White Paper

Emerging from the Shadows: A New Era for NASH

Opportunities and challenges as innovators race to the market

MARKUS GORES, Vice President, EMEA Thought Leadership, IQVIA
KIRSTIE SCOTT, Senior Consultant, EMEA Thought Leadership, IQVIA

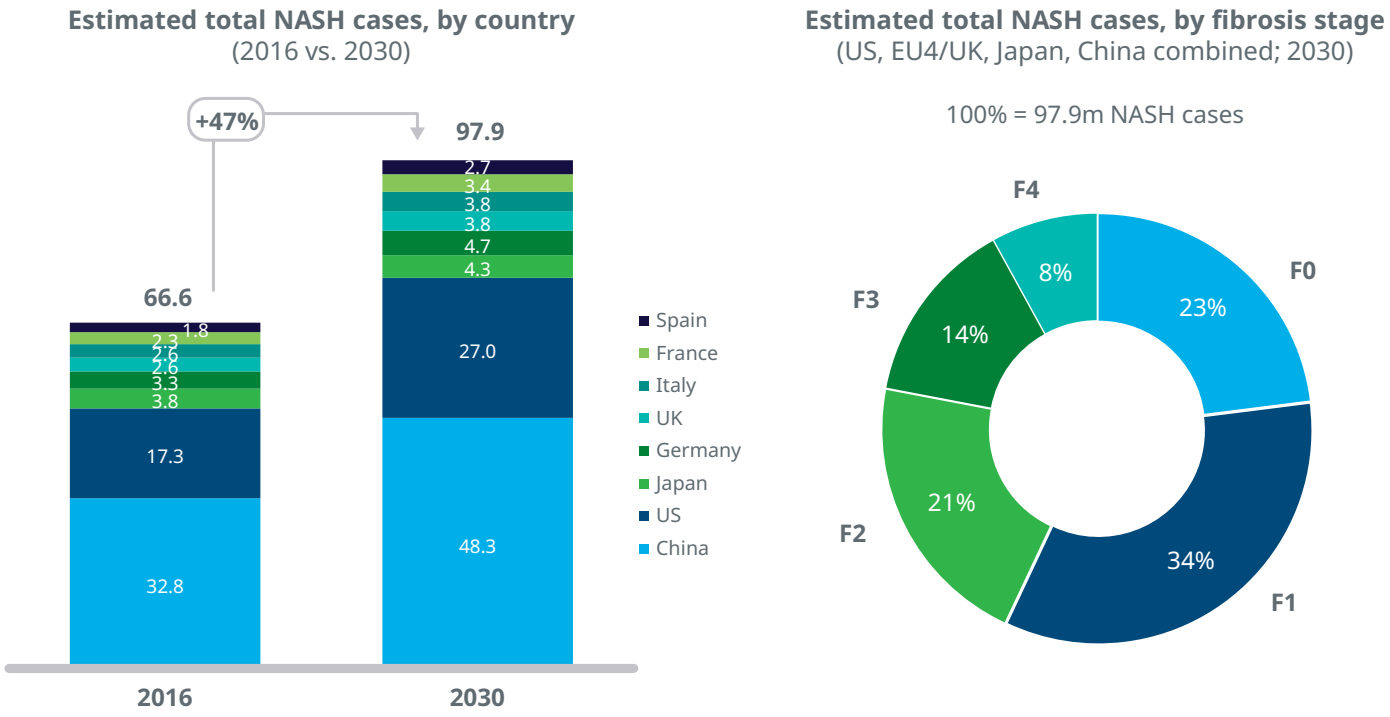
Table of contents

Introduction

Non-alcoholic fatty liver disease (NAFLD), including its progressive form non-alcoholic steatohepatitis (NASH), has largely been a silent epidemic in the shadows of more prominent diseases which have captured the public's imagination and healthcare resources, such as cancer or Alzheimer's.

This is in stark contrast to the significant global burden of disease that NAFLD, including NASH, represents as the most common chronic liver disease worldwide and the leading cause of liver-related morbidity and mortality. NAFLD is estimated to affect about 25% of the general population, while prevalence estimates for NASH vary between 1.5% and 6.5%.[1] By 2030, across 8 countries, including the US, EU4/UK, Japan and China, the total number of NASH cases has been estimated to reach 98 million, an increase of 47% since 2016, driven by factors such as growing prevalence of obesity, diabetes and an aging population (see Figure 1).[2]

Figure 1: NASH represents a large and growing public health burden



Source: Estes C, Anstee QM, Arias-Loste MT, et al. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016–2030. Journal of Hepatology. 2018;69(4):896-904

Unmet need remains high, despite decades of R&D efforts by the pharmaceutical industry focused on NASH, which have yet to deliver a disease-specific therapy to the market, in a field that has been beset by high profile failures, delays and disappointments. However, we are at the cusp of a new era of hope for NASH patients, as several late-stage assets race to cross the regulatory finish line.

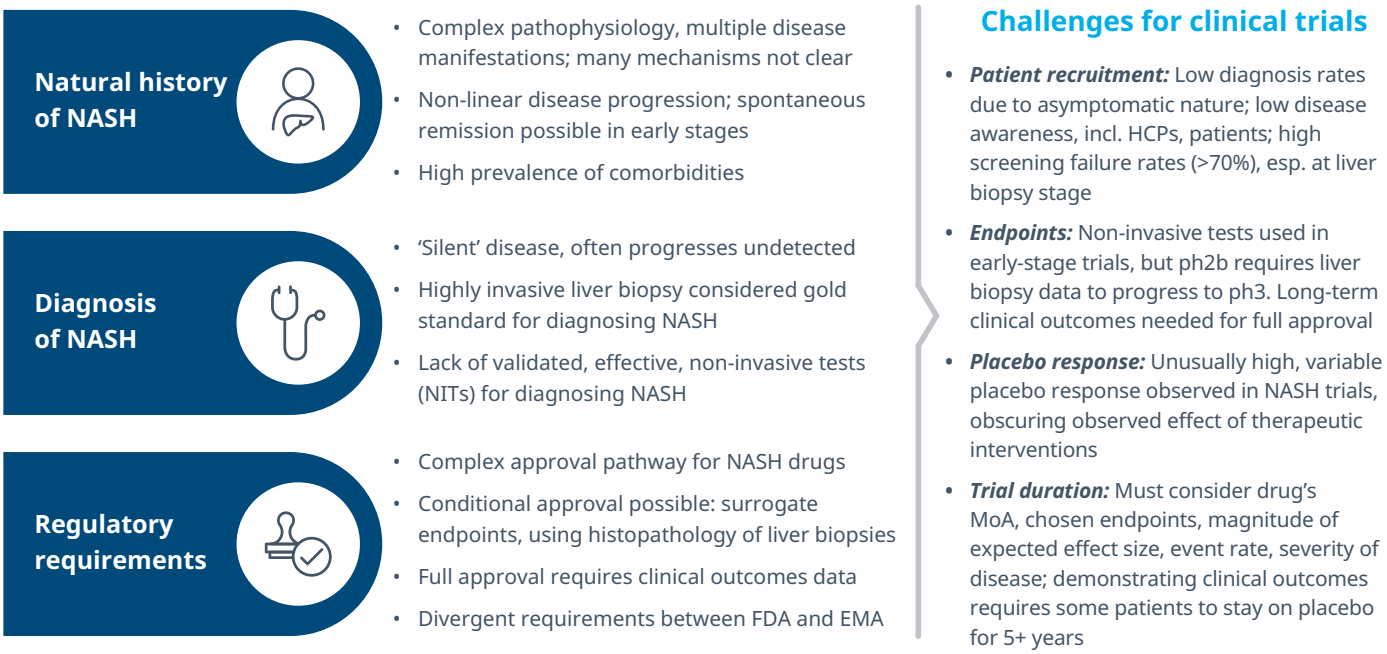
In this white paper, we will explore the latest trends in the NASH innovation landscape and the outlook for the commercial opportunity in NASH. Furthermore, we will identify critical success factors for innovators to overcome barriers in both development and commercialisation to ensure approval, access and the adoption of novel NASH therapies to benefit all eligible patients desperately waiting for much needed treatments.

