FDA **U.S. FOOD & DRUG** ADMINISTRATION

Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics VI (GREAT VI):

Workshop on Celiac Disease

July 22, 2021
Division of Gastroenterology (DG)
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research, FDA

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Disclosure Statement

- Nothing to disclose.
- The purpose of this presentation is to contribute to a scientific discussion of these issues.
- The views expressed in this presentation are those of the speaker, and do not necessarily represent an official FDA position.

Overview

- Regulatory framework for establishing substantial evidence of effectiveness
- Highlights from GREAT III workshop on celiac disease – March 31, 2015
- Considerations for drug development in celiac disease
  - Patient population
  - Trial design
  - Assessment of clinical benefit
  - Pediatric considerations

Regulatory Framework:
Establishing Substantial Evidence of Effectiveness

- "Evidence consisting of **adequate and well-controlled investigations**, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that **the drug will have the effect it purports or is represented to have** under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

- Requires that studies are designed well enough "to distinguish the effect of a drug from other influences, such as spontaneous change…placebo effect, or biased observation" (21 CFR 314.126)

Section 505(d) of the FD&C Act

Characteristics of an Adequate and Well-Controlled Trial

- Clear statement of objectives
- Appropriate control for comparison
- Appropriate selection of patients with disease/condition or at risk of disease (prevention)
- Baseline comparability (e.g., randomization)
- Methods to minimize bias (e.g., blinding)
- Appropriate methods for assessment of response
- Appropriate methods of analysis

21 CFR 314.126 (b)

Clinical Benefit

- Clinical benefit is a favorable effect on a meaningful aspect of how a **patient feels, functions, or survives** as a result of treatment.

- Clinical benefit must be clinically meaningful, measurable, and interpretable.

- Observed clinical benefit is described in labeling as a claim using words that represent the concept measured (should be meaningful and understandable to prescribers and patients).

Stakeholder Collaboration: GREAT III Workshop

AGA CLINICAL PRACTICE UPDATE: MEETING SUMMARY

Development of Celiac Disease Therapeutics: Report of the Third Gastroenterology Regulatory Endpoints and Advancement of Therapeutics Workshop

Daniel Leffler,[1,*] **Sonia S. Kupfer**,[2,*] Benjamin Lebwohl,[3] Kevin Bugin,[4] Donna Griebel,[4] Julia Tait Lathrop,[4] Jessica J. Lee,[4] Andrew E. Mulberg,[4] Elektra Papadopoulos,[4] Juli Tomaino,[4] and Sheila E. Crowe[5]

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Highlights from the GREAT III Workshop on Celiac Disease, March 31, 2015

- Considerations for defining the patient population
  - Ensure that signs and symptoms experienced by patients are indeed due to active celiac disease by ruling out other etiologies (e.g., based on endoscopic evaluation); large overlap in signs and symptoms among GI diseases.
- Clinical benefit is demonstrated through improvement in:
  - Disease-related GI signs and symptoms
  - Small intestinal histology
- Potential roles of celiac serologies in clinical trials
  - As part of the disease diagnosis for enrollment (celiac serologies have been cleared by the Center for Devices and Radiological Health only as an aid in diagnosis of celiac disease).
  - Serologies have not been cleared for monitoring disease progression or drug response in a clinical trial.

Stakeholder Collaboration: Listening Session

- Listening session with patients with celiac disease and caregivers – February 20, 2019
- Topics discussed:
  - Impactful symptoms
  - What would ideal treatments for celiac disease target?
    - Patients were generally open to the idea of a treatment for accidental exposure to gluten such as cross-contamination in food. If such a treatment was available, the patients indicated they would continue to maintain a strict gluten-free diet.
    - Patients were generally not open to the idea of a treatment intended to be taken regularly that does not promote healing of the underlying disease.
  - Patients generally expressed that they were not willing to ingest gluten for the purpose of a clinical trial.
  - FDA link to the summary for this listening session https://www.fda.gov/patientlisteningsessions

Trial Design Considerations:
General Approach

- Randomized, double-blind, placebo-controlled design to promote interpretability of data

- Trial design informed by the intended use of the product (e.g., adjunctive treatment to gluten free diet, monotherapy, etc.)

- Patient Population
  - Sufficiently symptomatic at baseline
  - Active histologic disease (EGD with biopsy during the screening period)

Trial Design Considerations: Duration

- Trial duration and timing of efficacy assessments should be guided by:
  - Anticipated onset of action
  - Goal of therapy (i.e., desired treatment outcome)
- Drugs intended for chronic administration should:
  - Characterize the long-term safety profile
  - Assess durability of response

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Trial Design Considerations: Clinical Benefit

- Improvement in
  - Clinically important signs and symptoms, using a well-defined and reliable patient-reported outcome (PRO) assessment
    - An assessment based on a report that comes <u>directly from the patient</u> without interpretation.
  - Histology, assessed by endoscopy with biopsy
    - Explore changes in a variety of histologic outcomes and scales, which incorporate evaluation of villous atrophy, crypt hyperplasia, and lymphocytic infiltration.
- Justify the magnitude of improvement in the relevant signs/symptoms and histology that reflect clinical benefit in the patients.

Trial Design Considerations: Gluten challenge

- When and why is it necessary to include gluten exposure in a clinical trial?

- What is the dose and duration of gluten exposure that elicits an immune (clinical and histologic) response?

- What is the timing of development of clinical symptoms and changes in histology in relation to the gluten exposure?

- What safety monitoring is needed to ensure the safety of patients during the trial?

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Pediatric Drug Development

- Extrapolation of efficacy is an approach to improve efficiency and success of pediatric drug development

- Relies on a series of evidence-based assumptions that reference adult or other pediatric trials, and targets pediatric populations that would be expected to have sufficiently similar

  – Disease course

  and

  – Expected response to therapy

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Pediatric Considerations

- Understand mechanism of action of the drug and its target to the pathophysiology of disease
  - Is the underlying pathophysiology and response to treatment sufficiently similar between adults and children?
  - Is it different for infants, children and adolescents?
  - Is the exposure-response sufficiently similar between adults and children?
- Are the core signs and symptoms that define the disease similar between adults and children?
- Would a clinically meaningful outcome be similar between adults and children?
- What is the age range of pediatric patients who might benefit from the therapy?
- What uncertainties and/or limitations are in existing data (e.g., clinical or historical data and published literature) and about pediatric population?

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Conclusion

- Early planning in the drug development process is critical to meet challenges associated with defining the target population and outcome measurement.

- Identify clinically meaningful, measurable, and understandable endpoints based on improvement in both key signs/symptoms as well as underlying disease (e.g., histology).

- Frequent communications and collaborations among the FDA, industry sponsors, academic investigators/clinicians, and patients will likely result in successful development of celiac disease treatment.

Acknowledgements

FDA

- Julie Beitz, MD

- Jessica Lee, MD, MMSc

- Juli Tomaino, MD, MS

- Suna Seo, MD, MSc

SESSION 1-
HISTOLOGIC ASSESSMENT IN THE
EVALUATION OF THE UNDERLYING
**DISEASE AND TREATMENT BENEFIT**
IN CELIAC DISEASE

Normal duodenal mucosa — Duodenal mucosa in celiac disease

Gluten →

← Gluten-Free Diet

Green and Cellier. N Engl J Med 2007;357:1731-1743.
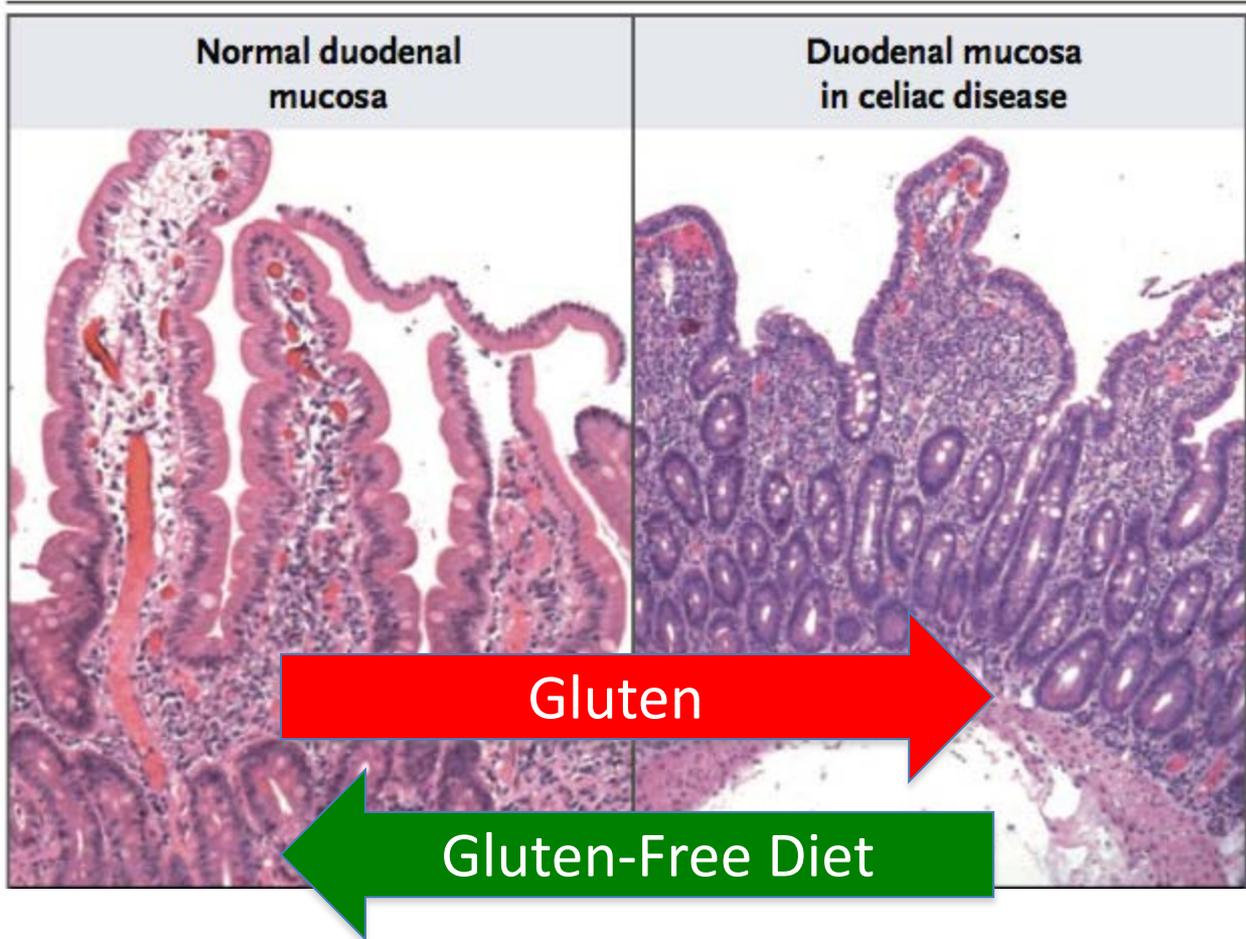
Why Do a Follow-Up Biopsy? Symptomatic Patients

- Identify whether gluten exposure is contributing to symptoms

- Diagnose or rule out refractory celiac disease

Why Do a Follow-Up Biopsy?
Asymptomatic Patients

- Assess dietary adherence
  - Confirm effectiveness of current precautions

- Triage patients for intensive dietitian follow-up

- Risk-stratify patients with regard to complications

Four Pillars of Monitoring Response to the Gluten-Free Diet

- Symptoms
- Dietitian's assessment
- Serologies
- Histology

Consequences of Persistent Villus Atrophy

Outcome	Hazard Ratio (95% CI)	Interpretation
Mortality (Aliment Pharmacol Ther 2013;37:332-9.)	1.01 (0.86-1.19)	No increased risk
Ischemic Heart Disease (PLOS One 2015; 30;10:e0117529.)	0.97 (0.73-1.30)	No increased risk
Low Birth Weight (Clin Gastroenterol Hepatol 2015;13:1111-7.)	0.98 (0.41-2.39)	No increased risk
Lymphoproliferative Malignancy (Ann Intern Med 2013;159:169-75.)	2.26 (1.18-4.34)	Increased risk
Hip Fracture (J Clin Endocrinol Metab 2014;99:609-16.)	1.67 (1.05-2.66)	Increased risk

Optimising delivery of care in coeliac disease – comparison of the benefits of repeat biopsy and serological follow-up

L. M. Sharkey*, G. Corbett*, E. Currie[†], J. Lee[†], N. Sweeney[‡] & J. M. Woodward*

- 391 patients underwent follow-up biopsy

- Median time to repeat biopsy: 11 months

- 57% with normal villi
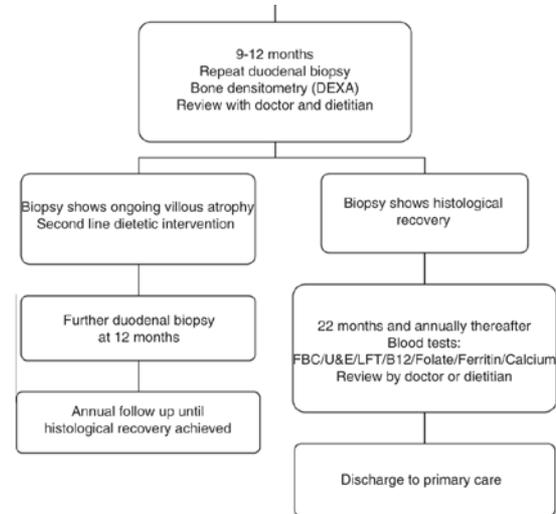

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Aliment Pharmacol Ther 2013;38:1278-91.

Optimising delivery of care in coeliac disease – comparison of the benefits of repeat biopsy and serological follow-up

L. M. Sharkey*, G. Corbett*, E. Currie[†], J. Lee[†], N. Sweeney[‡] & J. M. Woodward*
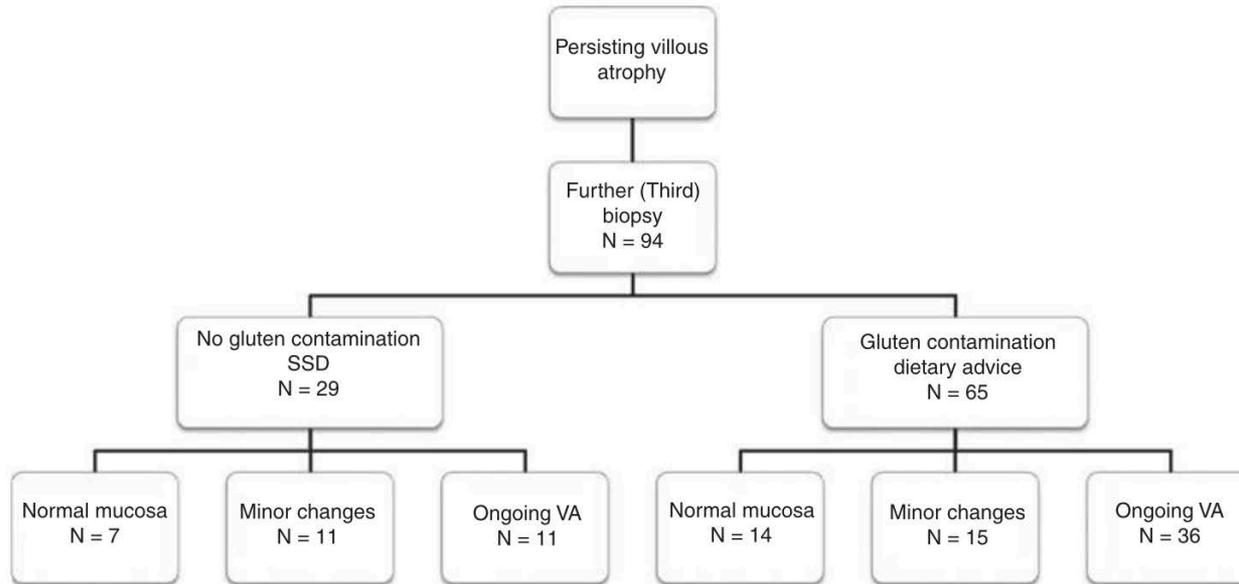
Expected Time to Healing
Clinical Trial Experience (adults)

Mahadev, et al. Aliment Pharmacol Ther 2017;45:1084-1093.

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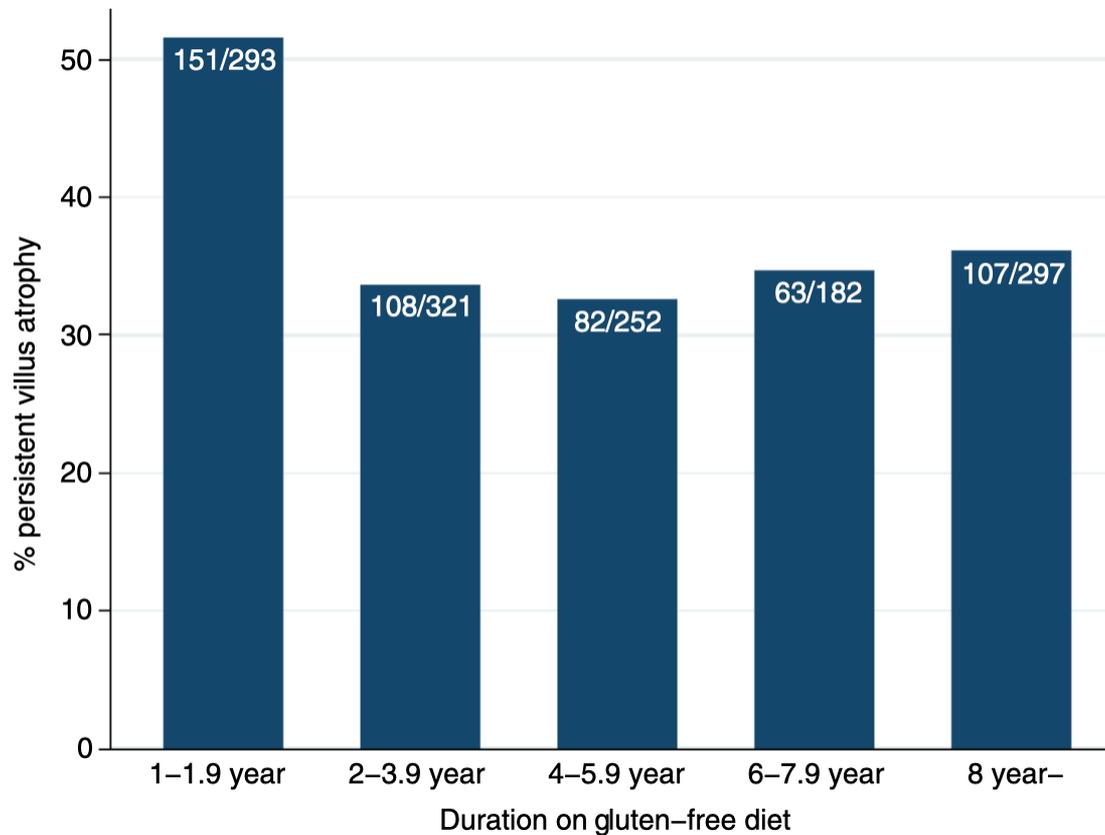
Gluten in Stool is Poorly Predictive of Persistent Villus Atrophy

- Multicenter study in Spain (76 subjects, 8 sites)

- Follow-up biopsy at 2 years

- Persistent villus atrophy: 53%
  - Age ≤30: 32%
  - Age >30: 67%

- Excellent adherence in majority on dietitian evaluation
  - But 69% had evidence of gluten in stool

- No association between gluten in stool and persistent atrophy
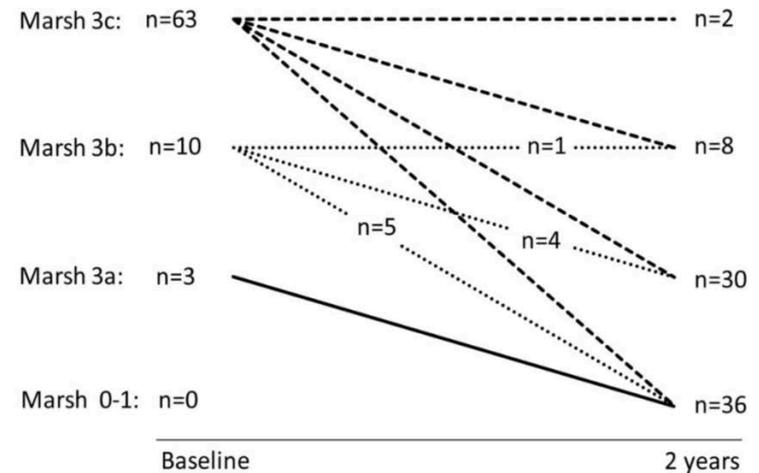
Figure 1. Evolution of histological damage according to the Marsh-Oberhuber classification.

