

# NASH: A Growing Public Health Burden



A Series by [REALWORLDHEALTHCARE.org](https://www.RealWorldHealthCare.org)

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Non-Alcoholic SteatoHepatitis (NASH) is the most severe form of non-alcoholic fatty liver disease and a growing concern in the medical community because of its potential consequences for patients and its high prevalence in the population.

***NASH: A Growing Public Health Burden*** is a recently published series of articles that spotlights the organizations and efforts dedicated to finding safe, effective treatments of the disease and supporting patients with education and other services. Please accept this complimentary copy as our way of thanking you for your commitment to raising awareness for NASH and advocating for healthier futures.

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# NASH: Fighting a Silent Epidemic

By Emily Burke, Ph.D., Director of Curriculum Development, BiotechPrimer.com

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Consider the liver. It's just one of the jumble of stuff inside that makes us tick, right? What do you really know about it though—other than it's "vital?" In fact, the liver is your largest internal organ, and plays vital roles in neutralizing toxins, fighting infections, manufacturing proteins and hormones, controlling blood sugar, and helping to clot the blood.

It may just be time to start giving our livers a little more thought. We don't just mean by taking it easy on the cocktails either. Liver disease is a growing health concern worldwide. A big part of the problem is that that the most common liver disease in developed countries, non-alcoholic fatty liver disease (NAFLD), often has no symptoms. Its onset is associated with obesity and type 2 diabetes—two conditions that are also on the rise.

In 2017, NAFLD was estimated to affect nearly one quarter of people worldwide. About 30 to 40 percent of people in the United States are thought to be affected, and about 3 to 12 percent of American adults suffer from the advanced form of the condition, non-alcoholic steatohepatitis (NASH). Currently, its only treatment is liver transplantation. However, a number of biopharma companies are tackling this growing concern. Let's take a closer look.



Emily Burke, BiotechPrimer.com

## Easily Confused: NAFLD VS. NASH

NAFLD occurs when excess fat accumulates in the liver of people who drink little to no alcohol. NASH, the more severe form of the disease, is characterized by liver inflammation and scarring. As scar tissue accumulates, it impairs liver function. It's the number one cause of non-alcohol related cirrhosis (severe, late stage scarring) which in turn can lead to liver failure.

People with diabetes, obesity, or metabolic syndrome run the risk of developing NAFLD and eventually, NASH. Treatments in the works largely focus on reducing inflammation and improving how the liver metabolizes fats.

## When White Cells Run Amok

Livers can only handle so much fat. Too much, and liver cells release inflammation-inducing signaling molecules, known as cytokines. These proteins trigger a series of events, the end result of which is the “attack of the white blood cells.” We think of these hemocytes as “good,” but not so with NASH. White blood cells, such as macrophages, invade the liver, increasing the chances that liver cells will die and damaging scar tissue will form. Here are a few small molecule drugs in the pipeline being developed to control inflammation:

- Now in Phase II clinical studies, an inhibitor of the vascular adhesion protein 1 (VAP1). VAP1 helps white blood cells to migrate into the liver. Inhibiting VAP1 reduces this migration. Ta-da—decreased inflammation!
- Selonsertib, currently in Phase III trials, takes a slightly different approach to inflammation. It inhibits the activation of two enzymes involved in cellular pathways leading to inflammation, liver cell injury, and scarring.
- Cenicriviroc takes aim at liver inflammation by inhibiting receptors on the surface of white blood cells called chemokine receptors. Chemokines are chemical messengers that stimulate movement of cells towards the source of their release—typically damaged or infected tissue. This chemokine APB often helps the body fight infection. However, with NASH, this just damages the already inflamed liver further. Cenicriviroc is in Phase III clinical studies.

