Celiac Disease: Pop quiz

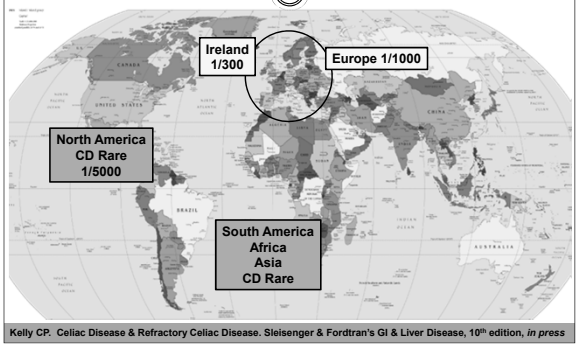
BIDMC HMS

True or False?

Celiac disease is:

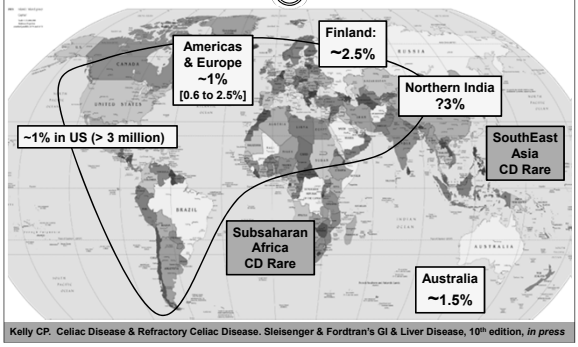
1. An uncommon condition in the US (~1:5000) that is more common in Europe (~1:500) ***False***
2. Usually presents with severe diarrhea and malabsorption ***False***
3. Usually a pediatric diagnosis ***False***
4. Diagnosed by clinical improvement following treatment with gluten free diet ***False***

The World View of Celiac Disease circa 1990



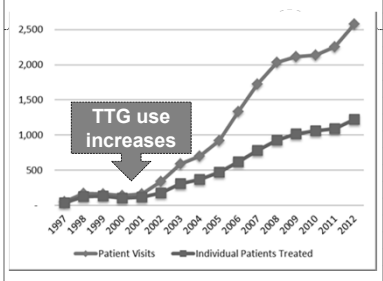
Kelly CP. Celiac Disease & Refractory Celiac Disease. Sleisenger & Fordtran's GI & Liver Disease, 10th edition, *in press*

Today's World View of Celiac Disease Common & Not Limited to Europeans



Kelly CP. Celiac Disease & Refractory Celiac Disease. Sleisenger & Fordtran's GI & Liver Disease, 10th edition, *in press*

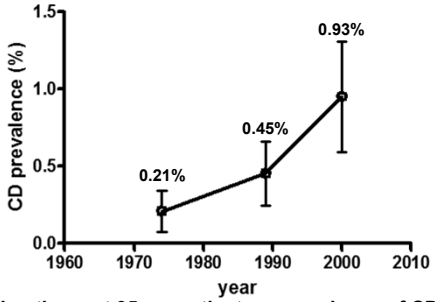
Celiac disease at BIDMC Boston Patient and Visit Volumes - 1997 to 2012



Year	Patient Visits	Fold increase	Individual Patients Treated
1997	47	1	38
1998	167	4	125
1999	160	3	131
2000	136	3	102
2001	160	3	119
2002	338	7	176
2003	590	13	304
2004	698	15	370
2005	919	20	471
2006	1,336	28	615
2007	1,720	37	780
2008	2,034	43	928
2009	2,118	45	1,016
2010	2,137	45	1,058
2011	2,257	48	1,088
2012	2,576	55	1,222

Increased Prevalence Over Time in U.S.A.

(in Line with Other Autoimmune Diseases)



During the past 35 years the true prevalence of CD in USA doubled every 15 years.

