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GASTROENTEROLOGY DATA TRENDS 2023

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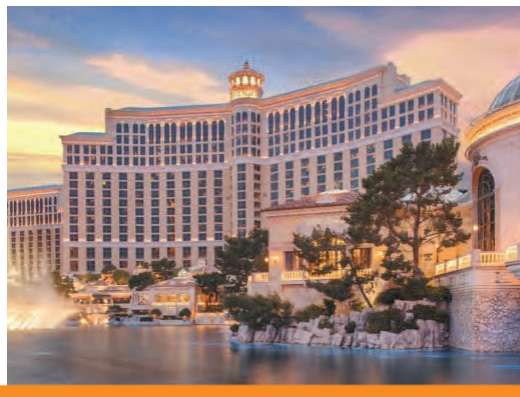

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Common Abbreviations

AGA, American Gastroenterological Association; **AI,** artificial intelligence; **BMI**, body mass index; **CRC**, colorectal cancer; **CT**, computed tomography; **FDA,** US Food and Drug Administration; **GERD**, gastroesophageal reflux disease; **GI**, gastroenterology or gastrointestinal; **IBD**, inflammatory bowel disease; **IBS**, irritable bowel syndrome; **ICU**, intensive care unit; **MR**, magnetic resonance; **WHO**, World Health Organization.

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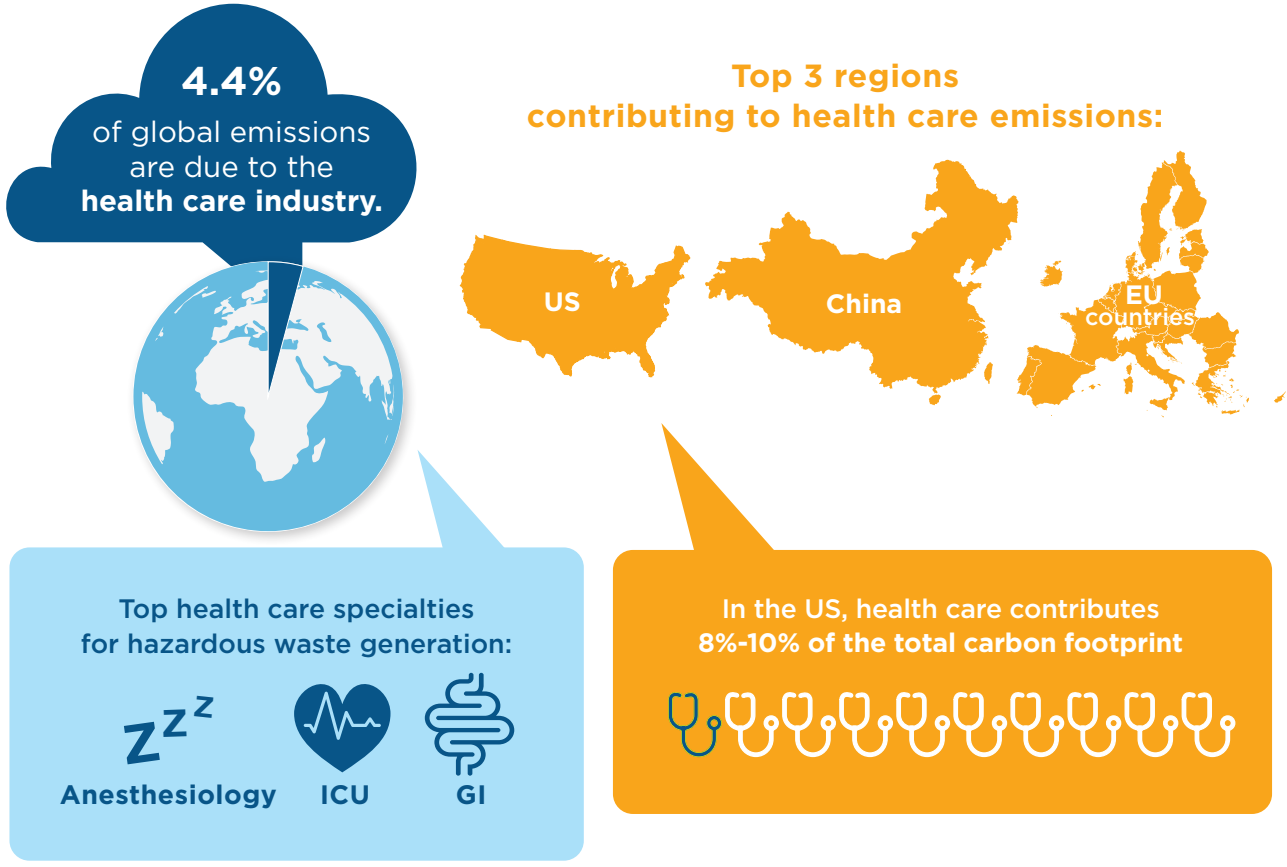
Gastroenterology and Climate Change:
Assessing and Mitigating Impacts

Swapna Gayam, MD, FACG

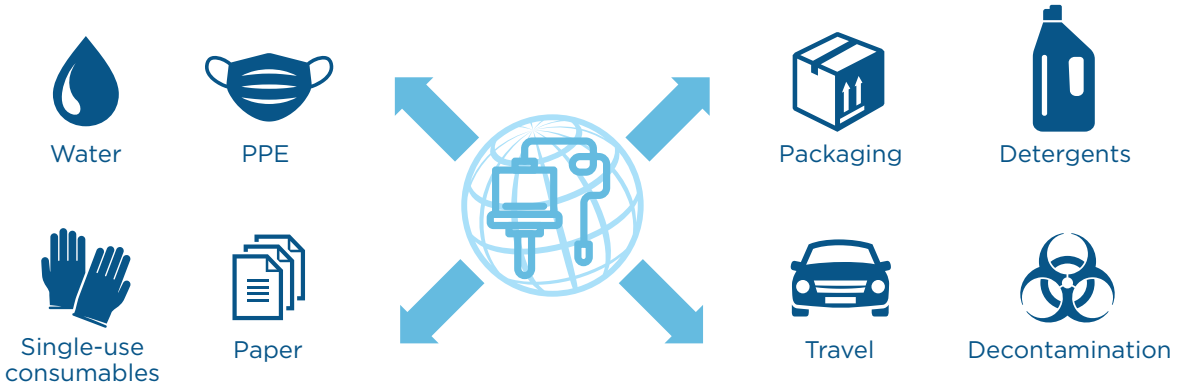
The health care industry, particularly in the United States, is a large contributor to climate change, with the field of GI being one of the top contributors to overall and hazardous waste emissions.[1,2] One of the most important components of the carbon footprint of GI is the sheer volume of procedures performed. More than 18 million endoscopic procedures are performed each year in the US alone, and a significant portion are of low-value.[3,4] Every endoscopic procedure uses substantial resources, including single-use consumables, water (including sterile water bottles), electricity, paper, and personal protective equipment (PPE), among others.[5-7] Within the field of endoscopy, disposable endoscopes are an important area of concern; a complete switch to disposables could increase waste by up to 40%.[8] Along with the impact of GI on climate change, there is also a bidirectional effect—climate change affects GI and liver health, worsening symptoms for many.[9-11]

To combat the contribution of GI to climate change, a GI multisociety task force was formed comprising members from 4 major US societies, including the AGA.[12] A strategic plan was proposed to decrease the carbon footprint of GI, similar to a plan proposed by European and British societies.[13,14] Multiple recent studies have shown positive effects of interventions such as waste segregation in reducing overall endoscopic waste and increasing recycled waste.[15] Such measures also have been shown to have financial benefits, with estimated cost savings of around $5.4 billion dollars in 5 years.[16]

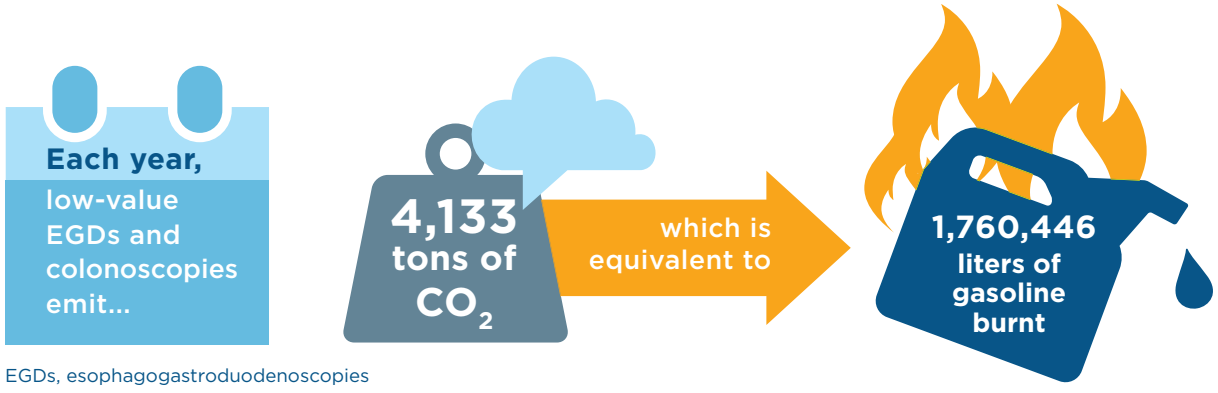
Health Care and GI Carbon Footprint[1,2]



Factors Contributing to Carbon Footprint of Endoscopy[5]

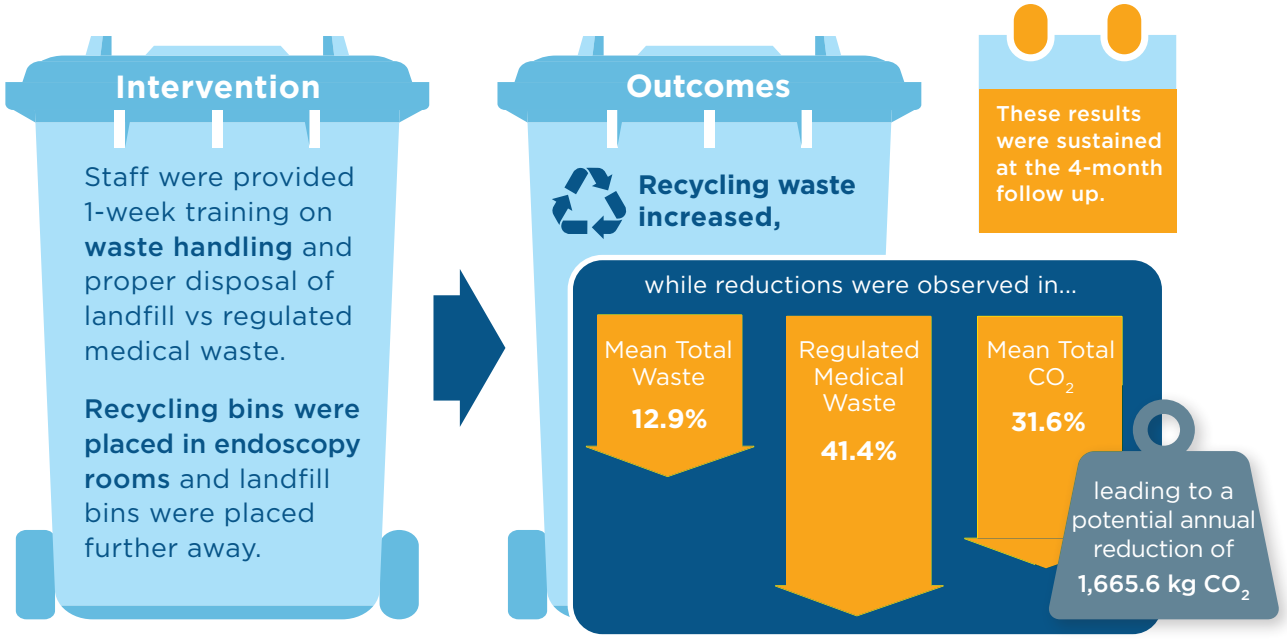


Carbon Footprint of Low-Value GI Endoscopy Procedures[4]

