BSC_CON_2.17	Genetic Testing: Gastroenterologic Disorders (Non-Cancerous)		
Original Policy Date:	May 1, 2024	**Effective Date:**	February 1, 2025
Section:	2.0 Medicine	**Page:**	Page 1 of 19

Example Test Table

The tests, associated laboratories, CPT codes, and ICD codes contained within this document serve only as examples to help users navigate claims and corresponding coverage 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.

Policy Statement Sections	Example Tests (Labs)	Common CPT Codes
Celiac Disease		
HLA-DQ Genotyping Analysis	Celiac HLA DQ Association (Labcorp)	81375, 81376, 81377, 81382, 81383
	HLA Typing for Celiac Disease (Quest Diagnostics)	
Hereditary Hemochromatosis		
HFE C282Y and H63D Genotyping	Hereditary Hemochromatosis DNA Mutation Analysis (Quest Diagnostics)	81256
	HFE Targeted Variant - Single Test (GeneDx)	
Hereditary Pancreatitis		
Hereditary Pancreatitis Multigene Panel	Hereditary Pancreatitis Panel (GeneDx)	81222, 81223, 81404, 81405, 81479
Inflammatory Bowel Disease		
Inflammatory Bowel Disease / Crohn's Disease Diagnostic Algorithmic Tests	Prometheus IBD sgi Diagnostic (Prometheus Laboratories)	81479, 82397, 83520, 86140, 88346, 88350
Inflammatory Bowel Disease / Crohn's 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 (Invitae)	81479, 81321, 81406, 81407
	Very Early Onset Inflammatory Bowel (VEO-IBD) 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
	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

Policy Statement

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) may be considered **medically necessary** when **BOTH** of the following criteria are met:
   A. The member is being evaluated for celiac disease, **AND any** of the following:
      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.

HEREDITARY HEMOCHROMATOSIS
HFE C282Y and H63D Genotyping

III. *HFE* C282Y and H63D genotyping (81256) to establish a diagnosis of hereditary hemochromatosis may be considered **medically necessary** when **EITHER** of the following criteria is met:
   A. The member has abnormal serum iron indices (e.g., elevated serum transferrin-iron saturation and/or elevated serum ferritin concentration, indicating iron overload), **OR**
   B. The member has a first-degree relative with a diagnosis of hereditary hemochromatosis.

IV. *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.

HEREDITARY PANCREATITIS
Hereditary Pancreatitis Multigene Panel

V. Hereditary pancreatitis multigene panel analysis (81222, 81223, 81404, 81405, 81479) to establish a diagnosis of hereditary pancreatitis may be considered **medically necessary** when **ALL** of the following criteria are met:
   A. The member has a personal history of pancreatitis, **AND**
   B. The member meets **at least one** of the following:
      1. Unexplained episode of acute pancreatitis in childhood (18 years or younger), **OR**
      2. Recurrent (two or more separate, documented) acute attacks of pancreatitis for which there is no explanation (i.e., anatomical anomalies, ampullary or main pancreatic strictures, trauma, viral infection, gallstones, alcohol, drugs, hyperlipidemia, etc.), **OR**
      3. Chronic pancreatitis of unknown cause, particularly with onset before age 35 years without a history of heavy alcohol use, **OR**
      4. At least one close relative with recurrent acute pancreatitis, chronic pancreatitis of unknown cause, or childhood pancreatitis of unknown cause, **AND**
   C. The panel includes, at a minimum, the following genes: *PRSS1*, *SPINK*, *CFTR*, and *CTRC*.

VI. Hereditary pancreatitis multigene panel analysis (81222, 81223, 81404, 81405, 81479) to establish a diagnosis of hereditary pancreatitis is considered **investigational** for all other indications.

INFLAMMATORY BOWEL DISEASE

Inflammatory Bowel Disease / Crohn's Disease Diagnostic Algorithmic Tests

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

Inflammatory Bowel Disease / Crohn's Disease Prognostic Algorithmic Tests

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

Hereditary Inflammatory Bowel Disease / Crohn's Disease Panel Tests

IX. Genetic testing for inflammatory bowel disease, including Crohn's disease, via a multigene panel (81479, 81321, 81406, 81407) may be considered **medically necessary** when **EITHER** of the following criteria is met:
   A. The member was diagnosed with infantile-onset inflammatory bowel disease (Infantile-IBD) before age 2 years, **OR**
   B. The member was diagnosed with very early onset inflammatory bowel disease (VEO-IBD) before age 6 years, **AND any** of the following:
      1. **At least one** of the following:
         a. The member has congenital multiple intestinal atresias, **OR**
         b. The member has congenital diarrhea, **OR**
         c. The member has a diagnosis of malignancy under age 25, **OR**
         d. The member has features of an inborn error of immunity such as susceptibility to infections, **OR**
         e. The member has complex autoimmune features, **OR**
         f. The member has a close relative meeting any of the above criteria, **OR**
      2. The member is undergoing stem cell transplant, **OR**
      3. The member has a history of multiple intestinal resections.

