# Monitoring IBD in 2021

## Combined, objective, scores?

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# Disclosures

- **PLL has been a speaker and/or advisory board member: AbbVie, Amgen, Arena Pharmaceuticals, Fresenius Kabi, Genetech, Gilead, Janssen, Merck, Mylan, Pharmacosmos, Pfizer, Roche, Takeda, Tillots and Viatris**

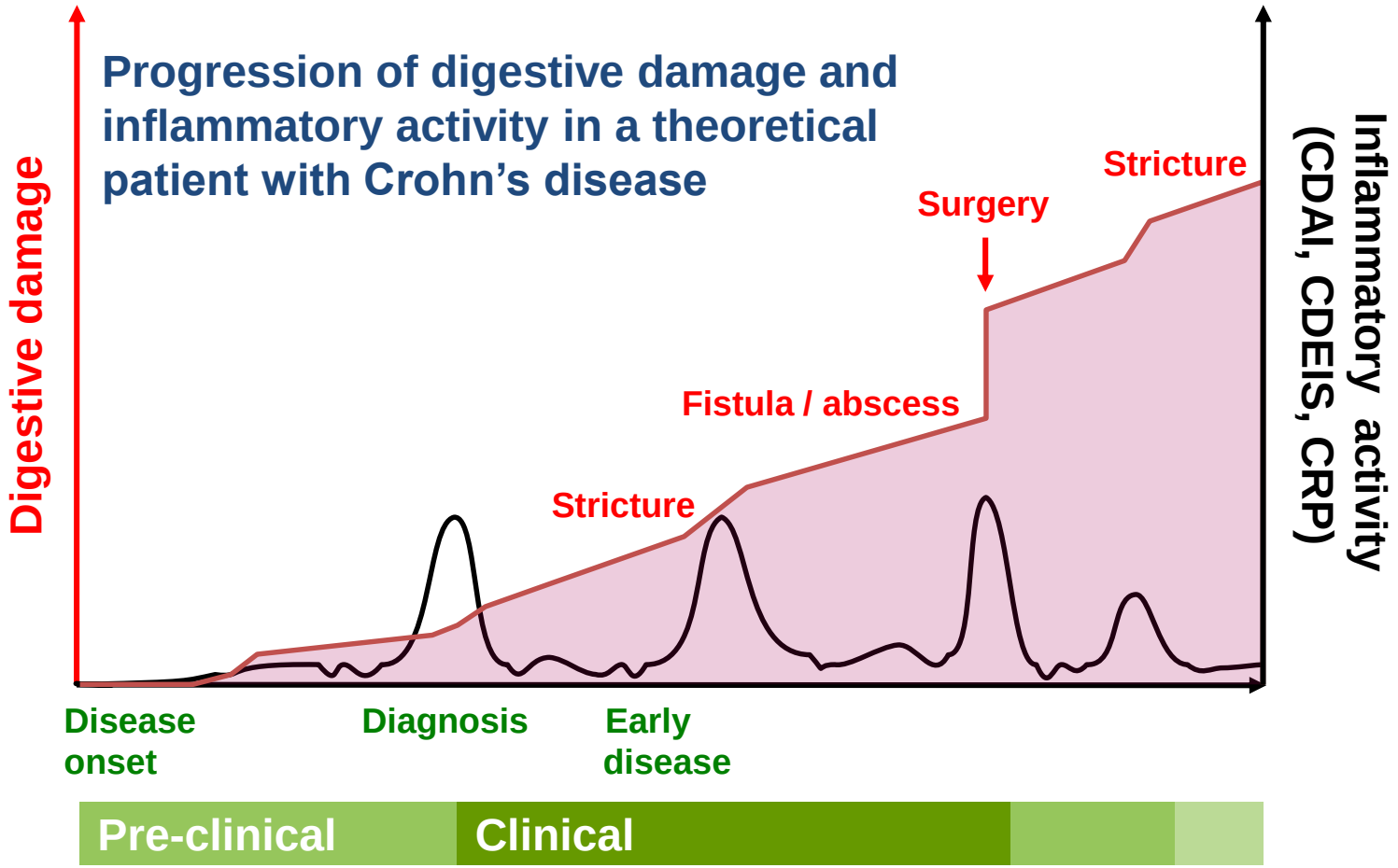
- **and has received unrestricted research grant: AbbVie, MSD and Pfizer.**

# Objectives

- To discuss
- Importance of patient stratification: natural Hx
- Maximise outcomes: Set treatment goals!
- How to monitor/engage our patients?

# Do IBD patients progress? „natural history”

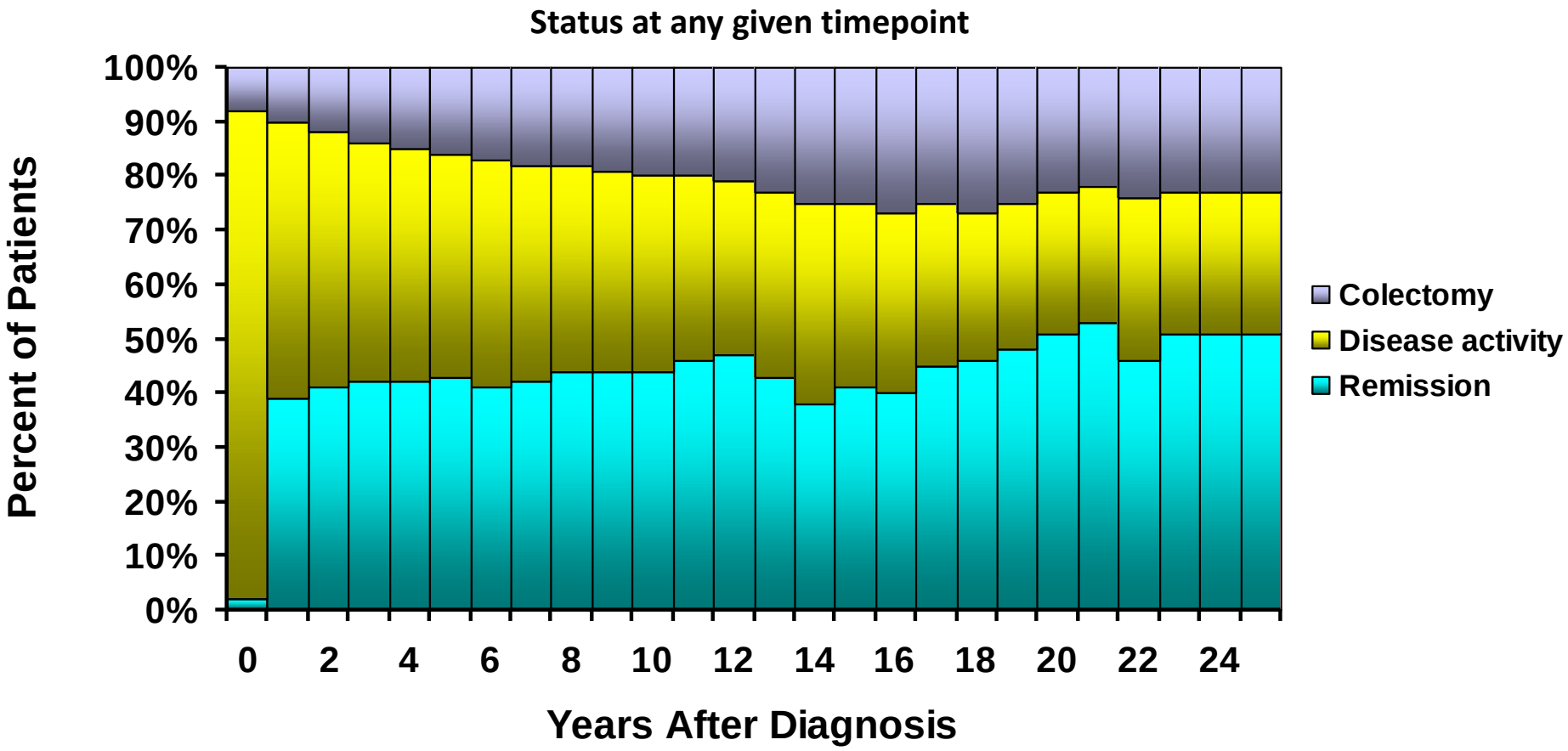
# Inflammation is ongoing and resulting tissue damage is cumulative




**CDAI: Crohn's disease activity index; CDEIS: Crohn's disease endoscopic index of severity; CRP: C-reactive protein**

**Pariente B, *et al. Inflamm Bowel Dis* 2011**

# Natural History of Ulcerative Colitis*



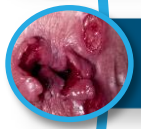

Langholz E et al. Gastroenterology. 1994;107:3.

# PREDICTORS: Possible factors associated with severe course of Crohn's disease have been proposed

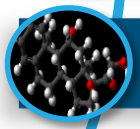
**Young-adult age** (Beaugerie L, *et al. Gastroenterology* 2006;130:650–6; Franchimont DP, *et al. Eur J Gastroenterol Hepatol* 1998;10: 821–5)

**Smoking** (Franchimont DP, *et al. Eur J Gastroenterol Hepatol* 1998;10: 821–5; Lakatos P, *et al. Inflamm Bowel Dis* 2013;19:1010–7)

**Extensive small bowel disease** (Munkholm P, *et al. Gastroenterology* 1993;105:1716–23)

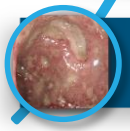


**Perianal disease** (Beaugerie L, *et al. Gastroenterology* 2006;130:650–6; Loly C, *et al. Scand J Gastro* 2008;43:948–54)



**Steroids at diagnosis** (Beaugerie L, *et al. Gastroenterology* 2006;130:650–6; Loly C, *et al. Scand J Gastr* 2008;43:948–54

**Weight loss** (Loly C, *et al. Scand J Gastro* 2008;43:948–54)



**Deep ulcerations at endoscopy** (Allez M, *et al. Am J Gastroenterol* 2002;97:947–53)

# How to monitor/engage our patients better?

# Where during the course of IBD are markers needed?

- Diagnosis and differential diagnosis?

- **Short term prediction**:
  - Assessement of disease activity?

- **Long term prediction**:
  - Prognosis and risk for complications?
  - Optimazing drug therapy and side effects?
  - Risk for post-operative recurrence?

# What are the clinical activity indices – validated and used in CD?

- IOIBD Position papers –"guidance"

GASTROENTEROLOGY 2002;122:512–530

## SPECIAL REPORTS AND REVIEWS

### A Review of Activity Indices and Efficacy Endpoints for Clinical Trials of Medical Therapy in Adults With Crohn's Disease

WILLIAM J. SANDBORN,*,† BRIAN G. FEAGAN,§ STEPHEN B. HANAUER,*,† HERBERT LOCHS,* ROBERT LÖFBERG,* ROBERT MODIGLIANI,*,‖ DANIEL H. PRESENT,*,† PAUL RUTGEERTS,* JURGEN SCHÖLMERICH,* EDUARD F. STANGE,* and LLOYD R. SUTHERLAND*

*The Clinical Trials Task Force of the International Organization of Inflammatory Bowel Disease (IOIBD), †The Clinical Alliance of the Cr and Colitis Foundation of America, the §Clinical Network of the Crohn's and Colitis Foundation of Canada, and the ‖Groupe d'Etude Therapeutique des Affections Inflammatoires Digestives. See Appendix I for institutional affiliations for each author and for the comple membership of the IOIBD Clinical Trials Task Force

## CDAI

**Table 1.** Crohn's Disease Activity Index

| Variable no. | Variable description | Multiplier | Total |
|---|---|---|---|
| 1 | No. of liquid or soft stools (each day for 7 days) | ×2 | |
| 2 | Abdominal pain, sum of 7 daily ratings (0 = none, 1 = mild, 2 = moderate, 3 = severe) | ×5 | |
| 3 | General well-being, sum of 7 daily ratings (0 = generally well, 1 = slightly under par, 2 = poor, 3 = very poor, 4 = terrible) | ×7 | |
| 4 | Number of listed complications (arthritis or arthralgia, iritis or uveitis, erythema nodosum or pyoderma gangrenosum or aphthous stomatitis, anal fissure or fistula or abscess, other fistula, fever over 37.8°C [100°F]) | ×20 | |
| 5 | Use of diphenoxylate or loperamide for diarrhea (0 = no, 1 = yes) | ×30 | |
| 6 | Abdominal mass (0 = no, 2 = questionable, 5 = definite) | ×10 | |
| 7 | Hematocrit (males, 47-Hct [%], females, 42-Hct [%]) | ×6 | |
| 8 | Body weight (1-weight/standard weight) × 100 (add or subtract according to sign) | ×1 | |
| CDAI score | | | |

Adapted with permission from Best WR, Becktel JM, Singleton JW. Rederived values of the eight coefficients of the Crohn's Disease Activity Index (CDAI). Gastroenterology 1979;77:843–846.

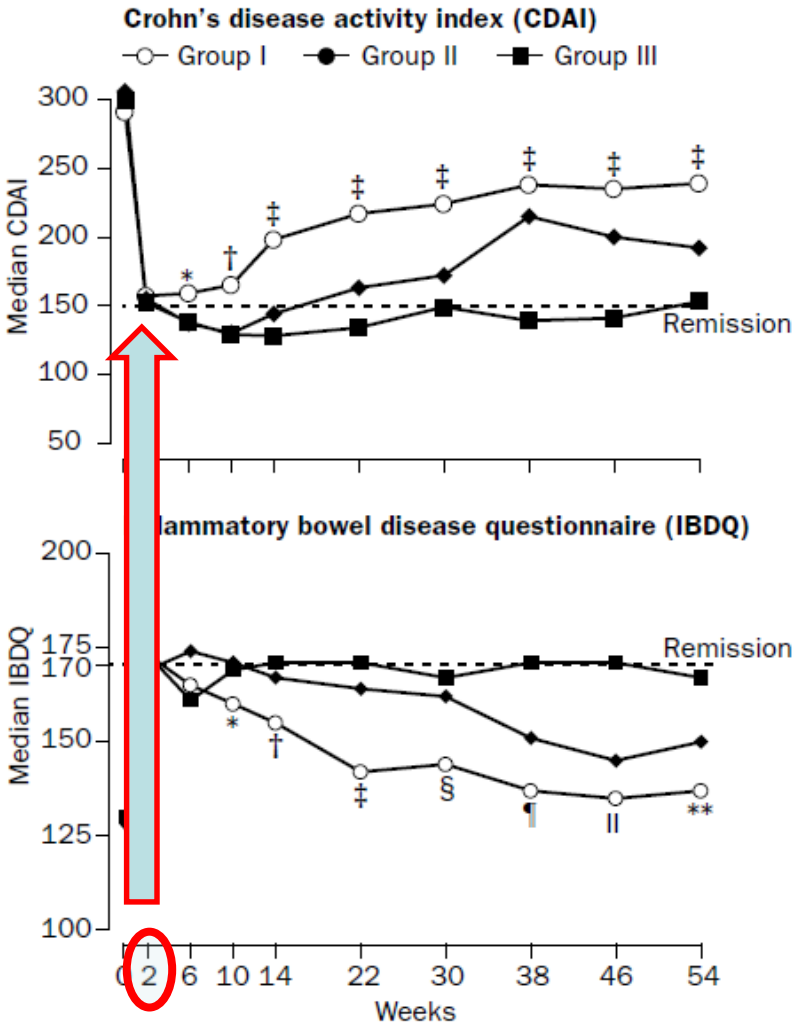
## HBI

**Table 2.** Harvey Bradshaw Index (HBI, Simple Index)

| Variable no. | Variable description | Total |
|---|---|---|
| 1 | General well being (0 = very well, 1 = slightly below par, 2 = poor, 3 = very poor, 4 = terrible) | |
| 2 | Abdominal pain (0 = none, 1 = mild, 2 = moderate, 3 = severe) | |
| 3 | Number of liquid stools daily | |
| 4 | Abdominal mass (0 = none, 1 = dubious, 2 = definite, 3 = definite and tender) | |
| 5 | Complications: arthralgia, uveitis, erythema nodosum, apthous ulcer, pyoderma gangrenosum, anal fissure, new fistula, abscess (score 1 per item) | |
| HBI Score | | |

Adapted with permission from Harvey RF, Bradshaw JM. A simple clinical index of Crohn's disease activity. Lancet 1980;1:514.

