

GENETIC TESTING: GASTROENTEROLOGIC DISORDERS (NON-CANCEROUS)

OVERVIEW

Genetic testing for gastroenterologic (non-cancerous) disorders may be used to confirm a diagnosis in a patient who has signs and/or symptoms of a specific gastroenterologic disorder. Confirming the diagnosis may alter aspects of management and may eliminate the need for further diagnostic workup. This document addresses genetic testing for common gastroenterologic (non-cancerous) conditions.

POLICY REFERENCE TABLE

Below is a list of higher volume tests and the associated laboratories for each coverage criteria section. This list is not all inclusive.

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Known Familial Variant Analysis for Gastroenterologic Disorders				
Known Familial Variant Analysis for Gastroenterologic Disorders	Targeted Mutation Analysis for a Known Familial Variant	81403		16
Celiac Disease				
HLA-DQ Variant Analysis	HLA DQ Association (LabCorp)	81370, 81375, 81376, 81377,	K90.0, R10.0-R10.13, R10.3-	4, 5, 6
	HLA DRB1,3,4,5,DQB1, Low Resolution (Quest Diagnostics)	81382, 81383		

	HLA Typing for Celiac Disease (Quest Diagnostics)		R10.829, R10.84-R10.9	
Hereditary Hemochromatosis				
HFE Sequencing and/or Deletion/Duplication Analysis	Hereditary Hemochromatosis via the <i>HFE</i> Gene (PreventionGenetics)	81479	E83.110, E83.118, E83.119, R79.0, E83.19, R16.0	1, 7
	Hereditary Hemochromatosis DNA Mutation Analysis (Quest Diagnostics)	81256		
Lactase Insufficiency				
MCM6 Targeted Variant Analysis	Lactose intolerance (polymorphisms-13910C>T; c.1917+326C>T and 22018G>A; 1362+117G>A on <i>MCM6</i> gene) (CGC Genetics)	81479	E73.1	14, 15
Hereditary Pancreatitis				
Hereditary Pancreatitis Multigene Panel	Hereditary Pancreatitis Panel (GeneDx)	81222, 81223, 81404, 81405, 81479	K85.0-K85.9, K86.1, Z83.79	2, 3
Inflammatory Bowel Disease				
Inflammatory Bowel Disease / Crohn's Disease Diagnostic Algorithmic Tests	Prometheus IBD sgi Diagnostic (Prometheus Laboratories)	81479, 82397, 83520, 86140, 88346, 88350	K50-K52	8
	IBD sgi Diagnostic (Children's Hospital of Philadelphia-Division of Genomic Diagnostics)	83520, 82397, 86140, 88342, 81479		
Inflammatory Bowel Disease / Crohn's Disease Prognostic Algorithmic Tests	PredictSURE IBD (KSL Diagnostics)	0203U	K50-K52	9
	Crohn's Disease Prognostic Panel (ARUP Laboratories)	83516, 86671		
	Prometheus Crohn's Prognostic (Prometheus Laboratories)	81401, 83520, 88346, 88350		
Hereditary Inflammatory Bowel	Monogenic Inflammatory Bowel Disease Panel-Primary Genes (Invitae)	81479	K50-K52	10, 11, 12

Disease / Crohn's Disease Panel Tests	Very Early Onset Inflammatory Bowel Genomic Panel (Children's Hospital of Philadelphia-Division of Genomic Diagnostics)			
Test Specific Not Covered Gastroenterologic Disorders Tests				
Test Specific Not Covered Gastroenterologic Disorders Tests	ASH FibroSURE (LabCorp)	0002M	K22.7, K74, K75,	13
	NASH FibroSURE (LabCorp)	0003M		
	EsoGuard (Lucid Diagnostics)	0114U		

OTHER RELATED POLICIES

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

- **Genetic Testing: Hereditary Cancer Susceptibility Syndromes** 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 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.

COVERAGE CRITERIA

KNOWN FAMILIAL VARIANT ANALYSIS FOR GASTROENTEROLOGIC DISORDERS

- I. Targeted mutation analysis for a known familial variant (81403) for a gastroenterologic disorder is considered **medically necessary** when:
 - A. The member has a [close relative](#) with a known pathogenic or likely pathogenic variant causing the condition.
- II. Targeted mutation analysis for a known familial variant (81403) for a gastroenterologic disorder is considered **investigational** for all other indications.

