GI ReConnect

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GI Health Foundation

GI ReConnect

Applying Treat to Target in Clinical Practice

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Faculty Disclosure

Uma Mahadevan, MD

- Consultant: Abbvie, Janssen, Pfizer, Takeda, Gilead, BMS, Arena, Lilly
- DSMB: Prometheus

Treat to Target

WHAT:

- Going beyond just symptomatic improvement or remission
  - Using clearly defined and objective biomarkers and endoscopy/radiology to prevent progressive bowel damage and complication

HOW:

- Clarify disease activity and severity
- Induce remission rapidly – defined by both patient-reported outcomes and objective markers
  - Crohn's disease PRO: absence of pain and diarrhea/altered bowel habits
  - Ulcerative colitis PRO: absence of rectal bleeding and diarrhea/altered bowel habits
- Maintain steroid-free remission

WHY:

- Change the natural history of IBD
  - Avoid hospitalization and surgery
  - Avoid drug-related and disease-related complications
  - Reduce costs of care

Rubin DT et al. *Am J Gastroenterol Suppl*. 2016;3:4-7; Peyrin-Biroulet L et al. *Am J Gastroenterol*. 2015;110(9):1324-1338.

Monday Morning Office Hours

- 20 M with new diagnosis of moderate to severe pan-UC started on vedolizumab 8 weeks ago, improving.
  - Wants to know when he will be well enough to resume competitive swimming at University
- 42 F with 10 year history of fistulizing and stricturing Crohn's disease.
  - Ileocolonic resection 5 years ago. On infliximab monotherapy
  - Self-discontinued therapy March 2020 and only now returning to care with abdominal pain and anemia

WHAT IS THE TARGET?

What Is the Target for Your Patient?

Desired outcomes of T2T approach

Early disease: Complete absence of symptoms, no disease progression, no complications or disability, and normal QoL

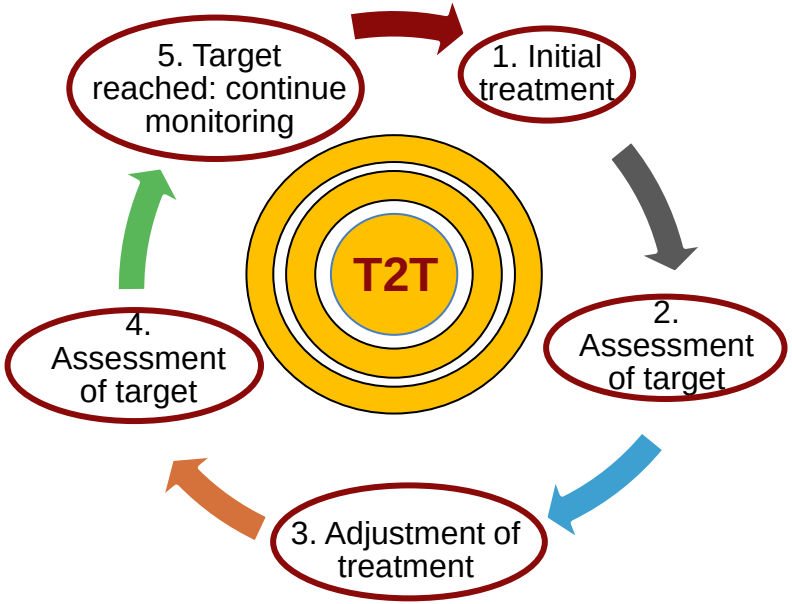
Late-stage disease: Stabilization of noninflammatory symptoms, no progression of damage or disability, and improved QoL

QoL, quality of life.

1. Panaccione R et al. *Inflamm Bowel Dis.* 2013;19(8):1645-1653; 2. Peyrin-Biroulet L et al. *Am J Gastroenterol.* 2015;110(9):1324-1338; 3. Peyrin-Biroulet L et al. *Nat Rev Gastroenterol Hepatol.* 2013;10(6):345-351.

Treat to Target (T2T) Is Rationale-Based Approach to Treatment Selection Using Systematic Adjustments