## Fight the Fat

An alternate approach to treating NASH works on improving a patient’s lipid metabolism. Control the fat that accumulates in the liver, control the disease. Here are two more small molecule drugs that work to control fat accumulation:

- Obeticholic acid has begun Phase III clinical studies. This product works by binding the nuclear receptor FXR. This is a type of receptor protein that is present inside of cells, rather than on their surface, like most other receptor proteins. When activated by the appropriate signaling molecule, the nuclear receptor moves inside the cell’s nucleus, where it binds DNA at a specific location, turning on the expression of particular genes. Obeticholic acid specifically binds to and activates FXR, which modulates the expression of genes involved in lipid metabolism and glucose regulation. Researchers hope this change may disrupt the progression of NASH.
- Yet another nuclear receptor activator is elafibranor. This drug works on the receptors PPAR  $\alpha/\sigma$ . Activating these receptors switches on genes that increase the metabolism of fatty acids, decreasing liver fat and improving lipid profiles—as well as increasing insulin sensitivity and anti-inflammatory activities. The drug is now in Phase II clinical studies for advanced NASH patients.

Several other NASH drugs are coming down the pike, including a small molecule conjugate of cholic acid and arachidic acid (inhibits fatty acid synthesis; Phase II) and a small molecule drug that inhibits inflammation-promoting caspase enzymes (Phase II).

Let's hope that 2019 sees at least one FDA approval from the handful of Phase III candidates out there to step up the fight against this silent epidemic.

## **About the Author**

Dr. Emily Burke is the Director of Curriculum for Biotech Primer and is responsible for customizing client training, delivering training sessions and writing the [Biotech Primer WEEKLY](#), a free electronic newsletter that explains the science behind the headlines. She received her B.S. in biological sciences from Carnegie Mellon University and her Ph.D. in molecular biology from the University of Southern Alabama.

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**Categories:** [General](#), [Nonalcoholic Steatohepatitis](#)

**Tags:** [Diabetes](#), [fatty liver disease](#), [liver](#), [NAFLD](#), [NASH](#), [obesity](#)

# NASH: A Disease without Symptoms but Lots of Hope

By Wayne Eskridge, President & CEO, Fatty Liver Foundation

What if you had a liver disease but nobody told you until it was too late?

Typically, nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are silent diseases. They have no symptoms. Even if cirrhosis has developed, there are often no symptoms until the liver has become so damaged that the only option is a liver transplant.

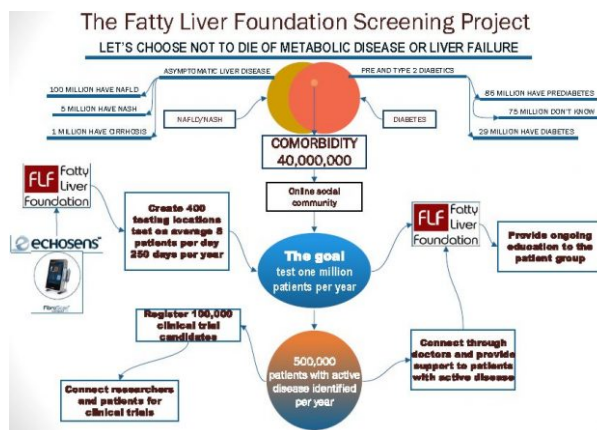
Early screening for NASH is essential, but obstacles abound. While there is a quick, easy and economical method to screen for fatty liver disease, it is not widely available and screening in the absence of symptoms is often not part of standard medical practice policy. Medical coverage for the test also may not be available if the patient isn't sick or doesn't have symptoms.



Wayne Eskridge, Fatty Liver Foundation

## Fatty Liver Foundation Screening Project

The Fatty Liver Foundation advocates for early screening. Our plan is to deliver liver care screening for the estimated 40 million comorbid diabetes/NAFLD/NASH patients. This patient group is our initial target for screening because up to 70 percent of type 2 diabetics have undiagnosed liver disease. The project's long-term goal is to have 400 testing locations seeing one million patients a year.



