aga American Gastroenterological Association

*Official newspaper of the AGA Institute*

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# GI&Hepatology News

December 2022

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SHAPECHARGE/E+/GETTY IMAGES

## Mentorship key to improving workforce diversity

**BY TARA HAELLE**
*MDedge News*

Increasing mentorship opportunities for gastroenterology and hepatology residents and medical students from populations underrepresented in medicine is essential to increase diversity in the specialty and improve health disparities among patients, according to a special report published simultaneously in Gastroenterology (2022 Oct 11. doi: 10.1053/j.gastro.2022.06.059) and three other journals.

"This study helps to establish priorities for diversity, equity and inclusion in our field and informs future interventions to improve workforce diversity and eliminate health care disparities among the patients we serve," Folasade P. May, MD, PhD, MPhil, the study's corresponding author and an associate professor of medicine at the University of California, Los Angeles, said in a prepared statement.

The report, the result of a partnership between researchers at UCLA and the Intersociety Group on Diversity, reveals the findings of a survey aimed at

*See* **Diversity** · *page 11*

## New AGA guidelines address antiobesity medications

**BY TARA HAELLE**
*MDedge News*

Adults with obesity who do not respond adequately to lifestyle interventions alone should be offered one of four suggested medications to treat obesity according to new guidelines published by the American Gastroenterological Association in Gastorenterology ((doi.org/10.1053/j.gastro.2022.08.045).

Recommended first-line medications include semaglutide, liraglutide, phentermine-topiramate extended-release (ER), and naltrexone-buproprion ER, based on moderate-certainty evidence. Also recommended, albeit based on lower-certainty evidence, are phentermine and diethylpropion. The guidelines suggest avoiding use of orlistat. Evidence was insufficient for Gelesis100 superabsorbent hydrogel.

The substantial increase in obesity prevalence in the United States – from 30.5% to 41.9% in just the 2 decades from 2000 to 2020 – has likely contributed to increases in various obesity-related complications, wrote Eduardo Grunvald, MD, of the

*See* **Antiobesity** · *page 10*

## First RCT evaluates benefits of colonoscopy screening

**BY BECKY MCCALL**
*MDedge News*

VIENNA – The real-world risk of colorectal cancer and associated mortality was lower among people who underwent a single screening colonoscopy than among those who did not have a colonoscopy, though only modestly so, the 10-year follow-up of the large, multicenter, randomized Northern-European Initiative on Colorectal Cancer (NordICC) trial shows.

In effect, this means the number needed to invite to undergo screening to prevent one case of colorectal cancer is 455 (95%

*See* **RCT** · *page 12*


INSIDE





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# GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

## LETTER FROM THE EDITOR

# *GIHN's Crystal Anniversary: Reflecting on the future of GI*

Our December 2022 issue marks the conclusion of GIHN's 15th Anniversary Series. We hope you have enjoyed these special articles intended to celebrate the success of AGA's official newspaper since its launch in 2007, mirroring equally rapid advances in our field. Over the past year, GIHN's esteemed Associate Editors and former Editors-in-Chief have helped us "look back" on how the fields of gastroenterology and hepatology have changed since the newspaper's inception, including advances in our understanding of the microbiome, innovations in endoscopic practice, changes in the demographics of the GI workforce, and breakthroughs in the treatment of hepatitis C. Now, as we conclude our 15th anniversary year, it is only fitting that we "look forward" and consider the type of innovative coverage that will grace GIHN's pages in the future. To that end, we asked a distinguished group of AGA thought leaders, representing various backgrounds and practice settings, to share their perspectives on what are likely to be the biggest change(s) in the field of GI over the next 15 years. We hope you find their answers inspiring as you consider your own reflections on this question.


Dr. Adams

**Now as we conclude our 15th anniversary year, it is only fitting that we "look forward" and consider the type of innovative coverage that will grace GIHN's pages in the future.**

As we close out 2022, we also wish to extend a big "thank you" to all the individuals who have provided thoughtful commentary to our coverage, helping us to understand the implications of innovative research findings on clinical practice and how changes in health policy impact our practices and our patients. I would also like to acknowledge our hardworking AGA and Frontline Medical Communications editorial teams, without whom this publication would not be possible. We wish you all a restful holiday season with your family and friends and look forward to reconnecting in 2023 – stay tuned for the launch of an exciting new GIHN initiative as part of our January issue!

***Megan A. Adams, MD, JD, MSc***
***Editor-in-Chief***

# Look forward: 15 years into the future of GI

As we close GI & Hepatology News' 15th anniversary year, we wanted to pause and reflect not only on the last 15 years, but also on what the next 15 years will bring.

To that end, we asked leaders in the field to share their reflections on GI's next chapter.

"I think that the biggest changes moving forward will be the following: utilizing artificial intelligence to enhance diagnosis in endoscopy and pathology along with streamlined information harvesting from the EMR and truly personalized medicine so that we can predict which patients will benefit optimally from the increasing number of biologic treatments in IBD and EoE."

*Gary Falk, MD, MS, AGAF*
*Professor of medicine and codirector, GI Motility/Physiology Program*
*University of Pennsylvania Perelman School of Medicine*
*Committees: AGA Council Diversity, Equity and Inclusion Subcommittee; AGA Institute Council; Techniques and Innovations in Gastrointestinal Endoscopy Editors*

"I anticipate seeing a shift in how we communicate with patients, with increased touchpoints between visits through symptom monitoring applications, social media, and more integrated electronic records systems. I also think we will see a growing influx of advanced practitioners joining our care teams both in the clinic and endoscopy space, and the role of the gastroenterologist will include even greater

*Continued on page 26*

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# Assessed medications

**Antiobesity** *from page 1*

University of California San Diego, and colleagues. These include CV disease, stroke, stroke, type 2 diabetes mellitus, nonalcoholic steatohepatitis, obstructive sleep apnea, osteoarthritis, and certain types of cancer, such as colorectal cancer.

"Lifestyle intervention is the foundation in the management of obesity, but it has limited effectiveness and durability for most individuals," the authors wrote. Despite a range of highly effective pharmacological therapies developed for long-term management of obesity, these agents are not widely used in routine clinical care, and practice variability is wide. There is a "small number of providers responsible for more than 90% of the prescriptions, partly due to lack of familiarity and limited access and insurance coverage," the authors wrote.

A multidisciplinary panel of 10 experts and one patient representative, therefore, developed the guidelines by first prioritizing key clinical questions, identifying patient-centered outcomes, and conducting an evidence review of the following interventions: semaglutide 2.4 mg, liraglutide 3.0 mg, phentermine-topiramate extended-release (ER), naltrexone-bupropion ER, orlistat, phentermine, diethylpropion, and Gelesis100 superabsorbent hydrogel. The guideline panel then developed recommendations and provided clinical practice considerations regarding each of the pharmacologic interventions.

The authors focused on adults, noting that pharmacologic treatment of childhood obesity is beyond the scope of these guidelines. The evidence synthesis yielded nine recommendations for the pharmacological management of obesity by gastroenterologists, primary care clinicians, endocrinologists, and other providers caring for patients with overweight or obesity. The target audience of the guidelines, however, includes patients and policymakers, the authors wrote.

"These guidelines are not intended to impose a standard of care, but rather, they provide the basis for rational, informed decisions for patients and health care professionals," the authors wrote. "No recommendation can include all the unique individual circumstances that must be considered when making recommendations for individual patients. However, discussions around benefits and harms can be used for shared decision-making, especially for conditional recommendations where patients' values and preferences are important to consider."

**"These guidelines are not intended to impose a standard of care, but rather, they provide the basis for rational, informed decisions for patients and health care professionals."**

The panel conducted a systematic review and meta-analysis of randomized controlled trials of Food and Drug Administration–approved obesity medications through Jan. 1, 2022. Though they primarily included studies with at least 48 weeks' follow-up, they included studies with a follow-up of less than a year if one with 48 weeks' outcomes did not exist.

The first of the nine recommendations was to add pharmacological agents to lifestyle interventions in treating adults with obesity or overweight and weight-related complications who have not adequately responded to lifestyle interventions alone. This strong recommendation was based on moderate-certainty evidence.

"Antiobesity medications generally need to be used chronically, and the selection of the medication or intervention should be based on the clinical profile and needs of the patient, including, but not limited

*Continued on page 26*

## CLINICAL CHALLENGES AND IMAGES

# What's your diagnosis?

**BY JANA G. HASHASH, MD, DIMA IBRAHIM, MD, AND NESRINE A. RIZK, MD**

*Previously published in Gastroenterology (2019 May 1;156[6]:1574-5).*

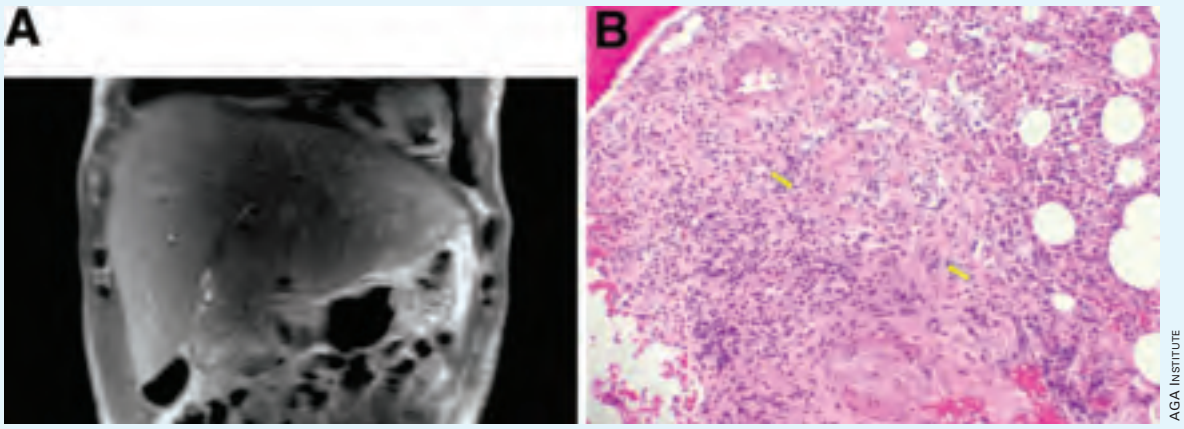
A 48-year-old man with HIV infection (PCR undetectable CD4 483) who used cocaine and was a heavy user of alcohol presented with jaundice, fever, and acute-onset left–upper quadrant abdominal pain. The pain was exacerbated by breathing. He had associated intermittent fevers and weight loss starting 3 weeks before presentation. He denied chest pain, nausea, vomiting, or a change in bowel habits. Home medications included dolutegravir, emtricitabine, tenofovir disoproxil fumarate, and recent intake of tamoxifen, clomiphene, and chorionic gonadotropin to counteract the effects of anabolic steroids that were used 4 months before presentation.

