

Defining Treatment Targets in IBD: Where Should We Be Aiming?

Jami Kinnucan, MD

Mayo Clinic Florida

Kinnucan.Jami@mayo.edu

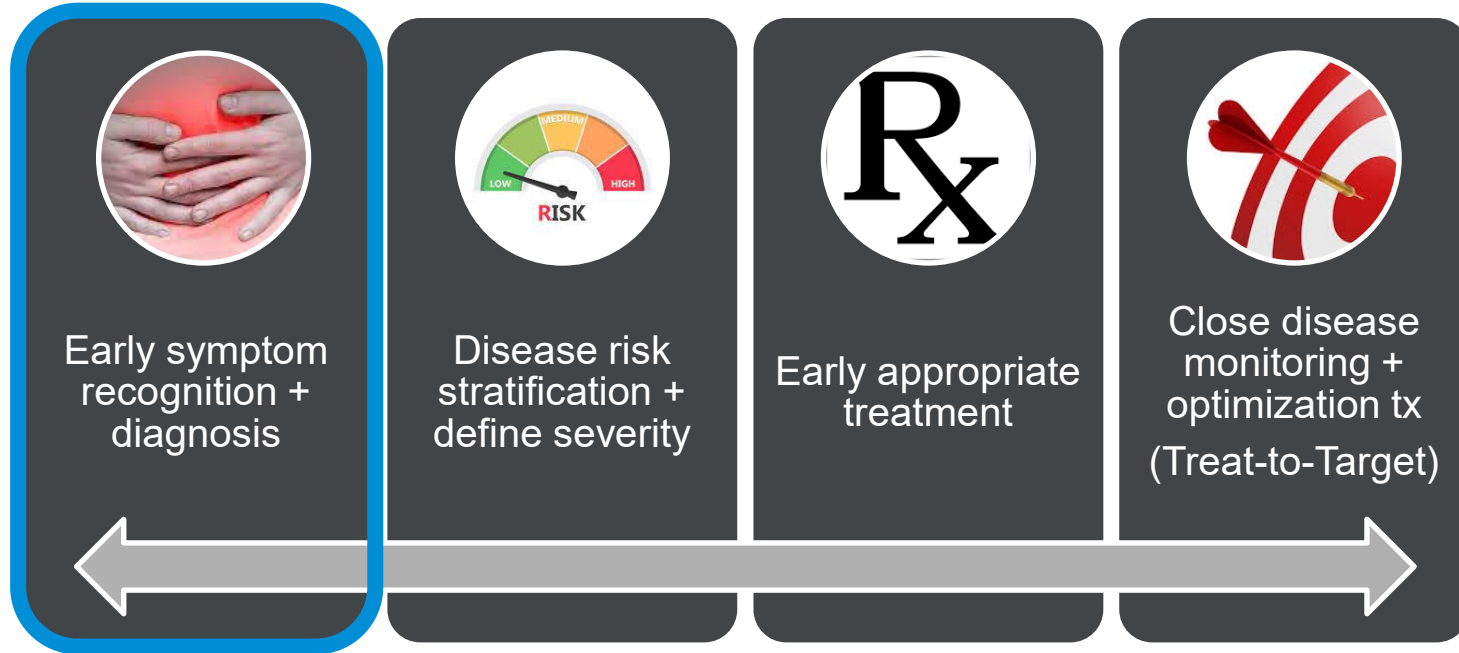
Disclosures

- Advisory Board/Consultant
 - AbbVie, Janssen, Pfizer, BMS, Fresenius Kabi, Takeda

Outline

- Early recognition of diagnosis
- Defining disease severity & prognosis
- Personalized approach to treatment selection
- Treat-to-target approach to care
- Changing short- and long-term outcomes

Delays During Diagnosis and Management Negatively Impact Patient Outcomes



Delays in Diagnosis Are Common


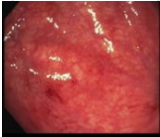

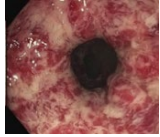
- Delay in reporting symptoms
- Delay in recognition of symptoms
- Uncertain or wrong diagnosis initially
- Delays in referral to gastroenterologist or specialist
- Delays in diagnostic evaluations

How can we better identify those individuals who are at risk BEFORE they develop symptoms?

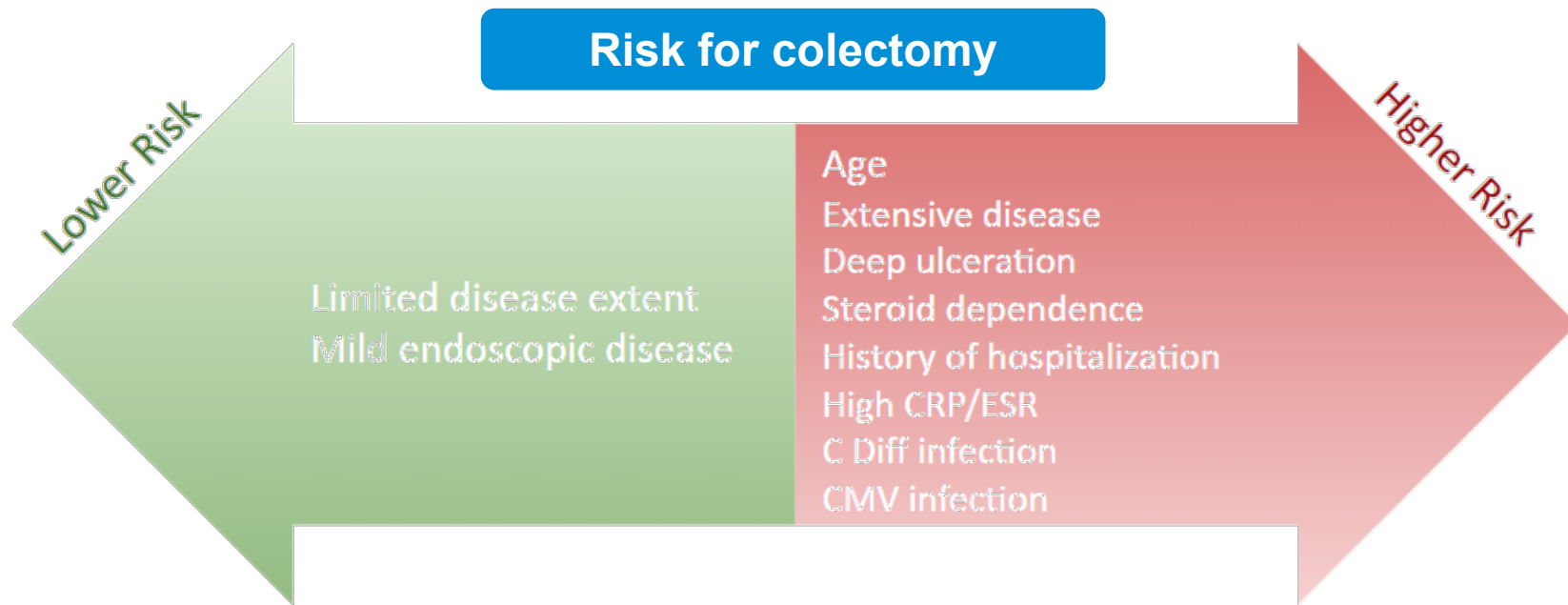
Delays During Diagnosis and Management Negatively Impact Patient Outcomes



