People Shall Not Live On Bread Alone: The Role Of A Gluten Free Diet To Improve Health

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CELIAC RESEARCH PROGRAM
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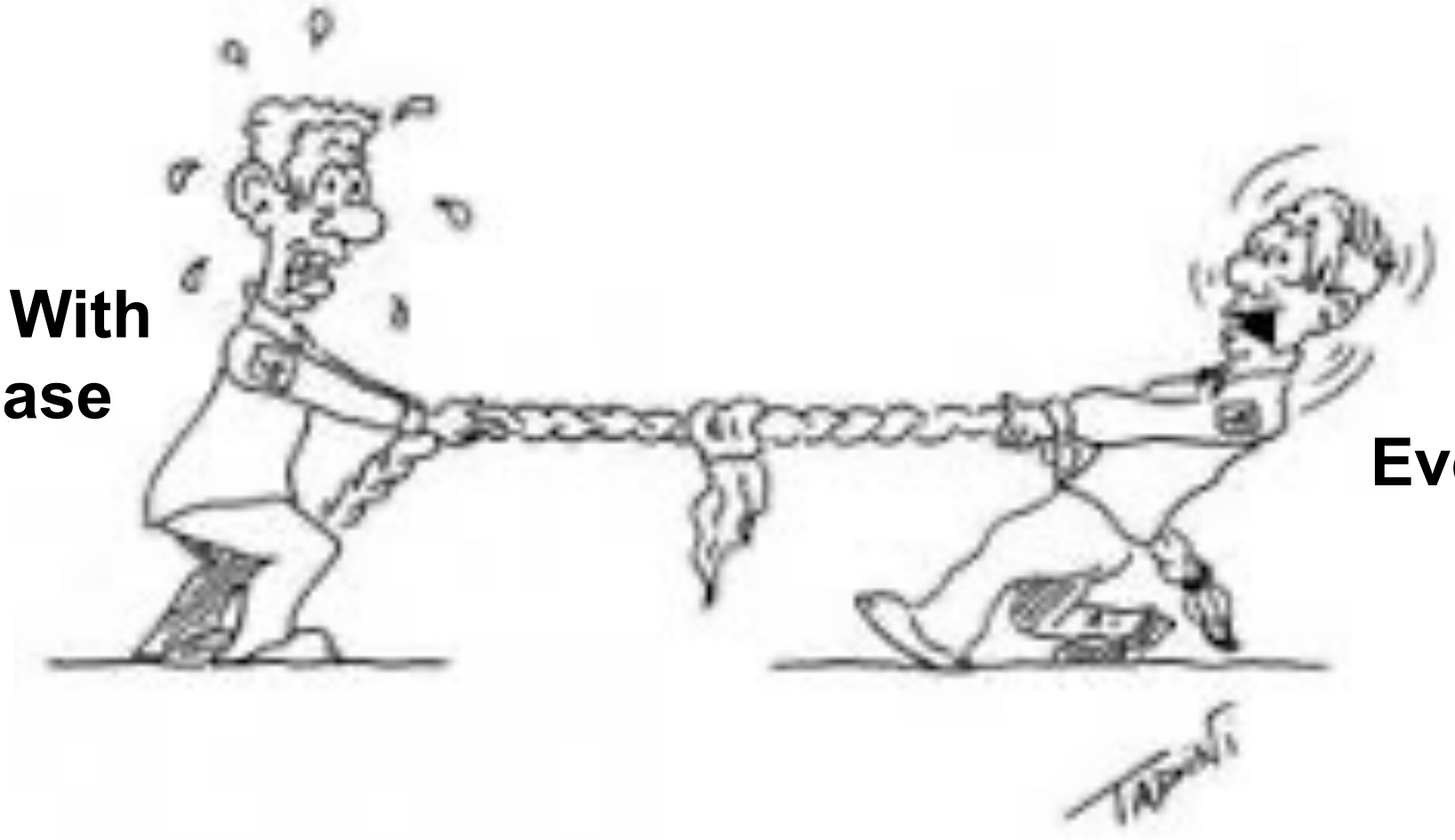
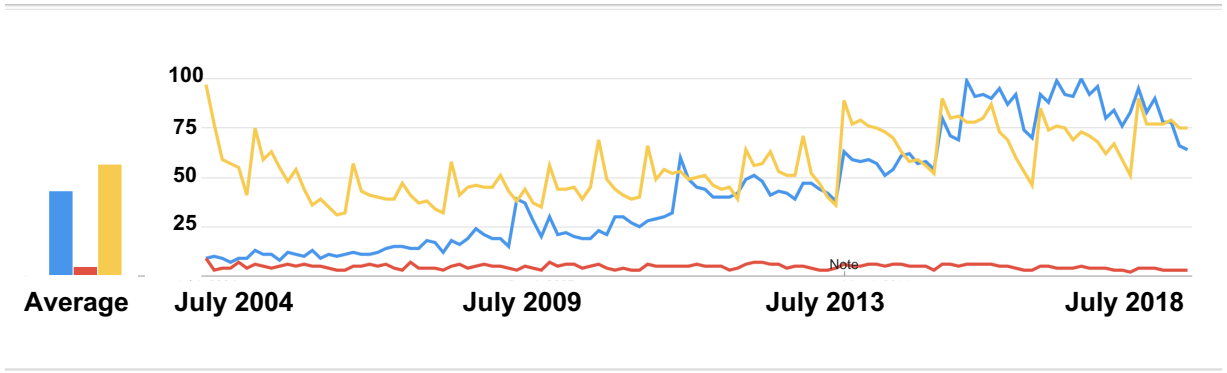
The Controversy On Who Should Be On A GFD