An uphill struggle: Barriers to NASH innovation

The persistent, high unmet need in NASH has attracted increasing interest from biotech and big pharma companies alike. However, despite significant investment in R&D to find novel, disease-specific therapies for NASH, many attempts were hit by major setbacks or even ended in high profile failures.

All innovators tackling NASH face a daunting combination of scientific/clinical, regulatory and practical barriers (see Figure 2).

Figure 2: An uphill struggle — barriers to NASH innovation



Source: IQVIA EMEA Thought Leadership

NATURAL HISTORY OF NASH

The natural history of NASH is complex, involving multiple pathogenetic mechanisms and disease manifestations. NASH is the progressive form of NAFLD, which itself spans a wide spectrum of histological features ranging from simple steatosis, characterised by excessive hepatic fat accumulation, to non-alcoholic steatohepatitis (NASH), associated with varying degrees of ballooning of hepatocytes, lobular inflammation, and/or different fibrosis stages, which may progress to liver cirrhosis and ultimately hepatocellular carcinoma.[3]

Despite advances in understanding the mechanisms responsible for NAFLD, e.g., the role of insulin resistance in fat accumulation, those associated with disease progression are less clear.[4] The complex pathophysiology of NASH implies a large number of potential drug targets and mechanisms of action for innovators to explore, while also making the development and validation of diagnostic tests more difficult.

To complicate matters further, disease progression is non-linear, and in the early stages of NASH can be bi-directional, i.e., both disease progression and spontaneous remission can occur, often resulting in high placebo response and thus confounding the effect of pharmacotherapeutic interventions being investigated in clinical studies.[5]

The prevalence of comorbidities associated with NASH is high, including obesity, type 2 diabetes and cardiovascular disease,[6] which complicates diagnosis and stratification of patients, e.g., when defining coherent, meaningful patient populations for clinical trials, since the presence of comorbidities may affect the therapeutic response.

DIAGNOSIS

NASH is commonly described as an asymptomatic disease. It may present with symptoms such as tiredness or developing pain in the upper right side of the abdomen,[7] however, their non-specific nature means the disease often progresses undetected.

There are currently no validated, effective, non-invasive diagnostic tests (NITs) for the diagnosis of NASH. Highly invasive liver biopsy is considered the gold standard for NASH diagnosis despite its numerous challenges and limitations, e.g., accuracy due to significant variability between pathologists' interpretations; providing only a small snapshot of the liver, at one point in time, for a progressive disease; its burden on patients, patient safety and cost.

Given the pivotal role that accurate, effective and scalable diagnostic tests play in the success of clinical trials and in enabling the wide adoption of novel NASH therapies in routine medical practice, we will elaborate in more detail on the latest trends and the future outlook for NASH diagnostics in a dedicated deep dive section below.

REGULATORY REQUIREMENTS

The regulatory approval pathway for NASH drugs is complex, with divergent requirements between the FDA and EMA adding further challenges for innovators.

For full regulatory approval, NASH drug candidates must demonstrate the ability to prevent or delay disease progression, as measured by a composite endpoint including progression to cirrhosis, liver-related outcome events (ascites, hepatic encephalopathy, upper gastrointestinal bleeding) and all-cause death.[8]

However, recognising the high unmet need in NASH, regulators have provided a pathway for conditional approval based on histopathological assessments of liver biopsies as a surrogate endpoint, while generation of clinical outcomes data must be in progress. Specifically, for conditional approval the FDA accepts as primary endpoint either the improvement of ≥1 stage in fibrosis with no worsening of NASH or improvement in NASH resolution with no worsening of fibrosis.[9,10] The EMA, on the other hand, requires that both endpoints are met, i.e., resolution of NASH and improvement in fibrosis.[11]

CLINICAL TRIALS: IMPLICATIONS AND PRACTICAL CHALLENGES

These NASH-specific complexities have profound implications for sponsors of clinical trials investigating NASH drug candidates,[12] including:

- *Patient recruitment:* Given NASH is asymptomatic, or at best presents with non-specific symptoms until its later stages, few patients are aware of their condition, which makes patient recruitment very difficult. Limited awareness of NASH among HCPs, especially primary care physicians, also contributes to low diagnosis rates.

  Furthermore, precise stratification is critical to ensure inclusion of patients who will benefit and/or in whom the natural history can be improved. Eligibility criteria for NASH clinical trials are usually sequentially assessed, including medical history, co-morbidities, laboratory values (e.g., AST, HbA1c, eGFR, platelets, bilirubin), imaging and liver biopsy, with the latter representing the main hurdle in the screening process. Overall screening failure rates of >70% are not uncommon,[13] making timely patient enrolment very challenging.

  Early-stage trials often choose to enrol patients considered highly likely of having NASH, due to the presence of multiple risk factors, e.g., fatty liver, type 2 diabetes or metabolic syndrome, but without biopsy confirmation. While such patients are easier and faster to recruit, they are likely to be different from the patient population in focus of late-phase trials, creating a disconnect and possibly increasing the risk of late-stage failure

Overall screening failure rates of >70% are not uncommon, making timely patient enrolment very challenging for NASH trials

- *Endpoints:* For pre-cirrhotic patients, resolution of NASH (with no worsening of fibrosis) or improvement of fibrosis (with no further deterioration of NASH) are the key endpoints to achieve. In the cirrhotic population, the main goal is avoiding decompensated cirrhosis, hepatocellular carcinoma, liver transplant and mortality.

  While non-invasive tests (NITs) are increasingly used in many early stage trials until phase 2a, liver biopsy data — with all the challenges and limitations elaborated on earlier — are required in phase 2b to inform progression to phase 3. At the time of conditional approval, assessment of clinical outcomes must also already be underway, including all-cause mortality, progression to cirrhosis and liver events.

  Beyond liver-related endpoints, multiple other factors need to be assessed to determine the net benefit of a new therapy, e.g., its effect on cardiovascular risk factors as major confounders

- *Placebo response:* Mitigating unusually high and variable placebo response observed in NASH trials is critical for accurately assessing drug efficacy.[14] For example, this may require weight stabilisation before liver biopsy, verification of alcohol consumption, controlling for other lifestyle factors, e.g., diet, exercise, which may be impacted by structured programmes advised as 'first-line treatment' for NAFLD/NASH, or exploring non-invasive tests (NITs) to overcome the well-documented inconsistency in pathologists' readings of liver biopsies

- *Trial duration:* Determining the appropriate trial duration must consider many factors, e.g., a drug's mechanism of action, chosen endpoints, magnitude of expected effect size or severity of disease (e.g., F2-F3 versus cirrhosis). For example, in NASH cirrhosis trials, the histological endpoint of fibrosis regression by one stage without worsening of NASH may be challenging to achieve in the typical duration of phase 2b trials.

  For full regulatory approval clinical outcomes must be demonstrated, including all-cause mortality, progression to cirrhosis and liver events. This requires committing resources for longer term monitoring and follow-up, while the uncertainty of removal from the market remains should a conditionally approved product fail its confirmatory trial(s). It also means some patients will need to agree to stay on placebo for 5+ years, even when treatments become available

Given the complexities of NASH, there is a role for adaptive trial designs, for example, using interim analyses to refine target populations to demonstrate better efficacy in a patient sub-set of high-responders.

Equally, ongoing innovation in diagnostics will eventually help address many challenges faced in NASH trials, e.g., new, validated biomarkers for non-invasive tests to diagnose NASH or to assess fibrosis stage. While such non-invasive tests (NITs) still need to reach maturity, sponsors should continue to embed experimental NITs in their trials, alongside established techniques, to gain valuable information about their utility and validity. This will help accelerate the innovation of novel diagnostics, with the ultimate goal of being able to measure robust endpoints that are not dependent on liver biopsies.

Innovative approaches are needed to improve and speed up patient enrolment, given the low diagnosis rates for NASH. For example, use of real world data, combined with education activities aimed at both patients and HCPs, can help identify pools of potential patients suitable for NASH trials, e.g., locating such patients in the healthcare system via general practitioners or community-based specialist, followed by confirmatory diagnosis using non-invasive tests.[15]

Innovation landscape for NASH

NASH has enjoyed considerable interest from the biopharmaceutical industry, resulting in a rich pipeline of 80 clinical-stage assets, as at December 2023, which target a wide range of over 40 mechanisms of action (MoA), (see Figure 3).

