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aga American Gastroenterological Association

Official newspaper of the AGA Institute

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GI&Hepatology News

July 2024

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Are Direct-to-Consumer Microbiome Tests Clinically Useful?

DENYS KOVALOV/DREAMSTIME

BY MARILYNN LARKIN

Companies selling gut microbiome tests directly to consumers offer a variety of claims to promote their products.

"We analyze the trillions of microbes in your gut microflora and craft a unique formula for your unique gut needs," one says. "Get actionable dietary, supplement, and lifestyle recommendations from our microbiome experts based on your results, tailored to mom and baby's biomarkers. ... Any family member like dads or siblings are welcome too," says another.

The companies assert that they can improve gut health by offering individuals personalized treatments based on their gut microbiome test results. The trouble is, no provider, company, or technology can reliably do that yet.

Clinical Implications, Not Applications

The microbiome is the "constellation of microorganisms that call the human body home," including many strains of bacteria, fungi, and viruses. That constellation comprises some 39 trillion cells.

Although knowledge is increasing on the oral, cutaneous, and vaginal microbiomes, the gut microbiome is arguably the most studied. However, while research is increasingly demonstrating that the gut microbiome has clinical implications, much work needs to be done before reliable applications based on

See **Microbiome** · *page 20*

Advice, Support for Entrepreneurs at AGA Tech 2024

Leveraging next-gen tech for GI

BY JIM KLING
MDedge News

FROM THE 2024 AGA TECH SUMMIT

CHICAGO — Have a great tech idea to improve gastroenterology? Start-up companies have the potential to transform the practice of medicine, and to make founders a nice pot of money, but it is a difficult road. At the 2024 AGA Tech Summit, held at the Chicago headquarters of MATTER, a global healthcare startup incubator, investors and gastroenterologists discussed some of the key challenges and opportunities for GI startups.

Mr. Fraser

The road is daunting, and founders must be dedicated to their companies but also maintain life balance. "It is very easy, following your passion, for your life to get out of check. I don't know what the divorce rate is for entrepreneurs, but I personally was a victim of that. The culture that we built was addictive and it became all encompassing, and at the same time [I neglected] my home life," Scott Fraser, managing director of the consulting company Fraser Healthcare, said during a "Scars and Stripes" panel at the summit.

For those willing to navigate those waters, there is help. Investors are prepared to provide seed money for companies with good ideas and a strong market. AGA itself has stepped into the investment field with

See **Entrepreneurs** · *page 16*

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LETTER FROM THE EDITOR

Dubious Medicine

Interest in and knowledge of the gut microbiome, and its role in health and disease, has increased exponentially in the past decade. Billions of dollars have been invested in gut microbiome research since release of the National Institutes of Health's Human Microbiome Project's reference database in 2012, aimed at not only better understanding pathology and disease mechanisms, but also promoting development of novel diagnostic and therapeutic interventions. However, it is fair to say that gut microbiome research is still in its infancy, and there is still much to be learned.

Dr. Adams

Our quarterly Perspectives column tackles the issue of GLP-1 receptor agonists in GI endoscopy.

Despite this, a global, and largely unregulated, industry of direct-to-consumer (DTC) microbiome tests has emerged. These (often costly) tests are now widely available to our patients via retail outlets and online — in exchange for a stool sample, consumers receive a detailed report comparing their microbiome to a "healthy" reference patient and recommending various interventions such as follow-up testing, special diets, or nutritional supplements. By now, we likely all have been handed one of these reports in clinic identifying a patient's "abnormal" microbiome and asked to weigh in on its dubious results. A special feature article in this month's issue outlines the controversies surrounding these DTC microbiome tests, which currently lack analytic and clinical validity, and highlights recent calls for increased regulation in this space.

Also in our July issue, we continue our coverage of DDW 2024 and this year's AGA Tech Summit, and report on innovative science published in our leading GI journals. We invite you to learn more about the exceptional Dr. Maria Abreu of the University of Miami, who recently assumed her new role as AGA President. Our quarterly Perspectives column tackles the issue of GLP-1 receptor agonists in GI endoscopy — gastroenterologist Jana Al Hashash and anesthesiologists Thomas Hickey and Ryan Pouliot offer contrasting perspectives on this topic drawn from AGA and American Society of Anesthesiologists guidance.

Finally, our July Member Spotlight features Dr. Lisa Mathew of South Denver Gastroenterology who shares her perspectives on hosting a GI podcast, why private practice is a fantastic laboratory for clinical innovation, and how she found her "tribe" in the field of gastroenterology. ■

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

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GI&Hepatology News

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AGA Clinical Guideline Stresses Patient Preferences in Barrett's Treatment

BY DIANA SWIFT
MDedge News

FROM GASTROENTEROLOGY

The American Gastroenterological Association has released updated evidence-based recommendations on the endoscopic eradication therapy (EET) of Barrett's esophagus (BE) and related neoplasms.

Published in *Gastroenterology* (2024 May 17. doi: 10.1053/j.gastro.2024.03.019), the clinical practice guideline makes five main recommendations — one strong and four conditional — based on very low to moderate evidence. It also stresses that providers should practice shared decision-making according to patient preferences and risk perception.


Dr. Rubenstein


Dr. Sawas

For the most part, the new guideline is not a significant departure from the way expert endoscopists are currently practicing EET for BE and related neoplasia, gastroenterologist Joel H. Rubenstein, MD, MSc, AGAF, of the Barrett's Esophagus Program in the Division of Gastroenterology at University of Michigan Medical School at Ann Arbor, said in an interview. One of three first authors of the guideline, Dr. Rubenstein added, "There is, however, considerable variability in how endoscopists practice, and we hope this guidance will serve as a useful resource to refer to for best practices."

Added gastroenterologist Tarek Sawas, MD, MPH, assistant professor of internal medicine at UT Southwestern Medical Center in Dallas, Texas, "we hope the update will provide some clarity for practice and for implementation, while allowing gastroenterologists the freedom to decide what is best for patients based on lesion characteristics."

Dr. Sawas added that one of the differences in the new guideline relates to the approach to low-grade dysplasia. While earlier guidance favored treatment over surveillance, patient preferences should now be factored into management. "Some patients are risk-averse and prefer to wait and watch, while others place more value on treatment and just want to get on with it," he said.

When this guideline was circulated for public comment, "the areas prompting the most feedback was on our current suggestions against the routine use of EET in nondysplastic BE and for the use of either endoscopic mucosal resection [EMR] or endoscopic submucosal dissection [ESD] for resection — with the expectation that the vast majority may be managed with EMR," Dr. Rubenstein said.

"We felt that ESD would work best for larger lesions," explained Dr. Sawas. "There aren't a lot data in this area, just some observational studies, but we should have more data for comparison in the next few years."

The incidence of esophageal adenocarcinoma continues to rise and an update was deemed in order since the AGA's last formal guidance on this subject using the systematic GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology was issued in 2011. "In the following time span, there's been a lot of research, particularly with regard to management of low-grade dysplasia and endoscopic resection techniques," Dr. Rubenstein said.

Key Recommendations

The 14 guideline panelists made the following suggestions for treatment and implementation based on different levels of certainty of evidence (CoE):

1. If high-grade dysplasia (HGD) is present, EET is recommended over surveillance, with subsequent surveillance performed at 3, 6, and 12 months, and annually thereafter. (Strong recommendation, moderate CoE).

Surveillance endoscopies should obtain targeted tissue samples of visible lesions and random biopsies of the cardia and distal 2 cm of the tubular esophagus.

2. In patients with low-grade dysplasia, EET is also preferred to surveillance. But for those placing a higher value on the certain harms and a lower value on the uncertain benefits of EET for reducing mortality, surveillance endoscopy is a reasonable option. (Conditional recommendation, low CoE).

Following EET, clinicians should perform surveillance at years 1 and 3 after complete eradication of intestinal metaplasia, then revert to the surveillance intervals used in nondysplastic BE.

3. For nondysplastic BE, the AGA advises against the routine use of EET. (Conditional recommendation, low CoE).

4. Patients undergoing EET should have resection of visible lesions followed by ablation of the remaining BE segment rather than resection of the entire segment.

In patients with only a small area of BE beyond the visible lesion, endoscopic resection is acceptable and may be preferred over repeated ablation. Radiofrequency ablation is the preferred ablative modality. (Conditional recommendation, very low CoE).

5. For treating visible neoplastic lesions the AGA suggests either EMR or ESD based on lesion characteristics. (Conditional recommendation, very low CoE).

Patients with suspected T1 esophageal adenocarcinoma (EAC) should be considered for EET. Endoscopic resection is recommended over endoscopic ultrasound for distinguishing EAC from HGD and for staging depth of invasion.

The vast majority of neoplastic lesions may be managed with EMR rather than ESD. Patients who have bulky lesions, or lesions highly suspicious of at least T1b invasion and are deemed candidates for endoscopic resection might benefit from ESD over EMR. Those with previously failed EMR might benefit from ESD.

As to the generally low quality of the supporting evidence, Dr. Rubenstein said, "Unfortunately, very few decisions we make in medicine are supported by high certainty of evidence, but we still have to make a decision." He pointed out that the guideline highlights areas for future research that could help strengthen or change the guideline's recommendations.

Considering benefits and harms, the panelists concluded that overall CoE across critical desirable outcomes of disease progression to EAC was moderate. Patient-important outcomes informing the harms were strictures, major bleeding perforation, and serious adverse events.

Lifestyle

The guidance also urges providers to counsel BE patients on tobacco cessation and weight loss if needed, and notes the specter of cancer may incentivize patients to make lifestyle changes.

The most common causes of death in EET patients are cardiovascular disease and other cancers, for which tobacco use and obesity are also major risk factors, and tobacco is associated with strictures, the panelists wrote. "The prospect of progression to cancer in patients with dysplastic BE often holds greater valence than prior counseling attempts, and patients may re-commit to such efforts following consultation for EET."

Going Forward

Areas for future attention include:

- Identifying populations with nondysplastic BE whose risk warrants EET
- Balancing risk and benefit of EET in low-grade dysplasia
- Comparing EMR and ESD in higher-risk lesions in randomized controlled trials
- Managing post-EET pain optimally
- Preventing and controlling stricture
- Managing resistant/recurrent disease beyond reflux control
- Using optimal surveillance and biopsy strategies following EET

This guideline was supported by the National Institutes of Health, the Department of Defense, the Veterans Administration Health Services and Research Division, and the Katy O. and Paul M. Rady Endowed Chair in Esophageal Cancer Research at the University of Colorado.

Dr. Sawas had no competing interests to disclose. Dr. Rubenstein reported research funding from Lucid Diagnostics.

Several other panelists reported research funding or consultation fees from various pharmaceutical and biotechnology companies.

Congratulations to the 2024 AGA Research Foundation Awardees!

The American Gastroenterological Association is proud to announce that it has selected 79 recipients to receive research funding through the annual AGA Research Foundation Awards Program. The program serves as a catalyst for discovery and career growth among the most promising researchers in gastroenterology and hepatology.

"This year's awardees are an exceptional group of investigators who are committed to furthering patient care through research," said Michael Camilleri, MD, AGAF, chair, AGA Research Foundation. "The AGA Research Foundation is proud to fund these investigators and their ongoing efforts to advance GI research at a critical time in their careers. We believe the Foundation's investment will ultimately enable new discoveries in gastroenterology and hepatology that will benefit patients."

