Gluten-Related Disorders in 2015

November 9, 2015

Stefano Guandalini, MD
Professor of Pediatrics

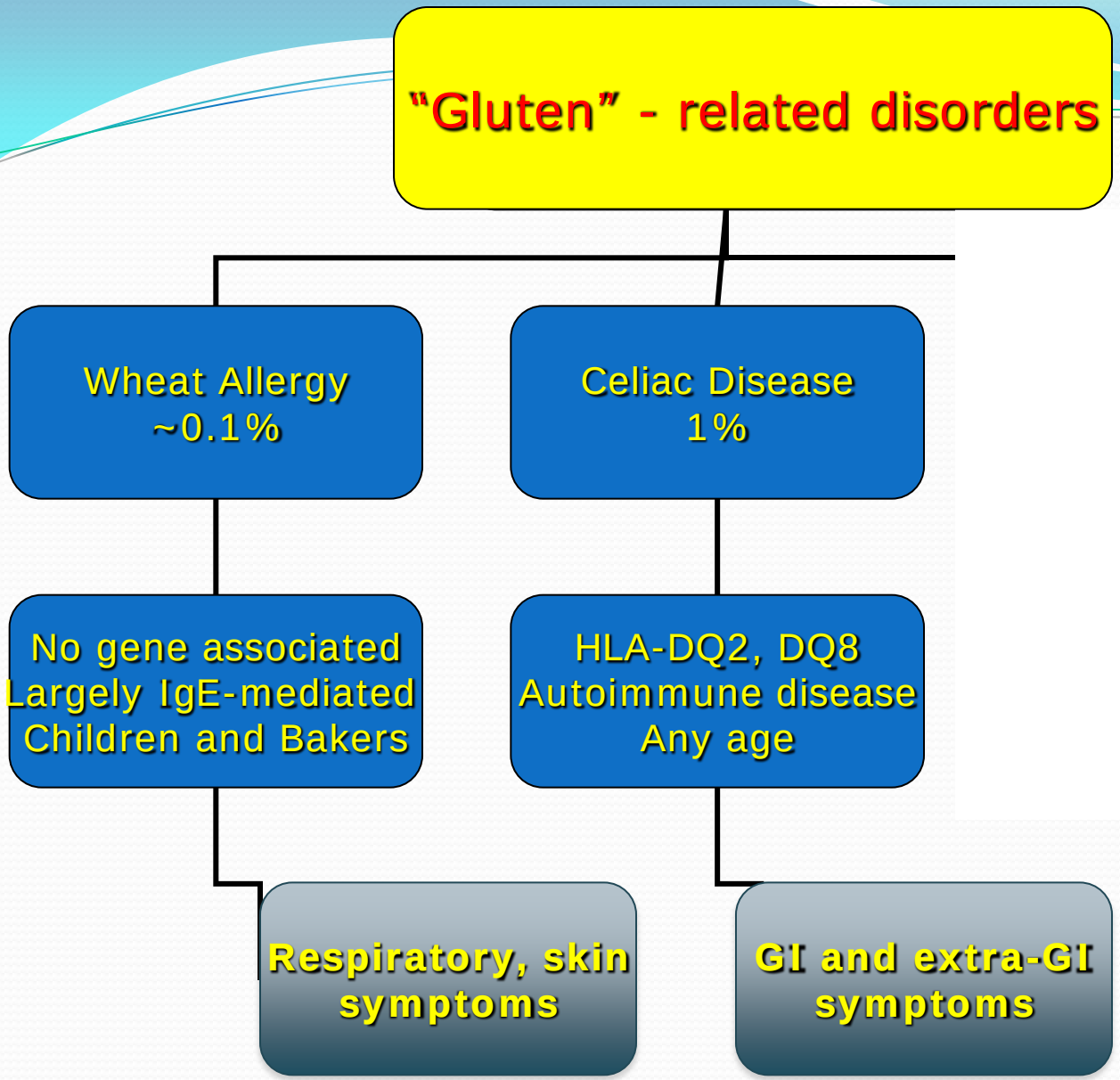
THE UNIVERSITY OF CHICAGO MEDICINE
Celiac Disease Center
cureceliacdisease.org

THE UNIVERSITY OF CHICAGO MEDICINE
Comer Children's Hospital
CELEBRATING 10 YEARS

Learning Objectives

- Distinguish between wheat allergy, celiac disease and non-celiac gluten sensitivity
- Analyze and define testing requirements to aid in the diagnosis of wheat allergy and gluten related disorders
- Advocate for accurate and timely diagnosis to improve patients quality of life
- Review literature to better understand the presentation of symptom, challenges of diagnosis and treatment options

“Gluten” - related disorders



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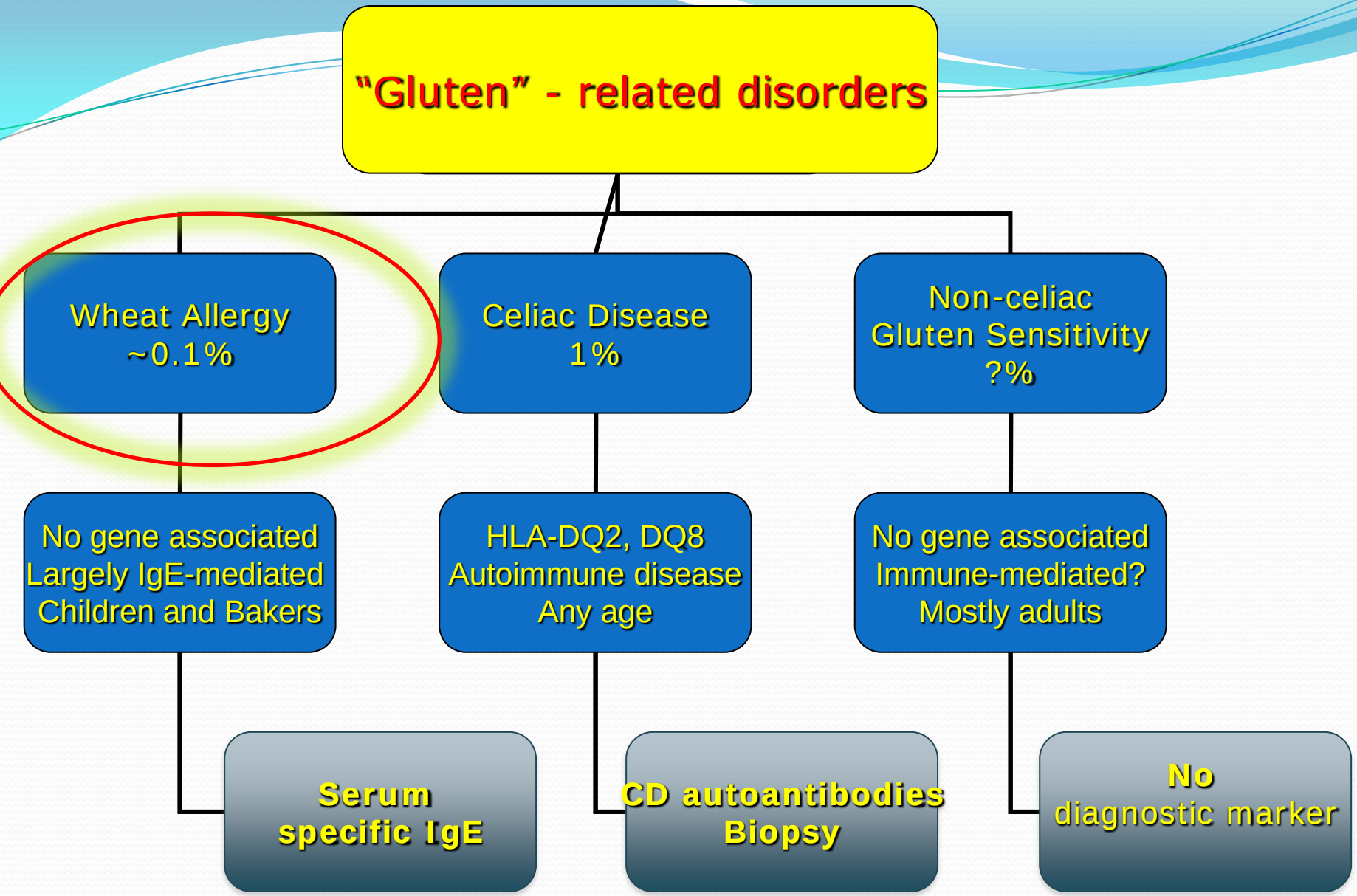

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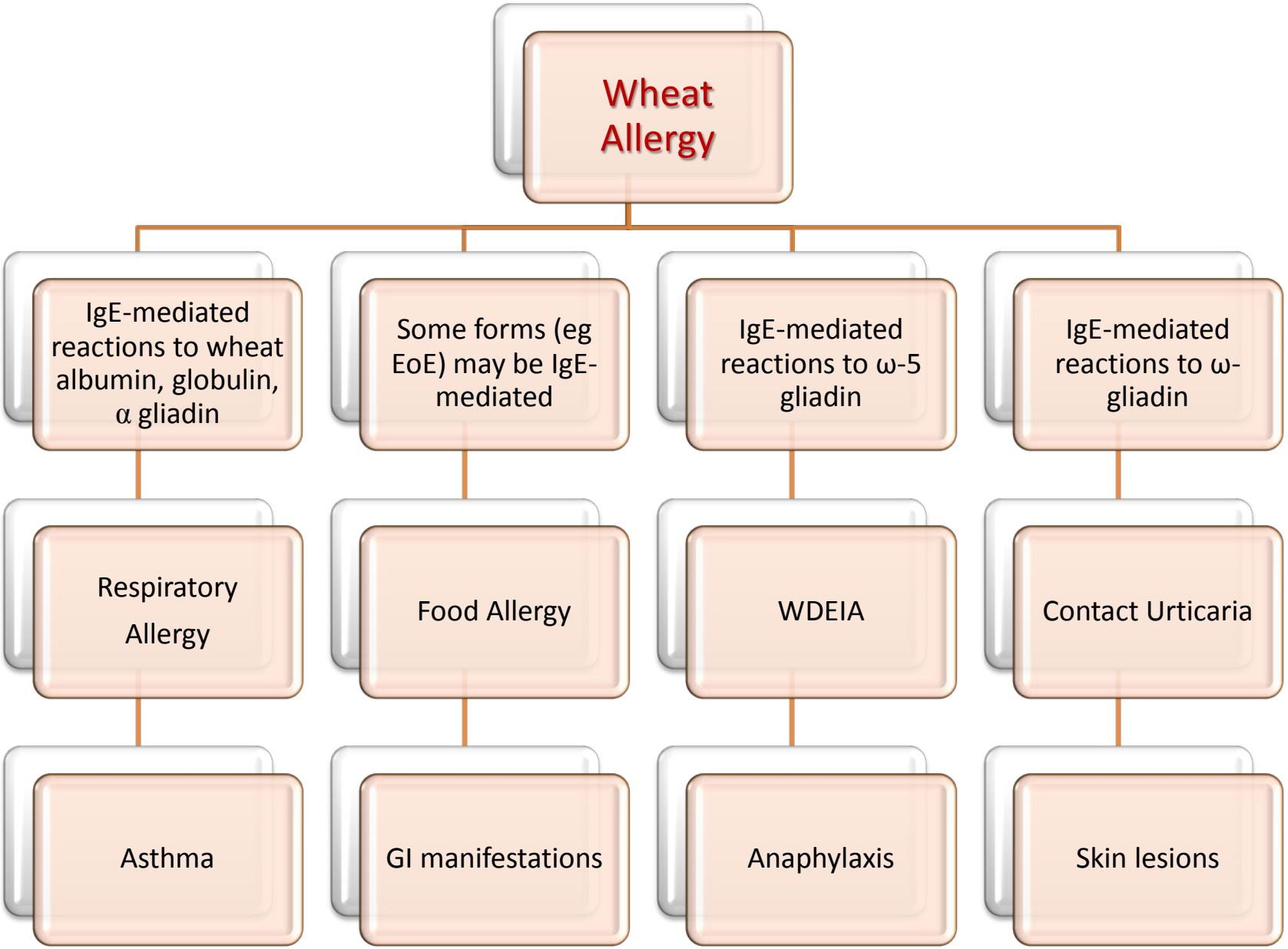
Wheat Allergy - Definition

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)

Hill I, Fasano A, Guandalini S et al., Diagnosis and Treatment of Gluten Related Disorder. *Manuscript submitted*


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
Food Allergy
WDEIA
Contact Urticaria
Asthma
GI manifestations
Anaphylaxis
Skin lesions

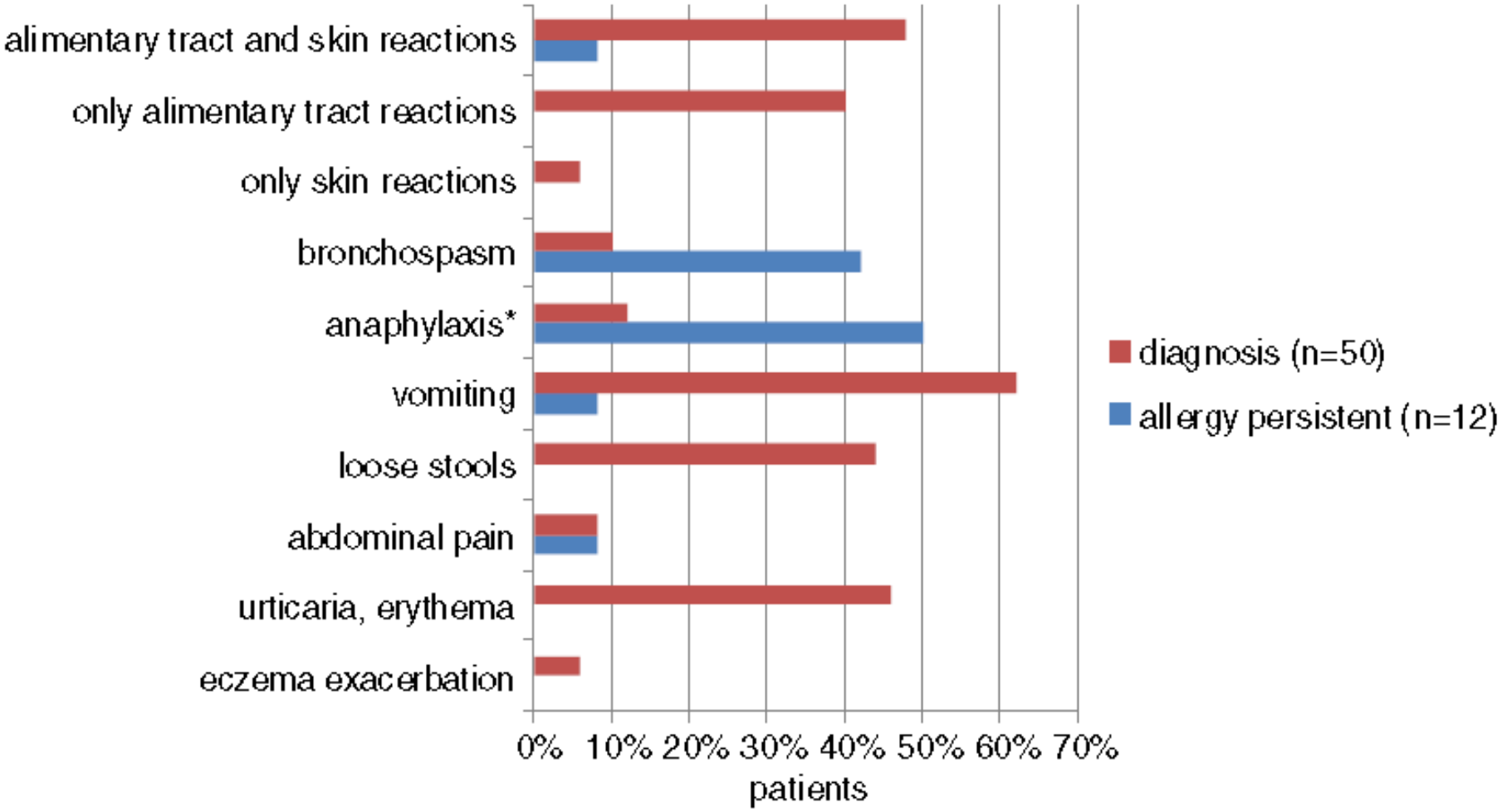
Wheat Allergy in Children

Characteristics	No. (%) of patients; n = 50
Sex: male/female	32 (64)/18 (36)
Other atopic diseases*	
Eczema	39 (78)
Asthma	24 (48)
Allergic rhinitis	17 (34)
Eosinophyllic gastrointestinal disease*	6 (12)
Eosinophilic oesophagitis	5 (10)
Other food allergies*	
Milk	40 (80)
White egg	36 (72)
Soy	12 (24)
Fish	14 (28)
Peanut	25 (50)
Tree nuts	13 (26)
Number of food allergens:*	Median 4; range: 3-7
3	4 (8)
4	33 (66)
≥5	13 (26)
Family history of atopy	50 (100)
1 parents	9 (18)
Both parents	41 (82)
Siblings	24 (62)

*throughout the whole observation period.

