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GASTROENTEROLOGY DATA TRENDS 2021

aga American Gastroenterological Association

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Official newspaper of the AGA Institute

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GI&Hepatology News

Produced in collaboration with the **American Gastroenterological Association**.

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GASTROENTEROLOGY DATA TRENDS 2021

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Digital health *in managing GI diseases*

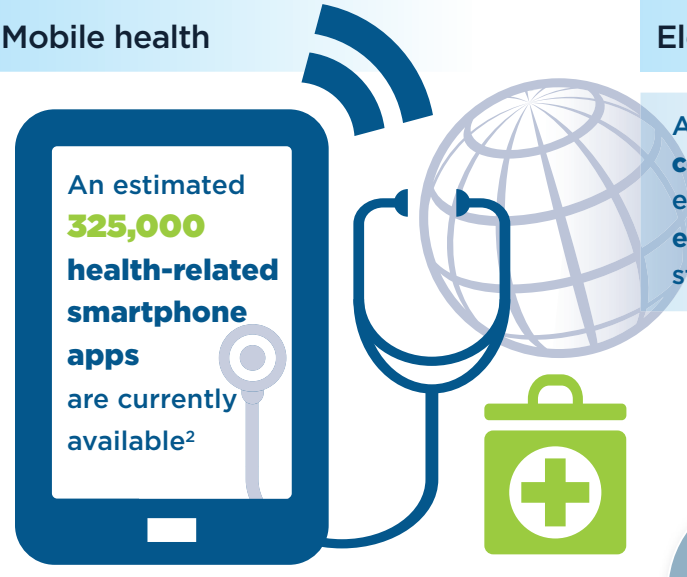
Dennis Shung, MD, MHS, and Lin Shen, MD, MBI

We conceptualize a framework for digital health technologies based on the workflow for machine learning: (1) **Input,** including data/information sources from which clinical insight can be derived; (2) **Blackbox,** involving algorithms that synthesize actionable insights via machine learning; and (3) **Output,** the methods by which insights are delivered clinically in a usable format.

Most GI companies and products focus on the **Blackbox**, developing algorithms like convolutional neural networks to analyze endoscopic videos to detect/classify abnormal tissue areas, to enhance endoscopist performance in removing suspicious polyps and preventing colorectal cancer.[1-3] While these algorithms have resulted in multiple randomized controlled trials with skilled endoscopists, real-world studies evaluating costs of implementation, maintenance, and effect on endoscopist and unit efficiency are needed. Algorithms have been developed to use data from electronic health records (EHRs) to predict outcomes for patients with acute GI bleeding, leveraging the wealth of clinical, demographic, and user-generated information stored in the EHR.[4] However, these predictions have not been validated retrospectively or prospectively.

Products and services focused on the **Input** stage have potential to enhance care quality by improving monitoring, treatment, and follow-up phases of care. Different data sources include digital biomarkers, information transmitted over telemedicine or mobile health apps (MHAs), and electronic devices. These are used to personalize treatment, enhance follow-up, and allow for early detection and referral. Collection of digital biomarkers (eg, vital signs, patterns of sleep, movement), patient input and history (eg, dietary and symptom logs), integration of visit and laboratory records from EHRs, and quick access to care guidelines help provide a complete and continuous picture of therapeutic choices.[5,6] Telemedicine has led to better treatment of hepatitis C and hepatocellular carcinoma (HCC) through improved access to physicians who can

Mobile health



An estimated **325,000 health-related smartphone apps** are currently available[2]

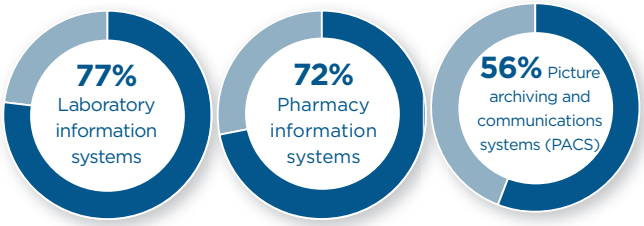
A survey of 135 gastroenterology patients found that...[11]

- **66%** agreed MHAs could help their doctor better manage their medical problems
- **64%** were concerned that personal information could "get into the wrong hands"
- **58%** were willing to use an MHA for up to 5 minutes per day

Electronic health records

About **58% of countries** have an existing **national eHealth policy or strategy**[14]

Most countries with national EHR systems reported integration with:



48% decrease in likelihood of medication errors[15] **when using a computerized order entry in conjunction with a bar-coded medication management system**

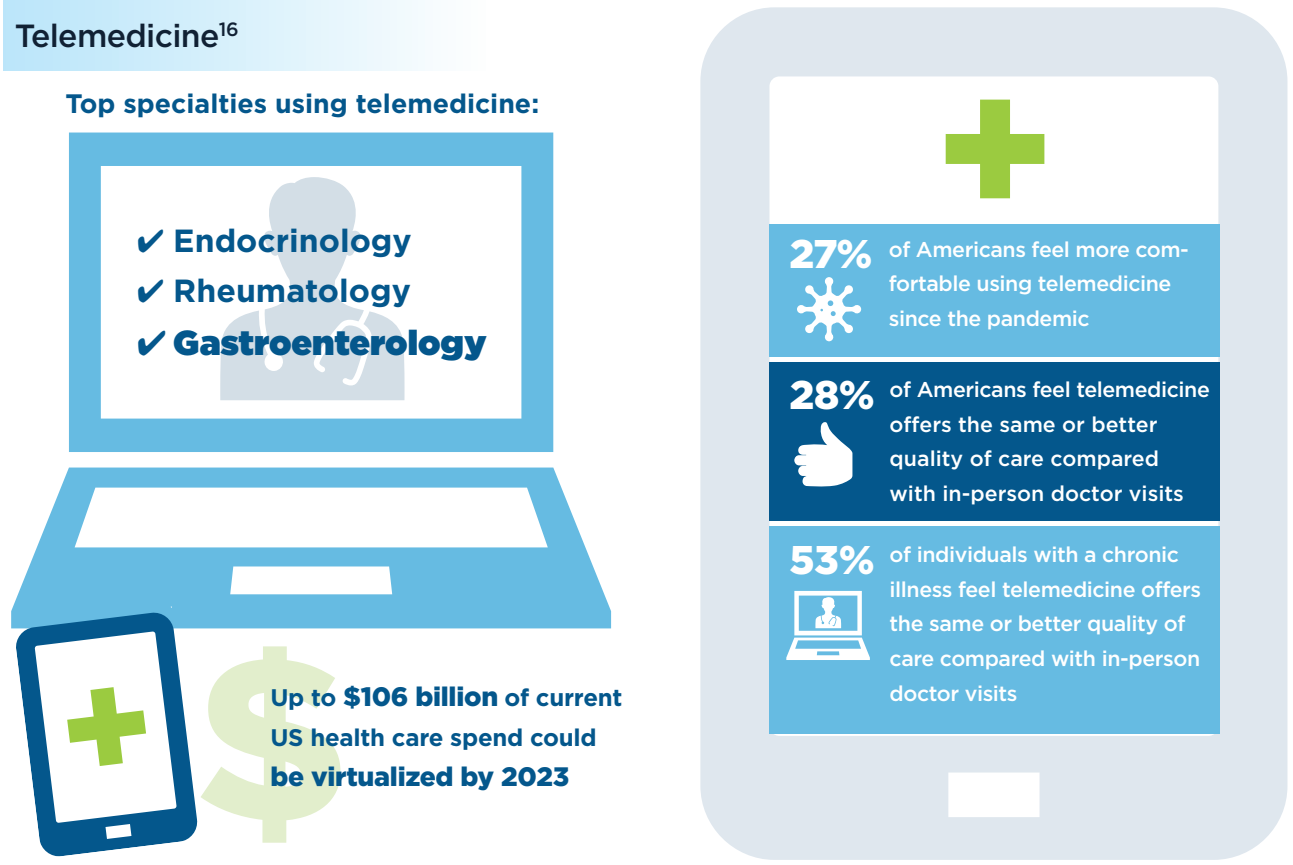
prescribe treatment, and multidisciplinary tumor boards.[7] Smartphone data and wearable tracking devices enable MHAs to monitor symptoms and guide management.[5,6]

Areas of positive impact are education, monitoring, treatment, follow-up, and improving patient satisfaction.[6] MHAs have tackled the problem of health literacy by helping patients with their bowel regimen before colonoscopy to improve preparation, and by helping patients manage their inflammatory bowel disease (IBD).[8,9] More IBD apps have become available, with many corresponding with improved quality of life (QoL) (eg, Constant Care, TECCU).[6] One study of the IBD HealthPROMISE app, a cloud-based platform available through the AGA Digital Transformation Network that tracks validated QoL and symptom scores, found that flagged interventions resulted in a significant decrease of yearly emergency department/hospitalization rates (from 25% to 3%, $P = .03$).[8] Noninvasive devices that capture novel information are promising for early disease detection, such as an ingestible microbioelectronic device to detect upper GI bleed, gut inflammation, and infectious microbes, and toilets that identify biomarkers in urine or feces to detect early malignancy.[10]

The greatest value for health care systems is in the **Output** stage. Implementation of algorithms improves clinically relevant outcomes and creates value through cost savings, compliance with metrics, and reduction in unnecessary use. Challenges include interpretability and bias when using machine learning algorithms in real-world practice, and no studies evaluating the implementation of GI-specific algorithms in health care systems exist.[11]

The future for digital health in gastroenterology will focus primarily on enhancement of endoscopic procedures, but many tools will provide decision support and enhanced symptom monitoring for IBD, management of hepatitis C and HCC, patient-facing applications for optimizing bowel preparation, and triage for acute GI bleeding. An underappreciated but critical area is the development of capture technologies that enhance the clinician experience. These tools aim to decrease the burden of documentation on physicians by collecting and collating data to minimize charting time, automate billing, and directly process information from endoscopy images and interventions.[12,13]

Telemedicine[16]



Emergence of live biotherapeutic products

for C. difficile and beyond

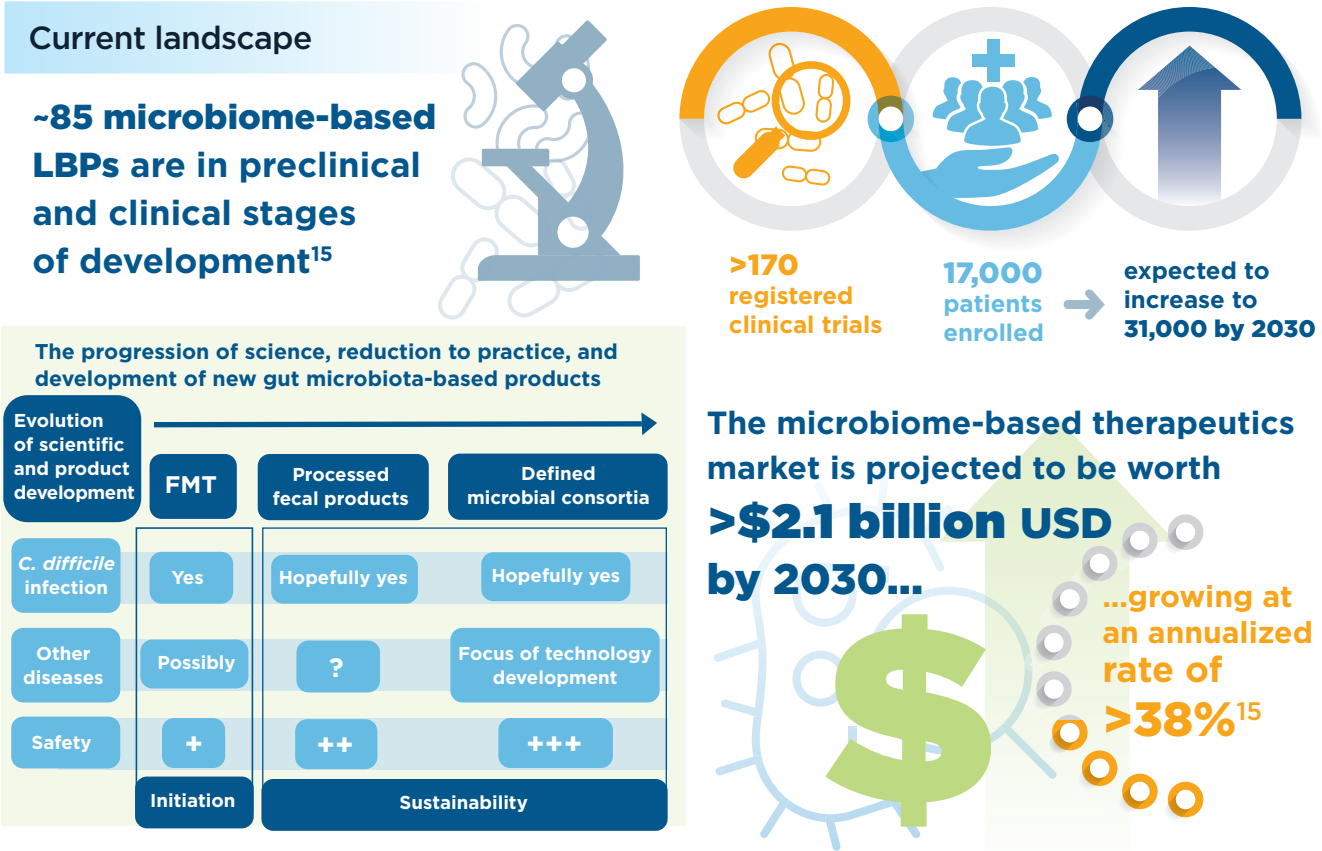
Gary D. Wu, MD, AGAF

The benefits of fecal microbiota transplant (FMT) have been described in literature for decades. Such studies have increased interest in the effect of the gut microbiota on a variety of physiological processes and diseases in humans.[1] The data suggest that processed microbiota can be developed into "live biotherapeutic products" (LBPs) that can be used as safe adjuncts to traditional medications for patients with a host of diseases.[2-4]

Observations that GI conditions such as inflammatory bowel disease are associated with alterations in the composition of the gut microbiota (commonly referred to as "dysbiosis") as well as with poor outcomes with cancer treatments, sparked interest in FMT as a potential therapeutic intervention. For this use, largely unprocessed stool from a healthy donor is transferred to a patient by a variety of methods.[1,3-5] FMT has also been studied in autism spectrum disorders, with one study reporting that FMT led to improved GI symptoms as well as social communication and behavior up to two years later.[5] Similar intriguing observations after FMT have been documented with other diseases such as ulcerative colitis.[6-9] However, many more studies are needed.

