CLDF Payer Coalition Practicum on Metabolic Dysfunction-Associated Steatohepatitis

CLDF
Chronic Liver Disease Foundation

Introduction

The Chronic Liver Disease Foundation (CLDF) is a nonprofit organization led by liver disease experts whose purpose is to raise awareness of the effects of chronic liver disease. In 2022, the CLDF formed the "CLDF Health Outcomes Coalition," comprised of stakeholders with expertise in liver disease, pharmacoeconomics, public health, health outcomes, managed care organizations, and innovative models of chronic care. In 2022, the coalition held a symposium to address current issues in the management of cirrhosis from overall health outcome and managed care perspectives and published the summary of this symposium, "Addressing Health Outcomes and Rising Costs in the Management of Chronic Liver Disease/Cirrhosis" on the CLDF website, https://www.chronicliverdisease.org/ (1).

In a follow-up to this symposium, the Coalition regrouped at the 3rd annual Liver Connect meeting and held a 3-hour Payer Solutions Workshop on Metabolic Dysfunction-Associated Steatohepatitis (MASH). Additional details on the participants can be found in Appendix A. The objectives of this meeting were to review the current management of MASH and its expected evolution, discuss best practices, and identify opportunities for the CLDF to support educational activities at managed care plans. An overview of the agenda is detailed here.

Update on Activities Following the 2022 Workshop	**JP Benya** President of Focus Payer Solutions Parsippany, New Jersey
AACE & AASLD Guidelines; Expected Impact on Improving the Patient Journey	**Scott Isaacs, MD** Atlanta Endocrine Associates Atlanta, GA
Roundtable on the Use of MASH NITs for Screening, Diagnosing, and Staging MASH in Lieu of Liver Biopsy – Potential Healthcare Cost Impact	**Rohit Loomba, MD, MHSc** UC San Diego Health San Diego, CA
Group Feedback & Discussion	**Moderators:** **Marcelo Kugelmas, MD** South Denver Gastroenterology, PC Englewood, Colorado **Timothy Ritter, MD** GI Alliance Southlake, TX **Hetal Karsan, MD** Atlanta Gastroenterology Associates Atlanta, GA

The presentations and subsequent discussions that took place and panel recommendations that were communicated during this roundtable are summarized throughout this whitepaper. It is important to note that, in June 2023 (3 months after the roundtable took place), the American Association for the Study of Liver Diseases (AASLD) announced a new nomenclature for fatty liver disease. The terms *metabolic dysfunction-associated steatotic liver disease* (MASLD) and *metabolic dysfunction-associated steatohepatitis* (MASH) now replace the terms *nonalcoholic fatty liver disease* (NAFLD) and *nonalcoholic steatohepatitis* (NASH) (2). This summary will use the most updated terminology wherever possible. Titles of published guidelines and papers that were published prior to June 2023 include the previous nomenclature, which are retained here for accuracy.

Update on Activities Following the 2022 Workshop

At the 2022 Coalition meeting, participants found that healthcare providers (HCPs) do not follow disease management guidelines because they are often not in complete alignment across different medical societies, are complex and difficult to "translate" to real world practice, and are outdated. Actions have been taken in other disease states in response to this feedback. For example, the CLDF created and published updated, comprehensive, step-by-step approaches to the management of hepatorenal syndrome-acute kidney injury (HRS-AKI) (3) and primary biliary cholangitis (PBC) (4), which streamline society guidelines for more practical use. Ultimately, Focus Payers Solutions was established in November 2022 to implement CLDF educational programs on behalf of disease management paradigms for payers by network providers within a network and members within a network. With HRS-AKI and PBC, the process of guideline reviews and tool creation has occurred; however, Focus Payers Solutions is still pursuing support for the dissemination of these tools.

AACE & AASLD Guidelines: Expected Impact on Improving the Patient Journey

A review of available guidelines on MAFLD/MASH align with the Coalition's perspective on guidelines in general:

Guidelines are often not in complete alignment across different medical societies

The most recent guidelines on MAFLD/MASH include EASL-EASD-EASO 2016, Clinical Care Pathway 2021,

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AACE 2022, ADA 2023, and AASLD 2023. The table below shows a detailed comparison of two of these guidelines (5, 6), which validates this feedback from the Coalition.