Czaja-Bulsa and Bulsa, Allergy, Asthma & Clinical Immunology 2014

Clinical Manifestations of Wheat Allergy in Children



Czaja-Bulsa and Bulsa, Allergy, Asthma & Clinical Immunology 2014

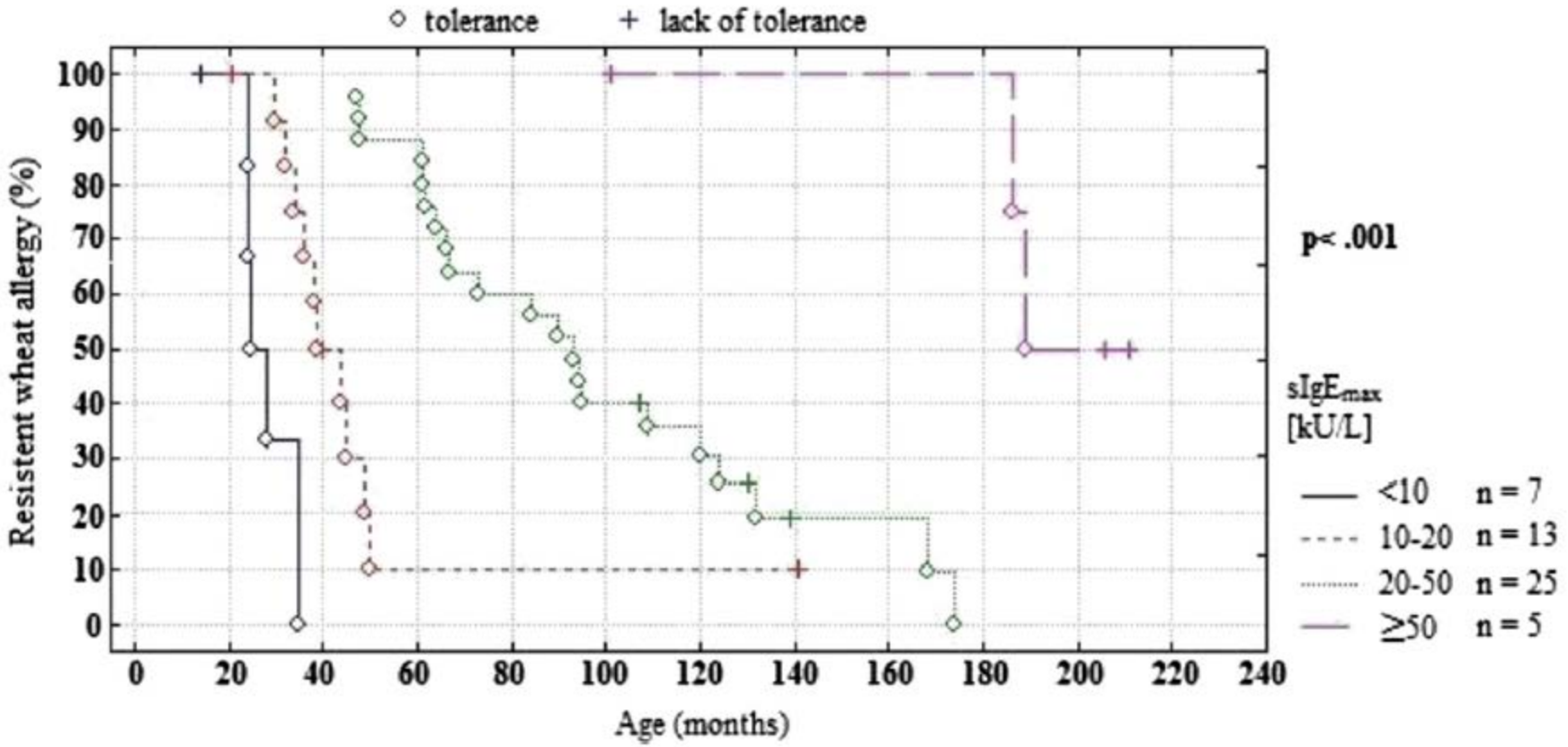
Median Wheat IgE levels in patients with persistent or resolved wheat allergy

Age (years)	Wheat specific IgE (kU/L)		p value*
	Outgrown	Persistent	
0-2	9	19	.04
2-4	10	27	.03
4-6	7	49	.03
6-8	6	46	.04
8-10	6	42	.04
10-12	5	36	.05
12-14	4	35	.07
14-16	4	33	.14
16-18	4	30	.36

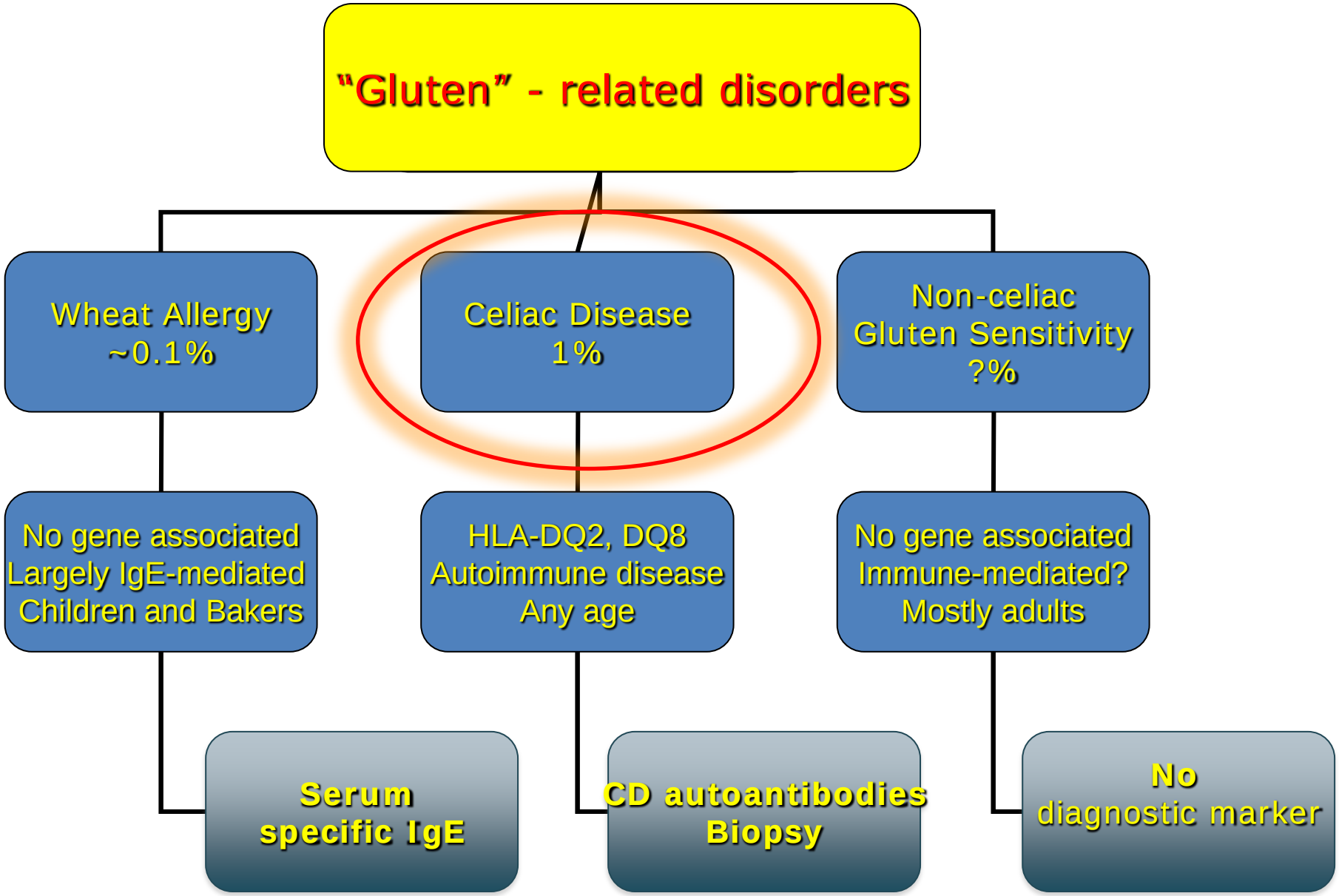
*Mann-Whitney test.

Czaja-Bulsa and Bulsa, Allergy, Asthma & Clinical Immunology 2014

Relationship of peak wheat IgE level to persistence of wheat allergy during the first 18 years of life



Czaja-Bulsa and Bulsa, Allergy, Asthma & Clinical Immunology 2014



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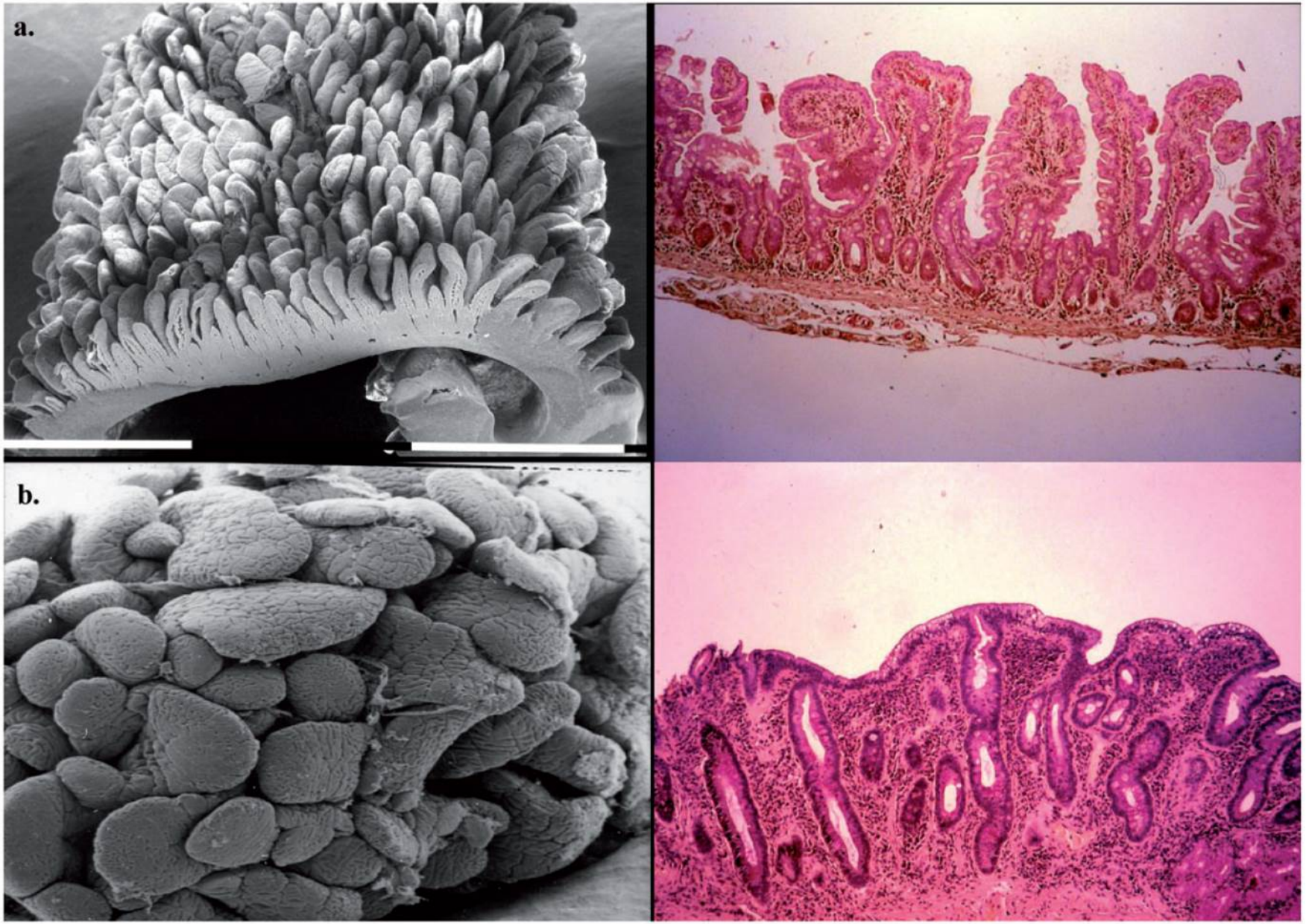
Celiac Disease

- An immune-mediated systemic disorder elicited by gluten and related prolamines in genetically susceptible individuals
- Characterized by a variable combination of:
  - Gluten-dependent clinical manifestations
  - CD-specific antibodies (autoantibodies against TG2, endomysial antibodies (EMA), and antibodies against deamidated forms of gliadin peptides (DGP)
  - HLA-DQ2 or HLA-DQ8 haplotypes; and
  - Enteropathy.

ESPGHAN Guidelines – Husby S et al., JPGN 2012



Gasbarrini GB and Mangiola F - UEG Journal 2014

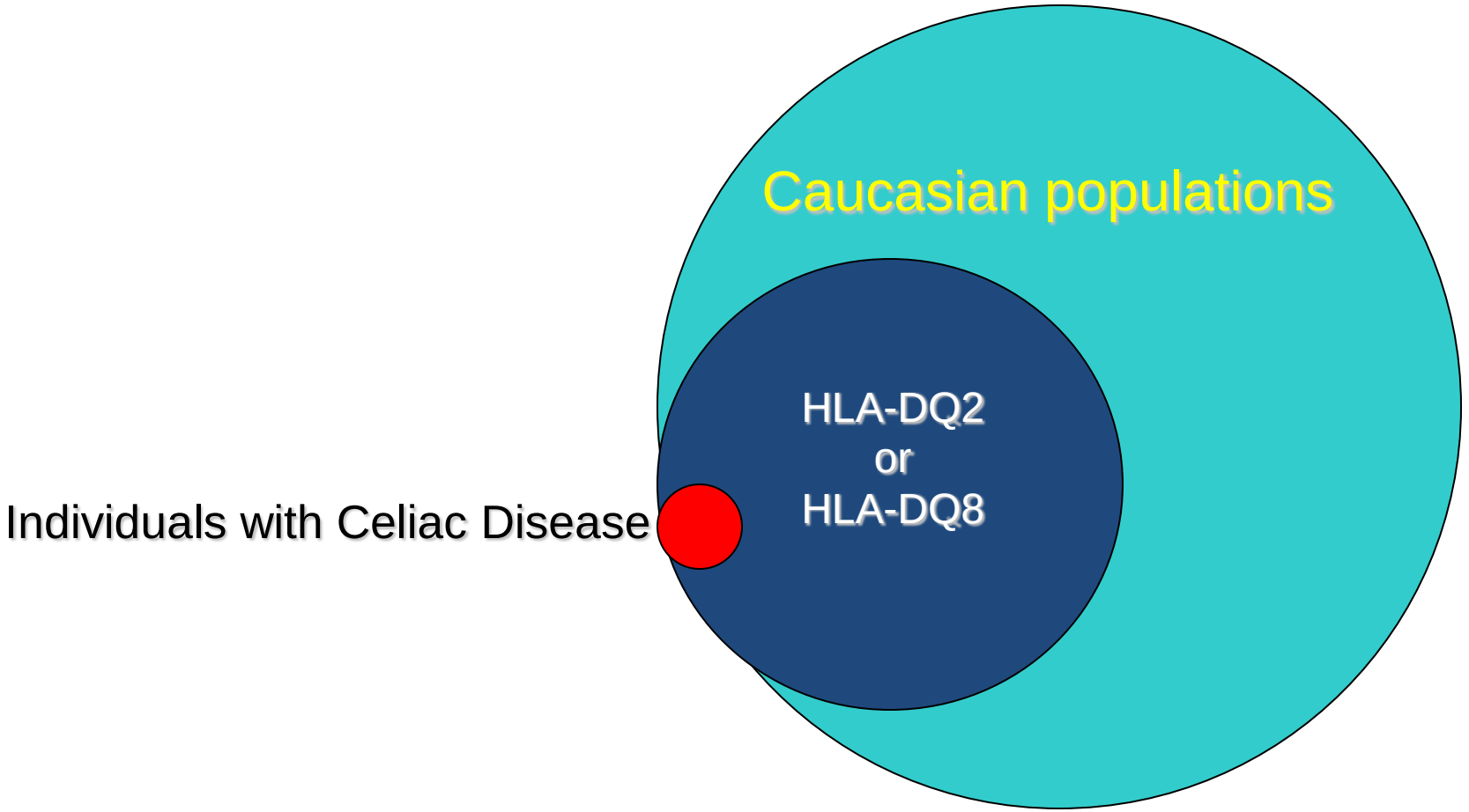
What Causes Celiac Disease?

