ROPER ST. FRANCIS HEALTHCARE

Metabolic dysfunction associated steatotic liver disease

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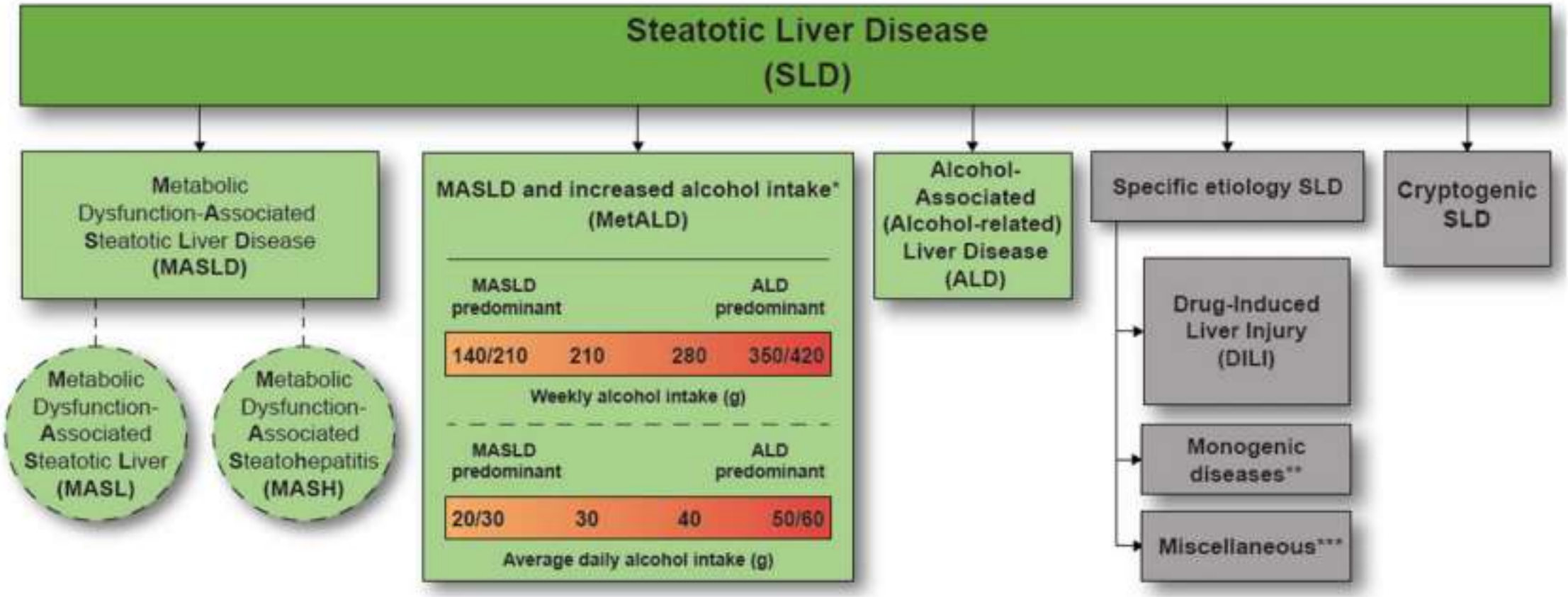
- The overarching term of steatotic liver disease (SLD) was chosen to classify individuals with hepatic steatosis due to various etiologies.
- The Delphi panel recommended the term steatosis in lieu of the term fatty because the latter was considered to be stigmatizing.
- The overarching term and its derivatives were based on “steatotic liver disease.”
- This overarching term encompasses MASLD and a new overlap category that includes individuals with cardiometabolic risk factors and a spectrum of alcohol consumption (metabolic dysfunction and alcohol-associated steatotic liver disease, MetALD), while continuing to recognize other causes of hepatic steatosis including alcohol-associated liver disease (ALD) with or without metabolic risk factors, drug-induced liver injury, monogenic diseases, and other etiologies.



Kanwal, Fasiha1,2,3; Neuschwander-Tetri, Brent A.4; Loomba, Rohit5; Rinella, Mary E.6. Metabolic dysfunction–associated steatotic liver disease: Update and impact of new nomenclature on the American Association for the Study of Liver Diseases practice guidance on nonalcoholic fatty liver disease. Hepatology 79(5):p 1212-1219, May 2024.

