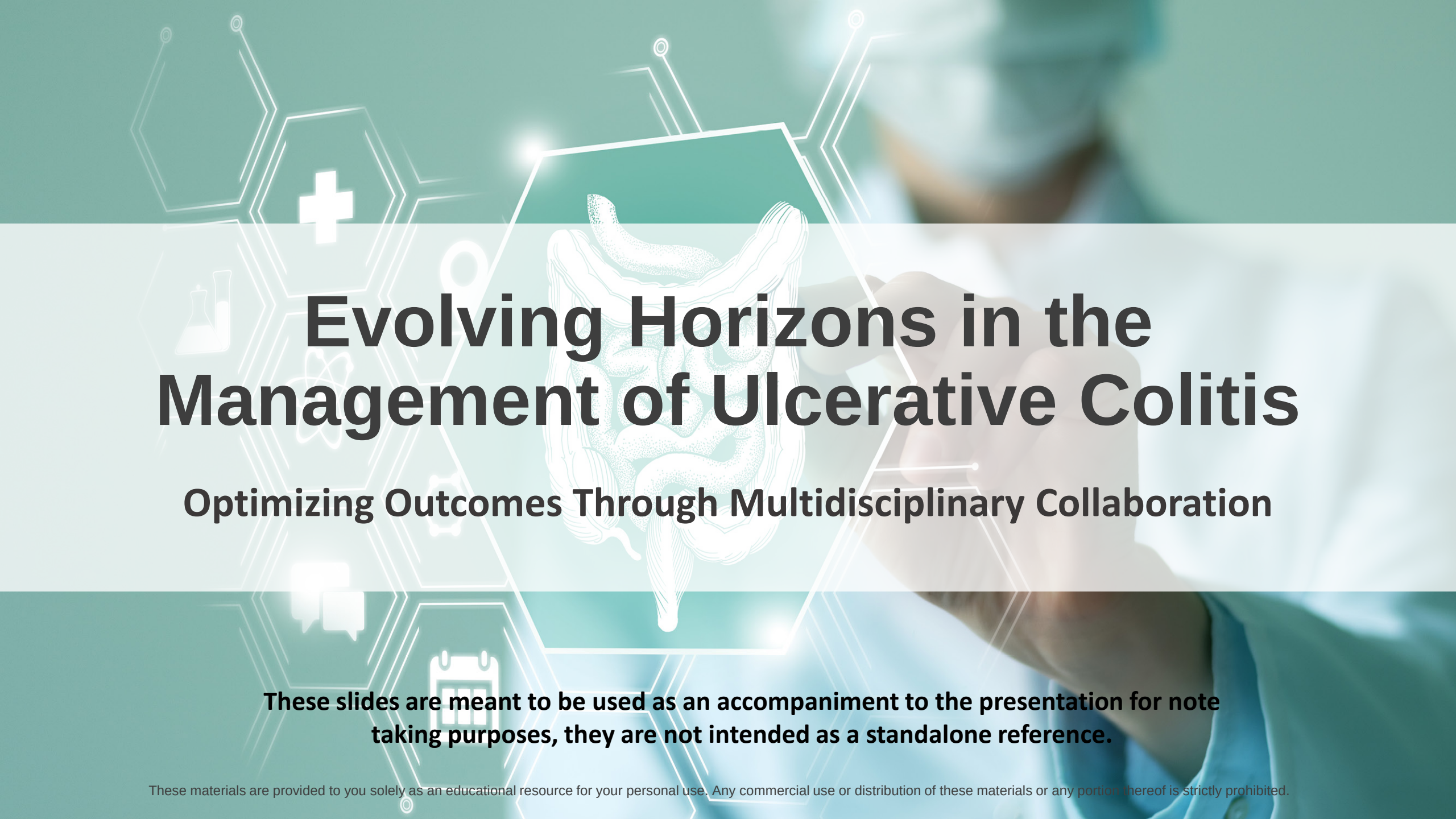
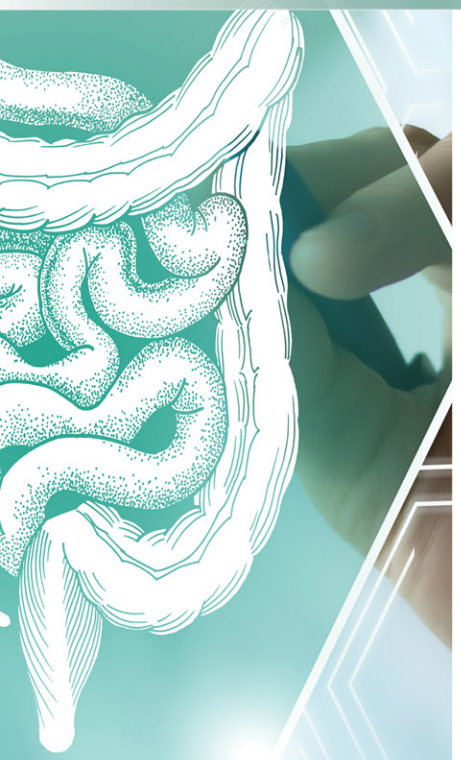


Evolving Horizons in the Management of Ulcerative Colitis

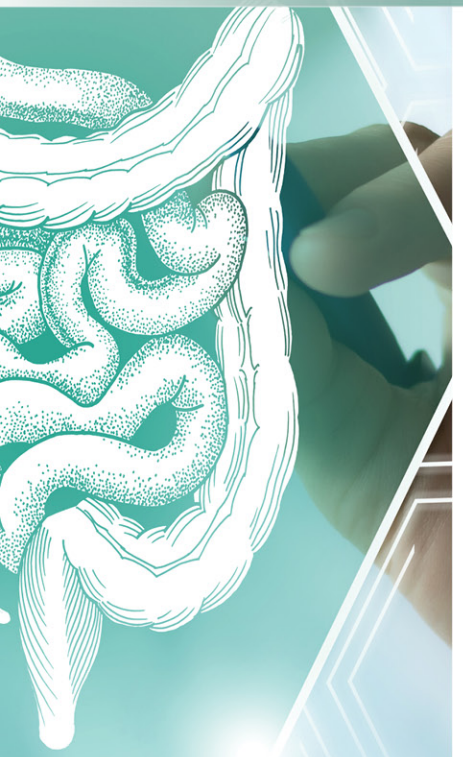
Optimizing Outcomes Through Multidisciplinary Collaboration

These slides are meant to be used as an accompaniment to the presentation for note taking purposes, they are not intended as a standalone reference.



This educational activity is jointly accredited for physicians, nurses, and pharmacists and is supported by an independent educational grant from Bristol Myers Squibb.

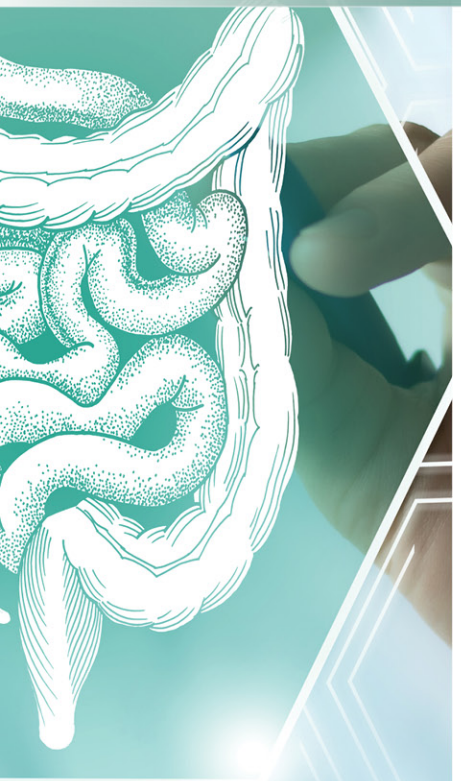
Faculty



Shubha Bhat, PharmD, MS, FCCP, BCACP
Clinical Pharmacy Specialist, Gastroenterology
Cleveland Clinic
Cleveland, OH

Shubha Bhat is a clinical pharmacy specialist in gastroenterology. In her clinical practice, she oversees the medication experience, including education, safety monitoring, and adverse effect management of patients with digestive conditions. In addition to clinical practice, Dr. Bhat also partakes in research and teaching. She earned her doctor of pharmacy degree from Northeastern University in Boston, and master's degree in clinical sciences from University of Colorado. She completed a PGY1 Pharmacy Residency at Boston Medical Center, PGY2 Ambulatory Care Residency at UIC, and Ambulatory Care Outcomes Fellowship at University of Colorado.

