


<b>MEDICAL POLICY</b>	<b>Inflammatory Bowel Disease: Serologic Testing and Therapeutic Monitoring</b>
<b>Effective Date: 9/1/2021</b>   <div style="text-align: right;">9/1/2021</div>	Medical Policy Number: 218
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Medical Officer	Date

See Policy CPT CODE section below for any prior authorization requirements

**SCOPE:**

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as “Company” and collectively as “Companies”).

**APPLIES TO:**

All lines of business

**BENEFIT APPLICATION**

Medicaid Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

**POLICY CRITERIA**

**Thiopurine Methyltransferase (TPMT) Genetic Testing**

- I. Initial genotype testing (i.e., Prometheus TPMT Genetics) *OR* phenotype testing (i.e., Prometheus TPMT Enzyme) of thiopurine methyltransferase (TPMT) may be considered **medically necessary and covered** prior to initiating treatment with 6-mercaptopurine or azathioprine.
- II. The use of both genotype testing (i.e., Prometheus TPMT Genetics) and phenotype testing (i.e., Prometheus TPMT Enzyme) of thiopurine methyltransferase is considered **not medically necessary and is not covered**.

**Thiopurine Therapeutic Drug Monitoring**

- III. The measurement of 6-thioguanine nucleotide (6-TGN) and 6-methylmercaptopurine nucleotide (6-MMPN) (i.e., Prometheus Thiopurine Metabolites) is considered **medically necessary and covered** when **at least one** of the following (A. or B.) criteria are met:
- A. In patients who previously developed leukopenia or elevated liver biochemical tests while taking 6-mercaptopurine or azathioprine; **or**
  - B. To monitor compliance and/or dosage in patients not responding to 6-mercaptopurine or azathioprine.

**Fecal Calprotectin Testing**

- IV. Fecal calprotectin testing may be considered **medically necessary and covered** for the differential diagnosis and/or management of inflammatory bowel disease.

**Serological Markers for Diagnosing/Managing Inflammatory Bowel Disease**

- V. Testing for serological markers for the diagnosis and/or management of inflammatory bowel disease, including Crohn's disease or ulcerative colitis, is considered **investigational and is not covered**. Tests/panels include, but are not limited to, the following (A.-H.):
- A. Anti-Saccharomyces cerevisiae antibodies (ASCA)
  - B. Anti-glycan-associated Saccharomyces cerevisiae antibodies (gASCA)
  - C. Anti-neutrophilic cytoplasmic antibody (ANCA)
  - D. Perinuclear antineutrophil cytoplasmic autoantibodies (pANCA)
  - E. Anti-outer membrane porin protein C of Escherichia coli antibodies (anti-OmpC)
  - F. Anti-chitobioside carbohydrate antibodies (ACCA)
  - G. Anti-laminaribioside carbohydrate antibodies (ALCA)
  - H. Anti-mannobioside carbohydrate antibodies (AMCA)

**NOD/CARD15 Genetic Testing**

- VI. NOD2/CARD15 genetic testing (e.g. 81401) for the diagnosis and management of inflammatory bowel disease is considered **investigational and is not covered**.

**NUDT15 Genetic Testing**

- VII. NUDT15 genetic testing (e.g. 0034U) for the diagnosis and management of inflammatory bowel disease is considered **investigational and is not covered**.

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**Quantitative Polymerase Chain Reaction (PCR) Testing**

VIII. Quantitative PCR testing (e.g. 0203U) for the diagnosis and management of inflammatory bowel disease is considered **investigational and is not covered**.

**Panel Testing**

IX. Combination panel testing of serologic, genetic, and inflammatory markers for the diagnosis and/or management of inflammatory bowel disease is considered **not medically necessary and is not covered**. Tests/panels include, but are not limited to, the following:

- A. Prometheus IBD sgi Diagnostic
- B. Prometheus Crohn’s Prognostic
- C. IBS-Smart

Note: If a panel includes any serologic, genetic, or inflammatory marker which is not covered, the entire panel is considered not covered.

Link to [Policy Summary](#)

**BILLING GUIDELINES**

Only one genotypic (CPT code: 81401) or phenotypic (CPT codes: 82542 and 82657) assay of TPMT is considered medically necessary, per individual, per lifetime.

When CPT codes 83520, 82397, 86140, 88346, 88350, 81479 (i.e., Prometheus IBD sgi Diagnostic) or CPT codes 83520, 88346, 88350, 81401 (i.e., Prometheus Crohn’s Prognostic) are billed together they will be denied as not medically necessary and not covered (see criterion VIII. above).

