

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) Care Guide

September 2026



Information contained in the Care Guide is not a substitute for a health care professional's clinical judgment. Tailor evaluation and treatment to the individual patient and the clinical circumstances. Furthermore, using this information will not guarantee a specific outcome for each patient. Refer to "Disclaimer Regarding Care Guides" for further clarification.

<https://cchcs.ca.gov/clinical-resources/>

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GOALS

- ✓ Recognize the health impacts of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) and Metabolic Dysfunction-Associated Steatohepatitis (MASH) go beyond the liver. There are cardiac, kidney and cancer adverse outcomes among other negative health effects.
- ✓ Screen patients with or at risk for MASLD for those at high risk for advanced fibrosis with scores and non-invasive testing (NIT).
- ✓ Recognize the very high rates of MASLD and MASH in patients with Diabetes; monitor the Fibrosis-4 (FIB-4).
- ✓ Fibrosis $\geq$ F2 for intervention. All-cause mortality starts to rise significantly at this level of fibrosis.
- ✓ Recognize cardiometabolic risk factors and how they integrate into the management of patients with MASLD and mitigate.

ALERTS

- FIB-4 cut-off values for the indeterminant range requiring additional screening tests starts at ≥ 1.3 (See Algorithm 1, page 6).
- The FIB-4 cutoff for risk for advanced fibrosis is > 2.67 which identifies $\geq$ F2 fibrosis and is the cutoff for intervention, but address lifestyle changes early and for all with MASLD.
- The FIB-4 cutoff for cirrhosis is ≥ 3.48 and requires clinical corroboration.
- The preferred method to evaluate liver fibrosis for suspected MASLD/MASH is the Enhanced Liver Fibrosis (ELF). FibroScan may be used if needed. (FibroTest is NOT used as it is not validated in MASLD and is inferior to other tests).
- Liver transaminases can be normal in patients with MASLD and cannot be used to exclude the presence of clinically significant fibrosis. High liver function tests (LFTs) herald risk for progression.
- Ultrasound (US) has low sensitivity across the MASLD spectrum, and the absence of US findings does not rule out MASLD. Although steatosis is used in the definition of MASLD, US is not needed to proceed with fibrosis risk assessment.

DEFINITION/BACKGROUND ^{1,2,3}**NOMENCLATURE**

Steatosis is the accumulation of excess fat in the liver and is the common pathology associated with all liver diseases. Steatotic Liver Disease (SLD) is the overarching category for which metabolic, alcoholic, mixed metabolic and alcoholic and other liver injurious states are a subcategory.

As of June 2023, the American Association for the Study of Liver Diseases (AASLD) has changed the nomenclature for steatotic liver diseases.

1. Non-alcoholic fatty liver disease (NAFLD) is now called MASLD.
 - a. MALSD encompasses the entire spectrum of metabolic associated steatotic liver disease including hepatosteatorosis, steatohepatitis, and cirrhosis.
 - b. Nonalcoholic steatohepatitis (NASH) is now called MASH.
 - c. Metabolic dysfunction-associated and alcohol-associated Liver Disease (MetALD) refers to patients with MASLD and increased alcohol intake and can be metabolic or alcohol predominant.
 - i. See [page 8](#) on alcohol amounts.
 - ii. Note: Alcoholic liver disease (ALD) is not under MALSD and refers to alcohol associated steatotic liver disease associated with heavy drinking.

DEFINITION/BACKGROUND (CONT'D)**DEFINITION OF MASLD**

Metabolic dysfunction-associated steatotic liver disease (MASLD): The presence of hepatic steatosis on imaging in conjunction with one cardiometabolic risk factor (CMRF) and no other discernible cause, minimal or no alcohol consumption. (See [page 7](#)).

MASLD is a metabolic disease which causes metabolic stress, hepatic lipotoxicity and fibrosis. It also causes systemic inflammation which affects not only the liver, but heart, pancreas, intestines, kidney, and possibly the brain as well. MASLD is part of a syndemic of metabolic factors and pathology that are not only interrelated but interacting negatively with each other to result in Type 2 diabetes (T2D), obesity, atherosclerotic vascular disease, liver fibrosis and kidney disease. There is an etiologic interplay of genetic and environmental factors in metabolic syndrome and MASLD that has not yet been completely elucidated by science.

Metabolic dysfunction-associated steatohepatitis (MASH): The progressive form of MASLD, previously termed nonalcoholic steatohepatitis (NASH), is characterized by inflammation from steatosis resulting in hepatocyte ballooning, and an influx of inflammatory cells. As MASH progresses, hepatocytes lyse and the liver becomes fibrotic, leading to cirrhosis, possible hepatocellular carcinoma (HCC), liver failure and the need for liver transplantation.

ALD: Patients with steatosis and heavy alcohol use.

Natural History of MASLD

Of patients with MASLD 15-40% will progress to MASH (50% in patients with diabetes)

Of patients with MASH 20-30% progress to advanced fibrosis

Of patients with MASH fibrosis 15-25% will progress to cirrhosis

Of patients with cirrhosis 7% will develop HCC (2-4% per year)

Patients with MASLD have high rates of cardiovascular disease, followed by extrahepatic cancers and then liver-related deaths. Overall mortality and cardiovascular mortality increase with and are highly correlated to fibrosis stage.

Fibrosis stages are classified histologically as the following:

- F0 – no fibrosis
- F1 – mild
- F2 – moderate (clinically significant)
- F3 – severe (advanced)
- F4 – cirrhosis

PREVALENCE

In the United States (U.S.), MASLD is one of the most common causes of liver disease. Between 30-40% of adults in the U.S. have the disorder, with higher prevalence in males compared with females. The incidence of MASLD is increasing over time and is considered an epidemic. It is expected to increase by 63% between 2015 and 2030⁴³. In the U.S., the proportion of liver transplant for MASH increased from 2.5% in 2004 to 20.4% in 2019 and has only increased since then⁴⁴. MASLD is the leading and fastest-growing cause of HCC and the second most common reason for liver transplantation, following ALD. As of 2023, ALD accounted for 41.1% of liver transplant recipients, followed by MASH at 20.3%.

DEFINITION/BACKGROUND (CONT'D)**RISK FACTORS FOR MASLD**

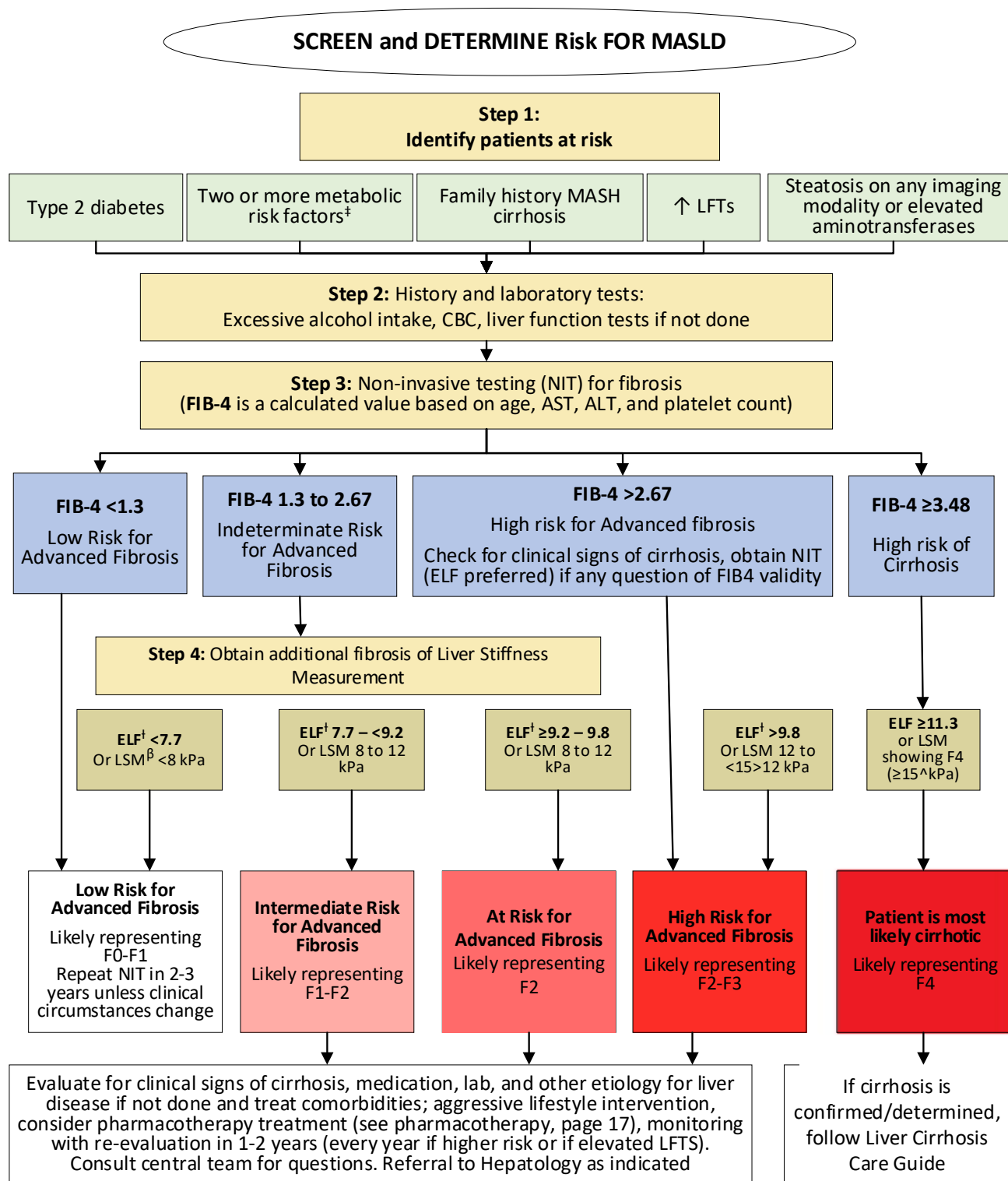
Risk factors and associated conditions Patients with MASLD often have one or more components of the metabolic syndrome including:

- Insulin resistance or overt T2D
 - T2D is a major risk factor for the development of MASLD
 - Approximately 55-70% of adults with T2D in the U.S. have MASLD
 - Of those with T2D and MASLD, 50% are estimated to have steatohepatitis (MASH)
 - Of those with T2D and MASH, it is estimated between 12% -20% have had sufficient inflammatory hepatitis to result in clinically significant fibrosis ($\geq$ F2)
 - T2D is also a major risk factor for fibrosis progression to cirrhosis, and HCC
- Obesity
- Systemic hypertension
- Dyslipidemia [low high-density lipoprotein (HDL) and elevated triglycerides (TG)]
- Human Immunodeficiency Virus (HIV) infection and certain HIV anti-retroviral medications

Other comorbid conditions include but are not limited to:

- Obstructive sleep apnea
- Cardiovascular disease (CVD)
- Chronic kidney disease (CKD)
- Polycystic ovarian syndrome (PCOS)
- Hypogonadism

There is a stepwise approach to screening and managing MASLD. Please see Figure 1 which shows an overview, for which details will follow in subsequent pages.

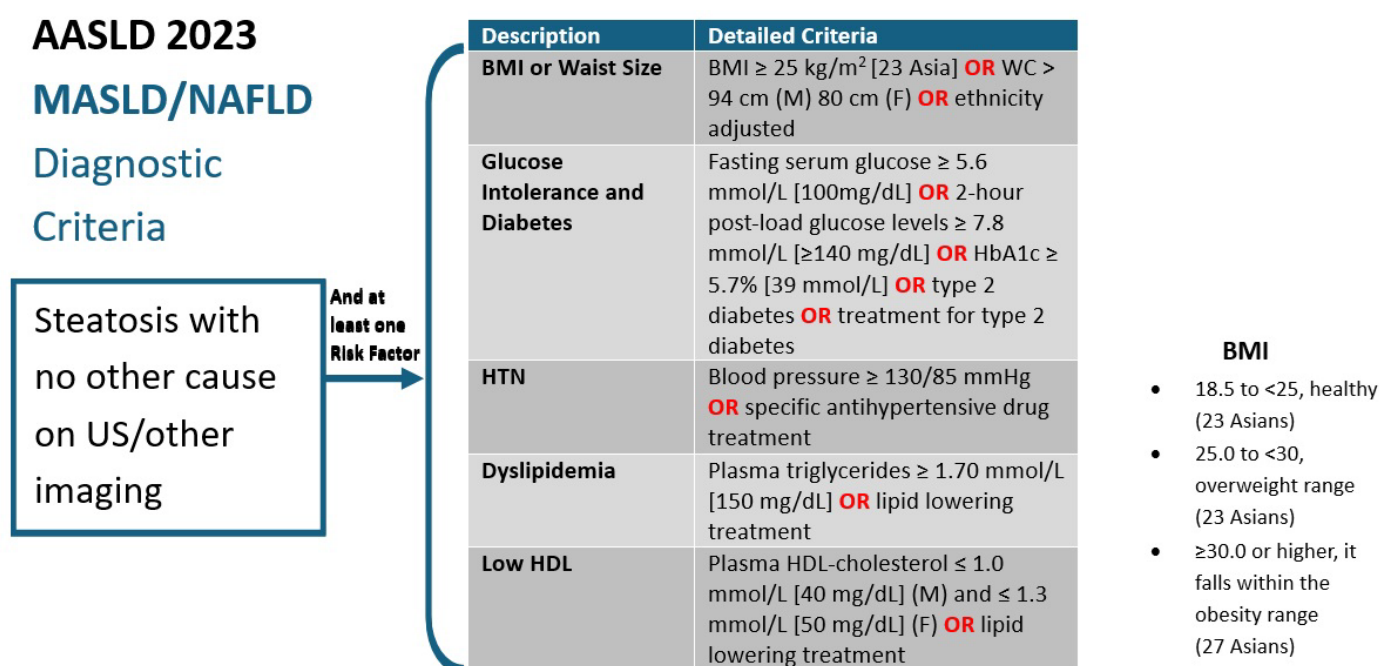
Figure 1: Algorithm**SCREENING FOR ADVANCED FIBROSIS RELATED TO MASLD ALGORITHM**[‡] Metabolic risk factors central obesity, obesity, high triglycerides, low HDL cholesterol, hypertension, prediabetes or insulin resistance, or HIV.[†] Preferred method of determining Liver Stiffness Measurement (LSM)[§] LSM cut-off values for the fibrosis stages in MASLD are different than those for HCV and other causes. For patients 65+, use FIB-4 <2.0 as the lower cut-off. Higher cut-off does not change. LSM measured by FibroScan. F0-F4, liver fibrosis staging levels. See [page 13](#) for details.[^] Controversy exists on kPa for cutoff for cirrhosis in MASH, with some entities using up to 20 kPa as a cutoff. Corroborate the diagnosis of cirrhosis with other clinical data when the kPa is 15-20 kPa.Adapted and revised from AGA Kanwal et al. 2021⁶ Figure 1 AASLD NAFLD guidance 2023¹ Figure 2, AASLD² Figure 2, and AASLD³ Figure 1

DIAGNOSIS ^{1,2,3,4,5}

The diagnosis of MASLD technically requires biopsy or the presence of steatosis on imaging along with at least 1 cardiometabolic risk factor (Diabetes Mellitus (DM), Prediabetes Mellitus (PreDM), obesity, central obesity, insulin resistance (IR), hypertension (HTN), low levels of HDL, or high triglycerides) and no other predominating cause of steatosis. However, a diagnosis is not necessary to proceed with a work-up of patients at risk for MASLD and as such it is recommended^{2,6} to focus on identification of risk and risk stratification for interventions. Note also that the presence of steatosis on imaging is not necessary for at-risk work up as described in the screening section below.

MASLD cannot be formally diagnosed when there is active viral or non-metabolic related hepatitis. However, patients with chronic liver injurious states (autoimmune, Hepatitis B Virus (HBV) etc.) and risk factors for MASLD may have mixed etiology of liver inflammation and are at increased risk of progression to advanced liver disease. Thus, it is critical to address metabolic issues in such patients to lower their overall risk.

Figure 2: Algorithm



The diagnosis of MASLD requires excessive alcohol use to be excluded.

Establish diagnosis of MASLD versus MetALD versus ALD.

If **MASLD** is suspected, assess alcohol consumption in a clinical interview, AUDIT tool and/or phosphatidylethanol (PEth) testing (Quest Misc. Test: test code 12198 - only if will change management), if applicable.

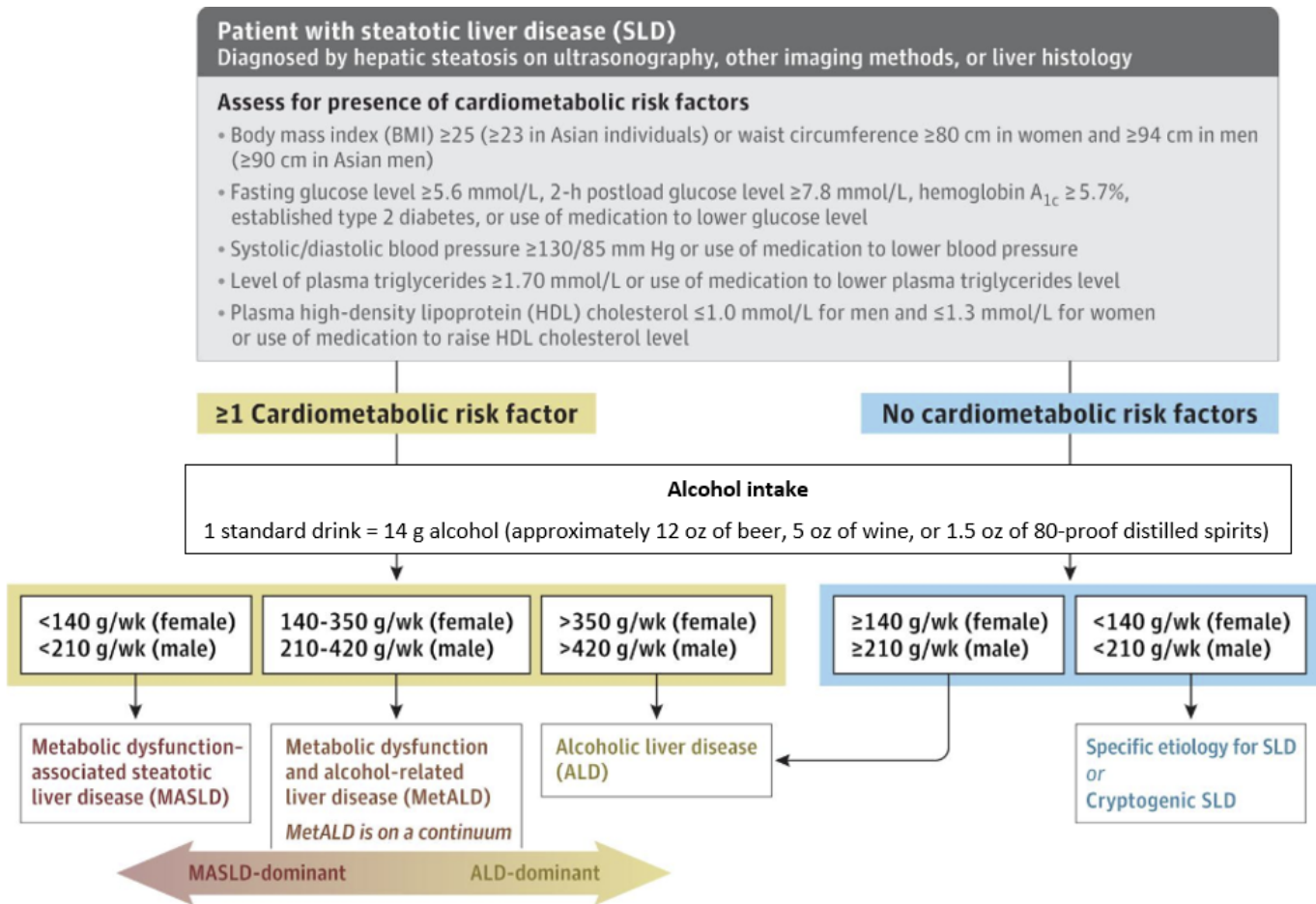
Alcohol intake

1 standard drink = 14 g alcohol (approximately 12 oz of beer, 5 oz of wine, or 1.5 oz of 80-proof distilled spirits)

