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GI&Hepatology News

December 2023

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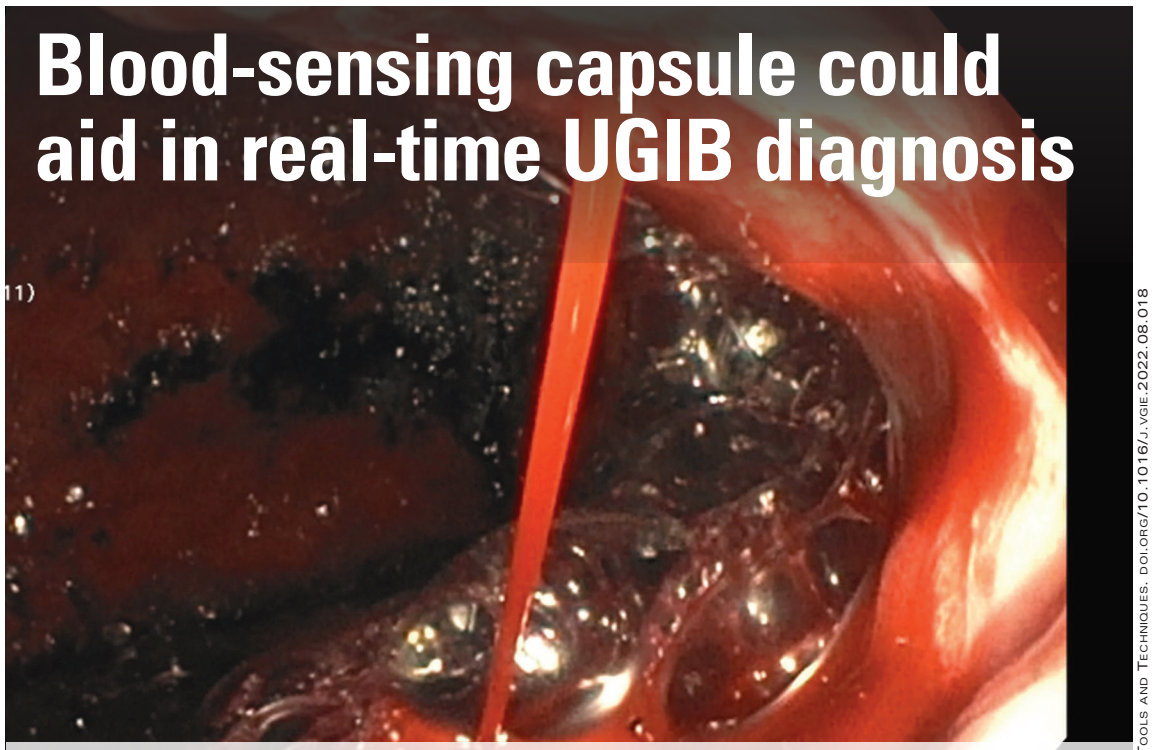
Blood-sensing capsule could aid in real-time UGIB diagnosis



Mahmoud T et al. Tools and Techniques. doi.org/10.1016/j.vgie.2022.08.018

In VideoGIE (doi:10.1016/j.vgie.2022.08.018), Mahmoud et al. posted a video and images of a disposable oral optical sensor capsule that detects gastrointestinal bleeding. This image shows an active spurting varix at the gastroesophageal junction as seen on esophagogastroduodenoscopy.

BY BECKY MCCALL

AT UEG WEEK 2023

COPENHAGEN – A real-time, blood-sensing capsule that detects upper gastrointestinal bleeding (UGIB) is safe and effective for patients before undergoing upper endoscopy, according to results from the first U.S.-based open-label, single-arm comparative clinical trial of a novel bleeding sensor for patients with suspected UGIB.

The capsule (PillSense, EnteraSense) is rapidly deployed, safe to use, and easy to interpret, study researchers say. In under 7 minutes, it correctly detected the presence of blood in 26 of 28 patients and its absence in 87 of 96 patients, as confirmed afterward by esophagogastroduodenoscopy (EGD).

"The use of the PillSense system will positively impact patient outcomes by providing early diagnosis, triaging, and directing care for UGIB," said Karl Akiki, MD, study lead, who is in the division of gastroenterology and hepatology at the Mayo Clinic, Rochester, Minn. He presented the results at the annual United European Gastroenterology Week.

"Due to its ability to rapidly diagnose UGIB, it helps us, as doctors, expedite accurate clinical decision-making while also optimizing

See **Capsule** · *page 7*

Risankizumab ups endoscopic remission in CD

BY BECKY MCCALL

AT UEG WEEK 2023

COPENHAGEN – Risankizumab shows noninferiority for clinical remission at week 24, and superiority of endoscopic remission at week 48 when compared with ustekinumab in patients with moderately to severely active Crohn's disease (CD) who failed one or more anti–tumor necrosis factor (anti-TNF) therapies, show results from the phase 3 SEQUENCE trial.

Secondary endpoints – presented for the first time at the United European Gastroenterology Week 2023 – showed superiority of risankizumab (Skyrizi, AbbVie), an interleulin-23 inhibitor, over ustekinumab (Stelara), an IL-12 and IL-23 inhibitor, for clinical remission at week 48 (60.8% vs. 40.8%) and a statistically significant endoscopic response favoring risankizumab at weeks 24 and 48.

"With endoscopic remission we see that with a single agent we have doubled the endoscopic remission rate by moving from 16% to 31% with risankizumab [at week 48]," said Laurent Peyrin-Biroulet, MD, PhD, a gastroenterologist specializing in inflammatory bowel disease at Nancy University Hospital, France. "This sort of thing happens once in your career," noted Dr. Peyrin-Biroulet, who presented the results of the study at the meeting. "It's totally amazing that everything you see here was in favor of risankizumab. Already we see the efficacy signal in the proportion of premature discontinuations at 2% vs. 13% due to lack of efficacy [in risankizumab and ustekinumab, respectively]," he said. "This is due to drug failure."

Risankizumab is an IL-23 inhibitor that selectively blocks the cytokine IL-23, thought to be linked to a

See **Crohn's disease** · *page 7*

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LETTER FROM THE EDITOR

Making an impact beyond medicine

When we launched GIHN's monthly Member Spotlight column in January of this year, our vision was to provide a platform to recognize AGA members' unique accomplishments across all career stages and practice settings, highlight the diversity of our membership, and build a sense of community by learning more about one another.


Dr. Adams

As physicians, we are fortunate to have the opportunity to meaningfully impact the lives of our patients through the practice of clinical medicine, or by spearheading groundbreaking research that improves patient outcomes. However, some physicians arguably make their greatest mark outside of medicine.

To close out the inaugural year of our Member Spotlight feature, we introduce you to gastroenterologist Eric Esrailian, MD, MPH, chair of the division of gastroenterology at UCLA who is an Emmy-nominated film producer and distinguished human rights advocate. His story is inspirational, and poignantly highlights how one's impact as a physician can extend far beyond the walls of the hospital. We hope to continue to feature exceptional individuals like Dr. Esrailian who leverage their unique talents for societal good, and we appreciate your continued nominations as we plan our 2024 coverage.

Also, in the December issue, we summarize the results of a pivotal, head-to-head trial of risankizumab (Skyrizi) and ustekinumab (Stelara) for Crohn's disease, which were presented in October at United European Gastroenterology (UEG) Week in Copenhagen.

We also highlight the FDA's recent approval of vonoprazan, a new pharmacologic treatment for erosive esophagitis expected to be available in the United States sometime this month. Finally, Dr. Lauren Feld explains how gastroenterologists can advocate for more robust parental leave and return to work policies at their institutions and why it matters.

We wish you all a wonderful holiday season and look forward to seeing you again in the New Year. ■

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

New treatment OK'd for erosive GERD

BY MEGAN BROOKS

In November, the Food and Drug Administration approved vonoprazan (Voquenza, Phathom Pharmaceuticals) 10-mg and 20-mg tablets for all grades of erosive esophagitis, also known as erosive gastroesophageal reflux disease (GERD), as well as relief of associated heartburn, the company announced. Vonoprazan, an oral potassium-competitive acid blocker (PCAB), provides more potent inhibition of gastric acid than do proton pump inhibitors (PPIs) and is seen as a potential alternative.

The approval of vonoprazan for erosive GERD was based on results from the phase 3 PHALCON-EE study.

The randomized, double-blind, multicenter study enrolled 1,024 patients with erosive GERD in the United States and Europe and compared vonoprazan with the PPI lansoprazole (Prevacid, Takeda) in the healing and maintenance of erosive GERD and associated heartburn.

Vonoprazan 20 mg was noninferior to lansoprazole 30 mg for complete healing by week 8 in patients with all grades of erosive GERD, with healing rates of 93% vs. 85% for lansoprazole.

In addition, vonoprazan showed superior rates of healing in patients with moderate to severe disease (LA Grade C/D) at week 2 (70% vs. 53% with lansoprazole). Vonoprazan was noninferior to lansoprazole in terms of heartburn-free days over the healing period.

In the maintenance phase of the trial, vonoprazan 10 mg was superior to lansoprazole 15 mg in maintaining healing at 6 months in all patients who were randomly assigned (79% vs. 72%) and in the subset of patients with moderate to severe erosive GERD (75% vs. 61%).