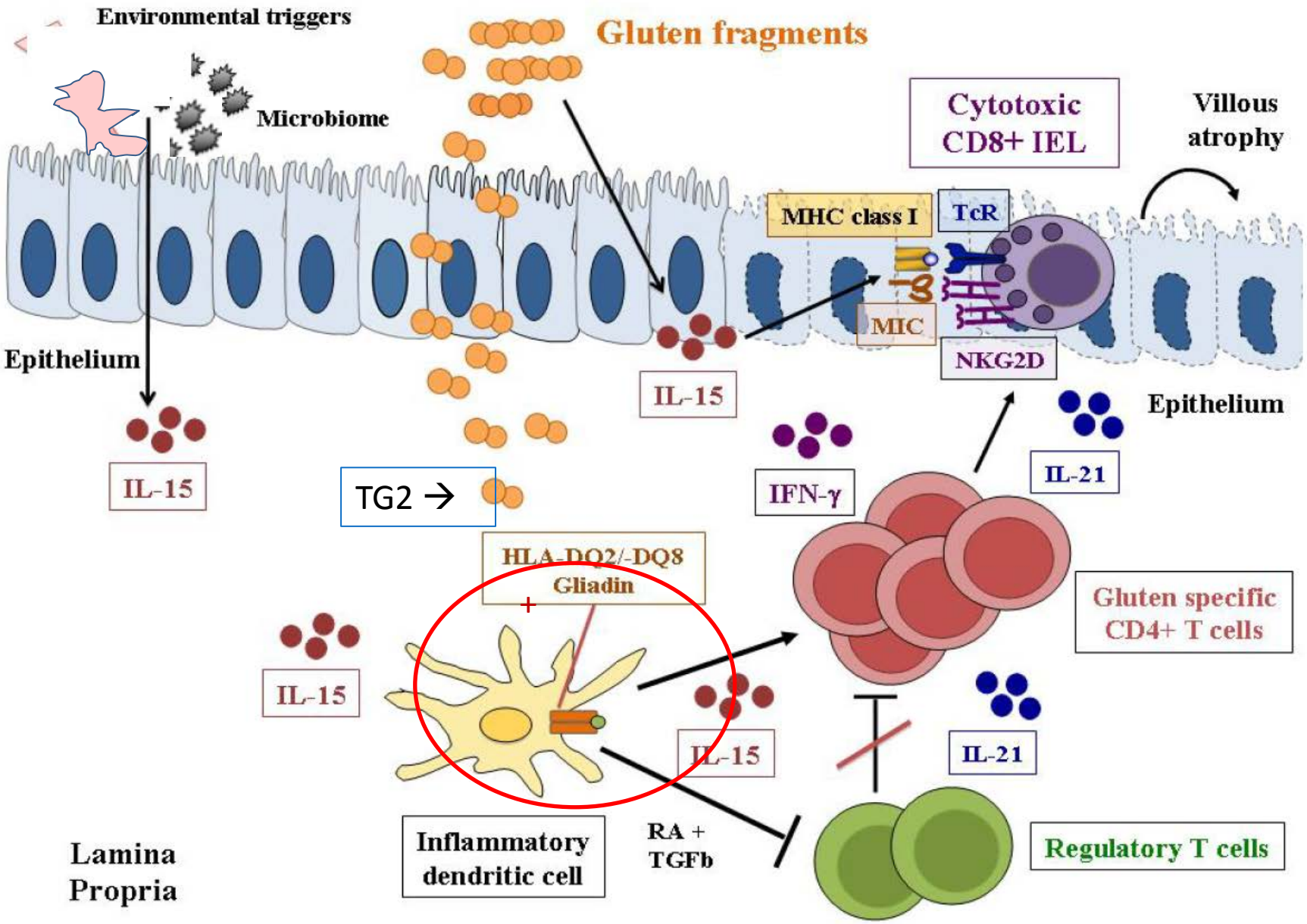
The Genes

- HLA-DQ2 (95% of celiacs)
- HLA-DQ8 (5% of celiacs)

Note: You **must** have one of these genes to be celiac;
But if you have them, you may or may not develop celiac

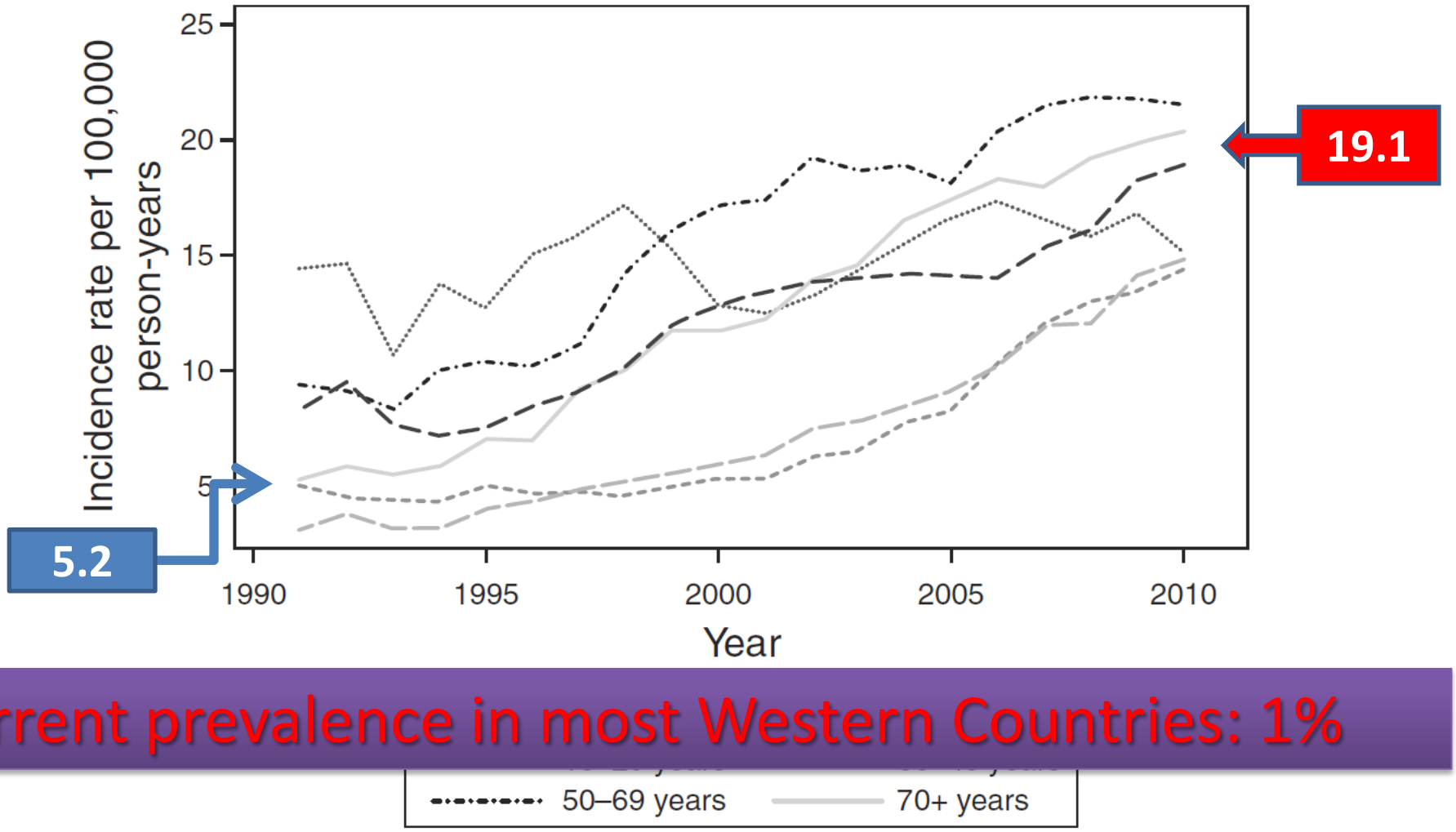
DQ2 or DQ8 Necessary but Not Sufficient





Guandalini S, Discepolo V, Newland C and Kupfer S
In: A Clinical Guide to Gluten-related Disorders 2014

Rapidly Increasing Incidence of CD



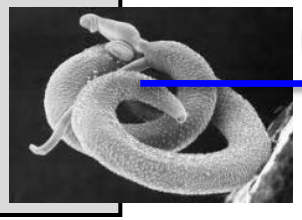
Current prevalence in most Western Countries: 1%

West J et al., Am J Gastroenterol 2014

Antibiotics

Western Diet

Elimination of enteropathogens (*H. pylori*, Helmints)



Vaccines/reduced exposure to infections

C-sections /infant feeding (?)

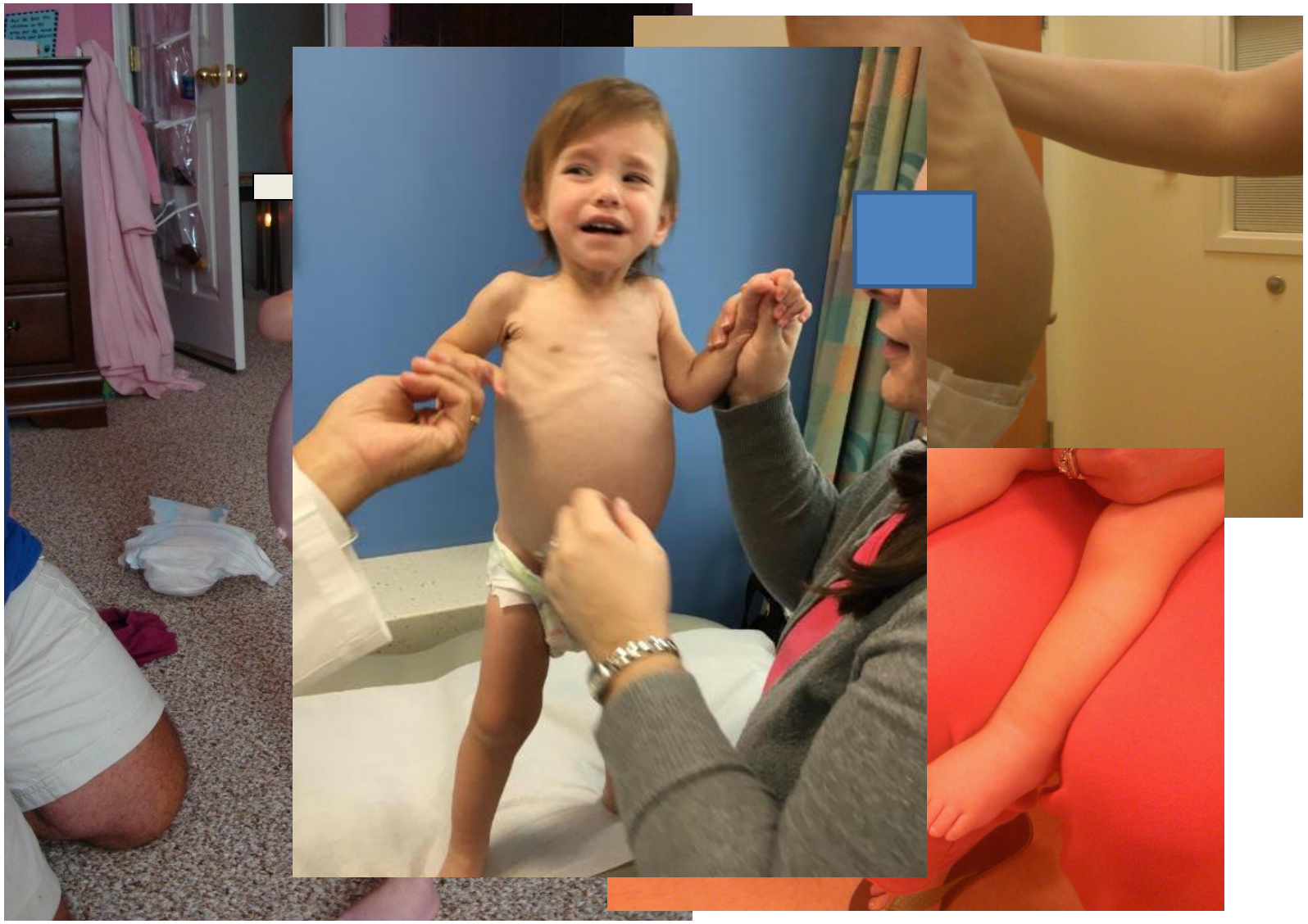
Changes in microbiota "Dysbiosis"

*Celiac Disease
*Autoimmunity
*Food Allergies

Genetically susceptible individual

Feehley et al *Seminars in Immunopathology* 2012

“Typical” Celiac Children



Clinical Presentations

	Serology (tTG or EMA)	Symptoms	Pathology
Symptomatic "Typical"	Positive	• Diarrhea • Abdominal Pain • Distention • Vomiting • Anorexia • Constipation	Marsh 2-3
Symptomatic "Atypical"	Positive	Extra-intestinal	Marsh 1-3
Silent	Positive	None	Marsh 1-3
Potential	Positive	• None • Gastrointestinal • Extra-intestinal	Marsh 0-1

Possible Presentations

- GI (“Typical”) or Extra-GI (“Atypical”)
- Silent
  - Positive antibodies
  - Intestinal damage at biopsy
  - ***No symptoms***
- Potential
  - Positive antibodies
  - ***No intestinal damage at biopsy***
  - **±** Symptoms

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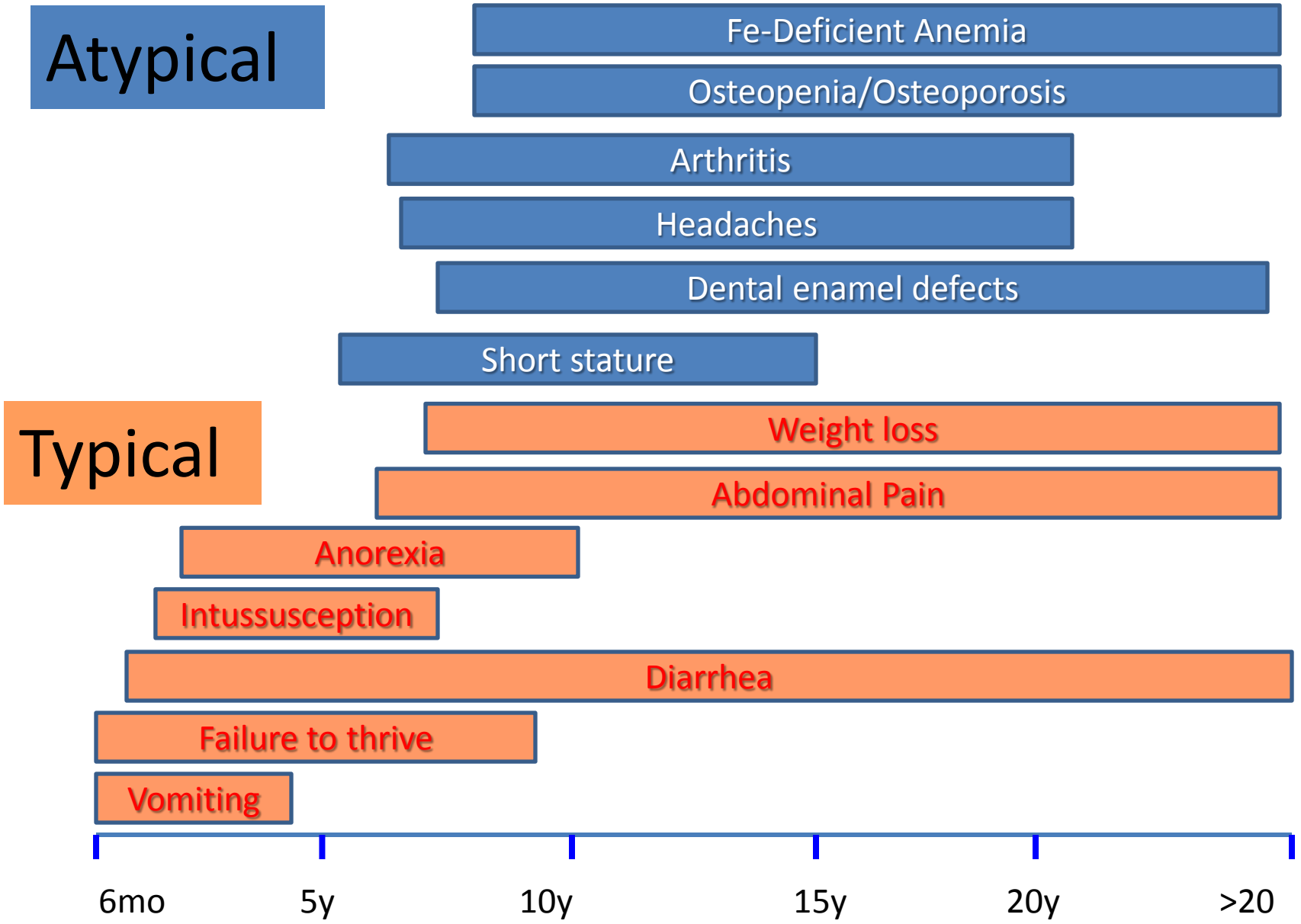
The “Typical” (GI) Presentations

- Diarrhea
- Vomiting
- Failure to thrive or weight loss
- Abdominal bloating/pain
- Constipation