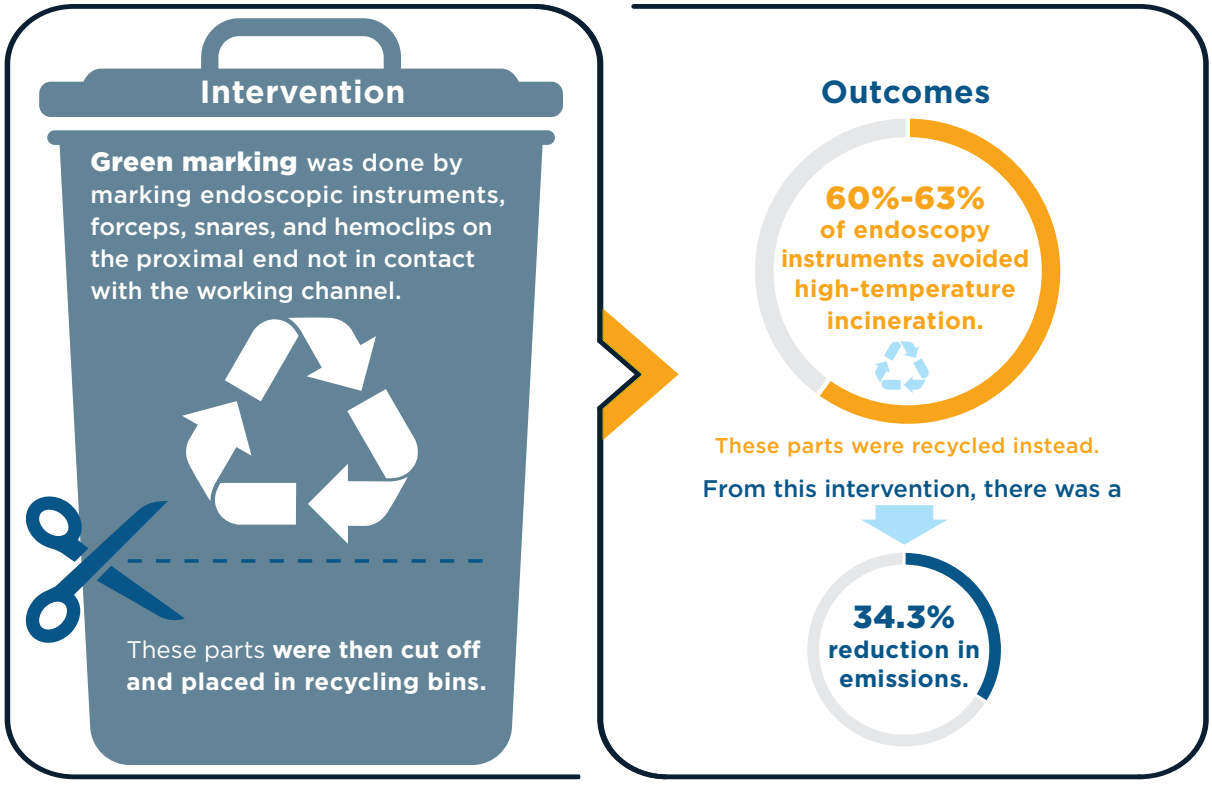


EGDs, esophagogastroduodenoscopies

Intervention to Decrease Endoscopy Waste Generation[15]



Impact of Sustainability Intervention to Reduce Instrument Landfill Waste[17]



GI Multisociety Task Force Plan to Improve Sustainability[12]

Clinical setting	Assess **carbon footprint and waste generation in clinical practice** and encourage implementation of **environmentally friendly practices** and sustainability metrics
Education	**Educate health care leadership, practitioners, and patients** about the effects of **GI on climate change and effects of climate change on GI health**
Research	Promote **research on the effect of climate change on GI health** and on **low-cost practices to improve carbon footprint** of GI
Society efforts	Implement **organizational measures across all societies** to decrease carbon footprint
Intersociety efforts	**Collaborate with other GI societies nationally and globally** to promote sustainability
Industry	Work with **industry to encourage environmentally friendly** product design and sustainability
Advocacy	Educate and advocate for **policies in government agencies**

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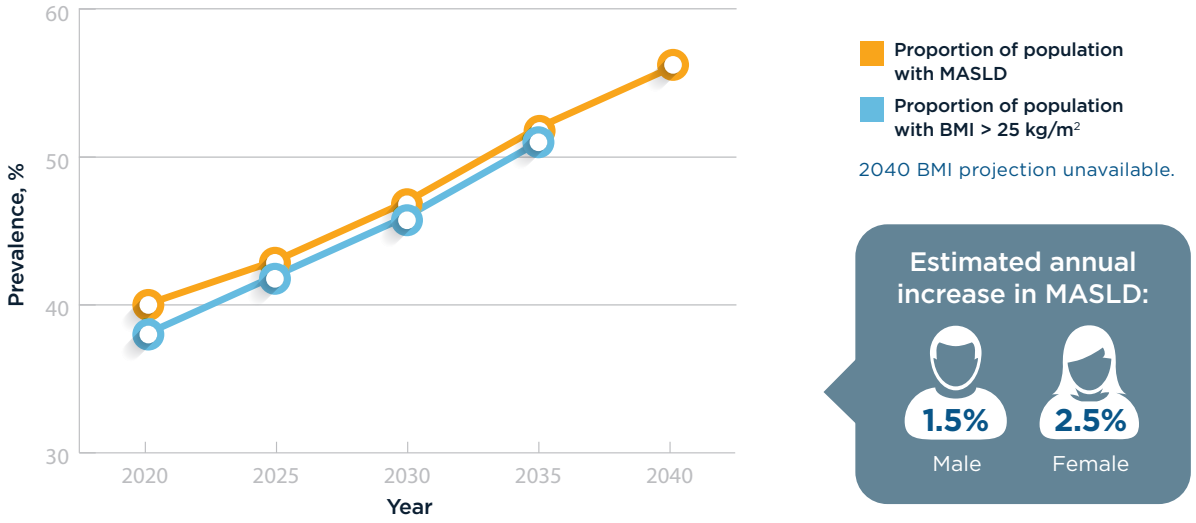
MASLD/MASH and Weight Loss

Arpan Mohanty, MD, MSc

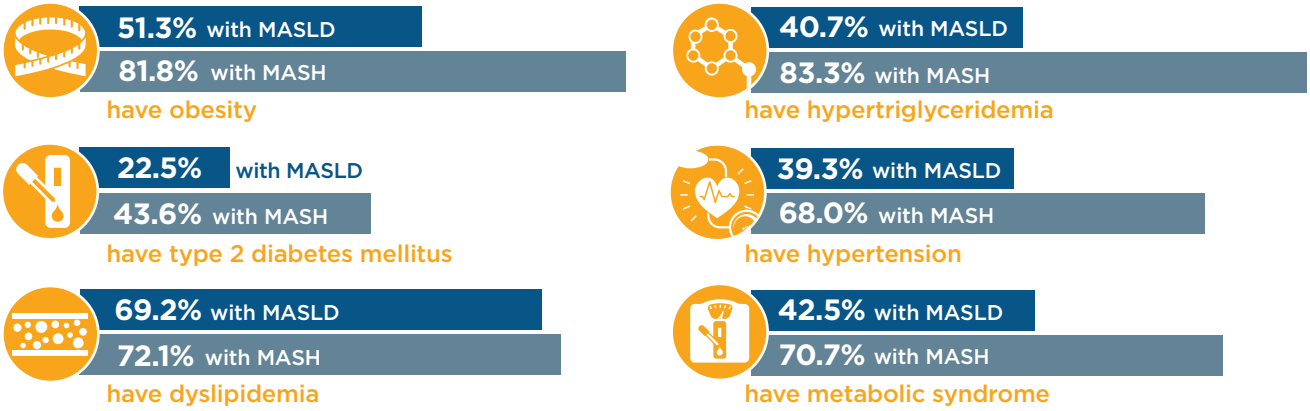
Metabolic dysfunction–associated steatotic liver disease (MASLD), formerly known as nonalcoholic fatty liver disease (NAFLD), affects about 20% to 30% of the world population. About 1 in 4 of these patients have metabolic dysfunction–associated steatohepatitis (MASH; formerly known as nonalcoholic steatohepatitis)—which is associated with significant morbidity and mortality. Although they affect the liver, these conditions are associated with extrahepatic diseases such as obesity, type 2 diabetes mellitus, and cardiovascular disease, which contribute to poor outcomes. Evidence has shown that weight loss is a key intervention for reduction of steatosis, MASH, and fibrosis in both lean and obese patients with MASLD. Modifications recommended for weight loss include potential pharmacological, surgical, or endoscopic approaches (in cases of severe obesity) that can prevent progression of MASLD as well as improve diabetes and reduce cardiovascular events.[1-3]

Global MASLD Prevalence Forecast, 2020–2040[4,5]

The projected increase in prevalence of MASLD mirrors that of overweight/obesity.

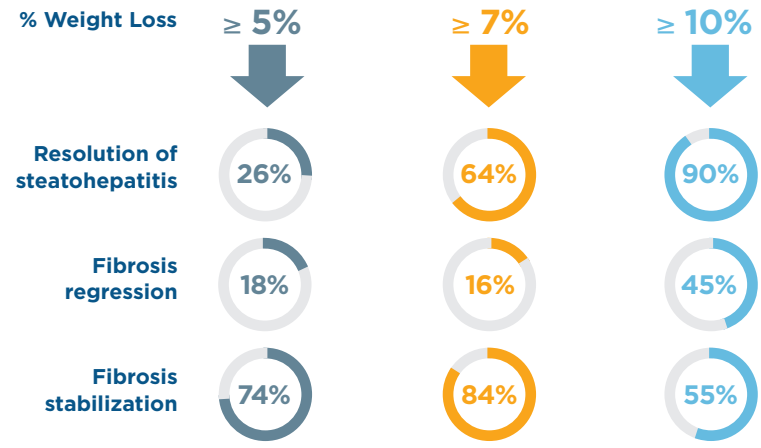


Prevalence of Metabolic Comorbidities With MASLD and MASH[1]



The AGA recommends that all patients with MASH and metabolic comorbidities be treated per American College of Cardiology/American Heart Association guidelines along with weight management strategies.[1]

Potential Weight Loss Benefits in Patients With MASH[6,7]



% of patients who achieved these results after 1 year of weight loss interventions

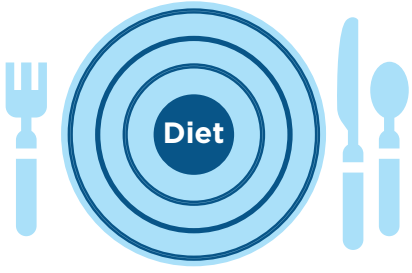
A systematic review[7] of studies of behavioral interventions, pharmacotherapy, and surgery estimated that every **1 kg of weight loss is associated with a...**

- ☑ **0.83-U/L reduction in ALT**
- ☑ **0.56-U/L reduction in AST**
- ☑ **0.77% point reduction in steatosis**

As assessed by histology or radiology

Weight Loss Interventions[1,8-13]

Lifestyle modifications[1,8,9]



Patients should target

1,200 daily kcals

1,500 daily kcals

or **500-1,000** kcal daily deficit

Following the **Mediterranean Diet** is associated with less liver fat accumulation and reduced risk of new fatty liver.[7]

Structured weight loss programs and anti-obesity medications tend to be more successful than clinician and dietician advice during visits.[9]

Patients should target

150-300 minutes of moderate-intensity aerobic exercise per week

75-150 minutes of vigorous-intensity aerobic exercise per week

Pharmacotherapy[10-13]

There are no FDA-approved medications for MASLD. However, many pharmacologic therapies for type 2 diabetes mellitus and weight loss may be beneficial to the liver and should be considered in select patients. These drugs have additional extrahepatic effects such as improvement in insulin sensitivity and cardiovascular risk reduction.

Hepatic Effects of Drugs Known to Cause Weight Loss

Drug	Primary comorbid indication	Known hepatic effect (patient population)	Expected mean weight loss
GLP1 receptor agonist			
Semaglutide[10]	T2DM, weight management	Improvement in steatosis and steatohepatitis, no proven effect on fibrosis (in patients with MASLD)	**4.8%-12.5%**[a]
Liraglutide[11]	T2DM, weight management	Improvement in steatohepatitis, no proven effect on fibrosis (in patients with MASLD)	**5.5%**
Tirzepatide[12]	T2DM	Improvement in steatosis on MRI (in patients with T2DM)	**7.9%-11.7%**[a]
SGLT2 inhibitor			
Empagliflozin[13]	T2DM, chronic kidney disease, heart failure	Improvement in steatosis on MRI (in patients with T2DM)	**2.8%**

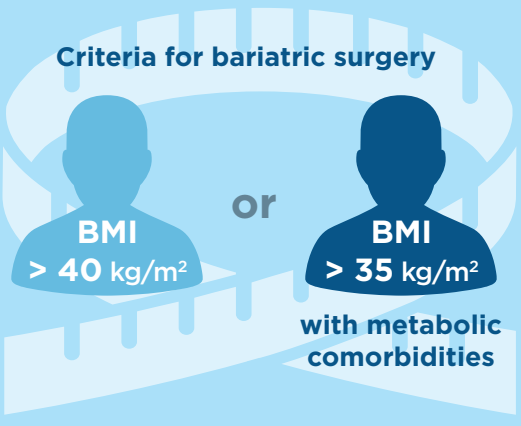
These drugs have been studied in phase 2 trials in patients with NAFLD (now called MASLD) or in T2DM and have not yet received FDA approval for MASLD.

GLP1, glucagon like peptide-1: SGLT2, sodium glucose cotransporter: T2DM, type 2 diabetes mellitus

[a]Depending on dosage of drug.

Bariatric surgery[1]

Bariatric surgery can resolve MASH, improve hepatic fibrosis, and lead to sustained weight loss. Currently MASLD is not an indication for bariatric surgery, but such **surgery should be considered in patients with MASLD without cirrhosis who meet criteria for surgery.** Evidence about the effectiveness of endoscopic bariatric techniques, particularly for liver disease, is still insufficient.