# How-quickly are they changeing meaningfully??




*Hanauer Lancet 2002 ACCENT I*

# Activity indices for UC

| | | |
|---|---|---|
| 1. | Truelove and Witts' | *BMJ* 1955;2:1041-8 |
| 2. | Powell Tuck/St Marks | *Scand J Gastro* 1978;13:833-7 |
| 3. | Sutherland/DAI/UCDAI | *Gastroenterology* 1987;92:1894-8 |
| 4. | Mayo/Disease Activity Index | *NEJM* 1987;317:1625-9 |
| 5. | Clinical Activity Index/CAI/Rachmilewitz | *BMJ* 1989;298:82-6 |
| 6. | Lichtiger/Modified T&W Severity Index | *Lancet* 1990;336:16-9 |
| 7. | Activity Index/Seo | *Am J Gastro* 1992;87:971-6 |
| 8. | Simple Clinical Colitis Index/Walmsley | *Gut* 1998;43:29-32 |
| 9. | Ulcerative Colitis Clinical Score | *NEJM* 2005;352:2499-507 |

**Number of different indices:**

**9 Clinical and biochemical activity**

**9 Endoscopic activity**

**4 Clinical and endoscopic**

**2 Quality of life**

**9 Histological activity**

***D'Haens & Sandborn et al Gastroenterology 2006***

# PRO outcomes: is the future now?

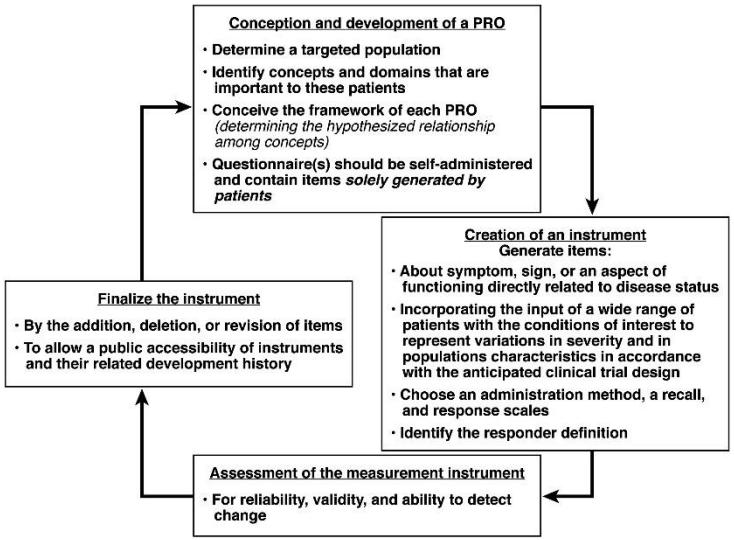
**Patients reported outcomes (PRO)**

- **New requirements from FDA**
- **The aim is to decrease the subjectivity of the clinical scores**
- **However, they pick only components of existing scores**
  - **Suggested for CD: abdominal pain and stool frequency (the same for IBS!)**
  - **Suggested for UC: stool frequency and bloody stool number**
- **The future is not clear**
- **How to use them in clinical practice?**
- **Not ready for prime time**

**Supplementary Table 1.** PRO Instruments Identified in a PubMed Literature Search From January 1966 to October 2013

| PRO | Instruments | Study | No. of studies in IBD |
|---|---|---|---|
| Quality of life | | | |
| | IBDQ-32 | Guyatt et al, 1989[3] | 214 |
| | IBDQ-36 | Love et al, 1992[4] | |
| | Short IBDQ (SIBDQ) | Irvine et al, 1996[5] | 28 |
| | RFIPC | Drossman et al, 1991[13] | 35 |
| | SF-36 | Ware and Sherbourne, 1992[14] | 106 |
| | EuroQol-5D | Jenkinson et al, 1997[15] | 36 |
| | Cleveland | Kiran et al, 2003[16] | 17 |
| | Visual analogue scale | Grunberg et al, 1996[17] | 20 |
| | IMPACT questionnaire | Otley et al, 2002[18] | 6 |
| | PedsQL | Varni et al, 1999[19] | 5 |
| Work productivity | | | |
| | WPAI(:CD) | Reilly et al, 1993[7] and 2008[8] | 9 |
| Disability | | | |
| | IBD Disability Index | Peyrin-Biroulet et al, 2012[12] | 1 |
| Fatigue | | | |
| | Fatigue questionnaire | | 4 |
| | MFI | Smets et al, 1995[20] | 7 |
| | FACIT | Yellen et al, 1997[6] | 2 |
| | Piper Fatigue scale | Piper, 1990[21] | 1 |
| | Fatigue impact scale | Fisk et al, 1994[22] | 6 |
| Depression and anxiety | | | |
| | HADS | Zigmond and Snaith, 1983[10] | 51 |
| | BDI | Beck et al, 1961[11] | 18 |
| | Z-self rating depression scale | Zung, 1972[9] | 3 |
| | State trait anxiety inventory | Spielberg et al, 1970[23] | 6 |

BDI, Beck's Depression Inventory; HADS, Hospital Anxiety and Depression Scale; MFI, Multidimensional Fatigue Inventory; RFIPC, rating form of IBD patient concerns.




*http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf*

*Willet N Clin Gastroent Hepatol 2014;12:1246*

# What are the endoscopic activity indices – validated and used in CD?

- IOIBD Position papers –"guidance"

GASTROENTEROLOGY 2002;122:512–530

## SPECIAL REPORTS AND REVIEWS

### A Review of Activity Indices and Efficacy Endpoints for Clinical Trials of Medical Therapy in Adults With Crohn's Disease

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## PDAI

**Table 3.** Perianal Crohn's Disease Activity Index

| Categories affected by fistulas | Score |
|---|---|
| Discharge | |
| No discharge | 0 |
| Minimal mucous discharge | 1 |
| Moderate mucous or purulent discharge | 2 |
| Substantial discharge | 3 |
| Gross fecal soiling | 4 |
| Pain/restriction of activities | |
| No activity restriction | 0 |
| Mild discomfort, no restriction | 1 |
| Moderate discomfort, some limitation of activities | 2 |
| Marked discomfort, marked limitation | 3 |
| Severe pain, severe limitation | 4 |
| Restriction of sexual activity | |
| No restriction sexual activity | 0 |
| Slight restriction sexual activity | 1 |
| Moderate limitation sexual activity | 2 |
| Marked limitation sexual activity | 3 |
| Unable to engage in sexual activity | 4 |
| Type of perianal disease | |
| No perianal disease/skin tags | 0 |
| Anal fissure or mucosal tear | 1 |
| <3 Perianal fistulae | 2 |
| ≥3 Perianal fistulae | 3 |
| Anal sphincter ulceration or fistulae with significant undermining of skin | 4 |
| Degree of induration | |
| No induration | 0 |
| Minimal induration | 1 |
| Moderate induration | 2 |
| Substantial induration | 3 |
| Gross fluctuance/abscess | 4 |

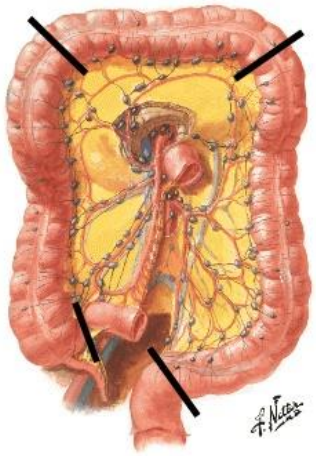
Reprinted from Irvine EJ. Usual therapy improves perianal Crohn's disease as measured by a new disease activity index. McMaster IBD Study Group. J Clin Gastroenterol 1995;20:27–32.

## CDEIS-SES-CD and Rutgeerts score

**Table 5.** Crohn's Disease Endoscopic Index of Severity

| Variable no. | Variable description | Weighing factor | Total |
|---|---|---|---|
| 1 | Number of rectocolonic segments (rectum, sigmoid and left colon, transverse colon, right colon, ileum) that deep ulcerations are seen in divided by the number of segments examined | 12 | |
| 2 | Number of rectocolonic segments (rectum, sigmoid and left colon, transverse colon, right colon, ileum) that superficial ulcerations are seen in divided by the number of segments examined | 6 | |
| 3 | Segmental surfaces involved by disease. The degree of disease involvement in each segment is determined by examining each segment for the following 9 lesions (pseudopolyps, healed ulcerations, frank erythema, frank mucosal swelling, aphthoid ulcers, superficial ulcers, deep ulcers, nonulcerated stenosis, ulcerated stenosis) and estimating the number of cm of involvement (1 or more lesions present) in a representative 10 cm portion from each segment. The average segmental surface involved by disease is calculated by dividing the sum of each of the individual segmental surfaces involved by disease by the number of segments examined | 1 | |
| 4 | Segmental surfaces involved by ulcerations. The degree of ulceration in each segment is determined by examining each segment for ulceration (aphthoid ulcers, superficial ulcers, deep ulcers, ulcerated stenosis) and estimating the number of cm of intestine involved by ulceration in a representative 10 cm portion from each segment. The average segmental surface involved by ulceration is calculated by dividing the sum of each of the individual segmental surfaces involved by ulceration by the number of segments examined | 1 | |
| 5 | Presence of a nonulcerated stenosis in any of the segments examined | 3 | |
| 6 | Presence of an ulcerated stenosis in any of the segments examined | 3 | |
| Total CDEIS | | | |

Adapted with permission from Groupe D'Etudes Therapeutiques Des Affections Inflammatories Du Tube Digestif (GTEAID) presented by Mary JY, Modigliani R. Development and validation of an endoscopic index of the severity for Crohn's disease: a prospective multicentre study. Gut 1989;30:983–989.



## Improvement vs Remission

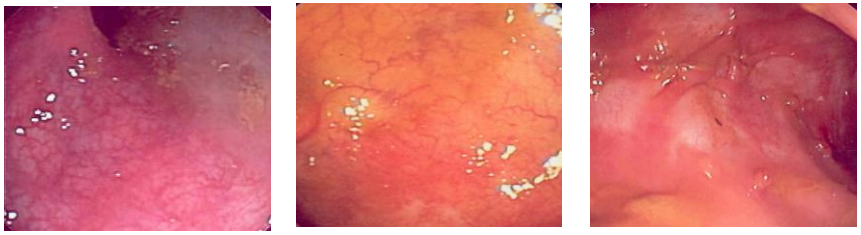
**Table 4.** Fistula Drainage Assessment

| Endpoint | Definition |
|---|---|
| Improvement | Closure of individual fistulas defined as no fistula drainage despite gentle finger compression. Improvement defined as a decrease from baseline in the number of open draining fistulas of ≥50% for at least 2 consecutive visits (i.e., at least 4 weeks) |
| Remission | Closure of individual fistulas defined as no fistula drainage despite gentle finger compression. Remission defined as closure of all fistulas that were draining at baseline for at least 2 consecutive visits (i.e., at least 4 weeks) |

Modified with permission from Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999;340:1398–1405.

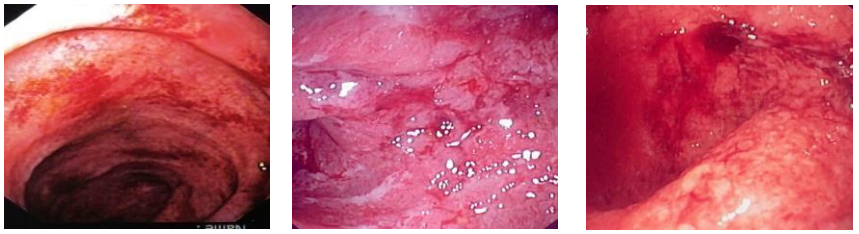
# Mayo sub-Score (DAI)

**score 0** — normal or healed mucosa

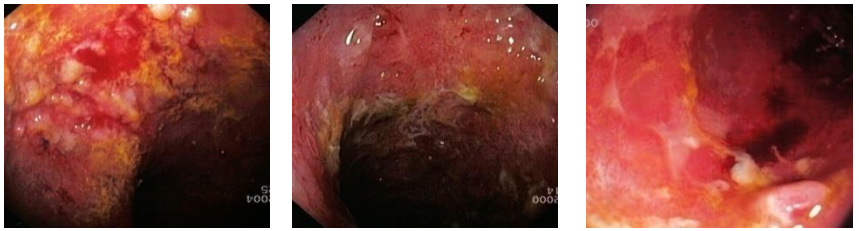


**score 1** — faded vascular pattern
mild friability
erythema

**score 2** — absent vascular pattern
marked friability
erosions



**score 3** — spontaneous bleeding
large ulcers



Schroeder KW et al, NEJM, 1987

# The definition of MH is still heterogenous

## Crohn's disease

- No mucosal ulceration in any of 5 segments
- Absence of mucosal ulceration
- Disappearance of all ulcerative lesions
- CDEIS ≤2, ≤3, ≤4, ≤6
- SES-CD ≤5
- Rutgeerts score ≤i1

## Ulcerative colitis

- Normal, improved, no change or worse
- Severity of bleeding without considering ulcers
- UC-DAI≤1
- Mayo≤1

Need for homogenous definition of mucosal healing
No score available for small bowel disease

# Current definitions of MH in IBD proposed for clinical trials

## Crohn's disease

- Endoscopic response:
  - >50% decrese of SES-CD
- Endoscopic remission:
  - SES-CD ≤2
- Post-surgery:
  - Rutgeerts score ≤i1

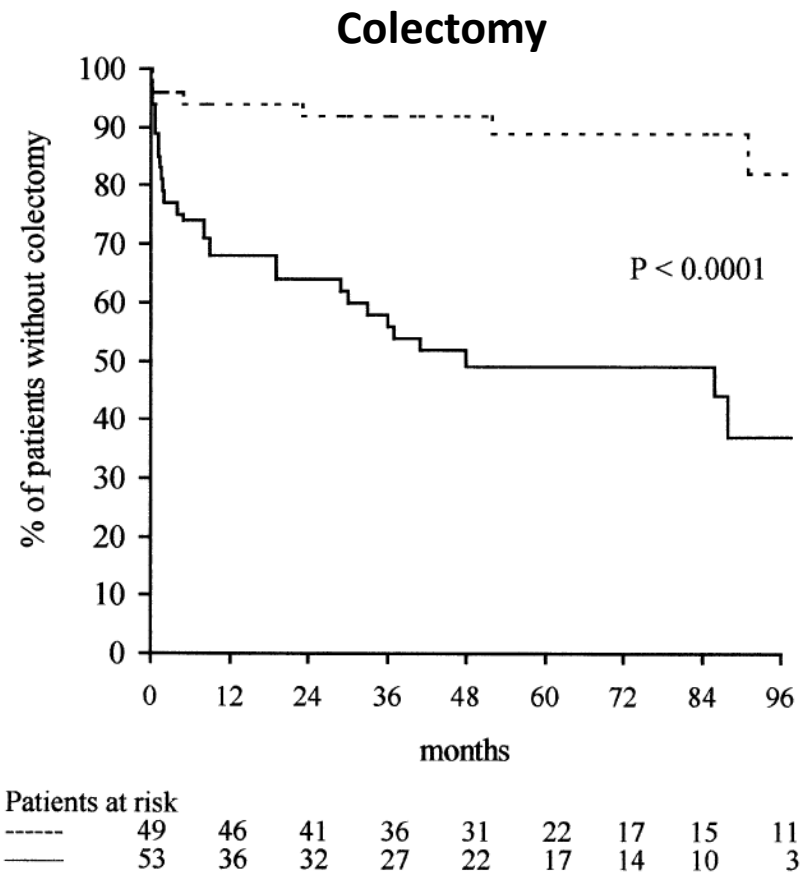
## Ulcerative colitis

- Endoscopic response
  - Improvement of Mayo ≥1 grade or UCEIS ≥2 points
- Endoscopic remission
  - UCEIS: 0

Vuitton L et al IOIBD GUT 2016:65:1447

Vuitton L et al APT 2017:45:801

# Severity of Endoscopic Lesions and Long Term Outcome in CD

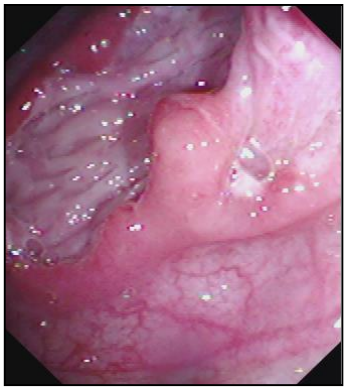



**Severe Endoscopic Lesions:**
**Deep ulcerations > 10% surface of one segment**

- **Independent risk factors for colectomy:**
  - **Severe endoscopic lesions RR: 5.43 (2.64 –11.18)**
  - **CDAI > 288**

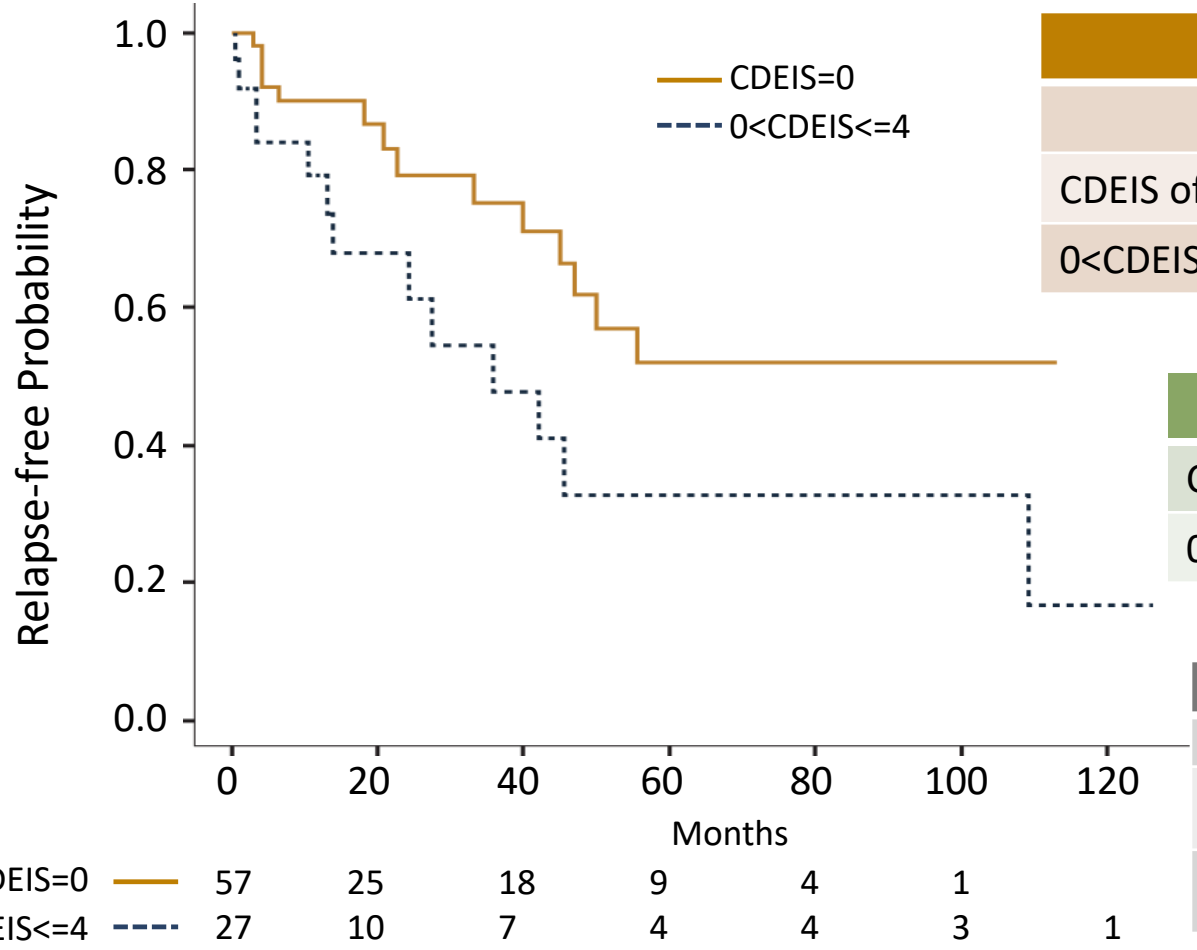
    **RR 2.21 (1.09–4.47)**
  - **No immunosuppressive therapy**

