Hepatitis C

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Best Practices
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Disclosures

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No disclosures
HCV Outline

- Prevalence
- Transmission
- Prevention
- Screening
- Treatment
- Extrahepatic Manifestations
- HCC screening
- Perinatal Transmission
- Adolescents
- Coffee, Herbs and Supplements
- Alcohol
- Cannabis
Learning Objectives

- Describe the prevalence and transmission of HCV
- Describe the extrahepatic manifestations of HCV
- Describe the process of HCC screening
- Describe the risks and benefits of herbs, supplements, coffee and cannabis
Based on NHANES data, Hepatitis C is the most common blood borne infection. 

NHANES from 2003-2010 estimates a prevalence of 2.7 million persons with chronic Hepatitis C. However this data excludes homeless, military, incarcerated, nursing home and immigrants. 

Because of the populations excluded, others estimate prevalence at 3.5-5.2 million


Worldwide Prevalence of HCV

Anti-HCV Prevalence (Reported + Extrapolated)

Worldwide distribution of HCV Genotypes
Chronic Hepatitis C – Age Distribution of Newly Reported Cases, California, 2007 and 2015

2007*

2015†

*N = 41,037; excludes 547 cases with missing age or sex information.
†N = 33,454; excludes 294 cases with missing age or sex information.
"BY THE WAY, I HAVE HEPATITIS C"
Transmission of HCV

Routes of Transmission

- Injecting drug use: 60%
- Sexual: 15%
- Transfusion: 10% (before screening)
- Occupational: 4%
- Other: 1% (*)
- Unknown: 10%

* Nosocomial; iatrogenic; perinatal

Source: Centers for Disease Control and Prevention
Hepatitis C is transmitted from blood to blood contact.

It is **not** transmitted from casual household contacts, hugging, kissing, sharing drinks, consuming alcohol.

HCV is primarily transmitted by:
- Sharing equipment used for injection drug use

Other risks include:
- Blood transfusion prior to 1992
- Clotting factors or organ transplants prior to 1987
- Hemodialysis (in settings with poor infection control)
- Tattoos in unregulated settings (especially prisons)
- Needle stick injury
- Perinatal transmission 5%; 15-20% if HIV/HCV coinfected
- Higher risk of sexual transmission among people living with HIV (especially men who have sex with men)
HCV infection from a contaminated syringe is 5-20-fold higher than it is for HIV.

HCV has been detected in all manner of drug using equipment: cookers, cotton, water, filters, even alcohol wipes.

Source: Thibault V, JID 2011
Ideally, a person has a new syringe and all other injecting equipment (cooker, cotton, water, etc.) for each use.

- Bleach does kill HCV 99% of the time, so it is better than not cleaning if no other options.
- Rubbing alcohol (70% isopropanol) also kills HCV, but you have to rinse and repeat the process 3 times:
  - e.g. draw up the alcohol, rinse it and do that at least 2 more times.

Source: Binka, OFID 2015
To Prevent HCV Transmission
 Avoid sharing used toothbrushes, razors, etc.
 Prevent blood contact to non-intact skin/mucous membrane/etc.
 Encourage harm reduction and treatment service access for people who inject drugs, including MAT (i.e. buprenorphine/methadone) for people with opioid use disorders
 “Safe sex” (i.e. condoms + lubricant) recommended generally, but sexual transmission is rare if HIV negative

Other Messages
 Avoid/limit alcohol consumption
 Test for HIV, test & vaccinate for HAV/HBV
 Encourage screening of family members, as applicable
 Potential household exposure, kids born after HCV infection, all “baby boomers”
 Stage of fibrosis important to determine long term prognosis, treatment options, monitoring
 Great treatment options available to cure HCV

1998: CDC recommends risk-based testing
2012: CDC expands recommendations to include one-time screening for “Baby Boomers” born between 1945 and 1965
Some are already screening all persons over the age of 13

Source: CDC and Prevention. MMWR. 2012. RR61:1-32
AASLD/IDSA Risk Based Screening Recommendations

