Monitoring IBD: can we abandon endoscopy?

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Disclosures

- E Louis has received fees for:
  - **Research Grant:** Takeda, Pfizer
  - **Educational Grant:** Abbvie, MSD, Takeda, Janssen
  - **Speaker Fees:** Abbvie, Ferring, MSD, Falk, Takeda, Hospira, Janssen, Pfizer, Celgene
  - **Advisory Board:** Abbvie, Ferring, MSD, Takeda, Celltrion, Celgene, Hospira, Janssen
  - **Consultant:** Abbvie

Disclaimer

- This is a medical education event with the support of Janssen-Cilag NV.
- This presentation represents the opinion of the speaker and not necessarily the opinion of Janssen.
- This presentation may include discussions on off-label use of drugs.

What is treat to target (T2T)?

Aim	Concept	Strategy	Additional principles
To avoid development of serious complications and disability in patients with chronic conditions	Treating to a pre-defined treatment target that is associated with optimal long-term outcomes (goal-oriented approach)	Ongoing and regular monitoring of the target and/or surrogate marker, with optimisation of treatment when the target is not met	All components – target, treatment and monitoring – are tailored to the needs of the individual patient De-escalation of therapy may be considered when treatment goals are achieved

A T2T approach involves pre-defining a treatment target, in consultation with the patient, continuously monitoring disease activity, and modifying treatment until the target is reached

1. Turner D, et al. Gastroenterology. 2021;160:1570-83.
2. Le Berre C, et al. Gastroenterology, 2022, online ahead of print.

TREAT TO TARGET

STRIDE 1 (2015) -> STRIDE 2 (2020)

Gastroenterology. 2020 Dec 21;S0016-5085(20)35572-4. doi: 10.1053/j.gastro.2020.12.031.
Online ahead of print.

STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD

Dan Turner [1], Amanda Ricciuto [2], Ayanna Lewis [3], Ferdinando D'Amico [4], Jasbir Dhaliwal [5], Anne M Griffiths [2], Dominik Bettenworth [6], William J Sandborn [7], Bruce E Sands [8], Walter Reinisch [9], Jürgen Schölmerich [10], Willem Bemelman [11], Silvio Danese [4], Jean Yves Mary [12], David Rubin [13], Jean-Frederic Colombel [14], Laurent Peyrin-Biroulet [15], Iris Dotan [16], Maria T Abreu [3], Axel Dignass [17], International Organization for the Study of IBD

STRIDE-II

- confirmed STRIDE-I long-term targets of clinical remission and endoscopic healing
- added absence of disability, restoration of quality of life and normal growth in children
- symptomatic relief and normalization of serum and fecal markers are short-term targets
- transmural healing in CD and histological healing in UC are not formal targets but should be assessed as measures of the remission depth

- **Control inflammation**
  - CRP
  - Fecal Calpro
  - …

↓

- **Intestinal healing**
  - Ultrasound
  - Endoscopy
  - …

↓

- **Avoid intestinal damage**
  - MRI
  - Histology
  - …

↓

➢ **Avoid disability and impairment of quality of life**

Symptoms control

Endoscopy is still necessary in some occasions, but…

- It is not that well accepted by the patients…
- We don’t see all the same things…
- It can be replaced by non-invasive first line tests in a substantial proportion of patients…
  - Calpro
  - US
- It does not tell us all the truth…and other techniques may bring more relevant information…
  - Biomarkers
  - Immunostat
  - Transmural and extramural inflammation…

Endoscopy is still necessary in some occasions, but

We are doing too many of them and we should, and increasingly will, replace a substantial number of them by stool/blood markers and cross-sectional imaging

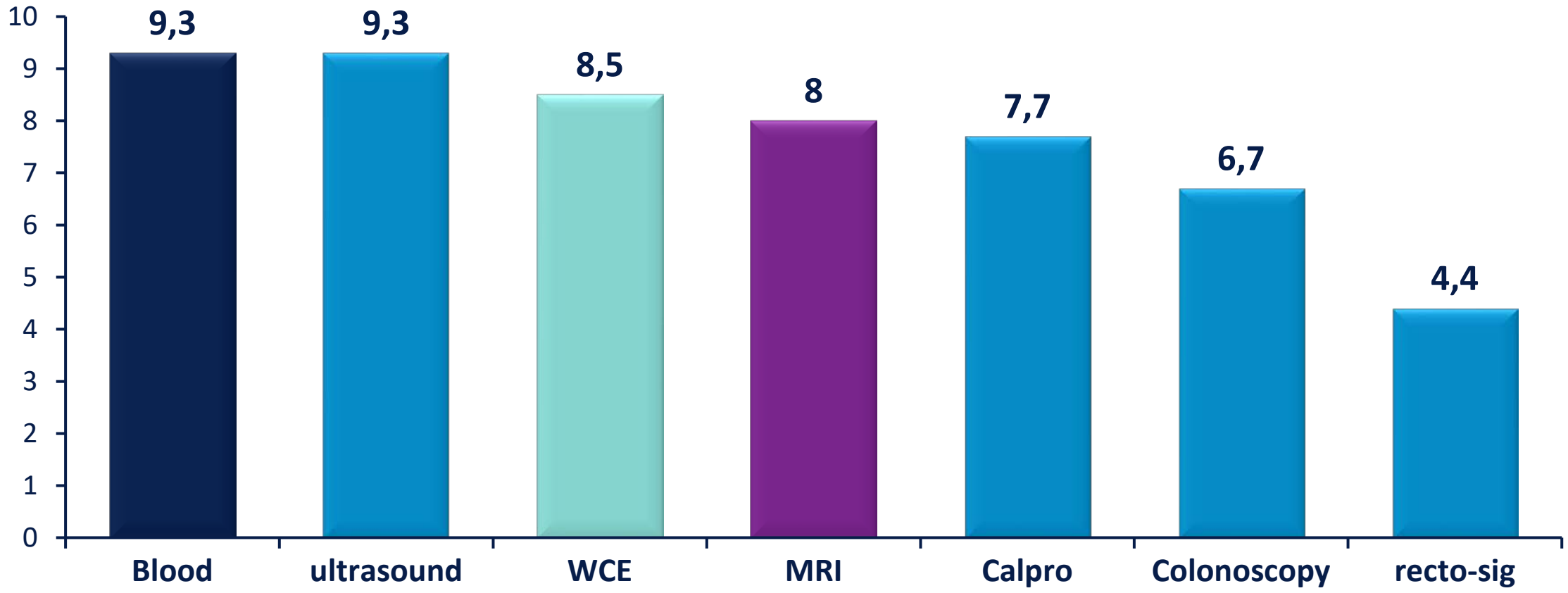
bring more relevant information…

- Biomarkers
- Immunostat
- Transmural and extramural inflammation…

Definition of an optimal monitoring tool

- Non-invasive
- Cheap
- Well accepted by the patient
- Reproducible
- Enough granularity to capture relevant changes
- Good correlation with the target

Patient-reported acceptability (618 patients with CD scored by VAS)



VAS, visual analogue scale

Buisson, et al. *Inflammatory Bowel Dis* 2017;23:1425

Moderate inter-observer agreements for endoscopic scores in IBD

- Rutgeerts Score (RS)
- RS0-RS4: kappa 0.43±0.05 (0.33–0.52) 'moderate' agreement.
- RS cut-off i2: kappa 0.47±0.10 (0.28–0.65) 'moderate' agreement
- RS >i2: Kappa 0.64±0.11 (0.42–0.85) 'substantial' agreement

- Endoscopic Mayo: kappas 0.53 (0.47-0.56) and 0.71 (0.67-0.76) 'Suboptimal' agreement
- Rutgeerts score: kappas 0.57 (0.51-0.65) and 0.67 (0.60-0.72) 'Fair agreement'
- CDEIS: intraclass correlation coefficients 0.83 (0.54-1.00) and 0.67 (0.36-0.97) 'good' agreement
- SES-CD: intraclass correlation coefficients 0.93 (0.76-1.00) and 0.68 (0.35-0.97) 'good' agreement

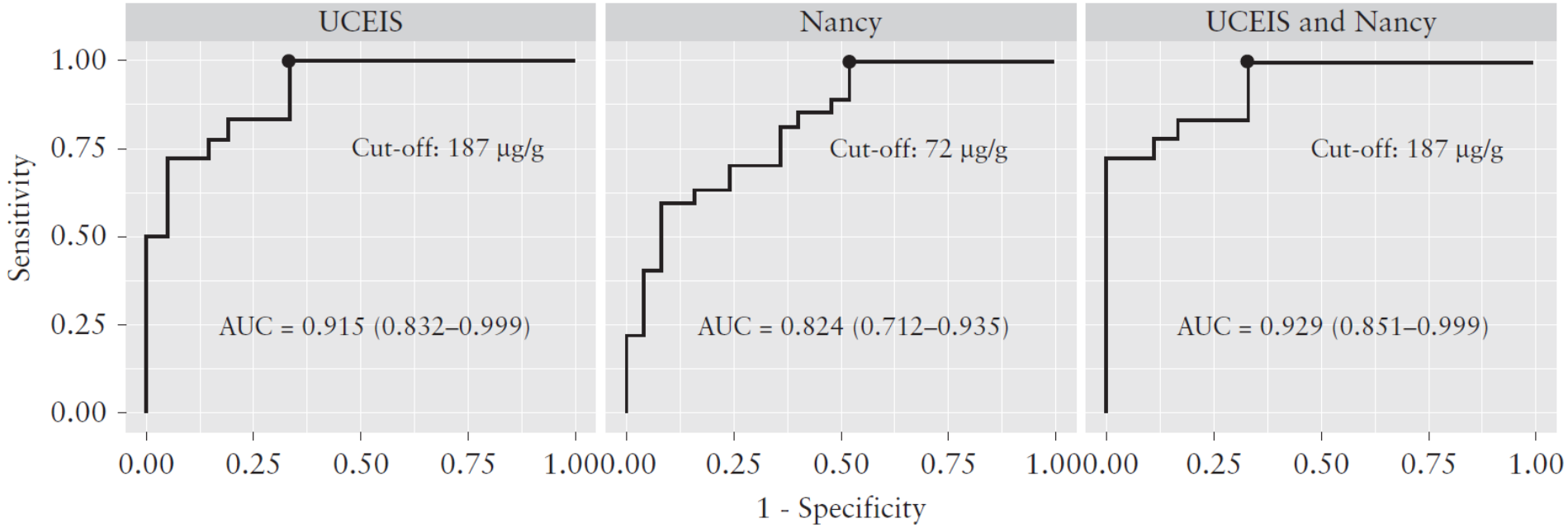
Marteau et al. J Crohns Colitis. 2016 Sep;10(9):1001-5