1. If the patient's daily alcohol consumption is no more than 20 g for women or 30 g for men, a diagnosis of MASLD can be made. This equates to 1 drink a day for women and 2 drinks a day for men.
2. If the patients have daily alcohol consumption >20 g and <50 g for women and >30 g <60 g for men, then the diagnosis of MetALD will be made. This equates to approximately 2 - 3 ½ drinks per day for women and 3 - 4 1/3 drinks a day for men. Consider the combination of metabolic-based and alcohol-based (MetALD) liver disease.

DIAGNOSIS (CONT'D)

3. In the presence or absence of metabolic dysfunction, if alcohol consumption ≥ 50 g for women or ≥ 60 g for men, diagnosis of ALD will be made and treatment guidance for ALD should be followed. This equates to anything more than 3 1/2 drinks a day for women and 4 1/3 drinks a day for men. Suspect ALD—and treat these individuals according to the ALD guidelines, not MASLD guidelines.
4. Ask your patients in a nonjudgemental manner and be sure to convey to them that the information is medical and will not be shared with custody. Patients at CCHCS are drinking alcohol. It is important for MASLD patients to stop.

Figure 3: Algorithm

DIAGNOSIS (CONT'D)**RISK ASSESSMENT****STEPWISE APPROACH TO RISK STRATIFY IN SUSPECTED MASLD****Step 1: Risk assess for suspected MASLD for patients with risk factors****Step 2: Conduct History and Blood Tests to Obtain Key Measures****Step 3: Conduct Noninvasive Testing for Liver Fibrosis Using FIB-4****Step 4: Obtain additional fibrosis testing if indicated****STEP 1: RISK ASSESS FOR SUSPECTED MASLD if any one of the following conditions are present:****Table 1: Assess for Suspected MASLD**

Group 1:	Group 2:	Group 3:	Group 4:	Group 5:
Patients with Type 2 Diabetes OR PreDM (A1c $\geq$ 5.7) OR 2-hour post-load glucose levels $\geq$ 140 mg/dL OR Insulin resistance: $\uparrow$ fasting plasma glucose, between 100 mg/dL and 125 mg/dL OR Other evidence of glucose intolerance	Patients with two or more metabolic conditions including: • Obesity • Body Mass Index (BMI) $\geq$25kg/m² ($\geq$23 kg/m² for Asians) - OR • Central obesity (also known as abdominal obesity, waist circumference $>$35 inches in women and $>$40 inches in men). • $\uparrow$ Triglycerides $\geq$150 mg/dL, or specific treatment for hypertriglyceridemia • $\downarrow$ Reduced HDL $<$40 mg/dL in men, $<$50 mg/dL in women, or specific treatment • Hypertension, systolic blood pressure $\geq$130 mm Hg or diastolic blood pressure $\geq$85 mm Hg, or specific treatment • Patients living with human immunodeficiency virus (HIV) While not in the guidelines yet, research shows that HIV is considered an independent risk factor for MASLD, both due to direct adverse effects of antiretroviral therapy (ART) and inflammatory and mitochondrial dysfunction associated with HIV infection itself	$\uparrow$ Aminotransferases Persistent elevation of aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) for $\geq$ 6 months (in minimum of 2 tests, at least 4 weeks apart) indicates the need for all causes of SLD to be ruled out before investigating for MASLD. It's important to note that after successful HCV treatment with sustained virologic response (SVR), liver function tests (LFTs) nearly always return to normal. If they do not, repeat the LFTs 1 month later and if they remain elevated, evaluate for other causes of hepatic inflammation, including MASLD.	Hepatic steatosis on any imaging modality and one CMRF from Group 1 or 2	Family history of MASH cirrhosis

Table 1 adapted from [2023 AASLD MASLD Guidelines](#)

EVALUATION

STEP 2: Conduct History and Blood Tests to Obtain Key Measures

Screen all at-risk patients identified in Step 1 for liver insults and advanced fibrosis related to MASLD with the following:

1. Conduct standard history, (to include alcohol intake history, viral hepatitis risk factors, autoimmune history, hepatotoxic medications including supplements, family history of MASH-cirrhosis), pertinent review of systems, physical exam, and clinical signs of advanced liver disease or cirrhosis.
2. Order screening labs to rule out other causes of liver disease, treating the underlying etiology if applicable, and to calculate FIB-4 fibrosis score. Keep in mind that age, acute hepatitis, and thrombocytopenia of autoimmune etiology (as opposed to cirrhosis) may spuriously affect FIB-4.

HISTORY

Screen patients for alcohol use (See [page 8](#)).

Most patients with MASLD are asymptomatic, although some patients with MASLD may complain of fatigue, malaise, and vague right upper abdominal discomfort.

Evaluate for known causes of liver disease, such as viral hepatitis, long-term use of steatogenic medication, and hepatotoxic medications. Consider secondary causes of liver inflammation, such as autoimmune hepatitis. Ask about itchy skin if biliary autoimmune disease is suspected.

Common hepatotoxic or steatogenic medications include: Nonsteroidal anti-inflammatory drugs (NSAIDs), amoxicillin-clavulanate, nitrofurantoin, sulfonamides, isoniazid, pyrazinamide, rifampin, amiodarone, ketoconazole, carbamazepine, valproate, phenytoin, corticosteroids, azathioprine, methotrexate, tamoxifen, 5-Fluorouracil (5-FU), infliximab, and irinotecan. See [National Institute of Health \(NIH\) LiverTox Website](#).

Patients with celiac disease and bypass surgeries or Crohn's or other diseases with small bowel resections may have nutritional deficits that can lead to steatohepatitis.

If not already done, assess for common comorbidities such as CVD, T2D, dyslipidemia, and kidney disease. Individualize assessments for sarcopenia, hypothyroidism, hypogonadism, growth hormone deficiency, polycystic ovary syndrome, and sleep apnea.

Assess for CVD risk using an accepted CVD screening tool such as the [AHA* PREVENT Cardiovascular Risk Calculator](#) which has replaced the ACC AHA [ASCVD Risk Calculator](#) for most patients. For patients living with HIV, use the older [ACC* AHA* Risk Estimator Plus](#) and not the PREVENT calculator which has been shown to underestimate risk in HIV.

These calculators are available in the Electronic Health Record System (EHRS) under Evidence-Based Medicine Calculator (EBMCalc) button, on the blue main menu in the chart. Be sure to scroll down and click "Record", so that it saves to "Assessments" inside "Results Review" in the patient's chart.

PHYSICAL FINDINGS

Patients with MASLD may have hepatomegaly on physical examination due to fatty infiltration of the liver, but the reported prevalence of hepatomegaly in patients with MASLD is highly variable. Patients who have developed cirrhosis may have stigmata of chronic liver disease (e.g., palmar erythema, spider angioma, ascites, peripheral edema).

Abdominal obesity is common. However, there are patients with MASLD who are lean. This is more commonly seen in persons of Hispanic or Asian origin and is thought to have a genetic component to the MASLD etiology.

If patients have MASLD or MASH and are lean and are without metabolic risk factors, search for other etiologies of liver disease. Patients who are lean with MASLD/MASH and have CMRFs tend to have worse prognosis for non-liver related outcomes even compared to those who are obese⁴⁵.

