



# Metabolic Dysfunction–Associated Steatotic Liver Disease (MASLD) in People With Diabetes: The Need for Screening and Early Intervention. A Consensus Report of the American Diabetes Association

*Diabetes Care* 2025;48:1057–1082 | <https://doi.org/10.2337/dci24-0094>

Metabolic dysfunction–associated steatotic liver disease (MASLD), formerly referred to as nonalcoholic fatty liver disease (NAFLD), is a growing but often unrecognized medical problem for people with diabetes (particularly type 2 diabetes, especially when associated with obesity). Liver health has not been at the forefront of complications tracked for disease prevention, as traditionally done for diabetic retinopathy, nephropathy, or neuropathy. However, liver steatosis affects approximately two out of three people with type 2 diabetes and places them at an increased risk for metabolic dysfunction–associated steatohepatitis (MASH), cirrhosis, hepatocellular carcinoma (HCC), and overall liver-related mortality. MASLD is also associated with extrahepatic cancers, atherosclerotic cardiovascular disease, and progression from prediabetes to type 2 diabetes and negatively impacts health-related quality of life. However, most individuals and their health care professionals remain unaware of the severe hepatic or extrahepatic health risks associated with MASLD and the need for early identification. In recognition of this knowledge gap and the rising prevalence of MASLD, this consensus report is a call to action to screen for liver fibrosis and risk stratify people with prediabetes or type 2 diabetes, in particular if obesity is also present. This consensus report explains the rationale for the recent MASLD nomenclature change, how to best risk stratify, current treatment and long-term monitoring options, the value of an interprofessional approach to disease management, and the impact of alcohol intake on liver health. More awareness about the health risks associated with MASLD and broad adoption of screening for liver fibrosis as a new standard of care hold promise for a future without cirrhosis for people with prediabetes and type 2 diabetes.

Until recently, liver health has been somewhat overlooked in the context of prediabetes and type 2 diabetes. The growing prevalence and serious health implications of metabolic dysfunction–associated steatotic liver disease (MASLD), formerly referred to as nonalcoholic fatty liver disease (NAFLD), have prompted a call to action

Kenneth Cusi,<sup>1</sup> Manal F. Abdelmalek,<sup>2</sup> Caroline M. Apovian,<sup>3</sup> Kirthikaa Balapattabi,<sup>4</sup> Raveendhara R. Bannuru,<sup>4</sup> Diana Barb,<sup>1</sup> Joan K. Bardsley,<sup>5</sup> Elizabeth A. Beverly,<sup>6,7</sup> Karen D. Corbin,<sup>8</sup> Nuha A. ElSayed,<sup>4,9</sup> Scott Isaacs,<sup>10</sup> Fasiha Kanwal,<sup>11</sup> Elizabeth J. Pegas,<sup>4</sup> Caroline R. Richardson,<sup>12</sup> Michael Roden,<sup>13,14,15</sup> Arun J. Sanyal,<sup>16</sup> Jay H. Shubrook,<sup>17</sup> Zobair M. Younossi,<sup>18,19</sup> and Mandeep Bajaj<sup>11</sup>

<sup>1</sup>Division of Endocrinology, Diabetes and Metabolism, University of Florida, Gainesville, FL

<sup>2</sup>Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN

<sup>3</sup>Division of Endocrinology, Diabetes and Hypertension, Brigham and Women's Hospital, Boston, MA

<sup>4</sup>American Diabetes Association, Arlington, VA

<sup>5</sup>MedStar Diabetes Institute, Washington, DC

<sup>6</sup>Heritage College of Osteopathic Medicine, Ohio University, Athens, OH

<sup>7</sup>Diabetes Institute, Ohio University, Athens, OH

<sup>8</sup>AdventHealth Translational Research Institute, Orlando, FL

<sup>9</sup>Harvard Medical School, Boston, MA

<sup>10</sup>Division of Endocrinology, Metabolism, and Lipids, Emory School of Medicine, Emory University, Atlanta, GA

<sup>11</sup>Department of Medicine, Baylor College of Medicine, Houston, TX

<sup>12</sup>The Warren Alpert Medical School of Brown University, Providence, RI

<sup>13</sup>Department of Endocrinology and Diabetology, Medical Faculty, and University Hospital Düsseldorf, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany

<sup>14</sup>Institute for Clinical Diabetology, German Diabetes Center - Leibniz Center for Diabetes Research at Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany

<sup>15</sup>German Center for Diabetes Research, Partner Düsseldorf, München-Neuherberg, Düsseldorf, Germany

<sup>16</sup>Virginia Commonwealth University School of Medicine, Richmond, VA

<sup>17</sup>Department of Clinical Sciences and Community Health, College of Osteopathic Medicine, Touro University California, Vallejo, CA

<sup>18</sup>The Global NASH Council, Washington, DC

<sup>19</sup>Beatty Liver and Obesity Research Program, Inova Health System, Falls Church, VA

Corresponding author: Kenneth Cusi, [kenneth.cusi@medicine.ufl.edu](mailto:kenneth.cusi@medicine.ufl.edu)

Received 22 October 2024 and accepted 25 March 2025

This article contains supplementary material online at <https://doi.org/10.2337/figshare.28673327>.

by the American Diabetes Association (ADA). The overarching goal of this consensus report is to provide guidance to health care professionals for the care and prevention of liver disease for people with prediabetes or diabetes.

Table 1 summarizes the clinical implications for adults with prediabetes or diabetes of having MASLD. In the U.S., the prevalence of MASLD among people with type 2 diabetes is  $\geq 70\%$ , with approximately half having the more progressive form with metabolic dysfunction–associated steatohepatitis (MASH) and about one in five having advanced liver fibrosis (1–3). Similar trends are observed worldwide in adults with type 2 diabetes (4–6). The presence of MASH markedly increases the risk of developing liver-related complications such as cirrhosis, hepatocellular carcinoma (HCC), and overall mortality. MASLD is one of the most common indications for liver transplantation in the U.S. (7), and having type 2 diabetes is independently associated with higher posttransplantation mortality, especially after kidney transplantation (8). Having MASLD significantly increases the likelihood of developing type 2 diabetes, cardiovascular disease, and extrahepatic malignancies (6). Finally, MASLD has a major negative impact on health-related quality of life and has become a significant economic burden (9).

Despite these alarming trends, a significant lack of awareness remains among both people at risk and clinicians regarding the health perils associated with MASLD and how best to manage it, often resulting in the condition being overlooked and untreated. There is a pressing need for heightened awareness, early diagnosis, and comprehensive management. This consensus report aims to address this knowledge gap with a clinical care pathway to manage people with prediabetes or diabetes and MASLD. Health care professionals must recognize that an early diagnosis is possible by using noninvasive tests (NITs) to stratify people for their

risk of developing cirrhosis. A timely diagnosis can encourage the adoption of healthier lifestyle habits or the initiation of pharmacological treatments for obesity and type 2 diabetes, which can prevent disease progression and, ultimately, cirrhosis. Numerous medications are currently under development to treat MASH. In 2024 the U.S. Food and Drug Administration approved resmetirom as the first pharmacological agent for people with MASH (10). Improvements in steatohepatitis and liver fibrosis were reported with semaglutide after 72 weeks of treatment in a phase 3 clinical trial, supporting an upcoming indication for MASH (11).

This guidance also covers the best practices for monitoring MASLD once diagnosed or in response to treatment. Because managing both hepatic and extrahepatic conditions associated with diabetes and MASLD is challenging, this guidance recommends the development of interprofessional teams that support the primary care physician and endocrinologist, including professionals such as registered dietitian nutritionists (RDNs), diabetes care and education specialists (DCES), behavioral health specialists, obesity management teams, pharmacists, hepatologists, and other specialists. Currently, numerous health care barriers hinder the delivery of optimal person-centered care for MASLD in primary care settings (12). This guidance also discusses integrating management pathways into electronic medical records (EMRs) to enhance care and the impact of alcohol intake on liver health and provides considerations for managing diabetes in individuals with cirrhosis and HCC.

Cirrhosis from MASLD is preventable in people with diabetes through early diagnosis, proper treatment, and long-term monitoring, similar to the management of care for diabetes-related microvascular complications (retinopathy, nephropathy, or neuropathy) or cardiovascular disease. With increased

clinician awareness and action, individualized education, more effective care models, and robust public health policies (13,14), we aim to catalyze a shift in clinical practice that will improve outcomes and the quality of life of people with diabetes and MASLD.

## RESEARCH DESIGN AND METHODS

The ADA convened a technical expert panel of health care professionals who play a key role in the prevention and management of diabetes and MASLD, and an experienced member of the panel was chosen as a chair to lead the development of the report. Panelist inclusion was based on excellence in clinical care, research, leadership, collaboration, and writing and editing; commitment to evidence-based practice; and availability to volunteer (unpaid) for the report development process. The number of panelists was chosen based on consideration of the health care professionals likely to be included as a part of diabetes and MASLD care teams (e.g., primary care physicians, endocrinologists, hepatologists, behavioral health specialists, obesity management specialists, RDNs, DCES, etc.). ADA solicited nominations from the pool of experts on record and from other relevant societies. ADA led the selection process and invited the experts to join this panel. In the event of invited panel members opting not to participate, the subsequent nominee on the list was invited. A preliminary version of this report was presented at the ADA 84th Scientific Sessions, and public feedback received during and after that session was incorporated into the subsequent versions of this report.

Prior to the initiation of evidence review and writing, the panel was convened in a virtual meeting and agreed on the proposed goal, content, methodology, and rigor to be followed for this consensus report. An additional virtual meeting was held for discussion of sub-

---

*This consensus report was reviewed and approved by the American Diabetes Association (ADA) Professional Practice Committee (PPC) in March 2025.*

*An ADA consensus report is a document on a particular topic that is authored by a technical expert panel under the auspices of ADA. The document does not reflect the official ADA position but rather represents the panel's collective analysis, evaluation, and expert*

*opinion. The primary objective of a consensus report is to provide clarity and insight on a medical or scientific matter related to diabetes for which the evidence is contradictory, emerging, or incomplete. The report also aims to highlight evidence gaps and to propose avenues for future research. Consensus reports undergo a formal review process, including external peer review and review by the ADA PPC and ADA scientific team, for publication.*

*This article is featured in a podcast available at [diabetescareonair.libsyn.com/site](https://diabetescareonair.libsyn.com/site).*

© 2025 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at <https://www.diabetesjournals.org/journals/pages/license>.

**Table 1—Clinical implications of MASLD in people with prediabetes and diabetes**

|                                                                                       |                                                                                                                                                                                         |
|---------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Adults with prediabetes and type 2 diabetes have the highest risk of developing MASLD | Adults with prediabetes and type 2 diabetes, especially those with obesity, should be risk stratified for having MASLD and liver fibrosis.                                              |
| Increased risk of severe liver disease                                                | MASLD with clinically significant fibrosis (stage $\geq$ F2) raises the risk of cirrhosis, liver cancer, and overall liver-related mortality.                                           |
| Leading cause for liver transplantation                                               | Approximately one in five people with type 2 diabetes are at high risk of developing cirrhosis due to MASLD, making it one of the leading reasons for liver transplantation in the U.S. |
| Higher likelihood of developing a broad spectrum of comorbidities                     | MASLD increases risk of progression from prediabetes to type 2 diabetes, development of cardiovascular disease, and extrahepatic malignancies.                                          |
| Negatively impacts quality of life                                                    | MASLD significantly impacts health-related quality of life and represents a significant economic burden.                                                                                |
| Importance of an early diagnosis                                                      | Timely identification and proper management can prevent the progression of fibrosis to cirrhosis in people with MASLD.                                                                  |

sections and writing teams to contribute to the sections of the report. The technical expert panel, with the assistance of a methodologist, conducted literature searches in PubMed and the Cochrane Library using related medical subject headings and terms to identify studies published in English through April 2024. The literature search was updated in November 2024. To identify appropriate evidence, the panel prioritized information from systematic reviews, randomized controlled trials, and observational studies. Questions related to clinical practice and interprofessional team collaboration for the prevention and care of liver disease in people with diabetes or prediabetes provide the foundation of this report. This document includes recent information about nomenclature and clinical definition, epidemiology, diagnosis, treatment, and topics of special consideration (e.g., development of interprofessional teams, cirrhosis, and alcohol intake).

Monthly virtual meetings were held between December 2023 and November 2024 along with email and Web-based collaboration as needed. An in-person meeting was conducted in April 2024 to finalize discussion of evidence, reach consensus on the present guidance, discuss the tables and graphic design elements, and finalize writing content. Meetings were recorded, and meeting summaries were provided to panel members via an online collaboration platform and email.

This consensus guidance was developed under the auspices of ADA and represents the technical expert panel's collective analysis and evaluation. ADA

and the panel were committed to fostering a collaborative environment of respectful communication. Panel members were asked to focus on evidence-based discussion and clinical judgement rather than personal opinions or biases, which warranted supplying supporting evidence for their discussions. ADA scientific team members were present for all discussions and helped ensure that all perspectives were taken into account. These principles were conducive to mitigating conflict, respectful discussion, and consensus building.

The nominal group technique was used to reach consensus on the guidance presented in this document, which was facilitated by the consensus report chair and the ADA scientific team. Topic areas and questions were posed to the full group by the chair and other panel members during virtual and in-person meetings. The panel used discussion in a roundtable or similar fashion to take all ideas into account. These discussions were carried out in detail so as to clarify meaning, resolve questions and/or clarifications, and bring forth new ideas. The technical expert panel collectively finalized the topic areas and reached consensus on the guidance covered in this document in a nonanonymous group setting during the virtual and in-person meetings, where each member "agreed" or "strongly agreed" in a rotating sequence, ensuring that all voices were heard before a decision was made. Verbal responses were aggregated in real time during these meetings and in written fashion from comments on collaborative documents. At the end of each meeting, the panel members were

provided with qualitative summaries, including topic areas for which consensus was reached and topics that required further attention on an ongoing basis.

The nominal group technique presented several strengths and some limitations. This methodology was used to encourage equal participation by all panel members and to facilitate discussion of diverse ideas. This allowed the panel to discuss viewpoints of all members of the interprofessional care team. Though this methodology had its advantages, time periodically posed a concern. Every effort was made to give topics ample time for deliberation. Complex topics were given priority at meetings to allow full discussion of insights and perspectives. The qualitative meeting summaries shared with the panel after each meeting allowed for reflection and opportunity to bring forth further discussion points throughout the development of the report until consensus on these topics was reached.

## SECTION 1. CLINICAL DEFINITIONS AND NOMENCLATURE CHANGE FROM NAFLD TO MASLD

Table 2 summarizes the current nomenclature with the most relevant clinical definitions. In Supplementary Table 1, we describe the mortality risk associated with each liver disease stage, the most commonly used NITs, and the optimal setting for health care professionals managing care for people with MASLD.

Three multinational liver associations recently agreed to modify the nomenclature from NAFLD to MASLD (15). MASLD was

**Table 2—MASLD nomenclature, histological grades, and fibrosis staging**

| Nomenclature                                                      | Definition                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Steatotic liver disease (SLD)                                     | <ul style="list-style-type: none"> <li>An “umbrella” term encompassing different disease subcategories, characterized by predominantly hepatic macrovesicular steatosis</li> </ul>                                                                                                                                                                                                                                                  |
| Metabolic dysfunction–associated steatotic liver disease (MASLD)* | <ul style="list-style-type: none"> <li>Presence of SLD with at least one metabolic risk factor (overweight or obesity or waist circumference &gt;95th percentile, hypertension, prediabetes or type 2 diabetes, elevated triglycerides, or low HDL cholesterol) and either no alcohol consumption or consumption in amounts not likely to directly lead to liver outcomes (&lt;20 g/day for women, &lt;30 g/day for men)</li> </ul> |
| Metabolic dysfunction–associated steatotic liver (MASL)           | <ul style="list-style-type: none"> <li>Steatosis with either no or minimal lobular inflammation and without ballooning and alcohol consumption below thresholds noted above</li> </ul>                                                                                                                                                                                                                                              |
| Metabolic dysfunction–associated steatohepatitis (MASH)           | <ul style="list-style-type: none"> <li>Presence of steatohepatitis and at least one metabolic risk factor for SLD and no alcohol consumption or consumption in amounts not considered likely to cause liver outcomes by itself as noted above</li> </ul>                                                                                                                                                                            |
| At-risk MASH                                                      | <ul style="list-style-type: none"> <li>Steatohepatitis (with histological MASLD activity score [MAS] <math>\geq 4</math>) and fibrosis stage <math>\geq F2</math> (i.e., people who are at a higher risk of developing future cirrhosis) (see below)</li> </ul>                                                                                                                                                                     |
| MASLD activity score (MAS)**                                      | <ul style="list-style-type: none"> <li>Sum of scores for steatosis (0–3) plus hepatocellular ballooning (0–2) plus lobular inflammation (0–3)</li> </ul>                                                                                                                                                                                                                                                                            |
| Fibrosis stages                                                   | <ul style="list-style-type: none"> <li>Based on severity and distribution of scar tissue</li> <li>Mild fibrosis: stage F1 (i.e., fibrosis in hepatic sinusoids in pericellular location)</li> <li>Moderate fibrosis: stage F2 (i.e., sinusoidal and portal fibrosis)</li> <li>Advanced fibrosis: stage F3 (i.e., bridging fibrosis, usually central-to-portal or central-to-central bridges) or stage F4 (cirrhosis)**</li> </ul>   |
| Clinically significant fibrosis                                   | <ul style="list-style-type: none"> <li>Fibrosis stage <math>\geq F2</math></li> </ul>                                                                                                                                                                                                                                                                                                                                               |

\*The definition of MASLD implies either no alcohol consumption or consumption in amounts not considered to lead to liver outcomes by itself. \*\*Extensive disruption of liver architecture with regenerative nodules with encirclement by fibrotic bands.

defined as steatotic liver disease (SLD) in the presence of at least one cardiometabolic risk factor (such as prediabetes or type 2 diabetes) without other identifiable secondary cause of steatosis (15) (Fig. 1). Likewise, the term nonalcoholic steatohepatitis (NASH) has been replaced with MASH (15). The aim of the new names (MASLD and MASH) is to highlight the pathogenic role of insulin resistance and metabolic dysfunction, remove any potential stigma from the terms nonalcoholic and fatty, and serve as a pragmatic diagnostic aid by virtue of inclusion of at least one of the cardiometabolic risk factors in the definition, these being already well known to the health care community in the context of metabolic syndrome and type 2 diabetes.

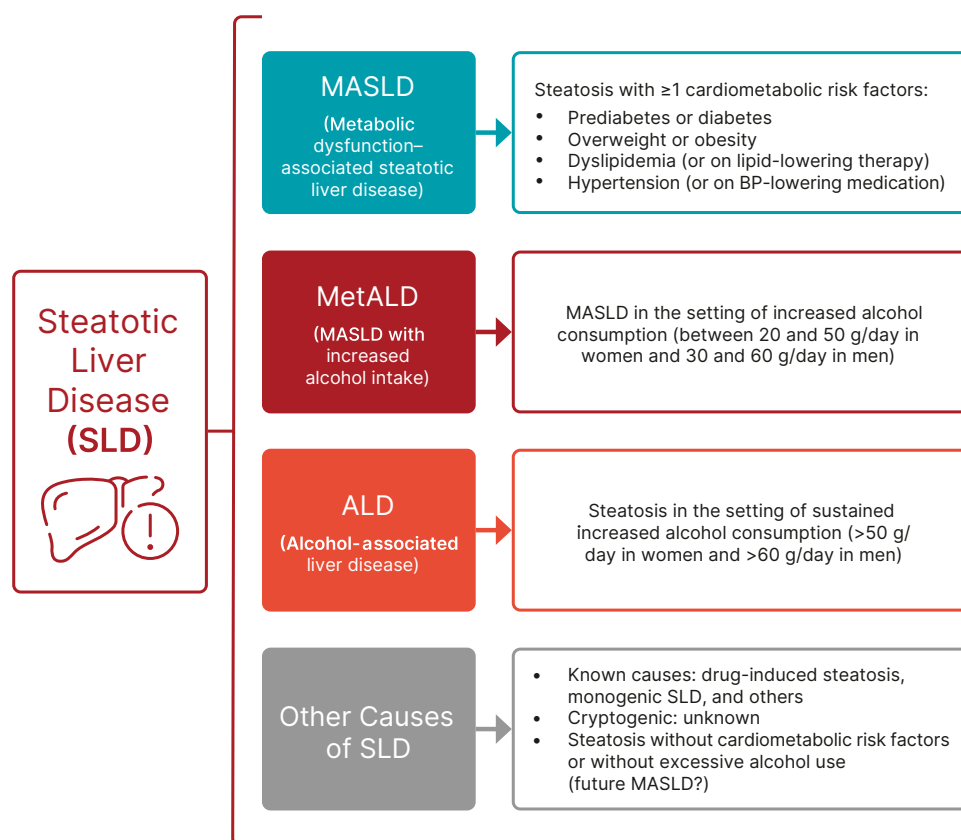
Table 3 summarizes the contributions of the new terminology and current knowledge gaps. There is a high correlation between NAFLD and MASLD in population-based studies (16–18). In comparing their concordance among 12,519 eligible participants from the National Health and Nutrition Examination Survey (NHANES) III, only 5.3% of NAFLD cases did not meet MASLD criteria. Of 6,429 adults with NAFLD, 99% met MASLD criteria, with 95% doing so on the basis of BMI only (17). The high concordance between NAFLD

and MASLD is attributable to the very high prevalence of overweight or obesity in the general population and that 85% of adults, even without steatosis, have at least one cardiometabolic risk factor (18).

