Management of Hepatitis C in Primary Care

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Objective

Epidemiology

Screening criteria

Appropriate work up

Treatment Guidelines

HCC screening

Follow up post treatment

Background

Hepatitis C virus infection is the most common blood borne infection in the US

70-85% will become chronically infected with HCV after initial infection

CDC estimates 2.4million persons are living with HCV infection in the US

- Compared to 2.2million persons living with HBV infection in the US
- Compared to 1.24million person 13yrs and older living with HIV in the US

- In 2016, a total of 2,967 cases of acute hepatitis C were reported to CDC from 42 states

Background

Gentoype 1: 75%

- 1a: 55%; 1b: 35%

Genotype 2 & 3: 15-20%

Genotype 3, 4, 5: 5%

RISK FACTORS

Ivdu

Transfusions prior 1992

Solid organ transplant

Hemophilia

MSM

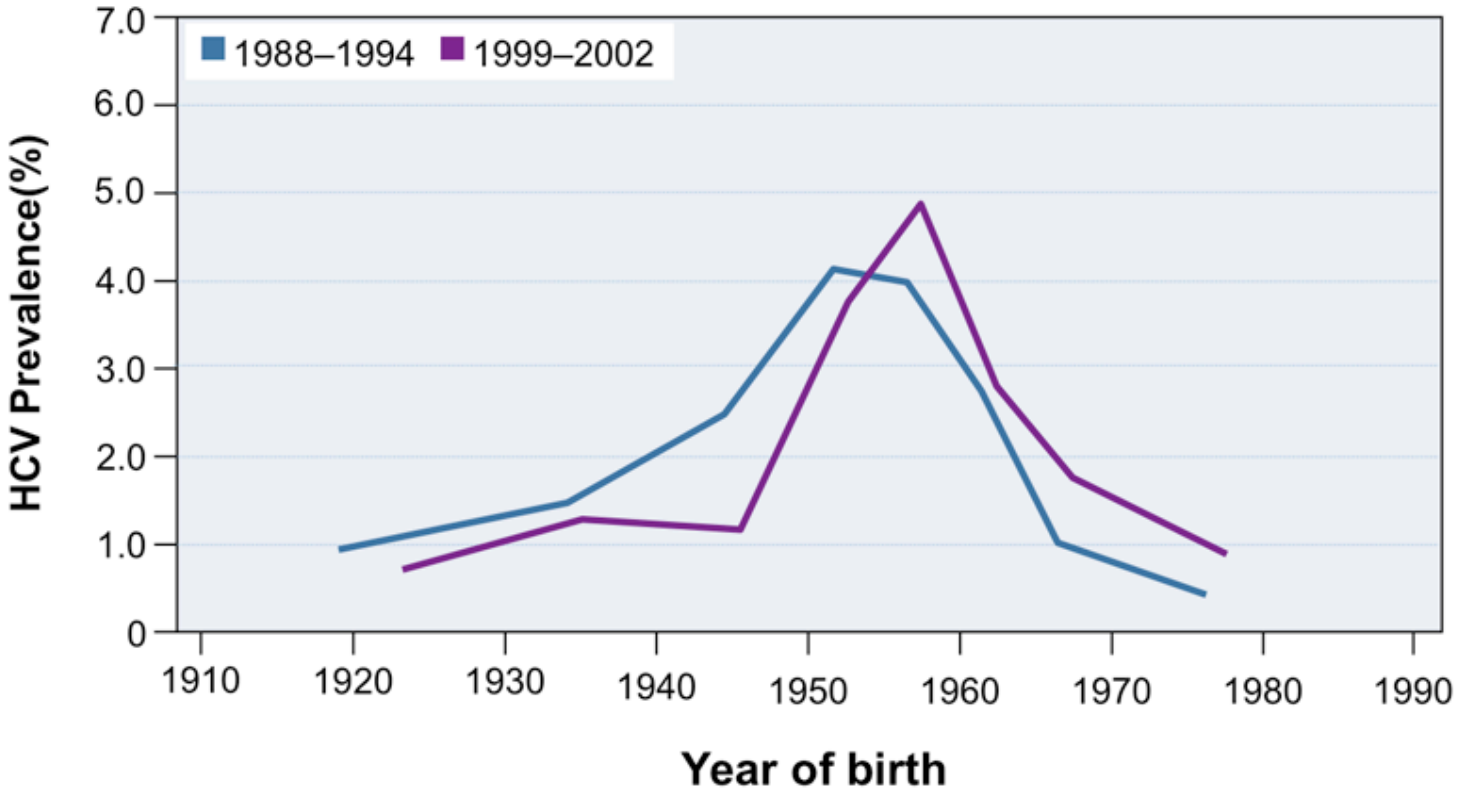
Body tattoos

Intranasal cocaine use

Hemodialysis: Prevalence increases to 8% (5x the general population)

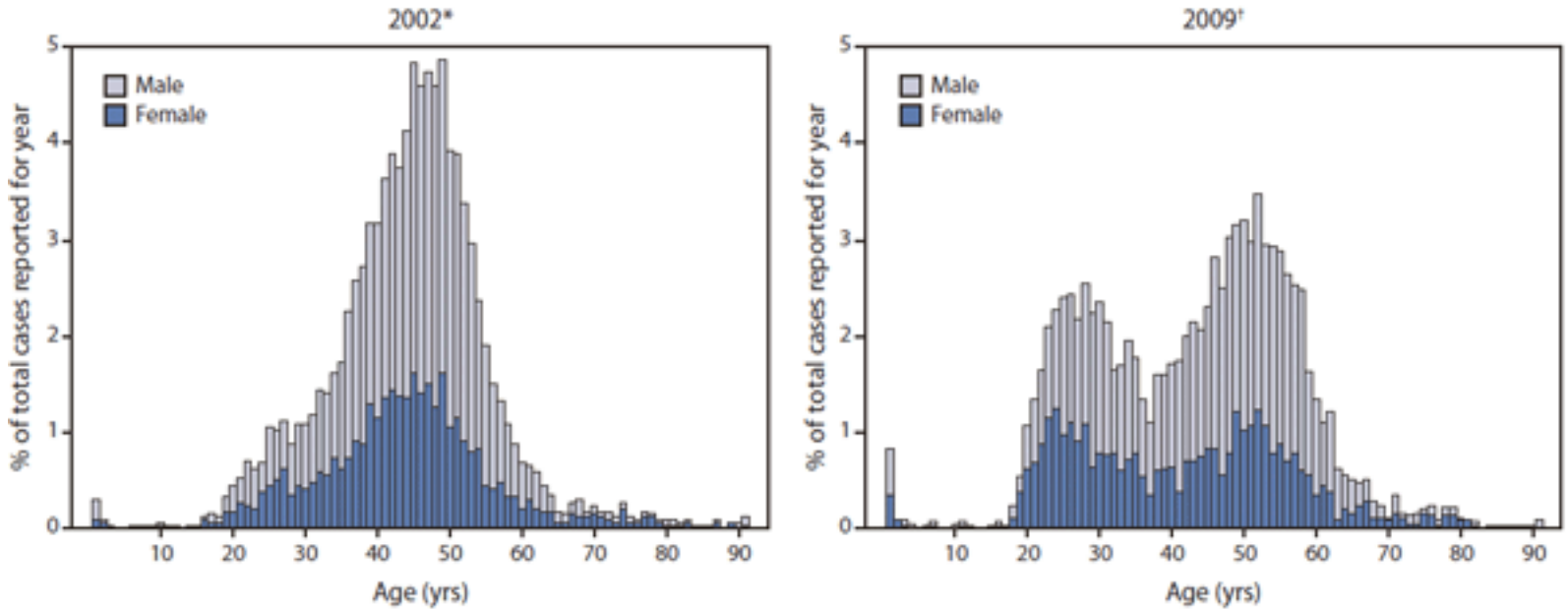
PERINATAL- about 5%

Background



HCV prevalence is highest among persons born during 1945 to 1965

Background


2002*
2009†
Male
Female
% of total cases reported for year
Age (yrs)
0
1
2
3
4
5
10
20
30
40
50
60
70
80
90

Morbidity/Mortality

ALL cause mortality 2x> than in HCV negative patients

Attributes to about 15,000 deaths per year

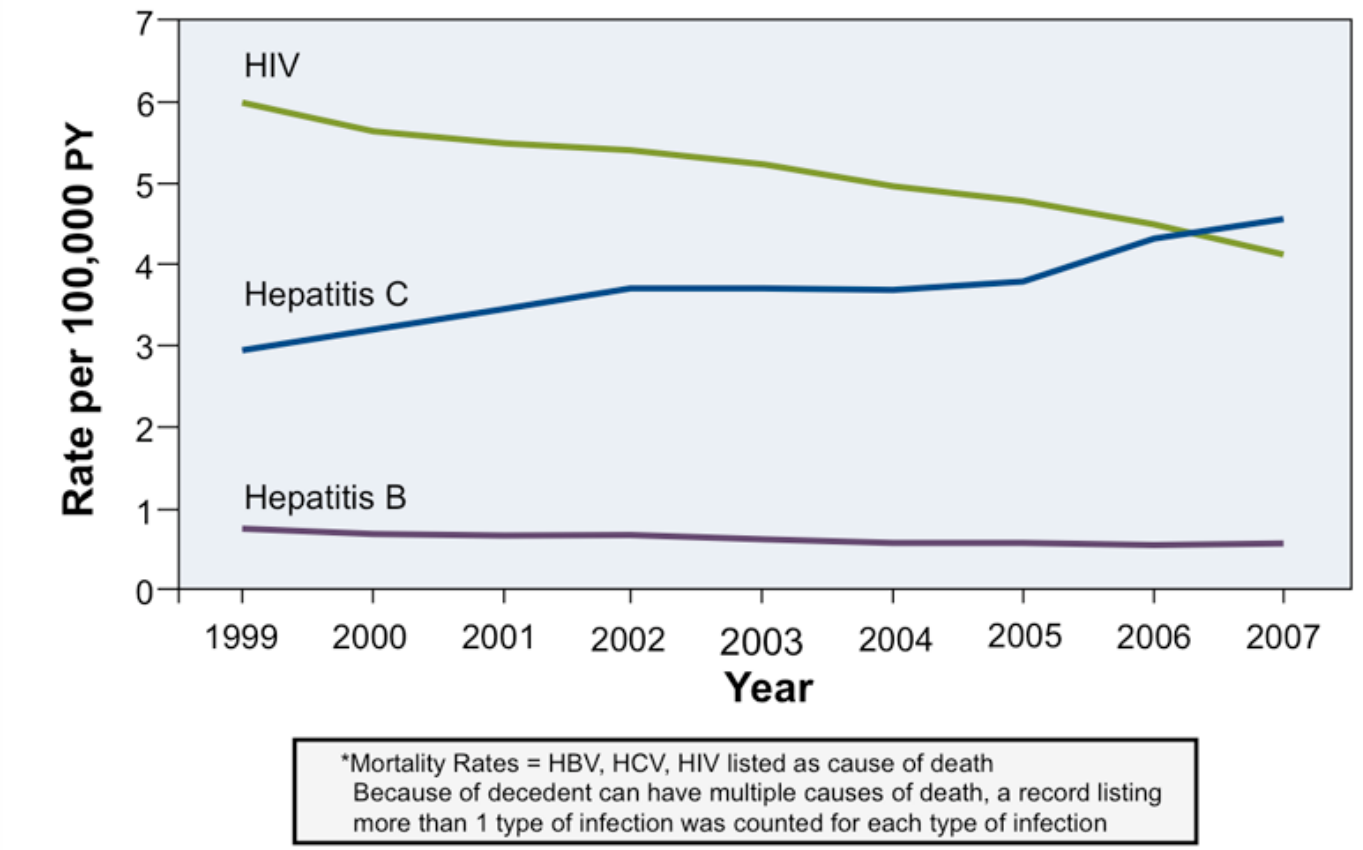
Mortality rate 12x than general population

