

# **Expert Updates in Celiac Disease and Gluten Intolerance**

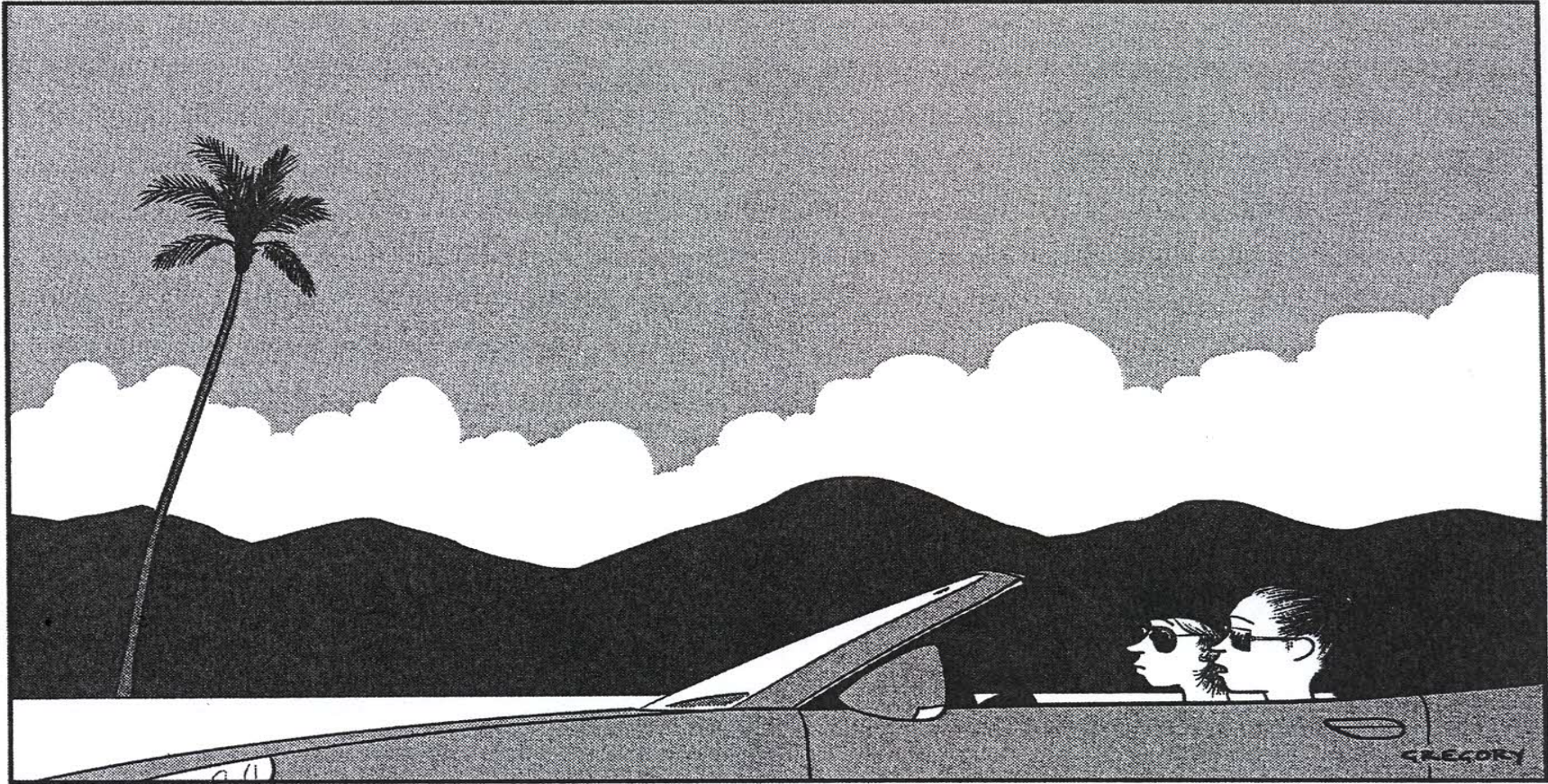
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# Definitions and Terminology

- **Celiac disease (CD)**: a chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals
- Other terms including celiac sprue, sprue, gluten intolerance and gluten-sensitive enteropathy **are no longer recommended**
- **Gluten sensitivity = gluten intolerance ~ NCGS**
- **Gluten** is a protein in many grains wheat, rye, triticale
- **Wheat starch** is the other key component of wheat



*“I have no idea what gluten is, either, but I’m avoiding it, just to be safe.”*



# Impact of Gluten-Free Eating

- The gluten-free (GF) market is expected to reach \$15 billion in annual sales by 2016<sup>1</sup>
- Portion of households reporting purchases of GF increased from 5% in 2010 to 11% in 2013<sup>1</sup>
- Common brands now available as GF
- Increase in labeling of foods as GF that are naturally GF from vodka, water, to meats and poultry
- The Onion reported in April 2014 “14% of Americans now intolerant to word “gluten”

*1. New York Times articles, Feb 17, 2014, Oct 6, 2014*



# Forms of Gluten Sensitivity?

## Oslo Definitions

**Gluten Sensitivity Due to Celiac Disease (CD)**

**A chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals**

**Non-Celiac Gluten Sensitivity (NCGS)**

**One or more immunological, morphological and/or symptomatic alterations triggered by gluten ingestion in individuals in whom celiac disease has been excluded**

# A Gluten-Sensitive Patient

- A 28 yr old woman comes to see me for food intolerances and gluten sensitivity. She reports abdominal bloating and discomfort after eating gluten containing foods, with abdominal cramping and loose stools ranging from 2 to 3 per day without blood for the past year. Symptoms are relieved by passage of stool. She also complains of fatigue.
- She went on a gluten free diet two months ago. She feels better but now finds that some other foods are also leading to bloating, pain and loose stools. She is concerned about food allergies and asks if she can be tested for celiac disease.

