I.R.C.C.S. Ospedale San Raffaele

Integrating IUS into the Therapeutic Pathway for UC

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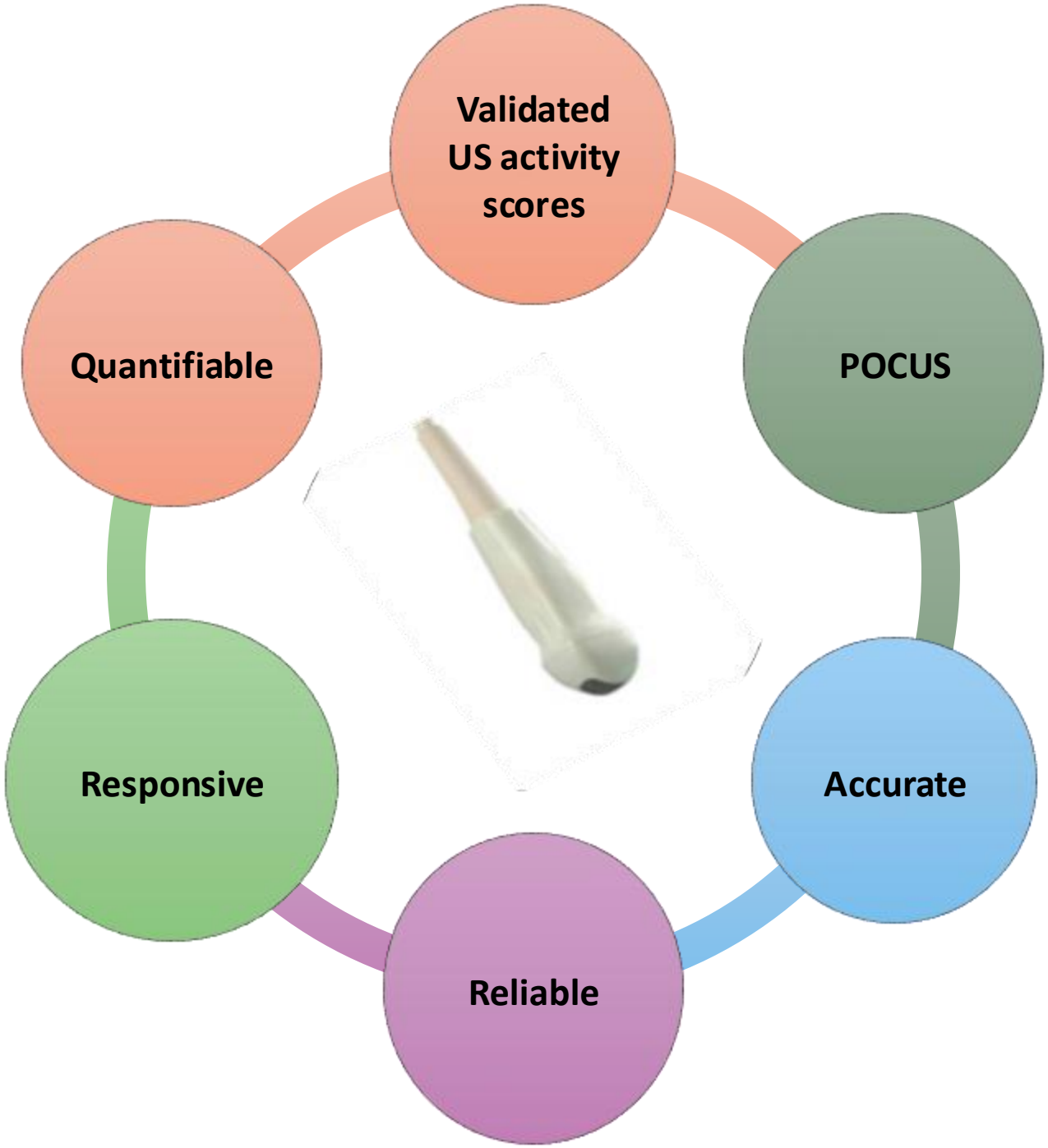
Disclosure of Conflicts of Interest

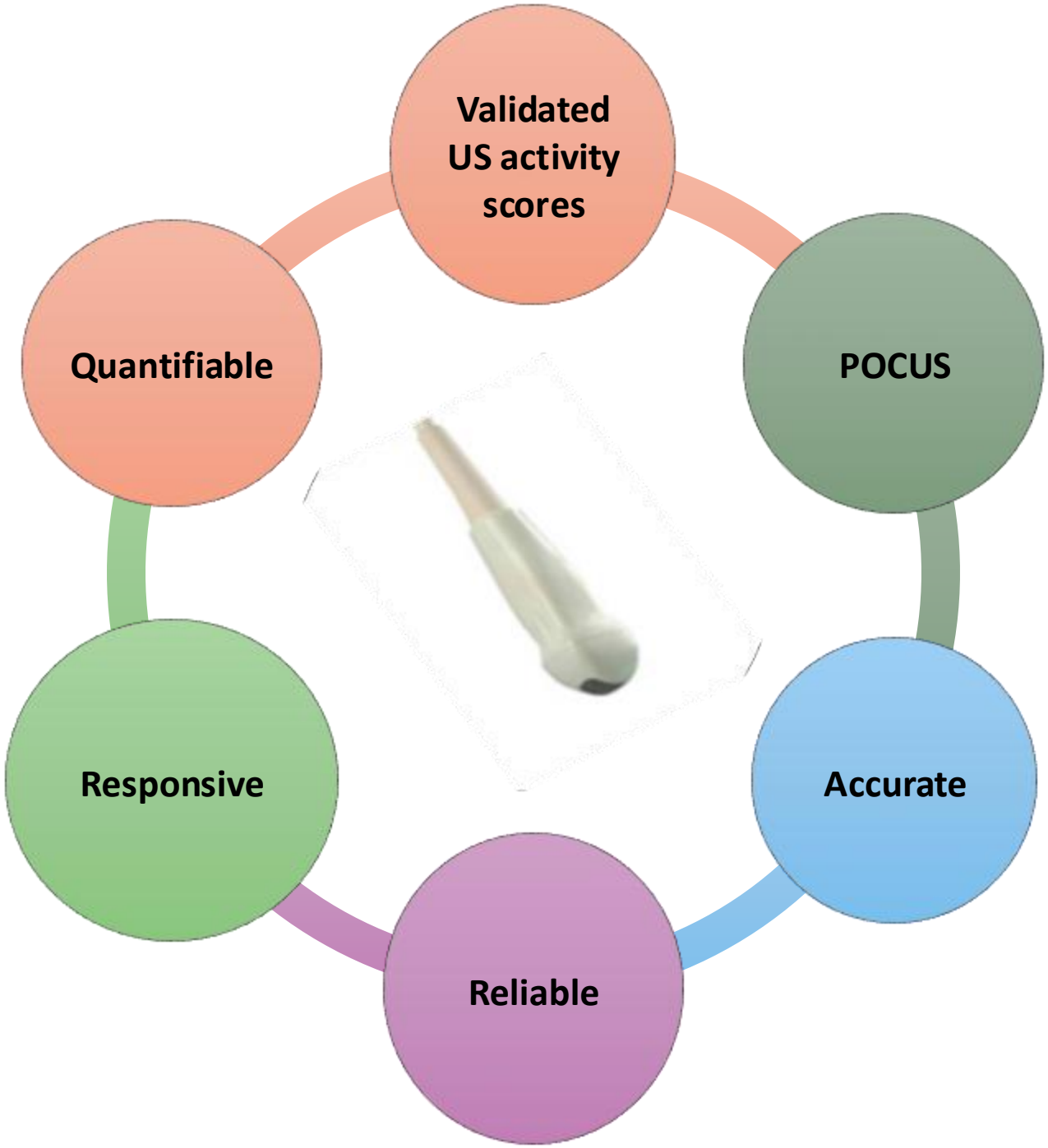
Dr. Mariangela Allocca received consulting fees from Nikkiso Europe, Mundipharma, Janssen, Abbvie, Ferring, Galapagos, Lilly, Alfasigma, Sandoz and Pfizer

Are we ready to incorporate intestinal ultrasound into clinical practice/clinical trials for UC?

Overview of IUS in UC



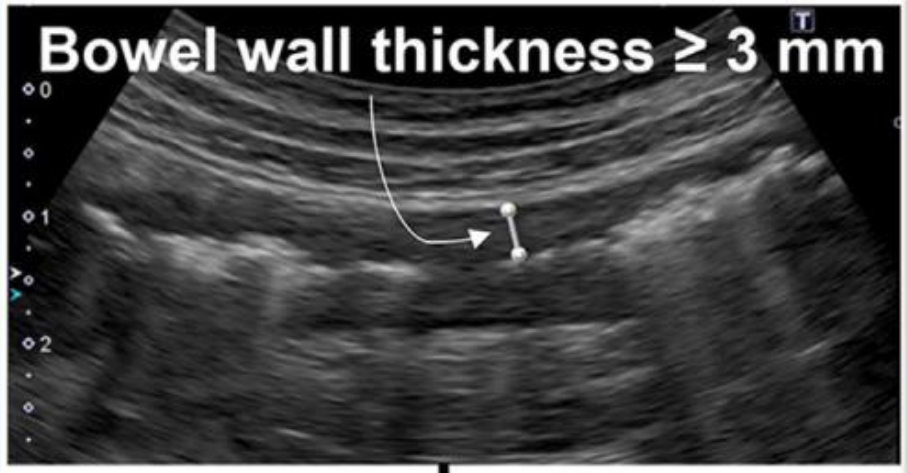
Accuracy of IUS in UC



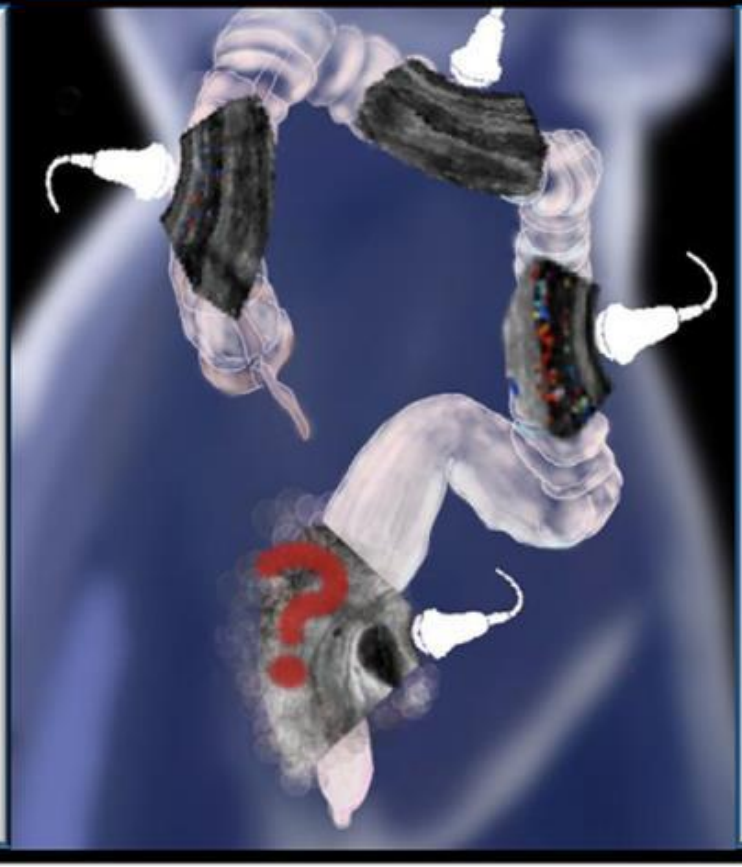
BWT ≥ 3 mm detects colonic inflammation with 86% of sensitivity and 88% of specificity: Comparable to colonoscopy

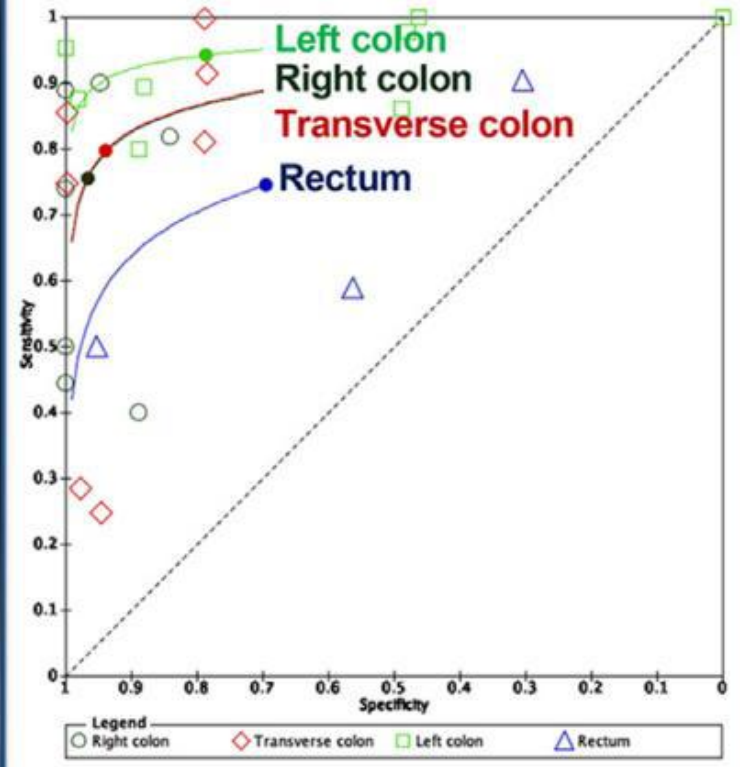
Accuracy

Systematic review and meta-analysis: Accuracy of ultrasound for the evaluation of colorectal segment in inflammatory bowel disease



Diagnostic accuracy detecting active disease in inflammatory bowel disease were high overall colon, but lower in the rectum.





Sagami S et al. CGH 2022

Transperineal US detects endoscopic activity in proctitis

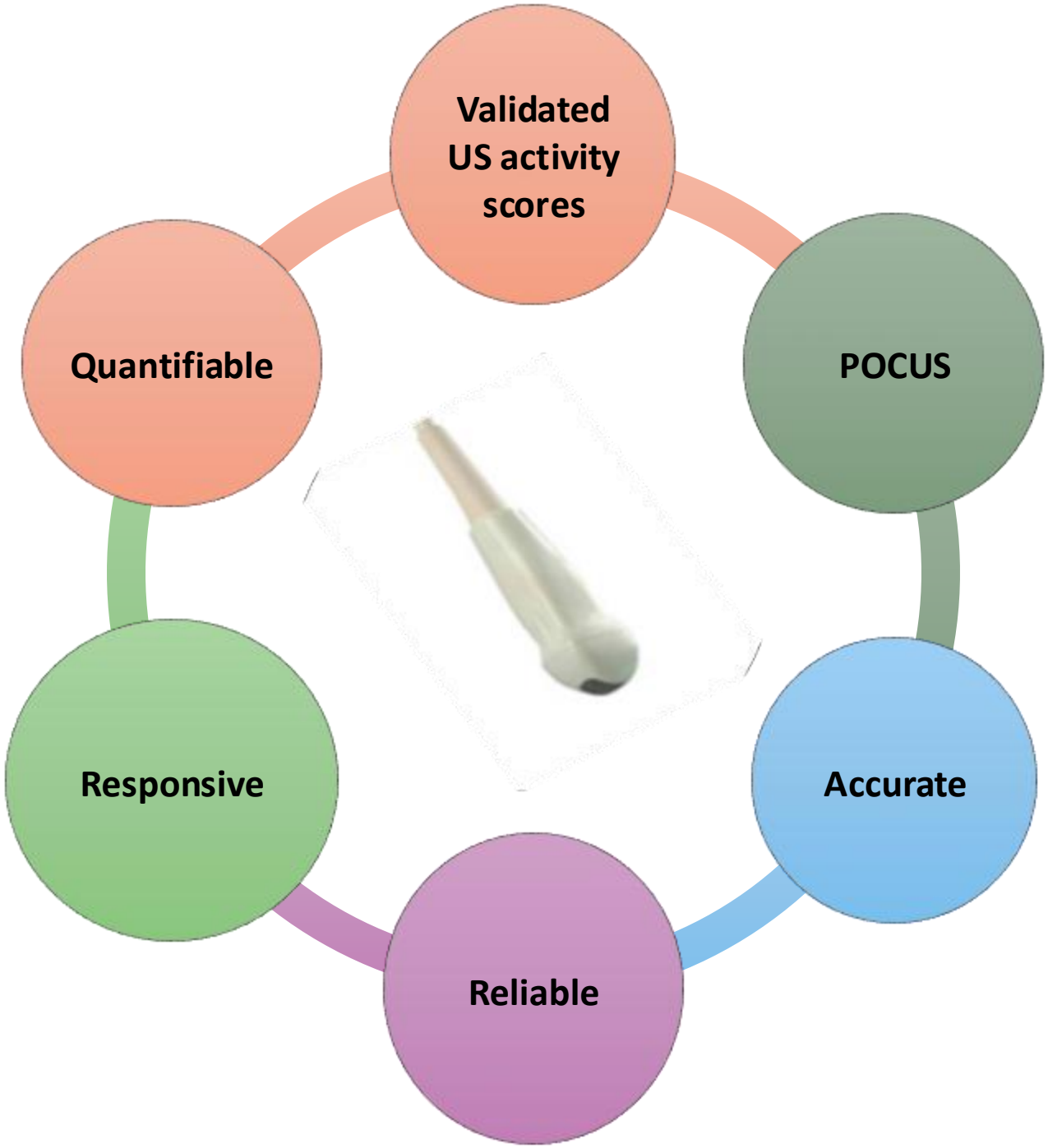
Accuracy

TABLE 3 Logistic regression analysis for predicting rectal endoscopic activity (Mayo endoscopic subscore in rectum >1; n = 53)

		Univariate			Multivariable		
	Variable	OR	95% CI	*P* value	Adjusted OR	95% CI	*P* value
TPUS	Bowel wall thickness (mm)	4.21[a]	2.00-8.84[a]	0.0002*	3.18[a]	1.43-7.06[a]	0.0003*
	Bowel wall flow[c] (LS 0-1 vs 2-3)	13.78	3.59-52.84	0.0001*	4.07	0.79-23.1	0.1044
Faecal calprotectin		1.41[b]	0.94-2.12[b]	0.0993	1.17[b]	0.91-1.52[b]	0.2208

Sagami et al., APT 2020

Reliability of IUS in UC



IUS is……..operator-dependent

Reliable

There was almost perfect reliability for BWT (ICC: 0.96, 95% CI 0.92–0.98) and for CDS (not present or present, κ = 0.83, 95% CI 074–0.92)

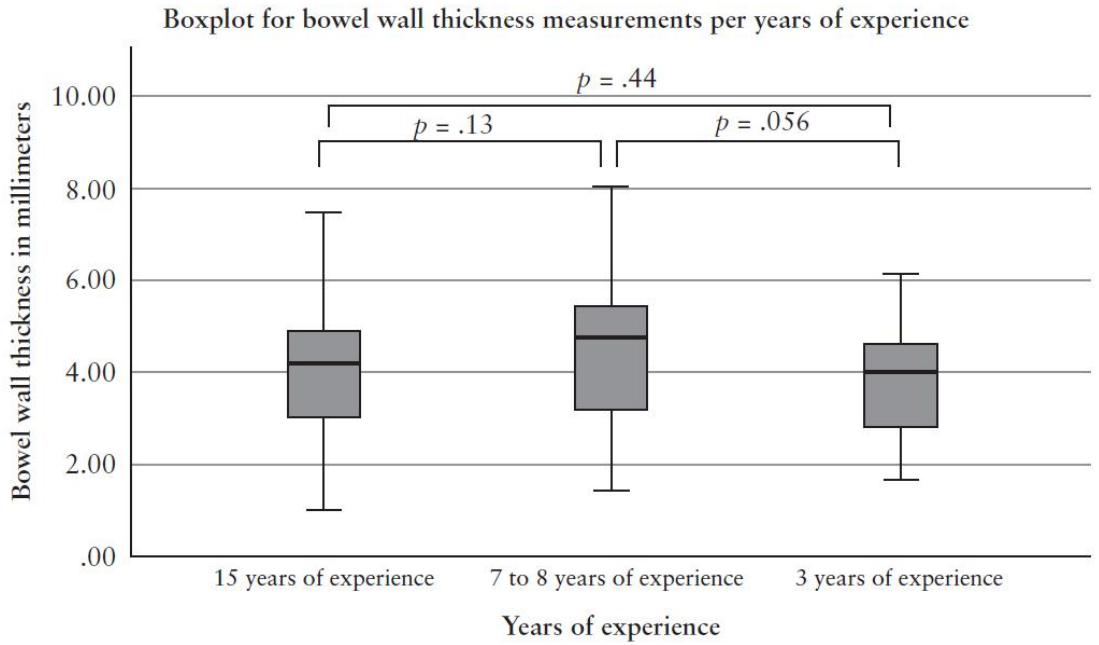


Table 3. Expert-derived blinded voting results: inter-rater reliability for IUS parameters during first and second round of voting.

