ARRAY 4

ARRAY 4 – Antibody

GLUTEN-ASSOCIATED CROSS-REACTIVE FOODS & FOODS SENSITIVITY™

CYREX™ Laboratories

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GLUTEN-ASSOCIATED CROSS-REACTIVE FOODS AND FOODS SENSITIVITY™

OVERVIEW

Once a patient is properly diagnosed as Gluten-Sensitive or having Celiac disease, he/she is instructed to adhere to a gluten-free diet. Brochures, books and websites help the patient with this seemingly difficult process. However, a significant percentage of these patients will continue to have gluten-like complaints even after being on a gluten-free diet for months. Most countries define "gluten-free" products based on the recommendation of the Food and Agricultural Organization of the United Nations and World Health Organization. This codex alimentarius allows the inclusion of up to 0.3% protein from gluten containing grains in foods labeled "gluten-free." If the sensitive body is exposed to 0.3% protein, the immune system will recognize and react to the protein.

There exists antigenic similarity, or cross-reaction, among many grains, and other dietary proteins such as casein with gluten. Based on biological individuality of immune response against a repertoire of gliadin or gluten peptides, any number of patients may produce antibodies against a single gluten antigen or a combination of gluten antigens, some of which may be cross-reactive with other food antigens.

A problem with digesting dairy, casein in particular,[1] may be a feature in about 50% of patients with Celiac disease and may, therefore, contribute to persistent symptoms in patients who are on a gluten-free diet.

Additionally, patients who are new to the gluten-free diet (GFD) encounter new foods and/or over-consume old favorites to compensate for the lack of wheat in the diet. Gluten-free cookies, crackers, breads and cakes often contain copious amounts of rice, amaranth, sorghum and other substitutes. Some of these new-to-the-patient foods may illicit an adverse reaction. Other foods that are often introduced to the patient on the GFD are quinoa, buckwheat and hemp. Some patients may turn to the "ancient" grains (Polish wheat, spelt, barley, rye), not knowing that these contain gluten. Another problem patients often face on the GFD is the over-consumption of another starch to make up for the loss of wheat. They turn to potato, rice or corn as a substitute. This can lead to the development of a new sensitivity or the enhancement of old sensitivities.

Array 4 can assist the clinician by detecting both sensitivities and cross-reactions and thus reveal the possible cause of this continued gluten-like reaction in the patient.

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Antibody Array 4

Testing for Gluten-Associated Cross-Reactive Foods and Foods Sensitivity in this array can assist the clinician in revealing the possible cause of this continued gluten-like reaction in the patient. Patients with Gluten-Sensitivity or Celiac disease are sensitized to a **broad range** of dietary proteins, due to enzyme dysfunction, villi damage, or other disorders. **Therefore, it is crucial to identify not only sensitivities to foods that are often recommended for patients on the GFD, but also the food antigens that cross-react to gluten peptides in the patient. Without biochemically individualized dietary intervention, the Gluten-Sensitive patient may develop additional reactivity and autoimmunity.**

Although the majority of individuals with Celiac disease (CD) have substantial improvement within the first few weeks of gluten withdrawal, between 7% and 30% continue to have symptoms or clinical manifestations suggestive of CD despite being on a gluten-free diet.[2]

Non-responsive Celiac Disease (NRCD) was defined as:

(1) Referral to a clinician specializing in CD for the evaluation of a lack of response to a gluten-free diet

(2) Failure of clinical symptoms or laboratory abnormalities typical of CD to improve within 6 months of gluten withdrawal

(3) Recurrence of symptoms and/or laboratory abnormalities typical of CD while on a gluten-free diet. Of the 12 identified causes of NRCD, the most common cause was (inadvertent) gluten exposure, accounting for 36% of patients.[3] What about the other 64%? An all-too-common contributor to NRCD is cross-reactivity with other foods. Antibody cross-reactivity between different foods or between food and aeroallergens, such as trees and grasses, occurs much more readily than clinically evident cross-reactivity.[4] The patient often is unable to 'feel' the immune response to cross-reactive food.

