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Medical Policy

Subject:	**Gene Expression Profiling for Risk Stratification of Inflammatory Bowel Disease (IBD) Severity**		
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Description/Scope

This document addresses risk stratification of inflammatory bowel disease (IBD) severity using gene expression profiling from peripheral blood biomarkers, including the use of PredictSURE IBD™ (PredictImmune, LTD., Cambridge, United Kingdom). This document does not address initial irritable bowel syndrome (IBS), IBD diagnosis, ongoing IBD disease management nor the use of inflammatory markers, fecal samples or tissue biopsies for risk stratification of IBD disease severity.

Note: Please see the following related documents for additional information:

- **CG-MED-59 Upper Gastrointestinal Endoscopy in Adults**
- **CG-MED-70 Wireless Capsule Endoscopy for Gastrointestinal Imaging and the Patency Capsule**
- **CG-SURG-01 Colonoscopy**
- **LAB.00016 Fecal Analysis in the Diagnosis of Intestinal Disorders**
- **LAB.00037 Serologic Testing for Biomarkers of Irritable Bowel Syndrome (IBS)**

Position Statement

Investigational and Not Medically Necessary:

Gene expression profiling for risk stratification of inflammatory bowel disease (IBD) severity, including use of PredictSURE IBD, is considered investigational and not medically necessary for all indications.

Rationale

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Inflammatory bowel disease (IBD) is an umbrella term which includes two conditions, Crohn's disease (CD) and ulcerative colitis (UC); both are characterized by chronic inflammation of the gastrointestinal (GI) tract. Diagnosing IBD presents a clinical challenge for practitioners and necessitates a combination of approaches which may include a detailed health history, imaging (endoscopy/colonoscopy), mucosal biopsies, fecal samples and serologic tests. The severity of IBD varies widely and an area of recent research has focused on identifying reliable prognostic markers to tailor treatment in early disease states with the aim of reducing morbidity and potentially permanent GI damage that may result.

PredictSURE

PredictSURE is a prognostic whole blood test that uses CD8 T cells to stratify newly diagnosed IBD cases into two distinct subgroups, termed IBD1 (moderate to severe) and IBD2 (mild to moderate). The foundational research for the basis of the PredictSURE test was published in a prospective study by Lee and colleagues (2011) in which 35 (23 newly diagnosed) individuals with active CD and 32 (16 newly diagnosed) with active UC, were enrolled. At enrollment, CD4 and CD8 T cells were selected from peripheral mononuclear blood cells (PMBCs) for exploration of association via whole-genome transcriptional analyses. Study enrollees were then managed with conventional therapy and followed for up to 2 years. A significant difference was detected in CD8 T cell activation status between what was later defined as the IBD1 and IBD2 cohorts (p=0.048). Furthermore, a substantially higher incidence of frequently relapsing disease (more severe) was experienced by the cohort (IBD1) defined by elevated expression of genes involved in antigen-dependent T cell responses (p=0.003; based on Kaplan-Meier survival curve long-rank tests). To calculate a direct estimate of the prognostic utility of the resulting gene signature, the specificity (CD, 89%; UC, 84%) and sensitivity (CD, 59%; UC, 77%) of its ability to predict treatment escalation was determined. Authors noted that it was not possible within the design of the study to fully explain the biological differences that gave rise to the transcriptional variation seen between cohorts but such understanding may provide novel therapeutic targets for further investigation. Authors also note that that the clinical relevance of the prognostic gene signature identified necessitates confirmation in a prospective clinical trial.

In 2019, Biasci and colleagues conducted a prospective clinical trial which enrolled 123 treatment-naïve individuals (93% newly diagnosed), 18 years or older, diagnosed with active IBD (CD=66, UC=57). The study aimed to build upon Lee and colleagues (2011) previous work by achieving cell separation and microarray-based gene expression analysis to enable use of the previously identified gene signature in the clinical practice setting. Microarray analyses of RNA were performed on purified CD8 T cells or whole blood, and phenotype data were collected. Median follow-up was 1.9 years. The IBD1 and IBD2 cohorts were

identified by consensus clustering of CD8 T cell transcriptomes. An initial list of 39 candidate and 3 reference genes was narrowed down to a final 15 informative and 2 reference genes, generating the 17-gene classifier known as the PredictSURE. Study investigators determined, irrespective of IBD-type (CD or UC), the IBD1 cohort experienced significantly more aggressive disease than the IBD2 cohort and were more likely to necessitate earlier treatment escalation (hazard ratio [HR]=2.65 [CD], =3.12 [UC]) and more escalations over time (multiple escalations within 18 months: sensitivity=72.7% [CD], =100% [UC]; negative predictive value=90.9% [CD], =100% [UC]). Authors conclude, while performance characteristics of the assay support its use as a potential prognostic biomarker, an interventional study is warranted to determine if stratifying newly diagnosed IBD cases based on the PredictSURE test would improve clinical outcomes equivalent to currently accepted standards of risk prediction.