Daperno et al. Dig Liver Dis. 2014 Nov;46(11):969-73

Faecal Calprotectin Tresholds as a Surrogate for Endoscopic and Histological Disease Activity in UC—a Prospective Analysis

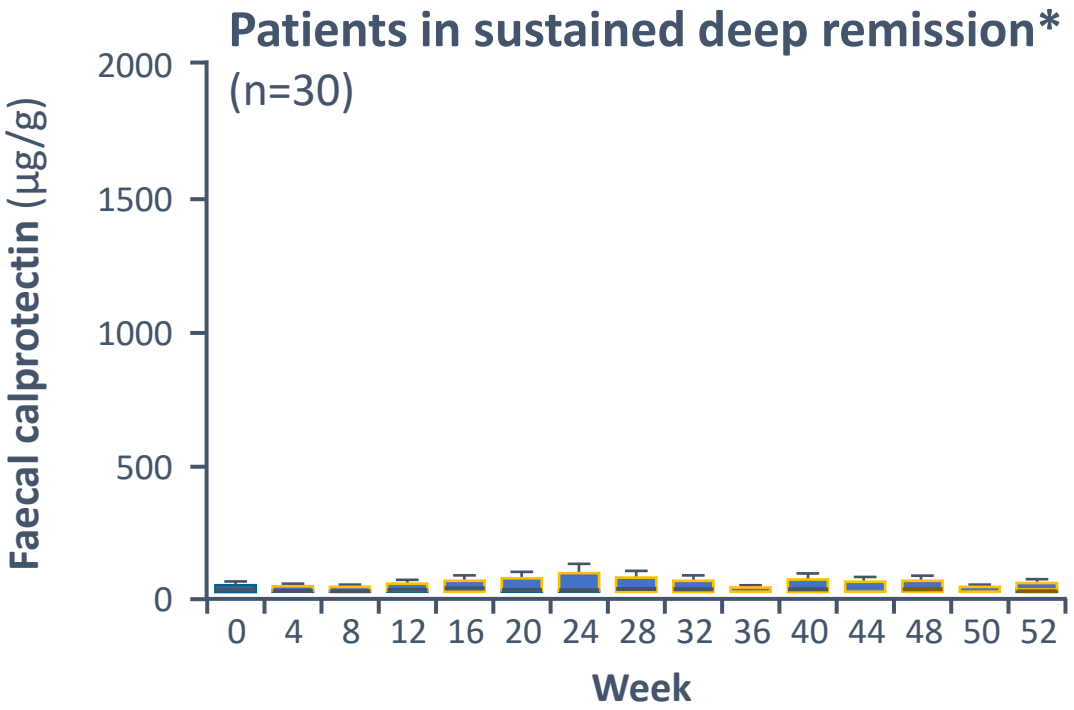
Table 4. Correlation coefficients between the levels of FCal and indices.

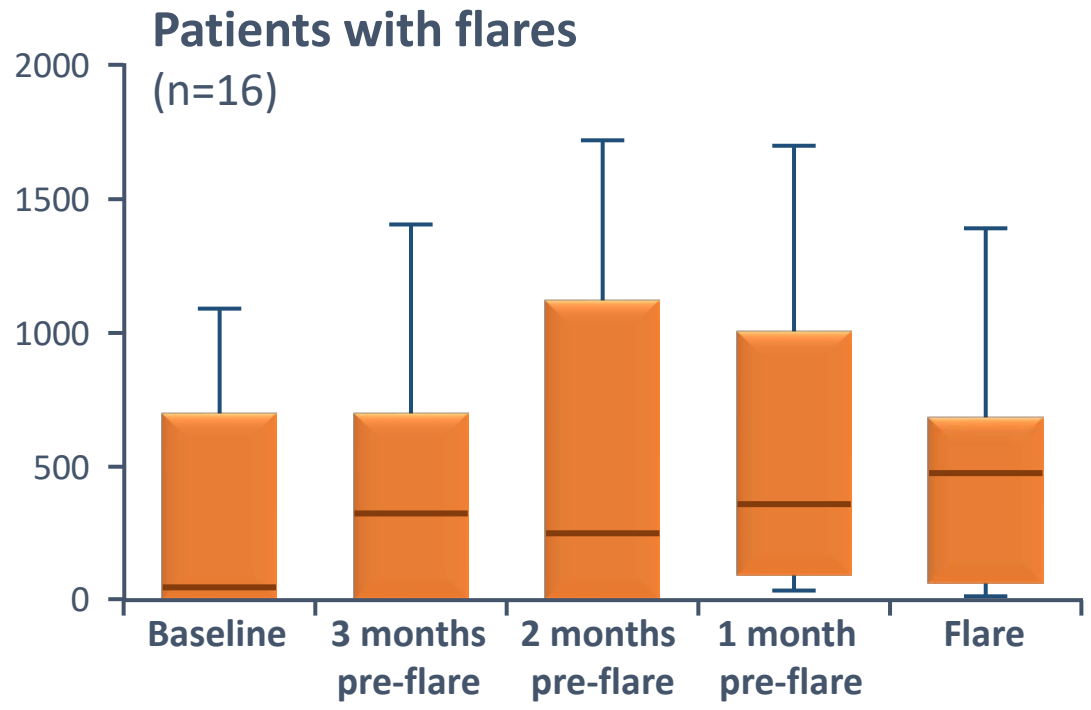
	r	95%CI	*p*-value
SCCAI	0.271	[0.114, 0.415]	<0.001
UCEIS	0.741	[0.289, 0.922]	<0.003
Nancy	0.876	[0.605, 0.965]	<0.0001



Walsh A, et al. J Crohns Colitis 2019;13:424-30

Two consecutive faecal calprotectin measurements of >300 µg/g with 1-month interval were the best predictor of flare





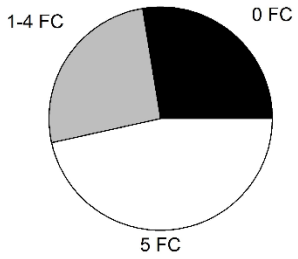
Prospective study of adult patients with UC in clinical remission with IFX maintenance

*Partial Mayo score <3 at all points and an endoscopic Mayo score 0 at week 52.
FCP, faecal calprotectin; IFX, infliximab.

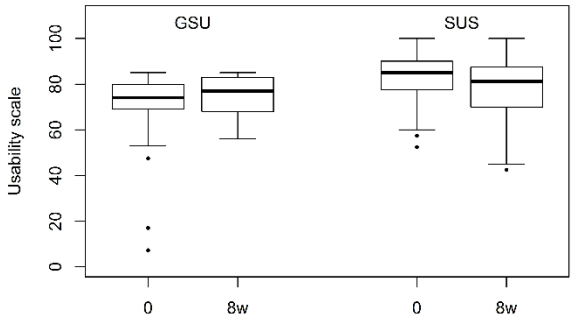
De Vos M, et al. *Inflamm Bowel Dis* 2013;19:2111–7

Usability of IBDoc a home-based self test for fecal calprotectin

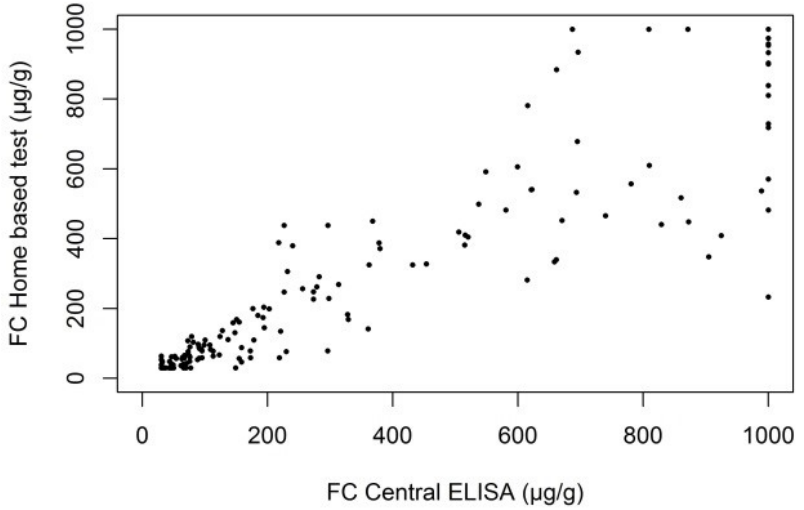
Adherence to the planned measurements
(n of measures performed)