Faculty

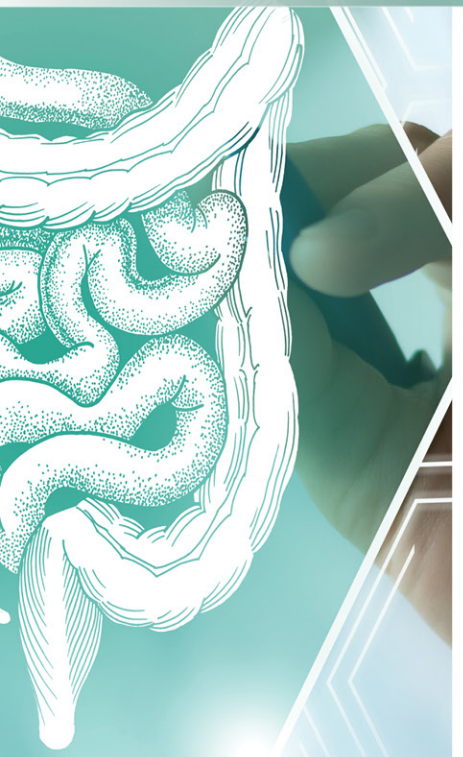


Francis A. Farraye, MD, MSc

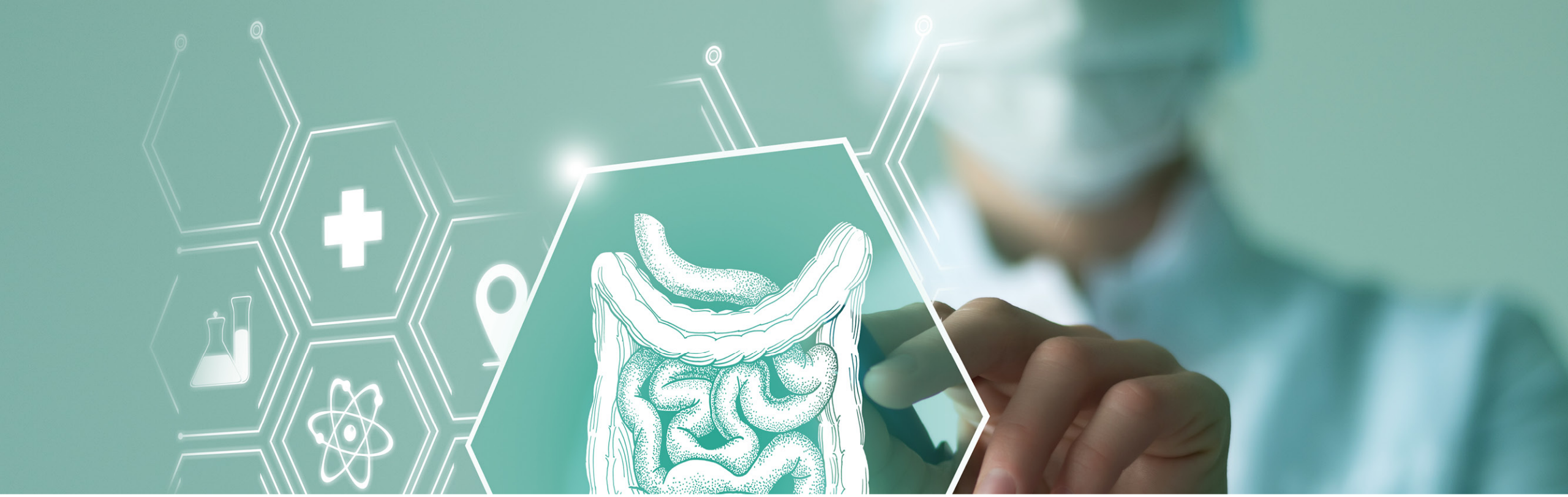
Director, Inflammatory Bowel Disease Center
Professor of Medicine
Division of Gastroenterology and Hepatology
Mayo Clinic College of Medicine and Science
Jacksonville, FL

Francis A. Farraye, MD, MSc, is the Director of the Inflammatory Bowel Disease Center at the Mayo Clinic in Jacksonville, Florida, where he is a professor of medicine. Dr. Farraye has authored or co-authored over 450 original scientific manuscripts, chapters, reviews, and abstracts. He is the Editor-in-Chief for *IBD Journal Scan*, which is published weekly by the American Society of Gastrointestinal Endoscopy. His most recent book is *Mayo Clinic on Crohn's Disease & Ulcerative Colitis*.

Learning Objectives



- **Describe** the goals of therapy for patients with ulcerative colitis (UC), including relevant clinical, endoscopic, and patient-reported outcomes
- **Summarize** current treatment options for UC and limitations associated with their use
- **Discuss** novel treatment options for UC, with a focus on the role and use of sphingosine-1-phosphate receptor modulators
- **Formulate** a collaborative, multidisciplinary plan of care for a patient with UC



Introduction to Ulcerative Colitis

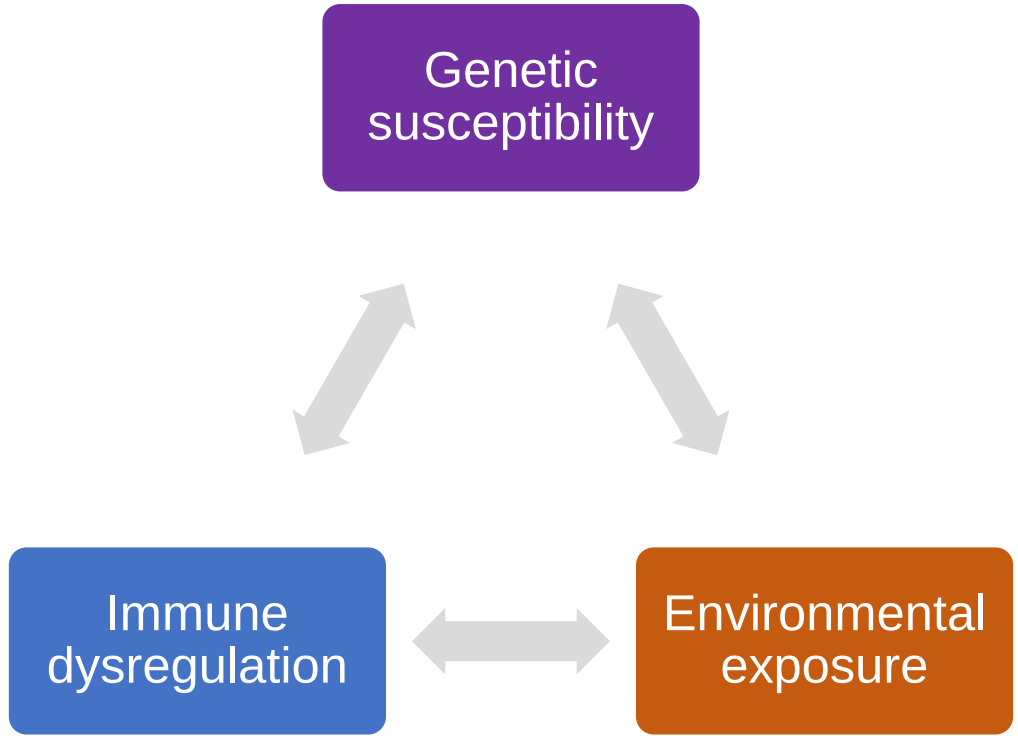
Ulcerative Colitis

- Chronic idiopathic inflammatory disease of the colon
- Peak of onset: adults aged 30-40 years
- Incidence and prevalence increasing worldwide
  - 3.7 million worldwide in 1990 → 6.8 million in 2017
- 15% of patients will require surgical intervention
- Disability + higher healthcare resource utilization
  - $11,029 higher direct costs per patient per year

Kaplan GG, Windsor JW. *Nat Rev Gastroenterol; Hepatol*. 2021;18(1):56-66. Ungaro R, et al. *Lancet*. 2017;389(10080):1756-1770. Pilon D, et al. *Curr Med Res Opin*. 2020;36(8):1285-1294.

Pathophysiology

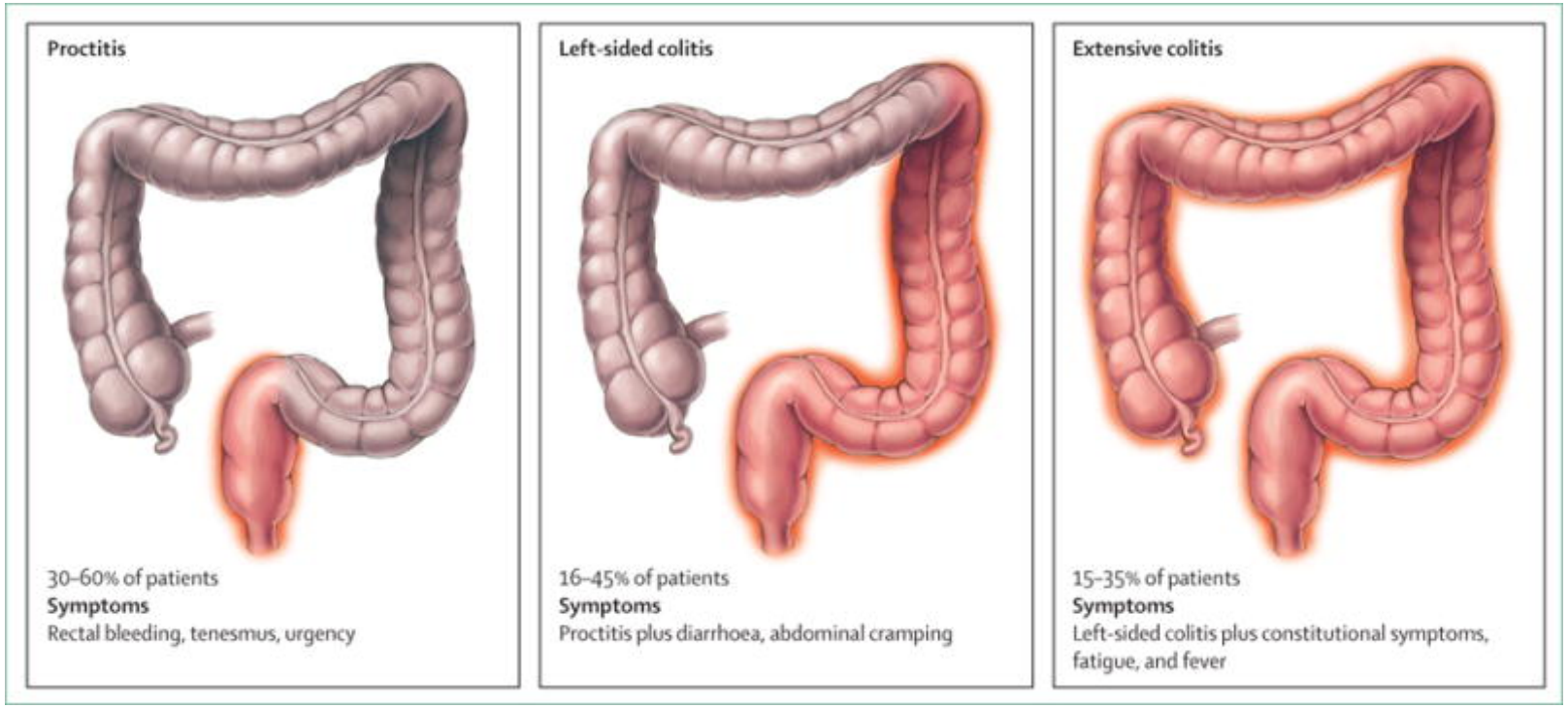
- Exact pathophysiology is not completely understood
  - Defects in colonic epithelial cells, mucosal barrier, and epithelial barrier
  - Family history of IBD, ≈200 identified risk loci, cigarette use, all ethnicities affected



IBD: inflammatory bowel disease.
Ungaro R, et al. *Lancet*. 2017;389(10080):1756-1770.

