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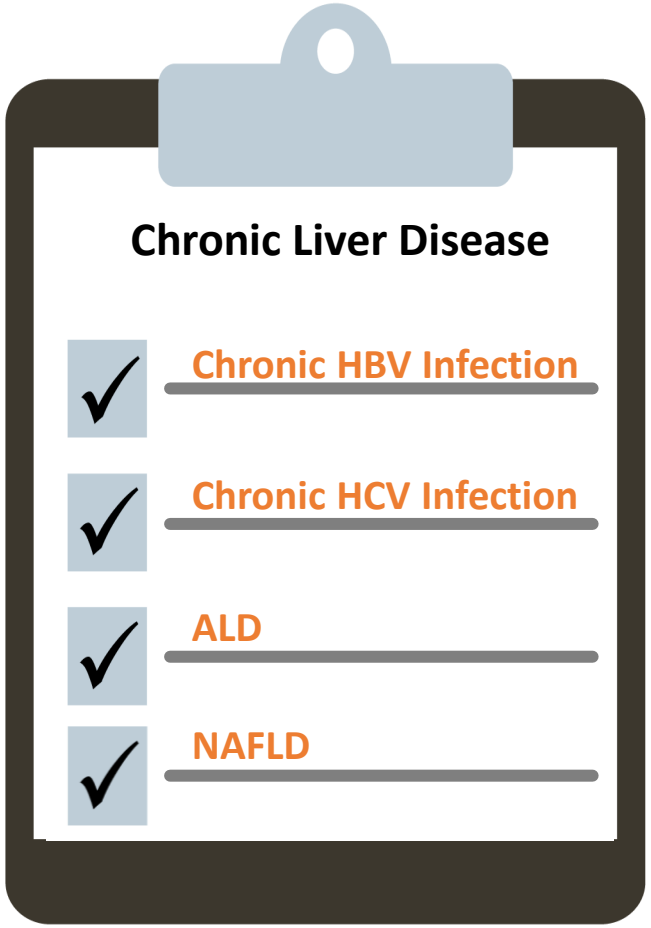
Chronic Liver Disease:
What the Laboratory Should Know

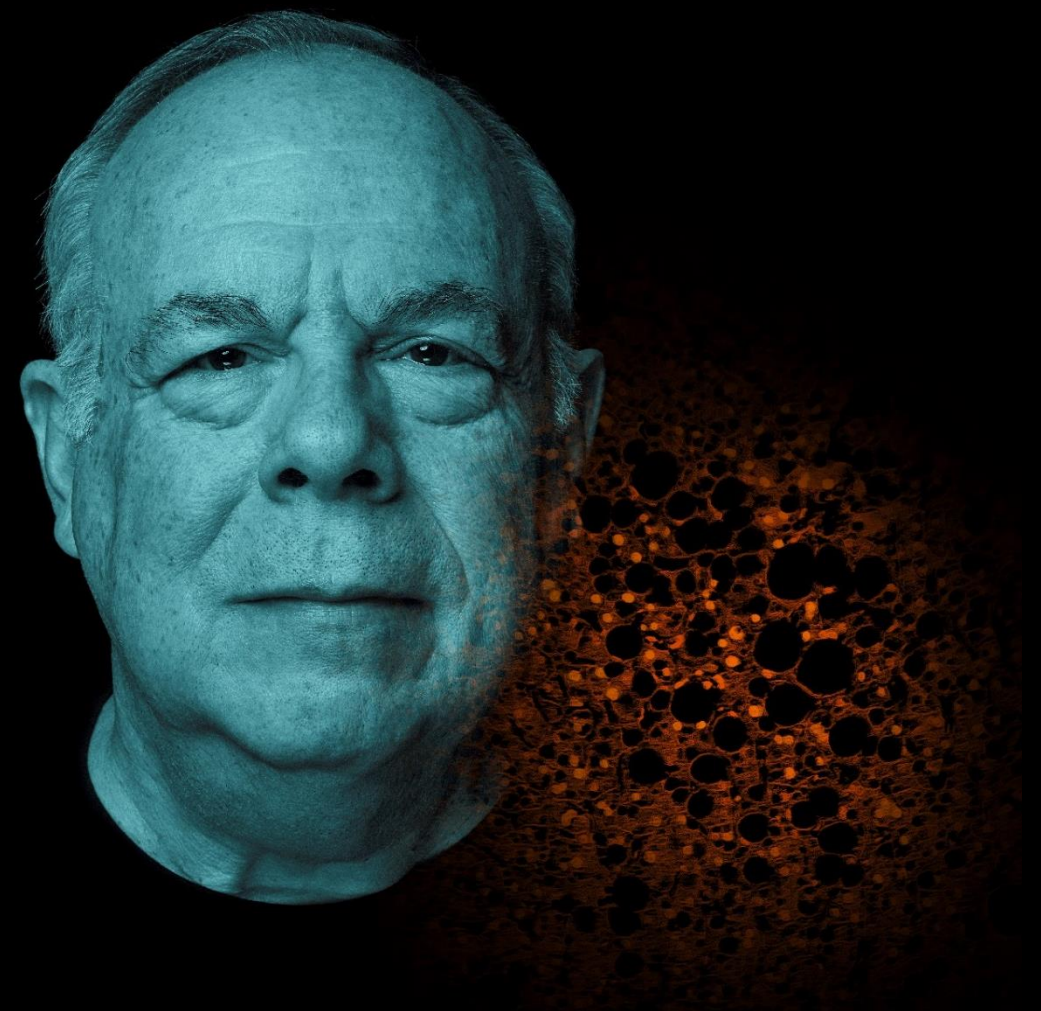
Jim Aguanno, PhD
Senior Clinical Consultant
Medical and Scientific Affairs

Agenda



- Epidemiology of chronic liver disease
- Definition of terms and staging
- Clinical aspects of chronic liver disease in general
- Discuss the clinical aspects and diagnosis of some of the common causes of chronic liver disease
  - Chronic Hepatitis B infection
  - Chronic Hepatitis C infection
  - Alcoholic Liver Disease (ALD)
  - Non-Alcoholic Liver Disease (NAFLD)

Chronic Liver Disease
Epidemiology

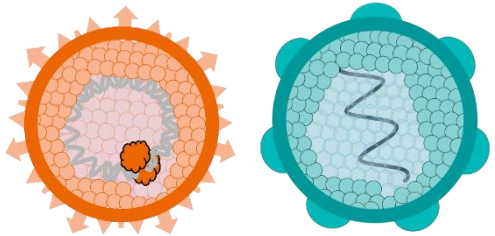


Epidemiology of Liver Disease

- More than 100 million people in the U.S. have some form of liver disease.
- 4.5 million U.S. adults (1.8%) have been diagnosed with liver disease. But it is estimated that 80-100 million adults in the U.S. have fatty liver disease, and many do not know they have it.
- In 2019, chronic liver disease was the 8th leading cause of death for non-Hispanic African American/Black people aged 45–64 years old.
- Left untreated, liver disease can lead to liver failure and liver cancer.
- In 2020, 51,642 adults in the U.S. died from liver disease (15.7 per 100,000 population).
- Chronic liver disease/cirrhosis was the 12th leading cause of death in the U.S in 2020.
- Cirrhosis is a long-term liver disease. Cirrhosis is scarring of the liver, when scar tissue replaces healthy tissue, causing damage and thereby reducing liver function. Cirrhosis is most often caused by: hepatitis and other viruses; long-term alcohol abuse; and nonalcoholic fatty liver disease (NAFLD).

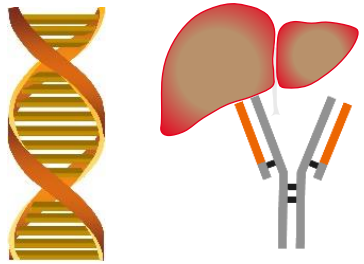
https://liverfoundation.org/about-your-liver/facts-about-liver-disease/how-many-people-have-liver-disease/

Chronic liver disease (CLD) has many etiologies



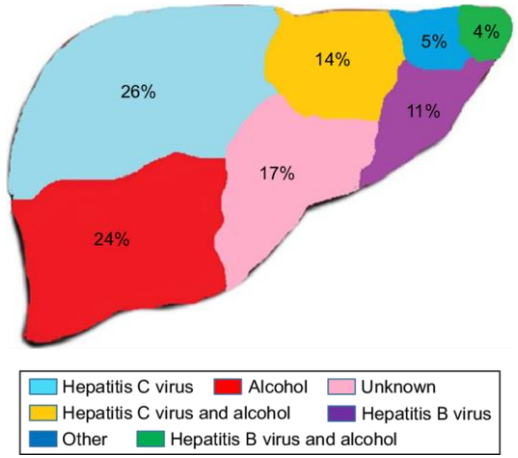
HBV HCV

Viral Hepatitis
(including HIV/HCV coinfections)



Primary biliary cirrhosis, autoimmune hepatitis, hemochromatosis, Wilson's disease

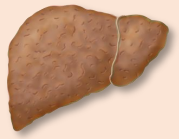
Alcoholic Liver Disease



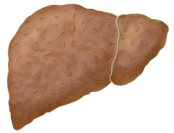
Non-Alcoholic Fatty Liver Disease

International Journal of Nanomedicine 2017:12 6997–7006
Moon, AM., et al. Clin Gastroenterol Hepatol 2020;18(12): 2650-66.

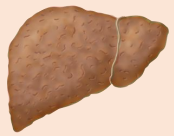
Liver Disease Definitions



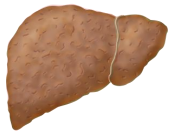
Acute liver failure is loss of liver function that occurs quickly — in days or weeks — usually in a person who has no preexisting liver disease.



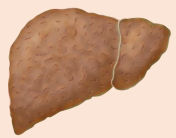
Chronic Liver Disease (CLD) is a progressive deterioration of liver function for more than six months.



Acute on Chronic Liver Disease (ACLD) is a clinical syndrome of sudden hepatic decompensation observed in patients with pre-existing chronic liver disease. Acute on chronic liver failure is a serious condition with very high morbidity and mortality.



Cirrhosis is scarring of the liver, when scar tissue replaces healthy tissue, causing damage and reducing the liver function.

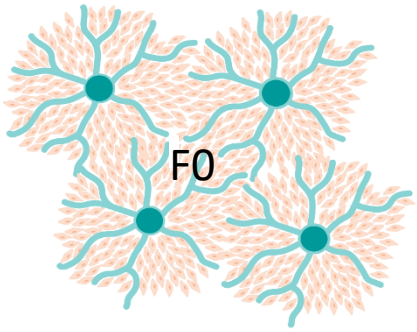


Decompensated Cirrhosis is defined as an acute deterioration in liver function in a patient with cirrhosis and is characterized by jaundice, ascites, hepatic encephalopathy, hepatorenal syndrome or variceal hemorrhage.

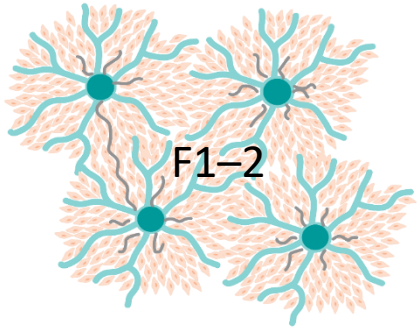
Fibrosis Staging Indicates Degree of Fibrosis

Fibrosis staging is defined by histological characteristics determined through biopsy.
Multiple staging scales are in use and provide a categorical score of fibrosis.
F3 and F4 are considered to be advanced fibrosis.

F0: None

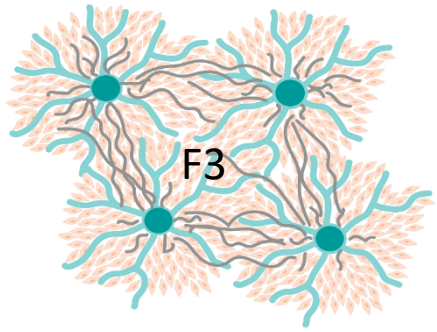


F1: Perisinusoidal fibrosis
AND/OR
F2: Periportal fibrosis

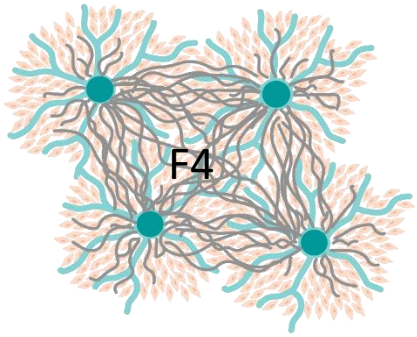


Advanced fibrosis

F3: Bridging Fibrosis

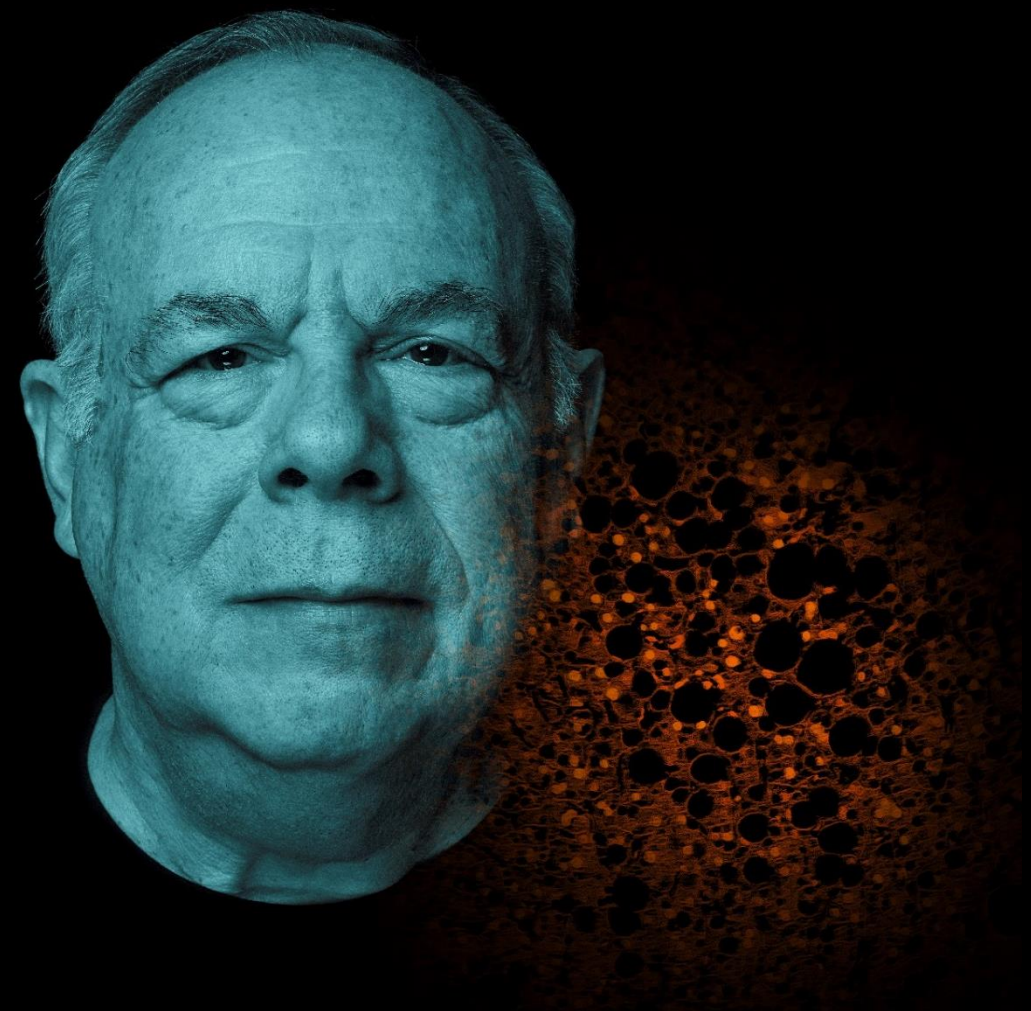


F4: Cirrhosis



1*described by Kleiner, Brunt, et al.*
Theise ND. Mod Pathol 2007;20 Suppl 1:S3-14.
Ferrell, L. https://www.ucsfcme.com/2013/MAP1301A/slides/13FerrellLiverUpdateOnStagingOfFibrosisAndCirrhosis.pdf Accessed Aug. 18, 2021

Chronic Liver Disease
Clinical Aspects



Risk Factors and Causes for Development of Liver Disease

Risk Factors for Liver Disease
• Heavy alcohol use
• Obesity
• Type 2 diabetes
• Tattoos or body piercings
• Injecting drugs using shared needles
• Blood transfusion before 1992*
• Exposure to blood or body fluids
• Unprotected sex
• Exposure to certain toxins
• Family history of liver disease

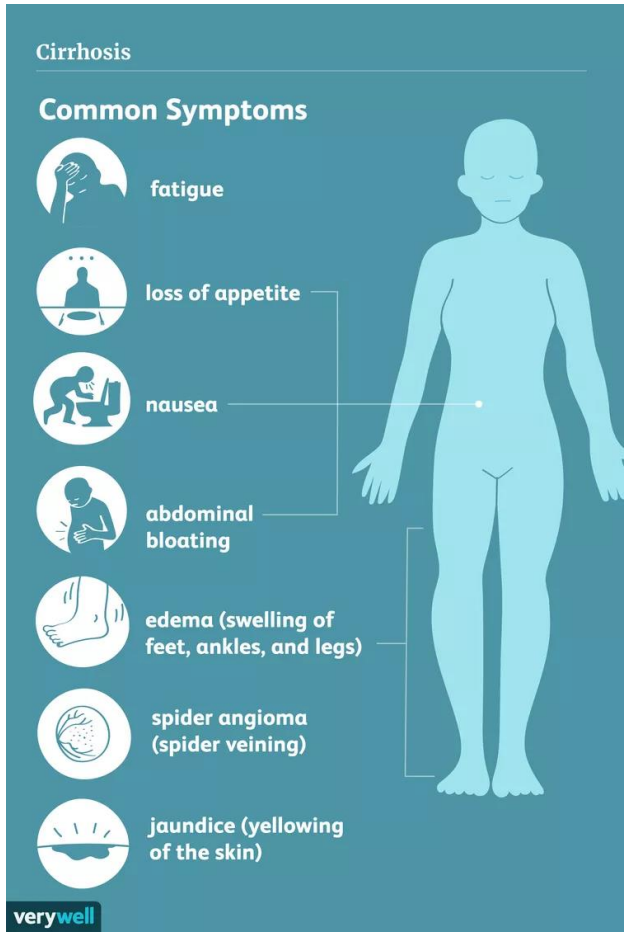
*In 1992 blood donor screening was completely implemented.

Causes of Chronic Liver Disease
Viral Causes
• Hepatitis B
• Hepatitis C
CMV, EBV, and yellow fever viruses cause acute hepatitis
Toxins and Drugs
• Alcoholic Liver Disease (ALD)
• Rarely drug induced liver disease from methotrexate, amiodarone, and others
Acetaminophen causes acute liver damage
Metabolic Causes
• Non-Alcoholic Fatty Liver Disease (NAFLD)
• Hemochromatosis
• Wilson's Disease
• Alpha-1-antitrypsin Deficiency
Autoimmune Causes
• Primary Biliary Cholangitis (PBC)
• Primary Sclerosing Cholangitis (PSC)
• Autoimmune Hepatitis
Cryptogenic Cirrhosis

https://en.wikipedia.org/wiki/Chronic_liver_disease

https://www.mayoclinic.org/diseases-conditions/liver-problems/symptoms-causes/syc-20374502

Signs and Symptoms of Chronic Liver Disease



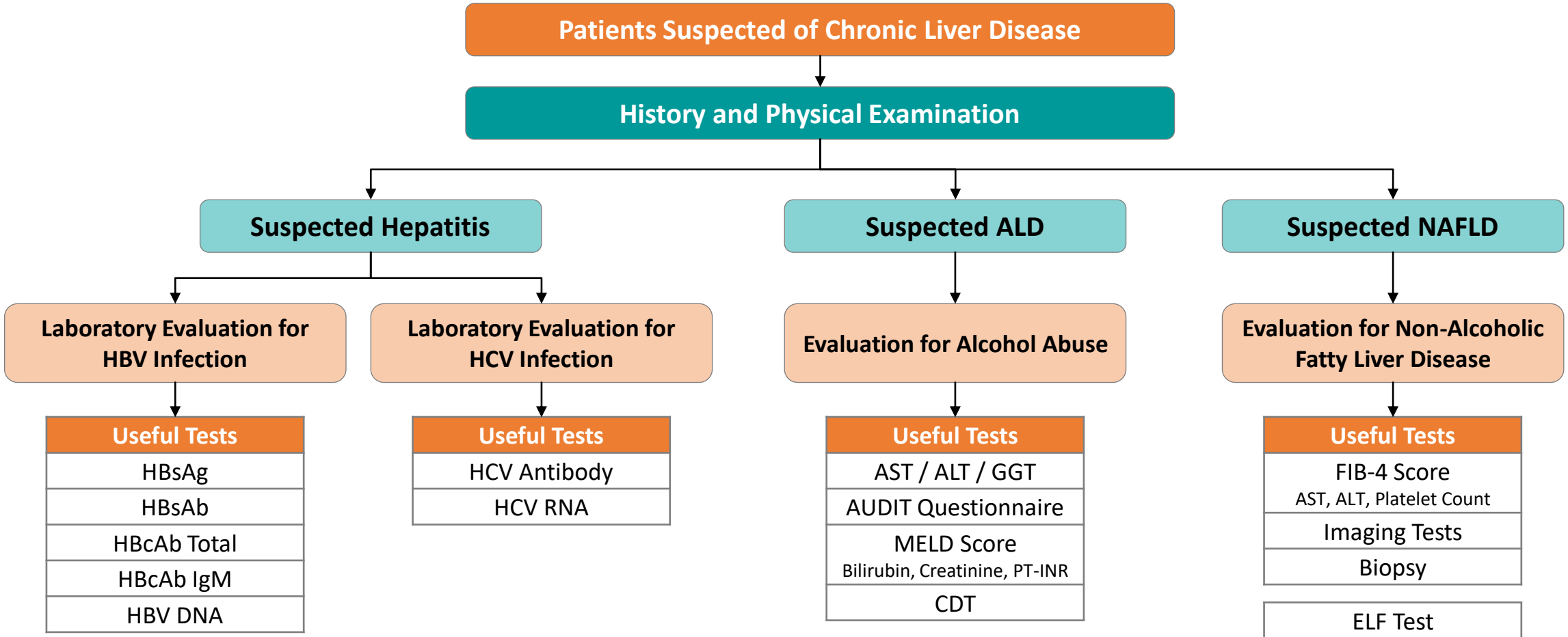
Signs and Symptoms of Chronic Liver Disease
• Chronic fatigue
• Loss of appetite
• Nausea and/or vomiting
• Abdominal pain
• Jaundice
• Easy bruising or bleeding
• Disorientation
• Severely itching skin
• Dark urine color
• Pale stool color
• Swelling in the arms, legs or abdomen

https://www.verywellhealth.com/cirrhosis-what-you-need-to-know-1759889

https://www.mayoclinic.org/diseases-conditions/liver-problems/symptoms-causes/syc-20374502

https://www.hopkinsmedicine.org/health/conditions-and-diseases/chronic-liver-disease-cirrhosis