Adverse event (AE) rates for vonoprazan were comparable to lansoprazole. The most common AEs in the healing phase

Continued on following page

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GI & Hepatology News is the official newspaper of the American Gastroenterological Association (AGA) Institute and provides the gastroenterologist with timely and relevant news and commentary about clinical developments and about the impact of health care policy. Content for **GI & Hepatology News** is developed through a partnership of the newspaper's medical board of editors (Editor in Chief and Associate Editors), Frontline Medical Communications Inc. and the AGA Institute Staff. "News from the AGA" is provided exclusively by the AGA, AGA Institute, and AGA Research Foundation. All content is reviewed by the medical board of editors for accuracy, timeliness, and pertinence. To add clarity and context to important developments in the field, select content is reviewed by and commented on by external experts selected by the board of editors.

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Editorial Director Kathy Scarbeck, MA
Editor Amy Reyes
Creative Director Louise A. Koenig
Director, Production/Manufacturing Rebecca Slebodnik
Director, Business Development Cheryl Wall
978-356-0032 cwall@mdedge.com

E-mail ginews@gastro.org

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New CPT codes for telemedicine in 2025

BY THE COVERAGE AND REIMBURSEMENT SUBCOMMITTEE OF THE AGA GOVERNMENT AFFAIRS COMMITTEE

In a significant move that will fundamentally change the way clinicians bill for telemedicine services, the American Medical Association has unveiled 17 new Evaluation and Management (E/M) Current Procedural Terminology (CPT) codes specifically for telemedicine visits, scheduled for release in CPT 2025. The AMA says the new codes are designed to bring the coding system up to date with the changing landscape of health care and reflect the realities of modern medical practice.

The 17 new CPT codes will encompass a variety of telemedicine services. While the official language of the codes has not been released yet, codes for telemedicine visits using a real-time audio-visual platform could be organized similarly to existing office/outpatient E/M visits (99202-99205, 99212-99215). As part of these revisions, the current telephone E/M codes (99441-99443) will be deleted and replaced with new codes for audio-only E/M.

Implementation of so many codes will require health care providers and systems to adapt their documentation and coding practices. Typically, the exact language and code numbers for new and revised codes are not released to the public until fall of the preceding year, leaving only a few months for practices to educate their physicians and coding staff and prepare their internal systems for implementation starting Jan. 1, 2025. However, given the significant education and systems changes that will be necessary to prepare for so many new codes, we will advocate that the AMA release this information in early 2024.

Luis Alvarez/DigitalVision/Getty Images

Additionally, the reimbursement for telemedicine services may not ultimately be the same as for in-person E/M office visits. The AMA/Specialty Society RVS Update Committee (RUC) provides recommendations to the Centers for Medicare & Medicaid Services (CMS) for consideration in developing Relative Value Units (RVUs) for new procedures, including the telemedicine codes. The RUC's recommendations for the telemedicine codes are not yet publicly available. However, it is important to note that, regardless of the RUC recommendations, CMS makes all final decisions about Medicare payment. CMS could decide to set the payments for the telemedicine codes at parity with in-person office E/M visits or less than, more than, or some combination at the individual code level.

If payments for telemedicine visits are set at parity with or higher than office E/M visits, practices can focus primarily on physician and staff education and system implementation of the new codes. However, if telemedicine visit payments are less than in-person E/M office visits, it would have significant implications for practices, providers, and patients. Providers might be discouraged from offering virtual care, leading to a disparity in the availability of telehealth services, with patients in some areas or with certain conditions having limited access. Additionally, not all patients have access to a smartphone or stable internet. Research has shown increased use of audio-only visits among marginalized groups including African Americans, non–English speakers, older patients, those with public insurance as opposed to private insurance, and patients living in rural communities and communities with low broadband access. For these patients, audio-only is a lifeline that allows them to access needed care.[1,2] If payment for audio-only is significantly less than in-person office E/M payments, practices may not offer this option furthering health care inequities.

Beyond the extensive preparation needed and the financial implications, there could be impacts to coverage policies. Currently, telemedicine coverage is triggered by reporting the appropriate office E/M level visit with telemedicine modifier 95. If the new telemedicine codes are no longer tied to the in-person codes, laws requiring payers to provide coverage and parity may need to be adjusted accordingly or they could become less effective. If coverage parity is not maintained, that may lead to changes in practice that could also worsen access and health disparities. Some insurers have already started rolling back coverage. Recently, Aetna decided to stop covering telemedicine visits as of Dec. 1, 2023.[3] Other insurers may follow suit.

Dr. Gunaratnam

"I think payment parity between in person and telemedicine visits is extremely important. If telemedicine is reimbursed at lower rates, then many of the advantages of telemedicine will be lost. This will affect the marginalized population the most and we will see fewer innovations in their care."

— Naresh T. Gunaratnam, MD, AGAF, Huron Gastroenterology Associates, Ypsilanti, Mich. Dr. Gunaratnam serves as an AGA Practice Councillor.

As practices prepare for 2024, tracking insurance coverage policies for telemedicine, staying alert for information from the AMA about the new telemedicine CPT codes, and monitoring the proposed payments for telemedicine that CMS will release in late June to early July in the 2025 Medicare Physician Fee Schedule proposed rule will be important. Participation in advocacy efforts will be critical once the full details are released by the AMA and CMS about the new telemedicine codes and their proposed values. The AGA is monitoring this issue and will continue to fight to reduce burden to physicians and practices, which includes fighting for payment parity with in-person office E/M visits and maintaining coverage benefits for patients.

The authors have reported no conflicts of interest. ■

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2. Chen J et al. J Gen Intern Med. 2022 Apr;37(5):1138-1144.

3. Aetna. Liberalized COVID-19 telemedicine services no longer covered effective 12/01/2023. https://shorturl.at/G1346

Continued from previous page

(≥ 2% with vonoprazan) were gastritis, diarrhea, abdominal distention, abdominal pain, and nausea.

The most common AEs in the maintenance phase (≥ 3% with vonoprazan) were gastritis, abdominal pain, dyspepsia, hypertension, and urinary tract infection.

"For many GERD patients with erosive esophagitis, the response to current treatment is suboptimal, leaving them with incomplete healing and ongoing symptoms," Colin W. Howden, MD, professor emeritus, University of Tennessee, Memphis, said in the news release.

Vonoprazan provides clinicians with a "new first-in-class therapeutic option that demonstrated faster healing in the more difficult-to-treat GERD patients with erosive esophagitis," Dr. Howden added.

Vonoprazan is expected to be available in the United States in December.

The FDA also recently approved reformulated vonoprazan tablets for Voquezna Triple Pak (vonoprazan, amoxicillin, clarithromycin) and Voquezna Dual Pak (vonoprazan, amoxicillin) for the treatment of *Helicobacter pylori* infection in adults, Phathom Pharmaceuticals announced.

In February, the FDA put both the vonoprazan new drug application for erosive esophagitis and the postapproval supplement for *H. pylori* on hold until the company addressed concerns over the presence of nitrosamine impurities. ■

Diagnostic tool aids in triage

Capsule *from page 1*

services to ensure the maximum number of patients obtain the best outcome. There are some pre-endoscopic assessment scores, like the Rockell or the Glasgow-Blatchford score, but they have limited clinical utility in predicting and confirming bleeding in suspected patients," Dr. Akiki said. He highlighted the need for a novel rapid, accurate, and safe devcice. He said despite being the gold standard for diagnosis, EGD is challenging in terms of time, personnel, and resources. PillSense and EGD supplement each other, he said. "It's not a device to replace the EGD itself," he explained, but given the results from the capsule, it will act "as a kind of a bridge that helps us to determine which patients should undergo EGD."

PillSense is based on optical sensing technology that uses an optical signature of blood in the gut. The device differentiates blood from any other liquids that may be present. After 5-7 minutes, it gathers and transmits data wirelessly to an external, handheld receiver that processes binary data and indicates either "blood detected" or "no blood detected" in the upper GI tract.

Optical sensing technology

Researchers aimed to assess the safety and efficacy of the PillSense system for patients with suspected UGIB. They enrolled 131 patients (mean age 62 years, 60% men). The most common presenting symptoms for UGIB were melena (52%), anemia (41%), and hematemesis (15%). The intent-to-treat population included 124 patients with 110 completing the study. Patients were asked to swallow the capsule and to lay on their left side. After the capsule reading, patients underwent EGD within 4 hours. This enabled researchers to compare data between the two modalities. Follow-up visits were conducted on days 7, 14, and 21 to ensure the capsule had passed from the body. Endoscopists were blinded to the capsule result when reading the EGD.

Primary endpoints were the sensitivity and specificity of the device; secondary endpoints were positive predictive value, negative predictive value, successful passage of the capsule, and safety. Researchers determined the efficiency of the capsule in correctly detecting a UGIB. The capsule's positive and negative predictive values were 74.3% and 97.8%, respectively.

"We achieved a sensitivity of around 93% (92.9%; $P = 0.024$) with the PillSense capsule and a specificity of 91% (90.6%; $P < .001$), which were pretty good. We also detected a range from minimal bleeding – so, speckles of blood to large amounts of active bleeding covering the entire stomach," Dr. Akiki said.

There were no differences in terms of patient demographics, laboratory results, or concomitant use of medications. PillSense recording time was a mean of 6.71 minutes, the time from capsule ingestion to EGD was a mean of 55 minutes, and the time to capsule passage through the GI tract was 3.6 days. Most bleeds were found to be in the stomach (18/30; 60%), followed by the duodenum (5/30; 16.6%).

Various capsules for detecting UGIB are under development or are already available, but unlike some of the others, "[the PillSense] is not a video capsule," said Dr. Akiki. "It does not take pictures at all but is more of a photo sensor capsule that measures the absorption of wavelengths."

This explains why PillSense was so rapid – results were available in around 7 minutes and did not require an interpretation by a physician, he explained. "Trained nonphysician personnel can use it, and this is where it differs from other devices, such as video capsules that require someone highly trained to interpret the output."

