Focused Recommendations for the Management of Metabolic Dysfunction-Associated Steatohepatitis (MASH) by Advanced Practice Providers in the United States

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Abstract: Metabolic dysfunction-associated steatohepatitis (MASH) has become the dominant cause of liver disease in the United States. With the growing burden of this disease in gastroenterology practices, the identification and treatment of those at risk of developing adverse outcomes (cirrhosis, hepatocellular carcinoma, or liver-related death) has become urgent. In recent years, the development of noninvasive tests (NITs) to identify "at-risk MASH" patients have provided cost-effective algorithms to identify these patients. Although treatment has historically been limited to lifestyle modification, recent FDA approval of resmetirom for noncirrhosis MASH with stages 2 and 3 fibrosis has provided a new opportunity in the United States to provide these patients with novel treatment options. Other new effective treatment regimens are on the horizon. Given that gastroenterology and hepatology practices in the United States heavily rely on advanced practice providers (APPs) to manage patients with MASLD, the APP Committee of the Global NASH/MASH Council has curated the essentials of day-to-day MASH management for our busy gastrohepatology providers and their APP colleagues. The goal of this document is to equip and mobilize more GI providers with the requisite competencies for the management of at-risk MASH, given the rapidly evolving MASH treatment landscape.

Key Words: metabolic dysfunction-associated steatotic liver disease, metabolic dysfunction-associated steatohepatitis, GI advanced practice provider, nurse practitioner, physician assistant

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Metabolic dysfunction-associated steatotic liver disease (MASLD) is increasingly recognized as the most common liver disease in the United States and other regions of the world.[1,2] In fact, clinical practices of hepatology and gastroenterology in the US are now inundated with patients with MASLD.[3] MASLD encompasses a spectrum ranging from hepatic steatosis on the low-risk end to the progressive subtype of metabolic dysfunction-associated steatohepatitis (MASH) which is the progressive form of MASLD.[4–10] These entities were previously known as NAFLD and NASH until the terminology was updated in 2023.[9] Moreover, in the recent years, identification of high-risk MASLD and managing their metabolic risks with lifestyle modification and medical treatment of metabolic risks has been an important part of the gastroenterology and hepatology practices. In this context, the urgency of identifying at-risk MASH has become even more critical after the approval of the first MASH-targeted therapy in the United States.[11]

In the United States, the outpatient practice of MASLD and MASH relies heavily on the care provided by advanced practice providers (APPs) in gastroenterology and hepatology practices. These APPs are driving many of the day-to-day clinical care and treatment choices for patients with MASLD. While a close working and collaborative relationship between APPs and their physician colleagues will be crucial to providing optimal care, many of the day-to-day care delivery decisions are made by the APPs with close collaboration with their physician colleagues.[12] In most GI and hepatology practices with strong APP-physician working relationships, the initial management of patients with MASLD are deferred to APPs. Although experienced GI-hepatology APPs have the experience and knowledge to provide the care, the younger APP graduates require more close collaboration with their supervising gastroenterologists. In this context, MASH has become a career-shaping liver disease for APPs for the foreseeable future. Given the continuing increase in the prevalence of MASLD/MASH and the shortage of clinicians in gastroenterology and hepatology, we must equip and mobilize the next generation of gastrohepatology APPs to be efficient to address this common liver disease.[13–15]

Although several excellent guidance statements on MASLD management are already published for

TABLE 1. Five Cardiometabolic Risk Factors (CMRs)

1. Obesity is defined as a BMI ≥ 30 kg/m^2 (25 kg/m^2 for Asia) or waist circumference $\geq 102/88$ cm for men and women (90/80 cm for Asia).
2. Fasting serum glucose of ≥ 100 mg/dL or HbA1c of $\geq 5.7\%$.
3. Blood pressure $\geq 130/85$ mm Hg or specific antihypertensive drug treatment.
4. Triglycerides ≥ 150 mg/dL or lipid-lowering treatment.
5. HDL-cholesterol < 40 mg/dL for men and < 50 mg/dL for women or lipid-lowering treatment.

gastroenterologists, the new and busy APP clinician can benefit from a condensed and efficient summary to address the growing volume of MASLD/MASH in clinical practices.[16–18] Most gastrohepatology APPs manage a broad range of gastrointestinal (GI) and liver diseases, which makes it difficult for APPs entering the gastrohepatology specialty to simultaneously develop competencies in inflammatory bowel disease, reflux disorders, generalized abdominal pain, and various liver diseases. To incorporate MASH care in these varied and busy practices and in response to the growing needs and dynamics, the Global NASH Council's APP Committee has curated the essentials of MASH management for APP clinicians.

The following section outlines the steps undertaken to provide this guidance document for the APP clinician. The process started by selecting gastrohepatology APP members of GNC with recognized experience and expertize in academic and clinical practices in the United States. This Steering Committee reviewed the literature to identify recent guidelines, guidances, and expert opinions on the management of MASLD (2018 to 2024). GI and hepatology APP members of the Steering Committee reviewed and presented select portions of the data to the group for input. These summaries were collated to distill the most pertinent aspects into a useful and easily consumable set of peer-level expert recommendations.

SUMMARY OF ASSESSMENTS AND RECOMMENDATIONS

Definition and Initial Assessment of MASLD and MASH

MASLD is defined as the presence of hepatic steatosis with at least one cardiometabolic risk (CMR) in the absence of other identifiable causes of liver disease or hepatic steatosis Table 1.[9] Given the very high prevalence of MASLD in patients with type 2 diabetes (T2D), it has been assumed that most individuals with T2D have MASLD and the next step in risk stratification of these individuals is warranted.