Some Common Causes of Chronic Liver Disease

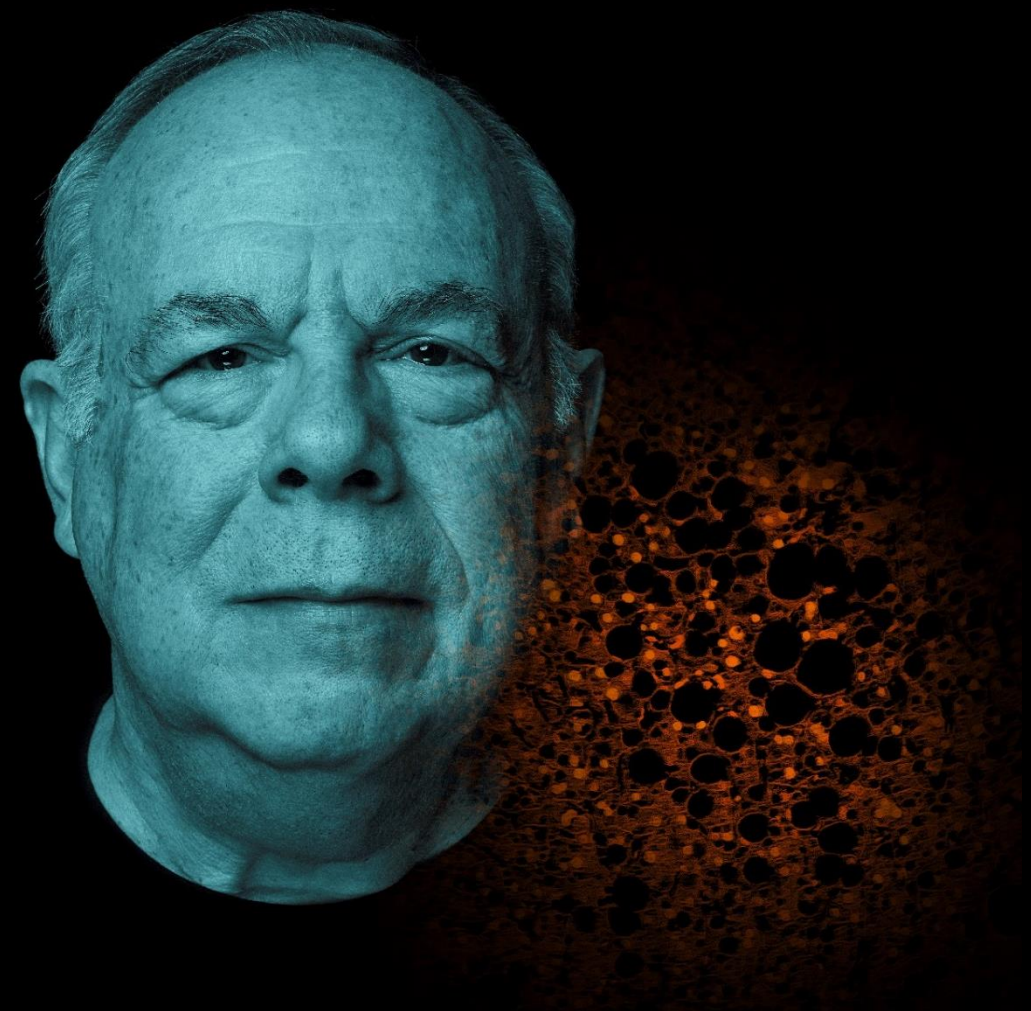


AUDIT: Alcohol Use Inventory Test
MELD: Model for End-Stage Liver Disease
CDT: Carbohydrate Deficient Transferrin

FIB-4: Fibrosis-4 Score
ELF: Enhanced Liver Fibrosis

Chronic Liver Disease

Hepatitis B



HBV Infection

Transmission	Percutaneous or permucosal contact with infectious blood or body fluids (e.g., semen and saliva).
Incubation Period	If symptoms occur, they begin an average of 90 days (range: 60–150 days) after exposure to HBV.
Symptom Duration	Symptoms typically last for several weeks but can persist for up to 6 months.
HBsAg Detection	HBsAg will be detected in an infected person's blood an average of 4 weeks (range: 1–9 weeks) after exposure to the virus. About half of patients will no longer be infectious by 7 weeks after onset of symptoms, and all patients who do not remain chronically infected will be HBsAg-negative by 15 weeks after onset of symptoms
Chronic Infections - Risk	The risk for chronic infection varies according to the age at infection and is greatest among young children. Approximately 90% of infants and 25%–50% of children aged 1–5 years will remain chronically infected with HBV. By contrast, approximately 95% of adults recover completely from HBV infection and do not become chronically infected.
Chronic Infections - Outcome	Approximately 25% of people who become chronically infected during childhood and 15% of those who become chronically infected after childhood die prematurely from cirrhosis or liver cancer, and most remain asymptomatic until onset of cirrhosis or end-stage liver disease
Environmental Survival	HBV can survive outside the body and remains infectious for at least 7 days.
Vaccine Availability	Yes
Treatment	People with acute infection are provided supportive treatment depending on their symptoms. For people with chronic infection, several antiviral medications are available

HBV Transmission

HBC Transmission

HBV is transmitted through activities that involve percutaneous or permucosal contact with infectious blood or body fluids (e.g., semen and saliva), including:

- sex with a partner who has HBV infection;
- injection drug use that involves sharing needles, syringes, or drug-preparation equipment;
- birth to a person who has HBV infection;
- contact with blood from or open sores on a person who has HBV infection;
- exposures to needle sticks or sharp instruments; and
- sharing certain items with a person who has HBV infection that can break the skin or mucous membranes (e.g., razors, toothbrushes, and glucose monitoring equipment), potentially resulting in exposure to blood.

Statistics

- Between 880,000 to 1.89 million people are living with HBV infection in the United States; two-thirds of whom may be unaware of their infection.
- Chronic hepatitis B disproportionately affects people born outside the United States; while accounting for only 14% of the US general population, non–US-born people account for 69% of the US population living with chronic HBV infection.
- In 2018, a total of 1,649 US death certificates had HBV recorded as an underlying or contributing cause of death. However, this is a conservative estimate.

https://www.cdc.gov/hepatitis/hbv/hbvfaq.htm#treatment

Chronic Hepatitis B Infection - Definition

Chronic HBV Infection
Clinical Description
No symptoms are required. Persons with chronic hepatitis B virus (HBV) infection may have no evidence of liver disease or may have a spectrum of disease ranging from chronic hepatitis to cirrhosis or liver cancer.
Laboratory Criteria For Diagnosis
• Positive HBcAb-IgM, **AND** • Positive result for one of the following tests: HBsAg, HBeAg, or HBV DNA (including qualitative, quantitative and genotype testing), **OR** • HBsAg positive or HBV DNA positive (including qualitative, quantitative and genotype testing) or HBeAg positive two times at least 6 months apart (Any combination of these tests performed 6 months apart is acceptable)

Chronic HBV Infection
Probable
A person with a single HBsAg positive or HBV DNA positive (including qualitative, quantitative and genotype testing) or HBeAg positive lab result and does not meet the case definition for acute hepatitis B.
Confirmed
A person who meets either of the laboratory criteria for diagnosis.
Comments
• Multiple laboratory tests indicative of chronic HBV infection may be performed simultaneously on the same patient specimen as part of a "hepatitis panel." Testing performed in this manner may lead to seemingly discordant results, e.g., HBsAg-negative **AND** HBV DNA-positive. • For the purposes of this case definition, any positive result among the three laboratory tests mentioned above is acceptable, regardless of other testing results. Negative HBeAg results and HBV DNA levels below positive cutoff level do not confirm the absence of HBV infection.

https://www.cdc.gov/hepatitis/hbv/hbvfaq.htm#treatment

Hepatitis B Infection – Risk Factors

The following populations are at increased risk for becoming infected with HBV:
• Infants born to people with HBV infection
• Sex partners of people with HBV infection
• Men who have sex with men
• People who inject drugs
• Household contacts or sexual partners of known people with chronic HBV infection
• Health care and public safety workers at risk for occupational exposure to blood or blood-contaminated body fluids
• Patients on hemodialysis

CDC recommends that the following people be screened for HBV infection
• People born in countries with prevalence of HBV infection ≥2%
• People born in the United States not vaccinated as infants whose parents were born in regions with high rates of HBV infection (HBsAg prevalence of ≥8%)
• Men who have sex with men
• People who inject drugs
• People with HIV
• Household and sexual contacts of people with HBV infection
• People requiring immunosuppressive therapy
• People with end-stage renal disease (including patients on hemodialysis)
• Blood and tissue donors
• People with elevated alanine aminotransferase levels (≥19 IU/L for women and ≥30 IU/L for men)
• Pregnant women HBsAg only is recommended
• Infants born to women with HBV infection (HBsAg and HBsAb only are recommended

https://www.cdc.gov/hepatitis/hbv/hbvfaq.htm#treatment

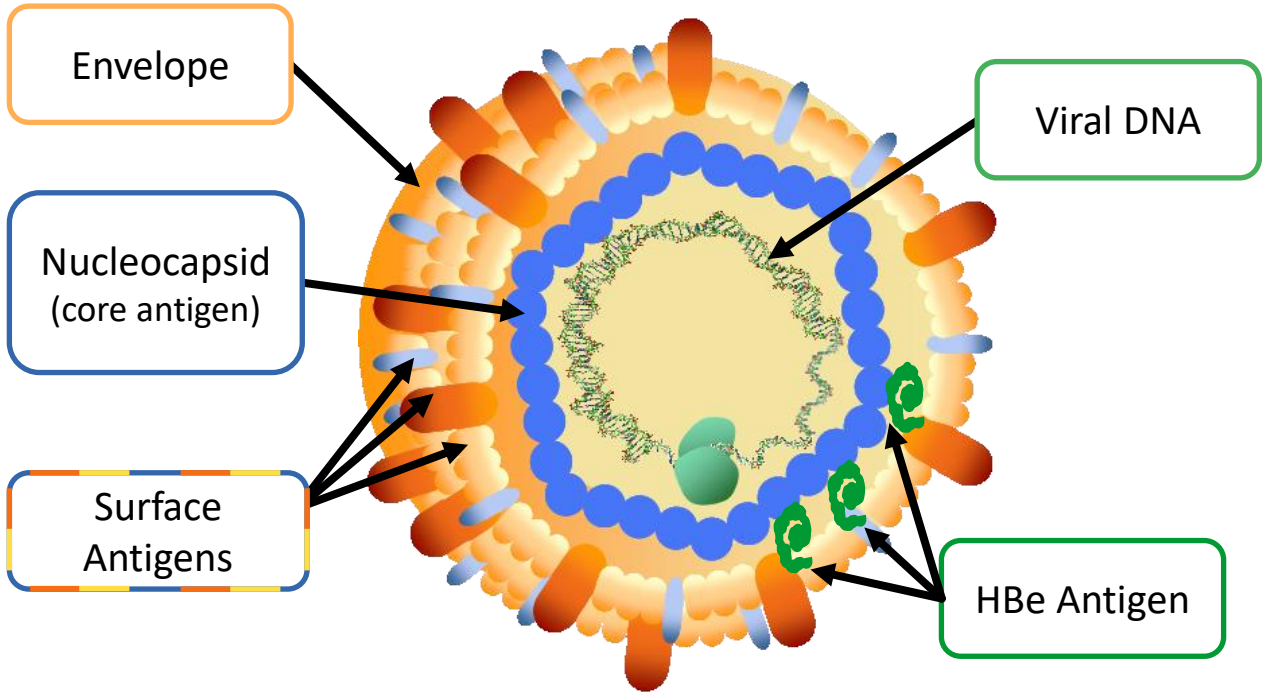
Hepatitis B – Signs and Symptoms

Signs and Symptoms of Acute HBV Infection
• Fever
• Fatigue
• Loss of appetite
• Nausea
• Vomiting
• Abdominal pain
• Dark Urine
• Clay-colored stool
• Joint pain
• Jaundice

- Not all people with acute HBV infection have symptoms. The presence of signs and symptoms varies by age.
- Most children <5 years of age and newly infected immunosuppressed adults are generally asymptomatic, whereas 30%–50% of people age ≥5 years have signs and symptoms.
- Most people with chronic HBV infection are asymptomatic and have no evidence of liver disease or injury.
- However, some people develop chronic hepatitis (elevation of AST/ALT), cirrhosis, or hepatocellular carcinoma (i.e., primary liver cancer).

https://www.cdc.gov/hepatitis/hbv/hbvfaq.htm#treatment

Hepatitis B Virus Structure



Hepatitis B Surface Antigen	HBsAg
Antibody to Hepatitis B Antigen	HBsAb
Antibody to Hepatitis B Core Antigen	HBcAb-IgM HBcAb Total
Hepatitis B Envelope Antigen	HBeAg
Antibody to Hepatitis B Envelope Antigen	HBeAb
Hepatitis B DNA	HBV DNA

HBV Markers

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Hepatitis B Surface Antigen (HBsAg)

HBsAg is the first serologic marker to be detected following initial infection. HBsAg seroconversion is the development of antibodies against HBsAg which it indicates the clearance of HBsAg and the resolution of infection. The presence of HBsAg always implies active infection, while persistence of HBsAg for more than six months indicates chronic infection.

Antibody to Hepatitis B Surface Antigen (HBsAb)

HBsAb is the antibody produced by the host in response to HBsAg (HBsAg seroconversion). The presence of HBsAb without HBsAg indicates two possible scenarios: either previous, cleared infection or vaccination against hepatitis B virus. Distinguishing between these two scenarios is possible with further serological testing. Generally, HBsAb remains in serum for life and indicates immunity to HBV.

Hepatitis B Core Antigen (HBcAg)

HBcAg is part of the nucleocapsid within HBV and it is not routinely measured in clinical practice. However, the body produces a corresponding antibody to this antigen called hepatitis B core antibody (HBcAb), which is clinically relevant. In the lab, we can measure, HBcAb-IgM which is a marker of acute infection and after a class-shift we begin making HBcAb-IgG but typically we measure HBcAb Total (IgM and IgG).

Antibody to Hepatitis B Core Antigen (HBcAb)

HBcAb is the antibody produced by the host in response to HBcAg. Depending on which immunoglobulin type is present indicates the time frame since infection. The presence HBcAb-IgM indicates recent infection within the last six months. Over time, IgM is gradually replaced by HBcAb-IgG; therefore, anti-HBc is seen in patients with resolved infection and those with chronic infection.

Hepatitis B Envelope Antigen (HBeAg)

The hepatitis B envelope antigen (HBeAg) is found between the core and lipid envelope within HBV and is present in both acute and chronic infection. The presence of HBeAg in serum indicates active viral replication and a higher risk of transmissibility. HBeAg can be therefore used to distinguish between active chronic infection and inactive chronic infection.

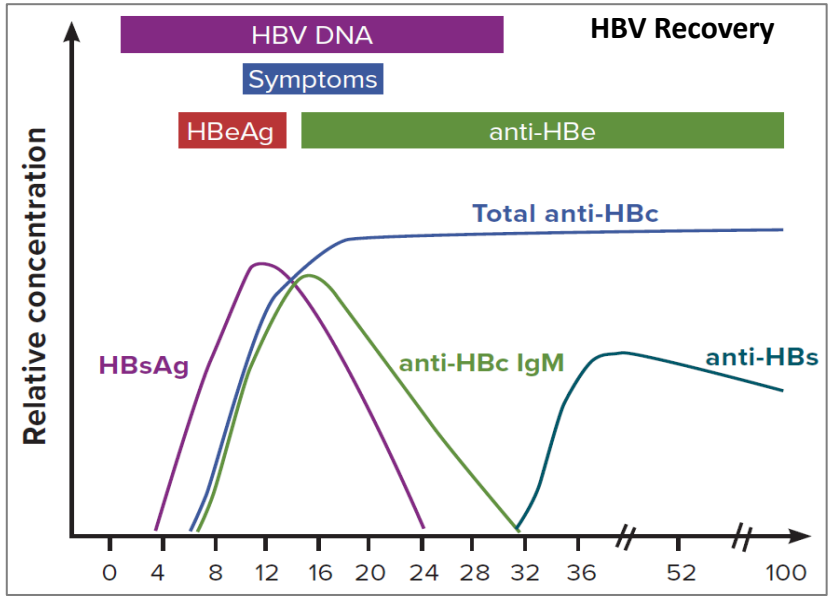
Hepatitis B Envelope Antibody (HBeAb)

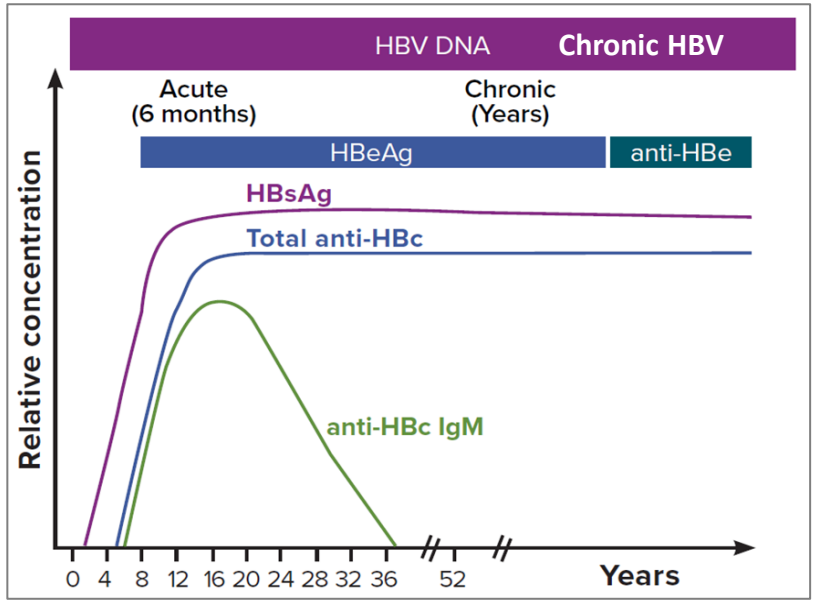
HBeAg seroconversion is the development of antibodies against HBeAg (HBeAb); it marks a transition from active disease to an inactive ‘carrier’ state. HBeAb remains in serum for life and indicates acquired, natural immunity (i.e. immunity from a previous infection only).

Hepatitis B Virus DNA (HBV-DNA)

In patients with serological markers indicating infection, quantification of HBV-DNA is often performed. A high HBV-DNA viral load is associated with an increased risk of progression to cirrhosis and hepatocellular carcinoma (HCC). In patients with active chronic infection, a higher HBV-DNA viral load is expected.

Serologic Testing for HBV Infection



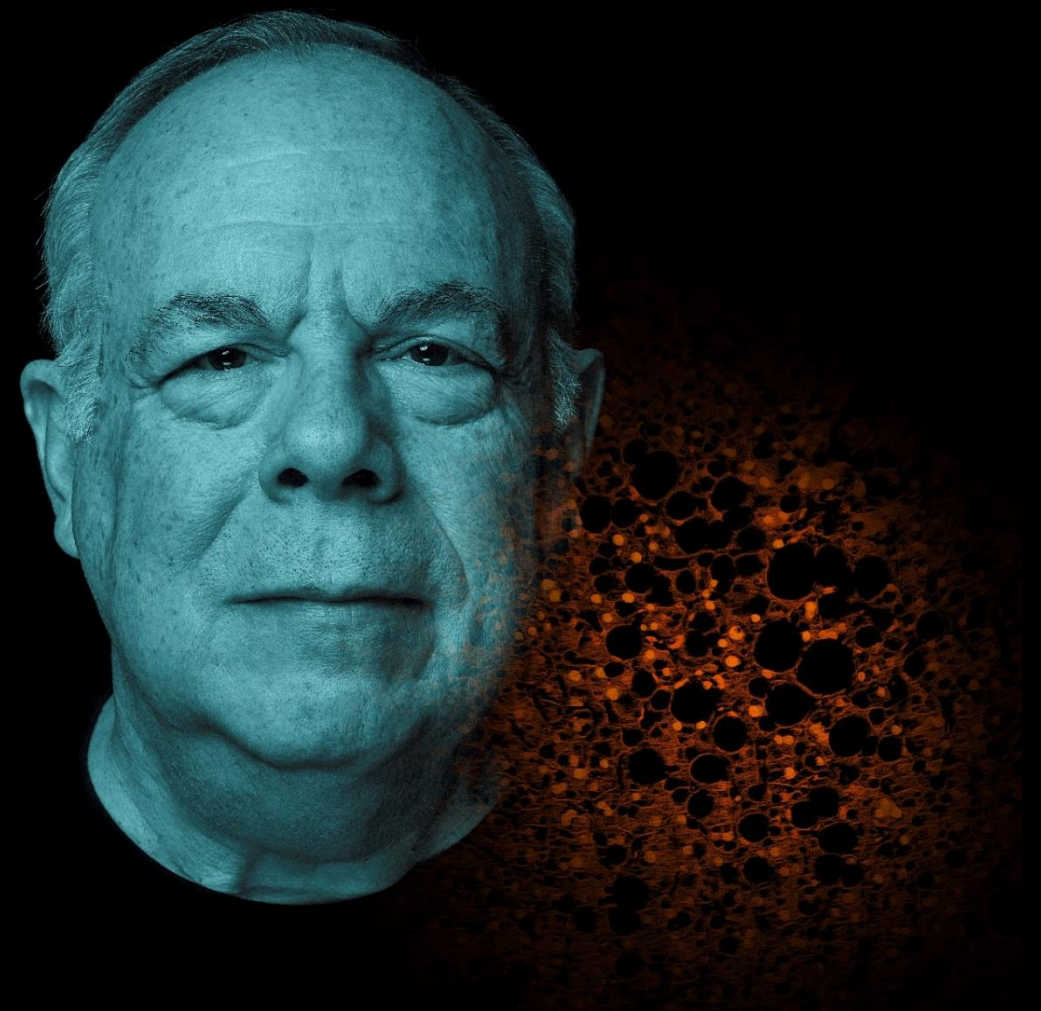


Condition	HBsAg	HBsAb	HBeAg	HBeAb	HBcAb-IgM	HBcAb Total	HBV DNA	AST/ALT
Acute Infection	+	--	+	--	+	+	+	Elevated
Chronic Infection (active)	+	--	+	--	--	+	++	Elevated
Chronic Infection (inactive, carrier)	+	--	--	+ or --	--	+	+	Normal
Immunity Past Infection	--	+	--	+ or --	--	+	--	Elevated or Normal
Immunity Vaccination	--	+	--	--	--	--	--	Normal

https://www.cdc.gov/hepatitis/statistics/surveillanceguidance/HepatitisB.htm

Chronic Liver Disease

Hepatitis C



HCV Infection

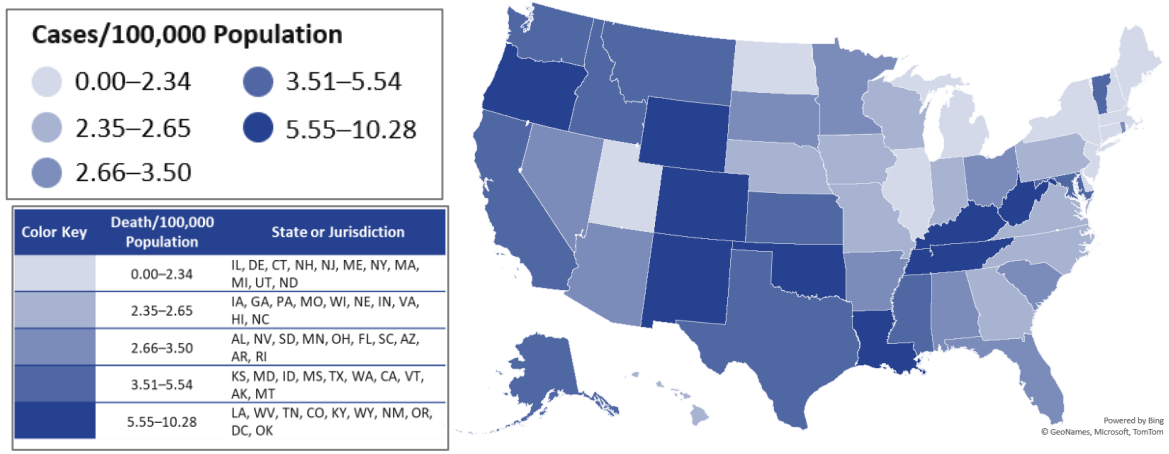
Transmission	Percutaneous or permucosal contact with infectious blood or body fluids (e.g., semen and saliva).
Incubation Period	Approximately 80% of people do not exhibit any symptoms. In those people who do develop symptoms, the average period from exposure to symptom onset is 2–12 weeks (range: 2–26 weeks).
HCV Antibody Detection	Anti-HCV seroconversion occurs an average of 8–11 weeks after exposure, although cases of delayed seroconversion have been documented in people who are immunosuppressed (e.g., those with HIV infection).
HCV RNA Detection	People with recently acquired acute infection typically have detectable HCV RNA levels as early as 1–2 weeks after exposure to the virus
Symptom Duration	Around 30% (15–45%) of infected persons spontaneously clear the virus within 6 months of infection without any treatment.
Chronic Infections	About 70% (55–85%) of persons will develop chronic HCV infection. Of those with chronic HCV infection, the risk of cirrhosis ranges from 15% to 30% within 20 years.
Environmental Survival	The hepatitis C virus can live outside the human body — and for quite some time. If blood containing the virus ends up on a surface, the virus can remain viable for up to 3 weeks
Vaccine Availability	No
Treatment	Over 90% of people infected with HCV can be cured of their infection, regardless of HCV genotype, with 8–12 weeks of oral therapy.