Criteria to define MASLD

- In the presence of hepatic steatosis, the finding of any cardiometabolic risk factor would confer a diagnosis of MASLD if there are no other causes of hepatic steatosis.
- In the case of alcohol, this is termed MetALD or ALD, depending on the extent of alcohol intake

Adult Criteria

At least 1 out of 5:

- ☐ BMI ≥ 25 kg/m² [23 Asia] **OR** WC > 94 cm (M) 80 cm (F) **OR** ethnicity adjusted equivalent
- ☐ Fasting serum glucose ≥ 5.6 mmol/L [100 mg/dL] **OR** 2-hour post-load glucose levels ≥ 7.8 mmol/L [≥140 mg/dL] **OR** HbA1c ≥ 5.7% [39 mmol/L] **OR** type 2 diabetes **OR** treatment for type 2 diabetes
- ☐ Blood pressure ≥ 130/85 mmHg **OR** specific antihypertensive drug treatment
- ☐ Plasma triglycerides ≥ 1.70 mmol/L [150 mg/dL] **OR** lipid lowering treatment
- ☐ Plasma HDL-cholesterol ≤ 1.0 mmol/L [40 mg/dL] (M) and ≤ 1.3 mmol/L [50 mg/dL] (F) **OR** lipid lowering treatment

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Clinical Suspicion for Steatotic Liver Disease

- Patients with steatosis noted on imaging or for whom there is a clinical suspicion of MASLD, such as those with metabolic risk factors or unexplained elevation in liver chemistries, should undergo further evaluation.

What next?

- In low-prevalence settings, such as in the primary care setting, the emphasis is on excluding advanced fibrosis using a test with a high negative predictive value.

FIB-4 calculation

- When the FIB-4 is <1.3, the patients can be followed in the primary care setting and reassessed periodically.
- Patients without prediabetes/T2DM and < 2 metabolic risk factors can be reassessed every 2–3 years.
- Patients with prediabetes/T2DM or 2 or more metabolic risk factors are at higher risk for disease progression, and more frequent FIB-4 monitoring (eg, every 1–2 y) should be considered.
- In patients older than age 65, an FIB-4 cutoff of >2.0 should be used.

Reminders

- FIB-4 has low accuracy in those under the age of 35 years; thus, secondary assessment should be considered in those < 35 years of age with increased metabolic risk or elevated liver chemistries.
- FIB-4 should not be used in acutely ill patients.

FIB-4 >1.3, NOW WHAT? Do I refer to gastroenterology?

No

Secondary assessment

- In patients with FIB-4 ≥1.3, a secondary assessment should be done (preferentially vibration controlled transient elastography (VCTE) or enhanced liver fibrosis testing (ELF) initially).
- However, direct referral to gastroenterology/hepatology should be considered in those with aminotransferases persistently (>6 months) above normal to exclude other causes of liver disease or when FIB-4 >2.67 due to the increased risk of clinically significant fibrosis.

Fibroscan

VCTE < 8 → low risk

- FIB-4 every 1-2 years if T2DM/preT2DM or ≥ 2 more metabolic risk factors
- FIB-4 every 2-3 years if no T2DM or < 2 metabolic risk factors

VCTE 8 – 12 → intermediate risk

- Treatment and repeat fibroscan in 1 year

VCTE > 12 → high risk

- Refer to gastroenterology for additional testing/biopsy

Enhanced Liver Fibrosis (ELF) Testing

< 7.7 → low risk

- FIB-4 every 1-2 years if T2DM/preT2DM or ≥ 2 more metabolic risk factors
- FIB-4 every 2-3 years if no T2DM or < 2 metabolic risk factors

7.7-9.8 → intermediate risk

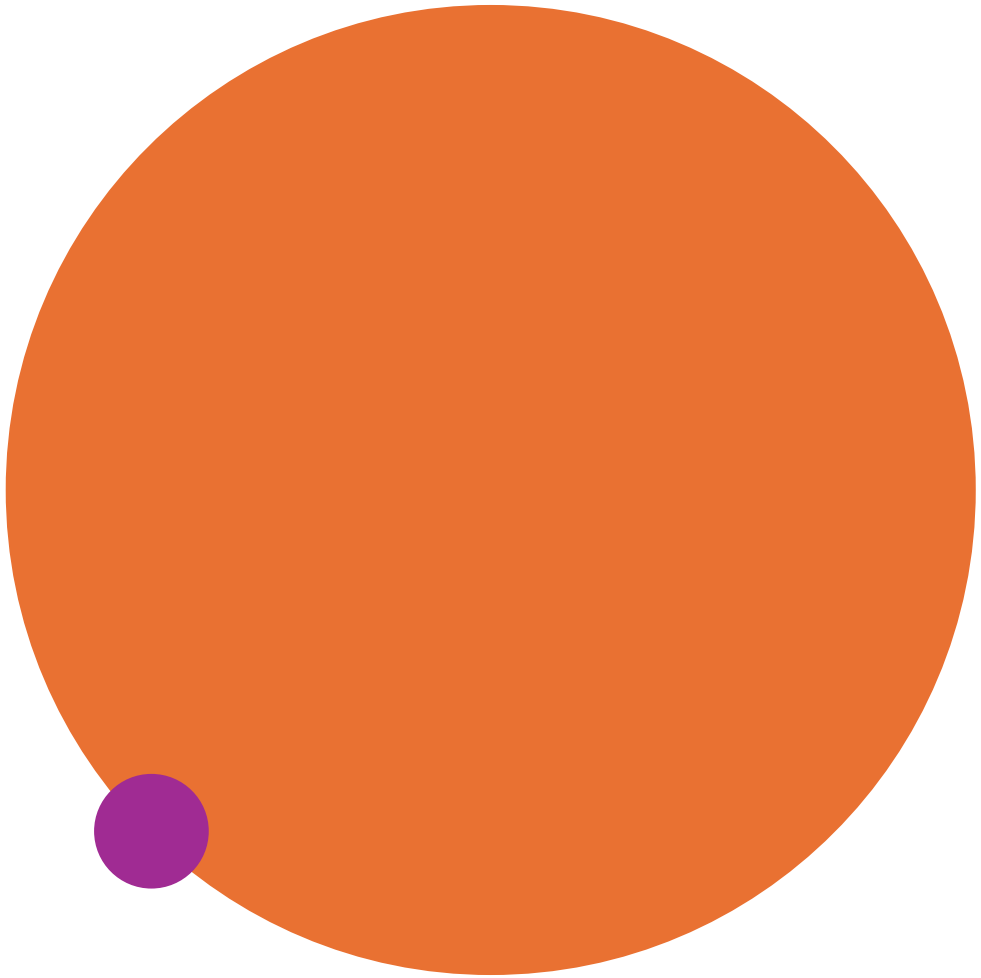
- Treatment and repeat testing in 1 year