On examination, his temperature was 39° C, he was jaundiced, and he had icteric sclera. The abdomen was soft and nondistended with minimal left–upper quadrant tenderness. Blood work showed a white blood cell count of 7,800/mcL, hemoglobin of 12.2 g/dL, platelets of 378,000/mcL, alanine aminotransferase 236 IU/L (upper limit of normal [ULN], 65 IU/L), aspartate aminotransferase 166 IU/L (ULN, 50 IU/L), total bilirubin 3.4 mg/dL (ULN, 1.2 mg/dL), direct bilirubin 2.6 mg/dL (ULN, 0.3 mg/dL), alkaline phosphatase 1,064 IU/L (ULN, 120 IU/L), gamma-glutamyl transferase (GGT) of 655 (ULN, 50 IU/L), protein of 73 g/L, and albumin of 34 g/L. Lipase, lactate dehydrogenase, and international normalized ratio were normal. Blood smear was unrevealing. A contrasted computed tomography scan showed multiple subcentimetric mesenteric and multiple retroperitoneal lymph nodes, the largest of which was 1.3 cm in the aortocaval area. All medications were discontinued. Hepatitis A, B, and C serologies were negative, including hepatitis B and C PCR. Epstein-Barr virus IgM was negative and cytomegalovirus IgM was equivocal.

During this hospitalization, his cholestatic liver enzymes continued to rise, reaching a maximum value of total bilirubin of 7.8 mg/dL, direct bilirubin of 6.5 mg/dL, and 3 days later, alkaline phosphatase of 1,637 IU/L and GGT of 1,171 IU/L. Alanine aminotransferase and aspartate aminotransferase slowly downtrended during the hospitalization. Magnetic resonance cholangiopancreatography showed an edematous enlarged liver with minimal peripheral intrahepatic dilatation without an obstructing mass or extrahepatic biliary ductal dilatation (Figure A). Comprehensive autoimmune hepatic serology, iron studies, ceruloplasmin, and alpha-1 antitrypsin labs were negative. The patient remained febrile, so a positron emission tomography computed tomography scan was done and it showed active and enlarged (2.8-cm) portocaval and porta hepatis lymph nodes. Bone marrow biopsy showed no lymphoproliferative disorder, but there was a small poorly formed granuloma (Figure B, between the arrows).

What other testing would you obtain to evaluate this patient's fever and abnormal liver enzymes?

*The answer is on page 25.*

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# Lack of representation at issue

**Diversity** *from page 1*

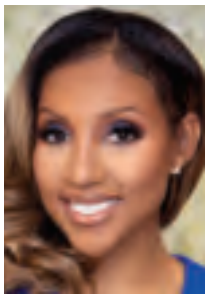
assessing current perspectives on individuals underrepresented in medicine and health equity within gastroenterology and hepatology. The collaboration involved five gastroenterology professional societies: the American Association for the Study of Liver Diseases; American College of Gastroenterology; American Gastroenterological Association; American Society of Gastrointestinal Endoscopy; and North American Society for Pediatric Gastroenterology, Hepatology and Nutrition.

"The current racial and ethnic composition of the GI and hepatology workforce does not reflect the population of patients served or the current matriculants in medicine," Harman K. Rahal, MD, of UCLA and Cedars-Sinai Medical Center, Los Angeles, and James H. Tabibian, MD, PhD, of UCLA and Olive View–UCLA Medical Center, and colleagues wrote. "As there are several conditions in GI and hepatology with disparities in incidence, treatment, and outcomes, representation of UIM [underrepresented in medicine] individuals is critical to address health disparities."

The term "underrepresented in medicine" is defined by the Association of American Medical Colleges (https://www.aamc.org/what-we-do/equity-diversity-inclusion/underrepresented-in-medicine ) as "those racial and ethnic populations that are underrepresented in the medical profession relative to their numbers in the general population." The authors explained that these groups "have traditionally included Latino (i.e., Latino/a/x), Black (or African American), Native American (namely, American Indian, Alaska Native, and Native Hawaiian), Pacific Islander, and mainland Puerto Rican individuals."

The five gastroenterology and hepatology societies partnered with investigators at UCLA to develop a 33-question electronic survey "to determine perspectives of current racial, ethnic, and gender diversity within GI and hepatology; to assess current views on interventions needed to increase racial, ethnic, and gender diversity in the field; and to collect data on the experiences of UIM individuals and women in our field," according to the report's authors. The survey was then distributed to members of those societies, with 1,219 respondents.

The report found that inadequate representation of people from those underrepresented groups in the education and training pipeline was the most frequently reported barrier to improving racial and ethnic diversity in the field (35.4%), followed by insufficient racial and ethnic minority group representation in professional leadership (27.9%) and insufficient racial and ethnic minority group representation among practicing GI and hepatology professionals in the workplace (26.6%). Only 9% of fellows in GI and hepatology are from groups underrepresented in medicine, according to data from the Accreditation Council for Graduate Medical Education (http://www.acgme.org/About-Us/Publications-and-Resources/Graduate-Medical-Education-Data- Resource-Book). Furthermore, one study has shown that the proportion of UIM in academic faculty has never exceeded 10% at each academic rank (Gastroenterology. 2019 Mar;156[4]:829-33); there has even been a decline recently among junior academic faculty positions. That study also found that only 9% of academic gastroenterologists in the United States identify as underrepresented in medicine, with little change over the last decade.



Dr. McCutchen

Potential contributors to this low level of representation, the authors wrote, include "lack of racial and ethnic diversity in the medical training pipeline, nondiverse leadership, bias, racial discrimination, and the notion that UIM physicians may be less likely to promote themselves or be promoted."

Another potential contributor, however, may be complacency within the field about the need to improve diversity and taking actions to do so.

A majority of White physicians (78%) were very or somewhat satisfied with current levels of workforce diversity, compared with a majority of Black physicians (63%) feeling very or somewhat unsatisfied.

This disconnect was not surprising to Aja McCutchen, MD, a partner at Atlanta Gastroenterology Associates who was not involved in the survey.

"One cannot discount the lived experience of a [person underrepresented in medicine] as it relates to recognizing conscious and unconscious biases, microaggression recognition, and absence of [underrepresented clinicians] in key positions. This is a reality that I do see on a daily basis," Dr. McCutchen said in an interview.

Only 35% of respondents felt there is "insufficient racial and ethnic representation in education and training," and just over a quarter (28%) felt the same about representation in leadership. In fact, most respondents (59.7%) thought that racial and ethnic diversity had increased over the past 5 years even though data show no change, the authors noted.

Although Dr. McCutchen appreciated the broad recognition from respondents, regardless of background, to improve diversity in the pipeline, she noted that "retention of current talent and future talent would also require cultural shifts in understanding the challenges of the [underrepresented] members," Dr. McCutchen said.

**"Diversity in medicine also leads to greater diversity in thoughts, better returns on investments, increased scholarly activities related to health equity, to name a few."**

Again, however, the majority of the respondents (64.6%) were themselves not members of underrepresented groups. Nearly half the respondents (48.7%) were non-Hispanic White, and one in five (22.5%) were Asian, Native Hawaiian, or Pacific Islander. The remaining respondents, making up less than a third of the total, were Hispanic (10.6%), Black (9.1%), American Indian or Alaskan Native (0.2%), another race/ethnicity (3.3%), or preferred not to answer (5.7%).

Dr. McCutchen said she had mixed feelings about the survey overall.

"On the one hand, I was eager to read the perceptions of survey respondents as it relates to diversity, equity and inclusion in the GI space as very little cross-organizational data exists," said Dr. McCutchen. "On the other hand, the responses reminded me that there is a lot of work to be done as I expected more dissatisfaction with the current GI workforce in both academia and private practice respondents."

She was surprised, for example, that nearly three-quarters of the respondents were somewhat or very satisfied, and that a majority thought racial and ethnic diversity had increased.

Studies on provider-patient concordance have shown that patients feel it's important to share common ground with their physicians particularly in terms of race, ethnicity and language, the authors noted.

"This patient preference underscores the need to recruit and train a more diverse cohort of trainees into GI and hepatology fellowships if the desired goal is to optimize patient care and combat health disparities," they wrote. They pointed out that cultural understanding can influence how patients perceive their health, symptoms, and concerns, which can then affect providers' diagnostic accuracy and treatment recommendations. In turn, patients may have better adherence to treatment recommendations when they share a similar background as their clinician.

