Challenges with Celiac Disease and Gluten Intolerances

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Objectives

- Differentiate celiac disease from other wheat-related ailments.
- Understand the appropriate use and limitations of available screening tests for celiac disease.
- Be aware of emerging therapeutic options for celiac disease.
- Provide family-centered support for those affected by celiac disease and other gluten intolerances.

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What is celiac disease?

Celiac disease is an immune-mediated enteropathy caused by a permanent sensitivity to gluten in genetically susceptible individuals.

It occurs in symptomatic people with gastrointestinal and non-gastrointestinal symptoms, and in some asymptomatic individuals, including people affected by:

- Type 1 diabetes
- Down syndrome
- Turner syndrome
- Williams syndrome
- Selective IgA deficiency
- First degree relatives of individuals with celiac disease

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What is celiac disease?

Prior aliases:

Celiac sprue
Gluten-sensitive enteropathy

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What is *not* celiac disease?

- ***Wheat allergy***
  - IgE-mediated food allergy
  - Diagnosed by RAST, skin prick or patch testing, dietary elimination/challenge

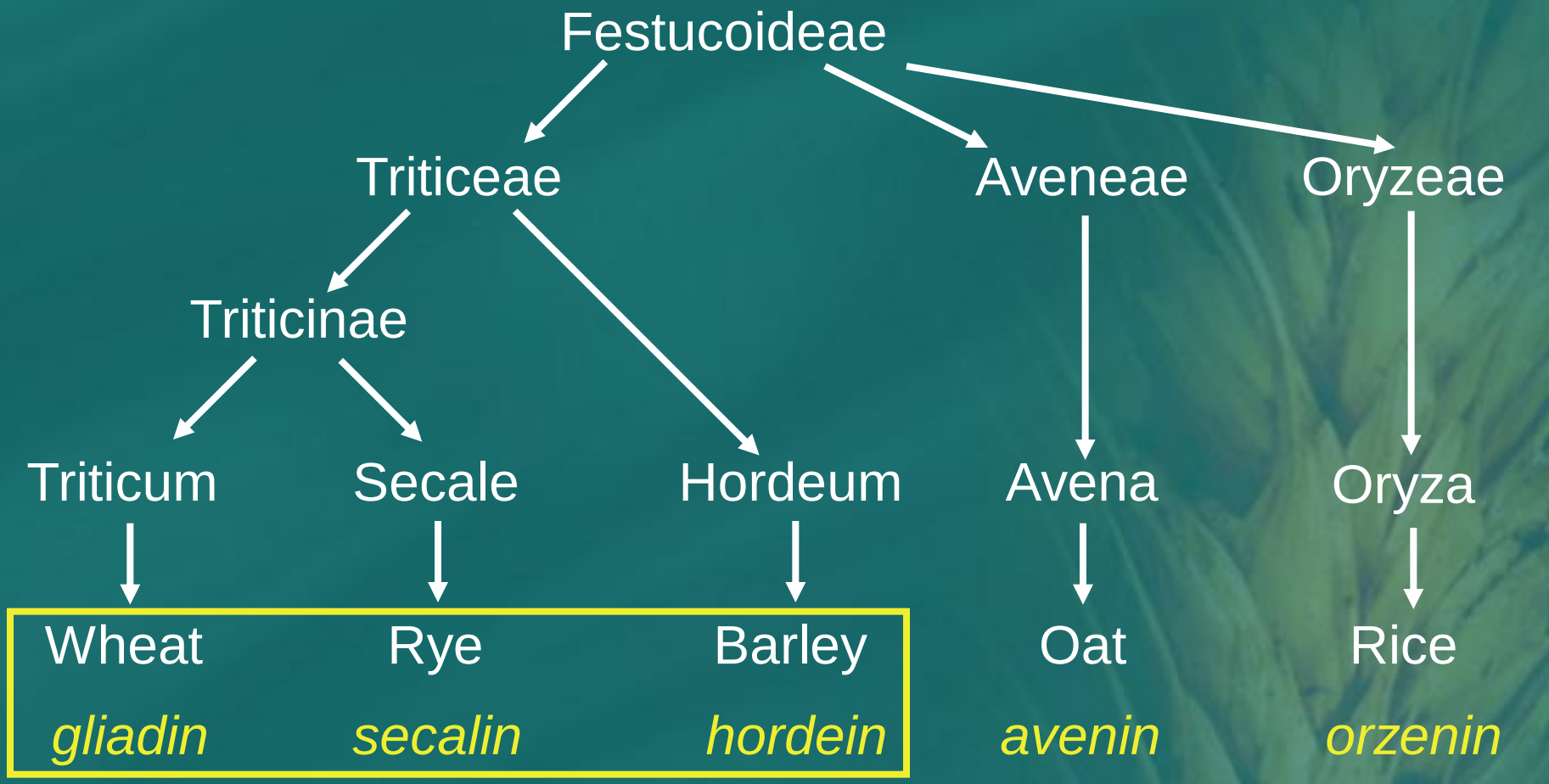
- ***Fructan sensitivity***
  - Bothersome gastrointestinal symptoms related to ingestion of fructans. Frequently associated with irritable bowel syndrome.

- ***Gluten sensitivity***
  - GI or systemic symptoms that improve on gluten-free diet in an individual who *does not* meet objective criteria for the diagnosis of celiac disease

What is gluten?

- Broad term for various proteins, called *prolamin(e)s*
- Each grain has its own specific prolamin
  - Wheat: gliadin
  - Rye: secalin
  - Barley: hordein
  - Oat: avenin

Major cereal grains in US and their prolamins



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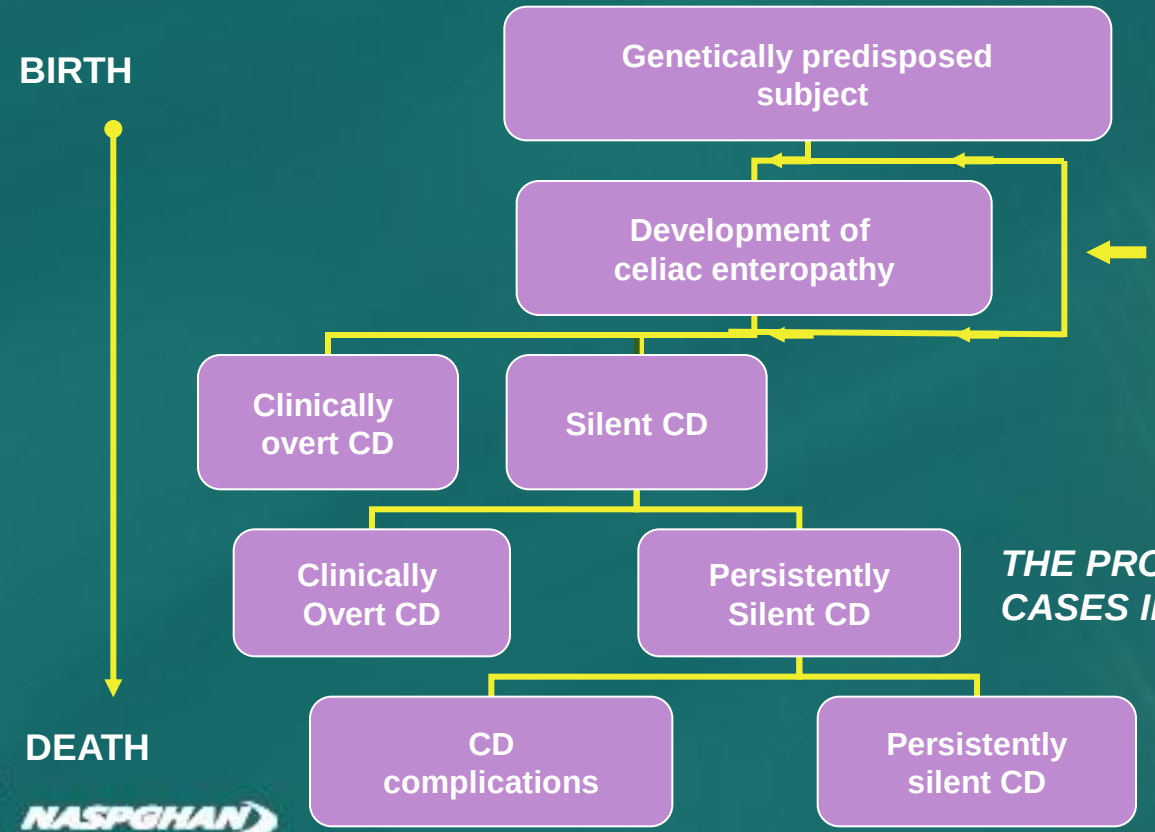
Natural History Of Celiac Disease At Glance