Clinical Presentation

- **Blood in stool**, **diarrhea**, urgency, incontinence, fatigue, increased frequency, mucus discharge, nocturnal defecations, weight loss, and abdominal discomfort



Ungaro R, et al. *Lancet*. 2017;389(10080):1756-1770.

Disease Severity Classification

	Remission	Mild	Moderate to Severe	Fulminant
Stools per day, n	Formed	<4	>6	>10
Blood in stool	None	Intermittent	Frequent	Continuous
Urgency	None	Mild, occasional	Often	Continuous
Hemoglobin	Normal	Normal	<75% of normal	Transfusion
Erythrocyte sedimentation rate (ESR), mm/h	<30	<30	>30	>30
C-reactive protein (CRP)	Normal	Increased	Increased	Increased
Fecal calprotectin (FCP), mg/kg	<150-200	>150-200	>150-200	>150-200
Mayo subscore (endoscopy)	0-1	1	2-3	3
UC Endoscopic Index of Severity	0-1	2-4	5-8	7-8

Rubin DT, et al. *Am J Gastroenterol*. 2019;114(3):384-413.
Pabla BS, Schwartz DA. *Gastroenterol Clin North Am*. 2020;49(4):671-688.

Patient Impact

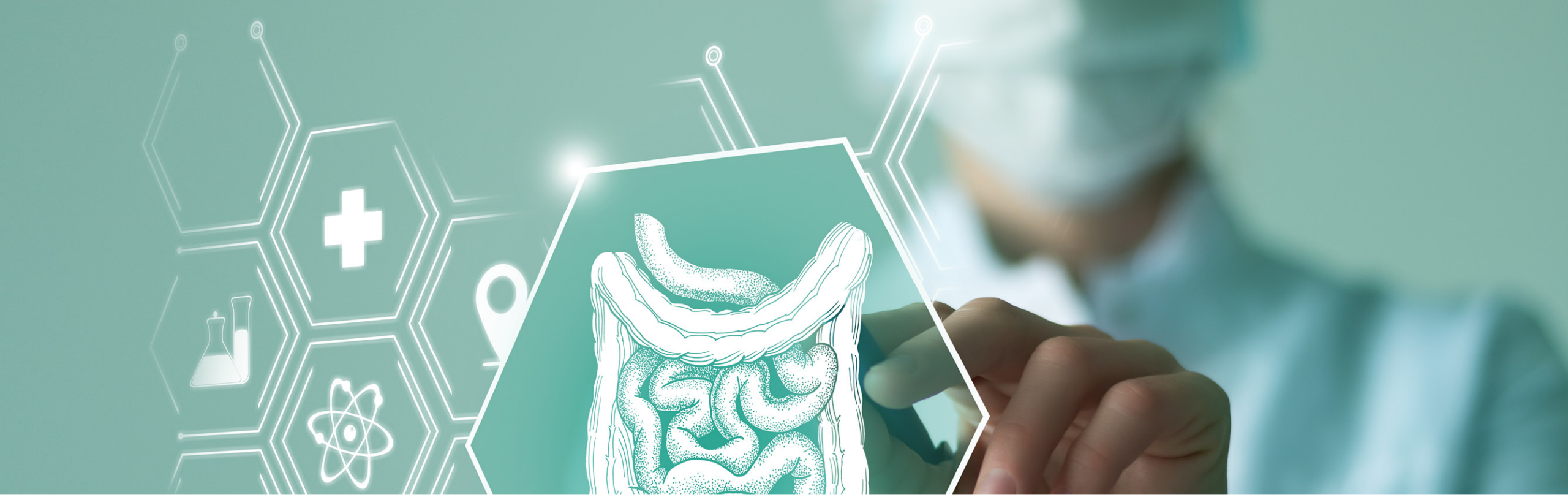
Complications

- Anemia
- Colorectal cancer
- Toxic megacolon
- Venous thromboembolism
- Malnutrition

Reduced quality of life

- Depression/anxiety
- Severe impairment of social/professional activities
- More sick leave/higher unemployment
- Sexual functioning
- Body image dissatisfaction

Armuzzi A, Liguori G. *Dig Liver Dis*. 2021;53(7):803-808.



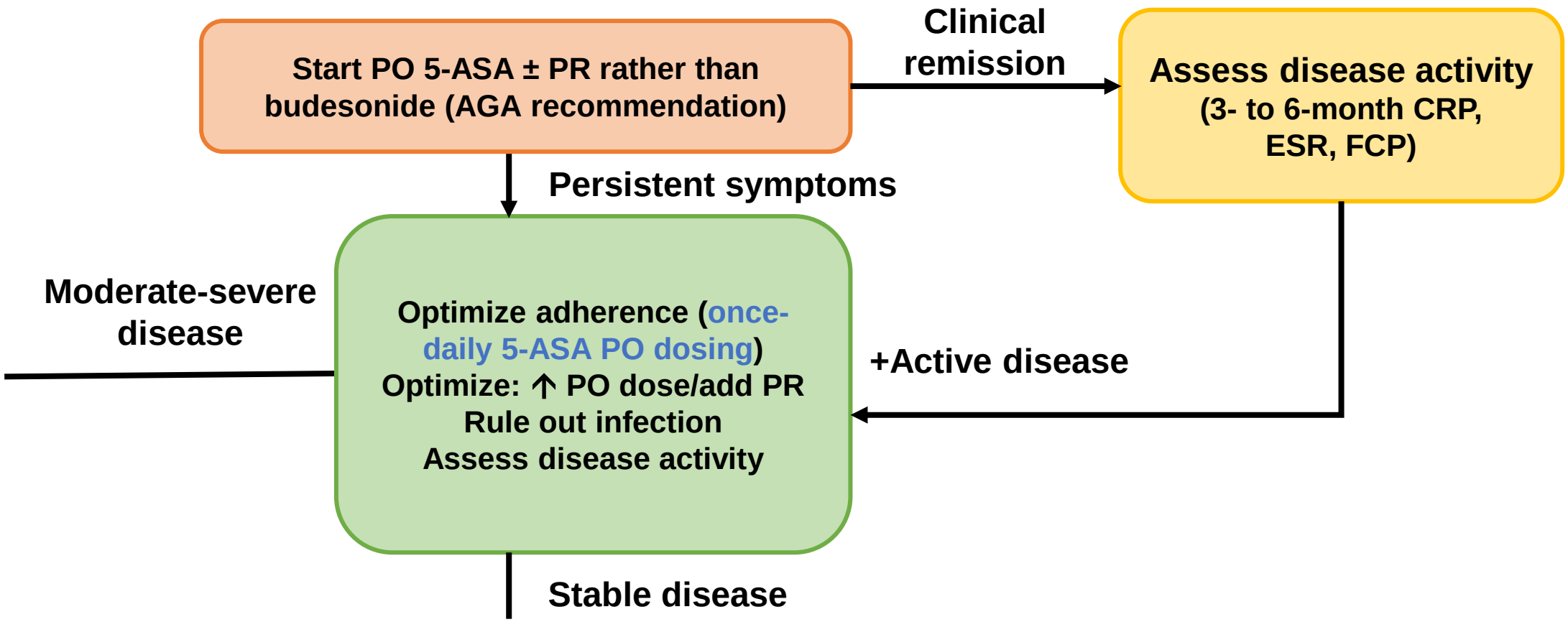
Treatment Considerations

Goals of Therapy

- Induce and maintain clinical and endoscopic remission
- Maintain steroid-free remission
- Improve quality of life
- Prevent complications, hospitalizations, and surgery

Armuzzi A, Liguori G. *Dig Liver Dis*. 2021;53(7):803-808.

Mild to Moderate UC Treatment Algorithm



5-ASA: 5-aminosalicylates; AGA: American Gastroenterological Association; PO: oral; PR: rectal.

Diaz G. GrepMed. https://www.grepmed.com/images/9608/moderate-algorithm-management-colitis-treatment-

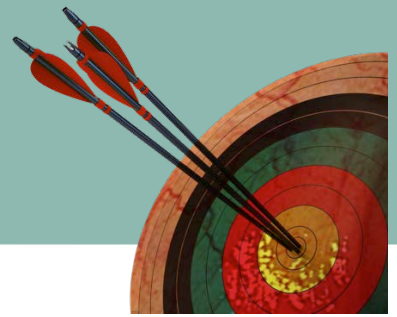
Ko CW, et al. *Gastroenterology*. 2019;156(3):748-764.

