aga American Gastroenterological Association

Official newspaper of the AGA Institute

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GI&Hepatology News

February 2023

Volume 17 / Number 2

Member SPOTLIGHT

Gastroenterologist Simon C. Mathews, MD, assistant professor of medicine at Johns Hopkins Medicine in Baltimore, sees bringing greater visibility to digital health technologies and improving their quality as part of his life's work.

Setting higher standards for digital health technologies

BY JENNIFER LUBELL

MDedge News

Gastroenterologist Simon C. Mathews, MD, sees himself as a disciple of patient safety and quality improvement.

"It's influenced the way I see medicine and the work that I do around identifying quality, not in the conventional context in a hospital or a clinic, but applying that lens to the world of technology," said Dr. Mathews, assistant professor of medicine at Johns Hopkins Medicine in Baltimore.

Bringing greater visibility to digital health technologies is part of his life's work.

"There is now an expectation that high quality must be part of the development process of these new technologies," said Dr. Mathews.

In particular, he'd like to see noninvasive diagnostic technologies in the gastroenterology world become more patient-centric.

Bringing somebody into the hospital is often inconvenient and disruptive. The field is heading toward technologies that can be used in the home or in an

See **Technologies** · *page 7*

Dietary interventions can support IBD

Additional data are needed

BY CAROLYN CRIST

Some solid-food diets may aid in the treatment of inflammatory bowel disease (IBD), though the overall quality of evidence remains low and additional data are needed, according to a new report.

For Crohn's disease, a diet low in refined carbohydrates and a symptoms-guided diet appeared to help with remission, yet reduction of refined carbohydrates or red meat didn't reduce the risk of relapse. For ulcerative colitis, solid-food diets were similar to control measures.

"The Internet has a dizzying array of diet variants touted to benefit inflammation and IBD, which has led to much confusion among patients, and even clinicians, over what is truly effective or not," Berkeley Limketkai, MD, PhD, AGAF, director of clinical research at the Center for Inflammatory Bowel Disease at the University of California, Los Angeles, said in an interview.

"Even experiences shared by well-meaning individuals might not be generalizable to others," he said. "The lack of clarity on what is or is not effective motivated us to perform

See **IBD** · *page 8*

Oral FMT on par for recurrent *C. diff*

BY MEGAN BROOKS

A real-world analysis confirms that fecal microbiota transplantation (FMT) is highly effective for recurrent *Clostridioides difficile* infection (rCDI) – and there is no difference between delivery by capsule (cap-FMT) and colonoscopy (colo-FMT).

"We present one of the largest cohorts involving people who received capsule FMT. The finding that capsule FMT is as safe and effective as colonoscopy FMT has practical implications for anyone suffering with rCDI today," Byron Vaughn, MD, with the division of gastroenterology, hepatology, and nutrition, University of Minnesota, Minneapolis, said in an interview.

The study was published online in Clinical Gastroenterology and Hepatology

See **FMT** · *page 9*

INSIDE

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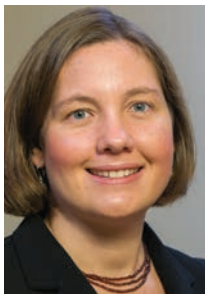
LETTER FROM THE EDITOR

Investing in GI innovation; new Member Spotlight

BY MEGAN A. ADAMS, MD, JD, MSC



Dr. Adams

In this issue, we are pleased to highlight AGA's GI Opportunity Fund, a new investment vehicle that provides AGA members and others a direct pathway to support development of promising, early-stage innovations.

Innovations in biomedical technology – from modern endoscopic devices and techniques to harnessing the microbiome to prevent and treat disease – have fundamentally changed the way in which we practice medicine and significantly improved the lives of our patients.

In our February issue, we are pleased to highlight AGA's GI Opportunity Fund, a new investment vehicle that provides AGA members and others a direct pathway to support development of promising, early-stage innovations by funding carefully vetted, cutting-edge start-up companies. We hope you will enjoy learning more about this exciting new initiative, which recently made its first major investment.

In our February Member Spotlight column, we feature Dr. Simon Mathews and his work to bring greater visibility to digital health technologies and their use in gastroenterology and beyond. I want to thank GIHN Associate Editor Dr. Janice Jou for agreeing to spearhead this new column as its section editor – again, we invite you to nominate your colleagues, mentees, and others to be featured in future Member Spotlight columns.

We also highlight several recent papers published in AGA's flagship journals, including a study assessing clinical outcomes and adverse events in patients receiving oral vs. colonic fecal microbiota transplant for recurrent *C. difficile* infection, and another evaluating the cost-effectiveness of earlier colorectal cancer screening in patients with obesity.

On the policy front, we summarize GI-relevant portions of the $1.7 trillion FY 2023 Omnibus Appropriations bill, signed into law on Dec. 30, 2022, by President Biden, and assess its impact on Medicare payments, continuation of support for telehealth/virtual care, and NIH funding.

We hope you enjoy reading these and other articles presented in our February issue.

Don't forget to register for DDW 2023, May 6-9, 2023, in Chicago – general registration is now open!

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

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GI&Hepatology News

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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The AGA Institute headquarters is located at 4930 Del Ray Avenue, Bethesda, MD 20814, ginews@gastro.org.

GI & Hepatology News (ISSN 1934-3450) is published monthly for $230.00 per year by Frontline Medical Communications Inc., 283-299 Market Street (2 Gateway Building), 4th Floor, Newark, NJ 07102. Phone 973-206-3434

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Advancing quality

Technologies *from page 1*

outpatient setting. "I have some research in that area, and I'd love to see it ultimately reach the patient at the bedside, if possible."

Dr. Mathews is a member of the AGA Center for GI Innovation and Technology and a previous mentee in the Future Leaders Program.

In an interview, Dr. Mathews discussed his push to validate health technologies in the GI field and to make them more transparent to physicians and patients.

Question: Why did you choose GI?
Answer: I think the world of gastroenterology offers a tremendous amount of diversity in the way we manage and treat patients. There's a huge spectrum of disease. There's also the procedural aspect, which is very different from a lot of other medical specialties. For me particularly, there's the opportunity to work on technology as it relates to GI, as well as research in that space.

Q: It seems like gastroenterology involves a lot of detective work. Would you say that's true?
A: When you think of something like abdominal pain or GI symptoms, any place in the body can cause those symptoms to be present. You have to think broadly about all of the contributing factors, the whole patient as it relates to travel, pets, exposures, food, diet. You really can't be myopic when you think about all the potential causes.

The name of the game is to provide answers whenever possible, but I will settle for getting someone feeling better, even if we don't have the answer etched in stone.

Q: What gives you the most joy in your day-to-day practice?
A: I work in an academic institution at Johns Hopkins. I really enjoy the direct connection with patients. I've switched mostly to a hospital-based practice, which means I'm getting patients at their sickest. It's really a privilege to provide an opportunity for improvement or support in that context. I also enjoy the teaching and training of the next generation of folks that are going into this field. There's so much to learn, and I think trying to set that example and teach by doing is a great opportunity, and I really enjoy that as well.

Q: Describe your biggest practice-related challenge and what you're doing to address it.
A: One of my focus areas on the research front is about providing greater transparency and validation around health technologies. How do patients know which health technologies to use? How do doctors know which ones to recommend or advocate for?

Q: Can you give an example of a technology of concern?
A: Looking at oncology and mobile apps, I coauthored one study in 2021 that found well over half did not meet physician or patient expectations. These were the most popular and highest-rated apps available at the time. It shows that there's a real disconnect between what the end users – the doctors and the patients – want from these solutions and what's actually being provided.

There's a flood of different solutions that are out there, and there really isn't a streamlined way to know, as a clinician or as a patient, which ones really make a difference clinically and which ones are going to be helpful for you. And that's been the focus of my research – understanding ways to evaluate technologies that are not so burdensome as to be purely in the realm of academics, but to be pragmatic.

Q: Who has had the strongest influence on your life?
A: I would say my spouse. She's an academic physician at Hopkins. One of the things she has shown me is the importance of finding alignment in what you do professionally with the sort of goals that you have or the values that you hold as an individual. That's why I've done some nontraditional things in my academic career. It's really been in search of finding that alignment that matches my interests and goals, as opposed to just doing something because it's a popular thing to do. ■

Dr. Mathews is on LinkedIn (https://www.linkedin.com/in/simon-mathews/). His health tech blog is Digital Differential (https://www.digitaldifferential.com).

Lightning Round

Favorite sport?
Soccer

What song do you have to sing along with when you hear it?
80s pop music

Introvert or extrovert?
Introvert

Favorite holiday?
Christmas

Optimist or pessimist?
Realist

CLINICAL CHALLENGES AND IMAGES

What's your diagnosis?

