

## Overview

Food is obviously the foundation of nutrition and its quality and quantity will determine how healthy or how sick an individual will be. But what happens when one has an adverse reaction to the very thing they require to live? Basically, an adverse reaction to food appears to be either toxic (e.g. food poisoning) or non-toxic. A non-toxic adverse reaction takes one of three forms: Food allergy, food intolerance, or food sensitivity.<sup>1</sup>

Food allergy is mediated by IgE antibodies (specific adaptive immunity) and may be so severe as to be life threatening (e.g. anaphylactic shock). This type of reaction is considered a “classic allergy” or “type 1 hypersensitivity reaction.”

Food intolerance refers to an inability to metabolize, digest, or absorb a food component (e.g. lactose intolerance due to lack of lactase enzyme). A pathophysiological food intolerance does not involve the immune system. Food intolerance symptoms tend to be confined to the GI tract (gas, bloating, abdominal distension).

Food sensitivity is currently defined as an adverse reaction to a food that is not due to an IgE-mediated reaction or a metabolic deficiency. It does, however, appear to involve an immune inflammatory reaction that may be local or systemic. Food sensitivities may also be referred to as delayed food hypersensitivities or even “hidden food allergies.”<sup>2</sup>

For simplification, consider that food intolerance refers to non-immune based reactions while food sensitivity refers to immune- based reactions that are non-IgE mediated. The terms food intolerance and food sensitivity have been used interchangeably in the past so don't be surprised if you feel bewildered. Also keep in mind that some food sensitivity symptoms may mimic food allergy, so it is important to rule out IgE-mediated food allergies when assessing for sensitivities.<sup>3</sup>

This FYI focuses on food sensitivity testing and

the most current research behind available testing methods. It does not address food intolerance or food allergy.

## Associated Content

An adverse reaction to a food is often noticed because of the distressing nature of the symptoms, especially those that are gastrointestinal (GI) neurological, respiratory, or dermatological in nature. See “Signs and symptoms of food sensitivities.”

Food sensitivity symptoms often involve the GI tract but can also be systemic. Related symptoms may be delayed and can occur hours or even days after exposure, making the primary “trigger” difficult to identify. In addition, “biochemical individuality” can influence how one reacts to a certain food or food component. This individuality may be influenced over time by many factors including the health of the gastrointestinal tract; the diversity of the GI microbiome; stress and psychological factors; physical activity; and even hormonal changes.<sup>8</sup>

An overburdened immune system can contribute to an “overreaction” of the immune system and can manifest as food sensitivities. This phenomenon is known as toxicant-induced loss of tolerance (TILT). In effect, TILT is due to an “overloaded” immune system, a phenomenon that can occur when a certain threshold of exposure to toxins, chemicals, radiation, etc. has been surpassed. The immune system then becomes dysfunctional and loses tolerance to seemingly harmless compounds including foods.<sup>9</sup>

Sensitization to foods may manifest as a “true” food allergy which is mediated by IgE antibodies from the adaptive/specific immune system. However, food components can also activate the innate/non-specific immune system without the involvement of antibodies. Activation of the innate system triggers a series of immune mechanisms, especially inflammation. Non-celiac gluten sensitivity is believed to be such an innate immune response.<sup>10 11</sup>

## Signs and Symptoms of Food Sensitivities <sup>4 5 6</sup>

### Cognitive/Neurological

Ataxia  
Autism spectrum disorders (ASDs)  
Behavioral problems  
Disorganized or disturbed thinking and feeling  
Headaches, migraines  
Memory and concentration disturbances  
Peripheral neuropathy  
Psychological disturbances (anxiety, depression, panic attacks)

### Gastrointestinal

Abdominal pain  
Bloating  
Constipation  
Diarrhea, loose stools  
Heartburn  
Indigestion  
Nausea  
Vomiting

### Musculoskeletal, joints, muscles, connective tissue

Arthritis  
Inflammatory myopathies, myelopathies  
Joint discomfort, pain, stiffness, swelling  
Musculoskeletal discomfort

### Respiratory

Food-induced bronchitis and asthma  
Sneezing

### Skin

Dryness  
Itching  
Rashes  
Redness  
Scaling (as in eczema or psoriasis)  
Swelling  
Thickening