Prediabetes and diabetes are now identified as important cardiometabolic risk factors for the development of MASLD, advanced fibrosis, and cirrhosis (19). However, randomized controlled trials (RCTs) will be needed for understanding of the role of hyperglycemia in the development and progression of MASLD, as findings of some studies have been of an association between suboptimal glycemic management and steatosis or fibrosis (20), while in others either a modest or no association was observed (4,21). In addition, there are no RCTs on the role of optimal glycemic management in liver outcomes in MASLD, independent of improving insulin resistance (e.g., with pioglitazone) or promoting weight loss (e.g., glucagon-like peptide 1 receptor agonists [GLP-1RA]). It must also be recognized that diabetes encompasses a spectrum of etiologies, including many where insulin deficiency rather than insulin resistance predominates (e.g., type 1 diabetes, cystic fibrosis–related diabetes, and pancreatogenic diabetes, along with

others) and where the risk of steatohepatitis with clinically significant fibrosis is overall low (4,22). Recent studies have identified novel diabetes subtypes that appear more prone to development of MASLD (23). With factors taken together, future studies should include risk stratification and careful assessment of the natural history of MASLD in individuals with different subtypes of diabetes.

Several additional aspects of adopting the new nomenclature should be considered (24). Future studies should be conducted for examination of the relative specificity of each cardiometabolic risk factor included in the definition of MASLD to predict liver outcomes. Type 2 diabetes and obesity among them have the strongest diagnostic concordance with MASLD and atherogenic dyslipidemia has the least. One should bear in mind that some of these cardiometabolic risk factors may develop through mechanisms unrelated to insulin resistance (25) and, under such circumstances, be of less value for consideration in association with MASLD. Nevertheless, linking steatosis with these cardiometabolic risk factors may improve clinicians' disease awareness and referral patterns, which deserve future investigation. Clinicians should be careful in attributing steatosis to



**Figure 1**—Nomenclature changes in SLD. BP, blood pressure; MetALD, metabolic dysfunction and alcoholic liver disease.

MASLD by virtue of the presence of one of these cardiometabolic risk factors and be aware of alternate causes of steatosis, for many of which specific therapies are available. (See diagnostic considerations in *SECTION 3. DIAGNOSIS* and Supplementary Table 2). Finally, while recent data confirm that obesity worsens the risk of hepatic fibrosis in young adults (aged 18–44 years) with type 2 diabetes (26), at the other end of the spectrum young adults may have isolated steatosis with insulin resistance without obesity or evident cardiometabolic disease (27). Clinicians should not miss the opportunity for these individuals with presumable “early” MASLD to risk stratify and encourage lifestyle intervention.

The perception of stigma arising from obesity, and in some cases from the term fatty in NAFLD, affects a significant number of people with this disease and is highly variable among affected individuals and their clinicians and across geographic regions (28). While the new nomenclature MASLD may function to reduce stigma, much work remains in eliminating additional contributing factors. Finally, a separate category named

MetALD has been created for individuals with MASLD and an alcohol intake that is greater than that for MASLD classification but less than in alcohol-associated liver disease (ALD) (15) (Fig. 1). Future studies will be needed to help determine its natural history and the impact of lifestyle interventions and pharmacotherapy to prevent cirrhosis from MetALD.

## SECTION 2. EPIDEMIOLOGY: MAGNITUDE OF THE PROBLEM

### Prevalence of MASLD in Prediabetes and Type 2 Diabetes

MASLD has become the most common cause of chronic liver disease, affecting >38% (2016–2019) of the world’s adult population and 7%–14% of children and adolescents (6,29). The prevalence of MASH among the general population is estimated at 5%–7%, while the prevalence of MASLD-related cirrhosis is 1.8% (6). These rates are much higher in people with type 2 diabetes, with estimated prevalence of ~70% for MASLD, ~35% for MASH, and ~7% for MASLD-related cirrhosis (1–6,30,31).

Recent data also suggest that the prevalence of MASLD among those with

prediabetes is between ~37% and 50% (32). In fact, people with prediabetes are 2.5 times more likely than those without prediabetes to have MASLD, 8.5 times more likely to have significant fibrosis, and almost 6 times more likely to have advanced fibrosis (32).

### Incidence of MASLD in Prediabetes and Type 2 Diabetes

The incidence rate of MASLD has been reported to be 49 per 1,000 person-years (6). The bidirectional association of type 2 diabetes and MASLD is suggested by the twofold higher incidence of type 2 diabetes among those with MASLD (33,34). The most important predictors for prediabetes and type 2 diabetes are having overweight or obesity and MASLD (34).

Additionally, having type 2 diabetes is associated with an increased relative risk of fibrosis progression (35–37), while 15%–38% of people with type 2 diabetes have MASH with clinically significant liver fibrosis or cirrhosis (also known as at-risk MASH [see fibrosis stage definitions in Table 2 and Supplementary Table 1]) (1–6,26,31,38). The presence of MASLD



**Table 3—Contributions of the nomenclature change to MASLD and areas of future research**

| Contributions of the new term MASLD                                                                                                                                                      | Areas of future research                                                                                                                                                                                                                                                              |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| The term metabolic dysfunction highlights the key role of insulin resistance and metabolic alterations in the pathophysiology of MASLD.                                                  | • Examine disease heterogeneity regarding insulin resistance and other metabolic factors in people with MASLD.                                                                                                                                                                        |
| Prediabetes and diabetes are now clearly defined as cardiometabolic risk factors for MASLD.                                                                                              | • Understand the role of prediabetes and of suboptimally managed diabetes in the development and progression of MASLD.<br>• Establish the role of different diabetes types (e.g., type 1 diabetes, cystic fibrosis–related diabetes, other) and of novel diabetes subtypes/endotypes. |
| Steatosis plus ≥1 cardiometabolic risk factors (MASLD) offers a “positive” diagnosis and clinical correlate for metabolic dysfunction, as compared with the previous definition (NAFLD). | • Investigate the concordance of steatosis with various cardiometabolic risk factors and their specificity to predict future clinical outcomes (hepatic and extrahepatic).<br>• Assess whether MASLD improves clinician’s diagnostic and referral patterns.                           |
| High concordance between MASLD and NAFLD in population-based studies allows the use of previous research results.                                                                        | • Define the natural history and role of lifestyle intervention for isolated steatosis, as observed in young adults in primary care settings.                                                                                                                                         |
| The change from the term fatty to steatotic removes potential stigma.                                                                                                                    | • Explore factors associated with stigma across ethnic, cultural, and socioeconomic backgrounds.                                                                                                                                                                                      |
| The new subgroup MetALD enables categorization of individuals with alcohol use and cardiometabolic factors.                                                                              | • Study the natural history of MetALD and the role of different interventions to halt or ameliorate liver disease progression.                                                                                                                                                        |

has been associated with increased incidence of other metabolic-related diseases such as cardiovascular disease (43% increase), prediabetes (69%), chronic kidney disease (38%), and all cancers (54%) (39).

**Prevalence of MASLD in Prediabetes and Type 2 Diabetes According to World Region and Ethnicity**

Beyond metabolic comorbidities, diverse genetic, environmental, and socioeconomic determinants of health explain the heterogeneous prevalence of MASLD around the world. In people with type 2 diabetes, the prevalence of MASLD is highest in Eastern Europe (80%), followed by the Middle East (71%), and lowest in Africa (53%) (40). In the U.S., MASLD prevalence differs by ethnicity and is highest for Hispanic, especially Mexican American, and lowest for Black individuals. These differences are most likely explained by differences in acquired risk factors (e.g., prevalence of obesity, diabetes, and socioeconomic determinants of health) and the genetic polymorphisms of *PNPLA3*, *TM6SF2*, and *MBOAT*, among others (41). The prevalence of MASLD usually increases among men until age 50 years; then, risk for women begins to be higher for MASH and advanced fibrosis (42). In this context, MASH can cause a significant burden for women

and is currently the number one cause of liver transplantation among women (43). Lastly, socioeconomic disparities also exist for MASLD disease burden. In particular, food insecurity (the limited or uncertain access to nutritionally adequate foods) is associated with higher odds among adults of developing MASLD and MASLD-associated advanced fibrosis independent of poverty status, education level, race, and ethnicity (44). Similar findings were reported among teenagers from food insecure homes (45).

**Clinical Outcomes and Quality of Life in People With MASLD**

Although the presence of liver fibrosis is the most significant predictor of mortality for those with MASLD, it is well known that the severity of metabolic abnormalities, especially in the case of type 2 diabetes, is a major driver of mortality among MASLD (30,32). In this context, the presence of an increasing number of metabolic abnormalities leads to increasing risk of mortality in MASLD, with the highest risk of mortality among people with type 2 diabetes (4.0-fold increase in risk) followed by those with prediabetes (3.4-fold increase in risk) (32).

In addition to cirrhosis, HCC is an important consequence of MASLD. Although

the presence of cirrhosis in MASLD substantially increases the risk of HCC, those with MASLD without cirrhosis can also develop HCC (46). In this context, as type 2 diabetes predisposes to MASLD, diabetes seems to be a risk factor for developing HCC. Dysregulated glucose homeostasis, hyperinsulinemia, and lipid accumulation in the liver can activate pathways promoting hepatic tumor development in individuals with MASLD and type 2 diabetes (37,38). MASH-related HCC is now the number one indication for liver transplantation among those listed for HCC (47). In the context of liver transplant, it is important to note that the presence of diabetes prior to transplant, the receipt of a liver from a donor with diabetes, or developing diabetes posttransplant are all associated with higher risk of mortality and graft loss (48).

In addition to the clinical outcomes, MASLD is also associated with decreased health-related quality of life. The ability to be physically active is the domain most adversely affected, possibly due to fatigue (49). Finally, MASLD has significant economic consequences for society due to increased health care use and decreased quality of life, particularly among those with more metabolic comorbidities (49).

### SECTION 3. DIAGNOSIS

#### Rationale for Screening for Hepatic Fibrosis in Prediabetes and Diabetes

The rationale for any screening strategy is applying adequate diagnostic tools to eventually treat a condition that may lead to serious morbidity and mortality. This is the case for people with type 2 diabetes with at-risk MASH (defined as steatohepatitis with clinically significant fibrosis or fibrosis stage  $\geq 2$ ) (50,51) (Table 2 and Supplementary Table 1). In at-risk MASH, hepatic fibrosis is the target of screening because it is the most important determinant of liver and non-liver outcomes in people with MASLD, with the risk demonstrably higher for people with at-risk MASH (52). Several professional societies (53–58), including the ADA (59), recommend screening high-risk individuals for at-risk MASH to prevent fibrosis progression and cirrhosis. Screening followed by intensive lifestyle intervention or pioglitazone has been suggested to be cost-effective (60).

#### Steatosis in Individuals With Prediabetes and Type 2 Diabetes

Diagnosing hepatic steatosis begins with obtaining a medical history and laboratory testing. While a liver ultrasound has in the past been widely used to diagnose hepatic steatosis, the presence of an echogenic liver itself is not highly specific, as its diagnosis is operator dependent and ultrasound has poor sensitivity for mild steatosis (61). Because having obesity and prediabetes or type 2 diabetes is associated with a high pre-test probability of hepatic steatosis ( $\geq 70\%$ ) (1–6), one may proceed directly to fibrosis risk assessment without an ultrasound to confirm steatosis. (See *PREVALENCE OF MASLD IN PREDIABETES AND TYPE 2 DIABETES ACCORDING TO WORLD REGION AND ETHNICITY*.) Further, management is impacted by the diagnosis of clinically significant fibrosis and not by the diagnosis of steatosis per se. Therefore, the focus has shifted toward detection of fibrosis severity (i.e., at-risk MASH), which is closely linked to the risk of clinical outcomes (Supplementary Table 1 and Fig. 2). Within the workup to establish the presence of fibrosis, or as part of secondary testing when there is diagnostic uncertainty because of abnormal plasma aminotransferases (ALT or AST), steatosis can be diagnosed with the controlled attenuation parameter from a vibration-controlled

transient elastography (VCTE) examination. Values  $>280$  dB/m are highly likely indicative of having steatosis. MRI is the gold standard for confirmation of steatosis (i.e., MRI-derived proton density fat fraction PDFF [MRI-PDFF] or  $^1\text{H-MRS}$ ) (62,63).

Some individuals may have abnormal plasma aminotransferase levels. In people with MASLD, having an elevated ALT level is suggestive of steatohepatitis but not necessarily of more severe liver fibrosis or cirrhosis (1,64–66). In such cases, alternate causes of liver disease, such as hepatitis B or C and ALD, need to be excluded (Supplementary Table 2). The Centers for Disease Control and Prevention recommend universal screening at least once for hepatitis B (67) and C (68) for all adults  $>18$  years of age. Hepatitis C is now curable in virtually all individuals. Alcohol consumption is widespread in many communities and has a synergistic effect with obesity for liver-related morbidity and mortality. All clinicians should be able to perform an alcohol-related liver disease assessment (Supplementary Table 3). The presence of both, metabolic risk factors and alcohol use (20–50 g/day for women and 30–60 g/day for men), should be considered indicative of the possibility of underlying MetALD (Fig. 1). People who consume alcohol regularly should be counseled, with appropriate management. (See *SECTION 8. ALCOHOL INTAKE AND LIVER HEALTH*.) Workup of uncommon causes of increased plasma aminotransferase levels may require referral to a liver specialist (Supplementary Table 3).

Another important consideration is awareness by the health care team about how to best deliver the diagnosis of MASLD as it may affect a person's acceptance of their condition and their ability to manage it. Thus, engaging in a clear, open conversation to explain the clinical implications of MASLD is essential. Understanding and acceptance of their condition often allow for adoption of proactive and problem-solving coping strategies that may reduce psychosocial concerns and support engagement in lifestyle modification and the treatment plan.

#### Fibrosis Risk Stratification

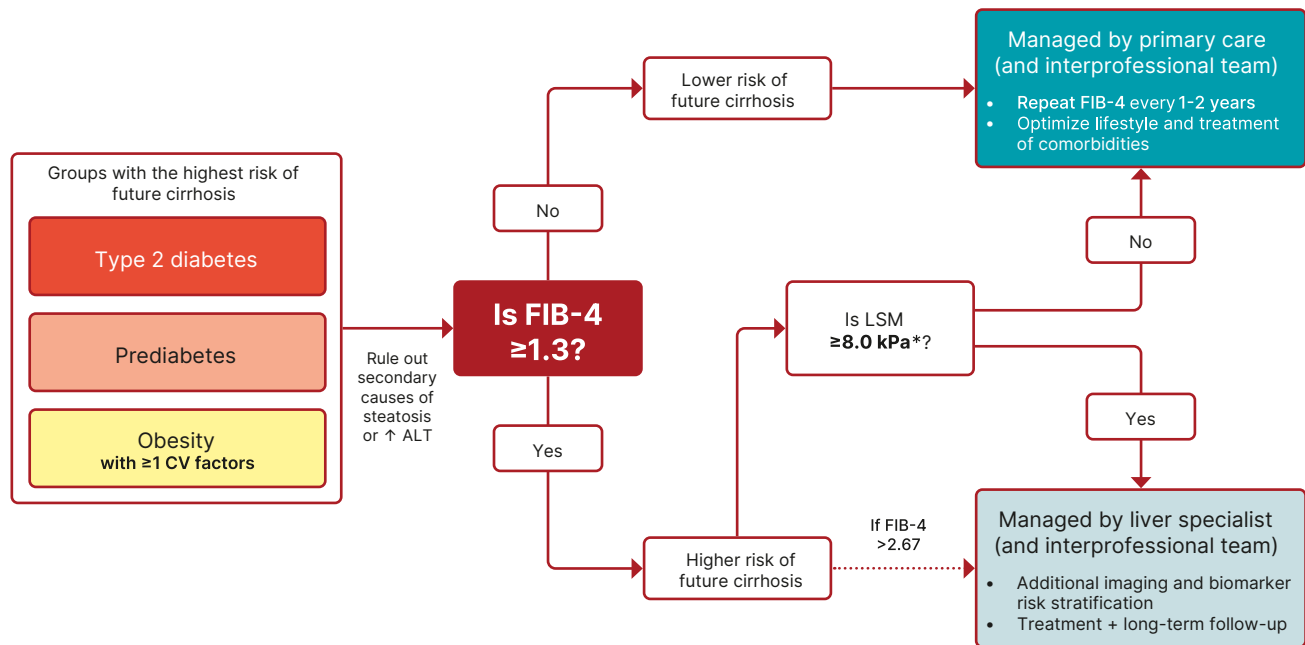
Adults with type 2 diabetes should undergo a two-tier process for assessment

for diagnosing at-risk MASH because fibrosis stage reflects proximity to development of liver cirrhosis and is thus a strong prognostic biomarker. Figure 2 summarizes the preferred NITs for the initial and secondary fibrosis risk stratification and optimal management setting for people at high risk for MASLD. (See also Supplementary Table 1 and Table 4.)

The first step in this two-tier process begins with laboratory testing, which should include a comprehensive metabolic panel and complete blood count; plasma aminotransferase levels (ALT and AST), platelet count, and age allow for calculation of a simple noninvasive marker of liver fibrosis, the fibrosis-4 index (FIB-4) (Fig. 2 and Table 4). FIB-4 as the first-tier test has several advantages: it is simple and inexpensive to use, a robust negative predictive value of a FIB-4 score for exclusion of advanced fibrosis (69,70), and, most importantly, test results at baseline as well as longitudinal changes in FIB-4 predict clinical outcomes in people with MASLD (71–76), including in individuals with type 2 diabetes (77). In a recent comparative study, overall diagnostic accuracy of FIB-4 was found to be similar to that of most other proprietary and nonproprietary biomarkers among individuals with biopsy-confirmed MASLD included in the Liver Investigation: Testing Marker Utility in Steatohepatitis (LITMUS) cohort (78).

A FIB-4 score  $<1.3$  can reliably be used to exclude advanced fibrosis (Fig. 2), with a negative predictive value of  $\geq 90\%$  (69). Individuals with values below this cutoff do not need further evaluation (in particular, with a FIB-4 score  $<1.0$ ). With age as a contributor to the FIB-4 score calculation, its performance may be affected for people  $\leq 35$  or  $\geq 65$  years of age. One study recommended using a cutoff of 2.0 to rule out clinically significant fibrosis in people  $\geq 65$  years old (57). However, there are limited data that confirm the 2.0 cutoff. Hence, we suggest using a simplified approach that relies on a threshold of 1.3 for considering a second-tier test (79,80).

Approximately 30%–40% of individuals with obesity and prediabetes or type 2 diabetes may have a FIB-4 score  $>1.3$ , and they should undergo a second test for further risk stratification as part of the two-tier approach (1–3). Individuals with a FIB-4 score  $>2.67$  ( $\leq 5\%$  of individuals with type 2 diabetes in nonhepatology



**Figure 2**—Diagnostic algorithm for risk stratification and the prevention of cirrhosis in individuals with MASLD. \*In the absence of LSM, consider the blood-based ELF test as a diagnostic alternative. If ELF score is  $\geq 9.8$ , a referral to a liver specialist is recommended, as there is a high risk of MASH with advanced liver fibrosis. Adapted from “Standards of Care of Diabetes—2025” (59).

settings) are at increased risk for advanced fibrosis, with a positive predictive value for clinically significant fibrosis ranging from 60% to 80% (81). These individuals can be directly referred (without the need of additional risk stratification at the primary care level) to gastroenterologists and hepatologists to assess for the presence of at-risk MASH or cirrhosis (Fig. 2). Most clinical care pathways endorse the use of liver stiffness measurement

(LSM), most commonly with transient elastography (VCTE), as the second step in the two-tier approach (Fig. 2). A stepwise FIB-4 plus VCTE-based algorithm performed well in stratifying the risk of future liver-related events in a recent multicenter cohort (80). A VCTE-derived LSM of  $<8.0$  kPa rules out advanced fibrosis accurately most times (81) and is associated with a low risk of liver outcomes (82,83), and people with LSM  $<8.0$  kPa should

be followed in primary care and endocrinology clinics with repeat surveillance in 1–2 years (see *LONG-TERM MONITORING*). Individuals with LSM  $>8.0$  kPa should be referred to gastroenterology or hepatology specialists for additional diagnostic testing. Shear wave elastography, point shear wave elastography, and other ultrasound-based methods can also be used for initial risk stratification, but they are not as well validated as VCTE.

**Table 4**—Preferred tests for the initial (FIB-4) and secondary (VCTE, ELF) liver fibrosis risk stratification of people at high risk for MASLD\*

|       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| FIB-4 | Calculated with the following inputs: age, AST and ALT levels, and platelet count.<br>First-line screening test for clinically significant fibrosis (stage $\geq F2$ ).<br>If FIB-4 score is $>1.3$ , additional risk stratification is needed.<br>Calculator: <a href="https://www.mdcalc.com/calc/2200/fibrosis-4-fib-4-index-liver-fibrosis">https://www.mdcalc.com/calc/2200/fibrosis-4-fib-4-index-liver-fibrosis</a>                                                                                                                                                                                                                      |
| VCTE  | Imaging technique for LSM, extensively validated with liver histology as a surrogate of liver fibrosis stage.<br>Second-line screening test for clinically significant fibrosis (stage $\geq F2$ ).<br>Diagnostic cutoffs:*<br><ul style="list-style-type: none"> <li>• LSM score <math>&gt;8</math> kPa = stage <math>\geq F2</math> (clinically significant fibrosis)</li> <li>• LSM score <math>&gt;10</math> kPa = stage F3 or F4 (advanced fibrosis)</li> <li>• LSM score <math>&gt;15</math> kPa = stage F4 (cirrhosis)</li> </ul>                                                                                                        |
| ELF   | A blood test that helps identify individuals with advanced fibrosis and at risk of developing cirrhosis or liver-related outcomes.<br>A score obtained from three proteins linked to liver fibrosis (hyaluronic acid, amino-terminal propeptide of type III procollagen [PIIINP], and tissue inhibitor of metalloproteinase-1 [TIMP-1]).<br>Second-line screening test for clinically significant fibrosis (stage $>F2$ ).<br>Diagnostic cutoffs:*<br><ul style="list-style-type: none"> <li>• ELF score <math>&gt;9.8</math> = stage F3 or F4 (advanced fibrosis)</li> <li>• ELF score <math>&gt;11.2</math> = stage F4 (cirrhosis)</li> </ul> |

\*Since NITs have significant interindividual variability and overlapping CIs across fibrosis stages, it is best to consider results in the context of having a “probability” of a given liver disease stage rather than the certainty that only a liver biopsy can provide.