BY AI LI, FEI-XUE CHEN, AND YAN-QING LI

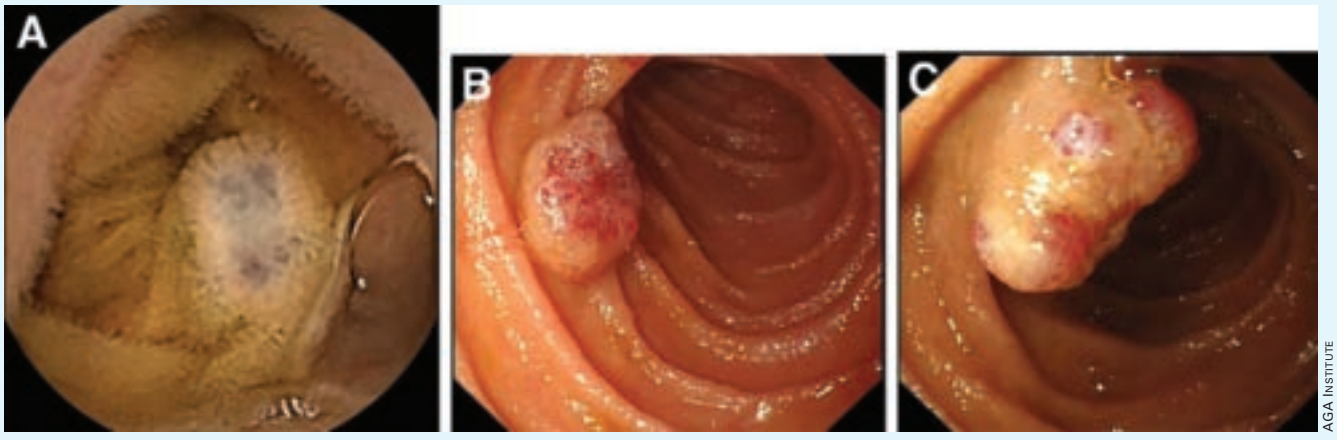
Previously published in Gastroenterology (2019;157:311-2).

A 13-year-old boy presented with recurrent melena for 10 years accompanied with dizziness and fatigue. This patient had no history of nonsteroidal anti-inflammatory drug use, peptic ulcer, or chronic liver disease, and no family history of gastrointestinal bleeding. He was born with a right foot hemangioma that was resected when he was 2 years old. Additionally, he had received multiple blood transfusions for iron deficiency anemia since childhood. The body mass index was 16.5 kg/m^2 and physical examination revealed active bowel sounds.

Laboratory examinations showed severe iron deficiency anemia (the lowest hemoglobin available was 36 g/L) and positive stool occult blood. Gastroscopy unveiled superficial gastritis and colonoscopy was normal. Second-look examinations showed the same results. No clinically important signs were observed on computed tomography scan. Given these results, small-intestinal bleeding was considered. Therefore, a video capsule endoscopy was carried out and revealed multifocal hemangioma-like purplish blue lesions in jejunum and ileum (Figure A). Then a single-balloon enteroscopy was performed, which showed multifocal vascular lesions ranging between 1.0 and 2.0 cm in the jejunum and ileum (Figure B, C).

Based on these findings, what is your diagnosis? What is the next step in management for this patient?

The answer is on page 22.



Dietary interventions

IBD *from page 1*

this systematic review and meta-analysis."

The study was published online in Clinical Gastroenterology and Hepatology (2022 Dec 2. doi: 10.1016/j.cgh.2022.11.026).

Some nutritional therapies, such as exclusive enteral nutrition, have good evidence to support their use in the treatment of IBD, Dr. Limketkai said. However, patients often find maintaining a liquid diet difficult, particularly over a long period of time, so clinicians and patients have been interested in solid-food diets to treat IBD.

In 2019, Dr. Limketkai and colleagues conducted a systematic review and meta-analysis of randomized controlled trials focused on solid-food diets for IBD that was published with the Cochrane Collaboration. At that time, the data were considered sparse, and the certainty of evidence was very low or low. Since then, several high-quality trials have been published.

For this study, Dr. Limketkai and colleagues conducted an updated review of 36 studies and a meta-analysis of 27 studies that compared a solid-food diet with a control diet in patients with Crohn's disease or ulcerative colitis. The intervention arm had to involve a well-defined diet, not merely a "usual" diet.

Among the studies, 12 evaluated dietary interventions for inducing clinical remission in patients with active Crohn's disease, and 639 patients were involved. Overall, a low–refined carbohydrate diet was superior to a high-carbohydrate diet or a low-fiber diet. In addition, a symptoms-guided diet, which sequentially eliminated foods that aggravated a patient's symptoms, was superior to conventional nutrition advice. However, the studies had serious imprecisions and very low certainty of evidence.

Compared with respective controls, a highly restrictive organic diet, a low-microparticle diet, and a low-calcium diet were ineffective at inducing Crohn's disease remission. Studies of immunoglobulin G–based measures were inconsistent.

In a comparison of diets touted to benefit patients with Crohn's disease, the Specific Carbohydrate Diet was similar to the Mediterranean diet and the whole-food diet, though the certainty of evidence was low. Partial enteral nutrition was similar to exclusive enteral nutrition, though there was substantial heterogeneity between studies and very low certainty of evidence.

For maintaining Crohn's disease remission, researchers evaluated 14 studies that included 1,211 patients with inactive disease. Partial enteral nutrition appeared to reduce the risk of relapse, although evidence certainty was very low. In contrast, reducing red meat or refined carbohydrates did not lower the risk of relapse.

Dr. Lewis

"These findings seemingly contradict our belief that red meat and refined carbohydrates have proinflammatory effects, although there are other studies that appear to show inconsistent, weak, or no association between consumption of unprocessed red meat and disease," Dr. Limketkai said. "The caveat is that our findings are based on weak evidence, which may change as more studies are performed over time."

For induction of remission in ulcerative colitis, researchers evaluated three studies that included 124 participants with active disease. When compared with participants' usual diet, there was no benefit from a diet that excluded symptom-provoking foods, fried foods, refined carbohydrates, additives, preservatives, most condiments, spices, and beverages other than boiled water. Other studies found no benefit from eliminating cow milk protein or gluten.

For maintaining ulcerative colitis remission, they looked at four studies that included 101 patients with inactive disease. Overall, there was no benefit from a carrageenan-free, anti-inflammatory, or cow milk protein–elimination diet.

Although the certainty of evidence remains very low or low for most dietary trials in IBD, the emerging data suggest that nutrition plays an important role in IBD management and should be considered in the overall treatment plan for patients, the study authors wrote.

"Patients continue to look for ways to control their IBD, particularly with diet. Providers continue to struggle with making evidence-based recommendations about dietary interventions for IBD. This systematic review is a useful tool for providers to advise their patients," James D. Lewis, MD, AGAF, associate director of the inflammatory bowel diseases program at the University of Pennsylvania, Philadelphia, said in an interview. Dr. Lewis, who wasn't involved with this study, has researched dietary interventions for IBD. He and his colleagues have found that reducing red meat does not lower the rate of Crohn's disease flares and that the Mediterranean diet and Specific Carbohydrate Diet appear to be similar for inducing clinical remission.

Based on this review, partial enteral nutrition could be an option for patients with Crohn's disease, Dr. Lewis said. "Partial enteral nutrition is much easier than exclusive enteral nutrition for patients," he added. "However, there remains uncertainty as to whether the solid-food component of a partial enteral nutrition approach impacts outcomes."

"While certain diets may be helpful and effective for IBD, different diets work differently in different people. This concept is no different than the fact that different IBD medications work differently in different individuals," Dr. Limketkai said. "However, given the current state of evidence for dietary interventions in IBD, we still have a long path of research ahead of us."

The study received no funding. The study authors reported no conflicts of interest. Dr. Lewis reported no relevant disclosures.

AGA venture capital fund makes first investment

BY THOMAS R. COLLINS

The American Gastroenterological Association has made the first investment through its new venture capital fund – an initiative that gives gastroenterologists a financial opportunity combined with a chance to help corporations trying to make a difference in the field.

The fund – called the GI Opportunity Fund 1 – invests in fast-growing, early-stage companies, with the goal of hastening innovation that could ultimately help patients with digestive diseases. It was established in partnership with Varia Ventures.

The AGA recently announced the fund's first investment with Carlsbad, Calif.–based Virgo Surgical Video Solutions, which offers endoscopy video recording that uses artificial intelligence for ease of use during procedures, for reviewing video later, and for using video to connect trial investigators with potential candidates.

Dr. Kosinski

"While AGA has long guided innovators who share our goal of improving digestive health care, we have doubled down on this commitment by establishing the GI Opportunity Fund," said Lawrence Kosinski, MD, AGAF, AGA Governing Board Councilor for Development and Growth. "The fund's first investment – Virgo – exemplifies our pursuit of improved clinical care." He said the fund gives physicians a chance to work closely with AGA to invest in difference-making ventures.

"Through our venture fund, gastroenterologists can join AGA to invest in fast-growing, early-stage companies that are transforming care for patients with digestive disease," Dr. Kosinski said.

Virgo CEO Matthew Z. Schwartz said the company's product is intended to fill an important need.

"We recognized that it was really difficult for doctors to capture endoscopy procedures video in high-definition at scale," he said. "Generally, they were just taking still images. And the images were often not of great quality."

Virgo offers a small device that connects to existing endoscopy equipment, plugging into the back of a video processor, securely compressing and encrypting video and sending it to Virgo's HIPAA-compliant cloud storage Web portal. Once it's plugged in, it's "set it and forget it. We try to make it as easy as possible for doctors to record their video – which means we don't want them to have to do anything different about their normal clinical workflow in order to generate these videos," Mr. Schwartz said. Physicians don't even have to press a start or stop button – Virgo's machine-learning algorithm detects when to start and stop recording by

Continued on following page

Oral vs. colonic

FMT *from page 1*

(2022 Sep 17. doi: 10.1016/j.cgh.2022.09.008).

The Food and Drug Administration allows FMT to be used for patients who have failed standard treatment for rCDI under a policy of enforcement discretion.