Fernandez-Bañares, et al. Am J Gastroenterol 2021;116:1036-1043.

Rej, et al. Am J Gastroenterol 2021;116:946-948.
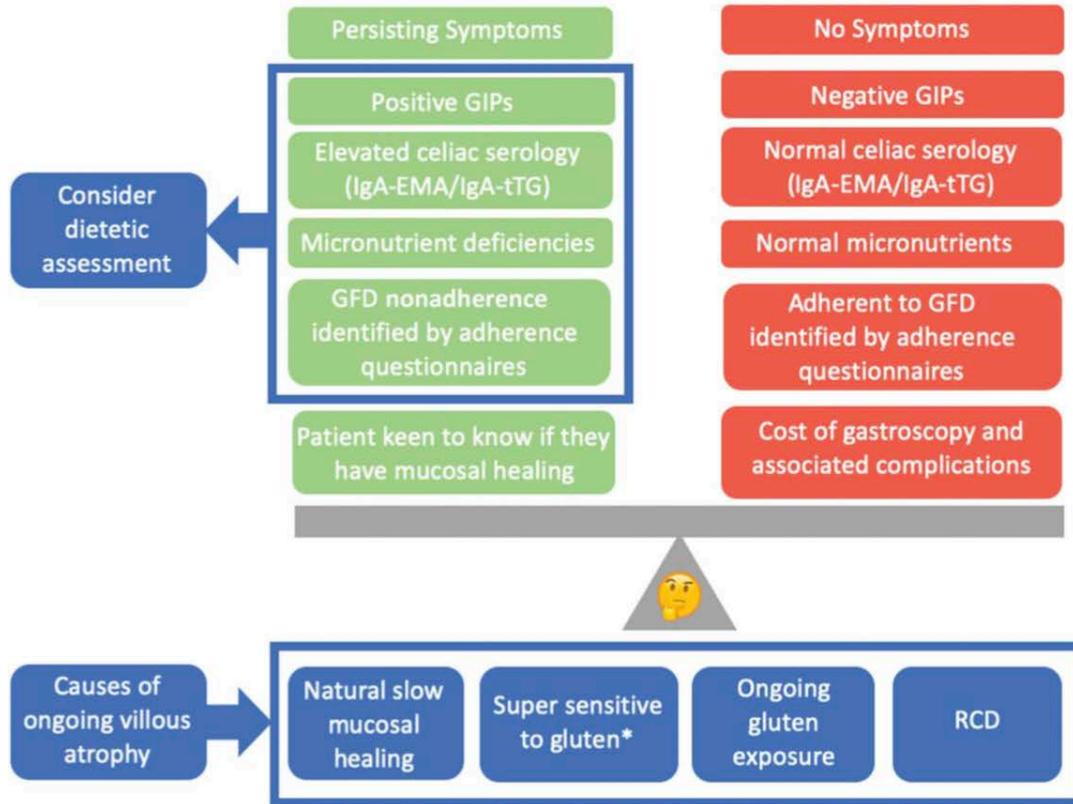
Age Has Become an Important Predictor of Histology

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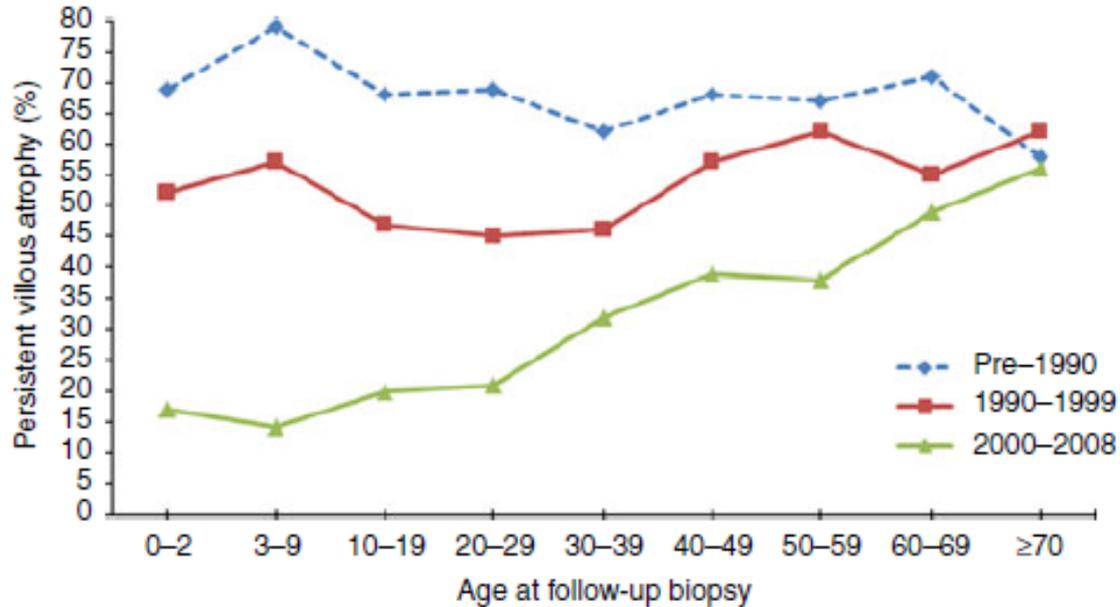
Symptoms are Poorly Predictive of Histology in Non-Responsive Celiac Disease

Symptoms	Proportion with villus atrophy (VH:CD ≤2)		P
	Present	Absent	
Bloating	431/1167 (36.9)	80/178 (44.9)	0.04
Abdominal pain	410/1134 (36.2)	101/211 (47.9)	0.001
Tiredness	421/1129 (37.3)	90/216 (41.7)	0.23
Diarrhoea	375/1018 (36.8)	136/327 (41.6)	0.12
Nausea	239/690 (34.6)	272/655 (41.5)	0.009
Constipation	263/684 (38.5)	248/661 (37.5)	0.73
Depression/anxiety	173/431 (40.1)	338/914 (37.0)	0.27
Heartburn	140/326 (42.8)	371/1018 (36.4)	0.04
Headache	112/320 (35.0)	399/1025 (38.9)	0.21
Anaemia	114/262 (43.5)	397/1083 (36.7)	0.04
Hypertension	80/179 (44.7)	431/1166 (37.0)	0.05
Dermatitis herpetiformis	31/89 (34.8)	480/1256 (38.2)	0.52

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Mahadev, et al. Aliment Pharmacol Ther 2017;45:1084-1093.

Tests for Serum Transglutaminase and Endomysial Antibodies Do Not Detect Most Patients With Celiac Disease and Persistent Villous Atrophy on Gluten-free Diets: a Meta-analysis

Jocelyn A. Silvester,[1,2,3,4,*] **Satya Kurada**,[2,4,*] Andrea Szwajcer,[5] Ciarán P. Kelly,[2,4] Daniel A. Leffler,[2,4] and Donald R. Duerksen[1]

- TTG IgA in follow-up

- 11 studies, 7 countries

- Identification of persistent villus atrophy:

  - Sensitivity 50%

  - Specificity 83%

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What is Well-Controlled Celiac Disease?

- Improved (resolved?) symptoms

- Adequately adherent according to dietitian's assessment

- Serologic normalization or near-normalization
  - Difficult to interpret during first year

- Histology
  - Difficult to interpret during first two years

Marsh Score

- In widespread clinical practice
- Used in pathology reports
- "Villus blunting" = Marsh 3
- Used for celiac vs. not
- Used for healed vs. not

- But
  - Gradations not used
  - Ignores intraepithelial lymphocytes

Adelman, et al. Am J Gastroenterol 2018; 113:339–347.

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Number of subjects
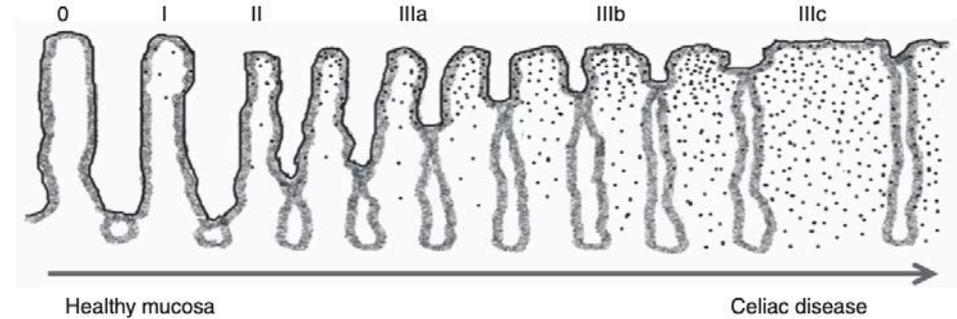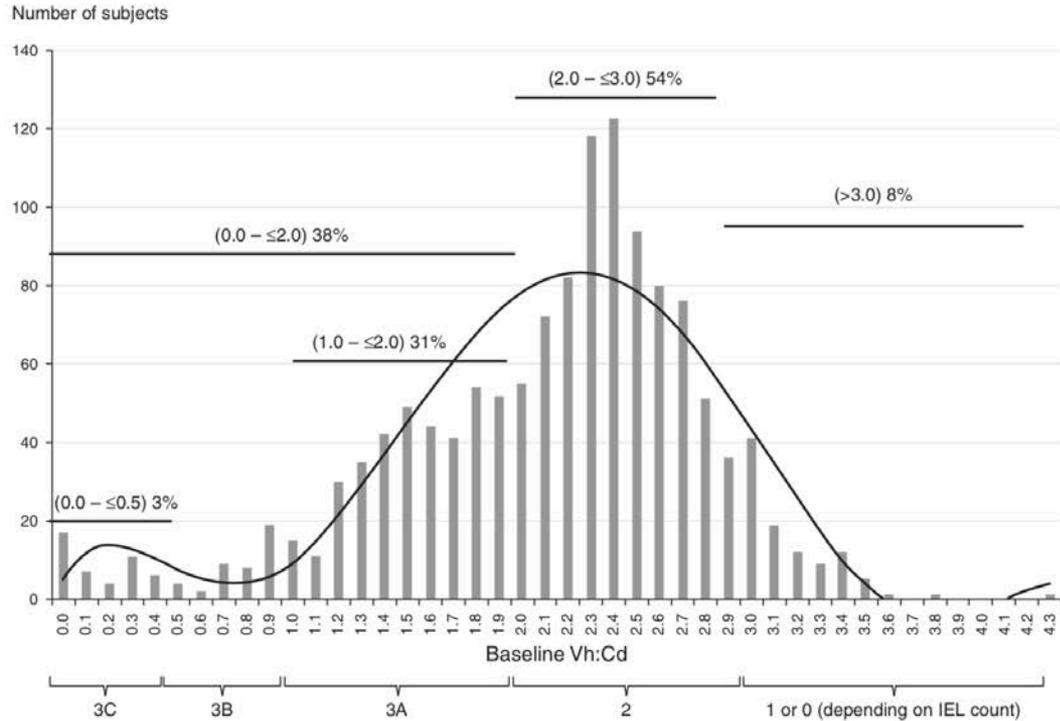
Figure 3. Villus height to crypt depth (Vh:Cd) frequency distribution of 1,345 patients with self-reported moderate or severe celiac disease-associated symptoms. Frequency distribution of Vh:Cd in duodenal biopsies taken from 1,348 patient with celiac disease on treatment with a gluten-free diet but with continuing moderate or severe celiac-associated symptoms (from CeliAction Study) (24). Proposed Quantitative-Mucosal Algorithmic Rules for Scoring Histology scores are illustrated.

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Adelman, et al. Am J Gastroenterol 2018; 113:339–347.

Follow-Up Biopsy in Clinical Practice

- Offered at 1-3 years after starting the gluten-free diet
  - Not mandated by guidelines
  - "It is reasonable to do follow-up biopsy in adults after 2 years of starting a GFD to assess for mucosal healing" –ACG 2013

- Healed result offers validation of patient's current precautions

- Persistent atrophy suggests ongoing gluten exposure

- In clinical practice we dichotomize, but there is a continuum (VH:CD)

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theceliacsociety.org
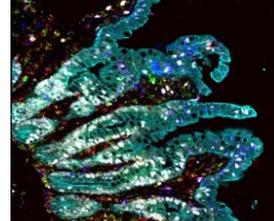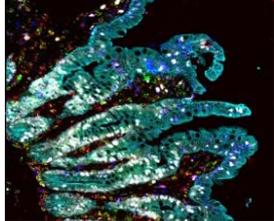
Unique considerations for using histologic assessments to monitor disease in pediatric patients

Jocelyn Silvester, MD PhD

22 July 2021

Disclosures

- Consulting: Takeda Pharmaceuticals, Teva Pharmaceuticals
- Site-PI for research study: Cour Pharmaceuticals, Takeda Pharmaceuticals, Amgen
- Investigator initiated study: Glutenostics LLC, Inova Diagnostics, Milky Way Life Sciences

Overview

- Why do a diagnostic biopsy?
- Mucosal recovery – are kids just little adults or are they better?
- Special considerations for pediatric endoscopy
- Implications for clinical practice (and research)

Celiac diagnosis circa 1979 – As easy as 1,2,3!

Biopsy #1　　　　**Biopsy #2**　　　　**Biopsy#3**

McNeish et al. Arch Dis Childhood 1979;54:783.

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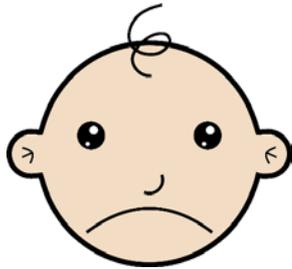
Celiac diagnosis, circa 1990
Focus on treatment response

Biopsy #1　　　　**Biopsy #2**　　　　**Biopsy#3**
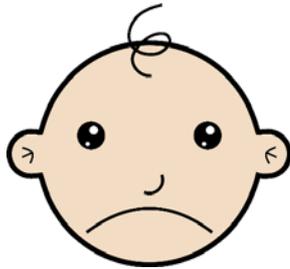
*Recommended if < 2 years old or asymptomatic at diagnosis

Walker-Smith et al. Arch Dis Childhood 1990;65:99.

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Celiac diagnosis, circa 2012
Focus on symptoms, autoimmunity, genetic risk
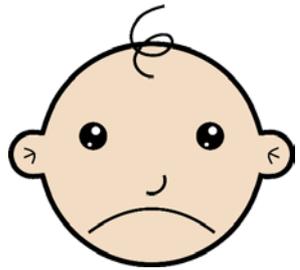
Husby et al. *JPGN* 2012;54:136.

Celiac diagnosis, circa 2020
Focus on autoimmunity

Husby et al. *JPGN* 2020;70:141.
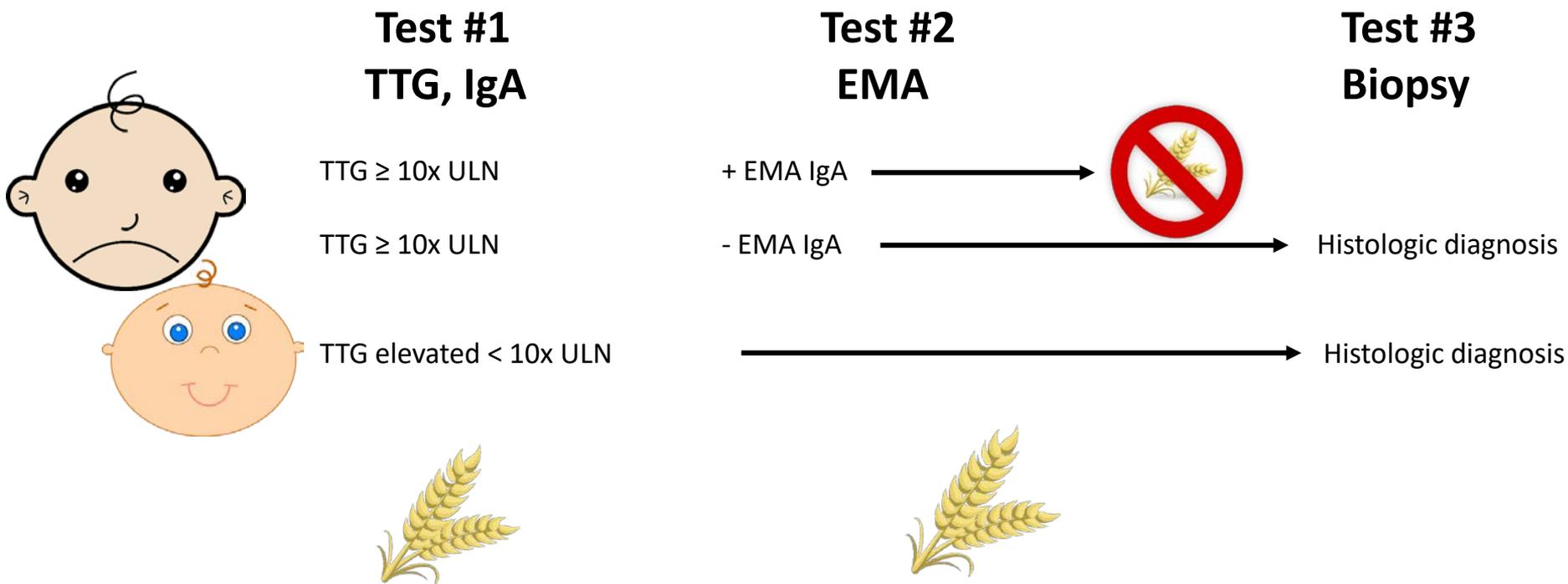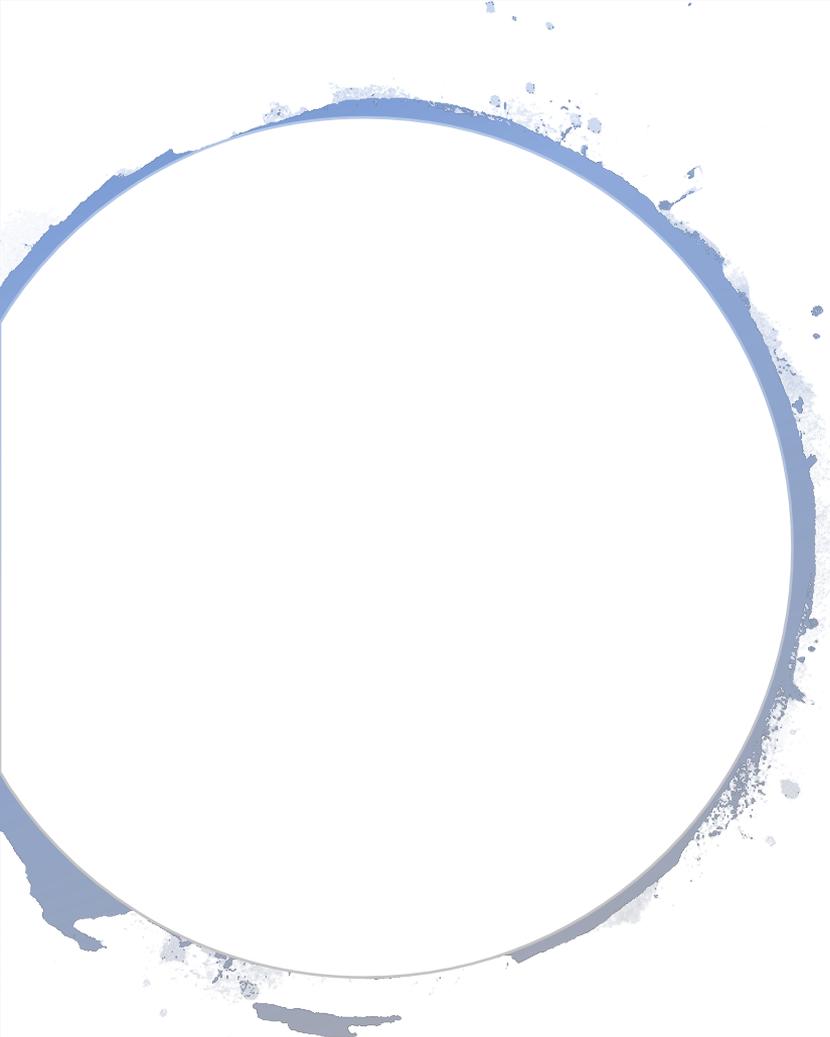
Intestinal biopsy to assess mucosal recovery on a gluten-free diet in children, circa 2021