Once an individual is identified as having or being at risk for hepatic steatosis (eg, T2D), the next step is to exclude the role of excessive alcohol consumption. As a part of a recent international consensus, the umbrella term "steatotic liver disease" (SLD) includes MASLD, Met-ALD, and alcohol-associated liver disease (ALD). Therefore, to establish the subtypes of SLD, correct assessment of alcohol consumption is imperative as noted in Table 2.[9]

These distinctions are important given that the progression of MASH to adverse liver-related outcomes and liver failure can occur more rapidly in the presence of alcohol intake.[19,20] As such, it is important to use several methods to obtain an accurate estimate of alcohol consumption. These methods include a clinical interview and the use of the Alcohol Use Disorder Identification Test—Concise (AUDIT C) questionnaire. In clinical practice, the AUDIT-C calculator can be accessed here: AUDIT-C calculator. The AUDIT-C score ranges from 0 to 12. A score of ≥ 4 for men or ≥ 3 for women indicates significant alcohol-related risk (Table 3).[21]

Increasingly, a new blood-based biomarker phosphatidylethanol (PEth) test can be used to quantify alcohol consumption over the past 4 weeks. In this context, if patients provide any indication of alcohol use, a PEth test may be indicated. Furthermore, PEth can be used for monitoring alcohol consumption in a similar fashion to HbA1c for management of patients with T2D (Table 3).[21,22]

Key Points

- MASLD is defined by hepatic steatosis in the presence of at least 1 cardiometabolic risk factor (CMR): obesity, prediabetes/diabetes, hypertension, high triglycerides, or low HDL-cholesterol, without other causes of liver steatosis and alcohol consumption < 20 g/day for females and 30 g/day for males.
- Met-ALD is MASLD with alcohol consumption between 20 g to 50 g a day for females and 30 g to 60 g a day for males.
- ALD is alcohol consumption > 50 g a day for females and > 60 g a day for males regardless of CMRs.
- Use clinical interviewing, the AUDIT-C, and whole blood PEth testing to accurately quantify alcohol consumption.
- It is important to rule out other liver diseases when appropriate.
- Assess for the presence of medications that may contribute to hepatic steatosis.

Epidemiology and Natural History

Globally, the prevalence of MASLD is ~38%.[9,10] Roughly 10% to 25% of patients with MASLD can have MASH, and 15% to 25% of patients with MASH develop cirrhosis over 2-3 decades. While the presence of cirrhosis greatly increases the risk of developing hepatocellular carcinoma (HCC), HCC can also occur in MASLD without cirrhosis.[9,10] However, the risk of HCC in noncirrhotic MASLD is below the threshold for recommended screening

TABLE 2. Degree of Alcohol Use in Steatotic Liver Disease (SLD)

Subtype of SLD	Number of standard 10 g drinks per day for men	Number of standard 10 g drinks per day for women
MASLD (metabolic dysfunction-associated steatotic liver disease)	≤ 3	≤ 2
Met ALD (MASLD with increased alcohol use)	3-6	2-5
ALD (alcohol-associated liver disease)	> 6	> 5

TABLE 3. AUDIT-C Scores and Phosphatidyl Ethanol (PEth) Thresholds

AUDIT-C	Scores
Q1. How often did you have a drink containing alcohol in the past year?	
Answer	Points
Never	0
Monthly or less	1
2-4 times a month	2
2-3 times a week	3
4 or more times a week	4
Q2: How many drinks did you have on a typical day when you were drinking in the past year?	
Answer	Points
No, I do not drink	0
1 or 2	0
3 or 4	1
5 or 6	2
7 or 9	3
10 or more	4
Q3: How often did you have 6 or more drinks on 1 occasion in the past year?	
Answer	Points
Never	0
Less than monthly	1
Monthly	2
Weekly	3
Daily or almost daily	4
AUDIT-C interpretation	Total score
Significant alcohol consumption level that is affecting health and safety	≥4 for men ≥3 for women
PEth interpretation	**PEth level**
Light or no alcohol consumption	<20 ng/mL
Moderate alcohol consumption (ie, 2-4 drinks several days a week)	20-200 ng/mL
Heavy alcohol consumption	>200 ng/mL

for HCC by ultrasound. In this context, we recommend all cirrhotic with MASH to be screened for HCC according to established guidelines.[16–18] Noncirrhotic HCC "case-finding" should be individualized by clinicians based on the presence of other risks, such as the family history of HCC, and other HCC risks.[17]

In addition, MASLD has been found to be independently associated with an increased risk of cardiovascular disease (CVD), sarcopenia, chronic kidney disease, and extrahepatic cancer.[23–26] In fact, CVD is the number one cause of death in patients with MASLD, followed by extrahepatic cancers and then liver-related mortality.[23,25] In this context, some risk assessment for CVD may be warranted. As noted previously, MASH-related HCC is very common and is the most common indication for liver transplant among individuals who are listed for liver transplant with HCC and is the second indication for all liver transplants in the United States.[27] It is important to remember that in addition to its growing clinical burden, MASLD is associated with decreased health-related quality of life and is responsible for a substantial economic burden.[28,29]

Main Considerations for GH APPs

1. Urgency: over 1/3 of Americans have MASLD. We should focus first on patients with "at-risk MASH" (those with stages 2 or 3 fibrosis) for treatment consideration and on patients with MASH-cirrhosis (stage 4 fibrosis) for HCC screening.
2. Identification: noninvasive tests (NITs) should be used to identify and follow patients with "at-risk MASH." We recommend FIB-4 as the first line NIT followed by transient elastography or enhanced liver fibrosis (ELF) test based on availability and costs.
3. Treatment of underlying metabolic diseases: treatment of T2D, obesity, dyslipidemia, and other cardiometabolic risks (CMRs) should be undertaken with lifestyle modification with or without medications approved for these indications.
4. Treatment of MASH: in the United States, resmetirom is now FDA-approved and indicated for adults without cirrhosis with at-risk MASH (stages 2 and 3 fibrosis). This determination should be made with NITs.
5. Priorities: of the many important aspects of managing MASH and the associated metabolic diseases, we recommend developing these high-impact competencies first*:
   - Risk stratification using NITs.
   - Growth in the ability to advocate for diet, exercise, and alcohol cessation.
   - Experience with the use of resmetirom in MASH.
   - Familiarity with the use of approved medications to treat T2D and obesity such as GLP-1RA or dual agonists.

