GI Alliance

Advancing GI Patient Care 2021

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Treat to Target in Inflammatory Bowel Disease

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Faculty Disclosures

Bincy P. Abraham, MD, MS, AGAF, FACG

Dr. Abraham has disclosed that she serves as a consultant for AbbVie, Takeda, BMS, Janssen, Lilly, Ferring, Medtronic, Pfizer, and Samsung Bioepis. She also serves on advisory boards and as a speaker for AbbVie, Janssen, Takeda, BMS, and Pfizer.

Learning Objectives

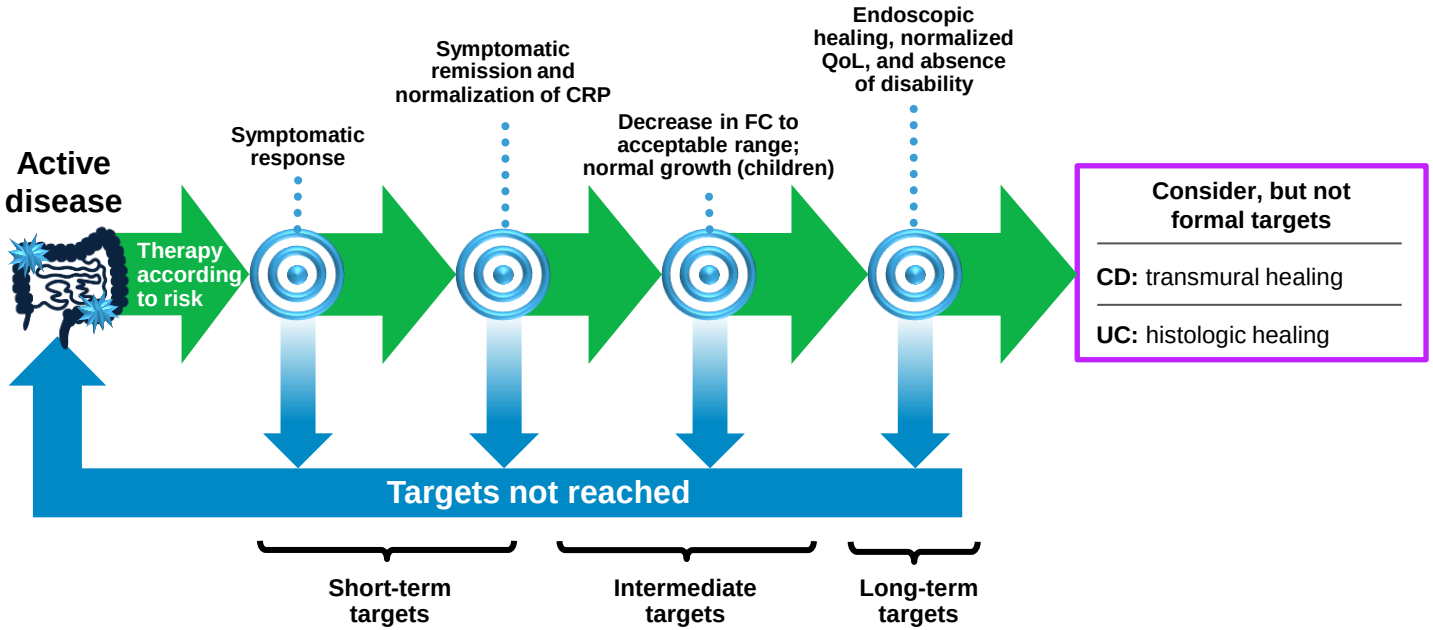
1. Understand the utility of treat to target strategy to simplify the management of IBD patients.
2. Assess targets of mucosal healing used in treat-to-target strategies.
3. Understand the evidence that exists to support the use of these strategies in IBD patients.

Treating to Target in IBD

Treating to Target in IBD

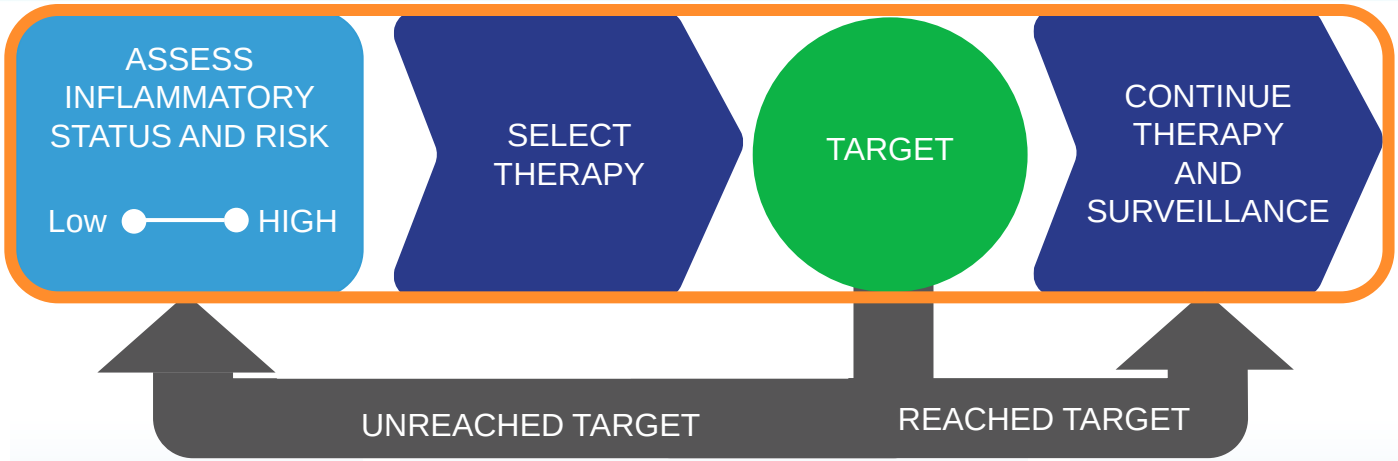
That's what I thought too until I started to follow the Treat to Target Strategy!

Update to STRIDE (STRIDE-II): Treatment Targets in Both CD and UC



Turner D et al. *Gastroenterology*. 2020;Dec 21:S0016-5085(20)35572-4. Epub ahead of print.

Treat to Target



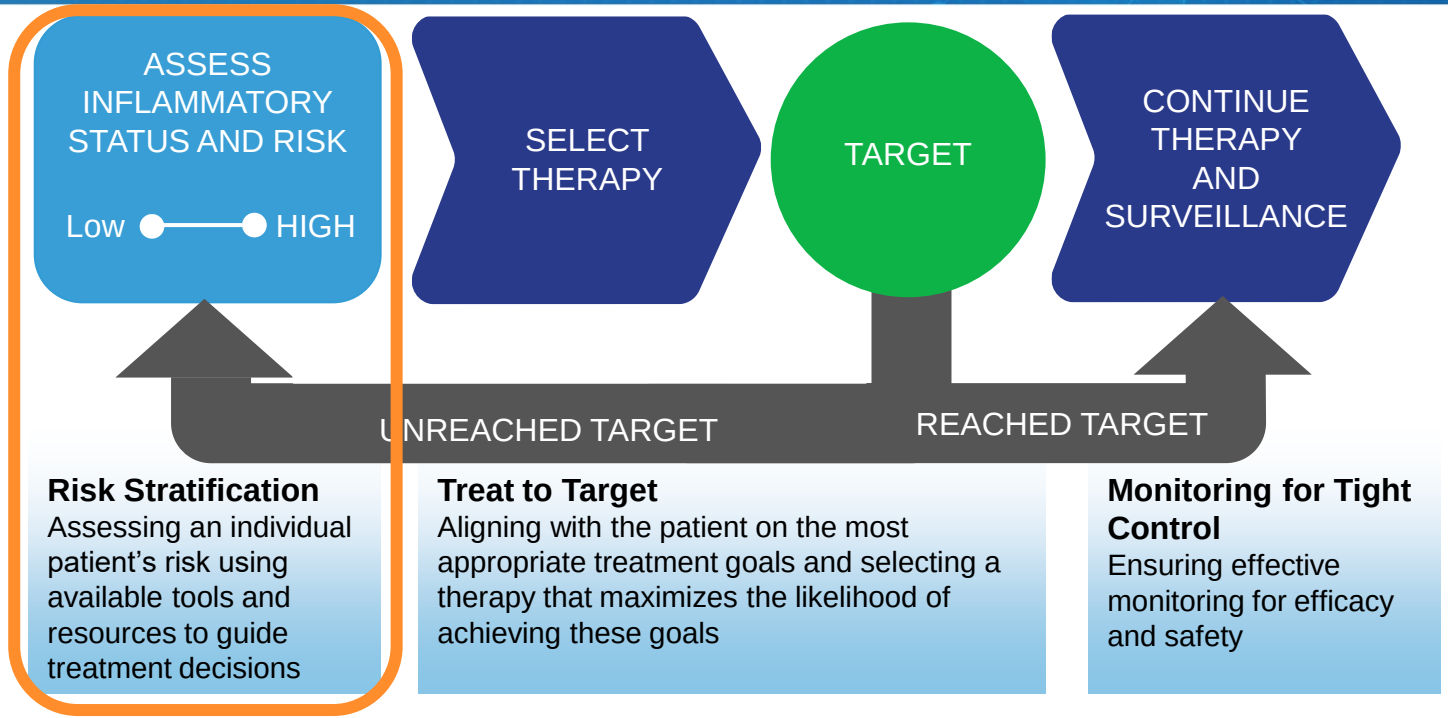
Risk Stratification
Assessing an individual patient's risk using available tools and resources to guide treatment decisions

Treat to Target
Aligning with the patient on the most appropriate treatment goals and selecting a therapy that maximizes the likelihood of achieving these goals

Monitoring for Tight Control
Ensuring effective monitoring for efficacy and safety

Bouguen et al. *Clin Gastroenterol Hepatol*. 2015; Colombel J-F et al. *Gastroenterology*. 2017; Dassopoulous T et al. *Gastroenterol*. 2015; Sandborn WJ. *Gastroenterology*. 2014; Bossuyt P et al. *Curr Treat Options Gastroenterol*. 2016.

