AGA Clinical Practice Guidelines on the Laboratory Evaluation of Functional Diarrhea and Diarrhea-Predominant Irritable Bowel Syndrome in Adults (IBS-D)

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1Department of Medicine, Division of Gastroenterology, Vanderbilt University School of Medicine, Nashville, Tennessee; 2Veterans Affairs Tennessee Valley Health Care System, Nashville, Tennessee; 3Departments of Medicine and Gastroenterology, Case Western Reserve University, Cleveland, Ohio; 4Veterans Affairs Northeast Ohio Health System, Cleveland, Ohio; 5Department of Dentistry, University of Chile, Santiago, Chile; 6Center for Evidence-Based Dentistry for the immunocompetent patient with or IBS-D. These guidelines apply to the evaluation of the diagnoses in the setting of suspected functional diarrhea choosing appropriate laboratory tests to exclude other expire in 5 years.

The focus of this guideline is to aid clinicians in choosing appropriate laboratory tests to exclude other diagnoses in the setting of suspected functional diarrhea or IBS-D. These guidelines apply to the evaluation of the immunocompetent patient with "watery" diarrhea of at least 4 weeks duration. This would exclude those patients with bloody diarrhea; diarrhea with signs of fat malabsorption; presentations with alarm features, such as weight loss, anemia, and hypoalbuminemia; those patients with a family history of inflammatory bowel disease (IBD), colon cancer, or celiac disease; and those with a travel history to regions with recognized specific diarrhea-related pathogens.

This guideline was developed using a process outlined elsewhere. Briefly, the AGA Institute process for developing clinical practice guidelines incorporates GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology and best practices as outlined by the Institute of Medicine. GRADE methodology was used to prepare the background information for the guideline and the technical review that accompanies it. Optimal understanding of this guideline will be enhanced by reading applicable portions of the technical review. The guideline panel and the authors of the technical review met face-to-face on September 8, 2017 to discuss the quality of evidence (Tables 1 and 2) and consider other factors relevant for the risk–benefit assessment of the recommendations. The guideline panel included 2 members of the AGA Clinical Practice Guidelines Committee (WS, SW, YFY), a GRADE methodologist (AC-L), and a primary care physician (CFY). The members of the guidelines panel subsequently formulated the recommendations by consensus. Although quality of evidence was a key factor in determining the strength of each recommendation (Table 2), the panel also considered the balance between the benefit and harm of interventions, patients’ values and preferences, and resource utilization. Development of this guideline and its accompanying technical review was fully funded by the AGA Institute with no additional outside funding.

Recommendation 1: In patients presenting with chronic diarrhea, the AGA suggests the use of either fecal calprotectin or fecal lactoferrin to screen for IBD. Conditional recommendation; low-quality evidence.

Comment: A threshold value of 50 μg/g for fecal calprotectin is recommended to optimize sensitivity for IBD. Threshold values in the range of 4.0–7.25 μg/g for fecal lactoferrin are recommended to optimize sensitivity.

Calprotectin and fecal lactoferrin have been proposed as markers for inflammatory conditions, such as IBD. There are several studies using fecal calprotectin with different threshold values to identify persons with IBD. Based on a review of the available data, it appears that using fecal calprotectin with a threshold of 50 μg/g yields the optimal performance. Among studies using this threshold, the pooled sensitivity for IBD was 0.81 (95% confidence interval [CI], 0.75–0.86) and the pooled specificity was 0.87 (95% CI, 0.78–0.92). Risk of bias and statistical imprecision

Abbreviations used in this paper: AGA, American Gastroenterological Association; CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; IBD, inflammatory bowel disease; IBS-D, diarrhea-predominant irritable bowel syndrome.
Both erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have been tested in populations with diarrhea to identify patient with IBD. In studies using a value of 5–6 mg/L as a threshold for CRP level, the pooled sensitivity was 0.73 (95% CI, 0.64–0.80) and the pooled specificity was 0.78 (95% CI, 0.58–0.91). Studies of similar design utilizing threshold values of 10–15 mm/h for ESR resulted in lower estimates of diagnostic accuracy for IBD.

While there are few settings where ESR should be considered as an appropriate screening test for IBD, there are some settings where the use of CRP might be a rational option. For example, if testing for fecal lactoferrin or calprotectin are either not available or not covered by insurance, the use of CRP might be considered to be a reasonable option to screen for IBD.