"Diversity in medicine also leads to greater diversity in thoughts, better returns on investments, increased scholarly activities related to health equity, to name a few," Dr. McCutchen said.

The top recommendations from respondents for improving representation of currently underrepresented individuals in GI and hepatology were to increase mentorship opportunities for residents (45%) and medical students (43%) from these groups and to increase representation of professionals from these backgrounds in program and professional society leadership (39%). A third of respondents also recommended increasing shadowing opportunities for undergraduate students from these underrepresented populations.

Dr. McCutchen expressed optimism regarding the initiatives to improve diversity, equity and inclusion across the gastroenterology spectrum.

"It is incumbent upon all of us to continue to be the driving force of change, which will be a journey and not a destination," Dr. McCutchen said. "In the future, diversity, equity, and inclusion will be the expectation, and we will ultimately move closer to the goal of completely eliminating health care inequities."

The research was funded by the National Cancer Institute, the UCLA Jonsson Comprehensive Cancer Center, and Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research Ablon Scholars Program. The authors reported no conflicts of interest. Dr. McCutchen disclosed relationships with Bristol-Myers Squibb and Redhill Biopharmaceuticals. ■

# Colonoscopy screening studied

**RCT** *from page 1*

confidence interval, 270-1,429), the researchers determined.

The results were presented at the United European Gastroenterology Week 2022 meeting and were published simultaneously in The New England Journal of Medicine (2022 Oct 9. doi: 10.1056/NEJMoa2208375). The study, which was designed to be truly population based and to mimic national colorectal cancer screening programs, estimated the effect of screening colonoscopy in the general population.

The primary outcome was determined on an intention-to-screen basis. All persons invited to colonoscopy screening were compared with those recieving usual care.

At UEG 2022, the researchers presented the interim 10-year colorectal cancer risk, which was found to be 0.98%, compared to 1.20%. This represents a risk reduction of 18% among colonoscopy invitees (risk ratio, 0.82; 95% CI, 0.70-0.93). During the study period, 259 cases of colorectal cancer were diagnosed in the invited group versus622 in the usual-care group.

The risk of death from colorectal cancer was 0.28% in the invited group and 0.31% in the usual-care group (RR, 0.90; 95% CI, 0.64-1.16). The risk of death from any cause was similar in both the invited group and the usual-care group, at 11.03% and 11.04%, respectively (RR, 0.99; 95% CI, 0.96-1.04).

The authors noted that the benefit would have been greater had more people undergone screening; only 42% of those who were invited actually underwent colonoscopy. In an adjusted analysis, had all those who had been invited to undergo screening undergone colonoscopy, the 10-year risk of colorectal cancer would have decreased from 1.22% to 0.84%, and the risk of colorectal cancer–related death would have fallen from 0.30% to 0.15%.

The researchers, led by gastroenterologist Michael Bretthauer, MD, from the department of medicine, gastrointestinal endoscopy, University of Oslo, acknowledged that, despite the "observed appreciable reductions in relative risks, the absolute risks of the risk of colorectal cancer and even more so of colorectal cancer–related death were lower than those in previous screening trials and lower than what we anticipated when the trial was planned."

However, they add that "optimism related to the effects of screening on colorectal cancer–related death may be warranted in light of the 50% decrease observed in adjusted per-protocol analyses."

With his coauthors, Dr. Bretthauer wrote that even their adjusted findings "probably underestimated the benefit because, as in most other large-scale trials of colorectal cancer screening, we could not adjust for all important confounders in all countries." Dr. Bretthauer noted that results were similar to those achieved through sigmoidoscopy screening. By close comparison, sigmoidoscopy studies show the risk of colorectal cancer is reduced between 33% and 40%, according to per protocol analyses. "These results suggest that colonoscopy screening might not be substantially better in reducing the risk of colorectal cancer than sigmoidoscopy."

NordICC is an ongoing, pragmatic study and is the first randomized trial to quantify the possible benefit of colonoscopy screening on risk of colorectal cancer and related death.

Researchers recruited healthy men and women from registries in Poland, Norway, Sweden, and the Netherlands between 2009 and 2014. Most participants came from Poland (54,258), followed by Norway (26,411) and Sweden (3,646). Netherlands' data could not be included owing to protection law.

At baseline, 84,585 participants aged 55-64 years were randomly assigned in a 1:2 ratio to be invited to undergo a single screening colonoscopy (28,220; invited) or to undergo usual care in each participant country (56,365; no invitation or screening). Any colorectal cancer lesions detected were removed, when possible. Primary endpoints were risks of colorectal cancer and colorectal cancer–related death. The secondary endpoint was death from any cause.

In an accompanying editorial (N Engl J Med. 2022 Oct 9. doi: 10.1056/NEJMe2211595), Jason A. Dominitz, MD, AGAF, from the division of gastroenterology, University of Washington, Seattle, and Douglas J. Robertson, MD, AGAF, from White River Junction (Vt.) Veterans Affairs Medical Center, commented on the possible reasons for the low reduction in incident cancer and deaths seen in NordICC.

They pointed out that cohort studies suggest a 40%-69% decrease in the incidence of colorectal cancer and a 29%-88% decrease in the risk of death with colonoscopy. However, they noted that "cohort studies probably overestimate the real-world effectiveness of colonoscopy because of the inability to adjust for important factors such as incomplete adherence to testing and the tendency of healthier persons to seek preventive care."

Dr. Dominitz and Dr. Robertson added that, in the United States, colonoscopy is the predominant form of screening for colorectal cancer and that in countries where colonoscopy is less established, participation may be very different.

"The actual effectiveness of colonoscopy in populations that are more accepting of colonoscopy could more closely resemble the effectiveness shown in the per-protocol analysis in this trial," they wrote.

The editorialists pointed out that the benefits of screening take time to be realized "because the incidence of colorectal cancer is initially increased when presymptomatic cancers are identified." A repeat and final analysis of the NordICC data are due at 15 years' follow-up.

In addition, they noted that "colonoscopy is highly operator dependent" and that the adenoma detection rate is variable and affects cancer risk and related mortality.

Given the "modest effectiveness" of screening colonoscopy in the trial, they asserted that, "if the trial truly represents the real-world performance of population-based screening colonoscopy, it might be hard to justify the risk and expense of this form of screening when simpler, less-invasive strategies (e.g., sigmoidoscopy and FIT [fecal immunochemical test]) are available."

However, they also noted that "additional analyses, including longer follow up and results from other ongoing comparative effectiveness trials, will help us to fully understand the benefits of this test."

Also commenting on the study was Michiel Maas, MD, from the department of gastroenterology and hepatology, Radboud UMC, Nijmegen, the Netherlands. He told this news organization that he agreed that the absolute effect on colorectal cancer risk or colorectal cancer–related death was not as high as expected and may be disappointing.

He added that "around half of the patients in the study did not undergo colonoscopy, which may have negatively impacted the results. "An additional factor, which can be influential in colonoscopy studies, is the potential variability in detection rates between operators/endoscopists," he said. In future, "AI [artificial intelligence] or computer-aided detection can level this playing field in detection rates. Nevertheless, this is a very interesting study, which sheds a new light on the efficacy on screening colonoscopies," he said.

Dr. Bretthauer has relationships with Paion, Cybernet, and the Norwegian Council of Research. Dr. Dominitz is cochair of VA Cooperative Studies Program #577, funded by the Department of Veterans Affairs. Dr. Robertson is national cochair (with Dr. Dominitz) of the CONFIRM trial and received personal fees from Freenome outside of the submitted work. Dr. Maas reported no relevant conflicts. ■

This study's data show that colonoscopy is effective – if it is completed. Only 42% of patients randomized to colonoscopy completed the test; among patients who actually got a colonoscopy, results are much more impressive in colorectal cancer (CRC) prevention (31% decrease) and mortality (50% decrease).

In this study, many endoscopists had ADRs below the 25% benchmark, and low ADRs are associated with a higher risk of postcolonoscopy CRC. Differences between the two groups may increase with longer follow-up, which is planned, because detection and removal of polyps via colonoscopy prevents future cancers.

Remind your patients that they shouldn't let media headlines guide your health care decisions.

Dr. Lieberman

You should also explain how colonoscopy can detect and remove polyps, which prevents those polyps from developing into cancer. Most of the patients in the Norway study skipped their colonoscopy, but the test can't prevent cancers if it isn't performed! Lastly, colonoscopy is effective in a U.S. population and can cut their risk of dying from CRC.

*David Lieberman, MD, AGAF, is a professor of medicine in the division of gastroenterology and hepatology at Oregon Health and Science University, Portland. He disclosed being a consultant for Freenome and Check-Cap.*

# An appeal from Michael Camilleri, MD, DSc, AGAF

This holiday season is a good time to reflect on our many blessings and thank those who have helped make our lives and careers worthwhile, successful, and prosperous. What better way than to pass on something to those who will ensure that gastroenterology will advance in decades to come?

Progress in this lifesaving work is made possible by the generosity of many supporters, like you, who understand the devastating physical, emotional, and financial costs of digestive diseases. We simply cannot allow a slowdown in the pace of GI research, and we cannot afford to lose talent when research offers so much promise for the future.

**You can make a difference to ensure the progress continues.**

The AGA Research Foundation funds promising young investigators who might not receive funding otherwise at crucial times in their early careers. The research of these talented individuals, while important to the field, if left unfunded, could end prematurely. That's something the field can't afford, and that's why I've supported the AGA Research Foundation over the years through my donations.