Chronic Hepatitis C - Definition

CDC Definition of Chronic Hepatitis C
Clinical Criteria (one or more of the following) All hepatitis C virus cases in each classification category should be > 36 months of age, unless known to have been exposed non-perinatally.
• Jaundice, **OR**
• Peak elevated total bilirubin ≥ 3.0 mg/dL, **OR**
• Peak elevated ALT ≥ 200 IU/L
AND
The absence of a more likely diagnosis (which may include evidence of acute liver disease due to other causes or advanced liver disease due to pre-existing chronic Hepatitis C virus (HCV) infection or other causes, such as alcohol exposure, other viral hepatitis, hemochromatosis, etc.)
Laboratory Criteria
Confirmatory Laboratory Evidence • Positive hepatitis C virus detection test: Nucleic acid test (NAT) for HCV RNA positive (including qualitative, quantitative, or genotype testing), **OR** • A positive test indicating presence of hepatitis C viral antigen(s) (HCV antigen)
Presumptive laboratory evidence: • A positive test for antibodies to hepatitis C virus (anti-HCV)

https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#section1

Rates of death with hepatitis C virus infection listed as a cause of death



Color Key	Death/100,000 Population	State or Jurisdiction
	0.00–2.34	IL, DE, CT, NH, NJ, ME, NY, MA, MI, UT, ND
	2.35–2.65	IA, GA, PA, MO, WI, NE, IN, VA, HI, NC
	2.66–3.50	AL, NV, SD, MN, OH, FL, SC, AZ, AR, RI
	3.51–5.54	KS, MD, ID, MS, TX, WA, CA, VT, AK, MT
	5.55–10.28	LA, WV, TN, CO, KY, WY, NM, OR, DC, OK

- Globally an estimated 70 million people are infected with HCV contributing to around 400,000 deaths annually.
- An estimated 2.4 million people in the United States were living with hepatitis C during 2013–2016
- During 2020, 64% of newly reported chronic HCV cases occurred among men
- In 2018, a total of 15,713 U.S. death certificates had hepatitis C recorded as an underlying or contributing cause of death. This number is considered a conservative estimate; data indicate that most people who die from hepatitis C lack documentation of HCV infection on their death certificates.
- Chronic hepatitis C affects multiple generations with infections highest among two age groups: 20 – 39 and 55 – 70 years.

Hepatitis C Infection - Risks and Screening

The following people are at increased risk for HCV
• People with HIV infection
• Current or former people who use injection drugs, including those who injected only once many years ago
• People with selected medical conditions, including those who ever received maintenance hemodialysis
• Recipients of transfusions or organ transplants prior to 1992[1] and people who were notified that they received blood from a donor who later tested positive for HCV infection
• People who received clotting factor concentrates produced before 1987[2]
• Health care, emergency medical, and public safety personnel after needle sticks, sharps, or mucosal exposures to HCV-positive blood
• Children born to mothers with HCV infection

1. Before 1992 (the year that blood screening became available), blood transfusion was a leading cause of hepatitis C virus transmission
2. Before 1987 (the year of viral inactivation methods were introduced), most recipients of clotting factor concentrates developed non-A, non-B hepatitis following their initial exposure.

CDC HCV Screening Recommendations
CDC now recommends universal hepatitis C screening for all U.S. adults and all pregnant women during every pregnancy, except in settings where the prevalence of HCV infection is <0.1%.
All adults aged 18 years and older
All pregnant women during each pregnancy
People who ever injected drugs and shared needles, syringes, or other drug preparation equipment, including those who injected once or a few times many years ago
People with HIV
People who have ever received maintenance hemodialysis
People with persistently abnormal ALT levels
People who received clotting factor concentrates produced before 1987[2]
People who received a transfusion of blood or blood components before July 1992[1]
People who received an organ transplant before July 1992[1]
People who were notified that they received blood from a donor who later tested positive for HCV
Health care, emergency medical, and public safety personnel after needle sticks, sharps, or mucosal exposures to HCV-positive blood
Children born to mothers with HCV infection
Any person who requests hepatitis C testing

https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#section1

HCV Infection – Signs and Symptoms

More than half of people who become infected with HCV will develop chronic infection.

HCV Infection Signs and Symptoms
People with newly acquired HCV infection usually are asymptomatic or have mild symptoms that are unlikely to prompt a visit to a health-care professional. When symptoms do occur, they can include:
• Fever
• Fatigue
• Dark urine
• Clay-colored stools
• Abdominal pain
• Loss of appetite
• Nausea
• Vomiting
• Joint pain
• Jaundice
In those people who do develop symptoms, the average period from exposure to symptom onset is 2–12 weeks (range: 2–26 weeks)

Signs and symptoms of chronic HCV infection

- Most people with chronic HCV infection are asymptomatic or have non-specific symptoms such as chronic fatigue and depression.
- Many eventually develop chronic liver disease, which can range from mild to severe, including cirrhosis and liver cancer.
- Chronic liver disease in HCV-infected people is usually insidious, progressing slowly without any signs or symptoms for several decades.
- In fact, HCV infection is often not recognized until asymptomatic people are identified as HCV-positive when screened for blood donation or when elevated alanine aminotransferase (ALT, a liver enzyme) levels are detected during routine examinations.

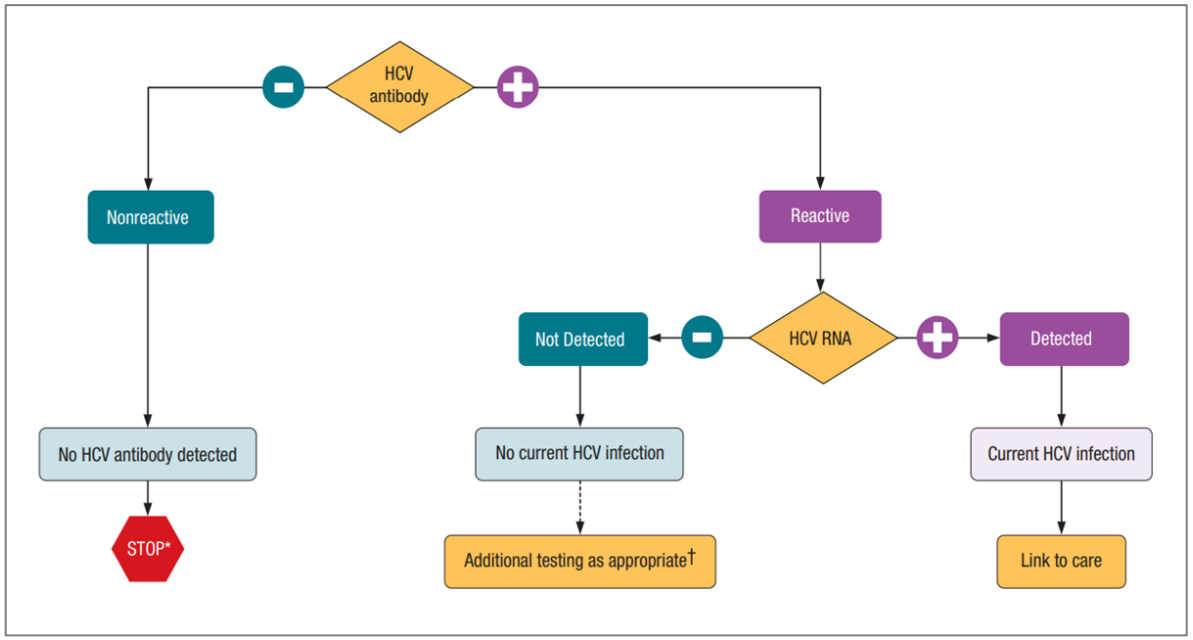
Progression to Cirrhosis

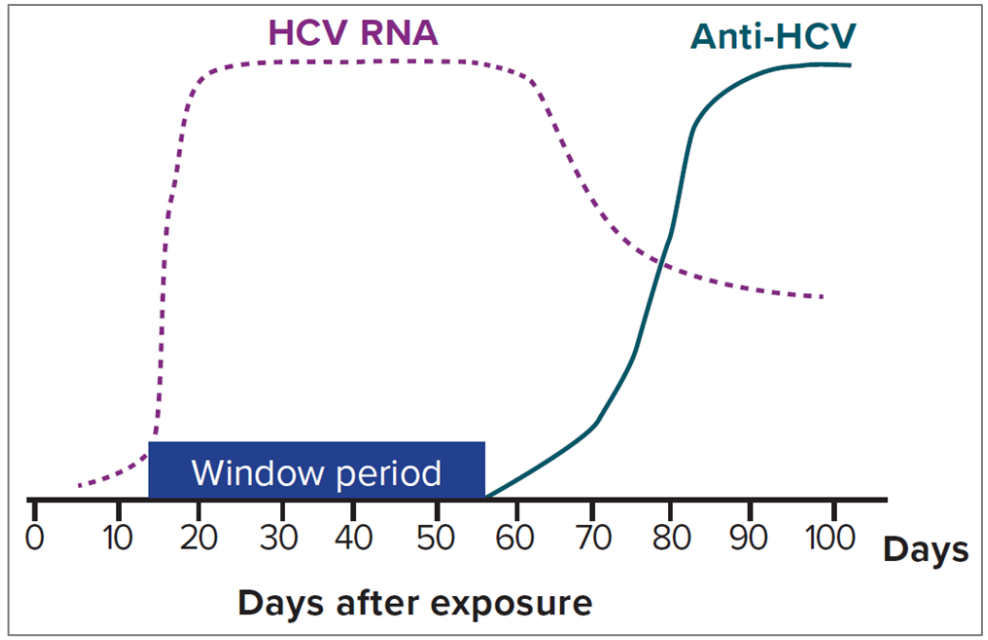
Rates of progression to cirrhosis are increased in the presence of a variety of factors, including:

- Being male
- Being age >50 years
- Consuming alcohol
- Having nonalcoholic fatty liver disease, HBV, or HIV coinfection
- Receiving immunosuppressive therapy

https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#section1

Recommended Testing Sequence for Identifying Current HCV Infection





- For diagnosis of current initial HCV infection, begin with HCV-antibody testing.
- For recurrent HCV infection, begin with HCV-RNA testing.
- 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 should be performed.
- For persons who are immunocompromised, testing for HCV RNA should be performed.
- 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.

https://www.cdc.gov/hepatitis/statistics/surveillanceguidance/HepatitisC.htm

Interpretation of Results of Tests for Hepatitis C Virus (HCV) Infection and Further Actions

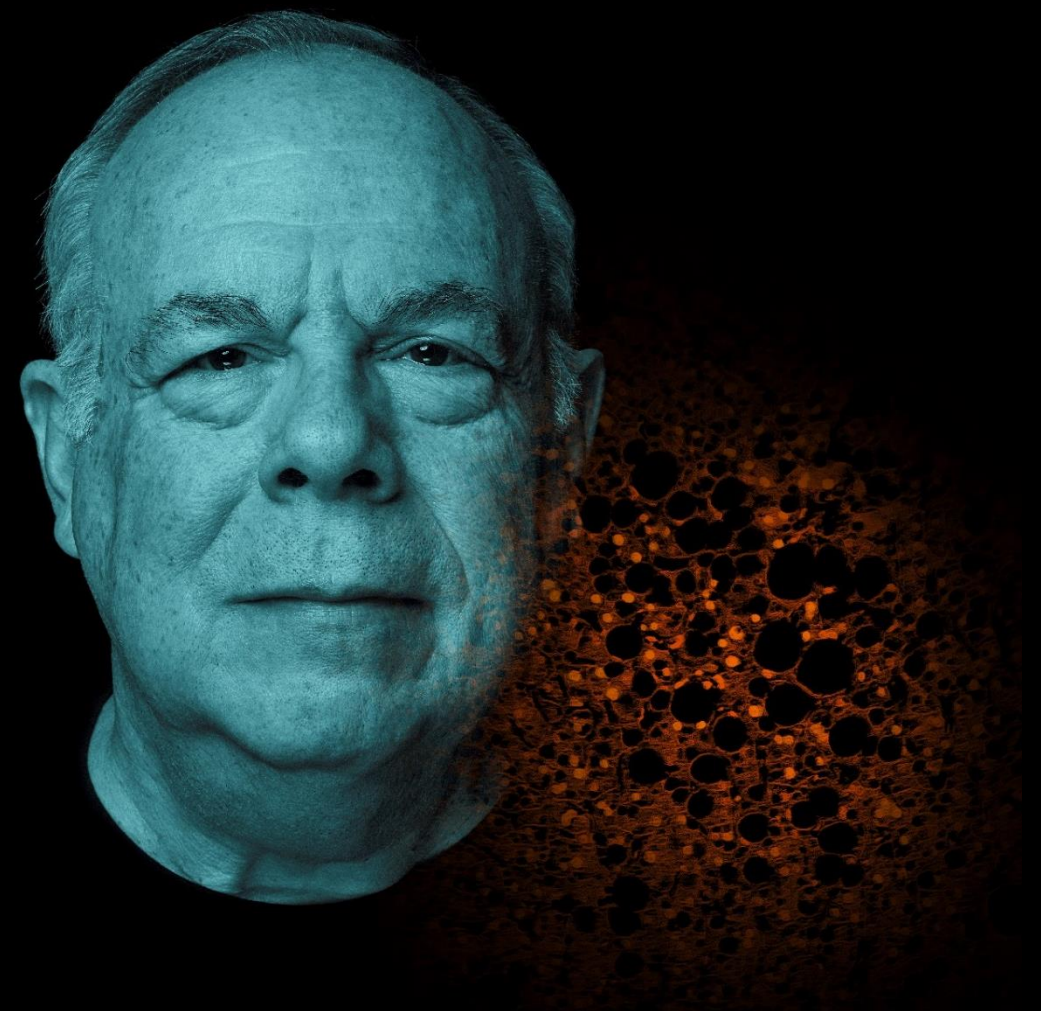
Test Result	Interpretation	Further Action
HCV Antibody **Nonreactive**	No HCV antibody detected	Sample can be reported as nonreactive for HCV antibody. No further action required. If recent exposure in person tested is suspected, test for HCV RNA.[1]
HCV Antibody **Reactive**	Presumptive HCV infection	A repeatedly reactive result is consistent with current HCV infection, or past HCV infection that has resolved, or biologic false positivity for HCV antibody. Test for HCV RNA to identify current infection.
HCV Antibody **Reactive** HCV RNA **Detected**	Current HCV infection	Provide person tested with appropriate counseling and link person tested to care and treatment.[2]
HCV Antibody **Reactive** HCV RNA **Not Detected**	No current HCV infection	No further action required in most cases. If distinction between true positivity and biologic false positivity for HCV antibody is desired, and if sample is repeatedly reactive in the initial test, test with another HCV antibody assay. In certain situations,[3] follow up with HCV RNA testing and appropriate counseling.

1. If HCV RNA testing is not feasible and person tested is not immunocompromised, do follow-up testing for HCV antibody to demonstrate seroconversion. If the person tested is immunocompromised, consider testing for HCV RNA.
2. It is recommended before initiating antiviral therapy to retest for HCV RNA in a subsequent blood sample to confirm HCV RNA positivity.
3. If the person tested is suspected of having 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.

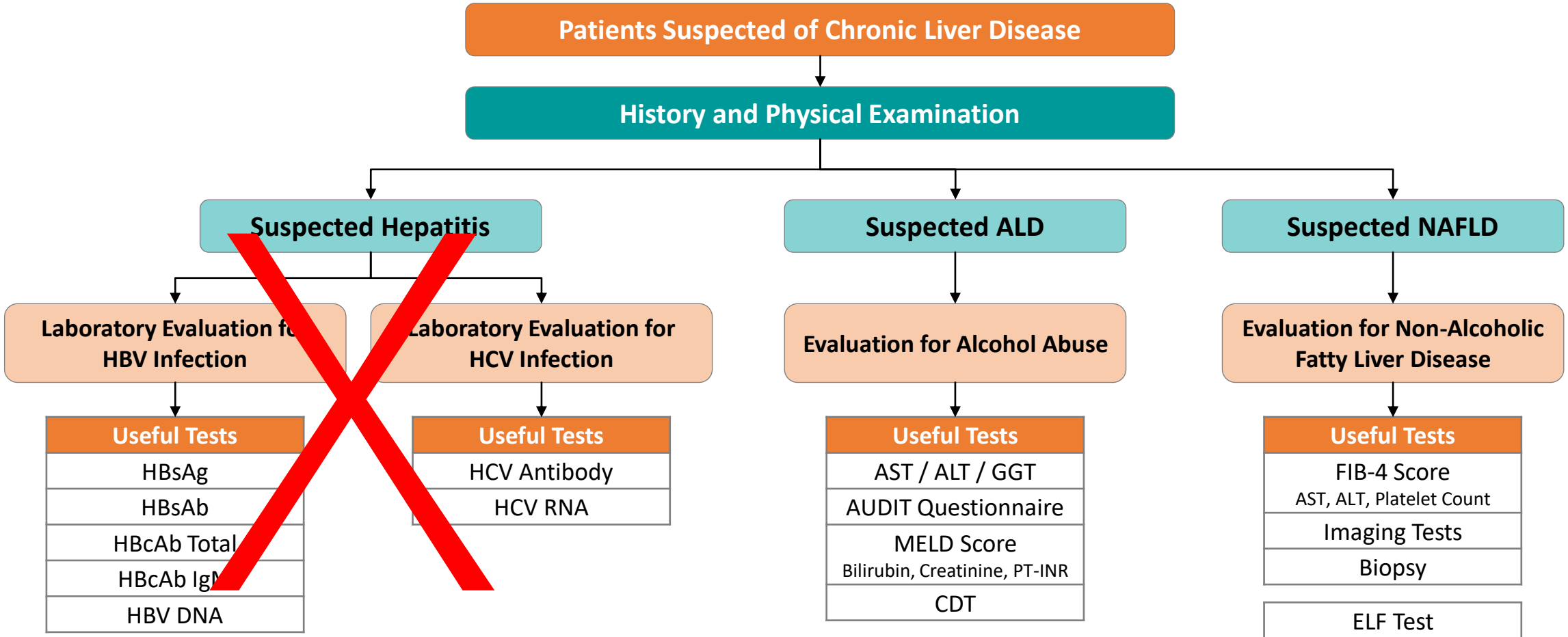
https://www.cdc.gov/Hepatitis/HCV/PDFs/hcv_graph.pdf

Chronic Liver Disease

Alcoholic Liver Disease



Some Common Causes of Chronic Liver Disease



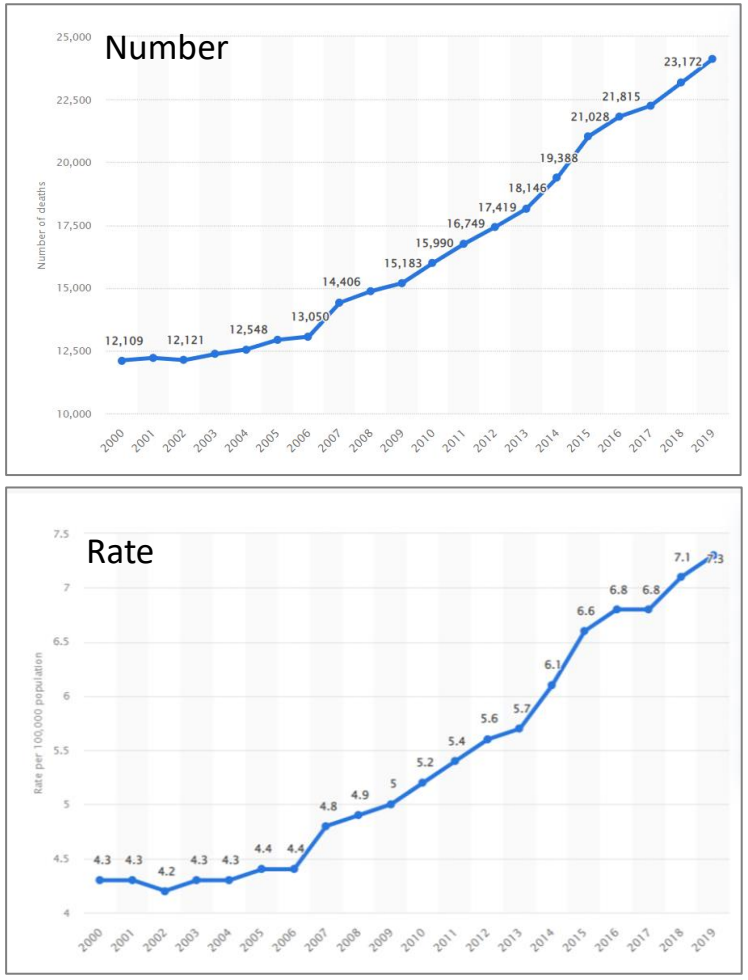
AUDIT: Alcohol Use Inventory Test
MELD: Model for End-Stage Liver Disease
CDT: Carbohydrate Deficient Transferrin