Risk Exposures
- Long Term hemodialysis (ever)
- Getting a tattoo in an unregulated setting
- Healthcare/occupational exposure to HCV-infected blood
- Children born to HCV-infected women
- Prior recipients of transfusion or organ transplant
  - Notified that they received blood from HCV+ donor
  - Blood product or organ transplant prior to July 1992
  - Clotting factor concentrate produced before 1987
- Persons who were ever incarcerated

Risk Behaviors
- Injection Drug Use (current or ever)
- Intranasal illicit drug use

Other
- HIV infection
- Unexplained chronic liver disease including elevated ALT
- Solid organ donors (deceased and living)

Source: AASLD/IDSA Recommendations for Testing, Managing and Treating Hepatitis C (www.hcvguidelines.org)
**HCV Screening Tests**

**Hepatitis C Antibody (Ab)**
- If positive, tells you that the patient has been exposed to hepatitis C
- Requires follow-up blood draw for confirmatory RNA test
- Antibody is not protective, does not offer any immunity to Hepatitis C

**Hepatitis C RNA (by PCR quantitative)**
- If positive, tells you whether the patient is currently infected or not
- ~15-25% of individuals clear HCV infection naturally

**Hepatitis C Ab with Reflex to RNA**
- Best screening test as it gives you the antibody screening and, if positive, automatically runs the RNA test confirming active infection (without additional blood draw)

**Q: What about rapid tests?**
- Can be used for quick turn around in 20 minutes for antibody only
- If positive, requires confirmatory blood draw for RNA test
# FDA-Approved

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Source: [www.hepatitisc.uw.edu](http://www.hepatitisc.uw.edu); Accessed January 2, 2018
Progression of Liver Disease

- Normal Liver
- Chronic Hepatitis
- Cirrhosis
- HCC/ESLD

- HCV Infection: 75-85%
- Cirrhosis: 20-30%
- HCC/ESLD: 2-7% per year
Benefits of Treating HCV

SVR and All-Cause Mortality Benefits in Cirrhotics Treated With IFN-Based Therapy

- All-cause Mortality
- Liver-related Mortality or Liver Transplantation
- Hepatocellular Carcinoma
- Liver Failure

### Table 1. Extrahepatic manifestations of chronic HCV infection.

<table>
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<th>Reported conditions</th>
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<td>Cardiovascular and circulatory</td>
<td>MC vasculitis</td>
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<td></td>
<td>Coronary artery disease</td>
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<td>Carotid atherosclerosis</td>
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<td></td>
<td>Ischemic heart disease with coronary vasculitis, mitral valvular damage, pericarditis, and congestive heart failure</td>
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<td>Endocrine</td>
<td>Insulin resistance</td>
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<td>T2D</td>
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<td>Type I diabetes mellitus</td>
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<td>Immune</td>
<td>MC</td>
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<td></td>
<td>B-cell lymphoproliferative diseases</td>
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<td>Autoantibodies</td>
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<td>Monoclonal gammopathies</td>
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<tr>
<td>Integumentary and exocrine</td>
<td>Purpura (main dermatological condition related to MC vasculitis)</td>
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<tr>
<td></td>
<td>Raynaud’s syndrome, acrocyanosis, livedo reticularis (less frequent)</td>
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<td>PCT</td>
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<td>Lichen planus</td>
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<td>Pruritus, psoriasis, polyarteritis nodosa, necrolytic acral erythema, HCV-related sicca syndrome</td>
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<tr>
<td>Musculoskeletal</td>
<td>Fatigue, arthralgia (main joint condition related to MC vasculitis)</td>
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<td>HCV polyarthritis /mono-oligoarthritis (less frequent)</td>
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<tr>
<td>Nervous</td>
<td>Cognitive impairment</td>
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<td>Fatigue</td>
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<td>Depression</td>
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<td>Sensory or sensory-motor polyneuropathy</td>
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<td>Renal</td>
<td>MC glomerulonephritis (MPG type I)</td>
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<td>Membranoproliferative glomerulonephritis without MC</td>
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<td>Membranous nephropathy</td>
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<td>Glomerulonephritis, focal segmental glomerulosclerosis, IgA nephropathy, fibrillar or immunotactoid glomerulopathy</td>
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<td>Renal insufficiency</td>
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<tr>
<td>Respiratory</td>
<td>Subclinical alveolitis</td>
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<td></td>
<td>Pulmonary intra-alveolar hemorrhages</td>
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MC: mixed-cryoglobulinemia; MPG: membranoproliferative glomerulonephritis; T2D: type II diabetes mellitus; PCT: porphyria cutanea tarda; HCV: hepatitis C virus.
Leads to development of immunologic, autoimmune, and viral phenomena throughout the body

