Advances in Diagnostic Strategies for IBD

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Learning Objectives:

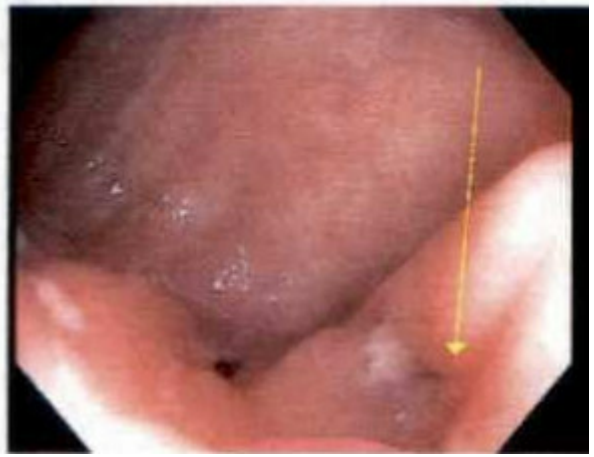
- To explore the latest advancements in diagnostic techniques for IBD
- To focus on innovative tools and methodologies that enhance early and accurate detection of inflammation
- To understand the role of non-invasive monitoring in treat to target
- To understand current applications of personalized diagnostic approaches in IBD

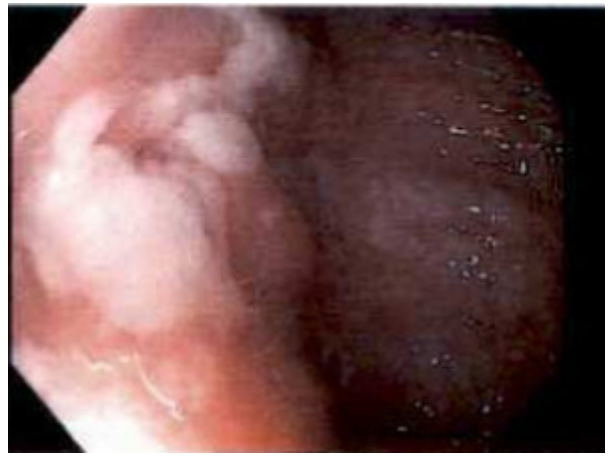
Case

- 25 year old woman was diagnosed with ileal Crohn's disease 3 months prior
- At time of diagnosis, she presented with partial obstructive symptoms, weight loss, anemia
- Colonoscopy at the time demonstrated inflamed, stenosed IC valve(could not intubate, moderate chronic-active enteritis), CT with ~15 cm of ileal inflammation/thickening (no pre-stenotic dilation)
- She was treated with corticosteroids, anti-TNF/aza, but continued to have symptoms, calpro remained elevated at 345 ug/g
- She underwent ileocecal resection w/ direct anastomosis

What monitoring strategy should be utilized post op?

Does she need medications?





IBD Diagnosis

Diagnosis of CD and UC

- Diagnosis of UC requires a lower gastrointestinal endoscopic examination with histologic confirmation
- CD is diagnosed clinically. Endoscopic, radiographic, and histologic criteria with evidence of chronic intestinal inflammation will be present.
- Adjunct measures such as intestinal ultrasound, MRE and biomarkers can support diagnosis and/pr response to therapy

Rubin DT, et al. Am J Gastroenterol 2025.
Lichtenstein GR, et al. Am J Gastroenterol 2025.

Defining Disease Severity in UC

- Standard assessment of UC activity (mild, moderate, severe) insufficient in guiding selection of therapy
- Need to assess risk for colectomy (severity)

Low Risk for Colectomy

- **Limited anatomic extent**
- **Mild endoscopic disease**

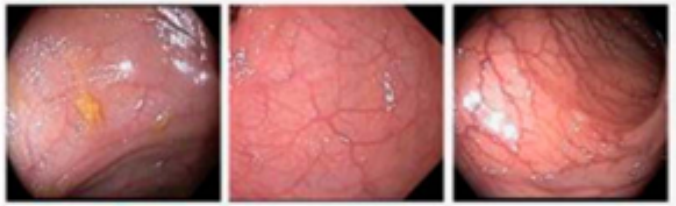
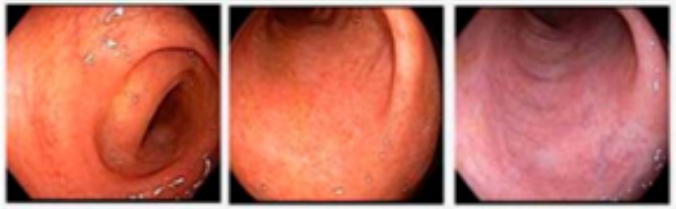
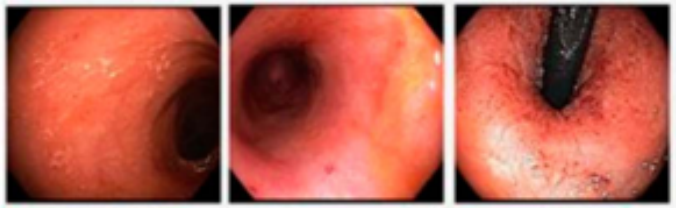
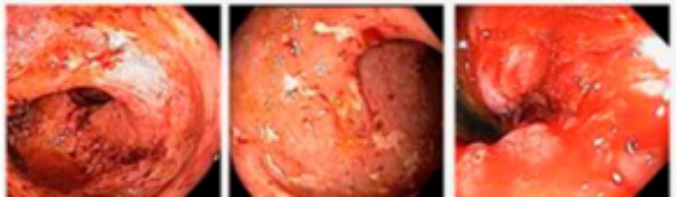
High Risk for Colectomy

- **Extensive colitis**
- **Deep ulcers**
- **Age <40**
- **High CRP and ESR**
- **Low albumin**

Dassopoulos T, et al. *Gastroenterology.* 2015;149(1):238-45.
Rubin DT, et al. *Am J Gastroenterol*. 2019;114(3):384-413.

Endoscopic Scales and Disease Severity in UC

Include Endoscopic Scoring

Endoscopic Assessment of Disease Activity	UCEIS Score	Mayo Score	Endoscopic Features
	0	0	Normal
	1-3	1	Erythema, decreased vascular pattern, mild friability
	4-6	2	Marked erythema, absent vascular pattern, friability, erosions
	7-8	3	Spontaneous bleeding, ulceration

Rubin DT, et al. Am J Gastroenterol. 2025 Jun 3;120(6):1187-1224.

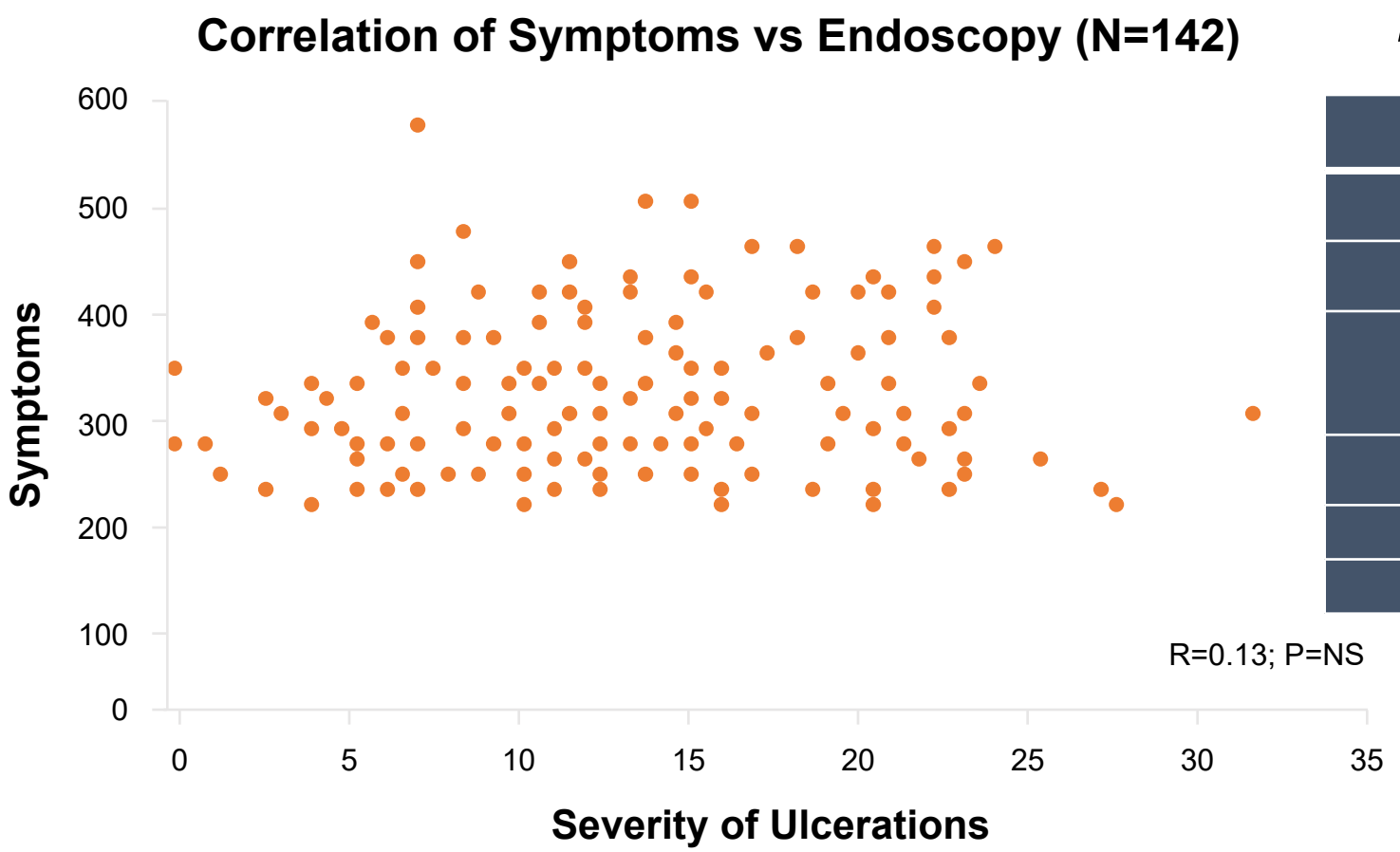
ACG: UC Activity Index

Table 4. American College of Gastroenterology Ulcerative Colitis Activity Index (modified from Ref. 66)

	Remission	Mild	Moderate-severe	Fulminant
Stools (#/day)	Formed stools	<4	>6	>10
Blood in stools	None	Intermittent	Frequent	Continuous
Urgency	None	Mild, occasional	Often	Continuous
Hemoglobin	Normal	Normal	<75% of normal	Transfusion required
ESR	<30	<30	>30	>30
CRP (mg/L)	Normal	Elevated	Elevated	Elevated
Fecal calprotectin (μg/g)	<150–200	>150–200	>150–200	>150–200
Endoscopy (MES)	0–1	1	2–3	3
Endoscopy (UCEIS)	0–1	2–4	5–8	7–8
Intestinal ultrasound	Colonic BWT≤3 mm Rectal BWT ≤4 mm mLimberg = 0		Colonic BWT >3 mm Rectal BWT >4 mm mLimberg >0	

Rubin DT, et al. Am J Gastroenterol. 2025 Jun 3;120(6):1187-1224.

Crohn's Disease Severity



NS = not significant.

Factors associated with severity

Poor Prognostic factors
Young age
Extensive bowel involvement
Perianal/ Severe Rectal Disease
Penetrating/stenosing at diagnosis
Deep ulcers
Prior surgery

The greater the number of poor prognostic factors, the worse the prognosis

Only 20-30% of CD patients will have an indolent course

Modigliani R, et al. *Gastroenterology*. 1990;98(4):811-818.

CD Activity vs. Severity

Disease Activity	Disease Severity	Disease Risk
• A **snapshot** of symptoms, perhaps also objective measures, that patient is experiencing now (eg, mild, moderate, or severe; mild to moderate; or moderate to severe) • Not sufficient to guide selection of therapy	• Newer concept, reflecting entire course of disease: **"the movie"** • Wide range of variables that includes not only symptoms, but also objective findings, past treatment experience, surgery, biomarkers, functional aspects	• Factors associated with worse long-term outcomes, warranting early use of most effective therapies – In CD: Unfavorable outcomes such as complicated disease behavior, surgery, disability

Peyrin-Biroulet. Clin Gastroenterol Hepatol. 2016;14:348.

IBD Goals:
How Can Diagnostic Strategies Help?

Evolving Goals (in IBD)

Early/prompt diagnosis

Define EIMS

Improve QoL

Induction of symptomatic remission

- No blood
- No pain
- Normal stool frequency
- No urgency
- No nocturnal symptoms

Induction of deep remission

- Endoscopic improvement
- Normalized labs
- Normalized growth, development
- Histologic remission?
- Transmural remission?