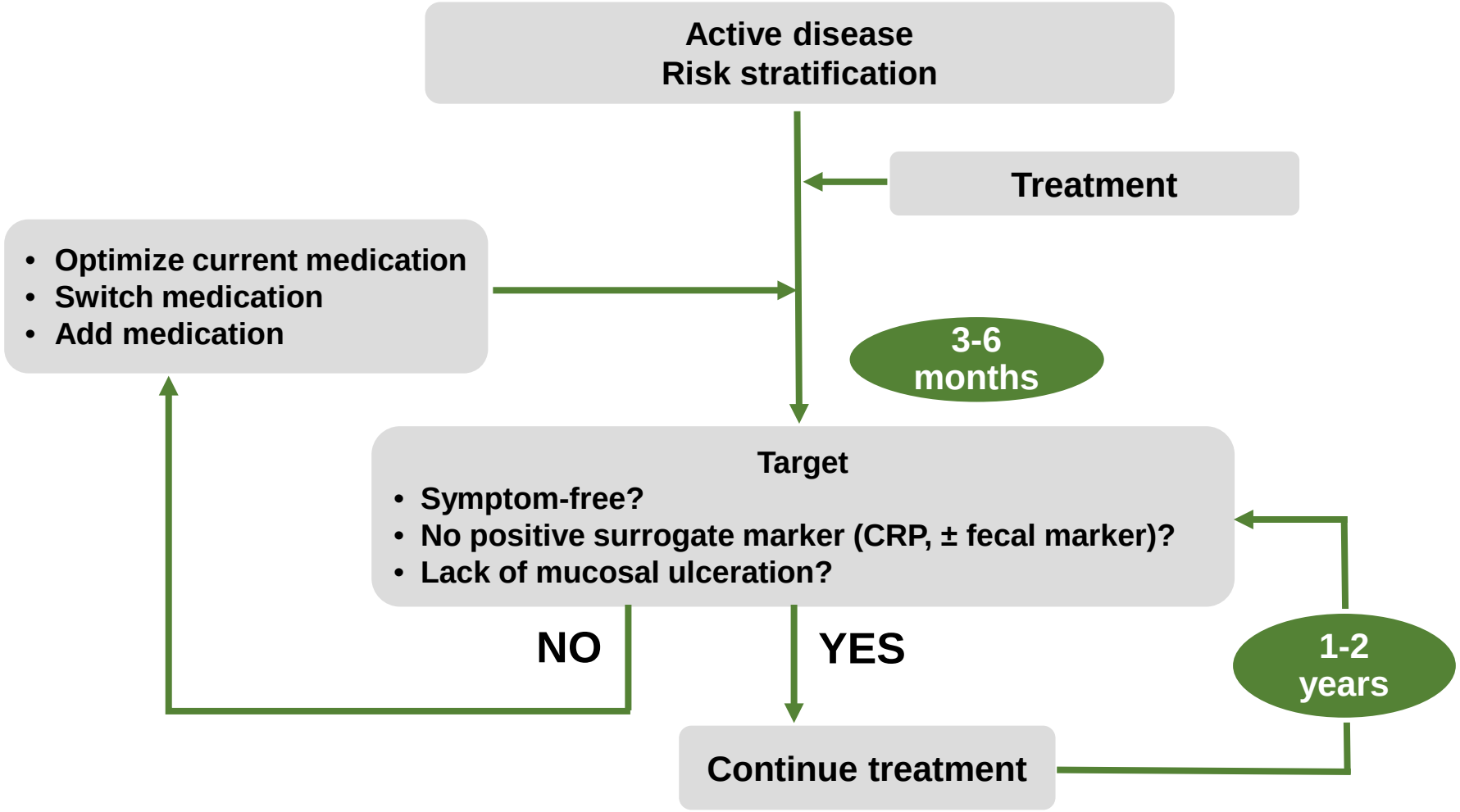
Moderate to Severe UC Treatment

- Biologics or small molecules
- Concomitant immunomodulator to decrease immunogenicity ± alternative mechanism of action
- Assess clinical response and remission
- Repeat imaging, surrogate markers (FCP, CRP), and/or sigmoidoscopy/colonoscopy for endoscopic ± histologic response/remission within 3 to 6 months of initiating treatment
- Periodic surveillance

Feuerstein JD, et al. *Gastroenterology*. 2020;158(5):1450-1461.

Treat-to-Target Approach



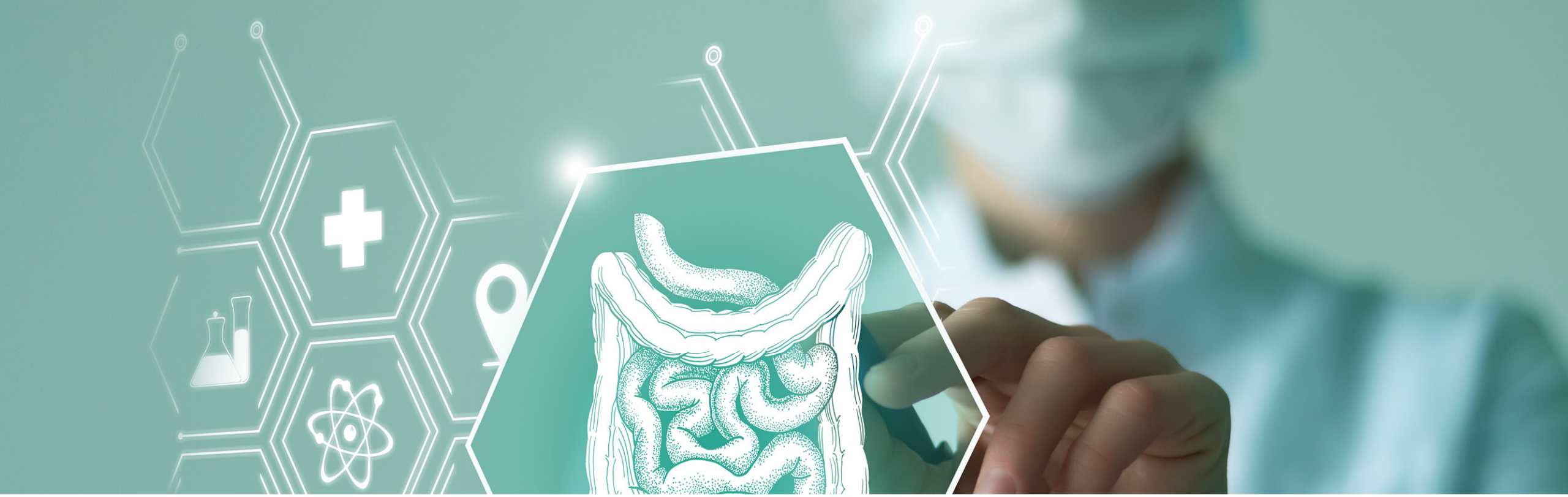


Bouguen G, et al. *Clin Gastroenterol Hepatol*. 2015;13(6):1042-1050.e2.

Patient/Treatment Considerations

- Disease severity
- Colonic extension
- Prior UC treatment history
- Age
- Comorbidities
- Lifestyle (oral vs injectables vs infusions)
- Drug interactions
- Insurance coverage

Armuzzi A, Liguori G. *Dig Liver Dis*. 2021;53(7):803-808.



Current Treatment Options

Brief Overview

Corticosteroids

5-ASA

Thiopurines

Biologics

Small Molecules

Corticosteroids

- Prednisone, budesonide (oral); methylprednisolone, hydrocortisone (parental)
- Used only for ***induction***, NOT maintenance of remission
- Associated with numerous AEs
  - Short-term: acne, insomnia, weight gain, irritability, and Cushingoid features
  - Long-term: osteoporosis, glaucoma, infection, diabetes mellitus, and mortality

AE: adverse event.

Faubion WA Jr, et al. *Gastroenterology*. 2001;121(2):255-260.

5-ASA

	Mesalamine (Several Products Available)	Balsalazide	Sulfasalazine
Chemical structure	5-ASA	Prodrug converted to 5-ASA in the colon	Prodrug converted to 5-ASA and sulfapyridine moieties in the colon
Dosage	• Low dose = <2 g/d • Standard dose = 2-3 g/d • High dose = >3 g/d	6.75 g provides approximately 2.4 g of 5-ASA	4 g provides approximately 1.6 g of 5-ASA
AEs	• Rare idiosyncratic worsening of colitis, presumed hypersensitivity syndrome • Rare: interstitial nephritis		• Folate metabolism interference • Male infertility • Rare serious cutaneous side effects, such as Stevens-Johnson syndrome • Anemia, leukopenia, and thrombocytopenia • Pneumonitis • Hepatitis
Monitoring	Renal function periodically		• CBC and LFTs periodically • Recommend folic acid supplement

CBC: complete blood count; LFT: liver function test.

Ko CW, et al. *Gastroenterology*. 2019;156(3):748-764.

Thiopurines: Azathioprine, 6-Mercaptopurine

- Inhibit proliferation of rapidly dividing cells (lymphocytes)
- Maintenance of remission
  - Typically, slower onset: ≈3 months
  - Often used in combination with biologics
- Dosing is weight based, *TPMT/NUD15* dependent
- Frequent (every-3-month) laboratory monitoring (CBC, LFTs) recommended

Drug Interaction:
Allopurinol

AEs:
Nausea, vomiting, fever, malaise, leukopenia, thrombocytopenia, pancreatitis, and hepatotoxicity

Rare AEs:
Non-Hodgkin lymphoma, hepatosplenic T-cell lymphoma

Feuerstein JD, Cheifetz AS. *Mayo Clin Proc*. 2014;89(11):1553-1163.

