

**Diagnos-Techs™**  
Clinical & Research Laboratory  
Quarterly Newsletter

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## Fecal Calprotectin: A New Marker of Intestinal Inflammation

Lisa Canar, ND; John J. White, MD CM;  
Jeremy Celver, PhD; and  
John Reinhard, PhD



**Assessing the severity and extent of intestinal inflammation** is an essential component in the workup of patients with such common digestive complaints as abdominal pain and cramping, bowel movement disturbances, bloating, and flatulence. Assessing intestinal inflammation is also indicated for patients with complaints such as fever, weight loss, or fatigue, because these symptoms are often associated with inflammatory bowel disease (IBD) and other inflammatory intestinal disorders.

Because intestinal inflammation is not directly observable by patients or clinicians, laboratory assays can provide a critical piece of information in helping to determine the presence, location, and magnitude of such inflammation. Laboratory stool analysis is the most convenient and non-invasive means of assessing inflammation in the intestinal tract. Elevated stool inflammatory biomarkers point to an active process of intestinal mucosal cell damage. Such damage may be associated with a variety of causes, including acute or chronic intestinal infection (viral, bacterial or parasitic), inflammatory bowel disease, diverticulitis, celiac disease, NSAID-induced enteropathy, and colorectal cancer.

Diagnos-Techs™ has offered stool markers of intestinal inflammation for some time, and we are now pleased to announce the addition of a new test for the marker **calprotectin**. Calprotectin is an abundant neutrophil protein, and its presence in stool is indicative of neutrophilic infiltration into the gut lumen associated with inflammatory processes. Elevated concentrations of fecal calprotectin have been demonstrated in numerous studies of patients with both infectious and inflammatory conditions, including those with IBD.<sup>1</sup> As a diagnostic test, fecal calprotectin has shown a 95% sensitivity and 91% specificity for identifying IBD patients.<sup>2</sup>

IBD, which includes Crohn's disease and ulcerative colitis, is marked by chronic, recurrent episodes of inflammation in the gastrointestinal tract. Because this inflammation underlies many of the symptoms and signs of IBD, its detection and monitoring are key to proper clinical management. Fecal calprotectin can aid in this detection and monitoring, as well as provide a non-invasive means to

## **Fecal Calprotectin** *continued from front cover.*

track disease activity, risk of relapse, and response to treatment. Fecal calprotectin values have been shown to correlate with endoscopic and histological assessment of disease activity in IBD patients.<sup>3</sup> Levels of fecal calprotectin correlate well with radio-labeled leukocyte scanning, a costly and invasive procedure used to assess active intestinal inflammation in Crohn's disease.<sup>4</sup> Overall, fecal calprotectin strongly outperforms serum C-reactive protein (CRP) and other inflammatory markers in assessing IBD treatment efficacy and in predicting relapse.<sup>5</sup>

A key problem in gastroenterology is the differentiation of IBD from irritable bowel syndrome (IBS). Because IBS is a functional disorder with no demonstrable pathology, the absence of biomarkers of intestinal inflammation such as fecal calprotectin can point toward an IBS diagnosis. In most patients presenting with common intestinal symptoms, a normal fecal calprotectin can help clinicians to rule out IBD. In a study of 602 patient referrals to a gastroenterology clinic who had symptoms suggestive of either IBS or inflammatory intestinal disease, the sensitivity and specificity of calprotectin for predicting inflammatory disease were 89% and 79%, respectively.<sup>6</sup> Meta-analysis of multiple similar studies involving nearly 6000 participants has demonstrated that using a fecal calprotectin cut-off limit of 50µg/g accurately differentiates IBD from IBS.<sup>7</sup> Because the clinical differentiation of IBD and IBS remains problematic, many patients in the IBS category are routinely investigated with extensive and invasive imaging tests


to rule out IBD. Fecal calprotectin provides a convenient and non-invasive marker of intestinal mucosal inflammation, and assessing fecal calprotectin first can help clinicians identify patients with abdominal symptoms who will more likely benefit from these further diagnostic procedures.

Fecal calprotectin is not specific for IBD but rather indicates immune cell infiltration into the gut lumen. Calprotectin levels can therefore be elevated in a variety of inflammatory conditions including celiac disease, infectious diarrhea, diverticulitis, NSAID-induced enteropathy, and some gastrointestinal malignancies. A positive fecal calprotectin test should be evaluated in the context of the patient's clinical presentation and will likely warrant further testing.