Prevention of relapse

- Avoid steroids

Prevention of complications

Cost-effective care

Tight control of immediate, intermediate, and long-term targets, alongside regular monitoring towards mucosal healing, is the goal[1]

STRIDE-II[1]

Short-term targets

Clinical response[2]
Clinical remission (steroid-free)[3]

Intermediate targets

Biomarker normalization[1]
Normal growth in children[2]

Long-term targets

Endoscopic healing
Returning to a normal life: Disability, QoL[2]

Adjunctive measure

Histological healing as a potential target in UC only[2]

SPIRIT[2]

Preventing disease/ long-term complications, e.g. flares, surgery, cancer prevention,[2] fibrosis,[4] and disability[5]

Concept of the 'therapeutic window of opportunity'[2]

Time

A selection of monitoring solutions are available:

Endoscopy[1,6]

IUS,[6] radiographic imaging[6,7]

Biomarkers[1]

QoL[6]

Next-gen monitoring tools:

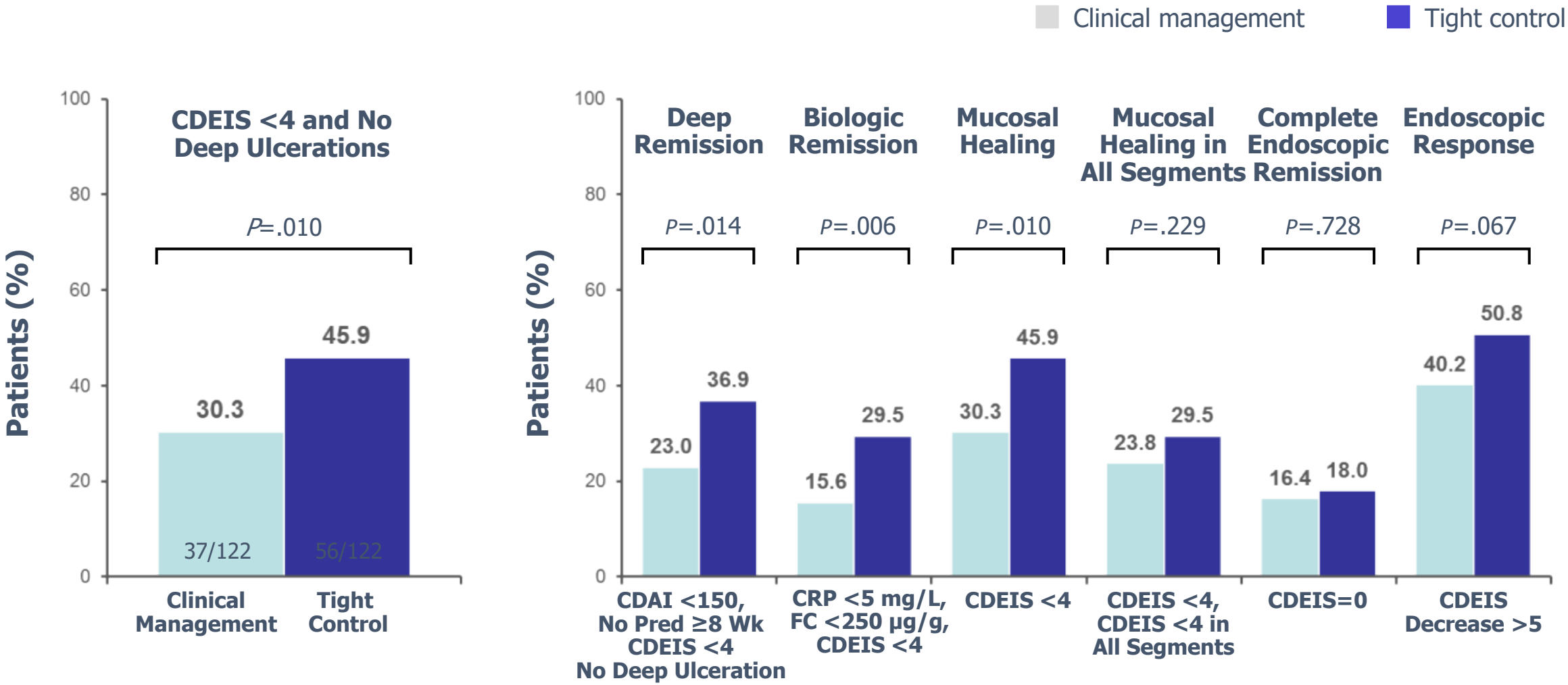
Wearable devices†[8,9]

Molecular endoscopy[10]

Figure adapted from Turner D, et al. *Gastroenterology*. 2021;160:1570–831 and Le Berre C, et al. *Gastroenterology.* 2022;162:1424–38. †Physiological metrics obtained from wearable devices include heart rate, resting heart rate, heart rate varaiblity, steps, and oxygenation.[9]
IUS, intestinal ultrasound; QoL, quality of life; SPIRIT, Selecting Endpoints for Disease-Modification Trials; STRIDE, Selecting Therapeutic Targets in Inflammatory Bowel Disease.

1. Turner D, et al. *Gastroenterology*. 2021;160:1570–83; 2. Le Berre C, et al. *Gastroenterology*. 2022;162:1424–38; 3. D'Amico F, et al. *United European Gastroenterol J*. 2024;12:705–16; 4. Solitano V, et al. *J Clin Med*. 2020;9:2646; 5. Allen PB, et al. *Therap Adv Gastroenterol.* 2017;10:865–76; 6. Garcia NM, et al. *United European Gastroenterol J*. 2022;10:1121–8; 7. Maccioni F, et al. *Diagnostics (Basel)*. 2023;13:2410; 8. Reddy KD and Chawla S. *J Clin Med*. 2025;14:2403; 9. Hirten RP, et al. *Gastroenterology*. 2025;168:939–51; 10. Zammarchi I, et al. *Diagnostics (Basel).* 2023;13:2547.

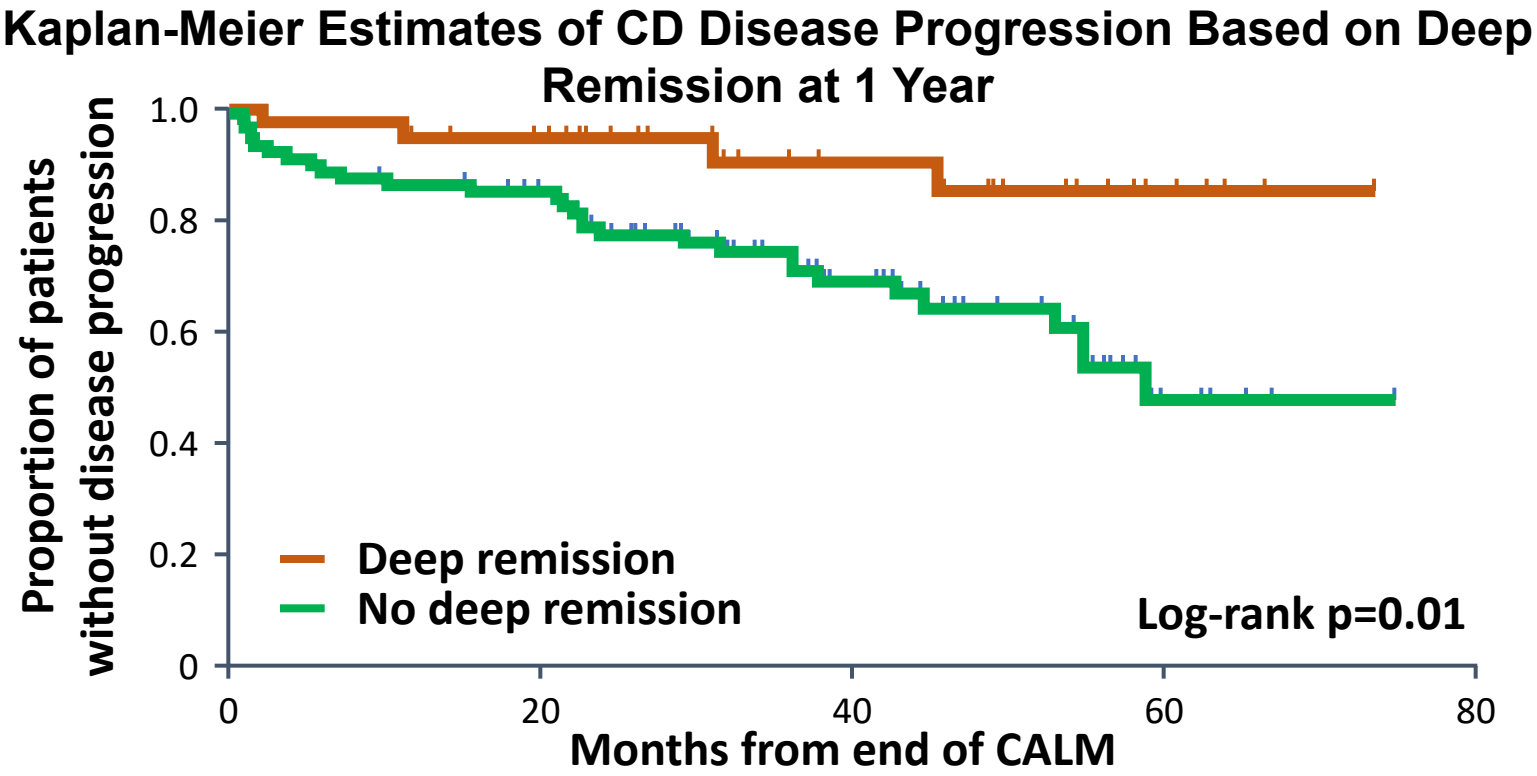
Why Does Tight Control Matter? CALM Study



CDEIS = Crohn's disease endoscopic index of severity; CRP = C-reactive protein; FC = fecal calprotectin; Wk = weeks.
Colombel JF, et al. *Lancet.* 2018;390:2779-2789.

Why Does Tight Control Matter? CALM Study Long Term Follow Up

CD patients achieving endoscopic or deep remission after 1Y of tight control are less likely to have disease progression* over a median of 3Y

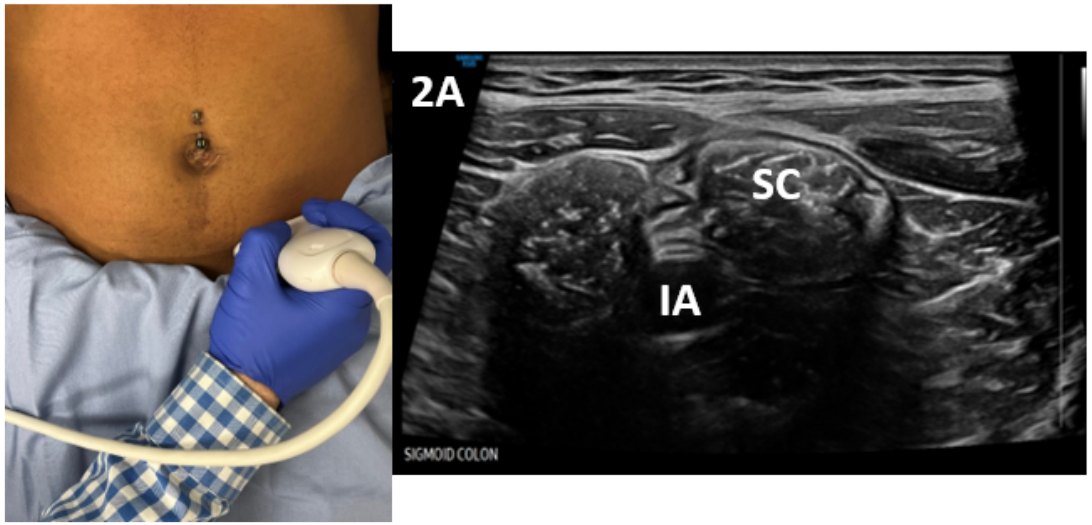


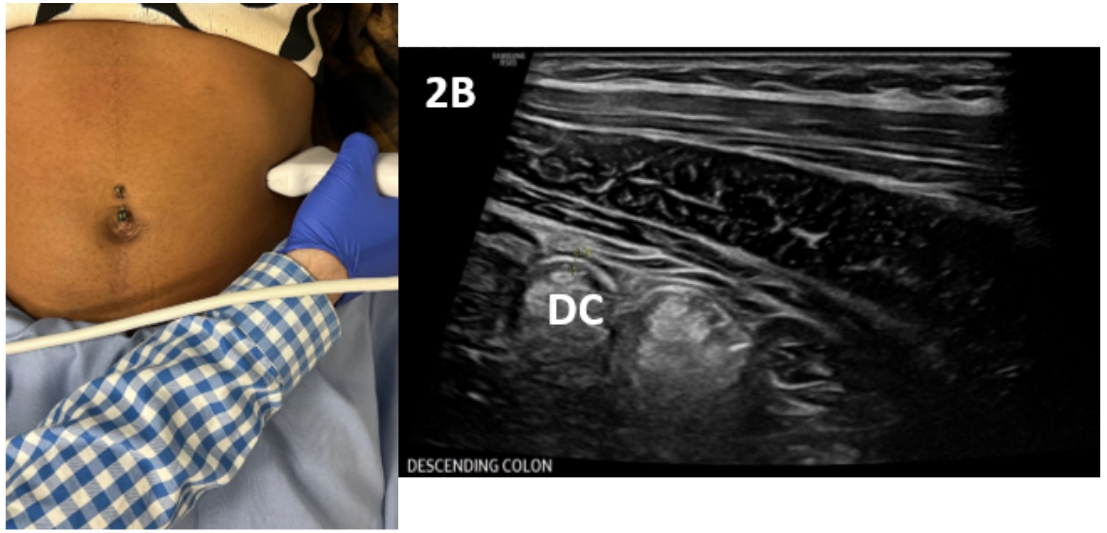
*Disease progression defined as composite of new internal fistula/abscess, stricture, perianal fistula/ abscess, CD hospitalization, or CD surgery since end of CALM

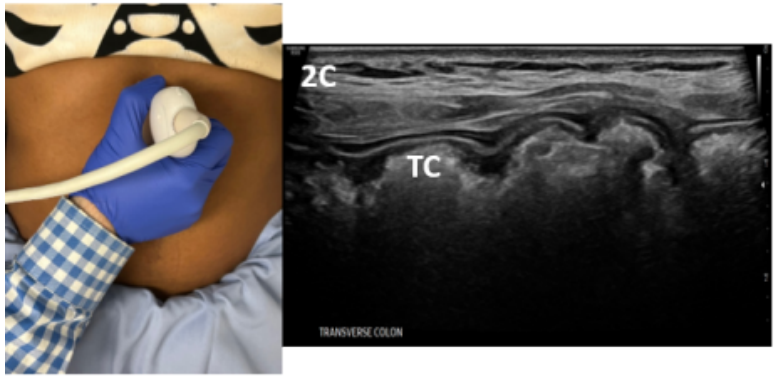
Ungaro R et al Gastroenterology. 2020 Mar 26:S0016-5085(20)30390-.