Treat to Target



Bouguen et al. *Clin Gastroenterol Hepatol*. 2015; Colombel J-F et al. *Gastroenterology*. 2017; Dassopoulous T et al. *Gastroenterol*. 2015; Sandborn WJ. *Gastroenterology*. 2014; Bossuyt P et al. *Curr Treat Options Gastroenterol*. 2016.

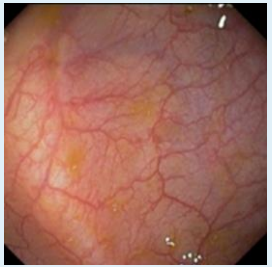
UC Disease Severity

Poor prognostic factors

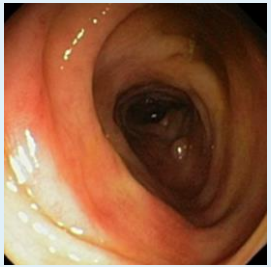
- Age <40 years
- Extensive colitis
- Severe endoscopic disease (Mayo endoscopic subscore 3, UCEIS ≥7)
- Hospitalization for colitis
- Elevated CRP levels
- Low serum albumin levels

The greater the number of poor prognostic factors, the worse the prognosis as measured by likelihood of colectomy

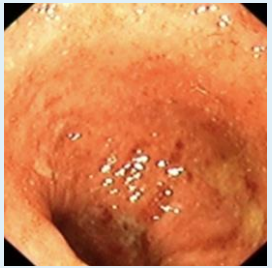
Mayo Endoscopic Subscore (0-3)



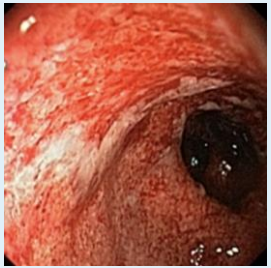
0
Normal or inactive disease



1
Mild disease (erythema, decreased vascular pattern, mild friability)



2
Moderate disease (marked erythema, absent vascular pattern, friability, erosions)



3
Severe disease (spontaneous bleeding, ulcerations)

UCEIS, Ulcerative Colitis Endoscopic Index of Severity.

Kornbluth A et al. *Am J Gastroenterol*. 2010;105(3):501-524; Dassopoulos T et al. *Gastroenterology*. 2015;149(1):238-245; Rubin DT et al. *Am J Gastroenterol*. 2019;114(3):384-413; de Lange T et al. *BMC Gastroenterol.* 2004;4:9. Licensee BioMed Central Ltd; e Chambrun GP et al. *Nat Rev Gastroetnerol Hepatol.* 2010;7:15-29.

ACG Guideline UC Severity Definitions (Symptoms and Endoscopy)

	Remission	Mild	Moderate to severe	Fulminant
Stools per day	Formed stools	<4	>6	>10
Blood in stools	None	Intermittent	Frequent	Continuous
Urgency	None	Mild, occasional	Often	Continuous
Hemoglobin	Normal	Normal	<75% of normal	Transfusion required
ESR (mm/h)	<30	<30	>30	>30
CRP (mg/L)	Normal	Elevated	Elevated	Elevated
FC (µg/g)	<150-200	>150-200	>150-200	>150-200
Endoscopy (Mayo subscore)	0-1	1	2-3	3
UCEIS	0-1	2-4	5-8	7-8

ACG, American College of Gastroenterology; ESR, erythrocyte sedimentation rate.

Rubin DT et al. *Am J Gastroenterol*. 2019;114(3):384-413.

CD Disease Severity

SES-CD Score

Variable	0	1	2	3
Size of ulcers (cm)	None	Aphthous ulcers (diameter 0.1-0.5)	Large ulcers (diameter 0.5-2)	Very large ulcers (diameter >2)
Ulcerated surface	None	<10%	10%-30%	>30%
Affected surface	Unaffected segment	<50%	50%-75%	>75%
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

SES-CD = sum of all variables for the 5 bowel segments.

Segments
- Rectum
- Left colon
- Transverse
- Right colon
- Ileum

Scoring
Inactive
≤6: mild
7-15: moderate
≥16: severe

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

Consider Prognosis

Poor prognostic factors

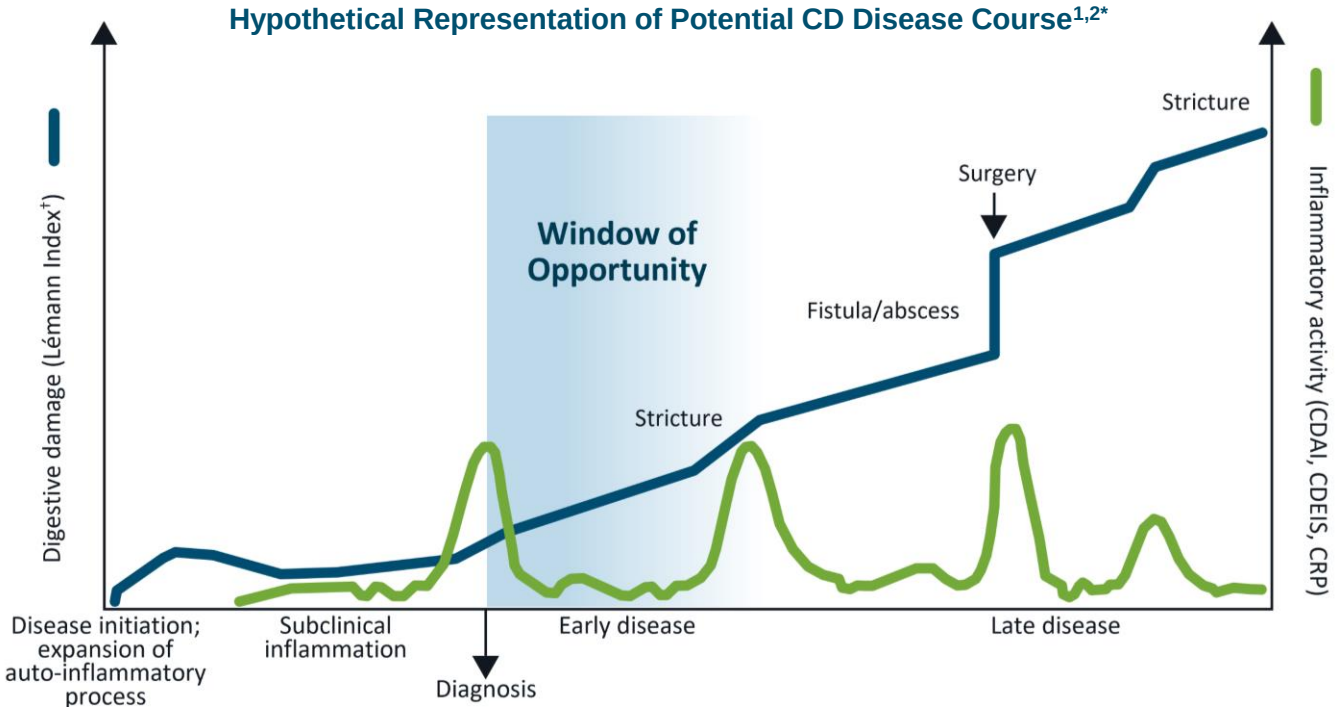
- Young age
- Initial extensive bowel involvement
- Perianal or severe rectal disease
- Penetrating or stenosing at diagnosis