X. 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.

NON-INVASIVE LIVER FIBROSIS SERUM TESTS

Non-Invasive Liver Fibrosis Serum Tests

XI. Non-invasive liver fibrosis serum tests (0002M, 0003M, 84450, 84460, 85049) to rule out liver fibrosis may be considered **medically necessary** when the member meets **BOTH** of the following:
   A. The member 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 had previous fibrosis-4 index (FIB-4) testing with a score of greater than 1.3.

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

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

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.

Coding
See the Codes table for details.

Description

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.

Related Policies

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

- ***Genetic Testing: Hereditary Cancer Susceptibility*** for coverage criteria related to germline testing for hereditary cancer syndromes, including Lynch/HNPCC syndrome.
- ***Genetic Testing: Prenatal and Preconception Carrier Screening*** for coverage 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 coverage criteria related to diagnostic genetic testing for conditions affecting multiple organ systems.
- ***Genetic Testing: Metabolic, Endocrine, and Mitochondrial Disorders*** for coverage criteria related to genetic testing for *MTHFR*.
- ***Genetic Testing: General Approach to Genetic and Molecular Testing*** for coverage 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.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Rationale

Background

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 (e.g., due to recurrent sinopulmonary infections, systemic infections, meningitis, gastrointestinal infections, or cutaneous infections) in the presence of abnormal laboratory tests (e.g., congenital lymphopenia or neutropenia, or combined immunoglobulin concentration abnormalities) meeting diagnostic criteria of an inborn error of immunity (i.e., 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)

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Documentation for Clinical Review

Please provide the following documentation:

- Name of the test being requested or the Concert Genetics GTU identifier.
  The Concert Genetics GTU can be found at https://app.concertgenetics.com
- CPT codes to be billed for the particular genetic test (GTU required for unlisted codes)
- History and physical and/or consultation notes including:
  - Clinical findings:
    - Signs/symptoms leading to a suspicion of genetic condition
    - Family history if applicable
  - Prior evaluation/treatment:
    - Previous test results (i.e., imagining, lab work, etc.) related to reason for genetic testing

- Family member's genetic test result, if applicable
- Rationale
  - Reason for performing test
  - How test result will impact clinical decision making

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	81222	CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; duplication/deletion variants
	81223	CFTR (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; full gene sequence
	81256	HFE (hemochromatosis) (e.g., hereditary hemochromatosis) gene analysis, common variants (e.g., C282Y, H63D)
	81321	PTEN (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
	81375	HLA Class II typing, low resolution (e.g., antigen equivalents); HLA-DRB1/3/4/5 and -DQB1
	81376	HLA Class II typing, low resolution (e.g., antigen equivalents); one locus (e.g., HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each
	81377	HLA Class II typing, low resolution (e.g., antigen equivalents); one antigen equivalent, each
	81382	HLA Class II typing, high resolution (i.e., alleles or allele groups); one locus (e.g., HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each
	81383	HLA Class II typing, high resolution (i.e., alleles or allele groups); one allele or allele group (e.g., HLA-DQB1*06:02P), each
	81401	Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
	81404	Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
	81405	Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
	81406	Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)

