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CELIAC DISEASE

Distinguishing Gluten Intolerance from Gluten Sensitivity

Whitepaper

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Distinguishing Gluten Intolerance from Gluten Sensitivity

Gluten-related illness affects *at least* three million people in America, and 90% of them don't know they have it. Among children and adults with gluten intolerance, half are asymptomatic.[1]

Among those who don't yet realize that gluten intolerance is causing their symptoms, 4 out of 5 who later become diagnosed with celiac disease (CD) learn of the problem between the ages of 30 and 70.

This is a sad statistic because gluten intolerance can ruin quality of life in several ways. It can also shorten your life span by a decade or two. These problems can be averted with early diagnosis and personalized support for transitioning to a gluten-free lifestyle and care plan.

Confusion reigns as to the difference between celiac disease (CD), gluten intolerance, and gluten sensitivity. At the present time, a consensus understanding on how to make a diagnosis of gluten intolerance or gluten sensitivity does not exist within the medical profession. All three conditions can exist without obvious signs or symptoms of illness.

CD is always preceded and caused by gluten intolerance. CD is the severe end of a gluten-mediated spectrum of illness that begins when gluten intolerance begins. Gluten sensitivity can accompany almost any form of chronic illness, but it does not cause CD.

There is great need for clarity on this subject. This Whitepaper describes a patient-centered approach to distinguishing between CD, gluten intolerance, and gluten sensitivity.

Making the Diagnosis

The main point of this Whitepaper is that the early detection of gluten intolerance is far more preferable than waiting to make a diagnosis of celiac disease.

In usual and customary medical practice, the diagnosis of CD relies almost entirely on a specific set of blood markers known as the *celiac disease panel*. If this test is positive, most gastroenterologists agree that the diagnosis should be confirmed with a small

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bowel biopsy. Most clinical systems biologists are prone to disagree with this advice, since a positive celiac disease panel predicts a positive biopsy finding 95% of the time.

In the case of an abnormal celiac disease panel, 95 out of 100 biopsies would show that the lush wetlands of your small intestinal border are being worn down, you have CD and the basket of problems that comes with it – most of which will begin to heal with a strict avoidance of gluten-containing foods as the focal point of an integrative care plan.

All people with CD are gluten intolerant, and all gluten intolerant people are on a track that permits them to evolve toward an official diagnosis of CD at some point in their lives. Current practice in most medical settings prefers that you earn a diagnosis of CD by getting sick enough first.

CD is fairly easy to diagnose. The problem lies in knowing what to do when the celiac disease panel is negative in a patient whose chronic illness remains medically unexplained.

Many patients are hung out to dry at this point because the physician mistakenly stops suspecting gluten intolerance when the celiac disease panel is negative – even if the patient's history screams for a more systematic evaluation.

Why is it so easy for CD and gluten intolerance to evade detection for decades? Why are they among the most commonly missed diagnoses in the world?

The answer is multiple vague symptoms that yield apparently normal blood tests. The early detection of gluten intolerance is not straightforward or precise; it is not based on a single test, and it usually requires a gluten-free trial.

And if you think gluten intolerance has to produce gut symptoms, you're wrong. For every gluten intolerant person with gut symptoms, there are eight gluten intolerant people who have symptoms that *do not seem* to involve the gut.[1]

Even the most systematic approach to detecting gluten intolerance can wind to an ambiguous conclusion. But in most cases of systematic assessment, the evidence for or against the presence of gluten intolerance will meet a reasonable person standard.

Let's say you're unusually tired, have trouble concentrating, sleep poorly, and suffer with a bowel that produces variations on cramping, bloating, and pain. Standard tests are within normal limits (this concept often misleads because a reference range is not a normal range).

Odds are you'll be offered medications for anxiety and insomnia, and for your irritable bowel syndrome you'll be advised to add more fiber and water to your daily intake, exercise regularly, and learn some relaxation methods.

You faithfully follow this advice for 3 to 6 months. You're sleeping but you're still really tired during the day, you feel less anxious but not without the pill, and your bowel remains a problem. Your doctor checks you for CD by running the gold standard panel: blood antibody markers.

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Technically, the panel measures IgA antibodies against tissue trans-glutaminase, and enzyme involved in the gut wall reaction to gluten, and IgA antibodies to gliadin – the indigestible portion of gluten that triggers most of the trouble.

When these markers aren't present, you are likely to be told that you are not gluten intolerant. This is incorrect. Years go by. You develop new chronic health problems and they all seem to progress no matter you do. You've received half a dozen diagnoses and a dozen medications, yet no treatment seems to hit the mark.