Shared Patient Decision Making



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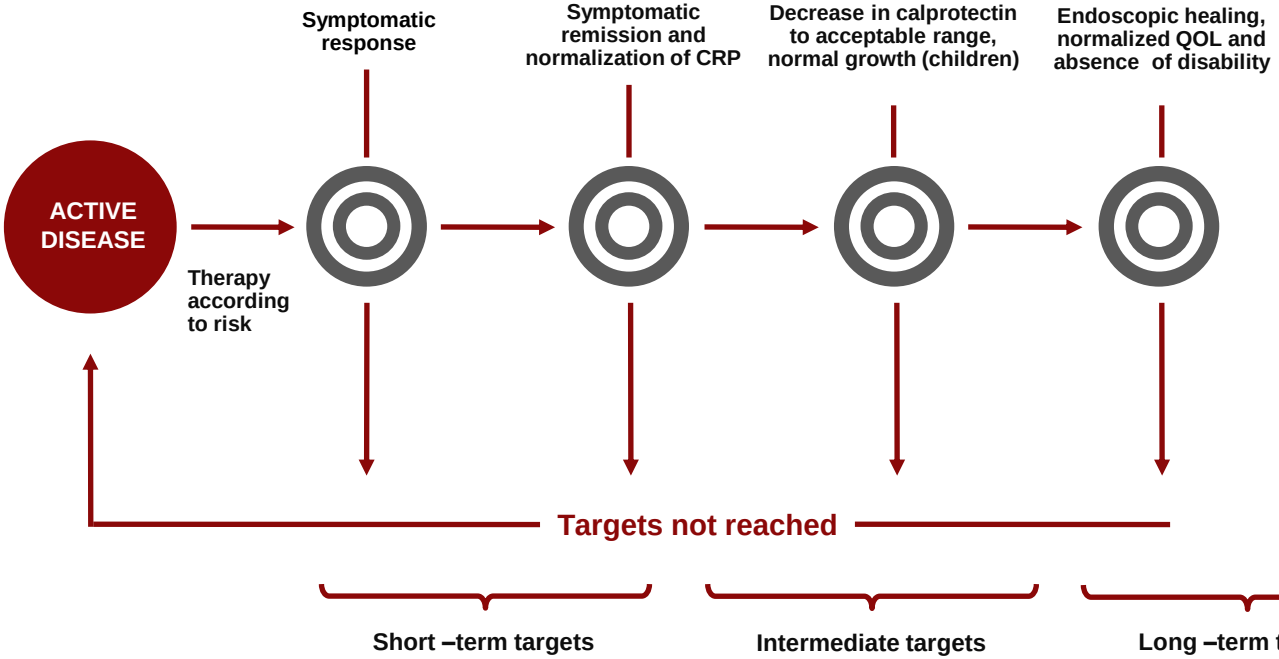
What Target Should I Use?

(STRIDE 2) Treatment Targets in Both CD and UC



Consider but not formal targets:

- Transmural healing: Crohn's Disease
- Histological healing: Ulcerative Colitis

Turner D et al. *Gastroenterology.* 2020.

Overview of Biomarkers in IBD

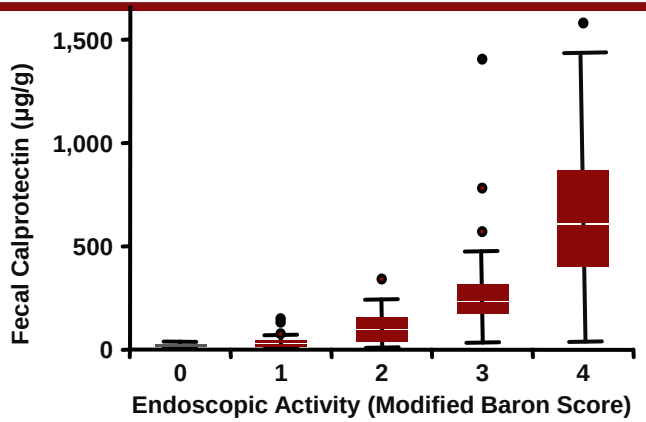
Biomarker	Description	Clinical Considerations
Calprotecin[1,2]	Granulocyte cytosolic protein Stable in feces for days	• Elevated in NSAID enteropathy, cancer, celiac disease, microscopic colitis • Sensitivity and specificity vary greatly based on cutoff value
Lactoferrin[1,2]	Neutrophil granule protein Stable in feces	
C-reactive protein (CRP)[1]	Acute-phase protein Produced in liver under influence of IL-6/TNF-α/IL-1β Short half-life (~19 hours)	• May be more elevated in CD than in UC • Elevated in other conditions (eg, infections, obesity, CAD) • May be low in ileal disease or those with low BMI, even in active disease • Minimal or no CRP response in 10%-40% • May be influenced by genetic polymorphisms
Erythrocyte sedimentation rate (ESR)[1]	Rate RBCs settle in 1 hour	• Influenced by anemia, gender, pregnancy • Peaks less rapidly than CRP • Resolves more slowly than CRP

CD, Crohn's disease; CAD, coronary artery disease; CRP, C-reactive protein; IL, interleukin; NSAID, nonsteroidal antiinflammatory drug; RBC, red blood cell;
TNF, tumor necrosis factor.

1. Montalto M et al. *Eur Rev Med Pharmacol Sci*. 2013;17:1569-1582; 2. Vermeire S et al. *Gut*.2006;55:426-431.

Fecal Calprotectin Correlates With Endoscopic Activity in UC

- 228 UC patients undergoing colonoscopy
- Endoscopic findings correlated with:
  - Clinical assessment (Lichtiger Index)
  - Biomarkers (FC, CRP)
- FC best correlated with endoscopy (better than clinical index, CRP)
- FC also useful in distinguishing degree of inflammation in UC



Baron Index	FC (µg/g)
0	16
2	102
4	611

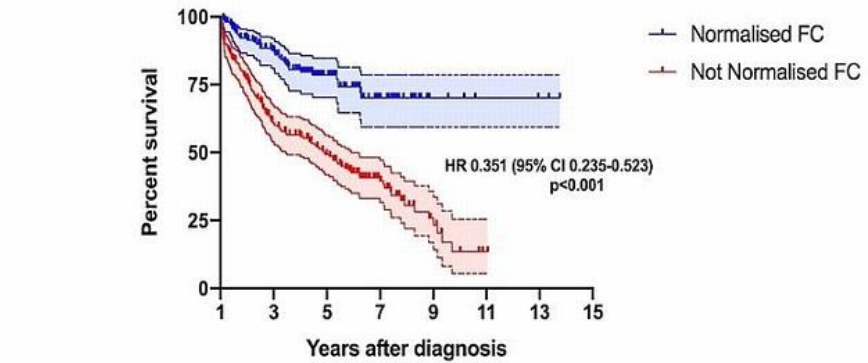
	Sensitivity (%)	Specificity (%)	ROC Area
Calprotectin ≥ 57 µg/g	91	90	0.939
Lichter Index ≥ 4	82	74	0.841
CRP ≥ 6 mg/L	68	72	0.778