PillSense has value in improving workflow, Dr. Akiki said. "If we had someone come in during the night with a suspected upper GI bleed, we could give them the capsule, determine if they need an EGD or not, and potentially postpone it to a time – say, the morning, when more resources are available – freeing up the night for emergency cases. It helps me, as a physician, to determine which patients to send to EGD immediately or which to wait."

More research is needed in the postmarketing phase. PillSense was approved by the Food and Drug Administration in February. No related adverse events or deaths have been reported.

Co-moderator, Philip Chiu, MD, a gastroenterologist from the Chinese University of Hong Kong, said, "It's an interesting study, because sometimes we can't differentiate by clinical symptoms as to whether this is a problem of continuous bleeding or something else. The capsule might help us in our decision-making in this respect and help determine whether we should scope the patients or just manage conservatively."

Mahmoud T et al. Tools and Techniques. doi.org/10.1016/j.vgie.2022.08.018

The FDA approved PillSense in February.

Dr. Akiki and Dr. Chiu have disclosed no relevant financial relationships. ■

Results lean toward risankizumab

Crohn's disease, *from page 1*

number of chronic immune-mediated diseases, by binding to its p19 subunit. It is the first IL-23 inhibitor to receive approval from the Food and Drug Administration (June 2022) for moderately to severely active CD based on data from the ADVANCE, MOTIVATE, and FORTIFY trials.

The phase 3, open-label, multicenter, randomized clinical trial evaluated risankizumab vs. ustekinumab through week 48 in patients with moderately to severely active CD. Participants were required to have a CD Activity Index (CDAI) score of 220-450 at baseline, a Simple Endoscopic Score for Crohn's Disease (SES-CD) of 6 or more for ileocolonic or colonic disease (and of 4 or more for isolated ileal disease), excluding the presence of a narrowing component, plus an average daily stool frequency of 4 or more and/or average daily abdominal pain score of 2 or more. They were also required to have previously failed 1 or more anti-TNF therapies.

Randomization was stratified by the number of anti-TNF therapies failed (at least 1 or more) and steroid use at baseline (which were tapered from week 2). Two primary endpoints comprised clinical remission at week 24 (defined as CDAI < 150, noninferiority margin within 10% of risankizumab vs. ustekinumab in 50% of participants), and also endoscopic remission (SES-CD of 4 or less, and at least a 2-point reduction vs. baseline and no subscore greater than 1 in any individual component) at week 48 demonstrating superiority of risankizumab vs. ustekinumab.

Secondary endpoints included clinical remission at week 48, endoscopic response at weeks 48 and 24, steroid-free endoscopic remission at week 48, and steroid-free clinical remission at week 48 (all tested for superiority of risankizumab vs. ustekinumab).

Intravenous risankizumab at 600 mg was given at weeks 0, 4 , and 8 followed by subcutaneous risankizumab at a 360-mg maintenance dose every 8 weeks through week 48 (n = 255). Participants who completed the week-48 visit continued on subcutaneous risankizumab for up to an additional 220 weeks. Ustekinumab was given as a weight-based, intravenous induction dose at week 0 followed by a 90-mg subcutaneous dose every 8 weeks, starting at week 8 through week 48 (n = 265). Participants received open-label drug administration but efficacy assessment was blinded.

Superiority of risankizumab

Both primary endpoints were met. For clinical remission at week 24, rates were 58.6% (75/128) for risankizumab and 39.5% (54/137) for ustekinumab, for a difference of 18.4% [95% confidence interval, 6.6-30.3], meaning that noninferiority was met within the predefined margin of 10%.

The second primary endpoint of endoscopic remission at week 48 showed rates of 31.8% (81/255) for risankizumab and 16.2% (43/265) for ustekinumab ($P < .0001$ for superiority). Risankizumab was found to be superior to ustekinumab for all secondary endpoints (all with $P < .0001$). Steroid-free endoscopic remission at week 48 showed a 16% difference, and steroid-free clinical remission at week 48 showed a 20% difference – both in favor of risankizumab.

No funding for this study was disclosed. Dr. Peyrin-Biroulet disclosed receiving fees from various companies, but not associated with this study. ■

A letter from Michael Camilleri, MD, DSc, AGAF, AGA Research Foundation chair

As a member of the AGA, you understand the physical, emotional, and financial costs of digestive diseases. And you understand the tremendous value of research to advance patient care.

We are in a time of major scientific breakthroughs; however, there is a growing gap in federal funding for research. Without gastroenterology and hepatology research, there would be no discoveries to develop new diagnostic and therapeutic approaches and to improve our understanding of the pathogenesis of digestive diseases.

The AGA Research Foundation funds promising GI investigators who don't receive funding at crucial times in their early careers. The research of these talented individuals, while important to the field, could end prematurely if they are left unfunded. That's something the fields of gastroenterology and hepatology can't afford, and that's why, as an AGA member, I'm making a year-end donation to the AGA Research Foundation.

You can help fill the funding gap and protect the next generation of investigators by joining me in supporting the AGA Research Foundation through a personal year-end gift.

Gifts to the AGA Research Foundation this past year directly supported 71 investigators. Despite this success, close to 245 other promising research proposals were not funded.

We must continue to foster the careers of talented scientists and clinicians, and protect the GI research pipeline. A financial contribution to the AGA Research Foundation is the opportunity for you to help foster the careers of talented scientists and protect the GI research pipeline.

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

Dr. Camilleri is a past AGA Institute president.

Applications for AGA Research Foundation awards are open

View complete award details, including sample applications and tips for applying, online here: https://shorturl.at/mANX3.

Don't let this opportunity pass you by. Mark the deadlines in your calendar today, and start working on your application to become a part of AGA's prestigious awardee community.

Author Q&A: GI needs better parental leave policies

In October, the Diversity, Equity, and Inclusion in GI section of Gastroenterology (doi: 10.1053/j.gastro.2023.08.014) and Clinical Gastroenterology and Hepatology featured the article, "Parental Leave and Return-to-Work Policies: A Practical Model for Implementation in Gastroenterology."

The authors note that this article can serve as a roadmap for institutions and practices to create a parental leave policy and return-to-work environment that attracts talent and supports a diverse and thriving workforce.

Despite a joint statement by the four main gastroenterology societies more than 25 years ago, few structural changes have been implemented to mandate a minimum of 12 weeks of parental leave for gastroenterologists.

We asked one of the article's authors, Lauren D. Feld, MD, a specialist in gastroenterology and transplant hepatology at UMass Memorial Medical Center, in Worcester, Mass., a few questions about the motivation behind this article and the movement at large.

Q: What motivated you and the coauthors to write this article?

A: It was a pleasure working with my coauthors – an incredible team of gender equity experts – Dr. Amy S. Oxentenko, Dr. Dawn Sears, Dr. Aline Charabaty, Dr. Loren G. Rabinowitz, and Dr. Julie K. Silver. I'm grateful to Dr. May and Dr. Quezada for the invitation to write about the important topic of creating family-friendly work environments. My coauthors and I have noticed increasing support for women in gastroenterology.

Q: Why is this issue important?

A: Nationwide, women are leaving clinical and academic medicine at alarming rates. The incompatibility of parenthood with a traditional medical career has been identified as a major driver of retention issues across specialties.

Dr. Feld

In addition to impacting retention, incompatibility with pregnancy and parenthood also impacts recruitment. Survey studies of internal medicine residents have identified concerns about family life as a major barrier to choosing gastroenterology as a specialty. Women in medicine have worked too hard to get to where they are to be excluded from or driven out of our field.

Beyond the impact on the physicians, there is a major impact on patients. Studies have identified that women patients' preference for a woman endoscopist as well as the difficulty in finding women endoscopists has created a barrier to colon cancer screening for women. Areas of research have also gone understudied because they primarily impact women patients. We must work towards equity for the benefit of both physicians and patients.

Q: What actions can practicing GI doctors take now to help support better parental leave and return to work policies?

A: Start by reviewing the article and asking human resources for your employer's policies in this area. If your employer doesn't have a parental leave policy, or if their policy is inadequate, discuss the importance of this with your leadership. Describing the cost impact of physicians leaving practice is a good way to justify the cost investment to support family-friendly policies.

The authors recommend policies outlined in the paper be consistent across genders with attention to equity for the LGBTQ+ community. The blueprint for parental leave and return to work department policies includes:

- Policies to support physicians during pregnancy, including endoscopy ergonomic accommodations.
- Components of a parental leave policy such as duration and adjusted RVUs to account for leave.
- Coverage models to consider during leave.
- How to create a family-friendly return to work, including modified overnight call during post partum and autonomy over schedule.
- Training considerations, such as competency-based assessments instead of time-based. ■

AGA provides leadership development for women in GI

As a part of AGA's ongoing goal to support women in GI and advance gender equity in gastroenterology, we hosted nearly 60 women executives in GI for the inaugural Women's Executive Leadership Conference recently held in Denver.

The two-day conference brought together leaders from different practice settings – academia, hospital systems, and private practice – for seminars on strengthening leadership skills and career progression, along with opportunities for networking and socializing with other women in the AGA Gastro Squad.

Women on the AGA governing board, including Kim E. Barrett, PhD, AGAF, and Sheryl Pfeil, MD, AGAF, led sessions on how to best communicate as a leader and pathways to society leadership. In addition, other leaders such as Aja McCutchen, MD, and Gyongyi Szabo, MD, PhD, shared their best practices for leadership and managing others.

Thank you to Fasiha Kanwal, MD, MSHS, and Aimee Lucas, MD, MS, cochairs of the AGA Women's Executive Leadership Conference, for leading the weekend, and to everyone who contributed to a productive weekend. Stay tuned for more opportunities to engage with the AGA Gastro Squad. ■

AGA

Thank you to our 60 women executives in GI for an engaging and productive weekend of leadership development.

