MASH



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Metabolic dysfunction-associated steatohepatitis (MASH) is a dangerously progressive liver disease not linked to alcohol consumption. It is the leading cause of cirrhosis and liver transplant.

MASH is a recently published series of articles that shines a spotlight on this increasingly prevalent disease and the efforts underway to serve the MASH patient population.

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Contents

| MASH | 101: What You Need to Know About an Emerging Liver Disease | 3 |
|--------|--|----|
| | American Liver Foundation | |
| What i | if You Had Fatty Liver Disease (MASH) and Didn't Know It? | 7 |
| | Fatty Liver Foundation | |
| Impro | ving the Lives of Veterans with Liver Diseases | 10 |
| | Global Liver Institute | |
| Taking | Support for MASH Patients into the Community | 13 |
| | Community Liver Alliance | |

MASH 101: What You Need to Know About an Emerging Liver Disease

Read or hear the words "liver disease" and most people probably think of alcohol-associated liver disease: the fatty liver, hepatitis and cirrhosis that can develop among people who drink excessively, usually over a long period of time.

But did you know there are serious liver diseases that are not linked to alcohol consumption? One is metabolic dysfunction-associated steatotic liver disease (MASLD), a condition in which fat builds up in the liver. The more severe form of the disease is called MASH, or metabolic dysfunction-associated steatohepatitis, a dangerously progressive form of MASLD in which patients have inflammation of the liver and liver damage in addition to excess fat. Cirrhosis (scar buildup) can develop if MASH advances.

"As our body's filter, the liver is a miraculous organ deserving of more attention," said Lorraine Stiehl, CEO, <u>American Liver Foundation</u> (ALF). "If our liver is unhealthy, it can affect other major systems including our kidneys and heart and lead to liver fibrosis and cirrhosis, which in turn, can potentially lead to the need for a liver transplant, liver cancer or even early death."



Lorraine Stiehl

MASH: The Leading Cause of Cirrhosis and Liver Transplant

According to ALF, about 100 million people (or 25%) in the United States have MASLD (most are between the ages of 40 and 60) and about 1.5 to 6.5 percent of U.S. adults have MASH. One estimate is that nine to 15 million adults have MASH. However, children can also have MAFLD and MASH. Close to 10 percent of those ages 2 to 19 (about six million children) are estimated to have MAFLD, in part due to the growing epidemic of childhood obesity.

The prevalence of MASH is projected to increase by 63 percent by 2030, and it is expected to become a leading cause of liver transplant in the U.S. by 2025. MASH is also one of the leading causes of cirrhosis in adults. Up to 25% of adults with MASH may have cirrhosis.

"MASLD and MASH are a looming public health crisis," Stiehl said, noting that ALF and the entire MASLD/MASH community look forward to gaining an even better understanding of the prevalence, diagnostic practices, treatment modalities, and potential complications of the disease through the <u>first-ever study on NAFLD</u>.

NASH To MASH: Same Disease with a New Name

Until recently, MASH was known by the name NASH, or nonalcoholic steatohepatitis, and MASLD was known as NAFLD, or nonalcoholic fatty liver disease. The updated names focus on the newly understood metabolic dysfunction-related drivers of the diseases. Those with metabolic syndrome are more likely to develop MASLD and MASH than those without metabolic syndrome. In order to be diagnosed with metabolic syndrome, any three of the following conditions must be present:

- Large waist size
- · High blood pressure
- High blood sugar (glucose)
- High levels of triglycerides in the blood
- Low levels of "good" (HDL) cholesterol in the blood

The updated names also give health care providers more targeted guidance for early screening of individuals with other metabolic conditions like overweight, obesity, high cholesterol, and type 2 diabetes, as well as those with lifestyle-related issues like poor diet and exercise. Noting that diseases aren't siloed in the human body, Stiehl said she hopes the nomenclature change will prompt typically siloed medical specialties like endocrinology, gastroenterology, cardiology, and hepatology to work more closely together to address liver-related metabolic issues.

"Patients, providers, scientists, non-profits, and advocates in the worldwide liver community came together last year to modify the way we talk about NASH – now MASH – in an effort to better identify who has the disease or is at risk for the disease," Stiehl said. "The name change also removes some of the stigma associated with the terms 'fatty' and 'alcoholic', which can create barriers to screening, diagnosis and appropriate treatment through medications and lifestyle modification."