FIB-4: Fibrosis-4 Score
ELF: Enhanced Liver Fibrosis

Natural History of Alcohol-Associated Liver Disease

SIEMENS Healthineers

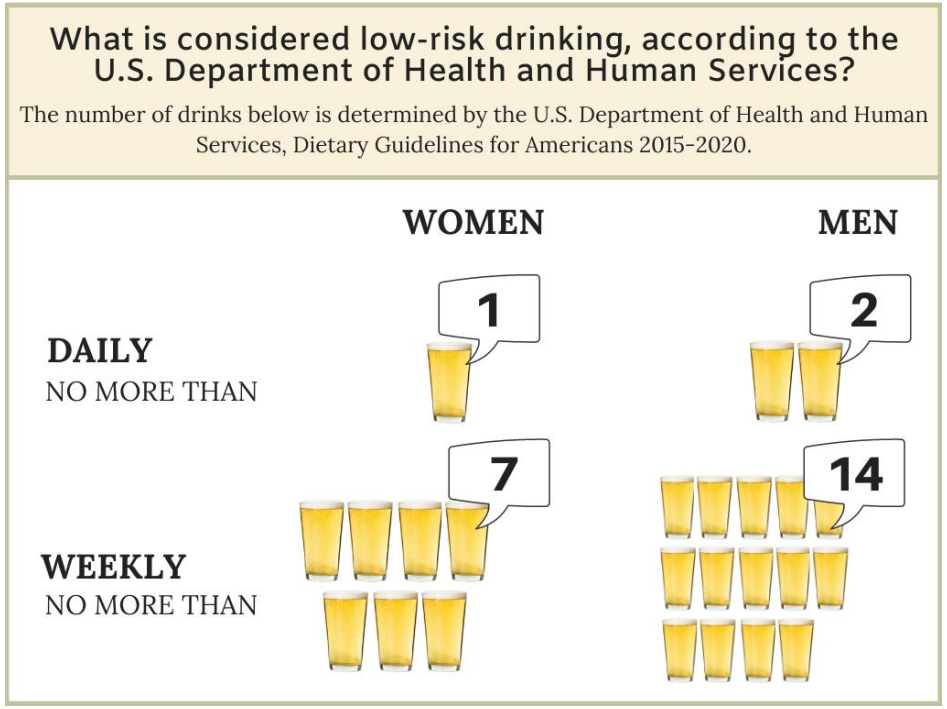
Number and Rate of alcohol-related liver cirrhosis deaths in the U.S. from 2000-2019



- Heavy alcohol consumption, which is defined as the consumption of >40g of pure alcohol per day over a sustained period, is a major cause of mortality and morbidity.
- Alcohol is one of the most common causes of liver diseases worldwide and causes a wide spectrum of direct liver injury ranging from steatosis, alcoholic hepatitis, cirrhosis and hepatocellular carcinoma.
- One-quarter of the global deaths due to cirrhosis in 2019 were associated with alcohol.
- Liver cancer is now the third-leading cause of cancer death worldwide. In 2019, alcohol was associated with an estimated 19% of deaths from liver cancer globally.
- These trends are projected to continue to increase.

https://www.statista.com/statistics/827488/alcohol-related-liver-cirrhosis-death-numbers-us-by-year/

Alcohol Consumption Guidelines



The U.S. Dietary Guidelines for American adults recommends that if alcohol is consumed, it should only be consumed in moderation — up to 1 drink per day for women and 2 drinks per day for men. This is not intended as an average over several days, but rather the amount consumed in any single day.

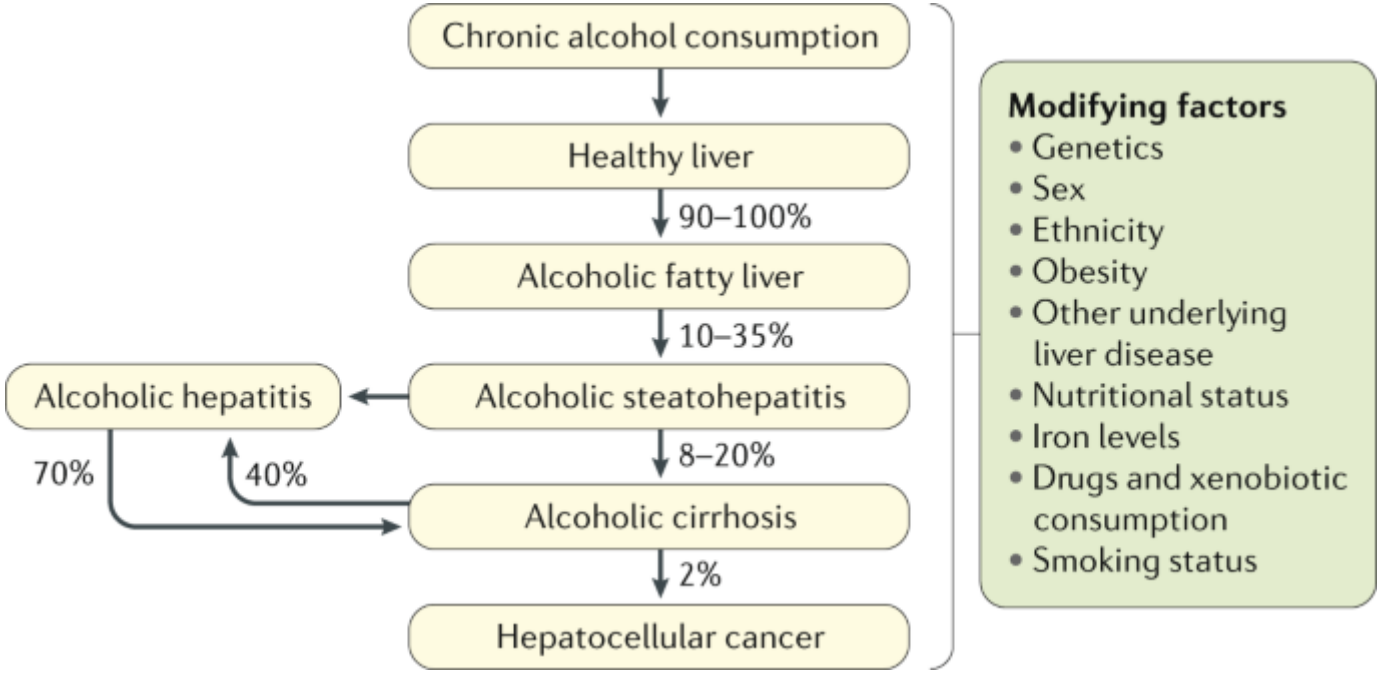
No amount of alcohol consumption is safe or without risk. The U.S. government, however, defines and recommends levels of alcohol consumption that have been found to generally carry only low to moderate risk for the general population. It is never recommended that individuals who do not drink alcohol begin to drink alcohol based on these guidelines. Women should be aware that even moderate drinking may increase the risk of breast cancer.

https://www.recoveryanswers.org/resource/guide-drinking-levels/

Progression of Alcohol Related Liver Disease

SIEMENS Healthineers

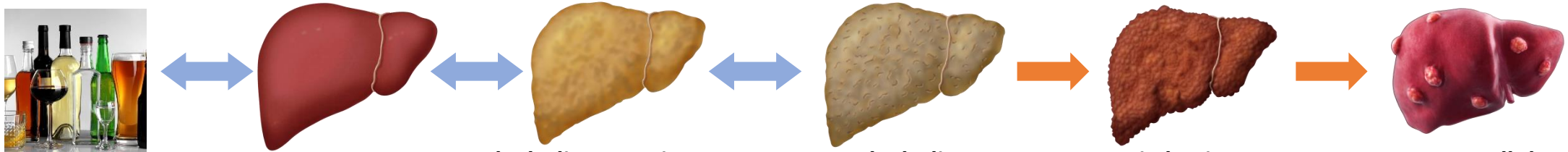
Alcoholic Liver Disease (ALD) or Alcohol-Related Liver Disease (ARLD) refers to liver damage caused by excess alcohol intake.



Symptoms of ALD can include:

- Feeling sick
- Weight loss
- Loss of appetite
- Jaundice
- Edema / ascites
- Confusion or drowsiness
- Vomiting blood or bloody stools

ALD does not usually cause any symptoms until the liver has been severely damaged which means ALD is frequently diagnosed during tests for other conditions, or at a stage of advanced liver damage



Healthy Liver

Alcoholic Fatty Liver Disease (AFLD)
Fat accumulation > 5%

Alcoholic Steatohepatitis (ASH)

Cirrhosis

Hepatocellular Carcinoma (HCC)
Liver Failure / Death

https://www.nature.com/articles/s41572-018-0014-7

Diagnostic Criteria for Alcohol Use Disorder (AUD)

SIEMENS Healthineers

Your Experience in the Past Year

1. Alcohol is often taken in larger amounts or over a longer period than intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control alcohol use.
3. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects.
4. Craving, or a strong desire or urge to use alcohol.
5. Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol.
7. Important social, occupational, or recreational activities are given up or reduced because of alcohol use.
8. Recurrent alcohol use in situations in which it is physically hazardous.
9. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.
10. Tolerance, defined as either of the following:
    A Need for markedly increased amounts of alcohol to achieve intoxication or desired effect; or
    B Markedly diminished effect with continued use of the same amount of alcohol.
11. Withdrawal, as manifested by either of the following:
    A The characteristic alcohol withdrawal syndrome; or
    B Alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms.

The presence of at least 2 of these symptoms indicates an AUD:
- **Mild:** 2-3 symptoms
- **Moderate:** 4-5 symptoms
- **Severe:** 6 or more symptoms

- The NIAAA, National Institute on Alcohol Abuse and Alcoholism, recommends a one-question initial screen: “How many times in the past year have you had 5 or more drinks in a day (for men) or 4 or more drinks in a day (for women)?”
- This is the NIAAA definition of binge drinking (five drinks in men; four in women over 2 hours).
- If the patient reports even a single episode, performing the Alcohol Use Disorders Inventory Test (AUDIT) is recommended. The AUDIT is used widely and is recommended by the USPSTF (US Preventive Services Task Force).
- The AUDIT-C (concise) version as a more efficient means of screening for problem alcohol use, but this shorter form does not provide information on more severe alcohol use problems.

AUDIT-C Screening Questions

1. How often do you have a drink containing alcohol?
   Never (0) Monthly or less (1) Two to four time per month (2) Two to three times per week (3) Four or more times per week (4)
2. How many drinks containing alcohol do you have on a typical day when you are drinking?
   1 or 2 (0) 3 or 4 (1) 5 or 6 (2) 7 to 9 (3) 10 or more (4)
3. How often do you have six or more drinks on one occasion?
   Never (0) Less than monthly (1) Monthly (2) two to three times per week (3) Four or more times per week (4)

The maximum score is 12. A score ≥4 identifies 86% of men who drink too much or have AUD. A score of >2 identifies 84% of women who drink more than is safe or have AUD.

PRACTICE GUIDANCE | Hepatology, VOL. 71, NO. 1, 2020

The MELD Score (Model for End-Stage Liver Disease)

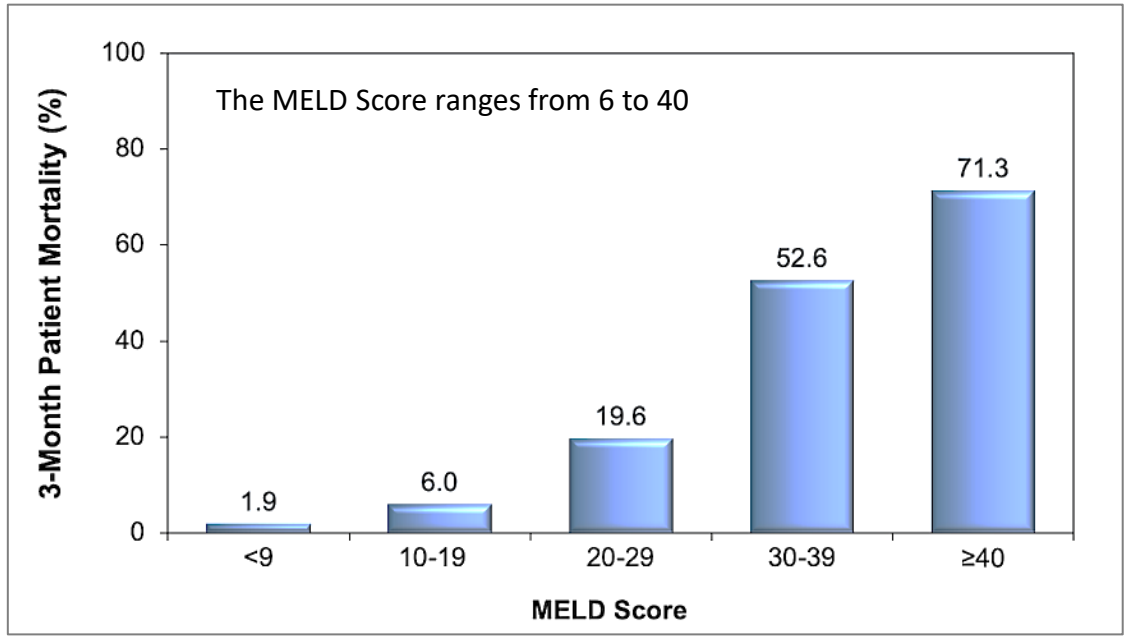
The MELD Score has been validated as predictor of survival in patients with cirrhosis, alcoholic hepatitis, acute liver failure, and in patients with acute hepatitis. The MELD score, which estimates the survival probability of a patient with end-stage liver disease, is based on three commonly obtained laboratory tests: serum bilirubin, serum creatinine, and PT-INR.

Model for End-Stage Liver Disease (MELD) Score

MELD = 3.78 x $\log_e$ serum bilirubin (mg/dL) +
11.20 x $\log_e$ INR +
9.57 x $\log_e$ serum creatinine (mg/dL) +
6.43 (constant for liver disease etiology)

NOTES:

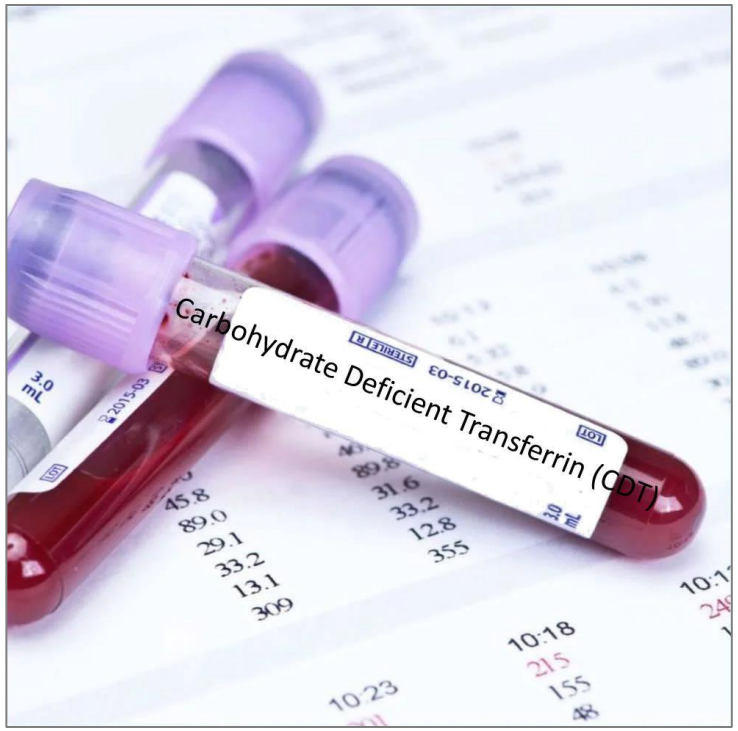
- If the patient has been dialyzed twice within the last 7 days, then the value for serum creatinine used should be 4.0
- Any value less than one is given a value of 1 (i.e. if bilirubin is 0.8, a value of 1.0 is used) to prevent the occurrence of scores below 0 (the natural logarithm of 1 is 0, and any value below 1 would yield a negative result)



https://www.hepatitisc.uw.edu/pdf/evaluation-staging-monitoring/evaluation-prognosis-cirrhosis/core-concept/all

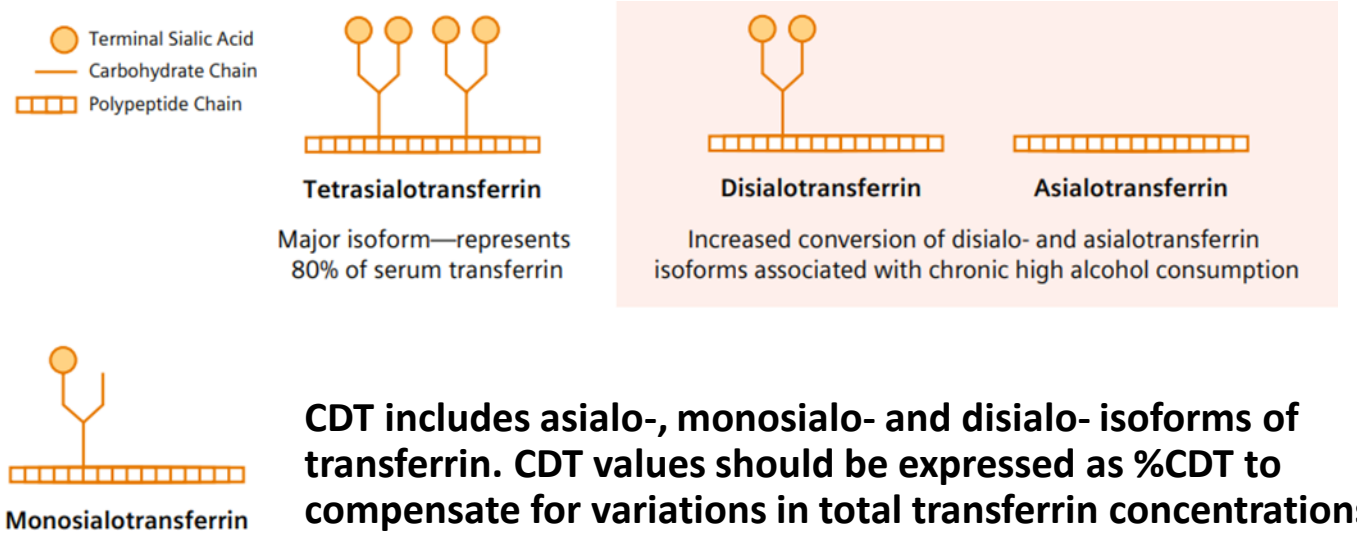
What is Carbohydrate Deficient Transferrin (CDT)?

- The formation of CDT is directly proportional to alcohol intake: ethanol (or its metabolites) appears to inhibit sialyl transferase which is the enzyme responsible for addition of the carbohydrate side-chains and induce sialidase the enzyme that removes the terminal sialic acid residues from the side-chains.
- CDT testing can be an effective tool for the early diagnosis of chronic alcohol misuse, for the detection of patients addicted to alcohol, and for the follow-up of treatment and diagnosis of alcohol relapse.
- CDT quantitation is useful in detecting abusive alcohol consumption (defined as ethanol consumption >40 mL per day for at least two weeks) and a more specific marker for alcohol exposure than other available markers, such as GGT.
- It enables early detection of alcohol misuses and follow-up of alcoholic patients.
- CDT has been shown to be more useful than other widely available biochemical tests for alcohol abuse.



What is Carbohydrate Deficient Transferrin (CDT)?

- Structurally, transferrin is a polypeptide with two N-linked polysaccharide chains, branched with sialic acid residues.
- According to the level of sialylation, there are various forms of transferrin, tetrasialotransferrin being predominant.
- The proportion of transferrin with zero, one or two sialic acid chains increases with alcohol to the so-called carbohydrate deficient transferrin.
- CDT is not affected by liver diseases other than those induced by alcohol abuse (except for biliary cirrhosis and chronic active hepatitis).

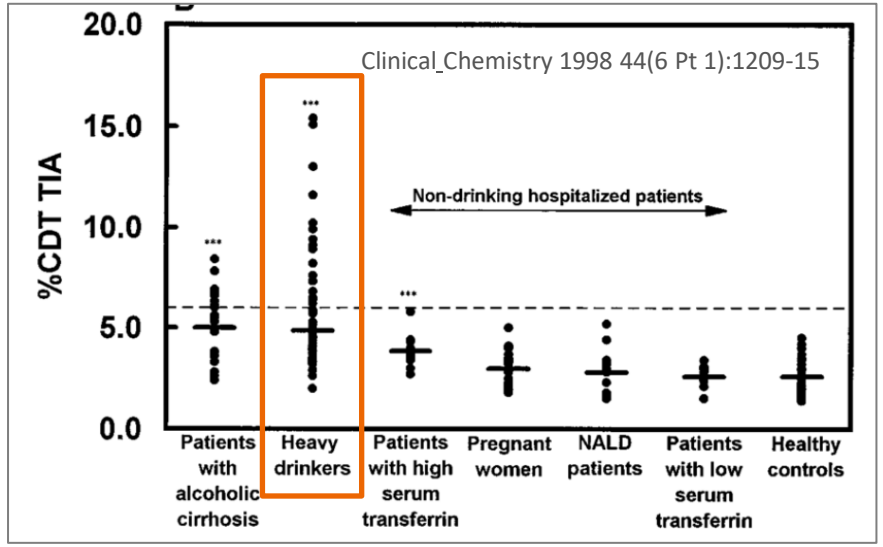


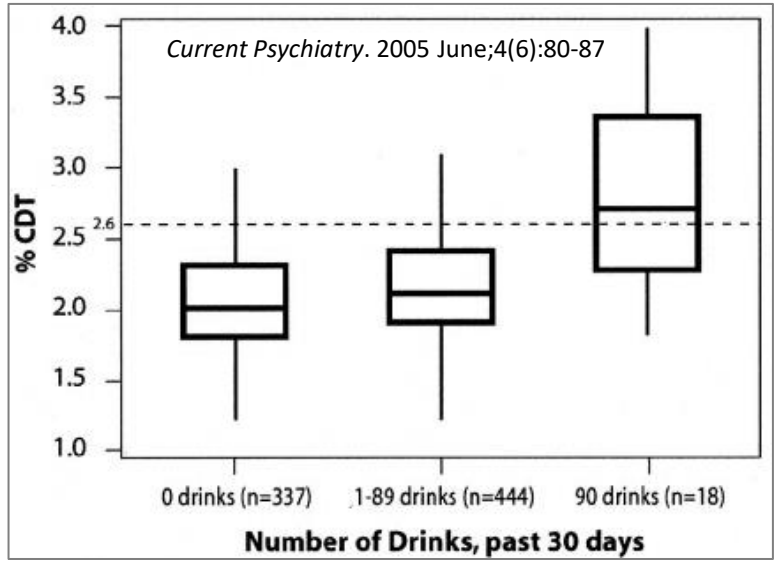
CDT includes asialo-, monosialo- and disialo- isoforms of transferrin. CDT values should be expressed as %CDT to compensate for variations in total transferrin concentrations.