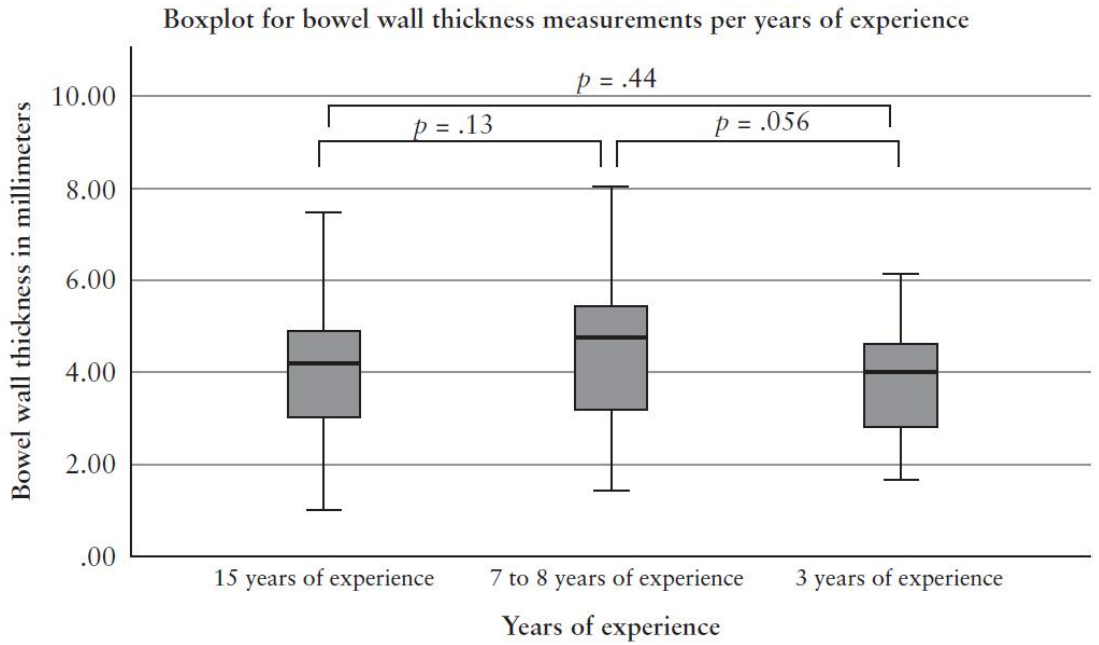
	Coefficient 1st round	Coefficient 2nd round	*p*-value
BWT	NA	0.96 [0.94–0.98]*	NA
CDS	0.62 [0.42–0.82]	0.60 [0.48–0.72]	0.776
i-fat	0.45 [0.27–0.64]	0.51 [0.34–0.67]	0.531
BWS	0.50 [0.29–0.71]	0.39 [0.24–0.53]	0.120
Confidence	0.06 [0.0–0.16]	0.08 [0.0–0.17]	0.534
Quality	0.15 [0.05–0.25]	0.14 [0.04–0.23]	0.776
Activity	0.92 [0.82–0.98]	0.96 [0.94–0.98]*	0.005
Severity	0.97 [0.91–0.99]	0.93 [0.87–0.97]*	0.980

De Voogd et al. JCC 2021; Novak et al. JCC 2021

IUS is NOT operator-dependent

Reliable

There was almost perfect reliability for BWT (ICC: 0.96, 95% CI 0.92–0.98) and for CDS (not present or present, κ = 0.83, 95% CI 074–0.92)



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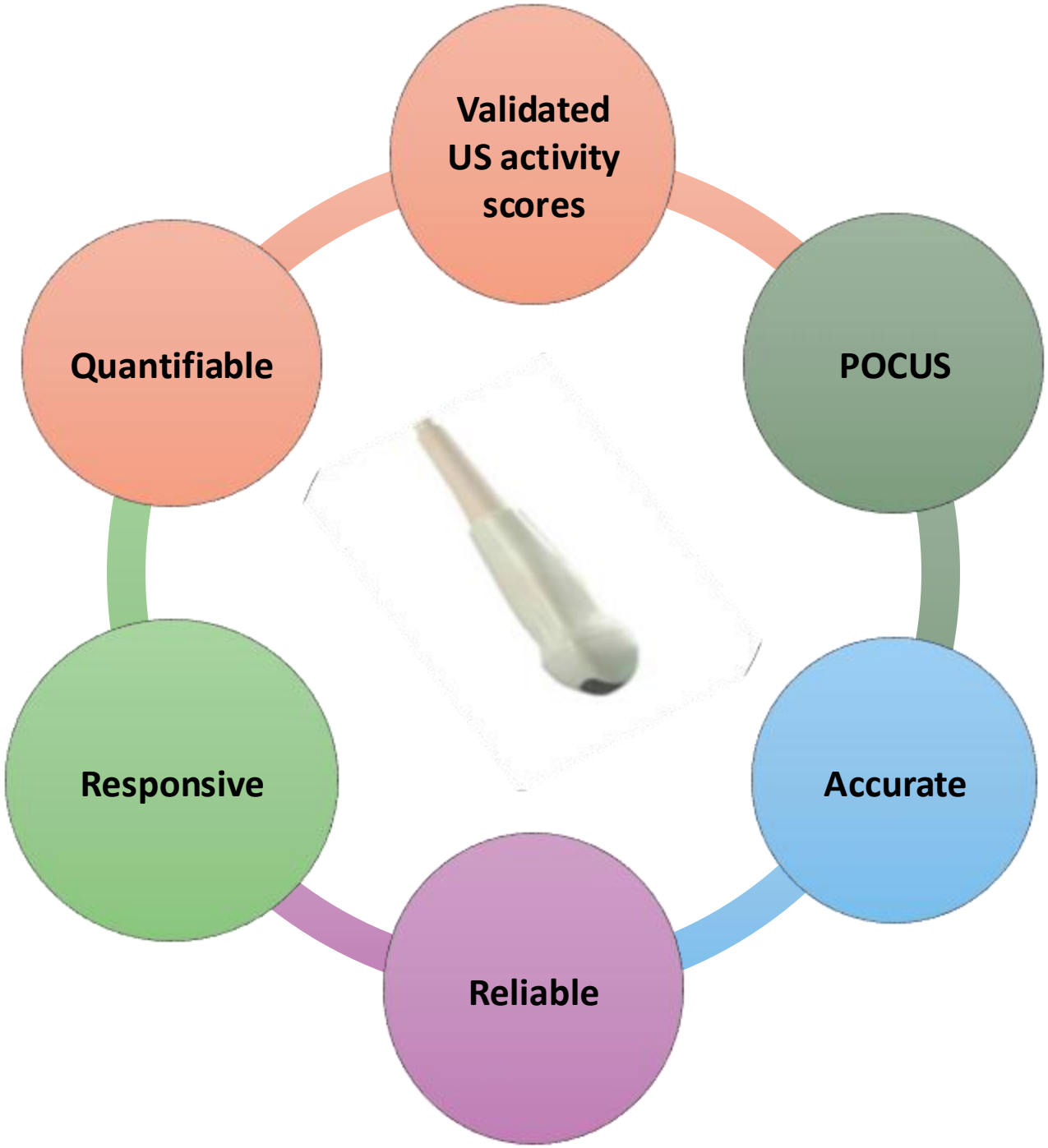
De Voogd et al. JCC 2021; Novak et al. JCC 2021