8x> than HBV related deaths

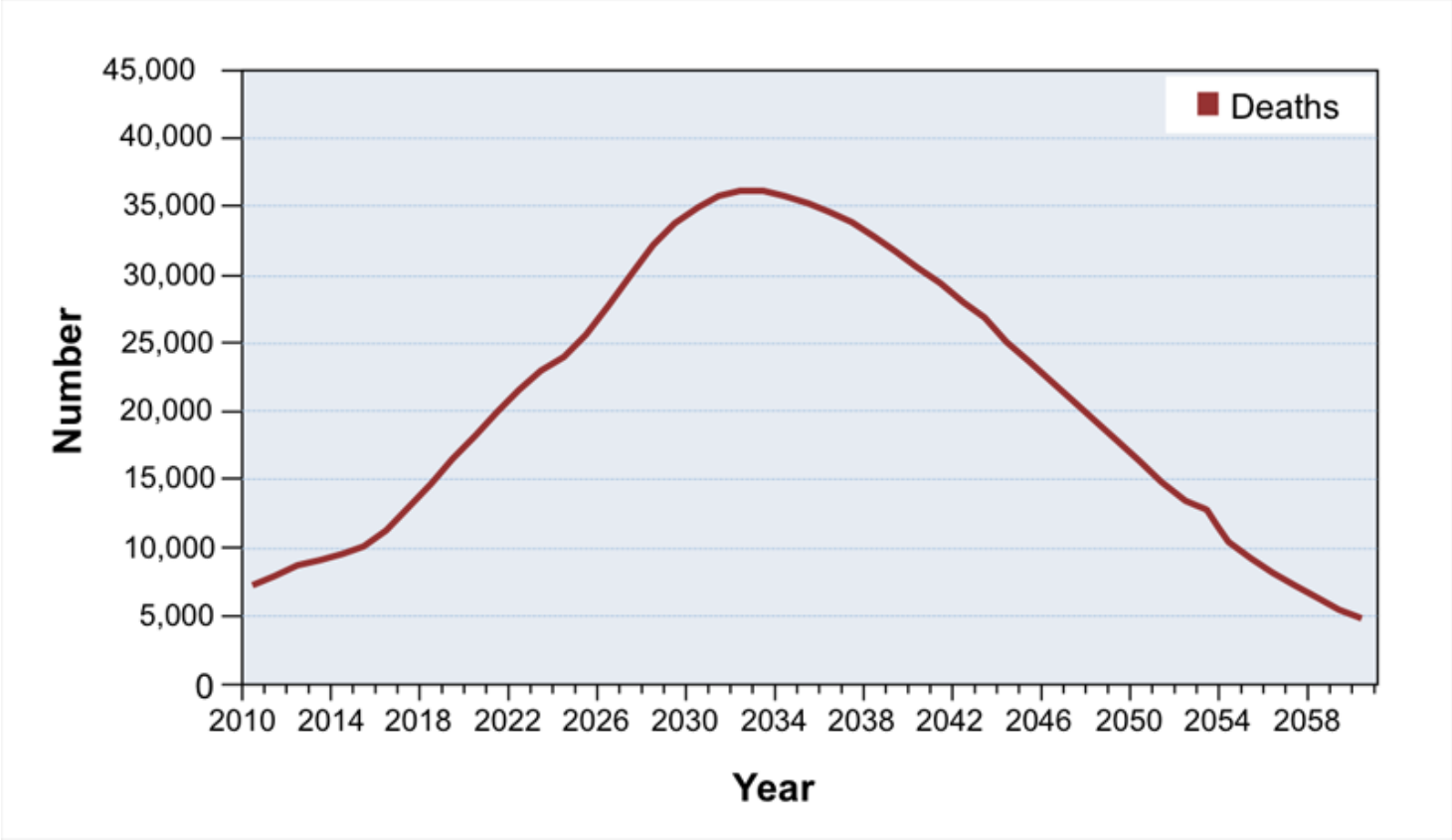
20% if not treated will develop cirrhosis after 20yrs of infection

1/3 of all persons on liver transplant list have HCV associated liver disease

Morbidity/Mortality



Morbidity/Mortality



Natural History

Factors associated with viral clearance

- Younger age
- Female gender
- Nonblack race
- Symptomatic acute infection
- Normal immune status

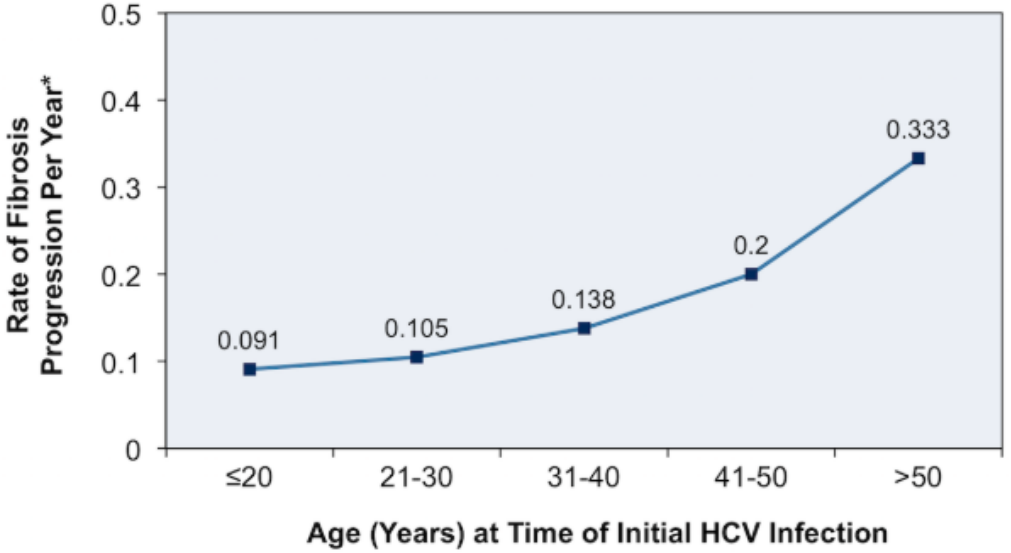
Natural History

Factors impacting rate of progression of fibrosis

- Older age: Acquisition after 40 associated with more rapid fibrosis progression
- Gender: MALE
- Coinfection with HIV:
- Coinfection with HBV
- Metabolic Factors: obesity, insulin resistance, steatosis
- Alcohol use
- Marijuana use

No impact

- HCV RNA VL or Genotype unlike HIV

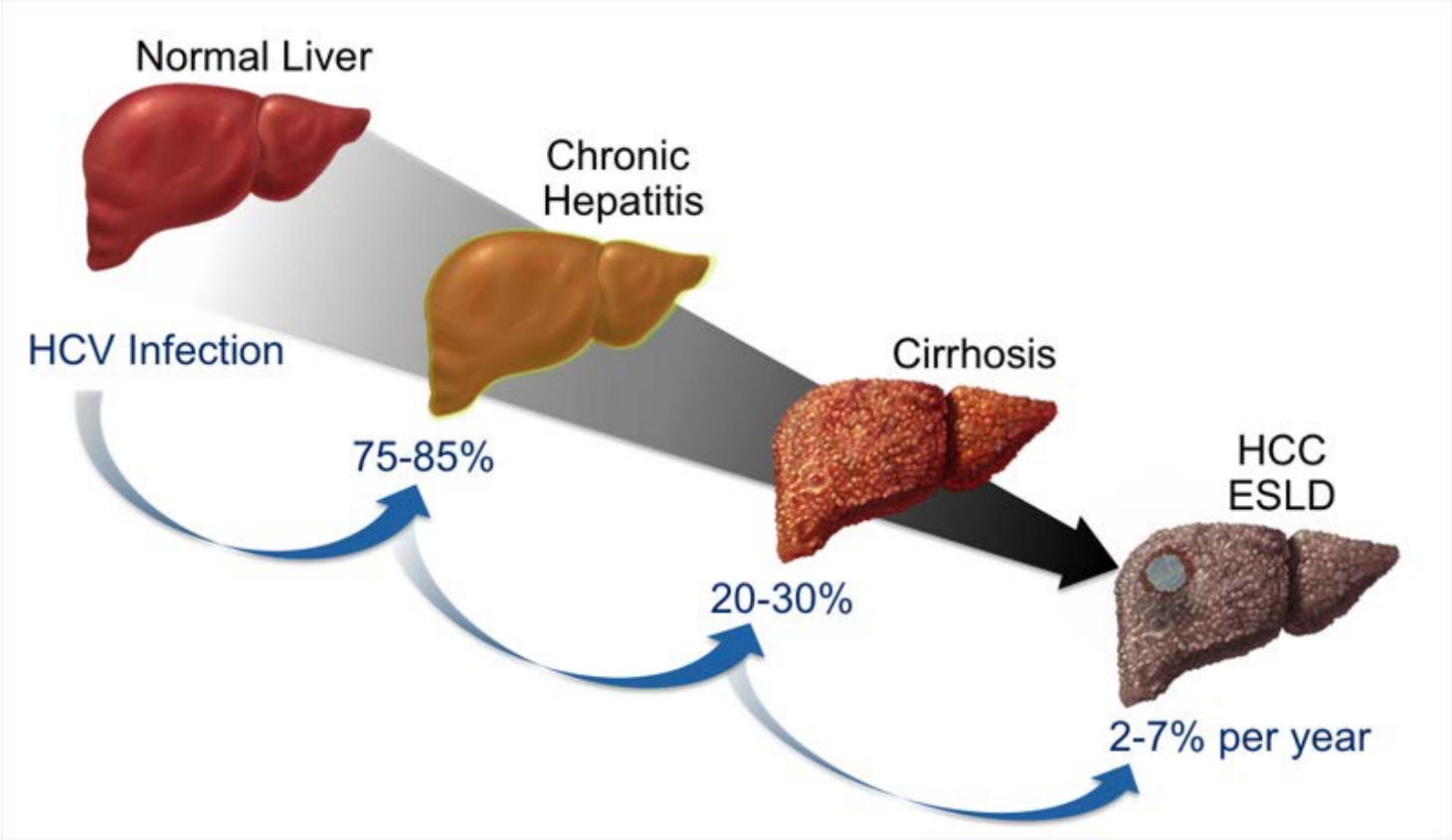


*Fibrosis progression per year = ratio between fibrosis stage in Metavir units and the duration of infection