For now, use of FMT for the treatment of any disease other than recurrent *Clostridioides difficile* infection should be considered experimental. The ultimate hope is that FMT will be replaced by US Food and Drug Administration (FDA)-approved commercial LBPs that capitalize on the ability of the gut microbiota to alter disease.[2,3]

Studies using LBPs for the treatment of *C. difficile* infection are advancing. LBPs compete with *C. difficile*



for the same nutrition source, effectively "starving" the pathogen or leading to alterations in bile acid composition in the gut to reduce its viability.[2,10] LBPs are also being developed to improve outcomes in cancer treatment. Studies focused on response to immune checkpoint inhibitor therapy targeting programmed cell death protein-1 (PD-1) for the treatment of melanoma revealed that the composition of the human gut microbiota was associated with treatment outcomes and immune responsiveness.[4,5] This finding led to two studies using donor fecal material from complete anti-PD-1 responders as source material for transplant into melanoma patients who had progression either during or after PD-1 antibody therapy. A 30% to 50% clinical response was safely achieved, although some discussion surrounds the possibility of a delayed response to the anti-PD-1 treatment.[11,12]

However, the use of undefined fecal material to treat disease may lead to potential complications such as the transmission of antibiotic-resistant organisms or pathogens from the donor to the recipient.[13] The hope is that technological advances will lead to the development of LBPs with more defined and consistent microbial populations to reduce these risks and lead to FDA approval.[3] Important issues will need to be addressed such as the proper "dose" that will produce a predictable favorable outcome.[2,12] LBPs are currently being developed for the treatment of recurrent *C. difficile* infection, graft-vs-host disease, autism, inflammatory bowel diseases, cancers, and metabolic syndrome.[2,12]

Ultimately, LBPs or alternative modalities to alter the gut microbiota could be developed to alter the interaction of the microbiome on drug kinetics and dynamics, based on the concept of pharmacomicrobiomics.[14] The genome of particular bacterial strains code for a myriad of enzymes that can inactivate or enhance the performance of small molecule drugs.[14] Other interesting studies have suggested that nonantibiotics could be developed to mitigate these drug-microbiome relationships.[14] The true challenge will be to efficiently translate the fundamental mechanistic research in basic science to clinically valuable applications that meet regulatory standards.[10,14]

2010 — The FDA is the first authority to consider drug status for LBPs with a first guideline draft[16]

2012 — The FDA publishes guidelines and officially creates the LBP category[16]

2019 — The European Directorate for the Quality of Medicines and Health Care publishes the European Pharmacopoeia monograph and officially accepts LBPs as a new medicinal category for the European market[16]

C. difficile

Initial antibiotic treatment fails in 20%-35% of patients with *C. difficile* infection; 40%-60% have a second recurrence[17]

Phase 2 and 3 studies of microbiome therapeutics in development for *C. difficile* have shown:

74.5%-89% reduction in recurrence

compared with **59%-61.5% reduction** observed with placebo[2,3,18]

AI and machine learning *in GI practice*

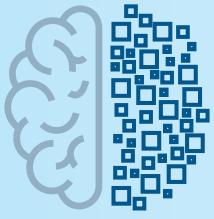
Dennis Shung, MD, MHS

The FDA approval of GI-Genius™ marks the arrival of artificial intelligence (AI) into daily GI practice.[1,2] Using deep convoluted neural network (DCNN) technology, computer-aided detection systems (CADe) improve accuracy in identifying precancerous areas and areas where biopsy is unnecessary.[1,3] Endoscopists may have different detection rates due to visual gaze patterns, "inattentional blindness," and "change blindness" within the context of the duality of manipulation and observation, which have been incompletely addressed by the addition of trained observers and improved camera technologies.[4] Randomized trial data in colonoscopy and upper endoscopy support that CADe improves detection, compliance with recommended time intervals, and documentation without significant increase in time expended.[1,3-5]

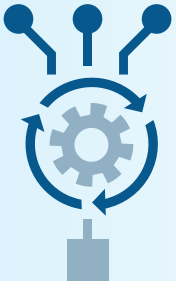
The deep learning needed to create CADe uses DCNNs trained with preprocessed images labeled and classified by experts.[6,7] Programs can integrate pretrained deep learning models with other non-polyp image data from large databases (AlexNet, VGG-16, DenseNet-169, ResNet-50, or Inception-v3).[3,6,7] The system is usually tested on new unlabeled images then deployed during colonoscopies.[6,7]

The randomized controlled trial that deployed GI-Genius™ focused on a population for whom screening and surveillance is recommended (age 40–80 years); other studies have enrolled patients as young as 18 years and showed improved polyp detection with AI assistance.[1,6] One study found a near doubling of adenoma detection rate (ADR) using a real-time automated system compared with standard colonoscopy, owing to improved identification of small (<10 mm) adenomas along with significant detection of hyperplastic polyps and minimal false-positive rates (0.075 per procedure).[8] The first double-blind, sham-controlled study evaluated the possibility that endoscopists using CADe may induce bias through increased vigilance and still found a benefit in polyp detection with the software system.[5] Another trial using back-to-back tandem colonoscopies found a lower

Artificial intelligence vs machine learning[12]



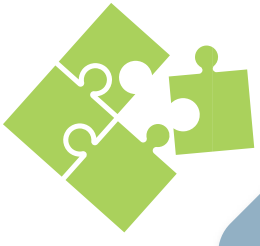
AI: Machine intelligence that has cognitive functions like those of humans, such as "learning" and "problem solving"

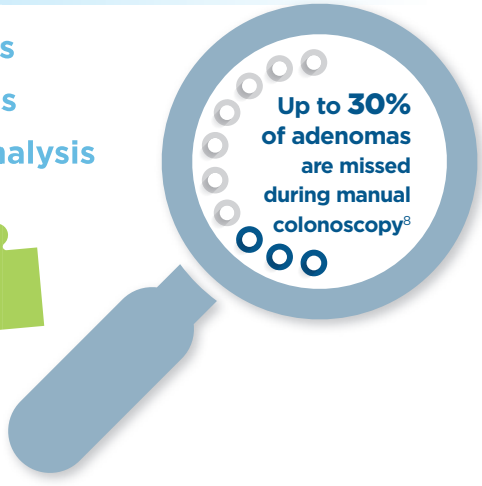


Machine learning: Mathematical algorithms that are automatically constructed from given data (known as input training data) and can predict or make decisions

AI and machine learning can help improve...[1]

- ✔ Diagnosis
- ✔ Prognosis
- ✔ Image analysis





In one study, **12% of patients with colorectal cancer were not diagnosed** at previous colonoscopies done within the previous 5 years[6]

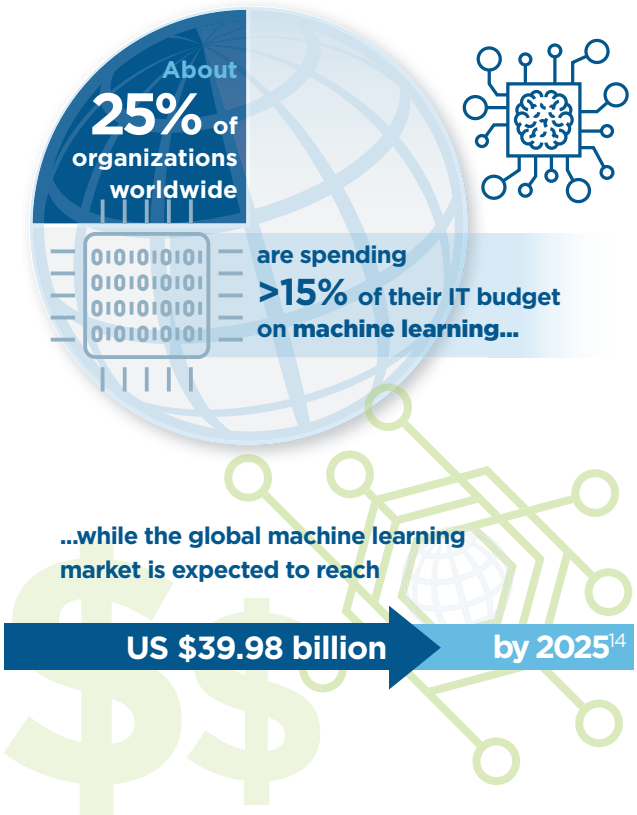
adenoma miss rate with CADe (18.39% vs 40%, $P < .0001$), with only 1.59% missed on review vs 24.21% missed with standard colonoscopy ($P < .001$).[4]

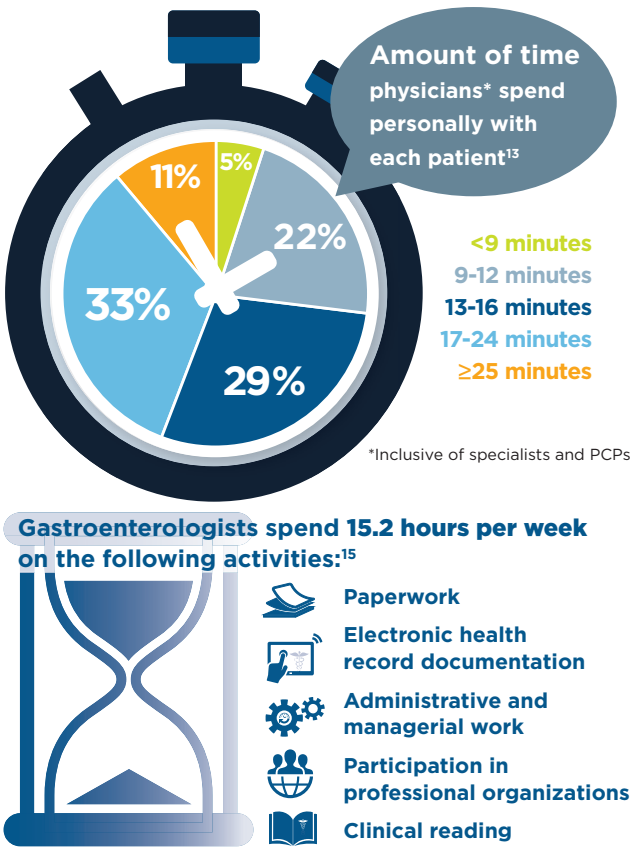
One study used real-time AI guidance to alert providers when landmarks were not photographed, withdrawal time was too short, or if blind spots were not evaluated, aiming to decrease interoperator variability.[6] As seen with the CADe studies, ADR rates improved withdrawal time and detection of slips that allowed for endoscopist recovery to visualize potential blind spots.[6]

Upper GI procedures may benefit from AI in screening for esophageal cancer and enhancing diagnostic capabilities. An ongoing trial of wide-area transepithelial sampling (WATS) assisted by 3-dimensional CAD (NCT02988934) strengthens detection of high-grade dysplasia/esophageal adenocarcinoma in Barrett's esophagus.[9,10] The WATS technique involves an abrasive brush that samples deep transepithelial cells, later analyzed by a computer-aided system designed specifically to detect esophageal mucosa abnormalities.[10] One trial also found that esophagogastroduodenoscopy significantly decreased blind-spot rates, increased inspection time, and augmented endoscopist photodocumentation.[3]

Despite the impressive performance of current AI systems, skilled endoscopists are still necessary to achieve the performance reported in published studies.[4] These systems have not been implemented widely, but multiple studies anticipate the need for ensuring that systems work across multiple types of endoscopic equipment.[1,5,6,8] Current AI systems are focused on improving endoscopist accuracy and reliability, but future products will also provide support to reduce documentation burden and provide real-time optical biopsies that can save time better used for physician-patient interaction.

