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Metabolic liver disease: A summary of major guidelines and identifying opportunities to improve future guidelines

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Abstract

The clinical management of metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) is undergoing rapid evolution, driven by advances in noninvasive diagnostics and the recent approval of liver-directed therapies. Multiple professional societies have issued guidelines and clinical care pathways to address screening, risk stratification, treatment initiation, and monitoring; however, substantial heterogeneity exists across these documents. In this review, we systematically compare major contemporary guidelines from hepatology, gastroenterology, endocrinology, and diabetes societies, highlighting areas of consensus as well as key differences in target populations for screening, noninvasive test thresholds, treatment eligibility criteria, and monitoring strategies. We analyse the methodological underpinnings of these recommendations, emphasising important limitations related to reliance on trial-derived populations, the absence of head-to-head comparisons, and the use of noninvasive test cutoffs extrapolated from highly selected randomised controlled trials. We also discuss how subjective interpretation of emerging evidence, variable consideration of cardiometabolic comorbidities, and limited integration of cost and access considerations contribute to divergent recommendations. Finally, we propose a framework for improving future guidelines, including greater transparency regarding evidence limitations, adoption of prevalence- and outcome-informed thresholds, clearer guidance on therapy sequencing and combination strategies, and a more holistic approach that aligns liver-specific outcomes with broader cardiometabolic risk reduction. As the therapeutic landscape continues to expand, more adaptive and objective guideline frameworks will be essential to optimise real-world implementation and equity of care.

1 | INTRODUCTION

Over the last few years, awareness of metabolic dysfunction-associated steatotic liver disease (MASLD) has increased substantially.[1] This progress has been driven by an improved understanding of the disease's metabolic underpinnings, as well as by unprecedented activity in clinical research and policy development. Since 2022, several major societies have published updated guidelines for the diagnosis and management of MASLD, providing greater clarity and consistency in clinical practice[2–6] (Figure 1). Importantly, two pharmacologic agents have now received regulatory approval for the treatment of metabolic dysfunction-associated steatohepatitis (MASH), marking a milestone in a field that for decades lacked effective therapy.[7,8] Parallel to these developments, scientific publications on MASLD have grown exponentially, reflecting a rapidly expanding research community and increasing global recognition of the disease's public health relevance.[9]

Despite this progress, substantial gaps remain. While liver biopsy is still recognised as the gold standard for the clinical diagnosis of MASH, it is an invasive procedure unsuitable for widespread screening or disease monitoring.[10] Current noninvasive approaches, mostly focused on using a two-step screening strategy

Plain Language Summary

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a common liver condition linked to obesity, type 2 diabetes, and other metabolic problems. In some people, MASLD can progress to a more serious form called metabolic dysfunction-associated steatohepatitis (MASH), which can lead to liver scarring (fibrosis), cirrhosis, liver failure, or death. Over the past few years, awareness of this disease has grown, new noninvasive tests have become available, and for the first time, medications specifically for MASH have been approved.

Several medical organizations have published guidelines to help physicians decide who should be screened, how liver disease should be diagnosed, and when treatment should begin. However, these guidelines often differ in important ways, which can be confusing for both clinicians and patients. This review compares the major current guidelines and explains where they agree, where they differ, and why those differences exist.

The review highlights that many recommendations are based on limited evidence and expert judgment rather than long-term outcome data. It proposes that future guidelines should be clearer about their limitations, better reflect real-world patients, and take into account access, cost, and overall cardiometabolic health. This approach could lead to more consistent, practical, and equitable care for people with MASH.

with the fibrosis-4 (FIB-4) index as the initial triage test, are limited in accuracy and emphasise fibrosis detection rather than early disease identification.[11,12] This narrow focus risks missing patients with MASH without or with only mild fibrosis who might benefit most from preventive interventions. Moreover, while guideline development has accelerated, most recommendations are still based on cross-sectional or surrogate outcomes rather than outcome-driven evidence.[2–6] Indeed, while guidelines are presented as evidence-based, evidence rarely dictates conclusions on its own. Interpretation, weighting of endpoints, and expert opinion often fill the gaps left by imperfect data. These subjective elements can significantly influence how evidence is translated into clinical recommendations. Consequently, clinicians navigating MASLD guidelines may encounter meaningful differences in recommended pathways, despite reliance on largely overlapping evidence. A more comprehensive approach (one that integrates metabolic risk assessment, early detection strategies, and prevention of disease progression alongside fibrosis staging) is needed for the management of patients with MASLD. This review summarises and contrasts recently published MASLD guidelines, highlighting points of convergence and divergence, and discusses opportunities to refine future recommendations towards a more holistic, objective, and outcome-oriented management strategy.

2 | FROM NAFLD TO MASLD: NOT JUST A CHANGE IN SEMANTICS

The terminology surrounding 'fatty' liver disease has undergone profound revision in recent years[13,14] (Figure 1), reflecting a shift towards definitions that better capture disease biology and reduce stigma. The long-standing term nonalcoholic fatty liver disease (NAFLD) defined the condition by exclusion, requiring hepatic steatosis and the absence of significant alcohol consumption and other liver diseases.[15] While conceptually useful, this definition centred on what the disease *was not* and failed to recognise its close association with metabolic dysfunction.

In 2020, an international consensus group proposed the term metabolic dysfunction-associated fatty liver disease (MAFLD) to establish a positive, inclusion-based diagnosis.[13] The MAFLD definition required evidence of hepatic steatosis in addition to overweight/obesity, type 2 diabetes, or metabolic dysregulation (i.e., two cardiometabolic risk factors), shifting the focus towards the metabolic drivers of liver injury. This change aligned nomenclature with pathophysiologic understanding and reduced the stigma implicit in 'nonalcoholic'.

Building on this concept, a multisociety consensus in 2023 introduced MASLD as the preferred terminology.[14] The definition was changed to include hepatic steatosis in the presence of at least one cardiometabolic risk factor, after exclusion of other causes of liver disease. MASLD aimed to harmonise prior proposals and ensure compatibility with existing research infrastructure, while MASH replaced NASH to describe its inflammatory and fibrotic form. At the same time, a new category called MetALD (metabolic dysfunction-associated alcohol-related liver disease) was introduced to describe individuals meeting MASLD metabolic criteria but with moderate alcohol consumption. Although conceptually important, MetALD has yet to be fully integrated into most clinical guidelines, and its operational definition remains debated.[16,17]

While the evolution from NAFLD to MASLD represents an important conceptual advance, the rapid succession of changes has also generated confusion. Divergent definitions across studies complicate data interpretation, hinder comparability of epidemiologic estimates and clinical trial data, and challenge clinicians attempting to apply evolving criteria in practice. Achieving consensus and harmonisation across research and clinical practice remains an urgent priority.

3 | GUIDELINES AGREE ON THE NEED TO SCREEN FOR LIVER FIBROSIS

In at-risk groups, such as individuals with type 2 diabetes, the prevalence of MASLD exceeds 50%,[18] making broad screening for steatosis impractical and of limited clinical utility. Consequently, contemporary strategies have focused on identifying the subset of patients who have progressed to clinically significant liver fibrosis (F2 or higher) or advanced fibrosis (F3 or higher). This approach reflects the recognition that fibrosis stage, rather than the presence of steatosis or even mild inflammation, is the strongest determinant of long-term outcomes.[19]

However, current clinical practice guidelines show notable heterogeneity in how they define the target of MASLD screening[2–6,20]: some recommend identifying clinically significant fibrosis, whereas others focus on advanced fibrosis as the primary outcome (Table 1). Despite this conceptual difference, most guidelines still endorse the same non-invasive algorithms and