Dr. Camilleri

We must maintain a robust pipeline of research that will help safeguard the success of clinical medicine. **I urge you to support the future of GI with a generous donation to the AGA Research Foundation. Your investment of $100, $250, $500, $1,000, or any amount you can give today will make a difference.**

Help close the gap in research funding and make a difference. Make your tax-deductible donation online at www.gastro.org/donateonline.

Thank you in advance for support and best wishes for a happy, healthy holiday season and prosperous New Year. ■

*Dr. Camilleri is chair of the AGA Research Foundation, past-president of the AGA Institute, and a consultant in the division of gastroenterology and hepatology, Mayo Clinic, Rochester, Minn.*

**Three easy ways to give**

Online: www.gastro.org/donateonline

Through the mail:
AGA Research Foundation
4930 Del Ray Avenue
Bethesda, MD 20814

Over the phone: 301-222-4002

All gifts are tax-deductible to the fullest extent of U.S. law.

# What to know about 2023 Medicare payments

The Centers for Medicare and Medicaid Services released its final rules for 2023 Medicare payments.

**Good news! The full CRC continuum will be covered in Medicare.**

In a win for patients and thanks to our collective advocacy efforts from AGA and partner societies, CMS expanded the regulatory definition of "colorectal cancer screening tests" and will waive cost sharing for a necessary follow-up colonoscopy after a positive stool-based screening test.

**Bad news: Looming cuts on the horizon, GI societies to take action.**

The rule finalizes more than 4% in mandated Medicare physician reimbursement cuts through decreases in the conversion factor and expiration of temporary fixes passed by Congress. The CY 2023 conversion factor is $33.06, an unacceptable cut for our members. The GI societies continue to work with a coalition of national and state medical societies to urge Congress to prevent these cuts before Jan. 1, 2023.

**Good news: ASC + hospital payments on the rise.**

ASC payments and facility fee payments increase 3.8% for institutions that meet quality reporting requirements. The CY 2023 ASC conversion factor is $51.854 and the hospital outpatient conversion factor is $85.585.

CMS removed motility codes 91117 and 91122 from APC 5731, where their payments would have been cut 21%, and finalized their placement in APC 5722, where they get a 3% payment increase beginning Jan. 1, 2023. Thank you to the motility community for helping us secure this win.

CMS raises the hospital payment for ESD code C9779 to $3,260.69, a $765.65 increase from 2022. We continue to work with CMS on our request for separate codes for lower ESD and upper ESD and payments that better reflect their unique resource costs. ■

# New AGA guideline ranks the most effective drugs for weight loss

AGA released new evidence-based guidelines strongly recommending patients with obesity use recently approved medications paired with lifestyle changes. The following medications, paired with healthy eating and regular physical activity, are first-line medical options and result in moderate weight loss as noted as a percentage of body weight (reported as the difference compared to percent weight loss seen in the placebo group).

- Semaglutide (Wegovy®), weight loss percentage: 10.8%
- Phentermine-topiramate ER (Qsymia®), weight loss percentage: 8.5%
- Liraglutide (Saxenda®), weight loss percentage: 4.8%
- Naltrexone-bupropion ER (Contrave®), weight loss percentage: 3.0%

Read the AGA Clinical Guidelines on Pharmacological Interventions for Adults with Obesity for the complete recommendations.

(*See related story on page 1*). ■

# Joint society task force releases strategic plan on climate change

A task force of GIs from the four major GI societies – AGA, AASLD, ACG, and ASGE – has released a multisociety strategic plan outlining goals and milestones the GI specialty needs to achieve to reduce the environmental impact of the practice.

**Key takeaway:** As a procedure-intense subspecialty, gastroenterology, and in particular endoscopy, is a major contributor to health care's carbon footprint and other environmental impacts. Endoscopy is the third largest generator of medical waste in a hospital (2 kg total waste per procedure) with most ending in landfills. With this strategic plan, the participating societies are committed to promoting and supporting a sustainable, high-quality GI practice.

The U.S. GI multisociety strategic plan, which has also been endorsed by 23 GI societies globally, is a collaborative effort that invites members to undertake initiatives to establish an environmentally sustainable, high-quality practice and promote planetary health. Each society will prioritize and adapt their initiatives in accordance with their individual societal goals. Some initiatives may be undertaken by a single society, whereas other objectives and initiatives may be approached jointly. It is a 5-year plan that covers seven major domains:

- Clinical setting.
- Education.
- Research.
- Society efforts.
- Intersociety efforts.
- Industry.
- Advocacy.

The plan was developed by the U.S. Multi-GI Society Task Force on Climate Change, composed of leading experts from AASLD, ACG, AGA, and ASGE. For more information, view the full publication: GI Multisociety Strategic Plan on Environmental Sustainability, published in Gastroenterology, Gastrointestinal Endoscopy, HEPATOLOGY, and The American Journal of Gastroenterology

(*See related story on page 23*). ■

# Novel YouTube study detects colonoscopy misinformation, guides better content creation

**BY WILL PASS**
*MDedge News*

Don't just sit there. Post something.

To combat misinformation about colonoscopy, health care providers (HCPs) should engage more with social media platforms and create accurate, engaging educational videos, according to investigators.

An assessment of top-ranking YouTube videos about colonoscopy by both lay people and HCPs revealed numerous inaccuracies, which have potentially contributed to public hesitancy to undergo appropriate screening, reported lead author Austin L. Chiang, MD, MPH, of Thomas Jefferson University Hospitals, Philadelphia, and colleagues.

**More than half of the videos were low quality based on DISCERN (52.2%) and PEMAT (59.4%) criteria. Videos that featured an HCP scored significantly higher on both scales, while videos created by HCPs were more likely to meet minimum quality criteria.**

"The prevalence and predictors of misinformation among contents on social media platforms such as YouTube with regard to colonoscopy remain unknown," the investigators wrote in Gastro Hep Advances (2022 Jan 1. doi: 10.1016/j.gastha.2022.07.005). They noted that previous research characterized YouTube as a "suboptimal" resource for information about colonoscopy, although those studies did not use validated instruments.

For the present cohort study, Dr. Chiang and colleagues performed a YouTube search for "colonoscopy" on Nov. 21, 2020. Results with more than 250,000 views were included in the analysis, netting 69 videos. Of these, 39 were posted by lay people, while the remaining 30 were posted by HCPs.

Three board-certified gastroenterologists measured video quality with two validated instruments for evaluating consumer health information: DISCERN and the Patient Education Material Assessment Tool (PEMAT) understandability score. Any video with a DISCERN score less than 2 or a PEMAT score less than 50% was deemed "inaccurate or of low scientific quality per established standards." The investigators also scored likelihood of recommending a video to a patient on a 5-point Likert scale.

More than half of the videos were low quality based on DISCERN (52.2%) and PEMAT (59.4%) criteria. Videos that featured an HCP scored significantly higher on both scales, while videos created by HCPs were more likely to meet minimum quality criteria and be recommended to patients.

Specifically, only 20.5% of videos created by laypeople made the grade, compared with 66.7% (PMAT) and 83.3% (DISCERN) of videos made by HCPs, depending on the quality instrument.

It therefore follows that an HCP creator was the greatest predictive factor for a high-quality video, according to the area under the receiving operating characteristic curve.

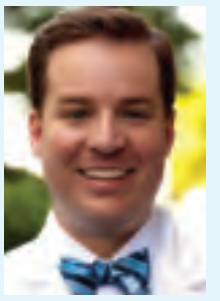
"Our analysis demonstrates a disturbing proportion of inaccuracies and poor scientific quality information among the most viewed YouTube videos around colonoscopy using validated instruments for consumer information," the investigators wrote.

Types of misinformation varied. Some of the videos contradicted current recommendations and intentionally overstated colonoscopy risk, while others called for screening every year.

"Although it is disheartening to imagine the influence of these inaccurate videos on millions of people, it may be helpful to learn from them and dissect why they have succeeded in attracting viewers," the investigators wrote.

So which videos had the most views? To put it bluntly, it was the funny, "gross" stuff. The top-ranking colonoscopy videos featured comedians talking about their colonoscopies or had shocking footage, like worms wiggling during an endoscopic exam of a patient with a parasitic infection.

The advent of social media ushered in the promise of a new age of information democratization. Unfortunately, the reality of increasingly accessible information – including misinformation – has disabused us of the notion that this increased accessibility is an unalloyed good. "Fake news" abounds, and in an era in which "truth" seems to be in the eye of the beholder – or influencer – medical misinformation appetizingly presented to the public is a particular hazard to public health. This is one of the first studies to offer an objective description of the medical information landscape as it pertains to the field of gastroenterology.


Dr. Brown

We must thank Dr. Austin Chiang and colleagues for their cohort study examining this misinformation landscape surrounding colonoscopy on YouTube. Although health care providers and laypeople were both guilty of poor-quality content creation, laypeople were more so, which, though not entirely surprising, is somewhat reassuring. Abiding the aphorism "know thy enemy," the authors suggest that perhaps the do-gooders can arm themselves with factual content that avoids complexity. Being "gross" or funny might help too. Focusing on at-risk populations and partnering both with professional societies and laypeople might be the right formula.

There is a tension between accessibility and quality of information within social media, the modern public forum. This study highlights that tension and serves both as a call-to-arms and a guide for experts on how to displace the amateurs and hucksters who are confusing those who've come to the forum not for entertainment but for information.

*Jason M. Brown, MD, is assistant professor and Grady site fellowship director, division of digestive diseases, Emory University School of Medicine, Atlanta. Dr. Brown reported no relevant conflicts of interest.*

## How to create better content

While these acts may be hard to follow for the average gastroenterologist-YouTuber, Dr. Chiang and colleagues did detect one video characteristic that should be avoided: complexity. Multivariate analysis showed that endoscopic footage was a negative effect modifier for clarity and understandability.