Biologics

Anti-Tumor Necrosis Factors (TNFs)

Interleukin (IL)-12/23 Inhibitor

Anti-Integrins

Anti-Tumor Necrosis Factor

	Infliximab	Adalimumab	Golimumab
Dosage	5 mg/kg IV at weeks 0, 2, and 6, then every 8 weeks	160 mg SQ on day 0, 80 mg on day 14, then 40 mg SQ every 2 weeks	200 mg SQ on week 0, 100 mg on week 2, 50 mg on week 4, then 50 mg (or 100 mg if >80 kg) every 4 weeks
AEs	• Infusion/injection site reactions • Hypersensitivity reactions • Infection • Malignancy • Hepatotoxicity • Demyelinating disease • Contraindicated in New York Heart Association III/IV heart failure		
Monitoring	• Hepatitis B and tuberculosis screening pretreatment • CBC and CMP periodically		

CMP: comprehensive metabolic panel; IV: intravenous;
SQ: subcutaneous.

Burri E, et al. *Digestion*. 2020;101(suppl 1):2-15.
Blonski W, et al. *Curr Opin Gastroenterol*. 2014;30(1):84-96.

IL-12/23 Inhibitor: Ustekinumab

- **Dose:** weight-based (260, 390, or 520 mg) IV induction x 1, then 90 mg SQ every 8 weeks
- **AEs:** infusion/injection site reaction, infection
- **Monitoring:** Hepatitis B panel + tuberculosis screen at baseline; CBC and CMP every 6 months

Stelara [package insert]. Horsham, PA: Janssen Biotech Inc.; 2022.

Anti-Integrin: Vedolizumab

- **Dose:** 300 mg IV at weeks 0, 2, and 6, then every 8 weeks thereafter
- **AEs:** infusion reaction, upper respiratory tract infections, and LFT elevation (transient)
- **Monitoring:** LFTs

Entyvio [package insert]. Lexington, MA: Takeda Pharmaceuticals USA, Inc.; 2022.

Small Molecules

Janus Kinase (JAK) Inhibitors

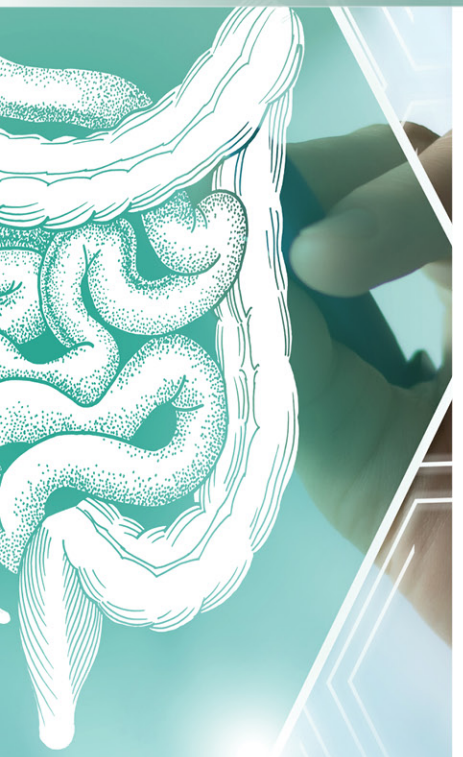
Sphinghosine-1-Phosphase Receptor (S1PR) Modulator

JAK Inhibitors

	Tofacitinib	Upadacitinib
Dosage	**Immediate release:** 10 mg PO twice daily x 8 weeks, then 5 mg PO twice daily for maintenance **Extended release:** 22 mg PO once daily x 8 weeks, then 11 mg PO once daily for maintenance	45 mg by mouth daily x 8 weeks, then 15 mg by mouth daily for maintenance. Can consider 30 mg by mouth daily for refractory disease.
AEs	• Infection (especially herpes zoster reactivation) • Black-box warning for major cardiovascular AEs in individuals aged ≥50 years with ≥1 cardiovascular risk factor, malignancy, and venous thromboembolism per ORAL Surveillance data • Lymphocyte abnormalities and anemia • Lipid elevation • Need to monitor for concurrent drug interactions (e.g., CYP3A4 inhibitor, CYP2C19 inhibitor) and renal/hepatic impairment	
Monitoring	• Hepatitis B and tuberculosis screening pretreatment • Lipid panel • CBC and CMP	

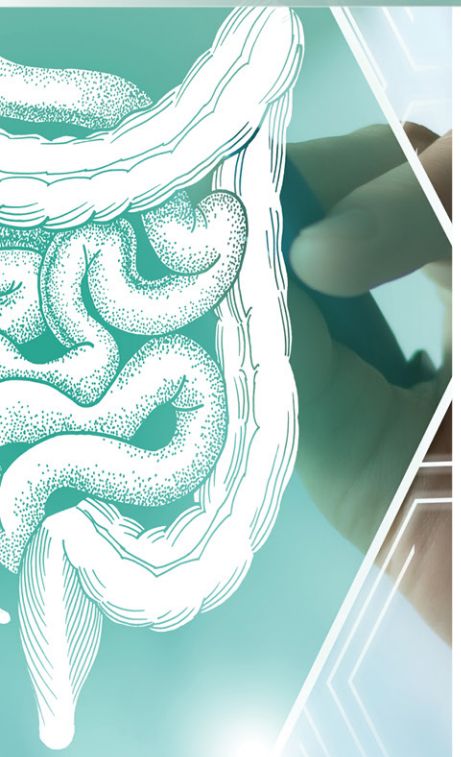
Xeljanz [package insert]. New York, NY: Pfizer, Inc.; 2022.
Rinvoq [package insert]. North Chicago, IL: AbbVie Inc.; 2022.

Treatment Limitations

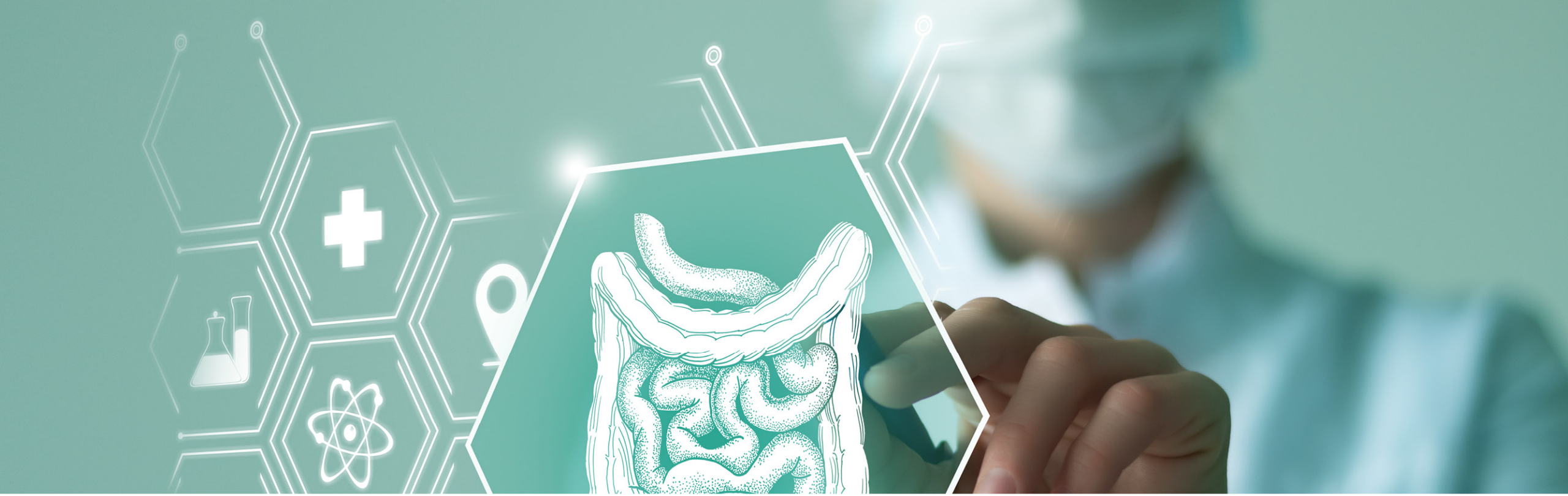


Corticosteroids	• Not intended for long-term use
Anti-TNF	• Systemic immunosuppression • Opportunistic infections • IV/SQ administration • Additional coordination of care (e.g., infusion center and refrigeration)

Treatment Limitations (cont)



Anti-Integrin	• Typically, slower onset of action • IV • Additional coordination of care (e.g., infusion center)
Anti–IL-12/23	• Systemic immunosuppression • IV/SQ administration • Additional coordination of care (e.g., infusion center and refrigeration)
JAK Inhibitors	• Systemic immunosuppression • Venous thromboembolism, major cardiovascular events • Herpes zoster • Not available as first-line therapy