In the future, biomarker-based assays integrating machine learning algorithms may play a more dominant role in guiding endoscopic therapies. Currently available "fluid" detection options that rely on biomarkers like DNA (eg, Cologuard®), methylated DNA (methylated septin 9, Epi proColon®), microRNA, low-molecular-weight metabolites, and gut microbiome shifts appear to have good diagnostic performance, but because of processing time and cost serve as adjunctive tests to endoscopy with biopsy.[8,11]





Eosinophilic esophagitis:

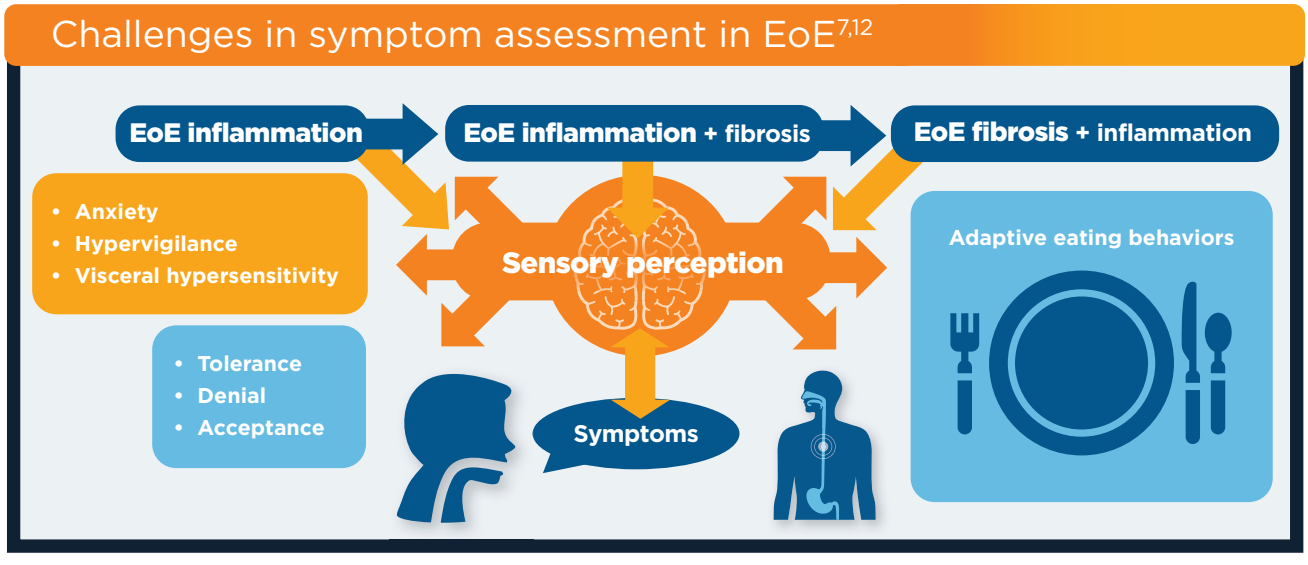
Addressing the rise in incidence and treatment options

Ikuo Hirano, MD, AGAF

Since characterized in small case series in the 1990s, eosinophilic esophagitis (EoE) has emerged as one of the most common etiologies for dysphagia in children and adults worldwide.[1,2] Esophageal eosinophilia had previously been viewed as a histologic feature of gastroesophageal reflux disease (GERD). Thus, initial diagnostic criteria for EoE required persistent eosinophilia (≥15 eosinophils/high power field [HPF]) following a course of high-dose proton pump inhibitor (PPI) therapy or normal esophageal acid exposure on reflux testing.[1] Recent recommendations eliminated the PPI trial requirement to acknowledge conceptual limitations and the fundamental similarities between "PPI-responsive esophageal eosinophilia" and EoE.[3]

The rise in EoE detection is a combination of an increase in disease incidence combined with heightened disease recognition by gastroenterologists, allergists, and pathologists through systematic biopsy protocols and histologic quantification of mucosal eosinophils in patients with characteristic symptoms and endoscopic signs.[1,4,5]

Research has identified several potential environmental, inherited, and inflammatory factors involved in the pathogenesis of EoE that revolve around a chronic T helper 2 (Th2)-type response to common food allergens.[3,4,6] Evidence of familial trends has generated interest in genetic and epigenetic links.[3,4,7] Candidate loci include thymic stromal lymphopoietin and CAPN14 (calcium-activated neutral proteinase 14). Early childhood antibiotic exposures are thought to epigenetically influence certain genes involved in proper tissue and immune regulation.[3,7] Associations between antibiotic-induced dysbiosis and other atopic diseases suggest a possible role in EoE as well. Population-based studies noted an inverse relationship between EoE and *Helicobacter pylori,* which may skew inflammation toward Th2 pathways or serve as an indicator of environmental factors involved in the



"hygiene hypothesis." Other changes in the microbiome include an enrichment of Proteobacteria *(Neisseria, Corynebacterium)* in active EoE esophagus disease plus *Granulicatella* and *Campylobacter* in the mucosa upon allergenic food introduction.[3,6] Implications of these mechanisms require further investigation.

Recurrent exposure to food allergens induces persistent eosinophil-predominant inflammation, resulting in progressive subepithelial esophageal remodeling that includes lamina propria fibrosis.[2,8] Progressive fibrosis results in major complications of EoE including food impaction and strictures requiring esophageal dilation, both associated with risk of esophageal perforation.

Management of EoE involves a treat-to-target approach that includes reduction in symptoms, normalization of histopathology, and improvement in endoscopic signs of inflammation and strictures. While symptom-based management is appealing to patients and clinicians, dissociation between symptoms and objective measures of endoscopic and histologic activity substantially limit this approach.[8] Fibrostenotic strictures responsible for food impactions often do not resolve with effective medical therapies directed at inflammation. Furthermore, a recent study identified anxiety and hypervigilance, rather than eosinophil density, as being important determinants of symptom severity in EoE.

Current treatment options for EoE include diet therapy, medications, and esophageal dilation. Although dilation is highly effective for improving dysphagia associated with strictures, it does not address the underlying inflammatory process responsible for disease progression.[9] Diet therapy has evolved from elemental formulas that remove dietary protein to allergy-testing–directed diet strategies to the empiric elimination of common food allergens. The six-food elimination diet (SFED) has demonstrable effectiveness for improving eosinophilic inflammation, but requires repeated endoscopies during food reintroduction to identify specific triggers. Recent studies have used less restrictive elimination diets that avoid the most common food triggers in a stepwise approach to reduce the burden

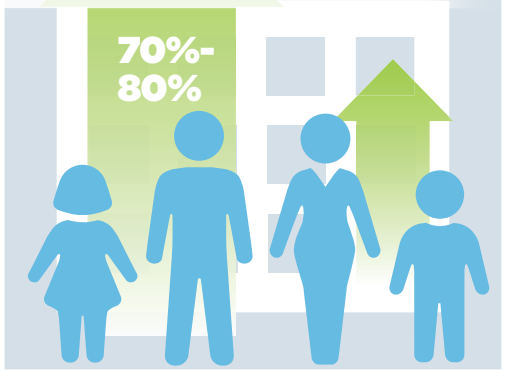
History of clinical criteria for EoE[9,16,17]

of endoscopy.[8,10,11] However, two recent trials (one randomizing children with EoE to milk elimination or a four-food elimination diet, and one randomizing adults with EoE to milk elimination or SFED) failed to demonstrate superiority of the more extensive diets over milk alone. Based on these data, an initial trial of milk elimination is reasonable prior to more extensive elimination diets for patients preferring diet therapy.[8]

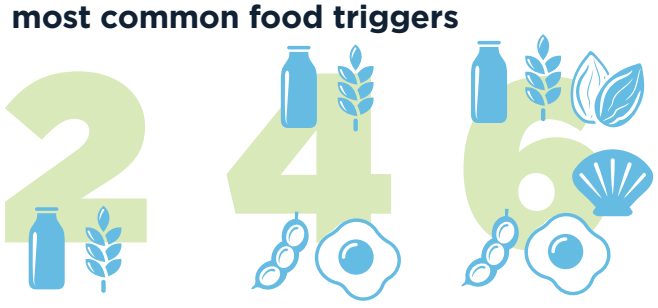
Swallowed topical corticosteroids are a mainstay of primary medical treatment of EoE and were the only medical therapy to receive a strong recommendation in the 2020 guidelines on the management of EoE by the AGA and the Joint Task Force on Allergy-Immunology Practice Parameters. Unlike PPIs and dietary therapies (also recommended in the guidelines), the efficacy of swallowed topical corticosteroids was supported by several double-blind, placebo-controlled trials. Current use of swallowed topical corticosteroids for patients with EoE in the United States is limited to off-label administration of steroid formulations developed for asthma or prepared by compounding pharmacies. Phase 3 US clinical trials are evaluating the efficacy and safety of swallowed topical budesonide and fluticasone preparations that have been optimized for esophageal delivery.[9]

Systemic therapies targeting immune mediators and cells central to the pathogenesis of EoE are in development.[2,7] Patients whose condition is refractory to treatment with PPIs, swallowed topical corticosteroids, and elimination diets are clear candidates for this approach. Use of systemically acting treatments also has conceptual advantages for patients with EoE who have multiple atopic diseases. While interleukin-5 (IL-5) antibodies have been studied with mixed results in children, a recent phase 2 trial using anti-IL-13 therapy demonstrated significant histologic and endoscopic improvements in adults, leading to an active phase 3 study.[2,3] Similarly, anti-IL-4Rα treatment is undergoing a phase 3 clinical trial based on favorable results from a phase 2 study in adults. Additional therapies more specifically targeting eosinophils by antibodies engaging the Siglec-8 receptor expressed on eosinophils (and mast cells) as well as the IL-5 receptor and an orally administered sphingosine 1-phosphate receptor modulator are being evaluated in active clinical trials.

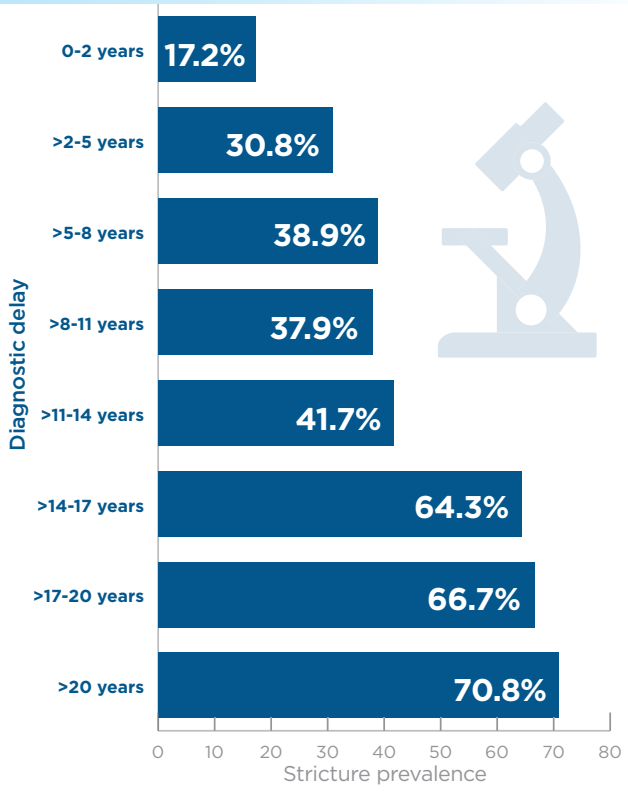
Sustained 1-year remission rates of approximately 70%-80% have been reported for standard dose PPI maintenance therapy among children and adults[13]



Elimination of two, four, and six **most common food triggers**



Prevalence of strictures in patients with EoE, by diagnostic delay period[18]



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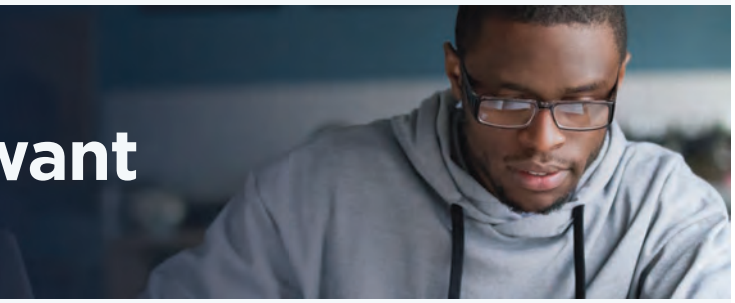

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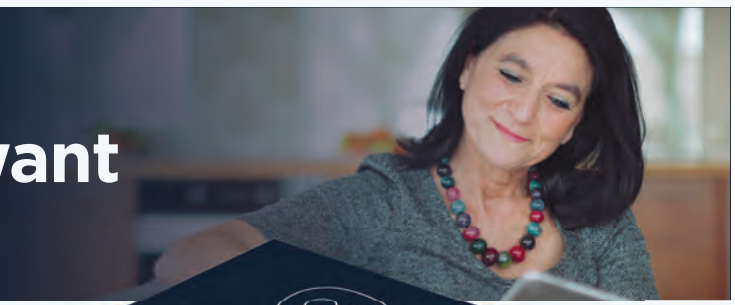