>9.8 → high risk

- Refer to gastroenterology for additional testing/biopsy

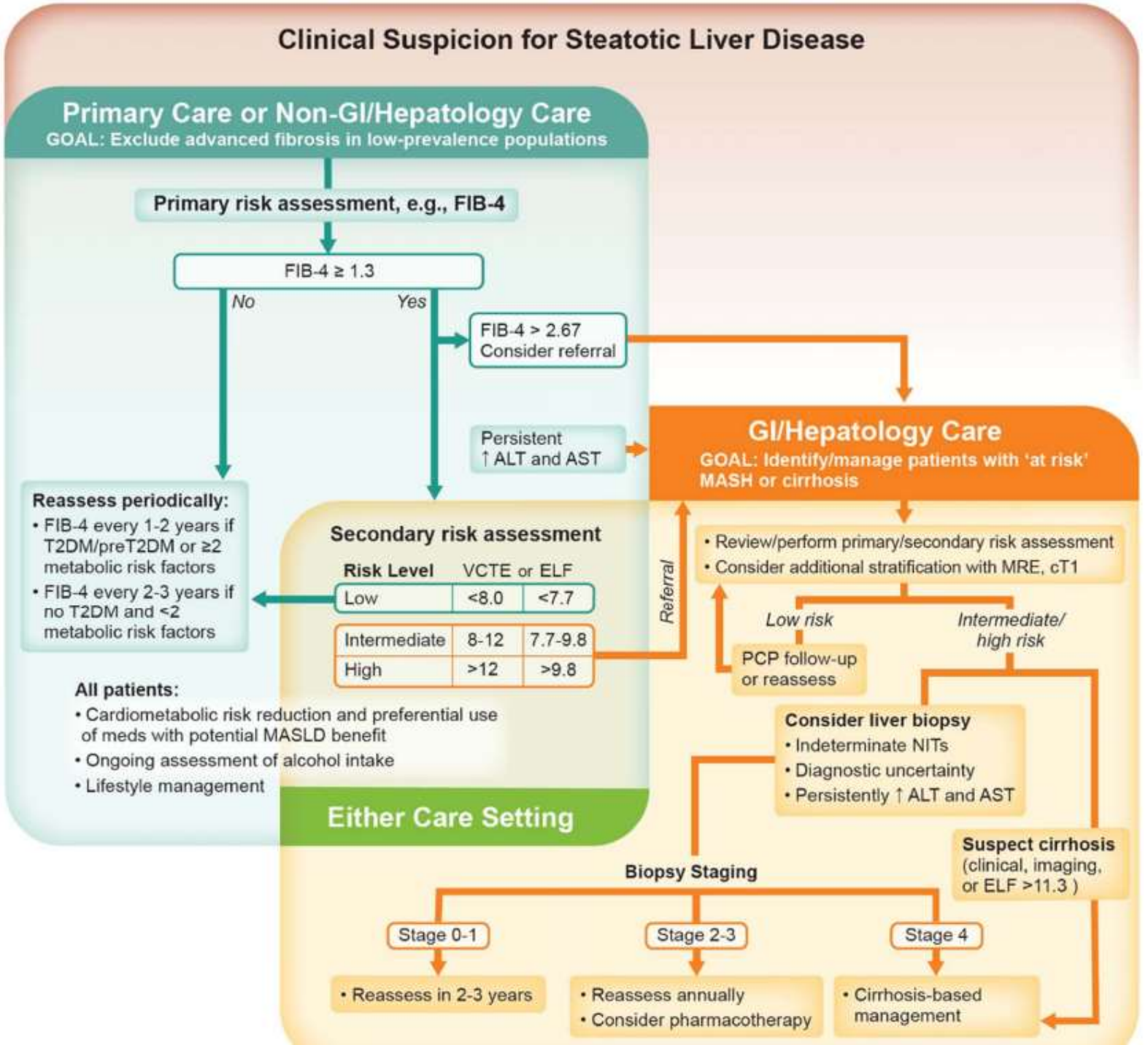
How to order ELF testing

- Miscellaneous lab orders
  - Type in Enhanced Liver Fibrosis (ELF) testing
  - Test number 550659
  - CPT 81517



