Revision log
Coding Implications

CONCERT GENETIC TESTING: GASTROENTEROLOGY

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

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.

POLICY REFERENCE TABLE

Coding Implications

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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. Please see the Concert Platform for additional registered tests.

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
	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	Monogenic Inflammatory Bowel Disease Panel	81321, 81406, 81407, 81479, K50-K52	7, 8

Disease Panel Tests	(Invitae)		
	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)		
	Enhanced Liver Fibrosis (ELF) Test - 81517 (Siemens Health Care Diagnostics)		

RELATED POLICIES

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

- ***Oncology Testing: Hereditary Cancer*** for criteria related to genetic testing for hereditary cancer predisposition syndromes.
- ***Reproductive Testing: Carrier Screening*** for criteria related to parental carrier screening for genetic disorders before or during pregnancy.
- ***Reproductive Testing: Prenatal Diagnosis*** for criteria related to fetal diagnostic testing for genetic disorders during pregnancy and following a pregnancy loss.
- ***Specialty Testing: Multisystem Genetic Conditions*** for
- 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 criteria related to diagnostic and serum biomarker tests for nutritional status and biochemical disorders.
- ***Specialty Testing: Immunology and Rheumatology*** for criteria related to diagnostic and biomarker tests for autoimmune conditions and inherited immunodeficiency disorders.
- ***General Approach to Laboratory Testing*** for 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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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:

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/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. Current evidence does not support *HFE* C282Y and H63D genotyping to establish a diagnosis of hereditary hemochromatosis 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/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. Current evidence does not support hereditary pancreatitis multigene panel analysis to establish a diagnosis of hereditary pancreatitis for all other indications.

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INFLAMMATORY BOWEL DISEASE

Inflammatory Bowel Disease / Crohn's Disease Diagnostic Algorithmic Tests

I. Current evidence does not support inflammatory bowel disease / Crohn's disease diagnostic algorithmic tests for all indications**.**

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Inflammatory Bowel Disease / Crohn's Disease Prognostic Algorithmic Tests

I. Current evidence does not support inflammatory bowel disease / Crohn's disease prognostic algorithmic tests 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/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**

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

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

II. Current evidence does not support genetic testing for inflammatory bowel disease, including Crohn's disease, via a multigene panel 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/enrollee 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/enrollee 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/enrollee 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. Current evidence does not support blood-based non-invasive liver disease algorithmic tests to rule out liver fibrosis 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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In the AAFP article, “Eating Disorders in Primary Care: Diagnosis and Management” (2021), amylase measurement is recommended for those with a suspected or diagnosed eating disorder (p. 26). Characteristics of eating disorders, as defined above, are outlined in table 1 (p. 23).

American College of Gastroenterology (ACG)

In the publication, “ACG Guidelines: Management of Acute pancreatitis” (2024) the authors conclude that due to poor sensitivity and negative predictive value, serum amylase cannot be

used reliably for the diagnosis of acute pancreatitis. Serum lipase is preferred. It is further noted that amylase may remain within normal range after an acute pancreatic event. Serum lipase is more specific and remains elevated longer than amylase following disease presentation. In absence of abdominal pain consistent with acute pancreatitis, elevations of amylase and lipase fail to predict the development of acute pancreatitis (p. 420-421).

In the article, "ACG Clinical Guideline: Diagnosis and Management of Pancreatic Cysts" (2018), the authors suggest that assessment of cyst fluid amylase levels can be helpful, as very low levels (<250 IU/l) exclude a pseudocyst in 98% of cases (p. 471). Excluding a pseudocyst is clinically useful because pseudocysts do not require surveillance or treatment when they are asymptomatic, as they have no malignant potential (p. 465).

Rao

There are no formally established, universally accepted guidelines for clinical surveillance after pancreas transplantation. However, assessment of pancreatic enzymes and metabolic markers is routinely performed to monitor for complications.
In the clinical practice resource, Pancreas Transplantation Treatment & Management, the authors state that following pancreas transplant, patients are monitored for the lifetime of the transplanted organ for signs of infection and rejection. Testing can include electrolytes, complete blood count, blood urea nitrogen (BUN) and serum creatinine, glucose, serum amylase and lipase, immunosuppressive drug blood levels, and surveillance for CMV, Epstein-Barr virus, and BK virus infection.

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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. **Signs/symptoms of an eating disorder** include food restriction/avoidance, binging and/or purging, body image distortion, intense fear of gaining weight or being "fat", misuse of laxatives or diuretics, significant unexplained weight loss, and nutritional deficiencies due to inadequate food intake.
3. **Signs/symptoms of liver dysfunction** can include jaundice, right upper quadrant abdominal pain/tenderness, anemia, thrombocytopenia, unexplained bleeding or bruising,

loose/fatty stools, unexplained fatigue, abdominal swelling, edema, itching, anorexia and nausea or vomiting.