Schoepfer A et al. *Inflamm Bowel Dis*. 2013;19(2):332-341; CRP, C-reactive protein; FC, fecal calprotectin

Normalization of Fecal Calprotectin Within 12 Months of Diagnosis Is Associated With a Reduced Risk of Disease Progression in CD

- Retrospective cohort study at tertiary IBD center
  - 375 patients with CD with FC >250 µg/g at diagnosis with ≥1 follow-up FC within first 12 months of diagnosis
- Patients who normalized FC within 12 months of diagnosis had significantly lower risk of composite disease progression
- Patients initiated on a biologic within 3 months of diagnosis significantly more likely to normalize FC within 12 months of diagnosis (OR 4.288; 95% CI 1.585-11.0601; *P*=0.004)

Composite disease progression[a] stratified by normalization of FC (<250 µg/g) within 12 months of diagnosis



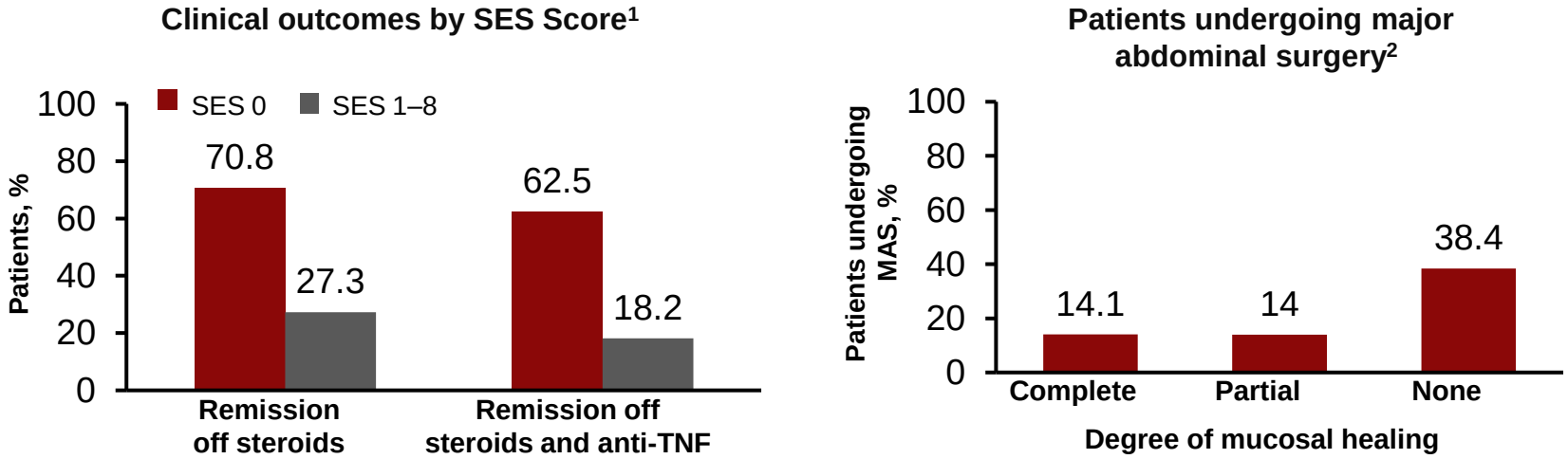
No. at risk

Normalised FC	163	108	61	28	7	4
Not Normalised FC	212	108	72	33	11	2

CI, confidence interval; FC, fecal calprotectin; HR, hazard ratio.
aProgression in Montreal behavior/new perianal disease or hospitalization or surgery.
Plevris N et al. Presented at DDW Virtual Conference 2020. May 3, 2020.

Mucosal Healing After Therapy Predicts Improved Outcomes in Crohn's Disease

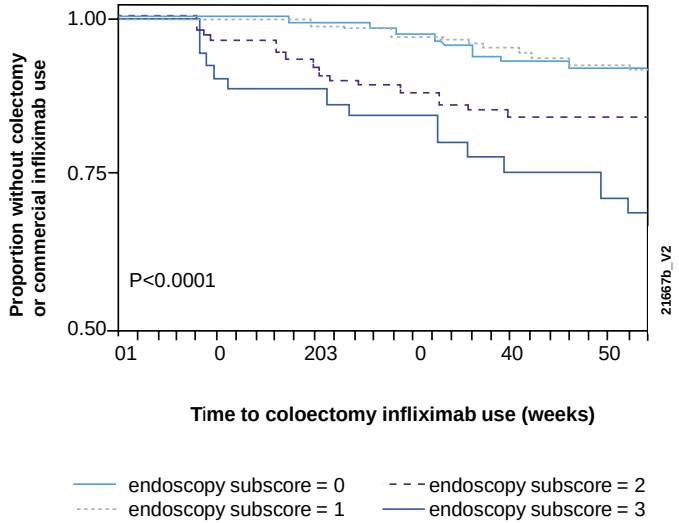
Degree of Mucosal Healing and Risk of Major Endoscopy Surgery[2]



