Rezdiffra and Wegovy are Just the Beginning: Vast Unmet Needs and Opportunities Remain in the Fight Against MASH

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Introduction

In 2023, the reclassification of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) to metabolic dysfunction-associated steatotic liver disease (MASLD) and steatohepatitis (MASH), respectively, represented a pivotal advancement in aligning terminology with pathophysiology. This updated terminology also removes the stigmatizing and often misleading reference to "alcoholic," a term that has historically impeded both patient understanding and clinical engagement.

Despite this important paradigm shift, metabolic dysfunction–associated steatotic liver disease remains markedly underdiagnosed and undertreated. The 2024 approval of Madrigal's *Rezdiffra* (resmetirom) as the first FDA-approved therapy for MASH signaled the beginning of a new era in disease management. This milestone not only established a long-awaited therapeutic option but also set the stage for a rapidly expanding pipeline of investigational treatments poised to transform the clinical landscape.

In August 2025, the U.S. Food and Drug Administration granted approval to Novo Nordisk's *Wegovy* (semaglutide 2.4 mg) as the second treatment for MASH, indicated for noncirrhotic patients with moderate to advanced fibrosis. This approval further broadens the therapeutic landscape and underscores a pivotal advancement in targeting the metabolic underpinnings of the disease, most notably type 2 diabetes and obesity.

Further disruption within the MASH landscape is anticipated as multiple pharmaceutical manufacturers advance toward market entry. The competitive momentum intensified in 2025 with a series of high-profile acquisitions that underscored the growing strategic importance of this therapeutic area. In May, GSK announced an agreement to acquire efimosfermin from Boston Pharmaceuticals, followed in September by Roche's planned acquisition of 89bio and its lead candidate, pegozafermin. One month later, Novo Nordisk, already an established player in the space, reinforced its commitment to MASH through the acquisition of Akero Therapeutics and its promising investigational agent, efruxafermin. Collectively, these transactions reflect sustained investment and confidence in diverse mechanistic approaches, including THR-β agonists, GLP-1 receptor agonists, and FGF21 analogs, all aimed at addressing the multifactorial nature of this complex disease.

This white paper explores physicians' early experiences with prescribing *Rezdiffra* and *Wegovy*, the barriers influencing clinical adoption, and the rapidly evolving therapeutic landscape shaping the management of MASH. It further provides strategic insights and recommendations for stakeholders as the landscape moves toward broader integration of novel, mechanism-driven therapies in clinical practice.

MASH: A Growing but Underrecognized Epidemic

Rising Prevalence and Burden

Metabolic dysfunction–associated steatohepatitis (MASH), the progressive and fibrotic form of metabolic dysfunction–associated steatotic liver disease (MASLD), represents a significant and growing public health concern. The condition is associated with substantial morbidity and mortality risks, including progression to cirrhosis, hepatocellular carcinoma (HCC), and liver-related death.

In 2020, an estimated 14.9 million U.S. adults were living with MASH, a figure projected to increase to 23.2 million by 2050. Of particular concern, cases with moderate to advanced fibrosis (F2–F4) are expected to rise from 6.7 million to 11.7 million during this same period. This escalating prevalence underscores the urgent need for earlier detection, improved risk stratification, and effective therapeutic strategies to mitigate long-term clinical and economic impact.[1,2,3]

Diagnostic Gaps: A Hidden Patient Population

Despite the mounting prevalence and clinical burden of MASH, diagnosis remains elusive for a substantial proportion of patients. Gastroenterologists and hepatologists estimate that approximately 40% of cases go undiagnosed, largely due to the disease's insidious,

asymptomatic nature and persistent gaps in recognition among primary care providers.[4] This diagnostic shortfall contributes to delayed intervention and missed opportunities for early therapeutic engagement, reinforcing the need for greater awareness, systematic screening, and cross-specialty collaboration.

