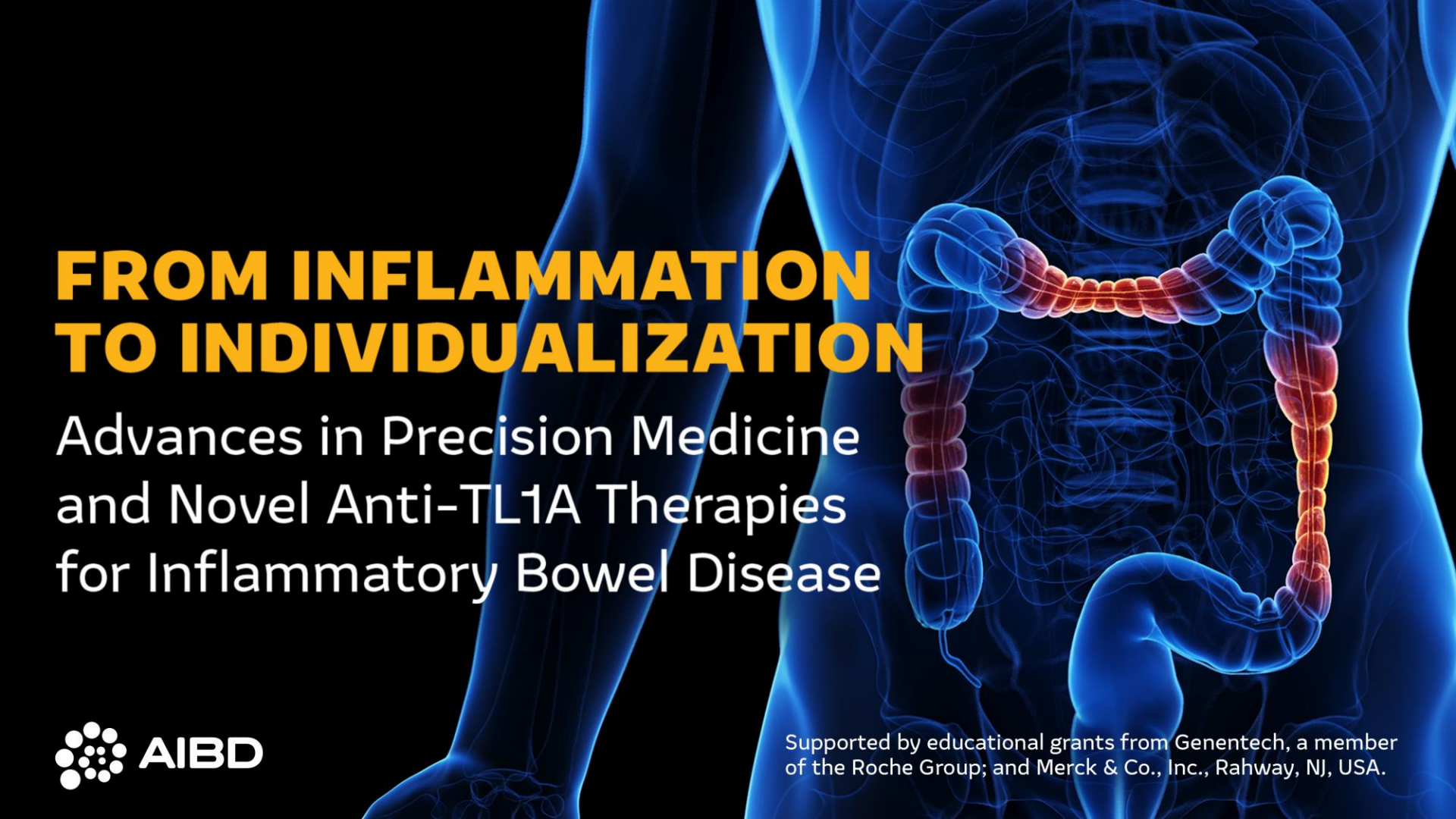
FROM INFLAMMATION TO INDIVIDUALIZATION

Advances in Precision Medicine and Novel Anti-TL1A Therapies for Inflammatory Bowel Disease



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Supported by educational grants from Genentech, a member of the Roche Group; and Merck & Co., Inc., Rahway, NJ, USA.

Learning Objectives

- Apply innovative technologies and precision medicine tools to accurately identify/characterize IBD, including CD and UC, and guide individualized therapeutic decisions
- Examine the impact of IBD disease heterogeneity, including chronic inflammation and complications such as strictures, on disease management and progression
- Evaluate the clinical data, therapeutic potential, and mechanisms of action of novel anti-TL1A monoclonal antibodies for the treatment of IBD
- Address the complexities of IBD through personalized management strategies that consider evidence-based risk stratification, biomarker utilization, TDM, and interdisciplinary care

TL1A = tumor necrosis factor-like cytokine 1A; TDM = therapeutic drug monitoring.

FROM INFLAMMATION TO INDIVIDUALIZATION

Advances in Precision Medicine and Novel Anti-TL1A Therapies for Inflammatory Bowel Disease

Untangling the Diagnostic Web: Precision Approaches to IBD

Corey A. Siegel, MD, MS

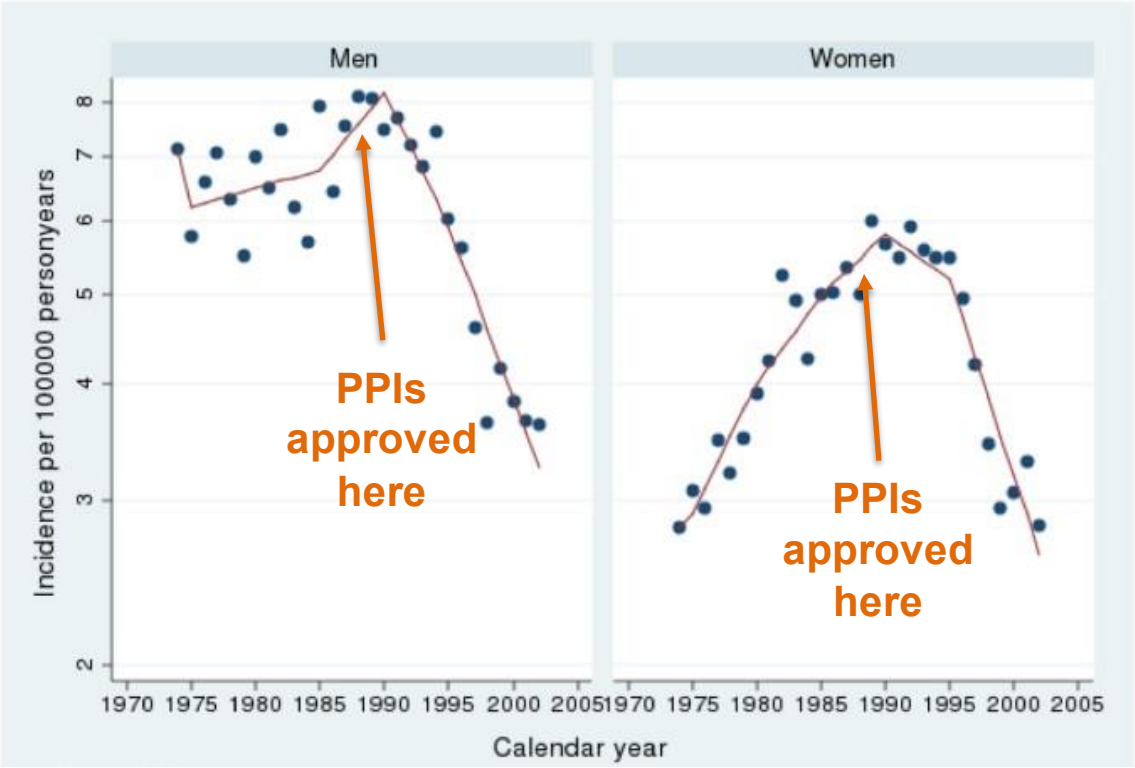
Director, Walter and Carole Young Center for Digestive Health
Dartmouth Hitchcock Medical Center
Lebanon, NH

Disclosures

- **Corey A. Siegel, MD, MS:** Consultant/Advisory Board – AbbVie, Boomerang, Celltrion, Johnson & Johnson, Lilly, Napo Pharmaceuticals, Path Healthcare, Pfizer, Prometheus Labs, Sanofi, Takeda, Trellus Health; Speaker for CME Activities – AbbVie, Johnson & Johnson, Pfizer, Takeda; Grant Support – AbbVie, Celltrion, Johnson & Johnson, Lilly, Pfizer, Takeda; Co-Founder – MiTest Health, LLC (software company that has developed technology licensed to Takeda); Intellectual Property – Patent for a “System and Method of Communicating Predicted Medical Outcomes”; Equity Interest – Path Healthcare, Trellus Health, MiTest Health, LLC

What Does IBD Need to Turn the Corner Like This?

Incidence of gastric perforated peptic ulcers in Sweden from 1974 to 2002



PPIs = proton pump inhibitors.

Hermansson M, et al. *BMC Gastroenterol*. 2009;9:25.

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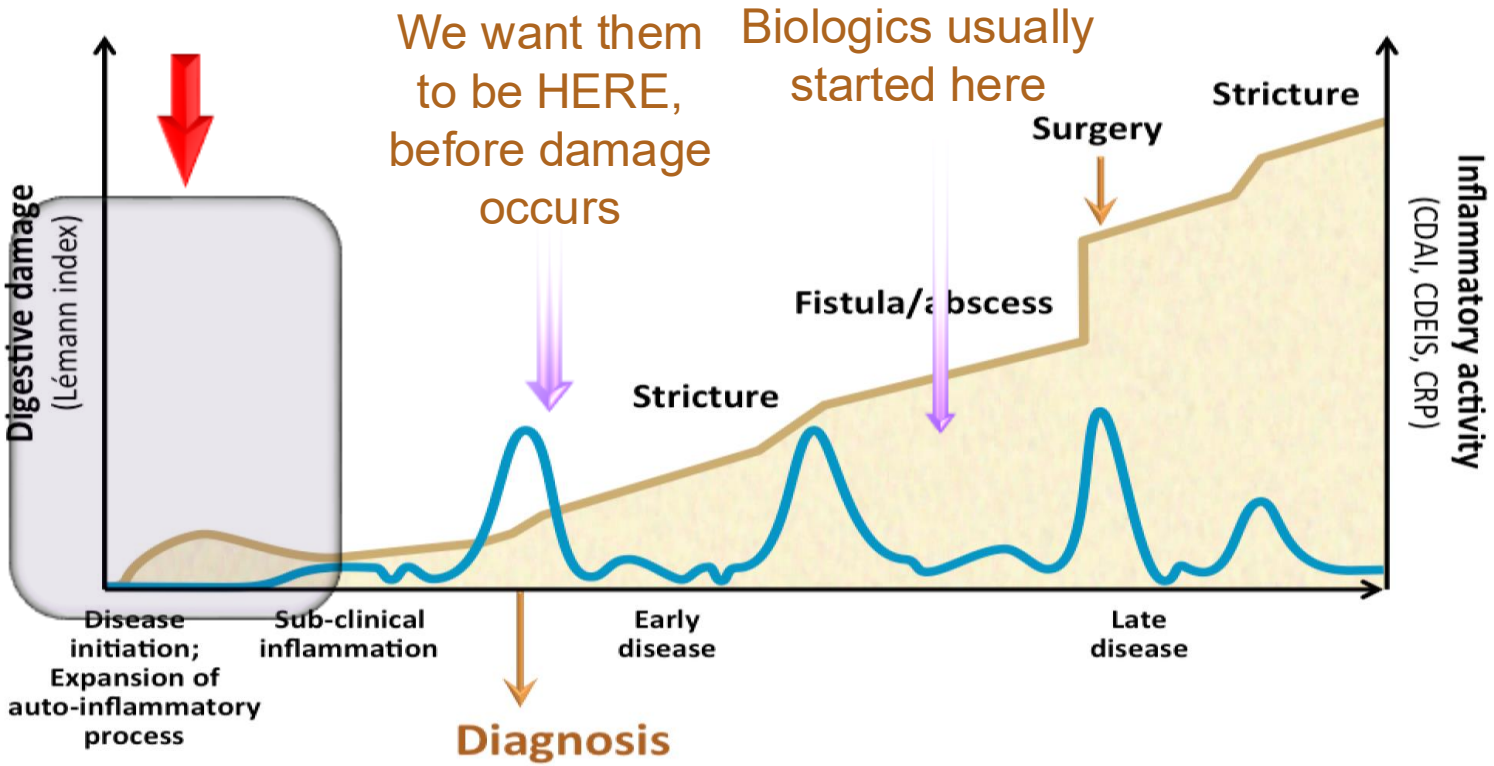
AIBD ADVANCES IN INFLAMMATORY BOWEL DISEASES

Early Diagnosis

Looking into the Future at Disease “Interception” and Prevention



CDAI = CD Activity Index; CDEIS = CD Endoscopic Index of Severity; CRP = C-reactive protein.
Pariente B, et al. *Inflamm Bowel Dis*. 2011;17(6):1415-1422.

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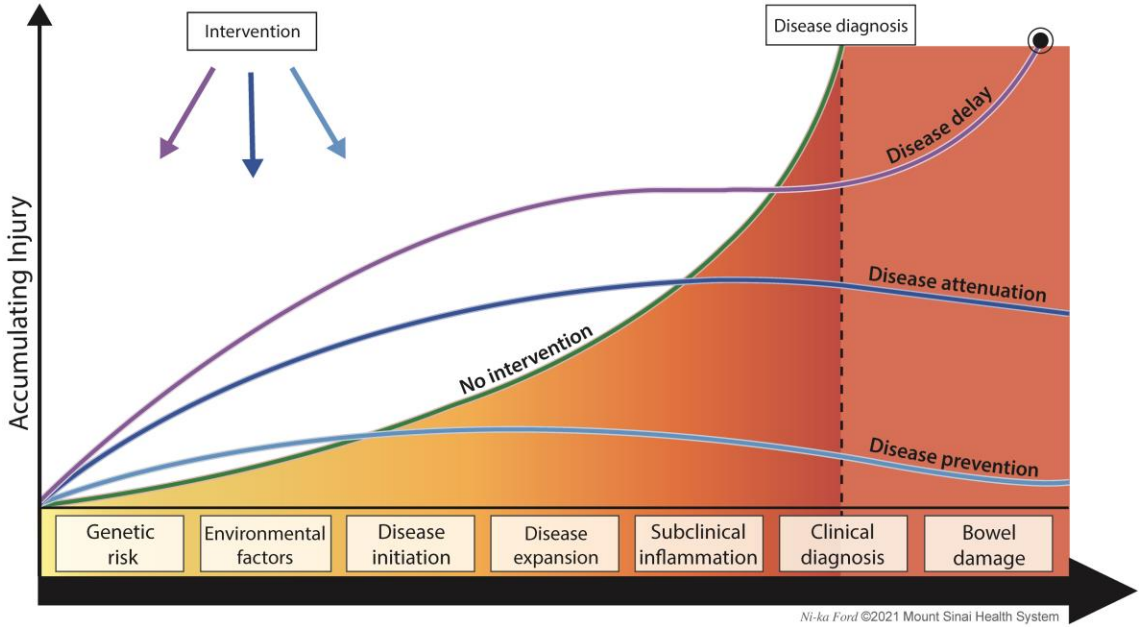
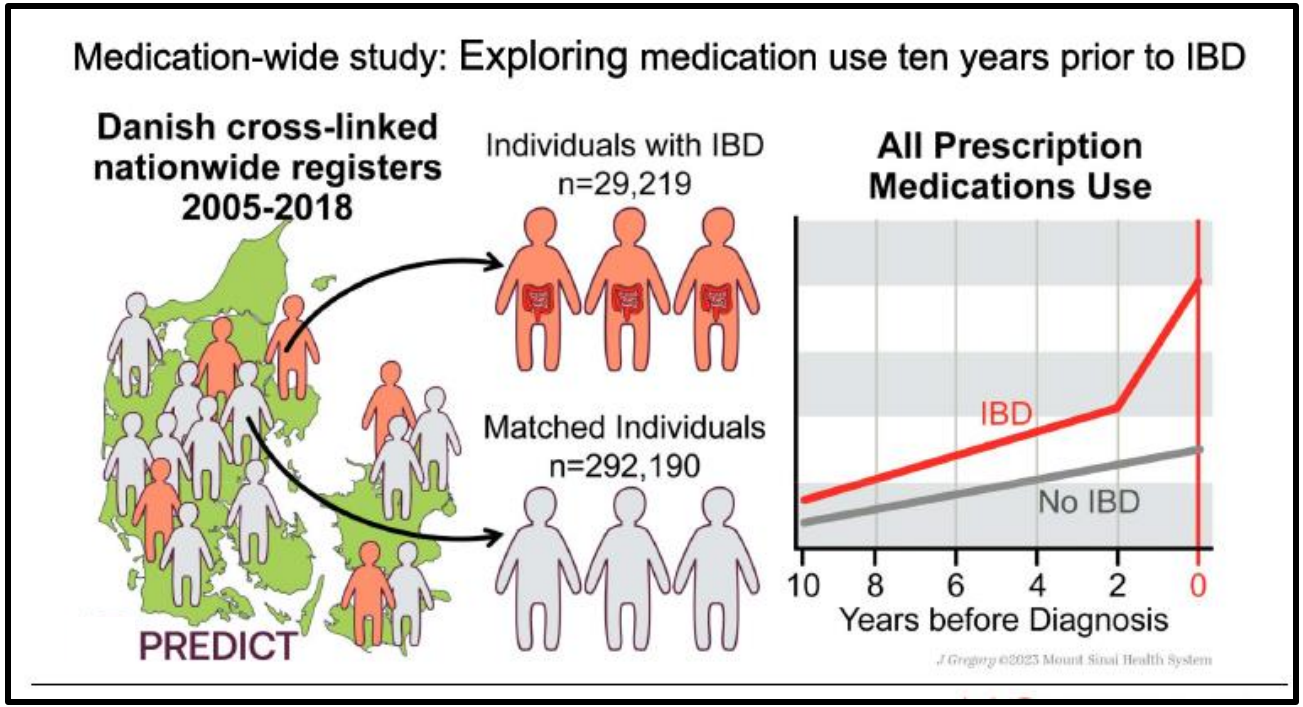
What Could Be the Impact of an Intervention in the Preclinical Stages of Disease?



Torres J, et al. *Gastroenterology*. 2022;162(5):1452-1455.

IBD Does Not Start at Diagnosis!



CD population
Immunosuppressants: X 2.7
Antianemic preparations: X 2.3
Analgesics: X 1.9
Psycholeptics: X 1.9
than the matched population 10 years before diagnosis (P<0.0001)

Bonfils L, et al. *Am J Gastroenterol*. 2023;118(12):2220-2229.

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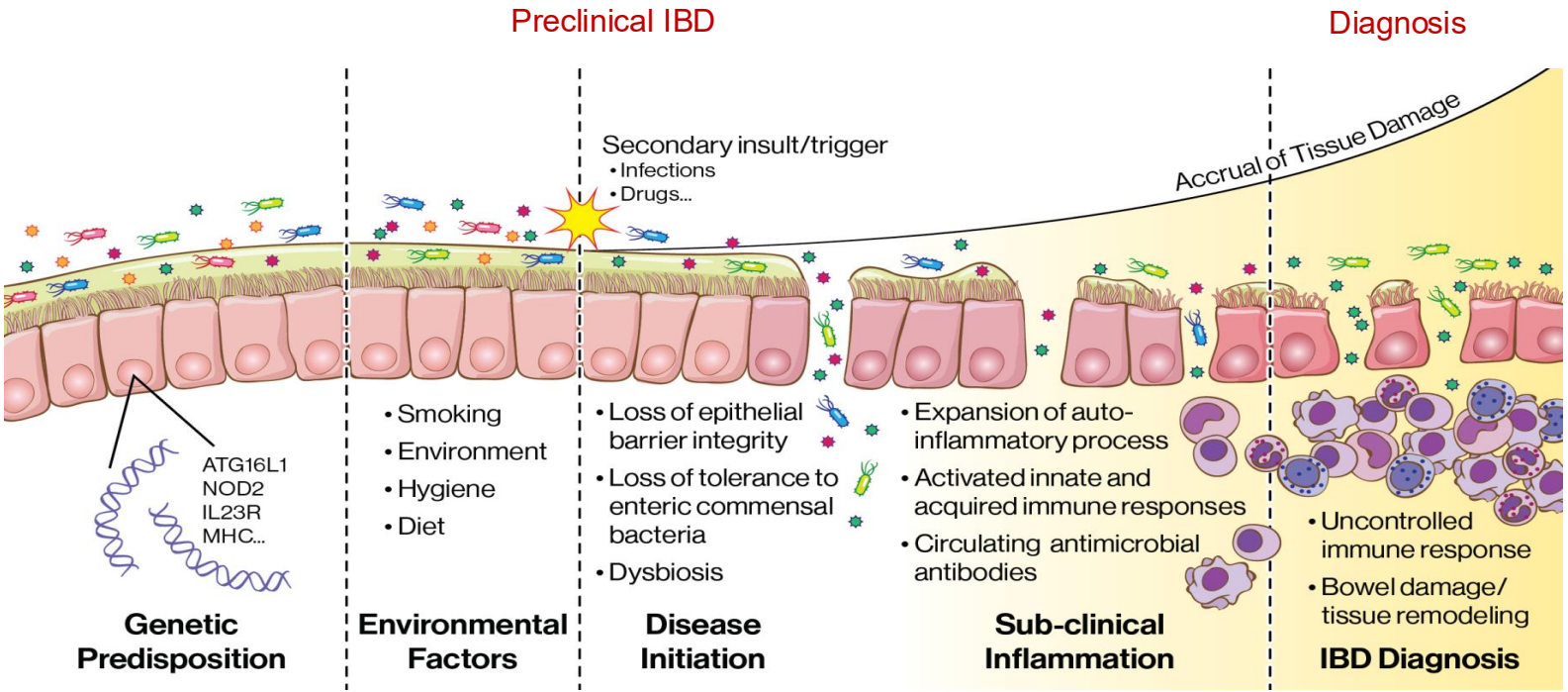
The Preclinical Phase of IBD: The New Window of Opportunity

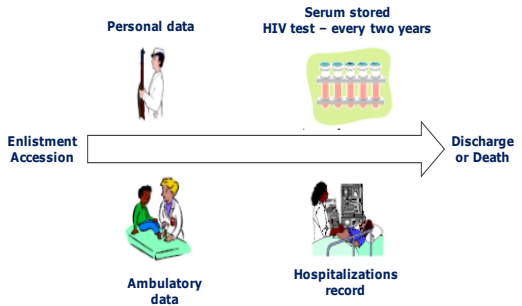


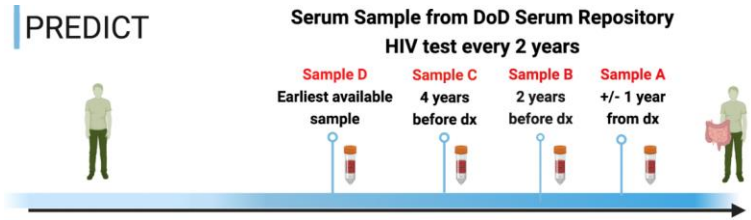
Torres J, et al. *Gut*. 2016;65(7):1061-1069.