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EDU19-45

Racial and social diversity *in GI practice*

Ibironke Oduyebo, MD

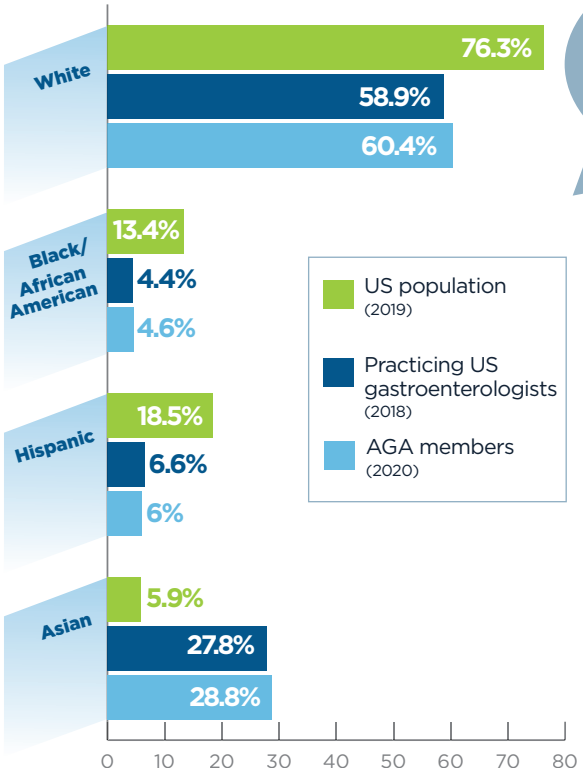
Hispanic, Black, Native American, and Alaska Native individuals comprise 33.2% of the US population—a proportion that is expected to continue to increase—yet minority representation in the medical workforce has not kept up with the diversity of the general population.[1,2] As the country diversifies, African American/Black, Native American/Alaska Native, and Latinx/Hispanic ethnic groups have actually seen declines in internal medicine residency and GI fellowships.[3] Only 5% of GI practitioners identify as Black, although Black individuals represent 13% of the US population.[4] In an internal survey, the AGA found only 11% of members self-reported as any of the populations underrepresented in medicine (UIM) (defined as Hispanic/Latinx, Black/African American, Native American [American Indian/Alaskan Native], or Hawaiian/Pacific Islander).[5]

Beyond race and ethnicity, barriers also exist against inclusion by gender and sexual identity as well as socioeconomic factors.[2,5] Data on lesbian, gay, bisexual, transgender, and queer (LGBTQ), disabled, and veteran individuals in the GI workforce have not been tracked, and general medicine has a lack of applicants (<6%) from the lowest income quintile.[1,2,6]

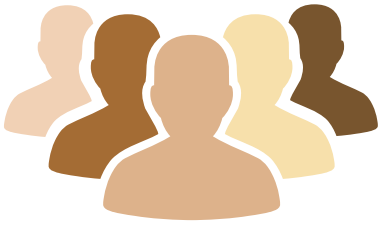
The importance of balancing these inequalities cannot be overstated. Underserved populations are more likely to accept advice coming from a medical expert of a similar ethnic background; additionally, overcoming language and cultural communication barriers can potentially improve diagnosis, therapy choices, and adherence.[1,3,4,7,8] Practitioners from lower socioeconomic or underserved populations are more likely to treat like-populations, bolstering rural and minority health care while fostering disparity research and providing mentorship that furthers advancement of UIMs into specialty arenas and leadership positions.[1,3,4,6,7,9]

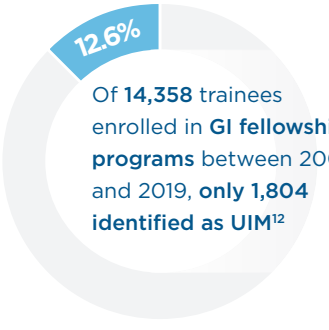
Race/Ethnicity

US Population vs Practicing Gastroenterologists and AGA Members[5,10,11]

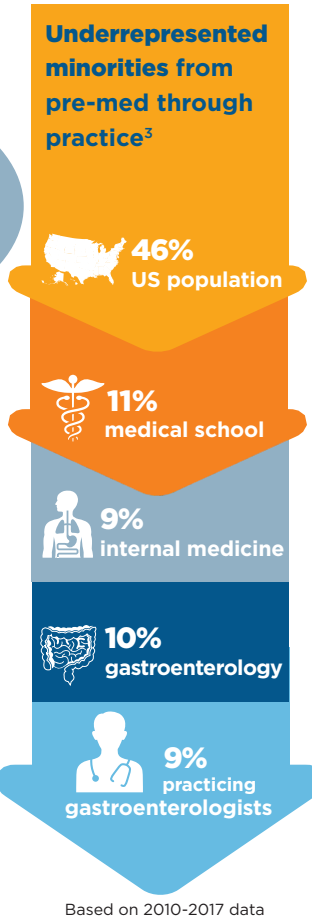


Native American and Hawaiian/Pacific Islander groups each represent <1.5% of US, GI, and AGA populations





Underrepresented minorities from pre-med through practice[3]

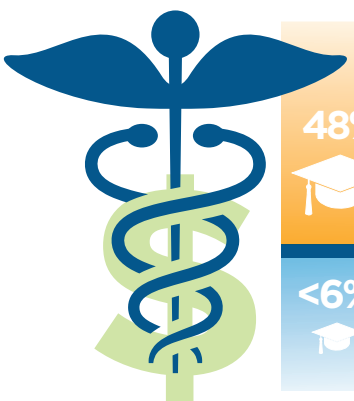


Based on 2010-2017 data

Establishing a framework for change must begin with an institutional review to determine where gaps occur and medical schools are positioned for such change.[3,6,7] Steps to improve inequalities based on race, ethnicity, gender, and sexual identity can include actively recruiting a more diverse pool of applicants, improving cultural competency curricula designed around ethnicity/race, gender, sexual preference, and low-income health care, establishing faculty representative of UIMs with strong mentorship programs, and allaying financial sacrifices of applicants (eg, decrease, supplement, or waive application fees and travel expenses).[1,3,5,6]

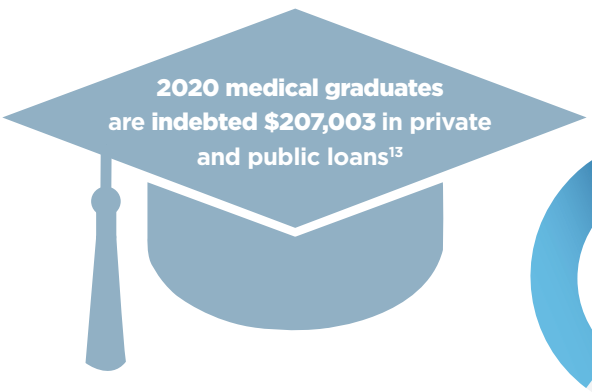
The GI specialty can further benefit from robust inclusiveness programs designed and supported by the various professional organizations.[1,4,5,9] The AGA has established an Equity Project Advisory Board to spearhead the AGA Equity Project (https://gastro.org/agaleadership/initiatives-and-programs/aga-equity-project/), an effort aimed at creating actionable strategies.[5] The Gastroenterology Women's Coalition, formed across four organizations (American Society for Gastrointestinal Endoscopy; AGA Institute; American Association for the Study of Liver Diseases; and North American Society for Pediatric Gastroenterology, Hepatology and Nutrition), sponsors programs to promote women's advancement in the profession.[1,3] An R25 grant program (Fostering Opportunities Resulting in Workforce And Research Diversity [FORWARD]), managed by the AGA, provides UIM physician scientists with tools to improve their success in a research career and opportunity for mentorship with UIM leaders. The AGA and other GI societies have created mentorships, awards, and high-school interactivity programs to forge interest in careers in GI.[1-3,5] Aside from these promising advances, challenges remain.[5] Collaboration with organizations representative of specific UIMs, such as the Association of Black Gastroenterologists and Hepatologists and the Gay and Lesbian Medical Association, allows sharing of resources. Individual practitioners can sign up for the Healthcare Equality Index (https://www.hrc.org/resources/healthcare-equality-index) or list businesses on specified provider directories to better tap into a diverse community.[4,8,9]

Socioeconomic factors



48% **medical students** who come from the **top income quintile**

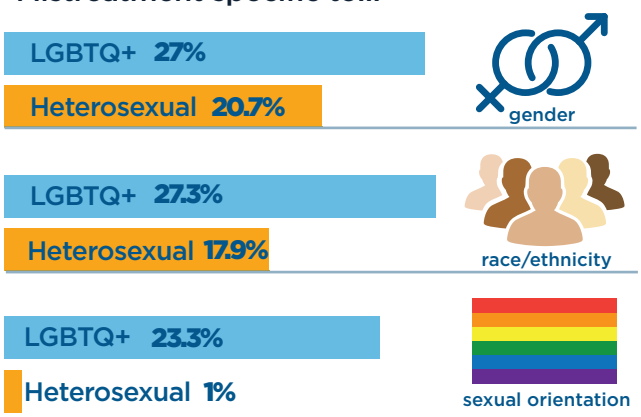
<6% **medical students** who come from the **lowest income quintile**[6]



LGBTQ+ students

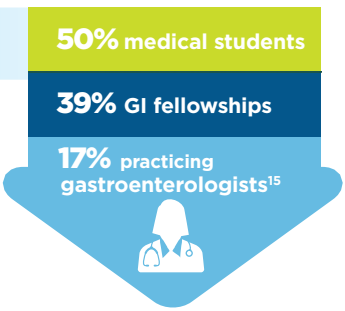
Experiences vs heterosexual students[14]

Mistreatment specific to...



Women

The proportion of women training in GI fellowship programs is decreasing, from **40.2%** in 2009-2010 to **35.44%** in 2018-2019[12]



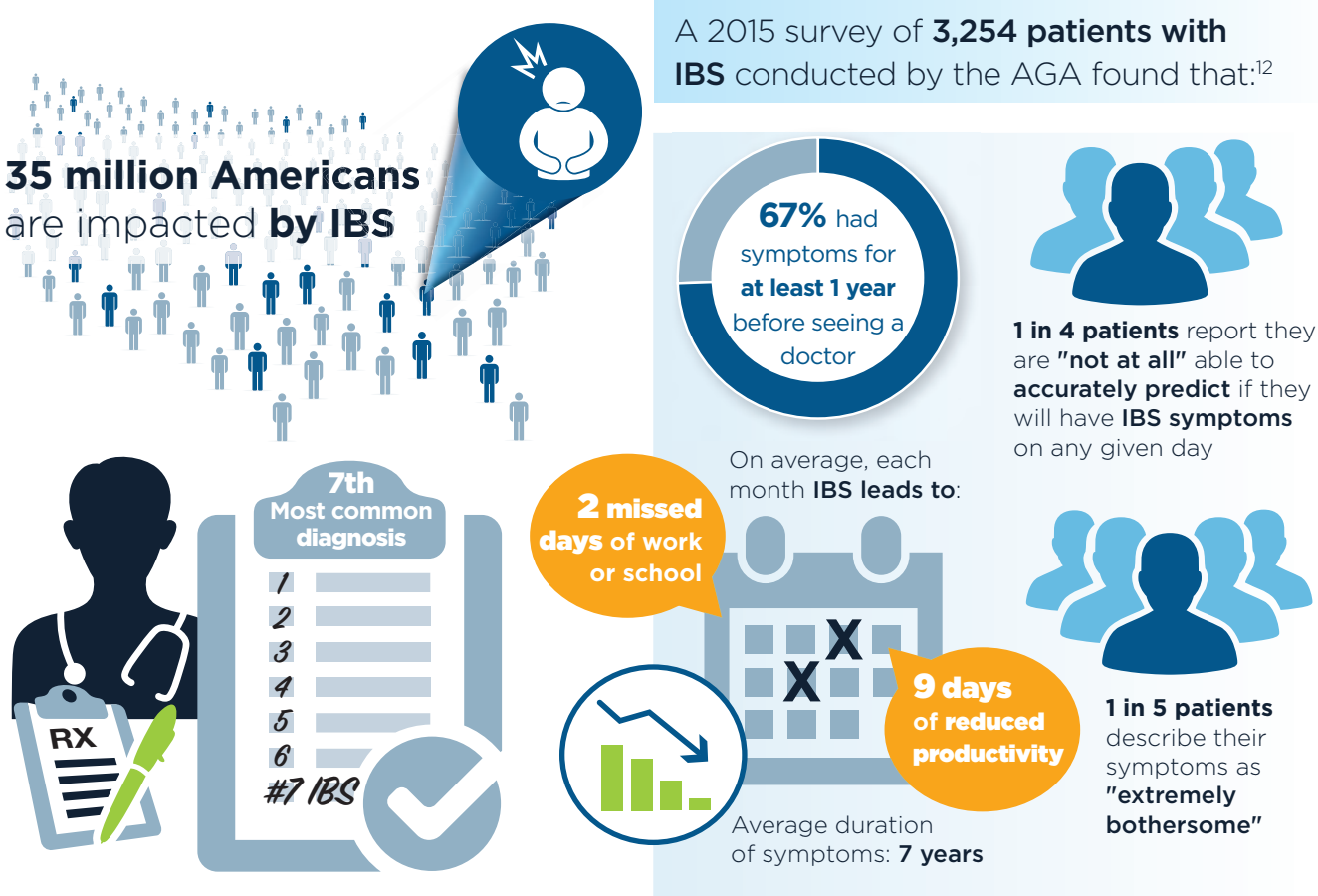
The gut-brain connection *in IBS*

Lin Chang, MD, AGAF

Irritable bowel syndrome (IBS) is one of several functional GI disorders lacking a reliable diagnostic biomarker. The syndrome is now believed to involve altered gut-brain axis communication through multiple possible etiologies, and has therefore been renamed "disorders of gut-brain interaction."[1-4] Diagnosis currently relies on symptomology (abdominal pain and altered bowel habits) meeting Rome IV criteria.[1-3] While the question of whether IBS originates from central nervous system (CNS) or GI abnormalities remains unanswered, recent evidence suggests substantial interplay of motility, epigenetic, microbiota, and immune mucosal disturbances, along with visceral pain hypersensitivity, psychosocial aspects, and altered brain processing.[1-3,5,6]