**CPT CODES**

All Lines of Business	
Prior Authorization Required	
81401	Molecular pathology procedure, Level 2 (eg, 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)
No Prior Authorization Required	
82542	Column chromatography, includes mass spectrometry, if performed (eg, HPLC, LC, LC/MS, LC/MS-MS, GC, GC/MS-MS, GC/MS, HPLC/MS), non-drug analyte(s) not elsewhere specified, qualitative or quantitative, each specimen

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82657	Enzyme activity in blood cells, cultured cells, or tissue, not elsewhere specified; nonradioactive substrate, each specimen
83993	Calprotectin, fecal
Not Covered	
0034U	TPMT (thiopurine S-methyltransferase), NUDT15 (nudix hydroxylase 15) (eg, thiopurine metabolism) gene analysis, common variants (ie, TPMT *2, *3A, *3B, *3C, *4, *5, *6, *8, *12; NUDT15 *3, *4, *5)
0169U	NUDT15 (nudix hydrolase 15) and TPMT (thiopurine S-methyltransferase) (eg, drug metabolism) gene analysis, common variants
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
81306	NUDT15 (nudix hydrolase 15) (eg, drug metabolism) gene analysis, common variant(s) (eg, *2, *3, *4, *5, *6)
Unlisted Codes	
All unlisted codes will be reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is billed related to services addressed in this policy then <b>prior-authorization is required.</b>	
80299	Quantitation of therapeutic drug, not elsewhere specified
81479	Unlisted molecular pathology procedure

## DESCRIPTION

### Inflammatory Bowel Disease (IBD)

According to Hayes, “(i)nflammatory bowel disease (IBD) is characterized by chronic inflammation of the gastrointestinal (GI) tract that can be painful, debilitating, and, sometimes, life-threatening. IBD consists of two major forms—ulcerative colitis (UC) and Crohn’s disease (CD).”<sup>1,2</sup> UC involves inflammation of the large intestine (colon and rectum), which causes ulcers. CD causes inflammation and subsequent swelling and irritation to any part of the GI tract from the mouth to the anus. This swelling disrupts normal GI function, which causes diarrhea, abdominal discomfort, bleeding, pus formation, fever, and anemia. Severe cases can lead to weight loss, nutritional deficiencies, and growth failure (in children). Furthermore, both diseases have also been associated with an increased risk for colorectal cancer. “Since there is no cure for UC or CD, treatment is aimed at reducing symptoms or repairing intestinal complications.”<sup>3</sup>

### Thiopurine Methyltransferase (TPMT) Genotyping and Phenotyping

TPMT is an enzyme involved in the metabolism of thiopurines (e.g., azathiopurine) used to treat inflammatory bowel disease (IBD).<sup>4</sup> There can be a wide variation in TPMT enzyme activity that is genetically determined by the TPMT gene. According to Hayes, “normal levels of TPMT enzyme activity are found in 89% of people, 11% have intermediate activity and approximately 0.3% have little or no

activity.”<sup>4</sup> People who have intermediate or no TPMT enzyme activity cannot undergo treatment with thiopurines. Treatment in these patients could cause severe, life threatening bone marrow toxicity. Genotyping determines the TPMT gene alleles that result in intermediate or deficient levels of the TPMT enzyme. Phenotyping determines the level of TPMT enzyme activity present in red blood cells. According to the U.S. Food and Drug Administration (FDA), TPMT genotyping or phenotyping can be used to identify patients who have low or intermediate TPMT activity.<sup>5-7</sup>

### **Thiopurine Metabolites**

Monitoring of thiopurine metabolites is used to evaluate 6-thioguanine (6-TG) levels in patients not responding to thiopurine therapy.<sup>8</sup> 6-TG levels have also been purported to correlate with therapeutic efficacy; however, this hypothesis has not been substantiated.<sup>9</sup> According to UpToDate, “(l)ow or absent 6-TG levels in non-responding patients may indicate noncompliance, use of a sub-therapeutic dose of azathioprine (AZA)/6-mercaptopurine (6-MP), or preferential metabolism to 6-methylmercaptopurine (6-MMP) instead of 6-TG (ie, 6-MP resistance).”<sup>10</sup> Evaluation of thiopurine metabolites is also indicated for patients who had previous leukopenia or elevated liver biochemical tests.

### **Serologic Markers of Inflammatory Bowel Disease**

According to Hayes, “(p)atients with inflammatory bowel disease (IBD) exhibit a serological response, or production of particular antibodies, to various microbial antigens and autoantigens.”<sup>1,2</sup> To offer an alternative to standard IBD testing, serologic markers have been identified that can diagnose and distinguish Crohn’s disease (CD) from ulcerative colitis (UC). Research has identified several serum biomarkers, including anti-Saccharomyces cerevisiae antibody(ies) (ASCA) and perinuclear antineutrophil cytoplasmic antibody (pANCA). “The presence and level of these antibodies is determined by testing blood samples using serological assays, particularly enzyme-linked immunosorbent assays (ELISAs) and indirect immunofluorescence assays (IFAs).”<sup>1,2</sup>

### **NOD2/CARD15 Genetic Testing**

According to Hayes, “(m)ultiple genes and environmental factors are believed to play a role in CD susceptibility.”<sup>11</sup> The nucleotide-binding oligomerization domain protein 2 (NOD2) (also known as caspase recruitment domain-containing protein 15 [CARD15]) was the first gene found to be associated with CD. Three variants in NOD2 are known to be associated with an increased risk for CD. The precise biochemical mechanism is unknown; however, it is thought that the variants in NOD2 result in an exaggerated immune response leading to chronic inflammation of the intestine.