Member SPOTLIGHT

Narrative medicine

Physician advocacy on the ground

BY JENNIFER LUBELL
MDedge News

In 2021, when Eric Esrailian, MD, MPH, was awarded the Benemerenti Medal from Pope Francis for his humanitarian work, he recognized other people worldwide who save lives daily – but without recognition. They're motivated for "the right reasons. To be clear, I do not deserve this honor. It is honestly overwhelming and humbling," he said in 2021 when news of the award reached him in Los Angeles where he holds the Lincy Foundation Chair in Clinical Gastroenterology at the University of California, Los Angeles. He also serves as chief of the Vatche and Tamar Manoukian Division of Digestive Diseases, and director of the Melvin and Bren Simon Digestive Diseases Center.

Dr. Esrailian, the son of Armenian immigrants, says that humanitarian work has been ingrained in him since childhood. His great-grandparents were Armenian genocide survivors and their struggles have never left him. He's devoted his life not only to medicine, but to documenting the history of the Armenian genocide and leading, or supporting, efforts to resolve humanitarian crises in Armenia and around the world. Earlier this year, he, with Kim Kardashian and singer/actor Cher, published op-eds that addressed a humanitarian crisis building as a result of Azerbaijan's blockade of the Lachin corridor – which is the only road that links Armenia to the ethnic Armenian–populated sections of Nagorno-Karabakh. In September, Armenia and Azerbaijan reached a tentative agreement to end the blockade, but more needs to be done, he says. Tragedies continue to unfold, and he is redoubling his efforts to bring more attention to this humanitarian crisis, he said.

Because storytelling is an important part of raising awareness, in 2016 Dr. Esrailian and partners produced two films about stories of perseverance, endurance, and the inextinguishable fire of the human spirit. The first film was "The Promise," a historical war drama set in the Ottoman Empire and released in 2016. In 2017, he and partners released "Intent to Destroy: Death, Denial, & Depiction," a documentary about the Armenian genocide. The documentary received an Emmy nomination for Outstanding Historical Documentary. And, in 2020, he produced "Francesco," a film about Pope Francis that documented his pilgrimage to Armenia in 2016.


UCLA
Dr. Esrailian

"The Promise" had such an impact on viewers that in 2017 Dr. Esrailian and the UCLA School of Law created The Promise Institute for Human Rights as a center of human rights education, research, and advocacy. In 2019, Dr. Esrailian and UCLA followed up with The Promise Armenian Institute as a place for academic research and teaching of Armenian studies, language, and culture. "The impact from building these two institutes has been transformational, and they will be part of UCLA forever," he said.

His philanthropic efforts connecting health, human rights, education, and the arts has had an impact worldwide. One person can make a difference, Dr. Esrailian said: "I've learned along the way that an individual can have more of an impact than ever imagined, but you have to dream big and never give up."

In this interview, he tells us more about his work.

Q: Not many doctors wear hats in medicine and filmmaking. Describe your journey as a filmmaker.

Dr. Esrailian: I've always been interested in storytelling. I was an English minor at Berkeley. My late mentor, Kirk Kerkorian, a legendary philanthropist, businessman, and entrepreneur, pushed me to take storytelling and do something that would potentially help secure Armenian Genocide recognition by the United States. Because of genocide denialists and geopolitical pressure, he felt the United States government was reluctant to recognize the Armenian Genocide. He thought having some visual materials for educational and outreach efforts would be transformational, and as it turns out, they were.

If you talk to any advocacy organization that tried for years to get Armenian Genocide recognition, they'd say that both films, "The Promise" (a feature film) and "Intent to Destroy" (a documentary), and the social impact media campaign we launched around them, were influential in moving the needle with legislators in the United States who, 3 years after "The Promise" was released, recognized the genocide. This was followed by the Library of Congress in 2020 and President Biden's executive branch in 2021.

Q: What has been your most rewarding accomplishment?

Dr. Esrailian: Giving a voice to people who don't have a voice is something that I'm proud of. Sometimes, it's questionable what impact it may have because we still see atrocities committed all over the world. In September, Azerbaijan completed an ethnic cleansing campaign of Armenians from a region called Artsakh, officially the Republic of Nagorno-Karabakh.

Despite having so many relationships with powerful people in government and in high-profile media, and despite our documentaries, op-eds, and interactions with influential leaders on a regular basis, it always feels like it's not enough. Obviously, the perpetrators are still able to abuse human rights and conduct these campaigns. Nevertheless, I don't think we should be deterred. Allowing human rights violations to occur with impunity only emboldens perpetrators even more. It takes a long time to bring people to justice through international courts, but it does happen – eventually. That's something I'm going to continue to work on.

Q: What should be the role of physicians in supporting human rights?

Dr. Esrailian: Physicians and health care providers play an important role in human rights. If you look back throughout history, whether it's the International Committee of the Red Cross, or Doctors Without Borders, or other organizations, physicians and health care professionals are often on the front lines, helping people. Unfortunately, physicians have also been part of human rights violations, like the Holocaust or other genocides. But I do think that in this day and age, with the reputation that physicians have, we can be policy advocates and upstanders in addition to taking care of patients. Telling our stories to the world is important so that people know what's actually happening on the ground. ■


Eric Esrailian, MD, MPH
Pope Francis with Eric Esrailian, MD, MPH.

Lightning round

Do you prefer texting or talking?
Talking

How many cups of coffee do you drink each day?
Two

What was the last movie you watched?
Mission Impossible

If you weren't a gastroenterologist, what would you be?
Entrepreneur

Who inspires you?
My family

CBD provides symptom relief in gastroparesis

BY CHRISTINE KILGORE
MDedge News

FROM CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Pharmaceutical-grade cannabidiol (CBD) relieved symptoms in patients with idiopathic and diabetic gastroparesis and increased tolerance of liquid nutrient intake after 4 weeks of treatment in a phase 2 randomized double-blinded, placebo-controlled study recently published in Clinical Gastroenterology and Hepatology (2023 Jul 22:S1542-3565[23]00543-8).

There is "significant unmet medical need in gastroparesis," and compared with cannabis, which has been used to relieve nausea and pain in patients with the condition, CBD has limited psychic effects with the added potential to reduce gut sensation and inflammation, wrote Ting Zheng, MD, and colleagues at Mayo Clinic in Rochester, Minn.

The researchers assessed the symptoms of 44 patients (21 randomized to receive CBD and 23 to receive placebo) – each of whom had nonsurgical gastroparesis with documented delayed gastric emptying of solids (GES) by scintigraphy for at least 3 months – with the American Neurogastroenterology and Motility Society's Gastroparesis Cardinal Symptom Index (GCSI) Daily Diary.

They measured GES at baseline, and at 4 weeks, they measured GES again as well as fasting and postprandial gastric volumes and satiation using a validated Ensure drink test. (Patients ingested Ensure [Abbott Laboratories] at a rate of 30 mL/min and recorded their sensations every 5 minutes.) The two treatment arms were compared via 2-way analysis of covariance that included body mass index and, when applicable, baseline measurements.

Patients in the CBD group received twice-daily oral Epidiolex (Jazz Pharmaceuticals, Dublin), which is Food and Drug Administration–approved for the treatment of seizures associated with two rare forms of epilepsy and with another rare genetic disease in patients 1 year of age and older.

The researchers documented significant improvements in the CBD group in total GCSI score (P = .0008) and in scores measuring the inability to finish a normal-sized meal (P = .029), number of vomiting episodes/24 hours (P = .006), and overall perceived severity of symptoms (P = .034).

CBD treatment was also associated with greater tolerated volume of Ensure – "without increases in scores for nausea, fullness, bloating, and pain" – and, in another component of the GCSI, there was "a borderline reduction in upper abdominal pain," Dr. Zheng and coauthors wrote.

There was a significant slowing of GES in the CBD group, however, and no significant differences were seen at 4 weeks in the fasting or accommodation gastric volumes between the two treatment groups. That beneficial effects of CBD were seen despite slowing of GES "raises the question of the contribution of the delayed GE of solids to development of symptoms in patients with gastroparesis, which is supported by some but not all meta-analyses on this topic," they noted.

Patients had a mean age of 44 and most were female. Of the 44 patients, 32 had idiopathic gastroparesis, 6 had type 1 diabetes, and 6 had type 2 diabetes. Four patients in the study did not tolerate the FDA-recommended full-dose escalation of CBD to 20 mg/kg per day, but completed the study on the highest tolerated dose.

Adverse effects (fatigue, headache, nausea) were distributed equally between the two groups, but diarrhea was more common in the CBD group. Diarrhea was the most common adverse event in a recently published analysis of 892 pediatric patients receiving Epidiolex over an estimated 1,755.7 patient-years of CBD exposure, the researchers noted.

Larger randomized controlled trials of longer-term administration of CBD in both idiopathic and diabetic gastroparesis are warranted, the investigators said.

The researchers disclosed no conflicts. The study was supported by a grant from the National Institutes of Health. ■

Report cards, additional observer improve ADRs

BY WILL PASS
MDedge News

FROM CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Endoscopy centers may be able to improve their adenoma detection rate (ADR) by employing report cards and ensuring that each procedure is attended by an additional observer, according to results of a recent systematic review meta-analysis.

Although multimodal interventions like extra training with periodic feedback showed some signs of improving ADR, withdrawal time monitoring was not significantly associated with a better detection rate, reported Anshul Arora, MD, of Western University, London, Ont., and colleagues.