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CELIAC DISEASE

HLA-DQ Genotyping Analysis

- I. *HLA-DQ2* and *HLA-DQ8* variant analysis (81370, 81375, 81376, 81377, 81382, 81383) to rule out celiac disease is considered **medically necessary** when:
 - A. The member meets one of the following:
 1. The member has equivocal small-bowel histological finding in seronegative patients, **OR**
 2. The member is on a gluten-free diet AND in whom no testing for CD was done before gluten-free diet, **OR**
 3. The member has discrepant celiac-specific serology and histology, **OR**

4. Patients with suspicion of refractory CD where the original diagnosis of celiac remains in question.
- II. *HLA-DQ2* and *HLA-DQ8* variant analysis (81370, 81375, 81376, 81377, 81382, 81383) to rule out celiac disease is considered **investigational** for all other indications.

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HEREDITARY HEMOCHROMATOSIS

HFE Sequencing and/or Deletion/Duplication Analysis

- I. *HFE* sequencing and/or deletion/duplication analysis (81256, 81479) to establish a diagnosis of hereditary hemochromatosis is considered **medically necessary** when:
 - A. The member has abnormal serum iron indices, especially 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, especially if the relative has Type I HH where the relative has two C282Y mutations (homozygous).
- II. *HFE* sequencing and/or deletion/duplication analysis (81256, 81479) to screen for hereditary hemochromatosis in the general population is considered **investigational**.
- III. *HFE* sequencing and/or deletion/duplication analysis (81256, 81479) to establish a diagnosis of hereditary hemochromatosis is considered **investigational** for all other indications.

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LACTASE INSUFFICIENCY

MCM6 Targeted Variant Analysis

- I. *MCM6* variant analysis (81479) for the prediction of lactase insufficiency is considered **investigational**.

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HEREDITARY PANCREATITIS

Hereditary Pancreatitis Multigene Panel

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

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

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INFLAMMATORY BOWEL DISEASE

Inflammatory Bowel Disease / Crohn's Disease Diagnostic Algorithmic Tests

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

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Inflammatory Bowel Disease / Crohn's Disease Prognostic Algorithmic Tests

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

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Hereditary Inflammatory Bowel Disease / Crohn's Disease Panel Tests

- I. Genetic testing for inflammatory bowel disease (81479), including Crohn's disease, via a multigene panel is considered **medically necessary** when:
 - A. The member has very early onset of [typical IBD symptoms](#) before age 2 years, **OR**
 - B. The member is under the age of 18 with [aggressive, refractory or unusual IBD presentation](#), **OR**
 - C. The member is under the age of 18 with IBD symptoms, and also has a family history of IBD or immunodeficiency.

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

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TEST-SPECIFIC NOT COVERED GASTROENTEROLOGIC DISORDERS TESTS

- I. The use of these specific gastroenterologic disorders tests are considered **investigational**:
 - A. ASH FibroSURE (0002M)
 - B. NASH FibroSURE (0003M)
 - C. EsoGuard (0114U)

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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

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BACKGROUND AND RATIONALE

Known Familial Variant Analysis for Gastroenterologic Disorders

Genetic Support Foundation

The Genetic Support Foundation's Genetics 101 information on inheritance patterns 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

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 Force (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* Sequencing and/or Deletion/Duplication Analysis

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 type 1 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.

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 transferrin-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 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)

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 pANCA and ASCA 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 IgA+.

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 (eg, 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 (eg, 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)

UpToDate (Snapper SB and McGovern DPB, 2021)

“Very early onset IBD — There is a diverse spectrum of rare genetic disorders that produce IBD-like intestinal inflammation caused by genetic variants that have a large effect on gene function and typically present in infancy. Over 60 unique monogenic IBD disorders have been described that affect mucosal homeostasis in diverse ways, including:

- Epithelial barrier and response defects (eg, IKBKG, TTC7, ADAM17)
- Dysfunction of neutrophil granulocytes (eg, NCF2, NCF4, SLC37A4)
- Hyper- and autoinflammatory disorders (eg, XIAP)
- Complex defects in T- and B-cell function (eg, LRBA, CD40LG; WAS)
- Regulatory T cells and IL-10 signaling (eg, IL10R, IL10, FOXP3)

Some of these disorders with gene defects that affect predominantly hematopoietic cells (eg, IL-10R, IL-10, XIAP, FOXP3) respond to stem cell transplantation.” (p. 3-4)

European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) (p. 24)

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

- 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

British Society of Gastroenterology

This source suggests that genetic testing for monogenic disorders should be considered in adolescents and young adults who have had early onset (before 5 years of age) or particularly aggressive, refractory or unusual IBD presentations. (p. 75)

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