Deciphering 2026 AGA Guidelines: Direct Impact on Point of Care Decision in PBC, Asymptomatic Celiac disease

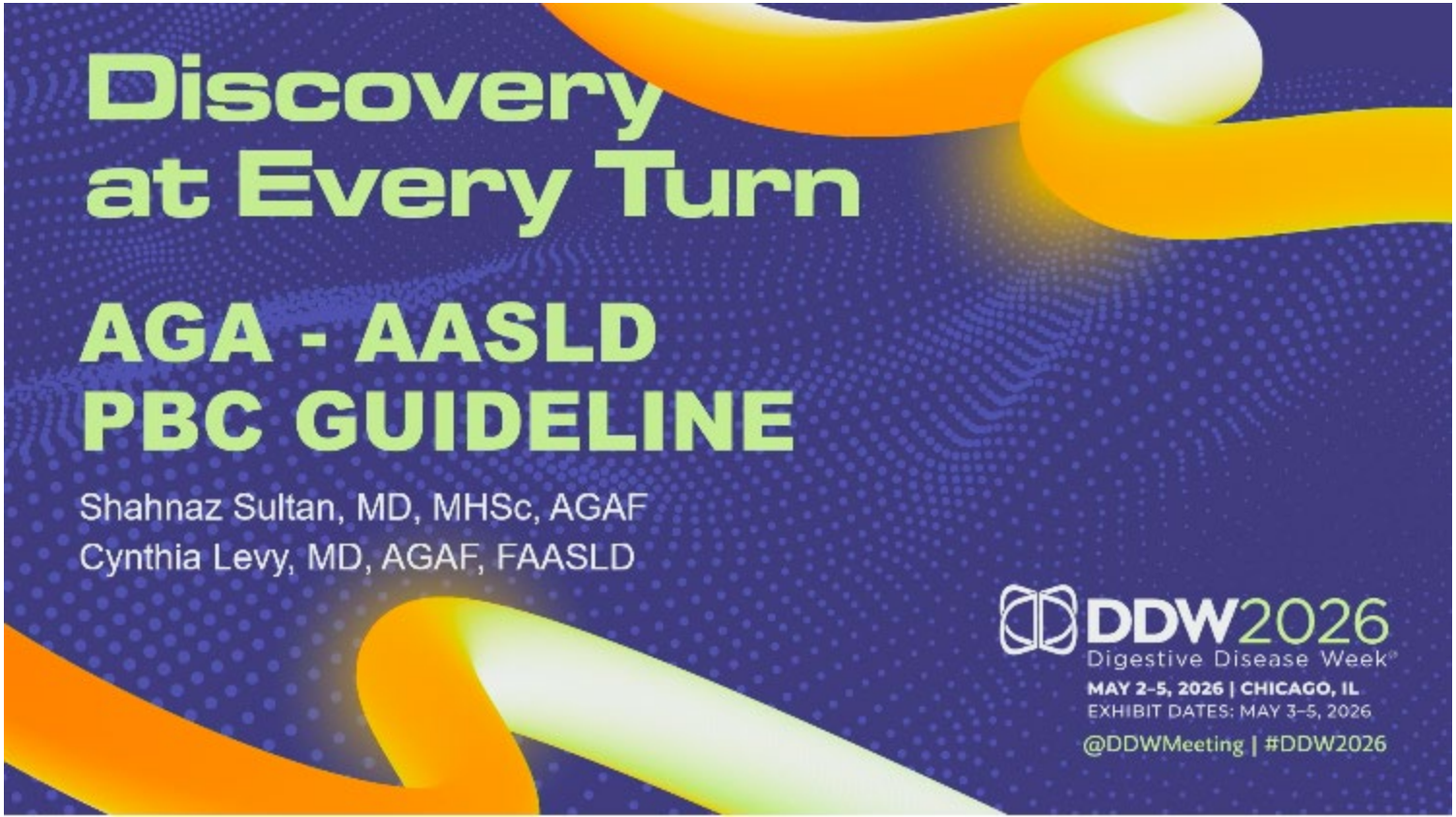
Venkata Rajesh Konjeti MD,FACP, DABOM

Financial Disclosure: None

Need/Practice Gap:
Rapidly evolving evidence and updated AGA guideline recommendations have changed the diagnosis, risk stratification, monitoring, and management of patients with primary biliary cholangitis (PBC) and asymptomatic celiac disease. Many clinicians remain uncertain about how to apply these recommendations in everyday practice, resulting in variability in patient evaluation, treatment selection, and follow-up care.

Objectives:
Discuss key 2026 AGA updates for PBC and asymptomatic celiac disease.
Compare new recommendations with prior standards of care.
Apply guideline recommendations to clinical practice.

Expected Outcome:
Participants will incorporate 2026 AGA recommendations into evidence-based care for PBC and asymptomatic celiac disease.


Discovery
at Every Turn
AGA - AASLD
PBC GUIDELINE
Shahnaz Sultan, MD, MHSc, AGAF
Cynthia Levy, MD, AGAF, FAASLD
DDW2026
Digestive Disease Week®
MAY 2–5, 2026 | CHICAGO, IL
EXHIBIT DATES: MAY 3–5, 2026
@DDWMeeting | #DDW2026

AGA - AASLD COLLABORATION

- **First joint AGA-AASLD guideline**
  - Harmonize recommendations between Societies
  - Facilitate high quality of care to patients
  - Ensure consistent messaging to all stakeholders
  - Reach a broader audience

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WHY WAS THIS GUIDELINE DEVELOPED?

-Prevalence 40.9/100,000 U.S., rising
-Worst quality of life among individuals with cholestatic conditions
-Important indication for LT in women

Diagnosis and Treatment

Patient Important Outcomes

Biochemical Response
Quality of life (Pruritus)
Decompensated Cirrhosis
Transplantation-free survival

DIAGNOSIS/RISK ASSESSMENT

Significant percentage have delays in diagnosis and initiation of treatment
Inadequate risk stratification contributes to worse outcomes
Inadequate symptom assessment impacts quality of life

TREATMENT

Under treatment: 20-40% of individuals have inadequate response to UDCA or are intolerant
Suboptimal management of pruritus (among most disabling symptoms of PBC)

Jie-Rae Tan et al CGH 2026, Levy et al Hepatology Communication 2025, Cançado et al Lancet 2025

HOW WAS THIS GUIDELINE DEVELOPED?

PANEL FORMATION

Based on:

- Expertise in management of PBC
- Representation from both organizations
- Group of GRADE methodologists
- Close attention to minimizing and managing COI

CLINICAL QUESTIONS

6 **clinically-relevant questions**

PICO format (population, intervention, comparison, outcome)

- Role of PBC specific ANA
- Role of LSM for prognostication
- PPAR agonists as 2nd Line
- Linerixibat for itching
- Urso as 1st line therapy and for prevention of rPBC

EVIDENCE SYNTHESIS

Evidence summary for each PICO question via systematic review of health effects plus:

- Net benefits/harms
- Certainty of evidence
- Patient values
- Resource use
- Equity
- Feasibility
- Acceptability

MAKING RECOMMENDATIONS

Recommendations made by guideline panel members based on evidence and structured framework for moving from decision to recommendation after achieving consensus among all panel members

CASE

- 54 y.o. female referred for evaluation of chronic liver enzyme elevation. Reports dry eyes and dry mouth, mild pruritus, no skin rash.
- She is not taking any medication except levothyroxine for hypothyroidism, does not smoke cigarettes, reports occasional alcohol use.
- She had an ultrasound of the abdomen with normal liver/spleen morphology and without bile duct dilatation
- Labs: TB 0.6, AST 65, ALT 72, ALP 358. Negative viral hepatitis panel

  AMA negative, ANA positive 1:80, ASMA negative

Should we order anti sp100 and/or gp210 antibodies?

