CHALLENGES AND OPPORTUNITIES IN THE MANAGEMENT OF ADVANCED FIBROSIS DUE TO NONALCOHOLIC STEATOHEPATITIS (NASH)

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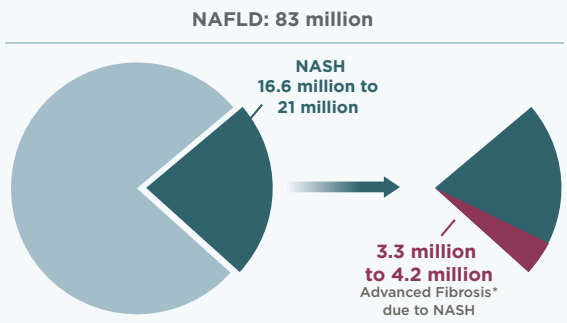
Disease-state background and epidemiology

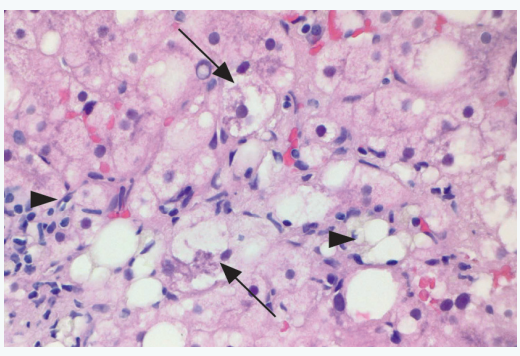
Nonalcoholic fatty liver disease (NAFLD) describes the entire spectrum of fatty liver diseases in individuals without significant alcohol consumption,[1] with which an estimated 83 million Americans are affected.[2,3] Between 16.6 to 21 million of these NAFLD patients have a more complex type of fatty liver disease known as NASH, and between 3.3 and 4.2 million of NASH patients will have Advanced Fibrosis due to NASH **(see Figure 1)**.[2,3] NASH is characterized by the presence of steatosis (the accumulation of fat in 5% or more of hepatocytes), hepatocellular ballooning, and inflammation.[4] In NASH, lipotoxic hepatocytes result in the production of factors that promote wound healing as an attempt to replace dying hepatocytes.[5] The presence of chronic and/or aberrant inflammation can lead to scar tissue deposition and the development of fibrosis and hepatocellular carcinoma (HCC).[3] NASH can be distinguished from simple steatosis—the predominant form of NAFLD—by the presence of lobular inflammation and hepatocellular ballooning in addition to fat in the liver **(see Figure 2)**.[3,4]

Figure 1. Prevalence of Advanced Fibrosis due to NASH in the United States[2,3]



The number of patients under treatment is likely smaller than the prevalence of each subtype of NAFLD.

Figure 2. Histologic features of NASH[3]



This figure shows characteristic histologic features of NASH from a liver-biopsy specimen: ballooned hepatocytes (arrows) and inflammatory infiltrate (arrowheads).
Source: Diehl et al (2017).

*For this figure, Advanced Fibrosis is defined as F3 and F4 fibrosis.

This white paper was developed and sponsored by Intercept Pharmaceuticals,Inc.

Patients with NASH can develop Advanced Fibrosis. As patients progress in fibrosis stage their risk of mortality increases.[6,7] Some patients with NASH will develop cirrhosis.[2] In a study of patients with histologically confirmed NASH, in which 217 patients had stage 3 fibrosis (F3) and 258 had compensated cirrhosis[8]:

- 22% (48/217) with F3 progressed to cirrhosis at median follow-up of 29 months
- 19% (50/258) of cirrhotic patients had a clinical event, such as ascites, hepatic encephalopathy, variceal bleeding, or death at median follow-up of 31 months

This study found that some patients may progress from F3 to cirrhosis in as few as approximately 2.5 years.[8]

Identification of Advanced Fibrosis

Biopsy has traditionally been used for identification of Advanced Fibrosis but is associated with numerous limitations, risks, and costs. Biopsy is not ideal for initial diagnosis of Advanced Fibrosis or monitoring patients over time due to its invasive nature and the accompanying risks of rare but life-threatening complications.[4,9,10] Liver biopsy is a subjective procedure; it analyzes only a small sample and can result in sampling errors.[11] Interpretation is based on pathologist readings. Thus, biopsy has poor inter-intra-observer reproducibility in fibrosis staging. It also requires specialized physicians, making it a costly procedure.[4,12]