Treatment options for digestive diseases begin with vigorous research. The AGA Research Foundation supports medical investigators as they advance our understanding of gastrointestinal and liver conditions. Here are this year's award recipients:

RESEARCH SCHOLAR AWARDS

AGA Research Scholar Award
- Karen Jane Dunbar, PhD, Columbia University, New York, New York
- Aaron Hecht, MD, PhD, Hospital of the University of Pennsylvania, Philadelphia
- Sarah Maxwell, MD, University of California, San Francisco
- Chung Sang Tse, MD, University of Pennsylvania, Philadelphia
- Jason (Yanjia) Zhang, MD, PhD, Boston Children's Hospital, Massachusetts

AGA-Bristol Myers Squibb Research Scholar Award in Inflammatory Bowel Disease
- Joseph R. Burclaff, PhD, University of North Carolina at Chapel Hill

SPECIALTY AWARDS

AGA-Caroline Craig Augustyn & Damian Augustyn Award in Digestive Cancer
- Swathi Eluri, MD, MSCR, Mayo Clinic, Rochester, Minnesota

AGA-R. Robert & Sally Funderburg Research Award in Gastric Cancer
- Jianwen Que, MD, PhD, Columbia University, New York, New York

AGA-Pfizer Fellowship-to-Faculty Transition Award
- Lianna Wood, MD, PhD, Boston Children's Hospital, Massachusetts

AGA-Ironwood Fellowship-to-Faculty Transition Award
- ZeNan Li Chang, MD, PhD, Washington University School of Medicine, St. Louis, Missouri

PILOT AWARDS

AGA Pilot Research Award
- Linda C. Cummings, MD, MS, University Hospitals Cleveland Medical Center, Cleveland, Ohio
- Pooja Mehta, MD, MSCS, University of Colorado, Denver
- Guilherme Piovezani Ramos, MD, Boston Children's Hospital, Massachusetts
- Simon Schwoerer, PhD, University of Chicago, Illinois
- Yankai Wen, PhD, University of Texas Health Science Center at Houston

AGA-Pfizer Pilot Research Award in Non-Alcoholic Steatohepatitis
- Alice Cheng, PhD, Stanford University, California
- Petra Hirsova, PhD, PharmD, Mayo Clinic, Rochester, Minnesota
- Sarah Maxwell, MD, University of California, San Francisco

AGA-Pfizer Pilot Research Award in Inflammatory Bowel Disease
- David Boone, PhD, Indiana University, Indianapolis
- Sara Chloe Di Rienzi, PhD, Baylor College of Medicine, Houston, Texas
- Jared Andrew Sninsky, MD, MSCR, Baylor College of Medicine, Houston, Texas

UNDERGRADUATE RESEARCH AWARDS

AGA-Aman Armaan Ahmed Family Surf for Success Program
- Eli Burstein, Yeshiva University, New York, New York
- Chloe Carlisle, University of Florida, Gainesville
- Adna Hassan, University of Minnesota, Rochester
- Nicole Rodriguez Hilario, Barry University, Miami, Florida
- Maryam Jimoh, College of Wooster, Ohio
- Viktoriya Kalinina, Brandeis University, Waltham, Massachusetts

AGA-Dr. Harvey Young Education & Development Foundation's Young Guts Scholar Program
- Rafaella Lavalle Lacerda de Almeida, Michigan State University, East Lansing
- Lara Cheesman, John's Hopkins University School of Medicine, Baltimore, Maryland
- Cass Condray, University of Oklahoma, Norman
- Daniel Juarez, Columbia University, New York
- Jason Lin, University of Michigan, Ann Arbor
- Riya Malhotra, Case Western Reserve University, Cleveland, Ohio
- Brian Nguyen, Brown University, Providence, Rhode Island
- Mahmoud (Moudy) Salem, Stony Brook University, New York

ABSTRACT AWARDS

AGA Fellow Abstract of the Year Award
- Andrea Tou, MD, Children's Hospital of Philadelphia, Pennsylvania

AGA Fellow Abstract Awards
- Manik Aggarwal, MBBS, Mayo Clinic, Rochester, Minnesota
- Kole Buckley, PhD, University of Pennsylvania, Philadelphia
- Jane Ha, MD, Massachusetts General Hospital, Boston
- Brent Hiramoto, MD, Brigham and Women's Hospital, Boston, Massachusetts
- Md Obaidul Islam, PhD, University of Miami, Coral Gables, Florida
- Kanak Kennedy, MD, MPH, Children's Hospital of Philadelphia, Pennsylvania
- Hanseul Kim, PhD, MS, Massachusetts General Hospital, Boston
- Chiraag Kulkarni, MD, Stanford University, California
- Su-Hyung Lee, PhD, DVM, Vanderbilt University Medical Center, Nashville, Tennessee
- Caroline Muiler, PhD, Yale School of Medicine, New Haven, Connecticut
- Sarah Najjar, PhD, New York University, New York
- Ronaldo Panganiban, MD, PhD, Penn State Hershey Medical Center, Hershey, Pennsylvania
- Perseus Patel, MD, Stanford University, California
- Hassan Sinan, MD, Johns Hopkins University, Baltimore, Maryland
- Patricia Snarski, PhD, Tulane University, New Orleans, Louisiana
- Fernando Vicentini, PhD, MS, McMaster University, Hamilton, Ontario, Canada
- Remington Winter, MD, University of Manitoba – Health Sciences Centre, Winnipeg, Canada
- Tiaosi Xing, PhD, MBBS, MS, Penn State College of Medicine, Hershey, Pennsylvania

AGA Student Abstract of the Year Award
- Jazmyne Jackson, Temple University, Philadelphia, Pennsylvania

AGA Student Abstract Award
- Valentina Alvarez, University of Washington School of Medicine, Seattle
- Yasaman Bahojb Habibyan, MS, University of Calgary, Alberta, Canada
- Tessa Herman, MD, University of Minnesota, Minneapolis-Saint Paul
- Jason Jin, Yale School of Medicine, New Haven, Connecticut
- Frederikke Larsen, Western University, London, Ontario, Canada
- Kara McNamara, Vanderbilt University, Nashville, Tennessee
- Julia Sessions, MD, University of Virginia, Charlottesville
- Scott Silvey, MS, Virginia Commonwealth University, Richmond
- Vijaya Sundaram, Marshall University School of Medicine, Huntington, West Virginia
- Kafayat Yusuf, MS, University of Kansas Medical Center, Kansas City

AGA–Eric Esrailian Student Abstract Prize
- Brent Gawey, MD, MS, Mayo Clinic, Rochester, Minnesota

Continued on following page

Introducing the 119th AGA President: Dr. Maria T. Abreu

Maria T. Abreu, MD, AGAF, has been inducted as the 119th president of the AGA Institute. She currently serves as the Martin Kalser Endowed Chair of Gastroenterology; professor of medicine, microbiology, and immunology; and director of the Crohn's and Colitis Center at the University of Miami. Dr. Abreu is the fifth woman to lead AGA as president.

Born in New York and raised in New Jersey, Dr. Abreu grew up surrounded by a strong, tight-knit Cuban community. Her family moved to Miami when she was in the ninth grade. She later entered the 6-year medical program at the University of Miami, which was the beginning of her unparalleled academic and professional excellence in medicine.

Dr. Maria T. Abreu

UNIVERSITY OF MIAMI

Dr. Abreu is a leader in inflammatory bowel disease patient care, and she was honored by the prestigious Sherman Prize in 2019. Her service to AGA is lengthy and begins when she took on the role of fellow representative for the Research Grant Committee. She has since sat on both the Government Advocacy and Diversity Committees.

She also served as the chair of the Immunology, Microbiology and Inflammatory Bowel Diseases Section of the AGA Council, and later as chair of the full AGA Council. While chair she developed a more streamlined in-person planning committee meeting to better organize DDW.

When asked about goals for her presidency, Dr. Abreu wants to make DDW a better experience for the modern gastroenterologist. This includes finding that perfect balance between digesting the latest education and science with networking and socializing. She plans to collaborate with the presidents of the other societies to make this come to fruition.

Perhaps the area that Dr. Abreu is most passionate about is welcoming and fostering the growth of women in gastroenterology. She wants to support women who want to succeed in academics and in practice, who want ergonomics to match their work needs, and who want to have families.

"Maria is the ultimate 'triple threat': master scientist, master clinician, and devoted mentor. She has not only been a major player advancing knowledge in IBD, but also motivating and pushing others to develop successful careers," said Andres Yarur, MD, AGAF, associate professor of medicine at Cedars-Sinai Medical Center. "Her work, brilliance, passion, and charm inspire all of us and will continue to inspire many generations to come." ■

AGA

Dr. Maria T. Abreu, left, is the 119th president of the AGA Institute. Pictured here with her family, Dr. Abreu is the fifth woman to lead AGA.


AGA

Dr. Maria T. Abreu, second from left, stands with other women leaders in IBD research: Dr. Iris Dotan, Dr. Uma Mahadevan, and Dr. Marla Dubinsky.

Continued from previous page

- Fei Li, MBBS, MS, University of Michigan, Ann Arbor
- Emily Wong, University of Toronto, Ontario, Canada
- Jordan Woodard, MD, Prisma Health – Upstate, Greenville, South Carolina

AGA–Radhika Srinivasan Student Abstract Prize

- Raz Abdulqadir, MS, Penn State College of Medicine, Hershey, Pennsylvania
- Rebecca Ekeanyanwu, MHS, Meharry Medical College, Nashville, Tennessee
- Jared Morris, MD, University of Manitoba, Winnipeg City, Canada
- Rachel Stubler, Medical University of South Carolina, Charleston

AGA Abstract Award for Health Disparities Research

- Saqr Alsakarneh, MD University of Missouri-Kansas City
- Marco Noriega, MD, Beth Israel Deaconess Medical Center, Boston, Massachusetts
- Temitope Olasehinde, MD, University Hospitals/Case Western Reserve University, Cleveland, Ohio
- Gabrielle Waclawik, MD, MPH, University of Wisconsin, Madison

AGA-Moti L. & Kamla Rustgi International Travel Award

- W. Keith Tan, MBChB, University of Cambridge, England
- Elsa van Liere, MD Amsterdam Universitair Medische Centra, Amsterdam, Netherlands ■

Targeting Enteroendocrine Cells in IBD Research

BY WILL PASS
MDedge News

FROM CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

Colitis-induced small intestinal hypomotility is closely linked to the loss of enteroendocrine cells (EECs) in mice, revealing a potential therapeutic strategy for patients with inflammatory bowel disease (IBD), according to investigators.

These findings suggest that restoring EEC function could alleviate some of the more general abdominal symptoms associated with IBD, reported lead author Zachariah Raouf, MD, of Johns Hopkins University School of Medicine, Baltimore, and colleagues.

"The symptoms experienced by patients with IBD, especially ulcerative colitis, may include those that are colonic in nature, such as bloody stools, abdominal pain, and weight loss, as well as those that are more general in nature, such as severe nausea and abdominal bloating," the investigators wrote in *Cellular and Molecular Gastroenterology and Hepatology* (2024 Mar. doi: 10.1016/j.jcmgh.2024.02.017). "Although the first set of symptoms may be attributable to the effects of colonic inflammation itself, those that are more vague seem to overlap with the symptoms that patients with small intestinal dysmotility experience, such as occur in response to medications, or diabetes."

Supporting this notion, several previous studies have reported the onset of intestinal dysmotility in experimental models of colitis, which is believed to be caused by impaired enteric nervous system function. But the precise mechanisms behind the impaired intestinal motility observed in colitis patients remain unclear.

To learn more, Dr. Raouf and colleagues conducted experiments involving three groups of mice: wild-type mice, mice genetically engineered to overexpress EECs, and mice lacking EECs.

