KRESSER INSTITUTE
FOR FUNCTIONAL AND EVOLUTIONARY MEDICINE

Gut Diagnosis Cyrex Array 3X Review

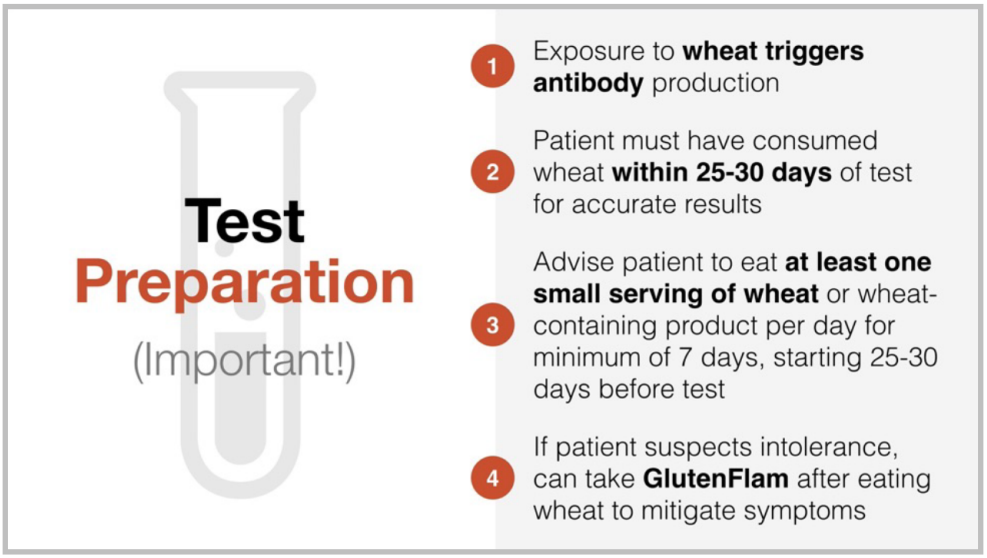
Testing for Wheat and Gluten Sensitivity

Typically, gastroenterologists screen for celiac disease with antibodies to alpha-gliadin, transglutaminase-2, and sometimes deamidated gliadin and endomysium. If the tests are positive, a biopsy might be performed to determine if tissue damage or enteropathy is present.

However, patients are often missed if these are the only markers tested. Research shows that people can and do react to several other components in wheat. These include other epitopes of gliadin like beta-gliadin, gamma-gliadin, and omega-gliadin; glutenin; wheat germ agglutinin; gluteomorphin; other types of tissue transglutaminase aside from tGT-2, including type 3, which is primarily found in the skin, and type 6, which is primarily found in the brain and nervous system tissue.

Who should be tested?

1. Anybody who is currently eating wheat and gluten.
2. Anyone who wants to eat wheat and gluten, even if only occasionally.



Patients may not have GI symptoms!

CYREX ARRAY 3X MARKERS

Wheat IgG/IgA	**Associated conditions:** celiac disease, Baker's asthma, dermatitis herpitiformis, gluten-sensitive enteropathy, type 1 diabetes, wheat allergy, wheat-triggered exercise-induced anaphylaxis Typically **cross-reacts** with rye, barley, and soy One study showed people **genetically susceptible to T1D** have higher risk of developing when exposed to wheat antigens with pro-inflammatory GI environment If wheat antibodies elevated, consider **intestinal permeability screen**

If a patient is only reacting to wheat and nothing else, it could indicate wheat sensitivity due to poor digestive function, not necessarily gluten intolerance. This is why an intestinal permeability screen may be warranted. In this case, a wheat-free diet, healing the gut, and then re-testing might reveal that those antibodies to wheat have decreased.

