APRIL 15, 2023

VALLEY-MOUNT SINAI CHILDREN'S SYMPOSIUM

The ABC's (and tTG's) of Celiac Disease Screening

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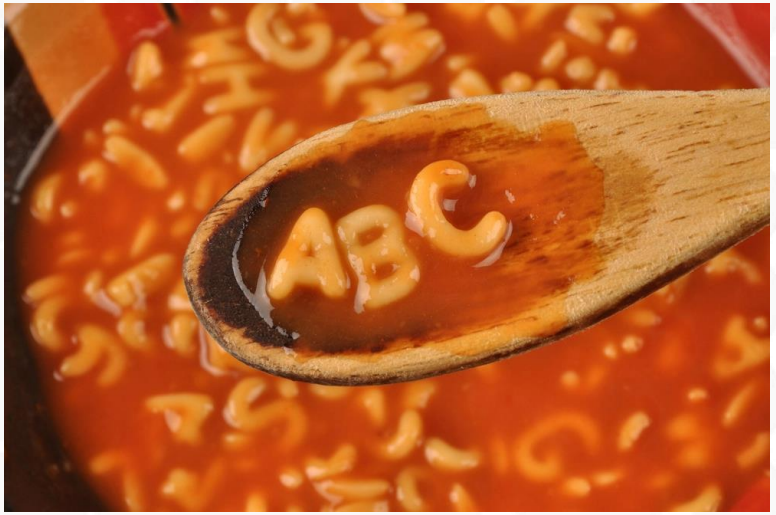
Colorado Center for Celiac Disease



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Faculty Disclosure

- There are no commercial products or services being discussed
- Consultant for Takeda and Pfizer (DSMB and Advisory Board for Celiac Disease)
- No unlabeled use of a product is being discussed

The Valley Hospital
Valley Health System

Objectives

1. Describe the alphabet soup of celiac disease screening and review the accuracy of different available serologic and genetic testing.
2. Describe the management including healthcare maintenance for children with celiac disease.
3. Review approaches to non-celiac gluten sensitivity and concomitant irritable bowel syndrome for the primary care provider.

Celiac Disease Alphabet Soup

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Who Has Celiac Disease?

Classic

Non-Classic

Subclinical of Asymptomatic

They all do! The presentation of modern day celiac disease is heterogeneous.

Ludvigsson,et al, *Gut,* 2013

It’s no longer just the classic presentation…

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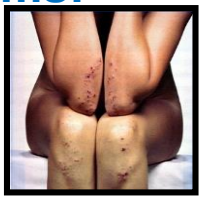
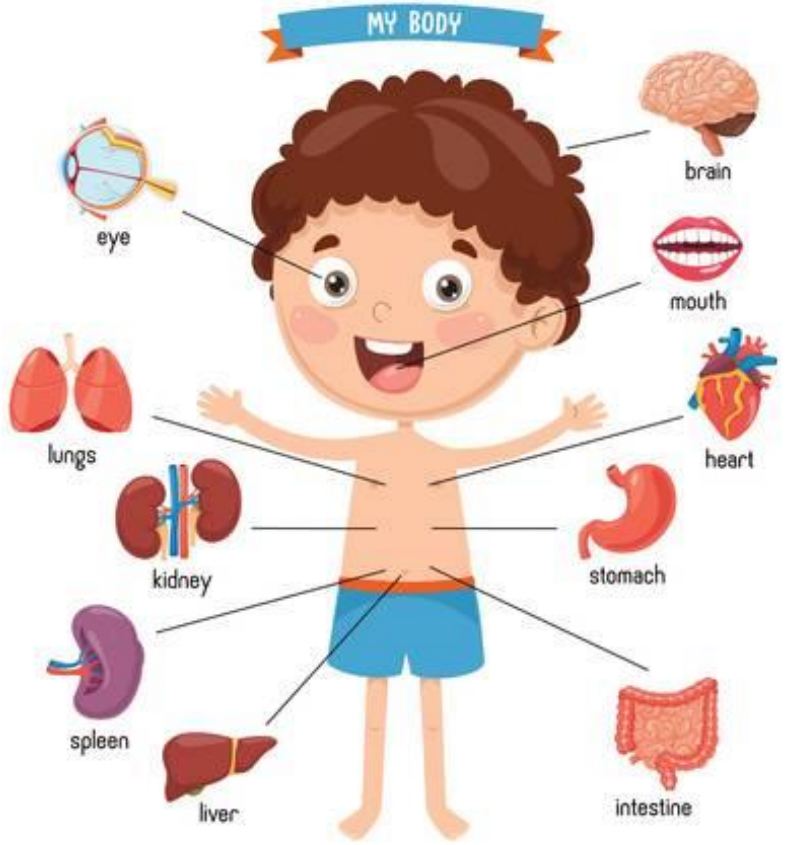
Riznik, *JPGN*, 2021

Symptoms Can Be Non-Specific

Other Non-GI Symptoms:



Anemia
Fatigue
Rash
Bone Fractures
Fertility Issues
Delayed Puberty



Headaches
Brain Fog
Seizures
Ataxia

Oral ulcers
Dental Enamel Defects

Carditis

GI symptoms:
Diarrhea
Constipation
Abdominal Pain
Bloating/Gas
Weight Loss
Growth Issues

