Local Coverage Determination (LCD):
MolDX: Prometheus IBD sgi Diagnostic Policy (L37299)

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Contractor Information

CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATE(S)
Noridian Healthcare Solutions, LLC	A and B MAC	01111 - MAC A	J - E	California - Entire State
Noridian Healthcare Solutions, LLC	A and B MAC	01112 - MAC B	J - E	California - Northern
Noridian Healthcare Solutions, LLC	A and B MAC	01182 - MAC B	J - E	California - Southern
Noridian Healthcare Solutions, LLC	A and B MAC	01211 - MAC A	J - E	American Samoa Guam Hawaii Northern Mariana Islands
Noridian Healthcare Solutions, LLC	A and B MAC	01212 - MAC B	J - E	American Samoa Guam Hawaii Northern Mariana Islands
Noridian Healthcare Solutions, LLC	A and B MAC	01311 - MAC A	J - E	Nevada
Noridian Healthcare Solutions, LLC	A and B MAC	01312 - MAC B	J - E	Nevada
Noridian Healthcare Solutions, LLC	A and B MAC	01911 - MAC A	J - E	American Samoa California - Entire State Guam Hawaii Nevada Northern Mariana Islands

LCD Information

Document Information

LCD ID **Original Effective Date**

L37299

LCD Title
MolDX: Prometheus IBD sgi Diagnostic Policy

Proposed LCD in Comment Period
N/A

Source Proposed LCD
DL37299

AMA CPT / ADA CDT / AHA NUBC Copyright Statement

For services performed on or after 01/30/2018

Revision Effective Date
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N/A

Retirement Date
N/A

Notice Period Start Date
12/14/2017

Notice Period End Date
01/29/2018

CMS National Coverage Policy

Title XVIII of the Social Security Act, §1862(a)(1)(A). Allows coverage and payment for only those services that are

considered to be reasonable and necessary.

42 Code of Federal Regulations (CFR) 410.32(a). Diagnostic x-ray tests, diagnostic laboratory tests, and other diagnostic tests: Conditions.

CMS On-Line Manual, Publication 100-02, *Medicare Benefit Policy Manual,* Chapter 15, §§80.0, 80.1.1, 80.2. Clinical Laboratory services.

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

This is a non-coverage policy for the Prometheus IBD sgi Diagnostic test. The intended use of this test is to aid healthcare providers in the differentiating inflammatory bowel disease (IBD) vs non-IBD, and Crohn's disease (CD) vs UC in a comprehensive blood test. The test includes nine serological markers: ASCA IgA, ASCA IgG, anti-OmpC IgA, anti-CBir1 IgG, anti-A4 Fla2 IgG, anti-FlaX IgG, IBD-specific pANCA auto-antibody, IBD-specific pANCA IFA (perinuclear pattern), IBD-specific pANCA IFA DNAse Sensitivity; four genetic immune response markers (SNPs): ATG16L1, STAT3, NKX2-3, and ECM1; and five inflammatory biomarkers: ICAM-1, VCAM-1, VEGF, CRP and SSA. A proprietary Smart Diagnostic Algorithm interprets patterns among the multiple assay values to produce an IBD score. The test results are reported as "consistent with IBD" (consistent with UC; consistent with CD, or inconclusive for UC vs CD) or "not consistent with IBD". In addition to the algorithmic test interpretation, the results of the 17 biomarkers are also individually reported.

Summary of Evidence

CD and UC represent the two main forms of idiopathic chronic IBD. While the etiology remains idiopathic, evidence suggests that the ongoing inflammation in IBD results from persistent overly aggressive inflammatory responses to a subset of commensal microorganisms in a genetically susceptible host with exposure to environmental triggers. CD is characterized by discontinuous, transmural regions of intestinal inflammation most frequently involving the terminal ileum and colon, but can affect any part of the gastrointestinal tract, with symptoms of abdominal pain, weight loss and variable degrees of diarrhea, and complications of intestinal fibrosis, strictures and fistula formation. In contrast, UC is limited to the mucosa and submucosa of the colon, with particular involvement of the rectum. Classic symptoms of active UC include diarrhea, hematochezia, tenesmus and defecatory urgency. Extra intestinal manifestations of IBD occur in up to 25% of patients. Joints, skin and eyes may be affected. In both CD and UC, disease activity is typically relapsing and remitting, although the disease course of CD is typically progressive. Although UC and CD can usually be differentiated on the basis of clinical, radiographic, endoscopic, and histologic findings, these conditions can be difficult to distinguish in about 10% to 15% of IBD patients.