What's wrong with this picture? Absence of evidence for celiac disease is not evidence of absence of gluten intolerance. This misunderstanding is responsible for years of suffering and lost time.

According to University of Maryland professor Alessio Fasano, MD, one of the world's foremost experts on celiac disease, three things need to happen for gluten intolerance to get started[2]:

1. **Gluten exposure.**
   A majority of the global population is now exposed to gluten on a regular basis.

2. **A celiac permissive genotype.**
   The gluten exposure must occur in someone whose genes program an overly aggressive immune response to gluten.

3. **Intestinal hyperpermeability.**
   The small bowel barrier must start lose enough functional integrity to permit the entry of undigested gluten fragments into its inner layer.

You can have a celiac permissive genotype and be exposed to gluten your entire life yet never become gluten intolerant unless you develop intestinal hyperpermeability.

This Whitepaper will use the term *leaky gut* rather than *intestinal hyperpermeability* because it means the same thing, it's not such a mouthful, and the average layperson can more easily relate to it.

A leaky gut throws the gluten intolerance switch in the genetically predisposed patient.

Gluten intolerance and CD are genetically driven. If your genetic markers are celiac permissive and you are suffering gluten-mediated damage to your small intestinal surface but you have no obvious symptoms, you have what is known as *silent* CD.

If your genetic markers are celiac permissive, and you're in the earlier stages of gluten intolerance, conventional wisdom insists that you don't have CD – you have the possibility of developing CD at a later date, a condition also known as *latent* CD.

Forget the fancy talk and research categorizations. The main point is to find out that you're gluten intolerant while it's in an early stage. Latent CD is a diagnosis made in retrospect. You want a prospective approach to early detection.

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If you have seen a physician or two and you're chronic illness remains medically unexplained, request the following:

1. A *celiac disease panel*.

2. A properly run *HLA DQ celiac genotype* test.

3. A *systematic review of your medical history* along *with testing to assess the likelihood that you have a leaky gut*.

If your doctor shows a look of consternation upon hearing such requests, odds are that they will not be granted because they require one or more of the following:

1. Deviating too much from practice's franchise mode.

2. Allocating more time than is available to medical history taking.

3. Befuddlement as to what you mean by *leaky gut*.

Another common error occurs when the doctor uses a negative celiac disease panel to mean that you are not gluten intolerant, but that you may be gluten sensitive, so go ahead and avoid gluten and see how you feel. What's missing in this scenario is a celiac genotype test. If your genotype is celiac permissive, it is reasonable to assume that you are gluten intolerant rather than gluten sensitive.

Gluten sensitivity is not genetically driven. It involves a different set of immune responses to gluten. In most cases, the problems caused by gluten sensitivity are not as severe as those caused when someone with a celiac permissive genotype and a leaky gut is repeatedly exposed to gluten.

Gluten intolerance and gluten sensitivity are similar in that healing from the effects of either usually occurs with strict adherence to a gluten-free diet over a matter of 3 to 6 months. The important difference is that staying well usually requires long-term gluten avoidance, whereas gluten sensitivity does not.

To draw the distinction between gluten intolerance and gluten sensitivity a celiac genotype is necessary but not sufficient. It is also necessary to correlate the medical history to at least one of several markers of immune system reactivity to gluten.

Getting properly evaluated for gluten intolerance is easier said than done in our health system. Unlike the presence of celiac disease, the presence of pre-celiac gluten intolerance is both hard to rule in, and hard to rule out using available testing methods, but it can be done in a way that greatly reduces the risk of a missed diagnosis.

First, the doctor has to think of gluten intolerance as a possible explanation for your health problems. Next, the doctor has to understand that the current gold standard blood test for making the diagnosis of CD requires significant intestinal damage – damage that has yet to occur in most gluten intolerant people.

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In cases of early gluten intolerance, the matter of its presence or absence cannot be settled without a systematic review of your medical history, a celiac genotype, and a look at other markers of a gluten-mediated illness process. These include:

1. **Markers of malabsorption.**

   Iron, protein, vitamin D, vitamin B12, magnesium and other mineral levels.

2. **Markers of a leaky gut**.

   Excessive antibody or lymphocyte responses to food antigens, signs of parasitic infection, yeast overgrowth or imbalanced bacterial populations in the gut, lactulose and mannitol levels in the urine following ingestion, and other tests soon to be available on the consumer market.

