BSC_CON_2.17	Genetic Testing: Gastroenterologic Disorders (Non-Cancerous)		
Original Policy Date:	May 1, 2024	**Effective Date:**	May 1, 2024
Section:	2.0 Medicine	**Page:**	Page 1 of 20

Example Test Table

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

Policy Statement Sections	Example Tests (Labs)	Common CPT Codes
Known Familial Variant Analysis for Gastroenterologic Disorders		
Known Familial Variant Analysis for Gastroenterologic Disorders	Targeted Mutation Analysis for a Known Familial Variant	81403
Celiac Disease		
HLA-DQ Variant Analysis	HLA DQ Association (Labcorp)	81370, 81375, 81376, 81377, 81382, 81383
	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
Lactase Insufficiency		
MCM6 Targeted Variant Analysis	Lactose intolerance (polymorphisms-13910C>T; c.1917+326C>T and 22018G>A; 1362+117G>A on *MCM6* gene) (CGC Genetics)	81479
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

Policy Statement Sections	Example Tests (Labs)	Common CPT Codes
	IBD sgi Diagnostic (Children's Hospital of Philadelphia-Division of Genomic Diagnostics)	83520, 82397, 86140, 88342, 81479
Inflammatory Bowel Disease / Crohn's Disease Prognostic Algorithmic Tests	PredictSURE IBD (KSL Diagnostics)	0203U
	Crohn's Disease Prognostic Panel (ARUP Laboratories)	83516, 86671
	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
	Very Early Onset Inflammatory Bowel Genomic Panel (Children's Hospital of Philadelphia-Division of Genomic Diagnostics)	
Non-invasive Liver Fibrosis Disease Serum Tests		
Non-invasive Liver Fibrosis Serum Tests	ASH FibroSURE	0002M
	NASH FibroSURE	0003M
	FIB-4 Index Panel with Reflex to Enhanced Liver Fibrosis (ELF) Score (Quest Diagnostics)	84450, 84460, 85049

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.

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**.

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.)
      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*.

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.

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 / Crohn's Disease Prognostic Algorithmic Tests

XI. Inflammatory bowel disease prognostic algorithmic tests (0203U, 81401, 83516, 83520, 86671, 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**
  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

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

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.

XV. Non-invasive liver fibrosis serum tests to rule out liver disease 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

NOTES AND 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. **Typical inflammatory bowel disease (IBD) symptoms** include diarrhea, abdominal pain, infections, and bleeding.
3. **Aggressive, refractory or unusual IBD presentation** includes:
   - a. Recurrent severe infections or atypical infections consistent with diagnostic criteria of a primary immunodeficiency,

   b. Hemophagocytic lymphohistiocytosis
   c. Autoimmune features in particular features of
      i. Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome
      ii. Malignancies or multiple intestinal atresias
   d. Unusual disease evolution
   e. Non-response to multiple IBD medications
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.

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.

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 ***(to be published)***
- ***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.

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.

Regulatory Status

- N/A

Rationale

Known Familial Variant Analysis for Gastroenterologic Disorders

Genetic Support Foundation

The Genetic Support Foundation's Genetics 101 information on genetic testing says the following about testing for familial pathogenic variants:

> Genetic testing for someone who may be at risk for an inherited disease is always easier if we know the specific genetic cause. Oftentimes, the best way to find the genetic cause is to start by testing someone in the family who is known or strongly suspected to have the disease. If their testing is positive, then we can say that we have found the familial pathogenic (harmful) variant. We can use this as a marker to test other members of the family to see who is also at risk.

