The Role of Non-Invasive Tests in MASH Drug Development Decision Making

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Background

Liver biopsy remains the gold standard for the assessment of histological endpoints and disease staging in metabolic dysfunction-associated steatohepatitis (MASH) drug development. However, its use in clinical trials is constrained by several well-recognized limitations, including its invasive nature, associated patient burden, sampling variability, and inter-observer variability in histological interpretation. In addition, reliance on biopsy can negatively impact patient recruitment and retention and limits the feasibility of repeated assessments for longitudinal monitoring.

Non-Invasive Tests (NITs) are increasingly integrated into MASH drug development to support proof-of-mechanism (PoM), inform dose selection, enable early efficacy assessment, with the potential to accelerate regulatory decision making. This shift is driven by the desire to mitigate the limitations and challenges of serial liver biopsies. Over time, a broad range of NIT modalities have demonstrated utility in assessing steatosis, inflammation, and fibrosis in patient with MASH. Despite the trends and progress, the relative performance of imaging-based techniques, serum biomarkers, and composite scoring systems across therapeutic classes and mechanisms of action remains incompletely characterized. This is especially the case for critical early decision making in MASH drug development, where robust, sensitive, and reproducible endpoints are critical to inform timely go/no-go decisions.

This analysis aims to evaluate the application and comparative utility of NITs in interventional pharmacology studies of MASLD/MASH therapies, with a focus on their role in early decision-making and their potential to complement or reduce reliance on liver biopsy.

Methods

A targeted literature and trial landscape review was performed using peer-reviewed publications, conference abstracts, ClinicalTrials.gov entries, and publicly available company data over the past 10 years through May 2026. Eligible Studies were interventional clinical trials in MASLD/MASH with a defined mechanism of action and quantifiable NIT endpoints. Observational studies, lifestyle-only interventions, and studies without measurable biomarker or imaging outcomes were excluded.

Fourteen representative trials were selected across key therapeutic classes, including THR-β agonists, FGF analogs, GLP-1–based therapies, FXR agonists, ACC inhibitors, and other metabolic or fibrosis-directed agents. This allowed for a structured cross-trial comparative analysis to characterize the relative performance of NITs across therapeutic classes.

Table 1: Outcomes across serum biomarkers, composite scores, imaging biomarkers

Category	NIT / Biomarker	Pathology	Proof-of-Mechanism (PoM) use	Dose / Exposure–Response	Early Efficacy Signal	Temporal Response	Key Strengths	Limitations
Serum Biomarkers	ALT, AST	Hepatocellular injury	Moderate – reflects liver injury and activity	Moderate (tracks dose-dependent changes)	Supportive, indirect	Rapid (weeks)	Widely available, dynamic, low cost	Limited specificity for MASH inflammation
	CK-18	Apoptosis	Variable – inconsistent signal	Limited	Weak/ inconsistent	Variable	Mechanistic relevance to cell death	Poor standardization, high variability
	PRO-C3	Fibrogenesis	Moderate – early signal anti-fibrotic activity	Limited–moderate	Emerging predictive value	Slow	Specific to collagen formation	Small early changes, less sensitive short-term
Composite Scores	Fibrosis-4 (FIB-4)	Fibrosis risk	Low for PoM	Limited	Low (short-term)	Slow	Simple, widely used, cost effective	Insensitive to short-term change
	Enhanced Liver Fibrosis (ELF) score	Fibrogenesis	Moderate	Limited	Moderate (longer-term)	Slow	Reflects ECM remodeling	Modest early changes
	Fibroscan-AST (FAST) score	Steatosis + inflammation + fibrosis	Limited as PD marker	Limited	Moderate (risk enrichment)	Moderate	Identifies "at-risk MASH" (F2–F3)	Limited validation for dynamic response
Imaging Biomarkers	MRI-PDFF	Hepatic steatosis	High – robust PoM marker	High – detects dose response	Strong predictor (≥30% reduction linked to histologic response)	Rapid (4-12 weeks)	Highly sensitive, reproducible	Focuses on fat, not fibrosis directly
	Magnetic Resonance Elastography (MRE)	Fibrosis (stiffness)	Moderate	Limited (short-term)	Moderate (long-term)	Slow	High sensitivity for fibrosis	Cost, accessibility constraints
	VCTE (FibroScan)	Fibrosis (stiffness)	Low-moderate	Limited	Limited	Slow	Widely available non-invasive, FDA accepted letter intent	Less sensitive than MRE, variability
	Iron-corrected T1 (cT1)	Inflammation + Fibrosis	Moderate	Moderate	Emerging predictive value	Moderate	Monitoring + risk stratification	Less standardized, fewer datasets than MRI-PDFF

Table 2: Recommended NITs across development decision points

Decision	Recommended NIT
PoM	MRI-PDFF
Dose Selection	MRI-PDFF
Early Efficacy	MRI-PDFF + ALT
Fibrosis	PRO-C3 + ELF; imaging adjunct as available
Histology Support	No standalone NIT recommended from study; multimodal assessment may be informative

Results

Detailed outcomes are summarized in Table 1 across serum biomarkers, composite scores, and imaging biomarkers

