Medical Policy

Subject:	Serologic Testing for Biomarkers of Irritable Bowel Syndrome (IBS)		
Document #:	LAB.00037	**Publish Date:**	01/03/2024
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Description/Scope

This document addresses the use of serological testing for biomarkers to aid in the screening, diagnosis and management of irritable bowel syndrome (IBS), including testing performed with IBSDetex™ (Quest Diagnostics, Secaucus, New Jersey), ibs-smart® (Gemelli Biotech, Los Angeles, CA) and IBSchek® (Commonwealth Diagnostics International, Inc, Salem, MA). This document does not address any other type of testing for IBS including breath tests, fecal analysis, gene expression profiling or imaging.

Note: For additional information regarding related documents, please see:

- LAB.00016 Fecal Analysis Panels in the Diagnosis of Intestinal Disorders
- LAB.00024 Immune Cell Function Assay

Position Statement

Investigational and Not Medically Necessary:

Serological testing for biomarkers of irritable bowel syndrome (for example, CdtB and anti-vinculin), using tests such as, IBSDetex, ibs-smart or IBSchek, is considered **investigational and not medically necessary** for screening, diagnosis or management of irritable bowel syndrome, and for all other indications.

Rationale

Diagnosing IBS and differentiating from other digestive disorders is a complex task for clinicians. Symptom-based diagnosis based on the Rome IV criteria is the most widely used method; however, the criteria have not been validated against laboratory or pathology disease markers. Therefore, there is great interest in identifying alternative tests or techniques to make more definitive diagnoses. One such method is the use of serologic markers. The IBSDetex, ibs-smart and IBSchek are three serologic marker tests currently on the market intended to aid providers in diagnosing and ruling out IBS through detection of circulating anti-cytolethal distending toxin B (anti-CdtB) and anti-vinculin antibodies.

In 2015, Pimentel and colleagues recruited 2375 subjects from a large-scale trial already underway (TARGET 3) with diarrhea-predominant IBS (IBS-D) based on Rome criteria, to assess circulating anti-CdtB and anti-vinculin antibodies as potential biomarkers for IBS-D. For comparison, additional subjects were recruited with inflammatory bowel disease (IBD) (n=142) and celiac disease (n=121), in addition to healthy controls (n=43). Enzyme-linked immunosorbent assay (ELISA) was used to determine plasma levels of anti-CdtB and anti-vinculin antibodies and then compared between groups. Relative to IBD, healthy controls and celiac disease, anti-CdtB and anti-vinculin plasma levels were significantly higher in IBS-D subjects ($p<0.001$; both). Both markers' specificity was lower in differentiating IBS from celiac disease. For anti-CdtB the specificity and sensitivity were 91.6% and 43.7,

respectively, and for anti-vinculin 83.8%, 32.6, respectively. Although results of this trial suggest that anti-CdtB and anti-vinculin antibodies are elevated in IBS-D compared to non-IBS subjects, their use in clinical practice remains undefined. Further investigation into cut-offs for confirmatory diagnosis, including characterizing variability within populations is warranted.

In 2017, a very similar study conducted by Rezaie and colleagues recruited subjects with IBS-D (n=2375) from the same TARGET 3 trial. Healthy controls (n=43) and individuals with mixed IBS (IBS-M) (n=25) or IBS with constipation (IBS-C) (n=30) were also recruited. Again, ELISA was used to analyze plasma levels of anti-CdtB and anti-vinculin antibodies. Plasma levels of anti-CdtB and anti-vinculin antibodies were highest in IBS-D and lowest in IBS-C and healthy controls ($p<0.001$), whereas plasma levels in IBS-C subjects were not statistically different from controls ($p>0.1$). Positivity for anti-CdtB or anti-vinculin resulted in a statistically significant negative gradient from IBS-D (58.1%) to IBS-M (44.0%), IBS-C (26.7%), and controls (16.3%) ($p<0.001$). Authors conclude that anti-CdtB and anti-vinculin antibodies may prove useful in the diagnosis of IBS-M and IBS-D, but their value in the diagnosis of IBS-C was not demonstrated in this trial. Further investigation into the clinical utility of these biomarkers is warranted.