Even with your genotype results, sometimes the best we can do is look at all the clinical data together – your personal history, family history, signs and symptoms, biomarkers, and genetics – and predict whether your health interests would be served by going gluten-free and following any other metabolic rehabilitation strategies that make sense in your case. These include:

1. **Nutritional repletion.**

   Iron, protein, vitamin D, vitamin B12, magnesium, and other minerals may be needed.

2. **Treatment of conditions that may have triggered a leaky gut.**

   Frequent or prolonged use of antibiotics, steroids, narcotic analgesics, or immune suppressants, intestinal yeast or bacterial overgrowth, intestinal parasitic infection, severe stress, excessive ingestion of sugar or alcohol, irritable or inflammatory bowel syndromes, or other potential triggers.

3. **Treatment of conditions that tagged along in the wake of gluten intolerance.**

   Sensitivity to dairy, yeast, soy, corn, sugar, or other foods, autoimmune activity, insulin resistance, excitatory neurotransmitter dominance, or other tag-alongs.

The truth is often learned in how your symptoms respond not just to a gluten-free diet but to a comprehensive regimen designed to rehabilitate the functional integrity of your gut wall and any other metabolic systems that have begun to struggle in the presence of gluten-mediated toxicity and nutrient depletion.

If your doctor checks for CD using the current standard method of screening, using blood antibody levels as markers of tissue injury and immune sensitivity, he or she is using a diagnostic protocol that could miss gluten-related illness in as many as 8 out of 9 cases.[1]

This sums up our current global dilemma: CD is just the tip of the iceberg. We're missing 90% of the world's gluten intolerant people because we can't see what we're not looking for. If 1% of the world population has CD, and 9 times that many are pre-celiac gluten intolerant people headed toward CD, the world health system has over 600 million cases to find and treat.

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CD and gluten intolerance are common and dangerous, and yet their under-diagnosis is increasingly hard to excuse. Doctors need to get real when it comes to suspecting, diagnosing, and managing this condition.

This is why it's essential that you seek the guidance of health professionals who have a current, sufficiently nuanced understanding of the genetics, disease mechanisms, and treatment of CD and gluten intolerance.

How Gluten Intolerance Results in Cascading Illness

Gluten is a complex protein found in several grains. The potentially damaging protein subunits of gluten are known as gliadins and glutenins. Wheat, rye, and barley contain the highest mixes of these indigestible and potentially damaging subunits of the gluten protein.

Current estimates are that one in every 100 people in the global population is genetically programmed to launch an immune system attack against these gluten-derived peptides when they come into contact with the cells lining the small intestine. Based on research thus far, gliadin appears to be the primary suspect.

When gliadin is detected by an immune system that is genetically programmed to overreact to its presence, chemical signals draw lymphocytes into the membrane's tissue spaces, where they fire bursts of molecules that are chemically to shred gluten into pieces. These parts are ingested and processed by dendrite cells and macrophages, cells that relay the message to other lymphocytes, which over time gear up the system's ability to attack gluten at the first sign of contact with the gut barrier.

This feedback loop produces progressive collateral damage to gut cells. Damage at this level then cascades into various forms of chronic illness, at various rates, depending on the genetically determined aggressiveness of the gluten intolerance.

This gut-related stress interacts with other metabolic systems in the body, amplifying weaknesses in other pathways, which can be influenced by other genetic circumstances, lifestyle factors, or environmental exposures.

One example of environmental exposure capable of triggering or perpetuating a leaky gut would be the mold toxin that you may ingest with your wheat-based cereal. Various mold toxins can survive food processing and have been shown to trigger a leaky gut in animal models.[3] Another environmental source of a leaky gut trigger could be the gliotoxin produced by some isolates of the yeast, *C. albicans*.[4]

It may take decades, years, or even months, but multidimensional chronic illness is the inevitable result unless a diagnosis is made and a gluten-free integrative care plan is implemented and monitored.

As the immune response to gluten becomes more widespread and amplified along your gut wall, the result is usually twin functional problems, each with its own type of pathological behavior:

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1. **Malabsorption.**

   Malabsorption of proteins, vitamins, and minerals creates subtle but sweeping nutritional deficiencies in cells and biochemical pathways. This occurs gradually as the small intestinal surface area for nutrient absorption is worn down by an overly aggressive reaction to gliadin.

2. **Gut-derived toxicity and immune system over-activation.**

   A leaky gut permits molecules with no business in your metabolism to gain entry, creating extra work for your immune system. If the immune system begins to falter and fall behind, toxic burdens accumulate, placing more inflammation and more stress on detoxification systems.

Some people seem to speed all the way to end-stage CD, with multiple, overlapping forms of malnutrition, toxicity, metabolic pathway disruption, autoimmune activity, and tissue damage that can occur in your gut, skin, liver, joints, muscles, bones, pancreas, thyroid, brain, or all of the above and a few more.

