ELF Test

Revolutionizing Liver Health Assessment by Optimizing Care Pathway to Hepatology Clinics

Value Proposition Framework

siemens-healthineers.com

Not for distribution in the United States. The ELF Test may not be commercially available in all countries. Its future availability cannot be guaranteed and is subject to local regulatory requirements.

SIEMENS Healthineers

Importance of a value proposition to introduce and successfully implement new laboratory medicine tests

Although clinical laboratories represent a small percentage of total healthcare spending, they can impact overall care costs, including hospitalizations and pharmaceutical expenses. Clinical laboratories contribute value by leveraging real-time, actionable data for executive decisions, care workflow, provider engagement, and patient treatment choices. St John et al., in their article "Developing a value proposition for high-sensitivity troponin testing",[1] emphasize several important topics.

First, the authors emphasize the current challenge of transforming healthcare management from an activity-based to a value-based approach, extending this paradigm shift to laboratory medicine services. For the authors, the trend for clinical laboratories over the last years has been to concentrate on expanding their test menu while reducing costs. Consequently, the authors point out that this has resulted in the introduction of new tests, often without a robust evidence basis. Predictably, this has led to significant variability in test adoption, even in the presence of established guidelines—there is evidence of both underutilization and overutilization of tests. They also underline that, due to the lack of effective communication between the clinical laboratory and other healthcare professionals, the uptake of some new tests can be sluggish.

The authors note that these issues can be addressed—at least for certain tests—by the development of value propositions, explaining how those tests can influence clinical pathways. Such value propositions will not only help clinical laboratories to demonstrate their high-value contribution to care pathways but also help optimize clinical benefits and process efficiencies, and improve patient outcomes, while also garnering appreciation from all stakeholders.[1,2]

The ELF value proposition framework

In their article, St John et al. specifically evaluate a value proposition framework in the context of adopting high-sensitivity troponin assays for managing patients with suspected acute coronary syndrome. In this document, we adopted the authors' methodology to develop a value proposition framework in the context of using the ELF Test to detect liver fibrosis in MASLD patients. We hope this value proposition framework for ELF will achieve the three objectives described by the authors: to support the presentation of business cases for this test, to guide its implementation, and to validate its adoption.

1. What is the unmet clinical need that the ELF Test can solve?

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as nonalcoholic fatty liver disease (NAFLD), was estimated to affect, with growing incidence, approximately 25 percent of the global population in 2016 and 30 percent in 2019, making it the most common cause of chronic liver disease and the second indication for liver transplants in the U.S.[3-5] (See more information on population in section 2). In addition, a smaller group of individuals can develop the progressive form of the disease called Metabolic dysfunction-associated steatohepatitis (MASH)—formerly known as NASH—which is one of the leading causes of cirrhosis in adults in the United States.[6]

Despite its prevalence, MASLD is a silent and largely undiagnosed condition, with less than 5 percent of individuals being aware of their condition[7] and with many cases of chronic liver disease detected only at an end-stage when the patients are admitted via the emergency department,[8] raising concerns among hepatologists.

Multiple studies have indicated the central role of fibrosis as the causative factor for MASLD progression.[9] Liver biopsy, the historical gold standard diagnostic method, is not conducive to the large-scale screening required for patients considered at risk, prompting the exploration of non-invasive alternatives.[10] Sequential use of non-invasive tests, such as serum biomarkers and vibration-controlled transient elastography (VCTE) to measure liver stiffness, has been proposed as a viable solution for screening and diagnosing patients at risk of advanced liver fibrosis. (See more information on tests and procedures to assess liver fibrosis in Table 1).

The unmet clinical need is primarily to efficiently detect in non-hepatology settings patients with advanced liver fibrosis who are at high-risk of developing clinical complications. However, VCTE is not widely available in those non-hepatology settings[11] and may not be scalable, given the size of the target population. This situation highlights the pressing need for easily accessible and widely available noninvasive liver fibrosis tests to address this unmet healthcare demand.

2. What patient population will benefit from the ELF Test?

In their recent Clinical Practice Guidelines on the management of MASLD in Europe, EASL-EASD-EASO propose to screen for MASLD with liver fibrosis in individuals with type 2 diabetes (T2D) or abdominal obesity and at least one additional metabolic risk factor(s) or abnormal liver function tests.[12]

For the American Clinical Practice Guidelines from AACE and AASLD in the United States,[13,14] the populations being considered for the intervention should also be high-risk people (both males and females), in particular those with T2D, obesity and/or 2 cardiometabolic risk factors, presence of hepatic steatosis on imaging or elevated serum aminotransaminases.

Most of those patients are seen in non-hepatology settings such as primary care (PCPs), endocrinology (incl. diabetes clinics), obesity medicine, and gastroenterology practices.

3. What is the ELF Test?

The Enhanced Liver Fibrosis (ELF) test is a blood test that utilizes three direct markers of liver fibrosis: hyaluronic acid (HA), amino-terminal propeptide of type III procollagen (PIIINP), and tissue inhibitor of metalloproteinase-1 (TIMP-1). The utility of the ELF Test is demonstrated for the assessment of severity of liver fibrosis in patients with signs, symptoms, or risk factors of chronic liver disease.[15,16]

How to interpret the ELF score?

An algorithm combines the results of the three biomarkers and generates a unitless ELF score.