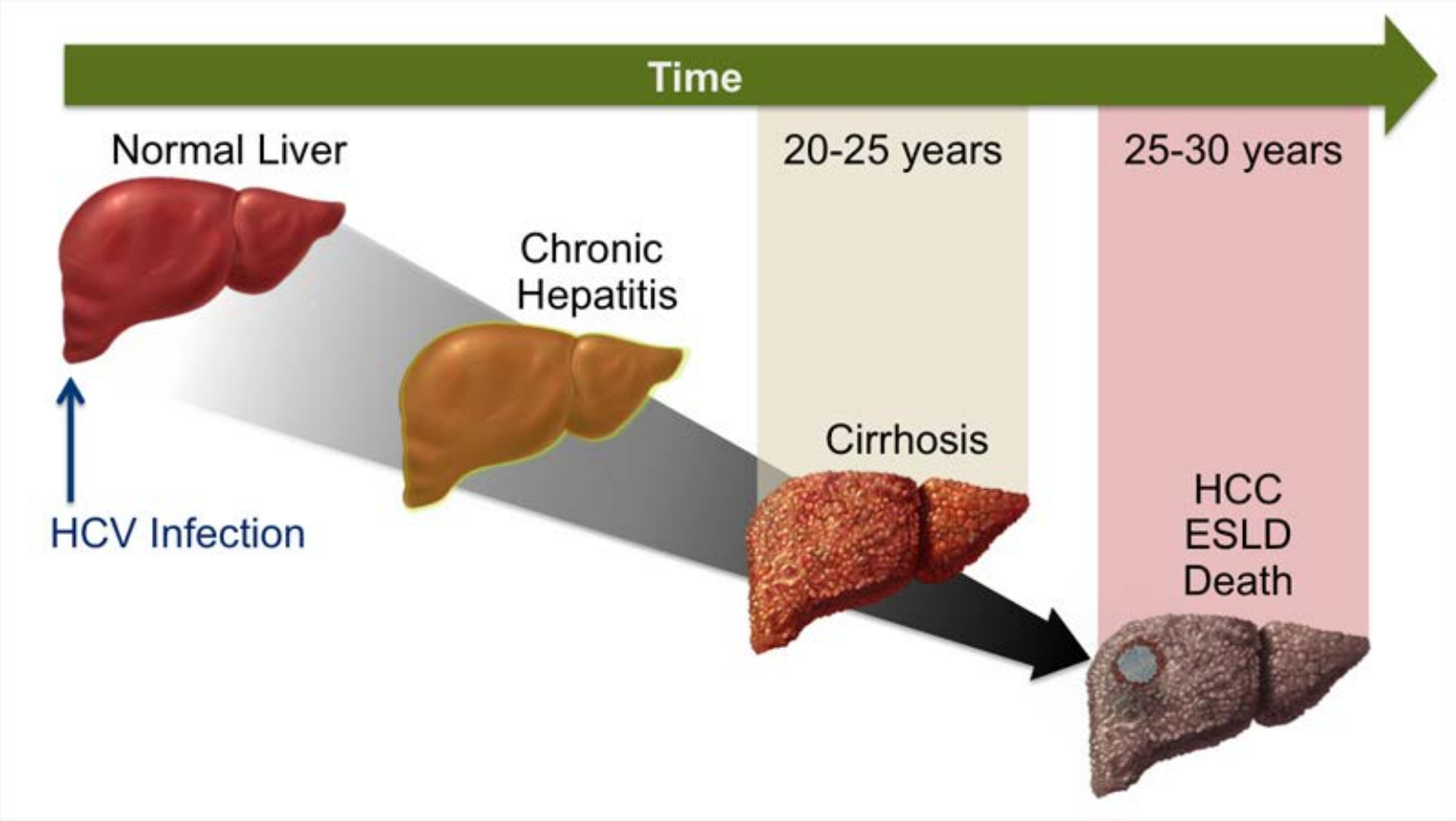
igure 4 - Impact of Age at the Time of Initial HCV Infection and Rate of Fibrosis
his graphic clearly shows higher rates of progression of hepatic fibrosis in patients who were older at the time f initial HCV infection.

ource: Poynard T, Bedossa P, Opolon P. Lancet. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The BSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet. 1997;349:825-32.

Background


Normal Liver
Chronic Hepatitis
HCV Infection
Cirrhosis
75-85%
HCC ESLD
20-30%
2-7% per year

Natural History

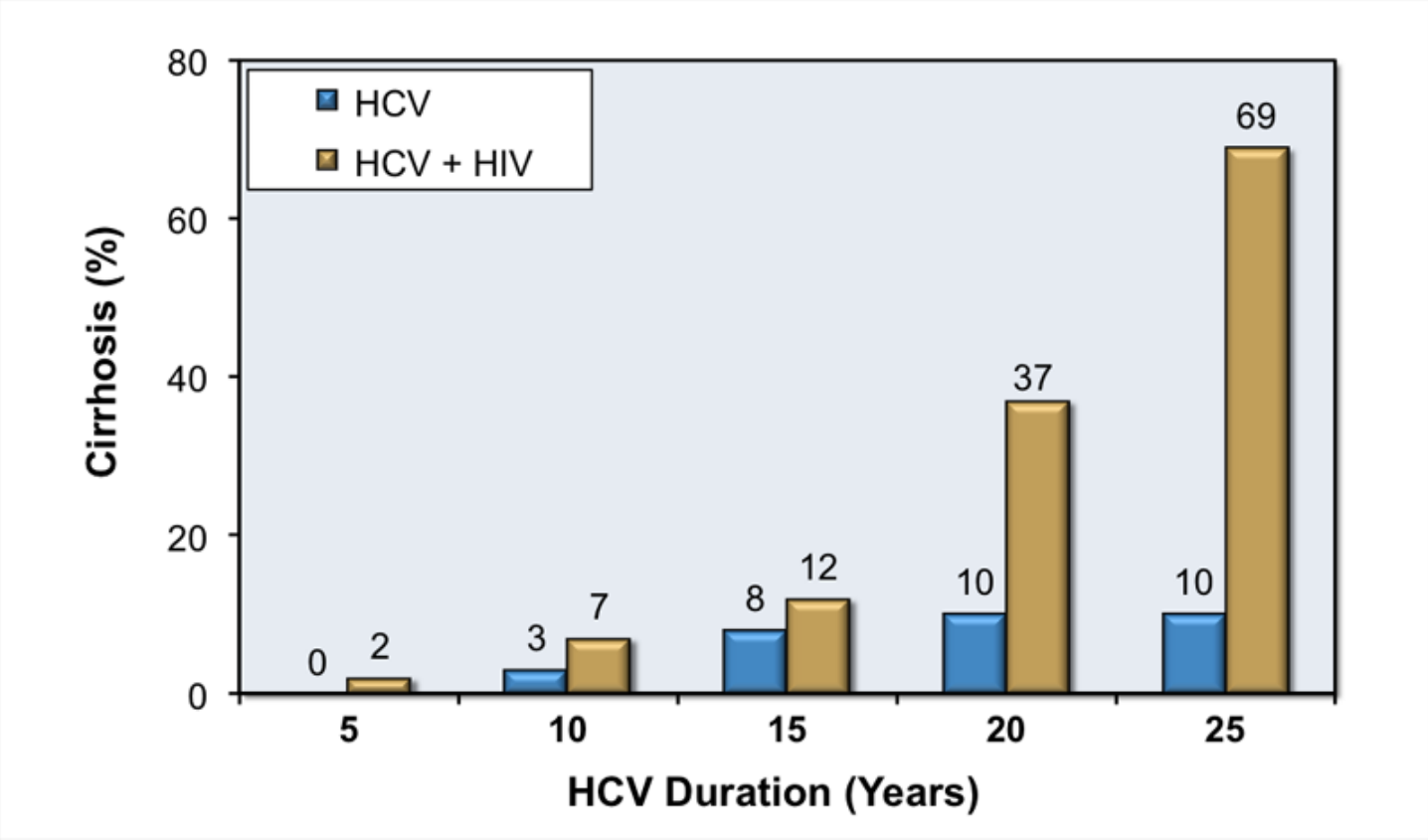


Natural History

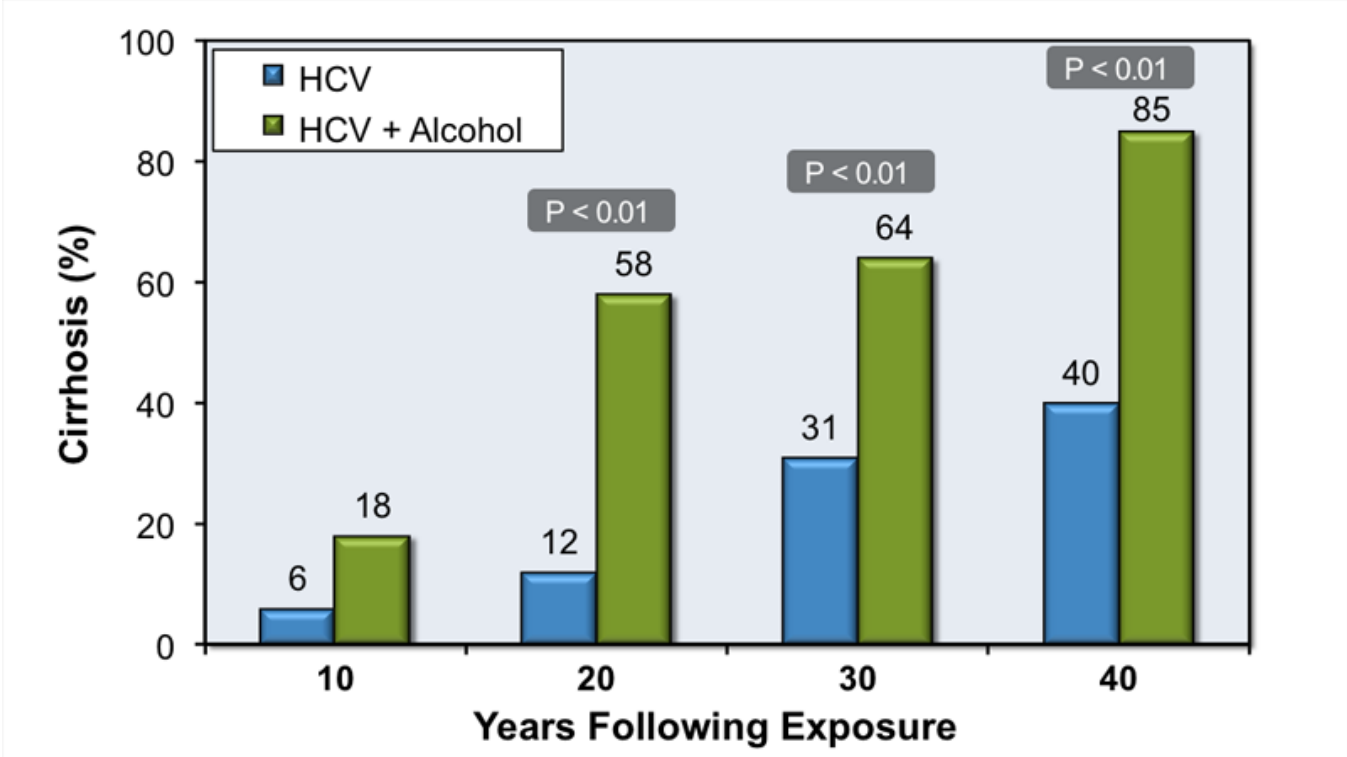
The Path to Fibrosis

- Dynamic scarring process with chronic inflammation
- Accumulation of collagen and ECMP
- Remodeling and regression of fibrous tissue via breakdown of matrix proteins