Digital Tools in the Management of IBS/Functional GI Disorders

Eric D. Shah, MD, MBA, FACG

IBS can be a highly debilitating condition that negatively affects a person's quality of life. The recent emergence of digital tools designed to help patients and caregivers better manage IBS and functional GI disorders has facilitated the formation of a new health care model with an ever-evolving landscape. These tools range from mobile apps, virtual health platforms, and wearable devices, to the use of AI and digital therapeutics.

These tools serve several purposes—such as telehealth services, symptom tracking, food journals, cognitive behavioral therapy, gut-directed hypnotherapy, and patient education—and can help increase patients' access to safe, effective treatments.[1,2] Further, AI-driven tools can assist health care providers in facilitating more accurate diagnoses and creating more personalized treatment plans.

Regular exercise, stress management, and low-FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) dietary strategies are often recommended as nonpharmacologic approaches to IBS management.[3-6] With the assistance of digital tools, patients can not only receive care, but also gain disease-specific knowledge, self-manage their diet, track physical activity, monitor stress and IBS symptoms remotely, and improve their quality of life with this new and expanding type of health care model.

Mobile and Web-Based Apps[7]

App features to help patients manage IBS:

- ✓ Symptom tracking
- ✓ Cognitive behavioral therapy
- ✓ Gut-directed hypnotherapy
- ✓ Food and symptom journals
- ✓ Meal planning
- ✓ Stress management techniques
- ✓ Medication reminders

FDA-cleared apps:

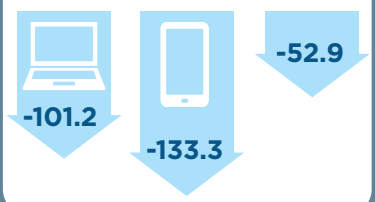
Mahana IBS (Mahana Therapeutics)[7]

Cognitive behavioral therapy program that helps adult patients address the psychological and emotional aspects of IBS

≤ **$90**/session

10 sessions/ 12 weeks

IBS-SSS reduction at 12 months (from cohort mean of 265 points):



Regulora (metaMe Health)[7]

Gut-directed hypnotherapy program that helps address IBS-related abdominal pain

≤ **$75**/session

7 sessions/ 12 weeks

31% reported a **≥ 30% reduction** in abdominal pain intensity

45% experienced a **≥ 30% improvement** in stools with normal consistency

IBS-SSS, IBS Symptom Severity Score.

Virtual Health Platforms[8]

A recent study assessed patient satisfaction with using telehealth services for IBS management[8]:

Of the 44,789 surveys sent:

- **5,832 (13.0%)** patients responded
- **1,632 (3.6%)** had Rome IV IBS

Among 1,314 (22.5%) respondents with IBS and prior telehealth use:

898 (68.3%) were satisfied

286 (21.8%) felt neutral

130 (9.9%) were dissatisfied

1033 (78.6%) would use telehealth services again

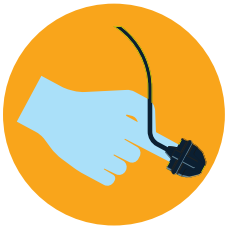
(Mean age: 52.6 years [17.4]; 84.9% female; and 59.4% non-Hispanic White, 29.0% Hispanic, and 5.6% non-Hispanic Black)

Wearable Devices[9,10]

Wearable devices are intended to provide insight into potential correlations between symptoms and lifestyle factors. To date, such claims have not been evaluated by the FDA.[9]

Smartwatches and fitness trackers[10]

Integrate with IBS management apps to monitor physical activity, sleep patterns, heart rate, and stress levels



Biofeedback devices[10]

Measure heart rate variability

Collect feedback on stress levels

Stress monitors[10]

Measure factors like heart rate, skin conductance, or temperature to provide insights into stress levels throughout the day

Artificial Intelligence[11-15]

AI and natural language processing algorithms are being evaluated to see if they can help:

Analyze symptom descriptions, food logs, and other data to create personalized recommendations[11]

Create predictive models to anticipate symptom flare-ups and suggest preventive measures[12]

Provide treatment decision support[12]

AI applications are being evaluated in research studies[13] to see if they can help with:

Mental health support:

Chatbots or virtual therapists could offer cognitive behavioral therapy, relaxation exercises, and stress management[14]

Remote monitoring:

Devices collect real-time health data, such as heart rate, blood glucose levels, or activity levels[15]

Treatment/medication adherence:

Provide reminders, track medication schedules, and offer educational resources[15]

Long COVID and the Gastrointestinal System: Emerging Evidence

Daniel E. Freedberg, MD, MS, and Lin Chang, MD, AGAF

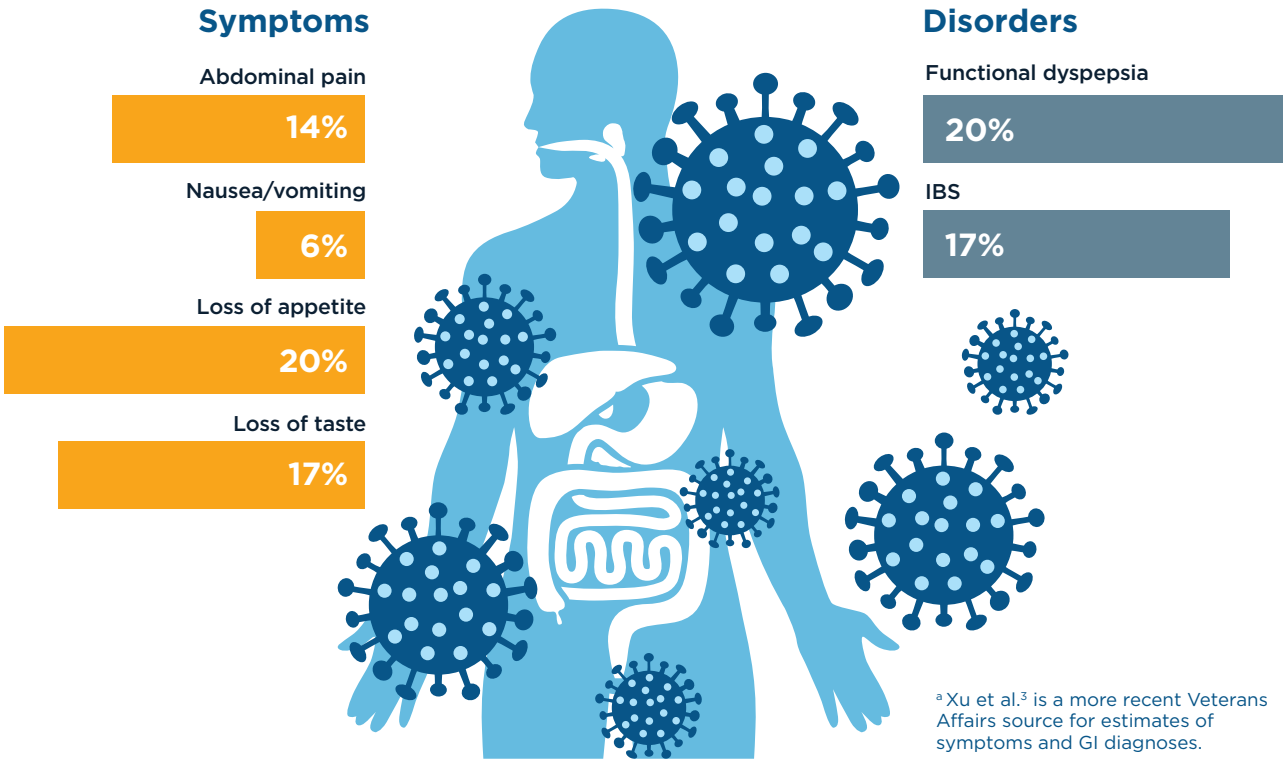
Long COVID is defined by WHO as the development or continuation of new symptoms 3 months after COVID-19 infection, with symptoms lasting for at least 2 months that have no alternative explanation.[1,2]

Long COVID often includes neuropsychiatric and GI symptoms.[1,2] GI manifestations are well known during acute COVID-19, but less understood in long COVID.[2] It is estimated that 12% of patients with long COVID have GI symptoms, which may include heartburn, constipation, abdominal pain, nausea and vomiting, and diarrhea.[2,3] Patients with long COVID also frequently receive new GI diagnoses, such as functional dyspepsia, IBS, GERD, peptic ulcer disease, and acute pancreatitis.[2,3]

Proposed causes of GI symptoms post-COVID are varied, including alterations in the gut microbiome and serotonergic signaling and changes downstream from the angiotensin-converting enzyme 2 receptor.[2,4] The serotonergic theory links the pathophysiology of long COVID GI symptoms to post-infection IBS and other disorders of gut-brain interaction. Like IBS, long COVID with GI symptoms is frequently associated with non-GI comorbidities, especially mental health comorbidities.[5]

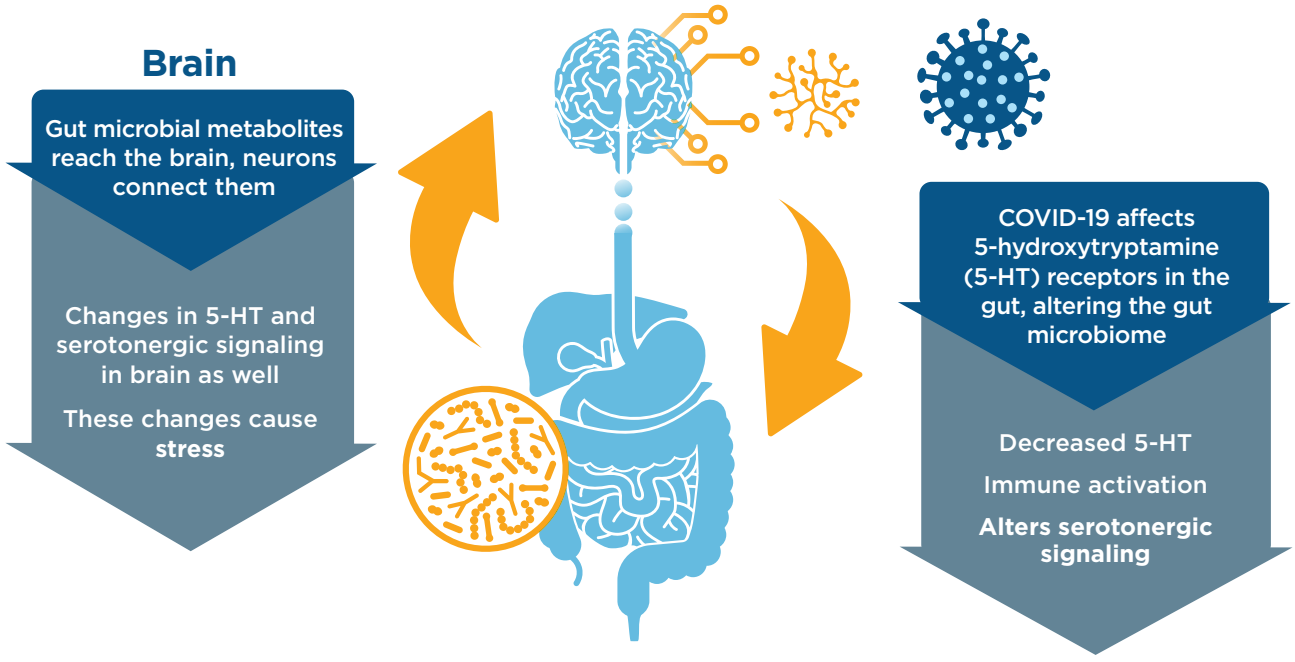
Currently, no specific treatments are endorsed for long COVID GI symptoms.[4] Management focuses on symptom relief and using protocols for the relevant GI disorders; when IBS is present, an integrated and multidisciplinary approach is recommended.[4,6] This multifaceted approach, when possible, can be especially helpful in patients with long COVID because of the number of comorbidities and varied symptoms.[1,4-6] Long COVID and its multitude of symptoms have a profound negative effect on productivity and quality of life in patients.[1,7] Thus, finding efficient treatment approaches is a top priority in navigating the complexity of long COVID and its GI manifestations.

Prevalence of GI Symptoms and Disorders Among Patients With Long COVID[2,a]



[a] Xu et al.[3] is a more recent Veterans Affairs source for estimates of symptoms and GI diagnoses.

Proposed Mechanism of Long COVID[4]

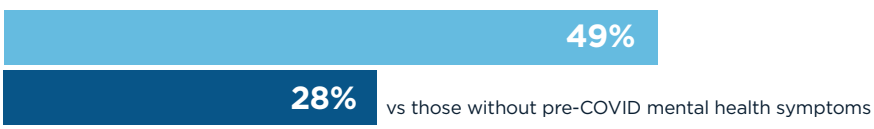


Mental Health and GI Symptoms After COVID-19 Recovery[5]

6 months after recovering from COVID-19:

- **37% reported mental health symptoms**
- **29% reported GI symptoms**

Patients with pre-COVID-19 mental health symptoms were more likely to report GI symptoms post-COVID:



Patients who reported sadness or anxiety post-COVID were more likely to have GI symptoms:

Overall, patients were more likely to have post-COVID GI symptoms if they had...

