Test Specific Guidelines

FibroTest/FibroSURE

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Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
HCV Fibrosure	81596
ASH Fibrosure	0002M
NASH Fibrosure	0003M

What Is FibroTest/FibroSURE?

Definition

Liver fibrosis is a condition that can lead to cirrhosis, liver failure, and portal hypertension; it is defined by the accumulation of excess proteins such as collagen, which leads to the buildup of scar tissue.[1]

There are many disease pathways that can lead to fibrosis, such as hepatitis B and C viruses (HBV and HCV, respectively), heavy alcohol use, and metabolic disease. Such diseases cause the liver cells (hepatocytes) to function improperly, which leads to the excess buildup of protein.

Evaluating the extent of liver fibrosis is an important factor for clinicians making treatment decisions for patients with hepatitis B and C. Liver biopsy is currently considered to be the gold standard for evaluating liver fibrosis; however, obtaining a liver biopsy involves invasive surgery. As a result, several non-invasive alternatives have been developed, including FibroTest.

FibroTest uses indirect markers to estimate the extent of fibrosis.[1] FibroTest (licensed in the United States as FibroSURE) was developed as an alternative to liver biopsy in the assessment of liver fibrosis. The remainder of this guideline will refer to the test as FibroSURE.

FibroSURE is a combination of five biochemical assays: alpha2-macroglobulin, haptoglobulin, apolipoprotein A1, gamma glutamyl transpeptidase (GGT) and total bilirubin. An additional component – alanine aminotransferase (ALT) – is infrequently used to test for necroinflammatory lesions. This addition is known as ActiTest. The results of these assays are factored together, along with patient

age, gender, height, and weight to produce a final FibroSURE score and/or ActiTest stage.[2]

FibroSURE is intended for patients with chronic viral hepatitis B or C, alcoholic liver disease, and non-alcoholic steatohepatitis (NASH). Under the broad brand name of NASH-FibroTest, there are five distinct test panels: FibroSURE, ActiTest, SteatoTest 2, NashTest 2, and AshTest.[3]

Test Information

FibroSURE™ is a serum biomarker test that is designed to assess liver fibrosis in patients with chronic viral hepatitis B or C, alcoholic liver disease, and metabolic steatohepatitis (for those who are overweight, have diabetes, or hyperlipidemia).

This test uses serum or plasma from a blood sample, preferably from a patient who has fasted or had a light meal prior to blood draw.

The specific assays performed are as follows:

Alpha-2-macroglobulin

Haptoglobin

Apolipoprotein A1

Gamma-glutamyl transpeptidase (GGT)

Total bilirubin

ALT (an additional component that, when performed, deems the panel ActiTest)

The FibroSURE score ranges from 0-1 and is proportional to the severity of fibrosis. FibroSURE scores have been assigned a corresponding METAVIR stage. Results are displayed using a five-color severity scheme along with the numeric score (dark green=no fibrosis, light green=minimal fibrosis, yellow=moderate fibrosis, orange=advanced fibrosis, and red=severe fibrosis (cirrhosis)).[4]

Guidelines and Evidence

American Association for the Study of Liver Disease

The American Association for the Study of Liver Disease published a practice guideline (2018) stating:[3]

“Liver stiffness measurements (elastography) are more accurate than serum fibrosis panels (e.g. aspartate aminotransferase [AST] to platelet ratio index or FIB-4) in predicting significant or advanced fibrosis.(123,124) Noninvasive methods overestimate fibrosis if high levels of necroinflammation, as reflected by elevated ALT, are present.”

“Liver biopsy offers the only means of assessing both fibrosis and inflammation.”

Of alternate/non-invasive methods, elastography is preferred.

American Gastroenterological Association Institute

The American Gastroenterological Association Institute (AGAI, 2017) guideline on the role of elastography in assessing liver fibrosis stated:[6]

"In patients with chronic hepatitis C, the AGA recommends VCTE, if available, rather than other nonproprietary, noninvasive serum tests (APRI, FIB-4) to detect cirrhosis. GRADE: Strong recommendation, moderate quality evidence."

British HIV Association

The British HIV Association (2013) stated:[7]

"The Writing Group suggests hepatic transient elastography (TE) (FibroScan ™ or Acoustic Radiation Force Impulse [ARFI]) as the non-invasive investigation of choice (2B) but if unavailable, or when reliable TE readings are not obtained, a blood panel test (aspartate transaminase to platelet ratio index [APRI], FIB-4, enhanced liver fibrosis [ELF], Fibrometer ™, Forns Index, FibroTest™) as an alternative (2C)."

European Association for the Study of the Liver

The European Association for the Study of the Liver (EASL, 2021) published a practice guideline on the use of non-invasive tests for assessment of liver disease that stated:[8]

"Non-invasive fibrosis tests should be used for ruling out rather than diagnosing advanced fibrosis in low prevalence populations (LoE 1, Strong recommendation)."

