CLINICAL APPLICATION GUIDE

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 diagnosed as Celiac Disease (CD) or having Gluten Reactivity, 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 (GFD) 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 CD and may, therefore, contribute to persistent symptoms in patients who are on a GFD.

Additionally, patients who are new to the 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.

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-Reactivity or CD 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-Reactive patient may develop additional sensitivity/intolerance and autoimmunity.

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Although the majority of individuals with 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) is 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-Reactive 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, and grains, such as spelt or barley** - 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] Wheat/gliadin is commonly added to foods as a "hidden" ingredient such as "Natural Flavor" or "Spices." A complete understanding of 'hidden wheat/gluten' sources is necessary to have a better outcome with the GFD. Additionally, education of gluten-containing grains, such as rye,[6][7] barley, [6][7] Polish wheat,[7][8][9] and spelt.[7][10][11][12][13]

2. **Problem with digesting dairy, 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 CD and may, therefore, contribute to persistent symptoms in Celiac patients who are on a gluten-free diet.[1][14] Casein also has been suggested as an environmental trigger of other autoimmune disorders such as Behçet's disease, type-1 diabetes, and systemic lupus erythematosus.[15][16][17]

3. **Cross-reaction among foods, or 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

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protein 2 and cell surface receptors (toll-like receptors), all cross-react with gliadin or Celiac peptide.[14] [18] [19] [20] Indeed, bovine milk caseins and transglutaminase-treated cereal prolamins, such as wheat and maize, are differentially recognized by IgA of CD patients.[21] Studies have identified food antigen cross-reactivity such as milk chocolate,[22] [23] rye,[6] [7] barley,[6] [7] Polish wheat,[7] [8] [9] spelt,[7] [10] [11] [12] [13] millet, [23] [64] corn, [23] rice,[23] yeast,[23] [24] [25] [26] [27] [28] oats,[29] [30] [31] [32] [33] [34] [35] instant coffee.[23] [36] [37] [38] [39] [40] The response to some of these food allergens parallels the response to gliadin and might be relevant to the pathogenesis of Gluten-Reactivity and CD by increased mucosal permeability, resulting in elevated antigen reabsorption, which can trigger immune activation with elevated levels of IgA antibodies.[41] 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.[42]

4. **Consumption of new foods and over-consumption of alternative starches**. Patients new to the GFD often begin to consume foods never eaten as a child when humans develop tolerance to foods. As an adult on a GFD, some of these gluten-alternatives (sesame,[43] [44] [45] [46] [47] hemp,[48] buckwheat,[49] [50] [51] [52] [53] [54] [55] [56] [57] sorghum,[58] [59] [60] [61] [62] millet,[63] [64] [65] [66] amaranth,[67] [68] [69] quinoa,[70] [71] [72] tapioca,[73] [74] [75] [76] teff[77] [78]) may cause the immune system to react against the new food as if it were a foreign antigen. Another common event is for a patient to develop food-sensitivity due to over-consumption of a specific food. People new to the GFD may substitute another starch to compensate for the loss of wheat in the diet. Thus, the development of reactions to corn,[79] [80] [81] rice,[82] [83] [84] [85] [86] and/or potato[87] [88] [89] is seen in some patients on a GFD.

5. **Common food sensitivities.** The gluten-reactive patient may also be reactive to common food antigens, such as hen's eggs[90] [91] [92] and soybean.[93] [94]

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.[1] [5] [95] [96]

Negative serology for transglutaminase, endomysium, or gliadin should not necessarily reassure the clinician[97] of neither negative immune activation nor pathology from Gluten Reactivity. Several reports[98] [99] [100] [101] [102] show that in the majority of Celiac patients, these antibodies may be negative or low but cross-reactive antibodies could be elevated. From the diagnostic and therapeutic point of view, it makes sense to define allergen clusters (cross-reactivity).[103]

INFLUENCING FACTORS

GENETIC

Close to 90% of CD patients carry the gene DQ2 (*DQA1*05/DQB1*02*), and a minority (10%) of the CD 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-Reactivity.[104] [105]