Alpha-gliadin	Alpha-gliadin is an **alcohol-soluble glycoprotein** **Gliadins and glutenins** are the major components of the gluten / protein fraction of the wheat seed Alpha-gliadin antibodies most likely to be elevated in **CD/NCGS** Antibodies to gliadin suggest **abnormal mucosal immune response** and intestinal barrier dysfunction

Alpha-gliadin **antibodies** associated with autism spectrum disorders, CD, wheat allergy

Known to **cross-react** with cerebellar proteins (can be confirmed with Cyrex Array 5)

If antibodies to transglutaminase 2 also present, patient most likely has **CD**; should be confirmed with biopsy

If gliadin **positive** but TTG negative, indicates gluten reactivity w/o autoimmunity

Omega-gliadin

Omega-gliadin is another **epitope of gliadin**

Omega-gliadin **associated with** celiac disease, celiac sprue, exercise-induced anaphylaxis, and wheat allergy

Omega- and gamma-gliadin **antibodies** are not tested for in conventional settings

If your patient only **tests positive** for omega- or gamma-gliadin, but not alpha-, they will be false negative on conventional tests

Glutenin

Glutenin is the other major fraction of **gluten protein** (with gliadin)

It comprises **47% of the wheat protein**

Antibodies IgG and IgA to glutenin are found in patients with celiac disease

IgA antibodies to glutenin found in dermatitis herpetiformis

Glutenin is known to **cross-react** with dermal elastin (skin) and rice globulin

In functional medicine, most equivocal results should be considered positive.

Wheat-germ agglutinin (WGA)

Wheat-germ agglutinin (WGA) is **lectin** (carbohydrate-binding protein) with capacity to **bind multiple cells/ tissue antigens**

WGAs interfere with enzymes and digestive function; also **enhance** antibody production against tissues that it binds (such as islet cells)

Antibodies to WGA associated with CD, diabetes, GI disorders, and IgA nephropathy

If WGA antibodies elevated, consider **intestinal permeability screen**

Non-Gluten Proteins (A and B)

Non-gluten proteins make-up the remainder of the **wheat proteome.** Several non-gluten proteins, including α-amylase/protease inhibitor, thiol reductase, serine protease inhibitor (serpin), and β-amylase have been identified as **potent allergens** in IgE-mediated wheat allergy and/or baker's asthma

Some research suggests involvement in the pathogenesis of Irritable Bowel Syndrome (IBS) and is often associated with **triggers of allergic disorders.**

Gliadin Toxic Peptides

This peptide lies within the larger gluten protein and has proven to be exceptionally **resistant to digestion.**

A **strong indicator** of possible Celiac disease, Crohn's disease and other chronic inflammatory processes.

The ability to identify a reaction to gliadin toxic peptide allows patients to **remove the trigger** before the intestinal barrier becomes damaged and causes serious long-term health issues.

Deamidated gliadin

Native & deamidated gliadin is produced by **acid or enzymatic treatment of gluten**

Natural byproduct of **gluten digestion in** humans; also in processed food (allows gluten to be more easily mixed w/other foods)

Mayo Clinic no longer tests for normal alpha-gliadin because of low sensitivity/ specificity; they now test deamidated gliadin instead

Associated with CD, autism spectrum disorder, wheat allergy

Cross-reacts with numerous tissues and proteins, including myelin basic protein, synapsin, myocardial peptide, dairy products, corn, oats

Gamma-gliadin

Gamma-gliadin third major **epitope** (along with alpha- and omega-) of gliadin that Cyrex tests for

Suspected to play a significant role in **pathogenesis of CD**

Gluteomorphin + Prodynorphin

Gluteomorphin: opioid peptide formed from **undigested gliadin from gluten protein**

Prodynorphin (PDYN) is an **opioid polypeptide;** building block for endorphins

Exogenous PDYN can compete with endogenous PDYN for **receptor sites**

Gluteomorphin & PDYN **associated with** autism spectrum disorder, CD, NCGS, PANDAS

Cross-reacts with enkaphalin (peptide involved in pain sensation)