EVIDENCE REVIEW

Systematic review of 12 studies (3729 individuals)

- *Case-control design (risk of bias), not all studies reported liver biopsy results*
- *Sensitivity of both anti sp100 and anti gp210 were inconsistent, both tests highly specific*
- *Anti gp210 had fewer false positives, but lower true positives*

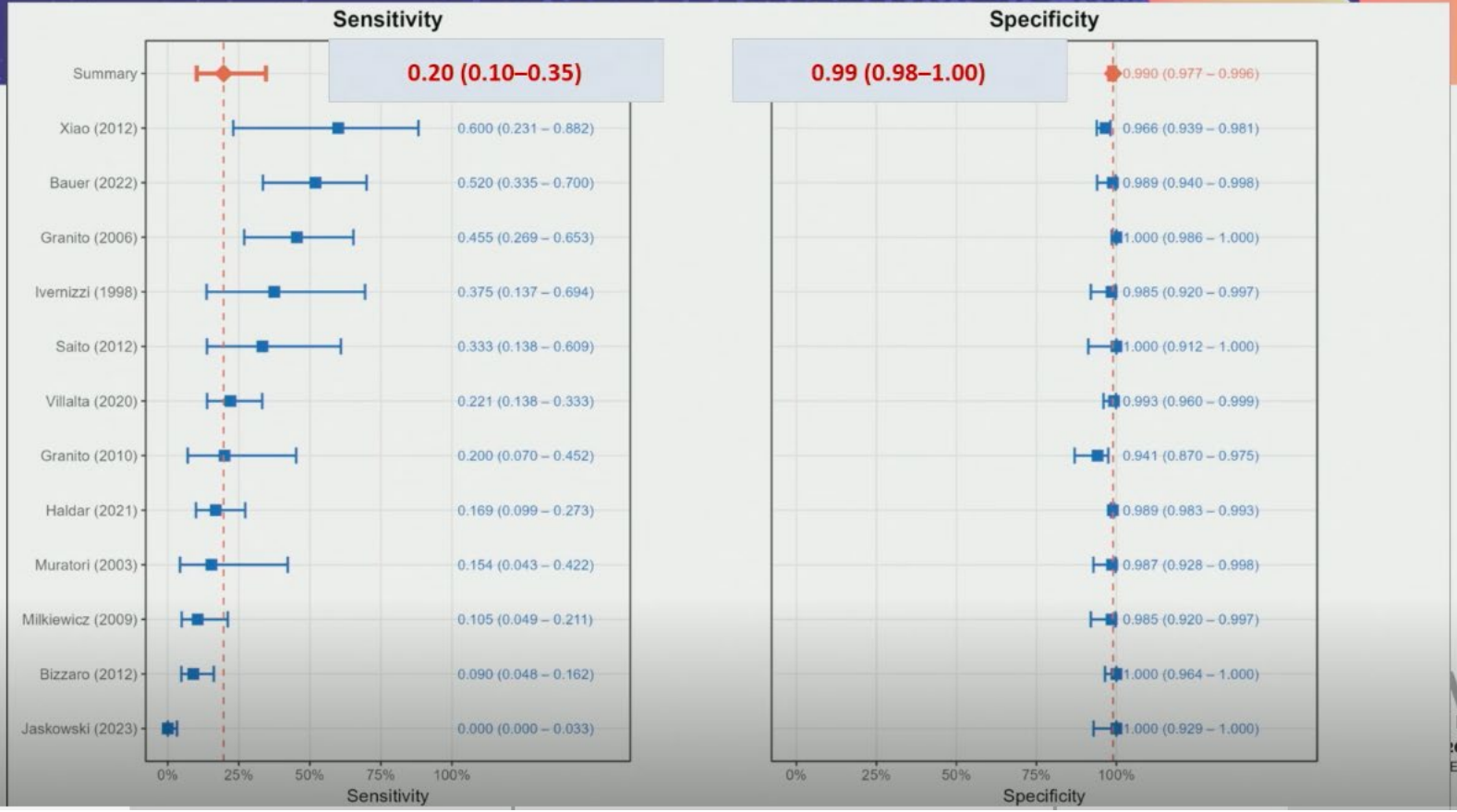
Outcome (per 100,000)	Anti gp210	Anti sp100
True Positives	197 (102-346)	227 (129-366)
False Negatives	803 (654–898)	773 (634–871)
True Negatives	98010 (96723–98604)	95535 (92961–97020)
False Positives	990 (396–2277)	3465 (1980–6039)
Pooled Se (95% CI)	0.20 (0.10–0.35)	0.23 (0.13–0.37)
Pooled Sp (95% CI)	0.99 (0.98–1.00)	0.96 (0.94–0.98)
Prevalence 1% #	⊕⊕◯◯ LOW/ ⊕⊕⊕◯ MODERATE	⊕◯◯◯ VERY LOW/ ⊕⊕◯◯ LOW

Benefits and Harms:

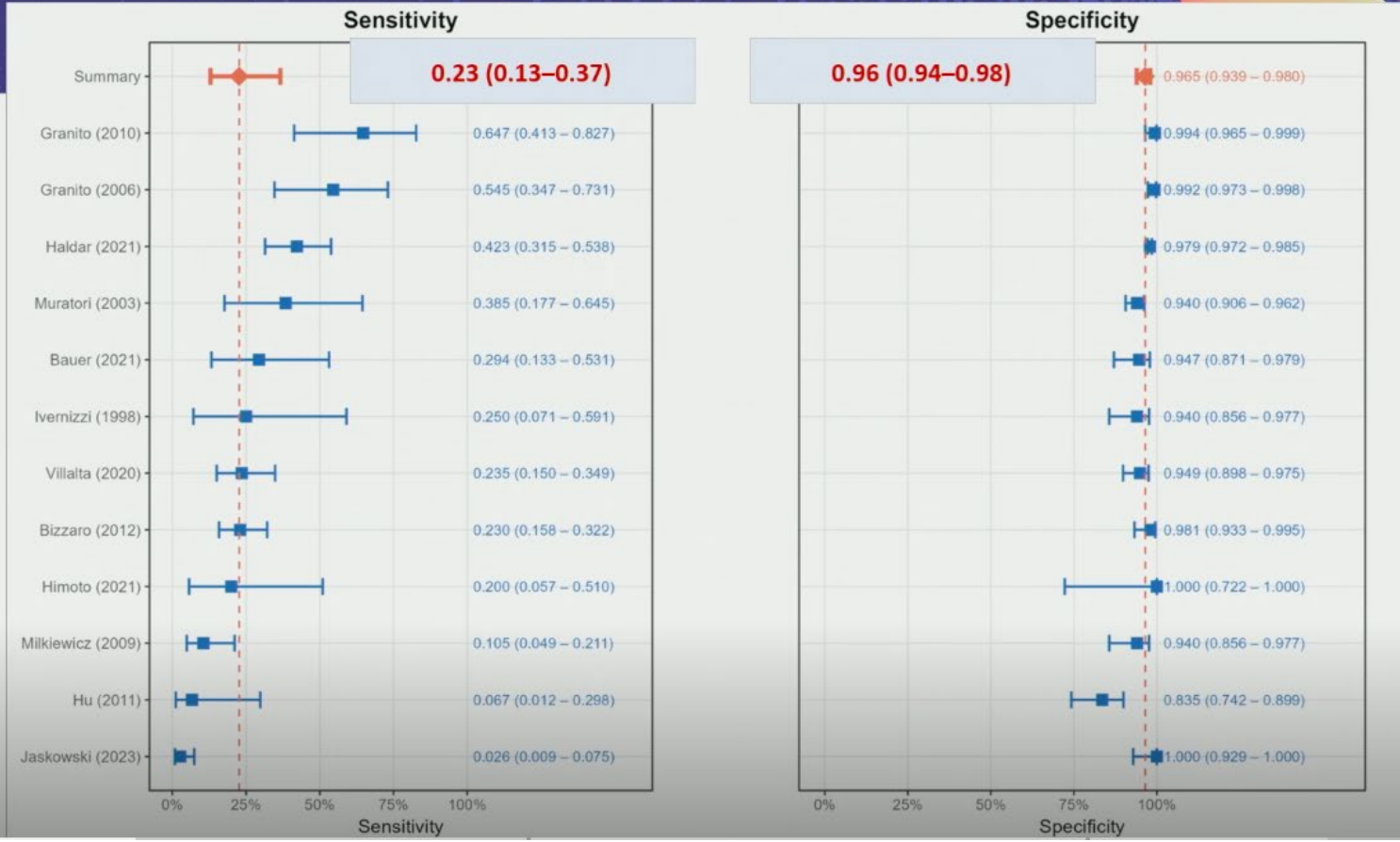
- *Prevent 227 liver biopsy per 100,000 patients tested*
- *Expedited diagnosis and early treatment initiation*
- *Cost savings (biopsy is expensive)*
- *Harm/undesirable effect: risk of missing other diagnosis*

EXHIBIT DATES: MAY 3-5, 2026

ANTI GP210- FOREST PLOTS



ANTI SP100- FOREST PLOTS



ROLE OF PBC-SPECIFIC ANTINUCLEAR ANTIBODY TESTING

Recommendation: In patients with cholestatic liver disease and negative anti-mitochondrial antibody (AMA), consider checking PBC-specific ANAs (anti sp100 and anti gp210 antibodies) (conditional recommendation with very low certainty of evidence)

Implementation Remarks:

- Anti sp100 and anti gp210 antibodies should be tested prior to obtaining a liver biopsy in patients with cholestatic liver disease and negative AMA, as a positive result may obviate the need for liver biopsy and allow for early initiation of therapy
- If both anti sp100 and gp210 antibodies are negative in a patient with strong clinical suspicion for PBC, liver biopsy remains appropriate to establish or refute the diagnosis, since the sensitivity of these tests is low.
- These tests are best applied in the evaluation of a cholestatic liver disease, rather than general population screening

Rationale: The recommendation is conditional given the low sensitivity of the test and potential for many false positives. Overall, there is a meaningful number of biopsies that are avoided in the 5-10 % of patients who are AMA negative.