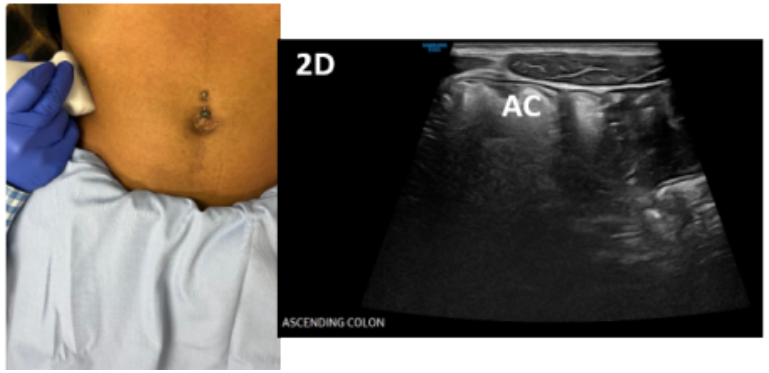
Non-Invasive Monitoring Options

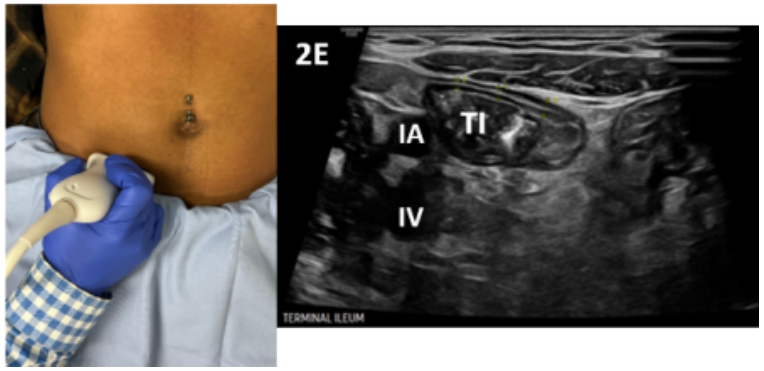
Intestinal Ultrasound as Point of Care Assessment of TI or Colon





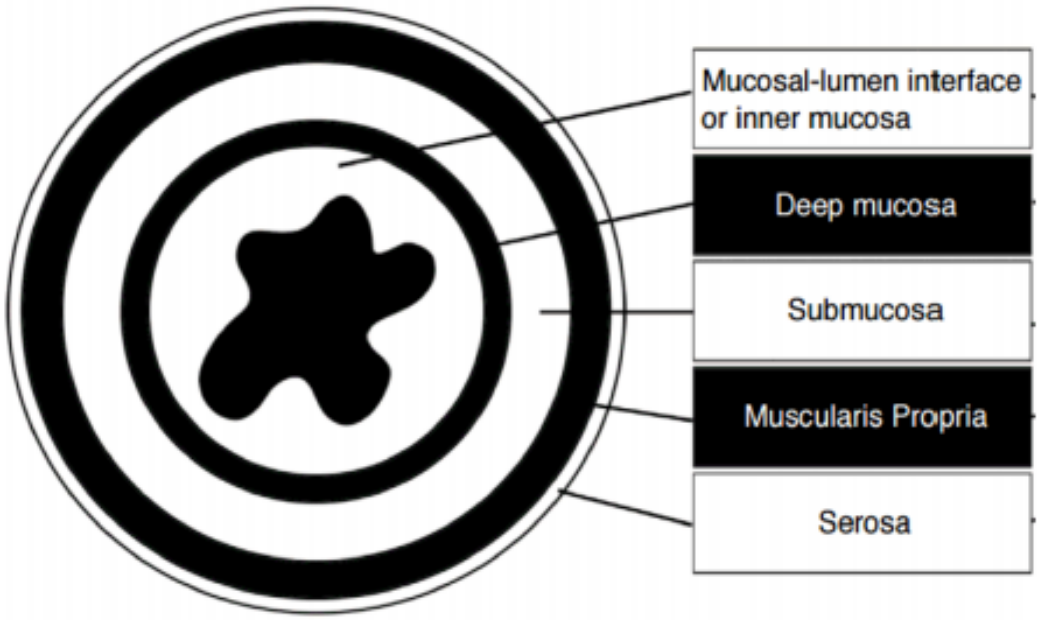


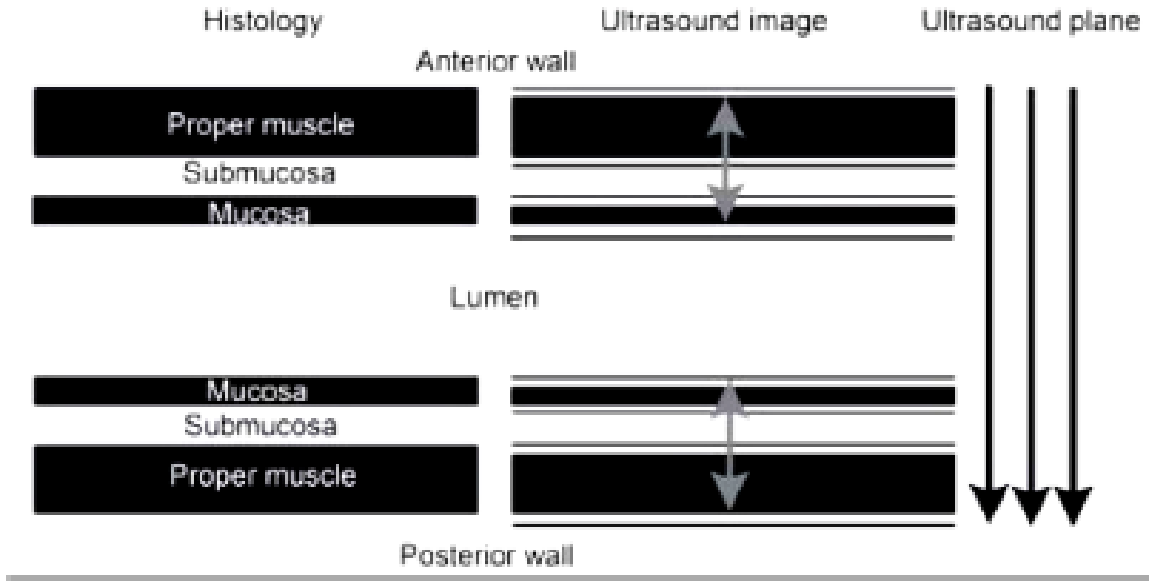




Kellar A and Dolinger M et al., *JPGN*, 2022

Bowel Layers on IUS

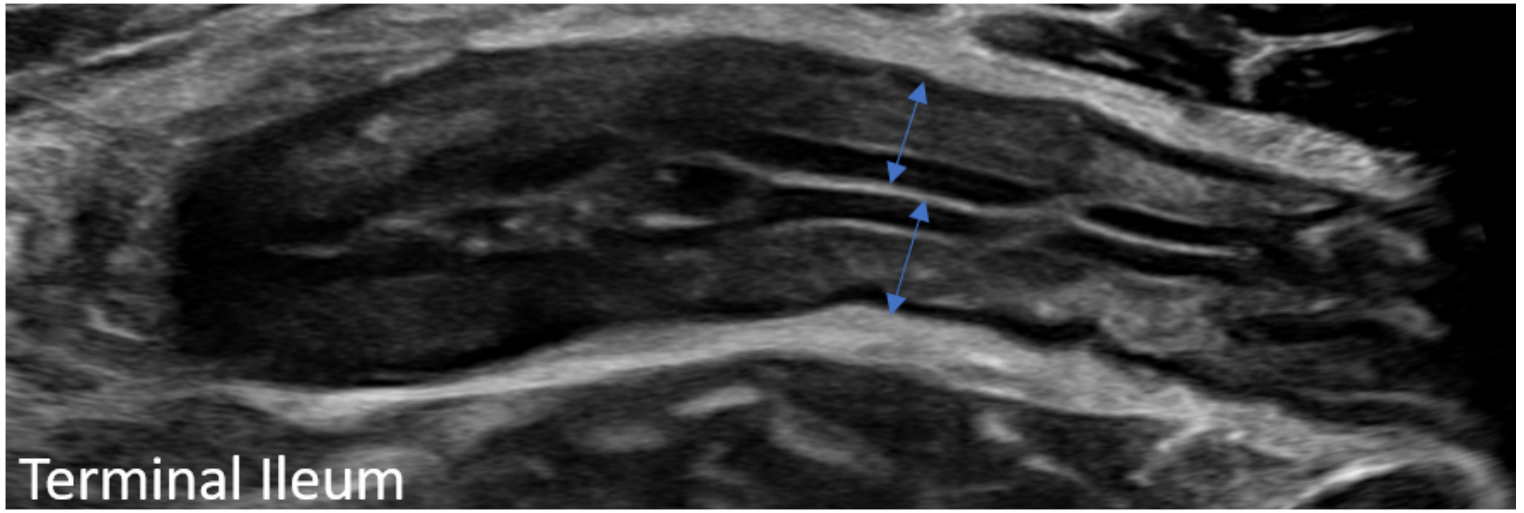




Measures of Inflammation on IUS

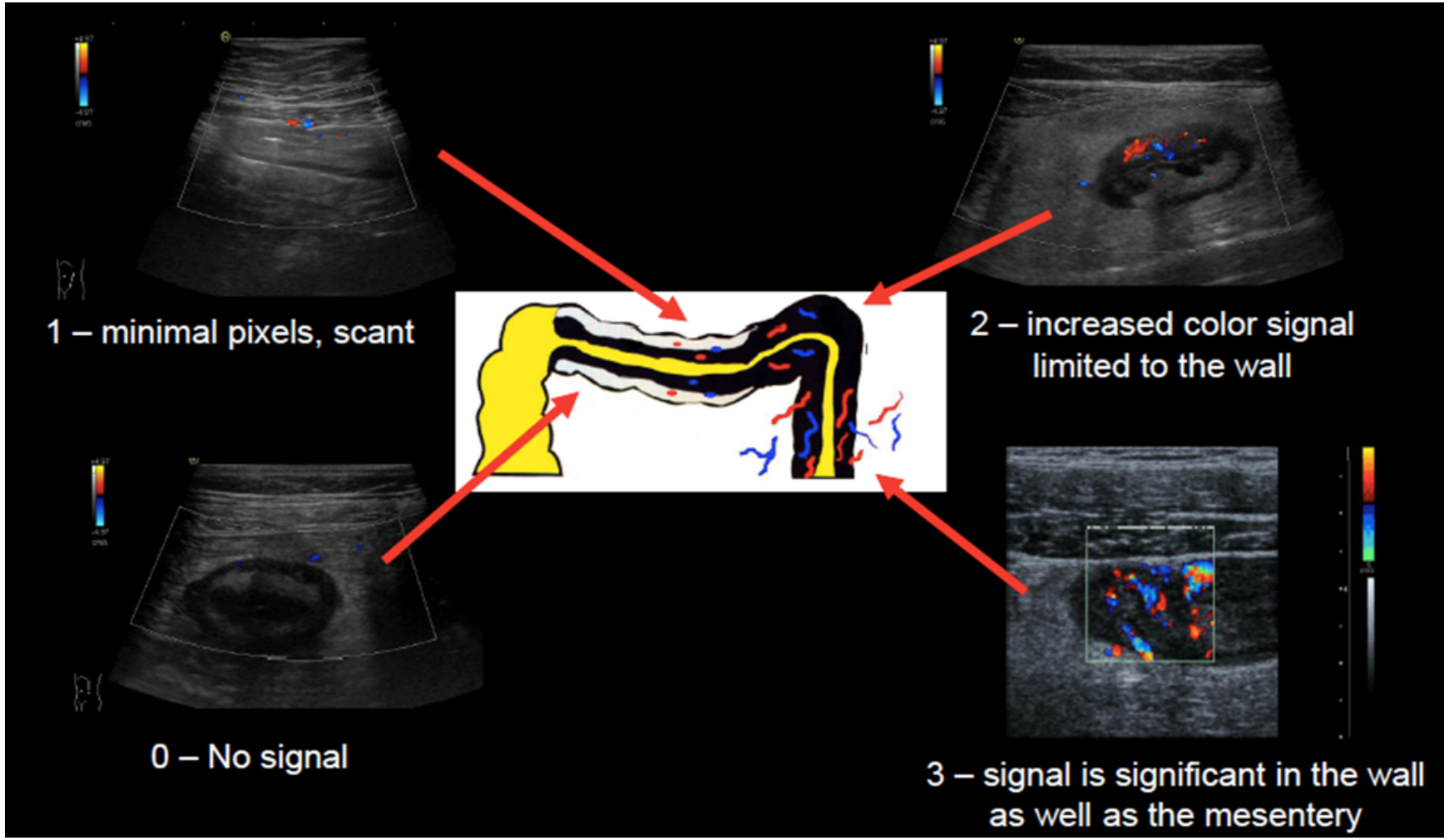
- Bowel wall thickness
- Bowel wall hyperemia
- Bowel wall stratification
- Inflammatory fat stranding
- Lymphadenopathy
- Complications

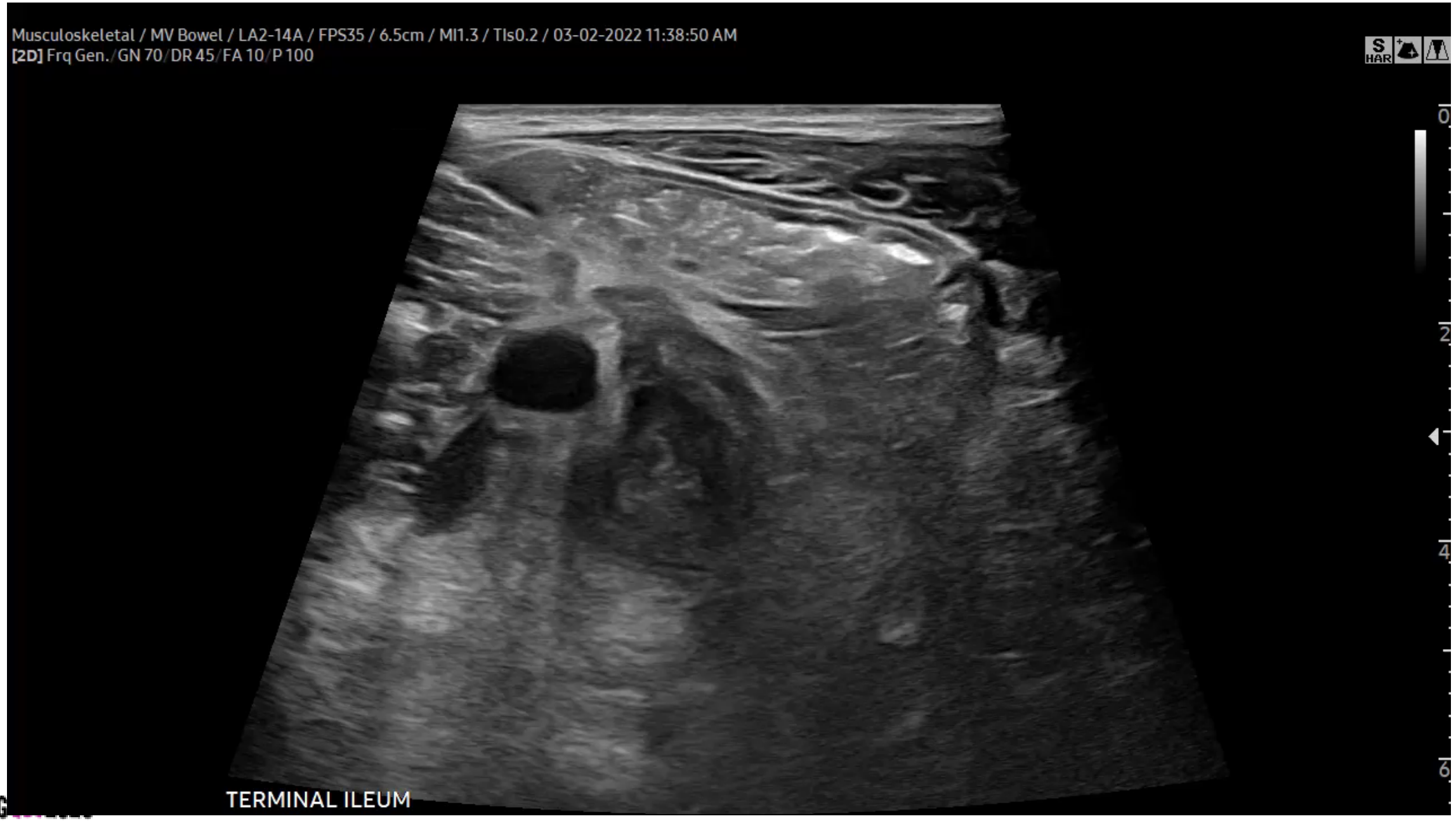
Bowel Wall Thickness is the Most Important Measure

