INFINITE ALLERGY LABS

The Emerging Role in Comprehensive Assessment of Food Sensitivity and Allergy Screening

Why measurement if IgE, IgG Total, IgG4 and Complement are Important Collectively for Understanding a Reaction to Food.

What Complement Proteins Should Be Measured?

Worldwide, there is significant increase in allergies and sensitivities, and the rate of increase is not slowing down. The past 50 years have resulted in a dramatic increase in incidents. The significant change in rate of allergies indicates that there must be an environmental influence, as genetics do not shift in such a short period of time. There are estimates that speculate the sensitization rate to one or more allergens in school children is approaching 40-50%. Currently, 32 million people in the United States have food allergies. The CDC states there has been a 50% increase from 1997 to 2011, and the rate of tree nut allergy has as much as tripled in the last two decades. [1] [2] [3] The increase is due to increase in respiratory environmental exposure, changes in what we eat, pesticides in food and over exposure to smaller amounts of food. Also, theories such as the "hygiene" hypothesis explain that as we have become more hygienic, our immune system is less able to become tolerant to exposures increasing allergies. Other factors include excessive use of acetaminophen, antibiotics, Vitamin D deficiency and obesity. [4]

The most familiar allergic reaction is the IgE mediated response. When IgE binds to mast cells or eosinophils it triggers an allergic reaction causing a release of histamine, or other inflammatory mediators. IgE can be measured in both the serum and on the skin, via skin prick testing. Results should be similar, but they will not correlate 100%, given there are slight differences in the immune environment of the skin vs the blood. An IgE mediated reaction is measured to confirm the presence of an allergy. In the strictest sense, an allergy is a clinical diagnosis, meaning it is based 100% on the presence of a reaction after a particular exposure. IgE testing is then used to confirm this allergic response and verify that the suspected allergen in the patient. It is well established that IgE will only be present 50% of the time when there is a reaction to an allergen, such as a food like dairy and wheat. IgE testing alone, will only identify 50% the global reactivity and subsequent food related symptoms a person is experiencing.

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2. United States Census Bureau Quick Facts (2015 and 2016 estimates).
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4. https://www.aaaai.org/conditions-and-treatments/library/allergy-library/prevalence-of-allergies-andasthma#:~:text=A%20leading%20theory%20behind%20the,between%20harmless%20and%20harmful%20irritants

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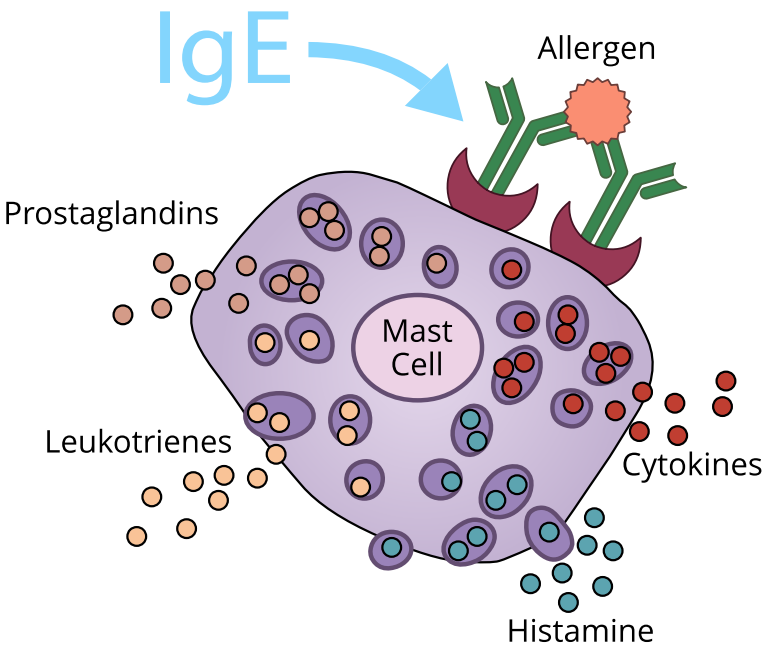

There are a number of reasons that an IgE titer is only positive 50% of the time. One is that not all responses to foods are allergies. An IgE reaction is known as a Type I Hypersensitivity reaction. A type I Hypersensitivity reaction is designed to protect the body from invasion by a pathogen. The normal response to an invading pathogen occurs when an IgE antibody binds to the pathogen and signals a cascade of other immune compounds to be to the area, and ultimately lyse (secrete enzymes to break down) or kill the invader.