How can you tell the difference between celiac disease, non-celiac gluten sensitivity, IBS or some other disorder?

# Changing Prevalence of Celiac Disease

- Prevalence of up to ~1:100 in most genetically susceptible populations, 0.71% in NHANES study
- Less than 10-15% of current cases of CD have been diagnosed in the US
- CD is 4 to 4.5 times more prevalent than 50 yrs ago
- Cause of “CD epidemic” unknown
  - Dietary – grains with increased gluten, increased wheat in diets worldwide
  - Other environmental
  - Microbiota

*Fasano et al, Arch Int Med, 163:286, 2003*

*Rubio-Tapa et al, Gastroenterology, 137: 88, 2009*

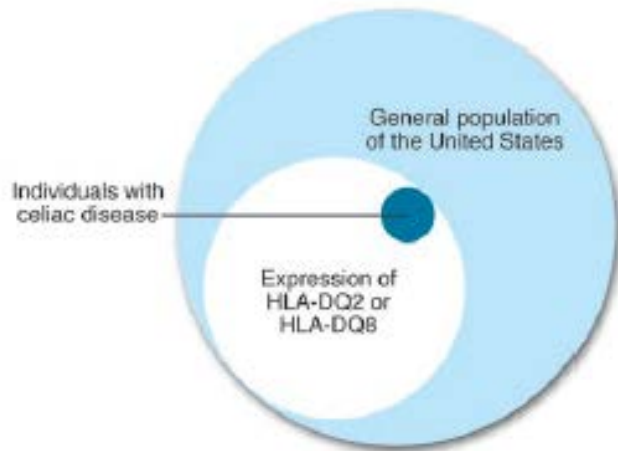
*AGA Technical Review, Gastroenterology, 131:1981, 2006*