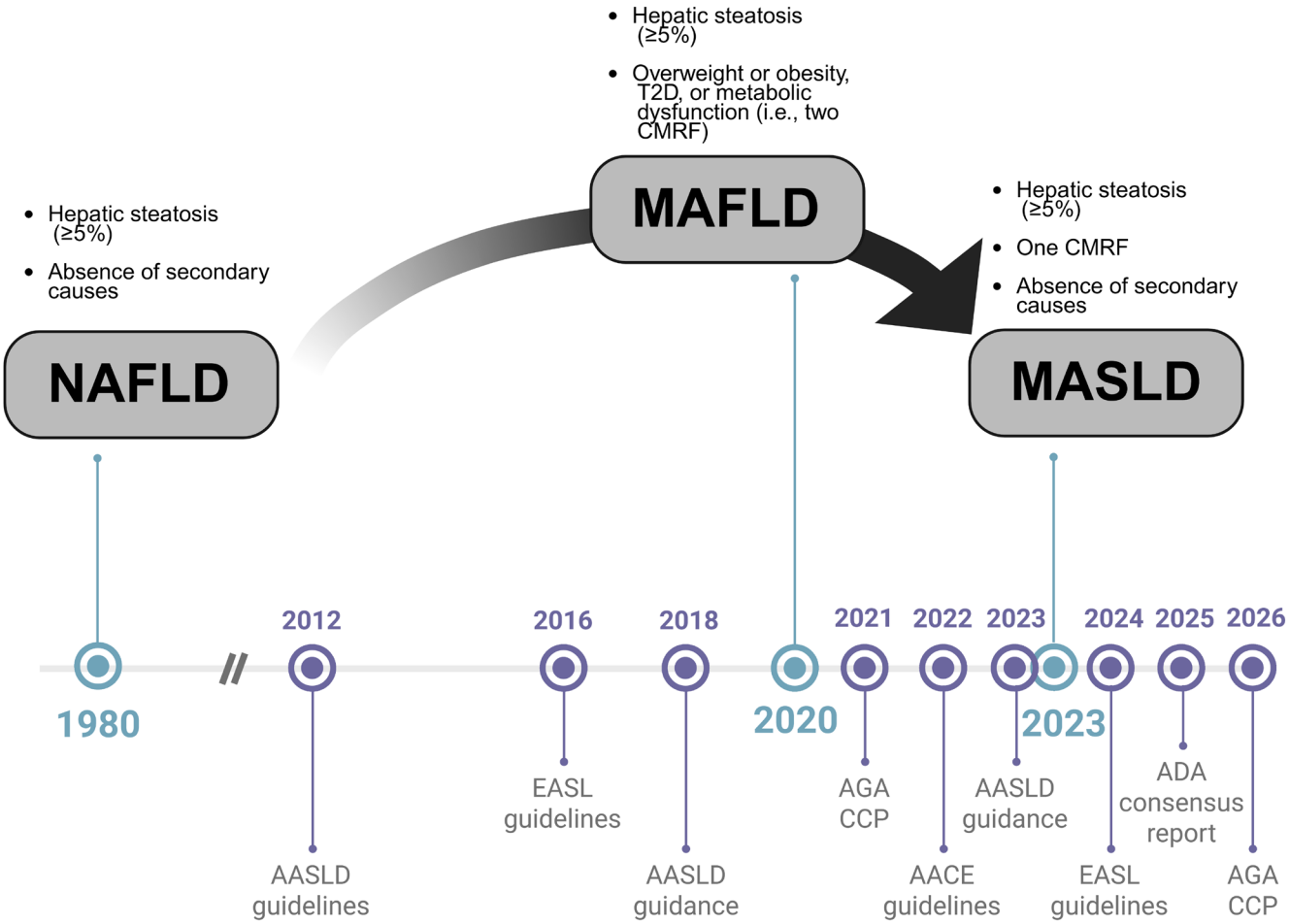

FIGURE 1 | Chronology of recent changes in nomenclature, definitions, and guidelines. This figure illustrates the conceptual transition from NAFLD to MAFLD and MASLD, highlighting changes in diagnostic criteria and the temporal relationship with major international guideline publications (1980–2026). AASLD, American Association for the Study of Liver Diseases; AACE, American Association of Clinical Endocrinology; ADA, American Diabetes Association; AGA, American Gastroenterological Association; CCP, Clinical Care Pathway; CMRF, cardiometabolic risk factor; EASL, European Association for the Study of the Liver; MAFLD, metabolic-associated fatty liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, nonalcoholic fatty liver disease.

cut-off points, such as FIB-4 followed by confirmatory testing (VCTE or ELF). Using similar algorithms to detect different fibrosis stages (i.e., clinically significant vs. advanced liver fibrosis) inevitably leads to different false-positive and false-negative rates, since a tool calibrated to rule out advanced fibrosis will perform differently when applied to clinically significant fibrosis as elegantly shown by Vidal-Trécan et al.[21] This inconsistency highlights an important gap in guideline harmonisation and underscores the need for stage-specific test calibration. However, given that both FDA-approved medications to treat MASH have been approved for individuals with MASH and F2 or F3,[7,8] it makes sense to focus recommendations to identify those patients that would benefit from specific pharmacological treatment.

A robust body of literature consistently demonstrates that the degree of liver fibrosis is the main predictor of overall mortality, liver-related adverse events, and hepatic decompensation in MASLD.[19,22,23] Large longitudinal studies show that as fibrosis advances from F1 to F4, the risk of liver-related morbidity rises exponentially, and fibrosis stage remains independently associated with all-cause mortality even after adjustment for metabolic comorbidities.[23,24] As such, the primary goal of MASLD screening programmes should be to detect liver fibrosis at earlier stages, when interventions (i.e., lifestyle modification, cardiometabolic optimization, and emerging pharmacotherapies) are most effective at halting or reversing disease progression. A recent cost-effectiveness analysis conducted for 12 countries concluded that screening for liver fibrosis followed by lifestyle interventions and pharmacological treatments was cost-effective for most countries.[25]

An additional consideration is whether screening for MASH, the inflammatory and progressive form of MASLD, may offer further benefit. Early identification of MASH, independently of the presence of liver fibrosis, could allow timely therapeutic interventions before advanced fibrotic remodelling occurs. The potential to prevent progression to advanced fibrosis, cirrhosis, and liver-related complications underscores the clinical appeal of such a strategy. Moreover, patients with MASH have a worse metabolic profile and may have increased cardiovascular risk independently of the stage of fibrosis.[26,27] However, widespread implementation of MASH-focused screening is currently limited by the lack of accurate non-invasive tests capable of reliably diagnosing MASH.[12,28] While biomarkers, imaging modalities,

TABLE 1 | Comparison of recent guidance and clinical care pathways regarding screening recommendations.

	AACE 2022	AASLD 2023	EASL-EASD-EASO 2024	ADA2025	AGA 2026
What do they screen for?	F2+	F3+	F3+	F2+	F2+
First-step in screening algorithm	FIB-4	FIB-4	FIB-4	FIB-4	FIB-4
Skip FIB-4 in T2D if VCTE readily available?	-	-	-	-	Yes
Is there a FIB-4 'indeterminate' group (i.e., 1.30 to 2.67) or just a high-risk group (i.e., ≥1.30)?	Indeterminate	Just high-risk	Indeterminate	Just high-risk	Just high-risk
Is FIB-4 ≥ 2.0 recommended as the threshold for individuals 65+ years?	No	Yes	Yes	No	Yes
Confirmatory testing recommended?	VCTE or ELF	VCTE or ELF	VCTE or others	VCTE or ELF	VCTE or ELF
Option to reassess FIB-4 after intensified management of comorbidities in the indeterminate group?	No	No	Yes	No	No
VCTE threshold to refer to hepatology?	8.0	8.0	8.0	8.0	8.0
ELF threshold to refer to hepatology?	7.7	7.7	7.7	9.8	9.2
Other types of elastography mentioned (MRE, SWE)?	Yes	Yes	Yes	Yes	Yes
How often to repeat in low risk?	2 years	1–3 years	1–3 years	1–2 years	1–3 years

Abbreviations: AACE, American Association of Clinical Endocrinology; AASLD, American Association for the Study of Liver Diseases; ADA, American Diabetes Association; AGA, American Gastroenterological Association; EASL, European Association for the Study of the Liver; EASD, European Association for the Study of Diabetes; EASO, European Association for the Study of Obesity; ELF, enhanced liver fibrosis test; FIB-4, Fibrosis-4 index; MRE, magnetic resonance elastography; SWE, shear wave elastography; T2D, type 2 diabetes; VCTE, vibration-controlled transient elastography.

and composite scores show promise, none have sufficient sensitivity and specificity to replace liver biopsy for definitive diagnosis. As a result, current guidelines prioritise fibrosis assessment rather than direct MASH detection. Advances in non-invasive diagnostics and the approval of targeted therapies may ultimately shift this paradigm,[28] but until then, fibrosis-centred screening remains the cornerstone of MASLD management.

Within the broader framework of cardiovascular-kidney-metabolic (CKM) syndrome,[29] fibrosis screening may additionally serve purposes that extend beyond the prevention of liver-related outcomes. Identification of liver fibrosis could help risk-stratify patients with MASLD who frequently harbour a high burden of cardiometabolic comorbidities and are at increased risk for cardiovascular events, the leading cause of mortality in this population.[27] However, whether liver fibrosis per se contributes to cardiovascular mortality remains uncertain. The observed associations between MASLD and/or MASH, and cardiovascular outcomes may largely reflect shared upstream drivers, particularly insulin resistance, hyperglycemia, and/or systemic inflammation, rather than a causal effect of hepatic fibrosis per se. This concept is supported, for example, by genetic and rare disease models in which insulin resistance and cardiovascular risk dissociate from hepatic steatosis and fibrosis. For example, individuals with insulin receptor mutations exhibit profound insulin resistance and markedly elevated cardiovascular risk, despite absence of MASLD or progressive liver fibrosis.[30] In contrast, patients with familial hypobetalipoproteinemia frequently develop hepatic steatosis and may progress to cirrhosis despite preserved insulin sensitivity and lower cardiovascular risk.[31] Accordingly, within the CKM paradigm, fibrosis screening is not just for the prevention of liver-related outcomes. It should also be viewed as a tool for integrated risk stratification and identifying patients with advanced metabolic dysfunction, who may benefit from intensified cardiometabolic interventions. However, there is no evidence that hepatic fibrosis itself is the principal driver of cardiovascular risk.

4 | DISCREPANCIES BETWEEN GUIDELINES ON WHO TO SCREEN: TOWARDS AN OBJECTIVE AND REPRODUCIBLE FRAMEWORK

All major professional societies agree that universal screening for clinically significant liver fibrosis is not recommended in

the general population[2–6,20] (Figure 2). When the prevalence of clinically significant fibrosis is low (i.e., 5%), and assuming FIB-4 index ≥1.3 has a sensitivity and specificity of 60%–70%,[32] the PPV would be approximately 7%–10%. This would mean that among those with a positive FIB-4 test, fewer than one in 10 would have ≥F2 fibrosis and roughly 9–14 confirmatory tests (such as VCTE or ELF) may be required per true positive. Consequently, large numbers of individuals would undergo unnecessary confirmatory testing or specialist referral for each true positive case identified. Instead, current guidance favours targeted, or 'case-finding', strategies that focus on individuals with higher pre-test probability of clinically significant fibrosis (Figure 2). The challenge, however, lies in determining which subgroups are sufficiently 'at risk' to justify structured fibrosis assessment, since guidelines use somewhat subjective criteria to define this.