EVALUATION (CONT'D)

LABS

For patients with suspected MASLD, obtain the following laboratory studies to assess liver function and comorbid conditions:

- Complete Metabolic Profile: Alanine aminotransferase (ALT) and aspartate aminotransferase (AST), Alkaline phosphatase (Alk Phos), Total bilirubin (BR), Serum albumin (ALB), and Glucose (GLU)
- Prothrombin time (PT)/international normalized ratio (INR)
- Complete blood count with platelets (CBC)
- Glycated hemoglobin (A1c)
- Fasting Lipid Profile (FLP) (Total, HDL, LDL, TG)
- Thyroid stimulating hormone (TSH)

Rule out other causes of liver disease, especially if liver function tests (LFTs) are elevated, the patient is lean or is found to have at-risk fibrosis (see below). If elevated transaminases or if there is suspicion of other chronic liver and biliary disease:

- For all patients: order labs to evaluate viral etiology, e.g., Hepatitis C Virus (HCV), HBV
- Hepatitis C Virus Antibodies (HCV Ab) with reflex testing of ribonucleic acid of the HCV, or HCV ribonucleic acid (RNA), (or HCV RNA for those with prior positive Ab)
- Hepatitis B serology: Surface antigen and antibody and core antibody (Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (HBsAb), Hepatitis B core antibody (HBcAb))
- If clinically indicated, when there are chronically unexplained elevated liver function tests and if high risk for fibrosis, or suggestive medical history or clinical picture, evaluate for other causes such as medication-induced hepatitis, Wilson Disease, Hereditary Hemochromatosis, Autoimmune Hepatitis, etc.
- Plasma iron, ferritin, and total iron binding capacity
- Antinuclear antibodies (ANA), Immunoglobulin G, anti-smooth muscle antibodies (ASMA)
- Antimitochondrial antibodies (AMA)
- Ceruloplasmin (liver disease usually begins under age 50)
- Alpha-1 antitrypsin (AAT) level
- Anti-tissue transglutaminase antibody (Ttg-IgA)

Transaminases	Patients with MASLD may have mild or moderate elevations in the AST and ALT, although normal aminotransferase levels do not exclude MASLD. Persistently elevated transaminases require a workup for less common causes of liver injury. When elevated, the AST and ALT are typically 2-5 times the upper limit of normal, with an AST to ALT ratio of < 1 (similar to HCV, but unlike alcoholic fatty liver disease, which typically has a ratio > 2). Note that the AGA definition of a high ALT is >20 U/L for women and >30 U/L for men which is lower than Quest's reference range. Note: The degree of aminotransferase elevation does NOT predict the degree of hepatic inflammation or fibrosis, and a normal alanine aminotransferase does not exclude clinically important histologic injury.
Alkaline phosphatase	May be elevated to 2-3 times the upper limit of normal. Keep a high index of suspicion for autoimmune biliary disease such as (primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC)).
Serum albumin	Typically, within the normal range, but may be abnormal in patients who have developed cirrhosis.
Bilirubin	Typically, within the normal range, but may be abnormal in patients who have developed cirrhosis.
Serum ferritin or transferrin saturation	May be elevated in patients with MASLD. In addition, a serum ferritin greater than 1.5 times the upper limit of normal in patients with MASLD has been associated with increased risk of steatohepatitis and advanced fibrosis.

EVALUATION (CONT'D)

RADIOGRAPHIC FINDINGS

Because obesity and T2D confer a high pretest probability of hepatic steatosis ($\geq 70\%$), current guidelines recommend proceeding directly to fibrosis risk assessment using FIB-4 without first confirming steatosis by imaging.

Radiographic findings in patients with MASLD include increased echogenicity on ultrasound, decreased hepatic attenuation on computed tomography (CT), and an increased fat signal on magnetic resonance imaging (MRI). Note that abdominal ultrasound (US) has good accuracy for detecting moderate and severe steatosis but has suboptimal sensitivity for detecting mild steatosis or evaluating the stages of fibrosis. Further, US has only approximately 50-70% sensitivity for diagnosing cirrhosis depending on the study (when nodularity consistent with cirrhosis is specifically read on US imaging, it is specific however, for identifying cirrhosis with a specificity of 74-95% depending on the study). Lack of US findings is not necessary to proceed with risk evaluation.

LIVER BIOPSY

Liver biopsy is currently the only reliable means to diagnose MASLD and is the reference standard for fibrosis staging. However, liver biopsy may not be feasible to obtain in a significant number of patients. Besides the accompanied pain, discomfort, and small risk of complications due to its invasive nature, liver biopsy is associated with potential sampling error and interobserver variation. It is also impractical to repeatedly perform liver biopsy to assess disease progression. Therefore, national guidelines (i.e., [American Gastroenterological Association \(AGA\) Guidelines page 7](#), Figure 2 and [AASLD Guidelines page 8](#), Figure 3) recommend further workup and noninvasive efforts to predict and evaluate the stage of hepatic fibrosis.

LEAN MASLD

It is estimated that 7-20% of patients with MASLD have a lean body habitus. The AGA defines Lean MASLD as patients with MASLD but a body mass index below the BMI cut offs for overweight or obese (<25 kg/m² (non-Asian race) or body mass index <23 kg/m² (Asian race).

The pathophysiology of lean MASLD differs from obesity-related MASLD in several ways. These patients characteristically exhibit visceral adiposity and sarcopenia rather than generalized obesity. Despite lower overall adiposity, lean individuals demonstrate adipose tissue dysfunction and insulin resistance that trigger lipid overflow to the liver, resulting in undesired liver injury.

More importantly, Lean MASLD carries similar or even elevated risks compared to obese MASLD for adverse outcomes. This paradox underscores that normal BMI does not confer protection against disease progression in the presence of metabolic dysfunction.

Hence, it is critical to identify patients with metabolic derangements, or incidentally noted steatosis, who are not overweight, and to risk stratify them.

Once again, assess alcohol use, as this could be its occult presentation and chart review and patient interview to look for secondary causes of liver disease are needed.

[AGA Clinical Practice Update: Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Lean Individuals: Expert Review](#)

EVALUATION (CONT'D)

STEP 3: Conduct Noninvasive Testing for Liver Fibrosis Using Simple Scores

Hepatic fibrosis is the most important determinant of liver and non-liver outcomes in patients with MASLD. Identifying patients with clinically significant hepatic fibrosis (F2 or higher) is important for targeted efforts at preventing disease progression. [Research](#)¹⁹ has shown that patients with MASLD have significantly elevated all-cause mortality in addition to liver related mortality once F2 fibrosis is reached. This research is what has led to the F2 cut off for “at risk” fibrosis and the goal to identify such persons early.

Alert: Unlike HCV, F2 fibrosis in MASLD is significant and increases risk of death and portends progression.

Note: Patients who have either spontaneously recovered from HCV infection, or had sustained viral response from HCV treatment, can also develop liver fibrosis related to MASLD when they have risk factors such as T2D and/or obesity. If these patients have not been evaluated regarding their liver fibrosis, screen for advanced fibrosis related to MASLD. Consult central care team for questions, (order is “Consult to MASLD” in the EHRs).

Calculate [Fibrosis-4 index \(FIB-4\)](#) score which has been validated for MASLD. (NOTE: decision thresholds for FIB-4 used for MASLD are different than that used for HCV). *Keep in mind that age, acute hepatitis, and autoimmune thrombocytopenia may spuriously affect FIB-4.*

Table 2: Interpretation of FIB-4 score in patients with MASLD

FIB-4 in Patients with MASLD	Interpretation^{2,6,9} Fibrosis staging system (NASH Clinical Research Network (CRN) staging system) for NAFLD⁴⁶ Note that the FIB-4 score may overrepresent the extent of liver fibrosis in the setting of advanced age and/or low platelet count⁷, even in the absence of liver disease. It is important to consider the cause of low platelets, as it may not be due to cirrhosis. Liver enzymes can be affected by several conditions. (See Liver biochemical tests that detect injury to hepatocytes (UpToDate) for more details). Moreover, the value of AST and ALT may be markedly elevated during acute hepatic injury⁸ from acute viral illnesses, alcohol or spice binges, medications or other acute injurious states. Thus, it is important to consider why the LFTs are elevated and monitor the lab values over time, and the calculation may need to be repeated to see if the FIB-4 score is consistently elevated.
<1.3*	Unlikely to have advanced fibrosis Likely representing: F0- No fibrosis F1- Mild fibrosis
1.3*-2.67	Indeterminate range, further evaluation required (See Step 4)
>2.67	Likely to have advanced fibrosis and likely representing: F2- Clinically significant fibrosis F3- Advanced fibrosis F4- Cirrhosis

* For patients 65+, use FIB-4 <2.0 as the lower cutoff. Higher cutoff does not change⁶.

In MASLD, the FIB-4 cutoff for cirrhosis is higher than for HCV at 3.48 instead of 3.25. For those patients who are considered to have cirrhosis (clinically or based on non-invasive testing (NIT) or liver biopsy), follow the appropriate management, including HCC and esophageal variceal determination/screening and advance care planning. (Refer to [Liver Cirrhosis Care Guide](#) for details.)

EVALUATION (CONT'D)

STEP 4: Obtain Additional Fibrosis Testing or Liver Stiffness Measurement

Based on the FIB-4 score, patients will be determined as having low, indeterminate, or high risk of having advanced fibrosis related to MASLD and then followed-up and managed accordingly.

Low Risk FIB-4 <1.3	Indeterminate Risk FIB-4 1.3 to 2.67 (2.0 – 2.67 for patients 65+)	High Risk FIB-4 >2.67
Repeat NIT in 2-3 years unless clinical circumstances change	Complete ELF testing (or FibroScan if discordant NITS or special circumstances)	Check for clinical signs of cirrhosis, obtain ELF or FibroScan testing as needed

Patients without clinical signs of cirrhosis and with indeterminate or high risk of advanced fibrosis need additional assessment using the ELF blood test (preferred) or liver stiffness measurement by FibroScan to further stratify their liver fibrosis level and identify those with increased risk of MASH and advanced fibrosis who require aggressive treatment¹¹.

- **Enhanced Liver Fibrosis (ELF) test** is a noninvasive blood test of blood-derived biomarkers consisting of three components:
 - Type III procollagen peptide,
 - Hyaluronic acid, **AND**
 - Tissue inhibitor of metalloproteinase-1

Providers can order the ELF test in the EHRS: *Enhanced Liver Fibrosis (ELF) score (Quest Test code 10350)*.

****IMPORTANT**** Note: The *FibroTest (ActiTest or FibroSure)* blood test, which is used for HCV, is **NOT** recommended to evaluate for MASLD.