Ulcerative Colitis: Defining Acute Severity

	Remission	Mild	Moderate-Severe	Fulminant
Clinical	<ul style="list-style-type: none"> Formed stool No blood No urgency 	<ul style="list-style-type: none"> <4 bm/day Intermittent blood Mild urgency 	<ul style="list-style-type: none"> >6 bm/day Frequent blood Often urgency 	<ul style="list-style-type: none"> >10 bm/day Constant blood Constant urgency
Biomarkers	<ul style="list-style-type: none"> HgB normal ESR <30 Normal CRP FCP <150-200 	<ul style="list-style-type: none"> HgB normal ESR <30 CRP elevated FCP >150-200 	<ul style="list-style-type: none"> HgB <75% nl ESR >30 CRP elevated FCP >150-200 	<ul style="list-style-type: none"> Transfusion req ESR >30 CRP elevated FCP >150-200
Endoscopy Mayo Score (UCEIS Score)	Mayo Score 0 (0-1) 	Mayo Score 1 (2-4) 	Mayo Score 2-3 (5-8) 	Mayo Score 3 (7-8) 

Ulcerative Colitis: Understanding Disease Prognosis Through Severity



CMV = cytomegalovirus.

Dassopoulos T et al. *Gastroenterology*. 2015;149(1):238-245.

Crohn's Disease: Defining Acute Severity

Clinical Symptoms

Crohn's disease activity index (CDAI)

<i>Variable</i>	<i>Quantity</i>	<i>Multiple</i>	<i>Total</i>
Number of liquid or soft stools per day		2	
Abdominal pain (0 = none, 1 = mild, 2 = moderate, 3 = severe)		5	
General well being (0 = well, 1 = slightly under par, 2 = poor, 3 = very poor, 4 = terrible)		7	
Number of complications: arthralgias, iritis, erythema nodosum, pyoderma gangrenosa, aphthous ulcerations, anal fissure, anal fistula, anal abscess, fever > 37° past week, intestinal obstruction		20	
Opiates for diarrhea (no = 0, yes = 1.)		30	
Abdominal mass (no = 0, questionable = 2, yes = 5)		10	
Deviation from normal hematocrit (N=42 for female, 47 for male)		6	
% deviation from standard weight		1	
Total CDAI			

Endoscopic Features

- Simple-endoscopic scoring system (SES-CD)
 - Remission: 0-2
 - Mild: 3-6
 - Moderate: 7-15
 - Severe: ≥ 16
- Rutgeert's score i0-i4

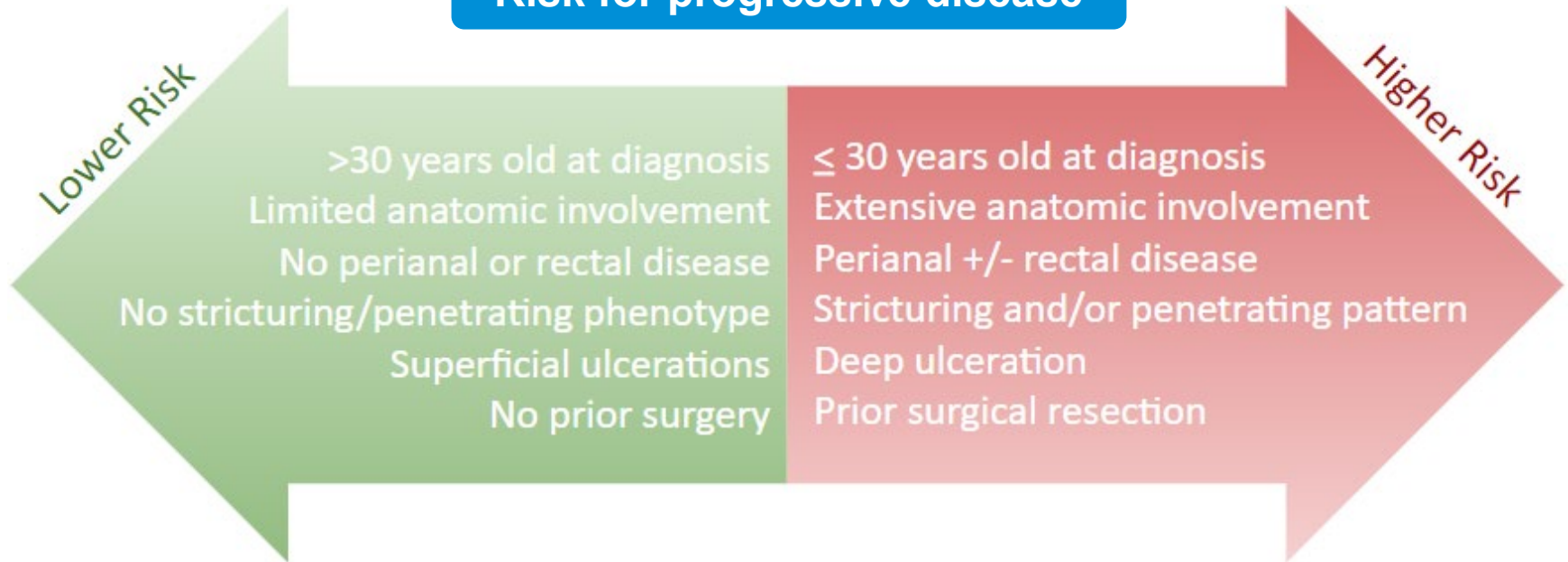
Mild <150
 Mild-Moderate 150-220
 Mod-Severe 220-450
 Severe >450

Additional Features

- Ambulation status
- Ability to tolerate oral
- Weight loss
- Absence of complications
- Dehydration
- Disability
- Impact on QOL

Crohn's Disease: Understanding Disease Prognosis Through Severity

Risk for progressive disease



Utilize Clinical Predictor Tools to Define Disease Severity

[AGA Crohn's Disease & Ulcerative Colitis Clinical Decision Support Tool](#)



IBD Clinical
Decision
Support Tool

Get Started!