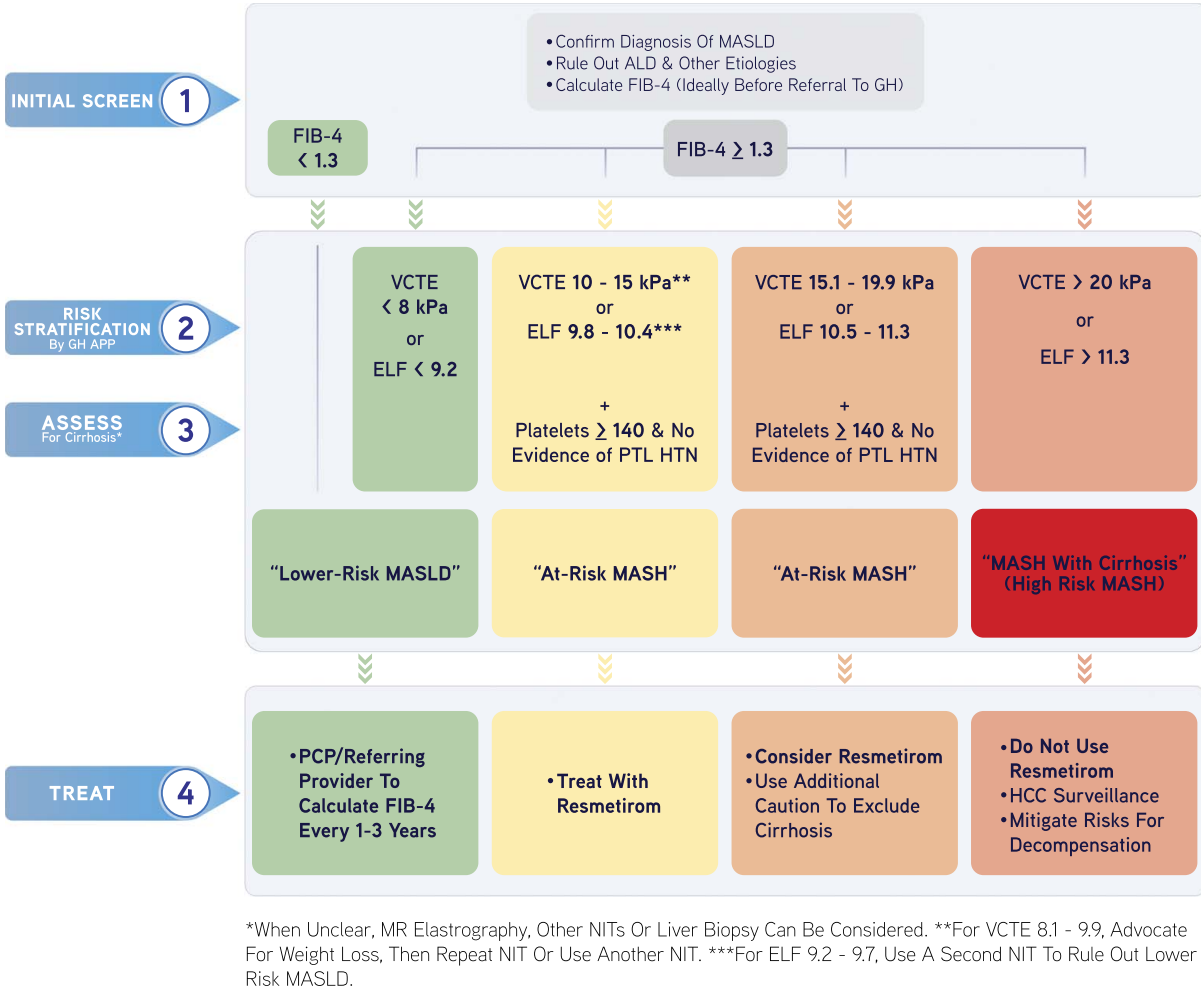
*Especially in resource-constrained settings where multidisciplinary team-based care is limited (Fig. 1).

Risk Stratification for MASLD

Individuals who are at risk for MASLD (individuals with T2D or obese with 1 CMR or with any other 2 CMR or individuals with chronically elevated aminotransferases (AST and ALT) should be considered for risk stratification using noninvasive tests (NITs). Distinguishing between "low-risk MASLD" and "at-risk MASH" allows for the concentration of limited resources on those with the greatest near-term risk for adverse outcomes. While liver biopsy has historically been the gold standard for staging fibrosis, current MASLD practice guidelines advocate for risk stratification using NITs, given that for most patients, a combination of NITs can assess risk with reasonable reliability.[16–18,30–33]

Step 1—Calculate the FIB-4 Score

Ideally, patients with MASLD should have a FIB-4 score calculated by primary care or endocrinology before referral to GI/hepatology; however, this will vary from setting to setting. Nevertheless, it is important to note that FIB-4 is a practical and easy first step that needs to be carried out in the primary care setting. FIB-4 is based on 4 simple data points: age, platelet count, AST, and ALT. Typically, these tests are available and should be performed by primary care providers in individuals at risk for MASLD, such as those with T2D and other risks as delineated in Table 1. The FIB-4 score is calculated as: (age×AST)/(platelets×square root of ALT) using FIB-4 calculators that can be found online and are often built into electronic medical record systems (click here for online FIB-4 calculator). A FIB-4 score ≥1.3 (≥2.0 for those 65 y and older) has been determined as the cutoff score as to when an individual with MASLD requires further evaluation. At a lower cutoff value of <1.3, the FIB-4 has a negative predictive value of ~95% meaning that the presence of



*When Unclear, MR Elastrography, Other NITs Or Liver Biopsy Can Be Considered. **For VCTE 8.1 - 9.9, Advocate For Weight Loss, Then Repeat NIT Or Use Another NIT. ***For ELF 9.2 - 9.7, Use A Second NIT To Rule Out Lower Risk MASLD.