AACE and AASLD Comparison

AACE (2022)

- Clinical practice guideline
- First NAFLD guideline
- Endocrinologists and primary care
- Adult and pediatric
- Cirrhosis prevention in high-risk groups
- Co-sponsored by AASLD

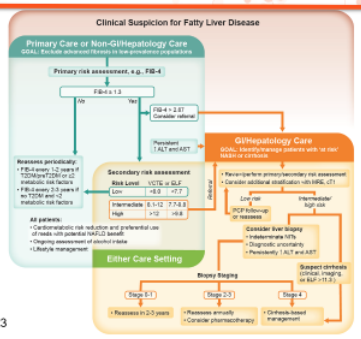
AASLD (2023)

- Practice guidance
- Revised from 2018
- Hepatologists and gastroenterologists
- Adult (pediatric separate)
- Screen NAFLD for T2D
- Some authors from AACE

Guidelines are complex and difficult to "translate" into real world practice

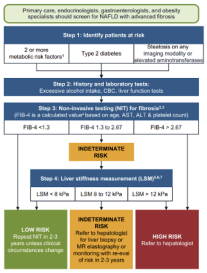
Images of the "AASLD Risk Stratification Algorithm (6)" and "AGA Clinical Care Pathway for the Risk Stratification and Management of Patients with NAFLD (7)" demonstrate the complexity of society guidelines.

AASLD Risk Stratification Algorithm



Rinella et al. Hepatology 2023

AGA Clinical Care Pathway for the Risk Stratification and Management of Patients With NAFLD



	LOW RISK FIB-4 < 1.3 or LSM < 8 kPa or liver biopsy F0-F1	INDETERMINATE RISK FIB-4 1.3 - 2.67 and/or LSM 8 - 12 kPa and liver biopsy not available	HIGH RISK[1] FIB-4 > 2.67 or LSM > 12 kPa or liver biopsy F2-F4
	Management by PCP, dietician, endocrinologist, cardiologist, others	Management by hepatologist with multidisciplinary team (PCP, dietician, endocrinologist, cardiologist, others)	
Lifestyle intervention[2]	Yes	Yes	Yes
Weight loss recommended if overweight or obese[3]	Yes May benefit from structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Greater need for structured weight loss programs, anti-obesity medications, bariatric surgery	Yes Strong need for structured weight loss programs, anti-obesity medications, bariatric surgery
Pharmacotherapy for NASH	Not recommended	Yes[4, 5, 6]	Yes[4, 5, 6, 7]
CVD risk reduction[3]	Yes	Yes	Yes
Diabetes care	Standard of care	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)	Prefer medications with efficacy in NASH (pioglitazone, GLP-1 RA)

Kanwal, et al. Gastroenterology. 2021

Guidelines are outdated

Some guidelines impart expiration dates, such as the AACE guidelines, which expire in 2027, 5 years from the publication date (5). However, with new MAFLD/MASH data rapidly emerging, these 2022 guidelines may already be outdated. Other guidelines such as the "EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease" date back to 2016 (8) and are surely in need of an update.

Roundtable on the Use of MASH NITs for Screening, Diagnosing, and Staging MASH in Lieu of Liver Biopsy – Potential Healthcare Cost Impact

Non-invasive assessment is now taking the center stage in risk stratification

MASH patients who are at the highest risk of progressive liver disease (i.e., fibrosis >F2 and/or NAS >4) must be identified early in the disease course (9). The limitations of liver biopsy have driven intense interest in the development of noninvasive testing methods (NITs) for assessing fibrosis in MAFLD/MASH. Serum-based algorithms or markers include the Fibrosis-4 (FIB-4) index (10, 11) and the Enhanced Liver Fibrosis (ELF) score (12), both of which are discussed in the figures below.

Central anchor: Fibrosis-4 (FIB-4) index

Fibrosis-4 (FIB-4) index

- **Predicts advanced fibrosis in the liver**
  - Age (years)
  - ALT (U/L)
  - AST (U/L)
  - Platelet count (x10^9/L)

Understanding the score:

Score <1.3 Rules out advanced fibrosis (Sn: 74%; Sp: 71%)	Indeterminate	Score >2.67 Predicts advanced fibrosis (Sn: 33%; Sp: 98%)

Shah AG, et al. Clin Gastroenterol Hepatol 2009;7:1104-12; Angulo P, et al. Hepatology 2007;45:846-54

Sn: sensitivity; Sp: specificity

Exploring non-invasive tests: Enhanced liver fibrosis (ELF) score

- **Proprietary blood test that delivers information on liver fibrosis severity**
- Algorithm incorporating 3 common serum biomarkers:
  - HA (hyaluronic acid)
  - PIIINP (amino-terminal propeptide of type III procollagen)
  - TIMP-1 (tissue inhibitor of metalloproteinase-1)

Understanding the score:

Score 7.7 Rules out fibrosis (Sn: 97%; Sp: 33%)	Score 9.8 Predicts fibrosis (Sn: 69%; Sp: 98%)	Score 11.3 Predicts cirrhosis (Sn: 83%; Sp: 97%)

Lichtinghagen R, et al. J Hepatol 2013;59:236-42; Fagan KJ, et al. Liver Int 2015;35:1673-81

The 2023 AASLD NALFD practice guidelines recommend the use of FIB-4, followed by ELF or vibration-controlled transient elastography (VCTE), an imaging-based NIT that uses liver stiffness measurement (LSM) to assess fibrosis (6). Liver biopsy should be considered when there is diagnostic uncertainty, as may occur with discordant or indeterminate NITs (6). **FIB-4 followed by ELF/VCTE may be cost-effective, but cut-points need to be developed for "at-risk" MASH for ELF.**

