# Concert Genetic Testing: Gastroenterologic Disorders (Non-Cancerous)

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Coding implications
Revision Log

**See Important Reminder at the end of this policy for important regulatory and legal information.**

# OVERVIEW

Genetic testing for gastroenterologic (non-cancerous) disorders may be used to confirm a diagnosis in a patient who has signs and/or symptoms of a specific gastroenterologic disorder. Confirming the diagnosis may alter aspects of management and may eliminate the need for further diagnostic workup. This document addresses genetic testing for common gastroenterologic (non-cancerous) conditions, such as Celiac disease, Crohn's disease, hereditary hemochromatosis, and many others.

# POLICY REFERENCE TABLE

### Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2023, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only and may not support medical necessity. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

The tests, associated laboratories, CPT codes, and ICD codes contained within this document serve only as examples to help users navigate claims and corresponding criteria; as such, they are not comprehensive and are not a guarantee of coverage or non-coverage. Please see the Concert Platform for a comprehensive list of registered tests.

**NOTE: Coverage is subject to each requested code's inclusion on the corresponding LDH fee schedule. Non-covered codes are denoted (*) and are reviewed for Medical Necessity for members under 21 years of age on a per case basis. The non-covered codes will only be denoted in the table below and not throughout the policy. Please only reference the policy reference table for covered and non-covered codes.**

| Criteria Sections | Example Tests (Labs) | Common CPT Codes | Common ICD Codes | Ref |
|---|---|---|---|---|
| **Celiac Disease** | | | | |
| *HLA-DQ* Genotyping Analysis | Celiac HLA DQ Association (Labcorp) | 81375*, 81376*, 81377*, 81382, 81383* | K90.0, R10.0-R10.13, R10.3-R10.829, R10.84-R10.9 | 4, 5, 6 |
| | HLA Typing for Celiac Disease (Quest Diagnostics) | | | |
| **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, 7, 12 |
| | HFE Targeted Variant - Single Test (GeneDx) | | | |
| **Hereditary Pancreatitis** | | | | |
| Hereditary Pancreatitis Multigene Panel | Hereditary Pancreatitis Panel (GeneDx) | 81222, 81223, 81404*, 81405*, 81479 | K85.0-K85.9, K86.1, Z83.79 | 2, 3, 13, 14 |
| **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 | 8 |
| Inflammatory Bowel Disease / Crohn's Disease Prognostic Algorithmic Tests | Prometheus Crohn's Prognostic (Prometheus Laboratories) | 81401*, 83520, 88346, 88350 | K50-K52 | 9 |
| Hereditary Inflammatory Bowel Disease / Crohn's Disease Panel Tests | Monogenic Inflammatory Bowel Disease Panel (Invitae) | 81479, 81321*, 81406*, 81407* | K50-K52 | 10, 11 |
| | Very Early Onset Inflammatory Bowel (VEO-IBD) Panel (Children's Hospital of Philadelphia - Division of Genomic Diagnostics) | | | |
| **Non-invasive Liver Fibrosis Serum Tests** | | | | |

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|---|---|---|---|---|
| Non-invasive Liver Fibrosis Serum Tests | ASH FibroSURE (LabCorp)<br>NASH FibroSURE (LabCorp) | 0002M*, 0003M* | K76.0, R74.8, R94.5, R79.89, I10 | 15, 16, 17, 18 |
| | FIB-4 Index Panel with Reflex to Enhanced Liver Fibrosis (ELF) Score (Quest Diagnostics) | 84450, 84460, 85049 | | |
| | Enhanced Liver Fibrosis (ELF) Test (Siemens Health Care Diagnostics) | 81517 | | |

# OTHER RELATED POLICIES

This policy document provides criteria for Genetic Testing for Gastroenterologic Conditions (Non-Cancerous). Please refer to:

- ***Genetic Testing: Hereditary Cancer Susceptibility Syndromes*** for criteria related to germline testing for hereditary cancer syndromes, including Lynch/HNPCC syndrome.
- ***Genetic Testing: Prenatal and Preconception Carrier Screening*** for criteria related to carrier screening in the prenatal, preimplantation, and preconception setting.
- ***Genetic Testing: Prenatal Diagnosis (via amniocentesis, CVS, or PUBS) and Pregnancy Loss*** for coverage related to prenatal and pregnancy loss diagnostic genetic testing for tests intended to diagnose genetic conditions following amniocentesis, chorionic villus sampling or pregnancy loss.
- ***Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for criteria related to diagnostic genetic testing for conditions affecting multiple organ systems.
- ***Genetic Testing: Metabolic, Endocrine, and Mitochondrial Disorders*** for criteria related to genetic testing for *MTHFR*.
- ***Genetic Testing: General Approach to Genetic and Molecular Testing*** for criteria related to genetic testing for any non-cancerous GI disorders that is not specifically discussed in this or another non-general policy, including known familial variant testing.

back to top

# CRITERIA

It is the policy of health plans affiliated with Centene Corporation® that the specific genetic testing noted below is **medically necessary** when meeting the related criteria:

# CELIAC DISEASE

## *HLA-DQ* Genotyping Analysis

I. *HLA-DQA1* and *HLA-DQB1* genotyping analysis (81375, 81376, 81377, 81382, 81383) to rule out celiac disease (CD) is considered **medically necessary** when:

   A. The member/enrollee is being evaluated for celiac disease, **AND**

      1. Had an inconclusive serology (antibody) result, **OR**
      2. Had an inconclusive histology (biopsy) result, **OR**
      3. Started a gluten-free diet before evaluation for celiac disease, **AND**

   B. *HLA-DQA1* and *HLA-DQB1* genotyping analysis has not been previously performed.

II. *HLA-DQA1* and *HLA-DQB1* genotyping analysis (81375, 81376, 81377, 81382, 81383) to rule out celiac disease is considered **investigational** for all other indications.

back to top

# HEREDITARY HEMOCHROMATOSIS

## *HFE* C282Y and H63D Genotyping

I. *HFE* C282Y and H63D genotyping (81256) to establish a diagnosis of hereditary hemochromatosis is considered **medically necessary** when:

   A. The member/enrollee 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/enrollee has a first-degree relative with a diagnosis of hereditary hemochromatosis.

II. *HFE* C282Y and H63D genotyping (81256) to establish a diagnosis of hereditary hemochromatosis is considered **investigational** for all other indications, including general population screening for hereditary hemochromatosis.

back to top

# HEREDITARY PANCREATITIS

## Hereditary Pancreatitis Multigene Panel

I. Hereditary pancreatitis multigene panel analysis (81222, 81223, 81404, 81405, 81479) to establish a diagnosis of hereditary pancreatitis is considered **medically necessary** when:

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

   B. The member/enrollee 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 (81222, 81223, 81404, 81405, 81479) to establish a diagnosis of hereditary pancreatitis is considered **investigational** for all other indications.

back to top

# INFLAMMATORY BOWEL DISEASE

## Inflammatory Bowel Disease / Crohn's Disease Diagnostic Algorithmic Tests

I. Inflammatory bowel disease diagnostic algorithmic tests (81479, 82397, 83520, 86140, 88346, 88350) are considered **investigational.**

back to top

## Inflammatory Bowel Disease / Crohn's Disease Prognostic Algorithmic Tests

I. Inflammatory bowel disease prognostic algorithmic tests (81401, 83520, 88346, 88350) are considered **investigational**.

back to top

## Hereditary Inflammatory Bowel Disease / Crohn's Disease Panel Tests

I. Genetic testing for inflammatory bowel disease, including Crohn's disease, via a multigene panel (81479, 81321, 81406, 81407) is considered **medically necessary** when:

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

B. The member/enrollee 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/enrollee has congenital multiple intestinal atresias, **OR**

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

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

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

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

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

2. The member/enrollee is undergoing stem cell transplant, **OR**

3. The member/enrollee has a history of multiple intestinal resections.

II. Genetic testing for inflammatory bowel disease (81479, 81321, 81406, 81407), including Crohn's disease, via a multigene panel is considered **investigational** for all other indications.

back to top

# NON-INVASIVE LIVER FIBROSIS SERUM TESTS

## Non-Invasive Liver Fibrosis Serum Tests

I. Non-invasive liver fibrosis serum tests (0002M, 0003M, 84450, 84460, 85049) to rule out liver fibrosis are considered **medically necessary** when:

   A. The member/enrollee has one of the following:

      1. Nonalcoholic fatty liver disease (NAFLD), also known as metabolic dysfunction-associated steatotic liver disease (MASLD), **OR**
      2. Nonalcoholic steatohepatitis (NASH), **OR**
      3. Type 2 diabetes, **OR**
      4. Obesity (BMI >25), **OR**
      5. Abnormal liver function tests, **OR**
      6. A history of alcohol use, **AND**

   B. The member/enrollee had previous fibrosis-4 index (FIB-4) testing with a score of greater than 1.3.

II. Non-invasive liver fibrosis serum tests (0002M, 0003M, 84450, 84460, 85049) to rule out liver fibrosis are considered **investigational** for all other indications.

back to top

# 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. **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)

3. **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)
4. **Fibrosis-4 index(FIB-4)** is a blood test that measures the probability of advanced liver fibrosis based on AST, ALT, platelets, and age.

back to top

# BACKGROUND AND RATIONALE

### *HLA-DQ* Genotyping Analysis

*American College of Gastroenterology (ACG)*

The guidelines from the American College of Gastroenterology (2023) addressing the diagnosis and management of celiac disease (CD) stated that genetic testing for CD- compatible HLA haplotype is not required for diagnosis in all cases but may be helpful in selected situations such as in the context of serology-histology discrepancy. If negative, celiac disease is ruled out. HLA testing is also central to the approach to CD testing for individuals who have already started a GFD (gluten free diet) before evaluation; in the presence of a CD-compatible haplotype, a gluten challenge can be offered. (p. 63-64)

*American Gastroenterological Association*

A clinical practice update on diagnosis and monitoring of celiac disease (2019) states that HLA testing has value in its negative predictive value to rule out CD in patients who are seronegative but have histologic changes or did not have serology at the time of diagnosis. HLA testing may be reserved for second line evaluation of patients with an equivocal diagnosis (inconclusive serology, histology or prior gluten free diet).

*U.S. Preventive Services Task Force*

The US Preventive Service Task Form (2017) released guidelines on screening adults and children for CD. These guidelines reviewed the use of tTG IgA testing followed by an intestinal biopsy to screen asymptomatic patients. Genotype testing was not discussed. The overall conclusion of this review was that the current balance of evidence was insufficient to assess benefits and harms resulting from screening for CD. (p. 1252)

### *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 a 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 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.

Per GeneReviews, "*HFE* hemochromatosis should be suspected in individuals with…clinical signs of advanced iron overload, biochemical evidence of hemochromatosis, and/or family history of *HFE* hemochromatosis."

**Hereditary Pancreatitis Multigene Panel**

*American College of Gastroenterology*

In 2013, the American College of Gastroenterology issued guidelines on management of acute pancreatitis and included the following statement: "Genetic testing may be considered in young patients (younger than 30 years old) if no cause [of acute pancreatitis] is evident, and a family history of pancreatic disease is present (conditional recommendation, low quality of evidence)." (p. 1402)

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, hyper- triglyceridemia 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

**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.

**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.

**Hereditary Inflammatory Bowel Disease / Crohn's Disease Panel Tests**

*UpToDate (Higuchi LM and Bousvaros A, 2022)*

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)
- 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)

**Non-invasive Liver Fibrosis Serum Tests**

*Wattacheril, et al*

The American Gastroenterological Association (AGA) released a clinical practice update expert review (2023) regarding the role of noninvasive biomarkers in the evaluation and management of nonalcoholic fatty liver disease. They produced several best practice advice statements including the following:

- "Non-invasive tests can be used for risk stratification in the diagnostic evaluation of patients with nonalcoholic fatty liver disease (NAFLD);
- Liver biopsy should be considered for patients with NIT results that are indeterminate or discordant; conflict with other clinical, laboratory, or radiologic findings; or when alternative etiologies for liver disease are suspected.
- 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." (p. 1080)

Although FIB-4 score does not outperform other proprietary fibrosis biomarkers (eg, FibroTest/FibroSure [eviCore Healthcare], FIBROSpect NASH [Prometheus Laboratories], Hepamet Fibrosis Score, a Pro-C3 based score [ADAPT], FibroMeter [ARUP Laboratories], and Hepascore), FIB-4 is recommended as a firstline assessment for practitioners based on its simplicity and low cost. (p. 1081)

