

How Low Can You Go?

Targeting of Deep Remission in the
Management of Crohn's Disease

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Integrate knowledge of the heterogeneity of CD in severity and manifestation into patient assessment and treatment.

LEARNING
OBJECTIVE

1



Utilize alternative diagnostic and evaluation tools beyond colonoscopy for evaluating symptoms in patients with CD.

LEARNING
OBJECTIVE

2



Incorporate histopathologic treatment targets as an objective measure of inflammation in CD to inform clinical decision-making.

LEARNING
OBJECTIVE

3





Disease Heterogeneity in CD

Marita Kametas, MSN, APN, FNP-BC, CMSRN, COCN

CD Classification and Risk Factors for Severe Disease



Risk Factors for Severe Disease

- ▶ Under age 30 at diagnosis
- ▶ Extensive anatomic involvement
- ▶ Perianal disease
- ▶ Severe rectal disease
- ▶ Deep ulcers
- ▶ Previous surgical resection
- ▶ Stricturing behavior
- ▶ Penetrating behavior

Montreal Classification

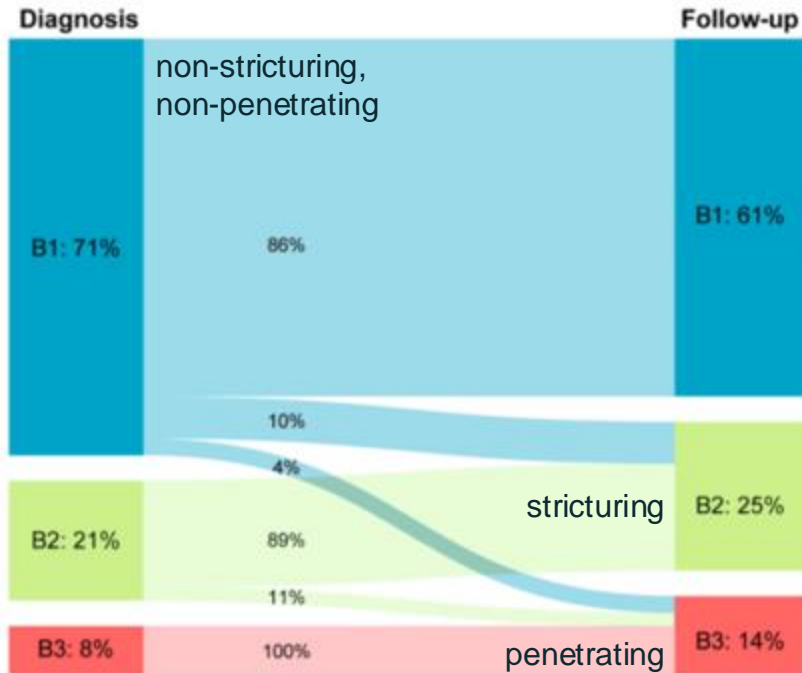
- ▶ Age at diagnosis
 - ▶ < 17
 - ▶ 17-40
 - ▶ > 40
- ▶ Location-terminal ileum +/- limited cecal disease, colonic, ileocolonic, isolated upper
- ▶ Behavior: stricturing, penetrating or perianal involvement

Disease Course Frequently Changes in CD

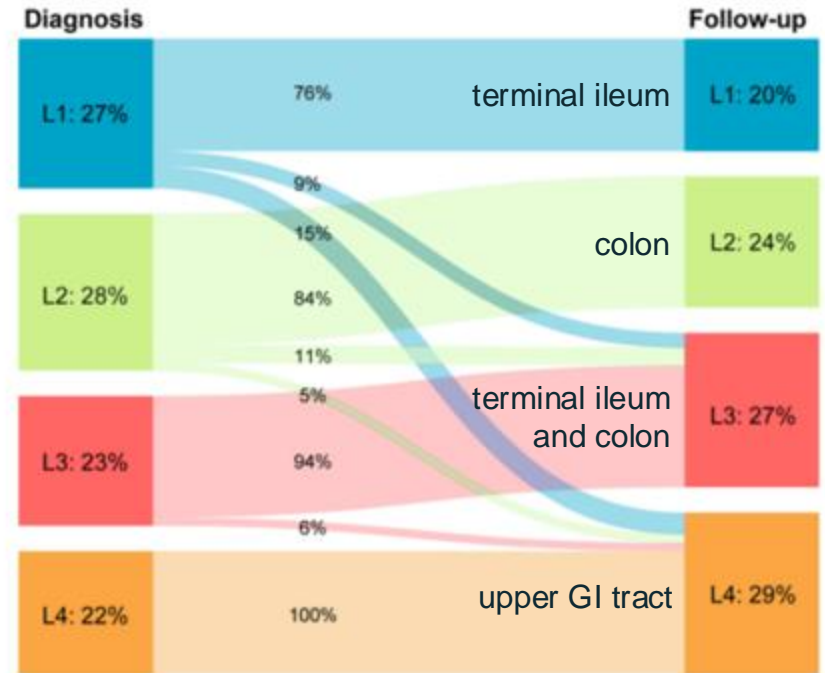


Epi-IBD Cohort: 5-Year Follow-Up of Patients with CD

Changes in Disease Behavior



Changes in Disease Location



CD Activity Versus Disease Severity



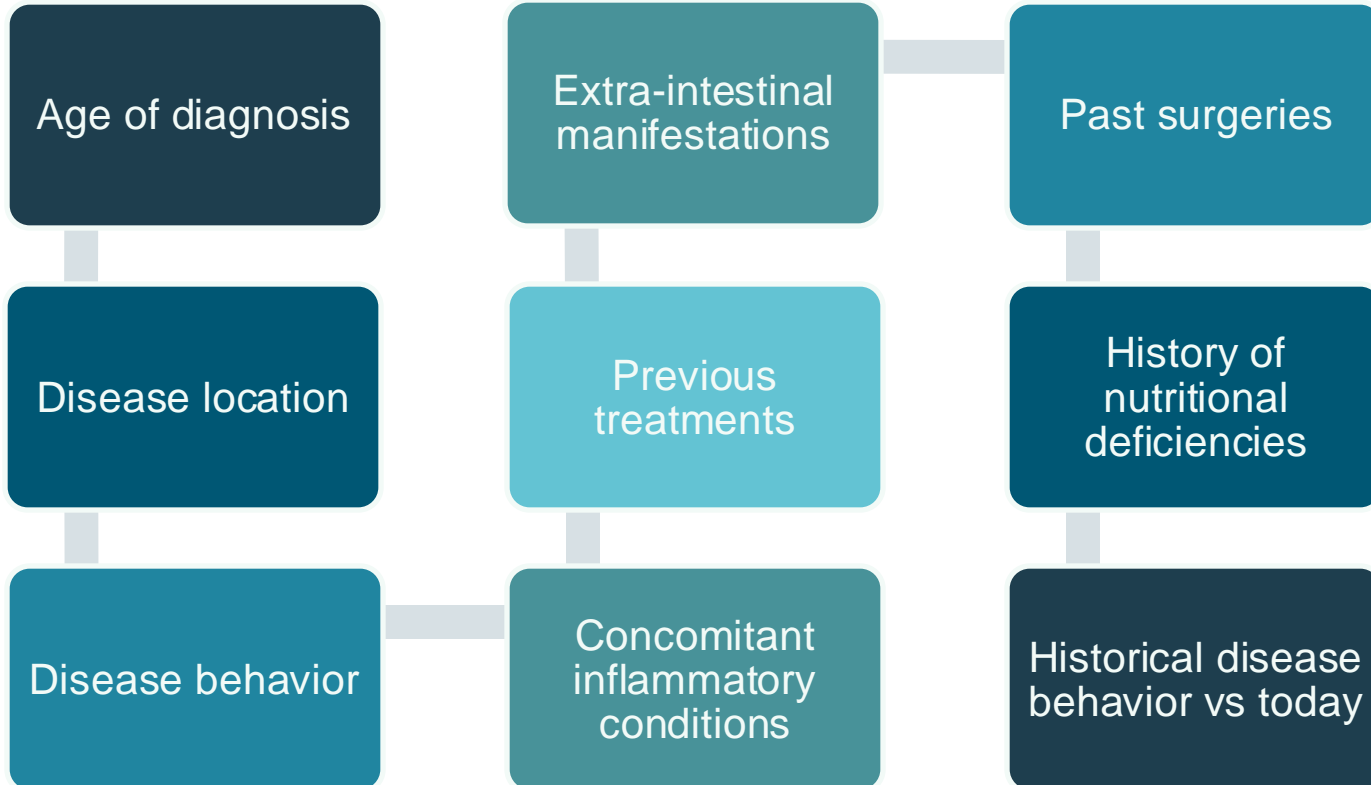
Activity

- Current inflammatory burden
- Current symptom burden
- Objective and subjective assessments of current activity

Severity

- Historical disease behavior
- Need for surgery
- Extent of bowel involvement
- Complications

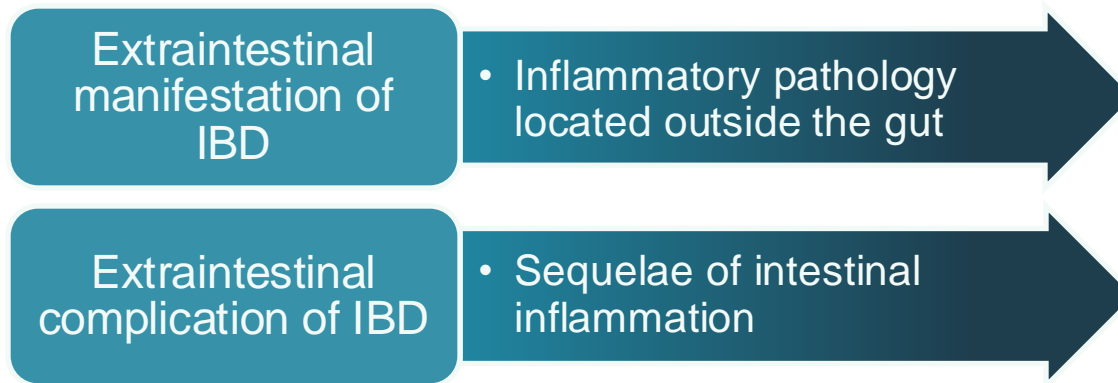
Complexity Complicates CD Monitoring and Treatment



Extraintestinal Manifestations (EIMs) are Unpredictable but Frequent in CD



- ▶ EIMs occur in varying frequency
 - ▶ Up to 50% of patients with IBD have at least 1 EIM
- ▶ EIMs can occur before or after diagnosis of IBD
 - ▶ One in four patients develop an EIM before diagnosis
- ▶ Can be dependent on or independent of intestinal inflammation



Treat-to-Target (T2T) Approach in IBD

Step 1: Disease control

Clinical response
Clinical remission



Biomarker normalization
Endoscopic healing
Normal growth



Returning to a normal life: disability, QoL



Step 2: Disease modification

Preventing disease complications



Reducing long-term complications



Disease onset

Historical:
Clinical response and remission

Current:
Clinical response and remission
CRP and calprotectin normalization
Endoscopic healing
Normal QoL and no disability

Future:
Histologic healing (UC)
Transmural healing (CD)



Historical:
No need for surgery/hospitalization

Current:
Normal QoL and no disability/incontinence
No need for surgery/hospitalization
No bowel damage (CD)/extension (UC)
No extra-intestinal manifestations
No permanent stoma or SBS

Future:
Reduced cancer and mortality risk



Outcomes Associated with Mucosal and Transmural Healing in CD



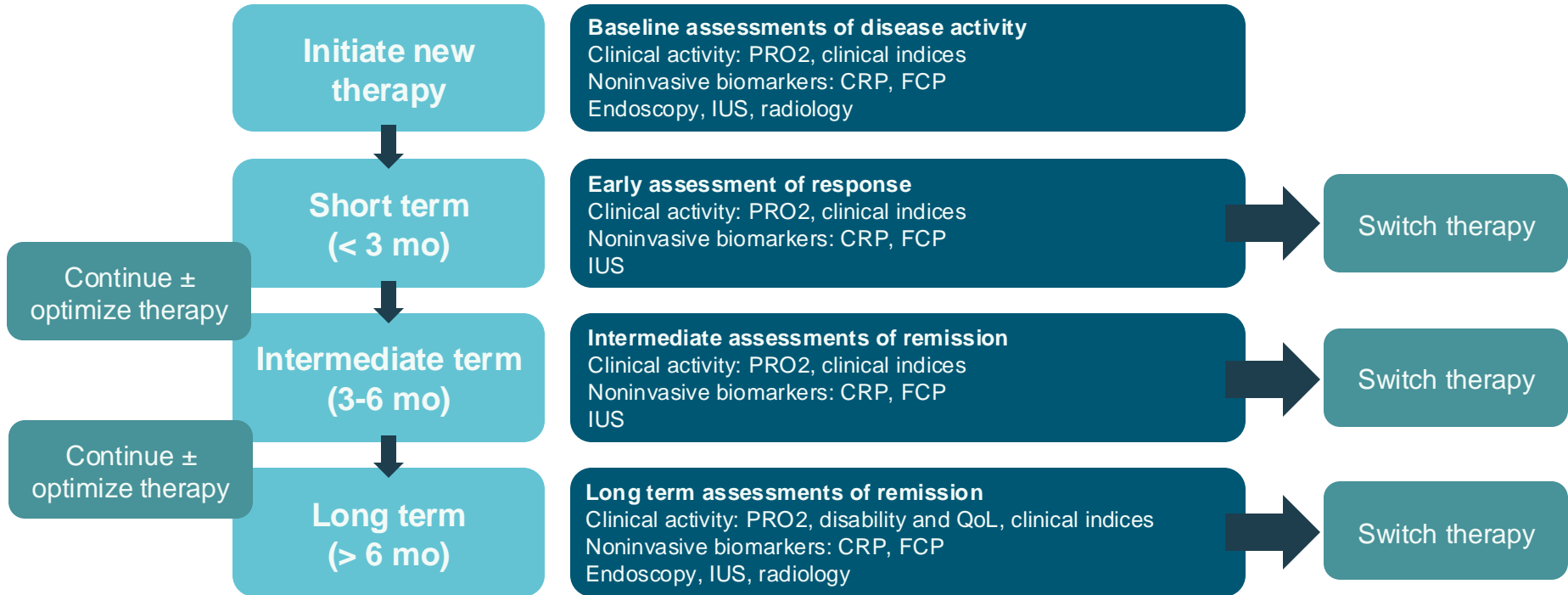
Lower rates of corticosteroid utilization