PREDICTS: The Multi-Omic Evaluation and Discovery in an IBD Cohort of Tri-Service Subjects Study

- History
  - Started in 1985 following universal, mandatory screening for HIV
- Current inventory: 62.5 million samples
- Location and management
  - Armed Forces Health Surveillance Branch, Silver Spring, MD

1. Case identification	2. Sample retrieval from DoD serum repository

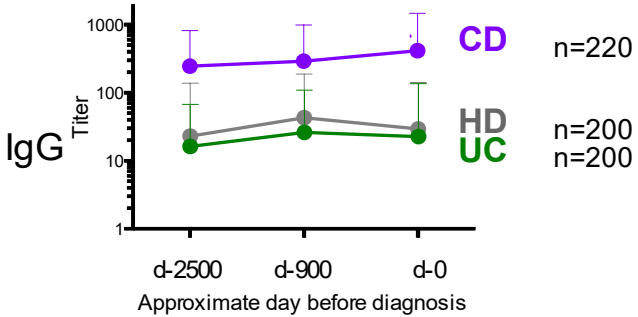


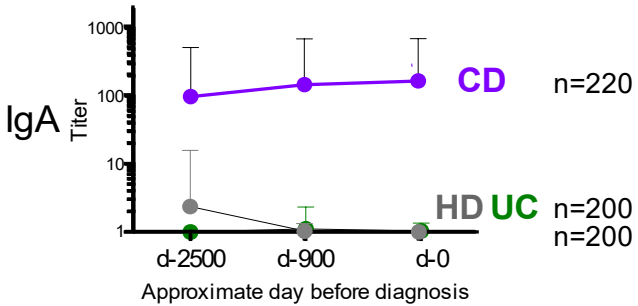


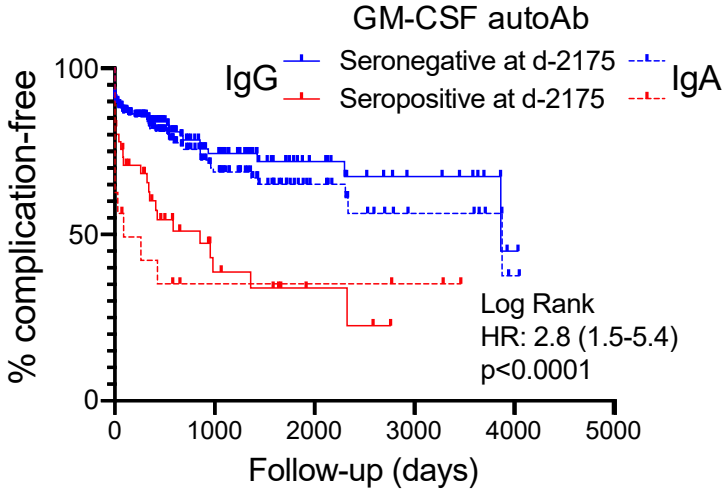
- For each patient, up to 3-4 serum samples are retrieved before diagnosis
- Controls were matched on timing of Sample A (± 1 year), age, gender, and race

Porter CK, et al. *Contemp Clin Trials Commun*. 2019;14:100345.

PREDICTS: GM-CSF Autoantibodies Are Present in Patients with CD Up to 10 Years before Diagnosis and Are Associated with Complicated Behavior







→ Higher anti-GM-CSF antibody prevalence and titers in CD than UC and HD

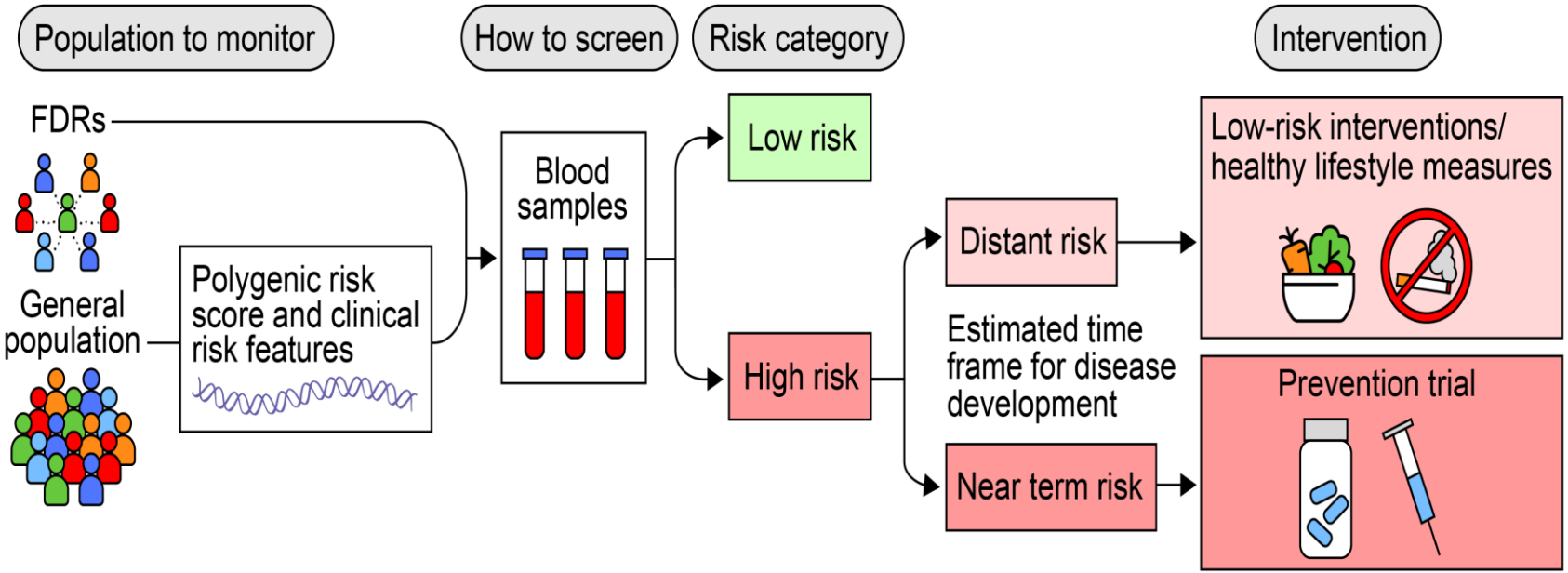
→ Increase in mean titers in CD only as diagnosis nears

→ Significantly higher IgG and IgA in cases **with ileal involvement**, overall complications, and IgA for perianal disease

GM-CSF = granulocyte-macrophage colony-stimulating factor; Ig = immunoglobulin; HD = healthy donors.

Mortha A, et al. *Gastroenterology*. 2022;163(3):659-670.

Prevention of IBD According to Risk



FDRs = first-degree relatives.

Lopes EW, et al. *Clin Gastroenterol Hepatol*. 2025;23(3):396-405.e1.

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Patients and FDRs Are Willing to Undergo Predictive Testing and Preventive Interventions

PREDICTIVE TESTING

85% accepted (for them/ their children)

Blood test	**78%**	n=1035
Stool test	**76%**	n=1012
Saliva test	**67%**	n=883
US	**57%**	n=761
MRI/CT scan	**46%/42%**	n=604/563
Colonoscopy	**37%**	n=490

PREVENTIVE INTERVENTIONS

97% accepted (for them/ their children)

n=1327

Diet modification	**86%**	n=1142
Physical exercise	**81%**	n=1071
Probiotics	**74%**	n=982
Diet supplements	**69%**	n=922
Quit smoking	**59%**	n=789
Fecal transplantation	**40%**	n=531
Immunosupressive oral drugs	**38%**	n=510
Oral antibiotics	**32%**	n=430
Immunosupressive IV/SC drugs	**32%**	n=423

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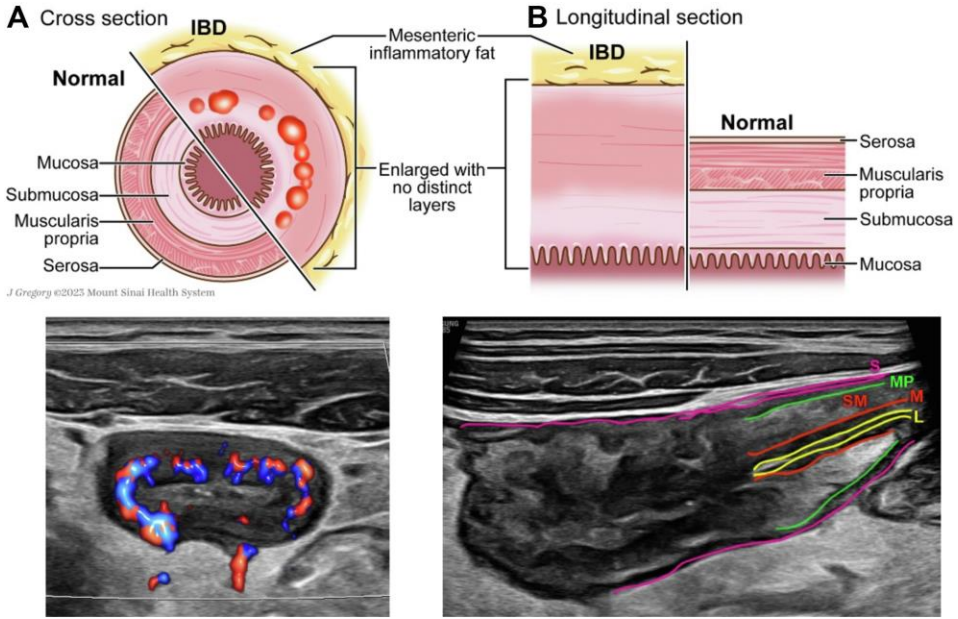
Bravo A, et al. *J Crohn Colitis*. 2024;18(Suppl 1):i2086.

The Benefits of Intestinal Ultrasound (IUS) for the Early Diagnosis of IBD



- Noninvasive, no radiation, no prep
- Real-time assessment
- Accurate in identifying the presence of inflammation, even in the absence of symptoms
- Easy to follow longitudinally
- Inexpensive
- A GREAT tool for assessment of high-risk individuals pre-diagnosis

Chavannes M, et al. *Clin Gastroenterol Hepatol*. 2024;22(9):1790-1795.e1.

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Currently Available Tools for Precision IBD Care

Our First Precision Diagnostic Tools in IBD

Thiopurines: TPMT, NUD15

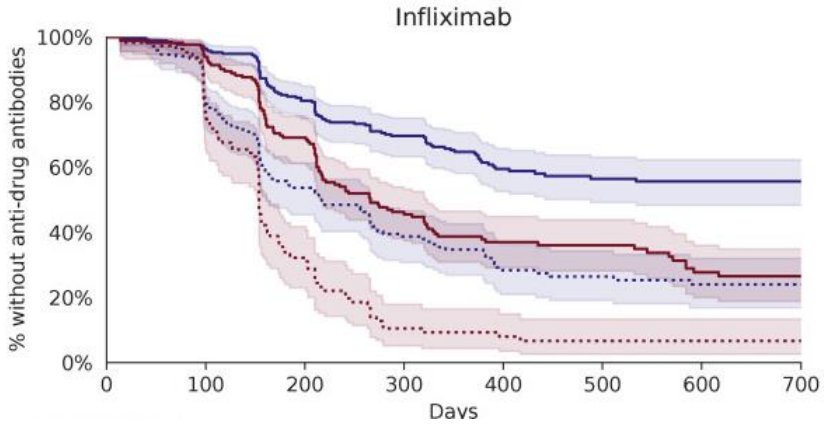
TPMT

Frequency	Enzyme Activity	Allele
89%	Normal to High	$TPMT^{H}/TPMT^{H}$
11%	Intermediate	$TPMT^{H}/TPMT^{L}$
0.33%	Low to Absent	$TPMT^{L}/TPMT^{L}$

NUD15

p.Arg139Cys Allele Frequency
Koreans: 10.4%
Japanese: 7%
Chinese: 13%
Mixed American: 2%

Anti-TNF: HLA-DQA1*05



Dotted lines = patients undergoing anti-TNF monotherapy

Solid lines = combination therapy with immunomodulators

Red = carriers of the HLA-DQA1*05 allele (1 or 2 copies)

Blue = noncarriers

TNF = tumor necrosis factor.

Beaugerie L, et al. *Lancet*. 2009;374(9701):1617-1625. Yang SK, et al. *Nat Genet*. 2014;46(9):1017-1020.
Sazonovs A, et al. *Gastroenterology*. 2020;158(1):189-199.

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TDM Is Precision Medicine for IBD

IBD patients at treatment failure
→ Confirm inflammation: Clinical assessment, biomarkers
→ Exclude infection and non compliance to treatment
→ Send for serum drug TLs and ADA levels

	Detectable ADAs	**Undetectable ADAs**
Sub-therapeutic drug levels	Immune mediated pharmacokinetic failure Insufficient bioavailability of drug as a result of indued immunogenicity with functional ADA resulting in increased drug clearance **Change to alternate drug, within the same class**	Non-immune mediated pharmacokinetic failure Insufficient availability of the drug as a result of non-immune mediated pharmacokinetic issues **Dose escalate**
Therapeutic drug levels	False positive Or Mechanistic failure Repeat TDM levels If repeat results consistent, **switch to out of class biologic agent**	Mechanistic failure Pharmacodynamic issues inhibition of inflammatory pathway not effective or inflammation driven by an alternate pathway **Switch to out of class biologic agent**

TLs = trough levels; ADAs = anti-drug antibodies.
Albader F, et al. *World J Gastroenterol*. 2021;27(37):6231-6247.

A Model to Predict Individualized Risk of Crohn's Disease Complications

- 695 adult patients with Crohn's disease
- Outcome = time to complication of Crohn's disease

Variable	Hazard Ratio, 95% CI
Small bowel disease	2.12, CI 1.05-4.29
Left colonic disease	0.73, CI 0.49-1.09
Perianal disease	4.12, CI 1.01-16.88
LogASCA	1.35, CI 1.16-1.58
LogCbir1	1.29, CI 1.07-1.55
LogANCA	0.77, CI 0.62-0.95
NOD 2 frameshift mutation	2.13, CI 1.33-3.40
Perianal*logASCA	0.63, CI 0.42-0.94

Model concordance
Calibration
Harrell's C=0.73

Adult Validation
Harrell's C=0.73

Pediatric Validation
Harrell's C=0.75

ASCA = anti-saccharomyces cerevisiae antibodies; ANCA = anti-neutrophil cytoplasmic antibodies.
Siegel CA, et al. *Aliment Pharmacol Ther*. 2016;43(2):262-271.

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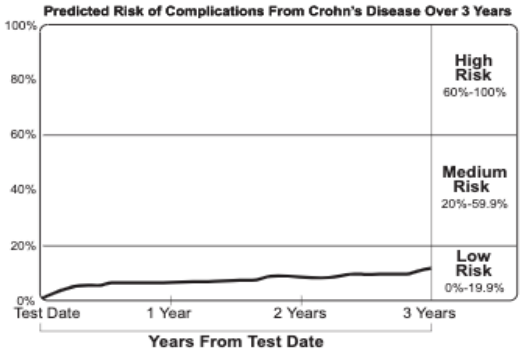
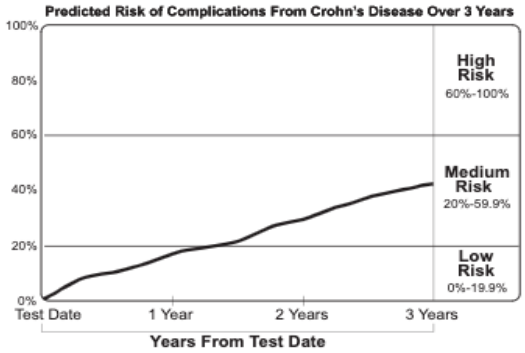
Transforming Clinical Decision Support Tool Results into an Individualized Risk Profile

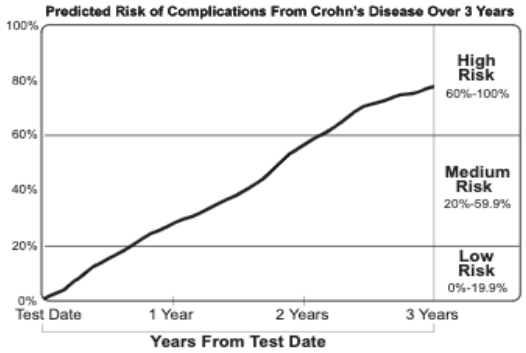
Example of LOW RISK result



Example of MEDIUM RISK result



Example of HIGH RISK result



Siegel CA, et al. *Aliment Pharmacol Ther*. 2016;43(2):262-271.

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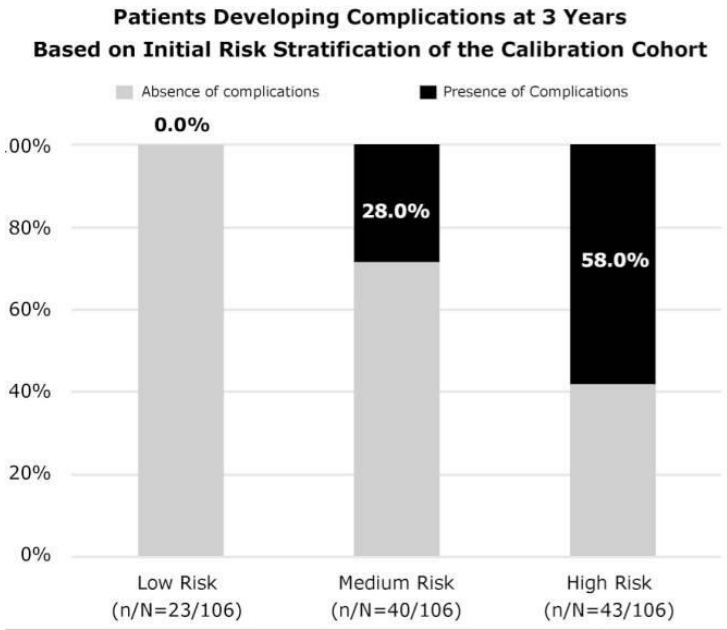
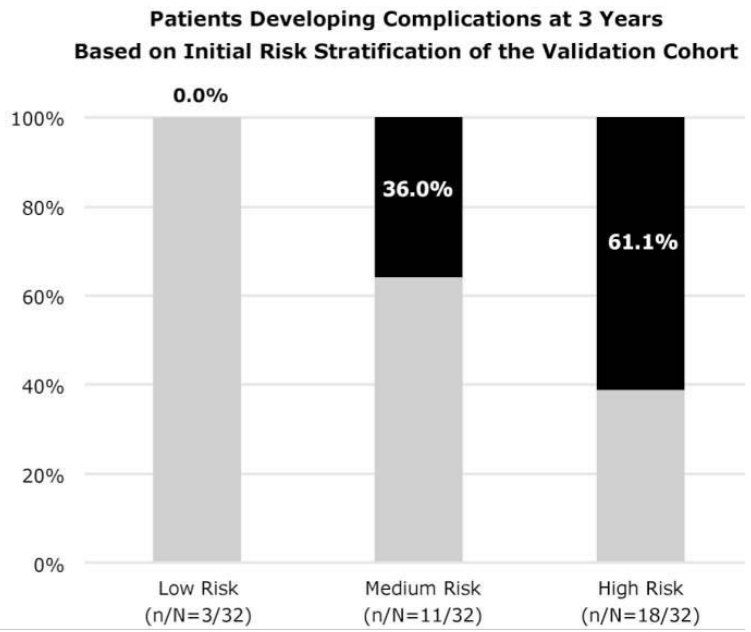
Calibration and Validation of Clinical Decision Support Tool to Predict Crohn's Disease Complications





Siegel CA, et al. *Crohns Colitis 360*. 2021;3(4):otab074.

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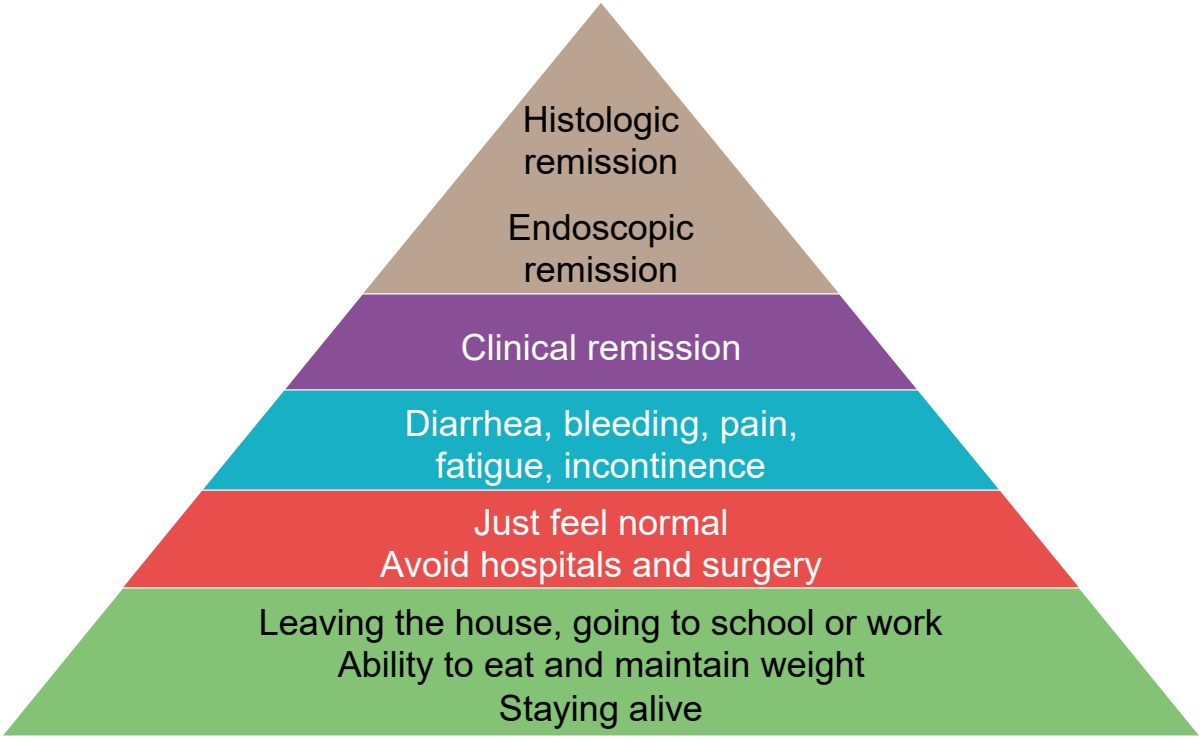
Patient Preferences Have to Be Part of Personalized IBD Care

Hierarchy of Needs for the Patient with IBD

Physician focus

Patient focus



Siegel CA. *Am J Gastroenterol*. 2019;114(3):382-383. Rubin DT, et al. *Am J Gastroenterol*. 2019;114(3):384-413. Al Khoury A, et al. *Dig Dis Sci*. 2022;67(6):1956-1974.