The use of ELISA testing for anti-CdtB and anti-vinculin in IBS-D diagnosis was found to suffer from epitope instability; as such, a trial was conducted by Morales and colleagues in 2019 incorporating epitope stabilization into testing. Plasma samples from a cohort of IBS-D subjects from the large-scale TARGET 3 clinical trial were retrospectively collected. After epitope stabilization, CdtB and vinculin were used in ELISA testing. Samples from 100 IBS-D and 31 IBD subjects were tested. IBS-D subjects had higher anti-CdtB titers ($p=0.0001$) and higher anti-vinculin titers ($p=0.004$) than IBD subjects. The specificity and sensitivity of anti-CdtB's ability to differentiate IBS-D from IBD were 93.5% and 43.0%, respectively. The specificity and sensitivity of anti-vinculin were 90.9% and 52.2%, respectively. Study authors concluded that performing epitope stabilization for CdtB and vinculin enhances the validity of ELISAs for anti-CdtB and anti-vinculin in distinguishing IBS-D from IBD. Epitope stabilization of ELISA testing may help further define what role, if any, anti-CdtB and anti-vinculin may play in understanding immunity in functional bowel diseases.

In 2019 a retrospective cohort study was published by Talley and colleagues which enrolled participants from 2 studies already in progress: (a) a random, population-based study with subjects diagnosed (using Rome criteria) with IBS (n=63) or functional diarrhea (FD) (n=61) and healthy control subjects (n=246), and (b) an outpatient-based study with subjects diagnosed with IBS (n=256) and/or FD (n=55) or organic gastrointestinal (GI) disease (n=182) diagnosed by an independent clinician. Using ELISA testing, serum levels of anti-CdtB and anti-vinculin antibodies were determined. Compared to healthy controls, individuals with symptoms of FD had a significantly higher mean value of anti-CdtB (mean=2.46 [Standard Deviation {SD}=0.72] vs mean=2.14 [SD=0.77]; $p=0.005$) and IBS/FD overlap versus healthy controls (mean=2.47 [SD=0.78] vs mean=2.14 [SD=0.77]; $p=0.02$). There were no significant differences in anti-CdtB levels in IBS and FD outpatients or IBS/FD subgroups compared with subjects with organic GI disease. Measurement of serum levels of anti-vinculin did not demonstrate significant differences between IBS and FD or healthy controls, or between IBS and FD or organic GI disease controls. This study did not demonstrate that anti-CdtB or anti-vinculin successfully distinguished IBS diarrhea from organic GI disease.

A meta-analysis conducted by Carrasco-Labra and colleagues (2019) searched the literature through 2017 and sought to summarize the available evidence on the usefulness of diagnostic tests to aid clinicians in differentiating

organic causes of chronic watery diarrhea (such as IBS), from FD. Although a total of 38 studies were included, only 2 included serologic tests of anti-CdtB and anti-vinculin antibodies. Authors concluded:

> Moderate to low certainty in the evidence indicates that available fecal and blood tests may play a role in the diagnostic workup of adult patients with functional diarrhea. At the moment, no tests are available to reliably rule in irritable bowel syndrome.

In 2021, Vasapolli and colleagues analyzed serum levels of anti-CdtB and anti-vinculin antibodies in individuals with functional gastrointestinal disorders (FGID). The study prospectively recruited 65 individuals with IBS-D (n=15), IBS-C (n=13), functional dyspepsia (n=15) and healthy controls (n=22). The study results demonstrated that "No bacteria markers showed significant differences between FGID subgroups and healthy controls. Neither anti-CdtB/anti-vinculin antibodies nor faecal microbial profiles allowed to discriminate between specific FGID subgroups."