Lower rates of hospitalization

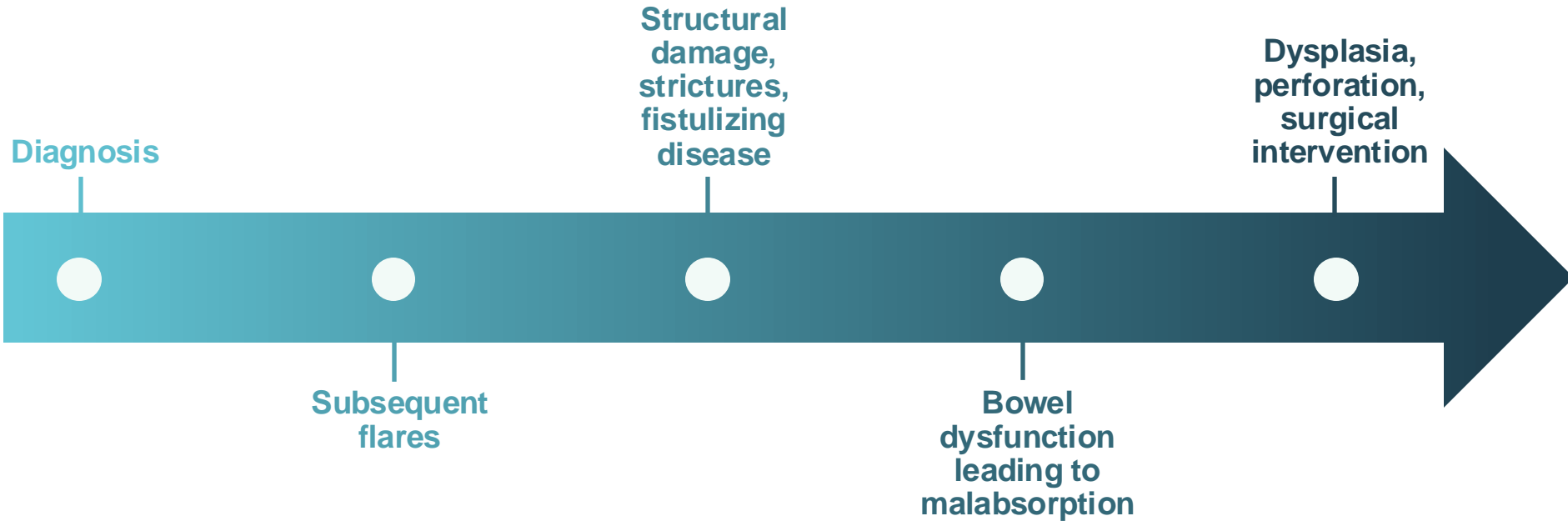
Decreased rates of relapse or need for treatment escalation

Decreased rate of surgical intervention

Evaluating Response Using a T2T Approach



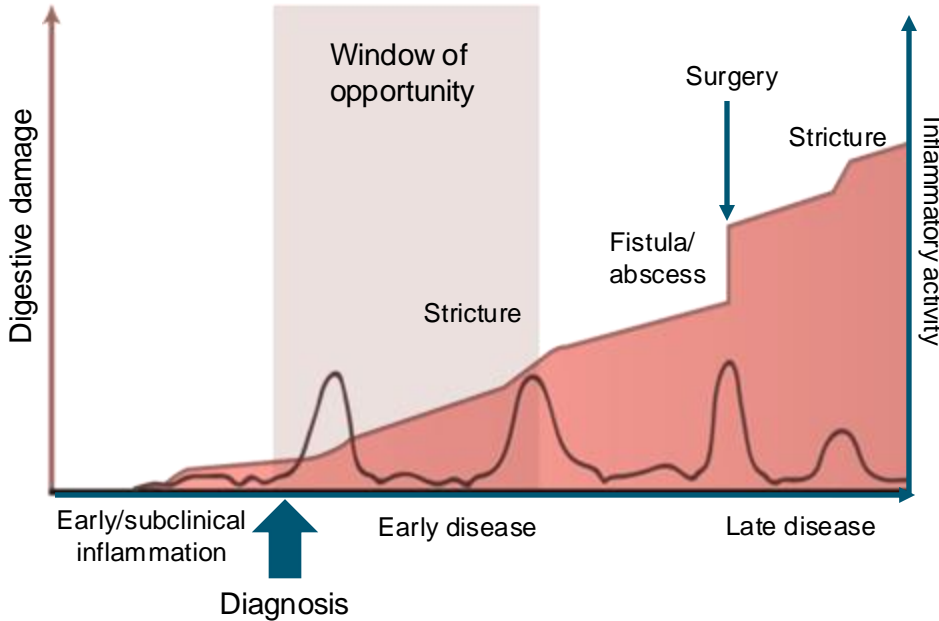
Consequences of Recurrent Inflammatory Activity



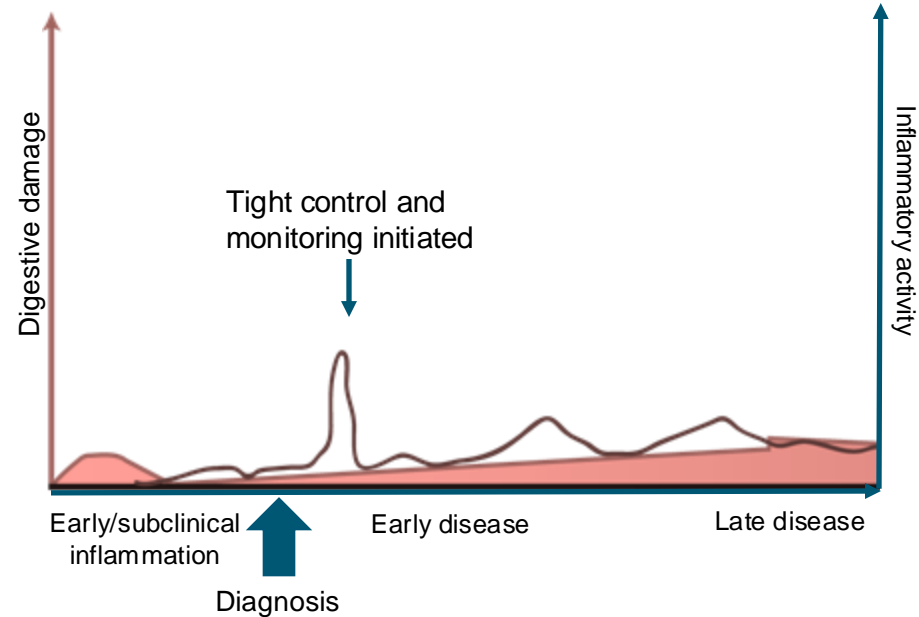
Early Diagnosis and Early Treatment are Key to Preventing Complications



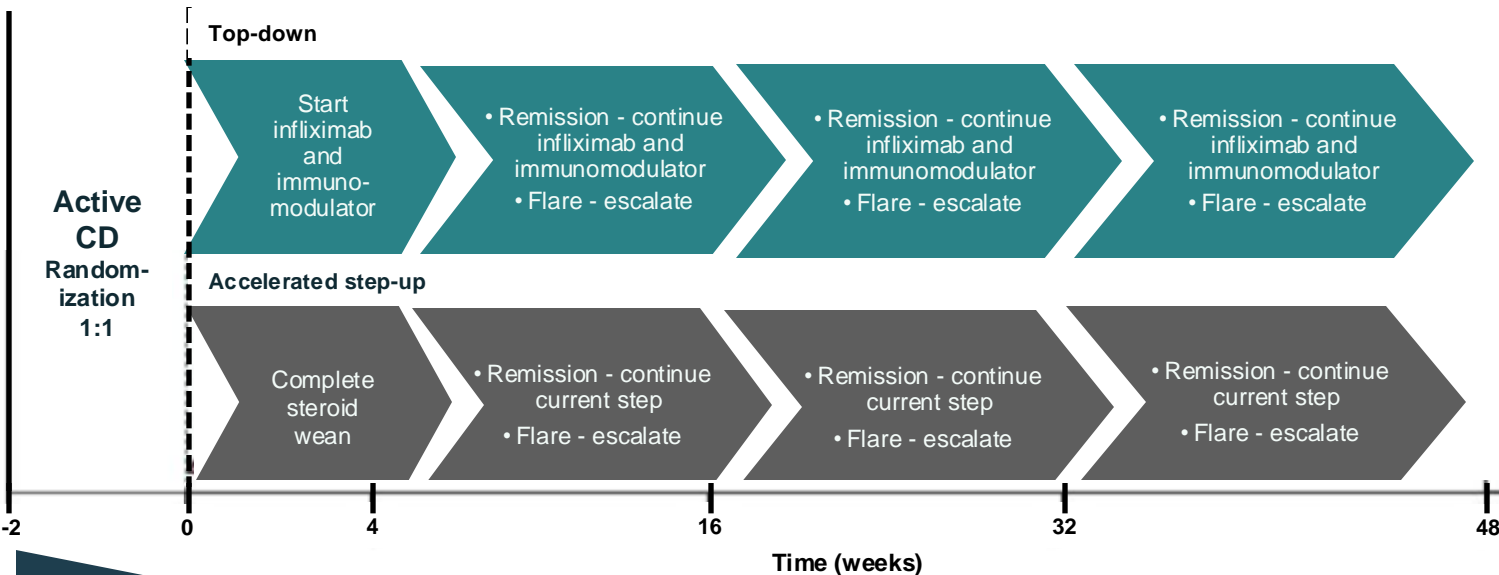
Natural Course of CD



Theoretical Impact of Early Intervention and Effective Treatment



PROFILE: Comparison of Two CD Treatment Strategies



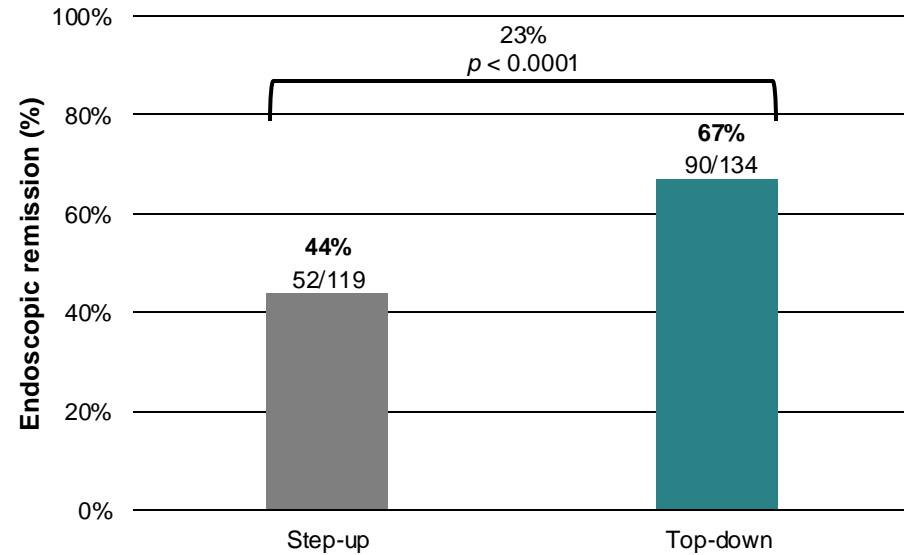
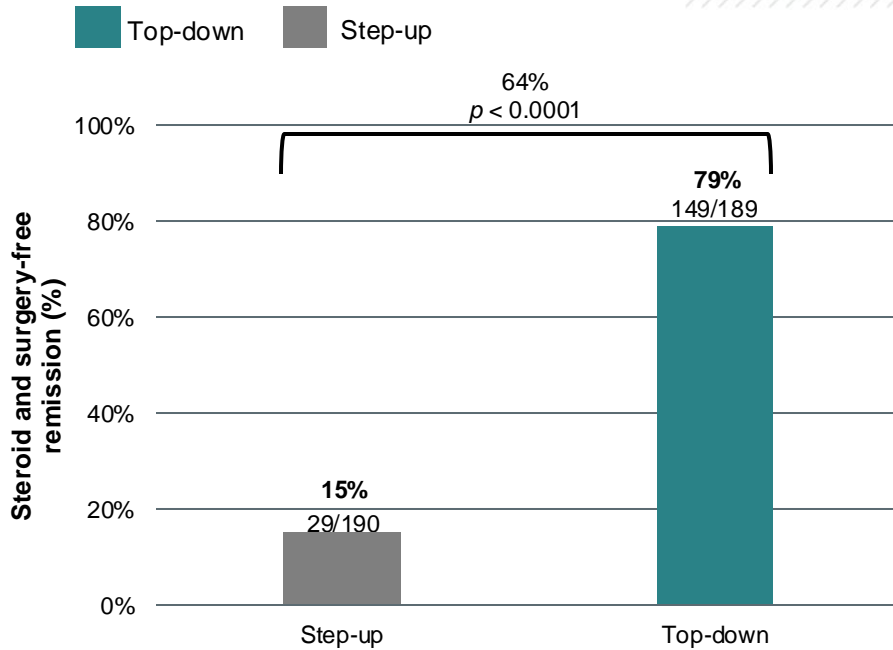
- Primary endpoint**
- ▶ Sustained surgery-free and steroid-free remission to week 48
- Secondary endpoints**
- ▶ Endoscopic remission
 - ▶ QoL
 - ▶ Surgeries and hospitalizations
 - ▶ Disease flares
 - ▶ Steroid courses

