THE UNIVERSITY OF CHICAGO MEDICINE

Digestive Diseases Center

Grains of Truth: Update on the Diagnosis and Management of Celiac Disease

Carol E. Semrad, M.D., FACG

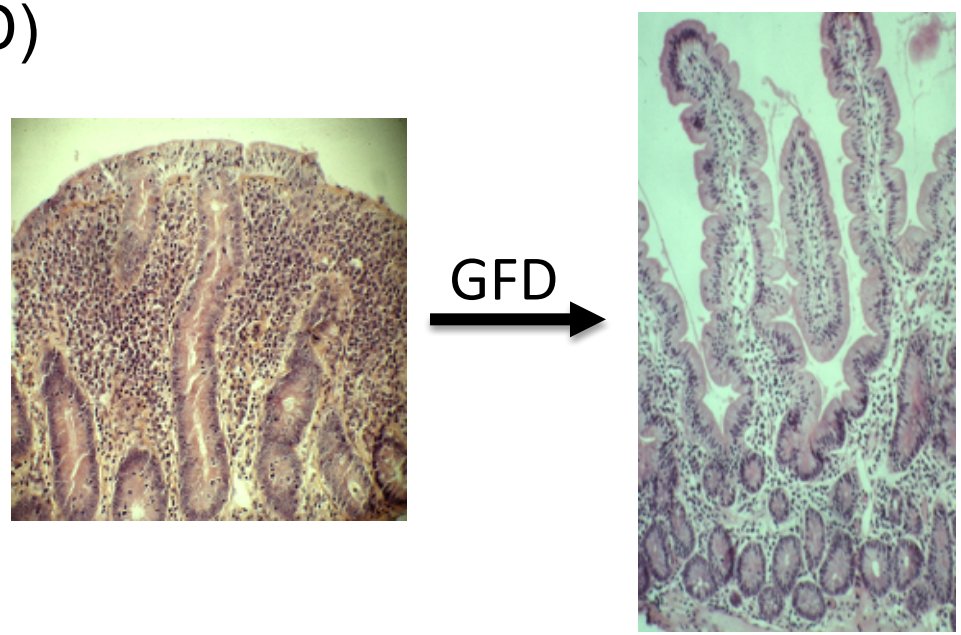
Professor of Medicine

CASE

- 28 y.o. Caucasian man
  - epigastric discomfort with eating, gas/bloating, altered bowel habits
  - sister with Celiac Disease
  - self-started a gluten-free diet 6 mo ago with partial improvement
  - wishes to know if he has celiac disease
- Laboratory tests: CBC, CMP normal
- What to do next?

Celiac Disease (CeD)

- T-cell mediated small bowel inflammation
- Triggered by gluten (wheat, rye, barley) in the diet
- High association with HLA DQ 2,8
- Nutrient malabsorption
- Histologic and clinical recovery on a gluten free diet (GFD)



