WHITE PAPER

Non-invasive biomarkers: Promising future to reduce patients' burden and accelerate drug development in MASH

A KEY QUESTION

How can non-invasive biomarkers reduce patient burden and accelerate drug development in MASH clinical trials?

KEYWORDS Non-Invasive Biomarkers, MASH Clinical Trials, Liver Biopsy Alternatives, Biomarker Validation, Hepatology

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Metabolic dysfunction-associated steatohepatitis (MASH) is one of the most pressing gaps in hepatology drug development, despite a rising global burden.[1] Therapeutic progress is hindered in part by the absence of non-invasive tools for the diagnosis and monitoring of the disease. Liver biopsy remains the standard for MASH diagnosis and efficacy assessment, but this method creates a significant barrier for patients.[2] The result is often high screen failure rates and slow enrollment in MASH trials.[3] Additionally, the potential sampling variability, subjectivity of the interpretation of the key features (with the consequent inter- and even intra-subject variability) and the need to have two or three experienced central readers poses several challenges in drug development. On Aug. 27, 2025, the FDA accepted a letter of intent for a non-invasive biomarker to be considered a surrogate endpoint reasonably likely (RLSE) to be associated with mortality and liver outcomes. This is the first step for a potential marketing authorization trial achieving accelerated approval with a NI RLSE, great milestone in the field. As biomarker science advances, these non-invasive alternatives have the potential to reduce burden, accelerate recruitment and create a more patient-centered approach to trial design and clinical care.

The current state of MASH therapeutic development

After decades of stalled progress, the MASH therapeutic landscape is beginning to shift. In 2024, the FDA approved the first therapy indicated specifically for patients with non-cirrhotic MASH with moderate to advanced fibrosis.[4] Most recently (Aug. 15, 2025), semaglutide was approved for the same indication, making it the first GLP-1 receptor agonist approved for MASH. These approvals validated the role of histological endpoints in assessing treatment efficacy. However, even as these approvals open the door to new therapeutic options, significant structural challenges remain, particularly around diagnosis, trial design and patient access.

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To date, liver biopsy remains the only method accepted by regulatory authorities as a "reasonably likely surrogate endpoint" (RLSE) that can lead to accelerated (conditional in EMEA) approval for MASH diagnosis.[2] Due to the high unmet medical need and the lack of approved therapies, resolution of MASH by histology and improvement in at least one stage in fibrosis were accepted as RLSE almost 12 years ago and led to the first marketing authorization trial in the indication at that point.[5]

During the last 10 years, dozens of programs were initiated to address the unmet medical need in this population. However, several studies failed at late stage in the development, including the first two: OCALIVA and elafibranor. Liver biopsy has become a hurdle in drug development in MASH, not only because of its invasiveness and unwillingness of patients to participate in a clinical trial requiring at least two liver biopsies in a relatively short time frame (typically within 48 weeks), but also due to the technical challenges.[6] The recent FDA acceptance of a letter of intent for a non-invasive, reasonably likely surrogate endpoint to predict all-cause mortality and liver-related events is a pivotal moment for the field and a critical step toward bringing safe and effective therapies to patients living with MASH.

Why liver biopsy alone falls short

Liver biopsy creates critical barriers across every phase of MASH drug development:

- **For patients:** The procedure is invasive, potentially painful and carries risk of complications;[2] these factors discourage participation, especially in early-phase studies where potential therapeutic benefit is uncertain[7]
- **For investigators (PIs):** Many physicians do not use liver biopsy to confirm diagnosis in clinical practice, and most of them do not request frequent liver biopsies as required in clinical trials. The pre-identification of patients that will ultimately be eligible in a trial is difficult and the high screen failure rate generates frustration for patients and PIs alike. Additionally, misalignment between local and central pathologist readings happens frequently and can demotivate site engagement
- **For sponsors:** High screen failure rates and procedural burden slow enrollment and increase trial costs;[8] requiring biopsy also narrows the pool of eligible sites and patients, undermining scalability. Subjectivity in central reading of biopsy slides creates ambiguity in endpoint analysis and makes it difficult to observe efficacy for some treatments

Limitations like these make it harder to generate the evidence needed to bring therapies to market and harder still to do so efficiently.

