



Literature Compendium Volume II

The Enhanced Liver Fibrosis (ELF) Test in NAFLD and NASH

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Introduction

NAFLD/NASH: a growing epidemic

Nonalcoholic fatty liver disease (NAFLD) is the most common form of chronic liver disease (CLD) globally, with a prevalence of ~25%.¹ NAFLD refers to a spectrum of diseases, from simple fatty liver to more aggressive non-alcoholic steatohepatitis (NASH). While patients with NASH are more likely to develop progressive disease, which can result in cirrhosis, liver failure, or hepatocarcinoma (HCC), patients without histological evidence of NASH are also at risk.² Progressive CLD typically lacks signs and symptoms, with many patients remaining undiagnosed until uncompensated disease presents. Liver fibrosis versus the inflammatory process is recognized as the key driver of pathogenicity in NAFLD/NASH.^{3,4} Early recognition of progressive fibrosis and intervention is key for improved outcomes. While weight loss and lifestyle modifications can help reverse disease, compliance can be a challenge.

Blood-based tests for liver fibrosis

Several therapies in late-stage development may offer a pharmacologic option if approved but this will require identification of patients at highest risk (i.e., patients with significant or advanced fibrosis). While tissue biopsy has been the historical standard, it is invasive, carries risk, has suboptimal accuracy, and is not amenable as a screening or routinely repeated test. Noninvasive tests (NITs)—both blood-based and imaging for liver elasticity—have emerged as alternatives, and growing data shows NITs could serve as an effective alternative to biopsy.^{5,6} Blood-based tests can readily support high-volume testing, do not require patient access to specialized imaging equipment or highly trained operators, and generally have lower incidence rates of failure and unreliable results reported for imaging modalities.^{7,8}

Blood-based tests for liver fibrosis include indirect and direct markers.⁹ Indirect markers may reflect elements of inflammation or damage, while direct markers measure analytes directly involved in fibrosis and turnover of the extracellular matrix (ECM). Since fibrosis is the key indicator of damage and CLD progression, direct assessment of fibrosis has proven valuable for identifying at-risk patients. The most widely studied direct marker is the Enhanced Liver Fibrosis (ELF™) Test, a fully automated immunoassay requiring only a single serum sample.

The ELF Test is a quantitative test that measures three major components directly involved in liver matrix metabolism: hyaluronic acid (HA), procollagen III amino-terminal peptide (PIIINP), and tissue inhibitor of matrix metalloproteinase 1 (TIMP-1). A simple-to-interpret numeric score helps identify patients at high risk of advancing to fibrosis or cirrhosis (Figure 1). The ELF Test is highly prognostic and has been shown to outperform both simple markers and biopsy for outcomes in CLD patients.¹⁰⁻¹²