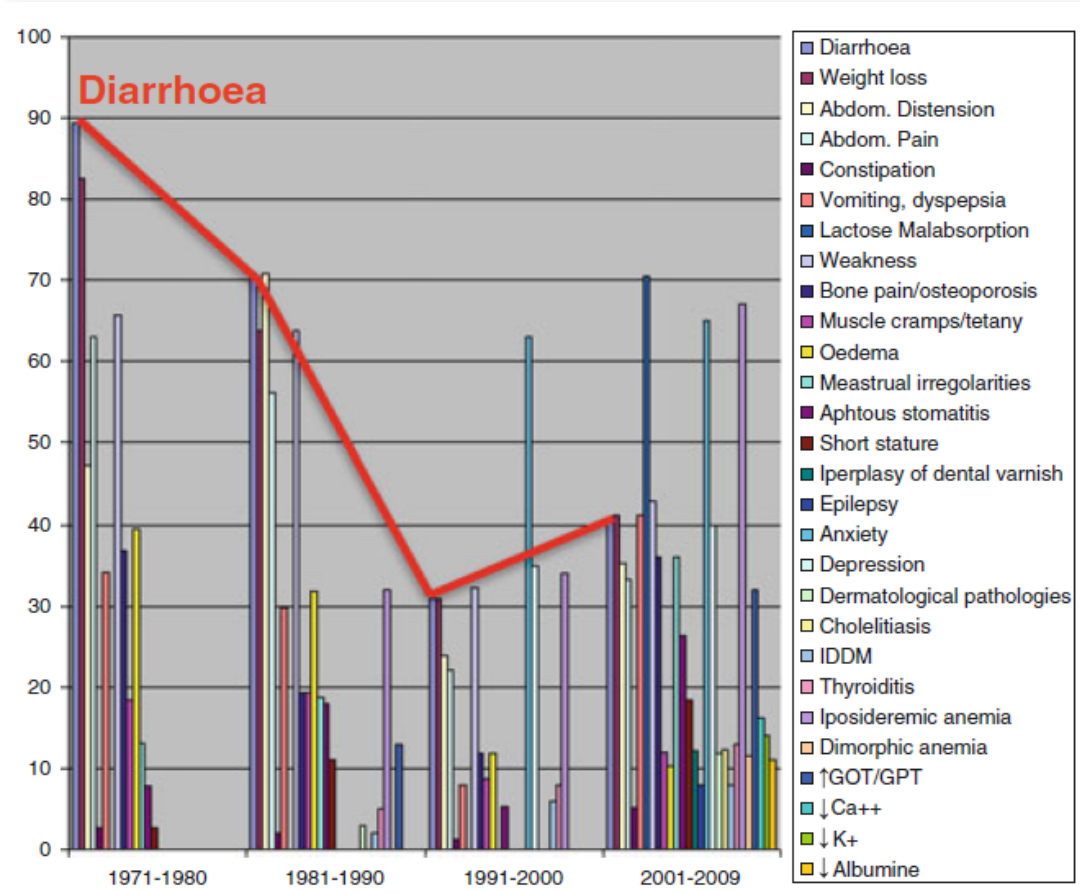
Main “Atypical”: Extra-Intestinal

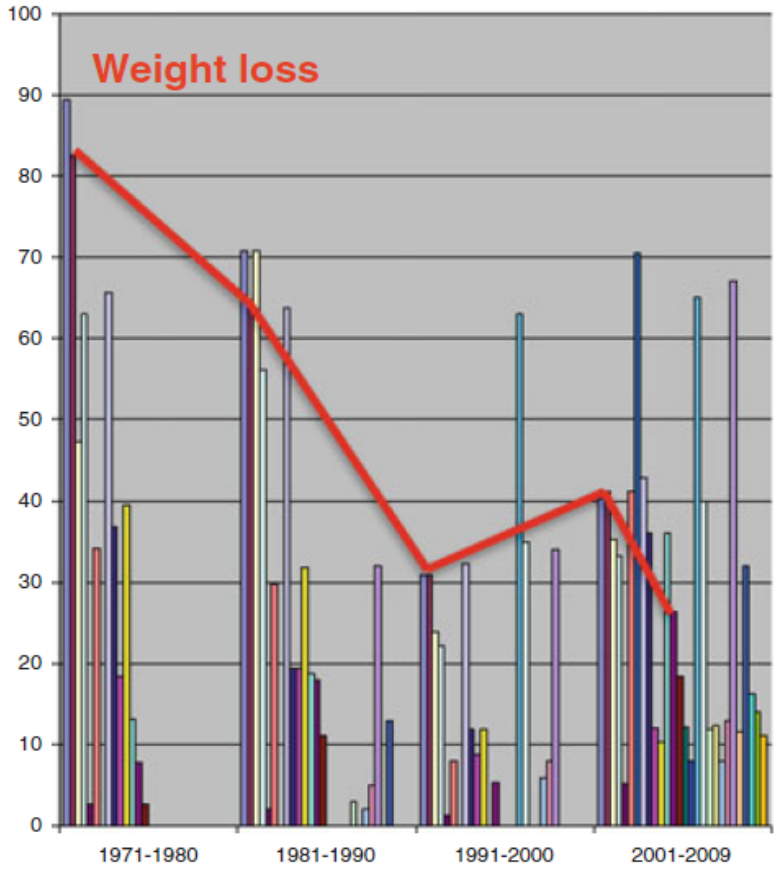
- Malnutrition Related
  - Short stature
  - Delayed puberty
  - Iron-deficient anemia resistant to oral Fe
- Recurrent stomatitis
- Liver and biliary tract disease
  - Autoimmune Liver Disease
  - Benign hypertransaminasemia
- Skin disorders
  - Dermatitis Herpetiformis
  - Alopecia Areata
- Osteopenia/Osteoporosis
- Arthritis/Arthralgia
- Neurological problems
  - Headache
  - Peripheral Neuropathy
  - Seizures with occipital calcifications
  - Gluten Ataxia
- Behavioral changes & psychiatric disorders
  - Poor mood
  - Anxiety
  - Depression
- Women: sub-infertility

Main GI and Extra-GI manifestations



The Decline of "Typical" CeD





Gasbarrini GB et al., Intern Emerg Med 2014

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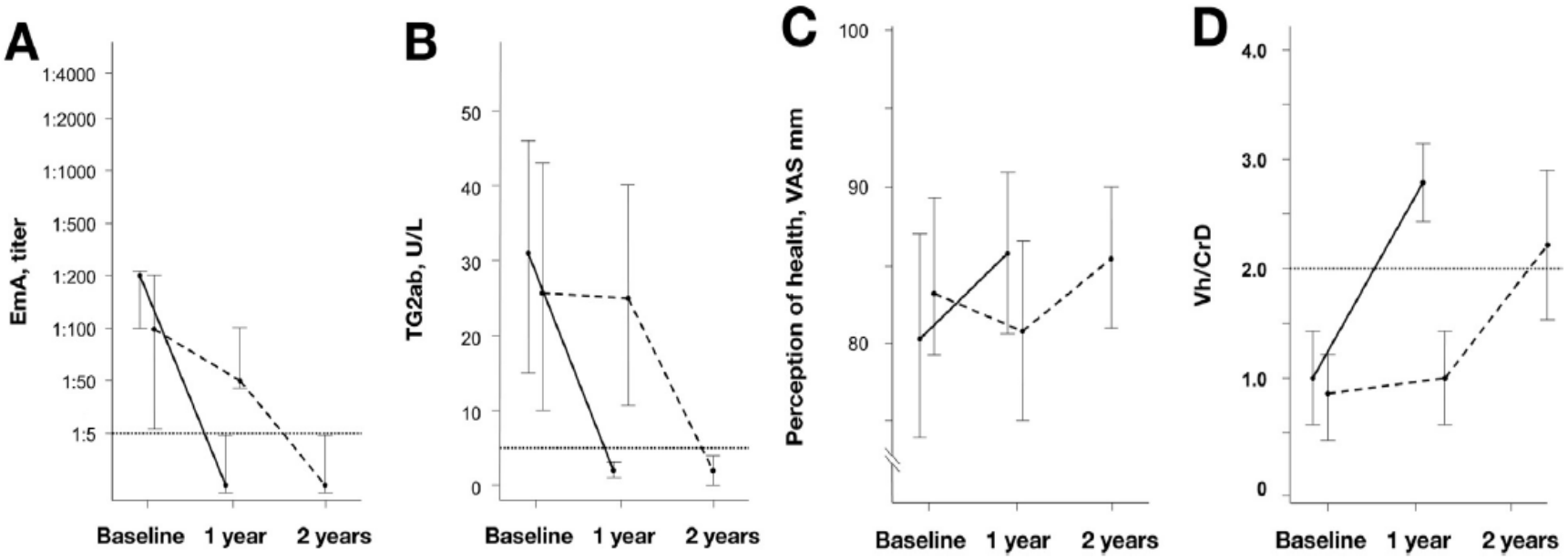
Silent CeD: to treat or not to treat



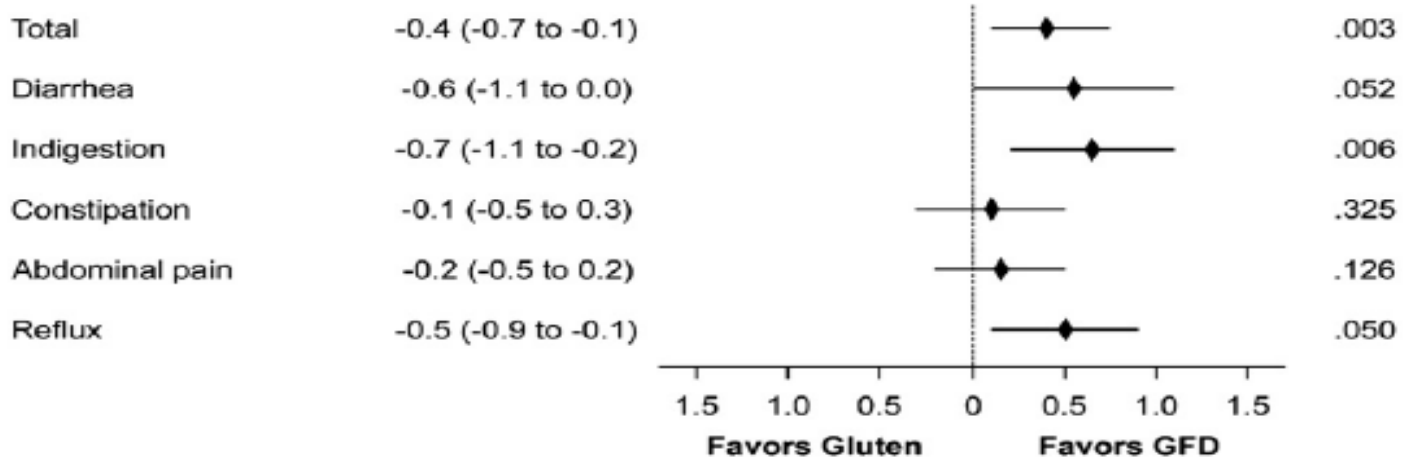
Autoantibodies

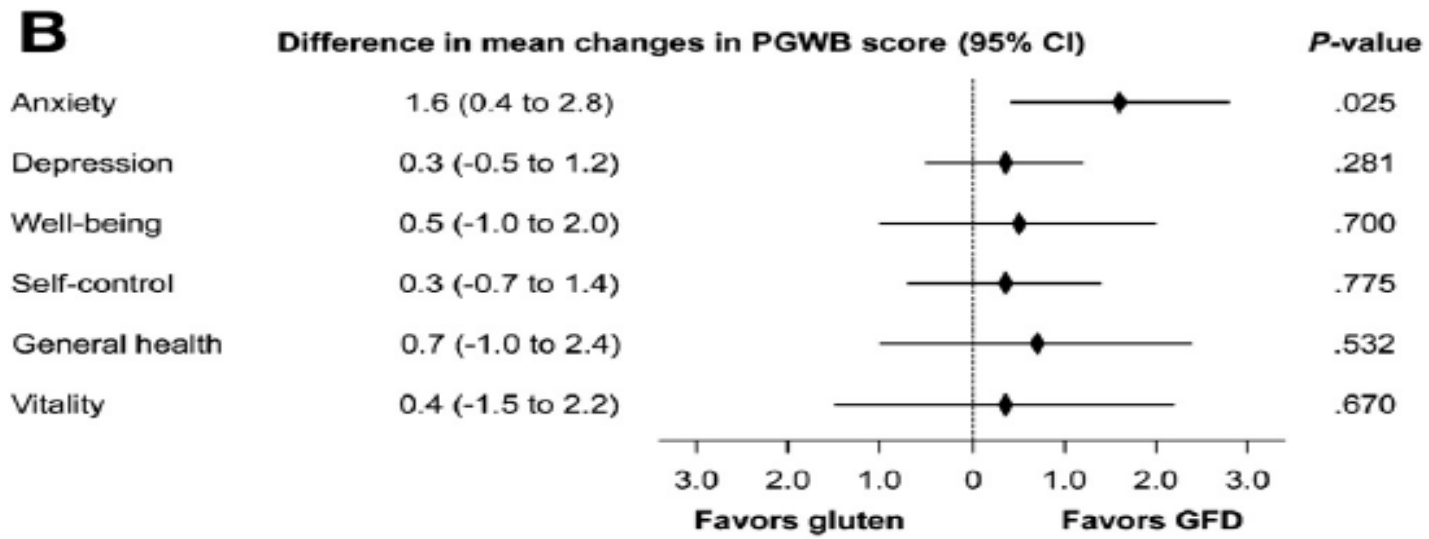
Health perception

Biopsy

Kurppa K et al., Gastroenterology 2014

Silent CeD: to treat or not to treat





Kurppa K et al., Gastroenterology 2014

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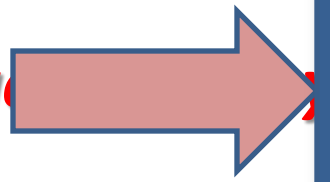


If left on gluten, almost 50% become full-blown celiacs in 3-5 years

Who Should be Tested?

- **Children and adolescents with otherwise unexplained GI symptoms and signs :**
  - Chronic or intermittent diarrhea
  - Nausea or vomiting
  - Chronic abdominal pain, cramping or distension
  - Chronic constipation
  - Failure to thrive, weight loss, stunted growth
  - Recurrent aphthous stomatitis

- **Children and adolescents with otherwise unexplained Extra-GI symptoms and signs :**
  - Short Stature; delayed puberty, amenorrhea
  - Iron-deficiency anemia, chronic fatigue
  - Dermatitis Herpetiformis–like rash
  - Fracture with inadequate traumas/osteopenia/osteoporosis
  - Abnormal liver biochemistry (elevated AST, ALT)

Who Should be Tested?

- **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)*

Celiac-specific Antibodies: the Best Biomarkers

	Positive likelihood ratio	Negative likelihood ratio
EMA /IgA	**31.8** *(18.6-54.3)*	**0.067** *(0.038-0.118)*
Anti-TG2 /IgA	**21.8** *(12.9-36.8)*	**0.060** *(0.040-0.090)*
Anti-DGP /IgG	**13.6** (8.1-22.8)	**0.061** *(0.017-0.221)*
Anti-DGP /IgA	**9.4** (6.8-13.1)	**0.121** *(0.072-0.203)*
AGA /IgA	**7.3** *(4.5-11.8)*	**0.186** *(0.095-0.362)*

Giersiepen K et al., JPGN 2012

How to Test for Celiac Disease

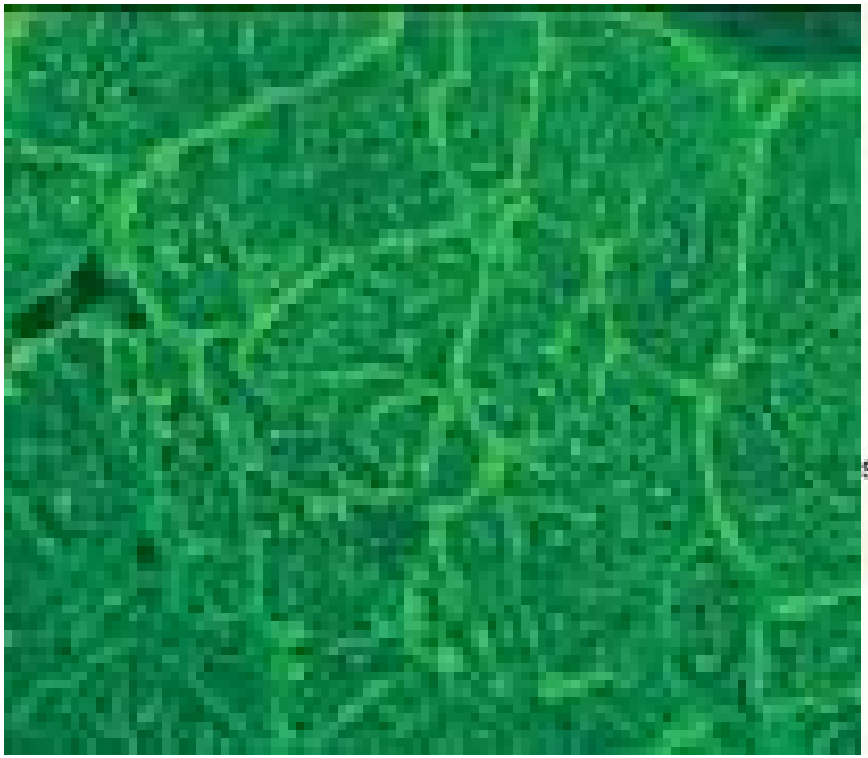
- **Serum anti-Tissue Transglutaminase IgA (TTG)**
  - Sensitivity: **98%** (74-100%) - beware of IgA-deficient! (*)
  - Specificity: **97%** (78-100% - correlating with titers)
  - *Beware of low titers: false positive often found in other conditions*