*Canivet, et al*

A review of screening for liver fibrosis in the general population (2022) stated that diagnostic studies using liver biopsy as a reference have demonstrated good rule-out sensitivity (80–90%) and good rule-in specificity (90–95%) of these NITs [noninvasive tests] for the diagnosis of advanced liver fibrosis in chronic liver diseases. Because these specialized blood tests include more expensive blood markers, they are best reserved for second-line evaluations of liver fibrosis, as recently proposed. (p. 7)

Type 2 diabetes mellitus (T2DM) was consistently associated with an increased risk of advanced liver fibrosis in the general population. (p. 2)

*Cusi, et al*

The American Association of Clinical Endocrinology (2022) produced a guideline that includes 34 evidence-based clinical practice recommendations for the diagnosis and management of persons with NAFLD and/or NASHin primary care and endocrinology clinical settings. They state that the following:

- "In persons at high risk of nonalcoholic fatty liver disease NAFLD (eg, type 2 diabetes mellitus, obesity, and metabolic syndrome), abdominal ultrasound is not required to diagnose hepatic steatosis, and it is reasonable to move directly to risk stratification after ruling out the secondary causes of liver disease." (p. 536)
- "Recommendation 2.1.1. Clinicians should consider persons with obesity and/or features of MetS, those with prediabetes or T2D, and those with hepatic steatosis on any imaging study and/or persistently elevated plasma aminotransferase levels (over 6 months) to be "high risk" and screen for NAFLD and advanced fibrosis." (p. 536)
- "Recommendation 2.2.1. Clinicians should use liver fibrosis prediction calculations to assess the risk of NAFLD with liver fibrosis. The preferred noninvasive initial test is the fibrosis-4 index (FIB-4)." (p. 537)
- "Recommendation 2.4.3: Clinicians should further risk stratify persons with T2D or T1D with cardiometabolic risk factors and/or elevated plasma aminotransferase levels (>30 U/L) using the FIB-4 elastography, and/or ELF test." (p. 538)
- "In high-risk populations (i.e., those with obesity and T2D), pharmacologic therapy to treat obesity or diabetes may also be considered in the presence of elevated plasma aminotransferase levels and/or FIB-4 scores of >1.3 and confirmatory imaging (ie, TE and MRE) or proprietary fibrosis biomarkers, such as the ELF test, when suggestive of clinically significant liver fibrosis, if imaging is not available." (p. 544)

*Rinella, et al*

The American Association for the Study of Liver Diseases issued a practice guideline (2023) for the clinical assessment and management of non alcoholic fatty liver disease. They recommend targeted screening of populations at increased risk for advanced liver disease, including individuals with type 2 diabetes, obesity with metabolic complications, family history of cirrhosis, or significant alcohol use, to identify and manage those with clinically significant fibrosis (stage 2 or higher). In the primary care setting, emphasis is on excluding advanced fibrosis using a test with a high negative predictive value such as FIB-4. (p. 1806-1807)