    **RR: 2.44 (1.20 –5.00).**



**Allez M et al. *Am J Gastroenterol* 2002;97:947–53.**

# Complete endoscopic healing is associated with better long-term outcomes than partial endoscopic healing




| Risk of treatment failure | | | |
|---|---|---|---|
| | Year 1 | Year 3 | *p* |
| CDEIS of 0 | 9% | 19% | 0.28 |
| 0<CDEIS<4 | 16% | 37% | 0.049 |

| Rates of treatment failure | | |
|---|---|---|
| CDEIS of 0 | 25% | |
| 0<CDEIS<4 | 48% | *p*=0.045 |

| Distribution of medications was as follows: | | | | |
|---|---|---|---|---|
| | IFX | ADA | VEDO | IS |
| CDEIS of 0 | 80.7 % | 15.8% | 3.5% | 38.6% |
| CDEIS 0 to < 4 | 74.1 % | 18.5% | 7.4% | 37% |

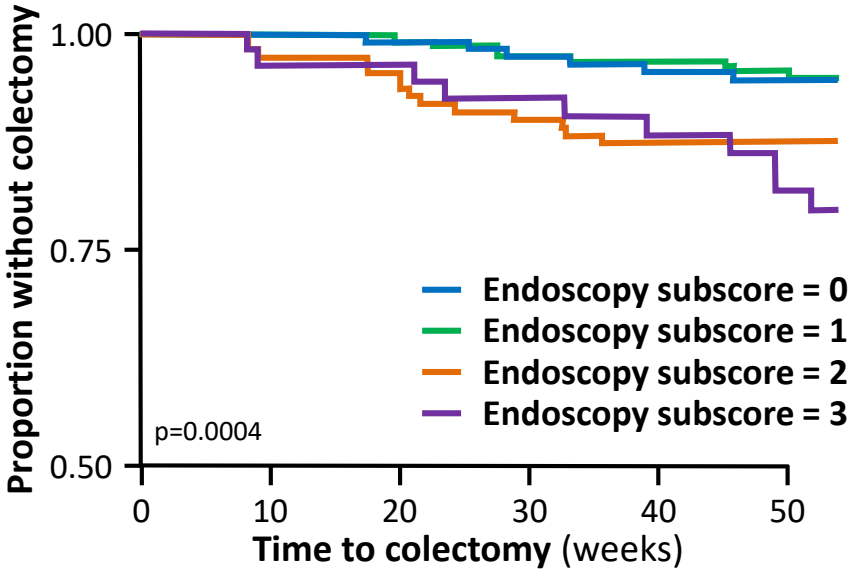
IFX: infliximab, ADA: adalimumab, VEDO: vedolizumab, IS: Immunosuppressant

CDEIS of 0: complete endoscopic healing; 0<CDEIS<4: partial endoscopic healing

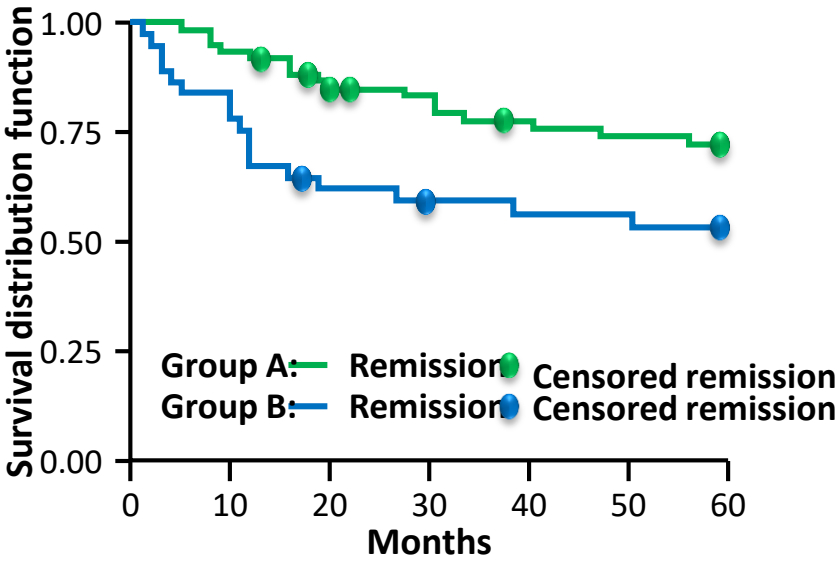
Yzet C, Diouf M, Le Mouel JP, et al. [published online ahead of print, 2019 Nov 16]. *Clin Gastroenterol Hepatol*. 2019;S1542-3565(19)31312-6.

# Early mucosal healing best predictor in steroid-dependent UC

**Kaplan-Meier curves of the proportion patients in the combined IFX group without a colectomy by endoscopy subgroup**




**Kaplan-Meier curves of freedom from combined endpoint of group A vs group B**

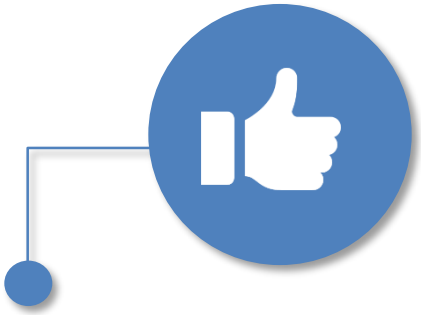



| Group | | Hospitalisation | Immunosuppressors | Colectomy | Combined endpoint |
|---|---|---|---|---|---|
| A | | 15 (25.0%) | 3 (5.0%) | 2 (3.3%) | 16 (26.7%) |
| B | | 19 (48.7%) | 10 (25.6%) | 7 (18.0%) | 19 (48.7%) |
| C | | 37 (63.8%) | 31 (53.5%) | 10 (17.2%) | 39 (67.2%) |
| p | | 0.0001 | <0.0001 | 0.0191 | <0.0001 |
| A + B vs C | p | 0.0003 | <0.0001 | 0.1307 | 0.0001 |
| | OR | 3.37 (1.71–6.63) | 7.60 (3.49–16.55) | 2.08 (0.79–5.48) | 3.75 (1.89–7.45) |
| A vs B | p | 0.0152 | 0.030 | 0.0265 | 0.0249 |
| | OR | 2.85 (1.21–6.72) | 6.55 (1.67–25.67) | 6.34 (1.24–32.37) | 2.61 (1.12–6.11) |

**IFX: infliximab**

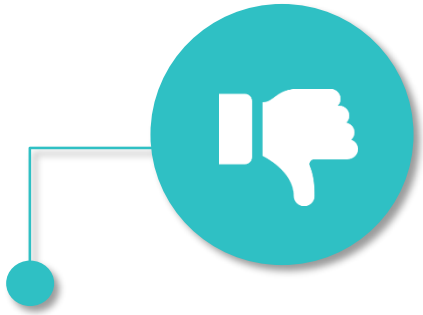
**Colombel JF, *et al*. *Gastroenterology* 2011;141:1194–1201; Ardizzone S, *et al. Clin Gastroenterol Hepatol* 2011; 9(6):483–489**

# Endoscopic measurement



**Pro**

- Gold standard
- Correlates with disease outcomes (surgery, hospitalisation)



**Con**

- Invasive
- Colon preparation
- Costly
- Incomplete procedures
- Scoring subjective

**Quality of the endoscopy is key:**
**prep, scoring, photo documentation, completeness**

# Can biomarkers predict mucosal healign? Biomarkers and their influence on clinical practice

## Marker with abnormal values in IBD

### Faecal

- Osteoprotegrin
- M2-Pyruvate Kinase
- Lactoferrin
- Myeloperoxidase
- Eosinophil Cationic Protein
- Calprotectin

### Serum

- S100A12, Calprotectin
- Nitrite, Neopterin
- suPAR, Ghrelin, Endothelin,
- IL-6, IL-17, sTNFRp55, sTNFRp75,
- CRP, hsCRP, Procalcitonin
- sCD14, Lipopolysaccharide Binding Protein
- Soluble ST2
- ASCA, ANCA, AMCA, ALCA,
- ACCA, anti-L, anti-C, anti-CBIR,
- anti-OMPC, anti-I2

## Markers with correlation to specific situations

### Faecal

- M2-Pyruvate Kinase
- Lactoferrin
- Calprotectin

### Serum

- IL-6, sTNFRp55, sTNFRp75,
- CRP, hsCRP, Procalcitonin
- ASCA, ANCA, AMCA, ALCA,
- ACCA, anti-L, anti-C, anti-CBIR,
- anti-OMPC, anti-I2

## Markers that INFLUENCE therapeutic decisions

### Faecal

- Calprotectin

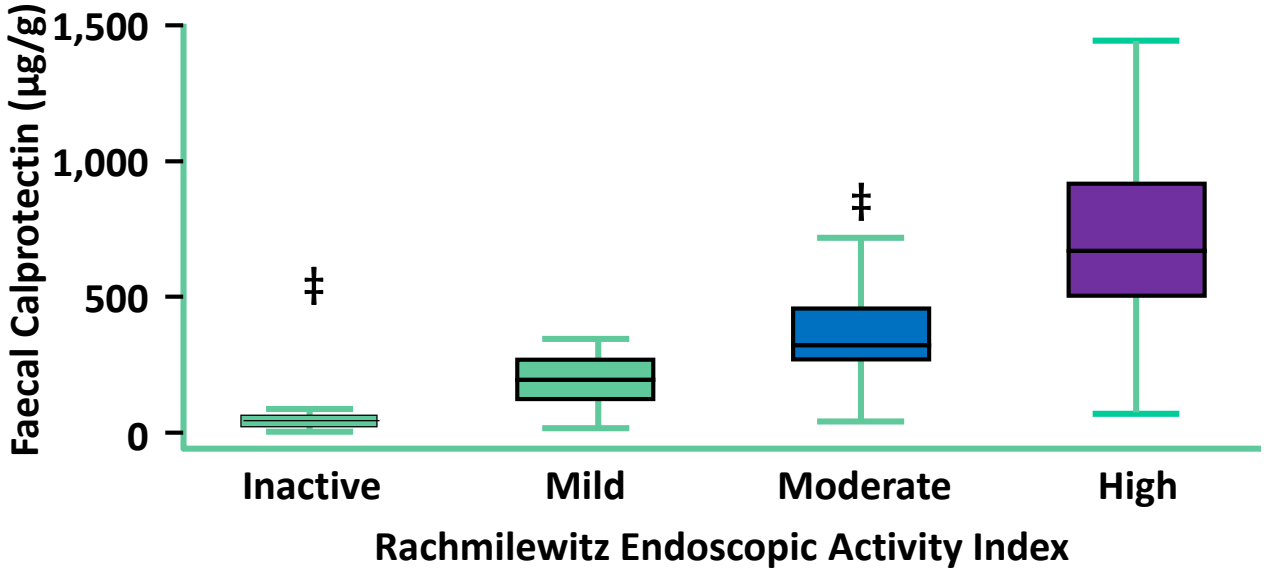
### Serum

- CRP

**ACCA: Anti-Chitobioside Carbohydrate Antibodies; ALCA: Anti-Laminaribioside Carbohydrate Antibodies; AMCA: Anti-Mannobioside Carbohydrate Antibodies; ANCA: Anti-Neutrophil Cytoplasmic Antibodies; Anti-C: Anti-Chitin; Anti-L: Anti-Laminarin; Anti-OmpC: Anti-Outer Membrane Porin C; ASCA: Anti-Saccharomyces Cerevisiae Antibodies; CRP: C-Reactive Protein; hsCRP: High Sensitivity CRP; IBD: Inflammatory Bowel Disease; IL: Interleukin; M2-Pyruvate Kinase: Muscle Pyruvate Kinase; S100A12: S100 Calcium-Binding Protein A12; suPAR: Soluble Urokinase-type Plasminogen Activator Receptor; sCD14: Soluble CD14; sTNFR: Anti-Human TNF Receptor.**

**Adapted from Murdoch T, *et al. Can J Gastroenterol Hepatol* 2015;29:203-208**

# Fecal Calprotectin Predicts Endoscopically Active Disease in UC




‡The values outside the whiskers represent individual outliers

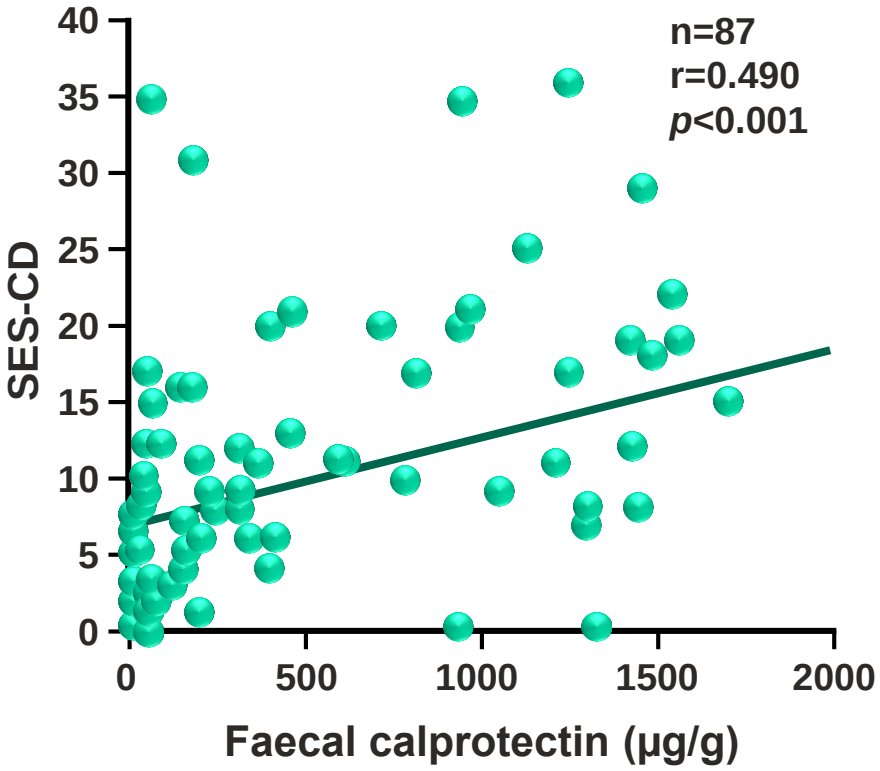
| | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Accuracy (%) |
|---|---|---|---|---|---|
| Calprotectin ≥ 50 µg/g | 93 | 71 | 91 | 81 | 89 |
| Calprotectin ≥ 100 µg/g | 86 | 88 | 96 | 65 | 86 |
| Clinical Activity Index ≥ 5 | 81 | 52 | 84 | 47 | 73 |
| CRP ≥ 5 mg/L | 60 | 67 | 84 | 37 | 62 |
| Blood Leukocytes ≥ 7.9 g/L | 59 | 62 | 82 | 34 | 60 |

PPV = Positive Predictive Value
NPV = Negative Predictive Value

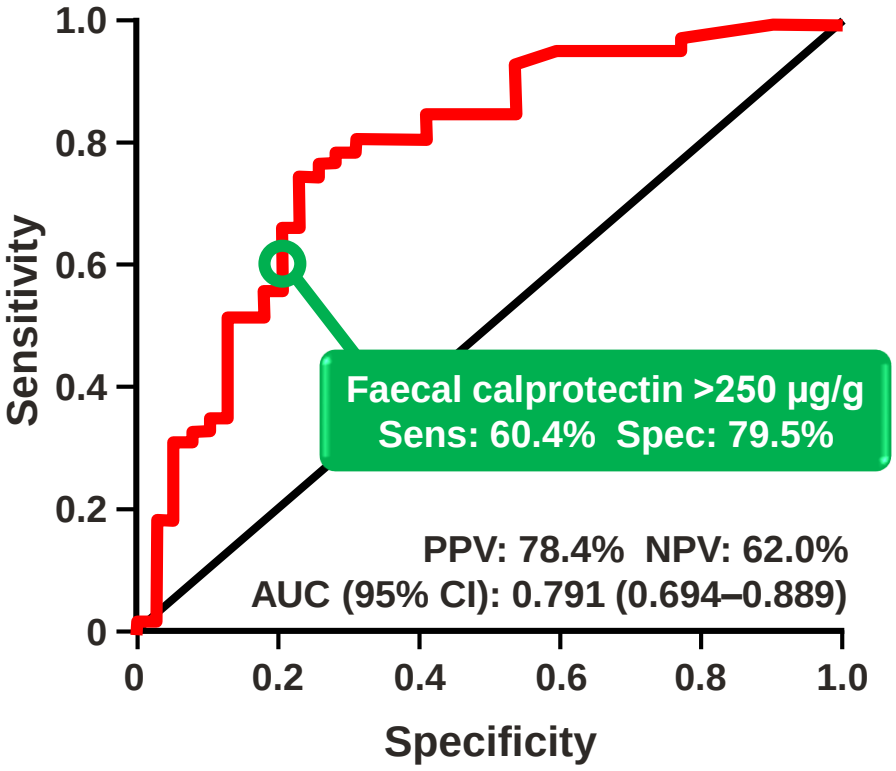
Schoepfer, AM. *Inlfamm Bowel Dis* 2009;15:1851–1858