Antibodies to gluteomorphin & PDYN indicate **gut permeability;** sign of undigested gluten molecules entering bloodstream

In brain: gluteomorphins bind to opioid receptors and block binding of endogenous opioids

Gluteomorphins also bind to lymphocytes and alter messages they send to brain; cause **cognitive/mood abnormalities**

PDYN **affects** pain sensation and has opioid effect due to interference with receptors

Patients with these antibodies may **feel "addicted" to wheat**

Gliadin-transglutaminase complex

Transglutaminase is the enzyme that **deamidates gliadin in the gut**

Tissue transglutaminase (tTG) f**orms covalent tTG-peptide** complexes with gliadin

These complexes can **adhere to intestinal walls,** where recognized by antigen-presenting cells and trigger immune response

This results in **autoantibodies** produced against the complex and pro-inflammatory response

Associated with CD, Crohn's disease

Microbial Transglutaminase

Microbial transglutaminase is an enzyme produced by bacteria, which can send signals **impacting brain and nervous system function.**

Microbial transglutaminase can be exceptionally antigenic in some patients. Patients who consume gluten substitutes like gluten-free pasta may have a reaction to the non-tissue transglutaminase contained within these foods—which may initiate autoimmune reactivity against the other transglutaminases.

May send signals impacting brain and nervous system function, **sometimes contributing to neurological disorders.**

Also, when found in gluten-free substitutes, may negate the effectiveness of a gluten-free diet in some patients.

Tissue-transglutaminase 2

Together with alpha-gliadin, **used to diagnose CD**

If tTG-2 antibodies present without antibodies to alpha-gliadin, indicates **autoimmunity not mediated by gluten** (investigate other causes)

Transglutaminases present in other tissues; **antibodies** to tTG-2 can cross react with tTG in skin, brain, elsewhere

Known to **cross-react** with fibrinogen in addition to tTG-3 & tTG-6

Transglutaminases are **structural enzymes** important to barrier formation

Transglutaminase 2 (tTG-2) found in gut; **converts glutamine to glutamic acid,** deamidation of gliadin

Food processors use transglutaminases to **bind proteins together in processed meats** (aka "meat glue")

Associated with CD, Crohn's disease, dermatitis herpetiformis, ulcerative colitis

Tissue-transglutaminase 3

tTG-3 expressed primarily in **epidermis,** to lesser degree in placenta and brain

tTG-3 **upregulated** in several degenerative diseases

tTG-3 **antibodies** common in dermatitis herpetiformis; also found in Huntington's disease, CD, esophageal cancer

Cross-reacts with tTG-2 & tTG-6

Tissue-transglutaminase 6

tTG-6 primarily expressed in the **brain and neural tissue**

Some research suggests **autoimmunity to tTG-6** results from early brain damage and inflammation

Patients with high tTG-6 antibodies may have **autoimmunity against neuronal tissue**

Associated with cerebral palsy, CD, gluten ataxia, idiopathic spontaneous ataxia, neurodegeneration, peripheral neuropathy

"Silent" celiac disease

Several studies show that the **majority of CD patients** don't test positive for antibodies to alpha-gliadin or transglutaminase-2

Especially true when **GI enteropathy** is mild

Some studies suggest **sensitivity** as low as 27-31% (with alpha-gliadin and TTG2) when villous atrophy is mild

1 in 2 new patients diagnosed with CD **doesn't have gut symptoms**

For every 1 case of diagnosed CD, there are **6.4 cases undiagnosed**

Silent CD every bit **as harmful as obvious CD** (possibly more, since unrecognized)

It's **associated with** 4-fold increase in mortality, as well as numerous chronic, inflammatory conditions

Affects skin (dermatitis herpetiformis, psoriatic arthritis), brain (gluten ataxia, schizophrenia, idiopathic neuropathies), endocrine system (diabetes, nephritis), metabolism (overweight/obesity) and more

Reason CD so often missed: tests rely only on alpha-gliadin and TTG2 antibodies