Usability score at baseline and week 8

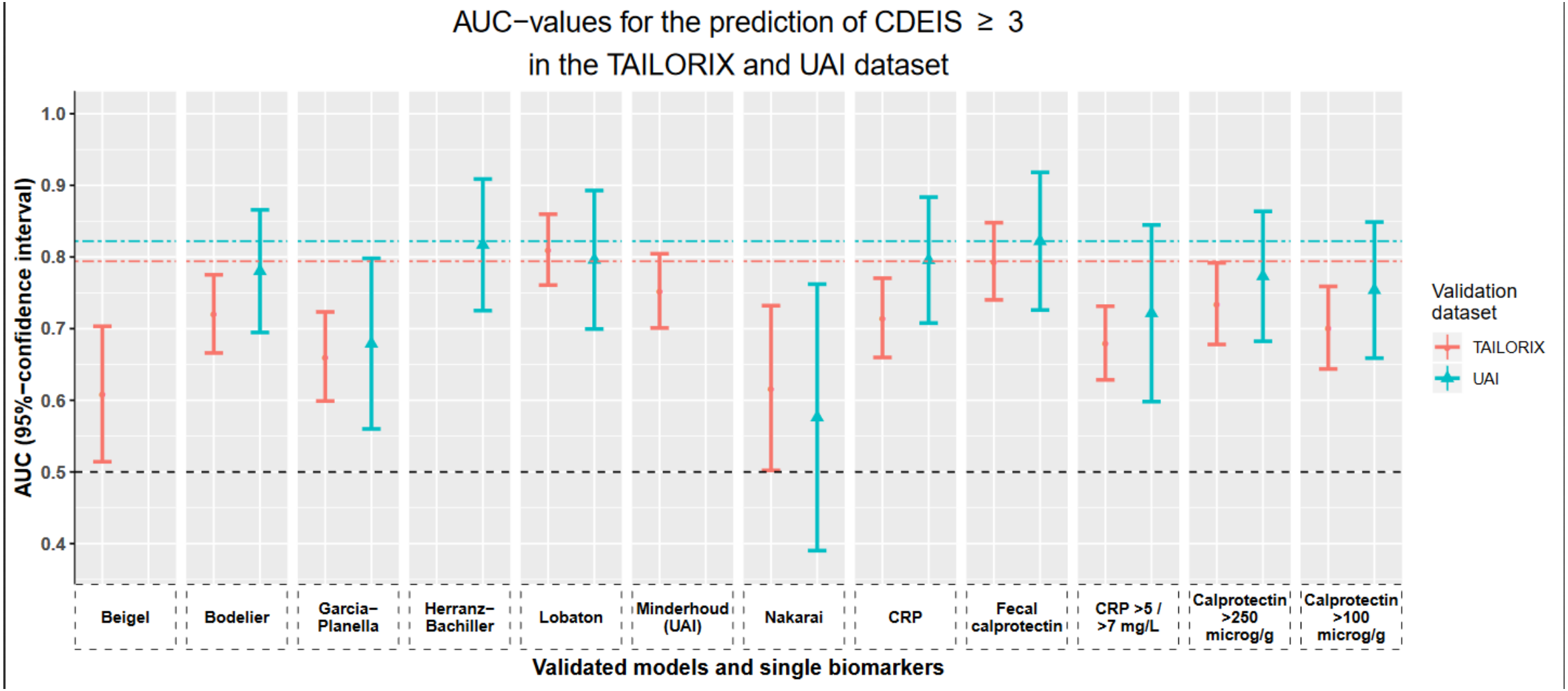


Correlation between the home self-test and the central ELISA



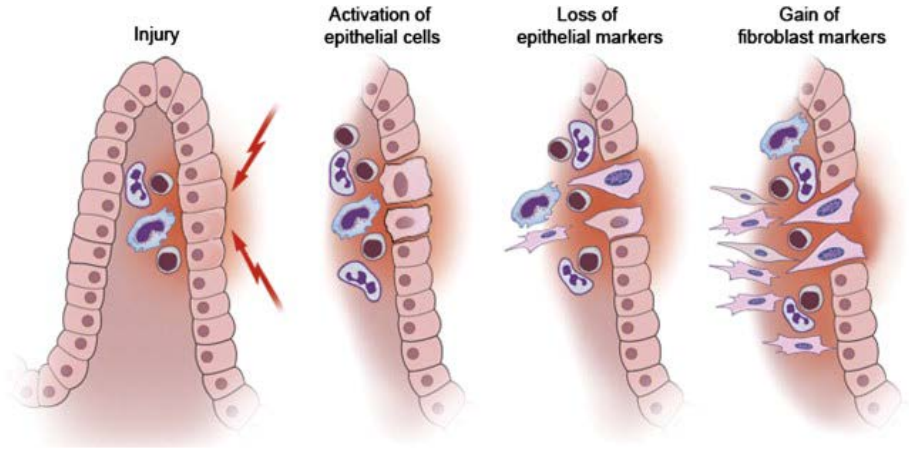
Bello C et al. Dig and Liver Dis 2017

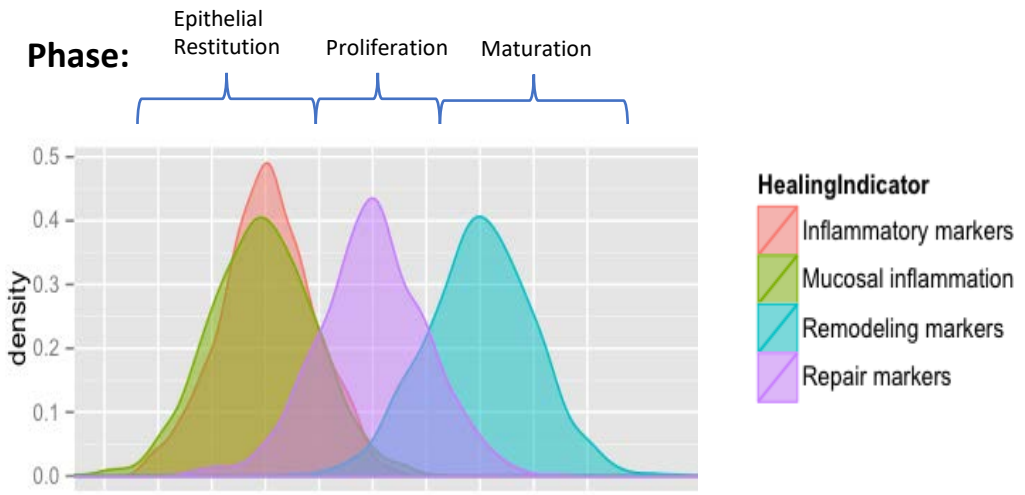
Systematic review and external validation of prediction models based on symptoms and biomarkers for identifying endoscopic activity in Crohn's disease.

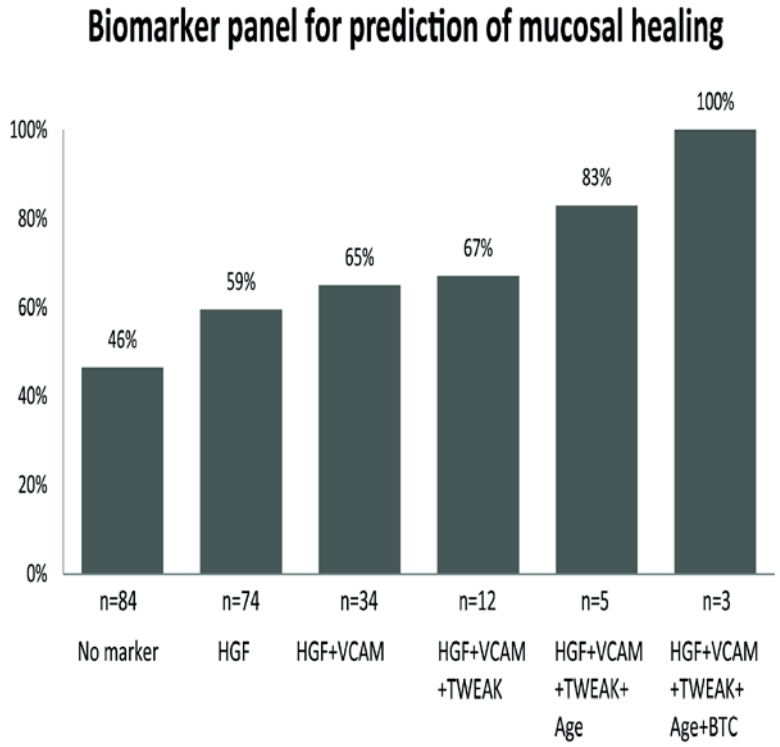


Brand et al. Clin Gastroenterol Hepatol. 2019 Dec 24. pii: S1542-3565(19)31493-4. doi: 10.1016/j.cgh.2019.12.014.

