ABOUT LIVER DISEASE

What Does Your Liver Do?

- Your liver is essential to your life. It is the largest internal organ, and gland, in the body. It is about the size of a football and weighs up to 4 pounds. It is located on your right side, just under your rib cage. [1, 2, 3, 4]

- The liver performs more than 500 functions, many vital, including filtering toxins from your blood, managing blood clotting, making bile to digest fat, storing and controlling blood sugar for energy (glucose/glycogen), making protein for blood plasma, storing your body's iron, creating proteins, eliminating old and damaged red blood cells, and helping fight off infections. [2, 5, 6, 7, 8]

What Is Liver Disease?

- Liver disease is also called hepatic disease. There are many kinds of liver diseases and conditions, the most common are hepatitis virus infections, metabolic dysfunction–associated steatotic liver disease (MASLD) which is formerly known as nonalcoholic fatty liver disease (NAFLD), immune system abnormalities, inherited (genetic) conditions, cancer, damage from alcohol and substance use disorders, and others. There are more than 100 types of liver disease, most of which are in groups of subtypes. [3, 9, 10, 11]

- Chronic liver disease (CLD)/cirrhosis (advanced liver scarring) are major causes of morbidity and mortality in the U.S. [12, 13]

- Chronic liver disease (CLD) has approximately **four stages:**[14]
    1. Hepatitis (liver inflammation)
    2. Fibrosis (scarring)
    3. Cirrhosis (advanced liver scarring)
    4. Liver failure

- Left untreated, liver disease can lead to liver failure and liver cancer. [3, 9, 15]

- People with advanced liver disease and chronic viral hepatitis B should undergo regular screening for liver cancer.[16]

- Liver disease has many causes such as: [3, 11, 14, 17, 18]
    - **Infections**: Viruses and parasites can infect the liver. The most common infections are hepatitis viruses (hepatitis A, B, and C). Liver-damaging viruses can spread through contaminated food or water (hepatitis A), unscreened blood transfusions (generally prior to 1992), sexual contact, exposure to blood/body fluids, and other ways.
    - **Immune system abnormalities**: Your immune system can attack parts of your body including your liver; this is called autoimmune disease. Autoimmune liver diseases include autoimmune hepatitis; primary biliary cholangitis; primary sclerosing cholangitis, and others.
    - **Genetics**: An inherited abnormal gene can cause liver damage. Genetic liver diseases include hemochromatosis; Wilson's disease; alpha-1 antitrypsin deficiency, and others.
    - **Cancer and other growths**: Including: hepatocellular carcinoma (liver cancer); cholangiocarcinoma (bile duct cancer); and liver adenoma (pre-cancerous mass).
    - **Other causes of liver disease**: long-term alcohol use; fat accumulation in the liver (metabolic dysfunction–associated steatotic liver disease (MASLD), formerly known as nonalcoholic fatty liver disease (NAFLD); or steatotic liver disease (SLD), formerly known as fatty liver disease; liver congestion related to heart disease (cardiac cirrhosis or congestive hepatopathy); some prescription or other medications; some herbal compounds; toxic chemicals, and others.

What Are the Risk Factors for Liver Disease?

- Risk factors include alcohol use, heavy or moderate; obesity; type 2 diabetes; high cholesterol; tattoos/body piercings; IV drug use, particularly with shared needles; blood transfusion pre-1992; exposure to blood and body fluids; unprotected sex; exposure to certain chemicals or toxins; family history of liver disease; overuse of certain pain relievers; and others. [3, 14, 19, 20]

How Many People Have Liver Disease?

- 4.5 million U.S. adults (1.8% of 18 yrs+) have been diagnosed with liver disease. (2018, National Health Interview Survey) [12]

- Estimates range from about 80 to 100 million people (or almost 1/3 of the population) in the U.S. having some form of liver disease, due to being overweight and having fat buildup in their liver, which is known as metabolic dysfunction–associated steatotic liver disease, (MASLD); metabolic dysfunction-associated steatohepatitis (MASH), formerly known as non-alcoholic steatohepatitis (NASH); or steatotic liver disease (SLD). One estimate cites 24% or about 1 in 4 adults. And it is on the rise. [9, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30]

- This condition often has no symptoms, and many do not know they have it. [3, 9, 26, 31]

- In 2022, 54,803 people in the U.S. died from liver disease (16.4per 100,000 population).[12]

- Chronic liver disease/cirrhosis was the 10th leading cause of death in the U.S in 2022.[12]

- Chronic liver disease was the 9th leading cause of death in 2020 for non-Hispanic Black people, aged 45-64. African American/Black men are also 60% more likely to have liver/bile duct cancer and die, compared to non-Hispanic White men. Also, African American/Black women are 30% more likely to get liver/bile duct cancer and die, compared to their White counterparts. [32]

- 1.5 billion cases of chronic liver disease were estimated worldwide in 2017.[33, 34]

- Worldwide, estimates of deaths caused by liver disease range from one to two million annually. Men account for about two-thirds of liver-related deaths. [33, 35, 36, 37, 38, 39]

- In addition to high-risk drinking, obesity, and the opioid epidemic, increases in rates of liver disease are also driven by health and healthcare inequities, and social determinants of liver health (SDOH). [40, 41]

- In 2022, liver disease was the 14th leading cause of death for Black people of all ages. It ranked 9th for Black people ages 35-64 years.[42]

Who Gets Liver Disease?

- Estimates of liver disease by race/ethnicity vary. The following studies show recent findings and possible trends:
    - A **2016 study** compared causes and prevalence rates of **general liver disease/cirrhosis racial/ethnic categories**, as follows:[43]
        - Chronic liver disease rates: Japanese Americans (6.9%); Hispanic/Latino persons (6.7%); White persons (4.1%); African American/Black and Native Hawaiian persons (3.9%).
        - Cause of liver disease/cause of cirrhosis: MASLD was the most common in <u>all</u> groups. The most common causes of cirrhosis by ethnicity were: MASLD in Japanese American, Native Hawaiian, and Hispanic/Latino persons; alcohol-associated liver disease (ALD;

alcohol-related liver disease (ARLD); alcoholic liver disease) in White persons; and hepatitis C in African American/Black persons.

- A 2017 **meta-analysis of 34 studies** of MASLD covering 368,569 unique patients found: MASLD prevalence was highest in Hispanic/Latino people, intermediate in Whites, and lowest in African American/Black people; risk of MASH was higher in Hispanic/Latino people and lower in African American/Black people than Whites.[44]

- A 2016 **study of prevalence of chronic liver disease (CLD)/cirrhosis in a sample of Medicare claims between 1999 and 2012** (*n*=106,458) found: In a total of 5,783 CLD cases (3,575 CLD without cirrhosis and 2,208 with cirrhosis), the prevalence of CLD was 3.9% in Black/African American and Native Hawaiian peoples, 4.1% in Whites, 6.7% in Hispanic/Latino and 6.9% in Japanese people. MASLD was the most common cause of CLD in all ethnicities combined (52%), followed by alcohol-associated liver disease (ALD (21%). The most common cause of cirrhosis in the entire sample was MASLD. By ethnicity, MASLD was the most common cirrhosis cause in Japanese Americans, Native Hawaiians, and Hispanic/Latino peoples (32%). ALD was the most common cirrhosis cause in White people (38.2%), and hepatitis C virus was the most common cause in Black/African American people (29.8%). [13]

- A study from the **American Association for the Study of Liver Disease (AASLD)'s workforce study group** reported that disparities in liver disease and treatment are persistent and could be related to gender, race, geography, socioeconomic status and behaviors leading to liver disease.[45]

- An analysis of CDC data for liver disease mortality trends in the US for 1999-2020 found that liver disease mortality improved for African American/Black people but worsened for Whites. There was a rise in alcohol-related liver disease and metabolic dysfunction–associated steatotic liver disease–related deaths among Whites, while there were also continuing liver cancer and viral hepatitis disparities in the Black population.[46]

Cirrhosis (scarring of the liver)

- **Cirrhosis** is a long-term liver disease. Cirrhosis is scarring of the liver, when scar tissue replaces healthy tissue, causing damage and reducing the liver's functioning. Cirrhosis is most often caused by hepatitis (liver inflammation) and other viruses; alcohol-associated liver disease (ALD); alcohol-related liver disease (ARLD); formerly alcoholic liver disease); and MASLD or steatotic liver disease.[47]

- **Currently, some studies indicate that cirrhosis may increase the risk for** stroke, others contradict or are inconclusive. [48, 49, 50, 51, 52, 53, 54, 55]

- **Rates of liver cirrhosis deaths** have been consistently higher for Black/African American men and women than their White counterparts since the 1950's. [56, 57, 58]

STEATOTIC (FATTY) LIVER DISEASE

- There have been recent changes to the **medical terminology covering "fatty" type liver disease** to reduce stigma. The term "fatty liver disease" (FLD) has been replaced by "steatotic liver disease" (SLD). SLD is an umbrella term covering "nonalcoholic fatty liver disease" (NAFLD)/"metabolic dysfunction-associated steatotic liver disease" (new term; MASLD); nonalcoholic steatohepatitis (NASH)/metabolic-associated steatohepatitis (new term; MASH); as well as alcohol-related liver disease (ARLD)/ alcohol-associated liver disease (new term; ALD), and the new category, Met+ALD (metabolic with alcohol-associated liver disease), a continuum which can have elements of MASLD and/or ALD. [59, 60, 61, 62, 63, 64, 65, 66, 67]

- Steatotic liver disease (SLD) as a disease category includes several conditions. "Steatosis" is a medical term that describes fat buildup in an organ (usually the liver). A normal liver contains a small amount of fat. When fat buildup goes over 5%-10% in the liver it becomes a health problem. [68]

- SLD classifications are as follows: [68]
    - Metabolic dysfunction-associated steatotic liver disease (MASLD); steatosis isn't associated with excess alcohol consumption but at least one cardiometabolic factor that poses risks to heart health. Cardiometabolic risks include type 2 diabetes mellitus (T2DM), hypertension, overweight (BMI > 25) or obesity (BMI >=30), and dyslipidemia (low HDL and/or high triglyceides).
    - Metabolic-associated steatohepatitis (MASH), a serious form of MASLD where fat buildup progresses to inflammation, then tissue damage and scarring (fibrosis)/cirrhosis.
    - Alcohol-related liver disease (ARLD)/ alcohol-associated liver disease (new term; ALD); occurring because of excessive alcohol consumption. Excess alcohol use is defined as at least 3 drinks/day (21 per week) in men and 2 drinks/day (14 per week) in women.
    - MASLD and increased alcohol intake (Met+ALD); both metabolic risk factors and excess alcohol consumption play a role in liver fat. Which contributes most to the fat buildup varies from person to person.
    - Other forms of SLD: For example, various medications and diseases. Sometimes, a specific cause can't be identified, and this is called "cryptogenic SLD."

- The majority of people with MASLD have steatotic liver disease (SLD). [69]

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly nonalcoholic fatty liver disease (NAFLD)

- There have been recent changes to the **medical terminology covering "fatty" type liver disease** to reduce stigma. The term "fatty liver disease" (FLD) has been replaced by "steatotic liver disease" (SLD). SLD is an umbrella term covering "nonalcoholic fatty liver disease" (NAFLD)/"metabolic dysfunction-associated steatotic liver disease" (new term; MASLD); nonalcoholic steatohepatitis (NASH)/metabolic-associated steatohepatitis (new term; MASH); as well as alcohol-related liver disease (ARLD)/ alcohol-associated liver disease(new term; ALD), and the new category, Met+ALD (metabolic with alcohol-associated liver disease), a continuum which can have elements of MASLD and/or ALD. [59, 60, 61, 62, 63, 64, 65, 66, 67]

- Metabolic dysfunction-associated steatotic liver disease (MASLD) is one of the most common causes of liver disease. [63,70, 71]

- Metabolic dysfunction-associated steatotic liver disease (MASLD) happens when excess fat builds up in the liver. It is a "silent" disease with few or no symptoms. Causes are still being studied, but research points to genetics, digestive disorders, and diet. [70, 71, 72]

- It is **not caused by heavy alcohol use** (alcohol-associated liver disease or ALD). **Causes** include diet and nutritional causes, genetics, being overweight/obesity, type 2 diabetes/ insulin resistance, high blood fat/triglyceride levels. One or more traits of metabolic syndrome (traits and medical conditions linked to overweight/obesity), and others. [70, 71, 72]

- **Risk factors** include family history, older age, growth hormone deficiency, high cholesterol/triglycerides, type 2 diabetes/insulin resistance, metabolic syndrome, obesity, polycystic ovary syndrome, sleep apnea, hypothyroidism, hypopituitarism. [70, 71, 72]

- **Some get MASLD even without risk factors.** [70, 71, 72]

- **Further information on risk factors:** [69, 72, 73, 74, 75, 76, 77]
  - Anyone, of all ages and races, can have MASLD. It's more common in Hispanic/Latino people, less common in African American/Black people.
  - Middle age, weight and diabetes are associated with MASLD.
  - MASLD is present in up to 75% of people with obesity or diabetes and up to 90% of people with advanced or class III obesity.

- MASLD is also caused by other factors experts are still trying to understand. [78]

- The majority of people with MASLD have SLD. [69]

- 50% of patients with obesity have MASLD. [79]

- 50%+ of type 2 diabetes patients have MASLD [79]

- **Metabolic dysfunction-associated steatohepatitis (MASH)** is a more advanced form of MASLD in which you have inflammation of the liver and liver damage, in addition to fat in your liver. (See next section.) It is difficult to tell MASLD from MASH; clinical evaluation and testing are needed. [70, 72, 80, 81, 82, 83]

- Weight loss can cause the more severe MASH to change to MASLD, and regaining weight may cause MASLD to switch to MASH. [70, 72, 80, 81, 82, 83]

- **MASLD is one of the most common causes of liver disease. About 24% of U.S. adults are estimated to have it.** An estimated 80-100 million people in the U.S. have MASLD. [69, 84, 85, 86, 87, 88, 89]

- Globally, MASLD is the most common liver disease, affecting about 25% to about a third of the world's population. [85, 89, 90, 91, 92, 93, 94, 95, 96]

- Worldwide prevalence of MASLD is increasing at an alarming rate. [93, 95, 96, 97, 98]

- The highest prevalence of MASLD is in Latin America at 44.37%. [97]

- One study (2020) states that worldwide cases of MASLD increased from 391.2 million in 1990 to 882.1 million in 2017. [95, 99]

- Global MASLD/SLD burdens parallel the increase in world obesity rates. [100, 101]

- The estimated global prevalence of MASLD among adults is higher among males than females. However, females' risk increases as they age. [93, 96, 102, 103]

- Hispanic/Latino people face a higher risk of developing MASLD than other racial or ethnic groups. And African American/Black people with MASLD or MASH are more likely to progress to liver cirrhosis. [104, 105]

- Study results of MASLD prevalence broken down by race/ethnicity vary but strongly indicate trends. Prevalence appears higher among Hispanics, then non-Hispanic Whites and Asians, and lastly, African Americans. [105]

- The prevalence of MASLD/MASH in the U.S. by race/ethnicity ranges as follows: Hispanic (37.0% to 21.2%); non-Hispanic Black population (24.7%-11.6%); non-Hispanic White population (29.3%-12.5%). [98, 106, 107, 108]
- Hispanic/Latino people face a higher risk of developing MASLD than other racial or ethnic groups, according to findings presented at the 2021 AASLD Liver Meeting. [104]
- Black people who develop MASLD or its more severe form, MASH, are more likely to progress to liver cirrhosis, also according to findings presented at the 2021 AASLD Liver Meeting. [104]
- MASLD prevalence in the US has been projected to increase by 21%, from 83.1 million in 2015 to 100.9 million in 2030. [94]
- Food insecurity may be linked to MASLD. [109], [110]
- On April 25, 2024, it was announced that the first national study to assess the prevalence of MASLD will be conducted by Federal Government. [111]
- People typically don't experience symptoms until MASLD progresses to MASH. It is hard to tell MASLD from MASH without clinical evaluation and testing. [70, 72]

Metabolic dysfunction-associated steatohepatitis (MASH), formerly nonalcoholic steatohepatitis (NASH)

There have been recent changes to the **medical terminology covering "fatty" type liver disease** to reduce stigma. The term "fatty liver disease" (FLD) has been replaced by "steatotic liver disease" (SLD). SLD is an umbrella term covering "nonalcoholic fatty liver disease" (NAFLD)/"metabolic dysfunction-associated steatotic liver disease" (new term; MASLD); nonalcoholic steatohepatitis (NASH)/metabolic-associated steatohepatitis (new term; MASH); as well as alcohol-related liver disease (ARLD)/ alcohol-associated liver disease(new term; ALD), and the new category, Met+ALD (metabolic with alcohol-associated liver disease), a continuum which can have elements of MASLD and/or ALD. [59, 60, 61, 62, 63, 64, 65, 66, 67]

- MASH is a dangerous and progressive form of MASLD in which patients have liver inflammation and damage, as well as excess fat. [25]
- **Estimates of MASH vary but fall within similar ranges: One study of 2017-2020 NHANES data estimated the prevalence of MASH among US adults in the range of 1.3% to 4.8%** (2017–March 2020 National Health and Nutrition Examination Survey (NHANES) data)**. Another analysis** (2016) **estimated 1.5% to 6.5% of U.S. adults as having MASH.** J. Hopkins Medicine estimates **about 2% to 5% have MASH.** [70, 112, 113, 114, 115]
- Approximately 24% of U.S. adults have MASLD/MASH, and about 1.5% to 6.5% adults have MASH. [25, 95]
- MASH annual incidence rate increased from 1.51% in 2010 to 2.79% in 2020. [116]
- From 2016 to 2020, >1.8 million patients in the US were diagnosed with MASH annually. [117]
- MASH is the number one cause for liver transplants in women and those 65+ in the US. [118]
- MASH is projected to become the leading reason for liver transplantation in all population categories. [118]

- MASH progression can result in cardiovascular disease; hepatocellular carcinoma (liver cancer); and liver-related/all-cause mortality. MASH progression is often slow, but some may have rapid progression from no fibrosis (development of fibrous tissue in the liver, similar to scarring) to advanced fibrosis in about 6 years. [118]

- MASH is difficult to identify until the late stages of the disease. [114]

- MASH Is the second most common and the most rapidly Increasing indication for liver transplantation in the US. [118]

- In the U.S., **MASLD affects between 80 and 100 million people**, **about 20-25% of them will progress to MASH**. Many do not know they have the disease. **11% of MASH patients will develop cirrhosis/liver failure.** [119, 120]

- MASH prevalence is projected to increase 63% between 2015 and 2030. One model estimates that by 2030, the number of MASH patients with advanced fibrosis (scarring) will double, resulting in 800,000 liver-related deaths. [94, 95, 114, 121, 122]

- Between 2015 and 2030, the prevalence of MASH is anticipated to increase by 63%. By 2030, modeling data estimates the number of patients with MASH-related advanced fibrosis (scarring) is expected to double, which will result in 800,000 liver-related deaths. [95, 123]

- The high rate of obesity in the US drives the burden of MASH. [124]

- 47% of MASH patients have diabetes mellitus (DM). [79, 116, 119, 125]

- **Breakdown of MASH prevalence by race/ethnicity/gender (2022 study of NHANES data for 5492 patients):** [126]
    - Overall prevalence of MASH was 7.6%.
    - Mexican Americans had the highest prevalence (10.6%), followed by other Hispanics (9.1%).
    - Non-Hispanic Whites had the lowest prevalence (6.8%).
    - Females had lower prevalence (4.8%) than males (10.4%).
    - Among males, Mexican Americans had the highest prevalence (14.3%), followed by African American/Blacks (11.3%)
    - "Other race" category had the lowest prevalence (7.7%).
    - Among males and females, there was no association between MASH and race/ethnicity.
    - The highest prevalence of MASH was among Mexican American males.