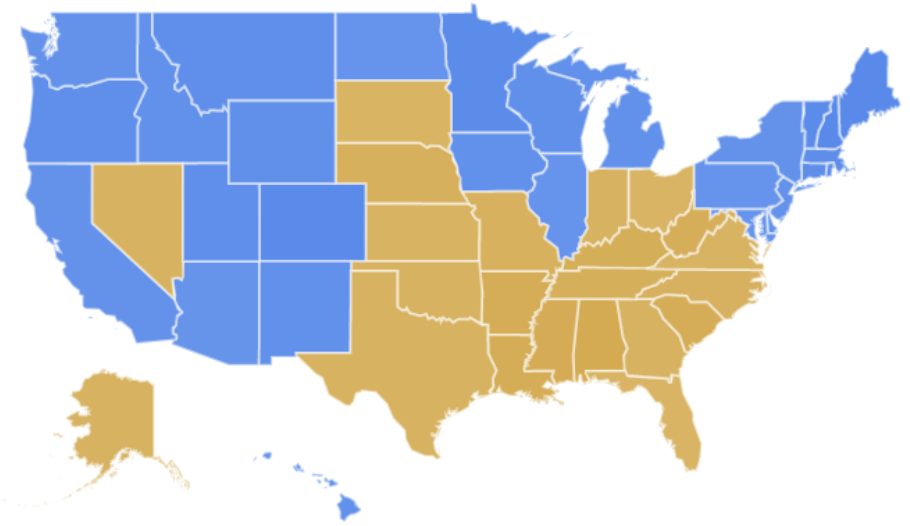
Only People With Celiac Disease

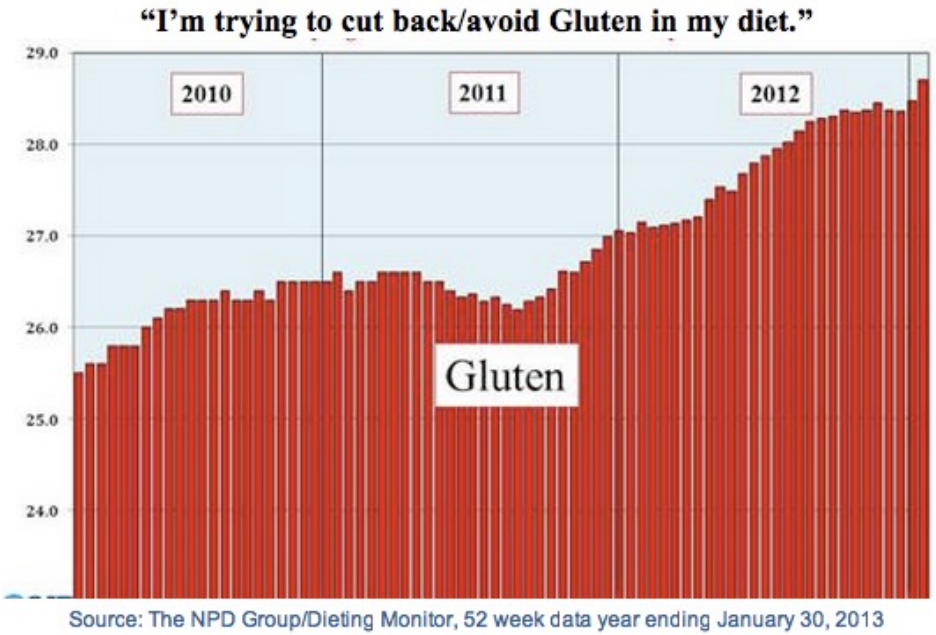


Everybody

Gluten Free Market



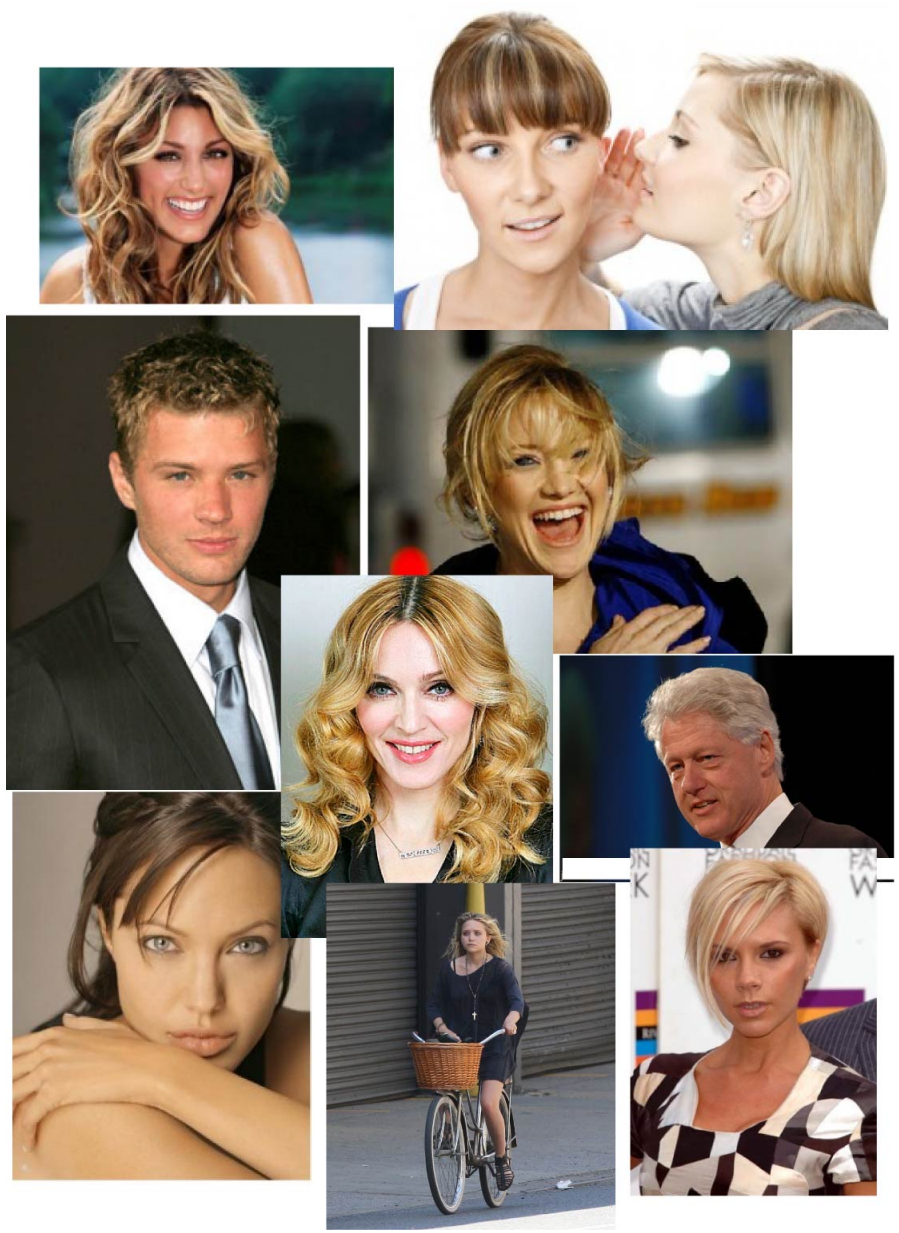


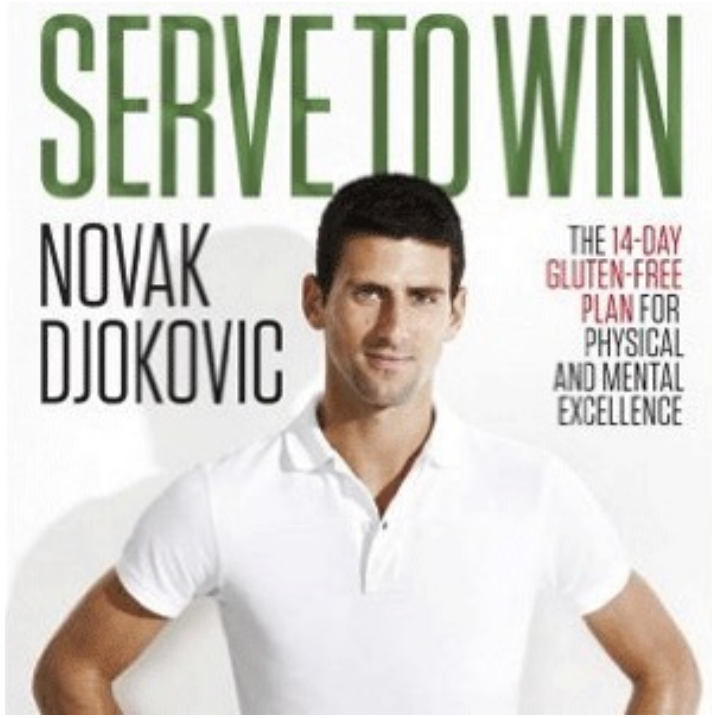


Source: The NPD Group/Dieting Monitor, 52 week data year ending January 30, 2013

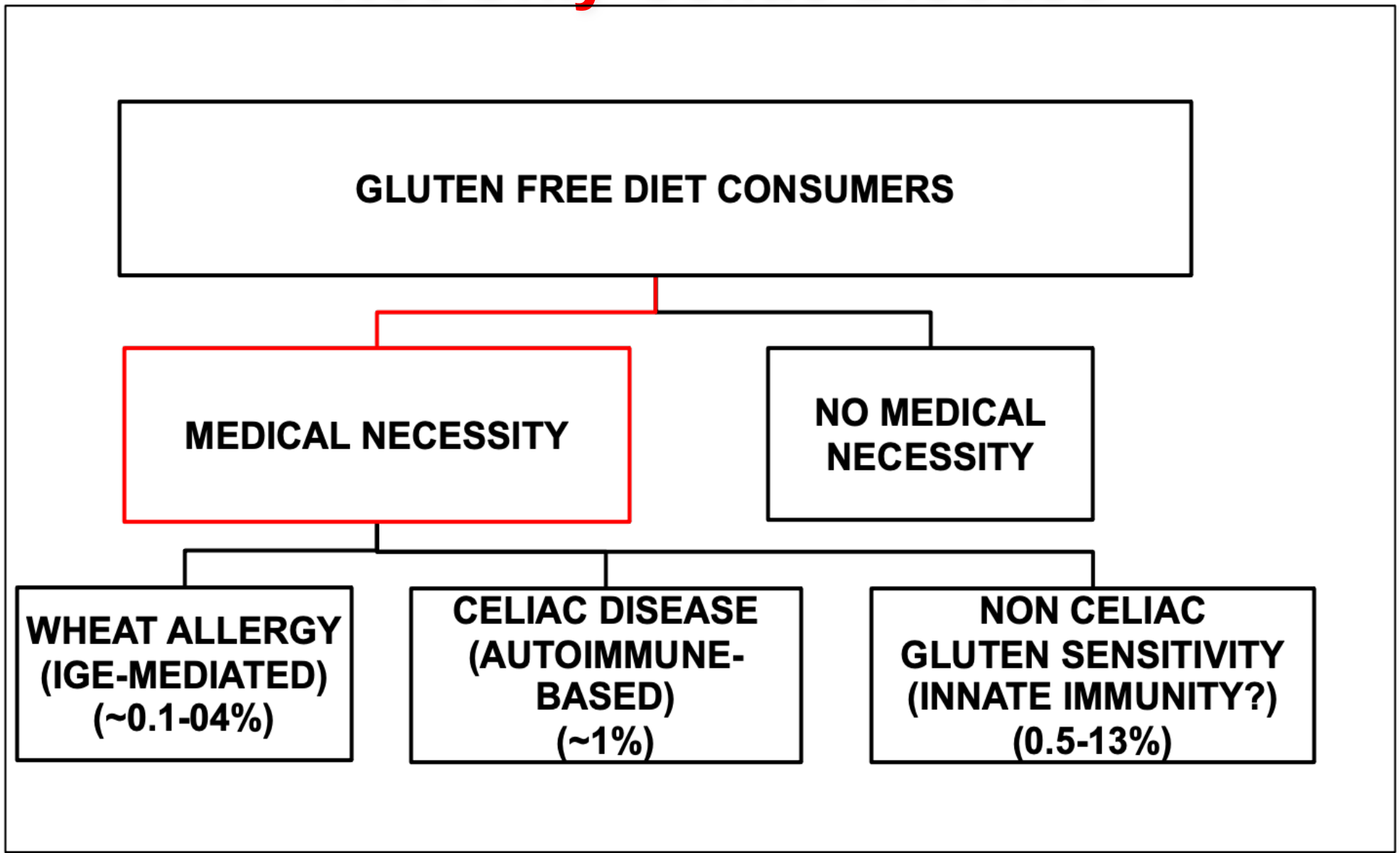
For the American general population adopting a gluten-free diet is becoming an increasingly popular solution. The market for gluten-free food and beverage products grew at a compound annual growth rate of 28 percent from 2009 to 2013, to finish with almost $11.6 billion in retail sales last year. By 2023 the market is expected to reach about $ 19.6 billion in sales.

