of hepatitis C virus. *Intervirology*. 1998;41(4-5):208-12. PMID: 10213898.
175. Zanetti AR, Tanzi E, Newell ML. Mother-to-infant transmission of hepatitis C virus. *J Hepatol, Supplement*. 1999;31(1):96-100. PMID: 10622569.
176. Tovo P-A, Lazier L, Versace A. Hepatitis B virus and hepatitis C virus infections in children. *Curr Opin Infect Dis*. 2005;18(3):261-6. PMID: 15864105.
177. European Paediatric Hepatitis C Virus Network. A significant sex--but not elective cesarean section--effect on mother-to-child transmission of hepatitis C virus infection. *J Infect Dis*. 2005;192(11):1872-9. PMID: 16267757.