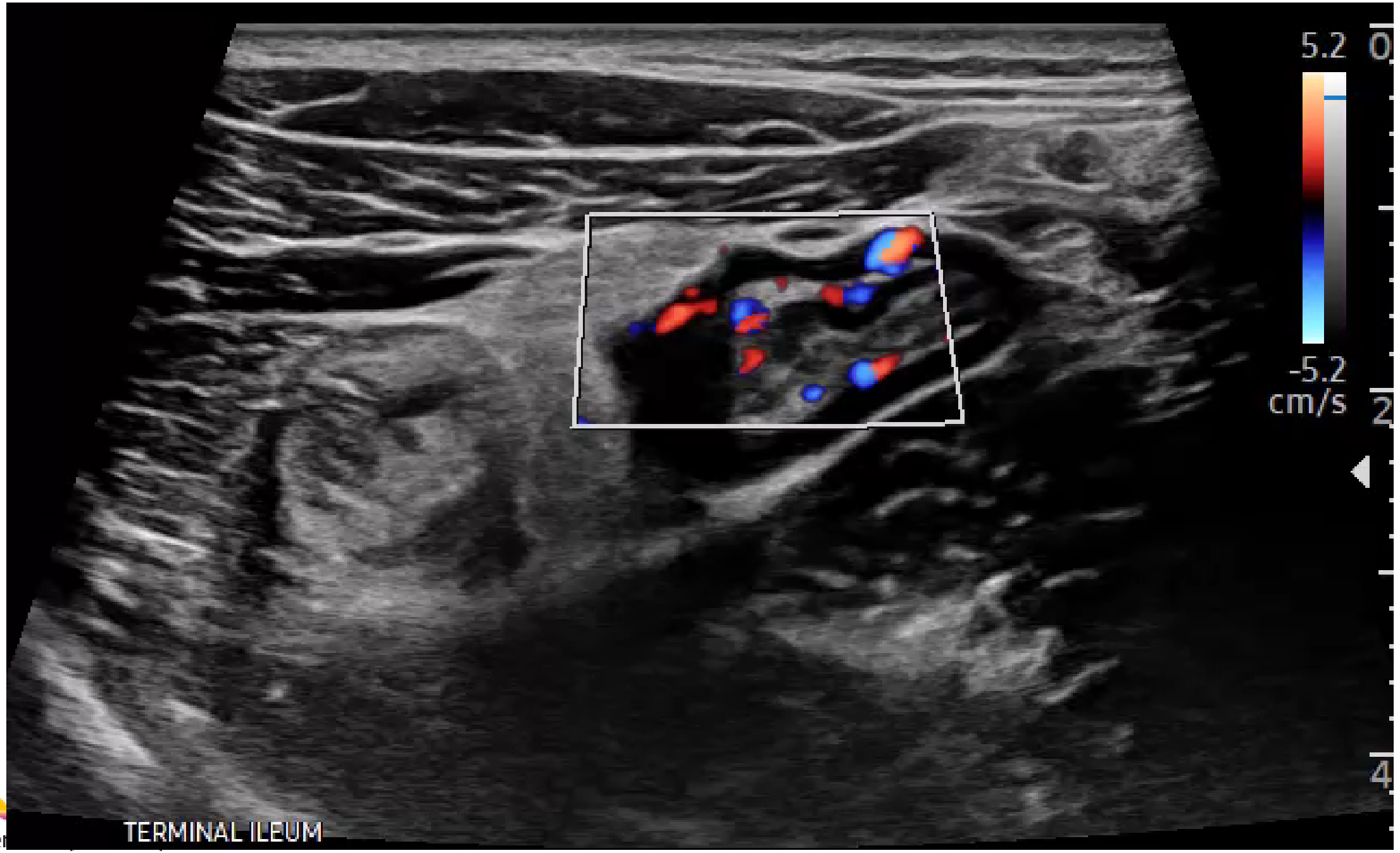


Kellar A and Dolinger M et al., *JPGN*, 2022

Bowel Wall Hyperemia is Measured by Modified Limberg Score




Musculoskeletal / MV Bowel / LA2-14A / FPS35 / 6.5cm / MI1.3 / TIs0.2 / 03-02-2022 11:38:50 AM
[2D] Frq Gen. / GN 70 / DR 45 / FA 10 / P 100
TERMINAL ILEUM


5.2
-5.2
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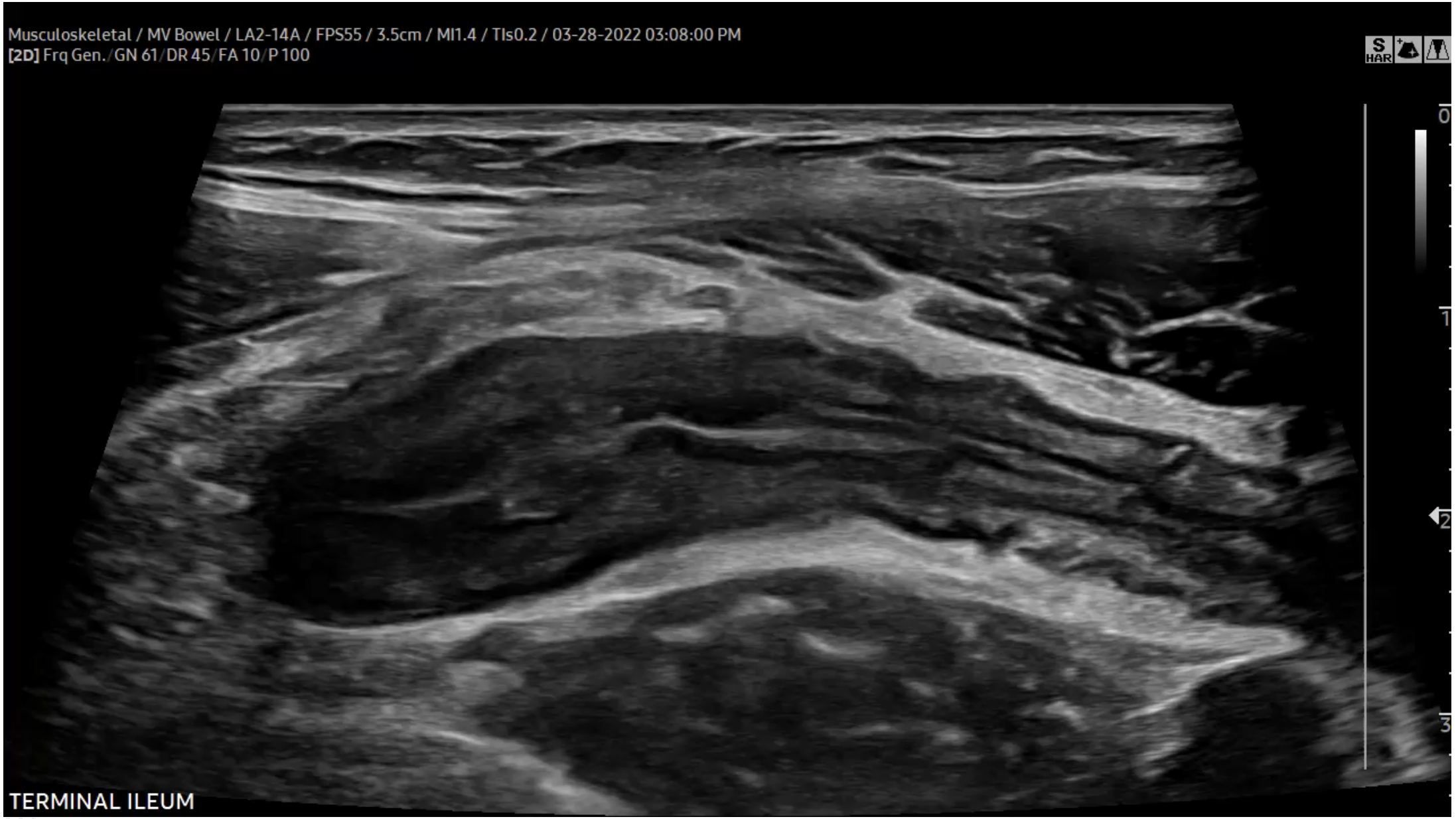
Musculoskeletal / MV Bowel / LA2-14A / FPS55 / 3.5cm / MI1.4 / TIs0.2 / 03-28-2022 03:08:00 PM
[2D] Frq Gen. / GN 61 / DR 45 / FA 10 / P 100
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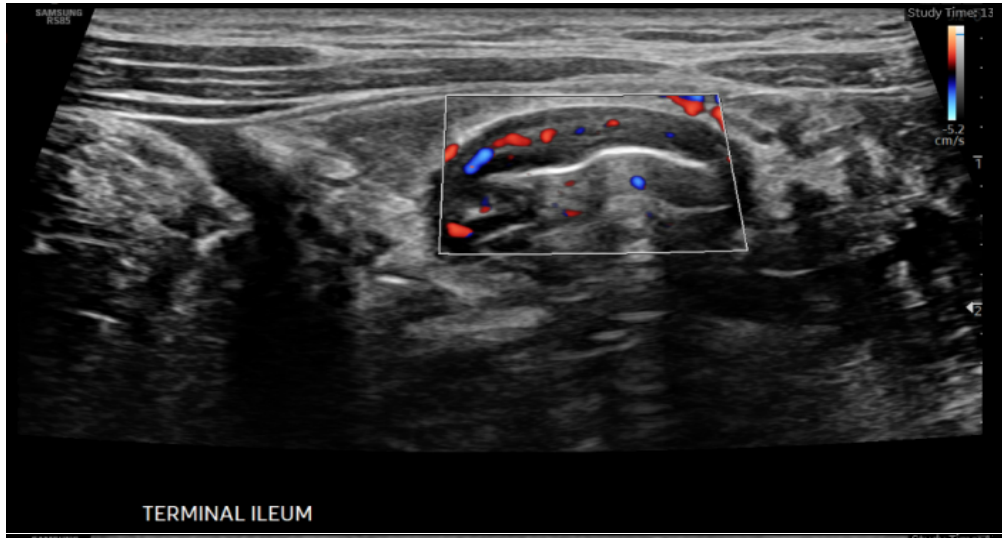
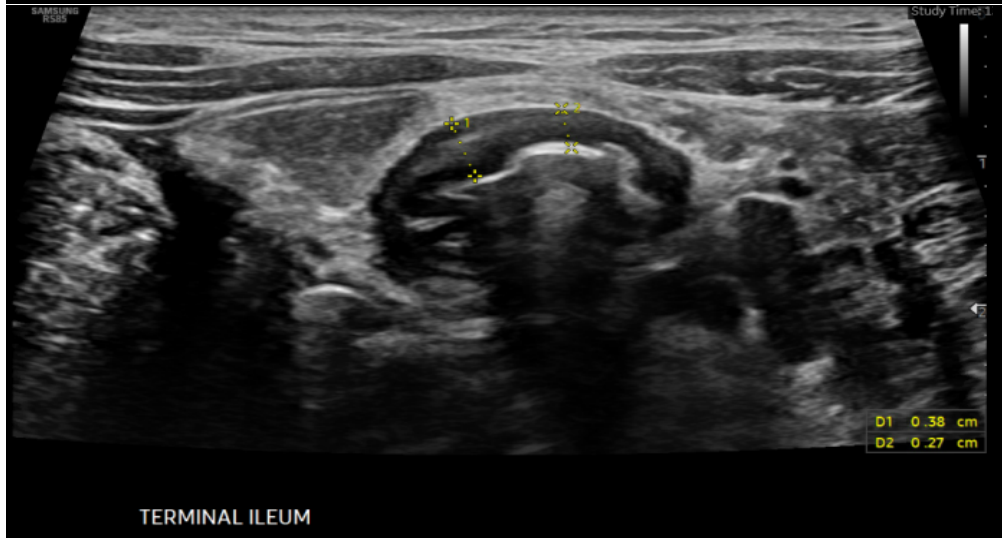
TERMINAL ILEUM