Metabolic Comorbidities Worsen the Outlook

Patients with type 2 diabetes and obesity are disproportionately affected by MASLD and its progressive form, MASH. Among individuals with diabetes, MASLD prevalence reaches approximately 70%, and up to 38% exhibit advanced fibrosis.[5] This population also faces more than double the rate of liver-related mortality compared with non-diabetic counterparts, underscoring the synergistic impact of metabolic dysfunction on disease progression and clinical outcomes.[5]

Rezdiffra's Debut: Clinical Promise Meets Practical Barriers

Strong Early Adoption and Positive Feedback

Since its approval, *Rezdiffra* has achieved strong early adoption within the hepatology and gastroenterology communities. Within its first year on the market, 80% of specialists surveyed reported prescribing the therapy.[6] While this rate now appears to be stabilizing, market insights suggest sustained momentum, with the total number of patients initiated on *Rezdiffra* continuing to rise.

Physician sentiment toward the therapy remains overwhelmingly positive—60% of current prescribers report being "extremely satisfied," citing expected efficacy as the primary driver of confidence.[6]

Rezdiffra's liver-directed mechanism, which selectively targets thyroid hormone receptor β (THR-β), demonstrates particular utility among patients with moderate to advanced fibrosis (F2–F3). These individuals are widely regarded as optimal candidates for treatment.[6] Early prescribing patterns indicate that the majority of patients initiated on *Rezdiffra* are males aged 35–64 with F2–F3 fibrosis and concurrent obesity.[6] While *Rezdiffra* is not yet indicated for patients with cirrhosis (F4), Madrigal is pursuing an expanded indication for those with compensated cirrhosis (F4c).[9]

Cost and Access: The Primary Friction Points

Despite its demonstrated clinical value, *Rezdiffra's* commercial rollout has been tempered by significant real-world access challenges. Out-of-pocket costs and complex prior authorization requirements are the most commonly cited barriers to treatment.[6] According to research, roughly 74% of patients prescribed require prior authorization.[6] Approximately

74% of patients prescribed *Rezdiffra* require prior authorization, and on average, physicians report that only 34 of 104 eligible patients per practice ultimately initiate therapy.[7]

Insurance denials and high copays have emerged as critical obstacles—not only limiting initiation but also contributing to treatment discontinuation.[6] As one gastroenterologist observed:

"They usually discontinue not for medical reasons, but because they can't afford it. Madrigal, probably because of an MBA somewhere, decided to charge $48,000 for the drug when semaglutide, another drug being tested for MASH, is a quarter of the price."[6]

Cost concerns are widespread: 24% of specialists characterize *Rezdiffra* as "very costly and difficult to access," while an additional 58% view it as "somewhat costly."[7] As a result, nearly one-third report "warehousing" patients—delaying initiation until reimbursement pathways improve or alternative therapies become available.[6]

Although access perceptions have improved modestly—supported by proactive field engagement and patient assistance initiatives—affordability and administrative burden continue to constrain uptake. Even so, specialists largely maintain confidence in *Rezdiffra*'s role as a foundational therapy for patients with F2–F3 fibrosis, emphasizing its proven antifibrotic efficacy and targeted, liver-specific mechanism of action.[6]

Wegovy's Entry: Expanding the Metabolic Frontline

A Long-Awaited Approval

The approval of *Wegovy* (semaglutide 2.4 mg) earlier this year marked a pivotal inflection point in the evolving management of MASH. As the first GLP-1 receptor agonist approved for noncirrhotic MASH, *Wegovy* introduces a treatment option with demonstrated benefits across key metabolic domains—weight reduction, glycemic control, and hepatic fat reduction—all central to addressing the multifactorial nature of the disease.[8] Importantly, it also enters the market at a substantially lower cost relative to *Rezdiffra*, further broadening its accessibility and appeal.