From a patient perspective, there may be concerns related to the invasive nature of the biopsy as well as the potential for pain, discomfort, and complications.[13]

Noninvasive tests (NITs), which are reproducible, widely available, and relatively low-cost, are an alternative to biopsy.[10,14,15] NITs present a safe and simple way to monitor disease over time and are cost-effective compared with biopsy **(see Table 1)**.[14]

Proposed as an alternative to biopsy, various biochemical markers and/or noninvasive imaging techniques are increasingly being used in clinical practice to identify patients with Advanced Fibrosis.[4] Noninvasive techniques allow the liver to be evaluated globally and decrease sampling error.[16] Current guidelines from the American Association for the Study of Liver Diseases see the increased value of using NITs to assess fibrosis.[4]

Commonly used NITS

NITs can be classified into 3 categories:

- Simple scores use a panel of standard values obtained from basic serum tests to help predict stages of liver fibrosis
- Proprietary predictive scores are based on patented tests for biomarkers specific to the liver
- Imaging techniques can be used to measure physical aspects of liver tissue

Table 1. NITs used to assess the level of fibrosis

Simple scores	Proprietary predictive scores	Imaging
• Nonalcoholic fatty liver disease fibrosis score (NFS) • Fibrosis-4 (FIB-4) • Aspartate aminotransferase/ platelet ratio index (APRI)	• FibroSure® • Enhanced Liver Fibrosis Test (ELF™) (not currently available in the US)	• Transient elastography (eg, FibroScan®) • Magnetic resonance elastography (MRE)

List of NITs provided above is not exhaustive.
ELF™ is a trademark of Siemens Healthineers™.
FibroScan® is a registered trademark of EchoSens™, Paris.
FibroSure® is distributed by LabCorp in the US.

Simple scores

Nonalcoholic fatty liver disease fibrosis score (NFS). NFS is an NIT that estimates the amount of scarring in the liver based on laboratory tests.[17] An NFS score is calculated using a patient's age, hyperglycemia, body mass index, platelet count, albumin level, and AST-to-ALT ratio. NFS has been proven several times to be externally valid and consistent in various populations with NAFLD.[11,17] In a 2016 study, risk stratification by the primary care provider using the NFS was estimated at $5,985 per quality-adjusted life year (QALY) in comparison with the cost of usual care at $7,229 per QALY. In the same study, the NFS was found to be the most cost-effective strategy in 94.2% of samples at a willingness-to-pay threshold of $100,000. Thus, NFS was found to be more cost-effective compared with usual care.[18]

Fibrosis-4 (FIB-4). The FIB-4 test, a noninvasive estimate of liver scarring, combines standard biochemical values with age. It is inexpensive in that the parameters used in the test are typically included in the diagnosis of any liver disease (ie, platelets, ALT, AST).[19] The calculations are relatively simple and immediate results can be communicated during the same patient visit.[20]

Aspartate aminotransferase/platelet ratio index (APRI). APRI is a noninvasive, readily available, and useful tool in assessing liver fibrosis that is based on routine lab tests and is therefore cost-effective and widely available. The APRI score utilizes a blood test that measures an enzyme, AST, that is produced by the liver. Liver damage is indicated by the AST level and the ratio of AST to platelets.[11] One study found that APRI values increase with the degree of fibrosis.[21]

Proprietary predictive scores

FibroSure®. FibroSure® is a noninvasive method of assessing liver fibrosis classified as the "biological" approach, which quantifies serum biomarkers in samples. It was the first algorithm to combine α-2-macroglobulin, γGT, apolipoprotein A1, haptoglobin, total bilirubin, age, and gender for quantifying serum biomarkers—particularly in patients with hepatitis C. FibroSure® is one of the most widely used and validated noninvasive approaches for assessing fibrosis level in patients with viral hepatitis C.[11]

Enhanced Liver Fibrosis (ELF™) Test. ELF™ is another biological noninvasive method of assessing liver fibrosis. Its formula combines age, hyaluronate, MMP-3, and TIMP-1 to quantify serum biomarkers.[11] ELF™ has shown diagnostic value in various chronic liver diseases alongside other serum biomarker tests such as FibroTest, APRI, and FIB-4.[11] The method is a patented diagnostic and is commercially available from Siemens Healthcare in Europe. ELF™ is pending approval in the United States and is not yet available for commercial use.[22]