MAS, major abdominal surgery; SES, Simple Endoscopic Score

1. Baert F et al. *Gastroenterology*. 2010;138:463-468; 2. Schnitzler F et al. *Inflamm Bowel Dis*. 2009;15:1295-1301.

Mucosal Healing and Time to Colectomy in Infliximab-Treated Patients

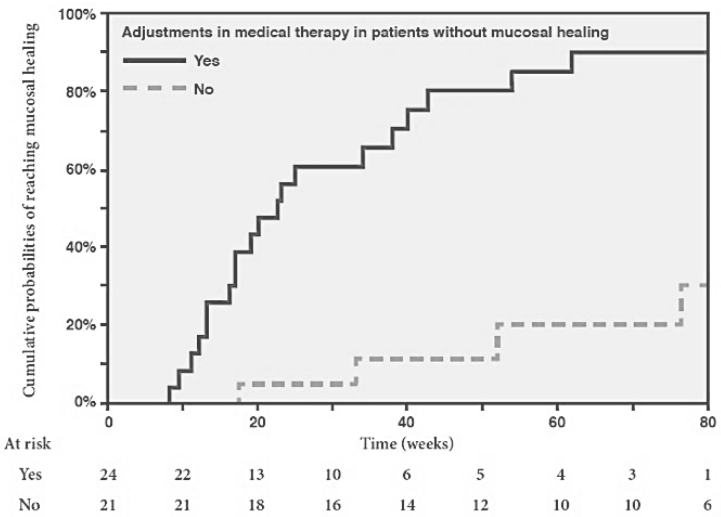


0 = NORMAL **1 = MILD** **2 = MODERATE** **3 = SEVERE**

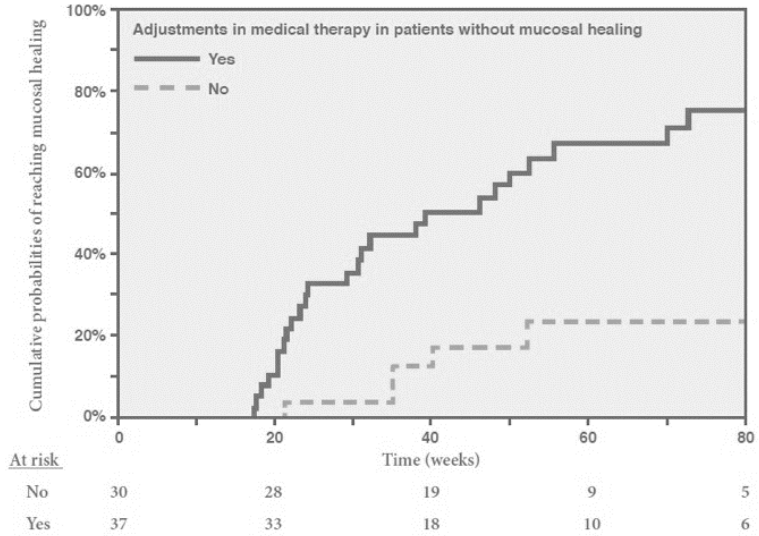
Colombel JF et al. *Gastroenterology.* 2011;141:1194-1201.

Retrospective Assessment of Treatment Adjustments Demonstrates Feasibility of Achieving MH in UC and CD

Ulcerative Colitis[1]