The Fad Factor of the GFD

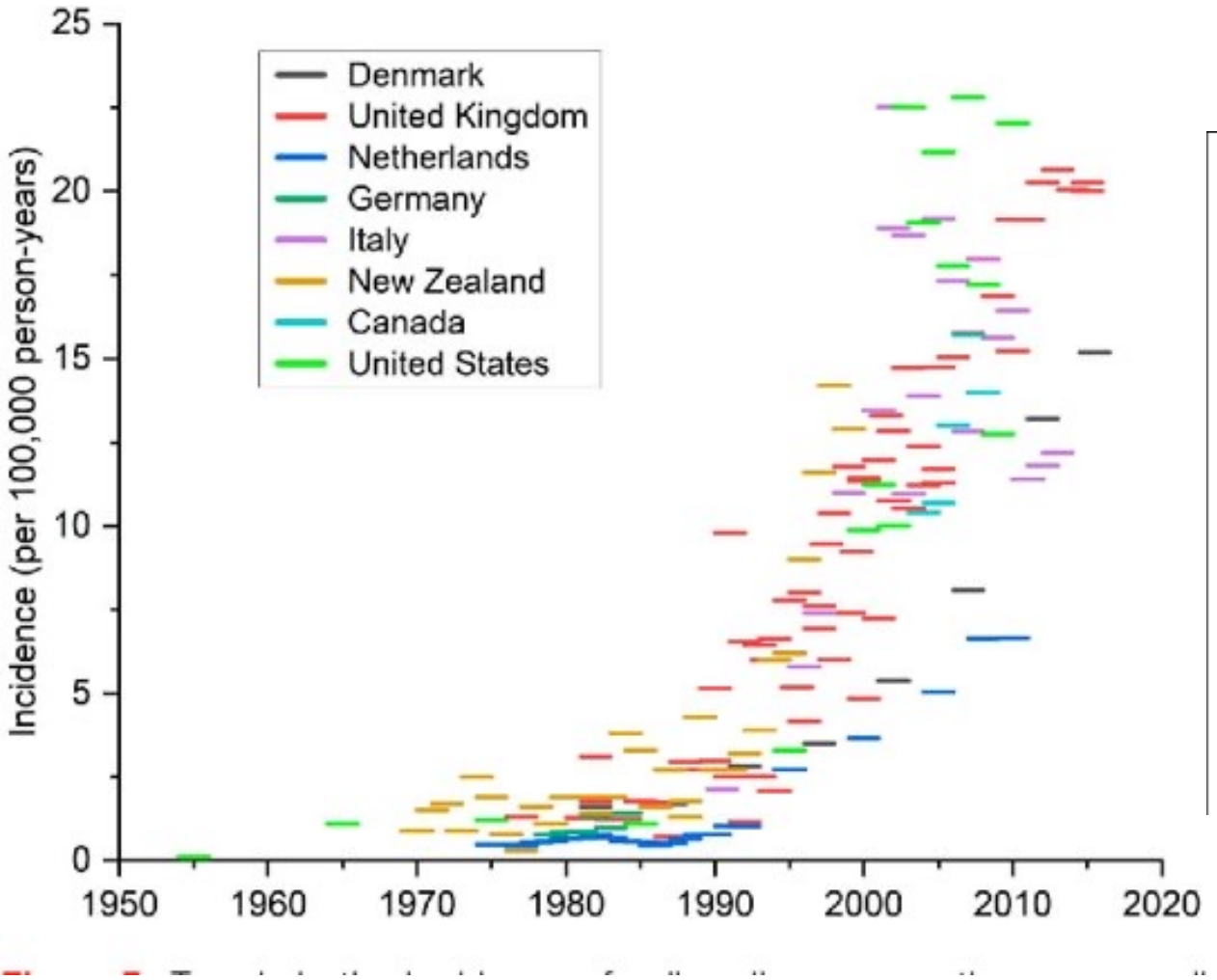


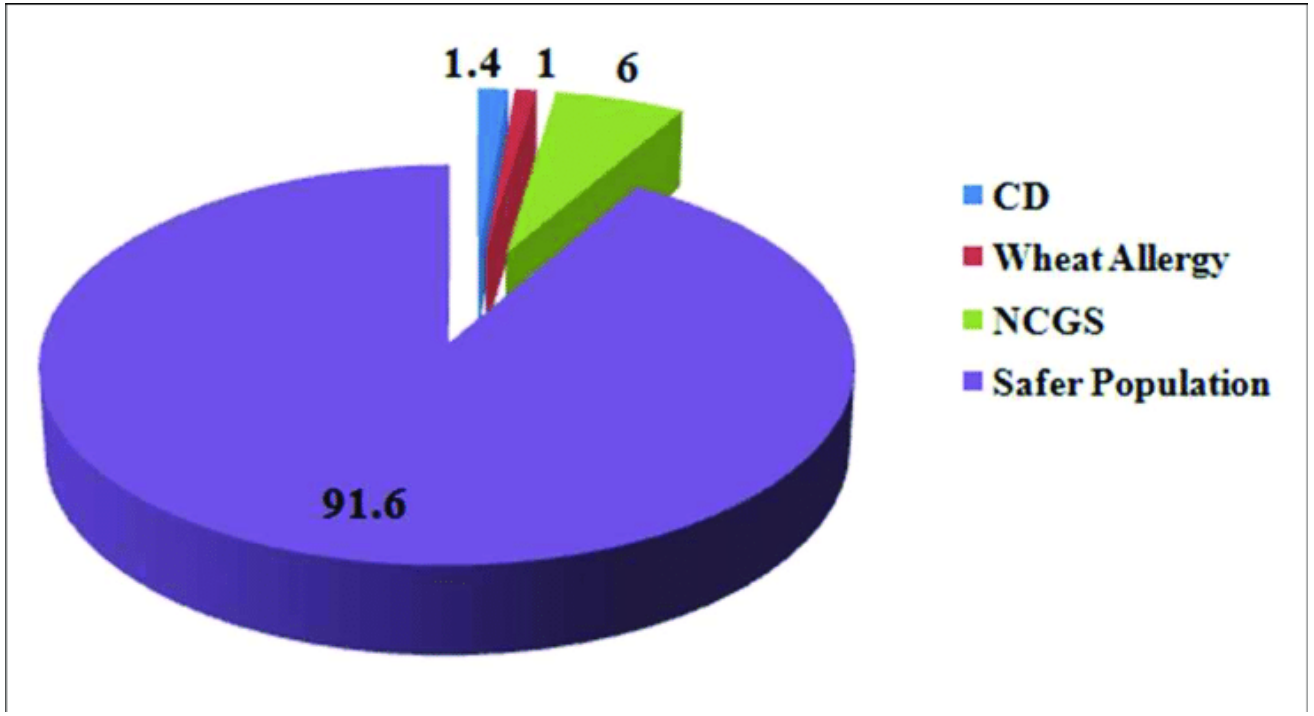


The Gluten Free Diet:
Not Only Celiac Disease



The Epidemics of GRD





The Epidemics Of Gluten Related Disorders

- **Quality of gluten: GE grains**
- **Quantity of gluten**
- **Gluten cannot be digested**

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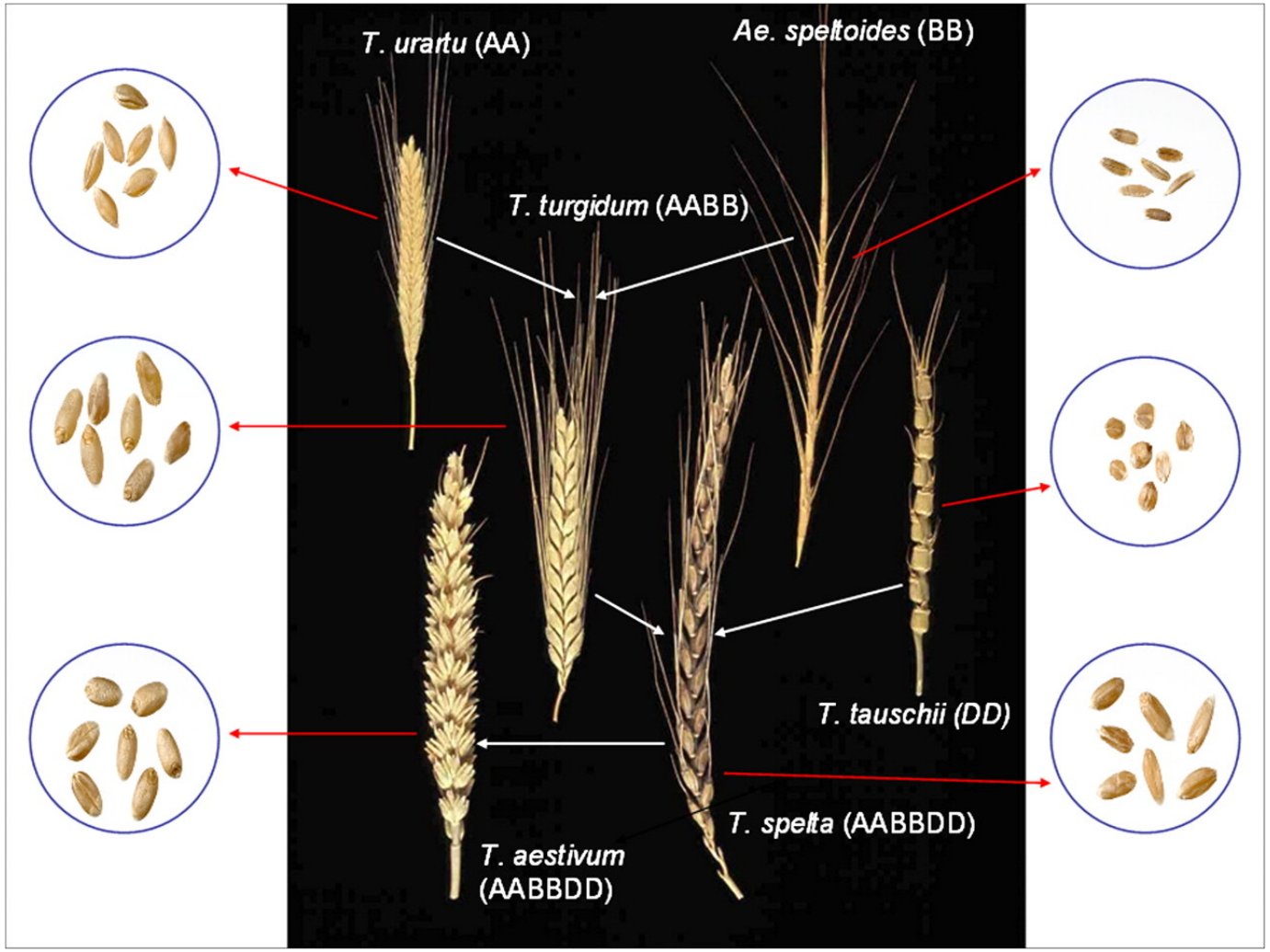
The evolutionary and genome relationships between cultivated bread and durum wheats and related wild diploid grasses, showing examples of spikes and grain.



Shewry P R J. Exp. Bot. 2009;60:1537-1553

JOURNAL OF
Experimental Botany

GMO Grains

+

T. turgidum AABB
28 chromosomes
100,000 genes

Aegilops tauschii DD
14 chromosomes
50,000 genes

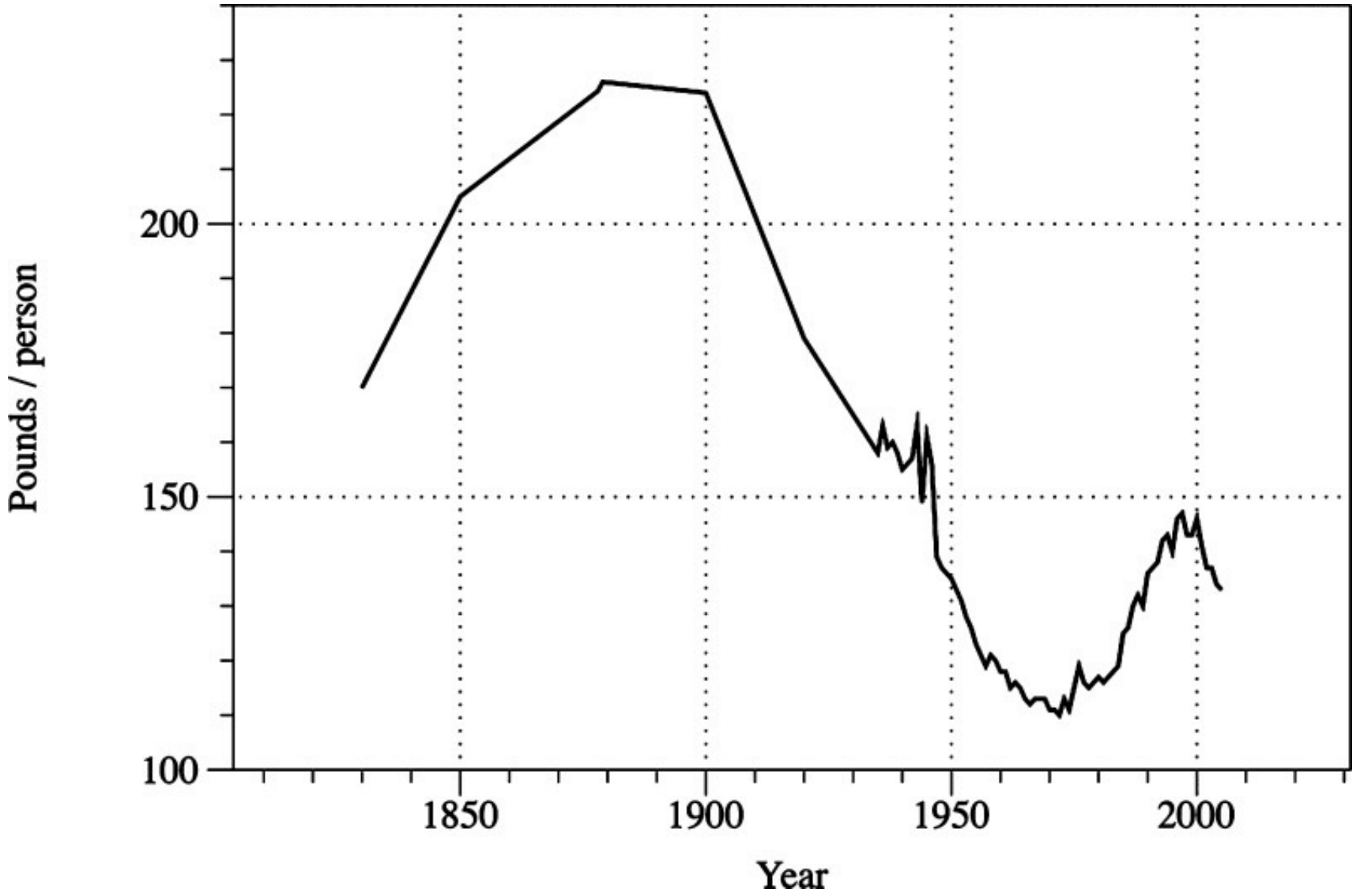
T. aestivum AABBDD
42 chromosomes
150,000 genes