back to top

| Reviews, Revisions, and Approvals | Revision Date | Approval Date | Effective Date |
|---|---|---|---|
| Converted corporate to local policy. | 09/23 | 11/27/23 | |
| Semi-annual review. Updated title to reflect V1.2024 version. Overview, coding, reference-table, background and references updated. Throughout policy: replaced "coverage criteria" with "criteria. For Policy Reference Table: changed "HFE Sequencing and/or…" to "HFE and/or…"; replaced "81479" with "81256"; under "Inflammatory Bowel Disease.." removed "86140" and "88342" and added "86140" and "88342". For Other Related Policies: added "Molecular". For Criteria; Known Familial Variant Analysis for Gastroenterologic Disorders Panel: under I. replaced "mutation" with "variant"; under I.A. added "close relative"; under II. replaced "mutation" with "variant"; For Celiac Disease: added "(CD)"; removed "in whom"; for Hereditary Hemochromatosis: changed title of panel from "HFE Sequencing and/or Deletion…" to "HFE C282Y and H63D Genotyping"; under I. added "HFE C282Y…"' under I.B. added "first-degree relative"; under II. removed "sequencing…" and added "C282Y…"; removed "III. HFE sequencing…"; For Hereditary Pancreatitis: under I.B.1. removed "The member/enrollee has an unexplained" and replaced with "Unexplained"; under I.B.2. removed "The member/enrollee has recurrent" and replaced with "Recurrent"; under I.B.4. removed "A history of at" and replaced with "At"; For Hereditary Inflammatory Bowel Disease/Crohn's Disease Panel Tests: under I.A. replaced "has" with "had" and removed "typical" and added "IBD symptoms"; under I.B. removed "is under the age of 18…" and added "had IBD symptoms before age 18 years…"; added I.B.1. "At least one of the following…"; added I.B.1.a. "Affected family…"; added I.B.1.b. "Multiple family members…"; added I.B.1.c. "Consanguinity…"; added I.B.1.d. "Recurrent infections…"; added I.B.1.e. "Hemophagocytic…"; added I.B.1.f. "Autoimmune features…"; added I.B.1.g. "Autoimmune and dermatological…"; added I.B.1.h. "Malignancy…"; added I.B.1.i. "Multiple intestinal atresias."; changed title of "Test-Specific Not Covered…" panel to "Other Not Covered….". For Notes and Definitions: added "4. Monogenic disorders…". For Background and Rationale: changed "inheritance patterns" to "genetic testing"; under Hereditary Hemochromatosis: added "HFE C282Y and H63D Genotyping…"; under Inflammatory Bowel Disease/Crohn's Disease Panel Tests: removed "UpToDate (Snapper SB…)"; and added "European Society of Paediatric…"; and removed "British Society of Gastroenterology…"; added "Other Not Covered Gastroenterologic Disorders Tests…". | 12/23 | 2/27/24 | |
| Semi-annual review. Updated title to reflect V2.2024 version. Non-Invasive Liver Fibrosis Serum Tests criteria is new, created criteria to align coverage with guidelines. In Known Familial Variant Analysis for Gastroenterologic Conditions criteria, moved criteria to policy "Genetic Testing: General Approach to Genetic and Molecular Testing" to consolidate criteria for known familial variant tests. In *HLA-DQ* Genotyping Analysis criteria, updated criteria to align coverage with new guidelines. In Hereditary Inflammatory Bowel Disease / Crohn's Disease Panel Tests criteria, changed age at diagnosis for Crohn's disease to align with updated guidelines criteria (see Redline document). In *MCM6* | 06/24 | 8/19/24 | 9/19/24 |

| Reviews, Revisions, and Approvals | Revision Date | Approval Date | Effective Date |
|---|---|---|---|
| Targeted Variant Analysis criteria, retired criteria set based on rarity of testing (low order volume and low claim volume). In Other Not Covered Gastroenterologic Disorders Tests criteria, FibroSure tests moved to the new Non-invasive Liver Fibrosis Serum Tests coverage criteria. Remaining tests moved to the General Genetic and Molecular Testing policy for consolidation. Minor rewording for clarity throughout. Coding, reference-table, background and references updated. | | | |
| Semi-annual review. Updated title to reflect V1.2025 version. Inflammatory Bowel Disease / Crohn's Disease Diagnostic Algorithmic Tests: Evidence review update performed (see separate PDF); Removed duplicate example test from Policy Reference Table; CPT code 88342 was removed from the Policy Reference Table and the criteria; Updated Background and Rationale to reflect updated Evidence Review; Updated evidence review dates in References. Inflammatory Bowel Disease / Crohn's Disease Prognostic Algorithmic Tests: Evidence review update performed (see separate PDF); Removed example tests from Policy Reference Table; Removed PLA code 0203U and CPT codes 81356 and 86671 from the Policy Reference Table and the criteria; Updated Background and Rationale to reflect updated Evidence Review; Updated evidence review dates in References. Non-invasive Liver Fibrosis Serum Tests: Added "also known as metabolic dysfunction-associated steatotic liver disease (MASLD)" to the criteria. Hereditary Pancreatitis Multigene Panel: Updated GeneReviews copyright dates in Reference list. Celiac Disease - HLA-DQ Genotyping Analysis: Added the following criterion: "HLA-DQA1 and HLA-DQB1 genotyping analysis has not been previously performed."; Updated alleles to their proper names: "HLA-DQA1 and HLA-DQB1"; Hereditary Inflammatory Bowel Disease / Crohn's Disease Panel Tests: Updated test examples in Policy Reference Table; Minor grammar changes in Background and Rationale. HFE C282Y and H63D Genotyping: Minor grammar changes to the investigational section; Minor formatting changes in Policy Reference Table; Streamlined portions of the Background and Rationale for clarity and brevity; Updated GeneReviews copyright dates in Reference list. | 1/25 | 3/31/25 | 5/1/25 |

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back to top