FIGURE 1. Algorithm for using noninvasive tests (NITs) to risk stratify and distinguish between and treat "lower-risk MASLD" (consistent with stage 1 fibrosis or less), "at-risk MASH" (consistent with stages 2 or 3 fibrosis), and MASH with cirrhosis. Step 1: the first-line NIT, FIB-4, should be calculated mostly in primary care/endocrinology but occasionally in GI/hepatology care settings. MASLD patients with a FIB-4 score ≥1.3 should be further assessed by GH APPs. The FIB-4 cutoff for ≥65 years is ≥2.0. Step 2: transient elastography/VCTE and ELF are the recommended second-line NITs. Patients with FIB-4 <1.3, OR VCTE <8 kPa or ELF <9.2 should be considered to have "lower-risk MASLD" and can follow up with PCP for optimization of cardiometabolic risk factors (CMRs) and repeat FIB-4 every 1 to 3 years. VCTE liver stiffness measurement (LSM) between 10 and 20 kPa or ELF between 9.8 and 11.3 is indicative of "at-risk MASH" (stages 2 or 3 fibrosis). Step 3: use additional caution to assess for cirrhosis if LSM >15 kPa or ELF >10.5 (assessing for the presence of thrombocytopenia, etc.). For ELF of 9.2 to 9.7, consider using a second NIT to confirm the diagnosis of at-risk MASH. For LSM >20 kPa or ELF >11.3, cirrhosis is likely, and management should be focused accordingly. Step 4: resmetirom is recommended for the treatment of at-risk MASH, where NITs are consistent with stage 2 or stage 3 fibrosis without cirrhosis. Resmetirom should be avoided in patients with lower-risk MASLD or in patients with cirrhosis.

advanced fibrosis is very low.[33] Those with low FIB-4 can be monitored by primary care providers with a repeat test every 1 to 3 years based on the presence of CMR. In contrast, FIB-4 score >2.67 strongly suggests the presence of advanced fibrosis. Nevertheless, most patients referred for further evaluation will have a FIB-4 ≥1.3. These patients require additional assessment by gastrohepatology APPs to assess further clinical decisions and interventions.[31] These NITs are considered second-line NITs and are discussed in step 2. Moving forward, it will be helpful for GH APPs to teach their referring clinicians to calculate FIB-4 before a referral to GH is made.

Step 2—Screen for At-Risk MASH Using Elastography or ELF

In the United States, liver stiffness measurement (LSM) by VCTE (vibration-controlled transient elastography) is the most common second-line NIT for assessing for at-risk MASH. There are several manufacturers, but FibroScan and Velacur are currently the most commonly used. These tests are noninvasive bedside procedures that can be performed in the clinic or ordered from radiology. The cutoffs for distinguishing between "lower-risk MASLD," (suggestive of stage 1 fibrosis or less) or "at-risk MASH" (suggestive of stages 2 or 3 fibrosis) and MASH with

cirrhosis (suggestive of stage 4 fibrosis) are provided in the key points below.[30–34]

It is important to note that patients must fast for 2 to 3 hours before VCTE. In addition, LSM scores can be elevated if there is cholestasis, recent alcohol use, liver congestion, or acute hepatic inflammation (AST or ALT > 100).[34]

The enhanced liver fibrosis test (ELF test) can be an alternative to VCTE as a second-line NIT and can be used to risk-stratify MASLD patients. ELF is a proprietary biomarker panel, based on the assessment of 3 products involved in fibrosis progression and regression: hyaluronic acid (HA), type III procollagen peptide (PIIINP), and tissue inhibitor of matrix metalloproteinase 1 (TIMP-1). ELF cutoffs are provided below. Coverage of ELF testing by commercial payers is generally reasonable, but discussing the potential costs with patients is advised.[34,35]

Recently, these NIT scores at baseline and changes over time have been associated with progression to cirrhosis and adverse liver-related outcomes.[36–40] Where available, LSM by MR elastography has also been used with greater sensitivity and specificity than VCTE but with limited access and greater costs.[31] The details on sensitivity, specificity, positive, and negative predictive values of these tests, as well of the other available NITs [FAST (FibroScan and AST), MAST (MRI and AST), and MEFIB (MRE and FIB-4), and others] are covered extensively in the recent review of NITs.[31]

Step 3—Assess for Cirrhosis

Regardless of the results of these NITs, ruling out cirrhosis and portal hypertension is critical. This is because cirrhosis requires additional assessment for HCC, risk of variceal bleeding, and liver failure. In addition, the presence of cirrhosis will negate the use of resmetirom in MASH. This assessment should include a review of platelet counts, INR, albumin levels, evidence of ascites on imaging, gastroesophageal varices, history of hepatic encephalopathy, firm liver, splenomegaly, prominent abdominal veins, gynecomastia, spider angiomata, and palmar erythema. Using NITs, VCTE ≥20 kPa, ELF ≥11.3, and MRE ≥5 kPa are highly suggestive of cirrhosis, which not only precludes the use of resmetirom but also requires a number of other preventative tests.[31]

In this context, these NIT cutoffs can also be used for triaging between patients to send back to primary care (lower-risk MASLD) and patients to refer to tertiary care hepatology with liver transplantation evaluation (evidence of advanced cirrhosis, HCC, or hepatic decompensation).

Although the NASH fibrosure blood test is widely available, it is not recommended or included in risk stratification algorithms by any of the recent MASLD guidance documents.[41]

Key Points

Use noninvasive tests (NITs) to risk stratify and distinguish between "lower-risk MASLD" (consistent with stage 1 fibrosis or less), "at-risk MASH" (consistent with stages 2 or 3 fibrosis), and MASH with cirrhosis.

Step 1 – FIB-4:

- The first-line NIT, FIB-4, should be calculated mostly in primary care/endocrinology but occasionally this step may occur in GI/hepatology care settings.
- MASLD patients with a FIB-4 score ≥1.3 should be further evaluated for at-risk MASH or cirrhosis, using VCTE. If unavailable, a serum ELF test is an alternative. In some center, MRE is more accessible and can be used as a second line test.