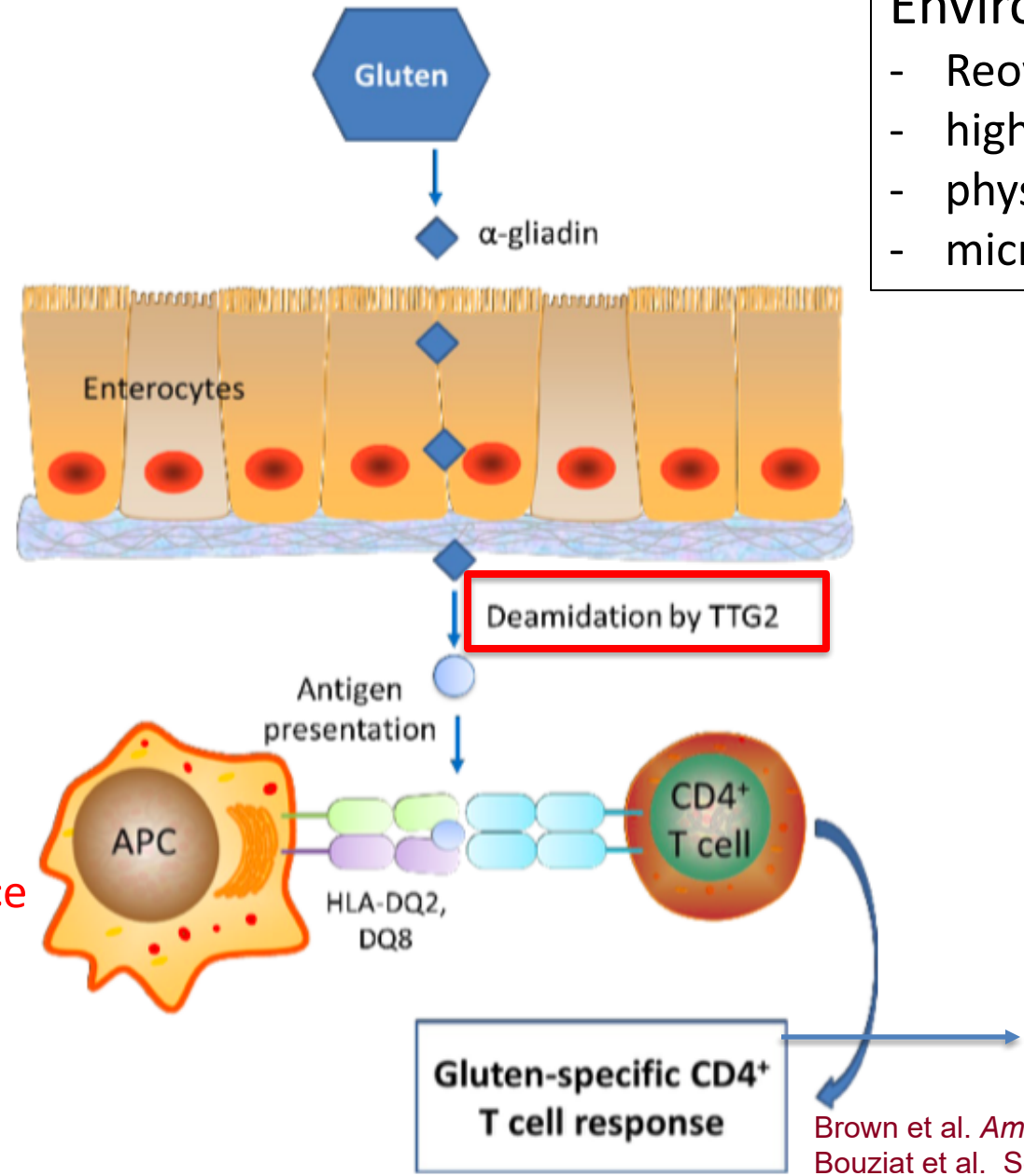
Targets for treatment

- ~~Oral proteases~~

- Tight junction modulator
  IMU-856 Phase 1
  Daveson Lancet Gast Hep 2025;10:44

- TG2 antibodies
  ZED1227 Phase 2b
  Schuppan et al. NEJM 2021;385:35

- Promote oral gluten tolerance
  TPM502 Phase 2a
  Lundin Oral presentation DDW 2025



Environmental Risk Factors