The past decade has seen an increase in the use of FMT in clinical practice, owing to an increase in cases of rCDI after failure of standard antibiotic therapy.

Unlike antibiotics, which perpetuate and worsen intestinal dysbiosis, FMT restores the diversity and function of host microbiota, effectively breaking the cycle of rCDI, the authors of the study noted. But it's been unclear whether the efficacy and safety of FMT vary by route of administration.

Effective without procedural risks

To investigate, Dr. Vaughn and colleagues evaluated clinical outcomes and adverse events in 170 patients with rCDI who underwent cap-FMT and 96 peers who underwent colo-FMT.

FMT was performed using one of two standardized formulations of microbiota manufactured by the University of Minnesota microbiota therapeutics program: freeze-dried/encapsulated or frozen-thawed/liquid.

Overall, the cure rates of CDI were 86% at 1 month and 81% at 2 months. There was no statistically significant difference at either time between cap-FMT and colo-FMT.

The 1-month cure rate was 84% with cap-FMT and 91% with colo-FMT; at 2 months, the cure rates were 81% and 83%, respectively.

Cap-FMT has a safety and effectiveness profile similar to that of colo-FMT, without the procedural risks of colonoscopy, the researchers concluded.

They cautioned that, although FMT is highly effective overall, patient selection is a key factor to optimizing FMT success.

Older age and hemodialysis were associated with FMT failure by 2 months on multivariate logistic regression.

"These risk factors can help determine if a patient should receive FMT or an alternative therapy for rCDI. This is not to say FMT should be avoided in older patients or those on dialysis, but clinicians should be aware of these associations in light of other options for rCDI," Dr. Vaughn said.

Confirming prior studies, antibiotic use after FMT was a major factor in its failure. Patient selection for FMT should include an assessment of the potential need for antibiotics after transplant, the researchers noted.

One serious adverse event (aspiration pneumonia) was related to colonoscopy; otherwise, no new safety signals were identified.

As reported in other studies, changes in bowel function, including diarrhea, constipation, gas, and bloating were common, although it's tough to disentangle gastrointestinal symptoms related to FMT from those after CDI, the researchers said. Importantly, no transmission of an infectious agent related to FMT was identified.

Two good options

The researchers said their findings are "highly generalizable" because the population reflects all FMT use by participating institutions and contains a mix of academic centers and private practices.

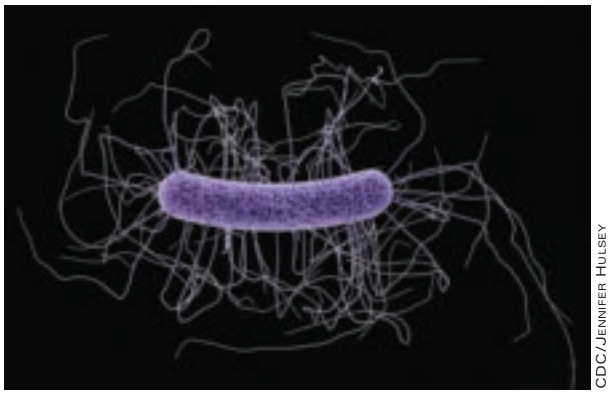
Many patients included in the study would not have been eligible for a clinical trial, owing to their having many comorbid conditions, including immune compromise and inflammatory bowel disease, the authors noted.

"FMT is recommended by major gastroenterology and infectious disease society guidelines," Dr. Vaughn said. "Our group, and others, have consistently found strategies that incorporate FMT as cost-effective strategies for treating rCDI."

However, lack of access to FMT products often is a barrier to treatment, he said.

"A stool banking model, similar to the nonprofit blood banking model, may be a useful solution to ensure equitable access to FMT to all who need it," Dr. Vaughn added.

Reached for comment, Majdi Osman, MD, MPH, told this news organization that the study is valuable, "as it nicely shows in a real-world setting that capsules and colonoscopy are good options for patients who need this."



CDC/Jennifer Hulsey

Dr. Osman is chief medical officer of OpenBiome, a nonprofit organization that operates a public stool bank and is the major FMT source in the United States. The organization has provided over 63,000 FMT treatments to over 1,200 hospitals in the United States.

"FMT has become standard of care for patients who failed antibiotic therapy, and certainly is being used widely as a treatment option for these patients who have often run out of existing options," Dr. Osman said.

Support for the study was provided by a donation from Achieving Cures Together, a nonprofit organization dedicated to advancing microbiome-based research. Dr. Vaughn receives grant support from Takeda, Roche, Celgene, and Diasorin and has received consulting fees from Prometheus and AbbVie. Dr. Osman reported no relevant financial relationships. ■

Continued from previous page

discerning when the scope is inserted and removed. "A goal of ours is to change the paradigm for endoscopy to help make sure that every procedure is captured in HD to the cloud."

The service also includes an "auto-highlight" feature that detects important moments in the procedure video. It automatically marks points in the video when the physician takes a still image and moments when an instrument, such as a snare or forceps, is present in the field of view. This, Mr. Schwartz said, makes it "easy in playback to focus on important aspects of the procedure."

There is also a clinical trial screening feature, called "auto IBD," that involves an algorithm that assesses videos to identify patients most likely to be eligible candidates for clinical trials. Mr. Schwartz said that procedures and patients who might go unconsidered – if they are performed at an affiliated community hospital or at an endoscopy center, for instance – can now be brought to the attention of trial investigators, without the need to comb through hundreds or thousands of candidates. "We believe there are many more patients with these diseases that are eligible for IBD clinical trials than are currently being exposed to research opportunities within large health systems."

Mr. Schwartz

Dr. Gellad

The proceeds from the AGA's Opportunity Fund will be used, in part, to expand Virgo's reach, he added. Virgo's connection with the AGA began with its participation in the AGA Tech Summit Shark Tank competition in 2018. "For us, the name of the game is getting Virgo in the hands of as many physicians and health systems as possible," Mr. Schwartz said. "So we'll be using these proceeds to build up the team and work on global distribution." The company is also "looking to refine machine-learning algorithms and build out new features and tools."

Ziad Gellad, MD, MPH, AGAF. associate professor of medicine in gastroenterology at Duke University, Durham, N.C., was one of the Opportunity Fund's earliest member investors. "I was looking for ways to diversify my portfolio, and this was an attractive way to get into an area of investment that is not easily accessible, and so I was excited about that," said Dr. Gellad, who himself is cofounder of a health start-up that develops software for patient navigation and outcomes collection but is not associated with the fund.

"As a start-up cofounder myself, I understand the needs of founders of companies, especially those in the GI space and appreciate the struggles they face," Dr. Gellad added. "The opportunity to contribute to that was appealing. "I also believe that specialty societies like the AGA need to diversify their funding strategy and I think this is a really innovative way to do that," he said

For more information about the fund, go to https://againvest.variacom. ■

What the omnibus bill means for GI

Congress filed its $1.7 trillion omnibus appropriations bill. The bill included positive news for GI and showcased the power of your voice in advocating for patient issues.
Here's what you need to know:

FRANCKREPORTER/THINKSTOCK

Medicare payment cuts

Unfortunately, physicians treating Medicare patients will face cuts this year.

It is disappointing that Congress failed to stop the full cuts. However, the Medicare payment cuts will be lower than the initially proposed 8.5% cut. Physicians will face a 2% cut because of the 4% in PAYGO relief for 2023 and 2024, plus an additional 2.5% in relief for the Centers for Medicare & Medicaid Services.

This is not an ideal outcome, but we are grateful to the more than 160 AGA members who raised their voices and sent over 600 messages to Congress. Your advocacy played a role in alleviating the final number of the cuts.

We will continue to urge Congress to stop the full cuts. Our top priority in 2023 remains addressing the Medicare reimbursement rates.

Two-year extension for telehealth

Good news! We have been ongoing supporters of telehealth expansion that resulted from the COVID-19 pandemic. The inclusion of this 2-year telehealth extension will allow doctors to continue to treat Medicare patients in a virtual setting. This is crucial since it allows patients to continue receiving treatment from their doctor in a virtual setting, and it provides patients and providers with certainty.

$2.5 billion increase for NIH

Good news! The omnibus allocates $47.5 billion for the National Institutes of Health's budget, a $2.5 billion increase from 2023. The increased federal research funding is something we advocated for with congressional offices during Advocacy Day and will support GI researchers who are conducting innovative research and developing treatment for digestive diseases and GI cancers.

AGA-submitted report language on IBD included

Good news! Two language requests submitted by AGA on inflammatory bowel disease (IBD) were included in the omnibus: one in the 2023 Department of Labor, Health and Human Services, Education, and Related Agencies funding bill and one in the 2023 Department of Agriculture, Rural Development, Food and Drug Administration, and Related Agencies funding bill.

The first reaffirms the Appropriations Committee's support for the NIH in funding basic, translational, and clinical studies on the diagnosis and treatment of IBD. The second encourages the FDA to improve diversity and patient-centricity in IBD clinical trials. The inclusion of these language requests in the omnibus highlights another successful advocacy effort by AGA. ■

Fast facts about gifts in a will and planned giving

Gifts to charitable organizations, such as the AGA Research Foundation, in your future plans ensure your support for our mission to fund young investigators continues even after your lifetime. See these three fast facts about planned giving.

TETRA IMAGES/GETTY IMAGES

1. Wills are not for older adults only.
Having a plan for the future is important – no matter your age. A will makes your wishes known and provides your loved ones with peace of mind.