The small intestinal surface bears the brunt of the damage because that's where the front lines are. As lymphocyte-derived friendly fire and antibody swat teams erode the velvety brush filters of your small intestinal surface – a condition known as villous atrophy – you enter the late stage of CD. Here, at long last, gold standard methods can make your diagnosis.

Gluten-related Health Problems

The list well-documented gluten-related health problems that follows explains why gluten intolerance is the reigning systems biology model for chronic illness:

1. **Malabsorption.** The proteins, vitamins, and minerals you're eating may not get fully absorbed because battle fatigue is disrupting the mechanisms that your gut uses to assimilate healthy nutrition.

2. **Leaky gut.** Some doctors prefer to call this *intestinal hyperpermeability* because it sounds more scientific that way. Whatever you call it, it means the barrier defenses of your small bowel are losing functional integrity – they're allowing gut-derived molecules with no business in your metabolism free passage into your system, where they can create havoc not just in your gut wall but also in other organs and tissues. Call it what you want, just get real.

3. **Food sensitivities.** Your small intestinal barrier defenses, already stressed by gluten-induced wreckage, develop various immune reactions to other foods that you're eating.

4. **Dysbiosis.** This means the ecological balance of friendly bacteria and yeasts in your gut has been disrupted. As the buckthorns start pushing out the maples, the biochemistry of your gut environment becomes more hostile to friendly bacteria and to well-coordinated gut function.

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5. **Gastrointestinal symptoms.** It's no surprise that chronic diarrhea, gas, bloating, recurrent abdominal pain, and irritable bowel syndrome may follow in the wake of gluten intolerance. What's more surprising is that as many as 8 out of 9 patients with CD do not develop obvious gut symptoms.

6. **Microscopic colitis.** Patients with the lymphocytic or collagenous forms of colitis are up to three times more likely to have celiac disease.[5]

7. **Iron deficiency anemia.** Low iron levels can result from poor absorption of iron and/or chronic, low-grade blood loss from a chemically stressed gut surface.

8. **Hepatitis.** If your liver enzymes run slightly high but nobody seems to know why, it is possible that your liver pathways are overwhelmed trying to keep up with the systemic effects of your gluten toxicity.

9. **Fatigue.** Your immune system is claiming a disproportionate share of protein and energy sources, and the pathways for turning oxygen, fatty acids, and glucose into energy may be adversely affected by toxic noise stemming from gluten intolerance.[6]

10. **Non-restorative sleep.** The mechanism may involve inflammation signals coming from gut inflammation zones pass the blood brain barrier to harass neuronal pathways, interfering with normal sleep chemistry.

11. **Migraine headaches.** Although the mechanism is unknown, many gluten sensitive patients report that their migraine headaches stop or lessen at some point after starting a gluten-free diet.

12. **Anxiety.** Studies show a higher risk for anxiety in people with CD compared to the general population. This anxiety typically resolves with a gluten-free diet.[6]

13. **Depression.** Studies show a higher risk for anxiety in people with CD compared to the general population. This anxiety typically resolves with a gluten-free diet.[6,7]

14. **Early cognitive decline and dementia.** The mechanism may involve the "spilling" of molecular toxicity related to gluten intolerance into the brain, producing regions of decreased oxygen and nutrition delivery. Neuronal pathways in those regions will not function up to their potential.[8]

15. **Attention deficit hyperactivity disorder.** ADD and ADHD-like symptoms are markedly higher in people with celiac disease compared to the general population.[9]

16. **Epilepsy.** Case reports describe people whose epilepsy was refractory to anti-epileptic drugs can experience remarkable improvement on a gluten-free diet.[10]

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17. **Cerebellar ataxia.** In ataxic syndromes (poor balance and coordination) without a definite cause, gluten sensitivity may account for more than 10% of cases.[11]

18. **Joint pains.** Gut-derived antigens (foreign proteins) enter your circulation, where they are chased and caught by antibodies and other immune system proteins, forming complexes that settle in the wear and tear zones of your joints, turning normal joint strain into inflammatory forms of arthritis, back, or neck pain.

19. **Autoimmune disease.** Toxic noise spreads to your thyroid, pancreas, brain, joints, or other tissues tripping an autoimmune response that disrupts systemic balance.[12]

20. **Diabetes.** Type 1 Diabetes is usually diagnosed in childhood. In one study, among 27 children who screened negative for celiac disease when diagnosed with Type 1 diabetes, 100% developed CD antibodies within four years.[13]

21. **Neuropathy.** People with CD are at higher risk for numbness, tingling, and peripheral nerve disease, with at least partial resolution after a gluten-free diet.[8]

22. **Obesity.** Mechanisms unclear, but gluten avoidance is often associated with significant weight loss in people who are gluten sensitive and carry extra weight.