MASH Has Few, If Any, Symptoms

"One of the biggest challenges with MASH is that it typically has very few symptoms," Stiehl said. "As a result, many with the disease only find out if they have a routine blood test or screening for another medical condition."

To help determine if someone has MASH, their doctor will perform a physical exam, conduct a blood test to check for high levels of liver enzymes and liver scarring, and/or do an ultrasound of the abdomen to see if it is enlarged. A liver biopsy may also be ordered.

If someone does have symptoms, they may feel tired or have pain in the upper right side of the abdomen, where the liver is. Those with severe scarring of the liver may have signs and symptoms of cirrhosis including:

- Intense itching
- A swollen belly

- Brusing and bleeding easily
- Yellowing of the skin and eyes
- Spider-like blood vessels just beneath the skin's surface
- Behavioral changes, slurred speech, and confusion

Support for People With MASH

ALF has several programs, services and initiatives to support the MASH patient community as well as those with other liver diseases, including:

- A toll-free helpline, 1-800-GO-LIVER, and a live chat at <u>liverfoundation.org</u>
- A MASH support group on Facebook
- <u>Caring Connections</u>, a peer-to-peer support programs that connects patients and caregivers with others facing similar challenges
- A <u>Caregiver Resources</u> page
- Help and information on <u>clinical trials</u> designed to find ways to more effectively prevent, diagnose or treat the disease
- Fact sheets and other educational resources
- A variety of on-demand <u>wellness webinars</u>
- A robust <u>research program</u>, which has provided nearly \$28 million in research funding since 1979

ALF is working to raise awareness of MASH among primary care providers by reaching out to nurse practitioners, physician assistants and other frontline health professionals. They currently have blood-draw screening programs in 50 clinics across 30 states to help people identify liver diseases earlier, before it's too late. These screenings check seven biomarkers that are highly predictive of risk for developing MASLD and MASH.

ALF also is exhibiting and presenting at primary care conferences and even screening primary care physicians for evidence of fat on their livers, to help drive home the importance of screening their own patients for such evidence.

ALF is taking its message directly to the public as well, at local festivals and events, where they have information booths and conduct free, non-invasive elastography ultrasound screenings of the liver, after which ALF connects screened individuals to the appropriate health care provider. In addition, ALF sponsors the Think Liver Think Life™ public health campaign, which aims to ensure every American understands their risk for liver disease, receives appropriate screening and care coordination, and feels well-informed and supported throughout their liver journey.

The Think Liver Think Life web site features a <u>liver health quiz</u> to help people see whether they or a loved one could be at risk for fatty liver disease. Since the quiz was launched last

year, 10,000 people have participated, and 92 percent found they are at risk or significant risk for liver disease.

Financial Help is Available for MASH Treatment

Earlier this year, the Food and Drug Administration (FDA) granted accelerated approval of the first-of-its-kind drug therapy for treatment of MASH in patients with fibrosis. However, accessing and paying for treatment with the new therapy and other medications, along with other associated costs related to treatment, may present a financial hurdle and dissuade adherence to the prescribed treatment regimen.

To help alleviate the financial burden, in May, the HealthWell Foundation launched a new MASH fund to provide financial assistance to patients living with MASH. Through the fund, HealthWell will provide up to \$8,000 in medication copayment or insurance premium assistance to eligible patients. The fund also provides financial assistance for doctor visits, disease-related laboratory testing, diagnostic testing, and transportation costs for treatment and monitoring.

"We applaud the new HealthWell MASH fund as it will serve the most marginalized groups affected by the disease and help alleviate some of the financial burdens these communities face in accessing new treatments and care," Stiehl said.

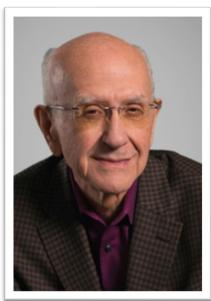
What if You Had Fatty Liver Disease (MASH) and Didn't Know It?

An estimated 100 million Americans have a fatty liver, and most don't know it. Twenty million of them will develop liver fibrosis disease or Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) and 5 million will progress to liver cirrhosis or Metabolic Dysfunction-Associated Steatohepatitis (MASH).