"Given the increased risk of postcolonoscopy colorectal cancer associated with low ADR, improving [this performance metric] has become a major focus for quality improvement," the investigators wrote in Clinical Gastroenterology and Hepatology (2023 Apr 18. doi: 10.1016/j.cgh.2023.03.049).

They noted that "numerous strategies" have been evaluated for this purpose, which may be sorted into three groups: endoscopy unit–level interventions (i.e., system changes), procedure-targeted interventions (i.e., technique changes), and technology-based interventions.

"Of these categories, endoscopy unit–level interventions are perhaps the easiest to implement widely because they generally require fewer changes in the technical aspect of how a colonoscopy is performed," the investigators wrote. "Thus, the objective of this study was to conduct a systematic review and meta-analysis to identify endoscopy unit–level interventions aimed at improving ADRs and their effectiveness."

To this end, Dr. Arora and colleagues analyzed data from 34 randomized controlled trials and observational studies involving 1,501 endoscopists and 371,041 procedures. They evaluated the relationship between ADR and implementation of four interventions: a performance report card, a multimodal intervention (e.g., training sessions with periodic feedback), presence of an additional observer, and withdrawal time monitoring.

Provision of report cards was associated with the greatest improvement in ADR, at 28% (odds ratio, 1.28; 95% confidence interval, 1.13-1.45; *P* less than .001), followed by presence of an additional observer, which bumped ADR by 25% (OR, 1.25; 95% CI, 1.09-1.43; *P* = .002). The impact of multimodal interventions was "borderline significant," the investigators wrote, with an 18% improvement in ADR (OR, 1.18; 95% CI, 1.00-1.40; *P* = .05). In contrast, withdrawal time monitoring showed no significant benefit (OR, 1.35; 95% CI, 0.93-1.96; *P* = .11).

Dr. Arora and colleagues offered guidance on the use of report cards, which were associated with the greatest improvement in ADR.

"We found that benchmarking individual endoscopists against their peers was important for improving ADR performance because this was the common thread among all report card–based interventions," they wrote. "In terms of the method of delivery for feedback, only one study used public reporting of colonoscopy quality indicators, whereas the rest delivered report cards privately to physicians. This suggests that confidential feedback did not impede self-improvement, which is desirable to avoid stigmatization of low ADR performers."

The findings also suggest that additional observers can boost ADR without specialized training.

"[The benefit of an additional observer] may be explained by the presence of a second set of eyes to identify polyps or, more pragmatically, by the Hawthorne effect, whereby endoscopists may be more careful because they know someone else is watching the screen," the investigators wrote. "Regardless, extra training for the observer does not seem to be necessary because the 3 randomized controlled trials [evaluating this intervention] all used endoscopy nurses who did not receive any additional polyp detection training. Thus, endoscopy unit nurses should be encouraged to speak up should they see a polyp the endoscopist missed."

The investigators disclosed no conflicts of interest. ■


Dr. Shaukat

The effectiveness of colonoscopy to prevent colorectal cancer depends on the quality of the exam. Adenoma detection rate (ADR) is a validated quality indicator, associated with lower risk of postcolonoscopy colorectal cancer. There are multiple interventions that can improve endoscopists' ADR, but it is unclear which ones are higher yield than others. This study summarizes the existing studies on various interventions and finds the largest increase in ADR with the use of physician report cards. This is not surprising, as report cards both provide measurement and are an intervention for improvement.

Interestingly, the included studies mostly used individual confidential report cards, and demonstrated an improvement in ADR. Having a second set of eyes looking at the monitor was also associated with increase in ADR. Whether it's the observer picking up missed polyps, or the endoscopist doing a more thorough exam because someone else is watching the screen, is unclear. This is the same principle that current computer assisted detection (CADe) devices help with. While having a second observer may not be practical or cost effective, and CADe is expensive, the takeaway is that there are multiple ways to improve ADR, and at the very least every physician should be receiving report cards or feedback on their quality indicators and working toward achieving and exceeding the minimum benchmarks.

Aasma Shaukat, MD, MPH, is the Robert M. and Mary H. Glickman professor of medicine, New York University Grossman School of Medicine where she also holds a professorship in population health. She serves as director of outcomes research in the division of gastroenterology and hepatology, and codirector of Translational Research Education and Careers (TREC). She disclosed serving as an adviser for Motus-GI and Iterative Health.

Liver-resident T cells protect against early *Listeria* infection

BY WILL PASS
MDedge News

FROM CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

Liver-resident gamma delta T cells that produce interleukin(IL)-17 coordinate with hepatic macrophages to offer early protection against *Listeria monocytogenes* infection, according to investigators.

These finding suggest that gamma delta T17 cells could be a target for novel cell-based therapies against liver diseases, reported lead author Yanan Wang, PhD, of Shandong University, Jinan, China, and colleagues.

"Gamma delta T cells are located in mucosal tissues and other peripheral lymphoid tissues and are considered to act as the first line of defense within the immune system," the investigators wrote in Cellular and Molecular Gastroenterology and Hepatology (2023 Aug 21. doi: 10.1016/j.jcmgh.2023.08.008). "Several studies have reported that IL-17A produced by gamma delta T cells plays a critical role in host defense after *Listeria monocytogenes* [infection] in the liver. However, in those studies, the details of the phenotypes, dynamic changes, proliferation activity, and cytokine production of the responding gamma delta T cell populations in the overall process of hepatic infection are unclear, and how they accumulated into the infection sites has not been elucidated."

To address this knowledge gap, Dr. Wang and colleagues conducted a series of experiments involving gamma delta T cells from murine liver samples.

First, using single-cell RNA sequencing (scRNA-seq), the investigators identified six

Continued on following page

Short course of opioids could risk IBD patient health

BY WILL PASS
MDedge News

FROM GASTRO HEP ADVANCES

Short- or long-term use of opioids may increase risk of poor outcomes in patients with inflammatory bowel disease (IBD), according to investigators.

These findings amplify the safety signal from previous inpatient studies by showing that even a short course of opioids in an outpatient setting may increase risks of corticosteroid use and emergency department utilization, prompting caution among prescribers, reported Laura Telfer, MS, of Penn State College of Medicine, Hershey, Pa., and colleagues.

"Opioids are frequently prescribed to treat pain associated with IBD," the investigators wrote in Gastro Hep Advances (2023 Sept 1. doi: 10.1016/j.gastha.2023.08.009). "Unfortunately, they are associated with many problems in IBD, including increased risk of emergency room visits, hospitalization, surgery, and mortality. Chronic opioid use may also exacerbate symptoms and induce IBD flares, prompting discontinuation, thus increasing the risk of opioid withdrawal syndrome. Ironically, there is no published evidence that opioids even help to improve abdominal pain in IBD, particularly in the long term. Notably, most studies investigating opioid use in IBD have been limited to hospitalized patients, and few have directly evaluated the impact of opioid prescription length."

To address this knowledge gap, Ms. Telfer and colleagues conducted a retrospective, population-based cohort study involving patients with IBD who were classified as either long-term opioid users, short-term opioid users, or nonusers. Drawing data from more than 80,000 patients in the TriNetX Diamond Network, the investigators evaluated relative, intergroup risks for corticosteroid use, emergency department utilization, mortality, and IBD-related surgery.

Comparing short-term opioid users and nonusers revealed that short-term use more than doubled the risk of corticosteroid prescription (relative risk, 2.517; *P* less than .001), and increased the risk of an emergency department visit by approximately 32% (RR, 1.315; *P* less than .001). Long-term use was associated with a similar doubling in risk of corticosteroid prescription (RR, 2.383; *P* less than .001), and an even greater risk of emergency department utilization (RR, 2.083; *P* less than .001). Risks of death or IBD-related surgery did not differ for either of these comparisons.

Next, the investigators compared long-term opioid use versus short-term opioid use. This suggested a duration-related effect, as long-term users were 57% more likely than were short-term users to utilize emergency department services (RR, 1.572; *P* less than .001). No significant differences for the other outcomes were detected in this comparison.

"Unlike previous studies, we did not find an association between opioid use and IBD-related surgery or death," the investigators wrote. "Notably, these [previously reported] associations utilized opioid dosage (e.g., morphine equivalent or number of prescriptions), rather than length of opioid prescription (as we did). We also focused on IBD outpatients, while prior studies evaluated (in part or completely) inpatient populations, who typically present with more severe illness."

Still, they added, the present findings should serve as a warning to prescribers considering even a short course of opioids for patients with IBD.

"This study demonstrates that prescribing opioids to IBD outpatients carries significant, specific risks, regardless of prescription length," Ms. Telfer and colleagues wrote. "Health care professionals should exercise caution before prescribing these agents."

The study was supported by the Peter and Marshia Carlino Early Career Professorship in Inflammatory Bowel Disease, the Margot E. Walrath Career Development Professorship in Gastroenterology, and the National Institutes of Health. The investigators disclosed no conflicts of interest. ■

Given that objective control of inflammation does not always correlate with improvement in abdominal pain scores, the use of opioids in patients with inflammatory bowel diseases (IBD) remains a difficult area of clinical practice and research. In this study, Telfer and colleagues performed a retrospective analysis using the TriNetX Diamond Network to assess the impact of opioid use on health-associated outcomes and evaluate for a differential impact on outcomes depending on the length of opioid prescription. When compared to non–opioid users, both short- and long-term opioid users were more likely to utilize corticosteroids and emergency department services. However, in contrast to prior studies, there was no increased risk for mortality demonstrated among those patients with short- or long-term opioid use.