Step 2 – VCTE or ELF:

- Transient elastography/VCTE is the most widely available form of elastography, which measures liver stiffness.
  - Stiffness between 10 and 20 kPa is indicative of at-risk MASH (stages 2 or 3 fibrosis).
  - Although stiffness >20 kPa can be predictive of cirrhosis, consider assessment for the possibility of cirrhosis, if stiffness is >15 kPa (assessing for the presence of thrombocytopenia, clinical evidence of cirrhosis or portal hypertension, etc.).
- An ELF score between 9.8 and 10.4 is indicative of at-risk MASH.
  - For ELF of 9.2 to 9.7, the diagnosis of at-risk MASH is highly liekly but additional testing and assessment may be needed.
  - For ELF >11.3, cirrhosis is likely, and management should be focused accordingly.
  - For ELF of 10.5 to 11.3, consider using a second NIT to rule out stage 4 fibrosis (cirrhosis) with some certainty.

Step 3 – other tests and screening for cirrhosis:

- MRE liver stiffness scores of 3.0 to 4.3 kPa are indicative of at-risk MASH.
  - For MRE scores of 4.4 to 4.9, additional tests should be done to rule out cirrhosis.
- A liver biopsy can be considered when NITs are inconclusive or discordant, or if any diagnostic uncertainty remains. Example of this uncertainty would be presence of high titer auto-antibodies highly suggestive of superimposed autoimmune liver disease.

NITs can be used for triage.

- Patients with "low-risk MASLD" (FIB-4 <1.3 or VCTE <8 kPa or ELF <9.2) can follow up with primary care as the likelihood for advanced fibrosis is negligible. Nevertheless, these patients should undergo an assessment with NIT calculation by primary care every 1 to 3 years with the duration based on the presence of CMR. The more components of CMR (especially T2D), the shorter the interval for retesting.
- Patients with "at-risk MASH" should be managed by gastrohepatology APPs in collaboration with their gastroenterology colleagues.
- For patients with MASH with advanced cirrhosis (VCTE ≥20 kPa or ELF >11.3 or MRE ≥5 kPa or evidence of portal hypertension), careful management of cirrhosis complications is recommended.

Management of MASLD

Comprehensive treatment goals for the patient with MASLD can be conceptually separated into 3 related branches:

1. Lifestyle changes that address both overall cardiometabolic risks (CMR) and liver-related risks.
2. CMR-focused drug management.
3. MASH-focused drug treatment.

It is important to note that management of CMR with lifestyle or medication should be considered at any point. In contrast, MASH-targeted therapy should be always considered for those who qualify for treatment without delay. This urgency is important because some patients with MASH can

progress quickly and are at risk for HCC even without advanced stages of hepatic fibrosis.

Lifestyle Management

The first line treatment for all patients with MASLD and MASH is lifestyle management, including diet and exercise. Body weight loss of 3% to 5% is associated with improvement in hepatic steatosis, 5% to 7% with improvement in steatohepatitis, and ≥10% body weight loss with improvement in hepatic fibrosis.[42] A caloric reduction of between 500 and 1000 kcal a day using a Mediterranean-based type of diet should be encouraged as well as the avoidance of ultra-processed foods, sweetened beverages and regular alcohol consumption. Notably, the Mediterranean diet has consistently shown hepatic and cardiovascular benefits, even in the absence of weight loss.[43] The Mediterranean diet is adaptable and can be considered more of an eating pattern than a strict diet. It emphasizes the consumption of whole, minimally processed foods, such as fruits, vegetables, whole grains, legumes, nuts, olive oil, and lean proteins like fish and poultry. It encourages moderation in dairy, while limiting red meat and processed foods. This flexible approach focuses on long-term, sustainable eating habits rather than rigid rules or calorie restrictions, making it more of a lifestyle than a traditional "diet" which can make it more approachable for patients.[44]

In contrast to dietary changes, the impact of exercise and activity on weight loss is mixed. Nevertheless, improving cardiovascular fitness reduces risks for cardiovascular diseases, and it also improves peripheral muscle tone, which is associated with improved insulin sensitivity and decreased risks for sarcopenia and frailty.[17,44] Patients with MASLD should increase their physical activity to achieve at least 150 minutes a week of moderate activity (movement where one can carry on a conversation) or 75 minutes of vigorous activity (movement where there is difficulty in having a conversation). In addition, smoking cessation and minimizing alcohol intake is recommended (Fig. 2).[41,45,46]

CMR-Focused Management

Identifying cardiometabolic comorbidities allows for a tailored approach to treatment, focusing on reducing the overall cardiometabolic risk burden. Managing cardiometabolic comorbidities in MASLD involves a multidisciplinary approach aimed at improving metabolic health and preventing adverse outcomes. Ideally, colleagues in primary care, endocrinology, cardiology, weight-loss medicine, dieticians, and exercise therapists/coaches should be involved in an integrated team approach potentially in a metabolic clinic. In this context, weight loss through lifestyle modification should be emphasized as the cornerstone of treating cardiometabolic stress. In addition, some pharmacotherapeutic agents help with weight loss and have the additional benefit of reducing major adverse cardiovascular events (Table 4). In addition to lifestyle and medications, endoscopic or metabolic surgical procedures have also been shown to lead to significant weight loss. These options should be considered for patients struggling with obesity and obesity-associated complications. Nevertheless, metabolic surgeries and endoscopic procedures are approved for managing obesity and T2D but not specifically approved for the treatment of MASLD/MASH.[16–18]

In addition to the management of obesity, pharmaceutical interventions for other cardiometabolic risks include statins, antihypertensives, and antidiabetic medications. It is important to note that currently only Semaglutide has shown efficacy in phase 3 clinical trials.