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

- Deep ulcerations on endoscopy
- SES-CD >6 is moderate/severe

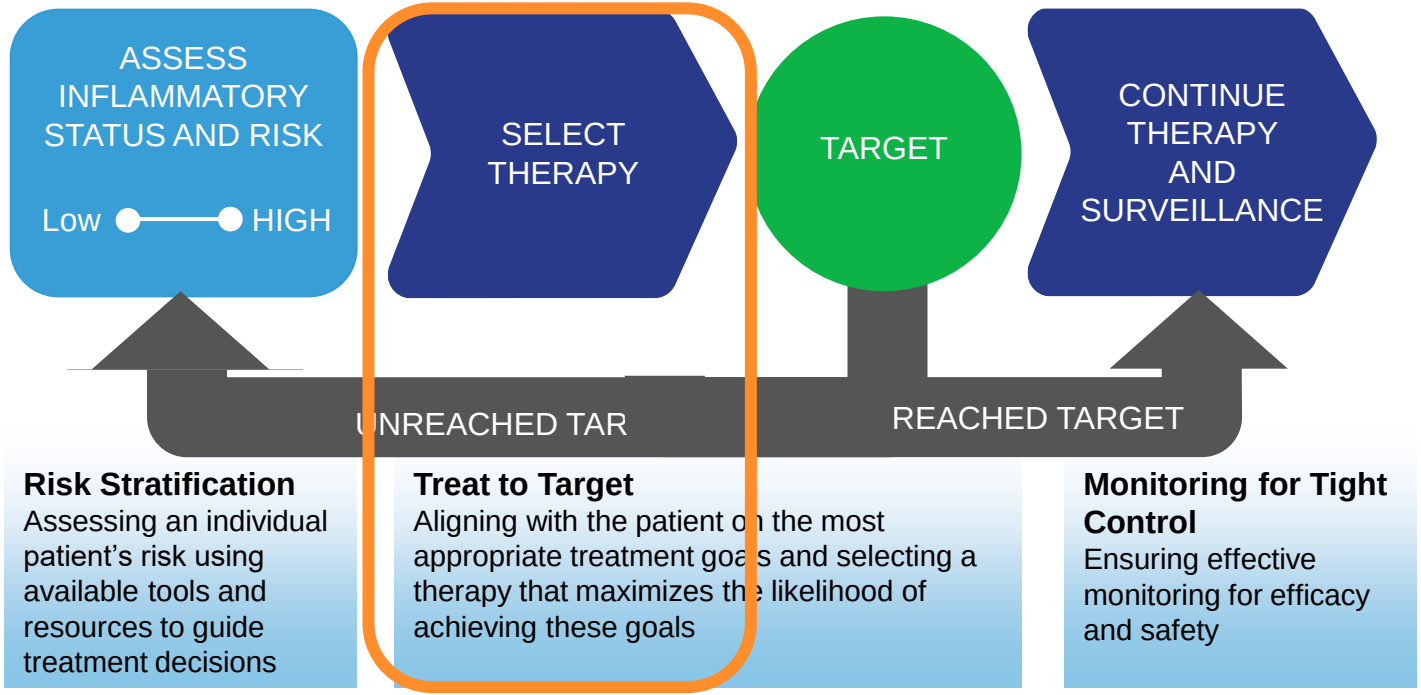
SES-CD, Simple Endoscopic Score for Crohn's disease.
Daperno M et al. *Gastrointest Endosc*. 2004;60(4):505-512. Reproduced with permission of ELSEVIER HEALTH SCIENCE JOURNALS via Copyright Clearance Center.
Lichtenstein GR et al. *Am J Gastroenterol*. 2018;113(4):481-517.

Crohn's Disease Progression



1. Pariente B et al. *Inflamm Bowel Dis*. 2011;17(6):1415-1422;
2. Colombel J-F et al. *Gastroenterology*. 2017;152(2):351-361.

Treat to Target



Bouguen et al. *Clin Gastroenterol Hepatol*. 2015; Colombel J-F et al. *Gastroenterology*. 2017; Dassopoulous T et al. *Gastroenterol*. 2015; Sandborn WJ. *Gastroenterology*. 2014; Bossuyt P et al. *Curr Treat Options Gastroenterol*. 2016.

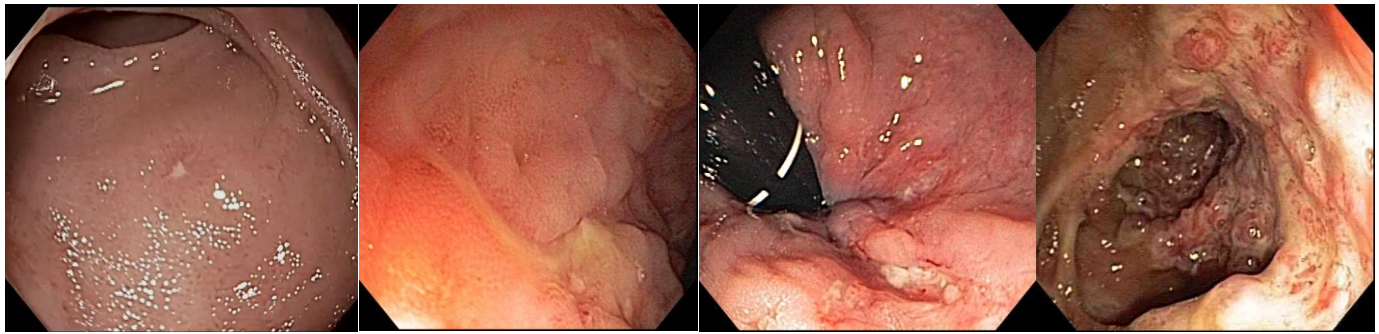
Treating to Targets

There are so many medications out there now. Where do I start?

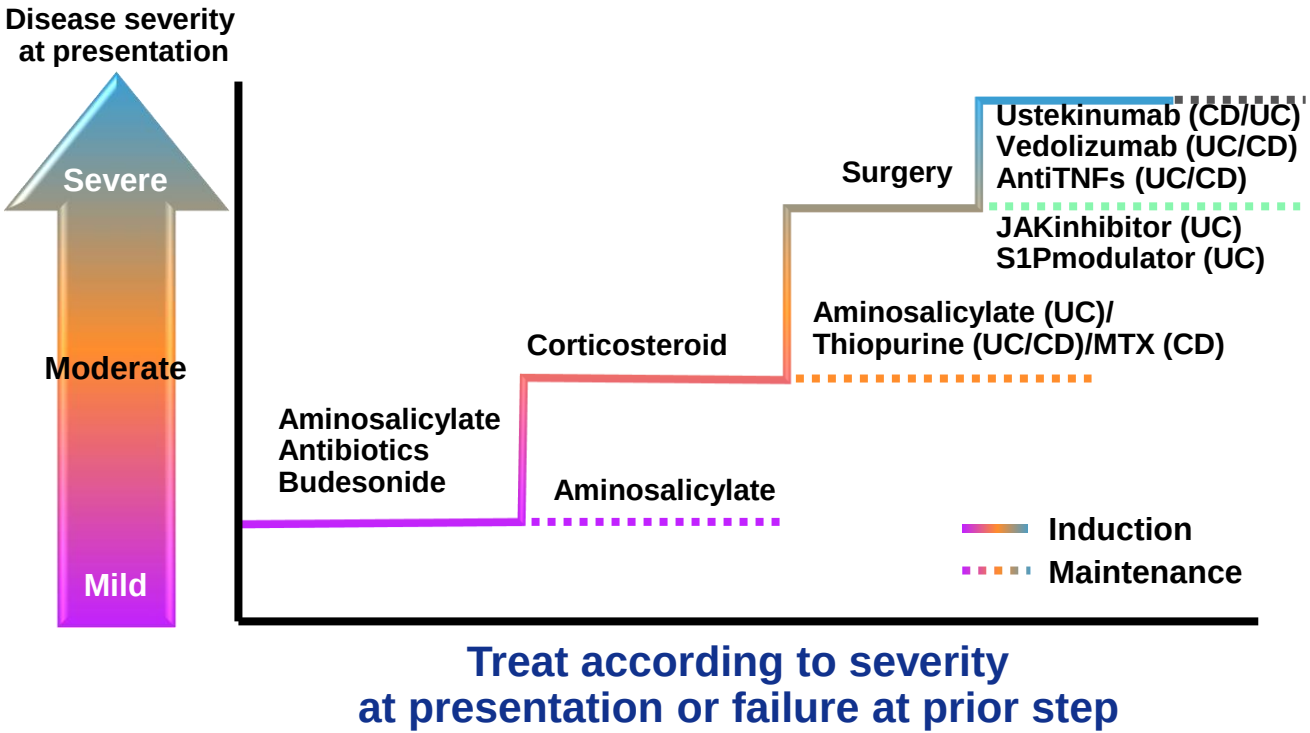
PERSONALIZE!

Personalizing IBD Treatment: Questions to Ask:

FIRST: EVALUATE THE DISEASE	
Disease Severity?	Mild/ Moderate/Severe Surgical History
Disease Location?	Colon/ Small Bowel/Perianal/Upper GI
Disease Extent?	Limited/Extensive
Disease Activity?	In remission/minimally active/active flare



IBD Therapies



MTX=methotrexate; TNF=tumor necrosis factor.
Hanauer SB. *Inflamm Bowel Dis*. 2009.

