Medica Central Coverage Policy

Policy Name:	**Genetic Testing - Specialty Testing: Gastroenterology**
Effective Date:	**July 1, 2025**

Important Information – Please Read Before Using This Policy
These services may or may not be covered by all Medica Central plans. Coverage is subject to requirements in applicable federal or state laws. Please refer to the member's plan document for other specific coverage information. If there is a difference between this general information and the member's plan document, the member's plan document will be used to determine coverage. With respect to Medicare, Medicaid, and other government programs, this policy will apply unless these programs require different coverage.
Members may contact Medica Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions may call the Provider Service Center. Please use the Quick Reference Guide on the Provider Communications page for the appropriate phone number. https://mo-central.medica.com/Providers/SSM-employee-health-plan-for-IL-MO-OK-providers

Medica Central coverage policies are not medical advice. Members should consult with appropriate health care providers to obtain needed medical advice, care, and treatment.

OVERVIEW

This policy addresses the use of tests for common gastroenterologic (non-cancerous) conditions, such as Crohn's disease, hereditary hemochromatosis, and others.
Pre-test and post-test genetic counseling that facilitates informed decision-making, addresses the possibility of secondary or incidental findings, and includes a plan for returning results before testing occurs is strongly advised.
For additional information see the Rationale section.
The tests, CPT codes, and ICD codes referenced in this policy are not comprehensive, and their inclusion does not represent a guarantee of coverage or non-coverage.

POLICY REFERENCE TABLE

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
Hereditary Hemochromatosis			
HFE C282Y and H63D Genotyping	Hereditary Hemochromatosis DNA Mutation Analysis (Quest Diagnostics)	81256, E83.110, E83.118, E83.119, R79.0, E83.19, R16.0	1, 4, 9

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
	HFE Targeted Variant - Single Test (GeneDx)		
Pancreatitis			
Hereditary Pancreatitis Multigene Panel	Hereditary Pancreatitis Panel (GeneDx)	81222, 81223, 81404, 81405, 81479, K85.0-K85.9, K86.1, Z83.79	2, 3, 10, 11
Inflammatory Bowel Disease			
Inflammatory Bowel Disease / Crohn's Disease Diagnostic Algorithmic Tests	Prometheus IBD sgi Diagnostic (Prometheus Laboratories)	81479, 82397, 83520, 86140, 88346, 88350, K50-K52	5, 7
Inflammatory Bowel Disease / Crohn's Disease Prognostic Algorithmic Tests	Prometheus Crohn's Prognostic (Prometheus Laboratories)	81401, 83520, 88346, 88350, 0203U, K50-K52	6
	PredictSURE IBD Test - 0203U (KSL Diagnostics)		
Hereditary Inflammatory Bowel Disease / Crohn's Disease Panel Tests	Monogenic Inflammatory Bowel Disease Panel (Invitae)	81321, 81406, 81407, 81479, K50-K52	7, 8
	Very Early Onset Inflammatory Bowel (VEO-IBD) Panel (Children's Hospital of Philadelphia - Division of Genomic Diagnostics)		
Noninvasive Liver Disease Tests			
Blood-based Noninvasive Liver Disease Algorithmic Tests	HCV FibroSURE, FibroTest - 81596 (BioPredictive S.A.S.)	81517, 81596, 0003M K76.0, R94.5	12, 13, 15, 16, 17, 18
	NASH FibroSURE - 0003M (LabCorp)		

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
	Enhanced Liver Fibrosis (ELF) Test - 81517 (Siemens Health Care Diagnostics)		

RELATED POLICIES

This policy document provides coverage criteria for non-cancerous gastroenterologic disorders. Please refer to:

- ***Oncology Testing: Hereditary Cancer*** for coverage criteria related to genetic testing for hereditary cancer predisposition syndromes.
- ***Reproductive Testing: Carrier Screening*** for coverage criteria related to parental carrier screening for genetic disorders before or during pregnancy.
- ***Reproductive Testing: Prenatal Diagnosis*** for coverage criteria related to fetal diagnostic testing for genetic disorders during pregnancy and following a pregnancy loss.
- ***Specialty Testing: Multisystem Genetic Conditions*** for coverage criteria related to diagnostic tests for genetic disorders that affect multiple organ systems (e.g. whole exome and genome sequencing, chromosomal microarray, and multigene panels for broad phenotypes).
- ***Specialty Testing: Nutrition and Metabolism*** for coverage criteria related to diagnostic and serum biomarker tests for nutritional status and biochemical disorders.
- ***Specialty Testing: Immunology and Rheumatology*** for coverage criteria related to diagnostic and biomarker tests for autoimmune conditions and inherited immunodeficiency disorders.
- ***General Approach to Laboratory Testing*** for coverage criteria related to non-cancerous gastroenterologic conditions, including known familial variant testing, that is not specifically discussed in this or another non-general policy.

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COVERAGE CRITERIA

HEREDITARY HEMOCHROMATOSIS

HFE C282Y and H63D Genotyping

I. *HFE* C282Y and H63D genotyping to establish a diagnosis of hereditary hemochromatosis is considered **medically necessary** when:

A. The member has abnormal serum iron indices (e.g., elevated serum transferrin-iron saturation and/or elevated serum ferritin concentration, indicating iron overload), **OR**

B. The member has a first-degree relative with a diagnosis of hereditary hemochromatosis.

II. *HFE* C282Y and H63D genotyping to establish a diagnosis of hereditary hemochromatosis is considered **investigational** for all other indications, including general population screening for hereditary hemochromatosis.

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PANCREATITIS

Hereditary Pancreatitis Multigene Panel

I. Hereditary pancreatitis multigene panel analysis to establish a diagnosis of hereditary pancreatitis is considered **medically necessary** when:

A. The member has a personal history of pancreatitis, **AND**

B. The member meets at least one of the following:

1. Unexplained episode of acute pancreatitis in childhood (18 years or younger), **OR**

2. Recurrent (two or more separate, documented) acute attacks of pancreatitis for which there is no explanation (i.e., anatomical anomalies, ampullary or main pancreatic strictures, trauma, viral infection, gallstones, alcohol, drugs, hyperlipidemia, etc.), **OR**

3. Chronic pancreatitis of unknown cause, particularly with onset before age 35 years without a history of heavy alcohol use, **OR**

4. At least one close relative with recurrent acute pancreatitis, chronic pancreatitis of unknown cause, or childhood pancreatitis of unknown cause, **AND**

C. The panel includes, at a minimum, the following genes: *PRSS1*, *SPINK, CFTR,* and *CTRC*.

II. Hereditary pancreatitis multigene panel analysis to establish a diagnosis of hereditary pancreatitis is considered **investigational** for all other indications.

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INFLAMMATORY BOWEL DISEASE

Inflammatory Bowel Disease / Crohn's Disease Diagnostic Algorithmic Tests

I. Inflammatory bowel disease / Crohn's disease diagnostic algorithmic tests are considered **investigational** for all indications**.**

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Inflammatory Bowel Disease / Crohn's Disease Prognostic Algorithmic Tests

I. Inflammatory bowel disease / Crohn's disease prognostic algorithmic tests are considered **investigational** for all indications.

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Hereditary Inflammatory Bowel Disease / Crohn's Disease Panel Tests

I. Genetic testing for inflammatory bowel disease, including Crohn's disease, via a multigene panel is considered **medically necessary** when:

A. The member was diagnosed with infantile-onset inflammatory bowel disease (Infantile-IBD) before age 2 years, **OR**

B. The member was diagnosed with very early onset inflammatory bowel disease (VEO-IBD) before age 6 years, **AND**

1. At least one of the following:

a) The member has congenital multiple intestinal atresias, **OR**

b) The member has congenital diarrhea, **OR**

c) The member has a diagnosis of malignancy under age 25, **OR**

d) The member has features of an inborn error of immunity such as susceptibility to infections, **OR**

e) The member has complex autoimmune features, **OR**

f) The member has a close relative meeting any of the above criteria, **OR**

g) The member is undergoing stem cell transplant, **OR**

h) The member has a history of multiple intestinal resections.