For induction of colitis, the mice were administered dextran sulfate sodium (DSS) in drinking water at concentrations of 2.5% or 5% for 7 days. Small intestinal motility was evaluated by measuring the transit of fluorescein isothiocyanate (FITC)-dextran. Immunohistochemical analyses were conducted to assess EEC number and differentiation, while quantitative reverse-transcriptase polymerase chain reaction was used to examine the expression of genes related to serotonin synthesis and transport.

The researchers examined colon length and signs of colonic inflammation, monitored weight loss, and measured the expression of proinflammatory cytokines. Histological analyses of colon and small intestine tissues were performed to further understand the effects of colitis. The presence and number of EEC cells was evaluated using chromogranin A (ChgA) staining, while apoptosis in EECs was measured via TUNEL staining. The expression of serotonin-related genes was also assessed.

These experiments revealed that DSS-induced colitis led to significant small-bowel hypomotility and a reduction in EEC density. Of note, genetic overexpression of EECs or treatment with prucalopride, a 5-hydroxytryptamine receptor 4 agonist, improved small intestinal motility.

"It is noteworthy that there were no significant changes in the density of other intestinal epithelial cells, or in other cell types that are linked to motility, such as enteric glia and neurons, suggesting the specificity of the effect," the investigators wrote. "Importantly, treatment with a serotonin agonist ameliorated the colitis-induced, small-bowel hypomotility and attenuated the severity of colitis, providing potential clinical relevance of the current findings. Taken together, these results identify mechanisms to explain the intestinal hypomotility observed in the setting of colitis."

Dr. Raouf and colleagues called for human clinical trials to expand their findings. Specifically, they suggested exploring therapies targeting enteroendocrine cells or serotonin pathways and examining the role of different EEC types in gut motility during inflammation.

The study was supported by the National Institutes of Health. The investigators disclosed no conflicts of interest.

Inflammatory bowel disease (IBD) typically manifests with colonic symptoms but is also associated with intestinal inflammation and dysmotility of the small intestine. Clinical research debates whether IBD causes small intestine hypermotility or hypomotility, but these motility dysfunctions are often attributed to alterations of the gut's intrinsic nervous system.


Dr. Gonzales

Dr. Raouf and colleagues focus on the role of enteroendocrine cells, an epithelial cell subtype with neuron-like features that secrete serotonin, one of the most important regulators of intestinal motility. Their population is reduced in colitis, and the subsequent alteration of serotonin signaling induces small intestine dysmotility. The observed loss of enteroendocrine cells in the small bowel may result from low-grade local inflammation increasing enteroendocrine cell apoptosis, or impaired gene expression in their differentiation pathways. However, more research is required to elucidate the underlying mechanisms of this loss.

Nevertheless, their findings provide valuable insights into small intestine dysmotility associated with IBD pathologies and suggest a therapeutic approach based on a pharmacologic serotonin agonist. Treatment with prucalopride, a serotonin type 4 receptor agonist already used in clinics with minimal adverse effects, restores small intestine motility and offers therapeutic benefits. Although the results are promising in dextran sodium sulfate models of colitis, the observed improvement in small intestinal motility needs to be confirmed in IBD patients.

This study enhances our understanding of the small intestine dysfunction associated with colitis and raises the exciting possibility of enteroendocrine cell–based therapeutic approaches in IBD.

Jacques A. Gonzales, PhD, is a postdoctoral fellow in the Gulbransen laboratory at Michigan State University, East Lansing. He has no conflicts of interest.

Fibrosis-4 Index Misclassifies Many Patients

BY WILL PASS
MDedge News

FROM CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

The Fibrosis-4 (FIB-4) index shows high discordance with liver stiffness measurement (LSM) via transient elastography, suggesting that many patients are misclassified, potentially impacting clinical decisions, according to investigators.

These findings call for a cautious interpretation of low-risk FIB-4 results among patients at greatest risk of misclassification, and/or use of alternative assessment strategies, reported Mazen Noureddin, MD, MHSc, of Houston Methodist Hospital, and coauthors.

"Currently, the [American Gastroenterological Association]/[American Association for the Study of Liver Diseases] Pathways recommends identifying patients at risk for metabolic dysfunction-associated steatotic liver disease (MASLD), then using sequential testing with FIB-4 followed by FibroScan to risk-stratify patients," the investigators wrote in *Clinical Gastroenterology and Hepatology* (2024 Feb 29. doi: 10.1016/j.cgh.2024.02.008).

Yet the performance of the FIB-4 index in this context remains unclear.

"Previous studies have shown FIB-4 to have low accuracy for screening liver fibrosis, especially among obese and diabetic patients," the investigators wrote. "Thus, there is a concern that classifying patients with FIB-4 can lead to misclassification and missed diagnosis."

To explore this concern, Dr. Noureddin and colleagues turned to data from the 2017-2020 National

Continued on following page

Autonomous AI Equals Humans in Optical Diagnosis of Colorectal Polyps

BY WILL PASS
MDedge News

FROM GASTROENTEROLOGY

Autonomous artificial intelligence (AI) can achieve similar accuracy to AI-assisted humans (AI-H) in the optical diagnosis of diminutive colorectal polyps, while providing greater alignment with pathology-based surveillance intervals, based on a randomized controlled trial.

These findings suggest that autonomous AI may one day replace histologic assessment of diminutive polyps, reported lead author Roupen Djinbachian, MD, of the Montreal University Hospital Research Center, Quebec, Canada, and colleagues.

Optical diagnosis of diminutive colorectal polyps has been proposed as a cost-effective alternative to histologic diagnosis, but its implementation in general clinical practice has been hindered by endoscopists' concerns about incorrect diagnoses, the investigators wrote in *Gastroenterology* (2024 Feb 7. doi: 10.1053/j.gastro.2024.01.044).

"AI-based systems (CADx) have been proposed as a solution to these barriers to implementation, with studies showing high adherence to Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI) thresholds when using AI-H," they wrote. "However, the efficacy and safety of autonomous AI-based diagnostic platforms have not yet been evaluated."

To address this knowledge gap, Dr. Djinbachian and colleagues conducted a randomized controlled noninferiority trial involving 467 patients, all of whom underwent elective colonoscopies at a single academic institution.

Participants were randomly assigned to one of two groups. The first group received an optical diagnosis of diminutive (1-5 mm) colorectal polyps using an autonomous AI-based CADx system without any human input. The second group had diagnoses performed by endoscopists who used AI-H to make their optical diagnoses.

The primary outcome was the accuracy of optical diagnosis compared with the gold standard of histologic evaluation. Secondarily, the investigators explored associations between pathology-based surveillance intervals and various measures of accuracy, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

The results showed that the accuracy of optical diagnosis for diminutive polyps was similar between the two groups, supporting noninferiority. Autonomous AI achieved an accuracy rate of 77.2%, while the AI-H group had an accuracy of 72.1%, which was not statistically significant ($P = .86$).

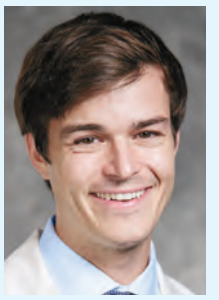
But when it came to pathology-based surveillance intervals, autonomous AI showed a clear advantage; the autonomous AI system achieved a 91.5% agreement rate, compared with 82.1% for the AI-H group ($P = .016$).

"These findings indicate that autonomous AI not only matches but also surpasses AI-H in accuracy for determining surveillance intervals," the investigators wrote, noting that this finding highlights the "complexities of human interaction with AI modules where human intervention could lead to worse outcomes."

Further analysis revealed that the sensitivity of autonomous AI for

Continued on following page

In the era of computer vision for endoscopy and colonoscopy, current paradigms rely on artificial intelligence (AI) as a co-pilot or second observer, with the physician serving as the final arbiter in procedure-related decision-making. This study by Djinbachian et al brings up the interesting wrinkle of autonomous AI as a potentially superior (or noninferior) option in narrow, task-specific use cases.


Dr. Glissen Brown

In this study, human input from the endoscopist after CADx diagnosis led to lower agreement between the AI-predicted diagnosis and corresponding surveillance intervals; human oversight more often incorrectly changed the resultant diagnosis and led to shorter than recommended surveillance intervals.

This study offers a small but very important update to the growing body of literature on CADx in colonoscopy. So far, prospective validation of CADx compared with the human eye for in-situ diagnosis of polyps has provided mixed results. This study is one of the first to examine the potential role of "automatic" CADx without additional human input and sheds light on the importance of the AI-human hybrid in medical care. How do the ways in which humans interact with the user interface and output of AI lead to changes in outcome? How can we optimize the AI-human interaction in order to provide optimal results?

In this case, the suggestion is that less is more when it comes to human interference with optical diagnosis, but further research is needed on how to best optimize this important relationship as well as how AI might (or might not) support diagnose-and-leave and diagnose-and-discard strategies in the United States and worldwide.

Jeremy R. Glissen Brown is an assistant professor in the Department of Internal Medicine and Division of Gastroenterology at Duke University Medical Center, Durham, North Carolina. He has served as a consultant for Medtronic and Olympus, and on the advisory board for Odin Vision.

Continued from previous page

Health and Nutrition Examination Surveys, including 5285 subjects at risk for MASLD. Exclusions were made for those with excessive alcohol intake or other liver diseases, resulting in a final cohort of 3741 individuals.

All subjects were classified as low, indeterminate, or high risk for advanced liver fibrosis based on FIB-4 scores. These scores were then compared with LSM obtained through transient elastography (FibroScan).

Out of 2776 subjects classified as low risk by FIB-4, 277 (10%) were reclassified as higher risk by LSM, including 75 (2.7%) who were found to be at high risk. Out of 879 subjects with indeterminate FIB-4 scores, 37 (4.2%) were at high risk according to LSM. Finally, among the 86 subjects classified as high risk by FIB-4, 68 (79.1%) were reclassified as lower risk by LSM, including 54 (62.8%) who were deemed low risk.

Subjects misclassified as low risk by FIB-4 were typically older and had higher waist circumferences, body mass indices, glycohemoglobin A1c levels, fasting glucose levels, liver enzyme levels, diastolic blood pressures, controlled attenuation parameter scores, white blood cell counts, and alkaline phosphatase levels, but lower high-density lipoprotein and albumin levels (all P less than .05). They were also more likely to have prediabetes or diabetes.

"[I]t is important to acknowledge that 10% of the subjects were misclassified as low risk by FIB-4," Dr. Noureddin and colleagues wrote, including 2.7% of patients who were actually high risk. "This misclassification of high-risk patients can lead to missed diagnoses, delaying crucial medical treatments or lifestyle interventions."

They therefore suggested cautious interpretation of low-risk FIB-4 results among patients with factors predicting misclassification, or even use of alternative diagnostic strategies.

"Some possible alternatives to FIB-4 include new serum tests such NIS-2+, MASEF, SAFE score, and machine learning methods," Dr. Noureddin and colleagues wrote. "However, additional confirmatory and cost-effective studies are required to validate the effectiveness of these tests, including studies conducted on the general population."

The investigators disclosed relationships with AbbVie, Corcept, Galectin, and others. ■

New Way to Gauge Mucosal Injury in Celiac Disease

BY DIANA SWIFT
MDedge News

FROM CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

A new two-measure metric seems to improve accuracy and statistical precision in assessing celiac disease (CeD) histology compared with either of two components alone, according to a study in *Clinical Gastroenterology and Hepatology* (2023 Nov. doi: 10.1016/j.cgh.2023.10.031).

The new morphometric duodenal biopsy mucosal scale joins together villous height-to-crypt depth ratio (Vh:Cd) and intraepithelial lymphocytes (IEL) — each key CeD histological measures of the small intestine — in a scale called VCIEL.