- Reovirus, other infections
- high gluten diet (known risk CD)
- physiologic stress
- microbiome

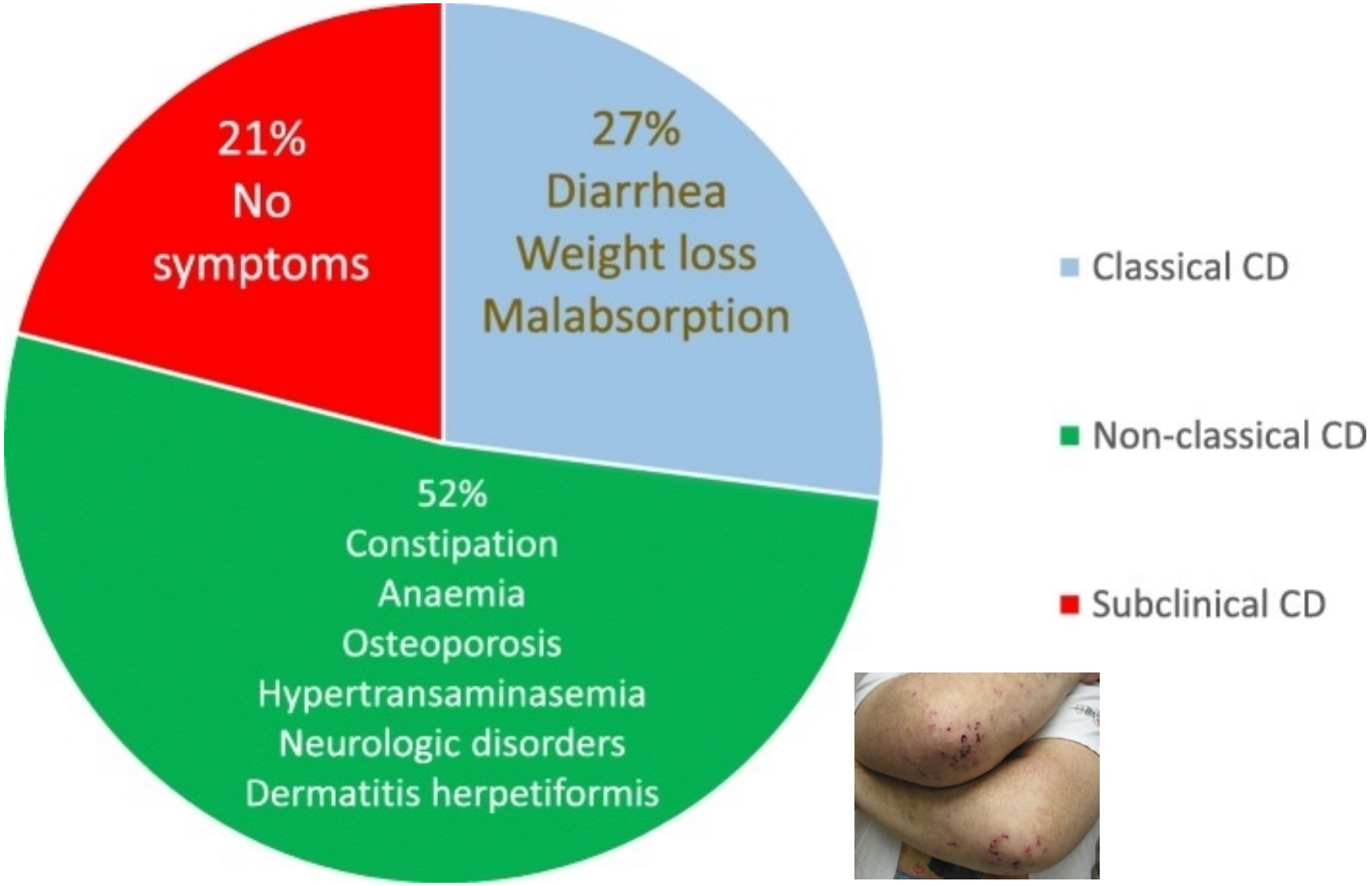
Brown et al. *Am J Gastroenterol* 2019;114:1587
Bouziat et al. Science 2017;356:44
Tsali et al. Eur J Gastroenterol Hepatol. 2024;36:1171
Szajewska H et al. J Pediatr Gastroenterol Nutr. 2024;79:438