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ENVIRONMENTAL (CHEMICALS, FOODS, BIOTOXINS, DRUGS…)

Environmental factors that have an important role in the development of CD have been suggested by epidemiologic studies. These include a protective effect of breast-feeding[106] and the introduction of gluten in relation to weaning.[107] [108]

Numerous environmental factors have been hypothesized as being catalysts for the development of not only the gluten enteropathy CD,[109] but also systemic manifestations of Gluten-Reactivity with or without the enteropathy. Some of these catalysts include bacteria,[110] viruses,[18] gut dysbiosis,[111] and cross-reactive foods.[112]

HISTORY (FAMILY, MEDICAL)

CD and Gluten-Reactivity 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).[113] [114] [115]

Clinical manifestations of Gluten-Reactivity and CD 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).[116] [117] [118]

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.

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 CD.

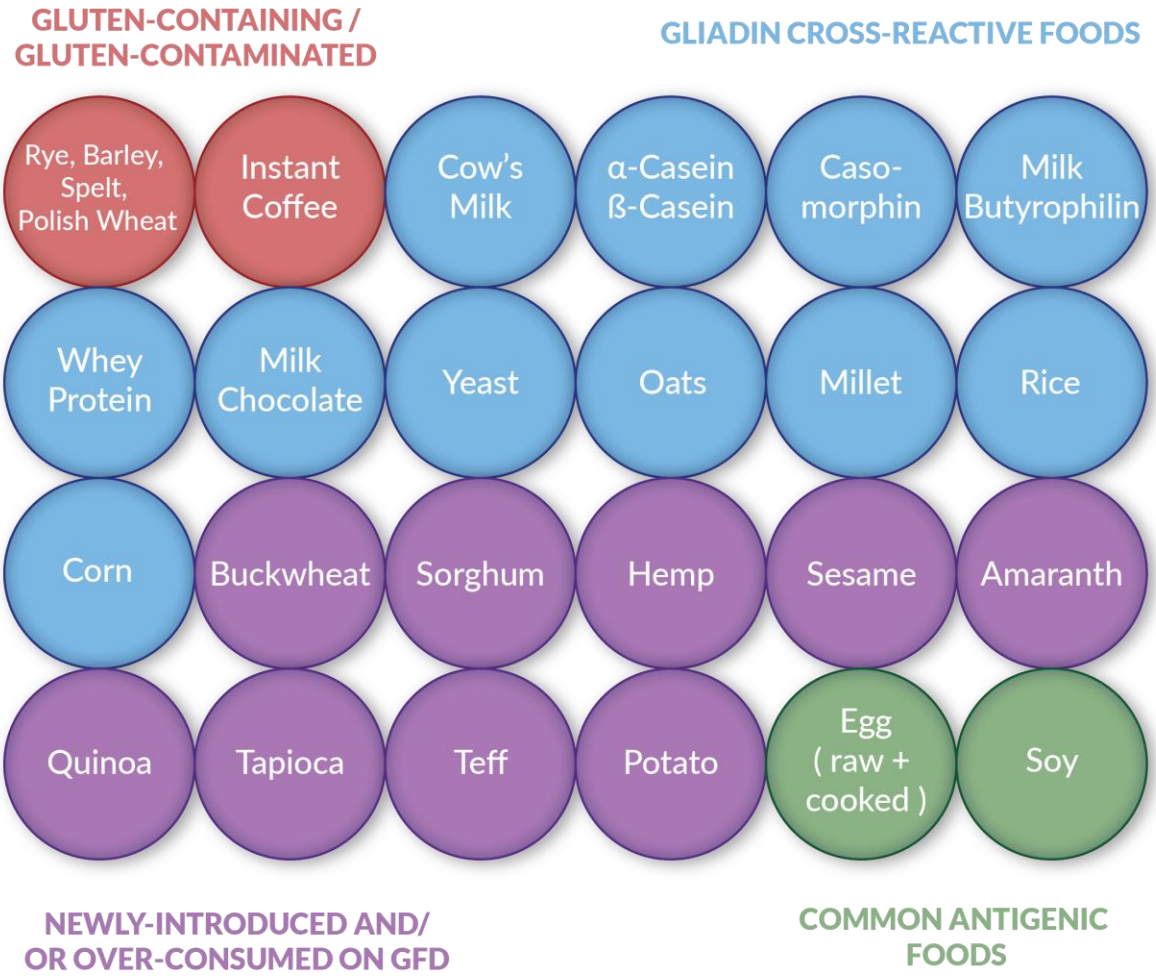
Reduced antibodies to gluten—after introduction of a gluten-free and cross-reactive food diet—probably reflects catabolism of pre-formed antibodies combined with lowered synthesis due to the lack of antigen stimulation. Concurrent reduction of antibodies to other dietary antigens may, therefore, be a 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.[119]