Non-invasive biomarkers are gaining ground in MASH trials

The field is still far from reaching a validated biomarker or panel of markers that can lead to final approval in MASH, but it is becoming one of the most anticipated areas of clinical development. A growing number of tools are being explored to diagnose disease, assess progression and evaluate response. A large amount of data has been generated in the last 10 years and a non-invasive algorithm is now recommended in clinical guidelines[9-10] (see Fig. 1). Receiving Fibroscan got an initial approval for noninvasive measurement of shear wave speed in the liver, that may be used as an aid to clinical management of patients with liver disease.[11] Most recently (2023) received an expanded indication to include more comprehensive diagnosis and management of liver disease. Furthermore, ELF (a Siemens panel composed by three extracellular matrix proteins) was approved as a marker of prognosis of progression to liver outcomes in 2021.[12] However, non of these biomarkers was accepted as a potential RLSE. Table 1 summarizes some of the imaging and serum biomarkers currently being explored as diagnosis, disease monitoring and/or prognosis of liver outcomes.

Figure 1(a): AASLD recommended algorithm for the evaluation of patients at risk for or with established MASLD across practice settings.[9]

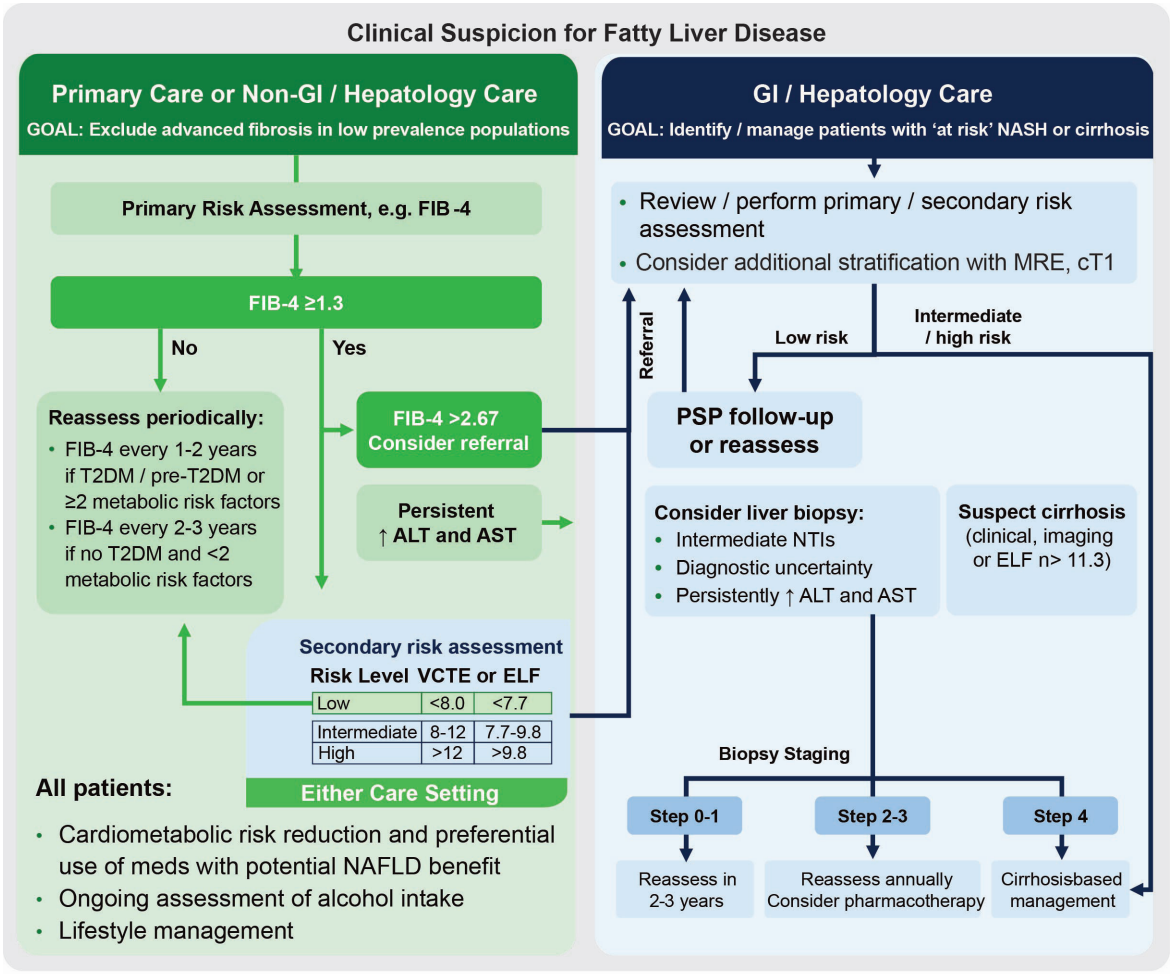

Figure 1(b): EASL–EASD–EASO proposed strategy for non-invasive assessment of the risk of advanced fibrosis and liver-related outcomes in individuals with metabolic risk factors or signs of SLD.[10]

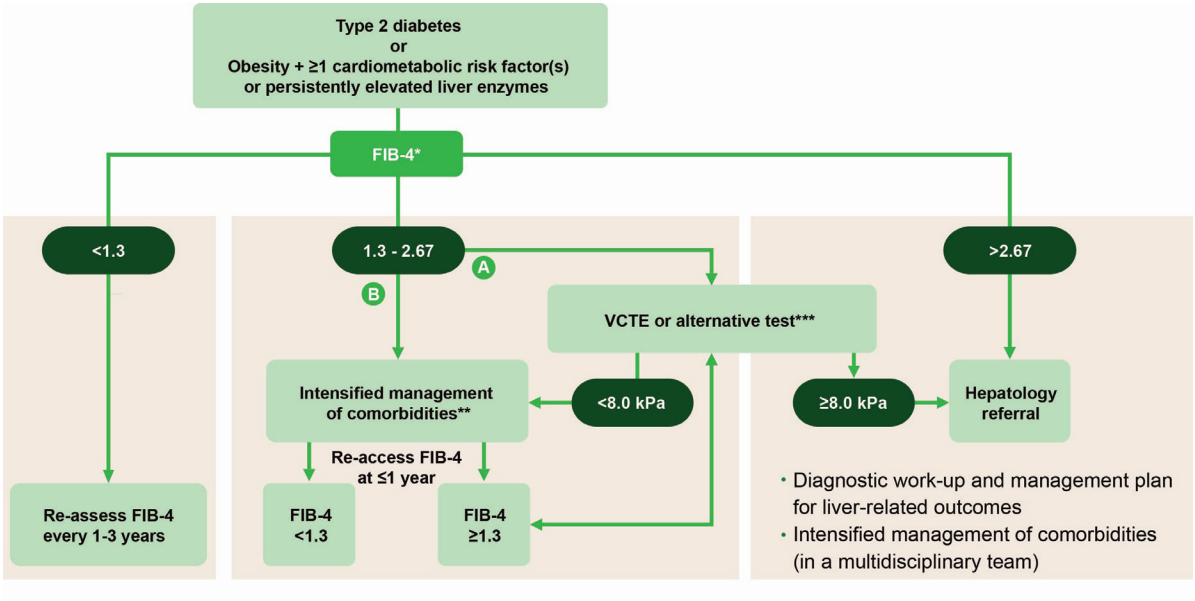

Table 1: Sensitivity and specificity of individual panels for their intended use assessed in the NIMBLE retrospective cohort.[13]