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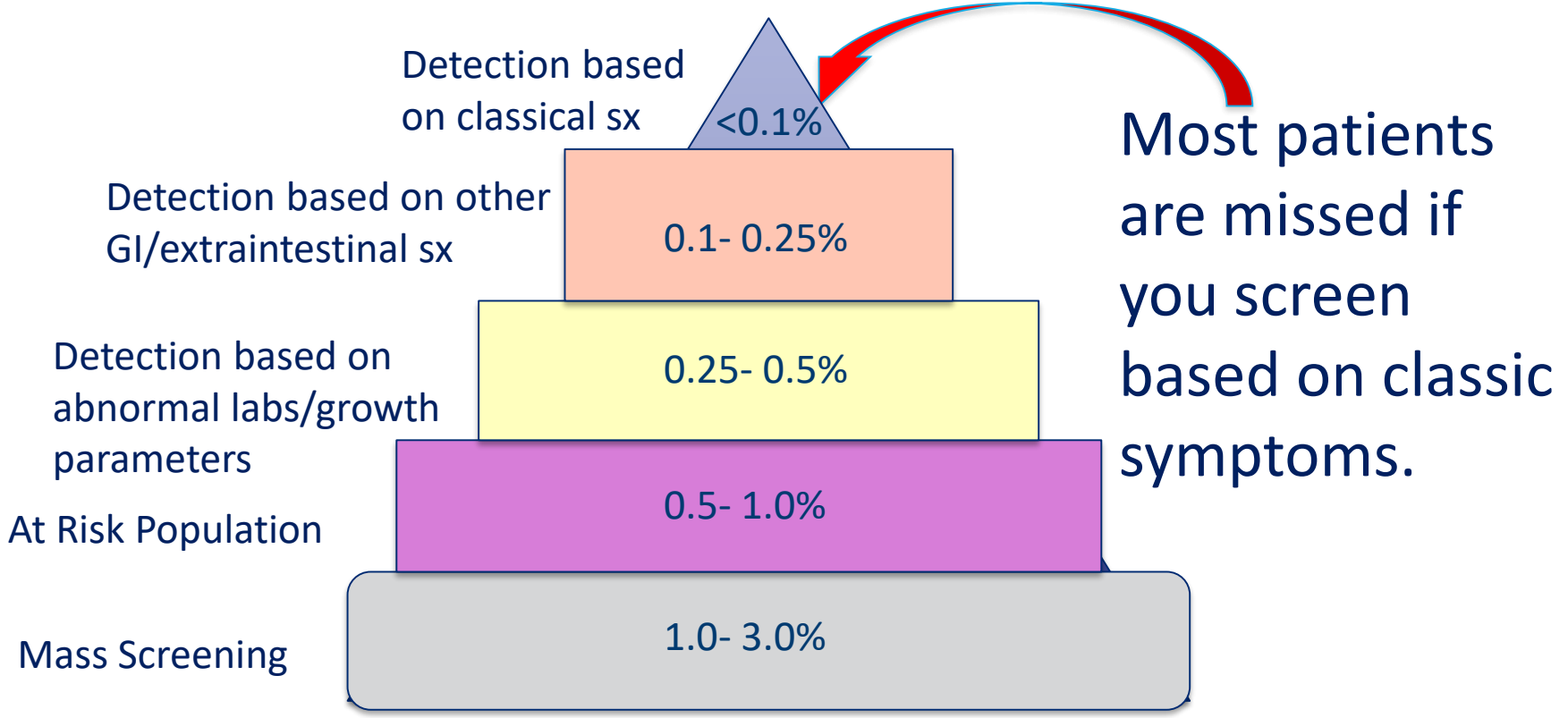
Who Should We Screen for Celiac Disease?



Most patients are missed if you screen based on classic symptoms.

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Kivela, L, *Acta Pediatrica*, 2018

Celiac Disease Screening

Test	Sensitivity	Specificity
Antigliadin Antibody IgA*	52-100	72-100
tTG IgG*	12.6-99.3	86.3-100
tTG IgA*	90-100	95-100
Endomysial Antibody IgA*	93-100	98-100
Deamidated Gliadin IgG*	88-95	86-98
HLA Screening	>99%	~60%

*Requires patient to be on a gluten-containing diet

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Adapted from:
NASPGHAN Guidelines, **JPGN**, 2016
Leonard, *JAMA*, 2017

How Do We Screen?

Test	Sensitivity	Specificity
tTG IgA and **total IgA** are the preferred first line screening tests for celiac disease		

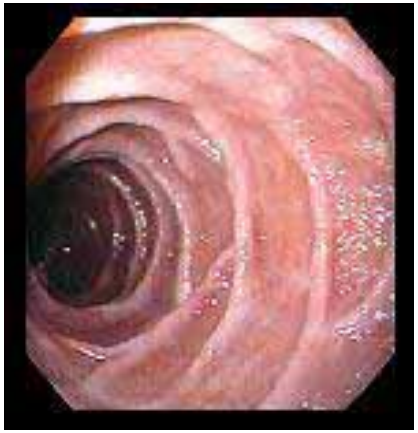
Adapted from:
NASPGHAN Guidelines, **JPGN**, 2016

Celiac Disease Diagnosis

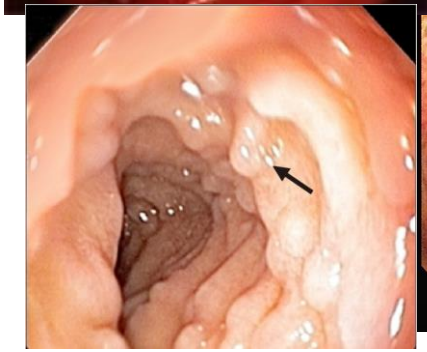
GI should always be involved in the diagnosis. Please refer tTG IgA positive children to GI.

