R.D. McKenna
2017 Memorial Lecture:

The Growing Problems of Food Allergies and Intolerances

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Division of Gastroenterology

University of California, San Diego

Dr. Richard D. McKenna

- August 30, 1911 - May 12, 1975
- Received MD from McGill University in 1938
- Trained at the Royal Victoria Hospital and the University of Pennsylvania under Henry Bockus
- Received FRCPS in Internal Medicine in 1947
- Staff/Faculty McGill University 1947-66
- Served as Treasurer of the AGA
- Founded CAG 1961, incorporated Jan 1962 – 1st president
- R. D. McKenna Lecture instituted in 1966, after retiring the McKenna Memorial Lecture was renamed

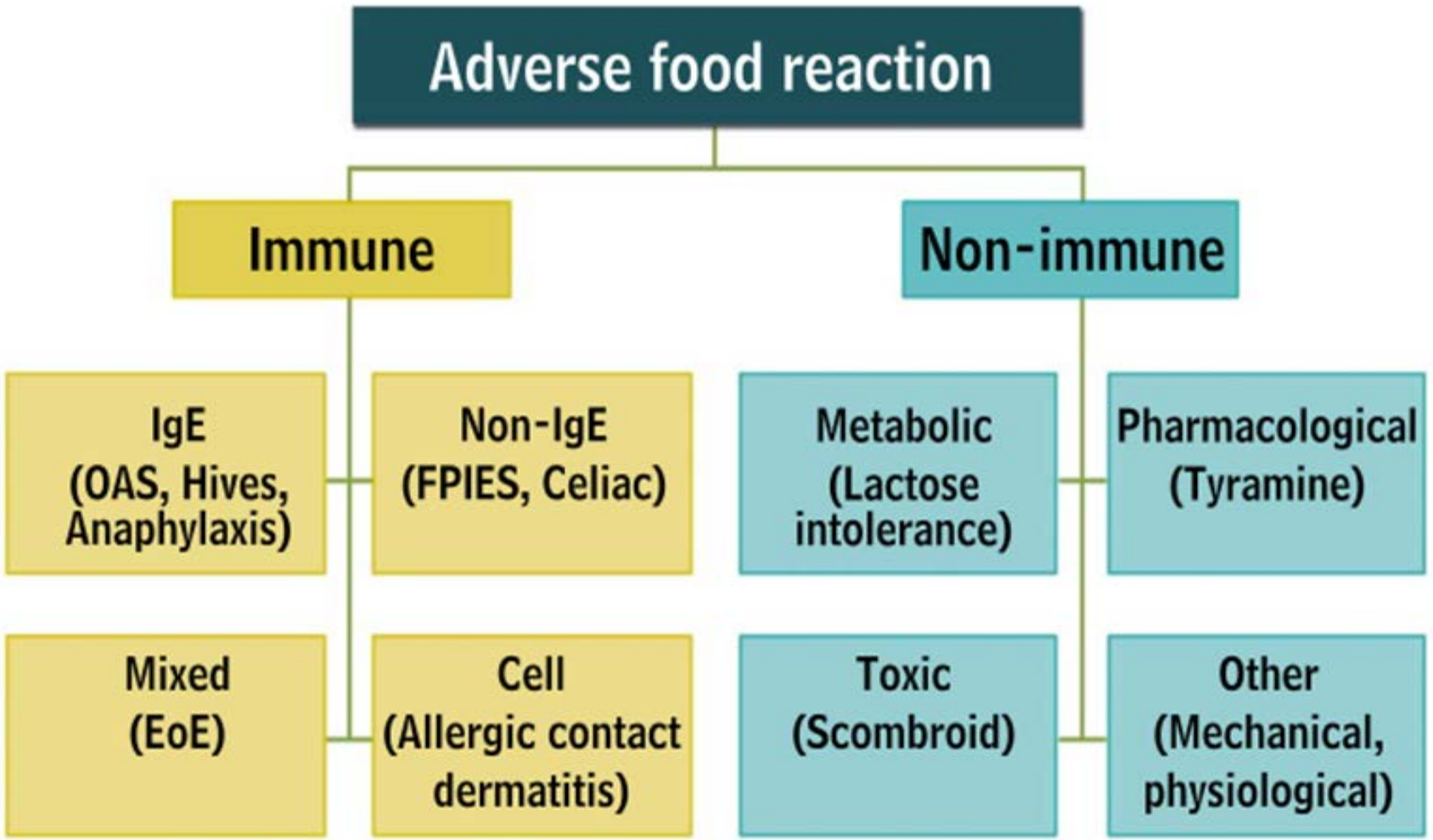
My Disclosures

- Co-author of “Celiac Disease for Dummies” – royalties
- UpToDate – author of *H. pylori* topics – honorarium
- Ferring, Inc. – Advisory Board – honorarium
- Celimmune – Site PI for a Clinical Trial with anti-IL-15 for Refractory Celiac Disease

A Change in Career

Crowe, SE & Perdue, MH, Gastrointestinal Food Hypersensitivity: Basic Mechanisms of Pathophysiology. Gastroenterology, 103:1075-95, 1992

Classification of Adverse Reactions to Food



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

Prevalence of Food Allergies

- Over 50 million Americans have allergies
- Up to 15 million have “food allergies”
- 1 in 13 children $\leq$ 18 yrs have food allergies
- $25 billion/year spent on allergies
- Over 85% of ARF are not food allergy
- A fifth of the US population self imposes diet modifications because of perceived ARF

Issues for Consideration as a Gastroenterologist

- Differentiating food allergies from food intolerances
- Why is there an increasing prevalence of celiac disease, peanut allergy, EoE and other food allergic conditions
- Managing eosinophilic food-related GI disorders
- Discuss forms of adverse reactions to wheat
- Consider varying forms of intolerances to milk
- Testing for food allergy and intolerences
- Upsides and downsides of various diets

What to Eat and What Not to Eat?

- Nearly every patient who sees a GI practitioner wants to know is it something they eat and/or is it something they are missing from their diet that is the cause of their GI and other health problems
- The popularity of many types of diets underscore the notion that what we eat is the key to health and wellbeing
- Marketing of food promoting potential health benefits is becoming more common

Good Grains and Bad Grains?

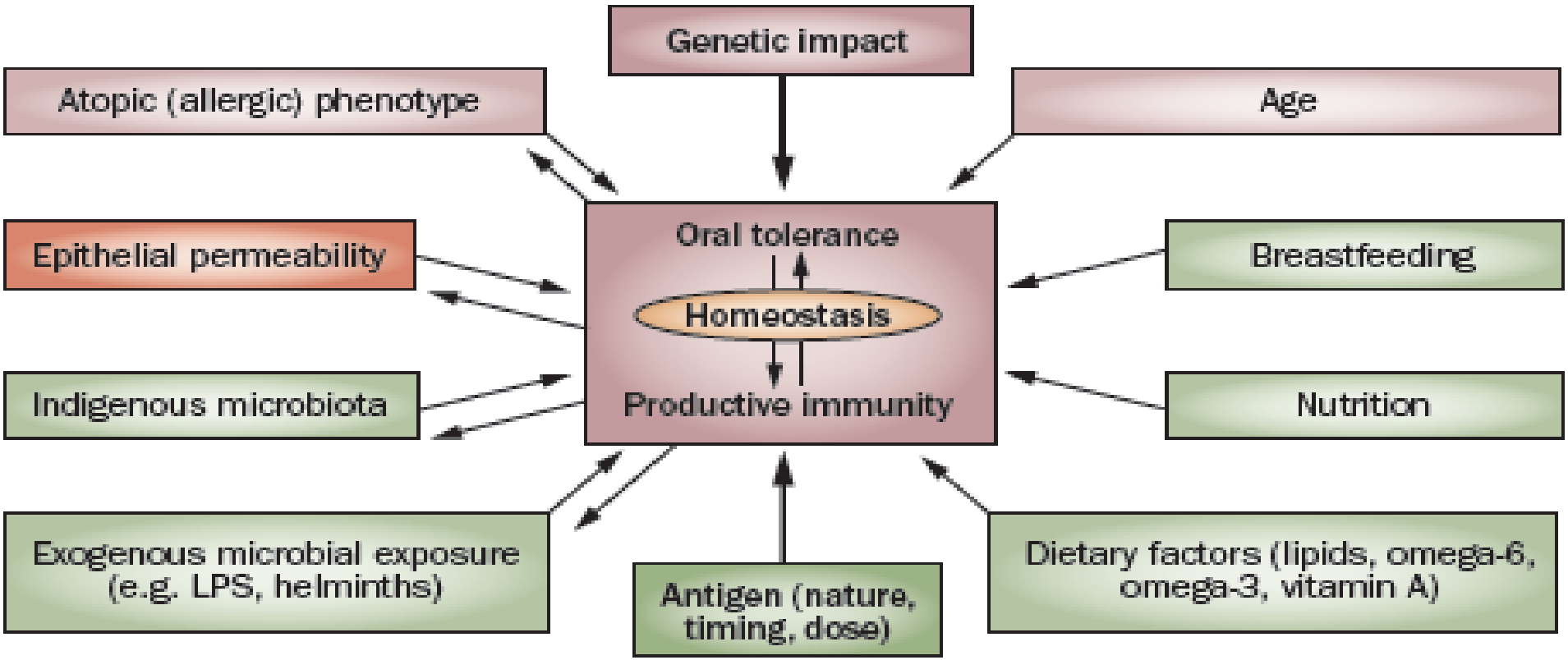
HIS AND HERS “SEX” CEREAL

THE DAILY CONSTITUTIONAL AID

Food and the Digestive Tract: Friend or Foe?