2. Planned gifts are not complicated or confusing.
They don't have to be. There are many types of planned gifts. Most are simple and affordable, like a gift in your will or living trust. You just need to find the one that best meets your needs.

3. Planned gifts are not for the wealthy only.
Anyone can make a planned gift. Gifts of all sizes make a difference at the AGA Research Foundation. In fact, you may even be able to make a bigger impact than you thought possible when you make a planned gift.

For 2023, consider including a gift to the AGA Research Foundation in your will. You will help support researchers and help spark future discoveries in GI.

Want to learn more about including a gift to the AGA Research Foundation in your future plans? Visit our website at https://gastro.planmylegacy.org or contact us at foundation@gastro.org. ■

Explaining sex differences in HBV-associated HCC

BY CAROLYN CRIST
MDedge News

In findings that point to a potential treatment strategy, researchers in China have discovered how two risk factors – male hormones and aflatoxin – may drive hepatocellular carcinoma (HCC). The liver cancer genetics and biology differ between men and women and help explain why aflatoxin exposure increases the risk of HCC in hepatitis B virus (HBV)–infected patients, particularly in men.

The researchers found evidence that androgen signaling increased aflatoxin metabolism and genotoxicity, reduced DNA repair capabilities, and quelled antitumor immunity, Chungui Xu, PhD, with the State Key Lab of Molecular Oncology at the National Cancer Center at Peking Union Medical College in Beijing, and colleagues wrote. The study was published in Cellular and Molecular Gastroenterology and Hepatology (2022 Oct 19. doi: 10.1016/j.jcmgh.2022.10.009).

"Androgen signaling in the context of genotoxic stress repressed DNA damage repair," the authors wrote. "The alteration caused more nuclear DNA leakage into cytosol to activate the cGAS-STING pathway, which increased T-cell infiltration into tumor mass." This might have improved anti–programmed cell death protein 1 [PD-1] immunotherapy in HCCs.

In the study, the researchers conducted genomic analyses of HCC tumor samples from people with HBV who were exposed to aflatoxin in Qidong, China, an area that until recently had some of the highest liver cancer rates in the world. In subsequent experiments in cell lines and mice, the team investigated how the genetic alterations and transcription dysfunctions reflected the combined carcinogenic effects of aflatoxin and HPV.

Dr. Xu and colleagues performed whole-genome, whole-exome, and RNA sequencing on tumor and matched nonneoplastic liver tissues from 101 HBV-related HCC patients (47 men and 54 women). The patients had received primary hepatectomy without systemic treatment or radiation therapy and were followed for 5 years. Aflatoxin exposure was confirmed by recording aflatoxin M1 in their urine 3-18 years before HCC diagnosis. For comparison, the research team analyzed 113 HBV-related HCC samples without aflatoxin exposure from the Cancer Genome Atlas database. They also looked at 181 Chinese HCC samples from the International Cancer Genome Consortium that had no record of aflatoxin exposure. They found no sex differences in mutation patterns for previously identified HCC driver genes, but the tumor mutation burden was higher in the Qidong set.

In the Qidong samples, the research team identified 71 genes with significantly different mutation frequencies by sex. Among those, 62 genes were associated more frequently with men, and 9 genes were associated with women. None of the genes have been reported previously as HCC drivers, although some have been found previously in other cancers, such as melanoma, lung cancer, and thyroid adenocarcinoma.

From whole-genome sequencing of 88 samples, the research team detected HBV integration in 37 samples and identified 110 breakpoints. No difference in HBV

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Earlier colorectal cancer screening appears cost-effective in overweight, obese patients

BY CAROLYN CRIST
MDedge News

Starting colorectal cancer screening earlier than age 50 appears to be cost-effective for both men and women across all body mass index measures, according to a study published in Clinical Gastroenterology and Hepatology (2022 Aug 4. doi: 10.1016/j.cgh.2022.07.028).

In particular, colonoscopy is cost-effective at age 45 for all BMI strata and at age 40 in obese men. In addition, fecal immunochemical testing (FIT) is highly cost-effective at ages 40 or 45 for all BMI values, wrote Aaron Yeoh, MD, a gastroenterologist at Stanford (Calif.) University, and colleagues.

Increased body fatness, defined as a high BMI, has increased sharply in recent decades and has been associated with a higher risk of colorectal cancer. Given the rising incidence of CRC in younger people, the American Cancer Society and U.S. Preventive Services Task Force now endorse screening at age 45. In previous analyses, Dr. Yeoh and colleagues suggested that the policy

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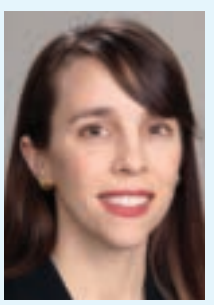
Obesity is associated with an increased risk of colorectal cancer, along with cancers of the breast, endometrium, and esophagus. Even maternal obesity is associated with higher offspring colorectal cancer rates. Key mechanisms that underlie these associations include high insulin levels in obesity that propel tumor growth, adipose tissue that secretes inflammatory cytokines, and high glucose levels that act as fuel for cancer proliferation.



Dr. McGill

With the recommended start of colorectal cancer screening now at age 45, and the U.S. demographic obesity problem worsening, Yeoh and his Stanford colleagues put their well-described cost-effectiveness model to work to analyze screening at different body mass indexes. The new inputs consider not only higher colorectal cancer risk among obese individuals, but also increased all-cause mortality.

For men with BMI over 35, moving the colonoscopy screening age earlier to age 40 was cost-effective. However, it's not clear that in practice the juice is worth the squeeze. Changing screening initiation times further based on personalized factors such as BMI could make screening more confusing for patients and physicians and may hurt uptake, a critical factor for the success of any screening program.

The study supports the current paradigm that screening starting at age 45 is cost-effective among men and women at all BMI ranges, a reassuring conclusion. It also serves as a sobering reminder that promoting metabolic health in our patients, our schools, and our communities is a valuable endeavor.

Sarah McGill, MD, MSc, FACG, FASGE, is associate professor medicine, gastroenterology, and hepatology at the University of North Carolina at Chapel Hill. She receives research funding from Olympus America, Finch Therapeutics, Genentech, Guardant Health, and Exact Sciences.

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breakpoint numbers was detected between the sexes, though there were differences in somatic mutation profiles and in HBV integration, and only men had HBV breakpoints binding to androgen receptors.

From RNA sequencing of 87 samples, the research team identified 3,070 significantly differentially expressed genes between men and women. The transcription levels of estrogen receptor 1 and 2 were similar between the sexes, but men expressed higher androgen receptor levels.

The researchers then analyzed the variation in gene expression between the male and female gene sets to understand HCC transcriptional dysfunction. The samples from men showed different biological capabilities, with several signaling pathways related to HCC development and progression that were upregulated. The male samples also showed repression of specific antitumor immunity.

Men's HCC tumor samples expressed higher levels of aflatoxin metabolism–related genes, such as AHR and CYP1A1, but lower levels of GSTM1 genes.

Turning to cell lines, the researchers used HBV-positive HepG2.2.15 cells and PLC/PRF/5 cells to test sex hormones in the regulation of AHR and CYP1A1 and how their interactions affected aflatoxin B1 cytotoxicity. After aflatoxin treatment, the addition of testosterone to the cultures significantly enhanced the transcription levels of AHR and CYP1A1. The aflatoxin dose needed to cause cell death was reduced by half in the presence of testosterone.

DNA damage from aflatoxin activates DNA repair mechanisms, so the research team analyzed different repair pathways. In the male tumor samples, the most downregulated pathway was NHEJ. The male samples expressed significantly lower levels of NHEJ factors than did the female samples, including XRCC4, MRE11, ATM, HRCC5, and NBN.

In cell lines, the researchers tested the effects of androgen alone and with aflatoxin on the regulation of NHEJ factors. The transcriptional levels of XRCC4, LIG4, and MRE11 were reduced significantly in cells treated with both aflatoxin and testosterone, compared with those treated with aflatoxin alone. Notably, the addition of 17beta-estradiol estrogen partially reversed the reduction of XRCC4 and MRE11 expression.

The tumor samples from men also showed different gene signatures of immune responses and inflammation from the samples from women. The genes related to interferon I signaling and response were upregulated significantly in male samples but not in female samples. In addition, the samples from men showed repression of antigen-specific antitumor immunity. The research team detected significantly increased CD8+T-cell infiltration in tumor tissues of men but not women, as well as higher transcriptional levels of PD-1 and CTLA-4, which are two immune checkpoint proteins on T cells that keep them from attacking the tumor. The data indicate that androgen signaling in established HBV-related HCCs contribute to the development of an immunosuppressive microenvironment, the authors wrote, which could render the tumor sensitive to anti–PD-1 immunotherapy.

In mice, the researchers examined the impact of a favorable androgen pathway on anti–PD-1 treatment effects against hepatoma. They administered tamoxifen to block ER signaling in syngeneic tumor–bearing mice. In both male and female mice, tamoxifen enhanced the anti–PD-1 effects to eradicate the tumor quickly. They also administered flutamide to tumor-bearing mice to block the androgen pathway and found no significant difference in tumor growth in female mice, but in male mice, tumors grew faster in the flutamide-treated mice.

"Therapeutics that favor androgen signaling and/or blocking estrogen signaling may provide a new strategy to improve the efficacy of immune checkpoint inhibitors against HCC in combination with radiotherapy or chemotherapy that induced DNA damage," the authors wrote. "The adjuvant effects of tamoxifen for favorable androgen signaling to boost the anti–PD-1 effect in HCC patients needs future study in a prospective HCC cohort."