	Sensitivity (%)	Specificity (%)	Youden index	AUROC (95% CI)	Significance (versus ALT or FIB4)
NASH Diagnosis					
ALT	63.2	64.8	0.28	0.678 (0.639, 0.717)	
NIS4	77.7	76.2	0.539	0.832 (0.801, 0.864)	<0.001
OWL	77.3	66.8	Categorical data	AUROC cannot be computed	
NAS ≥4					
ALT	71.1	64.1	0.352	0.726 (0.694, 0.759)	
NIS4	78.1	73.6	0.517	0.815 (0.786, 0.844)	<0.001
At-risk NASH					
ALT	71.1	64.1	0.352	0.726 (0.694, 0.759)	
FIB4	76.4	58.4	0.349	0.704 (0.671, 0.737)	
NIS4	78.1	73.6	0.517	0.815 (0.786, 0.844)	<0.001
Fibrosis stage ≥2					
FIB4	65.6	80.6	0.462	0.798 (0.768, 0.828)	
ELF	71.8	81.5	0.533	0.828 (0.08, 0.857)	0.013
NIS4	82.3	79.9	0.622	0.874 (0.848, 0.899)	<0.001
PROC3	69.8	81	0.507	0.809 (0.779, 0.839)	0.279
FibroMeter VCTE	66.7	86.4	0.53	0.841 (0.796, 0.886)	<0.001
Fibrosis stage ≥3					
FIB4	70.3	72.4	0.427	0.789 (0.758, 0.819)	
ELF	80.8	70.2	0.509	0.835 (0.807, 0.863)	<0.001
NIS4	72.9	74.8	0.476	0.788 (0.757, 0.820)	0.615
PROC3	71.4	71.4	0.428	0.764 (0.732, 0.795)	0.947
FibroMeter VCTE	76.2	81.3	0.575	0.858 (0.814, 0.902)	<0.001
Fibrosis stage 4					
FIB4	84.7	62.9	0.476	0.810 (0.770, 0.850)	
ELF	82.1	73.3	0.555	0.855 (0.818, 0.892)	<0.001
NIS4	78.1	61.4	0.395	0.725 (0.681, 0.760)	1
PROC3	66.2	68.5	0.346	0.728 (0.685, 0.770)	1
FibroMeter VCTE	94.2	70.4	0.646	0.897 (0.843, 0.951)	0.002

Progress beyond traditional tools

Today's most widely used non-invasive tools, such as FIB-4, ELF, FAST and imaging-based vibration-controlled transient elastography, can help stratify risk or exclude advanced fibrosis, but each comes with limitations in precision or accessibility.[2] A recent study has confirmed the repeatability and reproducibility for MR/based biomarkers.[14] In spite of the high sensitivity in quantifying liver stiffness (magnetic resonance elastography) and liver fat MRI-PDFF (proton density fat fraction), these more advanced imaging methods are restricted to research settings due to their limited availability, cost and complexity.[2]

Research is ongoing to expand the role of these tools and advancing next-generation options. Multi-analyte biomarker panels and emerging imaging-based metrics and the combination of each are also being studied for their potential to identify "at-risk" MASH and to monitor changes over time (Tables 1 and 2).[2] These innovations could allow sponsors, at this stage, to optimize patient selection and explore treatment response. Hopefully, the generation of data in studies such as NIMBLE and large-scale Phase III studies will help reach the required validation to be considered as RLSE. This would be a first step before the final validation of one or a combined set of biomarkers is achieved.