23. **Dermatitis herpetiformis.** This is the classic skin condition seen in people with gluten sensitivity – crops of itchy bumps triggered by immune complex deposits in the skin.

24. **Infertility or miscarriage**. Women who suffer one or more miscarriages or who have problems conceiving are more likely to have Celiac Disease of Gluten Sensitivity compared to the general population, though the mechanisms are unclear.[14]

25. **Osteoporosis.** Premenopausal women who develop unexplained osteoporosis are at substantially higher risk for Celiac Disease.[15]

This process of cascading illness can unfold over years or decades. Some people seem to speed all the way to end-stage CD within a decade or two. Others soldier on with slowly evolving gluten intolerance, going from doctor to doctor with an ever-growing list of symptoms and signs that just don't seem to fit any diagnosis in particular until someone proudly discovers that it's a gluten problem. By then, you may not be able to remember the names of your grandchildren.

CD is a classic example of how our health system lets sick people down. Specialists are rewarded for fragmenting the big picture and zooming in only on what they're paid to interpret. Harried generalists lose revenue if they take time to pan back and see the big picture. This needs to change.

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Wise health consumers realize that there is plenty of confusion to tackle when it comes to the early detection of gluten-related illness. They're looking for doctors who can apply good, old-fashioned problem solving methods using not just a health care relationship that is personalized and focused on getting positive health results – but also a clinical problem-solving mindset that is rooted in the complex reality of systems biology.

To practice this kind of medicine, an understanding of the underlying genetics of disease is indispensable.

The Genetics of Gluten Intolerance and Celiac Disease

What determines whether you react to gliadin like it's a foe rather than a friend? Genetics. We all have a region of our genome on chromosome 6 that codes for a special class of immune system proteins. These proteins, known as HLA markers, are used by lymphocytes and other white blood cells to communicate with each other.

Each of us inherits a set of HLA markers from each parent. The markers affecting risks for CD are called HLA-DQ genotypes. You receive one set of DQ markers from each parent. If you had a genetic test done, your pair of markers would be reported as DQ*x*, DQ*x* – where *x* is a number from *1* to *9* (because nine variations are known exist).

Roughly 90% percent of people with CD are thought to carry at least one DQ*2* marker. Most of the rest carry at least one DQ*8* marker. Thirty percent of the general population carries either one DQ*2* or one DQ*8*. While only 3 % of them develop biopsy-documented CD, a systems biology view of CD would suggest that this figure underestimates, perhaps by a vast amount, the number of people with a single DQ*2* or DQ*8* HLA gene who develop gluten-mediated illness.

As Fasano points out in his *Scientific American* review, the ability of gluten intolerance to produce chronic illness depends not just on genotype, but on interactions between lifestyles and environmental stresses, and whether these collaborate with genetic susceptibility to produce intestinal hyperpermeability, also known as leaky gut.[2]

You could live your entire life with a celiac permissive genotype and tons of gluten exposure and yet never develop gluten intolerance unless you develop a leaky gut along the way. The increased permeability is what allows gliadin to make its way into the gut wall, where your genetically programmed immune system is waiting for the chance to unleash its fury, treating the gliadin as if it is a dangerous toxin instead of a benign food protein. The leaky gut is what flips on the gluten intolerance switch.

Genotype associations are based on well-controlled research, but the field is evolving and identifying other DQ markers besides *DQ2* and DQ*8* that have been associated with biopsy-documented CD. Going by anti-tTG or anti-gliadin IgA antibody markers alone is clinical nonsense.

To determine your risk for CD it is essential to factor in your *genotype* – your *particular pair* of DQ markers – and to understand that the research literature on CD genetics is associating CD with markers other than the classic DQ2 and DQ8 genes.