- **FibroScan**
 - Liver Stiffness Measurement (LSM) by FibroScan is usually ordered in case-by-case situations by the Central Hepatitis Team or specialists when further evaluation is needed to rule in or rule out advanced fibrosis.
 - The LSM interpretation for fibrosis stages in MASLD in Table 2 below are cited from the American Association for the Study of Liver Disease (AASLD)¹, AGA⁶, and American Association of Clinical Endocrinology (AACE)², though various studies have reported other values^{12,13}. It is important to recognize that these are different than those for HCV¹⁴. **Thus, the FibroScan indication (MASLD vs HCV) needs to be specified on the EHRS order.**

EVALUATION (CONT'D)**Table 3: Advanced Fibrosis Risk Stratification**

MASLD Non-Invasive Test (NIT)	Low Risk	Moderate Risk		High Risk	Possible Cirrhosis	Probable Cirrhosis
FIB-4	FIB-4 <1.3	FIB-4 1.3 to 2.67 INDETERMINANT and needs secondary assessment (ELF preferred)		FIB-4 >2.67		Fib 4 ≥3.48
ELF	ELF 7.7	ELF 7.7 to <9.2	ELF ≥9.2 to 9.8	ELF >9.8		ELF >11.3
LSM	< 8kPa	Possibly ≥ 8 kPa	≥ 8 to < 12 kPa (F2)	≥12 kPa to <15 kPa (F3)	LSM 15-20 kPa (F3-F4)	LSM > 20 kPa
Metavir score	Likely representing F0 – F1	Likely representing F1 - F2	Likely F2	Likely F2 -F3 and high risk for advanced liver disease	Rule out cirrhosis	Likely F4
					Making MASH cirrhosis diagnosis between 15 and 20 kPa requires corroboration with other NITS or clinical data (such as platelets <150k) to confirm diagnosis of cirrhosis	While studies show FIB-4 ≥3.48 and ELF ≥11.3 and LSM by FibroScan >15 kPa correlate well with identifying patients with cirrhosis; some patients may be missed ¹ and some may be over diagnosed. Take the entire clinical picture into account. Further evaluation with magnetic resonance elastography or liver biopsy may be indicated in certain unique circumstances. Place consult to MASLD if considering biopsy or magnetic resonance elastography (MRE).

See the AGA algorithm below for screening and risk stratifying for advanced fibrosis related to MASLD with the goal of detecting those patients with clinically significant fibrosis early and starting intervention accordingly, on Figure 1, [page 6](#).

MANAGEMENT OF MASLD/MASH ^{1,2,3,6}

The most common causes of death in patients with MASLD are cardiovascular disease, non-hepatic malignancy, followed by liver disease. However, liver-related mortality increases exponentially with an increase in the stage of fibrosis and predominates in patients with advanced fibrosis.

While general measures such as lifestyle changes and weight loss are recommended for all patients with MASLD, intensity of treatment recommendations vary based on risk for or presence of advanced fibrosis. (See [Table 2: Management of MASLD](#) below)

General measures for all patients

The following measures apply to all patients with MASLD^{15, 16}:

Table 4: MASLD Interventions for All Patients

Abstain from alcohol	Avoid heavy alcohol use, which is associated with disease progression. Instruct patients with clinically significant liver fibrosis ($\geq F2$) to abstain from alcohol use completely ¹ .
Immunizations	Offer vaccination for Hepatitis A Virus and HBV to patients without serologic evidence of immunity. Additional vaccines for patients with chronic liver disease include pneumococcal vaccination and standard immunizations that are given to the general population (See Preventive Services Care Guide , Section 1) or the CDC website .
Manage and minimize metabolic risk factors Modify risk factors for cardiovascular disease	Optimize blood glucose control, lower blood pressure, improve the lipid profile, decrease weight. (Lean MASLD - still recommended to lose 5% of body weight if tolerated). Suppress TSH to be between 1-2.5 if possible, in patients with MASLD or MASH with hypothyroidism. It is recommended that we do not wait for TSH to be 10 for initiation of thyroid hormone replacement treatment in MASLD. Most patients with MASLD who have hyperlipidemia are candidates for lipid-lowering therapy. Optimize blood pressure control. Advocate for exercise and a healthy diet and healthy body weight. Dietary consult is recommended. Calculate the 10 year Cardiovascular Risk Percentage and offer appropriate interventions. If ASCVD, optimize all secondary prevention treatments. See Chronic Coronary Disease Care Guide . For patients living with HIV, use the Estimator Plus CV Risk Calculator.
Lifestyle interventions	Diet changes include the following recommendations: • Limit intake of fats (e.g., butter, cheese, red meat, sausage, bacon). • When available, replace foods with saturated and trans fats for those with unsaturated (poly and mono) fats, especially those high in omega-3 fatty acids. (e.g., vegetables, fruits, beans, nuts, whole grains, turkey, and fish). • Attempt to avoid foods with large amounts of fructose commonly found in canteen items. (e.g., honey buns, soda, sport drinks, juices). Regular physical activity, independent of weight loss, has hepatic and cardiometabolic benefit; and is recommended for patients with MASLD, with a target of 150-300 minutes of moderate-intensity or 75-150 minutes of vigorous-intensity aerobic exercise per week. • Resistance training exercise can be complementary to aerobic exercise and can have independent effects on MASLD. Twice a week is recommended. ○ The impact of exercise on MASLD can enhance the positive effect of hypocaloric diet. Note: There are conflicting studies in the literature that artificially sweetened beverages may be associated with increases in visceral adiposity and MASLD. This topic may have more guidance in the future pending more definitive research.

MANAGEMENT OF MASLD/MASH (CONT'D)**Table 4: MASLD interventions for All Patients (CONT'D)**

Weight loss	Weight loss has a profound impact on patients with MASLD. Weight loss is recommended for all patients who are overweight ([BMI] >25 kg/m², 23 kg/m² Asian) or have obesity (BMI >30 kg/m²). For patients with a normal BMI ("lean MASLD") - Reduction of 3-5% of total body weight to reduce visceral/intrahepatic fat. Lower body weight improves: • Liver biochemical tests, • Liver histology/regresses steatosis, • Insulin sensitivity • Cardiac risk, and • Quality of life in patients with MASLD. • Clinically significant weight loss generally requires a hypocaloric diet targeting 1200–1500 kcal/d or a reduction of 500–1000 kcal/d from baseline. (See Weight Management Care Guide for details.) Reduction of >=5% of total body weight to reduce liver fat. Reduction of 7-10% to improve liver inflammation. Reduction of >=10% to improve fibrosis. Bariatric procedures may be considered for those who do not meet weight loss goals after six months of weight loss management. (See Weight Management Care Guide for details.)
Avoid hepatotoxic medications	Common hepatotoxic or steatogenic medications include: NSAIDs, amoxicillin-clavulanate, nitrofurantoin, sulfonamides, isoniazid, pyrazinamide, rifampin, amiodarone, ketoconazole, carbamazepine, valproate, phenytoin, corticosteroids, azathioprine, methotrexate, tamoxifen, 5-FU, infliximab, and irinotecan. See National Institute of Health (NIH) LiverTox Website.

MANAGEMENT OF MASLD/MASH (CONT'D)

Table 5: Management of MASLD ^{1,2,6} Adapted and revised from Figure 2 in Kanwal et al. AGA 2021⁶

MASLD Management Intervention	Low Risk for Advanced Fibrosis	Indeterminate/Medium Risk for Advanced Fibrosis	High Risk for Advanced Fibrosis
	FIB-4 <1.3 or ELF [†] <7.7 or LSM [‡] <8 kPa by FibroScan (Likely representing F0 – F1)	FIB-4 1.3 - 2.67 and/or ELF [†] 7.7 - 9.8 or LSM 8 -12 kPa by FibroScan (Likely representing F1 - F2)	FIB-4 >2.67 or ELF [†] >9.8 or LSM > 12 kPa by FibroScan (Likely representing F2 and above)
	Management by PCP, dietician, and others	Management by central care team with multidisciplinary team	Management by central care team with multidisciplinary team
Lifestyle Intervention	Yes	Yes	Yes
Weight loss recommended if overweight or obese	Yes May benefit from structured weight loss programs, anti-obesity medications, possible bariatric surgery	Yes Greater need for structured weight loss programs, anti-obesity medications, possible bariatric surgery	Yes Strong need for structured weight loss programs, anti-obesity medications, possible bariatric surgery
Pharmacology for MASH	Not recommended	Consider worrisome rate of fibrosis rise, those with multiple risk factors or other concerning extenuating circumstances IMD [#] is recommended for ELF ≥9.2 and LSM of 8 or greater on FibroScan*	Yes (IMD, Resmetirom [@])
Diabetes with MASH	Standard of care	Prefer medications with efficacy in MASLD (IMD [#] , Resmetirom [@] , Pioglitazone) IMD [#] is recommended for ELF ≥9.2 and LSM of 8 or greater on FibroScan*	Prefer medications with efficacy in MASLD (IMD [#] , Resmetirom [@] , Pioglitazone)

[‡]Liver Stiffness Measurement (LSM) cut-off values for the fibrosis stages in MASLD/MASH are different than those for HCV and other causes of liver disease.

[†]Preferred method of determining LSM

[#]As of this writing, the only FDA approved medication for MASH is semaglutide. Semaglutide is first line therapy. AASLD notes in semaglutide guidance below that the [ESSENCE trial](#)²⁷ studies on semaglutide showed benefit in ELF ≥ 9.2.

* [November 2025 AASLD Guidance on Semaglutide in MASH](#)

@ Resmetirom has restricted use criteria see [page 22](#).

MONITORING

LABORATORY MONITORING¹⁶

Some experts obtain serum aminotransferases (ALT and aspartate aminotransferase) every 3-6 months after patients implement lifestyle interventions to achieve and maintain their weight loss goals. If the aminotransferases do not return to normal levels with weight loss or if they increase, consider evaluation for an alternative cause of liver disease. Keep in mind that elevated liver function tests are not necessary for significant MASH fibrosis to be occurring.