The Enhanced Liver Fibrosis (ELF) test can also be used as a second-tier test (84) (Fig. 2, Supplementary Table 1, and Table 4). ELF is a noninvasive blood-based proprietary test approved for prognostication when advanced fibrosis is suspected, although it can be ordered for secondary risk assessment, particularly because the availability of VCTE may be limited in some settings. The ELF test includes a panel of biomarkers consisting of three components: type III procollagen peptide, hyaluronic acid, and tissue inhibitor of metalloproteinase-1. An ELF score  $<7.7$  is associated with a very low risk of fibrosis, whereas a score  $\geq 9.8$  helps identify people with MASLD with advanced fibrosis and at increased risk of progression to cirrhosis and liver-related clinical events (85–88). An ELF score  $>11.3$  is associated with the highest risk of hepatic decompensation events, and such cases are best managed in a hepatology setting (89,90). ELF has proven useful in guiding referrals in primary care and diabetes clinic populations (91,92). An ELF score  $<9.8$  suggests a low risk of advanced liver fibrosis, which may be followed in primary care or endocrinology settings with repeat testing at  $\geq 2$  years. Individuals with ELF score  $\geq 9.8$  should be referred for secondary assessment due to the increased risk of liver-related events. Of note, the optimal ELF cutoff for use in nonhepatology clinics is evolving; management decisions should be individualized when the ELF score is between 9.2 and 9.7 based on clinical risk (i.e., testing may be needed more often in a high-risk individual with multiple cardiometabolic risk factors).

#### Referral Guidelines, Overview of Additional Tests by Specialists, and Role of Liver Biopsy

Individuals with a FIB-4 score  $>1.3$  and VCTE-derived LSM  $\geq 8.0$  kPa or an ELF score  $\geq 9.8$  should be considered for referral to liver specialty clinics (gastroenterology or hepatology) for additional assessment (Fig. 2). In liver clinic settings, imaging-based methods are usually used for better estimation of the fibrosis stage, including magnetic resonance elastography (MRE) (93) or multiparametric MRI-derived iron-corrected T1 (cT1) (which may identify people with at-risk MASH) (94). In head-to-head comparisons, MRE has higher accuracy in detecting liver fibrosis, especially in

earlier stages, than VCTE (95–97). While MRE may not be the initial choice for risk stratification due to cost and access considerations, it can serve as a valuable tool in specialty clinics, especially in cases of uncertainty or unreliable VCTE results. VCTE-derived LSM  $>10$  kPa and MRE-derived LSM  $>3.5$  kPa suggest advanced fibrosis (i.e., liver fibrosis stages 3 [F3] and 4 [F4]) and a value  $>15$  kPa and MRE values  $>4.4$  kPa are consistent with a high probability of cirrhosis (i.e., stage F4) (98). VCTE-derived LSM  $>25$  kPa (99), VCTE-derived LSM  $>20$  kPa with platelet counts  $\leq 150,000/\text{mm}^3$ , and MRE-derived LSM  $>5.7$  kPa are all reflective of likely having clinically significant portal hypertension (100) (Supplementary Table 1).

Liver biopsy is generally considered when noninvasive assessments are inconclusive or when alternative diagnoses are suspected. NIT results that may improve identification of advanced fibrosis or cirrhosis among individuals attending liver clinics and decrease the need for liver biopsy include transient elastography-based scores such as Agile 3+ (VCTE-LSM combined with AST-to-ALT ratio, platelet count, sex, diabetes status, and age) or Agile 4 (VCTE-LSM combined with AST-to-ALT ratio and platelet count for diagnosis of cirrhosis) (101–103), MRE-based measures such as MRI-AST (MAST) score (MRE plus AST) or MEFIB index (MRE plus FIB-4) (104,105), and used more recently to identify at-risk MASH, results from blood-based proprietary tests such as NIS2+ score (from a two-biomarker test derived from YKL-40 and miR-34a-5p corrected for sex) (102,103) or Metabolomics-Advanced Steatohepatitis Fibrosis Score (MASEF score) (a metabolomics-driven score) (106) and MRI-derived cT1 (94) (Supplementary Table 1).

#### Long-term Monitoring

The chronic nature and fluctuating course of MASLD require monitoring of the disease state in affected individuals. There is also a high possibility of de novo development of MASLD in individuals with diabetes, supporting the need for monitoring individuals without MASLD at the initial evaluation. Initiation of therapy also requires follow-up to assess treatment response. The best evidence-based guidance is summarized below.

#### Long-term Follow-up of Individuals With a FIB-4 Score $<1.3$ at Initial Evaluation

A growing body of literature indicates that most individuals with a FIB-4 score  $<1.3$  are unlikely to have increased liver-related outcomes or mortality within a 5-year time frame (76,107,108). These individuals may therefore be considered relatively low-risk, and management is usually focused on optimization of body weight, diabetes management, and underlying risk factors. However, there are limited data on how often to repeat FIB-4 testing because the natural history of fibrosis progression in MASH is not fully established and is highly variable among people with type 2 diabetes. In a prospective study from Hong Kong with use of repeated imaging (VCTE), worsening in LSM was found in 12% of participants after 3 years of follow-up (109). Of note, FIB-4 is a low-cost test with acceptable negative predictive value but with modest sensitivity and positive predictive value. With factors taken together, we recommend that individuals with an initial FIB-4 score  $<1.3$  be reassessed with repeat FIB-4 measurements in 1–2 years. Clinically significant fibrosis may be present in some adults with type 2 diabetes and FIB-4 values between 1.0 and 1.3, especially when type 2 diabetes is associated with obesity and multiple cardiometabolic risk factors. For instance, in a recent large phase 3 study with recruitment of people with MASLD with fibrosis stages F2 and F3, often with obesity and type 2 diabetes, the mean  $\pm$  SD of the FIB-4 score was  $1.4 \pm 0.7$  (10). This indicates that for some individuals with at-risk MASH FIB-4 score may be  $<1.3$ , especially in the context of obesity and type 2 diabetes. Therefore, a FIB-4 score cutoff of  $<1.3$  should be taken as a general guidance for assessment of having a lower risk of advanced fibrosis, but it does not replace clinical judgement. Case finding with eventual additional testing may be justified with a FIB-4 score between 1.0 and 1.3 in people with type 2 diabetes with obesity or other traditional cardiometabolic risk factors. For these cases transient elastography may also be of benefit as part of risk assessment. The risk of developing MASLD has been independently associated with insulin resistance, weight gain, obesity, and cardiometabolic risk factors (110–112). In contrast, individuals with type 2 diabetes without MASLD often have less

insulin resistance and a more favorable cardiometabolic profile in comparison with those with steatosis (113,114).

Once MASH with fibrosis develops, progression to more advanced stages is believed to occur at an average rate of 7 years per stage progression (115). Therefore, those whose FIB-4 score increases from  $<1.3$  to  $>1.3$  should be referred for transient elastography. Given the potential for underestimation of fibrosis severity in those with type 2 diabetes, those who progress from  $<1.0$  to values between 1.0 and 1.3 may also be considered for secondary assessment with VCTE or an ELF test (74–84).

#### **Long-term Follow-up of Individuals With a FIB-4 Score $\geq 1.3$ at Initial Evaluation**

In the majority ( $>90\%$ ) of people from primary care and endocrinology clinics, a FIB-4 score  $>1.3$  will range between 1.3 and 2.67. A FIB-4 score between 1.3 and 2.67 was initially considered indicative of “indeterminate risk” for having advanced fibrosis, reflecting the score range between a high-sensitivity cutoff for ruling out (FIB-4 score  $<1.3$ ) and a high-specificity cutoff for ruling in (FIB-4 score  $>2.67$ ) advanced fibrosis (116). However, more recent studies directly relating FIB-4 score between 1.3 and 2.67 to clinical outcomes indicate that, for people either with or without type 2 diabetes, rates of death, liver-related deaths, liver outcomes, and cardiovascular disease are higher among those with a FIB-4 score between 1.3 and 2.67 than among those with a FIB-4 score  $<1.3$  (76). Because of this increased risk of negative outcomes, it is recommended that for people with a FIB-4 score  $>1.3$  risk stratification with transient elastography be considered a requirement, as discussed above.

People with a FIB-4 score  $>1.3$  but VCTE-LSM  $<8.0$  kPa can be followed in non-liver specialty clinics with repeat surveillance in 1–2 years. Most guidelines (53–59) recommend LSM by VCTE as the leading disease monitoring tool, as it predicts future outcomes (83,117). In a global cohort of  $>16,000$  individuals, an increase in VCTE-LSM by  $\geq 30\%$  was associated with increased risk of adverse clinical outcomes (83). The transient elastography-based FibroScan-AST (FAST) score, for detection of at-risk MASH, and the Agile scores, for detection of advanced fibrosis or cirrhosis

(Supplementary Table 1), are additional scores that may be helpful in this regard (83,101,118,119). For these elastography-based scores VCTE-LSM is combined with routine blood parameters and clinical features. Although not representative of a substantial diagnostic improvement, these scores may help reduce the number of people with inconclusive results from VCTE-LSM alone (83,101,118,119).

People with a FIB-4 score  $>1.3$  and VCTE-LSM  $>8.0$  kPa should undergo more diagnostic testing in gastroenterology or hepatology specialty clinics for confirmation of at-risk MASH or cirrhosis. In individuals with cirrhosis, an increase in liver stiffness and a decrease in platelet counts to  $<150,000$  are associated with development of portal hypertension, which is a key driver of clinical decompensation (99). Annual transient elastography along with platelet counts may be considered for this subgroup. Screening for HCC and assessment of Model for End-Stage Liver Disease (MELD) score and complication(s) of portal hypertension should be performed every 6 months in individuals with cirrhosis to ensure timely diagnosis of HCC and referral for liver transplant for a rising MELD score, particularly to values of  $\geq 15$ .

Individuals with a FIB-4 score  $>2.67$  at initial evaluation are at high risk for advanced fibrosis, liver-related outcomes, and all-cause mortality. Approximately 3%–5% of people with type 2 diabetes and MASLD may have an initial FIB-4 score  $>2.67$  (1–3). Such individuals can be directly referred to gastroenterologists or hepatologists for evaluation of the presence or absence of cirrhosis and initiation of cirrhosis-related care for HCC surveillance, to prevent decompensation and delay the need for liver transplant, if indicated.

As the disease progresses, people with type 2 diabetes and MASLD may experience increased frustrations and worries about their future. The interprofessional team should consider screening for depressive symptoms and anxiety. As complications dominate, people need to learn to live with challenges that impact their usual level of activity and feeling of well-being.

#### **Assessment of Response to Treatment**

Individuals with a FIB-4 score  $>1.3$  and a second test (i.e., VCTE-LSM) confirming at-risk MASH may receive treatment

for obesity or type 2 diabetes (e.g., GLP-1RA, dual glucose-dependent insulinotropic polypeptide [GIP] and GLP-1 receptor agonist [dual GIP/GLP-1RA], or pioglitazone) that may also impact underlying MASH, or they may receive treatment specifically targeting MASH (e.g., resmetirom or semaglutide). FIB-4 is not very sensitive to fibrosis change, and its increase or decrease only occurs after substantial changes in fibrosis stage (69). Furthermore, short-term improvement (6–12 months) in FIB-4 likely reflects changes in inflammation (i.e., plasma aminotransferases) rather than fibrosis. On the other hand, several studies have shown that liver stiffness measures improve after effective drug intervention, and sustained improvement has been reported in clinical trial settings (120). These data support the use of transient elastography (VCTE-LSM) to evaluate responses to therapeutic intervention. Improvement by  $\geq 30\%$  represents therapeutic response, whereas an increase by  $\geq 30\%$  reflects disease progression (83). Referral to the gastroenterologist or hepatologist is warranted if there is a suggestion of disease progression.

#### **Assisting Implementation: Use of EMRs**

The value of EMR-integrated clinical decision support tools in MASLD is multifaceted. EMR use facilitates the incorporation of MASLD clinical practice guidelines into the clinical workflow. EMRs with FIB-4 scores can engage people through granting access to their data, empowering them in their health care journey. In EMR systems FIB-4 calculation can be automated, streamlining risk stratification in clinical practice (121). This can serve as a decision support tool in flagging people with high FIB-4 scores for further evaluation, aiding early detection, secondary testing, and referrals to the liver specialist and other members of the MASLD interprofessional team. EMR integration can assist in disease monitoring and tracking disease progression over time, providing insights for optimizing medical care. Additionally, this integration can contribute to research and population health management, from understanding the natural history of the disease in the “real world” to assessing the role of different lifestyle interventions and pharmacotherapy.

Overall, EMR-integrated clinical decision support tools will play an important

role for busy clinicians in screening implementation for high-risk individuals and improve clinical outcomes.

## SECTION 4. TREATMENT

Management of MASLD in adults involves an interprofessional team including but not limited to primary care physicians, endocrinologists, nurses, RDNs, DCES, behavioral health specialists, obesity management teams, pharmacists, and liver and other medical specialists. The comprehensive care plan includes lifestyle modification, weight management, and pharmacological treatment aimed at preventing cardiovascular disease and MASH cirrhosis (59).

### Lifestyle Modification

A healthy lifestyle is the foundation of treatment in people with type 2 diabetes and MASLD. Figure 3 summarizes a broad spectrum of useful lifestyle interventions. In people with overweight and obesity, the magnitude of weight loss correlates overall with improved glycemic management, insulin sensitivity, and histological improvement in MASH, including fibrosis (122,123). Among people with MASH, weight loss of  $\geq 5\%$  of total body weight decreases steatosis. Weight loss of  $>5\%$  usually is needed to reverse steatohepatitis (56,122,124,125). Many studies suggest that even more weight reduction ( $\geq 10\%$ ) is needed to improve

fibrosis and that the response can be highly variable (56,57,122,124). Of note, improvement in liver histology may be seen with lesser degrees of weight loss and, conversely, only modest improvement with significant weight loss.

When lifestyle modification includes individualized nutrition diagnosis, treatment, and behavior modification recommendations, it should be delivered by an RDN. However, all health care team members can reinforce general nutrition guidance. Furthermore, it is essential to use appropriate psychosocial care methods and provide access to diabetes self-management education and support (DSMES) services as a critical part of healthy lifestyle interventions for people with type 2 diabetes and MASLD (126).

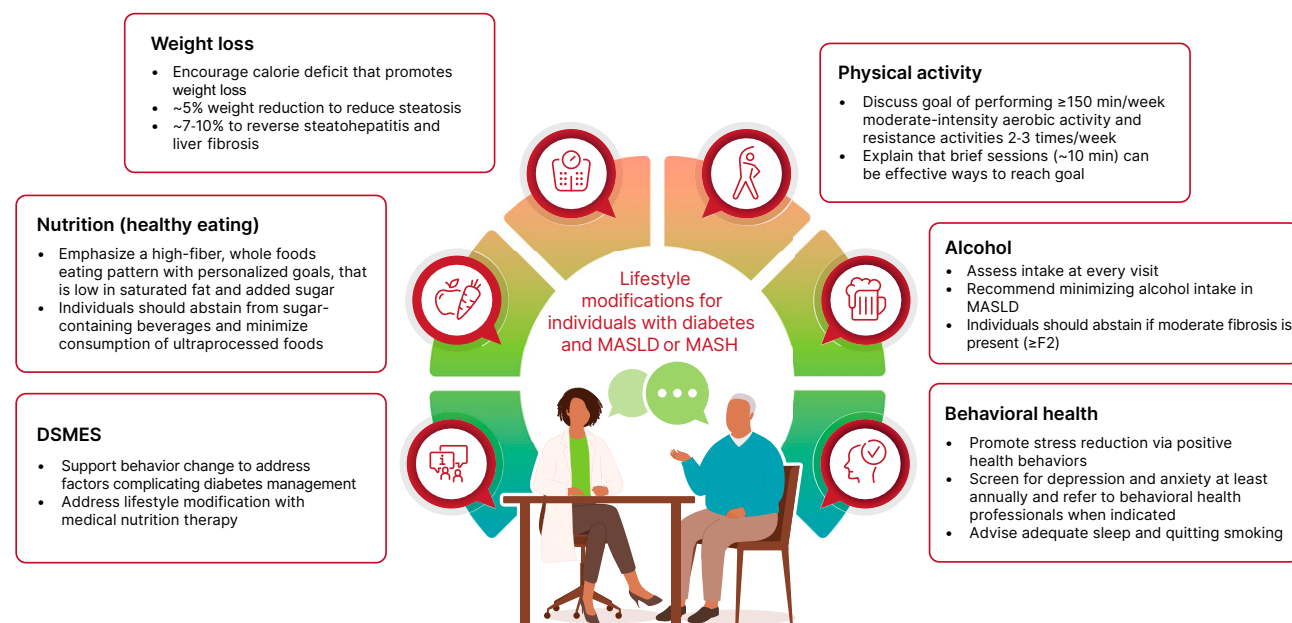
### Nutrition Plans

Nutrition plans should be tailored to the individual's social, work, cultural, and financial context and provided in a practical, implementable format. Given that MASLD often clusters in families, and family support is crucial for success, family counseling should be included (69). Evidence suggests that no ideal calorie percentage from carbohydrates, proteins, and fats can be broadly recommended for all people with prediabetes or diabetes (127). However, nutrition plans high in saturated fat and sugar (from sucrose and/or high-fructose corn syrup)

are associated with postprandial hypertriglyceridemia, insulin resistance, and higher risk of MASLD or MASH with fibrosis progression in high-risk individuals (122,128). Increased fructose consumption is associated with fibrosis severity, independent of total caloric intake (128). In macronutrient distribution avoidance of ultraprocessed foods and reduction in saturated fat and simple sugars and fructose consumption should be emphasized, as should an eating pattern enriched with high fiber and unsaturated fats (56,57,126,127).

Various nutritional approaches (e.g., low fat vs. low carbohydrate, Mediterranean diet, Dietary Approaches to Stop Hypertension [DASH] diet, high protein, meal replacement, and intermittent fasting, among others) seem comparable in their ability to improve steatosis (129,130), but their benefit for steatohepatitis and fibrosis have not been adequately studied (122). A (culturally appropriate) Mediterranean eating pattern (rich in fruits, vegetables, whole grains, and heart healthy fats) is preferred due to the best long-term data on beneficial cardiometabolic risk factor reduction and mortality benefit (122,129–131) and is endorsed in current MASLD guidelines (55,56,58,59,122).

Alcohol consumption increases the risk of cirrhosis and HCC (132). It should be avoided in individuals with at-risk MASH. (See *SECTION 8. ALCOHOL INTAKE AND LIVER HEALTH.*)



**Figure 3**—Lifestyle modification for individuals with prediabetes or diabetes and MASLD.

## Physical Activity

Structured exercise has been shown to decrease insulin resistance, plasma aminotransferases, and steatosis in individuals with MASLD (133–136). Different exercise types and intensities can produce different outcomes, with aerobic activity potentially offering greater hepatic benefits than other types (133,134) and high-intensity activity improving MASH and fibrosis (137).

Although current guidelines recommend accumulating at least 150 min of moderate- or 75 min of vigorous-intensity activity weekly and performing resistance activities two to three times per week for individuals with diabetes or MASLD or MASH (126,138), care teams should personalize activity plans based on individual needs, goals, and preferences as well as provide resources to support activity self-efficacy and long-term adoption (126). Minimizing sedentary time and engaging in brief sessions (~10 min) of simple activities such as walking with the goal of meeting activity guidelines should be encouraged (126). Resistance training may prevent sarcopenia and functional decline (133,139).

## Behavioral Health

Psychosocial care should be provided to all people with type 2 diabetes and MASLD to optimize health-related quality of life. There is a lack of large, high-quality studies for evidence-based best treatment recommendations for depression, anxiety, binge eating disorder, serious

mental illness, or substance use, specifically in MASLD (140). Drawing from the type 2 diabetes literature, evidence-based approaches include cognitive behavioral therapy, mindfulness-based therapy, and/or pharmacotherapy (126). All may be of help to treat mental health issues in adults with diabetes and MASLD that often overlap with obesity and its comorbidities, as well as with the use of obesogenic psychiatric medications. Behavioral health professionals should monitor outcomes systematically to assess progress and ongoing needs.

## DSMES

DSMES services provided by a DCES have been shown to support behavior change in people with type 2 diabetes. DSMES should be offered at least annually to people with type 2 diabetes and MASLD (for more details, refer to ADA “Standards of Care in Diabetes—2025” [Standards of Care] [126]). While basic healthy eating guidance is provided during DSMES sessions, coordination with the RDN ensures that specific nutrition therapy related to the person’s liver disease is addressed (141).