It is estimated that 40% to 74% of patients with chronic HCV will develop at least one extrahepatic manifestation throughout the course of their illness, leading to ↑ treatment cost and overall economic burden

I'm afraid my brain has left for the day.
Can lead to cognitive impairment (“brain fog”)
- Memory impairment, fluctuating disorientation, mental fatigue

Increases risk of cerebrovascular events, including stroke

TOP WAYS HEPATITIS C IMPACTS EDUCATION OR ABILITY TO WORK

- I am tired (fatigued) at work or school: 92%
- My brain feels foggy, it is difficult to concentrate and complete my work: 68%
- Physical symptoms affect my ability to work or study: 57%
- I am moody, irritable and short-tempered at work or school: 53%
HCV interferes at several steps in the signaling pathway via an increased proteasomal degradation of insulin receptors and other protein synthesis pathways (2,3).

There is evidence for both hepatic and peripheral insulin resistance, and this is in spite of the fact that HCV only directly infects the liver. (4,5)

Insulin resistance occurring in patients with HCV recognizes dual pathogenesis, both direct and/or indirect action of the virus and host factors. (4,5)

Insulin resistance is an independent risk factor for accelerated fibrogenesis and for the development of hepatocellular carcinoma (1).

DM, HTN, hyperlipidemia
- Obesity associated with accelerated fibrosis progression
- Aggressively manage metabolic syndrome risk factors
- Check lipid panel and HbA1c annually

Weight loss of 7-10% of total body weight improves both steatosis and inflammation
- Restrict caloric intake:
  - 1200 – 1500 kcal/day for women
  - 1500 to 1800 kcal/day for men
- Encourage aerobic exercise to decrease intrahepatic TG and increase hepatic insulin sensitivity
- Increase baseline steps per day to goal of 10-12,000 per day
- Exercise 2.5 hours aerobic plus resistance training per week for NAFLD

Pharmacotherapy (if indicated)
- Statins are OK in liver disease, monitor for increase in ALT
- Treat diabetes appropriately
- Vitamin E increases risk of cardiovascular events in persons with DM and NAFLD

Treat and cure HCV

Lower risk of Diabetes After SVR
Wide range of complications: includes frank auto-immune and rheumatic diseases (i.e. arthralgia, myalgia, arthritis, sicca syndrome, vasculitis)

- Mixed cryoglobulinemia vasculitis (CryoVas): systemic vasculitis → clinical manifestations ranging from purpura, arthralgia and fatigue to more serious lesions with neurologic and renal involvement

Circulating mixed cryoglobulins detected in 40–60% of patients with chronic HCV; overt CryoVas observed in only 5–10%.
~17-37% of people living with chronic HCV have HCV-related heart disease
Most common manifestations: cardiomyopathies, myocarditis, cardiovascular disease (stroke, atherosclerosis, coronary artery disease), peripheral artery disease

Primary (direct) pulmonary outcomes include: COPD, idiopathic pulmonary fibrosis, asthma, interstitial lung diseases

Can also indirectly affect lungs and pulmonary vasculature via mixed cryoglobulinemia, hepatopulmonary syndrome, portopulmonary hypertension

HCV and the Cardiovascular System

HCV: Increased cardiovascular mortality

Post SVR: Improved cardiovascular outcomes

Fig. 1. Spectrum of the current understanding of cardiovascular manifestations of HCV infection before (top panel) and after (bottom panel) sustained virological response (SVR). (Courtesy of Servier Medical Art, Suresnes, France [www.servier.fr].)
Renal involvement can be one of HCV’s most severe extrahepatic manifestations.