The Epidemics Of Gluten Related Disorders

- Quality of gluten: GE grains

- **Quantity of gluten**

- Gluten cannot be digested



Kasarda D. J Agric Food Chem. 2013;61: 1155–1159

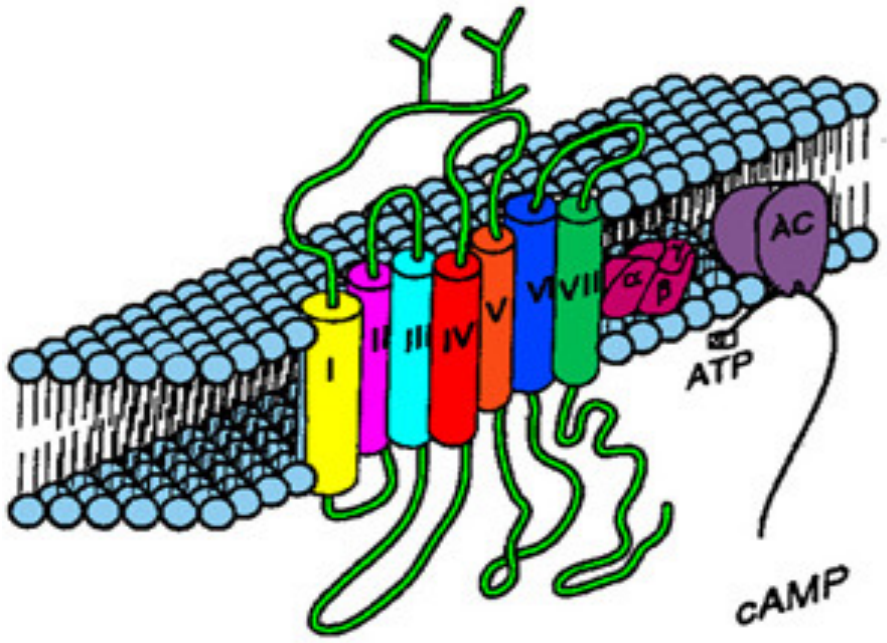
The Epidemics Of Gluten Related Disorders

- Quality of gluten: GE grains

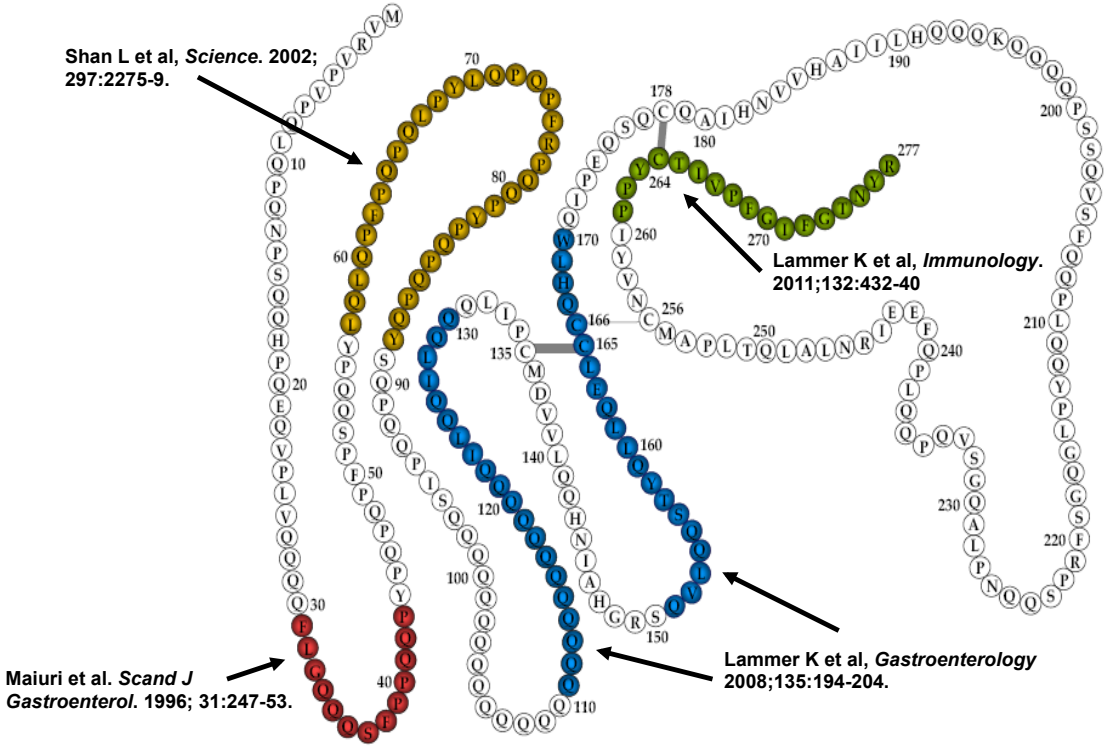
- Quantity of gluten

- **Gluten cannot be digested**

Understanding Why Gluten is Toxic



- CXCR-3 is a seven-transmembrane G couple protein receptor that is preferentially expressed on activated T lymphocytes and subset of B and NK cells.
- Three known CXCR3 ligands CXCL-9, -10, -11 are produced at the site of inflammation and elicit migration of pathological Th1 cells.
- CXCR3 has been implicated as a potential target for impeding T-cell-mediated destruction in autoimmune diseases such as multiple sclerosis and type 1 diabetes



Mapping of α-gliadin motifs exerting cytotoxic activity (red), immunomodulatory activity (light green), zonulin release and gut permeating activity (blue) and CXCR3-dependent IL8 release in CD patients (dark green).

Lammers K et al Gastroenterology 2008; 135:194-204

JAMA | Review

Celiac Disease and Nonceliac Gluten Sensitivity
A Review

Maureen M. Leonard, MD, MMSc; Anna Sapone, MD, PhD; Carlo Catassi, MD, MPH; Alessio Fasano, MD

IMPORTANCE The prevalence of gluten-related disorders is rising, and increasing numbers of individuals are empirically trying a gluten-free diet for a variety of signs and symptoms. This review aims to present current evidence regarding screening, diagnosis, and treatment for celiac disease and nonceliac gluten sensitivity.

OBSERVATIONS Celiac disease is a gluten-induced immune-mediated enteropathy characterized by a specific genetic genotype (*HLA-DQ2* and *HLA-DQ8* genes) and autoantibodies (antitissue transglutaminase and antiendomysial). Although the inflammatory process specifically targets the intestinal mucosa, patients may present with gastrointestinal signs or symptoms, extraintestinal signs or symptoms, or both, suggesting that celiac disease is a systemic disease. Nonceliac gluten sensitivity is diagnosed in individuals who do not have celiac disease or wheat allergy but who have intestinal symptoms, extraintestinal symptoms, or both, related to ingestion of gluten-containing grains, with symptomatic improvement on their withdrawal. The clinical variability and the lack of validated biomarkers for nonceliac gluten sensitivity make establishing the prevalence, reaching a diagnosis, and further study of this condition difficult. Nevertheless, it is possible to differentiate specific gluten-related disorders from other conditions, based on currently available investigations and algorithms. Clinicians cannot distinguish between celiac disease and nonceliac gluten sensitivity by symptoms, as they are similar in both. Therefore, screening for celiac disease must occur before a gluten-free diet is implemented, since once a patient initiates a gluten-free diet, testing for celiac disease is no longer accurate.

CONCLUSIONS AND RELEVANCE Celiac disease and nonceliac gluten sensitivity are common. Although both conditions are treated with a gluten-free diet, distinguishing between celiac disease and nonceliac gluten sensitivity is important for long-term therapy. Patients with celiac disease should be followed up closely for dietary adherence, nutritional deficiencies, and the development of possible comorbidities.

JAMA. 2017;318(7):647-656. doi:10.1001/jama.2017.9730

CME Quiz at
jamanetwork.com/learning

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Corresponding Author: Alessio Fasano, MD, Center for Celiac Research and Mucosal Immunology and Biology Research Center, Massachusetts General Hospital East, Bldg 114, 16th St (Mail Stop 114-3503), Charlestown, MA 02129-4404 (afasano@mgh.harvard.edu).

Section Editors: Edward Livingston, MD, Deputy Editor, and Mary McGrae McDermott, MD, Senior Editor.

Wheat Allergy

Signs and Symptoms

Nausea, Diarrhea, and Vomiting

Hives, Itchy rash or swelling of the skin

Nasal congestion, or Allergic rhinitis

Eczema, or Atopic dermatitis

Swelling, itching or irritation of the mouth or throat

IGE-MEDIATED WHEAT ALLERGY

- Food allergy, by definition, depends on an underlying immune-mediated process for its occurrence
- Food allergy is most common in the first year of life, decreasing in adolescence and adulthood
- Wheat is among the 10 most common allergens responsible for food allergy
- Clinical manifestations include: abdominal pain, nausea, vomiting, diarrhea, skin rashes, rhinitis, conjunctivitis

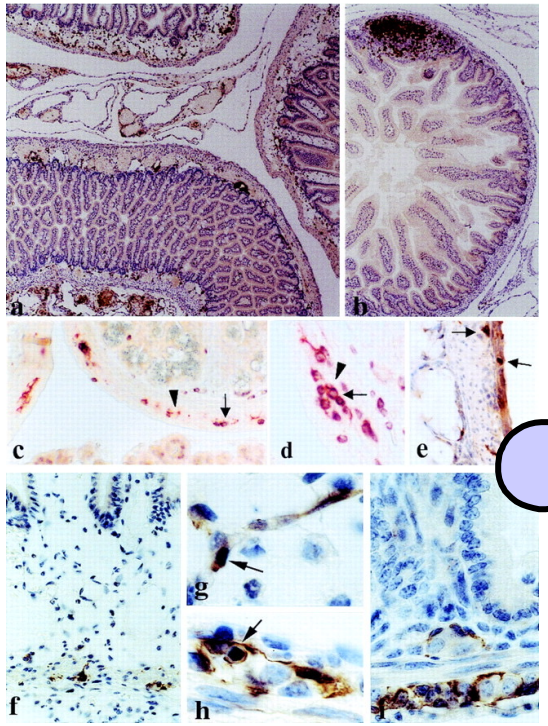
EOSINOPHILIC ESOPHAGITIS

- Increasing incidence world-wide
- Symptoms overlap GERD
- Suspect in cases of feeding aversion, dysphagia, food impaction
- Diagnosis made by endoscopy, biopsies
- Treatment involves elimination diets, topical steroids
- Complications include esophageal strictures, perforation