- The average human ingests a large amount of food in their lifetime
  - ~ 60,000 pounds - 27,273 kilograms - 30 tons
- The vast majority benefit from this ingestion but a small percentage develop complications:
  - Food poisoning
  - Food allergies
  - Food sensitivities
- There is a reported increase in food allergies, celiac disease and seemingly of food sensitivities

Biological Variables that Influence the Developing Immunophenotype of an Infant



Brandtzaeg, Nat Rev Gastroenterol Hepatol, 7: 380-400, 2010

Non-Immune Reactions to Food

- Mechanical, physiological
- Food toxicity/poisoning – microbes
- Anaphylactoid (pseudo-allergic) - strawberries
- Pharmacologic – tyramine, sulfates, etc
- Metabolic – lactase insufficiency
- Idiosyncratic –reactions without known cause
- Psychological

Immunological Reactions to Food

- Food hypersensitivity (IgE-mediated)
  - Oral allergy - pollens cross-reacting fruits, vegetables
  - Latex-food allergy – cross-reacting foods (bananas, etc)
- Celiac disease (T-cell mediated)
- Eosinophilic Esophagitis/Gastroenteritis (Eos)
- Food protein enteropathies (mixed)
    - Hypersensitivity
    - Immune complexes
    - T-cells

Peanut Allergy

- Increasing prevalence
- Occurs in 1 in 150-200 individuals
- Varying presentations
- Major cause of anaphylaxis
- Varying dose sensitivity
- Most react on first recognized exposure
- Up to 20% may lose sensitivity
- Associated with other food allergy, atopy

Risk of Anaphylaxis

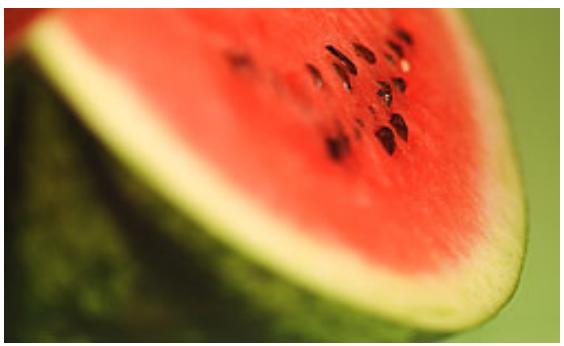
Food allergy is now the major cause of anaphylaxis in developed countries

Those with increased risk include those:

- with past history of anaphylaxis
- with reactions with respiratory tract symptoms
- with reactions to peanuts, tree nuts, fish, seafood
- taking B-blockers or ACE inhibitors

Oral Allergy Syndrome

- Localized IgE - Initial sensitization to pollens results in IgE that cross reacts with fruit and vegetables
- Raw fruit and vegetables
  - Birch pollen – apple, peach, pear, almond, hazelnut, potato, carrot
  - Ragweed pollen – melons, banana, gourd family
  - Mugwort pollen – celery, carrot, spices
  - Grass pollen - tomato
- Itching, ± swelling and/or tingling
- Confined to lips, tongue, roof of mouth and throat
- Affects patients with pollen allergy

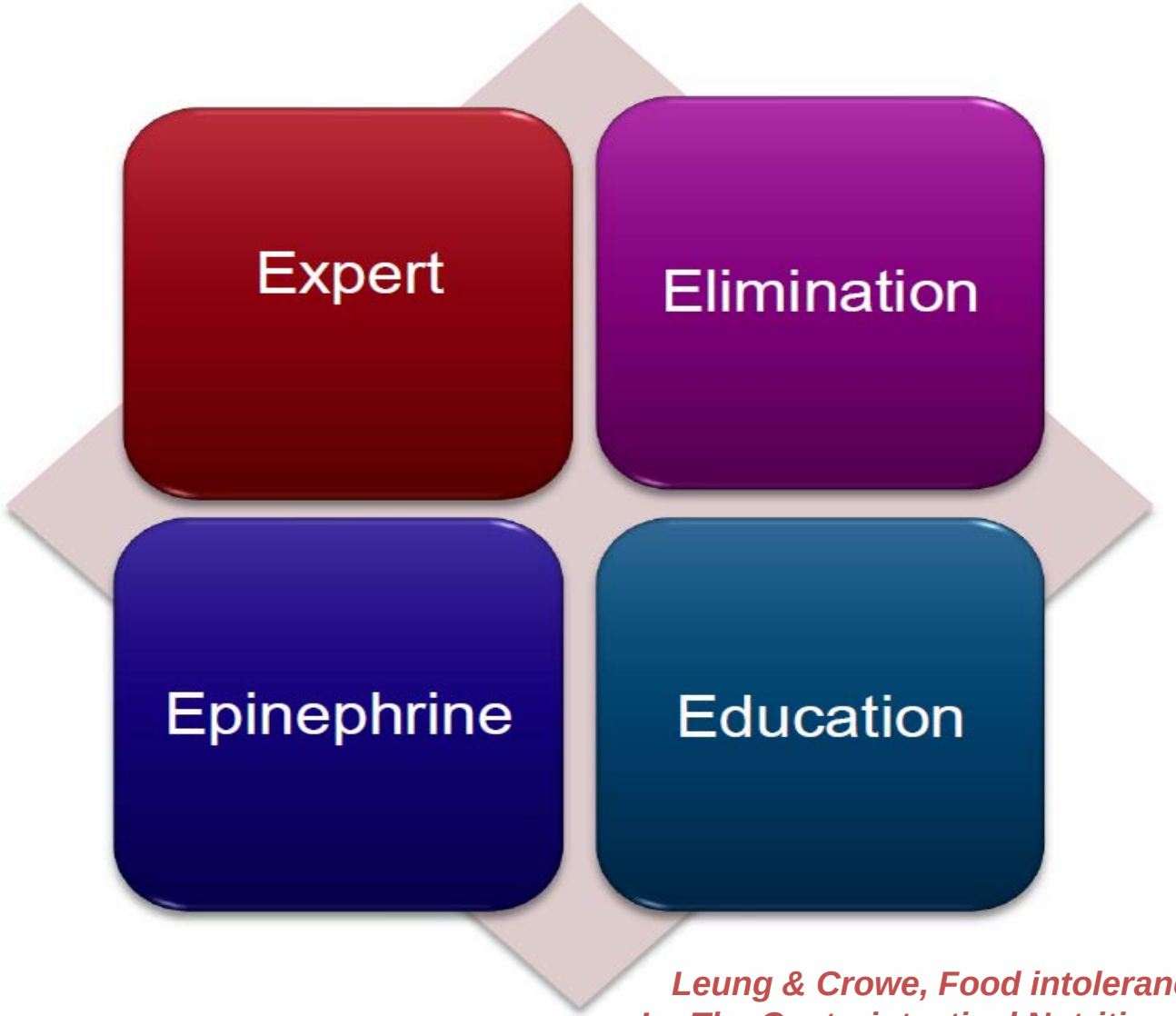


Hofmann A, et al. Curr Allergy Asthma Rep, 8(5):413, 2008

Latex – Food Allergy Syndrome

- Sensitization to latex results in IgE that cross reacts with fruit and vegetables
- Exposure to foods give same symptoms as latex
- Natural Rubber Latex contains over 200 proteins, 10 bind IgE (HEV b 1-10)
- Food associations:
  - Kiwi (5)
  - Potato, tomato (7)
  - Avocado, chestnut, banana (6)

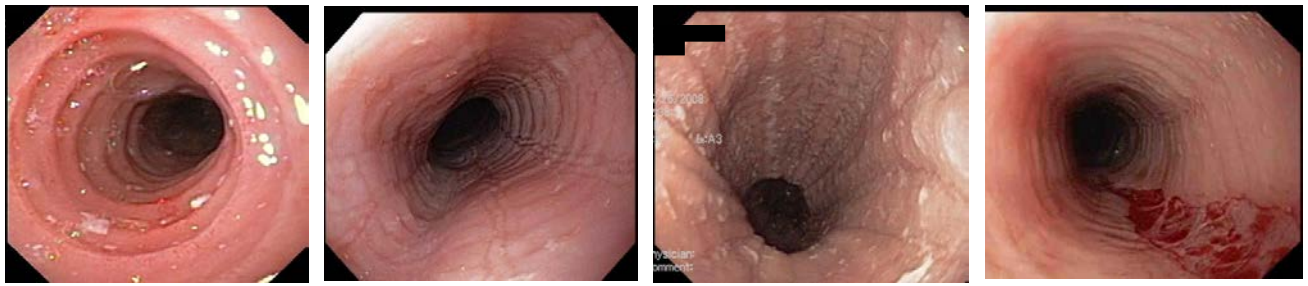
Treatment – the 4E's



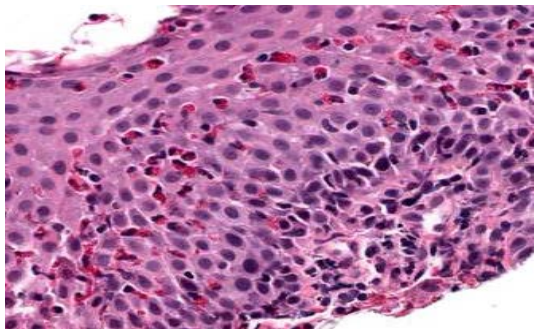
Leung & Crowe, Food intolerance and food allergy. In: The Gastrointestinal Nutrition Desk Reference, 2011

Eosinophilic Esophagitis (EoE)

- EoE is a clinicopathologic condition defined by:
  - Symptoms
    - **- Dysphagia**
    - **- Food impaction**
    - **- Heartburn**
  - Endoscopy



  - Pathology



Liacouras et al, JACI, 2011; Molina-Infante et al, CHG, 2011; Dellon, Gonsalves, Hirano, et al, AJG, 2013

Eosinophilic Esophagitis (EoE)

- **ACG Guidelines:** Definition
- Clinicopathologic disorder diagnosed based on both clinical and pathologic information
  - Symptoms related to esophageal dysfunction
  - Eosinophils in esophageal Bx's > 15 per high power field (HPF)
    - Isolated to esophagus
    - Persists after PPI treatment
  - Secondary causes ruled out

Dellon et al AJG 2013; 108:679-692

Eosinophilic Esophagitis (EoE) vs Eosinophilic Gastroenteritis (EGE)

- EGE affects upper and lower GI tract
  - Involves the mucosa, muscular layer and/or serosa
  - No change in prevalence, no gender difference
  - Food allergy is much less associated than in EoE
- EoE recognized in the early 1990s, a new disease
  - Prevalence increasing, 56.7/100,000 USA[2] (2008-11)
  - Male 65%, mean age 33.5[2]
  - Incidence 10,000 new cases/yr[3]

1-Liacouras CA et al. JACI, 128(1):3-20, 2011
2-Delllon, ES, CGH, 12;589, 2014
3-Dellon, ES, Gastroenterol, 147:1238, 2014

Diagnostic Tests for EoE

- Currently the only means to diagnose and follow treatment is esophageal mucosal Bx
- CBC, peripheral eosinophil count
- Patch test not helpful in adults
- Specific IgE levels (RAST, ELISA) not helpful
- Eosinophil markers (investigative)
- Swallowed sponge (studies in progress)

Treatment of EoE: The Three D's

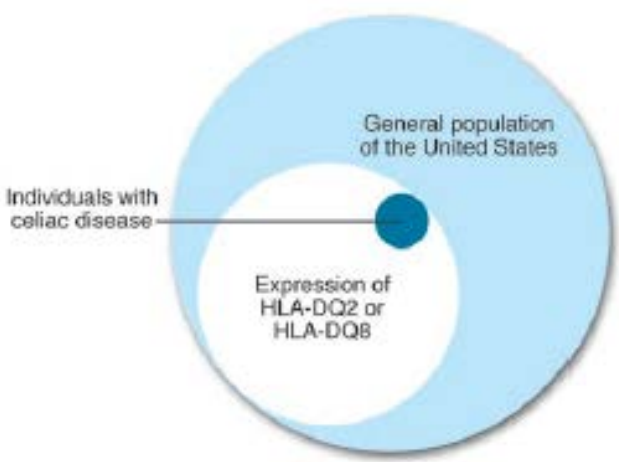
- **Drugs**
- 1) treat with PPI (20-40mg) of any PPI bid for 8 weeks
  - continue if beneficial
- 2) Topical steroids (first line)
  - Fluticasone or budesonide (swallowed) x 8 wks
- **Diet** - elimination (first line)
  - Elemental, empiric (6 or 4 food elimination), occasionally targeted
- **Dilation**
  - If persistent esophageal stricture post medical or dietary treatment
  - Type of stricture dictates the modality - Savory, balloon, bougie

