

Reimbursement Policy

Laboratory Testing for the Diagnosis of Inflammatory Bowel Disease

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I. Policy Description

Inflammatory bowel disease (IBD) is a class of inflammatory bowel disorders comprised of two major disorders: ulcerative colitis and Crohn's disease each with distinct pathologic and clinical characteristics (Peppercorn & Cheifetz, 2021).

Ulcerative colitis (UC) is a chronic inflammatory condition characterized by relapsing and remitting episodes of inflammation limited to the mucosal layer of the colon (Silverberg et al., 2005) beginning at the rectum and may extend in a proximal and continuous fashion to involve other parts of the colon (Peppercorn & Kane, 2022b).

Crohn's disease (CD) is characterized by patchy transmural inflammation (skip lesions) of the gastrointestinal tract resulting in sinus tracts, and ultimately microperforations and fistulae (Silverberg et al., 2005). It may also lead to fibrosis, strictures and to obstructive clinical presentations that are not typically seen in ulcerative colitis (Gasche et al., 2000; Peppercorn & Kane, 2022a).

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in Section VII of this policy document.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient's illness.

- 1) For the workup and monitoring of individuals with inflammatory bowel disease (IBD), the use of serologic markers, including, but not limited to, the following, **DOES NOT MEET COVERAGE CRITERIA**:
 - a) Anti-neutrophil cytoplasmic antibody (ANCA).
 - b) Anti-*Saccharomyces cerevisiae* antibody (ASCA).
 - c) Perinuclear anti-neutrophilic cytoplasmic antibody (pANCA).
 - d) Antibody to *Escherichia coli* outer membrane porin C (anti-OmpC).
 - e) Antibody to *Pseudomonas fluorescens*-associated sequence I2 (anti-I2).
 - f) Anti-CBir1 flagellin antibody (anti-cBir1).

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- g) Antichitobioside antibodies (ACCA IgA).
 - h) Antilaminaribioside antibodies (ALCA IgG).
 - i) Antimannobioside antibodies (AMCA IgG).
 - j) Pyruvate kinase M2 (PKM2).
- 2) For the diagnosis or monitoring of individuals with IBD, the use of diagnostic algorithm-based testing, including testing that combines serologic, genetic, and inflammation markers (such as Prometheus® testing), **DOES NOT MEET COVERAGE CRITERIA.**
- 3) Genetic testing for IBD **DOES NOT MEET COVERAGE CRITERIA.**

III. Table of Terminology

Term	Definition
7C4	7 α -hydroxy-4-cholesten-3-one
AAST	American Association for the Surgery of Trauma
ACCA	Anti-chitobioside carbohydrate antibody
ACG	American College of Gastroenterology
ACP	Antibodies to the Crohn's disease peptide
AGA	American Gastroenterological Association
ALCA	Laminaribioside
ALCA IgG	Antilaminaribioside antibodies
AMCA	Antimannobioside carbohydrate
AMCA IgG	Antimannobioside antibodies
ANCA	Anti-neutrophil cytoplasmic antibody
anti-cBir1	Anti-CBir1 flagellin antibody
anti-CUZD1	CUB and zona pellucida-like domains-containing protein 1
anti-GAB	Anti-goblet cell
anti-GP2	Anti-glycoprotein 2
anti-I2	Antibody to pseudomonas fluorescens-associated sequence I2
anti-LFS	Anti-DNA-bound-lactoferrin
anti-OmpC	Antibody to 2scherichia coli outer membrane porin C
APA	Anti-pancreatic antibodies
ASCA	Anti-saccharomyces cerevisiae antibody
<i>ATG16L1</i>	<i>Autophagy related 16 like 1 gene</i>
AUC	Area under the curve
B2-M	Beta 2-microglobulin
BD	Inflammatory bowel disease
BSG	British Society of Gastroenterology
CD	Crohn's disease
CD	Celiac disease
CGD	Chronic granulomatous disorder