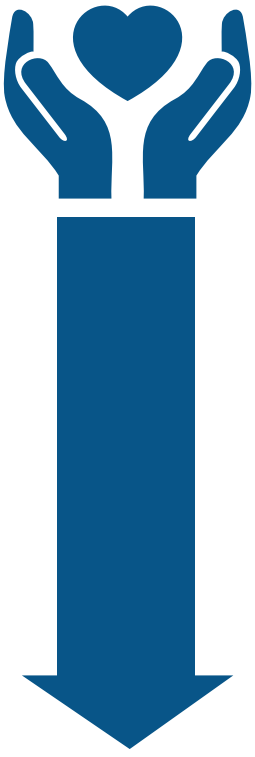
Both pre- and post-COVID mental health symptoms: 16.5x more likely

Only post-COVID mental health symptoms: 6.2x more likely

...compared to patients who had no mental health symptoms.

The Impact of Long COVID on Quality of Life and Economics[8-10]

Health-related quality-of-life impairments in those with self-identified long COVID



40.2%
Mobility problems

13.2%
Self-care-related impairment

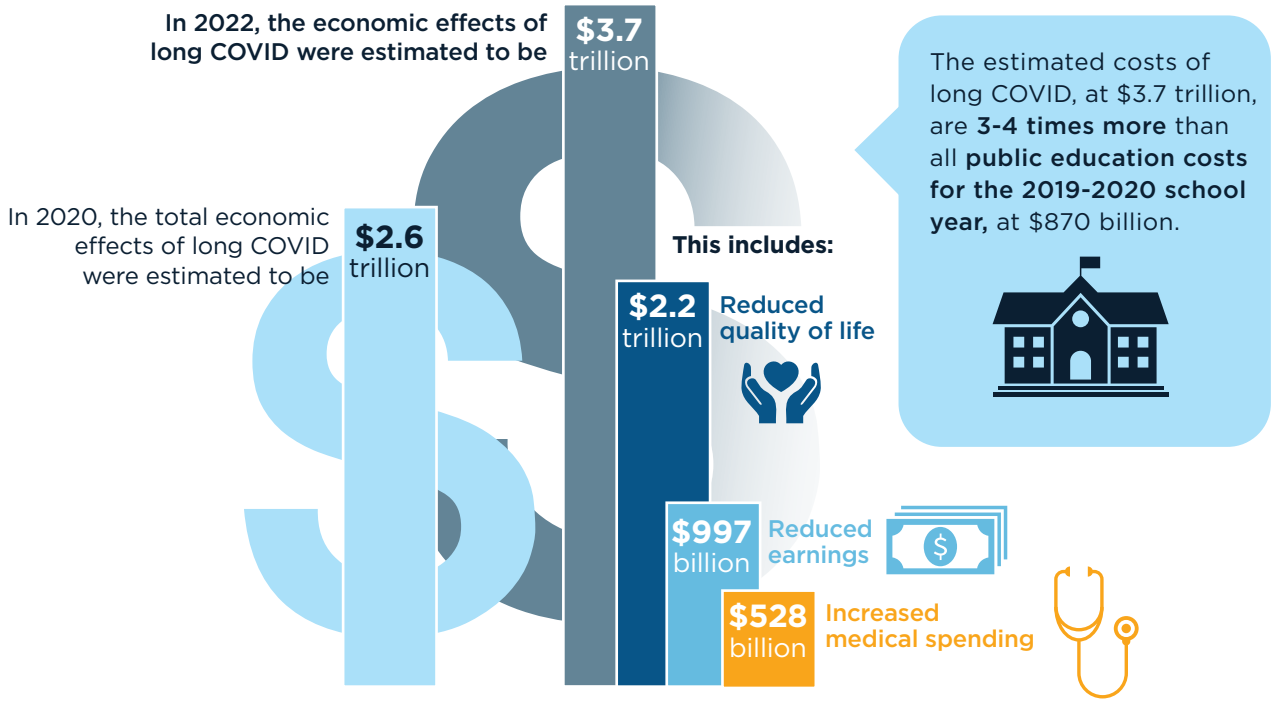
62.7%
Problems doing normal household activities

74.6%
Moderate pain and discomfort

15.0%
Extreme pain or discomfort

42.6%
Anxiety and depressive feelings

Economic effects of long COVID in the US



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Germline Genetic Testing in CRC:
Implications for Familial and Population-Based Testing

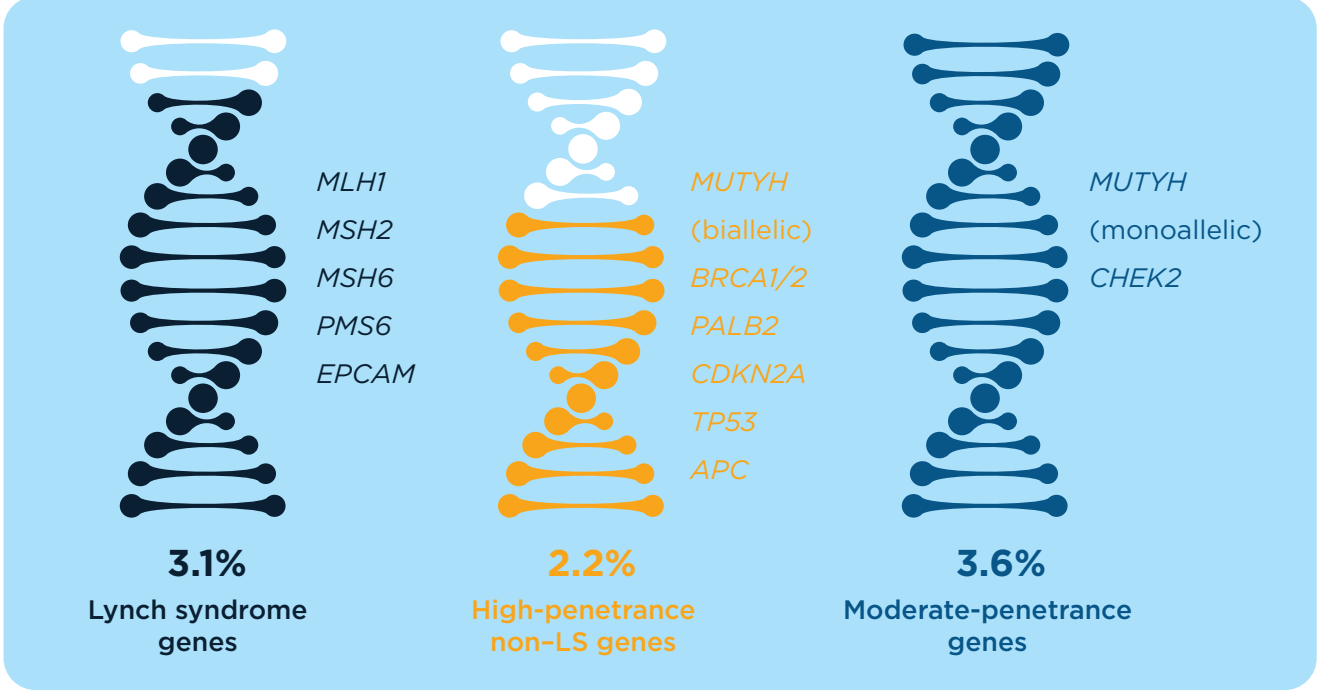
Fay Kastrinos, MD, MPH

Scientific advances in DNA sequencing technologies have allowed for the simultaneous testing of multiple genes associated with an inherited susceptibility of CRC. As a result, CRC screening and treatment protocols have been affected by results from germline multigene panel testing,[1,2] including but not limited to Lynch syndrome (LS), the most common inherited CRC syndrome, which is associated with mismatch repair deficiency and tumor microsatellite instability.[3]

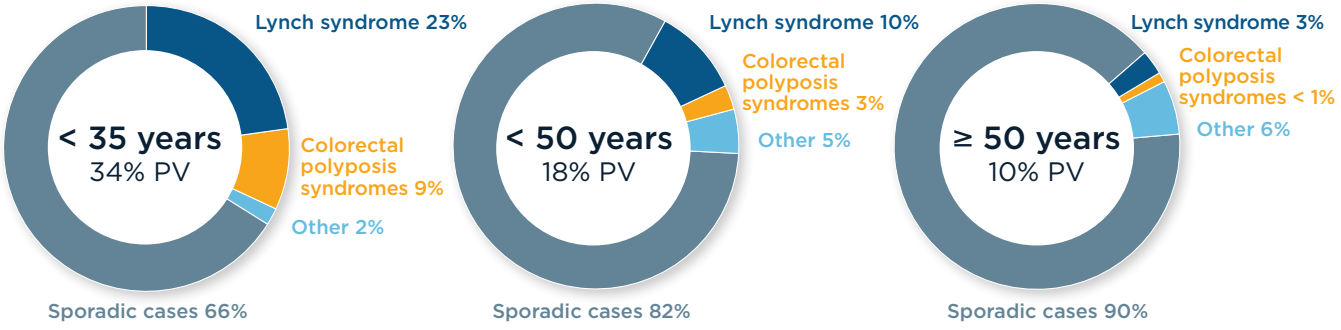
A demographic of concern for which systematic genetic risk assessment is recommended is the early-onset (EO) population—people diagnosed with CRC before age 50 years. More than 15% of EO-CRC cases are due to pathogenic variants in cancer susceptibility genes[3,4] irrespective of family cancer history, most of which are LS–related and most frequently detected as age at CRC diagnosis decreases.[5] Thus, multiple international guidelines recommend that all individuals diagnosed with EO-CRC undergo germline genetic testing[6]; these results have implications for at-risk relatives, particularly when a familial pathogenic variant is detected and specialized cancer screening or risk-reducing strategies can be pursued in family members, many of whom are cancer-free. The alarming increase in EO-CRC rates has led to a focus on the assessment of familial and inherited CRC risk to optimize screening recommendations among the general population.[7,8]

Furthermore, universal germline testing of *all* individuals with CRC is cost-effective and provides optimal surveillance for cancer survivors while also increasing the pool of at-risk, cancer-free relatives who benefit most from cancer screening and prevention protocols.[9] In fact, indications for universal germline testing for relatives of individuals with CRC to personalize screening recommendations also supports future consideration for population-based germline genetic testing for LS genes, as the prevalence of the condition is 1 in 279 individuals, with more than 1 million individuals in the United States affected but unaware of their diagnosis.[10,11]

Frequency of Germline Pathogenic Gene Variants in Patients with CRC[12]



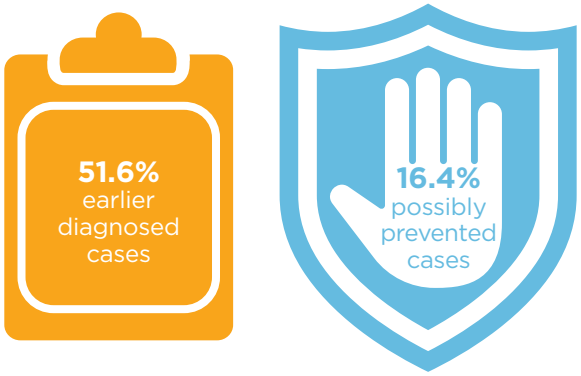
Frequency of LS in Patients With CRC[5,13,14]



PV, pathogenic variant

Early-Onset CRC: Familial and Genetic Risk Assessment[7,8]

In adults with CRC, it is estimated that applying **family history and hereditary screening guidelines or screening by age 45** would have resulted in:



1 in 4 patients with CRC aged 40-49 years **met early screening criteria** based on family history.

98.4% of these patients could have been **recommended screening initiation at a younger age** than when they were initially diagnosed.

CDC Recommendations for Population-Based Lynch Syndrome Testing[10,11]

Recommended universal population screening for: Lynch syndrome

Considerations to make this initiative effective:

1. Get carriers to act on screening recommendation
2. Assess availability of resources
3. Make sure screening does not affect current health care inequities

1 in 279 in the population carry mutations in mismatch repair genes *(MLH1, MSH2, MSH6, PMS2)*, which are all LS genes.