The screening project is currently in its pilot phase. The first installation is in the greater Houston area and the purpose is to gather real world data on self-selected patients

and to test methods and procedures to provide guidance to the larger project to follow. The study is being conducted as a formal study which can be read here as [NCT03726827 on ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03726827).

## **State of Liver Research**

While attending the 2018 meeting of the [American Association for the Study of Liver Diseases](#) (AASLD), I was struck by the sheer volume of research going into NAFLD/NASH/cirrhosis and how the evolution of new tools and probes coming from the broader arena of basic science is helping us along our journey to understand the liver.

The black box nature of many of the liver's functions is giving way to a real understanding of the specific chemical reactions between and within the cells. The study of lipids within the liver and body-wide is burgeoning, as fatty acids are both foundational molecules and dose-related substances involved with disease. The study of cellular response – such as how stellate cells are affected by different molecules – is robust.

Stepping up a level from how molecules work, researchers also are studying how the systems of body processes interact in ways that either lead toward health or toward dysfunction and illness. For example, scientists are investigating how liver fat responds to manipulation of certain thyroid hormones.

Then, we step out to see how body-wide functions like inflammation, wound management, tissue health, immune response and other processes lead to liver damage or may be recruited to promote healing. Here, the issue of comorbidity comes into focus as we look at the liver's relationship with cardiovascular and diabetic disease, as examples.

The meeting also showcased the significant work being undertaken on non-invasive markers for primary care-level triaging of patients with active disease, but who present as symptomatic. One of the most interesting developments was the documentation of the role that Fib-4 might play in the process. There is growing evidence that Fib-4, and several other blood-based candidates used as filters for screening, can help to determine referral to a specialist.

As a patient, being able to see the depth and breadth of the effort whose goal is to save my life, and that of the millions of patients like me, was both humbling and exhilarating. The knowledge that research will lead to solutions makes the day-to-day easier to bear and gives us patients a reason to find hope.

## **About the Fatty Liver Foundation**

The Fatty Liver Foundation is dedicated to identifying 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 progression of the disease. [Here is a link to a brief video about the Foundation.](#) Founder and CEO Wayne Eskridge was diagnosed with cirrhotic NASH in 2010 and since then has been dedicated to learning as much as possible about the disease and to helping other liver disease patients. For more information, visit the [Fatty Liver Foundation website](#), or connect via [Twitter](#).

**Categories:** [General](#), [Nonalcoholic Steatohepatitis](#)

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# Where Does NASH Stand on the Global Public Health Agenda?

By Real World Health Care Editorial Staff

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This week, Real World Health Care continues our series on [Non-Alcoholic Steatohepatitis](#) (NASH) by featuring an interview with [Donna Cryer](#), JD, president and CEO of the [Global Liver Institute](#) (GLI). Cryer founded the GLI on the 20<sup>th</sup> anniversary of her liver transplant due to an autoimmune disease. Today, four years later, GLI stands firm in its mission to improve the lives of individuals and families impacted by liver disease by promoting innovation, encouraging collaboration and scaling optimal approaches to help eradicate liver disease.

## A Vision for Liver Health

**Real World Health Care:** What was your vision when you set out to create the Global Liver Institute?

**Donna Cryer:** The GLI was designed to be patient-centric from the start. I wanted to make sure that other liver disease patients had access to the type of innovations and treatments that saved my life. At the time, I didn't see a lot of awareness around liver disease and liver health. There was a stigma attached to having liver disease, and there still is to a degree.

Our vision is for liver health to take its place on the global health agenda commensurate with its prevalence and impact. Half a billion people have liver disease, but the public health agendas for research, policy, and public knowledge and support don't reflect the scope of the disease.

We want to change the culture around liver disease to reduce stigma, change policies so patients have better access to care, and change health care delivery systems and reimbursement frameworks so new treatments get to the patients who need them.

