Differentiating Gluten-Related Disorders Through Diagnostic Methods

Stefano Guandalini, MD
Professor and Chief, Section of Pediatric Gastroenterology, Hepatology and Nutrition, University of Chicago
Director of the University of Chicago Celiac Disease Center, Chicago, IL

Alessio Fasano, MD
Professor of Pediatrics, Harvard Medical School
W. Allan Walker Chair of Pediatric Gastroenterology and Nutrition
Chief of the Division of Pediatric Gastroenterology and Nutrition
Director of the Mucosal Immunology and Biology Research Center
MassGeneral Hospital for Children
Gluten sensitivity
Also called: gluten intolerance

Usually self-diagnosed

Symptoms can include bloating, diarrhea, abdominal pain, tiredness, and skin rashes.

People may experience:

- **Pain areas**: in the abdomen or joints
- **Gastrointestinal**: bloating, diarrhea, fat in stool, heartburn, nausea, or flatulence
- **Also common**: anxiety, cramping, fatigue, mouth ulcer, skin rash, or weight loss

Consult a doctor for medical advice

**Sources**: Mayo Clinic and others. Learn more

Download PDF
The Controversy on Who Should Be on a GFD

Only People With Celiac Disease

Everybody
Sales of GFD Products in the US

<table>
<thead>
<tr>
<th>Year</th>
<th>Actual (million)</th>
<th>Forecast (million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>$11,609</td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td></td>
<td></td>
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<tr>
<td>2015</td>
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<tr>
<td>2016</td>
<td></td>
<td></td>
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<tr>
<td>2017</td>
<td></td>
<td></td>
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<tr>
<td>2018</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Best case (million)**: $31,228
- **Middle case (million)**: $21,701
- **Worst case (million)**: $14,175
How Many People in the US are Embracing a GFD

- Percentage of U.S. adults trying to cut down or avoid gluten in their diets reaches new high in 2013, Reports NPD

“I’m trying to cut back/avoid Gluten in my diet.”

Source: The NPD Group/Dieting Monitor, 52 week data year ending January 30, 2013
Want to Order Gluten-free Food at this Café?
Better Show Some Medical Proof
Because it is healthier
To lose weight
It resolved my GI symptoms
It resolved my extra-GI symptoms
Celiac disease

Approximately 50M
Approximately 24M
Approx 9M
Approx 7M
Approx 400,000

Based on internet interview users age 18y+ who eats GF food
Trends in the prevalence of total CD and undiagnosed CD from 2009 to 2014

Choung RS et al., *Mayo Clinic Proc* 2017
Trends

Trends in the prevalence of GFD in CD and in people without celiac disease avoiding gluten from 2009 to 2014

Choung RS et al., Mayo Clinic Proc 2017
The Gluten Free Diet: Not Only Celiac Disease

GLUTEN FREE DIET CONSUMERS

MEDICAL NECESSITY

WHEAT ALLERGY (IGE-MEDIATED) (~0.1%)

CELIAC DISEASE (AUTOIMMUNE-BASED) (~1%)

NON CELIAC GLUTEN (WHEAT) SENSITIVITY (INNATE IMMUNITY?) (?)

NO MEDICAL NECESSITY
Adverse Effects of Wheat Ingestion in Humans – Wheat Allergy

- Wheat Allergy
- Celiac Disease
- Non-Celiac Wheat Sensitivity
Wheat Allergy

• A hypersensitivity reaction to wheat proteins mediated through immune mechanisms and involving mast cell activation.

• The immune response can be IgE mediated, non-IgE mediated, or both.