- Patients at all stages of disease should be counseled on lifestyle modifications, and those with ≥F2 fibrosis targeted for pharmacologic interventions as they become available.

Algorithm for the evaluation of patients at risk for or with established SLD across practice settings



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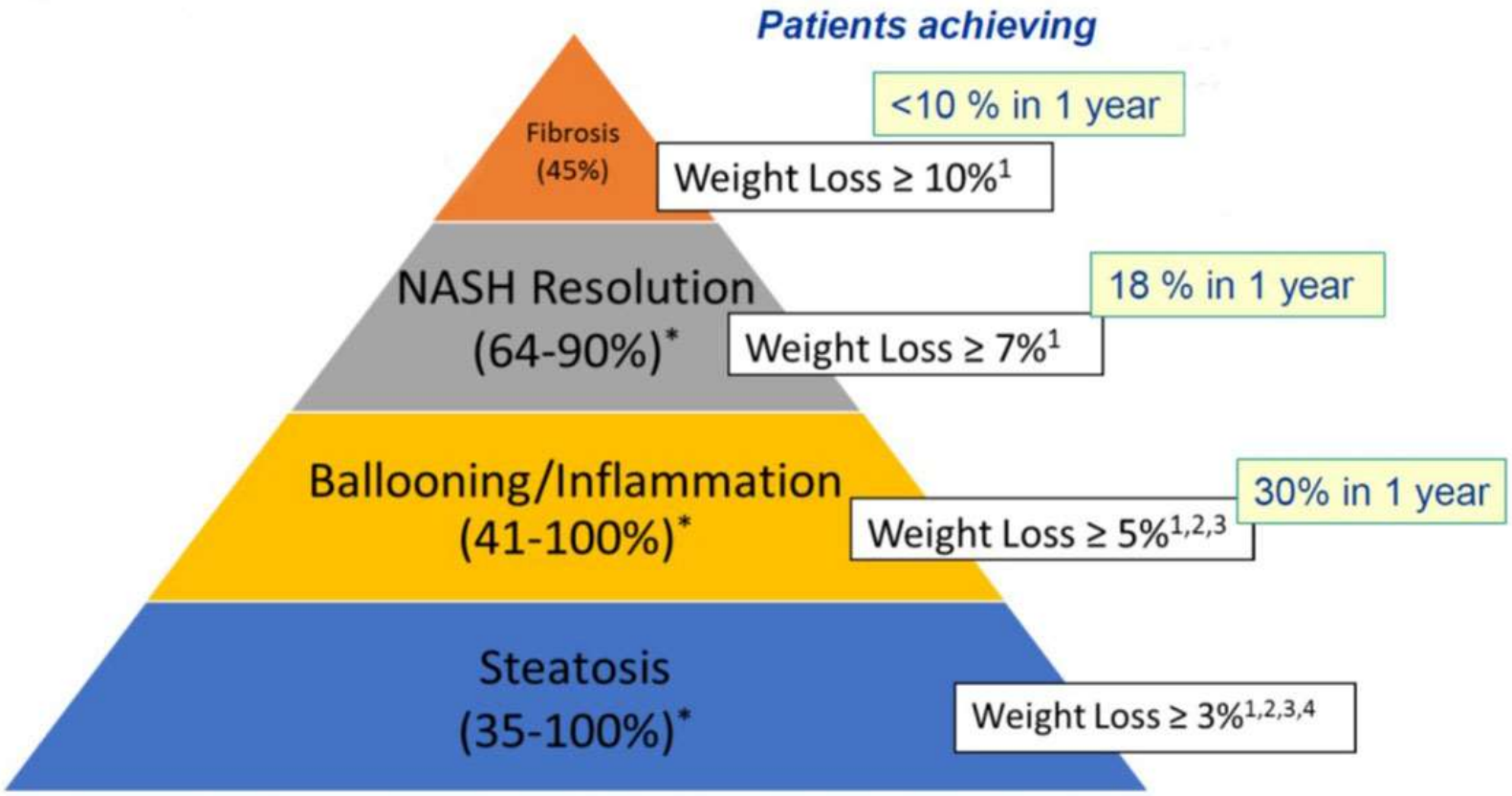
Treatment options

Lifestyle modifications

Slow weight loss of no more than 1-2 pounds per week with an initial goal of losing 10% of current body weight. Treating abnormal lipid and glucose levels with lifestyle modifications and/or medications is also important. If sleep apnea is present, it should be treated as well.