C. Catassi et al, Annal Med (on line ahead of print)

Celiac Disease: Age of presentation

- Classically after weaning
  - Peak #1: 4 to 7 years
- Symptoms often improve during adolescence
  - Celiac "honeymoon"
- Can present for the first time at any age
  - Most common - Peak #2: 30 to 50 years
  - BIDMC means:
    - 46 years - age at diagnosis
    - 11 years – interval from symptom onset to diagnosis
    - 6 years - interval from presentation to diagnosis

The protean clinical manifestations of celiac disease

Can presenting at any age to any medical specialty

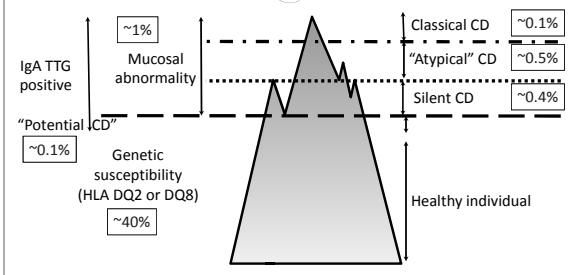
TABLE 1. THE SPECTRUM OF CLINICAL PRESENTATIONS OF CELIAC SPRUE.

COMMON FEATURES	LESS COMMON FEATURES	ASSOCIATED CONDITIONS	COMPLICATIONS
Adults	General features	Definite associations	Refractory sprue
Iron-deficiency anemia	Short stature	Dermatitis herpetiformis	Enteropathy-associated T-cell lymphoma
Diarrhea	Delayed puberty	IgA deficiency	Carcinoma of the oropharynx, esophagus, and small bowel
Children	Gastrointestinal features	Type 1 diabetes	Ulcerative jejunoileitis
Diarrhea	Recurrent aphthous stomatitis	Autoimmune thyroid disease	Collagenous sprue
Failure to thrive	Recurrent abdominal pain	Sjögren's syndrome	
Abdominal distention	Steatorrhea	Microscopic colitis	
	Extraintestinal features	Rheumatoid arthritis	
	Folate-deficiency anemia	Down's syndrome	
	Osteopenia or osteoporosis	IgA nephropathy	
	Dental-enamel hypoplasia	Possible associations	
	Vitamin K deficiency	Congenital heart disease	
	Hypertransaminasemia	Recurrent pericarditis	
	Thrombocytosis (hyposplenism)	Sarcoidosis	
	Arthralgia or arthropathy	Cystic fibrosis	
	Polyneuropathy	Fibrosing alveolitis	
	Ataxia	Lung cavities	
	Epilepsy (with or without cerebral calcification)	Pulmonary hemosiderosis	
	Infertility	Inflammatory bowel disease	
	Recurrent abortions	Autoimmune hepatitis	
	Anxiety and depression	Primary biliary cirrhosis	
	Follicular keratosis	Addison's disease	
	Alopecia	Systemic lupus erythematosus	
		Vasculitis	
		Polymyositis	
		Myasthenia gravis	
		Schizophrenia	

#1 Consider a diagnosis of celiac disease

RJ Farrell, CP Kelly N Engl J Med 2002; 346:183

The clinical spectrum of Celiac Disease



The celiac "iceberg"

Diversity of celiac disease:

Global, multiple symptoms, any age

- Who?
  - Common in many ethnic backgrounds
- When?
  - Any age after gluten ingestion
  - Average age at diagnosis ~45 yrs
- How?
  - Highly diverse presentations.
  - Average 11 years of symptoms prior to diagnosis

Green AJG 2001, Cranney DDS 2007

Who to test for celiac disease

Diarrhea +/- malabsorption
- IBS-like (especially D-IBS)
- Lactose (or fructose) Intolerance-like but not responding fully to dietary measures

Nutritional deficiencies
- Iron deficiency anemia (most common)
- B12, Folate (now rare)
- Vit D / osteopenia/osteoporosis

Other
- Dermatitis Herpetiformis
- Impaired fertility
- CNS: Ataxia, peripheral neuropathy
- Severe aphthous stomatitis
- Abnormal LFTs

How to diagnose Celiac disease

1. **Specific celiac serology**
   - **IgA tTG** (tissue TransGlutaminase) – the single best test
     - IgG tTG – less sensitive than IgA tTG
     - IgA DGP (Deamidated Gliadin Peptide)
     - IgG DGP – most accurate IgG-based assay
     - Total IgA – optional (IgG DGP more accurate)
2. **Characteristic histology** (EGD with biopsy)

Rubio-Tapia et al. ACG Clinical Guidelines on Celiac Disease. Am J Gastroenterol. 2013

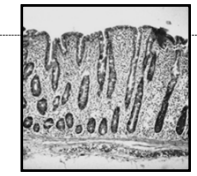
How NOT to diagnose Celiac disease

Common Pitfalls:

- Clinical response to GFD
- Positive serum IgG or IgA anti-gliadin antibodies
- Positive fecal anti-gliadin antibodies
- HLA DQ2 or DQ8 positivity (required but not sufficient)
- Flawed interpretation of biopsy histology:
  - Villus distortion and inflammation in duodenal bulb
  - Increased IELs [intraepithelial lymphocytes]
  - Villus atrophy from another cause (TTG & DGP negative)

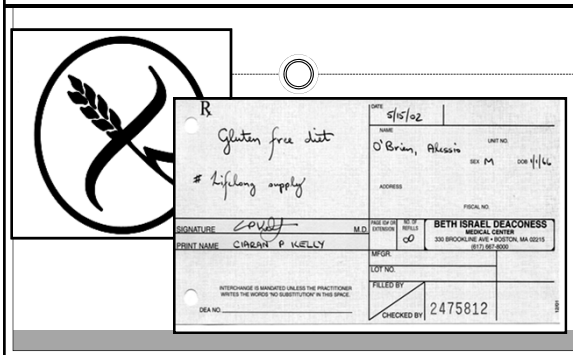
Is small intestinal biopsy still needed to diagnose celiac disease?

Yes because:



- Celiac disease is defined by enteropathy
- Biopsy is relatively simple and safe
- False positive serology does occur
- A false positive diagnosis is very costly in terms of the patient's lifelong treatment burden
- Symptom response to GFD is not reliable for diagnosis
- The diagnosis cannot be confirmed or refuted easily after treatment with a GFD (gluten free diet)

Treatment of Celiac Disease



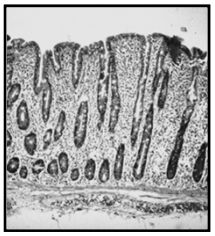
Management of Celiac Disease

NIH Celiac Disease Consensus Conference 2004

- **C**onsultation with a skilled celiac dietician
- **E**ducation about the disease
- **L**ifelong adherence to a gluten-free diet
- **I**dentification & treatment of nutritional deficiencies
- **A**ccess to a support and advocacy group
- **C**ontinuous long-term follow up by a multidisciplinary team

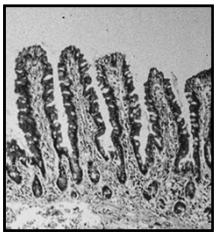
Celiac Disease: Response to GFD

tTG IgA > 100 units



Small intestinal villous atrophy & crypt hyperplasia

tTG IgA normal [<20 units]



Resolution of intestinal injury on gluten free diet

Non-Responsive Celiac Disease

Most patients with CD respond well to GFD

~10% are non-responsive:

Primary: Ongoing symptoms, signs or lab. abnormalities of CD after > six months of gluten withdrawal

Secondary: Recurrence of symptoms, signs or lab. abnormalities of CD after an initial response and while still on a strict GFD for > 6 months

Primary & Secondary:
Similar frequency
Similar demographics

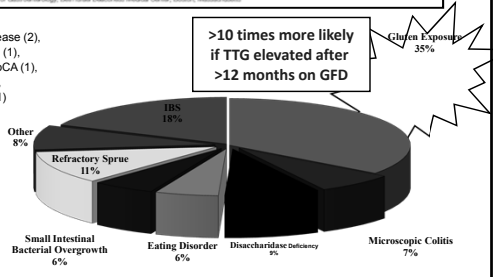
CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2007;5:445–450

Etiologies and Predictors of Diagnosis in Nonresponsive Celiac Disease

DANIEL A. LEFFLER, MELINDA DENNIS, BRIAN HYETT, EOIN KELLY, DETLEF SCHUPPAN, and CIARAN P. KELLY
Department of Gastroenterology, Beth Israel Deaconess Medical Center, Boston, Massachusetts

Other included:
Peptic ulcer disease (2),
Crohn's disease (1),
Duodenal adenoCA (1),
Food allergy (1),
Gastroparesis (1)

>10 times more likely if TTG elevated after >12 months on GFD



Gluten – *where will it hide next?*

- Toothpaste
- Envelope gum
- Lipstick
- Candy
- Flavorings
- Medications
- Vitamins & supplements
- **"Safe" gluten-free grains**