Evolution of IBD Testing

In the mid-2000s, two serologic markers – anti-Saccharomyces cerevisiae antibodies (ASCA) and perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) – were used to diagnose IBD, and distinguish between UC and CD. Studies had shown that patients with CD had significantly higher ASCA antibodies than did controls or patients with UC. The reason CD patients have both IgA and IgG-ASCA is unclear. Overall, the sensitivity for either IgA or IgG-ASCA is in the range of 55% with specificity of about 90%. On the other hand, pANCA, a true autoantibody, was observed to be associated with colonic forms of IBD, particularly UC, with a sensitivity of approximately 60-70%. However, these pANCA–positive CD patients typically have a clinical phenotype resembling left-sided UC, so pANCA

detection alone is of little value in distinguishing between UC and Crohn's colitis.

A second generation IBD panel (IBD First Step®) was marketed by Prometheus Laboratories (2000) consisting of more sensitive ASCA and pANCA assays and the addition of a second microbial antigen, OmpC. Anti-OmpC was added to increase the sensitivity for CD. Subsequently, a third generation serology panel (IBD Serology 7) was offered by Prometheus Laboratories in 2006. The panel is composed of the following markers: ASCA-IgA, ASCA-IgG, anti-OmpC-IgA, anti-CBir1-IgA, and three ANCA tests: pANCA, ANCA-IgG and DNAse-sensitive pANCA. The Smart Diagnostic Algorithm analyzes and correlated test results with patterns known to the database to be associated with IBD. It supposed can predict an IBD diagnosis even when all 7 of the parameters of the IBD Serology 7 panel would be considered normal on the basis of the reference ranges provided.[1] It was reported to identify another 20% or more of otherwise seronegative CD patients.[2] The IBD Serology 7 panel has a sensitivity of 93%, specificity of 95% and positive predictive value of 96% in population prevalence of 59% according to Prometheus. A positive anti-CBir1 can additionally help distinguish between UC and CD in pANCA positive patients. However, in a comparison study evaluating the predictive IBD Serology 7 with routine blood test (IgA-ASCA, IgG-ASCA) in a pediatric population referred for initial evaluation of suspected IBD, the sensitivity, specificity, positive predictive value, negative predictive value, and k value for the serologic panel was 67%, 76%, 63%,79% and 47%. The antiflagellin antibody assay had sensitivity of 50% and specificity of 53%. Despite the inclusion of antiflagellin in the IBD7 panel, the IBD7 panel had lower predictive values compared with routine laboratory tests in pediatric screening for IBD.[3]

Concern has been raised about serologic testing for IBD because the data evaluating the role of serologic testing were obtained in individuals with a known diagnosis of either CD or UC. In many of these studies, the controls were normal healthy individuals. The use of the Smart Diagnostic Algorithm based on pattern recognition has not been published in a peer-reviewed journal. Similarly, the characteristics of the validation cohort (age, gender, race) are not known or whether any of these patient characteristics affect serologic markers. However, the greatest uncertainly pertains to the precise role for serologic testing in the diagnosis of IBD patients. Austin, et al[1] state that "while there are no prospectively validated data on the accuracy of IBD serologic testing in patients with suspected IBD, the presence of positive serologic markers likely does increase the probability that the person has IBD compared with the general population". However, they note that when a physician has a reasonable index of suspicion for IBD, more definitive imaging and endoscopic studies are required to confirm or refute the diagnosis and plan treatment, regardless of the serologic results. When the physician has a low index of suspicion for IBD, a positive serologic test is likely to results in unnecessary evaluation, and a negative serologic test only adds additional expense without benefit. These authors specify that further research is required to develop the evidence that is necessary for rational use of serologic testing.

The American College of Gastroenterology, in its guideline on the clinical management of Crohn's Disease in adults, states that serologic tests are not routinely recommended to establish a diagnosis of CD.[4] The American College of Gastroenterology, in its "Ulcerative Colitis Practice Guidelines in Adults"[5] specifies that serologic testing (ANCA/ASCA) may be useful in the occasional patient in whom no other clinical or pathologic features allow a differential diagnosis between UC and CD. Additionally, serological studies evaluating anti-glycan antibodies and antibodies to microbial antigens are being studied to support the diagnosis of inflammatory bowel disease, but the reliability of these tests in helping establish a diagnosis is still not sufficient.[5]

The fourth iteration of Prometheus' IBD testing, IBD sgi Diagnostic test, combines serologic (n=8), genetic (n=4) and inflammatory biomarkers (n=5). In addition to the 7 serologic tests in the IBD Serology 7, two additional serologic markers: anti-Fla-X and anti-A4-FL2; four genetic markers: ATG16L1, ECM1, NKX2.3 and STAT3; and four inflammatory markers: VEGF, ICAM and VCAM, CRP and SAA are marked to increase the discriminatory ability of the assay to be an adjunct in the diagnosis of UC vs CD. The IBD sgi Diagnostic™ product monograph[6] includes an extensive bibliography that documents associations of the 17 component markers, individually and in combination, with UC and/or CD. Development and performance characteristics of the 17-marker panel are described without citation, and it is unclear what standard criterion was used for diagnosis. Overall sensitivity for IBD, UC, and CD is reported as 74%, 98%, and 89%, respectively; specificity is reported as 90%, 84%, and 81%, respectively; receiver operating characteristic (ROC) analysis showed greater discrimination with the 17-marker panel (area under the

curve [AUC], 0.871) compared with any individual marker (greatest AUC=0.690 for IgA anti-Saccharomyces cerevisiae antibodies [ASCA]). Test performance characteristics for distinguishing UC from CD were not provided.