Wayne Eskridge didn't even know what fatty liver was when his stage 4 disease was unexpectedly discovered during gallbladder surgery. He was so incensed that his doctors didn't alert him to his growing problem any earlier that in 2017, he founded the <u>Fatty Liver Foundation</u> (FLF) to help others facing the same fate.

"Unfortunately, when MASH is in its early stages, there are very few or very subtle symptoms, making it difficult to diagnose or ascribe the problems to the liver," Eskridge said. "As a result, historically people have not been screened for asymptomatic liver disease."

What started as a personal, lifesaving mission became a nationwide initiative to identify asymptomatic, undiagnosed Americans with liver fibrosis or early cirrhosis caused by fatty liver disease, and to educate them on the lifestyle changes needed to halt or minimize disease progression.



Wayne Eskridge

"Our goal is to be very focused on the issue of fat in the liver, why it matters, what it causes and how to deal with it," Eskridge said.

MASH: A Disease with No Symptoms

According to Eskridge, many people chalk up MASH symptoms to the process of aging. They may feel unwell, fatigued, or experience mild gastrointestinal upsets, but they don't really feel "sick." Even those with advanced liver damage (stage 4 with cirrhosis) may have no symptoms and completely normal liver test values. Moreover, MASH can take decades to develop; in the early part of disease development, it can take seven years to go from stage 1 to stage 2.

"Virtually everyone has some fat on their liver," he said. "Fat in itself is not harmful, but excess fat is. It kills liver cells and eventually leads to MASH if not treated. It can be 20 to 25 years of slow-motion accumulating damage with no real symptoms along the way. Countless people arrive at end stage liver disease without ever having a symptom of any kind because the liver is so robust and fatty liver was previously not thought to be very dangerous."

While MASH has no symptoms, there are several lifestyle factors that indicate whether someone may be at risk for having or developing the disease. One of the primary drivers is obesity, which affects over 42% of the adult population in the United States. Many with diabetes are also at risk of developing MASH.

"In terms of diet, too much sugar is as damaging to the liver as too much alcohol," Eskridge said. "It is the primary thing that turns to fat in the liver. Eating excess white flour, white rice and potatoes is almost the same as eating sugar. Saturated fats found in milk and red meat can cause inflammation, which also is bad for the liver."

Screening for MASH

As recently as 20 years ago, MASH could only be detected by an invasive, uncomfortable, and time-consuming liver biopsy, a procedure that most people want to avoid. Moreover, in the early stages of the disease, even a biopsy cannot confirm the presence of MASH with 100% confidence. Since liver damage can be patchy, it can depend on where the biopsy is taken and whether the sample size is adequate.

Today, doctors can check for signs of liver fibrosis with a simple blood test called Fibrosis-4 (FIB-4). FIB-4 blood results, in conjunction with a person's age, indicate whether someone is at high risk for liver fibrosis (FIB-4 \geq 3.25) or low risk (FIB-4 < 1.3). When FIB-4 panels are conducted over time, doctors can see changes taking place in the blood chemistry, allowing them to plan interventions to slow the progression of the disease.

Those with mid-level FIB-4 scores may be referred to additional screening with a special type of ultrasound called liver elastography, which measures liver stiffness (hardness) and fatty changes in the liver.

"Non-invasive screening methods are effective, accurate, and getting better all the time," Eskridge said. "Biopsy is no longer the gold standard and is no longer required for doctors to prescribe pharmacological treatments for MASH."

FLF is working to promote screening through a series of <u>Screening for Undiagnosed NAFLD/NASH (SUNN) studies</u>. (Editor's Note: NAFLD/NASH are previous disease nomenclatures that have been replaced by MAFLD/MASH.) SUNN-1 was implemented in Galveston County, Texas and successfully screened over 1,000 individuals using elastography machines at community locations. Approximately 15% of those screened were found to have NAFLD/NASH. FLF is in the planning and fundraising phase for SUNN-2, which will expand on the tactics and findings of SUNN-1 to screen more people while also connecting them to care and providing support.

New Treatment Options Available

Earlier this year, the first treatment for MASH was approved by the FDA. While not a cure, the drug is proven to reduce liver fibrosis among a percentage of people, when combined with diet and exercise.