Table 2. Grading of Recommendations Assessment, Development, and Evaluation Definitions of Strength of Recommendation and Guide to Interpretation

<table>
<thead>
<tr>
<th>Strength of recommendation</th>
<th>Wording in the guideline</th>
<th>For the patient</th>
<th>For the clinician</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>“The AGA recommends…”</td>
<td>Most individuals in this situation would want the recommended course and only a small proportion would not.</td>
<td>Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.</td>
</tr>
<tr>
<td>Conditional</td>
<td>“The AGA suggests…”</td>
<td>The majority of individuals in this situation would want the suggested course, but many would not.</td>
<td>Different choices would be appropriate for different patients. Decision aids may be useful in helping individuals in making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working toward a decision.</td>
</tr>
<tr>
<td>No recommendation</td>
<td>“The AGA makes no ...”</td>
<td></td>
<td>The confidence in the effect estimate is so low that any effect estimate is speculative at this time.</td>
</tr>
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</table>

Throughout the United States, *Giardia* is a common cause of watery diarrhea that can be readily treated. Modern diagnostic tests for *Giardia* have excellent performance characteristics, with many studies demonstrating sensitivity and specificity of >95%. The best available tests utilize either detection of *Giardia* antigens or polymerase chain

### Table 1. Grading of Recommendations Assessment, Development, and Evaluation Definitions of Quality and Certainty of the Evidence

<table>
<thead>
<tr>
<th>Quality grade</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>High</td>
<td>We are very confident that the true effect lies close to the estimate of the effect. The true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.</td>
</tr>
<tr>
<td>Moderate</td>
<td>We are moderately confident in the effect estimate. The true effect may be substantially different from the estimate of effect.</td>
</tr>
<tr>
<td>Low</td>
<td>Our confidence in the estimate is limited. The true effect may be substantially different from the estimate of effect.</td>
</tr>
<tr>
<td>Very low</td>
<td>We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.</td>
</tr>
<tr>
<td>Evidence gap</td>
<td>Available evidence is insufficient to determine true effect.</td>
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reaction for the \textit{Giardia} small subunit ribosomal RNA. Because treatments are straightforward, there is little risk in utilizing these tests in evaluation of chronic watery diarrhea.

\textbf{Recommendation 4:} In patients presenting with chronic diarrhea with no travel history to or recent immigration from high-risk areas, the AGA suggests against testing for ova and parasites (other than \textit{Giardia}). \textit{Conditional recommendation: low-quality evidence.}

In the absence of travel or immigration from high-risk areas, the practice of routinely testing the stool for ova and parasites is highly unlikely to identify important causes of chronic watery diarrhea. Guidance on testing and treating diarrhea among those who have been in a high-risk area can come from several sources.\textsuperscript{5,6}

\textbf{Recommendation 5:} In patients presenting with chronic diarrhea, the AGA recommends testing for celiac disease with IgA tissue transglutaminase and a second test to detect celiac disease in the setting of IgA deficiency. \textit{Strong recommendation: moderate-quality evidence.}

Comments: Testing options for IgA-deficient subjects include IgG tissue transglutaminase and IgG or IgA deaminated gliadin peptides.

Celiac disease is an important cause of chronic diarrhea and other manifestations. Among patients with chronic diarrhea who do not have IgA deficiency, use of serum IgA tissue transglutaminase (tTG) is a highly efficient strategy for determining the presence of celiac disease. In these patients, the sensitivity of serum IgA-tTG using thresholds in the 7–15 AU/mL range is typically >90% and the specificity is typically slightly higher. A positive test would warrant confirmation by duodenal biopsy.\textsuperscript{7}

\textbf{Recommendation 6:} In patients presenting with chronic diarrhea, the AGA suggests testing for bile acid diarrhea. \textit{Conditional recommendation: low-quality evidence.}

Comments: In settings with limited availability of commercial assays, an empiric trial of a bile acid binder could be considered.