The European Association for the Study of the Liver (EASL), together with the European Association for the Study of Diabetes (EASD) and the European Association for the Study of Obesity (EASO), recommend that fibrosis assessment be systematically considered in people with type 2 diabetes (T2D) or obesity with metabolic risk factors, as well as in individuals with abnormal liver enzymes or incidental imaging evidence of steatosis.[4] The American Association for the Study of Liver Diseases (AASLD) guidelines give similar advice, though the specific subgroups and operational pathways differ.[3] AASLD emphasises fibrosis assessment in individuals with T2D, medically complicated obesity, family history of MASH-cirrhosis, moderate alcohol intake, or those with hepatic steatosis or elevated aminotransferases. The American Association of Clinical Endocrinologists (AACE) has a broader recommendation to screen patients with prediabetes, T2D, obesity, two or more cardiometabolic risk factors, known hepatic steatosis, and persistently (6 months or longer) elevated ALT or AST.[2] Despite minor variations in terminology and cutoff values, these societies converge on a common principle: screening efforts should target groups in whom the prevalence of clinically significant fibrosis is high enough to make noninvasive tests (NIT)-based algorithms efficient and cost-effective (Figure 2).

Yet, the definition of 'at risk' remains qualitative rather than quantitative. Guidelines often refer to 'metabolic risk factors' or 'features of metabolic syndrome' without specifying an explicit prevalence threshold above which screening becomes worthwhile.[2–6,20] This introduces a degree of subjectivity, as the metabolic risk burden varies widely across populations, ages, and healthcare settings. As a result, clinicians must often rely on local epidemiology, pragmatic experience, and resource constraints to decide where systematic screening is worthwhile. This subjectivity could be reduced by adopting a prevalence-based framework, defining 'high-risk' as subgroups where the prevalence of clinically significant fibrosis is above a certain threshold. To move towards an objective framework, it is useful to ground the discussion in simple diagnostic mathematics: the relationship between disease

	AACE 2022	AASLD 2023	EASL-EASD-EASO 2024	ADA 2025	AGA 2026	"15% rule"
Prediabetes	✓	✗	✗	✓	✗	✗
Type 2 diabetes	✓	✓	✓	✓	✓	✓
Isolated overweight	✗	✗	✗	✗	✗	✗
Isolated obesity	✓	✗	✗	✗	✗	✗
Non-obese with two CMRFs	✓	✗	✗	✗	✗	✗
Obesity + CMRF	✓	✓	✓	✓	✓	✓
Steatosis on imaging*	✓	✓	✓	✗	✓	✓
Elevated ALT/AST	✓	✓	✓	✗	✓	✓
Moderate alcohol use	✗	✓	✗	✗	✗	✗
Family history of MASH-cirrhosis	✗	✓	✗	✗	✗	✓
People living with HIV	✗	✗	✗	✗	✗	✓

FIGURE 2 | Populations recommended for MASLD-related fibrosis screening across major clinical guidelines and clinical care pathways and a proposed prevalence-based strategy ('rule of 15%'). *Including patients that fulfil criteria for MetALD. AACE, American Association of Clinical Endocrinology; AASLD, American Association for the Study of Liver Diseases; ADA, American Diabetes Association; AGA, American Gastroenterological Association; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EASL, European Association for the Study of the Liver; EASD, European Association for the Study of Diabetes; EASO, European Association for the Study of Obesity; CMRF, cardiometabolic risk factor; HIV, human immunodeficiency virus; MASH, metabolic dysfunction-associated steatohepatitis.

prevalence, test performance, and predictive values. The PPV of a test depends strongly on the underlying disease prevalence: even a moderately accurate test yields many false positives in low-prevalence settings. Using Bayes' theorem, one can estimate the expected PPV and the downstream testing burden at various fibrosis prevalences. Assuming sensitivity and specificity of 60%–70%,[32] the PPV rises to around ~18% with a prevalence of 10%, requiring about six confirmatory tests for each true positive (a moderate yield). When prevalence increases to 15%, the PPV improves substantially (~27%), and only three to four confirmatory tests are needed per true case detected. In other words, the efficiency and clinical usefulness of a two-step screening strategy (FIB-4 followed by VCTE or ELF) rise sharply once the target subgroup has a baseline prevalence of ≥F2 fibrosis of 15%. Such an approach mirrors cost-effectiveness thresholds used in other screening domains, aligning diagnostic yield with health-system capacity. This numerical reasoning supports what guidelines have converged on empirically: screening is justified in subgroups with expected prevalence of clinically significant fibrosis ≥15%, which typically includes individuals with type 2 diabetes, and in many populations, those with obesity plus additional metabolic risk factors (hypertension, dyslipidemia, insulin resistance) (Figure 2). While several studies have agreed that screening for liver fibrosis with NITs is cost-effective in different subpopulations,[25,33] no prior study has focused on identifying a prevalence threshold at which cost-effectiveness is reached. It is possible that a lower prevalence of clinically significant fibrosis, (e.g., 10%–14%) is already cost-effective despite the higher number of confirmatory tests needed. Until this question is answered, providers will have to decide the need for screening based on patient's risk, resources available, and other individual risks.

In people with type 2 diabetes, studies report pooled prevalence of ≥F2 fibrosis between 15% and 25%,[18,34] depending on region and diagnostic modality, making T2D an efficient and justifiable target for fibrosis screening. In individuals with obesity and multiple metabolic risk factors, prevalence typically ranges from 10% to 20%, again exceeding the threshold.[18,35] Conversely, in the general population or in young adults with isolated obesity but without metabolic syndrome, prevalence of ≥F2 fibrosis is usually under 15%, which does not justify systematic screening.[36,37] Regarding incidental steatosis, among unselected individuals with steatotic liver disease in the NHANES population, the prevalence of clinically significant fibrosis was >15%,[18] justifying screening in this subgroup. Moderate drinkers, in the absence of prior knowledge of hepatic steatosis, have a prevalence of clinically significant fibrosis below this threshold[38] and therefore, should not be routinely screened. However, patients with MetALD are, by definition, part of the group with known hepatic steatosis, and should be screened for liver fibrosis given their increased risk.[39] Finally, among 272 consecutive patients with unexplained elevated ALT (at least 3 times with values above the upper limit of normal for at least 6 months) but without any previously known liver disease (i.e., viral, alcohol, drug, autoimmune, genetic), the prevalence of significant fibrosis was 27.4% (higher in those with a diagnosis of MASLD).[40] While this also suggests that patients with elevated aminotransferases should be screened for liver fibrosis, high heterogeneity exists regarding the cut-off points for abnormal AST/ALT, and the required duration of those elevations. Among first-degree relatives of individuals with MASLD and advanced fibrosis, the prevalence of advanced fibrosis was ~14%–17%,[41,42] implying that the prevalence of clinically significant fibrosis is >15%, and thus this group warrants liver fibrosis screening by the '15% rule'.

In summary, all major MASLD guidelines reject universal screening and instead advocate targeted fibrosis assessment in populations where disease prevalence is sufficiently high to make screening efficient and clinically meaningful. While the term 'at risk' remains loosely defined, an objective criterion can be derived from test performance characteristics: screening becomes worthwhile when the prevalence of clinically significant fibrosis is approximately >15%. This corresponds to patient groups such as those with T2D or obesity with additional metabolic risk factors.

5 | OTHER POTENTIAL 'AT-RISK' GROUPS EXCLUDED FROM CURRENT GUIDELINES

Several clinically important subgroups remain largely excluded from current 'at-risk' definitions for MASLD-related fibrosis screening, despite accumulating data that liver disease may be relevant in these populations.

5.1 | Polycystic ovary syndrome (PCOS)

PCOS affects ~13% of women of reproductive age.[43] From a pathophysiological standpoint, it shares with MASLD the presence of increased adipose tissue insulin resistance as an essential initiating process.[44] A meta-analysis showed a prevalence of MASLD of ~43% among women with PCOS,[45] similar to a recent study showing a prevalence of MASLD of ~36% based on MRI-PDFF in women with PCOS.[46] Moreover, this association with MASLD appears to be present even in lean women with PCOS.[47] Most studies have focused only on the relationship with hepatic steatosis and metabolic risk factors, rather than with the prevalence of clinically significant liver fibrosis. In 102 women with biopsy-confirmed MASLD, those with PCOS ($n = 37$) had a prevalence of advanced fibrosis of 16%.[48] However, this is a highly selected group of individuals in whom a liver biopsy was available. Among 241 consecutive patients with PCOS, the prevalence of clinically significant fibrosis, defined as liver stiffness measurement ≥8 kPa, was 22% in the United States.[49] Given this prevalence and following the '15% rule' described above, it seems that a priori this group of patients may benefit from screening for clinically significant fibrosis. However, individuals with PCOS identified in outpatient clinics are subject to referral bias and show higher rates of obesity and severe obesity compared to unselected individuals with PCOS.[50] Given the high rates of obesity and other cardiometabolic risk factors of patients included in the study by Scheetz et al.,[49] it is possible that MASLD and liver fibrosis were overrepresented in this cohort. It is also possible that all patients with PCOS and clinically significant fibrosis in this study would have already qualified for screening based on the presence of obesity with one cardiometabolic risk factor. In

a South Asian cohort from Canada with lower prevalence of obesity, the prevalence of clinically significant fibrosis among women with PCOS was only 6.9%.[51] Taken together, these heterogeneous findings, the strong overlap between PCOS and traditional cardiometabolic risk factors, and the limited number of well-designed studies specifically evaluating clinically significant fibrosis make it difficult to draw firm conclusions about whether all women with PCOS should undergo fibrosis screening. While mechanistic links support a biological rationale for increased liver risk, current data remain insufficient to justify universal screening in this subgroup of patients. Especially as the risk of liver fibrosis in women with PCOS may be driven by established metabolic comorbidities, rather than by PCOS itself. Larger, population-based studies with careful phenotyping will be required before definitive screening recommendations can be made for this population.