Although there are limited data on behavioral weight loss interventions in MASLD (142), structured nutrition and exercise intervention in addition to health education should be offered to all people with MASLD (57,126,143–145). These interventions share similarities with strategies for the management of obesity

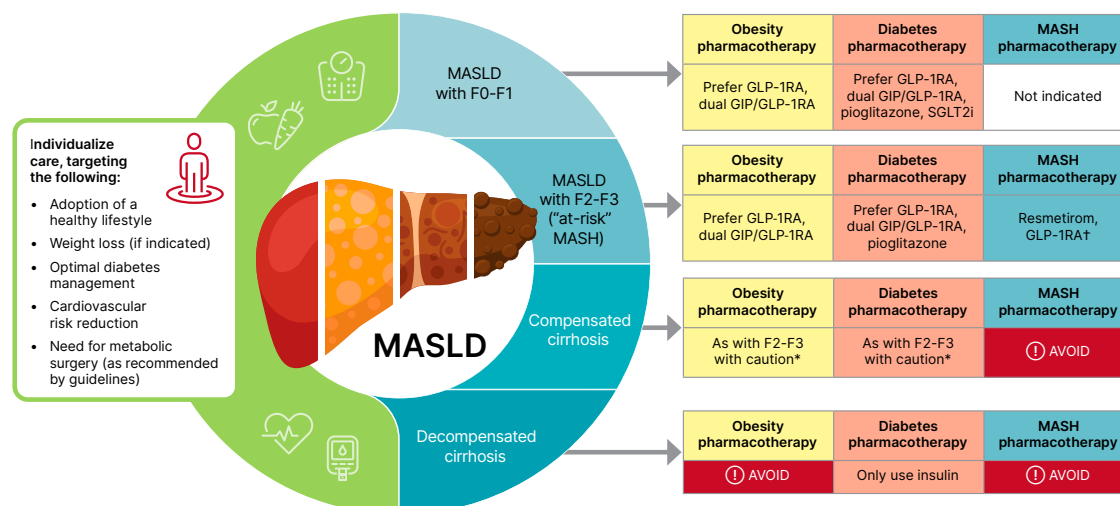
and for the prevention and treatment of type 2 diabetes (146). Literacy about fibrosis stage and risk of MASLD progression may improve adherence to lifestyle intervention (147–149).

## Pharmacological Treatment of Obesity and Role of Metabolic Surgery in MASLD

### Pharmacological Treatment of Obesity in MASLD

Together with lifestyle optimization, pharmacotherapy should always be considered in the management of people with diabetes with overweight or obesity and MASLD. Lifestyle modification alone often is unable to achieve or maintain long-term weight loss of the magnitude usually recommended to reverse steatohepatitis and fibrosis (>10%) (56,57,122).

Pharmacological therapy for obesity in MASLD should be individualized, potential risk-benefit and cost considered, and treatment strategies reassessed often over time. Figure 4 summarizes the management of MASLD in considering the severity of liver disease and the pharmacological options for obesity or type 2 diabetes with potential to reverse steatohepatitis, as well as MASH-specific therapies (i.e., resmetirom). GLP-1RA reduce cardiovascular disease, the main cause of death in MASLD (150), and offer renal protection to people with type 2 diabetes (see ADA Standards of Care [151,152]). Certain GLP-1RA also reduce cardiovascular disease in individuals



**Figure 4**—MASLD treatment algorithm for individuals with prediabetes or diabetes. Fibrosis stages: F0 and F1, mild or no liver fibrosis; F2, moderate fibrosis; F3, advanced fibrosis. CV, cardiovascular; SGLT2i, SGLT2 inhibitors. \*Individualized care and close monitoring is needed in compensated cirrhosis given limited safety data available. †Only semaglutide among GLP-1RA has been reported to be of benefit in a phase 3 RCT with histological outcomes in MASH. Adapted from “Standards of Care of Diabetes—2025” (59).

without diabetes with overweight or obesity and preexisting cardiovascular disease (153).

At present, no obesity pharmacotherapy has an approved indication for MASLD, but GLP-1RA have reported positive results in phase 2 RCTs and a phase 3 RCT. In a phase 2 RCT where 320 participants with MASH (65% with type 2 diabetes) received treatment with semaglutide, a GLP-1RA, MASH resolution without worsening of fibrosis occurred in 59% of individuals vs. 17% on placebo ( $P < 0.001$ ). Fibrosis did not improve (43% in the 0.4-mg group vs. 33% in the placebo group, respectively,  $P = 0.48$ ), but fewer individuals on semaglutide had worsening of fibrosis at 72 weeks (4.9% in the 0.4-mg group vs. 18.8% in the placebo group) (154). Recently, the phase 3 Effect of Semaglutide in Subjects with Non-cirrhotic Non-alcoholic Steatohepatitis (ESSENCE) trial in 800 participants with MASH (11) reported that for 36.8% of individuals treated for 72 weeks with semaglutide 2.4 mg s.c. once weekly improvement in liver fibrosis was achieved with no worsening of steatohepatitis, compared with 22.4% on placebo ( $P < 0.001$ ), while 62.9% achieved resolution of steatohepatitis with no worsening of liver fibrosis, compared with 34.3% on placebo ( $P < 0.001$ ) (11).

Tirzepatide, a dual GIP/GLP-1RA, has also been studied for the treatment of MASH. In an early study in adults with type 2 diabetes and MASLD, it had been reported that 52 weeks of treatment decreased liver fat by up to 47%, compared with 11% with insulin degludec ( $P < 0.001$ ) (155). In the phase 2 SYNERGY-NASH trial, treatment of 190 adults with overweight or obesity and MASH (50%–60% with diabetes) for 52 weeks with tirzepatide at doses of 5, 10, and 15 mg/day resulted in resolution of steatohepatitis without worsening of fibrosis in 44%, 56%, and 62% of participants, respectively, compared with 10% with administration of placebo ( $P < 0.001$  for all three comparisons) (156). The percentage of participants with an improvement of at least one fibrosis stage without worsening of MASH was 55%, 51%, and 51% of participants, respectively, compared with 30% with placebo. Finally, in an early proof-of-concept trial in individuals with MASH, the GLP-1RA liraglutide at a mean daily dose of 1.3 mg/day was reported to have positive

results after 48 weeks of treatment. MASH resolution occurred in 9 of 23 (39%) participants who were treated with liraglutide, compared with 2 of 22 (9%) in the placebo group ( $P = 0.019$ ) (157). Progression of fibrosis was seen in only 9% of those who received liraglutide compared with 36% in the placebo group ( $P = 0.04$ ).

Promising dual and triple agonists in the pipeline also include survodutide, a dual glucagon and GLP-1 receptor agonist. In 295 participants with overweight or obesity and MASH (clinical trial reg. no. NCT04771273, ClinicalTrials.gov), all doses of survodutide (2.4, 4.8, and 6.0 mg/day) met the primary outcome: a decrease of at least 2 points in NAFLD activity score without worsening of fibrosis, as well as MASH resolution. At the highest dose, significant improvement in liver fibrosis was seen in individuals with at-risk MASH ( $P < 0.001$ ) (158). Tests are also ongoing of retatrutide, a triple GIP receptor agonist, GLP-1RA, and glucagon receptor agonist, for the management of MASH. In phase 2 trials, retatrutide induced dose-dependent weight loss in people with type 2 diabetes (159) or obesity (160). In a subset of 98 people with obesity and MASLD ( $\geq 10\%$  liver fat, assessed with MRI-PDFF), the higher dose of retatrutide (12 mg s.c. once weekly) normalized liver fat in 90% of participants at the higher doses and improved biomarkers of steatohepatitis after 48 weeks of treatment (161).

For other U.S. Food and Drug Administration–approved weight management agents, i.e., orlistat (an oral lipase inhibitor), centrally acting oral combinations such as phentermine/topiramate ER or naltrexone/bupropion ER, or daily liraglutide 3 mg s.c., rigorous histological evidence of benefit in MASH is lacking, although they may reduce plasma aminotransferases or steatosis in the case of significant weight loss (56,162). There have been reports from several clinical trials that liraglutide at doses used to treat diabetes (up to 1.8 mg) or obesity (3.0 mg) (163,164) ameliorate steatosis, along with a report from a 48-week pilot study of histological improvement (157).

#### **Metabolic Surgery for the Treatment of MASLD**

Metabolic (also termed bariatric) surgery in people with diabetes improves glycemic management, promotes diabetes remission (165), and prevents cardiovascular

disease (146,166–168). Metabolic surgery improves steatosis in 70%–80% of individuals, with resolution of inflammation and hepatocyte ballooning (necrosis) in 50%–75% and fibrosis in 30%–40% (169,170). Metabolic surgery also reduces the risk of HCC (170,171) and other cancers (171). Although most data are from case-control observational studies, in an RCT in 288 adults with biopsy-confirmed MASH, lifestyle modification plus best medical care was compared with Roux-en-Y gastric bypass or sleeve gastrectomy (172). The primary outcome of resolution of MASH without worsening of fibrosis at 1 year of follow-up was achieved in 56% and 57% of the Roux-en-Y gastric bypass and sleeve gastrectomy groups, respectively, compared with 16% with lifestyle modification ( $P < 0.0001$ ). Among participants who completed the trial (82%), the primary outcome with either type of surgery was met in 70% of participants, compared with 19% with lifestyle modification ( $P < 0.0001$ ).

The long-term benefit of metabolic surgery for the treatment of MASH is possibly best illustrated with an observational study where 606 adults with obesity and MASH, but without cirrhosis, were matched to a nonsurgical control group ( $n = 550$ ) and followed for a median of 7 years (172). The metabolic surgery group showed more favorable long-term outcomes compared with the nonsurgical group, including significantly lower major adverse liver outcome occurrence (2.3% vs. 9.6%, respectively,  $P = 0.01$ ) and a significant reduction in cardiovascular events (8.5% vs. 15.7%, respectively,  $P = 0.007$ ). Thus, metabolic surgery can significantly reduce the risk of cirrhosis and cardiovascular disease, although lack of significant weight loss is associated with failure to reverse steatohepatitis or fibrosis. Endoscopic metabolic surgeries are less invasive options, but more robust evidence is needed for recommendations for their use to treat obesity in adults with MASLD (56,57).

Metabolic surgery should be recommended with caution in compensated cirrhosis from MASLD (i.e., asymptomatic stage of cirrhosis without associated liver complications), as the risk of hepatic decompensation appears comparable with that for individuals with less advanced liver disease when performed in experienced centers with interprofessional



teams (173,174). However, long-term studies are needed to better establish the safety and efficacy of metabolic surgeries and which type is best. There is significantly less information on procedures in people with clinically significant portal hypertension or decompensated cirrhosis (i.e., with complications such as variceal hemorrhage, ascites, hepatic encephalopathy, or jaundice), but overall these conditions are associated with worse outcomes and metabolic surgery should only be considered together with liver transplantation in tertiary centers. Therefore, metabolic surgery is not recommended in decompensated cirrhosis, given the limited outcome data available and the higher risk of postoperative liver-related complications (55–57).

#### Pharmacological Treatment of Type 2 Diabetes in MASLD

Approximately 15%–20% of adults with type 2 diabetes (1,2,4,21,175) have at-risk MASH and are on a path to develop cirrhosis if untreated (1,2,4,21,176,177). This high prevalence is comparable with or higher than that for other diabetes-related complications such as diabetic nephropathy, retinopathy, or neuropathy. Although no glucose-lowering medication

is approved for the treatment of MASLD, preference in treating diabetes should be given to those treatments with evidence of safety and effectiveness for steatohepatitis from high-quality phase 2 RCTs and a phase 3 RCT (e.g., GLP-1RA and/or pioglitazone, or dual GIP/GLP-1RA tirzepatide), with the dual purpose of treating hyperglycemia and steatohepatitis (154,178,179) (Fig. 4). Once cirrhosis is established there are currently no effective treatments. Table 5 summarizes our current knowledge about the effect of glucose-lowering medications in MASLD as well as their cardiorenal benefit.

As discussed above in *PHARMACOLOGICAL TREATMENT OF OBESITY IN MASLD*, semaglutide (11,154), tirzepatide (156), and liraglutide (157) improve MASLD in individuals without cirrhosis. Still, their long-term safety, tolerability, and efficacy remain to be established. The combination of gastrointestinal side effects, formulation as injectables, and high cost may limit long-term treatment adherence. Real-world data suggest discontinuation rates of ~50% and ~60% at 12 and 24 months, respectively—usually higher with daily versus weekly GLP-1RA dosing (180,181).

Pioglitazone may reverse steatohepatitis in people without diabetes (182–185) or with prediabetes or type 2 diabetes (186,187) (Table 5). The effect on fibrosis is modest; the placebo-subtracted proportion of people with improvement in fibrosis among different studies ranges from 9% to 22% (statistically significant in none) (182–187). Studies have been relatively small and underpowered for this outcome. Still, in some studies, fewer individuals exhibit fibrosis progression in comparison with placebo (185,187), and in a meta-analysis of available studies investigators concluded that pioglitazone may improve fibrosis (178). As a generic medication, pioglitazone may be a cost-effective alternative for the dual purpose of treating type 2 diabetes and MASH (60). Dose-dependent weight gain can be mitigated by prescribing lower doses (15 mg/day, weight gain 1%–2%) (188–190). Net weight loss is observed when pioglitazone is combined with a GLP-1RA (191–196) or a sodium–glucose cotransporter 2 (SGLT2) inhibitor (194,197–200). In addition, combined pioglitazone and GLP-1RA treatment is associated with a greater decrease in hepatic steatosis as compared with pioglitazone alone in people with type 2

**Table 5—Liver and cardiorenal effects of glucose-lowering medications**

| Medication        | Effect in MASLD and MASH* |                   |                     |                                   | Cardiovascular, renal, and other relevant clinical effects |            |                                           |               |
|-------------------|---------------------------|-------------------|---------------------|-----------------------------------|------------------------------------------------------------|------------|-------------------------------------------|---------------|
|                   | Hepatic steatosis         | Steatohepatitis   | Fibrosis regression | Reduction of fibrosis progression | ASCVD*                                                     | CKD*       | HF*                                       | Hypoglycemia¶ |
| Semaglutide**     | Beneficial                | Beneficial        | Beneficial          | Potential benefit                 | Beneficial                                                 | Beneficial | Beneficial                                | Low risk      |
| Tirzepatide***†   | Potential benefit         | Potential benefit | Potential benefit   | Potential benefit                 | ?                                                          | ?          | Beneficial                                | Low risk      |
| Pioglitazone†     | Potential benefit         | Potential benefit | Potential benefit   | Potential benefit                 | Beneficial                                                 | Neutral    | Not recommended in HF stage B, C, or D    | Low risk      |
| SGLT2 inhibitors  | Potential benefit         | ?                 | ?                   | ?                                 | Beneficial                                                 | Beneficial | Beneficial                                | Low risk      |
| Metformin¶        | Neutral                   | Neutral           | Neutral             | Neutral                           | Potential benefit?                                         | Neutral    | Neutral                                   | Low risk      |
| DPP-4 inhibitors¶ | Neutral                   | ?                 | ?                   | ?                                 | Neutral                                                    | Neutral    | Neutral (except saxagliptin, alogliptin?) | Low risk      |
| Insulin¶          | Potential benefit         | ?                 | ?                   | ?                                 | Neutral                                                    | Neutral    | Neutral                                   | High risk     |
| Sulfonylureas¶    | Neutral                   | ?                 | ?                   | ?                                 | Neutral                                                    | Neutral    | Neutral                                   | High risk     |

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; HF, heart failure. ? indicates unknown. \*Includes people with and without type 2 diabetes. ¶Only in people with type 2 diabetes. \*\*Only semaglutide among GLP-1RA has been reported to be of benefit in a phase 2 RCT (154) with improvement in steatohepatitis and more recently in a phase 3 RCT with histological outcomes in MASH, including improvements in steatohepatitis and fibrosis (11). Liraglutide may offer potential benefit, based on results of a phase 2 RCT (157). Other GLP-1RA have not been tested in RCTs with liver histological outcomes. \*\*\*Tirzepatide is the only dual GIP/GLP-1RA available and tested with histological outcomes in a phase 2 RCT in MASH (155). †Tirzepatide and pioglitazone are considered of potential benefit based on phase 2 trials.

diabetes (196,201). Pioglitazone improves left ventricular function (194,202) but may promote heart failure if inadvertently prescribed to individuals with preexisting congestive heart failure. Dose- and time-dependent increases in risk of fractures and bladder cancer have been reported, although the data for bladder cancer remain controversial (203).

Vitamin E may be considered for the treatment of MASH in selected individuals without diabetes (182), with effects significantly impacted by haptoglobin genotype (204), although when used in combination with pioglitazone in adults with diabetes it did not enhance pioglitazone's efficacy in comparison with earlier studies with the thiazolidinedione, and there is not enough evidence at this time for recommendation for people with type 2 diabetes (55–58,205). In a retrospective study in individuals with MASH and advanced fibrosis, it was reported that vitamin E was associated with less disease progression (206). However, controversy remains about a potential increase in hemorrhagic stroke and prostate cancer (207).

In at least six phase 2 RCTs, SGLT2 inhibitors were tested in individuals with type 2 diabetes and MASLD (dapagliflozin, empagliflozin, and canagliflozin, and smaller studies with others), and modest reductions in hepatic steatosis were consistently reported (e.g., mean of ~20% placebo-subtracted relative decrease in intrahepatic triglycerides) (164) (Table 5). Modest benefit was reported in an open-label trial with liver histological outcomes (208), while in another no improvement was noted (209). In a recent prospective study in 237 people with type 2 diabetes from diabetes clinics, with a mean follow up of ~4.5 years, it was reported that use of SGLT2 inhibitors was associated with less fibrosis progression (liver stiffness measured with transient elastography) (210). SGLT2 inhibitors have not been rigorously tested with histological outcomes in MASH, but their cardiometabolic benefits make them an attractive option for people with MASLD.

Glucose-lowering agents other than pioglitazone or GLP-1RA or dual GIP/GLP-1RA can be continued for glycemic management, as clinically indicated, but may not improve MASH (i.e., metformin) (56,57) or have not been tested in MASH

in paired liver biopsy trials (i.e., insulin, sulfonylureas, dipeptidyl peptidase 4 [DPP-4] inhibitors, meglitinides, or acarbose) (Table 5).

The prevalence of MASLD is increasing among people with type 1 diabetes, especially when associated with obesity (211), and weight gain appears to be linked to insulin resistance, hyperglycemia, and more difficult to manage diabetes (212). In one study an only 8% prevalence of steatosis was reported, measured with MRI, in adults with type 1 diabetes predominantly without obesity compared with an eightfold higher prevalence in those with type 2 diabetes (liver fibrosis was not measured) (213). A meta-analysis from 29 studies, including 390 individuals with type 1 diabetes and 10,487 individuals with type 2 diabetes, reported prevalence rates of fibrosis, measured with transient elastography, of 5.2% and 19.8%, respectively (4). The current recommendation is to screen for fibrosis in people with type 1 diabetes only in the context of risk factors for MASLD, in particular obesity, elevated plasma aminotransferases, or steatosis as an incidental finding (56,59). Treatment should focus on lifestyle modification that induces weight loss in individuals with overweight or obesity. Optimizing glycemic management with insulin therapy may reduce steatosis (155,164,214). Other diabetes medications (or resmetirom) have not been tested in this population.

#### **MASH Pharmacotherapy**

Resmetirom is a selective thyroid hormone receptor  $\beta$  (THR- $\beta$ ) agonist (215), approved in early 2024 for the treatment of MASH with fibrosis stages F2 and F3. Its THR- $\beta$  isoform selectivity (a receptor isoform with expression predominantly in liver, kidney, pituitary, and brain tissue) minimizes potential undesirable off-target THR- $\alpha$ -related effects in heart and bone tissues. Resmetirom decreases steatosis through not yet fully understood mechanisms such as enhancing mitochondrial function and improving the hepatic conversion of thyroxine (T4) to triiodothyronine. Administration for 52 weeks in 966 adults randomized 1:1:1 to oral resmetirom at a dose of 80 mg or 100 mg or placebo led to MASH resolution in up to 29.9% of participants receiving resmetirom compared with 9.7% on placebo ( $P < 0.001$ ) (10). Fibrosis

improved in up to 25.9% and 14.2%, respectively ( $P < 0.001$ ). Treatment initiation does not require a liver biopsy, and specific guidance has been developed for identification with NITs of adults with MASH with fibrosis stages F2 and F3 (i.e., LSM by imaging with VCTE or MRE) for whom therapy is suitable (216). Main exclusion criteria are compensated or decompensated cirrhosis, active liver diseases (i.e., autoimmune hepatitis or primary biliary cholangitis), suboptimally managed hypothyroidism or hyperthyroidism, or ongoing alcohol consumption of  $>20$  g/day for women or  $>30$  g/day for men. Nausea, vomiting, and diarrhea are the most frequent adverse events with resmetirom therapy. Resmetirom may lower free T4 levels by ~20% and increase two- to threefold sex hormone-binding globulin (SHBG) protein levels (10,216). Increasing SHBG in the setting of borderline or frank hypogonadism has the potential to exacerbate hypogonadism because it may alter the dynamics between bound and free testosterone, resulting in a decrease in biologically active hormone. Also, SHBG can potentially deliver testosterone directly to tissues with unknown biological effects on androgen-dependent organs (63,217). The long-term clinical significance of these hormonal changes remains to be determined (218). Baseline thyroid function testing prior to initiating therapy is recommended by the American Association for the Study of Liver Diseases (AASLD) (216), as hypothyroidism is common in the general population (~12%) and steatosis may be associated with hypothyroidism (55). Monitoring of thyroid function during resmetirom therapy should be based on clinical judgement. Of note, some people during the phase 3 trial had free T4 levels below normal (most often transient), needed resmetirom dose adjustments, or were started on levothyroxine (219). Because hypogonadism develops more often in older adults and in those with MASLD, clinicians should follow current guidelines (56,122,124) that recommend the evaluation of symptomatic individuals for hypogonadism on the basis of a fasting total testosterone and free testosterone concentration (ideally with liquid chromatography–mass spectrometry and equilibrium dialysis, respectively) (220) or consider an endocrinology consult.