• Most commonly a food allergy, but wheat can become a sensitizer when the exposure occurs through the skin or through the airways (Baker’s asthma)

Wheat Allergy

- IgE-mediated reactions to wheat albumin, globulin, α gliadin
- Some forms (eg EoE) may be IgE-mediated
- IgE-mediated reactions to ω-5 gliadin
- IgE-mediated reactions to ω-gliadin

Respiratory Allergy
- Asthma

Food Allergy
- GI manifestations

WDEIA
- Anaphylaxis

Contact Urticaria
- Skin lesions
Mr. Phillips

- 28 year old man, c/o watery eyes, itchy rash, occasional wheezing.
- Works at a bakery

Sounds like wheat allergy
Potential Testing Cascade

ImmunoCAP™ Complete Allergen

ImmunoCAP Allergen Components

- Tri a 14 (f433)*
  - Lipid transfer Protein (LPT)
  - Risk for clinical reactions

- Gliadin (f98)
  - Contains α, β, Y and omega-5
  - Risk marker for systemic reactions
  - Marker for wheat allergy persistence

- Tri a 19 (f416)*
  - Omega-5-Gliadin
  - Risk marker for systemic reactions
  - Marker for wheat allergy persistence

Gliadin gives high sensitivity for detecting wheat food allergy while Tri a 19 provides higher specificity

*These assays are only available in the United States through Phadia immunology Reference Laboratory (PiRL) as Laboratory Developed Tests.
Adverse Effects of Wheat Ingestion in Humans – Celiac Disease

- Wheat Allergy
- Celiac Disease
- Non-Celiac Wheat Intolerance Syndrome
• An immune-mediated systemic disorder triggered by gluten and related prolamines in genetically susceptible individuals (HLA-DQ2 or HLA-DQ8 haplotypes)

• Characterized by:
  • Inflammatory Enteropathy of variable severity
  • A wide range of gastrointestinal and/or systemic complaints
  • CD-specific antibodies
Microscopic Images and Histology

(a) normal cytoarchitectonic villus-crypt and absorbent epithelium of the small intestine scanning electron microscopy (left) and histology (right. Emat.cos.80x)

(b) subtotal villous atrophy in scanning electron microscopy (left) associated with hyperplasia of the crypts (right. Emat.cos.x80)
### Clinical Presentations

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Duodenal Biopsy</th>
<th>Serology</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI manifestations</td>
<td>Villous Atrophy</td>
<td>Positive</td>
<td>Typical</td>
</tr>
<tr>
<td>Extra-GI manifestations</td>
<td>Villous Atrophy</td>
<td>Positive</td>
<td>Atypical</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>Villous Atrophy</td>
<td>Positive</td>
<td>Silent</td>
</tr>
<tr>
<td>Symptoms present or absent</td>
<td>Normal or only increased intraepithelial lymphocytes</td>
<td>Positive</td>
<td>Potential</td>
</tr>
</tbody>
</table>
Typical CD in Children: GI Presentations

- Diarrhea
- Vomiting
- Failure to thrive or weight loss
- Abdominal bloating/pain
- Constipation
Main “Atypical”: Extra-Intestinal

- Malnutrition Related
  - Short stature
  - Delayed puberty
  - Iron-deficient anemia resistant to oral Fe
- Recurrent stomatitis
- Liver and biliary tract disease
  - Autoimmune Liver Disease
  - Benign hypertransaminasemia
- Skin disorders
  - Dermatitis Herpetiformis
  - Alopecia Areata
- Osteopenia/Osteoporosis
- Arthritis/Arthralgia
- Neurological problems
  - Headache
  - Peripheral Neuropathy
  - Seizures with occipital calcifications
  - Gluten Ataxia
- Behavioral changes & psychiatric disorders
  - Poor mood
  - Anxiety
  - Depression
  - Women: sub-infertility
Asymptomatic children and adolescents at increased risk for CD such as:
- Type 1 diabetes mellitus (T1DM)
- Autoimmune thyroid disease
- Down syndrome
- Turner syndrome
- Williams syndrome
- Selective immunoglobulin A (IgA) deficiency
- Autoimmune liver disease
- First-degree relatives with CD (overall prevalence 8.1%, varying from 13% in sisters, daughters to 3% in parents)
• 12 year old boy with type 1 diabetes; previously tested negative for celiac, but somewhat stunted growth in past couple years, increased irritability, some abdominal pain.