NASPGHAN Guidelines, *JPGN*, 2016
ESPGHAN Guidelines, *JPGN,* 2019

Endoscopic Diagnosis of Celiac Disease



Normal



Loss of folds
Scalloping
Blunted villi
Nodularity

General Population Screening

Why Consider Mass Screening for Celiac Disease?

WHO Criteria	Valid in CD
The disease is common and well defined	++
Screening tests are simple, safe and accurate	++
The screening test should be culturally acceptable	+++
Treatment is available	+++
Clinical detection is difficult	+++
If undiagnosed and untreated, the disease will lead to severe complications	+
Testing and treatment is cost-effective	+

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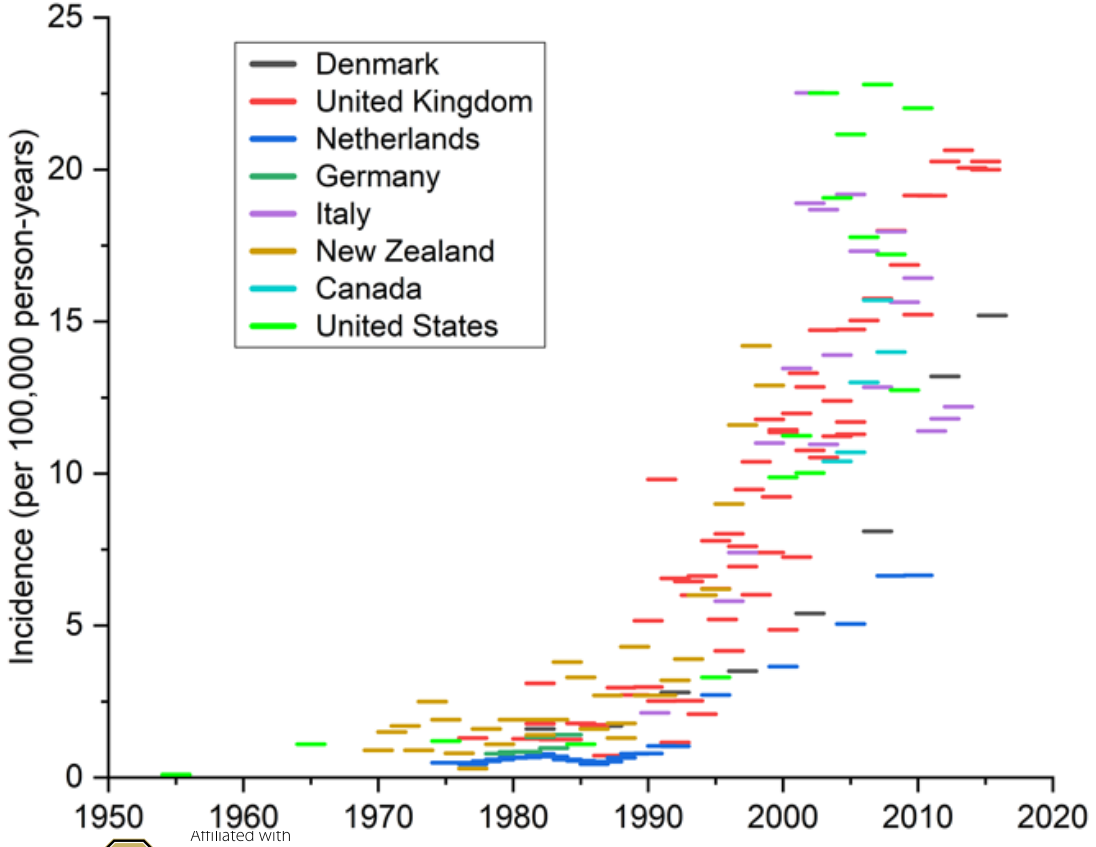
Ludvigsson J et al, United European Gastroenterol J 2015