Life-style modification to include routine physical activity of at least 20-30 minutes daily as well as dietary modification is necessary. Specifically, a Mediterranean style diet which is composed of fish, white meat, fresh fruit, vegetable, whole grains, and legumes was recommended. Foods enriched with excess refined sugars, such as high fructose corn syrup, and hydrogenated fats should be avoided.

Most patients cannot achieve significant weight loss



1 Vilar-Gomez. Gastroenterology 2015; 2 Promrat. Hepatology 2010; 3 Harrison. Hepatology 2009; 4 Wong. J Hepatol 2013

*Depending on degree of weight loss

Wegovy

- The Wegovy formulation whose main ingredient is semaglutide, received accelerated FDA approval in August 2025 for treating MASH with moderate to advanced fibrosis (consistent with stages F2-F3 fibrosis), based on interim results of the phase 3 ESSENCE trial where 72 weeks of 2.4 mg/week subcutaneous injection resulted in achievement of both primary histologic endpoints: 1) resolution of MASH without worsening of fibrosis (62.9% vs 34.3% placebo, p1 stage reduction in liver fibrosis without worsening of MASH (36.8% vs 22.4% placebo, $p<0.001$); final approval awaits long-term outcomes.

Patient Selection

- Candidates should have MASH with stage 2–3 fibrosis, identified using noninvasive tests (NITs) such as VCTE (8–15 kPa), MRE (3.1–4.4 kPa), or ELF (9.2–10.5), rather than liver biopsy, which is impractical and unnecessary for most patients.

Patient Selection

- In those with VCTE (15-20kPa),MRE (4.4-5kPa), or ELF (10.5-11.3), an individualized decision to treat should be based on exclusion of cirrhosis with another confirmatory NIT, or cross-sectional imaging excluding nodular-appearing liver contour and signs of portal hypertension, or a platelet count of <150,000/mm3.

Monitoring & Safety: Semaglutide

- Showed a favorable hepatic safety profile in the ESSENCE trial, with no discontinuations due to liver enzyme elevations.
- Routine hepatic panels are recommended only as clinically indicated.
- The most common adverse events were gastrointestinal (nausea, diarrhea, constipation, vomiting), generally mild and transient; patient education and dose titration help improve tolerance.
- Clinicians should monitor for rare but serious risks, including acute kidney injury (from dehydration), symptomatic gallbladder disease, pancreatitis, thyroid C-cell tumors, retinopathy progression, and lean mass loss.

Treatment Response & Concomitant Therapy

- Lifestyle modification remains the cornerstone of MASLD/MASH management alongside semaglutide.
- Combination use with resmetirom has not been studied.
- While no NITs reliably predict histologic response at the individual patient level, reductions from baseline to 72 weeks of treatment suggest significant improvement in MASH resolution (ALT >17U/L or >20%; CAP >30%) and fibrosis improvement (VCTE LSM >30%; MRE LSM >20%; ELF >0.5).
- Non-response may be suspected if ALT or NITs worsen.
- Benefit is uncertain if sub-optimal response and may require an individualized approach and further follow-up.

- Assessment of safety and response to semaglutide in MASH with moderate to advanced fibrosis (F2-F3)

Bansal, Meena B.1; Patton, Heather2,3; Morgan, Timothy R.4,5; Carr, Rotonya M.6; Dranoff, Jonathan A.7,8; Allen, Alina M.9. Semaglutide therapy for metabolic dysfunction-associated steatohepatitis: November 2025 updates to AASLD Practice Guidance. Hepatology ():10.1097/HEP.0000000000001608, November 7, 2025.