Personalizing IBD Treatment: Assess for EIMs

Other Organ System Involvement		Treatment

EIMs
 	
* More advanced inflammation.
	Joints
	Skin
	Eyes
	Hepatobiliary
	Others
		• Start: Moderate to Severe Treatment Options
		• *<u>IBD related?</u>*
		  - *Consider gut selective therapies (vedolizumab, ozanimod)*
		• *<u>Not-IBD related:</u>*
		  - *Consider anticytokine, immunomodulators, immunosuppression*

Personalizing IBD Treatment:

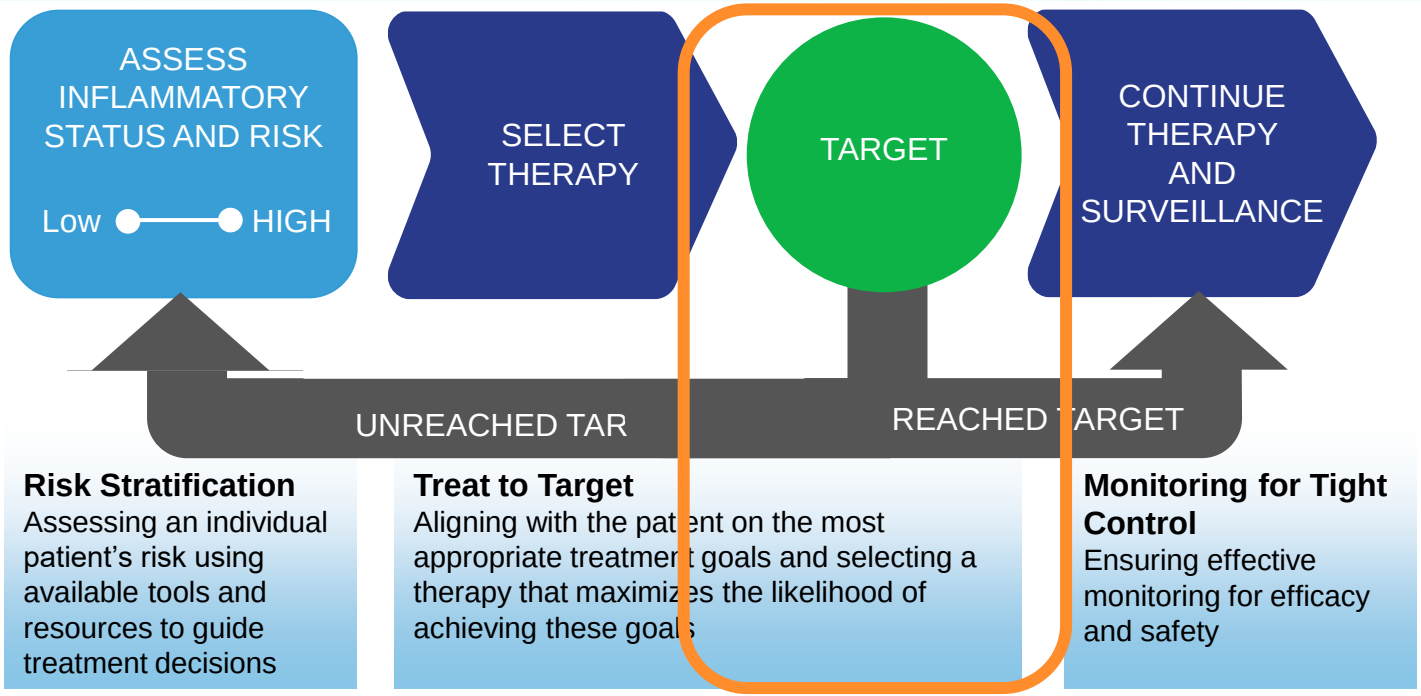
Patient Factors
Cost
Adherence → PO/IV/SQ
Social Support / Mental health
Patient Preferences (IV/SQ/PO)
Women of Childbearing Age
Age

Physician/ Healthcare Factors
Insurance
Ease of access
Infusion Facility
Ability to do TDM
Monitoring for adherence

Personalizing IBD Treatment: Assess Comorbidities

Comorbidities	Treatment
RA PsA Ankylosing Spondylitis Psoriasis Pustular Psoriasis	AntiTNFs, JAKi (No benefit with UST/VDZ) AntiTNFs/Ustekinumab AntiTNFs first line Ustekinumab >AntiTNFs Ustekinumab/Vedolizumab
NMSC	Avoid immunomodulators
Melanoma (PMHx/ FHx) CHF SLE Multiple Sclerosis	Avoid antiTNFs – Consider UST/VDZ Avoid antiTNFs Avoid antiTNFs Avoid antiTNFs – Consider natalizumab/VDZ
Frequent Infections History of other cancers Immunosuppression (congenital/ acquired (chemotherapy))	1st choice: vedolizumab Possibly: ustekinumab ?ozanimod Avoid AntiTNFS, JAKi

Treat to Target



Goals of Therapy in IBD

Clinical Remission

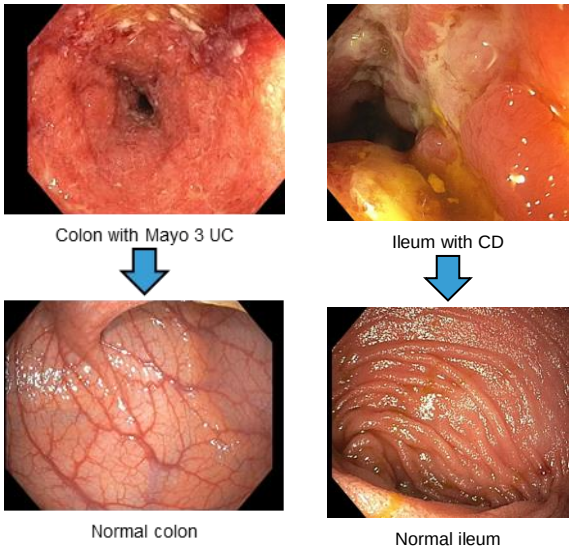
Lack of Symptoms | Improved Quality of Life

Endoscopic Remission

Reduce Hospitalizations & Surgery | Delay of Clinical Relapse

Histologic Healing

Reduce Dysplasia/Cancer risk



Bryant RV et al. *J Crohns Colitis*. 2014;8(12):1582-1597; Lichtenstein GR et al. *Am J Gastroenterol*. 2009;104(2):465-484; Talley NJ et al. *Am J Gastroenterol*. 2011;106 Suppl 1:S2-S26.

Treat-to-Target in UC: STRIDE Guidelines

Composite End Point

Clinical/PRO Remission	+	Endoscopic Remission
Defined as resolution of rectal bleeding and normalization of bowel habit • Should be assessed at minimum of 3 months during active disease • Patients' individual goals (e.g., QoL, mood disorders, fatigue, work productivity) should also be addressed, with normalization of QoL as the ultimate goal		**Defined as resolution of friability and ulceration with flexible sigmoidoscopy or colonoscopy (Mayo score 0 to 1)** • Should be assessed within 3 to 6 moths after start of therapy

Adjunctive Measures of Disease Activity (Useful in Selected Cases)

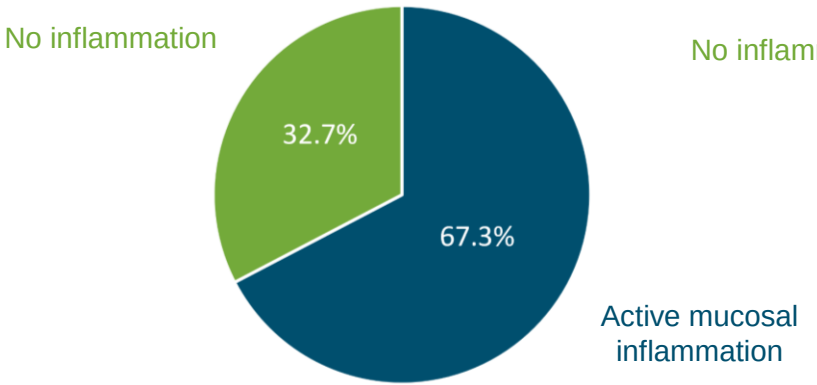
- **Biomarkers:** CRP and FC are adjunctive measures of inflammation—not targets—for monitoring UC
- **Histology** is a sensitive measure of inflammation but is not a target due to lack of evidence of clinical utility

Peyrin-Biroulet L et al. *Am J Gastroenterol*. 2015;110(9):1324-1338.