- African American/Black people who develop MASLD or its more severe form, MASH, are more likely to progress to liver cirrhosis, according to findings presented at the 2021 AASLD Liver Meeting. [104]

- Among patients with MASLD, risk of MASH was higher in Hispanic/Latino people and lower in African American/Black people than White people. [107]

- MASH was the second leading cause of liver transplant on waiting lists in the US (after alcohol-associated liver disease or ALD - 2022 data) and is projected to become the leading cause. [114, 127, 128, 129]

- In 2016, MASH emerged as the primary cause of liver transplantation in the US among people born 1945-1965. And a recent study found that MASH has become the primary cause of transplants in the over-65 population (2018-2020). [129]

- MASH is the leading cause of liver transplant in women. [129, 130]

- MASH may progress to hepatocellular cancer (HCC), the third leading cause of cancer-related death globally and also a leading cause of liver transplant. MASH was also determined to be both the leading and fastest-rising cause of HCC in liver transplant candidates. [131, 132]

- The 20% Rule of MASH Progression: Approximately 20% of patients with MASH will progress to cirrhosis or develop decompensation, over a 2-year period. [133]

- High-risk, or at-risk, MASH is defined as: Patients with MASH who have both substantial liver fibrosis (F2 or greater) and a MASLD activity score (MAS) of 4 or greater. It is imperative for clinicians to medically intervene with these patients. MAS can range from 0 to 8 and is calculated by the sum of scores of steatosis (0-3), lobular inflammation (0-3) and hepatocyte ballooning (0-2). In patients with MASLD, MAS score of ≥ 5 strongly correlated with a diagnosis of "definite MASH" whereas MAS ≤ 3 correlated with a diagnosis of "not MASH". [79, 134, 135, 136, 137]

- Though the global burden of MASH is on the rise, there is no single strategy to address this serious health crisis. [123, 124]

How MASLD/NAFLD Affects Children

- MASLD affects up to 38% of children with obesity in the US. However, not all children with MASLD have obesity. [97]

- One study of 408 children with obesity (mean age of 13.2 years; 2018), MASLD was present in nearly one-third of boys and one-fourth of girls. [138]

- MASLD is the most common form of pediatric liver disease in the U.S., more than doubling the past 20 years, in part because of increasing childhood obesity. Some Studies estimate 5% to 10% of children have MASLD. [139, 140, 141, 142, 143, 144, 145, 146, 147]

- Pediatric **MASLD is often associated with metabolic syndrome.** [145]

- **A recent story in the *Washington Post* (10/3/2023) covering the growing crisis of childhood liver disease highlighted the following facts**: [148]
    - Before the turn of the century, pediatric fatty liver disease was relatively rare. Now millions are affected; the journal *Clinical Liver Disease* estimates 5% to 10 % of all children in the US have MASLD — about as common as childhood asthma.
    - There were large jumps in MASLD incidence across all ages in the US; the steepest increase by far was in children (data 2017-2021).
    - The rate of MASLD diagnosis more than doubled in children up to age 17 (insurance claim data analyzed for The Post by Trilliant Health). Some of that increase is because of more vigilant reporting and testing recently. The trend, however, holds true.
    - The crisis is acute in the Southeast, where pediatric obesity rates are highest.
    - When more than 5% of liver cells contain fat, steatotic liver disease (SLD) is indicated (5-10%). Pediatric specialists are finding children with livers of 30-40% fat, even as high as 60% fat.
    - There is a rise in transplants for fatty liver in people in their 20s and 30s.
    - The story also highlighted the link between ultra-processed foods and pediatric/childhood obesity/MASLD.

- Studies estimate that 20% to 50% of children with MASLD have the MASH. [141, 149]

- When compared to people who develop MASLD during adulthood, people who develop MASLD during childhood are more likely to have MASH and its complications or liver disease as adults. [141, 150]

- Children with MASH can develop cirrhosis, but the complications of cirrhosis, such as liver failure and liver cancer, usually happen in adulthood. [141, 150]

- **MASLD is more common in boys than in girls.** [141, 148]

- **MASLD occurs in children of all races and ethnicities but is most common in Hispanic/Latino children and Asian American children, followed by White children.** [141, 148]

- **MASLD is less common in younger children, girls, and African American/Black children.** [141, 148]

- One study: Prevalence of MASLD in children broken down by race/ethnicity (2006 data): [146]
    - Children of Hispanic/Latino ethnicity (11.8%)
    - Asian children (10.2%)
    - White children (8.6%)
    - Black/African American children (estimate of 1.5%)

Met+ALD (metabolic with alcohol-associated liver disease)

- There is a **new category for people with alcohol-associated liver disease** (ALD) and MASLD, called **Met+ALD** (metabolic with alcohol-associated liver disease). It is a continuum which can have elements of MASLD and/or ALD. Met-ALD is the result of fat in the liver from alcohol use combined with MASLD. MetALD can result in liver inflammation, scarring, and cirrhosis. [59]

HEPATITIS

What is hepatitis?

- **Hepatitis is inflammation of the liver**, which causes liver damage, affecting vital functions. Hepatitis is often caused by hepatitis viruses (**viral hepatitis**); the most common in the U.S. are hepatitis A, B, and C. People can also get hepatitis from excess fat in the liver (MASLD; MASH; steatotic liver disease (SLD)), heavy alcohol use, drug use disorder, toxins, **other viral infections** (Epstein-Barr virus (EBV); cytomegalovirus (CMV)), some medications, and some medical conditions, such as diabetes, obesity, metabolic disorders, ischemia, and autoimmune disorders. Many people living with hepatitis are asymptomatic or don't know they are infected. Symptoms for **acute hepatitis** include light fever, fatigue, appetite loss, nausea, vomiting, belly pain, dark urine, light-colored/grey stools, muscle and joint pain, itchy skin, jaundice (yellow eyes/skin), and feeling unwell. Symptoms for **chronic viral hepatitis** can take anywhere from **2 weeks to 6 months, to even decades** to develop. [150, 151, 152, 153]

- Viral hepatitis is a serious, life-threatening public health crisis in the U.S. Testing is the first step to receiving life-saving treatment. All adults should be tested for hepatitis B and hepatitis C. [154, 155]

- There are five main strains of hepatitis: A, B, C, D, and E. Hepatitis B and C have the greatest impact on public health, affecting millions worldwide and in the U.S. [156]

- There are many other strains and sub-types of hepatitis. Among them are: hepatitis F (HFV); hepatitis G (HGV; GB virus; GBV-C); hepatitis TT viruses (transfusion transmitted virus (TTV), also known as Torque Teno virus) and hepatitis TT-like viruses); hepatitis SEN (SEN-V; two SEN-V variants (SENV-D and SENV-H)); non-A-E hepatitis (non-A to E hepatitis; sometimes referred to as hepatitis X; non-A-G hepatitis); autoimmune hepatitis (types I and II); neonatal hepatitis. [154, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175]

- What is the difference between hepatitis A, B, C, D, and E? What is Hepatitis F, G, TT, SEN, and Non-A-G viruses? [154, 156, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176]
    - **Hepatitis A, hepatitis B, and hepatitis C** are caused by three different viruses that cause liver damage. Each can produce similar symptoms, but they are spread in different ways and can affect the liver differently.
        - **Hepatitis A** is usually a short-term infection.
        - **Hepatitis B** and **hepatitis C** can begin as short-term, but in some people, the virus stays in the body, causing chronic infection and long-term problems with the liver.
        - There are vaccines to prevent hepatitis A and hepatitis B, but no vaccine for hepatitis C.
        - **Hepatitis D** (caused by HDV virus) and **E** (caused by HEV virus) are not common in the U.S. but do occur.
        - **Hepatitis F** is a hypothetical virus being researched, possibly linked to viral hepatitis.
        - **Hepatitis G** is a newly discovered form of liver inflammation caused by hepatitis G virus (HGV), believed to be a distant relative of the hepatitis C virus.
        - **Hepatitis TT** (Transfusion Transmitted Virus (TTV), also known as Torque Teno Virus) is a type of virus that passed through transfusions, possibly linked to liver damage, and currently under study.
        - **Hepatitis SEN** is another newly identified virus currently being studied.
        - **Non-A-G/Non-A-E hepatitis** consists of all of the hepatitis viruses awaiting identification.
        - **Autoimmune hepatitis** is when your body's infection-fighting system (immune system) attacks your liver cells.
        - **Neonatal hepatitis** is liver inflammation occurring only in early infancy, usually between one and two months after birth.

How does hepatitis spread? Is it contagious?

- Viral hepatitis is contagious. Viruses are all contagious and the most common cause of hepatitis worldwide. Other types of hepatitis (non-viral) are not contagious. The five main hepatitis viruses – A, B, C, D and E—spread in different ways: [176]
    - Hepatitis A and E spread through contaminated food and water.
    - Hepatitis B, C, and D can spread through contact with blood from an infected person. This happens when needles are shared during intravenous drug use.
    - Hepatitis B and D can also spread through other bodily fluids from sexual contact and from parent to child during childbirth.

- Many people with hepatitis in the United States do not know that they have hepatitis. **One in two people with hep B and one in three people with hep C are unaware they are infected**. Untreated, hep B and C can cause liver cancer and death. Infected people can also unknowingly transmit it to others. [155, 156, 160, 161, 177]
- The World Health Organization (WHO) states that, worldwide, most people with viral hepatitis don't know they have it. [178]

- The elimination of hepatitis is a national priority. In 2020, the Centers for Disease Control and Prevention (CDC) released universal hepatitis screening recommendations for adults. [179, 180]

- May 15 is Hispanic Hepatitis Awareness Day [181]

- World Hepatitis Day is observed on July 28. [182]

Hepatitis A (HAV; Hep A)

- Hepatitis A (HAV; Hep A) is a highly contagious, usually short-term, liver infection that can be spread person-to-person and through tainted food or drink. It can be found through testing and is preventable by vaccine. [183, 184, 185, 186]

- At risk for hepatitis A: People exposed to poor sanitation; people who use drugs (injection or non-injection; illegal drugs); people experiencing homelessness; men who have sex with men (MSM); incarcerated people; certain healthcare and lab workers; people with chronic liver disease; people who are HIV positive; international travelers; people in close contact with international adoptees; people who live with someone who has hep A. [187, 188, 189, 190]

- Persons aged 30–39 years had the highest rate of hepatitis A. [186, 191]

- In the US during 2022, there were 2,265 new cases and 4,500 estimated infections of hepatitis A reported, as well as 118 hepatitis A-related deaths. [186, 192]

- Since 2016, there have been multiple hepatitis A outbreaks in 37 states across the US, caused primarily by person-to-person spread among adults using drugs and experiencing homelessness. After annual increases from 2015, cases began to decrease in 2020. [186, 192]

- There was a 60% decrease of newly reported cases of hepatitis A from 2021–2022, but the number of 2022 cases remained 1.6 times higher than 2015. [186, 192]

- In 2022 58% of hepatitis A cases were among non-Hispanic White persons. [186, 192]

Hepatitis B (HBV; Hep B)

- **Hepatitis B (HBV; Hep B) is the most common serious liver infection and blood borne infection in the world.** Hepatitis B is a type of liver infection caused by the hepatitis B virus (HBV); it can be **short-term (acute) but** can progress to a **long-term or life-long illness (chronic)**, including liver disease/liver cancer. Hepatitis B is spread with blood, semen, or other body fluids, or can be passed through birth. It is preventable with vaccines. Testing is the only way to know if you are infected. Treatment can control hepatitis B in infected people. [192, 193, 194, 195, 196]

- Untreated long-term (chronic) hepatitis B and hepatitis C can cause cirrhosis, liver cancer (hepatocellular carcinoma (HCC)) and death. [16, 184, 195, 197, 198]

- **Around the world, two billion people (<u>one in three</u>) are estimated to have been infected with the hepatitis B virus.** [197]

- **The World Health Organization (WHO) has estimated that in 2022, 254 million people were living with chronic hepatitis B. The WHO also estimated that hepatitis B resulted in 1.1 million deaths that same year, and that there were 1.2 million new hepatitis B infections each year.** [194]

- **Hepatitis B disproportionately affects children**. The hep B virus can be passed on through the mother. However, hepatitis B can be prevented with a vaccine given soon after birth with boosters a few weeks later, offering nearly 100% protection against the virus. [194, 199, 200]

- According to the Centers for Disease Control and Prevention (CDC), during 2022: [201]
  - 2,126 new cases of acute hepatitis B.
  - 13,800 estimated acute HBV infections.
  - 16,729 cases of newly reported chronic hepatitis B.
  - 1,797 hepatitis B-related deaths.

- An estimated 660,000 adults are living with hepatitis B in the U.S. [184]

- Estimates of the number of adults living with hepatitis B infection in the U.S. range from 660,000 (CDC) to 2.4 million (chronic; Hepatitis B Foundation). [184, 195, 202, 203]

- **At risk for hepatitis B:** Anyone can get hepatitis B, but high-risk people include: people who inject drugs or share needles, syringes, drug equipment (the most common risk factor for acute HBV infection, because of the opioid crisis); infants of infected mothers; sex partners of infected people (esp. men who have sex with men); people exposed to blood, body fluids, or sores of someone who has hepatitis B (such as lab workers); people who have gotten tattoos with infected needles; anyone sharing contaminated items with someone who has hepatitis B infected person (toothbrushes, razors, or medical equipment (eg, glucose monitors)); people with certain medical conditions (e.g., HIV, chemotherapy, dialysis); people who live in households with some who has hepatitis B; people born in certain regions of the world with a high prevalence of hepatitis B; and rarely, dialysis/transplant patients and healthcare and public-safety workers exposed to blood or who work in facilities with inadequate infection control. [194, 195, 196, 204, 205, 206]

- **Hepatitis B symptoms include** abdominal pain; dark urine; fever; joint pain; appetite loss; nausea/vomiting; fatigue/weakness; jaundice (yellowing skin and whites of eyes); light or clay-colored stool; fluid swelling in belly or arms and legs. Not all people newly infected with HBV have symptoms. [196, 207, 208]

- **"Chronic" and "acute" hepatitis B:** HBV can be limited or life-long. When a person is first infected (sometimes for only a few weeks, with mild or no symptoms) it is called an **"acute infection" (or a new infection or short-term).** When the infection lasts more than six months, it is called a long-term or **"chronic infection"** (which can have no symptoms for decades, or immediate symptoms). A simple blood test can tell the difference. [196, 202, 208, 209, 210]

- 1 out of 2 people with hepatitis B are unaware. [184]

- A person can spread the hepatitis B virus and not know it. [196, 202]

- **HBV is highly transmissible** and infectious on surfaces for at least 7 days. [196]

- Approximately **50% of people living with chronic hepatitis B don't know they have it** and **can unknowingly transmit their infection to others**. [196]

- Approximately **50-70% of people with acute hepatitis B are not symptomatic**. [196]

- Acute hepatitis B symptoms usually appear about 1 to 4 months after infection but can appear as early as two weeks. [209]

- People who inject drugs have the highest rates of new (incident) hepatitis B and hepatitis C infections. [184]

- The acute hepatitis B rate remained stable during 2021-2022. [211]

- 52% of all acute hepatitis B cases were aged 40–59 years. [202]

- **89% of new (incident) chronic hepatitis B cases were in people 30 years and older.** [202]

- While the rate of **acute hepatitis B was lowest** among **non-Hispanic A/PI (Asian/Pacific Islander)** persons, the rate of **new (incident) chronic hepatitis B was highest** in this group. The rate of **new (incident) chronic hepatitis B cases among non-Hispanic A/PI persons was 11.2 times as high as** the rate among **non-Hispanic White persons**. [202]

- Highest rates of chronic hepatitis B infection in the US are among foreign-born individuals, especially people born in Asia, the Pacific Islands, and Africa. Foreign-born individuals account for 14% of the general population, but 69-70% of those with chronic HBV infection. [195, 212]

- Hepatitis B and the ensuing liver cancer are among the largest health disparity issues for these groups of foreign-born people in the US. [203]

- **A 2018 demographic breakdown of foreign-born people in the U.S. with chronic hepatitis B:** about 59% had emigrated from Asia, 19% from the Americas, and 15% from Africa. [203]

- The **rate of acute hepatitis B is highest in non-Hispanic Black populations**, increasing 11.1% during 2021–2022, and **was 1.7 times as high** as the rate among non-Hispanic White persons. [202]

- Asian/Pacific Islander (A/PI) populations have the highest rates of hepatitis B-related deaths. [184, 202]

- Hepatitis B-related deaths among non-Hispanic A/PI persons and non-Hispanic Black persons were 8.5 times and 2.6 times higher than among non-Hispanic White persons, respectively. [202]

- About 2% of people with HIV are coinfected with HBV and are at greater risk for complications and death from HBV infection. [195]

- **Hepatitis B disproportionately affects children**. Only 5% of adults who are infected by hep B develop a chronic infection, but 30% (1 in 3) of children under age 6 do. [196, 208]

- The younger a person's age when they are infected with Hep B, the greater the chance of the infection becoming chronic and lifelong, the risk goes down as a child gets older. The majority of children 6 and older infected with the hepatitis B virus recover completely. [196]

- Approximately 9 in 10 infants infected with hepatitis B will develop life-long, chronic infection. [196]

- **A one-time universal screening for hepatitis B could save 23,000 lives and nearly $600 million** in the U.S., according to a study in the journal *Clinical Infectious Diseases*. [213, 214]