CeD Remains Under-Diagnosed: How to Improve Detection?

- Clinical Detection, symptomatic patient
  - Wide clinical spectrum, changing clinical presentations
- Mass Screening[1]
  - At what age?
  - Harm in the asymptomatic?
  - Improves clinical outcomes?
  - Cost effective in the Netherlands
- **Case Finding Recommended[2]**
  - Screen those at increased risk for CeD
  - Based on common clinical presentations, family history, and associated conditions

[1]Chou et al. JAMA 2017;317:1258 Suasnabar et al. Gastroenterology 2024;167:1129
[2]Rubio-Tapia et al ACG Guidelines Update CeD. Am J Gastroenterol 2023;118:59

Clinical Presentations of CeD



Caio et al BMC Medicine 2019;17:142

Those at Increased Risk for CeD

Prevalence

- Western Countries 0.7%
- Europe 0.1-3%
- First Degree Relatives 5-10% lifetime risk

King et al Am J Gastroenterol 2020;115:507
Roberts et al. Aliment Pharmacol Ther 2021;54:109
Book et al. Am J Gastroenterol 2003;98:377

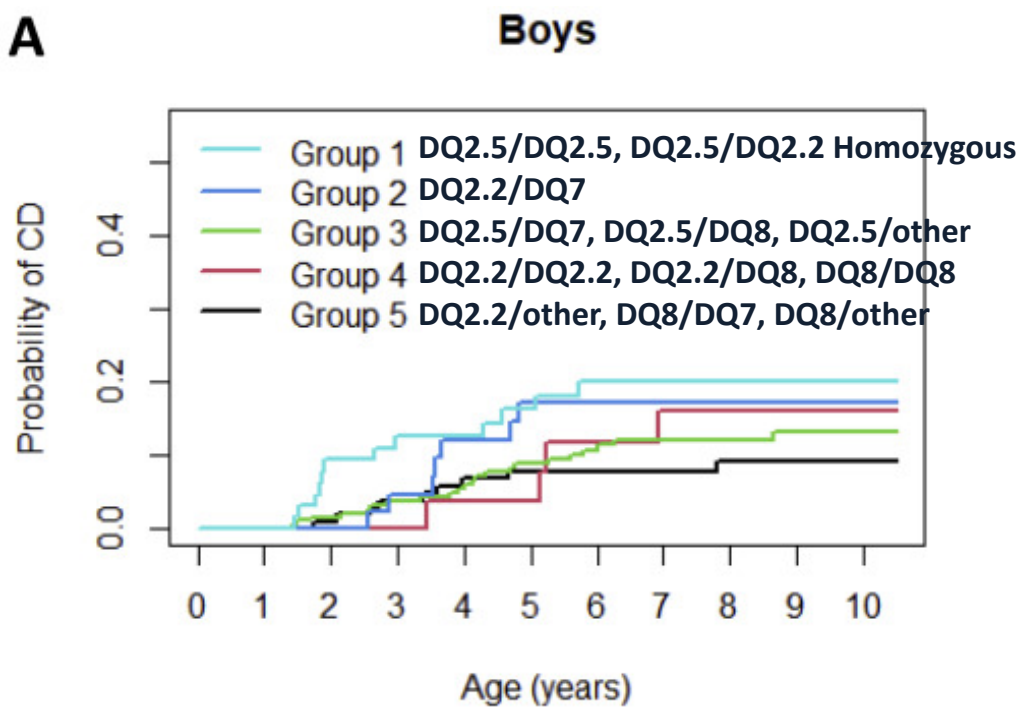
High Risk Groups

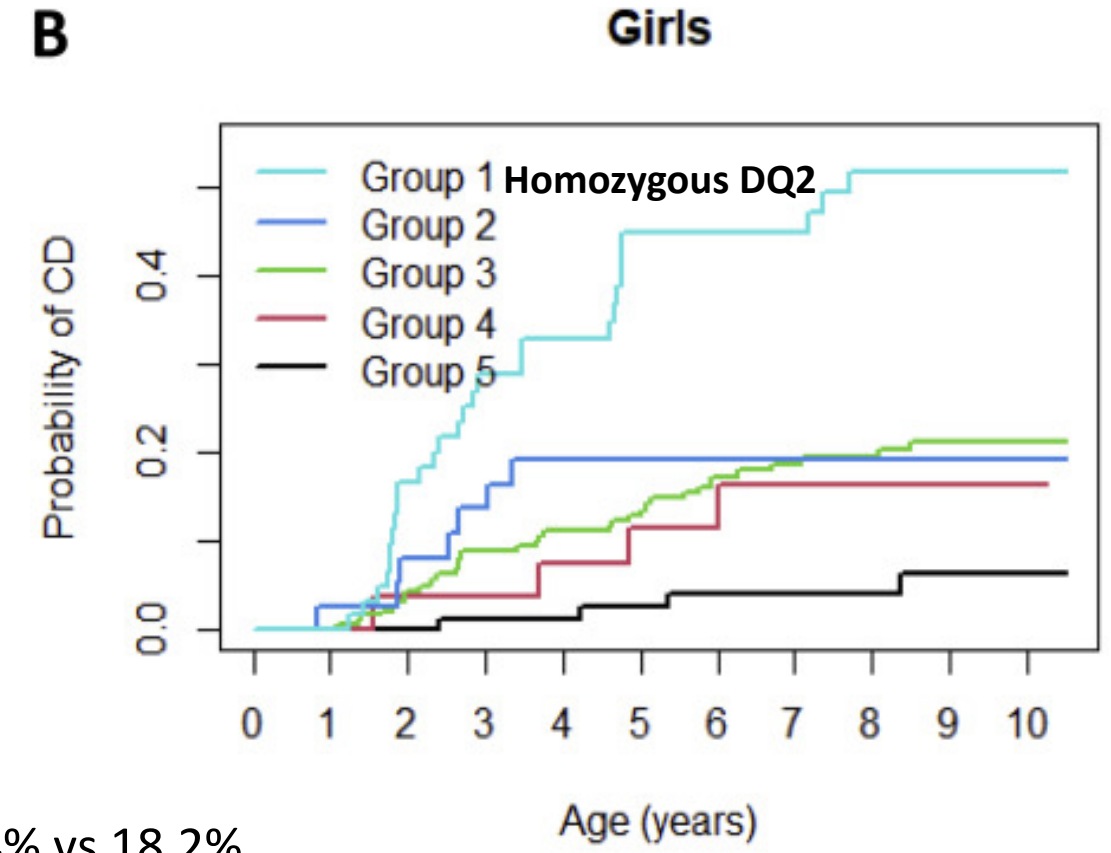
- Dermatitis herpetiformis
- Down, Turner syndromes
- Autoimmune thyroiditis/gastritis/hepatitis/Sjogren
- Selective IgA deficiency
- IBS, microscopic colitis
- Unexplained abnormal liver tests, pancreatitis
- Peripheral neuropathy, ataxia