Changing Prevalence of Celiac Disease

- Prevalence of up to ~1:100 in most genetically susceptible populations, 0.71% in NHANES study
- Estimated that 15 to 20% of current cases of CD have been diagnosed in the US, not aware of data in Canada
- CD is 4 to 4.5 times more prevalent than 50 yrs ago
- Increase in food allergies and autoimmune diseases as well
- 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 Gatroenterol, 44:933, 2009
Rubio-Tapia, Am J Gastroenterol, 2012

Who Develops Celiac Disease? Genetic and Other Factors



- 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)

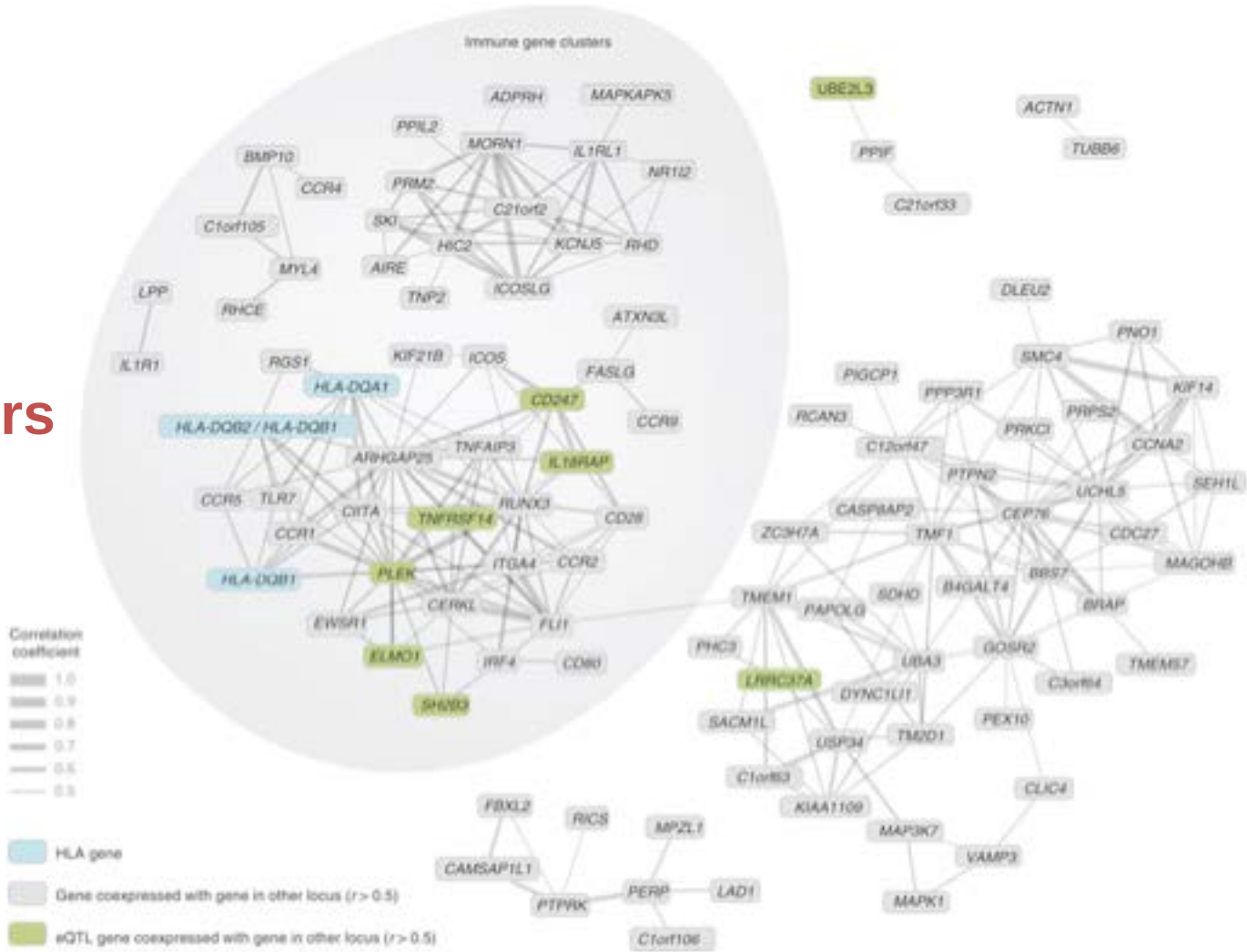
- 70% concordance in twins
- 10-15% prevalence in first degree relatives

- 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. pylor*i*

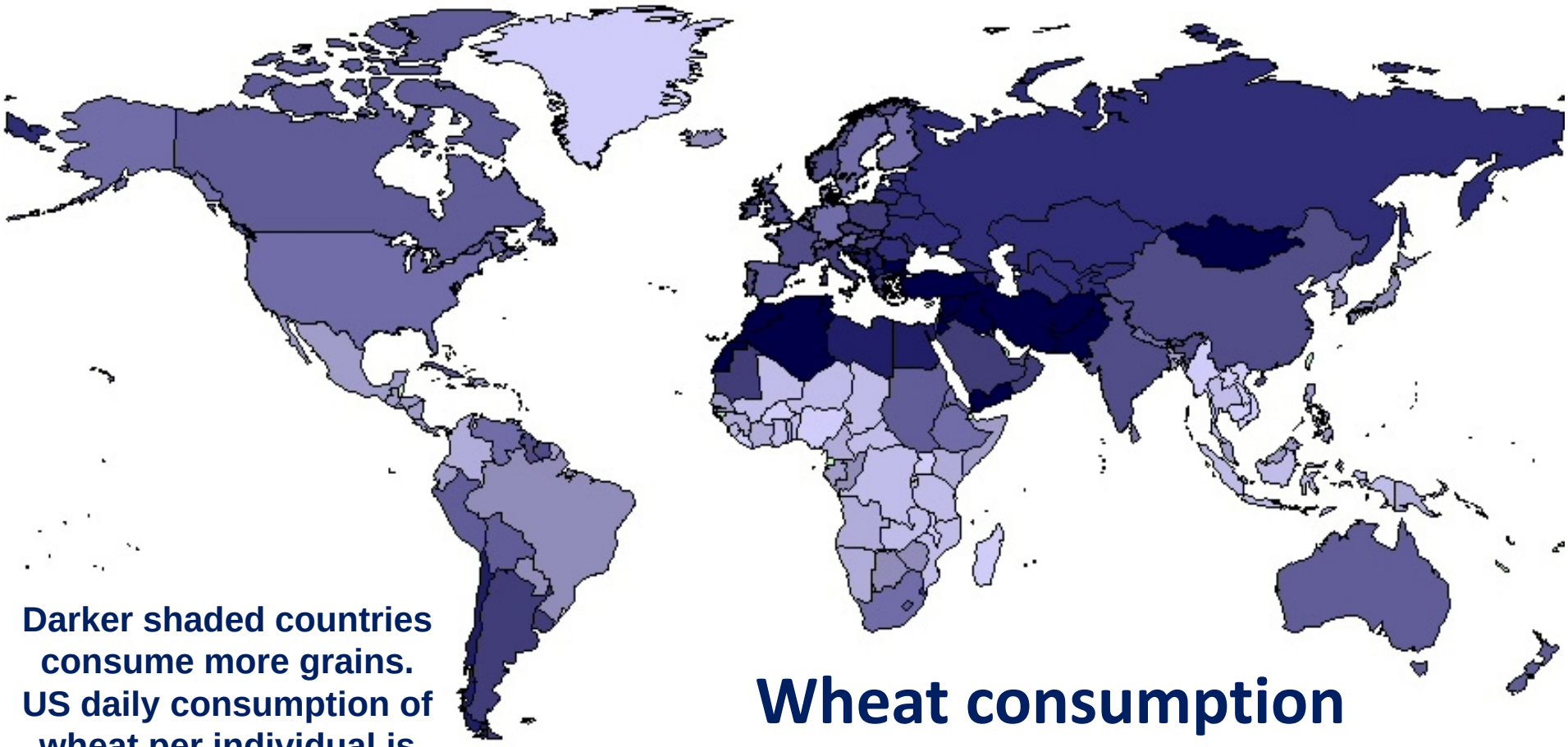
Coexpression Analysis of Genes Mapping to 40 GW Celiac Disease Regions

