Revision log
Coding Implications

CONCERT GENETICS GENETIC TESTING: GASTROENTEROLOGIC DISORDERS (NON-CANCEROUS)

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.

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. 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 and associated laboratories and CPT 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 Genetics Platform for a comprehensive list of registered tests.

Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Celiac Disease				
HLA-DQ Variant Analysis	HLA DQ Association (Labcorp)	81370, 81375, 81376, 81377, 81382, 81383	K90.0, R10.0-R10.13, R10.3-R10.829, R10.84-R10.9	4, 5, 6
	HLA DRB1,3,4,5,DQB1, Low Resolution (Quest Diagnostics)			
	HLA Typing for Celiac Disease (Quest Diagnostics)			
Hereditary Hemochromatosis				
HFE C282Y and/or H63D Genotyping	Hereditary Hemochromatosis DNA Mutation Analysis (Quest Diagnostics) HFE Targeted Variant - Single Test (GeneDx)	81256	E83.110, E83.118, E83.119, R79.0, E83.19, R16.0	1, 7, 12
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
	IBD sgi Diagnostic (Children's Hospital of Philadelphia-Division of Genomic Diagnostics)	83520, 82397, 86140, 88342, 81479		
Inflammatory Bowel Disease / Crohn's	PredictSURE IBD (KSL Diagnostics)	0203U	K50-K52	9
	Crohn's Disease Prognostic Panel (ARUP Laboratories)	83516, 86671		

Disease Prognostic Algorithmic Tests	Prometheus Crohn's Prognostic (Prometheus Laboratories)	81401, 83520, 88346, 88350		
Hereditary Inflammatory Bowel Disease / Crohn's Disease Panel Tests	Monogenic Inflammatory Bowel Disease Panel-Primary Genes (Invitae)	81479, 81321, 81406, 81407	K50-K52	10, 11
	Very Early Onset Inflammatory Bowel Genomic Panel (Children's Hospital of Philadelphia-Division of Genomic Diagnostics)			
Non-invasive Liver Fibrosis Serum Tests				
Non-invasive Liver Fibrosis Serum Tests	ASH FibroSURE (LabCorp) 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.

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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:

CELIAC DISEASE

HLA-DQ Genotyping Analysis

I. *HLA-DQ2* and *HLA-DQ8* variant analysis (81370, 81375, 81376, 81377, 81382, 81383) to rule out celiac disease (CD) is considered **medically necessary** when the member/enrollee meets one of the following:

   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.

II. *HLA-DQ2* and *HLA-DQ8* variant analysis (81370, 81375, 81376, 81377, 81382, 81383) to rule out celiac disease is considered **investigational** for all other indications.

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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 screen for hereditary hemochromatosis in the general population is considered **investigational** for all other indications.

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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 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 (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.

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INFLAMMATORY BOWEL DISEASE

Inflammatory Bowel Disease / Crohn's Disease Diagnostic Algorithmic Tests

I. Inflammatory bowel disease diagnostic algorithmic tests (81479, 82397, 83520, 86140, 88342, 88346, 88350) are considered **investigational.**

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Inflammatory Bowel Disease / Crohn's Disease Prognostic Algorithmic Tests

I. Inflammatory bowel disease prognostic algorithmic tests (0203U, 81401, 83516, 83520, 86671, 88346, 88350) are considered **investigational**.

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Hereditary Inflammatory Bowel Disease / Crohn's Disease Panel Tests

I. Genetic testing for inflammatory bowel disease (81479, 81321, 81406, 81407), 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**

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.

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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), **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.

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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. **Infantile-onset inflammatory bowel disease (Infantile-IBD)** is defined as clinical manifestations and/or receiving the diagnosis when younger than 2 years of age.[1]
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.[1]
4. **Monogenic disorders** are health conditions that are caused by mutations in a single gene.
5. **Fibrosis-4 (FIB-4)** is a blood test that measures the probability of advanced liver fibrosis based on AST, ALT, platelets, and age.

[1] 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.

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BACKGROUND AND RATIONALE

Celiac Disease - *HLA-DQ* Variant 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)

HEREDITARY HEMOCHROMATOSIS

HFE C282Y and H63D Genotyping

European Molecular Quality Network (EMQN)

Molecular genetic testing for hereditary hemochromatosis (HH) is recognized as a reference test to confirm the diagnosis of suspected HH or to predict its risk. The vast majority (typically >90%) of patients with clinically characterized HH are homozygous for the p.C282Y variant in the HFE gene, referred to as HFE-related HH. (p. 479)

The article includes guidelines, which state the following 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)
- Testing for p.S65C should not be offered

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).
- 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)

The ACG goes on to explain that there is evidence of cost-effectiveness of screening spouses of HH patients, as well as cost-effectiveness of genetic testing for children of HH patients when compared to serum screening (p. 1206).