- ELF ≥11.3 has high specificity for identifying cirrhosis (F4) as well as for predicting liver related events; a recent study shows that ELF ≥11.3 is associated with 5X greater risk of experiencing a liver related event within a year.[14,17-20]
- ELF ≥9.8 has high sensitivity for detecting advanced fibrosis with good performance (AUROC ≥0.8) for diagnosis of advanced fibrosis (≥F3); study data shows that patients with ELF scores ≥9.8 had elevated risk of a liver-related event compared to <9.8.[18,21-27]
- Data indicates that an ELF cutoff of ≥9.00 performs well in MASLD/MASH populations for the detection of patients with significant fibrosis (>F2).[17, 21-22]

Finally, in their meta-analysis from 2023, Hinkson et al.[28] studied the performance of ELF for different stages of fibrosis and cirrhosis and reported the following AUROCs: significant fibrosis (0.811), advanced fibrosis (0.812) and cirrhosis (0.810).

4. What is the ELF Test's utility?

Outside the United States, the ELF Test and score are CE marked for the assessment of liver fibrosis severity in patients with signs, symptoms, or risk factors of chronic liver disease to support fibrosis staging or to prognosticate the likelihood of progression to cirrhosis and liver-related clinical events.

In the United States, ELF received *De Novo* marketing authorization from the FDA to aid prognostic evaluation of disease progression (to cirrhosis and liver-related clinical events) in NASH (MASH) patients with advanced liver fibrosis.

It should be also noted that the ELF Test is not intended to monitor for MASH treatments but has been included as a monitoring biomarker in many clinical trials investigating new drugs for MASH treatments.[29-35]

How to use the ELF Test?

International Clinical Practice Guidelines recommend using sequential algorithms with non-invasive tests to triage patients at risk of advanced fibrosis and to limit the number of liver biopsies.[12-14] The first-line test recommended by those guidelines is the Fibrosis-4 (FIB-4) Index, a simple, inexpensive liver fibrosis score allowing for patient triage and to exclude advanced fibrosis in non-hepatology settings (see more information in Table 1). However, FIB-4 has some limitations (lower performances to detect fibrosis in an indeterminate range, in elderlies, and in individuals with T2D), requiring a second-line test to be performed for many patients.[36] If VCTE is the only "second-line" noninvasive test available, a scarcity of essential qualified staff—coupled with restricted availability of equipment for measuring VCTE—may impede the widespread adoption of these sequential algorithms.

McPherson et al. reported recently identical AUC for ELF and VCTE (0.86) and a good concordance between six hepatologists who had been asked to stage MASLD patients for advanced fibrosis (F0-2 vs F3-4) with noninvasive blood tests (FIB-4, ELF) and VCTE.[37]

In addition, a two-step algorithm consisting of Fibrosis-4 (FIB-4) and ELF (if required in the indeterminate zone) led to a substantial improvement in the detection of cases of advanced fibrosis and cirrhosis and a significant reduction of unnecessary referrals from primary care to secondary care.[38] So, major international clinical practice guidelines[12-14] now recommend employing VCTE or ELF Test as a second-line test for FIB-4 indeterminate results (1.3–2.67).

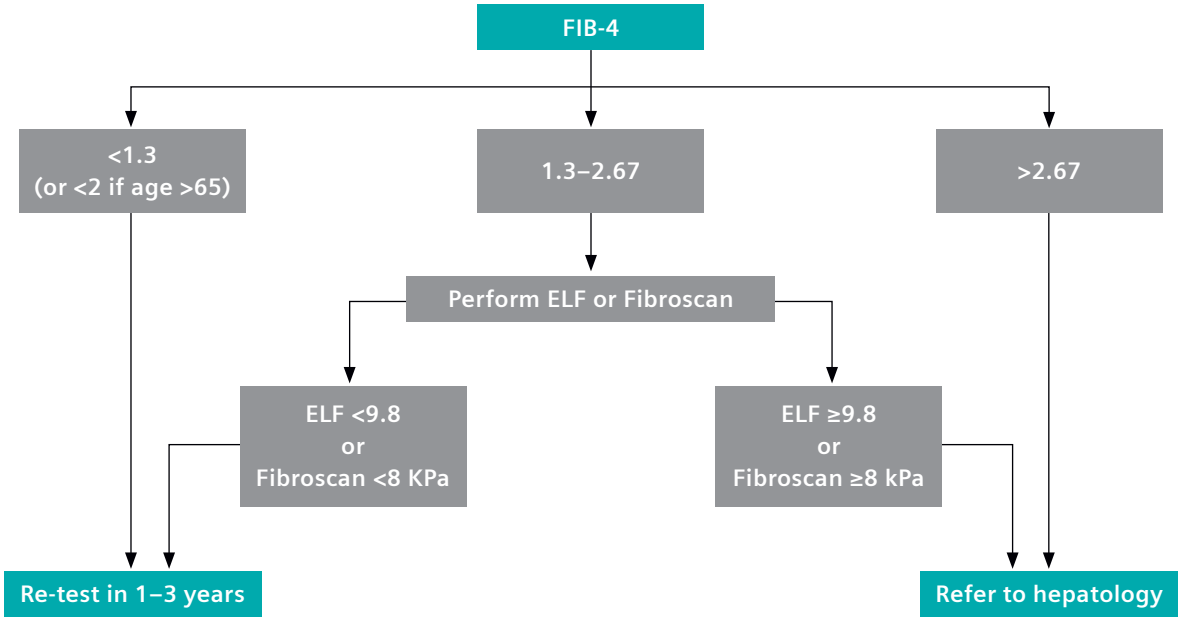


Figure 1. Example of a recommended use of noninvasive liver fibrosis tests in an algorithm for MASLD patients in non-hepatology settings—adapted from Zoncapè M. et al.[39]

