Worldwide Clinical Trials

Metabolic Dysfunction-Associated Steatohepatitis (MASH)

Global conceptualization of steatohepatitis is evolving from nonalcoholic steatohepatitis (NASH) nomenclature to a broader spectrum of hepatic conditions linked to metabolic disorders, now recognized as metabolic dysfunction-associated steatohepatitis (MASH). This infographic provides an overview of current and predicted MASH prevalence, its influence on regulatory changes, and updated clinical program design considerations. For a complete discussion, read our white paper.

Global MASH prevalence

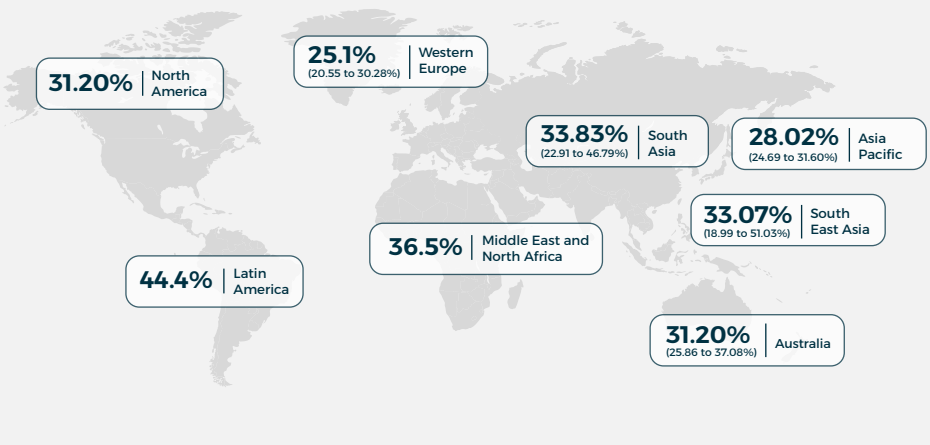
MASH is a global health concern, with regional variations and emerging markets.

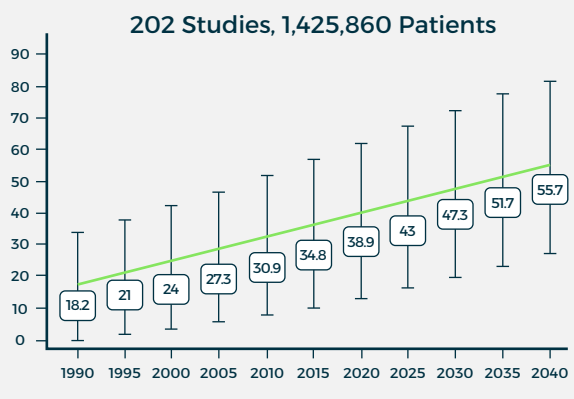
The prevalence is highest in the Americas and Asia.

Genetic factors, such as the PNPLA3 mutation, influence risk, particularly in Hispanic populations.

International patient populations are vital for fully understanding the condition and better informing patient stratification; various populations present symptoms differently, such as the higher proportion of lean MASH cases in Asia.