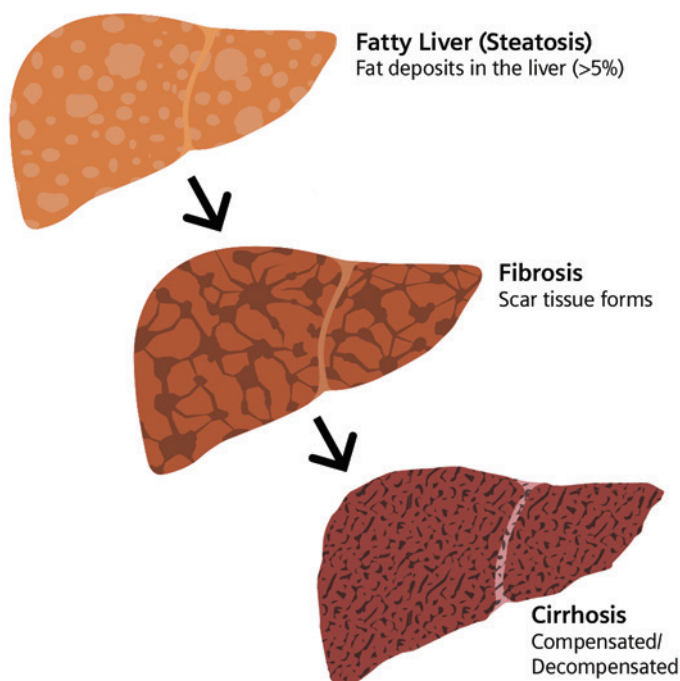


Figure 1: ELF score ≥ 9.8 indicates high risk of advanced fibrosis

Conclusion

ELF Test: a simple blood test for a complex process

Liver fibrosis is biochemically complex but is orchestrated primarily by activated hepatic stellate cells (HSCs). Activated HSCs produce components of the ECM that include proteins such as fibronectin, laminin, collagens, hyaluronic acid (HA), proteoglycans, and collagen types I, III, IV, and V that form scar tissue in the liver.¹³ Deposited ECM progressively accumulates and replaces normal liver tissue with scarring that damages hepatic architecture and drives dysfunction.

Fibrosis of the liver is a largely bidirectional process.^{15,16} Fibrosis and repair mechanisms have been linked to ECM-related pathways. HA and PIIINP are components of damage associated with progressive scarring. Regression and repair are associated with upregulation of matrix metalloproteinases (MMPs), which can degrade ECM deposition and therefore are central to healing. Levels of MMPs are inhibited by tissue inhibitors of metalloproteinases (TIMPs), which bind MMPs. TIMP-1 overexpression hinders degradation and clearance of the fibrotic matrix, leading to increased levels of interstitial ECM and progressive fibrosis.^{17,18} Additionally, low levels of TIMP-1 may promote hepatic stellate cell apoptosis.¹⁶ By testing for direct markers associated with both ECM deposition (PIIINP, HA) and inhibition of repair (TIMP-1), the ELF Test provides a direct quantitative measure for the assessment of fibrotic activity and ECM turnover.

The three direct markers of the ELF Test provide complementary information, and the combined score outperforms both the individual markers and simple scores such as APRI or FIB-4.^{11,19} The performance of the ELF Test for liver fibrosis has been well-established in the scientific literature, and ease of testing and interpretation support routine clinical use and an alternative to invasive biopsy. This compendium highlights a small subset of the extensive number of ELF publications in NAFLD and NASH patients, including recent studies evaluating therapies in development that used ELF testing.

The Enhanced Liver Fibrosis (ELF) Test in NAFLD and NASH

Noninvasive Tests Accurately Identify Advanced Fibrosis Due to NASH: Baseline Data from the STELLAR Trials

Anstee QM, et al. Hepatology. 2019 Nov;70(5):1521-30.

Objective

Evaluate the use and accuracy of NITs vs. biopsy in patients with nonalcoholic steatohepatitis (NASH) to better identify those with advanced fibrosis who could benefit from new therapies.

Methods

- Screening data from patients enrolled across 26 countries from two phase 3 studies exploring the potential efficacy of an apoptosis signal-regulating kinase 1 (ASK1) inhibitor for treatment were analyzed.
- The study population included patients with bridging fibrosis (F3) and compensated cirrhosis (F4).
- Area under the receiver operating characteristic curve (AUROC) was evaluated for alternate NITs for the discrimination of advanced fibrosis (compared to biopsy data).
- NITs compared included the NAFLD fibrosis score (NFS), Fibrosis-4 (FIB-4) index, Enhanced Liver Fibrosis (ELF) Test, and liver stiffness by vibration-controlled transient elastography (LS by VCTE).
- Novel optimal thresholds were determined for the individual NITs using evaluation/validation sets, and values from the scientific literature for the NITs were also examined.
- Approaches analyzed included a single test with one threshold, a single test with two thresholds, and simultaneous or sequential combinations with two tests.
- With the two-test approach, all patients were initially tested with a single test, and those falling into an indeterminate range were subsequently tested with a second test.