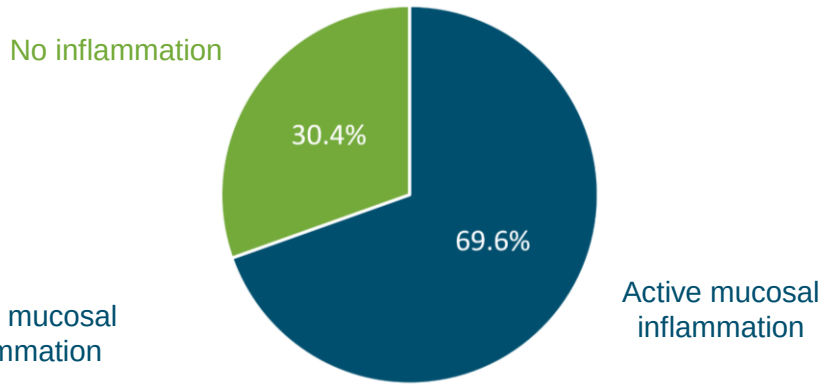
Importance of Mucosal Evaluation

A 3-year longitudinal study from the Netherlands identified UC (n=98) and CD patients (n=46) who underwent a surveillance colonoscopy* between 2001 and 2003 and found:

UC Patients in Clinical Remission (n=98)



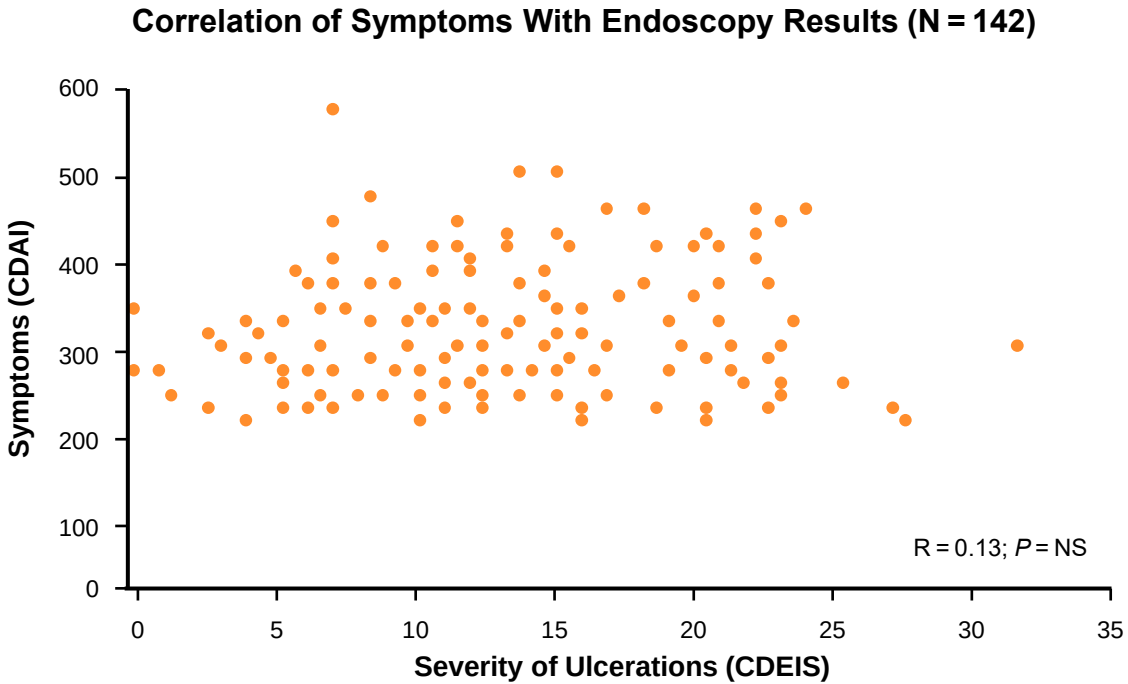
CD Patients in Clinical Remission (n=46)



CD=Crohn's disease; IBD=inflammatory bowel disease; UC=ulcerative colitis.

Baars JE et al. *Inflamm Bowel Dis*. 2012;18(9);1634-1640.

Symptoms Often Do Not Correlate With Inflammation



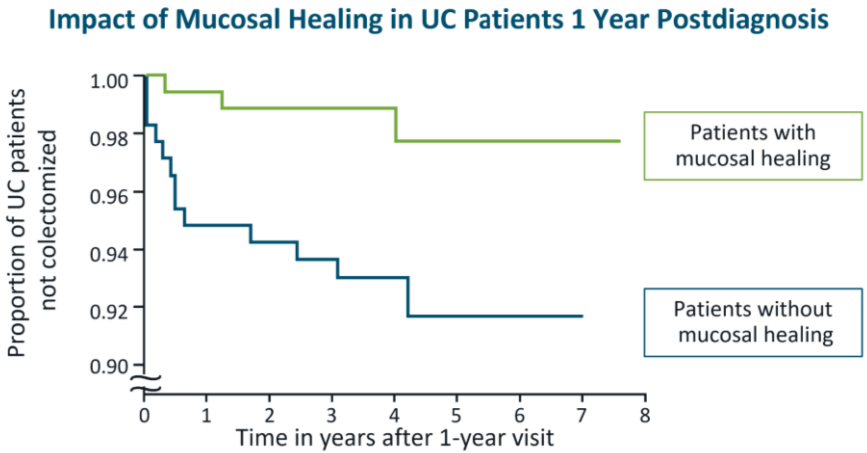
NS, not significant.

Modigliani R et al. *Gastroenterology*. 1990;98(4):811-818. Reproduced with permission of ELSEVIER HEALTH SCIENCE JOURNALS via Copyright Clearance Center.

Mucosal Healing Reduces Surgery Risk

In a prospective population-based study of 354 patients in Norway diagnosed with UC between 1990 and 1994

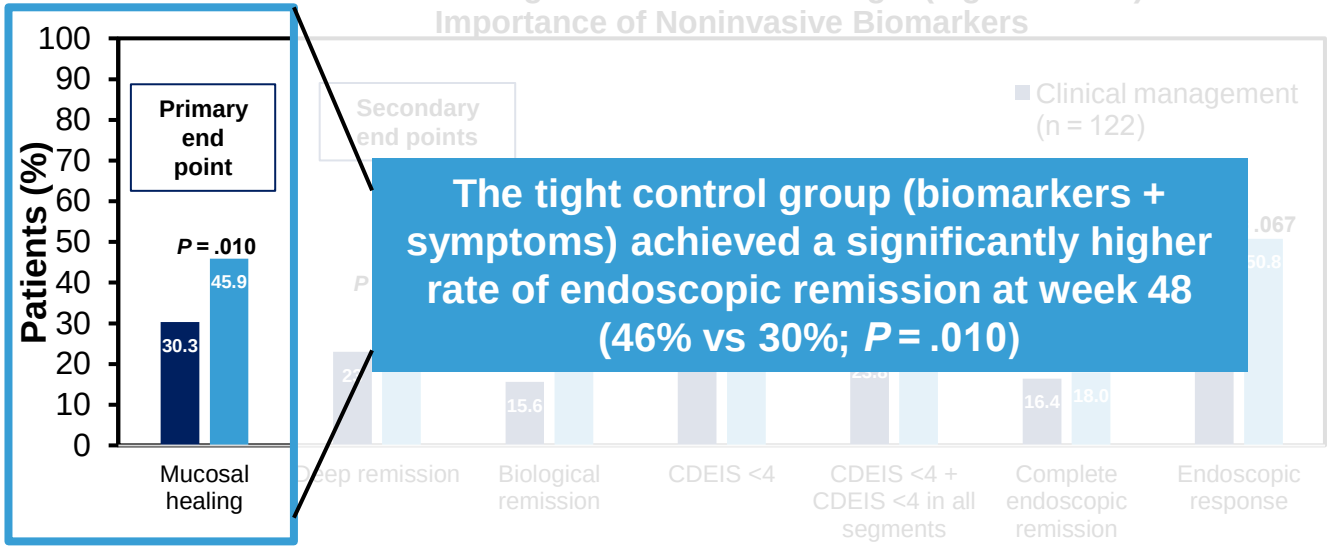
- Of patients with mucosal healing* at the 1-year follow-up, 3 were recorded as having undergone surgery at 5 years, compared with 13 in the group without mucosal healing at 1 year (*P*=0.02)



- Study controlled for variables that may influence colectomy rate (eg, age, smoking status, time to first visit, educational level, and disease extension)
- In CD, established mucosal healing after 1 year of treatment was similar to that of UC, although not significant

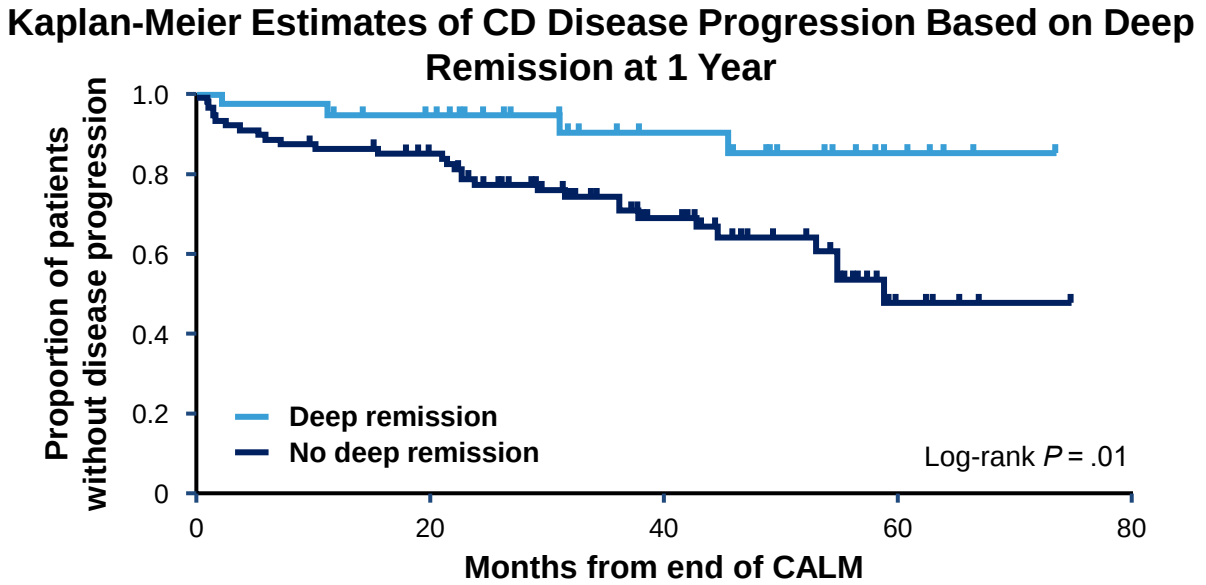
Frøslie KF et al. *Gastroenterology.* 2007;133:412-422.