A biomarker-stratified trial, based on PredictSURE, is currently underway in the United Kingdom with a target enrollment of 400 study participants. Participants will be randomized to receive treatment based on current standards of practice ('step-up' therapy), or based on earlier aggressive intervention ('top-down' therapy) in individuals predicted to have a more severe disease course (Parkes 2018).

Other Gene Expression Analyses in IBD

While a number of trials have investigated genomic analysis of intestinal mucosal biopsies for the purposes of diagnosing IBD or distinguishing UC from CD (Ansari, 2006; Bogaert, 2016; Cupi, 2014; Granlund, 2013; Iboshi, 2014; Labbé, 2012), none have investigated gene expression analysis of mucosa for prognosis. Other trials, similar to the foundational PredictSURE data, have used whole blood for genomic-wide, or gene-specific, transcriptional analysis as an exploratory technique in an attempt to further characterize the etiology of IBD but none to predict disease severity (Fonseca-Camarillo, 2015; McDermott, 2016).

In 2019, Someini and colleagues conducted a study in 164 pediatric cases (aged 1-17 years) diagnosed with CD who were followed for 5 years, and 74 non-IBD pediatric participants without intestinal inflammation or symptoms who served as controls. Gene expression analysis was conducted at the time of diagnosis and 1-3 years later. Study investigators sought to identify changes in DNA methylation patterns that might contribute to the development of, or result from, CD. CD-associated patterns of DNA methylation that were observed in blood samples were found to be a non-specific reflection of the inflammation present, rather than a marker of susceptibility to the development of CD or a reliable predictor of future severity. This was further confirmed when post-treatment methylation patterns in CD cases were indistinguishable from methylation patterns in controls. Authors conclude, " peripheral blood methylation profiles do not predict or

change in relevance to the evolution or presence of Crohn's disease complications." This trial, though relatively small and only inclusive of children, does not support the use of gene expression analysis from peripheral blood samples as a reliable prognostic tool in CD. Further investigation is warranted.

The American College of Gastroenterologists (ACG) clinical guideline on The Management of Crohn's Disease in Adults (2018) has the following recommendations:

- **Features that are associated with a high risk for progressive disease burden include young age at diagnosis, initial extensive bowel involvement, ileal/ileocolonic involvement, perianal/severe rectal disease, and patients presenting with a penetrating or stenosis disease phenotype. Visceral adiposity may be a marker for increased risk of penetrating disease.**
- **Genetic testing is not indicated to establish the diagnosis of Crohn's disease. Certain genetic variants are associated with different phenotypic expressions in Crohn's disease but testing remains a research tool at this time.**

The ACG's clinical guideline on Ulcerative Colitis in Adults (2019) has the following recommendations:

- **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.**
- **Definitions of disease severity are needed to guide treatment decisions; definitions should be based on (i) PROs (bleeding and normalization of bowel habits), (ii) inflammatory burden (endoscopic assessment including extent and severity and markers of inflammation), (iii) disease course (need for hospitalization, need for steroids, and failure to respond to medications), and (iv) disease impact (functionality and QoL),**

The American Gastroenterology Association (AGA) guidelines for both UC (2019, 2020) and CD (2014) recommend stratifying newly diagnosed IBD into a low-risk or high-risk category to guide disease management. According to the guidelines, a low-risk disease course for CD is predicted when an individual meets the following criteria: "Age at initial diagnosis > 30 years, limited anatomic involvement, no perianal and/or severe rectal disease, no superficial ulcers, no prior surgical resection, no stricturing and/or penetrating behavior" (AGA, 2014). A low-risk disease course for UC is predicted when an individual meets the following two criteria: "Limited anatomic extent and mild endoscopic disease" (AGA, 2019; AGA, 2020).