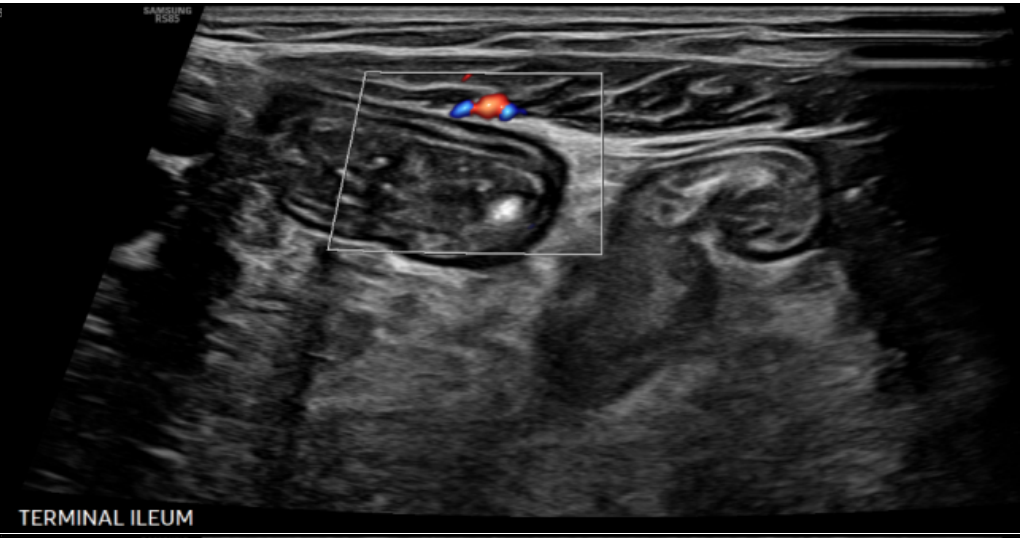
IUS to Monitor Induction Response

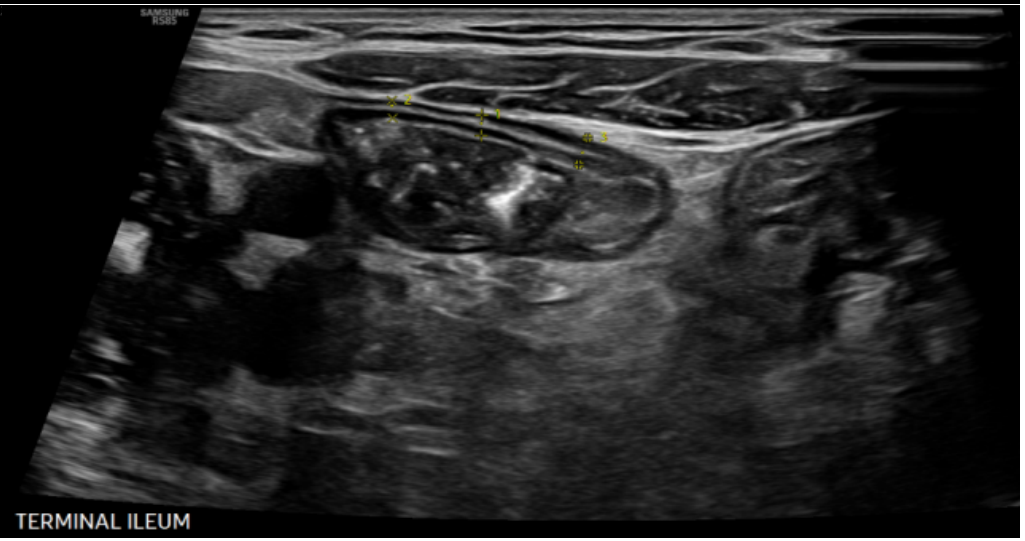
Pre-Induction



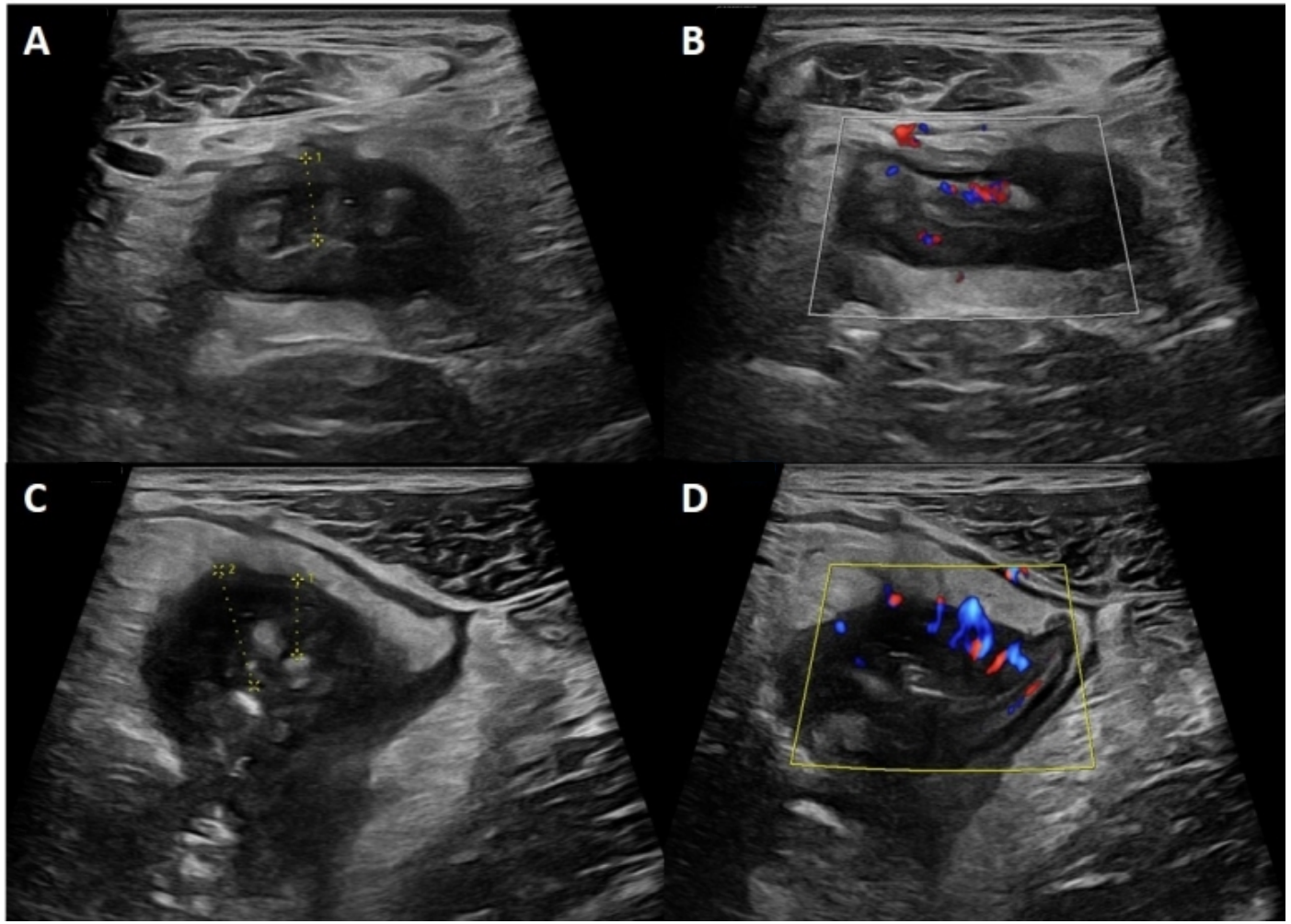


Post-Induction





IUS Monitors CD Recurrence After Surgery



Benefits and limitations of IUS in IBD

Benefits

- **Inexpensive** and **widely available**[1,2]
- **Non-invasive**[1]
- **Accurate**[1,2] **and sensitive**[3]
- Good agreement between **IUS** and **endoscopy** at determining most affected bowel segment[4]
- **Encourages patient's active engagement** in monitoring, as it is used at **PoC**[5,6]
- **Highly rated by patients** as a preferred monitoring approach[6]
- Long been established in **monitoring of CD**[7]
  - Recent studies and guidelines show **similar benefits** in patients with **UC**[7]

Limitations

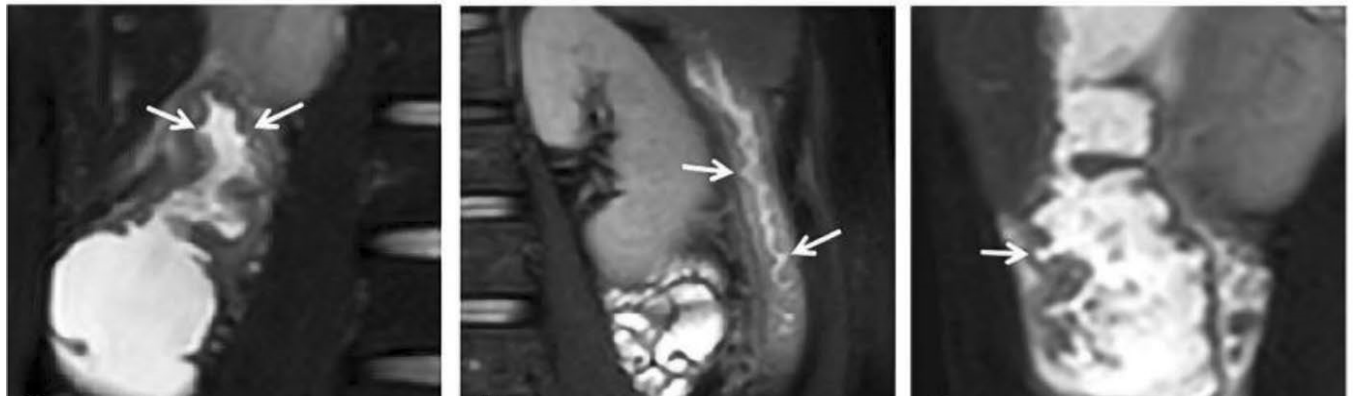
- Requires **experienced practitioners**[5]
- **Limited visualization:**[5,8]
  - Complete assessment of all bowel segments may be **challenging**, particularly in **overweight/obese** patients[5]
  - Overlying bowel gas may obscure **proximal (duodenal) disease**[8]
- Precise measurement of disease extent is difficult in **extensive small bowel CD**[8]
- **Standardized scoring systems** are not routinely used in **clinical practice**[8]

IUS, intestinal ultrasound; PoC, point-of-care.

1. Maaser C, et al. *J Crohns Colitis.* 2019;13:144–64; 2. Nardone OM, et al. *Front Med*. 2022;9:898092; 3. Cleveland NK. et al. *Curr Gastroenterol Rep*. 2024;26:31–40; 4. Kucharzik T, et al. *Clin Gastroenterol Hepatol*. 2023;21:153–63; 5. Wilkens R, et al. *Gastroenterology*. 2022;162:1476–92; 6. Rohatinsky N, et al. *Crohns Colitis 360.* 2023;5:1–11; 7. El-Nakeep S. *Egypt J Intern Med.* 2024;36:51; 8. Chavannes M, *Clin Gastroenterol Hepatol*. 2024;22:1790–95.

MRI can detect endoscopic ulcerations and be used to assess treatment response in CD[1–3]

Endoscopic ulcerations can be seen on MRI: CD[1]



The simplified magnetic resonance index of activity (MaRIA) can accurately evaluate the disease activity level of CD and is highly correlated with SES-CD and biomarkers:[1]

- MaRIA ≥1 detected segments with active CD with 90.80% specificity and 81.37% sensitivity, with good interrater analysis agreement[1]

MRI indices MaRIA and Clermont score are equally effective at detecting endoscopic ulcerations in CD[†2]

CD	MaRIA >7	MaRIA >11	Clermont >8.4	Clermont >12.5
Specificity, %	82.1	82.0	81.3	80.0
Sensitivity, %	51.8	90.9	54.4	90.9
AUROC (95% CI)	0.67 (0.60–0.74)	0.86 (0.77–0.95)	0.68 (0.61–0.75)	0.86 (0.76–0.95)

Studies have supported the ability of MRI/MRE to monitor treatment response and has led some experts to recommend use of MRI standards as the treatment endpoint in clinical practice[1–3]

Image of MRI scans from Tao Y, et al . *BMC Gastroenterol*. 2021;21:409.[1]

[†]Prospective data from a previous observational single-center cohort study of patients with CD who underwent consecutive DW-MREC and colonoscopy (N=44). [3]
AUROC, area under the receiver operating characteristic curve; CI, confidence interval; DW-MREC, diffusion-weighted magnetic resonance entero-colonography; MaRIA, magnetic resonance index of activity; MRE, magnetic resonance enterography.

1. Tao Y, et al . *BMC Gastroenterol*. 2021;21:409; 2. Buisson A, et al. *Dig Liver Dis*. 2017;49:1211–17; 3. Kumar S, et al. *J Crohns Colitis*, 2024;18:1450–63.

Biomarkers (FC and CRP) correlate with disease activity[1–4]

FC is a highly sensitive diagnostic tool in estimating endoscopic IBD activity; while CRP has higher specificity, it has lower sensitivity vs FC[1,2]

	Sensitivity†	Specificity†	AUC†
FC[3]	88% (84–90%)‡	73% (66–79%)‡	**0.89** (0.86–0.91)‡
CRP[3]	49% (34–64%)‡	92% (72–98%)‡	**0.72** (0.68–0.76)‡

Two measurements of **FC**, 1 month apart, may best predict flares before clinical symptoms[2]

A **combination** of **FC** with **clinical activity indices or CRP** may be better to assess endoscopic activity and healing vs FC alone[4]

†Meta-analysis of 19 studies (N=2,499) in patients with previously diagnosed UC or CD presenting with symptoms suggestive of endoscopically active disease.[3] ‡95% CI.[3]
AUC, area under the curve; CI, confidence interval; CRP, C-reactive protein; FC, fecal calprotectin.

1. Rokkas T, *J Gastrointestin Liver Dis.* 2018;27:299–306; 2. Turner D, et al. *Gastroenterology.* 2021;160:1570–83; 3. Mosli MH, et al. *Am J Gastroenterol. 2015*;110:802–19; 4. Bodelier A, et al. *Dig Dis Sci.* 2017;62:465–72.

ECCO guidelines recommend the use of biomarkers for disease monitoring[1]

For asymptomatic patients with CD or UC[1]

3–6 months

Consider detecting relapse with FC before clinical symptoms

For patients with CD[1]

≤12 weeks

Assess **clinical** and **biochemical response** to treatment

≤6 months

Assess endoscopic or **transmural** response

For patients with UC[1]

ND

Determine treatment response using clinical parameters, endoscopy, and **biomarkers**

3–6 months

Determine **mucosal healing endoscopically** or by **FC**

Before de-escalation of maintenance therapy, assess disease activity using clinical and **biochemical markers** and endoscopy and/or **cross-sectional imaging, including IUS**[1]

ECCO, European Crohn's and Colitis Organisation; ESGAR, European Society of Gastrointestinal and Abdominal Radiology; FC, fecal calprotectin; ND, no date; IUS, intestinal ultrasound.

