Food Sensitivity Facts

The facts regarding food specific antibody testing leads to the conclusion that many commercial claims of laboratories are misleading:

- Elevated levels of IgG antibodies to foods do **NOT mean that a hidden or delayed reaction to food is detected**
- Food-specific IgG antibody levels do **NOT necessarily correlate with chronic symptoms**
- IgG antibodies do **NOT cause inflammation or a leaky gut**
- IgG blood tests do **NOT detect Type III hypersensitivities**
- Diets based on IgG levels to foods have **NOT been shown to successfully diminish symptoms**

The origin of the IgG story – scientific appearance and revision

In 1982, Fagan *et al.* observed in an experiment that the IgG antibody subclass 4 degranulated basophils *in vitro* (1). Basophils and mast cells, which are central to type 1 allergic reactions, 'degranulate' and release histamine and other chemicals when activated by IgE antibodies. These chemicals produce the symptoms of an allergic reaction. Because of Fagan *et al.* it was assumed that IgG antibodies degranulate basophils and that IgG reacts in humans just like IgE. However, this **experiment could never be replicated** (2).

This is the original reason why IgG antibodies became a popular and promising research topic and why some food intolerance tests look at IgG4 levels specifically.

Immunologists had accepted that IgG was not a direct cause of allergic reactions and IgG4 in particular was cleared of its alleged involvement in any allergy; still, the initial observation needed to be explained (3-5). In 1992, Lichtenstein *et al.* revisited Fagan's work and uncovered the reason why IgG had appeared to be a regain (6). It turned out that IgG did not degranulate the basophils directly. Using the blood of allergic donors, Lichtenstein showed that IgE antibodies had IgG antibodies attached to them and this IgG had hidden the IgE in earlier experiments- the IgG antibodies were anti-IgE antibodies. Hidden IgE antibodies are not uncommon; in certain tests, the presence of IgG anti-IgE antibodies can give the appearance of increased IgG levels and decreased IgE levels for the same allergen (7).

Functions of IgG antibodies: Protective Immunity and Tolerance

The IgG antibody class has several specialties:

- **protective immunity**, which refers to the immune system's ability to recognize and remove invaders like viruses (this is what keeps us from getting chicken pox twice),
- **supports tolerance**, when the immune system remembers to suppress its reaction to

a foreign substance or to the body itself (tolerance is why the majority of us can eat whatever we want without fear of an allergic reaction; in many cases we have regulatory T cells, which invoke several helpers to suppress the immune response- these include IgG antibodies (8).

The **most advanced scientific knowledge** points to the conclusion that **food-specific IgG antibodies** in our blood **indicate exposure and tolerance, not *in*-tolerance**, to those foods (9, 10).

Food-specific IgG antibody levels do NOT cause inflammation and do NOT correlate with chronic symptoms.

There are four subclasses of IgG (IgG1 through IgG4), each with different roles. We know that some IgG antibodies have pro-inflammatory effects while others are anti-inflammatory (11); however, the protective immune response involves a finely choreographed balance between these players, along with many other antibodies and cells. **Overall, IgG antibodies are necessary to keep our immune system in check, and singling out one type of IgG to conclude that IgG antibodies cause inflammation is a gross oversimplification – and just plain wrong.**

Everyone produces IgG antibodies to food. Even though food intolerance blood tests rank IgG antibody concentrations for various foods as low, medium, and high, there is actually no such thing as a 'correct' level. IgG concentrations vary from person to person and depend on diet – perhaps even on how one was fed as an infant (8).

IgG- Summary and Evaluation:

- **IgG4** are considered as a **physiological, protective response of the immune system (not pro-inflammatory) following exposure** to food components and therefore indicate a tolerance, not intolerance (9, 10, 12, 13).
- Some laboratories investigate the presence of IgG1-3 antibodies or total IgG titers against foods- but is this clinically useful?
- **The IgG subclasses 1-3 can play a role in facilitating phagocytosis**. IgG formation is antigen-dependent, with the aim of neutralization pathogenic components. However, this is only one possible immune pathway**. Nevertheless, it is the phagocyte (such as neutrophils), which initiate inflammation and release pro-inflammatory mediators – NOT the antibodies.**

Conclusion:

IgG test results allow no clear determination and there is no scientific evidence that food-specific IgG-antibodies are associated with a definite diagnostic correlation (9, 10, 12, 13).