"This is a huge win for the patient community," Eskridge said. "Unfortunately, while the FDA said that a liver biopsy is not necessary for it to be prescribed, some medical insurers are

not covering the cost of the drug without a biopsy, thus adding to the significant cost and logistical barriers to treatment for many patients."

Eskridge praised the efforts of organizations like HealthWell, which helps to reduce financial barriers for MASH patients through its MASH Fund, which provides up to \$8,000 in medication copayment or insurance premium assistance to eligible patients. The fund also offers financial assistance for doctor visits, disease-related laboratory testing, diagnostic testing, and transportation costs for treatment and monitoring.

"As a liver disease patient, I understand firsthand the nuances and obstacles of living with MASH," he said. "Treatment and management of the disease requires multiple medications, diagnostic testing, and follow-up, leading to potentially overwhelming financial challenges. I applaud the HealthWell Foundation for recognizing this unique hardship for patients and for providing the financial resources to access and adhere to their treatment regimen."

Improving the Lives of Veterans with Liver Diseases

Last year, the <u>Global Liver Institute</u> (GLI) and the Department of Veterans Affairs (VA) announced a partnership to improve the lives of Veterans with liver disease. Through the collaboration, VA and GLI are providing educational materials and webinars to help increase Veteran awareness of liver disease, increase health care engagement of Veterans with a suspected or confirmed liver disease diagnosis, and ensure equitable access to information and care for Veterans from disadvantaged or underserved communities.

According to the VA, educating Veterans is a critical step toward preventing and improving care for liver disease. Current data suggests that more than 30 percent of Veterans receiving VA care have metabolic dysfunction-associated steatotic liver disease (MASLD, formerly known as non-alcoholic fatty liver disease), and VA is "determined to provide these Veterans with the world-class health care they have earned and deserved."

Like other populations in the United States, Veterans are seeing rising rates of obesity, diabetes, and metabolic syndrome – conditions that if left untreated, can lead to the development of MASLD and MASH (metabolic dysfunction-associated steatohepatitis, formerly known as NASH). Increased rates of depression and mental health conditions among Veterans may make them even more vulnerable and less successful in addressing their liver disease.

"Liver diseases significantly affect both our active duty and veteran armed forces, and even have an impact on armed services recruitment and our national security," said Donna Cryer, JD, founder and member of the Board of Directors of GLI. "It is our honor to help the military families who sacrifice so much to serve us and to do so in a way that advances the education, services, and messaging targeted to Veterans."



Donna Cryer

Promoting Liver Health

GLI has long taken a leadership position in the MASLD and MASH communities. In 2017, it established the NASH Council (now the Fatty Liver Disease Council) to help <u>communicate in plain English</u> about the importance of liver health as a public health issue. It created the <u>Advanced Advocacy Academy</u> (A3) in 2017 for patients, caregivers, and others. A3 features training programs and advocacy opportunities, with a hallmark annual four-day Learning Experience providing comprehensive advocacy preparation each September.

GLI also offers a wide variety of educational materials, many of which were developed in conjunction with A3 members and military families. Among those materials is a Liver Health for Veterans <u>YouTube Playlist</u>.

"We are thinking strategically about how to integrate the perspective of Veterans across all of our channels, assets, and programs," said Cryer. "Whether they engage with us on our website, social media accounts, or in person, they will be able to find easy-to-access and relevant information."

Enhancing Relationships Between Doctors and Patients

GLI stresses that liver conditions are often misunderstood, mischaracterized, and stigmatized, resulting in under-diagnosis, under-treatment, and unnecessarily poor outcomes around the globe. Part of the issue, said Cryer, is that traditionally, liver health issues were siloed to the field of hepatology.

"Everyone should be talking about their liver health with their primary physician," said Cryer. "There are multiple drivers for the accumulation of fat in the liver, so regardless of your leanness, diet, genetics, or lifestyle, liver health should be a normal part of the conversation, just like heart health is."

Cryer praised the VA for the way they view liver health holistically and encourages other health systems to do the same.

"The VA has been on the cutting edge of addressing liver cancer and hepatitis C among Veterans," said Cryer. "They were among the first health systems to conduct multidisciplinary tumor boards, for example. They understand the links between the environments Veterans live and work in, their lifestyles, and the development of fatty liver disease."