1. Maaser C, et al. *J Crohns Colitis*. 2019;13:144–64.

STRIDE-II recommends normalization of biomarkers as an intermediate treatment target[1]

FC and **CRP** are easy, low-cost, and **non-invasive** biomarkers that can be used post-induction and **regularly throughout a patient's disease** course[1]

FC and CRP **predict** endoscopic activity[1]

Recommended thresholds

FC (100–250 µg/g)

FC cutoff value is dependent on the desired outcome[1]

▲ **Higher FC values (<250 µg/g)** may reflect **less stringent outcomes** (e.g. MES of 0 or 1 in UC)[1]

▼ **Lower FC thresholds (<100 µg/g)** may reflect **endoscopic** and transmural healing (deep healing) or **histological healing**[1]

A post-induction FC concentration of ≤250 µg/g was associated with achieving:[2]

- Endoscopic improvement (OR: 4.24, 95% CI 2.96–6.06, p<0.0001)†
- Endoscopic remission (OR: 4.26, 95% CI 2.83–6.40, p<0.0001)†
- Histologic remission (OR: 6.42, 95% CI 4.02–10.26, p<0.0001)†

CRP (values under ULN)

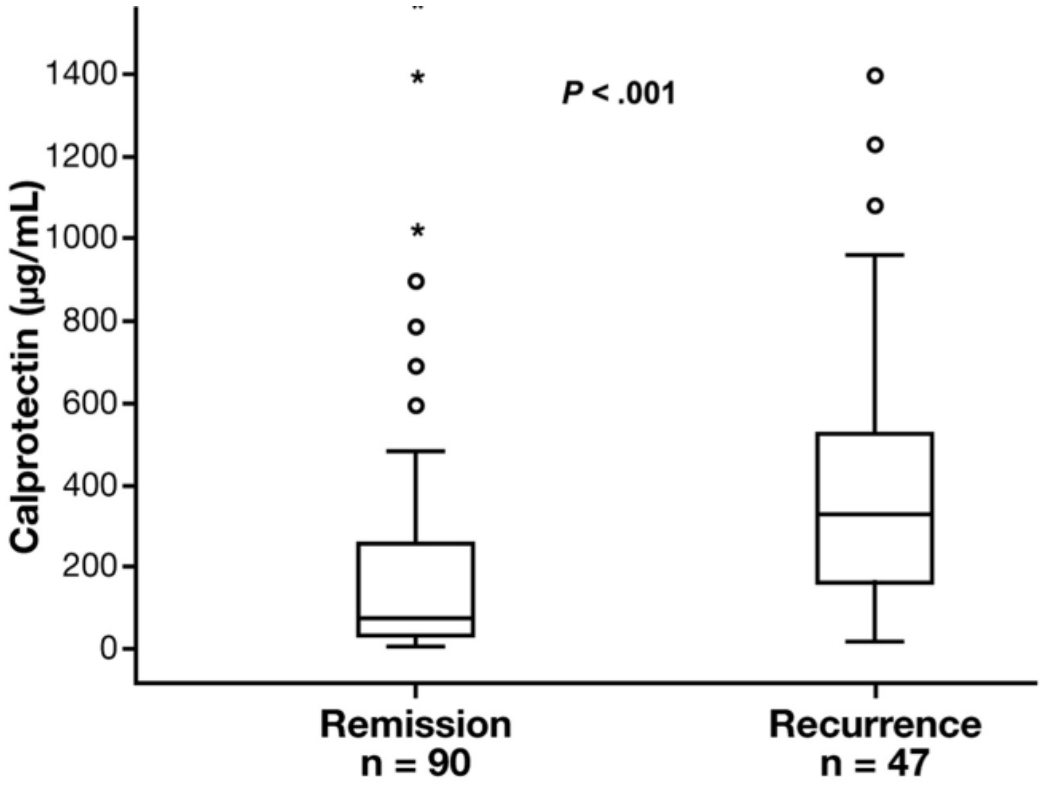
CRP cutoff of 5 mg/dL is typically endorsed[1]

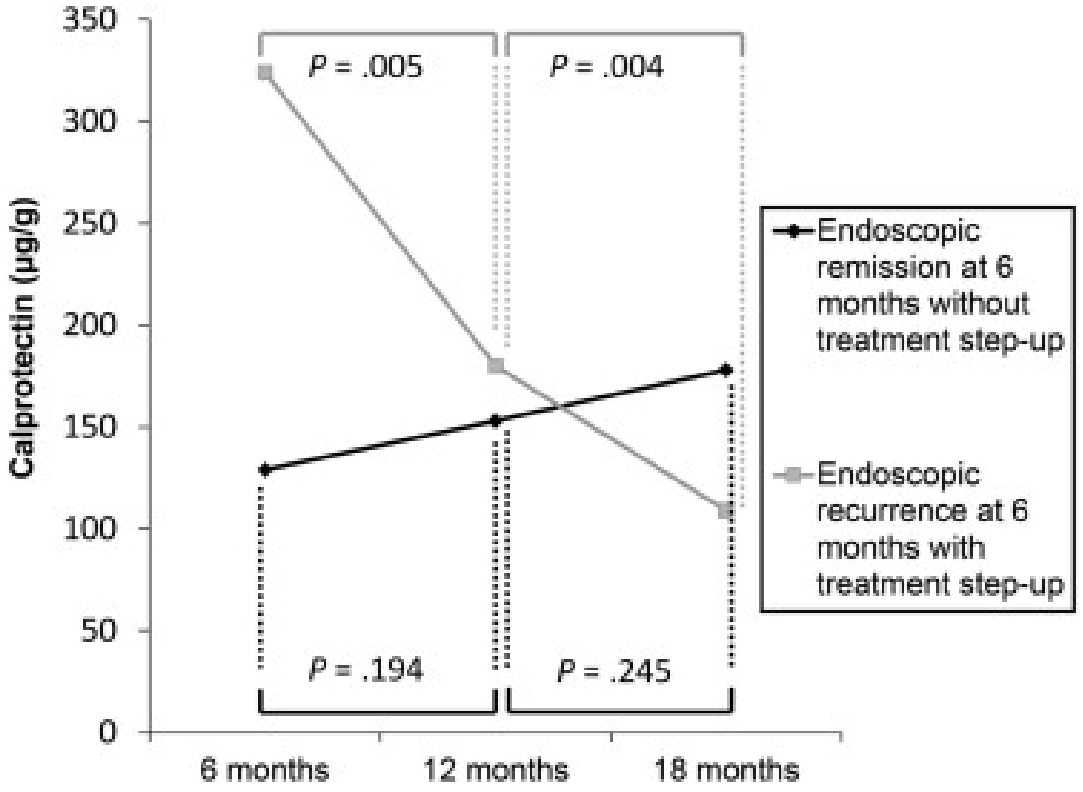
†ORs for Week 52 outcomes based on FC concentrations at Week 14 in a *post-hoc* analysis of the Phase III VARSITY study for VDZ and ADA.[2]

ADA, adalimumab; CI, confidence interval; CRP, C-reactive protein; FC, fecal calprotectin; MES, Mayo Endoscopic Subscore; OR, odds ratio; STRIDE, Selecting Therapeutic Targets in Inflammatory Bowel Disease; ULN, upper limit of normal; VDZ, vedolizumab.

1. Turner D, et al. *Gastroenterology*. 2021;160:1570–83 and supplementary data; 2. Dulai PS, et al. *Clin Gastro Hepatol*. 2023;21:456–66.

Specific Use Case of Fecal Calprotectin: CD Post Operative Recurrence

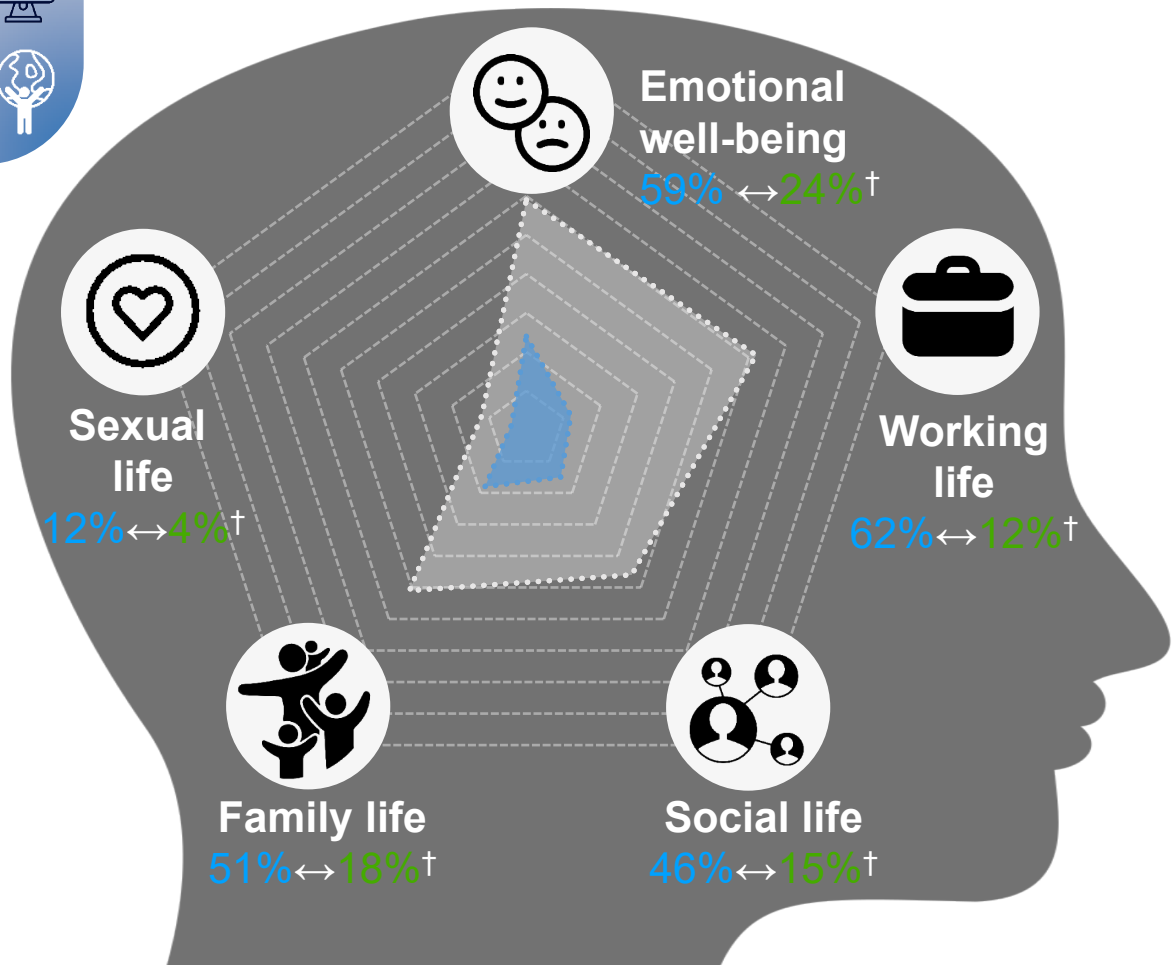




Calculated best cut-off at 6 mos to detect endoscopic POR: 135 ug/g → sens 91%, spec 62%
6 mo FC >100 ug/mL predicted 18 mo recurrence: AUROC 0.89

Wright EK, et al. *Gastroenterology*. 2015;148(5):938-947.

Holistic monitoring is important to recognize the impact of the disease on the lives of patients with IBD[1]



…But do we ask our patients questions beyond physical symptoms?

What do patients and physicians think?

How often patients feel they are asked about psychosocial aspects (n=903)[1]

How often HCPs ask their patients about these aspects (n=170)[1]

†p<0.05; chi-squared test for proportions.[1]

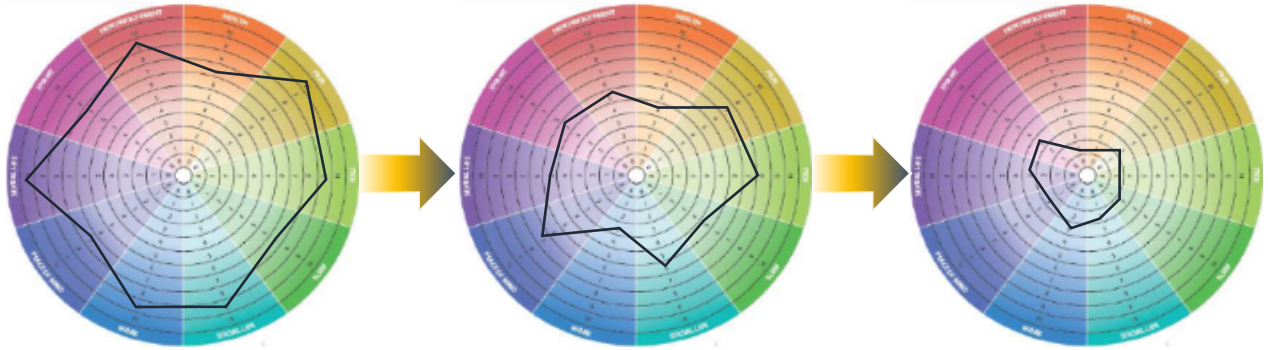
1. Marín-Jiménez I, et al. *Inflamm Bowel Dis.* 2017;23:1492–8.

IBD Disk can be used to assess patients' QoL[1]

Patients assess the **impact** of IBD on their **daily lives** using a **10-item questionnaire** with **VAS scores** (0–10) marked on a **colored disk**[1]

1. Abdominal pain
2. Regulating defecation
3. Interpersonal interactions
4. Education and work
5. Sleep
6. Energy
7. Emotions
8. Body image
9. Sexual functions
10. Joint pain

- ✓ Monitor IBD-associated disability
- ✓ Set short- and long-term goals
- ✓ Monitor treatment efficacy
- ✓ Encourage adherence
- ✓ Focus on specific issues of disability



Initial assessment
High scores/high disease burden

Therapeutic goal
Low scores/low disease burden

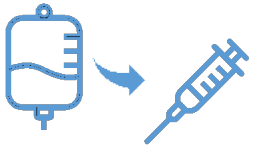
Figure taken from Ghosh S, et al. *Inflamm Bowel Dis*. 2017;23:333–40.
QoL, quality of life; VAS, visual analog scale.

1. Ghosh S, et al. *Inflamm Bowel Dis*. 2017;23:333–40.

Practical Algorithm for T2T in Practice

Induction of Remission

Endoscopy, IUS, Calpro Baseline



Therapy initiation according to risk

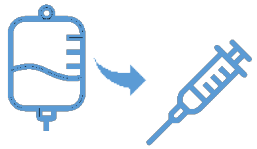
Calpro/IUS 8-12 weeks

Therapy adjustment

Endoscopy 6-9 months

Post-Operative CD

Surgery



Therapy initiation according to risk (2 wks)