- May be first biopsy if serologic diagnosis
- Not currently routine
- Follow-up biopsy more likely if:
  - New or persistent symptoms
  - Persistently elevated serology
  - Comorbidities which are assessed by endoscopy
    - Eosinophilic esophagitis
    - Inflammatory bowel disease

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Follow-up biopsy in Pediatric Clinical Practice

- 103 children with celiac disease (Marsh 3 at diagnosis) undergoing clinically indicated repeat endoscopy

Leonard et al. *JPGN* 2017;64:286-91.
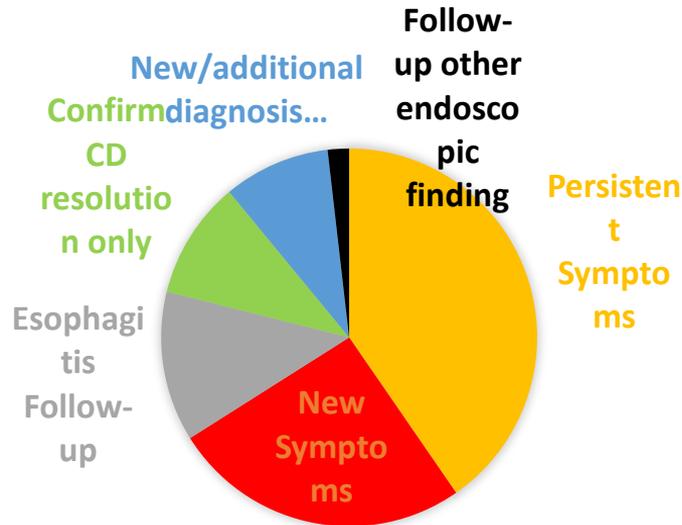
Follow-up biopsy in Pediatric Clinical Practice

- 103 children with celiac disease (Marsh 3 at diagnosis) undergoing clinically indicated repeat endoscopy between 2012-2015 at 2 hospitals

Leonard et al. *JPGN* 2017;64:286-91.
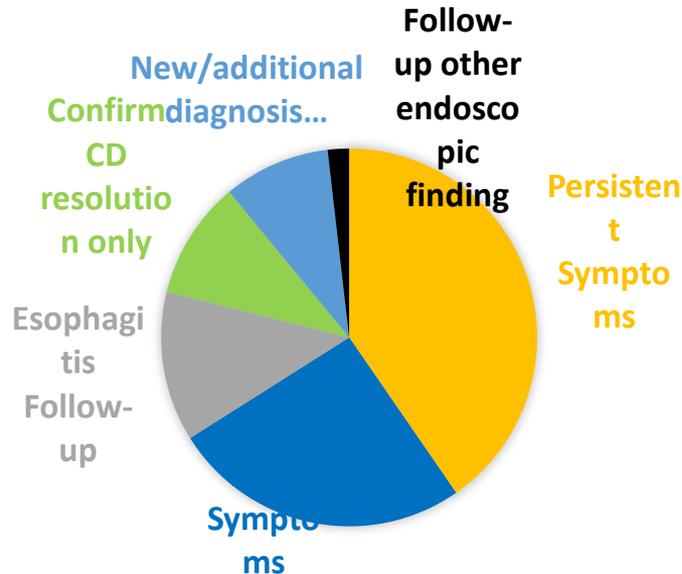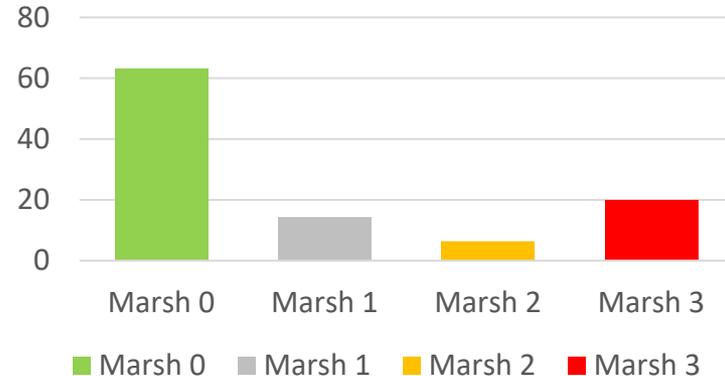
Proxies for histologic endpoints?

✖Serology (TTG IgA, DGP IgG, EMA IgA)

✖Stool/urine gluten immunogenic peptides

✖Symptoms

✖Self-reported gluten-free diet adherence
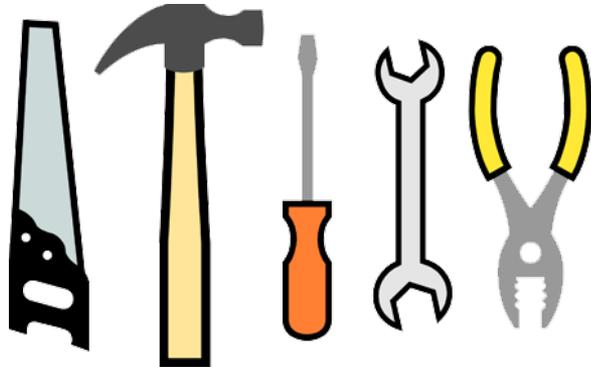
Additional considerations for endoscopy in children

- Endoscopy in pediatrics is a more significant undertaking
- Need for sedation entails higher risk
  - Impact on developing brain uncertain
- Unclear risks of more biopsies in smaller children

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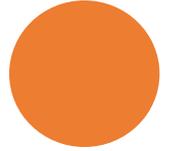
Additional considerations for endoscopy in children

- Endoscopy in pediatrics is a more significant undertaking
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  - Impact on developing brain uncertain
- Unclear risks of more biopsies in smaller children

Technological innovations could significantly impact practice (and risks)

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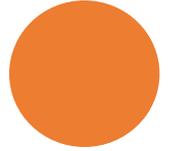
Re-imag(in)ing intestinal villi

a. HD with optimal band imaging
b. High definition (HD) endoscopy
c. Narrow band imaging (villi)
d. Narrow band imaging (absent vili)
e. HD endoscopy (vili)
f. HD endoscopy (subtotal villous atrophy)

Confocal imaging window
Objective lens
Instrument channel

Normal

Normal

Villous atrophy

Crypt hypertrophy

www.tearneylab.org
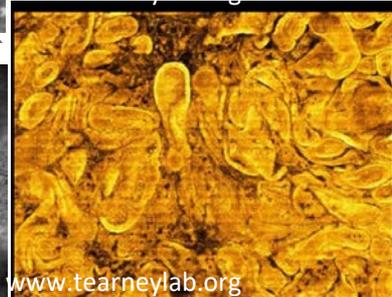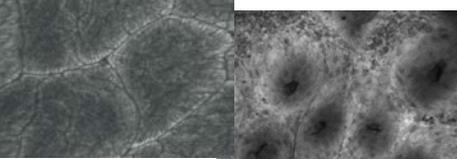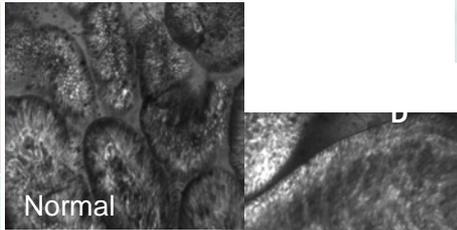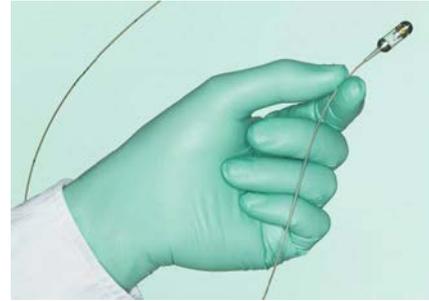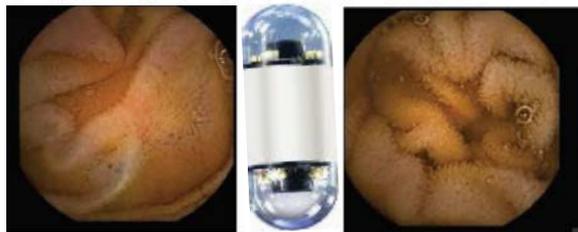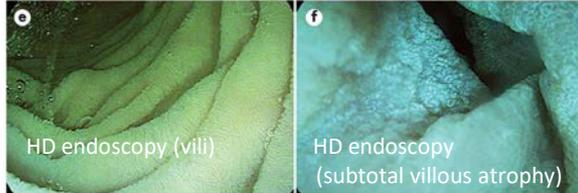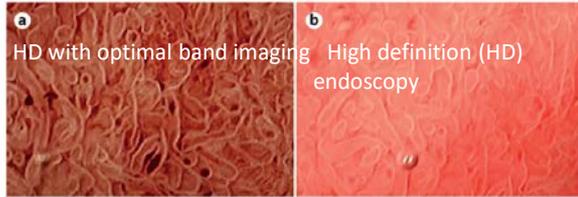
Thompson et al *Nat Rev Gastroenterol Hepatol* 2017;14:727-38.
Leong et al. *Gastroenterol* 2008;135:1870-76;

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Implications for clinical practice (and trials)

- Uncertain baseline histology
  - Follow-up biopsy may be the first biopsy
- Heavy reliance on "clinical" (signs and symptoms) endpoints yet there are no standardized measures or criteria
- Rate of mucosal recovery on a GFD in children on a "modern" GFD is uncertain but not universal
- Technological advances may shift risk-benefit equation for obtaining follow-up "look" at small intestinal histology

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Histologic Characteristics to Define Disease Severity and Remission

A Pathologist's Perspective

Marie E. Robert, M.D.

Yale University School of Medicine

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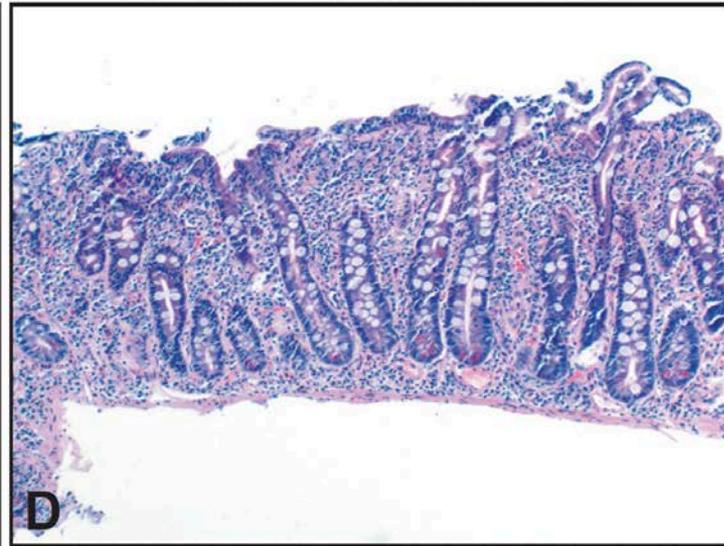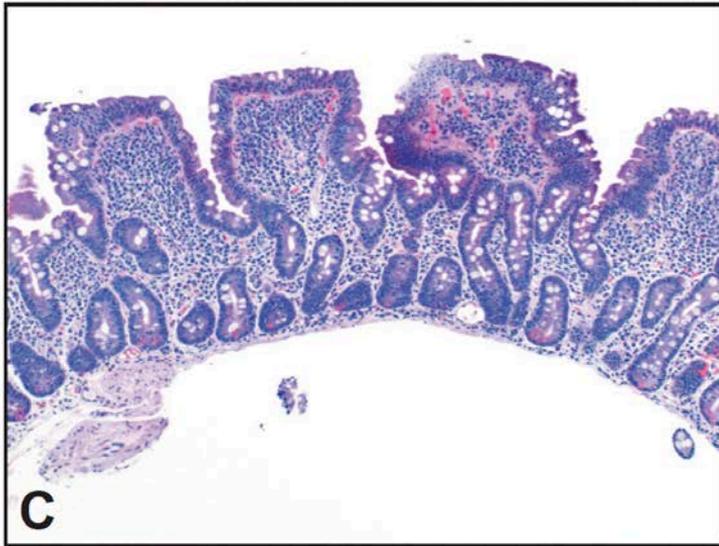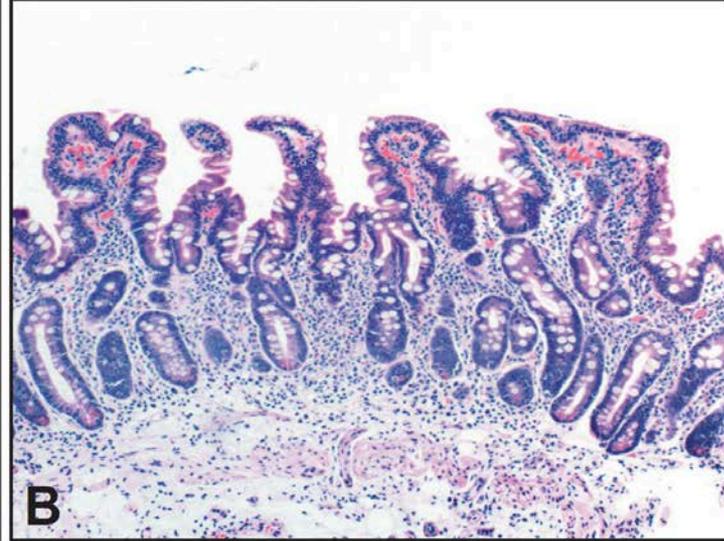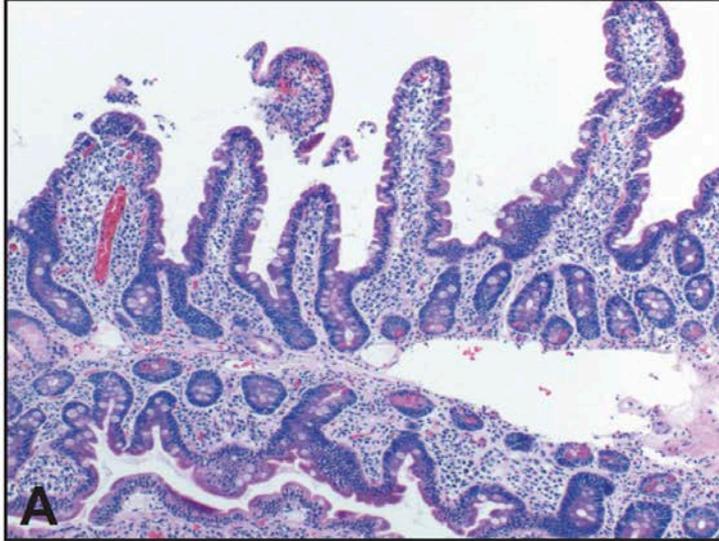
Celiac Disease Activity Indicators

Subjective and objective data points
- Symptoms
- Anti-IgA tTG titers, other serum markers
- Duodenal mucosal histology

Acknowledge imperfect correlation between clinical data and duodenal mucosal morphology.

Histology will always be a useful element in the tool kit of activity status indicators in CeD . . . Future holds promise for more.
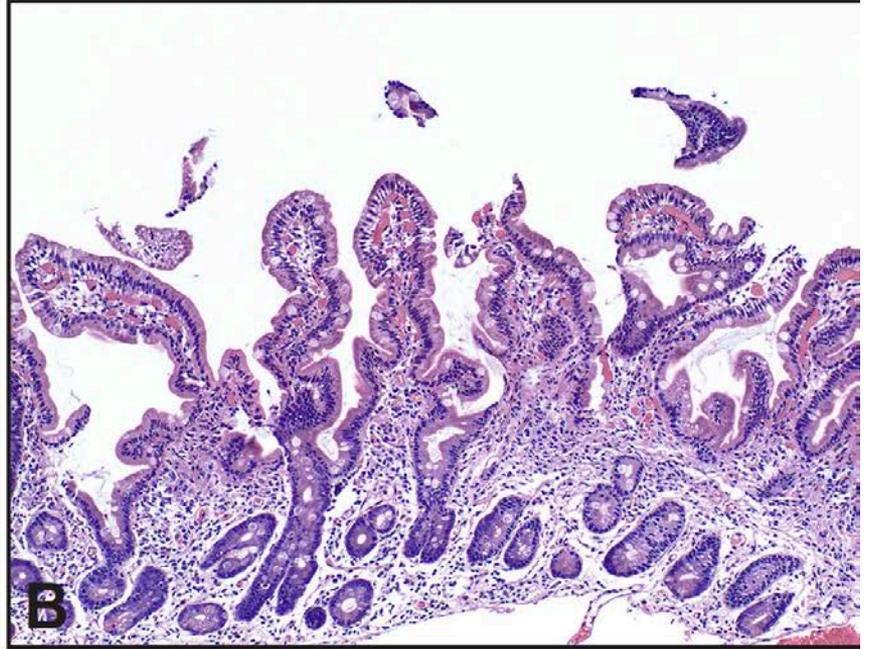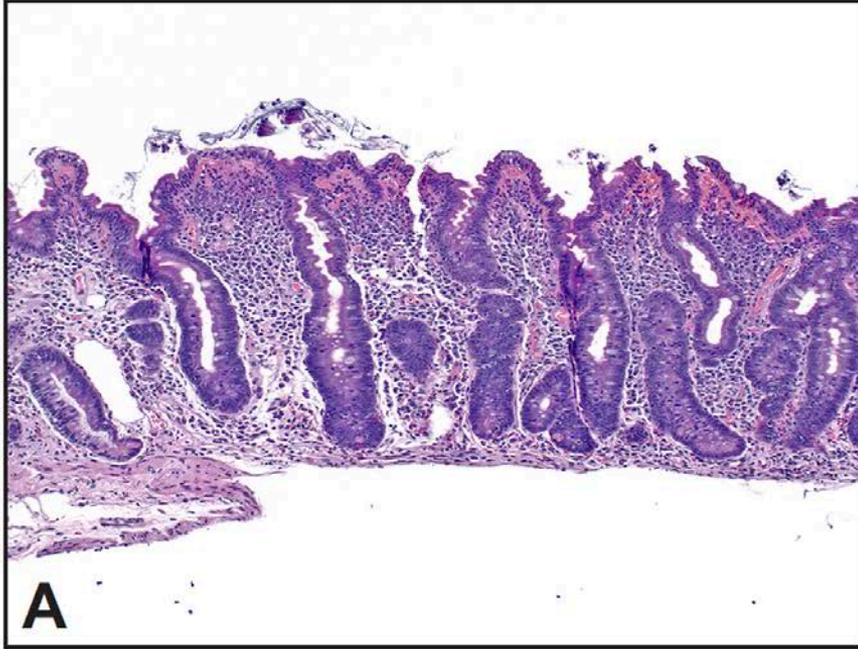
Expected histology at diagnosis and follow up

Normal: villous height/crypt depth ≥3:1, IELs ≤ 25/100 enterocytes

First diagnosis of celiac disease: Majority have diminution of Vh/Cd and increased IELs >40/100 or more.