Zingone F et al. Gastroenterology 2024;167:64

SCREEN FIRST DEGREE RELATIVES AND HIGH RISK GROUPS

First Degree Relatives - Prevent-CeD Cohort
Highest Risk in DQ2 homozygous girls





HLA-DQ2.5 homozygous cumulative incidence rate: 35.4% vs 18.2%

Meijer et al. Gastroenterology 2022;163:426

Diagnosis of Celiac Disease

- Serologic TTG IgA antibody and Total IgA level
  - Best test for diagnosis in children and adults
  - High quality assay
  - Must be eating gluten
  - DGP and/or TTG IgG antibody in those with IgA deficiency
- Duodenal biopsy
  - 4 distal duodenum, 2 bulb, well-oriented
  - clinical information and serology provided to pathologist
  - Always needed for diagnosis?
- HLA DQ 2,8 genetic testing
  - not diagnostic
  - best used to exclude disease when equivocal diagnosis or to predict risk

Rubio-Tapia et al. ACG CeD Guidelines Update Am J Gastroenterol 2023;118:59-76
Al-Toma et al. European Society Study CeD Update UEGJ 2025;00:1-32

TTG IgA > 10X Upper Limit Normal has a High Correlation with Villous Atrophy in Adults

Cohort	Sensitivity Value (95% CI)	Specificity Value (95% CI)	PPV Value (95% CI)	NPV Value (95% CI)
High suspicion (n=740, 93% CeD)	54% (51-58)	90% (78-97)	98.7% (97-99.4)	12.5% (11.2-13.9)
Low suspicion (n=532, 3% CeD)	50% (26-74)	100% (99-100)	100%	98.3% (96.8-99.2)
Retrospective 8 countries (n=145, 92% CeD)	30% (22-38)	83% (52-98)	95.2% (84.6-98.6)	9.5% (7.4-12.2)

Only 33% of adults had TTG IgA > 10x ULN

Penny at al. UK Gut 2021;70:876

Systemic Review and Meta-Analysis: Accuracy of no-biopsy approach to CeD in Adults

- 12,103 pts, 15 countries, pooled prevalence of CeD 62%
- 32% with TTG IgA $\geq$ 10 x ULN
- In those with high pretest probability
  - Summary sensitivity 51%, specificity 100%
  - PPV 99%

Shiha MG et al. Gastroenterology 2024;166:620

No Biopsy Approach for the Diagnosis of CeD in Adults

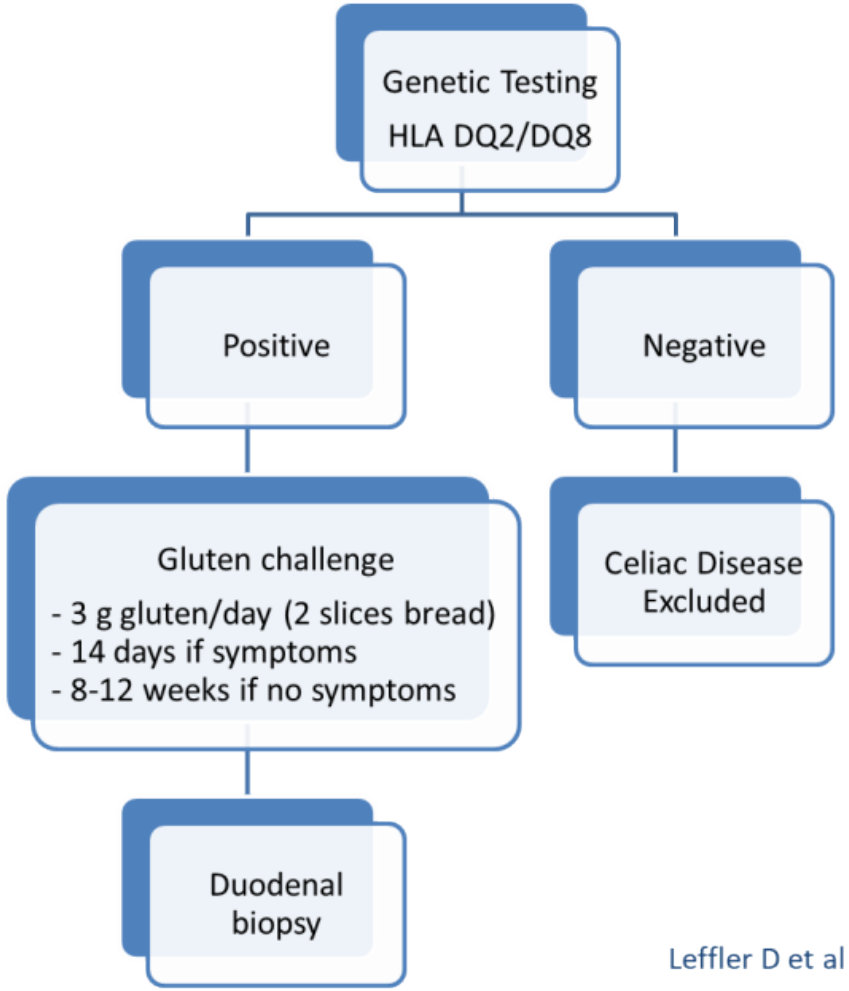
When initial TTG IgA antibody level ≥ 10 times the upper limit of normal