Advance in mucosal healing assessment
Combining relevant biomarkers



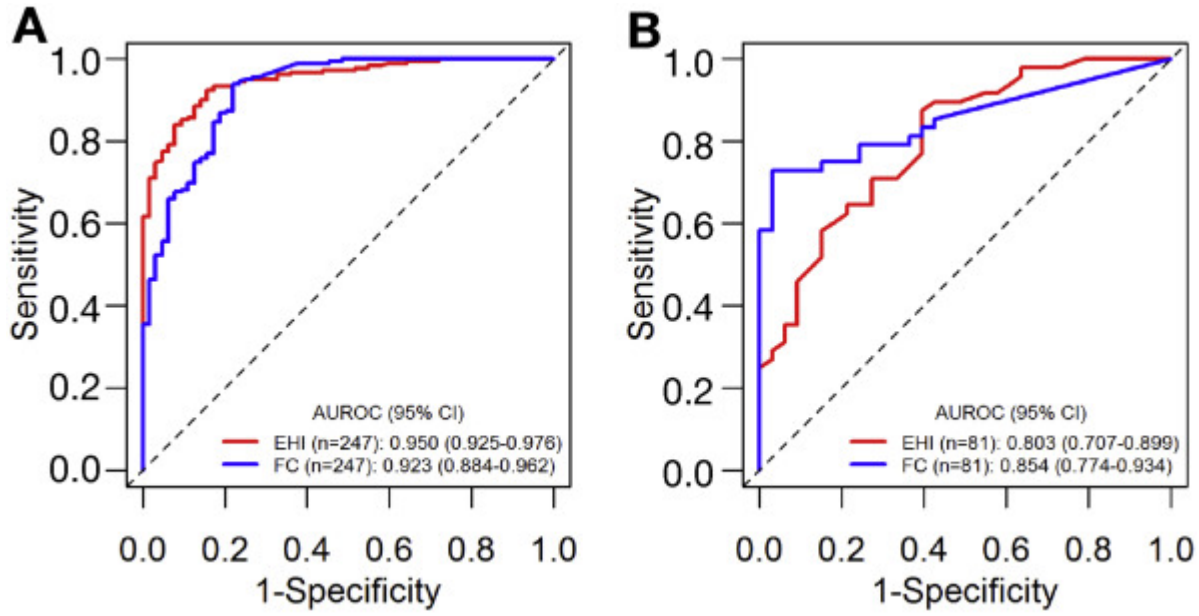




Prometheus Company ECCO February 2014

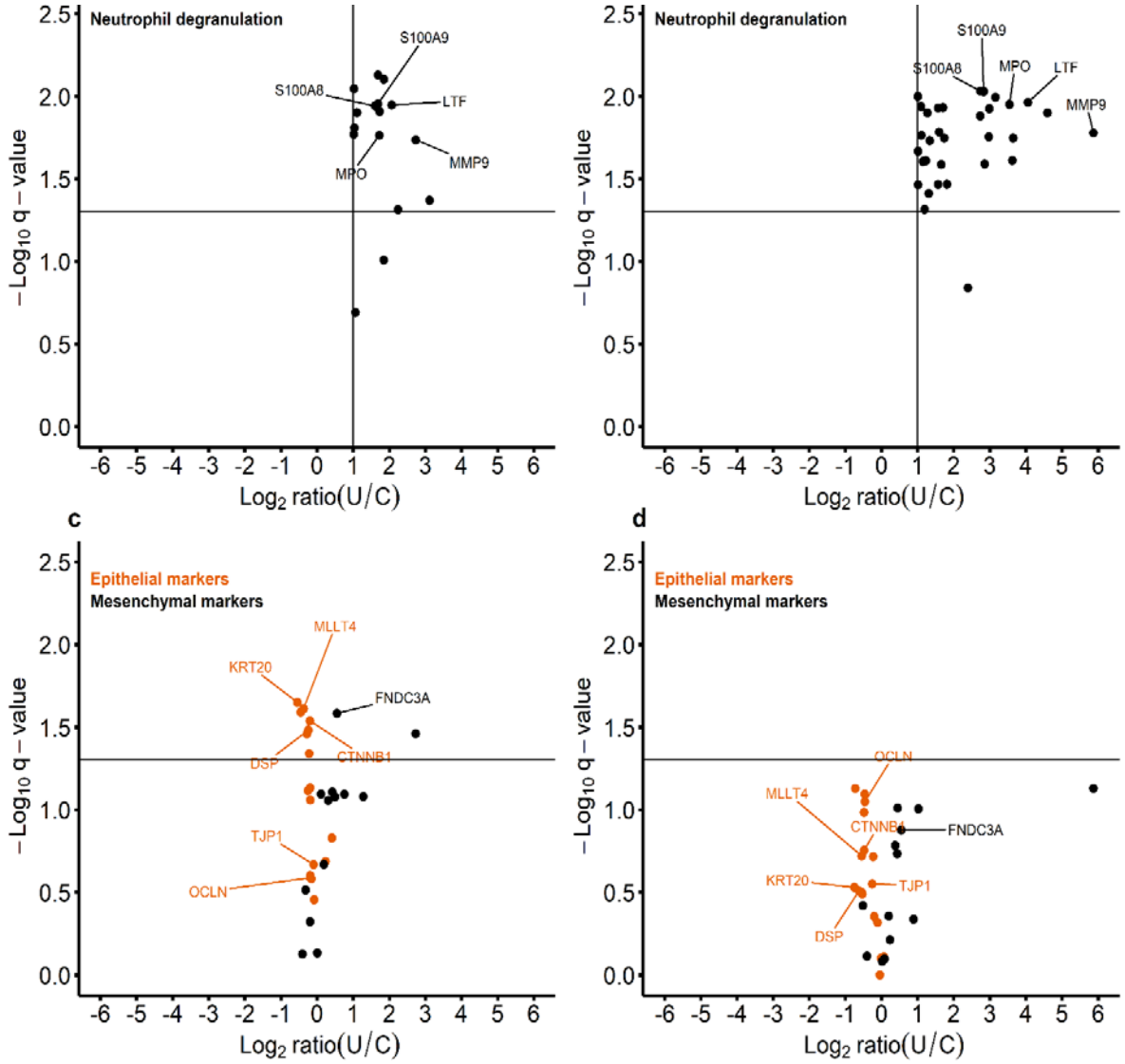
Blood biomarkers to predict endoscopic remission in Crohn

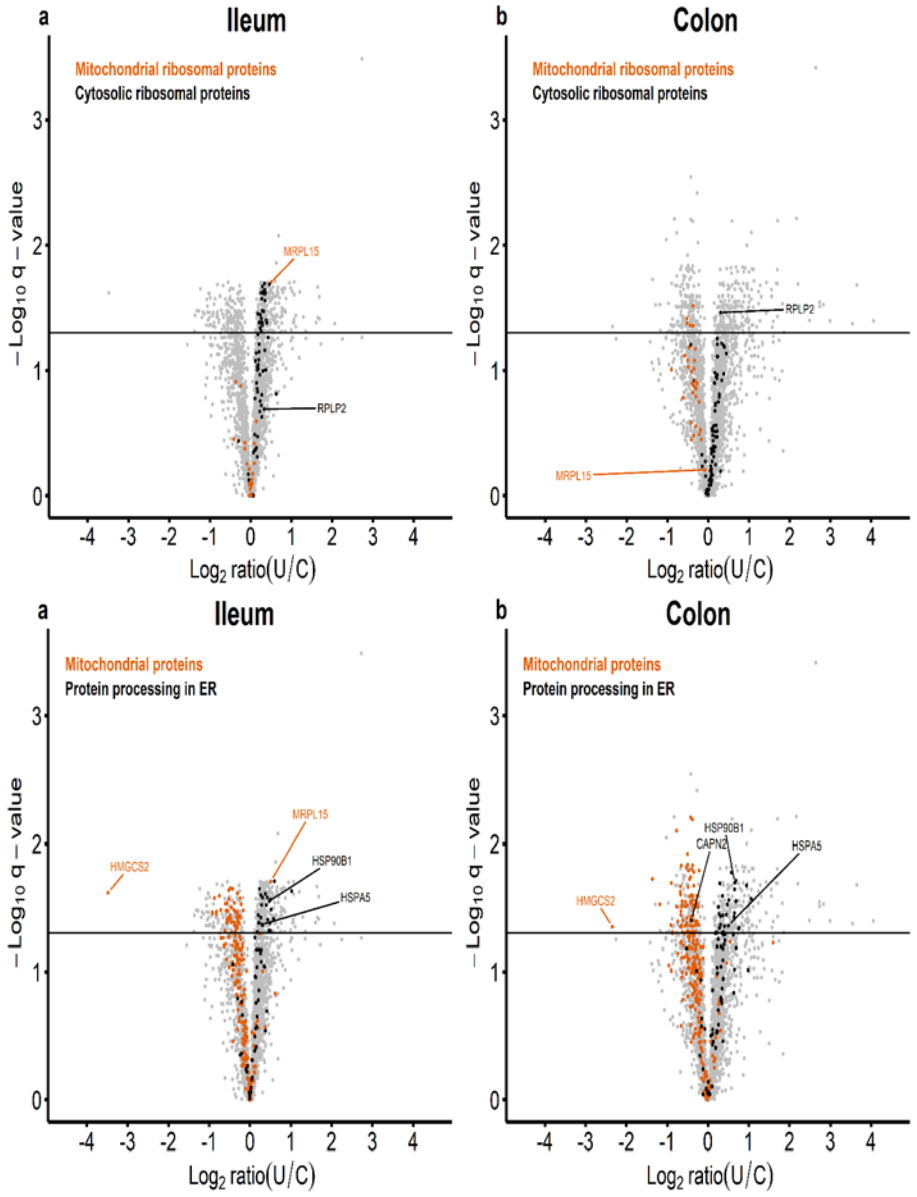
ROC curves of the EHI and FC for distinguishing active disease vs endoscopic remission in (*A*) validation cohort 1 and (*B*) validation cohort 2. In validation cohort 1, mixed logistic regression models with random intercepts for individual participants were used to combine multiple samples of the same participant.



D'haens et al. Gastroenterology. 2019 Nov 8. pii: S0016-5085(19)41525-4. doi: 10.1053/j.gastro.2019.10.034.