Steroid taper

Top-down n = 193	If in remission, continue infliximab and immunomodulator Flare 1, additional course of steroid medication Flare 2, consider non-response and trial withdrawal
Accelerated step-up n = 193	If in remission, continue current step of treatment Flare 1, start steroids and immunomodulator Flare 2, start infliximab alongside immunomodulator

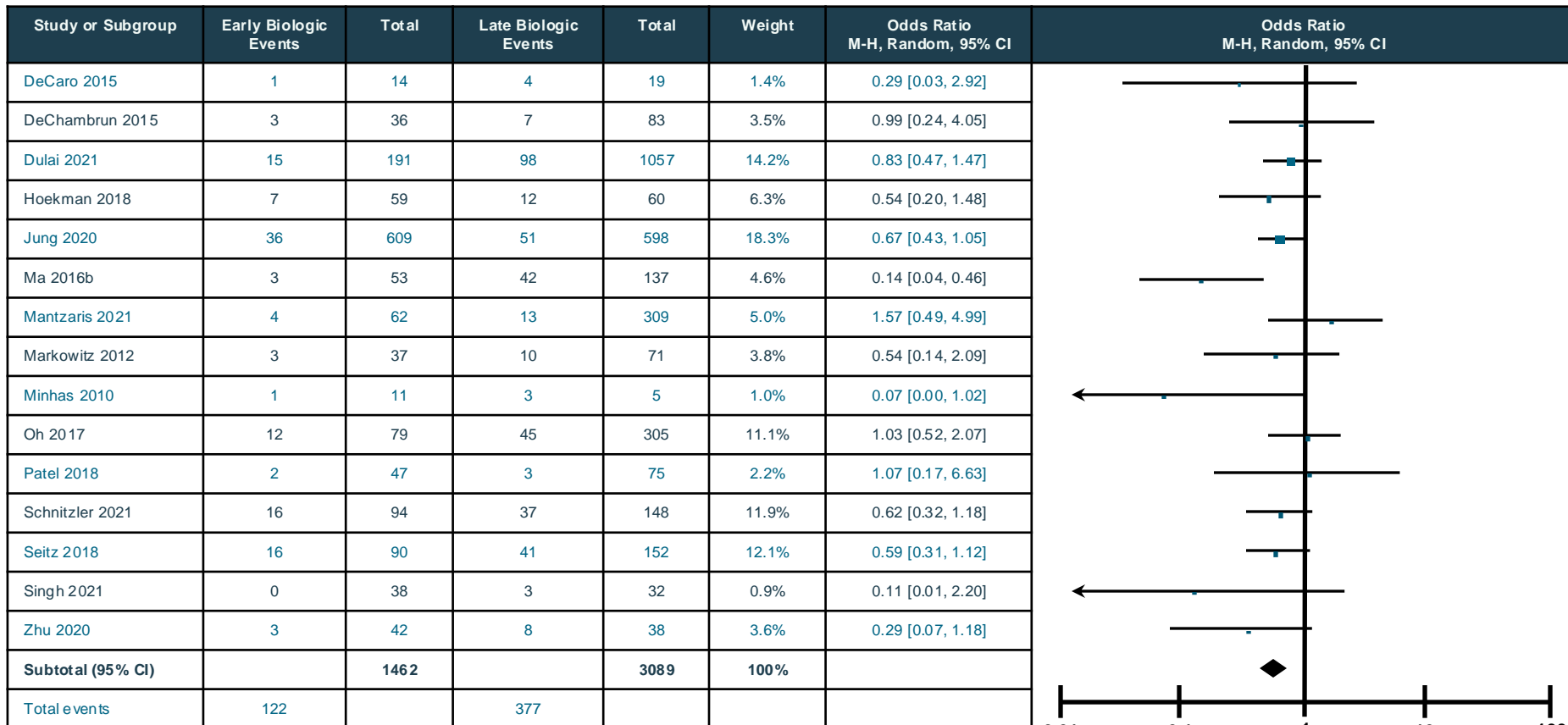


PROFILE: Top-Down Treatment Strategy of Infliximab + Immunomodulator Led to Improved Remission Rates



Requiring failure of conventional step therapy prior to advanced therapy is not recommended

Early Biologic Therapy Decreases the Risk of Surgery in CD



Heterogeneity: Tau² = 0.06; Chi² = 18.00, df = 14 (p = 0.21); I² = 22%.

Test for overall effect: Z = 3.18 (p = 0.001).

Early equates to < 3 years of diagnosis or top-down treatment; late equates to > 3 years of diagnosis or step-up treatment.

0.01 0.1 1 10 100
Favors Early Biologic Favors Late Biologic

CI = confidence interval.

Law CCY, et al. *Inflamm Bowel Dis.* 2024;30(7):1080-1086.



Summary



- ▶ Disease severity that considers a patient's overall disease course should drive treatment selection rather than current disease activity
- ▶ Tight control of inflammation can prevent complications in CD
- ▶ Early advanced therapy is appropriate without requiring failure of conventional step therapy



Faculty Discussion

What are some unmet needs in clinical practice or practice areas not addressed by guidelines?

A photograph of a doctor and a patient in a clinical setting, overlaid with a blue gradient and white text. The doctor is on the left, wearing a white lab coat and a stethoscope, looking towards the patient. The patient is on the right, wearing a striped shirt, looking towards the doctor. The background is a light blue wall with a window. The text is centered and reads:

Monitoring Beyond Endoscopy: Noninvasive Monitoring Tools in Gastroenterology Practice

Millie D. Long, MD, MPH

Limitations of Endoscopy in CD



Variability in scoring between observers

Disease activity below mucosal surface is not captured

Utility limited by patient's ability to access care and resources

Patients require preparation, time off work, and post-procedure support

Time-consuming

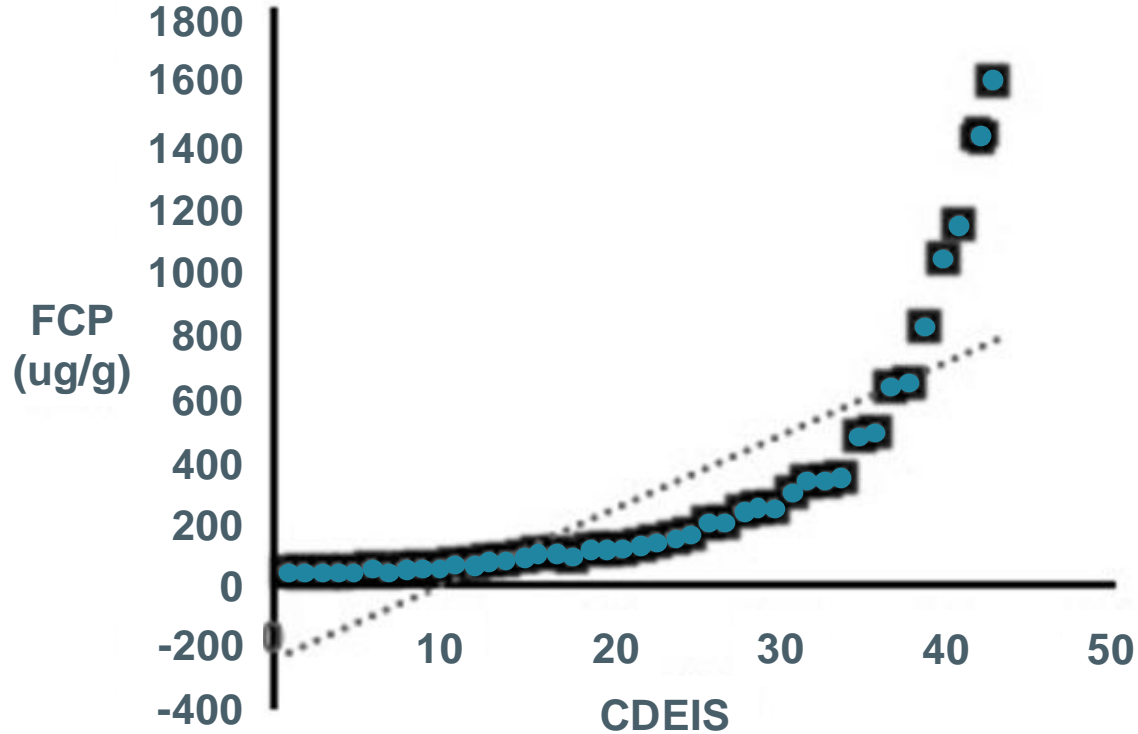
Delays can occur for many reasons (scheduling, cost, etc.)

Noninvasive Monitoring



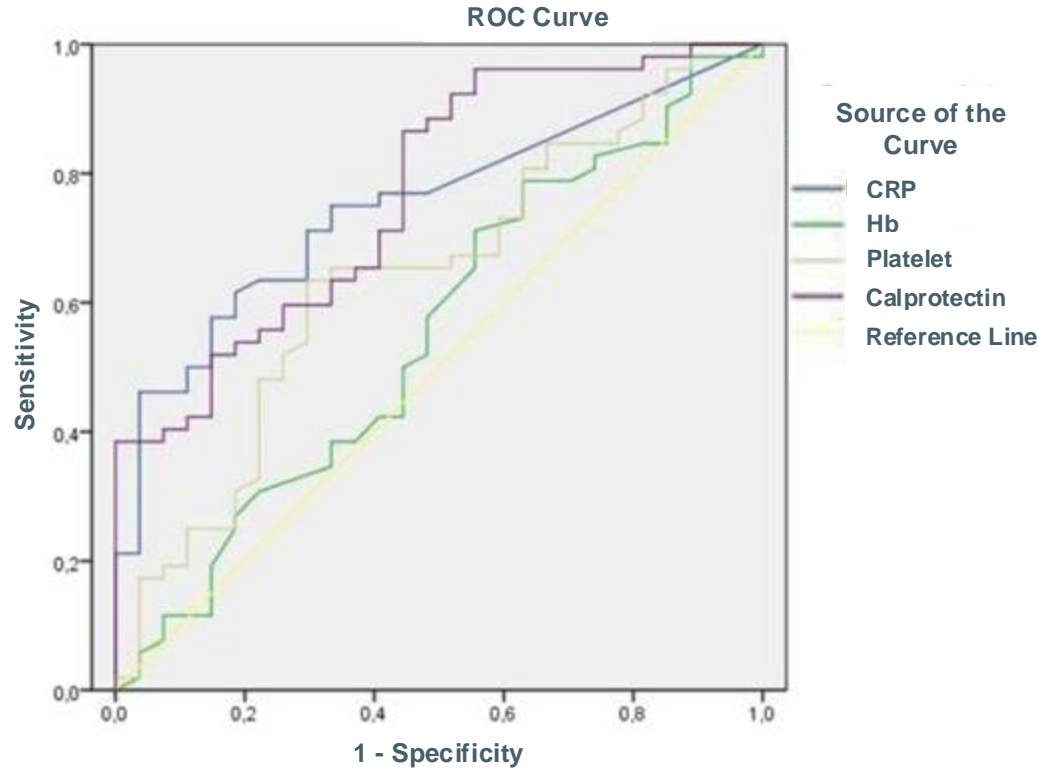
- ▶ Biomarkers
- ▶ Cross-sectional imaging
 - ▶ Magnetic resonance enterography (MRE)
 - ▶ Intestinal ultrasound (IUS)
 - ▶ Computed tomography enterography (CTE)
- ▶ Capsule endoscopy

FCP Levels Significantly Correlate with MRE Disease Activity in Colonic CD



CDEIS = Crohn's Disease Endoscopic Index of Severity.
Somwaru AS, et al. *BMC Gastroenterol.* 2019;19:210.