MONITORING FOR FIBROSIS^{1,6}

For patients who are at low risk for advanced fibrosis related to MASLD, repeating the NITs in 2-3 years is recommended, unless clinical circumstances change, indicating a need for sooner follow up. Encourage lifestyle changes to prevent progression.

For patients who are at indeterminate risk for advanced fibrosis, ensure fibrosis staging is sufficient and valid (not during acute hepatitis). Emphasize aggressive lifestyle change. Consider if other indications for incretin mimetic drugs (IMD) exist. Does patient have risk factors for progression of MASH to cirrhosis? Monitor fibrosis closely. Consult central care team for questions/guidance.

For patients at high risk of progression, especially if the staging is F3, consider Consult to MASLD. Pharmacologic therapy may be critical in addition to lifestyle changes¹⁷. Ensure ASCVD risk is also evaluated and risks mitigated, if possible, as the number one indicator of adverse cardiac outcomes and all-cause mortality is fibrosis stage, and outcomes worsen as fibrosis progresses.

MANAGEMENT OF MASLD: PHARMACOLOGIC INTERVENTIONS

PATIENTS WITH F4 - CIRRHOSIS (clinically or based on NIT or liver biopsy)

- Conduct HCC surveillance every 6 months with alpha fetoprotein and liver ultrasound.
- Screening for varices is recommended for patients with a platelet count of <150,000/microL or LSM >20 kPa by FibroScan, or decompensated cirrhosis (see [Liver Cirrhosis Care Guide](#)).

PHARMACOLOGIC MANAGEMENT

INCRETIN MIMETIC DRUGS (IMD):

The American Diabetes Association and the American Academy of Clinical Endocrinology²⁰ states that for patients with T2D and MASH with F2-F3 fibrosis, incretin mimetic medications are first line therapy in addition to lifestyle changes.

There is strong data²⁷⁻³⁰ for semaglutide [Glucagon Like Peptide (GLP)-1] and tirzepatide [(GLP-1/Glucose Insulinotropic peptide (GIP)] showing benefit in MASLD and MASH. Semaglutide injectable formulation (Wegovy®) currently is the only FDA approved IMD for MASH with or without diabetes.²⁶ For patients without diabetes and MASH with F3 fibrosis, strongly consider IMD therapy in addition to lifestyle changes.^{31,32} AASLD guidelines have been updated to include specific guidance regarding treatment of MASH with semaglutide.⁴²

While so far there is no strong data to show benefit of IMDs in patients with cirrhosis, there is no evidence of harm and safety has been demonstrated. Thus, it does not need to be discontinued if the patient is on the IMD for other indications. There are no studies at this time in decompensated cirrhosis, consult hepatologist.

- There is strong data²⁷⁻³⁰ for semaglutide (GLP-1) and tirzepatide (GLP-1/GIP) showing benefit in MASLD and MASH. Semaglutide injectable formulation (Wegovy®) has been FDA approved for MASLD with or without diabetes.

MANAGEMENT OF MASLD: PHARMACOLOGIC INTERVENTIONS (CONT'D)

- IMDs will be prescribed using a **pre-authorization process**. Certain criteria will allow for IMD use for patients with specific indications with just the order. Currently, all MASH indications will require the pre-authorization process and will be reviewed by the Hepatitis Central Team.
- For patients with T2D and MASLD/MASH with F2-F3 fibrosis, per the American Diabetes Association and the American Academy of Clinical Endocrinology²⁰⁻²⁶, **IMD medications are first line therapy**. Refer to the [CCHCS Diabetes Care Guide](#) for the use of these agents in patients with T2D.
- For patients without T2D and MASH with F3 fibrosis, **IMD medications are first line therapy**. The indications for treatment are as follows (NOTE: approval authorization policy may be different from treatment recommendations and is subject to change):

Table 6: Indications for Treatment for IMD Medications

Criteria	Requirement
Cirrhosis status	No active cirrhosis.
AND	
Platelet count	≥150K in the past 12 months (If patient has thrombocytopenia (TCP) or bone-marrow suppression of the megakaryocyte line that is NOT from cirrhosis, place the pre-authorization with explanation).
AND	
HCV status	HCV viral load negative for x 12 months to allow for regression of fibrosis. <i>Note</i> , commonly patients with pre-treatment assessments of >F4 will regress to <F4 after treatment.
AND	
FIB-4/ELF Score	FIB-4 >2.67 and <3.48 OR ELF score ≥9.2 and <11.3 OR FibroScan LSM ≥8 kPa and ≤15–20 kPa. If 15–20 kPa, patients with kPa 15 to 20 need corroborating evidence of cirrhosis.

- Note that some of the IMDs included in the MASH RCTs, such as tirzepatide, liraglutide and semaglutide, are non-formulary in CCHCS. More data on the formulary GLP-1 Receptor Agonists, GIP, dulaglutide, Glucagon and other IMDs, in MASH may become available in the future. Tirzepatide is completing phase 3 trials for FDA approval in MASH.
- [Semaglutide provider prescribing information \(package insert\)](#):
 - Start at 0.25 mg x 4 weeks, then 0.5 mg x 4 weeks, then 1 mg x 4 weeks, then 1.7 mg x 4 weeks, then 2.4 mg/week (maintenance).
 - The recommended maintenance dosage of WEGOVY® injection for the treatment of noncirrhotic MASH with moderate to advanced liver fibrosis in adults is 2.4 mg injected subcutaneously once weekly. If patients do not tolerate the maintenance dosage of 2.4 mg once weekly, the dosage can be decreased to 1.7 mg once weekly. Consider reescalation to 2.4 mg once weekly.
 - Blackbox warning – Contraindicated in patients with personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia, Type II.
 - Blackbox warning – In rodents: causes dose and duration-dependent thyroid C-Cell tumors. Unknown relevance in humans.
 - Not recommended in patients with gastroparesis.
 - Common side effects:
 - Lack of appetite
 - Nausea, diarrhea, constipation, vomiting, abdominal pain, esophageal reflux, and dyspepsia
 - Heart rate increase
 - Hypoglycemia in patients with diabetes, and possibly in those without diabetes
 - Headache and fatigue
 - Lean mass loss

MANAGEMENT OF MASLD: PHARMACOLOGIC INTERVENTIONS (CONT'D)

- Requirement for longer time before surgical anesthesia to avoid aspiration
- Hypotension and syncope, especially if on antihypertensive medication
- Monitor for rare but serious risks, including:
 - Acute kidney injury (from dehydration)
 - Symptomatic acute gallbladder disease
 - Pancreatitis
 - Thyroid C-cell tumors
 - Retinopathy progression
 - Suicidal ideation
 - Appendicitis
 - Hypersensitivity reactions

SEMAGLUTIDE			
MEDICATION	DOSING	ADVERSE EFFECTS/ INTERACTIONS*	COMMENTS
INCRETIN MIMETIC DRUGS (IMD)			
Semaglutide (Wegovy®) Injection solution: 0.25 mg, 0.5 mg, 1 mg, 1.7 mg, 2.4 mg \$\$\$\$\$ Note: Wegovy® is the only semaglutide formulation FDA-approved for MASH	Dosing: Initially, 0.25 mg subcutaneously once weekly x 4 weeks, then 0.5 mg weekly x 4 weeks, then 1 mg weekly x 4 weeks, then 1.7 mg weekly x 4 weeks; maintenance dose of 2.4 mg once weekly Note: If patients do not tolerate the maintenance dosage of 2.4 mg once weekly, the dosage can be decreased to 1.7 mg once weekly. Consider reescalation to 2.4 mg once weekly. Max dose: 2.4 mg/week Renal Impairment: No dosage adjustment needed Hepatic impairment: No dosage adjustment needed	Black Box Warning: Semaglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in animal studies. Relevance in humans has not been determined. <u>Adverse effects:</u> nausea, diarrhea, constipation, vomiting, abdominal pain, decreased appetite, dyspepsia, fatigue, heart rate increase • Serious but less common: pancreatitis, gastroparesis, acute kidney injury, retinopathy, cholelithiasis, AV block, angioedema, anaphylactoid reactions <u>Drug interactions:</u> • Chloroquine, sulfonyleureas, insulin, hydroxychloroquine • Semaglutide delays gastric emptying. May impact absorption of concomitantly administered oral medications • When initiating semaglutide, consider reducing the dose of concomitantly administered insulin secretagogues (e.g., sulfonyleureas) or insulin to reduce the risk of hypoglycemia	NON-FORMULARY USE CRITERIA: Not to be used solely for obesity and weight loss P&T approved indications (Wegovy®): • Atherosclerotic Cardiovascular Disease (ASCVD) with BMI ≥ 27 • Moderate-to-Advanced MASH with F2 or F3 fibrosis without cirrhosis Contraindications: Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia Syndrome type 2; severe gastroparesis; hypersensitivity to semaglutide or any of the product components Caution in the following: • Consider holding a week before elective procedure/surgery; if available follow recommendation from surgical team • Concomitant use with insulin or insulin secretagogues (e.g., sulfonyleureas); history of diabetic retinopathy, pancreatitis, hepatic impairment, gallbladder disease, cholelithiasis, renal impairment, gastroparesis • When using concomitantly with insulin, administer as separate injections. Do not mix together. Do not give injections adjacent to each other Pregnancy: Not recommended Lactation: Unknown effect, not recommended

*See prescribing information for complete description of dosing, adverse effects, and drug interactions.

The cost scale \$-\$\$\$\$\$ represents the relative cost of acquisition of medication only. When determining overall cost-effectiveness of treatment, consider frequency and complexity of medication administration (institution workload, effect on adherence).