5. What outcomes can be expected of a sequential algorithm including the ELF Test?*

The **clinical outcomes** of a sequential algorithm, combining FIB-4 as the first-line test and **ELF or VCTE** as the second-line tests, are:	1. **Improved diagnosis of advanced liver fibrosis** in patients with MASLD/MASH, with fewer liver biopsies needed and consequently fewer risks of side effects for patients. 2. **Improved stratification of patients at risk** of progressing to cirrhosis and liver-related events. 3. **Possibility to halt or reverse disease progression,** primarily through lifestyle changes but also recently through therapeutic intervention with Rezdiffra (Resmetirom), the first medication approved by the FDA in the United States for the treatment of patients with MASH with moderate to advanced liver fibrosis.[40]
The specific **operational outcomes** of a sequential algorithm that integrate FIB-4 as the first-line test and **ELF (not VCTE)** as the second-line test are:	1. **A decrease in the volume of referrals** for VCTE measurements to the limited number of hepatology departments which are already facing a shortage of specialists to care for at-risk patients and are already overburdened.[41] 2. **Shorter waiting lists for patients,** due to fewer unnecessary referrals, allow hepatologists to promptly attend to patients requiring specialized care. 3. **Widespread availability** of phlebotomy blood collection services provides ELF Testing at the scale required to address the population at risk. 4. **Result consistency** across the patient population regardless of body mass index (BMI), leading to less failure reported vs. imaging modalities.[42] 5. **Improved risk assessment** of patients and **improved longitudinal assessment of disease progression** due to ELF's good analytical performance and low imprecision as presented in the ELF Test instructions for use (IFU).[21] The ELF Test demonstrates good precision with coefficients of variation (CV) for repeatability and within-lab precision less than or equal to 5.4 percent and 8.5 percent respectively across the three assays. For the ELF score, coefficients of variation were less than or equal to 0.6 percent, less than or equal to 1.3 percent for repeatability and within-lab precision respectively, and less than or equal to 1.1 percent for reproducibility. In comparison, a high variability of VCTE measurements has been reported in the literature—at least 20 percent—as reported in multiple studies.[43-46]
The **economic outcomes** of a sequential algorithm that integrates FIB-4 as the first-line test and **ELF (not VCTE)** as the second-line test are:	1. **Short-term direct cost savings** due to the reduced number of unnecessary referrals of patients to hepatology clinics and additional exams in this setting, including VCTE.[47] 2. **Additional indirect cost savings** through clinical pathway efficiency gains, where a portion of the at-risk patients may be kept in primary care for management of their non hepatic conditions.

**The outcomes described herein are based on results that were achieved in a unique care setting. Because there is no typical hospital or laboratory and many variables exist (e.g., hospital size, sample mix, case mix, level of IT, and/or automation adoption), there can be no guarantee that other test users will achieve the same results.*

6. Where is the ELT test performed?

The Enhanced Liver Fibrosis (ELF) test is measured in laboratory settings on the Atellica IM Analyzer, Atellica CI Analyzer, or ADVIA Centaur XP and XPT systems and is therefore widely available. The reagent formulations used on the Atellica IM Analyzer are the same as those used on the ADVIA Centaur XP and XPT systems. Expected values were established using the ADVIA Centaur XP system and confirmed by assay comparison with Atellica IM Analyzer.[21]

An automatic reflex ELF Test can be triggered within the laboratory information management system using the same serum sample when a patient's FIB-4 value is in the range of 1.3–2.67, avoiding the need to draw an additional blood sample for the same patient.

7. What is the part of the care pathway where the ELF Test will be used?

As recommended in CPGs for MASLD/MASH, the ELF Test can be used as a diagnostic and prognostic marker in sequential algorithms as second line test after FIB-4, when FIB-4 results are in the indeterminate zone (in the range of 1.3–2.67).

8. What type of evidence is available?

See references in sections 3–5. The table below presents a selection of evidence describing the outcomes of a two-step algorithm with fibrosis-4 (FIB-4) and ELF.

Clinical evidence	• In the UK, a sequential pathway with FIB-4 and ELF (if required) improved the detection of cases of advanced fibrosis five-fold and cirrhosis three-fold.[38]
Process evidence	• Srivastava et al.[38] reported in 2019 that a pathway with FIB-4 followed by ELF (if required) reduced unnecessary referrals to hepatology clinics by 80 percent compared to FIB-4 alone.
Economic evidence	• In 2019, Srivastava et al.[47] published a probabilistic decisional model looking at a cohort of 1000 NAFLD patients over one year comparing five different scenarios from a healthcare-payer perspective: 1. Standard of care 2. FIB-4 followed by ELF for indeterminate FIB-4 results 3. FIB-4 followed by VCTE for indeterminate FIB-4 results 4. ELF alone,* and 5. VCTE alone. They concluded the use of noninvasive tests in primary care is cost efficient and reported the combination of FIB-4 and ELF provided the most cost savings. • In 2023, Kjaergraad et al. reported that a pathway with FIB-4 followed by ELF vs. FIB-4 alone would generate about 47 percent savings due to the reduction of unnecessary referrals for VCTE measurements.[48] • Finally, Z. Younossi et al. reported that, in the UK, a pathway combining FIB4 and ELF in patients with MASLD would be cost saving vs. other scenarios: 1. vs. standard of care; 2. vs. FIB4 alone; or 3. vs. FIB4 followed by VCTE.[49]