Celiac Disease - *HLA-DQ* Variant Analysis

American College of Gastroenterology (ACG)

The guidelines from the American College of Gastroenterology (2013) addressing the diagnosis and management of celiac disease (CD) stated the following on human leukocyte antigen (HLA) gene testing:

1. HLA-DQ2/DQ8 testing should not be used routinely in the initial diagnosis of CD [celiac disease] (Strong recommendation, moderate level of evidence).
2. HLA-DQ2/DQ8 genotyping testing should be used to effectively rule out the disease in selected clinical situations (Strong recommendation, moderate level of evidence).
3. Examples of such clinical situations include but are not limited to:
    a. Equivocal small-bowel histological finding (Marsh I-II) in seronegative patients
    b. Evaluation of patients on a gluten-free diet in whom no testing for CD was done before gluten-free diet
    c. Patients with discrepant celiac-specific serology and histology
    d. Patients with suspicion of refractory CD where the original diagnosis of celiac remains in question. (p. 9)

The 2013 guidelines from the American College of Gastroenterology do not recommend routine testing of family members, because of the high likelihood (>80%) of these individuals encoding HLA susceptibility. (p. 3)

American Gastroenterological Association Institute

The American Gastroenterological Association Institute (2006) issued a position statement on the diagnosis and management of CD. Regarding serologic testing, the Institute concluded that, in the primary care setting, the transglutaminase immunoglobulin (Ig) A antibody test is the most efficient single serologic test for diagnosing CD. The guidelines indicated that the antiendomysial antibodies IgA test is more time-consuming and operator dependent than the tissue transglutaminase (tTG). If IgA deficiency is strongly suspected, testing with IgG anti endomysial antibody (EMA) and/or tTG IgG antibody test is recommended. If serologic test results are negative and CD is still strongly suspected, providers can test for the presence of the disease-associated HLA alleles and, if present, perform a small intestinal mucosal biopsy. Alternatively, if signs and symptoms suggest that small intestinal biopsy is appropriate, patients can proceed to biopsy without testing for HLA alleles. (p. 4)

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.

Lactase Insufficiency - *MCM6* Targeted Variant Analysis

Obermayer-Pietsch et al 2004
LCT(T/C 13910) polymorphisms are associated with lactose intolerance and reduced bone density, and they predispose to bone fractures in postmenopausal women. Genetic testing for lactose intolerance may complement common indirect methods for the detection of individuals at risk for both lactose malabsorption and osteoporosis. (p. 42)

Mattar et al 2012
Genetic testing has been a new tool for the diagnosis of hypolactasia/lactase persistence but may not detect all the single nucleotide polymorphisms associated with this disorder. (p. 119)

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)

Inflammatory Bowel Disease / Crohn's Disease Diagnostic Algorithmic Tests

Concert Genetics - Evidence Review for Coverage Determination - Inflammatory Bowel Disease/Crohn's Diagnostic Algorithmic Tests

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 - Inflammatory Bowel Disease/Crohn's Disease Prognostic Algorithmic Tests
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 male 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)

European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)
The purpose of this statement was to demonstrate that genomic technologies should be considered an integral part of patient care to investigate patients at risk for monogenic forms of IBD. (p. 2) The majority of patients with monogenic IBD present in the first 6 years of life (i.e. very early-onset IBD). Consanguinity, a family history of autoimmune disease, and family history of suspected or confirmed monogenic disorders are associated with monogenic IBD. Several reviews have provided an overview of extraintestinal features of the diverse immunodeficiency and epithelial cell disorders that can present with intestinal inflammation. Those features include recurrent infections, hemophagocytic lymphohistiocytosis (HLH), autoimmune and dermatological features as well as development of malignancy. (p. 6-7)

According to the diagnostic algorithm for monogenic inflammatory bowel disease proposed by the position statement, patients with suspected monogenic IBD (either before age 2 years of IBD-onset or over age 2 years of IBD-onset with additional red flag features), a multidisciplinary team assessment will help to establish a diagnostic and therapeutic care plan. (p. 26)

Below is a summary of clinical features that should prompt considering a monogenic inflammatory bowel disease workup (Red flag signs) (p. 24):

- Age of inflammatory bowel disease (IBD) presentation
  - IBD symptom onset before age 2 years
  - IBD onset before age 6 years, in particular when other red flag signs are present
- Family history
  - Affected family member with a suspected monogenic disorder
  - Consanguinity
  - Multiple family members with early-onset IBD
- Comorbidity and extraintestinal manifestations are particularly relevant for monogenic IBD diagnostic considerations when rare or atypical for patient age irrespective of organ manifestation.
  - Recurrent severe infections or atypical infections consistent with diagnostic criteria of a primary immunodeficiency
  - Hemophagocytic lymphohistiocytosis
  - Autoimmune features in particular features of Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome
  - Malignancies
  - Multiple intestinal atresias

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 (e.g., 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.