Natural History

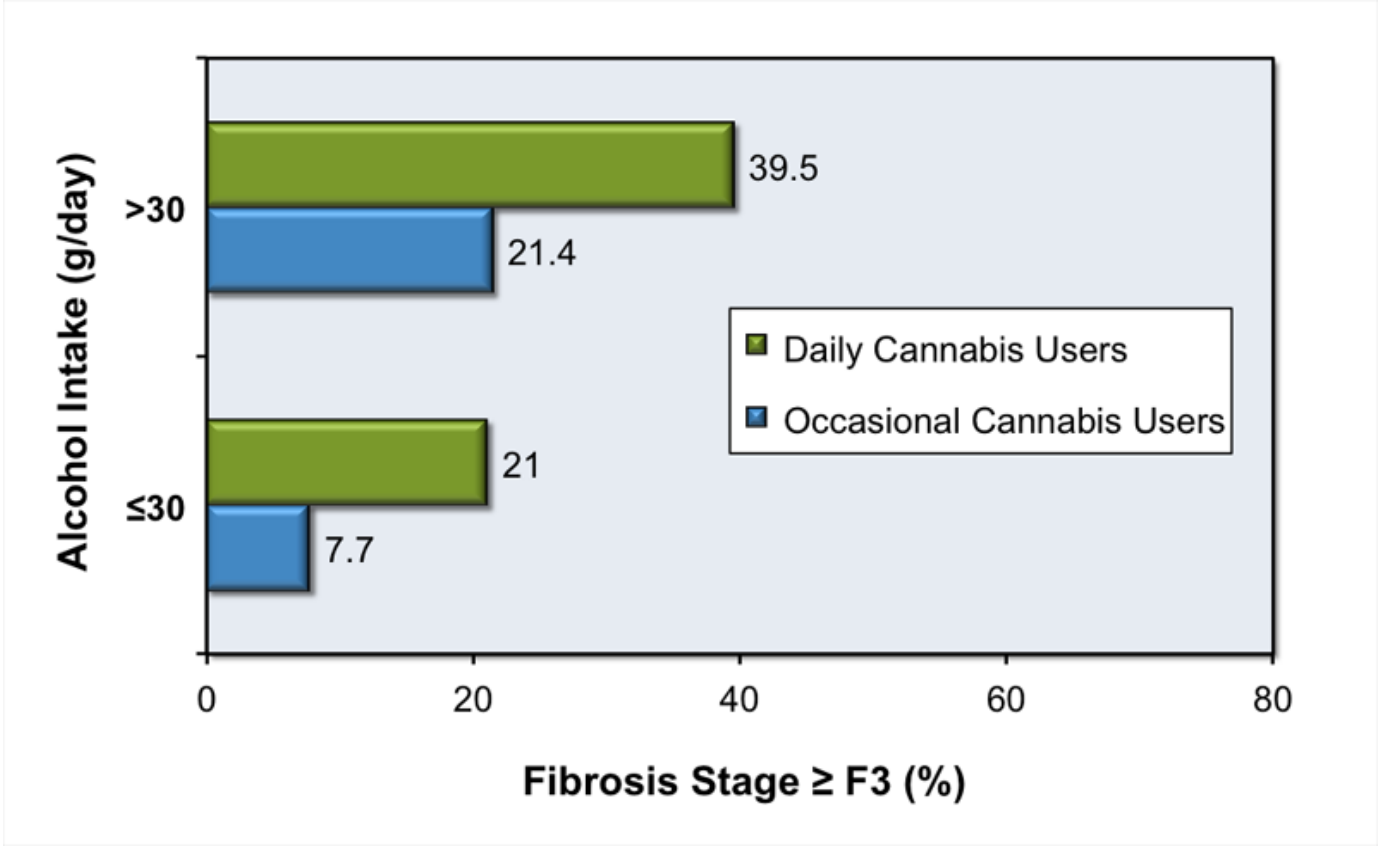


Natural History



*Excessive alcohol defined as > 40 g/day for women and > 60 g/day for men

Natural History



SCREENING

CDC, USPSTF, AASLD/IDSA

Routine Screening

- Active or Prior IDU
- People who have intimate contact with persons with HCV
- Medical Conditions
  - Received clotting factors prior 1987
  - Chronic hemodialysis
  - Persons with persistently abnormal ALT
  - HIV+

Prior recipient of transfusion or organ transplant

- Received transfusion of blood/blood products before 7/1992
- Received organ transplant before 7/1992
- Pts who received blood from a donor who was later tested Hep C Ab+

SCREENING

Screen based on exposure

- Healthcare, emergency medical, public safety worker after needle stick, sharps, or mucosal exposure to HCV+ blood
- Children born to HCV+ women
- Hx of incarceration
- Intranasal drug use

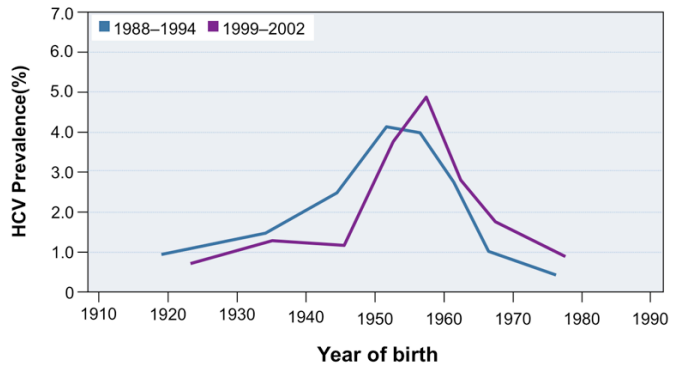
SCREENING-BABY BOOM

2012: CDC recommends screening for those born between 1945-1965

2013-USPSTF recommended 1 time screening for baby boomers

About 75% of persons living with HCV are in this cohort

Baby boomers make up about 23% of population, they account for 70% of Hep C related deaths



Diagnosis

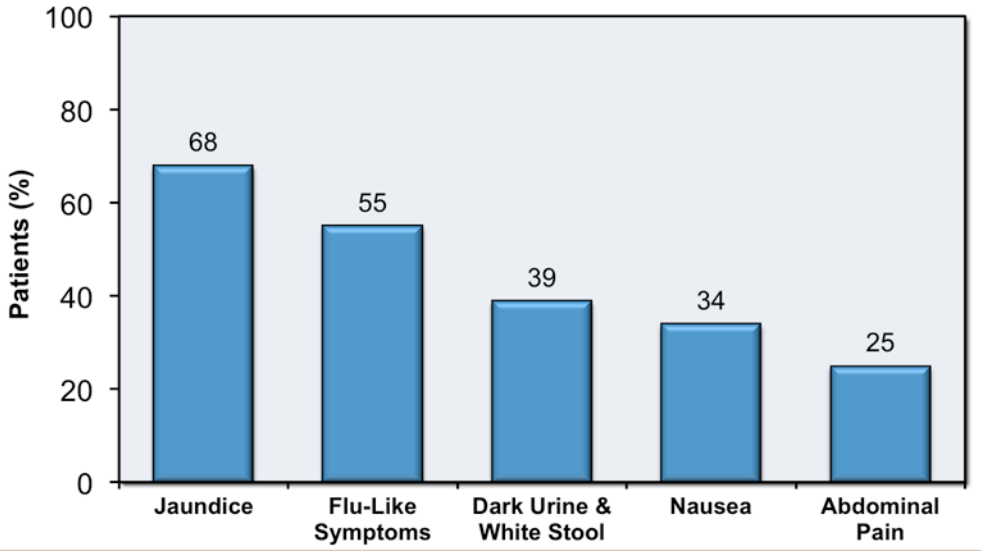
ACUTE HEP C- within 6 months of initial acquisition

- Clinical Criteria: an illness with discreet onset of any signs or symptom consistent with acute viral hepatitis (fever, headache, anorexia, n/v/d/abd pain)

  AND

- Jaundice OR peak ALT>200 IU/L during the period of acute illness

- Laboratory Criteria
  - Hep C Ab+: develops after 8-12wks of infection
  - Hep C RNA Detected
    - NAT(Quantitative, qualitative, or genotype testing
- Documented negative HCV Ab within 12 months