Evolution of Targeted Therapies
for *C difficile*

Sahil Khanna, MBBS, MS, FACG, AGAF

Clostridioides difficile (C difficile) is a gram-positive anaerobic bacillus that produces toxins (enterotoxin A [TcdA] and cytotoxin B [TcdB]) that can damage the lining of the gastrointestinal tract and cause potentially life-threatening disease of the large intestine.[1] *C difficile* infection (CDI) is not only a common nosocomial infection, but an increasing incidence is seen in the community with a high disease burden, as reinfection often occurs.[2] *C difficile* is very contagious and spreads easily via contaminated surfaces that act as reservoirs (especially in healthcare settings); the spores of this bacterium are very hard to kill.[3]

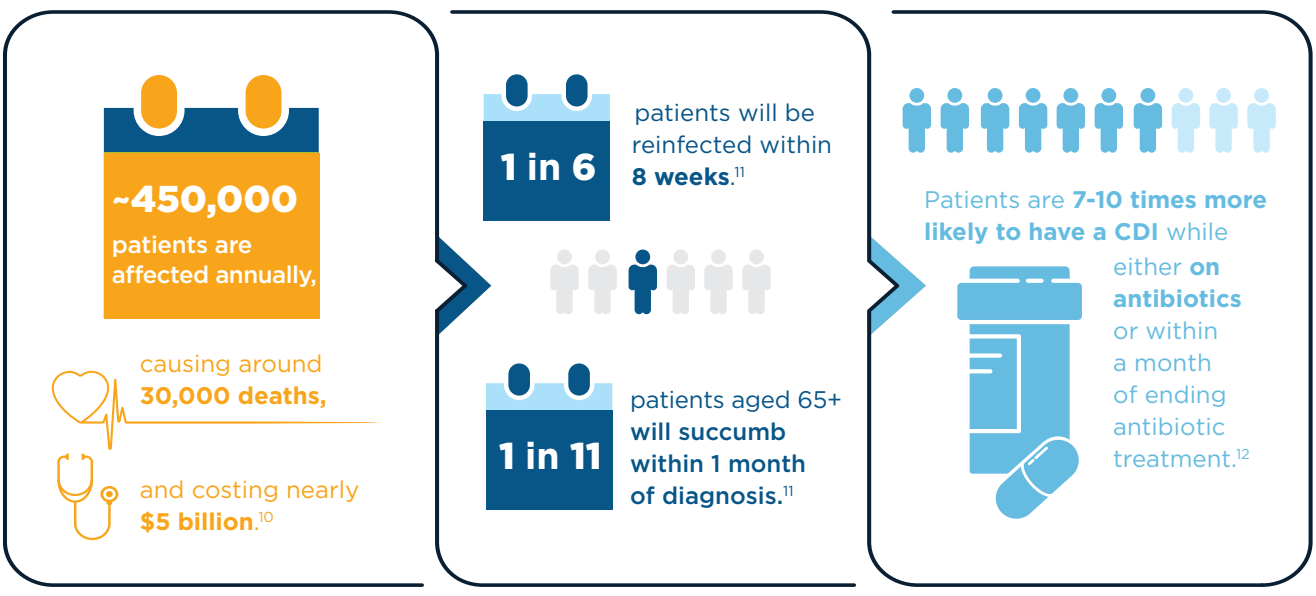
CDI often occurs either while the patient is taking antibiotics or soon after finishing them, as the intestinal (gut) microbiome and metabolism are altered, which allows for *C difficile* to proliferate.[4] People with a compromised immune system or other comorbid conditions, or who are older than 65 years of age, are especially prone to CDI.[1]

Antibiotics are the first-line treatment for primary and recurrent CDI (rCDI), although they do not always kill the spores,[3] and the dysbiosis caused by antibiotics within the gut environment still needs to be addressed.[4] A humanized monoclonal antibody (an immunoglobulin G against the cytotoxin B), in combination with antibiotics, has been shown to help prevent rCDI in a subset of patients.[5]

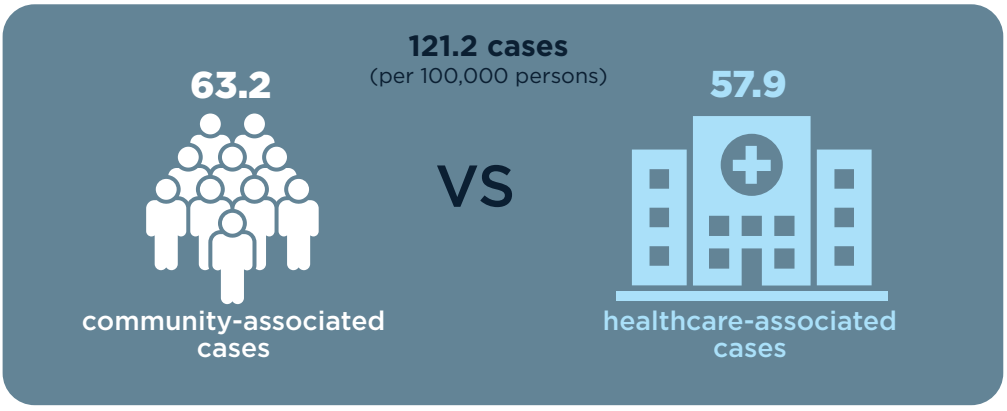
Therapies that help restore the gut microbiota to a eubiotic state, especially after antibiotic treatment for *C difficile,* have been shown to help manage and prevent future rCDI.[6] Experimental fecal microbiota transplantation (FMT) performed under enforcement discretion from the FDA is one such microbiota restoration therapy.[3] Microbes harvested from healthy donor stool are transplanted into the intestine of a recipient (usually via colonoscopy) to help restore the gut microbiome and prevent CDI.[7]

Two therapeutics are approved by the FDA for prevention of rCDI. The first one was approved in 2022 and is a rectal administration product derived from human donor stool (fecal microbiota live-jslm [Rebyota]).[8] The other is an oral capsule (fecal microbiota spores live-bprk [Vowst]) containing live spores from fecal microbiota.[6] With these exciting advances, we can now begin to address additional unmet needs with future research into microbiota restoration therapies.[9]

Burden of CDI in the United States[10-12]



Incidence Rate of CDI[13]

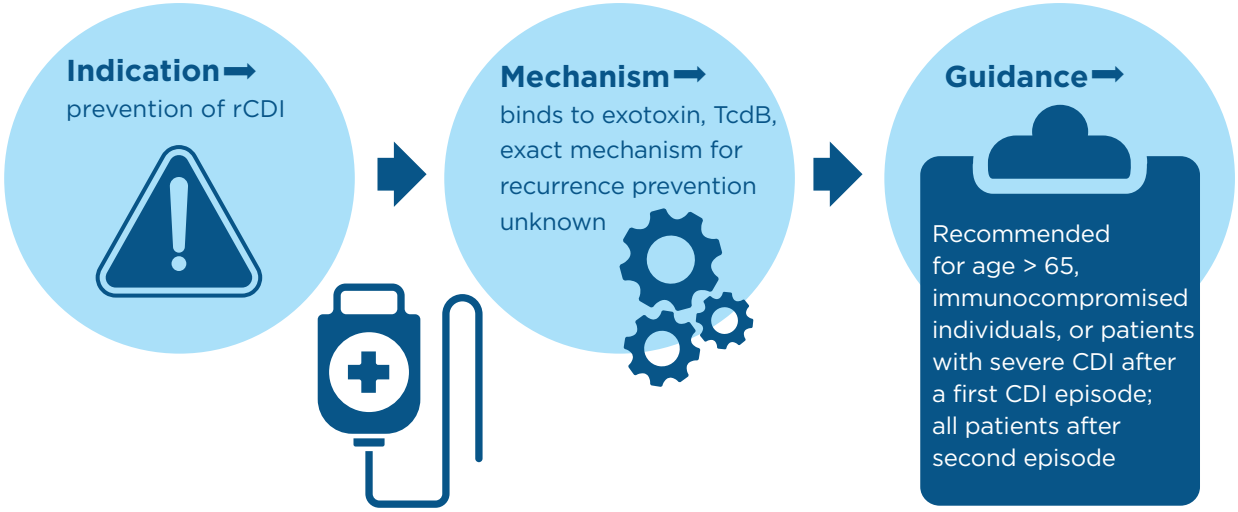


Antibiotics for Treating CDI[14-16]

	Indication	Guidance
Fidaxomicin[14] (Macrolide antibiotic)	First-line therapy for *C difficile* infection	Preferred agent for treating CDI
Vancomycin[14,15] (Glycopeptide antibiotic)	First-line therapy for *C difficile* infection	An acceptable alternative to fidaxomicin per Infectious Diseases Society of America guidelines[16]
Metronidazole[16] (Nitroimidazole antibiotic)	Not FDA-approved for *C difficile*	Recommended only for nonsevere CDI cases when fidaxomicin or vancomycin are unavailable

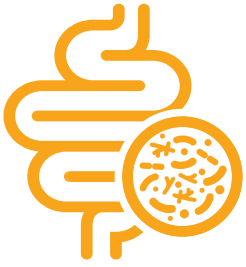
While antibiotics can kill *C difficile*, other beneficial bacteria also suffer, especially with use of vancomycin, throwing off the balance of the microbiome – and leaving the gut susceptible to rCDI.

Monoclonal Antibody for Treating CDI: Bezlotoxumab[17,18]



Solving the Underlying Issue: Restoring Gut Microbiota Through Microbiome Restoration[4,6]

The human gut microbiota comprises **~10^{13} bacterial cells ➡10×** more than the total number of human cells in the body.[4]



The colon is the most heavily colonized organ in the gastrointestinal tract ➡it contains **> 70% of all the microbes in the human body.**[4]

rCDI prevention **success rates are ≥ 90%** with **microbiota restoration** therapies vs ≤ 50% with courses of antibiotics.[6]

Standardized Microbiota Restoration Therapies to Prevent rCDI[6,8,19-21]

	Description	Status
Fecal microbiota spores live-bprk (Vowst)[6,8,19]	Orally administered, donor stool-derived capsule for the prevention of rCDI; improves the composition and abundance of the gut microbiota	**FDA-approved in 2023** based on results from phase 3 clinical trials ECOSPOR III
Fecal microbiota live-jslm (Rebyota)[20]	One-dose, microbiota-based enema therapy for rCDI; reduces rCDI and improves the composition and abundance of the gut microbiota	**FDA-approved in 2022** based on positive data from the phase 3 PUNCH CD3 study
VE303[6]	Oral capsules taken after antibiotic treatment for prevention of CDI	**FDA granted Orphan Drug Designation in 2017**; phase 2 CONSORTIUM published positive results in 2023; phase 3 trial is planned for 2023
RBX7455[21]	Nonfrozen, orally administered, investigational live biotherapeutic for rCDI	Positive phase 1 results announced in 2021; found to be safe and effective in preventing rCDI
CP101[6]	An investigational, orally administered microbiome therapeutic designed to prevent rCDI	Global phase 3 trial PRISM4 was discontinued as of 2022

Unmet needs of FMT[9]

- ➤ The number of FMT stool donor centers has been declining—especially since the pandemic.
- ➤ Studies of FMT have varied widely in stool quantity, preparation, storage, and administration procedures and more adverse events from FMT are being reported.
- ➤ Two standardized microbiota-based therapies are FDA-approved for rCDI fulfiling this unmet need.

Harnessing the Power of AI to Enhance Endoscopy: Promises and Pitfalls

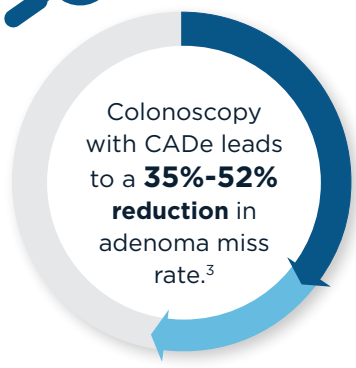
Eugenia Uche-Anya, MD, MPH

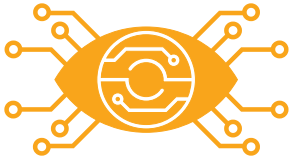
The availability of AI technologies to improve the overall quality of GI endoscopy has grown significantly over the last decade.[1] AI algorithms have shown promise in detecting malignant, infectious, and inflammatory diseases in both upper and lower GI endoscopy imaging.[2] Most AI research in endoscopy is currently focused on computer-aided detection (CADe) and diagnosis (CADx), but other computer vision tools are also in development, ranging from algorithms to measure IBD activity to dysplasia detection in Barrett's esophagus.[2,3]

Improved lesion detection and classification with AI can support clinical decision-making and lead to better patient outcomes, cost savings, clinician time management, and other efficiencies within the health care system.[2-7] However, some substantial barriers must be overcome and current projections must be validated with clinical and real-world trials before we can fully rely on AI in these settings.[8-11]

Where Are We Today?[3-6]

Detection With CADe





AI-assisted optical diagnosis without magnification can **diagnose > 90%** of diminutive (≤ 5 mm) rectosigmoid polyps.[4]

Diagnosis With CADx

Studies have shown high accuracy in diagnosing colorectal polyps compared to endoscopists[5,6]:

CADx – **~95%**

Expert endoscopists – **82%**

Novice endoscopists – **67%**

What Is the Potential Impact of AI?[7]

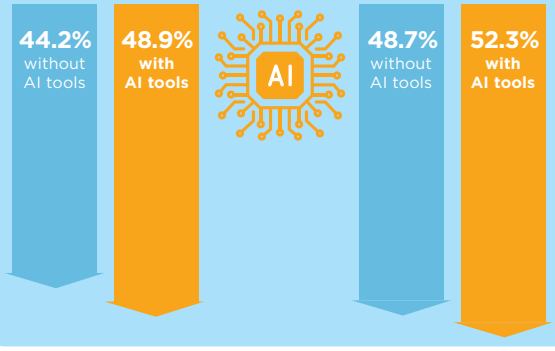
A simulation of AI implementation in colonoscopy screening for average-risk US patients estimates...