# Calprotectin as a surrogate marker of endoscopic activity in CD

**Correlation between SES-CD and calprotectin in Crohn's disease patients requiring colonoscopy** (n=87)

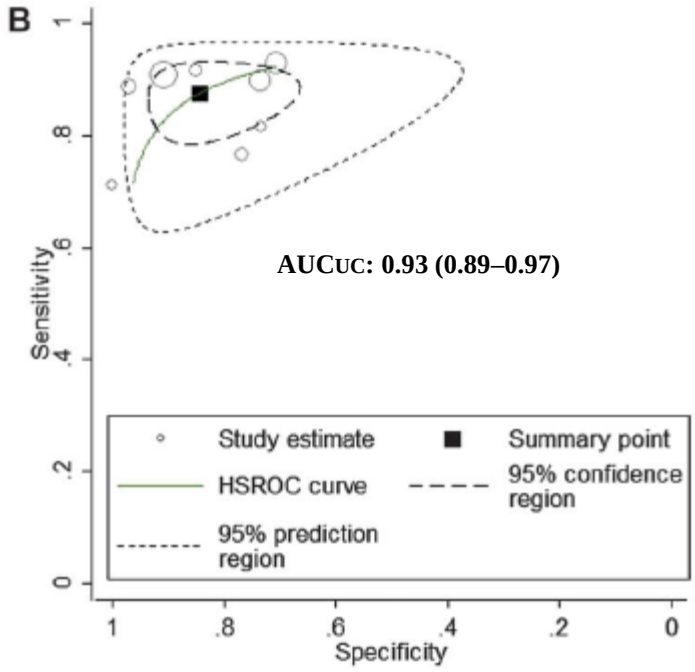



**SES-CD large ulcers** (n=48) **vs other** (n=39)

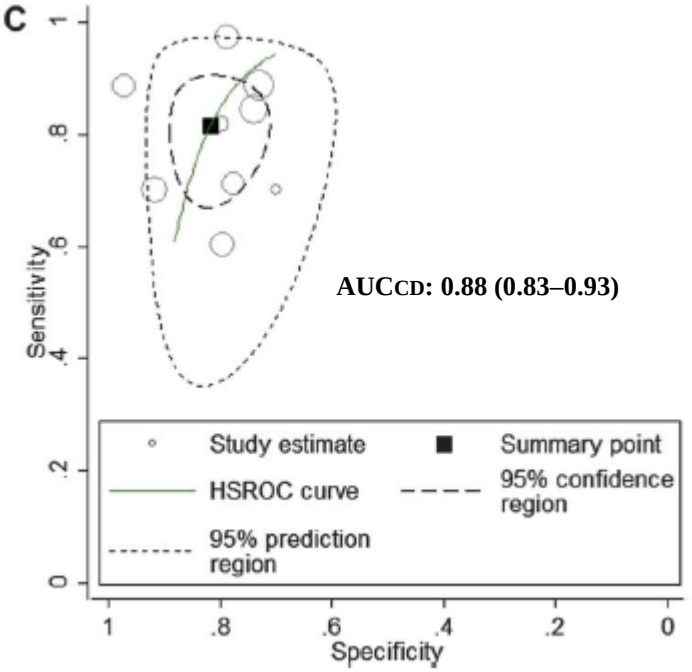



D'Haens G, *et al. Inflamm Bowel Dis* 2012;18:2218–24

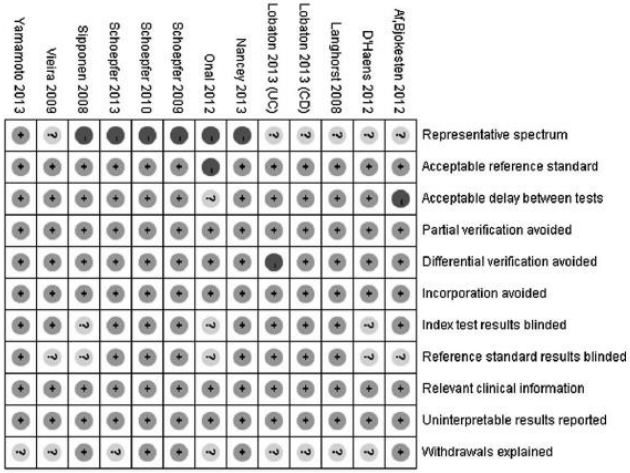
# Fecal Calprotectin Predicts active disease in patients with IBD: meta-analysis




**AUC$_{UC}$: 0.93 (0.89–0.97)**

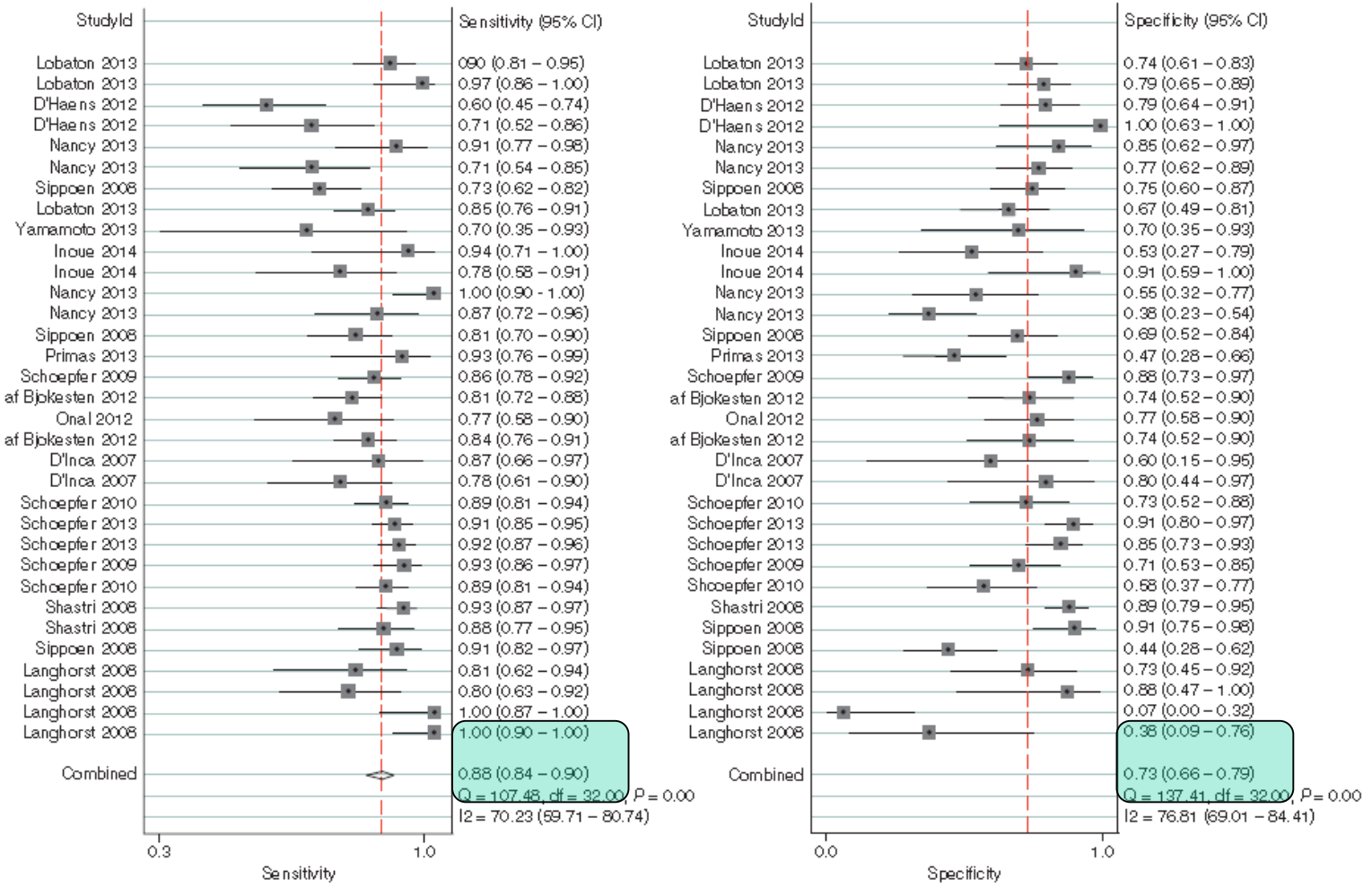



**AUC$_{CD}$: 0.88 (0.83–0.93)**




**Lin JF et al Inflamm Bowel Dis 2014**

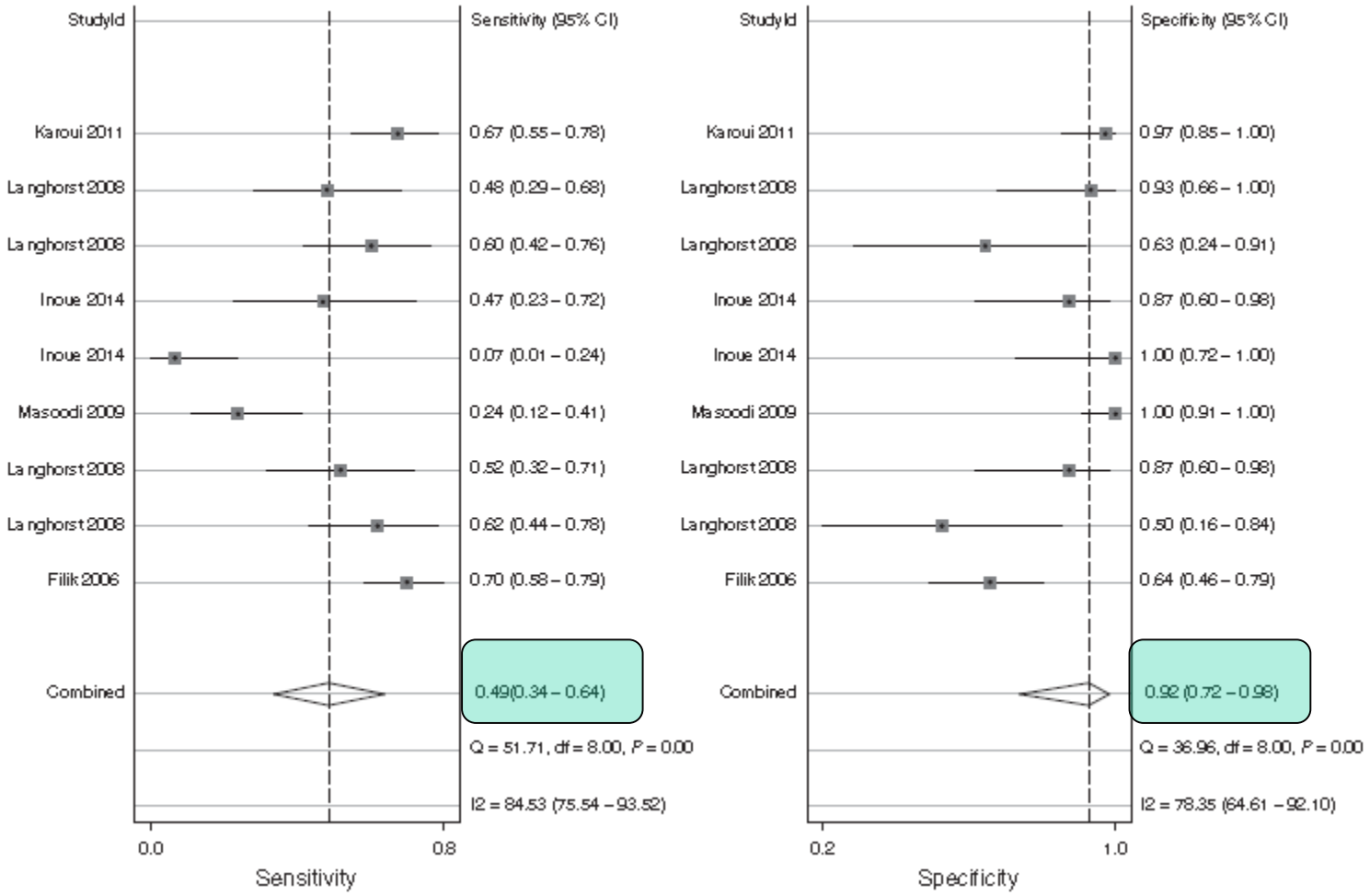
# Calprotectin and endoscopic activity: a metaanalysis




## Calprotectin

*Mosli MH AJG 2015;110:802*

# CRP and endoscopic activity: a metaanalysis




**CRP**

***Mosli MH AJG 2015;110:802***

# Accuracy of hs-CRP for identifying active disease during prospective follow-up

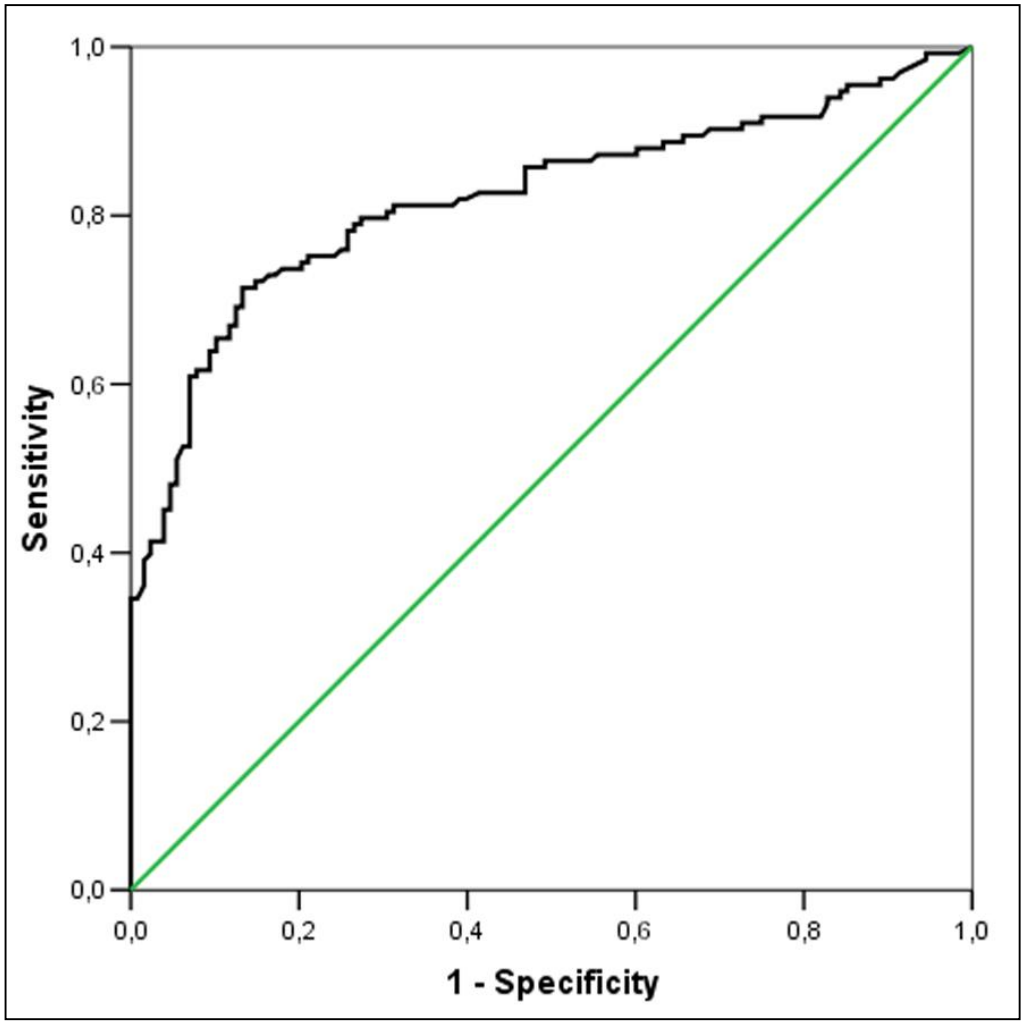
**app. 25-30% of CD patients are CRP negative at diagnosis**

**32.3% of the CD patients had normal hs-CRP at diagnosis.**

**Accuracy of hs-CRP to identify active disease:**

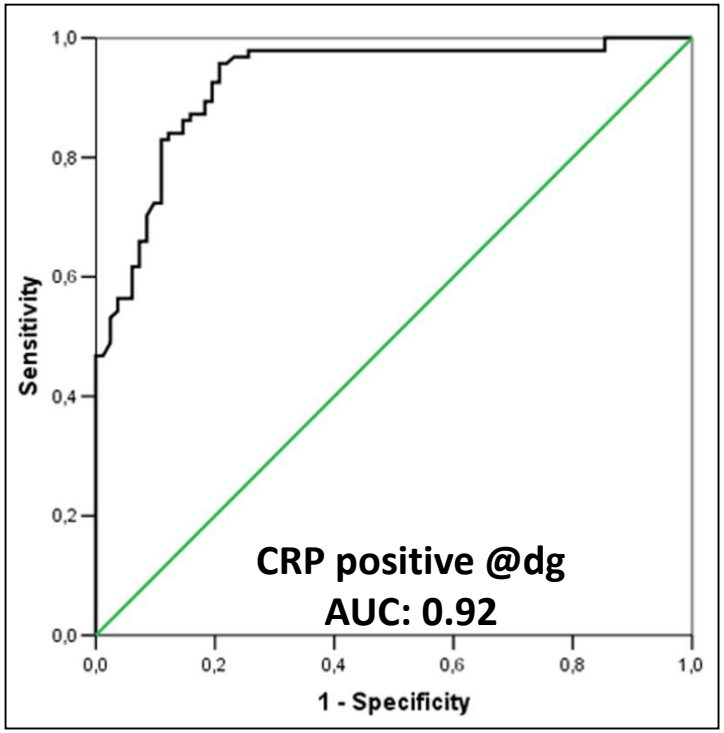
- **AUC: 0.82, 95%CI: 0.77-0.87**

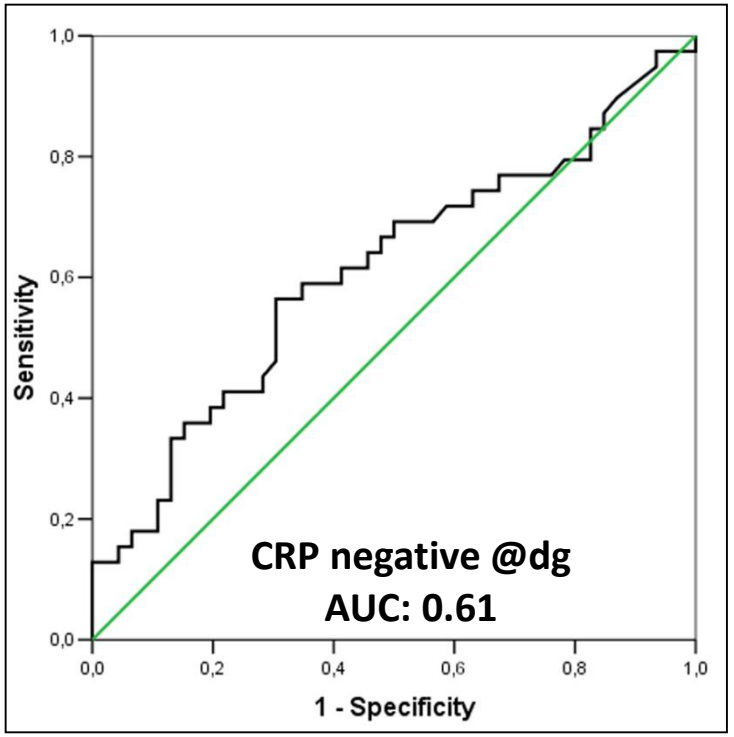
**Cut-off: 10.7 mg/L in the entire cohort.**