These are the confusing scenarios when a gluten-sensitive person will say, "What did I eat that was a problem? The packaging didn't reference any wheat products." This can be explained in the following:

1. **Consumption of gluten-containing foods such as beer or chewing gum** - Additionally, most countries define "gluten-free" products based on the recommendation of the Food and Agricultural organization of the United Nations and World Health Organization, which allows the inclusion of up to 0.3% protein from gluten-containing grains in foods labeled "gluten-free."[5]

2. **Problem with digesting diary, in particular, casein sensitivity to cow's, sheep's and goat's milk**. Casein sensitivity may be a feature in about 50% of patients with Celiac disease and may, therefore, contribute to persistent symptoms in Celiac patients who are on a gluten-free diet.[6] [7] Casein also has been suggested as an environmental trigger of other autoimmune disorders such as Behcet's disease, type-1 diabetes, and systemic lupus erythematosus.[8] [9] [10]

Cross-reaction among non-gluten grains, or even infectious agents, and products with gluten. For example, milk, casein, yeast and many other, as-yet-unidentified, food antigens, salmonella typhi, rotavirus and many other infectious agents, human tissue antigens, such as transglutaminase, heat shock protein, myotubularin-related protein 2 and cell surface receptors (toll-like receptors), all cross-react with gliadin or Celiac peptide.[11] [12] [13] [14] [15] Indeed, bovine milk caseins and transglutaminase-treated cereal prolamins, such as wheat and maize, are differentially recognized by IgA of

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Celiac disease patients.[16] Studies have identified cross-reactivity among gliadin and foods such as chocolate,[17] sesame,[18 19 20 21 22] hemp,[23] rye,[24] polish wheat,[25 26] buckwheat,[27 28 29 30 31 32 33 34 35] sorghum,[36 37 38 39 40] millet,[41 42 43 44] spelt,[45 46 47 48] amaranth,[49 50 51] quinoa,[52 53 54] yeast,[55 56 57 58 59] tapioca,[60 61 62 63] oats,[64 65 66 67 68 69] coffee,[70 71 72 73 74] corn,[75 76 77] rice,[78 79 80 81 82] and potato.[83 84 85] The response to some of these food allergens parallels the response to gliadin and might be relevant to the pathogenesis of Gluten Sensitivity and Celiac disease by increased mucosal permeability leading to increased antigen resorption, leading to increased immune activation with increased IgA antibodies.[86] Perhaps this is why as many as 40% of children on a well-managed gluten-free diet for at least 1 year still have elevated antibodies to gluten.[87]

3. Based on biological individuality and heterogeneity of immune responses, the spectrum of patients elicits a variety of intestinal T-cell responses to a repertoire of gliadin peptides;[88] and, therefore, any number of patients may produce antibodies against a single antigen or a combination of antigens. These antigens include gliadin, glutenin or agglutinins and their enzymatic digestions in a form of different peptide sizes, 33 MER, 24 MER, 17 MER, 15 MER, gluten exorphin, prodynorphin or dynorphins.[89]

4. From these data, it is conceivable that patients with Celiac disease are sensitized to a broad range of dietary proteins and peptides. Therefore, it is crucial to identify food antigens with a capacity to sensitized patients with Celiac and other autoimmune disorders.[90 91 92 93]

From the diagnostic and therapeutic point of view, it makes sense to define allergen clusters (cross-reactivity).[94]

Negative serology for transglutaminase, endomysium, or gliadin should not necessarily reassure the clinician[95] of neither negative immune activation nor pathology from Gluten Sensitivity. Several reports[96 97 98 99 100] show that in the majority of Celiac patients, these antibodies may be negative or low but cross-reactive antibodies could be elevated.