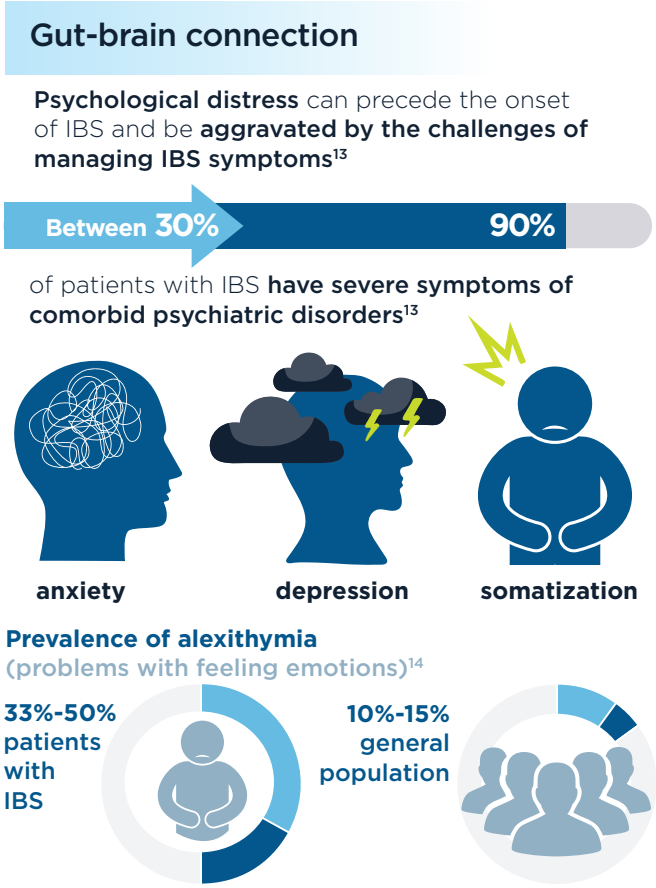
Within the GI tract, mucosal barrier dysfunction found in IBS may be mediated by immune activation.[2,6] Pioneering use of confocal laser endomicroscopy by Fritscher et al. has led to the discovery that 50% to 70% of patients testing negative for food allergens by traditional methods in fact developed significant mucosal permeability changes and an influx of intraepithelial lymphocytes within five minutes of direct exposure to common food antigens (eg, milk, wheat, yeast, soy, egg white).[7,8] In one small study, during a follow-up period of dietary restriction of the identified offender, most patients had complete or near remission after six months.[7] Research on microRNAs in IBS suggests a putative role for epigenetic factors that both disrupt membrane permeability (miR-219a-5p) and immune regulation (miR-338-3p), which can alter neurosensory pathways resulting in visceral hypersensitivity, offering potential treatment targets.[6] Increased activation of pain-mediating nerve fibers in intestinal tissue has been observed in IBS, some activated by proteases and histamine.[2]

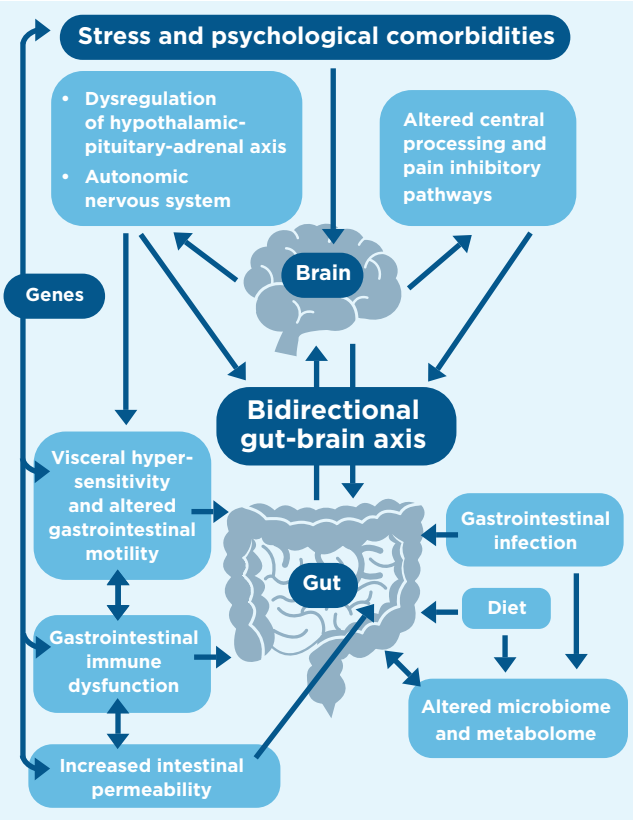
GI dysbiosis is a chronic suspect in IBS literature as a perpetrator of distorted motility.[2,5,9] In a systematic review of available data, an overall reduction in



microbial diversity, which is commonly seen in IBS, begs the question of whether preexisting immune activation in IBS promotes a greater abundance of certain bacteria *(Enterobacteriaceae, Lactobacillaceae, Bacteroides)* or if these bacteria ultimately mediate mucosal degradation, bloating due to fermentation, or production of neuroactive metabolites that facilitate pain.[9] However, beneficial bacteria *(Faecalibacterium, Bifidobacterium)* that have mucosal barrier protective or anti-inflammatory effects are decreased in IBS.[2,9] Integrated analysis of diet-microbiome interaction found important evidence that *Ruminococcus gnavus* and Lachnospiraceae species are potentially diagnostic of IBS, and the metabolome of patients with IBS can distinguish a subset of patients who actually have bile acid malabsorption.[5] Emerging research has shown bidirectional interactions between gut microbiota and the CNS through the brain-gut-microbiome axis, which may play an important role in IBS. Gut microbiota communicate with the CNS via metabolites and neural, immune, and endocrine pathways, while the CNS can influence the gut microbiome through the autonomic nervous system.[10]

At the CNS level, brain imaging studies support important differences in specific processing networks among patients with IBS, and these alterations can differ in men and women with IBS.[1,2,4] Areas of interest include salience ("expectancy") networks, biased threat appraisal ("catastrophizing"), emotional arousal ("anxiety, depression"), and central executive network ("symptom-focused attention").[4] Mapped differences include (1) sensorimotor cortex thickening, found to be greater in women; (2) anterior insula and amygdala connectivity alterations; (3) greater anterior and anterior midcingulate cortex engagement; (4) increased emotional center responsiveness; (5) decreased inhibitory feedback; and (6) increased central autonomic modulation.[2] While these alterations in IBS may be modulated by emotional (anxiety, depression, stress) and cognitive (attention, expectation) factors, they may also be a result of increased viscerosomatic signals to the brain.[2,4,11] No specific central neurotransmitter has yet been identified as a culprit, and centrally acting agents seem to also have an effect directly on the gut.[2,4]





Reference 15: Adapted by permission from Springer Nature: *Nature Reviews Gastroenterology & Hepatology.* Global burden of irritable bowel syndrome: trends, predictions and risk factors, Black CJ and Ford AC, 2020.

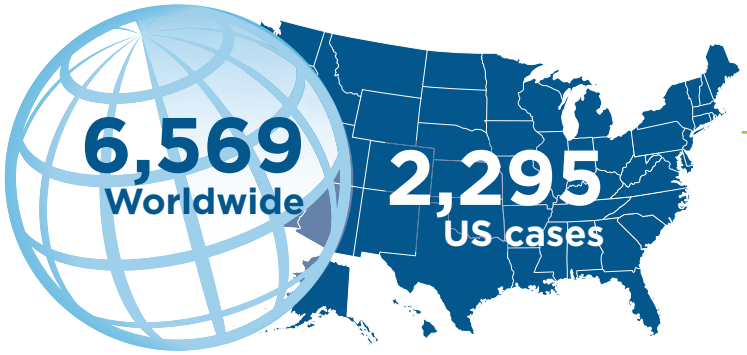
Managing IBD *in the backdrop of COVID-19*

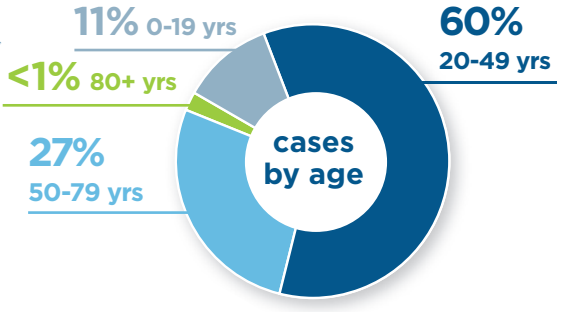
Stephen J. Bickston, MD, AGAF, FACG, FASGE

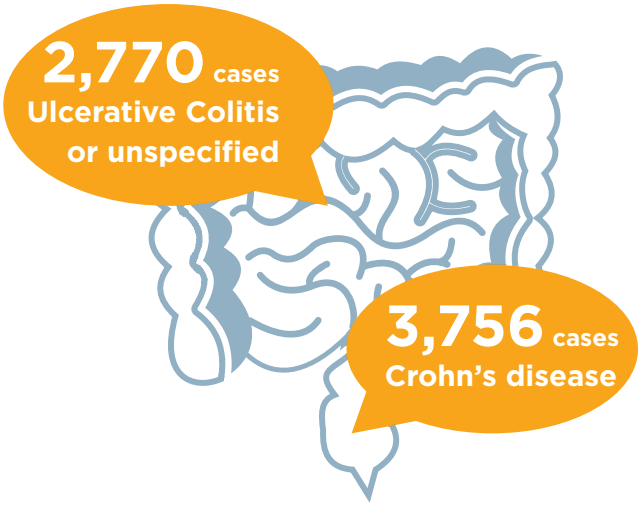
Challenges in caring for patients with inflammatory bowel disease (IBD) increased during the COVID-19 outbreak. The role of intestinal angiotensin-converting enzyme 2 (ACE2) in promoting coronavirus infection and immune-suppression treatments in these patients implies elevated risk of contracting COVID-19.[1-3] An Italian study showed an increased incidence of COVID-19 among patients with IBD compared to the general population, particularly in patients receiving steroid treatment.[1,4] Wary patients and providers delayed or discontinued therapy in an attempt to avoid exposure-inducing relapse of IBD and steroid use.[1,5] Additionally, advanced age, comorbidities, active disease, and nutritional status appear to worsen infection rates and outcomes.[1,4]

Initial data from the Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD) Registry connects thiopurine monotherapy to worse outcomes, as seen in other viral infections.[4] However, biologic monotherapy and combination therapy appear to mitigate infection severity and lessen vaccination adverse effects.[1,4,6] Mesalamine monotherapy has been linked to cases resulting in death, and little evidence supports its efficacy in Crohn's disease.[1,7] While changes in therapy are not

Reported **COVID-19 cases** among **patients with IBD** from the SECURE-IBD Registry[12]

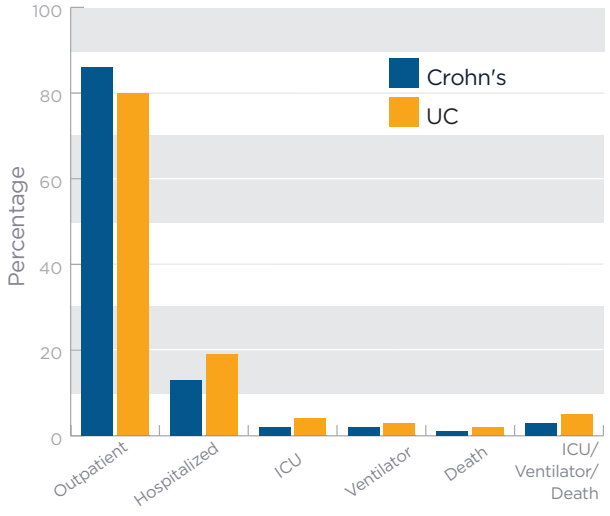






43 patients did not indicate their disease type.