*Kiss LS IBD 2012*

# CRP in Crohn's disease; are we using it properly?



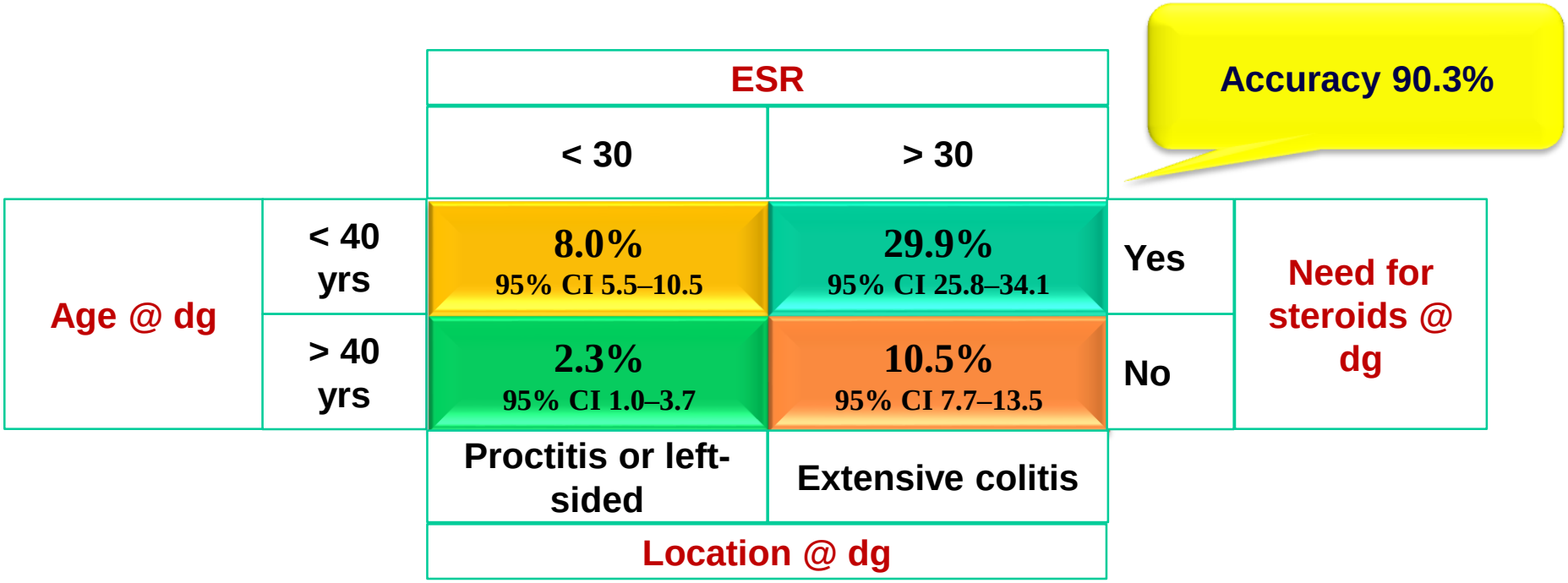

| | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|
| All CD patients | 71 | 85 | 83 | 75 |
| CD patients with a positive CRP @dg | 95 | 79 | 83 | 95 |
| CD patients with a negative CRP @ dg | 13 | 96 | 74 | 52 |

* Cut-off for hs-CRP 10mg/l

*Kiss LS IBD 2012*

# Cumulative Risk of Colectomy

## IBSEN




ESR = Erythrocyte sedimentation rate; HR = hazard ratio

Solberg IC, et al. *Scan J Gastroenterol* 2009;44(4):431–440

Cvancarova M *et al. Gut* 2010;59 Suppl III:A36

# Predicting the Outcome of Severe UC

- **85% of patients with :**
  - **Stool frequency >8/day**
    **or**
  - **C-reactive protein (CRP) >45mg/L and stool frequency 3–8/day on day 3 of intensive treatment required colectomy[1]**
- **Validated in 68 patients from 4 Scandinavian centres[2]:**
  - **Day 3 frequency >4 and CRP >25mg/L: 75% colectomy**
  - **Sweden index = stool frequency (0.14 x CRP)**
  - **When index >8, 72% came to colectomy**


1. Travis SP, et al. Gut 1996;38:905–910
2. Lindgren SC, et al. *Eur J Gastroenterol Hepatol* 1998;10:831–835

# How often? EVERY 6 weeks?
# CRP predicts short-term relapse in IBD

- 71 CD patients in medical remission
- CRP >20 mg/L and ESR >15 mm/h were selected as markers predictive of relapse
- A binary biological predictive score was derived: "negative" when both were lower than their limits, "positive" when otherwise
  - Sensitivity was 89%
  - Specificity was 43%

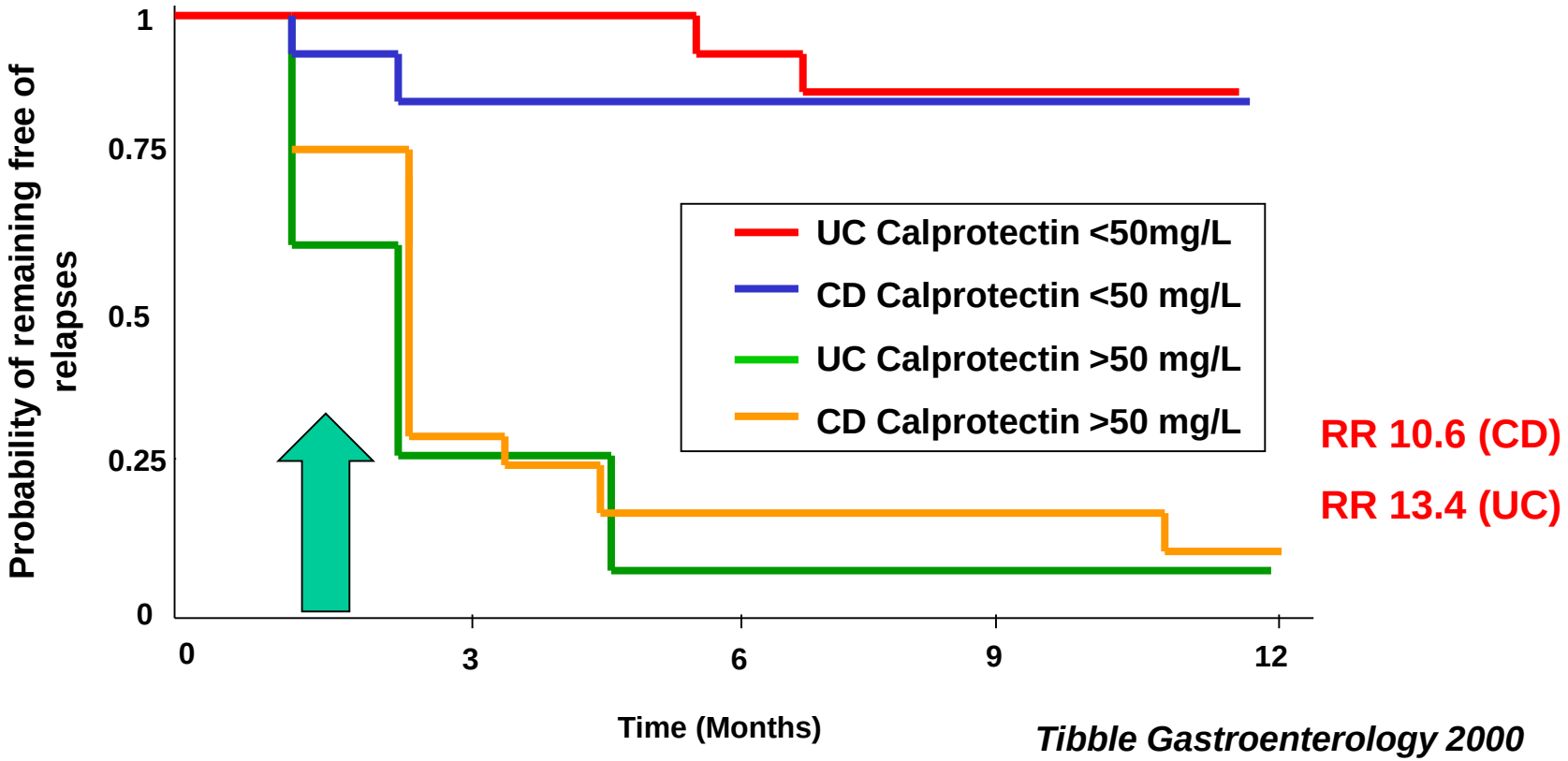
| | RR of relapse (95% CI) |
|---|---|
| CRP >20 mg/L only | 10.5 (2.3–48.1) |
| ESR >15 mm only | 6.1 (1.9–18.9) |
| Combined | 9.9 (3.3–29.7) |

*Consigny T et al. IBD 2006; 12:551-7*

# How often to measure: Every 12 weeks?

## Calprotectin predicts risk of relapses

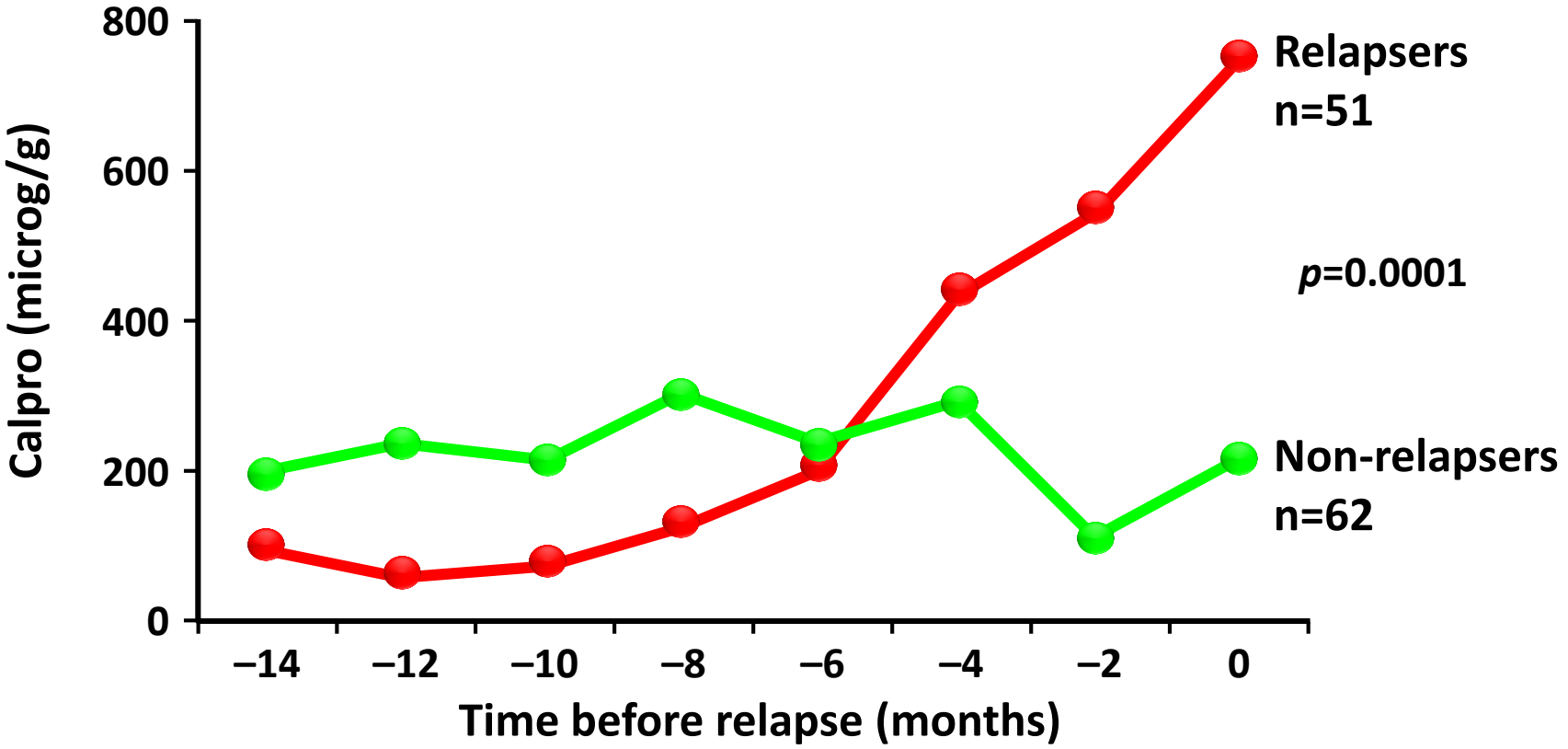
- 43 CD → 25 (58%) 12 month clinical relapse
- 37 UC → 19 (51%) 12 month clinical relapse
- After 1-4 months of clinical remission




*Tibble Gastroenterology 2000*

# Every 16 weeks?

## STORI sub-analysis: calprotectin levels months before relapse




**STORI enrolled 115 Crohn's disease patients who were treated with infliximab plus an immunomodulator for at least 1 year, and who were in stable remission for at least 6 months. Infliximab was discontinued, and 39% of patients relapsed within 1 year.**

De Suray N. ECCO 2012: P274

# Value of FC for predicting disease course

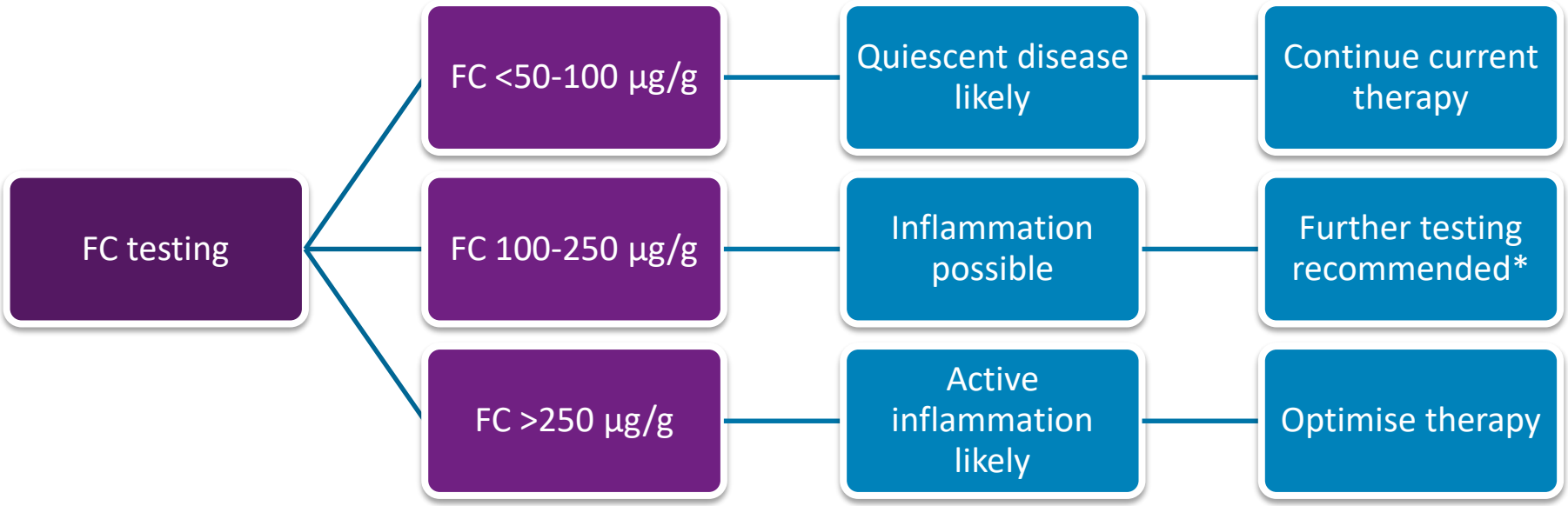
## Association between FC and relapse rate in IBD

| Study | Patients | Duration of remission at entry | Calprotectin elevated level | Relapse rate with low calprotectin | Relapse rate with high calprotectin |
|---|---|---|---|---|---|
| Gisbert et al. | UC | >6 months | >150 µg/g | 9% | 31% |
| Tibble et al. | UC | 1–4 months | >50 µg/g | 10% | 85% |
| Tibble et al. | CD | 1–4 months | >50 µg/g | 15% | 85% |
| Costa et al. | UC | 1–12 months | >150 µg/g | 10% | 81% |
| Costa et al. | CD | 1–12 months | >150 µg/g | 57% | 87% |
| D'Inca et al. | UC | 3–36 months | >130 µg/g | 30% | 79% |
| Sipponen et al. | UC +CD | >3 months (51% >12 months) | >100 µg/g | 25% | 39% |
| Walkiewicz et al. | CD | Not stated | >400 µg/g | 11% | 56% |

**FC: faecal calprotectin**

Lewis JD. *Gastroenterology* 2011;140:1817–1826

# Algorithm: Use of FC in disease monitoring




*Further testing may include additional FC tests, cross-sectional imaging, colonoscopy, or videocapsule endoscopy