Calpro 3 months

IUS 3-6 months

Endoscopy at 3 months if calpro >100

Endoscopy at 6 months if calpro <100

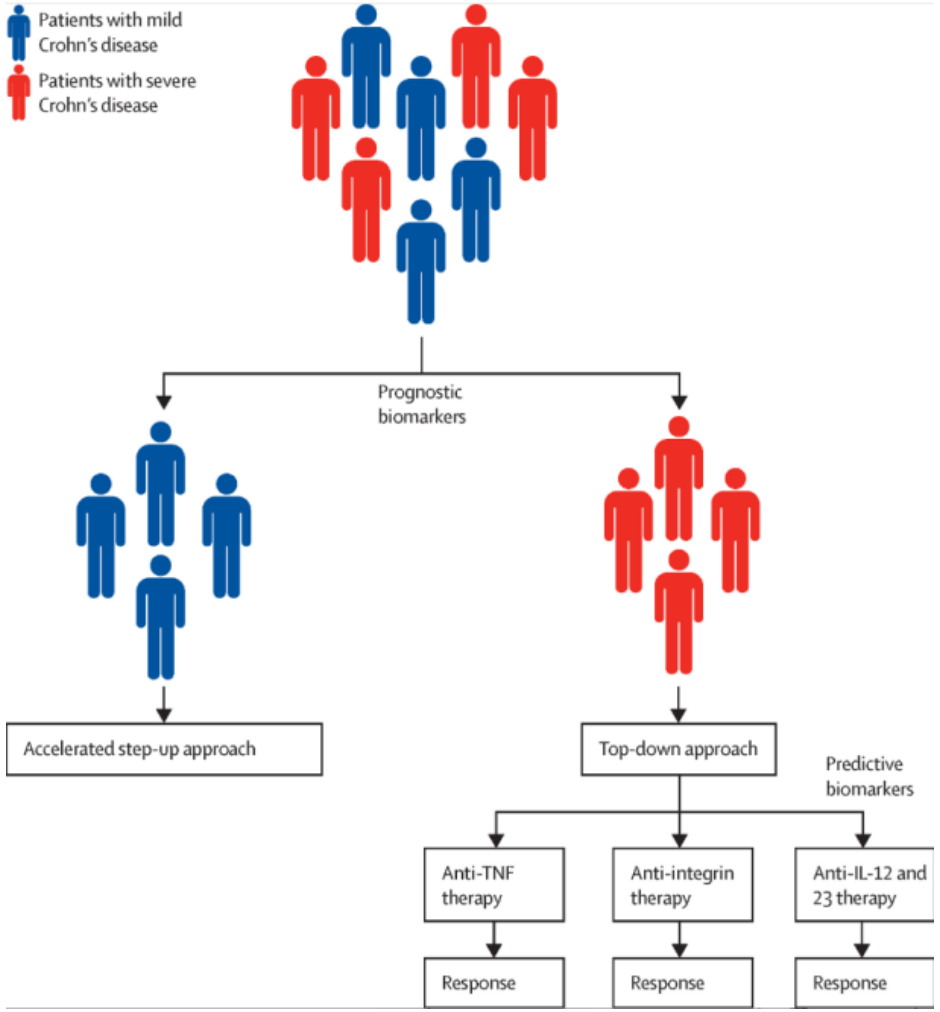
Therapy adjustment or continuation

Advances in Diagnostic Strategies: *Precision Medicine in IBD*

ACG 2025
October 24-29, Phoenix, AZ

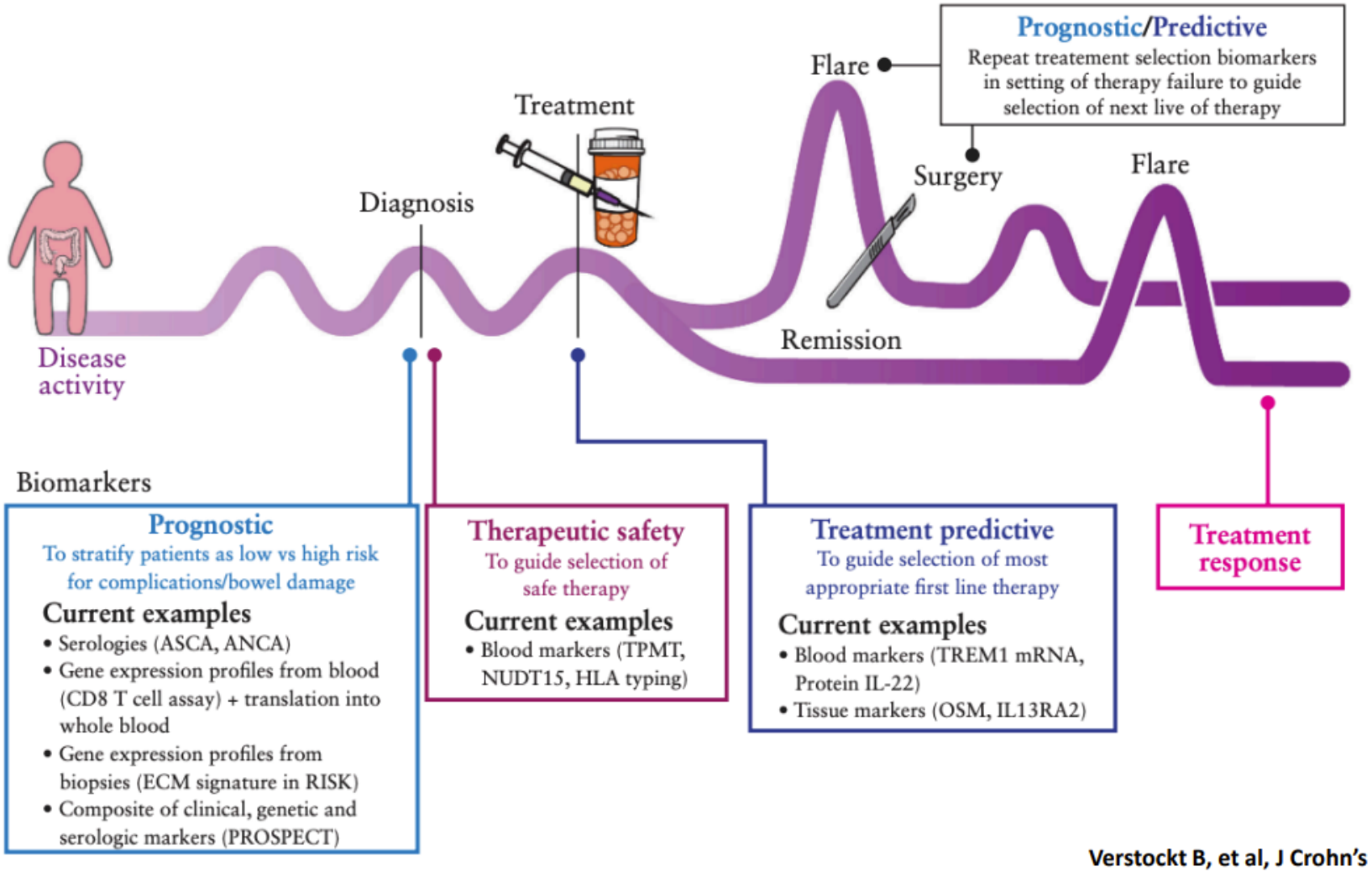
Advances in Diagnostic Strategies: Precision Medicine

- To incorporate **prognostic** and **predictive** biomarkers into clinical decision making to enable the most appropriate treatment
- **Prognostic biomarkers** could identify at the time of diagnosis which patients will have more aggressive disease and require **more potent therapy**
- **Predictive biomarkers** could be used to match patients to the most **appropriate therapy**



Noor NM, et al. Lancet Gastroenterol Hepatol. 2020 Jan;5(1):80-92.

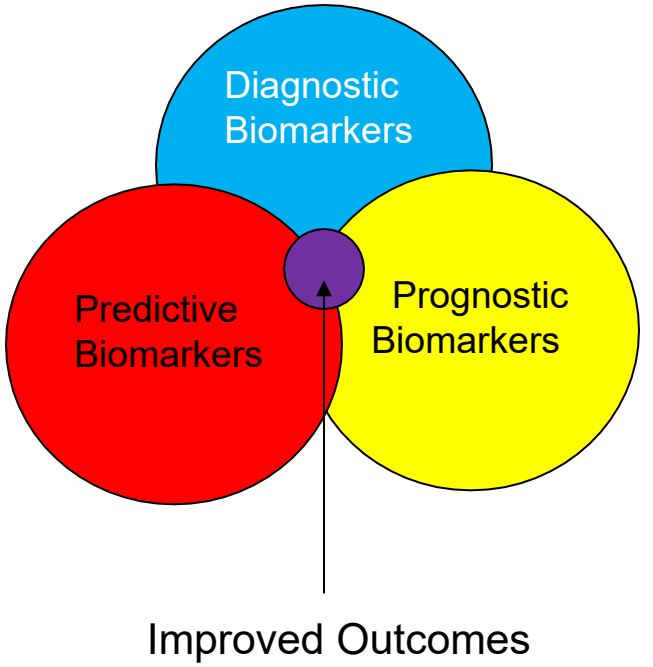
Applying Precision Medicine to IBD using Genetics



Verstockt B, et al, J Crohn's & Colitis. 2021:1431–1442

Prognostic Biomarkers

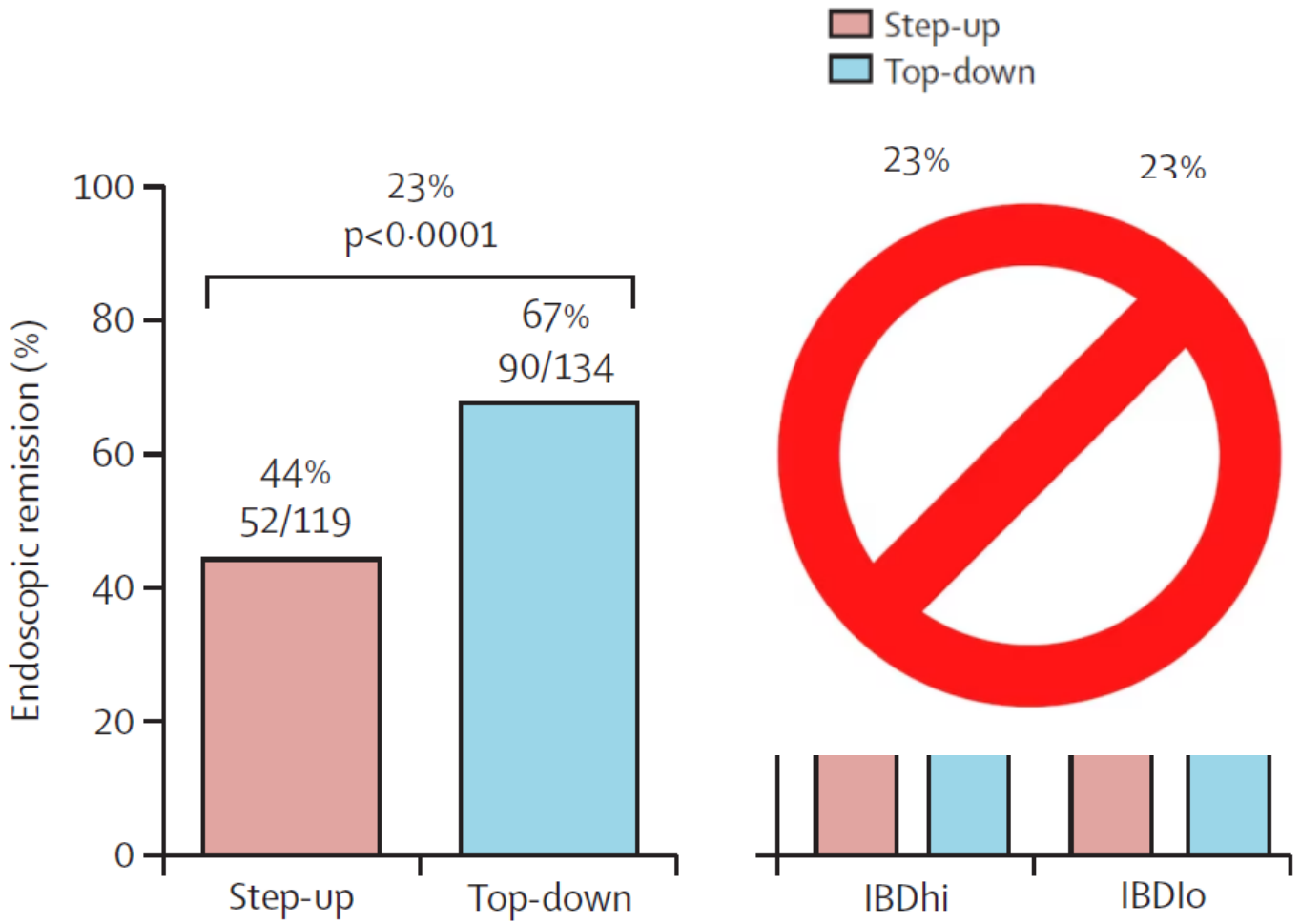
- Predictive biomarkers for diagnosis
  - PredictSURE IBD
- Prediction of adverse events
  - TPMT and thiopurine induced myelosuppression
  - NUDT-15 and thiopurine induced myelosuppression
- Prediction of response or non-response to therapy
  - HLA DQ A1*05 and immunogenicity
  - Companion diagnostics to Anti-TL1A



Noor NM, et al. Lancet Gastroenterol Hepatol. 2020 Jan;5(1):80-92.

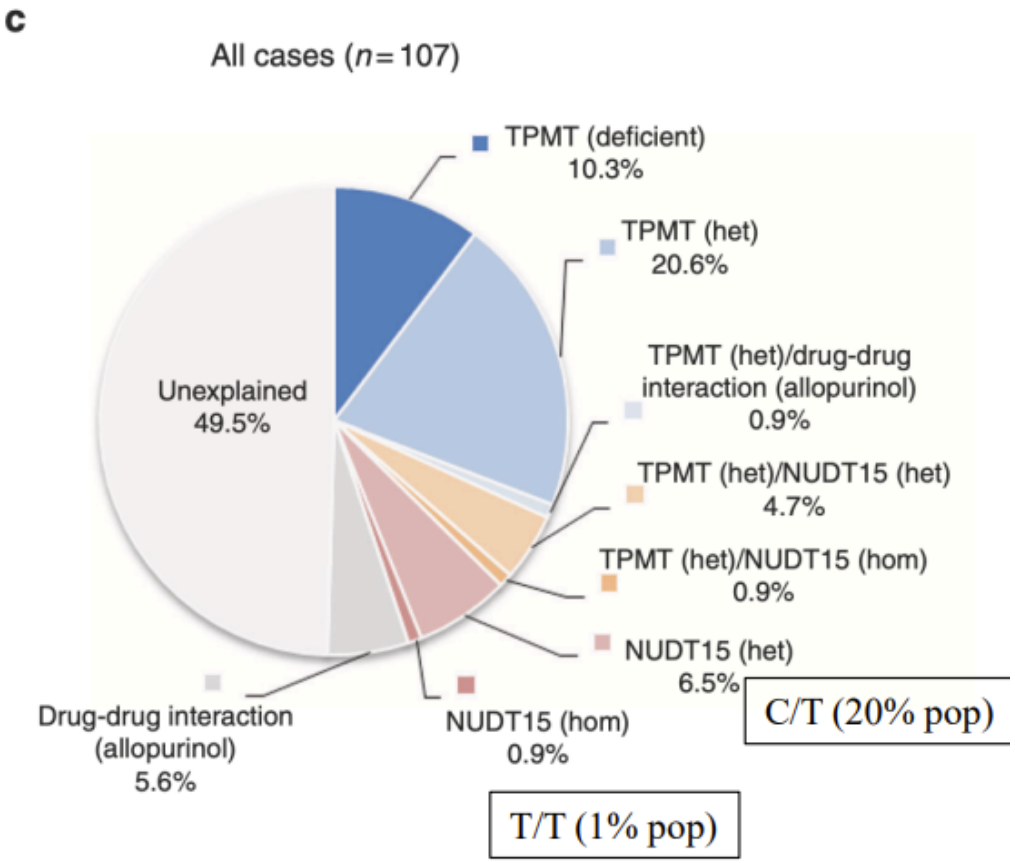
PROFILE UK Study of PredictSURE Biomarker and Top Down Therapy

- 386 patients randomized, 193 top down, 193 step up; biomarker stratified
- Newly diagnosed CD, within 2 weeks
- Biomarker: CD8 T cell gene expression signatures
- Steroid/surgery free remission improved in top down vs. step up (79% vs. 15%, p<0.001)
- No effect of biomarker



Noor N, et al. Clin Med (Lond). 2022 Jul; 22(Suppl 4): 22–23.
Noor NM, et al. Lancet Gastroenterology & Hepatology 2024;10.1016/s2468-1253(24)00034-7.