II. Genetic testing for inflammatory bowel disease, including Crohn's disease, via a multigene panel is considered **investigational** for all other indications.

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NONINVASIVE LIVER DISEASE TESTS

Blood-based Noninvasive Liver Disease Algorithmic Tests

I. Blood-based noninvasive liver disease[1] algorithmic tests are considered **medically necessary** when:

A. The member does **NOT** have a confirmed diagnosis of liver fibrosis, **AND**

B. This test has **NOT** been performed within the last year, **AND**

C. The member meets **BOTH** 1 and 2:

1. One of the following:

a) Untreated chronic hepatitis C virus (HCV) infection, **OR**

b) Suspected or confirmed metabolic dysfunction-associated steatotic liver disease (MASLD) (formerly, nonalcoholic fatty liver disease [NAFLD]), **AND**

(1) The member does **NOT** have chronic cholestatic liver disease, **AND**

2. One of the following:

a) An intermediate or high-risk Fibrosis-4 index (FIB-4) score (1.3 or greater for individuals younger than 65 years of age; 2.0 or greater for individuals 65 years of age or older), **OR**

b) A low-risk Fibrosis-4 index (FIB-4) score (less than 1.3 for individuals younger than 65 years of age; less than 2.0 for individuals 65 years of age or older), **AND**

(1) Prediabetes/type 2 diabetes, **OR**

(2) Two or more features of metabolic syndrome (e.g., abdominal obesity, high blood pressure, high triglyceride levels), **OR**

c) An indeterminate or high-risk score on the NAFLD fibrosis score (NFS) (less than -1.455).

II. Blood-based non-invasive liver disease algorithmic tests to rule out liver fibrosis are considered **investigational** for all other indications, including but not limited to:

A. Alcohol-associated steatotic liver disease (formerly, alcoholic fatty liver disease).

[1] Liver disease and liver fibrosis are not interchangeable terms; they describe separate, but often overlapping, disease states. Chronic liver diseases, such as MASLD, can lead to liver fibrosis. Liver fibrosis describes the accumulation of scar tissue in the liver.

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RATIONALE

HFE C282Y and H63D Genotyping

European Molecular Quality Network (EMQN)
In 2015, the EMQN developed best practice guidelines to guide criteria and strategies for molecular genetic testing for hereditary hemochromatosis (HH).
The article includes guidelines, which state the following evidence-based recommendations for *HFE* testing strategies:

- Laboratories providing testing for HFE-associated HH should test for p.C282Y (1A).
- According to local practice, p.H63D can be considered an optional complementary test that can be offered sequentially or simultaneously to p.C282Y testing (2C).
- Population screening for the p.C282Y variant is not currently recommended (1B).
- It is considered to be good practice to confirm elevated TS [transferrin saturation] before HFE genetic diagnosis testing (1B) (p. 489).

American College of Gastroenterology (ACG)
In 2019, practice guidelines from the ACG made the following statement on genetic testing for hereditary hemochromatosis (HH):

- "We recommend that family members, particularly first-degree relatives, of patients diagnosed with HH should be screened for HH (strong recommendation, moderate quality of evidence)" (p. 1203).
- "Selective screening of first-degree relatives of patients affected with type1 HH is suggested. Studies of patients with HH and their families have demonstrated that most homozygous relatives of probands demonstrate biochemical and clinical expression of the disease, not only due to the presence of the genetic mutation but also shared environmental factors that may increase the penetrance of the disease" (p. 1206).
- "We recommend that individuals with the H63D or S65C mutation in the absence of C282Y mutation should be counseled that they are not at increased risk of iron overload (conditional recommendation, very low quality of evidence)" (p. 1208).

Additionally, the ACG published a suggested algorithm for diagnosis and treatment in their 2019 practice guidelines. This algorithm includes evaluating a patient's serum transferrin iron saturation (TS) and serum ferritin (SF), and indicates *HFE* genotyping if TS is 45% or greater, and/or SF is elevated (p. 1212).
GeneReviews - HFE-Related *Hemochromatosis*
GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online.
Genereviews suggests that *HFE*-related hemochromatosis (*HFE*-HC) should be suspected in individuals with laboratory features consistent with *HFE*-HC (i.e., elevated transferrin saturation, and/or serum ferritin concentration, and/or higher Hg, MCH and MCV), clinical signs of advanced iron overload (i.e., weakness or chronic fatigue, abdominal pain, weight loss, etc), and/or a family history of *HFE*-HC.