The authors believe the VCIEL will enable a broader and more accurate measurement of mucosal health in CeD. It will be particularly useful for population analysis in clinical trials and could improve the powering of trial design. "Use of VCIEL may lead to better outcome measures for potential new therapeutic treatments benefiting patients," wrote Jocelyn A. Silvester, MD, PhD, a pediatrician at Boston Children's Hospital and an assistant professor at Harvard Medical School, and colleagues.

This chronic enteropathy affects about 1% of the world's population and requires a lifelong adherence to a gluten-free diet, the authors noted.

The authors pointed to weaknesses in the current quantitative and qualitative ways of measuring gluten-induced mucosal injury on biopsy

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identifying adenomas was 84.8%, slightly higher than the 83.6% sensitivity of the AI-H group. Specificity was 64.4% for autonomous AI vs 63.8% for AI-H. While PPV was higher in the autonomous AI group (85.6%), compared with the AI-H group (78.6%), NPV was lower for autonomous AI than AI-H (63.0% vs 71.0%).

Dr. Djinbachian and colleagues suggested that future research should focus on larger, multicenter trials to validate these findings and further explore the integration of autonomous AI systems in clinical practice. They also noted that improving AI algorithms to accurately diagnose sessile serrated lesions could enhance the overall effectiveness of AI-based optical diagnosis.

"The performance of autonomous AI in accurately diagnosing diminutive polyps and determining appropriate surveillance intervals suggests that it could play a crucial role in streamlining colorectal cancer screening processes, reducing the burden on pathologists, and potentially lowering healthcare costs," the investigators concluded.

The study was supported by Fujifilm, which had no role in the study design or data analysis. One coauthor reported additional research funding from Vantage and Fujifilm. ■


Dr. Silvester

for CeD. "Morphometry measures the injury continuum for architecture and inflammation, but these are used as separate outcomes," they wrote. "The original Marsh-Oberhuber [M-O] classifications are rather contrived approaches to assess a biologic continuum, forcing the injury in categorical groups of unclear clinical relevance and where clinically significant changes may occur within one single category."

Moreover, the quantitation of inflammation relies on binary assessment as normal or increased, which results in histology that is unscorable by M-O if villous atrophy persists without increased IELs, they added.

The Study

In the absence of a broadly accepted single measure of mucosal injury in CeD, the group assessed whether the composite metric could improve statistical precision for assessing histology.

Enter VCIEL, which combines the Vh:Cd and IEL for individual patients with equal weighting by converting each scale to a fraction of their standard deviation and summing the results.

The researchers applied the VCIEL formula in a reanalysis of four clinical gluten-challenge trials and compared the results for Vh:Cd and IEL separately with those for VCIEL for clinical significance (effect size) and statistical significance.

In reanalysis of the ALV003-1021 trial, for example, the researchers observed an effect size and *P* value (analysis of covariance) of 1.37 and .038 for a delta (difference) value of Vh:Cd 1.17 and .005 for IEL and 1.86 and .004 for VCIEL.

For the similar gluten-challenge IMGX003-NCCIH-1721 trial, the corresponding delta results were .76 and .057 for Vh:Cd, .98 and .018 for IEL, and 1.14 and .007 for VCIEL. Comparable improvements with VCIEL over individual Vh:Cd and IEL were observed for other studies, including a nontherapeutic gluten-challenge study.

In NCT03409796 trial data, the computation of VCIEL values showed an improved statistical significance relative to the component values of Vh:Cd and IEL by the within-group paired 2-tailed t test *P* values from baseline to day 15, particularly at a 10-g gluten-challenge dose: Vh:Cd, IEL, and VCIEL were .0050, .0031, and .0014, respectively.

Little correlation emerged between baseline values and changes with intervention for Vh:Cd and IEL on an individual patient basis.

The greater accuracy and statistical precision of the VCIEL scale are presumably due to averaging over some of the measurement uncertainty in individual patient and timepoint Vh:Cd and IEL values and creating a composite of different histologic properties, the authors noted.

This study was funded by ImmunogenX. First author Jack A. Syage, PhD, is a cofounder and shareholder in ImmunogenX. Dr. Silvester has served on an advisory board for Takeda Pharmaceuticals and has received research funding from Biomedal S.L., Cour Pharmaceuticals, and Glutenostics LLC. Several coauthors disclosed various financial ties to multiple private-sector pharmaceutical and biomedical companies, including ImmunogenX.

High-Quality Diet in Early Life May Ward Off Later IBD

BY DIANA SWIFT
MDedge News

Children who ate a high-quality diet at 1 year of age were at a 25% reduced risk of developing inflammatory bowel disease (IBD) in later life, prospective pooled data from two Scandinavian birth cohorts suggested.

It appears important to feed children a quality diet at a very young age, in particular one rich in vegetables and fish, since by age 3, only dietary fish intake had any impact on IBD risk.

Although high intakes of these two food categories in very early life correlated with lower IBD risk, exposure to sugar-sweetened beverages was associated with an increased risk. "While non-causal explanations for our results cannot be ruled out, these novel findings are consistent with the hypothesis that early-life diet, possibly mediated through changes in the gut microbiome, may affect the risk of developing IBD," wrote lead author Annie Guo, a PhD candidate in the Department of Pediatrics, University of Gothenburg, Sweden, and colleagues. The report was published in *Gut* (2024 Jan 30. doi: 10.1136/gutjnl-2023-330971).

"This is a population-based study investigating the risk for IBD, rather than the specific effect of diet," Ms. Guo said in an interview. "Therefore, the results are not enough on their own to be translated into individual advice that can be applicable in the clinic. However, the study supports current dietary guidelines for small children; that is, the intake of sugar should be limited and a higher intake of fish and vegetables is beneficial for overall health."

Two-Cohort Study

The investigators prospectively recorded food-group information on children (just under half were female) from the All Babies in Southeast Sweden and The Norwegian Mother, Father and Child Cohort Study to assess the diet quality using a Healthy Eating Index and intake frequency. Parents answered questions about their offspring's diet at ages 12-18 months and 30-36 months. Quality of diet was measured by intake of meat, fish, fruit, vegetables, dairy, sweets, snacks, and drinks.

The Swedish cohort included 21,700 children born between October 1997 and October 1999, while the Norwegian analysis included 114,500 children, 95,200 mothers, and 75,200 fathers recruited from across Norway from 1999 to 2008. In 1,304,433


Ms. Guo


Dr. Ananthakrishnan

person-years of follow-up, the researchers tracked 81,280 participants from birth to childhood and adolescence, with median follow-ups in the two cohorts ranging from 1 year of age to 21.3 years (Sweden) and to 15.2 years of age (Norway). Of these children, 307 were diagnosed with IBD: Crohn's disease (CD; n = 131); ulcerative colitis (UC; n = 97); and IBD unclassified (n = 79).

Adjusting for parental IBD history, sex, origin, education, and maternal comorbidities, the study found:

- Compared with low-quality diet, both medium- and high-quality diets at 1 year were associated with a roughly 25% reduced risk for IBD (pooled adjusted hazard ratio [aHR], 0.75 [95% CI, 0.58-0.98] and 0.75 [95% CI, 0.56-1.0], respectively).
- The pooled aHR per increase of category was 0.86 (95% CI, 0.74-0.99). The pooled aHR for IBD in 1-year-olds with high vs low fish intake was 0.70 (95% CI, 0.49-1.0), and this diet showed an association with a reduced risk for UC (pooled aHR, 0.46; 95% CI, 0.21-0.99). Higher vegetable intake at 1 year was also associated with a risk reduction in IBD (HR, 0.72; 95% CI, 0.55-0.95). It has been hypothesized that intake of vegetables and vegetable fibers may have programming effects on the immune system.
- With 72% of children reportedly consuming sugar-sweetened beverages at age 1, pooled aHRs showed that some vs no intake of sugar-sweetened beverages was associated with an increased risk for later IBD (pooled aHR, 1.42; 95% CI, 1.05-1.90).
- There were no obvious associations between overall IBD or CD/UC risk and meat, dairy, fruit, grains, potatoes, and foods high in sugar and/or fat. Diet at age 3 years was not associated with incident IBD (pooled aHR, 1.02; 95% CI, 0.76-1.37), suggesting that the risk impact of diet is greatest on very young and vulnerable microbiomes.

Ms. Guo noted that a Swedish national survey among 4-year-olds found a mean sugar-sweetened beverages consumption of 187 g/d with a mean frequency of once daily. The most desired changes in food habits are a lower intake of soft drinks, sweets, crisps, cakes, and biscuits and an increase in the intake of fruits and vegetables. A similar Norwegian survey among 2-year-olds showed that sugar-sweetened beverages were consumed by 36% of all children with a mean intake of 40 g/d.

The exact mechanism by which sugar affects the intestinal microbiota is not established. "However, what we do know is that an excessive intake of sugar can disrupt the balance of the gut microbiome," Ms. Guo said. "And if the child has a high intake of foods that are high in sugar, that also increases the chances that the child's overall diet has a lower intake of other foods that contribute to a diverse microbiome such as fruits and vegetables."

An 'Elegant' Study

In an accompanying editorial, gastroenterologist Ashwin N. Ananthakrishnan, MBBS, MPH, AGAF, of Mass General Brigham and the Mass General Research Institute, Boston, cautioned that accurately measuring food intake in very young children is difficult, and dietary questionnaires in this study did not address food additives and emulsifiers common in commercial baby food, which may play a role in the pathogenesis of IBD.

Another study limitation is that the dietary questionnaire used has not been qualitatively or quantitatively validated against other more conventional methods, said Dr. Ananthakrishnan, who was not involved in the research.

Nevertheless, he called the study "elegant" and expanding of the data on the importance of this period in IBD development. "Although in the present study there was no association between diet at 3 years and development of IBD (in contrast to the association observed for dietary intake at 1 year), other prospective cohorts of adult-onset IBD have demonstrated an inverse association between vegetable or fish intake and reduced risk for CD while sugar-sweetened beverages have been linked to a higher risk for IBD."

As to the question of recommending early preventive diet for IBD, "thus far, data on the impact of diet very early in childhood, outside of breastfeeding, on the risk for IBD has been lacking," Dr. Ananthakrishnan said in an interview. "This important study highlights that diet as early as 1 year can modify subsequent risk for IBD. This raises the intriguing possibility of whether early changes in diet could be used, particularly in those at higher risk, to reduce or even prevent future development of IBD. Of course, more works needs to be done to define modifiability of diet as a risk factor, but this is an important supportive data."

In his editorial, Dr. Ananthakrishnan stated that despite the absence of gold-standard interventional data demonstrating a benefit of dietary interventions, "in my opinion, it may still be reasonable to suggest such interventions to motivate individuals who incorporate several of the dietary patterns associated with lower risk for IBD from this and other studies. This includes ensuring adequate dietary fiber, particularly from fruits and vegetables, intake of fish, minimizing sugar-sweetened beverages and preferring fresh over processed and ultra-processed foods and snacks." According to the study authors, their novel findings support further research on the role of childhood diet in the prevention of IBD.

The All Babies in Southeast Sweden Study is supported by Barndiabetesfonden (Swedish Child Diabetes Foundation), the Swedish Council for Working Life and Social Research, the Swedish Research Council, the Medical Research Council of Southeast Sweden, the JDRF Wallenberg Foundation, ALF and LFoU grants from Region Östergötland and Linköping

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GLP-1s May Increase Post-Endoscopy Aspiration Pneumonia Risk: New Study

BY CAROLYN CRIST

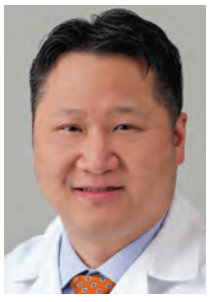
FROM GASTROENTEROLOGY

The use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) may lead to an increased risk for aspiration pneumonia after endoscopic procedures, according to a new large population-based study.