"The main challenge of any video content is striking a balance between brevity and accuracy/comprehensiveness," the investigators wrote. "When describing endoscopic videos to lay audiences, gastroenterologists must be careful to provide appropriate clinical context and use wording that is concise and easily comprehended."

More broadly, the investigators called for a three-pronged approach to combat misinformation by creating better content.

First, they advised HCPs to increase participation on social media channels, with a focus on promoting health equity among at-risk and non–English-speaking audiences.

Second, they asked professional societies such as the American Gastroenterological Association to assist HCPs with the fundamentals of content creation, including techniques in storytelling and videography. Finally, they proposed HCPs partner with lay creators, following a common strategy in traditional media in which celebrities share scientifically grounded medical information.

"Although the prevalence of inaccurate colonoscopy videos is concerning, an understanding of existing health misinformation and a proactive approach to cultivate professional content creation may help provide patients with high-quality information to help achieve colorectal cancer screening targets and improve health outcomes," the investigators concluded.

The study was partially funded by the National Institutes of Health. Dr. Chiang is an employee of Medtronic and holds a seat on the YouTube Health Advisory Board. The other investigators disclosed no competing interests. ■

# Invitations increased HCC surveillance screening

**BY TARA HAELLE**
*MDedge News*

Mailing invitations for hepatocellular carcinoma (HCC) surveillance screening to patients with cirrhosis increased ultrasound uptake by 13 percentage points, but the majority of patients still did not receive the recommended semiannual screenings, according to findings published in Clinical Gastroenterology and Hepatology (2021 Dec 10. doi: 10.1016/j.cgh.2021.12.014).

"These data highlight the need for more intensive interventions to further increase surveillance," wrote Amit Singal, MD, of University of Texas Southwestern Medical Center and Parkland Health Hospital System in Dallas, and colleagues. "The underuse of HCC surveillance has been attributed to a combination of patient- and provider-level barriers, which can serve as future additional intervention targets." These include transportation and financial barriers and possibly new blood-based screening modalities when they become available, thereby removing the need for a separate ultrasound appointment.

According to one study, more than 90% of hepatocellular carcinoma cases occur in people with chronic liver disease, and the cancer is a leading cause of death in those with compensated cirrhosis (Clin Gastroenterol Hepatol. 2011 Jan;9[1]:64-70). Multiple medical associations therefore recommend an abdominal ultrasound every 6 months with or without alpha-fetoprotein (AFP) for surveillance in at-risk patients, including anyone with cirrhosis of any kind, but too few patients receive these surveillance ultrasounds, the authors write.

The researchers therefore conducted a pragmatic randomized clinical trial from March 2018 to September 2019 to compare surveillance ultrasound uptake for two groups of people with cirrhosis: 1,436 people who were mailed invitations to get a surveillance ultrasound and 1,436 people who received usual care, with surveillance recommended only at usual visits. The patients all received care at one of three health systems: a tertiary care referral center, a safety-net health system, and a Veterans Affairs medical center. The primary outcome was semiannual surveillance in the patients over 1 year.

The researchers identified patients using ICD-9 and ICD-10 codes for cirrhosis and cirrhosis complications, as well as those with suspected but undocumented cirrhosis based on electronic medical record notes such as an elevated Fibrosis-4 index. They confirmed the diagnoses with chart review, confirmed that the patients had at least one outpatient visit in the previous year, and excluded those in whom surveillance is not recommended, who lacked contact information, or who spoke a language besides English or Spanish.

The mailing was a one-page letter in English and Spanish, written at a low literacy level, that explained hepatocellular carcinoma risk and recommended surveillance. Those who didn't respond to the mailed invitation within 2 weeks received a reminder call to undergo surveillance, and those who scheduled an ultrasound received a reminder call about a week before the visit. Primary/subspecialty providers were blinded to the patients' study arms.

"We conducted the study as a

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pragmatic trial whereby patients in either arm could also be offered HCC surveillance by primary or specialty care providers during clinic visits," the researchers wrote. "The frequency of the clinic visits and provider discussions regarding HCC surveillance were conducted per usual care and not dictated by the study protocol."

Two-thirds of the patients (67.7%) were men, with a median age of 61.2 years. Just over a third (37.0%) were white, 31.9% were Hispanic, and 27.6% were Black. More than half the patients had hepatitis C (56.4%), 18.1% had alcohol-related liver disease, 14.5% had nonalcoholic fatty liver disease, and 2.4% had hepatitis B. Most of the patients had compensated cirrhosis, including 36.7% with ascites and 17.1% with hepatic encephalopathy. Nearly a quarter of the patients in the outreach arm (23%) could not

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Hepatocellular carcinoma is a deadly cancer that is usually incurable unless detected at an early stage through regular surveillance. Current American guidelines support 6-monthly abdominal ultrasonography, with or without serum alpha-fetoprotein, for HCC surveillance in at-risk patients, such as those with cirrhosis. However, even in such a high-risk group, the uptake of and adherence to surveillance are far from satisfactory. This study by Dr. Singal and colleagues is therefore important and practical. Randomized controlled trials in HCC surveillance are rare. The authors clearly demonstrate that an outreach program comprising mail invitations followed by phone contacts if there was no response could increase the surveillance uptake by more than 10%.

Dr. Wong

Though the results are important, one cannot help but notice that, even in the outreach intervention group, more than half of the patients still did not undergo surveillance. Clearly, more needs to be done. As a first step, it would be helpful to understand factors associated with whether a patient would respond to mail and/or phone invitations. Additionally, the approach was likely labor intensive. With new developments in electronic health records and artificial intelligence, it would be interesting to see if the process can be automated in terms of patient identification and invitation. The efficacy of newer modes of communication should be explored.

None of these can work if chronic liver disease and cirrhosis are not diagnosed in the first place. Disease awareness, access to care (and racial discrepancies), and clinical care pathways are hurdles we need to overcome in order to make an impact on HCC mortality at the population level.

*Vincent Wong, MD, is an academic hepatologist at the Chinese University of Hong Kong. He does not have relevant conflicts of interest in this article.*

# Latiglutenase reduced symptoms in celiac patients

**BY CAROLYN CRIST**
*MDedge News*

In a gluten challenge trial, latiglutenase (IMGX003) reduced symptom severity and mucosal deterioration in patients with celiac disease, according to a new study published in Gastroenterology (2022 Aug 2. doi: 10.1053/j.gastro.2022.07.071).

Latiglutenase led to 95% gluten degradation in the stomach, as indicated by measurements of gluten-immunogenic peptides in urine, wrote Joseph A. Murray, MD, AGAF, a gastroenterologist at the Mayo Clinic, Rochester, Minn., and Jack A. Syage, PhD, CEO and cofounder of ImmunogenX, Newport Beach, Calif., and colleagues on behalf of the CeliacShield Study Group.

For patients with celiac disease, the only available treatment is a life-long gluten-free diet (GFD). Low levels of gluten exposure can lead to ongoing inflammation and the risk of complications, and about half of patients continue to experience moderate to severe symptoms.

"Although a GFD can reduce symptoms and intestinal damage, the diet is neither easy nor readily achievable by many patients and, furthermore, can be lacking in essential nutrients," the authors wrote.

In a randomized, double-blind, placebo-controlled gluten challenge study, the research team assessed the efficacy and safety of a 1,200-mg dose of IMGX003, formerly known as ALV003. The dual-enzyme supplementation therapy was "designed to mitigate the impact of gluten exposure in patients who are attempting to adhere to a GFD."

The phase 2 trial was conducted at the Mayo Clinic with adult patients (aged 18-80 years) who had physician-diagnosed and biopsy-confirmed celiac disease, followed a GFD for more than 1 year, and had histologically well-controlled disease. During the study, they were exposed to 2 g of gluten per day for 6 weeks.

The primary endpoint focused on the change in the ratio of villus height to crypt depth. The "secondary endpoints included density of intraepithelial lymphocytes and symptom severity. Additional endpoints included serology and gluten-immunogenic peptides in urine."

Among the 50 patients randomized, 43 completed the study, with 21 assigned to the IMGX003 group. About 74% of the participants were women; the mean age of all participants was 43.8 years.

Overall, the mean change in the ratio of villus height to crypt depth was –0.04 for IMGX003, compared with –0.35 for placebo. In addition, the mean change in the density of intraepithelial lymphocytes for IMGX003 was 9.8, compared with 24.8 for placebo. Based on the ratio of the means for both groups, the researchers estimated an 88% reduction of change in villus height to crypt depth and a 60% reduction of change in intraepithelial lymphocytes.

The mean changes, or worsening from baseline, in symptom severity for IMGX003 vs. placebo were 0.22 vs. 1.63 for abdominal pain, 0.96 vs. 3.29 for bloating, 0.02 vs. 3.2 for tiredness, and 0.64 vs. 2.27 for nonstool composite. The calculated symptom reduction values were 93% for abdominal pain, 53% for bloating, 99% for tiredness, and 70% for nonstool composite.

The mean change from baseline for symptom severity was evaluated over three 2-week periods, and the percent changes showed consistent reduction of symptom worsening during that time. Based on the effect size and trend significance, the *P* values were .014 for abdominal pain, .030 for bloating, .002 for tiredness, and < . 001 for nonstool composite.

The mean change in gluten-immunogenic peptides (GIP) in urine relative to baseline was 0.59 for IMGX003, compared with 11.53 for placebo. The researchers estimated an efficacy of gluten degradation in vivo of 95%.