Celiac Disease Incidence is Rising



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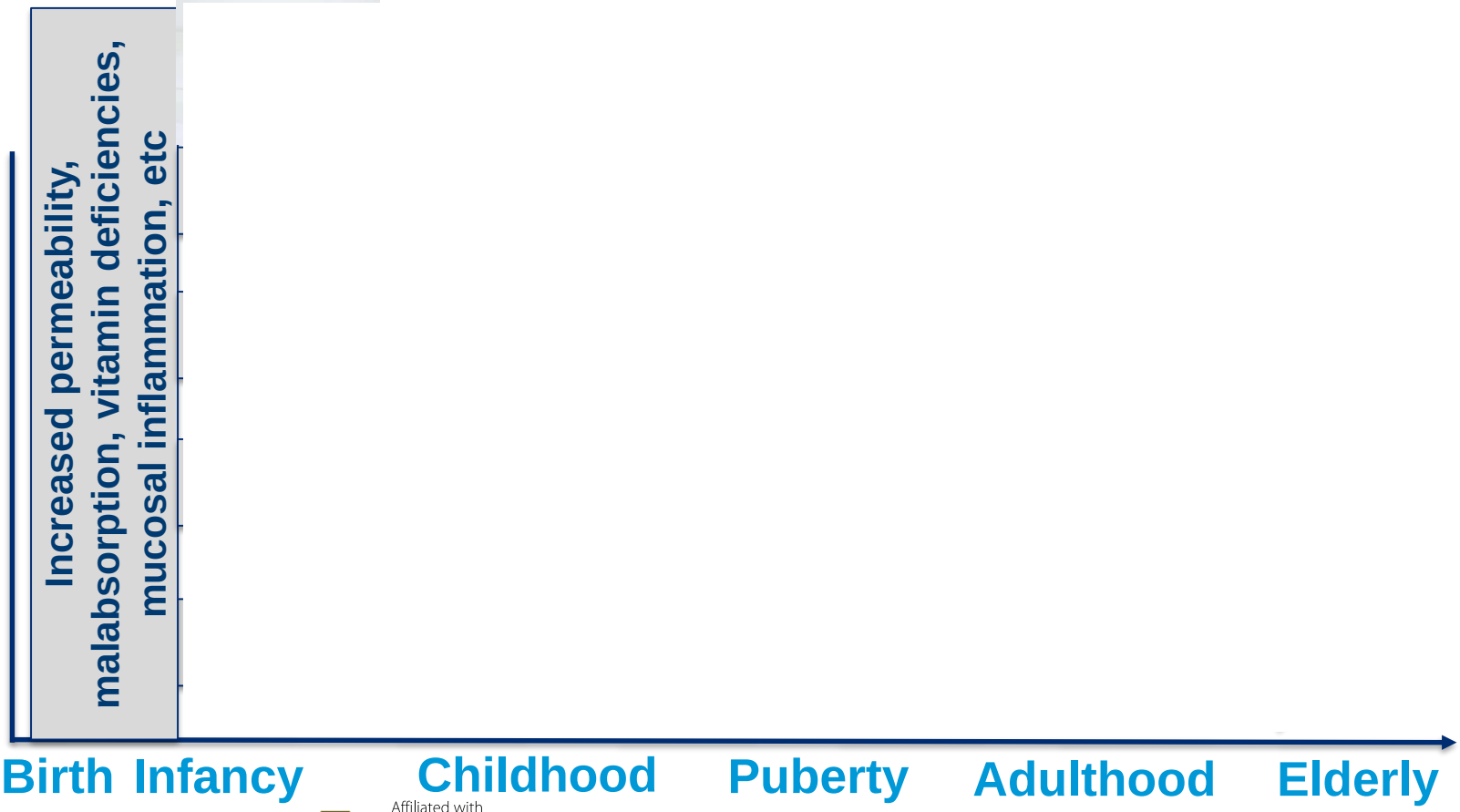
King, *AJG*, 2020

If Undiagnosed and Untreated, It Can Lead to Severe Complications…



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Kivela et al, *Acta Pediatrica,* 2018

If Undiagnosed and Untreated, It Can Lead to Severe Complications…

Increased permeability, malabsorption, vitamin deficiencies, mucosal inflammation, etc

Poor Dental Mineralization

Dental Enamel Defects

Birth Infancy Childhood Puberty Adulthood Elderly

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Kivela et al, *Acta Pediatrica*, 2018

If Undiagnosed and Untreated, It Can Lead to Severe Complications…

Increased permeability, malabsorption, vitamin deficiencies, mucosal inflammation, etc

Poor Dental Mineralization → Dental Enamel Defects

Lack of nutrients, GH Deficiency → Poor Growth → Short Stature

Birth Infancy Childhood Puberty Adulthood Elderly

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Kivela et al, *Acta Pediatrica,* 2018

If Undiagnosed and Untreated, It Can Lead to Severe Complications…

Increased permeability, malabsorption, vitamin deficiencies, mucosal inflammation, etc

Poor Dental Mineralization → **Dental Enamel Defects**

Lack of nutrients, GH Deficiency → Poor Growth → **Short Stature**

Vitamin Deficiency → Poor Bone Accrual → Osteoporosis → **Fractures**

Birth **Infancy** **Childhood** **Puberty** **Adulthood** **Elderly**

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Kivela et al, *Acta Pediatrica,* 2018

If Undiagnosed and Untreated, It Can Lead to Severe Complications…

Increased permeability, malabsorption, vitamin deficiencies, mucosal inflammation, etc

Treating early prevents complications later in life.

Poor Dental Mineralization → **Dental Enamel Defects**

Lack of nutrients, GH Deficiency → Poor Growth → **Short Stature**

Vitamin Deficiency → Poor Bone Accrual → Osteoporosis → **Fractures**

Continuous Inflammation. → Abnormal Cell Diff. Celiac Disease → Premalignancy → Refractory → **Intestinal Cancer**

Birth **Infancy** **Childhood** **Puberty** **Adulthood** **Elderly**

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Kivela et al, *Acta Pediatrica,* 2018

Complications of Screening-Identified Celiac Disease?