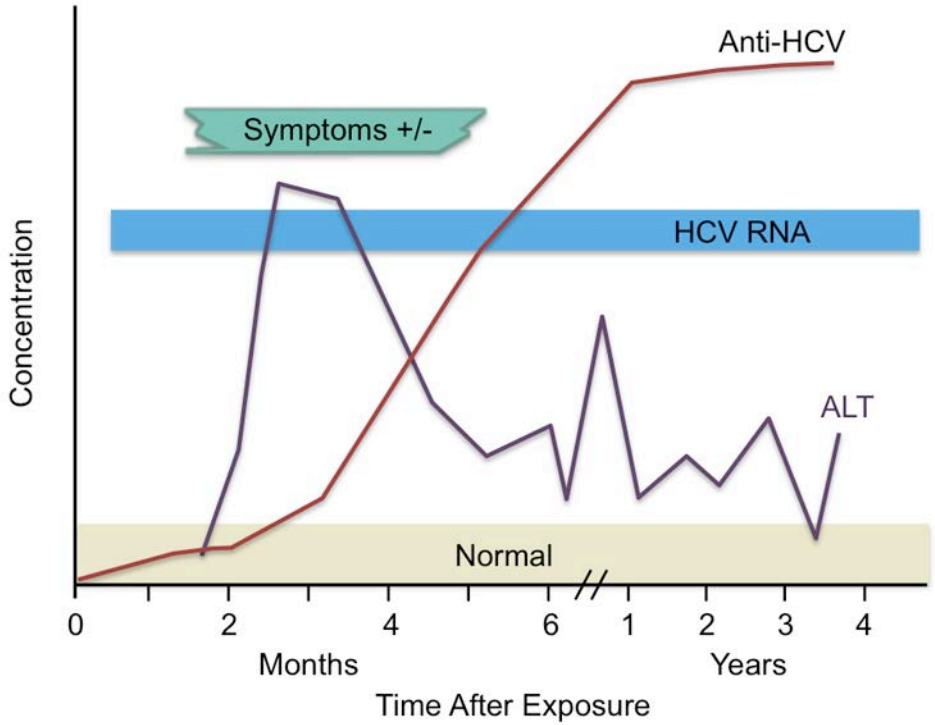


Diagnosis

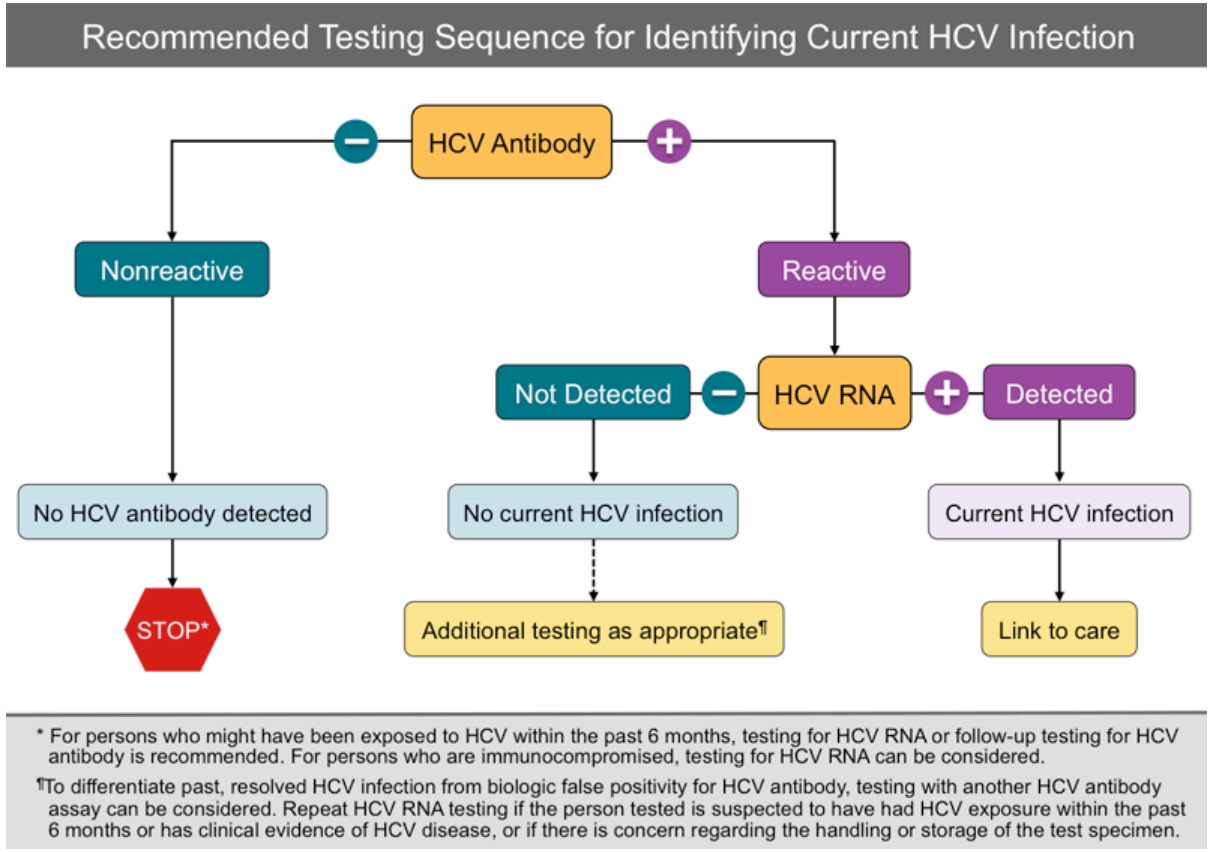
Chronic Hep C

- Clinical criteria: none; possible evidence of chronic liver disease

- Laboratory criteria
  - Hep C Ab+ > 6 months
  - Hep C RNA detected



Diagnosis


Recommended Testing Sequence for Identifying Current HCV Infection
HCV Antibody
Nonreactive
Reactive
Not Detected
HCV RNA
Detected
No HCV antibody detected
No current HCV infection
Current HCV infection
STOP*
Additional testing as appropriate¶
Link to care
* For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.
¶To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

Diagnosis

New Diagnosis of Hepatitis C Infection: Post-Test Counseling Messages

Persons infected with HCV can benefit from the following messages

- **Contact a health-care provider (either a primary-care clinician or specialist [e.g., in hepatology, gastroenterology, or infectious disease]), for**
  - medical evaluation of the presence or development of chronic liver disease;
  - advice on possible treatment options and strategies; and
  - advice on how to monitor liver health, even if treatment is not recommended.
- **Protect the liver from further harm by,**
  - considering hepatitis A and B vaccination if susceptible and if liver disease is present;
  - reducing or discontinuing alcohol consumption;
  - avoiding new medicines, including over-the-counter and herbal agents, without first checking with their health-care provider; and
  - obtaining HIV risk assessment and testing.
- **For persons who are overweight (BMI ≥25kg/m^2) or obese (BMI ≥30kg/m^2),**
  - consider weight management or losing weight and
  - follow a healthy diet and stay physically active.
- **To minimize the risk for transmission to others,**
  - do not donate blood, tissue, or semen and
  - do not share appliances that might come into contact with blood, such as toothbrushes, dental appliances, razors, and nail clippers.

Staging Fibrosis

Liver Biopsy: gold standard

- May incorrectly stage fibrosis in 20% of people; invasive
- Use if conflicting non-invasive results (FibroSure/Fibrotest/APRI)
- When suspecting concurrent liver disease (AIH, hemochromatosis)
- When non-invasive test aren’t available (Fibroscan)
- Determine whether to continue surveillance on HCC

FIBROSIS Staging

Aspartate Aminotransferase-to-Platelet ratio index (APRI):

FIB-4:

FibroIndex:

Forns Index

HepaScore:

FibroSure, FibroTest-ActiTest:

FIBROSIS Staging

$$\text{APRI} = \frac{\dfrac{\text{AST Level}}{\text{AST (Upper Limit of Normal)}}}{\text{Platelet Count } (10^9/\text{L})} \times 100$$

FIBROSIS Staging

$$\textbf{FIB-4} = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet Count } (10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}$$

FIBROSIS Staging

Comparative Scoring Systems for Histologic Stage (Fibrosis)			
Score	**IASL**	**Batts-Ludwig**	**Metavir**
0	No Fibrosis	No Fibrosis	No Fibrosis
1	Mild fibrosis	Fibrous portal expansion	Periportal fibrotic expansion
2	Moderate fibrosis	Rare bridges or septae	Periportal septae (> 1 septum)
3	Severe fibrosis	Numerous bridges or septae	Portal-central septae
4	Cirrhosis	Cirrhosis	Cirrhosis

FIBROSIS Staging

FibroSure

Contraindications for use of the FibroSure method for fibrosis staging include Gilbert's disease, acute hemolysis, extrahepatic cholestasis, post transplantation, or renal insufficiency, all of which may lead to inaccurate quantitative predictions

Radiologic Evaluation

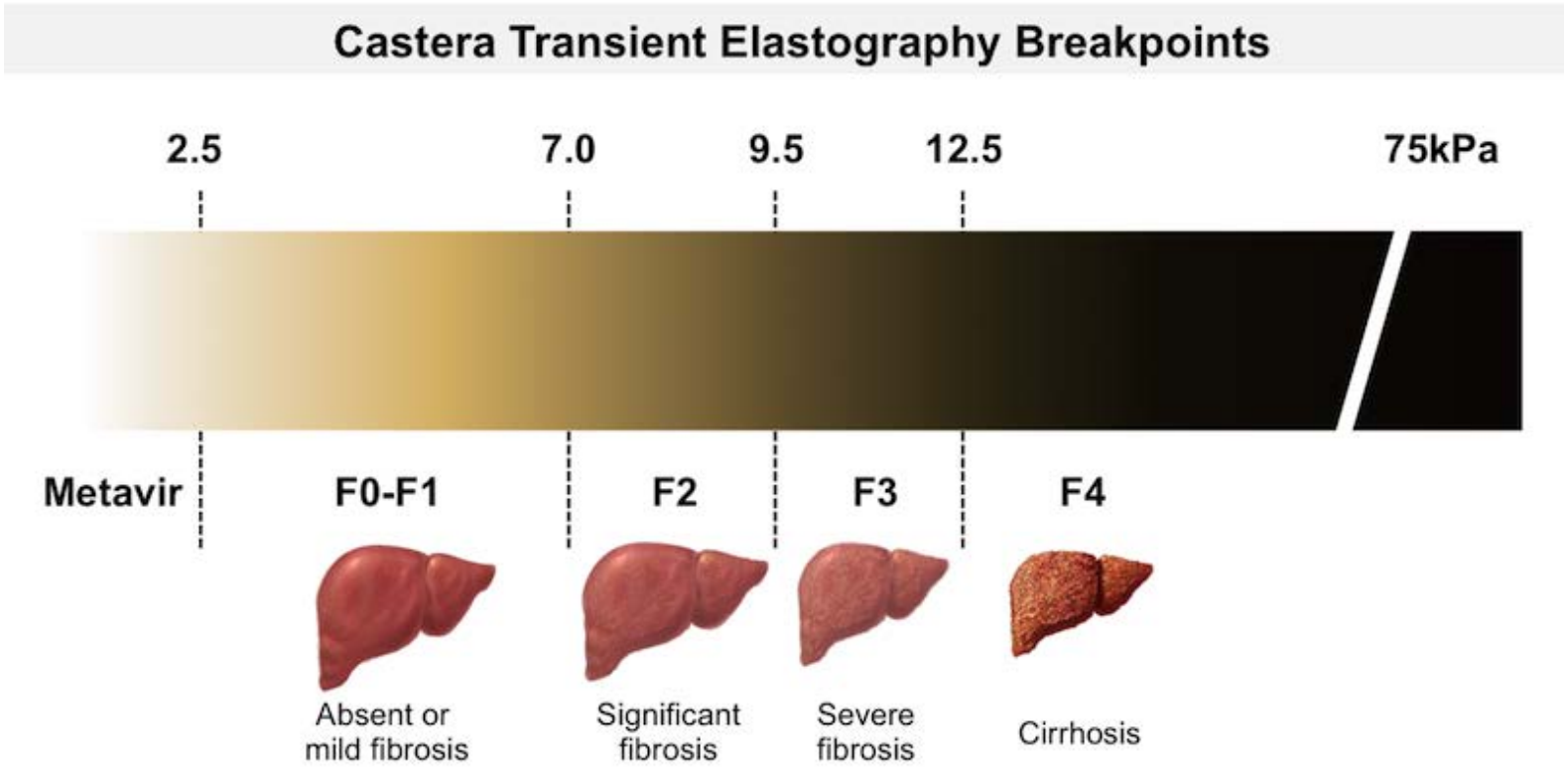
Hepatic Ultrasound-used to confirm overt cirrhosis and/or portal hypertension, and screen for hepatocellular carcinoma.