- 70% of adults in the US reported they were unvaccinated for HBV (2018). [213]

- 464,000 children's lives have been saved by hepatitis B vaccines since 1974. Every 10 seconds, one child's life is saved from a fatal disease by a vaccine. [215, 216]

Hepatitis C (HCV; Hep C)

- **Hepatitis C is a liver infection caused by the hepatitis C virus (HCV)** and is spread through contact with blood from an infected person. HCV is one of the most common types of viral hepatitis in the US. It is transmitted through blood. Most people become infected by sharing needles or other equipment used to prepare and inject drugs. For some, hepatitis C is a short-term illness, but for more than half (80%) it becomes a long-term, chronic infection. [184, 217, 218]

- Untreated, chronic hepatitis B and C can result in cirrhosis, liver cancer, and death. [184, 218, 219]

- **There is no HCV vaccine, but treatments, called direct acting antivirals (DAAs) can cure most persons with it (95%)**. Treatment is always needed for chronic hepatitis C. [198, 218, 219, 220]

- Acute vs. chronic HCV: People having HCV for a few weeks to a few months have "acute" hepatitis C. When people have hep C longer than 6 months, it becomes "chronic" hepatitis C, which can last for years and lead to serious liver damage. [221, 222]

- More than 2 million adults in the US are estimated to have hepatitis C. [184]

- 1 out of 3 people with hepatitis C are unaware. [184]

- **Estimates of the number of people with HCV can vary** because the National Health and Nutrition Examination Survey (NHANES), the main source of public health data in the US, does not sample certain populations, such as people who are incarcerated, homeless individuals, nursing home residents, persons on active military duty, and immigrants. [223]

- Globally, an estimated 50 million people have chronic hepatitis C virus infection, with about 1.0 million new infections occurring per year. [221]

- In 2022, approximately 242 000 people died from hepatitis C worldwide, mostly from cirrhosis and hepatocellular carcinoma (liver cancer), according to the WHO. [221]

- **HCV is the outstanding cause of non-A, non-B hepatitis.** [224]

- People with HCV who are unaware of their infection status can unknowingly transmit the virus to others. [225]

- **The hepatitis C virus is usually spread when someone comes into contact with blood from an infected person.** [219, 226, 227]

- **At risk for HCV:**

- Anyone who has ever injected, snorted or inhaled an illegal drug, especially those who shared drug injection/preparation equipment; people with unusual liver test results in which the cause wasn't found (including alanine aminotransferase (ALT) blood tests); children of mothers with HCV; healthcare, emergency medical, and public safety personnel exposed to HCV infected blood/needles or improper safety procedures; pregnant people, during the pregnancy; maintenance hemodialysis patients; people with hemophilia who received clotting factor before 1987; people who received transplants or blood transfusions before 1992; sexually active people; sexual partners of anyone with hepatitis C; men who have sex with men (MSM); people with HIV; anyone who has been in prison; people receiving piercings or tattoos in unclean environments or using unsterile equipment; people sharing glucose monitors, razors, nail clippers, toothbrushes, other items; and others. [219, 227, 228]

- **HCV is not spread through food, water, or mosquitoes.** [219, 227, 228]
- HCV is of particular concern for people with kidney disease. There is a much higher prevalence of HCV in people with chronic kidney disease (CKD) and end-stage kidney disease (ESKD) than in the general population. HCV can also cause kidney disease. [228]
- HCV is best prevented by avoiding behaviors that spread the virus. [229]
- IV drug users have the highest rates of new hepatitis B and hepatitis C infections. [184, 230]
- HCV/HIV coinfection: HCV/HIV coinfection means that a person has both viruses at the same time. For every 100 people with HIV, approximately 21 of them also have HCV. [231, 232]
- Approximately 5% of infants born to infected mothers will get hepatitis C (neonatal hepatitis C). [233]
- Acute **HCV symptoms** usually happen 2–12 weeks after exposure. Chronic hepatitis C usually has no symptoms for many years, and they appear only after the virus damages the liver enough to cause them. HCV symptoms include: chronic fatigue and depression; bleeding or bruising easily; loss of appetite; nausea and vomiting; stomach pain; fever; yellow skin and eyes (jaundice); dark urine; light colored stool; itchy skin; joint pain; fluid buildup in the abdomen (ascites); swelling in legs; weight loss; confusion, drowsiness and slurred speech (hepatic encephalopathy); spiderlike blood vessels on skin (spider angiomas). [219, 227]
- There were **93,805 newly reported cases** of **chronic HCV** during 2022. [231]
- There were **67,400** estimated **acute HCV infections** during **2022**, of which **4,848 cases were new.** [231]
- **Chronic HCV infections are highest among two age groups: 25–45 and 55–70 years.** [156, 231]
- **Persons aged 30–39 years had the highest rates of acute HCV.** [156, 231]
- Between 2013 and 2020, the number of acute HCV infections more than doubled. [198, 212, 231]
- Then in 2022, the estimated number of new HCV infections declined for the first time after more than a decade of consecutive annual increases but remained high at 67,400 cases. [198, 212, 231]
- However, in 2022, the number of acute hepatitis C cases was still 2 times as high as 2015. [198, 212, 231]

- 65% of new chronic HCV cases occurred among men (2022). [231]
- The rate of new chronic HCV cases was highest among non-Hispanic American Indian/Alaska Native (AI/AN) persons (2022). [231]
- Acute HCV was highest among males, people 30–39 years old, non-Hispanic AI/AN persons, and those in Eastern and Southeastern states (2022). [231]
- Rate of acute HCV is highest in non-Hispanic American Indian/Alaska Native (AI/AN) populations. [219]
- The rate of acute HCV in non-Hispanic White persons decreased but increased among non-Hispanic AI/AN persons 7.4% and was 1.9 times higher (2021–2022). [156, 231]
- **There were 12,717 hepatitis C-related deaths in 2022.** [231]
- **In 2022, the death rate for HCV decreased** (2022: 2.89 deaths per 100,000) (-9% from 2021: 3.18 deaths per 100,000) (-22% from 2018: 3.72 deaths per 100,000 population). [156, 184, 231]
- **HCV-related deaths are highest in non-Hispanic AI/AN and non-Hispanic Black persons.** [156, 184, 231]
- **HCV-related deaths were 3.3 times higher in non-Hispanic AI/AN people and 1.7 times higher in non-Hispanic Black persons than non-Hispanic White persons.** [156, 184, 231]

HBV & HCV/HIV Coinfection

- People with HIV and liver disease are at risk for severe hepatitis A virus (HAV) infection. [234]
- People with HIV with hepatitis B virus (HBV) or hepatitis C virus (HCV) are at increased risk for morbidity and mortality. [235]
- HBV or HCV can affect the management of HIV in patients. [235]
- HIV positive people should be vaccinated against hepatitis A and hepatitis B. [235]
- HIV positive people should be tested for hepatitis B and hepatitis C. [235]
- HCV/HIV coinfection means that a person has both viruses at the same time. For every 100 people with HIV, approximately 21 of them also have HCV. [232]

Hepatitis D (HDV; Hep D; “delta hepatitis”)

- Hepatitis D (HDV) is one of the five known hepatitis viruses. It was discovered in 1977 in patients with chronic hepatitis B (HBV). [235, 236]
- Globally, **hepatitis D (HDV)** is **most common** in Eastern Europe, Southern Europe, the Mediterranean region, the Middle East, West and Central Africa, East Asia, and the Amazon Basin in South America. **HDV is uncommon in the United States**; most cases occur among people who migrate or travel to the U.S. The number of HDV cases in the U.S. is unknown. [164, 237, 238, 239]
- HDV is known as a “satellite virus,” because it can only infect people with hepatitis B (HBV; “coinfection”). The illness can be short or long-term, coming in acute and chronic forms. [164, 238, 239, 240]

- People who have chronic hepatitis B and D develop complications more often and more quickly than people who have chronic hepatitis B alone. [238, 240]

- There is no vaccine for HDV; the hepatitis B vaccine can protect people from HDV infection, but treatment success is low. [238, 240]

- Globally, it is estimated that HDV affects nearly 5% of people who have chronic hepatitis B (HBV). [240]

- **HDV has similar risk factors/groups and symptoms to hepatitis A, B, and C.** Symptoms usually appear 3–7 weeks after first infection. [164, 238, 240]

- **HDV is not spread through food or water**, sharing eating utensils, breastfeeding, hugging, kissing, hand holding, coughing, or sneezing. HDV spreads the same way that hepatitis B spreads, through contact with an infected person's blood or other body fluids. [164, 238, 240]

- **HDV can only infect people who are also infected by the hepatitis B virus (HBV**); infection can occur simultaneously ("coinfection") or after infection with hep B ("superinfection"). HDV could be called a disease amplifier. It causes HBV to progress more rapidly, causing cirrhosis and liver failure, making it more deadly. [164, 238, 240]

Hepatitis E (HEV)

- **Hepatitis E** is a liver infection caused by the hepatitis E virus (HEV). HEV is found in the stool of HEV infected people. **It is uncommon in the U.S. and developed countries. It is most common in developing countries** with inadequate water supply and poor environmental sanitation; people often get HEV from drinking contaminated water. **People living in crowded camps or temporary housing, esp. refugees and displaced people, are at high risk.** Symptoms of HEV are similar to other forms of hepatitis; however, many people, especially young children, can have no symptoms. Most people with healthy immune systems fully recover. **There is no vaccine for HEV.** [168, 241, 242]

- There are an estimated 20 million HEV infections worldwide every year. 3.3 million of these infections become symptomatic HEV cases. [242]

- **For pregnant women, HEV can be a very serious illness**, with a mortality rate of up to 30% in their third trimester. **HEV is also a serious health threat to people with preexisting chronic liver disease and organ transplant recipients** on immunosuppressive therapy. [168, 243, 244]

A note on F, G, and TT viruses:

- Over the past decade, several hepatitis viruses have been identified, beyond hep A through E. Acute hepatitis not caused by hepatitis viruses A to E or alcohol, drugs, or autoimmune disease is important because 29% of these cases result in serious illnesses, such as fulminant hepatic failure, aplastic anemia, and progression to chronic hepatitis and cirrhosis. [245]

Hepatitis F (HFV)

- **Hepatitis F** virus (HFV) was identified in 1991. It is a hypothetical, poorly defined, virus of uncertain significance linked to viral hepatitis. Hepatitis F may be a mutant hepatitis C. [158, 162, 169, 246, 247]

Human pegivirus 1 (HPgV-1)

- Human pegivirus 1 (HPgV-1) was formerly known as "Hepatitis G" (HGV), hep G; GB virus; GB virus type C (GBV-C). [248, 249]

- HPgV-1 is transmitted by percutaneous injuries (PIs), contaminated blood and/or blood products, through sexual contact, and mother-to-child transmission, similar to HBV and HCV. [250]

- **HPgV-1** is believed to be a distant relative of the **HCV** virus. In its original classification, HGV, HPgV-1 was first described early in 1996. **HPgV-1 is still being studied. What is known is that transfused blood containing HPgV-1 has caused some cases of hepatitis. For this reason, patients who require large amounts of blood or blood products are at risk of HPgV-1.** [167]

- 3-15% of normal individuals have antibodies to HPgV-1. [173]

- Between one-sixth and 25% of the global population is estimated to be positive for HPgV-1 antibodies. [251, 252]

- It is estimated that 1% to 4% of blood donors worldwide are carriers of HPgV-1. [253]

- **Often patients with HPgV-1 are infected at the same time by the hepatitis B or C virus, or both.** In about 3 of every 1,000 patients with acute viral hepatitis, HPgV-1 is the only virus present. There is some indication that patients with HPgV-1 may continue to carry the virus in their blood for many years and so might be a source of infection in others. [167]

- Some recent studies indicate that HPgV-1 may actually have a beneficial clinical effect on many diseases, such as acquired immunodeficiency syndrome (AIDS) and HCV. [249, 251, 252]

Hepatitis TT Viruses (transfusion transmitted virus (TTV), Torque Teno Virus), and Hepatitis TT-like Viruses

- Hepatitis TT (transfusion transmitted) viruses were recently discovered in the late 20th century. Some studies indicate that they are passed on by blood transfusion. [253, 254]

- TTV is widespread, reaching 95% of healthy people in some regions of the world. [255]

- Studies indicate it can be spread in several ways: fecal-oral, parenteral, and sexual. [255]

- Some studies have associated TTV with different liver diseases, such as post-transfusion hepatitis, hepatitis B, and hepatitis C, but this is still under study. [255]

- Another study states that TTV appears to correlate with some acute and chronic hepatitis cases and may produce liver damage under specific circumstances. [170]

- However, the association between TTV and liver disease is disputed by some scientists. [246, 256, 256]

Hepatitis SEN (SEN-V; two SEN-V variants (SENV-D and SENV-H))

- SEN virus (SENV) is named after the initials of the patient with HIV from which it was first isolated. [257]

- Recent studies negated the link between SEN and post-transfusion hepatitis. Further studies may reveal more about its effects. [258]

- SEN's prevalence varies by geographic region. One sample detected SEN in as many as 30 percent of patients who received transfusions and 3 percent of patients who did not receive transfusions. [259]

- It appears to be transmitted by transfusion. One sample detected SEN in as many as 30 percent of patients who received transfusions, and 3 percent of patients who did not receive transfusions. [259]

Non-A-E Hepatitis (Non-A to E Hepatitis; "acute non HepA-E hepatitis"; sometimes referred to as Hepatitis X; Non-A-G hepatitis)

- "Non hepa A-E" of unknown origin is severe hepatitis not caused by the five strains of the virus (A-E). [259]
- The cause of non-A-E hepatitis is not currently known. [260]
- Non-A-G/Non-A-E hepatitis consists of all of the hepatitis viruses awaiting identification. [162]
- Non-A-E hepatitis is a "diagnosis of exclusion," made through process of elimination, when all other potential causes have been eliminated, and the diagnosis is based on the absence of any other identifiable condition. [261]
- Non-A-E hepatitis is similar to the other forms of acute hepatitis. In most cases, no source of exposure can be identified; some rare cases have been reported after blood transfusions. Non–A-E's lack of the regular risk factors for hepatitis suggests that some cases may be due to nonviral causes, such as an autoimmune process, environmental exposure, or drugs. [262]
- There is no treatment or preventative measures for non-A-E hepatitis. [262]
- Acute non-A-E-hepatitis in children is rare but severe, often resulting in acute liver failure. [261]

Autoimmune Hepatitis (types I and II)

- Autoimmune hepatitis is when the body's immune system attacks liver cells. It is a long-term chronic liver disease, causing inflammation and damage. [159, 262]
- Causes are unknown and it is more likely in people with other autoimmune conditions. [159, 263]
- Other viruses that can cause acute hepatitis: [260]
    - Epstein-Barr virus (EBV)
    - cytomegalovirus (CMV)
    - parvovirus
    - enteroviruses
    - adenoviruses (adenovirus type 41 (children)
    - rubella virus
    - herpes viruses (HHV-1, HHV-2, HHV-6, HH-7)
    - human immunodeficiency virus (HIV)
- Other infectious agents that may cause hepatitis: [260]
    - Brucella spp
    - Coxiella burnetiid
    - Leptospira
- Neonatal Hepatitis (neonatal hepatitis B/C/cytomegalovirus and others, neonatal HBV, congenital hepatitis) [171, 263]
- Neonatal hepatitis is liver inflammation occurring only in early infancy (one and two months after birth). [171, 264]

- Approximately 20% of infants with neonatal hepatitis were infected by a virus from their mother before birth or shortly after birth. These viruses include cytomegalovirus, rubella (measles) and hepatitis A, B or C viruses. In the other 80%, no specific virus can be identified as the cause, but many experts suspect a virus. [171, 264]

- Early diagnosis is critical. [264]

- There is no cure for neonatal hepatitis, but there are treatments. [264, 265]

Epstein-Barr virus (EBV)

- Epstein-Barr virus causes acute viral hepatitis, but most patients recover. [177, 265, 266]

Cytomegalovirus (CMV; human cytomegalovirus (HCMV))

- Cytomegalovirus (CMV) infection can cause acute viral hepatitis in immunocompromised individuals, particularly liver transplant patients. [177, 267]

- Human cytomegalovirus (HCMV) affects 40% to 100% of the world population. It is transmitted through close contact by body fluids (saliva, blood, urine, breast milk, semen and cervical secretions), and by organ transplantation. Most people with healthy immune systems are asymptomatic, but immuno-compromised people may experience severe complications. [177, 268]

- There are no specific guidelines for treatment, but the majority of patients recover on their own. [177, 268]

Toxic Hepatitis

- Toxic hepatitis causes include: [177, 268]
    - Industrial chemicals, including vinyl chloride, carbon tetrachloride and certain pesticides and herbicides.
    - Over the counter (OTC) medications, especially high doses of nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen (Tylenol®).
    - Prescription drugs, including statins, certain antibiotics and anti-seizure medications.
    - Non-prescribed drugs such as ecstasy, cocaine or off-label use of anabolic steroids.
    - Some herbs and supplements in large or frequent doses.

- Prevention: [177, 269]
    - Toxic hepatitis can't always be prevented. But you may reduce your risk if you:
        - Limit medications; look into nondrug options for common medical problems.
        - Take medications only as directed; don’t take too much.
        - Before taking herbs and supplements talk to your doctor.
        - Alcohol and drugs don’t mix.
        - Take precautions with chemicals.
        - Keep medicines and all chemicals away from children.