At follow up, at least one year on GFD: Three outcomes
- Improvement to normal range
- Improvement, still abnormal (Vh/Cd, IELs or both, question diet adherence)
- No improvement or deterioration (question diet adherence, rarely RCD)

How to grade change and define remission- preliminary considerations
- Eschew Marsh score for this purpose
- Dissociate villous architecture from IEL counts- treat as separate data points
- IELs lag behind villi in return to normal-even when asymptomatic with normal tTG
  - What is functional significance of remaining IELs?
  - IELs normal in the small bowel; not like counting eosinophils in EoE, or crypt abscesses in IBD

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Celiac Disease Follow Up Study

Patients in strict GFD group (N=142) with Improved Marsh scores/Normalization of IELs at follow up.*

*Includes only patients on a strict GFD who had proximal and distal duodenal biopsies at both diagnosis and follow up.

Age Group (years)	Proximal	Distal	Proximal	Distal
	Marsh improved from Marsh 3A-C to Marsh 0-2 N (%)		**Intraepithelial Lymphocytes Decreased from Elevated to Normal N (%)**	
All Patients	42/53 (79)	96/119 (81)	31/56 (55)	72/132 (54)
0-17	28/31 (90) p=0.036	32/34 (94) p=0.019	23/32 (72) p=0.023	27/40 (68) p=0.028
≥ 18	14/22 (64)	64/85 (75)	8/24 (33)	45/92 (49)

Patel et al. (2021) *in preparation (confidential-do not post)*

Marsh-Oberhuber Classification of Celiac Disease
Note: IEL cutoff for abnormal is now >25/100

TYPE	IEL' S* / 100 EPITHELIAL CELLS	CRYPTS	APPEARANCE OF VILLI
Pre-Infiltrative Type 0	Normal (Less than 40)	Normal	Normal
Infiltrative Type 1	Greater than 40	Normal	Normal
Hyperplastic Type 2	Greater than 40	Hypertrophic	Normal
Destructive Type 3a	Greater than 40	Hypertrophic	Mild Blunting
Destructive Type 3b	Greater than 40	Hypertrophic	Moderate Blunting
Destructive Type 3c	Greater than 40	Hypertrophic	Severe Blunting (Flat)
Hypoplastic Type 4	Greater than 40	Atrophic	Severe Blunting (Flat)

Classification Schemes for GSE
Not developed for Assessment of Therapeutics

Marsh 1992	Oberhuber 1999	Corazza and Vilanaci 2005	Ensari 2010
Type 1	Type 1	Grade A	Type 1
Type 2	Type 2	Grade A	Type 1
Type 3	Type 3A	Grade B1	Type 2
	Type 3B	Grade B1	Type 2
	Type 3C	Grade B2	Type 3
Type 4	Type 4	Obsolete	Obsolete

Duodenal Mucosal Histology For Clinical Trials:
Nitty Gritty of Endpoints

Location and Number:

- Take 4 or 6 biopsies from post ampullary duodenum only (D2, D3)
  - General agreement to avoid bulb and pre-ampullary region
  - Contrarian View: In clinical practice bulb and D1 always involved at diagnosis and may be only site to show histologic abnormalities
  - Each biopsy fragment in separate container

Fixation: Formalin, at least 8 hours, not longer than 1 week.

Orientation (for trials):

- Centralize laboratories to reduce variability, achieve best embedding
- Serial sections to allow for at least 3 perfectly oriented villus-crypt units per biopsy

Normal to mild decrease in Vh/Cd; Increased IELs

Normal

Flat

9
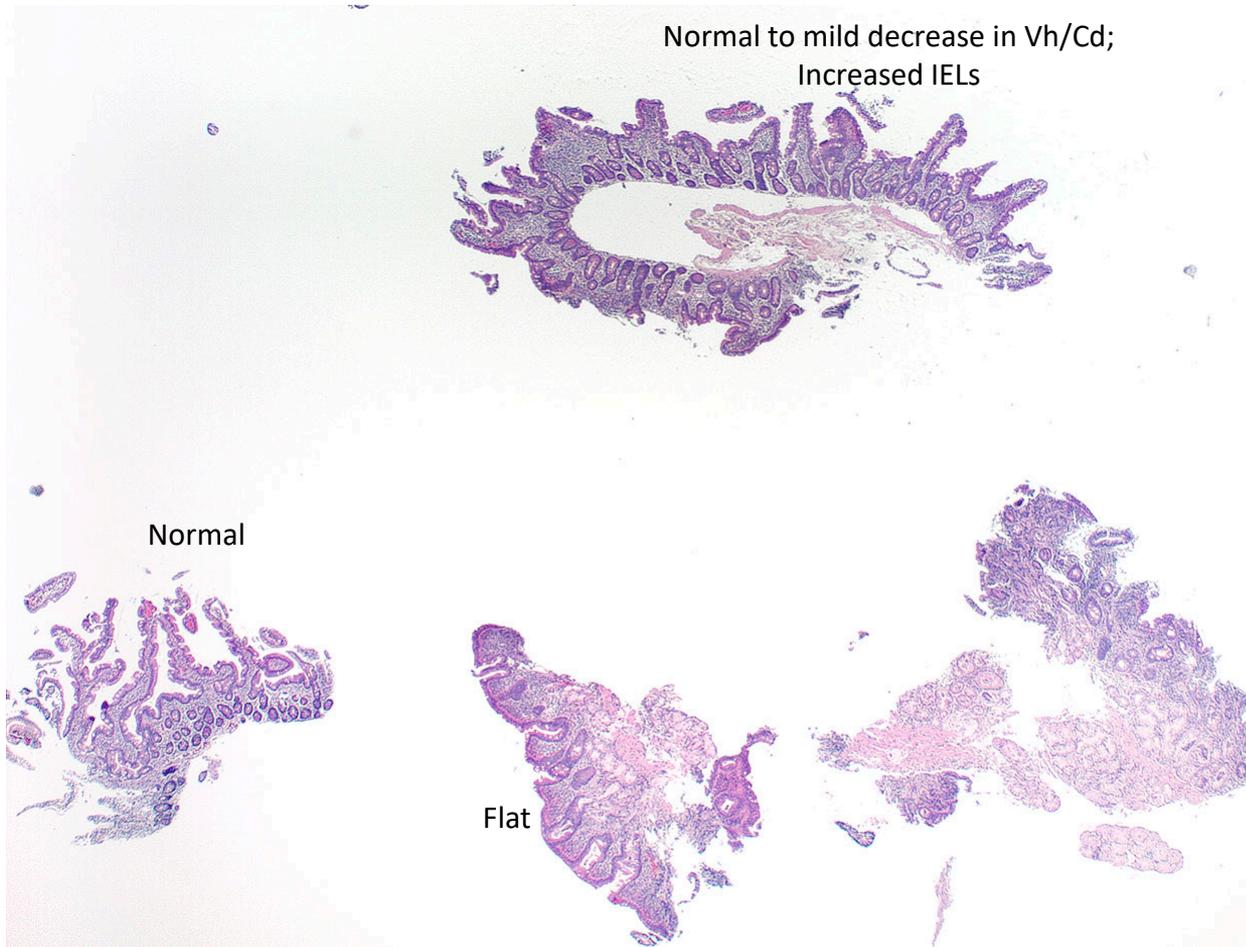
Child at first presentation: Variable degree of villous blunting, from severe in D1 (bulb) to normal in D3

Microscopic Evaluation for Clinical Trials
Endpoints

Collect Vh/Cd and IEL/100 enterocytes as separate data points
- Collect data only in well oriented villi, at least 3 per tissue fragment
  - Count all oriented villi present in each fragment, up to 10-12
- Standardize approach to IEL/100 enterocyte counting
  - CD3 immunohistochemistry vs Hematoxyln and Eosin stain
  - Automated (favored for trial) vs. light microscope
  - Villus tip vs villus tip and side (depends on degree of blunting)
- Score each biopsy fragment
  - Options: Range, average in each biopsy, and average across all samples per participant

Marsh or other scoring systems may not be appropriate for clinical trials
- Qualitative, not quantitative

Other Considerations and Exploratory Endpoints:
2021 and Beyond

- Ideally on the order of 6 months between pre and post trial biopsies (depends on trial design, may be unrealistic)

- How to define improvement, deterioration, or equivalency between timepoints?
  - Absolute change in Vh/Cd and IEL vs. achievement of pre-determined set point (Vh/Cd >3.0 and <25 IEL/100 enterocytes)

- Challenge: where does crypt end and villus begin? (help on the way)

- Other histology elements?
  - Villous height or width as stand-alone data points
  - Compare proximal, distal duodenum

Beyond H & E:

- IEL and lamina propria cell phenotypes and functional status in diagnostic and follow up biopsies
  - Multiplex immunofluorescence to co-localize

- Measures of IL-15 and other cytokines in mucosa, other inflammatory cell types

- RNA seq, proteomics and transcriptomics for signatures of disease state

Combination of histology and deeper analyses may maximize information from biopsy
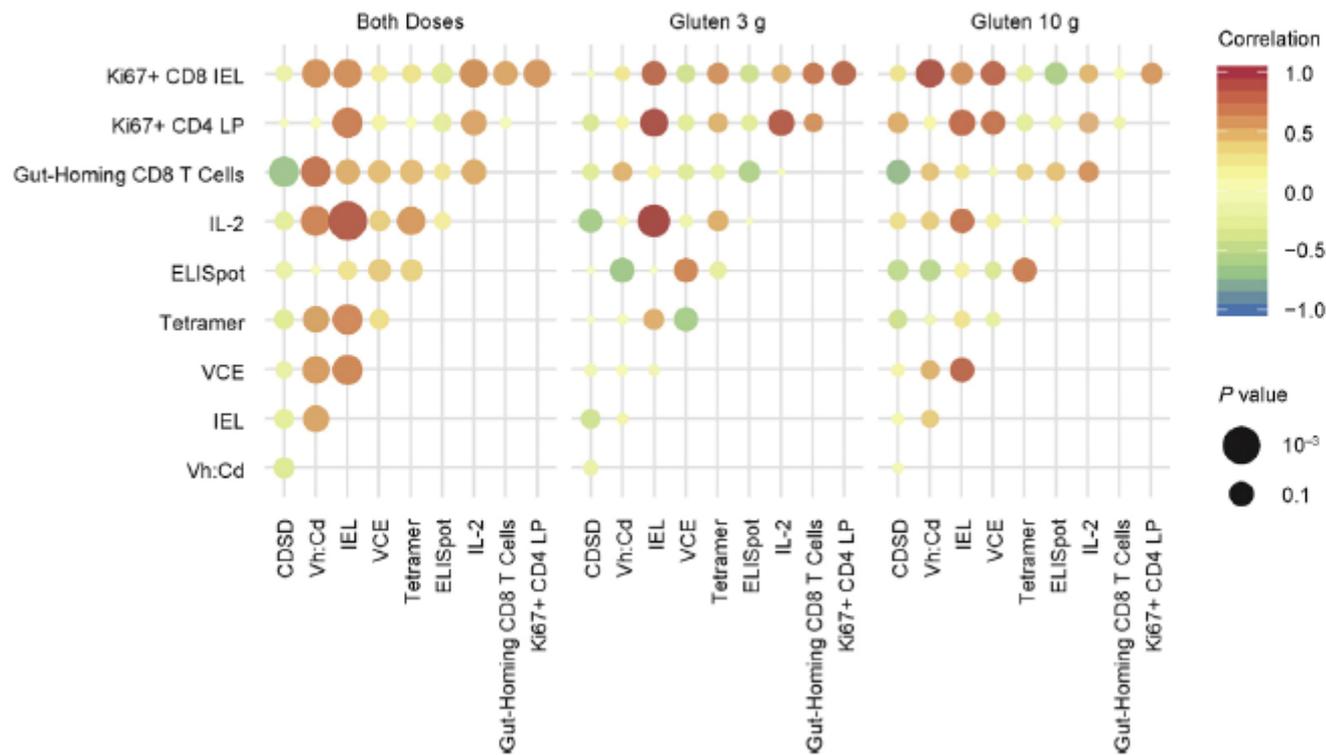
Figure 6. Data integration. Biomarker correlations. Maximum biomarker response was compared with both doses pooled and at each gluten dose by Spearman correlation. Vh:Cd change was inverted before calculating correlation because decreasing Vh:Cd signifies increasing severity, while for other markers increasing score reflects increasing severity.

Leonard et al. Gastroenterol, 2021

Contrast Trial with Clinical Practice

- What can pathologists be expected to report in a patient (on GFD or drug)

  - In US, many pathologists report mild, moderate, severe blunting with or without Marsh score (descriptive report)
    - Remember, many medications and other disorders lead to duodenal inflammation

  - IELs reported as normal or increased

  - If biopsies are available pathologists can compare pre- and post-treatment biopsies using their usual method
    - Vh/Cd not measured in routine practice
    - Requests to give precise IEL counts in practice faces challenges of uniformity of approach

High Level Summary Points
One Pathologist's view

- Three buckets: clinical practice, clinical trials, research to address knowledge gaps and advance patient care

- Ideally, clinical trials should collect data in a variety of ways to maximize scientific "take aways" to advance the field

- Can have predetermined histologic endpoints but still be nimble to correlate other data points/analyses (i.e. range vs average, multiple sites, molecular techniques) with PROs and other clinical endpoints to see what signal really matters.

- Maximize time interval to follow up biopsy to allow mucosa to register response to therapy or placebo. Pros and Cons?

- Future: Go beyond H&E and light microscopy for activity measures

PANEL DISCUSSION AND Q&A

SESSION 2- PEDIATRIC CELIAC DISEASE

Pediatric Extrapolation

Mona Khurana, M.D.

Pediatric Team Leader

Division of Pediatrics and Maternal Health

Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine

Office of New Drugs, CDER, FDA

Disclosure Statement

- I have no financial relationships to disclose relating to this presentation

- The views expressed in this talk represent my opinions and do not necessarily represent the views of FDA

FDA Evidentiary Standard

- Pediatric drug development held to same standard as adults for approval
  - Demonstrate substantial evidence of effectiveness for treatment of proposed indication
  - Adequate safety information must be included in the application to allow for appropriate risk benefit analysis
  - Manufacturing ensures product identity, strength, quality (purity)
  - Evidence-based labeling that adequately guides patients and prescribers how to use drug safely and effectively

Food Drug and Cosmetic [FDC] Act 505(d)

Flexibility

"While the statutory standards apply to all drugs, the many kinds of drugs...and wide range of uses for those drugs demand flexibility in applying the standards. Thus, FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards."

21 CFR 314.105

Substantial Evidence of Effectiveness

- Two adequate and well-controlled trials to independently substantiate clinical benefit in affected population (21 CFR 314.126)

- Single adequate and well-controlled trial plus "confirmatory evidence" in some instances (1997 FDA Modernization Act)

- Quantity and quality of clinical data constituting confirmatory evidence is program-specific

FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (May 1998)
Draft FDA Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (December 2019)

Unique Considerations: Pediatric Drug Development

- Relatively smaller pediatric population with disease/condition
- Global programs with geographical differences in
  - Regulatory requirements, standards of care, cultural expectations
- Ethical considerations
  - Scientific Necessity
  - Allowable risks in a clinical trial contingent on prospect of direct therapeutic benefit (21 CFR 50 Subpart D)

Extrapolation

- Instance of inferring an unknown from something that is known
- FDA finalized set of rules for extrapolation of efficacy data to pediatric population from adequate, well-controlled studies in adults (21 CFR 201.57(f)(9)(iv))
- Based on two fundamental assumptions
  - Similar disease course
  - Similar response to therapy
- Dosing and safety cannot be fully extrapolated

Pediatric Extrapolation: General Principles

- Common scientific approach

- Maintains evidentiary standard

- Maximizes use of existing data to support assumptions about disease and treatment response similarity between **source population (e.g. adults)** with disease or condition and **target population (e.g. pediatric patients)**

- Focus on filling gaps in existing knowledge

Assessment: Disease Course Similarity

Disease pathogenesis

Biological pathway

Etiology

Disease diagnosis and classification

Clinical presentation/course

Symptom time course

Comorbidities

Rate of progression

FDA Guidance for Industry: E11 (R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population (April 2018)

Assessment: Treatment Response Similarity

- Understand drug mechanism of action
- Consider maturational changes on drug disposition and action
  - Metabolizing capacity
  - Renal, biliary, pulmonary excretory pathways
  - Membrane transporters
- Determine relevance of clinical outcome(s) assessed in adult population to affected pediatric population

Draft FDA Guidance for Industry: General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products December 2014)

Assessment: Dose Response Similarity

• Is adult primary efficacy endpoint relevant to and measurable in pediatric population?

  Yes: Is a similar effect on endpoint expected with sufficient exposure in pediatric patients?

  No: Is there a predictive biomarker that could be measured in both adults and pediatric patients to bridge efficacy between both populations?

Pediatric Extrapolation: Framework

- How relevant is existing information in adults to pediatric population?

- What assumptions are being made in assessment of disease and treatment response similarity?

- What is level of confidence in these assumptions?

- Degree of confidence determines what additional data are needed to support pediatric approval

Level of Evidence Needed

Different	Dissimilar	Similar	Same
No overlap between adult and pediatric condition	Some degree of overlap with significant differences between adult and pediatric condition	Large degree of overlap with some differences between adult and pediatric condition	Significant overlap; no known significant differences between adult and pediatric condition

Increasing relevance of adult information to pediatric population with increasing confidence in similarity between adult and pediatric condition

Efficacy trial(s) — **Bridging Biomarker, Bayesian Borrowing, etc.** — Exposure Matchin

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Pediatric Extrapolation

- Must be scientifically and clinically justified
- Potential benefits
  - Avoid unnecessary pediatric clinical trials
  - Reduce testing burden to pediatric patients
  - Allow better allocation of resources

Faster availability of approved treatments

for pediatric population

Pediatric Extrapolation Framework: Successful Application

- [AAP News: Adult Drug Effective for Pediatric Patients with Dilated Cardiomyopathy and Heart Failure (October 2019)](#)

- [FDA Guidance for Industry: Drugs for Treatment of Partial Onset Seizures: Full Extrapolation of Efficacy from Adults to Pediatric Patients 2 Years of Age and Older (September 2019)](#)

- [FDA Guidance for Industry: Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment (November 2015)](#)

Thank You!

Living With Celiac Disease

My Daily Life Pre-Diagnosis

- Onslaught of symptoms that I would experience daily

Inclusive of...

        - Abdominal Pain

        - Nausea

        - Vomiting

        - Chronic Diarrhea

- With Gluten frequently within my system, the days my symptoms decided to show were irregular, turning days where I woke up in perfect health into days filled with pain and discomfort

My Diagnosis

- Lack of Social Awareness Regarding Disease Was A Huge Issue

- No Direction Towards Alternatives (Just A Basic Summary of What To Avoid)

- My Diagnosis Inspired Celiac Specific Testing Among Family And Friends (Ultimately leading to the discovery of 2 relatives who have Celiac Disease)

Symptoms Post-Diagnosis

- As an effect of strict adherence to the Gluten-Free diet, I no longer experience any of the initial symptoms

- Despite that, years passed since my diagnosis however I was barely growing (Celiac Disease had severely stunted my growth and becoming Gluten-Free did nothing to reverse that)

- Thankfully able to turn to growth hormones (salvaged my height but was met with another daily burden)

- Additionally, as a result of strict adherence, any unintentional gluten contamination currently magnifies any symptoms I had prior to my diagnosis
  - This means that my stable hold on Celiac Disease can flip upside down in a matter of a meal

The Daunting Gluten-Free Diet

- Countless foods I ate daily completely cut from my life

- Discouraging Gluten-Free substitutes and alternatives

- Initial lack of knowledge/misconceptions at restaurants (Cross-Contamination, "Fad" thinking)

- Only being able to trust food prepared within my own home

"Am I Ever Going to Be Able to Eat Out Again?"