4. **Risk factors for liver dysfunction** can include significant alcohol consumption, high risk sexual practices, cancer, recreational drug use, prescription drugs with potential for liver toxicity (e.g., anti-epileptics, statins, NSAIDs, corticosteroids), environmental exposure to liver toxicants, biliary ductal obstruction or disease, certain autoimmune diseases, obesity, infection with hepatitis viruses or other pathogens associated with liver dysfunction, dyslipidemia, and personal or family history of certain disorders such as Wilson disease, Celiac disease, hemochromatosis, and alpha-1 antitrypsin deficiency.
5. **Signs/symptoms of chronic liver disease** are often absent or very mild especially in early stages. When they do occur, pain in the upper right abdomen, weight loss, enlarged spleen, jaundice, abdominal swelling, and abnormal bruising are among the most common.
6. **Fibrosis-4 index (FIB-4)** is a blood test that calculates the probability of advanced liver fibrosis based on AST, ALT, platelets, and age.
7. **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.
8. **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)
9. **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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Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed.	03/23	03/23
Semi-annual review. Updated title to reflect V1.2024 version. Overview, coding, reference-table, background and references updated. Throughout policy: replaced	10/23	10/23

Reviews, Revisions, and Approvals	Revision Date	Approval Date
"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…".		
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* Targeted Variant Analysis criteria, retired criteria set based on rarity of testing (low order volume	04/24	04/24

Reviews, Revisions, and Approvals	Revision Date	Approval Date
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.	11/24	11/24
Annual review. Policy title changed from “Concert Genetic Testing: Gastroenterologic Disorders” to “Concert Genetic Testing: Gastroenterology.” Inflammatory Bowel Disease / Crohn’s Disease Diagnostic Algorithmic Tests: The term "Crohn's Disease" was added to criterion I. to be consistent with the title and the phrase "for all indications" was added. Non-invasive Liver Fibrosis Serum Tests- replaced with new criteria in Blood-based Noninvasive Liver Disease Algorithmic Tests. “Investigational” policy statements changed to note that “current evidence does not support…” Coding table, rationale, background, and references updated.	11/25	12/25

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
19. Levinthal, D, Staller, K, Thangam, V. AGA Clinical Practice Update on Diagnosis and Management of Cyclic Vomiting Syndrome: Commentary. Gastroenterology. 2024 Jul 16;167(4):804-811e1. https://doi.org/10.1053/j.gastro.2024.05.031
20. Oppenlander KE, Chadwick C, Carman K. Acute Pancreatitis: Rapid Evidence Review. Am Fam Physician. 2022;106(1):44-50.
21. National Institute of Diabetes and Digestive and Kidney Diseases. Pancreatitis: Symptoms & Causes of Pancreatitis. 2017. Accessed November 18 2024. Available at: https://www.niddk.nih.gov/health-information/digestive-diseases/pancreatitis/symptoms-causes
22. Coucke EM, Akbar H, Kahloon A, et al. Biliary Obstruction. [Updated 2022 Nov 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. Accessed November 18 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539698/

23. Misra D, Sood T. Pancreatic Pseudocyst. [Updated 2023 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. Accessed November 18 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557594/
24. Elta GH, Enestvedt BK, Sauer BG, Lennon AM. ACG Clinical Guideline: Diagnosis and Management of Pancreatic Cysts. *Am J Gastroenterol*. 2018;113(4):464-479. doi:10.1038/ajg.2018.14
25. Rao J. Pancreas Transplantation Treatment & Management. MedScape. April 13, 2022. Accessed November 27, 2024. https://emedicine.medscape.com/article/429408-treatment#d10
26. Klein D, Sylvester J, Schvey N. Eating Disorders in Primary Care: Diagnosis and Management. *Am Fam Physician*. 2021;103(1):22-32
27. Kwo PY, Cohen SM, Lim JK. ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries. Am J Gastroenterol. 2017;112(1):18-35. doi:10.1038/ajg.2016.517. Accessed December 2, 2024. Available at: https://journals.lww.com/ajg/fulltext/2017/01000/acg_clinical_guideline__evaluation_of_abnormal.13.aspx
28. Rinella M E, Neuschwander-Tetri B A, Siddiqui MS, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology 77(5):p 1797-1835, May 2023. DOI: 10.1097/HEP.0000000000000323
29. Centers for Medicare & Medicaid Services. Medicare Coverage Database: Local Coverage Determination (LCD). Hepatic (Liver) Function Panel. (L33907). Accessed December 2, 2024. Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdId=33907&ver=15
30. Tholey D. Evaluation of the Patient With a Liver Disorder. Merck Manual. 2023. Accessed December 10, 2024. Available at: https://www.merckmanuals.com/professional/hepatic-and-biliary-disorders/approach-to-the-patient-with-liver-disease/evaluation-of-the-patient-with-a-liver-disorder

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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is

consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care and are solely responsible for the medical advice and treatment of member/enrollees. This clinical policy is not intended to recommend treatment for member/enrollees. Member/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note: For Medicaid member/enrollees, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare member/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs and LCDs and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.