Study	Main Findings
Ad	
Pe	
Ce	in
Ge	
Exploring the Iceberg of Coeliacs in Saudi Arabia[5]	2/3 of screening-identified cases were symptomatic On average weighed less and shorter

Studies suggest that there may be complications particularly with respect to unrecognized symptoms, nutrition, and bone health.

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[1]Kurrpa, *Gastro*, 2014
[2]Van Koppen, *Pediatrics*, 2009
[3]Bjorck, *JPGN*, 2017
[4]Jansen, *J Gastro*, 2018; *Clin Gastro Hepa*tol 2015
[5]Al-Hussaini, *JPGN*, 2017

Cost Effectiveness of Screening?

Study	Main Findings
Hershicovici, et al.[1]	Cost effective based on QALY's
No	
Sh	
Kvamme, et al.[4]	One year adherence to GFD improved GI symptoms and health-related quality of life (HR-QOL) in Norway

Studies suggest may be cost-effective, but need the data in US pediatric population.

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[1]Hershicovici, *Aliment Pharma col*, 2010
[2]Norstrom, et al, BMC Gastroenterol, 2021
[3]Shamir, *Med Decis Making*,, 2006
[4]Kvamme, *Sci Rep*, 2022

Screening for Celiac Disease?

- The US Preventive Services Task Force (USPSTF) states that there is insufficient evidence to support general population screening for Celiac Disease.

Figure 2: Screening for Celiac Disease: Clinical Summary	
Population	**Asymptomatic adults, adolescents, and children**
Recommendation	**No Recommendation: Grade 1 (insufficient evidence)**

Adapted from "Screening for Celiac Disease: US Preventive Services Task Force Recommendation Statement." *JAMA* 2017.

Targeted Screening

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Who is “At Risk”?

- Based on Symptoms
- Asymptomatic with Following Features:
  - First Degree Relatives with Celiac Disease
  - Type 1 Diabetes
  - Autoimmune Thyroiditis
  - Autoimmune Liver Disease
  - Juvenile Chronic Arthritis
  - Selective IgA Deficiency
  - Down Syndrome
  - Turner Syndrome
  - William Syndrome

NASPGHAN Guidelines, *JPGN*, 2016
ESPGHAN Guidelines, *JPGN,* 2019

The Autoimmunity Screening for Kids (ASK) Study

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Autoimmunity Screening for Kids (ASK)

Pediatric Population Ages 1-17 yo

tTG IgA Screening
*Screening available at PCP offices, CHCO and satellite locations, At Home Kits

Initial Screening: Demographics and Family History, GFD data, Basic Symptom Questionnaire, Blood Draw for tTG IgA

Confirmation Screening: Extended Symptom Questionnaire, Blood Draw for tTG IgA

Other Important Considerations:

- IgA Deficiency
- Low Positive (<2x ULN)

31,000 children screened as of November 31, 2022

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Autoimmunity Screening for Kids
ASK
A SIMPLE TEST TO DETECT
Childhood Diabetes
+ Celiac Disease

Symptom Questionnaires

Symptom	Initial	Follow Up
Diarrhea	x	x
Abdominal pain	x	x
Constipation	x	x
Vomiting	x	x
Poor Weight Gain/Weight Loss	x	x
Short Stature	x	x
Gassy or bloated	x	x
Itching and/or rash		x
Edema		x

Symptom	Initial	Follow Up
Nausea		x
Brain fog		x
Mouth ulcers		x
Dizziness		x
Headaches		x
Joint Pain		x
Irritability		x
Decreased Energy		x
Bone Fractures		x
Pubertal Delay		x
Dental Problems		x

Autoimmunity Screening for Kids (ASK)

Pediatric Population Ages 1-17 yo

tTG IgA Screening
*Screening available at PCP offices, CHCO and satellite locations, At Home Kits

Initial Screening: Demographics and Family History, GFD data, Basic Symptom Questionnaire, Blood Draw for tTG IgA
Confirmation Screening: Extended Symptom Questionnaire, Blood Draw for tTG IgA

Primary Outcome: Persistent tTG IgA- elevated tTG IgA on 2 consecutive samples (initial and confirmation screening)
Secondary Outcome: Celiac Disease- Biopsy proven (Marsh 2 or greater) OR ESGPHAN Criteria

31,000 children screened as of November 31, 2022

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Childhood Diabetes + Celiac Disease

The Autoimmunity Screening for Kids (ASK) Study

Screening for type 1 diabetes & celiac disease

2.4% screened have undiagnosed celiac disease autoimmunity

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AJG The American Journal of GASTROENTEROLOGY

Stahl, et al. *Am J Gastroenterol*. 2021

The Autoimmunity Screening for Kids (ASK) Study

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AJG The American Journal of GASTROENTEROLOGY

Stahl, et al. *Am J Gastroenterol*. 2021

The Autoimmunity Screening for Kids (ASK) Study

Screening for type 1 diabetes & celiac disease

Only 10% have a family history

Autoimmunity Screening for Kids

ask

A SIMPLE TEST TO DETECT

Childhood Diabetes + Celiac Disease

2.4% screened have undiagnosed celiac disease autoimmunity

Only 30% have symptoms

-High prevalence of undiagnosed autoimmunity in Colorado

-Most identified would not have been caught by current screening practices

Created by TUXX from Noun Project

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AJG The American Journal of GASTROENTEROLOGY