*Virta et al, Scand J Gastroenterol, 44:933, 2009*

*Rubio-Tapia, Am J Gastroenterol, 2012*

# Who Develops Celiac Disease?

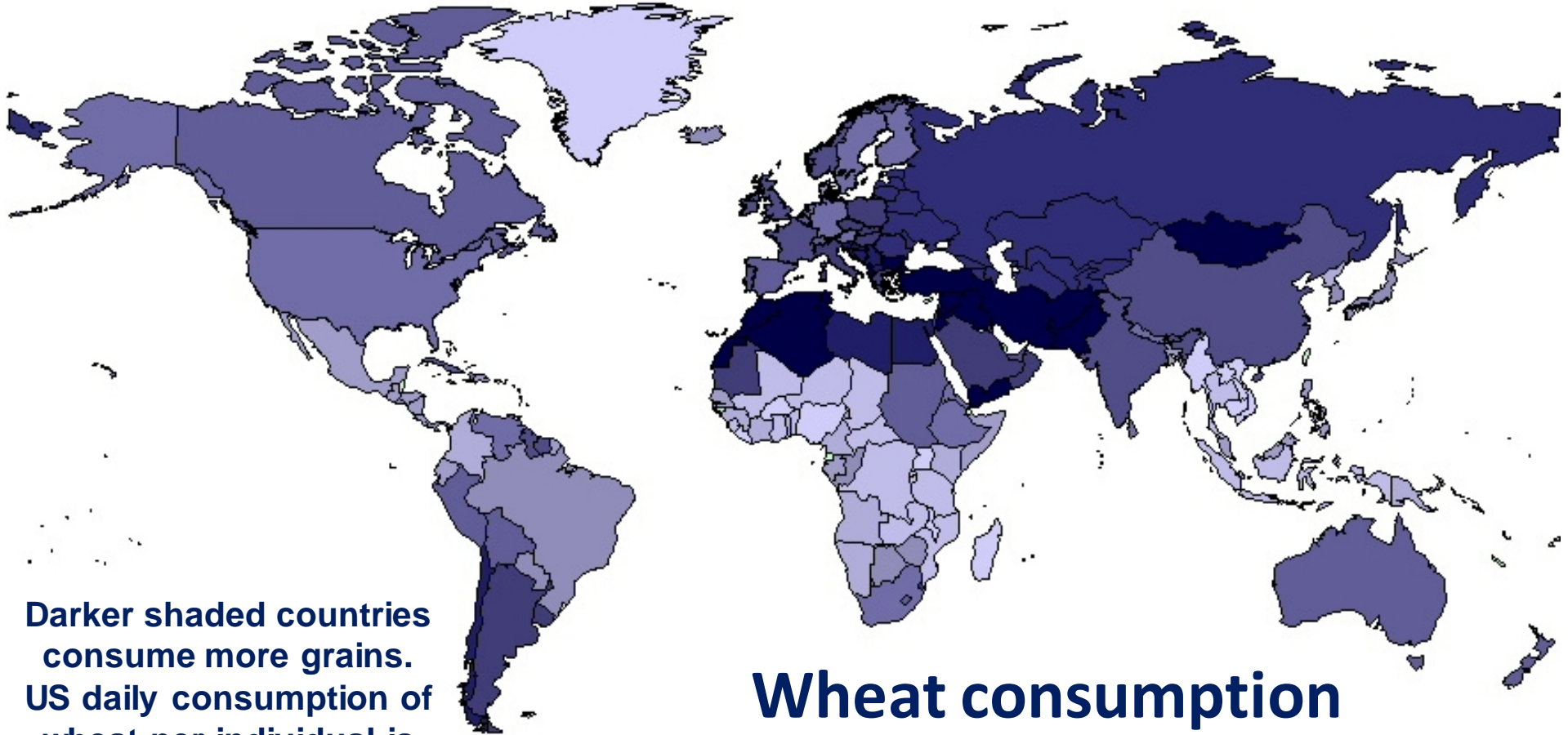
## Genetic and Other Factors



- 70% concordance in twins
- 10-15% prevalence in first degree relatives
- **Other genetic factors** - genes on chromosomes 5, 16, ?6
- GWAS have identified at least 26 celiac genetic risk variants
  - many contain immune-related genes controlling adaptive immune response
- **Environmental factors** - ? Infectious agents
  - Cytokines released during infection - Affecting APCs (e.g., dendritic cells)
  - Cross-reactive amino acid sequences - Adenovirus, *H. pylori*
- Increased frequency of **HLA haplotypes** - DR3-DQ2, DR5/7-DQ2, DR4-DQ8
- Other factors involved since most with these haplotypes do not get celiac disease (confer ~40% of risk)



# Risk Factors: The Grains

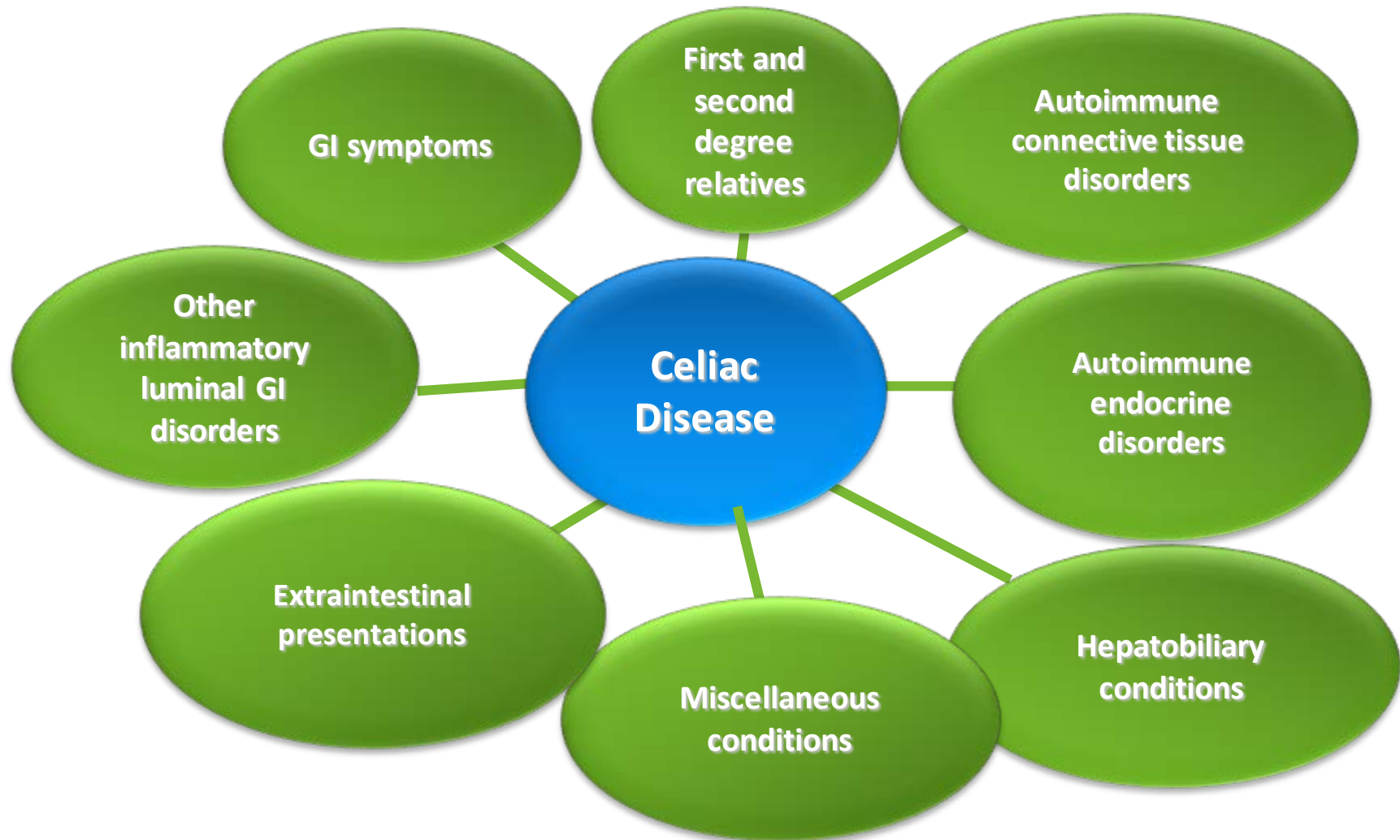


Darker shaded countries  
consume more grains.  
US daily consumption of  
wheat per individual is  
moderately high  
( $\approx$  24% to 32% of diet).