COVID-19 case severity among patients with IBD

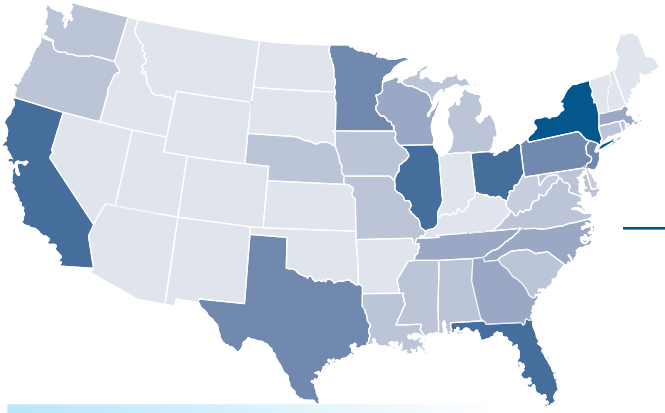


recommended for every patient, the risk-vs-benefit for steroids, thiopurines, and 5-aminosalicylic acid derivatives may need to be reconsidered for the elderly.[1,4]

Questions remain regarding whether biologics blunt serological response to COVID-19 vaccines, but consensus supports vaccination benefits as outweighing the risks, especially non-live, mRNA, and protein vaccines.[2,6,8] As with immunomodulators used for transplantation, thiopurine and methotrexate with or without concomitant anti-tumor necrosis factor drugs may necessitate a booster regimen. Mucosal-delivery vaccines in development may not produce an adequate response in patients taking vedolizumab.[8,9] GI specialists play an important role in assuring patients with IBD that current vaccine options are safe and should actively encourage patients most likely to decline immunization, such as minorities and patients with limited education, low income, or underinsurance.[2,6]

We must remain mindful of COVID-19's part in financial toxicity by avoiding medications with limited efficacy, maximizing the durable response to combinations, downward dosing of biologics, and using biosimilars.[7] An unexpected benefit from the pandemic may come in the form of step-therapy reform enacted across more than half of US states that will increase immediate access to effective therapies.[10] Children with IBD suffer the greatest cost increases, which could be further emphasized as their reduced immunization status places them at further COVID-19 risk.[11]

Distribution of COVID-19 cases by state among patients with IBD was similar to the general population[12]



New York had the most reported cases (297)

Vaccination response[6]

The **CORALE-IBD† study** longitudinally surveyed **postvaccination symptoms** after each vaccine dose in **246 adults with IBD**

Mean age 47.4 years

57% female

57% received Pfizer | 43% received Moderna

IBD diagnosis

67% Crohn's disease

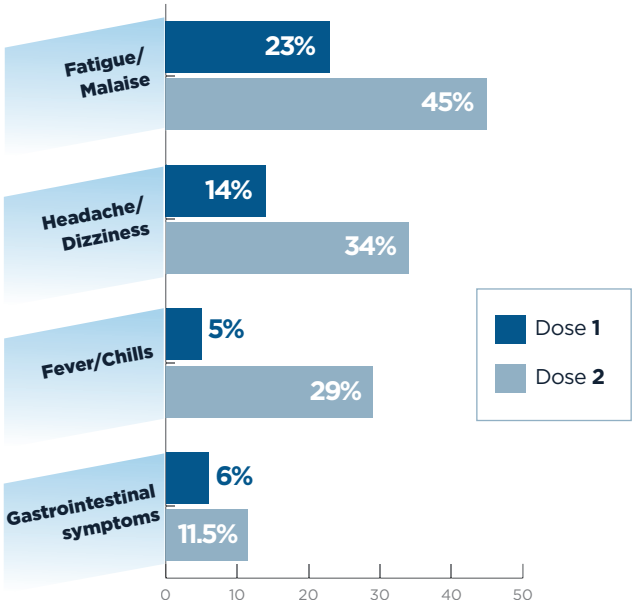
33% ulcerative/indeterminate colitis

Overall adverse event (AE) frequency

39% after Dose 1

62% after Dose 2

Most common systemic adverse events[6]



†Coronavirus Risk Associations and Longitudinal Evaluation-IBD study

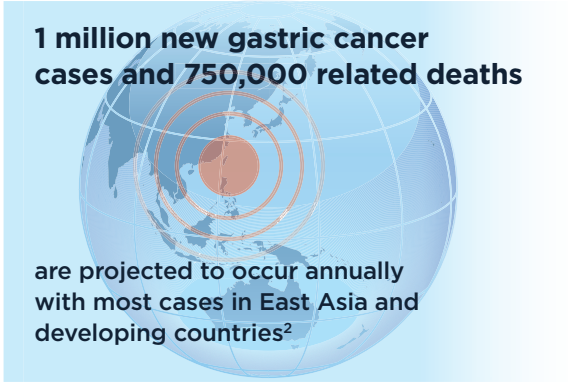
Noncardia gastric cancer risk:
Racial/ethnic disparity, gastric precancerous changes, and refractory H. pylori

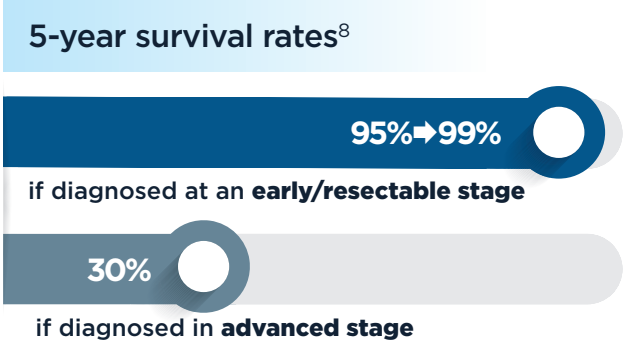
Shailja C. Shah, MD, MPH

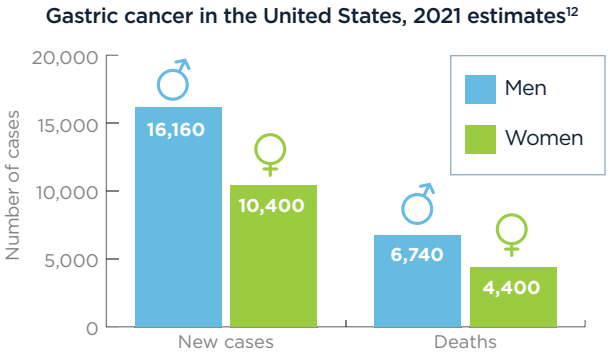
Atrophic gastritis and gastric intestinal metaplasia (GIM) represent precancerous mucosal changes in the stomach. The most common etiological trigger is chronic *Helicobacter pylori (H. pylori)* infection, with rarer causes such as autoimmunity.[1-4] A small minority of these patients experience progression, although the exact causes are not well understood.[2] The AGA conducted technical reviews focused on epidemiology and natural history to create the first US evidence-based GIM management guidelines, and recently published guidance focused on refractory *H. pylori* management and atrophic gastritis diagnosis and management.[1-4]

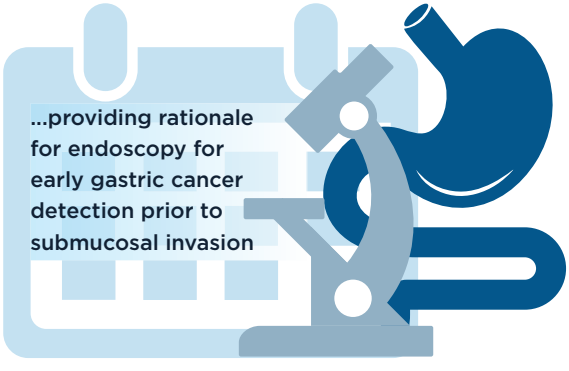
GIM is relatively common in the United States. Prevalence among patients undergoing endoscopy with biopsy is about 5%, and may approach 50% in higher-risk populations (including racial/ethnic minority groups and immigrants from areas where *H. pylori* and gastric cancer are endemic).[1,5] Estimated annual risk of GIM progression to gastric cancer is 0.16%, and ranges 2- to 4.5-fold higher depending on risk factors like family history of gastric cancer, extent of mucosal involvement, GIM histological subtype, and severity.[1,2,5] Smoking and dietary habits are likely relevant to progression risk, but data are limited.[1]

Although the AGA recommended against *routine* surveillance of GIM in all patients, they acknowledged that this is conditional based on low-quality evidence; they submitted that endoscopic surveillance for early detection is reasonable in patients with additional risk factors for progression and populations with higher risk of gastric cancer.[2] A follow-up analysis reported that noncardia gastric adenocarcinoma (GA) rates are higher in most non-White groups, with Korean American patients experiencing a significant increase; these incidence rates approached colorectal cancer rates.[6]





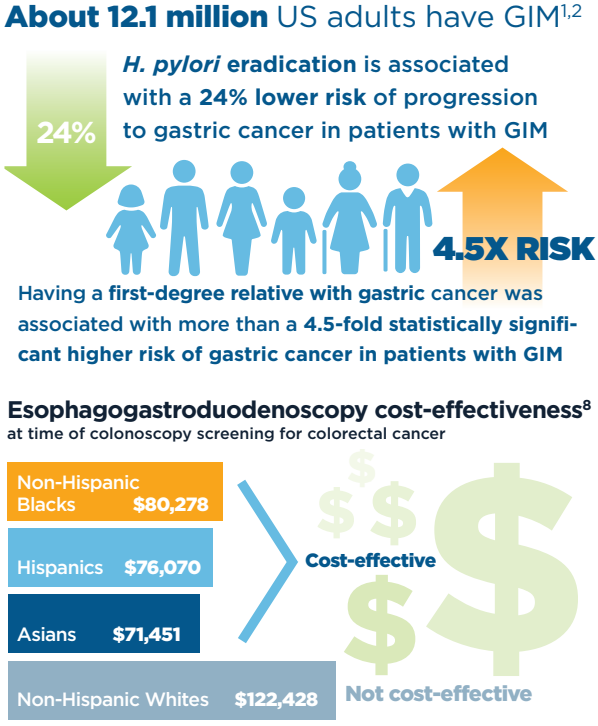




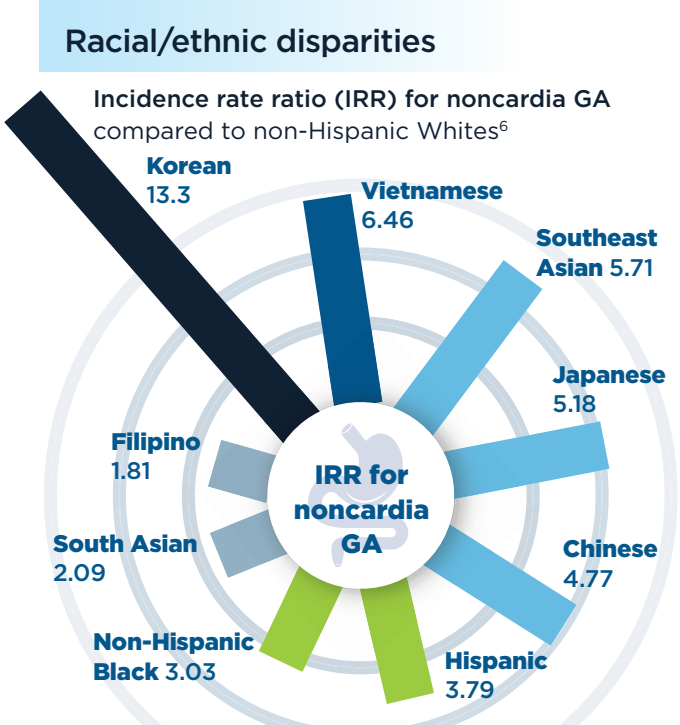
Unlike in some countries where noncardia GA has a universally higher incidence, the United States does not have evidence-based guidelines for gastric cancer screening, including among higher-risk groups. This is in contrast to endoscopic surveillance guidelines once premalignant changes are diagnosed.[7] Recent data support that targeted monitoring of at-risk minorities could be effective.[2] Data from decision model analyses also support the cost-effectiveness of endoscopy for gastric cancer screening at the time of colonoscopy for colorectal cancer (with continued surveillance of GIM if identified) in non-White racial and ethnic groups, including the most populous Asian American ethnic groups residing in the US.[1,2,6,8]

H. pylori treatment remains a challenge given global increases in antibiotic resistance and other factors leading to treatment failure.[3,9,10] Bismuth-containing quadruple therapy with metronidazole, tetracycline, and a proton pump inhibitor (PPI) (PBMT) offers the best empiric first-line approach in the face of rising clarithromycin resistance rates, but may be hampered by regimen complexity, expense, and side effects.[9] Antibiotic stewardship insists therapy be guided by established susceptibility; however, in the US, obtaining *H. pylori* susceptibility testing is challenging, not routinely available, requires endoscopy with biopsies to obtain samples for culture and susceptibility testing, and rarely provides useful results in real-world practice. Other limitations include discordant *in vitro* resistance and *in vivo* susceptibility observations.[3,9] Though, noninvasive molecular susceptibility testing may shift this narrative. These combined factors contribute to rising rates of refractory *H. pylori* infection, a strong risk factor for progression of premalignant changes in the stomach.[3]

The AGA's *H. pylori* guidance states that regimens with amoxicillin and/or rifabutin are favored for patients in whom PBMT has failed, as they are known to have minimal resistance. In patients with true penicillin allergy, the update offers alternative regimens. If low local resistance is confirmed, levofloxacin-containing regimens, with or without concomitant bismuth, may also be considered. The update also emphasized the importance of achieving adequate gastric acid suppression in successful *H. pylori* eradication. Due to the possibility that certain patients may be rapid PPI metabolizers, high-dose or high-potency PPIs should be considered.[3] Of note, potassium-competitive acid blockers (not yet approved for use in the US) are being evaluated in ongoing clinical trials as potent gastric acid suppressors in *H. pylori* eradication regimens; however, there is insufficient data to guide their placement in refractory *H. pylori* management.[3,9-11]



Given as costs per quality-adjusted life years. A threshold of $100,000 was used to determine cost-effectiveness of intervention. Compared with no gastric cancer screening, the current standard of practice.