Stahl, et al. *Am J Gastroenterol*. 2021

Healthcare Maintenance

Snyder Recommendations

Evidence-Informed Expert Recommendations for the Management of Celiac Disease in Children

John Snyder, MD,[a,†] J. Decker Butzner, MD,[b] Amy R. DeFelice, MD,[c] Alessio Fasano, MD,[d]
Stefano Guandalini, MD,[e] Edwin Liu, MD,[f] Kimberly P. Newton, MD[g]

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Snyder, et al. *Pediatrics*, 2016

Healthcare Maintenance and Surveillance

- CBC and ferritin
- 25-OH Vitamin D
- AST and ALT
- Thyroid
- Hepatitis B surface antibody and antigen- NOT ANYMORE!
- Repeat tTG IgA may take up to 2 years to normalize
- Counsel on signs and symptoms of Type 1 Diabetes
- Screening first-degree relatives
- Gluten-free multivitamin
- Vitamin D and iron supplementation when appropriate
- Glutenfreedrugs.com

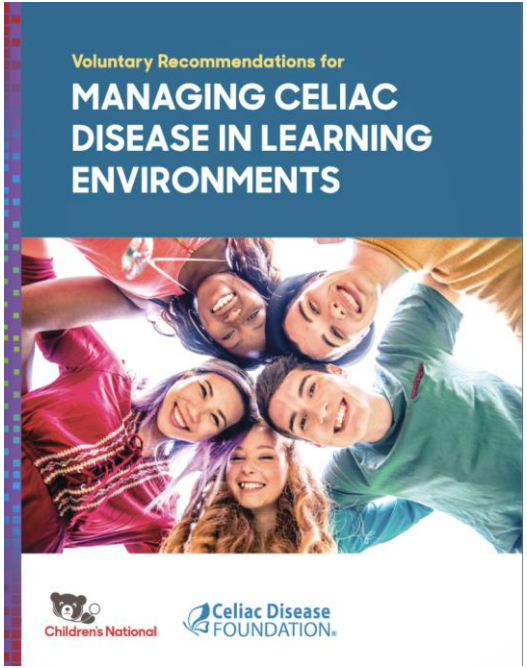
Snyder, *Pediatrics*, 2016

Hepatitis B Vaccination and Non-Response

- Previously would screen for non-immunity and recommend booster series for those non-immune
- Previous studies suggested connection between DQ2, gluten consumption, and non-immunity
- Recent study using NHANES data showed immune response to HBV vaccination similar between those with and without celiac disease
- No longer recommend checking antibody titers at diagnosis

Habash, *JPGN*, 2022
Noh, *Am J Gastro*, 2003

School Environments



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Weisbrod, *JPGN*, 2020
https://www.autoimmuneinstitute.org/celiac-education/managing-celiac-in-schools

What if it’s not just celiac?

Non-Celiac Gluten Sensitivity (NCGS)

- Clinical diagnosis based on symptom response to withdrawal of gluten
- Reported prevalence of 1.7% to 13%
- Proposed role of FODMAPs or amylase-tryptase inhibitors
- No current biomarkers

Lerner, et al. *DDS*, 2019

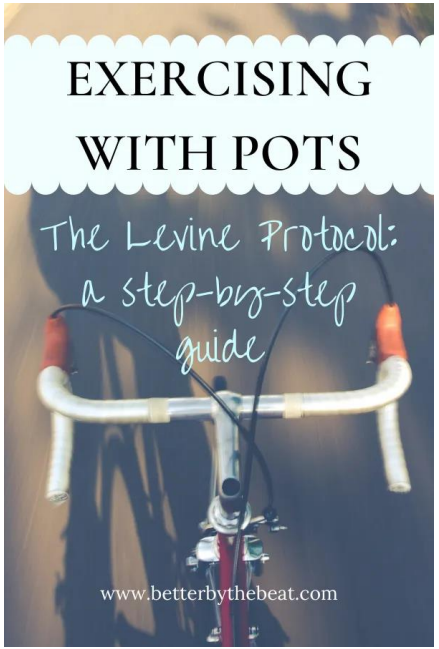
Irritable Bowel Syndrome

- One study of children with symptoms after 6 months of GFD:
  - 3% with IBS
  - 7% with functional abdominal pain
  - 20% with constipation
- Consider these gluten-free options:
  - IbGard
  - Iberogast
  - Miralax

Aziz, *Lancet*, 2021
Veeraraghavan, *World J Gastro*, 2021

Orthostatic Intolerance

- Link suggested between gluten sensitivity and POTS
- Light-headedness, dizziness, presyncope, headaches
- Nausea, bloating, diarrhea, constipation
- Potential Interventions:
  - Salt supplementation, fluid intake
  - Compression stockings
  - Physical Therapy- Levine Protocol



Penny, *Eur J Gastro Hepatol*, 2016

Conclusions

1. Describe the alphabet soup of celiac disease screening and review the accuracy of different available serologic and genetic testing.
   tTG IgA and total IgA level are best screening tests. DGP IgG and tTG IgG if IgA deficient (also ensure selective IgA deficiency).
2. Describe the management including healthcare maintenance for children with celiac disease.
   Monitor for adherence, complications, and support in different environments.
3. Review approaches to non-celiac gluten sensitivity and concomitant irritable bowel syndrome for the primary care provider.
   Consider other entities in children with ongoing symptoms.