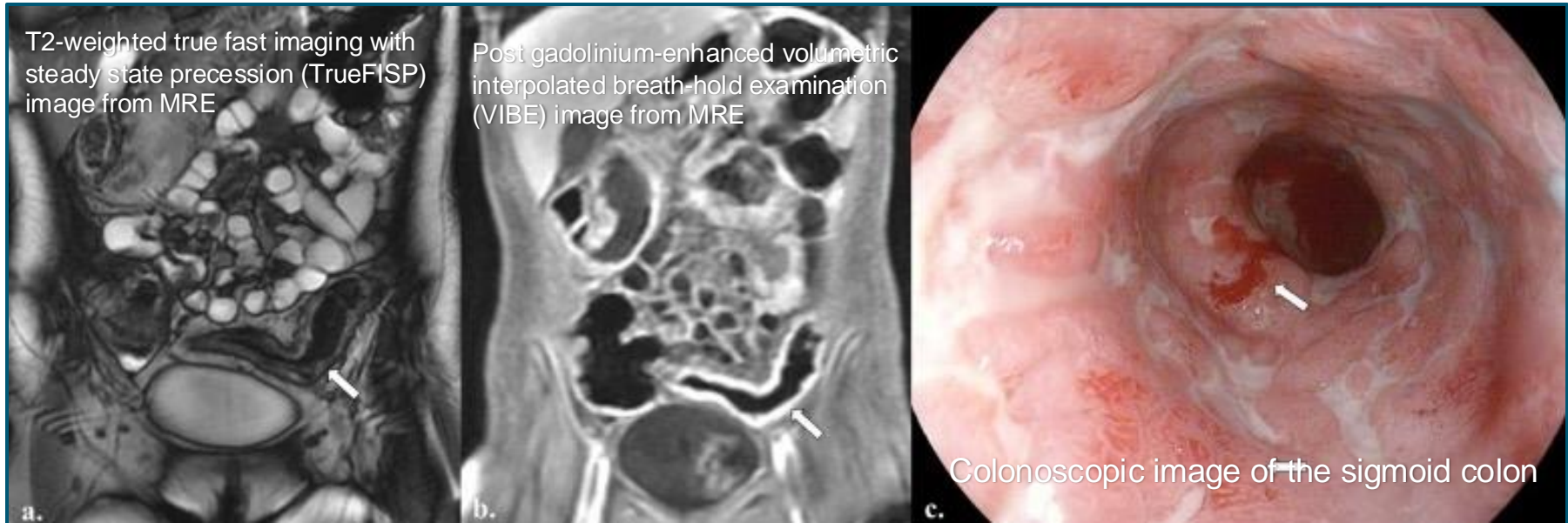
Fecal Calprotectin is the Best Biomarker for Assessing Overall CD Activity



FCP Levels Significantly Correlate with MRE Disease Activity in Colonic CD



- ▶ 27-year-old female with colonic CD and abdominal pain of increasing severity
- ▶ FCP of 436 $\mu\text{g/g}$, MaRIA score of 15 on MRE (severe), and CDEIS of 26 on colonoscopy



FCP < 50 µg/g in Post-Ileocolonic Resection Associated with Low Risk of Recurrence



	FCP < 50 µg/g (n = 15)	FCP ≥ 50 µg/g (n = 22)	p-value
Low-risk, n (%)	7 (47%)	13 (59%)	0.51
High-risk received prophylaxis, n (%)	8 (53%)	9 (41%)	
Median time to endoscopic recurrence, days	-	145 (56-217)	N/A
Ever endoscopic recurrence, n (%)	0 (0%)	9 (36%)	0.006
Median time to surgical recurrence, days	-	1416 (839-1677)	N/A
Ever surgical recurrence, n (%)	0 (0%)	3 (14%)	0.26

Multiple Factors and Conditions are Associated with Elevated FCP Levels



Infectious	Inflammatory Conditions
<ul style="list-style-type: none"> ▶ Bacterial dysentery ▶ Giardia lamblia ▶ <i>Helicobacter pylori</i> gastritis ▶ Infectious diarrhea ▶ Viral gastroenteritis 	<ul style="list-style-type: none"> ▶ Inflammatory bowel disease ▶ Autoimmune enteropathy ▶ Cirrhosis ▶ Cystic fibrosis ▶ Diverticulitis ▶ Eosinophilic colitis/enteritis ▶ Gastroesophageal reflux disease ▶ Juvenile polyp ▶ Microscopic colitis ▶ Peptic ulcer ▶ Untreated celiac disease
Neoplasms	Other
<ul style="list-style-type: none"> ▶ Colonic and gastric polyps ▶ Colorectal cancer ▶ Gastric carcinoma ▶ Intestinal lymphoma 	<ul style="list-style-type: none"> ▶ Age < 5 years ▶ Untreated food allergy
Drugs	
<ul style="list-style-type: none"> ▶ NSAIDs ▶ PPIs 	

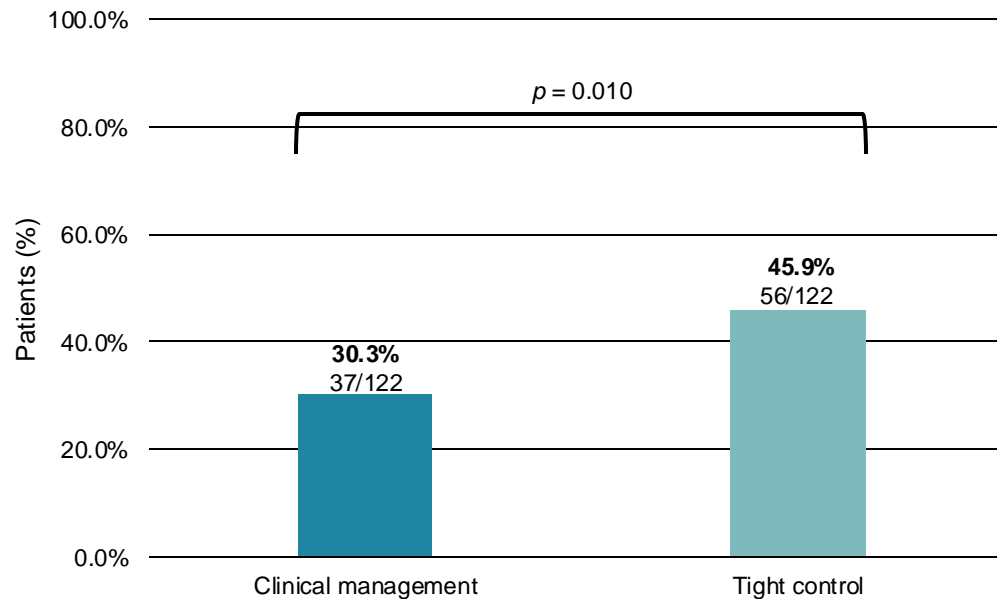
NSAIDs = nonsteroidal anti-inflammatory drugs; PPIs = proton pump inhibitors.

Bressler B, et al. *Can J Gastroenterol Hepatol.* 2015;29(7):369-372.

CALM: Tight Control Monitoring with Biomarkers is Better Than Symptoms Alone

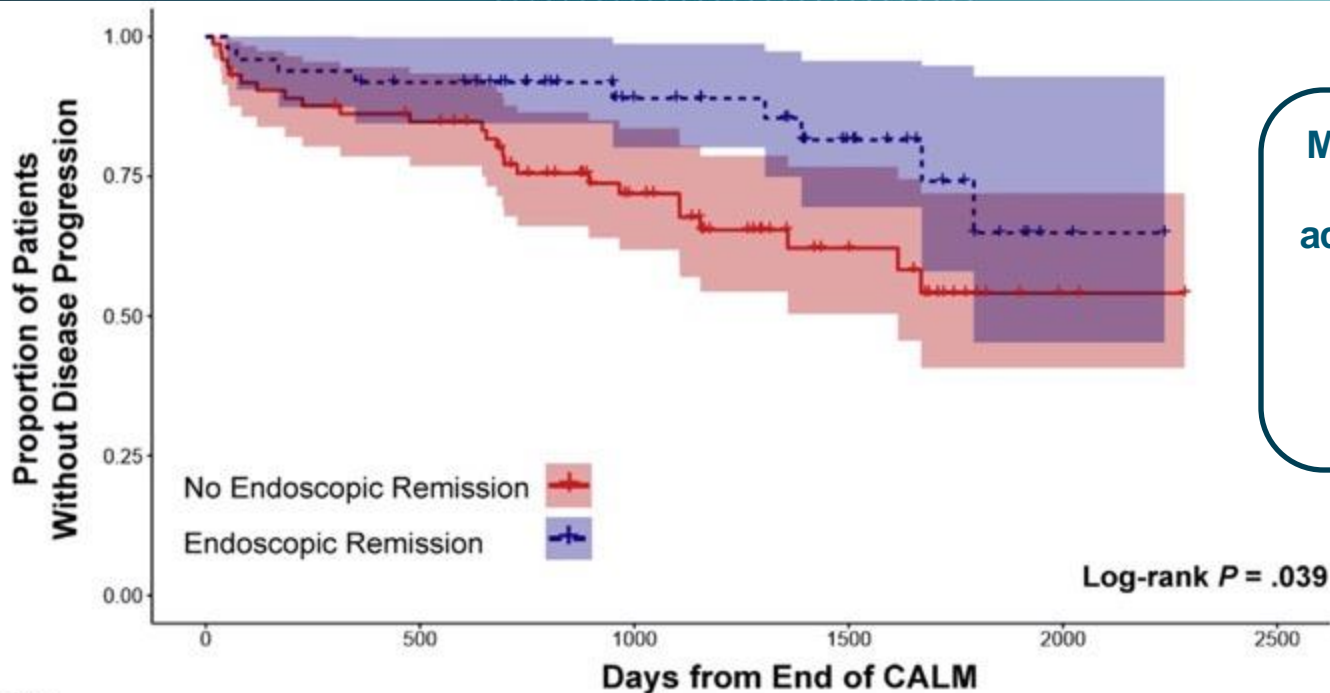


Primary outcome: CDEIS < 4 and no deep ulcers at week 48



More than half of patients in the tight control arm did not achieve mucosal healing

Patients Who Achieve Mucosal Healing Are Less Likely to Have Disease Progression



More than 1/4 of patients who achieve mucosal healing still experience disease progression

Number at risk:	0	500	1000	1500	2000	2500
No Endoscopic Remission	73	59	37	17	2	0
Endoscopic Remission	49	43	28	16	2	0

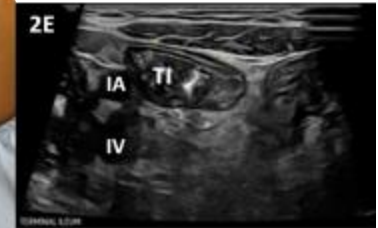
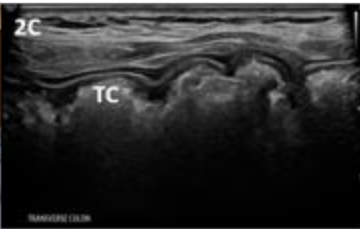
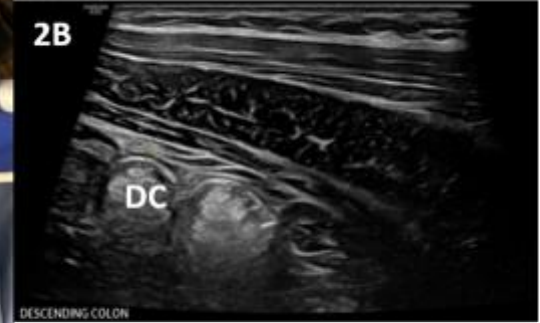
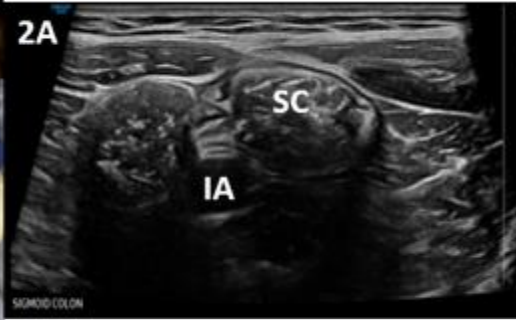
Deep remission defined as CD endoscopic index of severity scores < 4, with no deep ulcerations or steroid treatment, for 8 or more weeks.

Ungaro R. *Gastroenterology*. 2020;159(1):139-147.

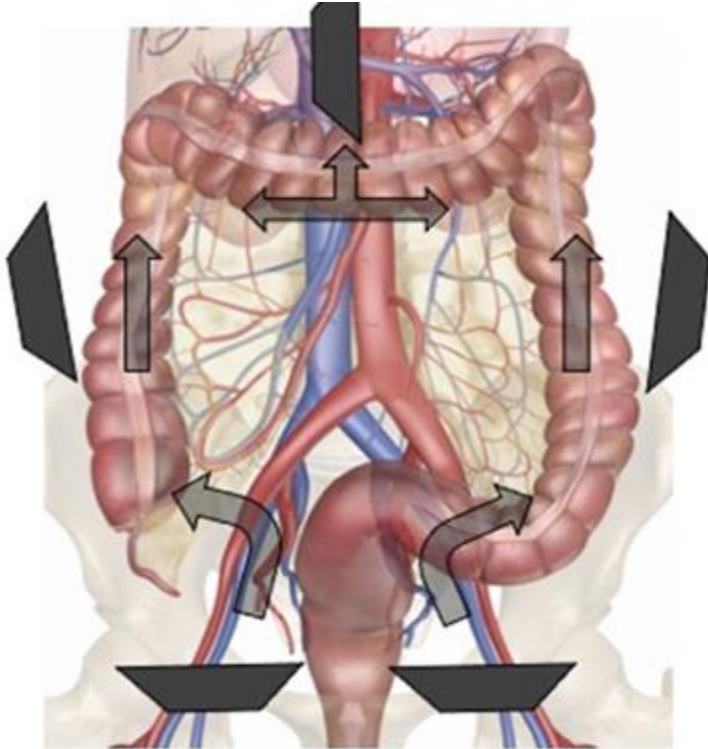
A photograph of a doctor in a white coat and stethoscope talking to a patient in a striped shirt. The image is overlaid with a semi-transparent blue filter. The text is centered in white. There are decorative white diagonal line patterns in the top and bottom corners.