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Stratification of newly diagnosed IBD is an important step in planning the most appropriate disease management approach for individuals. As such, specialty medical societies have established recommendations to aid clinicians in making prognostic determinations for new cases based on the most recent evidence and expert consensus. While use of biomarkers such as fecal calprotectin and serum CRP are established predictors of disease activity, the clinical utility of gene expression profiling from peripheral blood samples in the management of IBD remains to be established.

Background/Overview

Inflammatory bowel disease (IBD) is an idiopathic disease theorized to be caused by a dysregulated immune response. Though frequently confused with irritable bowel syndrome (IBS), they are distinct diagnoses with overlapping symptoms; IBD is typically more debilitating in nature. In 2015, an estimated 3 million US adults (1.3%) reported being diagnosed with IBD. There are two major types of IBD: ulcerative colitis (UC) and Crohn's disease (CD). UC is limited to inflammation of the colonic mucosa and is associated with ulceration, edema, bleeding, and fluid/electrolyte loss. CD inflammation can affect any segment of the gastrointestinal (GI) tract from the mouth to the anus (Centers for Disease Control [CDC] and Prevention, 2020). Although most new CD cases present with an inflammatory phenotype (low-risk), approximately 20% will rapidly progresses to a more complicated disease, which includes stricturing (high-risk) within 5 years (Somineni, 2019). While IBD may present at any age, pediatric-onset CD is more prevalent than UC and individuals diagnosed with CD in childhood are more likely to proceed to an aggressive disease course (Crohn's and Colitis Foundation, 2020) .

Inflammatory markers have been identified in IBD, and evidence suggests that these may play a role in the pathologic characteristics of the disease. IBD also features a genetic component and as result is more prevalent within members of the same family. IBD is diagnosed using a combination of endoscopy or colonoscopy and imaging. Stool samples, blood tests and mucosal biopsies are also routinely included in the diagnostic work-up. IBD is not curable but symptoms can typically be successfully managed through lifestyle changes and medical management. Several types of medications may be used to treat IBD depending on the severity of the condition: aminosalicylates, corticosteroids, immunomodulators, and biologics. IBD may require surgery in severe cases to remove damaged portions of the GI tract (CDC, 2020).

PredictSURE IBD uses a blood sample from individuals (16+ years) for the management of Crohn's disease and ulcerative colitis. PredictSURE uses a 17-gene algorithm designed to predict the severity of newly diagnosed IBD based on gene expression profiling of CD8 T cells; reportedly differentiating between an aggressive or milder form of the disease. At this time, the role of PredicSURE in the routine clinical management of IBD, has not been established.

Definitions

Gene expression profiling: The measurement of the activity of thousands of genes at once, to create a global picture of cellular function.

Penetrating disease: Abnormal connections between inflamed intestine and other parts of the intestine, bladder, skin, or vagina.

Stricturing: Narrowing of the intestine which can make it difficult for food matter to pass through.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services are Investigational and Not Medically Necessary:
For the following procedure codes, or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT	
81479	Unlisted molecular pathology procedure [when specified as a gene expression profiling test for IBD severity risk stratification]
81599	Unlisted multianalyte assay with algorithmic analysis [when specified as a gene expression profiling test for IBD severity risk stratification]
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
PredictSURE IBD™ Test, KSL Diagnostics, PredictImmune Ltd

ICD-10 Diagnosis

All diagnoses

References

Peer Reviewed Publications:

1. **Ansari N, Abdulla J, Zayyani N, et al. Comparison of RANTES expression in Crohn's disease and ulcerative colitis: an aid in the differential diagnosis? J Clin Pathol. 2006; 59(10):1066-1072.**
2. **Biasci D, Lee JC, Noor NM, et al. A blood-based prognostic biomarker in IBD. Gut. 2019; 68(8):1386-1395.**
3. **Bogaert S, Laukens D, Peeters H, et al. Differential mucosal expression of Th17-related genes between the inflamed colon and ileum of patients with inflammatory bowel disease. BMC Immunol. 2010;11:61.**
4. **Cupi ML, Sarra M, Marafini I, et al. Plasma cells in the mucosa of patients with inflammatory bowel disease produce granzyme B and possess cytotoxic activities. J Immunol. 2014; 192(12):6083-6091.**
5. **Fonseca-Camarillo G, Furuzawa-Carballeda J, Yamamoto-Furusho JK. Interleukin 35 (IL-35) and IL-37: intestinal and peripheral expression by T and B regulatory cells in patients with inflammatory bowel disease. Cytokine. 2015;75(2):389-402.**
6. **Granlund Av, Flatberg A, Østvik AE, et al. Whole genome gene expression meta-analysis of inflammatory bowel disease colon mucosa demonstrates lack of major differences between Crohn's disease and ulcerative colitis. PLoS One. 2013;8(2):e56818.**
7. **Iboshi Y, Nakamura K, Ihara E, et al. Multigene analysis unveils distinctive expression profiles of helper T-cell-related genes in the intestinal mucosa that discriminate between ulcerative colitis and Crohn's disease. Inflamm Bowel Dis. 2014; 20(6):967-977.**
8. **Labbé C, Boucher G, Foisy S, et al. Genome-wide expression profiling implicates a MAST3-regulated gene set in colonic mucosal inflammation of ulcerative colitis patients. Inflamm Bowel Dis. 2012; 18(6):1072-1080.**
9. **Lee JC, Lyons PA, McKinney EF, et al. Gene expression profiling of CD8+ T cells predicts prognosis in patients with Crohn disease and ulcerative colitis. J Clin Invest. 2011; 121(10):4170-4179.**