In 2022, Hanevik and colleagues evaluated serum levels of anti-flagellin and anti-CdtB in a cohort of individuals who developed fatigue syndromes and/or FGID, by comparing them with healthy controls .The study investigators did not find significant differences in circulating B-cell activating factor (BAFF), anti-CdtB, or anti-flagellin antibody levels between the cohorts and concluded, "… our results do not support a role for BAFF, anti-CdtB, or anti-flagellin antibodies as universal biomarkers for IBS or CFS."

Recent recommendations from the American Gastroenterological Association (AGA) on the Laboratory Evaluation of Functional Diarrhea and IBS-D in Adults include the following statement which highlights the lack of available evidence on the use of serologic biomarkers for management of IBS: "In patients presenting with chronic diarrhea, the AGA makes no recommendation for the use of currently available serologic tests for diagnosis of IBS. (No recommendation; knowledge gap)" (Smalley, 2019). Updated 2022 AGA guidelines on the pharmacological management of IBS with constipation and diarrhea, both state, "A continued unmet need in IBS clinical trials is the lack of a biomarker that can embody the different pathophysiologic mechanisms of IBS or that can reliably predict treatment response to medications that have different predominant mechanisms of action…" (Chang, 2022; Lembo, 2022).

The American College of Gastroenterology guidelines on the Management of Irritable Bowel Syndrome state that "A major shortfall in making the diagnosis of IBS is the absence of biomarkers" (Lacy, 2021). The clinical utility of biomarkers in the diagnosis and management of IBS remains to be established.

Summary
Confirmatory diagnosis of IBS presents an ongoing challenge for clinicians. Although use of serologic biomarkers, like anti-CdtB and anti-vinculin antibodies may hold promise, their association with IBS pathophysiology and clinical utility remain unclear.

Background/Overview

Irritable bowel syndrome (IBS) is a chronic condition that affects the large intestine. Signs and symptoms include cramping, abdominal pain, bloating, gas, diarrhea, and constipation. The prevalence of IBS in the United States is estimated to be 12-15%. Diagnosis of IBS is usually made based on a set of symptom-based criteria referred to as the Rome criteria. Some clinicians may employ biomarkers to aid in diagnosis, but their use varies widely and there

is a lack of guidance regarding their diagnostic role and clinical utility. The IBSDetex™, ibs-smart® and IBScheck® are three serologic marker tests currently on the market intended to aid providers in diagnosing and ruling out IBS through detection of circulating anti-CdtB and anti-vinculin antibodies. The IBSDetex and ibs-smart collection kits use a blood sample collected via venipuncture. The IBSchek is a home-based capillary blood sample collection. Both tests provide biomarker levels for clinician interpretation within approximately 2-3 days.

IBS is not curable. Treatment for IBS typically includes management of symptoms through changes in dietary practices in addition to pharmaceuticals, probiotics, and mental health support; treatment plans are tailored to the individual.

Definitions

Biomarker: A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic response to a therapeutic intervention.

Functional GI disorders: Gastrointestinal disorders that cause symptoms that are often debilitating, but are not currently associated with any physical damage, such as irritable bowel syndrome (IBS) and functional dyspepsia.

Organic GI disease: A gastrointestinal disease with measurable physiological changes, such as the villi damage caused by gluten in celiac disease and the intestinal inflammation found in Crohn's disease.

Rome criteria: An international effort to create criteria based on scientific data to help in the diagnosis and treatment of functional gastrointestinal disorders. These criteria include abdominal pain and discomfort lasting on average of at least 1 day a week in the last 3 months, associated with at least 2 of the following factors: Pain and discomfort are related to defecation, the frequency of defecation is altered, or stool consistency is altered.