Resmetirom

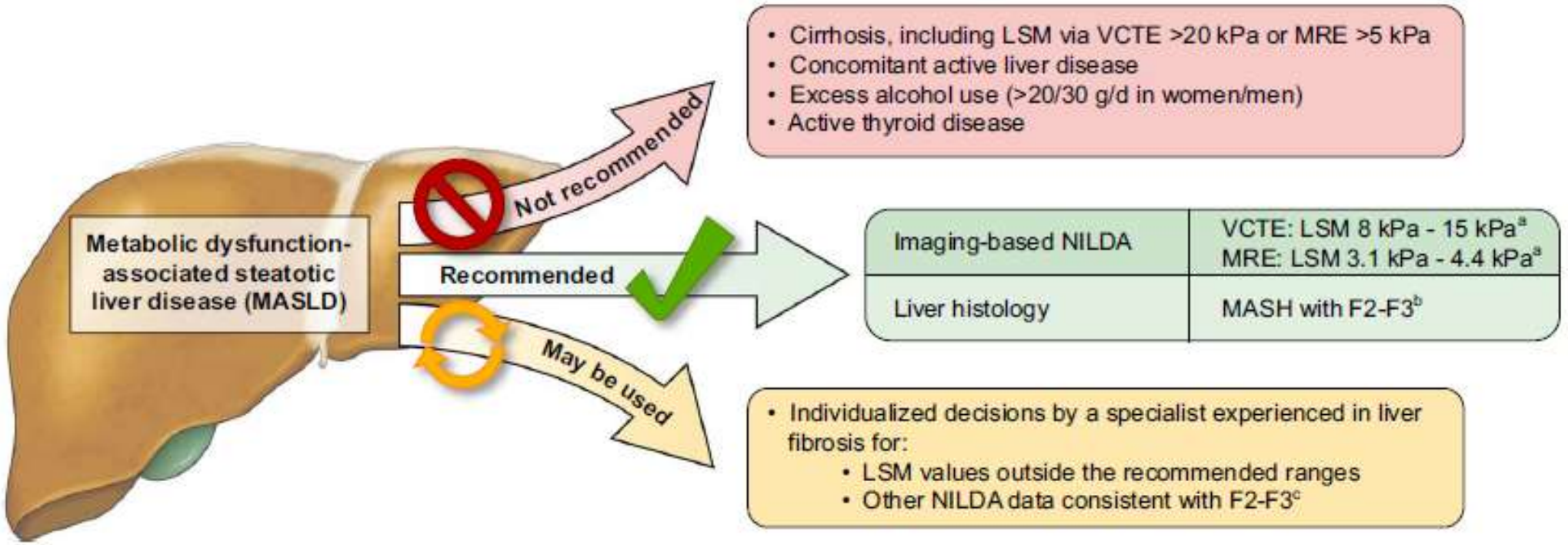
- Can be considered for treatment of adults with MASH and moderate to advanced liver fibrosis (consistent with F2-F3).
- The recommended dosage of resmetirom is 100 mg/d for persons who weigh 100 kg or more, or 80 mg/d for persons who weigh less than 100 kg.
- If resmetirom is used concurrently with a moderate cytochrome P450 2C8 inhibitor (eg, 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.

Pretreatment Considerations

- 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.

On treatment monitoring

- Hepatic function panel testing should be obtained at baseline and at periodic intervals (eg, 3, 6, and 12 months) to determine response and adverse events while on resmetirom therapy. Resmetirom should be discontinued if hepatotoxicity develops.
- There are insufficient data to make a recommendation on monitoring after 12 months of resmetirom treatment but continued monitoring with hepatic function panel testing every 6 months is suggested.
- Among persons with known thyroid disease, standard laboratory monitoring (eg, TSH and free T4) per established guidelines is recommended while receiving resmetirom therapy.
- Resmetirom can be used concurrently with statins; however, practitioners should 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.



[a] Modified from the AASLD NILDA guidelines.[5]
[b] Liver biopsy is not routinely recommended for staging of MASH.
[c] Imaging-based NILDA is preferred, eg, shear wave elastography (applying local standards for F2-F3) versus enhanced liver fibrosis score (9.2-10.4). The latter range is based on the interquartile range from the MAESTRO trial data; no recommendations are available from the AASLD NILDA guidelines.[6]

