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Opportunities and challenges following approval of resmetirom for MASH liver disease

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The US Food and Drug Administration (FDA) has approved the first drug, resmetirom, for metabolic dysfunction-associated steatohepatitis (MASH), but much work remains for the industry, practitioners and health systems so that this approval will benefit all patients.

Millions of people, and their doctors, have long wished for an approved pharmacological therapeutic to treat MASH (previously known as NASH). MASH represents a necroinflammatory variant of metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD)[1]. MASH is characterized by the presence of >5% hepatic steatosis, combined with the ballooning of hepatocytes and inflammation, measured histologically. An estimated 38.2% of the global adult population lives with MASLD[2]; 20–30% of those are estimated to have MASH. An estimated 5–10% of global children live with MASLD[3]. MASLD is the most prevalent chronic liver disease in human history, and so viable treatments are needed for MASH.

Notwithstanding years of promising clinical trials[4], until the approval of resmetirom by the FDA[5] on 14 March 2024, the global liver health community had long waited for MASH drugs to succeed.

Limited access

While effects of resmetirom rollout will be wide-ranging over time (Fig. 1), initially, resmetirom will probably be exclusively prescribed in gastroenterology and hepatology practices, which will provide important evidence of real-world effectiveness in relation to the reported efficacy[6,7]. Unless there are substantial changes in policy and better disease awareness, most people living with MASH — who are already relatively underserved or neglected — will not directly benefit from regulatory approval for the foreseeable future. The current registrational trial of resmetirom excluded people with cirrhosis, children and women of child-bearing age who may be planning a pregnancy or currently breastfeeding and so the drug will most likely not be available for these groups, which could exacerbate inequities.

MASH drug approval alone will not profoundly alter the course of rapidly growing metabolic dysfunction-associated non-communicable diseases, which coexist across all stages of MASLD. The pace of development and approval of new drugs across the spectrum of metabolic dysfunction warrants engagement of the industry with a range of healthcare providers, particularly given the potential polypharmacy burden experienced by people with MASH. Polypharmacy risks may further warrant the exploration of drug rationalization, de-escalation and discontinuation trials.

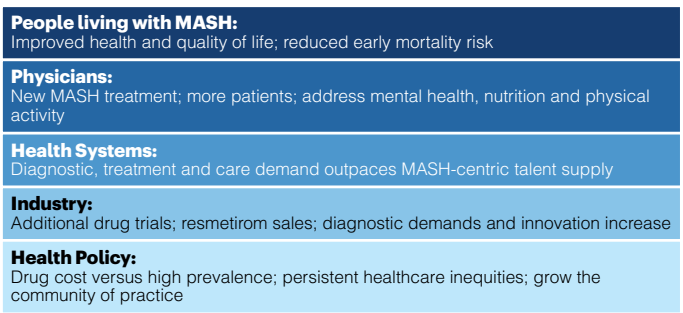

Fig. 1 | Cascading effects of the approval of resmetirom. In addition to directly affecting people living with MASH, resmetirom's approval will have implications that will influence practice, systems, industry and policy around the world.

Opportunities for people living with MASH

With the first MASH drug approval, treatment and care models will evolve, which should lead to longer life, improved quality of life and decreased total out-of-pocket medical expenditures for patients (Fig. 2).

However, the uptake of drugs for other liver diseases, such as hepatitis C, has not always led to disease elimination. For instance, despite widely available, safe, all-oral, direct acting, highly effective antiviral therapy, at least 57 million people living with hepatitis C (including over 800,000 in the USA) remain undiagnosed and untreated. Even with low-cost, curative drugs, few countries are on target to reach the World Health Organization goal of eliminating the hepatitis C virus by 2030.

The greatest effect from resmetirom will probably be seen if delivered in combination with non-pharmacological interventions (NPIs), such as nutrition, exercise, mental health and/or digital therapeutics, as seen with type 2 diabetes (T2D). To that end, the FDA noted resmetirom "to be used along with diet and exercise" as treatment options for patients with MASH[5]. Adherence to drug interventions and NPIs are influenced by numerous factors, including commercial[8] (such as food insecurity and marketing of low nutrition foods), social[9] (such as income level and effects of stigma) or related to vulnerabilities (such as for older people) and those at risk (such as children and marginalized populations). Special considerations must be given to these determinants and factors within the rollout of resmetirom or any other pharmaceutical to treat MASH.

Evolving hepatology practices

An increased understanding of the biological pathophysiology of MASLD and MASH in the last 30 years has implicated genomic and environmental determinants of disease. Along with improvements in disease pathogenesis come novel insights into diagnostic approaches, as well as increasingly precise treat-to-target drugs.