The manifestations and the pathophysiology of CD and Gluten-Reactivity 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 Gluten-Reactivity suffer an array of autoimmunity beyond the gastrointestinal system.

Cyrex Laboratories' Antibody Arrays for Gluten-Reactivity 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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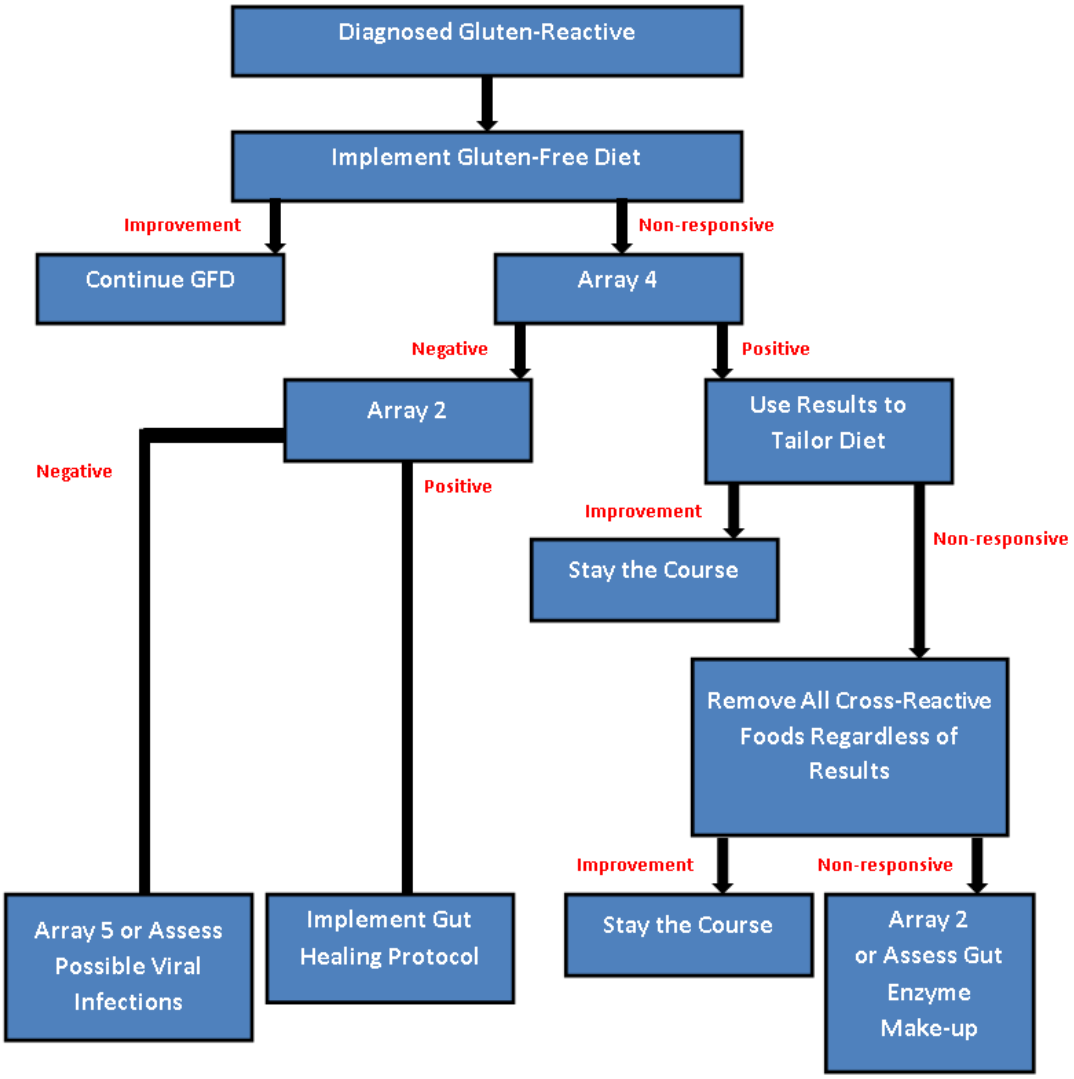
CLINICAL USE OF ANTIBODY ARRAY 4