The study was supported by the National Natural Science Foundation Fund of China, Innovation Fund for Medical Sciences of Chinese Academy of Medical Sciences, State Key Project for Infectious Diseases, and Peking Union Medical College. The authors disclosed no conflicts. ■

AGA Resource

To read an editorial that accompanied this study in Cellular and Molecular Gastroenterology and Hepatology, go to https://www.cmghjournal.org/article/S2352-345X(22)00234-X/fulltext.

Genomics data reveal promising PSC therapy target

BY TARA HAELLE
MDedge News

An investigation of genomics data related to primary sclerosing cholangitis (PSC) in published medical literature revealed several genes likely involved in the pathogenesis of this autoimmune diseases, according to a study published in Gastro Hep Advances (2023;2[1]:49-62).

PSC is very rare, with an incidence of 0-1.3 cases per 100,000 people per year. Because up to 80% of patients with PSC also have inflammatory bowel disease (IBD), a link along the gut-liver axis is suspected. So far, scientists have not understood the causes of PSC, the main complications of which include biliary cirrhosis, bacterial cholangitis, and cholangiocarcinoma.

No treatment is currently available for PSC, but the findings of this genomics study suggest several targets that may be worth pursuing, particularly the gene NR0B2.

"The therapeutic targeting of NR0B2 may potentiate that of FXR [farnesoid X receptor] and enable action on early events of the disease and prevent its progression," wrote Christophe Desterke, PhD, of the Paul-Brousse Hospital, the French National Institute of Health and Medical Research, and the University of Paris-Saclay in Villejuif, France, and his associates.

The researchers used an algorithmic tool to mine the MEDLINE/PubMed/National Center for

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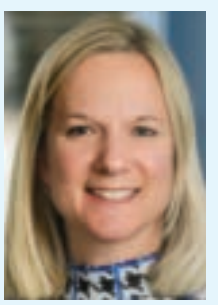
Primary sclerosing cholangitis (PSC) is a bile duct disease with few therapeutic options other than liver transplant, and thus its prognosis remains grim. Additionally, the factors that cause the disease are not well understood. Identifying the pathways and genes involved in PSC pathogenesis could help in the development of potential therapeutic targets.

In this report Desterke et al. mined public data sets to identify and define a PSC-specific network. Of the top genes in this list, NR0B2 stood out as a potential player in pathogenesis because of its involvement in regulating bile acid metabolism. The authors showed that upregulation of NR0B2 occurs early in the disease process and in patient tissues is independent of variables such as gender and sex. Interestingly, the authors showed that this upregulation occurs primarily in cholangiocytes, the cells lining the bile duct. Higher expression of NR0B2 results in reprogramming that alters the metabolic function of these cells and predisposes them to malignancy.



Dr. Nejak-Bowen

This study, which is the first to look at omics data for PSC, highlights the involvement of genes and pathways that were previously unrecognized in disease pathogenesis. By using data derived from human PSC liver biopsies and animal models of PSC, the authors were able to validate their findings across species, which strengthened their conclusions. This approach also showed that NR0B2 deregulation occurs primarily in cholangiocytes, suggesting that future therapies should be targeted to this cell type. These important findings will improve our understanding of this rare but clinically significant disease.

Kari Nejak-Bowen, PhD, MBA, is associate professor, department of pathology, University of Pittsburgh School of Medicine. She has no relevant conflicts of interest.

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is likely to be cost-effective, but they didn't explore the potential differences by BMI.

"Our results suggest that 45 years of age is a reasonable screening initiation age for women and men with BMI ranging from normal through all classes of obesity," the authors wrote. "Before changing screening policy, supportive data from clinical studies would be needed. Our approach can be applied to future efforts aiming to risk-stratify CRC screening based on multiple clinical factors or biomarkers."

The research team examined the potential effectiveness and cost-effectiveness of screening tailored to BMI starting as early as age 40 and ending at age 75 in 10 separate cohorts of men and women of normal weight (18.5 to <25 kg/m^2), overweight (25 to <30 kg/m^2), and three strata of obesity – obese I (30 to <35 kg/m^2), obese II (35 to <40 kg/m^2), and obese III (>40 kg/m^2).

For each cohort, the researchers estimated incremental costs per quality-adjusted life-year (QALY) gained by initiating screening at age 40 versus age 45 versus age 50, or by shortening colonoscopy intervals. They modeled screening colonoscopy every 10 years (Colo10) or every 5 years (Colo5), or annual FIT, offered from ages 40, 45, or 50 through age 75 with 100% adherence, with postpolypectomy surveillance through age 80.

For model inputs, the research team favored high-quality data from meta-analyses or large prospective trials. Screening, treatment, and complication costs were set at 2018 Centers for Medicare & Medicaid Services rates for ages 65 and older and modified to reflect commercial costs at ages 65 and younger. The authors assumed use of moderate sedation, and sensitivity analyses addressed possible increased costs and complications of colonoscopy under propofol.

Overall, without screening, sex-specific total CRC deaths were similar for people with overweight or obesity I-III and slightly higher than for people with normal BMI. For both men and women across all BMI strata, Colo10 or FIT starting at age 50 substantially decreased CRC incidence and mortality versus no screening, and the magnitude of the clinical impact was comparable across BMI.

For both sexes across BMI, Colo10 or FIT starting at age 50 was highly cost-effective. The cost per QALY gained for Colo10 compared with no screening became more favorable as BMI increased from normal to obesity III. FIT was cost-saving compared with no screening for all cohorts and was cost-saving or highly cost-effective, compared with Colo10 within each cohort.

Initiating Colo10 at age 45 showed incremental decreases in CRC incidence and mortality, which were modest compared with the gains of Colo10 at age 50 versus no screening. However, the incremental gains were achieved at acceptable incremental costs ranging from $64,500 to $85,900 per QALY gained in women and from $33,400 to $64,200 per QALY gained in men.

Initiating Colo10 at age 40 in women and men in the lowest three BMI strata was associated with high incremental costs per QALY gained. In contrast, Colo10 initiation at age 40 cost $80,400 per QALY gained in men with obesity III and $93,300 per QALY gained in men with obesity II.

FIT starting at ages 40 or 45 yielded progressively greater decreases in CRC incidence and mortality for both men and women across BMI strata, and it was highly cost-effective versus starting at later ages. Compared with Colo10, at every screening initiation age, FIT was cost-saving or preferred based on very high incremental costs per QALY, and FIT required substantially fewer colonoscopies per person.

Intensifying screening by shortening the colonoscopy interval to Colo5 was never preferred over shifting Colo10 to earlier screening initiation ages. In all cohorts, Colo5 was either less effective and more costly than Colo10 at a younger age, or when it was more effective, the cost per QALY gained was substantially higher than $100,000 per QALY gained.

Additional studies are needed to understand obesity-specific colonoscopy risks and costs, the authors wrote. In addition, obesity is only one of several factors that should be considered when tailoring CRC screening to the level of CRC risk, they wrote.

"As the search for a multifactor prediction tool that is ready for clinical application continues, we face the question of how to approach single CRC risk factors such as obesity," they wrote. "While screening guidelines based on BMI can be envisioned if supportive clinical data accumulate, clinical implementation must overcome operational challenges."

The study funding was not disclosed. One author reported advisory and consultant roles for several medical companies, and the remaining authors disclosed no conflicts. ■

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Biotechnology Information database using ththree key symptoms of PSC – biliary fibrosis, biliary inflammation, and biliary stasis – as their keywords. This approach allowed them to discover the genes and potential pathways related to PSC in published research text or in clinical, animal, and cellular models.

The researchers initially found 525 genes linked to PSC and then compared them to RNA data from liver biopsies taken from patients with liver disease from various causes. This process led to a ranking of the 10 best markers of PSC, based on the data-mining method and the genes' association with one or more of the three PSC symptoms.

At the top of the list is NR1H4, also called FXR, which ranks most highly with biliary fibrosis and biliary stasis. NR1H4 is already a clear target for cholestatic and fatty liver diseases, the authors noted. The other genes, in descending order of relevance, are ABCB4, ABCB11, TGFB1, IFNL3, PNPLA3, IL6, TLR4, GPBAR1, and IL17A. In addition, complications of PSC were significantly associated with upregulation of TNFRS12A, SOX9, ANXA2, MMP7, and LCN2.

Separately, investigation of the 525 initially identified genes in mouse models of PSC revealed that NR0B2 is also a key player in the pathogenesis of PSC.

"NR0B2 was upregulated in PSC livers independent of gender, age, and body mass index," the authors reported. "Importantly, it was not dependent on the severity of PSC in the prognostic cohort, suggesting that this may be an early event during the disease."

The researchers also found a possible pathway explaining the autoimmunity of PSC – the involvement of CD274, also known as the PDL1 immune checkpoint. The authors noted that the PDL1 inhibitor pembrolizumab has previously been reported as a cause of sclerosing cholangitis.

Further, the researchers discovered overexpression of FOXP3 in the livers of patients with PSC. Because FOXP3 determines what T-cell subtypes look like, the finding suggests that an "imbalance between Foxp3þ regulatory T cells and Th17 cells may be involved in IBD and PSC," they wrote.

At the top of the list is NR1H4, also called FXR, which ranks most highly with biliary fibrosis and biliary stasis. NR1H4 is already a clear target for cholestatic and fatty liver diseases.