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:
When the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary

CPT	
0164U	Gastroenterology (irritable bowel syndrome [IBS]), immunoassay for antiCdtB and anti-vinculin antibodies, utilizing plasma, algorithm for elevated or not elevated qualitative results ibs-smart™, Gemelli Biotech, Gemelli Biotech
0176U	Cytolethal distending toxin B (CdtB) and vinculin IgG antibodies by immunoassay (ie, ELISA) IBSchek®, Commonwealth Diagnostics International, Inc, Commonwealth Diagnostics International, Inc

ICD-10 Diagnosis

All diagnoses

References

Peer Reviewed Publications:

1. Hanevik K, Saghaug C, Aaland M, et al. No difference in serum levels of B-cell activating receptor and antibodies against cytolethal distending toxin B and flagellin in post-infectious irritable bowel syndrome and chronic fatigue syndrome after Giardia infection. JGH Open. 2022; 6(3):185-188.
2. Morales W, Rezaie A, Barlow G, Pimentel M. Second-generation biomarker testing for irritable bowel syndrome using plasma anti-CdtB and anti-vinculin levels. Dig Dis Sci. 2019; 64(11):3115-3121.
3. Pimentel M, Morales W, Rezaie A, et al. Development and validation of a biomarker for diarrhea-predominant irritable bowel syndrome in human subjects. PLoS One. 2015;10:e0126438.
4. Rezaie A, Park SC, Morales W, et al. Assessment of anti-vinculin and anti-cytolethal distending toxin B antibodies in subtypes of irritable bowel syndrome. Dig Dis Sci. 2017; 62(6):1480-1485.
5. Talley NJ, Holtmann G, Walker MM, et al. Circulating anti-cytolethal distending toxin B and anti-vinculin antibodies as biomarkers in community and healthcare populations with functional dyspepsia and irritable bowel syndrome. Clin Transl Gastroenterol. 2019; 10(7): e00064.
6. Vasapolli R, Schulz C, Schweden M, et al. Gut microbiota profiles and the role of anti-CdtB and anti-vinculin antibodies in patients with functional gastrointestinal disorders (FGID). Eur J Clin Invest. 2021; 51(12):e13666.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Carrasco-Labra Alonso, Lyubov Lytvyn, ,Yngve Falck-Ytte, et al. AGA technical review on the evaluation of functional diarrhea and diarrhea-predominant irritable bowel syndrome in adults (IBS-D). Gastroenterology. 2019; 157(3):859-880.
2. Chang L, Sultan S, Lembo A. AGA Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome With Constipation. 2022. Available at: https://www.gastrojournal.org/article/S0016-5085(22)00390-0/fulltext. Accessed on September 23, 2023.
3. Lacy BE, Pimentel M, Brenner DM, et al. American College of Gastroenterology (ACG) Clinical Guideline: Management of Irritable Bowel Syndrome. Am J Gastroenterol. 2021; 116(1):17-44.
4. Lembo A, Sultan S, Chang L. AGA Clinical Practice Guideline on the Pharmacological Management of Irritable Bowel Syndrome With Diarrhea. 2022. Available at: https://www.gastrojournal.org/article/S0016-5085(22)00391-2/fulltext. Accessed on September 23, 2023.
5. Smalley W, Falck-Ytter C, Carrasco-Labra A, et al. AGA Clinical practice guidelines on the laboratory evaluation of functional diarrhea and diarrhea-predominant irritable bowel syndrome in adults (IBS-D). Gastroenterology. 2019;157(3):851-854.

Websites for Additional Information

1. National Institutes of Health. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Irritable Bowel Syndrome (IBS). Available at: https://www.niddk.nih.gov/health-information/digestive-diseases/irritable-bowel-syndrome. Accessed on September 23, 2023.

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IBSchek
Ibs-smart

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
Reviewed	11/09/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Reference section.
Reviewed	11/10/2022	MPTAC review. Updated Rationale and References sections.
Reviewed	11/11/2021	MPTAC review. Updated Description/Scope, Rationale and References sections.
New	11/05/2020	MPTAC review. Initial document development.