MASH Global Prevalence

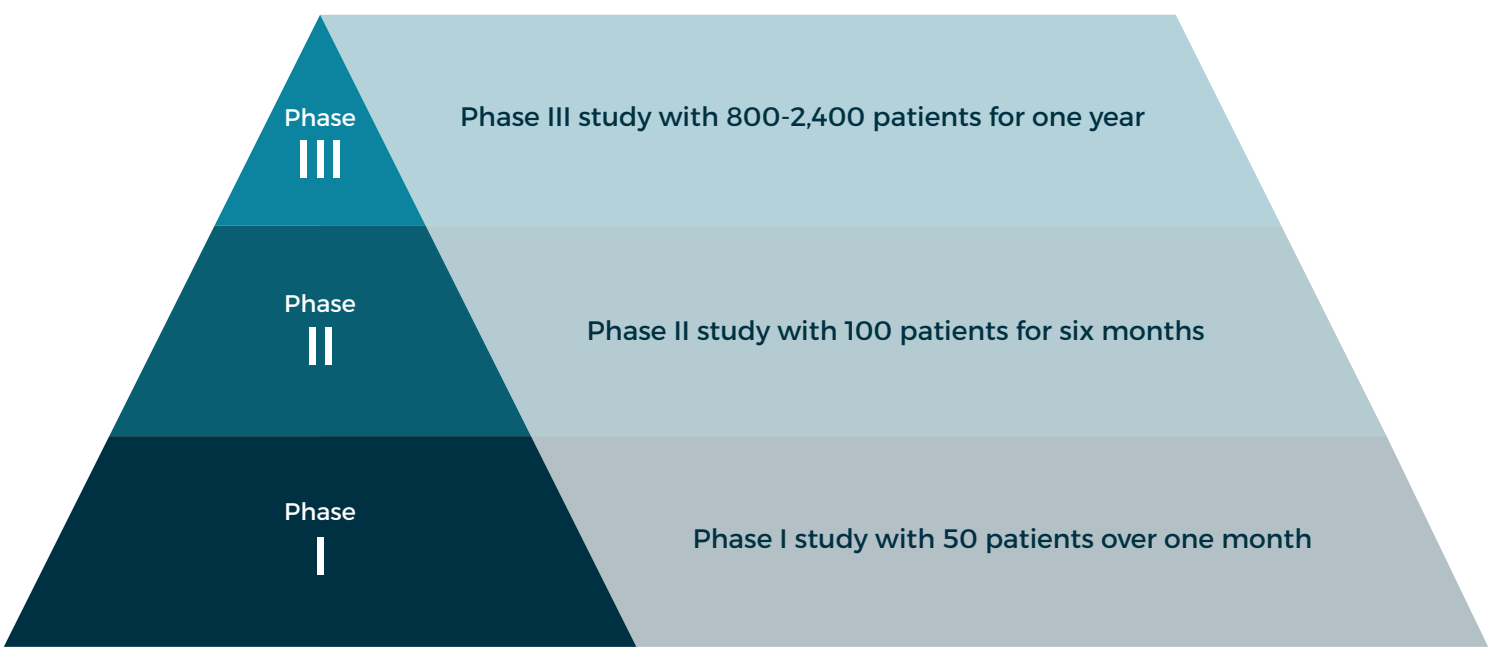




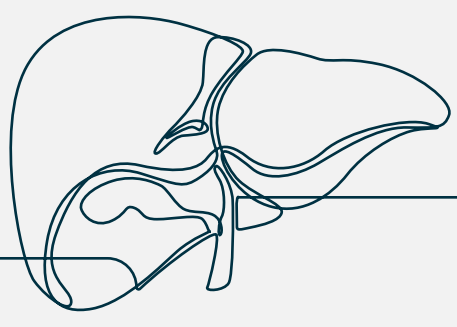
Studies in the space are growing, and the global incidence rate is expected to reach **56% by 2040**

Trial Design Recommendations

Typical MASH program may include:



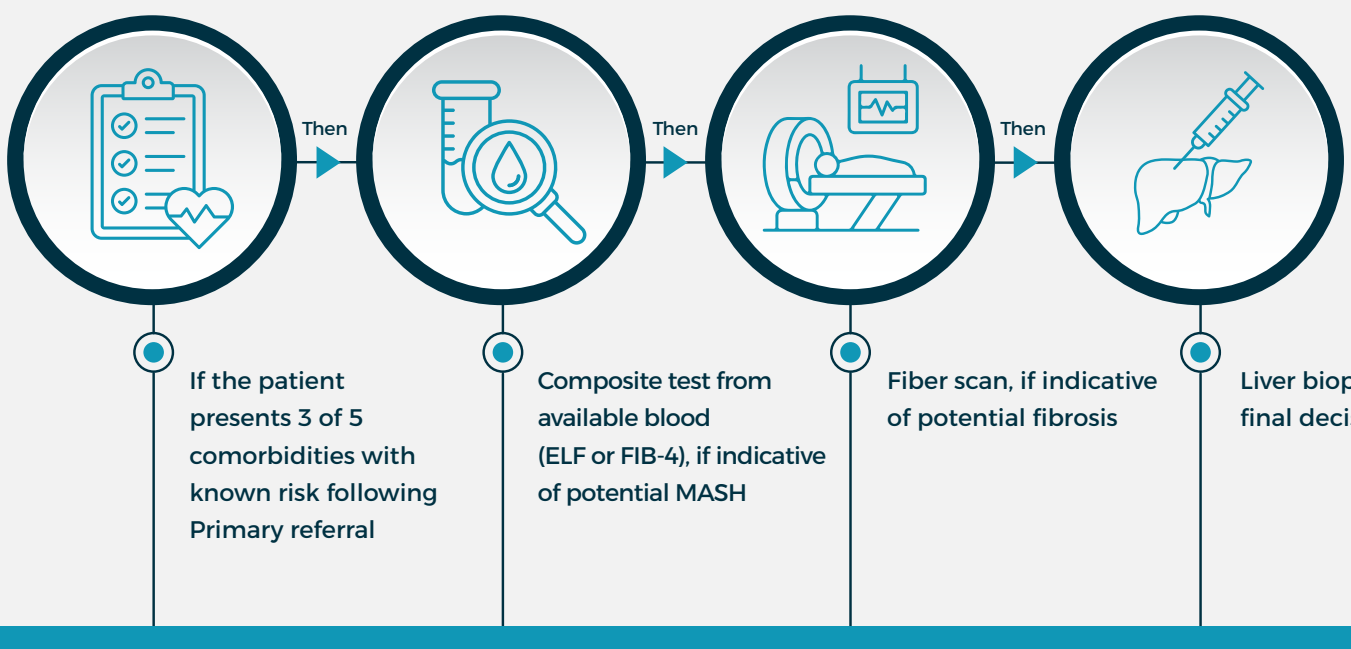
Screening Algorithms to Reduce Screen Fail Rate & Improve the Pathway to Diagnosis