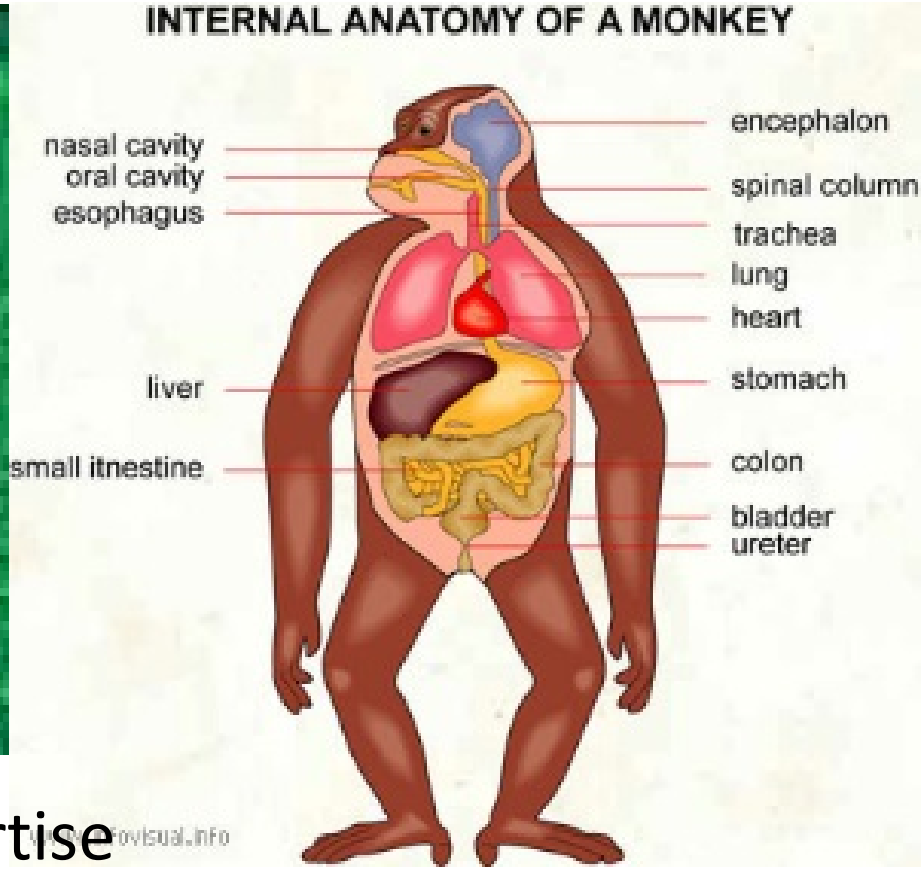
- **Serum anti-Endomysium Antibodies IgA (EMA)**
  - Low to moderate sensitivity (around 85%)
  - High specificity: 98.2% (97-100%)

(*) IgA deficient is a subject who has less than 20 mg/dl of total serum IgA : TTG-IgG should be performed ***only*** in these cases

Note: There is a very good correlation between serum titers of TTG-IgA or EMA and tissue damage - Husby S et al., JPGN 2012

Why anti-EMA is Not the Best Initial Test to Screen for Celiac Disease?





- Requires technical expertise
- Observer-dependent
- Costly and ecologically unfriendly

Careful!

Other causes of elevated TTG-IgA

- Liver Disease
- Any Autoimmune Condition (esp. T1DM!)
- Crohn's disease
- Tumors
- Viral Infections

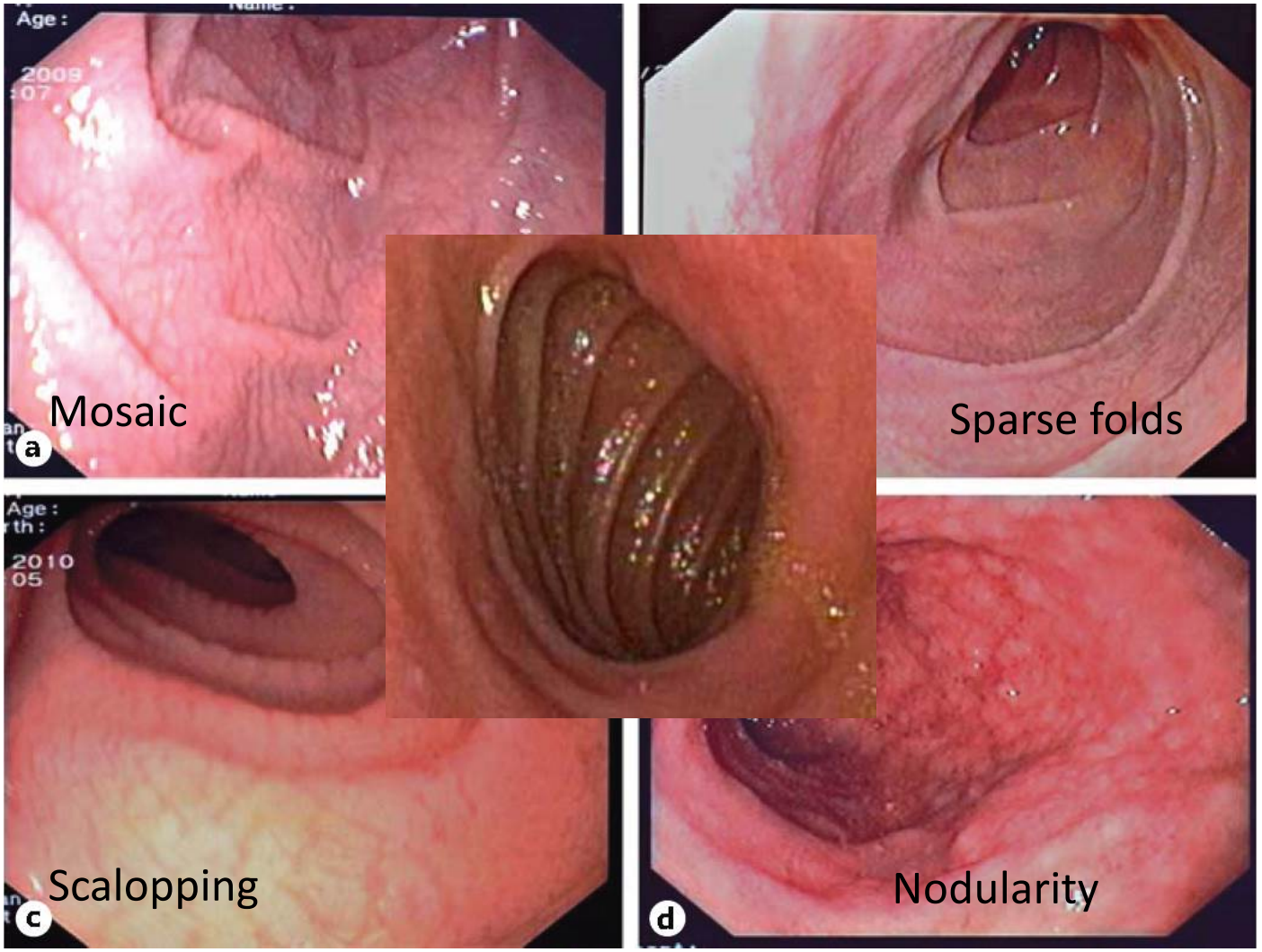
Deamidated Gliadin Peptides (DGP)

- DGP: sensitivity and specificity in screening for celiac disease similar to TTG-IgA
- DGP-IgG: better sensitivity and specificity than DGP-IgA

- DGP more often positive than TTG-IgA in very young children (below age 2), making them the preferred screening test for this age group

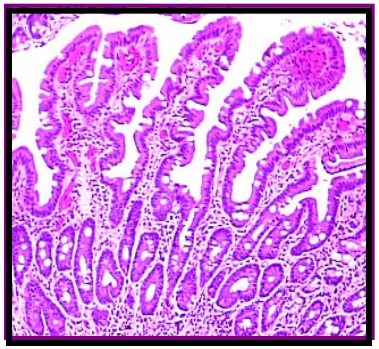
All serological tests for CD depend for diagnostic reliability on the patient being on gluten! Testing for serology someone who has been for ≥6 weeks on a strict gluten-free diet (GFD) is a common mistake that must be avoided, as levels of antibodies begin to decline 2-3 weeks after beginning GFD, and if the titers were only moderately elevated to being with, they may well be completely normal after 6 weeks on a GFD!

Endoscopic Changes in Celiac Disease

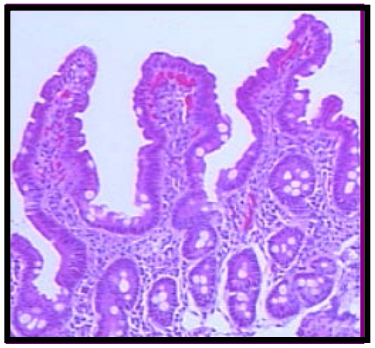


Pellegrino S et al., *Digestion* 2013

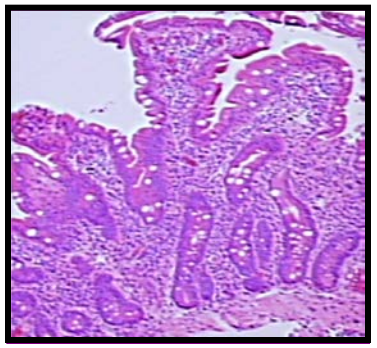
Mucosal damage is progressive:
the Marsh scoring system



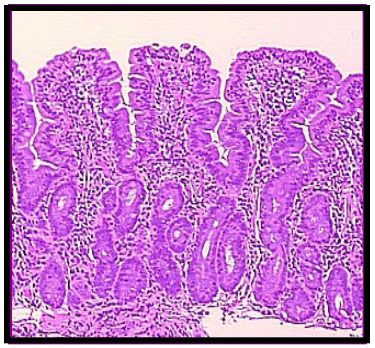
Normal 0



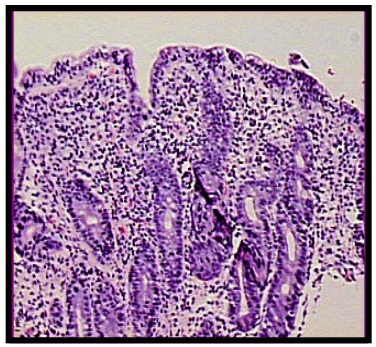
Infiltrative 1



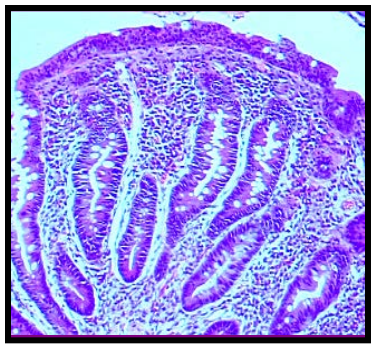
Hyperplastic 2



Partial atrophy 3a

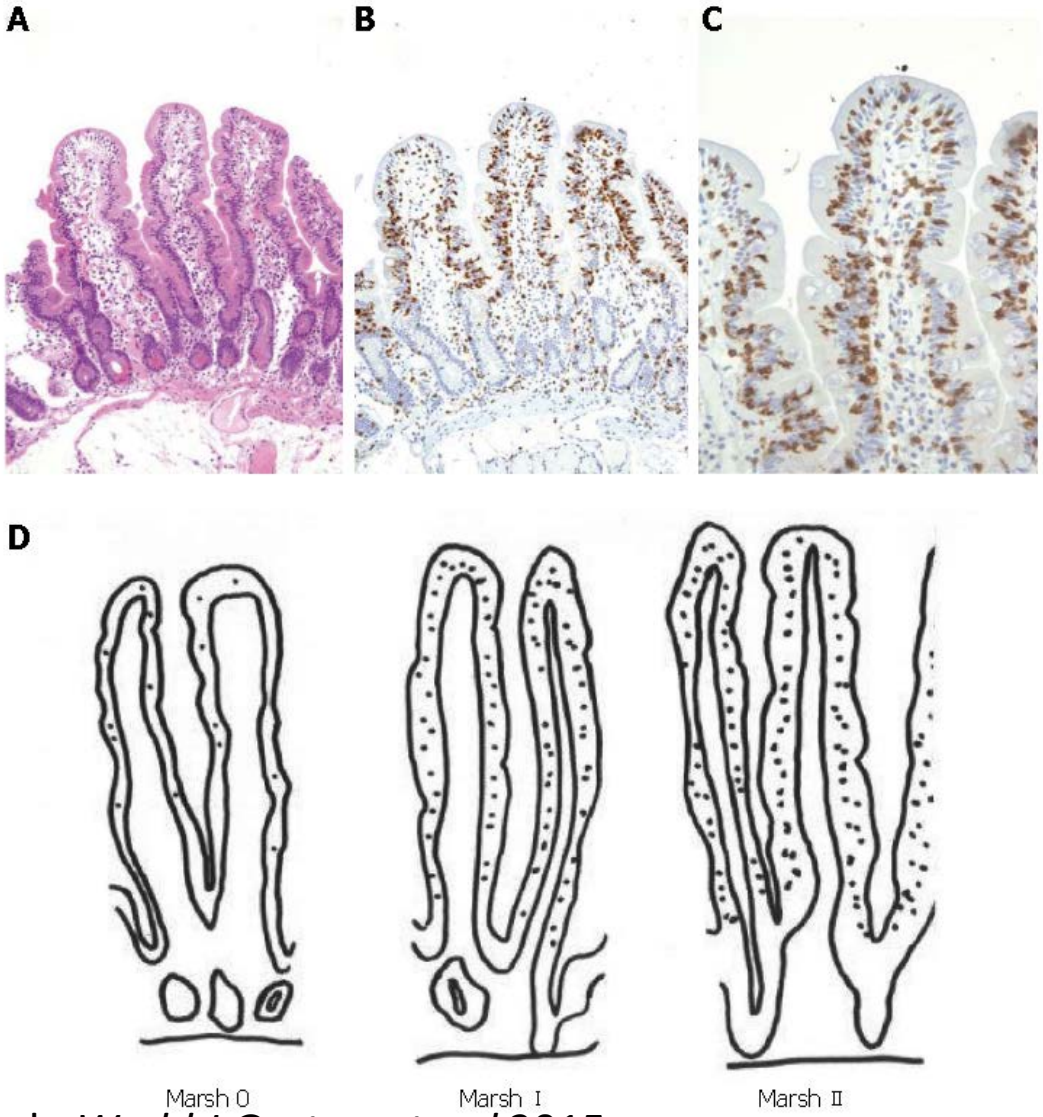


Subtotal atrophy 3b



Total atrophy 3c

Microscopic Enteritis (Marsh 1-2)



Rostami K et al., *World J Gastroenterol* 2015

Causes of Microscopic Enteritis

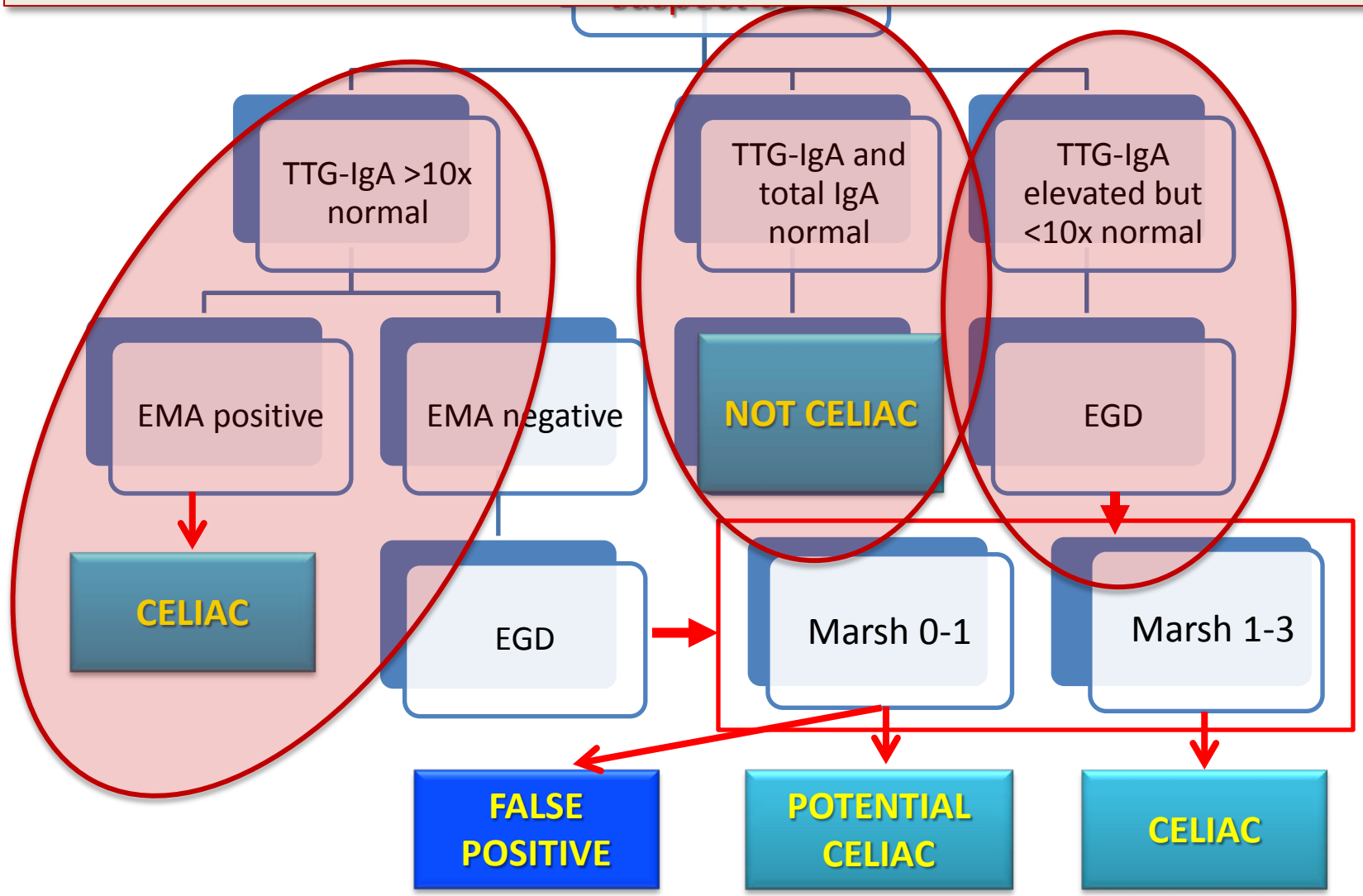
Conditions	Ref.
Coeliac disease	[7-8]
Non coeliac gluten sensitivity	[52-53]
Helicobacter pylori	[15,57]
Other infections, parasites	[92]
Non-steroidal anti-inflammatory drugs	[64]
Bacterial overgrowth	[58-60]
Common variable immunodeficiency	[13]
Eosinophilic gastroenteritis	[90]
Collageneous gastroenteritis	[1]
Microvillous inclusion disease	[12]
Autoimmune enteropathy	[68]
Autoimmune disorders	[2,15,68]
Irritable bowel syndrome	[3,75]
Inflammatory bowel disease	[16]
Food allergy	[93]
Food intolerances	[76]
Idiopathic	[94]

Rostami K et al., *World J Gastroenterol* 2015

Can we diagnose celiac disease without the histology?