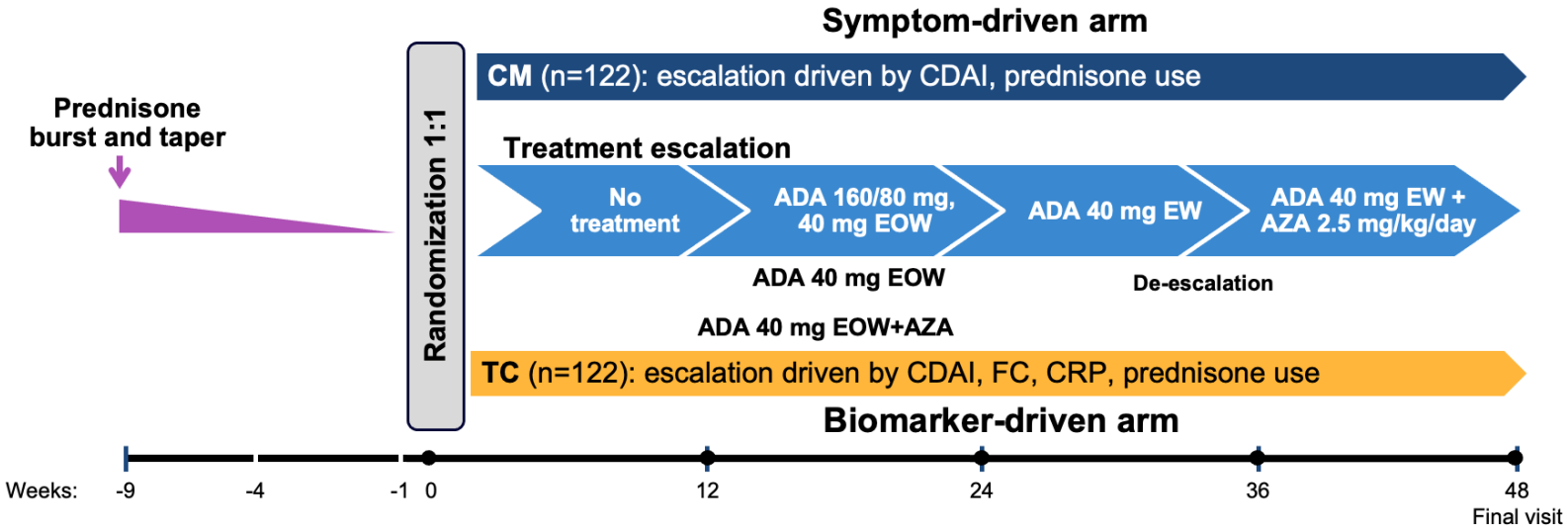


Crohn's Disease[2]



1. Bouguen G et al. *Inflamm Bowel Dis*. 2014;20(2):231-239;
2. Bouguen G et al. *Clin Gastroenterol Hepatol.* 2014;12(6):978-985.

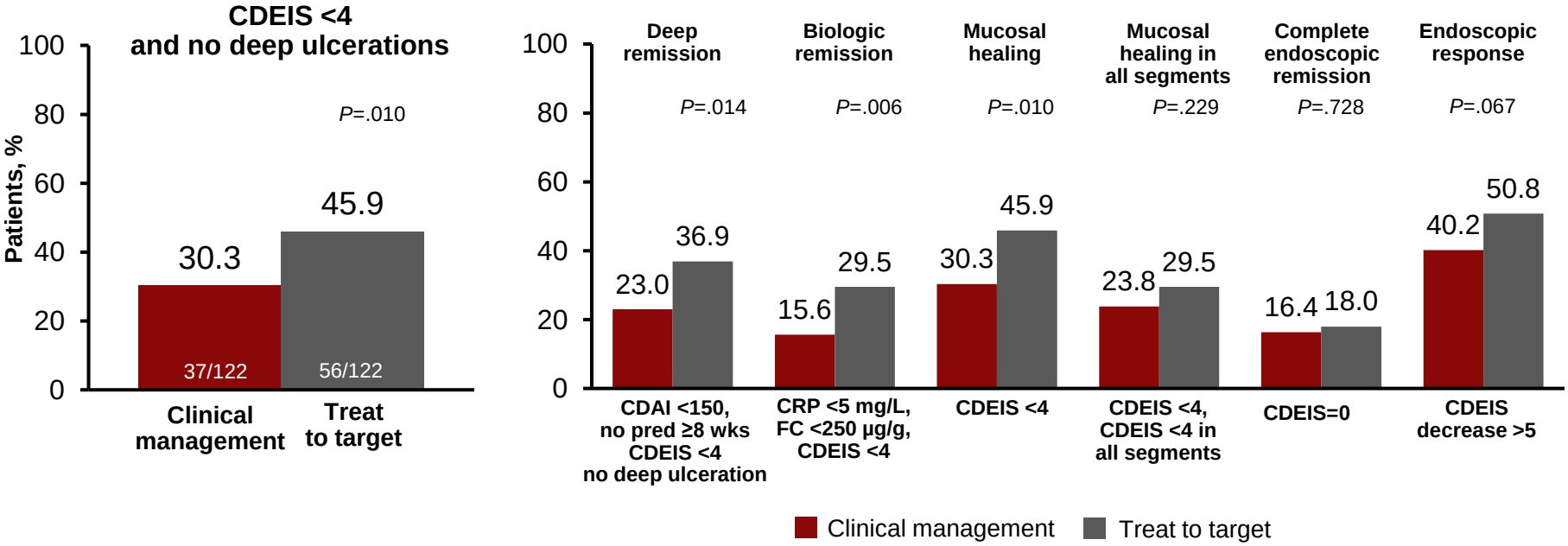
CALM: Study Design



ADA, adalimumab; AZA, azathioprine; CDAI, Crohn's disease activity index; CM, clinical management; CRP, C-reactive protein; EOW, every other week; EW, every week; FC, fecal calprotectin; TC, tight control.

Colombel JF et al. *Lancet.* 2018;390(10114):2779-89.

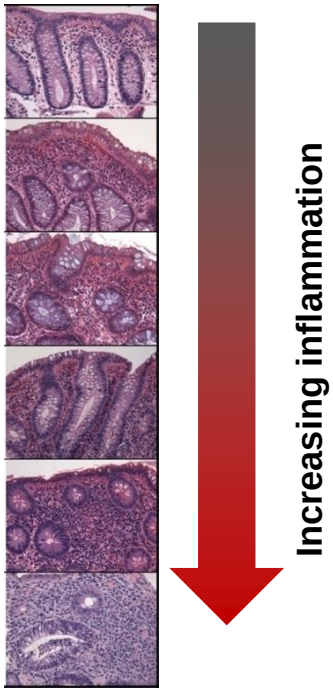
CALM: Primary and Secondary Endpoints



Colombel JF et al. *Lancet.* 2018;390(10114):2779-89.

Histopathology as a Marker of Mucosal Healing in IBD?

