

Array 3X – Part 1

The test I recommend for screening for gluten intolerance and celiac disease is Cyrex Array 3X, their wheat, gluten proteome reactivity and autoimmunity screening panel. Note that the slide says Cyrex Array 3. In 2018, Cyrex updated their test to be Cyrex Array 3X. They changed some markers and added some new markers, so throughout the presentation, the slides may say Array 3 but know that we are speaking of 3X, which is the test that they offer now, and we have provided some new slides that cover the new markers that were added in the Cyrex 3X panel.

This is the most advanced and sensitive way of testing for gluten intolerance that I am aware of, as of the time of this recording in 2018. Many gastroenterologists know how to screen for celiac disease. They will typically test for antibodies to alpha gliadin and transglutaminase 2, or if they are more current with the research, they might screen using deamidated gliadin and endomysium along with transglutaminase 2. If some of those are positive, they will do a biopsy to determine if tissue damage is present, and if it is, then that patient will be diagnosed with celiac. If it is negative, and those screening markers are negative, the patient is generally told that they don't have celiac or gluten intolerance, and they are sent away believing that they have no issue with gluten, and this is a grave mistake in some cases as you will learn as we go through this presentation because there are many other markers that are indicative of gluten intolerance on this Cyrex Array 3X panel that are not included in that conventional screening.

However, research clearly shows that people can and do react to several other components in wheat above and beyond alpha gliadin, the fraction of wheat that is involved in the pathogenesis of celiac disease, and these include other epitopes of gliadin such as beta gliadin, gamma gliadin, and omega gliadin; glutenin, which is the other major half of the wheat protein; wheat germ agglutinin, which is a lectin in wheat; gluteomorphin; and deamidated gliadin. What's more, people can react to other types of tissue transglutaminase aside from tTG2, including type 3, which is primarily found in the skin, and type 6, which is primarily in the brain and nervous system tissue. These patients will be completely missed by conventional testing. I can't emphasize that enough.

TEST	RESULT			
Array 3 – Wheat/Gluten Proteome Reactivity & Autoimmunity	IN RANGE (Normal)	EQUIVOCAL*	OUT OF RANGE	REFERENCE (ELISA Index)
Wheat IgG	0.46			0.3-1.5
Wheat IgA	0.59			0.1-1.2
Wheat Germ Agglutinin IgG	0.82			0.4-1.3
Wheat Germ Agglutinin IgA	0.63			0.2-1.1
Native & Deamidated Gliadin 33 IgG			2.18	0.2-1.2
Native & Deamidated Gliadin 33 IgA			1.40	0.1-1.1
Alpha Gliadin 17-mer IgG	0.63			0.1-1.5
Alpha Gliadin 17-mer IgA	0.32			0.1-1.1
Gamma Gliadin 15-mer IgG	<0.50			0.5-1.5
Gamma Gliadin 15-mer IgA	0.29			0.1-1.0
Omega Gliadin 17-mer IgG	0.68			0.3-1.2
Omega Gliadin 17-mer IgA	0.34			0.1-1.2
Glutenin 21-mer IgG			1.74	0.1-1.5
Glutenin 21-mer IgA	0.76			0.1-1.3
Gluteomorphin + Prodynorphin IgG			1.35	0.3-1.2
Gluteomorphin + Prodynorphin IgA	0.50			0.1-1.2
Gliadin-Transglutaminase Complex IgG			2.00	0.3-1.4
Gliadin-Transglutaminase Complex IgA	0.62			0.2-1.5
Transglutaminase-2 IgG	0.87			0.3-1.6
Transglutaminase-2 IgA	0.76			0.1-1.6
Transglutaminase-3 IgG			1.68	0.2-1.6
Transglutaminase-3 IgA	0.94			0.1-1.5
Transglutaminase-6 IgG			1.63	0.2-1.5
Transglutaminase-6 IgA	0.72			0.1-1.5

If you look at this panel here, you see that this patient is not producing antibodies to alpha gliadin, which is the epitope that is commonly tested for in conventional settings, nor are they producing antibodies to transglutaminase 2. Again, that is the enzyme that is tested for in conventional settings. But as you can see here, they are producing high amounts of antibodies to transglutaminase 3 and transglutaminase 6. They are producing antibodies to gliadin transglutaminase complex, which is what happens when gliadin AKA gluten binds to transglutaminase to the gluteomorphin prodynorphin, and also to glutenin, which is the other major half of the wheat protein and native in deamidated gliadin, so this is a strong reaction to wheat and the peptides in wheat, but this patient would be completely missed by conventional testing.

Who should get tested with Cyrex Array 3? I think there are 2 primary groups. Number one is anybody who is currently eating wheat and gluten. Number two is anyone who wants to be able to eat wheat and gluten, even if only occasionally. Let's say we have a patient who is following a Paleo template type of diet, but occasionally if they go out to a restaurant they are wondering if they can have a piece of bread once a month or once every couple weeks or something without significant consequences.