- Look up medications and supplements linked to liver damage at The National Institutes of Health LiverTox website. [269]

Alcohol-Induced Hepatitis

- Alcohol-induced hepatitis can be chronic or acute. You can get acute hepatitis after a short drinking binge or chronic hepatitis from chronic, heavy alcohol use (alcohol use disorder/AUD). [177]

Met+ALD (metabolic with alcohol-associated liver disease)

- There is a new category for people with alcohol-associated liver disease (ALD) and MASLD, called Met+ALD (metabolic with alcohol-associated liver disease). [177]

Steatotic Liver Disease (SLD)

- Steatohepatitis/steatotic liver disease (SLD) means hepatitis from fat. Information about the following conditions causing hepatitis can be accessed on the ALF site: [177, 269]
    - Steatotic liver disease (SLD)
    - Metabolic dysfunction-associated steatotic liver disease (MASLD)
    - Metabolic dysfunction-associated steatohepatitis (MASH)

Other Causes of Hepatitis:

- Cholestasis. Cholestasis means that bile doesn't flow through the liver's biliary tract. Then bile backs up into the liver, causing damage and hepatitis. It can happen suddenly (acute), due to an obstruction, or gradually (chronic), from a disease or condition. Pregnancy can also increase the risk for this condition. [177, 270]

- Inherited metabolic disorders (metabolic-liver-disease). Rare genetic disorders that affect metabolism can also affect the liver: Wilson disease; hemochromatosis; Gaucher disease; glycogen storage disease (GSD); and others. [177, 271]

- Ischemia (ischemic hepatitis, "shock liver"; ischemic hepatitis, hepatic infarction, and ischemic cholangiopathy). Ischemia is sudden or gradual loss of blood to an organ and can cause serious injury to the liver due to circulatory failure. It can also cause acute or chronic inflammation. [177, 272, 273]

- Causes of ischemia include sudden vasoconstriction, occlusions such as blood clots and arterial diseases that narrow arteries. Ischemia can also be a response to shock from a severe infection or organ failure. [177, 273, 274]

LIVER CANCER

- **Liver cancer** is due to excessive proliferation of tumor cells, cells with dysregulated replication mechanisms that eventually take over the liver's healthy cells. In adults, **the most common type of liver cancer is hepatocellular carcinoma (HCC).** [110, 274, 275, 276, 277, 278, 279]

- Liver cancer can be classified into **3 types**: [110, 275, 276, 277, 278, 279, 280]
    - **Primary liver cancer** occurs when the primary tumor originates from the hepatobiliary system. Some examples include hepatocellular carcinoma, **bile duct cancer** (intrahepatic cholangiocarcinoma); and **rarer forms of cancer** such as angiosarcoma, hemangiosarcoma, hepatoblastoma, and fibrolamellar carcinoma.
    - **Secondary liver cancer** (metastatic liver cancer) occurs when the tumor originates from another part of the body and spreads to the liver, either by hematogenous (blood circulation) or through lymphatic system.
    - The last group of liver cancers **include benign liver tumors** such as hemangioma, hepatic adenoma, and **focal nodular hyperplasia (FNH)**. These Are non-cancerous in nature and usually need monitoring or rarely, surgery because of pain, discomfort or mass effect (pushing on stomach or bile ducts).

- **Stages of Liver Cancer:** There are different liver cancer staging systems; These staging systems are not used uniformly among physicians. The one most commonly used liver cancer staging system in the United States is the AJCC (American Joint Committee on Cancer) **TNM system**. This staging system uses 3 pieces of information: [110, 280]
    - **Tumor size (T)**: How large is the cancer? Is there more than one liver tumor?
    - **Lymph node involvement (N)**: Has the cancer reached nearby lymph nodes?
    - **Tumor spread (metastasis; M)**: Has the cancer spread to nearby or distant lymph nodes, organs, or bones?

- **The primary <u>risk factors</u> of liver cancer:** [16, 281, 282, 283, 284]
    - Viruses, including hepatitis B virus (HBV) (the third leading cause of cancer deaths in the world) and hepatitis C virus (HCV)
    - cirrhosis/end stage liver disease
    - alcohol consumption
    - metabolic dysfunction-associated steatotic liver disease (MASLD)
    - metabolic dysfunction-associated steatohepatitis (MASH); some of the risk factors for MASH include diabetes and obesity
    - genetic/inherited liver diseases
    - exposure to some toxins
    - steroid use
    - hemochromatosis (condition where the body stores more iron than it needs),
    - other causes

- Globally, up to 80 percent of liver cancers are caused by hepatitis B (HBV) or hepatitis C virus (HCV). [277, 285, 286]

- **<u>Risk factors</u> for liver cancer**: [16, 284, 287, 288, 289]
    - Cirrhosis (scarring of the liver) from any cause (including chronic hepatitis B or C,
    - Metabolic dysfunction-associated steatotic liver disease (MASLD)
    - Metabolic dysfunction-associated steatohepatitis (MASH)
    - Alcohol-associated liver disease (ALD)
    - Met+ALD (metabolic with alcohol-associated liver disease)
    - Hereditary hemochromatosis (iron overload disorder)
    - Alpha 1 antitrypsin deficiency
    - Primary biliary cirrhosis (PBC)
    - Male gender
    - Being a member of certain racial/ethnic groups
    - Obesity
    - Older age
    - Tobacco use
    - Type 2 diabetes (T2D)
    - Steroid use
    - HIV/AIDS
    - Exposure to certain toxins/substances (e.g., aflatoxins (poisons produced by crop molds), vinyl chloride and thorium dioxide (thorotrast)
    - Family history of liver cancer
    - Certain rare diseases
    - Other factors

- Chronic viral hepatitis is a leading cause of liver cancer in the US. [290]

- Bile duct cancer (cholangiocarcinoma) occurs in the bile ducts, which are the tubes or channels that carry bile that's produced by the liver and helps with several important functions. Bile ducts drain the bile made in the liver to the gallbladder and small intestine. [291]

- There are two types of bile duct cancer based on where they originate: [292, 293]
    - Intrahepatic bile duct cancer (intrahepatic cholangiocarcinoma's): This type forms in the ducts inside the liver. Only a small number of bile duct cancers are intrahepatic, and the survival rate is very low.
    - Extrahepatic bile duct cancer: This type forms in the ducts outside the liver. There are two types of extrahepatic bile duct cancer: perihilar bile duct cancer (Klatskin tumor, perihilar cholangiocarcinoma) and distal bile duct cancer (extrahepatic cholangiocarcinoma).

- Prevalence of liver cancer: an estimated 108,247 people were living with liver and intrahepatic bile duct cancer in the US (2021). [294]

- Incidence (new cases) of liver and intrahepatic bile duct cancer: 9.4 per 100,000. (2017–2021). [295, 295, 296]

- **New cases of liver/bile duct cancer** (2024, estimated): 41,630 (2.1% of all new cancer cases). [295, 296, 297]

- **Liver/bile duct cancer deaths** (2024, estimated): 29,840 (4.9% of all cancer deaths for the year). [295, 296, 297]

- **5-Year liver and intrahepatic bile duct cancer survival rate:** 22% (2013-2019); 21.7% (2014–2020). [295, 296, 297]

- Liver cancer carries poor prognosis. [110]

- Liver cancer is rare compared to other cancers, making up only around 2% of all cancers in the United States. However, it accounts for about 4.8% of all cancer deaths in the country. The most common type of liver cancer is hepatocellular carcinoma (HCC). During the past few decades, the incidence and mortality of liver cancer has rapidly increased in the US. However, since 2017, the incidence rate has been declining, and the death rate has stabilized. That being said, liver cancer is still considered to have one of the worst survival rates, with an average five-year survival rate of 21.6%. [110]

- Worldwide, liver cancer is the sixth most common cancer and the third leading cause of cancer-related deaths. [284]

- In the US, "liver and intrahepatic bile duct cancer" is the sixth leading cause of cancer deaths. [297]

- The US liver cancer death rates:
    - 5.30 per 100,000 (2021) [296]
    - 6.6 per 100,000 (2018–2022) [295]

- Liver cancer is the 13th most common type of cancer overall in the U.S., with 41,630 estimated new (incident) cases (28,000 men; 13,630 women) and 29,840 estimated deaths (19,120 men; 10,720 women) in 2024. [289, 295, 298]

- Globally, more than 800,000 people are diagnosed with liver cancer each year. [299]

- Liver cancer is more common in sub-Saharan Africa and Southeast Asia than in the US. In fact, it is the most common type of cancer in those regions. [299]
- Worldwide, liver cancer is a leading cause of cancer deaths, with more than 700,000 deaths each year. [299]
- The rates of liver cancer are higher in Southwestern and Southeastern areas of the US, which have the highest populations of Black and Hispanic people. [110, 295]
- Liver cancer is one of the most rapidly growing causes of cancer related deaths in the U.S. [299]
- Liver cancer death rates have more than doubled since 1980. [299, 300, 301]
- Liver cancer incidence rates have more than tripled since 1980. [299, 301, 302]
- In some cases, even though the rate is going down, the number of new cases and deaths is going up. This is due to aging and increase in the population size. [110, 298, 302, 303]
- Liver cancer/hepatocellular carcinoma (HCC) is more common in men than women. [288, 295]
- In the US, Asian/Pacific Islander people have the highest liver cancer rates, followed by Hispanic/Latino, American Indian/Alaska Native, African American/Black, and White peoples. [288, 295]
- In the US, liver cancer incidence and mortality are approximately 1.5X to 2X higher in American Indian/Alaska Native (AIAN), Asian American, African American/Black, and Hispanic/Latino people than in the White people. [304]
- American Indian/Alaska Native men were almost 2X as likely to have liver and intrahepatic bile duct (IBD) cancer as non-Hispanic White men. (2014-2018) [305]
- American Indian/Alaska Native women are 2.3 X more likely to have liver and intrahepatic bile duct (IBD) cancer, and 2.2 X as likely to die from those diseases as non-Hispanic White women. (2014-2018) [306]
- In the US, liver cancer incidence (new cases) is higher among African American/Black people, compared to White people. (2017–2021) [295]
- African American/Black women are 30% more likely to die from liver/intrahepatic bile duct (IBD) cancer than non-Hispanic White women. (NCI 2022 Cancer Rates (2015-2019 data)) [306]
- African American/Black men are 60% more likely to get and die from liver/intrahepatic bile duct (IBD) cancer than non-Hispanic White men. (NCI 2022 Cancer Rates (2015-2019 data)) [307]
- During 2000–2019: the liver cancer mortality rate was highest in American Indian/Alaska Native people (10.5 deaths per 100,000), followed by Asian (7.5/100,000), African American/Black (7.6/100,000), and Hispanic/Latino (7.7/100,000) peoples, and was lowest for the White population (5.5/100,000). [307]
- The population with the highest liver cancer mortality rate changed from Asian people (2000) to American Indian/Alaska Native people (2019). [308]

- Liver cancer deaths among US males, ranked by demographic group as follows (2018–2022): [295]
  - Non-Hispanic American Indian/Alaska Native
  - Hispanic/Latino
  - Non-Hispanic African American/Black
  - Non-Hispanic Asian/Pacific Islander
  - Non-Hispanic White (NHWs)

- Liver cancer deaths among US females, ranked by demographic group as follows (2018–2022): [295]
  - Non-Hispanic American Indian/Alaska Native
  - Hispanic/Latino
  - Non-Hispanic Asian /Pacific Islander
  - Non-Hispanic African American/Black
  - Non-Hispanic White (NHWs)

- Incidence and mortality rates of liver and bile duct cancer (HCC/ICC) increased during 1975-2017, particularly in males, non-Hispanic African American/Black people, and older people. [308]

- A recent (2023) summary of Surveillance Epidemology and End Results Program (SEER)* data (2021) of liver/IBD cancer found the following racial/ethnic trends: [110]
  - Compared to non-Hispanic Whites (NHWs) (7.3%), all other racial/ethnic populations had higher liver cancer.
  - American Indian/Alaskan Native (AI/AN) people had the highest rates (17.8%), then Hispanic/Latino (14%), Asian American, Native Hawaiian/Pacific Islander (AANHPI) (10.6%), and African American/Black (9.5%) peoples.

  **The Surveillance, Epidemiology, and End Results Program (SEER), run by the National Cancer Institute, provides information on cancer incidence and mortality in different demographics.*

- Liver disease/liver cancer disproportionately affect certain groups: marginalized racial/ethnic, low socioeconomic status (SES), and other populations experiencing health disparities. Evidence ties social determinants of health (SDoH) to liver disease/cancer in people experiencing health disparities. [41, 110, 309]

- Food insecurity may be linked to the development of MASLD, one of the risk factors for liver cancer. [110, 295]

PEDIATRIC LIVER DISEASE

- 100+ liver diseases can affect children and young people; the signs and symptoms can vary greatly. [310, 311]

- Some liver disorders in children can be minor, others can be more serious, causing liver injury and cirrhosis, and can even lead to liver failure. Childhood liver disease can be life-threatening without treatment. [312]

- Causes of pediatric liver disease: autoimmune conditions, infections, metabolic disorders, genetic disorders, cardiovascular problems, medication reactions, anatomical issues, among others. [313]

- Early identification of pediatric liver disease is very important, with one goal being preservation of liver function. [313]

- Signs and symptoms of pediatric liver disease include: jaundice (yellowed skin/eyes); abdominal pain/bloating/swelling; change in sleep patterns; grey/white/pale stools; blood in the stools/urine; loss of appetite; nausea; poor weight gain; pruritus (general and persistent itching); fatigue/loss of stamina; vomiting, esp. of blood; persistent dark-colored urine; bruising/bleeding; higher than normal levels of liver enzymes. Any of these symptoms or a combination of them should be reported immediately to the child's doctor. [312, 314]

- Globally, the incidence of cirrhosis in children and adolescents increased from 204,767 in 1990 to 241,364 in 2019, a 17.9% increase. [315]

- Approximately 15,000 children are hospitalized each year in the U.S. with pediatric liver diseases or disorders (as of 2016). Due to the absence of symptoms, especially in early stages, these disorders continue to be under-recognized or diagnosed late. [316]

Alagille Syndrome

- Alagille Syndrome (ALGS), a genetic disorder, affects the liver, heart, skeleton/spine, eyes/face, blood vessels, skin (itchy skin, hard skin bumps), and kidneys. Most patients with ALGS have liver disease. [317, 318, 319, 320, 321, 322, 323, 324, 325]

- ALGS causes destruction of the bile ducts. Bile then builds up in the liver because there are too few ducts to drain bile, resulting in liver damage (cholestasis). [318, 319, 320, 321, 322, 323, 324, 325, 326]

- Children with ALGS can have unique facial characteristics: a pointy chin, broad brow, and widely spaced eyes. [318, 319, 320, 321, 322, 323, 324, 325, 326]

- Chronic itchy skin/hard skin bumps are often symptoms for people with ALGS. [318, 319, 320, 321, 322, 323, 324, 325, 326]

- ALGS is caused by abnormal development of many organs. [318, 319, 320, 321, 322, 323, 324, 325, 326]

- ALGS is usually diagnosed in infancy in about one of every 30,000 to 70,000 births but can also be diagnosed in early childhood. It affects both sexes and all races equally. [318, 319, 320, 321, 322, 323, 324, 325, 326]

- ALGS is the most common rare cholestatic (slowing or stalling of bile flow) liver disease. [318, 319, 320, 321, 322, 323, 324, 325, 326]

- ALGS has a mortality rate of 10-17%. [326, 327]

- About 75% of people diagnosed with ALGS in childhood live to at least age 20. [321]

Alpha-1 Antitrypsin Deficiency (AATD)

- **Alpha-1 Antitrypsin Deficiency** may also be referred to as AAT deficiency, AATD, Alpha-1, inherited emphysema, or genetic emphysema. [328, 329, 330, 331, 332, 333]

- Alpha-1 antitrypsin deficiency (AATD) is a rare, inherited genetic disorder that damages the liver and/or lungs, depending on the type of AATD inherited. [329, 330, 331, 332, 333, 334]

- AATD is characterized by low levels of a protein (alpha-1 antitrypsin (A1AT)) in the blood, causing several illnesses, most commonly lung disease (chronic obstructive pulmonary disease (COPD),

including bronchiectasis; emphysema) and liver disease (cirrhosis; hepatoma), or rarely, a skin condition (panniculitis). [329, 330, 331, 332, 333, 334]

- Patients with at-risk genes usually develop symptoms in adulthood, but childhood manifestations present a serious pediatric health problem. [329, 330, 331, 332, 333, 334]
- AATD is one of the most common genetic disorders among people with European ancestry. It is rare in non-European people, but all ethnicities can be affected. [329, 330, 331, 332, 333, 334]
- AATD has a global incidence of 1 in every 1500 to 3500 people with European ancestry. [329, 330, 331, 332, 333, 334]
- There is no known way to prevent AATD. There is a drug that replaces the antitrypsin that the body can't make. [329, 330, 331, 332, 333, 334]
- Patients with AATD may have reduced life expectancies. [329, 330, 331, 332, 333, 334]
- AATD affects 1 in every 3000 to 5000 people in the US. [330, 331, 334]
- AATD is often underdiagnosed or misdiagnosed. [330, 331, 335]
- Severe cases of AATD are estimated at 70,000 to 100,000 people in the US. It is projected that less than 10% have obtained an accurate diagnosis. [330, 331, 335]
- People with AATD are at increased risk for hepatocellular carcinoma (HCC). [335]

How AATD Affects Children

- AATD is the most frequent cause of genetic liver disease in infants and children and is the most common inherited indication for liver transplantation in children. [335, 336, 337, 338, 339]
- The first symptoms of AATD usually occur between 20 and 50 years, but some infants or children may be affected. **Children with AATD usually present with jaundice at birth,** white stools/dark urine, reduced stamina, wheezing, coughing, respiratory infections, fatigue, rapid heartbeat, vomiting, poor appetite, itching. Eventually, patients may develop emphysema. Some AATD patients develop **liver disease**, experiencing swollen abdomen, swollen feet or legs. [329]
- AATD is diagnosed with a simple blood test. [319]
- AATD affects about 1 in 2000 babies. [340]
- **Some infants born with AATD end up with severe liver damage or** cirrhosis. [336, 341]
- About 5-10% of patients with severe AATD eventually require a liver transplant. [338, 339]
- Emphysema in children with AATD is extremely rare. **AATD-associated liver disease (neonatal cholestasis) is present in only a small portion of affected children.** 10-15% present with neonatal cholestasis. The incidence of liver disease (cirrhosis and fibrosis) increases with age. [336, 342]
- AATD and its symptoms in infants and children may be overlooked. [343]

Autoimmune Liver Disease

- **Autoimmune hepatitis (AIH) and AIH/sclerosing cholangitis overlap syndrome known as autoimmune sclerosing cholangitis (ASC) (For general information see also section on Autoimmune Liver Disease).** [3, 344, 345]

- **Autoimmune Disorders:** Immune system abnormalities: Your immune system protects your body from germs and toxins. But that system can attack certain parts of your body (autoimmune), including your liver; this is called autoimmune disease. General examples of autoimmune diseases are rheumatoid arthritis and inflammatory bowel disease. Examples of autoimmune liver diseases include **autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, and others**. [3, 345, 346]

- **There are two types of autoimmune liver disease/hepatitis**, with different types of autoantibodies: [345, 346, 347]
    - **Type 1** – Anti-nuclear (ANA) and/or anti-smooth muscle (SMA) antibodies Type 1 makes up two out of three of all cases of AIH and the majority of ASC cases. Type I is by far the most common type of autoimmune hepatitis. In children, it most commonly presents in schoolchildren and teenagers.
    - **Type 2** – Liver kidney microsomal (LKM) antibodies Type 2 is less common, but **more likely to affect younger children** and can result in acute liver failure. Type 2 is rare in ASC.