Table 2: Performance of biomarkers at fixed sensitivity and specificity assessed in the NIMBLE retrospective cohort.[13]

	When constraining sensitivity to be at least 90%			When constraining specificity to be a least 90%		
	Cutpoint	Specificity (%)	Significance	Cutpoint	Sensitivity (%)	Significance
NASH Diagnosis						
ALT	≥22.0	26.9		≥72.0	26.3	
NIS4	≥0.20	55.9	<0.001	≥0.7	54.2	<0.001
NAS ≥4						
ALT	≥25.0	28.1		≥73.0	32.3	
NIS4	≥0.30	57.8	<0.001	≥0.80	46.2	<0.001
At-risk NASH						
ALT	≥23.0	25.7		≥73.0	27.1	
FIB4	≥0.8	44		≥1.7	46.1	
NIS4	≥0.2	64.4	<0.001	≥0.6	67.2	<0.001
Fibrosis stage ≥2						
FIB4	≥0.8	44		≥1.7	46.1	
NIS4	≥0.2	64.4	<0.001	≥0.6	67.2	<0.001
ELF	≥8.8	48.7	0.013	≥10.0	52.8	0.013
PROC3 (ELISA)	≥12.8	36.3	0.279	≥20.1	46.7	0.279
FibroMeter VCTE	≥0.2	50	<0.001	≥0.6	60.2	<0.001
Fibrosis stage ≥3						
FIB4	≥1.0	43.7		≥2.1	43.6	
NIS4	≥0.3	49.7	0.615	≥0.9	37	0.615
ELF	≥9.2	55.3	<0.001	≥10.4	50.3	<0.001
PROC3	≥13.6	34.6	0.947	≥25.0	42.5	0.947
FibroMeter VCTE	≥0.3	59.6	<0.001	≥0.8	54.2	<0.001
Fibrosis stage 4						
FIB4	≥1.3	50.5		≥2.6	42.3	
NIS4	≥0.5	46	1	≥0.9	23	1
ELF	≥9.7	60.5	<0.001	≥10.9	49	<0.001
PROC3	≥15.1	37.3	1	≥30.6	29.8	1
FibroMeter VCTE	≥0.7	72.5	0.002	≥0.9	66.7	0.002

Getting the first accepted RLSE is the first step. Validation is the next critical step

August 2025 marks an important milestone in drug development in MASH with the first letter of intent accepted. While the promise of biomarkers is clear, their use to lead to final approval depends on rigorous validation. Regulatory agencies have outlined frameworks for evaluating biomarkers as surrogate endpoints, but few tools have yet met the full standard for use in pivotal trials so far.[2]

For sponsors, early engagement in the biomarker validation process can offer a competitive advantage. Biomarkers that meet regulatory expectations could support marketing authorization trials, reduce reliance on biopsy and accelerate timelines. As more therapies enter the MASH pipeline, the ability to integrate well-validated biomarkers into protocol design may become a key differentiator in bringing new treatments to market efficiently.

Patient engagement strengthens biomarker validation

Patients bring life experience that can highlight unmet needs, such as the burden of liver biopsy, and help identify more tolerable, effective trial designs. Their insights have already driven interest in biomarkers and can continue to influence the validation process.

Involving patients earlier and more consistently offers several advantages:

- **Relevance:** Patients help ensure that biomarkers capture the full scope of disease impact, including fatigue, mental health and quality-of-life indicators often missed by traditional endpoints[8]
- **Feasibility:** Patient feedback informs the design of studies that are more inclusive, accessible and reflective of real-world disease management
- **Speed and scalability:** Trials that reduce procedural burden see faster enrollment and improved retention, two critical factors in bringing therapies to market efficiently

Fortrea supports the next generation of MASH trials

As MASH trials move toward a more patient-centric future, non-invasive biomarkers offer a pathway to reduce burden, increase access and accelerate development. Realizing their full potential requires a deep understanding of both liver disease and clinical trial operations.

Fortrea uses regulatory, operational and scientific insights from decades of hepatology research to help sponsors evaluate and implement the most appropriate biomarkers for their study design and mechanism of action with confidence. From early protocol design to site optimization and patient recruitment, we collaborate with you to build and deliver trials that are more efficient, scalable and patient-focused.

Contact us today to explore solutions to integrate non-invasive biomarkers in your MASH research.

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