**Note from the editor: ELF is not generally used as a standalone test, as it is often used in conjunction with other tests and clinical assessments to provide a comprehensive evaluation of liver health.*

9. What are the benefits and potential disadvantages of the ELF Test for each stakeholder involved in the care pathway?

Compared to VCTE, the ELF Test presents current benefits/disadvantages for each stakeholder.

	ELF Advantages	ELF Disadvantages
For the patient	• Improved satisfaction of patients who don't have to wait for an appointment in a hepatology clinic for VCTE measurements (with potentially longer wait times). ELF requires only a simple blood draw, taking just a few seconds, compared to the 15-minute process for VCTE, which includes five minutes on the examination bed before the procedure and 10 minutes for measuring liver stiffness.[50] • ELF can be widely accessible and available. Patients don't have to travel to a hepatology clinic. • ELF is a simple blood test. No need to fast before the blood sample collection. Patients must be fasting for at least three hours before having an VCTE examination.[51-53] • Possibility to include ELF in a panel of blood tests as part of a routine or annual check-up and to set up an automatic reflex testing of ELF after FIB-4 from the same blood sample, limiting blood draws for the patients	• The results of the ELF Test are not immediately available after the blood sample collection (vs. five minutes after examination by VCTE). • Possibility of rare and minor side effects similar to those that can occur after any blood draw vs. absence of side effects with VCTE.
For the clinical laboratory	• The opportunity to demonstrate the vital role and value of the clinical laboratory to have direct impact on MASLD patient care pathway, without a need for additional resources—it's noteworthy that conducting an ELF Test doesn't necessitate additional laboratory equipment or specialized personnel. • The opportunity to improve patients' outcomes and generate operational and financial benefits for the healthcare system.	• Need to allocate resources and time to educate and inform key stakeholders to ensure a successful implementation and use of the FIB-4/ELF Testing pathway.
For primary care (primary care physicians) and secondary care (endocrinologists)	• Possibility to identify patients at high risk of hepatic and extrahepatic adverse outcomes that were not detected before without having to refer all of them immediately to hepatology clinics for VCTE measurement. • Possibility to include the ELF Test in the panel of blood tests done for annual checkup of T2D patients.	• Managing the results of a new test like ELF will further increase their already substantial workload. • Need to get educated on MASLD/MASH disease and on the management of patients.
For tertiary care (hepatologists)	• Reduction of potentially too many referrals from primary and secondary care settings of patients having only minor liver fibrosis test abnormalities, freeing their resources and time for better use of VCTE equipment. • Capability of managing a larger number of at-risk patients, without being limited by the access and availability of VCTE equipment.	• Hepatologists may perceive ELF as a risk, leading to fewer VCTE measurements and, consequently, a reduction in their revenues.
For hospital/ healthcare provider	• Financial savings with the reduction of potentially unnecessary referrals and VTCE measurements at the hepatology clinic. • Possibility to implement an efficient MASLD pathway without the need to invest in the purchasing and maintenance of dedicated VCTE equipment in non-hepatology settings (endocrinology, primary care). • Can contribute to more efficient use of limited workforce (such as nurses). No need to train operators for VCTE in non-hepatology settings. (Operators shall be duly trained and certified to perform VCTE measurements).[50]	• Costs of laboratory reagents (ELF Test) may be perceived as an additional expenditure if not seen in the context of the patient care pathway.

10. What are the potential risks that may be associated with the introduction of the ELF Test? What are the mitigation strategies?

The slow adoption by prescribers of the ELF Test as a non-invasive, second-line test of the sequential pathway could lead to many patients having solely a FIB-4 result.

To mitigate this risk:

1. The clinical laboratory has the technical capability to implement a reflex-testing procedure, which automatically triggers an ELF Test for patients with an indeterminate FIB-4 result, thereby streamlining the ordering process.
2. Ensure accessibility of ELF Test to clinicians through the healthcare information system, allowing easy electronic requests to the clinical laboratory.
3. Organize educational meetings during the test-implementation phase where the laboratory staff can present and explain the new care pathway to clinicians.
4. Provide a short explanation in laboratory reports for easier interpretation of ELF Test results and guidance on patient management.

11. Resource/activity contributed by each of the service lines involved in the care pathway

Two situations can be anticipated:

- No MASLD care pathway is in place.

  The implementation of a sequential pathway will, therefore, introduce major changes for physicians seeing patients in non-hepatology settings and for the hepatologists to whom these patients are referred. The clinical laboratory will also have to implement two new tests, FIB-4 and ELF, in a sequential algorithm.

- FIB-4 results are already provided by the laboratory.