- IBDs (Crohn's disease and ulcerative colitis) are diseases of mucosal inflammation
- Histology is necessary (but not always sufficient) for accurate diagnosis of IBD
- Histologic degree of inflammation is associated with some clinical endpoints of interest
  - Time to relapse[1]
  - Risk of neoplasia[2,3]



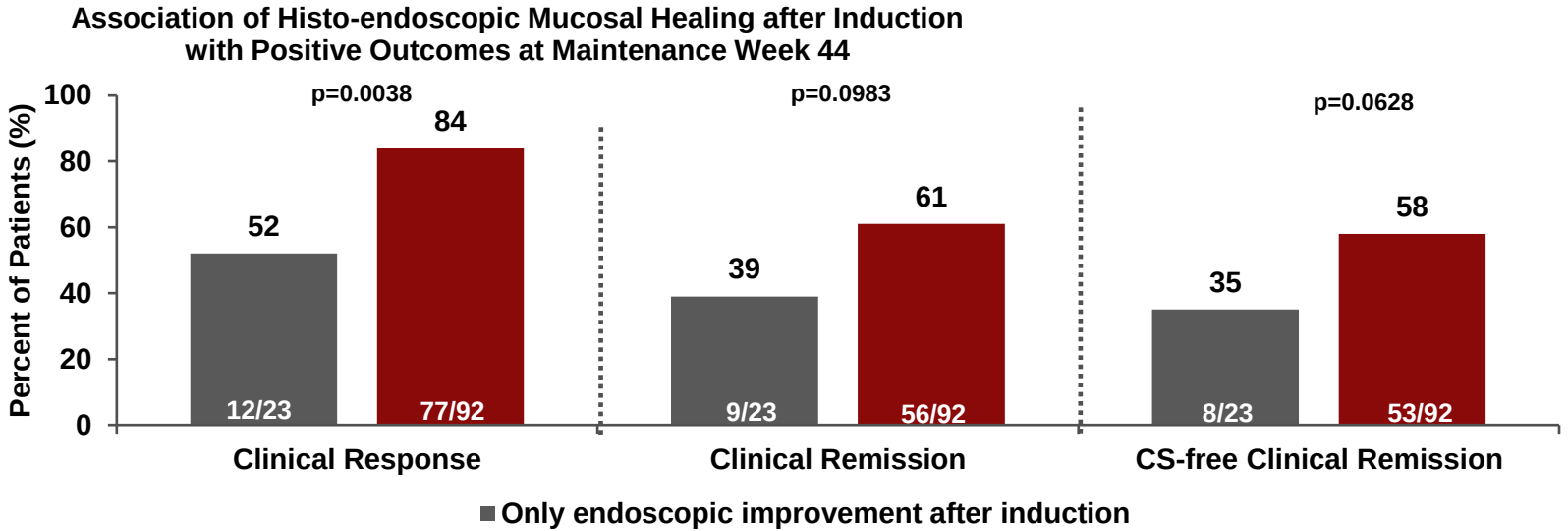
1. Riley et al. *Gut*. 1991;32:174-178; 2. Rutter et al. *Gastroenterology*. 2004;126:451-459;
3. Rubin et al. *Clin Gastroenterol Hepatol.* 2013.

Challenges to the Use of Histopathology to Assess Mucosal Healing in IBD

- Patchiness of disease activity (CD and UC)
- Represents a small surface area of mucosa
- Requires endoscopist “judgment” for sampling
  - In worst disease, tend to biopsy areas that are less involved
  - In milder disease, tend to biopsy areas that are more involved
- Requires multiple people and levels of expertise for processing and interpretation
- *“Don’t let perfect (histologic remission) be the enemy of good (endoscopic remission)”…and hard to interpret in Crohn’s disease*

1. Kim B et al. *Am J Gastroenterol.* 1999 Nov;94(11):3258-62; 2. Bernstein CN et. al. *Gastrointest Endosc.* 1995;42(3):232-7.

UNIFI: Histo-Endoscopic Mucosal Healing After Induction Is Associated With Positive Outcomes at Maintenance Week 44