Going forward, the antibody-antigen complex trains the immune system to recognize the antigen(invader) faster upon subsequent exposure. In the case of an allergen, the immune system is now recognizing something from the environment, either a food or environmental trigger, and this heightened sensitivity of immune reaction leads to the release of chemokines, cytokines, and other inflammatory compounds. These inflammatory compounds can lead to a variety of symptoms and even direct the patient's chemistry toward medical conditions.

An increase in inflammation can be driven by histamine reactions, and we know that histamine receptors are not just in the skin and lungs, but also in the brain, heart, kidneys, GI tract and uterus. This explains why histamine and allergies can have a wide-reaching effect on virtually every organ system in the body. Again, 50% of the time when an allergen causes a symptom, there is no positive IgE response. It is important to characterize the total immunologic response in order to help patients overcome their allergen and sensitivity symptoms and help them to improve their quality of life.

The immune system can react in a number of ways. Type I hypersensitivity is IgE driven, but another reaction known as Type II is IgG driven. Both parts of the immune system can be activated, so we can also mount an IgG response to foods. While an IgG response if not an allergy by definition, it still creates an inflammatory reaction to food and is known as a sensitivity response. It is different than an IgE response, in that the IgE reaction will result in symptoms immediately and can be anaphylactic, however the IgG mediated reactions will occur 3-72 hours later, in general. IgG will not create an anaphylactic response, but it upregulates on-going low-grade inflammation that can contribute to initiating symptoms or making many conditions worse.

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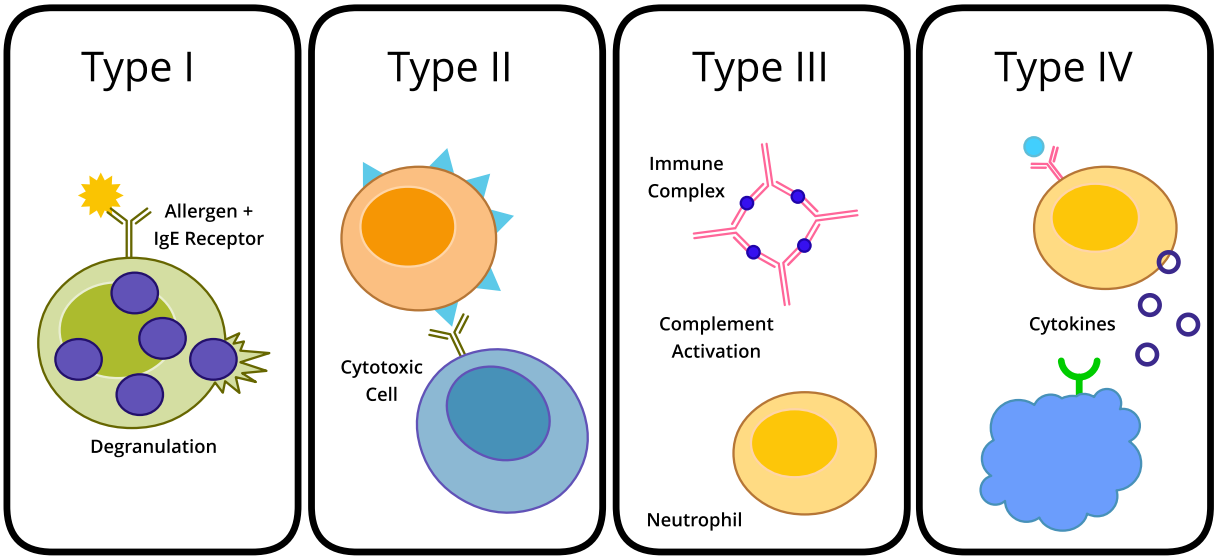
Type of Hypersensitivity Reactions



	Type I	Type II	Type III	Type IV
Mediators	IgE-Mediated	IgG or IgM Cytotoxic	Immune Complex Mediated	T-Cell Mediated
Onset	Within 1 Hour	Hours to Days	1-3 Weeks	Days to Weeks
Examples	Anaphylaxis	Hemolytic Anemia	Serum Sickness SLE	Rash SJS

Some practitioners dismiss IgG because IgG creates generalized inflammation and is not specific enough to consider. IgE reactions creates a smaller set of identifiable and in general immediate symptoms. IgG, because it increases inflammation, can make most underlying conditions worse. In essence, the value of IgG testing is that it helps determine another contributing factor to metabolic inflammation.