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CLIA '88	Clinical Laboratory Improvement Amendments of 1988
CMS	Centers for Medicare and Medicaid Services
CRP	C-reactive protein
DNA	Deoxyribonucleic acid
DOR	Diagnostic odds ratio
ECCO	European Crohn's and Colitis Organisation
ECM1	Extracellular matrix protein 1
ELISA	Enzyme-linked immunoassay
ESGAR	European Society of Gastrointestinal and Abdominal Radiology
ESR	Erythrocyte sedimentation rate
FC	Fecal calprotectin
FDA	Food and Drug Administration
GI	Gastrointestinal
HLH	Hemophagocytic lymphocytic histiocytosis
IBD	Inflammatory bowel disease
IBS	Irritable Bowel Syndrome
ICAM-1	Intercellular Adhesion Molecule 1
IL-10R	Interleukin-10 receptor
LDTs	Laboratory developed tests
mRNA	Messenger ribonucleic acid
NADPH	Reduced nicotinamide adenine dinucleotide phosphate
NASPGHAN	North American Society for Pediatric Gastroenterology, Hepatology, And Nutrition
NICE	National Institute for Health and Care Excellence
<i>NKX2-3</i>	<i>NK2 homeobox 3</i> gene
NPV	Negative predictive value
PAB	Pancreatic antibody
pANCA	Perinuclear anti-neutrophilic cytoplasmic antibody
PKM2	Pyruvate kinase M2
PPV	Positive predictive value
PROMs	Patient-reported outcome measures
SAA	Human serum amyloid A
SNPs	Single nucleotide polymorphisms
STAT3	Signal transducer and activator of transcription 3
UC	Ulcerative colitis
VCAM-1	Vascular cell adhesion protein 1
VEGF	Vascular endothelial growth factor
VEO-IBD	Very early onset inflammatory bowel disease
WES	Whole exome sequencing
WGO	World Gastroenterology Organisation
WGS	Whole genome sequencing
WSES	World society of emergency surgery
XIAP	X-linked inhibitor of apoptosis protein

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IV. Scientific Background

The diagnoses of Crohn's disease (CD) and ulcerative colitis (UC) depend on a combination of clinical, laboratory, radiographic, endoscopic, and histological criteria. Differential diagnosis can be challenging but is highly important toward treatment and prognosis. Serological markers could be of value in differentiating CD from UC, in cases of indeterminate colitis, and in predicting the disease course of IBD (Peppercorn & Cheifetz, 2021; Peppercorn & Kane, 2022a, 2022b).

Investigations based on animal models have led to the current theory that chronic intestinal inflammation is the result of an aberrant immunologic response to commensal bacteria within the gut lumen (Blumberg et al., 1999; Strober et al., 2002). Immune responses toward commensal enteric organisms have been investigated in CD and UC (Akasaka et al., 2015; D'Haens et al., 1998). Patients with IBD can have a loss of tolerance to specific bacterial antigens and autoantigens. These distinct antibody response patterns may indicate unique pathophysiological mechanisms in the progression of this complicated disease and may underlie the basis for the development of specific phenotypes (Landers et al., 2002; Peeters et al., 2001).

Numerous serological markers have been proposed as having utility in assessment of IBD patients. The most widely studied markers are the antineutrophil cytoplasmic antibodies (pANCA) and anti-*Saccharomyces cerevisiae* antibodies (ASCA), particularly for diagnosing IBD and distinguishing CD from ulcerative colitis (Higuchi, 2020; Peppercorn & Kane, 2022a). pANCA is thought to be an antibody corresponding to histone 1 whereas ASCA is an antibody against mannan from baker's yeast (Mitsuyama et al., 2016). Although there have been promising results regarding the clinical validity of these antibodies (Reese et al., 2006; Ruemmele et al., 1998; Sandborn et al., 2000), its utility in indeterminate bowel disease is uncertain (Joossens et al., 2002; Peeters et al., 2001). ASCA were present in 50 percent of patients with celiac disease and described in cystic fibrosis and intestinal tuberculosis, suggesting that they may reflect a nonspecific immune response in small bowel disease (Condino et al., 2005; Granito et al., 2005).

Additional antibody tests under investigation include laminaribioside (ALCA), chitobioside (ACCA), CBir1 flagellin, OmpC, and I2. ALCA and ACCA are antiglycan antibodies whereas the CBir1 flagellin comes from an indigenous species of bacteria (Dotan et al., 2006; Targan et al., 2005). OmpC is an antibody to an outer membrane protein of *E. coli* and I2 is an antibody against the I2 component of *Pseudomonas fluorescens* (Mitsuyama et al., 2016). The accuracy and predictive value of antibody tests is uncertain (Wang et al., 2017) and the prevalence of these antibodies in patients with a variety of inflammatory diseases affecting the gut has not been well-studied.

Additionally, bile acid deficiency--as indicated by serum 7 α -hydroxy-4-cholesten-3-one (7C4)--has been documented in patients with irritable bowel syndrome (IBS) (Donato et al., 2018; Vijayvargiya et al., 2018). This test has shown utility as an alternative test to measuring bile acids in stool (Walters & Pattni, 2010), but it is not recommended in the workup for IBD.