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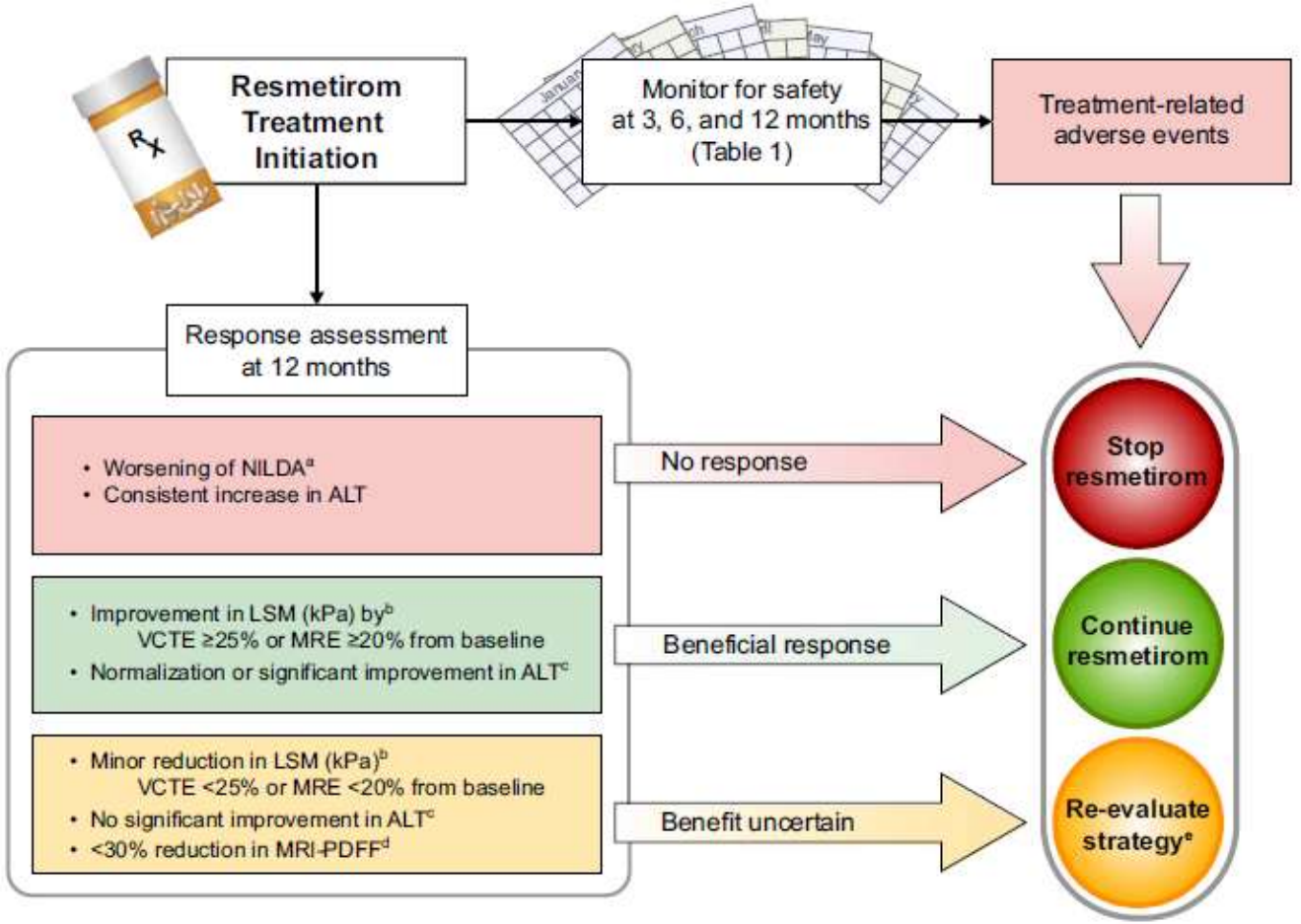
TABLE 1 Safety and efficacy assessments at baseline and during 12 months of treatment with resmetirom

	Safety/Efficacy assessments	Safety assessments		Efficacy assessments	
Timeframe	**Hepatic function panel[a]**	**Thyroid function[b]**	**Lipid profile[c]**	**Noninvasive measurement of liver stiffness[d]**	**MRI-PDFF[e]**
Before treatment initiation	✓	✓	✓	✓	Consider
3 months	✓				
6 months	✓	✓	✓		
12 months	✓	✓	✓	Repeat if imaging NILDA was used at baseline	Consider repeating if baseline data are available

Color Key Green: Recommended for all treated patients.
Blue: Recommended for a subset of patients for whom testing is appropriate.
Yellow: Optional assessments based on availability.

Chen, Vincent L.1; Morgan, Timothy R.2,3; Rotman, Yaron4; Patton, Heather M.5,6; Cusi, Kenneth7; Kanwal, Fasiha8,9,10; Kim, W. Ray11. Resmetirom therapy for metabolic dysfunction-associated steatotic liver disease: October 2024 updates to AASLD Practice Guidance. Hepatology 81(1):p 312-320, January 2025.



[a] Assess based on the same imaging-based or blood-based markers used to determine treatment eligibility.

[b] LSM improvement thresholds of VCTE ≥25% or MRE ≥20% are based on assay characteristics and not specifically validated for clinical decisions in resmetirom treatment patients. There are currently no comparable data to determine response in blood-based NILDAs.

[c] Applies to patients with elevated ALT at baseline. No specific ALT response cutoffs are available from the MAESTRO trial.

[d] MRI-PDFF reduction by >30% does not necessarily correlate with histologic response.

[e] Options may include re-optimizing lifestyle interventions and considering other therapy, with or without stopping resmetirom.