Dr. Barnes

In addition to demonstrating the potential risks associated with both short- and long-term opioid use among patients with IBD, this study also reemphasizes the need for appropriately addressing the drivers of pain in IBD and appropriate methods of treating this underlying pain. Despite the use of a well-constructed data source, given the retrospective nature of this manuscript it is difficult to untangle the cause vs. association of opioid use and increased corticosteroid use. However, the recognition there is an underlying driver of pain in patients with IBD that must be addressed should prompt continued analysis of the best method of pain control, the reasons for chronic opioid use in this population, and early treatment approaches to avoid opioid use and the related adverse IBD-related outcomes demonstrated in this study.

Edward L. Barnes, MD, MPH, is assistant professor of medicine at the University of North Carolina at Chapel Hill. He disclosed having served as a consultant for Target RWE (not relevant to this commentary).

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clusters of hepatic gamma delta T cells.

"[This first step] revealed the unique gene expression characteristics and indicated the possible important roles in immune responses of hepatic gamma delta T17 cells," they noted.

Next, the investigators measured expression of CD44 and CD27 in liver gamma delta cells.

Expression of CD44 and CD27 has been used to distinguish IL-17A–, interferon gamma–producing, and other subsets of gamma delta T cells in the thymus, lymph nodes, lungs, and other peripheral lymphoid tissues. These efforts revealed three subsets of hepatic gamma delta T cells, of which CD44hiCD27– gamma delta T cells were most abundant. Further analysis revealed expression profiles consistent with liver residency.

The next phases of the study characterized the immune roles of hepatic gamma delta T cells. A comparison of *L. monocytogenes* infection in wild-type versus T-cell antigen receptor knockout mice, for example, showed that knockout mice had significantly more weight loss than did wild-type mice, greater bacterial load in the liver, and shorter survival times.

"As expected, the proportion and absolute numbers of gamma delta T cells in the liver of wild-type mice increased at day 3 and reached a peak at day 7 after infection," the investigators wrote. "These data suggested that hepatic gamma delta T cells proliferated after infection and contributed to Lm clearance."

Parabiosis experiments showed that the increased number of CD44hiCD27–gamma delta T cells in the livers of *L. monocytogenes*–infected mice were due to migration and proliferation of liver-resident gamma delta T cells instead of circulating gamma delta T cells. A transwell assay revealed that Kupffer cells and monocyte-derived macrophages promoted migration of CD44hiCD27– gamma delta T cells upon infection.

"Our study provides additional insight into liver-resident lymphocytes and will aid in targeting such tissue-resident lymphocyte populations to promote local immune surveillance," the investigators concluded.

Investigators have no conflicts of interest. ■

A 4-year window for pancreatic cancer screening

BY WILL PASS
MDedge News

FROM GASTROENTEROLOGY

It takes an average of 4 years for a pancreatic lesion to progress from high-grade dysplasia (HGD) to cancer, suggesting a window of opportunity for screening, based on a microsimulation model.

To seize this opportunity, however, a greater understanding of natural disease course is needed, along with more sensitive screening tools, reported Brechtje D.M. Koopmann, MD, of Erasmus Medical Center, Rotterdam, the Netherlands, and colleagues.

Previous studies have suggested that the window of opportunity for pancreatic cancer screening may span decades, with estimates ranging from 12 to 50 years, the investigators wrote. Their report was published in Gastroenterology (2023 Aug 23. doi: 10.1053/j.gastro.2023.08.027).

"Unfortunately, the poor results of pancreatic cancer screening do not align with this assumption, leaving unanswered whether this large window of opportunity truly exists," they noted. "Microsimulation modeling, combined with available, if limited data, can provide new information on the natural disease course."

For the present study, the investigators used the Microsimulation Screening Analysis (MISCAN) model, which has guided development of screening programs around the world for cervical, breast, and colorectal cancer. The model incorporates natural disease course, screening, and demographic data, then uses observable inputs such as precursor lesion prevalence and cancer incidence to estimate unobservable outcomes like stage durations and precursor lesion onset.

Dr. Koopmann and colleagues programmed this model with Dutch pancreatic cancer incidence data and findings from Japanese autopsy cases without pancreatic cancer.

First, the model offered insights into precursor lesion prevalence.

The estimated prevalence of any cystic lesion in the pancreas was 6.1% for individuals 50 years of age and 29.6% for those 80 years of age. Solid precursor lesions (PanINs) were estimated to be mainly multifocal (three or more lesions) in individuals older than 80 years. By this age, almost 12% had at least two PanINs. For those lesions that eventually became cancerous, the mean time since cyst onset was estimated to be 8.8 years, and mean time since PanIN onset was 9.0 years.

However, less than 10% of cystic and PanIN lesions progress to become cancers. PanIN lesions are not visible on imaging, and therefore current screening focuses on finding cystic precursor lesions, although these represent only about 10% of pancreatic cancers.

"Given the low pancreatic cancer progression risk of cysts, evaluation of the efficiency of current surveillance guidelines is necessary," the investigators noted.

Screening should instead focus on identifying high-grade dysplastic lesions, they suggested. While these lesions may have a very low estimated prevalence, at just 0.3% among individuals 90 years of age, they present the greatest risk of pancreatic cancer.

For precursor cysts exhibiting HGD that progressed to pancreatic cancer, the mean interval between dysplasia and cancer was just 4 years. Among 13.7% of individuals, the interval was less than 1 year, suggesting an even shorter window of opportunity for screening.

Beyond this brief timeframe, low test sensitivity explains why screening efforts to date have fallen short, the investigators wrote.

Better tests are "urgently needed," they added, while acknowledging the challenges inherent to this endeavor. Previous research has shown that precursor lesions in the pancreas are often less than 5 mm in diameter, making them extremely challenging to detect. An effective tool would need to identify solid precursor lesions (PanINs) and also need to simultaneously determine grade of dysplasia.

"Biomarkers could be the future in this matter," the investigators suggested.

Dr. Koopmann and colleagues concluded by noting that more research is needed to characterize the pathophysiology of pancreatic cancer. On their part, "the current model will be validated, adjusted, and improved whenever new data from autopsy or prospective surveillance studies become available."

The study was funded in part by Maag Lever Darm Stichting. The investigators disclosed no conflicts of interest. ■

We continue to search for a way to effectively screen for and prevent pancreatic cancer. Most pancreatic cancers come from pancreatic intraepithelial neoplasms (PanINs), which are essentially invisible on imaging. Pancreatic cysts are relatively common, and only a small number will progress to cancer. Screening via MRI or EUS can look for high-risk features of visible cysts or find early-stage cancers, but whom to screen, how often, and what to do with the results remain unclear. Many of the steps from development of the initial cyst or PanIN to the transformation to cancer cannot be observed, and as such this is a perfect application for disease modeling that allows us to fill in the gaps of what can be observed and estimate what we cannot see. In this study, the Dutch Pancreatic Cancer Group has developed a model of the behavior of pancreatic precursor lesions (cysts and PanINs) that helps us understand the timeline of cancer development. This model substantiates that, although cysts and PanINs are common and increase with age, most (about 90%) will not transform into cancer. It also shows that high-grade dysplasia exists on average for 4 years before transformation, which could be a window of opportunity for screening and intervention. The challenge is how to detect these lesions. This model illustrates that biology is giving us a window of opportunity, but that we need to find the biomarkers to take advantage of that window.


Dr. Peters

Mary Linton B. Peters, MD, MS, is a medical oncologist specializing in hepatic and pancreatobiliary cancers at Beth Israel Deaconess Medical Center, Boston, an assistant professor at Harvard Medical School, and a senior scientist at the Institute for Technology Assessment of Massachusetts General Hospital. She reports unrelated institutional research funding from NuCana and Helsinn.

Many preoperative EAC biopsies fail to predict true tumor grade

BY WILL PASS
MDedge News

FROM TECHNIQUES AND INNOVATIONS IN GASTROINTESTINAL ENDOSCOPY

Preoperative biopsy results in patients with esophageal adenocarcinoma (EAC) often misrepresent true tumor grade, according to a recent retrospective study.

Inaccurate preoperative biopsy findings could mean that patients who are candidates for endoscopic resection (ER) are unnecessarily undergoing esophagectomy, a procedure with greater risks of morbidity and mortality, reported Ravi S. Shah, MD, of Cleveland Clinic, and colleagues.

"It is unclear how accurate tumor differentiation on endoscopic biopsies is and if it can be used for clinical decision-making," the investigators wrote in Techniques and Innovations in Gastrointestinal Endoscopy (2023 Jun 24. doi: 10.1016/j.tige.2023.06.001). "Given that tumors may be considerably heterogeneous in gland formation, the limited amount of tissue obtained from endoscopic forceps biopsies may not be representative of the entire tumor for pathologic grading, which may result in discrepant tumor grading between biopsy and resection specimens."

While previous studies have compared esophagogastroduodenoscopy-guided biopsy results with histological findings after surgical resection, scant evidence is available to compare biopsy findings with both surgically and

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New AGA CPU for AI in colon polyp diagnosis

BY WILL PASS
MDedge News

FROM GASTROENTEROLOGY

The American Gastroenterological Association has published a Clinical Practice Update (CPU) on artificial intelligence (AI) for diagnosing and managing colorectal polyps.

The CPU, authored by Jason Samarasena, MD, of UCI Health, Orange, Calif., and colleagues, draws on recent studies and clinical experience to discuss ways that AI is already reshaping colonoscopy, and what opportunities may lie ahead.

"As with any emerging technology, there are important questions and challenges that need to be addressed to ensure that AI tools are introduced safely and effectively into clinical endoscopic practice," the authors wrote in Gastroenterology (2023 Oct 17. doi: 10.1053/j.gastro.2023.07.010).

With advances in processing speed and deep-learning technology, AI "computer vision" can now analyze live video of a colonoscopy in progress, enabling computer-aided detection (CADe) and computer-aided diagnosis (CADx), which the panelists described as the two most important developments in the area.