It is not yet clear whether fecal calprotectin should begin to play a role in the diagnosis or management of celiac disease. A study of 29 children newly diagnosed with celiac disease (in its classic presentation including failure to thrive) found significantly elevated fecal calprotectin levels in patients relative to matched controls. In these patients calprotectin levels correlated with the severity of histopathologic findings at diagnosis. After one year on a gluten-free diet, calprotectin levels in these patients returned to levels found in healthy controls.<sup>8</sup> Another small study of children with celiac disease, evaluating both untreated (n=31) and treated (n=33) participants, noted similar findings.<sup>9</sup> Although these results appear promising, another small study in both adult and pediatric patients with chronic diarrhea from various causes found that

fecal calprotectin, while consistently reliable in identifying IBD patients, was not as reliable in distinguishing patients with celiac disease from those with IBS. Fecal calprotectin tests in patients with chronic diarrhea gave numerous false negative results in the case of celiac disease (i.e., many celiac disease patients were missed).<sup>10</sup> Given inconclusive research, we do not currently recommend that clinicians rely on fecal calprotectin levels to differentiate celiac disease from IBS. Similarly, a recommendation for use of fecal calprotectin to monitor diet adherence or disease improvement for those on a gluten-free diet must also await further study.

**Diagnos-Techs will offer fecal calprotectin as a stand-alone test and will soon incorporate this test into a new GI panel. Please call client services at 1-800-878-3787 to order the new Calprotectin test (CPT code 83993).**

In addition to the new fecal calprotectin test, Diagnos-Techs will continue to offer our current markers of intestinal inflammation—lysozyme and alpha anti-chymotrypsin—in addition to related markers of total intestinal secretory IgA (sIgA) and fecal occult blood. Together with our new fecal calprotectin test, these markers will help clinicians to quantify intestinal inflammation, differentiate inflammatory from functional causes of intestinal disturbance, and obtain a glimpse into intestinal mucosal immune function and epithelial integrity. 



## Food Intolerance vs. Food Allergy

Carrie C. McMillin, ND

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**Food intolerance, allergy, sensitivity and hypersensitivity** are often used interchangeably when referring to adverse food reactions. As these reactions become a more common topic of discussion, however, it is important that we standardize these definitions to avoid miscommunication and identify gaps in our understanding. In an effort to clarify these terms, several organizations have put forth additional definitions for various food reactions over the years.

In 2004, the World Allergy Organization released a report on allergy nomenclature, asserting that the term *food allergy* should be used when referring to food reactions in which an immunologic mechanism has been demonstrated.<sup>1</sup>

Elaborating further on the subject, the National Institute of Allergy and Infectious Diseases (NIAID), a component of the National Institutes of Health (NIH), released *Guidelines for the Diagnosis and Management of Food Allergy in the United States* in 2010.<sup>2</sup> These guidelines similarly define food reactions that are immune mediated as *food allergies*, and more specifically, they categorize adverse food reactions as follows:

### Adverse Food Reactions

#### Immune mediated (food allergy and celiac disease)

- IgE mediated (e.g., acute urticaria, oral allergy syndrome)
- Non-IgE mediated (e.g., food protein-induced enteropathy, celiac disease)
- Mixed IgE and Non-IgE mediated (e.g., eosinophilic gastroenteritis)

- Cell mediated (e.g., allergic contact dermatitis)

#### Non-immune mediated (primarily food intolerances)

- Metabolic (e.g., lactose intolerance)
- Pharmacologic (e.g., caffeine)
- Toxic (e.g., scombroid fish toxin)
- Other/idiopathic/undefined (e.g., sulfites)<sup>2</sup>

Although there is continued discussion on the specific mechanisms involved in adverse food reactions and the most appropriate methods of diagnosis, the consensus opinion is that those that are mediated by the immune system are most accurately termed *food allergies*. In keeping with this standard, we at Diagnos-Techs have instituted a change in our Food Intolerance Panel. This panel will now be called the Food Allergy (Sensitivity) Panel. We have chosen to include *sensitivity* in the title because we recognize that many providers use the term *food sensitivity* to differentiate immune-mediated food reactions that are not a Type I hypersensitivity from those that are. All components of the panel currently remain unchanged, although we are currently pursuing additional tests to aid in gaining a more complete understanding of patients. As always, we will keep our providers updated on new developments, and we welcome your feedback. 

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Food Allergy (Sensitivity) Test Kit



## Celiac Disease & Non-Celiac Gluten Sensitivity:

### Using Laboratory Measures to Clarify Etiology and Determine Course of Treatment

Bethany Glynn, ND



**The concept of gluten sensitivity** has been around for many years, but only recently has the term become ubiquitous. More patients than ever are entering clinics with self-diagnoses of various reactions to gluten, leaving practitioners to decipher the intricacies of gluten-induced symptoms. Gluten is found in common food items, prescriptions medications, supplements, and beauty products, making it difficult to isolate the source of gluten exposure. Adding to the confusion is the assumption by many that gluten sensitivity and its autoimmune counterpart, celiac disease, are the same disease entity.