There is limited information on combining resmetirom with medications often used for comorbidities in MASLD (e.g., pioglitazone, GLP-1RA, or dual GIP/GLP-1RA). People with obesity and type 2 diabetes should make it a priority to optimize lifestyle and medical management with a GLP-1RA, pioglitazone, or their combination or a dual GIP/GLP-1RA (tirzepatide) with potential benefits for steatohepatitis (59). Addition of resmetirom should be initiated by a hepatologist or gastroenterologist with expertise in MASH and within the context of an interprofessional team approach, cost-benefit assessment, and individual decision sharing. In monitoring resmetirom treatment recent guidance by AASLD should be followed (216).

## SECTION 5. THE NEED TO DEVELOP INTERPROFESSIONAL TEAMS

### Role of Primary Care

MASLD in type 2 diabetes is best managed by a coordinated health care team with expertise to address prevention, screening, diagnosis, lifestyle interventions, medication, and monitoring, led by the primary care physician (Fig. 5). Depending on the disease stage,

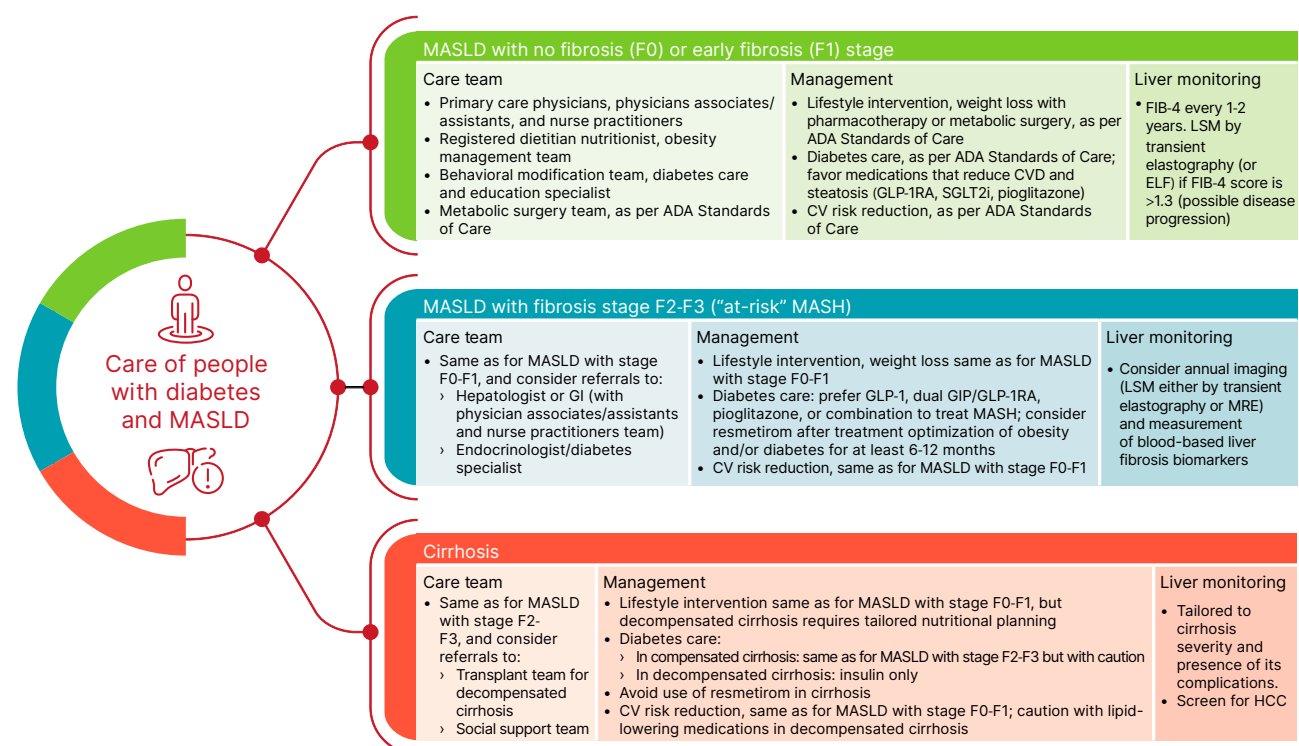
location, and resources in the area, the health care team may vary and even include expertise accessed remotely. Prevention is a critical first step, requiring awareness and expertise in managing diet, exercise, and obesity at the primary care level with support from dietitians, exercise physiologists, and behavioral health care professionals. Pharmacists can help by screening for obesogenic medications and suggesting pharmacologic interventions for obesity if appropriate. Diagnosis of early disease and eventual referral to a gastroenterologist or hepatologist, as per the diagnostic algorithm in Fig. 2, should become a routine component of type 2 diabetes care. A diagnosis of at-risk MASH may motivate behavior change and may be helpful for individuals for obtaining insurance coverage for more intensive behavioral and medical interventions.

Other valuable team members include obesity specialists in established weight loss programs and medical exercise programs, such as for cardiovascular or pulmonary rehabilitation. Mental health treatment and referral to behavioral health specialists can aid people with type 2 diabetes and MASLD who struggle with depression (140), which can hinder behavior change and weight

loss (Fig. 5). Suboptimally managed hyperglycemia should be managed with the combined efforts of an endocrinologist and diabetes educator. Even after an individual progresses to advanced fibrosis or cirrhosis and is under a liver specialist's care, the primary care and interprofessional teams must remain involved for management of behavioral and nutritional care and care for cardiometabolic risk factors and other MASLD-related comorbidities (56,57,59,126).

### Role of the Endocrinologist/Diabetes Care Specialist

The endocrinologist/diabetes care specialist is essential in managing MASLD in people with type 2 diabetes (56,57,221). Given the increased risk of cardiometabolic complications (150,222,223) and advanced liver fibrosis in this population (1,21), these professionals are at the front line of recognizing MASLD and treating its comorbidities (224). MASLD is found to occur more often in people attending diabetes clinics in comparison with primary care, possibly because longstanding type 2 diabetes is much more common. Therefore, the endocrinologist is in a unique position to 1) lead efforts to screen and risk stratify people at risk



**Figure 5**—Interprofessional teams, management, and liver monitoring for care of individuals with diabetes and MASLD. CV, cardiovascular; CVD, cardiovascular disease; F0, no fibrosis; F1, mild fibrosis; F3, advanced/severe fibrosis; GI, gastroenterologist; SGLT2i, SGLT2 inhibitors.

(Fig. 2), 2) promote lifestyle changes (Fig. 3) and initiate medications that benefit people with type 2 diabetes and MASLD (56,57) (Fig. 4), 3) develop interprofessional teams and manage referrals for optimal care (Fig. 5), and 4) stay engaged in the long-term follow-up of people with MASLD (12,224,225).

Of note, the endocrinologist should identify and treat other conditions associated with MASLD besides type 2 diabetes commonly seen in endocrinology clinics such as obesity (including secondary causes, e.g., Cushing syndrome), polycystic ovary syndrome, hypothyroidism (215), hypogonadism (frequent in older males), hypopituitarism, severe hypertriglyceridemia, and lipodystrophy (including that associated with HIV/highly active antiretroviral therapy), among others. The endocrinologist is often the first in line to exclude MASLD and diagnose secondary causes of liver disease (Supplementary Table 2).

### Role of Obesity Management Programs

Timely and appropriately structured lifestyle interventions remain crucial, with emphasis on weight loss as the principal strategy. Summary of pharmacological choices for obesity in MASLD in Fig. 4 and Table 5 follows the ADA Standards of Care that recommend weight loss using a GLP-1RA or a dual GIP/GLP-1RA (59).

As discussed earlier, metabolic surgery is recommended for suitable candidates, albeit with caution advised for people with compensated cirrhosis, and is not recommended in hepatic decompensated cirrhosis (59). Thus, a multifaceted approach involving lifestyle changes, pharmacotherapy, and potentially surgery is key to managing the intertwined issues of type 2 diabetes, obesity, and MASLD, with the aim of preventing progression to more severe liver diseases.

### Role of RDNs

DSMES is valuable in providing general nutritional recommendations as part of its comprehensive curriculum (141). We further recommend referral to an RDN to deliver medical nutrition therapy that can target the specific metabolic conditions relevant to each individual (226). There are several unique considerations for RDNs in caring for people with type 2 diabetes and MASLD. Even when a patient does not have elevated plasma

aminotransferases, RDNs need to consider whether at-risk MASH may be present in developing nutrition care plans for any adult within the high-risk groups, such as those with obesity, prediabetes, or type 2 diabetes or with a medical history of steatosis. Such plans should be formulated with the aim of managing weight, attaining glycemic goals, and addressing cardiometabolic risk factors to prevent hepatic and extrahepatic outcomes (57).

RDNs and DCES should consider a FIB-4 score calculation, if all components are available, for risk stratification and a better understanding of, along with educating people on, the importance of medical nutrition therapy for a person's liver health. Additionally, alcohol impacts both energy balance and disease progression, so suspicion of effects of alcohol should trigger an alcohol-related liver disease assessment (Supplementary Table 3) and be addressed during counseling sessions. (See *SECTION 8. ALCOHOL INTAKE AND LIVER HEALTH.*) Finally, communication with the referring provider about risk stratification, nutrition care plans, liver health outcomes, and new health conditions is essential to long-term success.

### Role of the Behavioral Modification Team

The behavioral modification team plays a foundational role in managing MASLD in people with diabetes in terms of both prevention and disease management. Primary care physicians and other clinicians can access additional support for lifestyle interventions through various behavioral health team members, including exercise physiologists, behavioral health professionals, and DCES. These professionals offer vital expertise in physical activity programs, body composition and weight management, psychosocial concerns, diabetes distress, substance use, education promoting positive lifestyle behaviors, and overcoming barriers (Supplementary Table 4).

### Role of the Gastroenterologist and Hepatologist

Gastroenterologists and hepatologists play an important role in managing clinically significant fibrosis, starting from the comprehensive fibrosis staging of the disease (clinically significant fibrosis, advanced fibrosis, or cirrhosis), then in developing stage-specific treatment plans, and then during

long-term follow-up, in collaboration with other members of the interprofessional team. As mentioned in *FIBROSIS RISK STRATIFICATION AND REFERRAL GUIDELINES, OVERVIEW OF ADDITIONAL TESTS BY SPECIALISTS, AND ROLE OF LIVER BIOPSY*, people at risk for fibrosis (based on FIB-4 or LSM scores) should be considered for referral to liver specialty clinics (gastroenterology or hepatology) where they may undergo imaging-based methods (MRE or cT1) or liver biopsy for final diagnosis. The liver specialists may also use evolving multimodal scores such as transient elastography-based scores (Agile 4 and Agile 3+), NIS2+ score (102,103), or MRE-based measures (MAST score, MEFIB index, and MASEF score) (104–106) for diagnosis of cirrhosis or advanced fibrosis.

People with cirrhosis also require ongoing HCC surveillance (liver ultrasound and  $\alpha$ -fetoprotein), screening and primary prophylaxis for esophageal varices, and monitoring for the need for liver transplantation. Treatment of comorbidities, such as type 2 diabetes, calls for joint care with endocrinologists/diabetes specialists in determining how to best tailor diabetes treatments and monitoring response accordingly (see below).

## SECTION 6. DIABETES MANAGEMENT IN CIRRHOSIS

Cirrhosis profoundly modifies the overall management of diabetes. Liver cirrhosis can worsen insulin resistance and glucose intolerance, explaining the higher prevalence of diabetes observed among people with cirrhosis (227)—highest among those with MASLD-cirrhosis or cryptogenic cirrhosis (56% and 51%, respectively) (228). In people with compensated cirrhosis, the presence of diabetes magnifies the risk for liver-related morbidity and mortality (3,20,229,230). In diabetes, many pathophysiological mechanisms have been invoked by which hyperglycemia may promote the development of MASH and progression to cirrhosis; however, these mechanisms remain poorly understood (203,231–233). Observational studies suggest lower rates of cirrhosis and adverse liver outcomes with GLP-1RA, SGLT2 inhibitors, and thiazolidinediones (234). In short-term clinical trials, glucose-lowering medications that stimulate weight loss (i.e., GLP-1RA) or improve insulin sensitivity (i.e., pioglitazone) may ameliorate

steatohepatitis, and eventually fibrosis progression, during the course of treatment (164) (Table 5). However, the role of hyperglycemia per se is unclear and robust evidence of cirrhosis prevention through optimizing glycemic management is lacking.

The diagnosis of diabetes can be challenging due to chronic anemia, hypersplenism, renal insufficiency, sarcopenia, or ascites, where there may be discordance between standard tests used in the diagnosis of diabetes (i.e., fasting glucose and A1C) (235). People with cirrhosis may have normal or near-normal fasting plasma glucose levels despite the presence of prediabetes or diabetes. An oral glucose tolerance test could “unmask” diabetes in the presence of an apparently normal A1C (236).

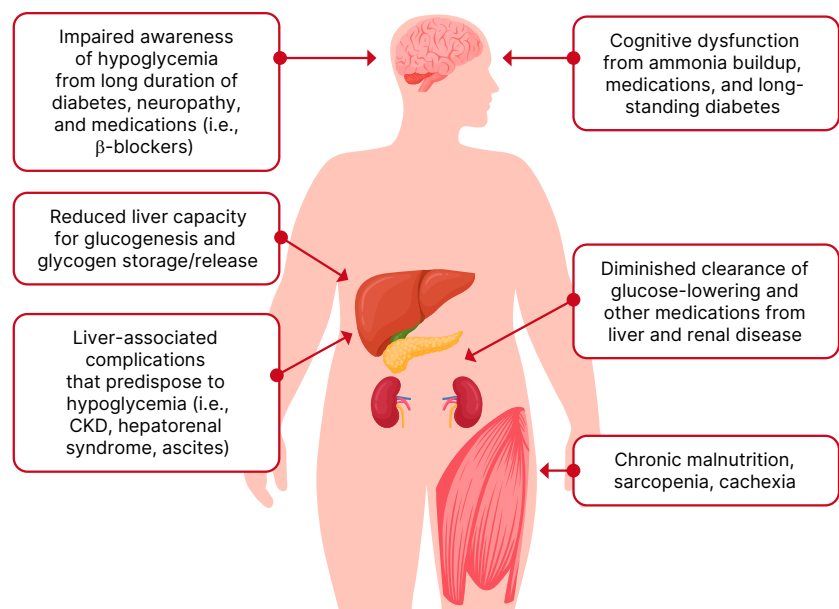
Management of diabetes presents unique challenges as well in people with cirrhosis. The approach to managing their diabetes is conditional on the presence of compensated or decompensated cirrhosis [i.e., with impaired liver synthetic function or complication(s) of portal hypertension] (19). One aspect of clinical relevance is that MASLD may be associated with higher risk of severe hypoglycemia in adults with type 2 diabetes (237). Among people with type 2 diabetes, those with cirrhosis had a much higher risk of severe hypoglycemia and overall mortality in comparison with those without liver cirrhosis (238). As summarized in Fig. 6, several risk factors combine in cirrhosis to promote severe hypoglycemia, such as impaired renal function and cachexia, frequent need of insulin (with diminished renal clearance in chronic kidney disease), and cognitive dysfunction with diminished alertness during hypoglycemia that could be misdiagnosed and mistreated as hepatic encephalopathy. Concomitant medications, such as nonselective  $\beta$ -blockers for portal hypertension, may also increase the risk for impaired awareness of hypoglycemia in masking signs and symptoms (i.e., tremor, tachycardia) because they block the effects of norepinephrine. Therefore, a less stringent and individualized glycemic goal may be considered for people with decompensated cirrhosis (239).

Formation of an interprofessional team (primary care, RDN, endocrinologist/diabetes care specialist, hepatologist, and others) is the best practice for

managing cirrhosis. Diabetes and nutrition education, with high protein intake (1.2–1.5 g/kg/day) and regular exercise, if feasible, may prevent sarcopenia, which is a common problem in people with cirrhosis (122,240). Education on glucagon administration to treat severe hypoglycemia, as well as the use of glucose monitoring devices (241), may decrease the overall risk of complications associated with hypoglycemia in cirrhosis from glucose-lowering medications. Continuous glucose monitoring systems await future greater use in this setting but have been validated and proven valuable in small proof-of-concept studies (241,242) and may be particularly useful in the case of having alerts for hypoglycemia.

Lifestyle modification including regular physical activity may improve diabetes, MASH (122,124), portal hypertension (243,244), and endurance and functional outcome measures in people with cirrhosis (245) and potentially decrease the risk for HCC (246,247). Compensated cirrhosis may be treated with caution using oral agents and GLP-1RA or dual incretin agonists, as in less severe stages of cirrhosis. Avoidance of sulfonylureas and metformin in the case of renal impairment is recommended due to the high risk of hypoglycemia and of lactic acidosis, respectively (248). However, rigorous long-term studies regarding the use of oral agents or GLP-1RA and dual incretin agonists in

people with compensated cirrhosis are limited. Short-term (28–48 weeks) studies in people with cirrhosis suggest that GLP-1RA-based therapies may be safe and also can improve glycemic management in people with MASH (249,250). In several short-term studies SGLT2 inhibitors have safely been tested in individuals with advanced fibrosis and cirrhosis (19). Pioglitazone should be avoided in decompensated cirrhosis from MASH because it is mainly metabolized in the liver by CYP2C8 and to a lesser extent by CYP3A4, and there is limited clinical experience. However, there was no increase in adverse events reported either in a meta-analysis that included adults with biopsy-proven MASH and advanced liver fibrosis or compensated cirrhosis treated with pioglitazone (178) or in a large population-based study (251). Insulin therapy is the preferred agent for the treatment of hyperglycemia in adults with type 2 diabetes with decompensated cirrhosis (59), given its safety and efficacy plus the lack of long-term data with oral agents or GLP-1RA (19). Future studies will be needed to reassess the role of different glucose-lowering medications in cirrhosis. A recent study from the Veterans Health Administration system in 16,058 individuals reported a 14% lower risk of cirrhosis with GLP-1RA treatment in comparison with DPP-4 inhibitor users (252). However, there was no benefit from GLP-1RA use in people with established cirrhosis (252).



**Figure 6**—Impaired awareness of hypoglycemia from risk factors in cirrhosis. CKD, chronic kidney disease. Adapted with permission from Castera and Cusi (19).



## SECTION 7. DIABETES AND HCC

In several retrospective and prospective studies, type 2 diabetes is independently associated with a two- to fourfold higher risk for HCC (31,177,253–257). Much of the association between diabetes and HCC may be explained by the development and progression of MASLD.

Although people with both diabetes and MASLD are among the highest-risk groups for HCC, the absolute risk of HCC is low and variable (258). Hence, current guidelines do not recommend screening for HCC in people with diabetes and MASLD unless there is evidence of cirrhosis. People with diabetes complications and/or suboptimal glycemic management, especially if they also have a high FIB-4 score, may be an important subgroup for close monitoring for future risk of cirrhosis (258,259). Duration of diabetes and other comorbid metabolic conditions also increased HCC risk in other studies.

Improved glycemic management to reduce cirrhosis and HCC burden in people with diabetes may hold promise but remains an understudied paradigm. Studies among individuals with type 2 diabetes have shown a reduction in HCC incidence with metformin but an increase with combination of metformin and a sulfonylurea or insulin, or a greater risk of HCC with oral agents combined with insulin therapy (259,260). Adequate glycemic management was associated with a 31% lower risk of HCC (259). The potential preventive effects of newer glucose-lowering medications for HCC are currently unknown, but this question warrants evaluation. While GLP-1RA, SGLT2 inhibitors, and pioglitazone are associated with lower rates of cirrhosis in population-based studies, their ability to prevent HCC is less clear (234,252,261). Overall, there is significant heterogeneity across observational studies, which, together with challenges in adjusting for multiple confounders, calls for caution in interpreting associations between diabetes medications and risk of HCC.

## SECTION 8. ALCOHOL INTAKE AND LIVER HEALTH

Initial evaluation of people with cirrhosis includes an assessment of alcohol intake (Supplementary Table 3). In people with preexisting obesity and diabetes, alcohol use has a synergistic effect for worsening insulin resistance, chronic liver

injury, cirrhosis, HCC, and liver-related morbidity and mortality (132). Any alcohol use should be avoided in people with diabetes and chronic liver disease. Mild-to-moderate alcohol intake can serve as a cofactor for the development of steatohepatitis and fibrosis progression. Heavy alcohol intake may increase the risk of type 2 diabetes in genetically predisposed individuals by inducing hepatic and peripheral (i.e., muscle) insulin resistance and promoting a chronic increase in pancreatic  $\beta$ -cell demand. Alcohol intake can be defined as mild if  $<20$  g/day for women and  $<30$  g/day for men, moderate if between 21 and 39 g/day for women and between 31 and 59 g/day for men, or heavy if  $\geq 40$  g/day for women and  $\geq 60$  g/day for men. While earlier studies suggested a protective effect of alcohol use on cardiometabolic risk factors (262,263), subsequent studies of moderate alcohol use (defined broadly as  $>20$  g/day) suggest lower odds of MASH resolution and increased risk for cirrhosis, HCC (264,265), and extrahepatic malignancies (266–268). Further, alcohol use may have a negative effect on glycemic management in people with diabetes (269,270), irrespective of the use of antidiabetes medications (271). Understanding of the impact of alcohol use (type, pattern, frequency, duration) in individuals with concomitant diabetes and liver disease is required.