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.

They point out the following regarding transferring-iron saturation (TS) levels in hereditary hemochromatosis (in the Clinical Characteristics section, Clinical Description-Heterozygotes):

> Although a threshold TS of 45% may be more sensitive than higher values for detecting HFE hemochromatosis, TS of 45% may also identify heterozygotes who are not at risk of developing other clinical abnormalities.

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 idio-pathic 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 Genetics - Evidence Review for Coverage Determination

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 body of literature includes few peer reviewed published studies on the clinical validity and clinical utility of Prometheus IBD sgi Diagnostic. The peer-reviewed 2013 validation study by Plevy et al used a 17 marker Prometheus panel and determined that this panel increased the discrimination between IBD and non-IBD, as well as Crohn's disease and ulcerative colitis compared to using serological markers alone. The current Prometheus offering, according to the laboratory website, has an additional serologic marker, to make 18 components. However, the website lists only seven serologic markers on the current panel. Given the different number of

components, it is unclear if the validation study of 2013 is applicable to the currently offered test. The Plevy validation study is not prospective, nor does it document the patient outcomes when Prometheus IBD sgi Diagnostic is used to base diagnostic decisions. This is appropriate for a validation study, however additional peer-reviewed studies showing prospective clinical utility outcomes have not been published. While studies on individual biomarkers are suggestive, the panel in question includes multiple markers with a proprietary algorithm, so evidence of the clinical usefulness must be from this same panel and algorithm. Further, Shirts et al. demonstrate that the predictive value of the Prometheus IBD sgi Diagnostic test primarily comes from the three widely available markers, pANCA+, ASCA-IgA+, and IG+.

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 Genetics Evidence Review for Coverage Determination

The results of the 2021 ECCO Scientific Workshop indicate that the PredictSURE IBD test is the only one that has sufficient evidence of clinical validity. Additionally, they point out that PredictSURE IBD currently has a clinical trial underway which may provide needed clinical utility evidence in the future. This group also has an ongoing clinical trial to further validate the biomarkers. 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.

Inflammatory bowel diseases are on a heterogenous spectrum that includes both ulcerative colitis and Crohn's disease. Two systematic reviews for serology biomarkers have been published recently, and indicate there is some promise in using these markers to distinguish ulcerative colitis from Crohn's disease, but studies show a marked heterogeneity in serological responses among populations. Another use of serological biomarkers is to predict future complications for individual patients, but these studies are similarly hampered by varied responses. It does appear that overall, multiple markers are more useful than single markers, but more well-designed studies are needed to support which markers are the most useful.

At the present time, Crohn's Prognostic Algorithmic tests, such as PredictSURE IBD, have INSUFFICIENT evidence in peer-reviewed publications to effectively result in improved health outcomes compared to the current standard of care. At this time, the current evidence does not

support health plan coverage due to a lack of evidence that prognostic serological IBD testing results in better outcomes than the current treatments.

Hereditary Inflammatory Bowel Disease / Crohn's Disease Panel Tests

UpToDate (Higuchi LM and Bousvaros A, 2021)

Clinical features that raise suspicion for monogenic IBD include:

- Young age of onset (e.g., younger than six years, particularly younger than age two years)
- Family history of IBD and/or immunodeficiency in multiple family members, particularly with those with a male reproductive system predominance, or consanguinity
- Recurrent infections or unexplained fever
- Associated features of autoimmunity (e.g., arthritis, primary sclerosing cholangitis, anemia, or endocrine dysfunction)
- Very severe IBD and/or resistance to conventional therapies for IBD
- Symptoms or signs suggesting hemophagocytic lymphohistiocytosis (hepatomegaly, fever, cytopenias, high ferritin)
- Lesions of the skin, nails, or hair
- Current or past history of cancer in the patient

Infants or young children presenting with these features warrant careful evaluation for monogenic IBD and consultation with an immunologist. (p. 7-8)

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 for the diagnosis and management of nonalcoholic fatty liver disease in primary care and endocrinology clinical settings. They state that the preferred noninvasive initial test is the fibrosis-4 index (FIB-4). (p. 537) 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)

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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 "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…".	10/23	10/23
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	04/24	04/24

guidelines criteria (see Redline document). In *MCM6* 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.		

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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.