According to a Spherix Global Insights pulse study (n=77) conducted one-week post-approval, only 42% of physicians reported unaided awareness of *Wegovy's* market entry. Nevertheless, early sentiment was highly optimistic: 65% of surveyed physicians indicated an intent to prescribe within three months, reflecting strong confidence in the therapy's clinical profile and familiarity derived from its established use in obesity and type 2 diabetes management.[8]

Distinct Roles for Wegovy and Rezdiffra

As clinical education and familiarity expand, *Wegovy* is expected to be prescribed alongside *Rezdiffra*, advancing a more integrated metabolic–hepatic strategy in the management of MASH. Physicians increasingly view the two agents as complementary, each addressing distinct pathophysiologic dimensions and fibrosis stages of the disease.

For patients with moderate fibrosis (F2), *Wegovy* monotherapy has emerged as the leading treatment preference among specialists, favored by 43% of respondents.[8] This preference is largely driven by the therapy's pronounced effects on weight reduction and metabolic improvement—key factors in mitigating disease progression. As one physician explained:

"*Wegovy causes weight loss, and weight loss is critical to reduce liver fat, liver fibrosis, and importantly the progression from F2 to F3 in MASH patients.*"[8]

Conversely, for patients with advanced fibrosis (F3), combination therapy with *Rezdiffra* and *Wegovy* is preferred by 43% of physicians, reflecting skepticism that monotherapy alone can adequately address more severe disease.[8] As one hepatologist observed:

"*We have known for several years that monotherapy is less likely to be the final answer for advanced MASH liver disease. The combination of Rezdiffra and Wegovy offers the possibility of preventing that progression, at least until we have more effective monotherapy.*"[8]

These perspectives highlight a growing consensus that MASH treatment will increasingly rely on multimodal strategies—integrating hepatocentric and metabolic mechanisms to achieve optimal outcomes across the disease continuum.

Projected Market Impact

With strong early prescribing intent and clearly differentiated clinical positioning, *Wegovy* is poised to rapidly solidify its role within the emerging MASH treatment paradigm. Physicians anticipate broad use among patients with metabolic comorbidities—particularly those with obesity or type 2 diabetes—citing its dual benefits on weight reduction and hepatic health.[8] As familiarity grows and access barriers ease, *Wegovy* is expected to become a cornerstone of metabolic-focused MASH management, complementing liver-directed therapies such as *Rezdiffra* to deliver more comprehensive patient outcomes.

Rezdiffra Positioning Among GLP-1 Agonists

As noted, *Rezdiffra* continues to be viewed as the superior option for direct hepatic benefit, while GLP-1 receptor agonists such as *Wegovy* are favored for patients with metabolic comorbidities. Ease of access, established prescriber familiarity, and the metabolic benefits of GLP-1s—particularly in patients with obesity and type 2 diabetes—have positioned them as a natural entry point into MASH care. Surveyed specialists report that a

greater proportion of their MASH patients are eligible for GLP-1 therapy (79%) compared with *Rezdiffra* (62%).[7]

The concept of a combination approach is rapidly gaining traction: 72% of specialists indicate a willingness to add *Rezdiffra* to a GLP-1-based regimen.[7] Such strategies are viewed as a promising means of addressing both hepatic pathology and underlying metabolic dysfunction in tandem.

Further insights from recent Spherix Global Insights' research underscore the evolving treatment paradigm. Following *Wegovy's* approval, physicians were asked to identify their preferred treatment approach across fibrosis stages. Results illustrate nuanced prescribing expectations and growing openness to combination therapy [8]:

	F0	F1	F2	F3	F4c	F4d
Rezdiffra Monotherapy	3%	4%	30%	19%	9%	5%
Wegovy Monotherapy	12%	48%	43%	34%	31%	19%
Non-Rx Treatment	81%	43%	9%	4%	14%	25%
Rezdiffra & Wegovy Combination	0%	1%	18%	43%	26%	16%
Other Rx Treatment	5%	4%	0%	0%	19%	35%

Future Outlook: Closing Gaps and Expanding the Toolbox

Addressing Cirrhotic MASH: A High-Need Frontier

The exclusion of patients with cirrhosis (F4) from *Rezdiffra's* current label highlights one of the most pressing unmet needs in MASH care—effective therapeutic options for those with the most advanced form of the disease. *Rezdiffra* is currently being investigated in patients with compensated cirrhosis (F4c), and Madrigal presented encouraging data from the MAESTRO-NASH OUTCOMES trial at the European Association for the Study of the Liver (EASL) Congress in May 2025.[9] Findings from this pivotal study suggest that *Rezdiffra* may confer meaningful benefits for compensated cirrhosis patients, including improvements in liver stiffness, fibrosis biomarkers, fibrosis scores, and portal hypertension.