## Wheat consumption

*Adapted from Fasano A, Catassi C. Gastroenterology. 2001;120:636-651.*

# Symptoms and Conditions That Should Prompt Consideration of Celiac Disease



# Common Symptoms in Celiac Disease: Overlap with Irritable Bowel Syndrome

- Altered bowel habits
  - Diarrhea, constipation and mixed pattern
- Fatigue
- Borborygmi, flatulence
- Abdominal discomfort or pain
- Weight loss
  - However patients with CD can be overweight and even obese
- Abdominal distention or bloating
- Note that there are many other presentations of celiac disease including an asymptomatic state

*Niewinski MM. J Am Diet Assoc. 2008;108:661-672.*

*Presuttii JR et al. Am Fam Physician. 2007;76:1795-1802.*

*Green PHR JAMA. 2009;302(11):1225-1226.*

*Crowe, SE, In The Clinic : Celiac Disease, Ann Int Med, 154:ITC5-14, 2011*

# How to Approach Gluten Sensitivity

- Is the problem gluten, other components of grains (wheat starch), or unrelated?
- Determine what type of reactions the patient experiences after eating gluten – GI, cognitive, other
- Do other foods cause similar symptoms?
- Associated autoimmune or allergic disorders
- Family history of autoimmune diseases
- Are they eating gluten-free and for how long?

# Physiological Food Reactions

- Large volume meals (overeating) cause distension, promote regurgitation
- Fatty foods delay gastric emptying, alter motility
- Legumes, cruciferous vegetables, garlic, onions, etc, may lead to flatus (farts)
- Non-absorbable or poorly absorbed sugars and carbohydrates (FODMAPs) can cause diarrhea, bloating, flatulence, etc
- However, intestinal gas is **NORMAL** (up to 20 farts/day)

# Non-Celiac Gluten Sensitivity

- Not a new entity, reported in 1980<sup>1</sup>
- Prevalence unknown, probably greater than celiac disease but no data
  - Varies from 0.548% (NHANES) to 30% of US!!
  - Studies reporting prevalence reflect referral bias
- Currently no specific criteria or validated tests for diagnosing NCGS!! Requires double blind challenge
- Reported in association with allergic diseases<sup>2</sup>

1. Cooper, BT, et al, *Gastroenterol*, 79; 801, 1980

2. Massari, S, et al, *Ine Arch Allergy Immunol*, 155;389, 2011

3. Sabatino, AD & Corazzo, GR, *Ann Intern Med*, 156, 309: 2012



# Putative Mechanisms of NCGS

- Elevated AGA IgA, IgG (up to 50% +AGA IgG)<sup>1</sup>
- No specific HLA association
- Some studies suggest gluten may activate the innate immune system (IL-6, IFN- $\gamma$ , etc) in NCGS<sup>2</sup>
- Increased permeability, mucosal inflammation, basophil activation but not found in a recent study<sup>3</sup>
- Other proposed mechanisms include immune complex, autoimmune, microbiota, wheat amylase trypsin inhibitors<sup>4</sup>, toxicity, false neurotransmitters, leaky gut....