Figure Illustration of different human transferrin glycoforms. Tetrasialotransferrin is the major isoform representing approximately 80% of serum transferrin in healthy adults. Heavy alcohol consumption causes an increase of disialo- and asialotransferrin isoforms.

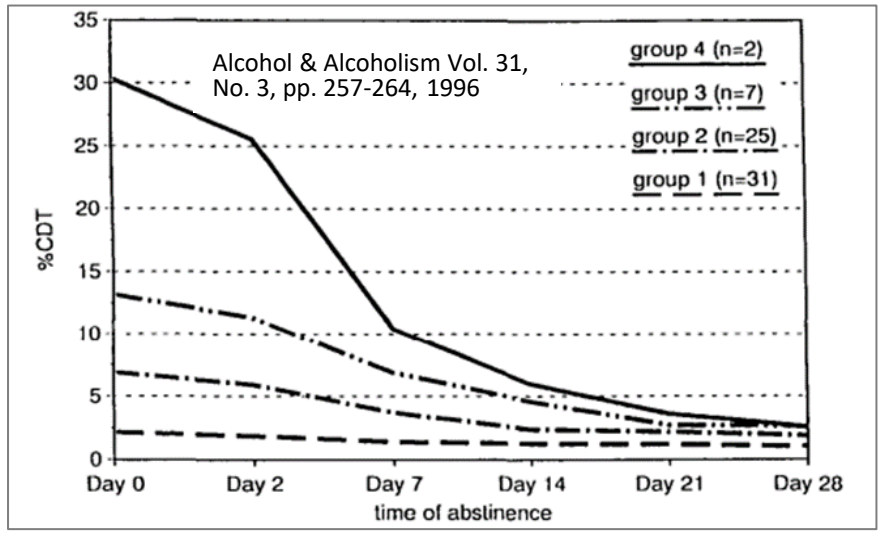
Clinical Performance of CDT

%CDT is elevated in heavy drinkers, independent of total transferrin level or non-alcoholic liver disease

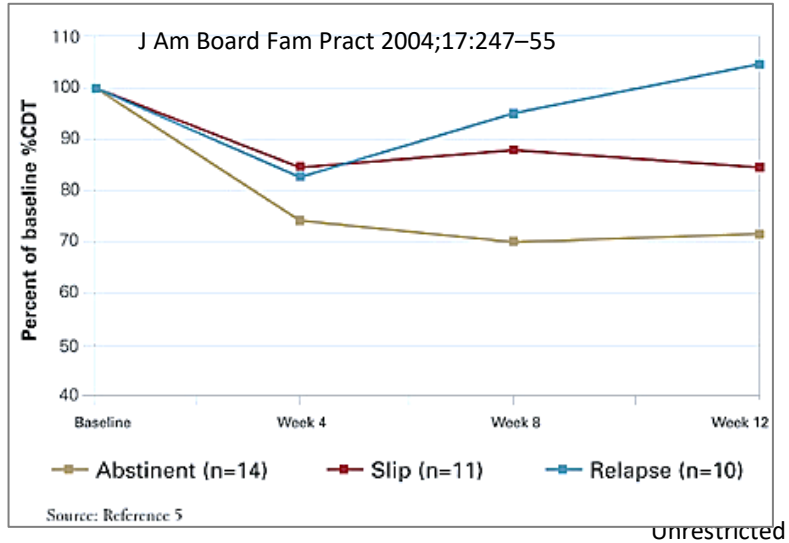




%CDT declined following abstinence from alcohol



%CDT increases after resuming alcohol use



Markers of Chronic Alcohol Consumption

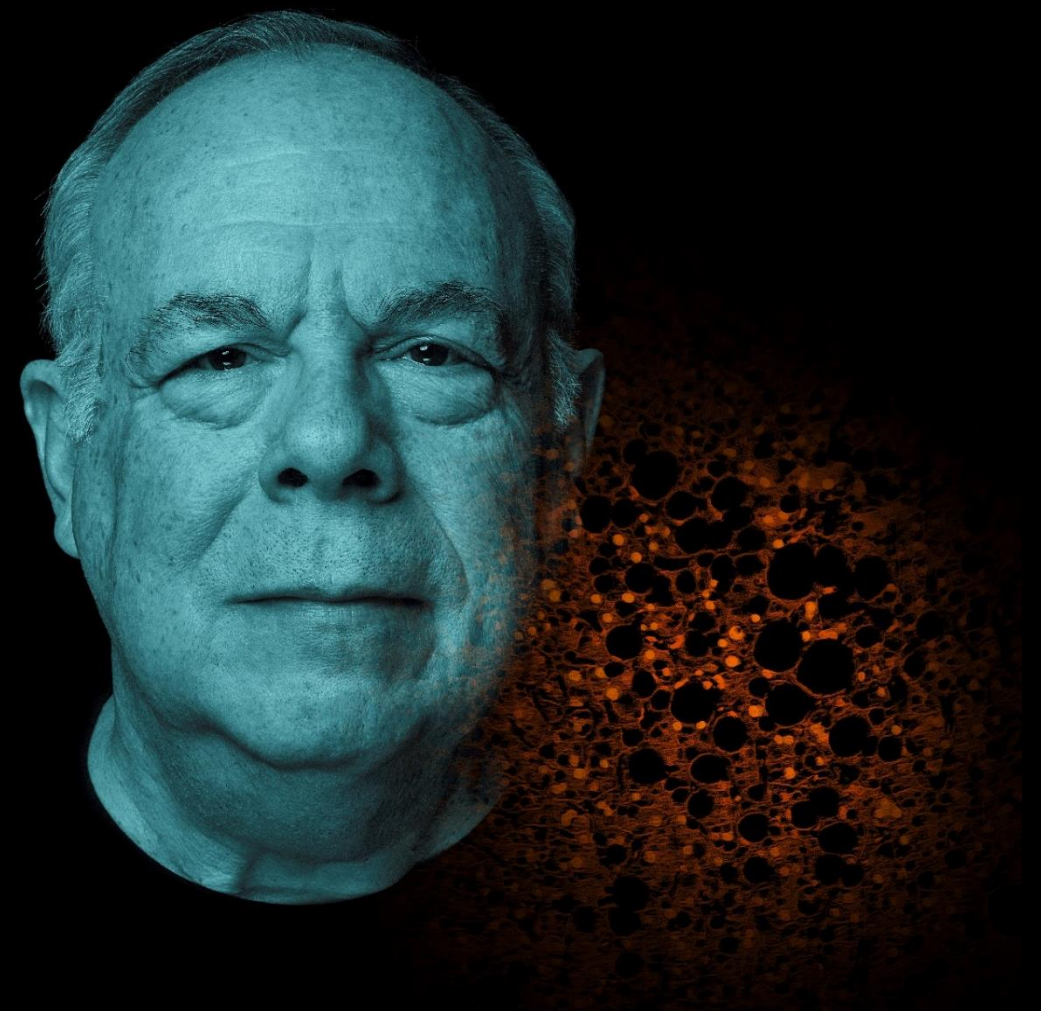
Biomarker	Strength	Possible Weakness
GGT	• Widely used • Standardized	• Low specificity (elevated in all types of liver disease, obesity, or with certain drugs) • Normalization only after 4-6 weeks of abstinence
MCV	• Liver-independent • Reflects toxic effects of alcohol	• Low sensitivity and specificity • Slow response (red blood cell half-life: 3 months
AST/ALT	• Indicates excessive alcohol consumption	• Insensitive and nonspecific if used without other markers
CDT (increases if alcohol consumption≥60 g/day for several weeks)	• High specificity • Returns to normal after 2-4 weeks	• Different technologies for quantification (IFCC standardization in 2018)

GGT: gamma-glutamyl transferase; MCV: mean cellular volume of red blood cells
AST: aspartate aminotransferase; ALT: alanine aminotransferase

Allen AP. Military Medicine. 2003;168:364-367.
Madhubala V, et al. J Clin Diagn Res. 2013;7:197-200.

Chronic Liver Disease

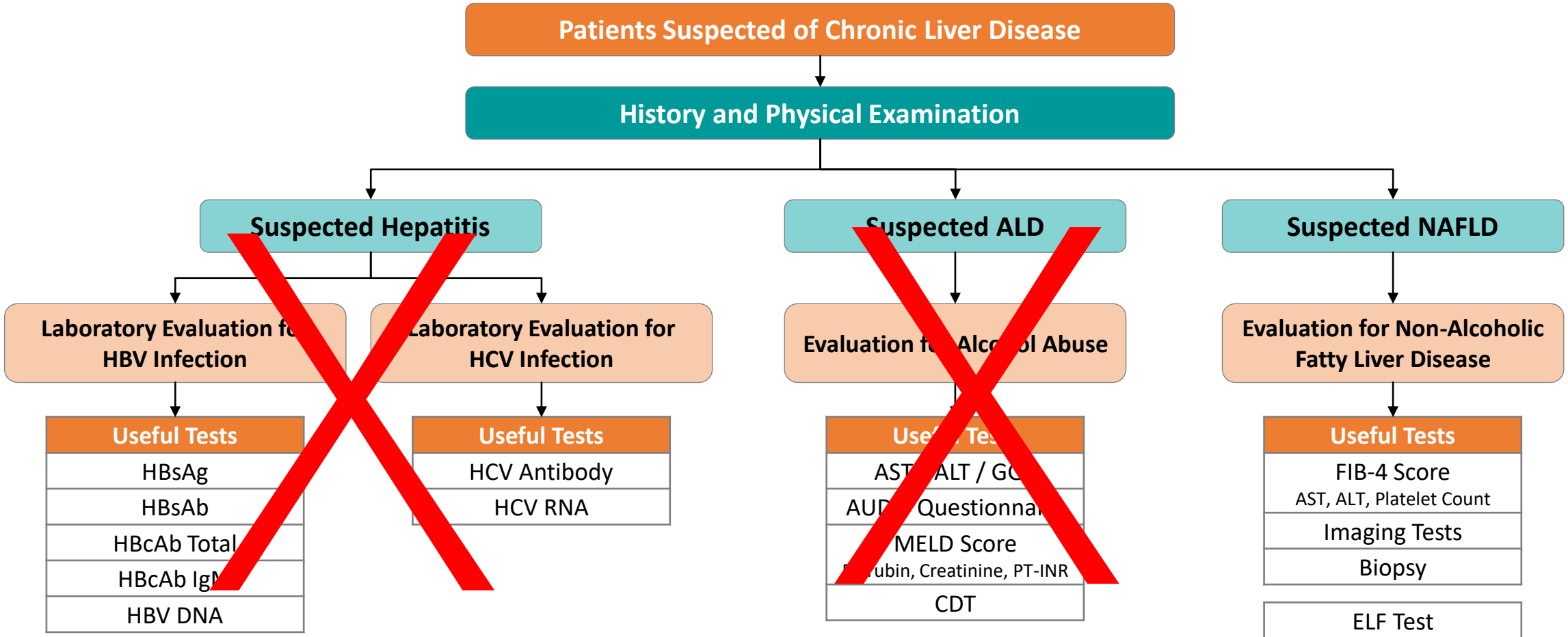
Non-Alcoholic Fatty Liver Disease (NAFLD)



New NAFLD Nomenclature

- **Steatotic Liver Disease or SLD** will now be used to encompass various causes of fat accumulation in the liver.
- **Metabolic Dysfunction-associated Steatotic Liver Disease (MASLD)** will replace non-alcohol related fatty liver disease (NAFLD).
- NASH the more serious form of NAFLD will now be called **Metabolic-associated steatohepatitis (MASH).**
- **Met-ALD** – this is a new name that has been created for people who have MASLD but who also drink alcohol.
- **Cryptogenic SLD** – this is the name used for fatty liver disease when the cause is unknown in people do not have any of the metabolic risk factors.

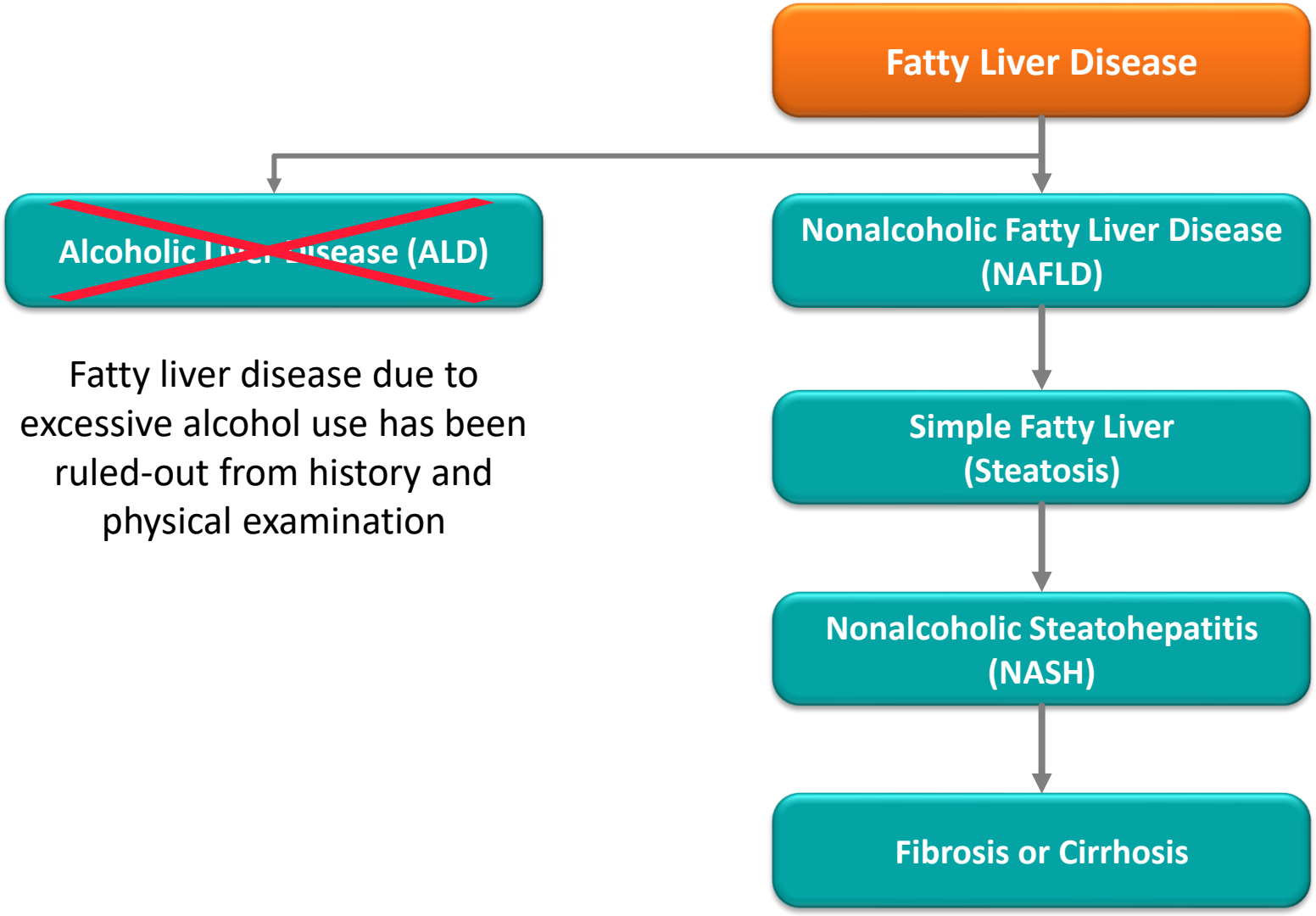
Some Common Causes of Chronic Liver Disease



AUDIT: Alcohol Use Inventory Test
MELD: Model for End-Stage Liver Disease
CDT: Carbohydrate Deficient Transferrin

FIB-4: Fibrosis-4 Score
ELF: Enhanced Liver Fibrosis

Types of Fatty Liver Disease



Fatty liver disease due to excessive alcohol use has been ruled-out from history and physical examination

The accumulation of liver fat in people who drink little or no alcohol. Risk factors include obesity, gastric bypass surgery, high cholesterol, and type 2 diabetes.

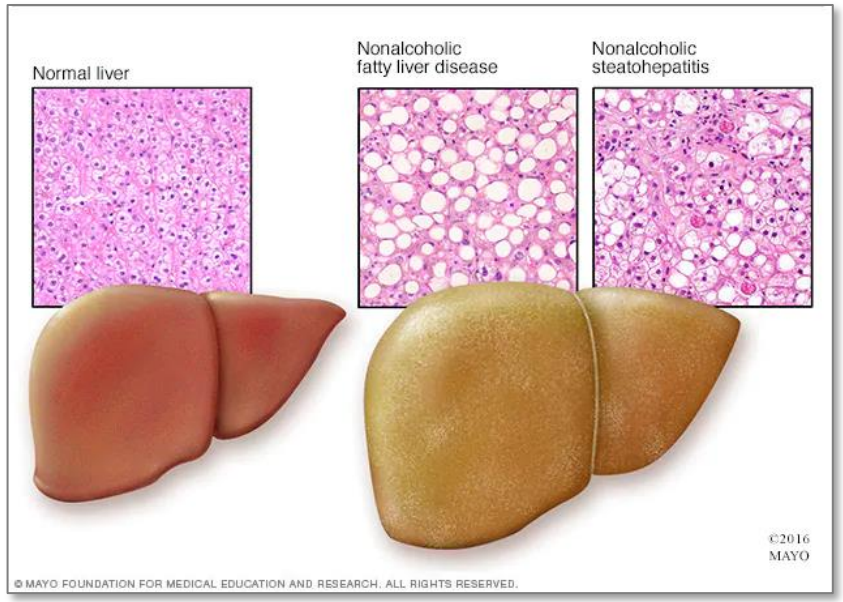
The deposition of fat in the liver without inflammation or cellular damage. Most people with NAFLD have simple fatty liver disease.

This is much more serious condition than a simple fatty liver. NASH is associated with liver inflammation which can cause serious problems such as fibrosis and cirrhosis. About 10-20% of people with NAFLD have NASH.

Fibrosis is the formation of an abnormally large amount of scar tissue in the liver.

Cirrhosis is long-standing scarring of the liver resulting in poor liver function and potentially liver failure.

Introduction



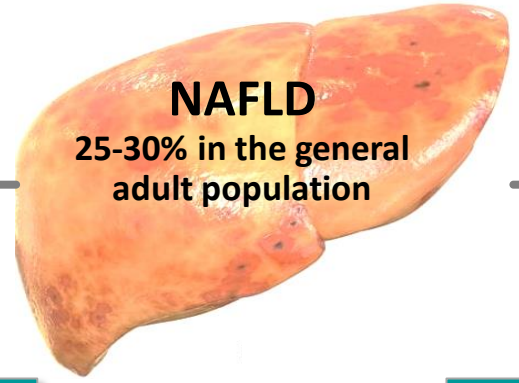
Nonalcoholic fatty liver disease (NAFLD) is an umbrella term for a range of liver conditions affecting people who drink little to no alcohol. As the name implies, the main characteristic of NAFLD is too much fat stored in liver cells.

NAFLD is increasingly common around the world, especially in Western nations. In the United States, it is the most common form of chronic liver disease, affecting about one-quarter of the population.

Some individuals with NAFLD can develop nonalcoholic steatohepatitis (NASH), an aggressive form of fatty liver disease, which is marked by liver inflammation and may progress to advanced scarring (cirrhosis) and liver failure. This damage is similar to the damage caused by heavy alcohol use.

It would be extremely useful to be able to determine which NASH patients with advanced fibrosis are more likely to progress to cirrhosis and more serious clinical conditions which can include complete liver failure and death. The *Enhanced Liver Fibrosis Test* or ELF™ can help physicians with that determination.

Progression of NAFLD



NAFLD
25-30% in the general adult population

- **Simple Steatosis (80-90%)**
  - **Stable Disease**
  - **Non-Cirrhotic HCC (<1%)**
- **NASH (10-20%)**
  - **Fibrosis (40%)**
    - **Cirrhosis (30%)**
      - **Decompensation (5-10%)**
      - **HCC (1-2%)**

HCC = Hepatocellular Carcinoma

AMONG ADULTS IN THE US

25%-30% HAVE **NAFLD**

10%-20% WITH **NAFLD** HAVE **NASH**

30%-40% WITH **NASH** WILL DEVELOP **FIBROSIS**

Hepatic encephalopathy is a nervous system disorder brought on by severe liver disease, toxins build up in the blood which can travel to the brain and affect brain function. People with hepatic encephalopathy may seem confused.

Hepatorenal syndrome represents the end-stage of a sequence of reductions in kidney perfusion induced by increasingly severe hepatic injury.

Variceal bleeding refers to bleeding of varices found throughout the gastrointestinal tract, such as in the esophagus, stomach, and rectum. Varices are dilated blood vessels in the esophagus or stomach caused by portal hypertension.

Decompensated cirrhosis is defined as an acute deterioration in liver function in a patient with cirrhosis and is characterized by jaundice, ascites, **hepatic encephalopathy, hepatorenal syndrome or variceal hemorrhage.**

Noninvasive tests improve care for patients at highest risk of progression to liver-related events

SIEMENS Healthineers

The Challenge: 100 million individuals in the United States are estimated to have NAFLD – which means that not all at-risk patients can undergo liver biopsy[1]

Disease identification starts with recognition of at-risk patients

- >50% of primary care providers **are unaware of noninvasive scoring methods, or the association of NAFLD with CVD mortality or the pathological criteria of NAFLD**.[1]
- Poor disease management is expected to contribute to a **178% increase** in liver deaths by 2030.[2,3]

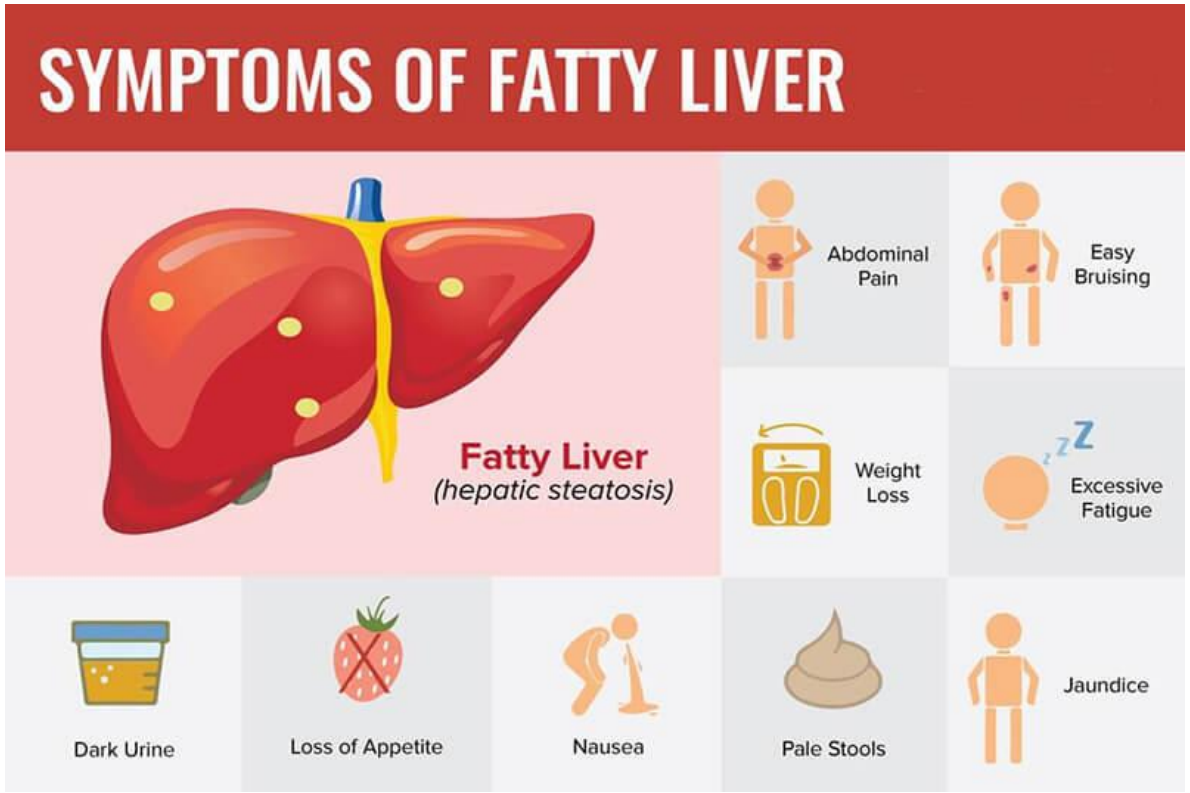
Noninvasive testing can help improve patient outcomes

- Opportunity to manage large patient populations, improve access to care, and allow for more accessible prognostic assessment, **results in better patient health outcomes and lowering direct costs**.[6,7]

1. Younossi ZM, et al. Clin Gastro Hepatol. 2021. DOI:10.1016/j.cgh.2021.06.048
2. Said A, et al. Ann Hepatol. 2013;12(5):758-65.
3. Estes C, et al. Hepatol. 2018;67(1):123-33.
4. Scaglione S, et al. J Clin Gastroenterol. 2015;49:690-6.
5. Wong RJ, et al. J Clin Gastroenterol. 2020 DOI: 10.1097/MCG.0000000000001409
6. Srivastava A, et al. BMC Gastroenterol. 2019; 19:122.
7. Srivastava A, et al. J Hepatol. 2019;71:371-8.