Broad spectrum of histopathologic lesions.

Clinical presentation ranges: completely asymptomatic (mild urinary abnormalities) → end-stage renal failure.

Need eGFR > 30 mL/min/1.73 mm² for some HCV treatment medication.
**Acetaminophen**
- NSAID w/minor effects on Cox-1 and Cox-2, produces analgesia by ↓ pain thresholds through inhibition of nitric oxide pathway
- Harmless at low doses, hepatotoxic >7.5g
- Therapeutic doses can → transient ↑LFT
- Injury due to direct toxic effect of high usually >15 gram dose.
- Hepatic injury starts in 24 to 72 hours with marked ↑ ALT and AST >2000 U/L, followed at 48 to 96 hours by: jaundice, confusion, hepatic failure and in some death. Possible renal insufficiency. LFT ↓ promptly, recovery is rapid if the injury is not too severe.

Acetaminophen is preferred over NSAID in liver disease, up to 2g a day.

**Ibuprofen**
- Potent inhibitor Cox-1 and Cox-2
- Can → asymptomatic flares of chronic HCV
- ↑ ALT occur full doses of 2,400 to 3,200 mg daily up to 16%
- Overdose >5-10 grams starts in 3 to 6 hours with agitation and stupor followed by coma, respiratory depression and lactic acidosis which can be fatal.
- Inhibits renal prostaglandins which → renal vasoconstriction and ↓ response to diuretics
- Can precipitate ARF
- ↑ Risk of GI bleed

**Avoid in all patients with cirrhosis**
- Livertox.nlm.nih.gov
Screen anyone with stage 3-4 fibrosis

Ultrasound with or without alpha-fetoprotein (AFP) every 6 months.

The added value of AFP to ultrasound in surveillance has been questioned. AFP no longer included in 2011 IDSA/AASLD guidelines.

Consider cross sectional imaging (MRI or CT if liver is dense and poorly penetrated by ultrasound)

IDSA/AASLD Guidelines

- In pts with chronic HCV, insufficient evidence to suggest surveillance before developing cirrhosis

HALT-C cohort: HCV positive patients with at least advanced fibrosis, median f/u nearly 7 years

- Of 427 pts w/cirrhosis: 11.2% developed HCC (Metavir F4/4, Ishak 6/6)
- Of 621 pts w/advanced fibrosis w/out cirrhosis, 6.4% developed HCC (Ishak 3-5/6)

- Tayob N, CGH 2015, epub ahead of print
- Bruix J & Sherman M - AASLD guidelines;
  - Hepatology 2005;42:1208-1236
Alpha-Fetoprotein (AFP)

- AFP as a screening test:
  - 40% with HCC have normal AFP
  - Up to 25% without HCC have abnormal AFP

- The higher the AFP, the more likely the diagnosis of HCC

- DCP (PIVKA-II) and AFP-L3 not better than AFP and don’t clearly add additional information

- Trevisani F, J Hepatol 2001;34:570; Marrero JA et al. Gastroenterology 2009;137:110-118
Perinatal HCV transmission

- Exact transmission timing during pregnancy unknown
- Occurs almost exclusively in women with HCV viremia

Major risk factors for perinatal transmission:
  - Maternal HIV co-infection
  - Detectable HCV viremia during pregnancy

Mother-to-child transmission has **NOT** been associated with mode of delivery or breastfeeding*

*Note: mothers with HCV should not breastfeed if damaged, cracked, or bleeding nipples
Infections acquired in infancy:
- 20-45% spontaneous clearance before age 2
- 6-12% after age 2

Markers of likely chronic infection
- + HCV RNA after 1-2 years of age; monitoring/assessing for perinatal HCV transmission is an area of active discussion
- Usually asymptomatic
- Usually with normal AST/ALT and liver function

