HTA Readiness for Emerging MASH Pharmacotherapies: Evaluation of Evidence Gaps and Payer Considerations Across the US, UK, France, and Germany

HTA329

Q. XU[1], N. MARTINOLI[1], A. MARCU[1] and M. KANG[2]
[1]Ipsos MORI, London, United Kingdom; [2]Ipsos Pte Ltd, Singapore, Singapore.

INTRODUCTION

- MASH is a progressive liver disease that can lead to cirrhosis, liver-related complications and increased healthcare resource use.
- With the emergence of novel therapies, HTA and reimbursement agencies will require robust evidence demonstrating clinical benefit, long-term outcomes and value for money. This creates a need to understand remaining evidence gaps that may influence future access decisions.

OBJECTIVE

- This review aimed to characterize the current MASH evidence base and identify key evidence gaps relevant to access decision-making across the United States, United Kingdom, France and Germany.
- The poster focuses on how disease burden, diagnostic access, clinical-trial evidence and early HTA or reimbursement signals may shape payer considerations for emerging MASH pharmacotherapies.

METHODS

- A targeted literature review was structured around pre-defined evidence domains: epidemiology, disease burden, unmet need, diagnosis, HTA, regulatory and reimbursement status, economic evidence, patient-reported outcomes and pivotal Phase II/III trials.
- Country-specific evidence from the US, UK, France and Germany was gathered from published sources, consolidated into a shared evidence summary framework and mapped against HTA-relevant decision domains to identify evidence gaps and payer considerations.

RESULTS

Table 1: Disease burden

MASLD affects around a third of adults worldwide[27]. In MASH, fibrosis stage is a key determinant of liver-related outcomes, with non-cirrhotic F2–F3 disease representing an important treatment target[3,6]. Healthcare costs increase with FIB-4 scores, with approximately twice the annual costs reported in the highest versus lowest FIB-4 groups in a US cohort[24]. However, substantial underdiagnosis and gaps in fibrosis risk stratification leave many potentially treatment-eligible patients unidentified, making early and reliable F2–F3 identification a key access challenge[17,23].

Country	Available Epidemiology and Disease Burden Data
UK	Recorded **prevalence in primary care has risen about five-fold in a decade but still reached only 2.42% of patients (283,762 people) in 2022**[17]— far below the roughly 25% expected from population estimates. Among patients who are identified, over about four years 8.6% progress to compensated cirrhosis and 6.5% to decompensated cirrhosis[18].
France	**Metabolic steatotic liver disease affects 16.7% of the population, around 8 million people**[19]. Within French cardio-metabolic care networks, advanced fibrosis was found in about 11% of these patients and was more common in men than in women[20]. Costs are highly concentrated: the highest-cost 10% of patients accounted for 58% of healthcare expenditure in the French MASLD cohort study[21].
Germany	**Metabolic steatohepatitis cases** are projected **to rise 42% (from 3.3 million to 4.7 million between 2016 and 2030)**[22]**.** About **75% of people with the condition remain undiagnosed**[23], pointing to late recognition.
US	An estimated 22 million adults have metabolic steatohepatitis, **of whom nearly 9 million are estimated to have F2–F3 disease**[24]**.** In people without cirrhosis, progression to cirrhosis occurs at a rate of **5.71 per 100 person-years**, and a Fibrosis-4 score above 2.67 is associated with a seven-fold higher risk of death[25].

Table 2: Diagnosis creates the access challenge

Guideline	Step 1 – FIB-4 blood score, rule-out	Step 2 – confirmatory test ELF / VCTE / other NIT	
NICE NG49[1], under revision to 2027	**Step 1 Gaps** • FIB-4 ≥1.3 showed only **57% sensitivity for fibrotic MASLD**, potentially excluding ~43% of cases from second-line testing[15]	**Step 2 Gaps** • Confirmatory NITs remain imperfect for ≥F2 fibrosis; reported sensitivity was ~72% for VCTE at ~8.5 kPa and ~80% for ELF at an optimized ~9.4 threshold[15,16] • ELF thresholds differ by country (10.51 in NICE NG49 vs 9.8 in EASL& AASLD)[1,3,5].	**Additional gaps in Biopsy** • **Limited guideline recommendations** • Low real-world liver biopsy use (28.6% in a UK MASH-coded cohort, 22.5% from a German specialist survey)[18,23]. • Non-invasive tests may misclassify the F2–F3 target relative to histology, so histology retains a confirmatory role.
AFEF 2020[2] + EASL 2024[3]			
DGVS S2k*[4] (2022 version lapsed 9/2026, update pending)			
AASLD[5] / AGA[6]			

German DGVS S2k guideline validity lapsed 30 Sep 2026; revision tendered Oct 2025, updated version pending.

Table 3: Pivotal programs comparability and PICO considerations

- Current MASH trials provide robust evidence of histological efficacy, with emerging data on non-invasive assessments and long-term outcomes.
- However, potential challenges remain for future HTA and EU JCA PICOs due to heterogeneous study populations, limited head-to-head or active-comparator evidence, and the ongoing maturation of patient-relevant outcomes data.
- Prespecified subgroup analyses, indirect treatment comparisons, and outcomes-based evidence will likely remain important to support future evidence submissions.