Annual prevention of

2,089
CRC-related deaths

7,194
additional CRC cases

Relative Reduction
(compared with no screening)



Projections are based on a modeling study. Future randomized clinical trials will provide clarity on the true impact of AI in practice.

What Barriers Still Remain?[1,8-11]

Technological barriers[1,8]

Unlike endoscopists who can multitask,

deep-learning models focus on 1 disease or task at a time.

It is difficult to identify inadequacies in training data until validation or clinical trial testing results are available.

Cost[7]

Upfront implementation of AI leads to some initial new costs. However, its long-term use has cost-saving benefits.

$57-94 per-person savings for colonoscopy screening with AI

$290 million yearly US savings due to decreased cases of CRC and related deaths

Endoscopist beliefs[9]

- Their current adenoma detection rate is sufficient
- CADe is too early in development
- Prices will drop once competition increases
- Wait and see what experts will do
- AI competes with physician expertise

A survey of US endoscopists found that only 40% are willing to perform optical diagnosis.[10]

Race and sex inequities[11]

Selective bias

Research efforts have focused largely on conditions impacting White populations, often overlooking populations of high unmet need.

Data collection

Algorithms have been developed from skewed data sets (ie, predominantly White and male), and may not have the same predictive power in other populations.

Variable selection

Many disease predictors are stronger in some populations than others. Including such factors in AI algorithms leads to discrepancies in patient outcomes.

Post-development considerations

AI tools developed with the best intentions may still lead to biased outcomes in real-life applications. Continued auditing and assessment of efficacy across subpopulations can lead to an improvement in racial disparities.

CADe models have lower sensitivity and higher miss rates for proximal polyps and sessile serrated lesions, which affect Black patients at higher rates.

Black patients have:

- **20% higher** CRC incidence
- **40% higher** CRC deaths
- **30% higher** interval CRC risk

The Future of AI in Medical Practice[12,13]

More large-scale AI applications on the horizon will continue to benefit both clinicians—aiding in informed decision-making and freeing up time—and patients, in the form of improved outcomes. However, many challenges must still be overcome before we can fully rely on these technologies.

Generalist Medical Artificial Intelligence (GMAI) Clinician-Based Solutions

Technology	Capabilities	Opportunities
Chatbots 	Chatbot-powered patient support apps can provide a holistic view of the patient's case by analyzing data like symptom descriptions, monitor readings, medication logs, and other self-reported information. Chatbots can reduce the need for clinician intervention, although the clinician would still be available.	Clear communication, using lay terms without compromising accuracy Diverse data collection Patient-collected data may be more prone to error or less reliable
Bedside decision support 	New bedside tools can provide more detailed explanations of changes to patient status and recommendations for future care using free-text explanations and data summaries.	Compare potential treatments and estimate possible effects while staying within therapeutic guidelines
Interactive notetaking 	AI models can preemptively draft reports by monitoring electronic records and clinician-patient conversations. This technology can reduce administrative overhead and give clinicians more time to spend with patients.	Accurate interpretation of speech signals, medical jargon, and abbreviations Proper contextualization of information
Text-to-image generation 	AI models such as GLIDE (Guided Language to Image Diffusion for generation Editing) could be used to generate histopathology images for research purposes using textual prompts.	In the future, text-to-image generative models such as GLIDE and subsequent improved model architectures could be used in medical image analysis applications, solving the problem of researchers having to train generative models on each niche domain.

Components that trigger paradigm shifts in AI and GMAI models

Key advantages: Controllability, Adaptability, Applicability

Key considerations: Validation, Verification, Social biases, Privacy, Scale

The Evolving Role of Surgery for IBD

Julie K.M. Thacker, MD, FACS, FASCRS

IBD can involve chronic inflammation of the GI tract that can lead to severe complications. Although surgery is not the first-line treatment for IBD, it may need to be considered in certain situations, such as when medication and other measures are ineffective, or in cases of certain disease manifestations.

Surgical options have evolved significantly over the years, with advancements in techniques, technologies, and perioperative care that have helped improve outcomes, reduce complications, and enhance quality of life for patients—especially with minimally invasive surgery (MIS) approaches. MIS procedures for IBD include multiport laparoscopy and robotics.[1,2] Now, colorectal surgeons have specialized to treat IBD—especially in MIS fashion when applicable.[3]

Successful IBD management requires a collaborative approach—and surgeons play a crucial role within this framework.[4] A multidisciplinary approach ensures that individuals with IBD receive comprehensive care that integrates medical, surgical, and supportive interventions (ie, nutrition, mental health, and peer support)—maximizing treatment outcomes, minimizing complications, and improving the overall quality of life for patients with IBD who require surgery.

Key Developments in the Field of Surgery for IBD[1-3,5]

Minimally invasive techniques[1,2]

Laparoscopic and robotic-assisted surgeries have revolutionized IBD surgery with several advantages over traditional open surgery.

Full-capacity recovery after minimally invasive surgery is often achieved in **2 to 4 weeks**.[3]

Stricturoplasty techniques[5]

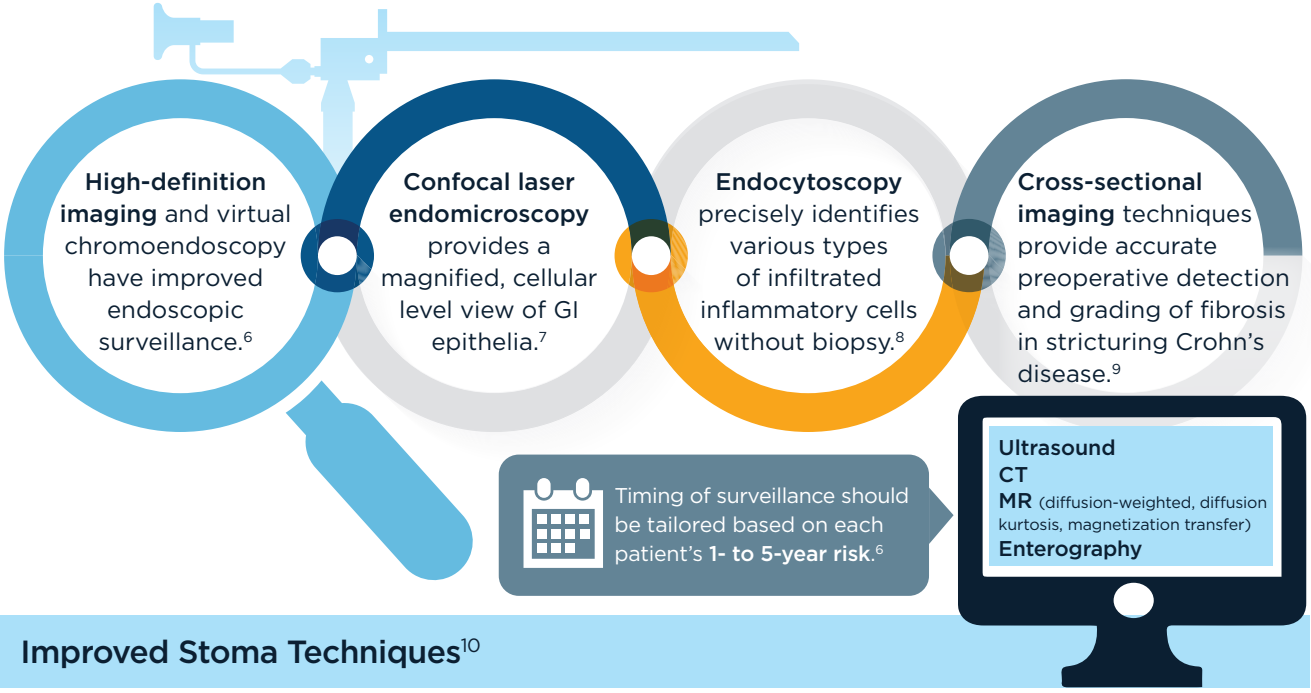
These procedures involve widening narrowed segments of the intestines in Crohn's disease.

Advancements allow for tailoring the procedure to the specific characteristics of the strictures.

Chronic strictures < 7 cm may sometimes be amenable to stricturoplasty rather than resection.

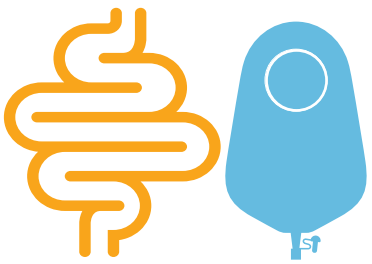
Enhanced Imaging and Preoperative Planning[6-9]

Advanced imaging modalities have improved the preoperative assessment of IBD by providing detailed information about disease location, extent, and complications.



Improved Stoma Techniques[10]

✓ Surgeons now have a good understanding of stoma placement, which can result in improved functionality and patient comfort.



✓ Advances in stoma care products have enhanced the management of ostomies, leading to better patient outcomes.[10]

Progress in Perioperative Management[11,12]

Perioperative management has drastically changed the experience of the early postoperative phase for patients with IBD.[11]

- Nutrition support
- Analgesia strategies
- Fluid resuscitation
- Rehabilitative exercise programs

Enhanced recovery after surgery (ERAS) protocols have been shown to improve long-term outcomes while reducing[12]:

- Complication rate **by 20%-50%**
- Length of hospital stays
- Need for ICU care

Multidisciplinary Team Follow-up[4-12]

Multidisciplinary team follow-up is crucial for optimizing the outcomes of IBD surgery—including coordination of care and information sharing across all team members.[4]



Diagnosis and preoperative assessment

Gastroenterologists play a central role in diagnosing and managing IBD by:

Working closely with surgeons to assess the severity and extent of disease

Evaluating treatment responses

Performing endoscopic procedures to visualize the GI tract and collecting tissue samples for pathology evaluation

Surgical planning and decision-making

Surgeons collaborate with gastroenterologists and nurses to:

Determine the appropriate timing for surgery

Develop a personalized surgical plan for patients

Assess the disease characteristics, medical history, response to medications, and overall health status to determine the optimal surgical approach

Radiologists:

Interpret imaging studies to provide detailed anatomical information that aids in surgical planning

Patient education and counseling

Specialized IBD nurses play a vital role in providing patient education and counseling before surgery:

Educate patients about the surgical procedure, potential risks and benefits, postoperative care, and lifestyle modifications

Offer emotional support, address concerns, and help patients navigate the entire surgical process

References

Gastroenterology and Climate Change: Assessing and Mitigating Impacts

1. Karliner J et al. *Eur J Public Health*. 2020;30(suppl 5):v311. doi:10.1093/eurpub/ckaa165.843
2. Vaccari M et al. *Waste Manag Res*. 2018;36(1):39-47. doi:10.1177/0734242X17739968
3. Peery AF et al. *Gastroenterology*. 2019;156(1):254-272.e11. doi:10.1053/j.gastro.2018.08.063
4. Sorge A et al. *Endoscopy*. 2023;55(suppl 2):S72-S73. doi:10.1055/s-0043-1765172
5. Maurice JB et al. *Lancet Gastroenterol Hepatol*. 2020;5(7):636-638. doi:10.1016/S2468-1253(20)30157-6
6. Gayam S. *Am J Gastroenterol*. 2020;115(12):1931-1932. doi:10.14309/ajg.0000000000001005
7. Siau K et al. *Tech Innov Gastrointest Endosc*. 2021;23(4):344-352. doi:10.1016/j.tige.2021.06.005
8. Namburar S et al. *Gut*. 2022;71(7):1326-1331. doi:10.1136/gutjnl-2021-324729
9. Haddock R et al. *Am J Gastroenterol*. 2022;117(3):394-400. doi:10.14309/ajg.0000000000001604
10. Donnelly MC et al. *J Hepatol*. 2022;76(5):995-1000. doi:10.1016/j.jhep.2022.02.012
11. Leddin D, Macrae F. *J Clin Gastroenterol*. 2020;54(5):393-397. doi:10.1097/MCG.0000000000001336.
12. Pohl H et al. *Hepatology*. 2022;76(6):1836-1844. doi:10.1002/hep.32810
13. Rodríguez de Santiago E et al. *Endoscopy*. 2022;54(8):797-826. doi:10.1055/a-1859-3726
14. Sebastian S et al. *Gut*. 2023;72(1):12-26. doi:10.1136/gutjnl-2022-328460
15. Cunha Neves JA et al. *Gut*. 2023;72(2):306-313. doi:10.1136/gutjnl-2022-327005
16. Kaplan S et al. *Issue Brief (Commonw Fund)*. 2012;29:1-14. PMID: 23214181.
17. López-Muñoz P et al. *Gut*. 2023;gutjnl-2023-329544. doi:10.1136/gutjnl-2023-329544