Celiac disease is an autoimmune digestive condition involving both humoral and cell-mediated immune responses to gluten, a protein in grains such as wheat, rye, and barley. Individuals with Non-Celiac Gluten Sensitivity (NCGS) may present with digestive symptoms similar to those with celiac disease, but without the autoimmune intestinal destruction. This

article will help to clarify the difference between these two conditions in reviewing symptoms, pathophysiology, and diagnosis in laboratory medicine.

#### Development and Identification of Celiac Disease

##### Symptoms and Pathophysiology

Symptoms of celiac disease can be highly variable, but often include abdominal pain, bloating, chronic diarrhea, vomiting, constipation, weight loss, and foul-smelling or fatty stool. The condition can also manifest with extra-intestinal symptoms such as ataxia,<sup>1</sup> peripheral neuropathy,<sup>2</sup> dermatitis herpetiformis,<sup>3</sup> anemia, muscle weakness, and osteopenia. Celiac disease was originally considered a childhood condition, but the mean age of diagnosis as of 2010 was 45 years.<sup>4</sup> The condition may be more common than most practitioners realize, as about 1 in 133 people in the United States have the disease. In patients with a first-degree relative with celiac disease, prevalence increases to 1 in 22.<sup>5</sup> It also has associations with other autoimmune diagnoses, including but not limited to type I diabetes mellitus, idiopathic pulmonary hemosiderosis, systemic lupus erythematosus, IgA nephropathy, polymyositis, and Sjögren's syndrome.<sup>4</sup> Malabsorption of important vitamins, minerals, and nutrients is common.

Celiac disease develops due to multiple factors, including genetic susceptibility, presence of antibodies to tissue transglutaminase (TTG) and/or deamidated gluten peptide (DGP), intestinal damage, and gluten as an environmental immunological trigger. Length of time spent breastfeeding, age of introduction of gluten-containing foods, and overall exposure to foods containing gluten are thought to have a role in celiac disease development.<sup>6</sup> The pathophysiology of the condition reveals that gluten leads to both 1) production of antibodies against TTG and 2) inflammatory cytokine release leading to enterocyte destruction. The process begins with gluten entering the tissue space of the small intestine through either paracellular or transcellular absorption. Gluten is then deamidated, forming DGP, or cross-linked to TTG, forming gluten-TTG. In the presence of HLA-DQ2 or HLA-DQ8 cell surface markers, DGP and gluten-TTG are presented to CD4+ Th1 cells by dendritic cells initiating a Type IV hypersensitivity reaction. These CD4+ cells release interferon- $\gamma$ , which leads to the activation of the humoral immune response through the clonal expansion of B-cells. The resulting plasma cells produce IgA and IgG to gliadin and TTG. The tissue destruction component of this process is also perpetuated by interferon- $\gamma$ , which subsequently triggers lamina propria cells and fibroblasts to secrete matrix metalloproteinases. The metalloproteinases begin to degrade cellular matrix and basement membrane, while simultaneously enhancing the cytotoxicity of intraepithelial lymphocytes and NK cells. The latter facilitate apoptosis of enterocytes,<sup>7</sup> ultimately leading to

decreased surface area of intestinal villi and symptoms of malabsorption.

### Diagnosis of Celiac Disease

New diagnostic criteria from the American College of Gastroenterology (ACG) recommend anti-TTG IgA as the most sensitive and specific serologic marker for celiac disease. They also assert the significance of assessing total IgA in the diagnostic process. Separate diagnostic guidelines are laid out for IgA deficiency and include assays of anti-TTG IgG and anti-DGP IgG. In children less than two years of age, anti-TTG IgG alone or in conjunction with anti-DGP IgG should be used due to high probability of insufficient total IgA. Confirmatory endoscopy and biopsy of the duodenum is still required.<sup>8</sup> A positive intestinal biopsy will reveal villous atrophy.<sup>3</sup>

The HLA-DQ2 and HLA-DQ8 genetic haplotypes also continue to be recommended as indicative of celiac disease under the new ACG guidelines. HLA-DQ2 is positive in ninety-five percent of those with biopsy-confirmed celiac disease, and the remaining five percent have HLA-DQ8.<sup>8</sup> These genes must be present in order for autoimmunity to develop, as they are essential to the process of generation of anti-TTG/anti-DGP antibodies and enterocyte destruction. While absence of these markers can be helpful in exclusion of celiac disease from a list of differential diagnoses, their presence is not diagnostic as they are common in individuals of Caucasian European descent.<sup>9</sup> Positive HLA-DQ2 is found in approximately 25-30% of these individuals, making the assay useful for—but not conclusive of—diagnosis of celiac disease. It is clear that celiac disease is a very specific, genetically-

influenced, autoimmune-mediated sequence of events under the umbrella of immune response to gluten, much like Hashimoto's thyroiditis in the overarching diagnostic category of thyroid disease.