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The research literature on CD continues to refine our understanding of how to relate your genotype to your risk of having gluten-related illness. The following table stratifies risks for gluten-related illness into categories based on genotyping. It is based on my clinical experience along with educated guesses as to where the current genetic literature on CD is pointing diagnosticians of CD and gluten intolerance.[1,8,17,18,19,20]

Table 1

HLA DQ Genotypes and Risk for Gluten Intolerance and Celiac Disease

Key:

CD = celiac disease
GI = gluten intolerance
DQ copy 1 = gene derived from parent #1
DQ copy 2 = gene derived from parent #2

High risk (CD common; gluten avoidance almost always helpful):

DQ copy 1	*DQ copy 2*
DQ*2.5*	DQ*2.5*
DQ*2.5*	DQ*2.2*
DQ*2.5*	DQ*8*
DQ*2.5*	DQ*7*
DQ*8*	DQ*8*
DQ*2.5*	Low risk

Moderate risk (GI common, CD reported; gluten avoidance often helpful):

DQ copy 1	*DQ copy 2*
DQ*2.2*	DQ*7*
DQ*8*	Low risk

Indeterminate risk (GI possible, CD unreported; gluten avoidance occasionally helpful):

DQ copy 1	*DQ copy 2*
DQ*2.2*	Low risk
DQ*7*	Low risk
DQ*A1*05*	*(only a single copy of the alpha subunit for DQ2.5 needed)*[18]
DQ*B1*0201*	*(only a single copy of the beta subunit for DQ2.5 needed)*[18]

Low risk (GI and CD unreported; gluten avoidance helpful for gluten sensitivity only)

DQ copy 1	*DQ copy 2*
DQ*4*	DQ*4*

Table derived from the celiac disease literature and author's clinical experience correlating clinical response to gluten free diet in patients with listed genotypes.

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Everyone gets two DQ gene copies, one from each parent. Each DQ marker has A (*alpha*) and B (*beta*) subtypes (also called subunits). An assessment of *both pairs* of DQ markers, including the specific alpha and beta subunits inherited, is needed to fully assess your genetic predisposition to CD.

If you or your doctor suspect that you have a gluten-related illness that is not associated with any of the risk markers listed in Table 1, you are not likely to be gluten intolerant but you could be gluten sensitive. In this case, testing for other food sensitivities should be considered (see discussion on food sensitivity testing below).

Some labs only report whether DQ*2* or DQ*8* markers are present or absent. Other labs report beta subunits only. This is no longer an acceptable method of reporting an individual's HLA DQ celiac genotype.

The DQ*5* marker is associated with gluten-related toxicities that tend to involve skin and neural tissues. According to data collected by Ken Fine, MD, unless you have a DQ*4* / DQ*4* marker pair, you *could* be gluten intolerant to some degree.[17]

When in doubt, a mild elevation of anti-gliadin IgA antibody in the blood, or moderate elevations of anti-gliadin IgA antibody in the saliva or stool, suggest either an early form of genetically driven gluten intolerance, or a gluten sensitivity driven by a separate immune system mechanism.

We can expect studies to yield more cost-effective methods for screening CD genetic risk. A more detailed genomic analysis may soon be available.[18] We can also expect to learn more about how CD risk is linked to genes on other chromosomes, and how this multi-factorial understanding of CD genetics should influence diagnosis and treatment.

Lab tests for Determining the Probability of CD or Earlier Stage Gluten Intolerance

Genetic testing

For starters, any patient for whom CDy is suspected should have genetic testing. To fully understand your risk for gluten-related illness your testing needs to be done by a lab that reports the full DQ genotype, including alpha and beta subunits for each DQ marker you have. Each DQ gene can code for one to four copies of a functioning HLA molecule, and this is determined by particular alpha-beta subunit combinations.[18]

If the lab merely reports the presence or absence of *DQ2* and DQ*8,* you're not getting enough information. You want to know exactly which two DQ markers you have, alpha and beta subunits included.

Quest Diagnostics identifies the alpha and beta subunit for each pair HLA-DQ markers. *Enterolabs* does not identify HLA-DQ alpha subunits as well as beta subunits, but it has the clinically useful ability to analyze cheek swab samples making a doctor's order unnecessary (as long as you're willing to pay out of pocket – the price is reasonable).

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Knowing alpha subunit types doesn't make or break the analysis, but be aware that CD genetic research is still well ahead of customary practice. Our understanding of the celiac permissiveness of HLA-DQ markers continues to evolve.

Research indicates that alpha-beta subunit combinations previously not suspected of being permissive for CD are indeed associated with increased risk for CD.[18]

Blood testing

The Standard Celiac Disease Panel

Anti-tTG IgA
The gold standard blood test for the diagnosis of CD measures anti-human tissue transglutaminase (anti-tTG) IgA antibody levels. For every100 people who test positive for anti-tTG IgA, and who go on to have an endoscopic small bowel biopsy by a gastroenterologist, 95 will have biopsies that show the characteristic tissue damage seen in CD.