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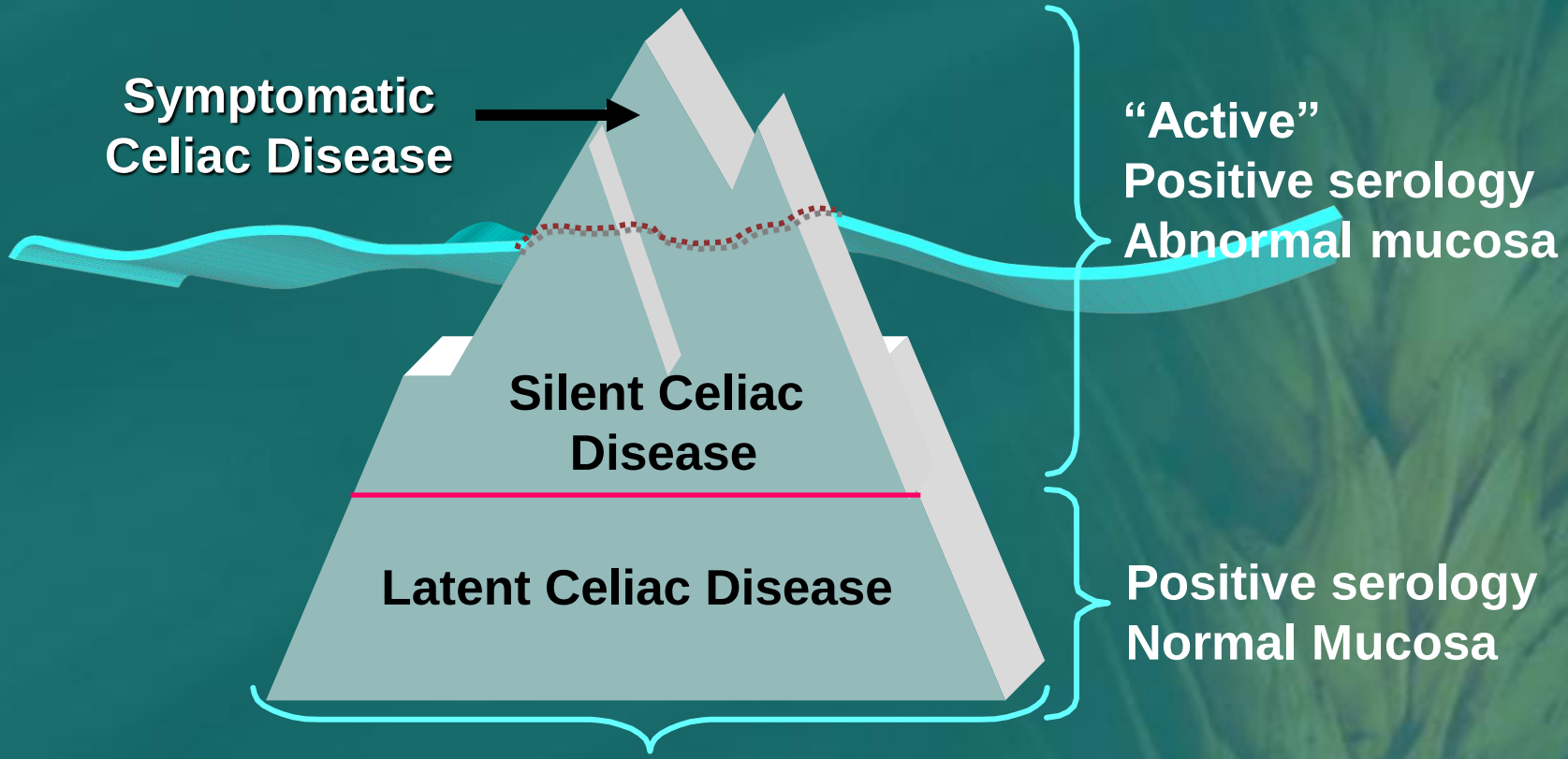
The Celiac Iceberg



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Asymptomatic

Latent **Silent**

- **Latent:**
  - ***No*** symptoms
  - ***Positive*** serology
  - ***Normal*** mucosa

  Do *not* have celiac disease

  May develop celiac disease in the future, under the "correct" environmental conditions

  AKA: False-positive serology

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Asymptomatic

Latent — **Silent**

- **Silent:**

  No or minimal symptoms

  Positive serology

  Damaged mucosa

  Identified by screening asymptomatic individuals from groups at risk such:

  - » First degree relatives
  - » Down syndrome patients
  - » Type 1 diabetes patients, etc.

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Symptomatic

- ***Significant*** symptoms
- ***Positive*** serology
- ***Damaged*** mucosa

Identified by screening symptomatic individuals

But….what are “symptoms”????

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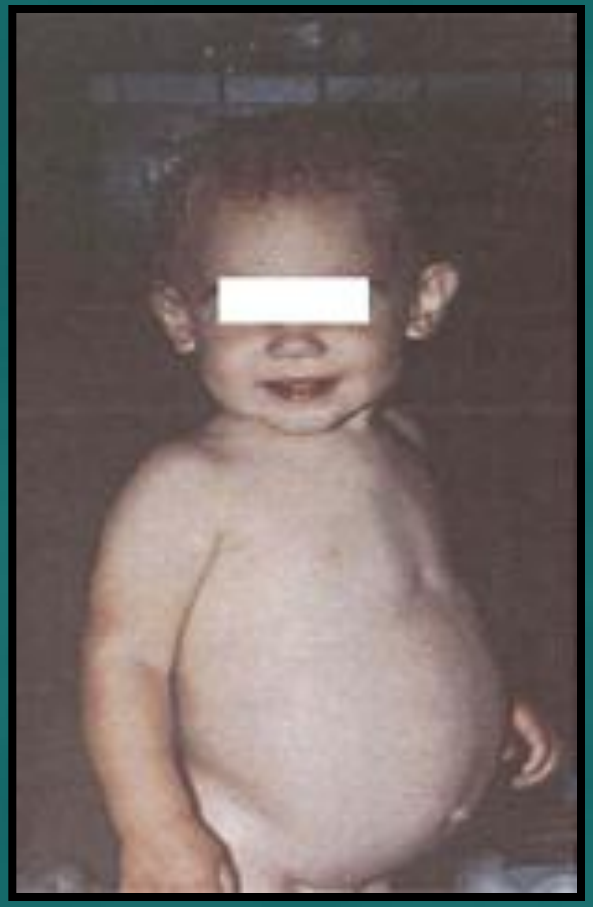
Gastrointestinal Manifestations ("Classic")

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
- Stomatitis

“Typical” Celiac Disease



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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-deficiency anemia
- Hepatitis
- Arthritis
- Infertility
- Neuropathies
- Epilepsy with occipital calcifications