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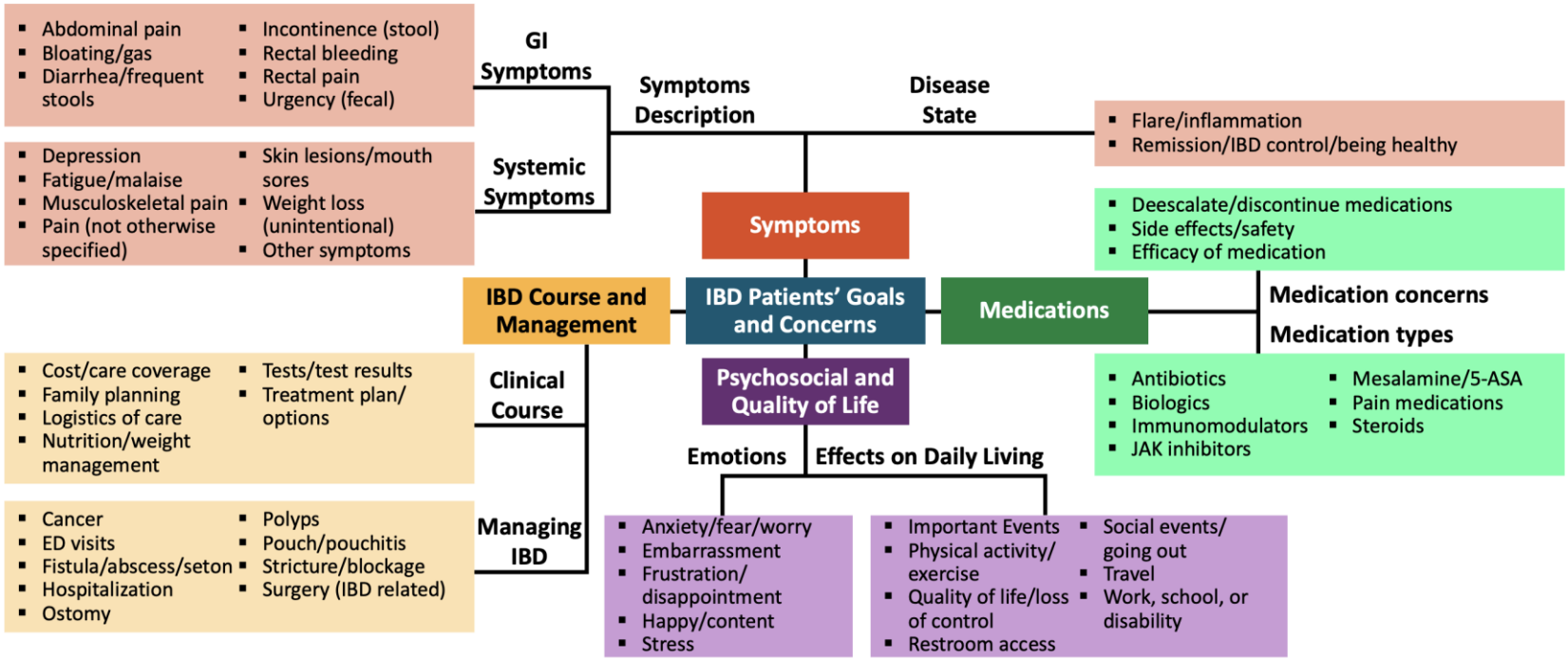
Just Ask the Patient about Their Goals?

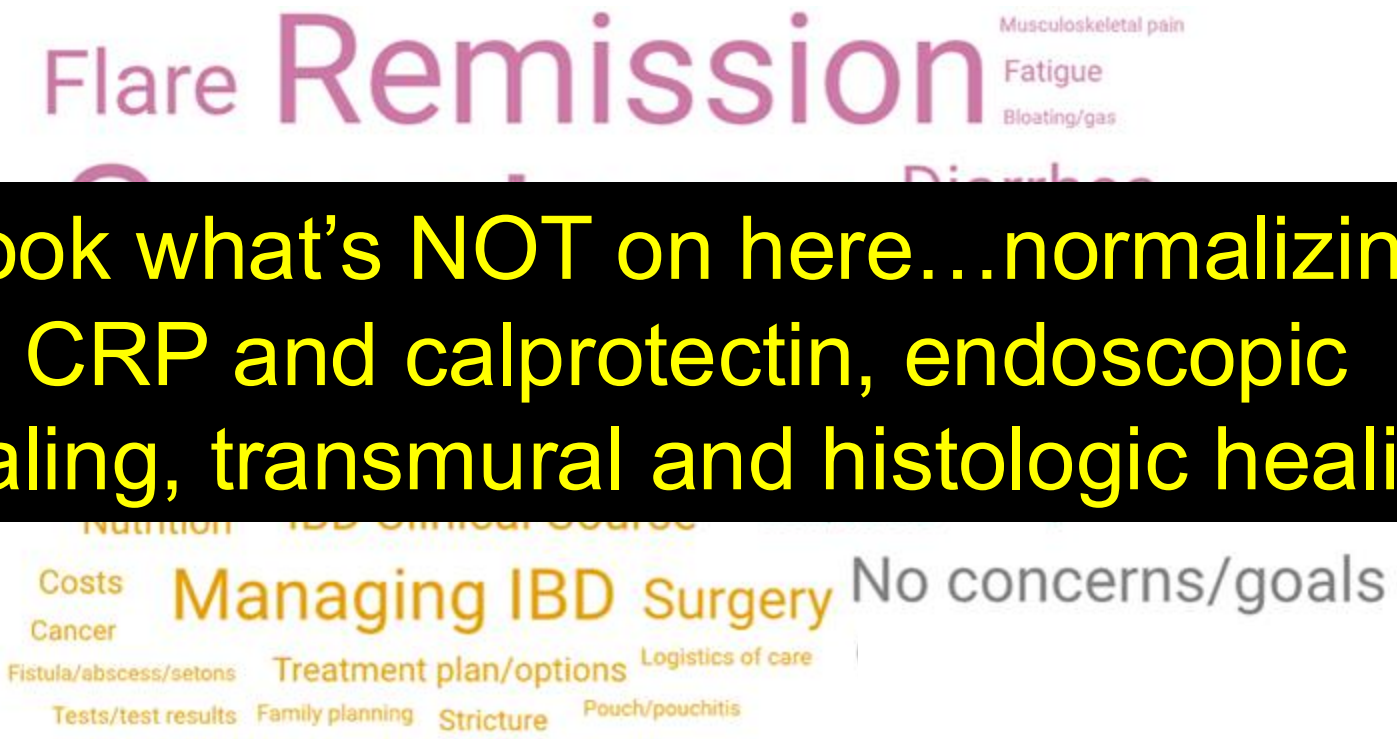
What is your number ONE concern or goal related to your IBD? This could be related to a specific symptom, worry for the future, or how IBD might impact an upcoming life event.

Patients' Goals Are Highly Variable



Tse CS, et al. *J Crohns Colitis*. 2022;16(3):379-388.

Patients' Goals Are Highly Variable



Tse CS, et al. *J Crohns Colitis*. 2022;16(3):379-388.

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This Is What We All Want!

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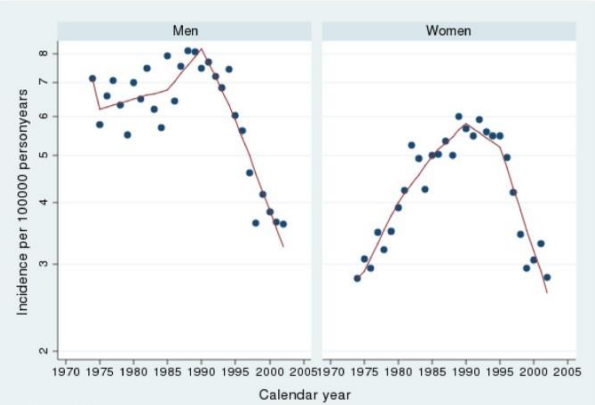
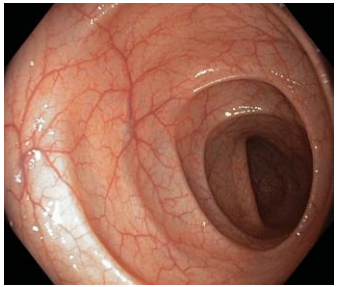
What Does IBD Need to Turn the Corner Like This?

- A cohort of recently diagnosed patients with early use of advanced therapy
- Treatment of a cohort of people at high risk of developing IBD
- Precision tools to risk-strategy patients and personalize medical therapy
- A new, different scientific breakthrough
- New mechanisms of action for therapeutics
- **Likely all of the above…**





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Hermansson M, et al. *BMC Gastroenterol*. 2009;9:25.

TL1A in IBD Pathogenesis and Anti-TL1A Agents in Clinical Trials

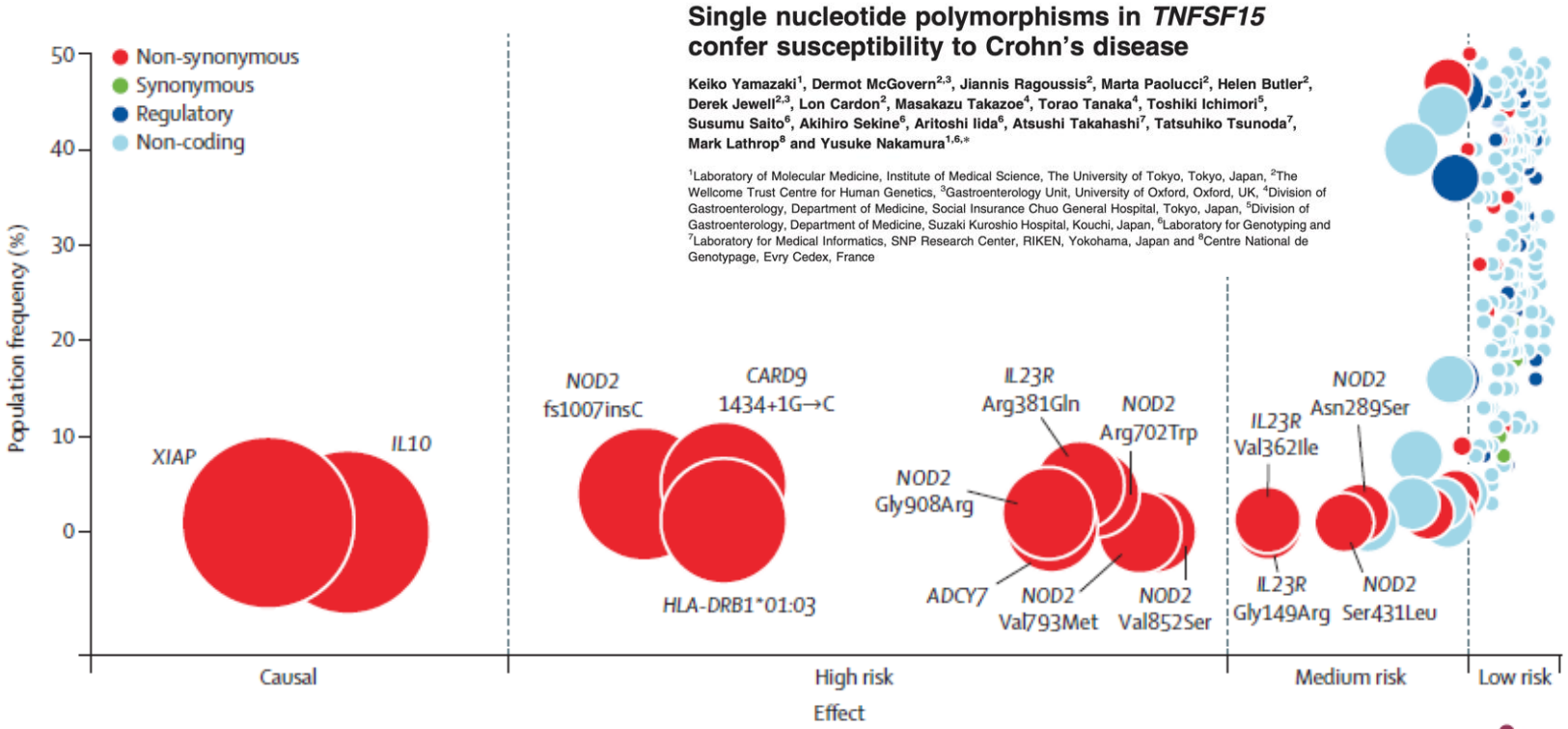
Bruce E. Sands, MD, MS, FACG

Chief, Division of Gastroenterology
Icahn School of Medicine at Mount Sinai

Disclosures

- **Bruce E. Sands, MD, MS, FACG:** Research Grants – Janssen; Consulting Fees – AbbVie, Alimentiv, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Celltrion, Eli Lilly and Company, Galapagos, Genentech, Gilead Sciences, GSK, Johnson & Johnson Innovative Medicine, Mitsubishi Tanabe, Merck & Co, Pfizer, Sanofi, Takeda, Teva; Speaking Fees – Abivax, Alimentiv, Bristol Myers Squibb, Celltrion, Eli Lilly and Company, Janssen, Merck & Co, Pfizer, Sanofi, Takeda; Stock & Stock Options – Ventyx Biosciences

GWAS Identify TNFSF15 (Encoding TL1A) as a Susceptibility Gene in Crohn's Disease



GWAS = genome-wide association studies.

Mirkov MU, et al. *Lancet Gastroenterol Hepatol*. 2017;2(3):224-234. Yamazaki K, et al. *Hum Mol Genet*. 2005;14(22):3499-3506.

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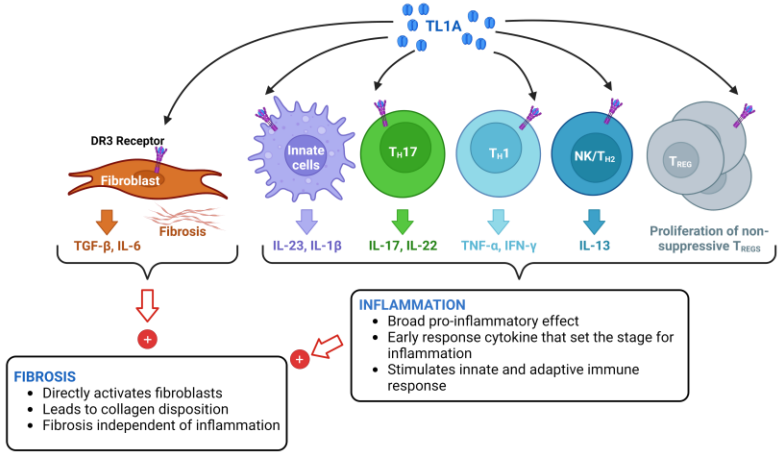
Tumor Necrosis Factor-Like Cytokine 1A (TL1A): First IBD Target That Mediates Inflammation and Fibrosis

- Member of the tumor necrosis factor (TNF) superfamily
- Implicated in the pathogenesis of inflammatory bowel disease (IBD)
- TL1A and its associated receptor (DR3) are significantly upregulated in inflamed intestinal tissues
- Mouse studies have validated TL1A as a target to treat colitis and intestinal fibrosis
- TL1A-encoding gene (TNFSF15) polymorphisms are associated with increased IBD risk



DR3 = death domain receptor 3; IL = interleukin; NK = natural killer; TGF = transforming growth factor; T_H = helper T cell; T_{REG} = regulatory T cell.

Xu X, et al. *J Biol Chem*. 1999;274(6):3549-3556. Furfaro F, et al. *Curr Drug Targets*. 2021;22(7):760-769. Xu WD, et al. *Front Immunol*. 2022;13:891328. Siakavellas S, Bamias G. *Inflamm Bowel Dis*. 2015;21(10):2441-2452. Bamias G, et al. *Clin Immunol*. 2010;137(2):242-249. Barrett R, et al. *Am J Pathol*. 2012;180(2):636-649. Takedatsu H, et al. *Gastroenterology*. 2008;135(2):552-567. Shih DQ, et al. *Mucosal Immunol*. 2014;7(6):1492-1503. Yamazaki K, et al. *Hum Mol Genet*. 2005;14(22):3499-3506. Jostins L, et al. *Nature*. 2012;491(7422):119-124.

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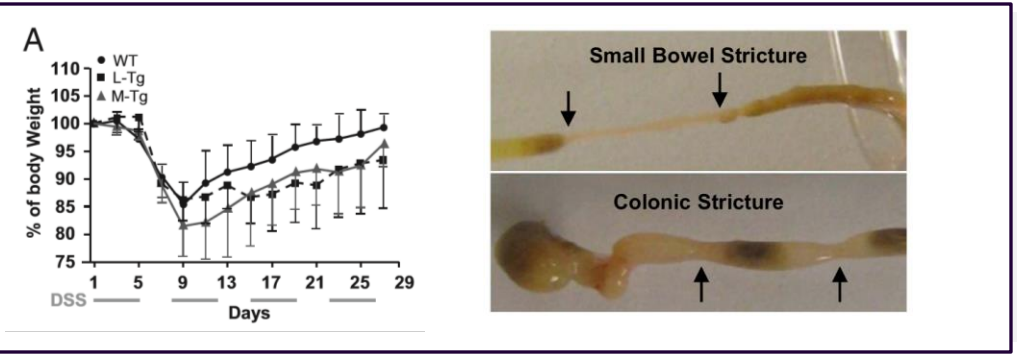
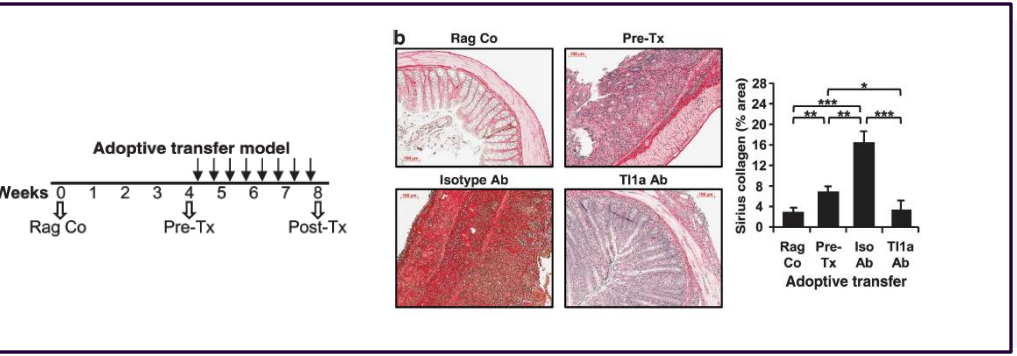
TL1A Signaling Is a Driver of Gut Inflammation and Fibrosis in Mouse Models of IBD





TL1A antibody treatment reverses established fibrosis in murine colitis

- This was observed in 2 different mouse models of chronic colitis

Barrett R, et al. *Am J Pathol*. 2012;180(2):636-649. Shih DQ, et al. *Mucosal Immunol*. 2014;7(6):1492-1503.

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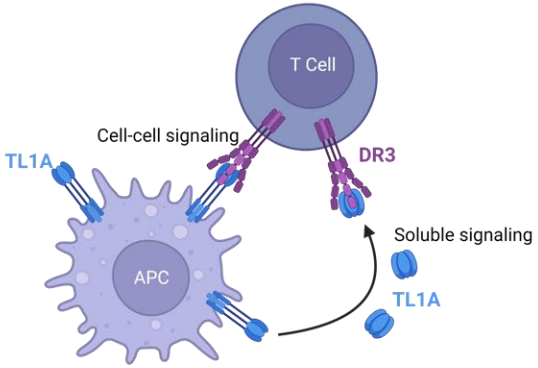
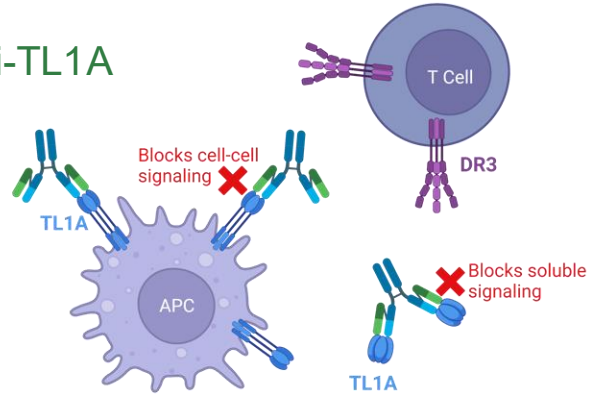
Anti-TL1A Therapy



Anti-TL1A



Sands BE, et al. Presented at: United European Gastroenterology Week (UEGW); October 14-17, 2023; Copenhagen, Denmark. Danese S, et al. Presented at: UEGW; October 14-17, 2023; Copenhagen, Denmark.