GLI is working with individual VA hospitals to optimize doctor-patient interactions relating to liver health. Together, they are working to incorporate "smart phrases" into patients' electronic health records (EHRs) and the My HealtheVet system, which provides tips and tools to help Veterans partner with their health care team and manage their health. Smart phrases are go-to phrases, recommendations, and responses that doctors can quickly apply when meeting with patients and charting their appointment. They are designed to help doctors quickly and accurately order diagnostic tests and develop treatment plans for fatty liver disease.

"The smart phrase model has been proven effective in the hepatitis C patient community and we want to replicate those results for the MASH community, especially now that there is a first-line treatment for the disease," said Cryer.

Supporting Other Patient Populations at Risk for MASH

Cryer stressed that GLI's support for MASH patients extends far beyond Veterans to other underserved patient groups and populations.

"All liver patients experience some form of stigma, discrimination, and barriers to care," she said. "Those barriers can result in delayed diagnosis and initiation of treatment."

Cryer pointed to the Black and Hispanic communities as an example and noted that these two patient groups tend to get diagnosed with MASH later than other groups, when their disease has already progressed to liver cancer or the need for transplant.

"There are wide disparities in insurance coverage, transportation access, and other social determinants of health that impede their access to primary care medical touchpoints," she said. "In addition, the quality of those touchpoints is not always where it needs to be in terms of appointment length and the need to focus on other health issues, meaning the liver doesn't always rise to the top of the discussion."

Because the prevalence of MASLD is around <u>70 percent</u> for people with diabetes, and diabetes is prevalent among the Black and Hispanic communities, GLI is working closely with diabetes advocates and endocrinology societies to expand the conversation around liver health.

"We're also addressing the alarming rise of MASH among infants, children, and teens," Cryer said. "It's important for families to know that there are non-invasive diagnostic tests that eliminate the need for painful, and quite honestly frightening, biopsies."

GLI's <u>Beyond the Biopsy program</u> is dedicated to accelerating the acceptance and adoption of non-invasive diagnostics as an alternative to biopsy, which has been a barrier to success in getting patients diagnosed and appropriately linked to care. These non-invasive alternatives potentially provide more information than a biopsy, through their ability to assess changes throughout the liver, rather than only in the relatively small amount of liver tissue typically obtained from a biopsy.

GLI's efforts and outreach, combined with the advent of non-invasive testing, has resulted in non-invasive testing replacing biopsy as the gold standard for MASH diagnosis. GLI also has worked closely with the American Board of Internal Medicine to change the rules around the number of biopsies a transplant specialist needs to perform to complete their fellowship, further influencing medical trainees to focus on non-invasive testing.

"We are incredibly excited about the role GLI has played in creating the infrastructure needed to address liver health head-on," Cryer concluded.

Taking Support for MASH Patients into the Community

The <u>Community Liver Alliance</u> (CLA) brands itself as an organization dedicated to global awareness and local impact. Even as the CLA has extended its beacon of hope to communities nationwide, the nonprofit still counts its hometown of Pittsburgh as its primary link to liver disease patients, providers, and caregivers.

CLA's mission to invest in local communities and give voice to patients and providers is reflected in the many ways the nonprofit supports the Metabolic Dysfunction-Associated Steatohepatitis (MASH) community in Pittsburgh and beyond.

"The MASH community faces significant unmet needs in terms of early diagnosis, awareness, and patient education," said Suzanna Masartis, Chief Executive Officer, CLA. "MASH is increasingly prevalent due to rising obesity rates and metabolic syndrome, but it remains underdiagnosed, with many patients unaware of their condition until advanced stages. The CLA aims to bridge these gaps by fostering awareness and providing resources to patients and health care providers to improve outcomes."



Suzanna Masartis

Understanding the MASH Patient's Journey

To better understand the MASH patient's journey, CLA conducts an ongoing <u>MASH patient survey</u>. In addition to making the survey available 24/7 online, CLA pushes it out through social media, patient and provider communications and programming, and to a coalition of MASH subject matter experts, patients, and caregivers. The survey collects information regarding MASH risk factors; symptoms; limitations; and social, economic, and psychological impacts; as well as barriers to improving liver health.