Bridging fibrosis/cirrhosis: 4-6%

 Decompensated cirrhosis: 2%

Risk factors for progression in pediatric patients not well-defined

FDA-Approved Treatment Regimens for HCV in Adolescents

- **Ledipasvir 90mg/sofosbuvir 400mg (Harvoni®)**
  - Genotype 1, 4, 5, 6
  - ≥12 years of age, ≥35 kg
  - Non-cirrhotic, or compensated cirrhosis
  - Treatment-naïve or experienced

- **Sofosbuvir 400mg (Sovaldi®) + Ribavirin**
  - Genotype 2 or 3

https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm551407.htm
Coffee
- HALT-C trial: 766 patients with bridging fibrosis/cirrhosis with food intake diary
- Coffee consumption (>3 cups/day) was associated with lower risk of disease progression

Herbs and Supplements
- No established role in liver disease.
- St. John’s Wort known to interact with HCV medications

Counseling Messages:
- Coffee seems to be hepato-protective
- Beware of potential hepatotoxicity of herbs & supplements
- Advise patients to stop all herbs & supplements during HCV treatment

Livertox.nlm.nih.gov

- Freedman, N. D., Everhart, J. E., Lindsay, K. L., et al.
Animal model data suggest hepatoprotection during varying liver insults
- SyNCH trial (2012): double-blind, placebo-controlled
- No change in serum ALT or HCV RNA during 24 weeks of silymarin
- HALT-C study (2008)
- No difference in anti-HCV efficacy or ALT, but somewhat better quality of life

**Counseling Message:**
Insufficient evidence to support milk thistle use, but appears to be safe.
Milk thistle should be stopped during HCV treatment

Safe level for those with underlying liver disease is unknown

Harmful drinking levels; strongly counsel against
- ≥ 2 drinks per day for women
- ≥ 4 drinks per day for men

Abstinence is recommended for all patients with significant fibrosis (F2 or higher)

Reduce to non-harmful levels in all

Daily cannabis use associated with progression of advanced liver disease and an independent risk factor for moderate to severe fibrosis

- Associated with a sevenfold higher odds of moderate to severe fibrosis compared to non-daily users
- Recommend non-daily use in those with advanced fibrosis who use

Not a requirement to stop using marijuana or alcohol before treating for HCV

U.S. prevalence of HCV: ~3.5-5.2 million
Transmission mainly via IDU
Many extra-hepatic manifestations can improve with cure
Interferon-free treatment for adolescents
HCC screening every 6 months if F3-4
The good, the bad and the borderline:
  • Good: Coffee, Acetaminophen
  • Bad: Herbs, Ibuprofen, Alcohol
  • Borderline: Cannabis
LOVE IS LIKE A VIRUS
IT CAN HAPPEN TO ANYBODY AT ANY TIME

Maya Angelou
Resources

- www.hcvguidelines.org
- www.hepatitisc.uw.edu
- Hep-druginteractions.org
- www.hcvdruginfo.ca/tables.html
- HCVECHO@ucsf.edu
- Livertox.nlh.nih.gov
- nccc.ucsf.edu: UCSF Clinical Consultation Center for HIV/HCV/substance use
## Comparison of various fibrosis assessment tools