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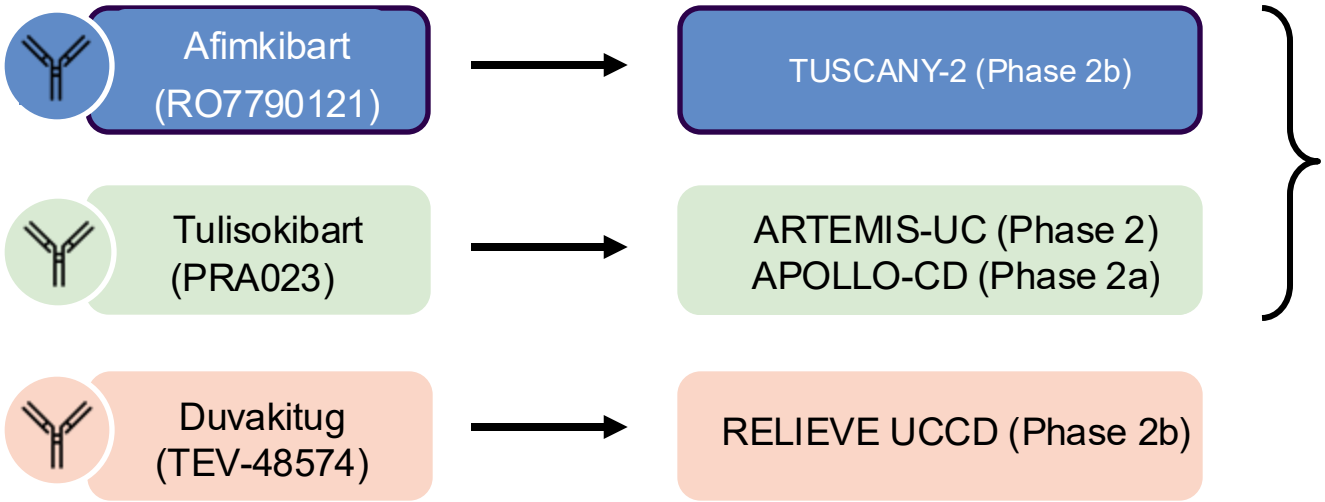
Novel Anti-TL1A Treatments Have Reported Positive Phase 2 Studies in IBD and Transitioned to Phase 3



ClinicalTrials.gov. Accessed December 1, 2025. https://clinicaltrials.gov/study/NCT04090411; https://clinicaltrials.gov/study/NCT04996797; https://clinicaltrials.gov/study/NCT05013905; https://clinicaltrials.gov/study/NCT05499130.

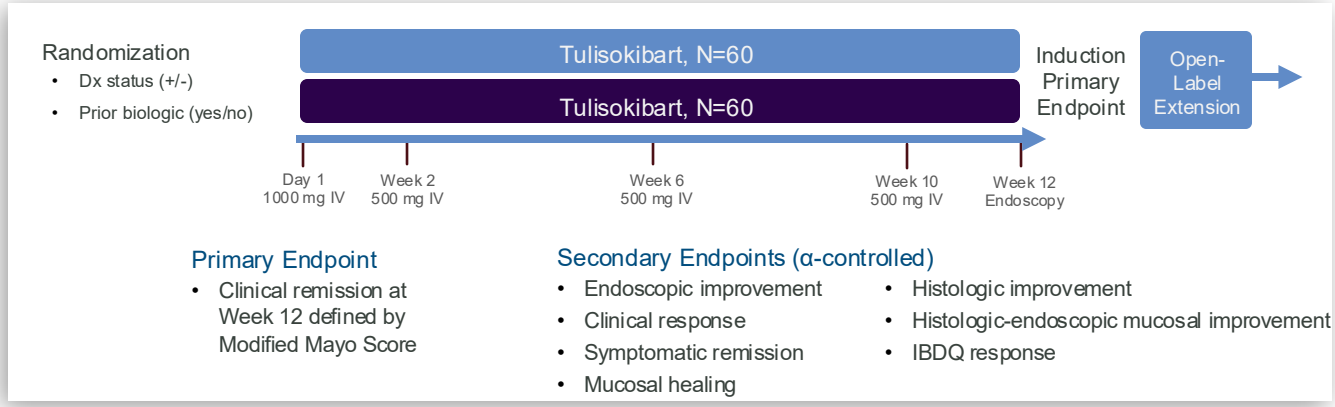
AIBD

ARTEMIS-UC: Phase 2 Study Design

Inclusion Criteria

- Moderately to severely active UC (modified Mayo Score 4-9)
- No/insufficient response, loss of response, and/or intolerance to conventional or advanced therapies
- Permitted prior medications
  - ≤4 approved advanced therapies (biologics and small molecule)
  - ≤3 classes of advanced therapies

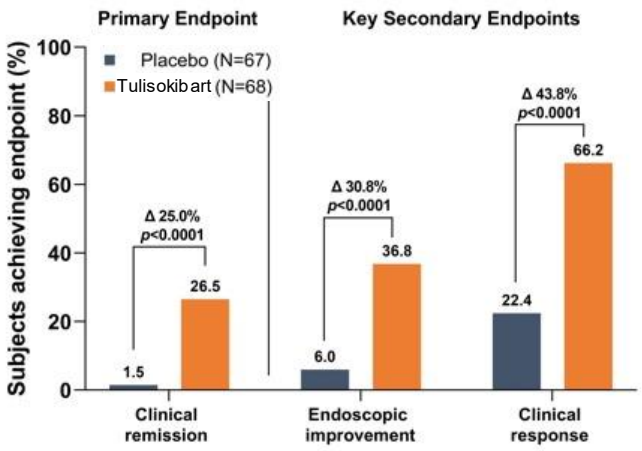
Demonstrate Efficacy of Tulisokibart

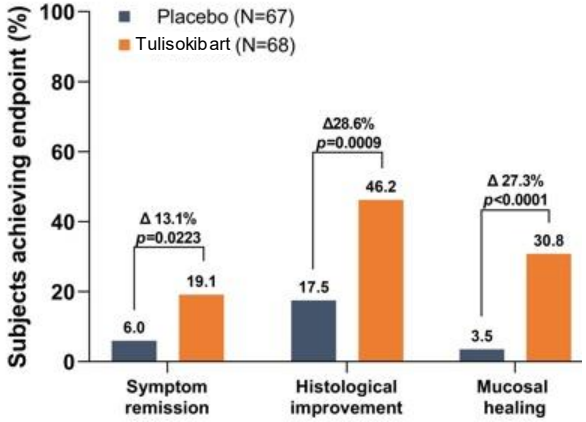


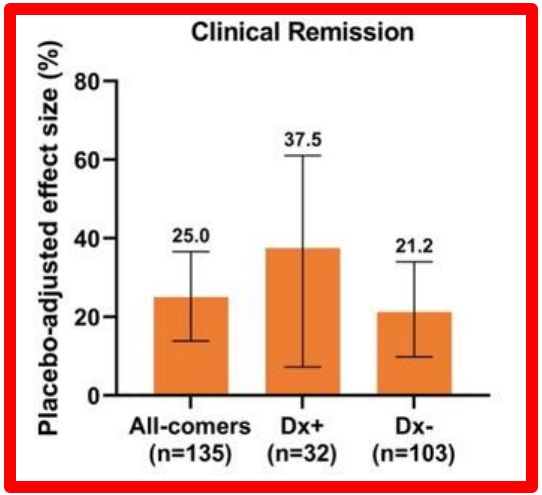
Dx = diagnostic test; DMC = data monitoring committee; IBDQ = Irritable Bowel Disease Questionnaire.

Sands BE, et al. *N Engl J Med*. 2024;391(12):1119-1129.

Tulisokibart (Anti-TL1A Antibody) for Moderate-Severe UC: ARTEMIS-UC Phase 2







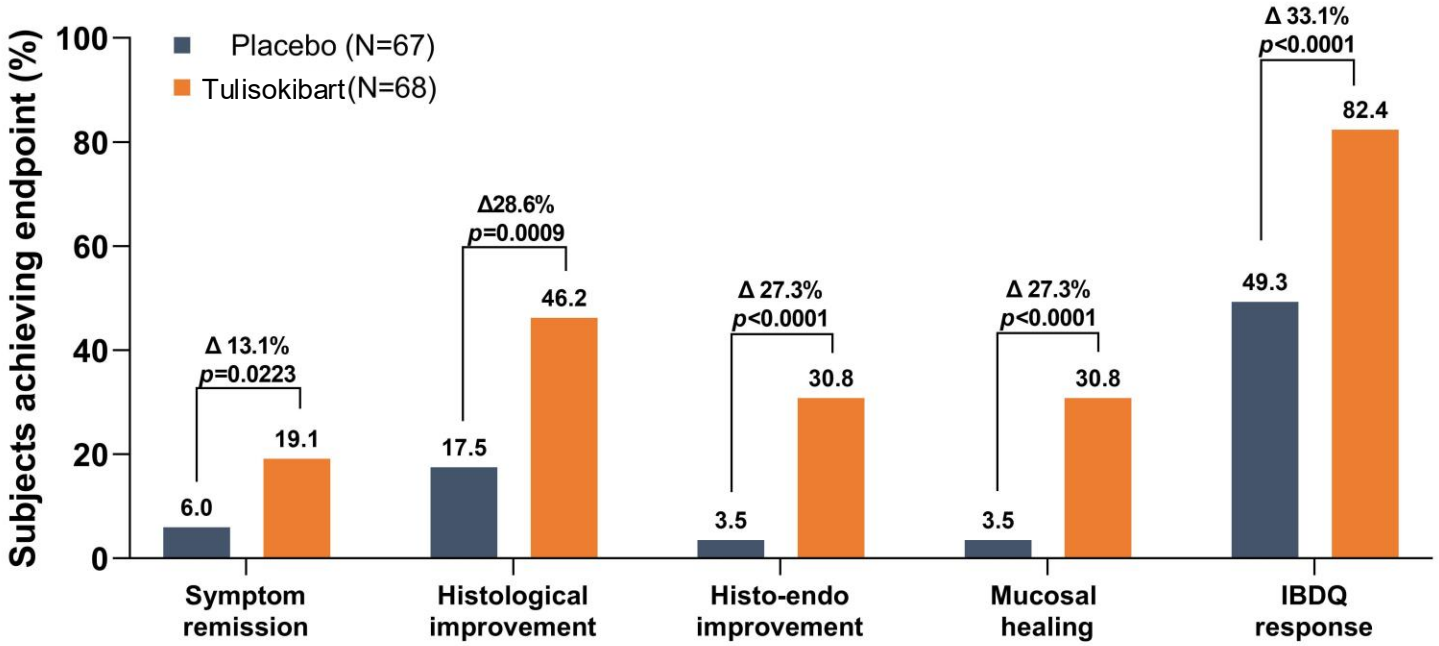
Conclusion

- Tulisokibart induction in UC was safe and improved clinical remission, endoscopic improvement, and mucosal healing
- Efficacy was consistent irrespective of prior advanced therapy use, concomitant IMM, or presence of ADA
- A positive genetically-based diagnostic test moderately increases likelihood of response

IMM = immunomodulator; ADA = adalimumab.

Sands BE, et al. *N Engl J Med*. 2024;391(12):1119-1129.

ARTEMIS-UC: Additional Secondary Endpoints

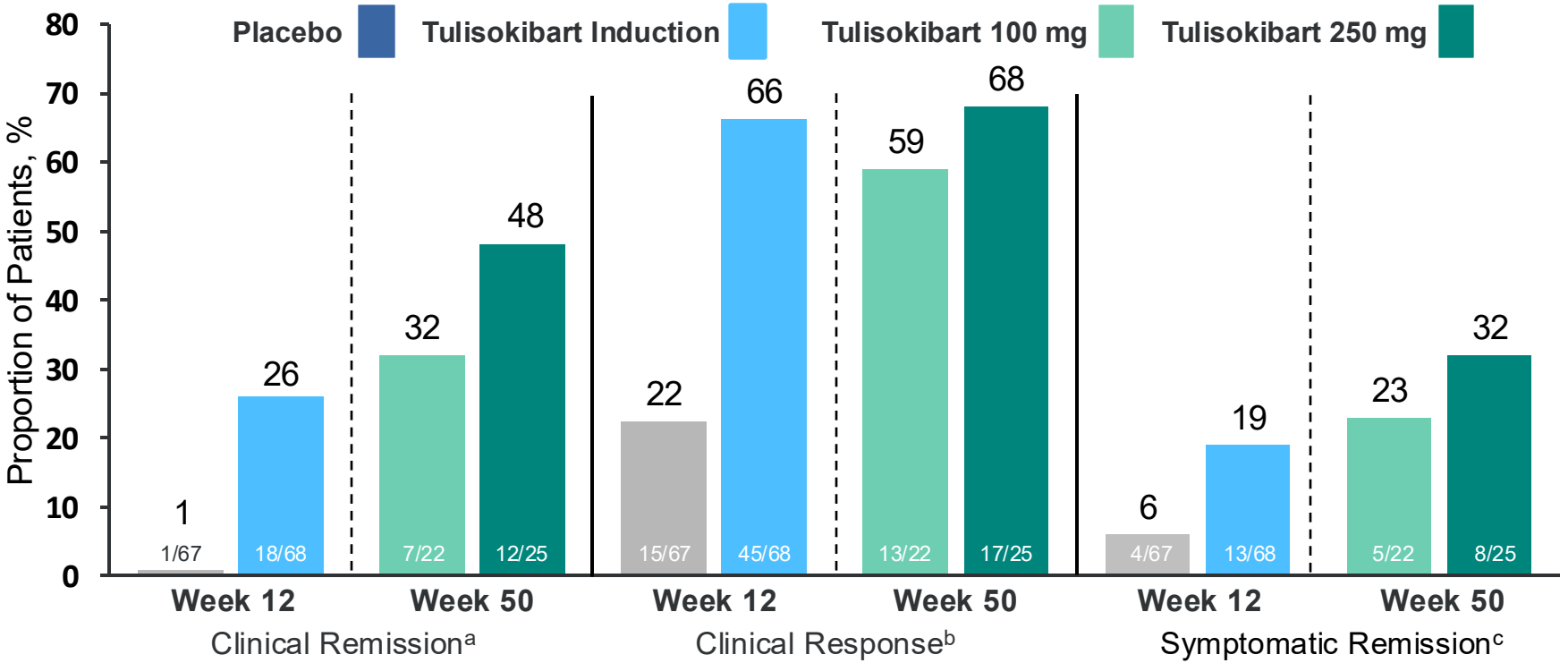


Symptomatic remission is defined as stool frequency subscore of 0 and rectal bleeding subscore of 0; Histologic improvement is defined as Geboes score ≤3.1; Histologic-endoscopic mucosal improvement is defined as Geboes score ≤3.1 and endoscopy subscore ≤1; Mucosal healing is defined as Geboes score ≤2B.1 and endoscopy subscore ≤1; IBD response is defined as IBD score increase of ≥16 points from Baseline. *P*-values for testing the treatment difference are based on Cochran-Mantel-Haenszel test adjusted for prior biologic exposure status and Dx status. All endpoints are statistically significant according to multiplicity-controlled 2-sided alpha of 0.05.

Sands BE, et al. *N Engl J Med*. 2024;391(12):1119-1129.

AIBD

At Week 50, Clinical Remission, Clinical Response, and Symptomatic Remission Rates Were Maintained, with Dose Response Observed



[a]Defined per mMS as endoscopic subscore of 0 or 1, RB subscore of 0, and SF subscore of 0 or 1 and not greater than baseline; [b]Defined per mMS as reduction from baseline ≥2 points and ≥30% in mMS, accompanied by a reduction ≥1 in RB subscore or absolute RB subscore ≤1; [c]Defined as rectal bleeding subscore of 0 and stool frequency subscore of 0. Analysis datasets include FAS for week 12 data in all participants who have been randomized and treated in cohort 1; MTAS for week 50 data in week 12 tulisokibart induction responders randomized and treated in the OLE. Week 12 and week 50 data were analyzed by non-responder imputation, where missing data are handled as non-responders. Data cutoff date: week 12, October 28, 2022; week 50, August 7, 2023.

FAS = full analysis set; mMS = 3-component Modified Mayo Score; MTAS = maintenance treatment analysis set; OLE = open-label extension; RB = rectal bleeding; SF = stool frequency.

Hoque S, et al. *Gut*. 2025;74(Suppl 1):A10-A11.

AIBD

ARTEMIS-UC: Tulisokibart Safety Summary

Treatment-Emergent Adverse Events, n (%)	Placebo N=67	Tulisokibart N=68
Subjects with any AE (n, %)	27 (40.3%)	28 (41.2%)
Subjects with any severe (Grade ≥3) AE	3 (4.5%)	0
Subjects with any drug-related AE	1 (1.5%)	3 (4.4%)†
Subjects with an AE leading to study drug discontinuation	3 (4.5%)	0
Subjects with any SAE	5 (7.5%)	0
Subjects with any drug-related SAE	0	0
Death	0	0
Subject with any AE of special interest	12 (17.9%)	10 (14.7%)
Acute infusion reaction*	0	0
Peri-infusion reaction^	1 (1.5)	0
Infection and infestation	11 (16.4%)	10 (14.7%)

***Acute infusion reaction: events as defined by the MedDRA hypersensitivity SMQ occurring within 1 hour of completion of infusion;**
^Peri-infusion reaction: events as defined by the MedDRA hypersensitivity SMQ occurring within 24 hour of completion of infusion;
†All mild to moderate AEs; all resolved as study drug continued.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious AE; SMQ = standardized MedDRA queries.
Sands BE, et al. *N Engl J Med*. 2024;391(12):1119-1129.

AIBD

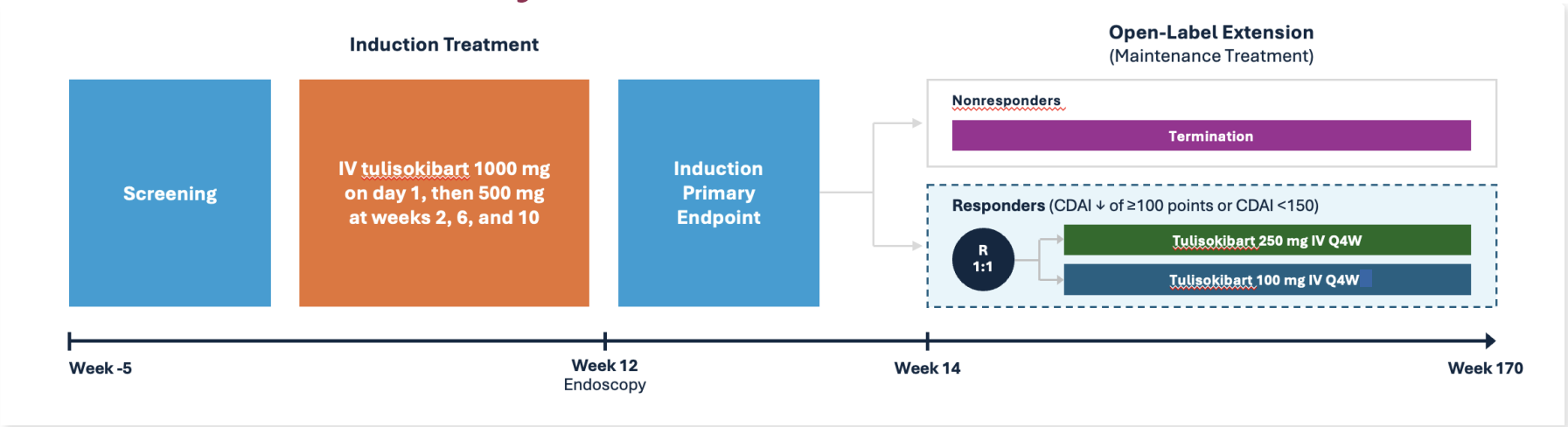
ARTEMIS-UC: Safety Summary during Induction and OLE

Event	Induction		OLE Tulisokibart	
	Placebo (N=88)	Tulisokibart (N=90)	100 mg (N=30)	250 mg (N=35)
AE, n (%)	38 (43)	41 (46)	23 (77)	22 (63)
• Treatment-related AE	1 (1)	4 (4)	3 (10)	4 (11)
• Serious AE	7 (8)	1 (1)	2 (7)	1 (3)
• Treatment-related serious AE	0	1 (1)	0	0
• AE leading to discontinuation	3 (3)	1 (1)	2 (7)	1 (3)
AE of special interest, n (%)				
• Acute infusion reaction	0	0	0	0
• Per-infusion reaction	1 (1)	0	0	0
• Infection and/or infestation	16 (18)	16 (18)	11 (37)	16 (46)
AEs occurring in ≥5% of patients in either group			NR	NR
• UC	9 (10)	1 (1)		
• COVID-19	4 (5)	5 (6)		

Sands BE, et al. *N Engl J Med*. 2024;391(12):1119-1129. Ma C, et al. Presented at: UEGW; October 12-15, 2024; Vienna, Austria. OP194.

AIBD

APOLLO-CD: Tulisokibart Phase 2a Study of Tulisokibart in CD



Key Inclusion Criteria

- Moderately to severely active CD (CDAI ≥220 and ≤450)
- Endoscopically active disease (SES-CD ≥6 [≥4 isolated ileal disease])
- History of insufficient response, loss of response, and/or intolerance to conventional and/or advanced therapies

Primary Efficacy Endpoint

- Endoscopic response at week 12

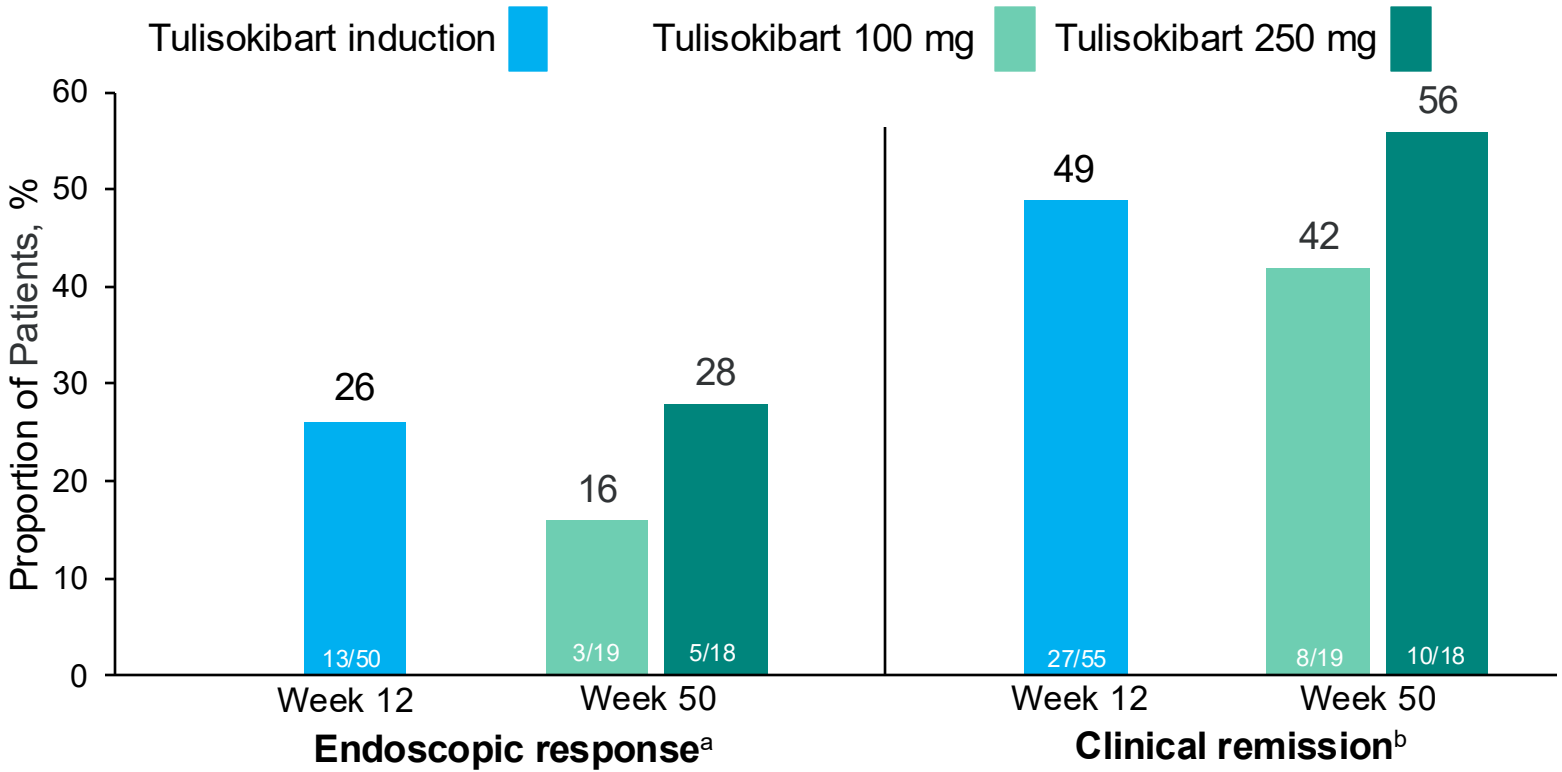
Selected Endpoints Evaluated at Week 50

- Endoscopic response
- Clinical remission, including CS-free clinical remission
- Clinical response
- Endoscopic and clinical response and/or clinical remission
- Biomarker (hsCRP, FC) and clinical response and/or clinical remission
- PRO-2 remission
- Normalization of hsCRP or FC among patients with elevated levels at baseline

AIBD

Siegel CA, et al. Presented at: UEGW; October 12-15, 2024; Vienna, Austria. OP078.