## CONCLUSIONS

It is now well established that adults with prediabetes or type 2 diabetes have the highest risk of developing MASLD. Approximately one in five people with type 2 diabetes have clinically significant fibrosis and are at high risk of developing cirrhosis from MASLD (i.e., has at-risk MASH), which is one of the leading reasons for liver transplantation in the U.S. MASLD is also associated with increased risk of HCC as well as extrahepatic malignancies and cardiovascular disease.

Individuals with prediabetes or type 2 diabetes should be risk stratified with a two-tier approach (FIB-4  $\pm$  VCTE-LSM) for assessment of their risk of having at-risk MASH with clinically significant liver fibrosis or cirrhosis. This consensus report delivers the message that timely identification and proper management can prevent the progression of fibrosis to cirrhosis in people with prediabetes

and type 2 diabetes in the same way as already accepted for diabetes-related microvascular complications (retinopathy, nephropathy or neuropathy) or cardiovascular disease. With interprofessional care teams and clinician awareness and action, education, development of proper models of care, and proactive public health policies we hope to catalyze a shift in clinical practice that will improve outcomes and the quality of life of people with diabetes and MASLD.

**Acknowledgments.** The authors thank Alexandra M. Yacoubian (ADA) for administrative assistance and Michael Bonar (Leicester Diabetes Centre, Leicester, U.K.) and Charlie Franklin (Leicester Diabetes Centre) for figure design.

**Funding.** This statement was funded by ADA general revenue. C.R.R. has received honoraria for travel and speaker engagements from the ADA. M.B. has received research funding (to institution) from the ADA.

No other entity, including industry, provided support for this statement.

**Duality of Interest.** K.C. has received research support (to institution) from Boehringer Ingelheim, Echosens, Inventiva, Labcorp, and Perspectum. K.C. has served as a consultant for Aligos Therapeutics, Arrowhead, AstraZeneca, 89bio, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Novo Nordisk, ProSciento, Sagimet Biosciences, Siemens USA, Zealand Pharma, and Terns Pharmaceuticals. M.F.A. has received research support (to institution) from Madrigal Pharmaceuticals, 89bio, Hanmi Pharmaceutical, Gilead Sciences, and Inventiva. M.F.A. has served as a consultant or advisory board member for Novo Nordisk, Hanmi Pharmaceutical, Inventiva, Madrigal Pharmaceuticals, and 89bio. C.M.A. has served as an advisory board member for Altimmune, BioAge Labs, Biolinq, CinFina Pharma, Cowen and Company, EPG Comm, Vida, Veru, Wave Life Sciences, Form Health, Fractyl Health, Gelesis, Eli Lilly, L-Nutra, NeuroBo Pharmaceuticals, Xeno, Novo Nordisk, Nutrisystem, Optum Rx, Pain Script, Palatin, The Pursuit By You, Redesign Health, and ReShape Lifesciences. D.B. has served as a co-investigator for clinical trials with Inventiva Pharma and Boehringer Ingelheim. D.B. also attended an advisory board meeting for Boehringer Ingelheim and has received honoraria for lectures from Novo Nordisk. K.D.C. has received research funding from BPGbio, Target RWE, and Merck. K.D.C. has served as an advisory board member or instructor/speaker for Target RWE. C.R.R. has been part of a focus group with Dexcom and is part of a steering committee funded by Boehringer Ingelheim and Eli Lilly. M.R. has received funding for travel, is part of a speaker's bureau, or served on advisory board for AstraZeneca, Boehringer Ingelheim, Echosens, Madrigal Pharmaceuticals, Merck Sharp & Dohme, Novo Nordisk, and Target RWE. A.J.S. has received consulting fees from Eli Lilly and has served as a consultant for Echosens, Abbott, Promed, GENFIT,

Satellite Bio, Corcept Therapeutics, Arrowhead, Boston Pharmaceuticals, Variant, Cascade, 89bio, AstraZeneca, Alnylam Pharmaceuticals, Regeneron Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Genentech, Gilead Sciences, Histoindex, Janssen, Lipocine, Madrigal Pharmaceuticals, Merck, GlaxoSmithKline, Novartis, Akero Therapeutics, Novo Nordisk, PathAI, Pfizer, Poxel, Salix Pharmaceuticals, Myovant Sciences, Median Technologies, Sequana Medical, Surrozen, Takeda Pharmaceuticals, Terns Pharmaceuticals, and Zydus Pharmaceuticals. A.J.S. has received grant funding (to institution) from AstraZeneca, Bristol-Myers Squibb, Gilead Sciences, Intercept Pharmaceuticals, Mallinckrodt Pharmaceuticals, Merck, Ocelot, Novartis, and Salix Pharmaceuticals. A.J.S. has received royalties from Elsevier and UpToDate. A.J.S. also has stock options in Duirect, GENFIT, Tiziana Life Sciences, and Inversago. J.H.S. has served as a consultant or advisory board member for Abbott, Bayer, Novo Nordisk, Sanofi, Eli Lilly, and Madrigal Pharmaceuticals. Z.M.Y. has received grant funding from Madrigal Pharmaceuticals and has served as a consultant for Madrigal Pharmaceuticals, Novo Nordisk, and Boehringer Ingelheim. No other potential conflicts of interest relevant to this article were reported.

**Prior Presentation.** Parts of this study were presented at the 84th Scientific Sessions of the ADA, Orlando, FL, 21–24 June 2024.

**Handling Editors.** The journal editor responsible for overseeing the review of the manuscript was John B. Buse.

## References

1. Lomonaco R, Godinez Leiva E, Bril F, et al. Advanced liver fibrosis is common in patients with type 2 diabetes followed in the outpatient setting: the need for systematic screening. *Diabetes Care* 2021;44:399–406
2. Harrison SA, Gawrieh S, Roberts K, et al. Prospective evaluation of the prevalence of non-alcoholic fatty liver disease and steatohepatitis in a large middle-aged US cohort. *J Hepatol* 2021;75:284–291
3. Ciardullo S, Monti T, Perseghin G. High prevalence of advanced liver fibrosis assessed by transient elastography among U.S. adults with type 2 diabetes. *Diabetes Care* 2021;44:519–525
4. Ciardullo S, Perseghin G. Prevalence of elevated liver stiffness in patients with type 1 and type 2 diabetes: a systematic review and meta-analysis. *Diabetes Res Clin Pract* 2022;190:109981
5. Stefan N, Cusi K. A global view of the interplay between non-alcoholic fatty liver disease and diabetes. *Lancet Diabetes Endocrinol* 2022;10:284–296
6. Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. *Hepatology* 2023;77:1335–1347
7. Younossi ZM, Stepanova M, Al Shabeeb R, et al. The changing epidemiology of adult liver transplantation in the United States in 2013–2022: the dominance of metabolic dysfunction-associated steatotic liver disease and alcohol-associated liver disease. *Hepatol Commun* 2024;8:e0352
8. Stepanova M, Kumar A, Brandt P, et al. Impact of type 2 diabetes on the outcomes of solid organ transplantations in the U.S.: data from a national registry. *Diabetes Care* 2023;46:2162–2170
9. Younossi ZM, Henry L. Understanding the burden of nonalcoholic fatty liver disease: time for action. *Diabetes Spectr* 2024;37:9–19
10. Harrison SA, Bedossa P, Guy CD, et al.; MAESTRO-NASH Investigators. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. *N Engl J Med* 2024;390:497–509
11. Sanyal AJ, Newsome PN, Kliers I, et al.; ESSENCE Study Group. Phase 3 trial: semaglutide in metabolic dysfunction-associated steatohepatitis. *N Engl J Med*. 30 April 2025 [Epub ahead of print]. DOI: 10.1056/NEJMoa2413258
12. Cusi K, Budd J, Johnson E, Shubrook J. Making sense of the nonalcoholic fatty liver disease clinical practice guidelines: what clinicians need to know. *Diabetes Spectr* 2024;37:29–38
13. Lazarus JV, Anstee QM, Hagström H, et al. Defining comprehensive models of care for NAFLD. *Nat Rev Gastroenterol Hepatol* 2021;18:717–729
14. Lazarus JV, Mark HE, Anstee QM, et al.; NAFLD Consensus Consortium. Advancing the global public health agenda for NAFLD: a consensus statement. *Nat Rev Gastroenterol Hepatol* 2022;19:60–78
15. Rinella ME, Lazarus JV, Ratzliff V, et al.; NAFLD Nomenclature consensus group. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *Hepatology* 2023;78:1966–1986
16. Song SJ, Lai JC-T, Wong GL-H, Wong VW-S, Yip TC-F. Can we use old NAFLD data under the new MASLD definition? *J Hepatol* 2024;80:e54–e56
17. Younossi ZM, Paik JM, Stepanova M, Ong J, Alqahtani S, Henry L. Clinical profiles and mortality rates are similar for metabolic dysfunction-associated steatotic liver disease and non-alcoholic fatty liver disease. *J Hepatol* 2024;80:694–701
18. Ciardullo S, Carbone M, Invernizzi P, Perseghin G. Exploring the landscape of steatotic liver disease in the general US population. *Liver Int* 2023;43:2425–2433
19. Castera L, Cusi K. Diabetes and cirrhosis: current concepts on diagnosis and management. *Hepatology* 2023;77:2128–2146
20. Alexopoulos A-S, Crowley MJ, Wang Y, et al. Glycemic control predicts severity of hepatocyte ballooning and hepatic fibrosis in nonalcoholic fatty liver disease. *Hepatology* 2021;74:1220–1233
21. Barb D, Repetto EM, Stokes ME, Shankar SS, Cusi K. Type 2 diabetes mellitus increases the risk of hepatic fibrosis in individuals with obesity and nonalcoholic fatty liver disease. *Obesity (Silver Spring)* 2021;29:1950–1960
22. Colomba J, Netedu SR, Lehoux-Dubois C, et al. Hepatic enzyme ALT as a marker of glucose abnormality in men with cystic fibrosis. *PLoS One* 2019;14:e0219855
23. Zaharia OP, Strassburger K, Strom A, et al.; German Diabetes Study Group. Risk of diabetes-associated diseases in subgroups of patients with recent-onset diabetes: a 5-year follow-up study. *Lancet Diabetes Endocrinol* 2019;7:684–694
24. Cusi K, Younossi Z, Roden M. From NAFLD to MASLD: promise and pitfalls of a new definition. *Hepatology* 2024;79:E13–E15
25. Simmons RK, Alberti KGMM, Gale EAM, et al. The metabolic syndrome: useful concept or clinical tool? Report of a WHO Expert Consultation. *Diabetologia* 2010;53:600–605
26. Sharma A, Godina Leiva E, Kalavalapalli S, et al. Obesity increases the risk of hepatic fibrosis in young adults with type 2 diabetes mellitus: the need to screen. *Obesity (Silver Spring)* 2024;32:1967–1974
27. Parcha V, Heindl B, Kalra R, et al. Insulin resistance and cardiometabolic risk profile among nondiabetic American young adults: insights from NHANES. *J Clin Endocrinol Metab* 2022;107:e25–e37
28. Younossi ZM, Alqahtani SA, Alswat K, et al.; Global NASH Council. Global survey of stigma among physicians and patients with nonalcoholic fatty liver disease. *J Hepatol* 2024;80:419–430
29. Paik JM, Kabbara K, Eberly KE, Younossi Y, Henry L, Younossi ZM. Global burden of NAFLD and chronic liver disease among adolescents and young adults. *Hepatology* 2022;75:1204–1217
30. Younossi ZM, Golabi P, Price JK, et al. The global epidemiology of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among patients with type 2 diabetes. *Clin Gastroenterol Hepatol* 2024;22:1999–2010.e8
31. En Li Cho E, Ang CZ, Quek J, et al. Global prevalence of non-alcoholic fatty liver disease in type 2 diabetes mellitus: an updated systematic review and meta-analysis. *Gut* 2023;72:2138–2148
32. Golabi P, Paik JM, Kumar A, et al. Nonalcoholic fatty liver disease (NAFLD) and associated mortality in individuals with type 2 diabetes, pre-diabetes, metabolically unhealthy, and metabolically healthy individuals in the United States. *Metabolism* 2023;146:155642
33. Bell JA, Kivimäki M, Hamer M. Metabolically healthy obesity and risk of incident type 2 diabetes: a meta-analysis of prospective cohort studies. *Obes Rev* 2014;15:504–515
34. Cuthbertson DJ, Koskinen J, Brown E, et al. Fatty liver index predicts incident risk of prediabetes, type 2 diabetes and non-alcoholic fatty liver disease (NAFLD). *Ann Med* 2021;53:1256–1264
35. Pais R, Charlotte F, Fedchuk L, et al.; LIDO Study Group. A systematic review of follow-up biopsies reveals disease progression in patients with non-alcoholic fatty liver. *J Hepatol* 2013;59:550–556
36. McPherson S, Hardy T, Henderson E, Burt AD, Day CP, Anstee QM. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. *J Hepatol* 2015;62:1148–1155
37. Huang DQ, Wilson LA, Behling C, et al.; NASH Clinical Research Network. Fibrosis progression rate in biopsy-proven nonalcoholic fatty liver disease among people with diabetes versus people without diabetes: a multicenter study. *Gastroenterology* 2023;165:463–472.e5
38. Castera L, Laouenan C, Vallet-Pichard A, et al.; QUID NASH investigators. High prevalence of NASH and advanced fibrosis in type 2 diabetes: a prospective study of 330 outpatients undergoing liver biopsies for elevated ALT, using a low threshold. *Diabetes Care* 2023;46:1354–1362
39. Le MH, Le DM, Baez TC, et al. Global incidence of adverse clinical events in non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Clin Mol Hepatol* 2024;30:235–246
40. Paik JM, Henry L, Younossi Y, Ong J, Alqahtani S, Younossi ZM. The burden of nonalcoholic fatty

liver disease (NAFLD) is rapidly growing in every region of the world from 1990 to 2019. *Hepatol Commun* 2023;7:e0251

41. Rich NE, Noureddin M, Kanwal F, Singal AG. Racial and ethnic disparities in non-alcoholic fatty liver disease in the USA. *Lancet Gastroenterol Hepatol* 2021;6:422–424

42. Henry L, Paik J, Younossi ZM. Review article: the epidemiologic burden of non-alcoholic fatty liver disease across the world. *Aliment Pharmacol Ther* 2022;56:942–956

43. Noureddin M, Vipani A, Bressee C, et al. NASH leading cause of liver transplant in women: updated analysis of indications for liver transplant and ethnic and gender variances. *Am J Gastroenterol* 2018;113:1649–1659

44. Kordashian A, Dodge JL, Terrault NA. Food insecurity is associated with mortality among U.S. adults with nonalcoholic fatty liver disease and advanced fibrosis. *Clin Gastroenterol Hepatol* 2022;20:2790–2799.e4

45. Paik JM, Duong S, Zelber-Sagi S, Lazarus JV, Henry L, Younossi ZM. Food insecurity, low household income, and low education level increase the risk of having metabolic dysfunction-associated fatty liver disease among adolescents in the United States. *Am J Gastroenterol* 2024;119:1089–1101

46. Orci LA, Sanduzzi-Zamparelli M, Caballol B, et al. Incidence of hepatocellular carcinoma in patients with nonalcoholic fatty liver disease: a systematic review, meta-analysis, and meta-regression. *Clin Gastroenterol Hepatol* 2022;20:283–292.e10

47. Younossi ZM, Stepanova M, Ong J, et al. Nonalcoholic steatohepatitis is the most rapidly increasing indication for liver transplantation in the United States. *Clin Gastroenterol Hepatol* 2021;19:580–589.e5

48. Younossi ZM, Stepanova M, Saab S, et al. The impact of type 2 diabetes and obesity on the long-term outcomes of more than 85 000 liver transplant recipients in the US. *Aliment Pharmacol Ther* 2014;40:686–694

49. Stepanova M, Henry L, Younossi ZM. Economic burden and patient-reported outcomes of nonalcoholic fatty liver disease. *Clin Liver Dis* 2023;27:483–513

50. Younossi ZM, Golabi P, de Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. *J Hepatol* 2019;71:793–801

51. Kanwal F, Kramer JR, Mapakshi S, et al. Risk of hepatocellular cancer in patients with non-alcoholic fatty liver disease. *Gastroenterology* 2018;155:1828–1837.e2

52. Dulai PS, Singh S, Patel J, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: systematic review and meta-analysis. *Hepatology* 2017;65:1557–1565

53. Arab JP, Dirchwolf M, Álvares-da-Silva MR, et al. Latin American Association for the study of the liver (ALEH) practice guidance for the diagnosis and treatment of non-alcoholic fatty liver disease. *Ann Hepatol* 2020;19:674–690

54. Eslam M, Sarin SK, Wong VW-S, et al. The Asian Pacific Association for the Study of the Liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease. *Hepatol Int* 2020;14:889–919

55. Kanwal F, Shubrook JH, Adams LA, et al. Clinical care pathway for the risk stratification

and management of patients with nonalcoholic fatty liver disease. *Gastroenterology* 2021;161:1657–1669

56. Cusi K, Isaacs S, Barb D, et al. American Association of Clinical Endocrinology clinical practice guideline for the diagnosis and management of nonalcoholic fatty liver disease in primary care and endocrinology clinical settings: co-sponsored by the American Association for the Study of Liver Diseases (AASLD). *Endocr Pract* 2022;28:528–562

57. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology* 2023;77:1797–1835

58. European Association for the Study of the Liver (EASL); European Association for the Study of Obesity (EASO). Clinical practice guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). *J Hepatol* 2024;81:492–542

59. American Diabetes Association Professional Practice Committee. 4. Comprehensive medical evaluation and assessment of comorbidities: Standards of Care in Diabetes—2025. *Diabetes Care* 2025;48(Suppl. 1):S59–S85

60. Noureddin M, Jones C, Alkhouri N, Gomez EV, Dieterich DT, Rinella ME; NASHNET. Screening for nonalcoholic fatty liver disease in persons with type 2 diabetes in the United States is cost-effective: a comprehensive cost-utility analysis. *Gastroenterology* 2020;159:1985–1987.e4

61. Bril F, Ortiz-Lopez C, Lomonaco R, et al. Clinical value of liver ultrasound for the diagnosis of nonalcoholic fatty liver disease in overweight and obese patients. *Liver Int* 2015;35:2139–2146

62. Heba ER, Desai A, Zand KA, et al. Accuracy and the effect of possible subject-based confounders of magnitude-based MRI for estimating hepatic proton density fat fraction in adults, using MR spectroscopy as reference. *J Magn Reson Imaging* 2016;43:398–406

63. Goldman AL, Bhasin S, Wu FCW, Krishna M, Matsumoto AM, Jasuja R. A reappraisal of testosterone's binding in circulation: physiological and clinical implications. *Endocr Rev* 2017;38:302–324

64. Mofrad P, Contos MJ, Haque M, et al. Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values. *Hepatology* 2003;37:1286–1292

65. Maximos M, Bril F, Portillo Sanchez P, et al. The role of liver fat and insulin resistance as determinants of plasma aminotransferase elevation in nonalcoholic fatty liver disease. *Hepatology* 2015;61:153–160

66. Verma S, Jensen D, Hart J, Mohanty SR. Predictive value of ALT levels for non-alcoholic steatohepatitis (NASH) and advanced fibrosis in non-alcoholic fatty liver disease (NAFLD). *Liver Int* 2013;33:1398–1405

67. Connors EE, Panagiotakopoulos L, Hofmeister MG, et al.; Contributors. Screening and testing for hepatitis B virus infection: CDC recommendations - United States, 2023. *MMWR Recomm Rep* 2023;72:1–25

68. Cartwright EJ, Patel P, Kamili S, Wester C. Updated operational guidance for implementing CDC's recommendations on testing for hepatitis C virus infection. *MMWR Morb Mortal Wkly Rep* 2023;72:766–768

69. Siddiqui MS, Yamada G, Vuppalanchi R, et al.; NASH Clinical Research Network. Diagnostic

accuracy of noninvasive fibrosis models to detect change in fibrosis stage. *Clin Gastroenterol Hepatol* 2019;17:1877–1885.e5

70. McPherson S, Stewart SF, Henderson E, Burt AD, Day CP. Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. *Gut* 2010;59:1265–1269

71. Unalp-Arida A, Ruhl CE. Liver fibrosis scores predict liver disease mortality in the United States population. *Hepatology* 2017;66:84–95

72. Hagström H, Talbäck M, Andreasson A, Walldius G, Hammar N. Repeated FIB-4 measurements can help identify individuals at risk of severe liver disease. *J Hepatol* 2020;73:1023–1029

73. Cholanikeri G, Kramer JR, Chu J, et al. Longitudinal changes in fibrosis markers are associated with risk of cirrhosis and hepatocellular carcinoma in non-alcoholic fatty liver disease. *J Hepatol* 2023;78:493–500

74. Lee J, Vali Y, Boursier J, et al. Prognostic accuracy of FIB-4, NAFLD fibrosis score and APRI for NAFLD-related events: a systematic review. *Liver Int* 2021;41:261–270

75. Kamada Y, Muneke K, Nakahara T, et al.; Japan Study Group of NAFLD (JSG-NAFLD). The FIB-4 index predicts the development of liver-related events, extrahepatic cancers, and coronary vascular disease in patients with NAFLD. *Nutrients* 2022;15:66

76. Sanyal AJ, Munoz B, Cusi K, et al.; TARGET-NASH Investigators. Validation of a clinical risk-based classification system in a large nonalcoholic fatty liver disease real-world cohort. *Clin Gastroenterol Hepatol* 2023;21:2889–2900.e10