Dr. Samarasena

CADe

"In the last several years, numerous prospective, multicenter studies have found that real-time use of AI CADe tools during colonoscopy leads to improvements in adenoma detection and other related performance metrics," Dr. Samarasena and colleagues wrote.

CADe has yielded mixed success in real-world practice, however, with some studies reporting worse detection metrics after implementing the new technology. Dr. Samarasena and colleagues offered a variety of possible explanations for these findings, including a "ceiling effect" among highly adept endoscopists, reduced operator vigilance caused by false confidence in the technology, and potential confounding inherent to unblinded trials.

CADe may also increase health care costs and burden, they suggested, as the technology tends to catch small benign polyps, prompting unnecessary resections and shortened colonoscopy surveillance intervals.

CADx

The above, unintended consequences of CADe may be counteracted by CADx, which uses computer vision to predict which lesions have benign histology, enabling "resect-and-discard" or "diagnose-and-leave" strategies.

Such approaches could significantly reduce rates of polypectomy and/or histopathology, saving an estimated $33 million–$150 million per year, according to the update.

Results of real-time CADx clinical trials have been "encouraging," Dr. Samarasena and colleagues wrote, noting that emerging technology–compatible white-light endoscopy can achieve a negative predictive value of almost 98% for lesions less than 5 mm in diameter, potentially reducing polypectomy rate by almost half.

"Increasing endoscopist confidence in optical diagnosis may be an important step toward broader implementation of leave in situ and resect-and-discard strategies, but successful implementation will also require CADx tools that seamlessly integrate the endoscopic work flow, without the need for image enhancement or magnification," the panelists wrote.

Reimbursement models may also need to be reworked, they suggested, as many GI practices depend on

AI CPU *Continued on following page*

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endoscopically resected tissue.

"Many patients with poorly differentiated EAC on preresection biopsy do not undergo ER, with the belief that the final resection pathology would be noncurative," the investigators noted.

Dr. Shah and colleagues conducted a retrospective study of 346 EAC lesions. Samples were drawn from 121 ERs and 225 esophagectomies performed at two tertiary referral centers. Preoperative and postoperative findings were compared for accuracy and for level of agreement via Gwet's AC2 interrater analysis. For all evaluable lesions, preoperative biopsy had an accuracy of 68%, with a "substantial" agreement coefficient. Accuracy in the esophagectomy group was similar, at 72%, again with "substantial" agreement (Gwet's AC2, 0.74; *P* less than .001). For the ER group, however, accuracy was just 56%, with a "moderate" level of agreement (Gwet's AC2, 0.60; *P* less than .001).

"We speculate that the discrepancy of tumor differentiation on endoscopic forceps biopsies and resection specimens is due to nonrepresentative sampling of tumors to accurately determine the percentage of gland formation and thus tumor grade," the investigators noted.

Upon final histology, 22.7% of moderately differentiated tumors were upgraded to poorly differentiated; 19.6% of poorly differentiated tumors were downgraded to moderately differentiated; and, 40% of T1a tumors were changed from poorly to moderately differentiated between pre- and postprocedural histology.

The investigators disclosed relationships with Medtronic, Lucid Diagnostics, and others. ■

AGA CPU focuses on exocrine pancreatic insufficiency

BY WILL PASS
MDedge News

FROM GASTROENTEROLOGY

The American Gastroenterological Association has published a Clinical Practice Update for managing exocrine pancreatic insufficiency (EPI). The update, which was led by Anna M. Buchner, MD, PhD, University of Pennsylvania, Philadelphia, includes 15 best practice advice statements based on available literature and expert opinion.

"EPI is frequently underdiagnosed and, as a result, patients are often not treated appropriately," the authors wrote in Gastroenterology (2023 Sept 20. doi: 10.1053/j.gastro.2023.07.007). "There is an urgent need to increase awareness of and treatment for this condition."

The authors offered guidance spanning the patient journey, with Best Practice Advice statements broadly grouped into four categories: clinical features and risk factors, diagnostic strategies, treatment approaches, and disease monitoring.

Clinical features and risk factors

The CPU begins by listing the key clinical features of EPI, including bloating, excessive flatulence, fat-soluble vitamin deficiencies, protein-calorie malnutrition, steatorrhea with or without diarrhea, and weight loss. They went on to suggest that EPI should also be considered in patients with high-risk clinical conditions, including previous pancreatic surgery, chronic pancreatitis, cystic fibrosis, pancreatic ductal adenocarcinoma, and relapsing acute pancreatitis. Similarly, suspicion should be increased for individuals with moderate-risk clinical conditions, such as prior intestinal surgery, Zollinger-Ellison syndrome, longstanding diabetes mellitus, and duodenal diseases like celiac and Crohn's disease.

Diagnostic strategies

The primary diagnostic tool for EPI is the fecal elastase test, according to the update. Levels below 100 mcg/g indicate EPI, whereas levels between 100 and 200 mcg/g are considered indeterminate. The investigators noted this test can be conducted even during pancreatic enzyme replacement therapy (PERT). Other tests for EPI are rarely used, such as fecal fat testing, which must be performed on a high-fat diet, and quantitative testing, which is generally impractical for routine clinical use. The authors noted that a therapeutic trial of PERT is an unreliable method for diagnosing EPI.

"Patients with nonspecific symptoms, such as bloating, excess gas, and foul-smelling or floating stools may note some improvement in these symptoms while taking PERT, but these symptoms are nonspecific and symptomatic

EPI CPU *Continued on following page*

AI CPU *Continued from previous page*
a steady stream of revenue from pathology services.

Computer-aided quality assessment systems

Beyond optical detection and diagnosis, AI tools are also being developed to improve colonoscopy technique. Investigators are studying quality assessment systems that use AI to offer feedback on a range of endoscopist skills, including colonic-fold evaluation, level of mucosal exposure, and withdrawal time, the latter of which is visualized by a "speedometer" that "paints" the mucosa with "a graphical representation of the colon."

"In the future, these types of AI-based systems may support trainees and lower-performing endoscopists to reduce exposure errors and, more broadly, may empower physician practices and hospital systems with more nuanced and actionable data on an array of factors that contribute to colonoscopy quality," the panelists wrote.

Looking ahead

Dr. Samarasena and colleagues concluded by suggesting that the AI tools in usage and development are just the beginning of a wave of technology that will revolutionize how colonoscopies are performed.

"Eventually, we predict an AI suite of tools for colonoscopy will seem indispensable, as a powerful adjunct to support safe and efficient clinical practice. As technological innovation progresses, we can expect that the future for AI in endoscopy will be a hybrid model, where the unique capabilities of physicians and our AI tools will be seamlessly intertwined to optimize patient care."

The CPU was commissioned by the AGA Institute CPU Committee and the AGA Governing Board. The investigators disclosed relationships with Olympus, Neptune Medical, Conmed, and others. ■

EPI CPU *Continued from previous page*
changes may be a placebo effect or masking other disorders, such as celiac disease, causing delays in a correct diagnosis," they wrote. While cross-sectional imaging methods like CT scans, MRI, and endoscopic ultrasound play a significant role in detecting other pancreatic diseases, they cannot identify EPI. Breath tests and direct pancreatic function tests hold promise, but are not widely available.

Treatment strategies

Once EPI is diagnosed, treatment with PERT is indicated to prevent complications related to fat malabsorption and malnutrition. PERT formulations are all equally effective at equivalent doses, according to the update, but non–enteric-coated preparations require concurrent H2 or proton pump inhibitor therapy. PERT should be taken during meals, with an initial adult dose of at least 40,000 USP units of lipase during each meal. Half that dose may be considered for snacks, with further dosage refinements based on meal size and fat content. Dietary modifications may include supplementation with fat-soluble vitamins alongside smaller, more frequent, low- to moderate-fat meals. Very-low-fat diets should be avoided, the authors cautioned.

Surveillance

EPI treatment success can be identified by reduction in steatorrhea and associated gastrointestinal symptoms, as well as weight gain, improved muscle mass and function, and enhanced fat-soluble vitamin levels, Dr. Whitcomb and colleagues wrote, noting that a dual-energy x-ray absorptiometry scan should be performed at baseline, then repeated every 1-2 years.

The update was commissioned by AGA. Investigators disclosed relationships with AbbVie, Nestlé, and others. ■

GLP-1 receptor agonist use prior to endoscopy

BY HEIDI SPLETE

FROM CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Popular new glucagon-like peptide 1 receptor agonists require some preprocedure considerations but not necessarily discontinuation of the drugs to support the success of endoscopic procedures, according to a new Clinical Practice Update (CPU) from the American Gastroenterological Association.

Use of glucagon-like peptide 1 receptor agonists (GLP-1 RAs) has been associated with delayed gastric emptying, which raises a clinical concern about performing endoscopic procedures, especially upper endoscopies in patients using these medications, wrote Jana G. Al Hashash, MD, MSc, of the Mayo Clinic, Jacksonville, Fla., and colleagues.

The Clinical Practice Update (CPU), published in Clinical Gastroenterology and Hepatology (2023 Nov 7. doi: 10.1016/j.cgh.2023.11.002), reviews the evidence and provides expert advice for clinicians on the evolving landscape of patients taking GLP-1 receptor agonists prior to endoscopic procedures. The CPU reflects on the most recent literature and the experience of the authors, all experts in bariatric medicine and/or endoscopy.

"If patients taking GLP-1 RAs solely for weight loss can be identified beforehand, a dose of the medication could be withheld prior to endoscopy with likely little harm, though this should not be considered mandatory or evidence-based."