Immune Gene Clusters



Dubois et al,
Nature Genetics, 2010

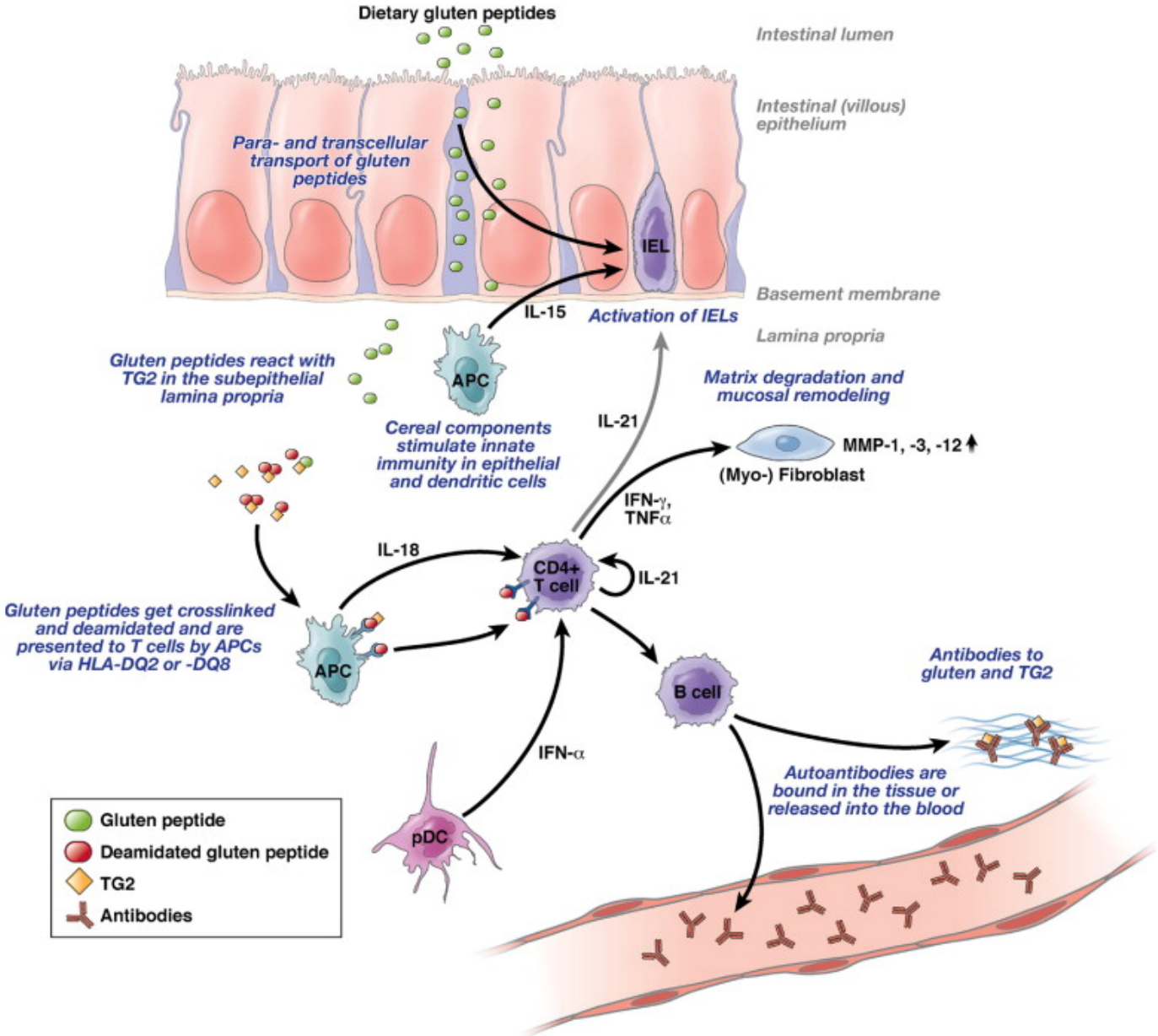
Risk Factors: The Grains



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

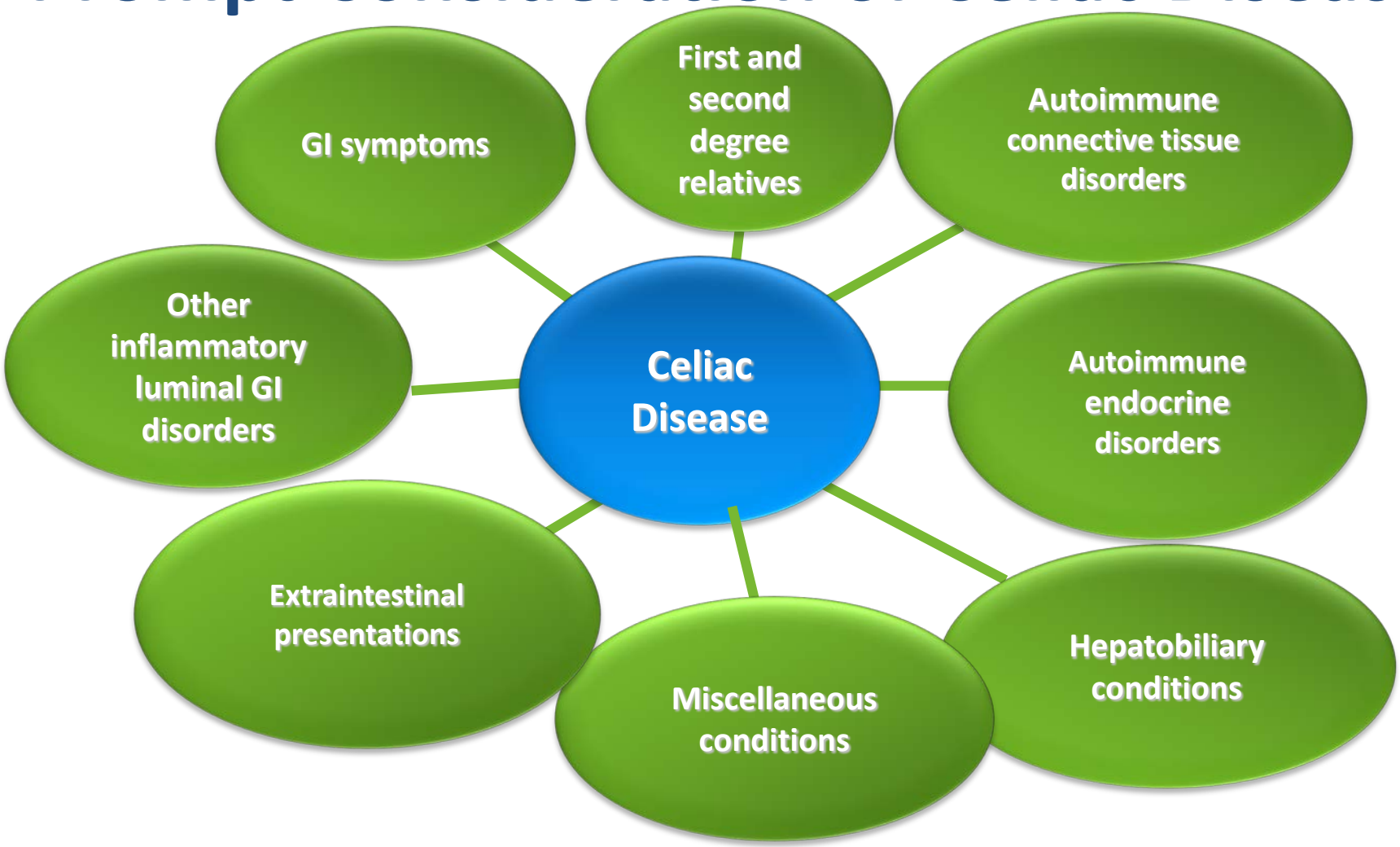
Wheat consumption

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



Schuppan et al, Gastroenterology, 137:1912, 2009

Symptoms and Conditions That Should Prompt Consideration of Celiac Disease



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

Changing Picture of Disease

- Classical form less prevalent now
- Average age of diagnosis in 5th decade
- Many are overweight, even super-obese
- Seroprevalence M=F, diagnosis M<F (1: 2 - 3)
- Other presentations are being increasingly recognized:
  - Reproductive problems
  - Neuropsychiatric manifestations
  - Related autoimmune conditions
  - Many others – true associations or chance?

Non-Responsive Celiac Disease (NRCD)

- Usually due to ongoing or recurrent gluten exposure
- Coincident disorders
  - Lactose intolerance
  - Pancreatic insufficiency
  - Small intestinal bacterial overgrowth
  - Microscopic colitis
  - **IBS (post-inflammatory or overlap of two common diseases)**
- Unrelated to celiac disease – incorrect or additional diagnoses
- Over or erroneous interpretation of the pathology
- Complications of celiac disease
  - Refractory celiac disease
  - Malignancy

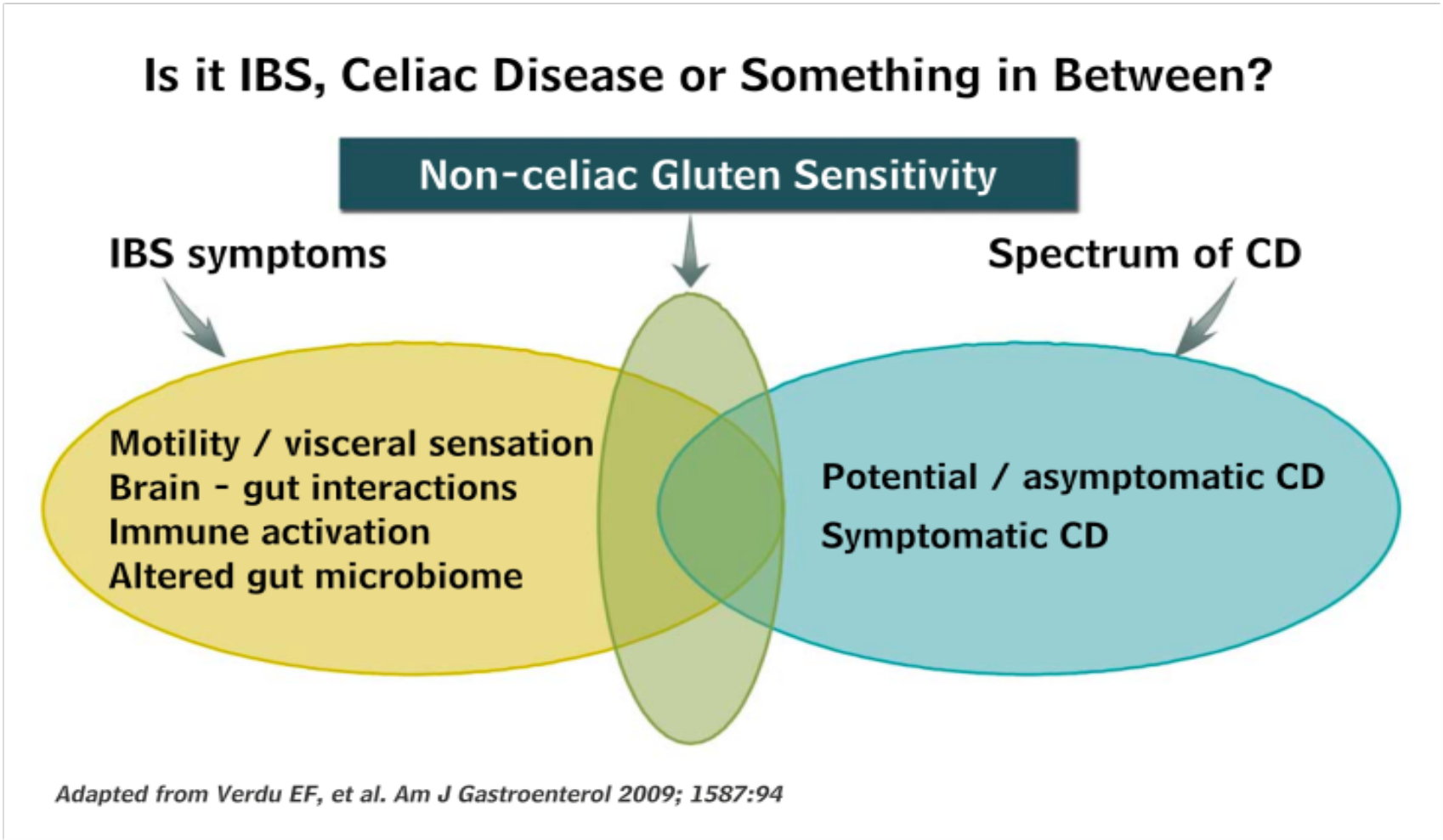
Krauss, GI Endosc Clin NA, 16: 317, 2006
Leffler, DA, et al. Clin Gastro & Hepatol, 5:445, 2007

Improvement on a Gluten Free Diet: What Does That Mean? Not always CD

- 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 – wheat starch
- Potentially other mechanisms explain benefit
- PPV of symptom improvement after gluten withdrawal for celiac disease only 36% in one study