MANAGEMENT OF MASLD: PHARMACOLOGIC INTERVENTIONS (CONT'D)

Evaluate for efficacy at approximately 6-month intervals and maximize doses if impact appears to be insufficient. AASLD notes that in current studies, the most robust benefit occurred in the initial 36 weeks. Based on current available data, a change of LSM of $\geq 30\%$ or ALT reduction of $\geq 20\%$ from baseline in 72 weeks likely represents a beneficial response⁴². If MASH is the only indication for the incretin mimetic drug (IMD) therapy, exercise caution in terminating for inefficacy, as even if the patient is progressing on IMD, it's possible the rate of progression is lower on medication. For a lack of improvement of fibrosis, consider discontinuing the medication, weighing the individual clinical data and keeping in mind dose and that some patients may require longer treatment times to benefit.

Also, when patients do not respond to medical therapy, patients may benefit from consideration of genetic causes of steatotic liver disease and may benefit from genetic sequencing lab analysis evaluation. E-consults to Hepatology are prudent. (These tests are now widely available and less expensive due to wide use in the pediatric cohorts with liver disease.)

RESMETIROM®

Restricted Use by Central Hepatitis Team. Please Order "Consult to MASLD"

In March of 2024, a novel THR- β agonist, Resmetirom®, was approved by the Food and Drug Administration (FDA) for treatment of MASH in patients with F2–F3 based on the MAESTRO-NASH trial²². The AASLD has added it to their 2024 MASLD practice guidelines^{24,25}.

Note: Resmetirom can only be prescribed by the Hepatitis Central Team. Place a "Consult to MASLD" if you think the patient may benefit from resmetirom. Try incretin mimetic medications first for 6-12 months. (See above).

- Non-formulary
- Dosage: 100 mg/d for people who weigh 100 kg or more, or 80 mg/d if weigh less than 100 kg
- Request by special order through Headquarters Pharmacy and Hepatitis Central Team

1. Criteria for Resmetirom® treatment eligibility include:

- Treated HCV at least 12 months from end of treatment (EOT) and SVR documented.
- MASH F2-F3 fibrosis without cirrhosis, regardless of BMI, DM or non-DM, AND those who have failed lifestyle and IMD medications with 6-12 month trial (or have contraindication or intolerance).
- At least 1-year post-HCV EOT F2-F3 fibrosis defined as any of the following:
 - ELF >9.8 but <11.3
 - FibroScan LSM >12 kPa and <15 kPa
 - FibroScan LSM 15-20 kPa and US with smooth liver contour and no significant splenomegaly (<14 cm), platelets ≥ 150 K, no other evidence of cirrhosis
 - Liver biopsy F2-3
 - Tie breaker NIT or resonance elastography (MRE) or Hepatology consult for patients with incongruent NITs

Do not use for:

- *FibroTest assessments (not validated in MASLD/MASH)*
- Any histologically active autoimmune liver disease by liver biopsy or suspected
- Fib 4 ≥ 3.48 (unless spuriously elevated due to acute hepatitis or advanced age etc.)
- ELF >11.3
- LSM > 20 kPa
- MRE >5
- Platelets <150 from chronic liver disease (not from autoimmune thrombocytopenia or bone marrow suppression of the megakaryocyte line)
- HIV infection (studies in progress)
- Active alcohol use
- Liver disease from other causes (such as, autoimmune hepatitis, HBV untreated or not suppressed 3 years, end of treatment HCV < 1 year, post liver transplant)

MANAGEMENT OF MASLD: PHARMACOLOGIC INTERVENTIONS (CONT'D)

- History of decompensated cirrhosis, even if regressed after HCV or other treatment
- IMD used within 6 months
- HCV EOT within 12 months
- Relative contraindication: chronic HBV. Some risk of reactivation on resmetirom – Treat HBV with antiviral medication and use resmetirom only in consultation with a tertiary care hepatologist/hepatology center

2. Dosing information - [Resmetirom prescribing information \(package insert\)](#).**3. Pretreatment considerations for Resmetirom®**

- Resmetirom is not recommended for persons with compensated or decompensated cirrhosis, concomitant uncontrolled active liver diseases (such as autoimmune hepatitis and primary biliary cholangitis), or ongoing alcohol consumption greater than 20 g/d for women or greater than 30 g/d for men.
- Thyroid function assessment is recommended before initiating resmetirom treatment. For persons with untreated hyperthyroidism or hypothyroidism, resmetirom initiation is not recommended until thyroid function is optimized.
- Resmetirom initiation is not recommended for patients with symptomatic gallstone-related conditions such as acute cholecystitis.
- If resmetirom is used concurrently with a moderate cytochrome P450 2C8 inhibitor (e.g., clopidogrel), the recommended dosage is 80 mg/d for persons who weigh 100 kg or more or 60 mg/d for persons who weigh less than 100 kg.

4. On-treatment monitoring for Resmetirom®

- Obtain hepatic function panel testing at baseline and at periodic intervals (e.g., 3, 6, and 12 months) to determine response and adverse events while on resmetirom therapy.
- Among persons with known thyroid disease, standard laboratory monitoring (e.g., TSH and free T₄).
- Resmetirom can be used concurrently with statins; however, be aware of the maximum recommended daily dosages, including atorvastatin 40 mg/d, pravastatin 40 mg/d, rosuvastatin 20 mg/d, and simvastatin 20 mg/d. Continued attention to comorbidity management including hyperlipidemia is recommended, particularly if the statin dose is modified at the outset of resmetirom therapy.

5. Determination of Efficacy and Futility for Resmetirom®

- In persons whose treatment candidacy was determined by liver stiffness measurements via ELF, vibration controlled transient elastography (VCTE) or MRE, a repeat measurement at 12 months of therapy is recommended to assess for treatment response. Meaningful change is currently approximately 20% improvement from baseline by expert opinion.
- Continuation of resmetirom treatment in persons with significant fibrosis improvement is recommended.
- Among persons with evidence of worsening liver disease at 12 months of treatment, strongly consider discontinuation of resmetirom. Document reasoning for any continuation.
- For a lack of improvement of fibrosis, consider discontinuing the medication, weighing the individual clinical data.

MANAGEMENT OF MASLD: PHARMACOLOGIC INTERVENTIONS (CONT'D)

RESMETIROM			
MEDICATION	DOSING	ADVERSE EFFECTS/ INTERACTIONS*	COMMENTS
Thyroid Hormone Receptor-beta Agonist			
Resmetirom (Rezdiffra™) Tablet: 60 mg, 80 mg, 100 mg \$\$\$\$\$	Dosing: based on actual body weight • < 100 kg: 80 mg orally once daily • ≥ 100 kg: 100 mg orally daily Max dose: 100 mg/day If using with moderate CYP2C8 inhibitors (e.g., clopidogrel): • 60 mg if < 100 kg • 80 mg if ≥ 100 kg Renal Impairment • Mild, moderate, or severe renal impairment: No dosage adjustment needed Hepatic Impairment • Mild hepatic impairment (Child-Pugh A): No dosage adjustment needed • Moderate to severe hepatic impairment (Child-Pugh B or C): Avoid use	Adverse effects: diarrhea, nausea, pruritus, vomiting, constipation, abdominal pain, dizziness, elevated AST and ALT, hepatotoxicity, cholelithiasis, acute cholecystitis, obstructive pancreatitis <u>Drug interactions:</u> atorvastatin, pravastatin, rosuvastatin, simvastatin, gemfibrozil, clopidogrel, clarithromycin, atazanavir, cobicistat, cyclosporine, rifampin, eltrombopag, erythromycin, fostemsavir, glecaprevir/pibrentasvir, sofosbuvir/velpatasvir, sofosbuvir/velpatasvir/voxilaprevir, sulfamethoxazole/trimethoprim	NON-FORMULARY USE CRITERIA: • Restricted use to Hepatitis Central Team (or tertiary care hepatologist after consult by Central Team), and • MASH F2 to F3 fibrosis without cirrhosis AND who have failed lifestyle changes AND failed a 6-to-12-month trial of incretin mimetic medication (or have a contraindication or intolerance) Pregnancy: Insufficient data, fetal risk cannot be ruled out Lactation: Present in breast milk Do not split, crush, or chew tablets

*See prescribing information for complete description of dosing, adverse effects, and drug interactions.

The cost scale \$-\$\$\$\$\$ represents the relative cost of acquisition of medication only. When determining overall cost-effectiveness of treatment, consider frequency and complexity of medication administration (institution workload, effect on adherence)

MANAGEMENT OF MASLD: PHARMACOLOGIC INTERVENTIONS (CONT'D)

PIOGLITAZONE

Pioglitazone has demonstrated histological improvement in randomized controlled trials (RCTs^{35,36}) in patients with MASLD

- For patients with T2D as a comorbidity, pioglitazone can be used, provided patients have no contraindications.
 - Pioglitazone improves insulin resistance by primarily targeting adipose tissue and improving lipid storage/redistribution and glucose utilization². However, it has side effects such as:
 - Dose-dependent weight gain (1% with pioglitazone 15mg/day up to 3-5% with 45mg/day)
 - Increased fracture risk
 - Heart failure, if used in persons with a preexisting heart disease
 - Bladder cancer
 - Peripheral edema (avoid in congestive heart failure and other fluid overload states)
 - Consider using pioglitazone together with other strategies that can lead to weight loss. It is to be avoided in patients with decompensated cirrhosis or peripheral edema.