### Systemic

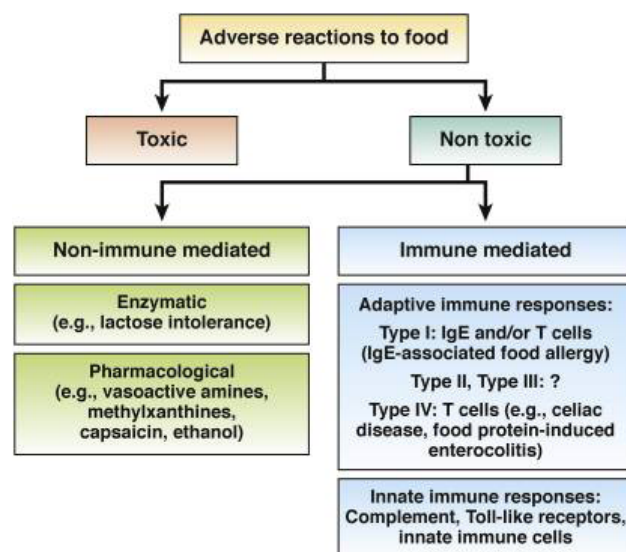
Chills  
Fatigue  
Fever  
Sweating  
Weakness  
Reduced exertional tolerance

“Clinically, complex health conditions without known cause are often found to improve by treating food sensitivities.”<sup>7</sup>

The innate immune system may become chronically activated as it functions as a “first responder” to a perceived threat. Innate immune cells, primarily neutrophils, release a cascade of pro-inflammatory mediators and reactive oxygen species that can contribute to chronic inflammation, cell dysfunction, and tissue damage.<sup>12 13</sup> Underlying “silent” inflammation can contribute to the multitude of symptoms associated with food sensitivity. The innate immune system can also recruit the adaptive system, compounding and magnifying food and chemical-related reactions.

The clinical imperative in food sensitivity testing is recognizing an immune inflammatory response and identifying which foods/compounds are actually causing that response.

Testing for food sensitivities has become increasingly popular for assisting individuals in the identification and elimination of food and chemical triggers. This brings us to the question of which test is best for reliably identifying food sensitivity triggers?



**Fig. 21-1. Classification of Food Intolerance.** Valenta R, Hochwallner H, Linhart B, Pahr S. Food allergies: the basics. *Gastroenterology*. 2015 May;148(6):1120-31. e4. doi: 10.1053/j.gastro.2015.02.006. Epub 2015 Feb 11. Review. PubMed PMID: 25680669; PubMed Central PMCID: PMC4414527. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4414527/>

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## Types of Food Sensitivity Testing

Currently, the most popular food sensitivity testing includes IgG immunoglobulin testing, leukocyte activation testing, and mediator release testing. Other testing may be available such as complement antigen testing, ELISA ACT lymphocyte response testing, and applied kinesiology. These tests are less common and less researched, and will not be covered here.

### IgG Antibody Testing

Immunoglobulin testing for food sensitivities measures IgG antibodies using the Enzyme Linked Immunosorbent Assay (ELISA) method. While some testing measures total IgG (IgG1, IgG2, IgG3, and IgG4), the IgG4 is appears to be the antibody that is associated with food exposure. Although testing may detect the presence of food-specific IgG4, it does not assess for or measure a pathological process.

Early research presumed that IgG antibodies were pathological and would trigger an adverse reaction and cause symptoms upon food exposure. Some research appeared to correlate symptoms with the presence of serum IgG.<sup>14 15 16 17</sup> However, the most contemporary research suggests that the presence of food-specific IgG antibodies may indicate not only exposure but tolerance to a particular food.<sup>18 19</sup> In fact, IgG4 antibodies may be protective and actually help sustain tolerance to a food or compound.<sup>20 21 22</sup> Antibodies of the IgG class may even serve to “block” negative effects of IgE antibodies, further serving a protective role versus a pathogenic role.<sup>23 24</sup>

Expert committees of international scientific societies do not recommend the use of IgG antibody testing for the detection of food allergies or food sensitivities.<sup>25</sup>

### The European Academy of Allergology and Clinical Immunology (EACCI):

- Titrating IgG4 against foods is not recommended as a diagnostic tool as IgG4 indicates repeated exposure to a food and is considered a marker of immune tolerance associated with the activity of regulatory T cells.
- “Specific IgG4 antibodies do not indicate food allergy or intolerance but a physiological response to the exposure to food.”