  The addition of an ELF Test will help to better document and to streamline referrals of patients to the hepatology clinics. This should result in more referrals of advanced cases and fewer futile referral cases.[38,48]

12. Reimbursement required for delivering the care pathway with and without (before and after) the test intervention

There may be extra costs associated with the addition of the ELF Test to services offered by the clinical laboratory. However, economic evaluations have demonstrated that the introduction of a sequential FIB-4/ELF pathway results in direct and short-term cost savings from the payer and society perspectives.[47,49] If relevant, the payment system for clinical laboratories should therefore be amended to reflect the broader societal impact of FIB-4/ELF and support the adoption of this pathway by covering the direct cost of the test from the provider's perspective.

13. Implementation plan including the metrics for monitoring appropriate adoption

1. Establishing the sequential algorithm combining FIB-4 and ELF Tests with appropriate cut-off values for the rule out and rule in of advanced fibrosis and cirrhosis.
2. Implementing and communicating the availability of the new care pathway outside and within the laboratory through educational activities.
3. Optimizing the patient pathway upstream in consultations where at-risk patients are seen (primary care, endocrine, obesity medicine, and gastroenterology practices) to ensure they are tested and referred according to clinical guidance.
4. Measuring downstream outcomes in hepatology clinics (number of referrals of at-risk patients and detected cases).
5. Audit of the complete care pathway at appropriate intervals.

Element of care pathway	Outcome measure (before vs. after implementation)
Clinical laboratory	• Number of FIB-4 tests/month • Number of ELF Tests/month with FIB-4 in indeterminate values and below or above ELF clinical thresholds (i.e.: >9.0; >9.8; >11.3) • Number of ELF Tests/month without FIB-4 results • Median ELF turnaround time
Clinical application	• Number of ELF Tests requested for MASLD/ MASH patients • Number of ELF Tests requested for other patients and conditions (e.g., Viral hepatitis, Alcohol Associated Liver Disease, PSC, PBC)
Change of practice	• Number of ELF Tests requested by non-hepatology settings (including diabetes clinics) • Number of patients referred from non-hepatology settings to hepatologists for further investigation • Number of consultations in nutrition clinic (to receive guidance for lifestyle changes) • Number of ELF Tests requested by hepatologists • Number of biopsies in hepatology clinic • Recruitment of patients into clinical trials
Clinical outcomes	Number of advanced fibrosis and cirrhosis cases detected
Economic outcomes	• Number of VCTE measurements in hepatology clinic • Costs saved by introducing the ELF Test as a second line test (i.e., patients who would have been referred if FIB-4 >1.3)
Process related outcomes	Average wait time for VCTE measurements at hepatology clinic before and after implementation of the sequential pathway

Table 1. Tests and procedures to assess liver fibrosis

FIB-4

FIB-4 is a blood-based test originally developed to detect liver fibrosis in patients with Hepatitis C and HIV and later in patients with MASLD/MASH. It can automatically be calculated from the values of patient age, platelet count, aspartate aminotransferase (AST), and alanine aminotransferase (ALT).

$$\text{FIB-4 index} = \frac{(\text{age} \times \text{AST})}{\text{platelet count} \times \sqrt{\text{ALT}}}$$

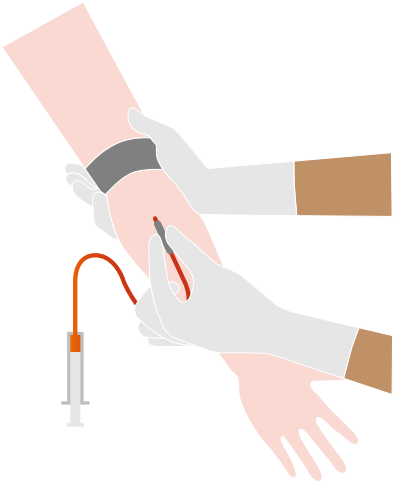
Age (yrs), ALT (U/L), AST (U/L) and platelet count (10^9/L)

FIB-4 <1.3: low risk for advanced liver fibrosis
1.3 ≤FIB-4 <2.67: indeterminate risk for advanced liver fibrosis
FIB-4 ≥2.67: high risk for advanced liver fibrosis

FIB-4 is a first-line and inexpensive liver fibrosis score, widely available in non-hepatology settings to help rule out with high sensitivity people who do not have advanced fibrosis (negative predictive value of 90–95 percent). When FIB-4 is above 2.67, FIB-4 can help to rule in advanced liver fibrosis (positive predictive value around 80 percent). Recent guidelines[12-14] recommend using a second NIT (VCTE or ELF) as a second-line test if FIB-4 is above 1.3 and below 2.67.

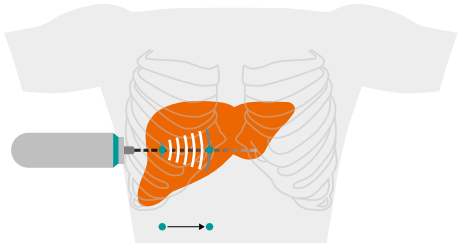
ELF

A blood sample was taken. Three important serum markers can be detected with an automated analyzer and the risk of disease progression can be derived from these.