Bile acid diarrhea may be due to excess production or decreased absorption of bile acids, which then reach the colon and can cause watery diarrhea. There are several tests that have been proposed to identify those persons who have bile acid diarrhea.\textsuperscript{7,5} Selenium homotaurocholic acid test is a nuclear medicine test used to identify those with diarrhea due to bile acid malabsorption and has moderate diagnostic efficiency. This test is used in Europe but is not available in North America. In the United States, other tests for bile acid diarrhea are measurement of total bile acids in a 48-hour stool collection (which would document increased fecal bile acids) and serum fibroblast growth factor 19, which measures defective feedback of bile acid synthesis. A test that is not yet available is measurement of serum levels of the marker 7a-hydroxy-4-cholesten-3-one—a measure of bile acid synthesis. Because these

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\textbf{Statement} & \textbf{Strength of recommendation} & \textbf{Quality of evidence} \\
\hline
Recommendation 1: In patients presenting with chronic diarrhea, the AGA suggests the use of either fecal calprotectin or fecal lactoferrin to screen for IBD. & Conditional & Low \\
Recommendation 2: In patients presenting with chronic diarrhea, the AGA suggests against the use of ESR or CRP to screen for IBD. & Conditional & Low \\
Recommendation 3: In patients presenting with chronic diarrhea, the AGA recommends testing for \textit{Giardia}. & Strong & High \\
Recommendation 4: In patients presenting with chronic diarrhea with no travel history to or recent immigration from high-risk areas, the AGA suggests against testing stools for ova and parasites (other than \textit{Giardia}). & Conditional & Low \\
Recommendation 5: In patients presenting with chronic diarrhea, the AGA recommends testing for celiac disease with IgA-tTG and a second test to detect celiac disease in the setting of IgA deficiency & Strong & Moderate \\
Recommendation 6: In patients presenting with chronic diarrhea, the AGA suggests testing for bile acid diarrhea. & Conditional & Low \\
Recommendation 7: In patients presenting with chronic diarrhea, the AGA makes no recommendation for the use of currently available serologic tests for diagnosis of IBS & None & Knowledge gap \\
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tests are not widely available or Food and Drug Administration–approved, it is reasonable to use an empiric trial of bile acid binders in patients in whom bile acid diarrhea is considered, with clinical response suggesting excess bile acids as the cause for diarrhea.

**Recommendation 7.** 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.**

IBS-D is a major cause of chronic watery diarrhea. Several tests have been proposed to identify those with IBS-D and who might benefit from IBS-D–specific therapy. Specifically, it has been postulated that a strategy of measuring antibodies to cytolethal distending toxin B and the gut mucosal protein, vinculin, might be used to identify persons who have post-infectious IBS-D.

The available data are sparse but suggest that the contemporary tests lack the diagnostic accuracy needed for routine use. In addition, the case–control design of the studies and the study setting used (secondary and tertiary care) likely inflate the estimates of the test characteristics compared to what is expected in a general population. The specificity in the 2 studies available for the technical review was in the 90% range, meaning that a positive test would indicate a high likelihood of IBS-D. However, the low sensitivity (20%–40%) would not be sufficient to employ these tests in routine use. More data will be helpful in determining the proper roles of these and similar tests.

**Summary**

These practice guideline recommendations for the evaluation of functional diarrhea and IBS-D with the intent of excluding other diagnoses in adults were developed using the GRADE framework and in adherence with the standards for guideline development set forth by the Institute of Medicine for the creation of trustworthy guidelines. These guidelines are intended to reduce practice variation and promote high-quality and high-value care for this patient population. Current evidence supports the use of fecal calprotectin or fecal lactoferrin and stool testing for *Giardia* in patients presenting with chronic diarrhea. The panel suggests against the use of blood tests ESR or CRP to screen for IBD. Our evidence profiles also strongly recommend testing for celiac disease with IgA-tTG and a second test to detect celiac disease in the setting of IgA deficiency. In addition, testing for bile acid diarrhea is suggested. The AGA makes no recommendation for the use of currently available serologic tests for the diagnosis of IBS and should be the focus of future research (Table 3). A clinical decision support tool is included to guide the evaluation of patients with chronic watery diarrhea (>4 weeks) (Figure 1).

**References**


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**Reprint requests**

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**Conflicts of interest**

All members were required to complete the disclosure statement. These statements are maintained at the AGA headquarters in Bethesda, Maryland, and pertinent disclosures are published with this report.

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