Imaging

Transient elastography (FibroScan®). Transient elastography (TE) is a noninvasive method of assessing liver fibrosis classified as the "physical" approach, which measures liver stiffness (LS). Fibrosis replaces healthy tissue with scar tissue and creates a stiffness in the liver. FibroScan® is a one-dimensional ultrasound transient elastography that measures the velocity of a low-frequency (50 Hz) elastic shear wave propagating through the liver, which is directly related to tissue stiffness. The faster the shear wave propagates, the stiffer the tissue is.[11]

Magnetic resonance elastography (MRE). MRE is a noninvasive method of measuring LS and is specifically a liver elasticity-based imaging technique.[11,15] It uses a variation of the phase-contrast method to image shear-wave characteristics within the liver and determines liver elasticity with a formula that quantifies shear modulus. LS is measured from the color-coded images of wave displacement

patterns.[15] MRE is expensive and not widely available in the United States.[11,23]

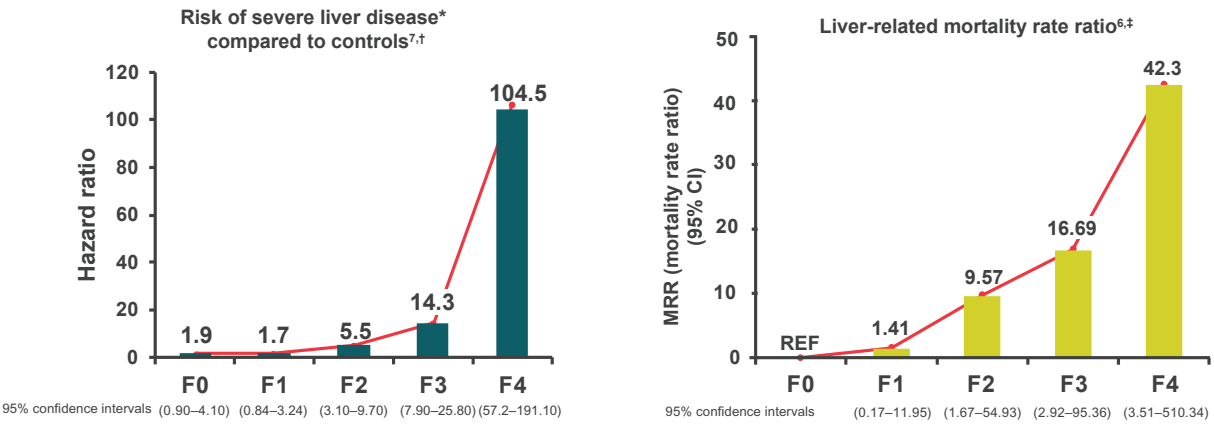
Disease burden

Clinical impact

While generally asymptomatic, NASH may progress to end-stage liver disease, HCC, liver transplant, and even death.[2,24]

- **End-stage liver disease (decompensated cirrhosis):** If underlying causes of cirrhosis are not treated, the liver will lose most of its function and complications can become life-threatening.[25,26] Thirty-one percent of patients with NASH-related cirrhosis have been shown to decompensate over an 8-year period.[27,28] Symptoms of end-stage liver disease include
  - **Portal hypertension:** an increase in pressure within the portal vein, which can lead to esophageal varices and the buildup of fluid in the abdomen (ascites).[25] Approximately 25% of patients with NASH-related cirrhosis are projected to develop major complications of portal hypertension within 3 years[29]
  - **Hepatic encephalopathy:** mental confusion and difficulty concentrating due to buildup of toxins in the bloodstream[25]
  - **Renal failure:** impairment to the kidneys that may require hemodialysis treatment[30]
- **HCC:** NASH is a major risk factor for developing HCC—even in patients without cirrhosis—and has been identified as one of the most common causes of HCC in the United States.[2,24,31] Seven percent of patients with NASH-related cirrhosis have been shown to develop HCC over 6.5 years of follow-up.[28]
- **Liver transplant:** NASH is the fastest-growing indication for liver transplantation in patients with HCC.[32,33] As early as 2020, NASH is projected to be the leading cause of liver transplantation in the United States.[34]
- **Death:** NASH is associated with increased risk of death due to liver-, CV-, and malignancy-related mortality.[35] By 2030, the number of deaths for patients with NASH is projected to nearly double from an estimated 370,000 to approximately 716,800.[2]

Figure 4. Impact of fibrosis stage on liver-related morbidity and mortality



*Severe liver disease is defined as cirrhosis, liver decompensation/failure, or hepatocellular carcinoma.
†From a retrospective cohort study of 646 biopsy-proven NAFLD patients, each matched to 10 controls.
‡From a meta-analysis of 5 multinational NAFLD cohorts (1495 NAFLD patients with 17,452 PYF). Liver-related mortality was a secondary outcome defined by investigators.
Figure of risk-related liver disease is adapted from Hagström H et al. *J Hepatol.* 2017;67:1265-1273.
Figure of liver-related mortality is adapted from Dulai PS et al. *Hepatology.* 2017;65(5):1557-1565.