77. Anstee QM, Berentzen TL, Nitze LM, et al. Prognostic utility of Fibrosis-4 Index for risk of subsequent liver and cardiovascular events, and all-cause mortality in individuals with obesity and/or type 2 diabetes: a longitudinal cohort study. *Lancet Reg Health Eur* 2024;36:100780

78. Vali Y, Lee J, Boursier J, et al.; Liver Investigation: Testing Marker Utility in Steatohepatitis (LITMUS) consortium investigators. Biomarkers for staging fibrosis and non-alcoholic steatohepatitis in non-alcoholic fatty liver disease (the LITMUS project): a comparative diagnostic accuracy study. *Lancet Gastroenterol Hepatol* 2023;8:714–725

79. Udompap P, Therneau TM, Canning RE, Benson JT, Allen AM. Performance of American Gastroenterological Association Clinical Care Pathway for the risk stratification of patients with nonalcoholic fatty liver disease in the US population. *Hepatology* 2023;77:931–941

80. Boursier J, Hagström H, Ekstedt M, et al. Non-invasive tests accurately stratify patients with NAFLD based on their risk of liver-related events. *J Hepatol* 2022;76:1013–1020

81. Mózes FE, Lee JA, Selvaraj EA, et al.; LITMUS Investigators. Diagnostic accuracy of non-invasive tests for advanced fibrosis in patients with NAFLD: an individual patient data meta-analysis. *Gut* 2022;71:1006–1019

82. Sanyal AJ, Castera L, Wong VW-S. Noninvasive assessment of liver fibrosis in NAFLD. *Clin Gastroenterol Hepatol* 2023;21:2026–2039

83. Lin H, Lee HW, Yip TC-F, et al.; VCTE-Prognosis Study Group. Vibration-controlled transient elastography scores to predict liver-related events in steatotic liver disease. *JAMA* 2024;331:1287–1297

84. Guha IN, Parkes J, Roderick P, et al. Noninvasive markers of fibrosis in nonalcoholic fatty liver disease: validating the European Liver Fibrosis Panel and exploring simple markers. *Hepatology* 2008;47:455–460
85. Lichtigthagen R, Pietsch D, Bantel H, Manns MP, Brand K, Bahr MJ. The Enhanced Liver Fibrosis (ELF) score: normal values, influence factors and proposed cut-off values. *J Hepatol* 2013;59:236–242
86. Vali Y, Lee J, Boursier J, et al.; LITMUS systematic review team. Enhanced liver fibrosis test for the non-invasive diagnosis of fibrosis in patients with NAFLD: a systematic review and meta-analysis. *J Hepatol* 2020;73:252–262
87. Sanyal AJ, Shankar SS, Yates KP, et al. Diagnostic performance of circulating biomarkers for non-alcoholic steatohepatitis. *Nat Med* 2023;29:2656–2664
88. Pearson M, Nobes J, Macpherson I, et al. Enhanced liver fibrosis (ELF) score predicts hepatic decompensation and mortality. *JHEP Rep* 2024;6:101062
89. Younossi ZM, Anstee QM, Wong VW-S, et al. The association of histologic and noninvasive tests with adverse clinical and patient-reported outcomes in patients with advanced fibrosis due to nonalcoholic steatohepatitis. *Gastroenterology* 2021;160:1608–1619.e13
90. Sanyal AJ, Harrison SA, Ratziu V, et al. The natural history of advanced fibrosis due to nonalcoholic steatohepatitis: data from the simtuzumab trials. *Hepatology* 2019;70:1913–1927
91. Patel P, Hossain F, Horsfall LU, et al. A pragmatic approach identifies a high rate of nonalcoholic fatty liver disease with advanced fibrosis in diabetes clinics and at-risk populations in primary care. *Hepatol Commun* 2018;2:893–905
92. Arai T, Takahashi H, Seko Y, et al.; Japan Study Group of Nonalcoholic Fatty Liver Disease (JSG-NAFLD). Accuracy of the enhanced liver fibrosis test in patients with type 2 diabetes mellitus and its clinical implications. *Clin Gastroenterol Hepatol* 2024;22:789–797.e8
93. Dulai PS, Sirlin CB, Loomba R. MRI and MRE for non-invasive quantitative assessment of hepatic steatosis and fibrosis in NAFLD and NASH: clinical trials to clinical practice. *J Hepatol* 2016;65:1006–1016
94. Andersson A, Kelly M, Imajo K, et al. Clinical utility of magnetic resonance imaging biomarkers for identifying nonalcoholic steatohepatitis patients at high risk of progression: a multicenter pooled data and meta-analysis. *Clin Gastroenterol Hepatol* 2022;20:2451–2461.e3
95. Park CC, Nguyen P, Hernandez C, et al. Magnetic resonance elastography vs transient elastography in detection of fibrosis and noninvasive measurement of steatosis in patients with biopsy-proven nonalcoholic fatty liver disease. *Gastroenterology* 2017;152:598–607.e2
96. Hsu C, Caussy C, Imajo K, et al. Magnetic resonance vs transient elastography analysis of patients with nonalcoholic fatty liver disease: a systematic review and pooled analysis of individual participants. *Clin Gastroenterol Hepatol* 2019;17:630–637.e8
97. Duman S, Kuru D, Gumusoy M, et al. A combination of non-invasive tests for the detection of significant fibrosis in patients with metabolic dysfunction-associated steatotic liver disease is not superior to magnetic resonance elastography alone. *Eur Radiol* 2024;34:3882–3888
98. Liang J-X, Ampuero J, Niu H, et al.; LITMUS Consortium Investigators. An individual patient data meta-analysis to determine cut-offs for and confounders of NAFLD-fibrosis staging with magnetic resonance elastography. *J Hepatol* 2023;79:592–604
99. de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C; Baveno VII Faculty. Baveno VII - renewing consensus in portal hypertension. *J Hepatol* 2022;76:959–974
100. Pons M, Augustin S, Scheiner B, et al. Noninvasive diagnosis of portal hypertension in patients with compensated advanced chronic liver disease. *Am J Gastroenterol* 2021;116:723–732
101. Sanyal AJ, Foucquier J, Younossi ZM, et al. Enhanced diagnosis of advanced fibrosis and cirrhosis in individuals with NAFLD using FibroScan-based Agile scores. *J Hepatol* 2023;78:247–259
102. Harrison SA, Ratziu V, Magnanensi J, et al. NIS2+, an optimisation of the blood-based biomarker NIS4 technology for the detection of at-risk NASH: a prospective derivation and validation study. *J Hepatol* 2023;79:758–767
103. Sanyal AJ, Magnanensi J, Majd Z, et al. NIS2+, an effective blood-based test for the diagnosis of at-risk nonalcoholic steatohepatitis in adults 65 years and older. *Hepatol Commun* 2023;7:e0223
104. Nouredin M, Truong E, Gornbein JA, et al. MRI-based (MAST) score accurately identifies patients with NASH and significant fibrosis. *J Hepatol* 2022;76:781–787
105. Nouredin N, Ajmera V, Bergstrom J, et al. MEFIB-Index and MAST-Score in the assessment of hepatic decompensation in metabolic dysfunction-associated steatosis liver disease-individual participant data meta-analyses. *Aliment Pharmacol Ther* 2023;58:856–865
106. Nouredin M, Truong E, Mayo R, et al. Serum identification of at-risk MASH: the metabolomics-advanced steatohepatitis fibrosis score (MASEF). *Hepatology* 2024;79:135–148
107. Vieira Barbosa J, Milligan S, Frick A, et al. Fibrosis-4 index as an independent predictor of mortality and liver-related outcomes in NAFLD. *Hepatol Commun* 2022;6:765–779
108. Guan L, Li L, Zou Y, Zhong J, Qiu L. Association between FIB-4, all-cause mortality, cardiovascular mortality, and cardiovascular disease risk among diabetic individuals: NHANES 1999–2008. *Front Cardiovasc Med* 2023;10:1172178
109. Lee HW, Wong GL-H, Kwok R, et al. Serial transient elastography examinations to monitor patients with type 2 diabetes: a prospective cohort study. *Hepatology* 2020;72:1230–1241
110. Targher G, Corey KE, Byrne CD, Roden M. The complex link between NAFLD and type 2 diabetes mellitus - mechanisms and treatments. *Nat Rev Gastroenterol Hepatol* 2021;18:599–612
111. Yuan S, Chen J, Li X, et al. Lifestyle and metabolic factors for nonalcoholic fatty liver disease: Mendelian randomization study. *Eur J Epidemiol* 2022;37:723–733
112. Shang Y, Grip ET, Modica A, et al. Metabolic syndrome traits increase the risk of major adverse liver outcomes in type 2 diabetes. *Diabetes Care* 2024;47:978–985
113. Ortiz-Lopez C, Lomonaco R, Orsak B, et al. Prevalence of prediabetes and diabetes and metabolic profile of patients with nonalcoholic fatty liver disease (NAFLD). *Diabetes Care* 2012;35:873–878
114. Lomonaco R, Bril F, Portillo-Sanchez P, et al. Metabolic impact of nonalcoholic steatohepatitis in obese patients with type 2 diabetes. *Diabetes Care* 2016;39:632–638
115. Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. *Clin Gastroenterol Hepatol* 2015;13:643–654.e1–e19; quiz e39–e40
116. Shah AG, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ; Nash Clinical Research Network. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol* 2009;7:1104–1112
117. Gawrieh S, Vilar-Gomez E, Wilson LA, et al.; NASH Clinical Research Network. Increases and decreases in liver stiffness measurement are independently associated with the risk of liver-related events in NAFLD. *J Hepatol* 2024;81:600–608
118. Pennisi G, Enea M, Falco V, et al. Noninvasive assessment of liver disease severity in patients with nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes. *Hepatology* 2023;78:195–211
119. Newsome PN, Sasso M, Deeks JJ, et al. FibroScan-AST (FAST) score for the non-invasive identification of patients with non-alcoholic steatohepatitis with significant activity and fibrosis: a prospective derivation and global validation study. *Lancet Gastroenterol Hepatol* 2020;5:362–373
120. Rinella ME, Dufour J-F, Anstee QM, et al. Non-invasive evaluation of response to obeticholic acid in patients with NASH: results from the REGENERATE study. *J Hepatol* 2022;76:536–548
121. Zhang X, Yip TC-F, Wong GL-H, et al. Clinical care pathway to detect advanced liver disease in patients with type 2 diabetes through automated fibrosis score calculation and electronic reminder messages: a randomised controlled trial. *Gut* 2023;72:2364–2371
122. Younossi ZM, Corey KE, Lim JK. AGA clinical practice update on lifestyle modification using diet and exercise to achieve weight loss in the management of nonalcoholic fatty liver disease: expert review. *Gastroenterology* 2021;160:912–918
123. Zelber-Sagi S, Moore JB. Practical lifestyle management of nonalcoholic fatty liver disease for busy clinicians. *Diabetes Spectr* 2024;37:39–47
124. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. *Gastroenterology* 2015;149:367–378.e5; quiz e14–e15
125. Promrat K, Kleiner DE, Niemeier HM, et al. Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. *Hepatology* 2010;51:121–129
126. American Diabetes Association Professional Practice Committee. 5. Facilitating positive health behaviors and well-being to improve health outcomes: Standards of Care in Diabetes—2025. *Diabetes Care* 2025;48(Suppl. 1):S86–S127

127. Evert AB, Dennison M, Gardner CD, et al. Nutrition therapy for adults with diabetes or prediabetes: a consensus report. *Diabetes Care* 2019;42:731–754
128. Jensen T, Abdelmalek MF, Sullivan S, et al. Fructose and sugar: a major mediator of non-alcoholic fatty liver disease. *J Hepatol* 2018;68:1063–1075
129. Pugliese N, Plaz Torres MC, Petta S, Valenti L, Giannini EG, Aghemo A. Is there an 'ideal' diet for patients with NAFLD? *Eur J Clin Invest* 2022;52:e13659
130. Properzi C, O'Sullivan TA, Sherriff JL, et al. Ad libitum Mediterranean and low-fat diets both significantly reduce hepatic steatosis: a randomized controlled trial. *Hepatology* 2018;68:1741–1754
131. Haigh L, Kirk C, El Gendy K, et al. The effectiveness and acceptability of Mediterranean diet and calorie restriction in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis. *Clin Nutr* 2022;41:1913–1931
132. Blomdahl J, Nasr P, Ekstedt M, Kechagias S. Moderate alcohol consumption is associated with advanced fibrosis in non-alcoholic fatty liver disease and shows a synergistic effect with type 2 diabetes mellitus. *Metabolism* 2021;115:154439
133. Sargeant JA, Gray LJ, Bodicoat DH, et al. The effect of exercise training on intrahepatic triglyceride and hepatic insulin sensitivity: a systematic review and meta-analysis. *Obes Rev* 2018;19:1446–1459
134. Nam H, Yoo J-J, Cho Y, et al. Effect of exercise-based interventions in nonalcoholic fatty liver disease: a systematic review with meta-analysis. *Dig Liver Dis* 2023;55:1178–1186
135. Stine JG, DiJoseph K, Pattison Z, et al. Exercise training is associated with treatment response in liver fat content by magnetic resonance imaging independent of clinically significant body weight loss in patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Am J Gastroenterol* 2023;118:1204–1213
136. Orci LA, Gariani K, Oldani G, Delaune V, Morel P, Toso C. Exercise-based interventions for nonalcoholic fatty liver disease: a meta-analysis and meta-regression. *Clin Gastroenterol Hepatol* 2016;14:1398–1411
137. Kistler KD, Brunt EM, Clark JM, Diehl AM, Sallis JF, Schwimmer JB; NASH CRN Research Group. Physical activity recommendations, exercise intensity, and histological severity of nonalcoholic fatty liver disease. *Am J Gastroenterol* 2011;106:460–468; quiz 469
138. Stine JG, Long MT, Corey KE, et al. Physical activity and nonalcoholic fatty liver disease: a roundtable statement from the American College of Sports Medicine. *Med Sci Sports Exerc* 2023;55:1717–1726
139. Hashida R, Kawaguchi T, Bekki M, et al. Aerobic vs. resistance exercise in non-alcoholic fatty liver disease: a systematic review. *J Hepatol* 2017;66:142–152
140. Shea S, Lionis C, Kite C, et al. Non-alcoholic fatty liver disease and coexisting depression, anxiety and/or stress in adults: a systematic review and meta-analysis. *Front Endocrinol (Lausanne)* 2024;15:1357664
141. Powers MA, Bardsley JK, Cypress M, et al. Diabetes self-management education and support in adults with type 2 diabetes: a consensus report of the American Diabetes Association, the Association of Diabetes Care & Education Specialists, the Academy of Nutrition and Dietetics, the American Academy of Family Physicians, the American Academy of PAs, the American Association of Nurse Practitioners, and the American Pharmacists Association. *Diabetes Care* 2020;43:1636–1649
142. Balakrishnan M, Liu K, Schmitt S, et al. Behavioral weight-loss interventions for patients with NAFLD: a systematic scoping review. *Hepatol Commun* 2023;7:e0224
143. Hamman RF, Wing RR, Edelstein SL, et al. Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes Care* 2006;29:2102–2107
144. Koutoukidis DA, Astbury NM, Tudor KE, et al. Association of weight loss interventions with changes in biomarkers of nonalcoholic fatty liver disease: a systematic review and meta-analysis. *JAMA Intern Med* 2019;179:1262–1271
145. Wadden TA, Neiberg RH, Wing RR, et al.; Look AHEAD Research Group. Four-year weight losses in the Look AHEAD study: factors associated with long-term success. *Obesity (Silver Spring)* 2011;19:1987–1998
146. American Diabetes Association Professional Practice Committee. 8. Obesity and weight management for the prevention and treatment of type 2 diabetes: Standards of Care in Diabetes—2025. *Diabetes Care* 2025;48(Suppl. 1):S167–S180
147. Carrieri P, Mourad A, Marcellin F, et al. Knowledge of liver fibrosis stage among adults with NAFLD/NASH improves adherence to lifestyle changes. *Liver Int* 2022;42:984–994
148. Haigh L, Bremner S, Houghton D, et al. Barriers and facilitators to Mediterranean diet adoption by patients with nonalcoholic fatty liver disease in Northern Europe. *Clin Gastroenterol Hepatol* 2019;17:1364–1371.e3
149. Zelber-Sagi S, Bord S, Dror-Lavi G, et al. Role of illness perception and self-efficacy in lifestyle modification among non-alcoholic fatty liver disease patients. *World J Gastroenterol* 2017;23:1881–1890
150. Mantovani A, Csermely A, Petracca G, et al. Non-alcoholic fatty liver disease and risk of fatal and non-fatal cardiovascular events: an updated systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2021;6:903–913
151. American Diabetes Association Professional Practice Committee. 10. Cardiovascular disease and risk management: Standards of Care in Diabetes—2025. *Diabetes Care* 2025;48(Suppl. 1):S207–S238
152. American Diabetes Association Professional Practice Committee. 11. Chronic kidney disease and risk management: Standards of Care in Diabetes—2025. *Diabetes Care* 2025;48(Suppl. 1):S239–S251
153. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al.; SELECT Trial Investigators. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med* 2023;389:2221–2232
154. Newsome PN, Buchholtz K, Cusi K, et al.; NN9931-4296 Investigators. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. *N Engl J Med* 2021;384:1113–1124
155. Gastaldelli A, Cusi K, Fernández Landó L, Bray R, Brouwers B, Rodríguez Á. Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial. *Lancet Diabetes Endocrinol* 2022;10:393–406
156. Loomba R, Hartman ML, Lawitz EJ, et al.; SYNERGY-NASH Investigators. Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis. *N Engl J Med* 2024;391:299–310
157. Armstrong MJ, Gaunt P, Aithal GP, et al.; LEAN trial team. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet* 2016;387:679–690
158. Sanyal AJ, Bedossa P, Fraessdorf M, et al.; 1404-0043 Trial Investigators. A phase 2 randomized trial of survodutide in MASH and fibrosis. *N Engl J Med* 2024;391:311–319
159. Rosenstock J, Frias J, Jastreboff AM, et al. Retatrutide, a GIP, GLP-1 and glucagon receptor agonist, for people with type 2 diabetes: a randomised, double-blind, placebo and active-controlled, parallel-group, phase 2 trial conducted in the USA. *Lancet* 2023;402:S29–S44
160. Jastreboff AM, Kaplan LM, Frias JP, et al.; Retatrutide Phase 2 Obesity Trial Investigators. Triple-hormone-receptor agonist retatrutide for obesity - a phase 2 trial. *N Engl J Med* 2023;389:514–526
161. Sanyal AJ, Kaplan LM, Frias JP, et al. Triple hormone receptor agonist retatrutide for metabolic dysfunction-associated steatotic liver disease: a randomized phase 2a trial. *Nat Med* 2024;30:2037–2048
162. Wang H, Wang L, Cheng Y, Xia Z, Liao Y, Cao J. Efficacy of orlistat in non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Biomed Rep* 2018;9:90–96
163. Patel Chavez C, Cusi K, Kadiyala S. The emerging role of glucagon-like peptide-1 receptor agonists for the management of NAFLD. *J Clin Endocrinol Metab* 2022;107:29–38
164. Genua I, Cusi K. Pharmacological approaches to nonalcoholic fatty liver disease: current and future therapies. *Diabetes Spectr* 2024;37:48–58
165. Courcoulas AP, Patti ME, Hu B, et al. Long-term outcomes of medical management vs bariatric surgery in type 2 diabetes. *JAMA* 2024;331:654–664
166. Sheng B, Truong K, Spitler H, Zhang L, Tong X, Chen L. The long-term effects of bariatric surgery on type 2 diabetes remission, microvascular and macrovascular complications, and mortality: a systematic review and meta-analysis. *Obes Surg* 2017;27:2724–2732
167. Lafarge J-C, Aron-Wisniewsky J, Pattou F, et al.; ARMMS-T2D Consortium. French National Authority for Health assessment of metabolic surgery for type 2 diabetes remission-a meta-analysis in patients with class I to III obesity. *Diabetes Metab* 2024;50:101495
168. Obeso-Fernández J, Millan-Alanis JM, Sáenz-Flores M, et al. Benefits of metabolic surgery on macrovascular outcomes in adult patients with type 2 diabetes: a systematic review and meta-analysis. *Surg Obes Relat Dis* 2024;20:202–212
169. Fakhry TK, Mhaskar R, Schwaitalla T, Muradova E, Gonzalvo JP, Murr MM. Bariatric surgery improves nonalcoholic fatty liver disease: a contemporary systematic review and meta-analysis. *Surg Obes Relat Dis* 2019;15:502–511