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

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 (i.e., 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)
	81370	HLA Class I and II typing, low resolution (e.g., antigen equivalents); HLA-A, -B, -C, -DRB1/3/4/5, and -DQB1
	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)
	81403	Molecular pathology procedure, Level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR

Type	Code	Description
		in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
	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)
	81479	Unlisted molecular pathology procedure
	82397	Chemiluminescent assay
	83516	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; qualitative or semiquantitative, multiple step method
	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;
	86671	Antibody; fungus, not elsewhere specified
	88342	Immunohistochemistry or immunocytochemistry, per specimen; initial single antibody stain procedure
	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)
	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)
	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
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.

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
New Policy	**Genetic Testing: Gastroenterologic Disorders (Non-Cancerous)** **BSC_CON_2.17**
Policy Statement:	**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.
Human Leukocyte Antigen Testing for Celiac Disease 2.04.95 I. Human leukocyte antigen *(HLA)-DQ2* and *HLA-DQ8* testing may be considered **medically necessary** to rule out celiac disease in: A. Individuals with persistent symptoms despite negative serology and histology B. Individuals with discordant serologic and histologic (biopsy) findings	**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.
II. *HLA-DQ2* and *HLA-DQ8* testing for celiac disease is considered **investigational** in all other situations.	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.

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
Genetic Testing for Hereditary Hemochromatosis 2.04.80 I. Genetic testing for human hemochromatosis (HFE) gene variants may be considered **medically necessary** for **either** of the following conditions: A. In an individual with abnormal serum iron indices indicating iron overload. B. In individuals with a family history of hemochromatosis in a first-degree relative. II. Genetic testing for hereditary hemochromatosis for screening of the general population is considered **investigational** **Genetic Testing for Lactase Insufficiency 2.04.94** I. The use of targeted *MCM6* -13910C>T variant analysis for the prediction of lactase insufficiency is considered **investigational**	**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**. **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.)

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
	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*. 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. **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 / Crohn's Disease Prognostic Algorithmic Tests** XI. Inflammatory bowel disease prognostic algorithmic tests (0203U, 81401, 83516, 83520, 86671, 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** 1. **At least one** of the following: a. Affected family member with a suspected monogenic disorder, who has not had genetic testing

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
	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 XIII. Genetic testing for inflammatory bowel disease (81479), including Crohn's disease, via a multigene panel is considered **investigational** for all other indications.
Noninvasive Techniques for the Evaluation and Monitoring of Patients With Chronic Liver Disease 2.04.41 I. A single FibroSURE multianalyte assay may be considered **medically necessary** once for the evaluation of individuals with chronic liver disease. II. FibroSURE multianalyte assays are considered **investigational** for monitoring of individuals with chronic liver disease. III. Other multianalyte assays with algorithmic analyses are considered **investigational** for the evaluation or monitoring of individuals with chronic liver disease. IV. Transient elastography (FibroScan) imaging may be considered **medically necessary** once for the evaluation of individuals with chronic liver disease. V. Transient elastography (FibroScan) imaging is considered **investigational** for monitoring of individuals with chronic liver disease.	**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. XV. Non-invasive liver fibrosis serum tests to rule out liver disease are considered **investigational** for all other indications.

POLICY STATEMENT	
BEFORE **Red font: Verbiage removed**	**AFTER** **Blue font: Verbiage Changes/Additions**
VI. The use of other noninvasive imaging is considered **investigational** for the evaluation or monitoring of individuals with chronic liver disease including but not limited to any of the following: A. Magnetic resonance elastography B. Multiparametric magnetic resonance imaging C. Acoustic radiation force impulse imaging (ARFI; e.g., acuson s2000) D. Real-time tissue elastography	