### **Fecal Calprotectin Testing**

Fecal calprotectin testing can be used to detect inflammation in the intestines associated with inflammatory bowel disease (IBD).<sup>12,13</sup> Calprotectin is a calcium-binding protein that is abundant in white blood cells (i.e., neutrophils). According to Hayes, “(d)uring active intestinal inflammation, neutrophils are recruited to the inflamed intestinal mucosa, and calprotectin is excreted into the stool through several proposed mechanisms, including active secretion, cell death, and leakage of neutrophils into the

intestinal lumen.”<sup>12,13</sup> The level of fecal calprotectin correlates with the amount of white blood cells in the gut; thus making it a marker for intestinal inflammation.

## REVIEW OF EVIDENCE

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of serologic testing and therapeutic monitoring for inflammatory bowel disease. Below is a summary of the available evidence identified through July 2021. Due to an extensive body of literature, the evidence supporting medical necessity of thiopurine methyltransferase genotyping and phenotyping and the measurement of thiopurine metabolites is based on the American College of Gastroenterology evidence-based clinical practice guidelines.

### Serologic Markers of Inflammatory Bowel Disease

- In 2017 (updated 2019), Hayes conducted an evidence review evaluating the analytical and clinical validity of Prometheus IBD sgi Diagnostic in distinguishing between IBD versus non-IBD and CD versus UC.<sup>14</sup> No studies were identified demonstrating the analytical validity of the test. One study was identified that used the test to screen for IBD, however, as no other test of diagnostic tool was used to confirm results, no evidence of clinical validity could be inferred. Hayes assigned the test a “D2” rating (insufficient evidence).
- In 2018 (reviewed in 2020), Hayes conducted an evidence review evaluating the clinical utility of genetic testing for inflammatory bowel disease (IBD).<sup>15</sup> As of May 1, 2018, no peer-reviewed studies were identified assessing the clinical utility of genetic testing for IBD. Hayes concluded that evidence was insufficient to support the clinical utility of genetic testing for IBD in symptomatic individuals with known or suspected IBD, or in asymptomatic individuals with a family history of IBD.
- In 2013 (archived in 2018), Hayes conducted an evidence review to evaluate serological assays for the diagnosis and management of inflammatory bowel disease— Crohn’s disease (CD).<sup>1</sup> The evidence review identified 22 studies (18 case-control design, 1 cross-sectional design, 1 pre-post design, and 2 were performed in parallel with randomized controlled trials) as eligible for inclusion, including 4,650 patients with CD, 2,138 patients with ulcerative colitis, 117 patients with indeterminate colitis, 564 patients with gastrointestinal diseases, and 1,671 health controls. The outcomes of interest in the selected studies were measures of diagnostic performance (sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]). No studies evaluated the clinical utility of serological markers for UC.

Findings from this body of evidence suggested that serological assays for UC have high specificity (typically  $\geq 85\%$ ); however, “the sensitivity of assays with these serological antibodies is too low (typically  $\leq 65\%$ ) to be effective for identifying the disease in question.”<sup>1</sup> There was also limited evidence that serological antibodies (individually or in combination) can predict disease phenotype or progression. “Furthermore, there is limited evidence regarding the use of

serological antibodies for predicting response to treatment.”<sup>1</sup> There was also no evidence that serological testing improves patient management or health outcomes for patients with UC.

The body of evidence was determined to be of low quality. There is a high risk of bias due to the majority of studies being of cross-sectional, retrospective design. Hayes also indicated there is potential for inflated estimates of accuracy due to a “high pretest probability of the disease since the patients were already diagnosed with UC or CD upon enrollment into the study.”<sup>1</sup> Furthermore, there is a lack of generalizability of these results since most of the studies were performed in Caucasian populations. Other limitations included, lack of reporting regarding blinding status, reporting of test sensitivity and specificity in subsets of patients rather than all patients combined, and failure to specify the statistical analysis used.