Crohn's Disease & Ulcerative Colitis
Clinical Decision Support Tool [CME Home](#)

Your Profile
Email Address: [CME Home](#)

Organization: [CME Home](#)

Select Specialty: **Crohn's Disease & Ulcerative Colitis** [CME Home](#)

Focus of F: GI Pro Other Primar GI Res [Update](#)

Data Usage:

Crohn's Disease Burden Assessment

Is there extensive anatomic involvement?
 Yes No

Is there perianal disease?
 Yes No

Is there severe rectal disease?
 Yes No

Are there deep ulcers?
 Yes No

Was there previous surgical resection?
 Yes No

Is there stricturing behavior?
 Yes No

Is there penetrating behavior?
 Yes No

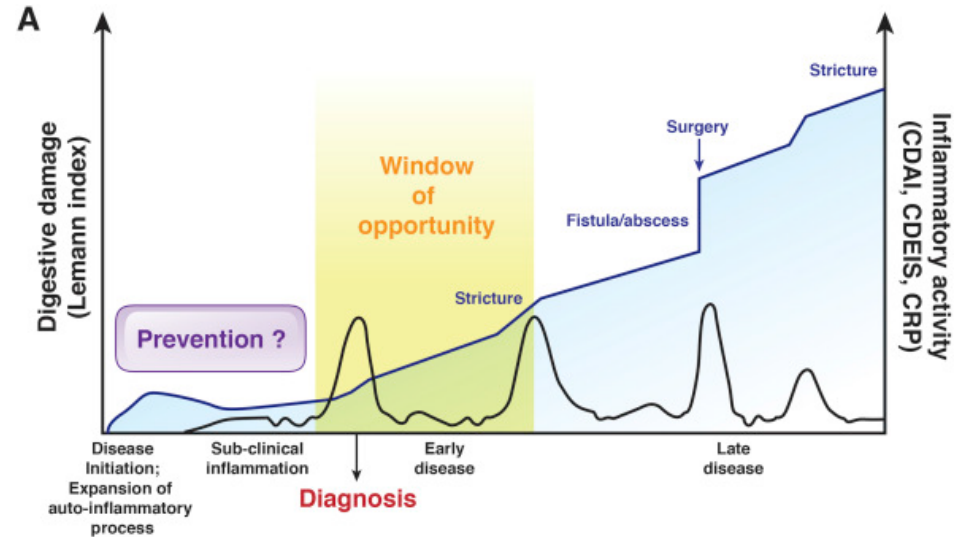
Crohn's Disease Burden Assessment

High risk for development of a disease related complication.

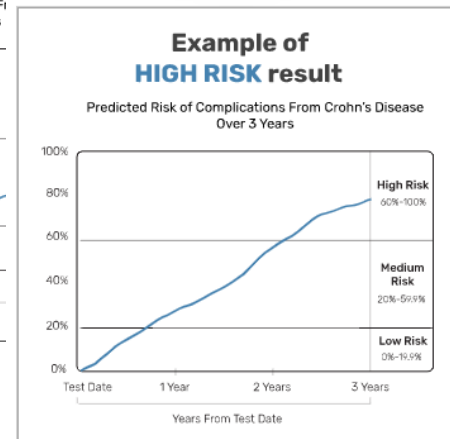
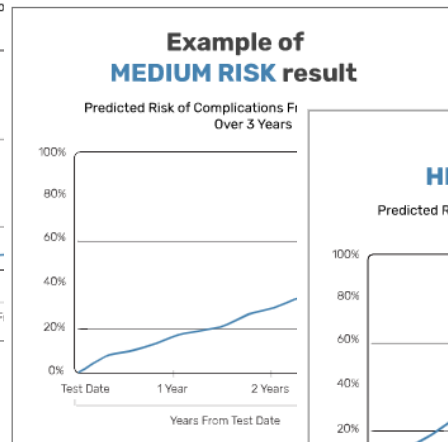
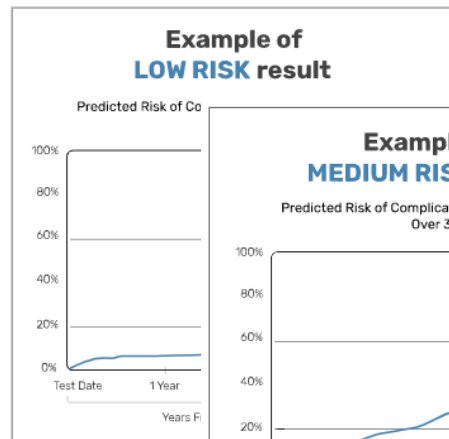
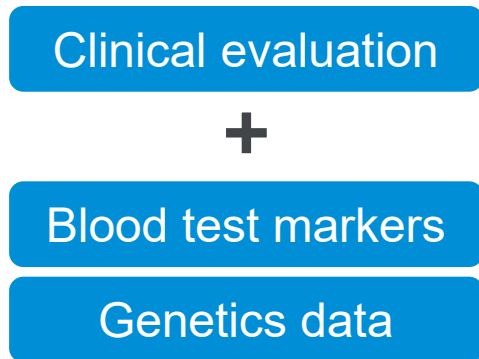
[Predictive Model](#) [Run Assessment Again](#) [Start Over](#)