Sounds like celiac
## Celiac-specific Antibodies

<table>
<thead>
<tr>
<th>Antibody Type</th>
<th>Positive likelihood ratio</th>
<th>Negative likelihood ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EMA / IgA</strong></td>
<td>31.8 (18.6 - 54.3)</td>
<td>0.067 (0.038 - 0.118)</td>
</tr>
<tr>
<td><strong>Anti-TG2 / IgA</strong></td>
<td>21.8 (12.9 - 36.8)</td>
<td>0.060 (0.040 - 0.090)</td>
</tr>
<tr>
<td><strong>Anti-DGP / IgG</strong></td>
<td>13.6 (8.1 - 22.8)</td>
<td>0.061 (0.017 - 0.221)</td>
</tr>
<tr>
<td><strong>Anti-DGP / IgA</strong></td>
<td>9.4 (6.8 - 13.1)</td>
<td>0.121 (0.072 - 0.203)</td>
</tr>
<tr>
<td><strong>AGA / IgA</strong></td>
<td>7.3 (4.5 - 11.8)</td>
<td>0.186 (0.095 - 0.362)</td>
</tr>
</tbody>
</table>

*EMA*: Endomysial Antibody  
*TG2*: anti transglutaminase-2  
*DGP*: anti-deamidated gliadin peptides  
*AGA*: anti-gliadin antibody
Assess for CD

**TTG-IgA**
- >10x normal

**TTG-IgA** and total IgA normal (*)

**TTG-IgA** elevated but <10x normal

**EMA**
- NOT CELIAC (NPV ~ 99%)

**CELIAC** (PPV 100%)

**EGD**
- Marsh 0-1
- Marsh 2-3

**FALSE POSITIVE**

**POTENTIAL CELIAC**

**CELIAC**

(*) if IgA-deficient: TTG-IgG or DGP-IgG normal

Adapted from NASPGHAN Clinical Guide for Pediatric Celiac Disease
However…

- All “adult” societies recommend biopsy confirmation of diagnosis of celiac disease
  - AGA
  - ACG
  - BSG
  - NICE

Am J Gastroenterol 108, 656-76 (2013)
Gut 63, 1210-28 (2014)
BMJ 351, h4513 (2015)*
Adverse Effects of Wheat Ingestion in Humans – Non-Celiac Wheat Sensitivity

- Wheat Allergy
- Celiac Disease
- Non-Celiac Wheat Sensitivity
12 Surprising Signs of Gluten Sensitivity

Psst! #5 & #6 will shock you.
Non-Celiac Wheat Sensitivity

- A poorly defined syndrome characterized by a variable combination of intestinal and extra-intestinal symptoms, typically occurring soon after the ingestion of gluten-containing foods and disappearing quickly upon their withdrawal, occurring in individuals where both CD and WA have been excluded.
NCWS: Definition

Cases of reaction to ingestion of wheat and possibly gluten-containing grains in which both allergic and autoimmune mechanisms have been ruled out (diagnosis by exclusion criteria)

- Triggered by the ingestion of gluten-containing grains
- Negative immuno-allergy tests to wheat
- Negative CD serology (EMA and/or tTG) and in which IgA deficiency has been ruled out
- Negative duodenal histopathology
- Possible presence of biomarkers of gluten immune-reaction (AGA+)
- Presence of clinical symptoms that can overlap with CD or wheat allergy symptomatology
- Resolution of the symptoms following implementation of a GFD and relapse after re-exposure to gluten-containing grains (double blind)