Campanella et al, Scand J Gastroenterol, 43:1311, 2008

Between Celiac Disease & IBS: The "No Man's Land" of Gluten Sensitivity



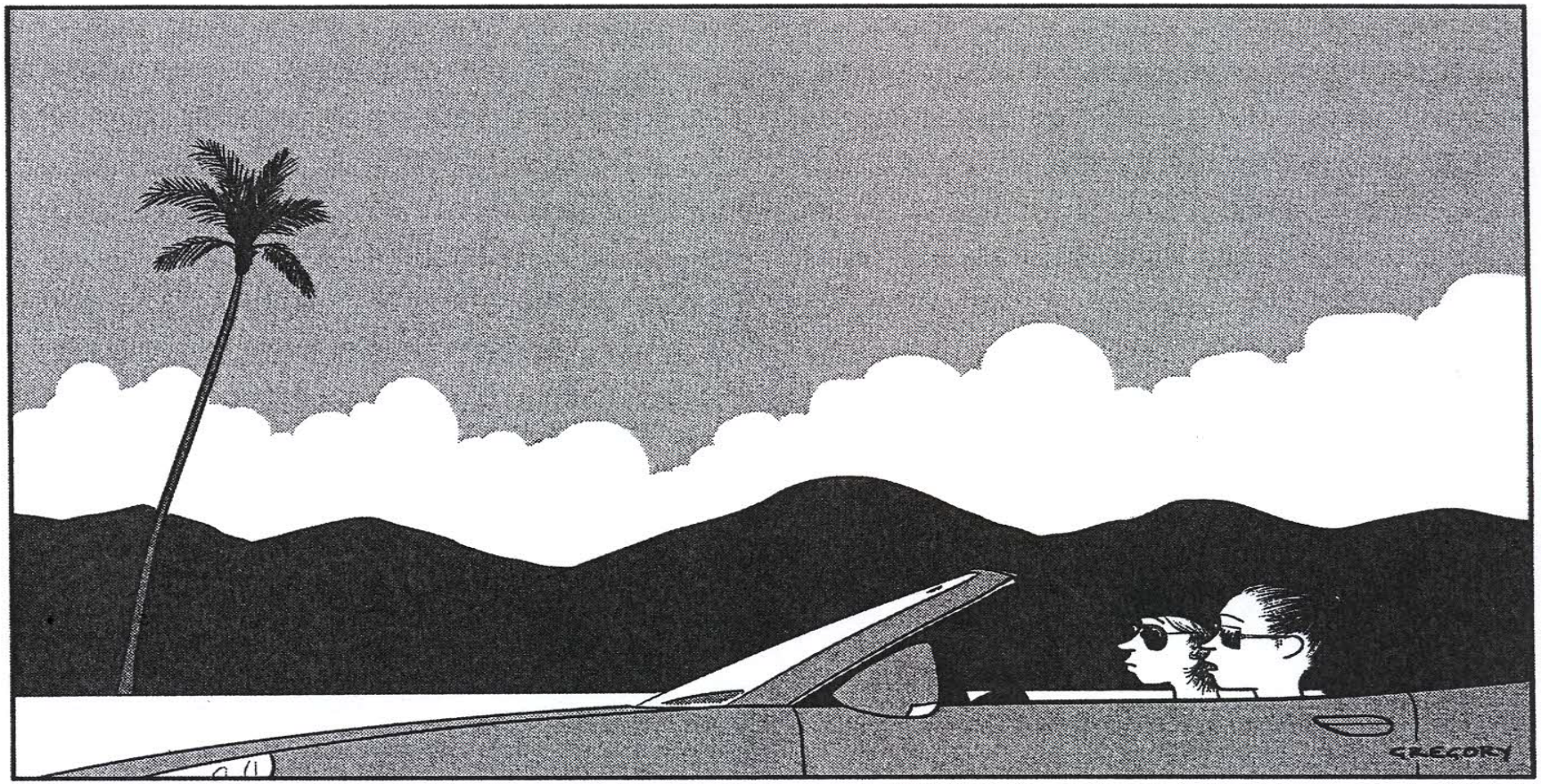
Non-Celiac Gluten Sensitivity

- Prevalence unknown
  - Varies from 0.548% (NHANES) to 30% of US (EnteroLab website)!!
  - Studies reporting prevalence reflect referral bias
- Currently no specific criteria or validated tests for diagnosing NCGS - requires double blind challenge
- Activation of innate immune system (IL-8, IFN-γ, etc), increased permeability, mucosal inflammation, basophil activation but not found in a recent study[1]
- Elevated AGA IgA, IgG (up to 50% +AGA IgG)[2]
- No specific HLA association
- Other proposed mechanisms include immune complex, autoimmune, microbiota, wheat amylase trypsin inhibitors[3], toxicity, false neurotransmitters, leaky gut….

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

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

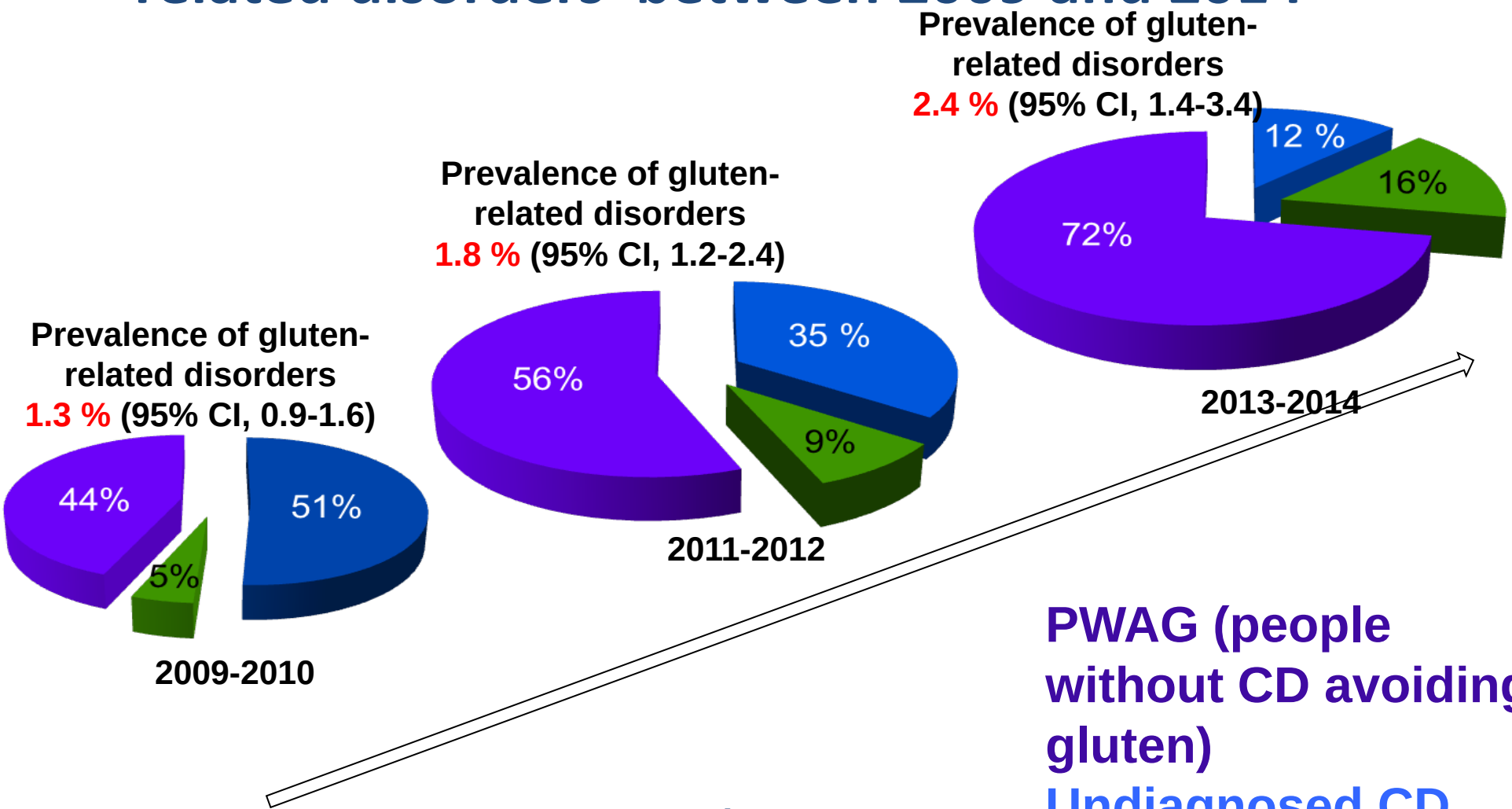
3. Junker, Y etal, J Exp Med, 209: 2395, 2013



"I have no idea what gluten is, either, but I'm avoiding it, just to be safe."

• •

Changes in prevalence and proportions of gluten-related disorders between 2009 and 2014



PWAG (people without CD avoiding gluten)

Undiagnosed CD

Diagnosed CD

DDW 2016 presentation

Hyun-Seok, K, et al. JAMA Int. Med., Sept 6,2016

Impact of Gluten-Free Eating

- The gluten-free (GF) market was expected to reach $15 billion in annual sales by 2016[1]
- Portion of households reporting purchases of GF increased from 5% in 2010 to 11% in 2013[1]
- 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