Thompson et al. J Am Diet Assoc 2010;110:937

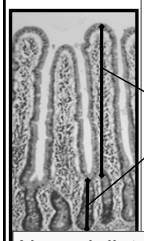
Table. Gluten content of inherently gluten-free grains, flours, and seeds not labeled gluten-free

Product	Allergen advisory statement	Extraction 1* ppm[a] gluten	Extraction 2 ppm gluten	Mean ppm
Millet flour	Yes	308.0	302.0	305.0
Millet flour	Yes	310.0	344.0	327.0
Millet grain	No	22.0	6.0	14.0
Millet grain	No	10.0	40.0	25.0
White rice flour	Yes	9.0	8.0	8.5
Buckwheat flour	No	66.0	64.0	65.0
Sorghum flour	Yes	238.0	230.0	234.0
Soy flour	No	3,000.0	2,850.0	2,925.0
Soy flour	No	96.0	88.0	92.0
Basmati rice	No	<5	<5	<5
Long-grain brown rice	No	<5	<5	<5
Enriched corn meal	No	<5	<5	<5
Instant polenta	No	<5	<5	<5
Rice flour	No	<5	<5	<5
Hulled buckwheat	No	<5	<5	<5
Buckwheat groats	Yes	<5	<5	<5
Amaranth flour	Yes	<5	<5	<5
Amaranth flour	No	<5	<5	<5
Flax seed	Yes	<5	<5	<5
Flax seed	No	<5	<5	<5
Amaranth seed	No	<5	<5	<5
Amaranth seed	No	<5	<5	<5

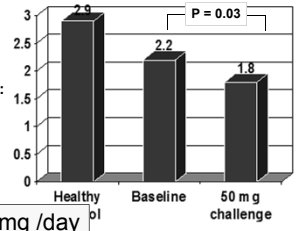
*Assay used: Sandwich R5 enzyme-linked immunosorbent assay with cocktail extrac-

Tiny gluten exposures perpetuate active disease

Histology post 90 day, 50 mg gluten/day microchallenge



Villus height: Crypt depth



Normal diet ~10,000 mg /day
Slice of bread ~2,000 mg
1/40th slice of bread ~50 mg

Catassi et al. Am J Clin Nutr 2007;85(1):160-6.

How to Evaluate GFD adherence

- **Patient self-report**
  - CDAT a Validated GFD adherence measure
    - Frequency of "cheating" & Confidence in ability to follow GFD when dining out
- **Serology**
  - focus on trajectory not absolute values
  - expect 50% drop every 2-4 months
  - NOT sensitive to dietary gluten
- **Expert dietician evaluation** = *"gold standard"*
- **Biopsy histology -** a measure of disease activity not GFD adherence
- **Measure gluten** in food, stool & urine

Leffler et al. *Clin Gastroenterol Hepatol* 2009;7:530-6.

Risk of neoplasia in celiac disease

- Sweden in-patient register
- 1964 to 1994
- 11,019 with CD
- 1,580 with DH
- * Standardized incidence ratio (SIR) for neoplasia
- SIR in DH 1.2
- Risks declined with time and duration of follow up

Site	SIR Celiac	% of cohort
All sites	**1.3***	2.3%
Oral	**2.3**	0.07%
Esophagus	**4.2**	0.05%
Small intest.	**10.0**	0.07%
Colon	**1.9**	**0.2%**
Lymphoma	**5.9**	**0.3%**
Hodgkin's	**4.6**	0.05%
NHL	**6.3**	**0.3%**

Askling et al. Gastroenterol 2002;123:1428-35

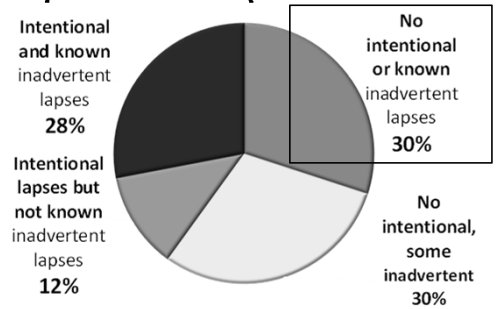
Do we need non-dietary treatments for Celiac Disease?