"Survey results to-date show that a large proportion of respondents are unaware of MASH prior to diagnosis and feel unprepared to manage the condition due to a lack of educational materials," Masartis said. "This feedback highlights the need for more accessible resources and clearer communication between health care providers and patients."

Masartis added that communication between providers and patients is especially crucial in the primary care setting so that more providers offer early screening to people at high risk for developing MASH and more high-risk patients know to ask for such screening if their doctor does not recommend it first. Indeed, current survey results show that more than 40% of MASH patients were diagnosed with fatty liver while being treated for another condition.

MASH Toolkits

To help improve patient-provider communication, CLA is partnering with gastrointestinal and internal medicine physicians at Allegheny Health Network (AHN) to develop downloadable patient-and provider-specific toolkits. The primary objective of the toolkit program is to foster collaboration that drives significant advancements in the understanding, diagnosis, treatment, and prevention of liver diseases. Further, the toolkits immerse AHN physicians in the core of the liver disease patient community, enriching their practical knowledge through hands-on, real-world experience.

"These toolkits are an excellent example of meeting people where they are," Masartis said. "The importance of patient engagement and education in their health care can hardly be overstated. It has a profound impact on health outcomes, patient satisfaction, and the overall effectiveness of health care delivery. When patients are well-informed about their conditions, treatment options, and preventive measures, they are better equipped to make decisions that align with their goals and values."

Once launched, the MASH Patient Toolkit will include information about:

- What MASH is
- How MASH is diagnosed
- How MASH is treated and managed
- Liver health strategies such as:
 - Healthy cooking
 - Physical activity
 - Mindfulness
- Resources available to MASH patients and caregivers

The MASH Provider Toolkit will provide primary care providers with the information and resources necessary to manage patients through their liver disease journey, including:

- An overview of MASH
- MASH pathophysiology and epidemiology
- MASH diagnosis
- MASH treatment and management
- Patient education and counseling

By early next year, both toolkits will be available nationwide and will be updated regularly as new research, resources, and guidelines become available.

MASH Challenge

Another way CLA is engaging with patients, providers and other stakeholders is through its MASH Challenge – a high-value health care program designed to improve patients' health through medical, physical, nutritional, and behavioral cornerstones. Developed in conjunction with physicians at AHN and experts from the MASH Coalition, the MASH Challenge just concluded a two-year pilot and was formally launched at CLA's annual Walk the Talk for Liver Health in mid-October.

Participants at the family-friendly Halloween-themed Walk had the opportunity to take part in a costume contest, see a chef demonstrate how to make healthy meals, build their own healthy breakfast from a parfait bar, be led in pre- and post-walk stretches by an exercise physiologist, and visit a variety of health information tents.

"The MASH Challenge achieved some good early milestones in patient recruitment and the development of personalized health management plans," Masartis said. "The program's focus on lifestyle interventions, including diet and physical activity, has shown promise in improving liver health markers. We're eager to see how patients will engage with the program as we continue to roll it out."

Addressing Disparities in Liver Disease

While fatty liver diseases such as MASH occur in people of all races and ethnicities, they are most common among Hispanic individuals, followed by non-Hispanic whites and Asian Americans.

To address health disparities in the MASH patient community, CLA held a virtual Addressing Disparities in Liver Disease program last month. The program was created to examine the differences that occur by gender, race, or ethnicity; education or income; disability; geographic location; or sexual orientation. It engaged patients and providers in diverse and high-risk communities and worked to build bridges to health care, services and resources.

"The conference highlighted the importance of culturally tailored interventions and addressed social determinants of health, such as food insecurity and physical activity, which contribute to higher rates of MASH in underserved populations," Masartis said, noting that a follow-up <u>conference</u> is scheduled for April 2025 to discuss concrete ways in which disparities can be overcome.

Engage with CLA

Masartis encourages providers, patients, and caregivers to engage with CLA, pointing to the organization's <u>video library</u>, which houses a series of short videos on topics such as nutrition, healthy meal preparation, and physical activity, along with videos from a variety of liver health conferences and events.

She also invited everyone in the MASH and liver diseases communities to connect with CLA on <u>Facebook</u>, <u>Instagram</u>, <u>X</u>, and <u>LinkedIn</u>.