Study of 10,265 GAs registered in the California Cancer Registry between 2011 and 2015 for individuals aged ≥20 years. IRR compared to non-Hispanic Whites to calculate IRR.

Rethinking management of alcohol-associated liver disease:

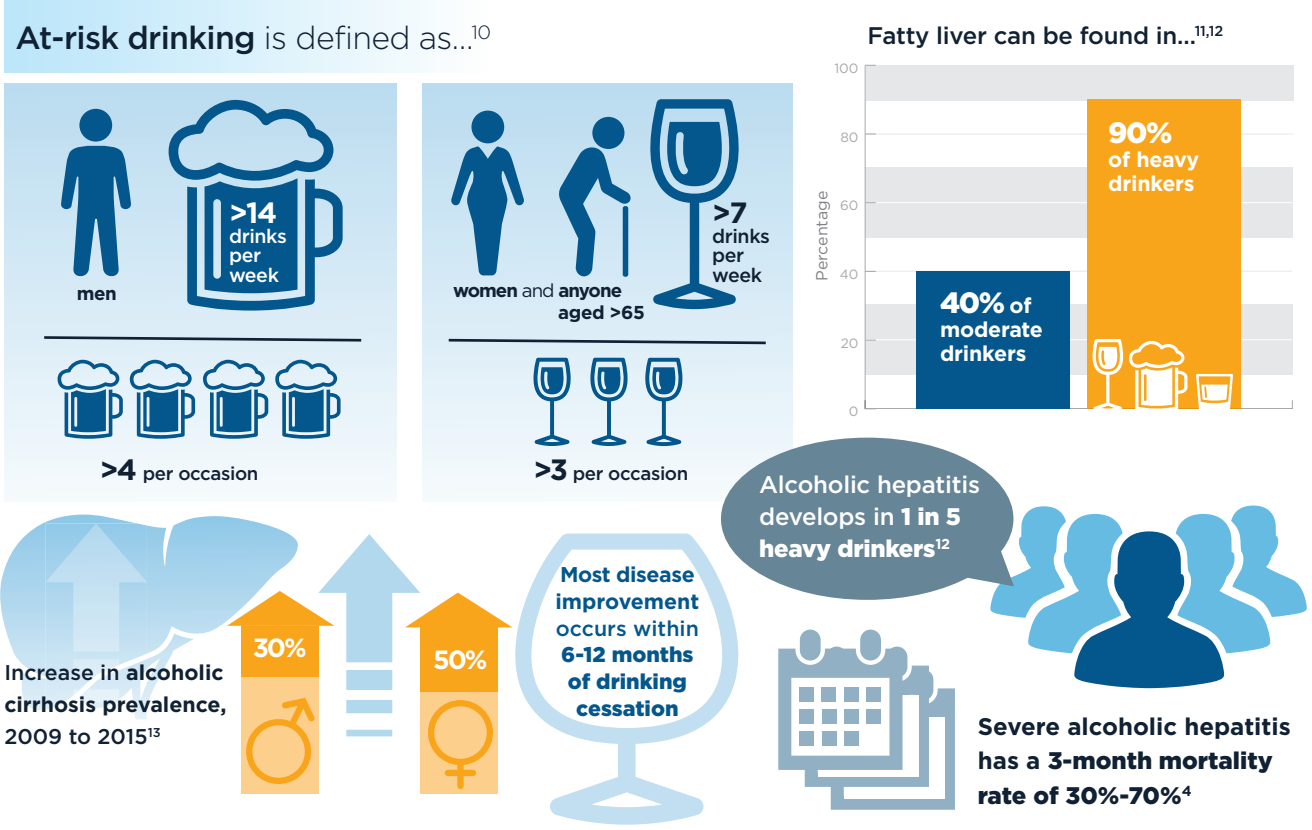
The other fatty liver epidemic

Mack C. Mitchell, MD, FAASLD

Liver-related morbidity and mortality has been rising and is now the fourth leading cause of death for those aged 45 to 64 years. Individuals with alcohol-associated liver disease (ALD) had the most significant increase in hospitalization (11.1%, $P < .001$) and the highest mortality between 2012 and 2016.[1] Concomitantly, nonalcoholic fatty liver disease (NAFLD) has a global prevalence of about 25%, a sharp increase from 2007, in part due to increases in obesity and type 2 diabetes.[2,3]

ALD and NAFLD were initially considered separate diseases based on the definition of ALD as alcohol consumption of at least 30 g/d in men or 20 g/d in women. Distinguishing between the two is hampered by overlapping clinical features and comorbidities, and the unmeasured effect of drinking on NAFLD.[2] Mild-to-moderate consumption was once thought to have a protective effect against developing NAFLD, but more recent evidence indicates any alcohol intake negatively influences fibrosis progression and development of hepatocellular cancer.[2] However, metabolic factors affect ALD, leading experts to consider a change in terminology reflecting a wider spectrum of disease in the hopes of improving natural history data.[2]

New advances abound for diagnostics and treatment of alcohol-associated hepatitis. High levels of accuracy associated with typical clinical assessments (ie, jaundice, bilirubin >5 mg/dL, AST:ALT > 2:1, neutrophilic leukocytosis, etc) preclude a need for routine biopsy, but transjugular sampling can help in cases of uncertainty.[4] Tests to detect alcohol use and assessment to determine disease presence and prognosis now include breath-sensing technologies (eg, trimethylamine and pentane [TAP]), molecular biomarkers (eg, TNFα, IL-6, etc), and new scoring systems (Model for End-Stage Liver Disease



[MELD] + Lille).[4] Among individuals with alcohol-associated hepatitis and suspected infection, polymerase chain reaction panels and metagenomic techniques may help confirm diagnosis and enhance antibiotic choice in the future.[5]

The Steroids or Pentoxifylline for Alcoholic Hepatitis (STOPAH) trial confirmed that neither pentoxifylline nor corticosteroids (CS) significantly improved survival beyond 30 days, although a different study showed superiority for CS over pentoxifylline and placebo.[4]

The therapeutic focus has shifted toward restorative measures addressing hepatic injury (eg, granulocyte-colony stimulating factor [G-CSF]) and a correction of dysbiosis and leaky gut.[4] N-Acetylcysteine and metadoxine with CS seem to offer short-term advantages while G-CSF improves 3-month survival, and ongoing studies are promising for zinc, anakinra (anti-IL1R), F-652 (IgG2 + IL-22), obeticholic acid (farnesoid X receptor [FXR] agonist), and simtuzumab (lysyl oxidase-like-2 antibody).[4] Prebiotics and probiotics are not as useful as hoped, but fecal microbial transplant and the use of bovine colostrum may reduce pathogens and improve beneficial microbiota, while active infections have been treated with bacteriophages to varying degrees of success in animal models.[4,5]

Choosing the time for liver transplantation can be difficult, but early intervention provides good outcomes for select patients.[4,5] One transplantation center studied the effects of the increase in ALD during COVID-19 and found that ALD relapse did not occur, supporting observations that transplantation in alcohol-associated hepatitis can be performed with an acceptably low risk of relapse.[4,6]

During the COVID-19 lockdown, many predicted increased alcohol consumption with downstream ALD effects.[6-8] Early stages saw surges in withdrawal, withdrawal-associated complications (eg, suicidality), and toxicity from methanol and other substitutes.[7] However, increased drinking and ALD then began trending upward, mostly with a younger demographic (35-53 years) and increased ethnic diversity.[6,8]

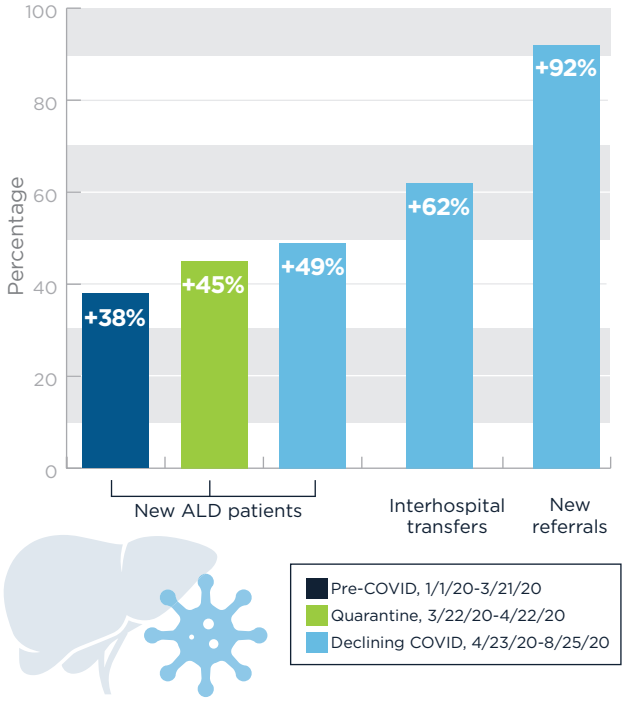
Patients with ALD share a higher risk of severe COVID-19 outcomes and preexisting immune suppression or other metabolic disorders, and an inclination to not heed social distancing.[7,9] Concerns that the virus would manifest liver damage appear largely unfounded and transient at best, although experimental treatments should be monitored.[9]

COVID-19 and alcohol consumption

Introducing a wider spectrum of terminology

- **MAFLD: metabolic-associated fatty liver disease**
- **AAFLD: alcohol-associated fatty liver disease**
- **ALD-MetS: ALD with metabolic factors**
- **BALFD: both alcohol- and metabolic-associated fatty liver disease**

Rise in ALD patients at an NYC liver transplantation center throughout COVID-19[6]



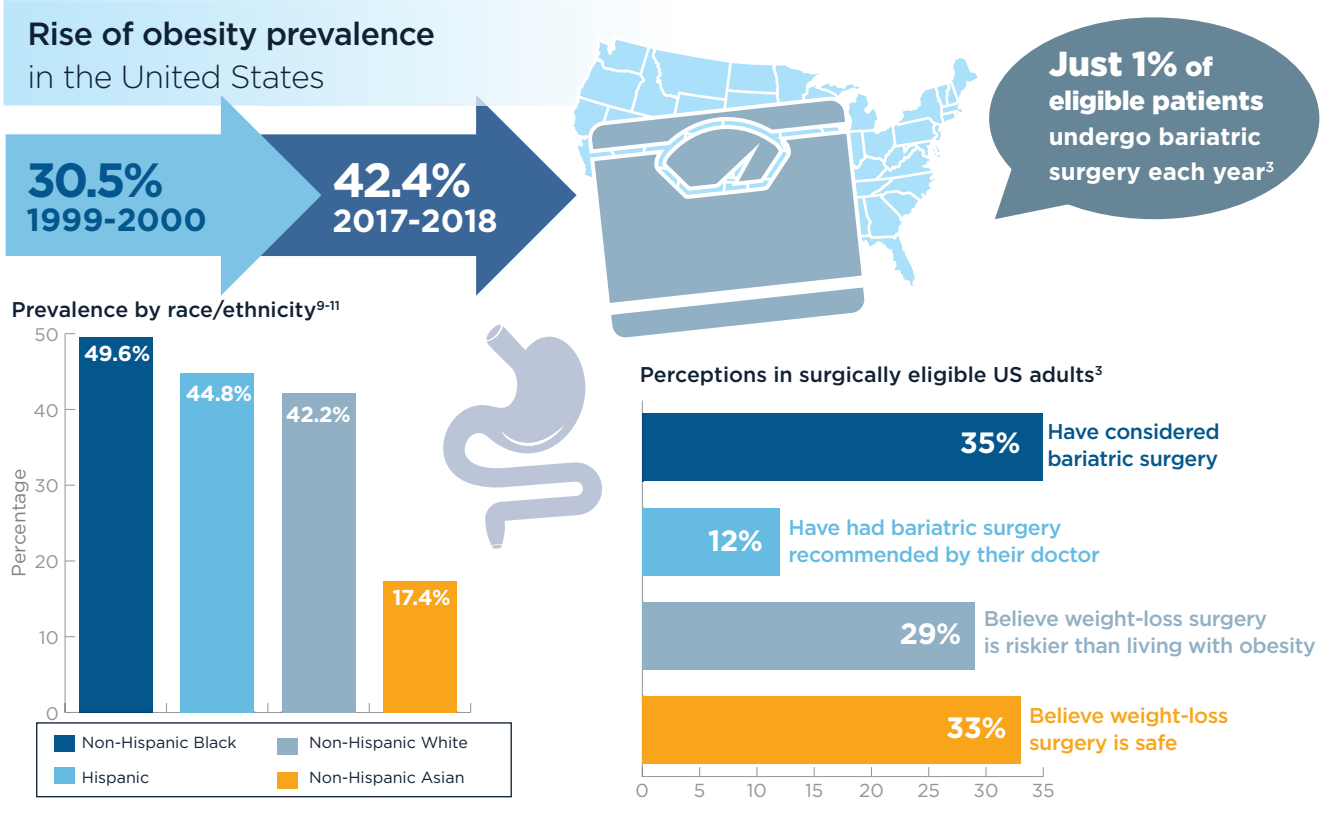
Endoscopic bariatric and metabolic therapies
for weight loss