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INFLUENCING FACTORS

GENETIC

Close to 90% of Celiac disease patients carry the gene DQ2 (*DQA1*05/DQB1*02*), and a minority (10%) of the Celiac disease patients carry DQ8 (*DQA1*03/DQB1*0302*). Typically, gluten peptides bind to the DQ2 and DQ8 molecules. Recent research however, has identified at least eight new genomic regions with robust levels of disease association to Gluten Sensitivity.[101 102]

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ENVIRONMENTAL (CHEMICALS, FOODS, BIOTOXINS, DRUGS…)

Environmental factors that have an important role in the development of Celiac disease have been suggested by epidemiologic studies. These include a protective effect of breast-feeding[103] and the introduction of gluten in relation to weaning.[104] [105]

Numerous environmental factors have been hypothesized as being catalysts for the development of not only the gluten enteropathy Celiac disease,[106] but also systemic manifestations of Gluten Sensitivity with or without the enteropathy. Some of these catalysts include bacteria,[107] viruses,[108] gut dysbiosis,[109] and cross-reactive foods.[110]

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HISTORY (FAMILY, MEDICAL)

Celiac disease and gluten sensitivity are characterized by a variety of clinical manifestations. These include the typical malabsorption syndrome (classic symptoms) and a spectrum of symptoms potentially affecting any organ or body system (non-classic symptoms).[111] [112] [113]

Clinical manifestations of gluten sensitivity and Celiac disease along with sensitivity to cross-reactive foods can present at any age:

- **Infancy** (less than 2 years old) – diarrhea, abdominal distention, failure to thrive (low weight, lack of fat, hair thinning), anorexia, vomiting, psychomotor impairment (muscle wasting)

- **Childhood** – diarrhea, constipation, anemia, loss of appetite, short stature, osteoporosis

- **Adulthood** – diarrhea, constipation, anemia, aphthous ulcers, sore tongue & mouth (mouth ulcers, glossitis, stomatitis), dyspepsia, abdominal pain, bloating (weight loss), fatigue, infertility, neuropsychiatric symptoms (anxiety, depression, etc.), bone pain (osteoporosis), weakness (myopathy, neuropathy).[114] [115] [116]

Reviewing current medications (antibiotics, steroids, NSAID's, etc.), supplements, diets, and a detailed medical history are critically important in determining who may have gluten sensitivity. The correlation between food ingestion and symptom onset is of great clinical importance.

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CLINICAL – SYSTEMIC IMMUNE EFFECTS

When cross-reactivity is present in a patient, gluten antibodies may be essentially normal, and antibodies to the particular antigenic food may be the sole indicator of a continued inflammatory response, triggering the symptomatology of Celiac disease.

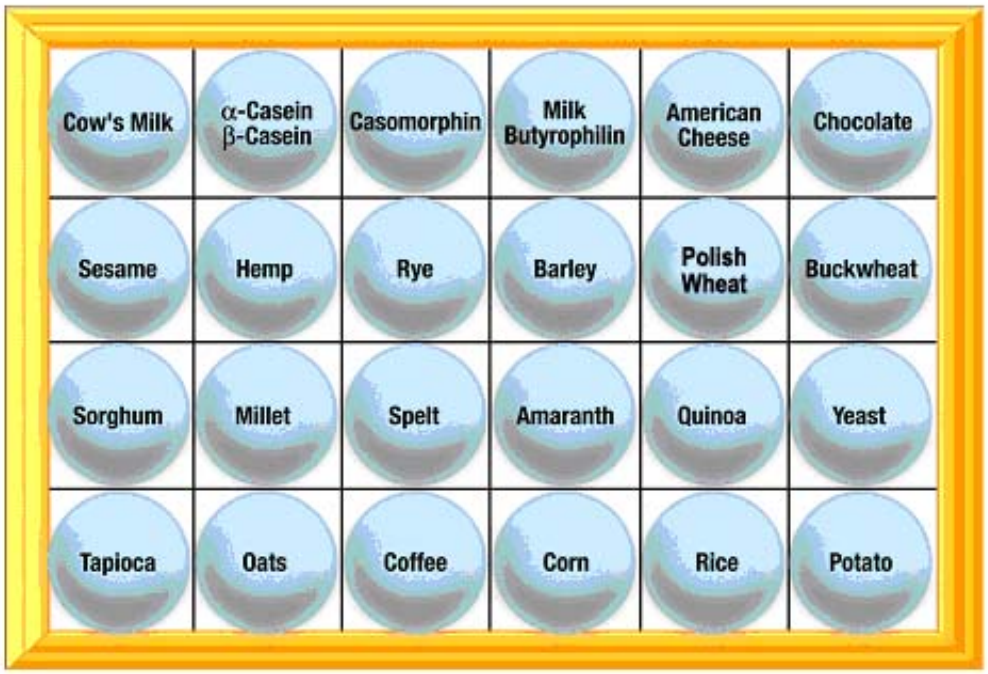
Reduced antibodies to gluten—after introduction of a gluten-free and cross-reactive food diet—probably reflects catabolism of pre-formed antibodies combined with lowered synthesis due to the lack of antigen stimulation. Concurrent reduction of antibodies to other dietary antigens may,