Comment:
The problem with relying on this test to diagnose gluten-related illness is that it could miss 90% of true cases of gluten-related illness. For this test to be positive, your gluten-mediated cascade of illness must have progressed enough to produce widespread villous atrophy. Only then will this marker of small bowel tissue injury to spill into the bloodstream in substantial amounts.

Anti-gliadin IgA and IgG
These tests are likely to show up positive in the blood before the anti-tTG IgA, but they, too, are better at detecting late stage gluten-related illness and missing early stage disease.

Comment:
Most patients who receive a diagnosis of CD have been symptomatic for 5 to 10 years and they've consulted several physicians, perhaps because these physicians were relying on the blood levels of anti-tTG IgA, or of anti-gliadin IgA and IgG, to make the diagnosis.

Total IgA
This test is usually run as a crosscheck on the trustworthiness of the anti-tTG and anti-gliadin IgA levels. IgA is class of antibody that serves as the front line of defense for your mucous membranes.

If those membranes have been under assault because your immune system views gliadin as a toxin, after a while your body's ability to produce IgA may wane. This would tend to make specific IgA levels run lower than they would if total IgA output were well within the reference range.

Comment:
This means that if you've been symptomatic for a while, your anti-tTG and anti-gliadin IgA levels may be artificially low because your system for producing IgA itself is worn down.

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Your doctor may look at the normal anti-tTG and anti-gliadin IgA levels alone and say, "You don't have celiac disease." If the doctor sees a low total IgA level, the proper response would be, "Hmm. Something's going on here. Let's take a deeper look."

The ALCAT Test

This lab analyzes how your lymphocytes respond when industry-certified specific antigens are added to tiny wells containing your blood. These antigens may come from foods, food additives, food preservatives, molds, or industrial chemicals.

After placing your blood into a series of wells, they use a light scanning technique to measure the average volume of your white blood cells before addition of specific antigens, and immediately after antigen addition. Previous research suggests that changes in lymphocyte volume – either a net increase or decrease – correlates closely with cytokine release. Cytokines are your immune system's way of communicating that a response to a toxin, antigen, or allergen is needed.

Comment:
This test is not covered by most health insurance plans, which cite a lack of prospective, controlled trials to support its clinical utility. We have found this to be a useful method for detecting cellular responses to gluten or gliadin, in that subsequent gluten-free trials based on ALCAT findings result in clinical improvements in roughly two-thirds of the time.

Because the initial response to the presence of gliadin involves lymphocytes, we believe this test offers another way to detect gluten-related illness sooner that standard blood antibody tests. It can also measure lymphocyte responses to food preservatives, chemicals, molds, and pharmaceuticals.

ALCAT results prove useful in clinical practice much of the time, but the method has critics concerned about issues of validity and reliability. Most health insurers elect not to cover the test.

Food-specific IgG Antibody Levels

These tests, while considered controversial in many allergy/immunology circles, are often useful to the clinician approaching the assessment of chronic illness from the perspective of systems biology.

A plate containing multiple wells, each holding a drop of your blood along with an antigen from a particular food, is analyzed to see if you blood is making low, moderate, or high levels of IgG antibody against that food.

IgG antibody is normally produced by the immune system to block an antigen that has a low risk of trouble and therefore less need for a full-power immune response. This represents a normal, physiologic response that helps the body decide which antigens to tolerate, and which to destroy.

Comment:
Many doctors reason that because IgG antibody serves a blocking function that levels lack clinical significance and are therefore of no use assessing people with medically unexplained illness. Yet a pattern of high IgG reactivity to certain foods as opposed to

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others, or a pattern of low to moderate IgG reactivity to several dozen foods, begs explanation. Why is the immune system working so hard to block food proteins?

The real concern in assessing patients for their likelihood of gluten intolerance is whether IgG sensitivities are causing or perpetuating intestinal hyperpermeability. If so, gluten avoidance might not be enough to help a leaky gut repair itself. To fully heal the patient might need to temporarily restrict other foods while also avoiding gluten.

This test helps the treating physician fine tune dietary restrictions to those that appear justified. It also helps the patient avoid unnecessary restriction of foods when gluten avoidance is already challenging enough.

Stool testing

Enterolab

Building on pioneering work done by the late Anne Ferguson and her group, proving that anti-gliadin antibodies in stool washings show up well before anti-gliadin antibodies in the blood of people with gluten-related illness, Ken Fine, MD, developed a series of measures from easily obtained stool specimens that provide patients and celiac diagnosticians another method of early detection.