**FC: faecal calprotectin**

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

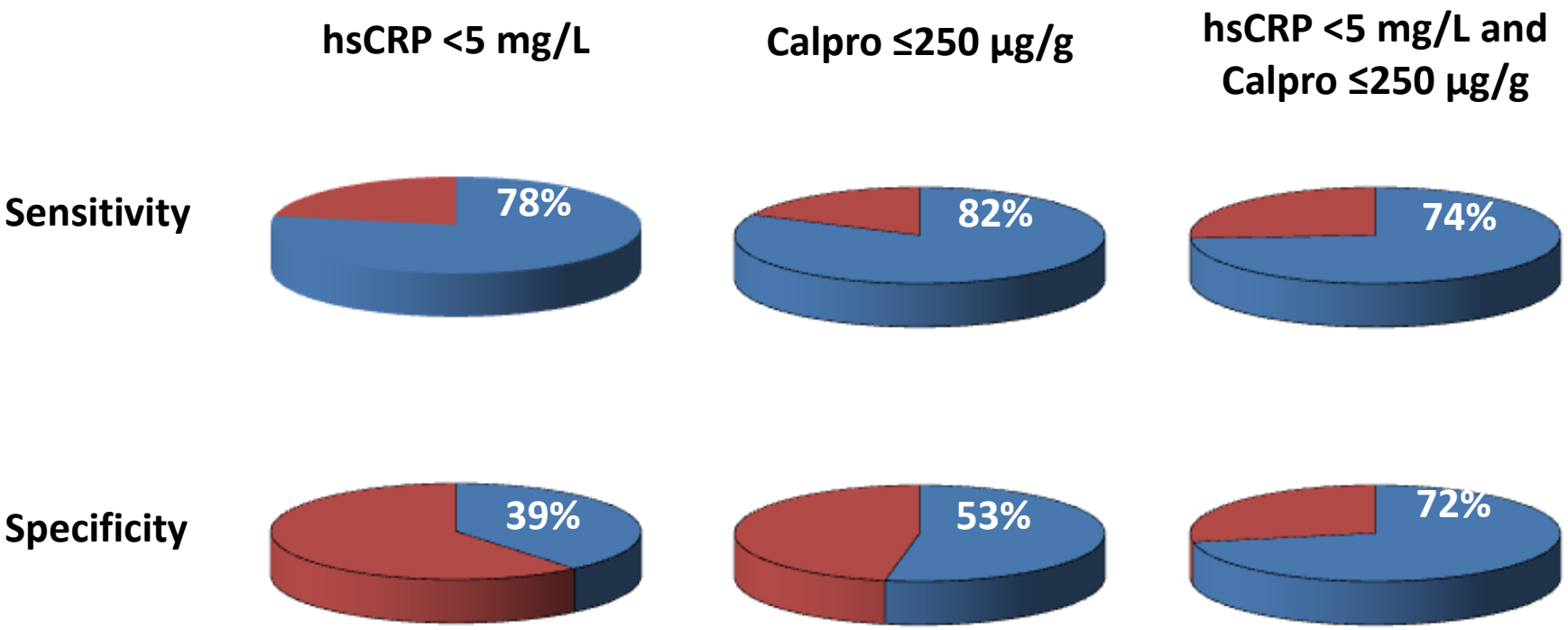
# CALPRO ‚light': „Homebrew"


Photo 4. Faecal calprotectin measurement in mg/kg is appearing on the phone screen 15 s after the picture has been sent to the server.

**Elkjaer M APT 2010;31:323-30**

# USE COMBO: faecal calprotectin and hsCRP to predict mucosal healing*

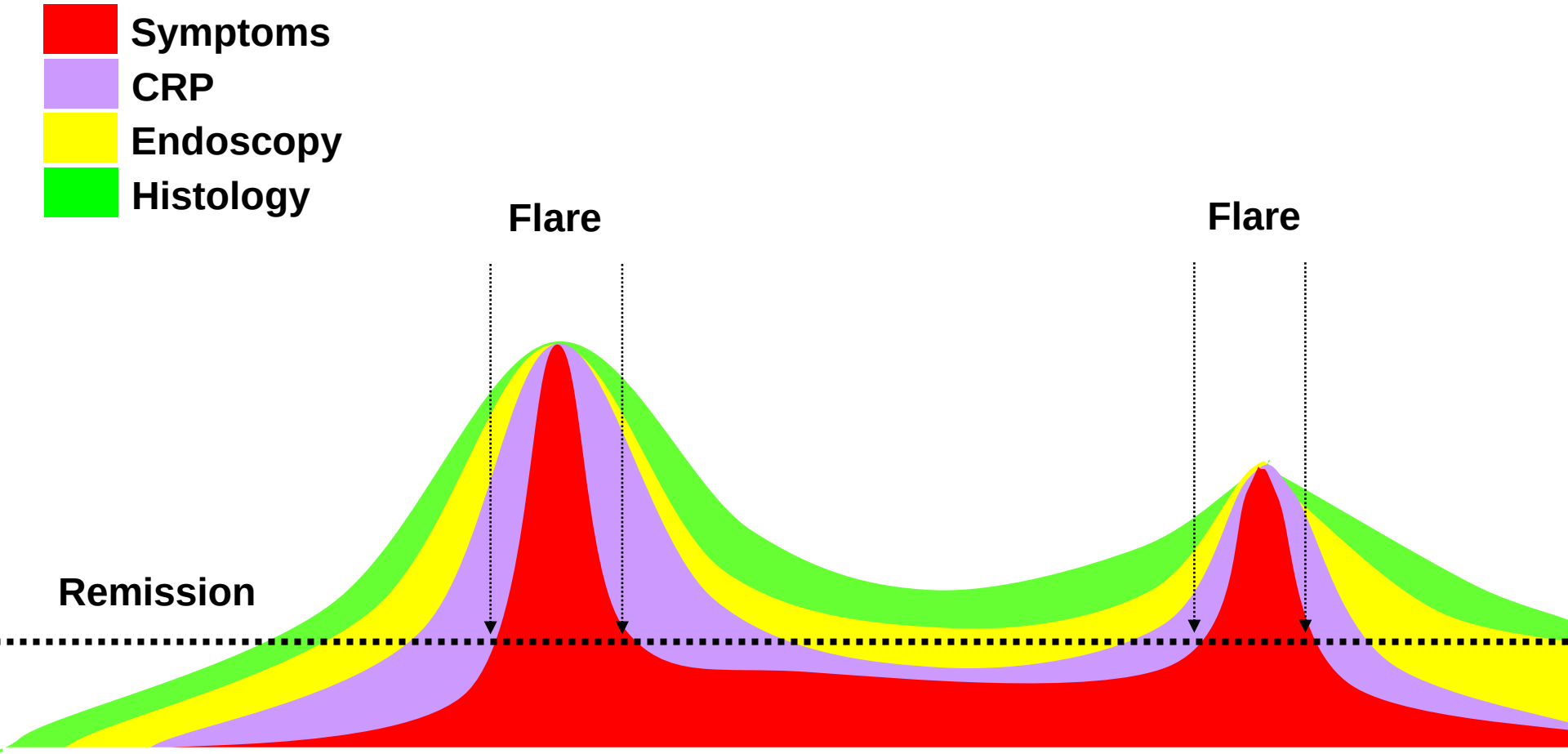
## Subanalysis of the STORI trial




* Defined as CDEIS ≤3

*Lémann M and the GETAID. Gut 2010;59(Suppl. III):A80:OP370 at UEGW 2010*

# IBD severity assessment



# What is the consensus target?

| Crohn's Disease | Ulcerative Colitis |
|---|---|
| **The consensus target is a combination of:** | |
| **Clinical / PRO remission defined as resolution of abdominal pain & diarrhoea / altered bowel habit which should be assessed at a minimum of 3 months during the active disease**<br>**and**<br>**Endoscopic remission defined as resolution of ulceration at ileocolonoscopy** (or resolution of findings of inflammation on cross-sectional imaging in patients who cannot be adequately assessed with ileocolonoscopy) **which should be assessed at 6–9 month intervals during the active phase** | **Clinical / PRO remission defined as resolution of rectal bleeding & diarrhoea / altered bowel habit which should be assessed at a minimum of 3 months during the active disease**<br>**and**<br>**Endoscopic remission defined as resolution of friability and ulceration at flexible sigmoidoscopy or colonoscopy† which should be assessed at 3–6 month intervals during the active phase** |
| **Adjunctive measures of disease activity that may be useful in the management of selected patients but are not a target include:** | |
| • **CRP**<br>• **Faecal calprotectin** | • **CRP**<br>• **Faecal calprotectin**<br>• **Histology** |
| **Measures of disease activity that are not a target:** | |
| • **Histology**<br>• **Cross-sectional imaging§** | • **Cross-sectional imaging** |

STRIDE
Selecting targets of remission in inflammatory bowel disease

* STRIDE initiated and under the auspices of the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD).
† While Mayo subscore of 0 may be defined as the target, there is currently insufficient evidence to recommend it in all patients; only Mayo subscore of 0–1 can be systematically recommended in practice.
§ When endoscopy cannot adequately evaluate inflammation, resolution of inflammation as assessed by cross-sectional imaging is a target

**PRO: patient-reported outcomes**

**Peyrin-Biroulet L, *et al*. *Am J Gastroenterol* 2015;110:1324–38**

| Recommendations | Voting results: Strength of recommendation[3] | Voting results: % votes 7-10 |
|---|---|---|
| *Clinical* | | |
| 1. **Clinical response is an immediate treatment target.** Consider changing treatment if this target has not been achieved[1]. | 9.0 | 94% |
| 2. Clinical response should be defined as:<br>a) CD: decrease of at least 50% in PRO2 (abdominal pain and stool frequency), and in children decrease in PCDAI of at least 12.5 points and in wPCDAI at least 17.5 points<br>b) UC: decrease of at least 50% in PRO2 (rectal bleeding and stool frequency), and in children decrease in PUCAI of at least 20 points | 8.3 | 84% |
| 3. **Clinical remission is an intermediate (i.e. medium-term) treatment target.** Consider changing treatment if this target has not been achieved[1]. | 8.7 | 94% |
| 4. Clinical remission should be defined as:<br>a) CD: PRO2 (abdominal pain≤1 and stool frequency≤3) or HBI<5; in children by PCDAI (<10 points or <7.5 excluding the height item) or wPCDAI (<12.5 points)<br>b) UC: PRO2 (rectal bleeding=0 and stool frequency=0) or partial Mayo (<3 and no score >1), and in children PUCAI<10 points | 8.5 | 81% |
| 5. Clinical response or remission are insufficient to be used as long term treatment targets | 8.3 | 80% |
| 6. **In children, restoration of normal growth is a long-term treatment target.** Consider changing treatment if this target has not been achieved. | 9.3 | 98% |
| *Endoscopic and transmural assessment* | | |
| 7. **Endoscopic healing is a long-term target**. Consider changing treatment if this target has not been achieved. | 8.7 | 87% |
| 8. **Assessment of endoscopic healing can be achieved by sigmoidoscopy or colonoscopy. When not feasible, alternatives in CD can be capsule endoscopy or balloon enteroscopy.** | 8.3 | 86% |
| 9. Endoscopic healing should be measured by:<br>a) CD: SES-CD<3 points or absence of ulcerations (e.g. SES-CD ulceration subscores=0)<br>b) UC: Mayo endoscopic subscore=0 points, or UCEIS≤1 points | 8.5 | 85% |
| 10. Histologic remission is not a treatment-target in either CD or UC. Nonetheless, in UC it could be used as an adjunct to endoscopic remission to represent a deeper level of healing. | 7.7 | 80% |
| 11. Transmural healing (assessed by CTE, MRE or bowel ultrasound) is not a treatment-target in either CD or UC. Nonetheless, in CD it should be used as an adjunct to endoscopic remission to represent a deeper level of healing. | 7.5 | 77% |



STRIDE
Selecting targets of remission in inflammatory bowel disease

**Treatment targets**
**Intermediate**
**Clinical**
**Biomarkers**

**Long term**
**Normal growth (in children)**
**Endoscopy**
**Quality of life**

**Histology and transmural healing are adjunct but NOT targets**

| | | |
|---|---|---|
| *Biomarkers* | | |
| 12. **Normalization of CRP (to values under the upper limit of normal) and fecal calprotectin (to 100-250 µg/g)[2] is an intermediate treatment target in UC and CD.** Consider changing treatment if this target has not been achieved. | 8.2 | 80% |
| *Quality of life and disability* | | |
| 13. **Absence of disability and normalized health-related quality of life are long-term treatment targets**. Consider changing treatment if this target has not been achieved. | 7.7 | 75% |

# AND: goals may be different in different stages of the disease

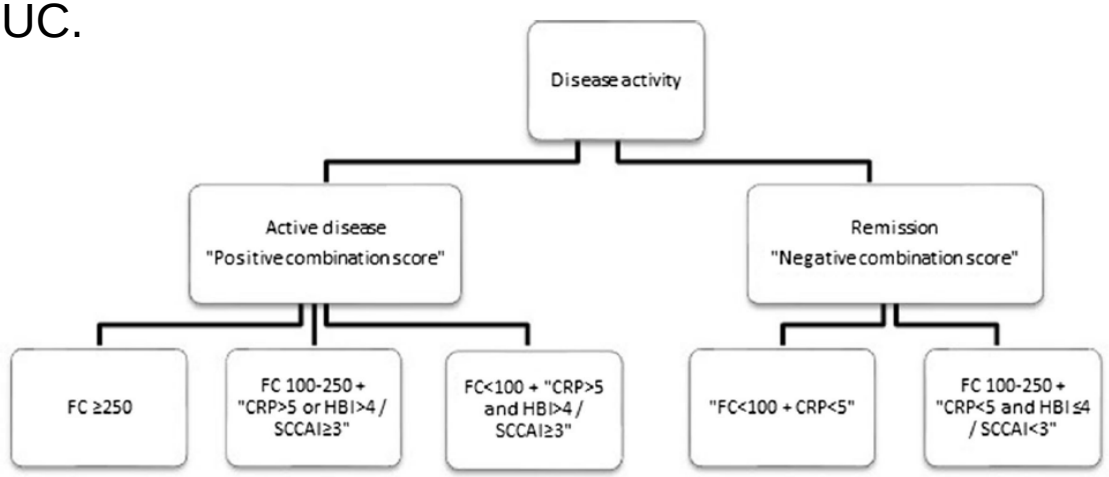
| Disease stage | Biological remission (Inflammation control) | Clinical remission (Symptom control) | Outcomes |
|---|---|---|---|
| **Early disease** | **Mucosal healing; colonoscopy: no ulcers** (with the exception of a certain number of aphthous ulcers <5 mm in diameter)<br>**Improvements in serum and faecal biomarkers of active inflammation: CRP: <5 mg/L; faecal calprotectin: <250 µg/g** | **Clinical practice: complete absence of symptoms; 1–2 formed stools per day without abdominal pain/cramping**<br>**Clinical trials: CDAI <150 points** | **Complete absence of symptoms; no disease progression; no complications; no disability; normal quality of life** |
| **Late disease** | **Mucosal healing; colonoscopy: no ulcers** (with the exception of a certain number of aphthous ulcers <5 mm in diameter)<br>**Improvements in serum and faecal biomarkers of active inflammation: CRP: <5 mg/L; faecal calprotectin: <250 µg/g** | **Clinical practice: inflammatory symptom improvement** (may experience residual symptoms of pain or diarrhoea because of previous surgical treatment or intestinal damage)<br>**Clinical trials: CDAI 150–220 points** | **Stabilisation of noninflammatory symptoms; no progression of structural damage; no progression of disability; improved quality of life** |

Panaccione R, *et al. Inflamm Bowel Dis* 2013;19:1645-53

# Composite clinical/ biomarker score to predict mucosal healing

**Clinical (HBI, MAYO) and CRP/FCAL**

Indefinite FC values were present in 24% of CD and 15% of UC.