therefore, be a better indication of improved mucosal integrity by reflecting decreased penetrability of antigens still available in the gut lumen.

Determination of serum IgA and IgG antibody activities to dietary proteins appears to be a valuable adjunct in the diagnosis and follow-up of diagnosed CD, both in children and adults. Increased IgA activities to other dietary antigens are likewise relatively characteristic of untreated CD; monitoring of such antibodies may be particularly helpful in evaluating the response of patients on a gluten- and cross-reactive food-free diet.[117]

The manifestations and the pathophysiology of CD and GS can be as unique as the individual himself. Identifying these triggers and cascades of autoimmunity is an important step in designing effective treatment and maintenance protocols for the patient. Therefore, patients with CD or GS suffer an array of autoimmunity beyond the gastrointestinal system.

Cyrex Laboratories' Antibody Arrays for Gluten Sensitivity are vital components to clinical practice. After establishing the patient on a gluten-free diet, many will return after adhering to this diet for months, and yet they still exhibit the same clinical complaints as they experienced with gluten-containing foods. Undoubtedly, these patients are having reactions to foods which cross-react with gluten antigens. Antibody Array 4 – Gluten-Associated Cross-Reactive Foods and Foods Sensitivity is designed to assess these select individuals. With results of this array, the practitioner can take a better, broader approach to developing a tailored diet plan for patients with Celiac disease or gluten sensitivity.



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CLINICAL USE OF ANTIBODY ARRAY 4

Patients with Gluten Sensitivity and Celiac disease are sensitized to a broad range of dietary proteins due to enzyme dysfunction, villi damage, or other disorders. A common problem is the digestion of dairy products, the casein protein, in particular. Consuming these food products will cause persistent symptoms and clinical complaints similar to the initial discomforts of the gluten sensitivity.

Complete normalization of gut lesions is very rare in adult patients with Celiac disease (8%), despite gluten-free diet compliance. Although a majority (65%) feels better, the ensuing inflammation in the gastrointestinal tract, due to cross-reactions with – and sensitization to – an array of food antigens, remains a cause for clinical concern. When the patient, despite adamant adherence to the gluten-free diet, is non-responsive, continues to exhibit clinical complaints or has therapy-resistant gut dysbiosis, an assessment of IgG + IgA antibodies to an array of food antigens associated with a gluten-free diet, or known to cross-react with gluten, can guide the Healthcare Practitioner in tailoring a recovery diet plan and preventing devastating autoimmune disorders.