Another proposed biomarker for IBD is serum pyruvate kinase M2 (PKM2), which is "emerging" in IBD as a mediator of inflammatory processes. Almousa et al. (2018) evaluated its association with IBD and its correlation with traditional IBD indices, BD disease type, and intestinal microbiota. The authors found that serum PKM2 levels were 6 times higher in IBD patients compared to healthy controls. However, no

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sensitivity to disease phenotype or localization of inflammation was observed. A positive correlation between PKM2 and *Bacteroidetes* was identified, as well as a negative correlation between PKM2 and *Actinobacteria*. The investigators concluded that their data “suggests PKM2 as a putative biomarker for IBD and the dysbiosis of microflora in CD,” but noted that further validation was required (Almoussa et al., 2018).

Genetic studies have identified over 200 distinct susceptibility loci for irritable bowel disease with a significant portion of these overlapping with Crohn’s and ulcerative colitis (Jostins et al., 2012; Liu et al., 2015). Most of these are located within introns, which more likely modulate the expression of proteins, with each only conferring a slight increase in risk (Snapper & Abraham, 2020). Altogether, the known loci only explain ~13% of variation in disease liability (Jostins et al., 2012). These results indicate that the genetic architecture of IBD represents that of multifactorial complex traits where a combination of multiple genes, along with the environment, lead to disease (Liu & Anderson, 2014). Given the low predictive value of individual genetic markers and high number of putative risk alleles, genetic testing does not currently offer much in terms of clinical utility (Lichtenstein et al., 2018; Liu & Anderson, 2014; McGovern et al., 2015; Shirts et al., 2012).

Laboratory evidence of inflammation is common in IBD. Fecal calprotectin, lactoferrin, ESR and CRP have each been correlated with disease activity (Lewis, 2011; Menees et al., 2015), but are not specific. Additional inflammatory markers including vascular endothelial growth factor, intercellular adhesion molecule, vascular adhesion molecule, and serum amyloid A offer no significant advantage (Shirts et al., 2012). Fecal calprotectin has been shown to be useful to help differentiate the presence of IBD from irritable bowel syndrome and in monitoring disease activity and response to treatment (Lichtenstein et al., 2018). Inflammation and calprotectin testing are discussed in greater detail in AHS-G2155 and AHS-G2061, respectively.

Clinical Utility and Validity

Panels to improve the predictive value of IBD testing incorporating serologic, genetic, and inflammation markers have been created (Plevy et al., 2013). The clinical validity and utility of antibody tests and panels of combinations of serologic tests for the diagnosis of IBD and the disease course and severity are still uncertain (Benor et al., 2010; Coukos et al., 2012; Kaul et al., 2012; Sura et al., 2014; Wang et al., 2017). For example, Prometheus Biosciences offers a series of tests intended for IBS. This series includes “IBDsgi Diagnostic,” which evaluates 17 biomarkers (serological and genetic markers, intended to provide “diagnostic and prognostic clarity,”(Prometheus, 2022a) “Crohn’s Prognostic” (evaluates “proprietary serologic (anti-CBir1, anti-OMPC, DNase sensitive pANCA) and genetic (NOD2 variants SNPs 8,12,13) markers”), and “Monitr” (evaluates 13 biomarkers to provide an “Endoscopic Healing Index Score” which represents endoscopic disease activity) (Prometheus, 2022b). In February 2022, Prometheus announced the release of PredictrPK IFX, a test that helps healthcare providers with biologic dose optimization by using individualized pharmacokinetic modeling. According to the Prometheus site, “PredictrPK IFX combines serology markers, patient-specific variables, current dosing information, and a proprietary machine-learning algorithm to provide individualized actionable insights to optimize the dose and interval for inflammatory bowel disease (IBD) patients treated with infliximab (IFX) or IFX biosimilars” (Prometheus, 2022c).

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Mitsuyama et al. (2014) conducted a multicenter study to explore the possible diagnostic utility of antibodies to the CD peptide (ACP) in patients with CD. A total of 196 patients with CD, 210 with UC, 98 with other intestinal conditions, and 183 healthy controls were examined. In CD patients, ACP had a higher sensitivity and specificity (63.3% and 91.0%, respectively) than ASCA (47.4% and 90.4%, respectively). ACP was also found to be negatively associated with disease duration. The authors concluded that “ACP, a newly proposed serologic marker, was significantly associated with CD and was highly diagnostic. Further investigation is needed across multiple populations of patients and ethnic groups, and more importantly, in prospective studies” (Mitsuyama et al., 2014).