10. **McDermott E, Ryan EJ, Tosetto M,et al. DNA methylation profiling in inflammatory bowel disease provides new insights into disease pathogenesis. J Crohns Colitis. 2016; 10(1):77-86.**
11. **Parkes M, Noor NM, Dowling F, et al. PRedicting Outcomes For Crohn's dIsease using a moLecular biomarkEr (PROFILE): protocol for a multicentre, randomised, biomarker-stratified trial. BMJ Open. 2018 Dec; 8(12):e026767.**
12. **Plevy S, Silverberg MS, Lockton S, et al. Combined serological, genetic, and inflammatory markers differentiate non-IBD, Crohn's disease, and ulcerative colitis patients. Inflamm Bowel Dis. 2013; 19(6):1139-1148.**
13. **Somineni HK, Venkateswaran S, Kilaru V, et al. Blood-derived DNA methylation signatures of Crohn's disease and severity of intestinal inflammation. Gastroenterology. 2019; 156(8):2254-2265.**
14. **Ye YL, Yin J, Hu T, et al. Increased circulating circular RNA_103516 is a novel biomarker for inflammatory bowel disease in adult patients. World J Gastroenterol. 2019; 25(41):6273-6288.**

Government Agency, Medical Society, and Other Authoritative Publications:

1. **American College of Gastroenterologists (ACG), Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol. 2018; 113(4):481-517.**
2. **ACG, Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG Clinical Guideline: Ulcerative Colitis in Adults. Am J Gastroenterol. 2019; 114(3):384-413.**
3. **AGA, Feuerstein JD, Isaacs KL, et al; AGA Institute Clinical Guidelines Committee. AGA Clinical Practice Guidelines on the Management of Moderate to Severe Ulcerative Colitis. Gastroenterology. 2020 Apr;158(5):1450-1461**
4. **AGA, Ko CW, Singh S, Feuerstein JD, et al. AGA Clinical Practice Guidelines on the Management of Mild-to-Moderate Ulcerative Colitis. Gastroenterology. 2019; 156(3):748-764.**
5. **AGA, Sandborn WJ. Crohn's disease evaluation and treatment: clinical decision tool. Gastroenterology. 2014; 147(3):702-705.**

Websites for Additional Information

1. **Centers for Disease Control and Prevention (CDC). Inflammatory Bowel Disease (IBD) in the United States. Updated August 11, 2020. Available at : https://www.cdc.gov/ibd/data-statistics.htm#:~:text=Inflammatory%20Bowel%20Disease%20Prevalence%20(IBD,%25%20or%202%20million%20adults). Accessed on September 28, 2020.**

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2. **Crohn's & Colitis Foundation. Inflammatory Bowel Diseases Clinical Primer and Care Pathway Tool Kit. 2020. Available at: https://www.crohnscolitisfoundation.org/sites/default/files/2020-03/Inflammatory%20Bowel%20Disease%20Clinical%20Primer%20and%20Care%20Pathway%20Tool%20Kit.pdf. Accessed on September 27, 2020.**
3. **Crohn's & Colitis Foundation. The Facts about Inflammatory Bowel Disease. 2014. Available at: https://www.crohnscolitisfoundation.org/sites/default/files/2019-02/Updated%20IBD%20Factbook.pdf. Accessed on September 27, 2020.**

Index

PredictSURE IBD™

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
New	11/05/2020	Medical Policy & Technology Assessment Committee (MPTAC) review. Initial document development.

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