Hayes assigned the following ratings:

- C (potential but unproven benefit) - For serological assays using a combination of antibodies (ASCA, gASCA, pANCA combined with anti-OmpC, ACCA, ALCA, AMCA, anti-C, and/or anti-L) as an adjunct to conventional diagnostic techniques in patients with suspected CD and to aid in classifying patients with indeterminate colitis. This rating reflects the evidence suggesting that these assays may provide confirmation for a CD diagnosis, the low quality of that evidence, the uncertainty regarding the optimal combination of antibodies, and the lack of evidence demonstrating a positive impact on patient management or outcomes.
- D1 (no proven benefit) - For serological assays using a combination of antibodies (ASCA, gASCA, pANCA combined with anti-OmpC, ACCA, ALCA, AMCA, anti-C, and/or anti-L) for population screening of CD in asymptomatic individuals. This rating reflects the evidence of low sensitivity of these assays for CD, which indicates they produce a relatively high percentage of false negative results.
- D2 (insufficient evidence) - For serological assays using a combination of antibodies (ASCA, gASCA, pANCA combined with anti-OmpC, ACCA, ALCA, AMCA, anti-C, and/or anti-L) to predict disease phenotype, disease progression, or response to treatment for patients with CD. This rating reflects the low-quality and/or limited evidence for these indications as well as the lack of studies evaluating the impact of assay results on patient management or outcomes.
- In 2013 (archived in 2018), Hayes conducted an evidence review to evaluate serologic assays for the diagnosis and management of inflammatory bowel disease—ulcerative colitis (UC).<sup>2</sup> The literature search identified 12 studies (8 case-control studies, 1 cross-section study, 2 case series, and 1 cohort study with a 10-year follow-up) as eligible for inclusion, including 1,951 patients with UC, 1,787 patients with Crohn’s disease (CD), 32 patients with indeterminate colitis, 188 patients with other gastrointestinal (GI) disease, and 764 health controls. The outcomes of interest in the selected studies were measures of diagnostic performance (sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]). No studies evaluated the clinical utility of serological markers for UC.

Findings from this body of evidence suggested that serological assays for UC have high specificity (typically  $\geq 85\%$ ); however, “the sensitivity of assays with these serological antibodies is too low (typically  $\leq 50\%$ ) to be effective for identifying the disease in question.”<sup>2</sup> There was also limited evidence that the presence of antibodies can predict disease phenotype or the progression of UC. “Furthermore, there is limited evidence regarding the use of serological antibodies for predicting response to treatment.”<sup>2</sup> There was also no evidence that serological testing improves patient management or health outcomes for patients with UC.

The body of evidence was determined to be of low quality. There is a high risk of bias due to the majority of studies being of cross-sectional, retrospective design. Hayes also indicated there is potential for inflated estimates of accuracy due to a “high pretest probability of the disease since the patients were already diagnosed with UC or CD upon enrollment into the study.”<sup>2</sup> Furthermore, there is a lack of generalizability of these results since most of the studies were performed in Caucasian populations. Other limitations included, lack of reporting regarding blinding status, reporting of test sensitivity and specificity in subsets of patients rather than all patients combined, and failure to specify the statistical analysis used.

Hayes assigned the following ratings:

- C (potential but unproven benefit) - For serological assays using perinuclear antineutrophil cytoplasmic antibodies (pANCA) and anti-Saccharomyces cerevisiae antibodies (ASCA) as an adjunct to conventional diagnostic techniques in patients with suspected ulcerative colitis (UC) and to aid in classifying patients with indeterminate colitis. This rating reflects the evidence suggesting that these assays may provide confirmation for a Crohn’s disease diagnosis, the low quality of that evidence, and the lack of evidence demonstrating a positive impact on patient management or outcomes.
- D1 (no proven benefit) - For serological assays using pANCA and ASCA for population screening of UC in asymptomatic individuals. This rating reflects the evidence of low sensitivity of these assays for UC, which indicates they produce a relatively high percentage of false-negative results.
- D2 (insufficient evidence) - For serological assays using pANCA and ASCA for predicting disease phenotype, disease progression, and/or response to treatment in patients with UC. This rating reflects the low-quality and/or limited evidence for these indications as well as the lack of studies evaluating the impact of assay results on patient management or outcomes.
- In 2017 (reviewed in 2020), Hayes conducted a genetic testing evaluation (GTE) and report of the Prometheus IBD sgi Diagnostic (Prometheus Laboratories, Inc.).<sup>14</sup> The GTE review was based on the ACCE model (Analytical validity; Clinical validity; Clinical utility; and Ethical, legal, and social implications) developed by the Centers for Disease Control and Prevention (CDC). The quality of evidence was determined to be insufficient or very low to evaluate the ACCE criteria; therefore, Hayes gave a D2 (insufficient evidence) rating for the Prometheus IBD sgi Diagnostic.