- Repeat test to assure no lab error
- Secondary Gastroenterology care setting
- Shared decision making
- No red flags (clinical severity or alternative symptoms)
- ≤ 45 years old

Certainty of Evidence Moderate
Conditional recommendation
95-100% agreement

Rubio-Tapia et al. ACG CeD Guidelines Update Am J Gastroenterol 2023;118:59-76
Al-Toma et al. European Society Study CeD Update UEGJ 2025 Sept 26.

Approach to CeD Diagnosis When Already on a GFD



Leffler D et al Gut 2013;62:996

On the horizon:

In vivo and *In vitro* whole-blood assay for the diagnosis of CeD

- single-dose gluten challenge (10 g)
- measure IL-2 release in blood
- 90% sensitivity, 95% specificity in HLA-DQ2.5

Moscatelli et al. Gastroenterology 2025:1-15

BACK TO CASE

- HLA DQ 2 Positive
- Gluten Challenge
  - 2 slices of gluten-containing bread in diet daily for 1 mo, worse symptoms
- EGD:
  - mild duodenal scalloping
  - obtained 4 biopsies from distal duodenum, 2 biopsies from bulb
  - Duodenal biopsy: increased intraepithelial lymphocytes, villous atrophy, increased lymphocytes and plasma cells in lamina propria
- TTG IgA positive

Celiac Disease: Treatment

- Gluten free diet remains the only treatment
- Education by doctor, registered dietitian and reliable Internet sites
- Allow Gluten-free oats but monitor
  - adds palatability, soluble fiber, laxation benefit
  - rare immune reactions to avenin oat protein
  - recent reports of contaminations of GF labeled oats
- Limit lactose to start

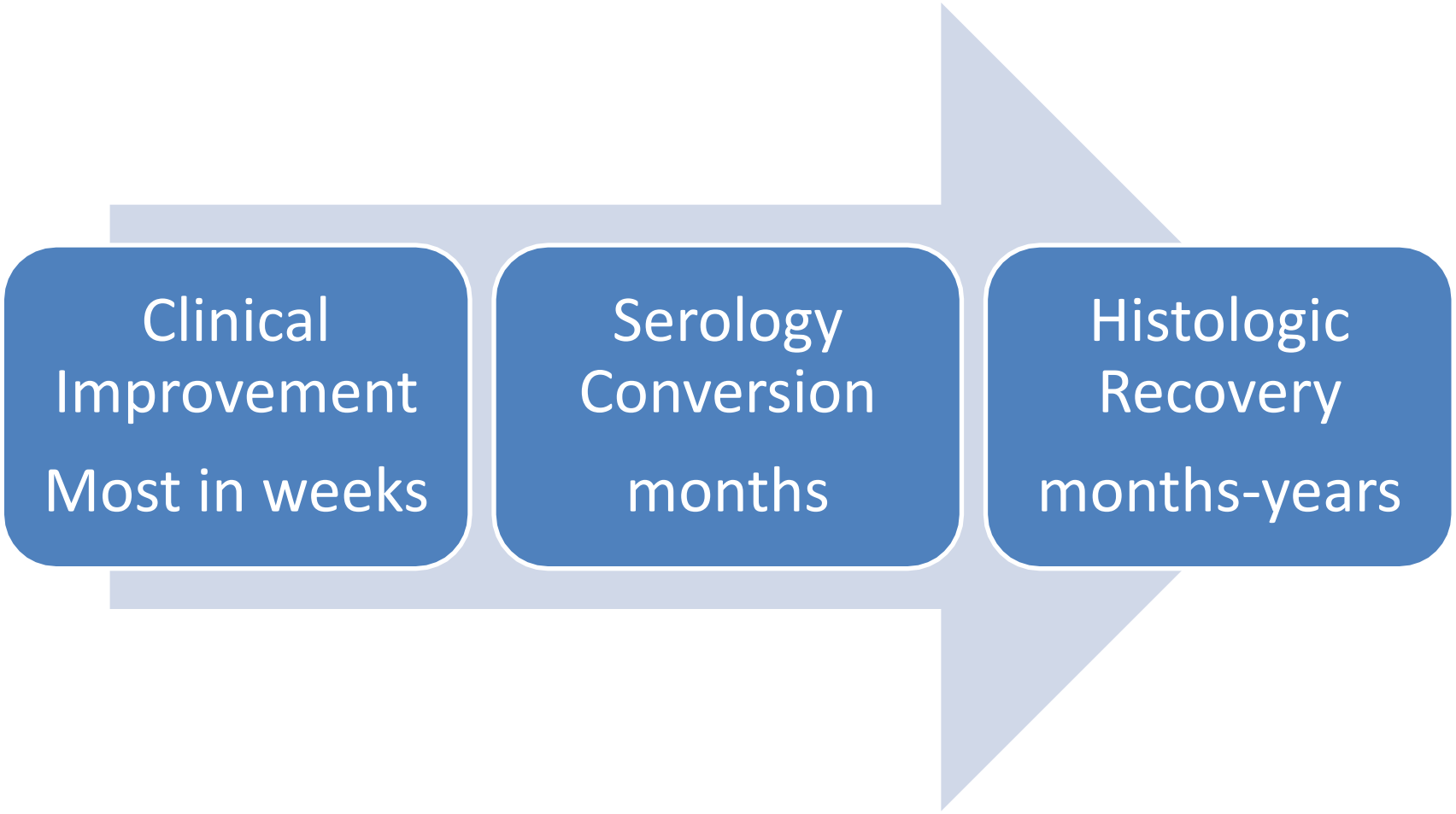
Aaltonen et al. Nutrients 2017;9:
Lionetti et al. J Pediatr 2018;194:116
Rubio Tapia Am J Gastroenterol 2023;118:59