MRI-PDFF: Most Sensitive Early Signal (Table 2)
- Strong evidence for detecting early pharmacodynamic activity
- Dose–response differentiation across therapeutic classes
- Supported early efficacy assessment
- ≥30% reduction consistently associated w/ subsequent histologic response

Imaging vs. Serum Biomarkers: Imaging-based endpoints outperformed serum biomarkers for
- Short-term studies (Figure 1)
- Dose and exposure–response characterization

Steatosis vs. Fibrosis Endpoints
Steatosis-based measures:
- Showed earlier and more consistent changes
- Highly informative for early-phase decision-making

Fibrosis/stiffness measures (MRE, VCTE):
- Demonstrated slower and less pronounced short-term responsiveness

Role of Fibrogenesis Biomarkers
- ELF, PRO-C3 provided supportive insights and are most valuable when used in combination with imaging biomarkers

Multimodal Approach (integrating imaging, serum biomarkers, composite scores) shows highest value:
- More comprehensive and clinically meaningful assessment
- Greater confidence vs. single endpoints

Composite Scores (Emerging Utility) (i.e. FAST score) found to be useful for:
- Corroborating histologic improvement
- Supporting post hoc analyses

Table 3: Relative utility of NIT modalities aligned to drug development objectives

NIT	Proof of Mechanism	Dose Response	Early Efficacy	Histology Linkage
MRI-PDFF	High	High	High	Moderate
MRE	Low-Moderate	Low	Low	Moderate
VCTE	Low	Low	Low	Moderate
ALT/AST	Moderate	Low	Moderate	Low
PRO-C3	Moderate	Low	Low	Moderate
ELF	Moderate	Low	Low	Moderate

Summary

- **14 representative** interventional trials reviewed
- **MRI-PDFF** demonstrated the most consistent early pharmacodynamic signal across all major therapeutic classes
- **~30%** relative MRI-PDFF reduction repeatedly associated with later histologic response
- **Multimodal NIT** strategies outperformed reliance on any single biomarker

Conclusion

The evaluation of 14 key clinical developments provided several impactful insights for the use of NIT in clinical development of MASH therapies.

The main findings demonstrated that:

- MRI-PDFF emerged as the most consistently responsive NIT for detecting early pharmacodynamic activity, characterizing dose-response relationships, and identifying early efficacy signals, whereas fibrosis-oriented biomarkers and stiffness-based measures exhibited slower and less consistent short-term responsiveness.
- Collectively, the evidence supports a multimodal NIT strategy integrating imaging, serum biomarkers, and composite indices to enhance interpretation of pharmacodynamic effects and early efficacy signals in MASH clinical trials (Table 3).
- Specific studies demonstrated associations between NIT changes and histologic outcomes; however, variability in study design and endpoint reporting highlights the continued need for prospective validation of NIT-biopsy relationships to support future drug-development and regulatory decision-making, and liver biopsy remains the reference standard.
- MRI-PDFF is the most sensitive NIT for detecting early pharmacodynamic effects and dose–response relationships
- Steatosis-based endpoints outperform fibrosis measures in early-phase studies
- Fibrosis and stiffness markers show slower, less consistent short-term responsiveness

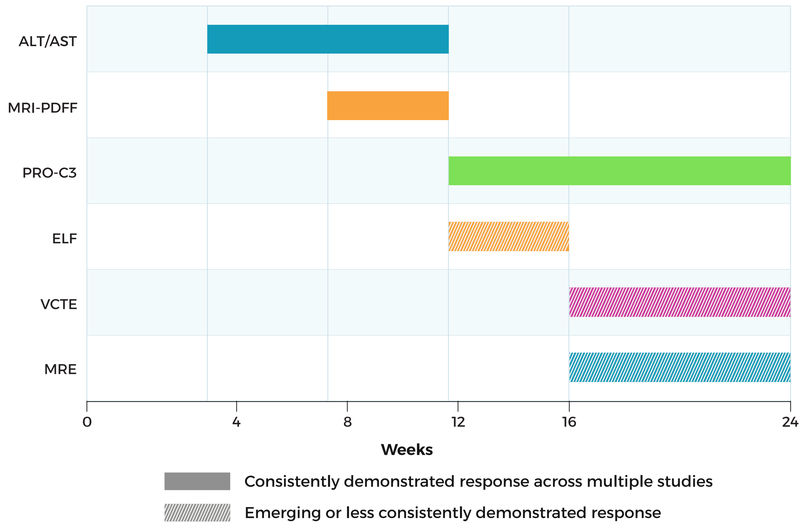
A multimodal approach (imaging + biomarkers + composite scores) provides the most clinically meaningful assessment

NITs show association with histologic outcomes, supporting their role in further development.

Limitations of this analysis:
- Cross-trial variability in design, endpoints, and reporting limited head-to-head comparisons of NIT modalities
- Predominantly short-term data; no long-term validation
- Need for prospective validation of NIT–biopsy relationships

Liver biopsy remains the reference standard for regulatory decision-making

Figure 1: Conceptual Timeline of NIT Response Windows in MASH Trials



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