Noninvasive Monitoring to Achieve Tight Control

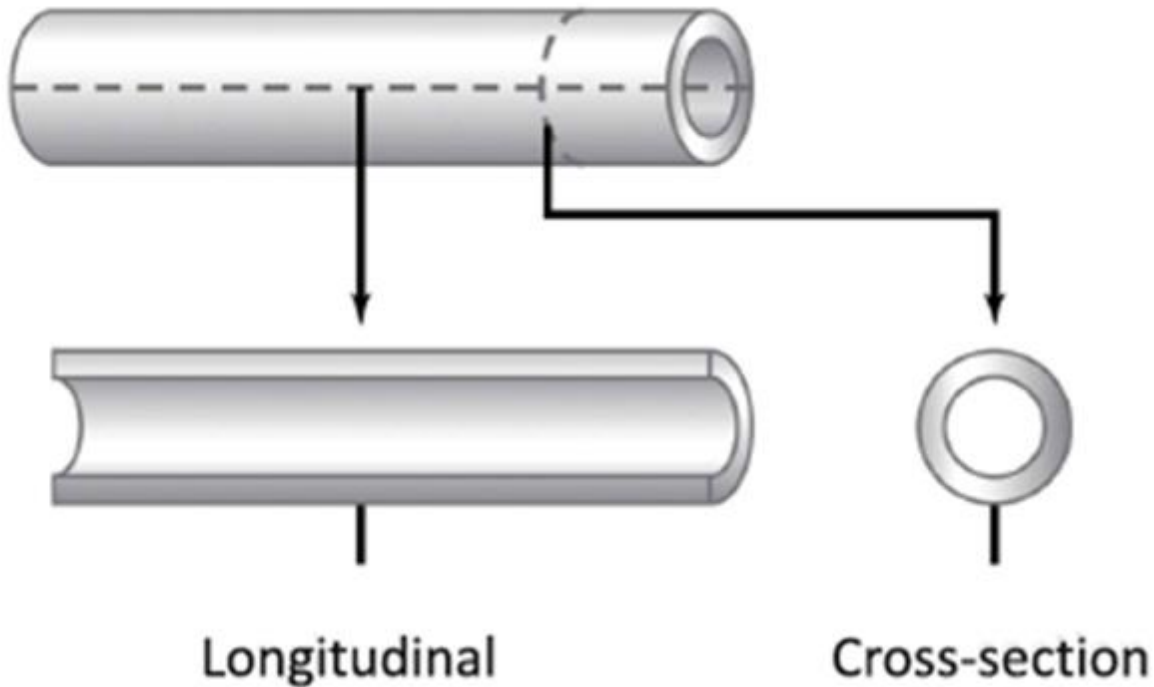
IUS Quickly Visualizes the Colon and Terminal Ileum



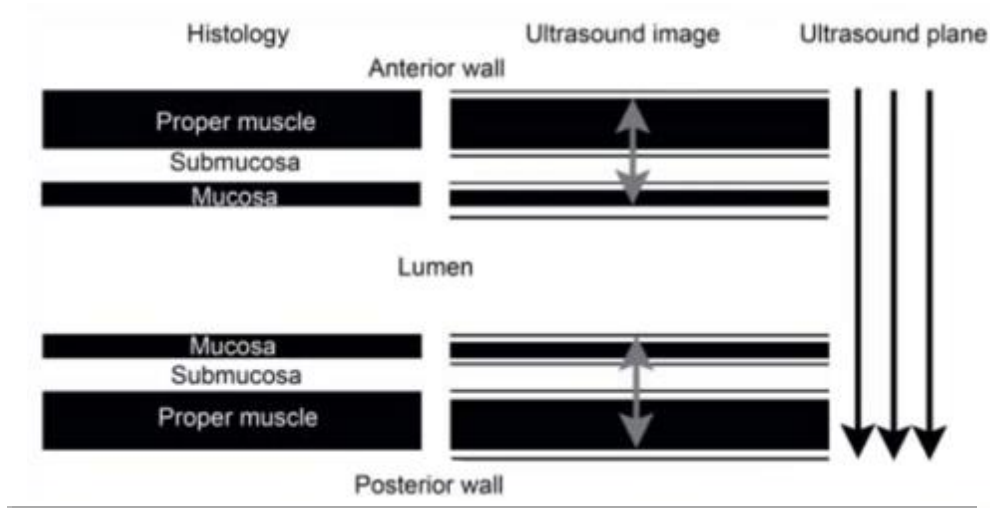
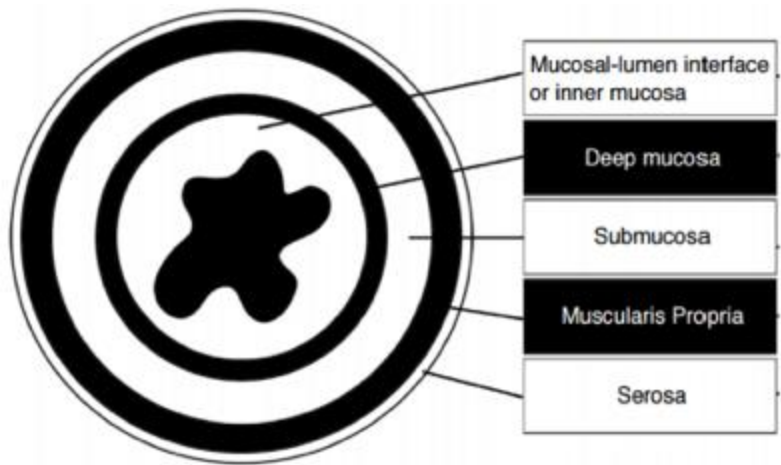
IUS Technique Follows the Same Standardized Approach Regardless of Disease Location



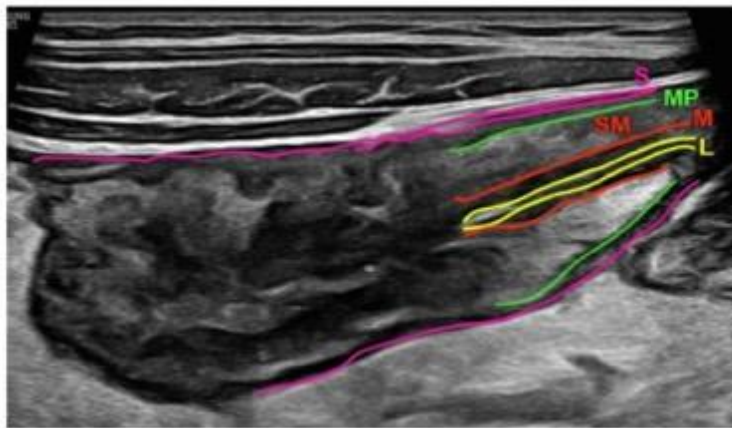
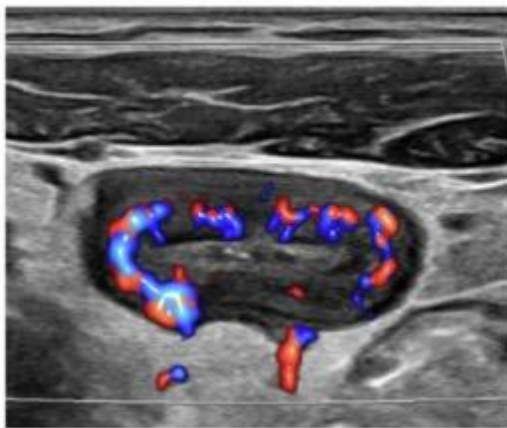
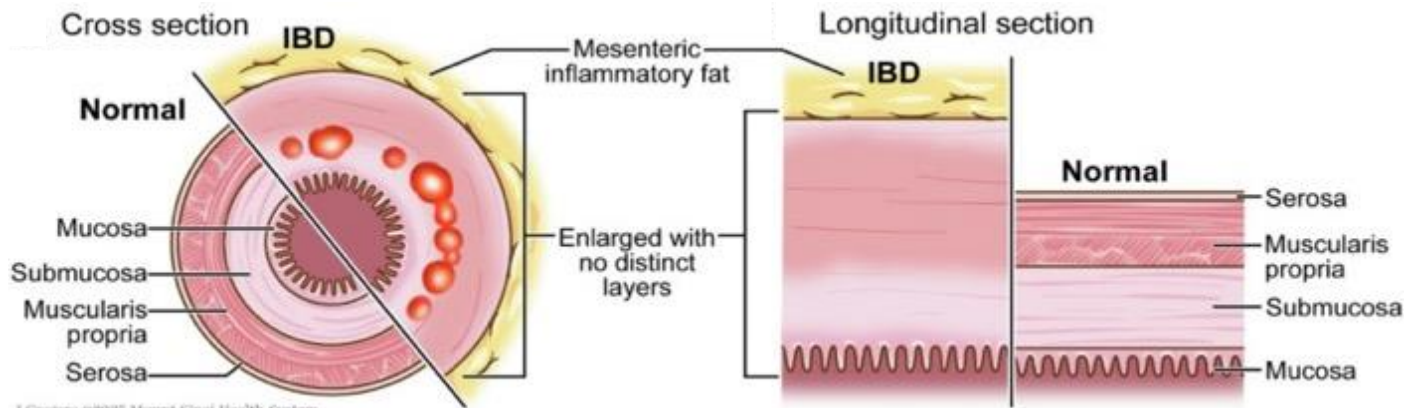
Two Major Scan Planes on IUS



Bowel Layers on IUS



Bowel Wall Layers and IUS Features of Active Disease



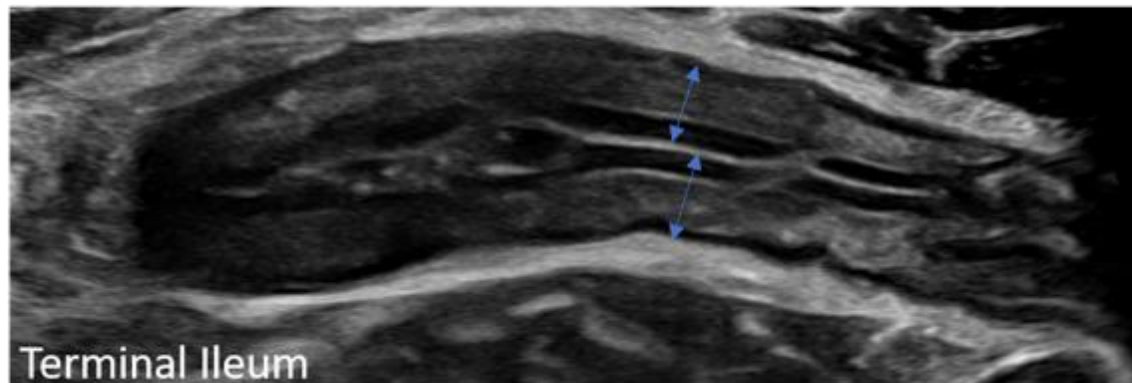
ARS Question



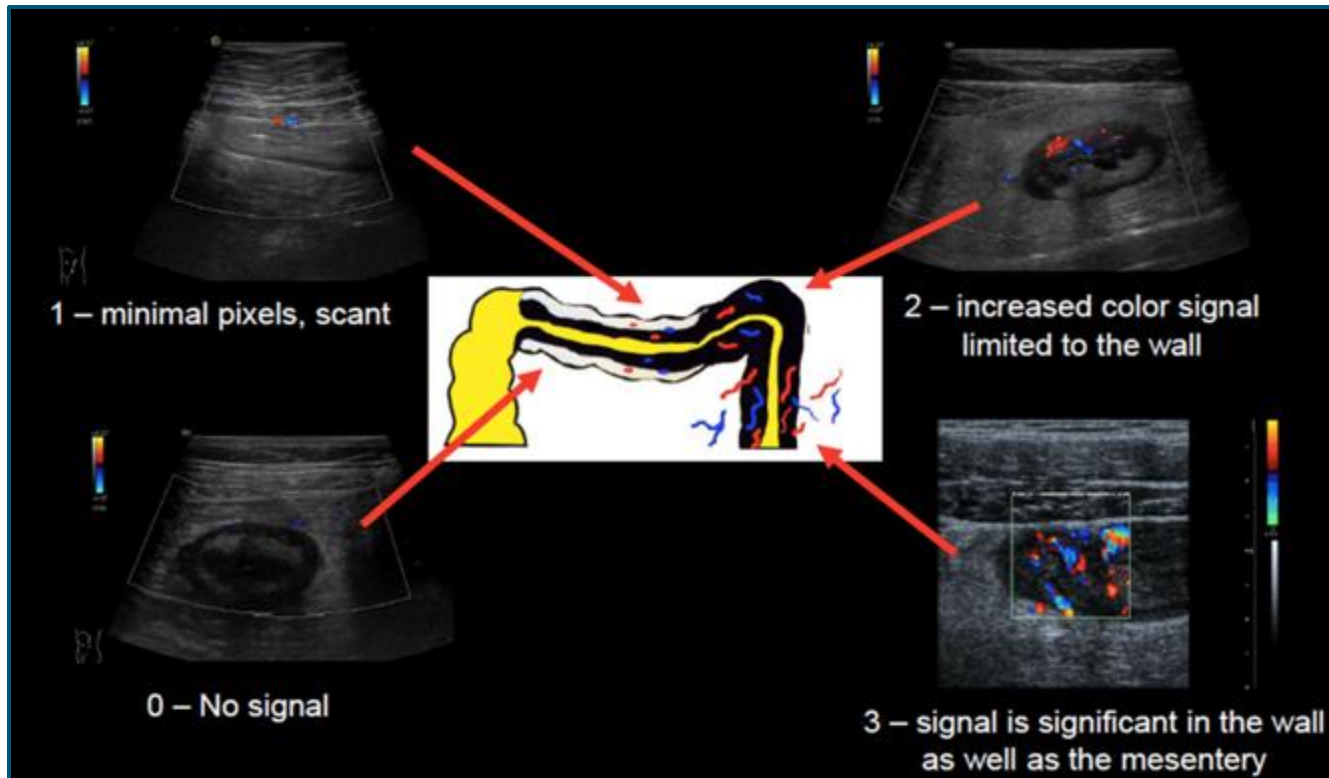
What are the measures of inflammation on IUS?