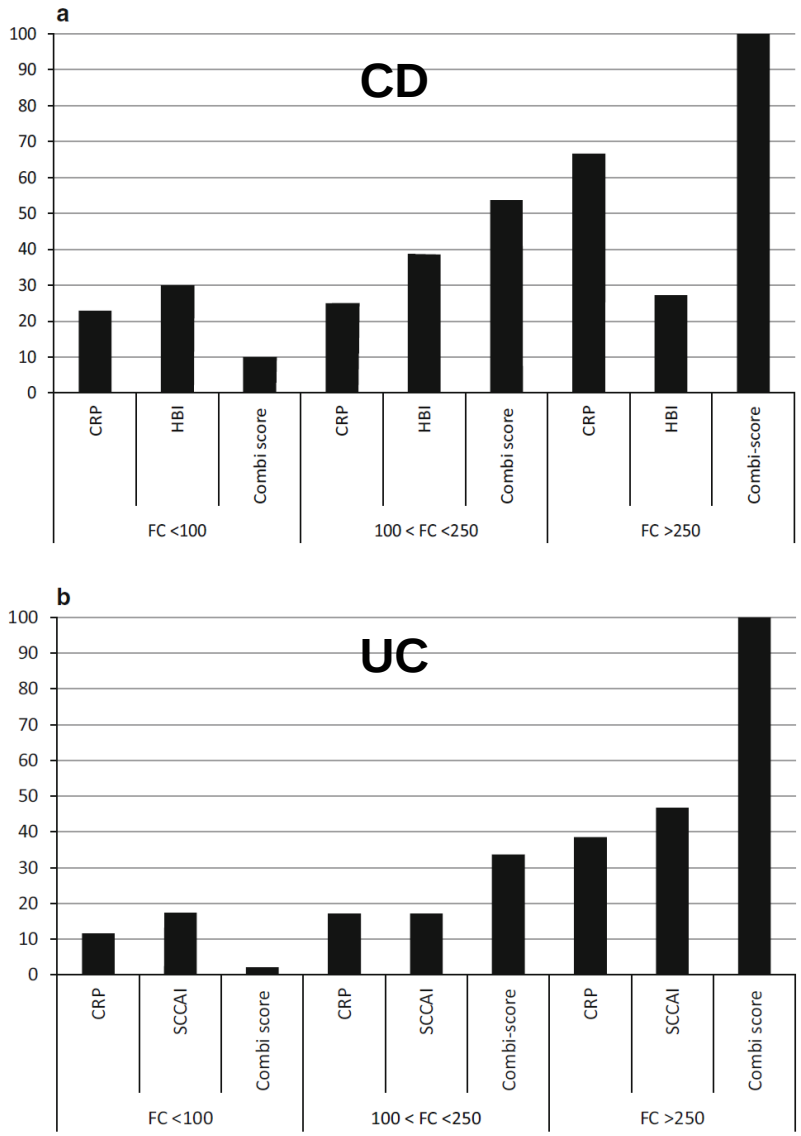



| | CD | | | | UC | | | |
|---|---|---|---|---|---|---|---|---|
| | Sensitivity | Specificity | PPV | NPV | Sensitivity | Specificity | PPV | NPV |
| Clinical activity index | 0.79 | 0.61 | 0.50 | 0.86 | 0.82 | 0.60 | 0.88 | 0.50 |
| Calprotectin >250 µg/g | 0.76 | 0.86 | 0.79 | 0.84 | 0.86 | 0.78 | 0.97 | 0.46 |
| CRP ≥5 mg/l | 0.56 | 0.65 | 0.32 | 0.83 | 0.50 | 0.65 | 0.39 | 0.74 |
| Combination score | 0.83 | 0.69 | 0.58 | 0.89 | 0.88 | 0.75 | 0.93 | 0.60 |

*PPV* positive predictive value, *NPV* negative predictive value

Bodelier et al.
DDS 2017;62:465-72

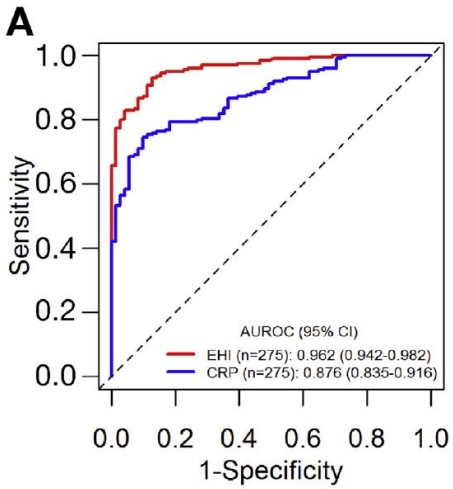
# Composite clinical/ biomarker score to predict mucosal healing

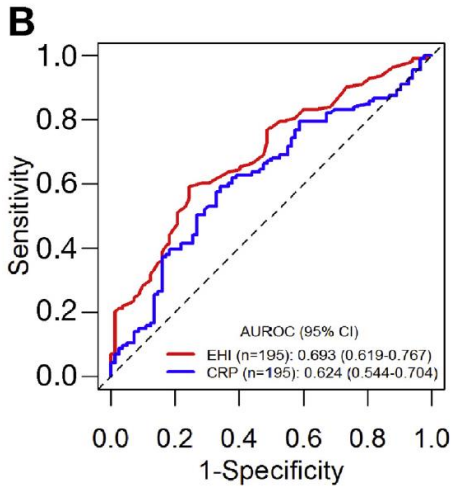


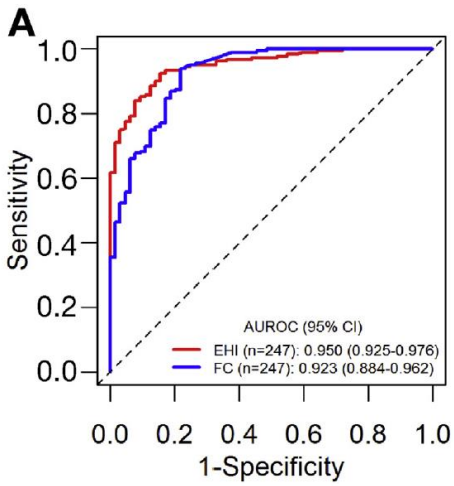

Bodelier et al.
DDS 2017;62:465-72

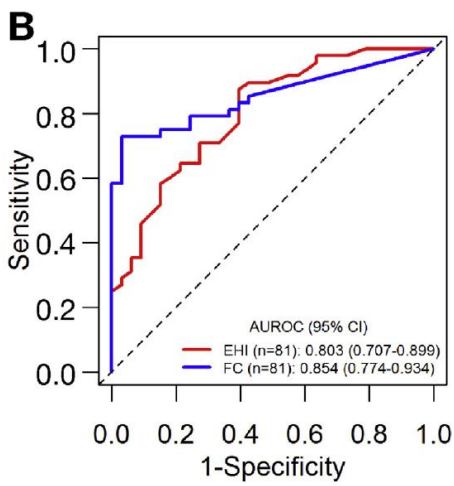
# Composite serum/ biomarker score to predict mucosal healing

**endoscopic healing index [EHI]** : 13 proteins in blood (ANG1, ANG2, CRP, SAA1, IL7, EMMPRIN, MMP1, MMP2, MMP3, MMP9, TGFA, CEACAM1, and VCAM1)




Mucosal healing definition
SES CD <3
CDEIS <3

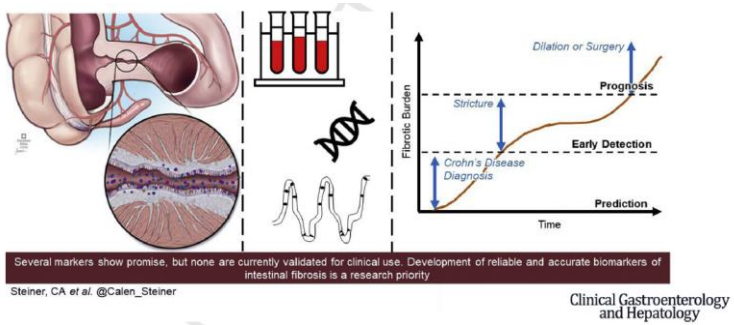
| Test | Threshold | MLG Probability[a] | TPs, n | TNs, n | Sensitivity, % (95% CI) | Specificity, % (95% CI) | PLR (95% CI) | NLR (95% CI) |
|---|---|---|---|---|---|---|---|---|
| EHI | 20 | 0.542 | 176 | 41 | 96.2 (92.3–98.4) | 64.1 (51.1–75.7) | 2.68 (1.93–3.72) | 0.06 (0.03–0.13) |
| | 30 | 0.728 | 153 | 59 | 83.6 (77.4–88.7) | 92.2 (82.7–97.4) | 10.70 (4.60–24.89) | 0.18 (0.13–0.25) |
| | 40 | 0.858 | 109 | 64 | 59.6 (52.1–66.7) | 100.0 (94.4–100.0) | INFINITY | 0.40 (0.34 0.48) |
| | 50 | 0.932 | 65 | 64 | 35.5 (28.6–42.9) | 100.0 (94.4–100.0) | INFINITY | 0.65 (0.58–0.72) |
| CRP, *mg/L* | 3 | 0.830 | 109 | 60 | 59.6 (52.1–66.7) | 93.8 (84.8–98.3) | 9.53 (3.66–24.80) | 0.43 (0.36–0.52) |
| | 5 | 0.868 | 81 | 62 | 44.3 (36.9–51.8) | 96.9 (89.2–99.6) | 14.16 (3.59–55.95) | 0.58 (0.50–0.66) |
| | 10 | 0.908 | 49 | 64 | 26.8 (20.5–33.8) | 100.0 (94.4–100.0) | Infinity | 0.73 (0.67–0.80) |
| FC, *µg/g* | 50 | 0.230 | 183 | 4 | 100.0 (98.0–100.0) | 6.2 (1.7–15.2) | 1.07 (1.00–1.14) | 0.00 (0.00) |
| | 150 | 0.624 | 144 | 53 | 78.7 (72.0–84.4) | 82.8 (71.3–91.1) | 4.58 (2.66–7.88) | 0.26 (0.19–0.35) |
| | 250 | 0.787 | 125 | 57 | 68.3 (61.0–75.0) | 89.1 (78.8–95.5) | 6.25 (3.08–12.65) | 0.36 (0.28–0.45) |

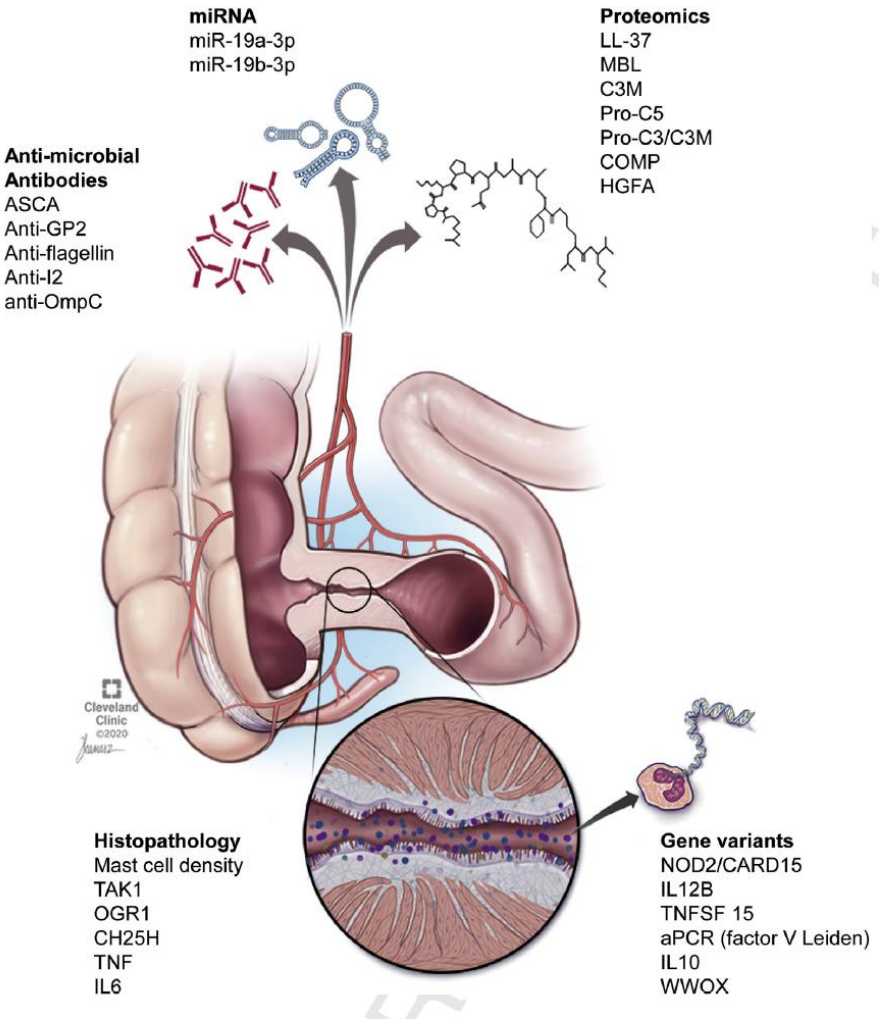
MLG, mixed logistic regression; NLR, negative likelihood ratio; PLR, positive likelihood ratio; TN, true negative; TP, true positive.
[a]The population-averaged probability from the MLG models.

Haens et al.
Gastroenterol 2020;158:515-26.

# Composite serum/ biomarker score to predict stricutring disease

**Thirty-five distinct biomarkers from 3 major groups were identified: serum (20 markers), genetic (9 markers), and histopathology (6 markers).**



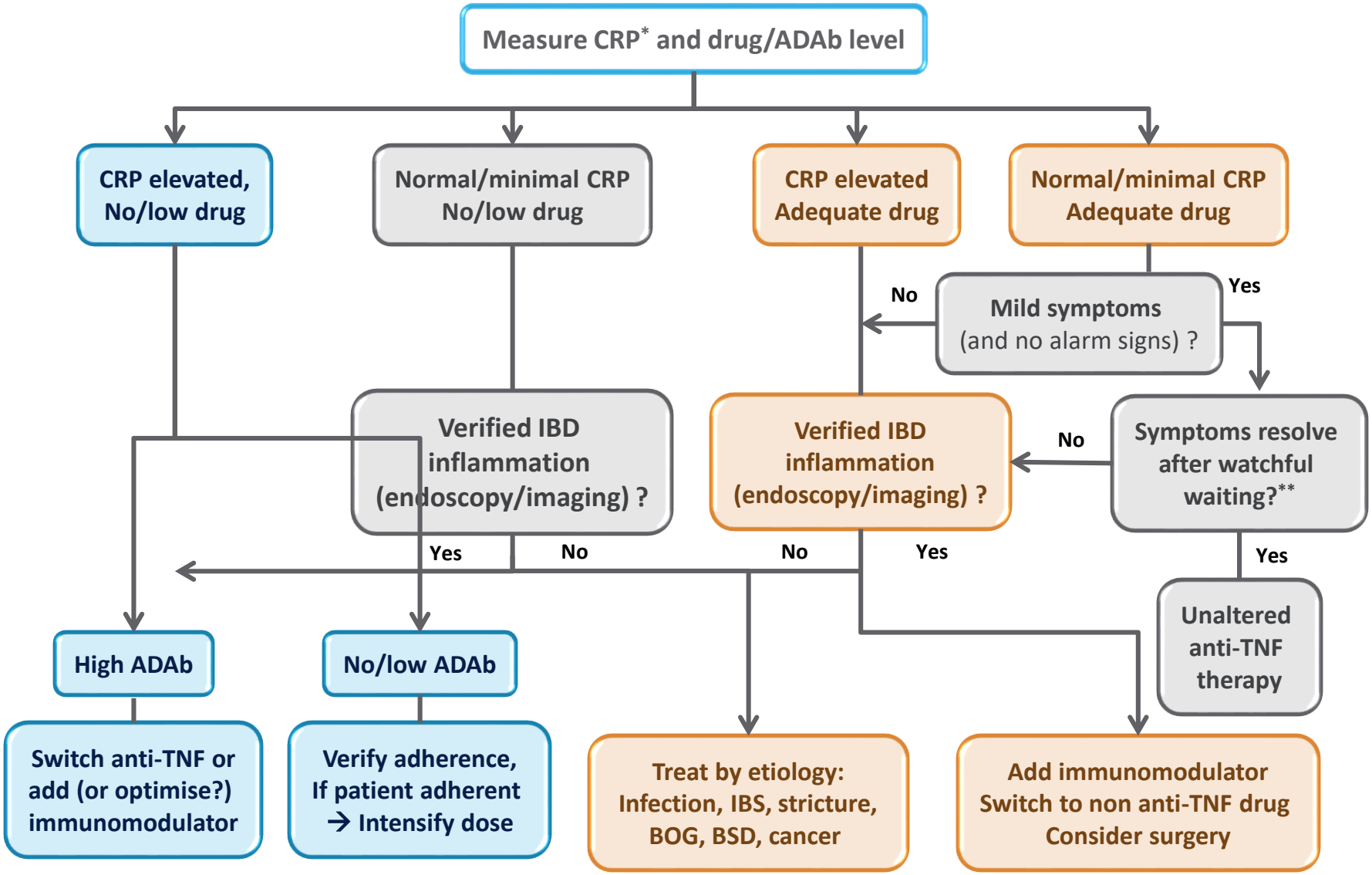




Steiner et al.

CGH 2021 online

**The NEW „era”:**
**T(herapeutic) D(rug) M(onitoring) tool or toy?**

# Tailoring anti-TNF and other biological therapies? in IBD




ADAb: anti-drug antibody

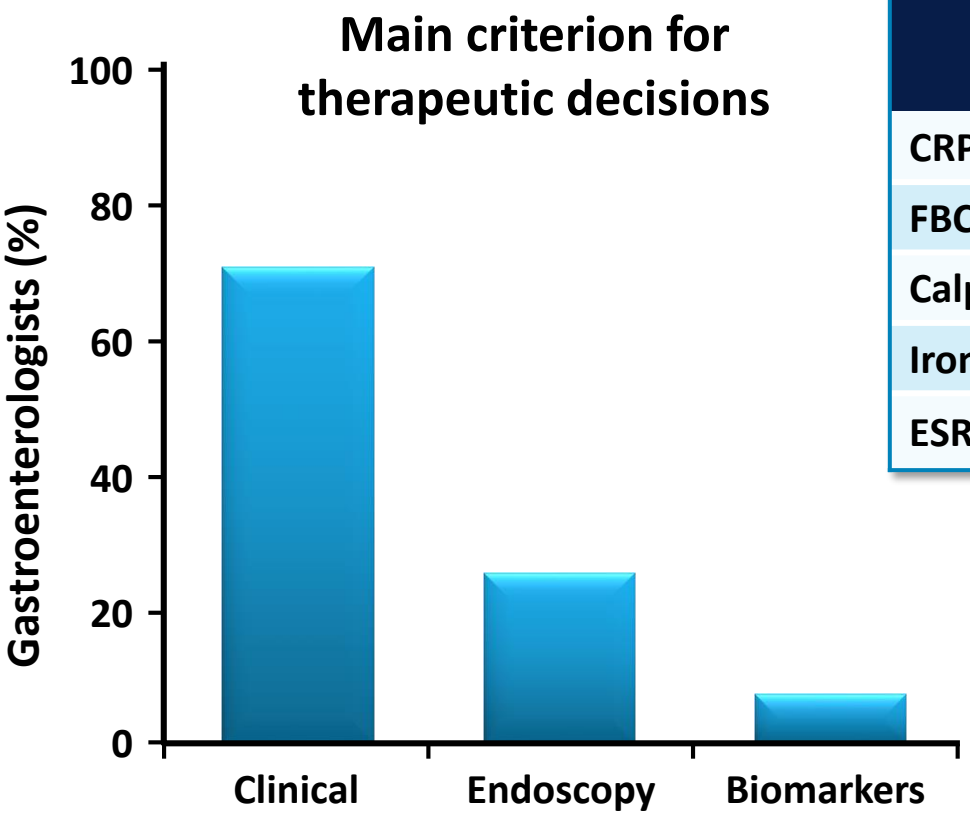
Ben-Horin S, Chowers Y. *Nature Rev Gastroenterol* 2014;11:243–55

# How do we monitor/manage or patients real life?

# What are clinicians thinking…?

## Clinical criteria are used by gastroenterologists to guide therapeutic decisions

**From a survey of 270 Swiss gastroenterologists...**




| Biomarkers used for IBD activity monitoring | Gastroenterologists (%) |
|---|---|
| CRP | 94 |
| FBC + differential | 78 |
| Calprotectin | 74 |
| Iron status | 63 |
| ESR | 3 |

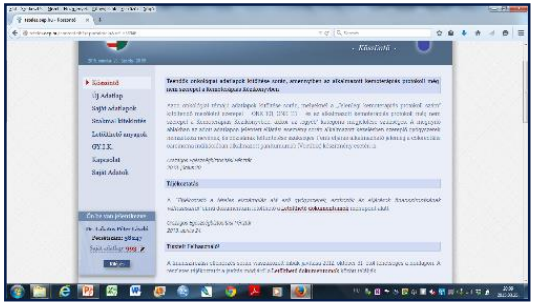
### What we do at Semmelweis?