Advanced Fibrosis due to NASH carries the greatest risk of liver-related morbidity and liver-related mortality **(see Figure 4)**.[6,7] In one study, F3 patients had an approximately 2 times greater liver-related mortality rate ratio compared with F2 patients, and F4 patients had an approximately 5 times greater liver-related mortality rate ratio compared with F2 patients.[6] Risk of liver-related mortality increases exponentially with increasing fibrosis stage, and patients with Advanced Fibrosis due to NASH are at the greatest risk.[6]

Economic impact

The current economic burden of treating patients with NASH is substantial and will continue to grow. In the United States, the annual predicted economic burden of NASH with and without fibrosis has been estimated at $7.35 billion, including direct costs and societal costs.[36] In one analysis, direct annual costs per patient (inflated from 2017 to 2019 period after currency), which includes inpatient, outpatient, professional services, emergency department, tests, and drug costs, directly relates to progression of disease[37]:

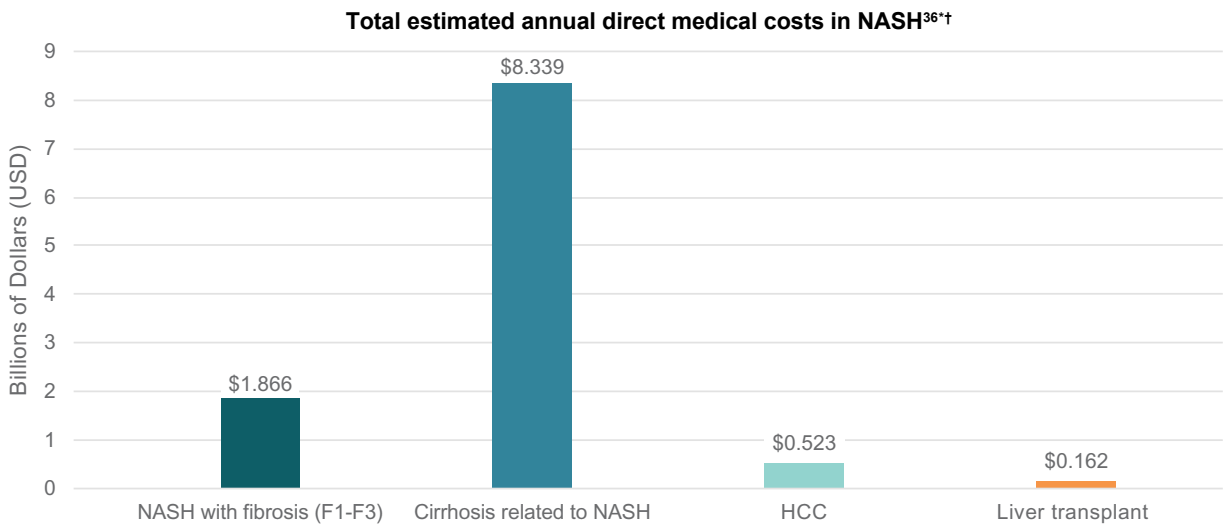
- Fibrosis F3: $551
- Compensated cirrhosis: $19,603
- Decompensated cirrhosis: $36,989
- HCC: $96,681
- Liver transplant: $368,149
- Post-liver transplant: $50,645

While liver transplant represents the highest cost per patient, overall economic burden is driven by patients progressing from fibrosis to cirrhosis. While only 8% of all NASH patients have cirrhosis, NASH with cirrhosis accounts for >80% of annual direct medical costs **(see Figure 5)**.[2,36] Although HCC and liver transplantation cost more per patient, their rate of incidence does not have the same impact as cirrhosis.[2,37] Such cost differences reflect the need for early treatment to avoid the downstream costs associated with cirrhosis.[2,37] Estimates of economic impact are based on existing clinical practice patterns and are not inclusive/predictive of new pharmacological treatments.

Societal impact

In the United States, the prevalence of NASH without fibrosis is highest among patients 65 years of age and older.[36] Following completion of the Short Form Health Survey, patients with NASH reported worse physical-component,

Figure 5. Costs are driven by patients progressing from fibrosis to cirrhosis



USD, United States dollars.