- Type 2 is very rare in the United States. This type of autoimmune hepatitis tends to be more severe and difficult to treat. It may appear at a younger age than Type 1. [345, 347, 348]

- Both types are only very rarely seen in infants. [345, 347, 348]

- **Autoimmune hepatitis (AIH)** with inflammation in the bile ducts can be further categorized into **AIH/sclerosing cholangitis** overlap syndrome or **ASC**. [345]

- **Childhood autoimmune liver disease can be difficult to diagnose** because the symptoms are similar to many other liver conditions. Manifestations can vary. Some children/young people may appear well, while others can be very ill. [345]

Autoimmune Hepatitis (AIH)

- A Canada-based study of AIH estimated its prevalence in children at 2.2–9.9 per 100,000. [348]

- The same study estimated the annual incidence of pediatric AIH to be between 0.1 and 0.23 per 100,000 children. [349]

Autoimmune Sclerosing Cholangitis (ASC)

- **Autoimmune sclerosing cholangitis (ASC), also known as "overlap syndrome (OS),"** refers to an autoimmune condition with characteristics of both autoimmune hepatitis (AIH) and primary sclerosing cholangitis (PSC) or primary biliary cholangitis (PBC). [349, 350, 351]

- The **prevalence of AIH-PSC overlap (ASC) in children** with AIH ranges from **20% to 49%**. [352]

- The **prevalence of AIH-PSC overlap (ASC) in adult patients** with AIH ranges from **1.7% to 10%**. [353]

- Autoimmune sclerosing cholangitis (ASC) in children is frequently associated with inflammatory bowel disease (IBD). [353]

Biliary Atresia (BA)

- Biliary atresia (BA) is a rare congenital disease, causing damage, scarring, and blockage of the bile ducts. It occurs in young infants (less than 3-4 months of age). The damage is progressive, so early diagnosis is important. BA is associated with significant morbidity and mortality. [354, 355, 356, 357, 358]
- BA is the most common cause of liver-related death in children. [358]
- Timely, early diagnosis is essential for best outcomes. [358]
- BA, though uncommon, is the leading indication for liver transplantation in the pediatric population. [357, 358, 359, 360]
- BA must be treated with surgery. [357, 358, 360, 361]
- BA usually affects girls more than boys. [357, 361]
- Biliary atresia (BA) is mostly seen in full-term infants, (not in premature babies). [362]
- However, according to one study, each year in the US, 400-500 newborns are diagnosed with BA, often in babies that are premature, female, and non-Caucasian. [361]
- BA can also cause other problems in the heart, spleen (polyclinic), intestine (malrotation) and kidneys (cysts). [362]
- About 10-20% of infants with biliary atresia have abnormalities in other organs, such as heart defects or issues with their spleen. [359, 362]
- Jaundice and pale stools starting in the first 4-8 weeks are the main signs of BA. [362]
- Jaundice is common in newborns and usually goes away in the first 1-2 weeks. Beyond 2 weeks, the doctor should order a test called direct or conjugated bilirubin to test for BA. Blood tests, abdominal ultrasound, and a liver biopsy may also be needed. [362]
- BA is rare, affecting 1 in 8,000 to 1 in 18,000 newborns worldwide. [359]
- **BA incidence in the US is estimated at 1 in 10,000 to 15,000 births.** Approximately 400-600 new cases of BA are found in the US each year. [359, 363, 364]
- We don't know the etiology of BA. There is emerging evidence that BA may start in utero and can be picked up at birth (but this is not proven yet). [363, 365, 366, 367]
- We do not know what causes BA, but the diagnosis of BA is time-sensitive, i.e., must occur as soon as possible. [363, 366, 368]
- Treatment of BA is surgical (Kasai procedure), and outcomes are better if the diagnosis and surgery occur as early as possible, before 30-45 days of life. [359, 362, 363, 369, 370, 371, 372]
- New clinical trials for treatment of BA are ongoing. [363, 373]

Budd-Chiari Syndrome (BCS)

- Budd-Chiari syndrome (BCS) occurs ***when the veins that carry blood away from your liver develop blockages (like*** clots) or become too narrow. Prompt treatment for Budd-Chiari syndrome is essential. BCS is a lethal disease. [374, 375]

- Budd-Chiari syndrome is rare, especially in children. [376]

- One study, taking place over a 19-year period, recorded the incidence of Budd Chiari increasing from 4.96 per 1,000,000 US population in 1998 to 10.44 per 1,000,000 in 2017. [377]

- Types of Budd-Chiari syndrome: acute syndrome with acute liver failure: acute without liver failure; subacute, the most common type; and chronic. Additionally, Budd-Chiari syndrome may be primary or secondary. [375]

- Budd-Chiari syndrome is treated with medications, nonsurgical procedures, and transplantation. [375]

- Oral contraceptives and pregnancy are responsible for about 20% of cases of Budd-Chiari syndrome. [378]

Crigler-Najjar Syndrome

- Crigler-Najjar syndrome may also be referred to as Glucuronyl transferase deficiency (type I Crigler-Najjar) and/or Arias syndrome (type II Crigler-Najjar). [379, 380]

- **Crigler-Najjar syndrome** is a rare genetic condition occurring when the liver can't break down bilirubin (a substance produced by the breakdown of red blood cells). Children with this condition have extended jaundice. Some symptoms are life-threatening. Too much bilirubin in the bloodstream causes irreversible nerve and brain damage if untreated. [380, 381]

- Crigler-Najjar syndrome is very rare, with an **incidence rate *of 0.6 to 1 in 1 million newborns worldwide.*** [381, 382]

- **There are two types of Crigler-Najjar syndrome** in pediatric patients. Both are treated with aggressive phototherapy (systematic exposure to intense blue LED light), which is needed throughout the patient's life. [380, 383, 383, 384]
    - **Type I** is more serious and life-threatening and may require a liver transplant before adolescence to prevent brain damage.
    - **Type II**, the milder version, is treated with the drug phenobarbital, blood transfusions. Children with type 2 have a normal life expectancy.

- **Children with Crigler-Najjar syndrome experience symptoms of kernicterus, a complication of jaundice:** clumsiness, spasms, sensory perception problems, problems with motor skills, twisting movements (choreoathetosis), underdeveloped teeth. Severe symptoms: hearing difficulties, fatigue, difficulties with feeding, fever, nausea/vomiting, weak (hypotonia) or tight muscles (hypertonia), cognitive issues. Pediatric patients may experience symptoms of kernicterus (high blood levels of bilirubin damaging the brain) if left untreated. [380]

- Early **treatment is imperative** in Crigler-Najjar syndrome type I to prevent the development of kernicterus during early life. [385]

Cystic Fibrosis Liver Disease

- **Cystic fibrosis (CF) is a hereditary condition** that causes damage to the lungs, digestive system and other organs. In the U.S., because of newborn screening, cystic fibrosis can be diagnosed within the first month of life. People born before the screenings became available may not be diagnosed until the symptoms appear later in life. CF affects the cells that make mucus, sweat and digestive juices, causing the secretions to become sticky and thick. The secretions then plug up pathways, in lungs, pancreas and liver. [386, 387, 388, 389, 390]

- With CF liver disease, bile ducts from the liver and gallbladder become blocked and inflamed, causing jaundice, fatty liver disease, cirrhosis (scarring; fibrosis), and gallstones. [387, 388, 389, 390, 391]

- CF gets worse over time and needs daily care, but people often have a better quality of life than in past decades. Improved treatments mean people with CF now may live into their mid- to late 50s or longer. [391]

Galactosemia, Classic galactosemia (CG)

- **Galactosemia** is an inborn pediatric metabolic liver disease, caused by a problem with the enzymes that break down the sugar galactose. Lactose, the main type of sugar in milk, is made up of glucose and galactose. Babies with galactosemia have high levels of galactose in their blood. Babies with galactosemia can't have milk and dairy products. There are three types of galactosemia; the most common and severe is called "classic galactosemia." [391, 392]

- **There are three types of galactosemia:** [393]
  - Type I: classic galactosemia
  - Type II: galactokinase deficiency galactosemia
  - Type III: epimerase-deficiency galactosemia

- **Galactosemia incidence:** [394, 395, 396, 397]
  - Type I: **Classic galactosemia** incidence: 1 in 30,000 to 60,000 newborns. One estimate of classic galactosemia in the US is 1 in 53,000 newborns. Galactosemia type II and type III are less common.
  - Type II estimated at fewer than 1 in 100,000 newborns.
  - Type III appears to be very rare.
  - Worldwide epidemiology of classic galactosemia: Incidence of type I varies geographically: 1 in 30,000 to 40,000 in Europe; 1 in 1,000,000 in Japan.

- Initial **symptoms** occur in first few weeks of life: refusal to feed, vomiting, lethargy, jaundice, diarrhea, cataracts, and sepsis (infection). [398]

- **Prompt treatment is essential.** The **only treatment for galactosemia** is avoiding foods that contain lactose and galactose. In order to prevent serious multiorgan involvement including death, a physician and a dietitian specializing in metabolic disorders need to create a special lactose-free diet for the child in the first 10 days. [399]

- After the first 10 days, the majority of untreated infants face life-threatening complications such as infection and liver failure. If they do survive the first month of life untreated, they develop cirrhosis. [399]

Hepatitis B (HBV) in Children and Mothers
(For general information, see also section on Hepatitis)

- The World Health Organization (WHO) estimates the global prevalence of all hepatitis B at 254 million people (2022). [399, 400]

- 12% of total hep B and C cases are in children under 18. [400, 401]

- **Hepatitis B (HBV; Hep B) is the most common liver infection in the world.** Hepatitis B is a type of liver infection caused by the hepatitis B virus (HBV); it can be **short-term (acute) but** can progress to a **long-term or life-long illness (chronic)**, including liver disease/liver cancer. Hepatitis B is spread with blood, semen, or other body fluids, or **can be passed through birth**. It is preventable with vaccines. Testing is the only way to know if you are infected. Treatment can control hepatitis B in infected people. [193, 194, 195, 196, 197]

- **Hepatitis B disproportionately affects children**. **Younger children are more prone to chronic hepatitis B.** The hep B virus can be passed on through the mother. However, hepatitis B can be prevented with a vaccine given soon after birth with boosters a few weeks later, offering nearly 100% protection against the virus. [194, 201, 401, 402]

- Untreated, hepatitis B and C can cause liver damage, cirrhosis, cancer, and death. [155]

- **At risk for HBV:** Anyone can get HBV, but among the highest-risk people are **infants of infected mothers.** [194, 196, 403, 403]

- **HBV in children is passed mostly during delivery and at birth**, as well as through contact with blood and body fluids. [194, 196, 403, 404]

- **Symptoms of acute HBV:** jaundice; fatigue; poor appetite; nausea, vomiting, abdominal pain; low fever; rash and itching; dark urine; joint pain. [403, 404]

- **Most children younger than 5 years of age with HBV have few or no symptoms.** Older children may develop symptoms 3 to 4 months after exposure if left untreated. [196, 201, 403, 405, 406, 407, 408, 409]

- **A child can't get HBV from hugging, kissing, coughing, or sneezing, if left untreated.** [196, 201, 403, 406, 407, 408, 409, 410]

- **Breastfeeding by a mother with HBV is safe if the child is treated at the time of birth.** [196, 201, 403, 406, 407, 408, 409, 410]

- **HBV comes in two forms, acute and chronic.** Acute hepatitis B does not cause any lasting problems. Chronic HBV is long-term and life-threatening and causes damage to the liver. [196, 201, 403, 406, 407, 408, 409, 410]

- If the body is able to fight acute HBV, children's symptoms end in weeks to 6 months. [196, 201, 403, 406, 407, 408, 409, 410]

- **If not vaccinated, 9 out of 10 infants infected with the hepatitis B virus at birth will develop chronic, life-threatening, HBV infections.** [196, 201, 403, 406, 407, 408, 409, 410]

- **Approximately one-third of children (under age 6) who get HBV develop the chronic form. A blood test after 6 months is used to diagnose chronic hepatitis B in children.** [196, 201, 403, 406, 407, 408, 409, 410]

- **Children can and should be tested for HBV if deemed at risk.** These tests can help diagnose: a new infection (acute HBV); chronic or long-term infection (chronic HBV); a past infection. [196, 201, 403, 406, 407, 408, 409, 410]
- **Treatment: Acute hepatitis B does not need treatment**; the child's immune system fights the disease. While the virus is present, the child can pass the virus onto others; special steps are needed to help prevent the disease from spreading. **Chronic hepatitis B needs treatment.** Treatment is to relieve any symptoms, preventing disease transmission, and preventing liver disease. [403]
- Around the world, two billion people (one in three) are estimated to have been infected with the hepatitis B virus. [197, 410]
- **1 out of 2 people with hepatitis B are unaware.** [194]
- **A person can spread the hepatitis B virus and not know it.** [196, 410]
- **Only 5% of adults who are infected by hep B develop a chronic infection, but 30% (1 in 3) of children under age 6 do.** [196, 201]
- The younger a person's age when they are infected with hep B, the greater the chance of the infection becoming chronic and lifelong, the risk going down as a child gets older. The majority of children 6 and older infected with the hepatitis B virus recover completely. Approximately 9 in 10 infants infected with hepatitis B will develop life-long, chronic infection. [196, 403, 410, 411]
- All pregnant women should be screened for HBV. [403, 406, 412, 413]
- Doctors recommend a series (2-3) doses of the hepatitis B shot for children as the best way to protect against hepatitis B. There is typically a 3-shot series for hep B for children from birth to 18 y/o. The first dose is given at birth. The hepatitis B shot is very safe and is effective. Side effects are usually mild and go away on their own. [403, 406, 413, 414]
- Children only receive immunoglobulins if they are born to a hep B positive mom. Newborns should get the first hepatitis B vaccine does and a dose of immunoglobulin (IG) in the first 12 hours. [403, 406, 413, 414]
- People who have not gotten vaccinated for HBV can and should get "catch-up" doses. [403, 406, 413, 414]
- 464,000 children's lives have been saved by hepatitis B vaccines since 1974. Every 10 seconds, one child's life is saved from a fatal disease by a vaccine. [216, 217]

Hepatitis C (HCV) in Children (neonatal hepatitis C)

(For general information, see also: Hepatitis)

- **Worldwide, hepatitis C virus (HCV) is a major public health problem and cause of chronic liver disease** that leads to approximately 399 000 deaths annually (2019). [414, 415]
- Only 21% of 58 million with chronic HCV had been diagnosed, and 13%, treated (2019). [415, 416]
- **1 out of 3 people with HCV in the US are unaware.** [155]

- **Hepatitis B and hepatitis C have similar symptoms**; they are both viral infections that attack the liver. The main difference between hepatitis B and C is that people may get hep B from contact with bodily fluids, **hep C is typically transmitted through blood-to-blood contact**. [222, 416, 417]

- Like hep B, hepatitis C comes in acute and chronic forms. [222, 417, 418]

- **75–85% of people with acute hepatitis C will also develop chronic hepatitis C, which can be a lifelong if left untreated.** [222, 417, 418]

- **Since 2013, doctors have been able to treat and even cure hepatitis C. Treatments can cure more than 95% of hepatitis C cases.** [222, 417, 418]

- **A pregnant woman can pass HCV to her baby (neonatal hepatitis C). If the mother has HCV, her baby should be tested for the virus.** [234]

- **Approximately 6% of infants born to infected mothers will get hep C. There is no treatment to prevent hep C at birth.** [226, 418, 419]

- **In addition to being born to an infected mother, children can also contract hepatitis C virus through** receiving virus-infected blood transfusions (before 1992) or blood-clotting products (before 1987); receiving a virus-infected organ transplant; kidney dialysis treatment; sharing personal hygiene items (such as toothbrushes, nail-clippers). [420]

- **Adolescents and teens can also get hepatitis C.** There are many causes of hepatitis C in teens, including: being stuck with an infected needle; contact with infected blood; using street drugs; unprotected sex; tattoos/acupuncture with infected needles. [419]

- Hepatitis C is not spread by breastfeeding, hugging, kissing, coughing, or sneezing. [419]

- **Hepatitis C is the most common cause of chronic viral hepatitis in children in industrialized nations.** [421]

- A factor that increases maternal transmission of HCV: IV drug use during pregnancy. [422]

- Hepatitis ***C goes away without treatment 25-40% of the time before a child's second birthday***. The virus has disappeared in some children as old as 7. [422, 422]

- After age two, the chance of spontaneous clearance prior to age 19 decreases to 6-12%. [422, 423]

- **All children suspected to be "at risk" should be tested for HCV.** [423]

- In 2020, because of continued increases in HCV infections in the US, CDC released screening recommendations, including screening for pregnant people. [420]

- Children make up a small percentage of hepatitis C virus (HCV) infections, compared to adults. [424]

- However, a significant number of children do have chronic HCV infection and are at risk of complications: cirrhosis, portal hypertension, hepatic decompensation with hepatic encephalopathy, and hepatocellular carcinoma (cancer) in adulthood. [425]

- Children with untreated chronic HCV infection should have regular physical exams, especially children with comorbidities such as coinfection with HIV or HBV infection. [425]

- **The CDC has designated the elimination of hepatitis C as a national priority.** [420]

Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD)
(See also general section on MASLD)

- There have been recent changes to the medical terminology covering "fatty" type liver disease to reduce stigma. The term "fatty liver disease" (FLD) has been replaced by "steatotic liver disease" (SLD). SLD is an umbrella term covering "nonalcoholic fatty liver disease" (NAFLD)/"metabolic dysfunction-associated steatotic liver disease" (new term; MASLD); nonalcoholic steatohepatitis (NASH)/metabolic-associated steatohepatitis (new term; MASH); as well as alcohol-related liver disease (ARLD)/ alcohol-associated liver disease(new term; ALD), and the new category, MetALD (metabolic with alcohol-associated liver disease), a continuum which can have elements of MASLD and/or ALD. [59, 60, 61, 62, 63, 64, 65, 66, 67]

- **Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common cause of liver disease.** [63, 70, 71]

- MASLD happens when excess fat builds up in the liver. It is a "silent" disease with few or no symptoms. Causes are still being studied, but research points to genetics, digestive disorders, and diet. [70, 71, 72]
    - **Causes** include diet and nutritional causes, genetics, being overweight/obesity, type 2 diabetes/ insulin resistance, high blood fat/triglyceride levels. One or more traits of metabolic syndrome (traits and medical conditions linked to overweight/obesity), and others.
    - **Risk factors** include family history, older age, growth hormone deficiency, high cholesterol/triglycerides, type 2 diabetes/insulin resistance, metabolic syndrome, obesity, polycystic ovary syndrome, sleep apnea, hypothyroidism, hypopituitarism.
    - **Some get MASLD even without risk factors.**
    - The **two basic kinds steatotic liver disease (SLD)** are metabolic dysfunction-associated steatotic liver disease (MASLD) and the more severe metabolic-dysfunction associated steatohepatitis (MASH). And there is also a **new category, MetALD** (metabolic with alcohol-associated liver disease), a continuum which can have elements of MASLD and/or ALD.