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Hereditary Pancreatitis Multigene Panel

American College of Gastroenterology
In 2024, the American College of Gastroenterology issued guidelines on management of acute pancreatitis, which included a statement that genetic testing may be helpful for patients with idiopathic pancreatitis with more than one affected family member (p. 424).
In 2020, the American College of Gastroenterology Clinical Guideline: Chronic pancreatitis (CP) recommended genetic testing in patients with clinical evidence of a pancreatitis-associated disorder or possible CP in which the etiology is unclear, especially in younger patients. At minimum, patients with idiopathic CP should be evaluated for *PRSS1, SPINK1, CFTR*, and *CTRC* gene mutation analysis, although more extended panels with over a dozen susceptibility and modifier genes, hypertriglyceridemia genes, and pharmacogenetics are available (p. 325 and 330).
American Pancreatic Association
In 2014, the American Pancreatic Association published Practice Guidelines in Chronic Pancreatitis: Evidence-Based Report on Diagnostic Guidelines. A classification guideline for the etiology of chronic pancreatitis (CP) includes genetic mutations in *PRSS1, CFTR, SPINK1*, and others (p. 7).
GeneReviews - Pancreatitis Overview
GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online.
According to GeneReviews, the evaluation of an at-risk individual for chronic pancreatitis should begin with the first episode of acute pancreatitis, after common causes such as gallstone, trauma, hypertriglyceridemia or hypercalcemia have been ruled out.
Molecular genetic testing for hereditary pancreatitis is indicated in a proband with pancreatitis and at least one of the following:

- An unexplained documented episode of acute pancreatitis in childhood
- Recurrent acute attacks of pancreatitis of unknown cause
- Chronic pancreatitis of unknown cause, particularly with onset before age 35 years without a history of heavy alcohol use (>5 drinks per day)
- A history of at least one relative with recurrent acute pancreatitis, chronic pancreatitis of unknown cause, or childhood pancreatitis of unknown cause

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Inflammatory Bowel Disease / Crohn's Disease Diagnostic Algorithmic Tests

Concert - Evidence Review for Coverage Determination (Published 07/1/2024)
There are several professional society guidelines that address appropriate diagnostic tools for IBD. These include the 2018 statement by the American College of Gastroenterology (ACG) on management of adult Crohn's Disease, the 2019 guideline on Ulcerative Colitis in Adults by ACG, and the 2017 guideline by the European Crohn's and Colitis Organization (ECCO) on Diagnosis and Management of Ulcerative Colitis. The ACG Crohn's Disease and Ulcerative Colitis guidelines indicated that routine serologic testing for either disease is not recommended, with the 2019 guideline stating "we recommend against serologic antibody testing to establish or rule out a diagnosis of UC (strong recommendation, very low quality of evidence)" (p. 486 [2018 guideline], p. 385 [2019 guideline]). The ECCO evidence review and consensus concluded that

the serological biomarker use of pANCAs and ASCAs for diagnosis and therapeutic decisions in ulcerative colitis is not clinically justified (p. 653).
This review focused on identification of peer-reviewed, published evidence of the clinical validity and utility of Prometheus IBD sgi Diagnostic from May 1, 2023 through May 2, 2024. A PubMed search was performed. Search terms included: Prometheus ibd sgi Diagnostic, inflammatory bowel disease, systematic review, meta-analysis, and guidelines. No new literature was identified to include in the evidence review.
At the present time, IBD Crohn's Diagnostic Algorithmic tests such as Prometheus IBD sgi Diagnostic, have **INSUFFICIENT EVIDENCE** in peer-reviewed publications to effectively result in improved health outcomes compared to the current standard of care.