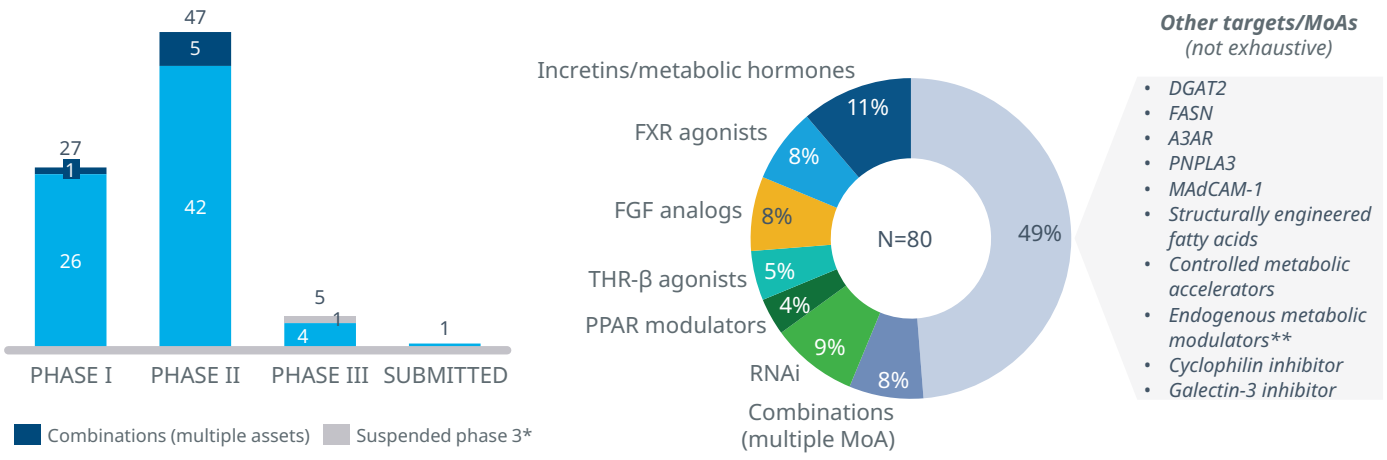
Drug candidates typically target a specific mechanism within the complex pathogenesis of NASH. Given the wide variation of NASH phenotypes between patients, a single drug is unlikely to work for every patient or address all manifestations of NASH. Consequently, there will be room for multiple MoAs, likely as part of combination therapies that are targeted at the best responding sub-populations.

Mechanisms of action in focus

The top 5 most investigated, discrete MoAs include metabolic hormones, such as GLP-1 or GIP receptor agonists, farnesoid X receptor (FXR) agonists, fibroblast growth factor (FGF) analogues, peroxisome proliferator-activated receptors (PPAR) modulators and thyroid hormone receptor-β (THR-β) agonist. Collectively, these top 5 MoAs represent 35% of the clinical-stage NASH pipeline.

Among the new generation of potent, incretin-based anti-obesity therapies, several candidates are being studied in NASH, e.g., semaglutide, tirzepatide or survodutide, because weight loss of >10% can lead to improved NASH outcomes and may reverse early-stage fibrosis in some patients.[16] GLP-1 receptor agonists represent a particularly promising MoA as they target insulin resistance, a key mechanism behind fat accumulation in the liver and a major issue for NASH patients.

Figure 3: The clinical-stage NASH pipeline is rich and maturing



*Ph3 ARMOR trial is suspended while Galmed reformulates Aramchol; **Mixture of amino acids designed to target metabolism, inflammation and fibrosis in NASH

Source: IQVIA EMEA Thought Leadership; IQVIA Pipeline Link; secondary research; Clinicaltrials.gov;

Other noteworthy MoAs include RNA interference, which account for 9% of the clinical-stage pipeline. These therapies are an example of a growing trend in personalised medicine, e.g., to target single-nucleotide polymorphisms in PNPLA3, GKCR, TM6SF2 or HSD17B13 that have been associated with NASH development or its progression.[17]

Some early-stage studies investigate cutting-edge advanced therapy medicinal products (ATMPs) for NASH, e.g., regenerative cell therapies to repair damage, reduce scarring and restore biliary structure and function.[18] Other interesting early-stage efforts focus on the potential of microbiome-based therapeutics.[19]

Given the complex pathophysiology of NASH, the future will likely belong to combination therapies which target different disease pathways and manifestations, e.g., metabolic drivers and comorbidities, inflammation, fibrosis or lipotoxicity and cell death. Complementary or synergistic MoAs should lead to better efficacy, which in turn may improve tolerability if dosing and administration frequency could be reduced.

The future will likely belong to combination therapies targeting different disease pathways and manifestations of NASH

While combinations of multiple MoAs currently account for only 8% of the clinical-stage NASH pipeline, we expect their prominence to increase significantly, especially as more of the over 40 MoAs being investigated emerge as validated therapeutic approaches.

Pipeline momentum

To date, no NASH drug has made it to the market, following a spate of high-profile failures, including erstwhile frontrunner, Intercept's obeticholic acid, being rejected by the FDA in June 2023 prior to the company's acquisition by Alfasigma three months later.[20]

Conversely, Madrigal's selective thyroid hormone receptor-β agonist resmetirom will most likely become the first ever NASH-specific drug to be approved in 2024.

In total, there are six late-stage assets in phase 3 development which are being studied across different NAFLD/NASH sub-populations (see Figure 4):

Figure 4: Several innovators race to cross the regulatory finish line in NASH

Product (Company)	NAFLD	NASH (F1)	NASH (F2)	NASH (F3)	NASH (Cirrhosis / F4)	Other notable, ongoing trials
Resmetirom (Madrigal)	MAESTRO-NAFLD-OLE, (ph3, safety study)		MAESTRO-NASH, (ph3, rolling data submission to FDA)		MAESTRO-NASH-OUTCOMES, (ph3)	
Semaglutide (Novo Nordisk)	NAFLD HEROES, (ph2)		ESSENCE, (ph3)		WAYFIND*, (ph2, sema/cilofexor/ firsocostat combination)	Ph2 combination trial (sema./ NNC0194 0499)
Lanifibranor (Inventiva)			NATiV3, (ph3)			LEGEND, (ph2 lanif./empagliflozin combo; NASH/T2D)
Belapactin (Galectin)					NAVIGATE, (ph2/3**)	
Aramchol (Galmed)		ARMOR, (ph3, suspended***)				
Oltipraz (PharmaKing)	Phase 3**** (small trial, S. Korea only)					

*Partnered with Gilead; **In prevention of oesophageal varices in NASH cirrhosis;
***Ph3 ARMOR trial is suspended while Galmed reformulates Aramchol;
****Not sufficient for approval in US/Europe
Source: IQVIA EMEA Thought Leadership; secondary research; clinicaltrials.gov

FDA priority review granted; review date: 14 March 2024

- **Resmetirom** (Madrigal): In December 2022, oral THR-β agonist resmetirom met its co-primary endpoints, NASH resolution and fibrosis improvement, in the pivotal MAESTRO NASH phase 3 trial, which focused on non-cirrhotic NASH patients with moderate-to-advanced fibrosis (F2-F3). This trial formed the basis of a rolling submission to the FDA seeking approval, which Madrigal initiated in July 2023.[21,22]

  Two additional phase 3 trials are underway: (i) MAESTRO-NASH-OUTCOMES, which investigates resmetirom in NASH patients with compensated cirrhosis;[23] (ii) MAESTRO-NAFLD-Open-Label-Extension, which evaluates safety and tolerability of resmetirom in NAFLD patients. Of note, this trial uses non-invasive imaging and biomarkers to assess secondary endpoints of hepatic fat fraction at different time points.[24]

- **Lanifibranor** (Inventiva): Ongoing, pivotal phase 3 trial NATiV3 evaluates efficacy and safety of pan-PPAR agonist lanifibranor in non-cirrhotic NASH patients with moderate-to-advanced fibrosis (F2-F3). Top-line data are expected in 2024.[25] Of note, lanifibranor is the only drug among phase 3 assets being evaluated against a dual efficacy endpoint of NASH resolution and fibrosis improvement.