5.2 | HIV

A large meta-analysis of MASLD in people living with HIV (PLWH) ($n = 8230$) reported a pooled prevalence of clinically significant fibrosis (≥F2) of 12% in HIV-monoinfected individuals, based on imaging-based non-invasive tests.[52] In a multicenter study in the United States ($n = 1065$), the prevalence of clinically significant fibrosis in PLWH was 15% independently of the presence of steatotic liver disease, and even higher (21%) if patients had MASLD.[53] Given this prevalence of clinically significant fibrosis, it is not surprising that several authors have suggested that PLWH should be included among those groups benefiting from screening for MASLD-related liver fibrosis.[54] Overall, these data suggest that PLWH represent a population in whom the burden of clinically significant fibrosis approaches (and in some settings exceeds) the proposed 15% screening threshold. Importantly, the elevated fibrosis risk appears to be present even in the absence of overt steatotic liver disease (8% in PLWH without hepatic steatosis), underscoring that HIV-related factors and metabolic dysfunction may compound liver injury independent of steatosis.[53] While additional population-based studies are still needed, the consistency of findings across large cohorts supports the rationale for including PLWH among high-risk groups warranting systematic fibrosis assessment. Targeted screening, particularly in those with coexisting cardiometabolic risk factors or MASLD, is therefore a reasonable and evidence-supported approach.

5.3 | Panhypopituitarism

Panhypopituitarism and adult growth hormone (GH) deficiency are consistently linked with MASLD. In a classic series, 77% of patients with panhypopituitarism had MASLD and the majority of biopsied cases (14 out of 16) had MASH,[55] with some case reports emphasising rapid progression to advanced fibrosis in this setting.[56,57] Among 76 patients with panhypopituitarism, 71% had MASLD compared to only 31% in patients without hypopituitarism ($n = 74$) even when BMI- and age-matched. A prevalence of 34% of 'liver fibrosis' was reported among patients with hypopituitarism, but there was no clear definition (i.e., LSM cut-off) of 'liver fibrosis' in this study.[58] Of note, these studies had high prevalence of liver disease despite including younger patients (mean~19 years)[58] and mostly non-obese individuals (mean BMI ~24–25 kg/m^2).[55,58] Although robust prevalence estimates of ≥F2 are lacking, the combination of very high MASLD frequency, MASH-predominant histology and multiple metabolic comorbidities makes it plausible that clinically significant fibrosis surpasses 15% in many hypopituitary cohorts. Overall, pros of screening in these 'orphan' groups include potential for early intervention and hormone replacement, while cons include limited fibrosis data, higher false-positive rates particularly in younger people if using imaging-based NITs, and lack of guideline support, arguing for a nuanced, individualised approach rather than blanket screening for all.

5.4 | Children

The 2025 AASLD Practice Statement on MASLD in children provides the first comprehensive, paediatric-specific framework for the evaluation and management of steatotic liver disease in youth.[59] Although conceptually aligned with adult guidelines, it diverges from them in several critical areas reflecting fundamental differences in disease epidemiology, diagnostic accuracy of available tools, natural history, and health-system considerations. The paediatric statement emphasises that MASLD in children is a biologically distinct disorder characterised by unique histopathologic patterns compared to the adult form, with predominance of zone 1 periportal inflammation and fibrosis (vs. the classic zone 3 pattern seen in adults). This distinction has meaningful implications for diagnostic thresholds, risk stratification, and biomarker performance when compared to adult guidelines.

Screening strategies differ substantially. All adult guidelines converge on screening individuals at high metabolic risk for liver fibrosis using sequential noninvasive tests.[2–6,20] In contrast, the paediatric guideline recommends screening for steatosis using ALT alone, beginning at age ≥10 years for children with overweight, obesity, or cardiometabolic risk factors.[59] Imaging-based screening (ultrasound, CAP, MRI) is not recommended due to limited accuracy, cost, or lack of validation in children. Unlike all adult guidelines, which treat ALT as a poor and unreliable signal of liver disease, the paediatric document continues to rely on ALT because paediatric NITs for fibrosis perform inadequately.[60,61] Moreover, the paediatric guideline explicitly states that no currently available NITs have adequate accuracy to detect clinically significant fibrosis and thus cannot replace liver biopsy for staging. This stands in contrast to adult practice, where non-invasive fibrosis pathways allow for widespread community-based screening and even initiation of pharmacological therapies. This raises the question as to whether NITs really perform worse in children, or it is just a matter of lack of validation. It is also possible that the underperformance of NITs (if real) in children may be related to the relatively low prevalence of clinically significant liver fibrosis in this population.[62]

The paediatric Practice Statement highlights unique risks, such as growth, puberty, and psychosocial morbidity, that are not addressed in adult guidelines. In contrast, the adult guidelines focus more heavily on cardiovascular morbidity, cirrhosis progression, and hepatocellular carcinoma. Finally, the paediatric

document places new emphasis on transition of care, recognising that youth with MASLD entering adulthood differ from patients with adult-onset disease. In summary, the 2025 AASLD paediatric Practice Statement illustrates that direct application of adult screening and diagnostic algorithms to children is inappropriate. While adult guidelines prioritise fibrosis-first risk stratification, the paediatric guideline remains steatosis-first, ALT-based, and biopsy-dependent due to fundamental differences in disease biology and the poor performance of current paediatric NITs.

6 | TOWARDS PRACTICE-SETTING-ADAPTED SCREENING ALGORITHMS FOR MASLD

A consistent theme across contemporary MASLD guidelines is the attempt to recommend a single, unified screening algorithm that can be applied across markedly heterogeneous clinical environments. While conceptually attractive, this 'one-size-fits-all' approach has important limitations. The feasibility, clinical yield, and downstream consequences of a given algorithm vary substantially depending on local resources, access to NITs, and patients' characteristics. As a result, current algorithms may be suboptimal when applied indiscriminately across practice settings.

In rural or community-based settings, access to confirmatory testing such as VCTE, MRE or even ELF is often limited or absent. In this context, insisting on a stepwise pathway that mandates confirmatory testing may delay care without meaningfully altering management in many cases. For individuals with a clearly elevated FIB-4, particularly those with obesity or type 2 diabetes, it may be reasonable to initiate lifestyle intervention and evidence-based metabolic therapies (including GLP-1RA, SGLT-2 inhibitors and/or pioglitazone when indicated), with reassessment after ~12 months. This, indeed, is supported only by the 2024 EASL guideline for FIB-4 between 1.30 and 2.67,[4] with no other guideline recognising the potential utility of this approach. Here, FIB-4 functions less as a gatekeeper to specialist referral and more as a pragmatic risk-enrichment tool that identifies patients who warrant intensified metabolic management, even in the absence of definitive fibrosis staging (Figure 3).

At the opposite end of the spectrum, tertiary or specialty centres often have ready access to VCTE, MRE, ELF and other advanced imaging-based NITs, as well as hepatology expertise. In these settings, particularly when evaluating individuals at very high risk (e.g., long-standing type 2 diabetes, severe obesity, or multiple cardiometabolic comorbidities), the incremental value of calculating FIB-4 may be limited. Proceeding directly to elastography or other high-performance NITs may improve diagnostic efficiency, reduce false reassurance related to low or indeterminate FIB-4 values, and accelerate clinical decision-making. Moreover, a strategy focused on liver fibrosis screening with VCTE only appears to be cost-effective in the primary care space, as well as in enriched at-risk populations.[63] The updated American Gastroenterological Association (AGA) MASH Clinical Care Pathway[20] specifically supports direct screening with VCTE in individuals with T2D if readily available.

Between these extremes lies a large and increasingly common hybrid or resource-variable practice setting ('referral-based').