1. Volta, U et al, *J Clin Gastroenterol*, 46: 680, 2012

2. Sabatino, AD & Corazzo, GR, *Ann Intern Med*, 156: 309, 2012

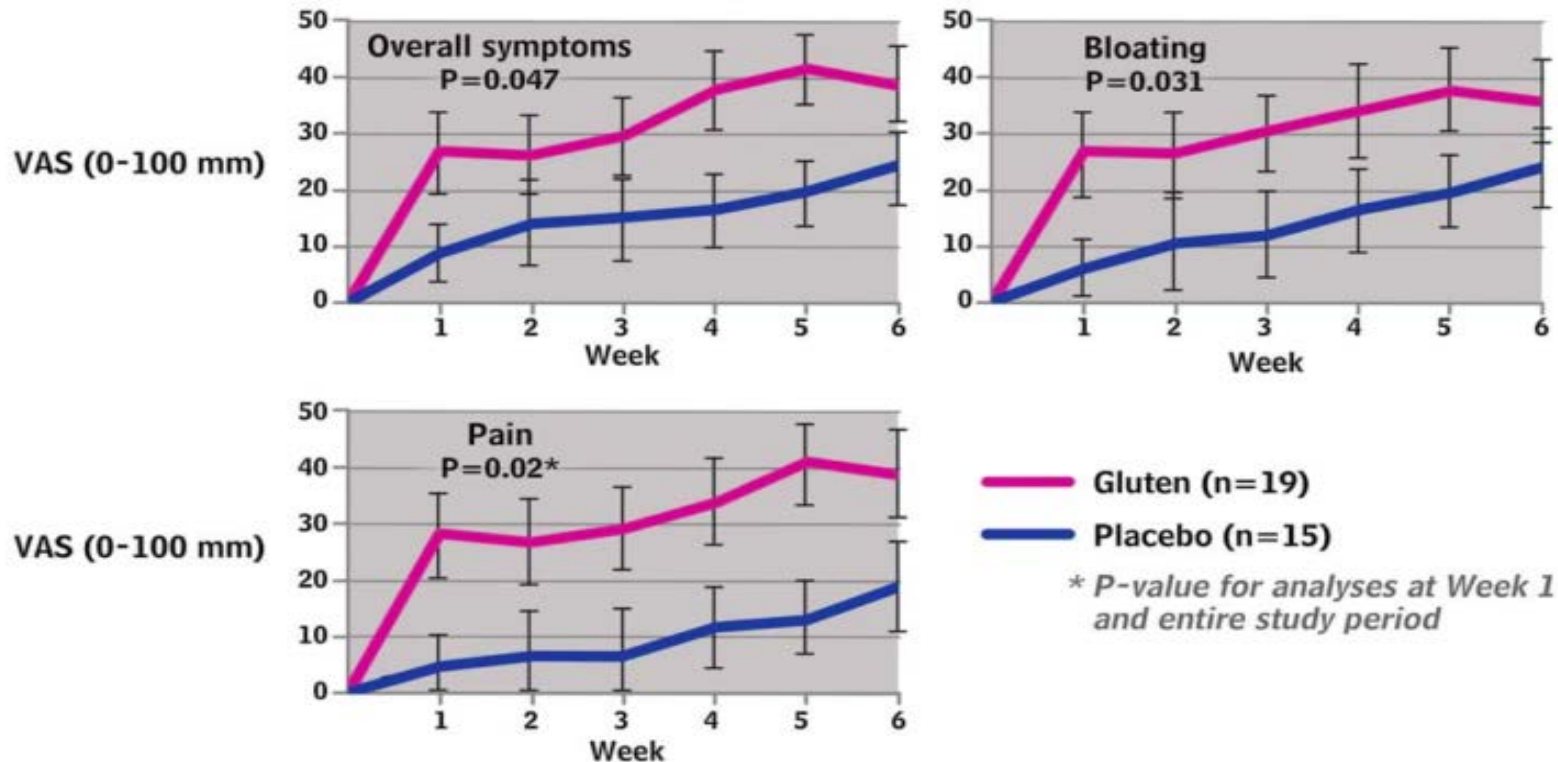
3. Bucci C, et al, *Clin Gastro Hepatol*, in press

4. Junker, Y et al, *J Exp Med*, 209: 2395, 2013

# Gluten Causes Symptoms in IBS Patients Without Celiac Disease

## Gluten Causes Symptoms in IBS Patients Without Celiac Disease

### Mean change in symptoms over 6 weeks



Adapted from Biesiekierski JR, et al. *Am J Gastroenterol*, Jan. 11, 2011 [Epub ahead of print]

# Adverse Reactions to FODMAPs

## Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols

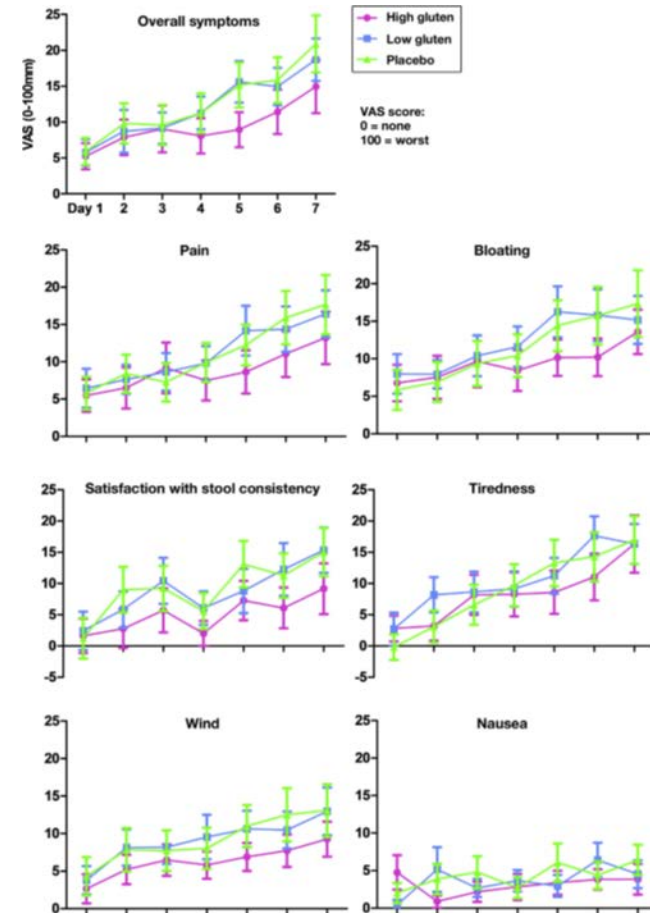
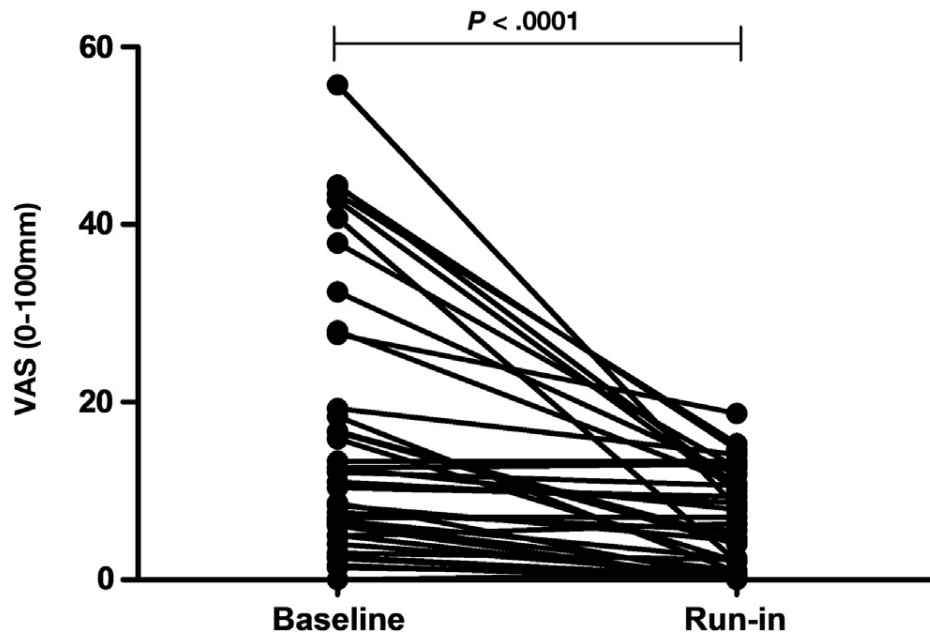
- Fructose and fructans
- Sorbitol
- Sucrose
- Lactose