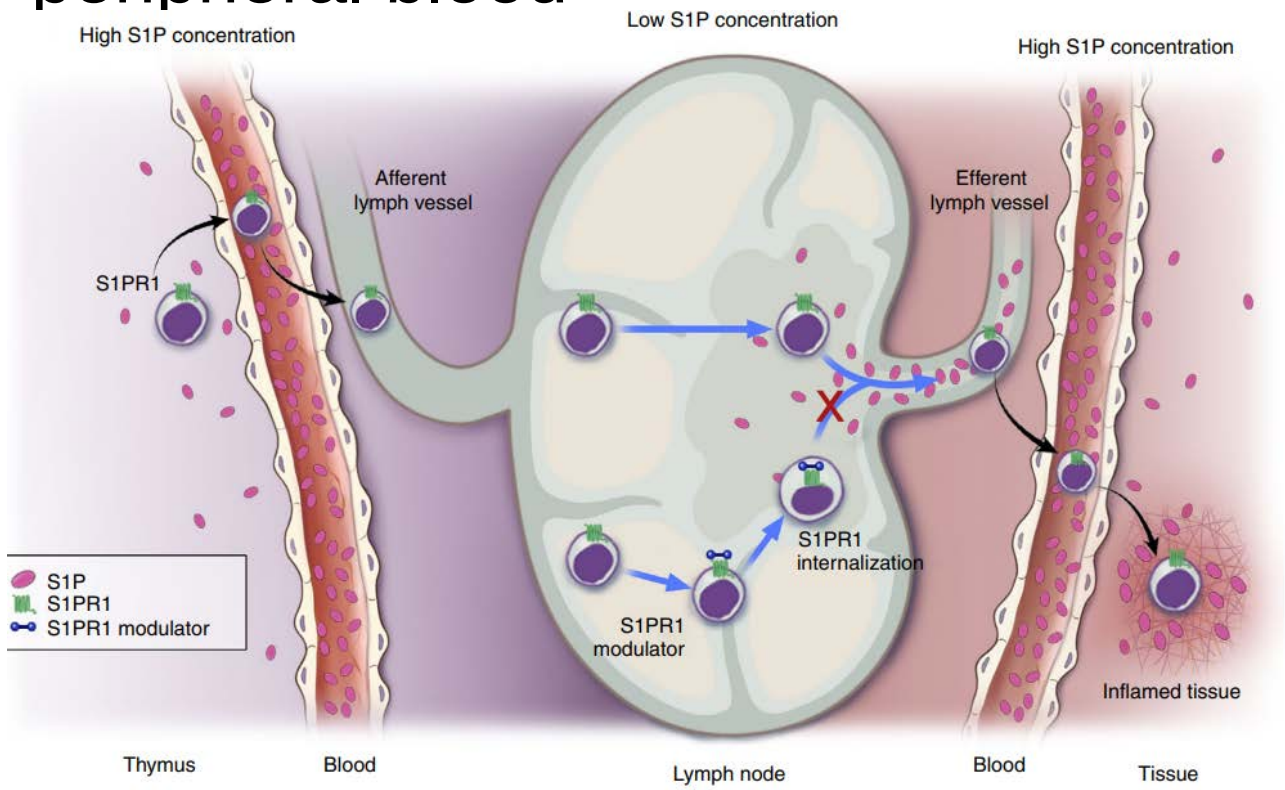


Novel Approved Treatment Options

Sphingosine-1-phosphate receptor modulators

S1PR Modulators: Background

- Limits egress of lymphocytes from lymph nodes to intestine via peripheral blood



Name	S1PR Target
Ozanimod[a]	1, 5
Etrasimod	1, 4, 5
Amiselimod	1, 4, 5
Fingolimod	1, 3, 4, 5
Siponimod	1, 5
Ponesimod	1
Cenerimod	1, 5

[a]Currently available on market for UC.

Wang J, et al. *Aliment Pharmacol Ther*. 2022;55(3):277-291.

Ozanimod: True North (Randomized-Controlled Trial)

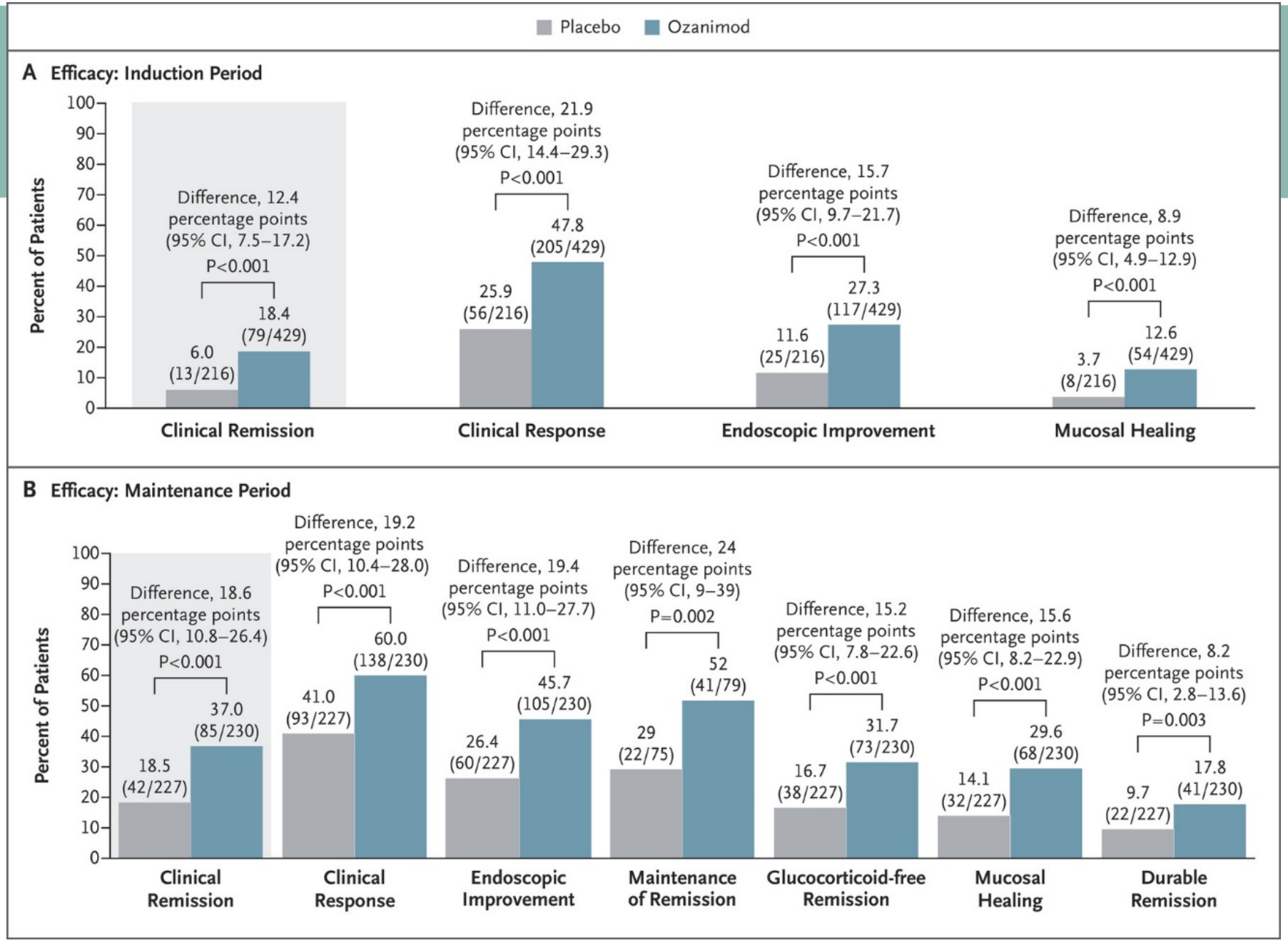
Induction

- Ozanimod 1 mg daily (n = 429) vs placebo (n = 216)
- 60% male, mean age = 42 years, mean disease duration = 7 years
- 30% with prior anti-TNF exposure
- Outcomes at week 10

Maintenance

- Ozanimod 1 mg daily (n = 230) vs placebo (n = 227)
- 31% with prior anti-TNF use
- Outcomes at week 52

Sandborn WJ, et al. *N Engl J Med*. 2021;385(14):1280-1291.



Sandborn WJ, et al. *N Engl J Med*. 2021;385(14):1280-1291.

Ozanimod Dosing

Starter Kit

- PO daily: 0.23 mg days 1-4, then 0.46 mg days 5-7

Maintenance

- 0.92 mg PO daily

Zeposia [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2022.

S1PR Modulator Safety

Receptor	Location	Function
$S1P_1$	Lymphocytes, neural, endothelial, atrial myocytes, and smooth muscles	Lymph node egression, neural cell migration/function, vasculature formation, endothelial barrier, and cardiovascular and nervous system development
$S1P_2$	Central nervous system, endothelial, and smooth muscle	Endothelial barrier, vascular tone, and hearing and balance
$S1P_3$	Neural, endothelial, and smooth muscle	Neural cell migration/function and endothelial barrier
$S1P_4$	Lymphocytes	Lymphoid tissue expression, dendritic cell modulation, and vasoconstriction
$S1P_5$	Central nervous system, oligodendrocytes, and natural killer cells	Oligodendrocyte function and natural killer cell migration

Subei AM, et al. *CNS Drugs*. 2015;29(7):565-575.

True North: Safety

- Incidence of infection (of any severity) with ozanimod was comparable during induction but higher in maintenance when compared with placebo
- <2%: serious infections, bradycardia, hypertension, and macular edema
- Elevations in liver function, headaches, and decrease in absolute lymphocyte count

Sandborn WJ, et al. *N Engl J Med*. 2021;385(14):1280-1291.

Ozanimod Initiation Checklist

Contraindications	
Recent history of a cardiac event within the past 6 months, including a myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or class III or IV heart failure	❑ No history
Second- or third-degree atrioventricular block, sick sinus syndrome, or sinoatrial block, unless the patient has a functioning pacemaker	❑ No history
History of untreated sleep apnea	❑ No history
Taking a MAO inhibitor • Nonselective type A and type B: isocarboxazid, phenelzine, or tranylcypromine • Type B: selegiline, rasagiline, or safinamide • Type A: moclobemide • Linezolid • Methylene blue	❑ Not taking

Baseline laboratory monitoring	
CBC with differential within the past 6 months	❑ Completed
Liver transaminases and bilirubin with the past 6 months	❑ Completed
Immunity documented to varicella zoster virus • Varicella zoster virus antibodies, or • History of varicella, or • Documentation of a full vaccination course	❑ Completed

Baseline examination	
Electrocardiogram • QTc ≤450 ms in male or ≤470 ms in female patients • Baseline heart rate >55 beats per minute	❑ Completed
Ophthalmic evaluation **only** in patients at high risk for macular edema (i.e., diabetes mellitus or history of uveitis)	❑ Completed Or ❑ Not needed

MAO: monoamine oxidase.

Choi D, et al. *Ann Pharmacother*. 2022;56(5):592-599.