Because IgG can contribute to a wide set of symptoms, this type of reaction may be dismissed as nonspecific. However, medical literature does clearly identify the fact that those with higher IgG reactions to foods, are likely to have more symptoms than those who have less. Additionally, there are particular conditions that tend to have an increased of an IgG response, and it makes sense to consider these reactions as a part of a treatment plan in order to reduce total immune burden on those conditions that show consistent IgG elevation.

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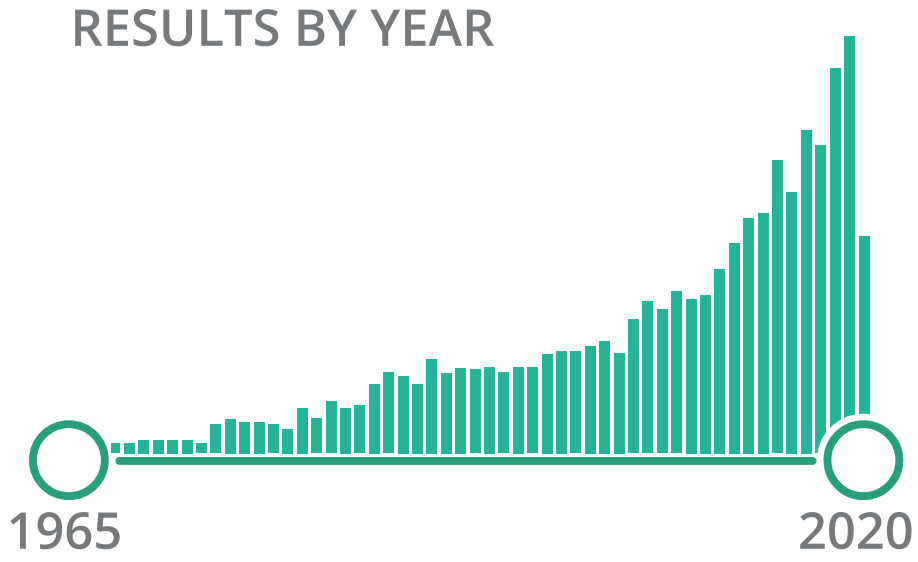
Critics say there is no data that supports the use of IgG in food reaction testing. Much of the evidence that is used to support that assumption is dated. Insurance companies for example, will often suggest that there is no association with IgG and pathology, but their references are generally from the 1980s or earlier. As our understanding of immunology improved so did our understanding of food reactions. Just like we learned that there was more than type I Hypersensitivity in response to infection, we learned that immune cross reactivity and heightened immune signaling that occurs in type I-IV Hypersensitivity. In Type II, IgG mediates a reaction, and just as our body mounts this response to infections, it can mount a similar response to foods. Type III and IV are also subsets of reactions driven by immune response in allergies and sensitivities. Current research has pointed to multiple examples of serum levels of IgG antibody testing to foods positively correlated to clinical symptom patterns and pathology.

The published evidence around IgG response is exploding, in 2019, there were over 400 publications around IgG reactions to foods. Whereas before 2000, there were generally around 100 publications a year. This demonstrates that our understanding of how IgG reacts to foods has grown enormously.



Graph from PubMed showing the increase in studies concerning IgG and reactions to foods.

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A study done in 2016 helps to confirm the role of IgG in unexplained symptoms as IgG was found elevated in patients presenting with allergic symptoms, but with no laboratory evidence of IgE antibodies. It was established that IgG was increased in patients with symptoms such as urticaria, typically believed to be mediated by IgE, compared to controls, demonstrating a role of IgG reactions in histaminergic reactions. They conclude that IgG antibodies play a role in allergic symptoms and should be measured when IgE is not present. [5] A number of studies show a connection between migraines and diet induced inflammation. [6] It has been increasingly identified that if patients who has migraines also has IBS, significant improvement is noted when IgG elimination style diets are utilized. This helps us to establish the connection between gut based inflammation and systemic symptoms. [7] IgG food reactions have been identified to be involved in ankylosing spondylitis, [8] abdominal pain, diarrhea, distention, stool shape and distress, [9] Non-celiac wheat sensitivity, [10] IBS, [11] IBD, [12 13 14 15 16] and Autism. [17]In Rheumatoid Arthritis, IgG antibodies to foods have been found in the synovial fluid at higher rates than in controls, demonstrating that IgG cross reactivity to food is involved in the autoimmune reaction in the joints. [18] IgG is also higher in atopic patients, but different subsets of IgG are higher depending on the food, again showing the importance of having measurements of multiple antibodies. [19]

Other connections that support the role of IgG being inflammatory are shown in a study in which subjects with diarrhea and constipation were measured for IgG antibodies to wheat and cereal. It was found that the group that higher levels of IgG also had higher levels of intraepithelial lymphocytes showing immune-inflammatory changes in the digestive tract, similar to levels seen in Celiac disease and Colitis. [20] While not diagnostic for Celiac disease, IgG antibodies have been shown to be increased in this condition, specifically IgG1 and IgG3, which is the majority of total IgG, with a decrease in IgG4. [21]

9. The value of eliminating foods according to food-specific immunoglobulin G antibodies in irritable bowel syndrome with diarrhoea. J Int Med Res. 2012;40(1):204-10.