Celiac Screening Clinical Pearls…

- **Who to Screen:** Symptoms and At-Risk Groups (Family History, Autoimmune Conditions, Genetic Syndromes)
- **How to Screen:** tTG IgA and total IgA, DGP/tTG IgG if IgA deficient
- **How to Diagnose:** Refer to GI

  *Patients must stay on gluten for diagnostic confirmation
- **Healthcare Maintenance:**
  - Adherence: tTG IgA; follow up dietitian and psychologist
  - Micronutrient/Vitamin Deficiencies: Vitamin D, Ferritin, CBC
  - Concurrent Autoimmune Disease: CMP, TSH, signs/symptoms of diabetes

Thank you!

Colorado Center for Celiac Disease and DHI: Ed Liu, Pooja Mehta, Mary Shull, Ed Hoffenberg, Monique Germone, Sadie Nagle, Isabel Griffith, and entire Celiac Research Team

Barbara Davis Center and ASK Team: Marian Rewers, Cristy Geno Rasmussen, Amber Baumgartner, Iman Taki, Jill Norris, and team

All of our research participants!

Funding provided: SSCD-Beyond Celiac Early Career Award

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Childhood Diabetes
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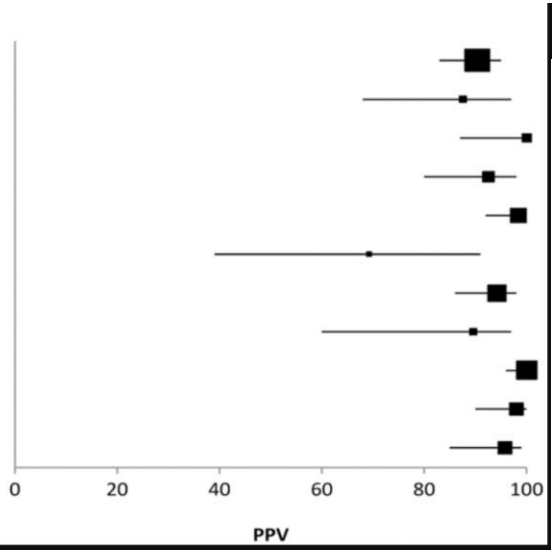
What about symptoms?

Study	TP	TP + FP	PPV (95%CIs)
Nevoral 2013	103	114	0.90 [0.83; 0.95]
Lionetti 2014	21	24	0.88 [0.68; 0.97]
Vriezinga 2014	27	27	1.00 [0.87; 1.00]
Trovato 2015	37	40	0.92 [0.80; 0.98]
Webb 2015	63	64	0.98 [0.92; 1.00]
Cilleruelo 2016	9	13	0.69 [0.39; 0.91]
Donat 2016	65	69	0.94 [0.86; 0.98]
Jansen 2017	16	19	0.84 [0.60; 0.97]
Paul 2017	84	84	1.00 [0.96; 1.00]
Werkstetter 2017	50	51	0.98 [0.90; 1.00]
Wolf 2017	45	47	0.96 [0.85; 0.99]



Positive Predictive Value of ESPGHAN criteria with NO symptoms

tTG IgA>10 x ULN
Including symptoms

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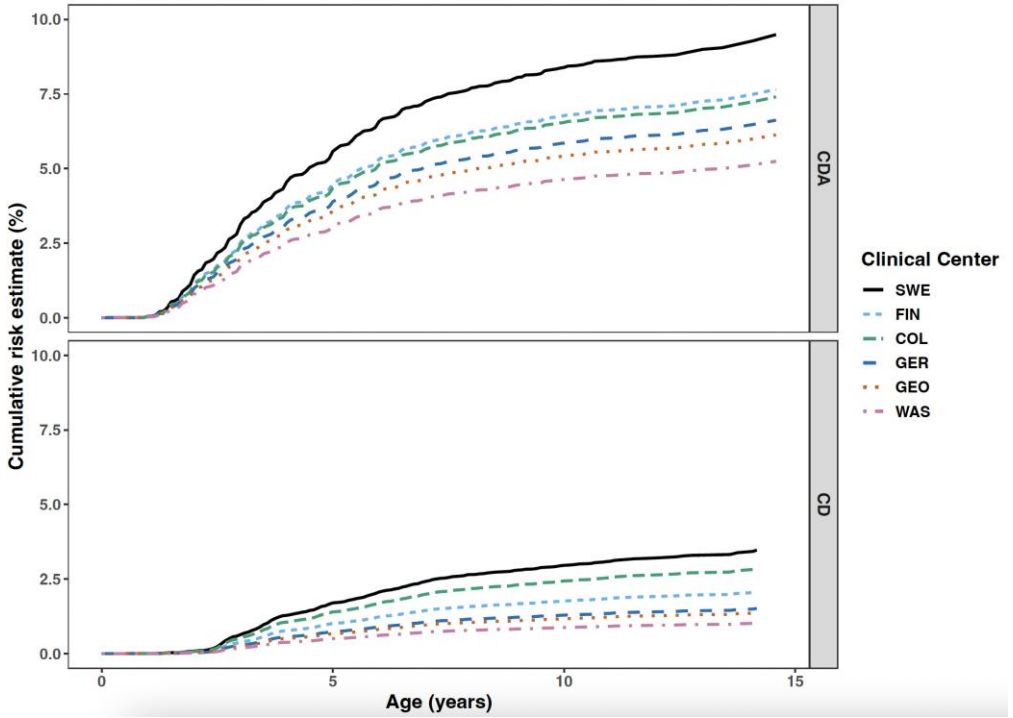
ESPGHAN Guidelines