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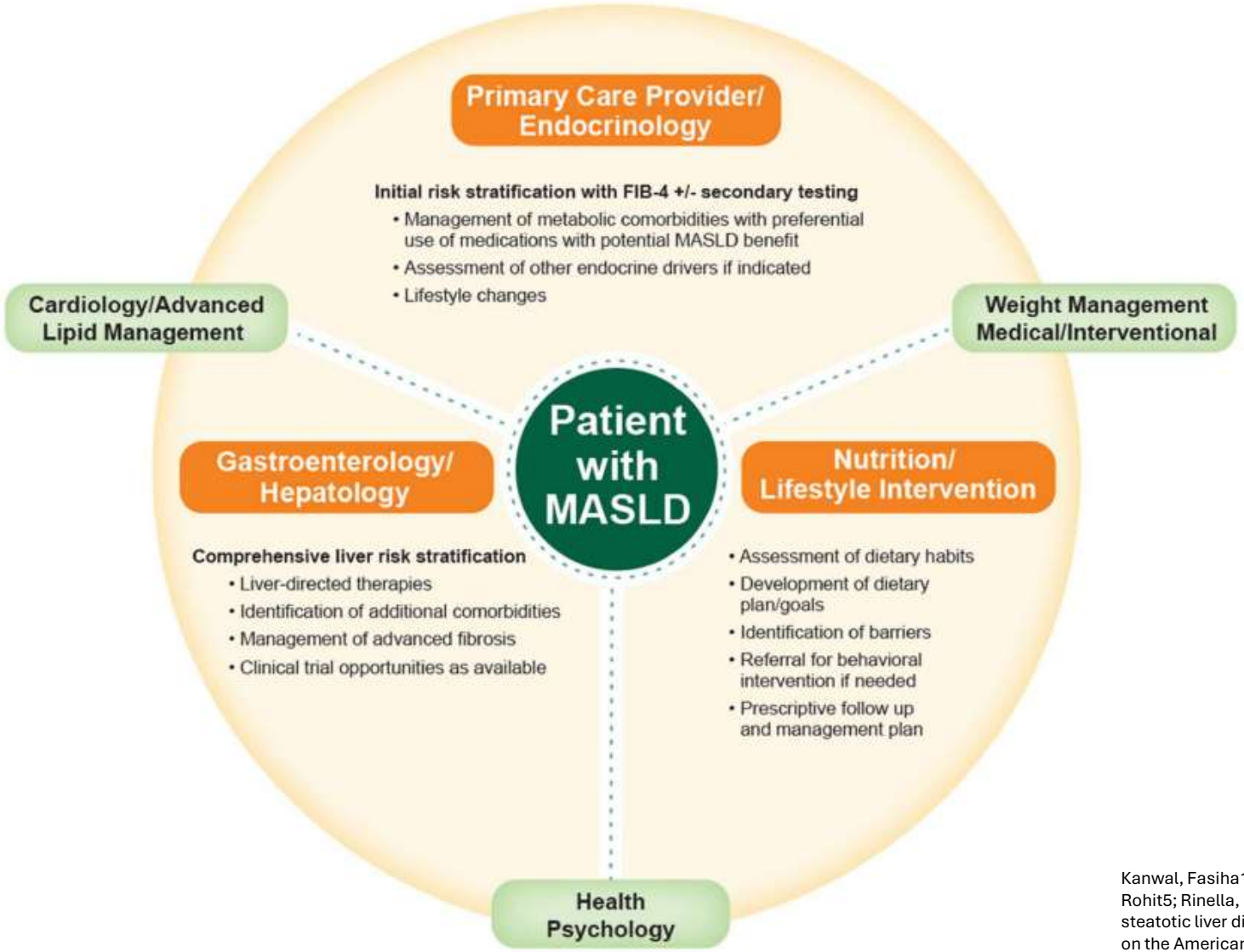

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In conclusion

- Optimal care of the patient with MASLD requires a multidisciplinary approach.
- The majority of patients are in the primary care/endocrine setting, in which the management of medical comorbidities should be optimized, with preference given to treatments for type 2 diabetes mellitus, hypertension, or obesity that likely also have beneficial effects on MASLD.
- In this setting, at-risk patients should be identified and initial risk stratification performed (ie, FIB-4 ± vibration-controlled elastography or enhanced liver fibrosis test (ELF)).
- The role of the gastroenterologist/hepatologist includes more comprehensive liver risk stratification, exclusion of other liver diseases, and a focus on liver-directed therapy.
- Close communication between gastroenterology/hepatology and primary care or endocrinology facilitates multidisciplinary management of metabolic comorbidities as well as the prioritization of medications or interventions that may also offer liver benefits.
- All patients should undergo dietary/nutritional assessment and a plan established for regular follow-up independent of gastroenterology/hepatology visits.
- The need for more specialized obesity management, including bariatric surgery referral, health psychology, and additional cardiology or lipid metabolic support, should be assessed on an individual basis

Weight loss works!

- > 5% - Improves steatosis
- > 7% - Improves inflammation
- > 10% - Improves fibrosis

MASLD IS NOT A LIVER DISEASE!

- It’s the hepatic manifestation of a systemic disease: Metabolic Syndrome - Obesity

References

- Bansal, Meena B.1; Patton, Heather2,3; Morgan, Timothy R.4,5; Carr, Rotonya M.6; Dranoff, Jonathan A.7,8; Allen, Alina M.9. Semaglutide therapy for metabolic dysfunction-associated steatohepatitis: November 2025 updates to AASLD Practice Guidance. Hepatology ():10.1097/HEP.0000000000001608, November 7, 2025. | DOI: 10.1097/HEP.0000000000001608
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Questions?