An Italian survey on 486 patients

Gastrointestinal symptoms

Extra-Gastrointestinal symptoms

Volta U et al., *BMC Medicine* 2014
### Clinical manifestations of NCWS

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Intestinal</th>
<th>Extra-intestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very Common</strong></td>
<td>Bloating</td>
<td>Lack of wellbeing</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>Tiredness</td>
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<tr>
<td></td>
<td>Diarrhea</td>
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<tr>
<td><strong>Common</strong></td>
<td>Epigastric pain</td>
<td>Anxiety</td>
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<tr>
<td></td>
<td>Nausea</td>
<td>Foggy mind</td>
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<td></td>
<td>Aerophagia</td>
<td>Numbness</td>
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<td></td>
<td>GER</td>
<td>Joint/muscle pain</td>
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<tr>
<td></td>
<td>Aphthous stomatitis</td>
<td>Skin rash/dermatitis</td>
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<tr>
<td></td>
<td>Alternating bowel habits</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td></td>
</tr>
<tr>
<td><strong>Undetermined</strong></td>
<td>Hematochezia</td>
<td>Weight loss</td>
</tr>
<tr>
<td></td>
<td>Anal fissures</td>
<td>Anemia</td>
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<tr>
<td></td>
<td></td>
<td>Loss of balance</td>
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<tr>
<td></td>
<td></td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rhinitis/asthma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight increase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Interstitial cystitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ingrown hairs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oligo or polimenorrhea</td>
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<tr>
<td></td>
<td></td>
<td>Sensory symptoms</td>
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<tr>
<td></td>
<td></td>
<td>Disturbed sleep pattern</td>
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<tr>
<td></td>
<td></td>
<td>Hallucinations</td>
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<tr>
<td></td>
<td></td>
<td>Mood swings</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Autism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Schizophrenia</td>
</tr>
</tbody>
</table>

The Salerno NCGS diagnostic criteria (Nutrients, 2015)
Open Questions

- Prevalence? (between 0.6-6%)
- Are children affected? (only 1 open-label paper published)
- Cause? (Gluten and/or other wheat components?)
- Pathophysiology? (Leaky gut? Innate/adaptive immunity?)
- Diagnosis? (No marker available)
- Complications? (Unknown)
- Treatment? (GFD or wheat-free diet? How strict? For how long?)
Open Questions

• Prevalence? (between 0.6-6%)
• Are children affected? (only 1 paper published)
• Cause? (Gluten and/or other wheat components?)
• Pathophysiology? (Leaky gut? Innate/adaptive immunity?)
• Natural history? (Permanent? Transient? Complications?)
• Diagnosis? (No marker available)
• Treatment? (GFD or wheat-free diet? How strict? For how long?)
Evidence for Gluten as Responsible for NCWS in IBS-type Adult Patients

- Di Sabatino et al., 2015: 5% of 59 pts
- Elli et al., 2016: 14% of 98 pts
- Zanini et al., 2016: 34% of 35 pts
- Weighted average: 9.8%
Antibodies to Native Gliadin in NCWS vs Celiac Disease (CD) and Healthy Controls

Both CD and NCWS pts had significantly higher levels of IgG, IgA and IgM AGA than healthy controls

- IgA AGA significantly higher in CD than in NCWS
- IgM AGA not significantly higher in NCWS than in CD and IgG AGA in CD than in NCWS

Uhde M et al. Gut 2016
Principal Component Analysis (PCA)

PCA score plot for the complete dataset of serological markers

- Anti-transglutaminase 2 (anti-TG2) IgA
- Anti-deamidated gliadin IgG and IgA
- Anti-gliadin IgG, IgA and IgM
- Lipopolysaccharide-binding protein (LBP)
- Soluble CD14 (sCD14)
- Endotoxin-core antibodies (EndoCAb) IgG, IgA and IgM
- Anti-flagellin IgG, IgA and IgM
- Fatty acid-binding protein 2 (FABP2) measured in healthy controls, patients with coeliac disease and individuals with non-celiac wheat intolerance syndrome (NCWS)
Other Potential Causes for NCWS: FODMAP