CALM: Substitution of Biomarkers for Endoscopy-Based Monitoring to Optimize Mucosal Healing[a]



[a]Mucosal healing defined as CDEIS <4 and no deep ulcerations 48 weeks post-randomization.

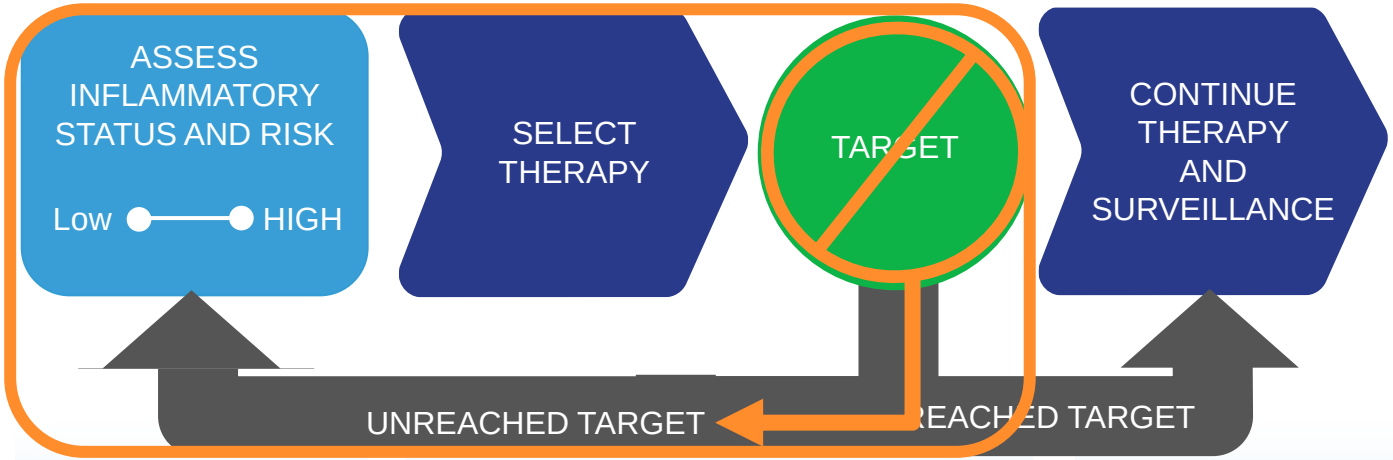
CALM Follow-Up: Impact of Induction of Deep Remission on Disease Progression in CD



CD patients achieving endoscopic or deep remission after 1 year of tight control are less likely to have disease progression[a] over a median of 3 years

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

Treat to Target



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Bouguen et al. *Clin Gastroenterol Hepatol*. 2015; Colombel J-F et al. *Gastroenterology*. 2017; Dassopoulous T et al. *Gastroenterol*. 2015; Sandborn WJ. *Gastroenterology*. 2014; Bossuyt P et al. *Curr Treat Options Gastroenterol*. 2016.

But Wait! Consider Alternatives:

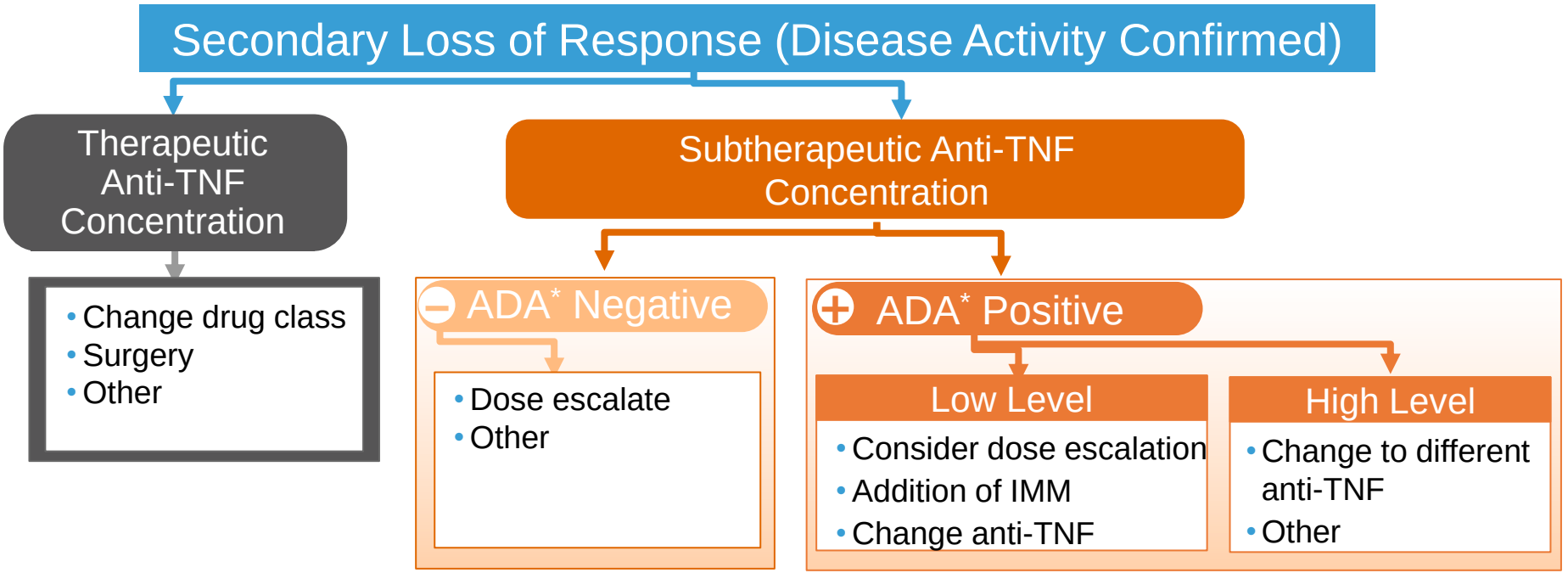
Don’t Start IBD Therapy:

- Indeterminate diagnosis (lack of chronicity on biopsies)
- IBS
- NSAID induced inflammation
- Infectious etiologies
  - *(Except *C. difficile* in the setting of disease activity)
- Bile Acid induced diarrhea
- Drug induced diarrhea
- Small intestinal bacterial overgrowth

Don’t Delay Surgery:

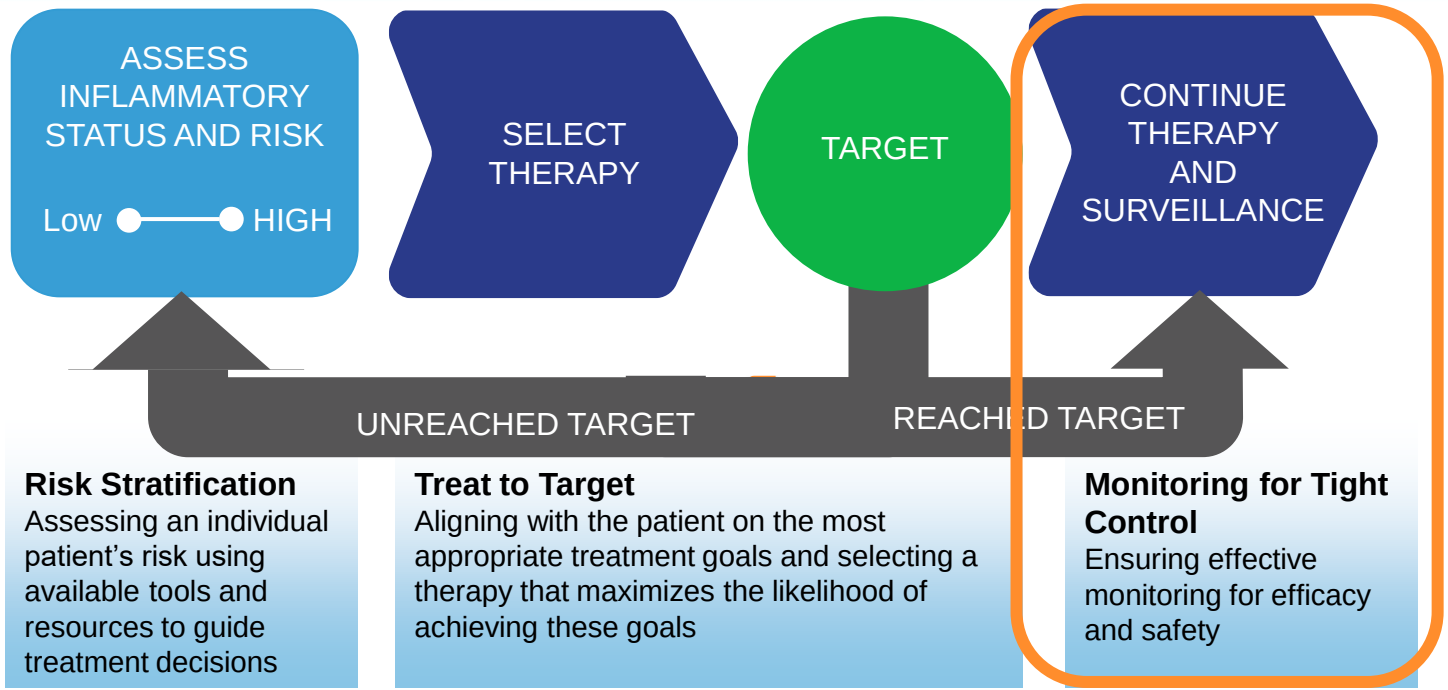
- Perforation/Hemorrhage
- Severe deep ulcers
- Fibrostenotic obstructing stricture
- Intestinal to hollow organ fistulas
- Complex fistulae/abscesses
- Dysplasia/Cancer
- Perianal complications