A Window of Opportunity in Crohn's Disease

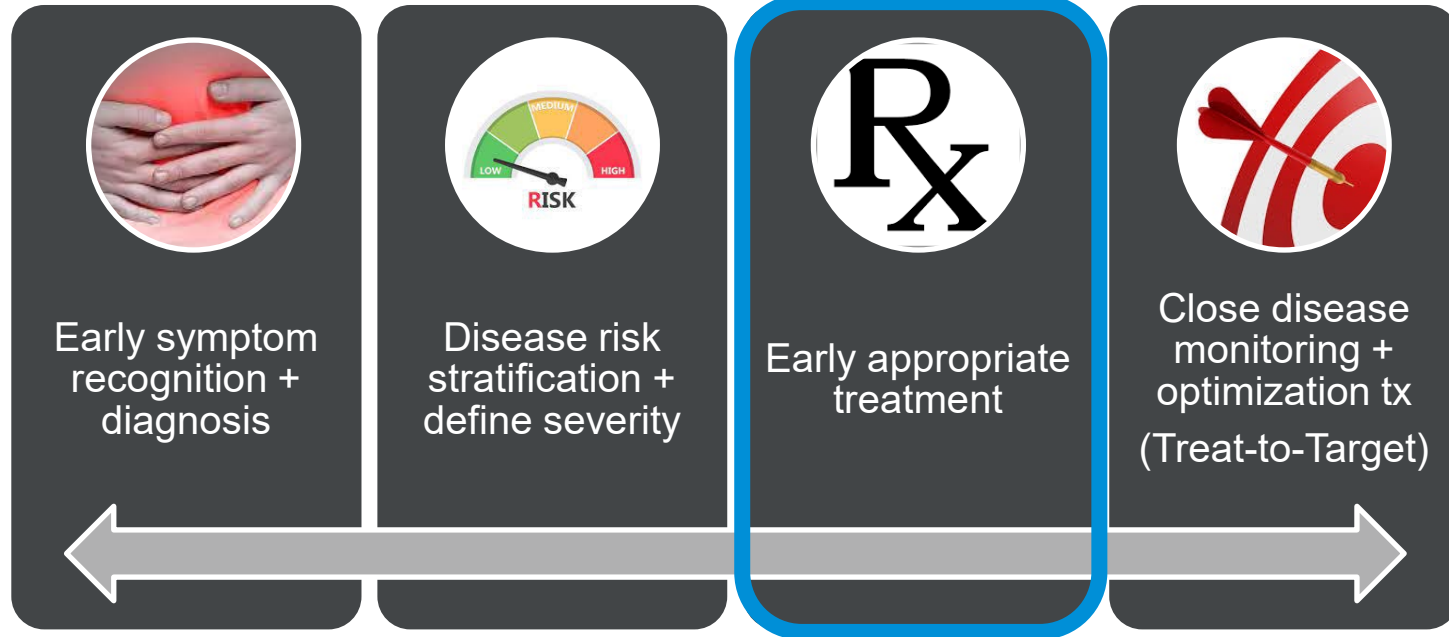
- Up to 80% of patients with Crohn's disease will require hospitalization
- 40-55% will require surgery at 10y
- Most patients will have progressive course without treatment
- Can we change that with a different approach to care?



What if a Blood Test Could Predict 3 Year Outcomes in Crohn's Disease?



Delays During Diagnosis and Management Negatively Impact Patient Outcomes



IBD Management Is No Longer a One Size Fits All Approach



**ONE SIZE
FITS ALL**



**MADE TO
MEASURE**

Positioning Therapies: Recent Network Meta-Analysis for Selecting IBD Treatments

[Updated Network Meta-Analysis in Moderate-Severe Ulcerative Colitis \(Singh S et al. CGH 2020\)*](#)

*upadacitinib not included

Clinical Gastroenterology
and Hepatology 

[Efficacy of biological therapies and small molecules in moderate to severe ulcerative colitis: systematic review and network meta-analysis \(Burr N et al. GUT 2021\)](#)

[Comparative efficacy and safety of biologic therapies for moderate-to-severe Crohn's disease \(Singh S et al. Lancet 2021\)](#)

THE LANCET
Gastroenterology & Hepatology

Positioning Therapies: A Few Head-to-Head Studies to Help Guide Us

Ulcerative Colitis

- VARSITY trial
- Adalimumab vs. vedolizumab
- Moderate to severe UC

Findings- week 52

- Vedolizumab was superior to adalimumab:
 - Clinical remission
 - Endoscopic improvement
- Vedolizumab was not superior for 52w steroid-free clinical remission

Crohn's disease

- SEAVUE trial
- Adalimumab vs. ustekinumab
- Moderate to severe bio-naïve CD

Findings – week 52

- Both adalimumab & ustekinumab:
 - Clinical remission
 - Steroid-free clinical remission
 - Clinical response
 - PRO-2 remission
 - Clinical remission (week 16)

Positioning Therapies: Use of Clinical Predictor Tools

AGA Crohn's Disease & Ulcerative Clinical Decision Support Tool



IBD Clinical
Decision
Support Tool

Get Started!

The banner features a red background with white text. At the top, there are three icons: a microscope, a target, and a test tube. At the bottom, there are three icons: a test tube, an eye, and a map of the United States.

Crohn's Disease & Ulcerative Colitis
Clinical Decision Support Tool

Crohn's Disease Predictive Model

Prior anti-TNF exposure?
 Yes No

Baseline Albumin Concentration - unit of measure g/dL (normal range 3.5 to 5.5)

Baseline CRP mg/L

Prior fistulizing disease?
 Yes No

Active fistulizing disease?
 Yes No

Prior Bowel Surgery?
 Yes No

Current or Prior Smoking?
 Yes No

Colonic or ileocolonic disease (not isolated ileal)?
 Yes No

Concomitant immunomodulator use?
 Yes No

Crohn's Disease Burden Assessment

High risk for development of a disease related complication.

Crohn's Disease

Vedolizumab

Probability of achieving clinical remission?	Intermediate
How quickly will the response be seen?	Within the first 2-3 months
Should I consider more frequent follow-ups and/or drug concentration monitoring?	You are at an intermediate risk for needing surgery or being hospitalized, and your drug concentrations are expected to be adequate.

Ustekinumab

Probability of achieving clinical remission?	Low
How quickly will the response be seen?	> 3 months
Should I consider more frequent follow-ups and/or drug concentration monitoring?	Your drug concentrations are expected to be inadequate.



Positioning Therapies: Consider Patient Specific Factors

	Anti-TNF	VDZ	UST/RISA	JAKi	S1P
Overall efficacy	+	+	+	+	+
Induction speed	++	-	+	+++	+
Perianal/fistulizing	++	+/-	+/-	++	NA
EIM	++	-	++	+	+
Serious infection	-	++	+	-	+
Malignancy	-	++	+	-	+
Pregnancy	+	+	+	-	-
Immunogenicity	-	+	+	++	++
TDM/ dose optimization	++	-	-	NA	NA