Segment specific pathophysiological processes in Crohn's disease





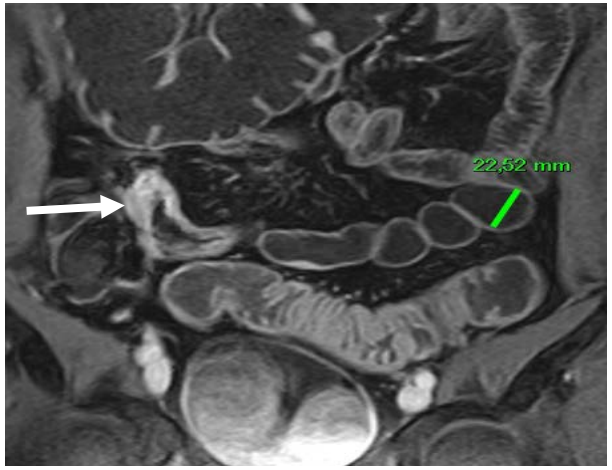
Pierre N. *et al.* J Crohns Colitis. 2019 Jul 8. pii: jjz130. doi: 10.1093/ecco-jcc/jjz130

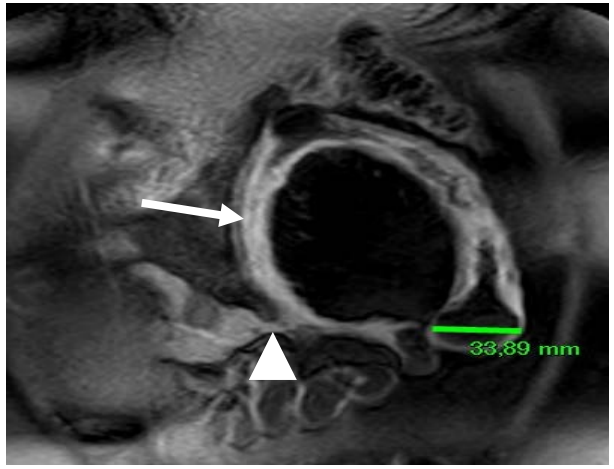
Success at week 24 in 93 patients with Crohn's disease and symptomatic small bowel strictures treated with adalimumab

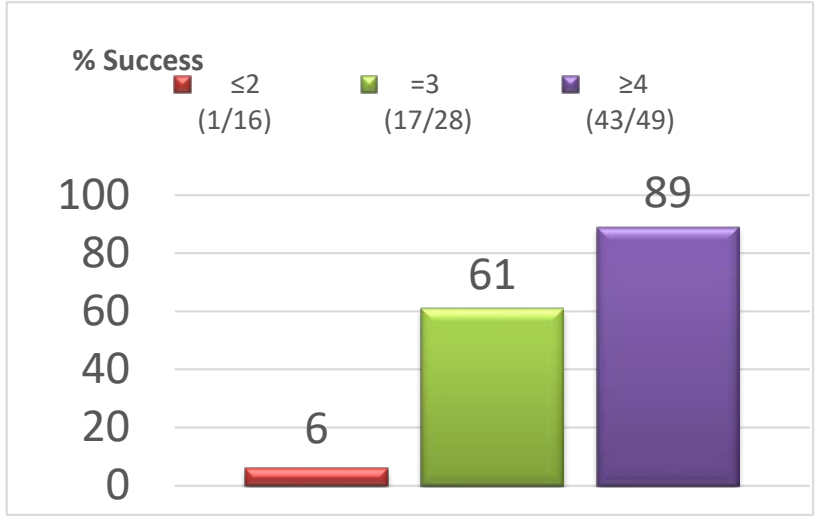
GETAID
CREOLE

Factor/Group at high rate of success	Coefficient estimate ± SE	Odds ratio estimate	p	Number of points
Immunosuppressor / Yes	1.23 ± 0.62	3.42	0.040	1
CDOS / > 4	1.25 ± 0.65	3.48	0.046	1
Duration obstructive symptoms (week) / < 5	1.79 ± 0.81	6.00	0.016	1
Length of stricture < 12 cm	1.80 ± 0.67	6.04	0.0042	1
Maximal proximal diameter (mm) / [18- 29]	1.99 ± 0.68	7.32	0.0013	1
T1 Delayed enhancement intensity / Severe	1.78 ± 0.66	5.92	0.0034	1
Fistula / No	1.55 ± 0.76	4.72	0.035	1

Bouhnik et al. Gut. 2018 Jan;67(1):53-60. doi: 10.1136/gutjnl-2016-312581.





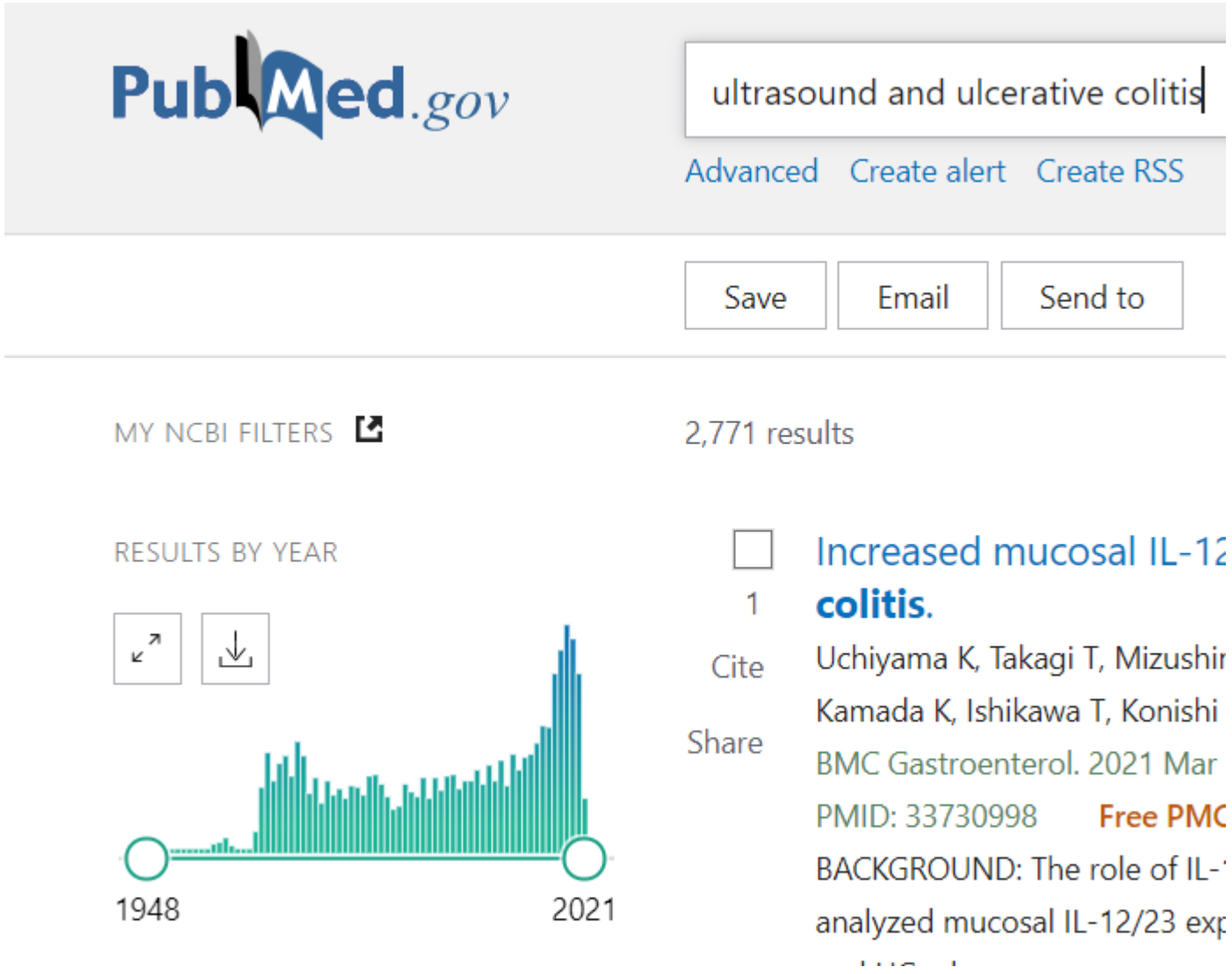


Review > Gut. 2018 May;67(5):973-985. doi: 10.1136/gutjnl-2017-315655. Epub 2018 Feb 3.

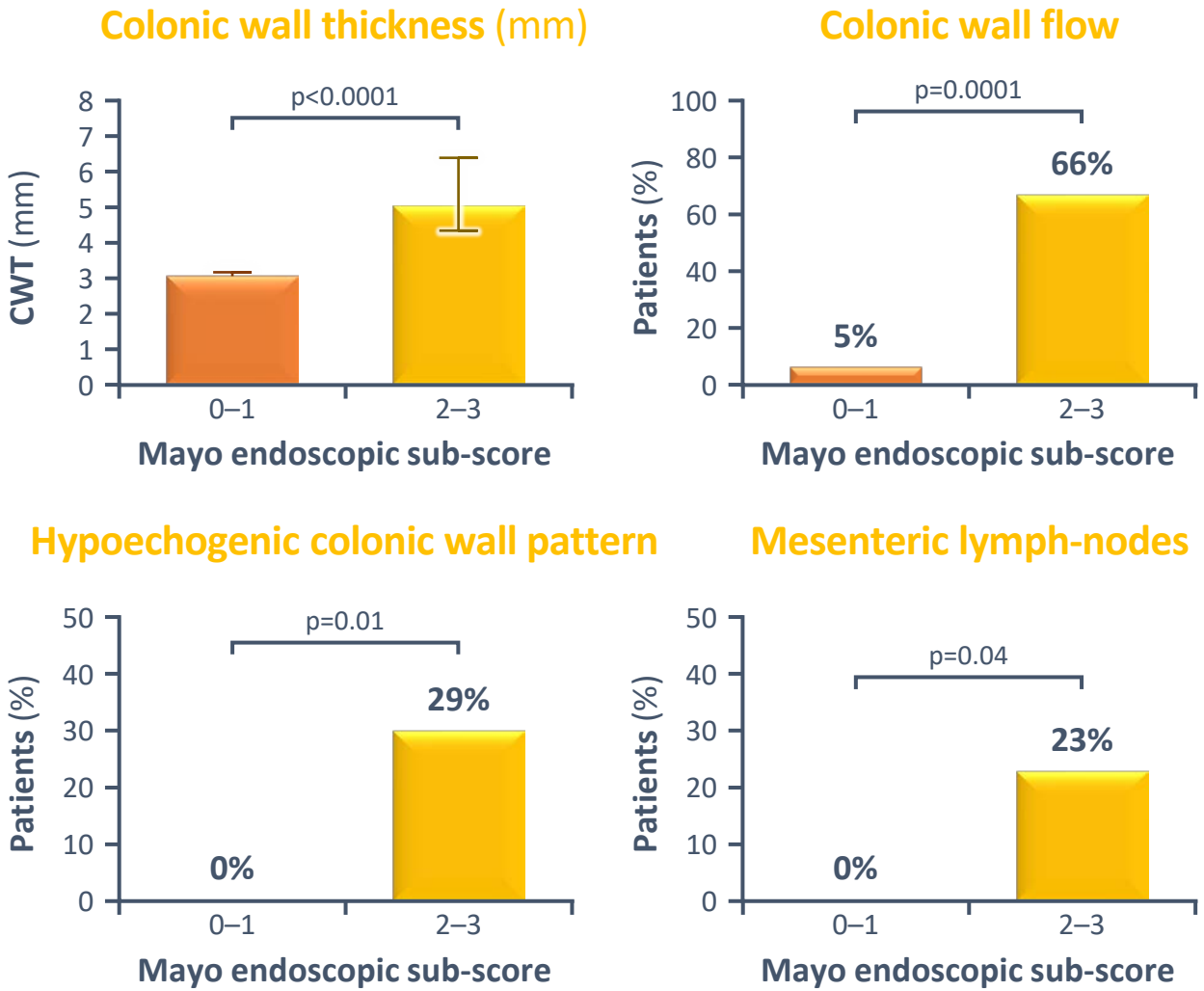
Gastrointestinal ultrasound in inflammatory bowel disease: an underused resource with potential paradigm-changing application