IgG4	***False Positives**, since measurement of exposure / protection (unsuitable parameter)*
IgG1-3	***False Negatives**, since only one immune pathway can/might be detected*
Total IgG Titer	***False Positives and False Negatives**, since the subclasses fractions are not distinguished*

Testing of other antibodies for food intolerance

IgA antibodies

IgA deficiency in the general population is about 1 in 700 and has no symptoms associated with it. However, IgA antibodies are a valuable marker whether the immune status of a person is sufficient or not: a low total-IgA-level can indicate if the persons' immune system is compromised or indicate if an inflammatory process is taking place. But it cannot tell you if there is individual food intolerance or not.
Unfortunately, laboratories do not explain that they measure only the total IgA-titer and don't stimulate the individual foods with IgA antibodies.

Aside from this, IgA antibodies have a less important role in antigen neutralization and rare role in opsonization. These antibodies are mainly present in secretion of epithelia, in the gut and respiratory tract, body surfaces that rarely contain the complement and phagocytes (important for inflammatory reactions).

IgA1	***False Negatives**, since only one immune pathway can/might be detected*
IgA2	***False Negatives,** since only one immune pathway can/might be detected*
Total-IgA Titer	***False Negatives**, since only one immune pathway can/might be detected*

IgM antibodies

IgM antibodies, first produced antibody during immune response, play a rare role in antigen neutralization (because of low affinity to antigens), opsonization and do not bind to phagocytes. They act as an indicator of current infection but also can inhibit inflammatory reactions. Why would you analyze an antibody class, which, first, inhibits inflammation (when you want to detect the source of inflammation) and, second, has a low affinity to certain food antigens?

Taken together, some of the antibody classes are in involved in recognizing harmful antigens (!) through

- facilitated neutralization
- opsonization, or
- complement activation

…but **phagocytes (like neutrophils) initiate inflammatory reactions** and release pro-inflammatory mediators, not antibodies.

IgG cannot detect sensitivities – then, how can it determine between "raw versus cooked" foods?

Lately a bizarre commercial field of "allergy" and potential cross reactivity was introduced to the market. To support claims, self-serving papers that would never pass a peer review process have been published in magazines and put on websites. Facts are mixed to commercially promote cooked and raw food test substances and introduce a "revolutionary new test"! There is only little true scientific evidence up today, hence these statements and claims are commercial and therefore should be taken carefully. We know that heating certain foods may diminish somewhat their allergenicity, but that is the only scientific evidence that we have.

What they don't tell is that they use a standard IgG test. It was discussed above that the measurement of **protective IgG antibodies is a false parameter and cannot detect food sensitivities.**

Papers, discussing the antigenicity (not allergenicity) of heated versus raw of various food conclude that there is very little difference between them. The best examples come from allergy to shrimp or peanut. The symptoms manifest whether the item is cooked or raw.

Although the structure of proteins may be modified by cooking food above 118F (protein denaturation), there is no data in the medical literature regarding the changes if food is boiled, broiled, baked, fried, or microwaved changes the protein in the same way or not or if it is from then on stable, which seems unlikely. To add to this, we do not know if cooking it to 130F, 140F, 150F, etc. changes the protein more or not. So, cooking the food essentially removes fat, and it is more important to check for the raw protein content which remains stable. Food antigens are not necessarily destroyed via heating (some food antigens might have increased allergenicity) but there is no uniform standard regarding allergenicity or antigenicity of cooked/modified foods.

According to the FDA and scientific literature it is not useful at all: "[…] Variable patient responses make it are allergic to a certain food item, knowing about potential cross reactivity is very important. A positive type 1 allergy test (skin test or blood test detecting IgE antibodies) can result, although the patient might be only allergic to the respective cross-reactive food.

difficult to conclude that a particular processing or cooking procedure affects allergenicity in all cases." (FDA, 07/2015). Nowak-Wegrzyn and Fiocchi state that "Heating and other methods of food processing have different effects on food allergens, even those contained in the same complex food. Structural homology does not reliably predict the effect of processing on allergenicity, and individual food allergens have to be tested. Interactions with other proteins, fat, and carbohydrates in the food matrix are complex and poorly understood." (14).