CASE CONTINUED

- Patient was diagnosed with AMA negative PBC after testing positive for sp-100.
- UDCA 15 mg/kg/day started

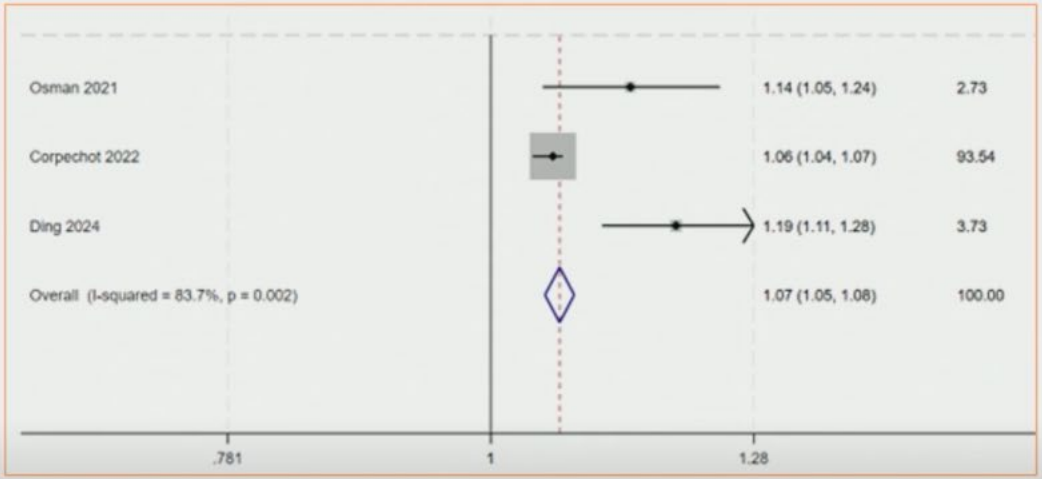
Should liver stiffness measurement be obtained? Will this help us understand our patient's prognosis?

EVIDENCE REVIEW

Panel chose to evaluate LSM by VCTE

- Osman et al evaluated MRE and TE in PBC and reported prognostic associations with both. However, study is limited to 3 US sites only.
- For SWE/pSWE/ARFI - PBC literature is largely focused on fibrosis staging and correlation with biopsy or other non-invasive markers and/or features of portal hypertension. There are no large PBC-specific studies evaluating prediction of liver-related outcomes.
- Large, externally validated, PBC-specific prognostic evidence is overwhelmingly for LSM by VCTE

EVIDENCE REVIEW-FORREST PLOT



All studies used composite outcomes (decompensation, liver transplant, death)

Binary cutoff analysis around LSM >10 kilopascals

- 30-46% hepatic decompensation vs 1%
- Different studies used cutoffs 9.3-11, harmonized to ~10 kPa

POOLED HR 1.07 per 1 kPa increase in LSM

ROLE OF LSM BY VCTE

Recommendation: In patients with PBC, the societies (AASLD/AGA) suggest assessing liver stiffness measurement by vibration-controlled transient elastography to improve prognostication (conditional recommendation with very low certainty of evidence)

Implementation Remarks:

- In patients with PBC, liver stiffness measurement (LSM) by VCTE can help with risk stratification. Patients with LSM ≥ 10 kPa are at increased risk of adverse clinical outcomes and therefore may deserve closer monitoring and/or possible therapy escalation
- When used serially, the most recent LSM appears to be more strongly associated with outcomes than the change in LSM between measures
- The BAVENO criteria can be applied to patients with PBC to identify those with clinically significant portal hypertension (CSPH): LSM < 15 kPa rules out CSPH, and LSM ≥ 25 kPa (or > 20 kPa AND platelet count < 150k) rules in CSPH

Rationale: Recommendation is conditional primarily due retrospective nature of studies using different composite endpoints. The panel also discussed concerns regarding variable access to this technology across different practice settings (academic vs. community, rural vs urban) and potential costs to patients (variable insurance coverage).

CASE CONTINUED

- 54 yo female with new diagnosis of AMA neg PBC, ALP 358.
- Underwent VCTE: LSM 8.5 kPa, CAP 189
- UDCA 15 mg/kg/day is prescribed and labs monitored quarterly

- She returns ~ a year later with the following results: Tb 0.5, AST 29, ALT 36, ALP 205 IU/L (ULN 130). Repeat LSM: 8 kPa

Should a PPAR agonist be added to UDCA?

TREATMENT GOALS (BIOCHEMICAL)

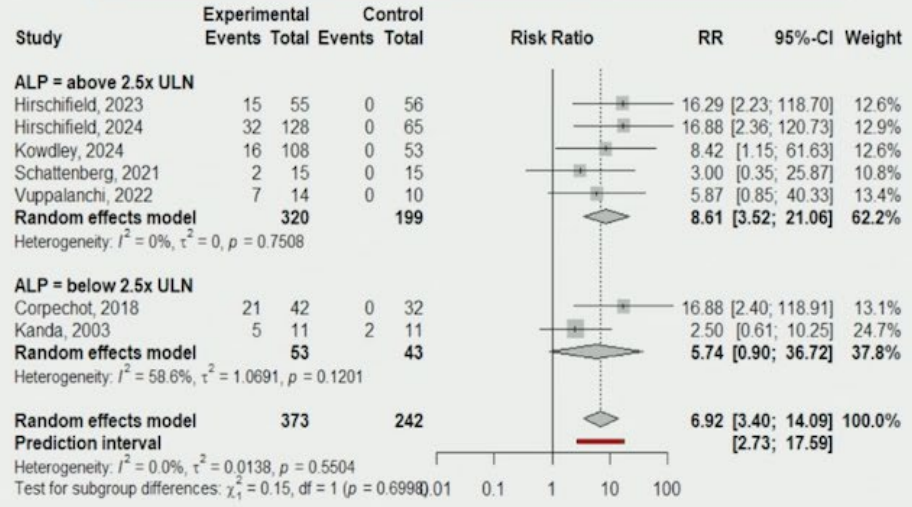
- Several UDCA-response criteria are available and correlate with long term outcomes[1]
- POISE criteria were utilized in pivotal phase 3 clinical trials investigating second line therapies:
  - Reduction in ALP by at least 15%
  - Reduction in ALP to < 1.67x ULN
  - Normal total bilirubin levels
- Adequate response: ALP < 1.5-1.67x ULN and Normal TB[2]
- Ideal response: Normal ALP and TB, suggested for high risk patients
- Inadequate biochemical response after 6 to 12 months of UDCA – and at any time thereafter – is associated with increased risk of poor clinical outcomes in patients with PBC[2].

1- Cançado et al. Lancet 2025; 2- EASL-AASLD Delphi consensus statement on surrogate endpoints and real-world evidence in primary biliary cholangitis, Journal of Hepatology and Hepatology, *in press*

FOREST PLOTS: PPAR OUTCOMES

7 RCTs, n=615 patients

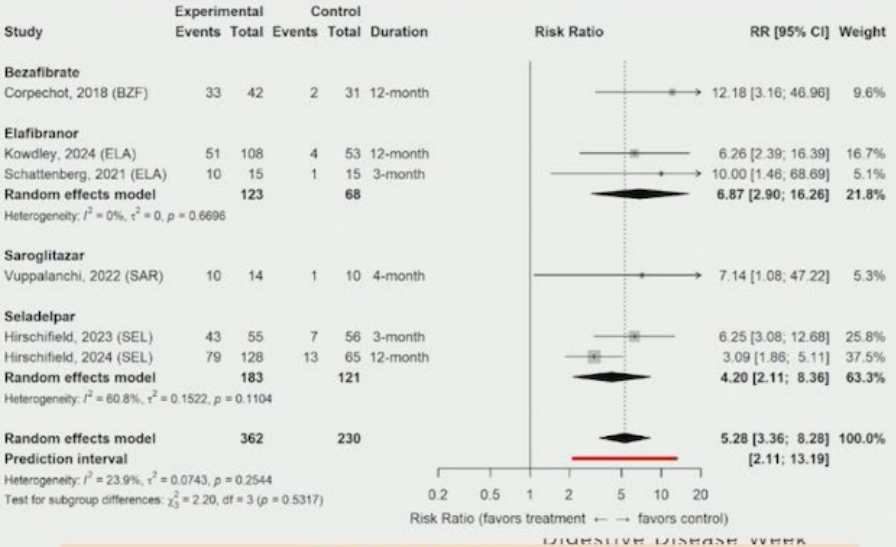
ALP normalization



RR 6.92 (3.40-14.09)
24 more 1,000 (10 more to 54 more)

