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Bowel Disorders Evaluation Rule-out Cascade

Applying exclusionary criteria to assist diagnosis

Disorders of the lower gastrointestinal tract in adults and children are among the most common conditions and may pose a difficult diagnostic problem. Approximately 1 in 20 of all general practitioners' consultations involve these conditions, and their symptoms are often ill-defined.[1] Those disorders include a wide range of pathologic conditions, including irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) that includes Crohn's disease (CD), ulcerative colitis (UC), and indeterminate colitis; microscopic colitis, infectious colitis, small intestinal bacterial overgrowth, celiac disease, and colon neoplasia (including colon cancer).[2]

The most prevalent condition is IBS. It is estimated that, in Europe and North America 10% to 15% of the population is affected.[3] Studies show that the incidence rate of Crohn's disease increased from 0.1 (three decades ago) to 4.6 (in 2003) per 100,000 children, and the incidence of UC from 0.5 to 3.2 per 100,000 children.[4] The prevalence of IBD among adults is approaching 0.3%.[5] Studies have shown that the prevalence of celiac disease increased at least four times during the last 50 years and approaches 1%.[6–8] It is estimated that less than 5% of celiac disease cases in the US are currently diagnosed.[8]

Recently, another condition termed "gluten sensitivity," distinct from celiac disease, emerged as an important and often underdiagnosed and undertreated disease.[8,9] It is reported that as much as 12% of the healthy population may have serological evidence of gluten sensitivity.[9]

Difficulties in differential diagnosis of those conditions often prompt clinicians to use an exclusion approach by performing tests to rule out the alternative etiologies.[2] Interestingly, one study shows that most of the celiac disease serological test requests now come from general practitioners rather than gastroenterologists.[10] Another study reports that 72% of general practitioners endorsed IBS as a diagnosis of exclusion.[2] The "gold standard" for diagnosing many of these conditions continues to be endoscopy with biopsies for histological examination.[11] In recent years, however, the introduction of a number of tests for new serological markers may allow for reduction in the number of intestinal biopsies.[12]

To assist clinicians — through the use of exclusionary criteria — in diagnosing bowel disorders, LabCorp has introduced the **Bowel Disorders Evaluation Rule-out Cascade.** (This profile is intended to be used only in conjunction with other clinical and laboratory findings as an aid in diagnosis.)

Bowel Disorders Cascade

STEP 1: Celiac Disease Screen

The cascade begins with a celiac screen that includes simultaneous detection of both IgA and IgG antibodies to both deamidated gliadin peptide (DGP) and human tissue transglutaminase (tTG). The screen performance is reported to achieve a clinical sensitivity of 98.6% and specificity of 97.0% for patients with celiac disease or controls.[12] When the result is positive, testing stops and the interpretive comment on the report would read:

Suggestive of celiac disease or other gluten-sensitive enteropathies. Subsequent testing for Endomysial Antibody, IgA (164996) and/or genetic testing for Celiac Disease HLA DQ Association (167082) may be indicated for further patient evaluation.

The Celiac Disease Screen may be negative if the patient is on a gluten-free diet because antibodies to tTG and DGP are usually no longer present.[12,13] A gluten challenge would be necessary to avoid false-negative results. Genetic testing for HLA DQ2/DQ8 may be considered if the patient does not wish to undergo a gluten challenge. A negative genetic test result effectively rules out celiac disease.[13,14] A positive genetic test result increases suspicion of celiac disease but is not diagnostic. A positive endomysial antibody test is highly specific for celiac disease. **When the result is negative, then testing reflexes to the second step.**

STEP 2: Inflammatory Bowel Disease (IBD) Screen

Inflammatory bowel disease screen includes testing for IgG antibodies to anti-*Saccharomyces cerevisiae* (ASCA), and atypical perinuclear antineutrophil cytoplasmic antibodies (pANCA). This panel of tests will aid in serological identification of patients with IBD and in differentiation between its three clinical forms: CD, UC, and indeterminate colitis. When the marker of CD (ASCA IgG) is positive, the clinical sensitivity for CD is reported to as high as 74.4% and specificity for IBD generally is reported to be as high as 95.9%.[15] When atypical pANCA (a marker of UC) is positive, the clinical sensitivity for UC is reported to be as high as 70% and the specificity as high as 80%.[16] The results of the ASCA and pANCA markers cannot rule out inflammatory bowel disease; neither can their presence strictly confirm its diagnosis.[17]

Testing for step two is described below and the interpretive comment on the report would be one of the following (depending on the combination of results): When ASCA IgG is positive and atypical pANCA is negative, testing stops and the comment would read:

Suggestive of Crohn's disease. Subsequent testing with the Crohn's Disease Prognostic Profile (162020) that includes antiglycan antibodies AMCA, ALCA, ACCA, and gASCA may aid in the differentiation of clinical forms of CD and prognosis of disease progression.

When ASCA IgG is negative or equivocal and atypical pANCA is positive testing stops and the comment would read:

Suggestive of ulcerative colitis.

When both, ASCA IgG and atypical pANCA, are positive testing stops and the comment would read:

Suggestive of IBD. Subsequent testing with the Crohn's Disease Prognostic Profile (162020) that includes antiglycan antibodies AMCA, ALCA, ACCA, and gASCA may aid in the differentiation of clinical forms of IBD and prognosis of disease progression.