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Inflammatory Bowel Disease / Crohn's Disease Prognostic Algorithmic Tests

Concert Evidence Review for Coverage Determination (Published 7/1/2024)
The 2018 statement by the American College of Gastroenterology (ACG) on management of adult Crohn's Disease states that certain genetic markers are associated with different phenotypic expressions in Crohn's disease but testing remains a research tool at this time" (p. 486). No other serological markers or prognostic algorithmic tests are mentioned in these guidelines.
This review focused on peer-reviewed, published evidence of the clinical utility and validity of Prometheus Crohn's Prognostic test from May 1, 2023 through May 8, 2024. A PubMed search was performed. Search terms included: Crohn's disease, prognostic, biomarker, inflammatory bowel disease, guidelines, genetic testing, Prometheus Crohn's, Prometheus, clinical validity, biomarkers in ulcerative colitis/Crohn's disease. No new literature was identified to include in the evidence review.
At the present time, Prometheus Crohn's Prognostic test has **INSUFFICIENT EVIDENCE** in peer-reviewed publications to effectively result in improved health outcomes compared to the current standard of care.

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Hereditary Inflammatory Bowel Disease/Crohn's Disease Panel Tests

UpToDate (Higuchi LM and Bousvaros A, 2024)
The following clinical features suggest the possibility of monogenic IBD:

- Onset under age 6, especially under age 2
- Family history of IBD and/or immunodeficiency in multiple relatives, especially in males or in families with consanguinity
- Recurrent infections or unexplained fever
- Associated autoimmune features (e.g., arthritis, primary sclerosing cholangitis, anemia, or endocrine dysfunction)
- Very severe IBD, complex fistulizing disease and/or resistance to conventional IBD treatment
- Symptoms or signs of hemophagocytic lymphohistiocytosis (hepatomegaly, fever, cytopenias, high ferritin)
- Lesions in the hair, nails, or skin
- Current or past history of cancer in the patient

- Endoscopic biopsies showing tissue eosinophilia and villous flattening without suggestion of celiac disease

Infants or young children presenting with these features should be referred to an immunologist for careful consideration of and evaluation for monogenic IBD. Testing may include panel, exome, or genome sequencing, and is recommended for all children under age 2, as well as for children under age 6 with the above clinical disease manifestations.
British Society of Gastroenterology and British Society of Paediatric Gastroenterology, Hepatology and Nutrition
This joint guideline (2023) states that monogenic causes of IBD should be considered in patients with IBD since optimal care pathways and treatment may differ from that of classical IBD (high quality evidence, strong recommendation). (p.18) In monogenic IBD, panel testing is favored due to the rarity of the disorders and heterogeneous phenotypes.
Clinicians should consider genomic testing in all patients with infantile onset IBD and in very-early-onset (defined as under age 6) IBD, particularly in the presence of one or more additional testing criteria (see below) (high quality evidence, strong recommendation). (p.25) Genomic testing should only be offered in exceptional circumstances to patients with onset after age 6 (moderate quality evidence, conditional recommendation).
The following testing criteria are proposed:

- Age of IBD onset: younger than 2 years or younger than 6 years particularly when additional criteria are observed
- Infection susceptibility (eg, due to recurrent sinopulmonary infections, systemic infections, meningitis, gastrointestinal infections, or cutaneous infections) in the presence of abnormal laboratory tests (eg, congenital lymphopenia or neutropenia, or combined immunoglobulin concentration abnormalities) meeting diagnostic criteria of an inborn error of immunity (ie, primary immunodeficiency)
- Inflammatory features indicative for an inborn error of immunity, such as complex autoimmune features (especially features of IPEX syndrome in the paediatric population or severe multiorgan autoimmune disease in the adult population) or haemophagocytic lymphohistiocytosis
- Congenital multiple intestinal atresias or congenital diarrhea
- Early-onset malignancy (age <25 years)
- Family history of suspected monogenic IBD (criteria 1–5)
- In advance of interventions or therapies with irreversible consequences and high risk for adverse outcome, such as haematopoietic stem-cell transplantation with transplantation-associated mortality or patients with a history of multiple intestinal resections and associated risk of short bowel syndrome, and total parenteral nutrition requirement (p. 8)

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Blood-based Noninvasive Liver Disease Algorithmic Tests

Wattacheril, et al
The American Gastroenterological Association (AGA) released a clinical practice update expert review (2023) containing several best practice advice statements regarding the role of blood-based and imaging-based noninvasive biomarkers in the evaluation and management of nonalcoholic fatty liver disease (NAFLD). Liver biopsy is complicated by sampling variability,

intra- and interobserver variability, and rare severe/fatal complications. Given these complications, and the high prevalence of NAFLD, noninvasive tests provide an alternative, validated tool to invasive biopsy testing.