Increased Discomfort When Eating Out

- No longer able to be spontaneous in my choices and meal plans

- No more sharing food with friends or partaking in special celebrations

- Had increased fears and anxiety when making the choice to eat out

    1) Having to have one-on-one conversations with the waitstaff

    2) Not wanting to come off as high maintenance or pushy

    3) Being nervous if they are going to take it seriously or if they might mess up

    4) Not wanting to end up at a restaurant where you have to settle instead of enjoy

Out of Town Uncertainties

- The un-comfortability is pushed even greater when travelling to an unfamiliar area

- 8th Grade Trip to Washington D.C. (4 Days and 3 Nights)

    - Packing an entire suitcase full of food

    - Having to request a certain room with a refrigerator

- Vacations in particular become more of a stressor than a relaxer (having to navigate not only 3 meals a day, but sometimes in an area where the native language is not my own or the types of cuisine are completely different)

Back To Square One

- The worst part of the process is a slip up

- It's bound to happen, regardless of the amount of precautions taken

- Dining confidence diminishes almost entirely and once again you're faced with the "Will I ever eat out again?" mentality

The Future of My Fear

- Eating is far too common a relationship developer to be ignored

  - Friends' Houses

  - Tennis Banquet

  - Prom

- Lack of high school and college social currency (This huge fixation on drinking)

- Having to have another area of criteria when choosing a college (3 meals a day + snacks for the entirety of the school year, I can't just choose any random school without considering the options for those who have a dietary restriction)

Perspective On Possible Treatment

- Monotherapy

  - Hands down the most desired option
  - Speaking for all those who I know that have Celiac, they would do anything to go back to a regular way of life (Regardless of what the future looks like, as long as gluten continues to damage my body, there won't be a time in which I forget about it or fail to accommodate for it)

- Adjunctive Therapy With a Gluten-Free Diet

  - Not ideal but is a step in the right direction
  - If some of that anxiety or physical side effects of possibly eating gluten could be lessened or avoided completely, the power that Celiac has over my decisions would shrink exponentially

Clinical manifestations, natural history, and unmet needs of pediatric celiac disease

Maureen M. Leonard MD, MMSc
Center For Celiac Research and Treatment at MGHfC

From a pediatric gastrointestinal disorder to a systemic autoimmune disease

1938

Today

Short Stature

Learning

Rash

Dental enamel defects

Delayed puberty

Fracture
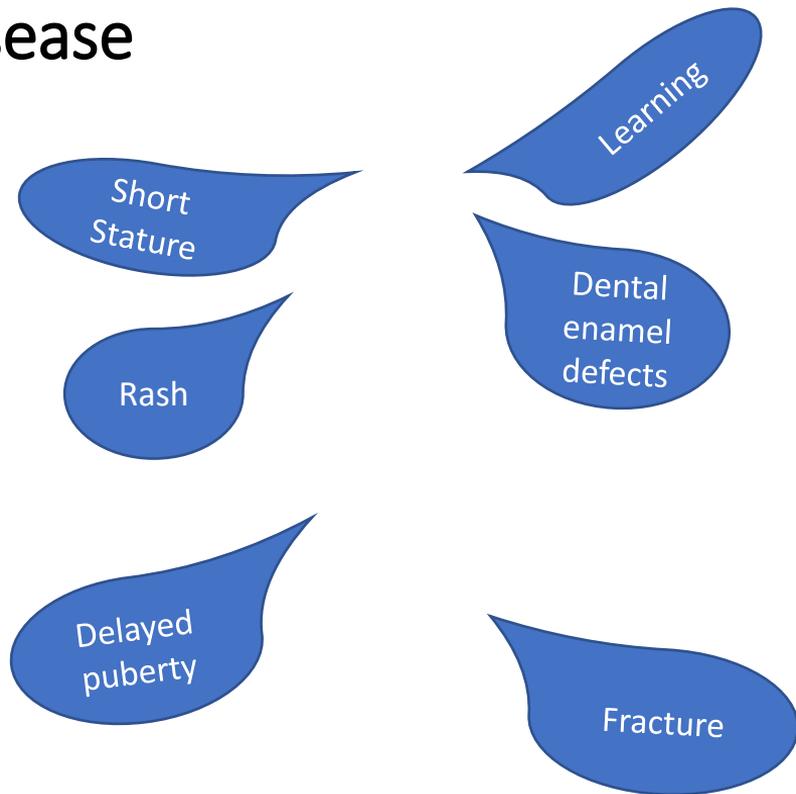
1. Jericho H & Guandalini S. PMID: 29895731
2. Nurminen S et al. PMID: 29569302

1

The clinical presentation of pediatric celiac disease has evolved

- Nearly 1 in 5 have overweight or obesity[2]

- Less severe presentation[1, 2]

- Older age at diagnosis; <3 years to age 9 [1,2]

- Extra-intestinal manifestations are becoming more frequent
  - Presenting symptom in 23-43 % of children[2,3,4]
  - Prevalent in 60% of children at diagnosis compared to 62% of adults[4]
  - Associated with
    - Slower rate of improvement than children with GI symptoms[4]
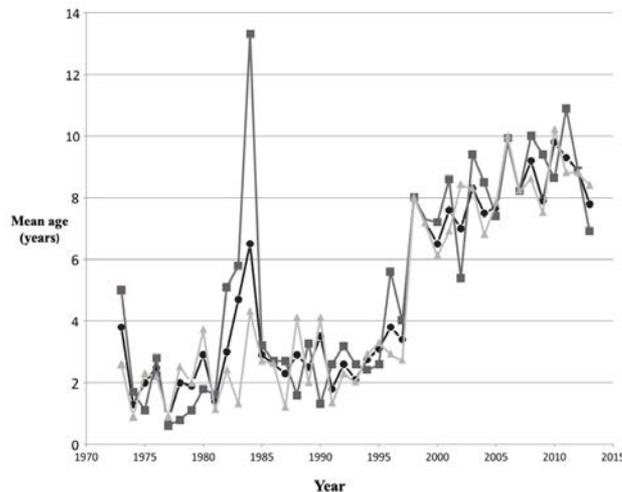
1. Tapsas et al. PMID: 26520057
2. Almallouhi et al. PMID: 28151767
3. Kivela et al. PMID: 26316370
4. Jericho H PMID: 29895731
5. Nurminen S et al. PMID: 29569302

Incidence and prevalence of CD in children continues to rise in Europe and the U.S.

Incidence (per 100,000 person-years) vs year (1950–2020)

Legend:
- Denmark
- United Kingdom
- Netherlands
- Germany
- Italy
- New Zealand
- Canada
- United States
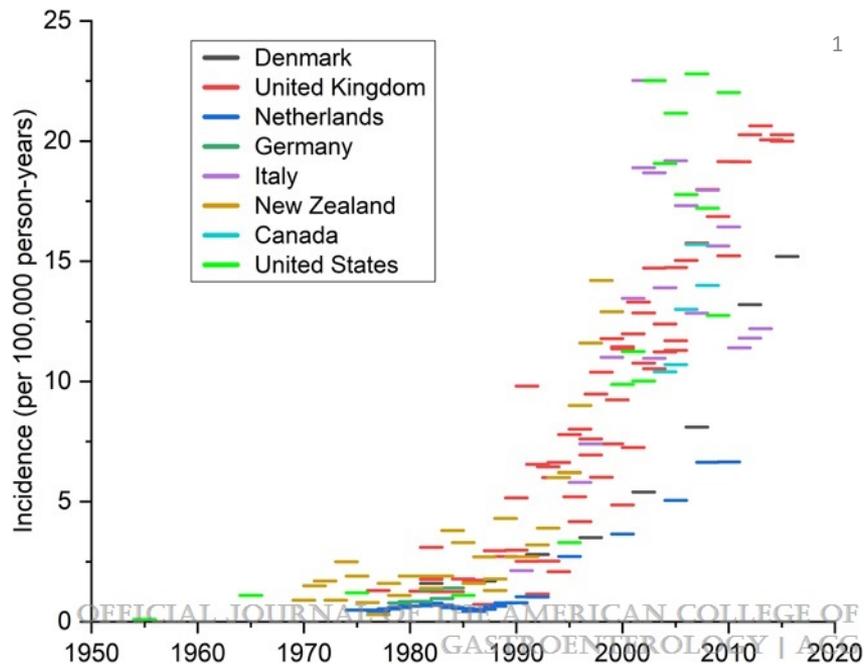
CD incidence

- Pooled incidence of pediatric CD in 21st century was 21.3/100,000 [1]
- Increased nearly three-fold between 2002 and 2014 (from 8.1 to 21.5 /100,000 person-years) in children in Olmsted County, Minnesota[2]

CD prevalence

- Increased by approximately two-fold between 1993–1995 (adjusted prevalence, 0.88%) and 2016 (estimated prevalence, 1.58%) in children in Italy[3]
- ASK study estimates up to 1.9% of children in Colorado may have tTG positivity[4]

1. King, JA. et al. 2020 PMID 32022718
2. Almallouhi et al. PMID: 28151767
3. Gatti S, et al. 2019 PMID : 31220637
4. Stahl MG. 2021 PMID: 32701732

3

A typical day in celiac disease clinic

Patient 1

12-y/o male with decreased height velocity

Patient 2

16-y/o female with delayed puberty and rash

Patient 3

18-y/o female with fatigue, headache and constipation

Patient 4

3-y/o female with family history of CD

Diagnostic approach to CD

Patients with symptoms or signs of CD or at high risk of CD (e.g. family history, T1D, Trisomy 21)

Measure total IgA and IgA tissue transglutaminase (tTG)

Positive IgA tTG

Positive IgA tTG

If IgA tTG<10xULN

If IgA tTG>10x ULN

Perform Endoscopy

Measure IgA EMA at a second time point

Celiac Disease

Celiac Disease

Diagnostic workup

Patient 1

12-y/o male with decreased height velocity referred by endocrinology

↓

tTG elevated

↓

Celiac Disease Confirmed

Patient 2

16-y/o female with delayed puberty and rash referred by dermatology

↓

tTG elevated

↓
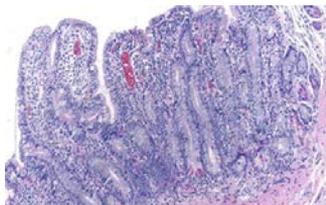
Celiac Disease Confirmed

Patient 3

18-y/o female with fatigue, headache and constipation

↓

tTG elevated

↓
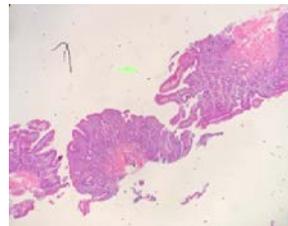
Celiac Disease Confirmed

Patient 4

3-y/o female with family history of CD

↓

tTG elevated

↓

tTG > 10 times ULN
&
EMA positive

Celiac Disease Confirmed

The gluten-free diet is the only available treatment for CD regardless of patient age, disease status, or symptoms

Patient 1

12-y/o male with decreased height velocity

⬇

Gluten-free diet

Patient 2

16-y/o female with delayed puberty, rash

⬇

Gluten-free diet

Patient 3

18-y/o female with fatigue, headache, and constipation,

⬇

Gluten-free diet

Patient 4

3-y/o female with family history of CD

⬇

Gluten-free diet

A gluten free diet is extremely difficult and almost impossible- especially for kids

School

Sleep overs

Birthday Parties

College

Dating

Affordability

8

Follow-up care: 6 months after diagnosis

Patient 1

12-y/o male with decreased height velocity

↓

tTG remains elevated

↓

Admits to gluten ingestion

Patient 2

16-y/o female with delayed puberty, rash

↓

tTG remains elevated

↓

Rash has improved; Hypervigilant; Underlying anxiety worsened

Patient 3

18-y/o female with fatigue, headache, and constipation

↓

tTG remains elevated

↓

Persistent symptoms

Lack of options at college

Patient 4

3-y/o female with a family history of CD

↓

tTG remains elevated

↓

Increased energy, seems happier

Celiac disease management requires a multidisciplinary team

Patient 1

12-y/o male with decreased height velocity

↓

tTG remains elevated

↓

Admits to gluten ingestion

Dietician
Psychologist
Social Worker
School intervention

Patient 2

16-y/o female with delayed puberty and rash

↓

tTG remains elevated

↓

Anxious
Disordered eating

Dietician
Psychologist
Psychiatrist

Patient 3

18-y/o female with fatigue, headache and constipation

↓

tTG remains elevated

↓

Persistent symptoms

Dietician
Psychologist
Social worker

Patient 4

3-y/o female with family history of CeD

↓

tTG remains elevated

↓

Symptom resolution

Dietician

How do we monitor improvement in children with CD?

- Symptom Improvement
  - 30% of patients may be asymptomatic
  - Symptoms don't correlate with mucosal damage

- Dietician Assessment

- Normalization of Serology
  - Tests poorly correlate with GFD adherence/ mucosal healing

- Mucosal Recovery
  - Only objective marker is endoscopy*

Performance of IgA tTG in predicting persistent villous atrophy at repeat biopsy

Group	N	Se	Sp	PPV	NPV	Accuracy
Overall	71	0.43	0.68	0.25	0.83	0.63
Symptomatic at repeat biopsy						
Yes	49	0.25	0.73	0.15	0.83	0.65
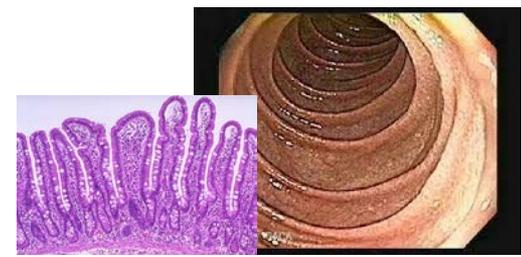
1. McGowan,2009. PMID: 19948628
2. Troncone, 1995 PMID: 8576818
3. Vahedi, 2003 PMID: 12809831 4.
Mahadev,2017PMID: 28220520
5. Leonard, 2017 PMID: 28112686
6. Silvester, 2017 PMID: 28545781

Is non-responsive celiac disease a problem in children?

Frequency of persistent villous atrophy

- Children: 4%-19%
  - median of 1.4-2.4 years

Frequency of non-responsive celiac disease

- Children: 15%

Potential consequences

1. Veeraraghaven,2021 PMID: 33833484
2. Bannister, 2014. PMID: 25070050
3. Vecsei, 2014. PMID: 24524430
4. Ghazzawi, 2014 PMID: 24691402
5. Leonard, 2017 PMID: 28112686

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One year after diagnosis

Patient 1	Patient 2	Patient 3	Patient 4
12-y/o male with decreased height velocity	16-y/o female with delayed puberty and rash	18-y/o female with fatigue, headache and constipation,	3-y/o female with family history of CeD tested due to routine screening
↓	↓	↓	↓
tTG remains elevated Admits to gluten ingestion	tTG normal	tTG normal	tTG normal
↓	↓	↓	↓
Continued counselling	Continued counselling	Persistent symptoms	Symptom resolution
• Dietician • Psychologist • School intervention	• Dietician • Psychologist • Psychiatrist	• Dietician	• Dietician

Repeat biopsy ?

Treatment* options for non-responsive CD in children

* Not FDA approved

Gluten contamination elimination diet[1,2]

	Acceptable Foods	Unacceptable Foods
Grains	Plain brown and white rice	Millet, sorghum, buckwheat, other gluten-free grains, seeds, flours
Fruits	All fresh fruits	Frozen, canned, or dried
Vegetables	All fresh vegetables	Frozen, canned, or dried
Proteins	Fresh meat, eggs, dried beans, unseasoned nuts in shell	Lunch meats, ham, bacon, other processed, self-basted or cured meats
Dairy	Butter, aged cheese, unflavored yogurt and milk	Seasoned or flavored dairy products, processed cheese
Condiments	Honey, Oil, vinegar, salt	Flavored and malt vinegars
Beverages	100% fruit/vegetable, gluten-free supplemental formula, gatorade, milk, water	

Budesonide

- Open Capsule Treatment[3]
  - 3mg, 3 times a day
  - 92% of patients w/ RCD-1 (N=43) had a clinical response (68% complete)
  - 89% of RCD-1 (N=43) patients had a histological response (67% complete)

1. Hollon et al, 2013. PMID: 23448408
2. Leonard, et al.2017. PMID: 29057833
3.. Mukewar, et al, , 2017 PMID: 28323276

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Similarities and differences between children and adults with CD

Adult

Response to GFD ~65-70%

Mucosal healing ~60%

1. Diarrhea
2. Anemia
3. Bloating (distention)
4. Osteoporosis

Comorbid Autoimmunity 16-30%

Adolescent

Comorbid Autoimmunity ~ 8%

Response to GFD ~85%

Mucosal healing >80% ???

>6 years old

1. Abdominal pain
2. Abdominal distention
3. Diarrhea
4. Asymptomatic

<3 years old

Mucosal healing ?Most?

1. Abdominal distention
2. Diarrhea
3. Growth Failure
4. Appetite loss

RižnikP, et al. JPGN 2021
Lebwohl &Rubio-Tapia. Gastro.2021
Cosnes et al. Clin Gastro. 2008.

15

Summary

- Signs and symptoms of CD differ according to age
  - Key pediatric clinical signs
    - Short stature, delayed puberty, behavioral changes impacting social development and learning

- Children face evolving challenges as they age
  - Toddlers, school age, adolescents, transition to independence

- We need accurate biomarkers to monitor disease
  - How frequent is NRCD? PE? Consequences?

- Children need alternative treatment options

FDA Reviewer Perspective: Defining Clinical Benefit in Pediatric Clinical Trials for Celiac Disease

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OND, CDER, FDA

Disclaimer

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

- No conflicts of interest to disclose.