Adults living with MASH and comorbidities begin pharmacological treatment with resmetirom

Challenges	Actions to optimise treatment
People living with MASH • Health literacy and infodemic • Stigma • Food insecurity • Polypharmacy • Social and commercial determinants of health	**People living with MASH** • Adopt a Mediterranean, plant-based or similar diet • Exercise • Behavioral treatment
Hepatologist • Management of polypharmacy • Measures to assess the effectiveness of treatment	**Hepatologist** • Account for the social and commercial determinants of health
Other clinical practices • Awareness of the treatment • Diagnosing MASLD	**Other clinical practices** • Interdisciplinary care models • Metabolic syndrome optimization
Public health • Lack of national policies, action plans and strategies • Limited human and economic burden studies • Inequitable healthcare access	**Public health** • Align payment models to support lifestyle interventions • Support non-pharmacological and pharmacological treatment

Fig. 2 | Challenges and actions in the implementation of resmetirom. Integrating resmetirom into clinical practice raises challenges and requires actions to enhance and optimize treatment outcomes.

Much can be extrapolated about resmetirom drug rollout success from T2D. Physicians have observed barriers to using therapies for T2D, such as SGLT2i, which include a lack of understanding of the drug's benefits, unclear and divergent guidelines, challenges in real-world application with patients who do not fit the exclusion and inclusion criteria of approval, and insufficiently addressed safety concerns.

MASLD and MASH exist within the wider continuum of the metabolic syndrome, which includes T2D, hypertension, hyperlipidemia and obesity. The management of MASLD and MASH should accompany optimal management of other components of metabolic syndrome and their shared cardiometabolic risks, as the two principal causes of mortality for patients with MASH are cardiovascular disease and solid organ malignancy. It will be important to observe whether resmetirom, as the first therapy for the treatment of MASH, improves long-term MASH outcomes that translate to reductions in major adverse liver outcomes and premature death owing to cardiovascular and cancer risks. To optimize for those outcomes, the liver field may prescribe the drug in conjunction with NPIs as a part of treatment and care, consistent with the FDA's observations. Gastroenterologists and hepatologists have not had to grapple with discerning prescription endpoints for MASH medication discontinuation in the past, but they will in the future.

Multidisciplinary treatment

Metabolic syndrome is complex and requires multidisciplinary treatment and care. The near-term focus of educational efforts will probably be largely directed toward USA-based gastroenterologists, hepatologists and associated advanced practice providers actively involved in the management of patients with MASLD, particularly those diagnosed with MASH, given resmetirom has only been approved in the USA. However, MASLD diagnostic tools and resmetirom-specific awareness should also be distributed to general practitioners and endocrinologists to engage them in identifying people with high-risk MASH so that they can prevent and treat risks associated with MASH. In addition, awareness and education should become universal, given the high MASLD and MASH prevalence around the world.

Mental health conditions, including depression, can hinder lifestyle modification and medicine adherence in patients with MASLD[10]. Resmetirom prescription should include mental health referrals, where necessary, for behavioral modification and to address underlying mental issues, mitigate feelings of self-ineffectiveness and improve their likelihood of adhering to other, concomitant interventions (such as nutrition, exercise and cognitive-based therapies)[9]. Over time, we anticipate interdisciplinary models of care will further emerge[11].

Health systems preparedness

Operational readiness, including forecasting and costing, is needed for the uptake of resmetirom, including anticipating increased demand for MASLD diagnoses. Implementation of NPIs will require coverage and payment models that support lifestyle interventions and include specific referral codes (such as for psychoeducation, behavioral change techniques and digital health interventions).

Liver biopsy is the 'gold standard' for MASH diagnosis, leading to high specialist practice costs for initial diagnoses and potential risks for patients. Because of the insufficient supply of hepatologists worldwide, health systems must task-shift non-invasive tests to other healthcare providers (for example, advanced practice providers and general practitioners and their allied health workers); this will preserve specialist time for those with advanced fibrosis and prescribing MASH treatment[12,13]. The MASLD and MASH community of practice should develop consensus around the appropriate non-invasive tests acceptable to initiate treatment and monitor progression. A large phase 3 clinical trial based solely on non-invasive tests (MAESTRO-NAFLD-1) has shown the potential benefit and use cases as part of the trial design for resmetirom.

Industry implications following approval

Resmetirom was developed by Madrigal Pharmaceuticals, who will need to scale up operations and educate the healthcare providers who already have a large number of patients with MASLD in their practice, such as gastroenterologists, hepatologists and their advanced practice providers. Similarly, they will need to quickly seek other global regulatory approvals given pre-existing mutual recognition agreements (for example, in the European Union and UK), expand trials for underrepresented populations (such as pediatrics), improve efficacy via drug rollout trials paired with nutrition, exercise and/or synergistic pharmacological therapeutics, and support patient and provider education initiatives.