Antidiabetic Medications in MASLD

Approved antidiabetic medications with potential efficacy in MASH include GLP-1 receptor agonists, dual agonists, or pioglitazone (Table 4). In addition, there are some recent data that SGLT 2 inhibitors may also be helpful. These drugs are approved for the treatment of T2D, but none are yet approved specifically for MASH. Nevertheless, the preliminary results of the phase 3 ESSENCE trial of semaglutide were released as a late-breaker at the 2024 AASLD Meeting.[47] In a double-blind fashion, 1200 participants with biopsy-proven steatohepatitis were randomized to placebo or semaglutide, titrated up to 2.4 mg/week. In the first 800 participants to reach the week 72 liver biopsy, 37.0% of those on semaglutide achieved improvement in hepatic fibrosis with no worsening of steatohepatitis, compared with 22.5% on placebo. In addition, 62.9% of those on semaglutide achieved resolution of steatohepatitis with no worsening of fibrosis, compared with 34.1% of those on placebo. Importantly, although semaglutide is currently not FDA-approved as a MASH-targeted treatment, it is expectd that the drug will undergo regulatory assessment in 2025 and may become available in 2026. Nevertheless, these drugs are associated with significant metabolic benefits . In this context, GLP-1RAs should be considered as one of the preferred drugs to manage T2D among patients with MASH.

Pioglitazone, a thiazolidinedione, acts as an agonist of peroxisome proliferator-activated receptor gamma (PPARγ). In relatively small-sized clinical trials, pioglitazone therapy has shown potential benefit in patients with MASH. Therefore, pioglitazone can be used as another preferred antidiabetic medication for patients with MASLD and MASH. (Table 4).[48]

In contrast to GLP-1 RAs and pioglitazone, other antidiabetic drugs (sulfonylurea, metformin, insulin, etc.) have not shown to have any potential liver benefits and are not preferred drugs for the treatment of T2D in MASH.[16–18] Although statins are not effective as MASH-targeted treatment, they are the drug of choice to manage dyslipidemia in patients with MASLD. Finally, ursodeoxycholic acid (UDCA) has not been associated with significant MASH improvement and should not be used.

Weight Loss Using GLP-1 and Antiobesity Medications

Similar to T2D, there is a very high prevalence of obesity among patients with MASH. Given that sustained weight loss through lifestyle modification alone eludes more than 90% of MASLD patients, antiobesity medications (AOMs) have become a part of the clinical management of obesity.[42,49–51] In this context, the pharmacotherapy agents that are suggested for use among adults who are overweight (body mass index ≥25 kg/m^2) or obese (body mass index ≥30 kg/m^2, or ≥27 kg/m^2) with weight-related complications, who have an inadequate response to lifestyle interventions include GLP-1 RAs and dual agonists.

Currently, 2 GLP-1 RAs (semaglutide and high-dose liraglutide) have been approved for the treatment of obesity.[49] In this context, once weekly semaglutide has been shown to have good efficacy for the treatment of obesity and confers additional cardiometabolic benefits.[16–18,47,49–52]

Diet Considerations

1. Increase water intake.
2. Reduce portion sizes and eat mindfully.
3. Minimize processed and red meat.
4. Limit ultra-processed foods (UPFs) and sugary drinks.
5. Reduce fried foods and saturated fats; opt for healthy fats.
6. Limit alcohol consumption.
7. Prioritize fiber and lean protein; consider the Mediterranean Diet.

Activity & Lifestyle Recommendations

1. Decrease sedentary time and increase daily movement.
2. Aim for 4,000–5,000 steps daily; gradually increase.
3. Engage in aerobic exercise 30-60 minutes, 3-5 times per week.
4. Incorporate resistance training 20-30 minutes, 2-3 times per week.
5. Commit to smoking cessation.
6. Prioritize restful sleep.
7. Track progress with journals or apps for accountability.

Other Recommendations

1. Meal plan to avoid unhealthy choices.
2. Shop the perimeter of the grocery store for fresh options.
3. Consult with a registered dietitian for personalized guidance.
4. Join group weight loss or exercise programs for support.
5. Set realistic and attainable goals for exercise.
6. Focus on small, consistent changes over time.
7. Make exercise enjoyable to enhance adherence.

FIGURE 2. Considerations for lifestyle modifications. Optimizing weight and CMRs are essential across the entire spectrum of steatotic liver disease (SLD). We provide several high-impact suggestions that can be tailored to the patient as part of a comprehensive treatment plan.

Although semaglutide can be used to treat obesity, the most recent phase 3 clinical trial also suggested efficacy for MASH. Once FDA approved, this drug may expand treatment choices for patients with MASH.

In addition to GLP-1 RAs, tirzepatide is a dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 RA and has been associated with a body weight reduction of greater than 20% in people with obesity as well as improved

TABLE 4. The Potential Impact of Diabetes Medications on MASH

Medication	Steatosis	Steatohepatitis	Fibrosis	Considerations	CV risk
Metformin	No change	No change	Neutral	Avoid in decompensated cirrhosis	Improves
Pioglitazone	Improved	Improved	Possibly	Potential weight gain, bone thinning, and worsened heart failure	Improves
Semaglutide	Improved	Improved	Improved	Improves weight. Risk of weight-loss associated cholecystitis	Improves
Tirzepatide	Improved	Improved	Possibly	Improves weight. Risk of weight-loss associated cholecystitis	Possibly
SGLT2 inhibitors	Improved	Unknown	Possibly	Improves renal outcomes. Risk of GU infections and bone thinning	Improves

cardiometabolic measures. Again, while not approved for the treatment of MASH, tirzepatide has shown to have potential benefit for MASH patients in phase 2 clinical trials.[53] Similar to GLP-1 RAs, currently, tirzepatide can be used for its approved metabolic indication but not specifically for the treatment of MASH. Although GLP1RA have shown to provide cardio-metabolic-kidney benefits, long term incidence and clinical implications of muscle loss (sarcopenia) requires additional data.[54–55]

Bariatric Surgery and Endobariatric Procedures

In addition, bariatric surgery can be considered for people living with noncirrhotic MASLD who meet the criteria for weight-loss surgery. Patient selection for bariatric surgery in those with MASLD should be done in collaboration with surgeons, hepatologists, social and mental health providers, and dieticians, and surgery should be performed in centers with sufficient volume.[49,56] The 2 main types of bariatric surgery most common for those with MASLD are sleeve gastrectomy and Roux-en-Y Gastric Bypass (RYGB). The benefits, burdens, risks, and indications for these surgeries are described elsewhere.[57]