Fibroscan-correlates directly with liver stiffness

- hepatic inflammation, obesity, ascites, and elevated central venous pressure and can influence the transient elastography result

Magnetic Resonance Elastography:

FIBROSIS Staging



CASES

Patient Evaluation

Medical History

- Asses for Alcohol Use,
- Illicit Drug use
- Medication Use
  - https://livertox.nlm.nih.gov/
- Comorbidities: HIV, Hepatitis B, DM, Obesity, Steatosis
- Psychiatric History
- ROS: abdominal swelling, edema, hematemesis, melena, AMS

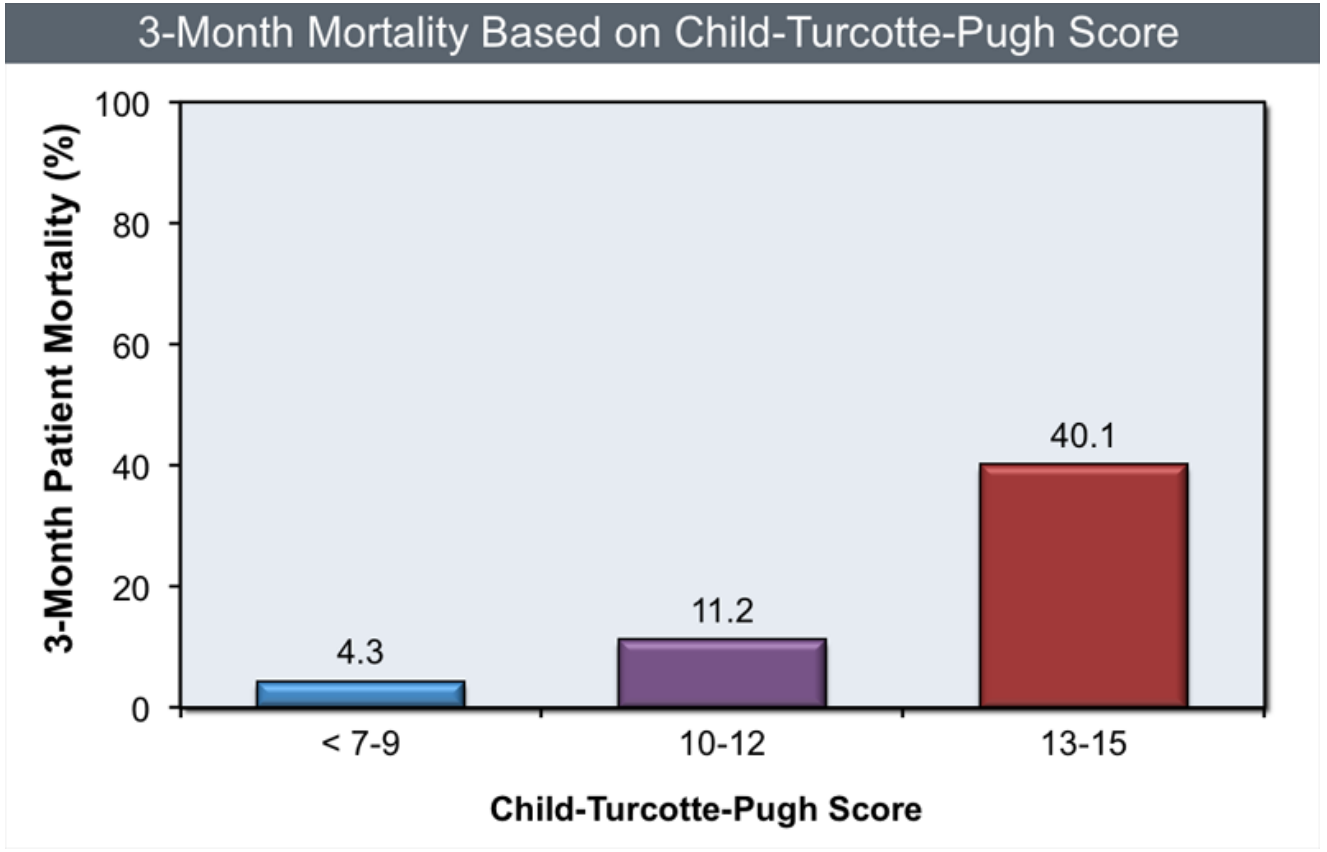
Patient Evaluation

Physical Exam

- BMI: BMI>25 at risk for NAFLD
- Wasting
- Scleral icterus
- Lower extremity edema
- Spider angiomata, Palmar erythema, gynecomastia, testicular atrophy
- Assess for Ascites: fluid wave and shifting dullness
- Mental status
- Asterixis and hepatic encephalopathy

Childs-Turcotte-Pugh

Child-Turcotte-Pugh Classification for Severity of Cirrhosis			
	Points*		
	1	2	3
Encephalopathy	None	Grade 1-2 (or precipitant induced)	Grade 3-4 (or chronic)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
INR	<1.7	1.7-2.3	>2.3
*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)			
Class A = 5 to 6 points (least severe liver disease)			
Class B = 7 to 9 points (moderately severe liver disease)			
Class C = 10 to 15 points (most severe liver disease)			


3-Month Mortality Based on Child-Turcotte-Pugh Score
3-Month Patient Mortality (%)
100
80
60
40
20
0
4.3
11.2
40.1
< 7-9
10-12
13-15
Child-Turcotte-Pugh Score

Work UP

CBC

LFT

INR

BMP

HCV genotype

HCV RNA (viral load)

Baseline Ultrasound

HIV

Hep B sAg/sAb/cAb: If negative Vaccinate

Hep A tAB: if negative vaccinate

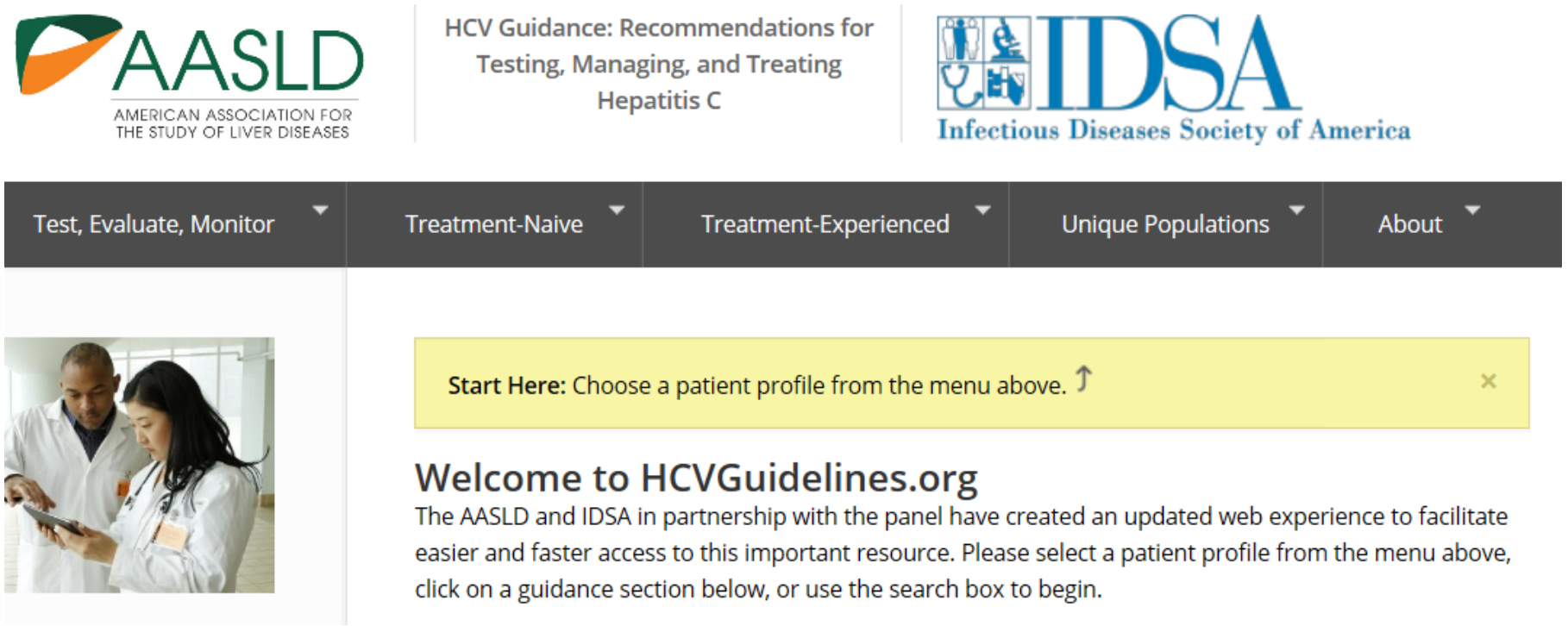
Treatment Contraindications

Absolute Contraindications

- Short life expectancy
- Pregnancy

    - Relative Contraindication
        - Active severe substance abuse
        - Uncontrolled psychiatric condition
        - Social issues that hinders adherence to therapy, monitor treatment safety, schedule office visits

Management

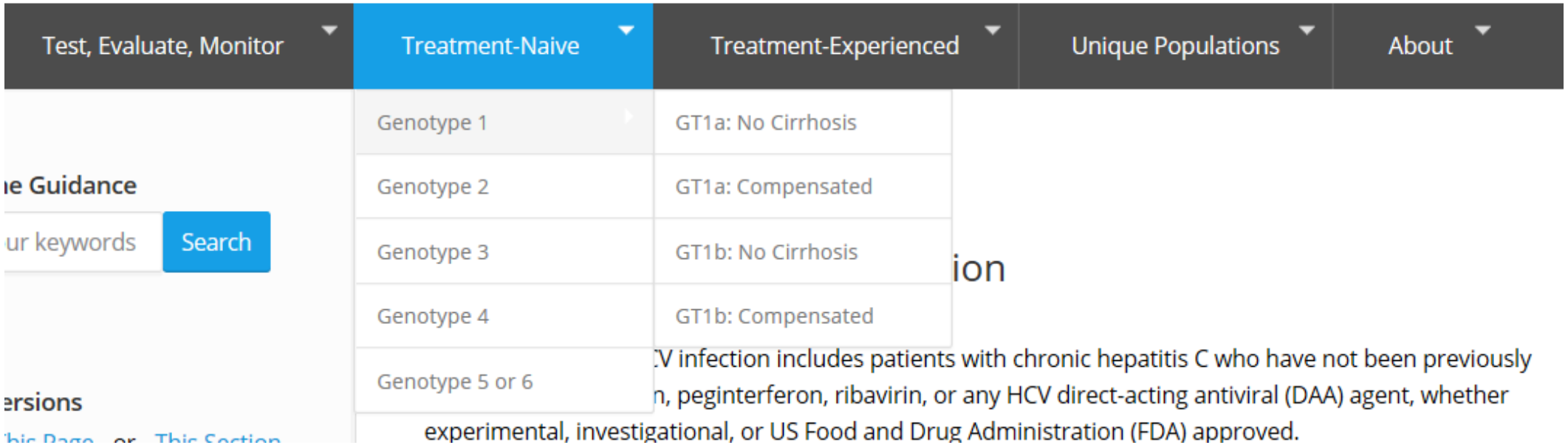

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES
HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C
IDSA
Infectious Diseases Society of America
Test, Evaluate, Monitor
Treatment-Naive
Treatment-Experienced
Unique Populations
About
Start Here: Choose a patient profile from the menu above.
Welcome to HCVGuidelines.org
The AASLD and IDSA in partnership with the panel have created an updated web experience to facilitate easier and faster access to this important resource. Please select a patient profile from the menu above, click on a guidance section below, or use the search box to begin.