6 RCTs, n=592 patients

POISE biochemical response



RR 5.28 (3.36-8.28)
521 more 1,000 (287 more to 886 more)

FOREST PLOTS: OUTCOMES

3 RCTs, n=145 patients

Improvement in pruritus by NRS

Alimentary Pharmacology & Therapeutics

WILEY

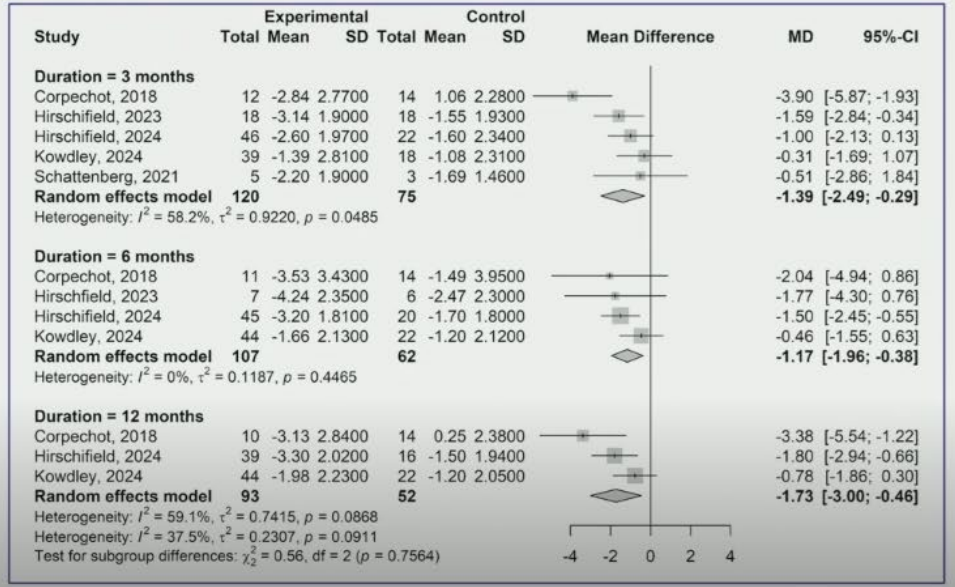
APT Alimentary Pharmacology & Therapeutics

META-ANALYSIS

Meta-Analysis: PPAR Agonists for Pruritus and Quality of Life in Primary Biliary Cholangitis

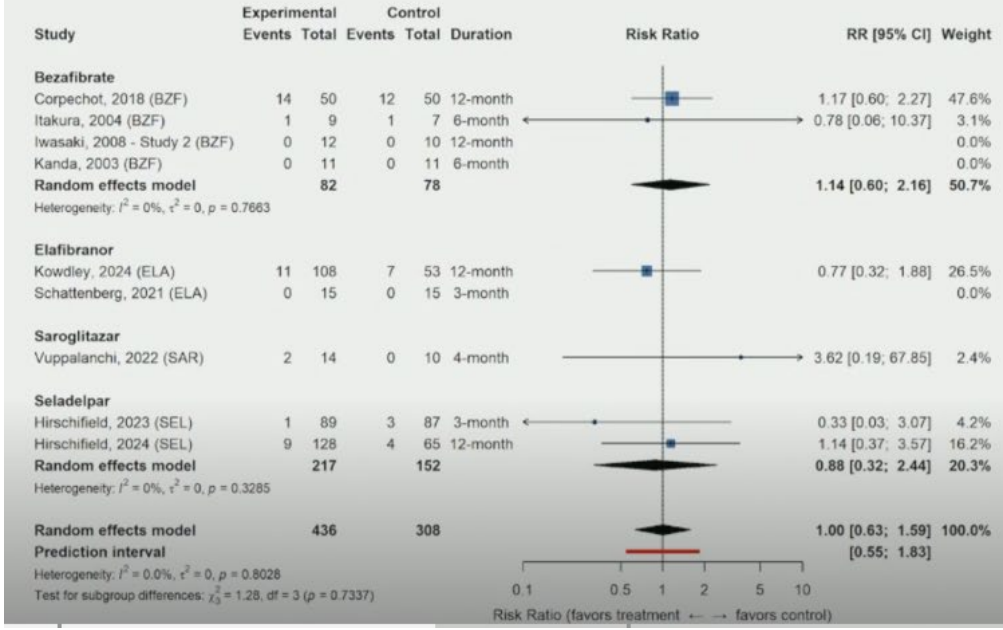
Adrielly Martins[1] | Nidah S. Khakoo[2] | Christophe Corpechot[3] | Alexandra Rousseau[4] | John M. Reynolds[5] | Andreas E. Kremer[6] | M. Hassan Murad[7] | Shahnaz Sultan[8] | Cynthia Levy[1,9]

MD 1.73 points lower on NRS scale
3.0 lower to 0.46 lower



FOREST PLOTS: SIDE EFFECTS

Serious Adverse Effects



Side effects [from RCT and non RCT]

- Myalgias 2-3%
- Rhabdomyolysis (rare, but serious)
- Creatinine rise (transient)
- ALT elevation >5x ULN –less with new PPAR agonists
- Bone fractures 4-6%
- Intolerability/drug discontinuation up to 25% in observational studies; much lower rates with new PPAR agonists

SHOULD A PPAR AGONIST BE ADDED TO PATIENTS WITH PBC AND INADEQUATE RESPONSE OR INTOLERANCE TO UDCA?

Recommendation: In patients with PBC and inadequate response or intolerance to UDCA monotherapy, the societies (AASLD, AGA) suggest the use of a PPAR agonist (elafibranor, seladelpar, fibrate) either as add-on therapy to UDCA or as monotherapy in cases of UDCA intolerance (conditional recommendation, low certainty of evidence)

Implementation Remarks:

- Biochemical response to UDCA should be evaluated after a minimum of 6 months, and no later than 12 months, after treatment initiation
- The following PPAR agonists have been evaluated for persons with PBC: bezafibrate, elafibranor, seladelpar and fenofibrate. Elafibranor and seladelpar have conditional FDA and EMA approval, whereas bezafibrate and fenofibrate remain available as off-label therapies
- In patients with PBC and moderate-to-severe pruritus, PPAR agonists reduce pruritus intensity. Efficacy data is clearer for bezafibrate and seladelpar*
- Once PPAR agonist has been initiated, treatment response and tolerability should be monitored longitudinally. The panel suggests quarterly laboratory testing during the first year, with less frequent monitoring once clinical benefit and tolerability have been established

PPAR AGONIST USE IN PBC

Implementation remarks, continued:

- Due to lack of efficacy and safety data, PPAR agonists should not be used in pregnancy, breastfeeding and decompensated cirrhosis.

RATIONALE: Recommendation was judged conditional based on the small number of trials, benefits based on biochemical endpoints (as opposed to liver-related outcomes). The panel acknowledged residual uncertainty about long term safety. There are ongoing studies looking at long term outcomes and additional data will be available in the future.

CASE CONTINUED

- You decided to add a PPAR agonist for your 54 yo female patient with AMA negative PBC and inadequate response to UDCA
- Patient returns for follow up yet another several months later
- Labs: TB 0.5, AST 22, ALT 24, ALP 134.
- She is happy to see these results but noted that lately she has not been functioning or sleeping well due to intensification of her pruritus. Her quality of life has deteriorated.

Will this patient with cholestatic pruritus benefit from using an IBAT inhibitor (linerixibat being the only FDA-approved IBAT inhibitor in PBC)?