"Measurement of GIP in urine demonstrated the purported mechanism of action of IMGX003, namely, degradation of gluten in the stomach, thereby preventing the triggering of the immunogenic autoimmune response," the authors wrote. "Targeting gluten by degrading the immunogenic peptides before absorption minimizes or abrogates the cascading innate and adaptive immune responses that characterize the inflammatory response to gluten in CeD [celiac disease]."

The study was sponsored by ImmunogenX, and partially funded by a grant from the National Center for Complementary and Integrative Health. The project was slso supported by grants from the National Center for Advancing Translational Sciences and the National Institute of Diabetes and Digestive and Kidney Diseases. Several authors reported grants from numerous funders, including ImmunogenX, and some reported being a cofounder, stockholder, or board director of the company. ■

From the perspective of patients affected by other chronic GI diseases requiring constant treatment with drugs, the life of celiac patients must appear "a piece of cake" (pun intended). But this is not the case. In fact, the burden of following a gluten-free diet (GFD) can profoundly impact their quality of life. Furthermore, a substantial portion of patients trying their best on a GFD do not experience full clinical and histologic remission, mainly because of ongoing involuntary gluten ingestion. Therefore, it's not surprising that several lines of research have been actively trying to address this unmet need.


Dr. Guandalini

In this phase 2 trial, the proprietary enzyme combination called IMGX003 (latiglutenase) was investigated for safety and efficacy. IMGX003 can digest gluten in the stomach, thus preventing its intact entry into the small intestine where it would trigger the immune reaction leading to the villi destruction. The study did indeed demonstrate that administering it to patients on GFD exposed to 2 grams of gluten daily (roughly the equivalent of half a slice of wheat bread) effectively reduced both the mucosal damage and symptom severity. Is this good news for patients with celiac? You bet it is! While not replacing the need for a GFD, having a safe drug that adds a substantial layer of protection to inadvertent gluten exposure or the so-called "cross-contamination" is surely to be welcome by them.

If and once approved for use, IMGX003 could be taken sporadically by patients on GFD: For instance, while eating out in "new" places, traveling, going to parties, or for younger patients, when having sleepovers, birthday celebrations, and so on. With the caveat, not to be forgotten, that this is not meant to be a wonder drug eliminating the need for vigilance; we still need to wait patiently for science to advance further for that.

*Stefano Guandalini, MD, AGAF, is professor emeritus of pediatrics at the University of Chicago and director emeritus of the University of Chicago Celiac Disease Center. He declares no relevant conflicts of interest.*

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be contacted or lacked working phone numbers, but they remained in the intent-to-screen analysis. Just over a third of the patients who received mailed outreach (35.1%; 95% confidence interval, 32.6%-37.6%) received semiannual surveillance, compared to 21.9% (95% CI, 19.8%-24.2%) of the usual-care patients. The increased surveillance in the outreach group applied to most subgroups, including race/ethnicity and cirrhosis severity based on the Child-Turcotte-Pugh class.

"However, we observed site-level differences in the intervention effect, with significant increases in semiannual surveillance at the VA and safety net health systems (both $P < .001$) but not at the tertiary care referral center ($P = .52$)," the authors wrote. "In a post hoc subgroup analysis among patients with at least 1 primary care or gastroenterology outpatient visit during the study period, mailed outreach continued to increase semiannual surveillance, compared with usual care (46.8% vs. 32.7%; $P < .001$)."

Despite the improved rates from the intervention, the majority of patients still did not receive semiannual surveillance across all three sites, and almost 30% underwent no surveillance the entire year.

The research was funded by the National Cancer Institute, the Cancer Prevention Research Institute of Texas, and the Center for Innovations in Quality, Effectiveness and Safety. Dr. Singal has consulted for or served on advisory boards of Bayer, FujiFilm Medical Sciences, Exact Sciences, Roche, Glycotest, and GRAIL. The other authors had no conflicts. ■

# Sex-linked IL-22 activity may affect NAFLD outcomes

**BY WILL PASS**
*MDedge News*

Interleukin-22 may mitigate nonalcoholic fatty liver disease (NAFLD)–related fibrosis in females but not males, suggesting a sex-linked hepatoprotective pathway, according to investigators.

These differences between men and women should be considered when conducting clinical trials for IL-22–targeting therapies, reported lead author Mohamed N. Abdelnabi, MSc, of the Centre de Recherche du Centre Hospitalier de l'Université de Montréal and colleagues.

"IL-22 is a pleiotropic cytokine with both inflammatory and protective effects during injury and repair in various tissues including the liver," the investigators wrote in Cellular and Molecular Gastroenterology and Hepatology (2022 Aug 13. doi: 10.1016/j.jcmgh.2022.08.001), noting that IL-22 activity has been linked with both antifibrotic and profibrotic outcomes in previous preclinical studies. "These different observations highlight the dual nature of IL-22 that likely is dictated by multiple factors including the tissue involved, pathologic environment, endogenous vs. exogenous IL-22 level, and the time of exposure."

Prior research has left some questions unanswered, the investigators noted, because many studies have relied on exogenous administration of IL-22 in mouse models, some of which lack all the metabolic abnormalities observed in human disease. Furthermore, these mice were all male, which has prevented detection of possible sex-linked differences in IL-22–related pathophysiology, they added.

To address these gaps, the investigators conducted a series of experiments involving men and women with NAFLD, plus mice of both sexes with NAFLD induced by a high-fat diet, both wild-type and with knockout of the IL-22 receptor.

## Human data

To characterize IL-22 activity in men versus women with NAFLD, the investigators first analyzed two publicly available microarray datasets. These revealed notable upregulation of hepatic IL-22 mRNA expression in the livers of males compared with females.

Supporting this finding, liver biopsies from 11 men and 9 women with NAFLD with similar levels of fibrosis showed significantly increased IL-22–producing cells in female patients compared with male patients.

"These results suggest a sexual dimorphic expression of IL-22 in the context of NAFLD," the investigators wrote.

## Mouse data

Echoing the human data, the livers of female wild-type mice with NAFLD had significantly greater IL-22 expression than male mice at both mRNA and protein levels.

Next, the investigators explored the effects of IL-22–receptor knockout. In addition to NAFLD, these knockout mice developed weight gain and metabolic alterations, especially insulin resistance, supporting previous work that highlighted the protective role of IL-22 against these outcomes. More relevant to the present study, female knockout mice had significantly worse hepatic liver injury, apoptosis, inflammation, and fibrosis than male knockout mice, suggesting that

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# Major U.S. GI societies issue strategic plan on environmental sustainability

**BY CAROLYN CRIST**
*MDedge News*

Four major professional medical societies in the United States have called for urgent action to create a more sustainable model for digestive health care that decreases the environmental impact of gastroenterology practice, according to a new joint strategic plan published simultaneously in Gastroenterology, Gastrointestinal Endoscopy, American Journal of Gastroenterology, and Hepatology.

The plan outlines numerous strategic goals and objectives across clinical care, education, research, and industry to support sustainable practices. With first author Heiko Pohl, MD, a gastroenterologist and hepatologist at the Veterans Affairs Medical Center in White River Junction, Vermont, and professor of medicine at the Geisel School of Medicine at Dartmouth, Hanover, N.H., the joint statement includes task force members from the American Association for the Study of Liver Diseases, American College of Gastroenterology, American Gastroenterological Association, and American Society for Gastrointestinal Endoscopy.


Dr. Pohl

"It is clear that the evolving climate crisis, with its deleterious effects on planetary ecosystems, also poses harm to the health of humankind," the authors wrote in Gastroenterology (2022 Oct 18. doi: 10.1053/j.gastro.2022.09.029).

"Climate change affects many social and environmental determinants of health, including water and food security, shelter, physical activity, and accessible health care," they added. These changes influence gastrointestinal practice (for example, increased risk of obesity and fatty liver disease, disruption of the microbiome, compromised gut immune function).

At the same time, health care delivery contributes to climate change and greenhouse gas emissions worldwide, they wrote. As a procedure-intensive specialty, digestive health care adds to the health care carbon footprint through single-use supplies and high levels of waste.

"As is the case for the impact of climate change by and on health care systems, there is a vicious cycle whereby climate change

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IL-22 signaling confers hepatoprotection in females but not males, the authors indicated.

"These observations may suggest a regulation of IL-22 expression by the female sex hormone estrogen," the investigators wrote. "Indeed, estrogen is known to modulate inflammatory responses in NAFLD, but the underlying mechanisms remain undefined. ... Further in vivo studies are warranted to investigate whether endogenous estrogen regulates hepatic IL-22 expression in the context of NAFLD."

In the meantime, the present data may steer drug development.

"These findings should be considered in clinical trials testing IL-22–based therapeutic approaches in treatment of female vs. male subjects with NAFLD," the investigators concluded.

The study was partially funded by the Canadian Liver Foundation and the Canadian Institutes of Health Research, the Bourse d'Exemption des Droits de Scolarité Supplémentaires from the Université de Montréal, the Canadian Network on Hepatitis, and others. The investigators disclosed no competing interests.

The cytokine interleukin-22 has potential as a therapeutic for nonalcoholic fatty liver disease, as it has been shown to decrease fat accumulation in hepatocytes and has various other liver protective effects such as prevention of cell death, enhancement of proliferation, and, importantly, reduction of liver fibrosis progression.


Dr. Wangensteen

Indeed, a recombinant derivative of IL-22 has been studied in a clinical trial of alcoholic liver disease and has been found to be safe. However, the beneficial effect of this cytokine is context dependent. High levels of IL-22 increased inflammation or fibrosis in hepatitis B infection and in toxic injury models in mouse models.