Kaul et al. (2012) performed a meta-analysis/systemic review aimed to evaluate the diagnostic value, as well as the association of anti-glycan biomarkers with IBD susceptible gene variants, disease complications, and the need for surgery in IBD. A total of 23 studies were included consisting of 14 in the review and 9 in the meta-analysis. They found that “individually, anti-Saccharomyces cerevisiae antibodies (ASCA) had the highest diagnostic odds ratio (DOR) for differentiating IBD from healthy (DOR 21.1), and CD from UC (DOR 10.2...)” (Kaul et al., 2012). The authors concluded, “ASCA had the highest diagnostic value among individual anti-glycan markers. While anti-chitobioside carbohydrate antibody (ACCA) had the highest association with complications, ASCA and ACCA associated equally with the need for surgery” (Kaul et al., 2012).

Schoepfer et al. (2008) aimed to determine the accuracy of fecal markers, C-reactive protein (CRP), blood leukocytes, and antibody panels for discriminating IBD from IBS. Sixty-four patients with IBD, 30 patients with IBS, and 42 healthy controls were included within the study. They found that “Overall accuracy of tests for discriminating IBD from IBS: IBD-SCAN 90%, PhiCal Test 89%, LEUKO-TEST 78%, Hexagon-OBTI 74%, CRP 73%, blood leukocytes 63%, CD antibodies (ASCA+/pANCA- or ASCA+/pANCA+) 55%, UC antibodies (pANCA+/ASCA-) 49%. ASCA and pANCA had an accuracy of 78% for detecting CD and 75% for detecting UC, respectively. The overall accuracy of IBD-SCAN and PhiCal Test combined with ASCA/pANCA for discriminating IBD from IBS was 92% and 91%, respectively” (Schoepfer et al., 2008).

Plevy et al. (2013) validated a diagnostic panel incorporating 17 markers. The markers were as follows: “8 serological markers (ASCA-IgA, ASCA-IgG, ANCA, pANCA, OmpC, CBir1, A4-Fla2, and FlaX), 4 genetic markers (ATG16L1, NKX2-3, ECM1, and STAT3), and 5 inflammatory markers (CRP, SAA, ICAM-1, VCAM-1, and VEGF).” A total of 572 patients with CD, 328 with UC, 427 non-IBD controls, and 183 controls were assessed. These results were compared to another panel with serological markers only. The extended panel increased the IBD vs non-IBD discrimination area under the curve from 0.80 to 0.87 and the CD vs UC from 0.78 to 0.93. The authors concluded that “incorporating a combination of serological, genetic, and inflammation markers into a diagnostic algorithm improved the accuracy of identifying IBD and differentiating CD from UC versus using serological markers alone” (Plevy et al., 2013).

Biasci et al. (2019) validated a 17-gene prognostic classifier. The classifier was intended to separate IBD patients into two subgroups of prognosis, IBD_{hi} (poorer prognosis) and IBD_{lo}. Two validation cohorts were used, one of CD (n=66) and one of UC (n=57). IBD_{hi} (separated by the classifier) patients experienced both an “earlier need for treatment escalation (hazard ratio=2.65 (CD), 3.12 (UC)) and more escalations over time (for multiple escalations within 18 months: sensitivity=72.7% (CD), 100% (UC); negative predictive value=90.9% (CD), 100% (UC))” (Biasci et al., 2019).

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Czub et al. (2014) compared PKM2 to fecal calprotectin (FC) as markers for mucosal inflammation in IBD. A total of 121 patients (75 with UC, 46 with CD) were compared to 35 healthy controls. The authors found that as a whole, PKM2 was “inferior” to FC. The differences in the area under curve were as follows: 0.10 (FC above PKM2, IBD), 0.14 (UC), and 0.03 (IBD). PKM2 was also considered inferior to FC in differentiating patients from mild UC from healthy patients by an AUC of 0.23 (Czub et al., 2014).