Similarly, Akero Therapeutics' SYMMETRY trial evaluating *efruxifermin* demonstrated statistically significant reversal of cirrhosis at 96 weeks, offering another promising signal in this high-need population.[10] Collectively, these data represent an important step toward expanding treatment eligibility to patients with compensated cirrhosis—potentially transforming care for one of the most vulnerable and underserved MASH subgroups.

The Push for Earlier Diagnosis

At present, only an estimated 315,000 diagnosed MASH patients are actively managed by approximately 14,000 specialists—a fraction of the projected eligible population.[9] Novo Nordisk anticipates up to 22 million Americans with F2-F4 MASH by 2030.[11] This widening gap between disease prevalence and diagnosis underscores the urgency of improving early detection and referral pathways.

Both Madrigal and Novo Nordisk are investing heavily in initiatives to expand physician awareness, improve diagnostic infrastructure, and advance the adoption of noninvasive testing modalities.[9 11] These coordinated efforts aim to close the diagnostic divide that continues to delay timely intervention and limit patient access to emerging therapies.

Pipeline Therapies on the Horizon

The MASH treatment pipeline remains highly active, with numerous late-stage programs advancing across diverse mechanisms of action. Collectively, these novel agents are poised to further redefine the therapeutic landscape and enable increasingly personalized treatment strategies. Key areas of innovation include:

- **Thyroid Hormone Receptor Beta Agonists**: *VK2809* (Viking Therapeutics)
- **FGF21 Analogs**: *Efruxifermin* (Novo Nordisk/Akero), *Pegozafermin* (Roche/89bio)
- **GLP-1 and Dual/Triple Agonists** *Tirzepatide* (Eli Lilly), *Survodutide* (Boehringer Ingelheim), *Retatrutide* (Eli Lilly)
- **PPAR Agonists**: *Lanifibranor* (Inventiva)
- **FGF19 Analogs**: *Efimosfermin* (GSK)

Among these, tirzepatide, lanifibranor, and efruxifermin are considered the most highly anticipated, given their robust clinical profiles and complementary mechanisms of action.[4] Surveyed physicians overwhelmingly expressed willingness to prescribe these agents upon approval, signaling strong market readiness and continued enthusiasm for innovation in MASH therapeutics.[4]

Conclusion and Strategic Recommendations

The introductions of *Rezdiffra* and *Wegovy* represent landmark milestones in the evolving management of MASH. Each therapy targets distinct yet complementary dimensions of the disease. *Rezdiffra* established the first hepatic-directed option aimed at reversing fibrosis, while *Wegovy's* recent approval underscores the central role of metabolic modulation in improving liver health. Together, they signal a paradigm shift toward more integrated,

patient-centered approaches that address both hepatic pathology and its metabolic drivers.

Yet the path toward comprehensive MASH management remains in its formative stages. Persistent challenges—most notably cost, access barriers, and the limited number of diagnosed patients—continue to constrain real-world impact. Nevertheless, rising physician enthusiasm, strong early prescribing intent for *Wegovy*, and a robust late-stage pipeline suggest that the market is poised for accelerated growth and deeper collaboration across hepatology, endocrinology, and primary care.

Recommendations for Stakeholders:

- **Enhance Early Identification:** Equip primary care and endocrine specialists with the tools and education necessary to identify at-risk patients earlier in the disease continuum.
- **Advance Access and Affordability:** Advocate for payer policies that reduce financial barriers and streamline prior authorization processes for *Rezdiffra*, *Wegovy*, and future therapies.
- **Promote Combination Strategies:** Support ongoing and future clinical trials, as well as real-world evidence initiatives, exploring combination regimens (e.g., *Rezdiffra* plus GLP-1 receptor agonists) that address hepatic and metabolic pathways simultaneously.
- **Drive Public Health Awareness:** Champion educational and public health campaigns to normalize MASLD/MASH screening, particularly among high-risk populations.