Also of note was the overexpression of SOX9 in the livers of patients with PSC whose profiles suggested the worst clinical prognoses.

Finally, the researchers identified three genes as potentially involved in development of cholangiocarcinoma: GSTA3, ID2 (which is overexpressed in biliary tract cancer), and especially TMEM45A, a protein in cells' Golgi apparatus that is already known to be involved in the development of several other cancers.

The research was funded by the French National Institute of Health and Medical Research. The authors reported no conflicts of interest.

IBD patients have limited protection against Omicron with third vaccine dose

BY TARA HAELLE
MDedge News

For people with inflammatory bowel disease (IBD) taking immunosuppressive medication, a third dose of a COVID-19 mRNA vaccine significantly increases neutralizing antibodies against the original SARS-CoV-2 strain, but the picture is more complicated for protection against the Omicron variant, according to a research letter published in Gastroenterology (2022 Oct 18. doi: 10.1053/j.gastro.2022.10.010).

Though IBD patients do mount a response against Omicron, the response is substantially lower for those taking tofacitinib or infliximab, particularly infliximab monotherapy.

"As further mutations in the viral genome accumulate over time, with the attendant risk of immune evasion, it remains important to continue to reappraise vaccination strategy, including the implementation of personalized approaches for some patients, such as those treated with anti-TNF drugs and JAK inhibitors," wrote Zhigang Liu, PhD, a research associate in the department of metabolism, digestion, and reproduction at Imperial College London, and his colleagues. "Preferential use of bivalent vaccines may be especially valuable in IBD patients taking anti–Tumor Necrosis Factor (TNF) agents or Janus Kinase (JAK) inhibitors," they wrote. Their study did not assess neutralizing antibodies resulting from use of the bivalent vaccine, however.

The researchers tracked 268 participants, including 49 healthy participants serving as controls, from May 2021 through March 2022. The other participants had IBD and included 51 patients taking thiopurines, 36 patients taking infliximab, 39 taking both infliximab and thiopurines, 39 taking ustekinumab, 38 taking vedolizumab, and 16 taking tofacitinib. The IBD patients were all enrolled in the SARS-CoV-2 Vaccination Immunogenicity in Immunosuppressed Inflammatory Bowel Disease Patients (VIP) cohort.

None of the participants had evidence of a SARS-CoV-2 infection at baseline. All had received two doses of an mRNA COVID-19 vaccine (all received Pfizer, except two controls who received Moderna) or two doses of the AstraZeneca vaccine as their primary vaccination. All received an mRNA vaccine for their third dose. Among the IBD patients, 137 received the AstraZeneca in their primary two-dose series, and 82 received Pfizer.

First the researchers assessed the participants' humoral response to the vaccine against the original SARS-CoV-2 strain and against the Omicron BA.1 variant. Neutralizing antibody titers rose significantly against both strains after the third vaccine dose for all participants.

"However, 50% neutralization titer (NT50) values were significantly lower against Omicron than against the ancestral strain in all study groups, irrespective of the immunosuppressive treatment regimen," the authors reported. NT50 values are a measure that reflect a vaccine-induced humoral immunity against SARS-CoV-2 after vaccination.

Compared to the healthy controls, individuals receiving infliximab, tofacitinib, or infliximab/thiopurine combination therapy showed significantly lower responses after the second and third vaccine doses. Thirteen patients did not generate NT50 against Omicron after the second vaccine dose, and seven of them were on infliximab monotherapy. They represented nearly 20% of all infliximab monotherapy participants.

Next the researchers assessed the risk of a breakthrough infection according to neutralizing titer thresholds. Individuals with an NT50 less than 500 had 1.6 times greater odds of a breakthrough infection than those with an NT50 above 500, they noted. After two vaccine doses, 46% of participants with IBD had an NT50 above 500 for the ancestral strain, which rose to 85% of those with IBD after a third dose.

In the healthy control group, 35% had an NT50 under 500 after two doses, and 14% of them had a breakthrough infection, all of which were mild and none of which required hospitalization. The NT50 in healthy controls, however, was not significantly associated with risk of breakthrough infection.

"In this study, neutralizing titers elicited against the omicron variant were generally poor for all individuals and were substantially lower in recipients of infliximab, infliximab/thiopurine combination, or tofacitinib therapy," the authors concluded. "This raises concerns about whether currently available vaccines will be sufficient to protect against continually evolving SARS-CoV-2 variants, especially in patients established on certain immunosuppressive drugs."

The small population sizes for each subgroup based on medication was one of the study's limitations. Another was the fact that it was underpowered to conclusively determine whether an increased risk of breakthrough infection exists in IBD patients who have lower titers of neutralizing antibodies. A limitation for generalization to U.S. patients is that just 64% of the IBD patients received the AstraZeneca vaccine, which is not offered in the U.S. for their first two doses before receiving the third mRNA (Pfizer) dose.

The study was funded by Pfizer in an independent research grant and by the National Institute for Health and Care Research Biomedical Research Centres in Imperial College London and Imperial College Healthcare NHS Trust and Cambridge, and the NIHR Clinical Research Facility Cambridge.

Dr. Liu and one other author had no disclosures. The other 18 authors have a range of disclosures related to various pharmaceutical companies, including Pfizer. ■

Understanding how inflammatory bowel disease (IBD) impacts COVID-19 infection risk and how IBD medications influence this risk remains an ever-evolving discussion, particularly with the emergence of new SARS-CoV-2 variants and booster vaccines. In this study, Liu et al. further shape this conversation: They show that a third mRNA COVID-19 vaccine dose increases neutralizing antibody levels against the Omicron variant in IBD patients compared to the level following a second vaccine dose, but that infliximab and tofacitinib significantly attenuate this response. They additionally suggest that IBD patients achieve lower neutralizing antibody levels after a third COVID-19 vaccine and may have a higher breakthrough infection risk, compared with healthy controls without IBD.


Dr. Brenner

Given the myriad health benefits of adequately controlling active IBD, few would argue that these results call for IBD patients to switch off infliximab or tofacitinib. Rather, the findings underscore the importance of multiple COVID-19 booster vaccinations for IBD patients, especially as most breakthrough COVID-19 infections take a mild course, even in the setting of immunosuppression.

Whether to change booster vaccination recommendations specifically for IBD patients on tofacitinib or infliximab, however, remains an unanswered question. The small sample of patients on tofacitinib precludes definitive conclusions regarding tofacitinib's impact on vaccine response. Moreover, this humoral antibody-based study tells only half the story: We need analyses of the cell-mediated booster vaccine response to truly understand vaccine efficacy during immunosuppressant use. Lastly, future studies including the bivalent booster will provide the most up-to-date information on protecting our IBD patients from the Omicron variant.

Dr. Erica J. Brenner, MD, MSCR, is an assistant professor, department of pediatrics, Division of Pediatric Gastroenterology, University of North Carolina School of Medicine; and a cofounder of the Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD) registry. She has no relevant financial conflicts of interest.

Proximal ADR could become new quality metric

BY CAROLYN CRIST
MDedge News

Measurement of the proximal adenoma detection rate may be an important new quality metric for screening colonoscopy, propose researchers in a study that found proportionately more adenomas detected in the right colon with increasing patient age.

As patients age, in fact, the rate of increase of proximal adenomas is far greater than for distal adenomas in both men and women and in all races, wrote Lawrence Kosinski, MD, AGAF, founder and chief medical officer of Sonar MD in Chicago, and colleagues.


Dr. Kosinski

Adenoma detection rate, the proportion of screening colonoscopies performed by a physician that detect at least one histologically confirmed colorectal adenoma or adenocarcinoma, has become an accepted quality metric because of the association of high ADR with lower rates of postcolonoscopy colorectal cancer (CRC). ADR varies widely among endoscopists, however, which could be related to differences in adenoma detection in different parts of the colon.

"An endoscopist could perform a high-quality examination of the distal colon and find one adenoma but at the same time miss important pathology in the proximal colon," the authors wrote. "These differences could be clinically important if CRC occurs after colonoscopy." The study was published in Techniques and Innovations in Gastrointestinal Endoscopy (2022 Oct 28. doi: 10.1016/j.tige.2022.10.006).

Dr. Kosinski and colleagues analyzed retrospective claims data from all colonoscopies performed between 2016 and 2018 submitted to Health Care Service, which is the exclusive Blue Cross Blue Shield licensee for Illinois, Texas, Oklahoma, New Mexico, and Montana. All 50 states were represented in the patient population, though Illinois and Texas accounted for 66% of the cases.

The research team limited the study group to include patients who underwent a screening colonoscopy, representing 30.9% of the total population. They further refined the data to include only screening colonoscopies performed by the 710 endoscopists with at least 100 screenings during the study period, representing 34.5% of the total patients. They also excluded 10,685 cases with family history because the high-risk patients could alter the results.

"An endoscopist could perform a high-quality examination of the distal colon and find one adenoma but at the same time miss important pathology in the proximal colon."

Using ICD-10 codes, the researchers identified the polyp detection locations and then calculated the ADR for the entire colon (T-ADR) and both the proximal (P-ADR) and distal (D-ADR) colon to determine differences in the ratio of P-ADR versus D-ADR by age, sex, and race. They were unable to determine whether the polyps were adenomas or sessile serrated lesions, so the ADR calculations include both.

The 182,296 screening colonoscopies included 93,164 women (51%) and 89,132 men (49%). About 79% of patients were aged 50-64 years, and 5.8% were under age 50. The dataset preceded the U.S. Preventive Services Task Force recommendation to initiate screening at age 45.