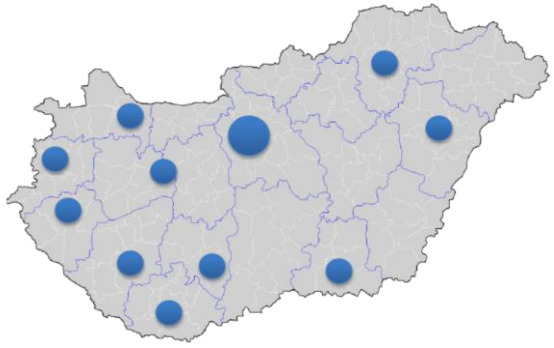
- **Laboratory every visit** (CRP, FBC, liver enzymes)
- **At relapse or every 12 months imaging/endoscopy: US/MRI/endoscopy**

Schoepfer AM, *et al. J Crohn's Colitis* 2012;6:412–8

# Monitoring of anti-TNF/biological treated patients is harmonised and schedule is mandatory in Hungary

| | Baseline | W14 | W30 | W54 |
|---|---|---|---|---|
| **Demographic data** | ✓ | | | |
| **Medication history** | ✓ | ✓ | ✓ | ✓ |
| **Clinical activity** CDAI / PDAI or partial Mayo | ✓ | ✓ | ✓ | ✓ |
| **Biochemical activity** WBC, CRP, ESR, albumin | ✓ | ✓ | ✓ | ✓ |
| **Endoscopic activity** SES-CD or Mayo | ✓ | | | ✓ |
| **Imaging** (perianal) MR or CT | ✓ | | | ✓ |
| **Adverse events** | ✓ | ✓ | ✓ | ✓ |



# MUHC McGill
# Rapid access clinic: outcomes
## Patient access and resource utilization

**June 2017 – March 2019**

**N=488 patients included**
(valid reason for contacting the RAC clinic)

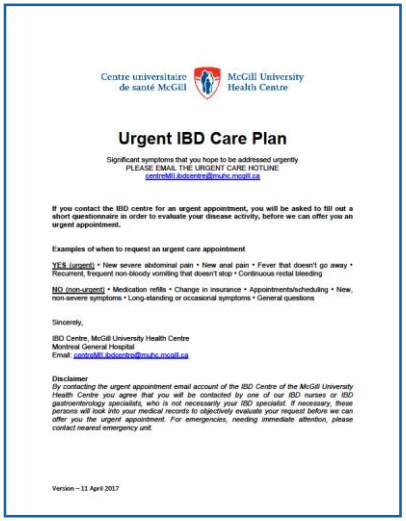
**N=333 (68.2%) MD visit**
patients having appointment with IBD specialist

**N=86 (17.6%) IBD nurse visit**
patients presenting at the IBD clinic and managed by nurse; MD notified

**N=69 (14.1%) no visit**
patient request managed via e-mail/telephone

Patient characteristic

| **Mean age (SD)** | **39.3 (14.8) years** |
|---|---|
| Men/Women (%) | 41.3/58.7 |
| CD/UC (%) | 68.4/31.6 |
| Age at onset A1/A2/A3 (%) | 30.3/60.4/9.3 |
| CD localization L1/L2/L3/L4 (%) | 25.1/27.9/46.0/1.0 |
| CD behavior B1/B2/B3 (%) | 66.7/17.6/15.7 |
| CD perianal (%) | 22.7 |
| UC localization (%) | 8.8/30.4/60.8% |
| Biological therapy (%) | 60.6 |
| Previous resective surgery (%) | 19.8 |



Centre universitaire de santé McGill — McGill University Health Centre

**Urgent IBD Care Plan**

Significant symptoms that you hope to be addressed urgently
PLEASE EMAIL THE URGENT CARE HOTLINE
centreMU.ibdcentre@muhc.mcgill.ca

If you contact the IBD centre for an urgent appointment, you will be asked to fill out a short questionnaire in order to evaluate your disease activity, before we can offer you an urgent appointment.

Examples of when to request an urgent care appointment

YES (urgent) • New severe abdominal pain • New anal pain • Fever that doesn't go away • Recurrent, frequent non-bloody vomiting that doesn't stop • Continuous rectal bleeding

NO (non-urgent) • Medication refills • Change in insurance • Appointments/scheduling • New, non-severe symptoms • Long-standing or occasional symptoms • General questions

Sincerely,

IBD Centre, McGill University Health Centre
Montreal General Hospital
Email: centreMU.ibdcentre@muhc.mcgill.ca

Disclaimer
*By contacting the urgent appointment email account of the IBD Centre of the McGill University Health Centre you agree that you will be contacted by one of our IBD nurses or IBD gastroenterology specialists, who is not necessarily your IBD specialist. If necessary, these persons will look into your medical records to objectively evaluate your request before we can offer you the urgent appointment. For emergencies, needing immediate attention, please contact nearest emergency unit.*

Version – 11 April 2017

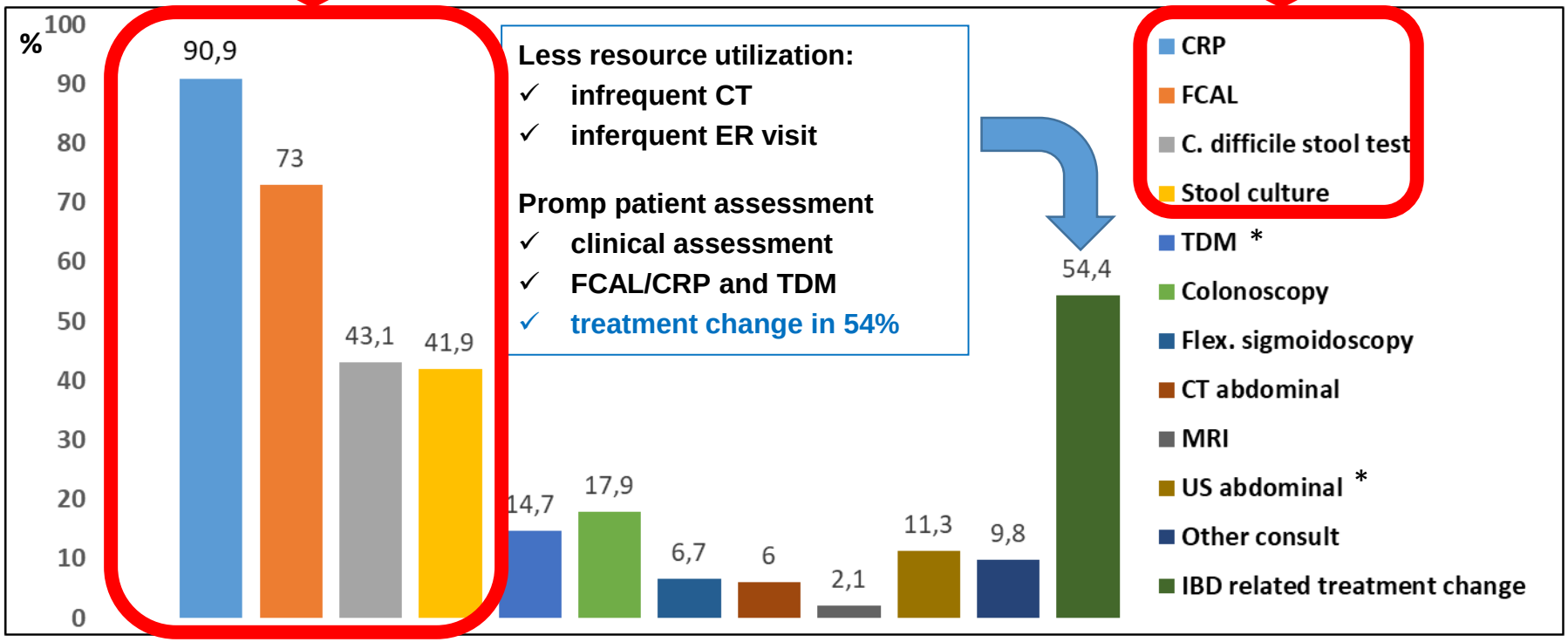
Nene S WJG 2020

Centre universitaire de santé McGill — McGill University Health Centre

# MUHC McGill
# Rapid access clinic: outcomes
## Patient access and resource utilization

**N=419 patients presenting for MD or nurse visit**

- **The reason for RAC appointment was potential disease flare in 71.6% of the patients**
- **The median time to RAC visit with MD was 2 days (IQR: 0-6 days) following the first point of contact by the patient**




* TDM measurement were evaluated in n=217 patients; US examinations were evaluated in n=160 patients

Nene S WJG 2020

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# Patient Management– our practice

**In the last several years we have embarked on**
**tight monitoring and objective outcome assessment in our IBD clinic:**

## Continuous access:

- **We provide 24/7 access** (email and daytime phone reply within 1-3 business day)

## Rapid appointments:

- **For patients with symptomatic relapse within the next 1–2 days**
- **Objective evaluation: laboratory same day, endoscopy-US-CT within 2-3 weeks**

## Close monitoring in patients in remission

- **Every 3–6 months follow-up, clinical/laboratory**
- **Every 12-24 month imaging/endoscopy: (US)/CT/MRI/endoscopy**

## Regular interdisciplinary meetings

- **With radiologists and surgeons**

## Close cooperation with other biological centers

- **2nd opinion if needed**

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McGill University Health Centre

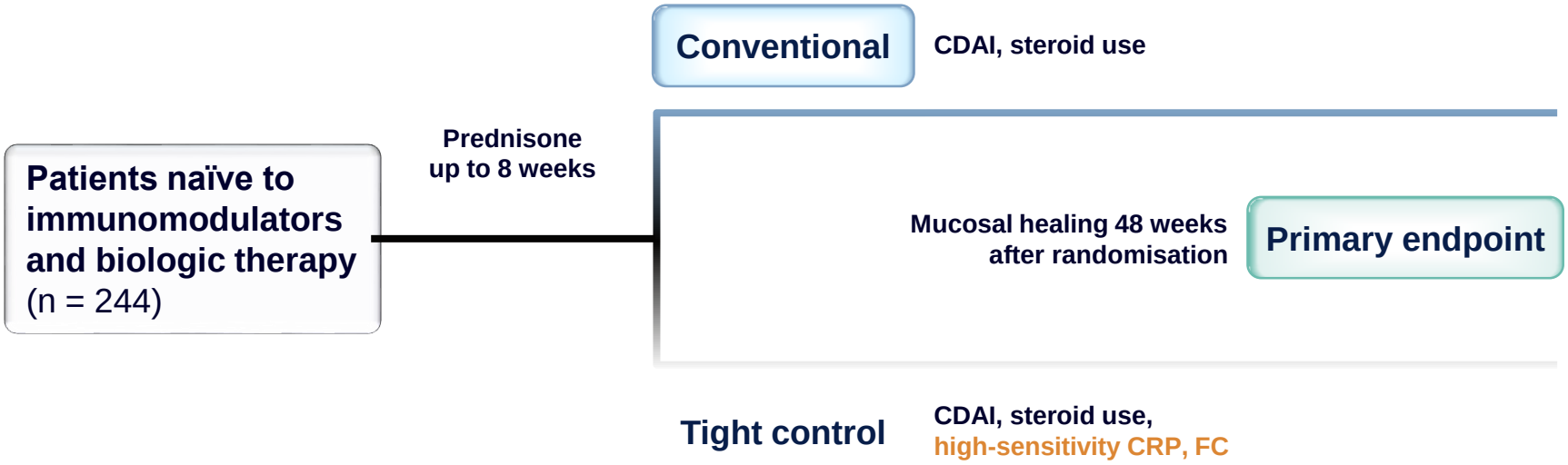
**Does therapeutic strategy/objective assessment and optimization actually modify outcomes?**

**Early, Combination, React, Calm or Pocer?**

# It is not just WHICH drug but HOW we use that!!

## **Keep CALM and measure objetively**: Study Design

Open-label, multicentre study in Europe and Canada
Evaluating two treatment algorithms in CD



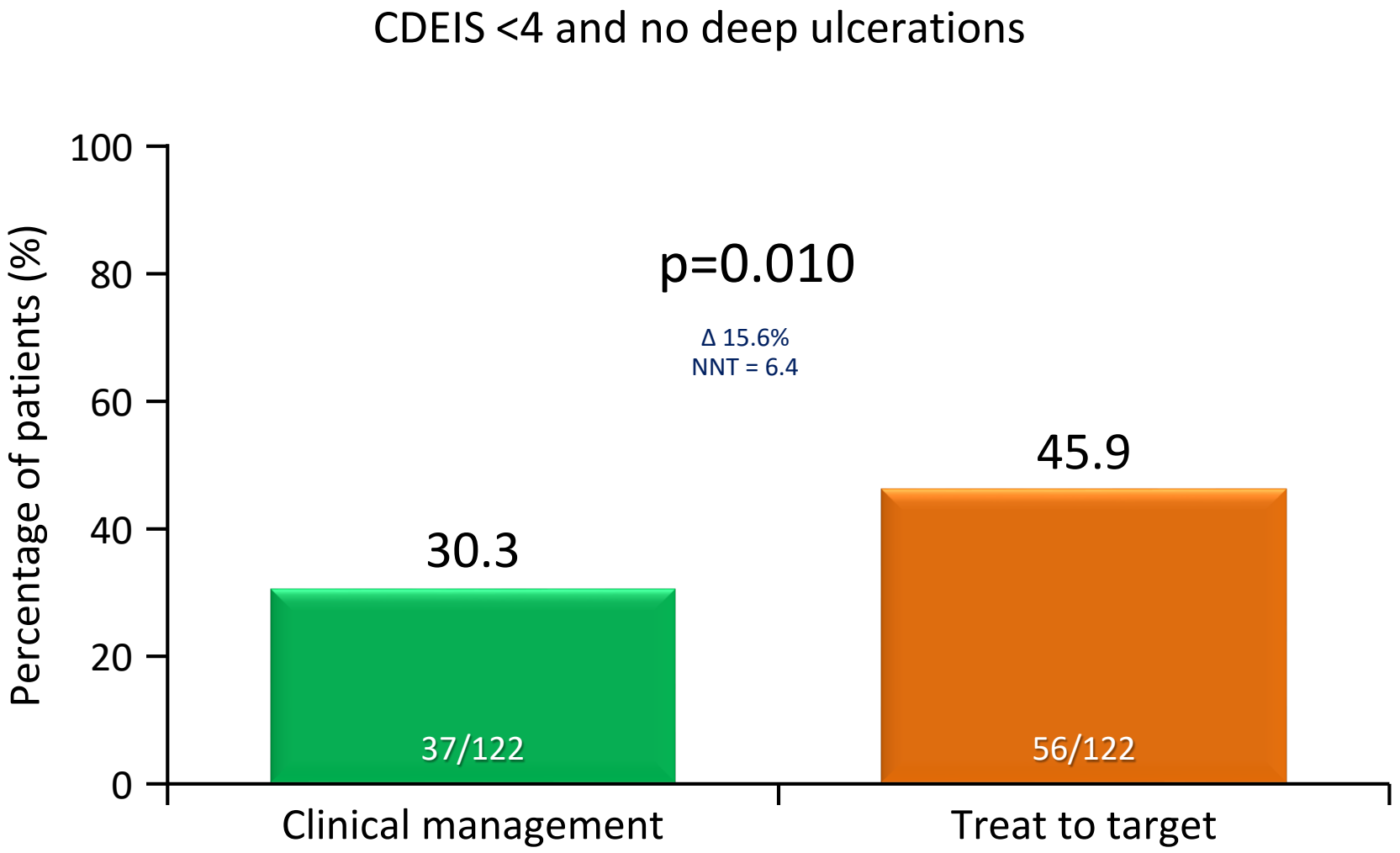

**Treatment intensification in both arms:**

1. **No treatment**
2. **Adalimumab every other week**
3. **Adalimumab weekly**
4. **Adalimumab weekly + azathioprine**


**CDAI: Crohn's disease activity index; CRP: C-reactive protein; FC: faecal calprotectin.**

Colombel JF *et al.* Oral 718, Tuesday May 8th, DDW 2017, Chicago

# Results: Primary Endpoint at 48 Weeks After Randomization




Colombel JF *et al.* Oral 718, Tuesday May 8th, DDW 2017, Chicago

# The art of IBD monitoring today

- **Assess patient prognosis objectively at diagnosis and during follow-up: adapt goals and therapeutic strategy if needed**
- **Discuss and set treatment goals with our patients: be realistic!**
- **Objective monitoring of multiple factors is needed**
- **Composite scores are fancy but not practical, neither more appropriate**
- **Involve our patients: patient empowerment, shared decision making, use MDT approach**
- **Apply 'tight monitoring' and optimise therapy as appropriate**
- **Patient stratification, appropriate timing and objective re-assessment are key elements of success!**

McGill UNIVERSITY

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McGill University Health Centre

# McGill Advanced IBD Fellowship

**One year fellowship**

- Aims: to offer candidates comprehensive and advanced training in the clinical and research aspects of IBD
- Education: in patient care relating to IBD will occur through one-to-one preceptorship with expert IBD clinicians.
- Clinical care (50% of time): The applicant (after 2 years of GI training) is expected to participate directly in the out- and inpatient care and endoscopy of IBD patients in conjunction with the IBD faculty
- Research (50% of time): will include clinical trials, observational studies, studies related to outcomes, decision analyses, and translational projects

**Inquire: Peter LAKATOS**
Director of IBD Centre
Professor of Medicine

McGill University Health Centre, Division of Gastroenterology
Montreal General Hospital, 1650 Ave. Cedar, D7.201, Montreal, QC, H3G 1A4
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