Other “Reasons” for Going Gluten-Free

Weight loss

Leaner

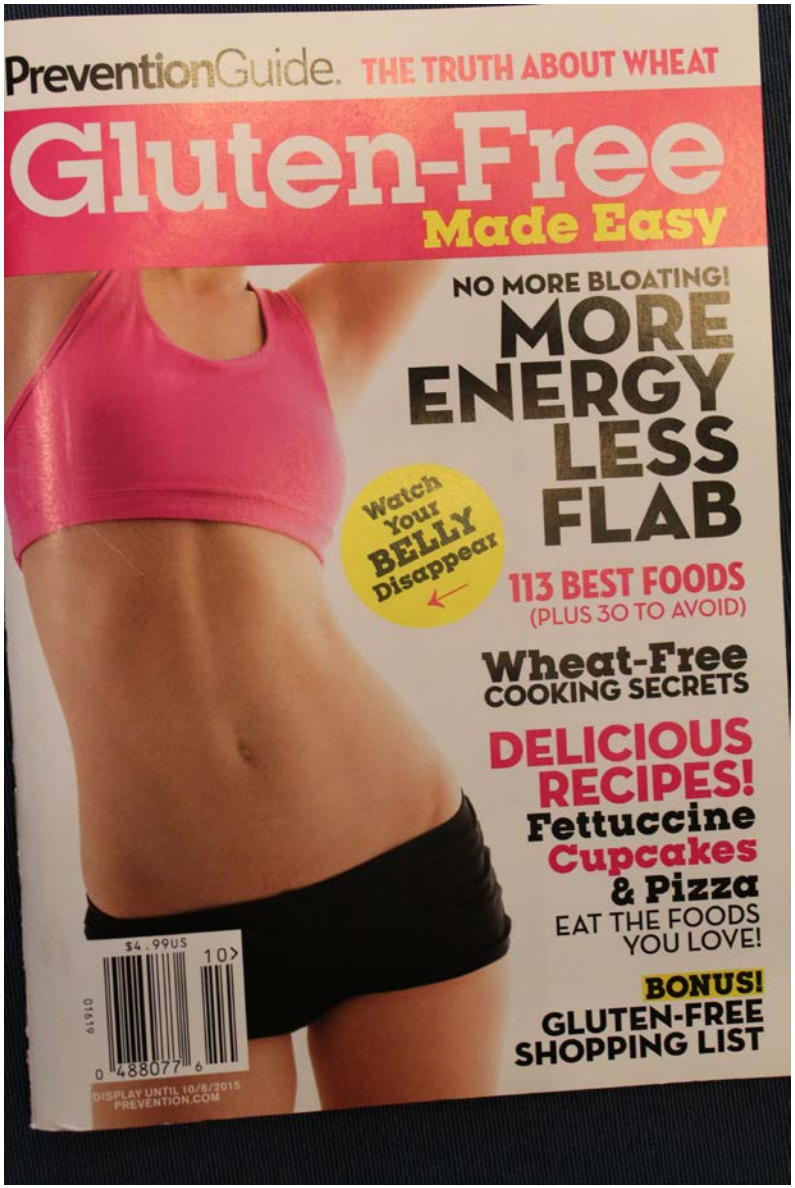
Less bloating

Decrease carbs

No GMOs

More natural

More energy



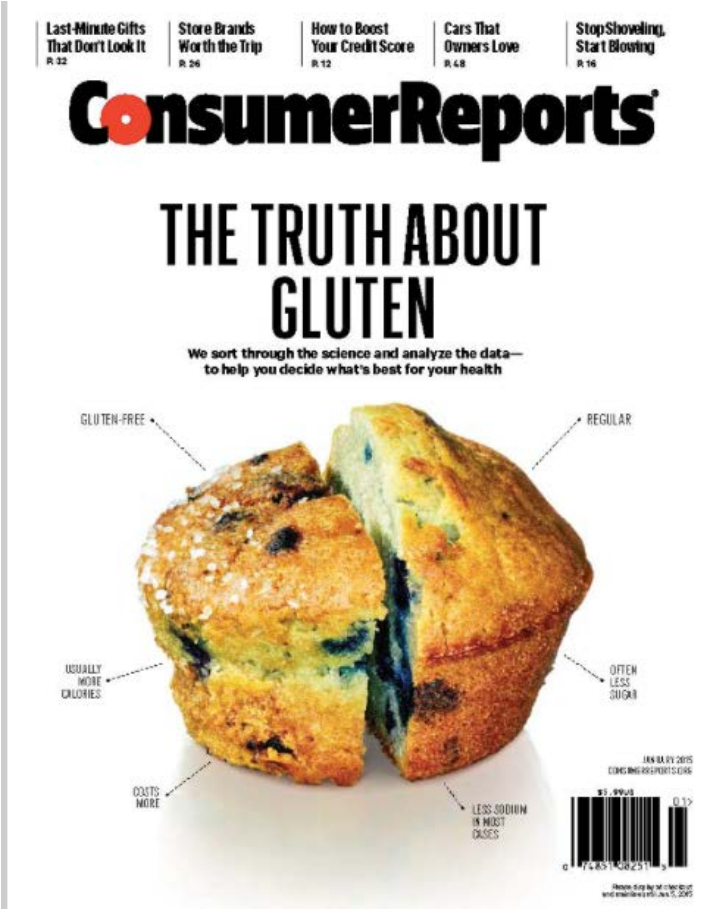
The Downside of Empiric Diets in Infants and Children

Gluten-Free, Vegan, Dairy-free, Paleolithic, Other diets

Reported adverse outcomes

- Malnutrition
- Deficiencies – vit B12, D
- Tooth and bone disease
- Death in rare instances
- Missed diagnoses

Downsides of Eating Gluten Free?



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

Does it Matter if it is Celiac Disease or Non-Celiac Gluten Sensitivity?

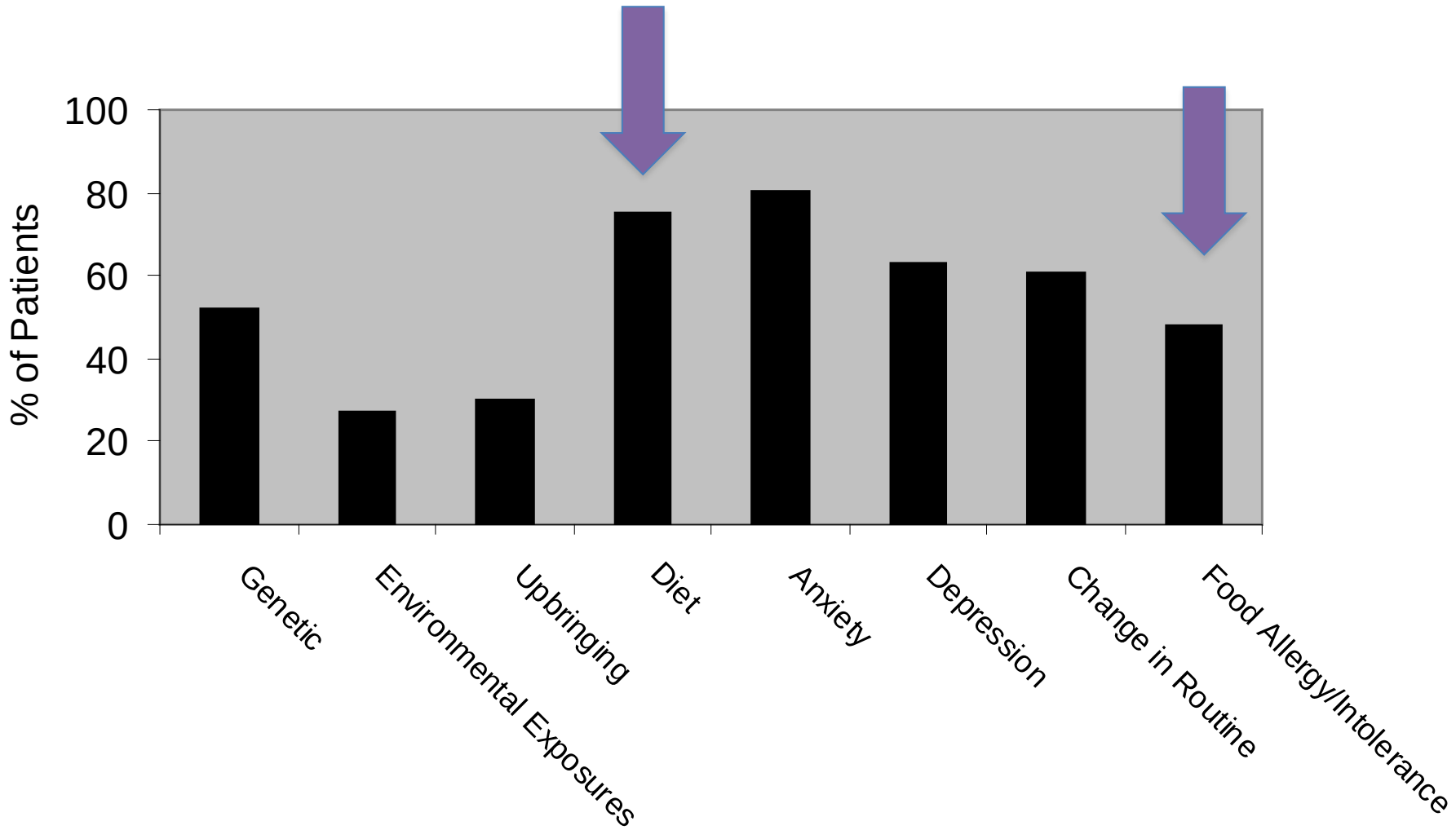
"She thinks she's so great cause she has real celiac disease."

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

Cause of IBS: Patients' Beliefs



Lacy, BE et al, Aliment Pharmacol Ther, 25:1329, 2007

Association of Diet, GI Symptoms & IBS

- Romanian study of 193 subjects assessed for eating habits and diet
  - 19.1% met criteria for IBS by Rome III
  - IBS subjects ate more canned food, processed meat, legumes, whole cereals, sweets, fruit compotes
- Swedish study of 197 IBS patients completed questionnaires for food, depression, anxiety, QoL, etc
  - 84% reported symptoms associated with ≥ 1 food
    - 70% carbs – dairy, legumes, apple, flour, plums
    - Histamine-releasing foods – milk, wine/beer, pork
    - Fried or fatty foods

Chirila, I. et al, J Gastrointestin Liver Dis, 21; 357, 2012.
Bohn, L, et al, Am J Gastroenterol, 108: 634, 2013

So What do We Know about Dietary Treatments for IBS and Other FGID?

Diet	Evidence for use
Low fat	Limited
Gluten-free	Limited
Low FODMAP	**Increasing data**
Histamine-free diet	Little to **none**
Paleolithic	Minimal
Candida	None
Elimination	Little to none

Limited evidence overall but for low FODMAP diet studies there are 6 randomized and 7 observational studies[1] plus a recent US RCT[3]

Only 3 of 17 elimination diets met eligibility criteria[2]

1-Nanayakkara, WS et al. Clin Exp Gastroenterol. 2016; 9:131

2-Moayyedi, P, et al, Clin Trans Gastroenterol, 2015; 6, e107

3-Eswaran, SL, Chey, WD, et al, Am J Gastroenterol, 2016

Mechanisms By Which Food Components Cause IBS Symptoms

- Components of food that cause altered pathophysiology and can lead to symptoms:
  - Fiber, fat, histamine, starches/sugars
- Stimulation of mechano- and chemoreceptors
- Release of hormones/peptides
- Alteration of the innate immune system
- In some genetically susceptible individuals food stimulates the adaptive immune system

Chey, WD, Am J Gastroenterol, 2016, 111, 366.