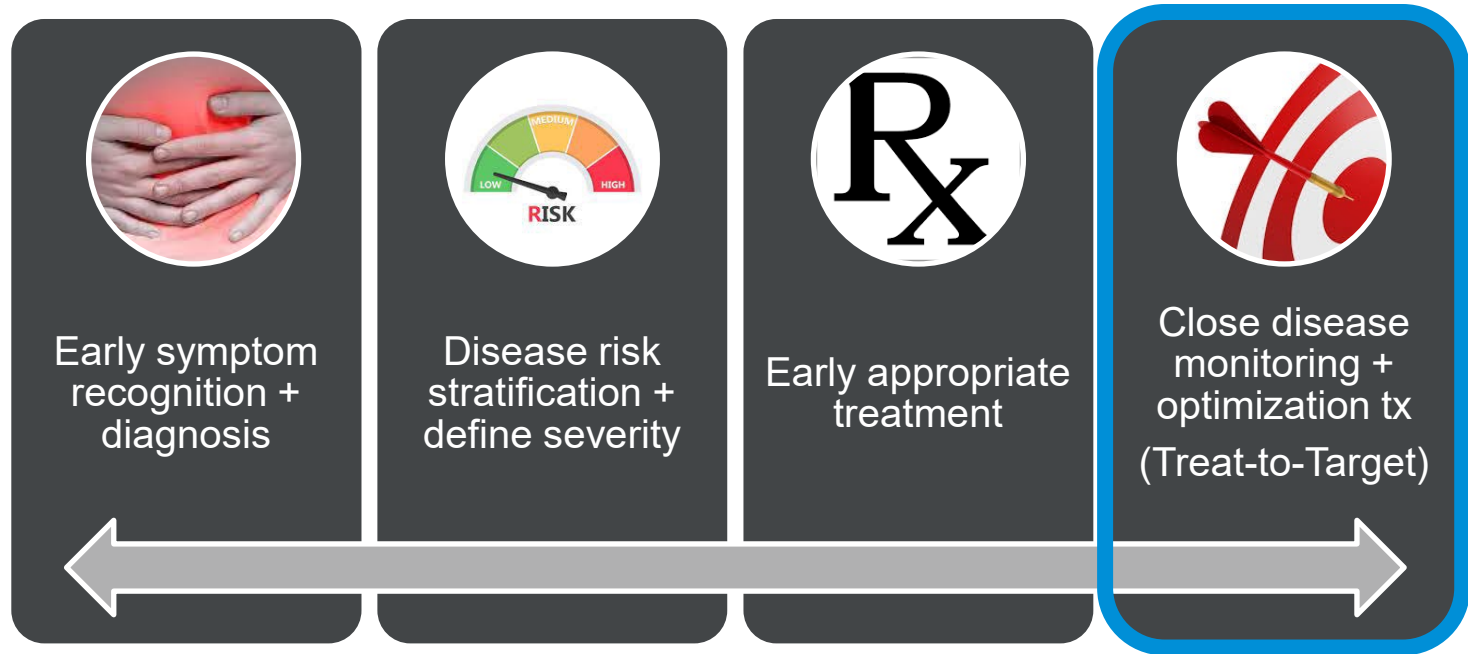
Initiating Therapy: How I Typically Review Treatment Options with Patients

Disease Activity

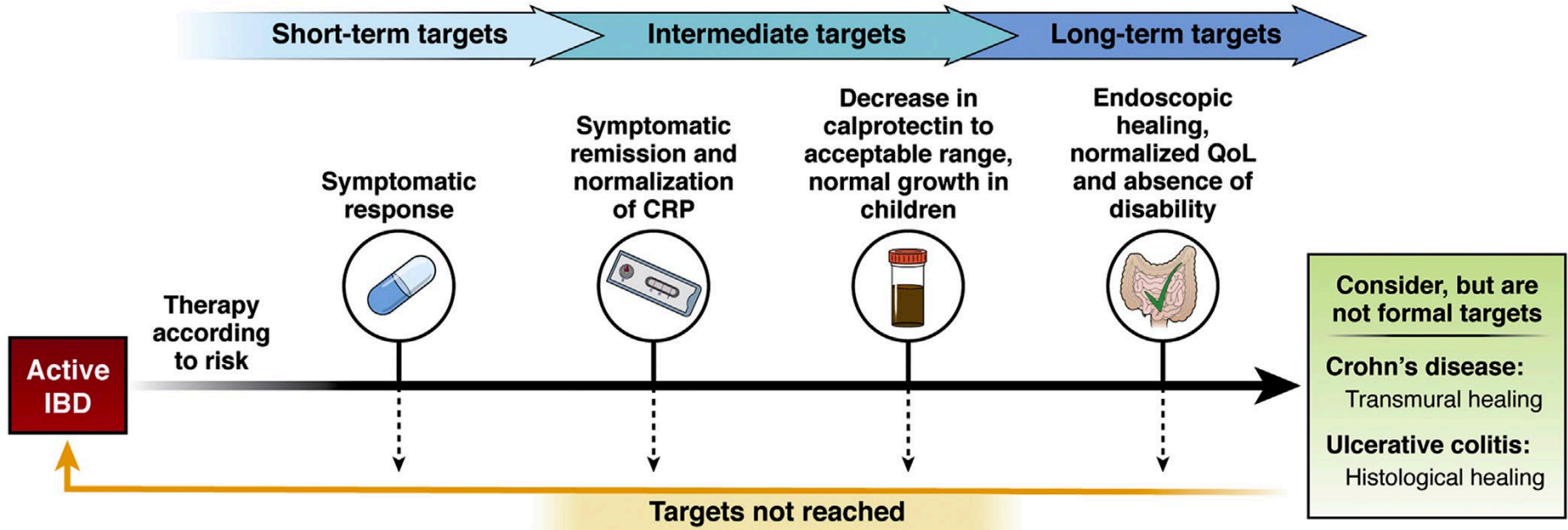
<p>Disease Prognosis + Comorbidities What is your risk if we do nothing? Undertreatment?</p>	<p>Patient preference What is your preference? What is important to you?</p>
<p>Medication efficacy Based on what we know about your disease, which drug would likely work best?</p>	<p>Medication Safety What is your risk of adverse event?</p>

Insurance Preference

Delays During Diagnosis and Management Negatively Impact Patient Outcomes



What Do We Mean by Treat-to-Target?



Defining Acute Disease Evaluations: Helping Define Our Targets

Patient reported outcomes

PRO2-CD (abd pain, stool freq)
PRO2-UC (rectal bleed, stool freq)
PRO3 (PRO2 + well-being)
SIBDQ (Short IBD QoL)
PSQI (sleep)
PHQ-9 (depression)
PROMIS Global Health (HRQoL)