Kovacs et al. (2018) investigated “prognostic potential of classic and novel serologic antibodies regarding unfavorable disease course in a prospective ulcerative colitis (UC) patient cohort”. They measured the auto-antibodies anti-neutrophil cytoplasmic (ANCA), anti-DNA-bound-lactoferrin (anti-LFS), anti-goblet cell (anti-GAB) and anti-pancreatic (pancreatic antibody (PAB): anti-CUZD1 and anti-GP2) and the anti-microbial antibodies anti-Saccharomyces cerevisiae (ASCA) IgG/IgA and anti-OMP Plus™ IgA. A total of 187 patients were included. The authors found a total of “73.6%, 62.4% and 11.2% of UC patients were positive for IgA/IgG type of atypical perinuclear-ANCA, anti-LFS and anti-GAB, respectively.” Occurrences of PABs were 9.6%, ASCA IgA/IgG was 17.6%, and anti-OMP IgA was 19.8%. IgA type PABs were found to be more prevalent in patients with primary sclerosing cholangitis (37.5% vs. 4.7% for anti-CUZD1 and 12.5% vs. 0% for anti-GP2). IgA type ASCA was associated with a higher risk for requiring long-term immunosuppressant therapy. The authors found that none of the autoantibodies, either alone or in combination, were associated with the “risk of development of extensive disease or colectomy,” although “multiple antibody positivity [≥ 3]” was associated with UC-related hospitalization. Overall, the authors concluded that “Even with low prevalence rates, present study gives further evidence to the role of certain antibodies as markers for distinct phenotype and disease outcome in UC. Considering the result of the multivariate analysis the novel antibodies investigated do not seem to be associated with poor clinical outcome in UC, only a classic antibody, IgA subtype ASCA remained an independent predictor of long-term immunosuppressive therapy” (Kovacs et al., 2018).

Ben-Shachar et al. (2019) evaluated the impact of genotype variations on serological biomarkers. The authors examined three *NOD2* variants (1007fs, G908R, R702W) and an *ATG16L1* variant (A300T). Then, the authors analyzed the antiglycan antibodies anti-Saccharomyces cerevisiae (ASCA), antilaminaribioside (ALCA), antichitobioside (ACCA), and antimannobioside carbohydrate (AMCA). A total of 308 IBD patients were included, “130 with Crohn’s Disease (CD), 67 with ulcerative colitis (UC), 111 with UC and an ileal pouch (UC-pouch), and 74 healthy controls.” ACCA was found to be “positive” in 28% of CD patients with the *ATG16L1* A300T variant, compared to only 3% in patients without the variant. ASCA was found to be positive in 86% of patients with the 1007fs variant, compared to 36% without the variant. UC-pouch patients with the 1007fs variant were also found to have “elevated” ASCA and ALCA levels compared to those without (50% vs 7% and 50% vs 8% respectively). The authors also found that the genetic variants were not associated with serologic responses in healthy controls and “unoperated” UC patients. The authors concluded that “Genetic variants may have disease-specific phenotypic (serotypic) effects. This implies that genetic risk factors may also be disease modifiers” (Ben-Shachar et al., 2019).

Ahmed et al. (2019) examined the association between six serological markers and Crohn’s Disease (CD) activity. The six markers evaluated were “ASCA-IgA, ASCA-IgG, anti-OmpC IgA, anti-CBir1 IgG, anti-A4Fla2 IgG and anti-FlaX IgG”. A total of 135 patients were included. The authors found that CD patients with high anti-Cbir1 IgG at baseline were 2.06 times more likely to have active clinical disease. The other five autoantibodies were not found to have significant impact on clinical course. The authors concluded

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that “High levels of anti-Cbir1 IgG appear to be associated with a greater likelihood of active CD. Whether routine baseline testing for anti-Cbir1 IgG to predict a more active clinical course is warranted needs more research” (Ahmed et al., 2020; Duarte-Silva et al., 2019).

Eltabbakh (2021) studied the diagnostic utility of beta 2-microglobulin (B2-M) as a biomarker in patients with IBS and UC. B2-M is a protein released by activated T and B lymphocytes and has shown to increase in inflammatory conditions. 40 patients with UC, 20 patients with IBS, and 20 healthy subjects were enrolled in the study. Overall, there was a higher mean of B2-M values in the UC patients (1.93) than IBS patients (1.51) or healthy subjects (1.43). At a cut off value of >1.5, sensitivity (75%), specificity (70%), PPV (83.3%), NPV (58.3%), and accuracy (0.753%) were measured. It was concluded that “B2-M level may have a diagnostic and differentiating utility between UC cases and IBS-D type as well as a potential indicator of disease activation in UC patients” (Eltabbakh, 2021).