Decompensated cirrhosis is defined as an acute deterioration in liver function in a patient with cirrhosis and is characterized by jaundice, ascites, hepatic encephalopathy, hepatorenal syndrome or variceal hemorrhage.

Symptoms of NAFLD



- NAFLD is known as the **'silent killer'** because it initially does not show any significant symptoms.
- However, some of the symptoms like the enlarged spleen, excess belly fat, high blood pressure, fatigue, pain in the abdomen, high levels of triglyceride and other symptoms, show that the liver is damaged, and fat has accumulated.
- The damaged liver cannot process glucose normally while responding to insulin, resulting in insulin resistance.
- The diagnosis of Non-alcoholic Fatty Liver Disease is made when high levels of fat (>5%) accumulates in a concentrated manner.

https://www.nash24x7.com/non-alcoholic-fatty-liver-disease-causes-symptoms-treatments/

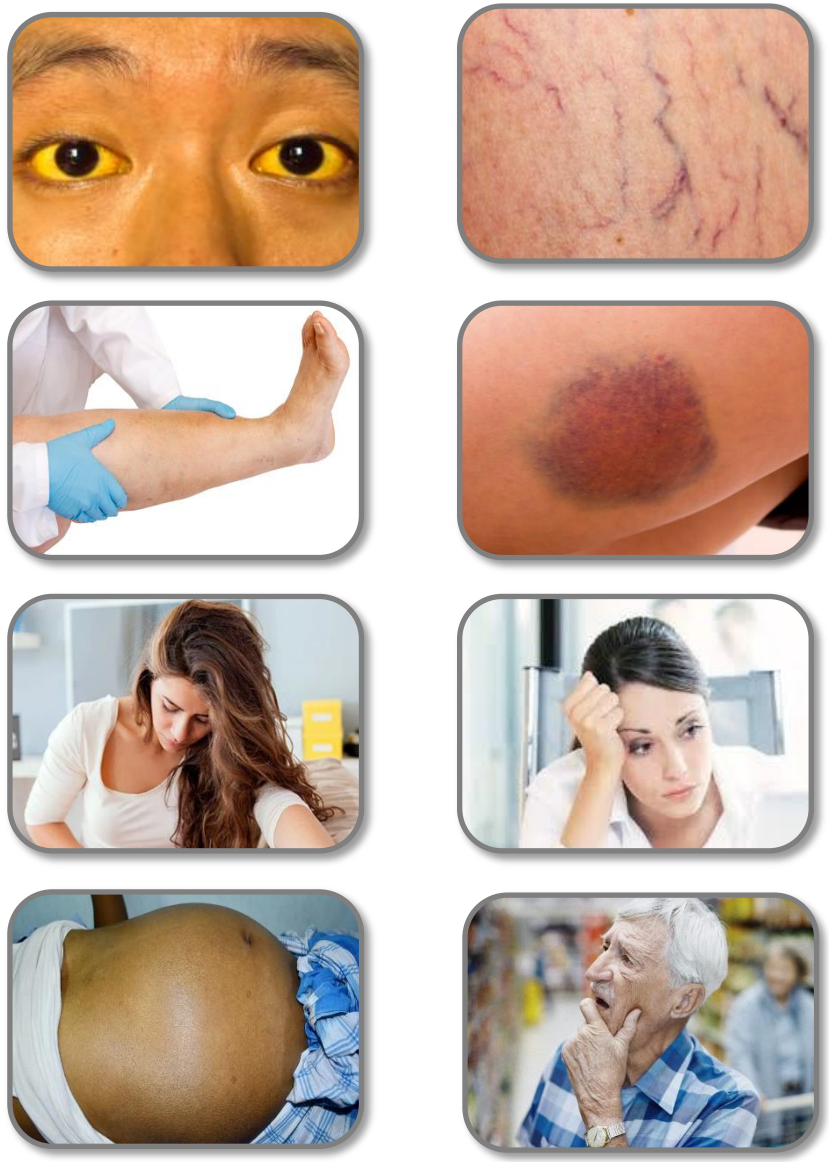
Symptoms of NASH

There are often no outward signs or symptoms associated with NASH. The most common symptoms are:

- Fatigue
- Pain in the upper right abdomen (usually mild)

NASH may lead to cirrhosis of the liver, causing one or more of the following symptoms as the condition progresses:

- Bleeding easily
- Bruising easily
- Itchy skin
- Yellow discoloration in the skin and eyes (Jaundice)
- Fluid accumulation in your abdomen (Ascites)
- Loss of appetite
- Nausea
- Swelling in your legs
- Confusion
- Drowsiness
- Slurred speech
- Spider-like blood vessels on your skin



Prevalence of comorbidities associated with NAFLD and NASH

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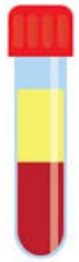
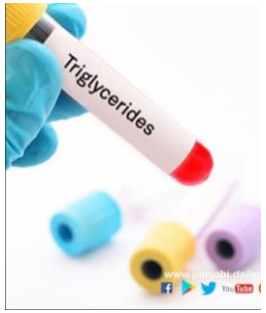
NAFLD is seen as the liver manifestation of metabolic syndrome and associated findings

Disease	Prevalence Estimates, %					
	Obesity (BMI ≥25)	Type 2 Diabetes	Hyperlipidemia	Hypertriglyceridemia	Metabolic Syndrome	Hypertension
NAFLD[a]	37–71%	14–37%	38–77%	55–68%	29–67%	33–67%
NASH[b]	**80%**	**25–54%**	**83%**	**83%**	**70-65%**	**77%**

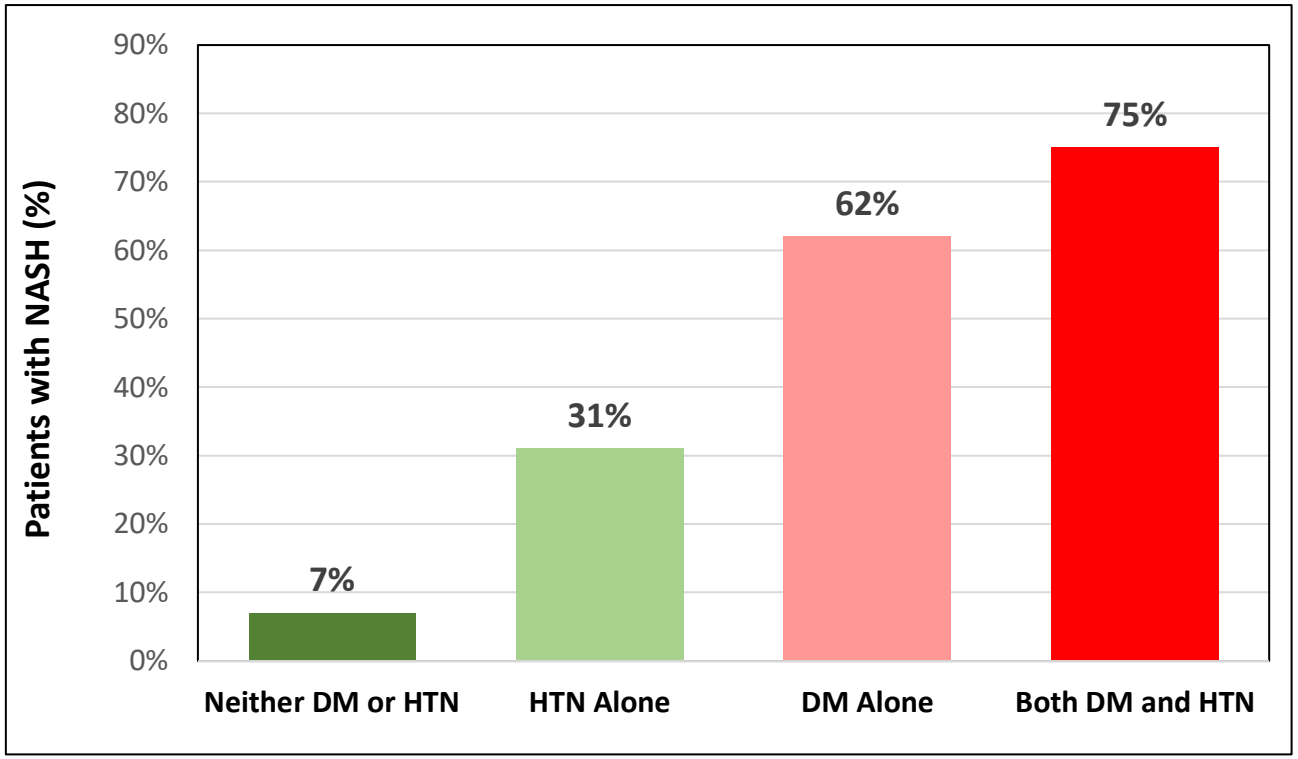


- The prevalence of comorbidity among those with NAFLD is very high, indicating that NAFLD is not a benign disease.
- Among those with NASH, which is the progressive form of the disease, comorbidity prevalence is even higher

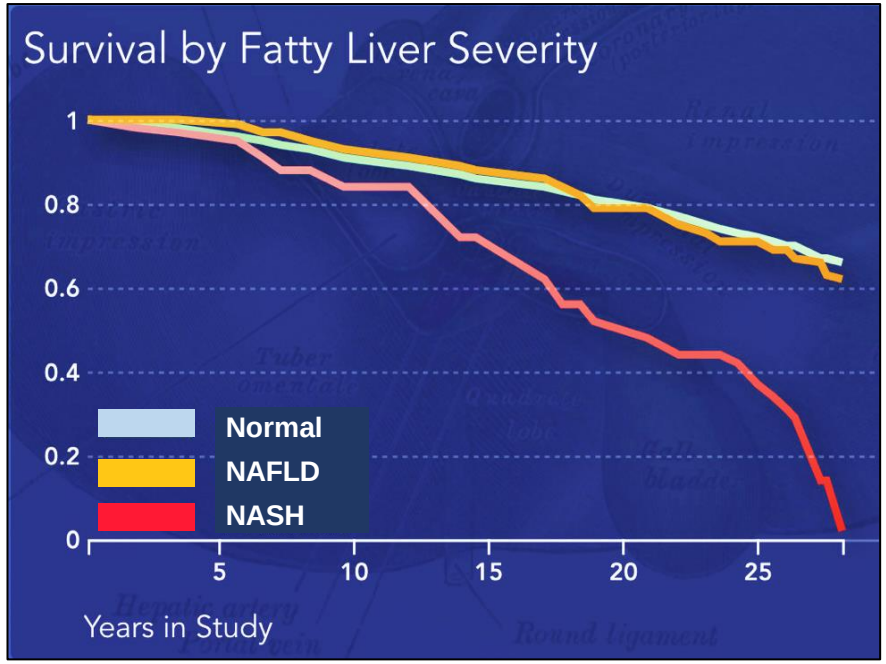
a. Ranges reflect various collection methods, which can include self-reporting, blood test, imaging, ICD code, and a mixture of methods
b. In biopsied patients
Younossi ZM, et al. Hepatology. 2016;64:73-84. Supplementary tables F and G.

Association Between NASH, Type 2 Diabetes (DM), and Hypertension (HTN) in Severely Obese (BMI > 30)



NAFLD vs NASH Mortality

Fatty Liver Disease by itself does not have significantly higher mortality. However, it can lead to NASH, which can be fatal.

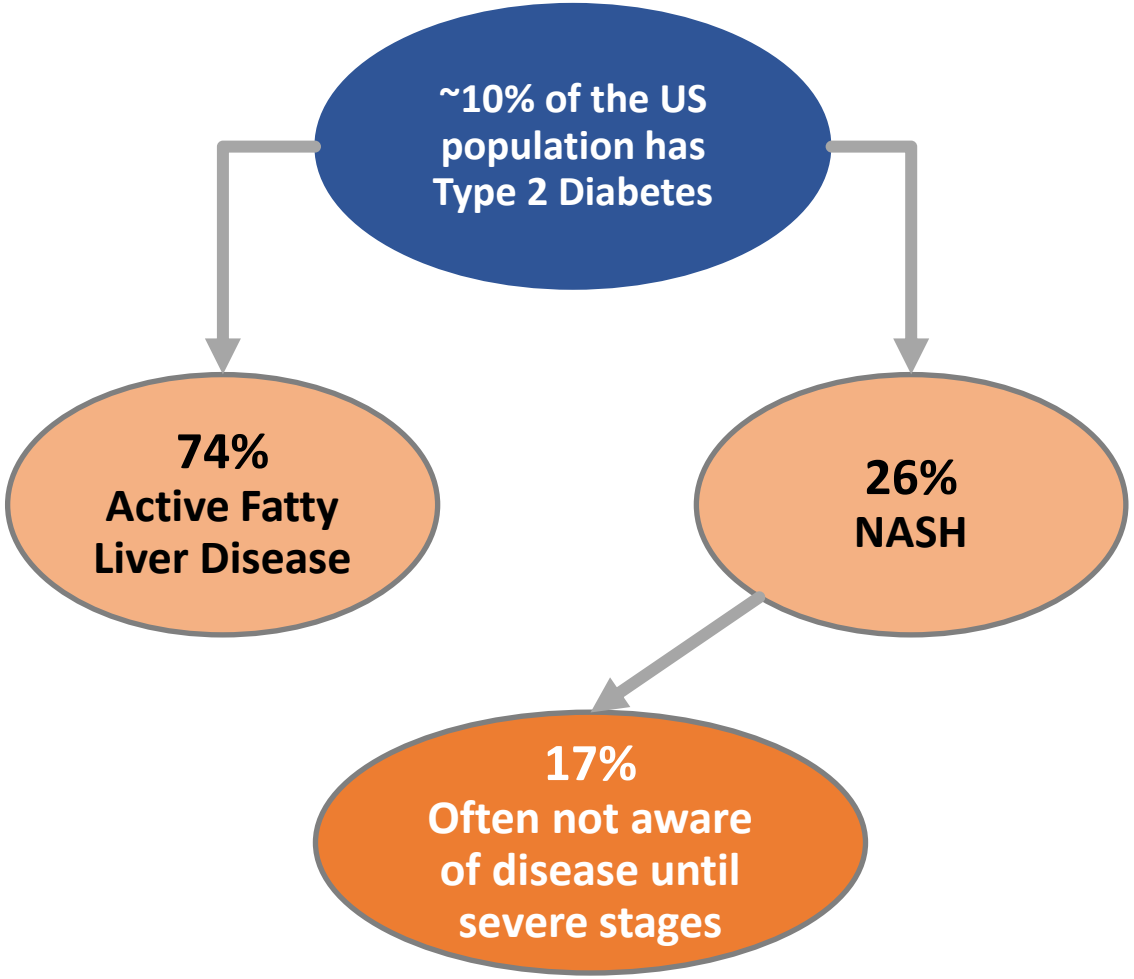


Dixon, JB et al. Gastroenterology 2001; 121: 91-100

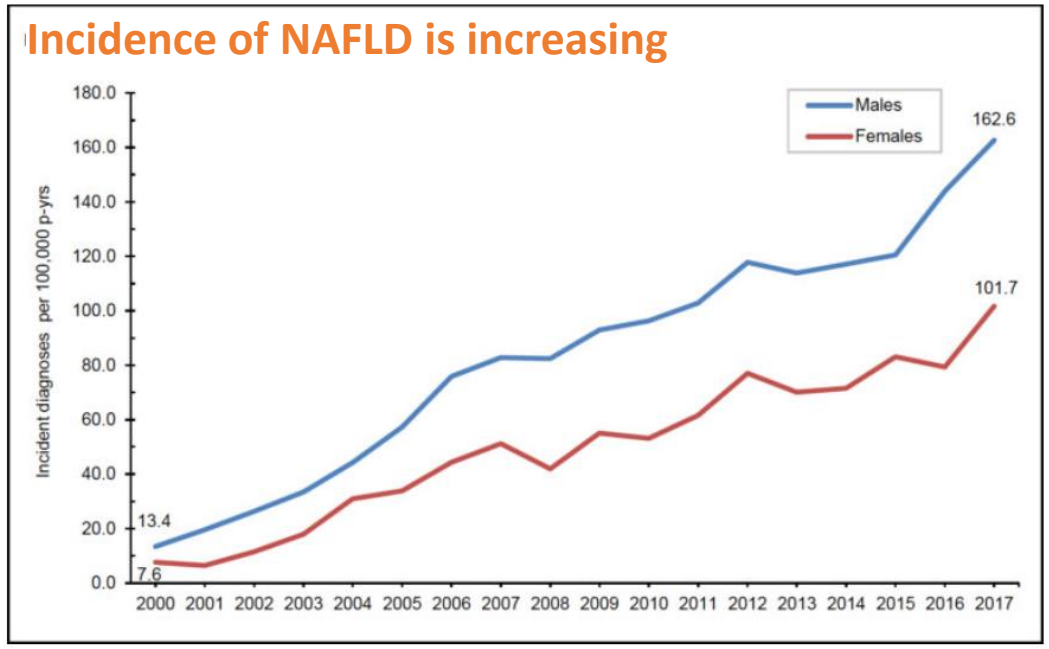
Type 2 diabetes drives and is driven by NAFLD

SIEMENS Healthineers

NAFLD is a silent disease and often not diagnosed until its most severe stage, at which time these individuals are often diagnosed with crypto or hidden cirrhosis



- Diabetes is also a key driver of NAFLD development. The global prevalence of NAFLD in patients with type 2 diabetes averages about 55% which is over 2-times the prevalence of NAFLD in the general population.
- The global prevalence of NASH in diabetics is about 37%. Again, this is almost double the prevalence of NASH found in the general population.

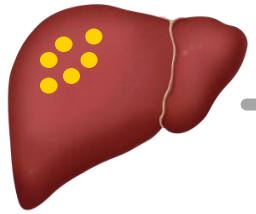


*** Among patients undergoing biopsy**

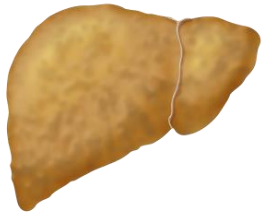
Younossi, Z. et al. Nat Ret Gastro Hepat. 2018;15:11–20.

Nonalcoholic fatty liver disease (NAFLD) is a continuum of disease

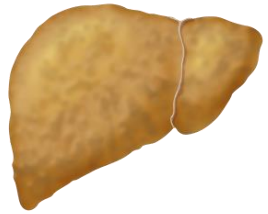
Non-alcoholic fatty liver disease (NAFLD)



Fat Accumulation

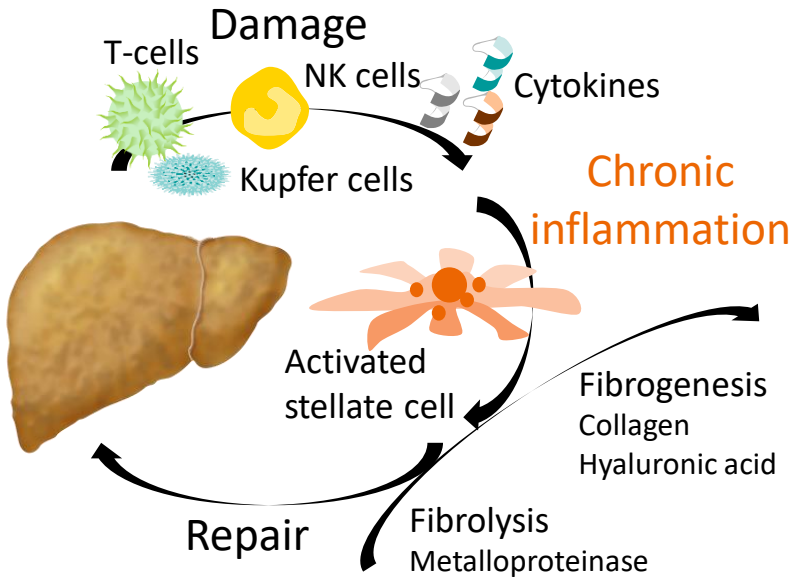


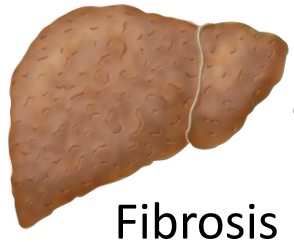
Fatty Liver > 5% fat accumulation



Stable or mild inflammation

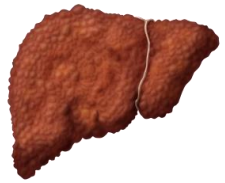
Nonalcoholic steatohepatitis (NASH)



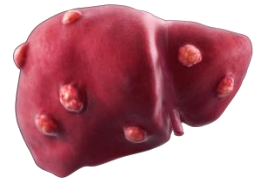


Fibrosis

Cirrhosis



Hepatocellular carcinoma (HCC)



Liver failure and death

Younossi ZM, et al. Hepatology. 2016;64:73-84.
Estes C, et al. Hepatology . 2018;67:123-33.
Divella R, et al. Int J Biol Sci. 2019;15(3):610-16.