Overview

1. Defining clinical benefit
2. Selecting fit-for-purpose clinical outcome assessments
3. Determining clinically meaningful change
   - Quantitative approaches
   - Qualitative approaches
4. Conclusions

Defining Clinical Benefit

- "A positive **clinically meaningful effect** of an intervention, i.e., a positive effect on how an individual feels, functions, or survives"*

- Feeling and functioning are measured using **clinical outcome assessments** (COAs), such as patient-reported outcome (PRO) assessments

- COAs should be **well-defined and reliable** in their specific context of use ("fit-for-purpose") to support regulatory decision-making

*FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource. https://www.ncbi.nlm.nih.gov/books/NBK338448/

3

Fit-For-Purpose COAs

- To support regulatory decision-making, COAs should have evidence to support their **content validity**, **measurement properties**, and interpretation of **meaningful change**

  – <u>Content validity</u>: Patient/caregiver input to show that the relevant concepts are captured by the COA, and the COA is understandable and usable as intended (qualitative)

  – <u>Measurement properties</u>: Psychometric analyses such as reliability, construct validity, ability to detect change, etc. (quantitative)

  – <u>Meaningful change</u>: Interpretation of what kind of change in COA scores is clinically meaningful (quantitative and qualitative)

Pediatric Considerations

- Consider PRO and/or caregiver-reported outcome measures, depending on the intended study population (e.g., depending on age)

- PROs intended for pediatric use should be tested in the intended age group prior to use in pivotal trials (i.e., not all age groups are the same)

- The 2013 ISPOR Task Force report on pediatric PROs* provides a useful overview of best practices

*Matza LS, Patrick D, Riley AW, et al. Pediatric patient-reported outcome instruments for research to support medical product labeling: report of the ISPOR PRO Good Research Practices for the Assessment of Children and Adolescents Task Force. Value Health. 2013; 16(4):461-479. Available from: https://pubmed.ncbi.nlm.nih.gov/23796280/

Determining Meaningful Change

- Statistical significance alone does not indicate whether individual patients have experienced meaningful clinical benefit

- FDA recommends **anchor-based methods** to assess meaningful within-patient changes in COA scores

- Qualitative evidence (e.g., from **exit interviews**) is also useful to inform meaningful change

Anchor-Based Methods

- Anchor-based methods involve comparing changes in a target COA measure to changes in an external (anchor) measure

- FDA recommends using anchor-based methods to assess meaningful within-patient changes in COA scores, supplemented by eCDF and PDF curves*

*eCDF = empirical cumulative distribution function
  PDF = probability density function

Selecting Anchor Scales

- We recommend including multiple **anchor scales**:
  - Global Impression of Severity
    - Assessing disease severity (e.g., none/mild/moderate/severe) over the time period matching the assessment period of the target COA endpoint (e.g., past 7 days, etc.)
  - Global Impression of Change
    - Assessing change in disease severity (e.g., much better/a little better/no change/a little worse/much worse) since beginning the study

- Consider including anchor scales from multiple perspectives:
  - Patient, if age-appropriate (generally ≥ 8 years) and cognitively able
  - Caregiver, if conducting a pediatric study
  - Clinician

eCDF Curve Example

Where change in score from baseline to primary timepoint = [score at primary timepoint] - [baseline score]
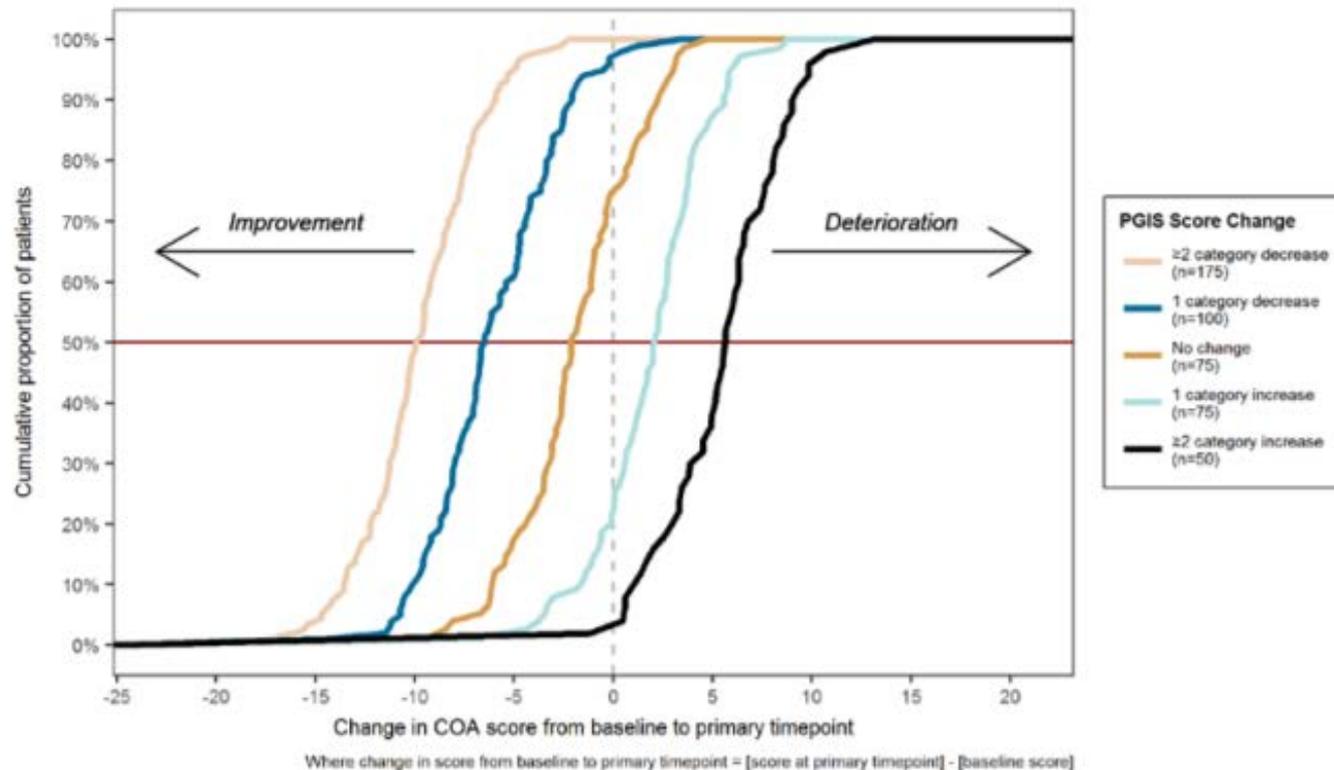
Properties of Anchor Scales

- Anchor scales should be easily interpretable
  - Verbal response scales are recommended over visual analogue scales and numeric rating scales

- Anchor scales should measure similar concepts as the target COA endpoint
  - Anchor scales should focus on the disease-related concepts of interest and not be overly general or vague (e.g., asking about "overall health")

- Anchor scale recall periods should be consistent with the assessment period of the target COA endpoint

Qualitative Approaches

- Qualitative data can provide valuable context and detail regarding patients' experiences with treatment, including how they did (or did not) experience clinical benefit

- Consider conducting exit interviews (or surveys)

- Qualitative data are especially useful when anchor-based analyses are difficult to interpret (e.g., if sample sizes are small)

Exit Interviews

- Exit interviews can explore, for example:
  - How patients (and their environment) changed during the trial
  - Whether patients believe they experienced meaningful improvement, worsening, or no change
  - Whether patients believe they were assigned to the treatment or placebo group
  - What "meaningful improvement" means for each sign/symptom/impact

Resources

- 2009 Patient-Reported Outcome Measures guidance*
- Patient-Focused Drug Development (PFDD) guidance series**
    - Guidance 1: Collecting Comprehensive and Representative Input
    - Guidance 2: Methods to Identify What is Important to Patients
    - Guidance 3: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments
    - Guidance 4: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision-Making

* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims

** https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

Conclusions

- Quantitative and qualitative approaches provide evidence to support COAs and inform determination of clinical benefit and meaningful change

- Talk with FDA early regarding plans to assess clinical benefit and meaningful change

- Refer to FDA's PFDD guidance documents when planning your COA measurement strategy

BREAK

15 MINUTES

PANEL DISCUSSION AND Q&A

Gluten Challenges and Unintentional Exposure in Clinical Care

Joe Murray, MD
Mayo Clinic

COI statement

- Dr. Joseph Murray has received study grants from Nexpep/ImmusanT, National Institutes of Health, Immunogenics, Johnson & Johnson, Kanyos/Anakion, Takeda Pharmaceutical, Allakos, 9Meters, Oberkotter, and Cour; consultancy fees from Bionix, UKKO, GSK, Amgen, Dren Bio, Dr. Schar USA, Chugai Pharma ; holds patents licensed to Evelo Biosciences; and receives royalties from Torax Medical.

Outline

- Clinical uses of prescribed gluten challenge
  - Initial diagnosis (pt on GFD)
  - Confirm permanent nature of gluten response
  - Uncertainty in diagnosis (seronegative, or sero not done)
- Gluten exposures in real life of patients with celiac disease
  - Threshold (FDA Codex < 20PPM,) microdose studies
  - Frequency, causes, detection, consequences
  - Verification
    - Dietary interview: CDAT
    - Histological and serological* effects
    - Measurement in Foods ingested
    - GIPS* in stool and urine
    - ARs* in plasma

*None of these have been FDA approved or cleared for Celiac disease management

Choung et al, APT, 2017;Leffler et al. CGH 2009;

Current use of Gluten Challenge in Diagnosing Patients on a Gluten Free Diet

- Reduced sensitivity of serology/bx
- HLA genotyping high NPV
- Consider complications of CeD, family hx, duration of GFD
- Medically directed gluten challenge
- Patients refusing or unsuitable for challenge managed as CeD

Leffler et al. Gut , 2013; Rubio-Tapia et al. AJG 108(5):656-676, 2013.
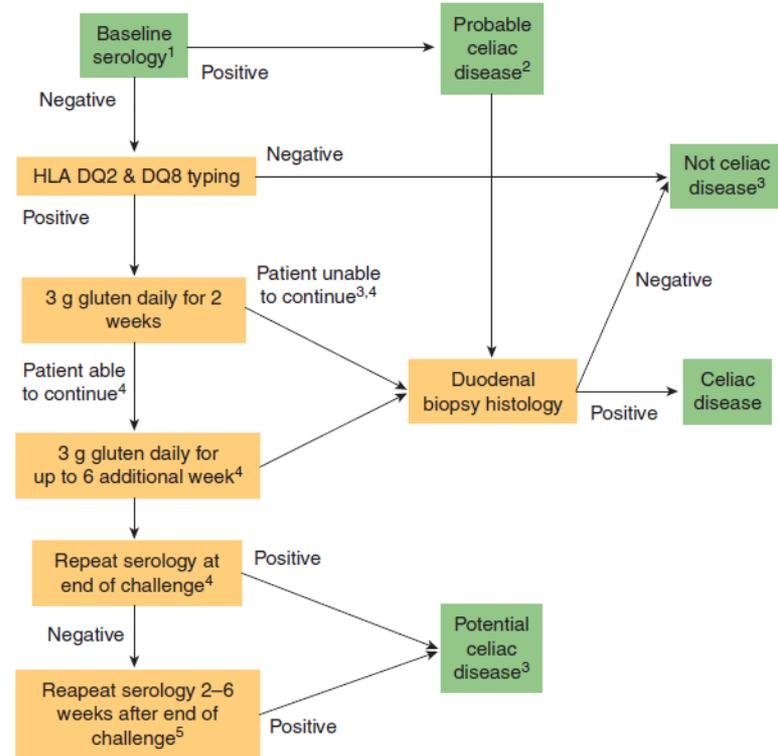
Contraindications to Challenge

- Anaphylactic response to gluten/ wheat
- Neurological associations pf celiac disease (ataxia, seizures, severe peripheral neuropathy, depression, cognitive impairment)
- Relative contraindications
  - ? Age critical to development or child bearing
  - Very severe or persistent symptoms reported with prior short term gluten exposure

- Do we really need to challenge the new adult? (diagnosed without biopsy as a child who met ESPGHAN criteria)

Husby et al.

Outcomes from Gluten Challenge

- Symptoms start < 6 hours after first dose:
  - Gi and Non-GI
  - Nocebo effect
  - Complex foods: FODMAPS , lactose, fat…
- Serology
  - Slow(weeks) and uncertain:
- Histology
  - Trade off between dose and duration (high dose for 2-4 weeks versus moderate dose (3-6grams) for 6 weeks)
  - Baseline biopsy might still show damage (avoid challenge) and is useful for comparison with post challenge
  - If no baseline biopsy then clear pathological changes are needed

Sarna ET AL, Gut 2018 Leffler 2012, Leonard et al. 2021

Recent Gluten Challenge Trial

Leonard. Silvester, J, et al. Gastro, 2021
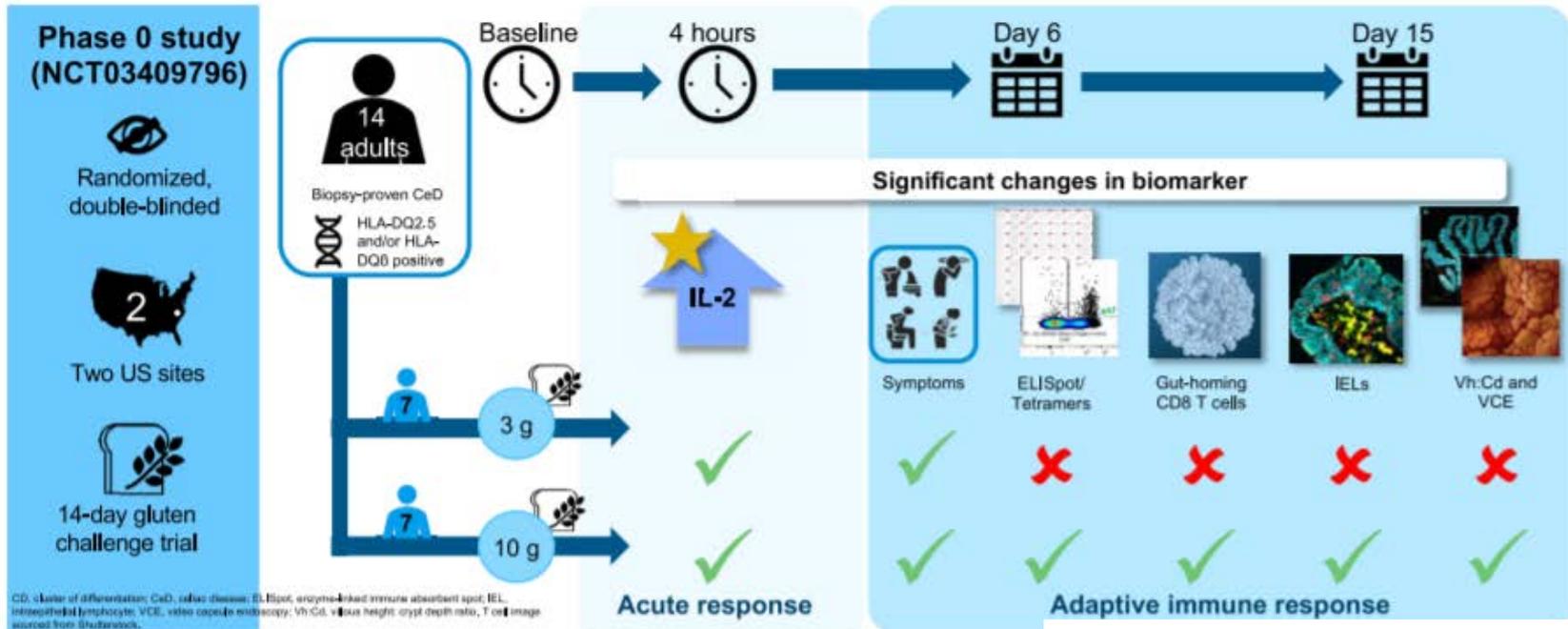
Follow Up Of Celiac Disease

- Symptoms resolve in 1-3 months
- Serology level fall substantially in 6 months and often negative at 1 year
- Biopsies improve more slowly in adults than children
- Re-biopsy in 1-2 year may be performed in adults
- Dietitian follow up for adherence is ideal but rarely done
- Physician interest is crucial
- In reality: little or no follow up is common

Murray et al, AJCN 2004, Herman et al. CGH 2012 Rubiotapia AJG 2012

Recommendations for Follow-Up bxs

‣ Routine biopsies may be considered in adults with CD,
         may identify patients at increased risk of lymphoma. (Grade B)

‣ Not mandatory for patients doing well on GFD and lack other features that suggest an increased risk of complications. (Grade C)

‣ Needed in patients with CD whose condition does not respond to a GFD. (Grade C)

Ludvigsson et al: Gut 2014
Rubiotapia etal. ACG Guidelines 2013

Non Responsive now known as "Slow-to-Respond " Celiac Disease

A patient with a diagnosis of celiac disease with persistent or recurrent symptoms despite self-declared adherence to a gluten free diet (GFD).

Al-toma et al. UEGJ, 2019

Non Responsive Celiac Disease

- *Primary*: no initial response to gluten free diet
- *Secondary*: relapse following initial response
- 17% of celiacs at a support group had diarrhea[1]
- 18.7% of a referral center population[2]
  - 9.9% of primary patients
  - 35% of referral patients

[1]*Fine et al. Gastro, 1997.* [2]*Leffler et al. CGH, 2007*

Symptoms In Non-responsive CD
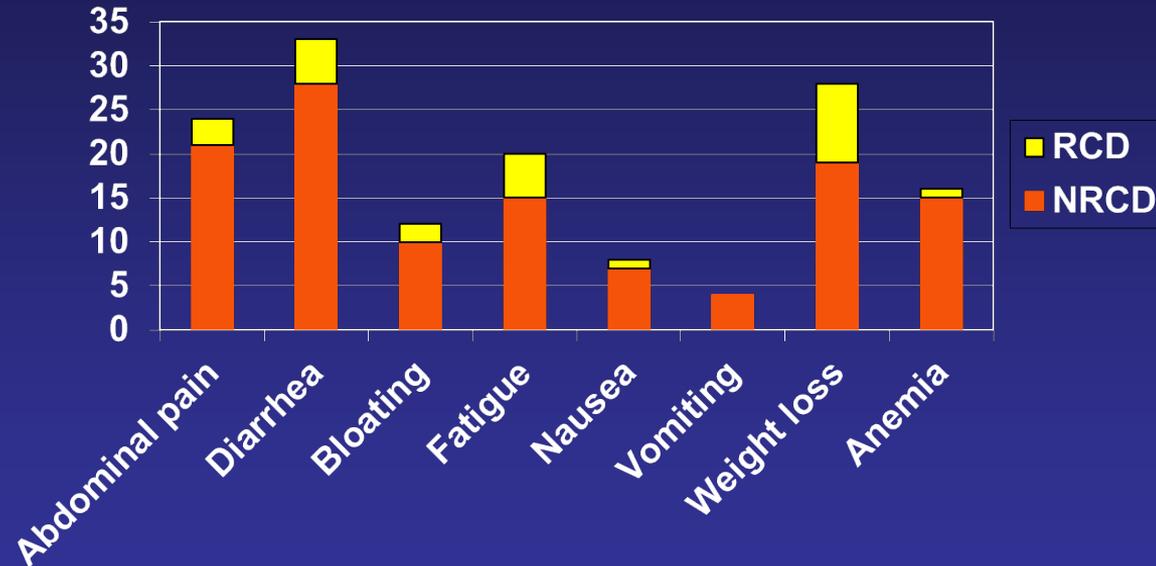
Abdulkarim et al. 2002
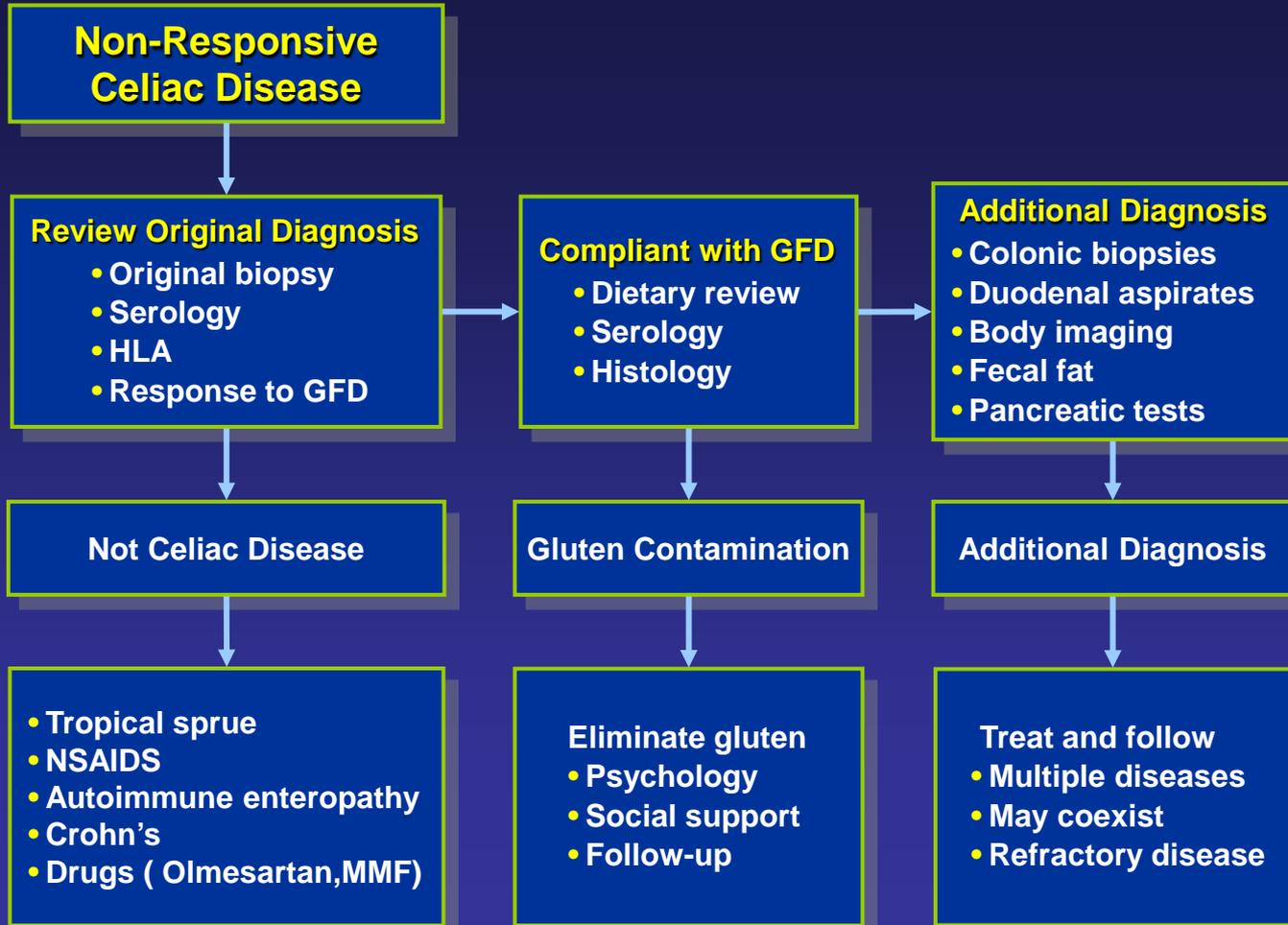
Rubio-tapia et al. CGH 2011