In June 2023, the American Society of Anesthesiologists (ASA) recommended holding GLP-1 RAs before an endoscopic or surgical procedure to reduce the risk for complications associated with anesthesia and delayed stomach emptying.

In response, the American Gastroenterological Association published a Rapid Clinical Practice Update in November 2023 that found insufficient evidence to support patients stopping the medications before endoscopic procedures.

Dr. Rezaie



Dr. Wang

"It is known that GLP-1 RAs significantly reduce the motility of the stomach and small bowel. As more and more patients are being started on GLP-1 RAs at higher doses and longer half-life, the question became whether the current recommended fasting durations are enough to reasonably assume the stomach is empty prior to procedures that require sedation," said senior author Ali Rezaie, MD, medical director of the GI Motility Program at Cedars-Sinai Medical Center in Los Angeles.

"We wanted to see if these medications in fact increased the chance of aspiration before the ASA suggestion went into effect," he said. "However, this is not an easy task, as aspiration is a rare event and a large sample size is needed to confidently answer that question. That is why we evaluated nearly 1 million cases."

The study was published online in *Gastroenterology* (2024 Mar 27. doi: 10.1053/j.gastro.2024.03.015).

Analyzing GLP-1 RA Use

Dr. Rezaie and colleagues conducted a population-based, retrospective cohort study of the TriNetX dataset, which includes 114 million deidentified individual health records from 80 healthcare organizations. The research team analyzed nearly 1 million records for adult patients between ages 21 and 70 who underwent upper and lower endoscopies between January 2018 and December 2020.

The researchers defined GLP-1 RA users as those who had the medication for more than 6 months and two or more refills within 6 months before the procedure. They adjusted for 59 factors that could affect gut motility or aspiration risks, such as obesity, numerous chronic diseases, and dozens of medications. The primary outcome was aspiration pneumonia within a month after the procedure.

Among 963,184 patients who underwent endoscopy, 46,935 (4.9%) were considered GLP-1 RA users. Among those, 20,099 GLP-1 RA users met the inclusion criteria and had their results compared with non-GLP-1 RA users.

After propensity score matching for the 59 potential confounders, GLP-1 RA use had a higher incidence rate of aspiration pneumonia (0.83% vs 0.63%) and was associated with a significantly higher risk for aspiration pneumonia, with a hazard ratio (HR) of 1.33.

An even higher risk was seen among patients with propofol-assisted endoscopies (HR, 1.49) but not among those without propofol (HR, 1.31).

In a subgroup analysis based on endoscopy type, an elevated risk was observed among patients who underwent upper endoscopy (HR, 1.82) and combined upper and lower endoscopy (HR, 2.26) but not lower endoscopy (HR, 0.56).

"The results were not necessarily surprising given the mechanism of action of GLP-1 RAs. However, for the first time, this was shown with a clinically relevant outcome, such as aspiration pneumonia," Dr. Rezaie said. "Aspiration during sedation can have devastating consequences, and the 0.2% difference in risk of aspiration can have a significant effect on healthcare as well."

More than 20 million endoscopies are performed across the United States annually. Based on the assumption that about 3% of those patients are taking GLP-1 RAs, about 1200 aspiration cases per year can be prevented by raising awareness, he said.

Considering Next Steps

The varying risk profiles observed with separate sedation and endoscopy types point to a need for more tailored guidance in managing GLP-1 RA use before a procedure, the study authors wrote.

Although holding the medications before endoscopy may disrupt diabetes management, the potential increased risk for aspiration could justify a change in practice, particularly for upper endoscopy and propofol-associated procedures, they added. At the same time, additional studies are needed to understand the optimal drug withholding windows before endoscopies and other procedures, they concluded.

"We will need more data on what is the optimal duration of holding GLP-1 RAs," Dr. Rezaie said. "But given our data and current ASA guidance, stopping these medications prior to elective procedures is the safe thing to do."

For now, AGA guidance remains the same as offered in the November 2023 update, suggesting an individual approach for each patient on a GLP-1 RA rather than a "blanket statement" on how to manage all patients taking these medications.

"Overall, I believe that this study is important, but we require more high-level data to inform clinical decision-making regarding patients using GLP-1 receptor agonists prior to gastrointestinal endoscopy," said Andrew Y. Wang, MD, AGAF, chief of gastroenterology and hepatology and director of interventional endoscopy at the University of Virginia in Charlottesville.

Dr. Wang, who wasn't involved with this study, coauthored the AGA Rapid Clinical Practice Update. He and colleagues advised continuing with a procedure as planned for patients on GLP-1 RAs who followed standard preprocedure fasting instructions and didn't have nausea, vomiting, dyspepsia, or abdominal distention.

Among patients with symptoms that suggest retained gastric contents, rapid sequence intubation may be considered, though it may not be possible in ambulatory or office-based endoscopy settings, the researchers wrote. As another option in lieu of stopping GLP-1 RAs, patients can be placed on a liquid diet for 1 day before the procedure.

"While this study found a signal suggesting that patients using GLP-1 RAs had an increased risk of aspiration pneumonia within 1 month following upper endoscopy or combined upper and lower endoscopy, it does not inform us if having patients stop GLP-1 RAs before endoscopic procedures — especially for a single dose — will mitigate this potential risk," Dr. Wang said.

"It was also interesting that these investigators found that patients taking GLP-1 RAs who underwent lower endoscopy alone were not at increased risk for aspiration pneumonia," Dr. Wang noted.

The authors didn't report a funding source and disclosed no potential conflicts. Dr. Wang reported no relevant disclosures. ■

Continued from previous page

University, and the Joanna Cocozza Foundation.

The Norwegian Mother, Father and Child Cohort Study is supported by the Norwegian Ministry of Health and Care Services and the Ministry of Education and Research.

Ms. Guo received grants from the Swedish Society for Medical Research and the Henning and Johan Throne-Holst Foundation to conduct this study. Co-author Karl Mårild has received funding from the Swedish Society for Medical Research, the Swedish Research Council, and ALF, Sweden's medical research and education co-ordinating body. The authors declared no competing interests.

Dr. Ananthakrishnan is supported by the National Institutes of Health, the Leona M. and Harry B. Helmsley Charitable Trust, and the Chleck Family Foundation. He has served on the scientific advisory board for Geneoscopy. ■

Practice-changing ideas posed

Entrepreneurs *from page 1*

its GI Opportunity Fund, which it launched in 2022 through a partnership with Varia Ventures. The fund's capital comes from AGA members, with a minimum investment of $25,000. To date, AGA has made investments in six companies, at around $100,000 per company. "It's not a large amount that we're investing. We're a lead investor that signals to other venture capital companies that this is a viable company," Tom Serena, CEO of AGA, said in an interview.

"I think that there's huge burnout among gastroenterologists, [partly because] some of the systems have been optimized to get the most out of each specialist. I think we just have to get back to making work more enjoyable."

The fund grew out of AGA's commitment to boosting early-stage companies in the gastroenterology space. AGA has always supported GI device and tech companies through its Center for GI Innovation and Technology, which sponsored the AGA Tech Summit. The center now provides resources and advice for GI innovators and startups. The AGA Tech Summit has created a gathering place for entrepreneurs and innovators to share their experiences and learn from one another. "But what we were missing was the last mile, which is getting funding to the companies," said Mr. Serena. The summit itself has been modified to increase the venture capital presence. "That's the networking we're trying to [create] here. Venture capitalists are well acquainted with these companies, but we feel that AGA can bring clinical due diligence, and the startups want to be exposed to venture capital," said Mr. Serena.

During the "Learn from VC [Venture Capital] Strategists" panel, investors shared advice for entrepreneurs. The emphasis throughout was on marketable ideas that can fundamentally change healthcare practice, though inventions may not have the whiz-bang appeal of some new technologies of years past.

"We're particularly focused on clinical models that actually work. There were a lot of companies for many years that were doing things that had minimal impact, or very incremental impact. Maybe they were helping identify certain patients, but they weren't actually engaging those patients. We're now looking very end-to-end and trying to make sure that it's not just a good idea, but one that you can actually roll out, engage patients, and see the [return on investment] in that patient data," said Kelsey Maguire, managing director of the Blue Venture Fund, which is a collaborative effort across Blue Cross Blue Shield companies.

Ms. Maguire

Dr. Jung

Part of the reason for that shift is that healthcare has evolved in a way that has put more pressure on physicians, according to Barbara H. Jung, MD, AGAF, past president of AGA, who was present for the session. "I think that there's huge burnout among gastroenterologists, [partly because] some of the systems have been optimized to get the most out of each specialist. I think we just have to get back to making work more enjoyable. [It could be less] fighting with the insurance companies; it could be that you spend less time typing after hours. It could be that it helps the team work more seamlessly, or it could be something that helps the patient prepare, so they have everything ready when they see the doctors. It's thinking about how healthcare is delivered, and really in a patient and physician-centric way," Dr. Jung said in an interview.

Anna Haghgooie, managing director of Valtruis, noted that, historically, new technology has been rewarded by the healthcare system. "It's part of why we find ourselves where we are as an industry: There was nobody in the marketplace that was incented to roll out a cost-reducing technology, and those weren't necessarily considered grand slams. But [I think] we're at a tipping point on cost, and as a country will start purchasing in pretty meaningfully different ways, which opens up a lot of opportunities for those practical solutions to be grand slams. Everything that we look at has a component of virtual care, leveraging technology, whether it's AI [artificial intelligence] or just better workflow tools, better data and intelligence to make business decisions," said Ms. Haghgooie. She did note that Valtruis does not work much with medical devices.

Specifically in the GI space, one panelist called for a shift away from novel colonoscopy technology. "I don't know how many more bells and whistles we can ask for colonoscopy, which we're very dependent on. Not that it's not important, but I don't think that's where the real innovation is going to come: when you think about the cognitive side of the GI business — new diagnostics, things that are predictive of disease states, things that monitor disease, things that help you to know what people's disease courses will be. I think as more and more interventions are done by endoscopists, you need more tools," said Thomas Shehab, MD, managing partner at Arboretum Ventures.

Ms. Haghgooie

Dr. Shehab

Finally, AI has become a central component to investment decisions. Ms. Haghgooie said that Valtruis is focused on the infrastructure surrounding AI, such as the data that it requires to make or help guide decisions. That data can vary widely in quality, is difficult to index, exists in various silos, and is subject to a number of regulatory constraints on how to move or aggregate it.

"We're focused on the systems and tools that can enable the next-gen application of AI. That's one piece of the puzzle. Every company that we've either invested in or are looking at investing in, we ask the question: How are you planning to incorporate and leverage this next-gen technology to drive your marginal cost-to-deliver down? In many cases you have to do that through business model redesign, because there is no fee-for-service code to get paid for leveraging AI to reduce your costs. You've got to have different payment structures in order to get the benefit of those types of technologies," she said. ■

FDA OKs Iqirvo, First-in-Class Proliferator-Activated Receptor Treatment for Primary Biliary Cholangitis

BY MEGAN BROOKS

The US Food and Drug Administration (FDA) has granted accelerated approval for Iqirvo (elafibranor; Ipsen) for treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults who do not respond adequately to UDCA or as monotherapy in patients unable to tolerate UDCA.

PBC is a rare, chronic cholestatic liver disease that destroys interlobular bile ducts and leads to cholestasis and liver fibrosis. Left untreated, the disease can worsen over time, leading to cirrhosis and liver transplant and, in some cases, premature death. PBC also harms quality of life, with patients often experiencing severe fatigue and pruritus.