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Epidemiology

The old world view:

- A rare disorder typical of infancy
- Wide incidence fluctuates in space (1/400 Ireland to 1/10000 Denmark) and in time
- A disease of essentially European origin

“Mines” of Celiac Disease Were Found Among:

Relatives

Patients with associated disorders

short stature, anemia, fatigue, hypertransaminasemia, autommune disorders, Down, IgA deficiency, neuropathies, osteoporosis, infertility

“Healthy” groups

blood donors, students, general population

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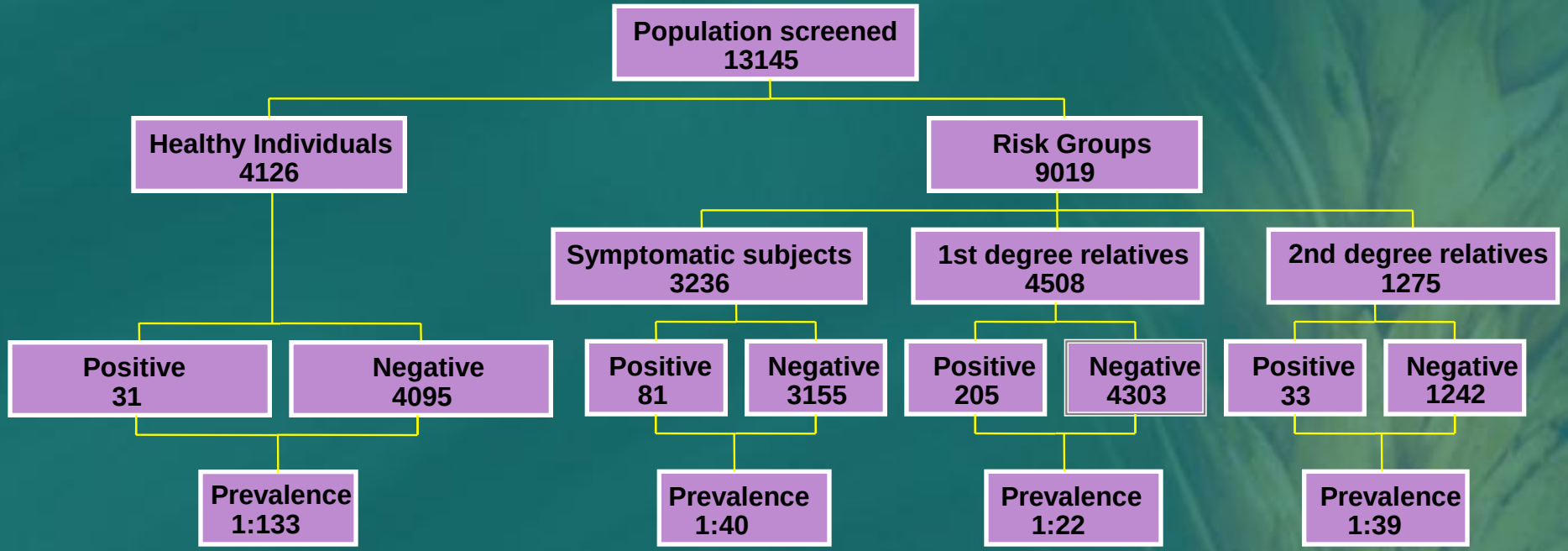
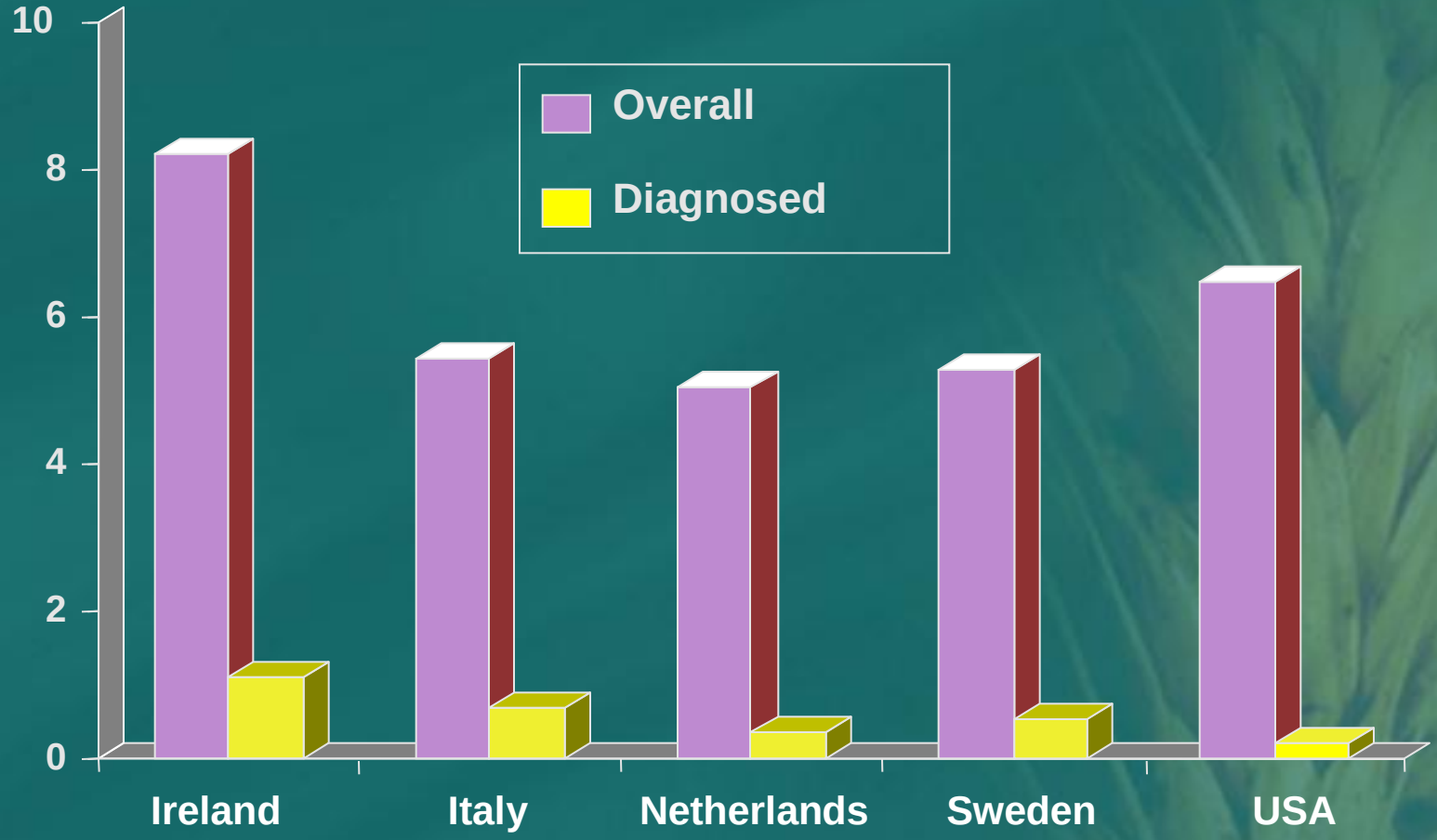
Celiac Disease Epidemiological Study in USA



Projected number of celiacs in the U.S.A.: 2,115,954
Actual number of known celiacs in the U.S.A.: 40,000
For each known celiac there are 53 undiagnosed patients.