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<th>Methodology</th>
<th>APRI or FIB-4</th>
<th>FibroSure™ FibroTest™</th>
<th>Transient elastography</th>
<th>Liver biopsy</th>
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<td><strong>Methodology</strong></td>
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<td>Direct observation of fibrosis</td>
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<tr>
<td><strong>Accuracy for detecting cirrhosis</strong></td>
<td>Moderate</td>
<td>High</td>
<td>High</td>
<td>High</td>
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<tr>
<td><strong>Accuracy for detecting intermediate fibrosis</strong></td>
<td>Low</td>
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<td>Moderate to high</td>
<td>High</td>
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<td><strong>Complication risk</strong></td>
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<td>Minimal</td>
<td>Minimal</td>
<td>Risk of pain/bleeding</td>
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<td><strong>Disadvantages</strong></td>
<td>Minimal (see limitations below)</td>
<td>Minimal (see limitations below)</td>
<td>Decreased accuracy if obesity and/or narrow rib spaces</td>
<td>Invasive; contraindicated if coagulopathy</td>
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<td><strong>Limitations</strong></td>
<td>Falsely elevated if acute hepatitis (of any etiology). Not good for detecting intermediate fibrosis.</td>
<td>Falsely elevated if hemolysis, inflammation, Gilbert’s, atazanavir use. Not good for detecting intermediate fibrosis</td>
<td>False-positives with inflammation, congestion</td>
<td>Sampling error; observer variation; not suitable for longitudinal monitoring</td>
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<td><strong>Cost</strong></td>
<td>Low per-test cost</td>
<td>Moderate</td>
<td>High initial equipment cost</td>
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<tr>
<td><strong>APRI</strong></td>
<td>&gt; 1.0: up to 76% sens and 72% spec for predicting cirrhosis. &gt; 1-1.5: assoc. with advanced fibrosis (METAVIR F3) &gt; 2.0: assoc. with cirrhosis (METAVIR F4): 46% sens, 91% spec</td>
<td>Good utility for predicting severe fibrosis/cirrhosis or low risk of significant fibrosis Doesn’t differentiate well between intermediate and either mild or severe fibrosis</td>
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<tr>
<td><strong>FIB-4</strong></td>
<td>&lt; 1.45: 74% sens and 80% spec in excluding significant fibrosis &gt; 3.25: 98% spec in confirming cirrhosis</td>
<td>Good at excluding or confirming cirrhosis If between 1.45 and 3.25, need another method to assess/predict fibrosis</td>
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<tr>
<td><strong>FibroSure</strong></td>
<td>Estimates grade and stage in report &lt; 0.31: 91% NPV for absence of clinically significant fibrosis &gt; 0.48: 61% PPV for presence of significant fibrosis (76% if use cutoff of 0.72)</td>
<td>Good at excluding or confirming cirrhosis; indeterminate for mid-range Cost; not widely available Not accurate if certain conditions (i.e. Gilbert’s, acute hemolysis, renal insufficiency, post-transplant)</td>
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</tbody>
</table>
Still gold standard, but obvious drawbacks! Provides objective, semi-quantitative info regarding amount and pattern of collagen or scar tissue

Report gives **grade** *(degree of inflammation reflecting ongoing liver disease injury)* and **stage** *(amount of currently established fibrosis)*

- Metavir (F0-F4) and Ishak (0-6) fibrosis scores commonly used to describe the amount of hepatic collagen.

**When to consider?** If 2 non-invasive markers discordant; when concurrent liver disease suspected (i.e. indirect markers or imaging shows more significant fibrosis than expected); can be considered when indirect, direct, and TE testing unavailable; also-- to help confirm if HCC surveillance indicated
### Table 13. Diagnosis of Compensated Cirrhosis for the Purpose of Identifying Treatment Candidates

<table>
<thead>
<tr>
<th>Method</th>
<th>Comment</th>
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<tbody>
<tr>
<td><strong>Clinical Findings</strong></td>
<td>• Physical exam findings (palpable left lobe, splenomegaly, palmar erythema) <strong>AND</strong></td>
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<tr>
<td></td>
<td>• Low platelet count (&lt;100,000/mm³) <strong>AND</strong></td>
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<td></td>
<td>• Abdominal imaging findings (see below)</td>
</tr>
<tr>
<td><strong>Abdominal Imaging</strong></td>
<td>• Surface abnormalities (e.g., nodularity, and left lobe/caudate lobe hypertrophy) are suggestive of cirrhosis.</td>
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<tr>
<td></td>
<td>• Features of portal hypertension (e.g., splenomegaly, recanalization of umbilical vein, collaterals) and ascites also are suggestive of cirrhosis.</td>
</tr>
<tr>
<td><strong>Liver Fibrosis Imaging</strong></td>
<td>• Both elastography and ARFI are FDA-approved, ultrasound-based techniques for estimating the extent of liver fibrosis.</td>
</tr>
<tr>
<td></td>
<td>• Fibroscan value of &gt;12.5 kilopascals has been associated with histologic cirrhosis.</td>
</tr>
<tr>
<td></td>
<td>• ARFI value of &gt;1.75 meters/second has been associated with histologic cirrhosis.</td>
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</table>