

**RESULTS: DRIED BLOOD SPOT TEST**

Accession #: 100035489 • Patient: JOHN SMITH

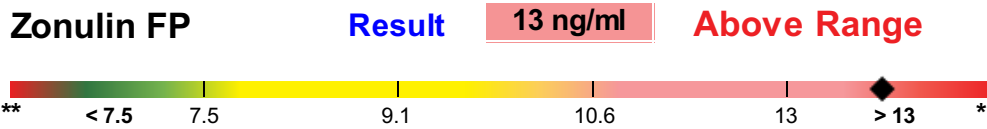
**Patient:** JOHN SMITH**Sex:** Male**Age:** 25 yr**Date of Birth:** 1998-05-14**Accession #:** 100035489

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**Health Care Professional:** Jane Smith

Sample collection: 2023-07-30

**ZONULIN FAMILY PEPTIDES (ZONULIN FP)**

\*The reference range represents a quintile distribution, each quintile being 20 % of a population determined from archival data.

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**GENERAL COMMENTARY Zonulin Family Peptides (Zonulin FP)**

The comments provided here are for educational purposes only. The results in this report should not be interpreted as diagnostic, nor should they be viewed as treatment recommendations. Those decisions are the responsibility of the health care professional. Moreover, the reference ranges shown in this report are derived from a normal distribution of results, that encompass 95% of randomly selected individuals in a population (see below).

The FLUIDS iQ Zonulin FP test, which uses the most advanced, polyclonal antibody immunoassay developed to date, is our test for Permeability. By its design, this test measures pre- haptoglobin 2 (see below), known as Zonulin, as well as other very closely related peptides implicated in intestinal permeability.

**Zonulin**

Zonulin is a protein found in intestinal cells, with production and release mimicking the effect of certain bacterial toxins on the tight junctions of the small intestine. Zonulin, and a small family of closely related peptides, bind to specific receptors only on the apical (luminal) surface of the intestinal epithelia and trigger a cascade of biochemical processes that induces tight junction (TJ) disassembly and a subsequent permeability increase of the intestinal epithelia.<sup>1</sup> This is often referred to as “leaky gut”.

Intestinal permeability changes due to Zonulin have been implicated in many diseases and dysfunction, notably in Celiac Disease and Type I Diabetes, but also in others including the brain, respiratory system and skin.

The gluten glycoprotein,  $\alpha$ -gliadin, can activate Zonulin signaling, irrespective of the genetic expression of autoimmunity. This generates a two-way response: Not only can fluid exit, but intestinal contents are able to gain entry in the opposite direction, into the bloodstream. This gliadin-Zonulin ‘leakage’ effect is longer and more pronounced (up to 5-fold greater) in the enterocytes, or intestinal cells, of people with Celiac Disease (CD).<sup>2</sup>

When intestinal tissue is taken from CDs in remission and from non-CD controls with digestive complaints, results show that CDs may produce up to 30 times as much Zonulin as non-CDs and have a three-fold greater intestinal permeability, even though the non-CDs are eating diets containing gluten, while the CDs have been gluten free for over two years.<sup>3</sup>

This strongly suggests that something besides gluten may be contributing to permeability changes in people with celiac disease. It may be that certain types of intestinal dysbiosis (improper balance of bacteria and yeasts in the intestines) prime genetically susceptible individuals to develop CD in response to gluten. In addition, many people who suffer from CD also suffer from other autoimmune disorders. Increased levels of Zonulin are implicated in corticosteroid use, as well as the pathogenesis of insulin dependent diabetes (type 1) and juvenile nonalcoholic fatty liver disease. There is also evidence of its implication in multiple sclerosis, rheumatoid arthritis, skin diseases, as well as inflammatory bowel disease and obesity.<sup>4,5</sup>

Zonulin also plays an important role in permeability changes in the brain, working as a gatekeeper, not only in the intestine, but also at the blood brain barrier (BBB). This is clearly in evidence when there is an intake of foods containing the  $\alpha$ -gliadin or similar proteins. The resulting high Zonulin levels leads to disassembly of the TJs in the vascular epithelium, permitting many molecules, including toxins, to slip through the BBB and resulting in activation of a cerebral inflammatory response.

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The resulting symptoms may include anxiety, depression, brain fog, slow mental processing, and emotional disturbances. Over time, this chronic inflammation may progress to neurodegenerative conditions such as dementia, Alzheimer's, and Parkinson's disease.<sup>6</sup>

Zonulin is also involved in the regulation of airway and lung permeability through its action on the TJs of the respiratory epithelial and/or endothelial barriers. This can be seen in Asthma, a complex clinical syndrome characterized by airflow obstruction, airway hyper responsiveness, and inflammation. Increased intestinal permeability in asthmatics may play a role in their susceptibility to environmental allergens. Serum Zonulin levels are high in a subset of subjects affected by Asthma, with 40% of asthmatic patients exhibiting increased intestinal permeability. This suggests that, besides inhalation, an alternative route for the presentation of specific antigens or irritants may occur through the gastrointestinal mucosal immune system, following their intercellular passage through the TJs.<sup>3</sup>

The effect of Zonulin is also evident in lung infections, including Acute Lung Injury (ALI). The role of Zonulin in ALI links the regulation of permeability with the inflammatory response through direct activation of the complement system.<sup>7</sup>

### Why Test for Zonulin FP?

Zonulin plays a pivotal role in the control of the tight junctions of the small intestine. As mentioned above, increased Zonulin levels are seen in many conditions and diseases associated with increased intestinal inflammation, with changes in permeability preceding clinical manifestations by up to a year.<sup>8,9</sup> For that reason Zonulin is gaining acceptance as a non-invasive marker of intestinal wall integrity and developing disorders.

Values smaller than 7.5 are considered as Optimal (green). If there are gut issues, they are not sufficient to have an effect on gut permeability.

However, this changes with values smaller than 1 (red), since extremely low levels of zonulin play a role in gut dysfunction

Values between 7.5 and 10.6 are Borderline (yellow-orange). The effects of gut inflammation, often caused by a combination of dysbiosis and enzyme imbalances, are beginning to have an effect on permeability.

Values greater than 10.6 are considered as Elevated (red). Within this red portion of the range one may find individuals showing signs and symptoms of enzyme deficiencies, dysbiosis, acute or chronic inflammatory disease and those with established autoimmune disorders.

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**References**

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