APOLLO-CD: Tulisokibart in CD – Endoscopic Response and Clinical Remission Rates Were Similar in 12-Week Responders at Week 50

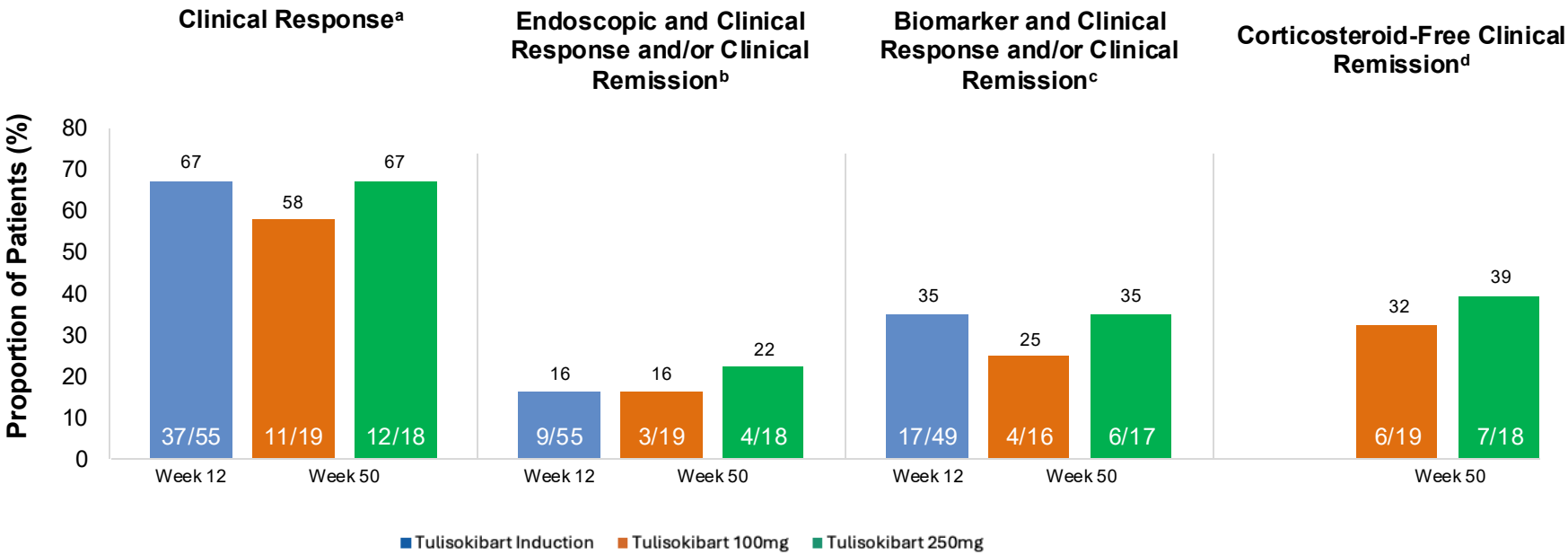


[a]Reduction of SES-CD by ≥50% from baseline. Endpoint assessed using per-protocol analysis set (all patients) at week 12 and the intention-to-treat analysis set at week 50 (12-week responders); [b]CDAI <150. Endpoint assessed using the full analysis set at week 12 (all patients) and the intention-to-treat analysis set at week 50 (12-week responders). Data cutoff date: week 12, October 6, 2022; week 50, June 28, 2023.

SES = Simple Endoscopic Score.

Siegel CA, et al. Presented at: Digestive Disease Week (DDW); May 3-6, 2025; San Diego, CA & virtual. Tu1883.

APOLLO-CD: Key Secondary Efficacy Outcomes with Tulisokibart at Week 50



[a]Decrease in CDAI of ≥100 points from baseline or CDAI <150; [b]Reduction of SES-CD by ≥50% from baseline and a decrease in CDAI of ≥100 points from baseline and/or CDAI <150; [c]Among patients with elevated hsCRP or FC levels at baseline, decrease in hsCRP or FC≥50% from baseline and a decrease in CDAI of ≥100 points from baseline and/or CDAI <150; [d]CDAI <150 and no concomitant use of corticosteroid within 12 weeks before week 50.

Siegel CA, et al. Presented at: DDW; May 3-6, 2025; San Diego, CA & virtual. Tu1883.

AIBD

APOLLO-CD: Safety Summary during Induction and OLE

Event	Induction	OLE Tulisokibart	
	Tulisokibart (N=55)	100 mg (N=19)	250 mg (N=18)
AE, n (%)	43 (78)	16 (84)	15 (83)
• Treatment-related AE	3 (5)	3 (16)	0
• Serious AE	8 (15)	2 (11)	1 (6)
• Treatment-related serious AE	0	0	0
• AE leading to discontinuation	2 (4)	4 (21)	2 (11)
AE of special interest, n (%)			
• Acute infusion reaction	0	0	0
• Per-infusion reaction	0	0	0
• Infection	25 (45)	12 (63)	11 (61)
Most frequent infections			
• UTI	NR	16%	11%
• COVID-19		11%	11%
• URTI		16%	6%

UTI = urinary tract infection; URTI = upper respiratory tract infection; NR = not reported.

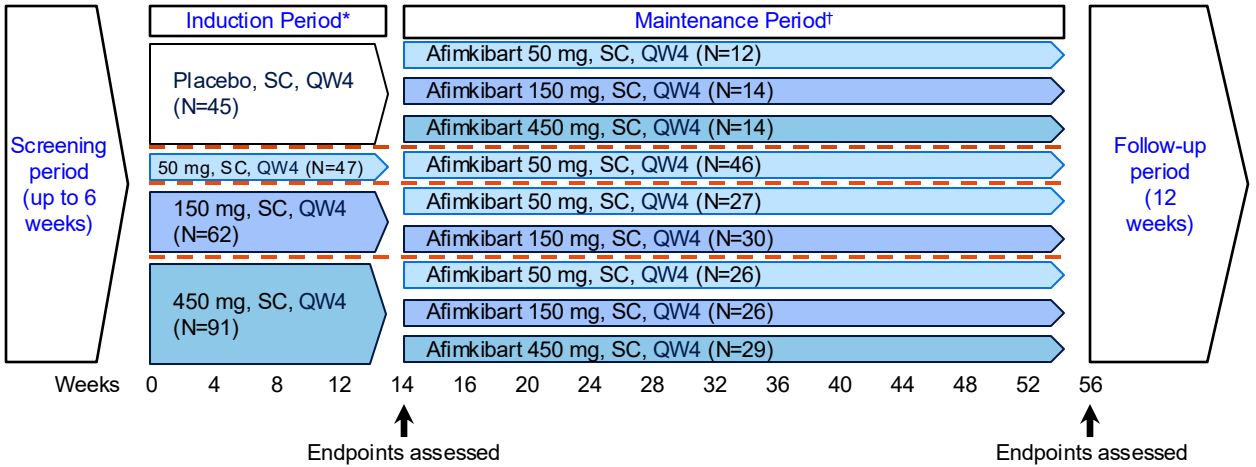
Siegel CA, et al. Presented at: DDW; May 3-6, 2025; San Diego, CA & virtual. Tu1883.

AIBD

TUSCANY-2: A Randomized, Double-Blind, Placebo-Controlled, Treat-Through, Dose-Ranging, Phase 2b Study

Key eligibility criteria

- Patients aged 18-75 years, with moderately to severely active UC (tMS ≥6, endoscopic subscore ≥2)
- Previously failed conventional or advanced therapy



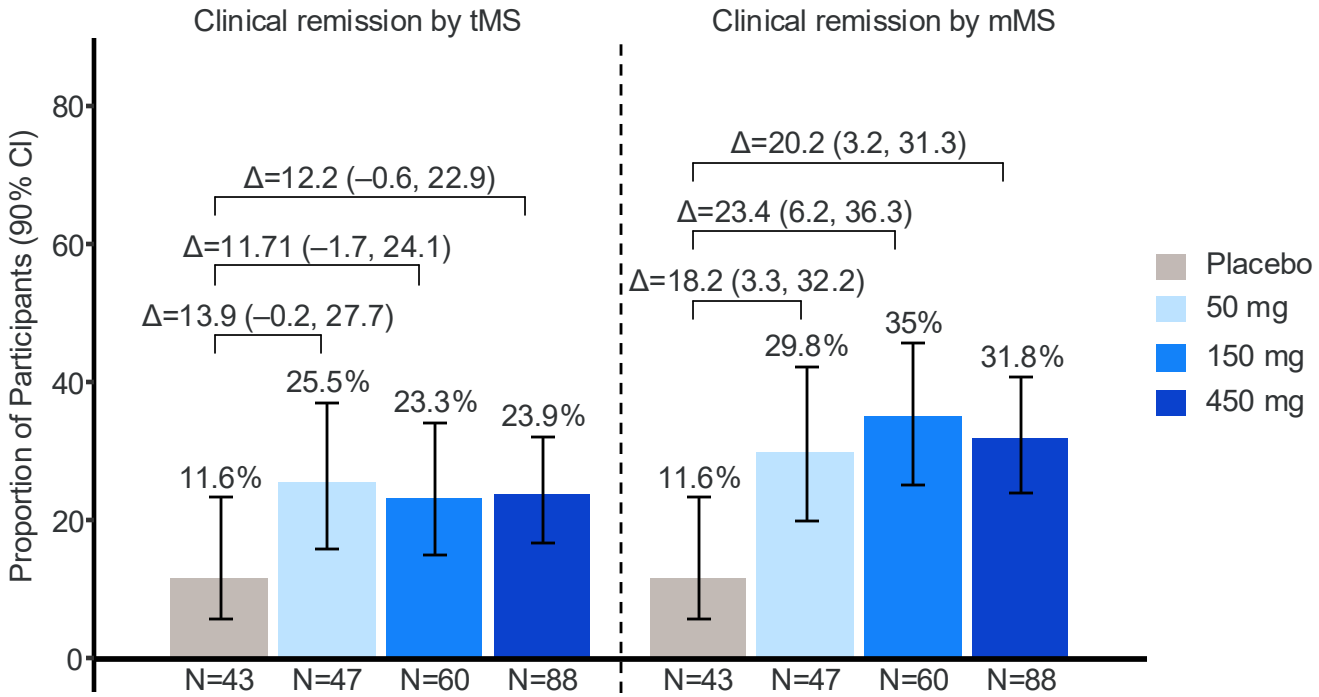
Primary endpoint	Secondary endpoints	Exploratory endpoint
• Clinical remission by tMS at week 14 • Safety	• Clinical remission by Modified Mayo Score (mMS) at week 14 • Clinical remission by tMS, mMS at week 56 • Endoscopic improvement at weeks 14 and 56	• Efficacy by pre-specified biomarker status

Clinical remission by tMS: tMS ≤2, with no individual subscore >1
Clinical remission by mMS: endoscopic subscore = 0 or 1, ≥1-point decrease from baseline to achieve a stool frequency subscore = 0 or 1, and rectal bleeding subscore = 0
Endoscopic improvement: endoscopic subscore = 0 or 1

***N=245 received at least one induction dose; †N=224 received at least one maintenance dose.**
Clinical trial identification: NCT04090411.
tMS = Total Mayo Score.
Danese S, et al. *Lancet Gastroenterol Hepatol*. 2025;10(10):882-895.

AIBD

TUSCANY-2: Clinical Remission with Afimkibart vs Placebo at Week 14

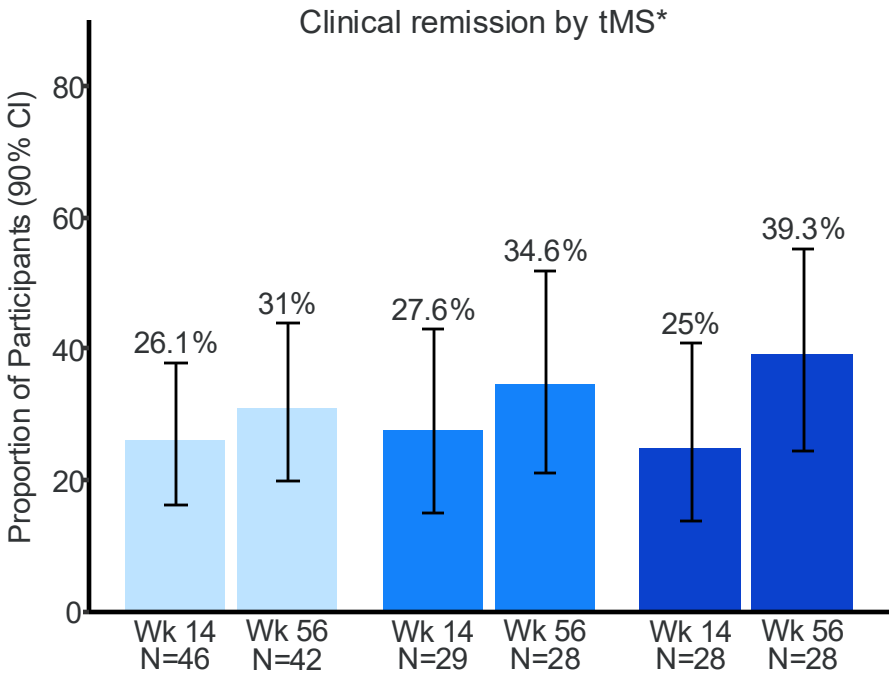


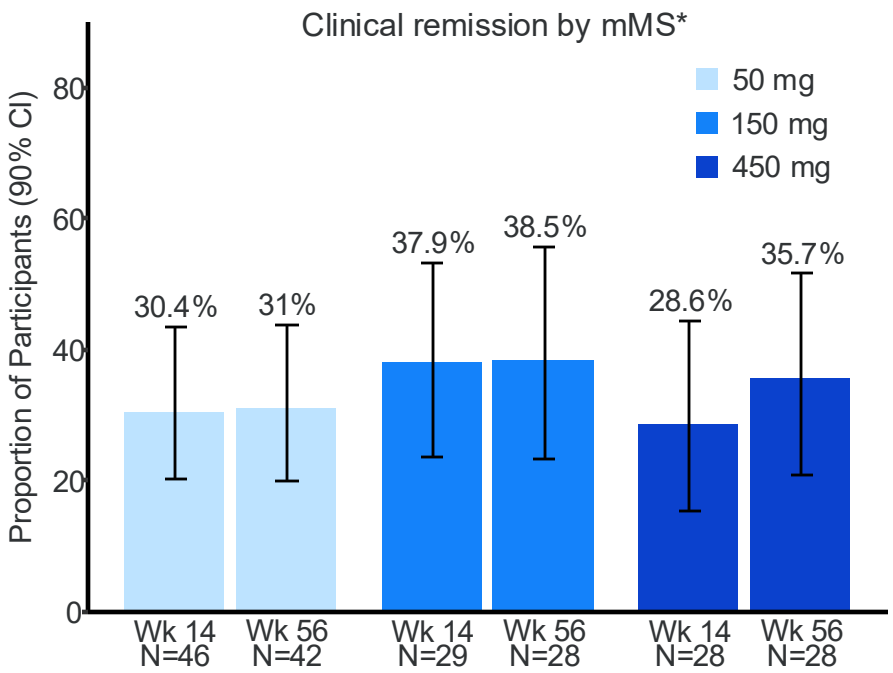
Clinical remission by tMS defined as tMS ≤2, with no individual subscore >1. Excluding 7 participants with missing data due to medical or operational complications resulting from COVID-19. Clinical remission by mMS defined as endoscopic subscore = 0 or 1, ≥1-point decrease from baseline achieve a stool frequency subscore = 0 or 1, and rectal bleeding subscore = 0.

CI = confidence interval.

Danese S, et al. *Lancet Gastroenterol Hepatol*. 2025;10(10):882-895.

TUSCANY-2: Remission Rates at Week 14 Were Sustained through Week 56 in Participants Treated with Afimkibart





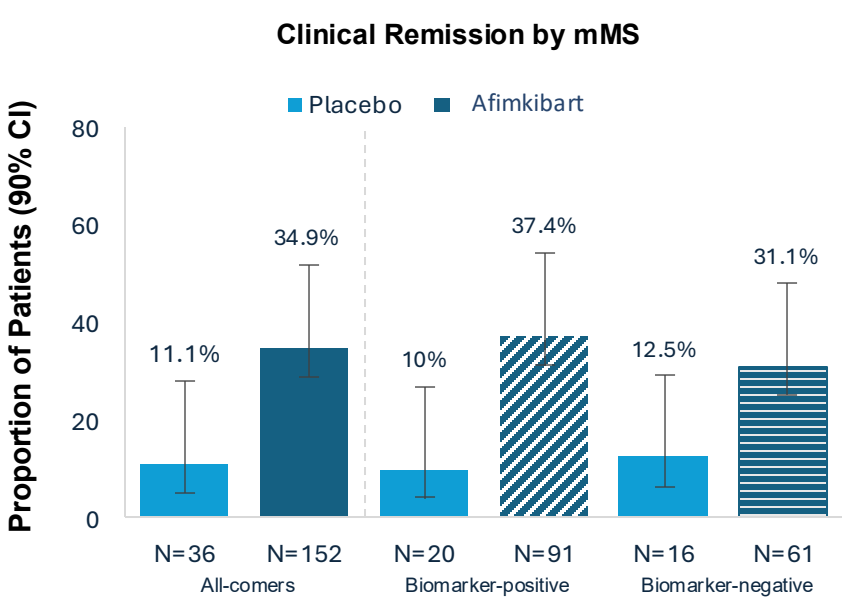
***Data shown for participants receiving the same afimkibart dose during both the induction and maintenance period of the study (50 mg → 50 mg; 150 mg → 150 mg; 450 mg → 450 mg).**

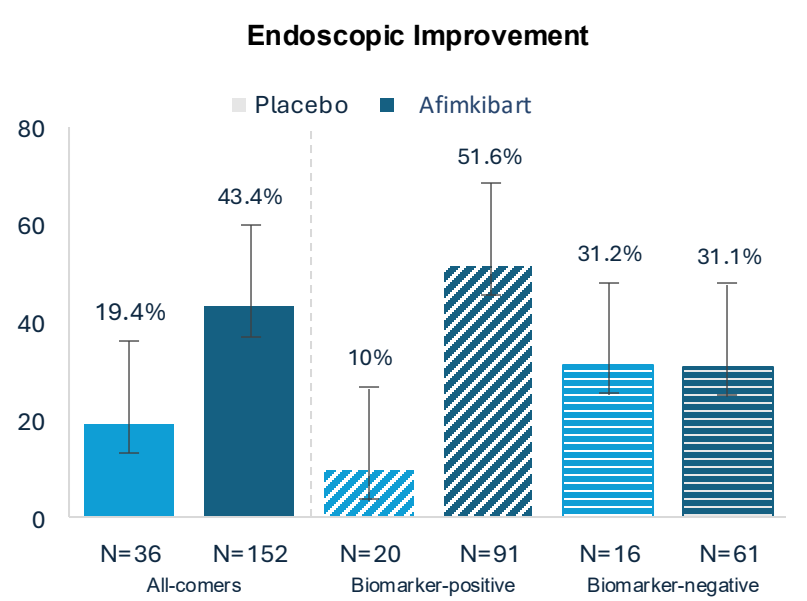
Clinical remission by tMS defined as tMS ≤2, with no individual subscore >1. Excluding participants with missing data due to medical or operational complications resulting from COVID-19. Clinical remission by mMS defined as endoscopic subscore = 0 or 1, ≥1-point decrease from baseline achieve a stool frequency subscore = 0 or 1, and rectal bleeding subscore = 0. The maintenance period of the study did not include a placebo arm.

Danese S, et al. *Lancet Gastroenterol Hepatol*. 2025;10(10):882-895.

AIBD

TUSCANY-2: Numerically Greater Treatment Effects Were Observed in Biomarker-Positive Participants Relative to All-Comers





Clinical remission by mMS defined as endoscopic subscore = 0 or 1, ≥1-point decrease from baseline achieve a stool frequency subscore = 0 or 1, and rectal bleeding subscore = 0.

Danese S, et al. *Lancet Gastroenterol Hepatol*. 2025;10(10):882-895.