We also want patients and their families to become better advocates so they can work more effectively to raise visibility and help change policy. To that end, we recently created an [Advanced Advocacy Academy](#), which connects liver patients and family members with the information, skills and opportunities they need to effectively advocate for liver health.



Donna Cryer, Global Liver Institute

## **NASH Council**

**RWHC:** How does the GLI's [NASH Council](#) help support patients with this advanced form of fatty liver disease?

**DC:** NASH is unique, partly because there are none of the underpinnings we typically see for other disease states. While research is starting to progress, the NASH patient community lacks education materials, support groups, and awareness efforts — despite the fact that one in four people around the world are estimated to have some form of fatty liver disease and 16 million people in the United States have NASH.

We created our NASH Council to fill that gap and to help define the NASH community more broadly than has been done with other liver diseases. Because NASH and other fatty liver disease patients often have concurrent metabolic conditions, NASH advocacy can't exist in a silo. That's why our NASH Council is reaching out to the obesity, diabetes and cardiovascular communities and conducting workgroup calls focused on patient education, clinical workflows and policy. Our 50-member council includes organizations with exponentially large reach, including the American College of Physicians and the American Heart Association.

Our latest efforts center on determining lifestyle interventions for NASH patients. We're working with physicians in hepatology, diabetes, cardiovascular and primary care to delineate how and by whom patients with NASH and other fatty liver diseases can be diagnosed earlier and referred to the appropriate specialist in a timely manner. Truly integrated care can't come fast enough.

## **Early NASH Disease Screening**

**RWHC:** Why is early screening so important for NASH patients?

**DC:** If fatty liver disease is found early, before it has a chance to cause significant fibrosis, the disease can be effectively reversed through lifestyle interventions, such as losing seven to ten percent of your body weight. Unfortunately, most NASH patients are diagnosed in advanced stages of the disease, when fibrosis and cirrhosis have caused extensive cellular damage. At that point, the only treatment option that currently exists is transplantation, which isn't feasible for this large patient population; there just aren't enough organs to go around.

Currently, the only way to truly define NASH is through a liver biopsy, which is both invasive and risky. In addition, because a biopsy may not capture the affected portion of the liver, it can't be considered a gold standard. Screening therefore needs to include metabolic syndrome risk factors and non-invasive technologies such as imaging and liver enzyme analysis.

## Promising NASH Developments

**RWHC:** Are there any screening or treatment approaches on the horizon that give you hope?

**DC:** In terms of screening, there are many existing imaging technologies and several more in development including large validation efforts by NIH in the US and consortia in the UK/Europe. One strategy that holds promise is simple: Moving existing hospital imaging capabilities into diabetes clinics. Just roll them down the hall! This would help to speed diagnosis for the estimated 80 percent of Type 2 diabetics who have fatty liver disease.

In terms of NASH treatment, there are several transformative candidates currently in Phase III trials that should be approved within the next year. This development is particularly exciting because the various therapies target different mechanisms. Some directly reduce fibrosis, while others reduce fat accumulation or overall inflammation. Some candidates address more than one mechanism, which will allow for greater therapy personalization and greater likelihood that a therapy will be effective for a wide population.

Therapies for fatty liver disease represent one of the most robust innovation areas in health care today. At a time when so many diseases still do not have cures, this outpouring of research holds hope and promise for liver patients like me.

**Categories:** General, Nonalcoholic Steatohepatitis

**Tags:** fatty liver disease, liver disease, NAFLD, NASH

# Obesity and Fatty Liver Disease: The Link Between Metabolic Disorders and NASH

By Real World Health Care Editorial Staff

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For decades, the general public has been aware of the many health risks of being obese, including diabetes, heart disease and certain cancers. However, many are not be aware that obesity is also linked to liver disease: specifically Non-Alcoholic Fatty Liver Disease (NAFLD), which in its most severe form, becomes Non-Alcoholic Steatohepatitis (NASH).