MASLD/MASH and Weight Loss

1. Younossi ZM et al. *Gastroenterology*. 2021;160(3):912-918. doi:10.1053/j.gastro.2020.11.051
2. Cusi K et al. *Endocr Pract*. 2022;28(5):528-562. doi:10.1016/j.eprac.2022.03.010.
3. Rinella ME et al. *Hepatology*. 2023;77(5):1797-1835. doi:10.1097/HEP.0000000000000323.
4. World obesity atlas 2023. World Obesity Day. Published March 2023. Accessed July 23, 2023. https://www.worldobesityday.org/assets/downloads/World_Obesity_Atlas_2023_Report.pdf
5. Le MH et al. *Clin Mol Hepatol*. 2022;28(4):841-850. doi:10.3350/cmh.2022.0239
6. Vilar-Gomez E et al. *Gastroenterology*. 2015;149(2):367-78.e5. doi:10.1053/j.gastro.2015.04.005
7. Koutoukidis DA et al. *Metabolism*. 2021;115:154455. doi:10.1016/j.metabol.2020.154455
8. Ma J et al. *Gastroenterology*. 2018;155(1):107-117. doi:10.1053/j.gastro.2018.03.038.
9. Ahern AL et al. *Lancet*. 2017;389(10085):2214-2225. doi:10.1016/S0140-6736(17)30647-5.
10. Newsome PN et al; NN9931-4296 Investigators. *N Engl J Med*. 2021;384(12):1113-1124. doi:10.1056/NEJMoa2028395
11. Armstrong MJ et al. *Lancet*. 2016;387(10019):679-690. doi:10.1016/S0140-6736(15)00803-X
12. Gastaldelli A et al. *Lancet Diabetes Endocrinol*. 2022;10(6):393-406. doi:10.1016/S2213-8587(22)00070-5
13. Kahl S et al. *Diabetes Care*. 2020;43(2):298-305. doi:10.2337/dc19-0641

Digital Tools in the Management of IBS/Functional GI Disorders

1. Hasan SS et al. *Neurogastroenterol Motil*. 2023;35(4):e14554. doi:10.1111/nmo.14554
2. Peters SL et al. *Neurogastroenterol Motil*. 2023;35(4):e14533. doi:10.1111/nmo.14533
3. Zhou C et al. *Neurogastroenterol Motil*. 2019;31(2):e13461. doi:10.1111/nmo.13461
4. Staudacher HM et al. *Nat Rev Gastroenterol Hepatol*. 2023;1-15. doi:10.1038/s41575-023-00794-z
5. Qin HY et al. *World J Gastroenterol*. 2014;20(39):14126-14131. doi:10.3748/wjg.v20.i39.14126
6. Varjú P et al. *PLoS One*. 2017;12(8):e0182942. doi:10.1371/journal.pone.0182942
7. Saleh ZM et al. *Am J Gastroenterol*. 2023. doi:10.14309/ajg.0000000000002220
8. Yu C et al. *Clin Transl Gastroenterol*. 2022;13(9):e00515. doi:10.14309/ctg.0000000000000515
9. Jagannath B et al. *Inflamm Bowel Dis*. 2020;26(10):1533-1542. doi:10.1093/ibd/izaa191
10. Zhang H et al. *J Nutr*. 2023;153(4):924-939. doi:10.1016/j.tjnut.2023.01.026
11. Karakan T et al. *Gut Microbes*. 2022;14(1):2138672. doi:10.1080/19490976.2022.2138672
12. Kordi M et al. *Inform Med Unlocked*. 2022;29:100891. doi:10.1016/j.imu.2022.100891
13. Gubatan J et al. *World J Gastroenterol*. 2021;27(17):1920-1935. doi:10.3748/wjg.v27.i17.1920
14. Boucher EM et al. *Expert Rev Med Devices*. 2021;18(suppl 1):37-49. doi:10.1080/17434440.2021.2013200
15. Babel A et al. *Front Digit Health*. 2021;3:669869. doi:10.3389/fdgth.2021.669869

Long COVID and the Gastrointestinal System: Emerging Evidence

1. Lutchmansingh DD et al. *Semin Respir Crit Care Med*. 2023;44(1):130-142. doi:10.1055/s-0042-1759568
2. Choudhury A et al. *Therap Adv Gastroenterol*. 2022;15:17562848221118403. doi:10.1177/17562848221118403
3. Xu E et al. *Nat Commun*. 2023;14(1):983. doi:10.1038/s41467-023-36223-7
4. Freedberg DE, Chang L. *Curr Opin Gastroenterol*. 2022;38(6):555-561. doi:10.1097/MOG.0000000000000876
5. Blackett JW et al. *Gastroenterology*. 2022;162(2):648-650.e2. doi:10.1053/j.gastro.2021.10.040
6. Chey WD et al. *Gastroenterology*. 2021;160(1):47-62. doi:10.1053/j.gastro.2020.06.099
7. Líška D et al. *Front Public Health*. 2022;10:975992. doi:10.3389/fpubh.2022.975992
8. Moens M et al. *Front Public Health*. 2022;10:991572. doi:10.3389/fpubh.2022.991572
9. Cutler DM. The economic cost of long COVID: an update. Scholars at Harvard. Published July 2022. Accessed July 20, 2023. https://scholar.harvard.edu/sites/scholar.harvard.edu/files/cutler/files/long_covid_update_7-22.pdf
10. National Center for Education Statistics (2023). Public School Expenditures. Condition of Education. US Department of Education, Institute of Education Sciences. Accessed August 4, 2023. https://nces.ed.gov/programs/coe/indicator/cmb

Germline Genetic Testing in CRC: Implications for Familial and Population-Based Testing

1. Weiss JM et al. *J Natl Compr Canc Netw*. 2021;19(10):1122-1132. doi:10.1164/jnccn.2021.0048
2. Samadder NJ et al. *JAMA Oncol*. 2021;7(2):230-237. doi:10.1001/jamaoncol.2020.6252
3. Pearlman R et al; Ohio Colorectal Cancer Prevention Initiative Study Group. *JAMA Oncol*. 2017;3(4):464-471. doi:10.1001/jamaoncol.2016.5194
4. Stoffel EM et al. *Gastroenterology*. 2018;154(4):897-905.e1. doi:10.1053/j.gastro.2017.11.004

5. Stoffel EM, Murphy CC. *Gastroenterology*. 2020;158(2):341-353. doi:10.1053/j.gastro.2019.07.055
6. Cavestro GM et al; Associazione Italiana Familiarità Ereditarietà Tumori; Collaborative Group of the Americas on Inherited Gastrointestinal Cancer; European Hereditary Tumour Group, and the International Society for Gastrointestinal Hereditary Tumours. *Clin Gastroenterol Hepatol*. 2023;21(3):581-603.e33. doi:10.1016/j.cgh.2022.12.006
7. Gupta S et al. *Cancer*. 2020;126(13):3013-3020. doi:10.1002/cncr.32851
8. Stanich PP et al. *Gastroenterology*. 2021;160(5):1850-1852. doi:10.1053/j.gastro.2020.12.009
9. Rustgi S et al. Universal screening strategies for the identification of Lynch syndrome in colorectal cancer patients and at-risk relatives. Research forum lecture #263 presented at: Digestive Disease Week (DDW) 2023; May 6-9, 2023; Chicago, IL.
10. Tier 1 genomic applications and their importance to public health. Centers for Disease Control and Prevention. Reviewed March 6, 2014. Accessed August 15, 2023. https://www.cdc.gov/genomics/implementation/toolkit/tier1.htm
11. Win AK et al. *Cancer Epidemiol Biomarkers Prev*. 2017;26(3):404-412. doi:10.1158/1055-9965.EPI-16-0693
12. Yurgelun MB et al. *J Clin Oncol*. 2017;35(10):1086-1095. doi:10.1200/JCO.2016.71.0012
13. Pearlman R et al. *JCO Precis Oncol*. 2021;5:PO.20.00525. doi:10.1200/PO.20.00525
14. Patel R, Hyer W. *Frontline Gastroenterol*. 2019;10(4):379-387. doi:10.1136/flgastro-2018-101053

Evolution of Targeted Therapies for *C difficile*

1. Di Bella S et al. *Toxins (Basel)*. 2016;8(5):134. doi:10.3390/toxins8050134
2. Turner NA, Anderson DJ. *Clin Colon Rectal Surg*. 2020;33(2):98-108. doi:10.1055/s-0040-1701234
3. Czepiel J et al. *Eur J Clin Microbiol Infect Dis*. 2019;38(7):1211-1221. doi:10.1007/s10096-019-03539-6
4. Sekirov I et al. Gut microbiota in health and disease. *Physiol Rev*. 2012;90(3):859-904. doi:10.1152/physrev.00045.2009
5. Posteraro B et al. *Expert Opin Biol Ther*. 2018;18(4):469-476. doi:10.1080/14712598.2018.1452908
6. Khanna S. *J Intern Med*. 2021;290(2):294-309. doi:10.1111/joim.13290
7. Seekatz AM et al. *Therap Adv Gastroenterol*. 2022;15:17562848221134396. doi:10.1177/17562848221134396
8. Federal Drug Administration. FDA approves first fecal microbiota product: Rebyota approved for the prevention of recurrence of *Clostridioides difficile* infection in adults [press release]. Published November 30, 2022. Accessed July 14, 2023. https://www.fda.gov/news-events/press-announcements/fda-approves-first-fecal-microbiota-product
9. Bafeta A et al. *Ann Intern Med*. 2017;167(1):34-39. doi:10.7326/M16-2810
10. Guh AY et al; Emerging Infections Program Clostridioides difficile Infection Working Group. *N Engl J Med*. 2020;382(14):1320-1330. doi:10.1056/NEJMoa1910215
11. Centers for Disease Control and Prevention. What is *C. diff*? Last reviewed September 7, 2022. Accessed July 14, 2023. https://www.cdc.gov/cdiff/what-is.html
12. Centers for Disease Control and Prevention. Patients and families: be antibiotics aware. *C. diff* infection—Am I at risk? Accessed July 14, 2023. https://www.cdc.gov/cdiff/pdf/FS-Cdiff-PatientsFamilies-508.pdf
13. Centers for Disease Control and Prevention. 2019 annual report for the emerging infections program for *Clostridioides difficile* infection. Last reviewed February 1, 2023. Accessed July 14, 2023. https://www.cdc.gov/hai/eip/Annual-CDI-Report-2019.html
14. Kelly CR et al. *Am J Gastroenterol*. 2021;116(6):1124-1147. doi: 10.14309/ajg.0000000000001278
15. Tariq R et al. *Therap Adv Gastroenterol*. 2021;14:1756284821994046. doi:10.1177/1756284821994046
16. McDonald LC et al. *Clin Infect Dis*. 2018;66(7):e1-e48. doi: 10.1093/cid/cix1085
17. Wilcox MH et al. *N Engl J Med*. 2017;376(4):305-317. doi:10.1056/NEJMoa1602615
18. Guilleman MM et al. *Gene Ther*. 2023;30:455-462. doi: 10.1038/s41434-021-00236-y
19. Sims MD et al; ECOSPOR IV Investigators. *JAMA Netw Open*. 2023;6(2):e2255758. doi:10.1001/jamanetworkopen.2022.55758
20. Microbiota Restoration Therapy for Recurrent *Clostridium Difficile* Infection (PUNCHCD2). ClinicalTrials.gov identifier: NCT02299570. Updated January 2021. Accessed August 2023. https://classic.clinicaltrials.gov/ct2/show/results/NCT02299570
21. Khanna S et al. *Clin Infect Dis*. 2021;73(7):e1613-e1620. doi:10.1093/cid/ciaa1430

Harnessing the Power of AI to Enhance Endoscopy: Promises and Pitfalls

1. Jin Z et al. *BioMed Eng OnLine*. 2022;21(1):12. doi:10.1186/s12938-022-00979-8
2. Buendgens L, Cifci D, Ghaffari Laleh N, et al. Weakly supervised end-to-end artificial intelligence in gastrointestinal endoscopy. *Sci Rep*. 2022;12(1):4829. doi:10.1038/s41598-022-08773-1
3. Uche-Anya EN, Berzin TM. Artificial intelligence applications in colonoscopy. *GI & Hepatology News*. January 24, 2023. https://www.mdedge.com/gihepnews/article/260769/mixed-topics/artificial-intelligence-applications-colonoscopy
4. Rondonotti E et al. *Endoscopy*. 2023;55(1):14-22. doi:10.1055/a-1852-0330
5. Antonelli G et al. *Ann Gastroenterol*. 2023;36(2):114-122. doi:10.20524/aog.2023.0781
6. van der Zander QEW et al. *Endoscopy*. 2021;53(12):1219-1226. doi:10.1055/a-1343-1597
7. Areia PM et al. *Lancet Digital Health*. 2022;4(6):e436-e444. doi:10.1016/S2589-7500(22)00042-5
8. Sumiyama K et al. *Dig Endosc*. 2021;33(2):218-230. doi:10.1111/den.13837
9. Berzin TM et al. *Gastrointest Endosc*. 2020;92(4):951-959. doi:10.1016/j.gie.2020.06.035
10. Mori Y et al. *Dig Endosc*. 2023;35(4):422-429. doi:10.1111/den.14531
11. Uche-Anya E et al. *Gut*. 2022;71(9):1909-1915. doi:10.1136/gutjnl-2021-326271
12. Moor M et al. *Nature*. 2023;616(7956):259-265. doi:10.1038/s41586-023-05881-413
13. Kather JN et al. *NPJ Digit Med*. 2022;5(1):90. doi:10.1038/s41746-022-00634-5