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EVIDENCE REVIEW- ITCHING

Primary outcome in the studies:
Mean Numeric Rating Scale (NRS) difference <0.78 points (0-10 scale)

				No linerixibat	Linerixibat
Itch – mean difference NRS EOT vs baseline Scale from: -10 to 10	296 (2 RCTs)	⊕⊕◯◯ Low[a,b]	-	MD 0.78 points lower (1.25 lower to 0.31 lower	
Itch - reduction in NRS by at least 2 points	296 (2 RCTs)	⊕⊕◯◯ Low[a,b]	**RR 1.11** (0.93 to 1.32)	584 per 1,000	**64 more per 1,000** (from 41 fewer to 187 more)
Itch - reduction in NRS by at least 3 points	237 (1 RCT)	⊕⊕◯◯ Low[a,b]	**RR 1.30** (1.00 to 1.69)	432 per 1,000	**130 more per 1,000** (from 0 fewer to 298 more)
Itch - mean difference PBC-40 Itch vs baseline Scale from: -12 to 12	296 (2 RCTs)	⊕⊕◯◯ Low[b]	-	MD 0.66 points lower (1.42 lower to 0.1 higher)	

≥2 point NRS reduction: modest improvement

≥3 point NRS reduction: limited to one study

PBC-40 itch domain: small, non-significant difference

≥ 3 point NRS reduction meaningful within patient change

EVIDENCE REVIEW – SLEEP INTERFERENCE (OUTCOME) AND SIDE EFFECTS

				No linerixibat	Linerixibat
Sleep interference - mean difference sleep NRS vs baseline Scale from: -10 to 10	296 (2 RCTs)	⊕⊕⊕◯ Moderate[b]	-	The mean sleep interference - mean difference sleep NRS vs baseline was **0** points	MD **0.52 points lower** (1.02 lower to 0.03 lower)
Diarrhea	296 (2 RCTs)	⊕⊕⊕◯ Moderate[b]	**RR 3.57** (2.43 to 5.23)	162 per 1,000	**417 more per 1,000** (from 232 more to 687 more)
Abdominal pain	296 (2 RCTs)	⊕⊕◯◯ Low[b]	**RR 3.67** (1.57 to 8.60)	45 per 1,000	**121 more per 1,000** (from 26 more to 345 more)
Increased ALT	237 (1 RCT)	⊕⊕◯◯ Low[b]	**RR 2.73** (0.89 to 8.32)	34 per 1,000	**59 more per 1,000** (from 4 fewer to 248 more)
Discontinuation due to AE	296 (2 RCTs)	⊕⊕◯◯ Low[b]	**RR 2.92** (1.24 to 6.90)	39 per 1,000	**75 more per 1,000** (from 9 more to 230 more)

Sleep interference: 0.52 point improvement

Adverse Events:

Diarrhea 417 more per 1,000
Abd pain 121 more per 1,000
Inc ALT 59 more per 1,000
Discontinuations 75 more per 1,000

SHOULD PATIENTS WITH PBC AND CHOLESTATIC PRURITUS BE TREATED WITH LINERIXIBAT

Recommendation: In patients with PBC and moderate-to-severe pruritus, the societies (AASLD, AGA) suggest use of linerixibat for the treatment of cholestatic pruritus. (conditional recommendation, low certainty of evidence)

Patients who place a higher value on avoiding potential gastrointestinal side effects or costs and a lower value on variable benefits may reasonably choose not to use linerixibat

Implementation Remarks:

- A 2-12 week trial of linerixibat 40 mg twice daily should be considered for patients experiencing moderate-to-severe itch, with consideration for continuation based on clinical response
- The trade-off between potential itch benefit and potential gastrointestinal effects of linerixibat should be discussed with the patient prior to treatment initiation

Rationale: Recommendation was conditional due to panel concerns about limited number of studies and small differences in proportion of patients achieving clinically meaningful improvements. In addition, the panel raised concerns about the high rate of GI side effects and treatment discontinuation and emphasized importance of shared decision making.

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OTHER RECOMMENDATIONS

1. In patients with treatment-naïve PBC, the societies (AASLD, AGA) recommend using ursodeoxycholic acid compared to no treatment (strong recommendation; moderate certainty of evidence)

2. In patients with PBC who have received a liver transplant, the societies (AASLD, AGA) suggest using ursodeoxycholic acid to prevent recurrent PBC and graft failure compared to no prophylaxis (conditional recommendation; very low certainty of evidence)

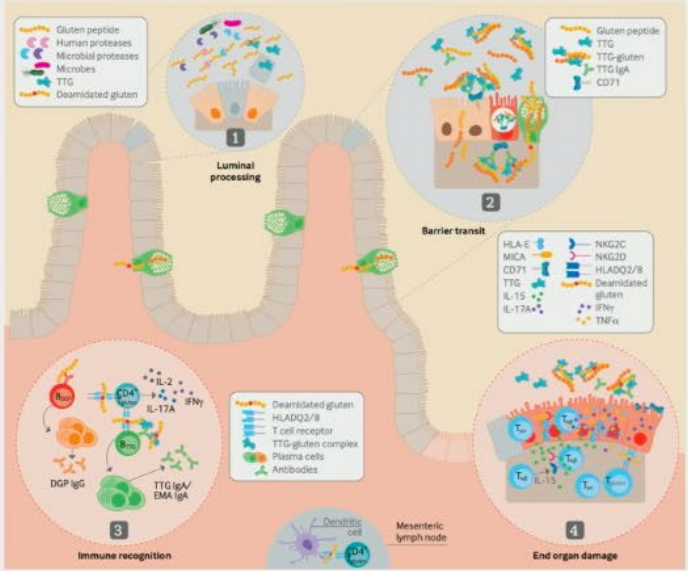
AGA/SSCD Clinical Practice Guideline on Treatment of Asymptomatic Celiac Disease

Benjamin Lebwohl and Osama Altayar

aga American Gastroenterological Association

Asymptomatic Celiac Disease

- Definition: “Celiac disease not accompanied by symptoms even in response to direct questioning at initial diagnosis”
- Gluten-free diet is generally recommended
  - Reversal of enteropathy may lead to decreased long-term morbidity
- The evidence basis for treating asymptomatic celiac disease has not been closely examined



Doyle JB, et al. . BMJ. 2025;391:e081353.
Ludvigsson JF, et al. . Gut. 2013;62:43-52.

PICO Questions

Category	Question Number	PICO Questions
Asymptomatic	1	In asymptomatic individuals diagnosed with celiac disease with **no extra-intestinal manifestations or associated conditions**, should gluten-free diet be used?
Asymptomatic, with signs of celiac disease	2-5	In asymptomatic individuals with **unexplained iron deficiency, metabolic bone disease, idiopathic abnormalities in LFTs, or short stature** diagnosed with celiac disease, should gluten-free diet be used?
Asymptomatic, with associated condition	6-8	In asymptomatic individuals with **type 1 diabetes mellitus, autoimmune thyroid disorders, or Down syndrome diagnosed** with celiac disease, should gluten-free diet be used?

The Challenge: Limited Data!

Two RCTs evaluated GFD vs no GFD in individuals with asymptomatic celiac disease

- ➔ Relied on observational studies:
  - ➔ Study designs:
    - ➔ Comparative: Studies that compared outcomes between patients on vs off GFD (preferred)
    - ➔ Pre-Post: Studies that compared outcomes before and after GFD
  - ➔ Population:
    - ➔ Asymptomatic individuals (preferred)
    - ➔ Anyone with celiac disease

PICO 1: Asymptomatic with no extra-intestinal manifestations or associated conditions

A 25-year-old man with no past medical history was found to have celiac disease. He was tested after his sister was found to have celiac disease as part of evaluation for chronic diarrhea.

He reports no abdominal pain, nausea, vomiting, diarrhea, constipation, bloating, or heartburn. He reports no headaches, joint pain, fatigue, or brain fog. He feels completely well.

His laboratory testing shows no evidence of anemia or LFT abnormalities. He had a normal TSH and a normal DEXA scan.

Should he start a gluten-free diet?

Benefits vs Harms

- *Quality of life better?*
- *Potential growth (children)?*
- *Less fragility fractures?*
- *Less intestinal malignancies?*
- *Less nutritional deficiencies?*

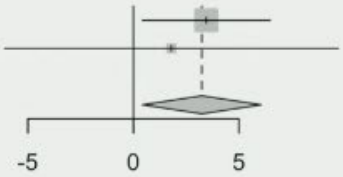
- *Quality of life worse?*
- *Quality of life for caregiver/family?*
- *New onset GI symptoms?*
- *More nutritional deficiencies?*
- *Worse food insecurity?*

The Evidence: Quality of Life

Two RCTs comparing GFD vs no GFD for 1 year

Study	outcome	range	Total	Mean	SD	MRAW	95%-CI	Weight
Kurppa 2014	PGWB	0-110	40	3.45	9.7676	3.45	[0.43; 6.48]	87.2%
Mahmud 2020	PQoLIGCS	0-100	51	1.80	28.8261	1.80	[-6.11; 9.71]	12.8%
Common effect model			**91**			**3.24**	**[0.42; 6.07]**	**100.0%**

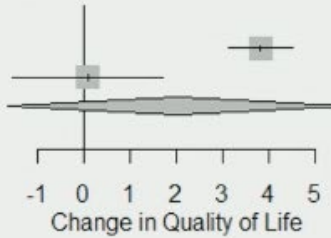
Heterogeneity: $I^2 = 0.0\%$, $\tau^2 = 0$, $p = 0.7018$



Two observational studies (change with GFD for 1 year)