170. Ramai D, Singh J, Lester J, et al. Systematic review with meta-analysis: bariatric surgery reduces the incidence of hepatocellular carcinoma. *Aliment Pharmacol Ther* 2021;53:977–984
171. Wilson RB, Lathigara D, Kaushal D. Systematic review and meta-analysis of the impact of bariatric surgery on future cancer risk. *Int J Mol Sci* 2023;24:6192
172. Aminian A, Al-Kurd A, Wilson R, et al. Association of bariatric surgery with major adverse liver and cardiovascular outcomes in patients with biopsy-proven nonalcoholic steatohepatitis. *JAMA* 2021;326:2031–2042
173. Agarwal L, Sahu AK, Bakshi A, Agarwal A, Aggarwal S. Safety of metabolic and bariatric surgery in obese patients with liver cirrhosis: a systematic review and meta-analysis. *Surg Obes Relat Dis* 2021;17:525–537
174. Feng G, Han Y, Yang W, et al. Recompensation in MASLD-related cirrhosis via metabolic bariatric surgery. *Trends Endocrinol Metab* 2025;36:118–132
175. Ajmera V, Cepin S, Tesfai K, et al. A prospective study on the prevalence of NAFLD, advanced fibrosis, cirrhosis and hepatocellular carcinoma in people with type 2 diabetes. *J Hepatol* 2023;78:471–478
176. Sanyal AJ, Van Natta ML, Clark J, et al.; NASH Clinical Research Network (CRN). Prospective study of outcomes in adults with nonalcoholic fatty liver disease. *N Engl J Med* 2021;385:1559–1569
177. Kanwal F, Kramer JR, Li L, et al. Effect of metabolic traits on the risk of cirrhosis and hepatocellular cancer in nonalcoholic fatty liver disease. *Hepatology* 2020;71:808–819
178. Musso G, Cassader M, Paschetta E, Gambino R. Thiazolidinediones and advanced liver fibrosis in nonalcoholic steatohepatitis: a meta-analysis. *JAMA Intern Med* 2017;177:633–640
179. Kahl S, Pützer J, Roden M. Novel antidiabetic strategies and diabetologists' views in nonalcoholic steatohepatitis. *Semin Liver Dis* 2022;42:48–60
180. Weiss T, Carr RD, Pal S, et al. Real-world adherence and discontinuation of glucagon-like peptide-1 receptor agonists therapy in type 2 diabetes mellitus patients in the United States. *Patient Prefer Adherence* 2020;14:2337–2345
181. Weiss T, Yang L, Carr RD, et al. Real-world weight change, adherence, and discontinuation among patients with type 2 diabetes initiating glucagon-like peptide-1 receptor agonists in the UK. *BMJ Open Diabetes Res Care* 2022;10:e002517
182. Sanyal AJ, Chalasani N, Kowdley KV, et al.; NASH CRN. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med* 2010;362:1675–1685
183. Aithal GP, Thomas JA, Kaye PV, et al. Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. *Gastroenterology* 2008;135:1176–1184
184. Huang J-F, Dai C-Y, Huang C-F, et al. First-in-Asian double-blind randomized trial to assess the efficacy and safety of insulin sensitizer in non-alcoholic steatohepatitis patients. *Hepatol Int* 2021;15:1136–1147
185. Bril F, Kalavalapalli S, Clark VC, et al. Response to pioglitazone in patients with non-alcoholic steatohepatitis with vs without type 2 diabetes. *Clin Gastroenterol Hepatol* 2018;16:558–566.e2
186. Belfort R, Harrison SA, Brown K, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med* 2006;355:2297–2307
187. Cusi K, Orsak B, Bril F, et al. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: a randomized trial. *Ann Intern Med* 2016;165:305–315
188. Aronoff S, Rosenblatt S, Braithwaite S, Egan JW, Mathisen AL, Schneider RL; The Pioglitazone 001 Study Group. Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. *Diabetes Care* 2000;23:1605–1611
189. Miyazaki Y, Matsuda M, DeFronzo RA. Dose-response effect of pioglitazone on insulin sensitivity and insulin secretion in type 2 diabetes. *Diabetes Care* 2002;25:517–523
190. Della Pepa G, Russo M, Vitale M, et al. Pioglitazone even at low dosage improves NAFLD in type 2 diabetes: clinical and pathophysiological insights from a subgroup of the TOSCA.IT randomised trial. *Diabetes Res Clin Pract* 2021;178:108984
191. Norwood P, Liutkus JF, Haber H, Pintilei E, Boardman MK, Trautmann ME. Safety of exenatide once weekly in patients with type 2 diabetes mellitus treated with a thiazolidinedione alone or in combination with metformin for 2 years. *Clin Ther* 2012;34:2082–2090
192. Wysham C, Blevins T, Arakaki R, et al. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). *Diabetes Care* 2014;37:2159–2167
193. Abdul-Ghani M, Migahid O, Megahed A, DeFronzo RA, Al-Ozairi E, Jayyousi A. Combination therapy with pioglitazone/exenatide improves beta-cell function and produces superior glycaemic control compared with basal/bolus insulin in poorly controlled type 2 diabetes: a 3-year follow-up of the Qatar study. *Diabetes Obes Metab* 2020;22:2287–2294
194. Anson M, Henney AE, Zhao SS, et al. Effect of combination pioglitazone with sodium-glucose cotransporter-2 inhibitors or glucagon-like peptide-1 receptor agonists on outcomes in type 2 diabetes: a systematic review, meta-analysis, and real-world study from an international federated database. *Diabetes Obes Metab* 2024;26:2606–2623
195. Ahrén B, Masmiquel L, Kumar H, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. *Lancet Diabetes Endocrinol* 2017;5:341–354
196. Lavynenko O, Abdul-Ghani M, Alatrach M, et al. Combination therapy with pioglitazone/exenatide/metformin reduces the prevalence of hepatic fibrosis and steatosis: the efficacy and durability of initial combination therapy for type 2 diabetes (EDICT). *Diabetes Obes Metab* 2022;24:899–907
197. Kovacs CS, Seshiah V, Swallow R, et al.; EMPA-REG PIO trial investigators. Empagliflozin improves glycaemic and weight control as add-on therapy to pioglitazone or pioglitazone plus metformin in patients with type 2 diabetes: a 24-week, randomized, placebo-controlled trial. *Diabetes Obes Metab* 2014;16:147–158
198. Kovacs CS, Seshiah V, Merker L, et al.; EMPA-REG EXTEND PIO investigators. Empagliflozin as add-on therapy to pioglitazone with or without metformin in patients with type 2 diabetes mellitus. *Clin Ther* 2015;37:1773–1788.e1
199. DeFronzo RA, Chilton R, Norton L, Clarke G, Ryder REJ, Abdul-Ghani M. Revitalization of pioglitazone: the optimum agent to be combined with a sodium-glucose co-transporter-2 inhibitor. *Diabetes Obes Metab* 2016;18:454–462
200. Yoneda M, Kobayashi T, Honda Y, et al. Combination of tofogliflozin and pioglitazone for NAFLD: extension to the ToPIND randomized controlled trial. *Hepatol Commun* 2022;6:2273–2285
201. Sathyanarayana P, Jogi M, Muthupillai R, Krishnamurthy R, Samson SL, Bajaj M. Effects of combined exenatide and pioglitazone therapy on hepatic fat content in type 2 diabetes. *Obesity (Silver Spring)* 2011;19:2310–2315
202. Attaran F, Emami S, Sohrabi M, et al. Effect of empagliflozin and pioglitazone on left ventricular function in patients with type two diabetes and nonalcoholic fatty liver disease without established cardiovascular disease: a randomized single-blind clinical trial. *BMC Gastroenterol* 2023;23:327
203. Gastaldelli A, Cusi K. From NASH to diabetes and from diabetes to NASH: mechanisms and treatment options. *JHEP Rep* 2019;1:312–328
204. Banini BA, Cazanave SC, Yates KP, et al.; Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN). Haptoglobin 2 allele is associated with histologic response to vitamin E in subjects with nonalcoholic steatohepatitis. *J Clin Gastroenterol* 2019;53:750–758
205. Bril F, Biernacki DM, Kalavalapalli S, et al. Role of vitamin E for nonalcoholic steatohepatitis in patients with type 2 diabetes: a randomized controlled trial. *Diabetes Care* 2019;42:1481–1488
206. Vilar-Gomez E, Vuppalanchi R, Gawrieh S, et al. Vitamin E improves transplant-free survival and hepatic decompensation among patients with nonalcoholic steatohepatitis and advanced fibrosis. *Hepatology* 2020;71:495–509
207. Neuhauser ML, Barnett MJ, Kristal AR, et al. Dietary supplement use and prostate cancer risk in the Carotene and Retinol Efficacy Trial. *Cancer Epidemiol Biomarkers Prev* 2009;18:2202–2206
208. Takahashi H, Kessoku T, Kawanaka M, et al. Ipragliflozin improves the hepatic outcomes of patients with diabetes with NAFLD. *Hepatol Commun* 2022;6:120–132
209. Takeshita Y, Honda M, Harada K, et al. Comparison of tofogliflozin and glimepiride effects on nonalcoholic fatty liver disease in participants with type 2 diabetes: a randomized, 48-week, open-label, active-controlled trial. *Diabetes Care* 2022;45:2064–2075
210. Lombardi R, Mantovani A, Cespiati A, et al. Evolution of liver fibrosis in diabetic patients with NAFLD in a follow-up study: hepatoprotective effects of sodium-glucose co-transporter-2 inhibitors. *Dig Liver Dis* 2024;56:551–558
211. Corbin KD, Driscoll KA, Pratley RE, Smith SR, Maahs DM, Mayer-Davis EJ; Advancing Care for Type 1 Diabetes and Obesity Network (ACT1ON). Obesity in type 1 diabetes: pathophysiology,

- clinical impact, and mechanisms. *Endocr Rev* 2018;39:629–663
212. Bailey R, Calhoun P, Garg SK. Weight gain and glycemic control in adults with type 1 diabetes in the T1D Exchange Registry. *Diabetes Technol Ther* 2024;26:156–160
213. Cusi K, Sanyal AJ, Zhang S, et al. Non-alcoholic fatty liver disease (NAFLD) prevalence and its metabolic associations in patients with type 1 diabetes and type 2 diabetes. *Diabetes Obes Metab* 2017;19:1630–1634
214. Cusi K, Sanyal AJ, Zhang S, et al. Different effects of basal insulin peglispro and insulin glargine on liver enzymes and liver fat content in patients with type 1 and type 2 diabetes. *Diabetes Obes Metab* 2016;18(Suppl. 2):50–58
215. Hatzigelaki E, Paschou SA, Schön M, Psaltopoulou T, Roden M. NAFLD and thyroid function: pathophysiological and therapeutic considerations. *Trends Endocrinol Metab* 2022;33:755–768
216. Chen VL, Morgan TR, Rotman Y, et al. Resmetirom therapy for metabolic dysfunction-associated steatotic liver disease: October 2024 updates to AASLD practice guidance. *Hepatology* 2025;81:312–320
217. Guzelce EC, Galbiati F, Goldman AL, Gattu AK, Basaria S, Bhasin S. Accurate measurement of total and free testosterone levels for the diagnosis of androgen disorders. *Best Pract Res Clin Endocrinol Metab* 2022;36:101683
218. Cusi K. Selective agonists of thyroid hormone receptor beta for the treatment of NASH. *N Engl J Med* 2024;390:559–561
219. Center for Drug Evaluation and Research. Application Number: 217785Orig1s000. NDA 217785: REZDIFFRA (Resmetirom): Integrated Review. U.S. Food & Drug Administration. Accessed 16 August 2024. Available from [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2024/217785Orig1s000IntegratedR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2024/217785Orig1s000IntegratedR.pdf)
220. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2018;103:1715–1744
221. Kanwal F, Shubrook JH, Younossi Z, et al. Preparing for the NASH epidemic: a call to action. *Metabolism* 2021;122:154822
222. Muzurović E, Peng CC-H, Belanger MJ, Sanoudou D, Mikhailidis DP, Mantzoros CS. Nonalcoholic fatty liver disease and cardiovascular disease: a review of shared cardiometabolic risk factors. *Hypertension* 2022;79:1319–1326
223. Long MT, Zhang X, Xu H, et al. Hepatic fibrosis associates with multiple cardiometabolic disease risk factors: the Framingham Heart Study. *Hepatology* 2021;73:548–559
224. Cusi K. Nonalcoholic fatty liver disease in diabetes: a call to action. *Diabetes Spectr* 2024;37:5–7
225. Younossi ZM, Henry L, Isaacs S, Cusi K. Identification of high-risk patients with nonalcoholic fatty liver disease in endocrinology clinics. *Endocr Pract* 2023;29:912–918
226. Academy Quality Management Committee. Academy of Nutrition and Dietetics: revised 2017 scope of practice for the registered dietitian nutritionist. *J Acad Nutr Diet* 2018;118:141–165
227. Wlazlo N, Beijers HJBH, Schoon EJ, Sauerwein HP, Stehouwer CDA, Bravenboer B. High prevalence of diabetes mellitus in patients with liver cirrhosis. *Diabet Med* 2010;27:1308–1311
228. Lee WG, Wells CI, McCall JL, Murphy R, Plank LD. Prevalence of diabetes in liver cirrhosis: a systematic review and meta-analysis. *Diabetes Metab Res Rev* 2019;35:e3157
229. Makol A, Kanthaje S, Dhiman RK, Kalra N, Chawla YK, Chakraborti A. Association of liver cirrhosis severity with type 2 diabetes mellitus in hepatocellular carcinoma. *Exp Biol Med (Maywood)* 2018;243:323–326
230. Chhabra S, Singh SP, Singh A, et al. Diabetes mellitus increases the risk of significant hepatic fibrosis in patients with non-alcoholic fatty liver disease. *J Clin Exp Hepatol* 2022;12:409–416
231. Mota M, Banini BA, Cazanave SC, Sanyal AJ. Molecular mechanisms of lipotoxicity and glucotoxicity in nonalcoholic fatty liver disease. *Metabolism* 2016;65:1049–1061
232. Ferdous S-E, Ferrell JM. Pathophysiological relationship between type 2 diabetes mellitus and metabolic dysfunction-associated steatotic liver disease: novel therapeutic approaches. *Int J Mol Sci* 2024;25:8731
233. Gancheva S, Roden M, Castera L. Diabetes as a risk factor for MASH progression. *Diabetes Res Clin Pract* 2024;217:111846
234. Khanmohammadi S, Habibzadeh A, Kamrul-Hasan ABM, Schuermans A, Kuchay MS. Glucose-lowering drugs and liver-related outcomes among individuals with type 2 diabetes: a systematic review of longitudinal population-based studies. *Diabet Med* 2024;41:e15437
235. American Diabetes Association Professional Practice Committee. 2. Diagnosis and classification of diabetes: Standards of Care in Diabetes—2025. *Diabetes Care* 2025;48(Suppl. 1):S27–S49
236. American Diabetes Association Professional Practice Committee. 7. Diabetes technology: Standards of Care in Diabetes—2025. *Diabetes Care* 2025;48(Suppl. 1):S146–S166
237. Lee J-Y, Kim Y-E, Han K, et al. Analysis of severe hypoglycemia among adults with type 2 diabetes and nonalcoholic fatty liver disease. *JAMA Netw Open* 2022;5:e202062
238. Yen F-S, Hou M-C, Liu J-S, Hsu C-C, Hwu C-M. Severe hypoglycemia in patients with liver cirrhosis and type 2 diabetes. *Front Med (Lausanne)* 2022;9:962337
239. American Diabetes Association Professional Practice Committee. 6. Glycemic goals and hypoglycemia: Standards of Care in Diabetes—2025. *Diabetes Care* 2025;48(Suppl. 1):S128–S145
240. Tuo S, Yeo YH, Chang R, et al. Prevalence of and associated factors for sarcopenia in patients with liver cirrhosis: a systematic review and meta-analysis. *Clin Nutr* 2024;43:84–94
241. Costa D, Lourenço J, Monteiro AM, et al. Clinical performance of flash glucose monitoring system in patients with liver cirrhosis and diabetes mellitus. *Sci Rep* 2020;10:7460
242. Honda F, Hiramatsu A, Hyogo H, et al. Evaluation of glycemic variability in chronic liver disease patients with type 2 diabetes mellitus using continuous glucose monitoring. *PLoS One* 2018;13:e0195028
243. Macías-Rodríguez RU, Illaraza-Lomeli H, Ruiz-Margáin A, et al. Changes in hepatic venous pressure gradient induced by physical exercise in cirrhosis: results of a pilot randomized open clinical trial. *Clin Transl Gastroenterol* 2016;7:e180
244. Berzigotti A, Albillos A, Villanueva C, et al.; Ciberehd SportDiet Collaborative Group. Effects of an intensive lifestyle intervention program on portal hypertension in patients with cirrhosis and obesity: the SportDiet study. *Hepatology* 2017;65:1293–1305
245. Locklear CT, Golabi P, Gerber L, Younossi ZM. Exercise as an intervention for patients with end-stage liver disease: systematic review. *Medicine (Baltimore)* 2018;97:e12774
246. Piguat A-C, Saran U, Simillion C, et al. Regular exercise decreases liver tumors development in hepatocyte-specific PTEN-deficient mice independently of steatosis. *J Hepatol* 2015;62:1296–1303
247. Zamanian-Azodi M, Khatoun Hajisayah S, Razzaghi M, Rezaei-Tavirani M. Introducing physical exercise as a potential strategy in liver cancer prevention and development. *Gastroenterol Hepatol Bed Bench* 2021;14:317–322
248. American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: Standards of Care in Diabetes—2025. *Diabetes Care* 2025;48(Suppl. 1):S181–S206
249. Looma R, Abdelmalek MF, Armstrong MJ, et al.; NN9931-4492 Investigators. Semaglutide 2.4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial. *Lancet Gastroenterol Hepatol* 2023;8:511–522
250. Lawitz EJ, Fraessdorf M, Neff GW, et al.; NCT05296733 Investigators. Efficacy, tolerability and pharmacokinetics of survodutide, a glucagon/glucagon-like peptide-1 receptor dual agonist, in cirrhosis. *J Hepatol* 2024;81:837–846
251. Kawamori R, Kadowaki T, Onji M, Seino Y, Akanuma Y, PRACTICAL Study Group. Hepatic safety profile and glycemic control of pioglitazone in more than 20,000 patients with type 2 diabetes mellitus: postmarketing surveillance study in Japan. *Diabetes Res Clin Pract* 2007;76:229–235
252. Kanwal F, Kramer JR, Li L, et al. GLP-1 receptor agonists and risk for cirrhosis and related complications in patients with metabolic dysfunction-associated steatotic liver disease. *JAMA Intern Med* 2024;184:1314–1323
253. El-Serag HB, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. *Clin Gastroenterol Hepatol* 2006;4:369–380
254. Simon TG, King LY, Chong DQ, et al. Diabetes, metabolic comorbidities, and risk of hepatocellular carcinoma: results from two prospective cohort studies. *Hepatology* 2018;67:1797–1806
255. Zoppini G, Fedeli U, Gennaro N, Saugo M, Targher G, Bonora E. Mortality from chronic liver diseases in diabetes. *Am J Gastroenterol* 2014;109:1020–1025
256. Llovet JM, Willoughby CE, Singal AG, et al. Nonalcoholic steatohepatitis-related hepatocellular carcinoma: pathogenesis and treatment. *Nat Rev Gastroenterol Hepatol* 2023;20:487–503
257. Huang DQ, Nouredin N, Ajmera V, et al. Type 2 diabetes, hepatic decompensation, and hepatocellular carcinoma in patients with non-alcoholic fatty liver disease: an individual participant-level data meta-analysis. *Lancet Gastroenterol Hepatol* 2023;8:829–836

258. Ye F, Chen L, Zheng X. Diabetes and the risk of cirrhosis and HCC: an analysis of the UK Biobank. *Hepatol Commun* 2023;7:e0280
259. Kramer JR, Natarajan Y, Dai J, et al. Effect of diabetes medications and glycemic control on risk of hepatocellular cancer in patients with nonalcoholic fatty liver disease. *Hepatology* 2022;75:1420–1428
260. Singh S, Singh PP, Singh AG, Murad MH, Sanchez W. Anti-diabetic medications and the risk of hepatocellular cancer: a systematic review and meta-analysis. *Am J Gastroenterol* 2013;108:881–891; quiz 892
261. Wester A, Shang Y, Toresson Grip E, Matthews AA, Hagström H. Glucagon-like peptide-1 receptor agonists and risk of major adverse liver outcomes in patients with chronic liver disease and type 2 diabetes. *Gut* 2024;73:835–843
262. Gepner Y, Golan R, Harman-Boehm I, et al. Effects of initiating moderate alcohol intake on cardiometabolic risk in adults with type 2 diabetes: a 2-year randomized, controlled trial. *Ann Intern Med* 2015;163:569–579
263. Baliunas DO, Taylor BJ, Irving H, et al. Alcohol as a risk factor for type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care* 2009;32:2123–2132
264. Yuan J-M, Govindarajan S, Arakawa K, Yu MC. Synergism of alcohol, diabetes, and viral hepatitis on the risk of hepatocellular carcinoma in blacks and whites in the U.S. *Cancer* 2004;101:1009–1017
265. Hassan MM, Hwang L-Y, Hatten CJ, et al. Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. *Hepatology* 2002;36:1206–1213
266. Agabio R, Madeddu C, Contu P, et al. Alcohol consumption is a modifiable risk factor for breast cancer: are women aware of this relationship? *Alcohol Alcohol* 2022;57:533–539
267. Bongaerts BWC, de Goeij AFPM, van den Brandt PA, Weijenberg MP. Alcohol and the risk of colon and rectal cancer with mutations in the K-ras gene. *Alcohol* 2006;38:147–154
268. Ortolá R, Sotos-Prieto M, García-Esquinas E, Galán I, Rodríguez-Artalejo F. Alcohol consumption patterns and mortality among older adults with health-related or socioeconomic risk factors. *JAMA Netw Open* 2024;7:e2424495
269. Mekary RA, Rimm EB, Giovannucci E, et al. Joint association of glycemic load and alcohol intake with type 2 diabetes incidence in women. *Am J Clin Nutr* 2011;94:1525–1532
270. Murata C, Suzuki Y, Muramatsu T, et al. Inactive aldehyde dehydrogenase 2 worsens glycemic control in patients with type 2 diabetes mellitus who drink low to moderate amounts of alcohol. *Alcohol Clin Exp Res* 2000;24:55–115
271. Ye Q, Ouyang X, Qin Z, et al. The association between alcohol drinking and glycemic management among people with type 2 diabetes in China. *J Diabetes Investig* 2024;15:237–244