- **MASLD is the most common cause of liver disease. Approximately 30%% of U.S. adults are estimated to have it.** An estimated 80-100 million people in the U.S. have MASLD. [25, 70, 85, 88, 89, 94, 96, 425, 426]

- **Globally, MASLD is the most common liver disease, affecting about 25% to about a third of the world's population.** [35, 85, 89, 90, 92, 93, 94, 95]

- **Worldwide prevalence of MASLD is increasing at an alarming rate.** [93, 95, 96, 97, 98]

How MASLD Affects Children

- MASLD affects up to 38% of children with obesity in the US. However, not all children with MASLD have obesity. [97, 427]

- One study of 408 children with obesity (mean age of 13.2 years; 2018), MASLD was present in nearly one-third of boys and one-fourth of girls. [139]

- MASLD is the most common form of pediatric liver disease in the U.S., more than doubling the past 20 years, in part because of increasing childhood obesity. [140, 141, 142, 143, 144, 145, 146, 147, 148, 428, 429]

- Some studies estimate 5% to 10% of children have MASLD. [140, 141, 142, 143, 144, 145, 146, 147, 148, 429, 430]

- MASLD is on the rise among children of all ethnicities, but especially Hispanic/Latino and Asian American children. [141, 430]

- In the next decade, untreated childhood MASLD will be a significant contributor to liver transplantation in adults (including some teenagers). [128, 141, 143, 147]

- MASH is the second most common reason for adult liver transplants, after alcohol-related liver disease. It recently superseded HCV as a cause. [128, 141, 143, 147]

- Pediatric MASLD is often associated with metabolic syndrome. [145, 431]

- A story in the *Washington Post* (10/3/2023) covering the growing crisis of childhood liver disease highlighted the following facts: [149]
    - Before the turn of the century, pediatric steatotic liver disease (formerly called fatty liver disease) was relatively rare. Now millions are affected; the journal *Clinical Liver Disease* estimates 5% to 10 % of all children in the US have MASLD — about as common as childhood asthma.
    - There were large jumps in MASLD incidence across all ages in the US; the steepest increase by far was in children (data 2017-2021).
    - The rate of MASLD diagnosis more than doubled in children up to age 17 (insurance claim data analyzed for The Post by Trilliant Health). Some of that increase is because of more vigilant reporting and testing recently. The trend, however, holds true.
    - The crisis is acute in the Southeast, where pediatric obesity rates are highest.
    - When more than 5% of liver cells contain fat, steatotic liver disease (SLD) is indicated (5-10%). Pediatric specialists are finding children with livers of 30-40% fat, or even as high as 60% fat.
    - There is a rise in transplants for steatotic liver disease in people in their 20s and 30s.
    - The story also highlighted the link between ultra-processed foods and pediatric/childhood obesity/MASLD.

- Studies estimate that 20% to 50% of children with MASLD have MASH. [141, 148, 150, 432]

- When compared to people who develop MASLD during adulthood, people who develop MASLD during childhood are more likely to have MASH and its complications or liver disease as adults. [141, 148, 150, 433]

- Children with MASH can develop cirrhosis, but the complications of cirrhosis, such as liver failure and liver cancer, usually happen in adulthood. [141, 148, 150, 433]

- MASLD is more common in boys than in girls. [141, 148]

- MASLD occurs in children of all races and ethnicities but is most common in Hispanic/Latino children and Asian American children, followed by White children. [141, 148]

- MASLD is less common in younger children and African American/Black children. [141, 148]

- **One study: Prevalence of MASLD in children broken down by race/ethnicity (2006 data):** [146]
    - Children of Hispanic/Latino ethnicity (11.8%)
    - Asian children (10.2%)
    - White children (8.6%)
    - Black/African American children (estimate of 1.5%)

Glycogen Storage Disease Type 1

- Glycogen storage disease type I (GSD I; Von Gierke disease) is an inherited disorder caused by deficiencies of enzymes, and the buildup of a sugar called glycogen in the body's cells. This accumulation of glycogen in organs and tissues, especially the liver, kidneys, and small intestines, impairs their function. [433]

- **GSD is hereditary, from parents to children**). It is seen mostly in babies and young children. Some forms of GSD may appear in adults. [434]

- **There are many types of glycogen storage disease (GSD) – at least 19 have been identified. The types of GSD are categorized by the enzyme missing in each one. Each GSD has its own symptoms and treatments.** [435, 435]

- **The most common types of GSD are types I, III, and IV.** [435, 436]

- GSD 1 is a serious, debilitating illness. Signs/symptoms of GSD 1 usually appear around age 3 or 4 months. Affected infants may have low blood sugar (hypoglycemia), which can result in seizures. They can also have a buildup of lactic acid (lactic acidosis); high levels of uric acid (hyperuricemia); and high fat levels in the blood (hyperlipidemia). [434, 437]

- Older children with GSD 1 can have thin arms/legs; short stature; enlarged liver with a protruding abdomen; enlarged kidneys; diarrhea and cholesterol deposits in the skin (xanthomas). [434, 438]

- Puberty in people with GSD 1 may be delayed. [434, 438]

- People with GSD 1 in young to mid-adulthood, can have osteoporosis; gout; kidney disease; and pulmonary hypertension. [434, 438]

- Females with GSD 1 can have abnormal development of the ovaries (polycystic ovaries). [434, 438]

- In teens and adults with GSD 1, tumors called adenomas may form in the liver. Adenomas are usually benign but can occasionally become cancerous (malignant). [434, 438]

- GSD 1 affects children's appearance. Afflicted people have doll-like faces and full cheeks, thin extremities, short height, and a protuberant belly. [438]

- **Incidence of type I glycogen storage disease is 1 in 100,000 births. The prevalence of GSD 1 in Ashkenazi Jews is estimated at 1 in 20,000.** [436, 439, 440]

- **GSD 1 affects males and females equally.** [436, 440, 441]

- **Type 1 accounts for 25% of all GSD cases in the U.S.** [436, 440, 441]

Primary Sclerosing Cholangitis (PSC)
(For general information see also section Autoimmune Disorders, PSC)

- Primary sclerosing cholangitis (PSC) is an autoimmune disorder, where the body's immune system attacks healthy cells. In an afflicted child, the bile ducts become narrow, slowing the bile flow out of the

liver. The abnormal flow and buildup of bile in the liver can cause chronic liver problems and damage. Over time, PSC can lead to cirrhosis and liver failure. [441, 442]

- PSC is usually accompanied by inflammatory bowel disease (IBD), often ulcerative colitis and sometimes Crohn's disease. This combination of PSC and IBD is found in about 80% of pediatric PSC patients. [443, 443]
- Children with PSC usually present without complications but often progress to end-stage liver disease (liver failure). Within 10 years of diagnosis, 50% of children will develop complications, with 30% requiring liver transplantation. [444, 444]
- PSC is rare, with a prevalence of 1.5 cases per 100,000 children. [442, 443, 445]
- Liver transplantation is the treatment for end-stage liver disease resulting from pediatric PSC. [446]
- PSC accounts for ~2% of all pediatric liver transplants in the U.S. [447]

Progressive Familial Intrahepatic Cholestasis (PFIC)

- Progressive familial intrahepatic cholestasis (PFIC) is a genetic disorder causing progressive liver disease, leading to liver failure. In PFIC, liver cells cannot secrete bile normally and the buildup of bile causes liver disease, or the secreted bile is abnormal and damages the bile ducts to injure the liver. [447]
- There are many types of PFIC - each type is classified by the specific genetic cause. The genetic mutations lead to "shortages" of particular proteins. [448, 448, 449]
- Prevalence of PFIC is unknown but estimates range from **1 in 50,000 to 1 in 100,000 births.** [450]
- Of all the cases of cholestasis in the pediatric population, scientists believe that nearly 10-15% are due to PFIC. [451]
- Approximately **10% of liver transplants in children result from this condition.** [451]

Gilbert's Syndrome

- **Gilbert (zheel-BAYR) syndrome is a common, harmless genetic liver condition in which the liver doesn't properly process bilirubin, produced by the breakdown of red blood cells.** [451, 452]
- **Gilbert syndrome requires no treatment.** [452, 453]
- **Doctors may consider Gilbert syndrome if patients have unexplained jaundice (yellowish skin and eyes) or if their level of bilirubin is elevated.** [452, 453]
- Gilbert syndrome can be discovered by accident because people may not know they have it. Approximately 1 in 3 people with Gilbert's syndrome don't have symptoms. [452, 454]
- People with Gilbert's can lead long, healthy lives and don't experience long-term health problems from the disease. [454]
- **Gilbert syndrome has a prevalence rate of 3%-16%.** [454, 454, 455, 456, 457, 458]
- Gilbert's Syndrome is more common in males than females, and affects all ages, races and ethnicities. [454]

- Symptoms of Gilbert syndrome can be similar to those of: Crigler-Najjar syndrome, Rotor syndrome, Dubin-Johnson syndrome. These diseases can also be similar in that all the diseases can cause jaundice, but the severity of jaundice and elevation of bilirubin are different. [459]

- According to one study, in children, Gilbert's syndrome manifests 2.22 times more often in boys than girls. [460]

- Gilbert syndrome may become more noticeable during puberty. [459]

- Gilbert syndrome can manifest during triggers such as fasting, hemolytic reactions, febrile illnesses, menstruation, and physical exertion. [459]

Pediatric Acute Liver Failure (PALF)

- Acute liver failure (ALF) happens when many cells in the liver die in a short period of time, or it becomes damaged, and the liver is no longer able to perform critical functions. Pediatric acute liver failure (PALF) is a complex, rapidly progressive syndrome that is the result of many conditions, some known and others to be identified. [128, 461, 462, 463, 464]

- Pediatric liver failure (PALF) is not as common as adult liver failure. Liver failure in children is very rare. [128, 462, 463, 464, 465]

- The frequency of ALF is estimated at 500-600 cases per year in the US, but the frequency in children is unknown. [128, 462, 463, 464, 465]

- PALF accounts for approximately 10 percent of pediatric liver transplants (LTs) in the US each year. [128, 462, 463, 464, 465]

- PALF is characterized by evidence of liver dysfunction within 8 weeks of onset of symptoms; no evidence of past or present chronic liver disease. [128, 462, 465, 466, 467, 468]

- Symptoms include fevers, abdominal pain, vomiting, lethargy, jaundice, confusion, enlarged liver/spleen, bleeding/bruising. [128, 462, 466, 467, 468, 469]

- Acute kidney injury (AKI) requiring continuous kidney replacement therapy (CKRT) may be a complication of PALF. [128, 462, 466, 467, 468, 469]

- Causes (etiologies) include viral hepatitis (A-G), infections, drug reactions, toxins, immune and metabolic disorders (including Wilson's disease), cardiovascular conditions. [128, 462, 466, 467, 468, 469]

- The cause of PALF is undetermined in 30-50% of cases. [128, 462, 466, 467, 468, 469]

- There is a separate entity of PALF called "indeterminate PALF" in which, after a thorough work up, the etiology is still not discovered. This is an area of exciting and active research within the field but thought to be driven by immune dysregulation. [128, 462, 466, 467, 468, 469]

- Sepsis (body overreacts to an infection, damaging healthy tissue/organs, leading to shock, organ failure) is a major cause of mortality in PALF in infants in which the underlying cause of PALF is infection. [128, 462, 466, 467, 468, 469]

- Other causes, such as severe hepatic dysfunction that leads to multiorgan failure (hepatic encephalopathy, cardiovascular and pulmonary failure) may be leading causes of mortality. [128, 462, 466, 467, 468, 469]

- Mortality may reach 80-90% without liver transplantation. [128, 462, 466, 467, 468, 469]

- PALF is a rapidly evolving disease state needing prompt recognition and management at an intensive care unit or pediatric liver transplant center. [469]

- PALF continues to be rare but potentially lethal in otherwise healthy children. [469]

Reye's Syndrome (RS; Reye Syndrome)

- Reye's syndrome, also known as Reye syndrome, is a very rare but serious condition that causes swelling in the liver and brain. [470, 471, 472]

- RS is generally a disease in children/young adults but can also occur at any age. [471, 472, 473]

- Reye's syndrome (RS) affects all organs of the body but is most harmful to the brain and the liver. It can cause an acute increase in pressure within the brain and massive fat accumulations in the liver and other organs. [471, 472, 473]

- RS generally occurs during recovery from a viral infection, such as the flu or chicken pox, but can develop 3 to 5 days after the onset of the viral illness. [471, 472, 473]

- RS is often misdiagnosed. [471, 472, 473]

- **Symptoms of RS include** vomiting; drowsiness/fatigue; confusion; behavior changes, irritability or aggression; breathing quickly/fast heart rate; difficulty breathing; seizures; loss of consciousness. [471]

- Most children and teenagers who have RS survive, but degrees of lasting brain damage are possible. [473]

- **Cause(s) of RS is unknown.** It has been **linked to certain medications (salicylates), particularly aspirin, children under 16, and young people**. Children with a rare genetic condition, (e.g., MCADD) can get Reye's syndrome. [471, 472]

- Because of this association between aspirin (salicylate) and the onset of Reye's syndrome, healthcare professionals do not recommend the use of aspirin for children. [472]

- RS has no cure. Treatment focuses on preventing brain damage. Recovery is related to the severity of brain swelling. Some recover, while others may have degrees of brain damage. [472]

- Reye syndrome is very rare. Fewer than 2 cases annually have been reported since 1994. [473]

- The incidence of RS may not be accurately known because reporting cases to the CDC is no longer mandatory. [474]

- The peak age for RS is 5 to 14 years; but cases have been reported in children of less than one year. Gender is not a risk factor for RS. [474]

- There is seasonal variation with RS. Most RS cases are reported from December through April. [474]

- Surveillance of RS in the US began in 1973. CDC reported 555 cases 1979 - 1980. December 1980 - November 1997, the CDC reported 1207 cases. The incidence fell from an average of 100 cases per year 1985-1986 to 36 cases per year 1987-1993. Incidence has fallen since 1991 with 0.2 to 1.1 cases per million reported in the US 1991-1994. [474]

Wilson Disease (WD)

- **Wilson disease is sometimes referred to as Wilson's Disease, hepatolenticular degeneration, hepatolenticular degeneration syndrome, or copper storage disease.** [284, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483]

- **Wilson disease is a rare, progressive, genetic disorder characterized by copper accumulating in body tissues, particularly the liver, brain, kidneys, and corneas.** If untreated, it can cause liver disease, nervous system dysfunction, and death. In summary, Wilson disease is a genetic defect that causes excessive copper accumulation in the liver or brain. The excess copper poisons the liver or brain, causing liver, neurologic or psychiatric symptoms. Wilson is a multisystem disorder. [284, 475, 476, 477, 478, 478, 479, 480, 481, 482, 483, 484]

- **Wilson disease is fatal unless detected and treated** before serious illness from copper poisoning develops. The mortality rate for Wilson disease complicated by acute liver failure (ALF) without liver transplantation is 95 percent, with death occurring in days to weeks. **However, liver transplantation cures Wilson disease with ALF, and prognosis following liver transplantation is excellent.** [284, 475, 476, 477, 478, 478, 479, 480, 481, 482, 483, 484]

- **Other organs can be involved**, including kidneys, heart, and skin. [284, 475, 476, 477, 478, 478, 479, 480, 481, 482, 483, 484]

- **Wilson disease carries a risk of liver cancer**. [284, 475, 476, 477, 478, 478, 479, 480, 481, 482, 483, 484]

- Symptoms start to appear at all ages, as early as 2-11 to 65+ years. **Symptoms usually appear in late adolescence to early adulthood**, but can also occur in early childhood, middle or old age. [284, 475, 476, 477, 478, 478, 479, 480, 481, 482, 483, 484]

- **Wilson disease symptoms**: weakness, abdominal pain, jaundice, personality change/ Psychiatric symptoms, seizures, migraine headaches, insomnia, tremors, Parkinsonian movement disorder, etc. [284, 475, 476, 477, 478, 478, 479, 480, 481, 482, 483, 484]

- In addition to liver injury, **patients can have neurological and mental health issues**. [284, 475, 476, 477, 478, 478, 479, 480, 481, 482, 483, 484]

- **Early diagnosis is crucial to prevent serious disability and life- threatening complications.** [284, 475, 476, 477, 478, 478, 479, 480, 481, 482, 483, 484]

- **Treatment** reduces the amount of copper in the body and focuses on maintaining normal levels. [284, 475, 476, 477, 478, 478, 479, 480, 481, 482, 483, 484]

- **If both parents carry a defective Wilson disease gene, there is a 25% chance each child will have the disorder.** [479]
- **Children with Wilson disease can have asymptomatic liver disease, cirrhosis, or acute liver failure (ALF), with or without neurological and psychiatric symptoms.** [484]

- **Fewer than 50,000 people in the U.S. have Wilson disease.** [475, 476, 478, 479, 480, 481, 482, 485, 485, 486, 487, 488]
- **Wilson disease affects males and females equally and is found in all races and ethnicities.** [475, 476, 478, 479, 480, 481, 482, 485, 486, 487, 488, 489]
- **Wilson disease incidence is approximately 1 in 30,000 to 40,000 people worldwide, though estimates vary.** [475, 476, 478, 479, 480, 481, 482, 485, 486, 487, 488, 489]
- **Wilson disease is more common in certain geographic areas, such as Sardinia, Sicilians, southern Italians, and some Eastern European countries.** [475, 476, 478, 479, 480, 481, 482, 485, 486, 487, 488, 489]
- **About 1 in 90 people may be carriers of Wilson disease, though estimates vary.** (One study puts the range at 1:90 to 1:150. Another study in the UK showed 1:7,000 have the Wilson disease gene mutation.) [475, 476, 478, 479, 480, 480, 481, 482, 485, 486, 487, 488, 489]
- **In younger children the liver is most often affected by Wilson disease.** [489, 489, 490, 491, 492, 493]
- In teens and adults, the brain may be more affected. [489, 490, 491, 492, 493, 494]
- Age of onset for WD is 5 to 35 years. [489, 490, 491, 492, 493, 494]
- **40-50% of WD patients experience liver disease as initial symptoms around the age of 15 years.** [489, 490, 491, 492, 493, 494]
- Other people with Wilson disease may be misdiagnosed with other neurological, liver or psychiatric disorders. Many doctors aren't familiar with Wilson symptoms that can be wide-ranging. [480, 482]
- **50-60% of Wilson patients present with liver symptoms. About 5% of patients with Wilson disease have acute liver failure** with severe liver damage. [475, 482, 494]
- 5% of acute liver failure is due to WD in adults. [495]
- 3.2% of acute liver failure is due to WD in pediatric population. [465]
- Approximately 20%–30% of WD patients present with ALF; most other untreated patients have chronic progressive hepatitis or cirrhosis. [485]
- One summary of studies of **organ-specific Wilson disease manifestations** at presentation: [483]
    - Liver disease: 18%-84% of patients
    - Neurologic symptoms: 18%-73%
    - Psychiatric symptoms: 10%-100%
    - Most symptomatic **pediatric patients (<18 years) present with liver disease alone**.
    - It is estimated that **35%-45% percent of patients have cirrhosis at diagnosis of Wilson disease**.