Management

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA
Infectious Diseases Society of America



Management

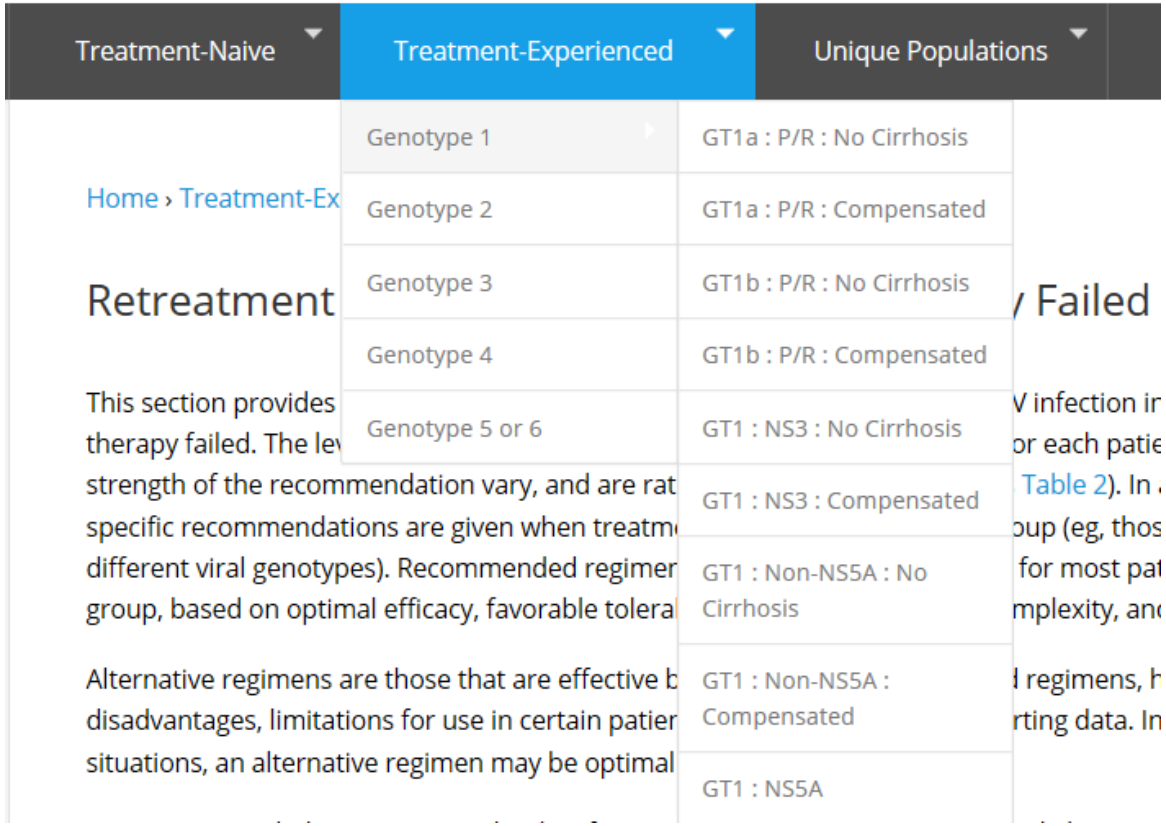
Treatment-Naive Genotype 1a Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 1a Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs[a] for elbasvir	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients who are non-black, HIV-uninfected, and whose HCV RNA level is <6 million IU/mL	8 weeks	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg), with weight-based ribavirin	12 weeks	I, A
Daily simeprevir (150 mg) plus sofosbuvir (400 mg)	12 weeks	I, A
Daily daclatasvir (60 mg)[c] plus sofosbuvir (400 mg)	12 weeks	I, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin for patients with baseline NS5A RASs[a] for elbasvir	16 weeks	IIa, B

Management


Treatment-Naive
Treatment-Experienced
Unique Populations
Genotype 1
Genotype 2
Genotype 3
Genotype 4
Genotype 5 or 6
GT1a : P/R : No Cirrhosis
GT1a : P/R : Compensated
GT1b : P/R : No Cirrhosis
GT1b : P/R : Compensated
GT1 : NS3 : No Cirrhosis
GT1 : NS3 : Compensated
GT1 : Non-NS5A : No Cirrhosis
GT1 : Non-NS5A : Compensated
GT1 : NS5A
Home › Treatment-Ex
Retreatment
Failed
This section provides
therapy failed. The le
strength of the recommendation vary, and are rat
specific recommendations are given when treatm
different viral genotypes). Recommended regimer
group, based on optimal efficacy, favorable tolera
Table 2). In
for most pat
Alternative regimens are those that are effective b
disadvantages, limitations for use in certain patier
situations, an alternative regimen may be optimal

Management

Peginterferon/Ribavirin-Experienced, Genotype 1a Patients Without Cirrhosis

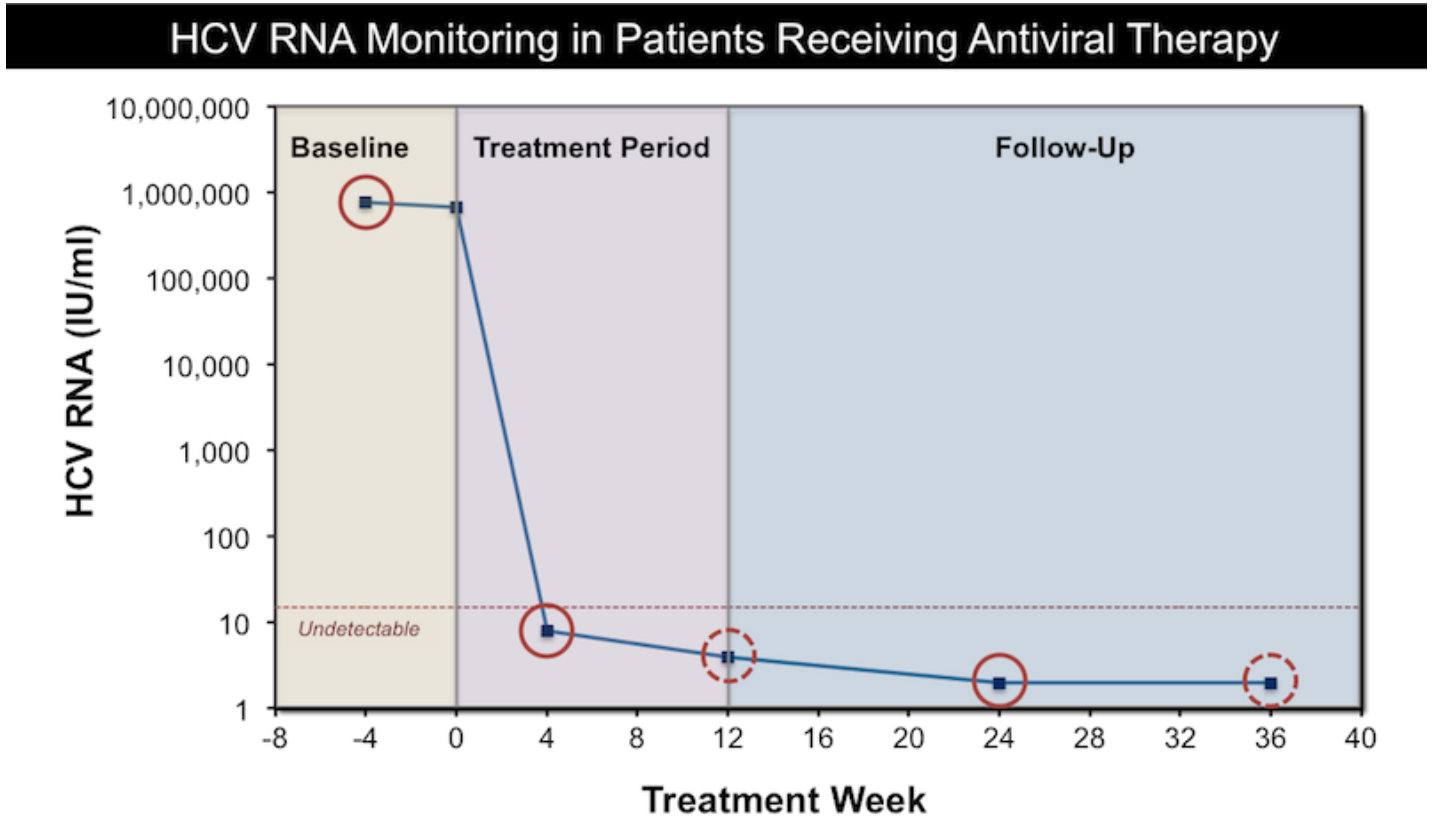
Recommended and alternative regimens listed by evidence level and alphabetically for:

Peginterferon/Ribavirin-Experienced, Genotype 1a Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs[a] for elbasvir	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg), and weight-based ribavirin	12 weeks	I, A
Daily simeprevir (150 mg) plus sofosbuvir (400 mg)	12 weeks	I, A
Daily daclatasvir (60 mg)[c] plus sofosbuvir (400 mg)	12 weeks	I, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for patients with baseline NS5A RASs[a] for elbasvir	16 weeks	IIa, B

[a] Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.
[c] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Management


HCV RNA Monitoring in Patients Receiving Antiviral Therapy
Baseline
Treatment Period
Follow-Up
Undetectable
HCV RNA (IU/ml)
10,000,000
1,000,000
100,000
10,000
1,000
100
10
1
-8
-4
0
4
8
12
16
20
24
28
32
36
40
Treatment Week