The new ESPGHAN guidelines

ESPGHAN diagnostic scheme



Decline of specific antibodies on the GFD

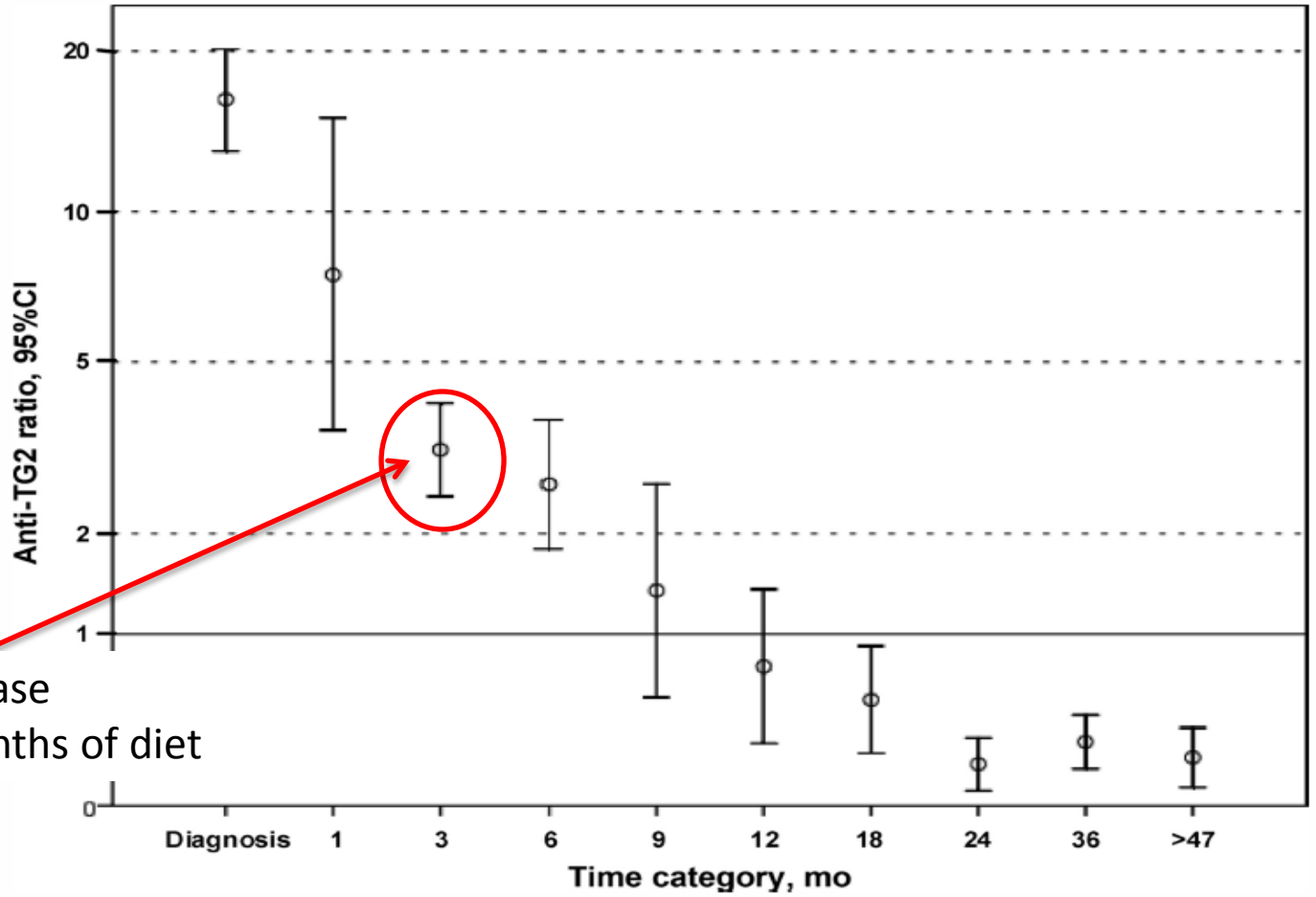
TABLE

Anti-TG2
EMA, %

[a] The ma

7 =

24
78
87



74% decrease
after 3 months of diet

FIGURE 2
Mean anti-TG2 levels (ratio, 95% CI) in children with CD on a gluten-free diet (in months).

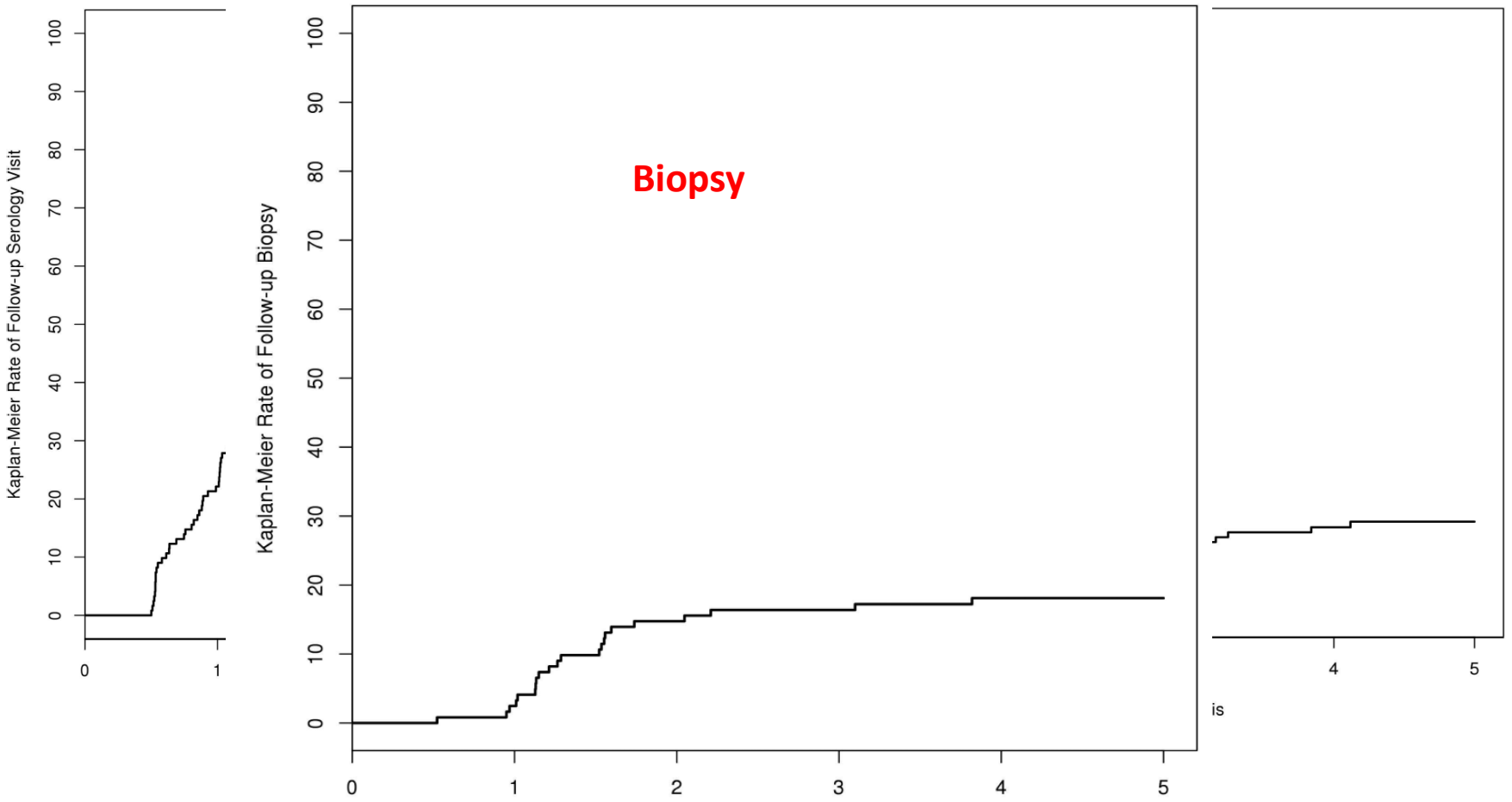
Hogen-Esch C. et al., Pediatrics 2011

Follow-up of Celiac Patients

	At diagnosis	At 3-6 months	Every 1-2 years	
EMA	●			
TTG-IgA	●	●	●	
DGP-IgG	●	●	●	
CBC	●			
Fe studies	●	●		
TSH+T4	●			
Vitamin D	●	●		
Dietitian review	●	●	●	
Cholesterol	●	●	●	
BMD	●		●	

+ Timely colon cancer screening

Follow-up often Inadequate



Herman et al. Clin Gastro Hep 2012;10:893


GLUTEN
FREE

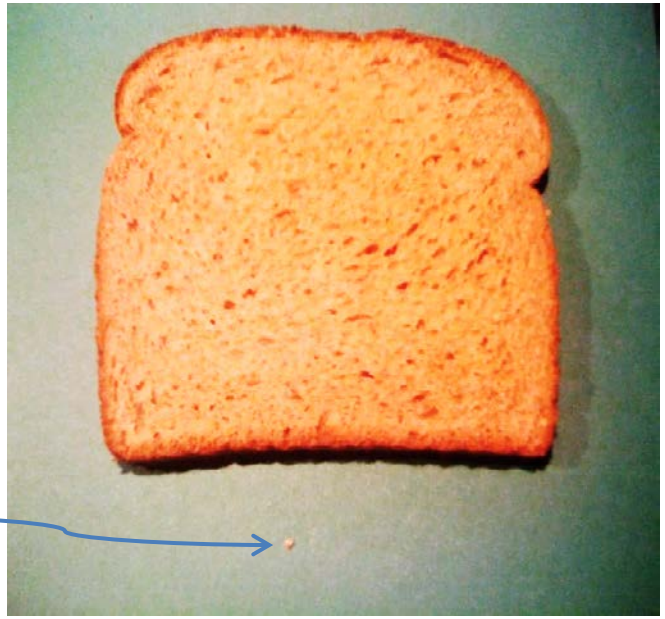
What is 20 ppm?

- *0.002% gluten or 2 mg/100gm*
- *20 mg gluten per 1 kg of food*
- *One minute in two years!*

- Study determined how much gluten may be tolerated
- 0, 10 or 50 mg gluten daily for 90 days

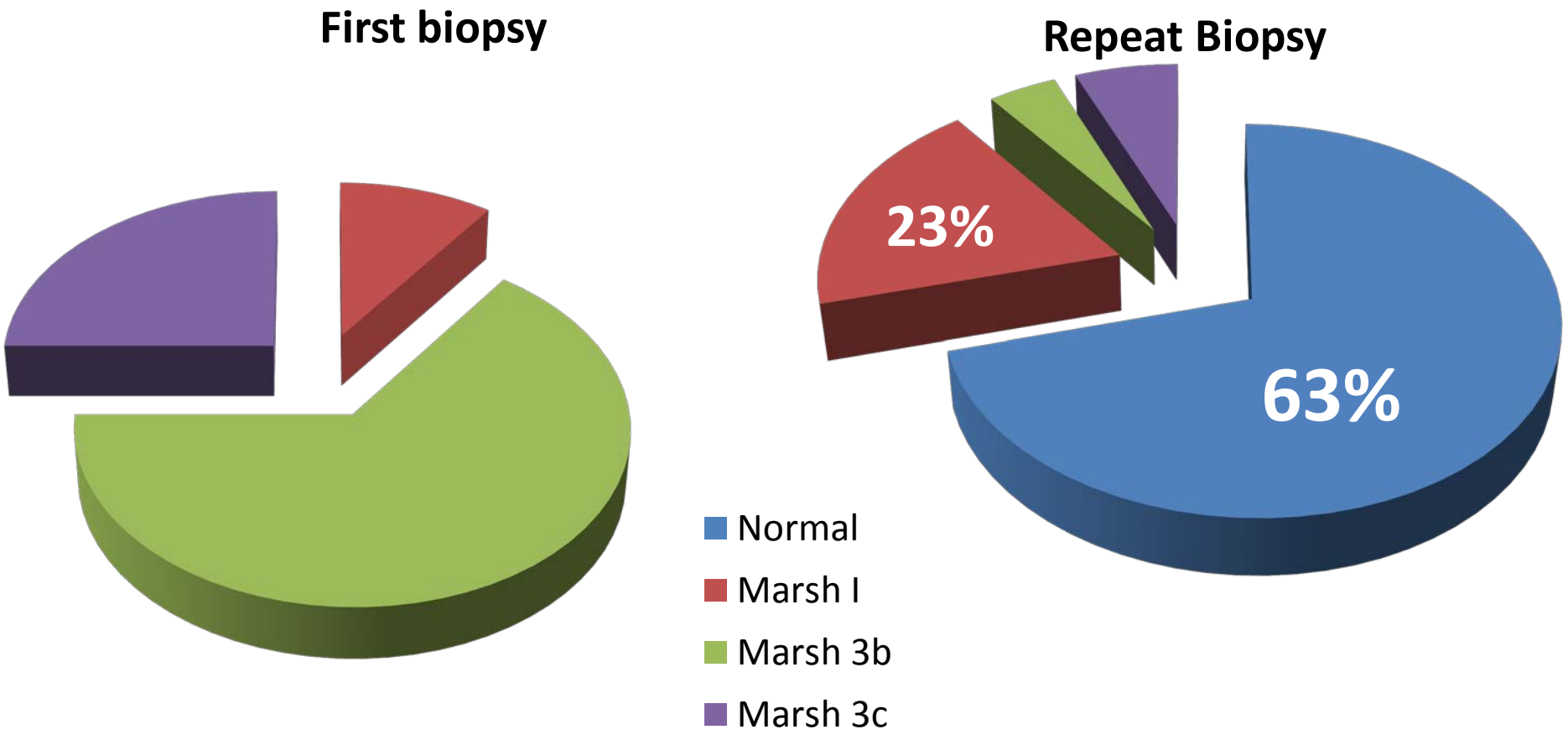
Conclusion:

- 50 mg or more of gluten induced villous damage



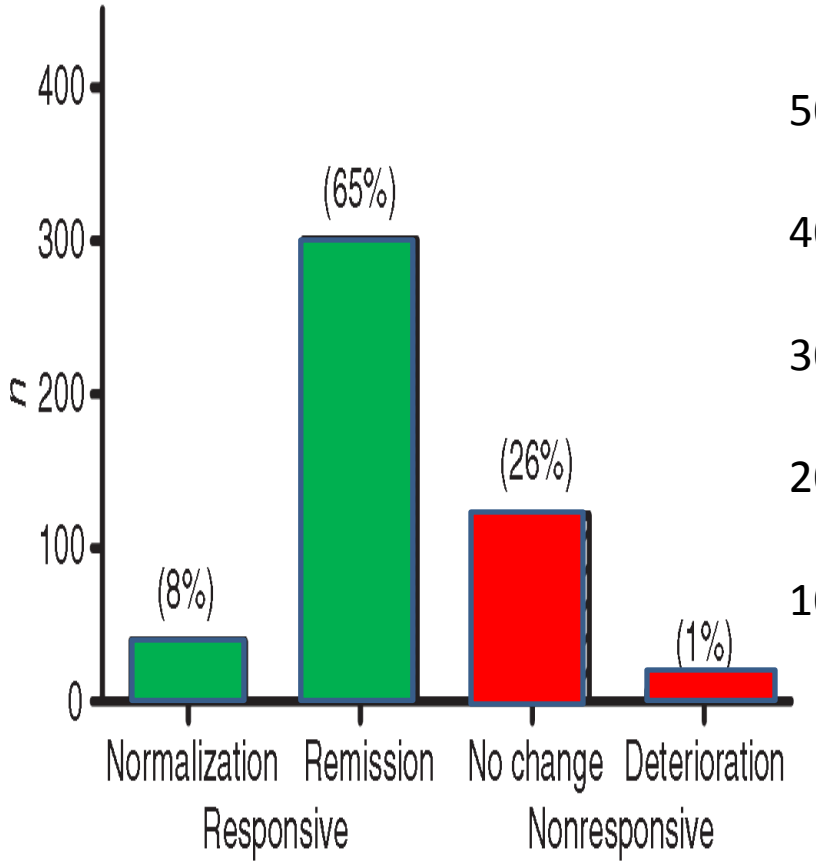
Catassi C, Am J Clin Nutr 2007;85:160

Healing of Intestine in Children

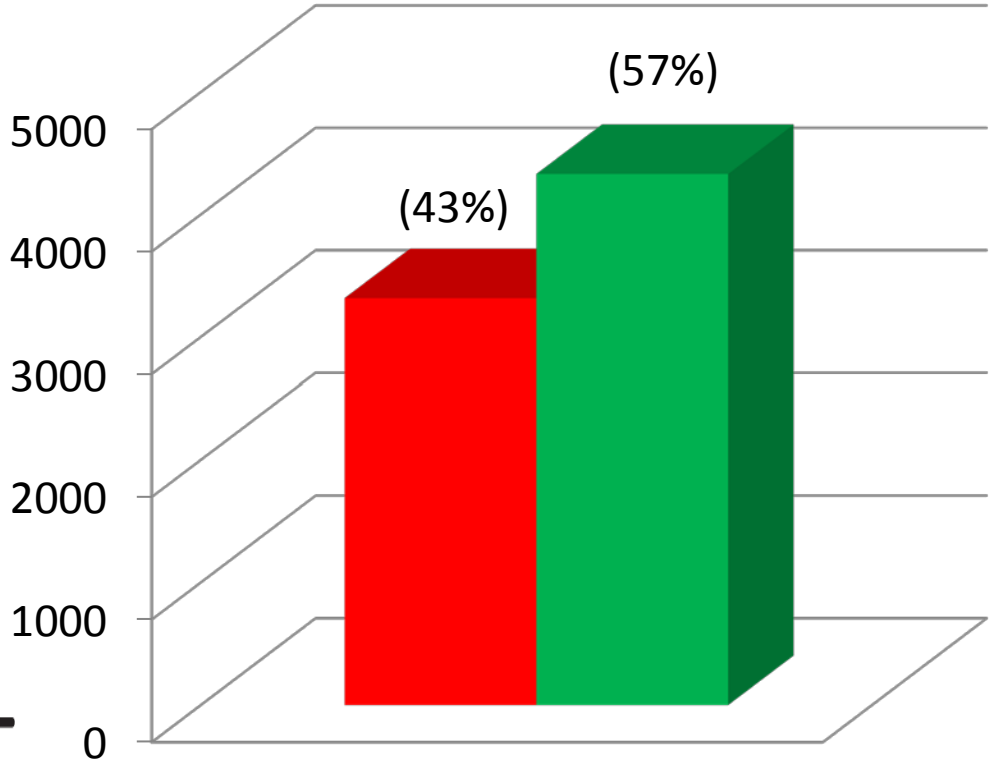


Ghazzawi Y at al., JPGN 2014

Healing of Intestine in Adults

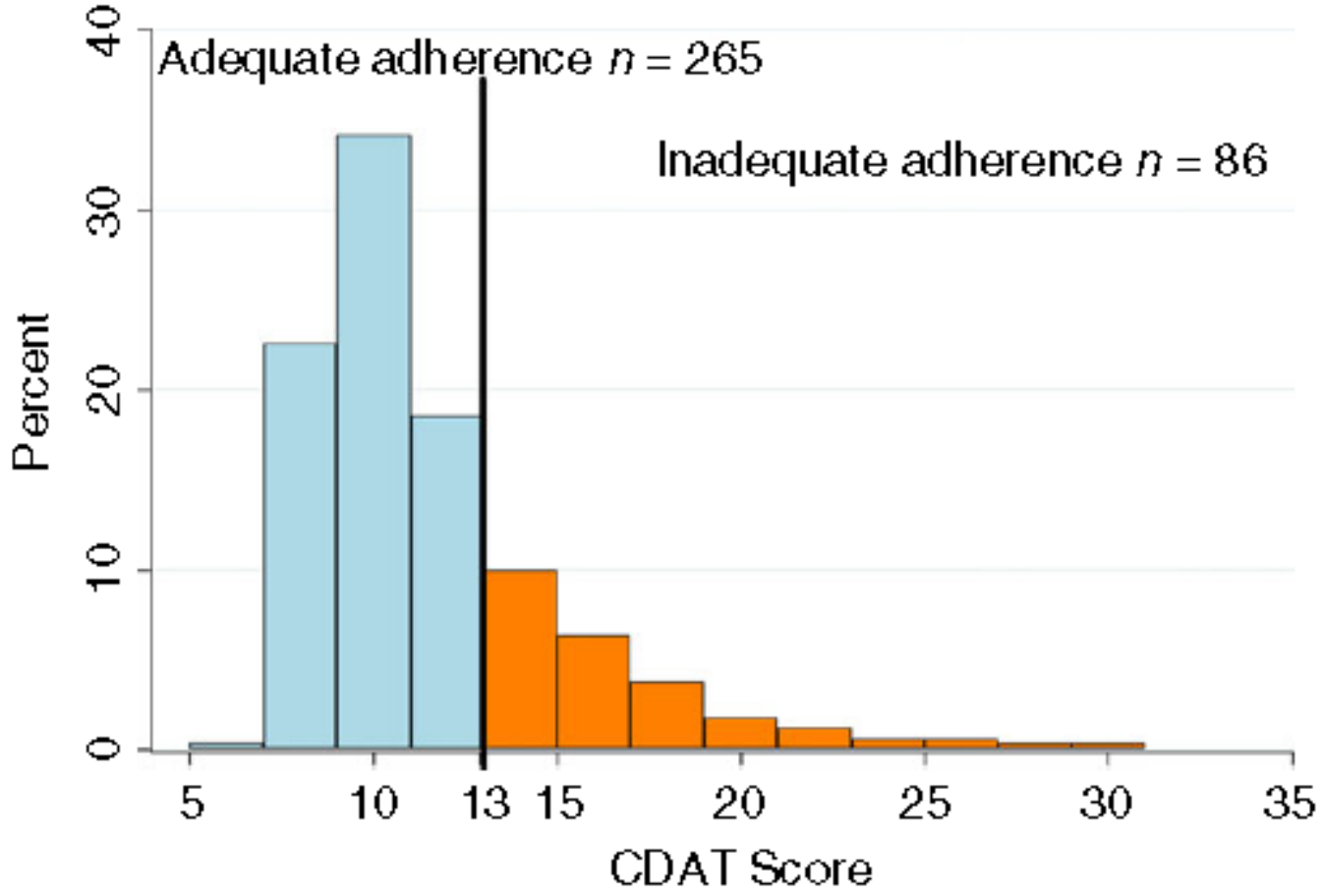


Lanzini A et al., Alim Pharmacol Ther 2009
Only adults

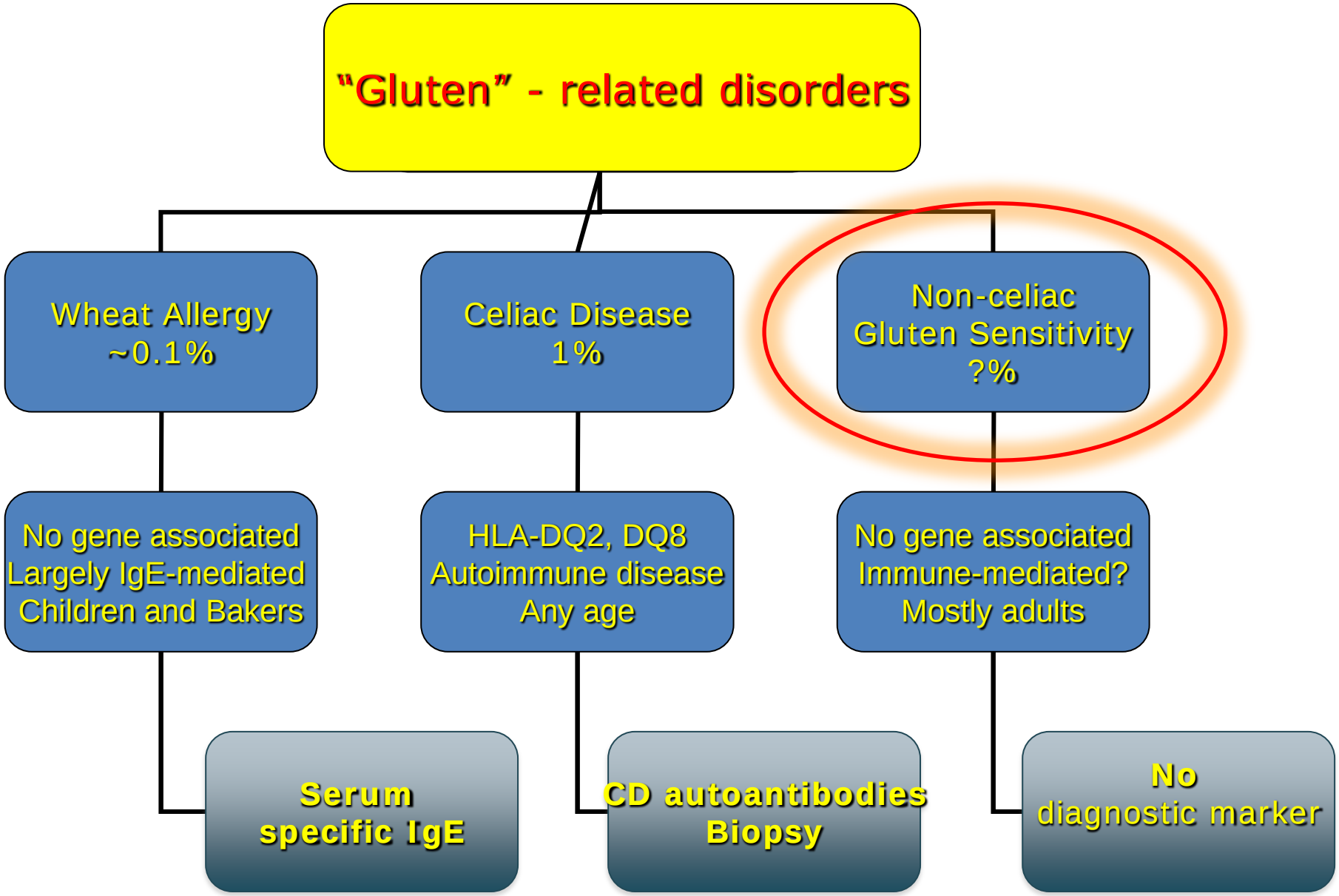


Lebwohl B. et al., Aliment Pharmacol Ther 2014
Adults and Children

Adherence to GFD in adults

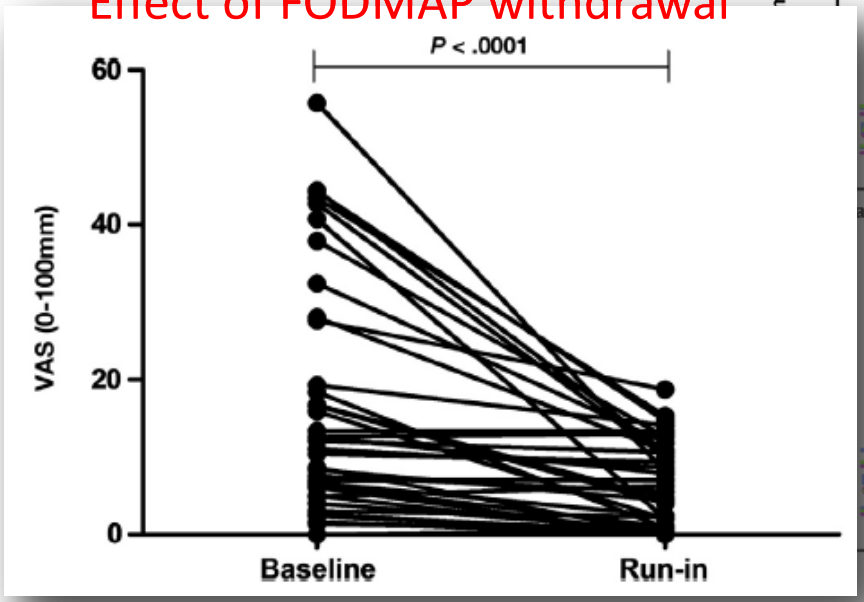


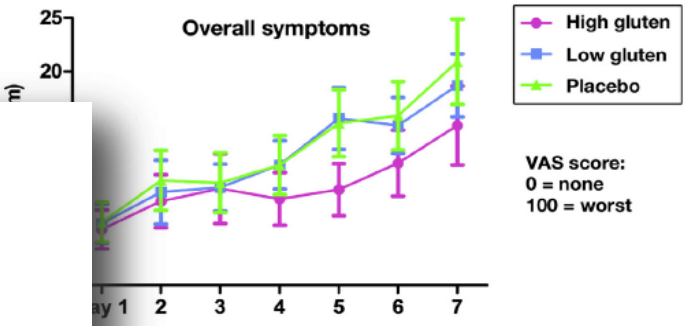
Leffler D et al., Am J Gastro 2015

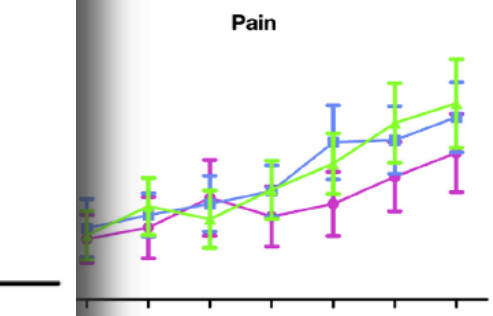


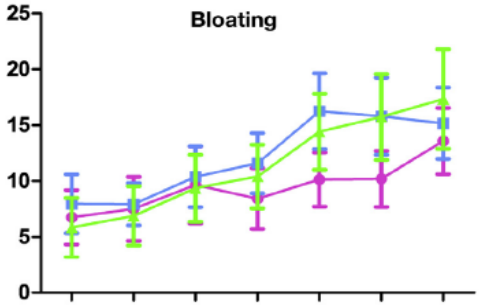
Biesekierski JR et al., Gastroenterology 2013