Dr Fine's work indicates the following:

Patient Condition	(+) stool anti-gliadin IgA	(+) for blood anti-gliadin IgA
Family member with celiac disease	79%	10 to 12%
Autoimmune disease	77%	10 to 12%
Microscopic colitis	76%	10 to 12%
Irritable bowel syndrome	57%	10 to 12%
Chronic diarrhea	50%	10 to 12%

Dr. Fine's work indicates that roughly 30% of at risk people (based on symptoms and/or genetics) whose stool is screened will show anti-gliadin antibody reactions.[14] Among these 30% to 40% have genotypes that include DQ2 or DQ8 markers. Most of them will not show the characteristic villous atrophy of late stage CD, but many will report symptomatic improvement on a gluten-free diet – additional evidence that we're missing diagnoses and prolonging illness by relying on standard blood tests alone.

Comment:
When convenient blood tests are negative in patients at risk for CD (based on symptoms and/or genetics), we run the stool test knowing that it can pick up immune reactivity to gliadin before standard blood tests will.

This test has several advantages. Compared to the standard blood antibody panels, it does a better job of early detection for gluten-related illness. The stool specimen collection kit can be delivered to your door and you don't need a doctor's order. Along with genetic testing, it should be used to evaluate symptoms that could be gluten-related, especially cases of irritable bowel syndrome or chronic diarrhea of unknown origin.

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Salivary testing

Diagnos-Techs

This kit measures salivary anti-gliadin IgA antibodies and is available with or without a doctor's order. Salivary anti-gliadin IgA levels are usually elevated in patients who are gluten sensitive, and may be one of the earliest early detection indicators of gluten sensitivity. These antibodies also decrease to within normal limits in most people on a gluten-free diet.

Comment:
In my opinion, this test has a useful role to play when evaluating people who are at risk for CD. The oral membrane is rich in dendrite cells, which are first responders to the presence of gluten. While the research has not yet been done, we can reasonably hypothesize that salivary anti-gliadin IgA levels would be among the earliest signs of a tendency toward CD.

Stay tuned

Research teams are working on simpler, less expensive methods of identifying celiac genotypes.[18] Other vendors are preparing new ways of identifying signs of gluten intolerance and of the intestinal hyperpermeability whose presence flips the switch from gluten tolerant to gluten intolerant.[21]

At *onebodymind.com*, we're committed to keeping you up to date with the best thinking on the diagnosis and treatment of this perplexing condition.

Going Gluten-Free

Imagine that you have received word that your illness is probably the result of gluten intolerance. You're excited to finally have some way to explain what's been wrong. Your feeling then morphs into anger at a medical profession that continues to miss earlier detection opportunities with a systematic approach to the evaluation of gluten sensitivity as a cause of illness. This anger then gets pushed away by a sense of fear and anxiety about what a gluten-free lifestyle is asking of you.

Good celiac diagnosticians should follow through with good support systems for helping patients and families go gluten-free. First on most people's list is finding an acceptable gluten-free bread substitute. After that it is figuring out how to dine out and remain gluten free. Learning the various places gluten hides in the processed foods we eat is another challenge.

Also on the to-do list for gluten-free newbies is developing a repertoire of gluten-free menu plans that are tasty enough for family members to *request it* even though they don't need to avoid gluten. It helps to minimize complexity for the cook. Support for people looking for help going gluten-free comes in several forms:

- Friends and family
- Nutrition counseling

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- Support groups
- Websites
- Books, magazines, and newsletters
- Lists of restaurants that can prepare gluten-free meals
- Recipes
- Mobile apps

For those who make the transition to a gluten-free diet, noticeable symptomatic improvements usually occur within 3 months (sometimes sooner). Some problems may get slightly better, while others go away altogether. Among previously untreated people with CD who avoid gluten close to 100% for one year, 70% will report moderate to major improvement in how they feel and function.

Why do 30% of gluten sensitive people who avoid gluten for one year *not* enjoy moderate to major improvement? In all likelihood this is explained by:

1. The presence of other medical conditions or sensitivities that are not relieved by gluten avoidance, and that need to be treated in their own way.
2. Failure to address the nutritional deficiencies that developed in the run-up to a diagnosis of gluten sensitivity.

For this reason, it is important to maintain regular contact with a health care team that is experienced in the diagnosis and treatment of celiac disease and gluten sensitivity.

At *onebodymind.com*, we view gluten intolerance and celiac disease the same way we view everything else: as a multidimensional metabolic rehabilitation project that applies specifically to you, and that is amenable to some degree to proper self-care.

Our system of self-assessment and care is consistent with an emerging understanding of the origins of chronic illness that is based on systems biology research. We believe that wise self-care methods should be part of any plan to get key your bodily systems working better together as a team.

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