The ELF score is calculated using the following equation:
ELF score = 2.278 + 0.851 ln(C_{HA}) + 0.751 ln(C_{PIIINP}) + 0.394 ln($C_{TIMP\text{-}1}$).
Concentrations (C) of each of the constituents are in ng/mL. The expected values of the ELF Test are reported in the test instructions for use[21] and were established on the ADVIA Centaur XP system with 594 samples from U.S. blood donors of known gender, ethnicity, and age (mean of 7.72, median of 7.74, fifth percentile of 6.51, and 95th percentile of 8.90). A published study conducted using 183 apparently healthy East Asian female and male subjects reported the following ELF scores: mean of 7.75, median of 7.82, fifth percentile of 5.95, and 95th percentile of 8.73.[54] The analytical performance of the ELF analytes and score on the Atellica IM Analyzer have been fully documented in the ELF instructions for use[21] and by Palladino et al.[55]

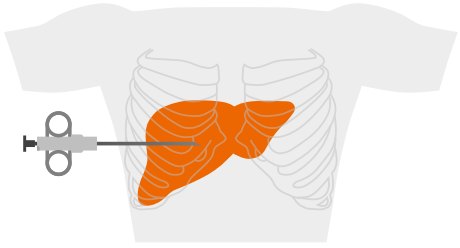
Vibration-Controlled Transient Elastography



A probe emits a mechanical pulse toward the liver. An integrated ultrasound transducer measures the velocity of the pulse wave between two points. The less elastic the liver tissue, the faster the pulse propagates through the liver.

While vibration-controlled transient elastography (VCTE) is a valuable tool in assessing liver health, it presents several limitations. False positives may occur in cases of acute hepatitis, inflammation, non-fasting conditions, exercise, hepatic venous congestion, inflammation or infiltration, excessive alcohol consumption, cholestasis, steatosis, and portal vein thrombosis. Furthermore, its failure rates surpass those of serum tests due to factors such as operator inexperience, narrow intercostal space, body habitus, and the presence of ascites.[57] To ensure the reliability of findings, it is recommended to conduct a minimum of 10 measurements. Proper patient positioning is equally crucial for obtaining accurate readings.[58]

Liver biopsy



A tissue sample is taken from the liver with a canula. The sample is then examined for scar tissue under a microscope.

Liver biopsy presents inherent limitations including its invasiveness and sampling variability, where the obtained specimen represents only a minute fraction (approximately 1/50,000) of the entire liver. Nonetheless, achieving consensus among readers in interpreting biopsy findings poses a significant challenge.[56] Other significant limitations concerning risk, cost, and resource allocation exist.[14]

References:

1. St John A, Cullen L, Jülicher P, Price CP. Developing a value proposition for high-sensitivity troponin testing. Clin Chim Acta. 2018 Feb;477:154-159.
2. Price CP, John AS, Christenson R, Scharnhorst V, Oellerich M, Jones P, Morris HA. Leveraging the real value of laboratory medicine with the value proposition. Clin Chim Acta. 2016 Nov 1;462:183-186.
3. Younossi ZM, Golabi P, Paik JM, et al. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatology (Baltimore, Md) 2023;77(4):1335–1347.
4. Quek J, Chan KE, Wong ZY, et al. Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2023;8(1):20–30.
5. Le MH, Le DM, Baez TC, et al. Global incidence of non-alcoholic fatty liver disease: a systematic review and meta-analysis of 63 studies and 1,201, 807 persons. J Hepatol 2023;79(2):287–295.
6. Younossi ZM, Stepanova M, Afendy M, et al. Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. Clin Gastroenterol Hepatol 2011; 9:524-530.
7. Alqahtani SA, Paik JM, Biswas R, Arshad T, Henry L, Younossi ZM. Poor awareness of liver disease among adults with NAFLD in the United States. Hepatol Commun. 2021;5(11):1833e1847.
8. Williams R, Aspinall R, Bellis M, et al. Addressing liver disease in the UK: a blueprint for attaining excellence in health care and reducing premature mortality from lifestyle issues of excess consumption of alcohol, obesity, and viral hepatitis. Lancet. 2014;384(9958):1953–1997.
9. Taylor RS et al. Association between Fibrosis Stage and Outcomes of Patients with NAFLD: A systematic Review and Analysis. Gastroenterology 2020;158:1611-1625
10. Castera L, Non-invasive tests for liver fibrosis in NAFLD: Creating pathways between primary healthcare and liver clinics Liver International. 2020;40(Suppl. 1):77–81
11. Tsochatzis EA. Screening for liver fibrosis - sequential non-invasive testing works best. J Hepatol. 2023 Aug;79(2):263-265.
12. EASL–EASD–EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD) Journal of Hepatology, July 2024. Available from https://doi.org/10.1016/j.jhep.2024.04.031
13. American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings. Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD). Endocrine Practice 28 (2022) 528e562. Available from https://doi.org/10.1016/j.eprac.2022.03.010
14. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease Hepatology. 2023 May 01; 77(5): 1797–1835.
15. Rosenberg W, Voelker M, Thiel R, et al. Serum markers detect the presence of liver fibrosis: A cohort study. Gastroenterology. 2004 Dec;127(6):1704–1713.
16. Patel PJ, Connoley D, Rhodes F, et al. A review of the clinical utility of the Enhanced Liver Fibrosis test in multiple aetiologies of chronic liver disease. Ann Clin Biochem. 2020;57(1):36–43
17. Younossi ZM, et al. The combination of the enhanced liver fibrosis and FIB-4 scores to determine significant fibrosis in patients with nonalcoholic fatty liver disease; Aliment Pharmacol Ther. 2023; DOI: 10.1111/apt.17472
18. Anstee QM, et al. Hepatology. 2019 Nov;70(5):1521-1530
19. Seko Y, et al. Diagnostic accuracy of enhanced liver fibrosis test for nonalcoholic steatohepatitis-related fibrosis: Multicenter study Hep Res. Hepatol Res. 2023 Apr;53(4):312-321
20. Sanyal AJ, Harrison SA, Ratziu V et al (2019) The natural history of advanced fibrosis due to nonalcoholic steatohepatitis: data From the Simtuzumab Trials. Hepatology 70:1913–1927. https://doi.org/10.1002/hep.30664
21. Siemens Healthineers ELF (Atellica IM) OUS IFU 11642660_EN Rev. 02, 2023-01
22. Staufer K, et al. Evaluation and comparison of six noninvasive tests for prediction of significant or advanced fibrosis in nonalcoholic fatty liver disease. Eur Gastro J. 2019;7(8):1113-1123.
23. Younossi ZM, et al. Performance of the Enhanced Liver Fibrosis Test to Estimate Advanced Fibrosis Among Patients with Nonalcoholic Fatty Liver Disease JAMA Netw Open. 2021;4:e2123923
24. Vali Y, Lee J, Boursier J, Petta S, Wonders K, Tiniakos D, et al. Biomarkers for staging fibrosis and non-alcoholic steatohepatitis in non-alcoholic fatty liver disease (the LITMUS project): a comparative diagnostic accuracy study. Lancet Gastroenterol Hepatol 2023;8:714–25.
25. Miele L, De Michele T, Marrone G, Isgr`o MA, Basile U, Cefalo C, et al. Enhanced liver fibrosis test as a reliable tool for assessing fibrosis in nonalcoholic fatty liver disease in a clinical setting. Int J Biol Markers 2017;32:e397–402.
26. Vali Y, Lee J, Boursier J, Spijker R, Löffler J, Verheij J, Brosnan MJ, Böcskei Z, Anstee QM, Bossuyt PM, Zafarmand MH; LITMUS systematic review team(†). Enhanced liver fibrosis test for the non-invasive diagnosis of fibrosis in patients with NAFLD: A systematic review and meta-analysis. J Hepatol. 2020 Aug;73(2):252-262.
27. Day J, Patel P, Parkes J, Rosengerg W. Derivation and performance of standardized enhanced liver fibrosis (ELF) test thresholds for the detection and prognosis of liver fibrosis. J Appl Lab Med 2019;3:815–26.
28. Hinkson et al. Meta-analysis: Enhanced liver fibrosis test to identify hepatic fibrosis in chronic liver diseases. AP&T Alimentary Pharmacology & Therapeutics, DOI: 10.1111/apt.17385
29. Rinella M, Dufour J-F, Anstee QM et al (2021) Non-invasive evaluation of response to obeticholic acid in patients with NASH: results from the REGENERATE study. J Hepatol 76:536–548. Available from https://doi.org/10.1016/j.jhep.2021.10.029
30. Gawrieh S, Harlow KE, Pike F et al (2021) Relationship of enhanced liver fibrosis score with pediatric nonalcoholic fatty liver disease histology and response to vitamin E or metformin. J Pediatrics 239:161-167.e5.