*Based on a model with an embedded disease-specific Markov structure that allowed patients to transition from NAFLD to different liver health states (eg, NASH without fibrosis, which could then progress to NASH with fibrosis; cirrhosis; etc).
†Direct medical costs include hospitalizations as well as costs of treating disease-related complications.

vitality, bodily pain, and general-health scores than NAFLD patients without NASH.[38] A significantly higher lifetime risk of depression and anxiety has been reported in a small study of patients with NASH compared with matched non-NASH controls.[38] Disease progression due to NASH may have a negative impact on productivity due to illness and disability. For instance, patients with NASH and cirrhosis generally demonstrated lower work productivity than those with NASH and F3 fibrosis, based on patient-reported scores on the Work Productivity and Activity Impairment: Specific Health Problem. Differences in work productivity impairment scores were not statistically significant between groups.[39]

Current treatment landscape

Currently, there are no pharmacologic therapies approved for the management of Advanced Fibrosis due to NASH.[40] Lifestyle modification, including changes such as diet, weight loss, and exercise, is recommended as a first-line treatment.[4] However, as lifestyle interventions require continuous support and regular monitoring to be successful, this approach can be limited by lack of patient compliance.[41]

Existing treatment interventions for Advanced Fibrosis due to NASH have suboptimal efficacy and safety.[42] Vitamin E and pioglitazone are non-indicated treatments that may be used in select patients. However, data are limited, and risks and benefits should be discussed with each patient before starting therapy.[4] Expected outcomes with treatments such as pioglitazone and vitamin E include reductions in disease activity, but they do not lead to the long-term resolution of Advanced Fibrosis due to NASH. The use of pioglitazone may be limited by adverse effects, such as weight gain, leg swelling, and exacerbation of heart failure.[43] Vitamin E may increase the risk of prostate cancer.[4]

There is a lack of effective therapies that are specifically approved for the treatment of Advanced Fibrosis due to NASH, including the reversal of fibrosis. Thus, a high unmet need remains for effective treatments that halt progression of fibrosis and prevent cirrhosis. New treatment options are therefore needed to halt the progression of Advanced Fibrosis due to NASH to prevent the onset of cirrhosis and its associated costs, HCC, or end-stage liver disease.

Drugs in development for the treatment of NASH

This is not a direct comparison of products.

Several pharmacological therapies have been evaluated in recent clinical trials for the treatment of NASH **(see Table 2)**. These efforts have targeted the processes involved in the pathogenesis and progression of NASH, including metabolic stress, inflammation, and fibrosis.[3]

ASK1 inhibitor

Selonsertib is a small-molecule inhibitor of apoptosis signal-regulating kinase 1 (ASK1), which regulates signaling for hepatic inflammation and fibrosis in settings of oxidative stress.[44]

Selonsertib has been investigated in combination with simtuzumab, a humanized monoclonal lysyl oxidase-like antibody that inhibits cross-linking of collagen in pathologic stroma.[44,45]

Dual CCR2/CCR5 antagonist

Cenicriviroc (CVC) is a dual C-C chemokine receptor type 2 and 5 (CCR2/CCR5) antagonist with nanomolar potency against both receptors. These receptors mediate the interactions that influence liver inflammation and fibrosis, therefore giving CVC an anti-inflammatory and antifibrotic effect.[46]

Table 2. Drugs in development for the treatment of NASH
This is not a direct comparison of products.