The current study makes a critical observation that sex influences the protective effect of IL-22. It finds that women with NAFLD tend to express higher levels of IL-22 than men. Similar results were found in female versus male mice fed with a high-fat diet. In a relevant mouse model, IL-22 signaling protected against fat-induced liver injury in females but not males.

The authors discuss evidence that estrogen may upregulate IL-22 to protect the liver.

This is in line with observations that progression to cirrhosis in NAFLD is greater after menopause. On the other hand, women are more likely to develop cirrhosis than men despite higher levels of IL-22, indicating more factors are at play in the progression of NAFLD.

Overall, this report should alert investigators to consider the sex-specific effects of emerging therapies for NAFLD. Future IL-22–based trials must include sex-based subgroup analyses.

*Kirk Wangensteen, MD, PhD, is with the department of medicine, division of gastroenterology and hepatology at the Mayo Clinic in Rochester, Minn. He declares no relevant conflicts of interest.*

# Pediatric celiac disease incidence varies by country

**BY CAROLYN CRIST**
*MDedge News*

The incidence of new celiac disease with onset by age 10 appears to be rising and varies widely by region, suggesting different environmental, genetic, and epigenetic influences within the United States, according to a new report. The overall high incidence among pediatric patients warrants a low threshold for screening and additional research on region-specific celiac disease triggers, the authors write.

"Determining the true incidence of celiac disease (CD) is not possible without nonbiased screening for the disease. This is because many cases occur with neither a family history nor with classic symptoms," write Edwin Liu, MD, a pediatric gastroenterologist at the Children's Hospital Colorado Anschutz Medical Campus and director of the Colorado Center for Celiac Disease, and colleagues.

"Individuals may have celiac disease autoimmunity without having CD if they have transient or fluctuating antibody levels, low antibody levels without biopsy evaluation, dietary modification influencing further evaluation, or potential celiac disease," they write. The study was published online in the American Journal of Gastroenterology (2022 Oct 10. doi: 10.14309/ajg.0000000000002056).

## The TEDDY study

The Environmental Determinants of Diabetes in the Young (TEDDY) study prospectively follows children born between 2004 and 2010 who are at genetic risk for both type 1 diabetes and CD at six clinical sites in four countries: the United States, Finland, Germany, and Sweden. In the United States, patients are enrolled in Colorado, Georgia, and Washington.

As part of TEDDY, children are longitudinally monitored for celiac disease autoimmunity (CDA) by assessment of autoantibodies to tissue transglutaminase (tTGA). The protocol analyzes the development of persistent tTGA positivity, CDA, and subsequent CD.

The study population contains various DQ2.5 and DQ8.1 combinations, which represent the highest-risk human leukocyte antigen (HLA) DQ haplogentotypes for CD.

From September 2004 through February 2010, more than 424,000 newborns were screened for specific HLA haplogenotypes, and 8,676 children were enrolled in TEDDY at the six clinical sites. The eligible haplogenotypes included DQ2.5/DQ2.5, DQ2.5/DQ8.1, DQ8.1/DQ8.1, and DQ8.1/DQ4.2. Blood samples were obtained and stored every 3 months until age 48 months and at least every 6 months after that. At age 2, participants were screened annually for tTGA.

## Disease incidence by country

Overall, the 10-year cumulative incidence was highest in Sweden, at 8.4% for CDA and 3% for CD. Within the United States, Colorado had the highest cumulative incidence for both endpoints, at 6.5% for CDA and 2.4% for CD. Washington had the lowest incidence across all sites, at 4.6% for CDA and 0.9% for CD.

"CDA and CD risk varied substantially by haplogenotype and by clinical center, but the relative risk by region was preserved regardless of the haplogenotype," the authors write. "For example, the disease burden for each region remained highest in Sweden and lowest in Washington state for all haplogenotypes."

In the HLA, sex, and family-adjusted model, Colorado children had a 2.5-fold higher risk of CD, compared with Washington children. Likewise, Swedish children had a 1.8-fold higher risk of CD than children in Germany, a 1.7-fold higher than children in the United States, and a 1.4-fold higher risk than children in Finland.

Among DQ2.5 participants, Sweden demonstrated the highest risk, with 63.1% of patients developing CDA by age 10 and 28.3% developing CD by age 10. Finland consistently had a higher incidence of CDA than Colorado, at 60.4% versus 50.9%, for DQ2.5 participants but a lower incidence of CD than Colorado, at 20.3% versus 22.6%., according to the authors.

Multiple environmental factors likely account for the differences in autoimmunity among regions, the authors write.

These variables include diet, chemical exposures, vaccination patterns, early-life gastrointestinal infections, and interactions among these factors. For instance, the Swedish site has the lowest rotavirus vaccination rates and the highest median gluten intake among the TEDDY sites.

The TEDDY study is funded by grants from the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Allergy and Infectious Diseases, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, the National Institute of Environmental Health Sciences, the Centers for Disease Control and Prevention, and the Juvenile Diabetes Research Foundation. The authors have disclosed no relevant financial relationships. ■

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negatively impacts individual digestive health, which accelerates specialized health care activity, which further contributes to the climate crisis," the authors wrote.

The multisociety task force noted the transition to a more sustainable model will be challenging and require major modification of current habits in practice. However, the long-term effects "will promote health, save cost, and ... correspond with a broader shared vision of planetary health," they wrote.

The strategic plan covers seven domains: clinical settings, education, research, society efforts, intersociety efforts, industry, and advocacy. Each domain has specific initiatives for 2023-2027. Years 1 and 2 are conceived as a period of self-assessment and planning, followed by implementation and assessment during years 3-5.

In the plan, clinical settings would assess the carbon footprint and waste within all areas of practice and identify low-carbon and low-waste alternatives, such as immediate, short-term, and long-term solutions. This involves creating a framework for GI practices to develop sustainability metrics and offer affordable testing and treatment alternatives with a favorable environmental impact.

Through education, the societies would raise awareness and share sustainability practices with health care leadership, practitioners, and patients regarding the interactions among climate change, digestive health, and health care services. This would include discussions about the professional and ethical implications of old and new patterns of shared resource utilization.

The societies also support raising and allocating resources for research related to the intersections of climate change, digestive health, and health care, with an emphasis on vulnerable groups. This would encourage the inclusion of environmental considerations in proposals.

At the GI society level, the groups suggest assessing and monitoring the current environmental impact of society-related activities. This entails identifying and implementing measures that would decrease the carbon footprint and reduce waste, as well as track financial costs and savings and environmental benefits from efforts included in a sustainability model.

At the intersociety level, the U.S. groups would collaborate with national and international GI and hepatology societies to support sustainability efforts and use validated metrics to evaluate their efforts. The multisociety plan has received endorsements from nearly two-dozen groups, including the Crohn's & Colitis Foundation, World Endoscopy Organization, and World Gastroenterology Organisation.

The plan calls for engagement with GI- and hepatology-focused industry and pharma partners to develop environmentally friendly products, publish information on carbon footprint implications, and promote reecycling options.

Through advocacy efforts, the societies would also identify and incorporate principles of sustainable health care among the goals of relevant political action committees, as well as leverage collaborative advocacy efforts with national and international health care and research agencies, political leaders, and payors.

"We are grateful that several other GI organizations have endorsed our plan, which reflects the importance and timeliness of the opportunity to work together and share best practices to overcome the burden of climate change on digestive health and help mitigate the environmental impact of GI practice," the authors concluded.

The authors did not declare a funding source for the report. Several of the authors declared financial relationships with pharmaceutical companies, serving as a consultant or receiving research funding. ■

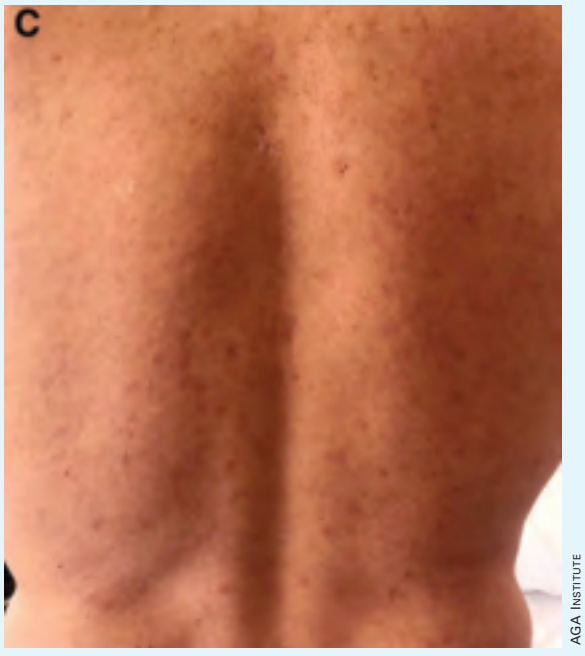
# The diagnosis

**Answer to "What's your diagnosis?" on page 10: Syphilis**

Although extremely rare, we checked a Venereal Disease Research Laboratory PCR, the results of which came back positive. A *Treponema pallidum* hemagglutination assay also returned positive with titers 1:5120 (ULN, < 1:80), confirming the diagnosis of syphilis. During his hospitalization, the patient developed a syphilitic skin rash on his back, chest, palms, feet, and soles (Figure C). The patient was started on penicillin G, 4 million units intravenously every 4 hours. The fever broke 36 hours after antibiotic initiation and 48 hours later, his bilirubin started to downtrend, followed by the alkaline phosphatase and GGT 3 days later. His rash completely disappeared 5 days after antibiotic initiation. He received a total of 2 weeks of penicillin G intravenously at 24 million units a day and his liver enzymes normalized 7 weeks later.