In a 2012 review of the monograph, Shirts et al[7] observed that serologic tests for ASCA-IgA, ASCA-IgG, and atypical perinuclear anti-neutrophil cytoplasmic antibody are standard of care in the diagnostic workup of IBD although not all investigators include these tests in recommended diagnostic strategies. These 3 markers are included in the 17-marker panel. Based on a meta-analysis of 60 studies (total N=11,608), pooled sensitivity and specificity of the 3-test panel were 63% and 93%, respectively, for diagnosing IBD. Because the product monograph does not include a comparison of the 17-marker panel with the 3- marker panel, incremental improvement in diagnosis with the 17-marker panel is unknown. Shirts et al calculated an AUC for the 3-marker panel of 0.899.

Analysis of Evidence
(Rationale for Determination)

Level of Evidence

Quality: Poor

Strength: Moderate

Weight: Moderate

Although manufacturer data supports clinical validity of the test for diagnosing IBD, this evidence is insufficient to support an indirect chain of evidence for clinical utility due to lack of details about study methodology and lack of replication of the findings. For distinguishing UC from CD, clinical validity has not been established. No studies examining the clinical utility of IBD sgi Diagnostic™ have been identified. Furthermore, there are no US Preventive Services Task Force (USPSTF) recommendations for genetic or molecular testing for inflammatory bowel diseases, and no recommendations for multi-marker panels that include genetic tests to facilitate diagnosis or prognosis of CD or UC.[4, 5] Consequently, this assay does not meet Medicare's reasonable and necessary criteria for coverage. Additionally, each of the individual components that comprise this assay, except ASCA-IgA, ASCA-IgG, and atypical perinuclear anti-neutrophil cytoplasmic antibody, are additionally non-covered for the diagnosis of IBD.

General Information

Associated Information

N/A

Sources of Information

N/A

Bibliography

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3. Benor S, Russell GH, Silver M, et al. Shortcomings of the inflammatory bowel disease Serology 7 Panel. Pediatrics, 2010;125(6):
4. Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol 2018; 113:481–517; doi: 10.1038/ajg.2018.27.
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6. https://www.prometheuslabs.com/Resources/IBDDiagnostic/IBD-sgi-Monograph.pdf
7. Shirts B, von Roon AC, Tebo AE. The entire predictive value of the Promethdus IBD sgi Diagnostic product may be due to the three least expensive and most available components. AJ Gastroentrol 2012;107:1760-1.

Revision History Information

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
12/01/2019	R5	The LCD is revised to remove CPT/HCPCS codes in the Keyword Section of the LCD. At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; and, therefore not all the fields included on the LCD are applicable as noted in this policy.	• Other (The LCD is revised to remove CPT/HCPCS codes in the Keyword Section of the LCD.)
12/01/2019	R4	12/01/2019: This LCD is being revised in order to adhere to CMS requirements per chapter 13, section 13.5.1 of the Program Integrity Manual. There has been no change in coverage with this LCD revision. Regulations regarding billing and coding were removed from the **CMS National Coverage Policy** section of this LCD and placed in the related Billing and Coding Article.	• Provider Education/Guidance
12/01/2019	R3	As required by CR 10901, all billing and coding information has been moved to the companion article, this article is linked to the LCD. At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination; and, therefore not all the fields included on the LCD are applicable as noted in this policy.	• Revisions Due To Code Removal

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
01/30/2018	R2	Link in bibliography entry #6 is corrected.	• Creation of Uniform LCDs With Other MAC Jurisdiction
01/30/2018	R1	The 5th biomarker, CRP, is added to the listing of biomarkers in the following sentence under Coverage Indications, Limitations and/or Medical Necessity: "…and five inflammatory biomarkers: ICAM-1, VCAM-1, VEGF, CRP and SSA."	• Creation of Uniform LCDs With Other MAC Jurisdiction

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Article(s)
A57516 - Billing and Coding: MolDX: Prometheus IBD sgi Diagnostic Policy
A55778 - Response to Comments: MolDX: Prometheus IBD sgi Diagnostic Policy
LCD(s)
DL37299
- (MCD Archive Site)

Related National Coverage Documents

N/A

Public Version(s)

Updated on 01/29/2020 with effective dates 12/01/2019 - N/A
Updated on 01/16/2020 with effective dates 12/01/2019 - N/A
Updated on 10/29/2019 with effective dates 12/01/2019 - N/A
Updated on 09/27/2018 with effective dates 01/30/2018 - 11/30/2019
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Updated on 12/01/2017 with effective dates 01/30/2018 - N/A

Keywords

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