Endoscopic bariatric procedures (intragastric balloons, placement of gastric bands or staples, and the insertion of endoscopic sleeves) can also use a minimally invasive approach to reduce food intake, restrict the absorption of nutrients, or both to facilitate weight loss. However, endoscopic procedures have a less clear role in the treatment of MASLD currently, but evidence is still emerging.[58]

Therefore, currently, both the RYGB and SG are the surgical options that are proven to be the most beneficial to those with MASLD and are associated with sustained and significant weight loss.[59,60] Regardless of the procedure performed, close follow up and management is necessary to help maintain weight loss and to follow for potential complications of surgery such as short bowel syndrome, dumping, hypoglycemia, vitamin and mineral deficiencies as well as hernias, intussusception, kidney stones, and renal dysfunction.[61,62]

Key Points:

- Weight loss, diet and exercise, and lifestyle modification are helpful for improving cardiometabolic risks and potentially for improving MASH and liver-related outcomes, in varying degrees. However, acheiving sustained weight loss with life style modification is relatively rare.
- For patients with type 2 diabetes,
  - GLP-1 receptor and dual agonists should be considered as a preferred treatment for T2D and/or obesity for individuals with MASLD.
  - Pioglitazone can be considered for treatment of T2D. Given improvements in steatohepatitis associated with pioglitazone treatment, this drug could be one of the preferred anti-diabetic agents for MASH.
- For obese patients who meet indications, AOM (anti-obesity medications), especially semaglutide and tirzepatide, and/or bariatric weight-loss procedures should be considered in patients with at-risk MASH. Further caution is required for the use of bariatric surgery/procedures in patients with cirrhosis due to MASH.
- Guidance on MASH-targeted therapy with vitamin E is mixed and the most recent guidelines recommend against its use.[17]
- UDCA or omega-3 fatty acids should not be considered for MASH-targeted therapy.
- Statins can be used safely in individuals with MASLD who meet the criteria for dyslipidemia treatment, across the spectrum from Lower-risk MASLD to compensated cirrhosis. Statin use in patients with decompensated cirrhosis is not well-studied and should be avoided or approached with caution.

Treatment of MASH With Resmetirom

While weight loss and lifestyle improvements remain important for the management of MASLD, the approval of a medication specifically indicated for at-risk MASH (stages 2 or 3 fibrosis) represents a significant advance in treatment. In March 2024, the FDA approved resmetirom, a liver-targeted thyroid hormone receptor-beta agonist (THR-β), for the treatment of patients with MASH with hepatic fibrosis consistent with stages 2 or 3, without cirrhosis. In the phase III MAESTRO-NASH trial, 888 adults with stages 2 or 3 fibrosis on liver biopsy were randomized to resmetirom 80 or 100 mg daily or placebo. At 52 weeks, compared with placebo, almost twice as many subjects on the 100 mg dose had improvement in fibrosis (25.9% improvement on 100 mg vs. 14.2% improvement on placebo).[11] As detailed in the risk stratification section above, once a patient is determined to have at-risk MASH (consistent with stages 2 or 3 fibrosis) without cirrhosis, treatment with resmetirom can be considered.[11] In addition to the clinical efficacy, resmetirom has shown to improve some aspects of health-related quality of life (HRQOL).[63,64] Regarding the use of resmetirom, several important points must be highlighted.

1. Indication: GH APPs must make sure that the patient with MASLD has disease consistent with fibrosis stages 2 or 3, given that resmetirom is not indicated for those with no or minimal fibrosis nor for those with cirrhosis. Given that liver biopsy is not indicated prior to initiation of treatment, NITs are used to identify patients who are candidates for treatment. The recent guidance documents suggest VCTE of 8 and 10 kPa as the NIT threshold to initiate treatment.[16–18,65] Given that VCTE of 10 kPa or higher indicates an increased risk of adverse outcomes and VCTE of 8 kPa may result in overtreating patients with MASH, we believe that VCTE of 10 kPa-20 kPa is more consistent with patients with at-risk MASH should be the threshold of choice. Nevertheless, it is imperative

that there is no indication that cirrhosis or portal hypertension is present. If one chooses the lower cutoff of 8 kPa, it is prudent to use a second NIT to assure patients have stage F2 or F3, rather than F0-F1 MASH.
2. Drug-drug interactions: the concomitant use of resmetirom with strong CYP2C8 inhibitors such as gemfibrozil or OATP1B1 and OATP1B3 substrates such as cyclosporine is not recommended. The use of resmetirom with moderate CYP2C8 inhibitors such as clopidogrel requires a dose reduction of resmetirom and close monitoring.
3. Statins: resmetirom may increase plasma concentrations of some statins so rosuvastatin or simvastatin should be limited to 20 mg per day, and pravastatin and atorvastatin should be limited to 40 mg per day.
4. Adverse effects: the most common adverse effects occurring in more than 5% of patients in the phase III MAESTRO-NASH trial were diarrhea, nausea, pruritus, vomiting, constipation, abdominal pain, or dizziness.

Resmetirom was approved by the FDA under accelerated approval based on improvements on liver biopsy after 52 weeks. Longer-term follow-up out to 4.5 years is ongoing. As data accrues, safety monitoring of resmetirom in the real world is essential. While no significant safety signal has been reported and none is expected, due diligence is warranted in the years immediately following FDA approval. As noted previously, resmetirom is not currently indicated for use in patients with cirrhosis. The phase 3 MAESTRO-NASH-OUTCOMES trial is enrolling 700 adults with compensated cirrhosis due to MASH to assess safety and efficacy in this population, so treatment options for patients with MASH and cirrhosis may evolve.