10. Frequency of determining markers of casein's inhability and gluten in children with disorders of autistic spectrum Bavykina IA, Popov VI, Zvyagin AA, Bavykin DV. Vopr Pitan. 2019;88(4):41-47. doi:10.24411/0042-8833-2019-10040

11. Atkinson W, Sheldon TA, Shaath N, Whorwell PJ. Food elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial. Gut. 2004;53(10):1459-1464. doi:10.1136/gut.2003.037697

12. Cai C, Shen J, Zhao D, et al. Serological investigation of food specific immunoglobulin G antibodies in patients with inflammatory bowel diseases. PLoS One. 2014;9(11):e112154. Published 2014 Nov 13. doi:10.1371/journal.pone.0112154

13. Jian L, Anqi H, Gang L, et al. Food Exclusion Based on IgG Antibodies Alleviates Symptoms in Ulcerative Colitis: A Prospective Study. Inflamm Bowel Dis. 2018;24(9):1918-1925. doi:10.1093/ibd/izy110

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15. Treating Irritable Bowel" by Drisko, et al Journal of American Nutrition Vol. 25 #6 514-522 Pub. 2006

16. "Delayed Onset Food Allergies" by Melletis, C. and Barker, J. Alternative and Complementary Therapies, Pg. 61-65 April 2003

17. Bavykina IA, Popov VI, Zvyagin AA, Bavykin DV. Vopr Pitan. 2019;88(4):41-47. doi:10.24411/0042-8833-2019-10040

18. 2006 Sep;55(9):1240-7. Feb 16. The gut-joint axis: cross reactive food antibodies in rheumatoid arthritis

19. Morris ER, Hampton SM, Morgan JB. IgG subclasses to food proteins in atopic and normal individuals. Ann Nutr Metab. 1993;37(1):39-43. doi:10.1159/000177747

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21. Hvatum M, Scott H, Brandtzaeg P. Serum IgG subclass antibodies to a variety of food antigens in patients with coeliac disease. Gut. 1992;33(5):632-638.

Another issue health care providers have with IgG reactions, is that IgG subtypes behave differently, are distinct and therefore you cannot effectively evaluate them when they are measured as a total group. This is demonstrated in the study above, in which Celiac patients had an increase of IgG1 and 3 but a decrease in IgG4. Antibody activity is distinct, and it is best to measure IgG4 separately. There are four isotypes of IgG, IgG 1-4. The understanding of various antibody response has grown with the increase in published studies.

Previously, our understanding of IgG was limited, leading to some misconceptions in food antibody testing. It was initially noted, that when IgE was higher, often IgG4 would be high as well. Because it correlated with IgE to some degree, and more than the other isotypes such as IgG1-3, some began to suggest that IgG4 might be the best marker for tracking sensitivity. Some labs even began running IgG4 and touting it as a stand-alone marker of sensitivity. As our understanding of immunology expanded, if was found that IgG4 could be seen with IgE because it is a response to IgE. It is not an allergic response or sensitivity reaction, but it blocks the effect of IgE and create immune tolerance. In fact, desensitization injections or allergy therapy work by increasing IgG4 via IL-10 modulated response, creating tolerance.

Desensitization to mediators released from mast cells and basophils to allergen exposure is the first change initiated with allergen immunotherapy. The mechanism responsible for this desensitization has yet to be elucidated. As allergen dosing is increased in the course of immunotherapy, the next response is a change in T cell subset distribution with the generation of allergen specific T regulatory (T reg) cells and a decrease in Th2 cells. Repeated allergen exposure stimulates IL-10 and TGF-β expression by allergen-specific, inducible, type 1, peripheral T regulatory (Tr1) cells, which act in an autocrine fashion to further activate these Tr1 cells and initiate peripheral tolerance.