### Considering Non-Celiac Gluten Sensitivity

Non-Celiac Gluten Sensitivity (NCGS) is a diagnosis of exclusion to consider in gluten-induced symptoms that improve on a gluten-free diet but lack genetic, immunologic, and endoscopic markers of celiac disease. IgG or IgA anti-gliadin antibodies may be present in this condition.<sup>10</sup> NCGS is not typically associated with intestinal damage and hyperpermeability, contrasted to the overt enterocyte destruction seen in celiac disease. Fecal lactoferrin levels and lactulose/mannitol tests that are frequently elevated in inflammatory bowel disease (IBD) and celiac disease are commonly normal in NCGS. A certain subset of irritable bowel syndrome (IBS) patients also have NCGS.<sup>11</sup>

### Differential Diagnosis of Gluten-Induced Symptoms in Laboratory Medicine

Because the presenting symptoms of gluten-related conditions can be complex, laboratory medicine can aid in differentiating autoimmune, allergic, and functional conditions.

#### Diagnos-Techs assays currently available:

- **Fecal calprotectin**—This stool assay can serve as a relatively non-invasive way to distinguish those patients urgently in need of biopsy (suspected celiac disease or IBD) from those with such functional digestive issues as IBS.<sup>12</sup> Calprotectin is a protein that is released from neutrophils during

active inflammatory states and has been found to correlate with degree of intestinal inflammation.

- **Intestinal inflammatory markers**—Lysozyme and alpha anti-chymotrypsin can also serve as non-specific markers of intestinal inflammation.
  - **Intestinal sIgA**—Total sIgA can aid in diagnosis of celiac disease or suggest immunological imbalance.
  - **IgA anti-gliadin antibodies**—These immunoglobulins are useful in the diagnosis of NCGS, and for identification of food allergy in individuals with IBS.
  - **Stool parasite and bacterial overgrowth panels**—The Gastrointestinal Health (GI-1 and GI-2) panels can be useful in ruling out infectious causes of digestive symptoms similar to those in celiac disease.
- Diagnos-Techs assays under development:**
- **IgA anti-TTG antibodies**—A positive result for this immunoglobulin, in the presence of genetic markers and positive biopsy results, constitutes the current diagnostic criteria for celiac disease.

### Gluten-Associated Conditions: Beyond the Gluten-Free Diet

Complaints of adverse physiologic reactions to gluten are becoming more common in medical offices. Many health professionals question whether this trend is due to an actual increase in incidence, an improvement in diagnostic methods, or simply a rise in awareness. Which of these is true remains to be clarified in research, but there is no doubt that our tools for identifying food allergies and furthering our understanding of the immune system are rapidly expanding.

*Continued on page 7.*



## Diagnos-Techs™ Introduces—

### Carrie C. McMillin, ND

#### Medical Support



After receiving a Bachelor's of Science in Biology at Oakland University, Dr. McMillin began her medical

education at Wayne State University School of Medicine in Detroit, MI. She has spent several years in clinical research, studying the use of *Serenoa repens* in the treatment of benign prostatic hyperplasia, as well as the pathophysiology and treatment of sleep apnea. Dr. McMillin received her Doctorate of Naturopathic Medicine from Bastyr University and is currently a licensed naturopathic physician in the state of Washington. She has extensive experience as a medical writer, anatomy and physiology instructor, and is an author of and contributor to several articles in the *Journal of Applied Physiology*. Dr. McMillin maintains a private practice in which she specializes in treating patients with anxiety, ADHD and autism spectrum disorders.

### Lisa Canar, ND

#### Medical Support



Dr. Canar received her Doctorate of Naturopathic Medicine from Bastyr University in 2001. Following medical school,

Dr. Canar practiced family medicine for three years before completing post-doctoral research training with the cancer prevention research group at the University of Michigan Comprehensive Cancer Center, where she participated in a variety of prevention studies involving dietary pattern changes, dietary supplementation, counseling, and lifestyle modification. More recently, Dr. Canar has served as an independent research physician and clinical research consultant, focusing on clinical research initiatives in health promotion, chronic disease prevention, and healthy aging.