Treatment Monitoring

- Signs and symptoms of infections
- CBC
- CMP
- Blood pressure
- Effective contraception during and 3 months post-treatment

Interactions

Medications

- Immunosuppressants
- Antiarrhythmics, beta blockers, and calcium channel blockers
- QT-prolonging agents
- Adrenergic and serotonergic
- CYP2C8 inducers/inhibitors
- MAO inhibitors

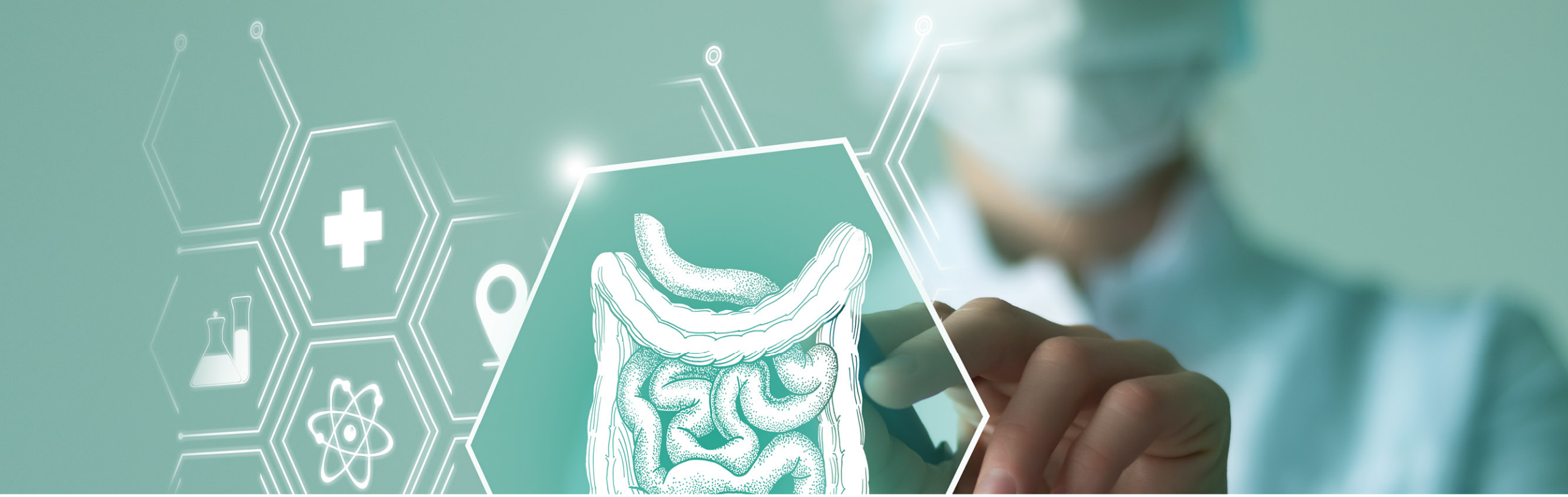
Vaccinations

- Avoid live

Tyramine

- >150 mg may lead to hypertension
- Aged, fermented, cured, smoked, and pickled foods
  - Cheddar, feta, gouda, and artisanal cheese
  - Kimchi
  - Sauerkraut
  - Beer
  - Soy sauce

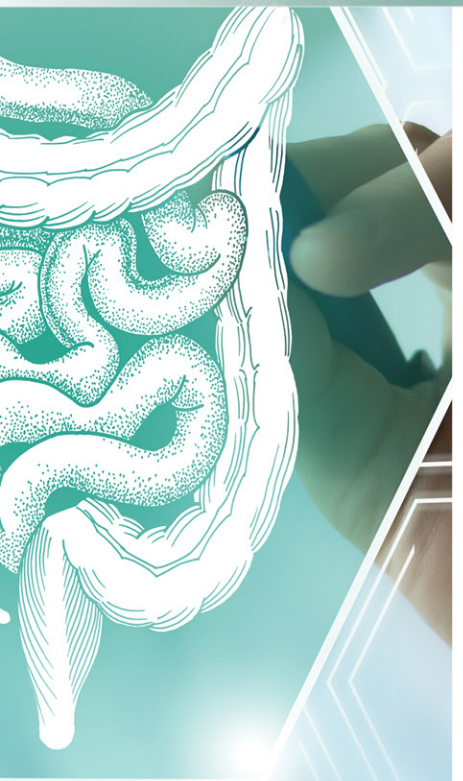
Zeposia [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2022.



Care Planning

Multidisciplinary

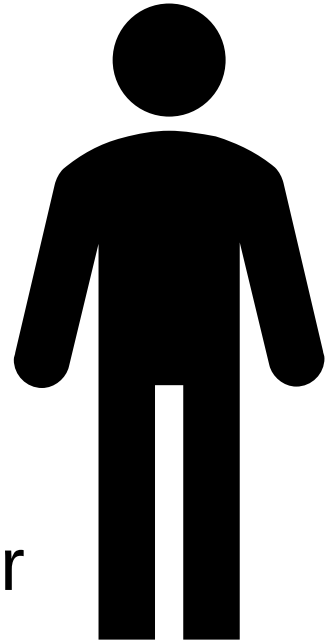
Multidisciplinary Team and Roles



Gastroenterologist

Dietitian

Surgeons



Psychologist
Psychiatrist

Nurses

Social worker

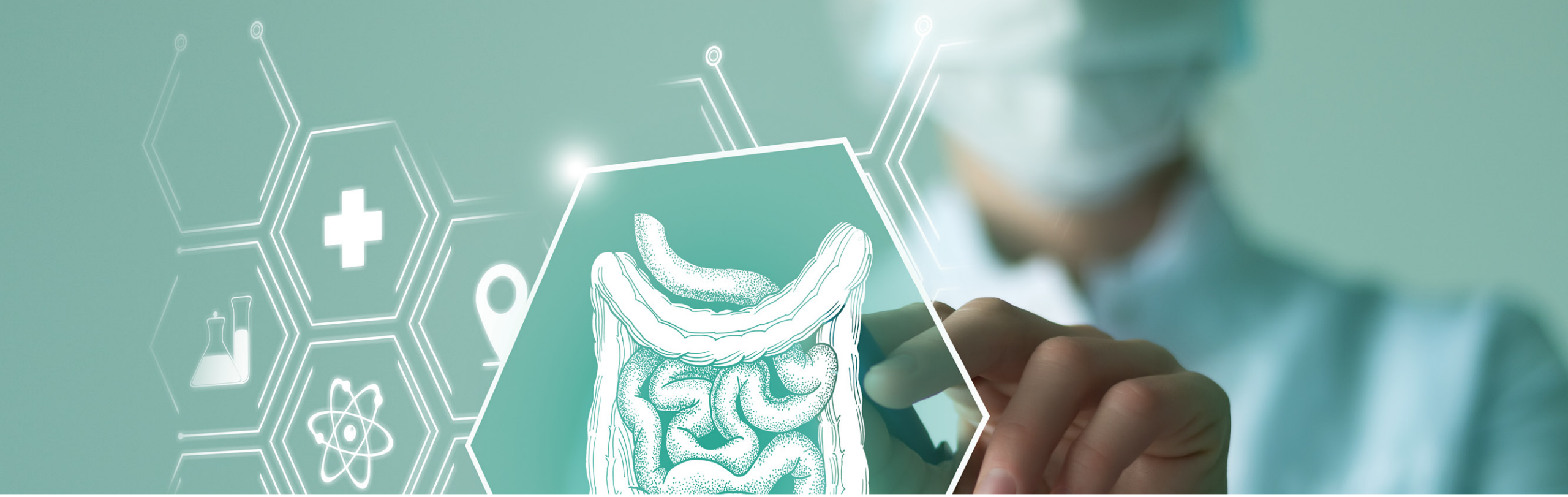
Physician
assistants

Clinical pharmacists

IBD Team Impact

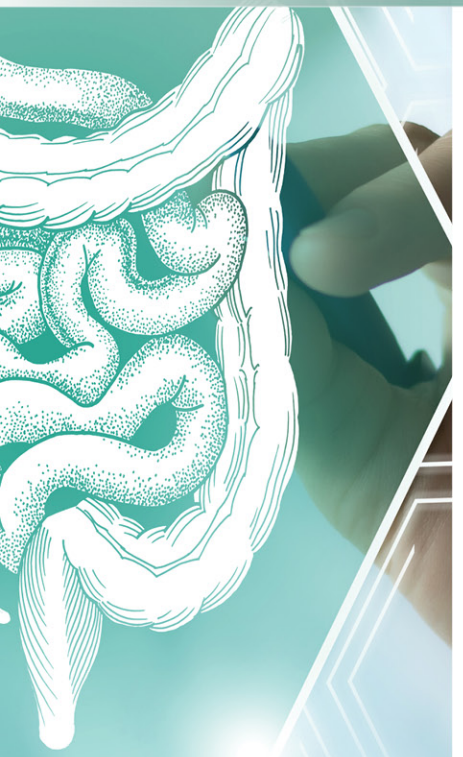
- N = 322 patients with IBD
- 47.3% reduction in emergency department visits
- 35.9% reduction in hospitalizations
- Decrease in UC activity index
- Increase in quality of life

Regueiro M, et al. *Clin Gastroenterol Hepatol*. 2018;16(11):1777-1785.