Through continued innovation, cross-specialty alignment, and a shared commitment to earlier diagnosis and equitable access, the next several years are poised to usher in a transformative era for liver–metabolic care—one defined by multidimensional treatment strategies and meaningful improvements in patient outcomes.

References

1. Phuc Le, PhD, MPH; Moosa Tatar, PhD; Srinivasan Dasarathy, MD, et al. Estimated Burden of Metabolic Dysfunction–Associated Steatotic Liver Disease in US Adults, 2020 to 2050. *JAMA Netw Open.* 2025;8;(1):e2454707. doi:10.1001/jamanetworkopen.2024.54707. Available from: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2829360
2. Younossi ZM, Henry L, Garrison R. Model Estimates Prevalence of MASLD Will Increase From 33.7% in 2020 to 41.4% in 2050. *Pharmacy Times*. 2024 April 2. Available from: https://www.pharmacytimes.com/view/model-estimates-prevalence-of-masld-will-increase-from-33-7-in-2020-to-41-4-in-2050
3. Tapper, E.B., Krieger, N., Przybysz, R. et al. The burden of nonalcoholic steatohepatitis (NASH) in the United States. BMC Gastroenterol 23, 109 (2023). https://doi.org/10.1186/s12876-023-02726-2. Available from: https://bmcgastroenterol.biomedcentral.com/articles/10.1186/s12876-023-02726-2
4. Spherix Global Insights. *Market Dynamix™: MASLD/MASH (US) 2024* [proprietary market research]. Exton (PA): Spherix Global Insights; 2024.
5. Ciardullo, S, Vergani M and Perseghin G. Nonalcoholic Fatty Liver Disease in Patients with Type 2 Diabetes: Screening, Diagnosis, and Treatment. Journal of Clinical Medicine 2023 Aug 27;12(17):5597. doi: 10.3390/jcm12175597. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC10488336/#:~:text=Abstract,signs%20of%20advanced%20liver%20fibrosis.
6. Spherix Global Insights. Launch Dynamix™: Rezdiffra in MASH (US) Deep Dive, Wave 5 [proprietary market research]. Exton (PA): Spherix Global Insights; 2025 Jul.
7. Spherix Global Insights. Patient Chart Dynamix™: MASLD/MASH (US) 2024 [proprietary market research]. Exton (PA): Spherix Global Insights; 2024.
8. Spherix Global Insights. Wegovy in MASH Pulse Survey. Exton, (PA): Spherix Global Insights; 28 August 2025 [cited 2025 Oct 16]. Related press release available from: https://www.spherixglobalinsights.com/despite-early-low-awareness-physicians-forecast-swift-adoption-of-novo-nordisks-wegovy-in-mash-according-to-spherix-global-insights/.
9. Madrigal Pharmaceuticals. Madrigal Pharmaceuticals Reports First-Quarter 2025 Financial Results and Provides Corporate Updates. Conshohocken (PA): Madrigal Pharmaceuticals; 2025 May 1 [cited 2025 Oct 16]. Available from:

https://ir.madrigalpharma.com/news-releases/news-release-details/madrigal-pharmaceuticals-reports-first-quarter-2025-financial.
10. Akero Therapeutics Inc. Akero Corporate Presentation. South San Francisco (CA): Akero Therapeutics, Inc. 2025 September [cited 2025 Oct 16]. Available from: https://ir.akerotx.com/events-presentations/presentations.
11. Novo Nordisk A/S. Investor presentation: first three months of 2025 [investor presentation]. Bagsværd (DK): Novo Nordisk A/S; 2025 May 2 [cited 2025 Oct 16]. Available from: https://investor.novonordisk.com/q1presentation2025/.