- Performance of the NITs alone or in combination as a method to discriminate advanced fibrosis were evaluated.
- Test performance relative to patient age ranges was also included.
- The authors note that assessment of LS by VCTE was optional, so evaluation included only a subset that was skewed toward those who qualified for enrollment.

Results

- ELF Test and LS by VCTE displayed the highest AUROC for use of a single NIT with one threshold to discriminate advanced fibrosis.
- NFS performed least well in the oldest age strata, while FIB-4 performed least well in the youngest age group. A trend for increased sensitivity but decreased specificity was seen with age for all NITs, though the authors noted that the ELF Test was generally more stable across age groups.
- Use of upper and lower thresholds for the inclusion or exclusion of advanced fibrosis had moderately high degrees of sensitivity and specificity but produced a large percentage falling into an indeterminate zone.
- Use of a sequential approach to better address indeterminate results significantly reduced the frequency of indeterminate results, with only a slight increase in misclassification.
- Novel thresholds derived from the trial data were found to perform similarly to existing literature-based NIT thresholds.
- No single threshold for any NIT was found to optimally balance sensitivity and specificity.

Significance

- Assessment for advanced fibrosis is critical for the proper evaluation of patients with known or suspected NASH, as fibrosis is the key independent predictor of disease progression. NITs can be readily used on large patient populations and lack the risk associated with biopsy.
- All NITs have the potential to miss some cases of advanced fibrosis (false negative) or incorrectly identify advanced fibrosis (false positive). Use of a sequential approach (e.g., FIB-4 followed by the ELF Test for indeterminates) may improve accuracy.
- Both the ELF score and FIB-4 can be readily obtained via a blood sample and therefore offer ease of use in both primary care and specialty settings where samples can be sent to available testing sites. Large numbers of patients could be expediently tested regardless of access to specialized imaging centers.
- This was a controlled study with a high prevalence of advanced fibrosis, so it may or may not reflect findings in a “real-world” population. The rule-in value used for the ELF Test was very high (11.3), so use of the manufacturer’s assigned value for severe fibrosis (≥ 9.8) was lacking.

Conclusion

NITs perform well in identifying NASH patients with advanced fibrosis. A sequential pathway (e.g., FIB-4 followed by the ELF Test) might improve detection while reducing inappropriate rule-ins.

ELF median in the F0-F2 population	9.2
ELF median in the F3-F4 population	10.39

Sequential performance of FIB-4 with the ELF Test to rule out (F0-F2) or rule in for advanced fibrosis (F3-F4):

Prevalence of F3-F4	72%
Thresholds used	FIB-4 1.3 and 2.67; ELF Test at 9.8 or 11.3
Sensitivity	69%
Specificity	92%

Cost-Comparison Analysis of FIB-4, ELF, and FibroScan in Community Pathways for Non- Alcoholic Fatty Liver Disease

Srivastava, et al. BMC Gastroenterology. 2019;19:122.

Objective

Assess the clinical and financial benefit of improved detection of advanced fibrosis in a primary care setting using alternative noninvasive testing NIT pathways compared to standard of care (SOC) in NAFLD patients with elevated liver function tests.