TUSCANY-2: Safety Results

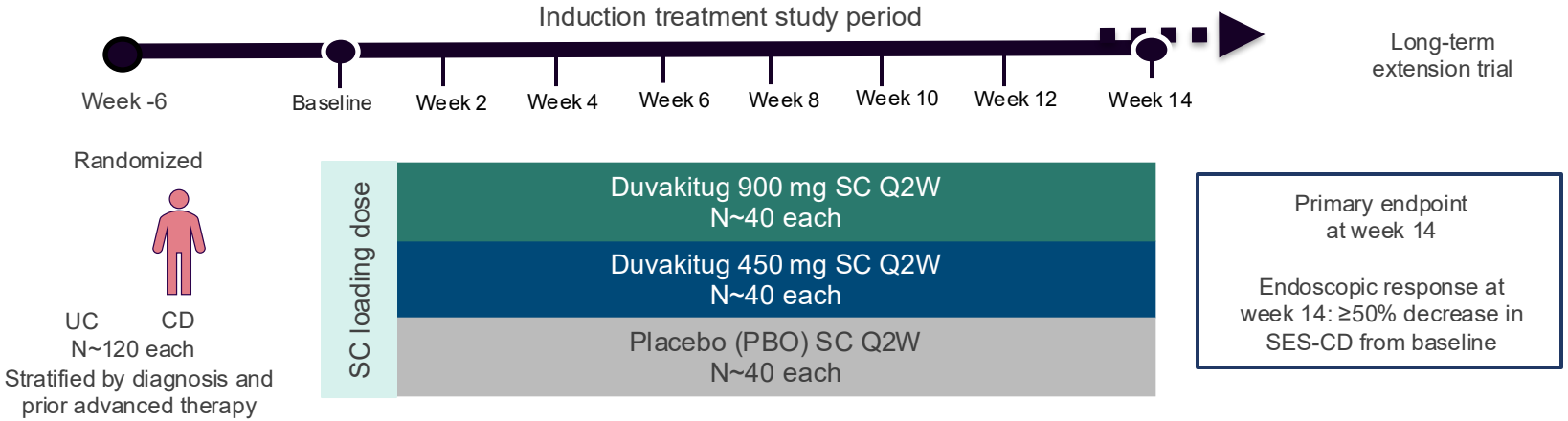
Induction				
Event, n (%)	**Placebo (N=45)**	**50 mg (N=47)**	**150 mg (N=62)**	**450 mg (N=91)**
Any AE	25 (56)	16 (34)	28 (45)	48 (53)
• Serious AE	4 (9)	3 (6)	0	3 (3)
• AE leading to discontinuation	3 (7)	1 (2)	1 (2)	1 (1)
• Treatment-related AE	4 (9)	6 (13)	9 (15)	13 (14)
• Treatment-related serious AE	1 (2)	0	0	1 (1)

Maintenance			
Event, n (%)	**50 mg (N=46)**	**150 mg (N=30)**	**450 mg (N=29)**
Any AE	28 (61)	15 (50)	19 (66)
• Serious AE	4 (9)	0	4 (14)
• AE leading to discontinuation	3 (7)	0	1 (3)
• Treatment-related AE	5 (11)	2 (7)	6 (3)
• Treatment-related serious AE	0	0	1 (3)

AIBD

Danese S, et al. *Lancet Gastroenterol Hepatol*. 2025;10(10):882-895.

RELIEVE UCCD: Induction Basket Trial



Study population

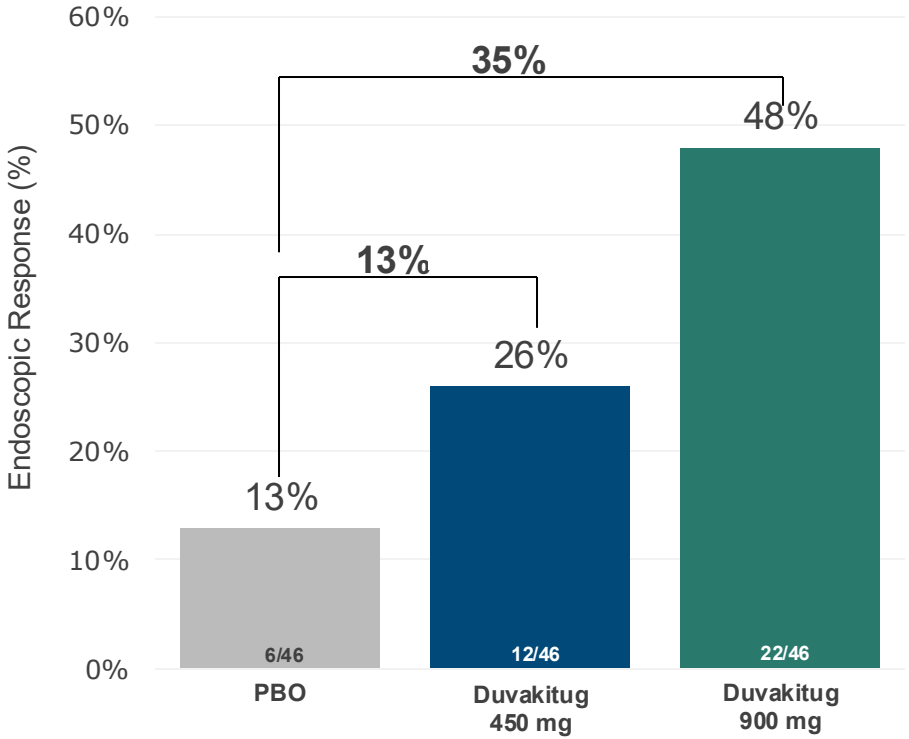
- Adults (18-75 years) with moderately to severely active CD (CDAI score ≥220 and ≤450); SES-CD score of ≥6 (≥4 for isolated ileal disease)
- Previous experience with conventional and/or advanced therapies (AT) permitted, irrespective of the number of advanced therapies within the same class
- Concomitant medications allowed
  - Stable doses of corticosteroids (prednisone equivalent of up to 20 mg/day), 5-ASA, and immunosuppressants (6-MP, AZA, MTX)

5-ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine; AZA = azathioprine; MTX = methotrexate.

Jairath V, et al. Presented at: European Crohn's and Colitis Organisation (ECCO) Congress; February 19-22, 2025; Berlin, Germany.

AIBD

RELIEVE UCCD: Duvakitug Primary Endpoint for CD – Endoscopic Response at Week 14



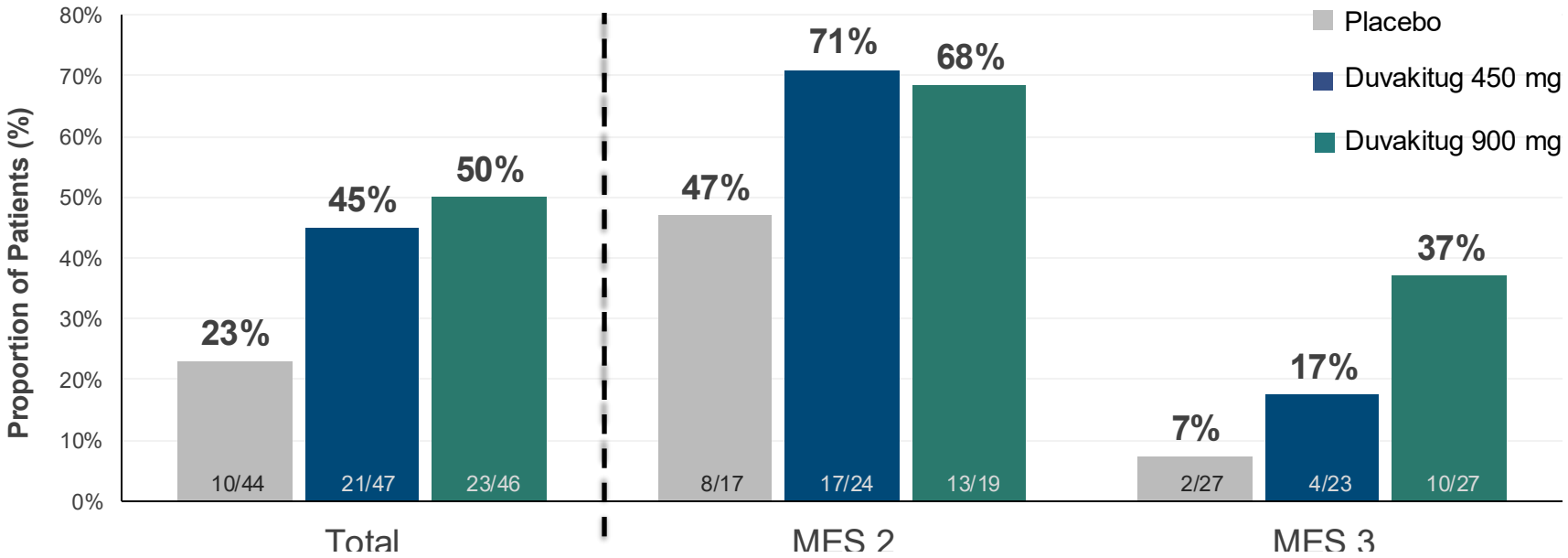
	Duvakitug 450 mg vs PBO	Duvakitug 900 mg vs PBO
Posterior probability	0.94	>0.99
Odds ratio	3.0 *P*=0.031	6.4 *P*<0.001

Jairath V, et al. Presented at: ECCO Congress; February 19-22, 2025; Berlin, Germany.

AIBD

RELIEVE UCCD: Duvakitug for UC – Endoscopic Improvement at Week 14 in Patients with Baseline MES 2 or MES 3

Greater rates of endoscopic improvement were observed for both doses of duvakitug vs placebo, regardless of baseline disease severity



Endoscopic improvement was defined as MES of 0 or 1 (where a score of 1 does not include "friability").
MES = Mayo Endoscopic Subscore.
Reinisch W, et al. Presented at: ECCO Congress; February 19-22, 2025; Berlin, Germany. OP40.

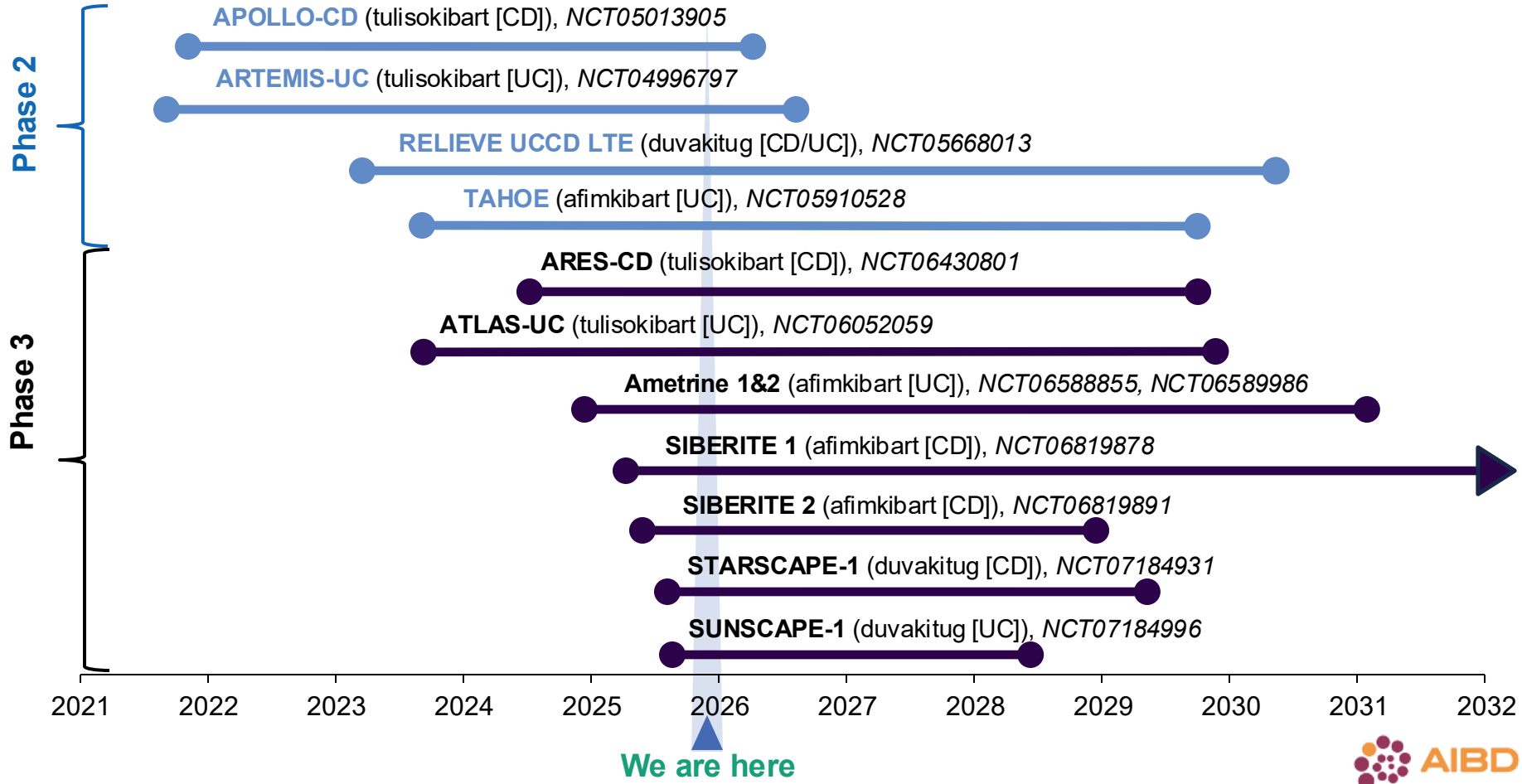
RELIEVE UCCD: Phase 2b Safety Results

Event	UC Cohort			CD Cohort		
	Placebo (N=44)	Duvakitug 450 mg (N=47)	Duvakitug 900 mg (N=46)	Placebo (N=46)	Duvakitug 450 mg (N=46)	Duvakitug 900 mg (N=46)
AE, n (%)	23 (52)	23 (49)	20 (43)	22 (48)	31 (67)	20 (43)
• Treatment-related AE	2 (5)	3 (6)	6 (13)	2 (4)	6 (13)	6 (13)
• Serious AE	1 (2)	0	1 (2)	5 (11)	6 (13)	1 (2)
• AE leading to discontinuation	2 (5)	0	1 (2)	1 (2)	4 (9)	1 (2)
AEs occurring in ≥2 participants in any arm						
• Anemia	3 (7)	1 (2)	1 (2)	1 (2)	3 (7)	0
• Headache	NR	NR	NR	4 (9)	4 (9)	1 (2)
• Nasopharyngitis	1 (2)	3 (6)	0	3 (7)	2 (4)	3 (7)
• URTI	1 (2)	3 (6)	1 (2)	NR	NR	NR
• Vomiting	0	3 (6)	0	NR	NR	NR

Reinisch W, et al. Presented at: ECCO Congress; February 19-22, 2025; Berlin, Germany. OP40.
Jairath V, et al. Presented at: ECCO Congress; February 19-22, 2025; Berlin, Germany. OP41.

AIBD

Ongoing Clinical Trials of TL1A Inhibitors in IBD



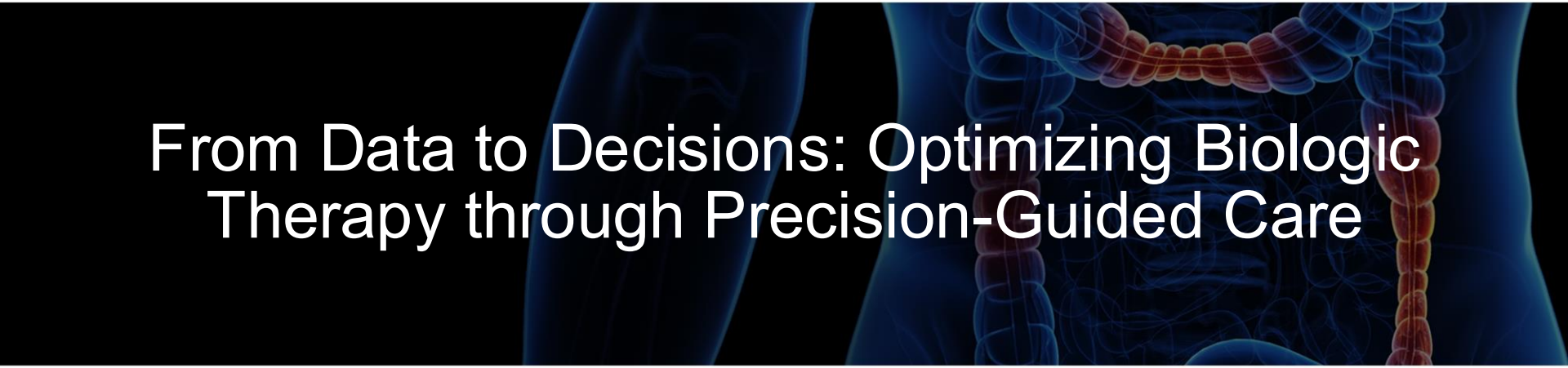
ClinicalTrials.gov. Accessed December 1, 2025. https://clinicaltrials.gov.

Conclusions

- TL1A emerging target for both forms of IBD
- Next steps: regulatory approval for different monoclonals
- Long-term safety?...new MOA
- Fibrosis?
- Single therapy?

MOA = mechanism of action.

AIBD



From Data to Decisions: Optimizing Biologic Therapy through Precision-Guided Care

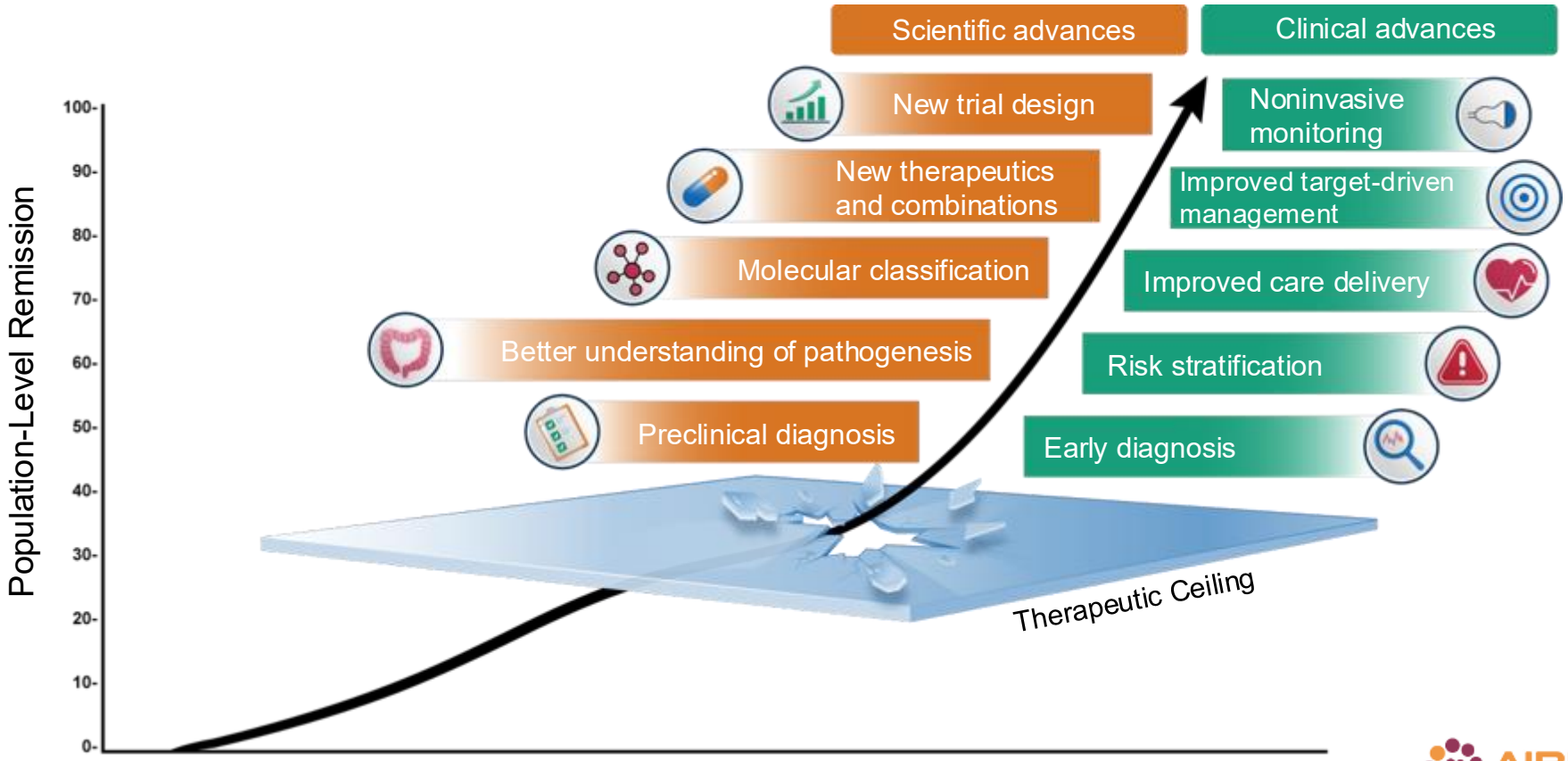
Jessica R. Allegretti, MD, MPH

Medical Director, Infusion Services
Director, Crohn's and Colitis Center
Director of Clinical Research
Director, Fecal Microbiota Transplant Program
Division of Gastroenterology, Hepatology, and Endoscopy
Brigham and Women's Hospital
Associate Professor of Medicine, Harvard Medical School

Disclosures

- **Jessica R. Allegretti, MD, MPH:** Consultant – AbbVie, Bristol Myers Squibb, Celltrion, Ferring, Genentech, GSK, Janssen, Merck, Pfizer, Roivant, Seres Therapeutics, Shattuck Labs, TRXBio, Vedanta, Xencor; Speaker's Bureau – AbbVie, Janssen

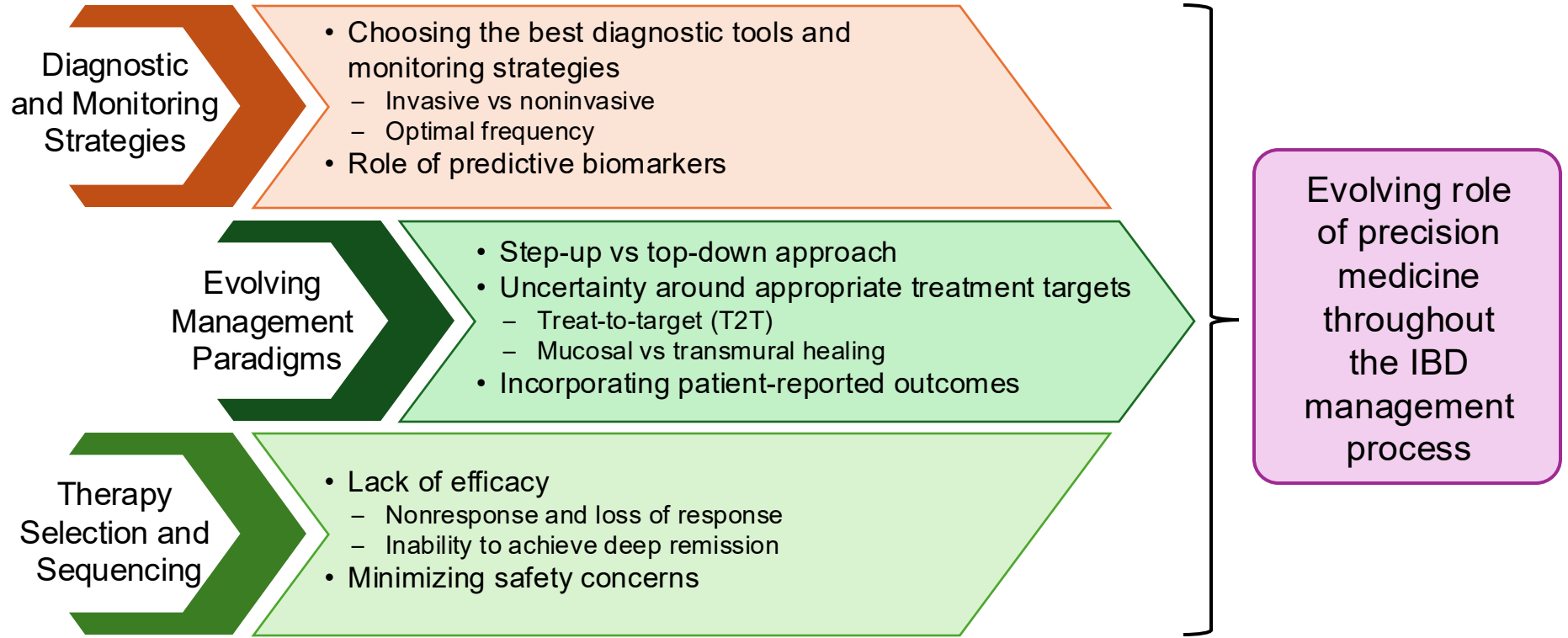
Where Do We Stand in IBD Care?