The Evolving Role of Surgery for IBD

1. Gul F et al. *Ann Med Surg (Lond)*. 2022;81:104476. doi:10.1016/j.amsu.2022.104476
2. Kotze PG et al. *Clin Colon Rectal Surg*. 2021;34(3):172-180. doi:10.1055/s-0040-1718685
3. Bemelman WA; S-ECCO collaborators. *J Crohns Colitis*. 2018;12(8):1005-1007. doi:10.1093/ecco-jcc/jjy056
4. Ricci C et al. *Dig Liver Dis*. 2008;40(suppl 2):S285-S288. doi:10.1016/S1590-8658(08)60539-3
5. Lin X et al. *Therap Adv Gastroenterol*. 2022;15:17562848221104951. doi:10.1177/17562848221104951
6. Parigi TL et al. *Dis Colon Rectum*. 2022;65(suppl 1):S119-S128. doi:10.1097/DCR.0000000000002548
7. Pilonis ND et al. *Transl Gastroenterol Hepatol*. 2022;7:7. doi:10.21037/tgh.2020.04.02
8. Misawa M et al. *Clin Endosc*. 2021;54(4):455-463. doi:10.5946/ce.2021.165
9. de Sousa HT et al. *Curr Opin Gastroenterol*. 2018 ;34(4):194-207. doi:10.1097/MOG.0000000000000440
10. Whitehead A, Cataldo PA. *Clin Colon Rectal Surg*. 2017;30(3):162-171. doi:10.1055/s-0037-1598156
11. Cannon LM. The use of enhanced recovery pathways in patients undergoing surgery for inflammatory bowel disease. In: Hyman N, Fleshner P, Strong S, eds *Mastery of IBD Surgery*. Chicago, IL: University of Chicago Press; 2019:29-38. doi:10.1007/978-3-030-16755-4_4
12. Ljungqvist O et al. *World J Surg*. 2020;44(10):3197–3198. doi:10.1007/s00268-020-05734-5

REBYOTA®
(fecal microbiota, live-jslm) suspension, for rectal use

REBYOTA® (fecal microbiota, live - jslm) suspension, for rectal use

Brief Summary Please consult package insert for full Prescribing Information

INDICATIONS
REBYOTA is indicated for the prevention of recurrence of *Clostridioides difficile* infection (CDI) in individuals 18 years of age and older following antibiotic treatment for recurrent CDI.
Limitation of Use: REBYOTA is not indicated for treatment of CDI.

CONTRAINDICATIONS
Do not administer REBYOTA to individuals with a history of a severe allergic reaction (e.g. anaphylaxis) to any of the known product components.

Each 150mL dose of REBYOTA contains between $1x10^8$ and $5x10^{10}$ colony forming units (CFU) per mL of fecal microbes including $>1x10^5$ CFU/mL of *Bacteroides*, and contains not greater than 5.97 grams of PEG3350 in saline.

WARNINGS AND PRECAUTIONS
Transmissible infectious agents: Because REBYOTA is manufactured from human fecal matter it may carry a risk of transmitting infectious agents. Any infection suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Ferring Pharmaceuticals Inc.

Management of acute allergic reactions: Appropriate medical treatment must be immediately available in the event an acute anaphylactic reaction occurs following administration of REBYOTA.

Potential presence of food allergens: REBYOTA is manufactured from human fecal matter and may contain food allergens. The potential for REBYOTA to cause adverse reactions due to food allergens is unknown.

ADVERSE REACTIONS
The most commonly reported (≥ 3%) adverse reactions occurring in adults following a single dose of REBYOTA were abdominal pain, (8.9%), diarrhea (7.2%), abdominal distention (3.9%), flatulence (3.3%), and nausea (3.3%).

Clinical Trials Experience: The safety of REBYOTA was evaluated in 2 randomized, double-blind clinical studies (Study 1 and Study 2) and 3 open-label clinical studies conducted in the United States and Canada. A total of 978 adults 18 years of age and older with a history of 1 or more recurrences of *Clostridioides difficile* (CDI) infection and whose symptoms were controlled 24 – 72 hours post-antibiotic treatment were enrolled and received 1 or more doses of REBYOTA; 595 of whom received a single dose of REBYOTA.

Adverse Reactions: Across the 5 clinical studies, participants recorded solicited adverse events in a diary for the first 7 days after each dose of REBYOTA or placebo. Participants were monitored for all other adverse events by queries during scheduled visits, with duration of follow-up ranging from 6 to 24 months after the last dose. In an analysis of solicited and unsolicited adverse events reported in Study 1, the most common adverse reactions (defined as adverse events assessed as definitely, possibly, or probably related to Investigational Product by the investigator) reported by ≥3% of REBYOTA recipients, and at a rate greater than that reported by placebo recipients, were abdominal pain, (8.9%), diarrhea (7.2%), abdominal distention (3.9%), flatulence (3.3%), and nausea (3.3%).Most adverse reactions occurred during the first 2 weeks after treatment. After this, the proportion of patients with adverse reactions declined in subsequent 2-week intervals. Beyond 2 weeks after treatment only a few single adverse reactions were reported. Most adverse drug reactions were mild to moderate in severity. No life-threatening adverse reaction was reported.

Serious Adverse Reactions - In a pooled analysis of the 5 clinical studies, 10.1% (60/595) of REBYOTA recipients (1 dose only) and 7.2% (6/83) of placebo recipients reported a serious adverse event within 6 months post last dose of investigational product. None of these events were considered related to the investigational product.

USE IN SPECIFIC POPULATIONS
Pregnancy: REBYOTA is not absorbed systemically following rectal administration, and maternal use is not expected to result in fetal exposure to the drug.

Lactation: REBYOTA is not absorbed systemically by the mother following rectal administration, and breastfeeding is not expected to result in exposure of the child to REBYOTA.

Pediatric Use: Safety and effectiveness of REBYOTA in individuals younger than 18 years of age have not been established.

Geriatric Use: Of the 978 adults who received REBYOTA, 48.8% were 65 years of age and over (n=477), and 25.7% were 75 years of age and over (n=251). Data from clinical studies of REBYOTA are not sufficient to determine if adults 65 years of age and older respond differently than younger adults.

For more information, visit www.REBYOTAHCP.com

You are encouraged to report negative side effects of prescription drugs to FDA. Visit www.FDA.gov/medwatch, or call 1-800-332-1088.

Manufactured for Ferring Pharmaceuticals by Rebiotix, Inc.
Roseville, MN 55113

FERRING
PHARMACEUTICALS

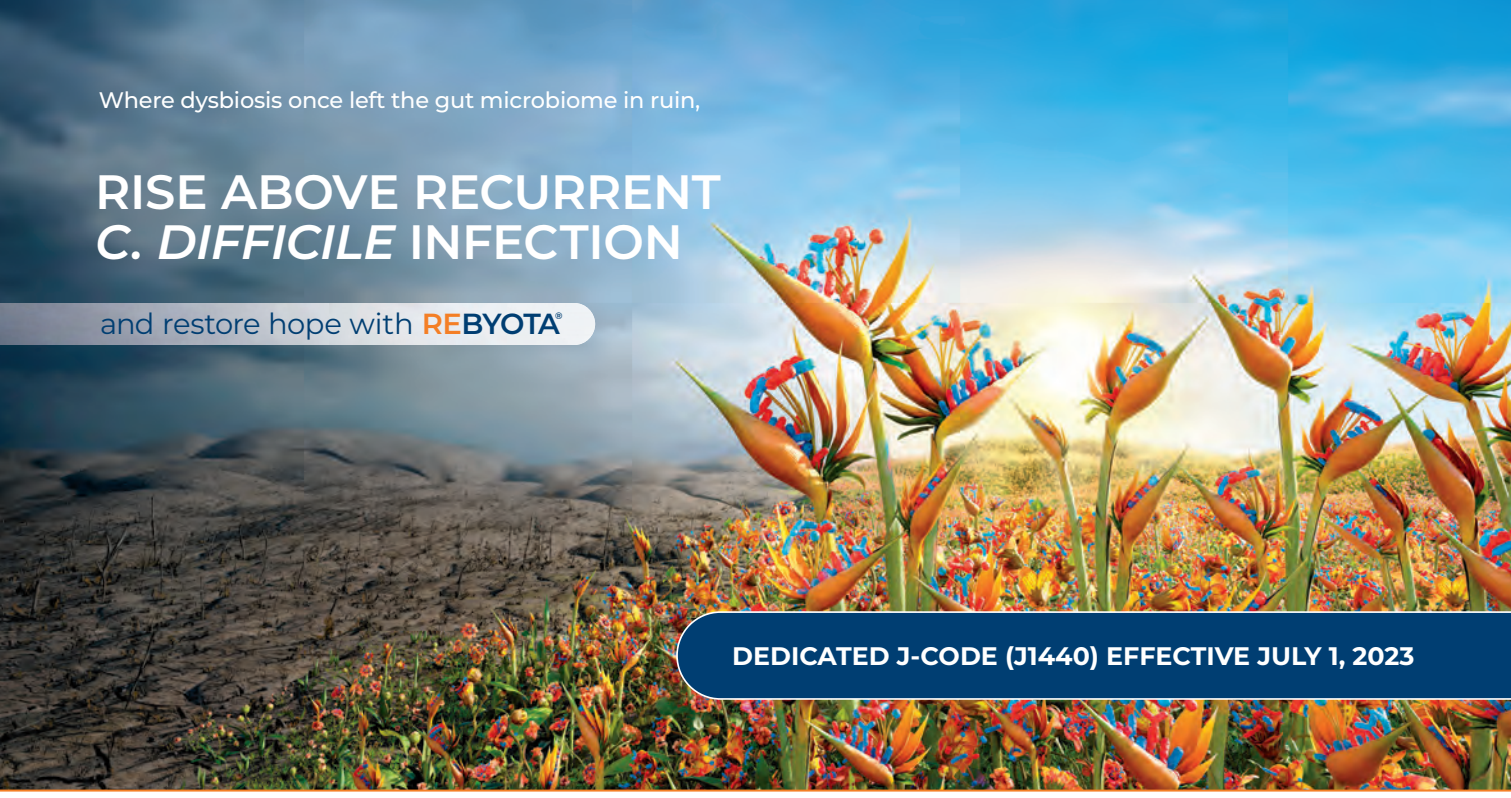
US License No. 2112

9009000002

Rx Only

This brief summary is based on full Rebyota Prescribing Information which can be found at www.RebyotaHCP.com

US-REB-2200277-V2



The first and only single-dose microbiota-based live biotherapeutic approved to prevent recurrence of *C. difficile* infection starting at first recurrence.[1,2,a]

Scan to visit website

[a]In the pivotal phase 3 trial, 32.8% of patients were treated at first recurrence of CDI following antibiotic treatment of CDI.[1]

INDICATION

REBYOTA (fecal microbiota, live - jslm) is indicated for the prevention of recurrence of *Clostridioides difficile* infection (CDI) in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI.

Limitation of Use

REBYOTA is not indicated for treatment of CDI.

IMPORTANT SAFETY INFORMATION

Contraindications

Do not administer REBYOTA to individuals with a history of a severe allergic reaction (eg, anaphylaxis) to any of the known product components.

Warnings and Precautions

Transmissible infectious agents

Because REBYOTA is manufactured from human fecal matter, it may carry a risk of transmitting infectious agents. Any infection suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Ferring Pharmaceuticals Inc.

Management of acute allergic reactions

Appropriate medical treatment must be immediately available in the event an acute anaphylactic reaction occurs following administration of REBYOTA.

Potential presence of food allergens

REBYOTA is manufactured from human fecal material and may contain food allergens. The potential for REBYOTA to cause adverse reactions due to food allergens is unknown.

Adverse Reactions

The most commonly reported (≥3%) adverse reactions occurring in adults following a single dose of REBYOTA were abdominal pain (8.9%), diarrhea (7.2%), abdominal distention (3.9%), flatulence (3.3%), and nausea (3.3%).

Use in Specific Populations

Pediatric Use

Safety and efficacy of REBYOTA in patients below 18 years of age have not been established.

Geriatric Use

Of the 978 adults who received REBYOTA, 48.8% were 65 years of age and over (n=477), and 25.7% were 75 years of age and over (n=251). Data from clinical studies of REBYOTA are not sufficient to determine if adults 65 years of age and older respond differently than younger adults.

You are encouraged to report negative side effects of prescription drugs to FDA. Visit www.FDA.gov/medwatch, or call 1-800-332-1088.

Please see Brief Summary on next page and full Prescribing Information at www.REBYOTAHCP.com.

References

1. REBYOTA. Prescribing Information. Parsippany, NJ: Ferring Pharmaceuticals; 2022. **2.** US Food and Drug Administration. FDA Approves First Fecal Microbiota Product. https://www.fda.gov/news-events/press-announcements/fda-approves-first-fecal-microbiota-product. Accessed December 1, 2022.

REBYOTA® (fecal microbiota, live-jslm) suspension, for rectal use

FERRING PHARMACEUTICALS Microbiome Therapeutics Development

RESTORE HOPE