### Bethany Glynn, ND

#### Medical Support



Dr. Glynn acquired her Doctorate of Naturopathic Medicine from Bastyr University with specialty training

in pediatrics, family health, neuropsychological conditions, autoimmunity, and environmental medicine. She is a licensed primary care physician to families living with autism, anxiety and ADHD in the Greater Seattle area. Dr. Glynn is passionate about integrating the innovations of modern science with the wisdom of traditional healing through the modalities of diet therapy, behavioral and emotional counseling, botanical medicine, nutritional supplement prescription, and biofeedback. During her time in the field of rehabilitative medicine, Dr. Glynn worked at Shriners' Hospital for Children in Spokane, with Patch Adams MD at his Gesundheit Institute, as a coach for junior Paralympic wheelchair sports competitors, and as a certified yoga instructor. She currently runs two active medical websites and hosts community outreach classes, summarizing and sharing the latest in natural health research with fellow practitioners and the public.

### Julie Krauss-Lucas, ND

#### Medical Support & InterPlexus Manager



Dr. Krauss was awarded her Doctorate of Naturopathic Medicine from Bastyr University after earning

her undergraduate degree in cell and molecular biology from Tulane University in New Orleans, LA. She has

worked in private practice with several prominent naturopathic physicians focusing on therapeutic lifestyle counseling and foundational medicine, including digestion, detoxification and nutrition. While working for a large digestive health company, she provided digestive wellness seminars and nutrition education for practitioners and consumers. Besides being an instructor of anatomy, physiology and pathology for massage students, Dr. Krauss was also a contributing author for a naturopathic nutrition book and

a weight loss guidebook, as she is a firm believer in empowerment through education. When she is not in the office, Dr. Krauss can be found in the kitchen experimenting with new recipes or hiking around the Puget Sound.

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### Celiac Disease & Non-Celiac Gluten Sensitivity continued from page 5.

With any food related symptoms or diagnoses, the astute clinician would recommend identification of and at least temporary removal of offending foods from the diet. And while it is essential to determine if gluten is a problematic food protein for patients, we must take further steps in laboratory diagnosis of varying facets of immunological response to gluten in order to develop appropriate treatment plans and prevent further tissue destruction. The importance of identifying celiac disease is paramount, because if left untreated it may contribute to infertility, development of other related autoimmune disorders, and a higher incidence of certain cancers including lymphomas.<sup>4</sup>

We have yet to fully understand the implications of genetic susceptibility in autoimmune diseases, but it is known that specific HLA haplotypes are also associated with type I diabetes mellitus, multiple sclerosis, and Graves' disease.<sup>13</sup> Because of the potential for food to be antigenic, the impact of diet and genetics on autoimmune conditions can be pivotal in shifting the immune response. While gluten-free diets can alleviate symptoms, it is important that we review the literature and use of diagnostic testing over time, as this is an evolving discussion and is sure to change in the future. Researchers continue to discover immunologic and genetic etiologies of gluten-induced symptoms, leading to important branching points in treatment approach. Oral or sublingual immunotherapy, for example, may be a possibility in the case of NCGS or IBS, while in celiac disease this therapy would be contraindicated due

to the potential for autoimmune gastrointestinal and systemic sequelae.<sup>14</sup> Identifying the exact pathophysiology and category of immune response for each individual can aid not only in determining the necessary length and course of a gluten-free diet, but also in preventing comorbidities and improving autoimmune prognosis. 

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## Coding Clues

John J. White, MD CM

Insurance claims require proper coding to be paid. Common Procedural Terminology (CPT) codes, called simply “procedure codes”, and International Classification of Diseases (ICD-9) codes, otherwise known as “diagnostic codes”, are necessary for reimbursement. Because stress, fatigue/malaise, and sleep disturbances are frequent indications for cortisol testing (e.g., the ASI or the TAP panels), the following might be appropriate ICD-9 codes:


<b>Fatigue, malaise</b>	<b>780.79</b>
<b>Mixed stress disorder</b>	<b>308.4</b>
<b>Stress with anxiety/depression</b>	<b>309.28</b>
<b>Sleep disturbances</b>	<b>307.4</b>
<b>Persistent sleep disorder/Idiopathic insomnia</b>	<b>307.42</b>


**Please note**, starting October 1, 2014, the ICD-9 codes will be replaced by new ICD-10 codes. After that date, proper insurance billing must reflect the revised codes to ensure reimbursement where applicable.

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