- A. Bowel wall thickness
- B. Bowel wall stratification
- C. Inflammatory fat stranding
- D. Bowel wall hyperemia
- E. All of the above
- F. I don't know

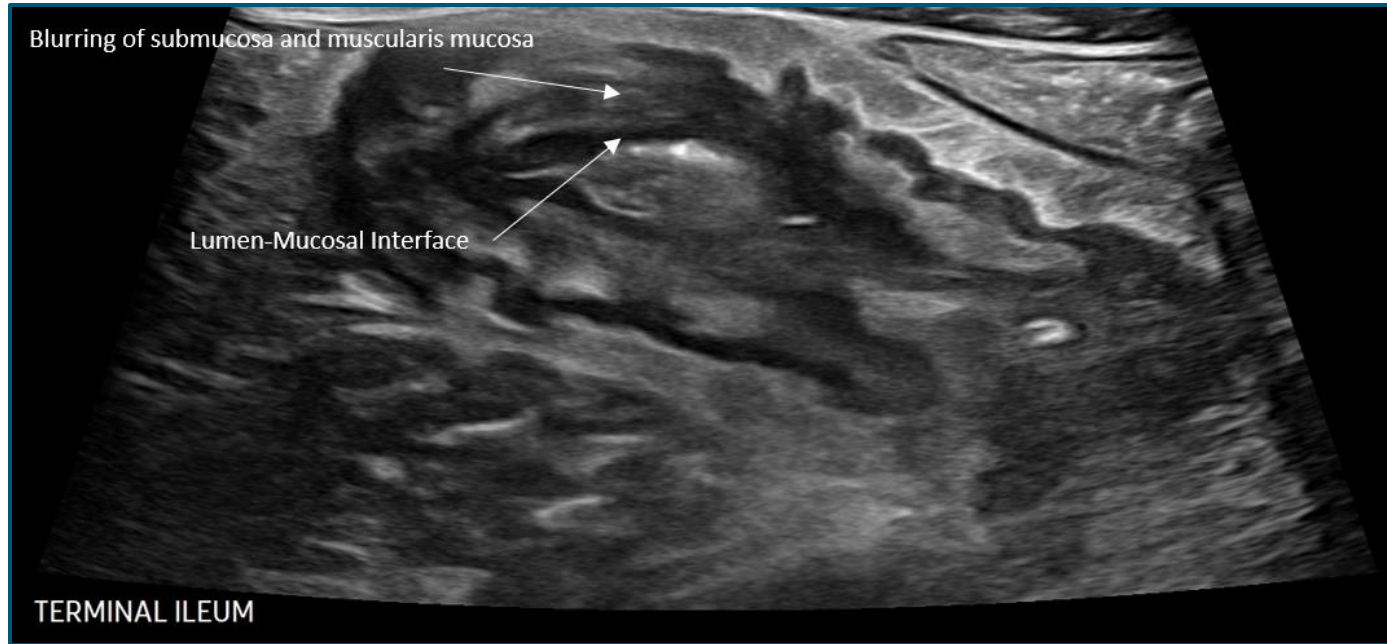
Bowel Wall Thickness is the Most Important Measure of IBD Activity



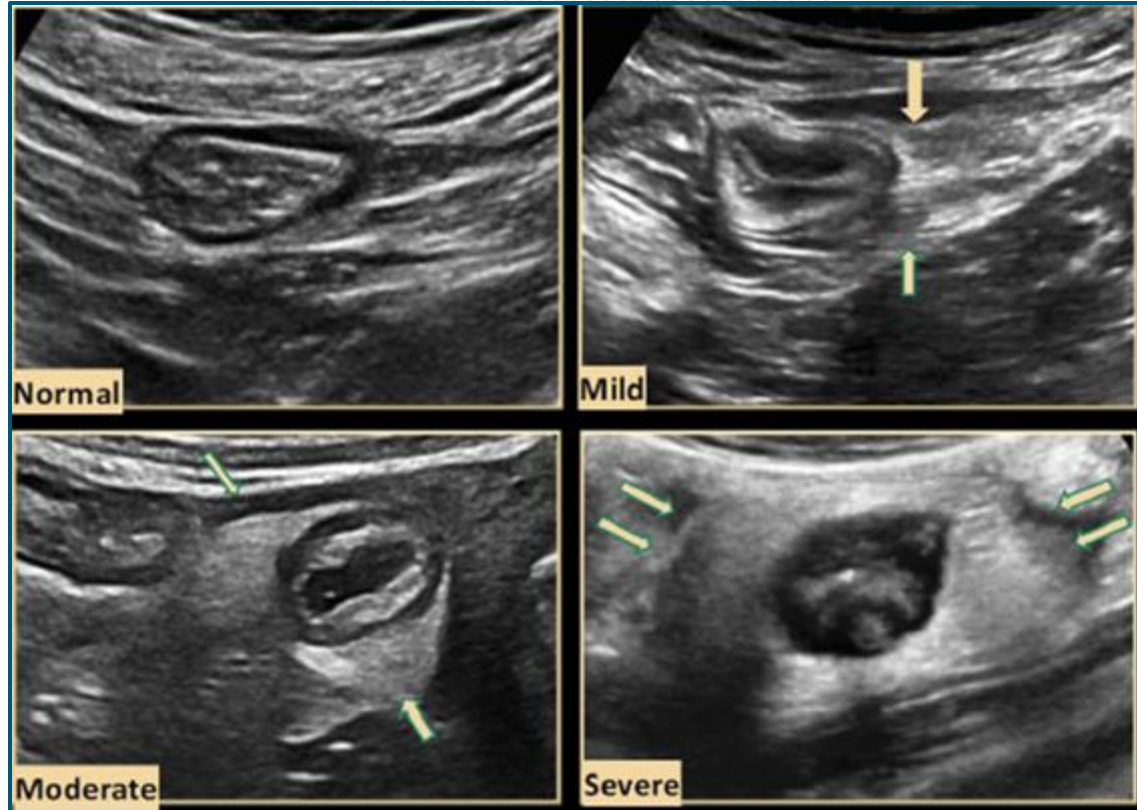
Bowel Wall Hyperemia is Graded by a Modified Limberg Score



Loss of Preservation of Bowel Wall Layer Stratification



Inflammatory Fat Presence on IUS as a Marker of IBD Activity and Chronicity

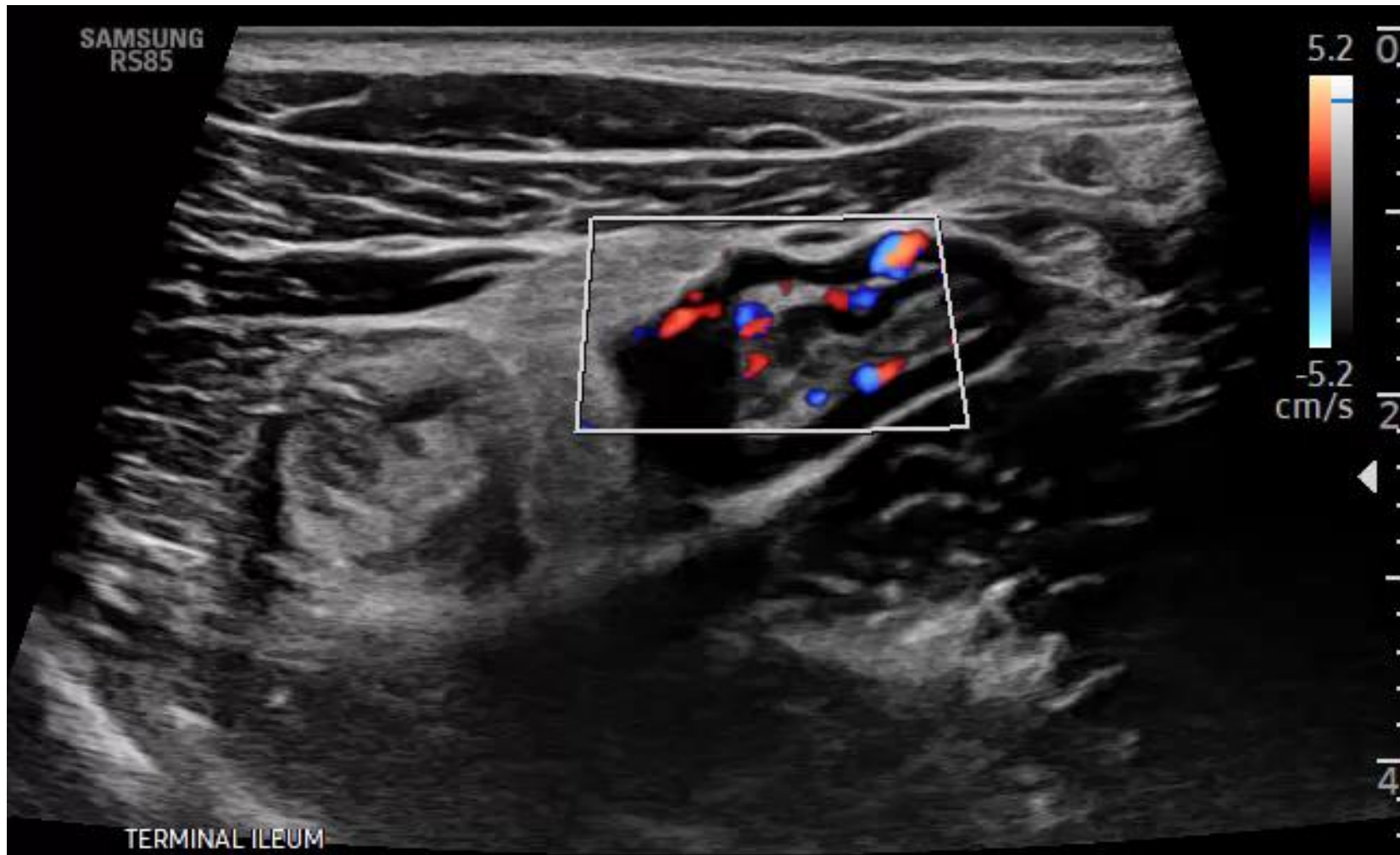


Images courtesy of Dr. Long.

SAMSUNG
RS85



TERMINAL ILEUM



[2D] Frq Gen./GN 61/DR 45/FA 10/P 100

S HAR

SAMSUNG
RS85

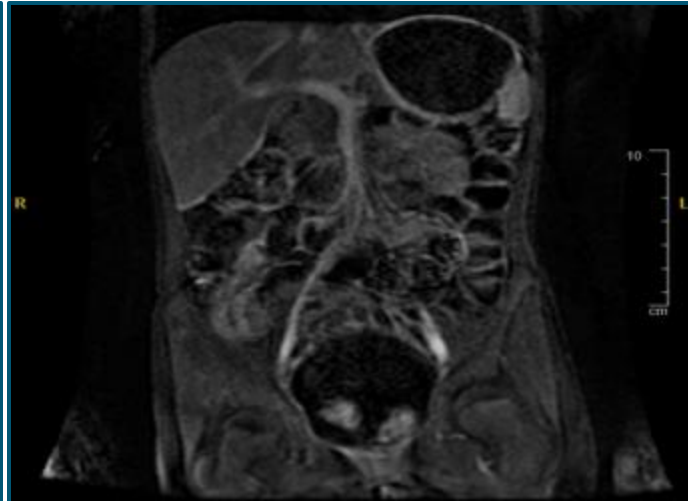
TERMINAL ILEUM

Who Should IUS Be Performed On?