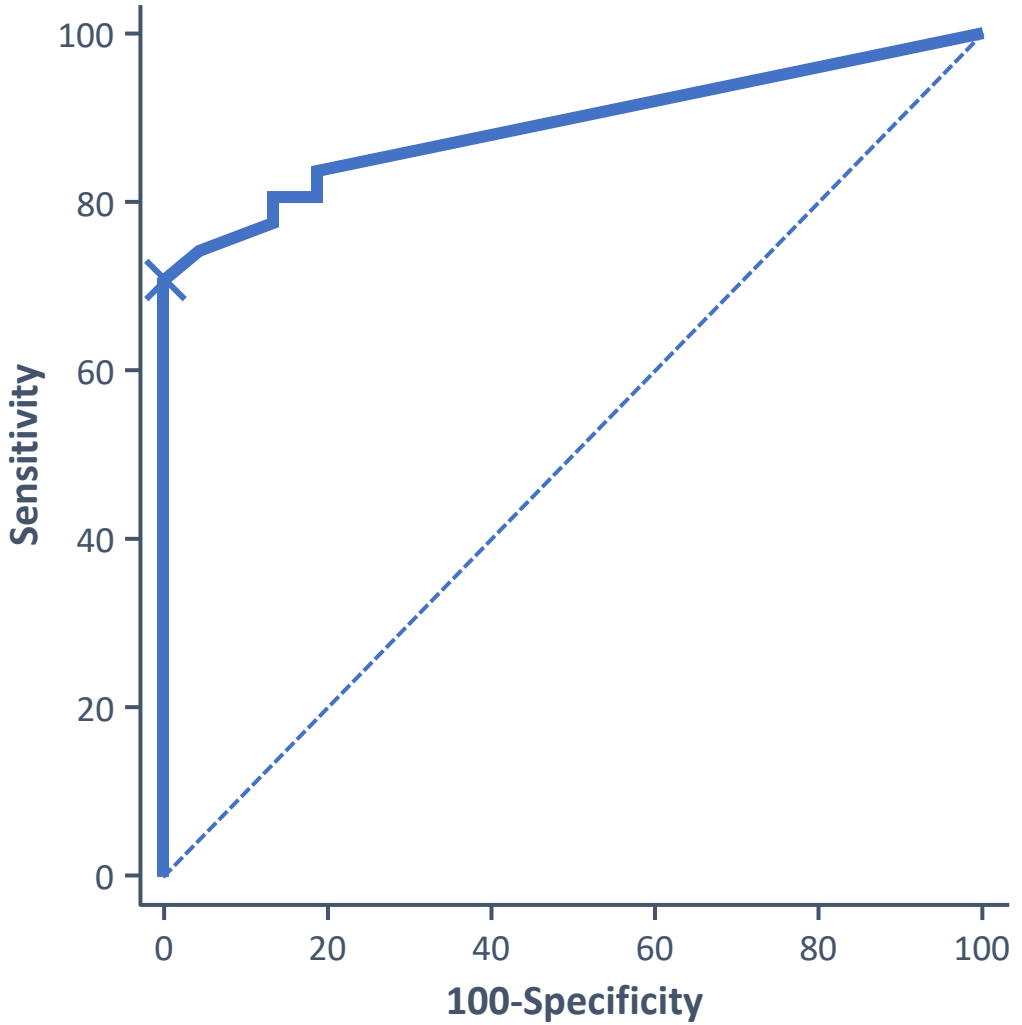
Robert Venning Bryant [1] [2], Antony B Friedman [3] [4], Emily Kate Wright [5] [6], Kirstin M Taylor [3] [4], Jakob Begun [7] [8], Giovanni Maconi [9], Christian Maaser [10], Kerri L Novak [11], Torsten Kucharzik [10], Nathan S S Atkinson [12], Anil Asthana [13], Peter R Gibson [3] [4]

Evolution des publications sur « Ulcerative colitis » and «Ultrasound »



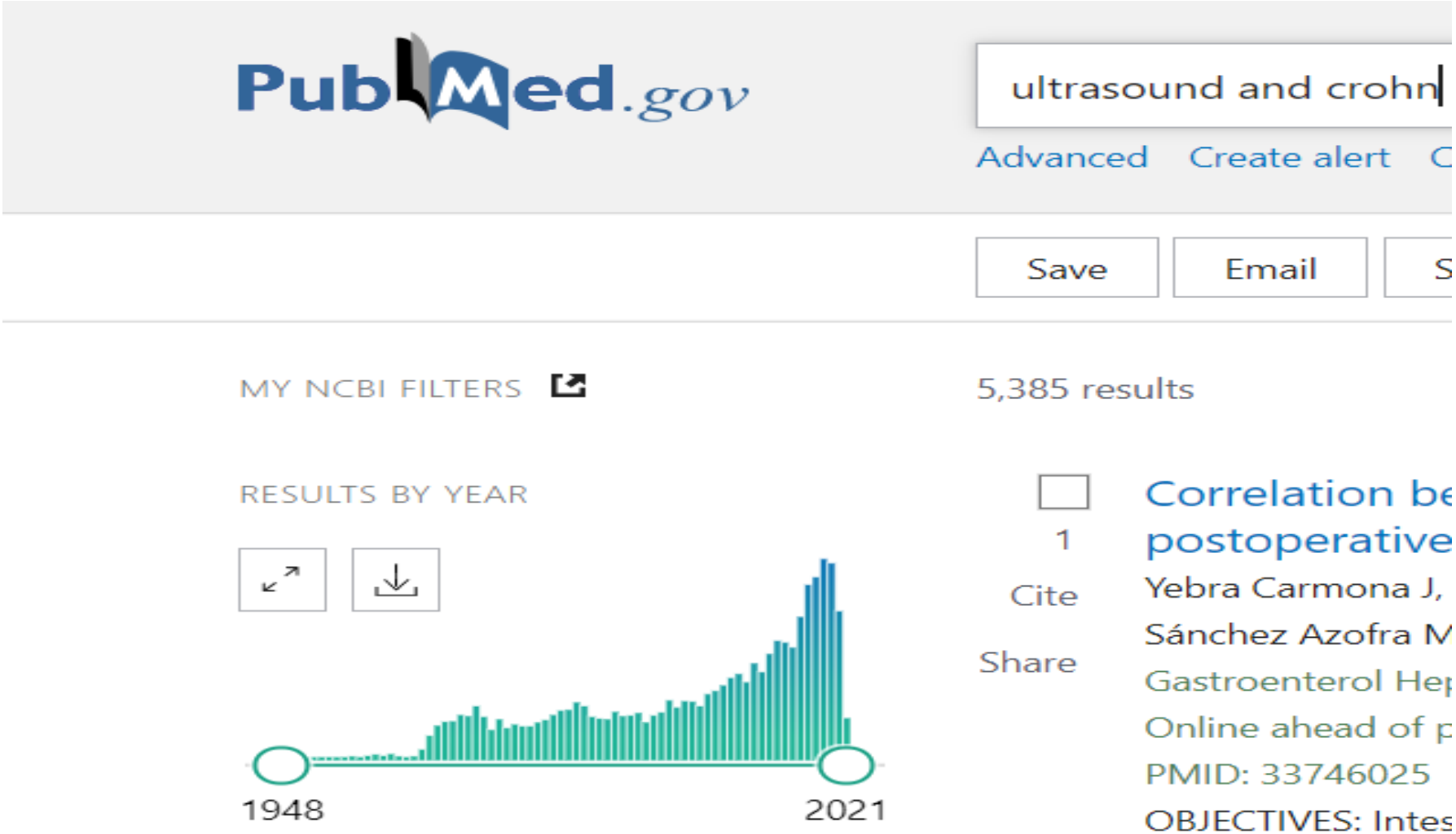
Ultrasound as a future monitoring tool for UC?