A. Fasano et al., *Arch Int Med* 2003;163:286-292.

Celiac Disease Icebergs



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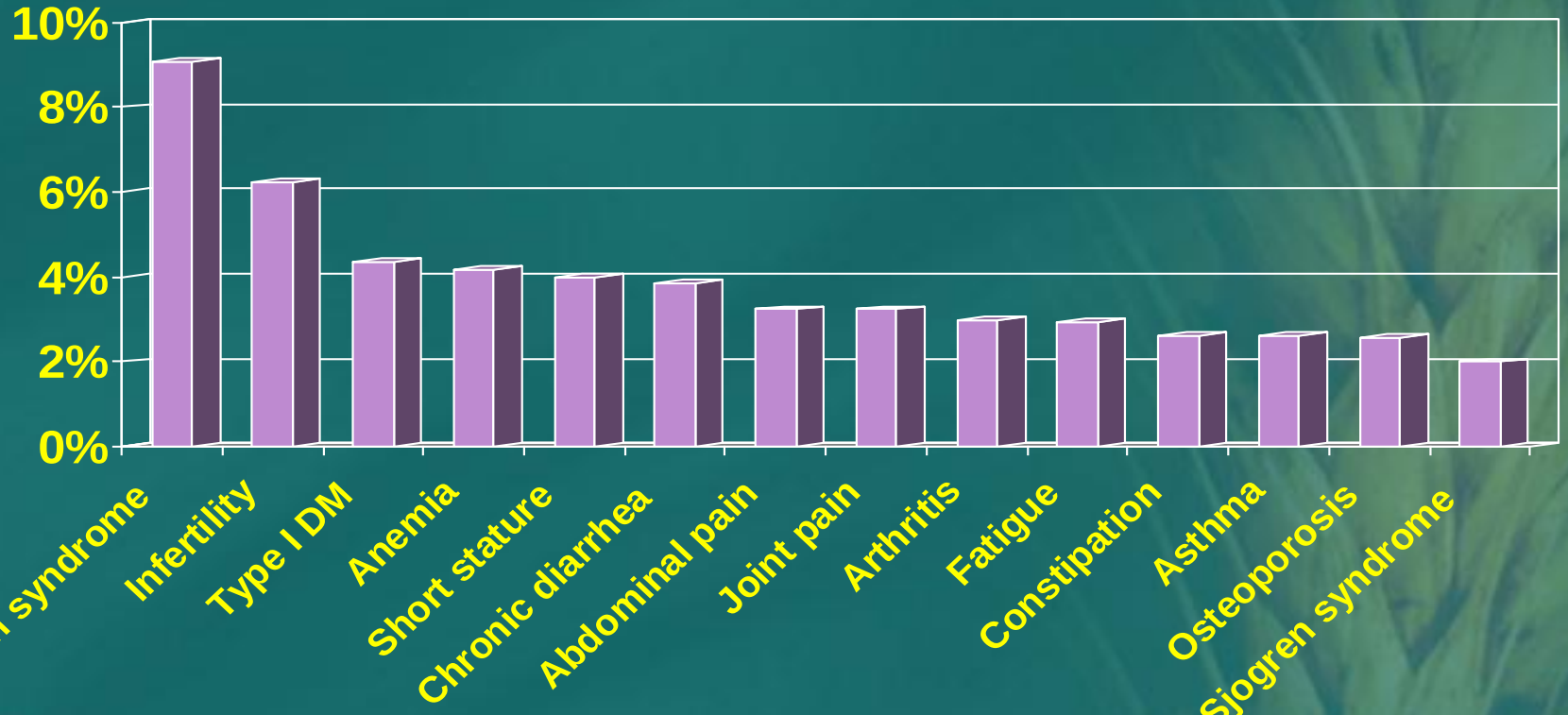
Associated Disorders/Symptoms



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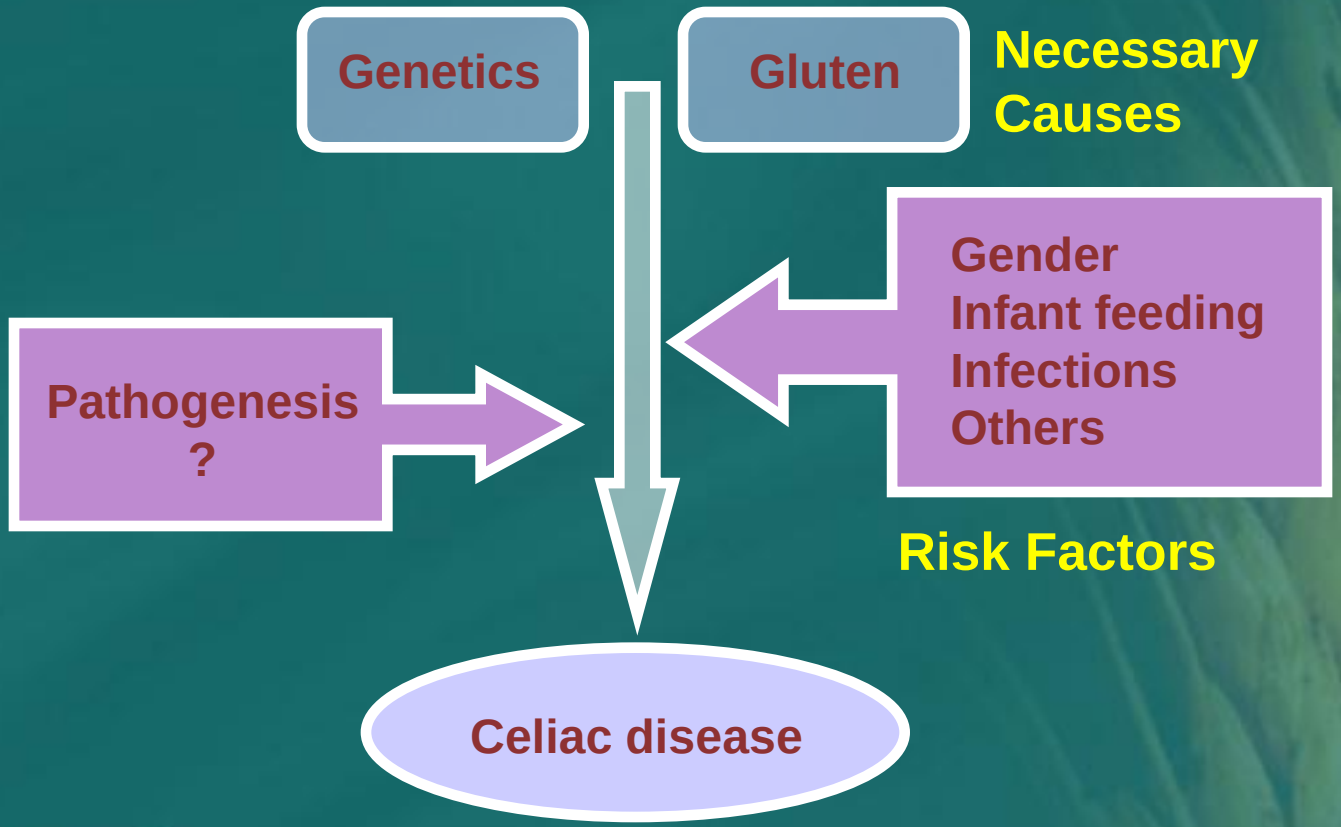
Associated Disorders/Symptoms

- **Moral of the story:**

Celiac disease is more common than we thought, but is still the answer only 2-5% of the time.