Best Performance	Most Difficult
Terminal ileum/ileum	Rectum
Sigmoid colon	Left flexure
Transverse colon	Duodenum
Ascending colon/cecum	Jejunum

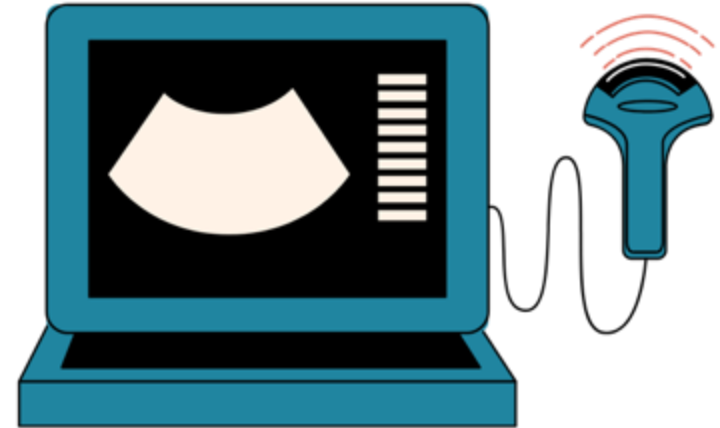
IUS is Accurate When Compared to MRI and Endoscopy



Advantages for IUS Evaluation of Disease Activity in CD



- Noninvasive
- Accurate
- Reproducible results
- Well-tolerated by patients
- Patient able to see scan results in real time
- No radiation exposure (monitoring option in pregnancy)



Limitations and Barriers for IUS



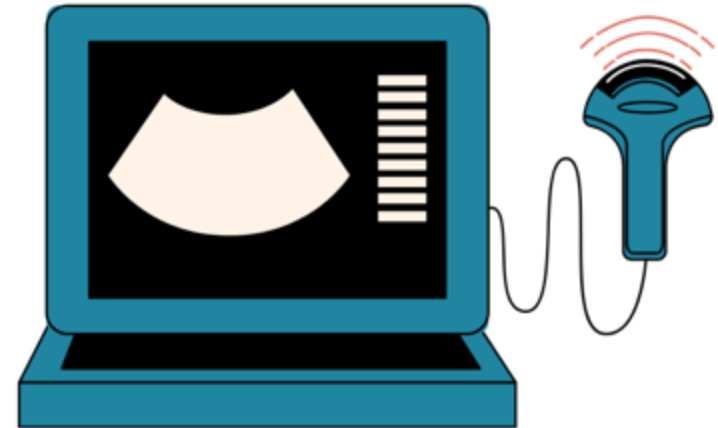
Needs specialized equipment

Image interpretation requires training

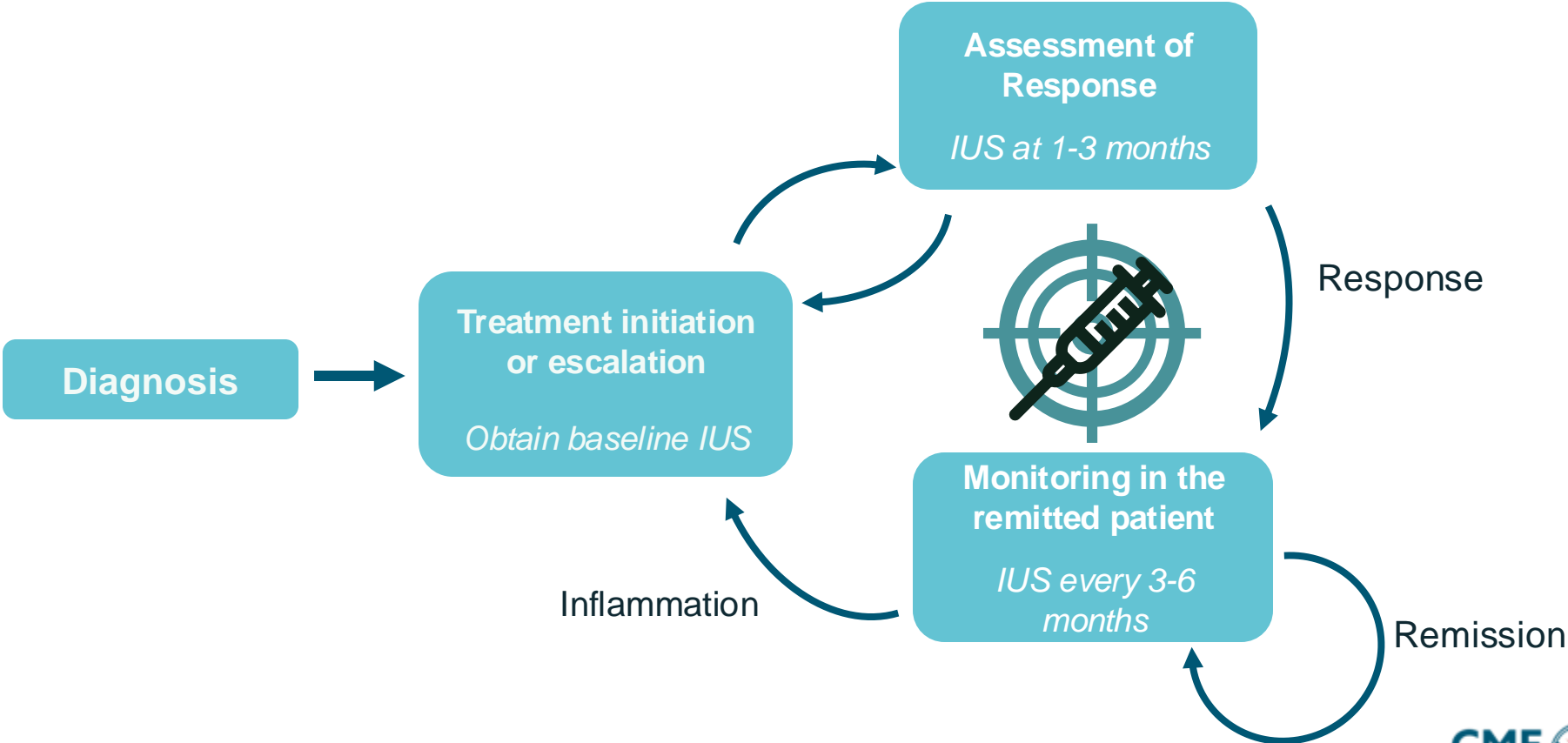
Scheduling and cleaning protocols

Poorer image quality in patients with obesity
(cannot use high frequency transducer)

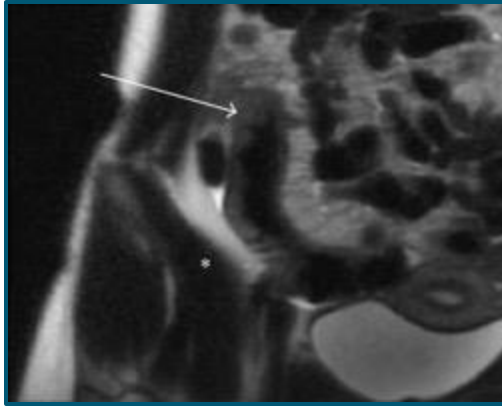
Cannot evaluate proximal small bowel



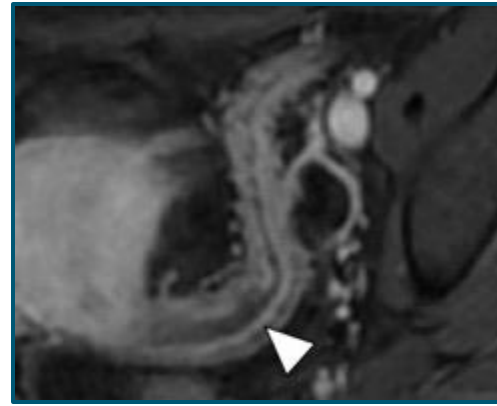
Monitoring Disease Activity in Practice Utilizing IUS



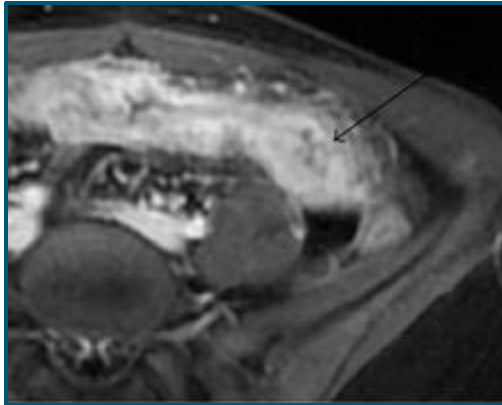
MRE Features of Active CD



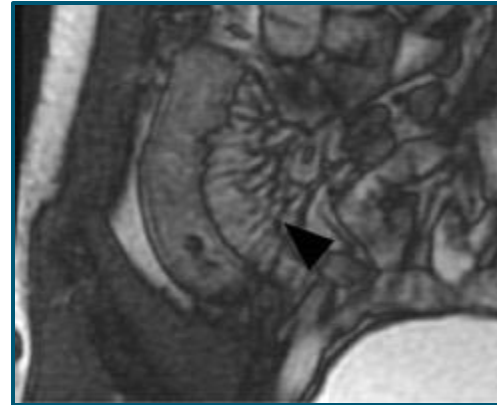
(a)



(b)

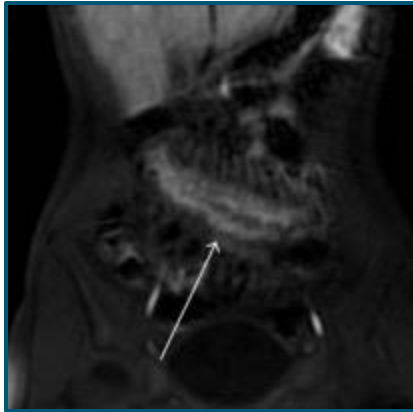


(c)

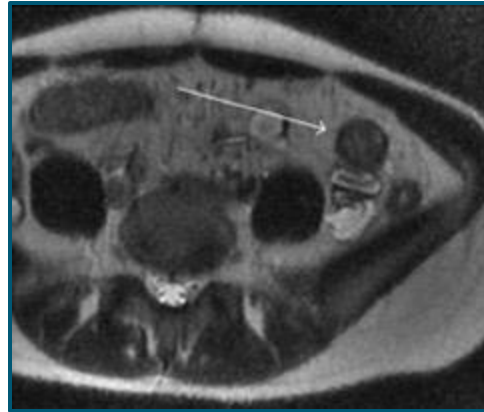


(d)

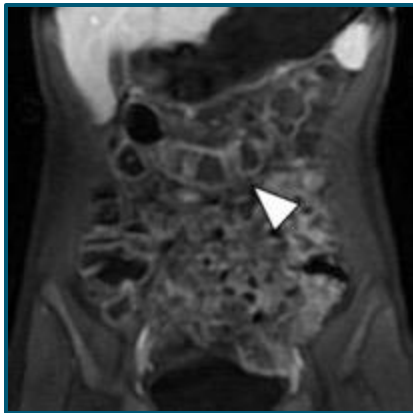
MRE Mucosal Healing in CD



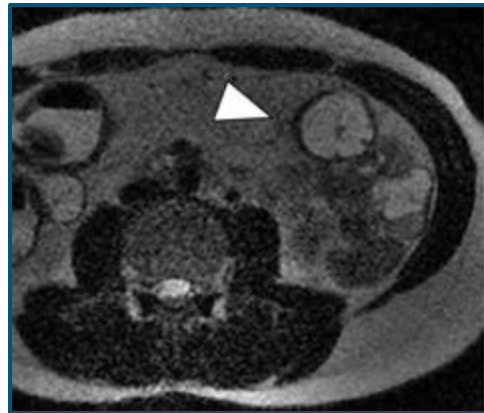
(a)



(b)



(c)



(d)

MRE is Not Accurate for the Colon

Ileocolonoscopy		MaRIA score 0	MaRIA score 1	MaRIA score ≥ 2
Transverse colon (n = 140)	Absence of lesions (n = 70)	70 (100)	0	0
	Inflammatory lesions without ulceration (n = 52)	49 (94)	1(2)	2 (4)
	Severe lesions (n = 18)	14 (78)	1 (5)	3 (17)
Descending colon (n = 140)	Absence of lesions (n = 63)	61 (96)	1 (2)	1 (2)
	Inflammatory lesions without ulceration (n = 59)	49 (83)	1 (2)	9 (15)
	Severe lesions (n = 18)	12 (67)	1(5)	5(28)
Sigmoid colon (n = 140)	Absence of lesions (n = 61)	58 (95)	0 (0)	3 (5)
	Inflammatory lesions without ulceration (n = 63)	51 (81)	0 (0)	12 (19)
	Severe lesions (n = 16)	10 (63)	1 (6)	5 (31)
Rectum (n = 140)	Absence of lesions (n = 62)	50 (81)	2 (3)	10 (16)
	Inflammatory lesions without ulceration (n = 65)	49 (75)	2 (3)	14 (22)
	Severe lesions (n = 13)	7 (54)	1 (8)	5 (38)

Advantages of MRE in CD

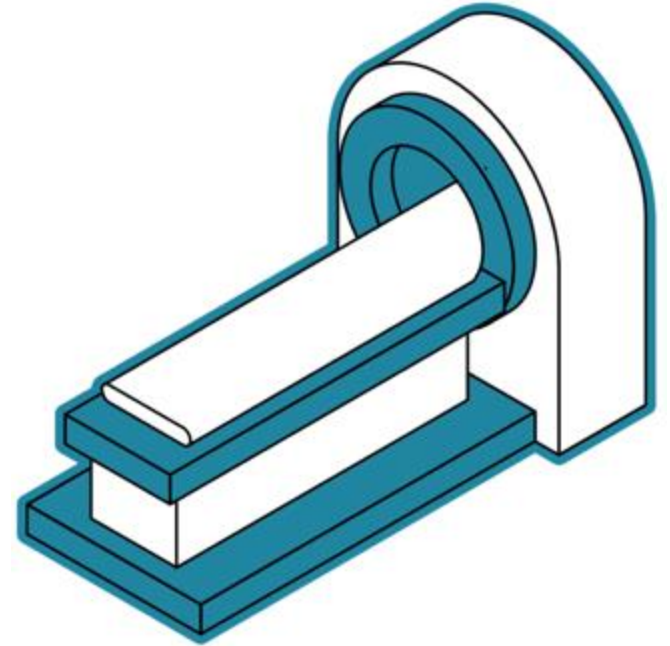


Identifies mural and extramural complications

No radiation exposure

Differentiates inflammation, stricturing, and penetrating disease

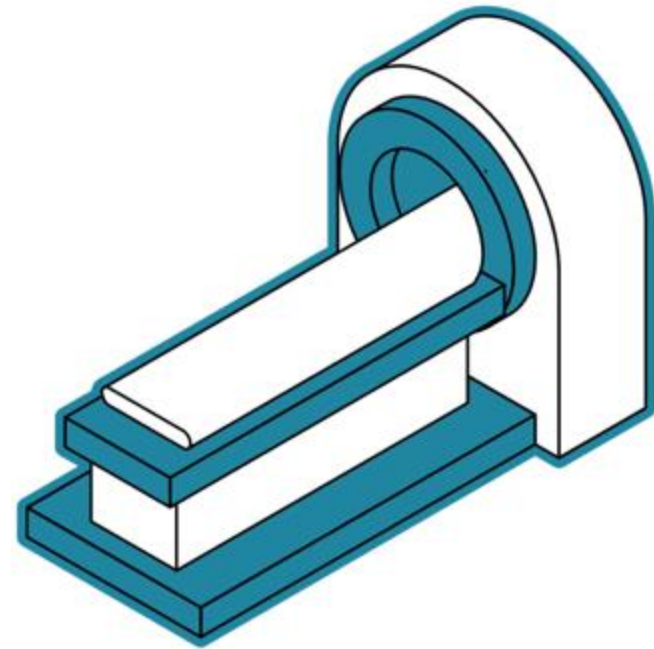
Useful for treatment/intervention planning



Limitations and Barriers for MRE



- Cost
- Limited accuracy in colonic disease
- Time requirement
- Difficult for patients with claustrophobia
- Differentiation of inflammation from fibrosis can be difficult



Video Capsule Endoscopy in CD



- ▶ Can be used in surveillance and diagnosis
- ▶ Particularly beneficial in patients with proximal small bowel disease and a normal ileocolonoscopy
- ▶ Risk of capsule retention with strictures
- ▶ Capsule endoscopy can support CD diagnosis in patients with normal upper and lower endoscopy studies
 - ▶ Ge et al. – 13/20 (65%) of patients examined
 - ▶ Herrerías et al. – 9/21 (43%) of patients examined

Summary



- ▶ Favor calprotectin over CRP in biomarker monitoring
- ▶ IUS can be utilized in point-of-care assessment in patients with CD
- ▶ Noninvasive monitoring through IUS, MRE, and capsule endoscopy is effective in tight control



Faculty Discussion

How have you incorporated noninvasive monitoring strategies into practice?