### Fecal Calprotectin Testing

- In 2021, ECRI published a systematic review evaluating the clinical utility of fecal calprotectin (FC) testing for monitoring inflammatory bowel disease (IBD).<sup>16</sup> Investigators examined meta-analyses of data on >7,000 patients in diagnostic cohort studies described in systematic reviews and 2 additional clinical studies. Findings suggested that FC testing's accuracy is fair to good for identifying likelihood of relapse upon endoscopy in patients with IBD. Accuracy was fair for detecting histologic remission in patients with ulcerative colitis (UC). Investigators concluded that data were nonetheless insufficient to determine FC's clinical utility for managing therapy. A retrospective clinical utility study reported no overall treatment changes after adopting FC testing in place of colonoscopy. Researchers called for additional prospective clinical utility studies to validate findings and determine how FC affects time to treatment, treatment success, and avoidance of unnecessary treatment. No study assessing these outcomes was identified.
- In 2018, Tham and colleagues conducted a systematic review and meta-analysis evaluating the use of fecal calprotectin for detection of postoperative endoscopic recurrence in Crohn's disease.<sup>17</sup> Independent investigators systematically searched the literature through July 2017, identified eligible studies, assessed study quality, extracted data and pooled results. Primary outcomes of interest included the degree of endoscopic recurrence – quantified by the Rutgeerts score (RS) – which correlates with risk of clinical and surgical recurrence and the accuracy of FC for detection of endoscopic recurrence. In total, 9 studies were included for review, and diagnostic accuracy was calculated for FC values of 50,100,150 and 200 µg/g. Investigators calculated pooled diagnostic sensitivity, specificity and diagnostic odds ratio for each available FC cut-off value. Analysis indicated that the optimal diagnostic accuracy was obtained for FC value of 150 µg/g with a pooled sensitivity of 70% (95% CI 59–81%, specificity 69% (95% CI 61–77%), and diagnostic OR 5.92 (95% CI 2.61–12.17). Investigators concluded FC to be an accurate surrogate marker of postoperative endoscopic recurrence in CD patients.
- In 2017, Heida and colleagues published a systematic review evaluating the clinical utility of repeated FC measurements in predicting IBD relapses among asymptomatic patients with IBD.<sup>18</sup> Independent investigators systematically searched the literature through April 2016, identified eligible studies, assessed study quality and extracted data. In total, 6 prospective studies were included for review, all of which followed patients with IBD in remission at baseline who had at least 2 consecutive FC measurements with a test interval of 2 weeks to 6 months. Sample sizes varied between 49 and 181 patients, and the total observation period was 10 to 18 months. The time interval between FC tests varied between 1 and 3 months.

Results indicated that patients who had repeated FC measurements above the study's cut-off level had a 53%-83% probability of relapsing within the next 2 to 3 months. In contrast, patients with repeated normal FC values had a 67-94% probability to remain in remission over the next 2 to 3 months. Only one study to date systematically investigated the prognostic value of repeat testing, finding that two consecutively elevated FC levels appeared to be the best predictor for relapse. An ideal cut-off could not be identified due to the limited number of studies included for review and heterogeneity across studies.

Limitations included the heterogeneity in included studies' patient characteristics, endpoints, cut-off levels, and quality of reporting. Investigators concluded that 2 consecutively elevated FC values were highly associated with disease relapse, and that a single FC measurement at baseline could not plausibly predict the clinical course over a 12-month period. Investigators called for more prospective data to determine if FC monitoring improve patient outcomes in the long-term.

- In 2017 (reviewed in 2020), Hayes conducted an evidence review to evaluate fecal calprotectin (FC) assay for monitoring disease activity in Crohn's disease (CD).<sup>13</sup> The literature search identified 16 studies (15 prospective cohort studies, 1 retrospective cross-sectional study) as eligible for inclusion, including 78 to 221 patients diagnosed with CD. Follow-up times varied from 0 to 20 months. The outcome measures included clinical validity (sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV], accuracy, area under the receiver operating characteristic curve [AUROC]) and clinical utility (change in patient management or health outcomes).

Findings from the body of evidence suggested FC testing may be able to monitor CD activity due to moderate-to-high diagnostic sensitivity; however, specificity, PPVs, and NPVs varied across studies (40% to 97% specificity, 48.5% to 98% PPV, and 40% to 96.6% NPV). Furthermore, there was no direct evidence to support the clinical utility of FC testing for monitoring disease activity in patients with CD. There was also insufficient evidence to establish definitive patient selection criteria for the use of FC testing.

The overall quality of evidence was determined to be low. "Major individual study limitations included small sample sizes; lack of blinding; no follow-up; unclear, extended, or varying lengths of time between FC stool sample collection and colonoscopy or clinical assessment; retrospective selection of optimal FC cutoff values; use of multiple techniques for the reference standard; limited reporting of other measures of clinical performance (e.g., PPV and NPV); lack of correction for multiplicity in analysis; and multiple endoscopic procedures per patient unaccounted for in the analysis."<sup>13</sup>

Hayes assigned the following ratings:

- C (potential but unproven benefit) - For the use of fecal calprotectin (FC) testing systems to predict and monitor disease activity in adult patients with Crohn disease (CD). This rating reflects a large body of low-quality evidence suggesting that FC testing is safe and, based on clinical validity data, may aid in the prediction of disease activity in adult patients with CD. This Rating also reflects substantial uncertainty regarding the clinical utility of FC testing to change patient management and/or improve clinical outcomes, and uncertainty regarding optimal FC cutoff levels for defining disease activity or remission.
- D2 (insufficient evidence) - For the use of FC testing systems to predict and monitor disease activity in children and adolescents with CD. This rating reflects the paucity of studies evaluating the use of FC testing in these patient populations.