For on-treatment monitoring and stopping criteria, routine DILI (drug-induced liver injury) parameters and tolerability should be assessed at 3 months on resmetirom. Mild liver enzyme increases at weeks 4 and 8 are occasionally noted. As long as significant liver enzyme elevation is not noted, dose adjustment or discontinuation is not recommended, given that improvement in liver enzymes typically occurs by week 12. Treatment monitoring should include liver enzymes (safety check) and VCTE (early response) at 6 months on resmetirom. At 12 months, continuation of resmetirom should be considered if patients have VCTE $>30\%$ drop in liver stiffness measurement (LSM). If there is no change in NITs, stability of liver disease may still be desirable, and continuation of resmetirom should be considered if there are no side effect concerns or coverage issues. In contrast, if there is significant and persistent worsening of 2 concordant NITs at 12 months, treatment futility is suspected and discontinuation should be considered.[31,66,67]

Key Points

- Resmetirom should be considered for patients with at-risk MASH and VCTE 10 to 15 kPa. Exclude cirrhosis with clinical evidence, platelets count, and liver stiffness imaging.
- Resmetirom can be considered for patients with at-risk MASH and VCTE 15.1 to 19.9 kPa or ELF 10.5 to 11.3. Further caution to exclude cirrhosis is recommended with these higher NIT scores. Most experts recommend 2 NITs to exclude cirrhosis for these patients.
- Do not prescribe resmetirom in patients with low-risk MASLD (NITs consistent with $\leq$stage 1 fibrosis).
- Do not prescribe resmetirom in patients with cirrhosis or any evidence of portal hypertension.
- Follow patients on resmetirom at 3-months, 6-months, and 12-months tests, including liver enzymes and NITs (VCTE). Other tests, such as TSH and lipid panel should be performed as indicated.
- At 12 months, resmetirom should be continued if patients have a VCTE $>30\%$ drop in liver stiffness measurement (LSM).
- At 12 months, if there is a significant worsening of NITs on resmetirom, which is confirmed by 2 tests, treatment discontinuation should be considered.
- At 12 months, if there stability of improvement less than 30%, is observed, continuation of resmetirom may be considered on a case by case basis.

Other Management Issues for Patients With MASH

Screening and surveillance for HCC is recommended for those with cirrhosis as recommended by HCC guidelines, which recommend liver imaging every 6 months with or without AFP.[68] Although noncirrhotics with MASH are at higher risk for HCC, current guidelines do not support routine surveillance.[17] In this context, certain risk factors (eg, T2DM, obesity, family history of HCC, age, alcohol intake, smoking status, and fibrosis markers) may increase the risk of HCC. Furthermore, clinical judgment and individual case findings should be considered when multiple risks are present.

TABLE 5. Phases 2 and 3 Investigational Agents for MASH

Class	Agent	Notes	Current trial phase
FASN inhibitor	Denifanstat		2
FGF21 agonists	Efruxifermin		3
	Pegozafermin		3
GLP1R agonists	Semaglutide	GLP-1 agonist	3
	Tirzepatide	Dual GLP1 and GIP agonist	2
	Survodutide	Dual GLP-1 and GCG agonist	3
	Pemvidutide	Dual GLP-1 and GCG agonist	2
PPAR agonist	Lanifibranor	Pan PPAR agonist	3
THR-β agonists	Resmetirom	Outcomes study for F2/F3 and compensated cirrhosis ongoing	3
	VK2809		3

National Library of Medicine. Accessed September 19, 2024. www.clinicaltrials.gov.
FASN indicates fatty acid synthase; FGF-21, fibroblast growth factor-21; GCG, glucagon receptor agonist; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide; PPAR, peroxisome proliferator-activated receptor.

Extrahepatic cancer screening should occur in line with current guidelines, and one's individual risk profile should also be considered given the higher incidence of extrahepatic cancer in those with MASLD. Vaccination against hepatitis A and hepatitis B is also recommended when feasible and applicable.[16–18]

CONCLUSIONS

For the GH APPs who work closely with their gastroenterology/hepatology counterparts, it is encouraging to finally have another option to supplement lifestyle modification and drugs for T2D and obesity to treat patients with MASH. In this context, the recent approval of resmetirom for noncirrhotic MASH with stages 2 and 3 fibrosis by NITs (at-risk MASH) is a major advancement.

It is important to remember that ~21 million Americans may have MASH (LSM >8.6 kPa), with 4.5 to 9 million having advanced fibrosis, and 0.6 million having cirrhosis.[10,68] Moreover, only 1.5 million of those with MASH have been diagnosed.[69] Furthermore, modeling studies suggest that the prevalence of MASH is anticipated to substantially increase by 2030.[70] Given these daunting statistics, the 3 messages should be emphasized to gastrohepatology APPs and other clinicians in gastroenterology, hepatology, primary care, endocrinology, and metabolic disease management:

1. Urgency: it is critical to get ahead of the impending wave of morbidity and mortality due to MASH.
2. Risk stratification: we must prioritize those with at-risk MASH (stages 2 or 3 fibrosis) and identify them using algorithms with NITs (noninvasive tests).
3. Treatment: we must become proficient in managing cardiometabolic risks with lifestyle modification, CMR-focused medications, and use resmetirom for MASH-focused intervention for patients with MASH with F2 and F3 without cirrhosis.

Two final points are also worth mentioning. First, with the approval of resmetirom, there is renewed interest in new MASH therapeutics, so the gastrohepatology APP should be aware that phases 2 and 3 trials are ongoing and that new options may become approved in the near future (Table 5). In fact, the recent data released about the phase 3 clinical trial of semaglutide provide even more enthusiasm for additional regimens for these patients. As with the heydays of hepatitis C treatment, regularly updated "living" guidance documents and expert recommendations for MASH management may become necessary.

Secondly, as care systems become more integrated, and as autonomous clinical management by APPs becomes more commonplace, some settings may benefit from the development of integrated multidisciplinary "metabolic clinics" led and staffed by APPs with competencies in hepatology, endocrinology, weight-management, cardio-kidney metabolic syndrome, and even mental health, which likely underlies most of our stunted efforts at lifestyle change. Integrated health systems with comprehensive EMRs are sitting on a wealth of data, and clearly, patients with significant risk have not been connected to care.[3,71] Establishing multidisciplinary APP run metabolic clinics could be an effective starting point for tackling this challenge.

There is plenty of work to do. Our hope is that this focused set of recommendations for APPs by APPs will equip us to address the great challenge ahead.

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