Raine T, Danese S. *Gastroenterology*. 2022;162(5):1507-1511.

AIBD

Unmet Needs in IBD Management

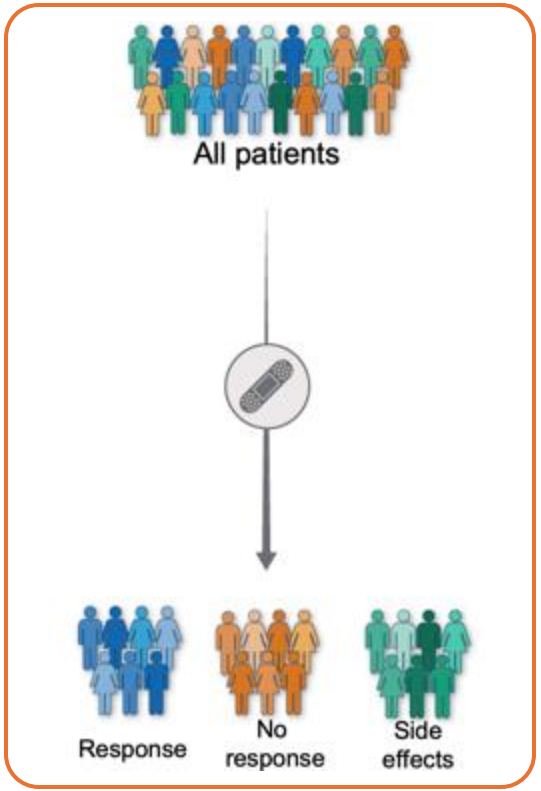


AIBD

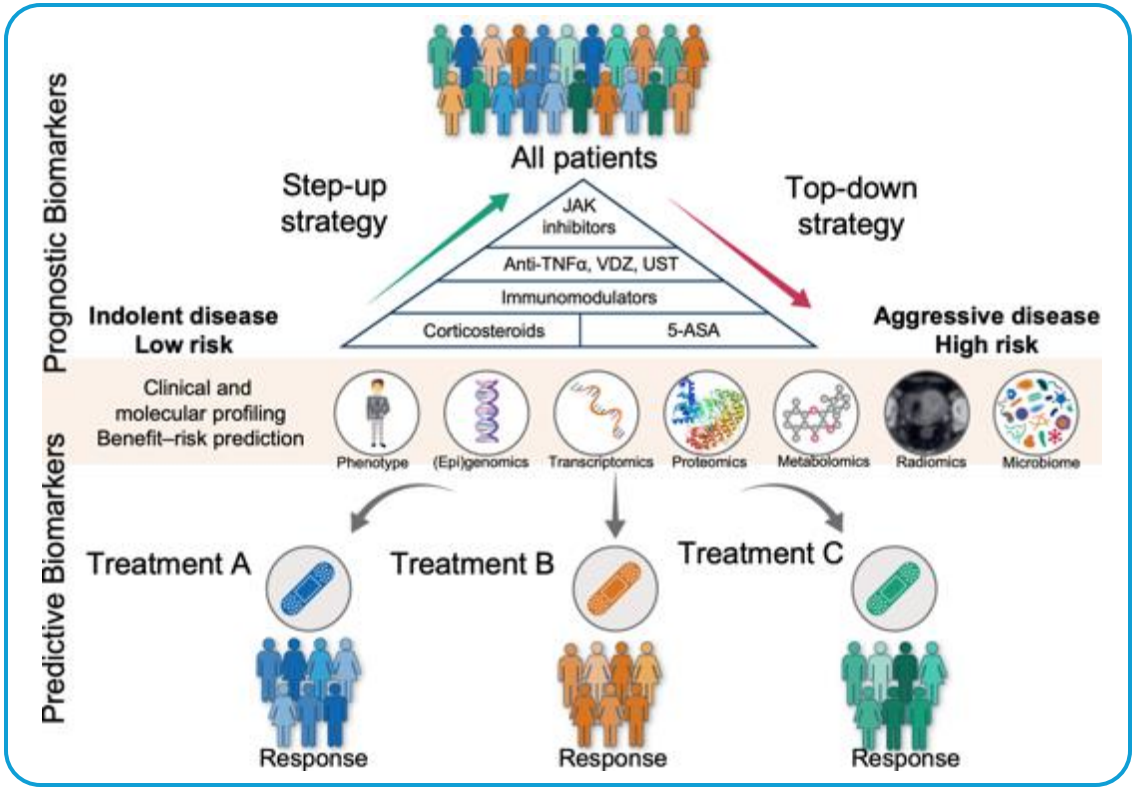
Danese S, et al. *Dig Dis*. 2019;37(4):266-283.

Past, Present, and Future Paradigms of Precision Medicine in IBD

Conventional Modern Medicine

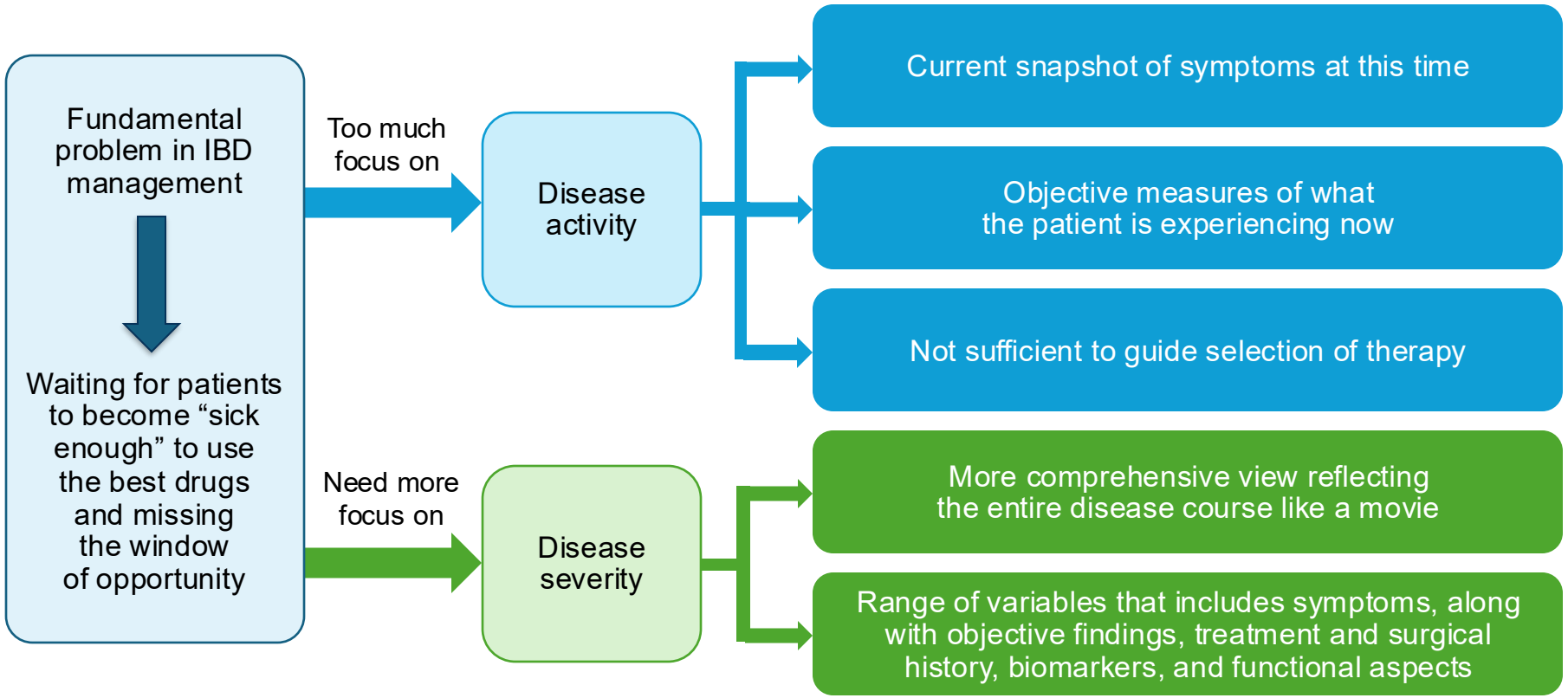


Future Precision Medicine



Vieujean S, Louis E. *Therap Adv Gastroenterol*. 2023;16:17562848231173331.

Getting the Full Picture: Comprehensive Assessment of IBD



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Peyrin-Biroulet L, et al. *Clin Gastroenterol Hepatol*. 2016;14(3):348-354.e17.

Clinical Trial Assessment Tools for IBD

CDAI (CD)

Composite of 8 Variables

- Stool frequency
- Abdominal pain
- General well-being
- Extraintestinal symptoms
- Use of anti-diarrheals
- Abdominal mass
- Hematocrit
- Body weight

Scoring

- <150: remission
- 150-219: mild
- 220-450: moderate to severe
- >450: severe

Mayo Score (UC)

Composite of 4 Variables

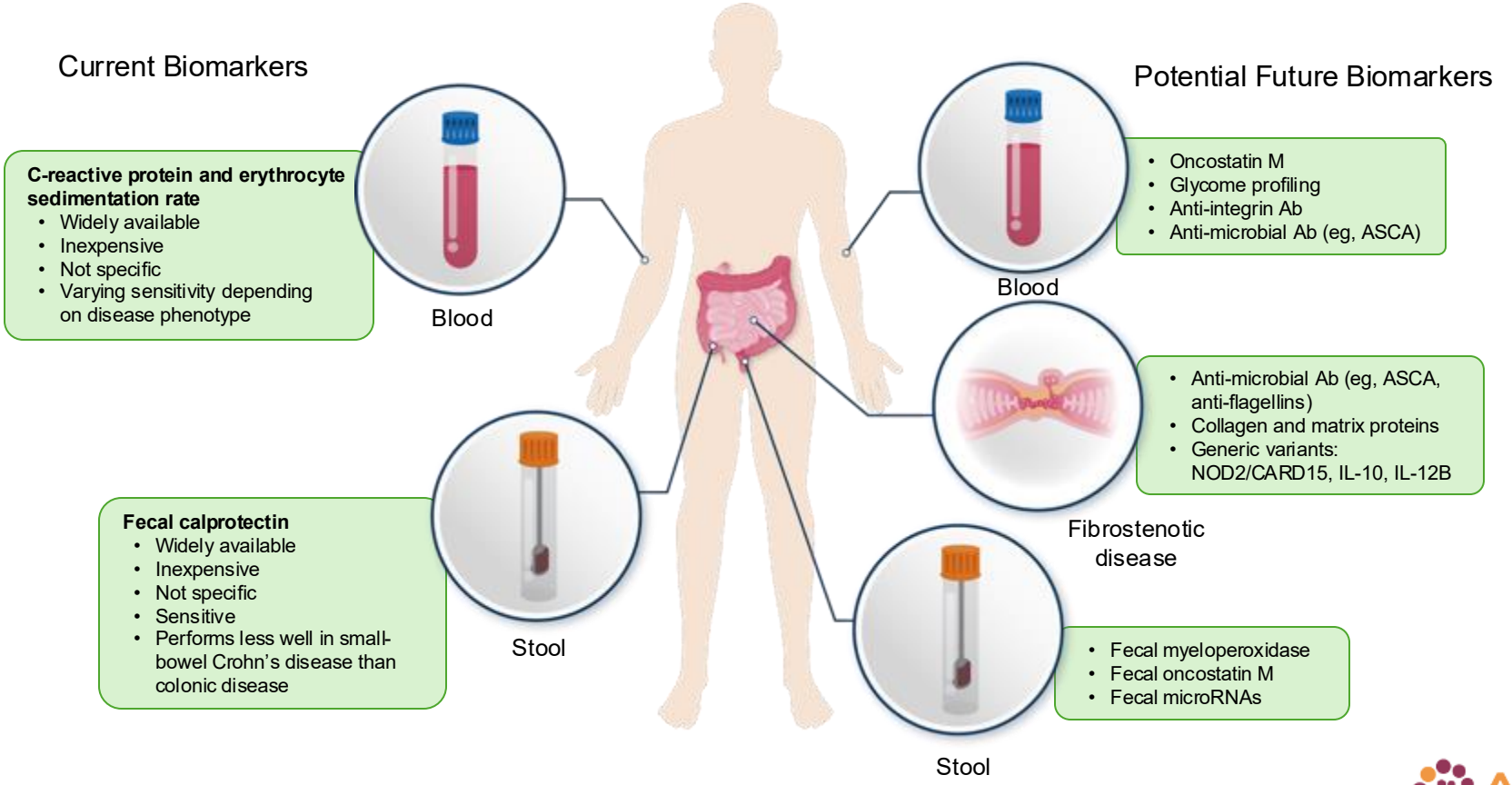
- Stool frequency
- Rectal bleeding
- Endoscopic findings
- Physician's global assessment

Scoring

- ≤2: remission
- 3-5: mild
- 6-10: moderate
- 11-12: severe

Lichtenstein GR, et al. *Am J Gastroenterol*. 2025;120(6):1225-1264. Rubin DT, et al. *Am J Gastroenterol*. 2025;120(6):1187-1224.

Clinical Indices and Biomarkers in IBD Assessment and Diagnosis



Clough J, et al. *Therap Adv Gastroenterol*. 2024;17:17562848241251600.

The Importance of Treating beyond Symptoms

- Goal of IBD treatment is to induce and maintain remission
- Historically, therapeutic decision-making was driven by the presence or absence of clinical symptoms

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Achieving this goal is not enough

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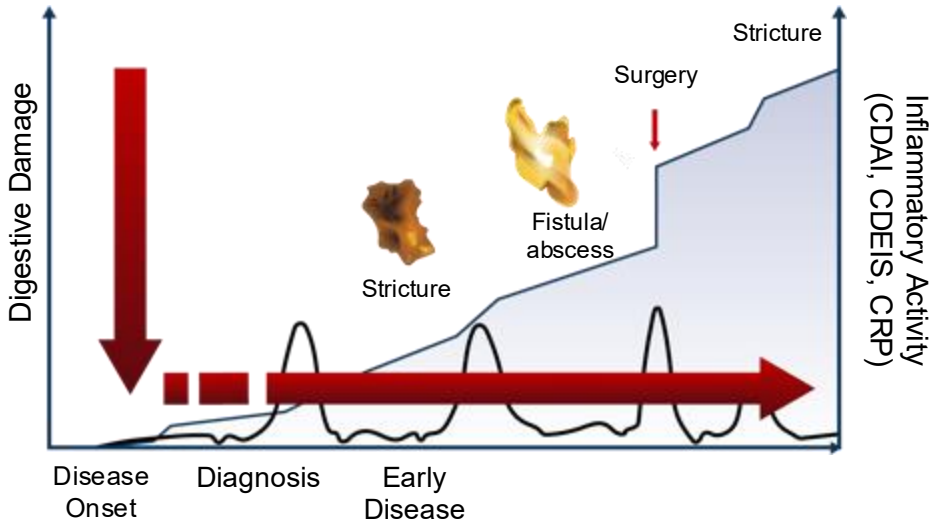
In the absence of timely and effective treatment, progressive and accumulative intestinal injury can lead to complications such as strictures, fistulae, loss of bowel function, surgery, cancer, resultant disability

Blocking Disease Progression and Damage to Improve Outcomes



Pariente B, et al. *Inflamm Bowel Dis*. 2011;17(6):1415-1422.

What Is T2T?

- Medical management strategy in IBD focused on deep remission: symptom control + objective markers (eg, CRP, fecal calprotectin)
- Target measurable outcome of mucosal healing in CD
- Continuous assessment and adjustment of therapy

Colombel JF, et al. *J Crohns Colitis*. 2020;14(2):254-266.

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Why Is T2T Important?

- Reduction of long-term disease complications
- Improvement in QoL
- Lower hospitalization and surgery rates
- Improved remission rates in IBD vs conventional therapy
- Aligns treatment goals with patient preferences and outcomes

QoL = quality of life.

Colombel JF, et al. *Gastroenterology*. 2017;152(2):351-361.e5.

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How Does T2T Work?

Initial assessment: establish baseline disease activity through clinical, endoscopic, and biomarker evaluations

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Define target: mucosal healing, normalized biomarkers, absence of symptoms

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Monitor regularly: schedule routine assessments (endoscopy, imaging, lab markers)

↓

Adjust therapy: escalate or modify treatment if target is not met

Peyrin-Biroulet L, et al. *Am J Gastroenterol*. 2015;110(9):1324-1338. Bouguen G, et al. *Clin Gastroenterol Hepatol*. 2015;13(6):1042-1050.e2. Agrawal M, Colombel JF. *Gastrointest Endosc Clin N Am*. 2019;29(3):421-436.

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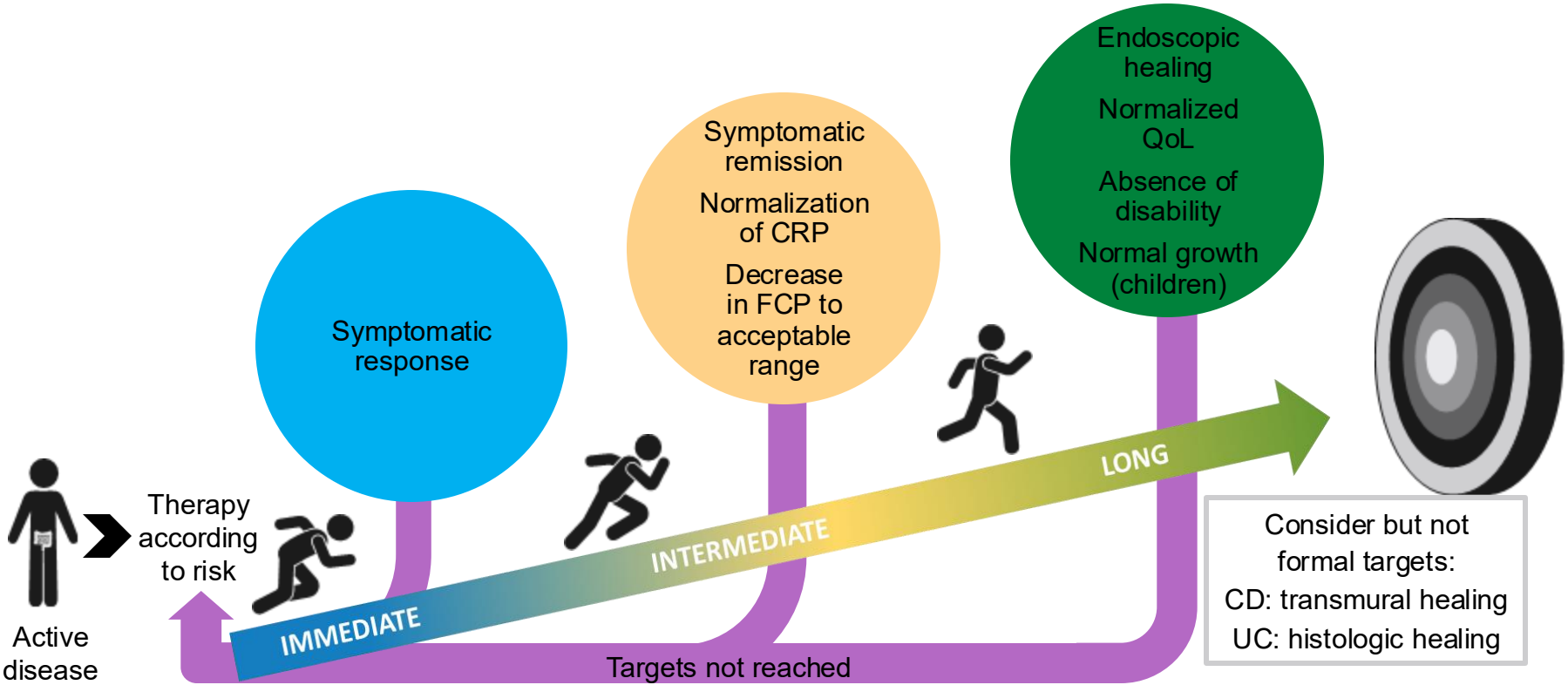
STRIDE-II: Dynamic T2T



FCP = fecal calprotectin.

Adapted from Turner D, et al. *Gastroenterology*. 2021;160(5):1570-1583.

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Goals and Timelines for Moderate to Severe CD

Clinical: Resolution of symptoms within 2-6 mo

Biomarkers: Normalization of CRP and fecal calprotectin within 2-6 mo

Endoscopic: Mucosal healing within 6-12 mo

Practical implications for monitoring: Ongoing assessment of biomarkers between cycles of imaging and/or endoscopy (depending on which is appropriate given disease extent and location)

Colombel JF, et al. *Dig Dis*. 2012;30(Suppl 3):107-111. Dignass A, et al. *Aliment Pharmacol Ther*. 2023;58(5):492-502. Srinivasan AR. *World J Gastroenterol*. 2024;30(1):50-69.