### COMMON FOODS CONTAINING FODMAPs

<table>
<thead>
<tr>
<th>EXCESS FRUCTOSE</th>
<th>LACTOSE</th>
<th>FRUCTANS</th>
<th>GALACTANS</th>
<th>POLYOLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fruits: apples, pears, nashi, mangoes, tinned fruit in natural juice, watermelon</td>
<td>Milk cow’s, goats’ and sheep’s milk, yoghurt, ice cream</td>
<td>Vegetables: artichokes, bok choy, carrots, celery, capers, chokos, choy sum, corn, eggplant, green beans, lettuce, chives, parsnips, pumpkins, silver beet, spring onions (green part only), tomatoes</td>
<td>Legumes: chickpeas, lentils, red kidney beans, baked beans</td>
<td>Fruits: apples, apricots, cherries, lychees, nashi, nectarines, pears, peaches, plums, prunes, watermelon</td>
</tr>
<tr>
<td>Sweeteners: fructose, high fructose corn syrup</td>
<td>Cereals: wheat and yew when eaten in large amounts (e.g. bread, pasta, couscous, crackers, biscuits)</td>
<td>Vegetables: avocados, mushrooms, sweeteners: sorbitol (420), mannitol (421), xylitol (967), maltitol (965), isomalt (953)</td>
<td></td>
<td>Cereals: watermelon, custard apples, persimmons</td>
</tr>
<tr>
<td>Large total fructose dose concentrated fruit sources, large servings of fruit, dried fruit, fruit juice</td>
<td>Cheese: soft and fresh (e.g. ricotta, cottage)</td>
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</tr>
<tr>
<td>Honey</td>
<td></td>
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</tr>
</tbody>
</table>

### SUITABLE ON A LOW-FODMAP DIET

<table>
<thead>
<tr>
<th>FRUIT</th>
<th>VEGETABLES</th>
<th>MILK PRODUCTS</th>
<th>GRAIN FOODS</th>
<th>OTHERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fruit: bananas, grapefruit, blueberries, grapes, honeydew melons, kiwifruit, lemons, limes, mandarins, oranges, pawpaw, passionfruit, tangelos, raspberries, rock-melons, strawberries, tangelos</td>
<td>Vegetables: bamboo shoots, bok choy, carrots, celery, capers, chokos, choy sum, corn, eggplant, green beans, lettuce, chives, parsnips, pumpkins, silver beet, spring onions (green part only), tomatoes</td>
<td>Milk: lactose-free, rice milk</td>
<td>Cereals: gluten-free bread, cereal products</td>
<td>Milk: lactose-free, rice milk</td>
</tr>
<tr>
<td>Rice</td>
<td>Ice-cream substitutes: gelato, sorbet</td>
<td>Rice: lactic acid</td>
<td>Ice-cream substitutes: gelato, sorbet</td>
<td>Ice-cream substitutes: gelato, sorbet</td>
</tr>
<tr>
<td>Oats</td>
<td>Butter substitutes: milk-free spread</td>
<td>Oats: carob, lentils</td>
<td>Butter substitutes: milk-free spread</td>
<td>Butter substitutes: milk-free spread</td>
</tr>
<tr>
<td>Polenta</td>
<td></td>
<td>Polenta: carob, lentils</td>
<td>Polenta: carob, lentils</td>
<td>Polenta: carob, lentils</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>FODMAP</th>
<th>Excess fructose</th>
<th>Lactose</th>
<th>Oligosaccharides (fructans and/or galactans)</th>
<th>Polyols</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Problem high FODMAP food source</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruits: apples, pears, nashi pears, clingstone peaches, mango, sugar snap peas, watermelon, tinned fruit in natural juice</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Honey</td>
<td></td>
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</tr>
<tr>
<td>Sweeteners: fructose, high fructose corn syrup</td>
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<tr>
<td><strong>Large total fructose dose:</strong> concentrated fruit sources; large serves of fruit, dried fruit, fruit juice</td>
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<tr>
<td><strong>Fruits:</strong></td>
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</tr>
<tr>
<td>Fruit: banana, blueberry, carambola, durian, grapefruit, grape, honeydew melon, kiwifruit, lemon, lime, mandarin, orange, passionfruit, paw paw, raspberry, rock melon, strawberry, tangelo.</td>
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<tr>
<td>Honey substitutes: maple syrup, golden syrup</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Sweeteners: any except polyols</td>
<td></td>
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<tr>
<td><strong>Suitable alternative low-FODMAP food source</strong></td>
<td></td>
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</tr>
<tr>
<td>Fruits: apples, pears, nashi pears, clingstone peaches, mango, sugar snap peas, watermelon, tinned fruit in natural juice</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Fruit: banana, blueberry, carambola, durian, grapefruit, grape, honeydew melon, kiwifruit, lemon, lime, mandarin, orange, passionfruit, paw paw, raspberry, rock melon, strawberry, tangelo.</td>
<td></td>
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</tr>
</tbody>
</table>

**Vegetables:** artichokes, asparagus, beetroot, Brussels sprout, broccoli, cabbage, fennel, garlic, leeks, okra, onions, peas, shallots.