WHEAT-DEPENDENT, EXERCISE-INDUCED ANAPHYLAXIS

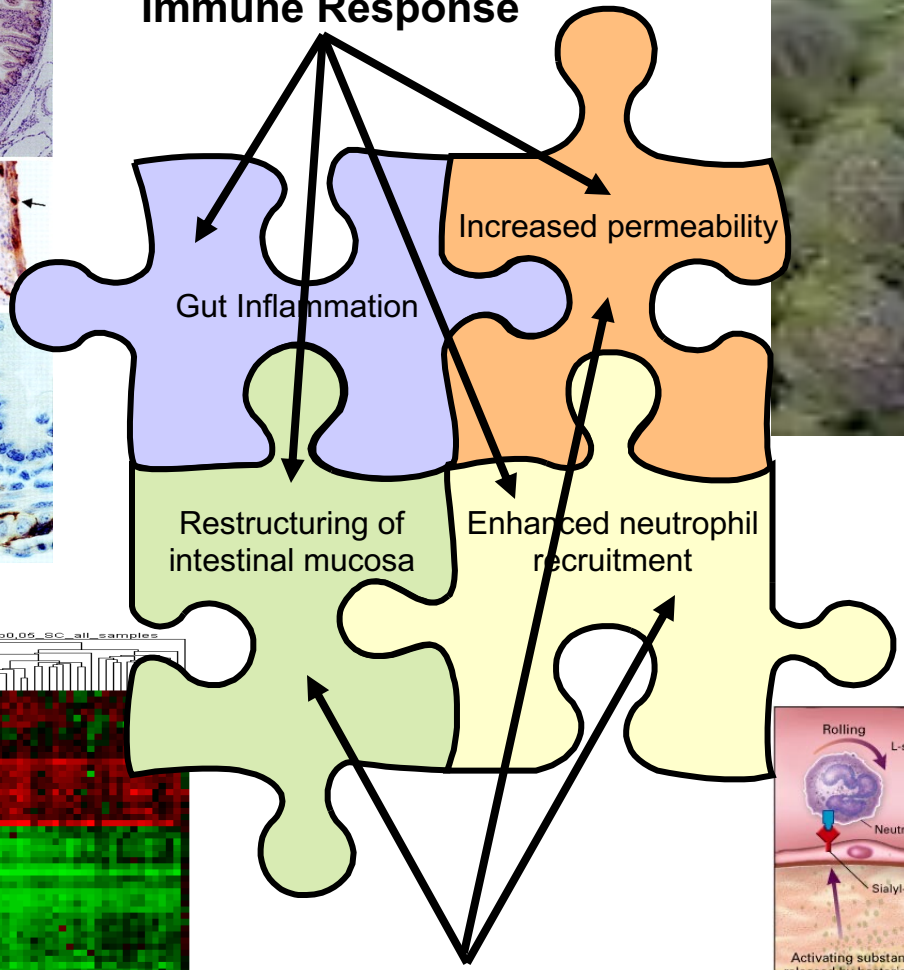
- High index of suspicion needed for diagnosis
- Ingestion of wheat is a pre-condition, but clinical picture does not manifest unless subject engages in exercise
- Intensity of exercise can be as mild as game of ping-pong or walking up hill
- Exercising within 2 hours carries high risk of unchaining immune reactions leading to anaphylaxis

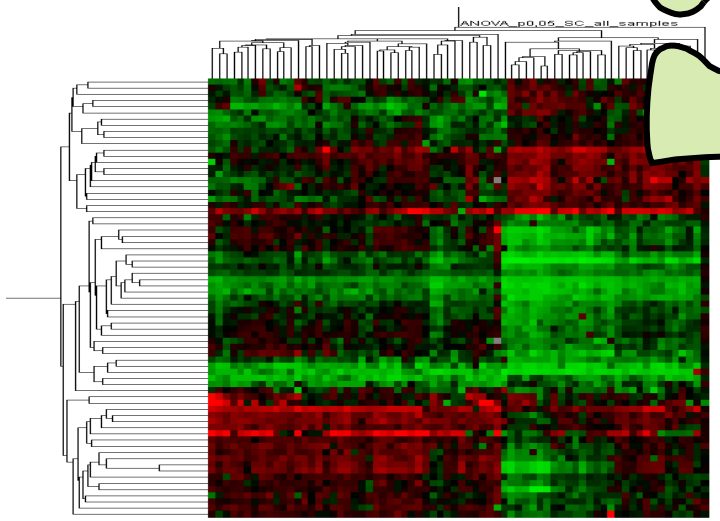
Mucosal Events of NCGS vs. Celiac Disease



CD

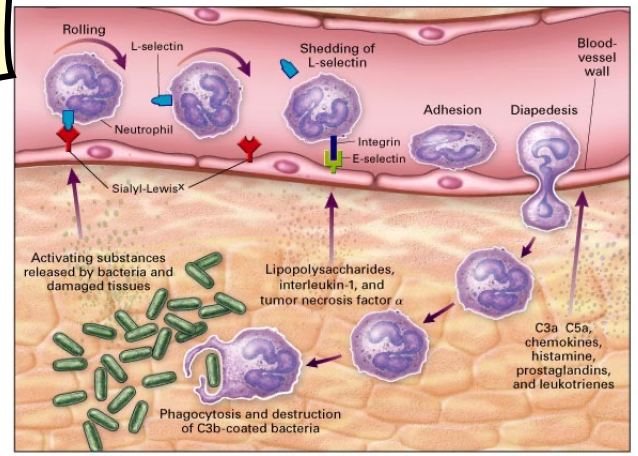
Innate + Adaptive Immune Response



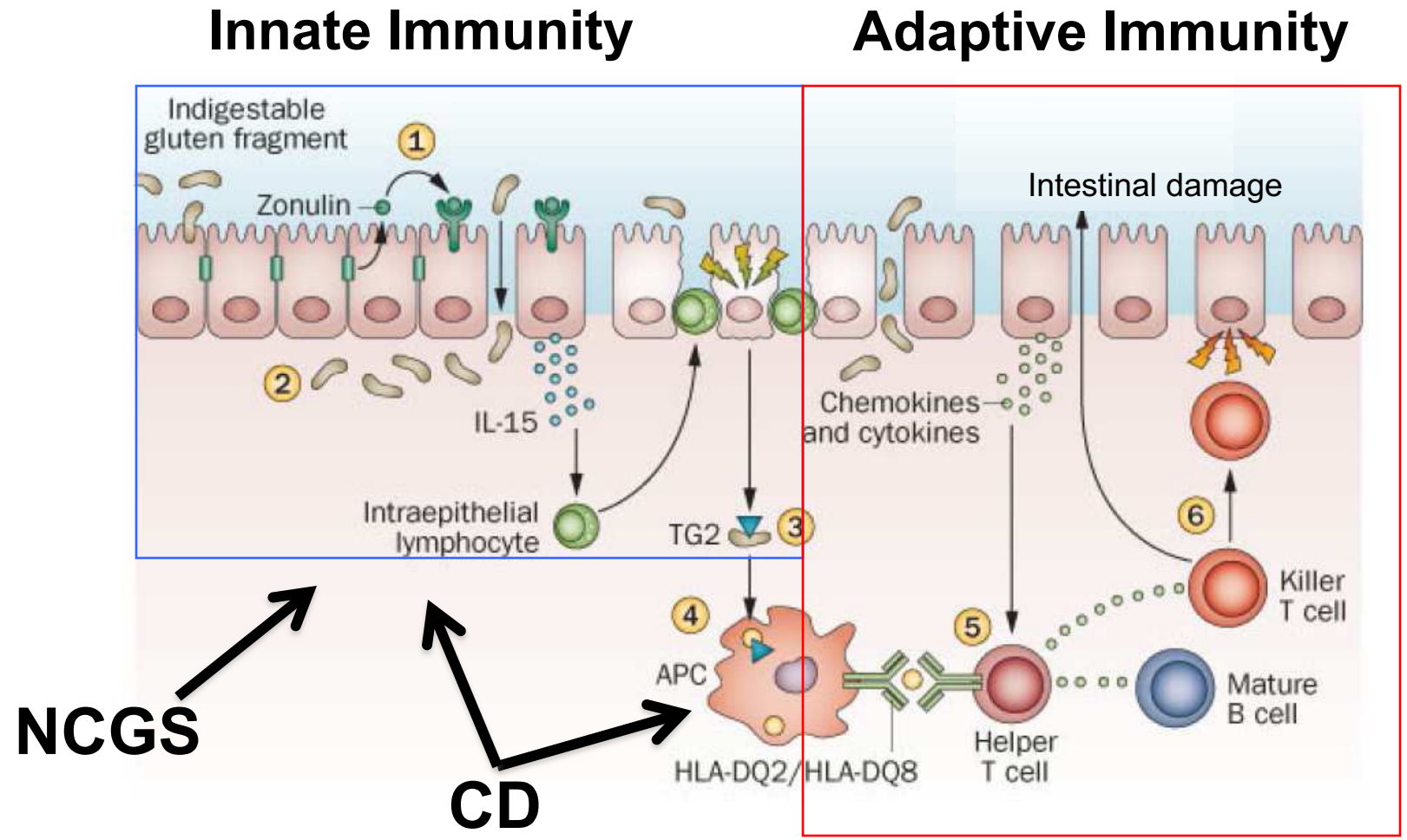


NCGS

Innate immune response



Innate Immunity is Common to Both NCGS and CD, While Adaptive Immunity Is Specific For Celiac Disease Pathogenesis



DA. Leffler et al. Nature Rewies Gastroenterology and Hepatology, 2015


Non Celiac
Gluten Sensitivity

Gluten Sensitivity (NCGS): Facts Definition

<u>Cases of reaction to ingestion of gluten-containing grains</u> 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)

Sapone A. et al BMC Med 2012, Ludvigsson JF et al Gut 2013, Catassi C. Et al, Nutrients 2013

Symptoms	Presence of Symptoms: Celiac Disease[b]	Nonceliac Gluten Sensitivity	
Intestinal			
Abdominal pain, %	+ (27.8)	+	(68)
Anorexia	+	–	
Bloating	+	+	
Constipation, %	+ (20.2)	+	
Diarrhea, %	+ (35.3)	+	(33)
Flatulence	+	+	
Lactose intolerance	+	–	
Nausea	+	–	
Gastroesophageal reflux	+	–	
Weight loss	+	–	
Vomiting	+	–	
Extraintestinal			
Anemia, %	+ (32)	+	(20)
Anxiety	+	+	
Arthralgia, %	+ (29.3)	+	(11)
Arthritis, %	+ (1.5)	+	
Ataxia	+	+	
Dental enamel hypoplasia	+	–	
Delayed puberty	+	–	
Dermatitis herpetiformis	+	–	
Depression	+	+	(22)
Elevated liver enzymes	+	–	
Rash (eg, eczema)	+	+	(40)
Fatigue, %	+ (26.3)	+	(33)
Cloudiness of consciousness	+	+	(34)
Headache	+	+	(35)
Infertility	+ (1.5)	–	
Irritability	+	+	
Iron-deficiency anemia	+	–	
Mouth sores	+	–	
Myalgias	+	+	
Osteoporosis, %	+ (5.5)	–	
Pancreatitis	+	–	
Peripheral neuropathy, %	+ (0.7)	+	
Short stature, %	+ (1.0)	–	

[a] Sources: Lionetti and Catassi[5] and Fasano et al.[6]

[b] Prevalence of celiac disease at presentation indicated in parentheses where available.[5,7]