Study	Total	Total	At CD Diagnosis	GFD for 1 yrs	MRAW	95%-CI
Measure = QoL						
Kurppa 2010	46	PGWB	103.20	107.40	3.82	[3.11; 4.52]
Ukkola 2011	23	PGWB	103.00	103.10	0.09	[-1.54; 1.72]
Random effects model	**69**				**2.03**	**[-1.62; 5.68]**

Heterogeneity: $I^2 = 94.1\%$, $\tau^2 = 6.5363$, $p < 0.0001$



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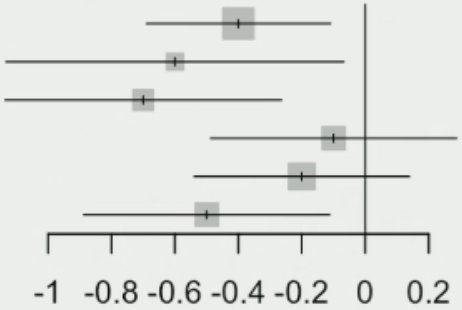
The Evidence: Symptoms

One RCT comparing GFD vs no GFD for 1 year

Study	outcome	range	Total	Mean	SD	MRAW	95%-CI
Kurppa 2014	GSRS	0-7	40	-0.40	0.9373	-0.40	[-0.69; -0.11]
Kurppa 2014	Diarrhea	0-7	40	-0.60	1.7183	-0.60	[-1.13; -0.07]
Kurppa 2014	Indigestion	0-7	40	-0.70	1.4059	-0.70	[-1.14; -0.26]
Kurppa 2014	Constipation	0-7	40	-0.10	1.2497	-0.10	[-0.49; 0.29]
Kurppa 2014	Abdominal pain	0-7	40	-0.20	1.0935	-0.20	[-0.54; 0.14]
Kurppa 2014	Reflux	0-7	40	-0.50	1.2497	-0.50	[-0.89; -0.11]

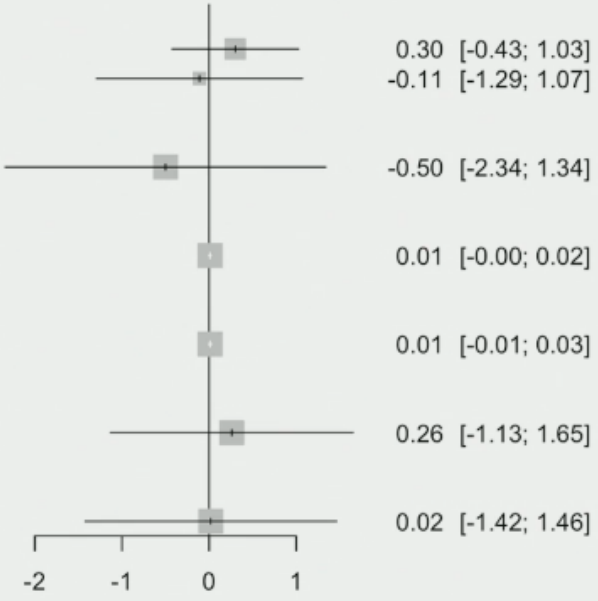


The Evidence: Growth and Bone Density

Two RCTs comparing GFD vs no GFD for 1 year

Study	outcome	Total	Mean	SD	MRAW	95%-CI
outcome = BMI						
Kurppa 2014	BMI	40	0.30	2.3431	0.30	[-0.43; 1.03]
Mahmud 2020	BMI	16	-0.11	2.4126	-0.11	[-1.29; 1.07]
outcome = Total body fat%						
Kurppa 2014	Total body fat%	40	-0.50	5.9359	-0.50	[-2.34; 1.34]
outcome = Lumbr spine BMD						
Kurppa 2014	Lumbr spine BMD	40	0.01	0.0469	0.01	[-0.00; 0.02]
outcome = Femur neck BMD						
Kurppa 2014	Femur neck BMD	40	0.01	0.0625	0.01	[-0.01; 0.03]
outcome = Height						
Mahmud 2020	Height	16	0.26	2.8442	0.26	[-1.13; 1.65]
outcome = Weight						
Mahmud 2020	Weight	16	0.02	2.9488	0.02	[-1.42; 1.46]

Heterogeneity: $I^2 = 0.0\%$, $\tau^2 = 0$, $p = 0.9828$



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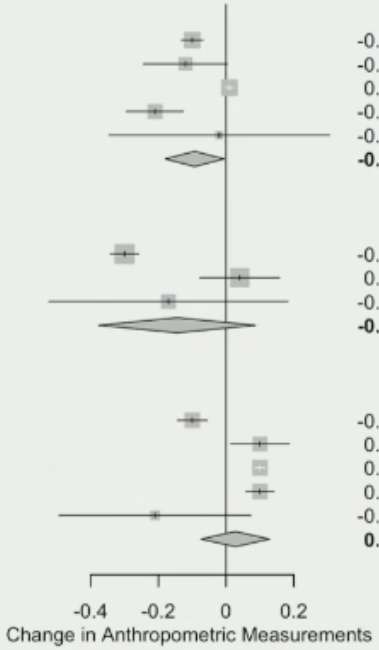
The Evidence: Growth

Observational Studies (Change with GFD for 2 years)

Study	Total	At CD Diagnosis	GFD for 2 yrs	MRAW	95%-CI
Measure = Height SDS					
Sun 2009	49	-0.20	-0.30	-0.10	[-0.13; -0.07]
Mackinder 2014	23	-0.26	-0.38	-0.12	[-0.24; 0.00]
Rami 2005	74	0.04	0.05	0.01	[-0.00; 0.02]
Valletta 2007	23	0.04	-0.17	-0.21	[-0.29; -0.13]
Mahmud 2020	8	0.27	0.25	-0.02	[-0.35; 0.31]
Random effects model	**177**			**-0.09**	**[-0.18; -0.01]**
Heterogeneity: I^2 = 94%, τ^2 = 0.0071, p < 0.0001					
Measure = Weight SDS					
Sun 2009	49	0.70	0.40	-0.30	[-0.34; -0.26]
Mackinder 2014	23	-0.19	-0.15	0.04	[-0.08; 0.16]
Mahmud 2020	8	0.76	0.59	-0.17	[-0.52; 0.18]
Random effects model	**80**			**-0.14**	**[-0.38; 0.09]**
Heterogeneity: I^2 = 93%, τ^2 = 0.0333, p < 0.0001					
Measure = BMI SDS					
Sun 2009	49	1.00	0.90	-0.10	[-0.14; -0.06]
Mackinder 2014	23	-0.03	0.07	0.10	[0.01; 0.19]
Rami 2005	74	0.33	0.43	0.10	[0.08; 0.12]
Valletta 2007	23	0.29	0.39	0.10	[0.06; 0.14]
Mahmud 2020	8	0.88	0.67	-0.21	[-0.49; 0.07]
Random effects model	**177**			**0.03**	**[-0.07; 0.13]**
Heterogeneity: I^2 = 94.7%, τ^2 = 0.0110, p < 0.0001					



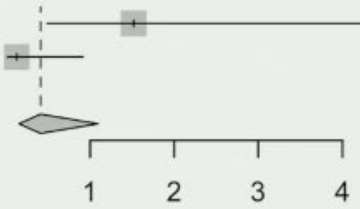
The Evidence: Malignancy

No studies on asymptomatic individuals but the incidence from all patients with celiac disease was pooled

Small bowel adenocarcinoma

Study	Location	Events	n	person-year	Events per 1000 person-years	Events	95%-CI
Green 2003	New York	3	381	1977		1.52	[0.49; 4.70]
Card 2004	Southern Debryshire, England	1	865	7742		0.13	[0.02; 0.92]
Common effect model			**1246**			**0.41**	**[0.15; 1.10]**

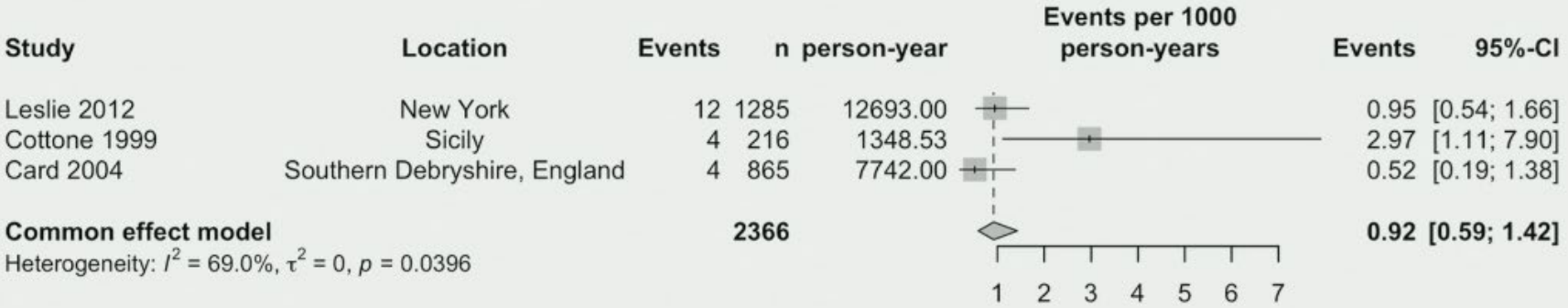
Heterogeneity: I^2 = 78.0%, τ^2 = 0.9780, p = 0.0329