**Cereals:** wheat & rye when eaten in large amounts (e.g. bread, pasta, couscous, crackers, biscuits)

**Legumes:** chickpeas, lentils, red kidney beans, baked beans

**Fruits:** watermelon, custard apple, white peaches, rambutan, persimmon

**Vegetables:** avocado, cauliflower, mushrooms, snow peas

**Sweeteners:** sorbitol(420), mannitol(421), xylitol(967), maltitol (965), isomalt (953) & others ending in ‘-ol’

**Fruits:** bananas, blueberry, carambola, durian, grapefruit, grape, honeydew melon, kiwifruit, lemon, lime, mandarin, orange, passionfruit, paw paw, raspberry, rock melon

**Sweeteners:** sugar (sucrose), glucose, other artificial sweeteners not ending in ‘-ol’

Definition of Food Reactions

(Consensus NIAID 2011)

- **Food intolerance** occurs when the body lacks a particular enzyme to digest nutrients, nutrients are too abundant to be completely digested, or a particular nutrient cannot be properly digested. Common examples are lactose intolerance, FODMAP intolerance, or lactulose intolerance (side effect of laxatives).

- **Food sensitivity**, an understudied area, are immune-mediated reaction to some nutrients and these reactions do not always occur in the same way when eating that particular nutrient.

- **Food allergy** is a very specific immune system response involving either the immunoglobulin E (IgE) antibody or T-cells. Both are immune system cells that react to a particular food protein, such as milk protein.
Pathogenesis Of IBS-Like Syndromes

Czaja-Bulsa G et al, Clin Nutr 2014
Other Potential Causes for NCWS

**Wheat Amylase-Trypsin Inhibitors (ATI)**

Zevallos VF et al., *Gastroenterology* 2017
Adverse Effects of Wheat Ingestion in Humans – Non-Celiac Wheat Sensitivity (cont’d)

- Wheat Allergy
- Celiac Disease
- Non-Celiac Wheat Sensitivity (still a mix bag)

- Gluten-sensitive (10%?)
- FODMAP-intolerant (40%?)
- Placebo effect (40%?)
- ATI-sensitive (5%?)
- Early stage celiac disease, wheat allergy (5%?)

True Non-Celiac Wheat Sensitivity
• 42 year old woman, who had headaches, foggy mind, some bloating, occasional abdominal pain. Much better when off wheat.

Sounds like NCWS
Diagnostic Algorithm for Suspected NCWS

Remember: NO biomarker!
The Diagnosis of NCWS

- **Self-diagnosis**
- **Elimination diagnosis**
- **Positive diagnosis**
  (clinical and DBPC test)
Proposed Algorithm for NCWS Diagnosis

Catassi C. et al. *Nutrients* 2015; 7:4966-77
Suspected NCWS (CD and WA excluded)

Patient on GFD for >1 month?

YES

Wheat exposure?

NO

No tests indicated No diagnosis possible

YES

Wheat for ≥ 3 months

NO

NCWS excluded

AGA-IgA, IgG

NO

NCWS confirmed

Symptoms recur?

YES

NO

NCWS excluded
Ms. Jones

• 25 year old lady, with c/o itching rash, headaches, bloating, nausea and occasional diarrhea when ingesting wheat foods

A wheat-related disorder, obviously. But… which one of the 3?
A Lab Approach to Generic Wheat-Related Disorders

- **TTG-IgA total IgA**
  - Positive: Follow CD algorithm
  - Consider challenge or wheat elimination
  - Negative: **Celiac excluded**
  - Negative: **Wheat allergy excluded**
  - Likely NCWS

- **f4**
  - Positive: Wheat sensitization confirmed
  - Consider challenge or wheat elimination
Thank you for your Attention Questions?