- "Best Practice Advice 1: Non-invasive tests (NITs) can be used for risk stratification in the diagnostic evaluation of patients with nonalcoholic fatty liver disease (NAFLD)."; FIB-4 is recommended as a first-line test because of its simplicity, low cost, and high negative predictive value (NPV). Serum-based fibrosis tests, such as the Enhanced Liver Fibrosis Test (ELF) or FibroTest/FibroSure, may be helpful in secondary risk assessment when elastography is not available." (p. 1081-1082)
- "Best Practice Advice 2: An FIB-4 score <1.3 is associated with strong NPV for advanced hepatic fibrosis and may be useful for exclusion of advanced hepatic fibrosis in patients with NAFLD."
- "Best Practice Advice 3: A combination of 2 or more NITs combining serum biomarkers and/or imaging-based biomarkers is preferred for staging and risk stratification of patients with NAFLD whose Fibrosis 4 Index score is >1.3." When imaging is not readily available, clinicians may consider use of a second serum test, such as ELF to improve sensitivity. Sequential testing of NITs has been shown to improve risk stratification and may reduce the need for liver biopsy (p. 1083).
- "Best Practice Advice 7: Serial longitudinal disease monitoring using NITs for assessment of disease progression or regression may inform clinical management." The authors contextualize this statement by noting that, while some studies have reported association of NIT monitoring with histological improvement, a strong, evidence-based recommendation is not possible for serial monitoring of NITs given the available data (p. 1084).

They propose a clinical workup for patients with suspected NAFLD that includes the following steps for individuals with elevated ALT (alanine aminotransferase; > 20 U/L for women and > 30 U/L in men) (p. 1084-1085):

- For patients with a FIB-4 less than 1.3 (or less than 2.0 for patients older than 65 years of age), who do NOT have type 2 diabetes or features of metabolic syndrome, repeat FIB-4 every 1-2 years.
- For patients with a FIB-4 less than 1.3 (or less than 2.0 for patients older than 65 years of age), who have type 2 diabetes or features of metabolic syndrome, perform a second NIT as accessible/feasible (ELF or imaging-based).
- For patients with a FIB-4 of 1.3 or greater, perform a second NIT as accessible/feasible (ELF or imaging-based).

American College of Gastroenterology (ACG)
The ACG Guideline: "Alcohol-Associated Liver Disease" (2024) includes the following recommendation regarding the use of noninvasive tests for assessing fibrosis severity in individuals with alcohol-associated liver disease:

- "Noninvasive blood and/or radiological tests (NITs) should be used to assess the severity of fibrosis in persons with asymptomatic ALD [alcohol-associated liver disease]. FIB-4 score, a blood-based marker, and hepatic transient elastography are best initial NITs of fibrosis among persons with ALD."

The guideline makes no formal recommendation regarding the use of proprietary noninvasive blood tests in the assessment of ALD. The guideline notes that the enhanced liver fibrosis (ELF) test and FibroTest have higher specificity of 80-90% (compared to 60-70% for FIB-4), while also noting the higher expense and more limited availability of these tests. They also point out that the ELF test is less well-validated in individuals with ALD as it is in those with metabolic-associated steatotic liver (MASLD) and hepatitis C virus-related liver diseases (p. 38-39).