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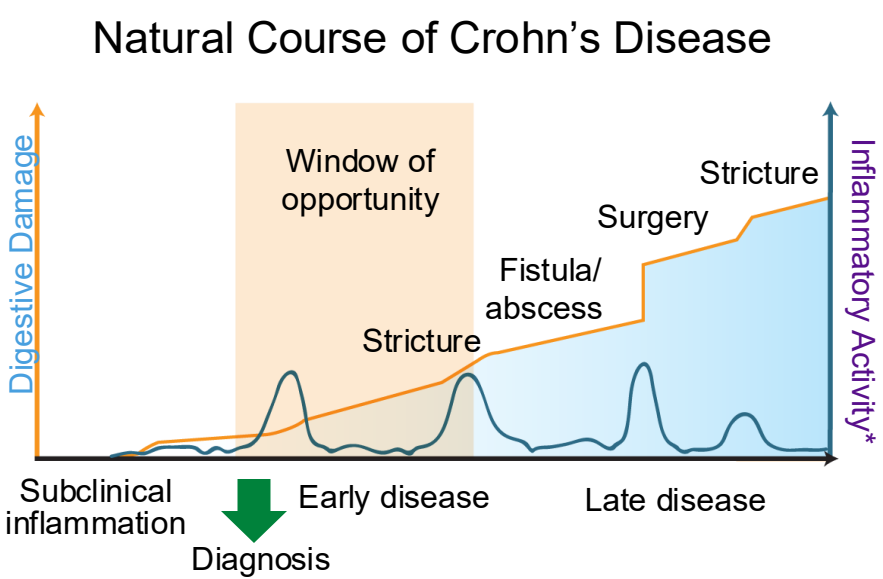
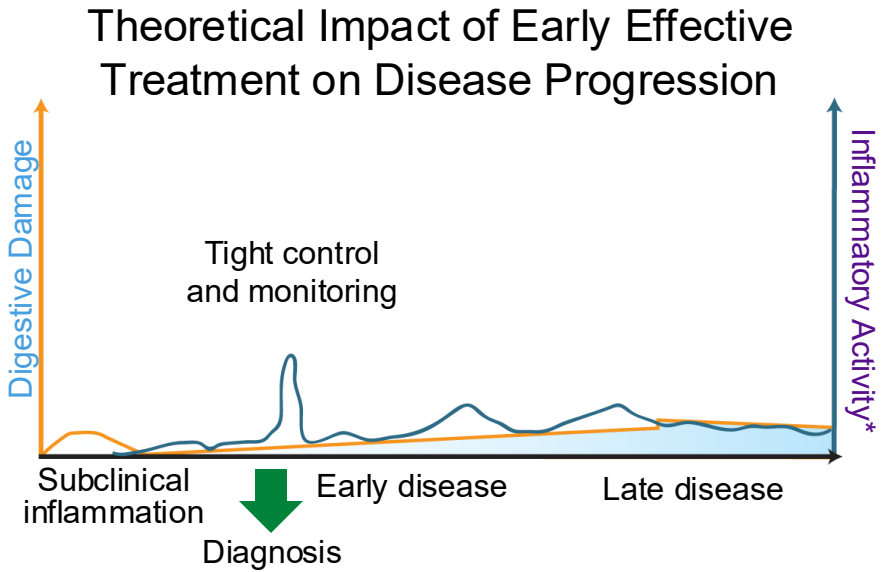
Why Is Early Treatment Important in Crohn's Disease?





- Similar principles in UC, but not as clear
- Effective treatment needed in UC and CD to provide adequate control of symptoms and mucosal inflammation (T2T approach)

***As measured by CDAI, CDEIS, CRP.**

Adapted from Colombel JF, et al. *Gastroenterology*. 2017;152(2):351-361.e5. Pariente B, et al. *Inflamm Bowel Dis*. 2011;17(6):1415-1422.

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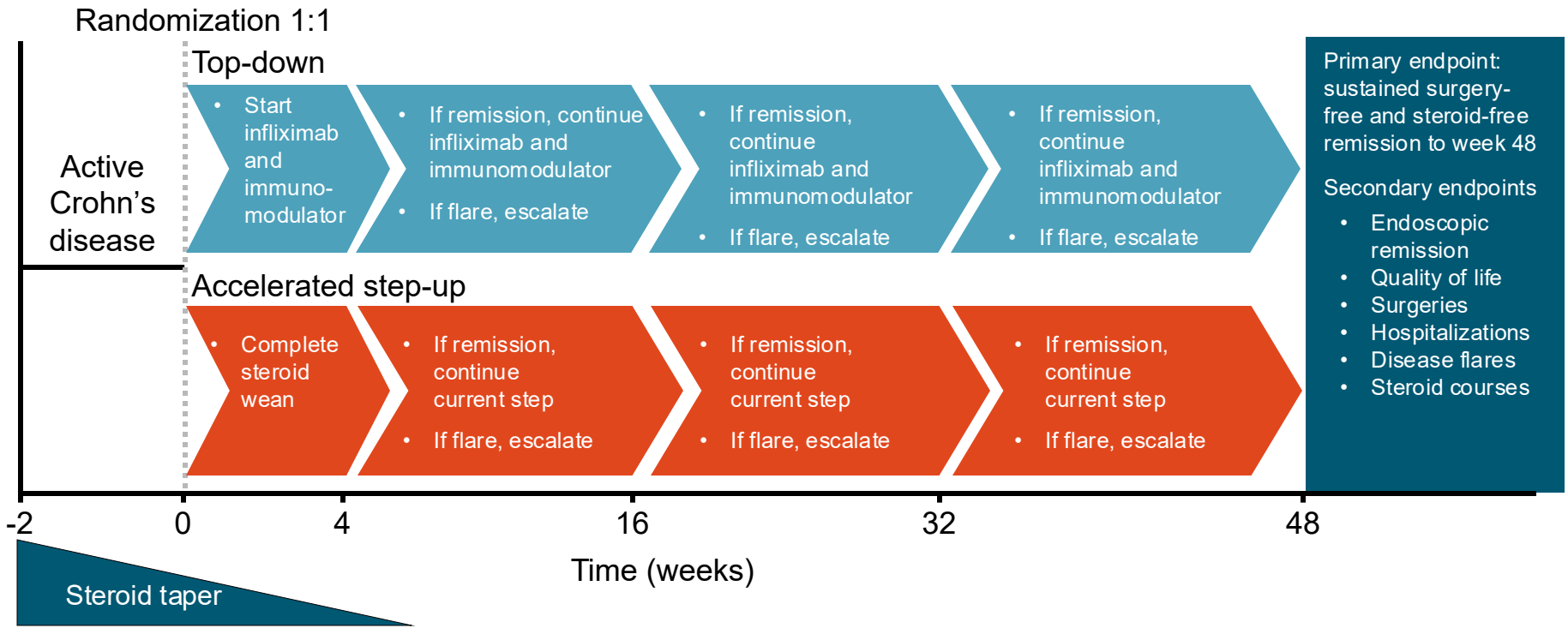
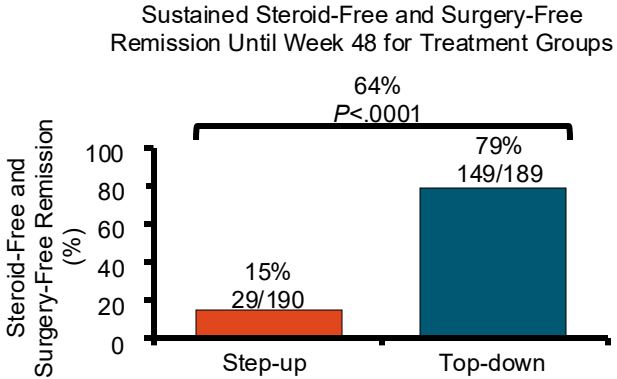
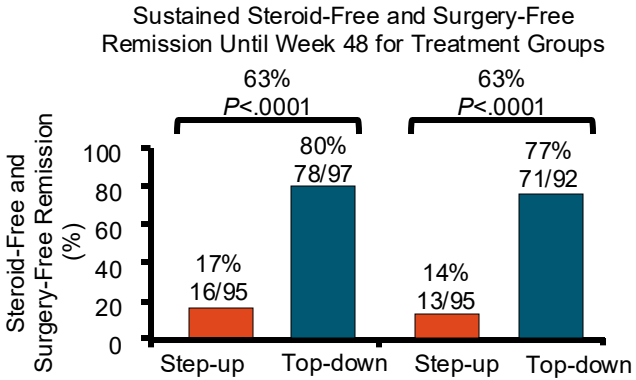
PROFILE Trial: Design

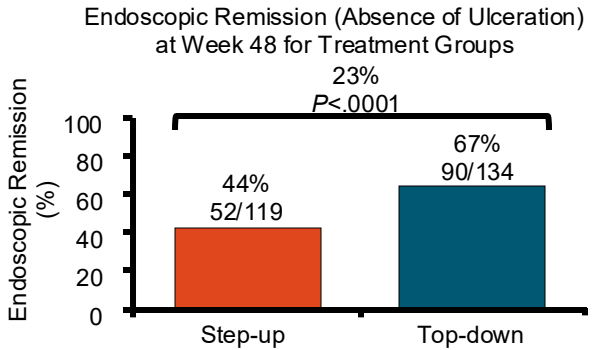


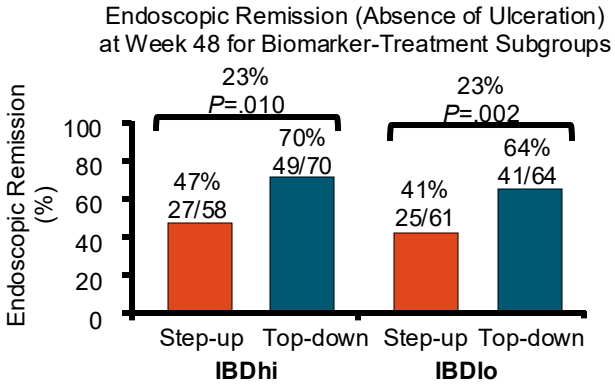
Noor NM, et al. *Lancet Gastroenterol Hepatol*. 2024;9(5):415-427.

PROFILE Trial: Primary Endpoint and Key Secondary Endpoint in CD









Noor NM, et al. *Lancet Gastroenterol Hepatol*. 2024;9(5):415-427.

CALM Trial

- Aim: compare endoscopic and clinical outcomes in patients with moderate to severe CD who were managed with a tight control algorithm using clinical symptoms and biomarkers vs patients managed with a clinical management algorithm
- Results
  - Patients in biomarker-driven treatment showed improved outcomes
  - Higher rates of mucosal healing
- Clinical implications: biomarker-driven adjustments improve long-term disease management

Colombel JF, et al. *Lancet*. 2017;390(10114):2779-2789.

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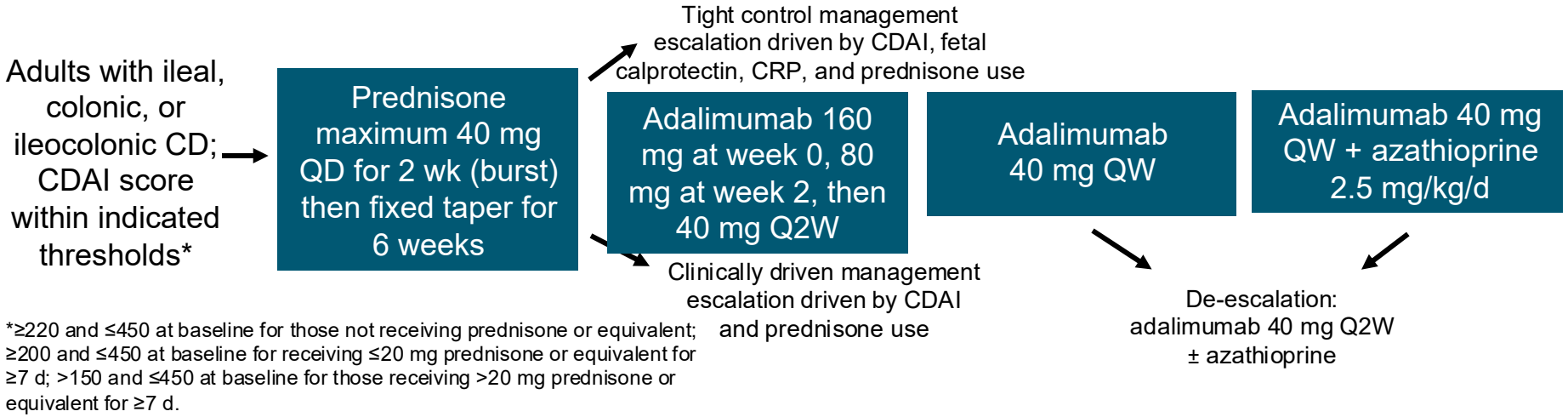
CALM: Study Design

- Multicenter, open-label, randomized phase 3 dose-escalation study



*≥220 and ≤450 at baseline for those not receiving prednisone or equivalent; ≥200 and ≤450 at baseline for receiving ≤20 mg prednisone or equivalent for ≥7 d; >150 and ≤450 at baseline for those receiving >20 mg prednisone or equivalent for ≥7 d.

- **Primary endpoint:** % of participants with mucosal healing and no deep ulcerations
- **Key secondary endpoints:** % of participants in deep remission, in biologic remission, with mucosal healing, and with complete mucosal healing 48 weeks after randomization

Colombel JF, et al. *Lancet*. 2017;390(10114):2779-2789. ClinicalTrials.gov. Accessed December 2, 2025. https://clinicaltrials.gov/study/NCT01235689?term=NCT01235689&rank=1.

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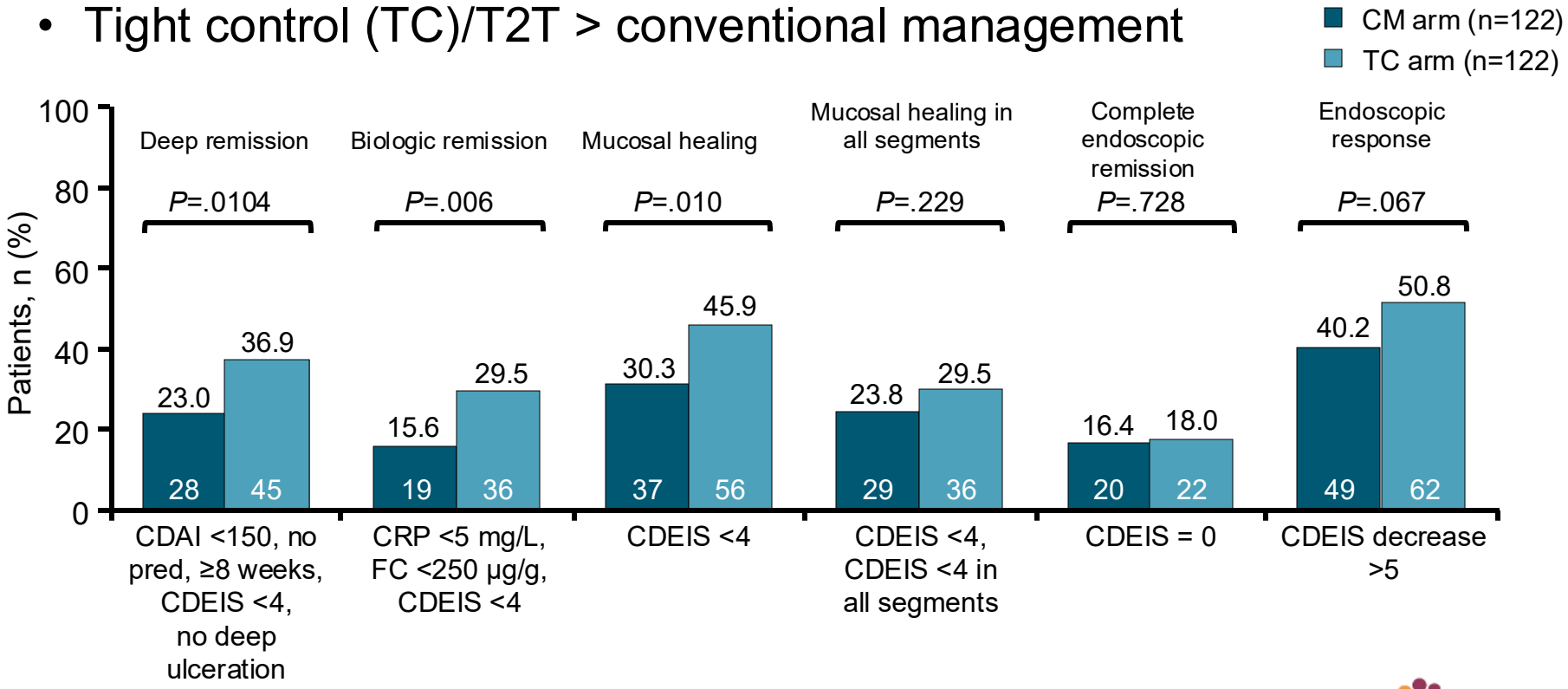
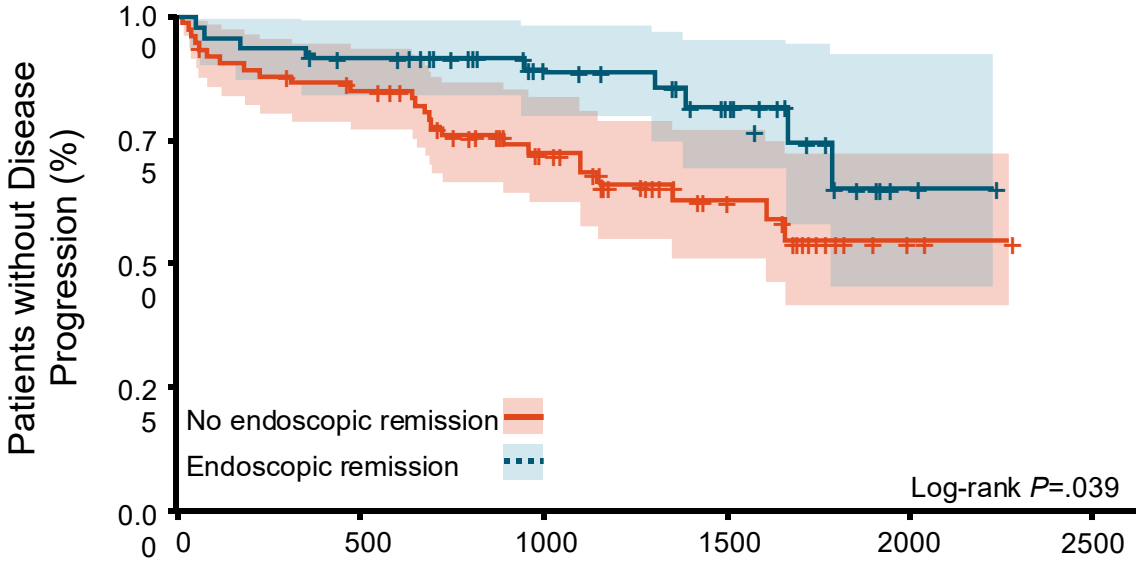
CALM: Endpoints in CD

- Tight control (TC)/T2T > conventional management



Colombel JF, et al. *Lancet*. 2017;390(10114):2779-2789.

Patients Who Achieve Mucosal Healing Are Less Likely to Have Disease Progression

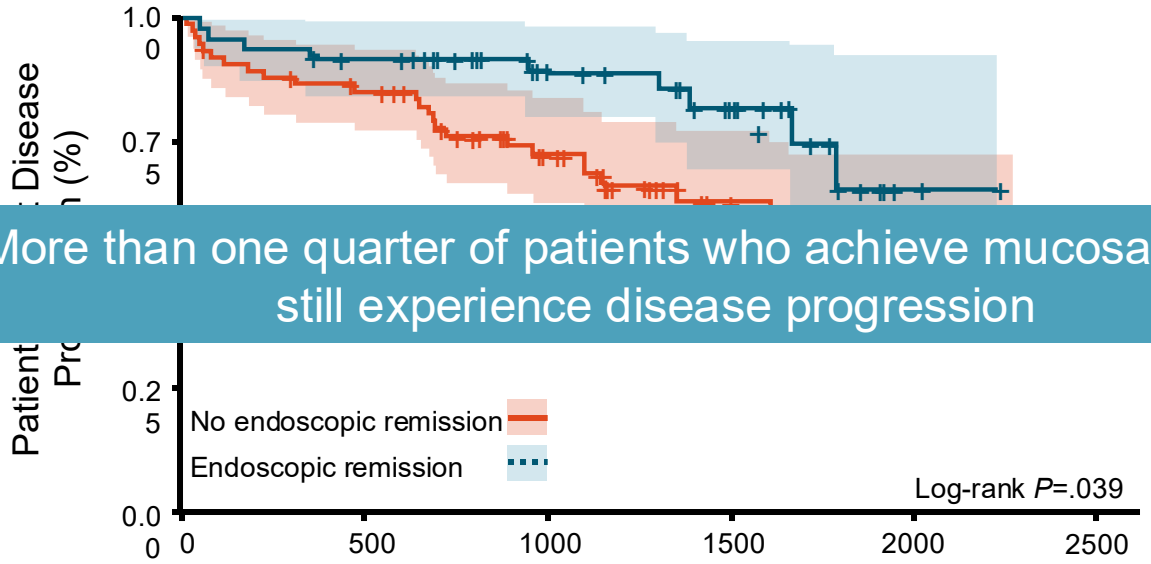


No. at risk:

No endoscopic remission	73	59	37	17	2	0
Endoscopic remission	49	43	28	16	2	0

Ungaro RC, et al. *Gastroenterology*. 2020;159(1):139-147.

Patients Who Achieve Mucosal Healing Are Less Likely to Have Disease Progression



More than one quarter of patients who achieve mucosal healing still experience disease progression

No. at risk:						
No endoscopic remission	73	59	37	17	2	0
Endoscopic remission	49	43	28	16	2	0

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Ungaro RC, et al. *Gastroenterology*. 2020;159(1):139-147.

Looking beyond STRIDE-II: Future Considerations

- Transmural healing: achieving normalization of all bowel layers
- Patient-centered goals: incorporating QoL metrics
- Emerging therapies: role of novel biologics and small molecules
- Spotlight on transmural healing
  - Using cross-sectional imaging (MRI or CT)
  - Evidence suggests transmural healing correlates with better long-term outcomes and reduced surgery rates
- Achieving improvement and normalization in histologic measurements of IBD disease activity

Wilkens R, et al. *Therap Adv Gastroenterol*. 2021;14:17562848211006672. Aladraj H, et al. *J Clin Med*. 2022;11(13):3743.

Key Learning Points

- **Precision medicine** enables earlier diagnosis and individualized IBD care
- **TL1A** is a promising new treatment target in both Crohn's disease and ulcerative colitis
- **Treat-to-target (T2T)** strategies improve long-term outcomes
- **Biomarkers and risk stratification** guide therapy choices
- **Patient-centered care** is essential for optimal management

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