Clinical Scores

CD: CDAI
CD: Harvey Bradshaw Index (HBI)
UC: Mayo Score
UC: SCCAI

Biomarkers

C-reactive protein (CRP)
Fecal calprotectin
Multiple biomarkers: Monitr®

Imaging

CT enterography
MR enterography (MaRIA)
Intestinal ultrasound

Endoscopy

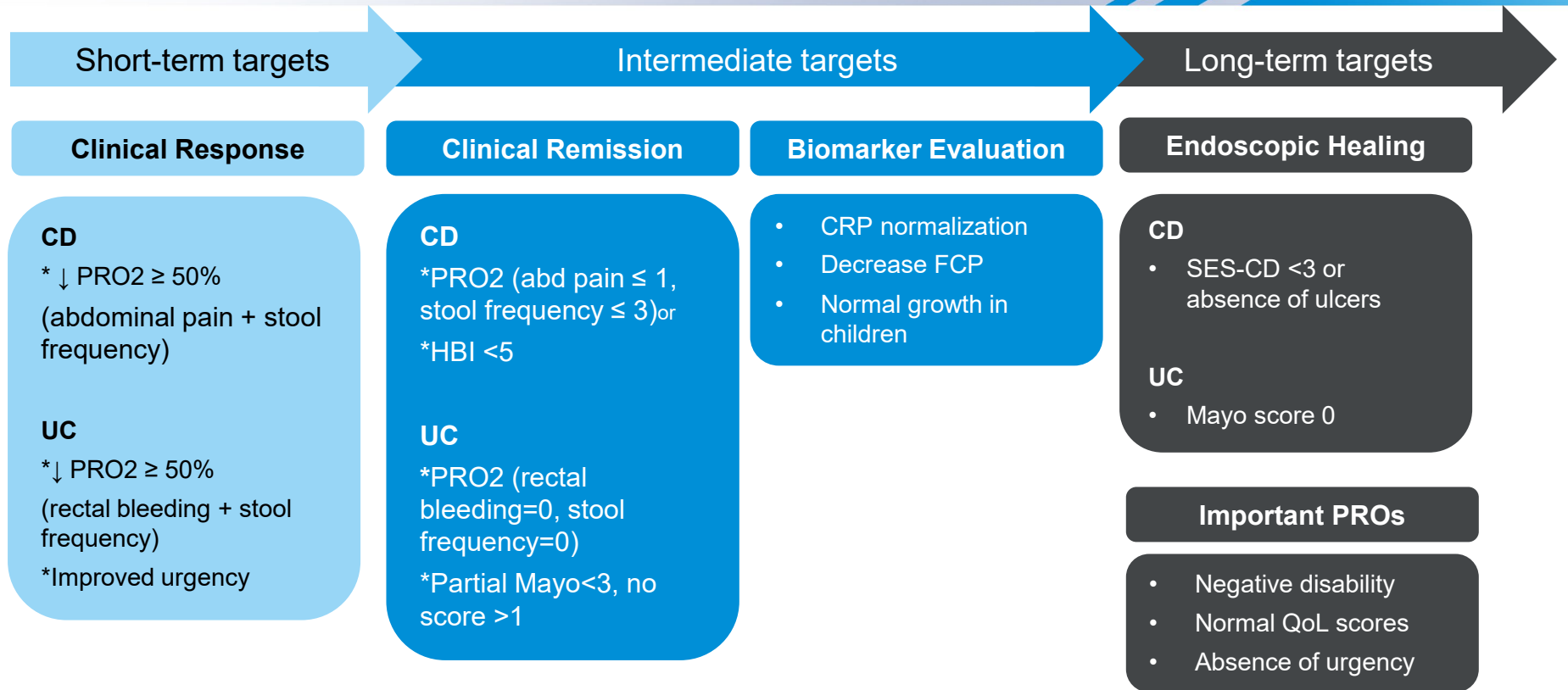
Video capsule endoscopy
CD: SES-CD
CD: CDEIS
UC: Mayo Score
UC: UCEIS

Histology

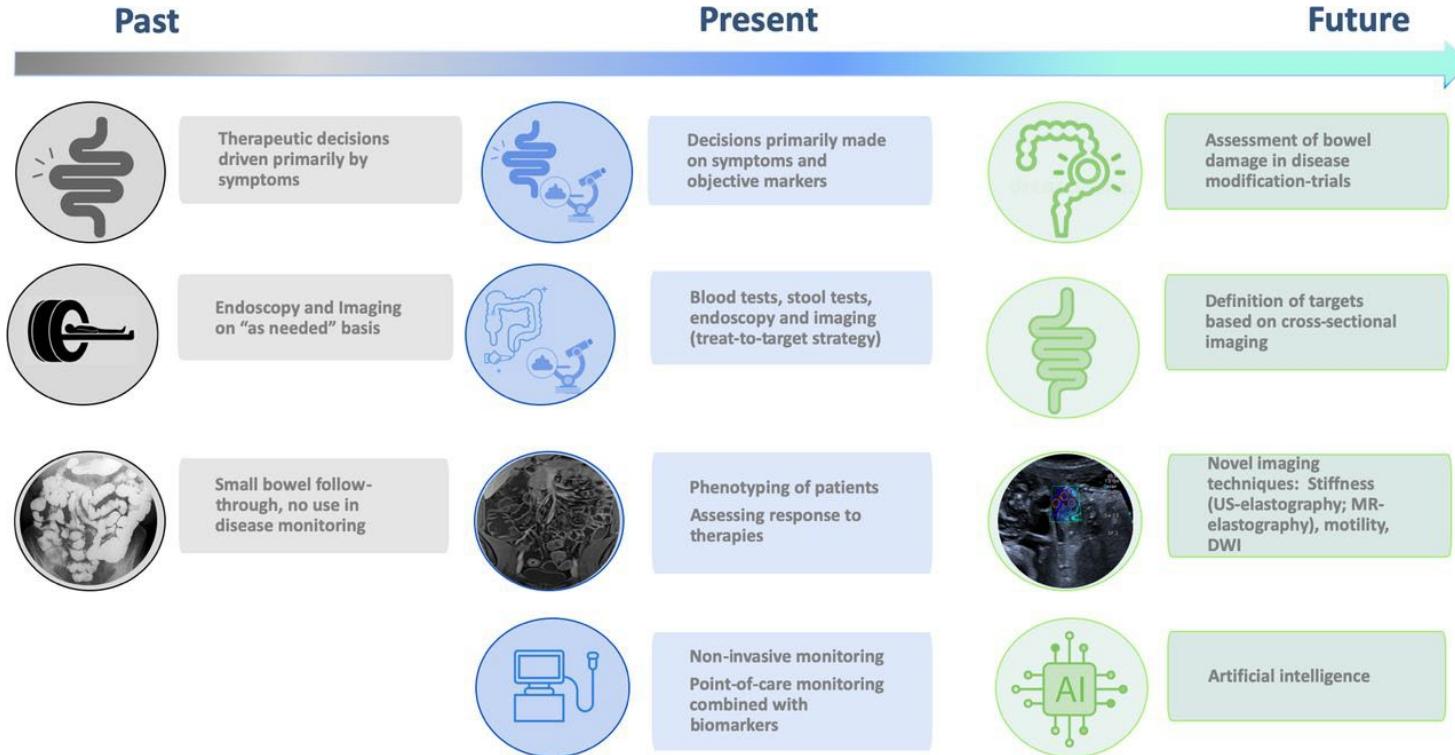
Histology healing (Geboes)
Histologic normalization

Where is urgency?