American Association for the Study of Liver Diseases (AASLD)

The AASLD Practice Guideline on blood-based noninvasive liver disease assessment of hepatic fibrosis and steatosis (2024) includes the following guidance statements:

- There is insufficient evidence to recommend blood-based noninvasive liver disease tests for staging fibrosis in patients with alcoholic liver disease or chronic cholestatic liver disease (p. 9).
- In patients with chronic untreated HCV, AASLD suggests a sequential combination of blood-based markers may perform better than a single biomarker for F2-4 or F4 (p. 15).
- In patients with NAFLD, AASLD suggests the sequential combination of blood-based NILDA may be considered for diagnosis of advanced fibrosis (F3-4) over using a single test alone (p. 15).
- AASLD suggests against the use of blood-based noninvasive tests to follow progression or regression of liver fibrosis over time (p. 16).

The AASLD generally recommends that fibrosis staging begins with simple, less costly, blood-based noninvasive liver disease assessment, such as the FIB-4 or NFS (NAFLD fibrosis score) over the more complex, proprietary tests, as they are readily available and performance is comparable. They note that proprietary tests can be used where available (p. 27).

Canivet, et al

A review of screening for liver fibrosis in the general population (2022) stated that of the specialized blood tests available for evaluation of liver fibrosis, the most-validated are the Enhanced Liver Fibrosis (ELF) test, FibroMeter, and Fibrotest. Diagnostic studies comparing these to liver biopsy have demonstrated good rule-out sensitivity of 80–90% and good rule-in specificity of 90–95% for the diagnosis of advanced liver fibrosis in chronic liver diseases. These specialized blood tests are more expensive, so they are best reserved for secondary evaluation of liver fibrosis, as proposed in figure 2, with those suspected of having NAFLD undergoing FIB-4 or NFS testing first, followed by either elastography or specialized blood test (ELF, FibroMeter, Fibrotest) (p. 6-7).

European Association for the Study of the Liver (EASL)

The EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis, updated in 2021, note that while the optimal interval to repeat noninvasive tests are not well-defined, it seems reasonable based on available studies to repeat them every 3 years in early stage fibrosis and annually in advanced stage nonalcoholic fatty liver disease (p. 670).

Angulo et al

In the article, “The NAFLD Fibrosis Score: A Noninvasive System That Identifies Liver Fibrosis in Patients with NAFLD” (2007), the authors determined the cutoff points for negative (>0.676), indeterminate (-1.455-0.676), and positive (<-1.455) results (p. 853).

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DEFINITIONS

1. **Close relatives** include first, second, and third degree blood relatives on the same side of the family:
    a. **First-degree relatives** are parents, siblings, and children
    b. **Second-degree relatives** are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings
    c. **Third-degree relatives** are great grandparents, great aunts, great uncles, great grandchildren, and first cousins
2. **Fibrosis-4 index (FIB-4)** is a blood test that calculates the probability of advanced liver fibrosis based on AST, ALT, platelets, and age.
3. **NAFLD fibrosis score (NFS)** is a blood test that calculates the probability of advanced liver fibrosis based on AST, ALT, albumin, age, body mass index (BMI), platelet count, and presence of impaired fasting glucose (IFG) or diabetes.
4. **Infantile-onset inflammatory bowel disease (Infantile-IBD)** is defined as clinical manifestations and/or receiving the diagnosis when younger than 2 years of age. (Ouahed, et al)
5. **Very early onset inflammatory bowel disease (VEO-IBD)** is defined as clinical manifestations and/or receiving the diagnosis when younger than 6 years of age. (Ouahed, et al)

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REFERENCES

1. Kowdley KV, Brown KE, Ahn J, Sundaram V. ACG Clinical Guideline: Hereditary Hemochromatosis [published correction appears in Am J Gastroenterol. 2019 Dec;114(12):1927]. *Am J Gastroenterol*. 2019;114(8):1202-1218. doi:10.14309/ajg.0000000000000315
2. Conwell DL, Lee LS, Yadav D, et al. American Pancreatic Association Practice Guidelines in Chronic Pancreatitis: evidence-based report on diagnostic guidelines. Pancreas. 2014;43(8):1143-1162. doi:10.1097/MPA.0000000000000237
3. Tenner S, Vege SS, Sheth SG, et al. American College of Gastroenterology Guidelines: Management of Acute Pancreatitis. The American Journal of Gastroenterology. 2023;119(3):419-437. doi:10.14309/ajg.0000000000002645
4. Barton JC, Edwards CQ. *HFE-Related* Hemochromatosis. 2000 Apr 3 [Updated 2024 April 11]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1440/
5. Concert Evidence Review for Coverage Determination. Inflammatory Bowel Disease/Crohn's Diagnostic Algorithmic Tests. Published 7/1/2024.