Many foods (grains including wheat starch, fruits, vegetables) contain FODMAPs

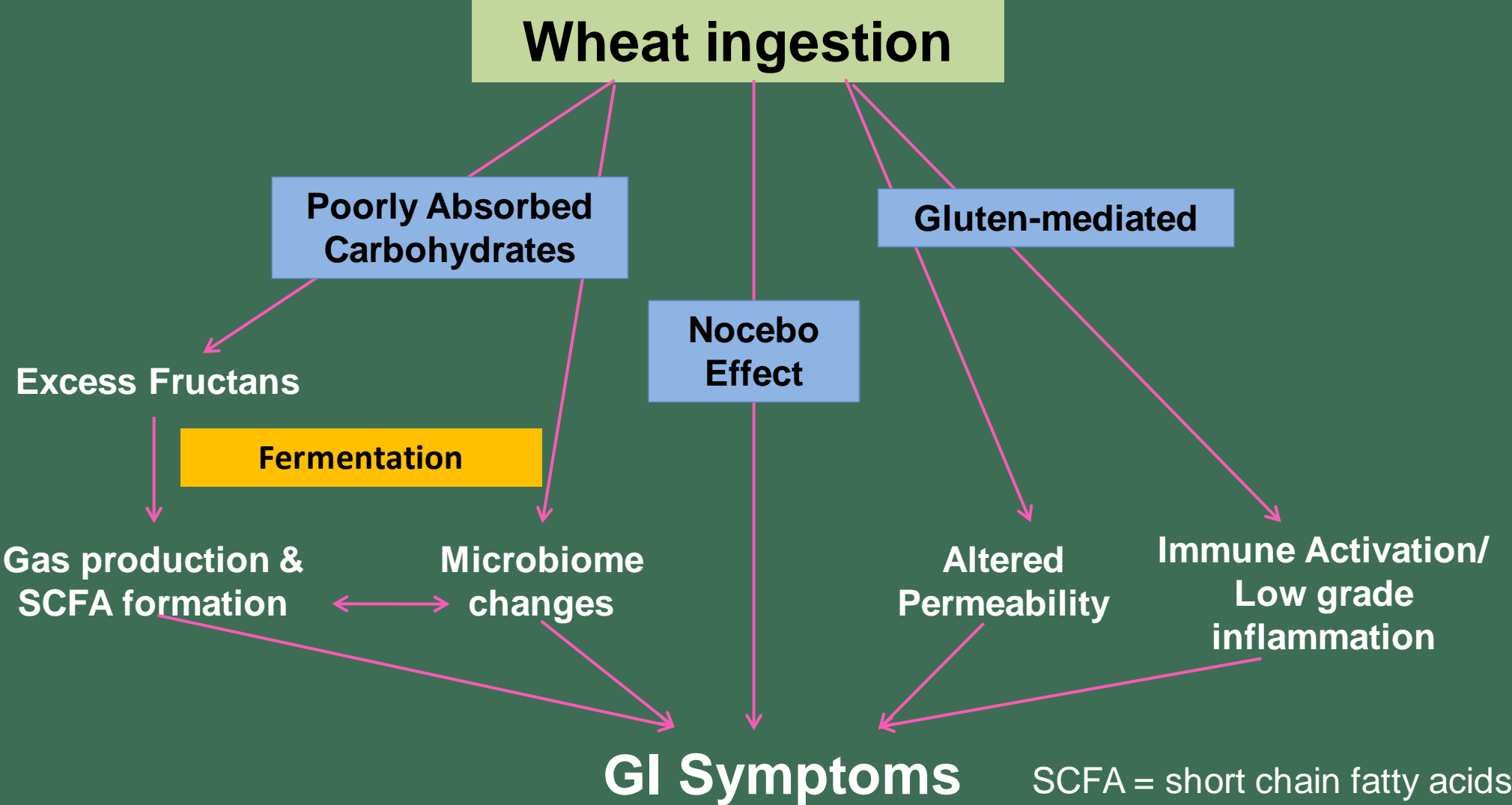
# No Effect of Gluten after Reduced FODMAP Diet in IBS Patients