## NAFLD/NASH Defined

According to the American Liver Foundation, it is normal for the liver to contain some fat. However, if more than five to ten percent of the liver's weight is fat, then it is considered to be a fatty liver (steatosis).

NAFLD is the build up of extra fat in liver cells that is not caused by alcohol. It is the most common form of liver disease in children and has more than doubled in the past 20 years, a statistic that's important to remember during September's National Childhood Obesity Awareness Month.

The more severe form of NAFLD is NASH, which causes the liver to swell and become damaged. NASH tends to develop in people who are overweight or obese, or have diabetes, high cholesterol or high triglycerides. However, some people have NASH even if they do not have any risk factors.

## Difficulties Diagnosing NASH

NASH often has no symptoms and people can have the disease for years before symptoms occur, making the disease difficult to diagnose.

"Fatty liver is quite common in the United States," said Sammy Saab, MD, MPH, AGAF, professor, Medicine and Surgery, Head, Outcomes Research in Hepatology, David Geffen School of Medicine, UCLA and co-chair of the National Medical Advisory Committee for the American Liver Foundation. "The hard part is identifying who has simple fat that doesn't cause serious liver problems and who has the more serious NASH."

Dr. Saab went on to note that the vast number of people with fatty liver makes it impractical to diagnose NASH using biopsy, an invasive technique with risks including pain, bleeding and sampling errors. Instead, he said that imaging and blood tests are the best and most non-invasive methods for detecting NASH.

He pointed to emerging imaging modalities such as ultrasound or magnetic resonance elastography, which can identify scar tissue and fibrosis, important predictors of outcomes in fatty liver. He also noted that blood tests, including AST-to-Platelet Ratio Index (APRI) and Fibrosis-4 (Fib4), can be used to easily estimate the chances of a patient having advanced fibrosis.

### **Treating Underlying Metabolic Problems**

According to Dr. Saab, NASH challenges don't end at the diagnosis stage.

“NASH can be a frustrating disease to treat,” he said. “First, we must identify and treat the underlying metabolic problem, whether that's obesity, diabetes, hypertension, high cholesterol, or a combination of these. If someone has poorly controlled diabetes, we recommend they get their blood sugar in line. If they are overweight, we recommend diet and exercise. But losing weight is difficult unless the patient is very determined, especially with the calorie-dense American diet.”

Because NASH patients typically have co-morbid conditions, an integrated, multi-disciplinary approach to care is crucial. To treat NASH patients, Dr. Saab regularly works with UCLA colleagues in primary care, endocrinology, nutrition, weight control, diabetes management and bariatrics, among other specialties.

“The idea of a hepatologist treating NASH by themselves is naïve...it must be a team effort,” he said. “Additionally, specialists in other medical fields need to increase their awareness of the links between metabolic issues and fatty liver disease so they better understand the significance of the problem and the importance of referring patients at risk for evaluation.”

### **Supporting the NASH Patient Community**

Dr. Saab's interest in fatty liver disease has led him to conduct clinical trials on NASH treatments and research related topics including the impact of obesity on liver transplant patient survival, safety and efficacy of liver transplants for NASH patients, food addiction in liver transplant recipients, and ethnic variations for fatty liver disease (NASH is the most common reason for liver transplants among Latina women).

He also holds a yearly seminar for patients and their caregivers to learn more about fatty liver disease and is in the process of publishing educational resources for both patients and caregivers with information on what fatty liver disease is, what it means, and what happens when patients have it.



Dr. Sammy Saab, David Geffen School of Medicine, UCLA

More information is also available through the American Liver Foundation (ALF), which provides patients, family members and the general public, as well as health care professionals, with direct access to [NASH education](#) and support services through a variety of programming initiatives, including [webinars](#), [in-person education programs](#), [published resources](#), and [online education](#). ALF's National Helpline, 1-800-GO-LIVER serves as an additional resource for information and support, and ALF offers an [online support group](#) for people affected by NASH.

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