

What Still Eludes Us in MASH Research?

Written by The Life Science Feed Editorial Team · Published 28 September 2026 · Edited by William Lopes

Metabolic dysfunction-associated steatohepatitis (MASH) represents a significant and growing global health challenge, driving liver-related morbidity and mortality. Despite its prevalence, key aspects of MASH pathophysiology, particularly the mechanisms underlying fibrosis progression, genetic influences, and reliable non-invasive biomarkers, remain poorly understood, complicating diagnosis and therapeutic development.

KEY TAKEAWAYS

- **The Pivot:** Despite advances, our understanding of MASH fibrogenesis, the role of genetics, and reliable non-invasive biomarkers remains incomplete, hindering targeted therapeutic development.
- **The Data:** PNPLA3 and TM6SF2 genetic variants are strongly associated with increased MASH risk, but their penetrance is variable.
- **The Action:** Clinicians should continue to rely on current guidelines for MASH diagnosis and staging, while advocating for and staying informed about emerging research in fibrosis mechanisms, genetic interplay, and novel biomarker development.

Unresolved Mechanisms of Fibrosis

The review highlights the central role of fibrosis in MASH-related morbidity and mortality. However, the precise molecular triggers that drive fibrogenesis remain incompletely understood. We know that hepatic stellate cells (HSCs) are key players in extracellular matrix deposition, but what are the upstream signals that activate them in the context of chronic metabolic stress? Furthermore, the heterogeneity of HSCs and their diverse responses to different stimuli complicate the picture. Are there specific HSC subpopulations that are more amenable to therapeutic intervention? This demands further investigation using single-cell RNA sequencing and spatial transcriptomics to map the cellular landscape of the MASH liver in high resolution.

Current guidelines, such as those from the American Association for the Study of Liver Diseases (AASLD), recommend liver biopsy for staging fibrosis in patients with suspected MASH, but this is invasive and subject to sampling error. Non-invasive markers of fibrosis, such as FibroScan and enhanced liver fibrosis (ELF) score, have limitations in accurately predicting disease progression, particularly in early stages. Therefore, a deeper understanding of the molecular mechanisms driving fibrosis is essential for developing more precise diagnostic and therapeutic strategies.

The Unclear Role of Genetics

Genetic predisposition plays a significant role in MASH susceptibility and progression, with variants in genes such as PNPLA3 and TM6SF2 being strongly associated with increased risk. However, the penetrance of these genetic variants is variable, and many individuals carrying these risk alleles do not develop advanced liver disease. What are the

environmental and epigenetic factors that modulate the impact of these genetic variants? Are there gene-environment interactions that explain the geographical and ethnic disparities in MASH prevalence? Large-scale multi-omics studies are needed to unravel the complex interplay between genetics, environment, and metabolism in MASH.

The European Association for the Study of the Liver (EASL) guidelines acknowledge the role of genetics in MASH but do not currently recommend routine genetic testing. This is partly due to the lack of evidence that genetic information can be used to guide clinical management. However, as our understanding of the genetic architecture of MASH improves, it is likely that genetic testing will become more integrated into clinical practice, particularly for identifying individuals at high risk of disease progression.

Biomarker Limitations in MASH

The development of reliable and non-invasive biomarkers for MASH diagnosis and monitoring remains a major challenge. While liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are commonly used in clinical practice, they lack sensitivity and specificity for detecting MASH. Emerging biomarkers such as cytokeratin-18 (CK-18) fragments and macrophage colony-stimulating factor (M-CSF) show promise, but their clinical utility needs to be validated in larger, prospective studies. Moreover, the lack of standardized assays and reference ranges for these biomarkers limits their widespread adoption.

We need to move beyond simple liver enzyme measurements and embrace more sophisticated approaches, such as metabolomics and proteomics, to identify novel biomarkers that reflect the underlying pathophysiology of MASH. The NIH-funded NASH Clinical Research Network (CRN) has made significant strides in biomarker discovery, but more investment is needed to translate these findings into clinically useful tools.

Choosing the Right Therapeutic Targets

Several therapeutic agents are currently being developed for MASH, targeting various aspects of the disease pathogenesis, including inflammation, fibrosis, and metabolic dysfunction. However, many of these agents have shown limited efficacy in clinical trials, highlighting the need for more rational target selection. Are we targeting the right pathways, and are we using the right endpoints to assess treatment response? Furthermore, the heterogeneity of MASH necessitates a personalized approach to therapy, tailoring treatment to the specific needs of each patient.

The review rightly points out the complex interplay of metabolic, inflammatory, and fibrotic pathways. It's like untangling a Gordian knot. The biggest catch? Many trials focus on surrogate endpoints like ALT reduction or steatosis improvement, without demonstrating a clear impact on long-term outcomes like cirrhosis, liver failure, or hepatocellular carcinoma. Until we see hard clinical endpoints consistently met, skepticism is warranted.

CLINICAL IMPLICATIONS

The persistent gaps in our understanding of MASH fibrosis mechanisms are a stark reminder of the challenges ahead for clinicians. Current reliance on invasive liver biopsy, as recommended by AASLD guidelines, is far from ideal. It is time for industry to invest heavily in non-invasive diagnostic tools that accurately stage fibrosis,

especially in early disease. This would allow for earlier intervention and better patient stratification for clinical trials.

Genetic insights, while acknowledged by EASL, are not yet actionable for patient management. This needs to change. Pharmaceutical companies developing MASH therapies should explore how genetic profiling, perhaps focusing on PNPLA3 and TM6SF2 variants, could identify patients most likely to respond to specific treatments. This precision medicine approach could significantly improve trial success rates and bring effective therapies to market faster.

The limitations of current MASH biomarkers are a critical bottleneck. Relying on liver enzymes like ALT and AST is simply not enough. We need a concerted effort from researchers and diagnostic companies to validate and standardize novel biomarkers, such as CK-18 fragments. Without robust, non-invasive markers, monitoring disease progression and treatment efficacy remains a significant hurdle for both patients and healthcare providers.

Ultimately, the fragmented understanding of MASH pathophysiology hinders the development of truly transformative therapies. Patients deserve better than the limited efficacy seen in many investigational agents. A deeper, collaborative effort across academia, industry, and regulatory bodies is essential to unravel the complex interplay of genetics, metabolism, and fibrosis. This will pave the way for more rational drug design and, crucially, more effective treatments for the millions living with MASH.

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