The Evidence: Malignancy

No studies on asymptomatic individuals but the incidence from all patients with celiac disease was pooled

Enteropathy-associated T-cell lymphoma



The Evidence: Summary

Effect of gluten-free diet in asymptomatic celiac disease

Quality of life	No / trivial improvement
Symptoms (asymptomatic at baseline)	Trivial improvement
Growth (normal at baseline)	No impact
Bone mineral density (normal at baseline)	No impact
Risk of malignancy	0.4–0.8 / 1,000 person-yr

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PICO 1 Recommendation

In individuals with asymptomatic celiac disease, the AGA/SSCD make no recommendation on the use of gluten-free diet [no recommendation, very low certainty of evidence]

- *Patients and/or caregivers who place a higher value on avoiding the potential risks of untreated celiac disease such as growth implications (for children), osteoporosis, and/or small intestinal malignancy may reasonably choose to gluten-free diet, whereas patients who place a higher value on the potential drawbacks of GFD such as cost and worsening quality of life may reasonably choose an unrestricted diet.*
- *Individuals who elect to not follow a gluten-free diet need to be monitored periodically for development of symptoms and disease complications.*

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PICO 3: Asymptomatic with metabolic bone disease

A 41-year-old woman with history of **spinal fracture** was found to have celiac disease. **She was tested as part of evaluation for secondary osteoporosis which was found due to the fragility fracture.**

She reports no abdominal pain, nausea, vomiting, diarrhea, constipation, bloating, or heartburn. He reports no headaches, joint pain, fatigue, or brain fog. She feels completely well aside from her back pain.

Her laboratory testing shows no evidence of LFT abnormalities or anemia. She had a normal TSH and hemoglobin A1c.

Should she start a gluten-free diet?

Benefits vs Harms

- *Less fragility fractures*
- *Change in bone mineral density*
- *Quality of life better?*
- *Potential growth (children)?*
- *Less intestinal malignancies?*
- *Less nutritional deficiencies?*

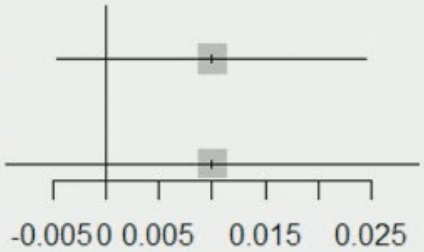
- *Quality of life worse?*
- *Quality of life for caregiver/family?*
- *New onset GI symptoms?*
- *More nutritional deficiencies?*
- *Worse food insecurity?*

The Evidence: Change in Bone Density

RCT comparing GFD vs no GFD for 1 year in Patients with Normal Bone Density at Baseline

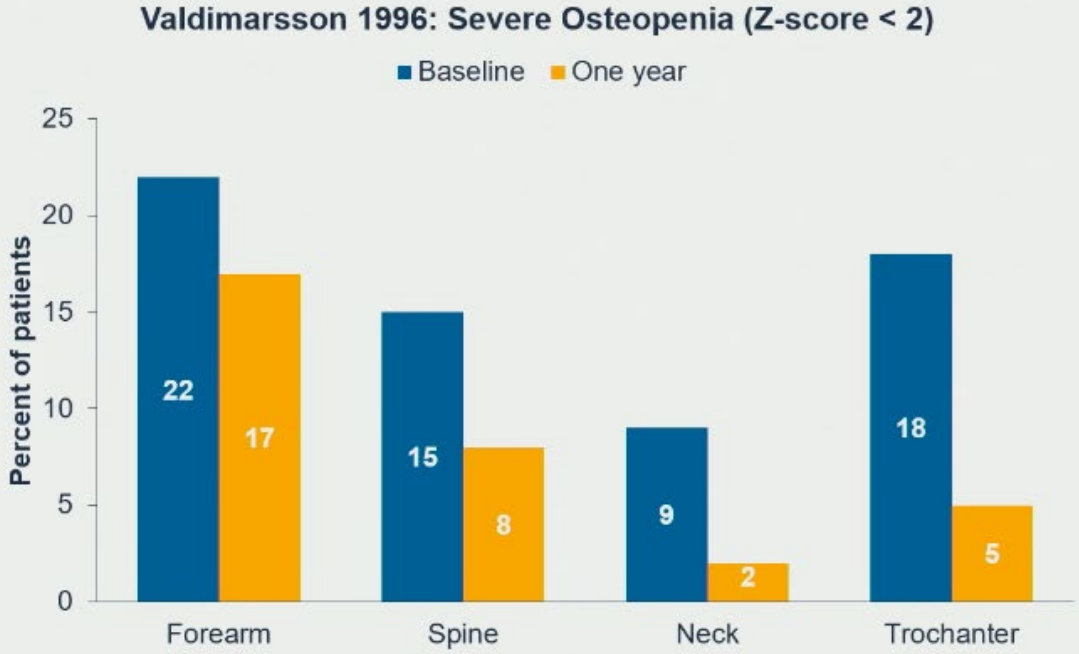
Study	outcome	Total	Mean	SD	Mean	MRAW	95%-CI
outcome = Lumbr spine BMD							
Kurppa 2014	Lumbr spine BMD	40	0.01	0.0469		0.01	[-0.00; 0.02]
outcome = Femur neck BMD							
Kurppa 2014	Femur neck BMD	40	0.01	0.0625		0.01	[-0.01; 0.03]

Heterogeneity: I^2 = 0.0%, τ^2 = 0, p = 1.0000



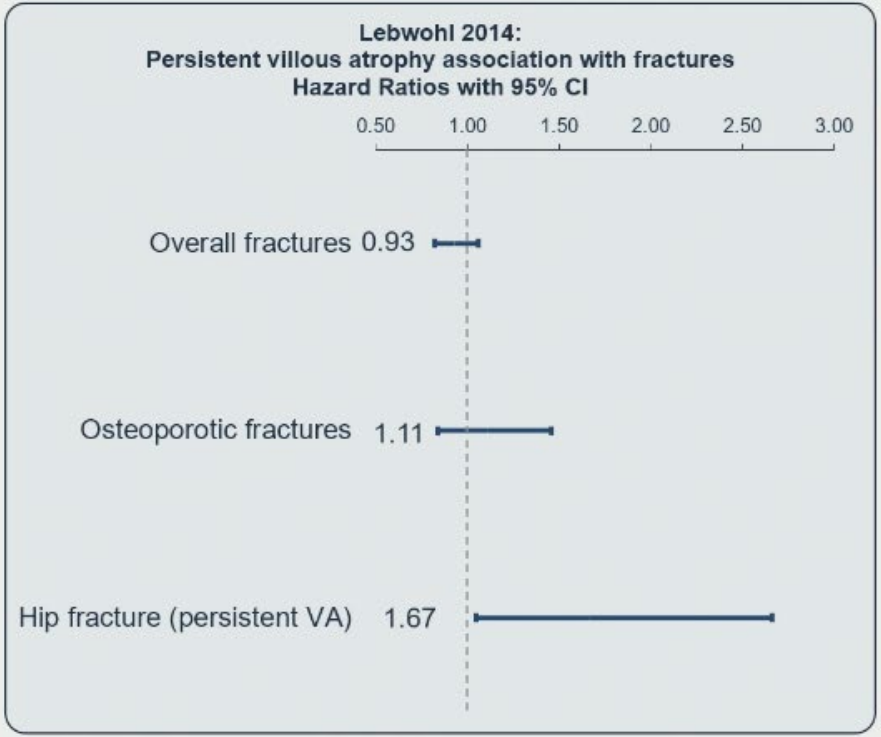
The Evidence: Change in Bone Density

Observational study (1 year of GFD including 29 symptomatic and 34 asymptomatic)



The Evidence: Risk of Fractures

Comparative observational study of all patients with celiac disease



PICO 3 Recommendation

In individuals with asymptomatic celiac disease with metabolic bone disease, the AGA/SSCD suggest for the use of gluten-free diet [conditional recommendation, very low certainty of evidence]

- *Given the uncertain relationship between imaging assessment of bone mineral density and pathologic fracture risk in this population and the uncertain benefit for skeletal benefit, implementation should be individualized with focus on patient values, baseline bone health, fracture risk, role of antiresorptive therapy, and tolerance for treatment burden.*

PICO 5: Asymptomatic with short stature

A prepubertal **8-year-old** girl with no past medical history was found to have celiac disease. **She was tested as part of evaluation for short stature.**

She reports no abdominal pain, nausea, vomiting, diarrhea, constipation, bloating, or heartburn. She reports no headaches, joint pain, fatigue, or brain fog. She feels completely well.