What about testing cross-reactive foods?

Cross reactivity means when the protein structure of one food item mimics that of another. Therefore the immune system recognizes them as the same. If you

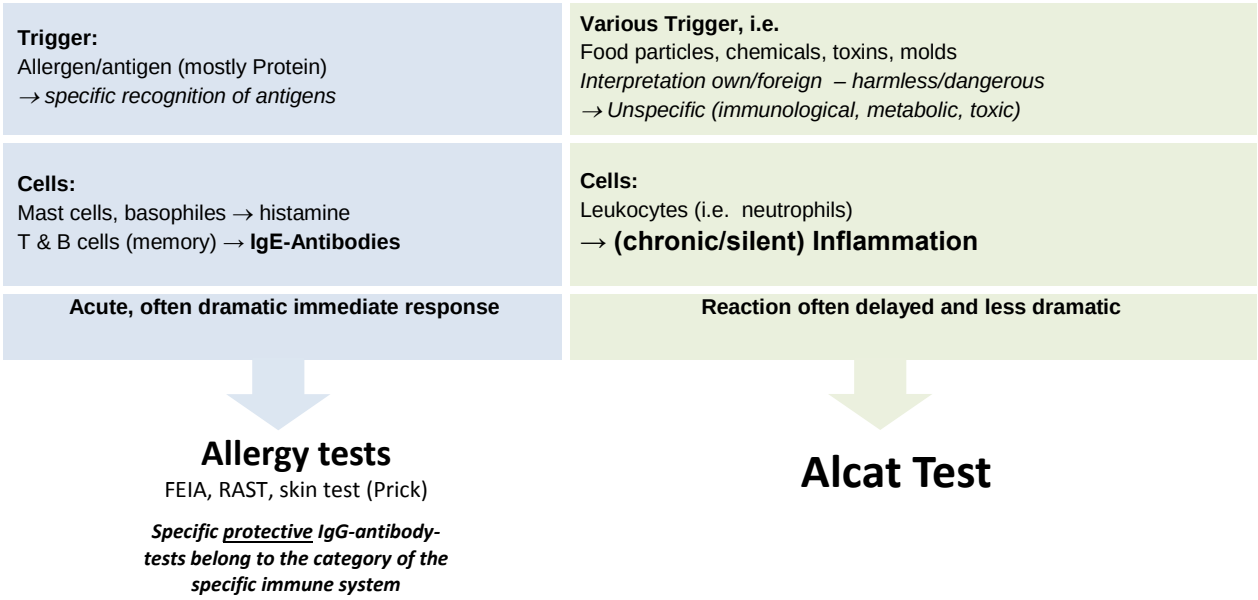
IgG antibodies do not detect food sensitivities; hence cross reactivity is a misleading claim in this context.

Other false premises and limitations of IgG and other antibody testing

1) **It is also unlikely that the adaptive/specific immune system recognizes antigens (mainly proteins) can detect fat, carbohydrates or other macromolecules.** Only the innate immune system could more likely detect other compounds such as artificial food colorings, preservatives, environmental chemicals and medications and produce an adverse reaction through initiating inflammatory reactions.

Table: Comparison of immunological reactions of Allergy and Intolerance

Food Allergy	Food/Chemical Sensitivity
Reaction of… Specific immune system	**Reaction** mostly **of…** Nonspecific/innate immune system



2) Brostoff and Gamlin (15) point out: *"**Given that the most common sources of food intolerance are wheat and milk, such therapists can achieve a reasonable success rate by diagnosing sensitivity to these two foods in all their patients. If eggs, oranges, chocolate, tea, and coffee are added to the list, they may well achieve success with 50% or more, and some patients will benefit from the placebo effect alone".*** And in 2001 a survey of UK residents, who had taken the YorkTest IgG blood test, only about 50% saw significant improvement in symptoms after eliminating their reported foods (16).