31. Newsome PN, Buchholtz K, Cusi K et al (2020) A placebo controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. New Engl J Med 384:1113–1124.
32. Loomba R, Noureddin M, Kowdley KV et al. Combination Therapies Including Cilofexor and Firsocostat for Bridging Fibrosis and Cirrhosis Attributable to NASH. Hepatology. 2021 Feb;73(2):625-643.
33. Harrison SA, Wong VW-S, Okanoue T et al (2020) Selonsertib for patients with bridging fibrosis or compensated cirrhosis due to NASH: results from randomized phase III STELLAR trials. J Hepatol 73:26–39.
34. Harrison SA, Rossi SJ, Paredes AH et al (2020) NGM282 improves liver fibrosis and histology in 12 weeks in patients with nonalcoholic steatohepatitis. Hepatology 71:1198–1212.
35. Harrison SA, et al. A randomized, double-blind, placebo-controlled phase IIa trial of efruxifermin for patients with compensated NASH cirrhosis. JHEP Rep. 2022 Aug 23;5(1):100563.
36. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. J Hepatol 2021;75(3):659–689.
37. McPherson S, Dyson JK, Jopson L, Masson S, Patel P, Anstee QM. How effective are experienced hepatologists at staging fibrosis using non-invasive fibrosis tests in patients with metabolic dysfunction-associated steatotic liver disease? Aliment Pharmacol Ther. 2024 Jul;60(2):267-273.
38. Srivastava A, Gailer R, Tanwar S, et al. Prospective evaluation of a primary care referral pathway for patients with non-alcoholic fatty liver disease. J Hepatol. 2019;71(2):371– 378.
39. Zoncapè M, Liguori A, Tsochatzis EA. Non-invasive testing and risk-stratification in patients with MASLD. Eur J Intern Med. 2024 Apr;122:11-19.
40. Madrigal Pharmaceuticals. Madrigal Pharmaceuticals announces FDA approval of Rezdiffra™ (resmetirom) for the treatment of patients with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver librosis. Available from: https://ir.madrigalpharma.com/news-releases/news-release-details/madrigal-pharmaceuticals-announces-fda-approval-rezdiffratm [Accessed 24 Nov 18].
41. Halegoua-De Marzio DL, Herrine SK. Training the next generation of hepatologist: What will they need to know? Clin Liver Dis (Hoboken). 2015 Jun 24;5(6):129-131.
42. Berger A, et al. Liver Stiffness Measurement With FibroScan: Use the Right Probe in the Right Conditions! Clin Transl Gastroenterol. 2019 Apr;10(4):e00023.
43. Nascimbeni F, et al. Significant variations in elastometry measurements made within short-term in patients with chronic liver diseases. Clin Gastroenterol Hepatol. 2015 Apr;13(4):763-71. e761-766.
44. Bradley CR, Cox EF, Palaniyappan N, Aithal GP, Francis ST, Guha IN. Variability of noninvasive MRI and biological markers in compensated cirrhosis: insights for assessing disease progression. Eur Radiol Exp. 2022 Oct 24;6(1):52.
45. Chow JC, et al. Repeating measurements by transient elastography in non-alcoholic fatty liver disease patients with high liver stiffness. J Gastroenterol Hepatol. 2019 Jan;34(1):241-248.
46. Anstee et al. Longitudinal variability of non-invasive tests of fibrosis: Implications for treatment response monitoring in patients with NASH J Hepatol. 2021;75(Suppl 2):S575-S576
47. A. Srivastava et al. Cost-comparison analysis of FIB-4, ELF and fibroscan in community pathways for non-alcoholic fatty liver disease. BMC Gastroenterology (2019) 19:122.
48. Kjaergaard M et al. Using the ELF Test, FIB-4 and NAFLD fibrosis score to screen the population for liver disease. Journal of Hepatology 2023. vol. 79 j 277–286
49. Z. Younossi et al. Health economics of the enhanced liver fibrosis test in the detection of advanced liver fibrosis in patients with non-alcoholic fatty liver disease in the UK. ILC 2023; poster SAT 116
50. Echosens. FibroScan® procedure for users. Available from https://www.echosens.com/fibroscanprocedure/ [accessed 24 Nov 18]
51. Mederacke I, Wursthorn K, Kirschner J, Rifai K, Manns MP, Wedemeyer H, Bahr MJ. Food intake increases liver stiffness in patients with chronic or resolved hepatitis C virus infection. Liver International 2009;29:1500-1506.
52. Arena U, Lupsor Platon M, Stasi C, Moscarella S, Assarat A, Bedogni G, Piazzolla V, et al. Liver stiffness is influenced by a standardized meal in patients with chronic hepatitis C virus at different stages of fibrotic evolution. Hepatology 2013;58:65-72.
53. Berzigotti A, De Gottardi A, Vukotic R, Siramolpiwat S, Abraldes JG, Garcia-Pagan JC, Bosch J. Effect of meal ingestion on liver stiffness in patients with cirrhosis and portal hypertension. PLoS One 2013;8:e58742.
54. Yoo EJ, Kim BK, Park JY, et al. Normal enhanced liver fibrosis (ELF) values in apparently healthy subjects undergoing a health check-up and in living liver donors in South Korea. Liver Int. 2013 May;33(5):706.
55. Palladino et al. Analytical performance of the Enhanced Liver Fibrosis (ELF) Test on the Atellica IM Analyzer Clin Chim Acta. 2023 Aug 1:548:117461.
56. Dufour J, Anstee QM, Bugianesi E, et al. Current therapies and new developments in NASH Gut 2022;71:2123-2134.
57. Patel K, Sebastiani G. Limitations of non-invasive tests for assessment of liver fibrosis. JHEP Reports, (2020). 2(2), 100067.
58. Kataria S., Juneja D, Singh O. Transient elastography (FibroScan) in critical care: Applications and limitations. World Journal of Meta-Analysis, (2023). 11(7), 340-350.