"Non-invasive fibrosis tests should be preferentially used in patients at risk of advanced liver fibrosis (such as patients with metabolic risk factors and/or harmful use of alcohol) and not in unselected general populations (LoE 2, Strong recommendation)."

"In patients patients with ALD, LSM by TE <8 kPa is recommended to rule-out advanced fibrosis in clinical practice, with the following NITs as alternatives, if TE is not available (LoE 3; strong recommendation).

Patented tests: ELF™ <9.8 or FibroMeter™ <0.45 or FibroTest® <0.48

Non-patented tests: FIB-4 <1.3"

The guideline described transient elastography as the most widely validated non-invasive technique.

World Health Organization

The WHO has published documents on several liver-related diseases.

Guidelines for the care and treatment of persons diagnosed with chronic hepatitis C virus infection (2018):[9]

"In resource-limited settings, WHO recommends that the assessment of liver fibrosis should be performed using non-invasive tests (e.g. aspartate/platelet ratio index (APRI) score or FIB-4 test, see existing recommendations, p. xvii). This can determine if there is cirrhosis before initiation of treatment."

Guidelines for the care and treatment of persons diagnosed with chronic hepatitis B virus infection (2015):[10]

"Aspartate aminotransferase (AST)-to-platelet ratio index (APRI) is recommended as the preferred non-invasive test (NIT) to assess for the presence of cirrhosis (APRI score >2 in adults) in resource-limited settings. Transient elastography (e.g., FibroScan) or FibroTest may be the preferred NITs in settings where they are available and cost is not a major constraint. (Conditional recommendation, low quality of evidence) "

World Gastroenterology Organisation

The World Gastroenterology Organisation has published documents on several liver-related diseases.

Hepatitis C (2017)[11]

The extent of hepatic fibrosis should be checked using noninvasive measures:

"Studies have demonstrated that FibroScan is a sensitive alternative to liver biopsy. The amount of fibrosis can be quantified very easily and reliably in more than 95% of the patients [45]. A correct interpretation of transient elastography must have an interquartile range/median values of < 30% and serum ALT < 5 × upper limit of normal. There should be no ongoing excessive alcohol intake, and the patient's BMI should be taken into account. If the BMI is over 30 kg/m2, using extralarge (XL) probes may be considered."

"In resource limited regions, and in places where FibroScan is not readily available, scores such as the fibrosis 4 index (FIB4), AST to platelet ratio index (APRI), and acoustic radiation force impulse (ARFI) can be used. An APRI score ≥ 2 can be used to predict the presence of cirrhosis. At its cut-off point, the ARFI score has a sensitivity of 48% but a specificity of 94% for predicting cirrhosis. It can also be used to predict the presence of significant fibrosis (stages 2–4). Using a cut-off value of 1.5, the sensitivity is 37% and the specificity is 95% for significant fibrosis [46,47]."

Hepatitis B (2015)[12]

"Measurement of liver fibrosis by serological testing, FibroScan (transient elastography), or liver biopsy."

Determination of the severity of liver disease:

"Laboratory tests for inflammation (ALT), hepatic function (bilirubin, albumin, coagulation factors and viral load (HBV DNA), if available"

"Hepatic ultrasound examination"

"Non-invasive methods to assess fibrosis (serum panels, transient elastography)"

Liver biopsy "can help exclude other coexistent causes of liver disease and clarify the diagnosis when ALT and HBV DNA levels are discordant."

Esophageal Varices (2014)[13]

In recommendations on "Esophageal varices", the WGO states that the "predictive accuracy is still unsatisfactory" for noninvasive markers such as FibroSURE.

Selected Relevant Publications

The evidence as a whole does not yet fully support using FibroSURE as a stand-alone test.[14-40] Limitations of the available studies include use of variable thresholds and heterogeneous patient populations. Many published studies are retrospective case-control studies subject to bias due to unclear methodology in patient selection and lack of blinding. Overall, there is a lack of direct comparative studies evaluating the impact of FibroSURE on clinical decision making and clinical outcomes to establish clinical utility.

Criteria

This test is considered investigational and/or experimental.

Investigational and experimental (I&E) molecular and genomic (MolGen) tests refer to assays involving chromosomes, DNA, RNA, or gene products that have insufficient data to determine the net health impact, which typically means there is insufficient data to support that a test accurately assesses the outcome of interest (analytical and clinical validity), significantly improves health outcomes (clinical utility), and/or performs better than an existing standard of care medical management option. Such tests are also not generally accepted as standard of care in the evaluation or management of a particular condition.

In the case of MolGen testing, FDA clearance is not a reliable standard given the number of laboratory developed tests that currently fall outside of FDA oversight and FDA clearance often does not assess clinical utility.

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