  Additionally, Inventiva is investigating lanifibranor in patients with type 2 diabetes and NAFLD. In June 2023, a phase 2 study in this population hit its primary endpoint, reduction in intrahepatic triglycerides.[26]

- **Semaglutide** (Novo Nordisk): The ESSSENCE phase 3 trial investigates Novo Nordisk's flagship asset, GLP-1 receptor agonist semaglutide, in NASH patients with moderate-to-advanced fibrosis (F2-F3). Histological data are expected in 2024, followed by long-term outcomes in 2028/29.[27] This trial follows a phase 2 study, in which semagultide demonstrated significant improvement of NASH resolution, while showing only numerical improvements of fibrosis and the progression of fibrosis.[28]

  Novo Nordisk is conducting additional phase 2 studies with semaglutide along the NAFLD/NASH severity spectrum: (i) NAFLD HEROES, investigating semaglutide in NAFLD patients;[29] (ii) WAYFIND, in partnership with Gilead, investigating semaglutide in combination with cilofexor/firsocostat in NASH patients with compensated cirrhosis (F4).[30] This trial follows a mid-stage setback in a phase 2 study investigating semaglutide in NASH patients with compensated cirrhosis (F4), which missed its primary endpoint (improvement in liver fibrosis) while hitting its secondary endpoint (resolution of NASH);[31] (iii) A phase 2 trial investigating a combination of semaglutide with Novo Nordisk's FGF21 stimulant NNC0194 0499 in NASH patients with moderate-to-severe fibrosis (F2-F4).[32]

- **Belapectin** (Galectin): NAVIGATE, an adaptive, two-stage, phase 2b/3 trial evaluates galectin-3 inhibitor belapectin in NASH patients with cirrhosis (F4), with focus on prevention of oesophageal varices only. Study completion is estimated in mid- to late 2024.[33]

This trial follows a failed phase 2b study, in which belapectin did not show significant improvement of fibrosis or hepatic venous pressure gradient (HVPG) in NASH patients with cirrhosis and portal hypertension. However, a subgroup analysis found that patients without esophageal varices achieved a statistically significant reduction in HVPG and development of varices.[34]

- **Aramchol** (Galmed): The ARMOR phase 3 trial includes two parts, an open-label and a randomized, double-controlled, placebo design. The open-label study evaluates treatment response kinetics, pharmacokinetics and safety of SCD1 inhibitor aramchol in NASH patients with liver fibrosis stage 1-3, while the randomized, double-blind, placebo-controlled part is designed to evaluate efficacy and safety of aramchol in NASH patients with moderate-to-advanced fibrosis (F2-F3).[35] An interim analysis for the open-label part showed it met its study objectives, which Galmed subsequently decided to discontinue. Galmed has also suspended the start of the randomized, double-blind part of ARMOR while it is exploring reformulation of aramchol to extend patent protection.[36]
- **Oltipraz** (PharmaKing): A phase 3 trial being conducted in South Korea evaluates LXRg and SREBP-c inhibitor oltipraz for liver fat reduction in patients with NAFLD.[37]

Looking beyond phase 3, the mid-stage NASH pipeline has also seen encouraging momentum, with some positive news flow in 2023 and further important trial readouts expected over the next 12 months (see Table 1). Selected highlights include:

POSITIVE PHASE 2 READOUTS IN 2023

- *Hepion Pharmaceuticals:* Cyclophilin B inhibitor rencofilstat demonstrated major reductions in liver stiffness in ALTITUDE-NASH phase 2 trial of advanced (F3) NASH, suggesting reduction in hepatic fibro-inflammation (November 2023)[38]. However, in December 2023 Hepion announced it would not enrol new patients for its ASCEND-NASH phase 2b trial until it has secured full future funding or completed a strategic transaction[39]
- *TERNS Pharmaceuticals:* THR-β agonist TERN-501 met primary endpoint (liver fat reduction) and all secondary endpoints (liver fibro-inflammation, lipid parameters) in phase 2a DUET trial (August 2023)[40]
- *Sagimet Biosciences:* FASN inhibitor denifanstat met primary endpoint (liver fat reduction) and statistically significant reduction of LDL in interim readout from FASCINATE-2 phase 2b trial (June 2023)[41]
- *Viking Therapeutics:* THR-β agonist VK2809 achieved primary endpoint (liver fat reduction) and statistically significant reductions of lipid parameters in phase 2b VOYAGE trial (May 2023)[42]
- *89bio:* Pegozafermin (FGF21) achieved statistical significance on both primary histology endpoints (fibrosis improvement, NASH resolution) in phase 2b ENLIVEN trial at 24 weeks (March 2023)[43]

Table 1: Key phase 2 readouts expected in 2024

COMPANY	ASSET	MOA	TRIAL
BI/Zealand	Survodutide	GLP-1/glucagon agonist	Ph2 NASH trial
Lilly	Mounjaro	GLP-1/GIP agonist	SYNERGY, NASH trial
Pfizer	Ervogastat/clesacostat	ACC/DGAT2 inhibitors	MIRNA, NASH trial
Ionis	ION224	DGAT2 inhibitor	Ph2 NASH trial
AstraZeneca	Mitiperstat	Myeloperoxidase inh	COSMOS, NASH trial
Novo	Semaglutide/NNC0194 0499	GLP-1/FGF21	Ph2 NASH trial
Gilead/Novo	Semaglutide, cilofexor/firsocostat	GLP-1/bile acid/ACC	WAYFIND, NASH/cirrhosis
Ascletis	ASC41	THR-β agonist	Ph2 NASH trial
Cascade	CS1059	FXR agonist	Ph2 NASH trial

NASH is heading for an inflection point in 2024. Current frontrunner Madrigal is expected to maintain its lead and hit the market with resmetirom, possibly some time in the first half of 2024, to introduce the first ever, disease-specific therapy for NASH. However, it may not enjoy its first mover status for too long.

With a handful of other NASH assets in phase 3 racing to cross the regulatory finish line, the prospect of Madrigal facing competitors in the near-term seems inevitable. At the same time, the mid-stage pipeline looks set to gain further momentum in 2024, thus setting the stage for second-generation therapies to arrive in the medium term. Assuming a steady rise of combination therapies to become the future standard of care, a complex and highly dynamic NASH market will eventually emerge.

Deal activity focused on NASH

Growing interest in NASH is also reflected in deal trends over the last decade. Biotech companies account for 64% of the clinical-stage NASH pipeline, which makes them attractive targets for larger players looking to external sources for access to innovation.

Since 2015, annual NASH-focused deal volume has been in double-digit figures, with the exception of 2023, reaching a peak of 25 and 27 transactions p.a. in 2019 and 2020, respectively (see Figure 5).

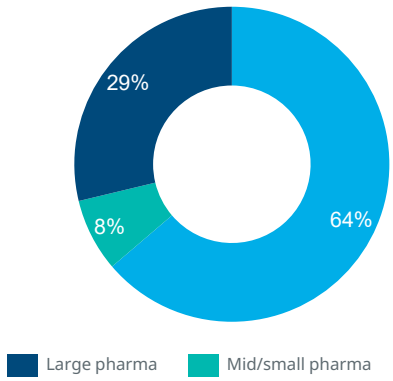
Interestingly, partnerships between drug developers and diagnostics players accounted for about 9% of deal volume over the past eight years. This reflects the critical role innovation in non-invasive diagnostic tests (NITs) plays in overcoming many of the challenges faced by sponsors of NASH trials we discussed earlier. Moreover, as biopharmaceutical companies progress their assets, many start thinking ahead to market shaping as a prerequisite for successful commercialisation, including the need to boost historically low NASH diagnosis rates in real world practice, which again will ultimately rely on accurate and scalable NITs being adopted.

Sluggish deal momentum in 2023 is likely a reflection of the industry-wide slowdown in M&A activity following a period of exuberance. As we discussed elsewhere, in 2023 large pharma dealmakers have also increasingly focussed on de-risked targets with assets which were at least in phase 3 or already on the market, at the expense of earlier stage candidates.[44] Given the high stakes of NASH innovation, with its many high profile failures, in the current sentiment potential dealmakers are likely to hold off, while waiting for high quality data for the asset of interest to emerge, before making their move.