PIOGLITAZONE			
MEDICATION	DOSING	ADVERSE EFFECTS/ INTERACTIONS	COMMENTS
Thiazolidinediones (TZDs)			
Pioglitazone (Actos®) Tablet: 15 mg, 30 mg, 45 mg \$	Dosing: 30 to 45 mg orally daily Max dose: 45 mg/day Concomitant CYP2C8 inhibitors (e.g., gemfibrozil) or HF (NYHA class I or II): Max dose 15 mg/day Renal Impairment: No dosage adjustment needed Hepatic impairment • Mild impairment with ALT ≤ 2.5X upper limit of normal (ULN): Use caution • Moderate or severe impairment: Avoid use	Black Box Warning: May cause or exacerbate heart failure (HF). Closely monitor for signs and symptoms of HF, especially after initiation or dose increase. If HF occurs, treat accordingly and consider dose reduction or discontinuation. <u>Adverse effects:</u> Weight gain, edema, HF, upper respiratory infection, headache, sinusitis, myalgia, pharyngitis, possible hepatic injury <u>Drug interactions:</u> Strong CYP2C8 inhibitors (e.g., gemfibrozil); CYP2C8 inducers (e.g., rifampin), insulin, insulin secretagogues (e.g., sulfonylureas), topiramate, chloroquine	Contraindications: Symptomatic HF; HF NYHA Class III or IV; hypersensitivity to pioglitazone or any of the product components Caution: Combination use with insulin in patients with HF and HF NYHA Class I and II; bladder cancer, hepatic disease, Monitor LFTs, avoid if ALT > 2.5 times normal before starting therapy, discontinue if ALT > 3 times normal during therapy Reduce insulin dose by 10% to 25% if hypoglycemia occurs; adjust insulin dose further based on glycemic response Reduce dose of sulfonylurea when used with TZDs to minimize hypoglycemia risk Pregnancy: Insufficient data, fetal risk cannot be ruled out Lactation: Unknown effect, not recommended

MANAGEMENT OF MASLD: PHARMACOLOGIC INTERVENTIONS (CONT'D)**VITAMIN E**

No studies have shown meaningful reduction in fibrosis. Although some research has shown histological improvement in biopsy proven MASH and lower rates of hepatic decompensation and transplant-free survival. Controversy exists in literature. Consider concerns for prostate cancer, bleeding risk and hemorrhagic stroke.

MANAGEMENT OF MASLD: MASH RELATED END STAGE LIVER DISEASE (ESLD)**Cirrhosis**

For patients with MASH or mixed MASH ESLD please follow the [Liver Cirrhosis Care Guide](#) management of compensated and decompensated cirrhosis.

MASH-Related Liver Transplant

Patients will first be identified by their primary care providers. Once the Transplant Center Hepatology has approved the patient for transplant evaluation, the central team will be supporting the process. (See steps below).

A. First assess whether a patient is a suitable candidate* for liver transplant.

***Considerations for liver transplant candidates**

- Will have access to Medi-Cal medical insurance on release.
 - Please consult current Medi-Cal eligibility rules at the time of request for transplant as patients who are not US citizens may be impacted.
- Not condemned.
 - Loma Linda University (LLU) is not offering liver transplant services to patients who are condemned.
- EPRD within 1-2 years may preclude candidacy due to inability to complete work up while here.
- Support after parole or community release, which has been shown in studies to be crucial to success.
- Able to understand risks, benefits, and alternatives of liver transplantation or has conservator.
- Substance Use Disorder (SUD) in remission (defined at minimum as no diagnostic criteria for SUD for 12 months or longer. Urine drug testing (UDS) testing is recommended).
- Cooperative and able to adhere to a treatment plan.
- Adherent with medical management.
- Stable mental health comorbidities.
- Absence of severely morbid end organ disease or poor prognosis for non-liver related 12-month survival (such as frailty not expected to be remediated by transplant, very low ejection fraction, untreatable coronary/peripheral/cerebral artery disease, terminal/uncontrolled HIV AIDS or non-liver related cancer).

MANAGEMENT OF MASLD: MASH RELATED END STAGE LIVER DISEASE (ESLD) (CONT'D)

B. If suitable, when a patient's **Model for End Stage Liver Disease (MELD) Score becomes 15**, it is the time to initiate a referral for consideration. Currently LLU Medical Center is our only liver transplant entity. For consideration for liver transplantation:

- 1) **Submit an electronic Request for Services (eRFS) for hepatology.** Put evaluation for liver transplantation in the order comments. Ensure pertinent patient records are uploaded for the appointment.
 - a. Please place **"LLU Hepatology and Liver Transplant Team"** in the special instructions of your eRFS.
- 2) **After the patient is seen and IF deemed a transplant candidate by LLU hepatology**, then submit an eRFS for liver transplant itself.
 - a. **Along with the eRFS for liver transplant, submit a Statewide Medical Authorization Review Team (SMART) referral** via the EHRS Ad Hoc Form, "SMART Requisition" Tab.
 - b. Currently, patients are evaluated on a case-by-case basis through the SMART Committee run by Utilization Management.
 - c. Proceed with the transplant center's requested work up for transplant.

The updated version of the Liver Cirrhosis Care Guide will have more information on Liver Transplant. For questions, please contact the Headquarters Transplant Coordinator at: CPHCSTransplantProgramCoordinator@cdcr.ca.gov.

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Revision History

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PATIENT EDUCATION

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): What to know

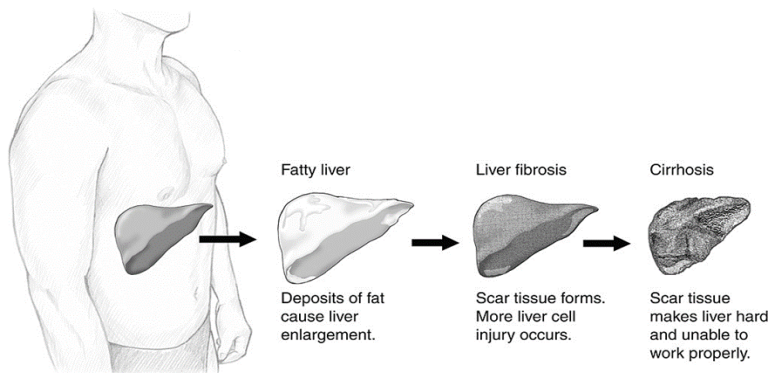
What is the liver?

- Your liver is one of the largest organs in the body.
- When the liver does not work well, you can get very sick or even die if your liver stops working.



What is MASLD?

- MASLD is the most common cause of chronic liver disease in the U.S.
- It is due to a buildup of fat in the liver (steatosis) that is not caused by drinking a lot of alcohol.
- If you are overweight, have diabetes, or high blood pressure, you are at risk for MASLD.
- A fatty liver alone does not damage the liver. However, a severe form of MASH, called Metabolic dysfunction-associated steatohepatitis can cause damage to the liver that can lead to cirrhosis (sir-o-sis).



How do you know if you have MASLD?

- At first, you may not notice any symptoms of MASLD.
- Some early symptoms are:
 - ◆ Feeling tired
 - ◆ Pain in the right upper stomach area



What to do if you have MASLD?

- The most important treatment for MASLD is to lose weight slowly along with healthy diet changes and regular exercise.
- The goal is to lose weight slowly, around 1-2 pounds per week, or 7-10% loss of body weight, over a year.
- You can help yourself manage MASLD by:
 - ◆ Increasing physical activity
 - ◆ Making healthy food choices
 - ◆ Slowly losing weight
 - ◆ Not drinking alcohol
 - ◆ Working with your health care team to keep all medical conditions under control



EDUCACIÓN DEL PACIENTE/AUTOCONTROL

Enfermedad hepática esteatótica asociada a disfunción metabólica (MASLD, por sus siglas en inglés): Lo que debe saber

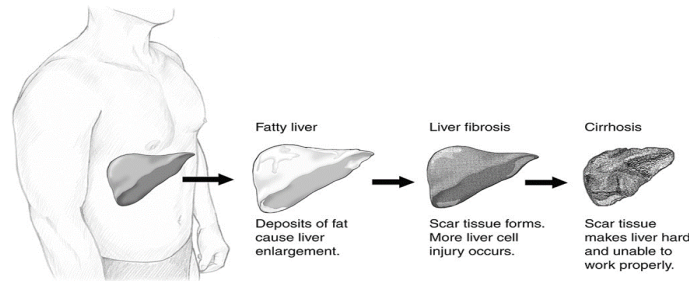
¿Qué es el hígado?

- El hígado es uno de los órganos más grandes del cuerpo.
- Cuando el hígado no funciona bien, la persona puede enfermarse gravemente o incluso morir si éste deja de funcionar.



¿Qué es la MASLD?

- La MASLD es la causa más común de enfermedad hepática crónica en EE. UU.
- Se debe a una acumulación de grasa en el hígado (esteatosis) que no es causada por beber alcohol en gran cantidad.
- Si tiene sobrepeso, diabetes o hipertensión, corre el riesgo de padecer la MASLD.
- Un hígado graso por sí solo no daña el hígado. Sin embargo, una forma grave de MASH, llamada esteatohepatitis asociada a disfunción metabólica asociada puede causar daños en el hígado que pueden derivar en cirrosis (sir-o-sis).



¿Cómo saber si padece la MASLD?

- Al principio, es posible que no note ningún síntoma de la MASLD.
- Algunos síntomas tempranos son:
 - ♦ Sensación de cansancio.
 - ♦ Dolor en la parte superior derecha del estómago.



¿Qué debe hacer si tiene MASLD?

- El tratamiento más importante para la MASLD es perder peso lentamente acompañado de cambios saludables en la dieta y hacer ejercicio con regularidad.
- El objetivo es perder peso lentamente, alrededor de 1/2 o 1 kilo por semana, o 7-10 % de pérdida de peso corporal, durante un año.
- Para controlar la MASLD puede:
 - ♦ Aumentar la actividad física
 - ♦ Tener una alimentación saludable
 - ♦ Perder peso lentamente
 - ♦ No consumir alcohol
 - ♦ Trabajar con el equipo médico para controlar todas las enfermedades