- In 2017 (reviewed in 2020), Hayes conducted an evidence review to evaluate fecal calprotectin (FC) assay for monitoring postoperative endoscopic recurrence (PER) of Crohn’s disease (CD).<sup>12</sup> The literature search identified 11 studies (8 prospective cohort studies, 2 retrospective cross-sectional studies, and 1 subgroup analysis of a randomized controlled trial) including 20 to 135 patients diagnosed with CD. Follow up times varied from 0 to 24 months. The outcome measures included clinical validity (sensitivity, specificity, positive predictive value [PPV], negative predictive value [NPV], accuracy) and clinical utility (change in patient management or health outcomes following FC testing).

This body of evidence suggested FC testing usually has high NPVs (ranging from 68% to 93%) and moderate sensitivity (ranging from 63% to 95%) for the prediction of PER in patients with CD; however, the specificity and PPV was low. The high NPVs indicate a high assurance that a negative result on an FC test indicates PER will not occur, but “additional research is needed to define uniform and optimal cutoffs for FC testing to predict and monitor PER of CD.”<sup>13</sup> Furthermore, there was no direct evidence regarding the clinical utility of FC testing and its potential impacts on patient management or health outcomes in postoperative CD patients.

Overall, the quality of evidence was determined to be low. “Major individual study limitations included small sample sizes; study design; lack of blinding; no follow-up; unclear, extended, or varying lengths time between FC stool sample collection and colonoscopy; lack of correction for multiplicity in analysis; multiple endoscopic procedures per patient unaccounted for in the analysis; and nonuniform postoperative treatment.”<sup>13</sup>

Hayes assigned the following ratings:

- C (potential but unproven benefit) - For fecal calprotectin (FC) tests to predict and monitor postoperative endoscopic recurrence (PER) in adult patients with Crohn disease (CD) who have previously undergone ileocolic resection due to refractory disease or complications. This Rating reflects low-quality evidence suggesting that FC testing may aid in the prediction of PER in patients with CD, as well as remaining uncertainties regarding optimal FC cutoff levels for defining PER and outcomes related to clinical utility.
- D2 (insufficient evidence) - For FC tests to predict and monitor PER in pediatric and adolescent patients with CD who have previously undergone ileocolic resection due to refractory disease or complications. This Rating reflects the paucity of studies evaluating the use of these tests in these patient populations.

**NOD2/CARD15 Genetic Testing**

Several historical studies were identified that evaluated the use of NOD2/CARD15 genetic testing for the diagnosis of Crohn’s disease (CD).<sup>19-24</sup> These studies suggested NOD2 genotyping may be predictive of an increased risk of CD; however, no studies assessed the analytical validity or clinical utility of genetic testing for CD. Present-day studies of good methodological quality are required to establish the analytical validity, clinical validity, and clinical utility of NOD2/CARD15 testing for CD.

**NUDT15 Genetic Testing**

Three studies (2 meta-analysis and 1 systematic review) examined the efficacy of genetic testing for NUDT15 for the diagnosis and management of inflammatory bowel disease; however, none of the studies assessed the clinical utility of NUDT15 TESTING.<sup>25-27</sup>

**CLINICAL PRACTICE GUIDELINES****Thiopurine Methyltransferase (TPMT) Genotyping and Phenotyping**American Gastroenterological Association (AGA)

In 2017, the AGA conditionally recommended routine TPMT testing (enzymatic activity or genotype) to guide thiopurine dosing in adult patients with IBD being started on thiopurines.<sup>28</sup> This recommendation was made on the basis of “low quality” evidence.

American College of Gastroenterology (ACG)

The 2010 ACG evidence-based clinical practice guideline for ulcerative colitis stated, “(a)lthough TPMT testing cannot substitute for complete blood count monitoring in patients being started on thiopurines, TPMT genotyping or phenotyping can be used to identify patients with absent or reduced TPMT activity. Because the phenotype assay reports a quantitative level of the TPMT enzyme activity, it is preferred to the genotype assay. A TPMT assay is therefore recommended by many authorities before initiating thiopurine therapy, to identify the rare patient who is at risk of developing severe myelotoxicity.”<sup>29</sup>

The 2018 ACG Clinical Guideline: Management of Crohn’s Disease in Adults offer the following recommendations: “Thiopurine methyltransferase (TPMT) testing should be considered before initial use of azathioprine or 6-mercaptopurine to treat patients with Crohn's disease (strong recommendation, low level of evidence).”<sup>30</sup>

**Thiopurine Metabolites**American Gastroenterological Association (AGA)

In 2017, the AGA conditionally recommended reactive therapeutic drug monitoring to guide treatment changes in adults with active IBD treated with anti-TNF agents.<sup>28</sup> The AGA made no recommendation for the use of routine proactive therapeutic drug monitoring in patients with quiescent IBD due to insufficient evidence.