Methods

- A working group comprising clinicians (primary and specialty), public health, and patient representatives was formed. Pathways incorporating NITs (imaging and blood-based) were developed to identify patients likely to have advanced fibrosis who would benefit from specialist referral. Pathways were compared to SOC using a probabilistic decision analytical simulation model.
- Four NIT pathways were defined:
 - Scenario 1: SOC
 - Scenario 2: FIB-4 (FIB-4 <1.30 remained in primary care and >3.25 were referred) followed by the ELF Test for indeterminates
 - Scenario 3: FIB-4 (FIB-4 <1.30 remained in primary care and >3.25 were referred) followed by FibroScan for indeterminates
 - Scenario 4: ELF Test alone
 - Scenario 5: FibroScan alone
- Advanced fibrosis was defined at an ELF value of ≥ 10.3 and a FibroScan value of ≥ 7.9 kPa.
- A 1-year time horizon was used to explore short-term benefits and a 5-year period for longer-term benefits.
- Healthcare costs were calculated for both primary and specialty care, and the impact of the pathways on healthcare spending was assessed.
- Clinical parameters included increased detection of advanced fibrosis and cirrhosis and a reduction in unnecessary referrals.
- Improved detection of cirrhosis over the 1-year timeframe was observed for all pathways compared to SOC, ranging between 113% and 136%.
- Clinical benefits noted included increased detection of advanced fibrosis, a decrease in rates of incurable HCC and variceal hemorrhage in the NIT pathways, and increased detection of curable HCC over the 1-year timeframe. The model demonstrated that management of cirrhosis in secondary care could reduce hospitalizations from CLD complications.
- Cost-outcome analysis showed savings with all NIT pathways compared to SOC over both the 1-year and 5-year horizons.
- The combination of FIB-4 and the ELF Test delivered the greatest cost savings.

Significance

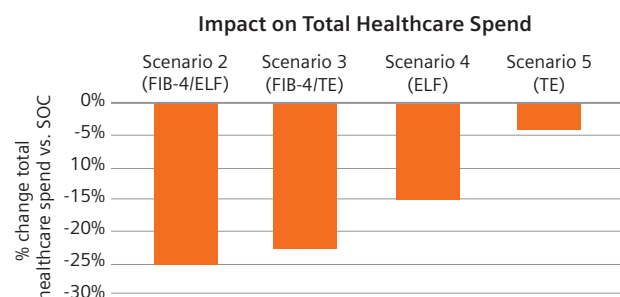
- Implementation of simple NIT pathways in a primary care setting has the potential to dramatically improve management and appropriate referral of NAFLD patients at greater risk of advancing disease and risk of liver-related outcomes.
- Blood-based testing (either FIB-4 followed by the ELF Test or ELF Test alone) offers the greatest opportunity to manage large patient populations or those with limited/no access to specialized imaging.
- Benefits may include improved patient outcomes, a reduction in unnecessary referrals, and significant reduction in healthcare spending.
- Resources could be allocated to patients at higher risk, and specialist evaluations could focus on those most likely to benefit.

Conclusion

"The model provides compelling evidence for clinicians, commissioners and policy makers to consider the formal introduction of non-invasive liver fibrosis testing in primary care, in line with other central policy statement."

Results

- All the NIT pathways reduced the unnecessary referral rate over the 1-year time horizon compared to SOC. FIB-4 followed by the ELF Test (Scenario 2) yielded the highest reduction rate (85%).
- The decrease in unnecessary referrals reduced the need for investigation in the secondary setting, yielding a cost savings for all pathways compared to SOC.



Direct Comparison of the Specialised Blood Fibrosis Tests FibroMeterV2G and Enhanced Liver Fibrosis Score in Patients with Non-alcoholic Fatty Liver Disease from Tertiary Care Centres

Guillaume M, et al. Aliment Pharmacol Ther. 2019 Dec;50(11-12):1214-22.

Objective

Compare the accuracy of two specialized blood tests (ELF Test and FibroMeterV2G) with each other, FIB-4, and the nonalcoholic fatty liver disease (NAFLD) fibrosis score (NFS) in NAFLD patients treated at two tertiary care centers.

Methods

- Patients with biopsy-proven NAFLD were tested with the ELF Test, FibroMeterV2G, NFS, and FIB4 and assessed for advanced fibrosis (F3/F4) relative to NASH CRN scoring as a primary endpoint.
- FibroMeterV2G includes HA (a direct marker of fibrosis), alpha2-macroglobulin, and indirect markers (AST, urea, platelets, prothrombin time) along with age and gender.
- FibroMeterV2G (developed for HCV) was used versus FibroMeter^{NAFLD} as the authors state it outperformed the FibroMeter^{NAFLD} in NAFLD patients. FibroMeter^{NAFLD} uses only indirect markers.
- Statistical analysis included method comparisons using the Obuchowski index and Youden index.