Allison R. Schulman, MD, MPH

Obesity, despite comorbid sequelae, has seen minimal uptake of bariatric surgical options for a variety of reasons, including cost, access, and adverse-event profile.[1-4] Furthermore, while bariatric surgery is the most effective strategy for weight loss, weight regain is increasingly recognized as a problem.[2,5] More recently, endoscopic bariatric and metabolic therapies (EBMTs) have evolved as less invasive alternatives and have proven to be safe, cost-effective, and often reversible and repeatable. EBMTs were initially thought to induce weight loss primarily through gastric restriction and/or overall reduction in caloric intake. With increasing experience, however, there is now recognition of improved gut hormonal changes, intestinal absorption modifications, and alterations in the incretin effect that may be associated with improved metabolic parameters beyond weight loss.[1,2,5,6] Many of these interventions have demonstrated improvement in such comorbidities as type 2 diabetes and nonalcoholic fatty liver disease.[2,3,6]

Three intragastric balloon (IGB) options are FDA-approved as space-occupying devices for patients with a BMI of 30 to 40 kg/m^2: Orbera® and ReShape™ are fluid-filled, while Obalon™ inflates with a nitrogen-mix gas.[1-2] As a group, IGBs produce a 6.6% to 13.2% total body weight loss (TBWL) at removal, depending on the type of balloon placed.[1-3,7] IGBs may also positively affect metabolic and cardiopulmonary comorbidities.[2] Reductions in weight and improvement in obesity-related comorbidities appear durable following removal, though adjuncts may be needed.[1-3,8] Common adverse events (mild or moderate) are nausea, vomiting, and reflux, for which proton pump inhibitors are commonly prescribed. Approximately 5% to 18% of patients require device removal due to intolerance or device failure.[3,8] Newer technologies hope to address volume adjustability, intolerance, placement, removal, and dwell time.[1-3]

Other gastric devices and interventions have also been studied. The recently approved oral superabsorbent



gel capsule (Plenity®) behaves similarly to IGBs by expanding in the stomach, maintaining its volume through to the colon. Nearly 59% of patients achieved 5% weight reduction, with 37.7% experiencing mild gastrointestinal effects, and many saw metabolic and blood-pressure improvements.[9] Approved in 2019 but still not commercially available, the TransPyloric Shuttle® uses peristalsis to set a small bulb into the duodenal opening, tethering a larger one across the pylorus in the stomach to diminish gastric emptying, with preliminary data indicating up to 50% excess body weight loss (EBWL) but also an approximately 10% occurrence of gastric ulceration.[1,3] Aspiration therapy (AspireAssist®) functions similarly to a percutaneous endoscopic gastrostomy (PEG) tube and is FDA-cleared for use in patients with a BMI of 35 to 55 kg/m². The tube allows aspiration of gastric contents after meals and is effective at providing about 30% to 50% EBWL. It remains in place for 1 year and then is either removed or exchanged. This device carries stomal-related risks such as cellulitis and persistent gastrocutaneous fistula.[1,3,6]

Endoscopic sleeve gastroplasty (ESG) using full-thickness suturing (OverStitch™, OverStitch SX™, Apollo Endosurgery™) produces lower %TBWL compared with laparoscopic gastroplasty (17.1% vs 23.6%) but exhibited significant improvements in adverse outcomes and length of stay.[1,3,6] One 5-year observational study found sustained EBWL at 45.3%, with the best success in younger patients and with more experienced endoscopists.[4] Other promising endoscopic procedures to watch include primary obesity surgery endoluminal (POSE) via the Incisionless Operating Platform™ and EndoZip™.[1,3,6]

Techniques such as endoluminal bypass liners (gastroduodenojejunal [endoluminal bypass] and the shorter duodenal-jejunal device [EndoBarrier®]) that deploy a fluoropolymer sleeve, and duodenal mucosal resurfacing (Revita®), which applies heat therapy to the duodenal intestinal barrier, are intended to produce metabolic change (with weight reduction as a secondary effect) and are awaiting FDA approval.[1,3,6] A particularly exciting newcomer, incisionless magnetic anastomosis, places opposing magnets in the proximal jejunum and distal ileum which force a compression anastomosis, with removal of the magnets through natural defecation. Test participants showed 40.2% EBWL at 1 year and a corresponding drop in HbA_{1c} (7.8 to 5.9).[1,3]

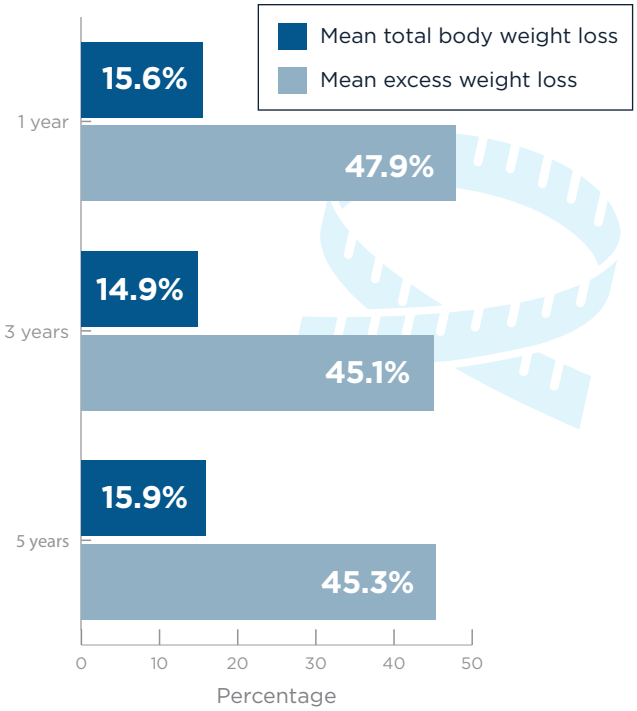
5-year data from a prospective cohort of 216 patients who underwent ESG[4]

Baseline characteristics:

- 68% female
- Mean age of 46 ± 13 years
- Mean BMI of 39 ± 6 kg/m²

Adverse events

- **32%** of patients had mild AEs
- **25%** experienced heartburn for up to 3 weeks after the procedure
- **19%** experienced nausea and/or vomiting after the procedure
- **31%** experienced epigastric pain beyond 24 hours after the procedure



The weight-loss journey
at University of Michigan

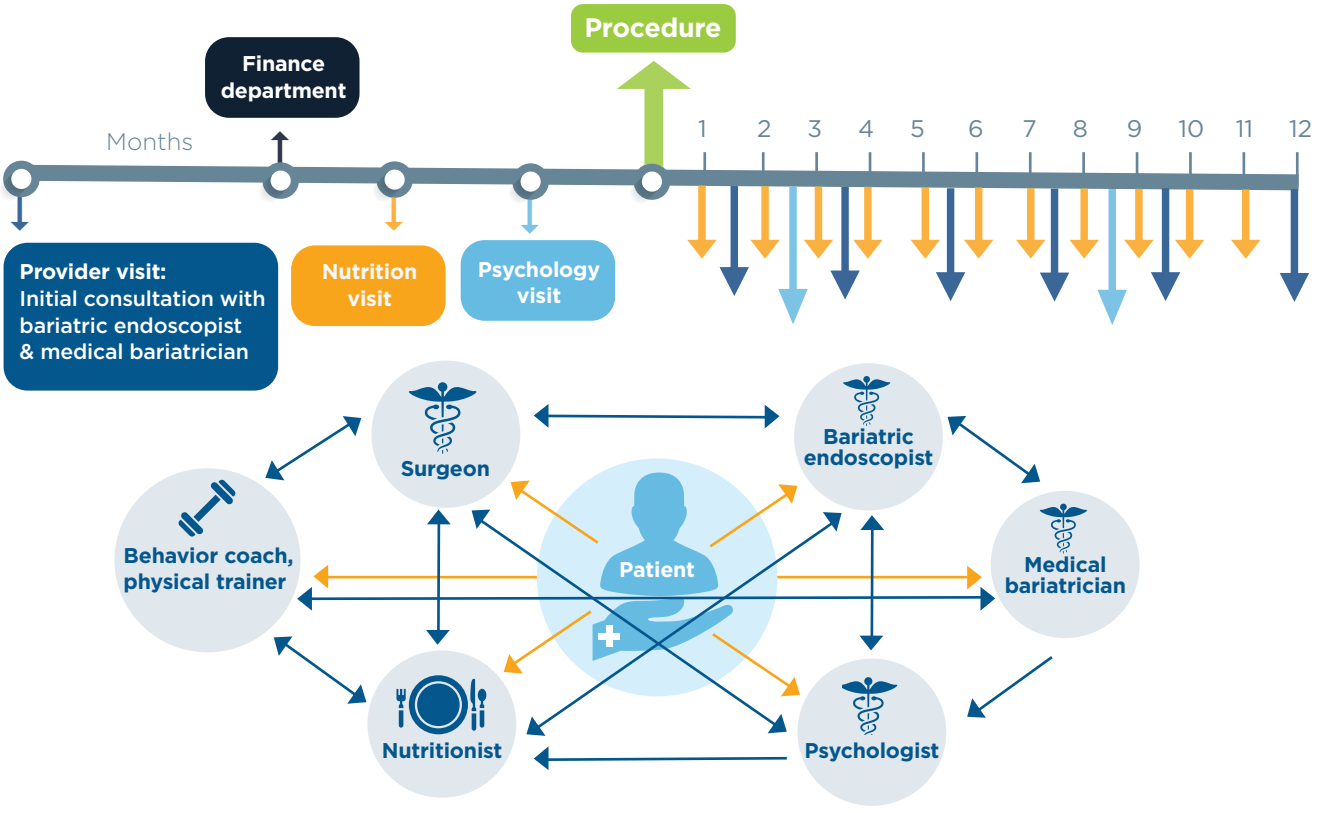
Allison R. Schulman, MD, MPH

Patients with obesity who seek to lose weight should be evaluated at a comprehensive weight loss center, where treatment options can involve a tailored, multimodal approach to each individual patient. At the University of Michigan, each potential candidate is reviewed by a highly trained team including a bariatric surgeon, a bariatric endoscopist, an obesity medicine physician, a behavioral psychologist, a registered dietician, a social worker, and often a behavioral coach and/or physical trainer. When there is consensus about the optimal approach for an individual patient, endoscopic bariatric metabolic therapy (EBMT) is considered.

EBMT has been developed to fill the gap between lifestyle interventions and surgical procedures. EBMT may be a less invasive option for people who have tried diet and exercise without success or who are not candidates for, or do not want to pursue, a surgical intervention. In certain situations, EBMT may also offer bridge therapy for patients who require weight loss prior to being considered for other types of surgery, including joint replacements or organ transplants. For patients who have undergone bariatric surgery but have regained weight, there are additional minimally invasive options for weight loss.

Because these procedures are not always covered by medical insurance, patients are referred to a University of Michigan financial counselor to review the costs involved. If a patient selects an endoscopic approach, the purchase price is inclusive of the procedure and 12 months of follow-up, including frequent visits with the multidisciplinary team. A dedicated bariatric clinical navigator, physician assistant, nurse, and scheduler also ensure individualized and accessible care. Since the prepaid program's implementation, tremendous growth has been seen over the past three years, with very compelling results.

Overview of primary EBMT at the University of Michigan



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Rethinking management of alcohol-associated liver disease: The other fatty liver epidemic

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