Allocca M, et al. *J Crohns Colitis* 2018;12:1385–1391

Publications sur « Crohn » and « Ultrasound »



IUS directly reflects transmural disease activity[1]

IUS parameters for disease activity:

Bowel wall thickness

Normal: terminal ileum:
≤2 mm; colon: ≤3 mm

Vascularization: colour Doppler signal

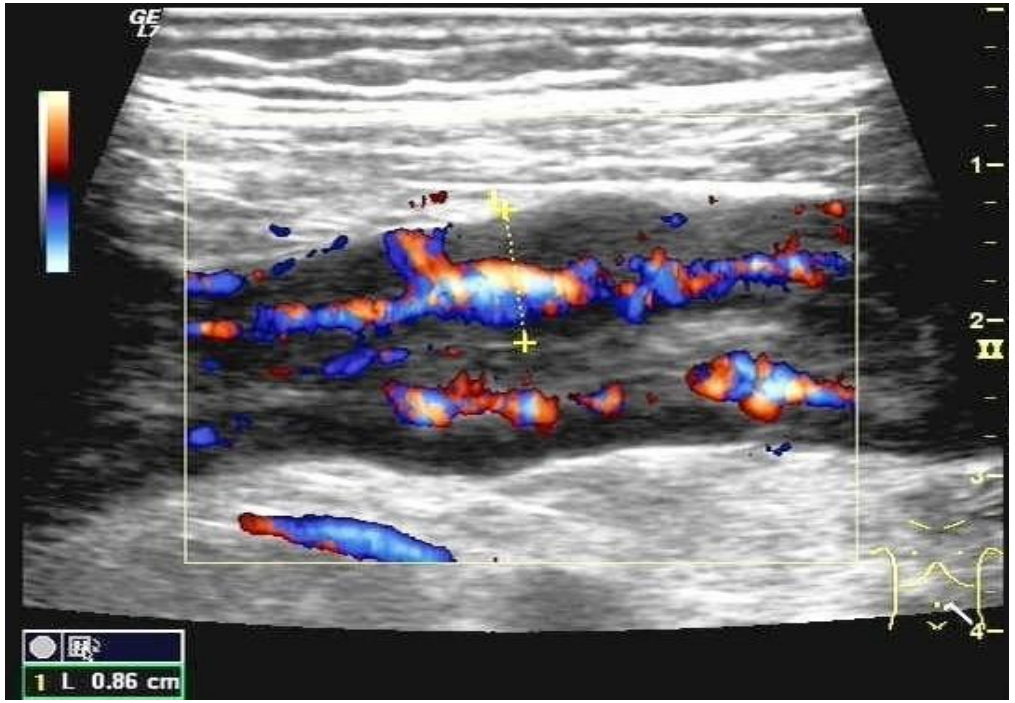
0 – No signal
1– Minimal pixels, scant
2– Increased colour signal limited to the wall
3 – Signal is significant in the wall as well as the mesentery

Echostratification assessment

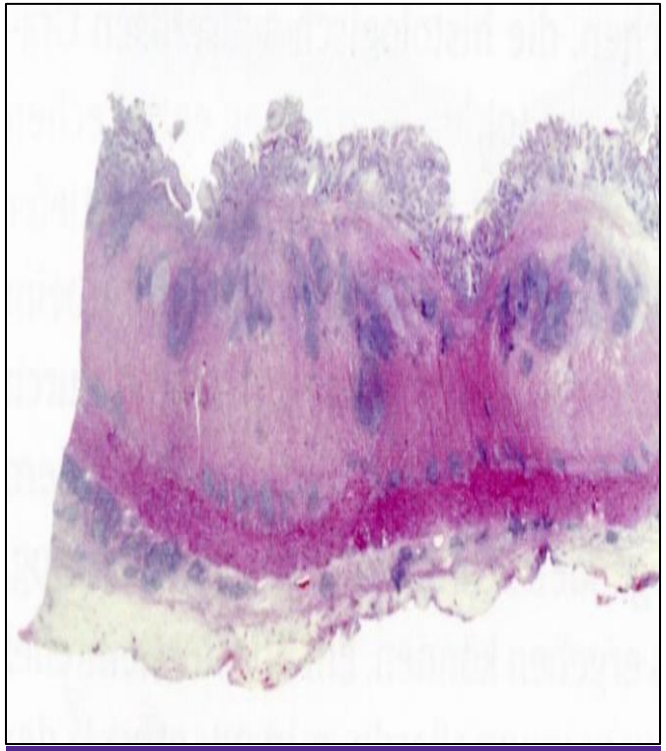
- Normal/preserved echostratification
- Uncertain presence of echostratification
- Focal disruption (<3 cm)
- Extensive disruption (>3 cm)

Inflammatory mesenteric fat assessment

- Absent
- Uncertain (increased fat is possible – either the image quality or the views are insufficient to determine the contribution)
- Present



IUS image of active CD



Histology of active CD

IUS remission (transmural healing): defined as normalization of BWT (terminal ileum: ≤2 mm; colon: ≤3 mm), vascularization (colour Doppler signal 0 or 1), normal echostratification and absent inflammatory mesenteric fat (based on most affected part of the bowel).

©ECCO 2020 Vienna Congress – Speaker: T. Kucharzik

1. Wilkens RT, et al. *J Crohn's Colitis.* 2020;14(suppl 1):S225–S226.

BWT, bowel wall thickness; CD, Crohn's disease; IUS, intestinal ultrasound

Aliment Pharmacol Ther. 2021 Apr;53(8):873-886. doi: 10.1111/apt.16288. Epub 2021 Feb 28.

Standardisation of intestinal ultrasound scoring in clinical trials for luminal Crohn's disease

Thomas M Goodsall [1], Vipul Jairath [2], Brian G Feagan [2], Claire E Parker [2], Tran M Nguyen [2], Leonardo Guizzetti [2], Anil K Asthana [3], Jakob Begun [4], Britt Christensen [3], Antony B Friedman [3], Torsten Kucharzik [5], Andrew Lee [4], Peter J Lewindon [4], Christian Maaser [5], Kerri L Novak [6], Jordi Rimola [7], Kirstin M Taylor [3], Stuart A Taylor [8], Lauren S White [4], Rune Wilkens [9], Stephanie R Wilson [6], Emily K Wright [3], Robert V Bryant [1], Christopher Ma [6]

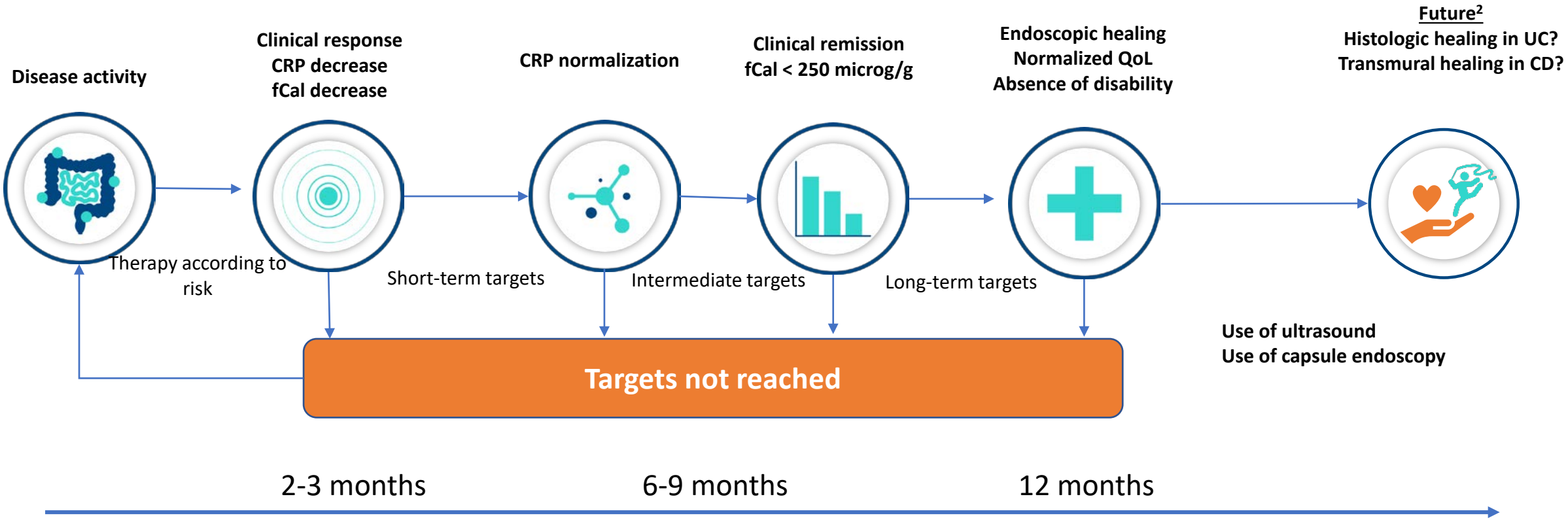
- Items considered appropriate measures of disease activity were:
  - bowel wall thickness (BWT)
  - vascularity
  - Stratification
  - mesenteric inflammatory fat
- There was uncertainty if any of the existing IUS disease activity indices were appropriate for use in CD clinical trials.
- At outcome assessment, remission endpoints including BWT and vascularity, with or without mesenteric inflammatory fat, were considered appropriate.

Definition of an optimal timing

- Avoid prolonged ineffective treatment
- Avoid to discard potentially effective treatment
- Avoid disease progression and cumulative tissue damage
- Avoid complications
- Ability to predict longer term outcome

Different monitoring tools at different time-points

Treat-to-target approach[1]



1. Turner D, et al. Gastroenterology. 2021;160:1570-83.
2. Le Berre C, et al. Gastroenterology, 2022, online ahead of print.