Results

- ELF Test and FibroMeterV2G had similar diagnostic accuracies for advanced fibrosis, though disagreement was observed in a percentage of cases. Both outperformed "simple" tests.
- Setting a 90% sensitivity and 90% specificity for both tests produced equivalent performance for the detection of advanced fibrosis. At these criteria, a "grey zone" was noted for both assays that could require subsequent evaluation (biopsy or other).
- Diagnostic algorithms using high and low thresholds were explored. An agreement-based algorithm between the two tests yielded good performance, with a diagnostic accuracy of 86% for advanced fibrosis.

- The authors discuss the potential for imaging as a second-line evaluation for grey-zone results. Alternatively, given the large numbers of patients in need of testing, the authors suggest simple markers such as FIB-4 or NFS could be used initially, with grey-zone results reflexing to the specialized tests. They caution that cost-effectiveness analyses might better identify the value for the initial use of simple vs. specialized blood tests to identify at-risk patients.

Significance

- Direct markers of liver fibrosis outperform indirect makers and simple tests.
- Testing can be applied both to primary and tertiary care populations to better identify patients with advanced fibrosis vs. those at lower risk. Setting a high criterion for both sensitivity and specificity (90%) performs well with both tests but results in a grey zone requiring additional analysis in a significant percent of samples.
- Diagnostic algorithms employing alternate NITs such as imaging or simple tests may further inform diagnosis and reduce grey-zone results.
- ELF Test offers the advantage of a single blood tube and an automated score vs. the diverse testing of analytes, patient demographic info, and data import for score calculation required for calculating the FibroMeterV2G score.

Conclusion

"In conclusion, the diagnostic accuracy of FibroMeterV2G and ELF Test is not significantly different in a population of NAFLD patients from tertiary care centres. These two specialized blood fibrosis tests including direct biomarkers of liver fibrosis perform significantly better than simple blood fibrosis tests such as FIB4 and the NFS."

Biopsy Stage	≥F2	≥F3	F4
ELF Test AUROC	0.721	0.793	0.852
FibroMeterV2G AUROC	0.726	0.804	0.818

The Natural History of Advanced Fibrosis Due to Nonalcoholic Steatohepatitis: Data from the Simtuzumab Trials

Sanyal AJ, et al. Hepatology. 2019 Dec;70(6):1913-27.

Objective

Analyze the control and trial arms of patients enrolled in a clinical trial for simtuzumab using serum markers of fibrosis and other testing parameters of NASH progression; assess changes and clinical outcomes.

Methods

- Patients with NASH and bridging fibrosis (F3) or compensated cirrhosis (F4) were enrolled. The treatment and trial arms were combined after 96 weeks due to lack of treatment efficacy to assess tests and outcomes.
- Outcomes analyzed included progression to cirrhosis in the F3 group and liver-related events in the F4 group.
- Tests included biopsy (with Ishak staging), ELF Test, FibroSure/FibroTest, FIB-4, APRI, NAFLD Activity Score (NAS), and hepatic collagen content and alpha-smooth muscle actin (by morphometry). Core biopsies were obtained at baseline and weeks 48 and 96 and staged using modified Ishak. Serum markers (including the ELF Test) were measured at baseline and every three months.
- Outcomes were assessed relative to baseline values of the ELF Test and other tests. Changes were also assessed over time.