Responsiveness of IUS in UC

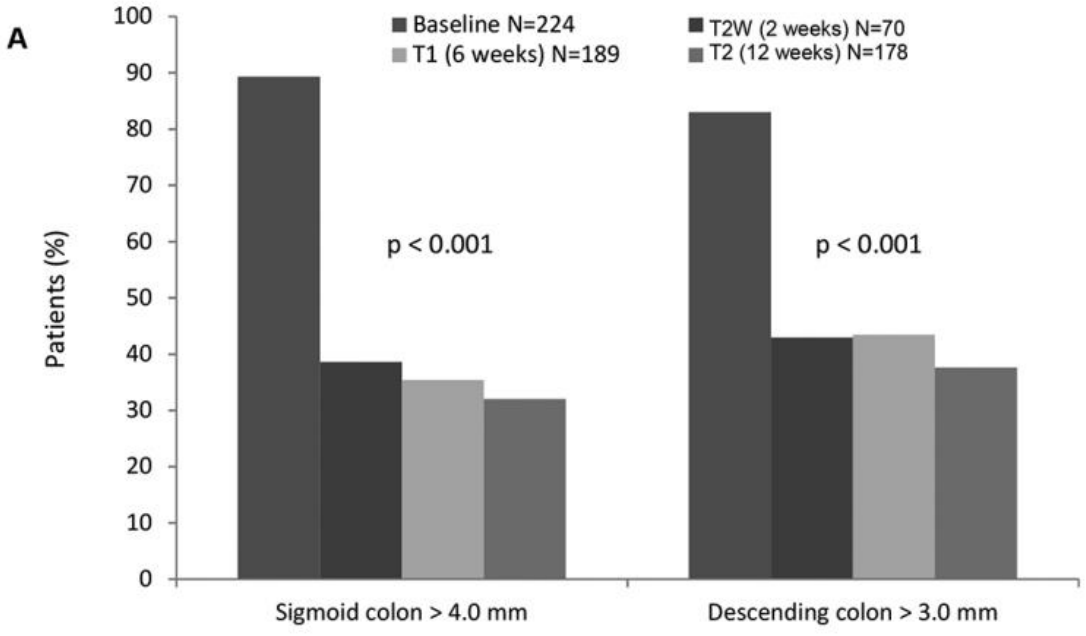


Ultrasound parameters are responsive to treatment

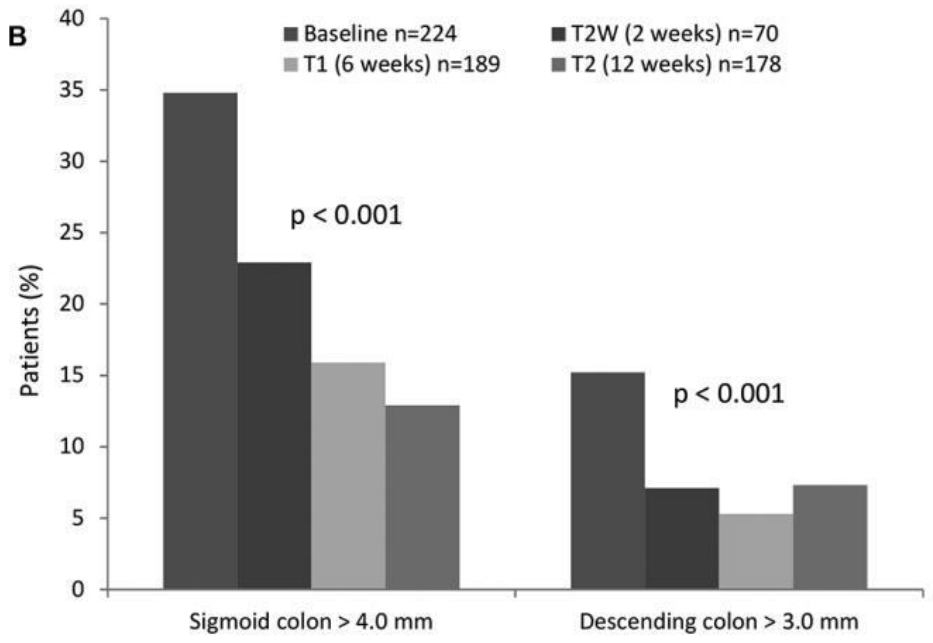
Responsive

Ulcerative colitis

BWT

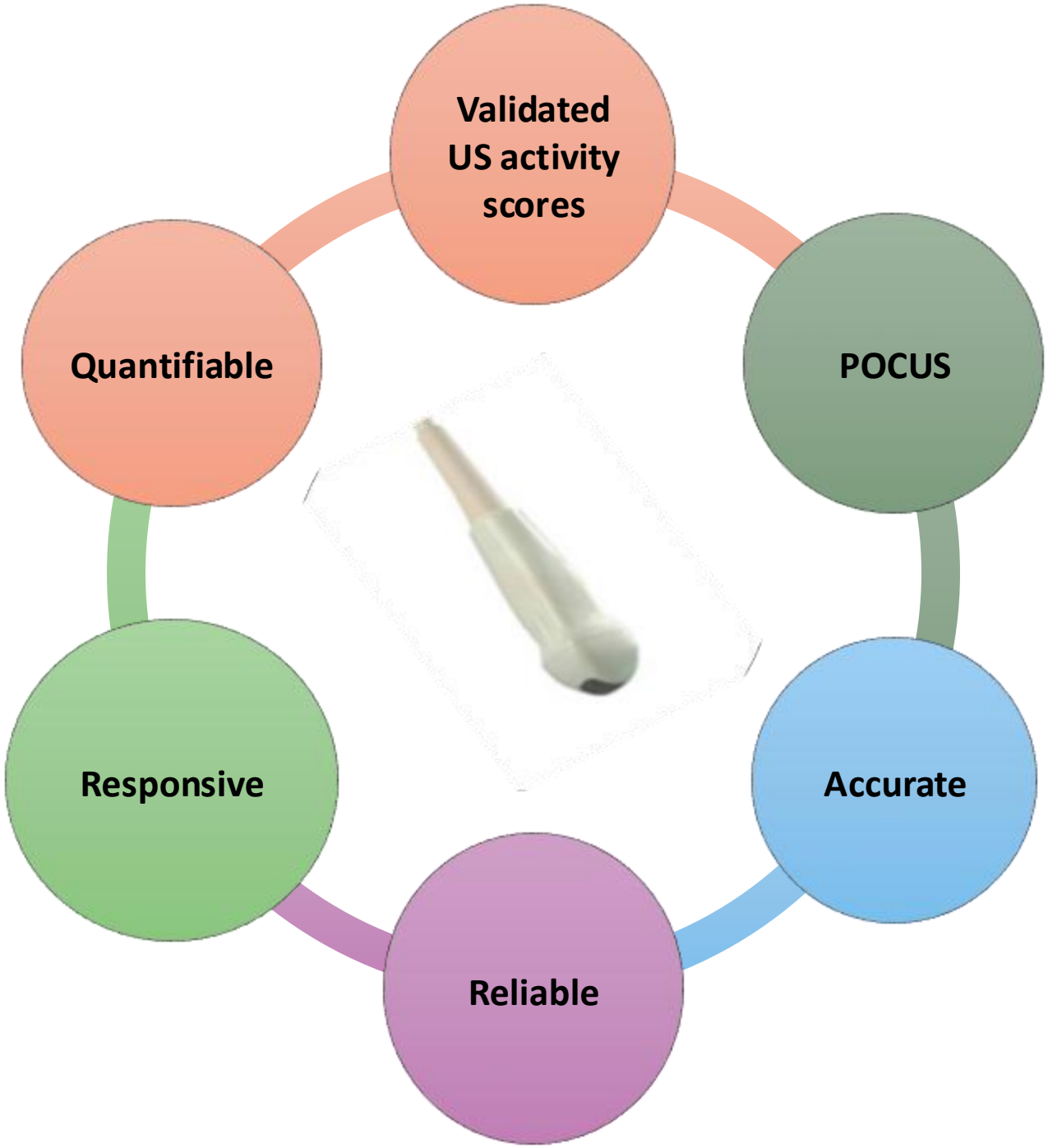


CDS



Maaser et al. GUT 2020

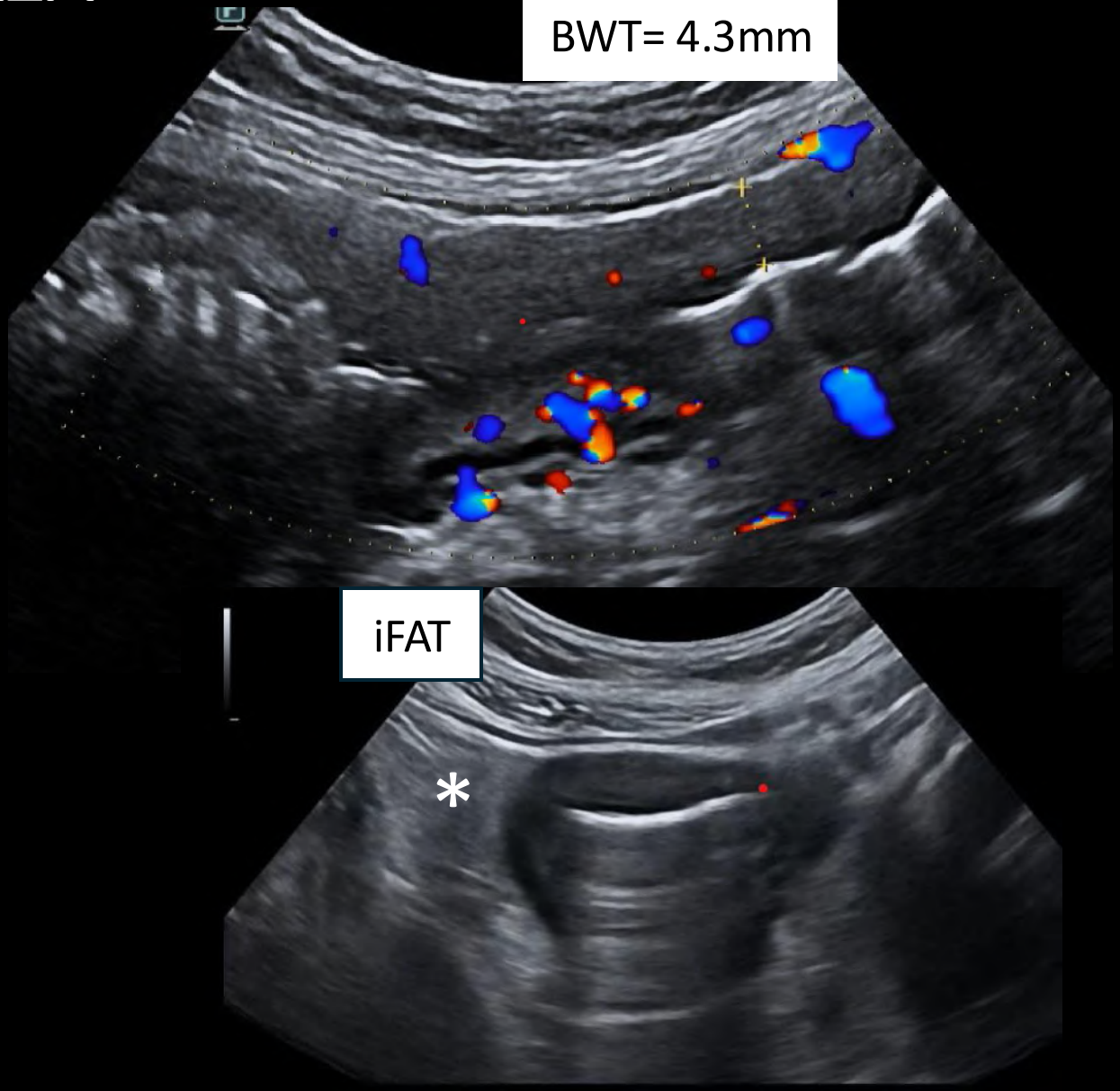
IUS findings are quantifiable

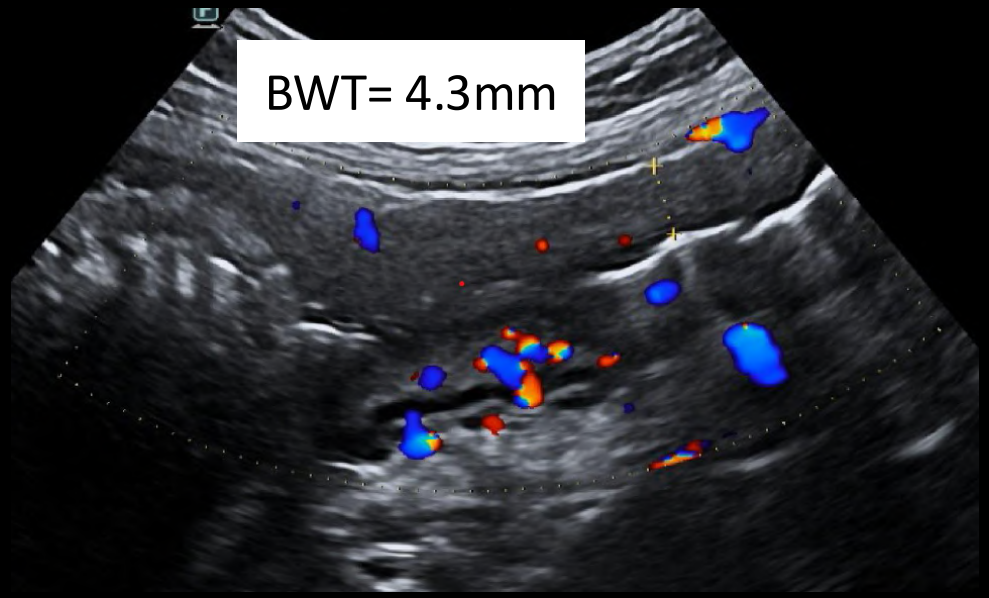


Ultrasound scoring systems in UC

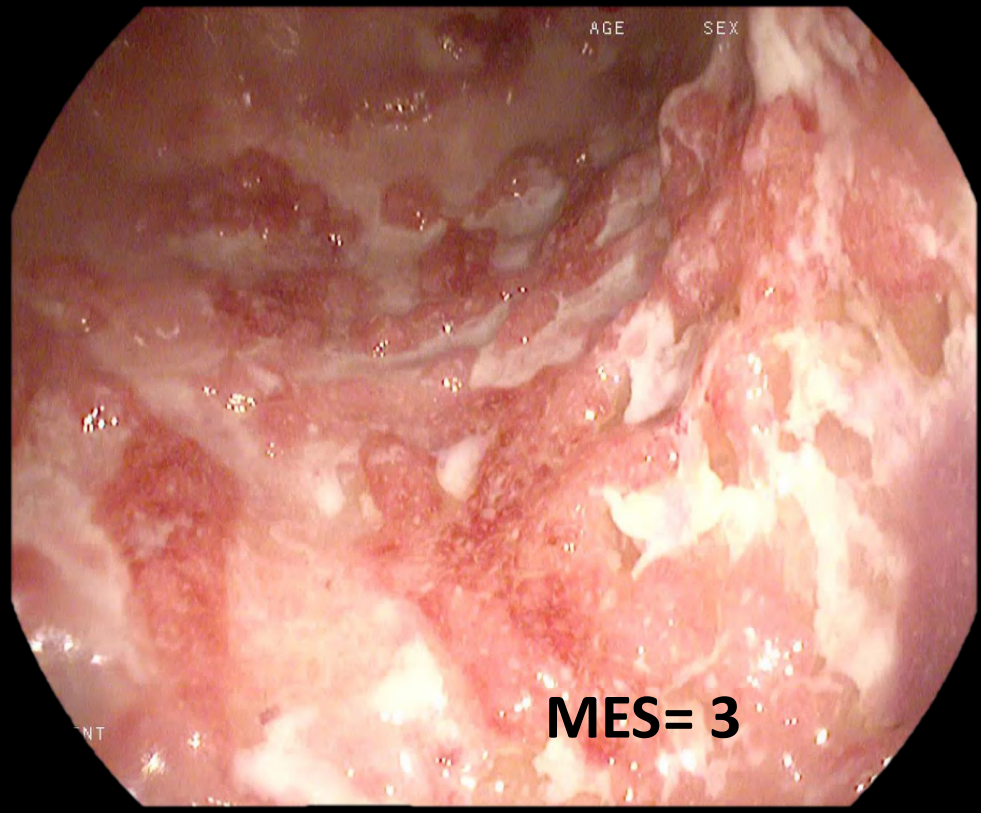
Scoring index for UC	Formula	Reference standard	Cohort N.	Validation	Sensitivity to change	Predictive value
MUC (Allocca, JCC 2018)	1.4 × BWT + 2 × CDS (1 if present, 0 if absent) **(Derived through logistic regression)**	**Colonoscopy** (MES > 1). **Cut-off values: > 6.2 for MES > 1; ≤ 4.3 for MES= 0**	53	**YES**, external cohorts	**YES**	**YES**
UC- IUS index (Bots, JCC 2021)	BWT + CDS + Haustra + iFAT	**Colonoscopy** (MES, UCEIS)	60	**YES**, external cohort	**NOT assessed**	**NOT assessed**
IBUS-SAS (Novak, JCC 2021; Innocenti, CGH 2024)	4 x BWT (mm) + 15 x i-fat + 7 x CDS + 4 x BWS **(Derived through logistic regression)**	Visual analogue scale	50	**YES**, external cohort	**NOT assessed**	**NOT assessed**

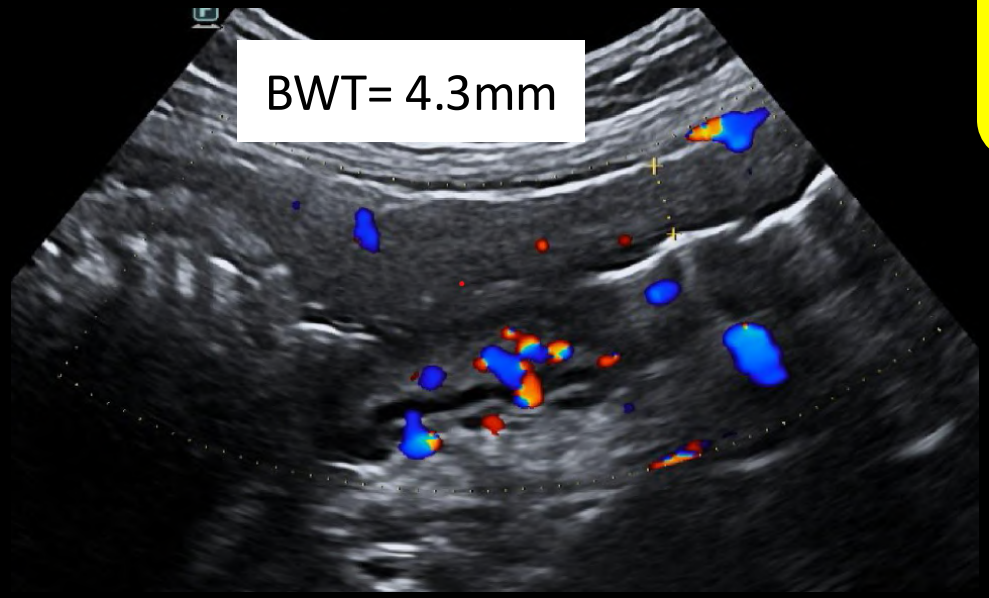
Michela, 40 years old, left side ulcerative colitis, failure to combo therapy with IFX and AZA





What score?

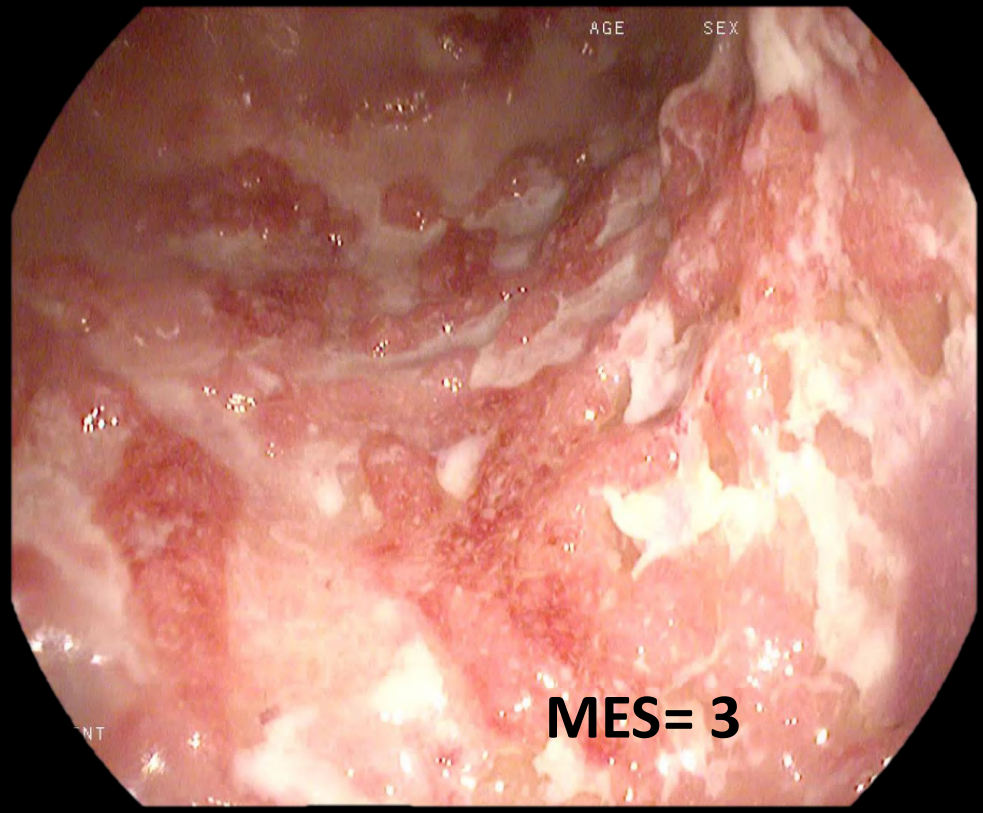


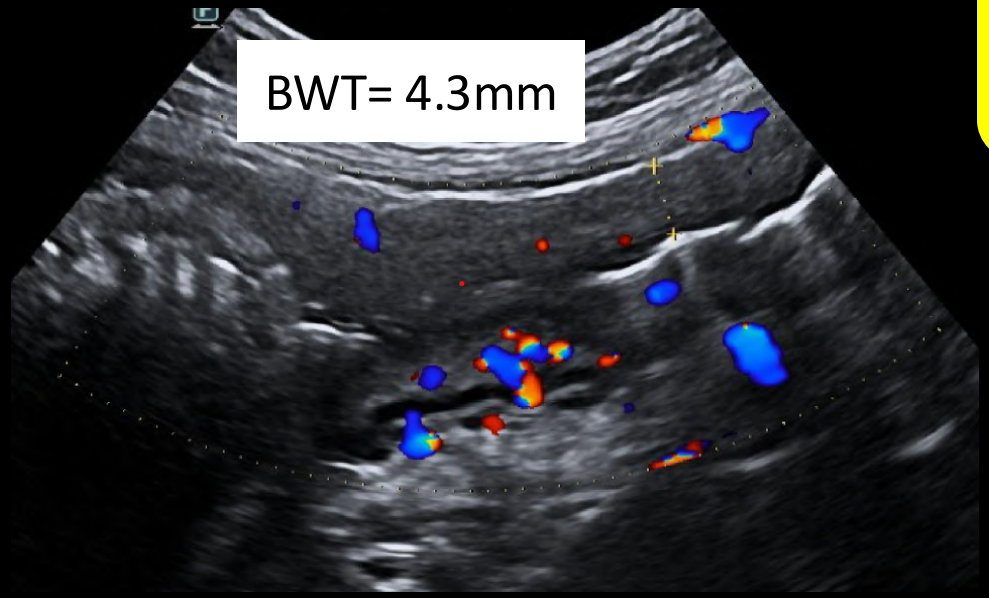


MUC= 1.4xBWT mm + 2xCDS=
(1.4x4.3) + 2=

What score?

CDS= 0 absent; **1 present**



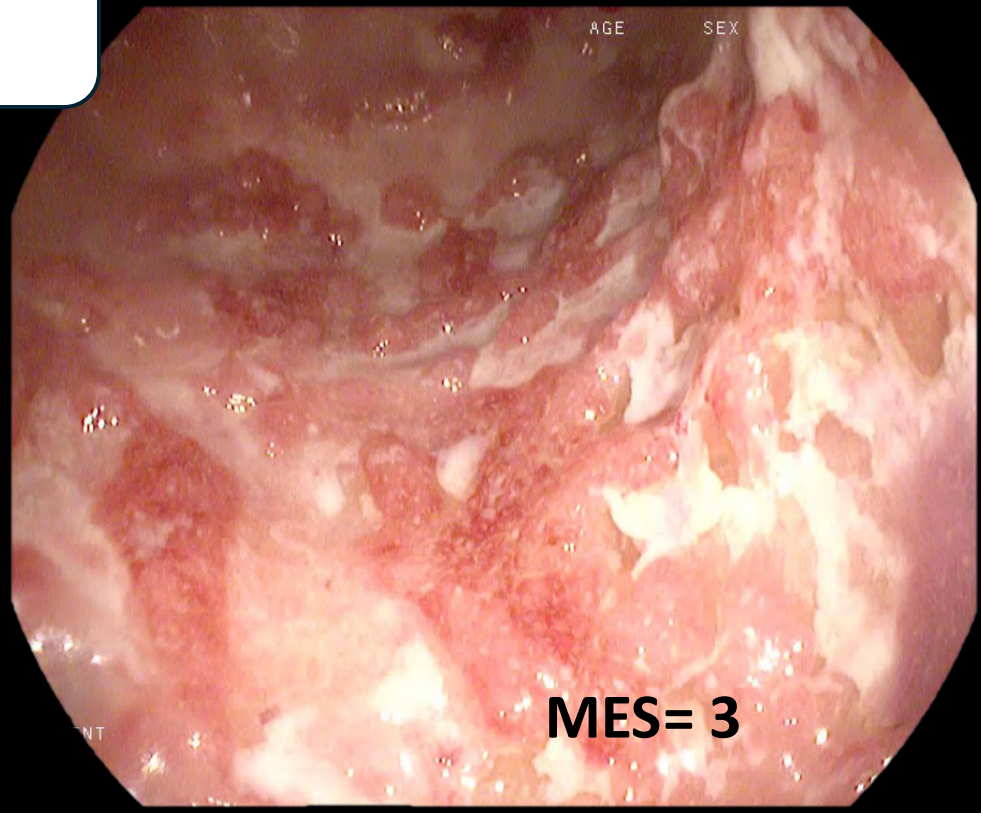


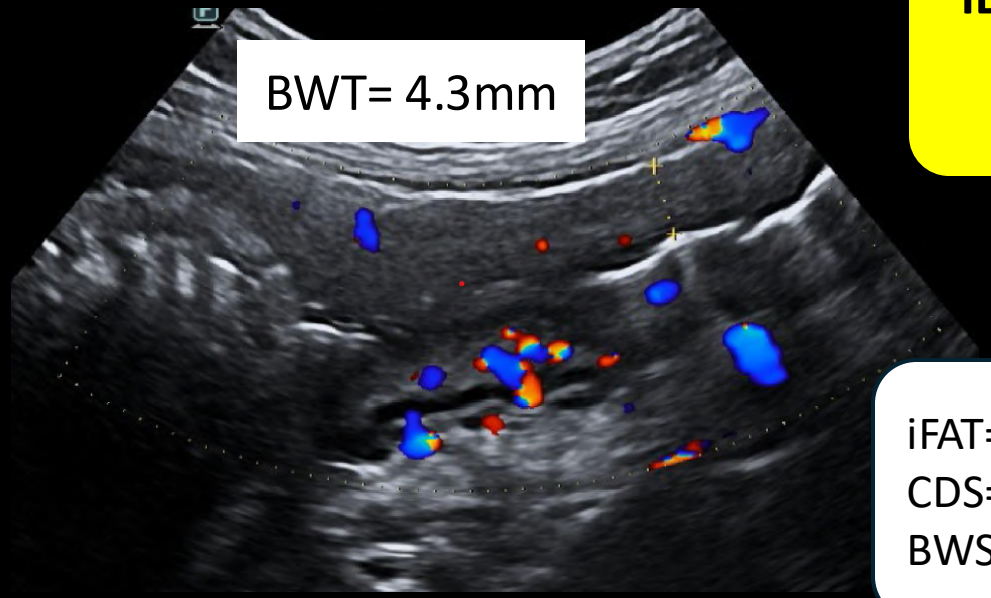
MUC= 1.4xBWT mm + 2xCDS=
(1.4x4.3) + 2= **8**

MUC >6.2 for MES >1

What score?