Notes

Notes

At Siemens Healthineers, we pioneer breakthroughs in healthcare. For everyone. Everywhere. Sustainably. As a leader in medical technology, we want to advance a world in which breakthroughs in healthcare create new possibilities with a minimal impact on our planet. By consistently bringing innovations to the market, we enable healthcare professionals to innovate personalized care, achieve operational excellence, and transform the system of care.

Our portfolio, spanning in vitro and in vivo diagnostics to image-guided therapy and cancer care, is crucial for clinical decision-making and treatment pathways. With the unique combination of our strengths in patient twinning,* precision therapy, as well as digital, data, and artificial intelligence (AI), we are well positioned to take on the greatest challenges in healthcare. We will continue to build on these strengths to help overcome the world's most threatening diseases, enable efficient operations, and expand access to care.

We are a team of more than 72,000 Healthineers in over 70 countries passionately pushing the boundaries of what is possible in healthcare to help improve the lives of people around the world.

**Personalization of diagnosis, therapy selection and monitoring, aftercare, and managing health.*

Siemens Healthineers Headquarters
Siemens Healthineers AG
Siemensstr. 3
91301 Forchheim, Germany
Phone: +49 9191 18-0
siemens-healthineers.com

Published by
Siemens Healthcare Diagnostics Inc.
Core Lab Solutions
511 Benedict Avenue
Tarrytown, NY 10591-5005
USA
Phone: +1 914-631-8000

Published by Siemens Healthcare Diagnostics Inc. · CLS-24-3812-76 · QR700019094 · 03-2025 · ©Siemens Healthcare Diagnostics Inc., 2025