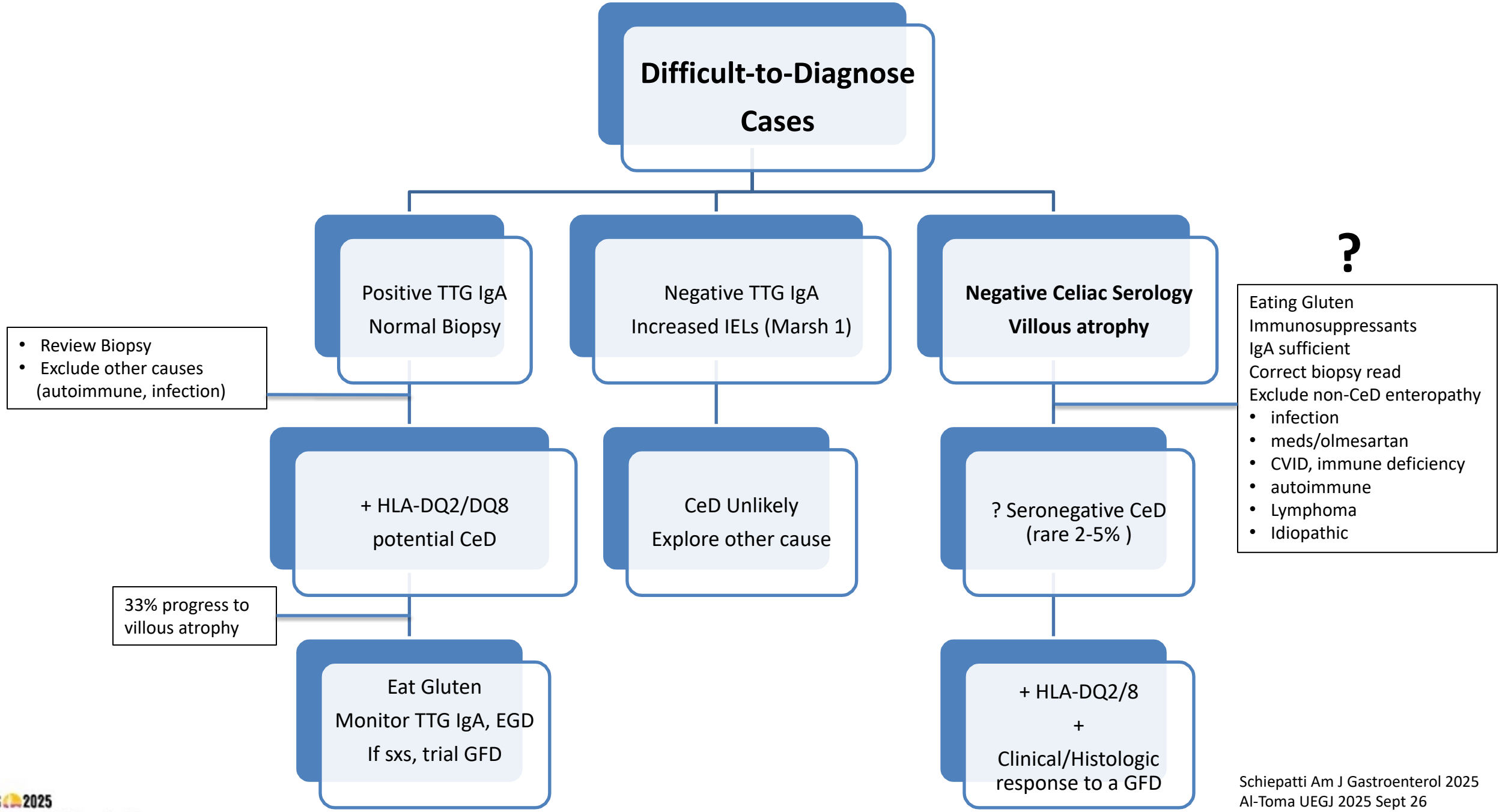
Management

- Initial
  - CBC, CMP, folate, iron, vitamin D
  - Diet adherence: clinic visit with repeat TTG IgA at 3 mo, 6-12 mo, then 1-2 yrs
  - Bone health: DEXA in adults
  - Weight, cholesterol
- Vaccinations: flu, pneumococcal
- No proven benefit for
  - probiotics
  - Gluten-detection devices to test food
  - Urine/stool gluten peptides may be useful to detect contamination
- Follow up biopsy on a GFD for histologic recovery
  - Not routinely recommended
  - Persistent symptoms/positive TTG or patient preference on a GFD

Rubio Tapia et al. Update ACG CeD. Am J Gastroenterol 2023;118:59
Elli et al. Nat Rev Gastroenterol Hepatol 2024;21:198
Simon et al Am J Med 2018;131:83

Celiac Disease Recovery





Schiepatti Am J Gastroenterol 2025
Al-Toma UEGJ 2025 Sept 26

Clinical Consequences of Persistent Villous Atrophy

- Occurs in 20% of pts with CeD
- Increased risk of complications
  - lymphoproliferative malignancy risk
  - hip fracture
  - refractory celiac disease
- Increased mortality due to related malignancies
- Predictors of persistent villous atrophy
  - age at diagnosis $\geq$ 45 yrs
  - classical CeD presentation
  - lack of clinical response or poor adherence to a GFD

Schiepatti et al. Gut 2023;72:2095
Lebwohl et al. Ann Intern Med 2013;159:169
Lebwohl et al. J Clin Endocrinol Metab 2014;99:609
Ludvigsson et al. JAMA 2009;302:1171

Persistent signs/symptoms on a GFD (7-30%)

Clinically stable, No red flags
Review biopsy, serology, HLA

- Wrong diagnosis further evaluate
- Secure diagnosis
  - gluten contamination (33%)
    - review diet (dietitian), TTG IgA Ab
    - gluten peptides (urine or stool)
    - stricter diet if needed
  - IBS 16%
  - constipation (gas/bloating)
  - co-existing problem
    - lactose or fructose intolerance