- 37 subjects with IBS (Rome III) reporting NCGS (celiac disease meticulously excluded) underwent double-blind cross-over study
- 2 wks low FODMAP diet resulted in significant improvement of GI symptoms and fatigue
- Challenge with gluten (high, low or control) did not result in symptomatic or biological changes
- Suggests sensitivity may not be due to gluten

# No Effect of Gluten after Reduced FODMAP Diet in IBS Patients



# Proposed Mechanisms - Non-Celiac Wheat Sensitivity



Adapted from Eswaran S, et al. Gastroenterol Hepatol 2013;9:85.  
Vazquez-Roque MI, et al. Gastroenterology 2013;144:903



# Forms of Adverse Reactions to Wheat or Gluten: Clinical Features

Type of ARF	Immediacy of symptoms/dose	Neurological & Psychological	Anemia/Lab abnormalities
Wheat allergy	Immediate Varying dose	No	No - anemia Yes (specific IgE)
Celiac disease	Delayed/Dose effect varies	Varies	Yes - anemia TTG, DGP Abs
Non-celiac gluten sensitivity	Varies Exquisite dose sensitivity	Yes	No anemia AGA IgG, Wheat IgG
Wheat starch intolerance	Varies, builds post-ingestion	Not typically	Typically not

# Role of Response to Gluten-Free Diet in Diagnosing Wheat/Gluten Disorders?

- Placebo response in IBS up to 70%
- Gluten (increased prolamines) is hard to digest, increases stool volume
- Gluten-free diet often eliminates other dietary factors (additives, preservatives)
- PPV of symptom improvement after gluten withdrawal for celiac disease only 36% in one study
- What else is improved by a gluten free-diet?

# Patients Already on Gluten Free Diet: How to Test for Celiac Disease?

- Depends of duration and stringency of the GFD
  - if truly on a GFD for years it is difficult to prove CD
  - many patients on a self-taught GFD are not truly gluten-free
- Serology can take over a year to normalize
  - Check TTG IgA +/- DGP IgA, IgG
- Histology can take several years plus to become normal
- If an undiagnosed patient wants an assessment for possible CD assess with serological tests, HLA DQ2/8 and EGD with biopsies within the first year on a GFD
- Absence of HLA DQ2.2, 2.5 or 8 effectively excludes CD now or in the future

*Sugal, E, et al, Digestive & Liver Disease, 42:352, 2010*

*Crowe, SE. In The Clinic : Celiac Disease, Ann Int Med,2011 154:ITC5-14,*

# How to Evaluate for Causes of Adverse Reactions to Food

- History - ? co-factors (exercise, drugs)
- Assess for lactose intolerance
- Assess for SIBO
- Skin testing for food allergens
- Diet diary
- Hypoallergenic diet trial
- Endoscopy and biopsy
- CBC, eosinophil count
- Quantitative immunoglobulins
- Specific IgE levels (RAST, ELISA)
- Serum IgG to foods – **No longer accepted**
- Celiac serology and/or HLA DQ assay
- Other tests for non-IgE mediated reactions

*Bischoff & Crowe, Gastroenterology, 128: 1089, 2005*

*DeGaetani & Crowe, CGH, 8: 755, 2010*

*Stapel SO, et al, EAACI Task Force Report. Allergy, 63:793, 2008*

# Alternate Tests for Food Sensitivity and Non-Celiac Gluten Sensitivity

- **LabCorp** – NCGS screen = IgG to native gliadin
- **ALCAT** – Gut Health Profile (tests specific genetic predisposition to celiac disease as well as antibody testing and immune system activation to food sensitivities), also leukocyte assays for food sensitivities
- **Cyrex** – Intestinal antigen permeability screen, Wheat/Gluten proteome reactivity/autoimmunity, Cross-reacting foods & food sensitivities (IgG & IgA)
- **Enterolab** – various stool panels (food Abs, gene tests, celiac Abs)
- **Genova Diagnostics** (Great Smokies Diagnostic Lab) – Blood for IgG4 to food, for celiac & gluten sensitivity, saliva for gliadin sensitivity

# Alternate Tests for Food Allergy or Food Intolerance

- **Many labs** – food allergies, IgG to food antigens\*
- **Cyrex, ALCAT** – as per previous slide\*
- **MRT/LEAP** – Measures release of immune mediators (histamine, cytokines, etc) via changes to the liquid/solids ratio of a blood sample after incubation with specific food, additive, or chemical\*
- **Applied kinesiology** – patient holds putative allergenic food while muscle strength is tested by the practitioner\*
- **Electrodermal skin testing** - machine measures electrical resistance at acupuncture points when allergen is placed in the electrical circuit\*

\* Expert NIH panel “recommends not using” this test for routine diagnosis of food allergy

*Boyce JA et al. JACI.2010;126(6):1105*



# Back to the Patient

## Lab test results

- Normal CBC & diff, CMP
- Stool studies negative for pathogens
- Celiac serology not elevated
- No HLA DQ susceptibility genes
- Specific IgE to wheat negative
- Glucose breath test – no rise in hydrogen or methane