Pathogenesis



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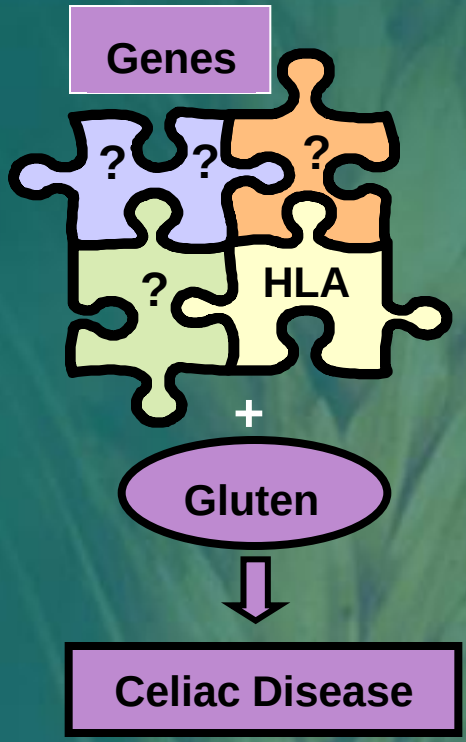
Genetics

- Several genes are involved
- The most consistent genetic component depends on the presence of HLA-DQ (DQ2 and / or DQ8) genes
- Other genes (not yet identified) account for 60 % of the inherited component of the disease
- HLA-DQ2 and / or DQ8 genes are necessary (No DQ2/8, no Celiac Disease!) but not sufficient for the development of the disease



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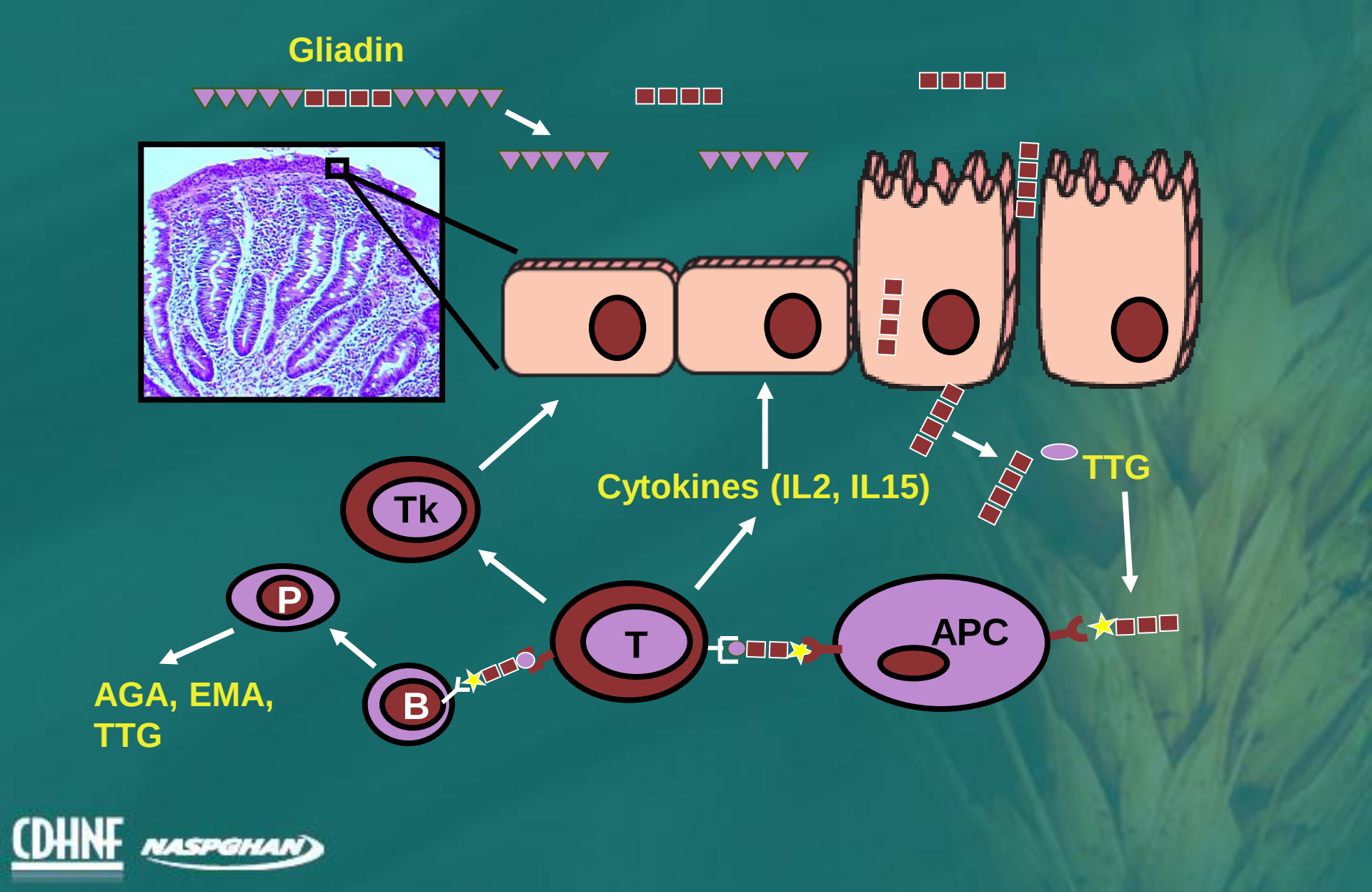
Genetics

- Non-HLA Related Factors
  - Concerns about HLA factors
    - **< 2% of all DQ2 carriers have Celiac Disease**
    - concordance for HLA matched siblings (30-40%) is lower than for monozygotic twins (~70%)
  - Data suggests additional non-HLA genes
  - Inheritance of Celiac Design most likely multigenic
  - Conflicting data for non-HLA genes