Histopathologic Remission in CD

Bruce E. Sands, MD, MS

Defining Histopathologic Remission



Disease Healing in IBD



ARS Question



Which of the following parameters can be measured by histopathologic evaluation in CD?

- A. Fibrosis
- B. Disease distribution
- C. Fistula formation
- D. Duration of disease
- E. I don't know

Geboes Score and Derived RHI



GS	Morphology	RHI
Grade 0: Architectural changes	0.0 No abnormality	0
	0.1 Mild abnormality	0
	0.2 Mild/moderate diffuse or multifocal abnormalities	0
	0.3 Severe diffuse or multifocal abnormalities	0
Grade 1: Chronic inflammatory infiltrate	1.0 No increase	0
	1.1 Mild but unequivocal increase	1
	1.2 Moderate increase	2
	1.3 Marked increase	3
Grade 2A: Eosinophils in lamina propria	2A.0 No increase	0
	2A.1 Mild but unequivocal increase	0
	2A.2 Moderate increase	0
	2A.3 Marked increase	0
Grade 2B: Neutrophils in lamina propria	2B.0 No increase	0
	2B.1 Mild but unequivocal increase	2
	2B.2 Moderate increase	4
	2B.3 Marked increase	6

GS = Geboes score; RHI = Roberts histopathological index. GS: histological remission ≤ 2.0 , histological response ≤ 3.0 .
 RHI: histological remission ≤ 3 , histological response ≤ 9 .
 Vespa E, et al. *J Clin Med*. 2022;11:939.

Geboes Score and Derived RHI



GS	Morphology	RHI
Grade 3: Neutrophils in epithelium	3.0 None	0
	3.1 < 5% crypts involved	3
	3.2 < 50% crypts involved	6
	3.3 > 50% crypts involved	9
Grade 4: Crypt destruction	4.0 None	0
	4.1 Probable - local excess of neutrophils in part of the crypts	0
	4.2 Probable - marked attenuation	0
Grade 5: Erosions and ulcerations	4.3 Unequivocal crypt destruction	0
	5.0 No erosion, ulceration or granulation tissue	0
	5.1 Recovering epithelium + adjacent inflammation	5
	5.2 Probable erosion – focally stripped	5
	5.3 Unequivocal erosion	10
	5.4 Ulcer or granulation tissue	15

Nancy Index (NI)



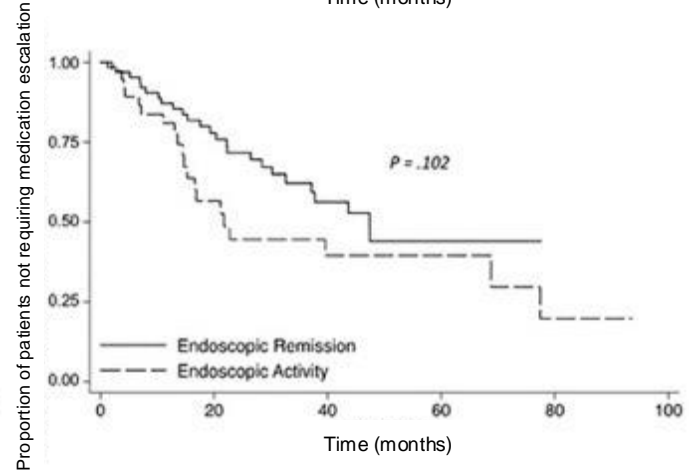
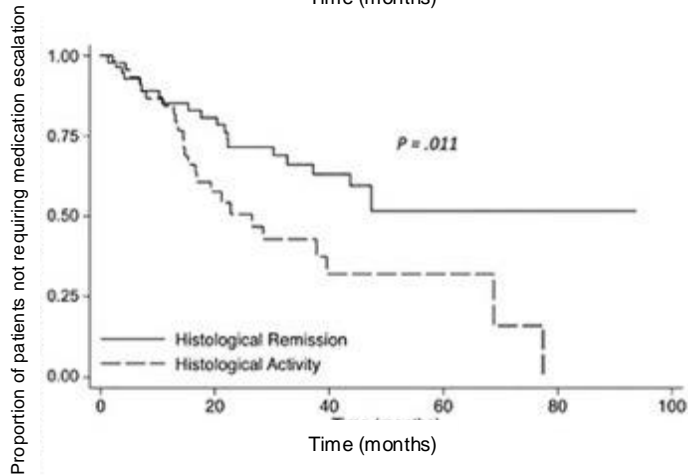
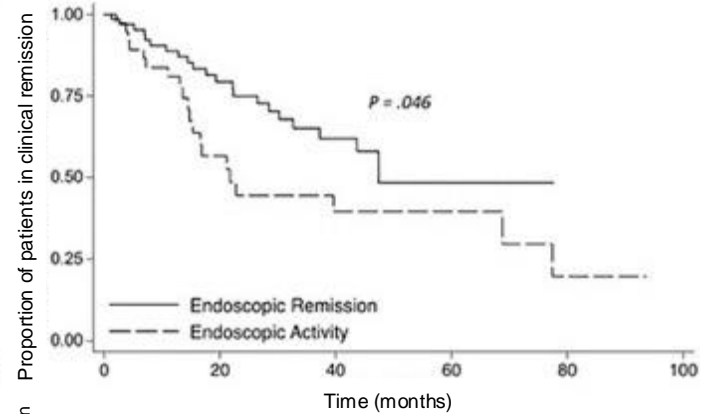
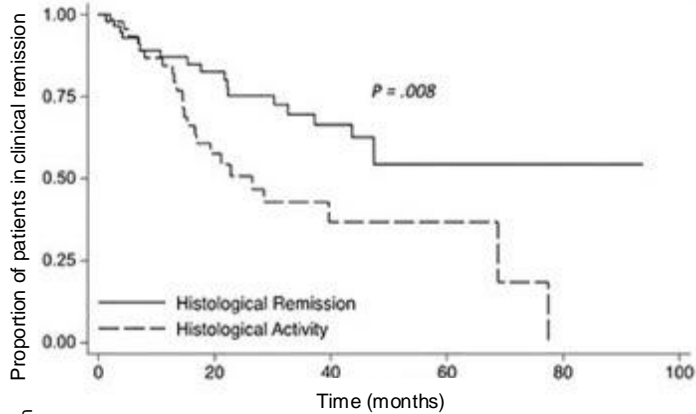
Grade	Morphology
0	No or only mild increase in chronic inflammatory cells
1	Moderate or severe increase in chronic inflammatory cells (lymphocytes, plasma cells, and eosinophils) defined as presence of an increase in chronic inflammatory cells that is easily apparent
2	Mild increase in neutrophils defined as few or rare neutrophils in lamina propria or in the epithelium that are difficult to see
3	Moderate or severe increase in neutrophils defined as presence of multiple clusters of neutrophils in lamina propria and/or in epithelium that are easily apparent
4	Ulcers or erosions defined as loss of colonic crypts replaced with “immature” granulation tissue (disorganized blood vessels with extravasated neutrophils) or the presence of fibrinopurulent exudate

Histologic Healing is Associated with Better Long-Term Outcomes in CD

Study	Type of Study	Disease	N Patients	Endoscopic Activity	Histological Index	Outcome
Brennan et al.	Retrospective cohort study	CD	62 patients, follow-up for at least 6 months. A total of 103 patients with CD underwent elective colonoscopies during clinical remission.	55 patients (53%) in endoscopic healing, 48 patients (47%) with active disease.	A semiquantitative score (0 to 3) was assigned for the histologic characteristics in each of the biopsy samples.	At 12 months, the rate of relapse was 25.5% in patients with histologic activity, compared with only 2.4% of patients without histologic activity at baseline. The presence of histological activity was associated with higher flare rates ($p < 0.05$).
Christensen et al.	Retrospective study	CD	101 patients, follow-up for a median of 21 months.	63% of patients with endoscopic remission.	55% of patients achieved histologic remission.	CR occurred in 42% (n = 42) of patients. Histologic healing was associated with a decreased risk of CR (HR 2.05; 95% CI, 1.07-3.94; $p = 0.031$).

Association between histological activity and the risk of clinical relapse. A p -value < 0.05 is considered statistically significant.

Improved Outcomes with Endoscopic and Histologic Healing in Ileal CD



Global Histologic Disease Activity Score (GHAS)



Epithelial damage	0 - Normal
	1 - Focal pathology
	2 - Extensive pathology
Architectural changes	0 - Normal
	1 - Moderately disturbed (< 50%)
	2 - Severely disturbed (> 50%)
Infiltration of mononuclear cells in the lamina propria	0 - Normal
	1 - Moderate increase
	2 - Severe increase
Infiltration of polymorphonuclear cells in the lamina propria	0 - Normal
	1 - Moderate increase
	2 - Severe increase
Polymorphonuclear cells in epithelium	1 - In surface epithelium
	2 - Cryptitis
	3 - Crypt abscess

Components of the IBD-DCA Score

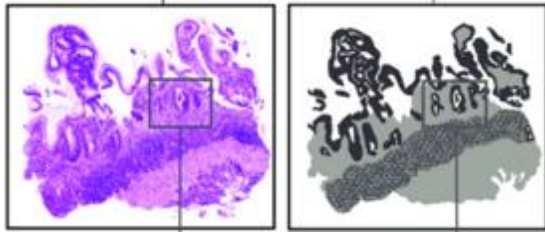
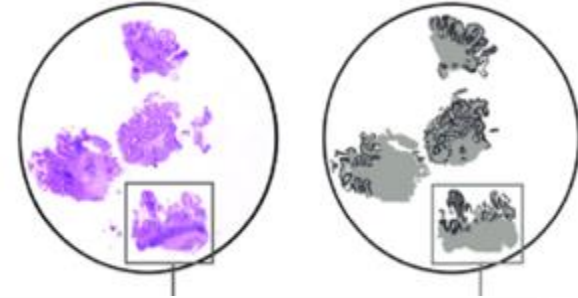


Variable	Classification
Distribution (D)	0 = Normal 1 = < 50% of the time tissue per same biopsy site 2 = \geq of tissue affected per same biopsy site
Chronic features (C)	0 = Normal 1 = Crypt distortion <i>and/or</i> mild lymphoplasmacytosis 2 = Marked lymphoplasmacytosis <i>and/or</i> marked basal plasmacytosis
Activity features (A)	0 = Normal 1 = Two or more neutrophils in lamina propria in one high-power field (HPF) <i>and/or</i> intraepithelial neutrophils (any number) 2 = Crypt abscesses, erosions, ulcers

IBD-DCA Scoring Example

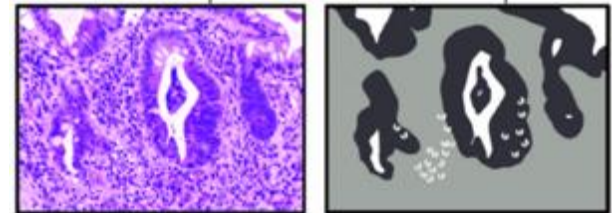


Distribution “D”: overall affected tissue in scanning magnification (2.5-4x). Ex. four biopsies, affected by inflammatory and architectural changes in > 50% of tissue = D2



Chronicity “C”: Assess in magnification 4 to 10x. Ex. shows architectural distortion as and prominent bandlike (lympho-) plasmacytosis = C2

Activity “A”: assess in higher magnification. Ex. shows cluster of neutrophilic granulocytes in tunica propria and some granulocytes in crypt epithelium = A1



Summary



- ▶ Several histopathologic indices exist for scoring disease activity in CD
- ▶ Several important long-term outcomes have been associated with histologic healing in CD



Faculty Discussion

What is the current state of incorporating histopathologic activity measures in patients with CD in practice?

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely



- ▶ Consider disease severity and a patient's overall disease course when making choices regarding treatment selection
- ▶ Utilize advanced therapies in patients with CD without first requiring failure or intolerance of conventional therapies
- ▶ Incorporate noninvasive monitoring strategies into the routine care of patients with CD



QUESTIONS & ANSWERS

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