### The International Consensus ON (ICON) document on food allergy (EAACI, American Academy of Allergy, Asthma & Immunology (AAAAI), and World Allergy Organization (WAO):

- Emphasizes that the titration of specific IgG against foods is not a recommended test in the diagnosis of food allergy.

### 2014 Food Allergy Guidelines prepared by experts from American Academy of Allergy, Asthma & Immunology (AAAAI), American College of Allergy, Asthma & Immunology (ACAAI), Joint Council of Allergy, Asthma & Immunology (JCAAI)

- State that titration of allergen-specific IgG and IgG4 is not recommended in the diagnosis of non-IgE-mediated food allergies.

**Yale University** research supports leukocyte activation testing as a screening tool to identify foods and compounds that cause the immune inflammatory reactions associated with food sensitivity.

### **Leukocyte activation testing provides foundation for individualized dietary plans effective in IBS.**

Patients with irritable bowel syndrome demonstrated significant improvements when they eliminated foods that tested as severely reactive on leukocyte activation testing. Symptom reduction correlated with a decrease in plasma elastase. Elastase, an inflammatory compound widely distributed in innate immune cells, can damage tissue, disrupt tight junctions, and potentially contribute to increased intestinal permeability.

-Ali A, Weiss TR, McKee D, Scherban A, Khan S, Fields MR, Apollo D, Mehal WZ. Efficacy of individualised diets in patients with irritable bowel syndrome: a randomised controlled trial. *BMJ Open Gastroenterol.* 2017 Sep 20;4(1):e000164. doi: 10.1136/bmjgast-2017-000164. eCollection 2017. PubMed PMID: 29018540; PubMed Central PMCID: PMC5628288. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5628288/>

Online presentation of study results: <https://livestream.com/cellscience/events/7935391/videos/166053245>

### **Leukocyte Activation Testing**

Leukocyte (white blood cell) activation testing identifies and measures immune cell responses to foods and other ingested compounds.

White blood cells (e.g. neutrophils which are most abundant, macrophages/monocytes, eosinophils, basophils, and lymphocytes) release a variety of pro-inflammatory mediators that cause the local and systemic symptoms of food and chemical sensitivity. When white blood cells are stimulated/activated by an offending trigger, they undergo measurable changes which can then be measured by leukocyte activation testing.

During testing, white blood cells from a patient sample are exposed to a wide array of extracts (foods, herbs, spices, chemicals, additives, etc.) while changes at the cellular level are recorded and measured. The testing utilizes impedance cytometry to detect cellular changes such as:

- Increase in cell volume (production of mediators, loss of segmentation)
- Decrease in cell volume (degranulation, initiation of apoptosis)
- Decrease in cell number (apoptosis, necrosis, pyroptosis, NETosis, cell burst, ejection of cell contents)

Remember, the immune cell response is designed to neutralize and eliminate threats such as pathogens, damaged proteins and DNA, cellular debris, etc. It is a potent reaction and can effectively rid the body of intruders and potentially damaging compounds. However, a

chronically activated or imbalanced immune system can mount a damaging response to seemingly harmless foods or food components. Leukocyte activation testing has a long history of clinical use, Early research, documented in professional medical presentations, correlated test outcomes with double-blind challenge results, providing early objective validation of this testing method.<sup>26 27 28 29 30</sup>

A widening base of research correlates leukocyte activation results with biomarkers indicative of an immune inflammatory response, perhaps providing the long sought-after “smoking gun” underlying food sensitivities.<sup>31 32 33</sup>

A comprehensive program will include elimination and controlled reintroduction of immune inflammatory triggers. If sensitivity to a food or compound persists (e.g. non-celiac gluten sensitivity), then lifelong elimination of that food or substance should be maintained.

### **Mediator Release Testing**

Mediator release testing for food sensitivities measures volumetric changes around white blood cells that occur when cells are exposed to a variety of substances. Mediator release testing

Is based on the premise that volumetric changes around immune cells reflect inflammatory activity. This method combines flow cytometry technology with an impedance-based “Ribbon Method.” Published clinical research is limited for this method.