Overall, T-ADR was consistent with accepted norms in both men (25.99%) and women (19.72%). Compared with women, men had a 4.5% higher prevalence of proximal adenomas and a 2.5% higher prevalence of distal adenomas at any age. The small cohort of Native Americans (296 patients) had a numerically higher T-ADR, P-ADR, and D-ADR than other groups.

By age, T-ADR increased significantly with advancing age, from 0.13 in patients under age 40 to 0.39 in ages 70 and older. The increase was driven by a sharp rise in P-ADR, particularly after age 60. There was a relatively small increase in D-ADR after ages 45-49.

Notably, the P-ADR/D-ADR ratio increased from 1.2 in patients under age 40 to 2.65 in ages 75 and older in both men and women.

Since the experience of the endoscopist affects ADR, the research team also calculated the ADR data by the number of total colonoscopies by endoscopist per decile. T-ADR, P-ADR, and D-ADR were associated directly in a linear relationship with the number of total colonoscopies performed. The slope of the P-ADR trendline was 2.3 times higher than the slope of the D-ADR trendline, indicating a higher volume of

ADR · *Continued on following page*

Lifestyle changes may reduce colorectal cancer risk

BY LAIRD HARRISON

Changes regarding smoking, drinking, body weight, and physical activity may alter the risk for colorectal cancer (CRC), the results of a study on a large European cohort suggest.

"This is a clear message that practicing clinicians and gastroenterologists could give to their patients and to CRC screening participants to improve CRC prevention," write Edoardo Botteri, PhD, Cancer Registry of Norway, Oslo, and colleagues in an article published in the American Journal of Gastroenterology (2022 Dec 2. doi: 10.14309/ajg.0000000000002065).

Previous studies have shown a correlation between cancer in general and unhealthy lifestyle factors. They have also shown an association between weight gain and an increased risk for CRC and a reduced risk with smoking cessation. But Dr. Botteri and colleagues could not find any published research on the association of other lifestyle factors and the risk for CRC specifically, they write.

To help fill this gap, they followed 295,865 people who participated in the European Prospective Investigation Into Cancer (EPIC) for a median of 7.8 years. The participants were mostly aged from 35 to 70 years and lived in Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom.

The researchers calculated a healthy lifestyle index (HLI) score on the basis of smoking status, alcohol consumption, body mass index, and physical activity. The median time between baseline and the follow-up questionnaire was 5.7 years.

They awarded points as indicated in the following table.

Participants' scores ranged from 0 to 16. At baseline, the mean HLI score was 10.04. It dipped slightly to 9.95 at follow-up.

Men had more favorable changes

Lifestyle · *Continued on following page*

Point system used to calculate healthy lifestyle index score

Smoking	Alcohol consumption	Physical activity*	BMI
Never smoked = 4	Less than 6.0 g/day = 4	Fifth quintile = 4	Less than 22 = 4
Stopped for more than 10 years = 3	6.0-11.9 g/day = 3	Fourth quintile = 3	22 to 23.9 = 3
Stopped for up to 10 years = 2	12.0-23.9 g/day = 2	Third quintile = 2	24 to 25.9 = 2
≤15 cigarettes per day = 1	24.0-59.9 g/day = 1	Second quintile = 1	26 to 29.9 = 1
>15 cigarettes per day = 0	≥60 g/day = 0	First quintile = 0	30 or higher = 0

*In metabolic equivalent tasks

Source: Am J Gastroenterol. 2022 Dec 2. doi: 10.14309/ajg.0000000000002065

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ADR · *Continued from previous page*

procedures directly related to higher polyp detection – specifically the P-ADR.

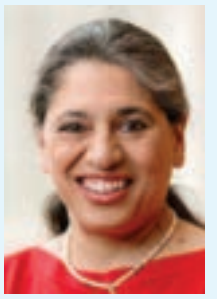
"Our data demonstrate that it is feasible to measure P-ADR in clinical practice," the authors wrote. "We propose that P-ADR be considered a quality metric for colonoscopy."

In addition, because of considerable variation in ADR based on age and sex, calculated ADR should be normalized by the age and sex of the specific patient profile of each endoscopist so relevant benchmarks can be established based on practice demographics, they wrote. For example, an endoscopist with a practice that includes predominantly younger women would have a different benchmark than a colleague with an older male population.

"With appropriate use of gender and age adjustments to ADR, endoscopists in need of further education and mentoring can be identified," they wrote.

The authors declared no funding for the study. One author reported advisory roles for several medical companies, and the remaining authors disclosed no conflicts.

"What gets measured gets managed" is a common mantra in quality improvement. Adenoma detection rate (ADR) is currently one measure of a "quality" colonoscopy and a metric that is studied to determine means for improvement. ADR is an imperfect measure as it does not necessarily reflect true risk of a postcolonoscopy cancer in all parts of the colon since many postcolonoscopy cancers are found in the proximal colon. To try to better understand potential differences in polyps found in different segments of the colon, and to determine if this was a metric that could be measured, Dr. Kosinski and colleagues studied a large claims database to understand the potential difference in ADR in the proximal versus distal colon.



Dr. Kane

Their main finding was that, with advancing age, the ADR for proximal lesions is far greater than for distal ones, especially after 60. They also found that experience of the colonoscopist as determined by the number of procedures performed made a difference in all forms of ADR. Given that proximal lesions tend to be more flat and potentially hard to see, it makes sense that experience is important. Determining an ADR for all parts of the colon rather than grouping it together makes sense since the pathology of polyps can differ based on location and is likely a metric that will find its way into the definition of acceptable colonoscopy practice.

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Lifestyle · *Continued from previous page*

than women, and the associations between the HLI score and CRC risk were statistically significant only among men.

Overall, a 1-unit increase in the HLI score was associated with a 3% lower risk for CRC.

When the HLI scores were grouped into tertiles, improvements from an "unfavorable lifestyle" (0-9) to a "favorable lifestyle" (12-16) were associated with a 23% lower risk for CRC (compared with no change). Likewise, a decline from a "favorable lifestyle" to an "unfavorable lifestyle" was associated with a 34% higher risk.

Changes in the BMI score from baseline showed a trend toward an association with CRC risk.

Decreases in alcohol consumption were significantly associated with a reduction in CRC risk among participants aged 55 years or younger at baseline.

Increases in physical activity were significantly associated with a lower risk for proximal colon cancer, especially in younger participants.

On the other hand, reductions in smoking were associated with an increase in CRC risk. This correlation might be the result of "inverse causation," the researchers note; that is, people may have quit smoking because they experienced early symptoms of CRC. Smoking had only a marginal influence on the HLI calculations in this study because only a small proportion of participants changed their smoking rates.

Information on diet was collected only at baseline, so changes in this factor could not be measured. The researchers adjusted their analysis for diet at baseline, but they acknowledge that their inability to incorporate diet into the HLI score was a limitation of the study.

Similarly, they used education as a marker of socioeconomic status but acknowledge that this is only a proxy.

"The HLI score may therefore not accurately capture the complex relationship between lifestyle habits and risk for CRC," they write.

If the results of this observational study are confirmed by other research, the findings could provide evidence to design intervention studies to prevent CRC.

Still, if the results of this observational study are confirmed by other research, the findings could provide evidence to design intervention studies to prevent CRC, they conclude.

The study was supported by the grant LIBERTY from the French Institut National du Cancer. Financial supporters of the national cohorts and the coordination of EPIC are listed in the published study. The researchers reported no relevant financial relationships.

Artificial intelligence applications in colonoscopy

In Focus
Brought To You By The New Gastroenterologist

BY EUGENIA N. UCHE-ANYA, MD, AND TYLER M. BERZIN, MD

Considerable advances in artificial intelligence (AI) and machine-learning (ML) methodologies have led to the emergence of promising tools in the field of gastrointestinal endoscopy. Computer vision is an application of AI/ML that has been successfully applied for the computer-aided detection (CADe) and computer-aided diagnosis (CADx) of colon polyps and numerous other conditions encountered during GI endoscopy. Outside of computer vision, a wide variety of other AI applications have been applied to gastroenterology, ranging from natural language processing (NLP) to optimize clinical documentation and endoscopy quality reporting to ML techniques that predict disease severity/treatment response and augment clinical decision-making. This article focuses on opportunities for AI applications in colonoscopy, reviews the existing data, describes the challenges limiting widespread adoption, and explores future directions.

Advances in deep learning and computer vision have led to the development of CADe systems that automatically detect polyps in real time during colonoscopy, resulting in reduced adenoma miss rates.