Fibrosis stage substantially increases the risk of severe liver disease and liver-related morbidity and mortality*

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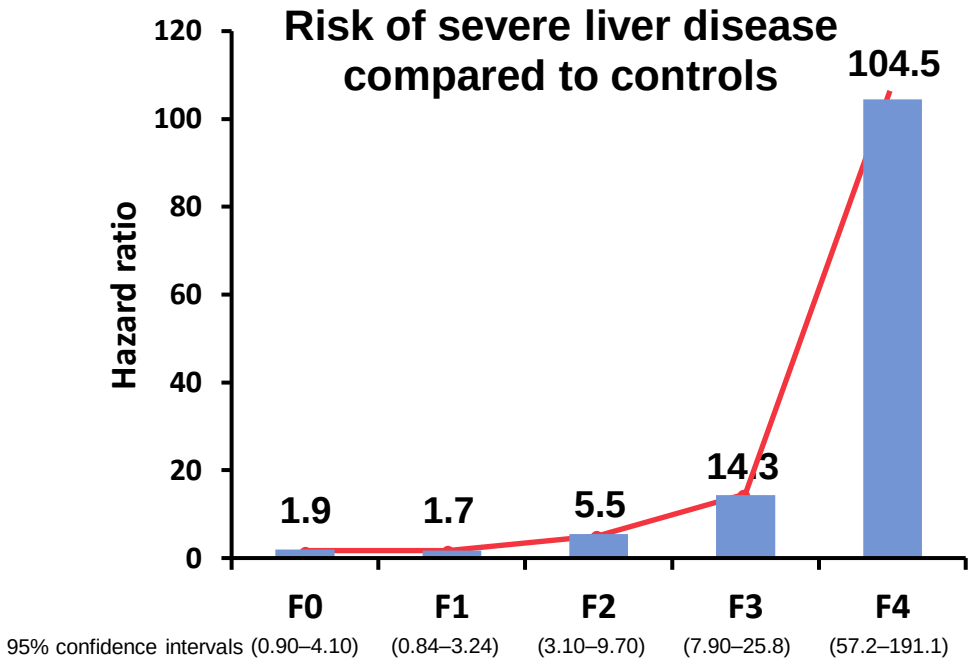
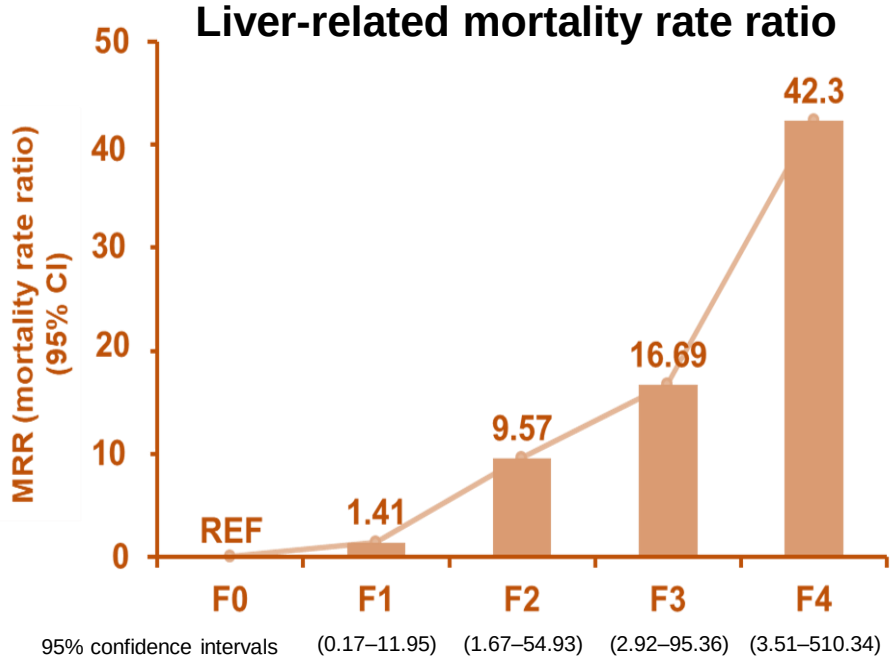
Risk of severe liver disease and liver-related mortality increases exponentially with increasing fibrosis stage and patients with advanced fibrosis are at the greatest risk



Adapted from Hagström H et al. *J Hepatol* 2017;67:1265 –1273



Adapted from Dulai PS et al. *Hepatology* 2017;65(5):1557–1565

***Findings based on differing study populations and analyses not intended for comparison purposes**

† From a retrospective cohort study of 646 biopsy-proven NAFLD patients, each matched to 10 controls. Severe liver disease was defined as cirrhosis, liver decompensation/failure or hepatocellular carcinoma

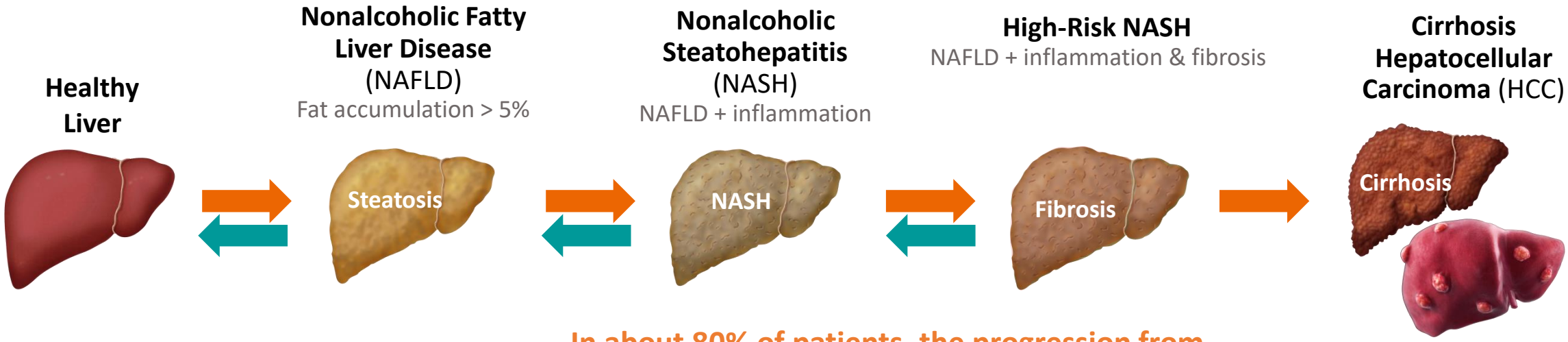
‡ From a meta-analysis of 5 multinational cohorts (1,495 NAFLD patients with 17,452 PYF). Liver-related mortality was a secondary outcome and was defined by investigators

NAFLD, nonalcoholic fatty liver disease; PYF, patient years of follow-up

1. Hagström H et al. *J Hepatol* 2017;67:1265 –1273; 2. Dulai PS et al. *Hepatology* 2017;65(5):1557–1565.

NAFLD progression: A two-way street with intervention

Liver fibrosis can be reversed, even in some cases of cirrhosis. Identification and intervention, which can include both lifestyle and drug therapies (when approved) could dramatically improve outcomes and quality of life and reduce the healthcare burden.



NAFLD progresses along a spectrum. Increasing risk of adverse outcomes accompanies each histological stage

In about 80% of patients, the progression from Steatosis to NASH to Fibrosis to Cirrhosis is slow

- Fortunately, the disease is stable or progresses slowly in most individuals.
- In those who do develop NASH progression can take a median of 14 years.
- Approximately 20 to 30% of those with NAFLD will develop NASH.
- up to 40% of those with NASH will develop some degree of fibrosis.

http://www.sydneynwgastro.com.au/services/liver-disease/fatty-liver
Wree A, et al. Nat Rev Gastroenterol Hepatol. 2013;10:627-36.
Vernon G, et al. Aliment Pharmacol Ther. 2011;34:274-85.
Schattenberg JM, et al. Curr Opin Lipidol. 2011;22:479-88.
Angulo P, et al. Hepatology. 1999;30:1356-62.

Surveillance Options

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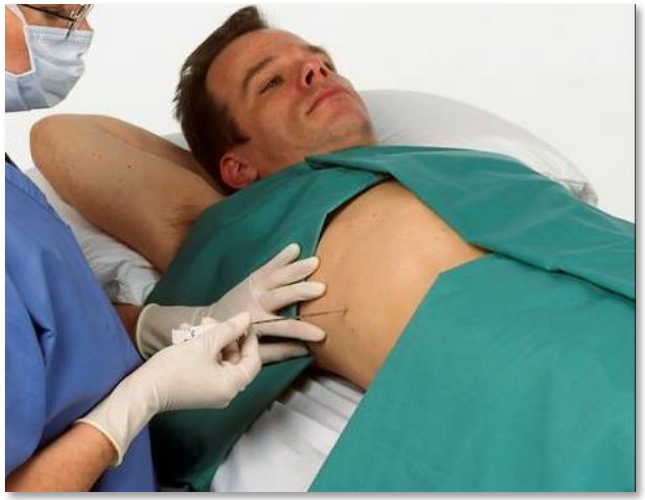
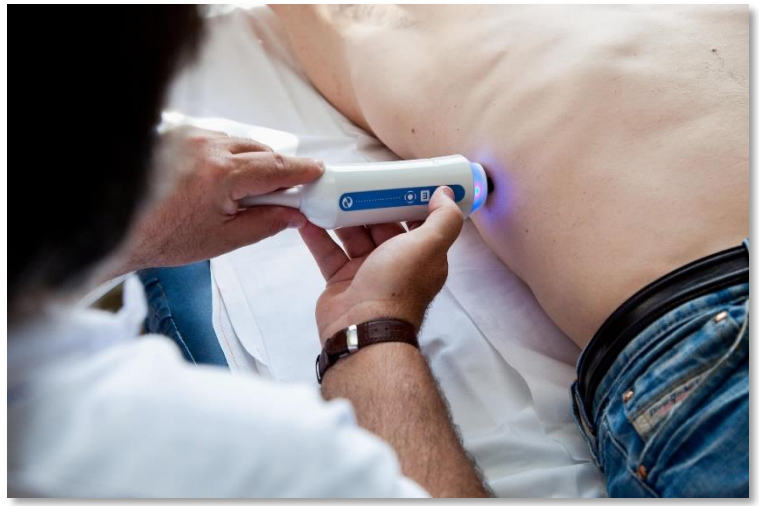
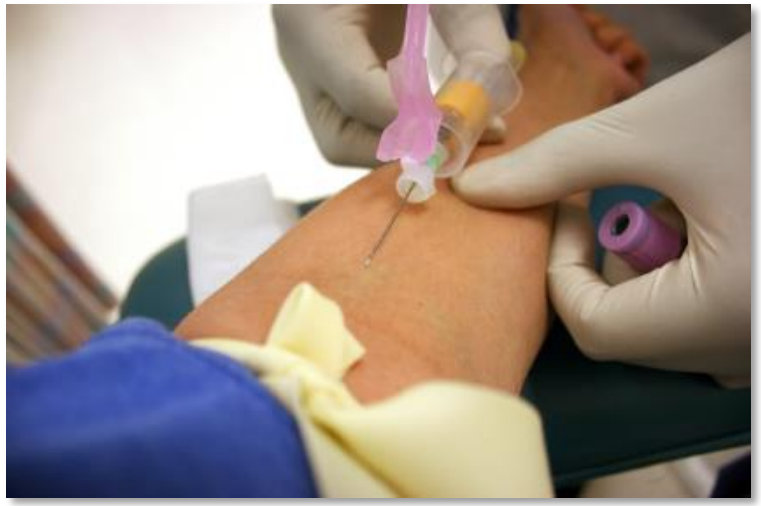
Biopsy



Imaging



Blood Test



Invasive Tests

Biopsy is generally considered the "Gold Standard"
Complications include:
Pain, Bleeding, Infection

Non-Invasive Tests (NIT)

Imaging methods use liver stiffness as a surrogate for fibrosis.

Blood tests are easy to access from virtually any hospital, doctor's office, or phlebotomy center. Even patients who are significantly remote from a specialty center generally have access to phlebotomy

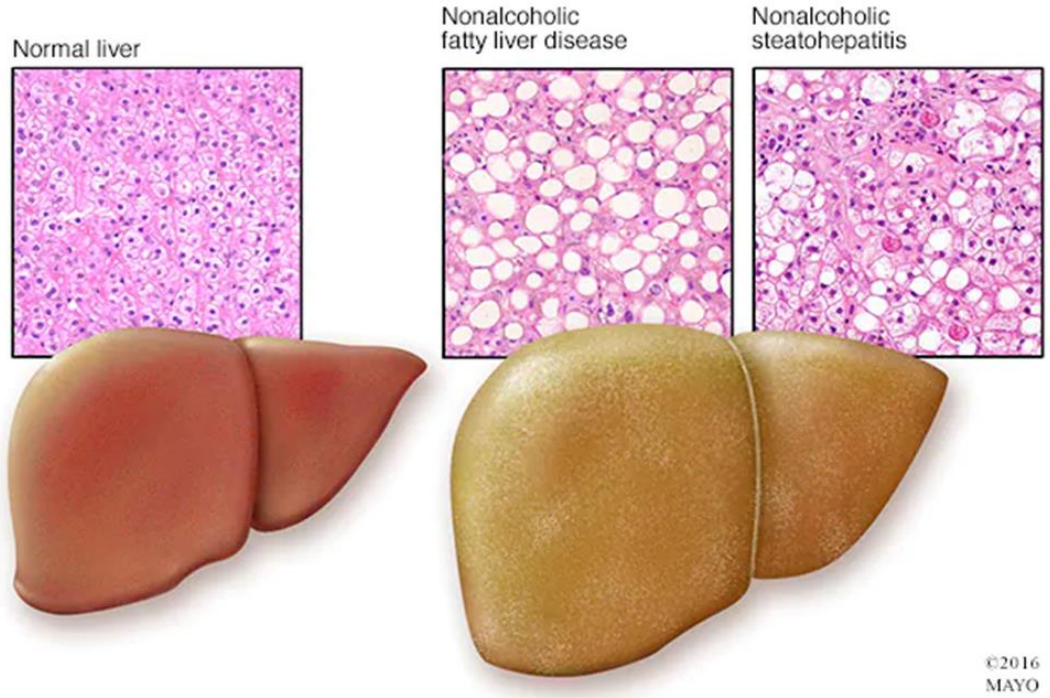
Younossi ZM, et al. Clinc Gastro and Hepatol. 2021. DOI 10.1016/j.cgh.2021.06.048.

Percutaneous Liver Biopsy

Percutaneous biopsy.

- The patient lies on their back and positions the right hand above the head on the table.
- Local anesthetic is used where the needle will be inserted.
- Ultrasound might be used during the biopsy to help guide the needle into the liver.
- A small incision is made near the bottom of the rib cage on the right side and the biopsy needle is inserted.
- The biopsy itself takes just a few seconds.
- The biopsy specimen will be viewed by a pathologist to grade the extent of fat accumulation and/or damage

Compared with a normal liver (left), a fatty liver (right) appears enlarged and discolored. Tissue samples reveal fat deposits in nonalcoholic fatty liver disease, while inflammation and advanced scarring (cirrhosis) are visible in nonalcoholic steatohepatitis.

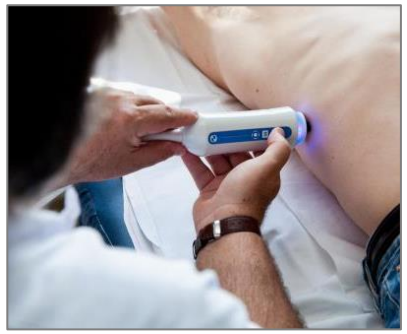


Non-Invasive Tests (NIT's) for liver fibrosis:

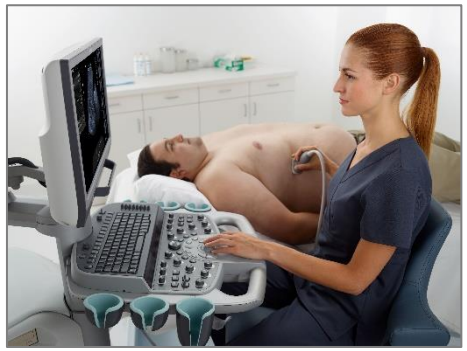
Imaging (Liver Elastography)

MR
Elastography

Vibration Controlled Transient
Elastography (VCTE)



Acoustic Radiation
Force Impulse (ARFI)



Blood Tests

HCV FibroSure

NASH FibroSure

Liver Fibrosis Panel

FibroMeter Virus

FibroMeter NAFLD

Fibrosis-4 (FIB-4)

Enhanced Liver Fibrosis (ELF) Test

FibroScan,® also called transient elastography, is a specialized ultrasound measures liver stiffness

Liver Fibrosis Blood Tests

SIEMENS Healthineers

Enhanced Liver Fibrosis (ELF): hyaluronic acid (HA), procollagen-3 N-terminal peptide (P3NP), and tissue inhibitor of metalloproteinase-1 (TIMP-1)

HCV FibroSure (LabCorp): alpha-2-macroglobulin, haptoglobin, apolipoprotein A-1, GGT, total bilirubin, AST

NASH FibroSure (LabCorp): alpha-2-macroglobulin, haptoglobin, apolipoprotein A-1, GGT, total bilirubin, AST, ALT, total cholesterol, triglycerides, fasting glucose

Liver Fibrosis Panel (Quest): Alpha-2-Macroglobulin, Haptoglobin, Apolipoprotein A-1, Total Bilirubin, GGT, ALT

FibroMeter Virus (ARUP): platelet count, prothrombin index, AST, alpha-2-macroglobulin, GGT, BUN, patient's age and gender

FibroMeter NAFLD (ARUP): ALT, AST, ferritin, glucose, platelet count, patient's weight

Fibrosis-4 (FIB-4): age, platelet count, AST and ALT

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

The scoring system creates a score - <1.45 has a negative predictive value of over 90% for advanced liver fibrosis of multiple etiologies. A score of **>3.25** has a positive predictive value of 65% for advanced fibrosis with a specificity of 97%.

The Enhanced Liver Fibrosis (ELF™) Test

SIEMENS Healthineers

The Enhanced Liver Fibrosis (ELF™) test is indicated as a **prognostic marker** in conjunction with other laboratory findings and clinical assessments in patients with advanced fibrosis (F3 or F4) due to non-alcoholic steatohepatitis (NASH) **to assess the likelihood of progression to cirrhosis and liver-related clinical events**

Hyaluronic acid (HA)

Procollagen III amino terminal peptide (PIIINP)

Tissue inhibitor metalloproteinase-1 (TIMP-1)

Liver-related events are generally defined as:
- Ascites,
- Variceal bleeding,
- Hepatorenal syndrome,
- Hepatic encephalopathy

$$\text{ELF score}^* = 2.278 + 0.851 \ln (C_{HA}) + 0.751 \ln (C_{PIIINP}) + 0.394 \ln (C_{TIMP\text{-}1})$$

Fully Automated: ELF Score Calculated and Reported

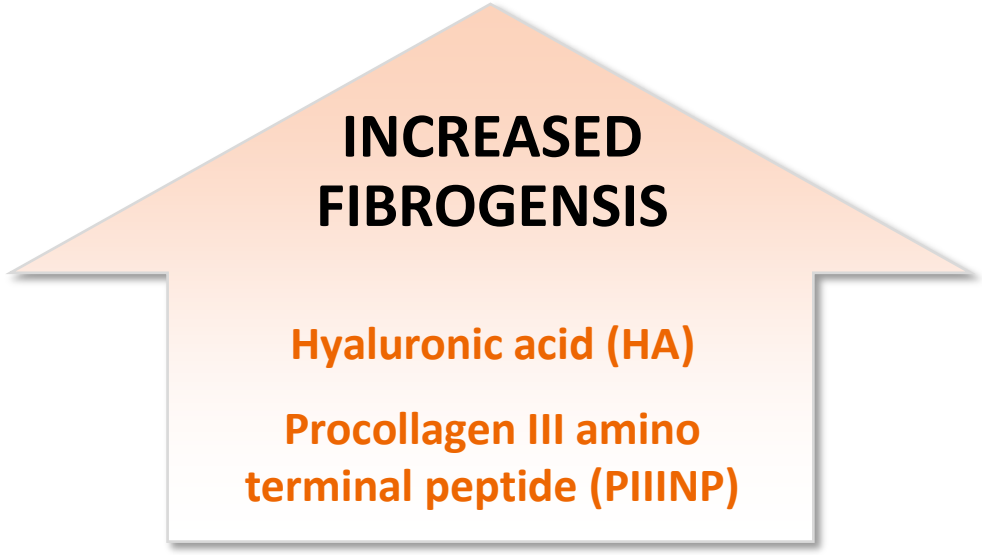
< 9.8	≥ 9.8 – < 11.3	≥ 11.3
Lower Risk	Mid Risk**	Higher Risk

.

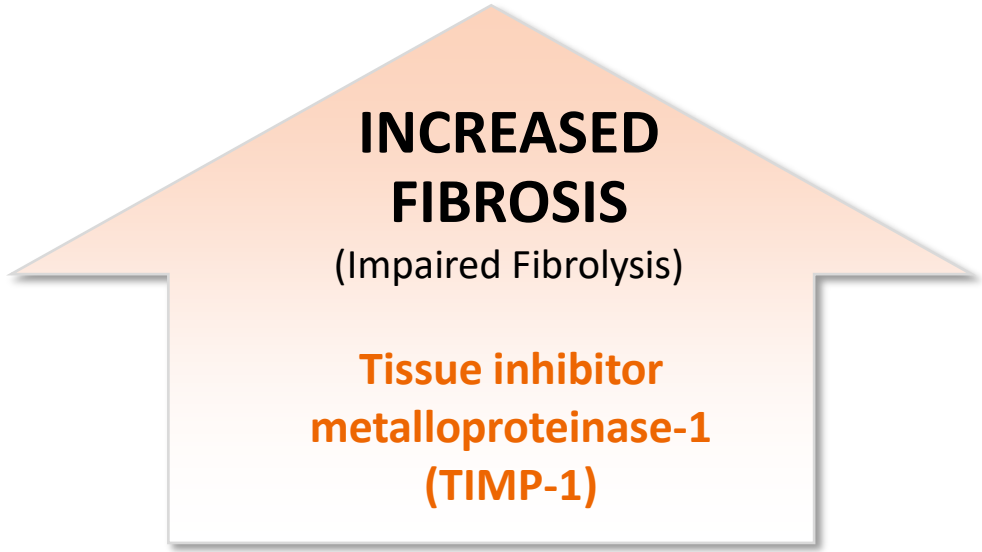
" Equation shown is for the ADVIA Centaur XP/XPT systems and Atellica IM Analyzer. **: "In the Mid group, the risk of disease progression is similar to the pre-test risk. Pre-test risk refers to the likelihood of disease progression in the overall intended use population without considering the ELF score."*

ELF IFU 11205858_EN Rev. 02, 2022-10

Siemens Healthineers Enhanced Liver Fibrosis (ELF™) Test and ELF Score for prognosis in advanced NASH



Markers of extracellular matrix (ECM) synthesis:
Elevated levels associated with **increased fibrogenesis**



Marker of ECM repair inhibition:
Elevated levels **impair fibrolysis** and **increase fibrosis**

- While HA and PIIINP are directly involved in fibrosis formation, TIMP-1 reflects damage associated with a reduced ability of the liver tissue to repair itself by degrading the scar tissue.
- TIMP-1 overexpression hinders the clearance of fibrotic matrix, mediated in part by matrix metalloproteinases (MMPs) which are the main enzymes implicated in ECM degradation. Increased inhibition of MMP's by TIMP's leads to extensive accumulation of interstitial ECM.
- Thus, the MMP and TIMP-1 imbalance is associated with progressive liver damage, and increased levels of TIMP-1 reflect disease progression as do HA and PIIINP.