Trial (Intervention vs Comparator)	Population	N / Duration	Primary endpoint / result	Key secondary endpoints / results	Safety
ESSENCE Semaglutide vs Placebo[11]	Adults ≥18 y; biopsy-confirmed NASH, F2–F3; NAS ≥4	1,197 (2021-2029, results at week 72, 240)	NASH resolution without fibrosis worsening: 62.9% vs 34.3%	Fibrosis improvement without NASH worsening: 36.8% vs 22.4% NASH resolution + fibrosis improvement: 32.7% vs 16.1%	GI AEs
MAESTRO-NASH Resmetirom vs Placebo[12]	Adults; biopsy-confirmed NASH, F1B–F3	966 (2019-2028, results at week 52, 54 months)	NASH resolution without fibrosis worsening: 25.9% / 29.9% vs 9.7%	≥1-stage fibrosis improvement without NAS worsening: 24.2% / 25.9% vs 14.2% LDL-C change at week 24: -13.6% / -16.3% vs +0.1%	Diarrhea, nausea
SYNERGY-NASH (Ph 2)[13] **Tirzepatide vs Placebo**	Biopsy-confirmed MASH, F2–F3	190 (2019-2024, results at week 52)	MASH resolution without fibrosis worsening: 44% / 56% / 62% vs 10%	≥1-stage fibrosis improvement without MASH worsening: 55% / 51% / 51% vs 30%	GI AEs
SYNERGY-Outcomes[14] **Tirzepatide; retatrutide vs Placebo**	Adults ≥18 y; high-risk MASLD; liver fat ≥8%, ELF 9–10.8, VCTE-LSM 10–<20 kPa; no biopsy required	4,500 (2025-2032, results at week 102 to 224)	Time to first MALO (cirrhosis, portal-hypertension complications, MELD progression, LT or death)	At week 104: ΔELF, ΔVCTE-LSM and %Δliver fat; other endpoints include cirrhosis progression, AST/ALT, weight and MACE-3	No results yet

Abbreviations: AE, adverse event; ELF, enhanced liver fibrosis; GI, gastrointestinal; LDL-C, low-density lipoprotein cholesterol; LSM, liver stiffness measurement; LT, liver transplantation; MACE-3, 3-point major adverse cardiovascular events; MALO, major adverse liver outcomes; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; MELD, Model for End-stage Liver Disease; NAS, NAFLD activity score; NASH, non-alcoholic steatohepatitis; VCTE, vibration-controlled transient elastography; FIB-4, Fibrosis-4 Index; F2 / F3 / F4, Fibrosis stages: F2 = significant fibrosis; F3 = advanced fibrosis; F4 = cirrhosis;

Table 4. Summary of Priority evidence gaps for HTA readiness and strategic implications

Topic	HTA Challenges	Strategic Implications
F2-F3 identification	Pivotal trials used liver biopsies for patient inclusion and outcomes while real-world clinical practice relies on NIT.	Bridging analyses or RWE demonstrating NIT accuracy/alignment with biopsy to justify real-world eligibility.
Surrogate Validation	Pivotal trials primary endpoints were short-term evaluating histological surrogates rather than overall survival, decompensated cirrhosis, or liver transplant avoidance.	Perform longitudinal extrapolation modeling linking surrogate histologic responses to long-term reductions in liver-related events. Leverage ongoing metabolic outcome data to support broader benefits.
Progression Avoidance	Some long-term outcome trials extend beyond 2030, HTA bodies cite uncertainty regarding true long-term disease progression avoidance.	Utilize early conditional access or coverage with evidence development while long-term outcome trials mature. Use natural history and health economic modeling to bridge short-term trial endpoints to long-term progression avoidance.
Quality of Life	Difficult to capture short-term HRQoL improvements in asymptomatic F2-F3 patients, making cost-effectiveness harder to demonstrate.	Collect prospective patient-reported outcomes and utilities sensitive to early MASH symptoms and comorbidity burden. Highlight HRQoL preservation by preventing progression to end-stage liver disease and liver transplantation.
Resource Use	High-cost MASH tracks closely with cardiovascular and metabolic comorbidities, making it difficult to distinguish MASH-attributable healthcare resource use from broader multimorbidity-related costs and creating uncertainty in economic value assessment.	Generate country-specific budget impact and cost-consequence models showing offset of high-cost advanced liver and cardiovascular complications. Focus value stories on high-risk, high-cost subgroups to maximize cost-effectiveness.
Comparative Value	Pivotal trials evaluated a single agent vs placebo over different time frame. HTA bodies considered Semaglutide/Resmetirom as comparator/emerging standard of care or background therapy.	Conduct NMAs or ITCs comparing these therapies against active background therapy. Tailor HTA submissions by region.

CONCLUSIONS

The MASH evidence base is rapidly evolving, but HTA readiness remains constrained by diagnostic fragmentation and uncertainty linking short-term histological or metabolic endpoints to long-term patient-relevant outcomes. Future evidence generation should prioritize reliable identification of eligible F2–F3 patients, validation of surrogate endpoints, prevention or delay of disease progression, quality-of-life and healthcare resource impact, and comparative effectiveness and value across liver-directed and metabolic treatment strategies.

CONTACT INFORMATION

Qin Xu, MPP
Ipsos MORI, London, United Kingdom
Celina.xu@ipsos.com

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