Gao & Zhang (2021) studied the use of serological markers for the diagnosis of Crohn’s disease. 196 suspected CD patients were enrolled in the study and ELISA was used to study the expression of various biomarkers including ASCA-IgG, ASCA-IgA, AYMA-IgG, AYCA-IgA, FI2Y-IgG, and pANCA. Overall, ASCA was found to be the most accurate serological marker for the differential diagnosis of CD. It was also noted that a combination of markers resulted in a higher sensitivity and NPV. There was no relation noted between the expression of ASCA and disease behavior at diagnosis (Gao & Zhang, 2021).

Nakov et al. (2022) performed a review of current studies related to IBS and IBD biomarker diagnosis and management, including how to distinguish IBS from IBD (as a note, IBS is a disorder of the gastrointestinal tract while IBD constitutes inflammation or destruction of the bowel wall. Crohn’s disease and ulcerative colitis fall under an IBD etiology). The authors focused on the most clinically validated biomarkers to-date and summarized the biological rationale, diagnostic, and clinical value. The authors wrote, “there are well-established serological markers that help differentiate IBS from IBD. These include ASCA, which facilitates the differential diagnosis of Crohn’s disease (CD) and ulcerative colitis (UC), predominantly in the disease’s early stages. The serum concentration of ASCA is considerably higher in patients with CD than in those with UC. Thus, ASCA can be employed in differentiating organic disease from IBS.” They also noted “the other autoantibodies that can be used in distinguishing IBS from IBD are the anti-neutrophil cytoplasmic antibody. They target antigens present in neutrophils and are positive in 50–80% of the UC patients”(Nakov et al., 2022).

Reese et al. (2006) performed a meta-analysis of dozens of studies to assess the diagnostic precision of ASCA and pANCA in pinpointing irritable bowel disease, as well as the role of these particular serum antibodies in differentiating Crohn’s from ulcerative colitis. Using 60 different studies, comprising 3,841 UC and 4,019 CD patients, they calculated sensitivity, specificity, and likelihood ratio for different test combinations. The ASCA+ with PANCA- test had the highest sensitivity for Crohn’s disease at 54.6%; the specificity was 92.8%. The sensitivity and specificity of pANCA+ tests for ulcerative colitis were 55.3% and 88.5%, respectively. Sensitivity and specificity of pANCA+ were improved in a pediatric subgroup when combined with an ASCA test. In the pediatric cohort, sensitivity was 70.3% and specificity was 93.4%. In conclusion, the authors write that “ASCA and pANCA testing are specific but not sensitive for CD and UC, but that it may be particularly useful for differentiating between CD and UC in the pediatric population” (Reese et al., 2006).

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V. Guidelines and Recommendations

American Gastroenterological Association

No guideline or position statement from AGA on specific use of immunologic or genetic markers for the diagnosis of inflammatory bowel disease was found. The AGA assessment algorithms used for both Crohn's disease and ulcerative colitis do not include genetic testing or combinatorial serologic-genetic testing approaches, such as the Prometheus® testing methodology (AGA, 2015).

In 2021, the AGA published a guideline on the medical management of severe luminal and perianal fistulizing Crohn's disease (Feuerstein et al., 2021). While the guideline focuses on therapeutic approaches (i.e., different drug classes for Crohn's disease), it does make a statement on perceived future research needs and evidence gaps. AGA notes: "There remains an urgent need for improved patient-specific predictors, clinical and biologic, of response and harm to a particular drug or drug class to improve the rational choice of initial and second-line therapeutic agents in a given patient. The need is especially great in special populations, such as those with fistulizing disease or aggressive and recurrent fibrostenosing disease. Overall, the data on risk-stratifying individual patients into low and high risk of disease complications and disability remain poor"(Feuerstein et al., 2021).

American College of Gastroenterology (ACG)

The ACG published guidelines (Lichtenstein et al., 2018) on the management of Crohn's disease which state:

- "The diagnosis of Crohn's disease (CD) is based on a combination of clinical presentation and endoscopic, radiologic, histologic, and pathologic findings that demonstrate some degree of focal, asymmetric, and transmural granulomatous inflammation of the luminal GI tract. Laboratory testing is complementary in assessing disease severity and complications of disease. There is no single laboratory test that can make an unequivocal diagnosis of CD. The sequence of testing is dependent on presenting clinical features."
- "Initial laboratory investigation should include evaluation for inflammation, anemia, dehydration, and malnutrition."
- "Genetic testing is not indicated to establish the diagnosis of Crohn's disease."
- "Routine use of serologic markers of IBD to establish the diagnosis of Crohn's disease is not indicated."