Management

Patient who do not achieve SVR

- Monitor LFT, CBC, INR q6-12month
- Consider re-treating

- IF F3-F4
  - HCC q6 months screening with US

PERINATAL TRANSMISSION

Approximately 5%-15% will transmit HCV (MTCT)
- CDC 4-7%
- Depends on HCV RNA viral load at time of delivery
- Co-infected with HIV and HCV- 2x higher risk
- Rare: Hep C Ab+ and HCV RNA –

Breastfeeding is not contraindicated in women with HCV

Screen infant at 18 months for HCV Ab and if + again after age 3

Women with HCV should be re-evaluated after delivery to assess for spontaneous clearance
- 10% with clearance

Treatment is contraindicated in Pregnancy

HCC Screening

Worldwide, hepatocellular carcinoma (HCC) is the sixth most common malignancy

2nd leading cause of cancer-related death

In 2012, there was an estimated 24,696 new cases of HCC diagnosed

1973: incidence was 1.51 cases per 100,000 persons

2011: incidence 6.20 cases per 100,000 persons

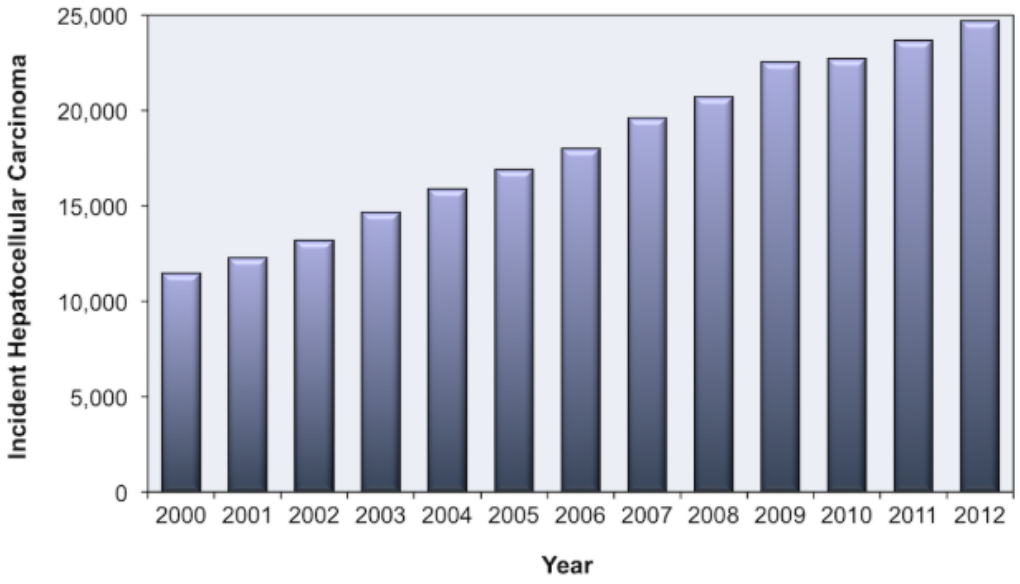
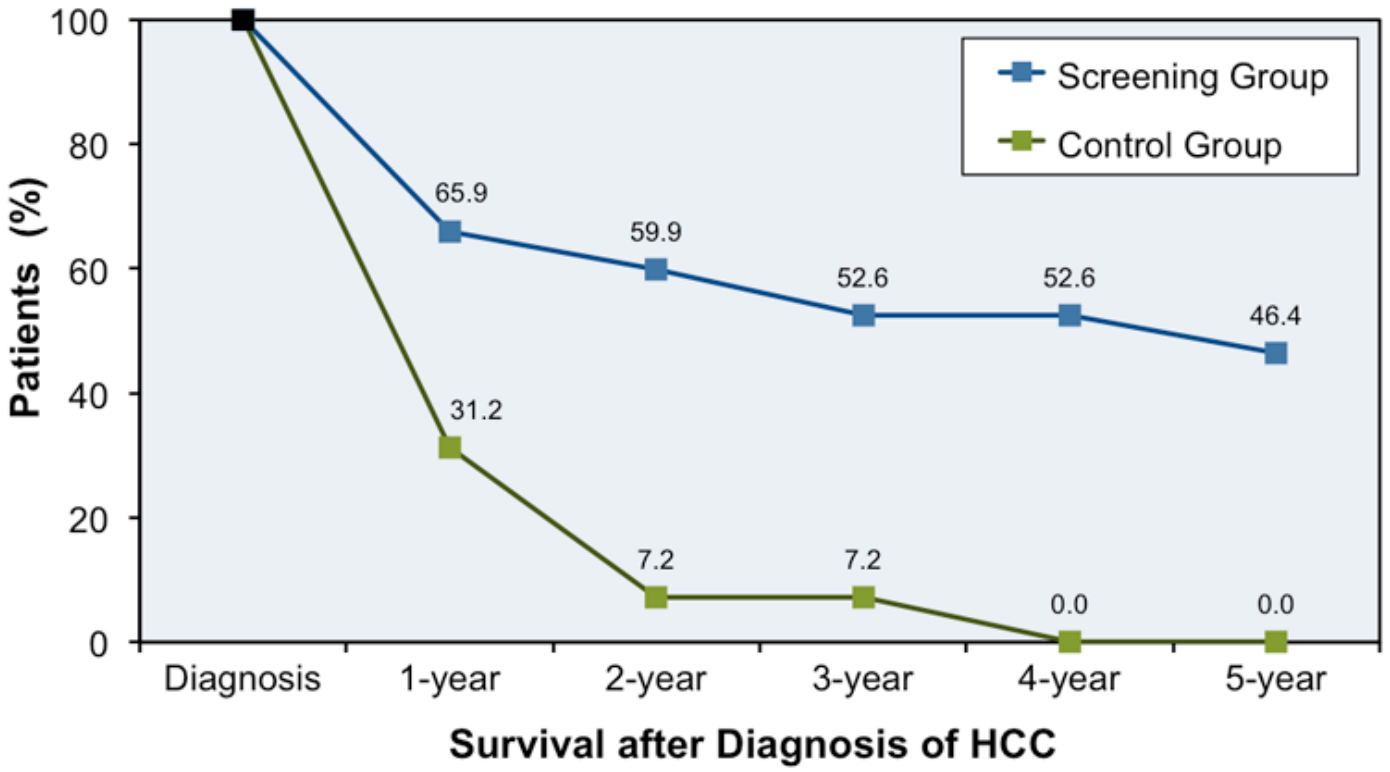


Figure 3 - Incident HCC in United States, 2000-2012
This graphic shows a steady increase in the number of new cases of hepatocellular carcinoma in the United States—from 11,469 cases cases in 2000 to 24,696 cases in 2012.

HCC Screening



HCC Screening

all adults with cirrhosis of any etiology

any patient with chronic HCV who has developed advanced fibrosis or cirrhosis (Metavir stage 3 or 4) even if treated and cured

- Rates decrease by 79% once cured but risk is still not 100% eliminated

recommend using a surveillance interval of 6 months.

If Coinfected with HBV

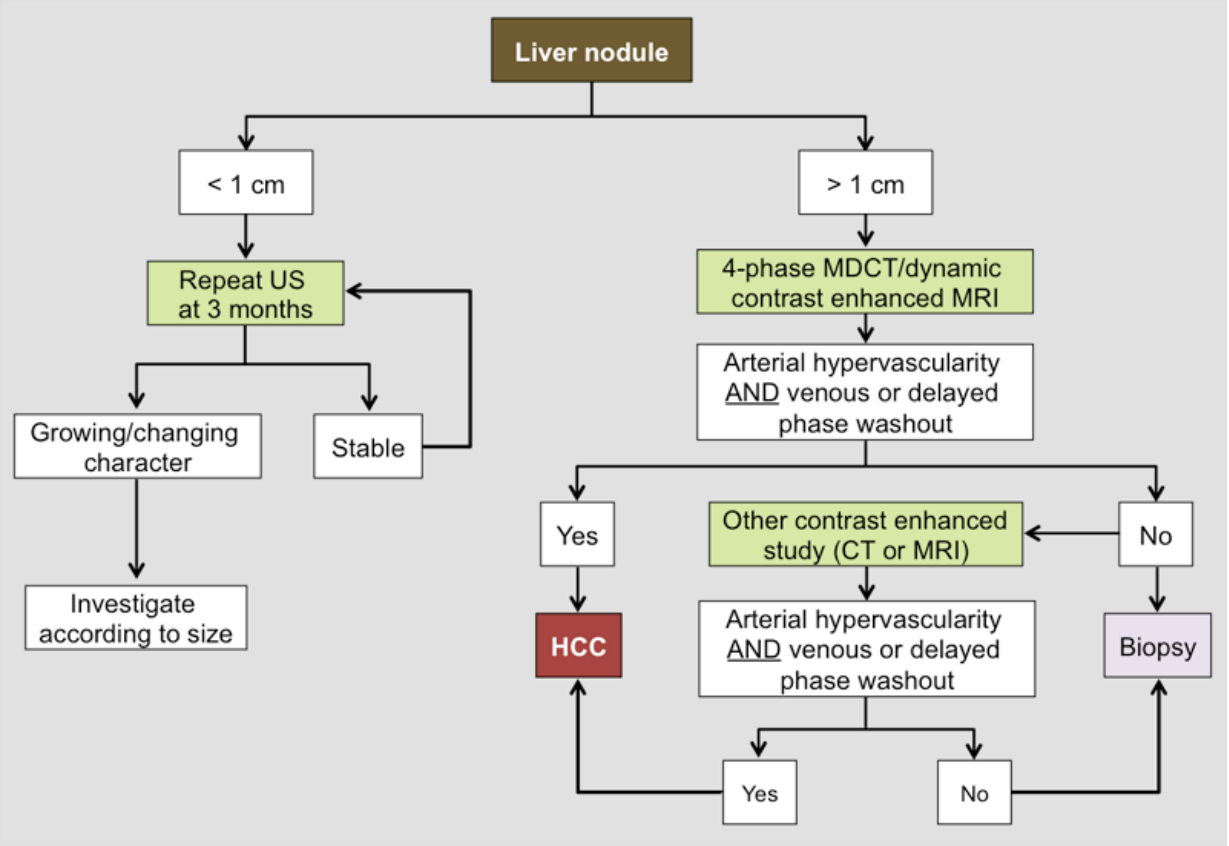
- Asian men 40 years of age or older
- Asian women 50 years of age or older
- Black men 40 years or older
- Patients with cirrhosis
- First degree family history of HCC
- Hepatitis D virus

HCC Screening

AFP is no longer recommended as a routine surveillance test

Hepatic US: sensitivity of 60 to 80% and specificity > 90% for detecting HCC at any stage

HCC Screening



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Team work makes the Dream Work!

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