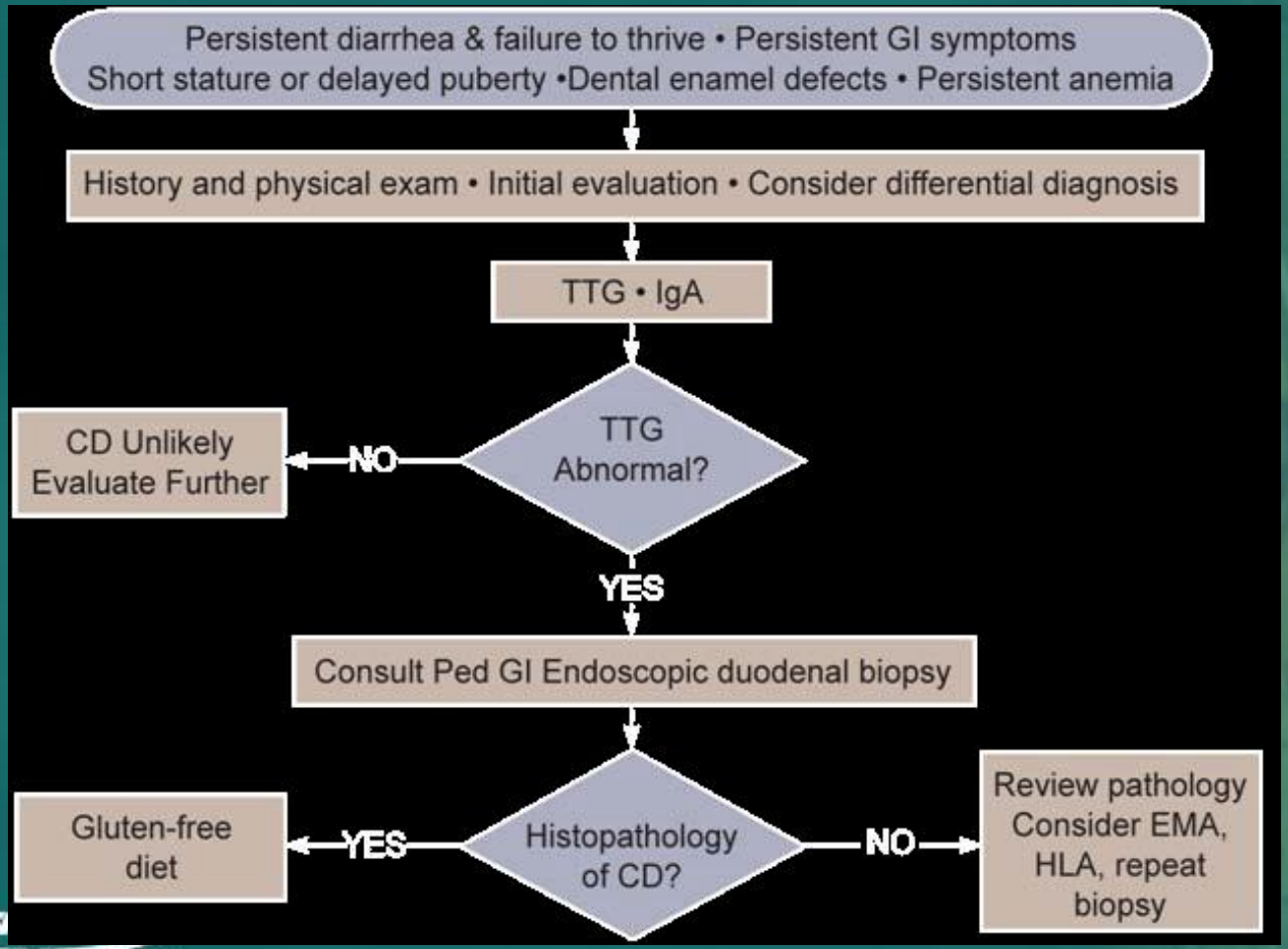

Gliadin
Tk
Cytokines (IL2, IL15)
TTG
P
T
APC
B
AGA, EMA,
TTG

Tests for Celiac Disease

- Serology
- Duodenal biopsy
- HLA typing
- Video capsule endoscopy
- Fecal testing

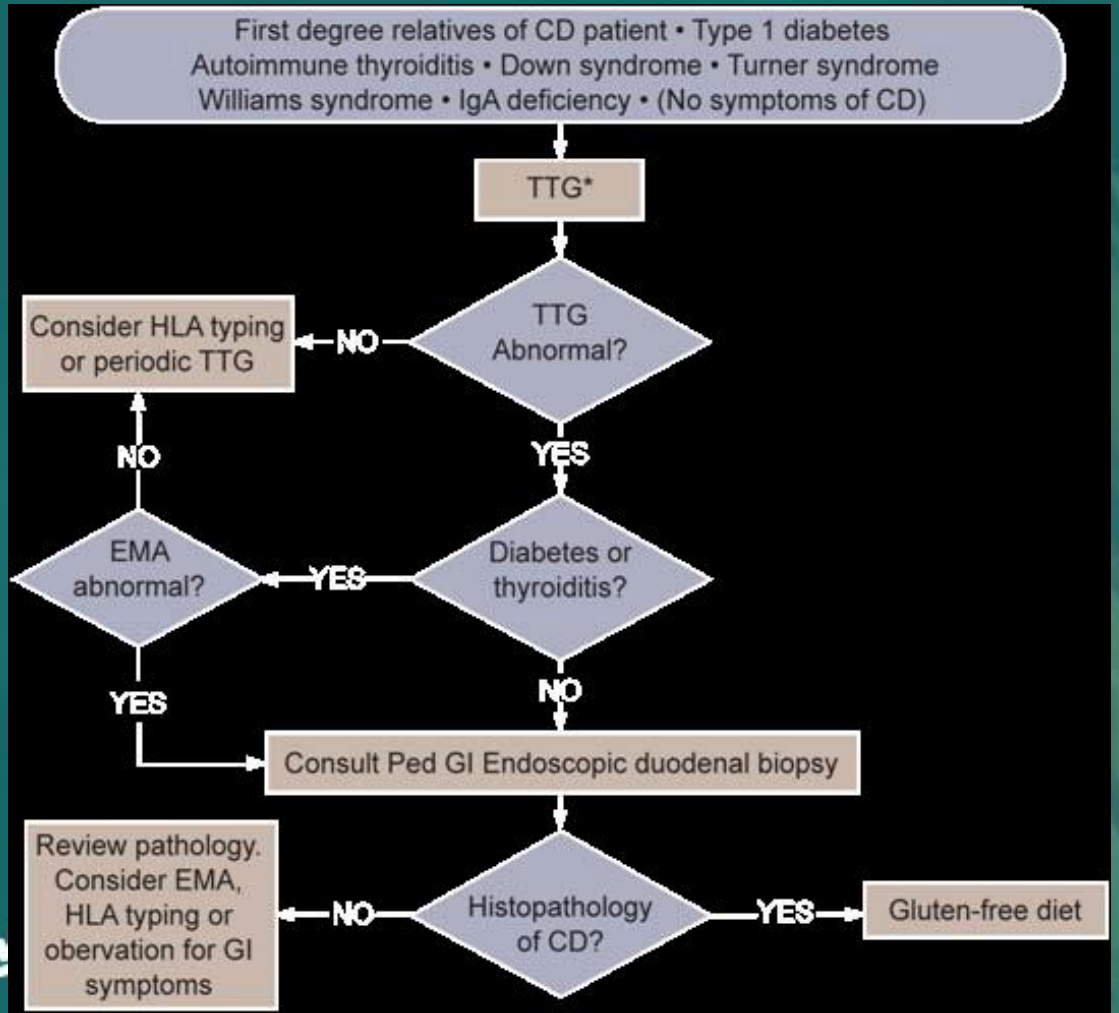
Screening algorithm

Symptomatic Child



Screening algorithm

At Risk Child



Serological Tests

- Anti-gliadin antibodies (AGA)
- Anti-endomysial antibodies (EMA)
- Anti-tissue transglutaminase antibodies (TTG)
- Anti-deamidated gliadin antibodies

Serological Tests

Role of serological tests:

- Identify symptomatic individuals who need a biopsy
- Screening of asymptomatic “at risk” individuals
- Monitoring dietary compliance

Serological Test Comparison

	Sensitivity (+ with CD)	Specificity (- w/o CD)	Cost
AGA IgG	69-85%	73-90%	$
AGA IgA	75-90%	82-95%	$
EMA IgA	88-99%	90-100%	$$$
TTG IgA	90-100%	94-100%	$$

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Caveats

- IgA deficiency
  - anti-TTG IgG or deamidated gliadin peptide IgG
  - consider QUIGs if failure to thrive, diarrhea
- <2 years of age
  - consider deamidated gliadin IgA + IgG if other serologies negative

Fecal antigen testing

- Non-specific, high false-positive rate
- Not incorporated in any national or international guidelines
- Not advised

Serological Tests

Diet and serologies

- All testing should be done on gluten *containing* diet
- Note: “limiting gluten” or “avoiding wheat” are usually *not* a gluten-free diet

Serological Tests

Diet and serologies

- Unclear how quickly serologies convert on gluten-free diet; frequently in 12 months
- Unclear how long they take to revert on gluten-containing diet

HLA Typing

- What's the deal with HLA typing and celiac disease?