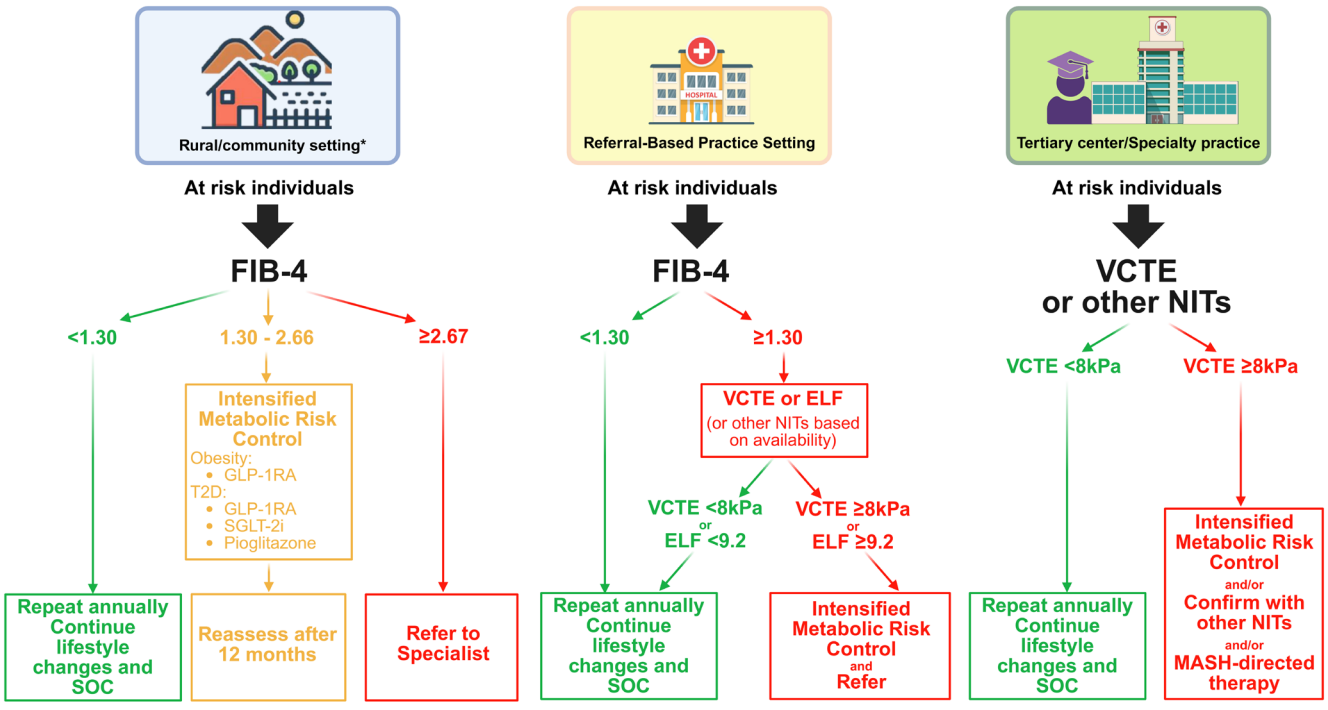

FIGURE 3 | Setting-specific screening, risk-stratification, and management algorithms for MASLD-related fibrosis in rural, referral-based, and tertiary/specialty centres. *Also applicable to referral-based practice setting if confirmatory testing is not available. ELF, enhanced liver fibrosis test; FIB-4, fibrosis-4 index; GLP-1RA, glucagon-like peptide-1 receptor agonist; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; NIT, noninvasive test; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; SOC, standard of care; T2D, type 2 diabetes; VCTE, vibration-controlled transient elastography.

In such environments, some confirmatory testing may be available, often through referral or limited on-site resources, but access is not universal or immediate. In this context, FIB-4 remains a valuable first-line triage tool to prioritise patients for confirmatory testing, reserving elastography or advanced biomarkers for those with indeterminate or high FIB-4 values, as recommended by most current guidelines. It is reasonable, even in these referral-based settings, to consider intensified metabolic risk control for patients with indeterminate FIB-4 results if confirmatory testing is not available.

Taken together, these considerations argue for a shift away from a single universal algorithm towards practice-setting-adapted screening pathways, as illustrated in Figure 3. Such an approach acknowledges real-world constraints, aligns diagnostic intensity with available resources, and may ultimately improve the efficiency and effectiveness of MASLD fibrosis detection across diverse healthcare systems.

7 | DIAGNOSTIC ALGORITHM: HOW STRONG IS THE EVIDENCE?

As previously mentioned, all major societies currently endorse a two-step, sequential diagnostic algorithm for MASLD-related fibrosis.[2–6,20] However, the strength supporting FIB-4 as the universal entry point into fibrosis screening is modest and increasingly questioned. FIB-4 was originally developed as a prognostic tool in viral hepatitis rather than as a screening test in MASLD, and its performance in contemporary, high-risk metabolic populations is suboptimal, particularly in type 2 diabetes.[12,64,65] In such populations, reliance on FIB-4 risks systematically missing patients most likely to benefit from further assessment.

Another important concern is the discordance between FIB-4 and VCTE. Several studies have shown a high rate of mismatch, with many patients displaying abnormal VCTE despite low FIB-4 values, or conversely elevated FIB-4 with normal liver stiffness.[66,67] This bidirectional discordance undermines the assumption that FIB-4 reliably enriches the population for second-line testing and raises questions about its role as an effective gatekeeper. Additional uncertainty relates to age-adjusted cutoffs, particularly in individuals older than 65 years. While some guidelines recommend increasing the FIB-4 threshold to 2.0 to improve specificity,[3,4,20] this adjustment is based on limited evidence[68] and introduces heterogeneity across algorithms. Race and ethnicity may also affect the performance of FIB-4.[69] Moreover, even in highly selected populations enrolled in large phase 3 randomised controlled trials (MAESTRO-NASH and ESSENCE), nearly half of participants with biopsy-confirmed MASH and fibrosis had FIB-4 values within the 'normal' range, highlighting the limited sensitivity of this marker even under trial conditions.[7,8] Taken together, these limitations suggest that FIB-4 is endorsed less because of strong intrinsic diagnostic performance and more because of its low cost, simplicity, and universal availability. If other non-invasive tests with superior accuracy were equally inexpensive and accessible, it is unlikely that FIB-4 would remain the preferred first-line tool.

Regarding individuals with MetALD, the optimal screening strategy for liver fibrosis has not been fully defined yet, as this population has been underrepresented in validation studies of NITs. Nevertheless, available evidence suggests that commonly used tools for MASLD, such as FIB-4, perform similarly in individuals with metabolic dysfunction and modest alcohol intake, and that standard cutoffs can be applied pragmatically in this subgroup.[70]

8 | CONFIRMATORY TESTING: PERFORMANCE, THRESHOLDS, CAVEATS, AND THEIR USE TO DECIDE ON TREATMENT INITIATION

Among confirmatory non-invasive tests, VCTE and ELF tests are the most frequently endorsed across contemporary MASLD guidelines.[2–6,20] Both have been extensively validated in the literature,[28,71] and the available evidence does not support a universal preference for one over the other in all settings. As a result, current guidelines generally position VCTE and ELF as complementary rather than competing tests, allowing either modality as second-line assessment after an abnormal first-step screen.

In general, elastography-based liver stiffness measurements tend to show strong diagnostic performance for advanced fibrosis when technically reliable. VCTE, while well validated, has important context-specific limitations that are particularly relevant to MASLD screening populations. Many individuals targeted for screening are severely obese or have coexisting cardiometabolic disease. In obesity, VCTE is associated with higher rates of technical failure and unreliable measurements, even if the XL probe is used.[72,73] In addition, liver stiffness can be falsely elevated in the setting of hepatic congestion, such as in patients with heart failure, leading to overestimation of fibrosis if clinical context is not carefully considered.[74]

In contrast, ELF offers a less operator-dependent, practical, blood-based alternative with good accuracy and particular utility when imaging capacity is limited or unreliable. A major challenge with ELF relates to threshold selection, which varies across guidelines and clinical contexts and has evolved over time (Table 1). Commonly cited cutoffs include ELF <7.7 to rule out advanced fibrosis, ≥9.2 to indicate a high likelihood of clinically significant fibrosis, ≥9.8 to indicate a high likelihood of advanced fibrosis, and ≥11.3 to identify individuals at particularly high risk of cirrhosis or liver-related events. Of note, ELF is FDA approved for its prognostic value and technically not as a diagnostic tool for liver fibrosis. This variability contributes to the perception that ELF cutoffs represent a 'moving target', potentially limiting clinician confidence and uniform adoption.

Taken together, existing evidence supports the use of either VCTE or ELF as confirmatory tests, and even other modalities, such as shear wave elastography or MRE, with selection guided by local resources, experience, patient characteristics, and clinical setting, rather than by a clear superiority of one modality over the other. Indeed, as NITs are now used to diagnose MASH with F2–F3 to guide treatment decisions, some of the guidelines recommend using more than one NIT in certain cases to confirm the diagnosis.[20,75]

While most guidelines[2–5] focused primarily on fibrosis detection and referral, recent AASLD practice guidance updates[75,76] and other expert consensus[6,77] provide explicit NIT thresholds to guide initiation and monitoring of resmetirom and semaglutide treatment, without requiring universal liver biopsy. As can be observed in Figure 4, there is partial agreement between these recommendations, with only small discrepancies, usually related to the ranges where confirmation with an additional NIT is recommended. An important limitation of these ranges is that many of these thresholds are derived from analysing baseline characteristics of the populations which have participated in the randomised controlled trials. In these trials, patients were highly selected, as multiple layers of screening were required in order to enrich for individuals with histologic F2–F3 disease and to minimise unnecessary liver biopsies. Depending on what criteria were used in each trial, the distribution of baseline NIT values will be significantly different, and it does not reflect the spectrum of disease seen in routine clinical practice. Because the observed NIT ranges are conditioned on prior screening and biopsy-selection criteria, they do not represent unbiased thresholds for identifying treatment-eligible patients in real-world populations. Moreover, if we compare the thresholds used to initiate treatment for MASH with F2–F3 (Figure 4) with the thresholds used to decide on hepatology referral in prior guidelines, we can observe marked differences, especially for ELF.[2–4] Future guideline frameworks will need to explicitly separate screening efficiency from treatment eligibility and incorporate population-level validation and outcome-based calibration of NIT thresholds. But until then, when faced with patients with borderline or discordant NIT values, clinicians will necessarily require individualised clinical judgement. Clinicians will have to decide whether to favour treatment initiation, confirmation