Results

- The primary determinant of disease progression in both patient subgroups was fibrosis as determined histologically or based on the ELF Test or other serum markers.
- During a mean follow-up of 29 months, patients with bridging fibrosis were evaluated for progression to cirrhosis (based on histologic findings, signs, or symptoms). Higher ELF scores at baseline or greater changes over time were significantly associated with disease progression.
- The optimal cutoff for baseline ELF score to predict disease progression (balancing sensitivity and specificity) was 9.76.
- 21% of patients with bridging fibrosis achieved ≥ 1 stage improvement over the 2-year follow-up. Lower ELF scores at baseline, but not FibroSure/FibroTest, NAS, or severity of steatosis and lobular inflammation, were associated with improvement/regression.

- During a mean follow-up of 30.9 months, 19% patients with compensated cirrhosis experienced a liver-related event. A higher ELF score at baseline, but not a greater increase over time, was associated with an increased risk of events.
- The optimal cutoff for baseline ELF score to predict clinical events (balancing sensitivity and specificity) was 11.27. Baseline ELF score outperformed biopsy for the prediction of liver-related events.
- Cirrhosis regression was achieved in 8.6% of patients through the end of the study and associated with lower baseline ELF score but not changes in ELF scores.

Significance

- The data supports that reductions in fibrosis may offer the greatest clinical benefit in a high-risk population.
- As a quantitative measure of direct markers of fibrosis, the baseline ELF score or changes over time could be used for risk assessment or evaluation for improvement or disease progression. As a blood-based NIT, an ELF score can be readily obtained using a routine serum sample.
- This study revealed a relatively more-rapid rate of disease progression over a 2-year period, suggesting the natural history of NASH may be faster than previously described. Identification of at-risk patients using easily obtained quantitative markers of fibrosis such as the ELF score might aid more expedient identification and trigger intervention.

Conclusion

"Unlike baseline Ishak fibrosis stage, which had no prognostic value in either cohort, the ELF score at baseline and its change over time was associated with disease progression in patients with bridging fibrosis and cirrhosis."

Evaluation and Comparison of Six Noninvasive Tests for Prediction of Significant or Advanced Fibrosis in Nonalcoholic Fatty Liver Disease

Stauer K, et al. United European Gastroenterol J. 2019 Oct;7(8):1113-23.

Objective

Compare the performance of NITs for the assessment of fibrosis in NAFLD patients with and without NASH.

Methods

- NAFLD patients with biopsy were tested with the ELF Test, liver stiffness measurement (LSM) using VCTE (FibroScan), and FibroMeter V2G and V3G. NAFLD fibrosis scores (NFS) and FIB-4 were also calculated.
- NIT results were compared for diagnostic accuracy.
- An ELF score threshold of 9.8 was used for advanced fibrosis and a value of 9.1 for significant fibrosis (the 9.1 value was derived from the Youden index within the study cohort).
- Any effect by age, diabetes, or high BMI on NIT performance was evaluated.

Results

- Failure rate was an issue for VCTE but not for the blood tests. VCTE failed due to technical reasons in 7% of patients and produced unreliable values in 12%, compromising ~20% of results. The proportion of failed/unreliable measurements was independent of the probe used (failures occurred with both the M and XL probes).
- Values for ELF, LSM, and the V2 and V3 versions of FibroMeter increased with fibrosis stage. A high diagnostic accuracy was observed for both the ELF test and the two versions of FibroMeter in NAFLD patients with NASH and advanced fibrosis.
- ROC analysis showed a high diagnostic accuracy for both $\geq F2$ and $\geq F3$ using the ELF Test, FibroMeter, and LSM. Inferior performance was observed for both FIB-4 and NFS.
- While an increased likelihood of fibrosis was associated with age, no major differences in the AUROC for advanced fibrosis with the ELF Test or other NITs were observed when patients were split into groups of <60 years of age and >60 years.

- When patients were split by BMI (<30 and >30), no significant differences were seen with the blood tests. In contrast, a clear impact on LSM was observed. Accuracy decreased with increasing BMI using LSM.
- No impact by diabetes was observed for any of the NITs.

Conclusion

"In conclusion, fibrosis stage in NAFLD is best assessed by the ELF Test, FibroMeterV2G/V3G, and/or VCTE."