The ACG guidelines on Ulcerative Colitis in adults (Rubin et al., 2019) state:

- "We recommend against serologic antibody testing to establish or rule out a diagnosis of UC (strong recommendation, very low quality of evidence)."
- "We recommend against serologic antibody testing to determine the prognosis of UC (strong recommendation, very low quality of evidence)."
- The ACG also mentions perinuclear antineutrophil cytoplasmic antibodies (pANCA) as a proposed serological marker, but they observe that "there is currently no role for such testing to determine the likelihood of disease evolution and prognosis" and that the marker has low sensitivity for diagnostic purposes.

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- Overall, “the yield of genetic or serologic markers in predicting severity and course of UC has been modest at best, and their use cannot be recommended in routine clinical practice based on available data” (Rubin et al., 2019).

The ACG released guidelines on management of IBS in adults. The recommendations state:

- “We recommend that serologic testing be performed to rule out celiac disease (CD) in patients with IBS and diarrhea symptoms.
- We suggest that either fecal calprotectin or fecal lactoferrin and C-reactive protein be checked in patients without alarm features and with suspected IBS and diarrhea symptoms to rule out inflammatory bowel disease.
- We recommend against routine stool testing for enteric pathogens in all patients with IBS” (Lacy et al., 2021).

European Crohn’s and Colitis Organisation (ECCO)

ECCO states that the Montréal classification of CD is advocated. Therefore, “genetic tests or serological markers should currently not be used to classify CD in clinical practice” (Gomollón et al., 2016).

In a 2017 update for UC, ECCO states that “the routine clinical use of genetic or serological molecular markers is not recommended for the classification of ulcerative colitis.” ECCO also notes that the most widely studied marker is the pANCA, but they have “limited sensitivity” and “their routine use for the diagnosis of UC and for therapeutic decisions is not clinically justified” (Magro et al., 2017).

ECCO also published a “harmonization of the approach to Ulcerative Colitis Histopathology.” A section titled “Correlation of Histological Scores with Biomarkers” is included. However, only fecal biomarkers (such as fecal lactoferrin and calprotectin) are mentioned, with no mention of serological biomarkers (Magro et al., 2020).

ECCO also published the “ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment.” While the guideline mainly focused on therapeutic agents, it does advocate for identification of important biomarkers to biologic effect. ECCO writes, “there is a clear need to identify biomarkers that could guide therapeutic choices, and to conduct appropriately sized head-to-head trials that could allow for the identification of patient subgroups who would benefit from a given biologic over the other” (Torres et al., 2019).

World Gastroenterology Organisation (WGO)

Concerning the use of p-ANCA and ASCA to diagnose UC and CD, the WGO states, “These tests are unnecessary as screening tests, particularly if endoscopy or imaging is going to be pursued for more definitive diagnoses. p-ANCA may be positive in Crohn’s colitis and hence may not be capable of distinguishing CD from UC in otherwise unclassified colitis. ASCA is more specific for CD. These tests may have added value when there may be subtly abnormal findings, but a definitive diagnosis of inflammatory bowel disease is lacking. They may also be helpful if considering more advanced endoscopic techniques such as capsule endoscopy or double-balloon endoscopy, such that a positive ASCA test may provide stronger reasons for evaluating the small bowel.” Later, the WGO also notes,

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“There are several other antibody tests, mostly for microbial antigens, that increase the likelihood of CD either singly, in combination, or as a sum score of the ELISA results for a cluster of antibodies. These tests are costly and not widely available. The presence of these antibodies, including a positive ASCA, would increase the likelihood that an unclassified IBD-like case represents Crohn’s disease” (Bernstein et al., 2016).

Working Group of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the Crohn’s and Colitis Foundation of America

A clinical report (Bousvaros et al., 2007) noted that:

“A positive ANCA does not differentiate between UC and Crohn colitis.”

“Genetic testing cannot as yet reliably differentiate UC from CD of the colon.”

The Working Group also observed that in the largest study of prospective markers for UC, the majority of patients remained seronegative for both ASCA and ANCA.