Type	Code	Description
	81407	Molecular pathology procedure, Level 8 (e.g., analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
	81479	Unlisted molecular pathology procedure
	81517	Liver disease, analysis of 3 biomarkers (hyaluronic acid [HA], procollagen III amino terminal peptide [PIIINP], tissue inhibitor of metalloproteinase 1 [TIMP-1]), using immunoassays, utilizing serum, prognostic algorithm reported as a risk score and risk of liver fibrosis and liver-related clinical events within 5 years
	82397	Chemiluminescent assay
	83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
	84450	Transferase; aspartate amino (AST) (SGOT)
	84460	Transferase; alanine amino (ALT) (SGPT)
	85049	Blood count; platelet, automated
	86140	C-reactive protein;
	88346	Immunofluorescence, per specimen; initial single antibody stain procedure
	88350	Immunofluorescence, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure)
	0203U	Autoimmune (inflammatory bowel disease), mRNA, gene expression profiling by quantitative RT-PCR, 17 genes (15 target and 2 reference genes), whole blood, reported as a continuous risk score and classification of inflammatory bowel disease aggressiveness
	0002M	Liver disease, ten biochemical assays (ALT, A2-macroglobulin, apolipoprotein A-1, total bilirubin, GGT, haptoglobin, AST, glucose, total cholesterol and triglycerides) utilizing serum, prognostic algorithm reported as quantitative scores for fibrosis, steatosis and alcoholic steatohepatitis (ASH)
	0003M	Liver disease, ten biochemical assays (ALT, A2-macroglobulin, apolipoprotein A-1, total bilirubin, GGT, haptoglobin, AST, glucose, total cholesterol and triglycerides) utilizing serum, prognostic algorithm reported as quantitative scores for fibrosis, steatosis and nonalcoholic steatohepatitis (NASH)
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
05/01/2024	New policy. Archived Blue Shield of California Medical Policy: 2.04.95, 2.04.80, 2.04.94, and 2.04.41.
02/01/2025	Annual review. Policy statement, guidelines and literature updated. Coding update.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
Genetic Testing: Gastroenterologic Disorders (Non-Cancerous) **BSC_CON_2.17** **Policy Statement:** KNOWN FAMILIAL VARIANT ANALYSIS FOR GASTROENTEROLOGIC DISORDERS I. Targeted variant analysis for a known familial variant (81403) for a gastroenterologic disorder may be considered **medically necessary** when: A. The member has a close relative with a known pathogenic or likely pathogenic variant causing the condition. II. Targeted variant analysis for a known familial variant (81403) for a gastroenterologic disorder is considered **investigational** for all other indications. CELIAC DISEASE ***HLA-DQ* Genotyping Analysis** III. *HLA-DQ2* and *HLA-DQ8* variant analysis (81370, 81375, 81376, 81377, 81382, 81383) to rule out celiac disease (CD) may be considered **medically necessary** when the member meets **one** of the following: A. The member has equivocal small-bowel histological finding in seronegative patients B. The member is on a gluten-free diet AND no testing for CD was done before gluten-free diet C. The member has discrepant celiac-specific serology and histology D. The member has suspicion of refractory CD where the original diagnosis of celiac remains in question. IV. *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.	**Genetic Testing: Gastroenterologic Disorders (Non-Cancerous)** **BSC_CON_2.17** **Policy Statement:** 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) may be considered **medically necessary** when **BOTH** of the following criteria are met: A. The member is being evaluated for celiac disease, **AND any** of the following: 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.

POLICY STATEMENT	
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HEREDITARY HEMOCHROMATOSIS ***HFE* C282Y and H63D Genotyping** V. *HFE* C282Y and H63D genotyping (81256) to establish a diagnosis of hereditary hemochromatosis may be considered **medically necessary** when **EITHER** of the following criteria is met: A. The member has abnormal serum iron indices, especially elevated serum transferrin-iron saturation and/or elevated serum ferritin concentration, indicating iron overload B. The member has a first-degree relative with a diagnosis of hereditary hemochromatosis, especially if the relative has Type I HH where the relative has two C282Y mutations (homozygous). VI. *HFE* C282Y and H63D genotyping (81256) to screen for hereditary hemochromatosis in the general population is considered **investigational**.	**HEREDITARY HEMOCHROMATOSIS** ***HFE* C282Y and H63D Genotyping** III. *HFE* C282Y and H63D genotyping (81256) to establish a diagnosis of hereditary hemochromatosis may be considered **medically necessary** when **EITHER** of the following criteria is met: A. The member has abnormal serum iron indices (e.g., elevated serum transferrin-iron saturation and/or elevated serum ferritin concentration, indicating iron overload), **OR** B. The member has a first-degree relative with a diagnosis of hereditary hemochromatosis. IV. *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.
LACTASE INSUFFICIENCY ***MCM6* Targeted Variant Analysis** VII. *MCM6* variant analysis (81479) for the prediction of lactase insufficiency is considered **investigational**.	
HEREDITARY PANCREATITIS **Hereditary Pancreatitis Multigene Panel** VIII. Hereditary pancreatitis multigene panel analysis (81222, 81223, 81404, 81405, 81479) to establish a diagnosis of hereditary pancreatitis may be considered **medically necessary** when **ALL** of the following criteria is met: A. The member has personal history of pancreatitis B. The member meets **at least one** of the following; 1. Unexplained episode of acute pancreatitis in childhood (18 years or younger) 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.)	**HEREDITARY PANCREATITIS** **Hereditary Pancreatitis Multigene Panel** V. Hereditary pancreatitis multigene panel analysis (81222, 81223, 81404, 81405, 81479) to establish a diagnosis of hereditary pancreatitis may be considered **medically necessary** when **ALL** of the following criteria are met: A. The member has a personal history of pancreatitis, **AND** B. The member meets **at least one** of the following: 1. Unexplained episode of acute pancreatitis in childhood (18 years or younger), **OR** 2. Recurrent (two or more separate, documented) acute attacks of pancreatitis for which there is no explanation (i.e., anatomical anomalies, ampullary or main pancreatic strictures, trauma, viral infection, gallstones, alcohol, drugs, hyperlipidemia, etc.), **OR**