AUTOIMMUNE LIVER DISEASES

Autoimmune Disorders

- **Immune system abnormalities**: Your immune system protects your body from germs and toxins. But that system can attack certain parts of your body (autoimmune), including your liver; this is called autoimmune disease. General examples of autoimmune diseases are rheumatoid arthritis and inflammatory bowel disease. Examples of autoimmune liver diseases include **autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, and others**. [3, 345, 346]

- **There are two types of autoimmune liver diseases, each with different types of autoantibodies:** [345]
  - **Type 1** (anti-nuclear (ANA) and/or anti-smooth muscle (SMA) antibodies) make up two out of three cases of autoimmune hepatitis (AIH) and most autoimmune sclerosing cholangitis (ASC) cases.
  - **Type 2** (liver kidney microsomal (LKM) antibodies) is less common, but **more likely to affect younger children** and can cause acute liver failure (ALF). Type 2 is rarely associated with ASC cases.

Primary Sclerosing Cholangitis (PSC)

- **Primary sclerosing (skluh-ROHS-ing) cholangitis (koh-lan-JIE-tis) (PSC)** is a rare chronic liver disease of the bile ducts. Bile ducts, located inside and outside the liver, carry bile from the liver to the small intestine for digestion. With PSC, the liver's bile ducts become inflamed and scarred, causing them to become narrowed or blocked, seriously damaging the liver. In 10 to 15 years, this can lead to liver failure. Many people with PSC also have inflammatory bowel disease (IBD), including ulcerative colitis or Crohn's disease. [496, 497, 498, 499]

- The causes of PSC are not clear. Indications are for an immune system reaction to an infection or toxin in people with a genetic predisposition to the disease. [499]

- PSC is rare. Incidence rates for PSC range from 1.3 per 100,000 to 1 in 10,000 people per year worldwide. [500, 500, 501, 502, 503]

- Prevalence rates for PSC are approximately 1 to 16 per 100,000 people in the U.S. [500, 501, 502, 503, 504]

- PSC is usually diagnosed between the ages of 30 and 40 years. It is more common in men, who have a two-fold risk compared to women. Family history of the disease is also a risk factor. [500, 501, 502, 503, 504]

- PSC is more common in North America and Northern Europe than in Asia. [500, 501, 502, 503, 504]

- PSC has no "type 1" or "type 2" distinctions; PSC diagnosis uses a system with stages 1-4, based on the progression of the disease. Stage 1 is minimal fibrosis (scarring) around the portal areas of the liver, eventually progressing to more advanced fibrosis and cirrhosis (stage 4) in later stages (stage 4) These stages are diagnosed using a liver biopsy. [504]

- **Stages of PSC:** [505, 506, 507, 508]
  - Stage 1 – A small amount of fibrosis limited mostly to portal regions of the liver.
  - Stage 2 – Fibrosis outside portal areas. The strands of fibrosis not connected.
  - Stage 3 – Fibrosis areas connecting to each other.
  - Stage 4 – Widespread honeycomb-like scarring, cirrhosis.

- **IMPORTANT:** Because of the similarity of the abbreviations/acronyms, **it is easy to confuse PSC with PBC.** Remember: PSC = primary sclerosing cholangitis; PBC = primary biliary cholangitis. [509]

Primary Biliary Cholangitis (PBC)

- **IMPORTANT: The full name of the disease "PBC" has been changed from "primary biliary cirrhosis" to "primary biliary cholangitis."** [506, 510]

- **Primary biliary cholangitis (PBC; formerly "primary biliary cirrhosis")** is a chronic disease of the small bile ducts in the liver. The ducts become injured and are eventually destroyed. When there are no bile ducts, bile backs up, causing liver damage. It can be life-threatening if left untreated. [511]

- **Possible causes of PBC include autoimmunity, infection, or genetic predisposition.** [512]

- **IMPORTANT:** Because of the similarity of the abbreviations/acronyms, **it is easy to confuse PSC with PBC.** Remember: PSC = primary sclerosing cholangitis; PBC = primary biliary cholangitis. [510]

- Primary biliary cholangitis (PBC) is rare. The reported prevalence varies from 19 to 402 cases per million people. [513, 513, 514]

- PBC mostly afflicts women (90%-95%). Women are affected 10 times more than men, but recent studies indicate that the ratio may be closer to 4:1 – 6:1. [513, 514, 515]

- Most people are diagnosed with PBC between ages 30 and 65 years, often in their 40s or 50s. The disease has also been reported in women aged 15 years and 93 years. [513, 514, 515]

- One 2014 study found a PBC prevalence of 58 in every 100,000 U.S. women, and approximately 15 out of every 100,000 U.S. men. [515]

- There is no cure for PBC, but treatment can help slow the disease's progression and prevent complications. [516]

- Cholestatic pruritus – severe, intense itching – is a key symptom of PBC, experienced by up to 81% of PBC patients. [517]

Autoimmune Hepatitis (AIH)

- Autoimmune hepatitis is when your immune system attacks your liver, causing inflammation, swelling, and liver damage. It is a chronic disease that can lead to cirrhosis and liver failure. [159, 518, 519, 520]

- The causes are unknown, but AIH is more likely in people with other autoimmune conditions. Genetic and environmental factors and some medications can trigger autoimmune hepatitis. [159, 519, 520, 521]

- AIH affects women more than men. [159, 519, 520, 521]

- If AIH is diagnosed and treated early, it can be controlled with medicines that suppress the immune system. The disease can go into remission. [159, 519, 520, 521]

- People with other autoimmune conditions have a 25-50% chance of developing another autoimmune disorder and are at higher risk for developing AIH. (data 2016, 2019) [263]

- There are two types of AIH: type 1 and type 2. Type 1 AIH, also called the "classic type," is typically diagnosed in adulthood; type 2 is diagnosed during childhood. [263]

- Life expectancy with autoimmune hepatitis: Without treatment, 50% within 5 years; with treatment, 90% in 10 years and 70% in 20. About 15% of people being treated eventually develop cirrhosis, usually after 10 to 20 years. [519]

- AIH incidence has been estimated at 1-2 per 100,000 people. (data 2016, 2019) [263]

- AIH prevalence has been estimated at 24 per 100,000. (data 2016, 2019) [263]

- Studies suggest that the incidence of AIH is increasing for unknown reasons. [263]

- An estimate of the prevalence of AIH in the US was 31.2/100,000. (2014-2019) [521]

- Result of a global pooled prevalence study of AIH was 15.65 cases per 100,000. (2023) [522]

- The incidence of AIH was greater in North America and Oceania (compared with Asia), among females, adults (vs. children). [523]

Autoimmune Sclerosing Cholangitis (ASC)

- Autoimmune sclerosing cholangitis (ASC), also known as "overlap syndrome (OS)," refers to an autoimmune condition with characteristics of both autoimmune hepatitis (AIH) and primary sclerosing cholangitis (PSC) or primary biliary cholangitis (PBC). [350, 351, 352]

- The prevalence of AIH-PSC overlap (ASC) ranges from 1.7%–10% in adult patients with AIH. [353]

- The prevalence of ASC in children is much higher ranging from 20%–to 49%. [353]

- Autoimmune sclerosing cholangitis (ASC) in children is frequently associated with inflammatory bowel syndrome (IBS). [523]

RARE LIVER DISEASES

- Per the FDA, The Orphan Drug Act defines a rare disease as a disease or condition that affects less than 200,000 people in the United States. [524, 525]

- There are many different types of rare liver diseases: acute hepatic porphyria (AHP); acute liver failure; Alagille syndrome; alpha-1 antitrypsin deficiency (ie, AAT deficiency, AATD, Alpha-1, inherited emphysema, genetic emphysema); autoimmune hepatitis; biliary atresia (BA); Budd–Chiari syndrome; cancers of the liver: hepatoblastoma, cholangiocarcinoma;; congenital hepatic fibrosis; Crigler-Najjar syndrome; galactosemia; glycogen storage disease; hemochromatosis (i.e., hereditary hemochromatosis, iron overload disorder); hepatic porphyria (acute hepatic porphyrias); immune-mediated and inflammatory diseases: primary sclerosing cholangitis (PSC), primary biliary cholangitis (PBC); intrahepatic cholestasis of pregnancy (ICP, cholestasis of pregnancy); lysosomal acid lipase deficiency (LAL-D); polycystic liver disease; progressive familial intrahepatic cholestasis (PFIC); Wilson disease. [526, 526, 527]

Acute Hepatic Porphyria (AHP)

- Acute hepatic porphyria (AHP) is a genetic disorder characterized by sudden "attacks" of symptoms in some people, which can be severe and life-threatening. AHP symptoms include nerve pain, abdominal pain, vomiting, neuropathy, and seizures. [528, 529]

- AHP begins in the liver and can eventually affect the nervous system: AHP occurs secondary to mutations that lead to abnormal pathways for production of proteins in the liver but can affect the nervous system. [529, 530]

- There are different types of AHP, representing different missing enzymes as a result of the disorder. From most to least common: acute intermittent porphyria (AIP); variegate porphyria (VP); hereditary coproporphyria (HCP); ALAD-deficiency porphyria (ADP). [529, 530]

- The genetic mutations that cause AIP, VP, HCP are equal in males and females, but it is females who are predominantly symptomatic. In ADP, all symptomatic patients have been male. [529, 530]

- AIP attacks have been reported five times more frequently in non-Hispanic females as compared with males. [530, 531]

- 80% of those who develop AHP/AIP symptoms are female and of childbearing age. [531, 532]

- Any race or ethnicity may inherit the AHP genetic mutation, from one or both parents. [531]

- AHP is often undiagnosed. [531]

- AHP symptoms are triggered by hormonal changes, some drugs, alcohol use, smoking, and severe stress. [531]

- Most people with the AHP gene mutation never develop symptoms, only 1 in 10. Worldwide, estimates for the prevalence of AHP range from 1 in 500 to 1 in 50,000 people. [531, 532]

- The US prevalence for AHP is 1 in 25,000 people. [531, 532]

- The mutation for AIP, the most common type of AHP, has an incidence of 1/1600 in Caucasians, but <10% of the at-risk population develops the disease. [531, 532]

- AHP is diagnosed with a genetic test. [529, 530, 531]

- Treatment mostly focuses on symptom relief, including anti-seizure medication in about 20% of cases. Precipitating factors, such as smoking and alcohol, should be eliminated during attacks. [529, 530, 531]

- People experiencing life-threatening AHP symptom attacks may be eligible for a liver transplant, which can cure them. However, this is rarely done because of the invasive nature of a liver transplant and the need for lifelong immunosuppressive treatment. [529, 530, 531]

Alagille Syndrome (ALGS)

- **Alagille Syndrome (ALGS) may also be referred to as syndromic bile duct paucity or syndromic bile duct paucity.** [318, 319, 320, 321, 322, 323, 324, 325, 326, 532]

- **Alagille Syndrome (ALGS), a progressive genetic disorder, affects the liver, heart, skeleton/spine, eyes/face, blood vessels, skin (itchy skin, hard skin bumps), and kidneys.** [318, 319, 320, 321, 322, 323, 324, 325, 326, 533]

- **Most patients with ALGS have liver disease.** [318, 319, 320, 321, 322, 323, 324, 325, 326, 533]

- ALGS causes destruction of the bile ducts. Bile then builds up in the liver because there are too few ducts to drain bile, resulting in liver damage (cholestasis). [318, 319, 320, 321, 322, 323, 324, 325, 326, 533]

- Children with ALGS can have unique facial characteristics: a pointy chin, broad brow, and widely spaced eyes. [318, 319, 320, 321, 322, 323, 324, 325, 326, 533]

- **Chronic itchy skin/hard skin bumps are often symptoms for people with ALGS.** [318, 319, 320, 321, 322, 323, 324, 325, 326, 533]

- ALGS is caused by abnormal development of many organs. [318, 319, 320, 321, 322, 323, 324, 325, 326, 533]

- ALGS is usually diagnosed at infancy in about one of every 30,000 to 70,000 births but can also be diagnosed in early childhood. It affects both sexes and all races equally. [318, 319, 320, 321, 322, 323, 324, 325, 326, 533]

- **More than 85% of patients with Alagille have liver disease.** [533]

- **ALGS has a mortality rate of 10-17%. Most of the mortality in ALGS is secondary to cardiac or vascular involvement.** [327, 328, 534]

- About 75% of people diagnosed with ALGS in childhood live to at least age 20. [321]

Alpha-1 Antitrypsin Deficiency (AATD)

- **Alpha-1 antitrypsin deficiency (AATD) may also be referred to as AAT deficiency, Alpha-1, inherited emphysema or genetic emphysema.** [530, 534]

- **Alpha-1 antitrypsin deficiency (AATD) is a rare, inherited genetic disorder that damages the liver and/or lungs, depending on the type of AATD inherited.** [530, 535]

- In a healthy person, A1AT protein is made by the liver, secreted into the blood stream, and travels to the lung where it helps to protect the lung. In people with AATD, however, the A1AT protein is underproduced or misfolded. This can result in buildup of the A1AT protein in the liver, leading to liver cell damage (cirrhosis; hepatoma) and/or decreased entry of A1AT in the lung, resulting in lung breakdown and chronic lung disease (chronic obstructive pulmonary disease (COPD), including bronchiectasis; emphysema). AATD can also, rarely, lead to a skin condition, panniculitis. [530, 535]

- AATD lung symptoms usually develop in adulthood, but liver symptoms can present in infants (up to 73%). [530, 535]

- Patients with at-risk genes can present with a range of liver or lung diseases. Liver disease usually presents in infancy while lung disease usually becomes apparent in early adulthood. [530, 535]

- Approximately 15% of patients with A1AT require liver transplant. [530, 535]

- Notably, lung disease is more dominant in most patients. [530, 535]

- AATD is one of the most common genetic disorders among people with European ancestry. It is rare in non-European people, but all ethnicities can be affected. [329, 330, 331, 332, 333, 334, 535]

- AATD has a global incidence of 1 in every 1500 to 3500 people with European ancestry. [329, 330, 331, 332, 333, 334, 535]

- There is no known way to prevent AATD. There is a drug that replaces the antitrypsin that the body can't make, but it only helps in the lung aspects of the disease, not the liver. Patients with AATD may have reduced life expectancies. [329, 330, 331, 332, 333, 334, 535]

- There is currently ongoing research on gene therapy for AATD that will treat all aspects of the disease if successful. [535]

- **AATD affects 1 in every 3000 to 5000 people in the U.S.** [330, 331, 335]

- **AATD is often underdiagnosed or misdiagnosed.** [330, 331, 335]

- Severe cases of AATD are estimated at 70,000 to 100,000 people in the US. It is projected that less than 10% have obtained an accurate diagnosis. [330, 331, 335]

- **People with AATD are at increased risk for hepatocellular carcinoma (HCC), as with virtually any liver disease.** [336]

Gilbert's Syndrome

- Gilbert (zheel-BAYR) syndrome is a common, harmless genetic liver condition in which the liver doesn't properly process bilirubin, produced by the breakdown of red blood cells. [452, 453]

- Gilbert syndrome requires no treatment. [452, 453]

- Doctors may consider Gilbert syndrome if patients have unexplained jaundice (yellowish skin and eyes) or if their level of bilirubin is elevated. [452, 454]

- Gilbert syndrome can be discovered by accident because people may not know they have it. Approximately 1 in 3 people with Gilbert's syndrome don’t have symptoms. [452, 454]

- People with Gilbert's can lead long, healthy lives and don’t experience long-term health problems from the disease. [454]

- Gilbert syndrome has a prevalence rate of 3%-16%. [454, 455, 456, 457, 458, 459]

- Gilbert's Syndrome is more common in males than females, and affects all ages, races, and ethnicities. [454]

- According to one study, in children, Gilbert's syndrome manifests 2.22 times more often in boys than girls. [461]

- Gilbert syndrome may become more noticeable during puberty. [536]

- Gilbert syndrome can manifest during triggers such as fasting, hemolytic reactions, febrile illnesses, menstruation, and physical exertion. [537]

Hereditary Hemochromatosis

- **Hereditary Hemochromatosis is sometimes referred to as,** bronze diabetes; bronzed cirrhosis; familial hemochromatosis; genetic hemochromatosis; haemochromatosis; HC; hemochromatosis; hereditary haemochromatosis; HH; HLAH; iron overload disorder; iron storage disorder; pigmentary cirrhosis; primary hemochromatosis; Troisier-Hanot-Chauffard syndrome; Von Recklenhausen-Applebaum disease) (See also "Liver Cancer") [530, 537, 538, 539, 540]

- **Hereditary Hemochromatosis (HH)** is a disorder causing **excess dietary iron to build up** in the body, damaging multiple organs including the liver, pancreas, heart, thyroid, joints, skin, gonads, and pituitary. [530, 538, 539, 540, 541]

- Too much iron from hemochromatosis can lead to life-threatening conditions, such as liver disease, heart problems, and diabetes. As hereditary hemochromatosis worsens, patients may develop arthritis, liver cirrhosis/cancer, diabetes, heart abnormalities, or skin discoloration. [530, 538, 539, 540, 541]

- In HH patients, there is an increased risk of **hepatocellular carcinoma or liver cancer**. [530, 538, 539, 540, 541]

- The most common cause of hemochromatosis is genetics, but excessive iron absorption can also cause this condition. [530, 538, 539, 540, 541]

- Hereditary hemochromatosis is the most common autosomal recessive disorder in White people. [530, 538, 539, 540, 541]

- **The prevalence** of hereditary hemochromatosis is estimated to be between 1/220-1/250 people of northern European descent. [530, 538, 539, 540, 541]

- **Men and women** are now being diagnosed equally with HCC. [530, 538, 539, 540, 541]

- **Symptoms** of hereditary hemochromatosis include extreme fatigue, joint and abdominal pain, weight loss, and lowered sex drive. Severity of symptoms can be affected by the environment and lifestyle, such as diet (iron), alcohol use, and infections. [541, 542, 543]

- There are a variety of genes mutations associated with HH, with C282Y being most common. [542, 543, 544]

- Hemochromatosis can be difficult to **diagnose** because early symptoms (stiff joints, fatigue) can mirror other conditions. Many patients don't have any symptoms other than high iron levels. It can also be found when screening family members of people with the disease. [538, 540, 541]

- There are **three key blood tests** for hemochromatosis: serum iron level; serum transferrin saturation; serum ferritin. Additional tests are made to confirm diagnosis: liver function tests; MRI; genetic tests; liver biopsy. [538, 540, 541]

- Doctors can **treat hereditary hemochromatosis** by periodically removing blood from the body (phlebotomy) to reduce iron levels to normal. [538, 540, 541]

- As with other liver diseases, **hereditary hemochromatosis is a risk factor and cause of liver cancer** (hepatocellular carcinoma (HCC), the most common form of liver cancer). (See also section on "Liver Cancer.") [288]

Lysosomal Acid Lipase Deficiency (LALD)

- **Lysosomal acid lipase deficiency (LALD) is a genetic condition** in which the body does not properly break down fats and cholesterol (lipid metabolism), causing harmful amounts of fats (lipids) to accumulate in cells and tissues leading to liver disease. [544, 545]

- **There are two forms of LALD:** [545, 546]
    1. **Infantile-onset LALD** – the most severe and rarest form. It begins in infancy.
        - LALD is often fatal within first 12 months of life.
        - Signs of the disease begin occurring shortly after birth as fat begins to accumulate in the body. Symptoms/signs of the disease can include severe malnutrition; abdominal distention; enlarged liver/spleen (hepatosplenomegaly); abnormalities in the adrenal glands; jaundice; delayed development; poor appetite; fatty stools (steatorrhea); vomiting; diarrhea; poor growth (weight/height) gain; anemia.
    2. **Late-onset LALD** – This form is more common than early-onset. It is less severe, and first symptoms occur at various ages, from mid-childhood to adolescence to late adulthood.
        - Symptoms/complications can include enlarged liver and spleen (hepatosplenomegaly); fatty stools (steatorrhea); vomiting; diarrhea; high cholesterol (hypercholesteremia); liver disease; fatty deposits in arteries (atherosclerosis).