Test Preparation (Important!)

- 1 Exposure to **wheat triggers antibody** production
- 2 Patient must have consumed wheat **within 25-30 days** of test for accurate results
- 3 Advise patient to eat **at least one small serving of wheat** or wheat-containing product per day for minimum of 7 days, starting 25-30 days before test
- 4 If patient suspects intolerance, can take **GlutenFlam** after eating wheat to mitigate symptoms

The test preparation for Cyrex Array 3 is really important, and we've provided a patient handout which you can give to your patients describing the process in detail. It's really crucial to do this, or else you can get unreliable results. The first thing to know is that exposure to wheat is what triggers the antibody production. I'm sure you do know that, but it's just an important reminder. If a patient is not eating wheat and hasn't eaten it for a very long time, then they may not be producing antibodies to it anymore, so if someone who's been on a Paleo-type diet, strict gluten-free for five years, takes Array 3, they might get a false negative result. The patient must have consumed wheat within 25 to 30 days of the test for accurate results. What we do is, we advise the patient to eat at least one small serving of wheat or wheat-containing product per day for a minimum of seven days, starting 25 to 30 days before the test.

Now you can see here that if someone already knows that they have gluten intolerance, and eating wheat or gluten as we're suggesting here would cause significant distress, then I don't think that this test is worthwhile because it's not really going to change the treatment protocol, which is to avoid gluten in those cases. Those people already know they have an issue. There is no point really in putting them through this unless there is some really specific reason to do it, and the test should be reserved for people who aren't clear whether they're reacting to wheat and gluten and want to be able to include it in their diet, or people who are currently eating it and for whom you're curious about the reaction. If they're eating it and they don't want to stop eating it, and you as a clinician suspect it might be contributing to their symptomatology and their pathology, then that's another reason to do this test.

Now if a patient suspects they are gluten-intolerant, and they may have a mild reaction, but they just really want to know for sure, they want to do this test, and they're willing to put up with the

potential symptoms or side effects of eating gluten during the preparation phase, they can take something like GlutenFlam, which is a product from Apex Energetics. It contains an enzyme that helps break down gluten after they eat the wheat to help mitigate the symptoms. Now, it's important to point out to them that this is not a get-out-of-jail-free card for gluten. If a patient is gluten-intolerant, they can't expect to eat pizza and then gobble down a few capsules of GlutenFlam and not experience any of the adverse effects of gluten intolerance, but we use this product more for people who know that they're gluten-intolerant. When they're traveling, they might be accidentally exposed to gluten, eating out at a restaurant or some cross-contamination or something like that, and we do use it in this situation just to help alleviate some of the discomfort for someone who suspects they're gluten-intolerant and still wants to get the test.

Array 3 and Celiac Disease

Alpha-gliadin

Transglutaminase 2

Deamidated gliadin

Endomysium

Before we jump into looking at actual lab results and case studies, I want to address a question that we're often asked about Array 3, which is, can you diagnose celiac disease with it? The short answer is no, but it is an excellent screening tool and starting place. I mentioned earlier that celiac is characterized by antibody production to alpha gliadin, transglutaminase 2 or tGT2, and deamidated gliadin, among others, and all three of these are on Cyrex Array 3. If you see those elevated, you might suspect celiac disease, and then at that point, you can do one of two things. You can refer out right away to a gastroenterologist, who will do an endoscopy to see if there's enteropathy and tissue damage, or you can also run antibodies to endomysium through LabCorp, which is a test that's fairly specific for celiac disease, and then refer to a gastroenterologist.

Another question we get a lot is, does it matter if they have celiac versus nonceliac gluten sensitivity? The answer to this is it depends on the patient. From our perspective, treatment for celiac and nonceliac gluten sensitivity is largely the same, which is avoiding wheat, gluten, and often other proteins that cross-react with wheat and gluten, or other foods that the patient is intolerant of, but you have to really look at this on a case-by-case basis.

Here are a couple of considerations. Number one, if you have a patient that kind of pooh-poohs nonceliac gluten sensitivity and doesn't take it seriously, and you suspect that they have markers for celiac and may have celiac, then you could definitely do a workup for celiac, and if you discover that they have it, they'll probably be more compliant because it's a much more recognized condition in mainstream medicine. Another thing is that although we don't fully understand the pathological mechanisms for nonceliac gluten sensitivity, and there may very well be some autoimmune involvement, we know that celiac is an autoimmune disease. We know that a lot of patients with celiac disease also have and produce antibodies to dairy products and other proteins. We know that removing gluten from the diet alone doesn't often resolve symptoms for patients with celiac, and they may need more attention and a more thorough workup and comprehensive testing and treatment plan than people with nonceliac gluten sensitivity. But having said that, I can also tell you that I've had many patients with nonceliac gluten sensitivity that have even more severe symptoms than some with celiac, so again, it really has to be a case-by-case evaluation.