Case Discussion

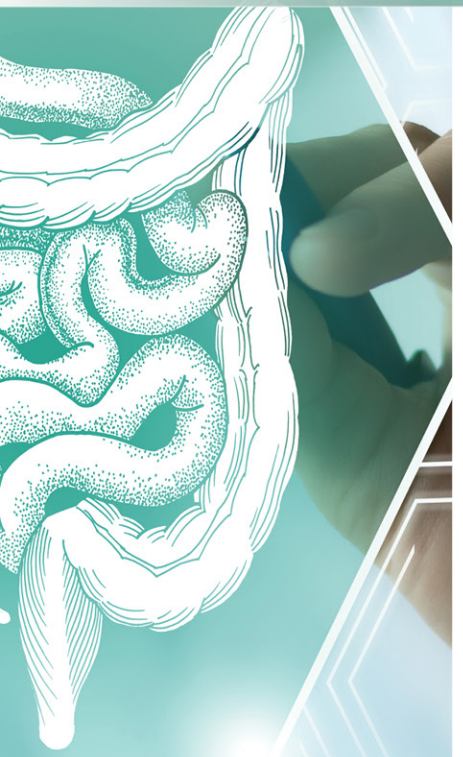
BK: A Case Study



- 34-year-old woman with a 2-month history of diarrhea (6-8 bowel movements/day), bleeding, and urgency
- No other medical history; nonsmoker
- Medications: oral contraceptive and occasional NSAID use for menstrual-related cramps
- Family history: brother has UC

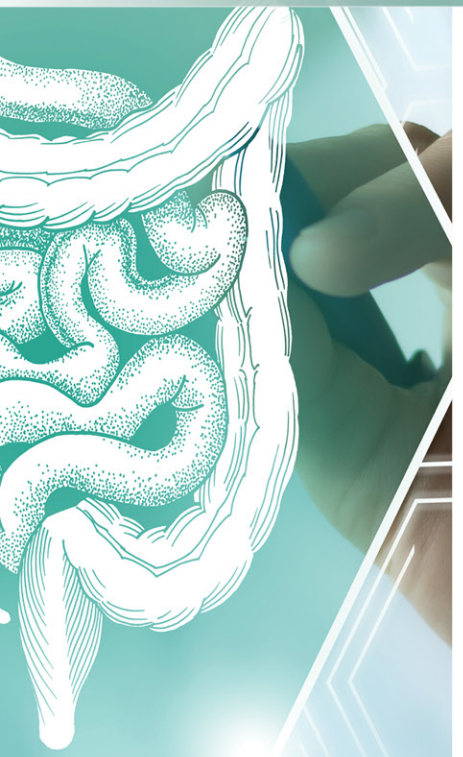
NSAID: nonsteroidal anti-inflammatory drug.

BK: Pertinent Laboratory Results

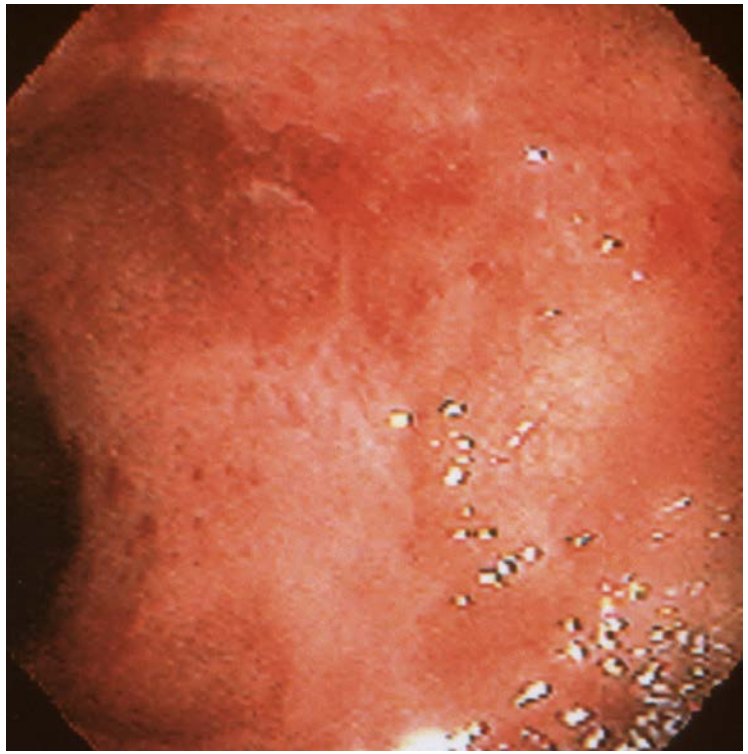


Parameter	Results
Hemoglobin, g/dL	11
Hematocrit, %	36
Platelets, k/uL	440
Creatinine, mg/dL	0.68
Alanine aminotransferase, U/L	10
Aspartate aminotransferase, U/L	15
CRP, mg/dL	1.9 (<0.3 is normal)
ESR, mm/h	45
FCP, mg/kg	324

BK: A Case Study



- Infectious stool studies negative
- Flexible sigmoidoscopy:
  - Erythema, friability, granularity, erosions in a continuous distribution to ≥50 cm (Mayo subscore 2)
- Biopsies:
  - Acute/chronic inflammation and crypt abscess
  - No granulomas



Disease Severity Classification

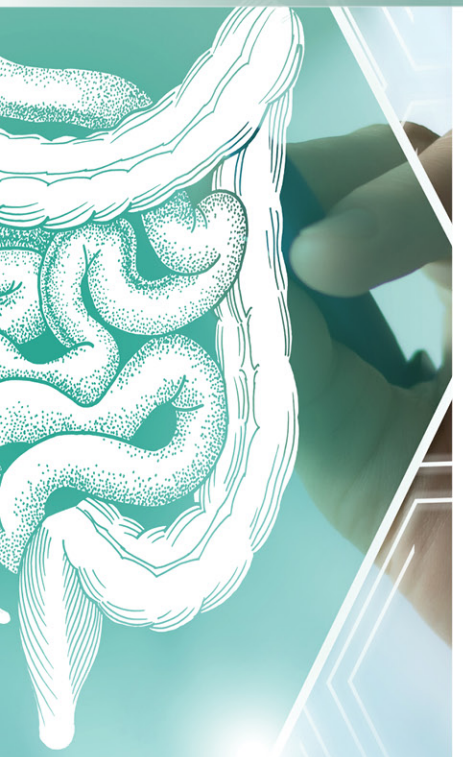
	Remission	Mild	Moderate to Severe	Fulminant
Stools per day, n	Formed	<4	>6	>10
Blood in stool	None	Intermittent	Frequent	Continuous
Urgency	None	Mild, occasional	Often	Continuous
Hemoglobin	Normal	Normal	<75% of normal	Transfusion
ESR, mm/h	<30	<30	>30	>30
CRP	Normal	Increased	Increased	Increased
FCP, mg/kg	<150-200	>150-200	>150-200	>150-200
Mayo subscore (endoscopy)	0-1	1	2-3	3
UC Endoscopic Index of Severity	0-1	2-4	5-8	7-8

Rubin DT, et al. *Am J Gastroenterol*. 2019;114(3):384-413.
Pabla BS, Schwartz DA. *Gastroenterol Clin North Am*. 2020;49(4):671-688.

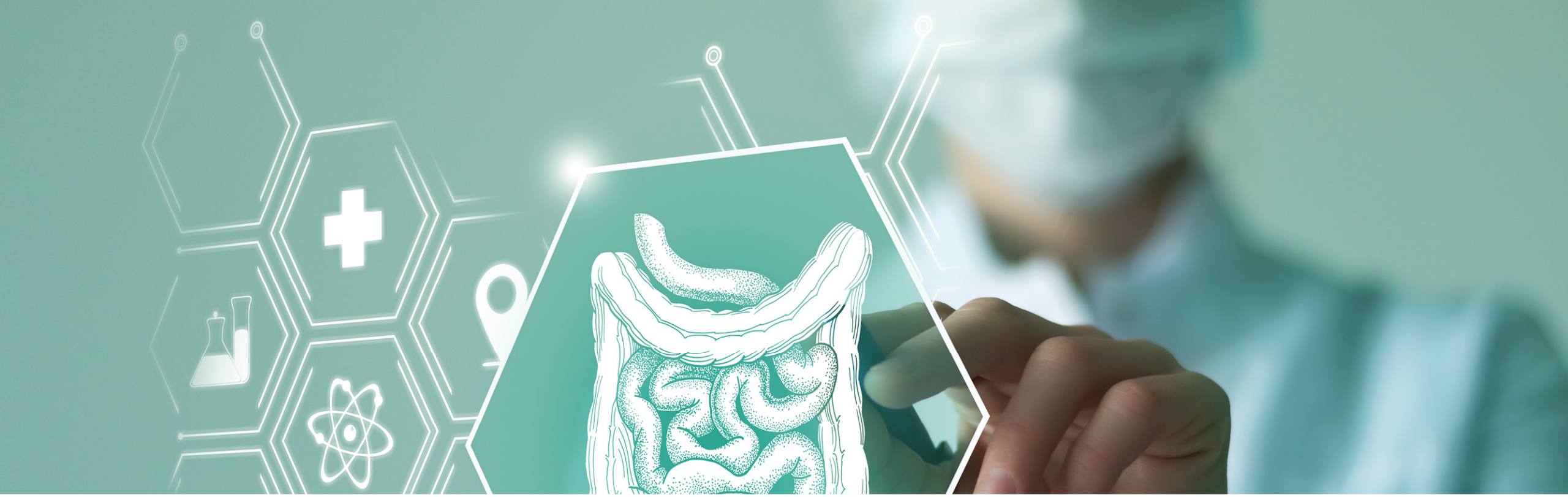
Discussion

1. What are potential treatment options?
2. What is the recommended monitoring plan?
3. What are the roles of the IBD team members?

Conclusion



- UC is a systemic chronic inflammatory condition with increasing incidence and prevalence and significant effect on quality of life
- Several treatment options are currently available, but have limitations
- S1PR modulators are a newer class of medications available for treatment of moderate to severe UC
- Management by an IBD multidisciplinary team can help improve patient outcomes



Thank you!