Iqirvo, an oral dual peroxisome proliferator–activated receptor (PPAR) alpha and delta agonist, is the first new drug approved in nearly a decade for treatment of PBC.

Accelerated approval of Iqirvo for PBC was based on data from the phase 3 ELATIVE trial published last year in *The New England Journal of Medicine*. The trial randomly assigned patients with PBC who had an inadequate response to or unacceptable side effects with UDCA to receive either once-daily elafibranor (80 mg) or placebo.

The primary endpoint was a biochemical response, defined as an alkaline phosphatase (ALP) level < 1.67 times the upper limit of the normal range, with a reduction ≥ 15% from baseline, as well as normal total bilirubin levels.

Among 161 patients, a biochemical response was seen in 55 of 108 (51%) who received elafibranor vs 2 of 53 (4%) who received placebo.

At week 52, the ALP level normalized in 15% of patients in the elafibranor group and none of the patients in the placebo group.

In a news release announcing approval of Iqirvo, the company notes that improvement in survival and prevention of liver decompensation events have not been demonstrated and that continued approval for PBC may be contingent upon verification and description of clinical benefit in confirmatory trials.

The most common adverse effects with Iqirvo, reported in ≥ 10% of study participants, were weight gain, abdominal pain, diarrhea, nausea, and vomiting. Iqirvo is not recommended for people who have or develop decompensated cirrhosis. Full prescribing information is available online.

The data show that Iqirvo is "an effective second-line treatment for patients with PBC with favorable benefit and risk data," Kris Kowdley, MD, AGAF, director of the Liver Institute Northwest in Seattle, Washington, and a primary investigator on the ELATIVE study, said in the news release.

The approval of Iqirvo "will allow healthcare providers in the US to address an unmet need with the potential to significantly reduce ALP levels for our patients with PBC," Dr. Kowdley said. ■

GLP-1 Receptor Agonists in Endoscopy

Dear colleagues,
Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are revolutionizing the field of obesity management and are now common medication in patients presenting for endoscopy. With their effect on gastric emptying, the American Society of Anesthesiologists has recommended cessation of such agents prior to endoscopy. However, is this necessary in patients who have been on a clear-liquid diet in preparation for a colonoscopy or who are undergoing moderate sedation? Additionally, there are risks to holding GLP-1 RAs, especially for those taking them for glycemic control.

In this issue of Perspectives, Dr. Thomas Hickey and Dr. Ryan Pouliot discuss the nuances of preprocedure cessation from an anesthesiologist's perspective. Dr. Jana Al Hashash provides a gastroenterologist's view, also highlighting the current paucity of evidence guiding management strategies. We hope these pieces will help your discussions in managing GLP-1 RAs prior to endoscopy in your own practice. We welcome your thoughts on this issue on X @AGA_GIHN.


Dr. Ketwaroo

Gyanprakash A. Ketwaroo, MD, MSc, is associate professor of medicine, Yale University, New Haven, Connecticut, and chief of endoscopy at West Haven (Connecticut) VA Medical Center. He is an associate editor for GI & Hepatology News.

GLP-1 Receptor Agonists: Anesthesiologists Weigh In

BY THOMAS R. HICKEY, MD; RYAN C. POULIOT, MD

In response to the recent dramatic increase in glucagon-like peptide 1 receptor agonist (GLP-1 RAs) prescribing and at the urging of its membership, the American Society of Anesthesiologists (ASA) issued guidance on the preoperative management of these medications. The big takeaways were recommendations that patients on daily dosing should hold their dose on the day of a procedure, and that patients on weekly dosing should hold their dose a week prior.


Dr. Hickey


Dr. Pouliot

The ASA guidance recognizes the sparse available evidence base and makes its recommendations in the spirit of patient safety, presuming that a more conservative approach will mitigate risk of rare but potentially devastating pulmonary aspiration, until prospective evidence informs the ideal approach. Until that approach is defined, whether more or less conservative, it is expected that anesthesiologists will adhere to their professional society's recommendations.

Meanwhile, the American Gastroenterological Association Institute Rapid Clinical Practice Update (CPU) makes little distinction in the management of the endoscopy patient on GLP-1 RAs. A key refrain throughout the CPU is that there is no actionable data to justify the harms that may come to patients from stopping these medications (eg, withdrawal of benefit to glycemic control and cardiovascular health) and in delaying or canceling procedures, which could lead to further stress on an overburdened workforce and add complexity to periprocedural processes.

Anesthesiologists should rightly consider themselves leaders in patient safety. As such, when a serious safety concern emerges they should be compelled to caution despite the possibility of other harms, until their concerns are mitigated by robust clinical evidence. Thankfully these questions are quite amenable to research, and prospective trials are already reporting compelling data that residual gastric contents, clearly a risk factor for aspiration, are increased in GLP-1 RA groups compared to controls. This is evident even while following recommended fasting times and abstinences

GLP-1 *continued on following page*

GLP-1 Receptor Agonists: The View From Gastroenterology

BY JANA G. AL HASHASH, MD, MSC, AGAF

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have been approved for the treatment of type 2 diabetes mellitus since 2005. They have become more widely used over the last couple of years for weight loss in individuals who suffer from adiposity-based chronic disease.


Dr. Al Hashash

The remarkable positive effects that GLP-1 RAs have had on weight loss as well as other medical conditions such as heart disease, hypertension, metabolic dysfunction–associated steatotic liver disease, among many others, have gained these drugs more traction. Even in situations when insurance companies deny coverage of GLP-1 RAs, many patients have been resorting to other routes to obtain these medications, commonly by purchasing them from online compounding pharmacies.

As such, more and more of our patients who present to endoscopy suites across the country are on one of the available GLP-1 RAs. This has necessitated endoscopists and anesthesiologists to become more familiar with the impact of GLP-1 RAs on patients undergoing endoscopic procedures.

Similar to narcotics, GLP-1 RAs affect gastrointestinal motility and delay gastric emptying. Common side effects of patients receiving GLP-1 RAs include nausea, vomiting, and increased satiety. Patients on GLP-1 RAs for weight loss may also have other contributing risk factors for gastroparesis such as diabetes mellitus which may further delay gastric emptying.

For endoscopists, our goals are to achieve the highest quality examination in the safest way possible. As such, being on a GLP-1 RAs could compromise both goals; but to date, the exact impact of these drugs on exam quality and patient safety is yet to be determined.

Studies have shown that patients on GLP-1 RAs have increased gastric residue on upper endoscopy compared with patients not on GLP-1 RAs. The effect of this increased residue on aspiration risk and clinically meaningful patient outcomes is being investigated, and the available published data are conflicting. Additionally, other published cases have shown that GLP-1 RAs are associated with increased solid gastric residue but not liquids, and that symptoms of dyspepsia and abdominal bloating

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GLP-1 *continued from previous page*
from these medications, and adjusting for confounders (eg, age, diabetes, body mass index).[1,2] It logically follows that large studies are likely to find an increased aspiration risk in GLP-1 RA populations. Indeed, this increased risk has already been identified in a large retrospective study of endoscopy patients.[3] These findings support the ASA's caution. Additional data indicate that standard fasting guidelines in this patient population may be inadequate.[4]

The ASA guidance does not differentiate between patients undergoing surgery in the operating room and procedures in the endoscopy suite.

"We also expect prospective trials will confirm retrospective findings that both propofol and procedures including upper endoscopy confer a higher risk for aspiration compared with conscious sedation and colonoscopy."

Part of our task is to provide perspective on whether GLP-1 RA management deserves different treatment for endoscopy patients. We can only speculate pending further data. For example, a prolonged fasting period including a full day of clears, with or without a bowel prep, intuitively protects against pulmonary aspiration. However, this is unlikely to mitigate an anesthesiologist's concern that administration of propofol, frequently to a state of general anesthesia with an unsecured airway and resulting in a patient devoid of airway protection reflexes, is an inherently higher risk scenario for aspiration compared to surgery in the operating room with a secured airway. We also expect prospective trials will confirm retrospective findings that both propofol and procedures including upper endoscopy confer a higher risk for aspiration compared with conscious sedation and colonoscopy.[3]

We suggest a reasonable approach based on society guidance and existing evidence, pending additional data. Endoscopists and anesthesiologists should continue this important conversation with a specific focus on risks and benefits in order to decrease conflict and achieve consensus. If anesthesia care is desired, the patient instructions should be updated to reflect ASA guidance. Special attention should be paid to the "gray area," for example those who did not hold the GLP-1 RA as recommended.

This category of patients can be considered on a case-by-case basis by the anesthesiologist, proceduralist, and patient, with a range of options including proceeding with endoscopist-directed sedation, proceeding with anesthesiology-administered conscious sedation, rescheduling the procedure, and proceeding with general anesthesia with rapid-sequence intubation. In addition to patient factors (eg, GI symptoms, urgency of procedure), this consideration would vary based on local resources (eg, presence or absence of anesthesia support staff, emergency airway equipment, nursing staff to comfort recovering patients after general endotracheal anesthesia), and aspiration risk inherent to the procedure (eg, upper and or combination upper and lower endoscopy vs colonoscopy alone).

Proficiency and availability of point-of-care ultrasound are rapidly increasing; adoption of a pre-procedure gastric ultrasound to assess for solids, thick liquids, or large volume of clear liquids may provide a less nuanced, more objective means to address this question.

While the question of periprocedural management of these medications has generated intense interest among anesthesiologists and endoscopists alike, it is worth noting the net positive health effects these drugs are likely to have on our patients, including improved glycemic control, significant weight loss, and decreased cardiovascular risk. We are eager to see whether these benefits translate into an overall improvement in periprocedural outcomes, including in our endoscopy patients. ■

Dr. Hickey is assistant professor of anesthesiology at the Yale University School of Medicine, New Haven, Connecticut, and the VA Connecticut Healthcare System. Dr. Pouliot is assistant professor of anesthesiology at the Geisel School of Medicine at Dartmouth, Hanover, New Hampshire, and Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire.

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are associated with an increased probability of residual gastric content.

Given the valid concern for increased gastric content residue, anesthesia specialists became more strict about which GLP-1 RA users they would agree to sedate, which ones they would intubate, and which procedures they would cancel. As one would imagine, cancellation and intubation rates have been increasing, and these have affected the schedules of patients, their families, and physicians.

The concern with GLP-1 RAs does not only apply to upper endoscopies, but also impacts colonoscopies. In addition to the concerns of aspiration and pneumonia, studies have shown that the use of GLP-1 RAs may be associated with a lower quality of bowel preparation and higher need for repeat colonoscopy.

A study, which I believe is critical, showed that patients on GLP-1 RAs who were scheduled for upper endoscopy and colonoscopy were found to have less gastric residue and less risk of complications when compared with patients who were having only an upper endoscopy. This study sets the stage for a modified prep for patients on GLP-1 RAs prior to their procedures, since patients who received a modified/extended liquid diet on the day prior to their procedure (those preparing for a colonoscopy), had a protective effect against retained gastric content.

Clearly, there is a knowledge gap and a need for guidance. In our recently published AGA Rapid Clinical Practice Update (CPU), we advised an individualized approach to managing patients on GLP-1 RAs in the pre-endoscopic setting. Factors to consider are the indication for the GLP-1 RAs, the dose being used, duration of use, and indication and urgency of the procedure, as well as the presence of symptoms in the preoperative area (ie, do patients have any nausea, vomiting, dyspepsia, etc). Also an important factor is the facility in which the endoscopy will be taking place, as certain centers have the capacity to act fast and prevent complications or address them in a timely manner while other centers may not be prepared.