HLA Tests

HLA alleles associated with Celiac Disease

- DQ2 found in 95% of celiac patients
- DQ8 found in remaining patients
- DQ2 found in ~30% of general population
- DQ8 found in ~10% of general population

Value of HLA testing

- **High negative predictive value**
  - Negativity for DQ2/DQ8 excludes diagnosis of Celiac Disease with 99% confidence

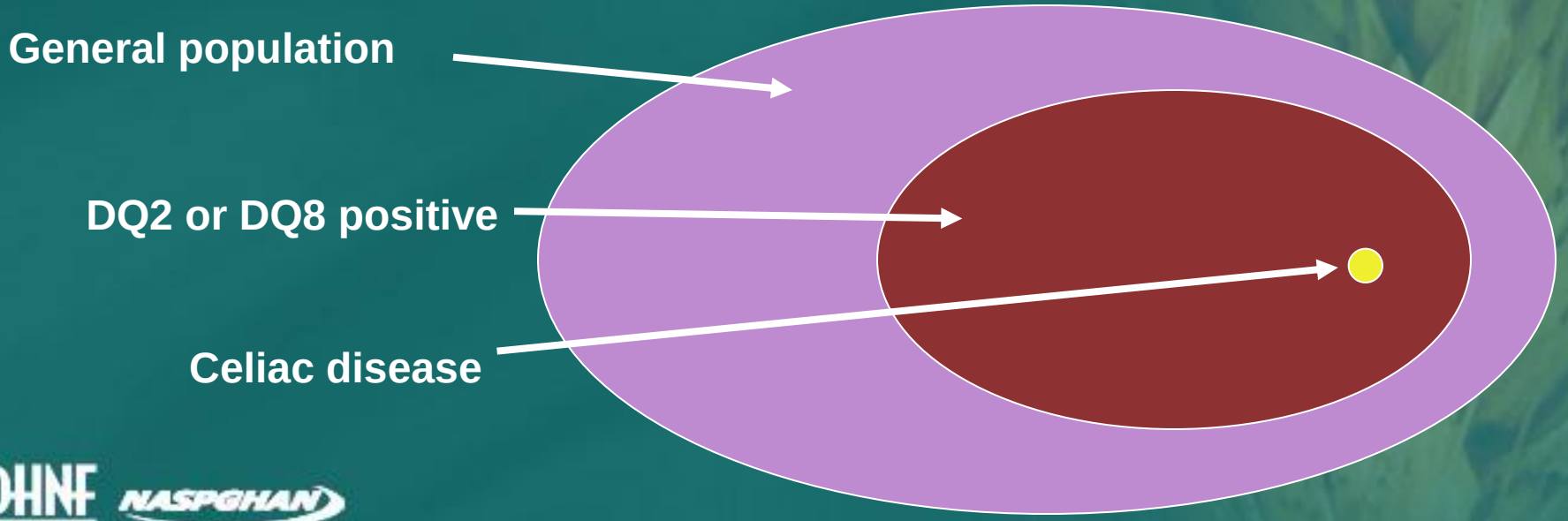
Schuppan. Gastroenterology 2000;119:234
Kaukinen. Am J Gastroenterol 2002;97:695

HLA Typing

- Having DQ2 or DQ8 does not mean you *have* disease
- Having DQ2 or DQ8 means that you are part of the 40% of the world that *may* one day develop celiac (and a host of other diseases)

HLA Typing

- Positive predicitive value is ***LOW***
- Negative predictive value is ***HIGH***



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HLA Typing

Considerations for HLA typing:

- May decrease need for regular blood testing for at-risk populations (e.g. Type I diabetes)
- May increase anxiety of both children and parents, esp. for those who are at low-risk (e.g. constipation, functional abdominal pain)
- Often not covered by insurance: genetic testing

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HLA Typing

Bottom Line:

- Do not include in routine work-up of symptomatic individuals
- Consider using to rule out asymptomatic high-risk individuals
- Consider in ‘challenging situations’

Pitfalls to Screening

- Not screening symptomatic patients
- Pursuing positive anti-gliadin antibodies in the face of negative EMA or TTG
- Obtaining HLA typing in symptomatic individuals
- Not screening before starting GFD

Optimal Screening

- Symptomatic
  - Anti-TTG IgA
  - Total serum IgA
- Asymptomatic, high-risk
  - Same +/- anti-EMA IgA
  - +/- HLA typing

Diagnosis

- Confirm diagnosis before treating
  - Diagnosis of Celiac Disease mandates a strict gluten-free diet for life
    - following the diet is not easy
    - QOL implications
  - Remember *low* PPV of serologies
- Failure to treat has potential long term adverse health consequences
    - increased morbidity and mortality
- Implications for family screening

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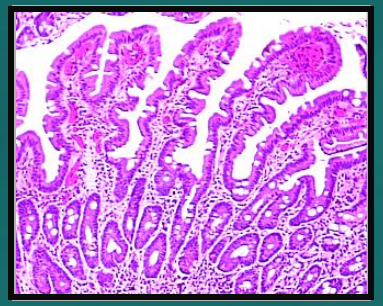
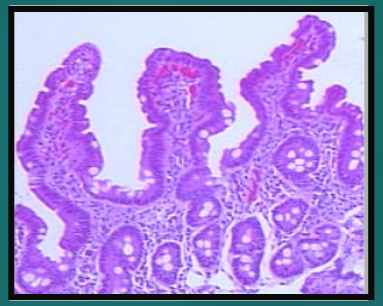
Biopsy

- Endoscopy and duodenal biopsy
  - Spectrum of endoscopic findings
    - Normal
    - Scalloping of duodenal folds
    - Mucosal fissures
    - Nodularity
  - Spectrum of histologic findings

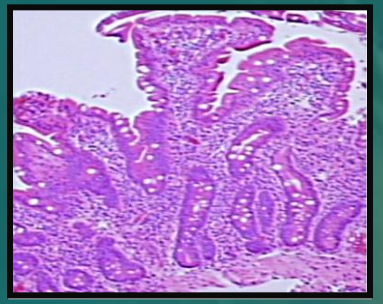
Histological Features



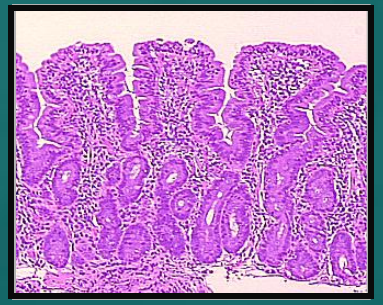
Normal 0



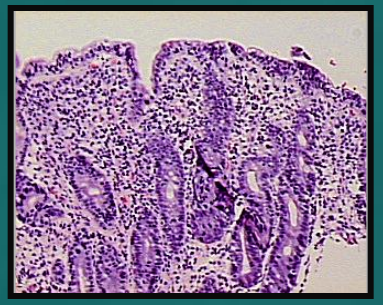
Infiltrative 1



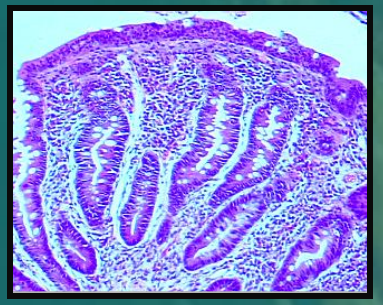
Hyperplastic 2



Partial atrophy 3a



Subtotal atrophy 3b



Total atrophy 3c

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Horvath K. Recent Advances in Pediatrics, 2002.

Histology

- Villous atrophy
- Villous blunting
- Increased intraepithelial lymphocytes
- Crypt hyperplasia

Diagnosis

- Based on combination of:
  - Clinical findings
  - Serology
  - Histology
  - Clinical improvement on gluten-free diet
- Routine repeat endoscopy *NOT* recommended

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Biopsy-Free Diagnosis?

- Maybe…
- ESPHGHAN guidelines: “in children and adolescents with signs or symptoms suggestive of celiac disease and a high anti-TTG with levels >10 times ULN…”
- Need confirmatory anti-EMA IgA prior to gluten-free diet
- Consider HLA typing

Diagnosis after GFD

- Pretreatment with GFD is not advised
- Baseline TTG IgA
- Consider HLA typing, if TTG IgA negative
- Challenge with >15g/day gluten until clinical or serologic relapse for maximum 2 years

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Treatment

- Only treatment for celiac disease is a gluten-free diet (GFD)
  - Strict, lifelong diet
  - Avoid:
    - Wheat
    - Rye
    - Barley
    - Contaminated oats

Sources of Gluten

- **OBVIOUS SOURCES**
  - **Bread**
  - **Bagels**
  - **Cakes**
  - **Cereal**
  - **Cookies**
  - **Pasta / noodles**
  - **Pastries / pies**
  - **Rolls**

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Sources of Gluten

- Not so obvious sources
  - OTC medications, including MVI
  - Hydrolyzed vegetable protein
  - Hydrolyzed plant protein
  - Soy sauce, imitation pepper, malt
  - Graham, bulgur, farina, spelt
  - Malted beverages, beer, ale, lager

A note on oats

- What about oats?
  - Avenin does not provoke an autoimmune response
  - Many sources of commercial oats are cross-contaminated with gluten grains

So what does that leave?