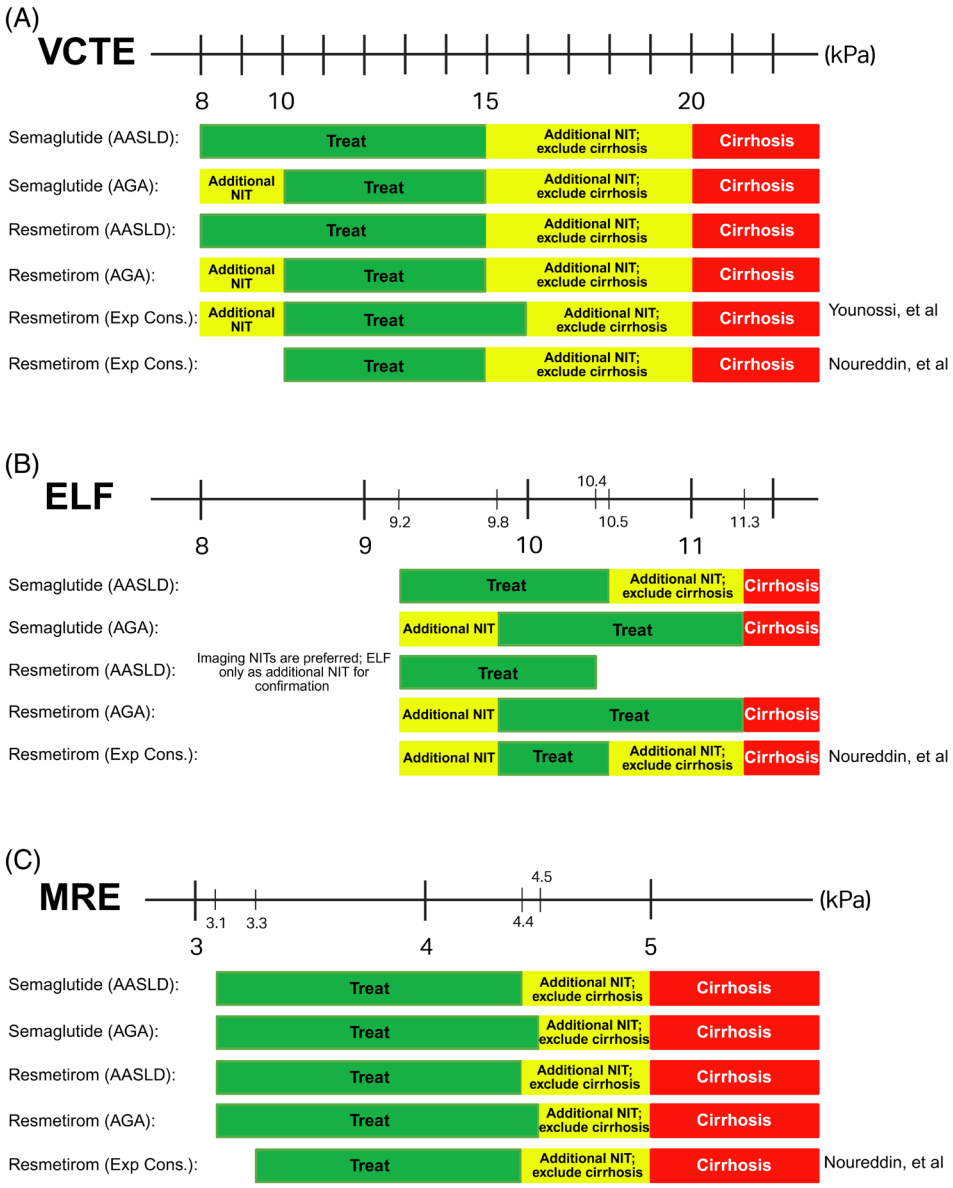

FIGURE 4 | VCTE (panel A), ELF (panel B), and MRE (panel C) thresholds to guide initiation of resmetirom and semaglutide treatment across major guidelines and expert consensus statements. AASLD, American Association for the Study of Liver Diseases; AGA, American Gastroenterological Association; ELF, enhanced liver fibrosis test; MASH, metabolic dysfunction-associated steatohepatitis; MRE, magnetic resonance elastography; NIT, noninvasive test; VCTE, vibration-controlled transient elastography.

with additional NITs, or active surveillance, taking into account the overall cardiometabolic risk profile, comorbidities, and therapeutic risk–benefit balance. From a pragmatic standpoint, when consideration is being given to GLP-1RAs, it may be reasonable to err towards treatment initiation, given their extensive long-term safety data, consistent weight loss efficacy,[78] and well-established cardiovascular[79] and renal benefits,[80] as well as their use across the spectrum of liver disease, including compensated cirrhosis.[81] In contrast, when resmetirom is under consideration, the absence of long-term outcome data and limited experience in patients with cirrhosis support a more conservative approach, in which confirmation with an additional NIT or short-interval reassessment may be appropriate before treatment initiation. This differentiated strategy may help clinicians navigate uncertainty at borderline thresholds while minimising both undertreatment and unnecessary exposure to therapies with narrower evidence bases.

9 | WHEN TO RULE OUT OTHER LIVER DISEASES AND WHO IS RESPONSIBLE FOR THIS?

Across major MASLD guidelines and consensus documents, there is broad agreement that alternative causes of liver disease should be excluded, but the specificity, timing, and ownership of this evaluation are inconsistently defined,[2–6] with the exception of the latest AGA MASH Clinical Care Pathway.[20] Most documents explicitly state that other liver diseases should be considered in the differential diagnosis. However, few provide a test-by-test checklist of what needs to be ordered, and they are also largely silent on when in the diagnostic pathway this evaluation should occur. This creates ambiguity as to whether comprehensive etiologic testing should precede NIT-based risk assessment, occur in parallel, or be deferred until abnormal or discordant results prompt referral. Finally, none of the guidelines clearly delineate who is responsible for ruling out alternative liver diseases at each stage of care. While primary care providers, endocrinologists, and obesity specialists are increasingly positioned as the entry point for MASLD screening, the guidelines do not specify which elements of the etiologic work-up are expected to occur before hepatology referral. In practice, this often leads to variability, with some clinicians ordering extensive panels upfront (sometimes with significant over-testing) and others deferring nearly all etiologic testing to hepatology referral. In turn, this lack of clarity can also lead to over-assumption of MASLD as the diagnosis, with the possibility of missing alternative diagnoses, which oftentimes coexist with MASLD. Together, these gaps highlight an important opportunity for future guidelines to more clearly define what to test for and when to test, while offering adaptable guidance on the role of non-hepatologists in excluding other etiologies of liver fibrosis, recognising that responsibilities will necessarily vary across healthcare settings and reimbursement environments. The 2026 update of the MASH Clinical Care Pathway[20] tried to overcome some of these limitations, by providing explicit guidance on these issues, including tools to screen for alcohol consumption (AUDIT-C or the National Institutes of Alcohol Abuse and Alcoholism [NIAAA] recommended single alcohol screening question), as well as detailed work-up needed to exclude other liver conditions. An AUDIT-C score ≥4 (men) or ≥3 (women) indicates a positive screen. Similarly, a response of "≥1" on the NIAAA single alcohol screening question also warrants follow-up.[20] Following a positive screen, additional questions should be asked to learn the typical weekly pattern and quantify alcohol intake. None of the guidelines devotes much consideration to serum markers of alcohol consumption (e.g., phosphatidyl ethanol [Peth]) despite its increased use in clinical practice, and this option was only mentioned in the newest guidance/consensus.[6,20]

10 | MANAGEMENT OF INDIVIDUALS WITH MASH WITH F2 AND F3

The management of MASLD and MASH is undergoing a period of unusually rapid evolution, driven by the emergence of effective pharmacologic therapies, expanding evidence for cardiometabolic interventions, and increasing reliance on NITs to guide treatment decisions. As a result, clinical guidelines are increasingly challenged to balance durability with relevance, and recommendations may become outdated within a short time frame as new trial data, regulatory approvals, and real-world experience accumulate. This dynamic environment partly explains the heterogeneity observed across contemporary guidelines, which often reflect different evidentiary cutoffs, regulatory contexts, and intended audiences. In this section, we compare areas of broad consensus and key points of divergence across guidelines with respect to lifestyle interventions, bariatric surgery, diabetes management, and MASH-directed therapies, highlighting where recommendations are robust and where future updates are likely to be required.