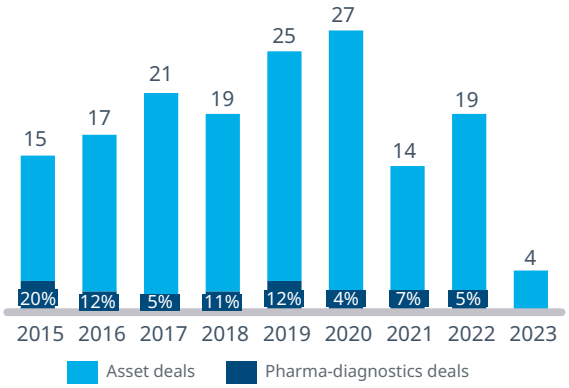
Notable examples of deals focused on NASH assets in recent years include the licensing agreement between GSK and Arrowhead, covering development and commercialisation of Arrowhead's investigational RNA interference therapeutic;[45] Merck's collaboration with Aligos Therapeutics to utilise their oligonucleotide platform technology in developing new drug candidates against NASH targets;[46] or Boehringer Ingelheim's licensing agreement with Yuhan centred on a fusion protein dual agonist against GLP-1 and liver hormone FGF21 in development for NASH.[47]

Figure 5: Trends in NASH-focused deal-making

Clinical NASH assets, by developer size
(Phase 1 – submitted)



Number of Industry NASH deals, by type
(2015-2023)



NOTE: Company breakdown does not indicate originator (included as large or mid/small pharma if partnerships exists)
Source: IQVIA EMEA Thought Leadership; IQVIA PharmaDeals; IQVIA Pipeline Link; secondary research; Clinicaltrials.gov; Includes Product and M&A deals

Deep Dive: Transforming the diagnosis of NASH

The reliance on highly invasive liver biopsies as the currently accepted gold standard for diagnosing NASH represents a major barrier to the development of new therapies for NASH and, ultimately, their future adoption by health systems in routine medical practice.

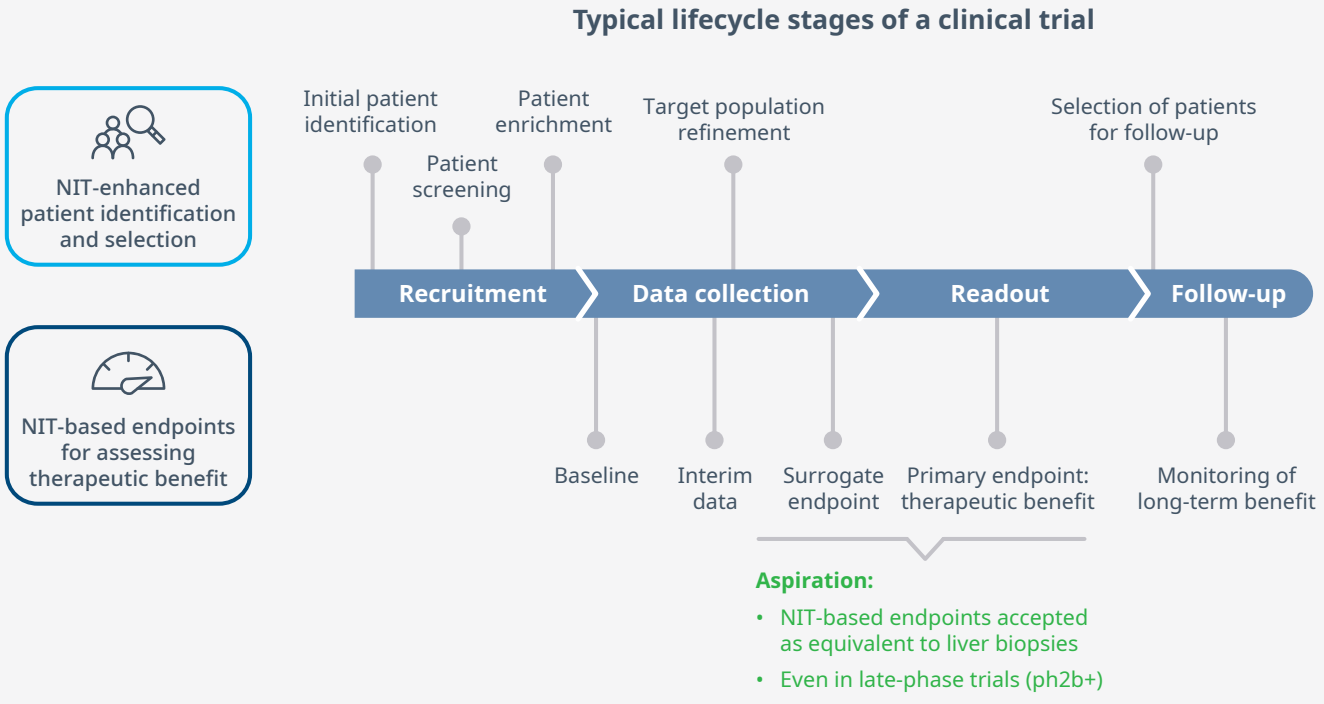
Instead, a practical, scalable and cost-effective approach is needed, based on sensitive, accurate and reliable, non-invasive diagnostic tests (NITs) for NASH.

The aspiration for NITs in medical practice includes their ability to enable:

- Diagnosing NAFLD/NASH, e.g., screening and initial diagnosis in a primary care setting
- Staging of fibrosis, e.g., identifying 'at-risk' NASH patients with a worsening prognosis
- Monitoring disease severity longitudinally, e.g., to assess disease progression or treatment response and achieved patient outcomes
- Predicting patients' response to therapeutic interventions

The immediate opportunity for NITs in NASH clinical trials lies in increasing potential patient pools for recruitment and to reduce screen failure rates, especially at the liver biopsy stage. Furthermore, NITs have found widespread use in early to mid-stage trials, e.g., magnetic resonance imaging-derived proton density fat fraction (MRI-PDFF) emerging as a common primary endpoint in phase 2a studies, especially with drugs targeting metabolic pathways (see Figure 6).[12]

Figure 6: Opportunities for NITs to improve clinical trials in NASH



NIT: Non-invasive tests
Source: IQVIA EMEA Thought Leadership

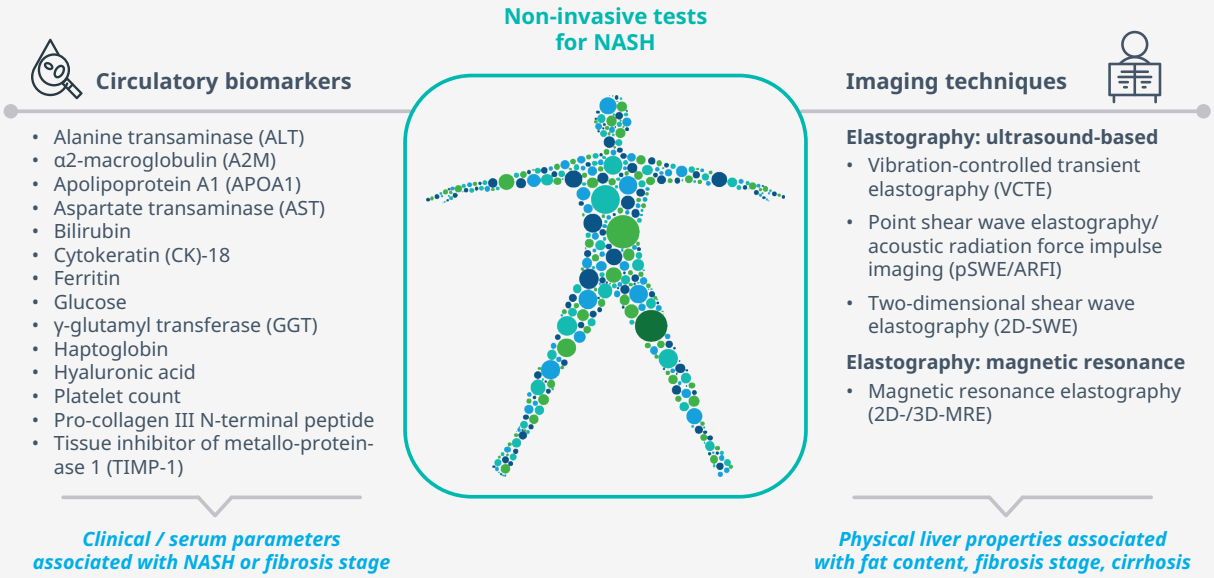
Their medium- to longer-term promise would see NIT-based efficacy endpoints accepted instead of histology (relying on liver biopsies) for the assessment of therapeutic benefit, including in late-phase trials.