The American Society of Anesthesiologists (ASA) issued guidance that reflects concerns for the risk of aspiration in sedated patients because of delayed gastric motility from the use of GLP-1 RAs. The ASA advises patients on daily doses of GLP-1 RAs to refrain from taking the medications on the day of a procedure; those on weekly dosing should hold the drugs for a week prior to surgery.

However, the ASA suggestions do not differentiate based on the indication for the drug or for the type of procedure, and questions remain as to whether these changes are necessary and/or effective, the CPU authors said. The ASA's guidance is based mainly on expert opinion, as not enough published evidence on this topic exists for a robust review and formal guideline, they added.

Recently, a multisociety statement from the AGA, AASLD, ACG, ASGE, and NASPGHAN noted that widespread implementation of the ASA guidance could be associated with unintended harms to patients.

Therefore, the AGA CPU suggests an individualized approach to managing patients on GLP-1 RAs in a pre-endoscopic setting.

For patients on GLP-1 RAs for diabetes management, discontinuing prior to endoscopic may not be worth the potential risk. Also, consider not only the dose and frequency of the GLP-1 RAs but also other comorbidities, medications, and potential gastrointestinal side effects.

"If patients taking GLP-1 RAs solely for weight loss can be identified beforehand, a dose of the

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Two multitarget stool tests show promise for CRC screening: Studies

BY DAMIAN MCNAMARA, MA

AT ACG 2023

VANCOUVER – Two multitarget stool tests in development compare favorably for colorectal cancer (CRC) screening in average-risk people, suggest two new studies.

In a blinded, prospective, cross-sectional study, researchers assessed a multitarget stool RNA test (mt-sRNA; Colosense, Geneoscopy) vs. colonoscopy for detection of advanced adenomas and CRC in average-risk individuals aged 45 years and older.

In a prospective, cross-sectional study, investigators evaluated the clinical performance of a next-generation multitarget stool DNA (mt-sDNA; Cologuard) and fecal hemoglobin assay for CRC screening in adults aged 40 years and older.

Both studies were presented at the ACG: American College of Gastroenterology 2023 Annual Scientific Meeting.

> "The critical part to all of these tests is that if a patient has a positive test, they need to get a colonoscopy. That doesn't always happen. We have to make sure there's appropriate education" for patients and providers.

RNA as a biomarker

For CRC-PREVENT, which evaluated the mt-sRNA test, David Lieberman, MD, professor of medicine and former chief of the division of gastroenterology and hepatology at the Oregon Health & Science University, Portland, and colleagues recruited a diverse group of 8,289 adults undergoing colonoscopy at 1 of more than 3,800 endoscopy centers nationwide. Recruitment included outreach through social media, which could be used to improve future screening rates, Dr. Lieberman said.

The full study findings of CRC-PREVENT were also published online in the Journal of the American Medical Association (2023 Oct 23. doi: 10.1001/jama.2023.22231).

Participants provided stool samples before colonoscopy. Colosense includes a commercially available fecal immunochemical test (FIT) and tests for eight different strands of RNA. The mt-sRNA test results were compared with the colonoscopy results.

The mt-sRNA test had 100% sensitivity for early, stage I cancers, which were detected in 12 patients. Advanced adenomas were detected with an overall sensitivity of 45%. When the advanced adenomas were ≥ 2 cm, sensitivity increased to 51%.

Specificity was 87% among patients with negative findings for hyperplastic polyps or lesions.

The mt-sRNA test showed significant improvements in sensitivity for CRC (94% vs. 77%; $P = .029$) and advanced adenomas (45% vs 29%; $P < .001$), when compared with the FIT results alone.

"This is the first large study to include the 45- to 49-year-old population, for whom screening is now recommended," Dr. Lieberman told this news organization.

Results show a sensitivity of 100% for detecting CRC and 44% for advanced adenomas in this younger age group. That performance is "excellent," said Dr. Lieberman.

Results also were reliable across all ages.

"The consistent performance across all age groups for whom screening is recommended is a key finding and was totally unknown" before this study, Dr. Lieberman said.

RNA-based testing may have an advantage over DNA biomarker tests, which can be prone to age-related DNA methylation changes, he added.

Detection by DNA

Thomas Imperiale, MD, distinguished professor of medicine at Indiana University, Indianapolis, and colleagues conducted the BLUE-C trial to validate the next-generation mt-sDNA test for CRC screening.

The mt-sDNA assay tests for three novel methylated DNA markers and fecal hemoglobin.

Dr. Imperiale and colleagues studied 20,176 adults (mean age, 63 years) scheduled for screening colonoscopy at 1 of 186 U.S. sites. Participants provided a stool sample for the mt-sDNA test and comparator FIT prior to colonoscopy preparation. They compared results to colonoscopy and FIT findings.

Colonoscopy revealed 98 people with CRC, 2,144 with advanced precancerous lesions, and 17,934 with no advanced neoplasia.

Sensitivity of the mt-sDNA test for detecting CRC was 93.9% (95% confidence interval, 87.1-97.7), advanced precancerous lesions was 43.4% (95% CI, 41.3-45.6), and advanced precancerous lesions with high-grade dysplasia was 74.6% (95% CI, 65.6-82.3).

Sensitivities of the mt-sDNA test for detecting CRC and advanced precancerous lesions were significantly higher than FIT ($P < .0001$).

In terms of specificity, the mt-sDNA test had a specificity of 90.6% (95% CI, 90.1-91.0) for the absence of advanced neoplasia. Specificity for nonneoplastic findings or negative colonoscopy was 92.7% (95% CI, 92.2-93.1).

The mt-sDNA test demonstrated high specificity and high CRC and advanced precancerous lesion sensitivity. The test outperformed FIT for these factors on sensitivity but not specificity, the authors noted.

Improved specificity was a goal of developing this next-generation assay. The BLUE-C trial demonstrated a 30% improvement in specificity that "will decrease the number of unnecessary colonoscopies performed for false-positive results," said Dr. Imperiale.

Improvements associated with this next-generation test could "help further reduce the incidence of and mortality from colorectal cancer."

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medication could be withheld prior to endoscopy with likely little harm, though this should not be considered mandatory or evidence-based," the CPU authors wrote.

However, withholding a single dose of medication may not be enough for an individual's gastric motility to return to normal, the authors emphasized.

Additionally, the ASA's suggestions for holding GLP-1 RAs add complexity to periprocedural medication management, which may strain resources and delay care.

The AGA CPU offers the following guidance for patients on GLP-1 RAs prior to endoscopy:

> The current CPU endorses the multisociety statement that puts patient safety first and encourages AGA members to follow best practices when performing endoscopies on patients who are using GLP-1 RAs, in the absence of actionable data, the authors concluded.

In general, patients using GLP-1 RAs who have followed the standard perioperative procedures, usually an 8-hour solid-food fast and 2-hour liquid fast, and who do not have symptoms such as ongoing nausea, vomiting, or abdominal distension, should proceed with upper and/or lower endoscopy.

For symptomatic patients who may experience negative clinical consequences of endoscopy if delayed, consider rapid-sequence intubation, but the authors acknowledge that this option may not be possible in most ambulatory or office-based endoscopy settings.

Finally, consider placing patients on a liquid diet the day before a sedated procedure instead of stopping GLP-1 RAs; this strategy is "more consistent with the holistic approach to preprocedural management of other similar conditions," the authors said.

The current CPU endorses the multisociety statement that puts patient safety first and encourages AGA members to follow best practices when performing endoscopies on patients who are using GLP-1 RAs, in the absence of actionable data, the authors concluded.

The Clinical Practice Update received no outside funding. Lead author Dr. Al Hashash had no financial conflicts to disclose. ■

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Tests to provide more noninvasive options

Both are "important studies" that look at a large, average-risk screening population in the United States, said Aasma Shaukat, MD, MPH, who was not affiliated with the research. "Both show high sensitivity for detecting CRC and decent specificity for advanced adenomas."

While we will have to wait for the full publications, U.S. Food and Drug Administration approvals, and insurance coverage, gastroenterologists can expect to see these tests in clinical use in the near future, added Dr. Shaukat, professor of medicine and population health at NYU Langone Health, New York, and lead author of the ACG 2021 Colorectal Cancer Screening Guidelines.

"These tests provide more noninvasive options for CRC screening and are more accurate, which hopefully will translate into increased screening and a reduced burden of CRC."

These tests provide more noninvasive options for CRC screening and are more accurate, which hopefully will translate into increased screening and a reduced burden of CRC, she said.

"We are always looking for ways to increase colon cancer screening uptake," said Brooks Cash, MD, professor and chief of the division of gastroenterology, hepatology, and nutrition at the University of Texas, Houston, who also was not affiliated with the research.

Certainly, the multitarget stool DNA is not a new concept with Cologuard, but it is a new assay, Dr. Cash said.

"It's significantly different than their previous version, and they were able to show improved sensitivity as well as specificity, which has been one of the concerns," he said. The multitarget stool RNA test "shows very similar results. Their predicate is that it's slightly different and actually may return very good sensitivity for older patients, where you don't have the same methylation issues with the DNA. The critical part to all of these tests is that, if a patient has a positive test, they need to get a colonoscopy. That doesn't always happen. We have to make sure there's appropriate education for not only patients but also providers, many of whom will not be gastroenterologists," he said.

Geneoscopy funded the CRC-PREVENT trial. Exact Sciences funded the BLUE-C trial. Dr. Lieberman is an adviser or review panel member for Geneoscopy.

Dr. Imperiale receives grant or research support from Exact Sciences. Dr. Shaukat reports no relevant financial relationships. Dr. Cash is on the advisory board for Exact Sciences. ■

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