10.1 | Lifestyle interventions and bariatric surgery

Across guidelines, lifestyle modification remains the cornerstone of MASLD/MASH management, yet recommendations are largely superficial. While various dietary approaches are endorsed (e.g., Mediterranean-style diets, low-carbohydrate diets, caloric restriction), no guideline recommends one specific dietary pattern over another based on head-to-head comparative evidence. This reflects the absence of adequately powered trials directly comparing dietary strategies with histological or fibrosis-related endpoints in MASLD/MASH. Consequently, recommendations emphasising one diet over another may be premature, and most guidelines appropriately focus on caloric reduction, sustainability, and patient preference rather than diet composition per se. In contrast, weight-loss targets are remarkably consistent, with most documents converging on ≥5% weight loss for steatosis improvement, ≥7% for histologic benefits, and ≥10% for fibrosis regression. Physical activity recommendations are similarly aligned, emphasising both aerobic and resistance exercise independent of weight loss.[2–6,20] A key question is whether any of the recommended lifestyle interventions is specific for individuals with MASLD/MASH, or if they are all applicable to individuals with obesity and/or T2D. Because lifestyle interventions usually target the shared upstream drivers (i.e., insulin resistance, increased adiposity, and overall cardiometabolic risk), most lifestyle recommendations in MASLD/MASH guidelines are essentially the same as for individuals

with obesity and T2D (e.g., caloric restriction, sustained weight loss, macronutrient composition, increased physical activity). Probably, the most 'liver-specific' lifestyle recommendations are alcohol avoidance (particularly once fibrosis is clinically significant) and coffee consumption (e.g., ~3 cups/day in the absence of contraindications), which is not a standard recommendation for obesity or diabetes care despite potentially beneficial for MASLD in epidemiologic data.[82] Most other lifestyle advice in MASLD/MASH, such as limiting sugar-sweetened beverages/refined carbohydrates, prioritising unsaturated fats/fibre, and structured physical activity, would generally be considered appropriate and beneficial irrespective of liver disease. An in-depth summary of lifestyle interventions and their evidence in MASLD/MASH is beyond the scope of this review, and readers are referred to several comprehensive reviews that detail the evidence supporting dietary modification, physical activity, and weight loss strategies, as well as their limitations and implementation challenges.[83–85]

All major guidelines[2–6,20] are largely concordant in their recommendations regarding bariatric (or metabolic) surgery in MASLD/MASH. They usually state that bariatric surgery may be considered in patients who meet standard surgical indications based on BMI and obesity-related comorbidities, and substantial evidence demonstrates improvements in steatosis, inflammation, and fibrosis following surgery.[86] However, MASH itself is not considered a primary indication for bariatric surgery, and surgery should not be pursued solely for the treatment of liver disease in the absence of established metabolic indications.[2–6,20] Rather, the hepatic benefits are viewed as an important secondary advantage of a procedure undertaken for obesity and its systemic complications. Guidelines further acknowledge that bariatric surgery may be performed safely in carefully selected individuals with compensated cirrhosis, provided that clinically significant portal hypertension is excluded and surgery is undertaken in experienced centres with multidisciplinary expertise.[87] A recent retrospective observational study in individuals with MASH-related compensated cirrhosis ($n = 168$) reported that bariatric surgery was associated with an 80% lower risk of progression to decompensation and a 72% lower risk of incident major liver-related outcomes.[88] Finally, except for the 2026 AGA MASH Clinical Care Pathway, current MASLD/MASH guidelines do not specifically address the recognised risk of incident alcohol misuse/AUD after bariatric procedures, which can particularly affect individuals with liver disease. Alcohol use should be systematically evaluated before bariatric surgery and reassessed during postoperative follow-up, with referral to addiction medicine specialists when appropriate.[20]

10.2 | Pharmacological management of diabetes in MASH and MASH-directed therapies

As discussed above, the therapeutic landscape of MASH is evolving at an unprecedented pace, highlighting a fundamental gap between the speed at which new evidence emerges and the timeline of guideline development. Indeed, with the exception of the AGA 2026 Updated MASH Clinical Care Pathway,[20] none of the major guidelines were published after the regulatory approval of both semaglutide and resmetirom. Consequently, existing documents provide limited guidance on practical questions such as which agent should be initiated first in patients with MASH and F2–F3 fibrosis.[2–6] This gap is not unexpected, but it underscores how quickly guidance can become outdated when new pharmacologic options enter clinical practice.

Despite being grounded in evidence-based medicine, guideline recommendations are inevitably shaped by differences in interpretation of trial data, weighting of endpoints, clinical priorities, and even personal or disciplinary perspectives of the authors. These differences become particularly apparent when evaluating therapies with heterogeneous trial designs, populations, durations, and primary outcomes. For example, if one focuses narrowly on fibrosis improvement in phase 3 histologic trials, both semaglutide and resmetirom appear to demonstrate comparable efficacy,[7,8] acknowledging that direct comparisons are not fair given the absence of head-to-head studies and substantial differences in trial design. From this perspective, a reasonable recommendation would be that either medication could be considered as first-line therapy in patients with noncirrhotic MASH and F2–F3 fibrosis. And this, unfortunately, seems to be the approach of the latest guidelines/recommendations.

Even when acknowledging the metabolic advantages of GLP-1RA, the most recent AGA 2026 Updated MASH Clinical Care Pathway[20] refrains from recommending a fixed sequence for initiating FDA-approved MASH therapies. Instead, it emphasises shared decision-making, implicitly recognising that clinical context, comorbidities, access, and patient preferences may outweigh any single hierarchy of drugs. This approach contrasts with the expectations of many clinicians, who often turn to guidelines specifically for help in making such prioritisation decisions. While a flexible framework may be philosophically defensible, it may also reduce the practical utility of guidelines for front-line decision-making. A similar pattern is seen in the approach followed by AASLD,[75,76] where independent updates for semaglutide and resmetirom are provided, yet no formal guidance is offered on how to choose between them.

Notably, although guidelines consistently emphasise the importance of a holistic (multidisciplinary) approach to MASH, accounting for cardiovascular disease, chronic kidney disease, heart failure with preserved ejection fraction, obstructive sleep apnea, and other obesity-related complications, these comorbidities are not always explicitly integrated into therapeutic prioritisation. This omission is particularly striking given that GLP-1RA (or dual agonists) have demonstrated benefits across many of these conditions.[79,80,89,90] From a pragmatic standpoint, it is difficult to argue against the use of GLP-1–based therapy as first-line treatment in patients with MASH who also have overweight, obesity, and/or type 2 diabetes, if no contraindications exist. In this context, the question becomes less whether a GLP-1RA should be used, and more which agent should be selected. And this is another question that is amenable to subjectivity.

Although fibrosis improvement was not the primary endpoint of the phase 2 trial of tirzepatide in MASH,[91] the magnitude of histologic improvement observed in this randomised, controlled trial has led several authors to view this as convincing evidence of antifibrotic benefit, warranting similar clinical consideration as semaglutide, as observed in the framework for the

pharmacological treatment of obesity from the EASO[92] or the AACE Consensus Statement on Obesity treatment from 2025.[93] Others may reasonably argue that tirzepatide must demonstrate comparable effects in a larger phase 3 trial before being positioned equivalently. This divergence highlights an important conceptual distinction between regulatory requirements for approval and statistical evidence of biological efficacy. Many therapies have demonstrated robust treatment effects in relatively small, well-conducted studies, raising the question of whether efficacy observed in ~150–200 patients should be discounted solely because it precedes a phase 3 trial enrolling ~1000 participants. The answer to this question is not purely scientific, but partly philosophical, and it helps explain variability across guideline recommendations. The choice between semaglutide and tirzepatide further illustrates the role of subjectivity in guideline development. A 'purist' approach may favour semaglutide based on phase 3 histologic data and regulatory approval for MASH. However, given the comparable magnitude of liver-related effects in phase 2 MASH trials and head-to-head studies demonstrating greater reductions in HbA1c[94] and body weight[78] with tirzepatide, it is reasonable to infer similar hepatic benefits, particularly since much of the liver improvement appears to be weight-loss mediated. Because semaglutide and tirzepatide are distinct molecules with different mechanisms of action, extrapolation must be cautious, yet the available data supports a clinically defensible approach in which both agents are considered broadly comparable from a liver perspective.

Within this context, the debate surrounding agent selection during guideline development goes beyond biological efficacy. Evidence-grading frameworks such as GRADE do not explicitly differentiate phase 2 from phase 3 trials, but they emphasise certainty of evidence, including risk of bias, consistency, and precision. Therefore, while phase 3 trials more readily support strong recommendations by virtue of larger sample size and narrower confidence intervals, phase 2 trials may support conditional recommendations based on moderate-certainty evidence. Importantly, earlier MASH guidelines incorporated agents such as pioglitazone and vitamin E on the basis of consistent phase 2 histologic data,[95] when phase 3 data was unavailable. In a similar manner, agents such as dapagliflozin and tirzepatide have demonstrated meaningful histologic signals in well-designed phase 2 trials,[91,96] alongside well-established benefits in metabolic, cardiovascular, and renal outcomes. Although these data may not meet the threshold for strong recommendations as MASH-directed therapies, GRADE methodology allows for their consideration as conditional options with lower certainty of evidence, particularly in appropriately selected patients with relevant comorbidities. Taken together, this distinction highlights the complementary, but non-identical, roles of regulatory approval and clinical practice guidelines in translating evolving evidence into individualised patient care.

The roles of SGLT-2 inhibitors and pioglitazone further highlight discrepancies between hepatology- and endocrinology-led guidance. These agents receive greater emphasis in AACE and ADA documents,[2,5] reflecting their proven benefits in diabetes, cardiovascular disease, chronic kidney disease, and heart failure. Given that proof of histological benefit on resolution of MASH and fibrosis improvement with dapagliflozin use is recent,[96] SGLT-2 inhibitors have not yet been incorporated into guidelines. Moreover, as standalone MASH-targeted therapies, they still require replication in a Phase 3 trial. However, they are an instrumental part of the holistic management of individuals with CKM syndrome given their extensive benefits, especially in those at high cardiovascular risk. Unlike GLP-1RA, their effects are likely not mediated by weight loss, making them an excellent possibility even in MASLD without increased adiposity. Pioglitazone, although supported by long-standing histologic data and low cost,[97–99] occupies an increasingly marginal role due to concerns about weight gain, edema, fractures, and potential malignancy risk.[100] Nevertheless, given its cardiovascular benefits[101] and liver efficacy that is numerically comparable to GLP-1RA,[97–99] pioglitazone remains a reasonable option in selected patients with diabetes, particularly where access to newer therapies is limited.