To date, there are no validated NITs that could entirely replace liver biopsies in either clinical trials or routine practice, however, several promising developments are underway.

Innovation trends for non-invasive diagnostic tests

Fundamentally, NITs rely on two different approaches (see Figure 7): (i) circulating biomarkers, e.g., measuring inflammation, apoptosis, oxidative stress or extracellular matrix turnover; and (ii) imaging techniques, such as ultrasound- or magnetic resonance-based elastography, to assess physical properties of the liver, e.g., its stiffness, attenuation or viscosity.[48]

Figure 7: Non-invasive tests for NASH – two fundamental approaches



Source: IQVIA EMEA Thought Leadership; desk research

While NITs currently lack the supporting evidence to be considered equivalent to histopathological assessments as standard efficacy endpoint in clinical trials, two major initiatives aim to close this gap for regulatory qualification of biomarkers:

- **LITMUS** (Liver Investigation: Testing Marker Utility in Steatohepatitis), funded by the European Innovative Medicines Initiative 2 Joint Undertaking, brings together clinicians, academia and pharmaceutical companies from the European Federation of Pharmaceutical Industries and Associations (EFPIA). The LITMUS initiative aims to develop, validate and advance towards regulatory qualification biomarkers that diagnose, risk stratify and/or monitor NAFLD/NASH progression and fibrosis stage[49]
- **NIMBLE** (Non-Invasive Biomarkers Of Metabolic Liver Disease) is a comprehensive, five-year public-private partnership collaboration to standardize, compare and qualify imaging and circulating biomarkers to diagnose NASH, assess disease stage and measure therapeutic response, for use in both clinical trials and medical practice. The initiative is conducted under the umbrella of the Foundation for the NIH (FNIH) Biomarkers Consortium and comprises academia, the FDA, biopharmaceutical and diagnostics companies[50]

In October 2023, LITMUS in collaboration with NIMBLE submitted an initial qualification package to the FDA, including biomarkers PRO-C3, ADAPT and the FAST score, with the context of use 'Diagnostic Enrichment'.[51]

Among the many potential circulating and imaging biomarkers being investigated, we want to highlight a selected few that have found more common use, albeit with well-documented and much discussed limitations (see Tables 2 and 3).[48,52]

Table 2: Circulating biomarkers

BIOMARKER	DETAIL	APPLICATION
ELF (Enhanced Liver Fibrosis)	Blood test that combines pro-collagen III N-terminal peptide, hyaluronic acid, tissue inhibitor of metallo-proteinase 1	Assess risk of NASH progression in patients with advanced fibrosis (F3-F4) to cirrhosis and liver-related clinical events; used as secondary endpoint for antifibrotic efficacy
FIB-4 (Fibrosis-4)	Algorithm that combines aspartate transaminase (AST), alanine transaminase (ALT), platelet count, age	Assess risk for advanced liver fibrosis (F3-F4)
NIS-4	Blood test that is a composite of microRNA 34A, alpha2 macro-globulin, HbA1c, YKL-40	Identify patients with at-risk NASH (higher risk of presession, eg cirrhosis)
NAFLD Fibrosis Score	Algorithm that combines age, BMI, fasting glucose/T2D, AST/ALT ratio, platelet count, albumin	Distinguish NAFLD patients with/without advanced fibrosis (F3-F4)
PRO-C3 (Pro-peptide type 3 collagen)	Blood test that measures fibrogenesis-specific peptide fragment; combining PRO-C3 with age, diabetes, platelet count (ADAPT) enhances accuracy	Identify patients with advanced fibrosis and active fibrogenesis; used as secondary endpoint for antifibrotic efficacy
OWLiver	Blood test that evaluates 28 biomarkers (metabolites) to determine liver activity	Staging of NAFLD/NASH; used in screening of at-risk population

Table 3: Imaging biomarkers

BIOMARKER	DETAIL	APPLICATION
MRI-PDFF (MRI-derived proton density fat fraction)	Quantifies fat content in the liver	Screening for NAFLD patients; used in many ph 2a trials to assess treatment response
MRE (Magnetic Resonance Elastography)	Measures stiffness of liver	Assess fibrosis stage; assess treatment response.
VCTE (Vibration-controlled Transient Elastography) stiffness measurement	Measures stiffness of liver	Diagnose and stage the presence and extent of liver fibrosis
VCTE CAP (Controlled Attenuation Parameter)	Measures fat content of the liver	Assess degree of steatosis (fat accumulation in liver)
FAST score (FibroScan-AST)	Combines two imaging biomarkers (liver stiffness, CAP), and circulating blood biomarker AST	Identify patients with at-risk NASH; used in pre-screening for trials

To date, predictive biomarkers for NASH, which identify likely responders for a given treatment who will benefit the most, remain a greatly under-developed area.

To further advance the field of NITs and overcome the challenges and limitations they face related to levels of sensitivity, specificity, accuracy and reliability, combinations of several biomarkers, including circulating and imaging ones, are the likely way forward.

More work is needed to achieve the full regulatory qualification of biomarkers for use in both clinical trials and routine practice, including establishing cut-off points for diagnosis and patient stratification, and confirming clinically meaningful changes in biomarker values that correspond to clinical outcomes in NAFLD/NASH.

Commercial landscape for liver NITs: Prominent diagnostics players

The urgent need for NITs to diagnose liver diseases has attracted numerous established and emerging diagnostics companies vying for a share of the sizeable business opportunity. The likely FDA approval of Madrigal's resmetirom in 2024, likely to be followed by other phase 3 NASH assets in the coming years, will further accelerate the need for the fast, accurate and convenient diagnosis of patients in routine medical practice, at scale.

Prominent diagnostics companies offering commercially available liver NIT solutions include:

- **Genfit/Labcorp:** In 2020, the two companies signed a licensing agreement for Labcorp to develop and commercialise a blood-based molecular diagnostic test powered by Genfit's NIS4™ technology in the U.S. and Canada. NIS4™ is Genfit's proprietary, non-invasive, blood-based diagnostic technology, which was developed to identify patients with at-risk NASH (F>2)[53]
- **Siemens Healthineers**, provide the commercially available, prognostic Enhanced Liver Fibrosis (ELF™) test, which measures three direct markers of fibrosis, to assess the risk of NASH progression in patients with advanced fibrosis (F3-F4) to cirrhosis and liver-related clinical events. In 2021, ELF was granted marketing authorisation by the FDA under the De Novo review pathway for novel medical devices[54]
- **Echosense:** Diagnostics company focused on liver health, offering proprietary FibroScan® device technology using ultra-sound based, vibration-controlled transient elastography (VCTE) to measure liver stiffness and fat content using CAP® (Controlled Attenuation Parameter) score. Combining the VCTE-derived liver stiffness and circulating biomarker aspartate aminotransferase (AST) level yields the FAST® (FibroScan-AST) score for the identification of at-risk NASH patients[55]
- **OWL Metabolomics:** Offers OWLiver® Panel, a non-invasive, in-vitro diagnostic test based on lipidomic analysis of fasting blood samples using high-resolution liquid chromatography coupled with mass spectrometry (UHPLC-MS). It evaluates a panel of 28 metabolites reflecting liver fat content, inflammation and fibrosis to estimate the stage of NAFLD[56]
- **Nordic Bioscience:** Focused on blood-based biomarker development across a wide range of therapy areas, building on its extracellular matrix (ECM) research. Their biomarker portfolio for liver disease includes PRO-C3, which detects the formation of type lll collagen as a predictor of fibrosis stage in NAFLD and allows identifying NASH patients with advanced fibrosis and active fibrogenesis[57]
- **Perspectum:** Offers LiverMultiScan®, a non-invasive MRI-based test that provides a comprehensive view of liver health and accurately assesses signs of liver disease, e.g., liver fat, iron concentration or fibro-inflammation, with application in clinical trials and as decision-support for practising physicians[58]

Biopharma-diagnostics partnerships

As discussed earlier, biopharmaceutical companies seek partnerships with diagnostics companies to advance the development of their potential NASH therapies. Such collaborations are mutually beneficial: They help sponsors overcome many of the unique challenges associated with NASH trials, while diagnostic players benefit from their NIT solutions being tested to expand the evidence base about their utility and validity, which in turn will accelerate NITs reaching maturity. In addition, biopharma-diagnostics partnerships help raise awareness among physicians to boost the diagnosis of NASH, especially at early disease stage, which historically has suffered from low diagnosis rates.