Patients with Gluten-Reactivity and CD 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-Reactivity 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 Alpha-Gliadin-33-Mer	
Cow's Milk	Gluten Grains*
α + β Casein	Yeast
Casomorphin	Oats
Milk Butyrophilin	Millet
Whey Protein	Rice
Milk Chocolate	Corn

** Rye, Barley, Spelt, Polish Wheat (Polish Wheat is also known as Camel's wheat, Egyptian wheat, Khorasan 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.

Newly-Introduced and Over-Consumed Foods on GFD	
Sesame	Quinoa
Buckwheat	Tapioca
Sorghum	Teff
Millet*	Rice*
Hemp	Corn*
Amaranth	Potato

**Also cross-reacts with alpha-gliadin-33-mer*

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 REACTIVITY**	**IN VITRO CROSS-REACTION TO α-GLIADIN**	**NEWLY INTRODUCED FOODS ON GFD**	**OVER-CONSUMED ON GFD**	**GLUTEN-CONTAINING/ GLUTEN-CONTAMINATED**	**COMMON ANTIGENIC FOODS**
Rye, Barley, Spelt, Polish Wheat*						
Instant Coffee						
Cow's Milk						
α-Casein + β-Casein						
Casomorphin						
Milk Butyrophilin						
Whey Protein						
Milk Chocolate						
Yeast						
Oats						
Millet						
Rice						
Corn						
Sesame						
Buckwheat						
Sorghum						
Hemp						
Amaranth						
Quinoa						
Tapioca						
Teff						
Potato						
Soy						
Egg						
**Polish Wheat is also known as Camel's wheat, Egyptian wheat, Khorasan wheat and Kamut®*						

Dairy Reactivity – if any of the 6 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. If the patient is already on a long-term (more than four months) GFD and is positive for gluten-containing grains, he/she is consuming 'hidden' sources of gluten.

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.

Wheat-Contaminated Foods – although oats in a recent study did not cross-react with purified alpha-glidain-33-mer,[23] researchers found that certain varieties of oats do cross-react with gliadin.[31] [35] It is recommended that gluten reactive patient's refrain from consuming oats not only because one does not know the variety of oats in the package purchased at the grocery store, but also due to the common wheat contamination of oats that occurs in the transportation, processing and packaging processes.[33] The coffee antigen used on Array 4 is instant coffee. In a recent study, [23] instant coffee was shown to cross-react with gliadin, but whole bean coffee was not. This indicates that coffee protein by itself does not cross-react with purified gliadin. The positive result for instant coffee shows that during the manufacturing of instant coffee, wheat is either added to the product or contaminates it. Gluten-reactive patient who test positive to instant coffee on Array 4 should eliminate all coffee for a period of time to heal the gut and quiet the immune response. Whole bean coffee can be reintroduced and the patient monitored for adverse reactions.

TREATMENT PROTOCOL

1. Tailor a more effective, individualized diet plan. Refer to antigen specification sheets for additional known cross-reactions for the best dietary outcome. Specification sheets are found under "Tests and Arrays" then click "Array 4" followed by the pdf symbol next to the food antigen.
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.
6. If antibody levels have not normalized, instruct the patient to avoid the positive foods for life.

Specimen Requirement

2 mL Serum
Ambient

Related Testing

Antibody Array 2 – Intestinal Antigenic Permeability Screen (Serum)

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