Class	Molecule	Company	Clinical trials	Phase 2 primary endpoints	Phase 3 primary endpoints
Dual CCR2/CCR5 antagonist[46]	CVC	Allergan	• Phase 2 completed[47] • Phase 3 ongoing[48]	• Percentage of patients with improvement in NAS by ≥2 points with at least 1-point reduction in either lobular inflammation or hepatocellular ballooning and no concurrent worsening of fibrosis at 12 months[47]	• Improvement in fibrosis by ≥1 stage and no worsening of steatohepatitis at 12 months[48] • Observed histopathologic progression to cirrhosis, liver-related clinical outcomes, and all-cause mortality (composite long-term outcome endpoint)[48]
ASK1 inhibitor[49]	SEL	Gilead	• Phase 2 completed[50] • Phase 3 completed; primary endpoint not achieved[51]	• Percentage of patients with ≥1 stage improvement in fibrosis at week 24[44]	• Percentage of patients with ≥1 stage improvement in fibrosis at week 48[51] • Event-free survival at week 240[51]
PPAR alpha-delta dual agonist[49]	ELA	Genfit SA	• Phase 2 completed[52] • Phase 3 ongoing[53]	• Predefined primary: reversal of NASH without worsening of fibrosis at week 52[52] • Modified primary: resolution of NASH without worsening of fibrosis at week 52[52]	• Percentage of patients achieving resolution of NASH without worsening of fibrosis at week 72[53] • Composite long-term outcome composed of all-cause mortality, cirrhosis, and liver-related clinical outcomes[53]
FXR agonist[42]	Obeticholic acid	Intercept Pharmaceuticals	• Phase 2 completed[54] • Phase 3 ongoing. Interim readout available[55]	• Percentage of patients with improvement in NAS by ≥2 points at week 72 and no worsening in fibrosis[54]	• Percentage of patients at 18 months – With ≥1 stage improvement in fibrosis with no worsening of NASH[55] or – Achieving NASH resolution with no worsening of liver fibrosis[55] • Long-term outcome (up to 7 years): treatment effect on all-cause mortality and liver-related clinical outcomes as measured by the time to first occurrence of prespecified clinical events[55]
THR beta-selective agonist[49]	MGL-3196	Madrigal	• Phase 2 completed[56] • Phase 3 ongoing[57]	• Relative reduction of liver fat on MRI-PDFF at 12 weeks[56]	• Percentage of patients with stage 2 or 3 fibrosis who achieved NASH resolution at 52 weeks[57] • Composite long-term outcome composed of all-cause mortality, cirrhosis, and liver-related clinical outcomes[57]

ASK1, apoptosis signal-regulating kinase 1; CCR-2/5, chemokine receptors-2/5; CVC, cenicriviroc; ELA, elafibranor; FXR, farnesoid X receptor; MRI-PDFF, magnetic resonance imaging-estimated proton density fat fraction; NAS, nonalcoholic fatty liver disease activity score; OCA, OCALIVA; PPAR, peroxisome proliferator-activated receptor; SEL, selonsertib; SIM, simtuzumab; THR, thyroid hormone receptor.

FXR agonist

Obeticholic acid (OCA) is a selective agonist of the farnesoid X receptor (FXR), a bile acid nuclear receptor. FXR is highly expressed in the liver and helps regulate lipid metabolism and inflammation—key underlying pathways that drive NASH and NASH-related fibrosis.[42,58] OCA is currently approved by the FDA for the treatment of primary biliary cholangitis and is being studied for NASH and other indications.[59,60]

PPAR alpha-delta dual agonist

Elafibranor is a peroxisome proliferator-activator receptor (PPAR) alpha-delta dual agonist. PPAR alpha agonists are involved in fatty-acid oxidation, whereas PPAR delta agonists have an anti-inflammatory effect.[49]

THR beta-agonist

MGL-3196 is a small-molecule, liver-directed thyroid hormone receptor (THR) beta-agonist.[49] The high selectivity for the beta-receptor subtype, the predominant isoform in the liver, aims to reduce the effects of extrahepatic thyroid receptor activation (via the alpha-receptor), such as increased respiration and cardiac tissue hypertrophy.[61]

Future outlook: intervention for the right patient at the right time

Advanced Fibrosis due to NASH is a progressive disease, but with a greater understanding of NASH pathogenesis, scientific research is now focusing on the potential of targeting multiple key pathways of the disease. With no indicated pharmacological treatments, the ability to manage Advanced Fibrosis due to NASH is limited, creating an urgent need for treatment options.

Conclusions

Advanced Fibrosis due to NASH is a progressive disease, with increasing risk associated with later stages of the disease.[3] It is associated with serious and costly consequences, with the main cost driver being cirrhosis.[37] Patients with Advanced Fibrosis due to NASH have the highest unmet need and represent a small fragment of the total population.[2]

Biopsy has traditionally been used for identification of Advanced Fibrosis due to NASH but is associated with numerous limitations.[4,9,10] As a result, biochemical markers and various noninvasive tests are increasingly being used to identify patients with Advanced Fibrosis.[4] The goal of treating these patients should be halting or reversing their fibrosis and thus preventing cirrhosis.[2,24]

There is a high unmet need for effective treatments that halt fibrosis and prevent cirrhosis. Although Advanced Fibrosis due to NASH is a more severe stage of the disease spectrum, the progression of disease can be halted or even reversed.[42,62] Academic and industry research is focused on different types of treatment options and mechanisms of action that address the pathophysiology of Advanced Fibrosis due to NASH.

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This white paper was developed and sponsored by Intercept Pharmaceuticals, Inc.

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