Syphilitic hepatitis is extremely rare and occurs in 0.2% of patients with secondary syphilis.[1] There are few cases of syphilitic hepatitis in HIV carriers reported in the literature. Of the described cases, only two patients had an undetectable viral load.[2,3] The clinical presentation of syphilitic hepatitis includes jaundice, pruritus, nausea, and vomiting, in addition to generalized symptoms of fatigue, malaise, and weight loss. Biochemically, alkaline phosphatase and GGT are predominantly elevated with mild elevation in the transaminases. Few cases describe an elevation in the bilirubin. Diagnosis is made based on treponemal testing and/or evaluation of tissue for spirochetes on liver biopsy. The majority of cases used penicillin G with excellent response. Doxycycline was also used in one case and ceftriaxone was used in another.

In our case, the patient had several other possible reasons for his liver enzyme elevation, including drug-induced liver injury, cocaine, and alcohol use, which could have contributed to his disturbed liver enzymes. The steady improvement in his cholestatic liver enzymes, fever, and rash, shortly after the initiation of penicillin G indicates that syphilis was the cause of his hepatitis. Given the improvement in his symptoms and biochemical markers, we refrained from obtaining a liver biopsy.

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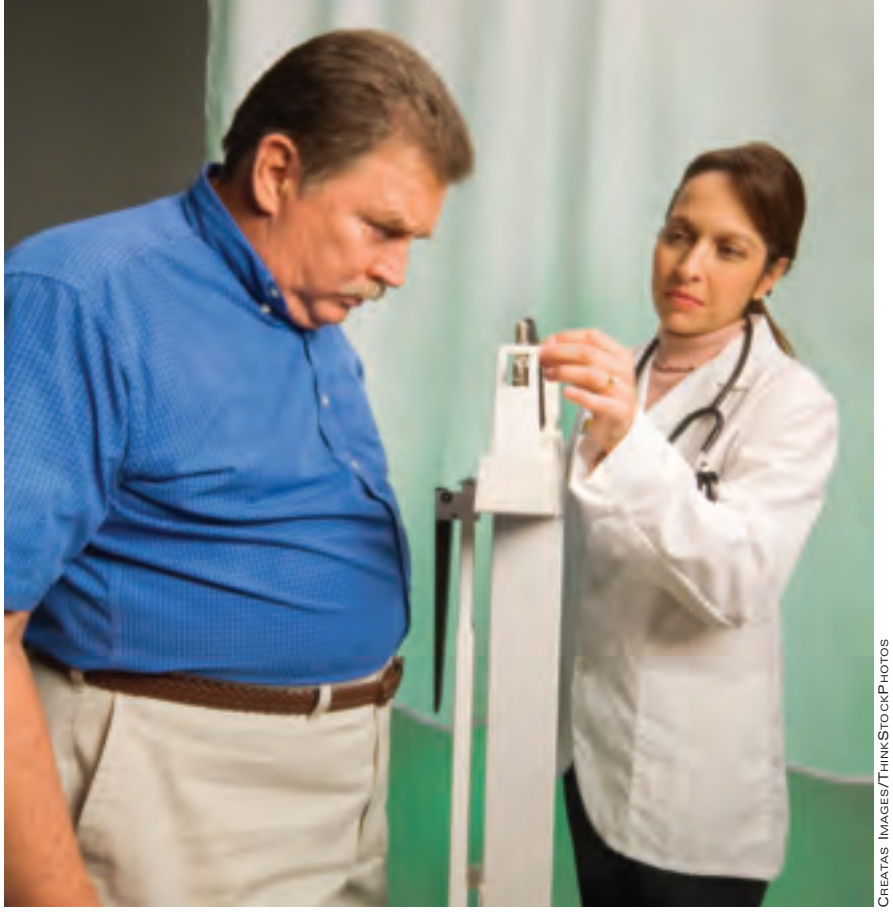
Continued from page 10

to, comorbidities, patients' preferences, costs, and access to the therapy," the authors wrote. Average difference in total body weight loss with the addition of medication to lifestyle interventions was 3%-10.8%, depending on the drug. Adverse event rates were low.

The panel's second recommendation discussed use of semaglutide along with lifestyle interventions in terms of its large magnitude of weight loss and low risk of discontinuation because of adverse events seen in trials. The remaining recommendations describes the use of each of the other medications based on their respective magnitude of effect and risk for adverse events.

These medications treat a biological disease, not a lifestyle problem," Dr. Grunvald said in a prepared statement. "Obesity is a disease that often does not respond to lifestyle interventions alone in the long term. Using medications as an option to assist with weight loss can improve weight-related complications like joint pain, diabetes, fatty liver, and hypertension."

The authors acknowledged that cost remains a concern, especially among vulnerable populations. They also noted that the medications should not be used in pregnant individuals or those with bulimia nervosa, and they should be used with caution in people with other eating disorders. Patients with type 2 diabetes taking insulin or sulfonylureas and patients taking antihypertensives may require dosage adjustments since these obesity medications may increase risk of hypoglycemia for the former and decrease blood pressure for the latter.



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The panel advised against orlistat, although it added that "patients who place a high value on the potential small weight-loss benefit and low value on gastrointestinal side effects may reasonably choose treatment with orlistat." Those patients should take a multivitamin daily that contains vitamins A, D, E, and K at least 2 hours apart from orlistat. The lack of available evidence for Gelesis100 oral superabsorbent hydrogel led the panel to suggest its use only in a clinical trial.

The AGA will update these guidelines no later than 2025 and may issue rapid guidance updates until then as new evidence comes to light.

The guidelines did not receive any external funding, being fully funded by the AGA. The guideline chair and guideline methodologists had no relevant or direct conflicts of interest. All conflict of interest disclosures are maintained by the AGA office. ■



Continued from page 9

supervisory responsibility and leadership skill sets."

*Sandra Quezada, MD, MS, AGAF*
*Associate Professor of Medicine at University of Maryland, School of Medicine*
*Pfizer Task Force*

"In the next 15 years, I believe we will see a significant increase in the application of artificial intelligence and machine-learning approaches to diagnosis and prognostication of digestive diseases. In addition, advances in our understanding of the microbiome and metabolomics should yield actionable information for the treatment of IBD and perhaps functional GI disorders."

*Kim Barrett, PhD, AGAF*
*Vice Dean for Research and Distinguished Professor of Medicine, UC Davis School of Medicine*
*AGA Governing Board; Trainee and Early Career Committee; Women's Committee; Appointments Committee; Diversity Committee; AGAI Governing Board*

"Over the next 15 years as risk management is moved from Medicare and commercial health plans on to providers, GI will need to find its value place in the cascading levels of accountability. Technological advances will also force GI to make the transition from a procedure-dominated specialty to one that is more cognitive and risk-focused as colon cancer screening transitions from colonoscopy to less invasive tools."

*Larry Kosinski, MD, MBA, AGAF*
*Chief Medical Officer at SonarMD*
*AGA Governing Board; Appointments Committee; Center for GI Innovation and Technology; AGA Institute Governing Board*

"I would offer these two biggest changes. One: There is going to be increasing importance afforded to a personalized precision medicine approach. While treatment options have expanded across

Continued on following page

Continued from previous page

disease states in GI, for equitable, cost-effective, and efficient use, we are going to have to get better at predicting which therapy works for which patient, particularly for chronic GI diseases, including IBD. The field is also going to have to tackle an increasing proportion of vulnerable populations with their unique health needs and risk-benefit balance, in particular, the elderly."

*Ashwin Ananthakrishnan, MPH, MBBS, MPH*
*Associate Professor of Medicine at Massachusetts General Hospital*
*AGAI Council; Clinical Guidelines Committee; Research Awards Panel*

"It is hard to imagine that there will not be some breakthrough on colon cancer and its precursors such that diagnostic testing will not involve colonoscopy. It would be tremendous for patients while revolutionary for our specialty."

*C. Mel Wilcox, MD, MSPH*
*Professor of Medicine at University of Alabama, Birmingham*
*Publications Committee; AGAI Council*

"The biggest change in GI will be that of precision medicine, based on results of aggregated databases involving the combination of human microbiome patterns, serum biomarkers, genomics, and computer-based pattern recognition for disease diagnosis and management. The gastroenterologist will [take on more] of a therapeutic role and [function as] an empathic interpreter of results derived from computer-derived algorithms and machine learning."

*Aja S. McCutchen, MD*
*Atlanta Gastroenterology Associates*
*Ethics Committee; AGA Research Foundation Executive Board*

"I believe the use of computer algorithms will increase to incorporate the large volume of molecular, microbial, and genetic data that will be collected on each patient to implement precision diagnosis and treatments. Chronic inflammation – as the root cause for most GI pathogenesis, prompting the use of a repertoire of anti-inflammatory agents for non-IBD disorders – will also loom large. Also, changes in the GI workforce to near parity for women will be achieved."

*Juanita Merchant, MD, PhD*
*Chief, Division of Gastroenterology, Professor of Medicine at University of Arizona College of Medicine*
*AGAI Council*

"I feel the biggest change in GI will be the use of artificial intelligence in the diagnosis and management of disease. Access to GI and hepatology care will improve with virtual visits. With the advancements in clinical and basic science research, there will be further improvements in the quality and strategies for colon cancer screening."

*Shanthi Srinivasan, MD, AGAF*
*Associate Professor of Medicine*
*Emory University School of Medicine*
*Division of Digestive Disease*
*AGAI Council*

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