When all results are negative, testing reflexes to the third step.

STEP 3: Nonceliac Gluten Sensitivity Screen

The nonceliac gluten sensitivity screen includes testing for IgG antibodies to native gliadin with reported clinical sensitivity of up to 87% (for untreated clinically defined celiac disease patients) and specificity of up to 91%.[18] Recent reports show that there is a significant subset of patients that has normal histology for celiac disease, negative for antibodies to DGP and tTG, positive for antigliadin antibodies and clinically undistinguishable from those with celiac disease. Those patients constitute the so-called nonceliac "gluten sensitivity" group and many of them will benefit from gluten-free diet. This group of patients is also reported to have increased mortality.[8] When the result is positive, the testing stops and the interpretive comment on the report would read:

Suggestive of nonceliac gluten sensitivity. The patient may benefit from a gluten-free diet.

When all results are negative, the testing stops and the interpretive comment on the report would read:

Suggestive of irritable bowel syndrome (IBS). Careful evaluation of the patient's history, physical examination, and application of Rome III diagnostic criteria may help to rule in or rule out the diagnosis of IBS. Subsequent testing for Fecal Calprotectin (123255) may be recommended. If IBD is strongly suspected, subsequent testing with the Crohn's Disease Prognostic Profile (162020) that includes antiglycan antibodies AMCA, ALCA, ACCA, and gASCA may aid in differential diagnosis.

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Additional Related Studies

Ball AJ, Hadjivassiliou M, Sanders DS. Is gluten sensitivity a "No Man's Land" or a "Fertile Crescent" for Research? *Am J Gastroenterol.* 2010 Jan; 105:222-223.
Ford R. Which serological tests best identify gluten reactions? Available at: http://www.drrodneyford.com.
Wangen S. Testing for non-celiac gluten intolerance. Available at: http://www.IBSTreatmentCenter.com. Accessed August 27, 2010.

STEP1 Celiac Disease Screen (Simultaneous Detection of tTG and DGP IgG/IgA)

Prevalence: Up to 1%	Clinical Sensitivity: 98.6%	Clinical Specificity: Up to 97%

- **<20 units** → (continue to Step 2)
- **≥ 20 units** → Stop → Suggestive of celiac disease or other gluten-sensitive enteropathies. Subsequent testing for Endomysial Antibody, IgA (164996) and/or genetic testing for Celiac Disease HLA DQ Association (167082) may be indicated for further patient evaluation.

STEP 2 Inflammatory Bowel Disease (IBD) Screen (ASCA IgG, Atypical pANCA)

Prevalence: Up to 0.3%	Clinical Sensitivity	Clinical Specificity
	ASCA IgG (CD): Up to 74.4%	ASCA IgG (IBD): Up to 95.9%
	Atypical pANCA: Up to 70% (Differential diagnosis of UC)	ASCA IgG: Up to 80% (Differential diagnosis of UC)

- **All Negative** → (continue to Step 3)
- **ASCA IgG: ≥25 units Atypical pANCA: Negative** → Stop → Suggestive of Crohn's disease. Subsequent testing with the Crohn's Disease Prognostic Profile (162020) that includes antiglycan antibodies AMCA, ALCA, ACCA, and gASCA may aid in the differentiation of clinical forms of CD and prognosis of disease progression.
- **ASCA IgG: <25 units Atypical pANCA: Positive** → Stop → Suggestive of ulcerative colitis.
- **ASCA IgG: ≥25 units Atypical pANCA: Positive** → Stop → Suggestive of IBD. Subsequent testing with the Crohn's Disease Prognostic Profile (162020) that includes antiglycan antibodies AMCA, ALCA, ACCA, and gASCA may aid in the differentiation of clinical forms of IBD and prognosis of disease progression.

STEP 3 Nonceliac Gluten Sensitivity Screen (Antigliadin IgG)

Prevalence: Up to 12%	Clinical Sensitivity: Up to 87%	Clinical Specificity: Up to 91%

- **<20 units** → Stop → Suggestive of irritable bowel syndrome (IBS). Careful evaluation of the patient's history, physical examination, and application of Rome III diagnostic criteria may help to rule in or rule out the diagnosis of IBS. Subsequent testing for Fecal Calprotectin (123255) may be recommended. If IBD is strongly suspected, subsequent testing with the Crohn's Disease Prognostic Profile (162020) that includes antiglycan antibodies AMCA, ALCA, ACCA, and gASCA may aid in differential diagnosis.
- **≥20 units** → Stop → Suggestive on nonceliac gluten sensitivity. The patient may benefit from a gluten-free diet.

Note: Biopsy with histological evaluation remains the "gold standard" for the diagnosis of many bowel disorders.[11]

Relevant Assays

Test Name	Test Number
Bowel Disorders Evaluation Rule-out Cascade	164085
Calprotectin, Fecal	123255
Celiac Disease HLA DQ Association	167082
Crohn's Disease Prognostic Profile	162020
Endomysial Antibody, IgA	164996

For the most current information regarding test options, including specimen requirements and CPT codes, please consult the online Test Menu at **www.LabCorp.com.**