   So it seems that common sense would have about a 50% chance of finding at least some of the relevant foods for people who, we assume, actually have a food sensitivity. That's the same odds as flipping a coin – any blood test would certainly need to do better than that.

3) **It cannot be said that diets based on IgG antibodies to foods have been shown to successfully diminish symptoms.** Some studies found no benefit (17), while others saw mild effectiveness (18). Atkinson *et al.* found out that a group of IBS sufferers that received the test diet saw a 26% improvement in symptoms over the group that received the control diet (18). However, while the test and control diets were both problematic, the most significant problem came from the control diet: most participants had high IgG levels antibodies to wheat and milk, so the test diets ended up being wheat-free and milk-free while the control diets generally contained these foods. This difference between the diets is significant because wheat and milk are known to aggravate IBS. Was the control group accidentally sabotaged by being given unfriendly foods? Experimental flaws aside, it is also worthwhile to get a sense of just what a "26% improvement in symptoms" means for an IBS study.

Summary IgG testing

In order to prove that food-specific IgG antibodies cause delayed reactions and chronic symptoms, one fundamental question would need to be answered: *"Do high levels of IgG against a food predict an adverse reaction to that food" (19).* In debunking the myths used to justify food intolerance blood tests, we have seen that there is no research that has provided a positive

answer to that question. **The evidence actually points to there being no association between IgG antibodies to foods and adverse reactions, making IgG blood tests for foods useless.**

Some might personalize the argument against IgG-mediated food reactions and see it as dismissing their symptoms or delayed reactions in general. This is not true. The issue here is whether IgG blood tests are worth 500 to 1000 USD and the inconvenience, risk, and expense of modifying one's diet – all possibly for nothing or for less improvement than could have been gained using a proper elimination diet and food challenges.

Remember that elimination diets and food challenges are already reliable means of diagnosing food sensitivities, even though spending a month or so tracking and testing your diet may not seem as attractive as a single blood test. Fortunately, the diet investigation process is not a shot in the dark – an experienced doctor or dietitian can use your personal history and your own suspicions to guide you through the process. Even though testing companies use rhetoric about 'hidden food intolerances,' there is usually nothing 'hidden' about food sensitivities at all.

But how can real food sensitivities be identifies?

ALCAT TEST: Advantages & Disadvantages of Cellular Testing for Food Intolerance

The Gold Standard for identifying food intolerance is the oral provocation test. Accordingly, the only alternative is an immunological blood test, which measures the effect of food substances on precisely those immune parameters that are responsible for the effector function.

The **Alcat Test**, a cell activation test, which detects when leukocytes react to foods, reliably identifies potentially harmful foods or xenobiotics by measuring the cellular changes of neutrophils, the first effector cells of innate immunity that initiates inflammatory reactions. In this way, the overall effect on various complex immune mechanisms and interactions involved in an intolerance reaction on blood cells can be detected.

The complex cell-cell communication and signaling within the total leukocyte population is therefore maintained, whereas the IgG test uses serum, which does not contain cellular components.

The innate immune system recognizes antigen-independent via various receptors for a wide range of substances (endogenous/exogenous). **Therefore, the Alcat Test is not limited to food testing. It can identify cellular changes caused by food ingredients (including protein and carbohydrate structures), as well as by chemical substances (organic and inorganic compounds).**

Fell and Brostoff conducted double-blind studies to test the clinical validity of the Alcat Test. Their findings showed that the average correlation between the Alcat Test and double blind oral challenge was 83.4% (20). In addition, they came to the conclusion that the Alcat Test can be used to develop a diet program for patients suffering from a wide range of symptoms due to food sensitivities.

The Alcat Test provides accurate and consistent results on what might causing inflammations and show reliable correlation to symptoms – no matter whether eaten raw or cooked.