Further Defining These Targets



These Targets Will Likely Continue to Evolve



Addressing Gaps in Care Will Ensure We Continue to Meet Our Patient's Needs

Patient reported outcomes

- PRO2 created as temporary measure to meet FDA requirements
- PROs should be developed to be used in clinical practice with high reliability, validity, responsiveness and feasibility

HRQoL*

- Developed as research tools and challenging to implement in clinical practice
- Develop validated shorter HRQoL assessment tool

*Health-related quality of life

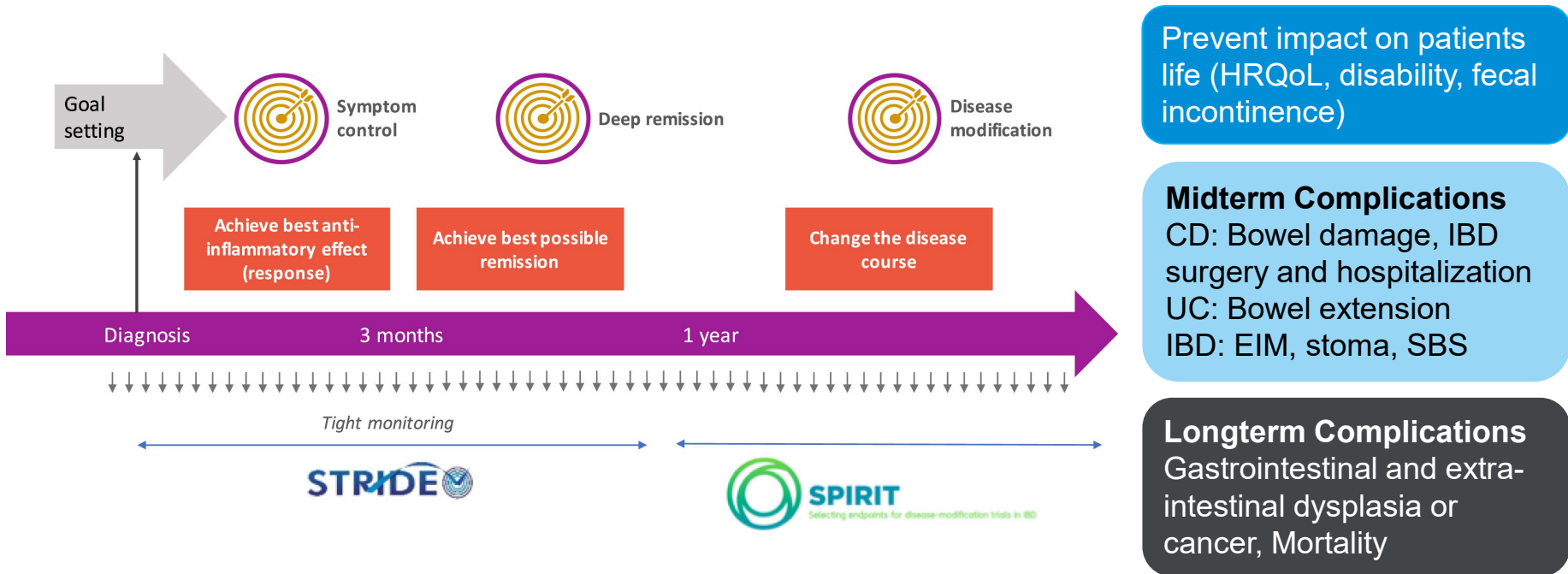
Endoscopic Healing

- Thresholds to define remission or response remain un-validated
- More studies needed to link optimal thresholds with best patient outcomes

Histology & Transmural Healing

- Unclear if significant enough to justify further optimization of medical treatment
- Prospective (ideally RCT) needed to explore these targets for optimal outcomes

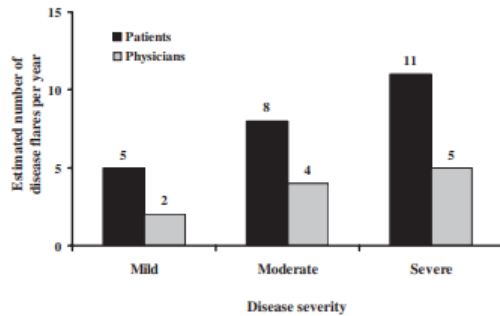
Tight Control Can Lead to Prevention of Complications in the Future



Do Your Patients' Goals Match Your Suggested Targets?



Patient-Physician Perspective: Frequency of flare



- Surveys identify clear disparities between physicians and patients' perceptions of impact of UC on patients' lives
- Calls for improved communication about goals

Patient-Physician Perspective: Burden of UC

Response	Respondents (%)	
	Patients' Response	Physicians' Estimate of Patients' Response
Symptom control		
"My symptoms were completely or mostly under control"	21	48
"My symptoms were present but did not interfere with my life"	19	24
"My symptoms caused some disruption to my activities, but my quality of life was okay"	42	17
"My symptoms negatively affected my life on a regular basis"	17	11
Interpretation of remission		
"Experiencing no symptoms, feeling similar to how they did before they developed the disease"	42	57
"Living with some symptoms, but managing life without interruption"	43	31
"Living with symptoms and interruptions to daily life, but with less severity, pain, and bleeding than during a flare"	15	13

Patient-Physician Perspective: QoL/Psychological

Impact of UC on Day-to-Day Lives	Respondents (%)	
	Patients' Response	Physicians' Estimate of Patients' Response
"I worry about the long-term health effects of having UC"	84	53
"UC makes life more stressful"	82	57
"UC makes it difficult to lead a normal life"	62	36
"UC is embarrassing"	70	33
"Going to the bathroom a lot has become an expected part of life"	84	52
"Not feeling well from UC has become an expected part of life"	73	37
"Living with UC is a daily struggle"	61	28
"UC has wrecked important moments in my life"	60	35
"Disruptive to life"	95	97

UC, ulcerative colitis.