Updated cardiometabolic diagnostic criteria now requires at least one of five select cardiometabolic factors, broadening the eligible patient population and highlighting the comorbidity with other cardiometabolic conditions.

Patients who have three of the five following comorbidities present a significant risk for MASH and should be screened:

- BMI ≥ 25, or WC > 94cm (Male), 80cm (Female), or ethnicity-adjusted correlate
- Fasting glucose ≥ 100 mg/dl, or 2-hour post-load glucose levels ≥ 140 mg/dl, orHbA1c ≥ 5.7%, or type 2 diabetes
- Blood pressure ≥ 130/85 mm/Hg, or taking antihypertensive drug
- Elevated plasma triglycerides (≥ 150 mg/dl)
- Elevated plasma HDL-cholesterol (≥ 40 mg/dl), or actively taking lipid lowering treatment



Reducing Screen Fail Rate

Central reader accuracy is essential for accurate adjudication for screening and treatment effects. Upcoming AI technology may help increase correct patient screening, enrollment, and study outcomes.

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Tale of Two Agencies: FDA & EMA Guidance

Recent FDA Approvals and Ongoing Programs

In 2024 the FDA granted accelerated approval for resmetirom (Rezdiffra™) and pegozafermin, illustrating progress in regulatory adaptations to the changes in the field.

Navigating the EMA

#1 Question

Q: What patient population should we target?

A: Programs should include patients with F 2-4. Endpoints and outcomes may vary depending on the stage of disease.

#2 Question

Q: Should we plan for a single or multi-study Phase III program?
A: Either. However, if taking a multi-study approach, each study should examine different fibrosis stages.

#3 Question

Q: Is a biopsy still required?
A: Yes. Although a sponsor should consider a biomarker and imaging-based algorithm for patient recruitment and management, confirmational biopsy for enrollment and efficacy remains necessary.

#4 Question

Q: Are intermediate endpoints acceptable?

A: Yes, for now. However, they are only acceptable if (1) an unmet need is still present, (2) the sponsor can conclude a positive benefit-risk ratio, and (3) the sponsor is able to provide comprehensive data post-marketing.

#5 Question

Q: What are the primary intermediate endpoints?
A: For non-cirrhotic NASH (F2-3), guidance suggests two composite endpoints as co-primary endpoints.

- NASH resolution and any grade of steatosis, along with the following: no ballooning, only minimal (grade 1) lobular inflammation, and no worsening of the fibrosis stage.
- Improvement of fibrosis by at least one stage without any worsening of NASH (no worsening of ballooning or lobular inflammation, not more than 1 grade increase in steatosis).

#6 Question

Q: What are the long-term efficacy endpoints?
A: For non-cirrhotic NASH, studies should assess long-term efficacy with a single composite endpoint including any of the following: all cause mortality, decompensation of liver disease (with a complete listing), (histology) diagnosis of (progression to) liver disease, and MELD ≥ 15.

Emerging Treatment & the Future

Targeting MASH, or Interrupting the Metabolic Pathway

GLP-1 and cardiovascular-kidney-metabolic studies are emerging as preventative and interventional treatments for metabolic syndrome before progression to MASH.

Changing Clinical and Regulatory Environment: The rapid development of MASH clinical trials and regulatory guidance reflects efforts to address the growing prevalence and complexity of these metabolic disorders.

The future will increasingly emphasize refining patient management strategies, enhancing early detection methods, and adapting trial designs to meet diverse patient needs.

Worldwide Clinical Trials

Worldwide's Cardiovascular Metabolic experts are ready to discuss your next MASLD/MASH trial, work with you in trial design, and offer continued guidance throughout your study.

For more information and resources, please contact us or visit worldwide.com