- Rice, corn, arrowroot, potato and nut flour
- Buckwheat, flax, sorghum, tapioca, millet
- Eggs, lentils, peas, beans, nuts, tofu
- Meat, fish, poultry
- Fruit, vegetables
- Popcorn, ice cream, corn chips, chocolate
- Wine, cider, distilled alcoholic beverages

Fructan sensitivity

- Fructans are chains of fructose molecules
- Those with short chains are called fructooligosaccharides
- Those with long chains are called inulins
- They occur in foods like beans, onions, garlic, peas, artichokes, asparagus, leeks, **wheat and rye**

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Fructan sensitivity

- Fructans are frequently incompletely digested in the small intestine
- Residual fructans are delivered to the colon and fermented by colonic bacteria
- Can result in excessive flatulence, bloating, constipation, diarrhea, nausea, abdominal pain

Fructan sensitivity

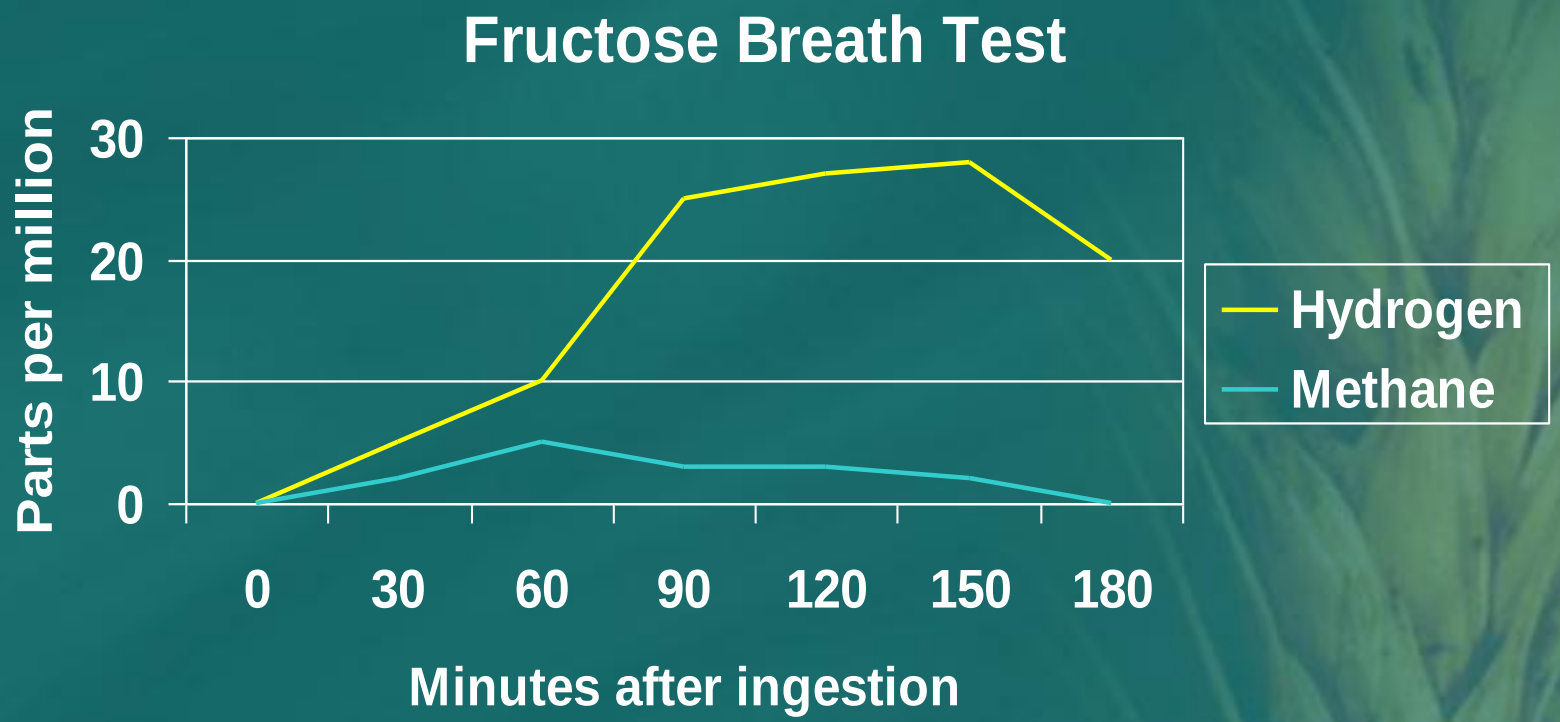
- **FODMAP: F**ermentable **O**ligosachharides, **D**isaccharides, **M**onosaccharides and **P**olyols

- **Oligos: fructans, galactans**
- **Disaccs: lactose**
- **Monos: fructose**
- **Polyols: sorbitol, mannitol, xylitol, isomalt**

Diagnosis

- Fructose breath test
- Lactose breath test
- Empiric elimination

Breath Test



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Treatment

- Reduction of FODMAP intake can reduce symptoms of IBS
- Often requires professional nutritional counseling
- Symptoms return with reintroduction of the offending foods

Barriers to Compliance

- Ability to manage emotions – depression, anxiety
- Ability to resist temptation – exercising restraint
- Feelings of deprivation
- Fear generated by inaccurate information

Factors that Improve Adherence

Internal Adherence Factors Include:

- Knowledge about the diet
- Understanding the risk factors and serious complications can occur to the patient
- Ability to break down big changes into smaller steps
  - Ability to simplify or make behavior routine
- Ability to reinforce positive changes internally
- Positive coping skills
- Ability to recognize and manage mental health issues
- Trust in physicians and dietitians

Emerging Therapies

- **Genetically modified gluten:** decreases gluten exposure by transamidation of gluten
- **Zonulin inhibitor:** larozotide acetate-decreases zonulin secretion and inhibits intestinal permeability, going into Phase III trials; preliminary data in celiac patients shows fewer symptoms after intentional gluten ingestion
- **Therapeutic vaccine:** Nexvax2: creates immune tolerance to gluten fragments and desensitizes celiac patients to their T-cell response to gluten; going into Phase IIa trial
- **Probiotics:** *Lactobacillus fermentum, Bifibobacterium lactis*-detoxify gliadin and promote intestinal healing
- **Tissue transglutaminase inhibitors:** stop TTGs from modifying gluten fragments, avoiding triggering an immune response

Health Maintenance

- **Initial**
  - **Weight gain and linear growth**
  - **Consider Bone density**
  - **Vitamin and mineral depletion**
  - **Dental check-up**
  - ***Screening of 1st and 2nd degree relatives***

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Health Maintenance

- Later
  - Yearly check-ups with serologies
  - Be on the alert for:
    - symptom recurrence
    - adherence issues
    - social difficulties
  - Be on the alert for other autoimmune diseases:
    - Type I DM
    - autoimmune thyroiditis
    - Sjögren's syndrome

Take Homes

- Celiac disease is more common than we thought, but still not *very* common.
- Problems with wheat don't always mean celiac disease.
- EMA and TTG are the best screening tests.
- Maintenance of a GFD requires on-going education and support.

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Thank you!