References:

1) Fagan DL, Slaughter CA, Capra JD, Sullivan TJ. Monoclonal antibodies to immunoglobulin G4 induce histamine release from human basophils in vitro. J Allergy Clin Immunol. 1982 Nov;70(5):399–404.
2) Hamilton RG. Relevance of (IgG anti-IgE)-IgE complexes, IgG subclass and modern IgG antibody autoanalyzers in the dying IgG reagin story. Allergy. 2009 Feb;64(2):317–8.
3) Van der Zee JS, Aalberse RC. The role of IgG in immediate-type hypersensitivity. Eur Respir J Suppl. 1991 Apr;13:91s–96s.
4) Shakib F, Smith SJ. In vitro basophil histamine-releasing activity of circulating IgG1 and IgG4 autoanti-IgE antibodies from asthma patients and the demonstration that anti-IgE modulates allergen-induced basophil activation. Clin Exp Allergy. 1994 Mar;24(3):270–5.
5) Aalberse RC, Van Milligen F, Tan KY, Stapel SO. Allergen-specific IgG4 in atopic disease. Allergy. 1993 Nov;48(8):559–69.
6) Lichtenstein LM, Kagey-Sobotka A, White JM, Hamilton RG. Anti-human IgG causes basophil histamine release by acting on IgG-IgE complexes bound to IgE receptors. J Immunol. 1992 Jun 15;148(12):3929–36.
7) Jensen-Jarolim E, de Weck AL, Stadler BM. Are allergen-specific IgG mainly IgG anti-IgE autoantibodies? Int Arch Allergy Appl Immunol. 1991;94(1-4):102–3.
8) Akdis CA, Akdis M. Mechanisms of allergen-specific immunotherapy. Journal of Allergy and Clinical Immunology. 2011 Jan;127(1):18–27.
9) Stapel SO, Asero R, Ballmer-Weber BK, Knol EF, Strobel S, Vieths S, et al. Testing for IgG4 against foods is not recommended as a diagnostic tool: EAACI Task Force Report. Allergy. 2008;63(7):793–6.
10) Tomicić S, Norrman G, Fälth-Magnusson K, Jenmalm MC, Devenney I, Böttcher MF. High levels of IgG4 antibodies to foods during infancy are associated with tolerance to corresponding foods later in life. Pediatr Allergy Immunol. 2009 Feb;20(1):35-41.
11) Collins AM, Jackson KJL. A Temporal Model of Human IgE and IgG Antibody Function. Front Immunol [Internet]. 2013 Aug 9 [cited 2014 Feb 24];4.
12) Jenkins M, Vickers A. Unreliability of IgE/IgG4 antibody testing as a diagnostic tool in food Intolerance. Clin Exp Allergy. 1998 Dec;28(12):1526-9.
13) Antico A, Pagani M, Vescovi PP, Bonadonna P, Senna G. Food-specific IgG4 lack diagnostic value in adult patients with chronic urticarial and other suspected allergy skin symptoms. Int Arch Allergy Immunol. 2011;155(1):52-6.
14) Nowak-Wegrzyn A, Fiocchi A. Rare, medium, or well done? The effect of heating and food matrix on food protein allergenicity. Curr Opin Allergy Clin Immunol. 2009 Jun;9(3):234-7.
15) Brostoff J, Gamlin L. Food Allergies and Food Intolerance: The Complete Guide to Their Identification and Treatment. Inner Traditions/Bear; 2000. 486 p.
16) Sheldon TA. Audit of the York Nutritional Laboratory Survey. Townsend Letter for Doctors and Patients [Internet]. [cited 2014 Mar 4];2002(August/September).
17) Mitchell N, Hewitt CE, Jayakody S, Islam M, Adamson J, Watt I, et al. Randomised controlled trial of food elimination diet based on IgG antibodies for the prevention of migraine like headaches. Nutr J. 2011 Aug 11;10:85.
18) Atkinson W, Sheldon TA, Shaath N, Whorwell PJ. Food elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial. Gut. 2004 Oct;53(10):1459–64.
19) Hunter JO. Food elimination in IBS: the case for IgG testing remains doubtful. Gut. 2005 Aug;54(8):1203.
20) Fell P, Brostoff J, Pasula MJ. High Correlation of the Alcat Test Results with Double Blind Challenge (DBC) in Food Sensitivity, in 45th Annual Congress of the American College of Allergy and Immunology1988, Annals of Allergy: Los Angeles.
21) FoodConnections.org – Food intolerance resource with a scientific twist