Reactive TDM Algorithm



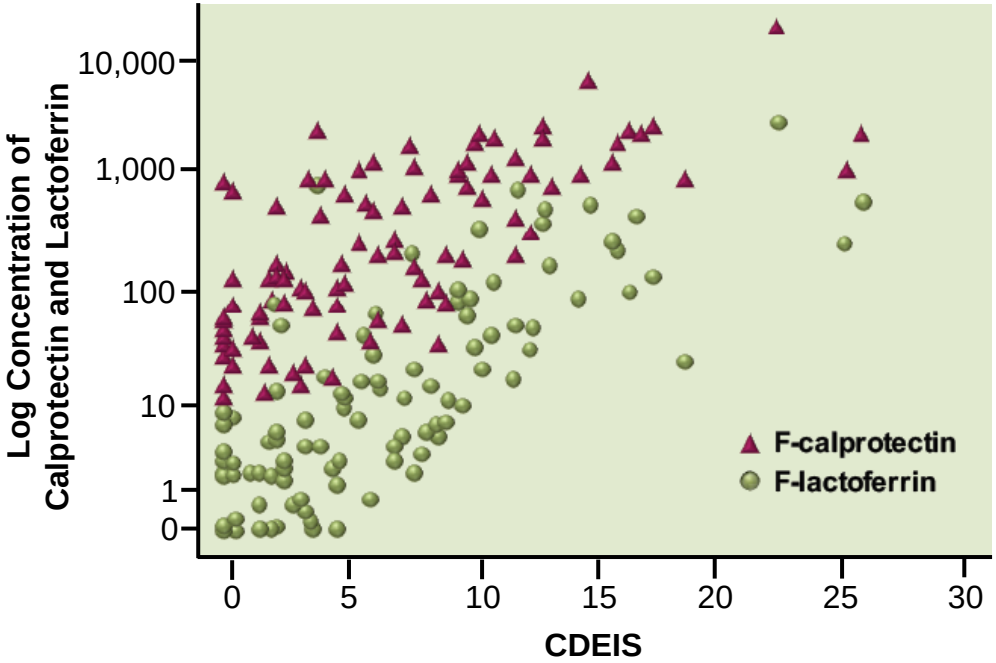
*ADA = Antidrug antibody

Treat to Target: How to Monitor?



Bouguen et al. *Clin Gastroenterol Hepatol*. 2015; Colombel J-F et al. *Gastroenterology*. 2017; Dassopoulous T et al. *Gastroenterol*. 2015; Sandborn WJ. *Gastroenterology*. 2014; Bossuyt P et al. *Curr Treat Options Gastroenterol*. 2016.

Fecal Calprotectin and Lactoferrin Correlate With Endoscopic Activity



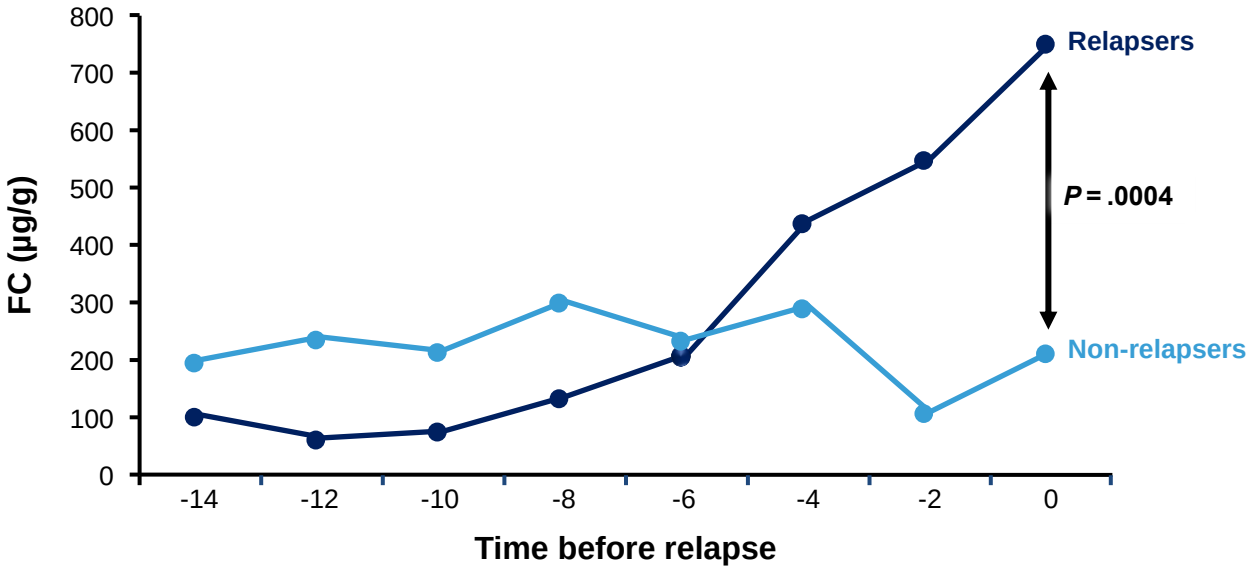
Correlations of fecal calprotectin and lactoferrin with CDEIS. Spearman's *r* for calprotectin 0.729 and for lactoferrin 0.773, *P*=0.001

CDEIS, Crohn's Disease Endoscopic Index of Severity.

Sipponen T et al. *Inflamm Bowel Dis*. 2008;14(1):40-46.

Consecutive FC Measurements for Early Prediction of Clinical Relapse

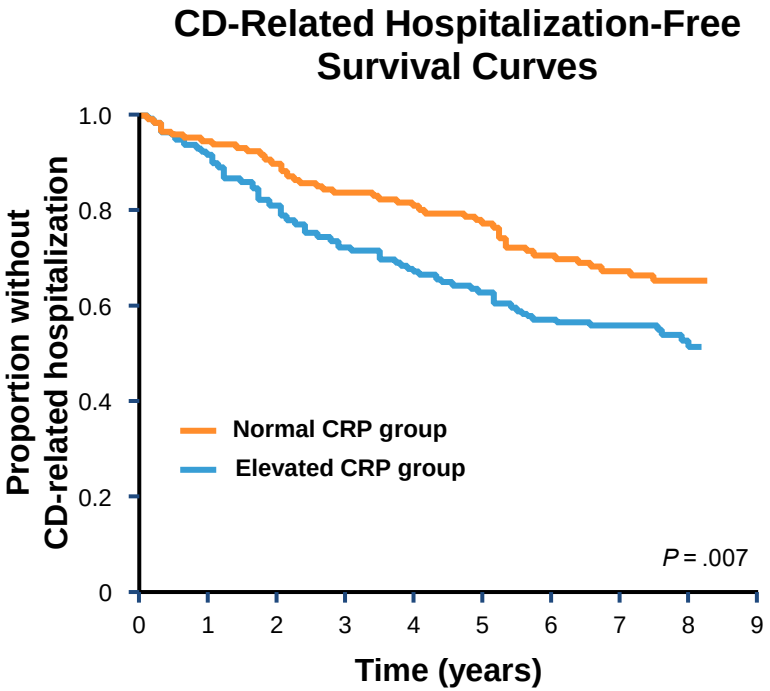
STORI Cohort Follow-up: Longitudinal FC Measurements[a]

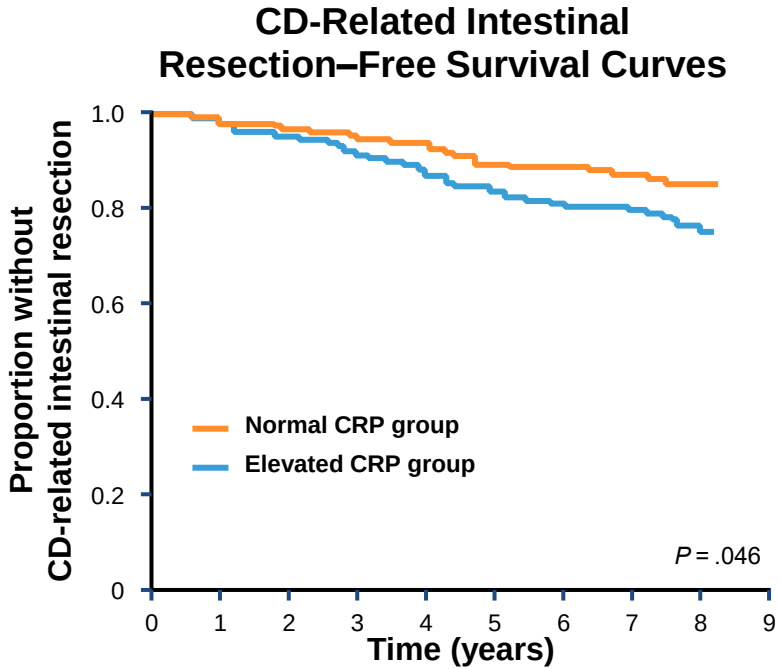


[a]In a study of 113 luminal CD patients treated with 1 year of infliximab plus immunosuppressant who were in stable remission without steroids for ≥6 months.