6. Concert Evidence Review for Coverage Determination. Inflammatory Bowel Disease/Crohn's Prognostic Algorithmic Tests. Published 7/1/2024.
7. Higuchi LM and Bousvaros A. Clinical presentation and diagnosis of inflammatory bowel disease in children. In: UpToDate, Connor RF (Ed), Wolters Kluwer. Accessed November 18, 2024. https://www.uptodate.com/contents/clinical-presentation-and-diagnosis-of-inflammatory-bowel-disease-in-children
8. Kammermeier J, Lamb CA, Jones KDJ, et al. Genomic diagnosis and care coordination for monogenic inflammatory bowel disease in children and adults: consensus guideline on behalf of the British Society of Gastroenterology and British Society of Paediatric Gastroenterology, Hepatology and Nutrition. *Lancet Gastroenterol Hepatol*. 2023;8(3):271-286. doi:10.1016/S2468-1253(22)00337-5
9. Porto G, Brissot P, Swinkels DW, et al. EMQN best practice guidelines for the molecular genetic diagnosis of hereditary hemochromatosis (HH). *Eur J Hum Genet*. 2016;24(4):479-495. doi:10.1038/ejhg.2015.128
10. Gardner, Timothy B. MD, MS, FACG1; Adler, Douglas G. MD, FACG2; Forsmark, Chris E. MD, FACG3; Sauer, Bryan G. MD, MSc (Clin Res), FACG (GRADE Methodologist)4; Taylor, Jason R. MD5; Whitcomb, David C. MD, PhD, FACG6. ACG Clinical Guideline: Chronic Pancreatitis. The American Journal of Gastroenterology 115(3):p 322-339, March 2020.
11. Shelton C, LaRusch J, Whitcomb DC. Pancreatitis Overview. 2014 Mar 13 [Updated 2020 Jul 2]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK190101/
12. Canivet CM, Boursier J. Screening for Liver Fibrosis in the General Population: Where Do We Stand in 2022?. Diagnostics (Basel). 2022;13(1):91. Published 2022 Dec 28. doi:10.3390/diagnostics13010091
13. Wattacheril JJ, Abdelmalek MF, Lim JK, Sanyal AJ. AGA Clinical Practice Update on the Role of Noninvasive Biomarkers in the Evaluation and Management of Nonalcoholic Fatty Liver Disease: Expert Review. Gastroenterology. 2023;165(4):1080-1088. doi:10.1053/j.gastro.2023.06.013
14. Ouahed J, Spencer E, Kotlarz D, et al. Very Early Onset Inflammatory Bowel Disease: A Clinical Approach With a Focus on the Role of Genetics and Underlying Immune Deficiencies. Inflamm Bowel Dis. 2020 May 12;26(6):820-842. doi: 10.1093/ibd/izz259. PMID: 31833544; PMCID: PMC7216773.
15. Sterling RK, Patel K, Duarte-Rojo A, et al. AASLD Practice Guideline on blood-based noninvasive liver disease assessment of hepatic fibrosis and steatosis. Hepatology. Published online March 15, 2024. doi:10.1097/HEP.0000000000000845
16. 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. doi:10.1016/j.jhep.2021.05.025
17. Jophlin LL, Singal AK, Bataller R, et al. ACG Clinical Guideline: Alcohol-Associated Liver Disease. Am J Gastroenterol. 2024;119(1):30-54. doi:10.14309/ajg.0000000000002572

18. Angulo P, Hui JM, Marchesini G, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology. 2007;45(4):846-854. doi:10.1002/hep.21496

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Note: The Health Plan uses the genetic testing clinical criteria developed by Concert Genetics, an industry-leader in genetic testing technology assessment and policy development.

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