CDS= 0 absent; 1 present

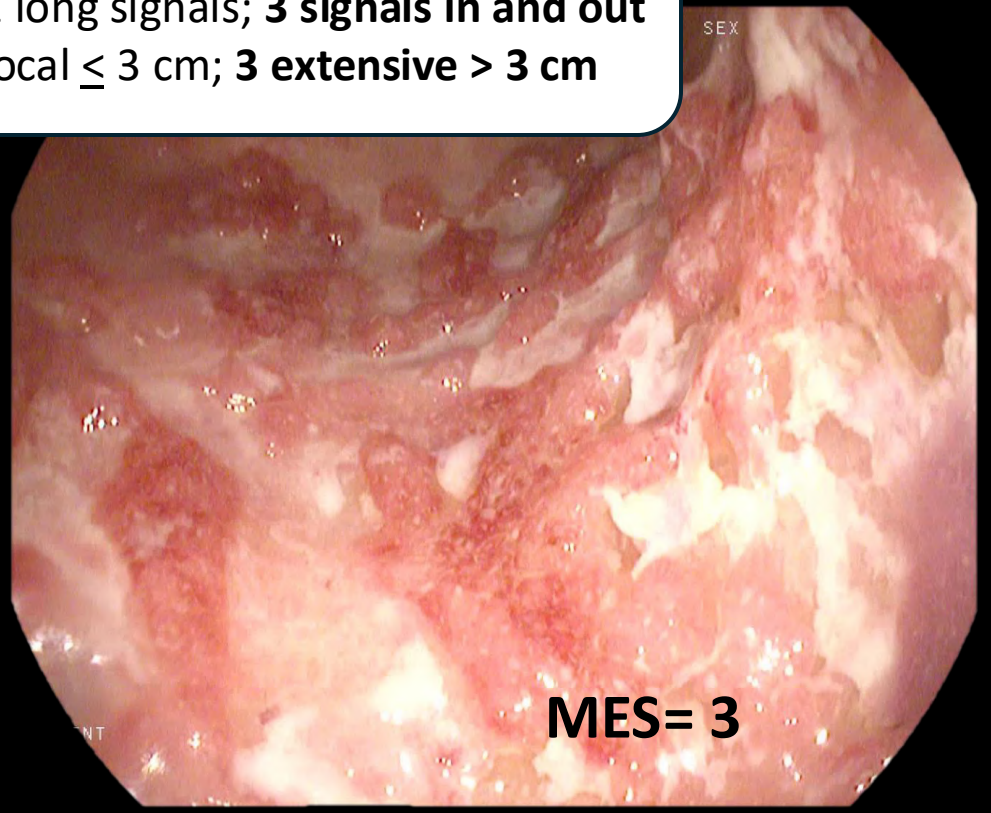


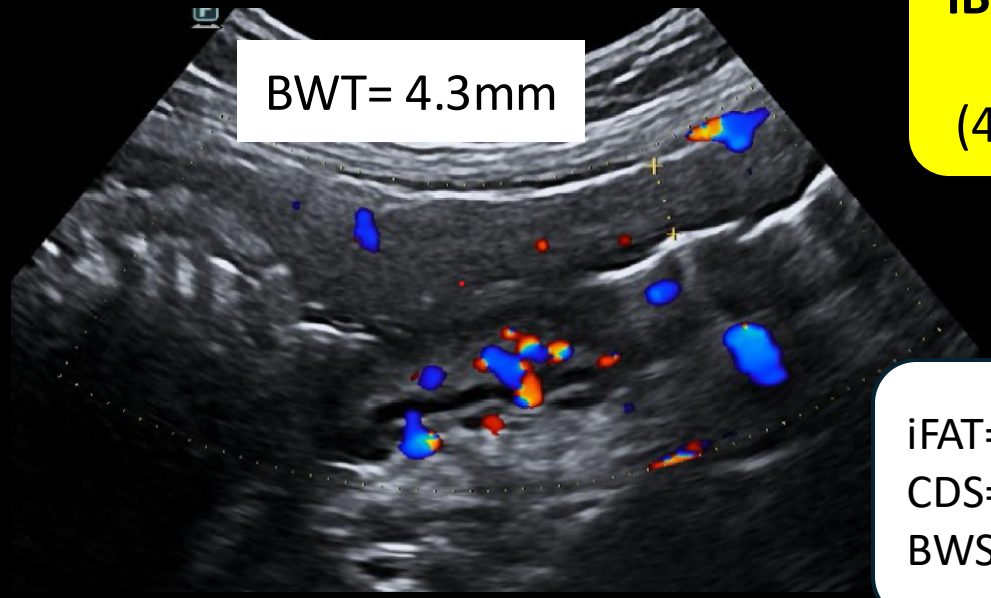


IBUS-SAS= (4xBWT mm) + (15xiFAT) + (7xCDS) + (4xBWS)=
(4x4.3) + (15x2) + (7x3) + (4x3)=

What score?

iFAT= 0 absent; 1 uncertain; **2 present**
CDS= 0 absent; 1 short signals; 2 long signals; **3 signals in and out**
BWS= 0 normal; 1 uncertain; 2 focal ≤ 3 cm; **3 extensive > 3 cm**

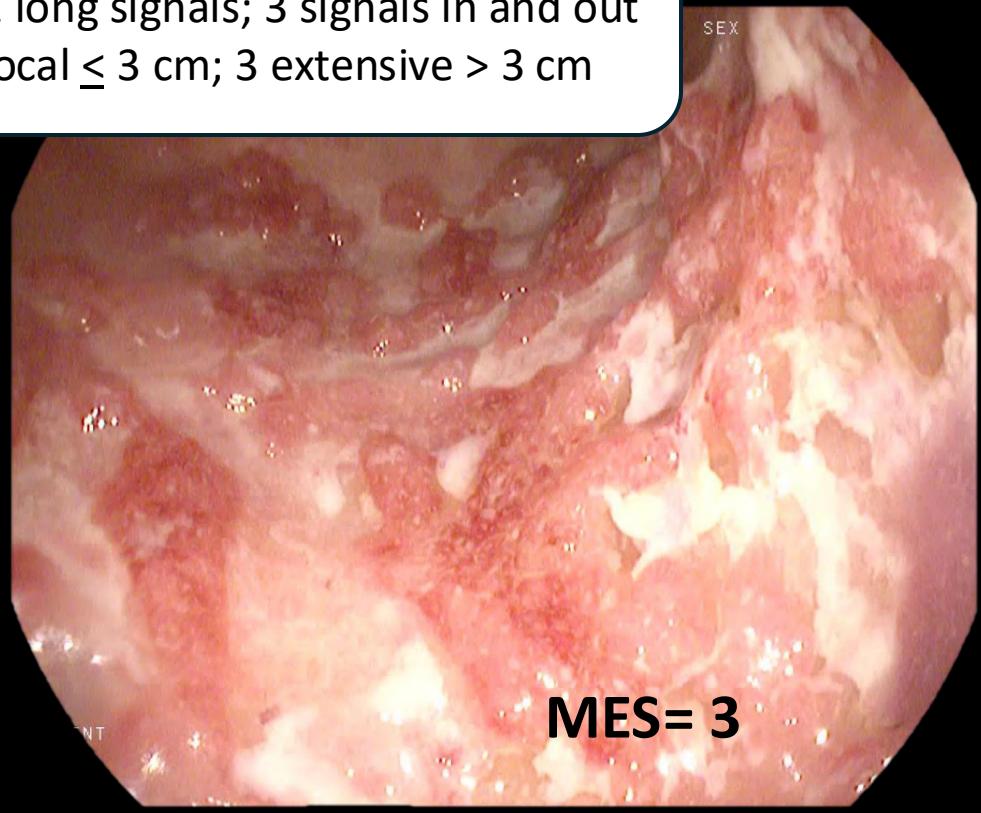




IBUS-SAS= (4xBWT mm) + (15xiFAT) + (7xCDS) + (4xBWS)=
(4x4.3) + (15x2) + (7x3) + (4x3)= **80.2**

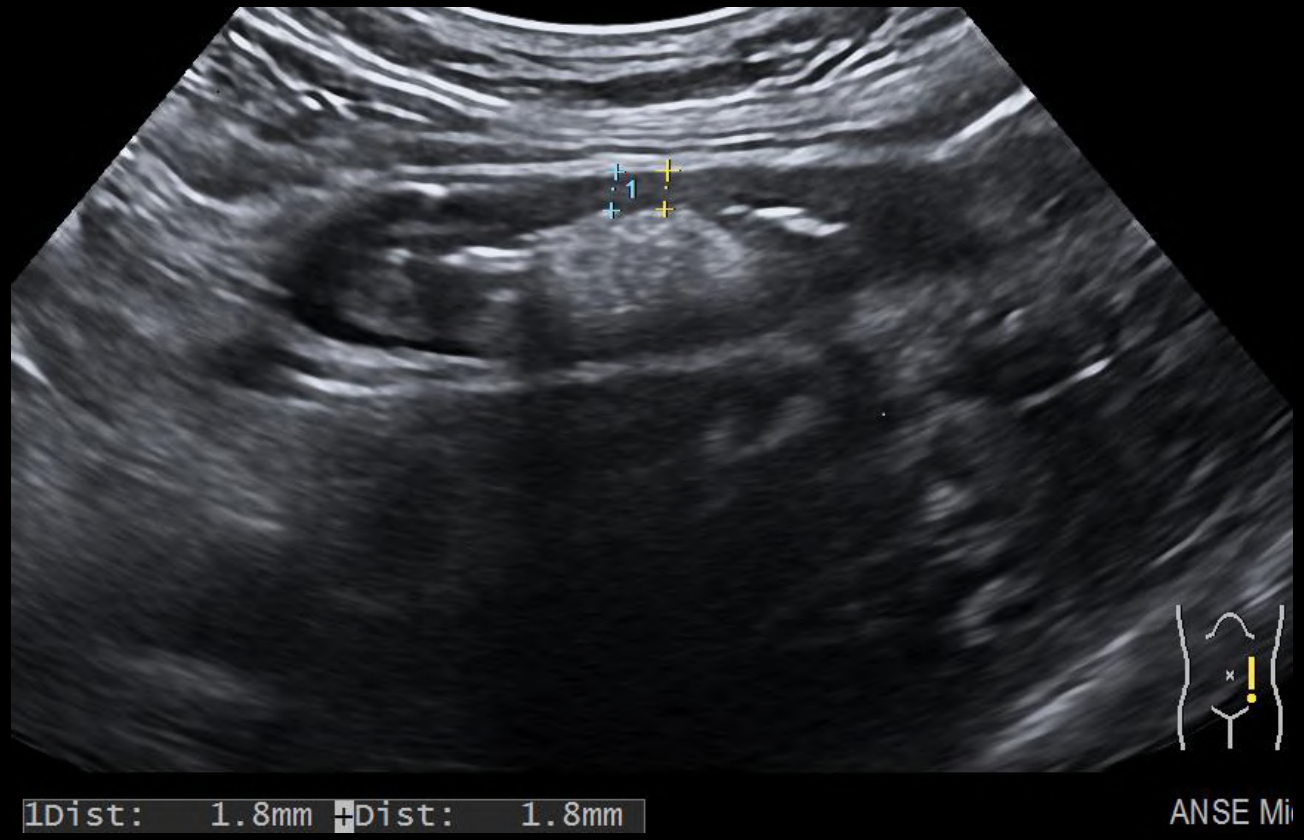
What score?

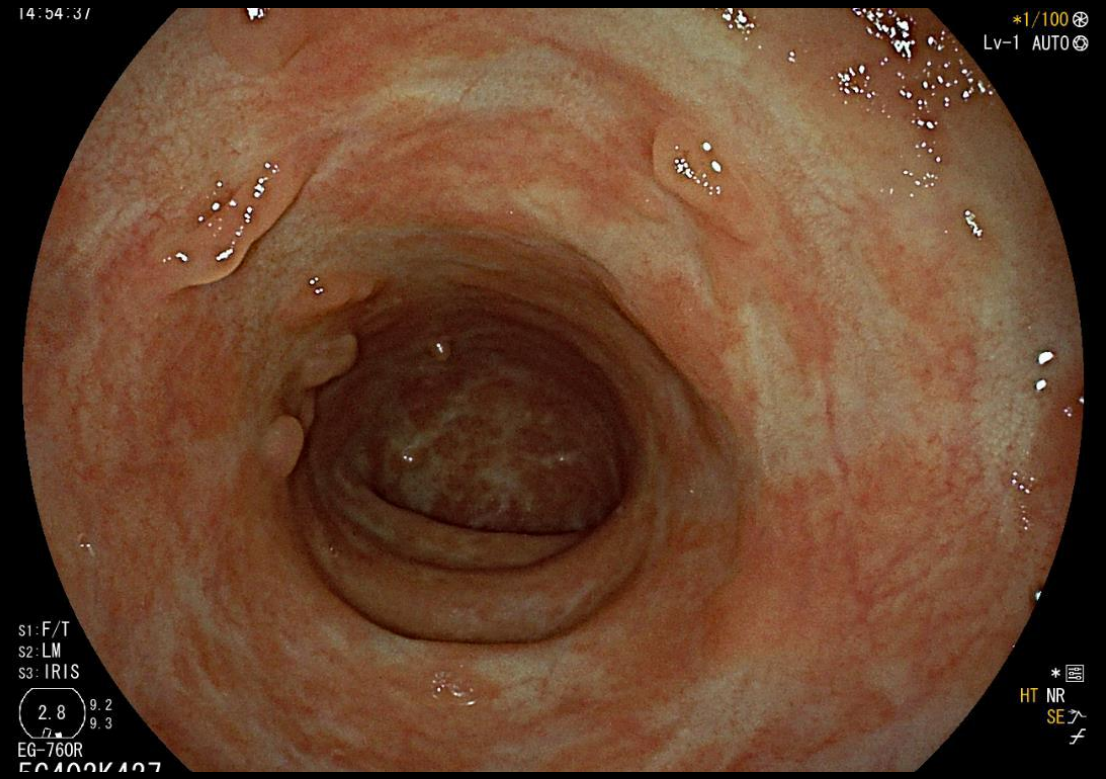
iFAT= 0 absent; 1 uncertain; 2 present
CDS= 0 absent; 1 short signals; 2 long signals; 3 signals in and out
BWS= 0 normal; 1 uncertain; 2 focal ≤ 3 cm; 3 extensive > 3 cm



6 Months after starting ustekinumab therapy

What score?



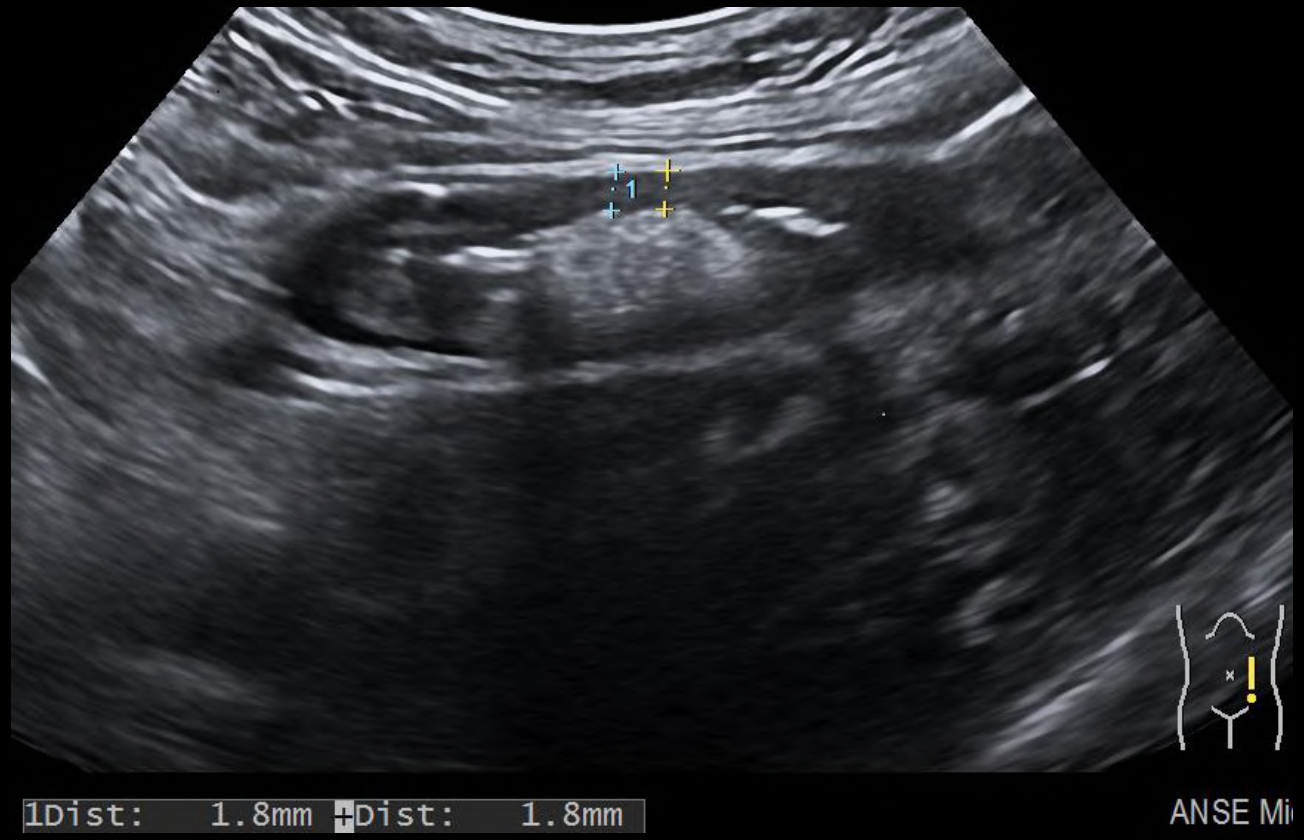


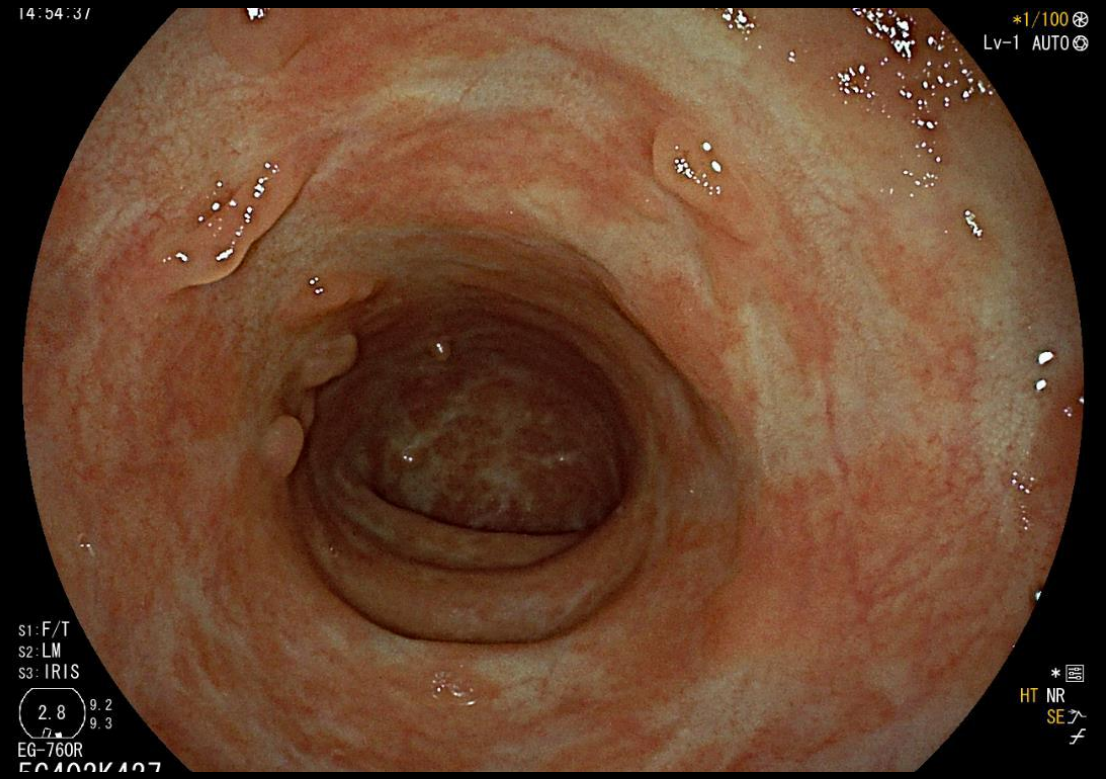
MES= 0

6 Months after starting ustekinumab therapy

MUC= 1.4xBWT mm + 2xCDS=
(1.4x1.8) + 2 x 0= **2.52**
≤6.2 for MES ≤1;
≤4.3 for MES= 0