Fecal calprotectin at Week 6 best predicts endoscopic remission at week 52 in CD patients treated with **ustekinumab**

677 CD patients included in UNITI/IMUNITI and treated with ustekinumab

Predictor	Unadjusted OR	*p*-value	Adjusted OR[b]	*p*-value	Adjusted OR[c] [including disease duration]	*p*-value
Week 6 FC <250	4.45 [1.78–11.13]	0.001	3.48 [1.31–9.28]	0.013	2.58 [0.75–8.90]	0.133
Week 6 clinical response	0.82 [0.35–1.88]	0.630	1.02 [0.42–2.49]	0.962	0.64 [0.19–2.16]	0.471
Week 6 clinical remission	0.91 [0.37–2.25]	0.844	1.45 [0.53–3.96]	0.466	0.32 [0.08–1.22]	0.095
Week 6 CRP <5	2.12 [0.90–5.00]	0.088	1.95 [0.80–4.77]	0.142	2.50 [0.72–8.65]	0.149
Week 6 ustekinumab drug level [continuous]	1.01 [0.96–1.08]	0.647	1.02 [0.96–1.09]	0.551	1.03 [0.94–1.14]	0.515
Week 6 FC <250 and Week 6 clinical response	3.03 [1.18–7.76]	0.021	2.98 [1.09–8.15]	0.033	1.47 [0.41–5.31]	0.559
Week 6 FC <250 and Week 6 clinical remission	1.71 [0.59–4.94]	0.320	1.74 [0.55–5.48]	0.347	0.45 [0.01–2.04]	0.303
Week 6 FC <250 and Week 6 CRP <5	3.34 [1.39–8.02]	0.007	2.68 [1.08–6.65]	0.034	2.49 [0.72–8.65]	0.152
Week 8 endoscopic response [SES-CD improvement >50%]	0.433 [0.107–1.757]	0.242	0.375 [0.088–1.599]	0.185	1.861 [0.056–62.202]	0.729

Narula et al. Journal of Crohn's and Colitis, 2021, 462–470

Fecal calprotectin at week 10 best predicts clinical remission at week 58 in IC patients treated with **filgotinib**

Table 3. Prognostic value of FC concentration and invasive and non-invasive assessments at week 10 for clinical remission at week 58 in patients receiving filgotinib 200 mg.

		Clinical remission				ROC curve	Logistic regression	
		Yes	No	PPV	NPV	AUC (95% CI)	Odds ratio (95% CI)	*p* value[a]
FC <250 µg/g	**Yes**	51 (47.2%)	57 (52.8%)	47.2%	–	0.606	2.440	0.0046
	No	22 (26.8%)	60 (73.2%)	–	73.2%	(0.536–0.676)	(1.316–4.525)	
pMCS remission	**Yes**	61 (42.1%)	84 (57.9%)	42.1%	–	0.576	2.290	0.0213
	No	13 (24.1%)	41 (75.9%)	–	75.9%	(0.516–0.636)	(1.131–4.638)	
Endoscopic response	**Yes**	37 (50.7%)	36 (49.3%)	50.7%	–	0.606	2.472	0.0030
	No	37 (29.4%)	89 (70.6%)	–	70.6%	(0.536–0.676)	(1.359–4.495)	
Geboes histological remission	**Yes**	32 (45.1%)	39 (54.9%)	45.1%	–	0.559	1.661	0.0953
	No	42 (33.1%)	85 (66.9%)	–	66.9%	(0.489–0.629)	(0.915–3.014)	
FC <250 µg/g and Geboes histological remission	**Yes**	27 (50.0%)	27 (50.0%)	50.0%	–	0.570	1.957	0.0401
	No	46 (33.8%)	90 (66.2%)	–	66.2%	(0.502–0.637)	(1.031–3.714)	
FC <250 µg/g and Geboes histological remission and endoscopic response	**Yes**	20 (60.6%)	13 (39.4%)	60.6%	–	0.581	3.018	0.0051
	No	53 (33.8%)	104 (66.2%)	–	66.2%	(0.523–0.640)	(1.394–6.536)	
FC <250 µg/g and pMCS remission	**Yes**	45 (51.7%)	42 (48.3%)	51.7%	–	0.629	2.870	0.0006
	No	28 (27.2%)	75 (72.8%)	–	72.8%	(0.558–0.700)	(1.568–5.252)	

[a]All *p* values are nominal.

AUC, area under the ROC curve; CI, confidence interval; FC, faecal calprotectin; NPV, negative predictive value; pMCS, partial Mayo Clinic Score; PPV, positive predictive value; ROC, receiver operating characteristic.

E Louis et al. UEGW 2022

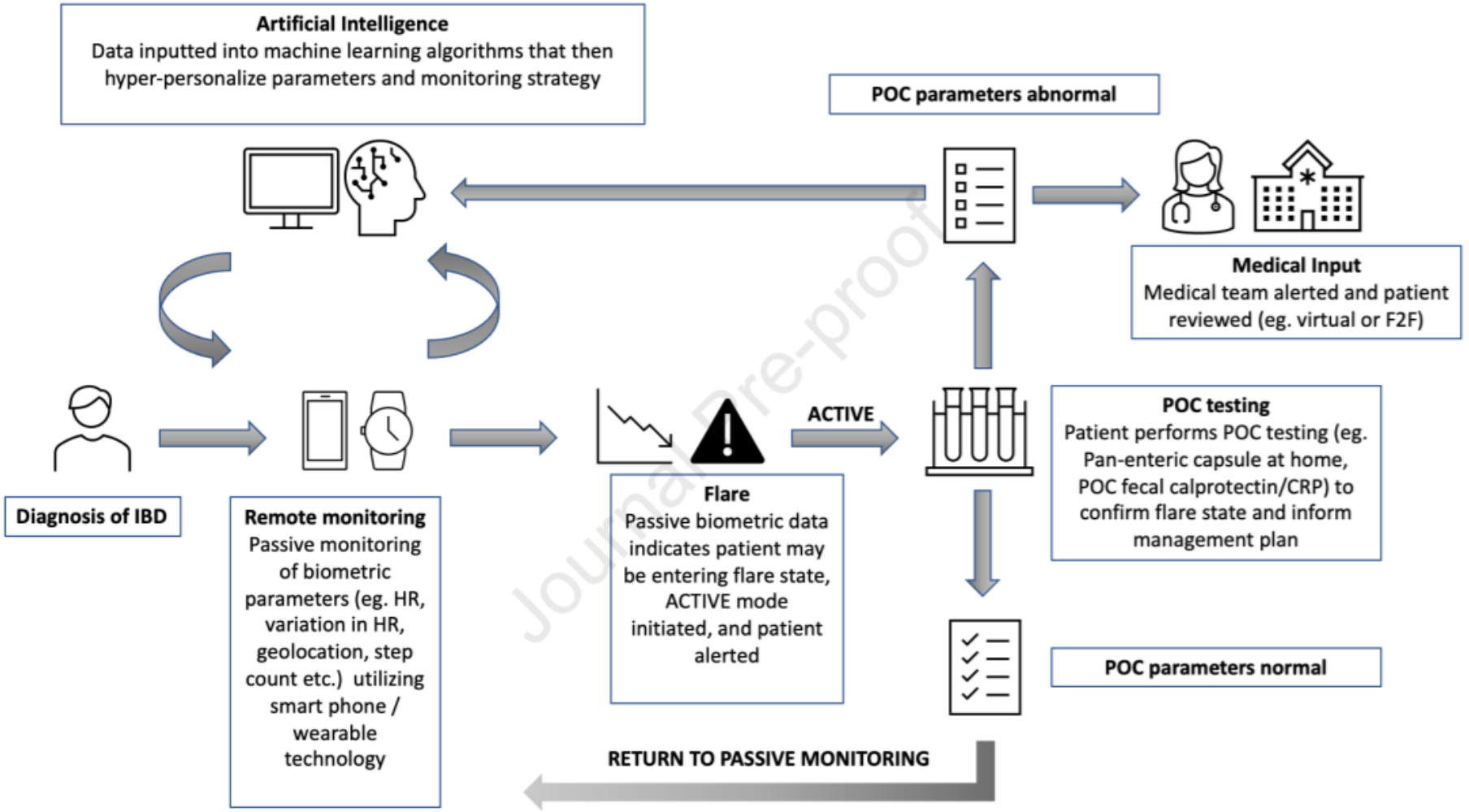
Monitoring strategy over the disease course: a tailored approach

- Before treatment start
  - CRP, fCal, US
  - Endoscopy, MRI
- Induction
  - CRP, fCal, US at 3 months and 6 months
- Maintenance
  - CRP, fCal, US every 6 months
  - Endoscopy/MRI at 12 months combined with non-invasive test and then non-invasive test
- De-escalation or elective switch
  - CRP, fCal, US
  - Endoscopy, MRI

  } Before change

  - CRP, fCal, US every 3 months for 1 year

The future of monitoring using AI



Journal Pre-proof

Plevris and Lees. Gastroenterology 2022 Jan 28;S0016-5085(22)00078-6.
doi: 10.1053/j.gastro.2022.01.024

Conclusions

Un monitoring optimal des MICI devrait combiner:

- Une utilisation régulière de tests et outils non invasifs à haute valeur informative (biomarqueurs sanguins, selles, échographie,...)
- Une utilisation plus occasionnelle de l'imagerie endoscopique ou IRM

Janssen IUS Course in IBD *(JIUS Course)*

- **What?**
  - Co-create **Medical Education Course of 1-year** with Philips ***(in English)***
  - 2 Introduction & 3 return days
- **Faculty**:
  - Prof. Dr. Pieter Dewint (AZ Maria Middelares)
  - Dr. Barbara Willandt (AZ Sint Jan Brugge)
  - Dr. Bram Verstockt (UZ Leuven)
- **3rd Edition (2023) due to great evaluation & Success !!**
  - Limited 8-10 places
  - Contact MSL Janssen (Cheyma Rhimi)
- **Needed for the course attendance:**
  - Dedication & Time
  - Enough resources to practice on your own
  - IUS Echo device in your hospital