"In our recently published AGA Rapid [CPU], we advised an individualized approach to managing patients on GLP-1 RAs in the pre-endoscopic setting. Factors to consider are the indication for the GLP-1 RAs, the dose being used, duration of use, and indication and urgency of the procedure."

We proposed that a modified liquid diet be considered in patients prior to their endoscopies by advising patients to adhere to a clear-liquid diet the day before the procedure, as this may help decrease gastric residue and be the safest and best approach for patients on GLP-1 RAs. Of course, it is important to note that more prospective studies are needed to inform clinical practice, and until then, we will have to individualize our approach and continue to put patient safety first. ■

Dr. Al Hashash is a gastroenterologist and associate professor of medicine at Mayo Clinic, Jacksonville, Florida.

Tests not yet reliable

Microbiome *from page 1*

that research are available.

But lack of scientific evidence and validity hasn't stopped a growing number of companies across the globe from offering direct-to-consumer (DTC) microbiome tests, Erik C. von Rosenvinge, MD, AGAF, a professor at the University of Maryland School of Medicine and chief of gastroenterology at the VA Maryland Health Care System, Baltimore, said in an interview.

Dr. von Rosenvinge

"If you go to their websites, even if it's not stated overtly, these companies at least give the impression that they're providing actionable, useful information," he said. "The sites recommend microbiome testing, and often supplements, probiotics, or other products that they sell. And consumers are told they need to be tested again once they start taking any of these products to see if they're receiving any benefit."

Dr. von Rosenvinge and colleagues authored a recent article in *Science* (2024 Mar 14. doi: 10.1126/science.adk427) arguing that DTC microbiome tests "lack analytical and clinical validity" — and yet regulation of the industry has been "generally ignored." They identified 31 companies globally, 17 of which are based in the United States, claiming to have products and/or services aimed at changing the intestinal microbiome.

Unreliable, Unregulated

The lack of reliability has been shown by experts who have tested the tests.

"People have taken the same stool sample, sent it to multiple companies, and gotten different results back," Dr. von Rosenvinge said. "People also have taken a stool sample and sent it to the same company under two different names and received two different results. If the test is unreliable at its foundational level, it's hard to use it in any clinical way."

Test users' methods and the companies' procedures can affect the results, Dina Kao, MD, a professor at the University of Alberta, Edmonton, Canada, explained in an interview.

"So many biases can be introduced at every single step of the way, starting from how the stool sample was collected and how it's preserved or not being preserved, because that can introduce a lot of noise that would change the analyses. Which primer they're using to amplify the signals and which bioinformatic pipeline they use are also important," commented Dr. Kao, who presented at the recent Gut Microbiota for Health World Summit, organized by the American Gastroenterological Association and the European Society of Neurogastroenterology and Motility.

Dr. Kao

Different investigators and companies use different technologies, so it's very difficult to compare them and to create a standard, said Mahmoud Ghannoum, PhD, a professor in the dermatology and pathology departments at Case Western Reserve University School of Medicine and director of the Center for Medical Mycology at University Hospitals in Cleveland.

The complexity of the gut microbiome makes test standardization more difficult than it is when just one organism is involved, Dr. Ghannoum, who chaired the antifungal subcommittee at the Clinical and Laboratory Standards Institute, said in an interview.

"Even though many researchers are focusing on bacteria, we also have fungi and viruses. We need standardization of methods for testing these organisms if we want to have regulations," said Dr. Ghannoum, a cofounder of BIOHM, a microbiome company that offers nondiagnostic tests and markets a variety of probiotics, prebiotics, and immunity supplements. BIOHM is 1 of the 31 companies identified by Dr. von Rosenvinge and colleagues, as noted above.

Dr. Ghannoum believes that taking a systematic approach could facilitate standardization and, ultimately, regulation of the DTC microbiome testing products. He and his colleagues described such an approach by outlining the stages for designing probiotics capable of modulating the microbiome in chronic diseases, using Crohn's disease as a model. Their strategy involved the following steps:

- Using primary microbiome data to identify, by abundance, the microorganisms underlying dysbiosis.
- Gaining insight into the interactions among the identified pathogens.
- Conducting a correlation analysis to identify potential lead probiotic strains that antagonize these pathogens and discovering metabolites that can interrupt their interactions.
- Creating a prototype formulation for testing.
- Validating the efficacy of the candidate formulation via preclinical in vitro and in vivo testing.
- Conducting clinical testing.

Dr. Ghannoum recommends that companies use a similar process "to provide evidence that what they are doing will be helpful, not only for them but also for the reputation of the whole industry."

Potential Pitfalls

Whether test results from commercial companies are positioned as wellness aids or diagnostic tools, providing advice based on the results "is where the danger can really come in," Dr. Kao said. "There is still so much we don't know about which microbial signatures are associated with each condition."

"Even when we have a solution, like the Crohn's exclusion diet, a physician doesn't know enough of the nuances to give advice to a patient," she said. "That really should be done under the guidance of an expert dietitian. And if a company is selling probiotics, I personally feel that's not ethical. I'm pretty sure there's always going to be some kind of conflict of interest."

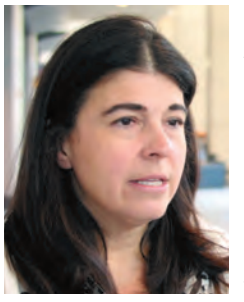
Supplements and probiotics are generally safe, but negative consequences can occur, Dr. von Rosenvinge noted.

"We occasionally see people who end up with liver problems as a result of certain supplements, and rarely, probiotics have been associated with infections from those organisms, usually in those with a compromised immune system," he said.

Other risks include people taking supplements or probiotics when they actually have a medically treatable condition or delays in diagnosis of a potentially serious underlying condition, such as colon cancer, he said. Some patients may stop taking their traditional medication in favor of taking supplements or may experience a drug-supplement interaction if they take both.

What to Tell Patients

"Doctors should be advising against this testing for their patients," gastroenterologist Colleen R. Kelly, MD, AGAF, Brigham and Women's Hospital, Boston, said in an interview. "I explain to patients that these tests are not validated and are clinically meaningless data and not worth the money. There is a reason they are not covered by insurance.



Dr. Kelly

"Recommendations to purchase probiotics or supplements manufactured by the testing company to 'restore a balanced or healthy microbiome' clearly seem like a scam," she added. "I believe some of these companies are capitalizing on patients who are desperate for answers to explain chronic symptoms, such as bloating in irritable bowel syndrome."

Dr. von Rosenvinge said that the message to patients "is that the science isn't there yet to support using the results of these tests in a meaningful way. We believe the microbiome is very important in health and disease, but the tests themselves in their current state are not as reliable and reproducible as we would like."

When patients come in with test results, the first question a clinician should ask is what led them to seek out this type of information in the first place, Dr. von Rosenvinge said.

"Our patient focus groups suggested that many have not gotten clear, satisfactory answers from traditional medicine," he said. "We don't have a single test that says, yes, you have irritable bowel syndrome, or no, you don't. We might suggest things that are helpful for some people and are less helpful for others."

Dr. Kelly said she worries that "there are snake oil salesmen and cons out there who will gladly take your money. These may be smart people, capable of doing very high-level testing, and even producing very detailed and accurate results, but that doesn't mean we know what to do with them."

She hopes to see a microbiome-based diagnostic test in the future, particularly if the ability to therapeutically manipulate the gut microbiome in various diseases becomes a reality.

Continued on following page

Mailed Outreach for CRC Screening Appeals Across Races and Ethnicities

BY CAROLYN CRIST
MDedge News

FROM DDW 2024

WASHINGTON — Mailing outreach notices for colonoscopies or fecal immunochemical test (FIT) kits may be a great way to increase colorectal cancer (CRC) screening in younger adults, according to a study presented at the annual Digestive Disease Week® (DDW).

In a comparison of four outreach approaches, sending a FIT kit to people between the ages of 45 and 49 via mail garnered better response rates than opt-in strategies to participate in FIT, inviting them to undergo colonoscopy, or asking them to choose between FIT or colonoscopy. At the same time, when given a choice between colonoscopy and FIT, colonoscopy was preferred across all racial and ethnic groups.

"At my institution, we have a large number of such patients [not on the digital portal] who tend to be of lower socioeconomic status and tend to be at higher risk of not getting screened."

"It is well known that colorectal cancer is the second-leading cause of cancer-related deaths in the United States. The good news is that for the past several decades, we've seen a decline in colorectal cancer incidence and mortality in ages 50 and above. However, there has been a recent rise in incidence and mortality in people younger than 50," said lead author Rebecca Ekeanyanwu, a third-year medical student at Meharry Medical College School of Medicine in Nashville, Tennessee. She was awarded the 2024 AGA Institute Council Healthcare

Ms. Ekeanyanwu

Disparities Research Award for the top oral presentation for research in racial and ethnic healthcare disparities.

CRC incidence, screening rates, and mortality also vary by race and ethnicity, with higher incidence and mortality rates seen among non-Hispanic Black patients, more late-stage diagnoses among Hispanic patients, and lower screening rates among Asian patients.

"There's no formal guidance on how to screen the population under age 50," she said. "With the disparities in race and ethnicity, it remains unclear what would be the best population health strategy to optimize colorectal screening participation in young minorities."

Ms. Ekeanyanwu and colleagues conducted a subanalysis of a 2022 randomized controlled trial at the University of California, Los Angeles (UCLA), that looked at screening strategies for average-risk patients between ages 45 and 49. The study population included patients who were assigned to a primary care provider in the UCLA Health system and had active electronic portal use and excluded those with a personal or family history of adenoma or CRC, history of inflammatory bowel disease or gastrointestinal cancer, and a prior FIT or colonoscopy.

In this study, the research team focused on the completion of any CRC screening at 26 weeks, stratified by race and ethnicity. They included four outreach scenarios: FIT invitation, colonoscopy invitation, a choice between FIT or colonoscopy invitation, or a default mailed FIT kit, which served as the control and typically is sent to UCLA patients overdue for screening among ages 50 and older. The researchers sent letters via US Postal Service and the online patient portal, as well as two texts about CRC screening.

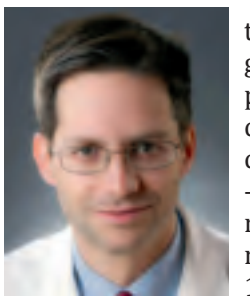
Among 20,509 patients, 8918 were White (43.5%), 2757 were Hispanic (13.4%), 2613 were Asian (12.7%), and 797 were Black (3.9%).

The overall screening participation rate was 18.6%, with the lowest percentage among Black participants at 16.7% and the highest among Asian participants at 23.8%. These numbers varied significantly from the 20% seen among both White and Hispanic participants.

"With the disparities in race and ethnicity, it remains unclear what would be the best population health strategy to optimize colorectal screening participation in young minorities."

The default mailed outreach approach had the highest uptake with higher screening rates, at 26.2% overall, and had the highest participation in each racial and ethnic group. The rates were 28.7% among White patients, 20.1% among Black patients, 27.5% among Hispanic patients, and 31% among Asian patients.

Participation was lowest among the colonoscopy invitation group — for White (14.8%), Hispanic (16%), and Asian (19.3%) patients. Among Black patients, participation was lowest in the FIT invitation group (12.8%).



Dr. Lebwohl

Notably, in the choice group, more participants chose colonoscopy above FIT — across all racial and ethnic groups — at 12.1% versus 5.6% overall. In addition, among both FIT groups, there was significant crossover to colonoscopy, with about 7%-14% among the racial and ethnic groups preferring colonoscopy.