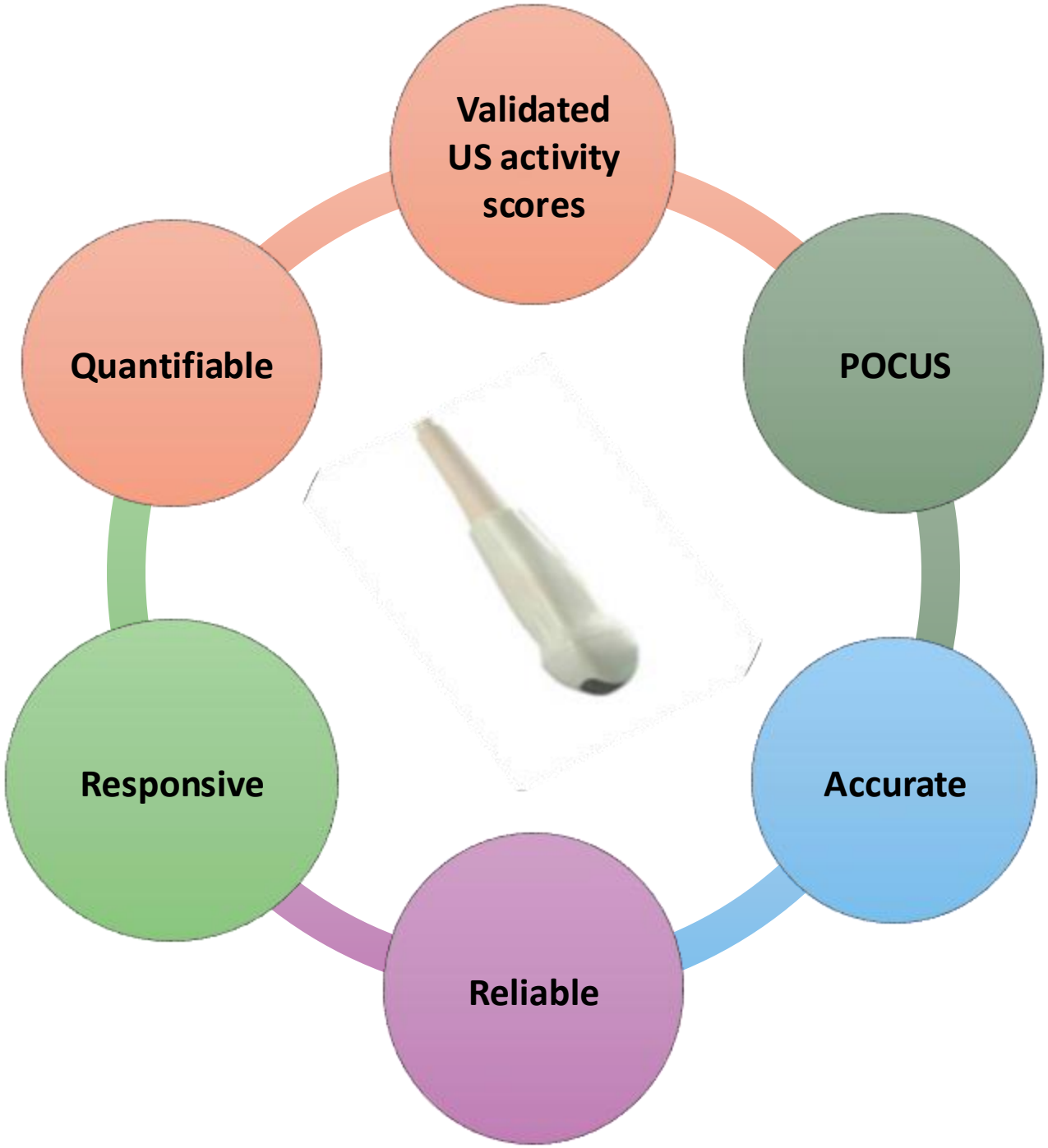
What score?





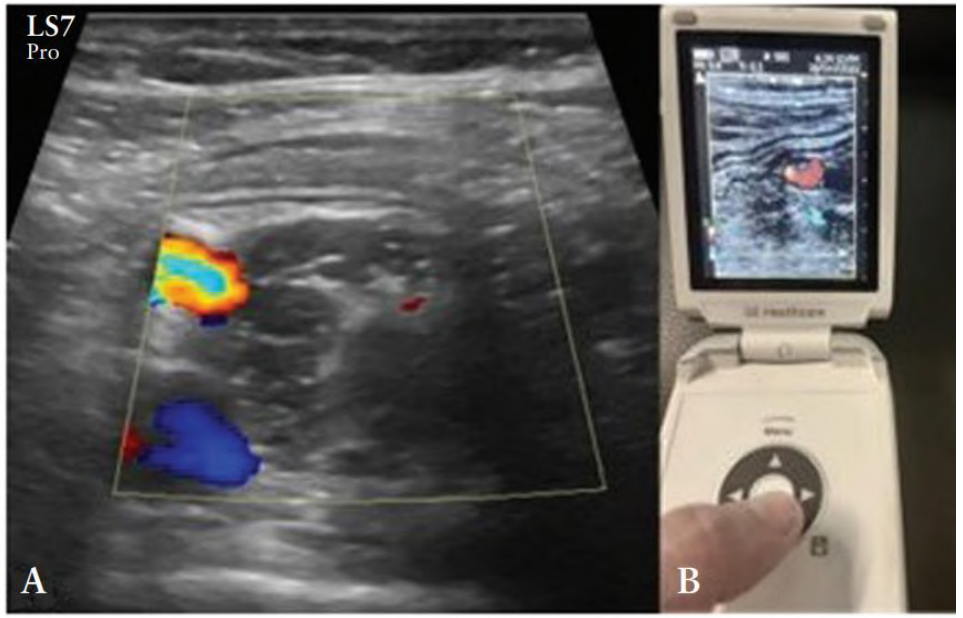
MES= 0

POCUS


Validated US activity scores
POCUS
Accurate
Reliable
Responsive
Quantifiable

Intestinal ultrasound is changing the current approach to managing patients with IBD

POCUS



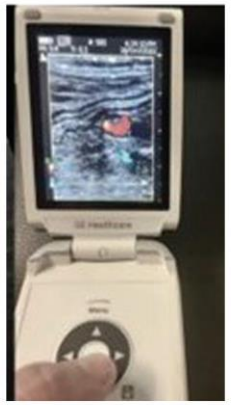
The diagnosis in your pocket

Journal of Crohn's and Colitis, 2023, **17**, 1089–1096
https://doi.org/10.1093/ecco-jcc/jjad024
Advance access publication 16 February 2023
Original Article

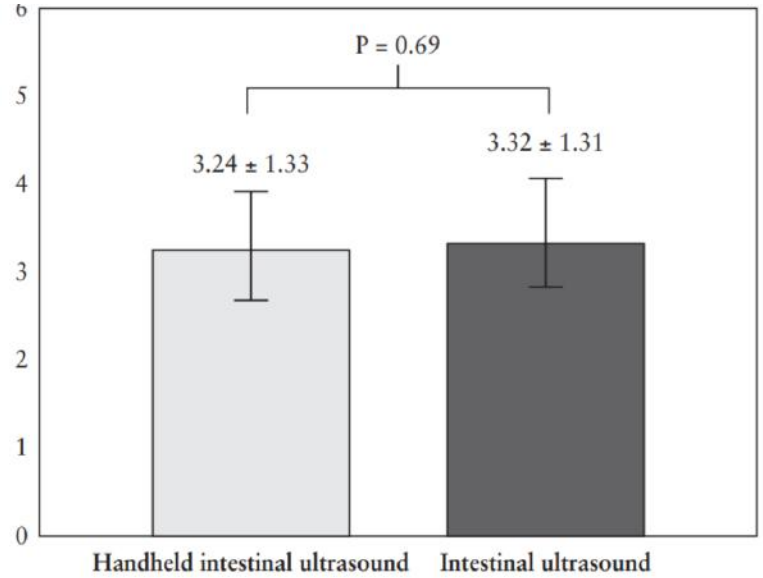
Hocus Pocus: the Role of Hand-held Ultrasonography in Predicting Disease Extension and Endoscopic Activity in Ulcerative Colitis

Antonio Rispo,[a] Giulio Calabrese,[a] Anna Testa,[a] Nicola Imperatore,[b] Marta Patturelli,[a] Mariangela Allocca,[c] Alessia Dalila Guarino,[a] Nicola Mattia Cantisani,[a] Benedetta Toro,[a] Fabiana Castiglione[a]

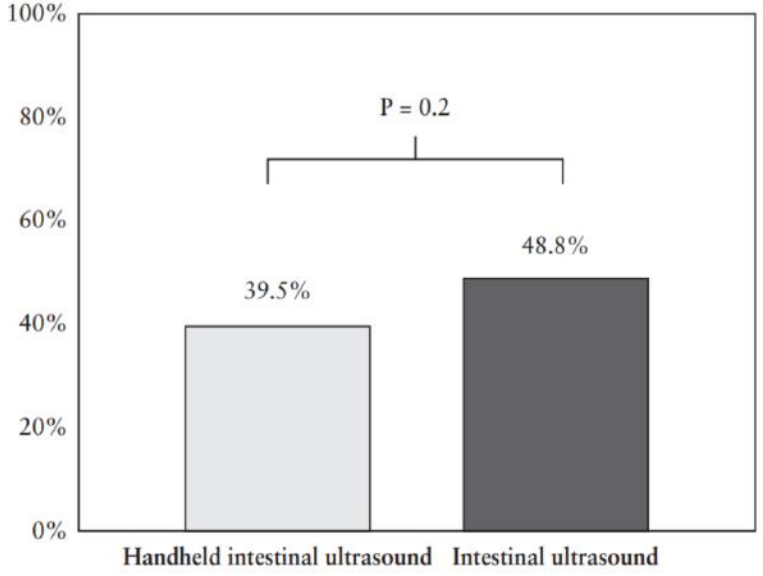
Hand-held IUS and IUS are comparable for the assessment of ultrasound parameters



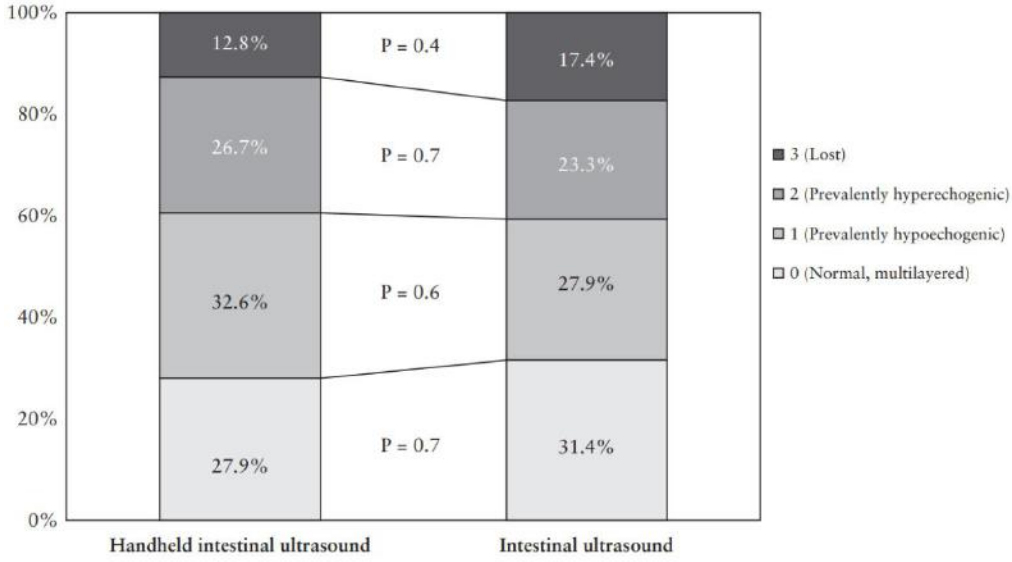
Bowel wall thickness



Color Doppler signals

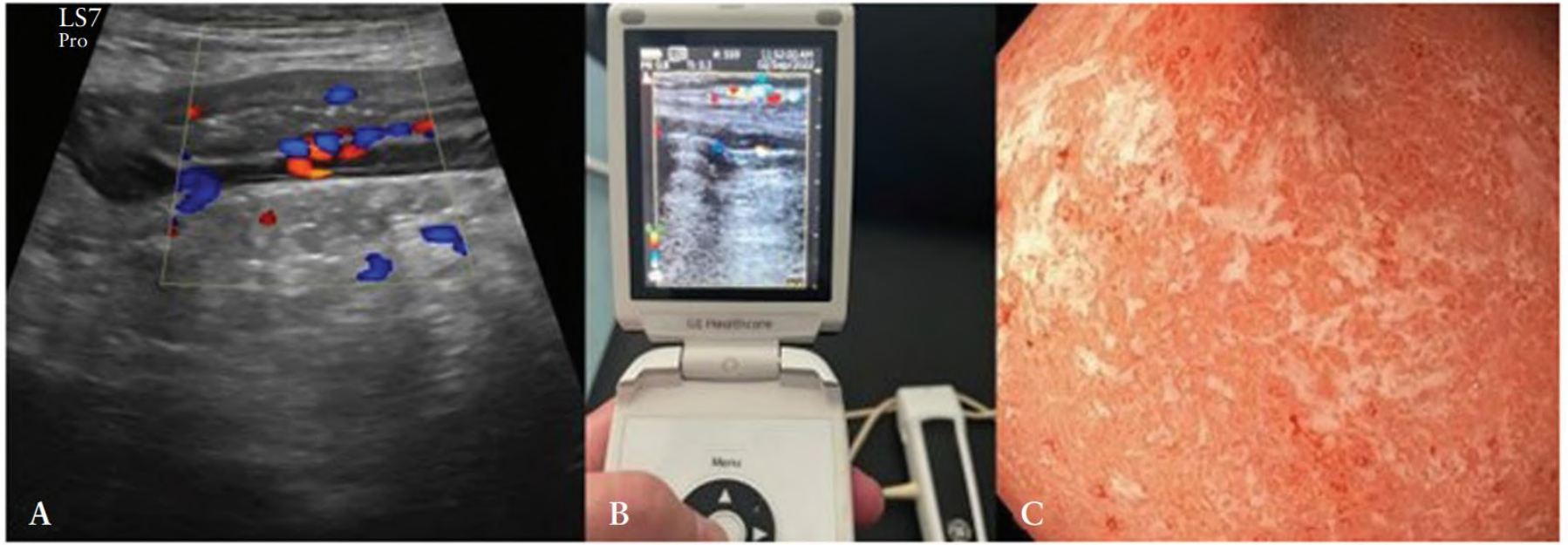


Bowel wall stratification



Rispo et al. JCC 2023

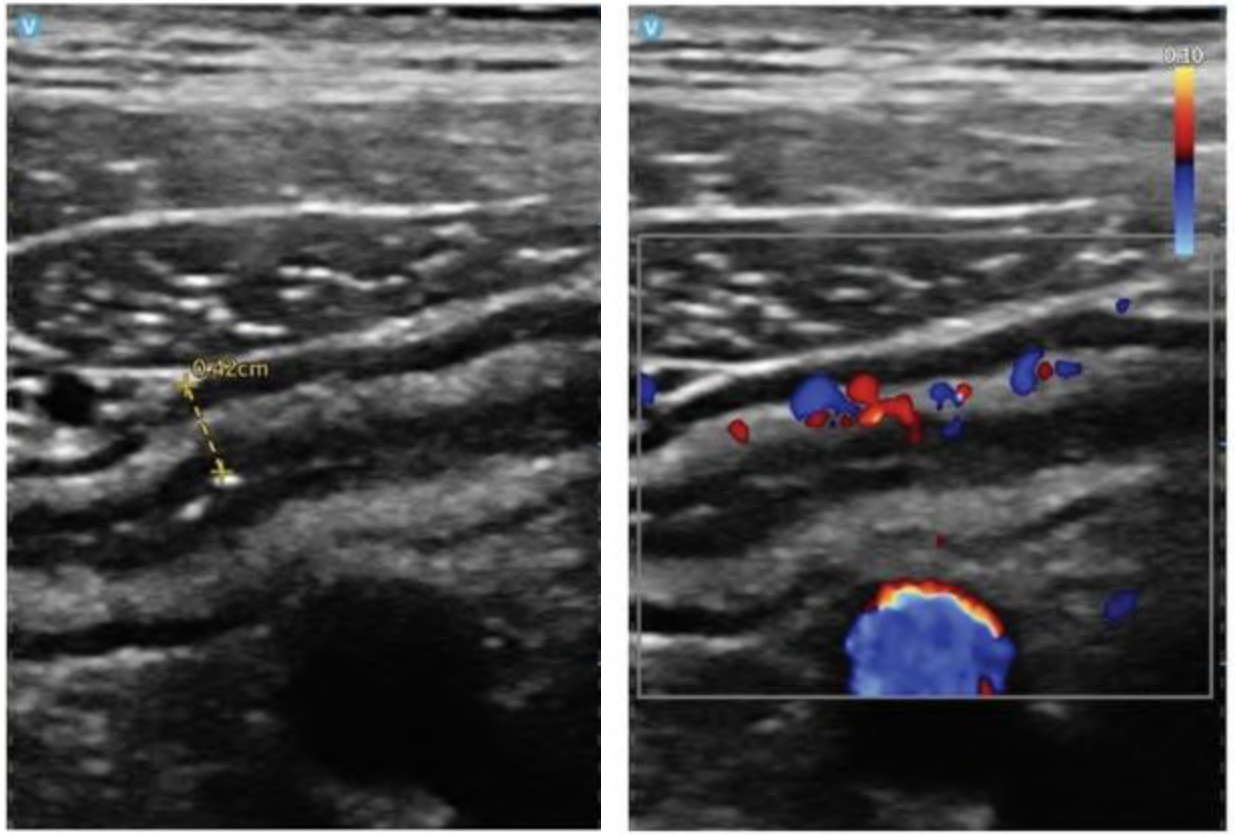
No significant differences in diagnostic accuracy between the two procedures