NIT	Cutoff	Sensitivity %	Specificity %
ELF Score	9.8	72	90
FMV2G	0.385	81	81
FMV3G	0.461	84	78
LSM	9.7	91	65
FIB-4 low	1.3	76	68
FIB-4 high	2.67	49	96

ELF Test: hyaluronic acid (HA), procollagen-III N-terminal peptide (PIIINP), and tissue inhibitor of metalloproteinase-1 (TIMP-1)

FMV2G: platelet count, prothrombin index, aspartate transaminase (AST), alpha-2-macroglobulin, HA, urea, age, and sex

FMV3G: platelet count, prothrombin index, aspartate transaminase (AST), alpha-2-macroglobulin, GGT, urea, age, and sex

LSM: Vibration-controlled transient elastography (VCTE). FibroScan 502 Touch

FIB-4: age, platelet count, AST, and ALT

NGM282 Improves Liver Fibrosis and Histology in 12 Weeks in Patients with Nonalcoholic Steatohepatitis

Harrison SA, et al. Hepatology. 2019 Feb 25. doi: 10.1002/hep.30590

Objective

Patients with biopsy-confirmed NASH were treated with an engineered fibroblast growth factor 19 analogue (NGM282) and assessed for histological improvement using biopsy, serum markers of fibrosis (ELF Test and Pro-C3), and other parameters.

Methods

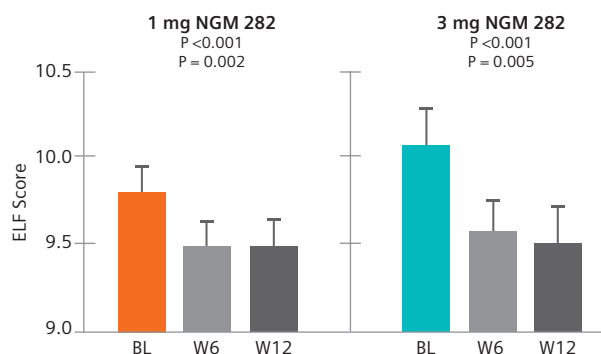
- NASH patients underwent biopsy within 3 months of screening and were treated with NGM282 (either 1 mg or 3 mg). A second biopsy was obtained at end of treatment (12 weeks).
- Histologic improvement was characterized by a decrease in NAS by at least 2 points without worsening of fibrosis or a decrease in fibrosis by at least one stage without worsening of NASH.
- Serum markers of fibrosis (ELF Test and Pro-C3) were collected at baseline and week 12. Imaging included MRI-PDFF and corrected T1 (cT1, a standardized, vendor-neutral imaging biomarker of hepatic fibroinflammatory disease).
- Treatment with NGM282 was associated with histological improvements, including a 2-point or greater improvement in NAS without worsening of fibrosis or improvement in fibrosis without worsening of NASH. A significant reduction in liver fat content was also observed with treatment.
- Significant reductions in both ELF score and Pro-C3 were reported for treatment responders.

Significance

- Despite the relatively short treatment period (12 weeks), significant improvement was seen with NGM282 treatment. Improvements were more pronounced in patients with baseline advanced fibrosis.
- Serum markers of fibrosis reflected biopsy findings and changes with therapy over the short term and could serve as an alternative to invasive biopsy.
- ELF testing or other direct markers of fibrosis may be useful to both identify candidates for therapy as well as aid in assessment of therapeutic response using a simple and easily collected blood sample.

Conclusion

"Levels of Pro-C3, ELF, and cT1 had greater reductions in patients with histological response compared with nonresponders."



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In the U.S., the ELF Test is indicated as a prognostic marker in conjunction with other laboratory findings and clinical assessments in patients with advanced fibrosis (F3 or F4) due to non-alcoholic steatohepatitis (NASH) to assess the likelihood of progression to cirrhosis and liver-related clinical events.

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