The GFD is highly effective in celiac disease BUT:

- > 10% Non-responsive to GFD
- 1 - 2% Refractory to GFD
- ~ 30% of adults on GFD for celiac disease have ongoing partial villous atrophy on biopsy
- Strict GFD difficult to maintain
  - At social events
  - For food prepared outside the home
    - When travelling
    - In restaurants & cafeterias
    - Take-out
  - For the elderly
  - For the illiterate
  - For those with mental or psychological impairment

Sanders JGLD 2011

70% of Celiac Disease Patients Report Gluten Exposures on GFD

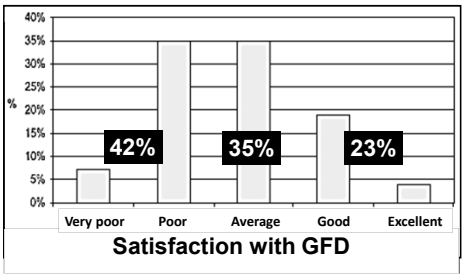


Reported intentional and inadvertent gluten consumption (n=269)

Hall NJ, Rubin GP, Charnock A, Intentional and Inadvertent Non Adherence in Adult Coeliac Disease. A Cross-Sectional Survey Appetite 68:56-62, 2013

Low satisfaction with the GFD amongst patients with Celiac disease

26



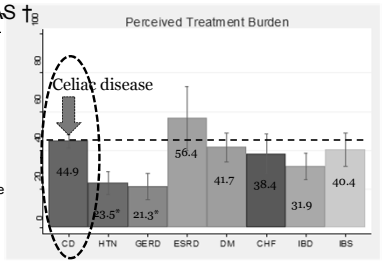
Sanders JGLD 2011

Perceived treatment burden is very high in Celiac disease

Renal disease on Hemodialysis = 56.4

Celiac disease = 44.9

Higher than:
- Insulin dependant diabetes
- Irritable bowel syndrome
- Congestive heart failure
- Inflammatory bowel disease
- Hypertension
- GERD



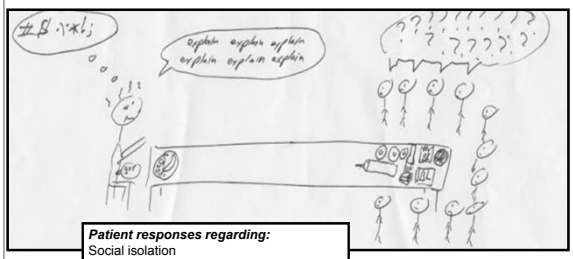
†VAS: 0 = Very Easy
100 = Very Difficult

*Compared with CeD, p<0.001

Shah S et al. Treatment burden in CeD. Am J Gastroenterol 2014;109:1304-11.

Social isolation is part of the treatment burden of CeD

28



Patient responses regarding:
Social isolation
Burden of requesting and explaining GFD
Inhibition of social interactions

Market Research, Alba Therapeutics & Double Helix

Homework Question: What having celiac disease means to you?

Pathogenesis of Celiac Disease & Potential Sites for Intervention

Wheat
Barley
Rye

Gluten / gliadin

1. Ingested
2. Survives digestion
3. Crosses gut lining
4. "Made tastier" by TTG
5. Taken up by "antigen presenting cells" (APCs)
6. Genetically encoded DQ2 or DQ8 present
7. Presented on DQ2/8
8. T cells activated
   - Inflammation
   - Antibody production
   - Tissue damage

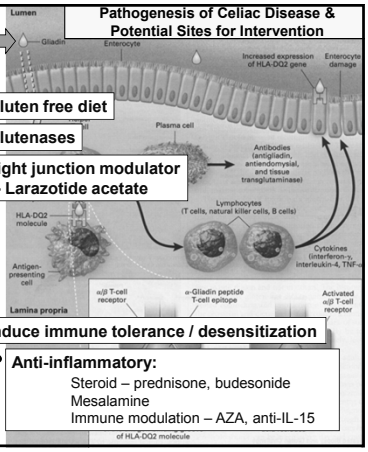
Gluten free diet

Glutenases

Tight junction modulator – Larazotide acetate

Induce immune tolerance / desensitization

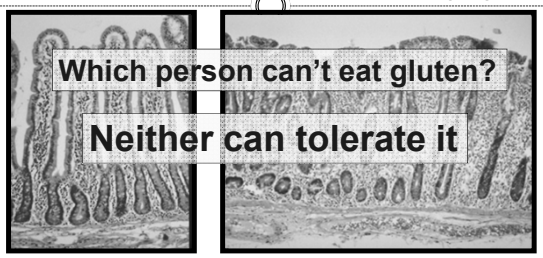
Anti-inflammatory:
Steroid – prednisone, budesonide
Mesalamine
Immune modulation – AZA, anti-IL-15