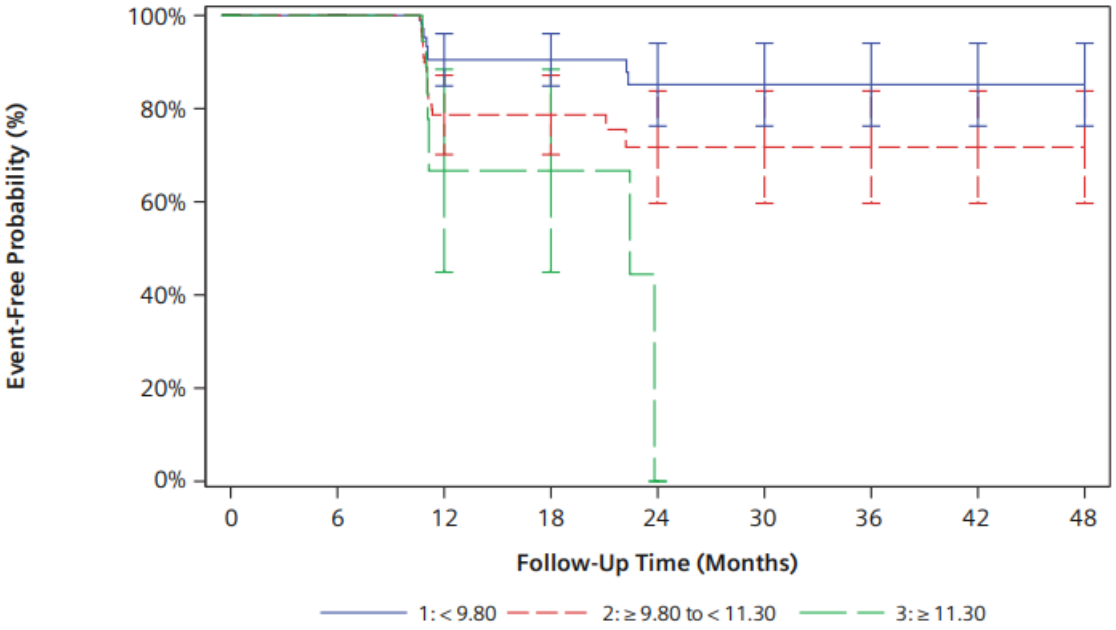
ELF is Prognostic

Supporting risk assessment of liver related events (LRE)

NASH F3 (Bridging Fibrosis)

An analysis of 212 subjects pooled from the placebo arms of these studies estimated the prognostic ability of ELF scores at baseline to predict the risk of progression to cirrhosis.

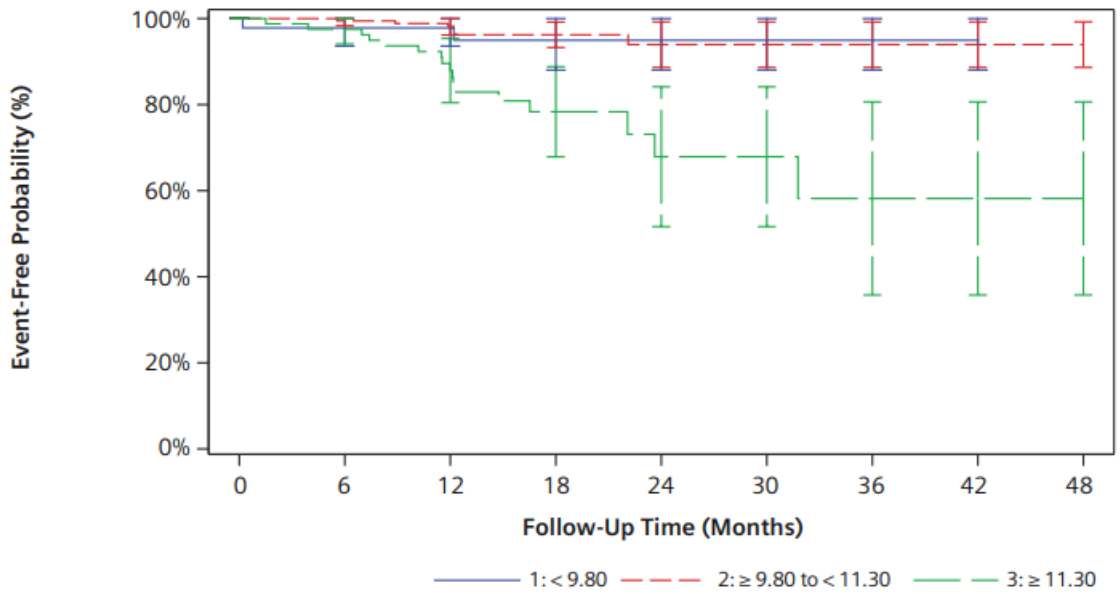
Kaplan-Meier curves up to 48 months were plotted for each of the risk groups to display the proportion of subjects without a liver-related event over time.



NASH F4 (Compensated Cirrhosis)

An analysis of 305 subjects estimated the prognostic ability of ELF scores at baseline to predict the risk of liver-related events up to 3.8 years following enrollment

Kaplan-Meier curves up to 48 months were plotted for each of the risk groups to display the proportion of subjects without a liver-related event over time.



Instructions For Use. Atellica IM Enhanced Liver Fibrosis (ELF). 11208118. Rev. 02, 2022-10

ELF Test is Now Included in Multiple Clinical Guidelines

SIEMENS Healthineers

American Association of Clinical Endocrinology

- ELF is included in the section focusing on the Comprehensive Medical evaluation and Assessment of Comorbidities: NAFLD
- ELF was strongly recommended for risk stratification

https://diabetesjournals.org/care/article/46/Supplement_1/s49/148058/4-Comprehensive-Medical-Evaluation-and-Assessment

American Gastroenterological Association

- ELF was included in the 2022 Clinical Practice Update: Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Lean Individuals: Expert Review
- An ELF score of ≥ 9.8 is valuable for prognostic decision making.

AGA Clinical Practice Update: Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Lean Individuals: Expert Review (gastrojournal.org)

American Association of Clinical Endocrinology

- ELF was strongly recommended in the 2022 NAFLD Clinical Practice Guidelines
- ELF testing can be incorporated into a clinical decision pathway to identify NASH patients at risk of progressing to cirrhosis.

American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings (endocrinepractice.org)

American Association for the Study of Liver Diseases

- An ELF score of ≥9.8 reliably identifies patients with NAFLD at increased risk of progression to cirrhosis and liver-related clinical events.
- In patients with confirmed or suspected advanced fibrosis, an ELF ≥11.3 is a predictor of future liver-related events and is approved for this purpose; use of other ELF cutoffs in secondary risk assessment is based on expert option.

AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology* 77(5):p 1797-1835, May 2023. | *DOI:* 10.1097/HEP.0000000000000323

In the U.S., the ELF Test is indicated as a prognostic marker in conjunction with other laboratory findings and clinical assessments in patients with advanced fibrosis (F3 or F4) due to non-alcoholic steatohepatitis (NASH) to assess the likelihood of progression to cirrhosis and liver-related clinical events. The test is not for use in the diagnosis of NASH or for the staging of fibrosis.

ELF is Clinically Valuable in NASH Prognostic Care

ELF can be integrated into patient management pathways once at-risk patients are identified in primary care

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PRIMARY CARE VISIT

EVIDENCE OF ≥1 OF THE FOLLOWING:

- Fatty Liver on Imaging?
- BMI ≥ 30?
- Type 2 Diabetes?
- Elevated LFTs?

"Some community sites have zero ability to do liver fibrosis assessments…Would feel confident if they had ELF to be able to give some indication of progression of disease."

- Chair of Hepatology, Large IDN

CALCULATE FIB-4* (*standard blood work*)

	Under 65	65 & Older	
LOW RISK	0-1.3	0-2.5	MONITOR
MEDIUM TO HIGH RISK	≥ 1.3[1]	≥ 2.5[1]	Confirmation of advanced fibrosis due to NASH

***FIB-4 is a simple calculation involving:**

1. Platelet count
2. Age
3. Liver Enzymes (ALT & AST)

ELF TEST

≥9.8 – 11.3	≥ 11.3
Mid risk for progression and liver-related events	Higher risk for progression and liver-related events

Further assessment
(may conduct additional tests)

This algorithm uses the ELF Test in conjunction with the FIB-4 Score to help determine which patients may need more intensive management of their liver disease. While there are no drug therapies available at this time, patient management may include intensive lifestyle change, hepatology consult, or further testing for potential liver-related events like decompensation.

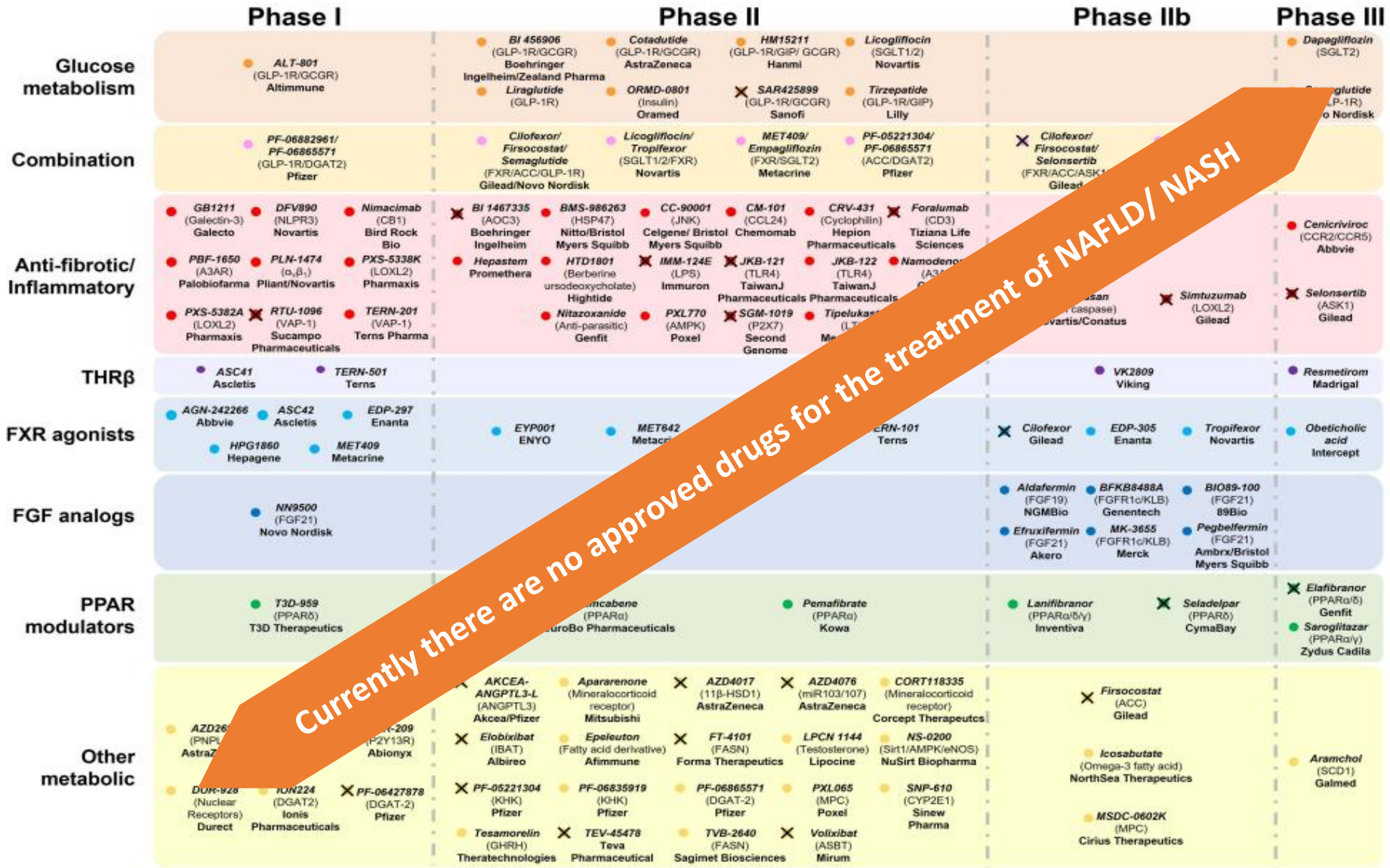
Start Therapy*

- **Intensive Lifestyle Intervention**
- **Change Therapy** *(if applicable)*
- **Refer to Clinical Trial** *(liver biopsy as appropriate)*

*Once therapies are available

1. Data on file. NAFLD/NASH NIT Market Research Interview. Siemens Healthcare GmbH; September 2020.

Therapeutic landscape for NAFLD/NASH with targeted pathways



A cross indicates that the drug has been discontinued for NASH therapy from the company's pipeline.

Drug Design, Development and Therapy 2021:15

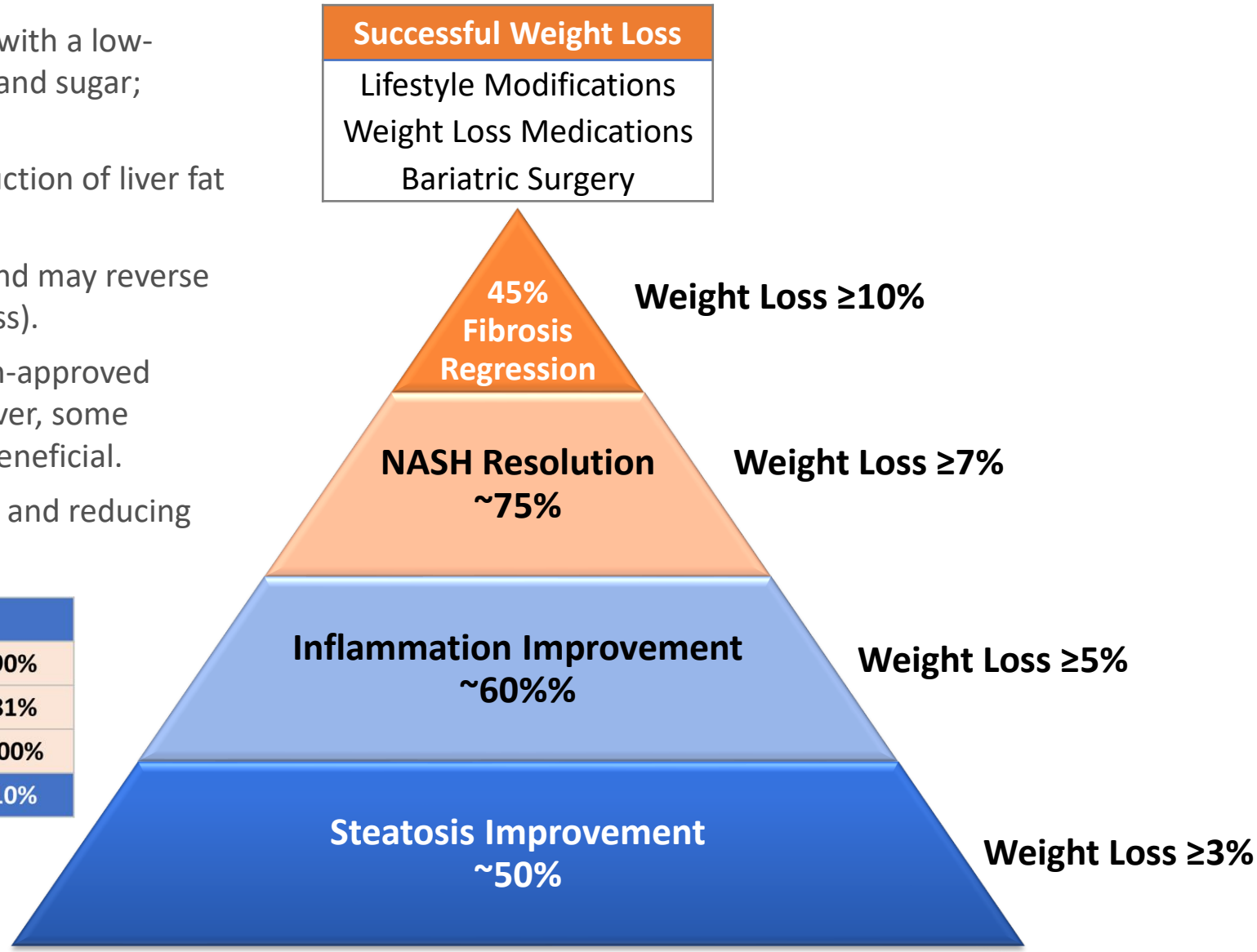
However, Weight Loss Works

- The primary treatment of NAFLD is weight loss with a low-calorie diet; restriction of saturated fat, starch, and sugar; improved eating patterns and exercise.
- Cardiovascular and metabolic benefits and reduction of liver fat can be observed with >5% weight loss.
- More weight loss provides increased benefits and may reverse steatohepatitis or liver fibrosis (≥10% weight loss).
- There are no U.S. Food and Drug Administration-approved medications for the treatment of NAFLD; however, some diabetes and anti-obesity medications can be beneficial.
- Bariatric surgery is also effective for weight loss and reducing liver fat in persons with severe obesity.

% Weight Loss (WL)	5%	7%	10%	
NASH Resolution	10%	26%	64%	90%
Fibrosis Regression	45%	38%	50%	81%
Steatosis Improvement	35%	65%	76%	100%
% Patients Achieving WL	70%	12%	9%	10%

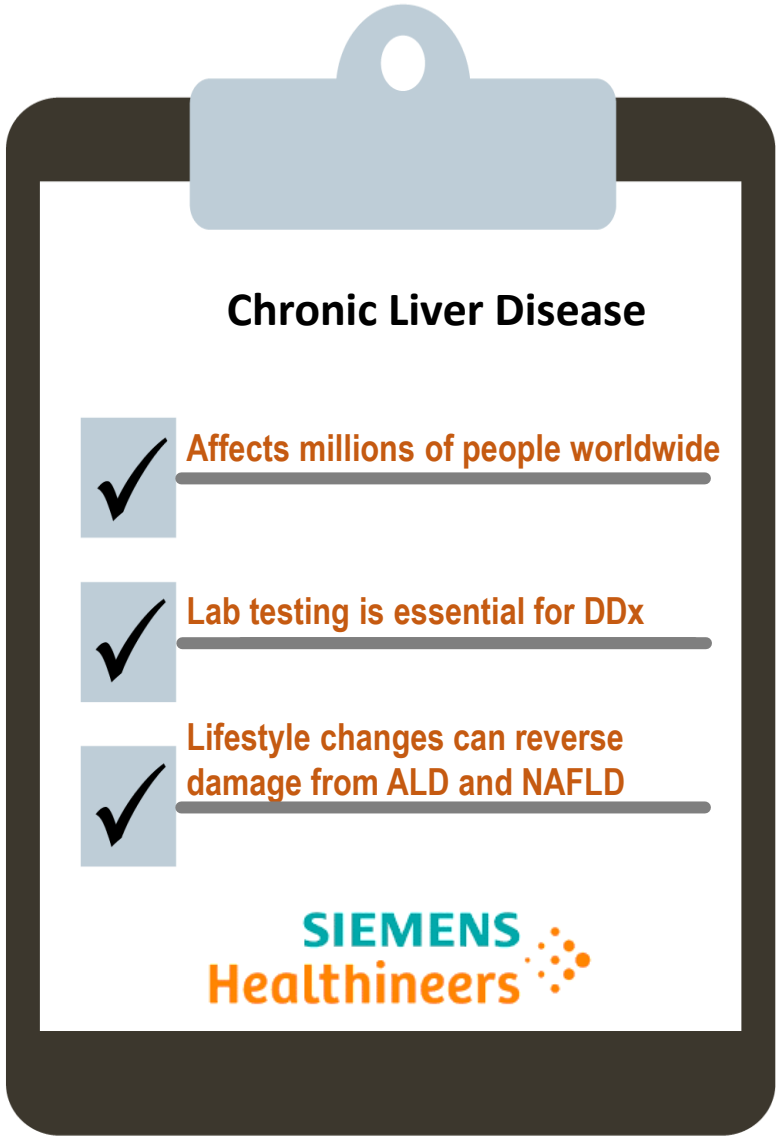
A study of 293 NAFLD/NASH patients demonstrating the benefits of weight loss over a one-year period

Journal of Hepatology 2017 vol. 67 j 829–846



Hannah WN. Et al. Clin Liver Dis 2016:20;329-350

Summary



Chronic Liver Disease (CLD) is a progressive deterioration of liver function for more than six months.

Four common causes of chronic liver disease include: infection from Hepatitis B or Hepatitis C, Alcoholic Liver Disease and Non-Alcoholic Liver Disease.

No matter the underlying cause, the clinical signs and symptoms of chronic liver disease are essentially identical making laboratory testing an essential component for the differential diagnosis.

Lifestyle changes can reverse the progression of disease and damage caused by alcoholic liver disease and non-alcoholic liver disease.

QR700001589

Contact Information

Jim Aguanno, PhD
Senior Clinical Consultant
Medical and Scientific Affairs
james.aguanno@siemens-healthineers.com
Cell: 972-567-7777

Extra Slides

Summary and Objectives

SIEMENS Healthineers

Summary

Chronic liver disease is a disease process of the liver that involves a process of progressive destruction and regeneration of the liver tissue leading to fibrosis and cirrhosis. "Chronic liver disease" refers to disease of the liver which lasts over a period of six months. It consists of a wide range of liver pathologies which include inflammation (chronic hepatitis), liver cirrhosis, and hepatocellular carcinoma. Liver fibrosis results from chronic damage to the liver in conjunction with the accumulation of extracellular cell matrix proteins, which is a characteristic of most types of chronic liver diseases. Cirrhosis and chronic liver failure are leading causes of morbidity and mortality in the United States, with the majority of preventable cases attributed to excessive alcohol consumption, viral hepatitis, or nonalcoholic fatty liver disease. Depending upon the study, these four disease states account for approximately 80% of all chronic liver disease. This presentation will focus on these four common causes of chronic liver disease and discuss the epidemiology, clinical aspects and diagnosis of each. This presentation will focus on these four common cause of chronic liver disease and discuss the epidemiology, signs and symptoms, and diagnosis of each disease. In addition, Since fibrosis is the key indicator of damage and chronic liver disease progression, direct assessment of fibrosis has proven valuable for identifying at-risk patients. This presentation will focus on the prognostic utility of the Enhanced Liver Fibrosis (ELF) Score in conjunction with other laboratory findings and clinical assessments in patients with advanced fibrosis due to non-alcoholic steatohepatitis to assess the likelihood of progression to cirrhosis and liver-related clinical events will also be discussed.

Objectives

By the end of this session participants will be able to:

1. Describe the four main causes of chronic liver disease
2. Describe the major risk factors for the development of chronic liver disease
3. Explain the clinical and laboratory findings associated with chronic liver disease
4. Explain the testing options that can assist in the differential diagnosis of chronic liver disease

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