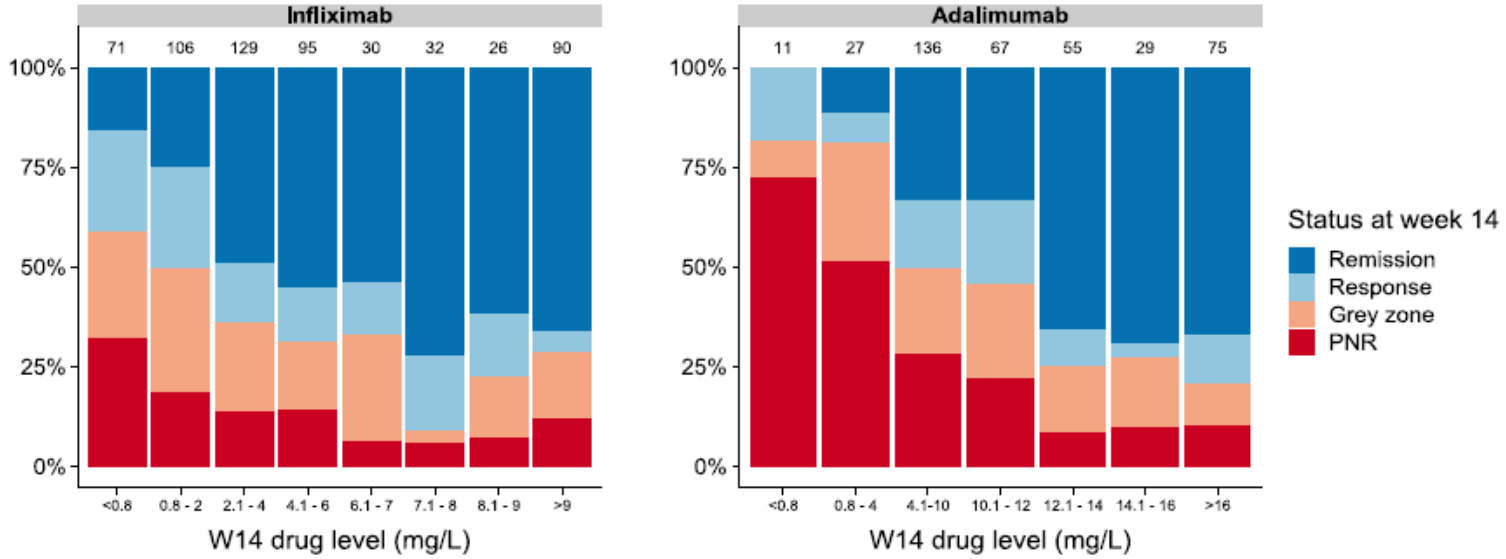
- Histologic improvement: Neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue
- Endoscopic improvement: Mayo Endoscopic Score 0 or 1
- Histo-endoscopic mucosal healing: Histologic and endoscopic improvement

Adapted from Li et al. *UEGW.* 2019 #P1008.

Proactive Therapeutic Drug Monitoring (TDM)

Definition	• Measurement of trough concentrations and antibody levels with the goal of optimizing drug concentrations to achieve a threshold drug concentration at specific time-points (eg, during induction, at end of induction or during maintenance)
Goals	• Improve response rates and prevent secondary loss of response by targeting drug concentrations considered to be in the optimal therapeutic range • Facilitate longer persistence of drug as well as improve other more objective outcomes
When to Implement	• During maintenance (most studies) • Optimized (biologic) monotherapy instead of combination with thiopurine or MTX • When stopping immunomodulator (in combination with anti-TNF) • Following reactive TDM • During induction or post-induction

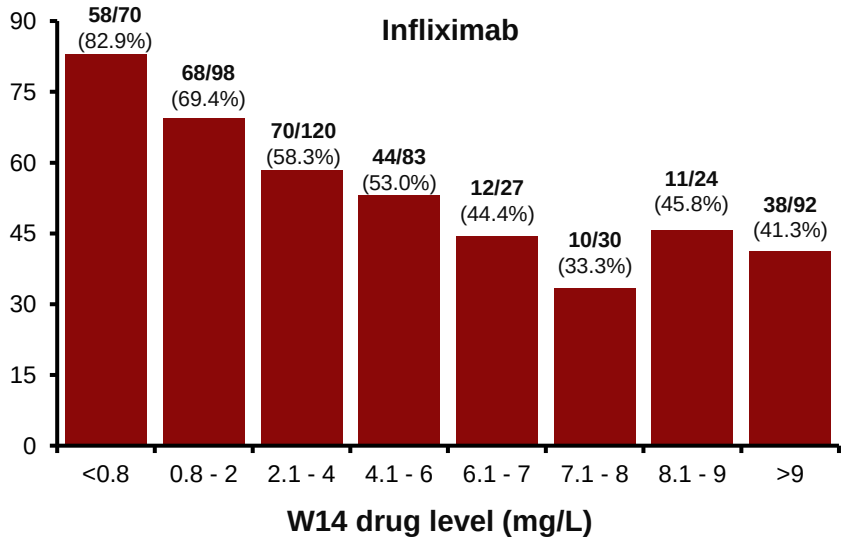
The Pants Study: Low Drug Concentrations at Week 14 Are Associated With Primary Non-Response (24% of Patients)

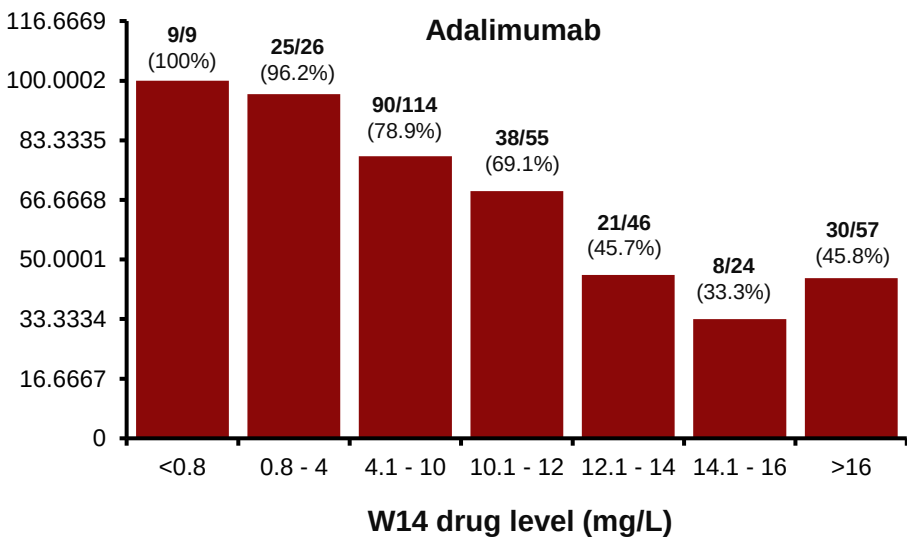


Optimal week 14 drug concentrations
infliximab 7 mg/L; adalimumab 12 mg/L

Kennedy et al. *Lancet Gastro Hepatology.* 2019. http://dx.doi.org/10.1016/ S2468-1253(19)30012-3.