Gluten Exposure in celiac disease patients

New York Times February 4, 2013

Adherence to the gluten-free diet
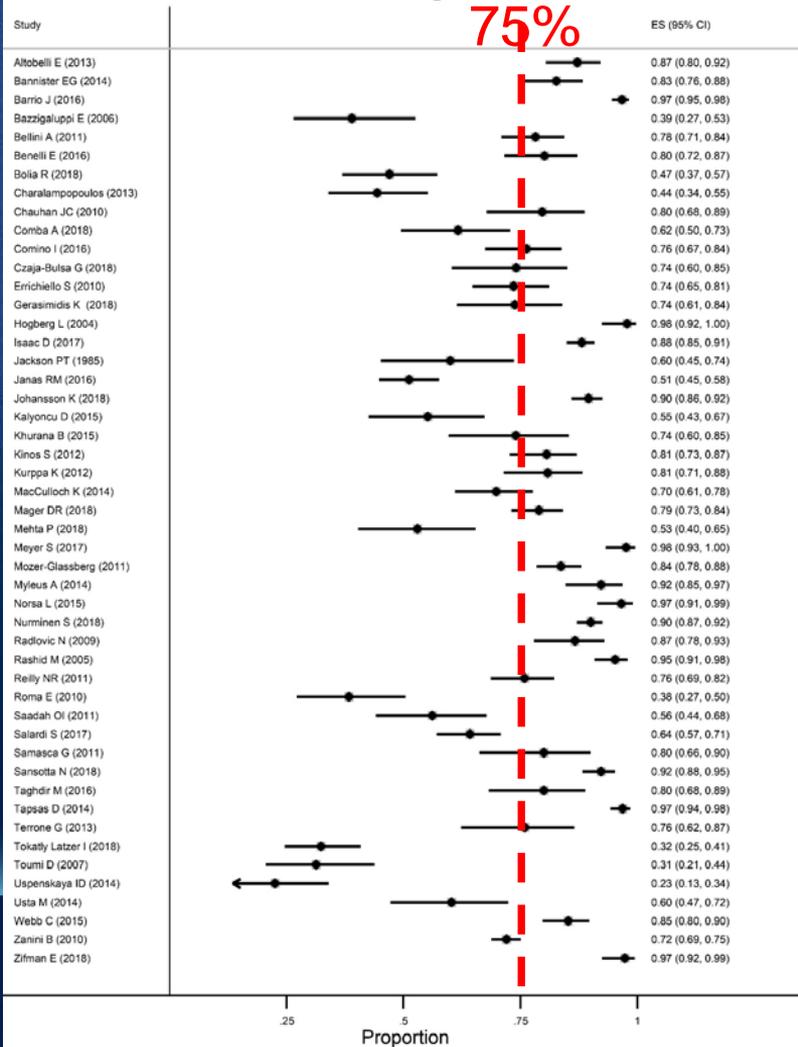
Adherence is highly variable
Accidental and/or deliberate are common

Biomarkers for contamination (Silvester)

Myleus , Reilly and Green ,
CGH 2020
Hall et al. Apatite, 2013

151

Why do gluten exposures occur?

- Deliberate or knowing intake
  - Taste, cost, depression, lack of support, risk taking, not wanting to be different , accessibility, hunger
  - Diagnosis in adolescence
  - Self regulatory efficacy

- Accidental
  - Eating out, labelling,
  - Missed ingredients
  - Prepared foods

Dowd et al.   J of Hu Nutr and Diet, 2015

Consequences of Gluten Exposure in Celiac Disease

Gluten	Single Dose	3-7 days	2-6 weeks	1 year +	Decades
Onset/duration	Immediate Short lived	Delayed/ variable	Slow/ prolonged	Variable chronic	Slow or abrupt/ catastrophic
Impact	-/+	+/++	+++	+++	++++
Mechanism	Tissue resident T-cells→cytokines	T- cell proliferation, B-cells expansion	Inflammation CD8 CTLs Enterocyte damage Villous damage	Ulcers, strictures, Dysmotility gastroparesis Vitamin depletion	Neoplastic transformation Neurological injury
Symptoms+ consequences	Abdominal pain, bloating, gas, nausea, vomiting*, diarrhea fatigue, headache	GI symptoms, headache, fatigue, DH	Lactose intolerance, steatorrhea, Weight loss, anemia, weakness, bruising bleeding,	Obstruction, gastroparesis, weight loss , Steatorrhea peripheral neuropathy,	EATL, Adenocarcinoma Dementia, ataxia,
Measures	Il-2 other cytokines	Peripheral responses	VH:CD, antibodies, enterocyte function	Imaging, VHCD, nutrients	Imaging, VH:CD, Molecular testing survival

Detection/Verification of Gluten Exposure

- Patient self report: admit to eating gluten
- ? Accidental: based on symptoms reported after eating out ?
- Collateral support for the actual gluten (review of ingredients, admission by food server, etc)
- Objective patient testing
  - Urine/stool testing for GIPS(available for pt use)
  - Alkyl resorcinols in plasma(research only)
  - Serology (widely used off label)
  - Biopsy (in symptomatic patients)
- Food analysis
  - Food safety lab (G12 or other testing) (used most often by food industry)
  - Self testing kits (occasional use but clunky)
  - Nima device (very sensitive)
  - Doggy bag study *

Choung et al. APT 2016
*Silvester et al. APT 2020

Serological Monitoring for Gluten Exposure

- Serology tested at diagnosis, 3-6 months, 12 months, and yearly thereafter and with symptoms

- Persistent positive 1 year serology usually indicates gluten exposure
  - Predicts ongoing histology damage

- Lacks sensitivity for damage

- Thresholds developed for diagnoses not for healing or gluten exposure

- High negative serology "detectable" may indicate higher likelihood of damage than undetectable*

rubiotapia etal. AJG 2013
*fang et al. APT 2017,

Management of Sequela of Gluten Exposures

- Many exposures likely have little or no acute symptoms
- Anti-diarrheals after clearance of gluten
- Anti emetic drugs
- Reflux, dyspepsia: antacids, acid blockers
- Headaches: acetaminophen….
- Weakness: hypokalemia, dehydration
- Rarely hospitalization for celiac crisis
  - IV fluids , steroids, HPN
- Long term: Dietary intervention

Celiac Crises: Jamma et al. , CGH 2010

Summary

- Gluten exposures are common and often recognized by patients
- Consequences are variable and uncertain
- Verification of the exposure is often been lacking
- In gluten challenges, symptoms often happen quickly (< 6 hours in 2/3rds of patients)
- Histological damage is dependent on dose and duration, (2 weeks at 10gm/day)
- Seroconversion is delayed for weeks
- Symptoms often preclude sufficient duration of challenge to produce damage in clinical practice

Leffler, AJG 2012,, Daveson et al. APT 2019 , Leonard, gastro 2021, Murray e al. Gastro 2017

Dose and duration of gluten exposure that elicits clinical signs/symptoms and changes in histology

Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics VI (GREAT VI) Workshop on Celiac Disease

July 22nd 2021

Jason Tye-Din MD, PhD, FRACP

Head, Coeliac Disease Research Lab, Walter and Eliza Hall Institute

Gastroenterologist, The Royal Melbourne Hospital

Principal Research Fellow, The University of Melbourne

Secretary, International Society for the Study of Celiac Disease

Chair, Medical Advisory Committee, Coeliac Australia

Disclosures

- JT-D is privately or via employer a consultant and/or an advisory board member for Chugai Pharmaceuticals, Genentech and Janssen and has undertaken sponsored research with ImmusanT Inc.

- Inventor on patents relating to the use of gluten peptides in celiac disease diagnosis and treatment

Gluten challenge in the literature

- **Gluten challenge** in treated celiac disease is a useful tool to examine symptoms, serologic, histologic and immune changes to gluten

  (i) Diagnostic evaluation
  (ii) Examine disease pathogenesis
  (iii) Pre-clinical drug discovery and validation
  (iv) Establish proof of concept (Ph. I) or examine efficacy and dose-ranging (Ph. II) of novel therapies that protect against gluten-induced effects

- Generally, does not mimic real life effects of treated CeD patients exposed to gluten i.e. higher dose, sustained *versus* lower dose, intermittent

- > 50 published studies employing gluten challenge in CeD/suspected CeD
- Wheat gluten: variable dose, duration and form
- Variable inclusion criteria e.g. age, time on GFD, baseline disease activity status

Histology with gluten challenge: academic studies
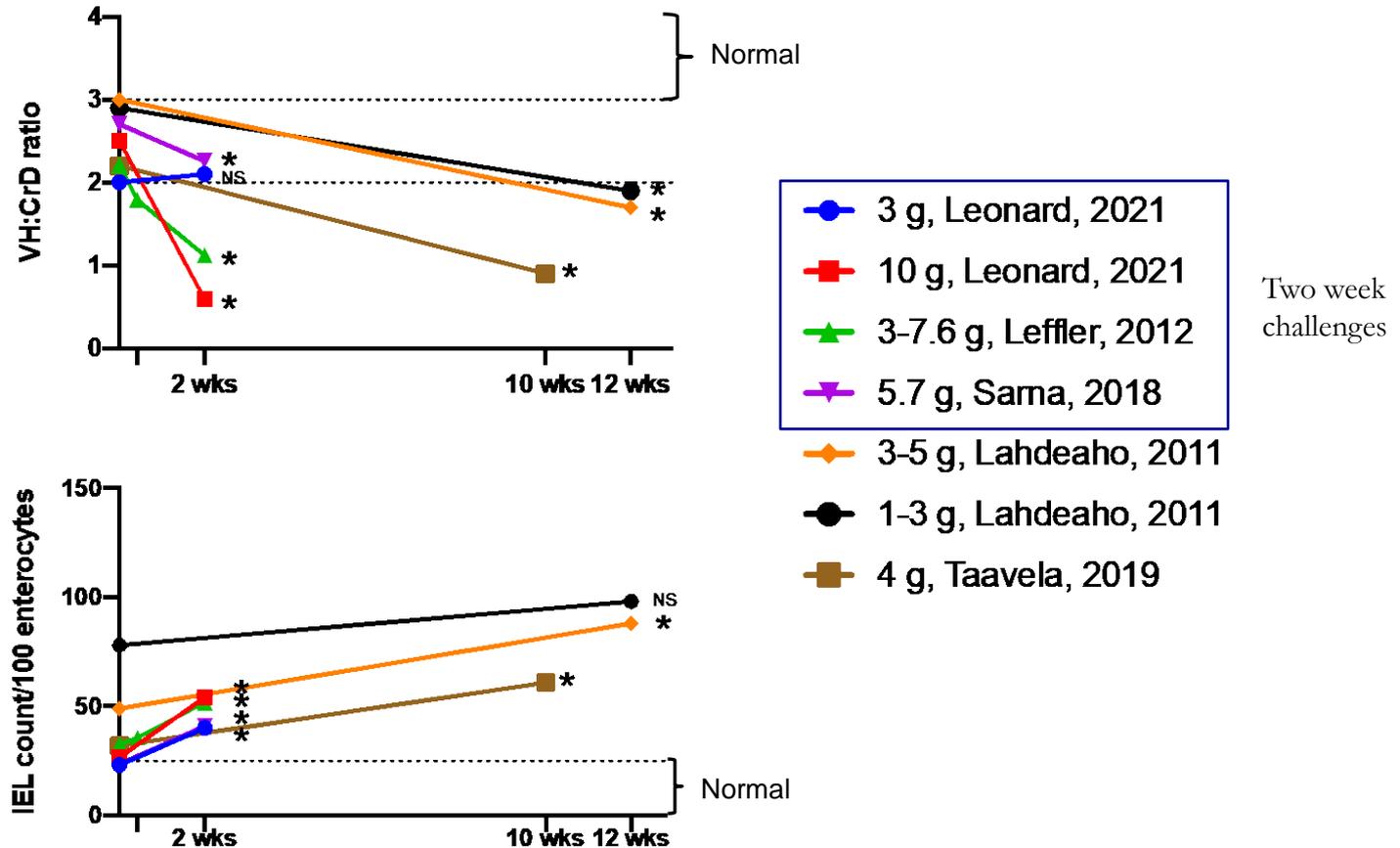
Lähdeaho et al, BMC Gastro 2011; Leffler et al, Gut 2012; Sarna et al, Gut 2018; Taavela et al, BMC Gastro 2019; Leonard et al, Gastroenterology 2021

Histology with gluten challenge: trials under GCP conditions
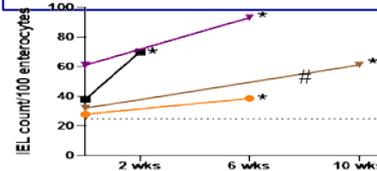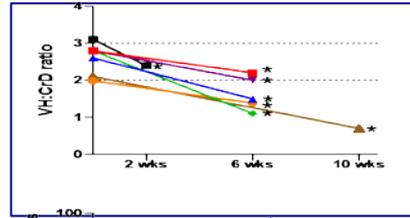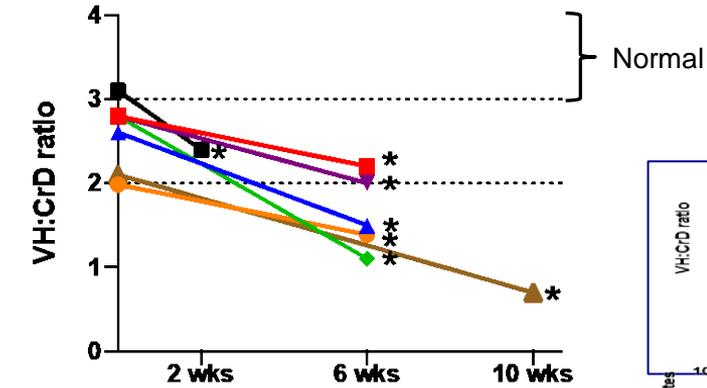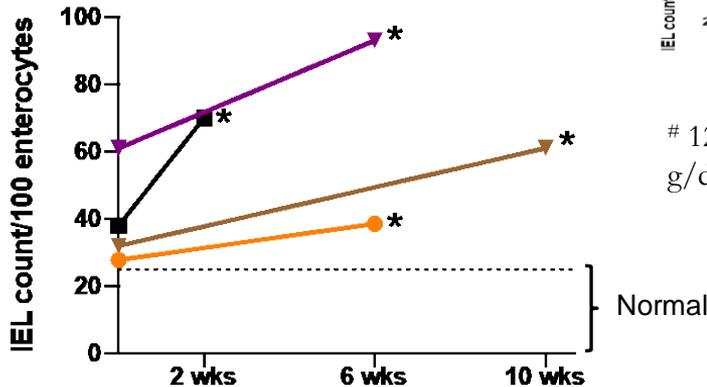
Observations

- High rate of baseline damage by "traditional" criteria

- Early responses detectable

- Mucosal relapse increases with **dose** and/or **duration** of challenge

- Heterogeneity

12 g/d for 3 days then 6 g/d

Lähdeaho et al, Gastro 2014; Lähdeaho et al, Lancet Gastro Hep 2019; Kelly et al, Gastroenterology 2021, Schuppan et al, NEJM 2021

Baseline disease activity: implications for challenge

- Baseline damage by "traditional" criteria of VH:CrD <3.0 is common – but normal cut-off may be lower using quantitative morphometry

- **CeliAction Study** *(Murray et al, Gastroenterology 2017; Adelman, Am J Gastro 2018)*
  - N=1345 treated, symptomatic CeD patients
  - Baseline: 38% VH:CrD ≤2.0

- **RESET-CeD Study** *(Daveson et al, Gastrohep 2019)*
  - N=93 <u>well treated</u> US, Australian, NZ CeD patients
  - Baseline: 60% VH:CrD <2.0; 90% negative tTG serology
- Altered intestinal transcriptional profile even in normal CeD mucosa *(Dotsenko, CMGH 2021)*

Complex non-linear relationship between VH and CrD *(Daveson, Gastrohep 2019)*

Baseline disease activity: implications for challenge

- Baseline damage by "traditional" criteria of VH:CrD <3.0 is common – but normal cut-off may be lower using quantitative morphometry

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- Altered intestinal transcriptional profile even in normal CeD mucosa *(Dotsenko, CMGH 2021)*

Complex non-linear relationship between VH and CrD *(Daveson, Gastrohep 2019)*

Baseline disease activity impacts response to gluten challenge
- In *Sarna, Gut 2018* cohort, histologic <u>responders</u> had low-level tissue inflammation at baseline with increased intestinal gluten specific T-cells and a low-level circulating inflammatory profile *(Stamnaes, Adv Sci 2021)*
- Stronger immune responses (interleukin-2) to single-dose gluten seen in CeD patients with greater baseline histologic activity *(Tye-Din, BMC Med 2021)*
- Longer gluten challenge regimens e.g. 10 weeks may provide more uniform mucosal response

Overcoming heterogeneity with histologic readouts

- **Gluten challenge factors**
  – Amount and duration of challenge: low doses and shorter periods more variable
  – How is gluten content measured? Need to harmonize methods *(Schall, Front in Plant Science 2020)*
  – Gluten formulation: food matrix effects e.g. liquid vs solid, composition

- **Analytical factors**
  – Site of biopsy collection (proximal vs distal), histological parameters, quantitative morphometry SOP, specialty provider

- **Patient factors**
  – Baseline disease activity
  – Biological sensitivity: consider HLA gene dose, ?sex, ?age
  – Medications e.g. NSAIDs, immunosuppressants

Symptoms with gluten challenge: trials under GCP conditions

Drug	Gluten	Dose / duration	Placebo gluten	PRO
Larazotide[1]	Gluten capsules (2, 3x/d)	2.4 g/d for **2 weeks**	Yes double-blind	GSRS, CeD GSRS
Larazotide[2]	Gluten capsules (2, 3x/d)	2.7 g/d for **6 weeks**	Yes double-blind	GSRS, CeD GSRS
ALV003/ Latiglutenase[3]	Baked gluten in meal 3x/d	2 g/d for **6 weeks**	No	GSRS
AMG 714[4]	Cookies (Rusks or cake breads) 2x/d	2-4 g/d for **10 weeks**	Yes single-blind prior to gluten	CeD GSRS
ZED1227[5]	Gluten biscuit	3 g/d for **6 weeks**	No	CSI
Nexvax2[6]	Gluten powder in flavored drink	11 g **single dose**	Yes double-blind and open-label	CeD PRO GloSS

[1]Leffler, Am J Gastro 2012; [2]Kelly, APT 2012; [3]Lahdeaho, Gastro 2014; [4]Lahdeaho, Lancet Gastro Hep 2019; [5]Schuppan, NEJM 2021; [6]Daveson, APT 2019; Tye-Din, APT 2019; Tye-Din, BMC Med 2020. TAK-101 data (Kelly, Gastro 2021) not included as symptom data not reported.