    - microscopic colitis (if diarrhea)
    - SIBO
    - pancreatic Insufficiency
    - other autoimmune diseases

Older, diarrhea/wt loss, low albumin
Immediate evaluation, may need PN

- ? Wrong Diagnosis
  - Olmesartan, autoimmune, CTLA4 other gene mutations
- Refractory CeD
  - Rare (0.04-1.5%)
- Rapid Evaluation
  - Duodenal biopsy (flow cytometry, immunohistochemistry)
  - Abd CT, capsule and deep enteroscopy
- RCD I
  - mixed lymphocyte population
  - stricter diet/budesonide/steroid
- RCD II
  - clonal population, early lymphoma
  - poor prognosis
  - chemotherapy/stem cell transplant

Aggarwal et al. J Gastroenterol Hepatol 2025;40:101
Elli et al. Nat Rev Gastroenterol Hepatol 2024;21:198 Al-Toma et al. ESsCD Guideline UEG J 2019;75:583
Rubio-Tapia et al. Am J Gastroenterol 2023;118:59. Van Wanrooij et al. Clin Transl Gastroenterol 2017;8:e218
Green et al. Gastroenterology 2022;163:1461

Celiac Disease: Take Home Points

- TTG IgA Ab is the best serology for the diagnosis of CeD in children and adults
  - Total IgA level needed to interpret a negative test
  - DGP and TTG IgG antibodies when IgA deficiency
  - Screen first degree relatives
- Duodenal biopsy still needed for diagnosis in most
  - No-biopsy approach in select patients when TTG IgA ≥ 10X ULN
- Seronegative CeD is rare, need to evaluate for other causes of villous atrophy
- Genetic testing is NOT diagnostic, best use is to exclude disease
- Gluten-free diet is the only effective treatment, most respond
- Education on GFD and monitoring are crucial for recovery
  - Histologic recovery is the goal, F/U biopsy not routinely recommended
  - Gluten contamination, most common cause persistent symptoms
  - Refractory celiac disease is rare, may be a misdiagnosis, needs immediate evaluation