American College of Gastroenterology (ACG)

The 2010 ACG evidence-based clinical practice guideline for ulcerative colitis stated thiopurine metabolite markers are of value in, “assessing whether a patient is noncompliant or preferentially metabolizes the drug to 6-methylmercaptopurine (6-MMP) instead of 6-thioguanine (6-TGN).”<sup>29</sup> The ACG

also stated that thiopurine metabolites may also, “be useful as an indication that maximal dosage has been achieved before abandoning the drug as a failure.”<sup>29</sup>

The 2018 ACG Clinical Guideline: Management of Crohn’s Disease in Adults offer the following recommendations: “Thiopurines (azathioprine, 6-mercaptopurine) may be effective and should be considered in treating fistulizing Crohn's disease (198) (strong recommendation, low level of evidence).”<sup>30</sup>

### **Serologic Markers of Inflammatory Bowel Disease**

#### American College of Gastroenterology

The 2019 ACG Clinical Guideline for Ulcerative Colitis in Adults offers the following recommendations:

- 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).<sup>31</sup>

The guideline also stated, “Serologic markers such as perinuclear antineutrophil cytoplasmic antibodies (pANCA) may be found in up to 70% of patients with UC, and combination of negative anti-Saccharomyces cerevisiae antibodies with elevated pANCA levels has been proposed to facilitate establishing a diagnosis of UC. However, the pooled sensitivity of antibody testing for diagnosis of UC is low, and such markers are not used for establishing or ruling out a diagnosis of UC. Although pANCA positivity has also been associated with treatment refractory UC, the evidence supporting this is limited, and there is currently no role for such testing to determine the likelihood of disease evolution and prognosis.”

The 2018 ACG Clinical Guideline for Management of Crohn’s Disease recommends against the use of serologic markers for diagnosing Crohn’s disease, stating, “Routine use of serologic markers of IBD to establish the diagnosis of Crohn's disease is not indicated (Summary Statement). Because of the heterogeneous nature of IBD there has been extensive research directed toward finding immunologic markers that would assist in disease diagnosis. These studies have focused on antibodies to microbial antigens and autoantibodies (Supplementary Information online). Anti-glycan antibodies are more prevalent in CD than in ulcerative colitis but have a low sensitivity, making their use in diagnosis less helpful.”<sup>30</sup>

The guideline also recommends against genetic testing as a diagnostic tool: “Genetic testing is not indicated to establish the diagnosis of Crohn's disease (Summary Statement). Certain genetic variants are associated with different phenotypic expressions in Crohn's disease but testing remains a research tool at this time.”

**NOD2/CARD15 Genetic Testing**

The 2018 ACG Clinical Guideline for Management of Crohn’s Disease recommends against the use of NOD2 for diagnosing Crohn’s disease.<sup>30</sup> Authors stated that “although identification of these [NOD2] variants may identify patients who are likely to have more aggressive CD, this laboratory test has not been routinely used clinically and remains a research tool.”

**Fecal Calprotectin Testing**American College of Gastroenterology (ACG)

In 2019, the ACG issued a clinical practice guideline on the management of ulcerative colitis in adults.<sup>31</sup> Authors concluded that “fecal calprotectin can be used in patients with UC as a noninvasive marker of diseases activity and to assess response to therapy and relapse.”<sup>31</sup>

In 2018, the ACG issued a clinical practice guideline on the management of Crohn’s disease in adults.<sup>30</sup> On the basis of “moderate evidence,” the ACG issued a strong recommendation for fecal calprotectin (FC) as a “helpful test that should be considered to help differentiate between the presence of IBD from IBS.”<sup>30</sup> The guideline did not address the clinical utility of FC or its impact on overall health outcomes, but did state that it “may have an adjunctive role in monitoring disease activity.”<sup>30</sup>

National Institute for Health and Care Excellence (NICE)

In 2013 (updated 2017), NICE issued a guidance for fecal calprotectin (FC) diagnostic tests for IBD. The guidance recommended FC testing as an option to support clinicians with the differential diagnosis of IBD or IBS in adults with recent onset lower gastrointestinal symptoms,” provided cancer is not suspected.<sup>32</sup> The guidance also recommended FC testing as option to support clinicians with the differential diagnosis of IBD or non-IBD (including IBS) in children with suspected IBD who have been referred for specialist assessment.

World Gastroenterology Organization (WGO)

In 2015, the WGO included fecal calprotectin tests in a list of “high resource level” diagnostics for distinguishing between IBD and IBS.<sup>33</sup>

**CENTERS FOR MEDICARE & MEDICAID**

As of July 2021, the Centers for Medicare & Medicaid (CMS) consider the Prometheus IBD sgi diagnostic test to be non-covered per Local Coverage Determination (LCD): MolDX: Prometheus IBD sgi Diagnostic® Policy (L37313).<sup>34</sup> No other coverage guidance was identified which addresses serologic testing or therapeutic monitoring for inflammatory bowel disease.