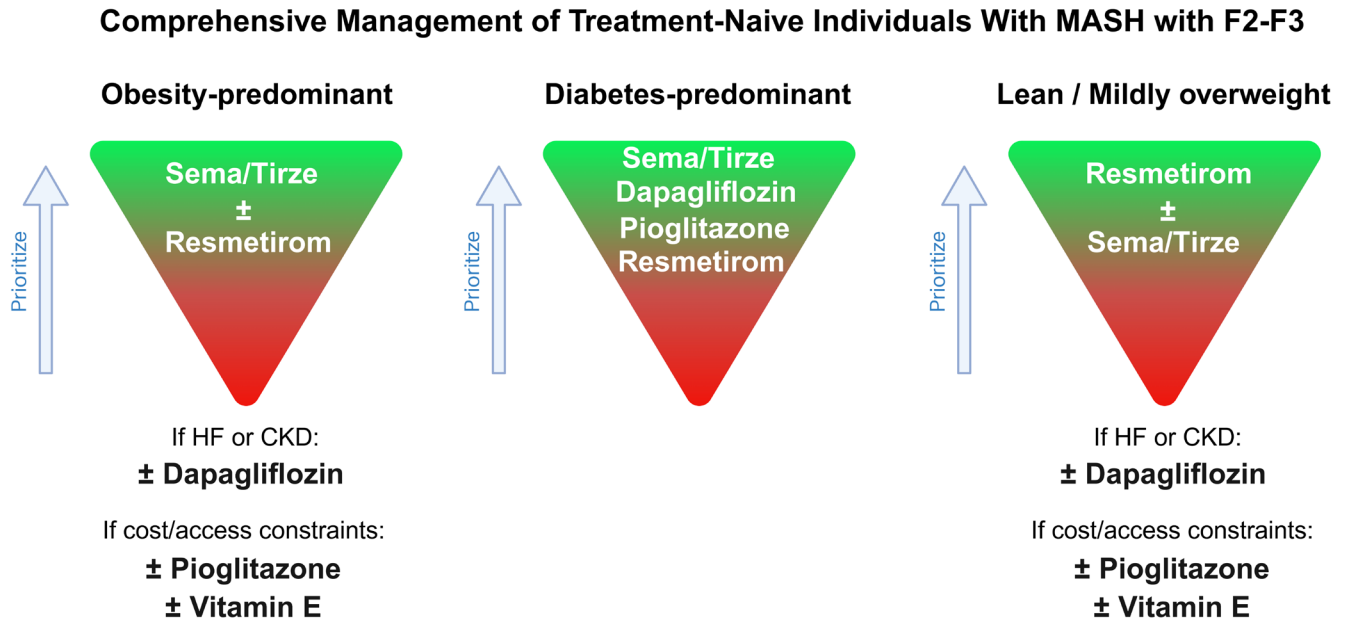

FIGURE 5 | Comprehensive, phenotype-based pharmacologic management of treatment-naïve patients with MASH and F2–F3 fibrosis. CKD, chronic kidney disease; HF, heart failure; MASH, metabolic dysfunction-associated steatohepatitis; Sema, semaglutide; Tirze, tirzepatide.

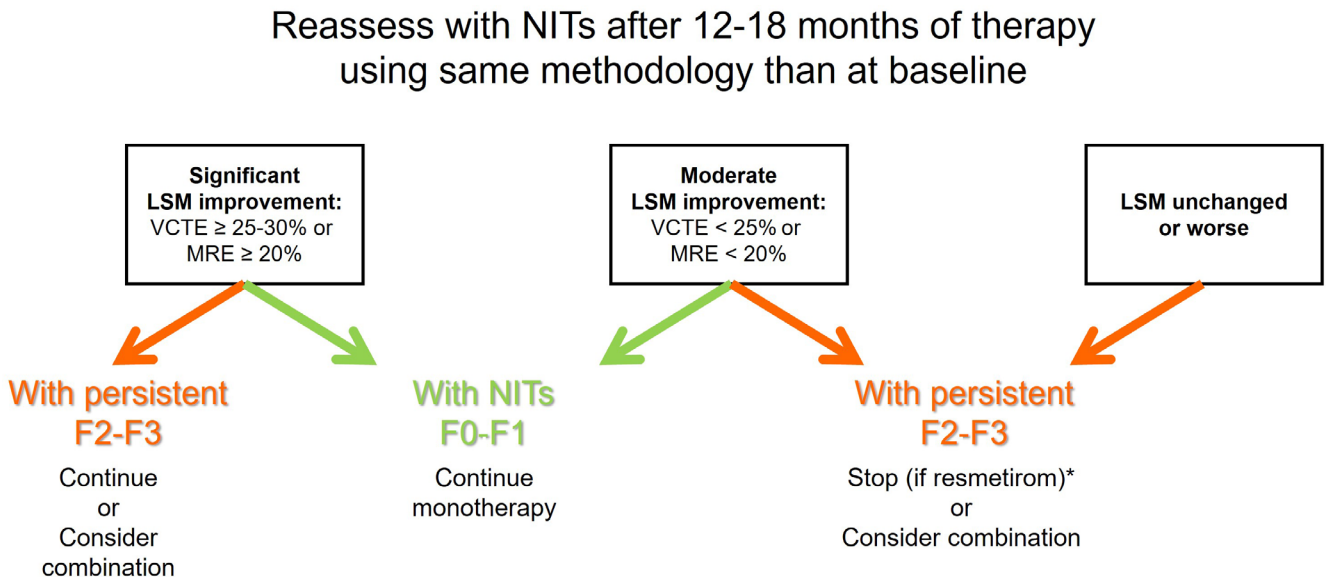

FIGURE 6 | Monitoring treatment response to MASH pharmacotherapy and deciding when to continue, stop, or combine medications based on relative reductions. *Decision to stop GLP-1RA should be done only if no metabolic or weight benefit. LSM, liver stiffness measurement; MRE, magnetic resonance elastography; NIT, noninvasive test; VCTE, vibration-controlled transient elastography; F0–F1, no to mild fibrosis; F2–F3, moderate to advanced fibrosis.

Finally, when MASH is approached in a manner analogous to hypertension, dyslipidemia, or diabetes, it becomes evident that combination therapy will increasingly represent standard practice. Although guidelines generally endorse combining therapies when appropriate, they provide little direction on optimal sequencing beyond a preference for sequential rather than simultaneous initiation. As the field moves towards combination regimens targeting complementary pathways, future guidelines will need to move beyond single-agent paradigms and more explicitly address how to integrate multiple therapies to maximise both hepatic and extrahepatic benefits. In line with this, a simplified algorithm of medication preference based on comorbidities (e.g., obesity, diabetes, chronic kidney disease, or heart failure) is provided in Figure 5. With current evidence, it would be premature to recommend simultaneous initiation of MASH-directed therapies, given the lack of evidence. There is general consensus that monotherapy is preferred with consideration of additional medications based on monitoring after 12–18 months.[6,20]

10.3 | Monitoring response to treatment

After initiation of MASH-directed pharmacotherapy, all current guidance agrees on the need for a monitoring strategy that is noninvasive, longitudinal, and anchored to the same NITs used to establish treatment eligibility, while also incorporating drug-specific safety surveillance. Early follow-up should prioritise assessment of tolerability and safety, particularly during dose escalation for incretin-based therapies and through structured laboratory monitoring for resmetirom. Beyond early safety, efficacy assessment should focus on changes over time rather than absolute thresholds, recognising biological variability and the absence of fully validated on-treatment cutoffs. Repeat fibrosis assessment using the same modality employed at baseline (e.g., VCTE, MRE, or ELF) is recommended to allow meaningful interpretation of trends, with reassessment typically performed at approximately 12 months for resmetirom or semaglutide[20,76] or even longer for semaglutide as recommended by AASLD (72 weeks consistent with the pivotal trial duration).[75]

Across documents, a clinically meaningful response is generally defined as a relative reduction in LSM exceeding expected test variability, commonly cited as a ≥25%–30% decrease in VCTE-derived LSM or a ≥20% decrease in MRE, with supportive changes in liver enzymes, ELF score, or MRI-PDFF when available. Improvement or stabilisation of fibrosis markers supports treatment continuation, whereas consistent worsening should prompt reassessment of adherence, metabolic control, and the possibility of disease progression or cirrhosis. Importantly, none of the guidelines recommend routine repeat liver biopsy for response monitoring; invasive reassessment is reserved for atypical or discordant cases. This flexible, trend-based approach reflects both the limitations of current biomarkers and the evolving therapeutic landscape, emphasising individualised decision-making over rigid stopping rules while maintaining a structured framework for longitudinal care (summarised in Figure 6).

11 | CONCLUSIONS

Contemporary MASLD/MASH guidelines reflect a rapidly advancing field, with increasing reliance on noninvasive tests, expanding pharmacologic options, and growing recognition of the need for multidisciplinary care. Across documents, there is broad agreement on core principles, including targeted screening, prioritisation of cardiometabolic risk reduction, initiation of MASH-directed therapy without mandatory liver biopsy, and longitudinal noninvasive monitoring. Nevertheless, substantial heterogeneity persists in how these principles are operationalised. Differences in target populations for screening,

NIT thresholds, treatment initiation strategies, and monitoring approaches often stem from reliance on trial-derived populations, subjectivity in interpreting emerging evidence, and the rapid pace at which new data are generated relative to guideline update cycles. Future guidelines would benefit from greater transparency regarding areas where evidence remains limited or evolving, clearer integration of comorbidities into therapeutic decision-making, and explicit consideration of cost and access. Moreover, guidance on therapy sequencing and combination strategies will be essential to address the growing burden of MASLD/MASH more effectively.

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