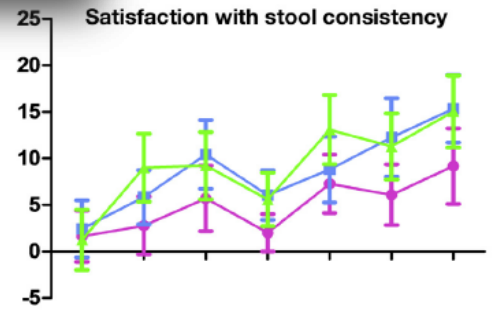
Effect of FODMAP withdrawal

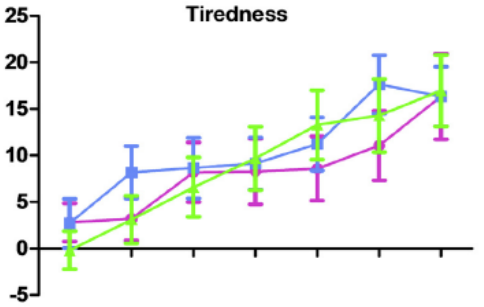


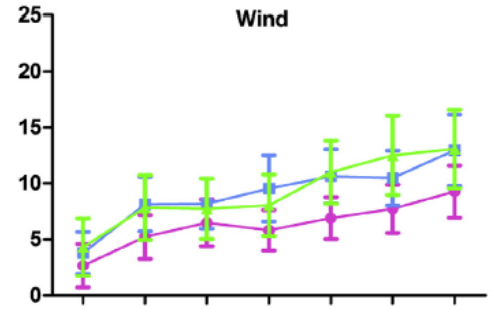


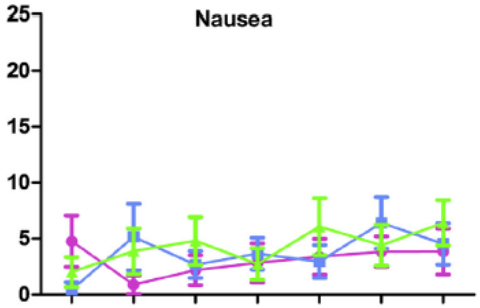












No effect of gluten

Biesekierski JR et al
Gastroenterology 2013

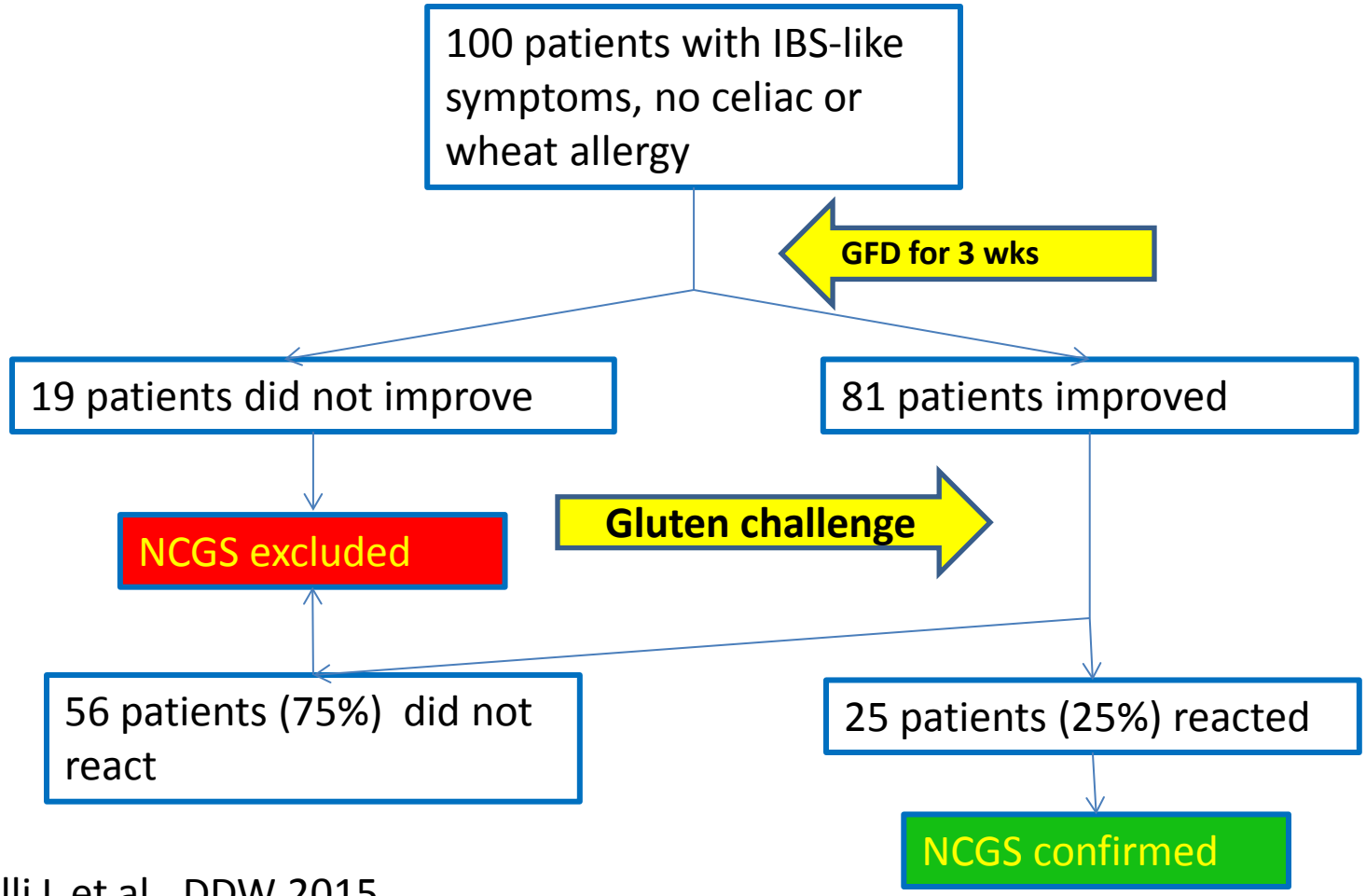
So: Is it Gluten or Not?

Number of studies so far published on NCGS that utilized pure gluten (not wheat) to challenge:

0 (Zero)

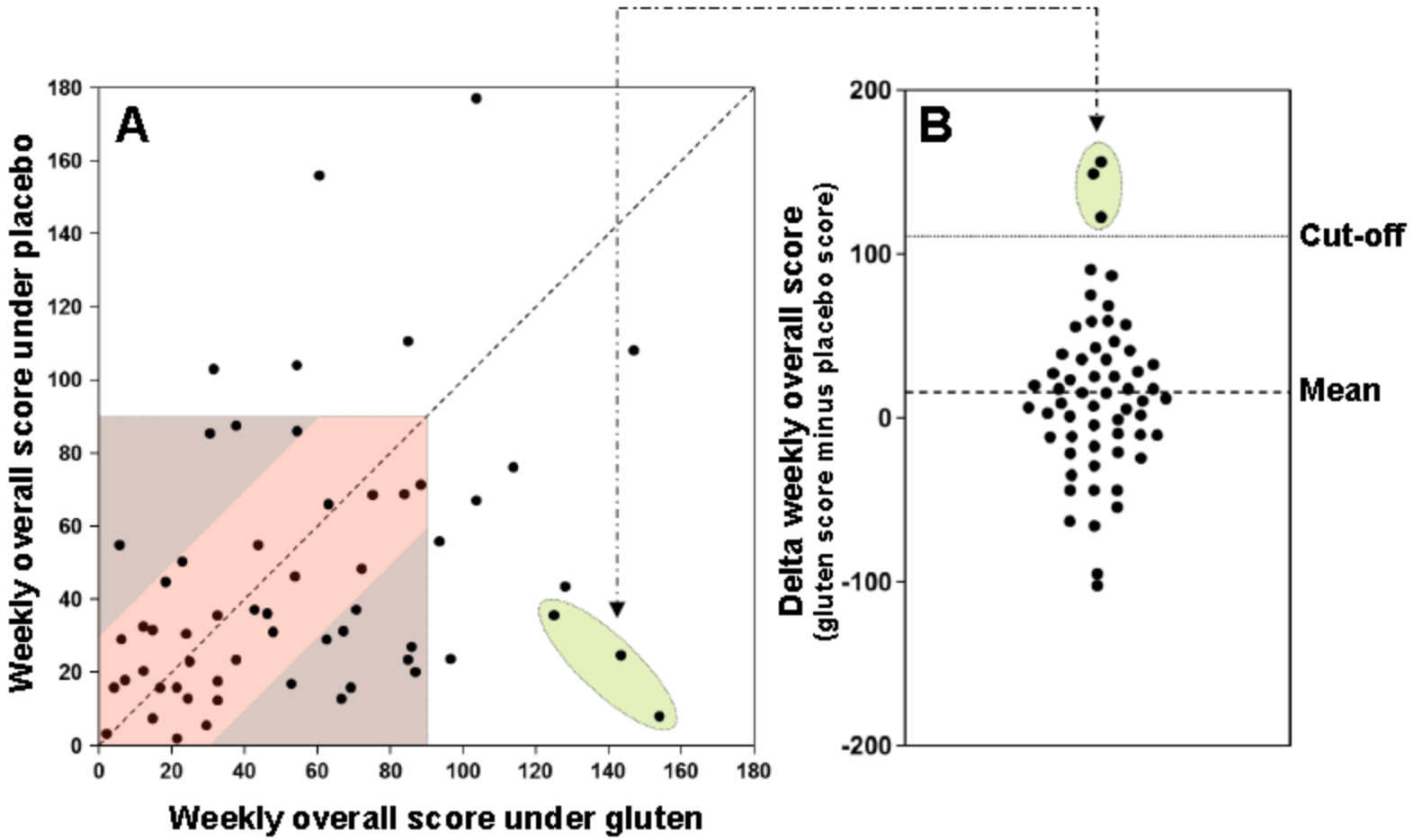
"Of note, no study on NCGS has specifically used as the re-challenging agent gluten or gliadin" – Molina-Infante J et al., Aliment Pharmacol Ther *April* 2015

The "GLUTOX" Trial: A Randomized, Double Blind, Placebo Controlled Crossover Study on "Non-Celiac Gluten Sensitivity"



Elli L et al., DDW 2015

The only published study testing the effect of gluten in NCGS



Di Sabatino A. et al., Clin Gastroenterol Hepatol, 2015

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MEDICAL PROGRESS

Nonceliac Gluten Sensitivity or Wheat Intolerance Syndrome?

Stefano Guandalini, MD[1], and Isabel Polanco, MD[2]

The increase in world-wide consumption of a Mediterranean diet, which includes a wide range of wheat-based foods, has possibly contributed to an alarming rise in the incidence of wheat (gluten?)-related disorders.[1,2] Gluten, the main protein complex in wheat, barley, and rye, is a mixture of alcohol-insoluble ("glutenins") and alcohol-soluble ("gliadins") proteins.[3] Gliadins are a group of proline and glutamine-rich proteins resistant to digestion in the gastrointestinal tract.

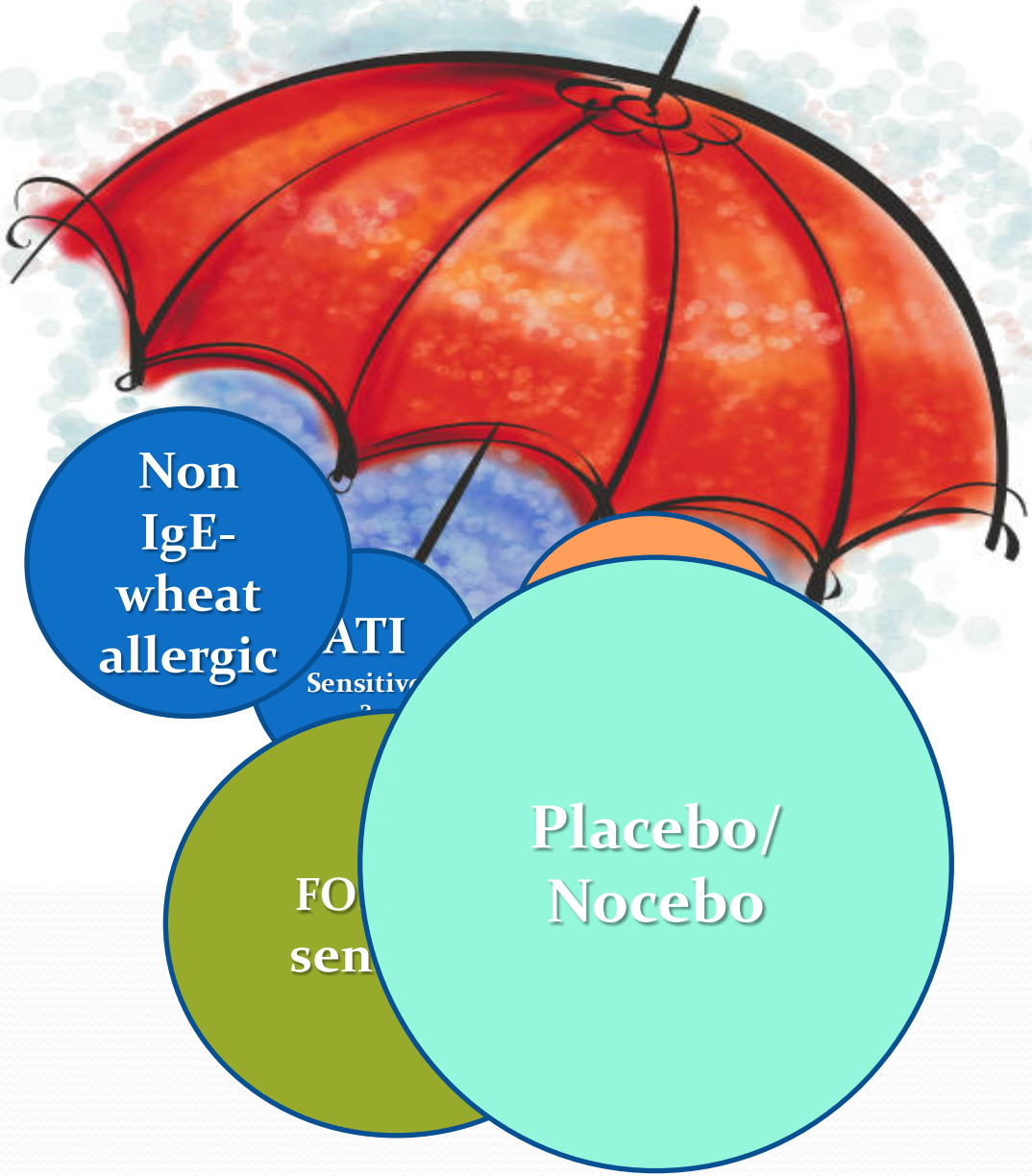
Gluten consumption has been linked to a wide range of

systemic manifestations were most commonly tiredness, headache, fibromyalgia-like joint/muscle pain, leg or arm numbness, 'foggy mind,' dermatitis or skin rash, depression, anxiety, and anemia. Of note, in this study, 95% of patients reported the appearance of symptoms every time or often after the ingestion of gluten containing food. In more than one-half of these patients, the symptoms occurred within 6 hours after gluten ingestion; in about 40%, between 6 and 24 hours after ingestion; and only in less than 10%, more than 24 hours after ingestion. Similar data had been published

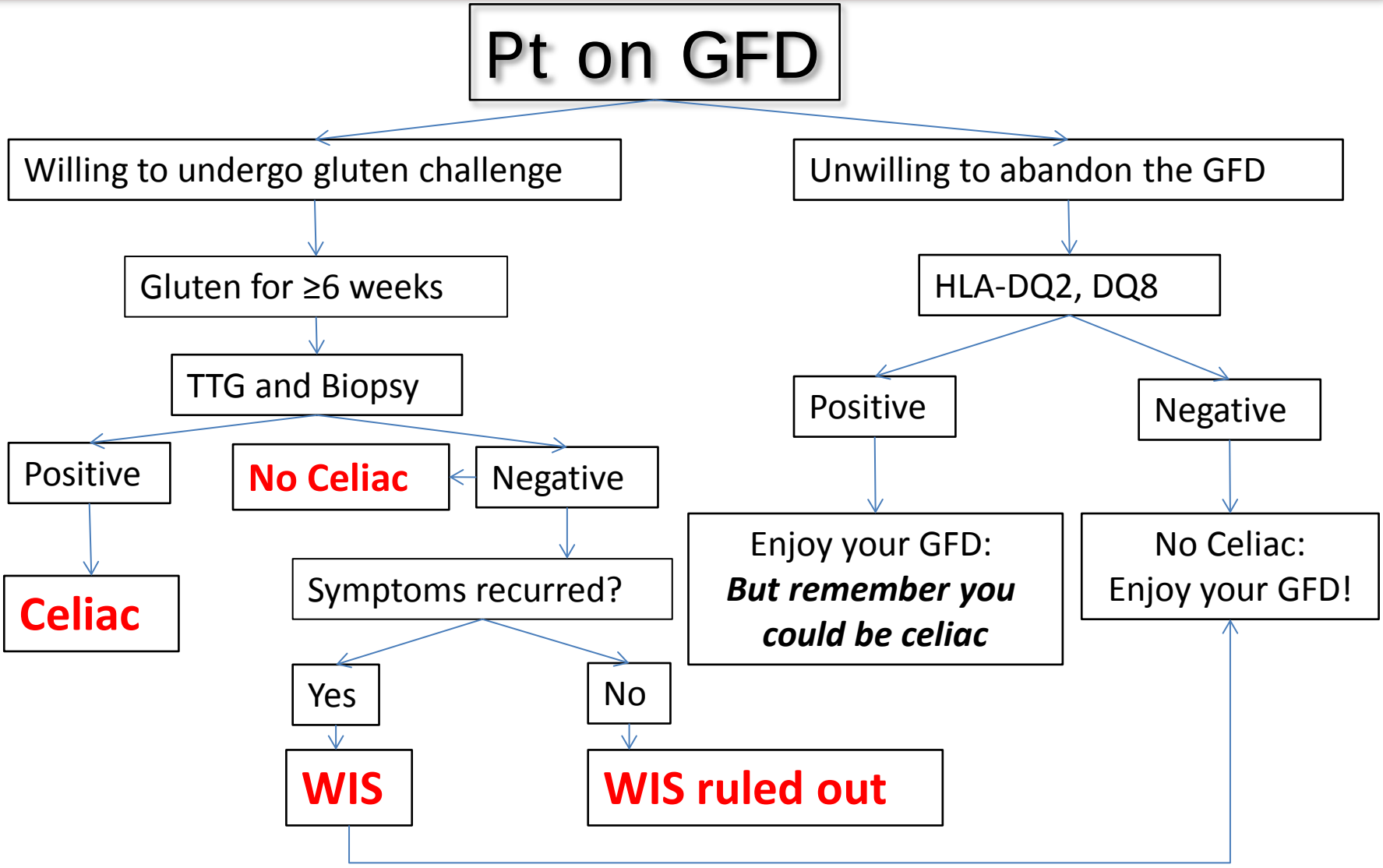
WHEAT INTOLERANCE SYNDROME

Guandalini S and Polanco I, J Pediatr 2015

The ndrome:



WIS – A Practical Approach



In conclusion

- Wheat Allergy
  - More common in children
  - Mostly IgE-mediated
- Celiac disease:
  - Fast increasing prevalence
  - Changing patterns of presentations
  - Celiac serology needed for diagnosis and follow-up
  - GFD more effective in children than in adults
- NCGS (or better "Wheat Intolerance Syndrome")
  - No diagnostic marker available
  - Likely a mixture of various conditions

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Celiac Disease Center

cureceliacdisease.org

Cureceliacdisease.org

Thank you