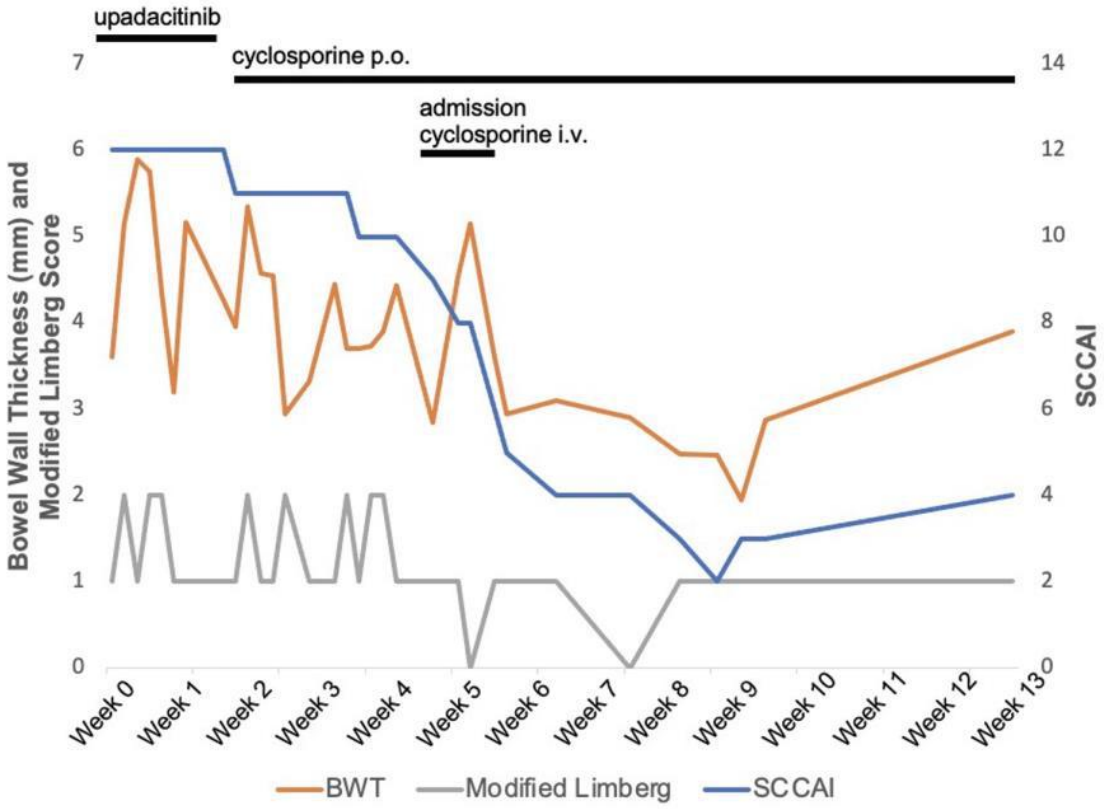


	Cut-off	Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy
IUS-MUC	>6.2	0.83 [95% CI 0.67–0.93]	0.90 [95% CI 0.78–0.97]	0.86 [95% CI 0.72–0.93]	0.88 [95% CI 0.78–0.94]	0.87 [95% CI 0.78–0.93]
HHIUS-MUC	>6.2	0.80 [95% CI 0.64–0.92]	0.88 [95% CI 0.76–0.95]	0.83 [95% CI 0.69–0.91]	0.86 [95% CI 0.76–0.92]	0.84 [95% CI 0.75–0.92]

Rispo et al. JCC 2023

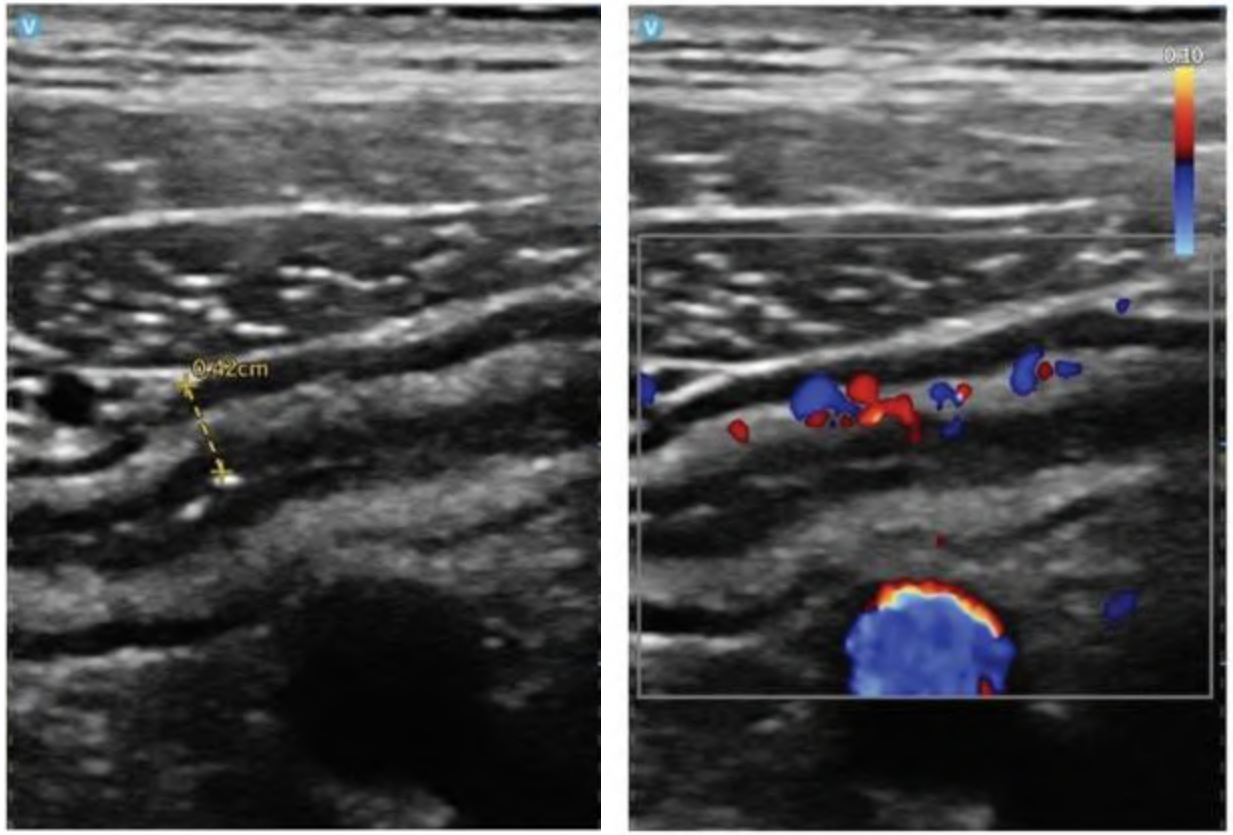
Hand-held US by a patient with UC for at-home monitoring

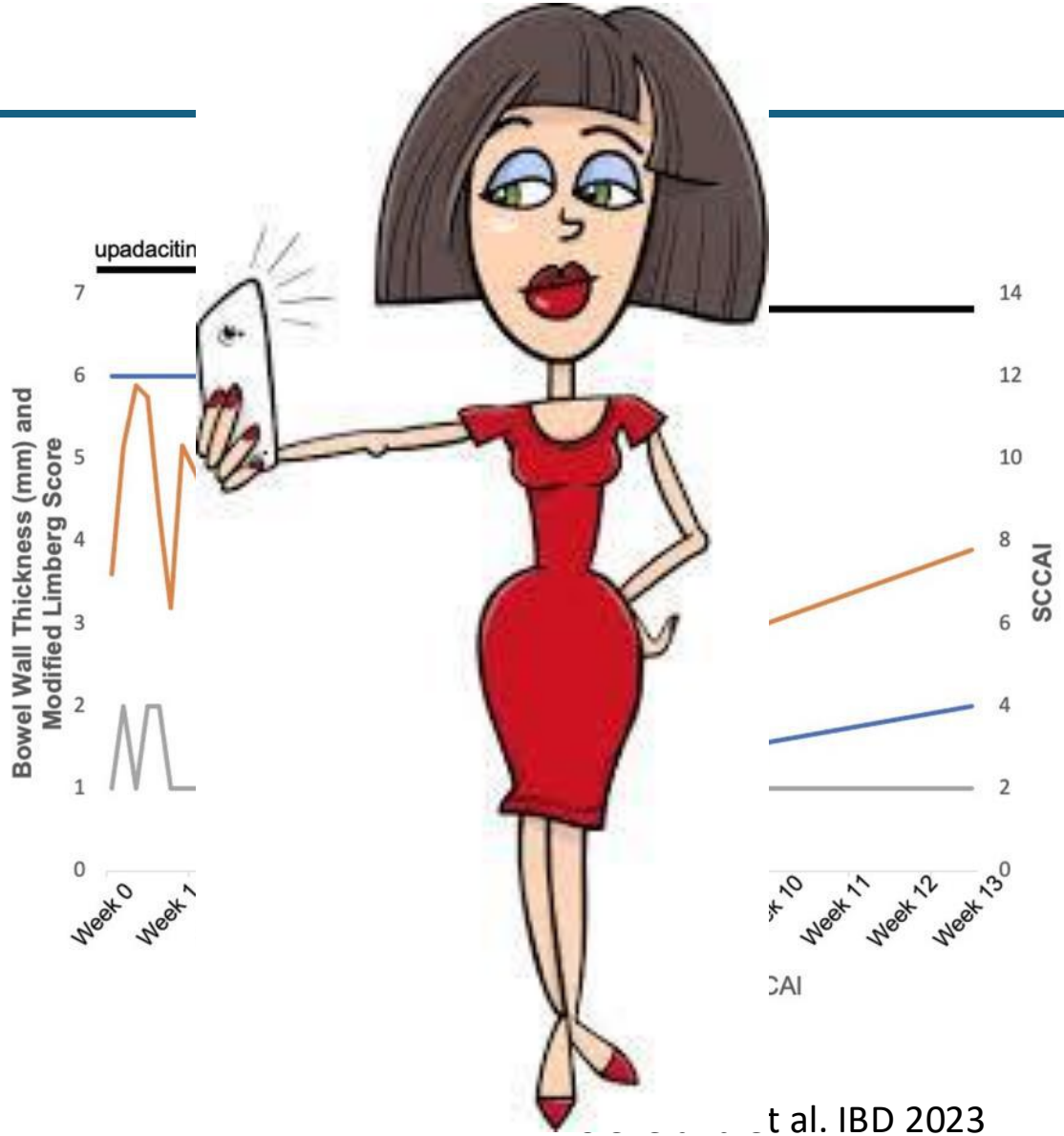




Cleveland et al. IBD 2023

Hand-held US by a patient with UC for at-home monitoring

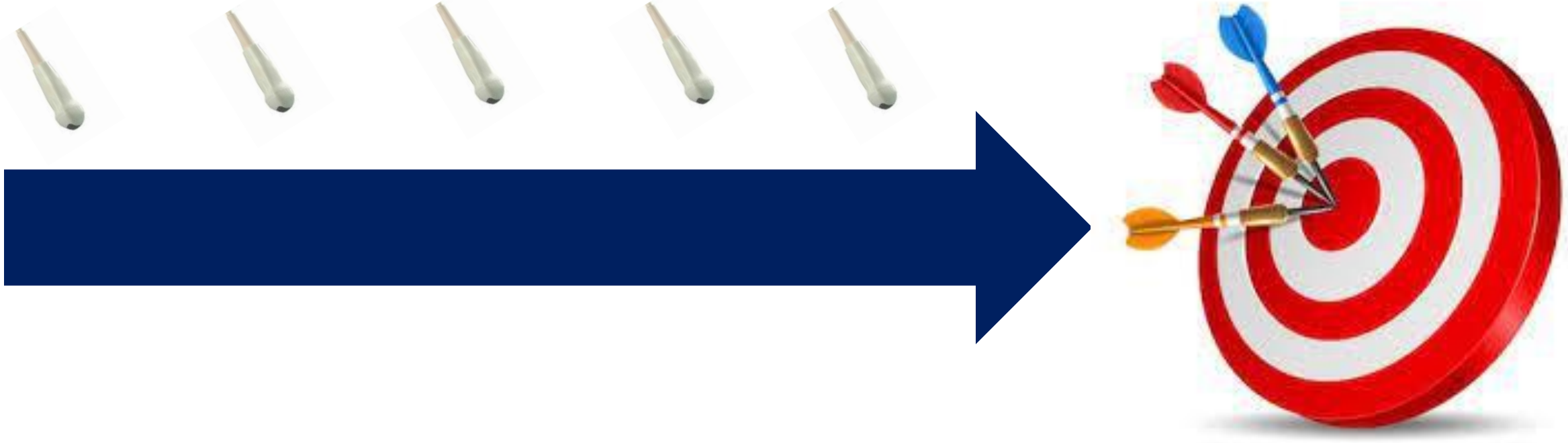




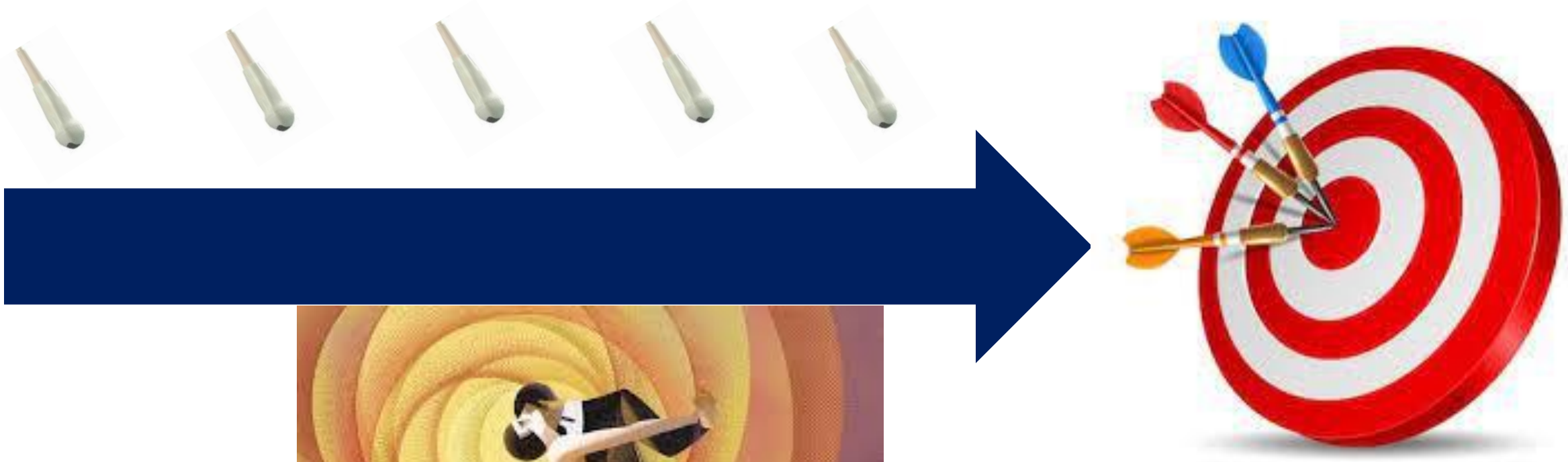
t al. IBD 2023

IUS is a perfect tool for monitoring patients and treatment response

From tight control to treatment target



From tight control to treatment target



Cohort of 49 patients with **ulcerative colitis** starting biologics

Allocca et al. JCC 2023

MUC ≤ 6.2 at week 12 was the only independent predictor for MES ≤ 1 and MES = 0 at reassessment

MUC= 1.4xBWT + 2xCDS

Supplementary Table 1. Influence of non-invasive tools at week 12 on the risk of endoscopic remission (MES = 0) at reassessment

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***
Parameters				
MUC ≤ 6.2	13.0 (1.40¬120.27)	***0.023***	10.41 (1.09¬99.29)	***0.041***
FC µg/g < 50 50-250 > 250	4.72 (0.75¬29.70) 0.52 (0.08-3.24)	***0.097*** 0.49		
CRP < 5 mg/dL				
PMS ≤ 2	6.33 (0.69¬57.90)	0.10		

Table 3. Influence of non-invasive tools at week 12 on the risk of endoscopic improvement [MES ≤ 1] at reassessment

Parameter	Univariable analysis		Multivariable analysis	
	OR [95% CI]	*p*	OR [95% CI]	*p*
MUC ≤ 6.2	7.0 [1.84–26.61]	*0.0043*	5.80 [1.49–22.47]	*0.010*
FC, µg/g <50 50–250 >250	6.0 [1.52–23.67] 0.44 [0.07–2.51] 0.30 [0.08–1.12]	*0.010* 0.35 0.074	—	—
CRP < 5 mg/L	2.03 [0.51–8.00]	0.31	—	—
PMS ≤ 2	3.54 [0.97–12.90]	0.054	—	—

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MUC ≤ 6.2 at week 12 was the only independent predictor for MES ≤ 1 and MES = 0 at reassessment

MUC= 1.4xBWT + 2xCDS

Supplementary Table 1. Influence of non-invasive tools at week 12 on the risk of endoscopic remission (MES = 0) at reassessment

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Parameters				
MUC ≤ 6.2	13.0 (1.40¬120.27)	***0.023***	10.41 (1.09¬99.29)	***0.041***
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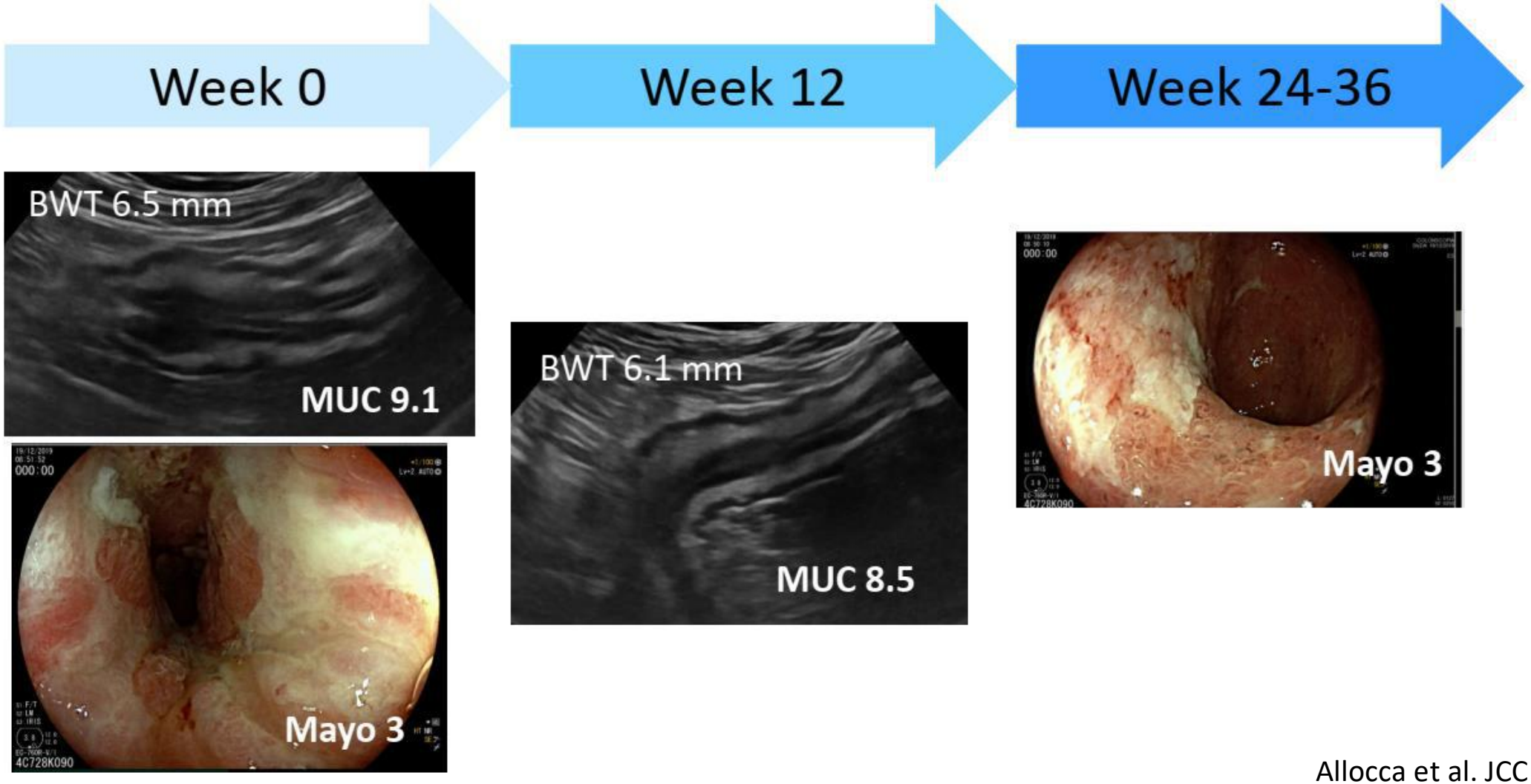
Failure to get ultrasound remission by 12 weeks was associated to failure to get long-term endoscopic remission in ulcerative colitis