Leonard M et al JAMA 2017

Clinical Manifestations of NCGS

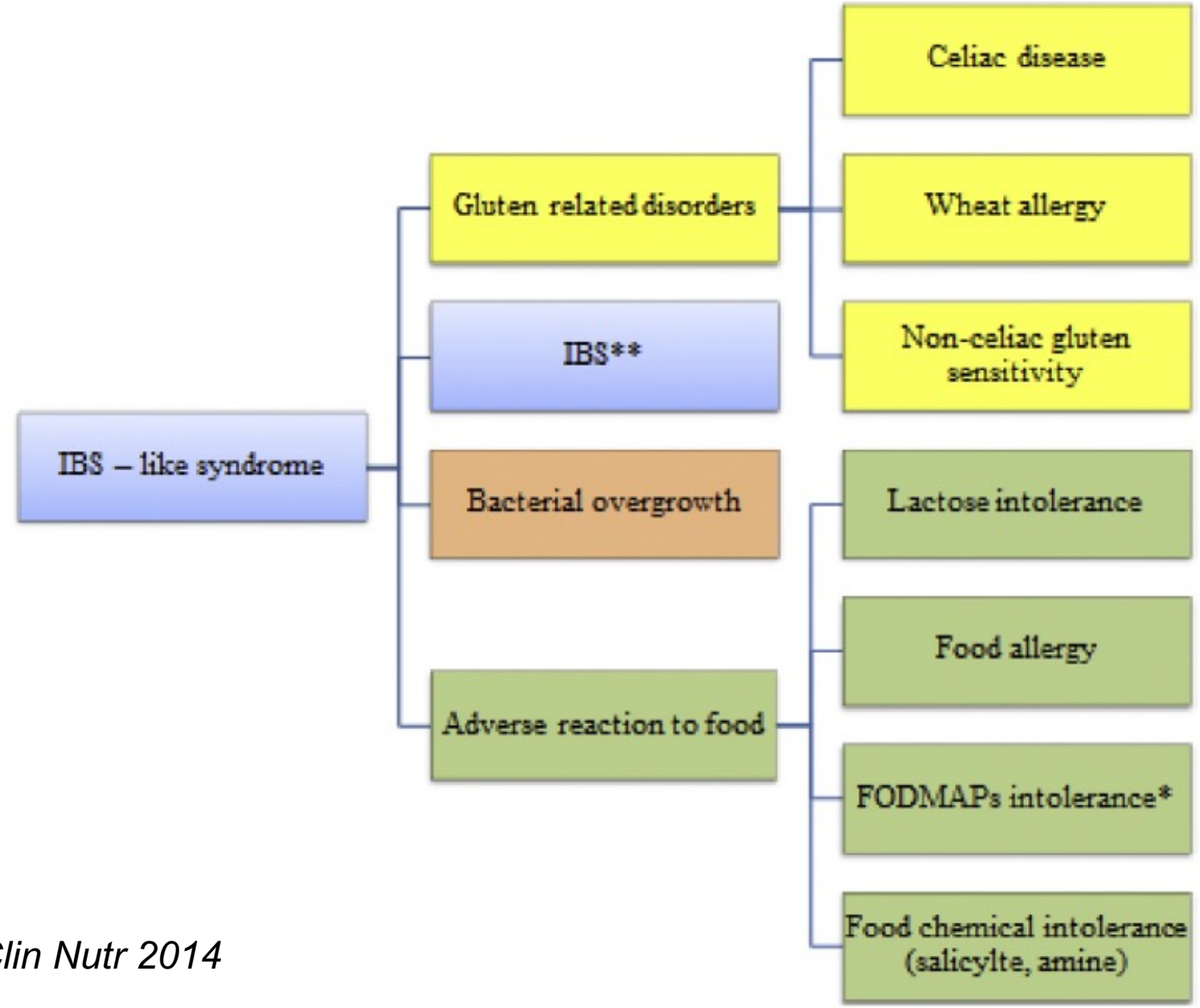
Frequency	Intestinal	Extra-intestinal
Very Common	Bloating	Lack of wellbeing
	Abdominal pain	Tiredness
Common	Diarrhea	Headache
	Epigastric pain	Anxiety
	Nausea	Foggy mind
	Aerophagia	Numbness
	GER	Joint/muscle pain
	Aphtous stomatitis	Skin rash/dermatitis
	Alternating bowel habits	
	Constipation	
Undetermined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

Sapone A. et al BMC Med 2012
Catassi C. Et al, Nutrients 2013

The Salerno NCGS diagnostic criteria (Nutrients, 2015)

Gluten Sensitivity and IBS

Pathogenesis Of IBS-Like Syndromes

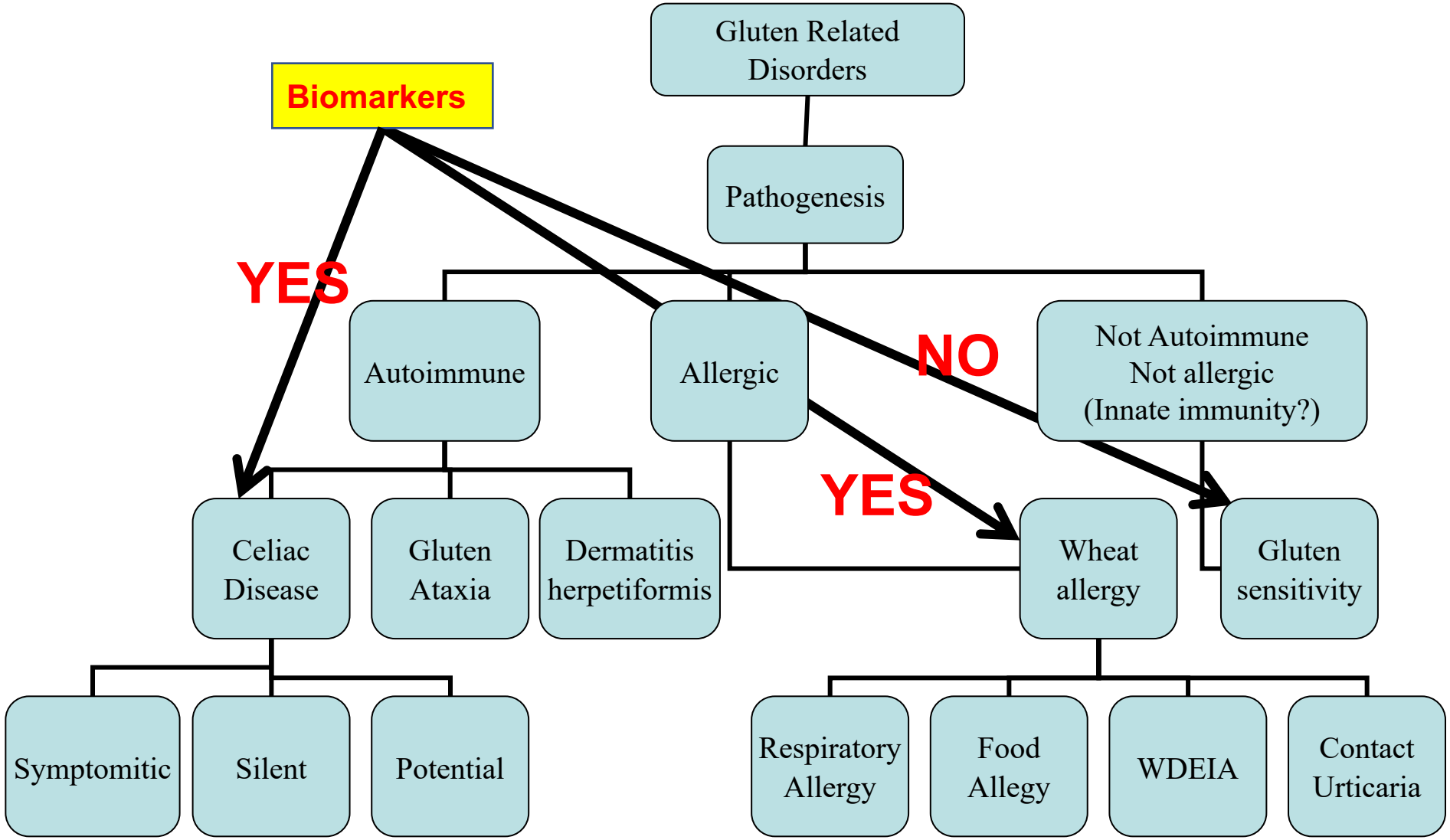


Czaja-Bulsa G et al, Clin Nutr 2014

Key Questions About Non-Celiac Gluten Sensitivity:

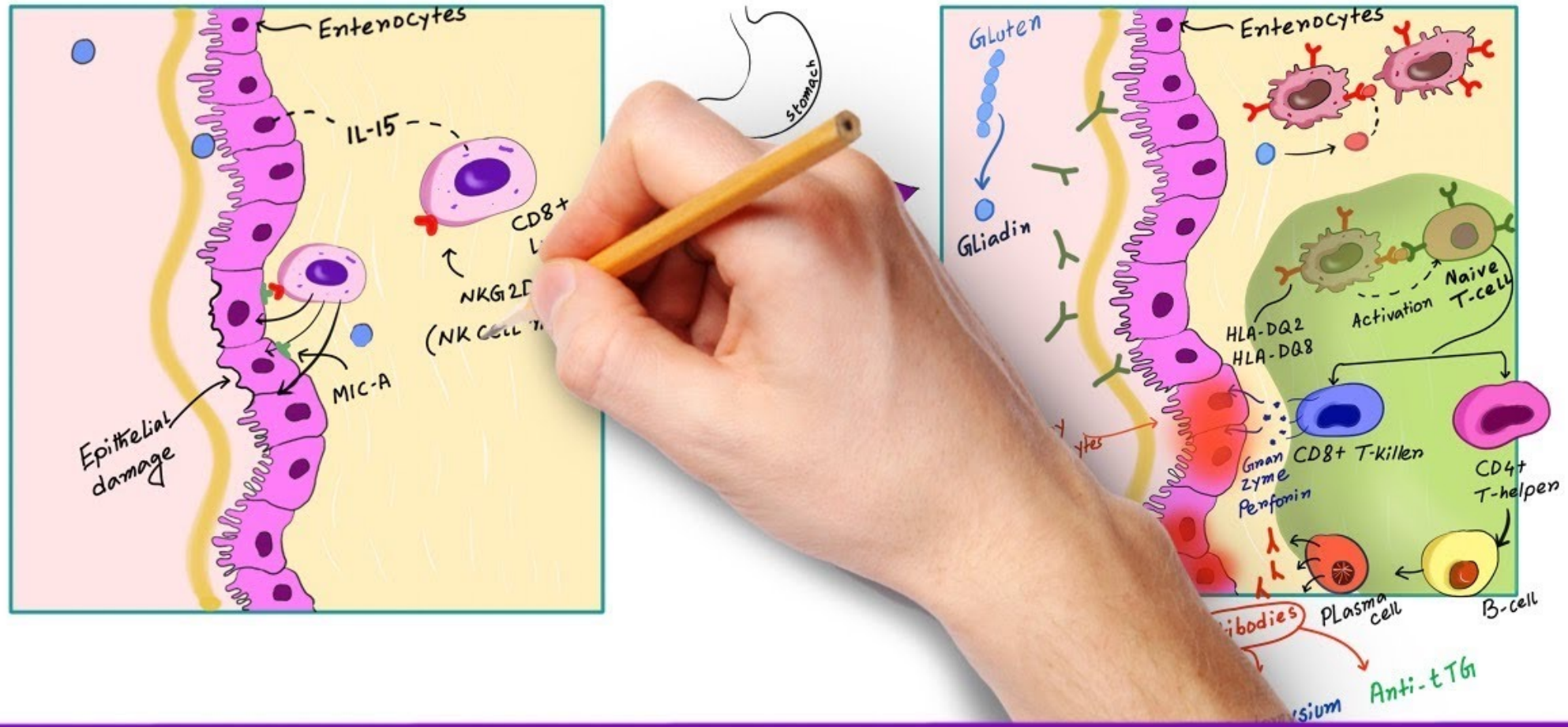
- **Are current diagnostic tools (dietary re-challenge – Salerno criteria) feasible in clinical practice?**
- **Are there any validated biomarkers for the diagnosis of NCGS?**
- **How gluten and possibly other wheat components cause symptoms on NCGS?**

Proposed New Classification of Gluten Related Disorders



Celiac Disease

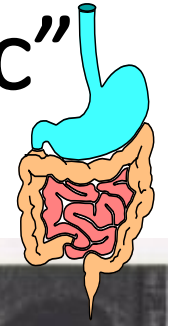
Celiac Disease Pathophysiology



Celiac Disease as a Unique Model of Autoimmunity

- **The only autoimmune disease in which specific MHC class II HLA (DQ2 and/or DQ8) are present in >95% of patients;**
- **The auto-antigen (tissue Transglutaminase) is known;**
- **The environmental trigger (gluten) is known;**
- **Elimination of the environmental trigger leads to a complete resolution of the autoimmune process that can be re-ignited following re-exposure to gluten**