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 can cause diarrhea, bloating, flatulence, etc
- However, intestinal gas is NORMAL (up to 20/day)

MD Levitt, et al, A. J. Gastroenterol., 1998: 93:2276

What are FODMAPs

Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols

- Fructose and fructans
- Sorbitol
- Sucrose
- Lactose

Many foods (grains, starches, fruits, vegetables, lactose, sweeteners) contain FODMAPs

Shepherd SJ, et al. Clin Gastro Hep. 2008;6:765
Shepherd SJ, Gibson PR. J Am Diet Assoc. 2006;106:1631

Milk Allergy and Lactose Intolerance

- Cows Milk Protein (CMP) allergy – rare in adulthood
- Symptoms due to lactose malabsorption resulting from lactose deficiency
  - Congenital deficiencies - rare
  - Constitutional lactase insufficiency
    - Genetically programmed decreased in lactase synthesis after weaning
    - Common in native NA, Asians, Africans, those from Mediterranean areas
  - Secondary lactase insufficiency
    - Gastroenteritis, Crohn's disease, celiac disease
- Most common ARF worldwide *Shaukat, A, et al Ann Int Med. 152:797, 2010*

Management of Lactose Intolerance

- Most individuals with lactose intolerance can tolerate 12-15 g lactose (8-10 oz of milk)
- Yoghurt, hard cheeses are naturally lactose-free
- Lactose better tolerated when taken in small, more frequent amounts and with other foods
- Lactase supplements helpful
- No proven benefit for probiotics, adaptation programs
- Triacylglycerol (fat) content of many milk products can cause GI symptoms unrelated to lactase insufficiency or cows milk protein (CMP) allergy

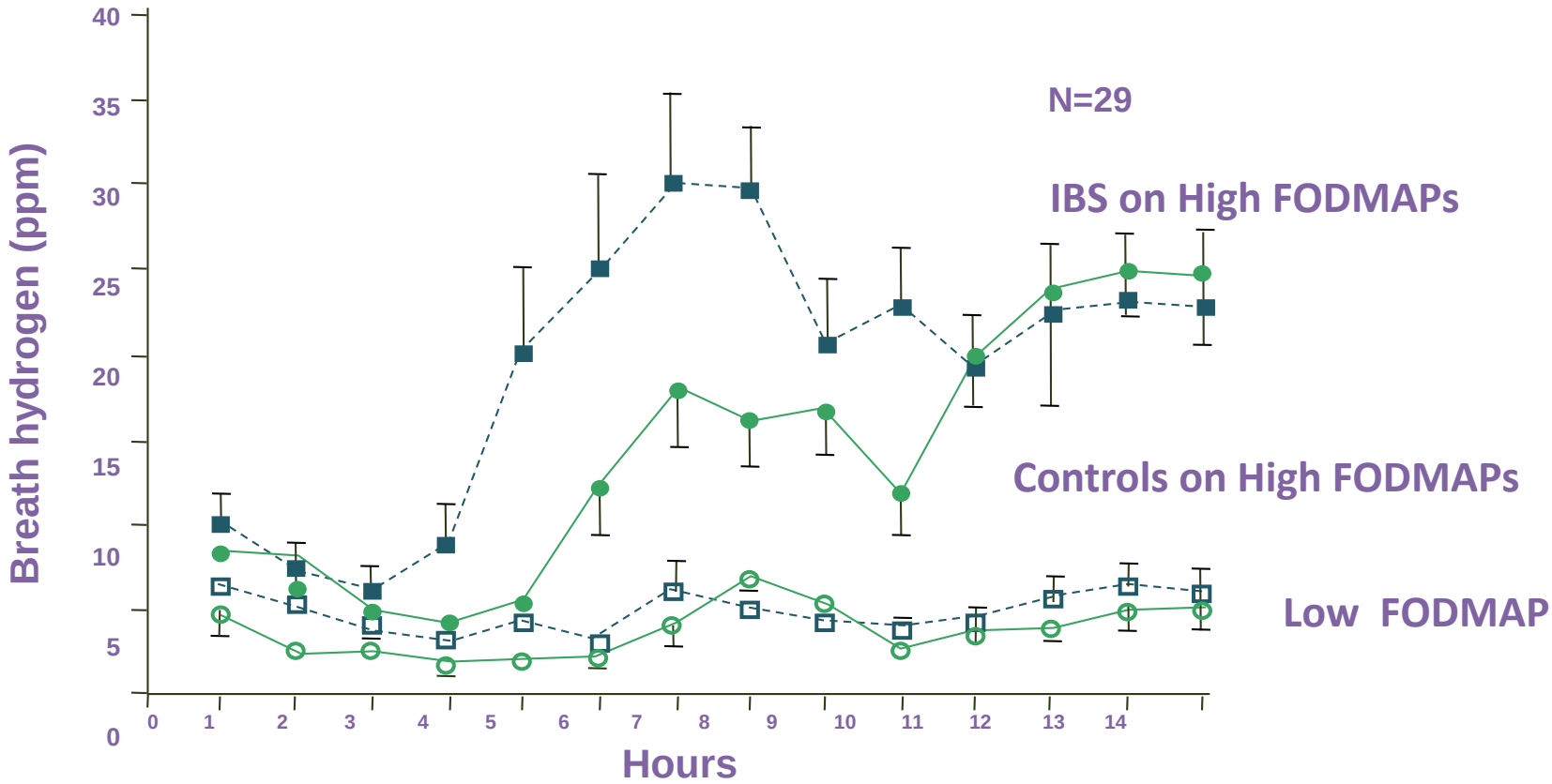
Shaukat, A, et al Ann Int Med. 152:797, 2010

Pathophysiology of FODMAPs

- Poor absorption in the small intestine
- Osmotic effects in the colon, increased water
- Fermentation with gas production
- Luminal distension
- Effects on microbiota
- Immune modulation
- Alteration of intestinal barrier

Chey, WD, Am J Gastroenterol, 2016, 111, 366

Effect of FODMAPs on Breath Hydrogen



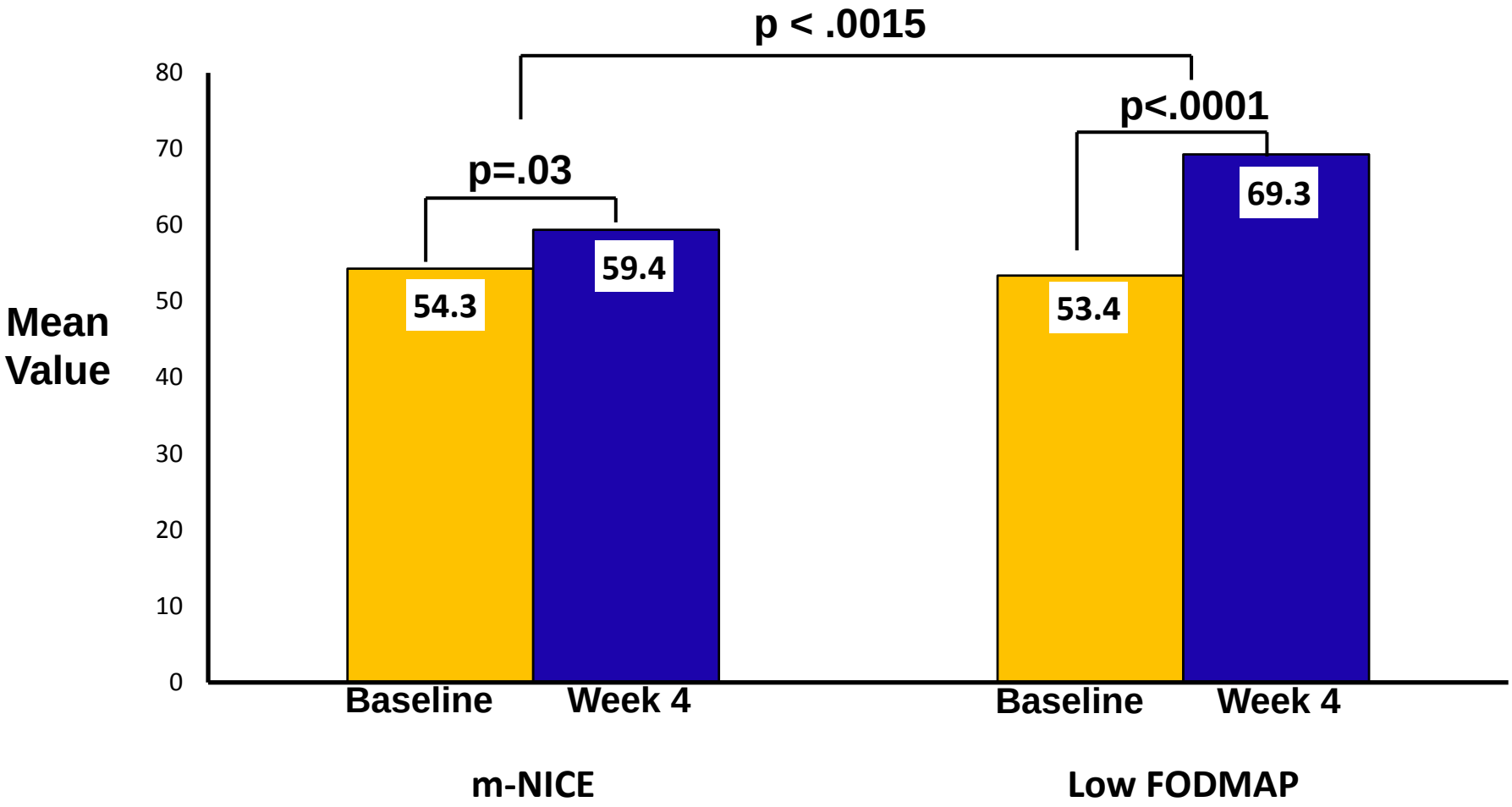
Ong DK et al. J Gastroenterol Hepatol. 2010;25:1366

Recent Canadian Study Suggests Benefits of Low FODMAP Diet

- 40 patients IBS Rome III controlled single blinded study for 3 weeks
  - 19/20 on low FODMAP, 18/20 high FODMAP diet completed
- Significant reduction of IBS symptoms (IBS-SSS)
- Significantly altered metabolic profile in urine (histamine, p-hydroxybenzoic acid, azelaic acid major determinants) and an 8-fold decrease of histamine levels in urine
- Increased Acetinobacteria in the microbiome
- This study suggests a benefit but more studies in different populations with larger numbers are needed to determine the true value of the low FODMAP diet

McIntosh, K, et al, Gut: 2016, ePub.

Overall IBS-QOL Scores



Eswaran, SL, Chey, WD, et al, Am J Gastroenterol, October 2016

Who Benefits From a Low FODMAP Diet?

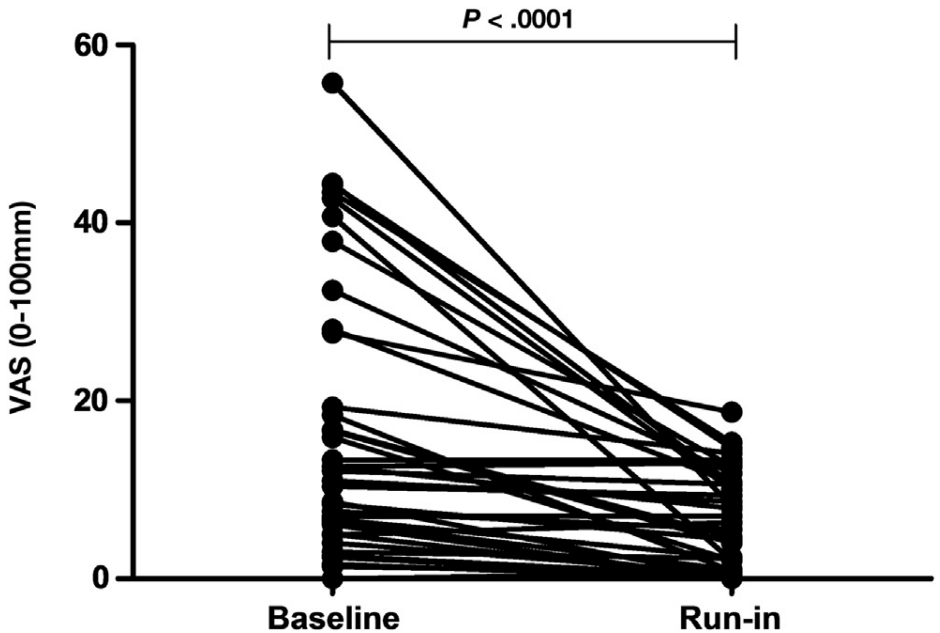
- Motivated, compliant, educated patients with IBS-D, M, C
- Other functional GI diseases may benefit from a low FODMAP diet
- NCGS and celiac disease patients on a GF diet (eliminates wheat starch with gluten, also some have increased FODMAPs in their diet)
- Low FODMAP diet reported to work better in IBD than IBS patients in one report[1]