Finally, the late changes include decrease in IgE production by B cells and an increase in IgG4 and IgA serum levels. These changes are responsible for the clinical effect of ameliorating allergy symptoms. [22] Probiotics and omega-3 fatty acids have been reported to work through increasing IL-10, helping with immune tolerance. [23] [24] The activity of IgG4 is quite distinct. It is smaller in size, and more thiol bonds which allow it to adhere to IgE receptors, blocking the ability of IgE to bind resulting in decreased reactions to allergens. IgG4 creates immune tolerance. In general, having levels of IgG4 indicates a tolerance to an allergen, rather than a sensitivity. However, there is a class of IgG-RD or IgG related disease, and if someone has a condition related to excessive production of IgG4, clinically it makes sense to remove foods that are creating heightened IgG4 production to the food.

22. Understanding the Mechanism of Allergen Immunotherapy, Amber Luong, MD, PhD, https://med.uth.edu/orl/2009/02/05/understanding-mechanism-allergen-immunotherapy/

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There is discussion that production of IgG antibodies can be generated to anything eaten if the gut is permeable. However, this is not the case. While exposure to the food, and gut based permeability could increase your chances of having both IgG reactions as well as IgE reactions, it is not the only cause and food exposure is not predictive alone. In general, individuals do not have sensitivity reactions to everything they eat. There are genetic or environmental reasons that cause the immune system to become sensitive to a particular food. Outside of permeability, there is an increased chance of food reactions based on immune response in the Peyer's patches, part of the lymphatic system of the gut. If there is improper immune queuing, the body will begin to mount an immune response to a food, even in the absence of permeability. Permeability is an important factor, but only one factor determining whether or not sensitivity to specific foods develop. Testing becomes essential because you cannot isolate reactions merely from diet history. Removing foods that create an inflammatory response helps normalize reactions, in addition, gut based therapies can normalize the microbiome, improve sIgA and reduce permeability is additionally helpful.

As stated, IgE will only have a positive titer 50% of the time when there is a known reaction to food. Outside of IgE and even IgG, there are other ways the body can create symptoms to foods including:

- Increase release serotonin,
- Increases in platelet activating factor
- Could have lower levels of complement receptors on their RBCs that clear inflammatory reactions causing them to be more reactive.

No methodology exists for isolating these responses to foods, so even the most complete test cannot measure every type of reaction to food.

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It is important to measure antibodies together because they do not act in isolation. It is commonly taught that IgE is a Type I hypersensitivity, creating immediate symptoms, and that IgG is Type II hypersensitivity creating delayed sensitivities 3-72 hours later. While this is generally the case, there is also an interaction between IgE, IgG, complement, and even sIgA antibodies. For example, if there is enough IgG present, it can cause more immediate symptoms. IgG can cause an additive effect to IgE antibodies, increasing mast cell degranulation. [25] Both IgE and IgG will become more reactive when complement is present. Another difference between IgG 1-3 and IgG4 is that IgG4 does not readily bind to complement, and this causes it to be less inflammatory compared to other IgG antibodies. Measuring both IgG and complement together further fine tunes results. Complement can augment the effect of IgG 1000 to 10,000-fold so it is important to look at IgG and complement together. [26] If sIgA, that lines the gut is low, this too effects IgG and IgE titers. IgG and IgE specific to foods, will stay elevated for longer, as the body responds to its first level of defense, sIgA being low. IgG and IgE increase to compensate for sIgA deficiencies. [27] All antibodies play a role, and they can interact to have a synergistic effect. This certainly means, that when you see multiple types of immune response to a food or antigen, you are isolating the more inflammatory challenge to the patient. Measuring multiple antibody reactions allows for a more comprehensive picture allows for discovery of the most clinically important responses.

While there are different methods of food allergy and sensitivity testing available, the type that is most represented in the literature is IgE and IgG testing. By far, the bulk of the research is done in this area. This makes sense given, the major reason for pathology is immune confusion that is augmented with antibody production. Production of antibodies and presentation of antigen-antibody complex in the presence of complement is how inflammation is most typically created. Measuring antibody response is the most direct way of measuring an inflammatory response to foods. While other methods exist, such as a live cell analysis, there is little peer-reviewed data exists tying this type of inflammation to pathology.

There is extensive research connecting a number of different pathologies to an increase in IgG antibodies, and in the case of allergies, IgE antibodies. Complement is also well defined to drive inflammation and damage to tissue, whereas there is little data exists to show that as a white blood cell increases in size in response to a food there is also an association with various conditions. Immune challenges creates confusion in immune response and is best documented with various antibodies, IgE, IgG 1-3, IgG4 and complement, so the most comprehensive evaluation of food reactions, is one that looks at multiple facets of the immune system together.

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