Louis E et al. *Gastroenterology*. 2012;142(1):63-e31.

“Silent” CD Associated With ~2x Higher Risk of Hospitalizations & Surgery

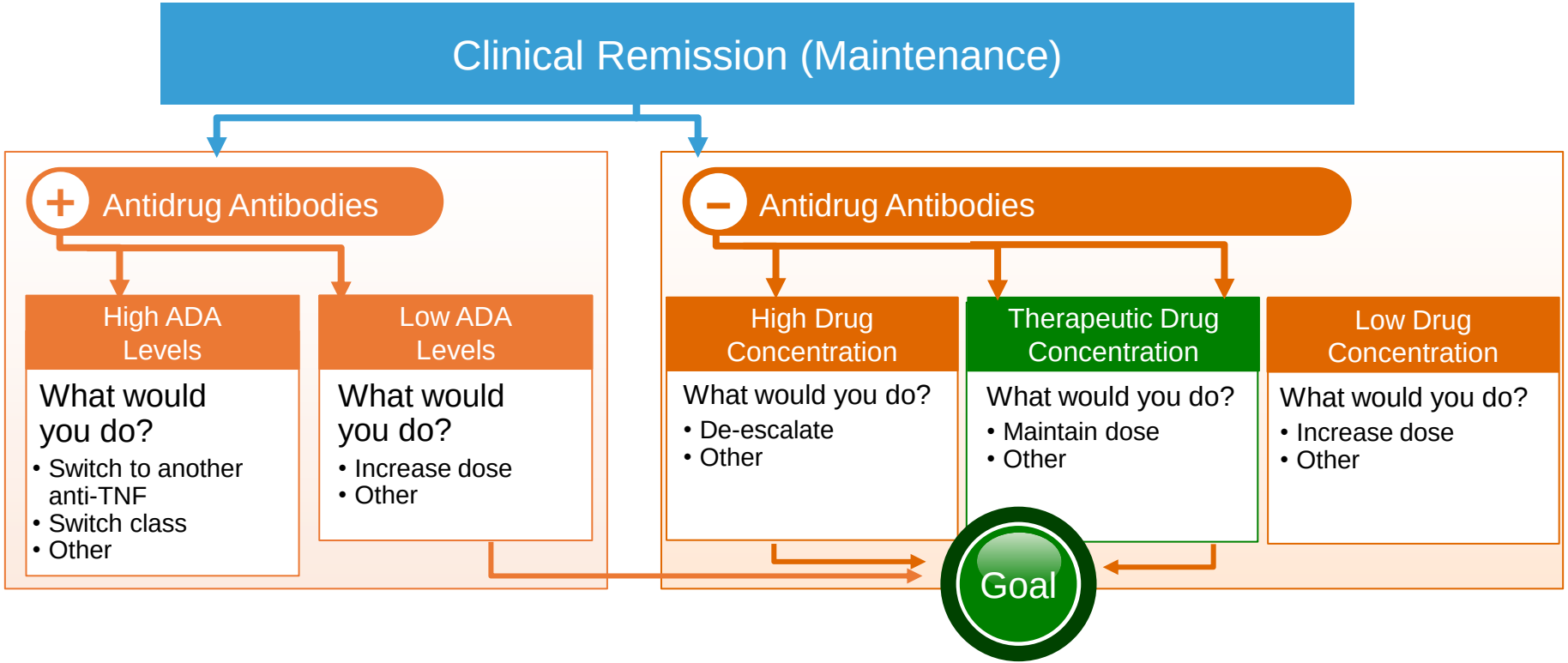




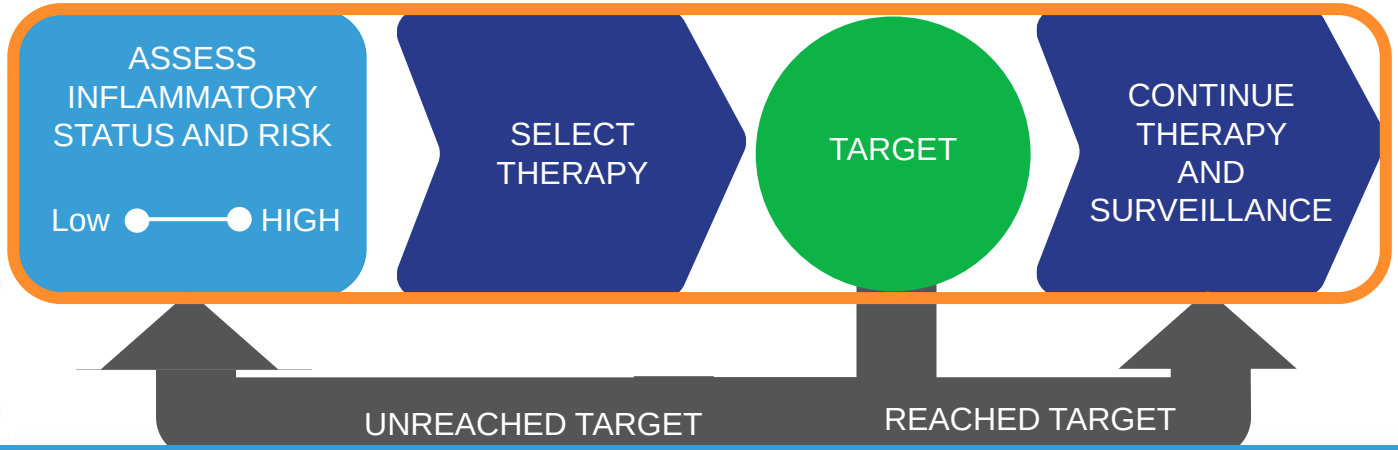
Quiescent patients with CRP elevation were at increased risk of relapse within 1-2 years

Oh K et al. *PLoS One.* 2017;12(6):e0179266.

Proactive TDM Algorithm: Time to De-Escalate?



Summary: Treating to Target in IBD Clinical Practice



- Determine disease severity to guide management of IBD
- Treat to Mucosal Healing (Endoscopic/ Adjunct markers)
- “Silent” inflammation is associated with disease complications
- Monitoring strategies (q6 months to yearly) to prevent disease

Bouguen et al. *Clin Gastroenterol Hepatol*. 2015; Colombel J-F et al. *Gastroenterology*. 2017; Dassopoulous T et al. *Gastroenterol*. 2015; Sandborn WJ. *Gastroenterology*. 2014; Bossuyt P et al. *Curr Treat Options Gastroenterol*. 2016.

What to Do When All Else Fails?

OPTIONS:

1. Phone call to IBD Specialist
2. Refer to IBD center
3. Consider clinical trials/ new agents
4. Combination therapy…

The IBD Pipeline

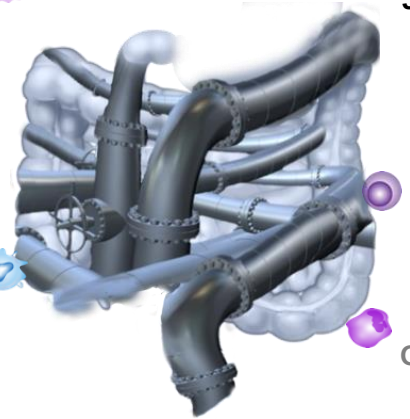
Anti–IL-23 Inhibitors

Risankizumab*
Guselkumab*
Mirikizumab
Brazikumab
PTG-200 (oral)

Lymphocyte Trafficking

Anti-integrins
Etrolizumab
PN-943 (oral)

S1PR modulator
Etrasimod
Amiselimod



Downstream signaling blockade

JAK-STAT pathway inhibitors
Upadacitinib*
Filgotinib
Deucravacitinib (TYK2)
Ritlecitinib (JAK3/TEC)
Brepocitinib (JAK1/TYK2)
TD-1473 (oral gut-selective pan-JAK)

PDE4 inhibitor
Apremilast*

Other

Stem cell therapy (perianal fistula)
Fecal transplant (intestinal microbiota transfer)
SER-287 (microbiome therapeutic)

*Approved for use in other indications.

ClinicalTrials.gov. Accessed December 2020. www.clinicaltrials.gov.

GI Alliance

Thank You!