Prediction of Adverse Events with Thiopurines



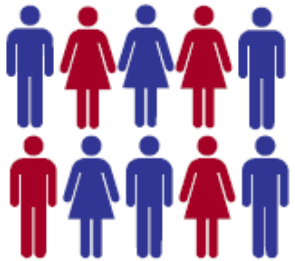
NUDT15 polymorphisms and **TPMT** mutations predict ~50% cases of severe thiopurine-induced leukopenia

Schaeffeler et al Genetics in Medicine 2019 Sep;21(9):2145-2150

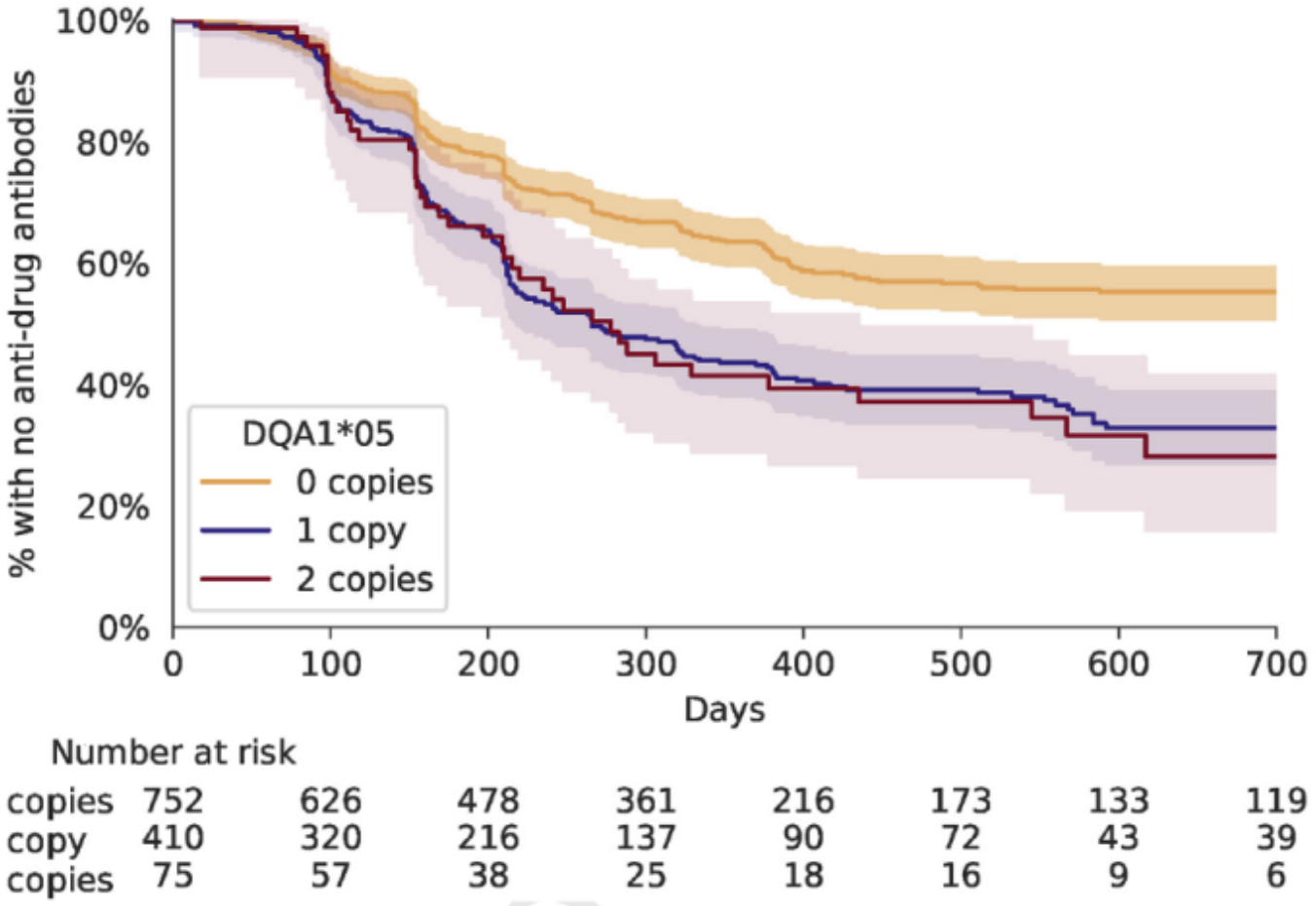
Maeda T et al Intestinal Research doi.org/10.5217/ir.2020.00133

Prediction of Response: Genetic Marker HLA DQ A1*05

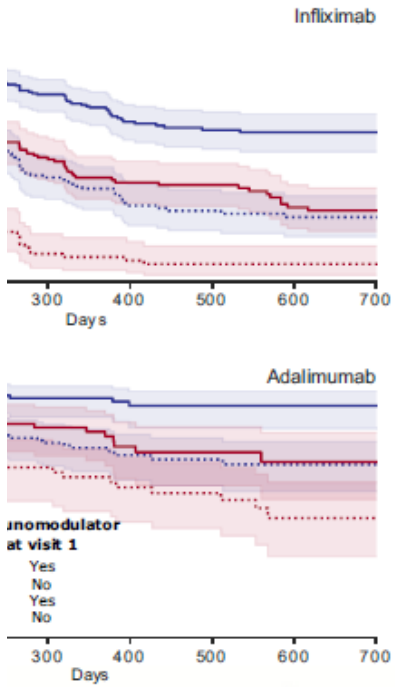
HLA-DQA1*
in biologic



1240 patients wit
Crohn's disease trea
with infliximab o
adalimumab
± immunomodulat



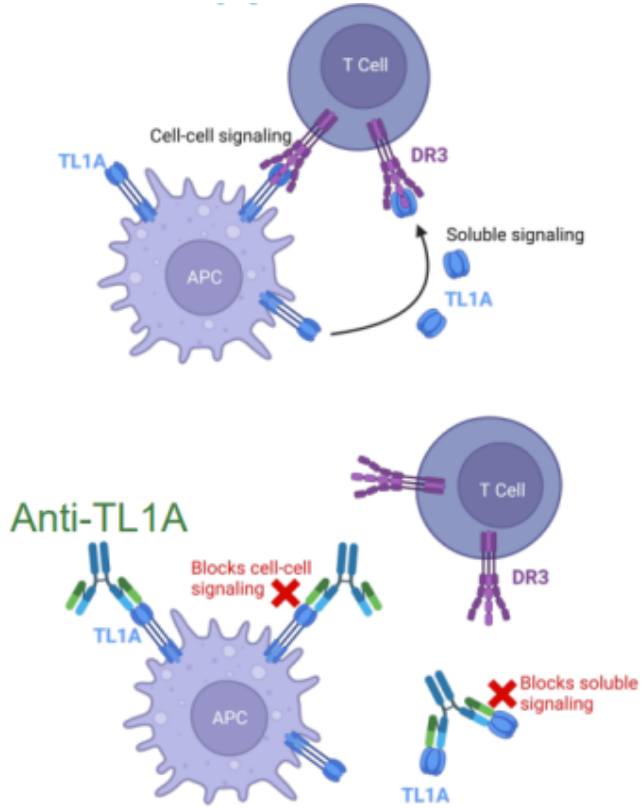
TNF therapy



stroenterology

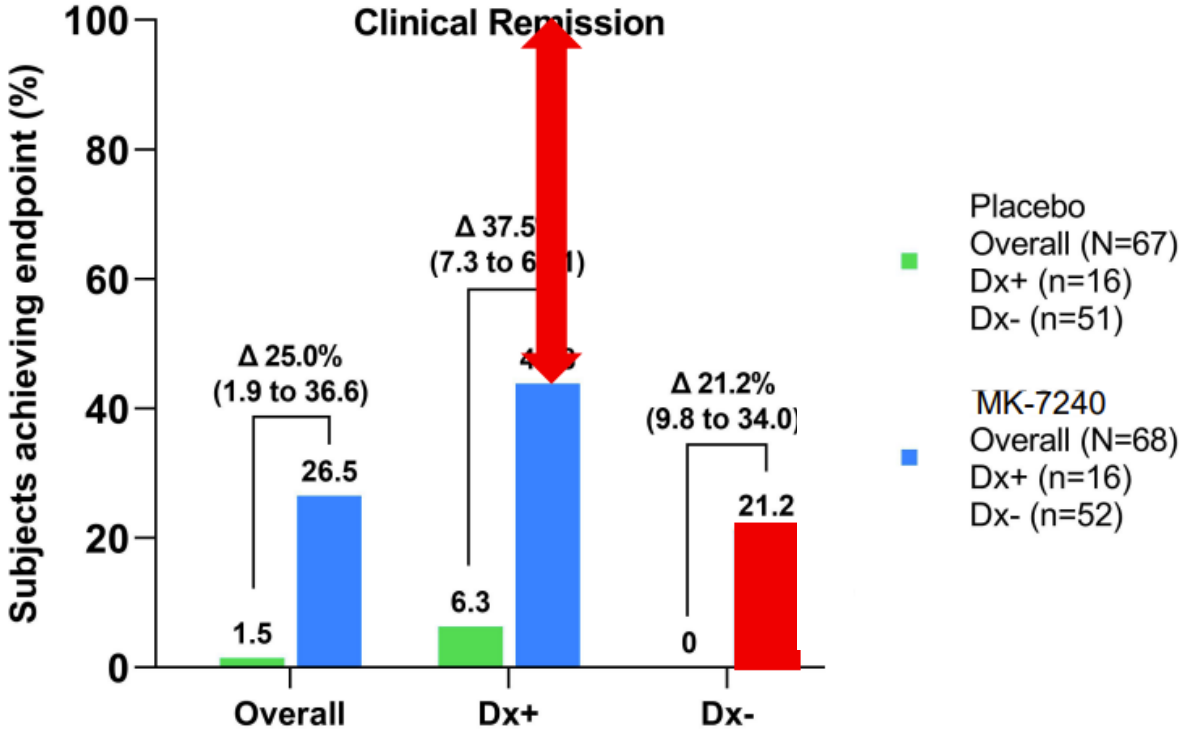
Example of Anti-TL1A and Personalized Medicine

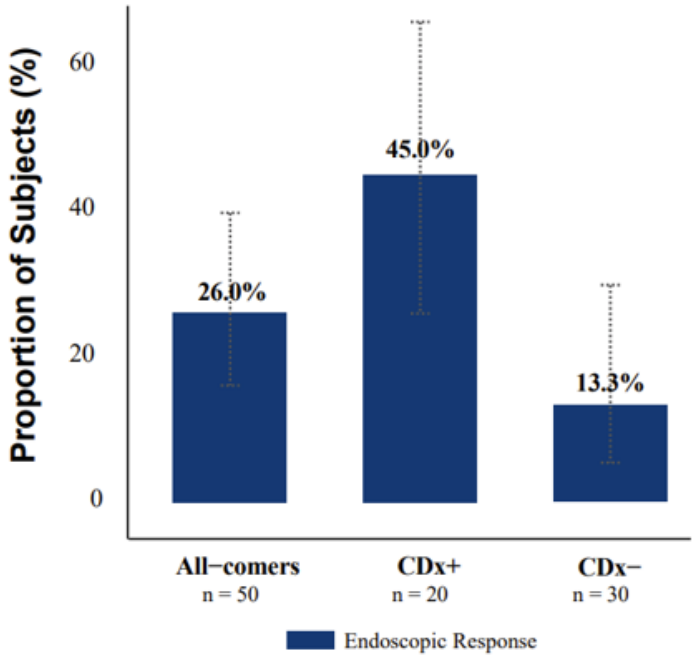
- First IBD target that may moderate inflammation and fibrosis
- TL1A and associated receptor (DR3) upregulated in inflamed intestinal tissue
- TL1A encoding gene (TNFSF15) polymorphisms are associated with increased IBD risk
- Possibility of a companion diagnostic test: in vitro test providing information on safe and effective use of therapeutic product



Furfaro et al. Curr Drug Targets 2021, Jostens et al, Nature 2012
Yamazaki et al, Hum Mol Genet 2005

Diagnostic Tools in ARTEMIS and APOLLO- Anti-TL1A

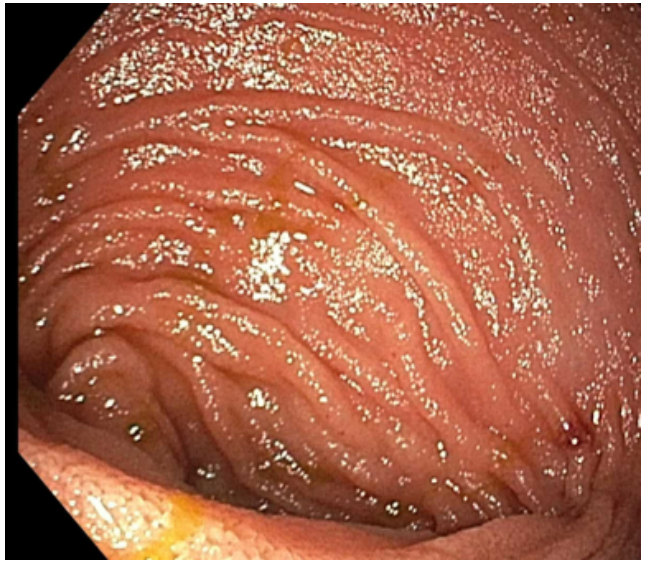




Sands BE, et al. DDW 2023
Fegan BG, et al. ECCO 2023

Case Wrap-Up

- Does well with ileocecal resection
- Risk factors for recurrence: young age, stenosing disease, prior surgery
- Continued on IFX/aza
- HLA DQ A*1 05 is negative, aza stopped
- IFX level post stopping aza: 12 ug/mL
- Calpro at 3 months <50 ug/g; IUS without recurrence
- Colonoscopy at 6 months: Rutgeert's I0



Summary: Advances in Diagnostic Strategies in IBD

- Diagnosis of IBD remains endoscopic/pathologic
- Non-invasive monitoring tools are increasingly important for monitoring and clinical decision-making in IBD, ensuring the delivery of patient-centered care
- Non-invasive monitoring enhances tight control and treat to target
- Currently TPMT/NUDT 15 is used to risk stratify prior to thiopurines; HLA DQ A1*05 can assess immunogenicity risk with anti-TNF
- Predictive biomarkers for risk stratification and drug response will be a major break-through to improve the IBD therapeutic ceiling (*none as of yet….*)
- Anti-TL1A therapies are the first development programs with potential companion diagnostics, although further study is needed
- Challenges to advances in predictive biomarkers include the need for a standardized approach, definitions, inclusion of large, diverse populations, and costs involved in development programs