## **POLICY SUMMARY**

Patients with intermediate or absent thiopurine methyltransferase (TPMT) enzyme activity who undergo thiopurine therapy can develop life-threatening drug toxicity; therefore, the American College of Gastroenterology (ACG) and the U.S. Food and Drug Administration (FDA) recommend genotype or phenotype testing of TPMT prior to initiating therapy with thiopurines. The ACG also recommends fecal calprotectin testing and monitoring thiopurine metabolites to assess lack of response to thiopurine therapy, evaluate liver enzymes, leukopenia, and evaluate patient adherence.

There is not enough evidence to support the analytic validity, clinical validity, or clinical utility of testing serologic markers for the diagnosis of inflammatory bowel disease (IBD). Further studies of good methodological quality are required to establish the reliability of these tests and assure they improve IBD management and health outcomes. In addition, the American College of Gastroenterology (ACG) does not recommend the use of antibody testing for IBD, and state that the low sensitivity of testing limit the usefulness of it as a diagnostic tool.

The evidence was insufficient to support the use of NOD2/CARD15 testing or NUDT15 genetic testing for the diagnosis of inflammatory bowel disease. Further studies of good methodological quality are required to establish the analytical validity, clinical validity, and clinical utility of these testing methodologies. Furthermore, no evidence-based clinical practice guidelines were identified that address these diagnostic tests for IBD.

## **INSTRUCTIONS FOR USE**

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days' notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

## **REGULATORY STATUS**

### U.S. Food and Drug Administration (FDA)

The FDA has approved the thiopurines Imuran (azathioprine) and Purinethol (mercaptopurine) for the treatment of inflammatory bowel disease, specifically Crohn's disease and ulcerative colitis.<sup>6,7</sup> Regarding thiopurine methyltransferase (TPMT) genotyping and phenotyping, the FDA states the following:

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“It is recommended that consideration be given to either genotype or phenotype patients for TPMT. Phenotyping and genotyping methods are commercially available. The most common non-functional alleles associated with reduced levels of TPMT activity are TPMT\*2, TPMT\*3A and TPMT\*3C. Patients with two nonfunctional alleles (homozygous) have low or absent TPMT activity and those with one non-functional allele (heterozygous) have intermediate activity. Accurate phenotyping (red blood cell TPMT activity) results are not possible in patients who have received recent blood transfusions. TPMT testing may also be considered in patients with abnormal CBC results that do not respond to dose reduction. Early drug discontinuation in these patients is advisable.”<sup>7</sup>

The following is a list of fecal calprotectin tests currently approved for use by the U.S. Food and Drug Administration. This list may not be complete. Users should refer to the FDA website for a list of all currently approved diagnostics.

Test Name	Manufacturer	Indications
<a href="#">ALPCO Calprotectin Chemiluminescence ELISA/ALPCO Easy Stool Extraction Device</a>	ALPCO	In vitro diagnostic use as an aid in the diagnosis of inflammatory bowel disease (IBD), specifically Crohn’s disease (CD) and ulcerative colitis (UC), and as an aid in the differentiation of IBD from irritable bowel syndrome (IBS) in conjunction with other clinical and laboratory findings.
<a href="#">Buhlmann FCAL Turbo and CALEX Cap</a>	Buhlmann Laboratories	Aids in the diagnosis of inflammatory bowel disease (IBD), specifically Crohn's disease (CD) and ulcerative colitis (UC) and aids in the differentiation of IBD from irritable bowel syndrome (IBS) in conjunction with other laboratory and clinical findings.
<a href="#">Calprest, EasyCAL</a>	Eurospital	Used as an in vitro diagnostic to aid in the diagnosis of Inflammatory Bowel Diseases (IBD, Crohn’s disease and ulcerative colitis) and to differentiate IBD from Irritable Bowel Syndrome (IBS) in conjunction with other clinical and laboratory findings.
<a href="#">Liaison Calprotectin assay</a> (control set, calibration verifiers, buffer, device)	Diasorin Inc.	As an aid in the diagnosis of inflammatory bowel diseases (IBD), specifically Crohn’s disease and ulcerative colitis, and as an aid in differentiation of IBD from irritable bowel syndrome (IBS). Test results are to be used in conjunction with information obtained from the patients’ clinical evaluation and other diagnostic procedures.
<a href="#">Quanta Flash Calprotectin assay</a>	Inova Diagnostics	Can aid in the diagnosis of inflammatory bowel disease (IBD) (ulcerative colitis and Crohn’s disease), and in the differentiation of IBD from irritable bowel syndrome (IBS).



Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

**MEDICAL POLICY CROSS REFERENCES**

- Inflammatory Bowel Disease: Measurement of Antibodies to Immunosuppressive Therapies
- Celiac Disease: Serologic Testing

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