- The incidence of LALD is unknown. LALD prevalence is estimated to be between 1:40,000 to 1:300,000 people, depending on ethnicity and geographical location. [545, 546]

- **There is no cure for LALD.** [547]

- **Treatment options** include enzyme replacement therapy (ERT) which replaces the enzyme lysosomal acid lipase (LAL) that is missing or not working in people with LALD. [548]

- Other treatments include lipid lowering agents, though these have not had great success. [530]

Wilson Disease (WD)

- Wilson disease may also be referred to as Wilson's Disease, hepatolenticular degeneration syndrome, hepatolenticular degeneration syndrome or copper storage disease. [284, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 491, 530, 548]

- **Wilson disease is a rare, progressive, genetic disorder characterized by excessive copper accumulating in body tissues, particularly the liver, brain, kidneys, heart, skin, and corneas.** If untreated, the excess copper poisons the liver or brain, causing liver, neurologic or psychiatric symptoms, and death. Wilson is a multisystem disorder. [284, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 491, 530, 549]

- **Wilson disease can be fatal unless detected and treated** before serious illness from copper poisoning develops. The mortality rate for Wilson disease complicated by acute liver failure (ALF) without liver transplantation is 95 percent, with death occurring in days to weeks. **However, liver transplantation cures Wilson disease with ALF, and prognosis following liver transplantation is excellent.** [284, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 491, 530, 549]

- **Wilson disease carries a risk of liver cancer**. [284, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 491, 530, 549]

- Symptoms start to appear at all ages, as early as 3-11 to 65+ years. **Symptoms usually appear in late adolescence to early adulthood**, but can also occur in early childhood, middle or old age (some patients are detected by genetic studies in their 70s or 80s). [284, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 491, 530, 549]

- **Wilson disease symptoms**: weakness, abdominal pain, jaundice, personality change/ Psychiatric symptoms, seizures, migraine headaches, insomnia, tremors, Parkinsonian movement disorder, etc. [284, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 491, 530, 549]

- **Early diagnosis is crucial to prevent serious disability and life- threatening complications.** [284, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 491, 530, 549]

- **Treatment** reduces the amount of copper in the body and focuses on maintaining normal levels. [284, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 491, 530, 549]

- **If both parents carry a defective Wilson disease gene, there is a 25% chance each child will have the disorder.** [479]

- **Children with Wilson disease can have asymptomatic liver disease, cirrhosis, or ALF, with or without neurological and psychiatric symptoms.** [485]

- **An estimated 8,300 to 11,000 people in the U.S. have Wilson disease.** [475, 476, 478, 479, 480, 481, 482, 485, 486, 487, 489, 549]

- **Wilson disease affects males and females equally and is found in all races and ethnicities.** [475, 476, 478, 479, 480, 481, 482, 485, 486, 487, 489, 549]

- **Wilson disease incidence is approximately 1 in 30,000 to 40,000 people worldwide, though estimates vary. Wilson disease is more common in certain geographic areas, such as Sardinia, Sicilians, southern Italians, and some Eastern European countries.** [475, 476, 478, 479, 480, 481, 482, 485, 486, 487, 489, 549]

- **About 1 in 90 people may be carriers of Wilson disease, though estimates vary.** (One study puts the range at 1:90 to 1:150. Another study in the UK showed 1:7,000 have the Wilson disease gene mutation.) [475, 476, 478, 479, 480, 481, 482, 485, 486, 487, 489, 549]

- **In younger children the liver is most often affected by Wilson disease.** [489, 490, 492, 493, 494]

- In adults, the brain may be more affected. [489, 490, 492, 493, 494]

- **40-50% of WD patients experience liver disease as initial symptoms around the age of 15 years.** [489, 490, 492, 493, 494]

- **Other people with Wilson disease may be misdiagnosed with other neurological, liver, or psychiatric disorders. Many doctors aren't familiar with Wilson symptoms that can be wide-ranging.** [480, 482]

- **WD patients can present with ALF; most other untreated patients have chronic progressive hepatitis or cirrhosis.** [485, 549]

- **50-60% of Wilson patients present with liver symptoms. About 5% of patients with Wilson disease have ALF with severe liver damage**. [475, 482, 495]

- **Of all causes of ALF in adults, 5% is due to Wilson disease.** [496]

- **Of all causes of ALF in the pediatric population, 3.2% is due to Wilson.** [465]

- One summary of studies of **organ-specific Wilson disease manifestations** at presentation: [483]
    - Liver disease: 18% - 84% of patients
    - Neurologic symptoms: 18%-73%
    - Psychiatric symptoms: 10% - 100 %.
    - Most symptomatic **pediatric patients (<18 years) present with liver disease alone**.

- It is estimated that **35%-45% percent of patients have cirrhosis at diagnosis of Wilson disease**. [483]

LIVER TRANSPLANT

What is Liver Transplantation?

- **A liver transplant** removes a liver no longer functioning properly due to chronic (end-stage chronic liver disease) or sudden, acute liver failure, replacing it with a healthy liver from a deceased donor or part of a healthy liver from a matching living donor. Liver transplantation is also a treatment option for other conditions, including some forms of liver cancer. [549, 550, 551]

- **The first successful liver transplant took place in 1967.** [552]

- **Major reasons for liver transplantation** include metabolic dysfunction-associated steatohepatitis (MASH); alcohol-associated liver disease; liver cancer (hepatocellular carcinoma (HCC)); bile duct cancer (cholangiocarcinoma); autoimmune hepatitis; primary biliary cholangitis, primary sclerosing cholangitis, Hepatitis B and C; acute liver failure; biliary atresia (children). [551, 553]

- **Major causes of cirrhosis leading to liver failure and liver transplantation** include alcohol-associated liver disease; MASH; hepatitis B and C; genetic diseases (e.g., hemochromatosis, Wilson's disease, alpha-1 antitrypsin); autoimmune hepatitis; diseases that affect bile ducts (e.g., primary biliary cirrhosis, primary sclerosing cholangitis, biliary atresia). [552, 554]

- Alcohol-associated liver disease and metabolic dysfunction-associated hepatitis are the most common reasons for liver transplantation among adults. [552, 555]

- Biliary atresia is the most common reason for liver transplantation among children. [552, 555]

- In 2024, there were 11,458 liver transplants in the US: 10,854 from deceased donors, 604 from living donors. [555]

- There are currently 9,065 people on the liver transplant waitlist. (June 2025). [556]

- There are more people who need a liver than the supply available. People continue to die while on the waiting list. [556]

- Only a small percentage of liver transplants each year are from living donors. [552]

- **Liver transplants have grown among adolescents/young adults.** [557]

- In the past decade, there has been a 25 percent increase in liver transplants in children 11 to 17 years old; transplants for young adults 18 to 34 more than doubled (United Network for Organ Sharing; UNOS). [558]

- The **waiting time for a deceased donor liver transplant** ranges from less than 30 days to more than 5 years. One source places the average wait time at 11 months. [558, 559]

- Of **adults added to the liver waiting list** (2021): 39.9% received a deceased donor liver transplant within 3 months; 45.7%, within 6 months; and 54.5%, within 1 year. [128, 555]

- **Waitlist candidates by sex distribution** (2023): 60.6% male; 39.4% female. [555]

- **Female liver transplant waitlist candidates had higher pretransplant mortality rates than male candidates** (2023). [555]

- **Racial and ethnic composition of liver waitlist candidates** (2023): 67.8% White, 19.0% Hispanic/Latino, 6.5% Black/African American, 4.5% Asian, 1.2% Native American, 0.6% Multiracial, and 0.3% unreported. [555]

- **Racial and ethnic composition of liver transplant recipients** (2023): 69.8% White, 17.5% Hispanic/Latino, 6.6% Black/African American, 4.1% Asian, 0.6% Multiracial, and 0.4% unreported. [555]

- **Liver transplants by age** (2023): 6.3% age 18-34 years; 20.1% 35-49 years; 46.7% 50-64 years; 26.9% 65 years or older. [555]

- There are good trends in liver transplantation that need to continue: [128, 560]
    - **In 2023, the number of liver transplants performed in the US reached another record high**: 10,659 overall, of which 10,125 (95.0%) were in adult recipients and 534 (5.0%) were in pediatric recipients.
      There was also growth in living donation: 5.7% of adult transplants and 14.6% of pediatric transplants were from living donors.
    - **Wait times are shorter**.

- About 75%-78% of people receiving a liver transplant live for at least five years and nearly 65% after 10 years. [552, 561]

- Survival rates can depend on age, overall health, and the original disease that made the transplant necessary (some diseases return or continue). [552]

- Recipients have been known to live a normal life more than 30 years after the transplant operation. [562]

- Because there are many more people who need a new liver than there are livers available for those people, researchers are looking for ways to increase the number of livers available for patients. [563, 564, 565]

- Liver machine perfusion technology was developed to expand the number of livers available for transplantation. [564, 565, 566]

- In 2024, Penn Medicine performed the first successful external liver perfusion with a gene-edited pig liver. Blood in a brain-dead patient was circulated through a gene-edited pig's liver that was outside the

body. The pig's liver showed no signs of inflammation for 72 hours during the test and the body remained stable. [564, 565, 566]

- Researchers have had successes with gene-edited pig kidneys and hearts, but liver transplants have proven more complicated. [564, 565, 566]
- This may be one solution to the shortage of livers for transplantation. [564, 565, 566]
- Recently, a gene-edited pig liver was transplanted into a brain-dead patient in China, functioning for 10 days; there were no signs of immune rejection or accumulation of inflammation. [566, 567]

ALCOHOL-ASSOCIATED LIVER DISEASE

- The terminology of this disease has been updated from alcohol-related liver disease to alcohol-associated liver disease. [568]
- **Alcohol-associated liver disease (ALD) is a major cause of alcohol-related morbidity and mortality through cirrhosis, liver cancer, and acute and chronic liver failure.** [569, 570, 571]
- **The amount of alcohol consumed placing an individual at risk is not known. A typical patient has consumed alcohol heavily for two or more decades, although sometimes heavy use may be for less than 10 years.** [570, 571, 572]
- **Alcohol-associated liver disease (ALD) is a spectrum of conditions, ranging from reversible fatty liver to alcoholic hepatitis (AH), cirrhosis, and hepatocellular carcinoma (HCC). AH is a distinct syndrome caused by long- term alcohol use and has poor prognosis.** [570, 571, 572]
- **Alcohol-associated liver disease (ALD) is common** but **preventable**. [572, 573]
- **ALD is caused by heavy alcohol use.** The liver breaks down alcohol. If a person drinks more than the liver can process, it can become seriously damaged. [573, 574]
- **The severity of ALD depends on how much alcohol is consumed and duration of heavy drinking**. [573, 574]
- However, some are more susceptible than others and can develop ALD from lower amounts of alcohol. [573, 574]
- **ALD is most common** between 40 and 50 years of age. Men are more likely than women to develop ALD. However. women can develop ALD after less exposure to alcohol than men. Also, the burden of ALD is rising in women. Some people may be genetically at higher risk of developing ALD. [574, 574, 575]
- **Hepatic steatosis, also known as "fatty liver", is the most common alcohol-induced liver problem.** [573]
- Obesity and high-fat diet also increase the risk of ALD. [574]
- **There are three types, or histologic stages, of alcohol-associated liver disease (ALD).** Many heavy drinkers progress through these three types over time: [37, 177, 570, 571, 572, 573, 574, 576, 577, 578, 579]

- **Steatosis (fatty liver; alcoholic fatty liver)** – Steatosis is build-up of fat inside liver cells (liver parenchyma), leading to an enlarged liver. It is the most common alcohol-induced liver problem.
- **Alcohol-Induced hepatitis (AIH; alcoholic hepatitis, AH)** – Alcoholic hepatitis, acute inflammation of the liver, results in death of liver cells, often with permanent scarring. It is an acute, severe problem that is often treated in the hospital. It can be treated but more severe cases lead to liver failure. AIH has poor prognosis.
- **Alcoholic cirrhosis** – Alcoholic cirrhosis is the irreversible destruction of normal liver tissue, leaving scar tissue in place of working tissue. Alcoholic cirrhosis leads to complications including liver failure, portal hypertension, ascites (swelling of the abdomen), infections, confusion, and bleeding in the stomach and esophagus. Alcoholic liver cirrhosis comprises the highest proportion of people in the ALD disease spectrum at 32.9%. **One of the 3 main causes of liver cirrhosis is alcohol** (others are hepatitis B/C & MASLD).

- Heavy drinkers can progress through these three stages over time. [37, 177, 570, 571, 572, 573, 574, 577, 578, 579, 580]

- **Alcohol use can worsen other disease states, including liver diseases but also heart disease and cancers.** [580]

- **Continuing alcohol consumption is a major factor decreasing the survival of patients with alcoholic hepatitis (AH).** [570]

- **The single best treatment for alcohol-related liver disease is abstinence from alcohol.** [578]

- **Participating in a treatment program while avoiding all alcohol can improve outcomes**. There are effective medications that can help people decrease cravings and consumption of alcohol. [573, 576, 581]

- **Alcohol use disorder (AUD) is a pattern of alcohol use that includes problems controlling drinking, preoccupation with alcohol or continued use of alcohol after it causes problems. This disorder also involves increasing tolerance and withdrawal symptoms. Alcohol use disorder includes alcoholism.** [582]

- The **National Institutes of Health defines heavy alcohol** use as: Men: 5+ drinks per day or 15+ drinks per week; women: 4+ drinks per day or 8+ drinks per week. **Heavy drinking increases the likelihood of ALD.** [573, 583]

- **Alcohol is the most frequently misused drug in the world** and in the US, where it is a leading cause of liver disease. It involves 61 % of the US population; 10 to 12 % of that 61% are heavy drinkers. [574]

- ALD prevalence is highest in Europe. [574]

- Globally, excessive alcohol use is a leading preventable risk factor for physical/social harm. [571]

- Excess alcohol consumption causes substantial medical, economic, and societal burdens. [584]

- Worldwide, approximately 5.3% of all deaths may be related to alcohol consumption. [585]

- Worldwide, alcohol associated liver disease (ALD) accounts for 5.1% of all diseases and injury. [585]

- **25% of cirrhosis deaths were associated with alcohol (2019).** [585]

- The global estimated age-standardized death rate (ASDR) for alcohol-associated cirrhosis was highest in Africa and lowest in the Western Pacific. [586]
- The annual global incidence rates of hepatocellular carcinoma (HCC, liver cancer) among patients with alcohol-associated cirrhosis ranged from 0.9% to 5.6% (2019). [586]
- Worldwide, alcohol was associated with approximately one-fifth of HCC-related deaths (2019). [586]
- **In the US, alcohol-related steatosis has been estimated at 4.3%** (NHANES). [585]
- **Alcohol-related fibrotic liver disease has increased in the US.** [585]
- In people with AUD, alcohol-related hepatitis prevalence has been estimated at 10–35%. [585]
- In the US, alcohol-related liver complications result in high healthcare cost burdens. [585]
- Worldwide, alcohol-associated cirrhosis prevalence has been estimated at 23.6 million in people with compensated cirrhosis and 2.46 million with decompensated cirrhosis. [585]
- ALD's contribution to global mortality and burden of liver-related deaths is considerable. **Liver disease related to alcohol contributed to 50% of the estimated liver disease deaths for age 15+ years** (2016)**.** [585]
- **Worldwide, the prevalence of ALD has been estimated at 4.8%.** The prevalence in males was 2.9%, which was higher than female (0.5%). [580]
- **68.9% of people with ALD were Caucasian** (2023). [580]
- **About 59.5% of ARLD patients were current or former smokers.** [580]
- **18.7% of ALD patients also had prior or current viral hepatitis infection.** [580]
- **ALD mortality was 23.9%, and liver-related mortality was 21.6%.** [580]
- **The global prevalence of ALD was 4.8%** (2023). [580]

MetALD (Met+ALD; Met-ALD; metabolic with alcohol-associated liver disease) (See also sections on MASLD and MASH)

- There is a **new category for people with alcohol-associated liver disease** (ALD; formerly alcohol-related liver disease (ARLD)) and MASLD, called **MetALD** (metabolic with alcohol-associated liver disease). It is a continuum which can have elements of MASLD and/or ALD. MetALD is the result of fat in the liver from alcohol use, combined with MASLD. MetALD can result in liver inflammation, scarring, and cirrhosis. [59, 67, 586, 587]

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