Gluten-Associated Cross-Reactive Foods and Foods Sensitivity assessment is recommended for patients who:

- Have gluten-sensitivity or Celiac disease
- Are non-responsive to the gluten-free diet
- Have gut dysbiosis, which appears to be resistant to standard therapy
- Have an autoimmune disorder

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CLINICAL INTERPRETATION OF ANTIBODY ARRAY 4

FOODS KNOWN TO CROSS-REACT WITH PURIFIED GLIADIN												
Cow's Milk	α + β Casein	Casomorphin	Milk Butyrophilin	American Cheese	Milk Chocolate	Rye	Barley	Polish Wheat*	Spelt	Yeast	Oats	Coffee
+	+	+	+	+	+	+	+	+	+	+	+	+
-	-	-	-	-	-	-	-	-	-	-	-	-

*Polish Wheat is also known as Camel's wheat, Egyptian wheat and Kamut®

For patients with known gluten reactions or Celiac disease (refer to results from Array 1 or Array 3), all cross-reactive foods should be removed from the patient's diet under a clinician's care.

FOODS CONSUMED ON A GLUTEN-FREE DIET										
Sesame	Hemp	Buckwheat	Sorghum	Millet	Amaranth	Quinoa	Tapioca	Corn	Rice	Potato
+	+	+	+	+	+	+	+	+	+	+
-	-	-	-	-	-	-	-	-	-	-

If any foods commonly consumed on the gluten-free diet result positive, the offending food should be eliminated from the patient's diet until the gut is healed. Slowly reintroduce the foods on a rotation diet after gut is healed. After at least two months on the rotation diet, Array 4 may be rerun on a fresh specimen.

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INTERPRETATION OF CROSS-REACTIVE AND FOOD ANTIGENS					
POSITIVE REACTION TO:	DAIRY-SENSITIVITY	GLUTEN-CONTAINING GRAINS	IN VITRO CROSS-REACTION TO GLIADIN	NEWLY INTRODUCED FOODS ON GFD	OVER-CONSUMED ON GFD
Cow's Milk					
α-Casein + β-Casein					
Casomorphin					
Milk Butyrophilin					
American Cheese					
Milk Chocolate					
Sesame					
Hemp					
Rye					
Barley					
Polish Wheat*					
Buckwheat					
Sorghum					
Millet					
Spelt					
Amaranth					
Quinoa					
Yeast					
Tapioca					
Oats					
Coffee					
Corn					
Rice					
Potato					

*Polish Wheat is also known as Camel's wheat, Egyptian wheat and Kamut®

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Dairy Sensitivity – if any of the 5 antigens are positive, the patient must be placed on a dairy-free diet.

Gluten-Containing Grains – if the patient is wheat-sensitive, but not gluten-sensitive, he/she may be able to tolerate these grains. If any of these are positive the patient must be on a gluten-free diet.

In Vitro Cross-Reaction to Gliadin – in the laboratory setting these foods were shown to be highly cross-reactive to purified gliadin. If the patient had antibodies to any of these foods based on the practitioner's recommendation, the foods should be eliminated from the patient's diet.

Newly Introduced Foods – when a patient goes on a gluten-free diet there are many exposures of foods the patient may not have eaten during the formative years, when humans develop their tolerance to foods, thus, the patient may have an adverse reaction to the new food. Positive antibodies to these foods means the foods should be avoided. After normalization of the immune response, these foods may be reintroduced on a rotation basis and rechecked for reactivated immune response after a minimum of 2 months fresh exposure.

Over-Consumed Foods – when a patient goes on a gluten-free diet, the patient often trades one sensitivity for another by over eating a different starch. The common substitutes tend to be potato, rice or corn. After normalization of the immune response, these foods may be reintroduced on a rotation basis and rechecked for reactivated immune response after a minimum of 2 months fresh exposure.

TREATMENT PROTOCOL

1. Tailor a more effective, individualized diet plan.
2. Heal the gut.
3. After confirmation that the gut is healed, using a rotation diet, slowly re-introduce the non-cross-reactive foods into the patient's diet regimen.
4. After fully re-introducing the foods, retest with Array 4.
5. If antibody levels have normalized, continue with the rotation plan.

If antibody levels have not normalized, instruct the patient to avoid the positive foods for life.

Specimen Requirement

2 mL Serum
Ambient

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Related Testing

Antibody Array 2 – Intestinal Antigenic Permeability Screen (Serum)

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