Ms. Ekeanyanwu noted the study may be limited by variations in sample size by race and ethnicity, as well as the socioeconomic status of typical patients at UCLA, who tend to fall in middle-class and affluent groups. Demographic and socioeconomic factors may play a part in patients' decision to get screened, she noted.

Patient participation in the digital portal may affect response rates as well, said Benjamin Lebwohl, MD, AGAF, an associate professor of medicine and epidemiology at Columbia University Medical Center, New York, who moderated the DDW session titled "Reducing the Burden of GI Cancers Through Early Interventions."

"At least at my institution, we have a large number of such patients [not on the digital portal] who tend to be of lower socioeconomic status and tend to be at higher risk of not getting screened," Dr. Lebwohl said. It would be important to consider "those who might need this intervention the most."

Ms. Ekeanyanwu declared no relevant disclosures. ■

Continued from previous page

Emphasize Education

More education is needed on the subject, so we can become "microbial clinicians," Dr. Kao said.

"The microbiome never came up when I was going through my medical education," she said, adding that current and future physicians "need to at least be able to understand the basics. Hopefully, one day, we will be in a position where we can have meaningful interpretations of the test results and make some kind of meaningful dietary interventions."

Dr. Ghannoum reiterated that companies offering microbiome tests and products also need to be educated and encouraged to use systematic approaches to product development and interpretation.

"Companies should be open to calls from clinicians and be ready to explain findings on a report, as well as the basis for any recommendations," he said.

Dr. von Rosenvinge, Dr. Kao, and Dr. Kelly had no relevant conflicts of interest. Dr. Ghannoum is a cofounder of BIOHM. ■

Mirikizumab Promising for Moderate to Severe CD

BY DAMIAN MCNAMARA

FROM DDW 2024

WASHINGTON — The selective interleukin (IL)–23p29 monoclonal antibody mirikizumab demonstrated safety and efficacy in people with moderate to severe Crohn's disease compared with placebo up to 52 weeks, according to results of the phase 3 randomized, double-blind, treat-through VIVID-1 study.

Bruce E. Sands, MD, AGAF, chief of gastroenterology at the Icahn School of Medicine at Mount Sinai in New York, reported the findings in a poster (Abstract Su1801) at the annual Digestive Disease Week® (DDW).

The Food and Drug Administration approved mirikizumab (Omvoh, Eli Lilly) to treat moderate to severe ulcerative colitis in October 2023.

Dr. Sands and a team of US and international collaborators studied 1065 adults with Crohn's disease or fistulizing Crohn's disease for 3 months or more, with a mean duration of more than 7 years. At baseline, participants had a Simple Endoscopic Score for Crohn's Disease (SES-CD) of 7 or more and reported an inadequate response, lost response, or intolerance to other therapy.

A total of 579 people were randomly assigned to mirikizumab and another 199 to placebo. Another 287 patients received ustekinumab; though they were not included in this current analysis, the findings were presented separately at DDW 2024.

Mean age of study participants was 30 years, and men comprised 57%-59% of the groups. Nearly half (49%) of each group previously failed biologic therapy.

Dr. Sands

Dr. Axelrad

A primary composite endpoint was clinical response at 12 weeks according to patient reported outcome and endoscopic response at 52 weeks measured with the SES-CD. A second primary endpoint was clinical response at 12 weeks by patient-reported outcome combined with clinical remission on Crohn's Disease Activity Index (CDAI) at 52 weeks.

Researchers also tracked 12 major secondary endpoints for mirikizumab vs placebo, including clinical response, endoscopic response, and clinical remission at week 12 and week 52.

A higher percentage of participants in the mirikizumab group achieved 12-week secondary endpoints compared with placebo. In the treatment group, 32.5% reached endoscopic response vs 12.6% in the placebo group, a statistically significant difference ($P < .000001$). In addition, 17.6% achieved endoscopic remission in the treatment group vs 7.0% in the placebo group at 12 weeks ($P < .000213$).

The "treat-through" results at 52 weeks revealed that a higher proportion of the group taking mirikizumab met the co-primary endpoints compared with placebo. A total of 48.4% in the mirikizumab group vs 9.0% in the placebo group achieved endoscopic response ($P < .000001$). Similarly, a higher proportion met clinical remission on the CDAI, 54.1% in the treatment group vs 19.6% in the placebo group ($P < .000001$).

Overall, 38% of mirikizumab-treated patients vs 9% of the placebo group reached a composite endpoint of patient-reported clinical response at week 12 and endoscopic response by SES-CD at week 52 ($P < .000001$).

Dr. Sands and colleagues also combined clinical response reported by patients at 12 weeks with CDAI findings for clinical remission at week 52. A total of 45.4% in the treatment group met the combined endpoint compared with 19.6% of the placebo group ($P < .000001$).

In an additional analysis, the researchers looked at this composite endpoint in patients in both groups who had failed or not failed a prior biologic for a total of 43.4% vs 12.4%, and 47.3% vs 26.5%, respectively.

"Mirikizumab demonstrated statistically significant and clinically meaningful improvements" in the co-primary endpoints and secondary endpoints compared with placebo, the researchers concluded.

Safety Findings

Safety outcomes during the 52-week study were "consistent with the known safety profile" of mirikizumab, the researchers noted.

Treatment-emergent adverse events occurred in 78.6% of mirikizumab participants vs 73.0% of the placebo group. The most common were COVID-19, anemia, and arthralgia. Serious adverse events were reported in 10.3% of the mirikizumab group vs 17.1% of the placebo group. There were seven opportunistic infections in the treatment group, including herpes zoster and *Candida*, compared with none in the placebo group.

One person in the placebo cohort died of a pulmonary embolism; there were no deaths in the mirikizumab group.

People randomly assigned to placebo without a response at 12 weeks were switched over to mirikizumab. However, the findings from this group between 12 and 52 weeks were excluded from the 1-year data presented at DDW 2024, including one death from worsening Crohn's disease.

Mirikizumab looked particularly robust in this study, and it may turn out to be a critically important option for our patients, said Jordan Axelrad, MD, MPH, co-director of the Inflammatory Bowel Disease Center at NYU Langone Health in New York City. Dr. Axelrad was not involved in this study.

Of importance, effect sizes were similar for "bio-naive and previously biologic-exposed patients," he added. These data "really underscore that therapies targeting IL-23 may be clinically useful for Crohn's disease patients with prior biologic failure, representing a significant departure from our previous experience with other biologic classes."

The study was funded by Eli Lilly. Dr. Sands is a consultant and receives grant funding from Lilly. Dr. Axelrad had no relevant disclosures. ■

Member SPOTLIGHT

For One Colorado GI, Private Practice Is Anything but Routine

BY JENNIFER LUBELL
MDedge News

Lisa Mathew, MD, wants to quell any misconceptions that private practice is dull or routine. "That has not been my experience at all," says Dr. Mathew, a partner with South Denver Gastroenterology in the suburbs of Denver, Colorado.

For Dr. Mathew, working in private practice offers a rich professional experience, not just in the day-to-day experiences of medicine, but in practice management innovation and patient care delivery. "It's an area within GI where we can be quite nimble in trialing new technologies, optimizing patients' access to care, and working to ensure a positive patient experience," she said.

Nationwide, a flourishing GI private practice community engages in ongoing dialogue about improvements, navigating a changing healthcare environment, and innovation. "That has been a surprising and wonderful twist in my career," she added.

Dr. Mathew fosters that dialogue through "Gastro Broadcast," a podcast she shares with several other GI physicians. Targeted toward private GI practice, it highlights innovations within the community, providing updates on practice management and other technological advances.

In an interview, she spoke frankly about her favorite recent podcast guest, the challenges she's faced in her career, and why her fellow GI specialists are her "tribe."

Q: Why did you choose GI?
Dr. Mathew: In medical school at Duke University, I was considering going into ob.gyn., but academically I was a little more drawn toward internal medicine. While I was in my residency at the University of Pennsylvania, I really clicked with the gastroenterologists. I enjoyed their sense of humor. They were dealing with complex medical issues but doing so with a sense of levity and enjoyment in their work. When I entered fellowship at the University of Washington, I felt like I found my tribe. This was a group of people who really love their work, love medicine, love being able to develop their procedural skills, and keep a sense of humor about themselves. I married a cardiologist (and he's a hilarious cardiologist), but the world of cardiology is a little more buttoned up. I like that GI is a little more relaxed.


South Denver Gastroenterology

Dr. Lisa Mathew

Q: What gives you the most joy in your day-to-day practice?
Dr. Mathew: My patients. They are funny and genuine, and they allow you into these moments of vulnerability — it's an honor to walk through that together. I'm always so grateful for the trust they put in me in those moments. As my practice has matured, it's been incredible to watch those relationships grow, as well as begin caring for husbands, wives, sons, and daughters of my patients. I enjoy being a part of my community.

Q: Can you talk about an interesting recent guest you had on your podcast? Who was it and why did he or she stand out?
Dr. Mathew: Russ Arjal, MD, AGAF, cofounder, chief medical officer, and president of Telebelly Health. He's been working on a platform for exclusively telehealth services that improves access to care; pairing patients with brick-and-mortar gastroenterology to provide any necessary procedural care, such as colonoscopy and upper endoscopy. It was a fantastic interview. I think it's so refreshing and inspiring to see how people innovate within the field of GI. On the procedural side, you see this all the time. With my advanced endoscopy colleagues, they're constantly pushing the boundaries of what we can do procedurally. My academic colleagues are constantly thinking through what the next best treatment is or how best can we optimize care. And, in the world of private practice, we're thinking about practice care delivery — how to improve access and make the experience of being a patient better, with the ultimate goal of improving health outcomes.

Q: What fears did you have to push past to get to where you are in your career?
Dr. Mathew: Imposter Syndrome is a very, very common issue, maybe somewhat more for women in GI. I think it's something that everybody wrestles with to some degree. For me, it was developing confidence not just in my clinical skills, but in learning all the complexities of running a small business. It takes time to develop confidence in your abilities and judgment. I think to some degree, that's normal. It just takes a while to settle into whatever your chosen career path is. Having a community and strong mentors to support me has made all the difference.

Q: Describe your biggest practice-related challenge and what you are doing to address it.
Dr. Mathew: One of the greatest challenges in my career has been navigating COVID — both with just the tremendous sea change it had on our ability to practice, as well as the financial consequences to someone in private practice. Those were very challenging times to deliver the care that was needed, protect staff, and to maintain a small business. Fortunately, as with many practices across the nation, we've emerged through that.

We pivoted; we innovated with telehealth and other services that allowed us to care for our patients. But there were a lot of lessons learned and a lot of difficult moments.

Q: What teacher or mentor had the greatest impact on you?
Dr. Mathew: My dad has taught me the value of hard work. Being a physician just comes in tandem with hard work. And my mom, who is a nurse, has always shown the importance of empathy. Without it, everything else is a little empty. Medicine is a combination of skill and hard work, but also an ability to connect with other people. Empathy is essential to that.

Q: Describe how you would spend a free Saturday afternoon.
Dr. Mathew: We have three children who are native Coloradans so skiing is their birthright. Our entire family are diehard skiers. This is our joy. When you talk about the beach versus mountains debate, we are firmly Team Mountains. On a perfect Saturday afternoon, I'm on the slopes with my little crew, just tearing it up, having a great time. ▮

LIGHTNING ROUND

Texting or talking?
Texting

Favorite city in U.S. besides the one you live in?
Washington, D.C.

Favorite breakfast?
Avocado toast

Place you most want to travel to?
South America

Favorite junk food?
Candy

Favorite season?
Winter

Number of cups of coffee you drink per day?
2 or 3

Dream profession if you weren't a gastroenterologist?
Ski coach

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