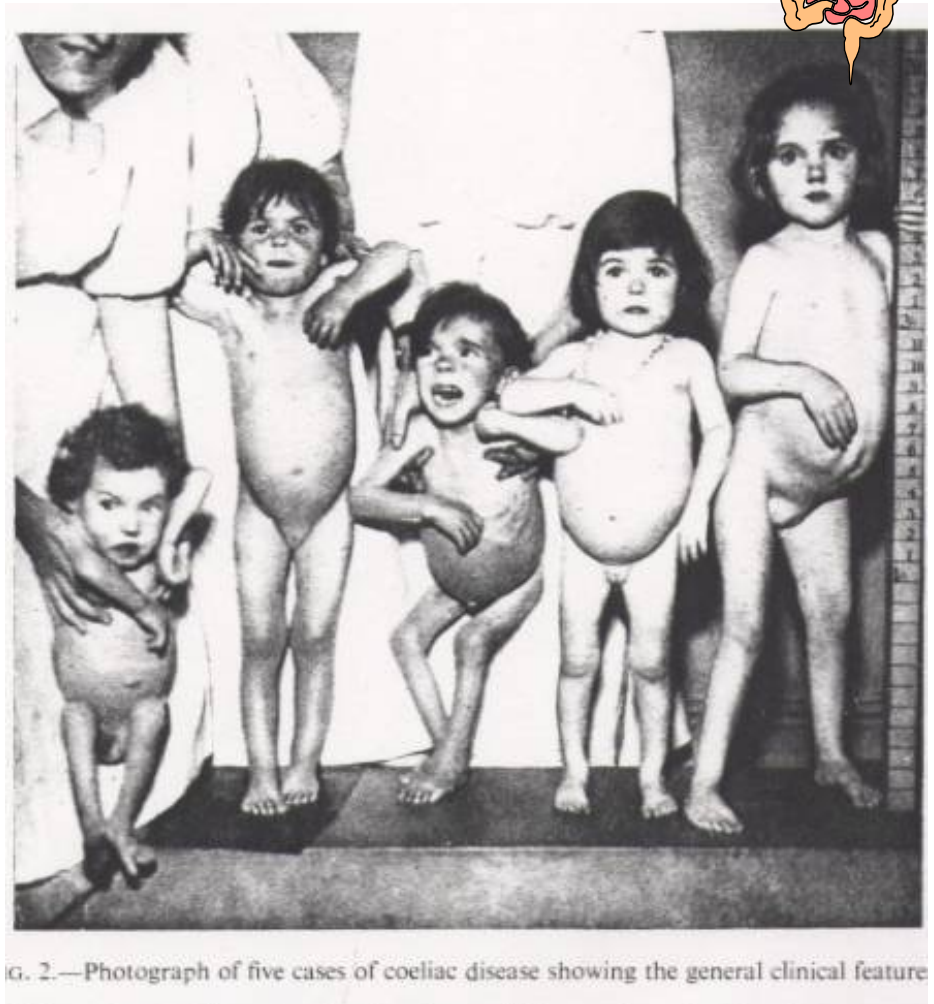
Gastrointestinal Manifestations: “Classic”



Most common age of presentation: 6-24 months

- Chronic or recurrent diarrhea
- Abdominal distension
- Anorexia
- Failure to thrive or weight loss
- Abdominal pain
- Vomiting
- Constipation
- Irritability

Rarely: Celiac crisis



G. 2.—Photograph of five cases of coeliac disease showing the general clinical feature

Non Gastrointestinal Manifestations

Most common age of presentation: older child to adult

- Dermatitis Herpetiformis
- Dental enamel hypoplasia of permanent teeth
- Osteopenia/Osteoporosis
- Short Stature
- Delayed Puberty

- Iron-deficient anemia resistant to oral Fe
- Hepatitis
- Arthritis
- Epilepsy with occipital calcifications

Listed in descending order of strength of evidence

Diagnosis

Serological Test Comparison

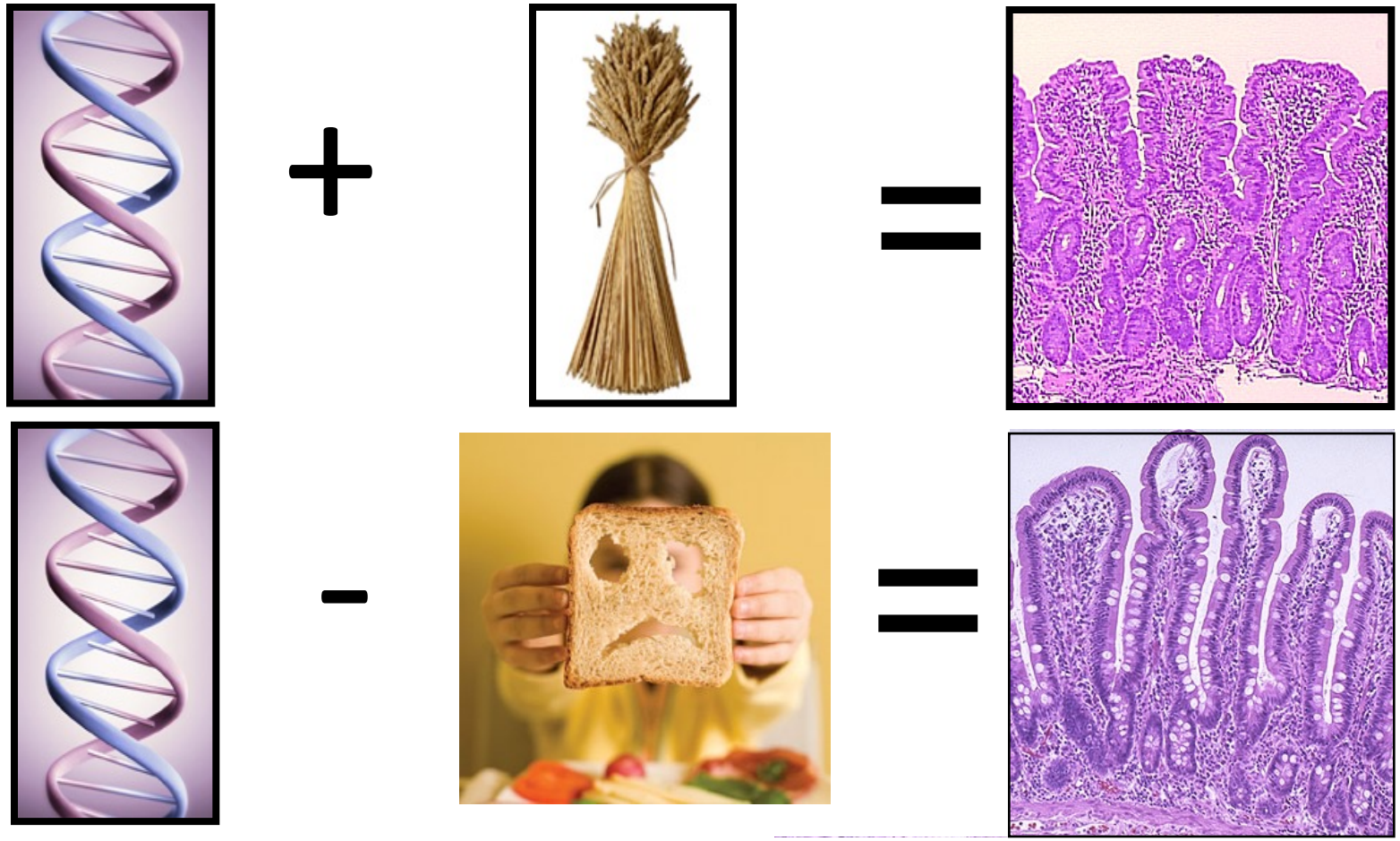
Table 1. Serum Tests for the Diagnosis of Celiac Disease.*

Test	Sensitivity (Range)	Specificity (Range)	Comments
	percent		
IgA anti-tTG antibodies	>95.0 (73.9–100)	>95.0 (77.8–100)	Recommended as first-level screening test
IgG anti-tTG antibodies	Widely variable (12.6–99.3)	Widely variable (86.3–100)	Useful in patients with IgA deficiency
IgA antiendomysial antibodies	>90.0 (82.6–100)	98.2 (94.7–100)	Useful in patients with an uncertain diagnosis
IgG DGP	>90.0 (80.1–98.6)	>90.0 (86.0–96.9)	Useful in patients with IgA deficiency and young children
HLA-DQ2 or *HLA-DQ8*	91.0 (82.6–97.0)	54.0 (12.0–68.0)	High negative predictive value

* Data are from Husby et al.[28] and Giersiepen et al.[29] DGP denotes deamidated gliadin peptides, and tTG tissue transglutaminase.

Fasano & Catassi NEJM 2012;367:2419-26

Celiac Disease Pathogenesis
Paradigm Of Autoimmunity

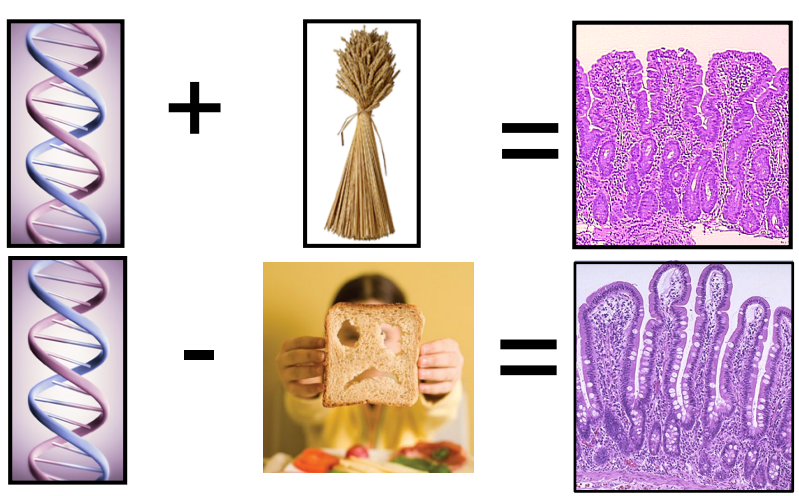


Necessary and Sufficient

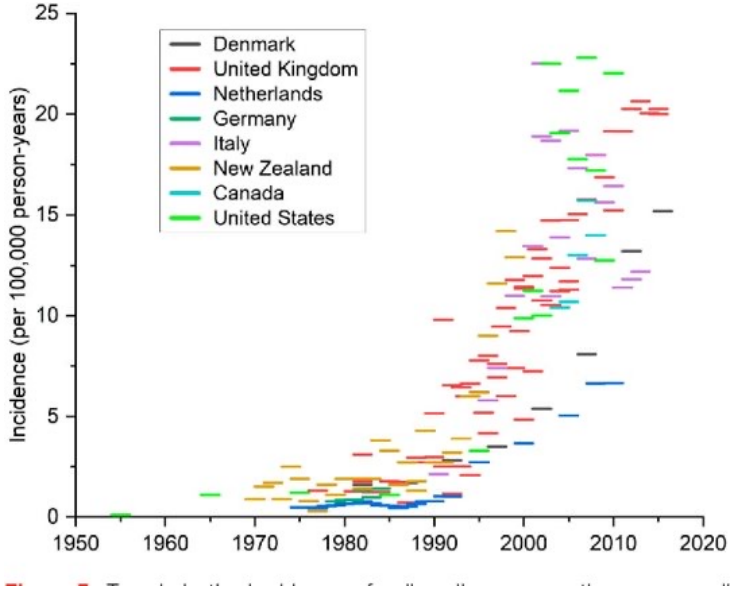
Clinical Factors at Odd With The CD Pathogenesis Paradigm