Her laboratory testing shows no evidence of anemia. She had normal TSH and LFTs.

Should she start a gluten-free diet?

Benefits vs Harms

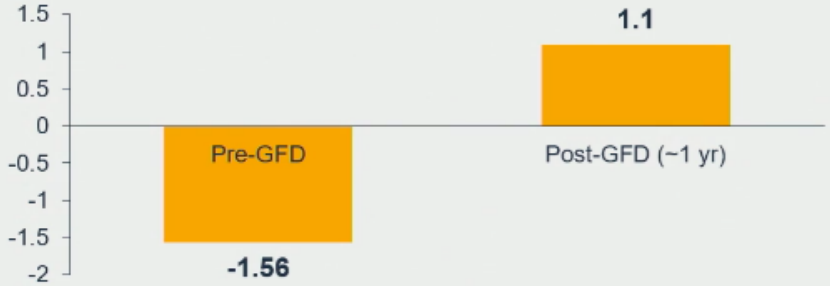
- *Catch up growth*
- *Quality of life better?*
- *Potential growth (children)?*
- *Less fragility fractures?*
- *Less intestinal malignancies?*
- *Less nutritional deficiencies?*

- *Quality of life worse?*
- *Quality of life for caregiver/family?*
- *New onset GI symptoms?*
- *More nutritional deficiencies?*
- *Worse food insecurity?*

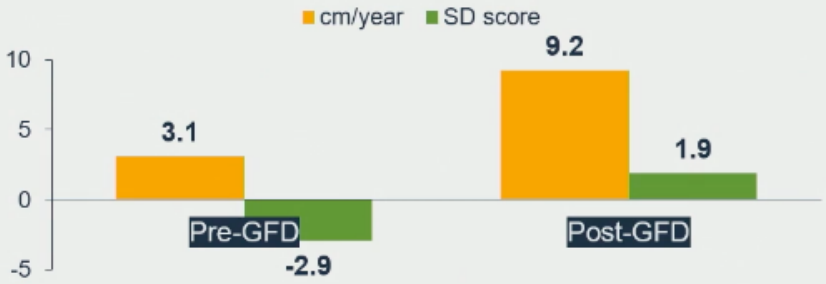
The Evidence: Change in Growth Velocity

Groll 1980 (n=6): Height Velocity Acceleration

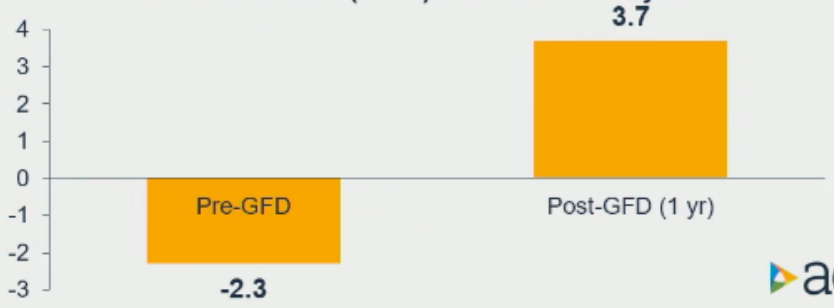
Cacciari 1985 (n=11): Growth Velocity SD



Rosenbach 1986 (n=11): Height Velocity



Bonamico 1992 (n=29): Growth Velocity SD



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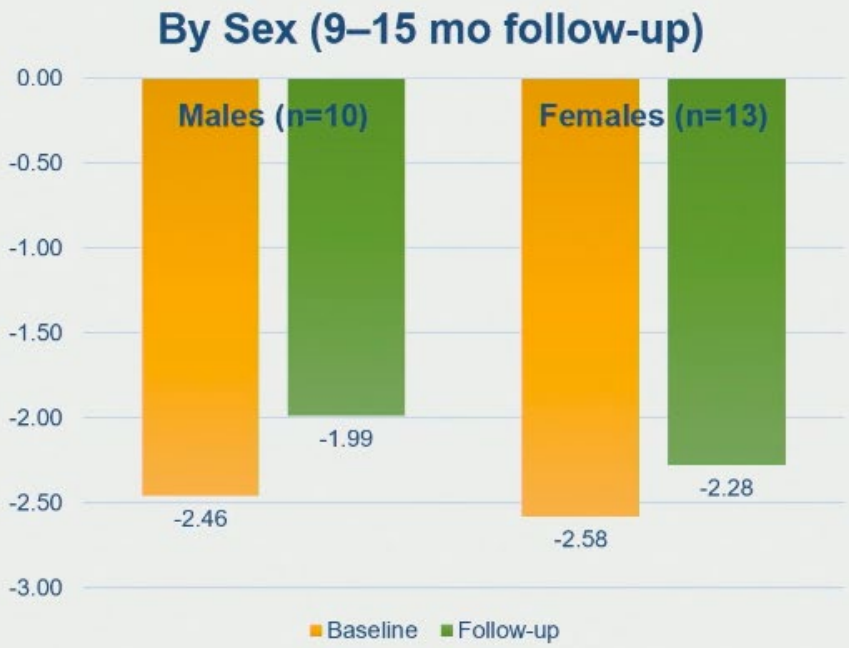
The Evidence: Change in Height Z-Score

Bosio 1990



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PICO 5 Recommendation

In prepubertal children or adolescents with asymptomatic celiac disease with short stature, the AGA/SSCD suggest for the use of gluten-free diet [conditional recommendation, very low certainty of evidence]

- *The impacts of even strict adherence to a gluten-free diet on catch up growth are variable and earlier intervention relative to puberty onset and bone age is suspected to improve the chances of greater catch-up*

PICO 8: Asymptomatic with Down Syndrome

A 19-year-old man with history of **Down syndrome** was found to have celiac disease. **He was tested as part of screening.**

He reports no abdominal pain, nausea, vomiting, diarrhea, constipation, bloating, or heartburn. He reports no headaches or joint pain. He feels well.

His laboratory testing shows no evidence of anemia. He had normal TSH and LFTs. He had a normal DEXA scan.

Should he start a gluten-free diet?

Benefits vs Harms

- *Improved behavioral outcomes*
- *Quality of life better?*
- *Potential growth (children)?*
- *Less fragility fractures?*
- *Less intestinal malignancies?*
- *Less nutritional deficiencies?*

- *Quality of life worse?*
- *Quality of life for caregiver/family?*
- *New onset GI symptoms?*
- *More nutritional deficiencies?*
- *Worse food insecurity?*

The Evidence

PICO 8 Recommendation

In individuals with asymptomatic celiac disease and Down syndrome, the AGA/SSCD make no recommendation on the use of gluten-free diet [no recommendation; knowledge gap]

- *The presentation of celiac disease can vary and individuals with Down syndrome may have difficulty recognizing or reporting symptoms. While symptom checklists for adults with Down syndrome (e.g. Global Down Syndrome Foundation checklist) have been developed and variably implemented, these under-recognized symptoms may not be appreciated until after treatment with a gluten-free diet.*
- *The challenges of the gluten-free diet including adherence may present barriers in patients with Down syndrome*

PICO Question	Patient	Recommendation	Strength of Recommendation	Certainty
1	Asymptomatic No EIM or associated conditions	The AGA/SSCD make **no recommendation** on the use of gluten-free diet	No recommendation	Very low
2	Asymptomatic with iron deficiency	The AGA/SSCD **suggest for** the use of gluten-free diet	Conditional	Very low
3	Asymptomatic with metabolic bone disease	The AGA/SSCD **suggest for** the use of gluten-free diet	Conditional	Very low
4	Asymptomatic with liver enzyme abnormalities	The AGA/SSCD **suggest for** the use of gluten-free diet	Conditional	Very low
5	Asymptomatic with short stature	The AGA/SSCD **suggest for** the use of gluten-free diet	Conditional	Very low
6	Asymptomatic with T1D	AGA/SSCD make **no recommendation** on the use of gluten-free diet	No recommendation	Very low
7	Asymptomatic with autoimmune thyroid disease	AGA/SSCD make **no recommendation** on the use of gluten-free diet	No recommendation	Very low
8	Asymptomatic with Down Syndrome	AGA/SSCD make **no recommendation** on the use of gluten-free diet	No recommendation	Knowledge gap