North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN)

NASPGHAN published a guideline regarding the management of patients with “Very Early-Onset Inflammatory Bowel Disease (VEO-IBD)”. This guideline defines this cohort as a patient of the pediatric IBD population presenting at under 6 years of age. The guideline makes the following remarks on evaluation of IBD in this population:

- “...genetic sequencing is often necessary to identify the specific monogenic forms of VEO-IBD, or to confirm a suspected defect.”
- “Targeted panels should be performed first in cases of infantile onset IBD, when the phenotype is consistent with a known defect, history of consanguinity, and abnormal immunology studies.”
- “Currently, WES is most often performed in the setting of a negative targeted panel, however, there are select cases in which WES may be indicated instead of a targeted panel, such as those patients who present with a phenotype that is not previously described.”
- “At this time, WGS should be reserved for cases in which WES is negative, yet there remains a high suspicion of a monogenic defect given the young age of onset, disease severity, family history, and complex phenotype including associated autoimmunity.”
- “In general, the gene defects that have been detected with the highest frequency in patients with VEO-IBD can prompt specific targeted therapies that include: defects that lead to CGD (NADPH complex defects), IL-10R and XIAP” (Kelsen et al., 2019).

National Institute for Health and Care Excellence

NICE does not mention any serological or genetic biomarkers in its reviews of management of UC or CD (NICE, 2019a, 2019b).

British Society of Gastroenterology (BSG)

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The BSG published guidelines on the “management of inflammatory bowel disease [IBD] in adults.” In it, they made the following comments regarding use of biomarkers in IBD:

- “...more evidence is also needed of the role of faecal calprotectin or other biomarkers as non-invasive surrogates for mucosal healing.”
- “Further studies are required to evaluate the use of drug levels and biomarkers to determine personalized dosing for patients.”
- “If a response [to treatment] is unclear, then measurement of biomarkers, serum C-reactive protein and faecal calprotectin, or comparison of disease activity scores or PROMs with baseline values, may be helpful.”
- “We suggest 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 (GRADE: weak recommendation, very low-quality evidence)” (Lamb et al., 2019).

In 2021, the BSG released guidelines on management of irritable bowel syndrome. The BSG suggests that “all patients presenting with symptoms of IBS for the first time in primary care should have a full blood count, C reactive protein or erythrocyte sedimentation rate, coeliac serology and, in patients <45 years of age with diarrhea, a faecal calprotectin to exclude inflammatory bowel disease. Local and national guidelines for colorectal and ovarian cancer screening should be followed, where indicated” (Vasant et al., 2021).

European Crohn’s and Colitis Organization (ECCO) and the European Society of Gastrointestinal and Abdominal Radiology (ESGAR)

- These joint guidelines include some relevant items on inflammatory bowel disease (IBD), which includes both Crohn’s disease (CD) and ulcerative colitis (UC). These items include:
- “A single reference standard for the diagnosis of Crohn’s disease [CD] or ulcerative colitis [UC] does not exist. The diagnosis of CD or UC is based on a combination of clinical, biochemical, stool, endoscopic, cross-sectional imaging, and histological investigations.”
- “Genetic or serological testing is currently not recommended for routine diagnosis of CD or UC.”
- “On diagnosis, complementary investigations should focus on markers of disease activity, malnutrition, or malabsorption.”
- “Serological markers may be used to support a diagnosis, though the accuracy of the best available tests [pANCA and ASCAs] is rather limited and hence ineffective at differentiating colonic CD from UC. Similarly, the additional diagnostic value of antiglycan and antimicrobial antibodies, such as anti-OmpC and CBir1, is small” (Maaser et al., 2018).

European Crohn’s and Colitis Organisation (ECCO) and European Society of Pediatric Gastroenterology, Hepatology and Nutrition (European Society for Paediatric Gastroenterology Hepatology and Nutrition)

This joint guideline was published regarding “Management of Paediatric Ulcerative Colitis” Although there was no mention of serological markers, the guideline did make this comment on “very early-onset inflammatory bowel disease presenting as colitis,” which is as follows:

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- “Unusual disease evolution, history of recurrent infections, HLH [hemophagocytic lymphocytic histiocytosis], and non-response to multiple IBD medications may indicate an underlying genetic defect which should prompt genetic and/or immunological analyses at any age during childhood” (Turner et al., 2018).

World Society of Emergency Surgery and the American Association for the Surgery of Trauma

WSES and AAST released joint guidelines on the management of inflammatory bowel disease in the emergency setting. When assessing an acute abdomen in patients with IBD, “laboratory tests including full blood count, electrolytes, liver enzymes, inflammatory biomarkers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and serum albumin and pre-albumin (to assess nutritional status and degree of inflammation) are mandatory” (De Simone et al., 2021).

VI. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: <https://www.cms.gov/medicare-coverage-database/search.aspx>. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

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