Make Sure You Have the Right Target: Not All Active Symptoms = Active Inflammation

Clinical remission
Endoscopic remission



Clinical response/remission
Biochemical inflammation



Subclinical inflammation

Almost there



Optimize treatment

Clinical symptoms
Endoscopic remission

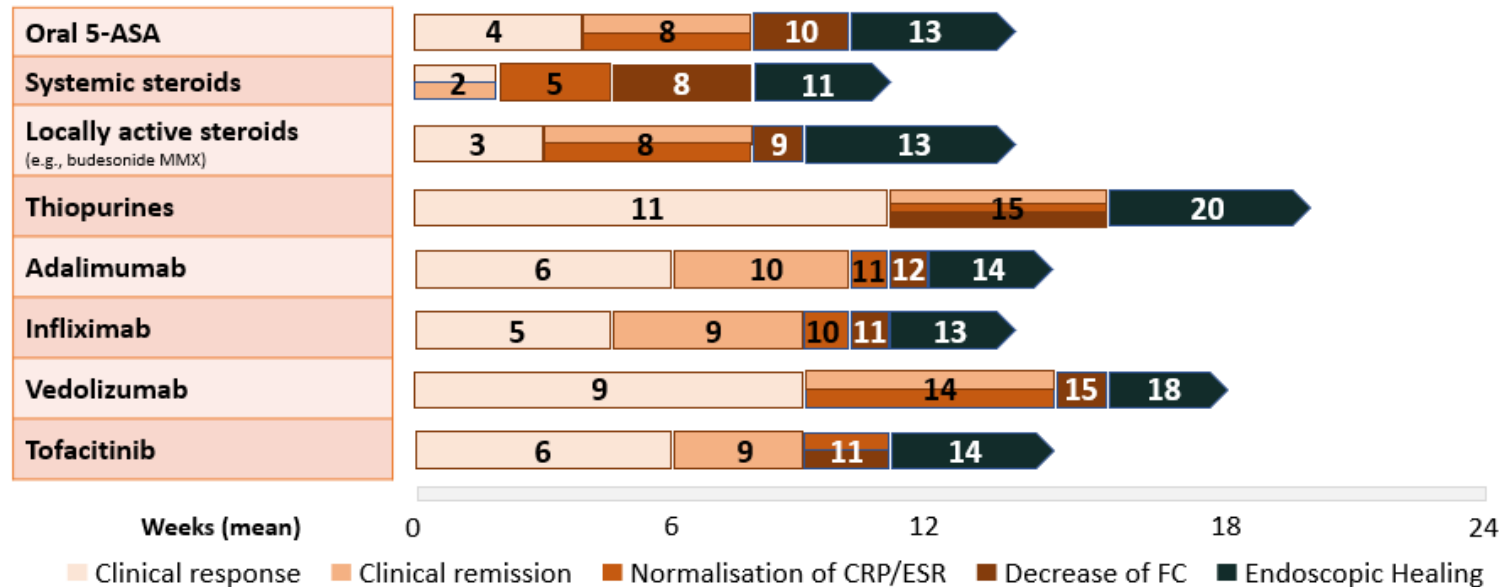


Non-inflammatory causes for symptoms



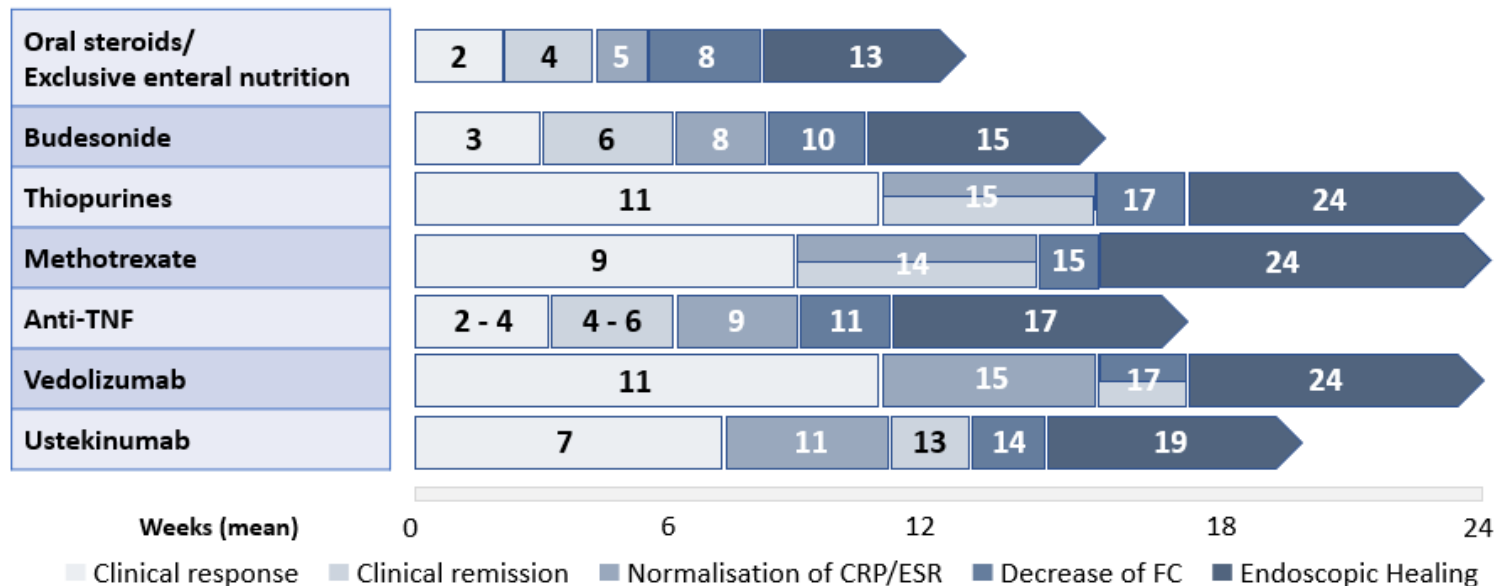
Ulcerative Colitis: Ensure You Give Your Patient Enough Time to Reach Targets

Mean Number of Weeks after Initiation of Therapy
(based on expert opinion)



Crohn's Disease: Ensure You Give Your Patient Enough Time To Reach Targets

Mean Number of Weeks after Initiation of Therapy
(based on expert opinion)



Defining Treatment Targets Should Be Individualized to Each Patient

Evidence guides more objective targets of disease control



Partner with your patient to determine which targets are important for them

Baseline assessment of disease severity*



Select targets with your patient-Partner!



Reassess the patient early in treatment (4-8w)**



Need more time vs. optimize your treatment plan



Reassess until you have reached your target

*benchmark CRP, FCP to endoscopy



**Know your treatment response times

Take Home Points for Your Practice

1. Undifferentiated patient with symptoms concerning for IBD → get your diagnostics early!
2. Diagnosis established – understand your patient's prognosis and disease severity – they are not always the same
3. Shared decision making to select the right treatment for your patient
4. Once you start therapy partner with your patient to define treatment targets
5. Have clear plan when to evaluate your targets including endoscopic assessment
6. When you aren't reaching your targets – ensure you have the right target
7. If ongoing inflammation despite time, optimize therapy or move to plan B

An aerial view of a city skyline, likely Atlanta, Georgia, featuring prominent skyscrapers like the Bank of America Tower. The image is overlaid with a large blue geometric shape that tapers from the top left towards the bottom right. The text "Thank You" is centered in the middle of the image in a blue, sans-serif font.

Thank You



@ibdgijami



Kinnucan.Jami@mayo.edu