Symptoms with gluten challenge: trials under GCP conditions

Drug	Gluten	Dose / duration	Placebo gluten	PRO	Most common symptoms	Onset	Tolerability
Larazotide[1]	Gluten capsules (2, 3x/d)	2.4 g/d for **2 weeks**	Yes double-blind	GSRS, CeD GSRS	50% symptomatic; Indigestion, abdominal pain, diarrhea	Increased rapidly over 14 days	Well tolerated; low sham gluten response
Larazotide[2]	Gluten capsules (2, 3x/d)	2.7 g/d for **6 weeks**	Yes double-blind	GSRS, CeD GSRS	80% symptomatic; Indigestion, abdominal pain, diarrhea, constipation	Increased over 3 weeks then plateaued	Early withdrawal of some
ALV003/ Latiglutenase[3]	Baked gluten in meal 3x/d	2 g/d for **6 weeks**	No	GSRS	Indigestion, abdominal pain	Consistent increases to wk 6	Drop outs at 1.5 g to 3g (none at 6 g) from nausea, vomiting, distension or diarrhea < 1 wk
AMG 714[4]	Cookies (Rusks or cake breads) 2x/d	2-4 g/d for **10 weeks**	Yes single-blind prior to gluten	CeD GSRS	Distension, pain, diarrhea	CeD PRO scores peaked at wk 8 then fell	1 drop out due to poor tolerability
ZED1227[5]	Gluten biscuit	3 g/d for **6 weeks**	No	CSI	Score increased to week 6 and returned to BSL at week 10	CSI increased to wk 6	1 withdrawal in placebo-treated gluten challenge arm
Nexvax2[6]	Gluten powder in flavored drink	11 g **single dose**	Yes double-blind and open-label	CeD PRO GloSS	Nausea (61%), vomiting (44%), diarrhea (28%), tiredness (22%), headache, pain	Symptoms peaked at 2-3 hours	Well tolerated; low sham gluten response (? Due to low FODMAP content)

[1]Leffler, Am J Gastro 2012; [2]Kelly, APT 2012; [3]Lahdeaho, Gastro 2014; [4]Lahdeaho, Lancet Gastro Hep 2019; [5]Schuppan, NEJM 2021; [6]Daveson, APT 2019; Tye-Din, APT 2019; Tye-Din, BMC Med 2020. TAK-101 data (Kelly, Gastro 2021) not included as symptom data not reported.

Overcoming heterogeneity with symptom readouts

- **Gluten challenge factors**
  - Amount and duration of challenge
  - Gluten formulation: food matrix effects, taste, effect of fasting

- **Patient-reported symptoms are not always caused by gluten**
  - IBS is common in CeD and can be triggered by non-gluten food components e.g. wheat fructan (a type of FODMAP) *(Halmos, Gastroenterology 2014; Roncoroni, Nutrients 2018)*
  - Controlling for FODMAP content important
  - Need to understand symptoms triggered by gluten-free FODMAPs in CeD

- **Patient expectations versus experience**
  - Patients often expected diarrhea after gluten but only nausea and vomiting were more common after gluten than placebo challenge and linked to immune activation *(Daveson, APT 2019; Tye-Din, APT 2019)*
  - Implications for PRO development based on patient recall of "exposure related symptoms"
  - Screening challenge at enrolment may help define symptomatology

Overcoming heterogeneity with symptom readouts

- **Nocebo effect**
  - Effects minimal in two studies employing double-blind, placebo-controlled gluten challenge *(Leffler, Am J Gastro 2012 (2 week challenge); Daveson, APT 2019 (single dose challenge)*
  - Patient anticipation will be impacted by likelihood of gluten intake and gluten dose

- **Effect of recent gluten exposure**
  - Symptoms and immune stimulation (interleukin-2) more prominent following a repeat gluten challenge 5 months later *(Tye-Din, BMC Med 2020)*. Boosting effect?
  - More data needed on effect of baseline disease activity on gluten-induced symptoms

- **Symptom heterogeneity means robust samples sizes important**

Immune readouts with gluten challenge

FDA: Not a primary outcome measure but provides important complementary data

- **CeD serology**
  - Key readout of disease activity
  - Response to gluten variable e.g. tTG/DGP seroconversion day 28 after 2 wk challenge (3 - 5.7 g/d) in 10 - 75% *(Leffler, Gut 2013; Sarna, Gut 2017);* tTG seroconversion after 6 wk challenge (3g/d) in 16% *(Schuppan, NEJM 2021)*
  - Dose-dependence: faster relapse with higher dose; time on GFD may impact time to relapse

- **Gluten-specific T cells** - the pathogenic cell driving CeD
  - Potential roles: Proof of concept, immunomonitoring, assessment of target engagement
  - Measurable in blood after short-term (3-day) gluten challenge *(Anderson, Nat Med 2000)*
  - Detectable without gluten challenge using tetramers *(Sarna, Gastroenterology 2018; Christophersen, UEGJ 2014)* or whole blood cytokine release assay *(Anderson, CEI 2021; Hardy, Frontiers in Immunology 2021)*
  - Circulating **interleukin-2** 4 hours after single-dose gluten challenge: first biomarker to correlate with onset and magnitude of symptoms to gluten *(Goel, Sci Adv 2019; Daveson, APT 2019; Tye-Din, APT 2019)*

Evaluating Responses to Gluten Challenge:
A Randomized, Double-Blind, 2-Dose Gluten Challenge Trial

From *Leonard et al, Gastroenterology 2021*
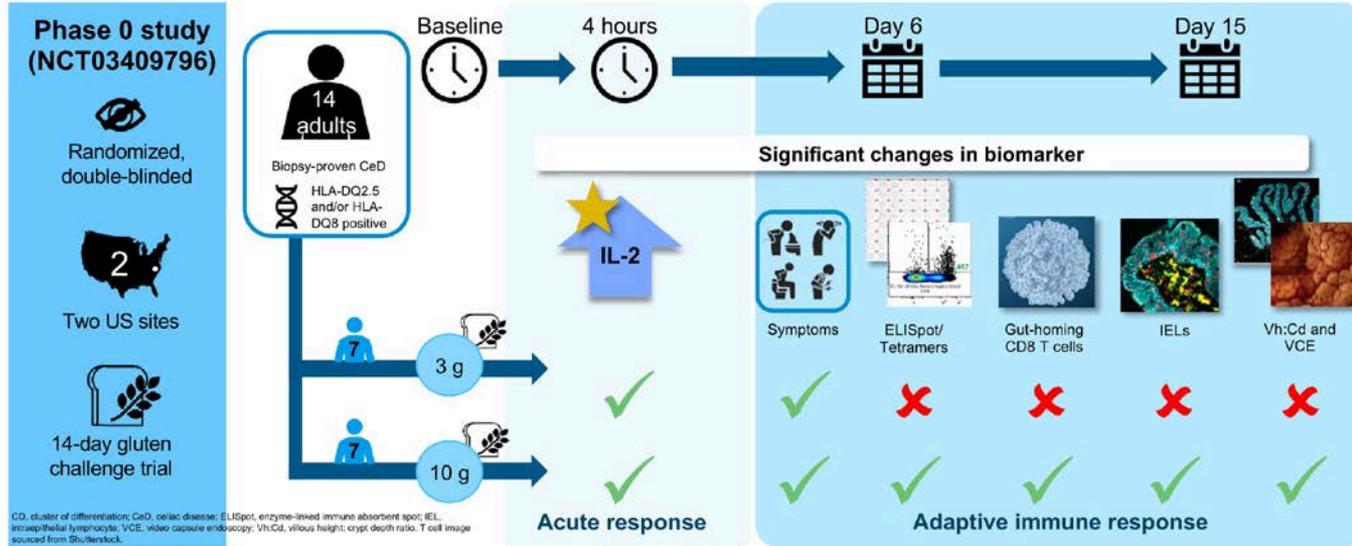
- Interleukin-2 (IL-2) response consistently measurable with low-dose gluten challenge
- Potential role as a secondary endpoint

How to make gluten challenge meaningful for drug development

- **A standardized and controlled approach to gluten challenge**
  - Minimise sources of heterogeneity
  - Need consensus on optimal readouts (index) for mucosal histology

- **Baseline healing rates are low and inflammation in "healed" mucosa is common**
  - Is gluten challenge needed when there is already damage present? If not, perhaps a better question is does the investigational product improve upon standard therapy?
  - How should baseline biopsies inform stratification?

- **PROs to reliably demonstrate changes in symptoms caused by gluten**
  - Acute gluten exposure PRO needed; verify symptoms are caused by gluten via placebo-controlled exposure +/- objective immune readout e.g. interleukin-2
  - Validation in pediatric populations
  - PROs that encompass extraintestinal manifestations of CeD

- **Optimization, validation and incorporation of gluten-specific biomarkers into trial design**

Incorporation of Gluten into Celiac Disease Clinical Trials: An Industry Perspective

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CELIAC RESEARCH PROGRAM
HARVARD MEDICAL SCHOOL

Disclosures

- Employee Takeda Pharmaceuticals
- Executive Committee Foundation for Celiac Disease Outcome Measures

A Patient Perspective

"Studies with gluten put more burden on patients, and investigators need to have the knowledge and resources to help with any issues. However, as much as I really didn't love having to eat gluten for the study, I don't think I would really trust the results of a study without gluten since I wouldn't know what it was treating or how much it would protect me from." Patient Advisor

Gluten Exposure has Always been a Critical Component of Celiac Disease Clinical Care and Research

Coeliac Disease

II. The Presence in Wheat of a Factor Having a Deleterious Effect in Cases of Coeliac Disease

by W. K. DICKE, H. A. WEIJERS and J. H. v. D. KAMER

basic principle of current opinion on the dietary treatment of
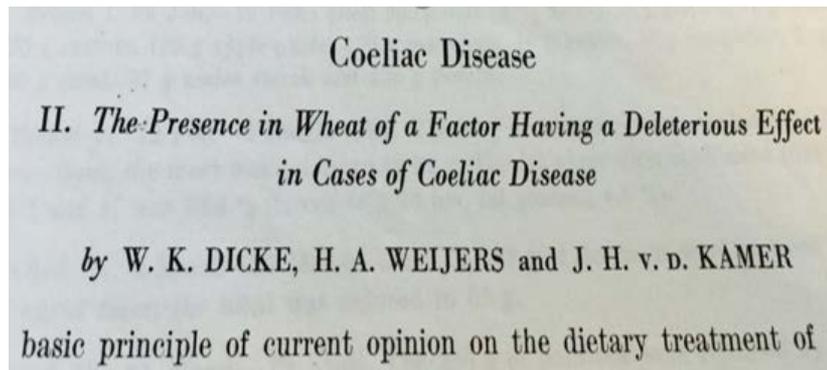
Source: Acta Paed 1953
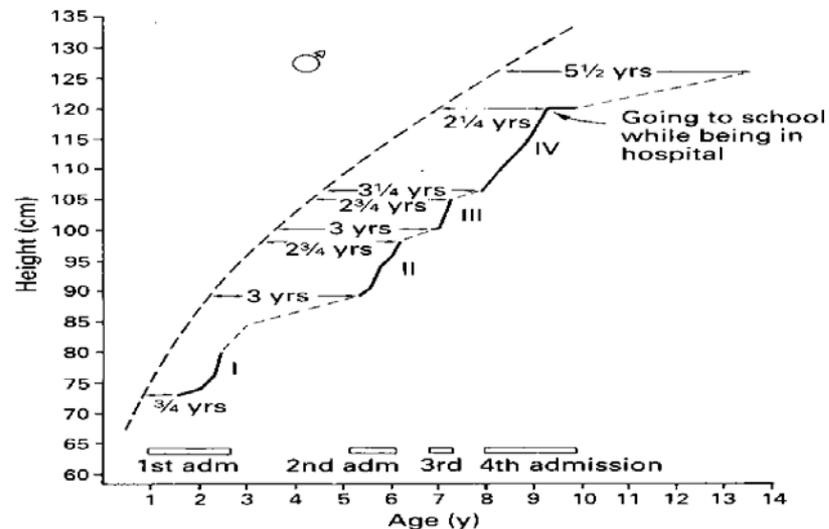
'the only decisive criteria are the abnormal morphology of the small intestinal mucosa, its normalisation on gluten withdrawal, and the reaction on reintroduction of gluten.'

McNeish et al Diagnosis of Coeliac Disease, Arch Dis Childhood 1979

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Monitored Gluten Exposure is Generally Safe

Acute damage ≠ chronic damage

Acute gluten exposure ≠ chronic gluten exposure

Gluten is one of the most important research tools in celiac disease and has been used for >70 years

Gluten exposure in a carefully monitored study is <u>safe</u>

What gluten exposure in a study can cause:

- Symptoms; GI and non-GI
- Immune activation
- Elevations in celiac serologies (tTG)
- Small intestinal mucosal injury

What gluten exposure in a study will not cause:

- Increased risk of long-term complications
- Permanent damage to the small intestine
- Ongoing symptoms after the study is complete

When is gluten challenge generally not recommended:

- If you are pregnant or planning on pregnancy in the near future
- If you have a severe celiac-related neurological condition such as gluten ataxia
- Type II Refractory Celiac Disease

GI, gastrointestinal.

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Lessons Learned from Clinical Trials in Celiac Disease to Date

- We can predict protection from gluten induced immune activation based on known CeD pathophysiology and effect in animal models
- Therapeutic effect in gluten challenge studies can be difficult to reproduce in active CeD treatment studies
  - Very large clinical trial effect
  - Very difficult to confirm that ongoing symptoms are to gluten/CeD
  - Mis-diagnosis of celiac disease
- Histologic response is both gluten dose and duration dependent but with diminishing returns with >14 days and >5 grams gluten/day
- Small intestinal mucosal assessment is critical to understanding the effect of therapy but questions remain about interpretation
- Histologic and symptomatic response to gluten challenge is highly variable due to both patient heterogeneity and inherent limitations of traditional histology but not due to gluten source
- Drop out of ~10% due to gluten related symptoms can be expected with gluten doses >1 gram per day. Drop out is generally in the first few days of exposure and does not appear to be highly gluten dose dependent
- Patients are engaged and willing to participate in celiac research; even in studies with gluten, invasive procedures and multiple visits, however appropriate support is required

Gluten Challenge vs. Gluten Exposure: Different Concepts with Different Goals

- Gluten challenge: Defined as <u>daily high dose gluten exposure</u> (3-12 grams / day; equivalent to 2-8 slices of bread/day) with the aim of <u>exacerbating disease activity</u>
  - Uses
    - Studies of the pathophysiology of celiac disease
    - Proof of Concept and dose findings studies assessing therapeutic protection against gluten induced disease activation

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    - Proof of Concept and dose findings studies assessing therapeutic protection against gluten induced disease activation
- Simulated inadvertent gluten exposure: Defined as <u>intermittent low dose gluten exposure</u> (100-500 mg of gluten 1-3x per week; equivalent to accidental gluten exposure) with the aim of <u>assessing therapeutic efficacy in a real-world-like setting</u>
  - Uses
    - Studies of later stage therapies abilities to protect against real-world accidental gluten exposure
    - Reducing clinical trial effects that lead to reduced gluten exposure

Examples of Gluten Challenge and Gluten Exposure Study Designs

Gluten Challenge Study

Study subjects:
Well-controlled CeD
n: 15-30/arm

Primary Endpoint:
Protection from worsening in duodenal histology

Secondary Endpoint:
Protection from worsening in CeD signs and symptoms

Screening

Duodenal biopsy

Run-out/ Safety follow up

~3-6g per day Gluten Challenge

X ← 2-12 weeks → X

X X X X X X X X X X X X X X X X X X X X X X X X

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X X X X X X X X X X X X X X X X X X X X X X X X

Gluten Exposure Study

Study subjects:
Ongoing Active CeD
n: 50-90/arm

Primary Endpoint:
Improvement in CeD signs
and symptoms

Secondary Endpoint:
Improvement in duodenal
histology

Screening

Duodenal biopsy

0.5-1.5g per week gluten in divided doses

Run-out/ Safety
follow up

X X X X X X X X X X X X X X X X X X X X X X X X

X ← 24-52 weeks → X

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Rationale for Simulated Inadvertent Gluten Exposure

- Most therapies under development in celiac disease aim to protect against disease activation due to accidental gluten exposures in patients on a GFD

- Major lifestyle changes, such as participation in a clinical trial (or a pandemic), reduce gluten exposure leading to two significant interpretation risks for trials without administered gluten

Risk 1:
  - Therapy is effective against the reduced amounts of gluten people are exposed in the setting of a trial but is ineffective against higher real-world exposures

Result
  - Drug is approved later found to be ineffective

Risk 2:
  - Therapy is ineffective in a trial as residual symptoms in a background of reduced gluten exposure are less likely to be gluten related, but may have been effective in a real world setting where patients have higher exposures

Result
 - Drug is not approved which may have had clinical benefit
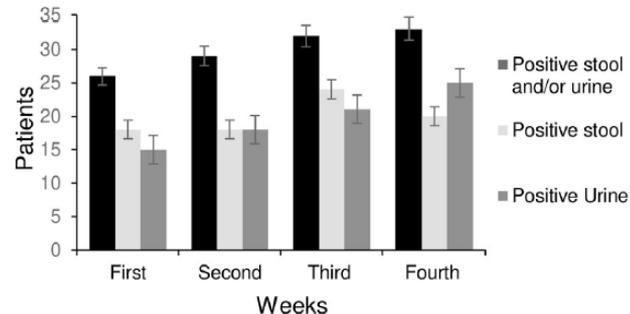
Figure 3. Number of cases excreting gluten immunogenic peptides (GIPs) at each week of the 4 weeks of the study. Patients excreting in stool and urine, or in stool or urine alone (urine: first vs fourth week excretions: $P < .05$).

Source: Stefanolo et al Clin Gastro and Hep 2021

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Operational Considerations for CeD Studies Utilizing Gluten

- Slower enrollment due to concerns with gluten exposure
  - Partnership with Patient Advocacy Groups to provide advice on study materials and recruitment strategy
  - Development of study specific awareness and educational materials
- Potential for missed gluten doses confounding data analysis
  - Emphasize and monitor compliance of gluten similar to drug
  - Use of objective gluten exposure tests e.g. urine and/or stool gluten testing*
- ~10% drop out rate due to gluten related symptoms
  - Site/investigator training to prepare patients and manage symptoms when needed
  - Ensure adequate study power
  - Consideration of strategies for missing data
- Lack of standardization of gluten amount and form
  - Acquire additional data as part of, or in addition to, therapeutic clinical trials
  - Source of gluten does not appear to be a cause of response variability

* These tests are not FDA cleared for monitoring compliance with gluten exposure

Conclusions

- Optimal design of CeD trials providing confidence that positive results will translate into meaningful real-world benefit are not currently established and at this stage, different designs, followed by Post Marketing Studies, may be appropriate
- Gluten exposure is a vital tool in celiac disease research and therapeutic development but when and how to use requires careful consideration
    - Highly valuable in assessing protection from the effects of gluten exposure in many phase 2 and 3 studies
    - Generally not needed/counter-productive in Phase 1 studies and in open label/Post Marketing Studies
- Interventions may have differential impact on histology vs. other endpoints
    - Initial studies with novel modalities should include an assessment of small intestinal mucosal injury
    - Once this correlation is shown, further studies may utilize non-invasive markers however, more studies are needed across multiple development programs to support the use of newer technologies, such as video capsule endoscopy and blood biomarkers
- Gluten challenge studies (precipitation of damage) should be differentiated from gluten exposure studies (maintenance of real-world conditions)
    - Gluten challenge remains the most efficient design for Proof-of-Concept studies and may assist with dose ranging
    - Gluten exposure studies may improve confidence in results of studies of treatment of ongoing active celiac disease

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PANEL DISCUSSION AND Q&A