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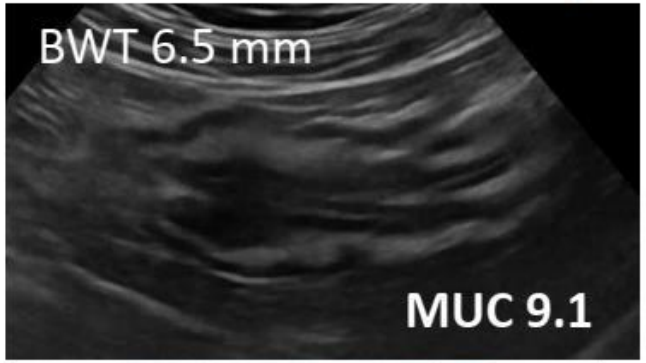
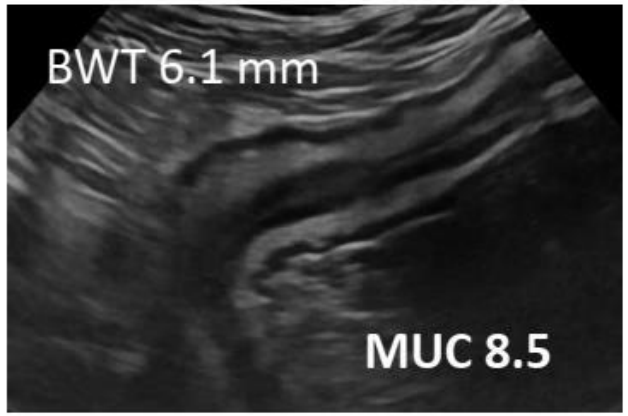
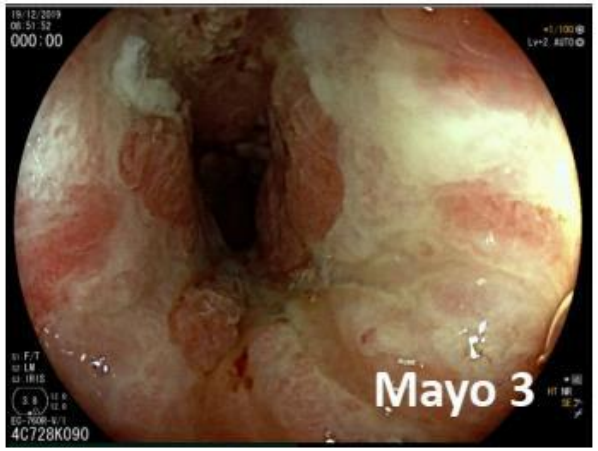


NPV 96%





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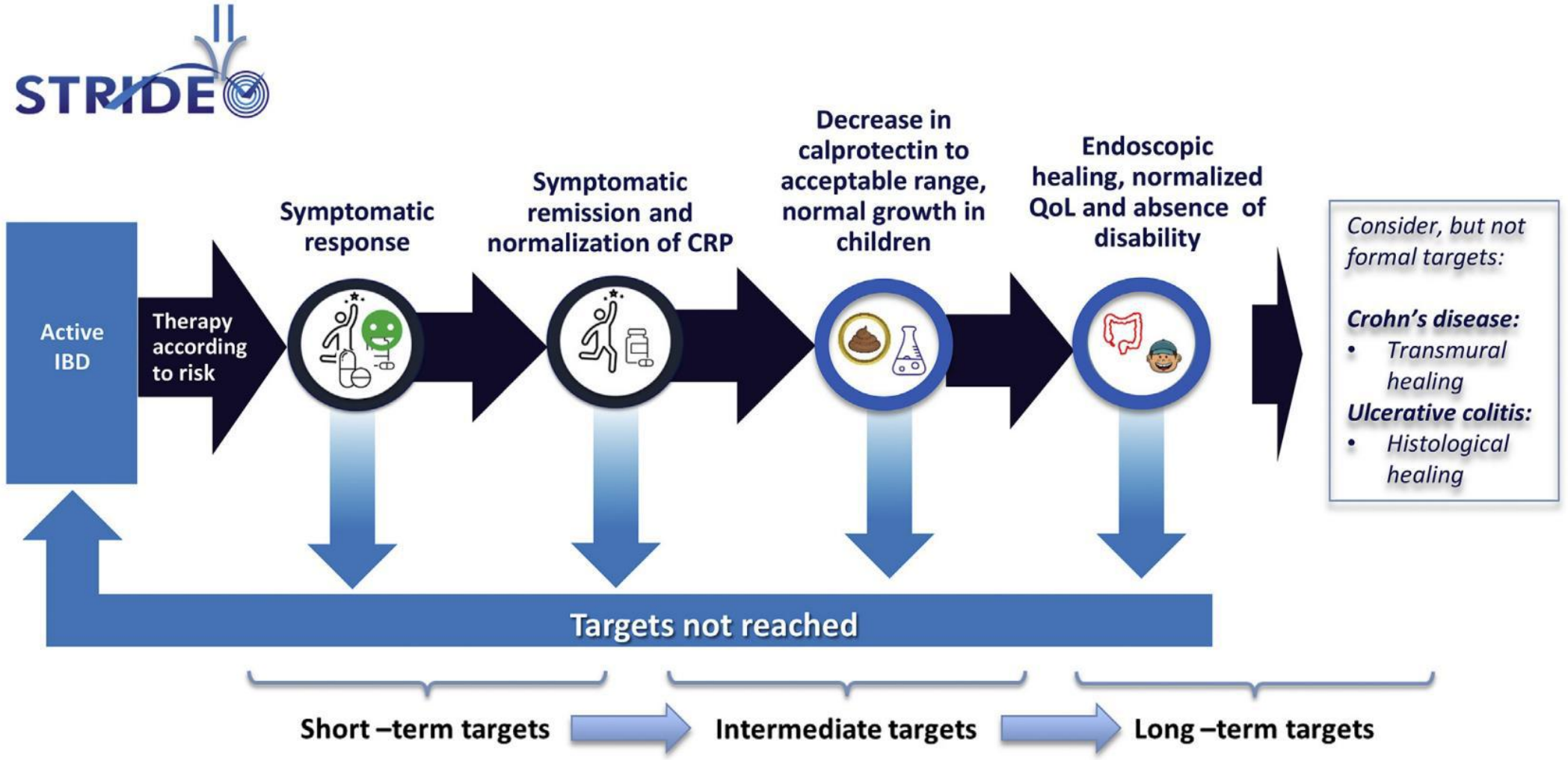
Ultrasound remission may be an early target in UC



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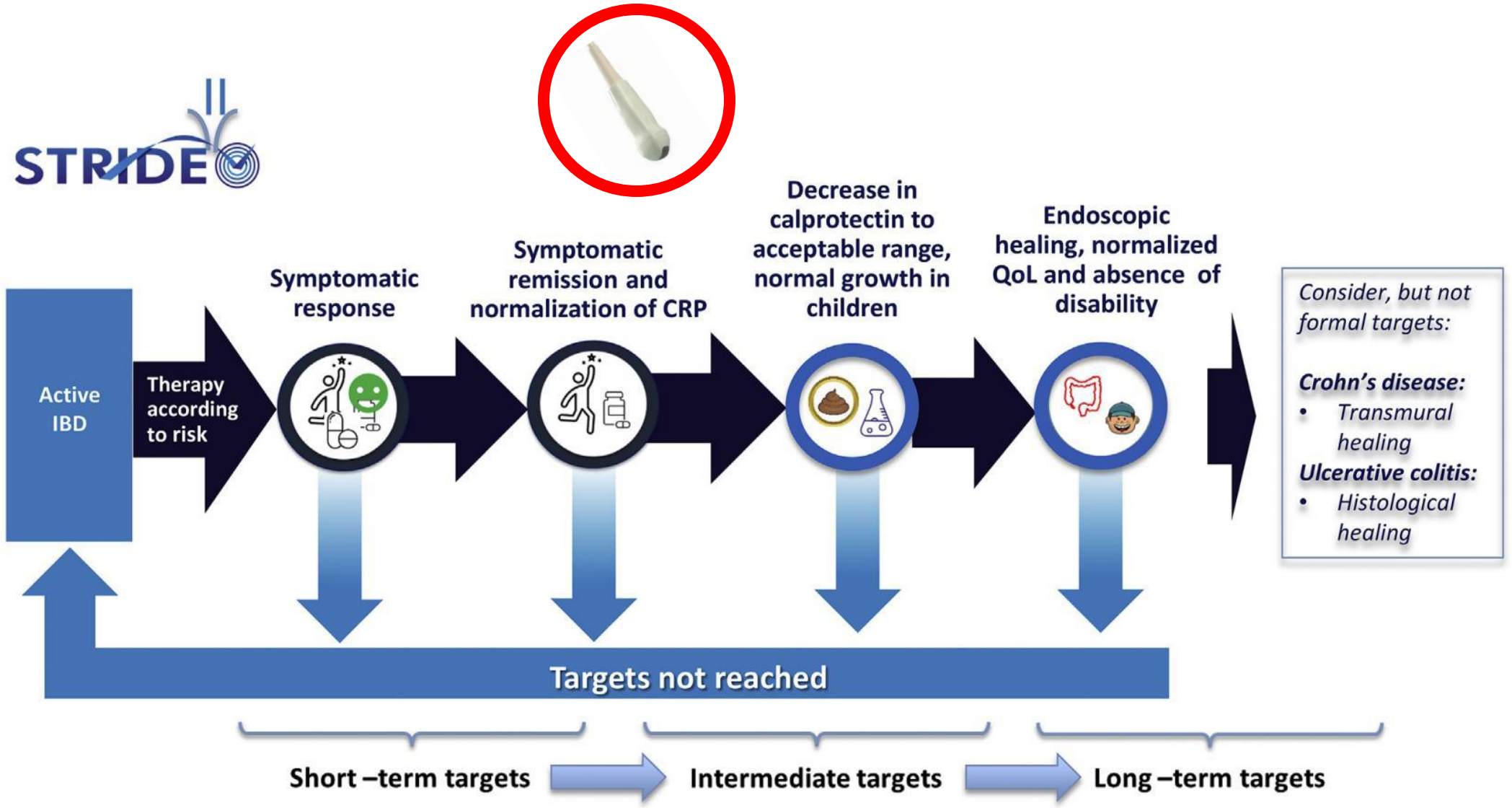

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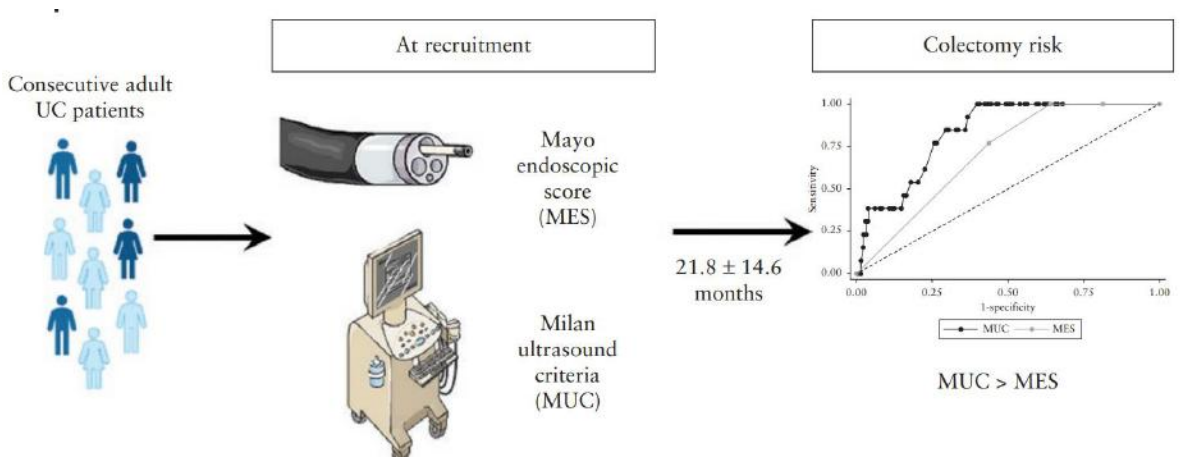
MUC, not MES, was independently associated with the risk of colectomy



Cohort of 141 patients with ulcerative colitis

MUC = 1.4xBWT + 2xCDS

Table 2. Influence of baseline characteristics on the risk of colectomy—Cox models

	Univariable Cox PH model		Multivariable Cox PH model	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
MUC	1.48 [1.19–1.76]	<0.001	1.46 [1.06–2.02]	0.02
Bowel wall thickness	1.68 [1.23–2.3]	<0.001		
Mayo Endoscopic Subscore	3.15 [1.18–8.37]	0.02	—	—
Partial Mayo Score	1.67 [1.27–2.19]	<0.001	1.63 [1.08–2.47]	0.02
Biological therapy	1.29 [1.05–1.58]	0.01	1.47 [1.12–1.94]	0.01
Steroids	0.83 [0.42–1.61]	0.58	—	—
Disease duration	0.93 [0.86–1.01]	0.08	0.91 [0.84–0.99]	0.03
CRP	1.01 [0.99–1.02]	0.07	—	—
Calprotectin	0.99 [0.99–1.00]	0.97	—	—

Piazza & Noviello et al. JCC 2023

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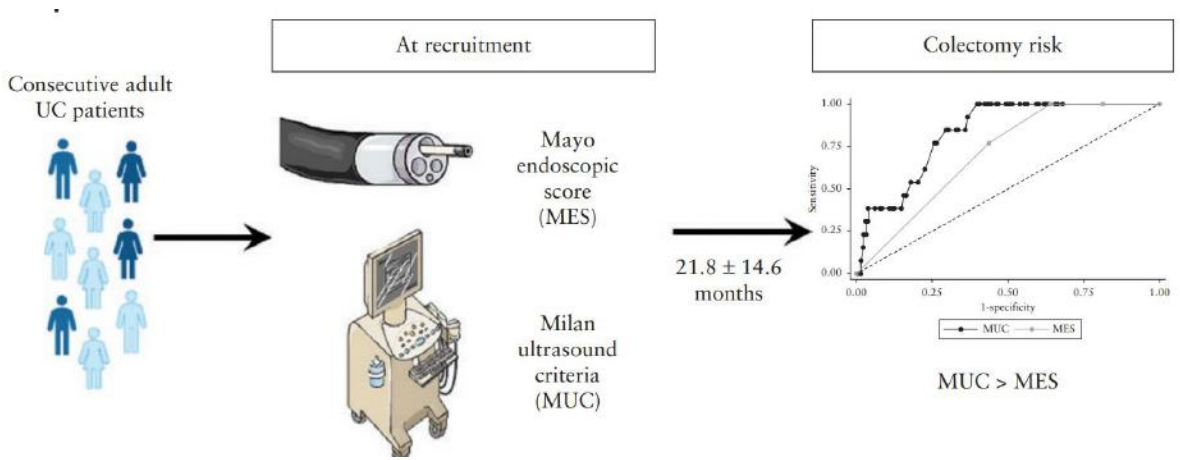

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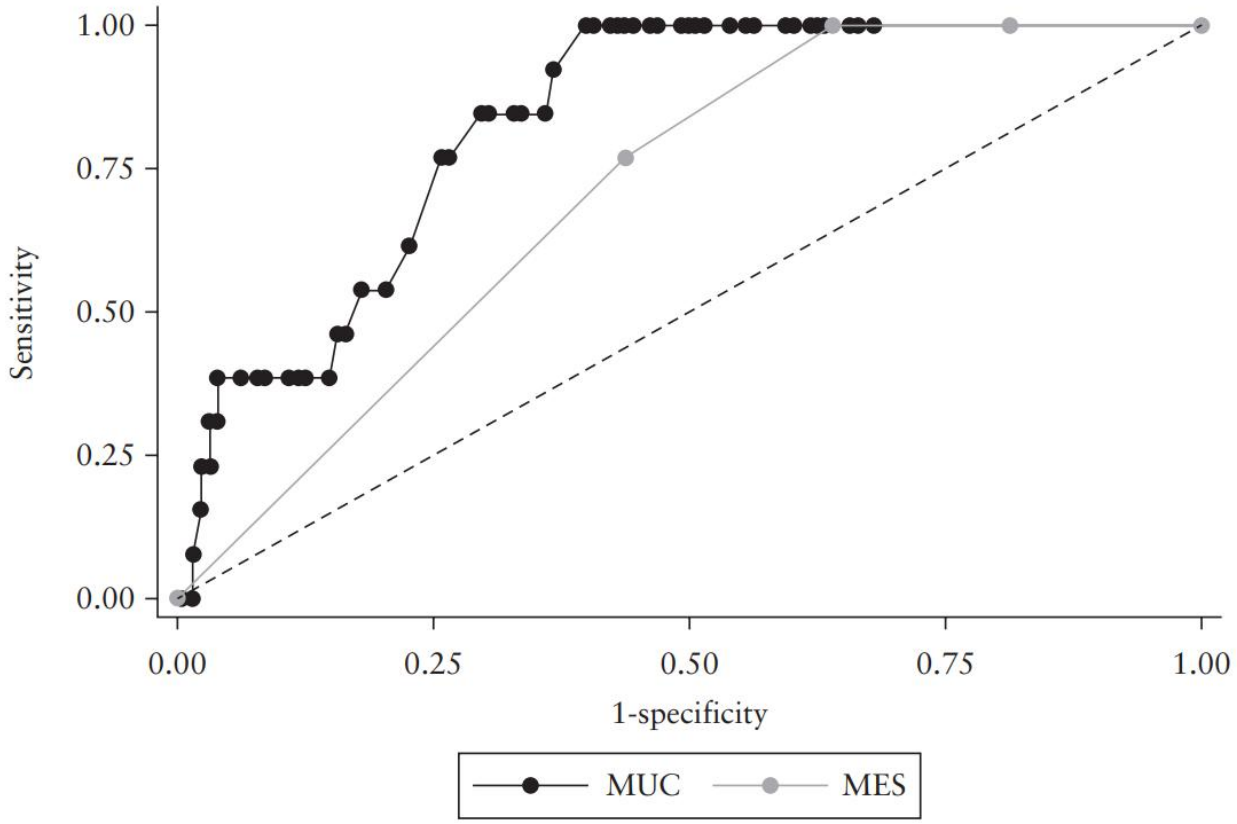
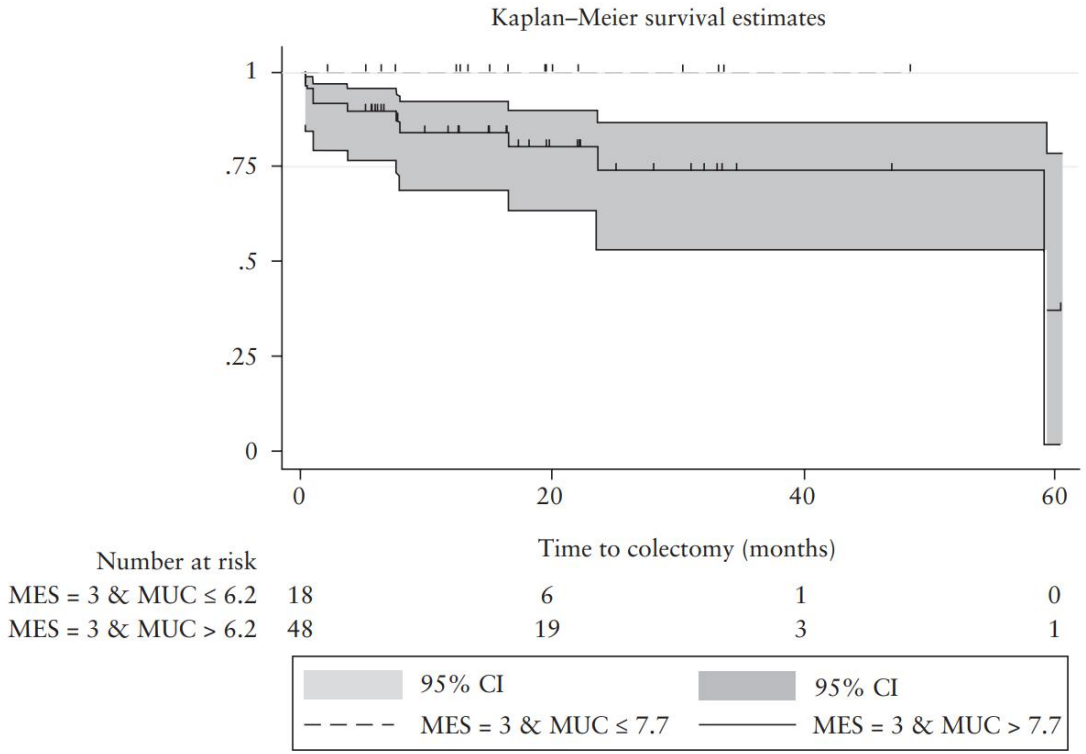
The optimal MUC cut-off value for predicting colectomy was 7.7