Farrell & Kelly N Engl J Med 2002;346:183

Small bowel biopsy of patients with diarrhea & bloating

Normal **Villous atrophy**



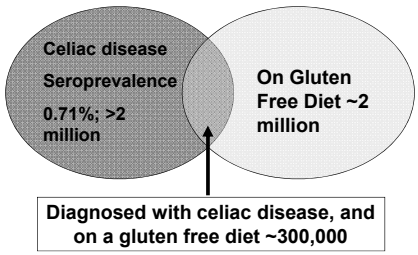
Which person can't eat gluten?

Neither can tolerate it

Slide Atlas of Gastronterology, Misiewicz et al, 1984

Epidemiology of Celiac Disease & Use of the Gluten free Diet in the US

Rubio-Tapia A et al. Am J Gastroenterol. 2012 Oct;107(10):1538-44;



Diagnosed with celiac disease, and on a gluten free diet ~300,000

- Most people in the US with CeD remain undiagnosed
- NCGS may be very common

Non-celiac Gluten Sensitivity: The new kid that's taking over the block?

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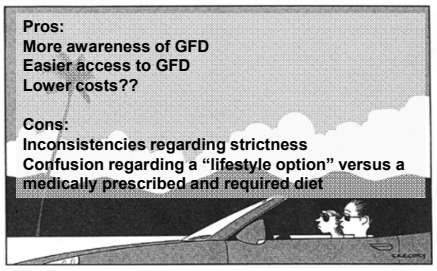
Pros:
More awareness of GFD
Easier access to GFD
Lower costs??

Cons:
Inconsistencies regarding strictness
Confusion regarding a "lifestyle option" versus a medically prescribed and required diet



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

New Yorker cartoon by GREGORY

Celiac disease *vs* NCGS Who cares? – or Does it even matter?

	Celiac disease	NCGS [Non-celiac gluten sensitivity]
Gluten exposure	< 20 ppm	Variable Titrate to symptoms
Implications for family	Relatives at high risk (esp. 1st degree)	None
Complications	Malignancies incl. Lymphoma Nutritional deficiencies	None
Long-term management	Recommended	Not needed

Diagnostic Testing in Celiac disease (CeD) versus Non-celiac Gluten Sensitivity (NCGS)

Finding	Untreated CeD	Treated CeD (on GFD)	NCGS
Symptoms after gluten ingestion	Yes	Yes	Yes
Specific CeD **serologies**	Yes	No (often)	No
Villous atrophy (biopsy changes)	Yes	No (often)	No
Celiac **genes** (HLA DQ2/8)	Yes	Yes	No in ~40%

ACG Clinical Guidelines. Am J Gastroenterol. 2013

CME

Celiac Disease or Non-Celiac Gluten Sensitivity? An Approach to Clinical Differential Diagnosis

Toufic A. Kabbani, MD, MPH[1,2], Rohini R. Vanga, MD[1], Daniel A. Leffler, MD, MS[1], Javier Villafuerte-Galvez, MD[1], Kumar Pallav, MD[1], Joshua Hansen, MS[1], Rupa Mukherjee, MD[1], Melinda Dennis, MS, RD, LDN[1] and Ciaran P. Kelly, MD[1]

Am J Gastroenterol 2014. 109:741-6. PMID:24619056.

Main points:

1. Positive serology (TTG, EMA or DGP) **at any time** - high PPV for Celiac disease
2. Negative serology **while on normal diet** - high NPV
3. **HLA DQ2 & 8 negative** essentially **excludes** Celiac disease
4. "**Gluten challenge**" sometimes needed

The many faces of Celiac Disease

- Common (~1% of population)
- Complex presentations
  - All ages
  - With or without
    - GI symptoms
    - Deficiency states
      - esp. iron deficiency
- Easy to diagnose (or exclude) prior to GFD by **IgA-tTG** (plus biopsy if positive)
- GFD is the only treatment
  - Usually effective
  - Often considered burdensome
  - Increasingly popular
    - esp for "*Non-celiac gluten sensitivity*"
  - Non-dietary treatments under investigation