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3. Chronic pancreatitis of unknown cause, particularly with onset before age 35 years without a history of heavy alcohol use 4. At least one close relative with recurrent acute pancreatitis, chronic pancreatitis of unknown cause, or childhood pancreatitis of unknown cause C. The panel includes, at a minimum, the following genes: *PRSS1*, *SPINK*, *CFTR* and *CTRC*.	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*.
IX. Hereditary pancreatitis multigene panel analysis (81222, 81223, 81404, 81405, 81479) to establish a diagnosis of hereditary pancreatitis is considered **investigational** for all other indications.	VI. Hereditary pancreatitis multigene panel analysis (81222, 81223, 81404, 81405, 81479) to establish a diagnosis of hereditary pancreatitis is considered **investigational** for all other indications.
INFLAMMATORY BOWEL DISEASE **Inflammatory Bowel Disease / Crohn's Disease Diagnostic Algorithmic Tests** X. Inflammatory bowel disease diagnostic algorithmic tests (81479, 82397, 83520, 86140, 88342, 88346, 88350) are considered **investigational.**	INFLAMMATORY BOWEL DISEASE **Inflammatory Bowel Disease / Crohn's Disease Diagnostic Algorithmic Tests** VII. Inflammatory bowel disease diagnostic algorithmic tests (81479, 82397, 83520, 86140, 88346, 88350) are considered **investigational.**
Inflammatory Bowel Disease / Crohn's Disease Prognostic Algorithmic Tests XI. Inflammatory bowel disease prognostic algorithmic tests (0203U, 81401, 83516, 83520, 86671, 88346, 88350) are considered **investigational**.	**Inflammatory Bowel Disease / Crohn's Disease Prognostic Algorithmic Tests** VIII. Inflammatory bowel disease prognostic algorithmic tests (81401, 83520, 88346, 88350) are considered **investigational**.
Hereditary Inflammatory Bowel Disease / Crohn's Disease Panel Tests XII. Genetic testing for inflammatory bowel disease (81479), including Crohn's disease, via a multigene panel may be considered **medically necessary** when **EITHER** of the following criteria is met: A. The member had very early onset of IBD symptoms before age 2 years B. The member had IBD symptoms before age 18 years, **AND**	**Hereditary Inflammatory Bowel Disease / Crohn's Disease Panel Tests** IX. Genetic testing for inflammatory bowel disease, including Crohn's disease, via a multigene panel (81479, 81321, 81406, 81407) may be considered **medically necessary** when **EITHER** of the following criteria is met: A. The member was diagnosed with infantile-onset inflammatory bowel disease (Infantile-IBD) before age 2 years, **OR** B. The member was diagnosed with very early onset inflammatory bowel disease (VEO-IBD) before age 6 years, **AND any** of the following:

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1. **At least one** of the following: a. Affected family member with a suspected monogenic disorder, who has not had genetic testing b. Multiple family members with early-onset IBD c. Consanguinity d. Recurrent infections e. Hemophagocytic lymphohistiocytosis (HLH) f. Autoimmune features g. Autoimmune and dermatological features h. Malignancy i. Multiple intestinal atresias	1. **At least one** of the following: a. The member has congenital multiple intestinal atresias, **OR** b. The member has congenital diarrhea, **OR** c. The member has a diagnosis of malignancy under age 25, **OR** d. The member has features of an inborn error of immunity such as susceptibility to infections, **OR** e. The member has complex autoimmune features, **OR** f. The member has a close relative meeting any of the above criteria, **OR** 2. The member is undergoing stem cell transplant, **OR** 3. The member has a history of multiple intestinal resections.
XIII. Genetic testing for inflammatory bowel disease (81479), including Crohn's disease, via a multigene panel is considered **investigational** for all other indications.	X. 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.
Non-invasive Liver Fibrosis Serum Tests	NON-INVASIVE LIVER FIBROSIS SERUM TESTS **Non-Invasive Liver Fibrosis Serum Tests**
XIV. Non-invasive liver fibrosis serum tests (0002M, 0003M, 84450, 84460, 85049) to rule out liver disease may be considered **medically necessary** when the member meets **BOTH** of the following: A. The member has **one** of the following: 1. Nonalcoholic fatty liver disease (NAFLD) 2. Nonalcoholic steatohepatitis (NASH) 3. Type 2 diabetes 4. Obesity (BMI >25) 5. Abnormal liver function tests 6. A history of alcohol use B. The member had previous fibrosis-4 index (FIB-4) testing with a score of greater than 1.3.	XI. Non-invasive liver fibrosis serum tests (0002M, 0003M, 84450, 84460, 85049) to rule out liver fibrosis may be considered **medically necessary** when the member meets **BOTH** of the following: A. The member 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 had previous fibrosis-4 index (FIB-4) testing with a score of greater than 1.3.

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