## **Commercial Food Sensitivity Testing**

### **IgG Antibody Testing**

Alletess Medical Laboratory

<https://foodallergy.com/tests/available-tests/>

Cyrex Laboratories

<https://www.cyrexlabs.com/>

<https://www.cyrexlabs.com/PatientHome/tabid/129/Default.aspx>

EverlyWell [https://www.everlywell.com/products/food-sensitivity/?gclid=Cj0KCQiAus\\_QBRDgARIsAIRGNGicM7wr6rg1Tejg4B0IUqylgXMpyIm6rSScYsblDww5qJw6JuCPCZwaAiSIEALw\\_wcB](https://www.everlywell.com/products/food-sensitivity/?gclid=Cj0KCQiAus_QBRDgARIsAIRGNGicM7wr6rg1Tejg4B0IUqylgXMpyIm6rSScYsblDww5qJw6JuCPCZwaAiSIEALw_wcB)

Genova Diagnostics IgG

<https://www.gdx.net/product/igg-food-antibodies-food-sensitivity-test-blood>

HEMOCODE

<https://www.hemocode.com/>

Immuno Labs

<http://www.immunolabs.com/patients/products/>

<http://www.betterhealthusa.com/public/282.cfm>

KBMO FIT

<https://kbmodiagnostics.com/>

Meridan Valley Lab

<http://meridianvalleylab.com/igg-food-allergy-testing>

Pinnertest

[https://pinnertest.com/?gclid=Cj0KCQiAus\\_QBRDgARIsAIRGNGjeopGdG0paCXYH3IK8tXk0G63UhmRsOco3emZIm\\_utDIWGymAH7TlaAswuEALw\\_wcB](https://pinnertest.com/?gclid=Cj0KCQiAus_QBRDgARIsAIRGNGjeopGdG0paCXYH3IK8tXk0G63UhmRsOco3emZIm_utDIWGymAH7TlaAswuEALw_wcB)

[https://pinnertest.com/?gclid=Cj0KCQiAus\\_QBRDgARIsAIRGNGjeopGdG0paCXYH3IK8tXk0G63UhmRsOco3emZIm\\_utDIWGymAH7TlaAswuEALw\\_wcB](https://pinnertest.com/?gclid=Cj0KCQiAus_QBRDgARIsAIRGNGjeopGdG0paCXYH3IK8tXk0G63UhmRsOco3emZIm_utDIWGymAH7TlaAswuEALw_wcB)

York

<http://www.yorktest.com/usa/index.html>

### **Leukocyte Activation Testing**

Cell Science Systems Alcat Test <https://cellsciencesystems.com/>

### **Mediator Release Testing**

Oxford Biomedical Technologies, MRT®, LEAP program <http://nowleap.com/>

### **Other**

Delayed Food Allergy Test Complement Antigen Testing.

<http://www.foodallergytest.com/programTest.html>

<http://www.foodallergytest.com/technology.html>

LRA (Lymphocyte Response Assay) by ELISA/ACT™

<https://www.elisaact.com/>

## Takeaways for Practitioners

Practitioners should maintain awareness that chronic immune inflammatory activity may be responsible for a wide variety of symptoms including those that affect gastrointestinal, neurological, musculoskeletal, and integumentary systems. When this underlying chronic inflammation is related to ingested food or chemicals, triggers should be identified and eliminated.

- A variety of testing for food sensitivities is available commercially. The most current and compelling research supports leukocyte activation testing for identification of specific food and chemical triggers.
- Although popular, IgG food sensitivity is not considered a diagnostic tool and may simply reflect exposure and tolerance, not a potential pathogenic trigger.
- Remember that food sensitivity testing does NOT test for IgE-mediated hypersensitivity reactions and will not detect an IgE-mediated food allergy.
- When food sensitivity symptoms are identified and even once triggers are being eliminated, remember to counsel the patient on an anti-inflammatory diet<sup>34 35</sup> high in:
  - Omega-3 fatty acids
    - Especially wild-caught cold-water fish, flaxseeds, chia seeds, hemp seeds, organic canola oil
  - Vegetables and fruits
    - Especially dark leafy greens, cruciferous vegetables, onions, tomatoes, avocados, berries, cherries, purple grapes, pomegranates, and citrus fruits
  - Herbs and spices
    - Especially turmeric, chili powder, saffron, ginger, garlic, parsley, sage, dill, basil, rosemary, oregano, bay leaf, caraway, anise, fennel, black pepper, lemongrass, mint, clove, coriander, cinnamon, nutmeg
  - Other
    - Cocoa, green and black tea, nuts and seeds (especially almonds, cashews, Brazil nuts, walnuts, pumpkin seeds, sunflower seeds, and sesame seeds)
  - Minimize or eliminate processed foods, commercial baked goods, commercial sweets, soda, trans fats, pesticide exposure/residues

## Foundational Resources

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