Low Drug Concentrations at Week 14 Are Associated With Non-Remission at Week 54 (and Non-Remission Seen in 60% of Patients)





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Kennedy et al. *Lancet Gastro Hepatology.* 2019. http://dx.doi.org/10.1016/ S2468-1253(19)30012-3.

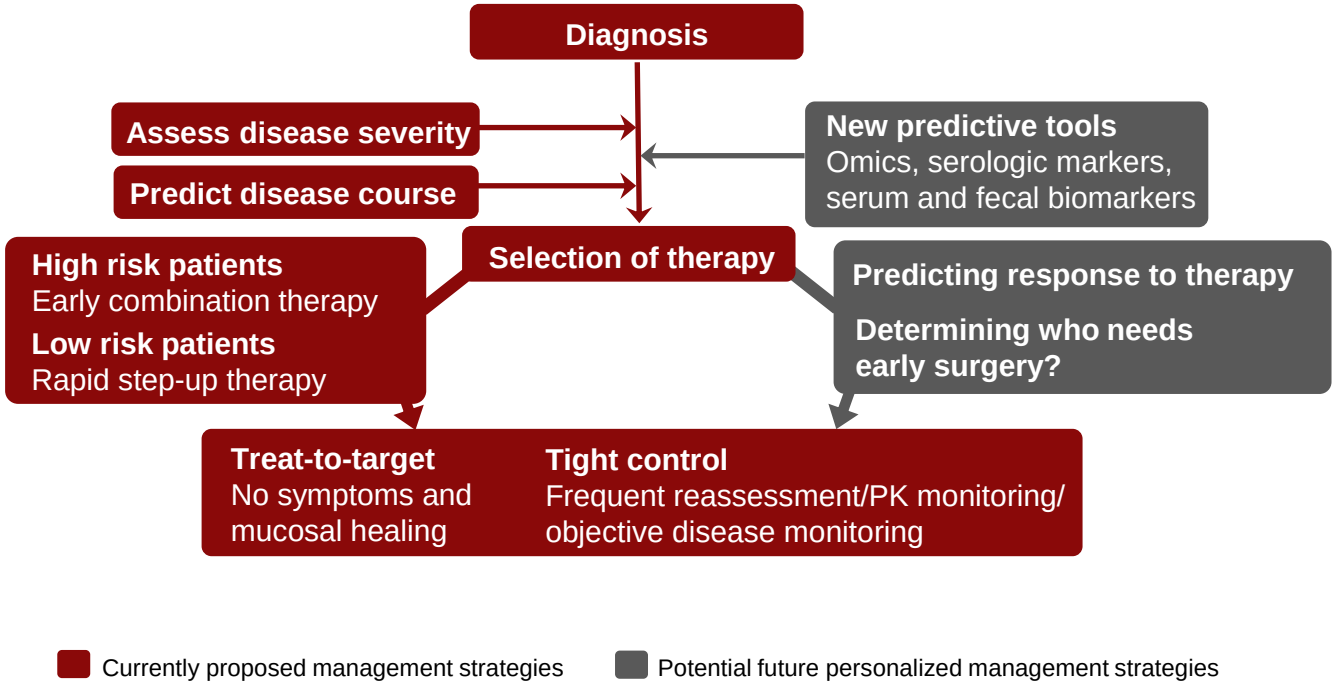
Monday Morning Office Hours

- 20 M with new diagnosis of moderate to severe pan-UC started on vedolizumab 8 weeks ago, improving. Competitive athlete
  - Flex sig at 8-14 weeks to confirm mucosal healing
    - Mayo 0: Every 6 month labs (CRP)
    - Mayo 2-3: adjust therapy and monitor
    - Mayo 1?:
      - Asymptomatic with good trough levels → follow calpro and symptoms
      - Symptomatic: TDM, adjust therapy (increase or change)
- 42 F with 10 year history of fistulizing and stricturing Crohn's disease.
  - Ileocolonic resection 5 years ago. Symptomatic off therapy for 1 year
    - Restart infliximab with TDM or change mechanism (scope/image prior to therapy)
    - Repeat colonoscopy 6 months after therapy. If active disease, TDM, adjust
    - Continue to follow with 6 months labs, CRP and/or calprotectin

Individualizing Care

- Make a plan for each patient based on disease and individual risk factors
- Decide up front what success looks like/ what are the goals for this patient
  - Pick something you will follow for each patient (targets)
  - UC: fecal calprotectin (sometimes elevated from pseudopolyps even when mucosal inflammation better), colon/flex sig
  - Symptoms track better in UC than CD
- Depending on the drug being used, the amount of time to achieve mucosal healing or clinical improvement will differ

The Future of IBD Therapy



Colombel JF et al. *Gastroenterology.* 2017;152:351–361.