Notable biopharma-diagnostics partnerships include:

- Novo Nordisk and Echosens entered a partnership to increase awareness and advance early diagnosis of NASH, with the aim to double diagnosis rates for NASH by 2025[59]
- Hepion Pharmaceuticals initiated a clinical collaboration with HepQuant, incorporating the HepQuant SHUNT test into a Phase 2b clinical trial in presumed NASH F3 patients to measure impact on hepatic function[60]
- Sagimet Biosciences entered into an agreement with OWL Metabolomics to use OWL's proprietary technology in the FASCINATE-2 phase 2b NASH trial to assess denifanstat's effect on the metabolomics profile[61]
- GSK is partnering with PathAI on a phase 2b NASH trial, deploying AI-powered pathology to generate, digitise and analyse liver biopsy slides for central pathologist evaluation, while also using the proprietary AI-based Measurement of NASH Histology (AIM-NASH) tool for histological evaluation[62]

As more NASH assets progress through the pipeline and approach the pre-launch phase, we expect to see a shift in focus of biopharma-diagnostics partnerships from clinical trials towards embedding NITs as new diagnostic standard to ensure health system readiness for future NASH launches, for example as illustrated by the Novo Nordisk-Echosens partnership.

Finally, beyond solving the scientific and technical challenges facing NITs, their successful, widespread adoption in real world medical practice depends on overcoming other barriers, e.g., care pathway re-configuration, building on established tests and biomarkers, incorporating NITs in guidelines, securing reimbursement of tests and educating HCPs and patients.

We will elaborate on how to address those challenges in the next section as part of the overall market shaping effort required for the successful commercialisation of novel NASH therapies.

Capturing the commercial opportunity in NASH

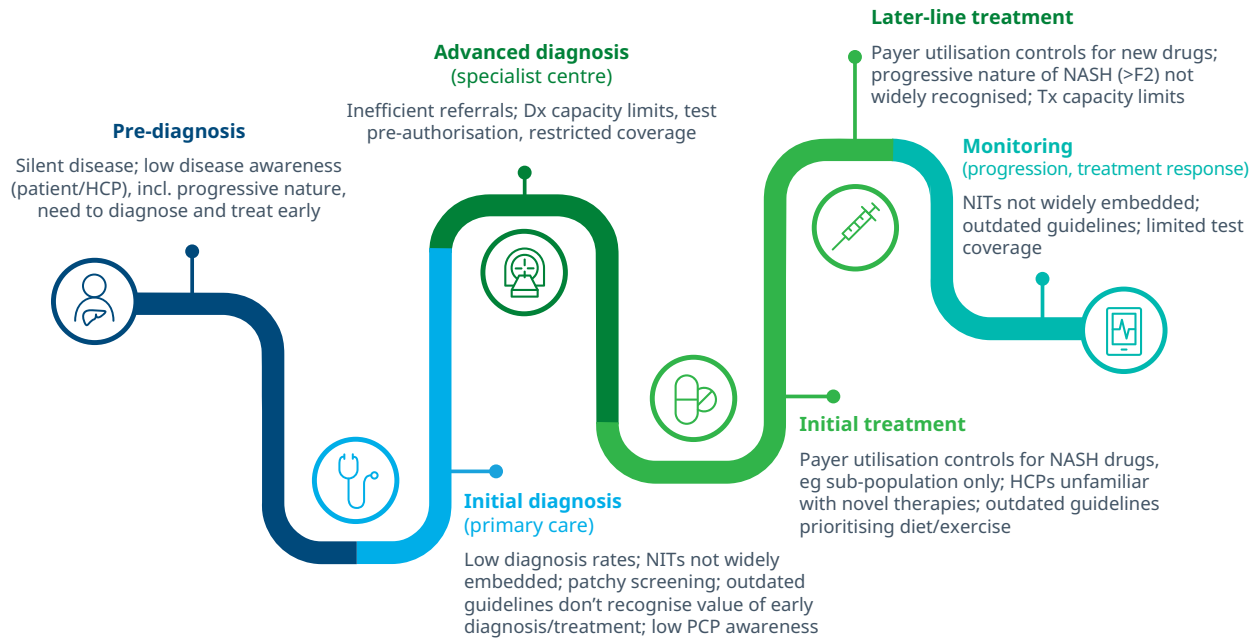
Estimates for the size of the future NASH market vary widely, however, strong underlying drivers of disease epidemiology suggest the potential commercial opportunity for innovators is considerable.

As discussed earlier, by 2030 close to 100 million patients are expected to live with NASH in the US, EU4/UK, Japan and China alone.[2] Uncertainty remains high around how this disease burden will translate into a market for pharmacotherapies to treat NASH, resulting in global market size estimates ranging from $10s of billion to over $100 billion by 2030.

This is a consequence of numerous barriers preventing an efficient NASH patient journey and a general lack of health system readiness in the absence of disease-specific treatment options to date (see Figure 8), including

- Low disease awareness among both patients and HCPs, including the progressive nature of NASH with potentially poor prognosis, e.g., severe fibrosis, compensated cirrhosis, need for liver transplants or increased mortality due to fatal liver events or cardiovascular disease
- Historically low diagnosis rates, not helped by highly invasive and costly liver biopsies being considered the diagnostic gold standard while non-invasive tests (NITs) are still establishing their validity and acceptance
- Guidelines not reflective of the latest developments in NASH, e.g., embedding broad use of NITs in clinical practice; or patient screening and referrals not systematically implemented
- Underdeveloped care pathways, including inefficient referrals across different settings of care, or lack of adequate capacity for screening, diagnosis and treatment
- Payers unprepared for the imminent NASH innovation wave; budget impact concerns given the uncertainty around the potential size of the NASH patient population, with vivid memories of their experience when hepatitis C treatments became available a decade ago. Uncertainty about real-word outcomes of NASH drugs granted conditional approval based on surrogate endpoint will likely prompt payers to restrict access even more tightly while confirmatory evidence is being generated
- NASH not being recognised as a public health priority that is adequately reflected in health policies and funding commitments, with the increasing noise around obesity diverting stakeholders' attention and possibly budgets