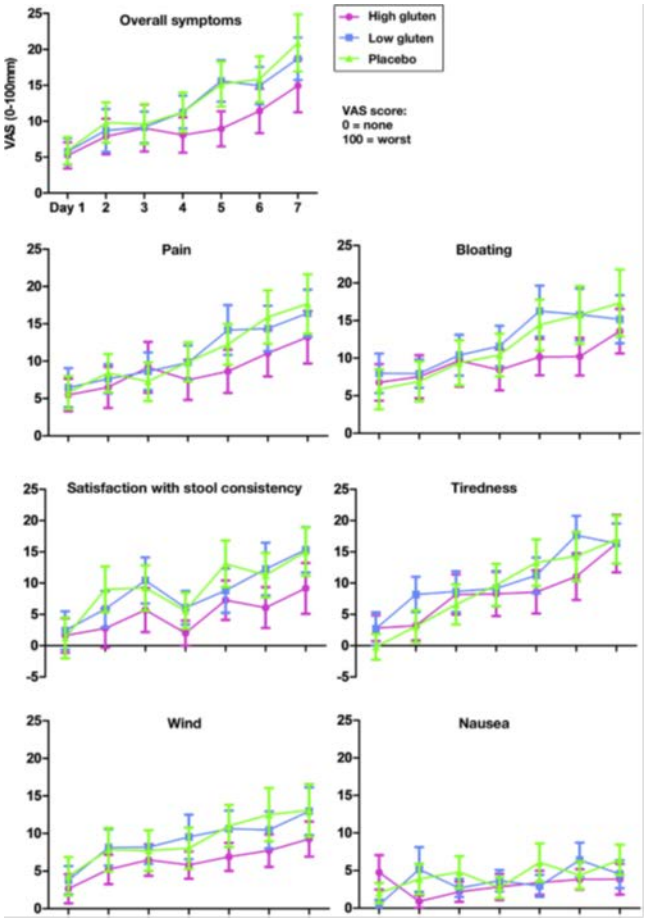
The downsides and unknowns of the diet

- Long term effects are not known
- Very stringent restrictions may have adverse effects
- Impact on the individual's microbiome

1- Maagaard, L, et al, World J. Gastroenterol: 2016, 22; 4009

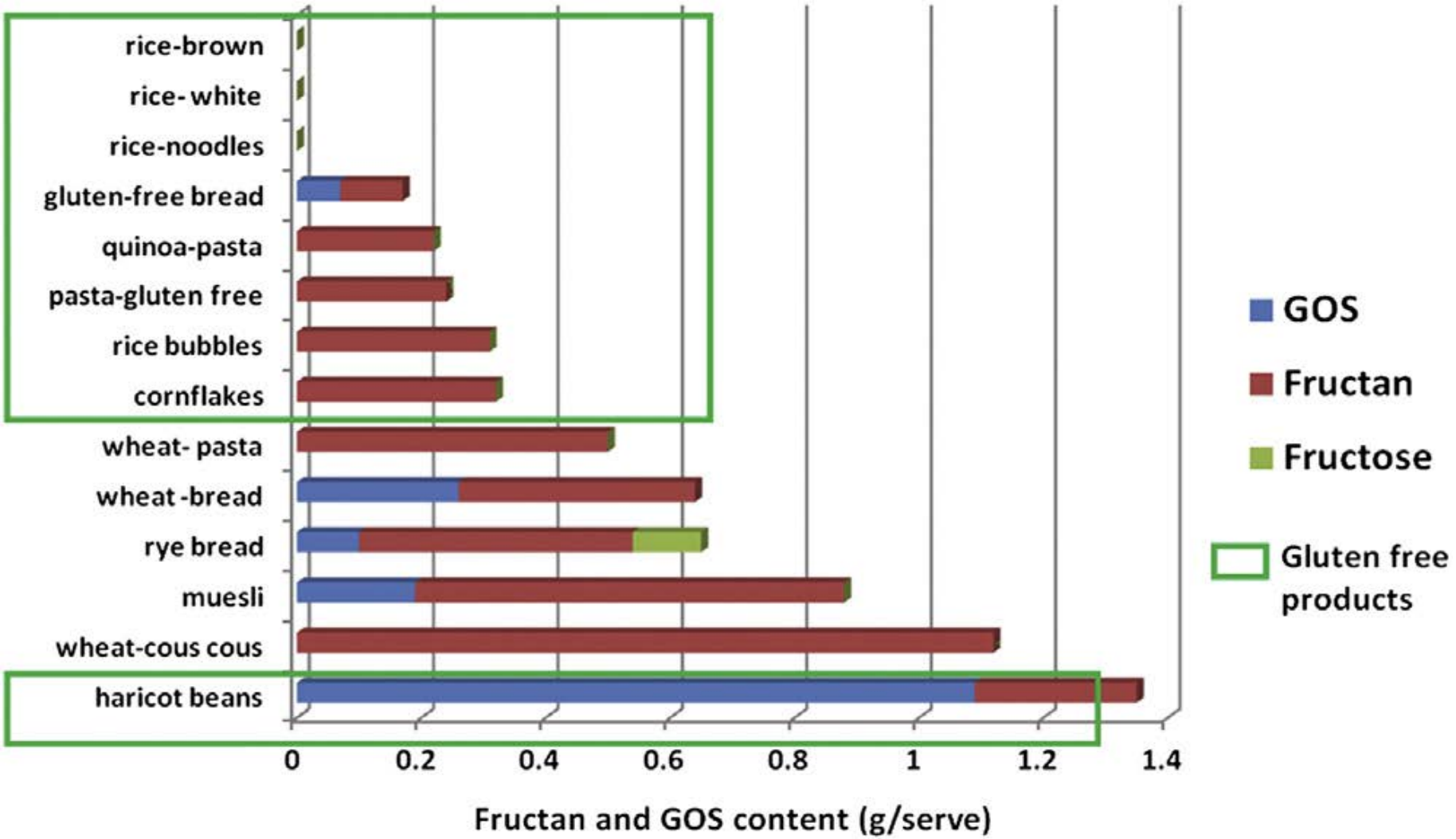
No Effect of Gluten after Reduced FODMAP Diet in IBS Patients





J. Biesiekierski, et al, Gastroenterol, 145:320, 2013

Foods +/- Gluten Coexist with Nonabsorbed Fructans and Other Saccharides



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 many years it is difficult to prove CD
  - many patients on a self-taught GFD are not truly or continually 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 Heath 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

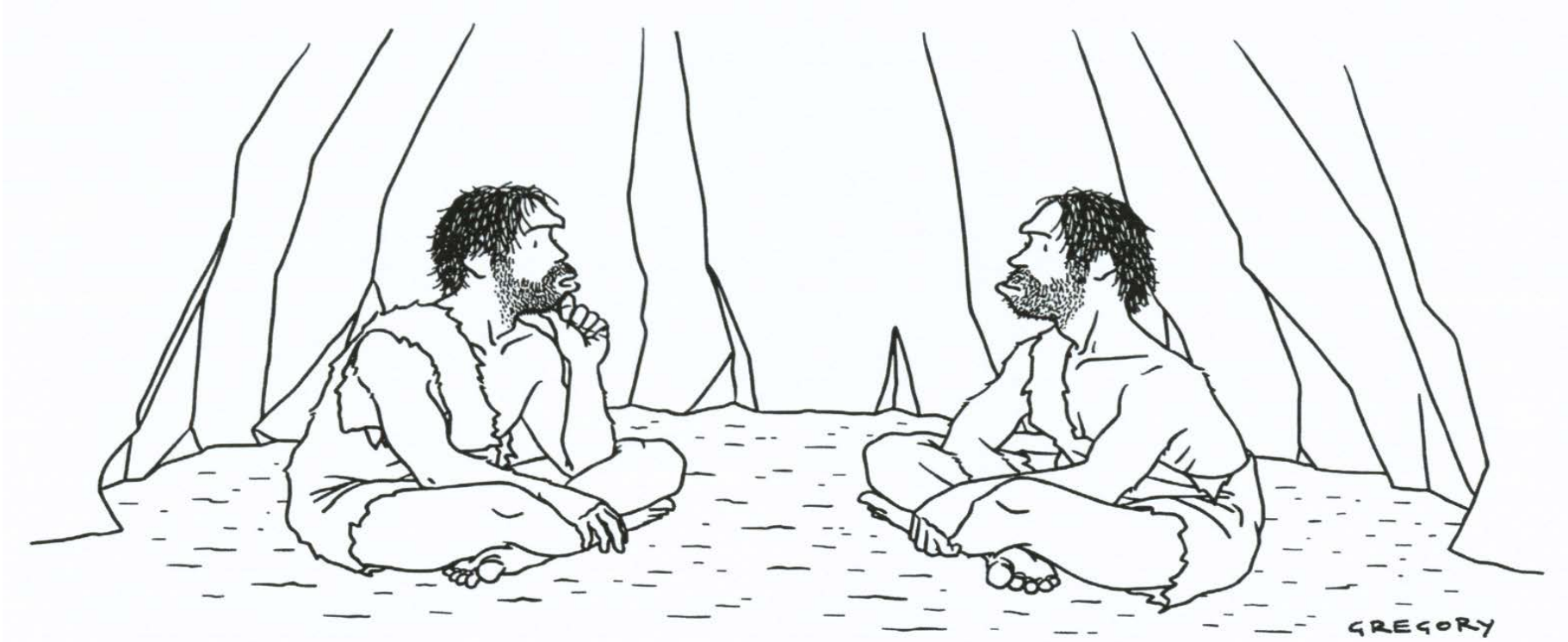
- **Many labs** – food allergies, IgG to food antigens*
- **Cyrex, ALCAT** – as per previous slide*
- **MRT/LEAP** – Measures release of immune mediators (histamine, cytokines, etc) via changes to the liquid/solids ratio of a blood sample after incubation with specific food, additive, or chemical*
- **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

Food Intolerances & Allergies
Take Home Messages

- Food ingestion is a significant factor in causing symptoms in patients with IBS and other FGID
- Culprits are often comfort foods (sweets/starches, fatty foods, histamine containing foods)
- Lactose in lactase deficient patients
- Non-celiac gluten sensitivity in some but may be due to coexisting dietary wheat starch
- Bacterial overgrowth, dysbiosis
- The low FODMAP diet does provide some benefit but difficult to adhere to long-term
- A minority will have food allergy or celiac disease – an overlap of common diseases (IBS affects 15% of the US population, 1% with celiac disease and 2-4 % of adults have food allergy)



"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."