## What to do next?

- Consider endoscopy/biopsy
- Check nutritional parameters
- Diet diary
- Referral to a knowledgeable RD
- Trial of low FODMAP diet
- Other dietary trials within reason
- Consider treating SIBO

# Downsides of Eating Gluten Free?



- Expense, availability
- Travel, dining out
- Increased fat, salt, sugars, calories in processed GF foods
- Exposure to arsenic with rice
- Potential nutritional deficiencies

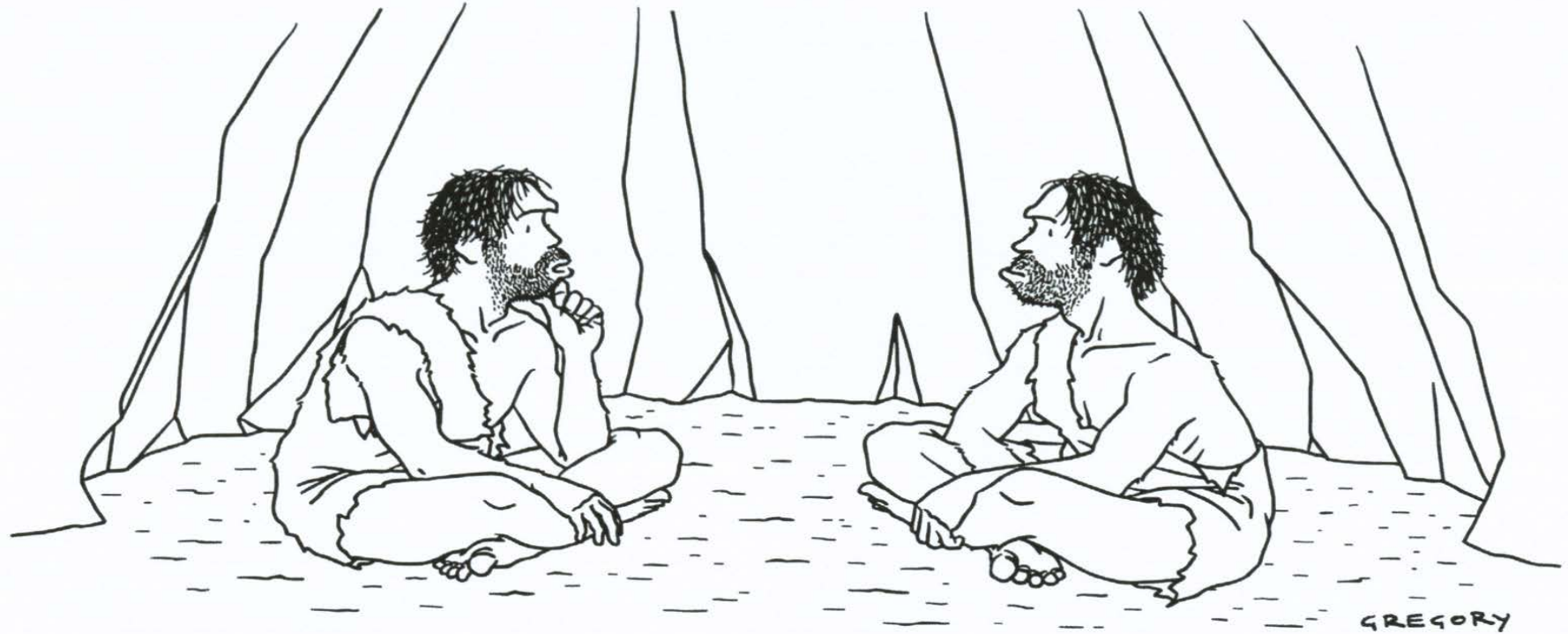
# Pros and Cons of Going Gluten Free Before Evaluating for Celiac Disease

## Pros

- Feeling better sooner
- Avoids the expense and time seeing health care providers
- Decrease consumption of GMOs
- Other perceived health benefits

## Cons

- Difficulty to subsequently confirm celiac disease
- Impact on assessing risk of celiac disease in relatives
- Potential nutritional deficiencies
- Social and economic issues for the entire family



*“Something’s just not right—our air is clean, our water is pure, we all get plenty of exercise, everything we eat is organic and free-range, and yet nobody lives past thirty.”*

# Summary of Adverse Reactions to Wheat or Gluten

Type of ARF	Immune mediated	Tissue damage	Genetic factors
Wheat hypersensitivity	IgE-mediated	Transient	Yes
Celiac disease	T cell mediated	Persistent with gluten ingestion	Yes
Non-celiac gluten sensitivity	Innate immune? AGA IgG Other mechanisms	Microscopic	Not yet identified May be more than one entity
Wheat starch intolerance	Non-immune	None apparent	Seemingly not

# Summary of Gluten Sensitivity

- Celiac disease is common and easily screened for
- Non-Celiac Gluten Sensitivity cannot necessarily be distinguished from celiac disease
- NCGS is not currently a specific definable entity
- Patients can have celiac disease, gluten or wheat sensitivity and also have a FGID
- The role of gluten, FODMAPs (wheat starch), and other foods in IBS/FGIDs remains unclear. However, identifying specific food intolerances can be beneficial for IBS patients
- The microbiome/SIBO also contribute to food intolerances