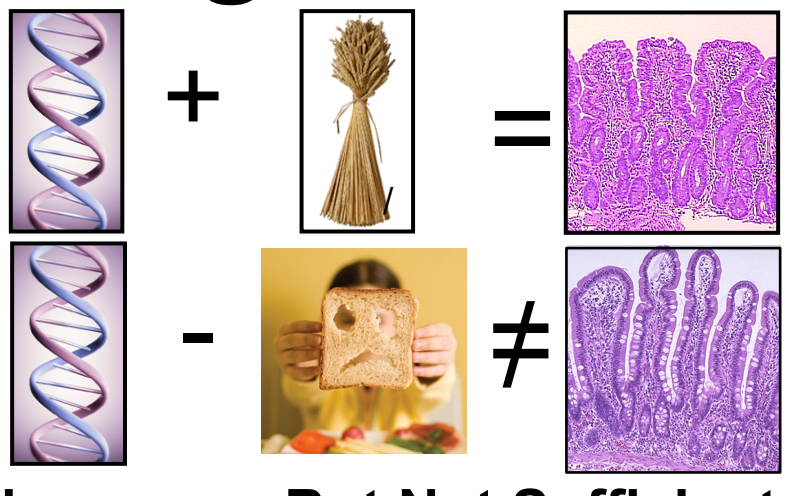
- Lack of 100% concordance in monozygotic twins;
- Difference age of onset of the disease;
- Differences in targeted organs/tissues and severity of the disease;
- Prospective studies in at-risk subjects showing sero-conversion over time;
- Epidemiology of CD showing an increase prevalence over time.

CD Pathogenesis: More Than Genes + Environment Paradigm

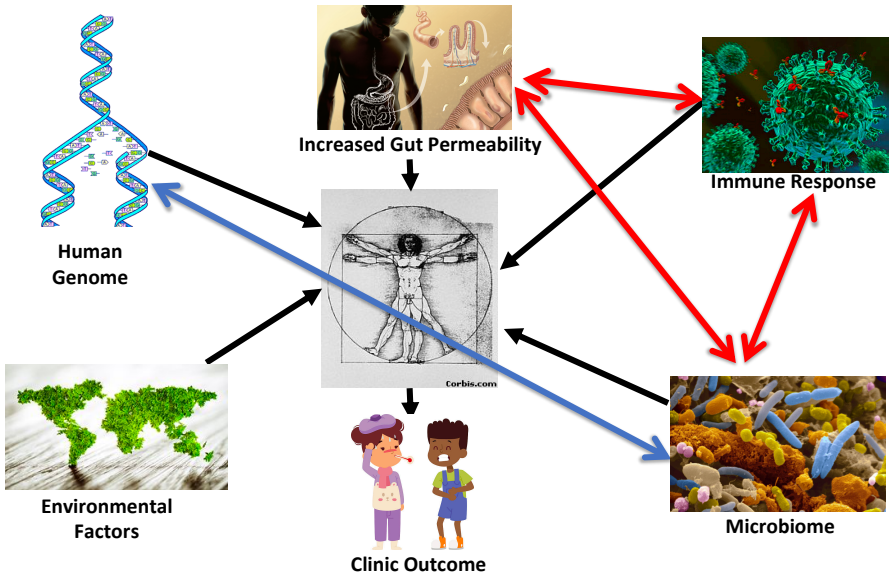


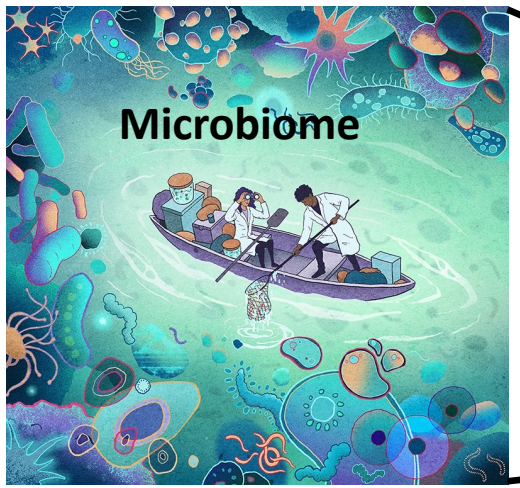
Necessary and Sufficient

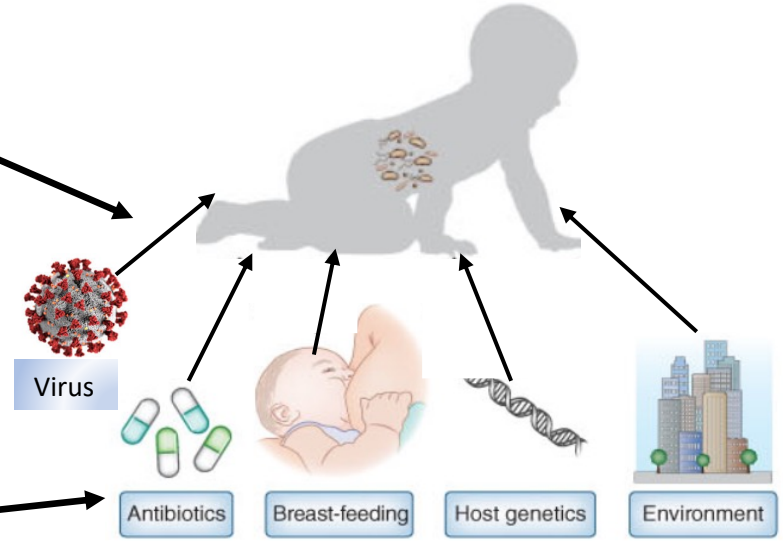




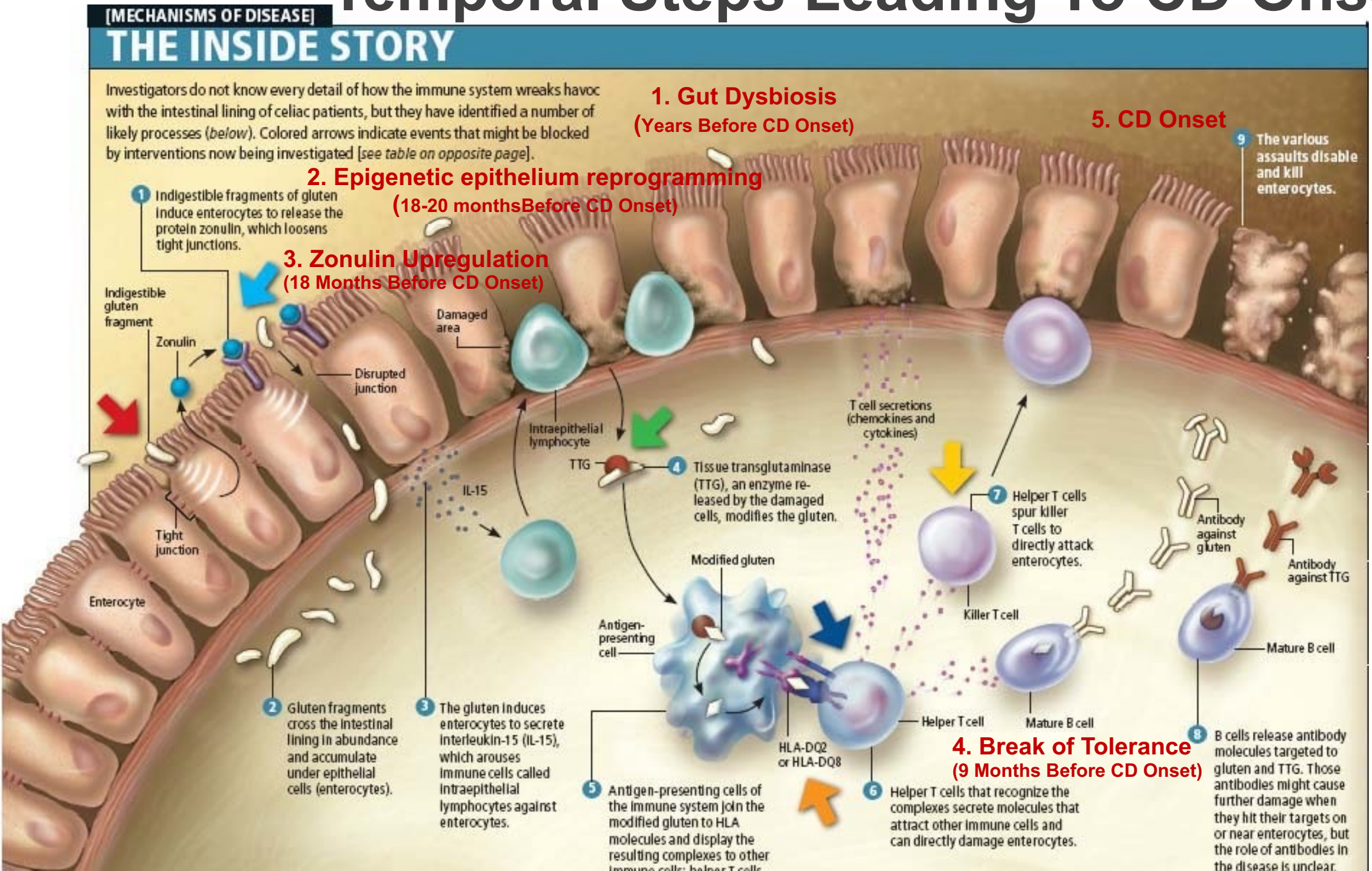
Necessary But Not Sufficient







Temporal Steps Leading To CD Onset



Fasano A, Sci Am, 2009

Key Open Questions Concerning Celiac Disease:

- Best diagnostic strategies?
- Endoscopy yes/no for diagnosis?
- How to properly follow up CD patients?
- Should CD patients be actively screened for other autoimmune diseases?
- How to manage CD patients with discrepancies between serology and histology?
- Are POC tests useful/appropriate for diagnosis and/or management of CD?
- Is the GFD highly effective in controlling CD?
- How to properly check for gluten cross-contamination?
- Are there any alternative/complementary treatments to the GFD at the horizon?

Differential Diagnosis Between CD, GS, and WA

	Celiac Disease	Gluten Sensitivity	Wheat Allergy
Time interval between gluten exposure and onset of symptoms	Weeks-Years	Hours-Days	Minutes-Hours
Pathogenesis	Autoimmunity (Innate+ Adaptive Immunity)	Immunity? (Innate Immunity?)	Allergic Immune Response
HLA	HLA DQ2/8 restricted (~97% positive cases)	Not-HLA DQ2/8 restricted (50% DQ2/8 positive cases)	Not-HLA DQ2/8 restricted (35-40% positive cases as in the general population)
Auto-antibodies	Almost always present	Always absent	Always absent
Enteropathy	Almost always present	Always absent (slight increase in IEL)	Always absent (eosinophils in the lamina propria)
Symptoms	Both intestinal and extra-intestinal (not distinguishable from GS and WA with GI symptoms)	Both intestinal and extra-intestinal (not distinguishable from CD and WA with GI symptoms)	Both intestinal and extra-intestinal (not distinguishable from CD and GS when presenting with GI symptoms)
Complications	Co-morbidities Long term complications	Absence of co-morbidities and long term complications (long follow up studies needed to confirm it)	Absence of co-morbidities. Short-term complications (incliuing anaphylaxis)

Thank you

GEMM's and their families

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