Figure 8: Many barriers prevent an efficient NASH patient journey



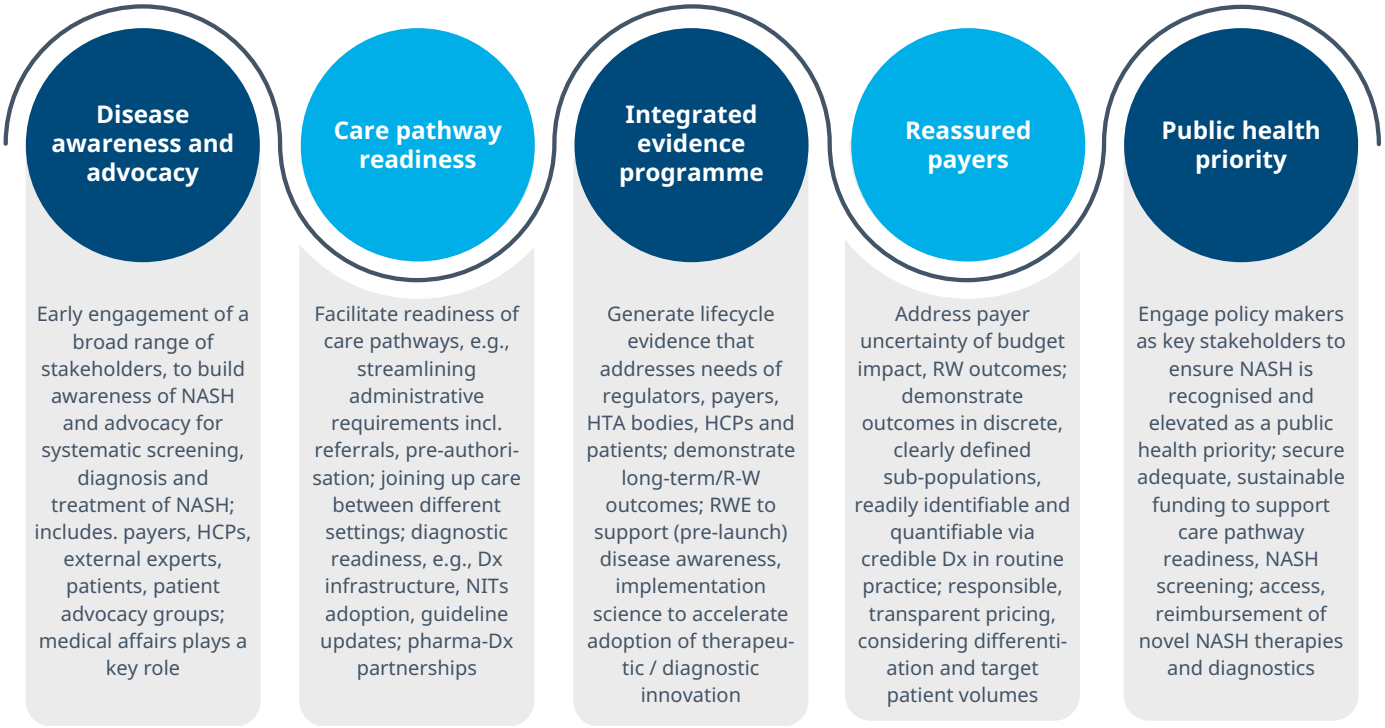
NITs: Non-invasive tests; PCP: Primary care physician
Source: IQVIA EMEA Thought Leadership

Innovators, especially early entrants, will therefore need to focus on extensive market development efforts to prepare the ground for seizing the commercial opportunity in NASH.

That task has become even more challenging recently as the wider cardio-metabolic treatment landscape is being transformed by the next generation of potent anti-obesity therapies. These treatments may emerge as backbone agents for overall CV risk management, thereby blurring, possibly even shrinking, the NASH opportunity if obesity is managed as an upstream intervention to avoid downstream co-morbidities, including NASH. This in turn represents a risk to 'NASH-only' treatments being relegated to later lines.

We have identified five strategic priorities for innovators to achieve commercial success in NASH (see Figure 9):

Figure 9: Achieving commercial success in NASH



Source: IQVIA EMEA Thought Leadership

1. **Disease awareness and advocacy:** Early engagement of a broad range of stakeholders is critical to build awareness of NASH and advocacy for systematic screening, diagnosis and treatment of NASH patients with novel therapies. These efforts must focus on payers, HCPs, external experts, patients and patient advocacy groups, with medical affairs playing a key role. Madrigal's unbranded campaign "Meet Olivia, Her Liver's #1 Fan" is a case in point for building patient-focused disease awareness.[63]

   Building disease awareness of NASH inevitably will happen in competition with the overwhelming noise and excitement surrounding obesity. Innovators therefore must carefully, and very clearly, position NASH within the broader context of cardiometabolic conditions and co-morbidities, including which patients need to be specifically treated for NASH and how, to avoid being engulfed by the surging obesity wave.

2. **Care pathway readiness:** Innovators must engage health systems to facilitate readiness of care pathways, e.g., streamlining administrative requirements such as referrals, pre-authorisation and joining up care between different settings. Diagnostic readiness is particularly important for a 'silent' condition like NASH to improve diagnosis rates which requires addressing diagnostic infrastructure bottlenecks by facilitating validation and adoption of non-invasive tests

(NITs) in guidelines and ultimately routine practice. Partnerships with diagnostics companies will be essential to embed novel, scalable solutions, possibly involving pre-competitive, cross-industry, multi-stakeholder consortia to set a new diagnostic standard for NASH.

There are important lessons to be learnt for NASH innovators from similar situations, for example, faced by first-generation checkpoint inhibitors. They also had to ensure diagnostic readiness of health systems for broad, routine testing of patients for the novel PD-L1 biomarker. Leading players not only partnered closely with key diagnostics players to address infrastructure bottlenecks, they also deployed dedicated field roles focused on diagnostic readiness, e.g., 'diagnostic science liaisons', training pathologists, guiding oncologists and working closely with specialist provider centres. However, given the size of the potential NASH population and the importance of the primary care setting, similar efforts will need to be delivered at a much grander scale.

3. **Integrated evidence programme:** Innovators must think beyond regulators and plan carefully for evidence that addresses the needs of payers, HTA bodies, physicians and patients to craft a comprehensive, compelling and differentiated value proposition. This includes generating long-term outcomes data under real-world conditions. Pre-launch RWE plays a key role in generating disease awareness and highlighting unmet needs, e.g., through studies exploring epidemiology, burden of illness or the natural history of disease. RWE is also needed as critical enabler of implementation science to accelerate the adoption of innovation, in both pharmacotherapies and diagnostics, and translating it into change in clinical practice on the ground.[64]

4. **Reassured payers:** Innovators must address two types of uncertainty payers face: (i) budget impact, as patient identification and disease progression make it hard to size the potential NASH target population; (ii) outcomes achieved in routine medical practice vs. those used for conditional approval of NASH drugs based on surrogate endpoints. Compelling evidence is key to address those payer concerns by demonstrating real world outcomes in clearly defined sub-populations, e.g., by fibrosis stage, risk profile, co-morbidities, that are identifiable in routine clinical practice, and can be quantified, via credible diagnostic approaches.

   Importantly, innovators will have to make the case for NASH to payers against competing demands from novel anti-obesity therapies, which requires educating payers that these are two distinct conditions that both need to be specifically treated, despite some population overlap.

   In addition, transparent, responsible pricing must take into account both the differential value of therapies and size of target patient populations.

5. **Public health priority:** Policy makers are particularly important stakeholders for innovators to engage, to ensure NASH is recognised and elevated as a public health priority. This in turn will help secure adequate and sustainable funding to support care pathway readiness, access to and reimbursement of novel NASH therapies, and diagnostics, for all eligible patients to benefit from much needed treatments. To address policy makers' needs, relevant evidence must help them understand the burden of NASH, unmet need and quantify beneficial health system impact of novel therapies, e.g., delivering cost-offsets by avoiding downstream complications from the progression of NAFLD/NASH such as liver transplants.

As the most common liver disease worldwide and the leading cause of liver-related morbidity and mortality, NAFLD/NASH represent a major and growing public health concern. This silent epidemic is at the cusp of emerging from the shadows, as innovators race to the market with novel, disease-specific therapies for NASH, heralding a new age of hope for patients.

However, for these innovations to fulfil their promise, a concerted, multi-stakeholder effort is needed, comprising biopharmaceutical and diagnostics innovators, policy makers, payers, healthcare professionals and patients. The time to act is now!

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About the authors

MARKUS GORES
Vice President,
EMEA Thought Leadership,
IQVIA

Markus has over 20 years of experience in life sciences, advising clients in all major geographies on a broad range of topics, including real world evidence strategy, launch readiness, go-to-market models, brand and commercial strategies, and building enabling organisational capabilities.

Markus is a frequent speaker on the latest industry trends and regularly engages with senior leadership teams of pharmaceutical companies.

Prior to his current role in Thought Leadership, he has held leadership positions within IQVIA Real World Solutions and QuintilesIMS Consulting Services (formerly the IMS Consulting Group).

Markus holds a PhD in Pharmaceutical Chemistry from the University of Hanover and has completed post-doctoral research at the University of California.

KIRSTIE SCOTT
Senior Consultant,
EMEA Thought Leadership,
IQVIA

Kirstie is a Senior Consultant in IQVIA's EMEA Thought Leadership team, based in London.

She has experience preparing white papers and delivering presentations across a range of priority healthcare topics such as Launch Excellence, the availability of medicines, and the impact of biosimilars in Europe. A particular recent focus is how companies with new launches can overcome the challenging post-pandemic environment to achieve launch success.

Kirstie has over 5 years' experience in healthcare and life sciences, previously providing clinical and commercial competitive insights for pharmaceutical companies with pipeline NASH assets, and working to support industry associations to influence health policy.

She holds a degree in Neuroscience from the University of Nottingham.

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CONTACT US

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