Additional NITs may be used to identify "at risk" MASH

The FibroScan AST (FAST) score uses LSM, controlled attenuation parameter (CAP), and AST to non-invasively identify patients at risk of progressive MASH. A 3-yr study of 350 patients with suspected MAFLD found that FAST provides an efficient way to noninvasively identify patients at risk of progressive MASH (13). In terms of cost, **FAST will have a lower upfront cost, but more patients will need to be evaluated and the lower precision may eventually increase costs.**

The MAST score combines magnetic resonance imaging-proton density fat fraction (MRI-PDFF) plus magnetic resonance elastography (MRE) and AST. MRI-PDFF response defined as ≥ 30% relative decline and serum ALT decline are associated with higher odds of MASH resolution. **MAST is associated with greater cost, but the higher sensitivity at a lower cut-point but may increase the cost.**

MEFIB combines MRE plus FIB-4. The combination of imaging and serum markers (MRE ≥ 3.3kPa and FIB-4 ≥ 1.6) yielded a high positive predictive value (97.1) for a clinician to rule in clinically significant disease that needs pharmacologic treatment in MAFLD (14). One study found that MEFIB is superior than MAST or FAST in the detection of F ≥ 2 among biopsy-proven MAFLD patients (15). **The most cost-effective approach to MEFIB is to perform an MRE only when FIB-4 ≥ 1.6.** This approach has a high PPV but low sensitivity.

Further advancements are needed in the field of NITs. The current standard of clinical practice is that patients with advanced fibrosis are serially monitored with NITs for progression to cirrhosis, but this warrants further testing and monitoring for hepatocellular carcinoma. MRI-based assessments need to be made more accessible and cost-effective. Finally, more disruptive proof-of-concept technologies are needed for liver disease assessment.

Despite these unmet needs, **MEFIB, MAST, and FAST may be used to identify "at-risk" MASH.**

Identifying Opportunities for the CLDF to Support Educational Activities at Managed Care Plans

It is clear that educational activities at managed care plans are warranted. In order to fulfill the final objective of the meeting (i.e., identify opportunities for the CLDF to support educational activities at managed care plans of the meeting), the approach needs to be considered from different perspectives, which are discussed in detail here.

Healthcare provider perspectives

The HCPs are currently not prepared with how to manage MASH patients if a treatment becomes available. They want help to identify these patients, but there is no one-size-fits-all, in part due to the large number of patients with MASH. HCPs need guidance on how to identify the right patients, but the hurdle, as discussed during this workshop, is that there is no single consensus guidance. HCPs also need to understand the evidence used to make payer decisions and how it should be interpreted. Finally, HCPs need to know what tests should be done and when. For example, the payer will say, "if the biopsy results show [a particular result], [a particular drug] will then be covered". However, the payer will not require a biopsy to be performed and may not cover the cost of the biopsy.

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Payer perspectives

It is important for external parties to understand that, when changes occur, it is very difficult for commercial plans to make enormous adjustments. Rates are set, and payers cannot "open the flood gates". If a drug does not have a certain indication and coverage is needed, payers need to see the data to support this use for coverage to be considered. This is also true for certain tests that are required. It is not ideal to solely use clinical trial data as evidence because rigorous criteria indicate the results may not apply to all patients. There are a lot of real-world data that would be of benefit

to payer decisions. Finally, there are data to demonstrate that nonpharmacological costs often outweigh the costs of the most expensive drugs, and this needs to be considered when we talk about informed coverage decisions.

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Patient perspectives

There are certain risk factors for MASH that patients do not consider. For example, patients will continue to use alcohol, although it is a contributor to chronic liver disease. They do not understand the connection. Patients are willing to pay to be cured, but this is not for all diagnoses. A patient will pay out-of-pocket for obesity drugs because the result is cosmetic, but that same patient will not pay out of pocket to get a tooth pulled.

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Conclusion

MASLD/MASH treatment guidelines need to be simplified and include the best available evidence for diagnosis, staging and risk assessment. Without this, HCPs are not ready to prescribe any drug(s) that become approved. It took 12 years for Medicaid to adjust to prescribing hepatitis drugs, and it is important this scenario not repeat with regard to MASH. The most important model will be the one that demonstrates that it is financially viable to treat MASH. Educational programs are needed to streamline and disseminate the current guidelines and must take into consideration the different perspectives from all stakeholders (HCPs, payers, and patients).

Appendix A: Coalition Workshop Participants

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Hetal Karsan, MD, FACG, FASGE, FAASLD, FACP	Atlanta Gastroenterology Associates Atlanta, Georgia
Edmund Pezalla	Enlightenment Bioconsult Founder and CEO Hartford, Connecticut

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