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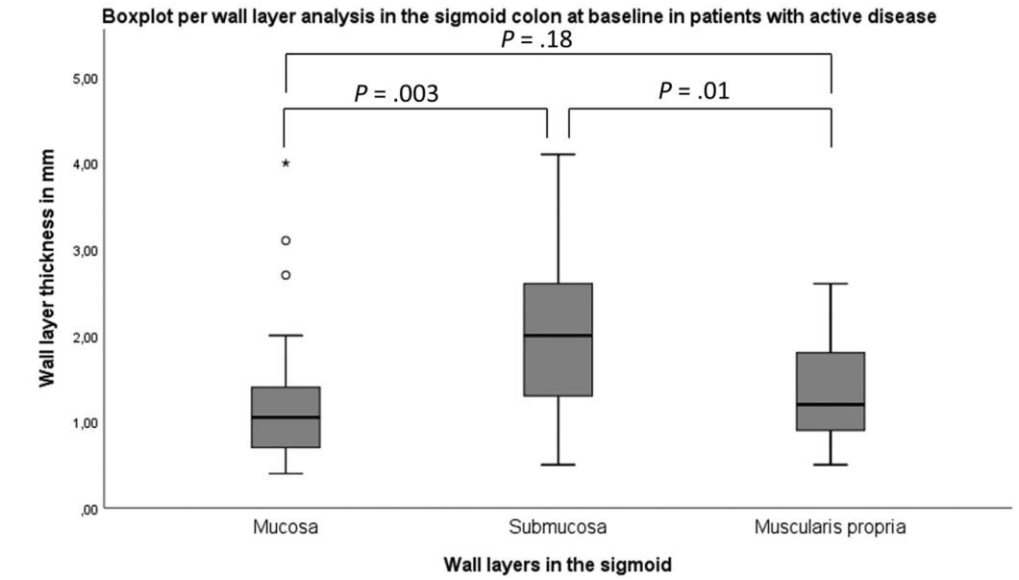
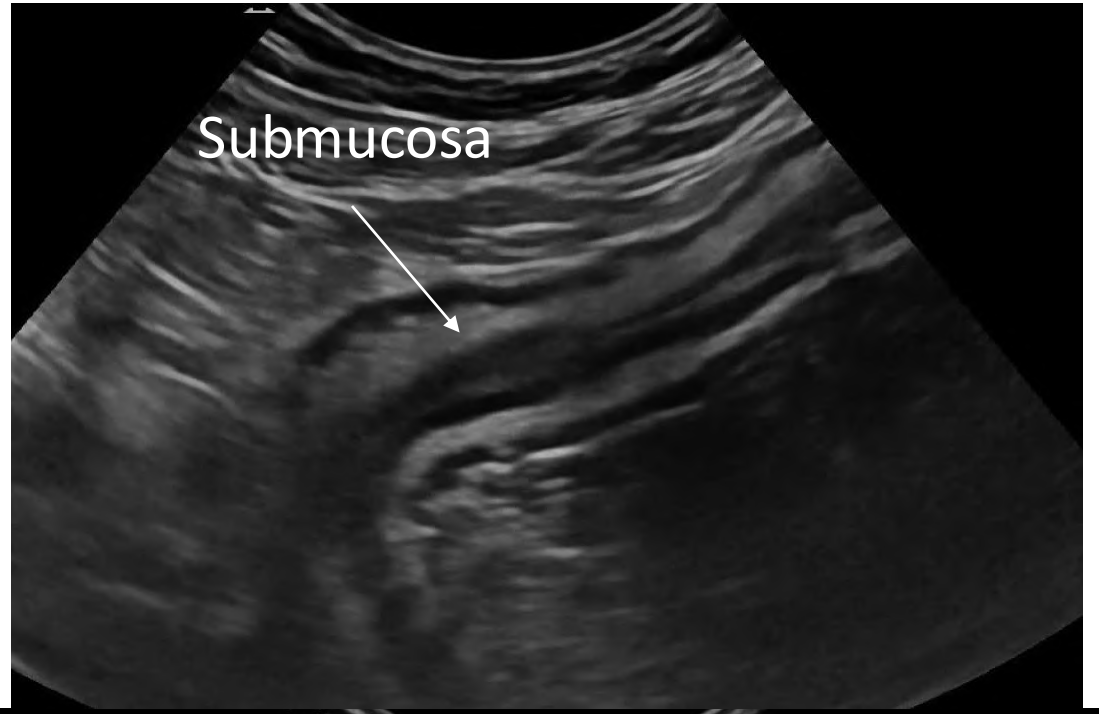
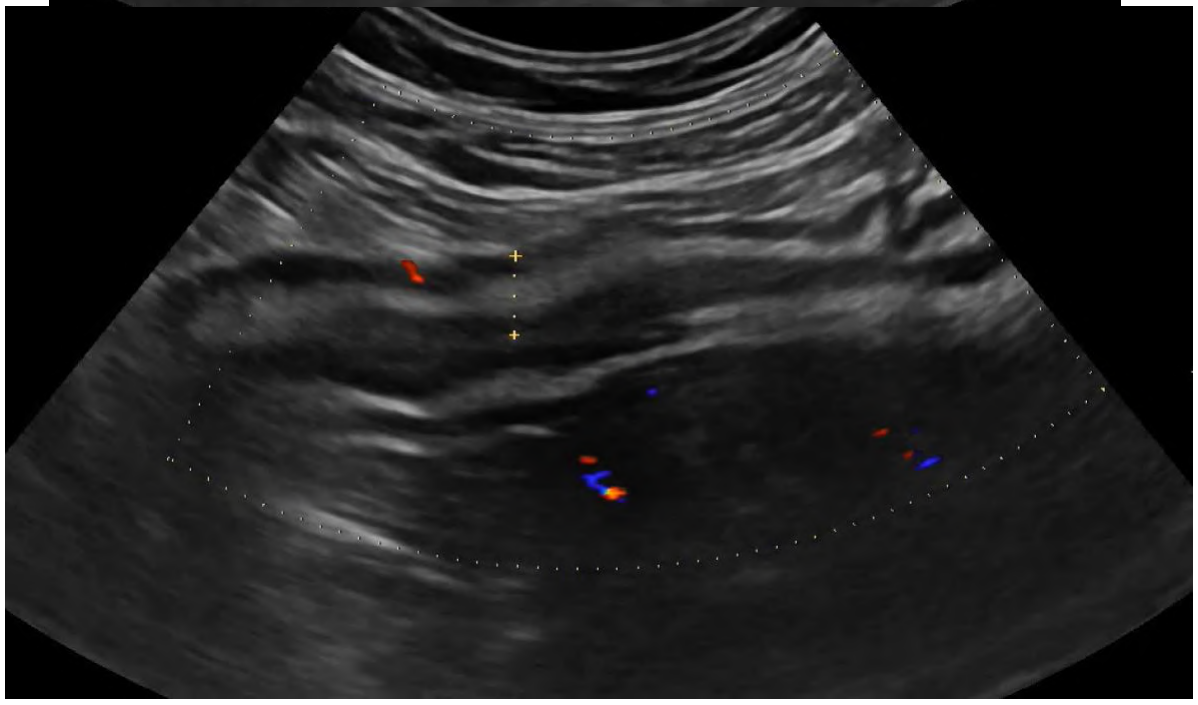
UC is not a “mucosal disease”: the submucosa is the thickest layer



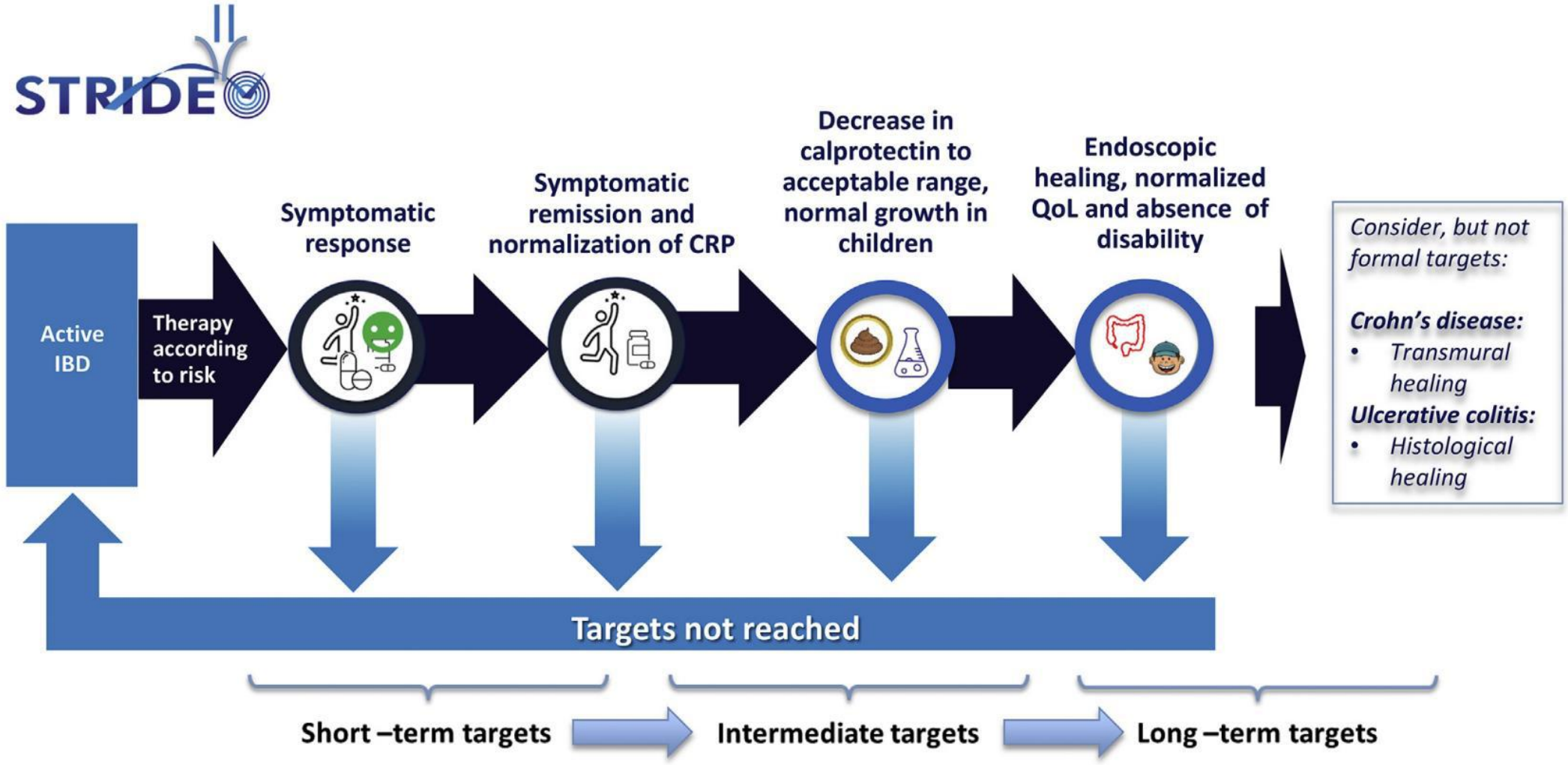
RCU patients with MES ≥ 2

De Voogd F, Gastroenterology 2022





Ultrasound remission may be a long-term target in UC



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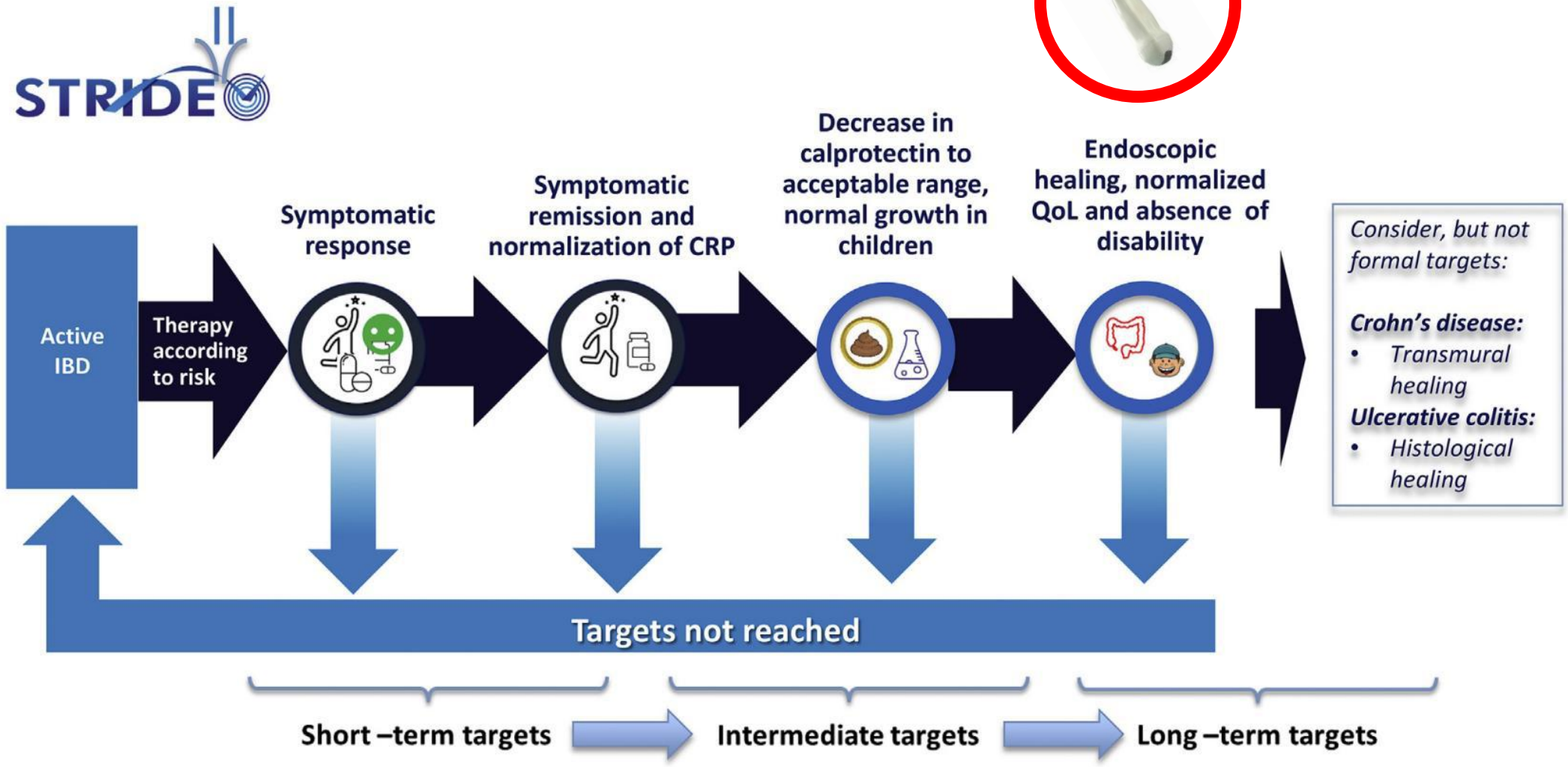

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Intestinal ultrasound in IBD

Indications	Unmet needs
Distinguish between IBD and irritable bowel syndrome[13]	International and validated ultrasound activity scores • Responsive to treatment • Predictive of outcomes
Assessment of disease activity (Milan Ultrasound Criteria, Simple Ultrasound Score for Crohn's Disease, Bowel Ultrasound Score, and International Bowel Ultrasound Segmental Activity Score)[4-6,19]	Treat-to-target strategy studies with point-of-care ultrasound • Is the diagnosis speedier? Does it lead to change in decision-making? Does this change lead to better patient outcome?
Assessment of complications and bowel damage (ultrasonography-based Léman index)[3]	Treat-to-target strategy studies with starting/optimization/change treatment according to IUS findings
Monitoring therapeutic response (transmural response and remission)[7-10,16]	Cost-effectiveness studies • IUS vs MRI and colonoscopy
Assessment of postoperative recurrence[3]	Defining IUS parameters for early postoperative recurrence
Predicting outcomes[6,10,14]	Predictive parameters for response and nonresponse Defining criteria for bowel damage in ulcerative colitis Evaluation of IBD in pregnant patients Evaluation of IBD in children Defining age-specific cutoff values for IUS parameters for pediatric patients

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Indications for IUS in IBD

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Areas for future research

- Large multicenter studies that confirm the accuracy, the reproducibility and the responsiveness of ultrasonographic-based activity scores;

- Maximize the use of IUS in treat-to-target strategies

Areas for future research

- Validation of ultrasonographic parameters to diagnose strictures and treatment response;

- Use of advanced techniques (CEUS, elastography, motility) and artificial intelligence to ultrasound imaging with extraction of novel imaging biomarkers of activity and fibrosis

Thank you