Prevalence Varies by Region



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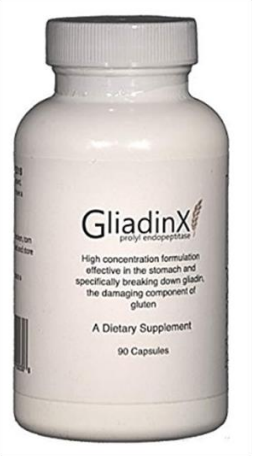
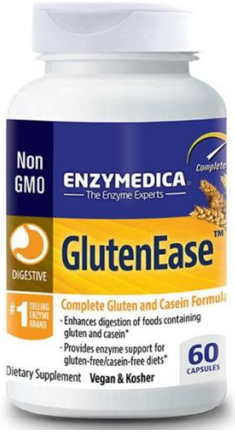
Stahl, et al, *Am J Gastroenterol*, 2022

Are there any other therapies?





Not yet!

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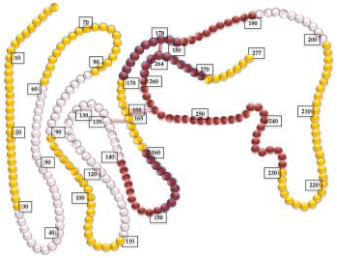
But there will be…



Drugs that Break Down Gluten: Endopeptidases (Latiglutenase)

Drugs that Strengthen the Barrier: Larazotide?? Maybe Not!

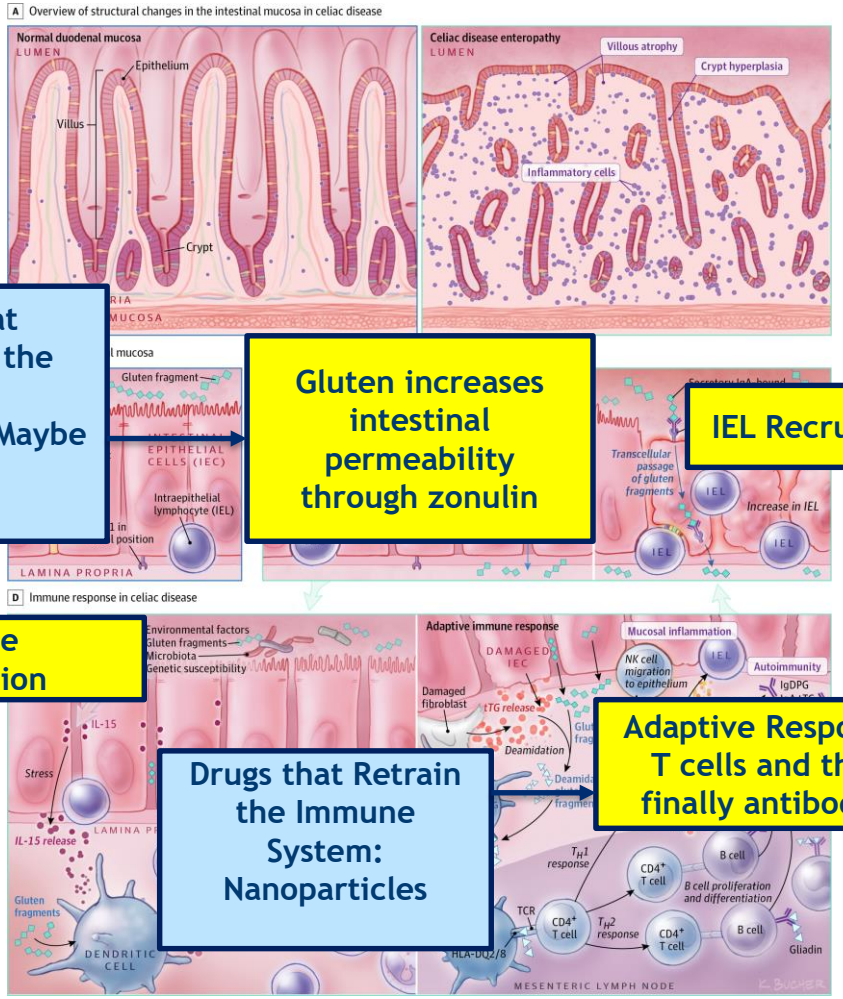
Gluten increases intestinal permeability through zonulin

IEL Recruitment

Innate Activation

Drugs that Retrain the Immune System: Nanoparticles

Adaptive Response- T cells and then finally antibodies



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