For medical technology companies focused on liver health testing and diagnostics, given that a liver biopsy is not required by the FDA to initiate treatment with resmetirom, there will probably be substantial increases in demand. These companies should take note of the field's need for greater accuracy in early-stage non-invasive testing, expanded access to diagnostics to close the gap between prevalence and diagnoses, and artificial intelligence-based tools and features for task-shifting and for enhanced productivity. For other pharmaceutical companies, several other hepatic-specific drugs are being tested in clinical trials, although many past trials have failed to achieve the requisite surrogate endpoints of MASH resolution and/or fibrosis improvement as stipulated by the FDA and European Medicines Agency.

Table 1 | Longer term implications following resmetirom approval in March 2024

Group	Long term implications
People living with MASH	• Scale-up awareness of MASH. • A near-future where biofeedback and diagnostics are increasingly directly in patients' hands. • Additional pharmacological and non-pharmacological treatments will be required as more is learnt about MASH, particularly its progression to cirrhosis and cancer and its bidirectional nature with other comorbidities. • Ceasing to refer to metabolic dysfunction-associated non-communicable diseases primarily as 'lifestyle' diseases, given the increasingly implicated role of genetic predisposition, social and commercial determinants, the inappropriate risk-shifting to individuals and the risk of inducing stigma or inviting discrimination.
Physician practices and health systems	• Address hepatology specialist talent supply-side challenges as demand from at-risk people increases. • Raise awareness, grow skills and task-shift some liver specialist work to general practitioners, endocrinologists, and advanced practice providers. • Expand people-centric practices and integrated models of cares, with closer coordination with other specialists focused on comorbidities, especially endocrinology, obesity management, clinical dietitians, and mental health. • Extend diagnostic and therapeutic opportunities, including the probable future displacement of highly invasive procedures such as liver biopsy as the focus moves to severe MASLD, advanced fibrosis, and onset of cirrhosis
Industry	• For the broader pharmaceutical industry, history shows that first to market is not necessarily best in terms of cost, efficacy or side-effects; continuation of other MASH-oriented trials to introduce alternative and competing or combination drugs remains important. • The pharmaceutical industry may experience price- or margin-erosion following the introduction of new drug approvals, regulated pricing, or price volume agreements. • Further inclusion of people living with MASH in the design of new clinical research and future trials to reflect real world challenges and benefit from lived experience
Public health policy	• The World Health Organization should publish a MASLD/MASH framework for member states with technical guidance, followed by a global action plan and strategy adopted by the World Health Assembly. • Public health researchers should expand the literature on the social gradient of health inequities compounded by social, structural, and commercial determinants of health. • Governments and health systems must enhance strategies to address the staggering costs of all forms of metabolic dysfunction-associated diseases. • The current MASLD/MASH community of practice must grow itself beyond hepatology and beyond medicine, to reach adjacent sectors, such as agriculture, food systems and broader health and non-communicable disease advocacy.

Public health policy for health systems

Patients and the MASLD community of practice can anticipate multiple reimbursement restrictions by payers, as approval of resmetirom could increase pharmacological costs to public and private third-party payers. Policymakers will need to reduce the socioeconomic burden and treat MASH through healthcare access, health insurance affordability, reduced food insecurity, expanded insurance affordability and support of non-pharmaceutical interventions.

Individuals with metabolic risk who also consume above recommended amounts of alcohol form a substantial cohort in the real world, including those previously diagnosed with MASLD (this condition is now termed metabolic and alcohol-associated liver disease, MetALD, a newly created steatotic liver disease subtype[1]). Policymakers must determine when treatment will be extended to people with MetALD, or, instead, whether combination therapies that focus on constituent pathophysiological processes (such as anti-steatotic, anti-fibrotic or anti-inflammatory) should be considered[14]. Medium- and long-term real-world outcomes of resmetirom are needed to support policymakers in decision-making; efforts should be focused on curating robust prospective data cohorts[13]. Policy implications of the approval of resmetirom do not occur in a vacuum and so policymaking in contexts with and without universal healthcare will be quite distinct.

Global access

The recent FDA approval of resmetirom presents a pathway to improved outcomes for patients eligible for resmetirom and their healthcare providers. Longer-term considerations are shown in Table 1.

Despite enthusiasm in the field, approval of resmetirom, in isolation, is not enough for many people; its use must be accompanied by awareness and education, pairing with non-pharmaceutical interventions and engagement across a range of disciplines to effectively treat comorbidities[9,15]. Healthcare providers, industry, and researchers must learn from resmetirom's effectiveness in real-world conditions. Greater access to this treatment must be addressed by international agencies, policymakers and public and private payers alike.

Outside the USA, people living with MASH in countries with mutual recognition agreements, such as the UK and Europe Union, should soon have access to resmetirom. However, once again, positive health outcomes will probably flow first to high-income countries, while patients with MASH elsewhere watch and wait.

As experts in liver disease and health systems, we have a sense of balanced optimism. Resmetirom, in the face of ever-rising MASH prevalence, offers positive glimpses of success in the fight against the most prevalent chronic liver disease in human history.

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Competing interests

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