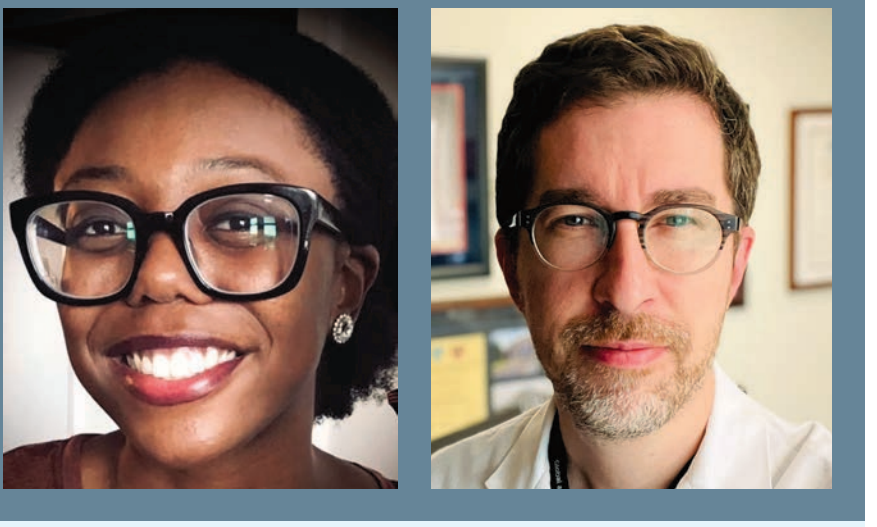
In the United States, colonoscopy is the standard for colon cancer screening and prevention; however, precancerous polyps can be missed for various reasons, ranging from subtle surface appearance of the polyp or location behind a colonic fold to operator-dependent reasons such as inadequate mucosal inspection. Though clinical practice guidelines have set adenoma detection rate (ADR) thresholds at 20% for women and 30% for men, studies have shown a 4- to 10-fold variation in ADR among physicians in clinical practice settings[1] with an estimated adenoma miss rate (AMR) of 25% and a false-negative colonoscopy rate of 12%.[2] Variability in adenoma detection affects the risk of interval colorectal cancer post colonoscopy.[3,4]

AI provides an opportunity for mitigating this risk. Advances in deep learning and computer vision have led to the development of CADe systems that automatically detect polyps in real time during colonoscopy, resulting in reduced adenoma miss rates (Table 1).
In addition to polyp detection, deep-learning technologies are also being used in CADx systems for polyp diagnosis and characterization of malignancy risk. This could aid therapeutic decision-making: Unnecessary resection or histopathologic analysis could be obviated for benign hyperplastic polyps. On the other end of the polyp spectrum, an AI tool that could predict the presence or absence of submucosal invasion could be a powerful tool when evaluating early colon cancers for consideration of endoscopic submucosal dissection vs. surgery. Examples of CADe polyp detection and CADx polyp characterization are shown in Figure 1.

Other potential computer vision applications that may improve colonoscopy quality include tools that help measure adequacy of mucosal exposure, segmental inspection time, and a variety of other parameters associated with polyp detection performance. These are promising areas for future research. Beyon d improving colonoscopy technique, natural-language processing tools already are being used to optimize clinical documentation as well as extract information from colonoscopy and pathology reports that can facilitate reporting of colonoscopy quality metrics such as ADR, cecal intubation rate, withdrawal time, and bowel preparation adequacy. AI-powered analytics may help unlock large-scale reporting of colonoscopy quality metrics on a health-systems level[5] or population level,[6] helping to ensure optimal performance and identifying avenues for colonoscopy quality improvement.

The majority of AI research in colonoscopy has focused on CADe for colon polyp detection and CADx for polyp diagnosis. Over the last few years, several randomized clinical trials – two in the United States – have shown that CADe significantly improves adenoma detection and reduces adenoma miss rates in comparison to standard colonoscopy. The existing data are s ummarized in Table 1, focusing on the two U.S. studies and an international meta-analysis.

In comparison, the data landscape for CADx is nascent and currently limited to several retrospective studies dating back to 2009 and a few prospective studies that have shown promising results.[10,11] There is an expectation that integrated CADx also may support the adoption of "resect and discard" or "diagnose and leave" strategies for low-risk polyps. About two-thirds of polyps identified on average-risk screening colonoscopies are diminutive polyps (less than 5 mm in size), which rarely have advanced histologic features (about 0.5%) and are sometimes nonneoplastic (30%). Malignancy risk is even lower in the distal colon.[12] As routine histopathologic assessment of such polyps is mostly of limited clinical utility and comes with added pathology costs, CADx technologies may offer a more



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Applications of artificial intelligence in gastroenterology and hepatology are vast, and investigators are seeking ways to enhance patient care and medical practice through emerging AI advances. The most developed AI systems in gastrointestinal endoscopy are applications of computer-aided detection and computer-aided diagnosis in colonoscopy.

In February's In Focus article, brought to you by The New Gastroenterologist, Dr. Eugenia N. Uche-Anya and Dr. Tyler M. Berzin review the evidence behind AI in colonoscopy, including how it can increase the adenoma detection rate, decrease unnecessary resection, and improve quality metrics analyses. They also highlight current obstacles to widespread adoption of AI in colonoscopy and discuss the future of AI in gastroenterology and hepatology.

Judy A. Trieu, MD, MPH
Editor in Chief
The New Gastroenterologist

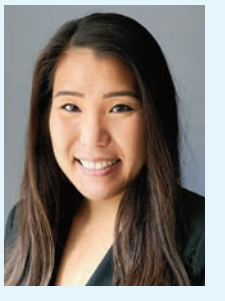

Table 1. Summary of current data for CADe in colonoscopy

Reference	Year	Country	Summary
Glissen Brown et al.[7]	2022	United States	Multicenter tandem screening or surveillance colonoscopy RCT in diverse population of 232 participants, randomized to colonoscopy with CADe first or standard colonoscopy first. The CADe-first group had a 35% reduction in AMR (P = .02) and an 83% reduction in sessile serrated lesion (SSL) miss rate. There was no statistically significant difference in miss rates when stratified by adenoma size.
Wallace et al.[8]	2022	United States, United Kingdom, Italy	Multicenter tandem screening or surveillance colonoscopy RCT with 230 participants randomized to colonoscopy with CADe first or standard colonoscopy first. The CADe-first group had a 52% reduction in AMR (P < .001). This was driven by increased detection of adenomas < 5 mm as there was no difference in miss rates for adenomas > 5 mm. Low prevalence of SSLs (< 3%) underpowered the study for assessment of SSL miss rate.
Hassan et al.[9]	2021	China, Italy	Metaanalysis of five moderate-quality RCTs with a total of 4,354 particpants. The CADe group had significantly higher pooled ADRs (25% vs. 36%), adenomas per colonoscopy regardless of size (except for advanced adenomas), and SSLs per colonoscopy.

MDedge News

Source: Dr. Uche-Anya, Dr. Berzin

cost-effective approach where polyps that are characterized in real time as low-risk adenomas or nonneoplastic are "resected and discarded" or "left in" respectively. In 2011, prior to the development of current AI tools, the American Society for Gastrointestinal Endoscopy set performance thresholds for technologies supporting real-time endoscopic assessment of the histology of diminutive colorectal polyps. The ASGE recommended 90% histopathologic concordance for "resect and discard" tools and 90% negative predictive value for adenomatous histology for "diagnose and leave," tools.[13] Narrow-band imaging (NBI), for example, has been shown to meet these benchmarks[14,15] with a modeling study suggesting that implementing "resect and discard" strategies with such tools could result in annual savings of $33 million without adversely affecting efficacy, although practical adoption has been limited.[16] More recent work has directly explored the feasibility of leveraging CADx to support "leave-in-situ" and "resect-and-discard" strategies.[17]

Similarly, while CADe use in colonoscopy is associated with additional up-front costs, a modeling study suggests that its associated gains in ADR (as detailed in Table 1) make it a cost-saving strategy for colorectal cancer prevention in the long term.[18] There is still uncertainty on whether the incremental CADe-associated gains in adenoma detection will necessarily translate to significant reductions in interval colorectal cancer risk, particularly for endoscopists who are already high-performing polyp detectors. A recent study suggests that, although higher ADRs were associated with lower rates of interval colorectal cancer, the gains in interval colorectal cancer risk reduction appeared to level off with ADRs above 35%-40% (this finding may be limited by statistical power).[19] Further, most of the data from CADe trials suggest that gains in adenoma detection are not driven by increased detection of advanced lesions with high malignancy risk but by small polyps with long latency periods of about 5-10 years, which may not significantly alter interval cancer risk. It remains to be determined whether adoption of CADe will have an impact on hard outcomes, most importantly interval colorectal cancer risk, or merely result in increased resource utilization without moving the needle on colorectal cancer prevention. To answer this question, the OperA study – a large-scale randomized clinical trial of 200,000 patients across 18 centers from 13 countries – was launched in 2022. It will investigate the effect of colonoscopy with CADe on a number of critical measures, including long-term interval colon cancer risk.[20]

Without mandatory requirements for ADR reporting or clinical practice guideline recommendations for CADe use, these systems may not be perceived as valuable or ready for prime time.

Despite commercial availability of regulatory-approved CADe systems and data supporting use for adenoma detection in colonoscopy, mainstream adoption in clinical practice has been sluggish. Physician survey studies have shown that, although there is considerable interest in integrating CADe into clinical practice, there are concerns about access, cost and reimbursement, integration into clinical work flow, increased procedural times, over-reliance on AI, and algorithmic bias leading to errors.[21,22] In addition, without mandatory requirements for ADR reporting or clinical practice guideline recommendations for CADe use, these systems may not be perceived as valuable or ready for prime time even though the evidence suggests otherwise.[23,24] For CADe systems to see widespread adoption in clinical practice, it is important that future research studies rigorously investigate and characterize these potential barriers to better inform strategies to address AI hesitancy and implementation challenges. Such efforts can provide an integration framework for future AI applications in gastroenterology beyond colonoscopy, such as CADe of esophageal and gastric premalignant lesions in upper endoscopy, CADx for pancreatic cysts and liver lesions on imaging, NLP tools to optimizing efficient clinical documentation and reporting, and many others. ■

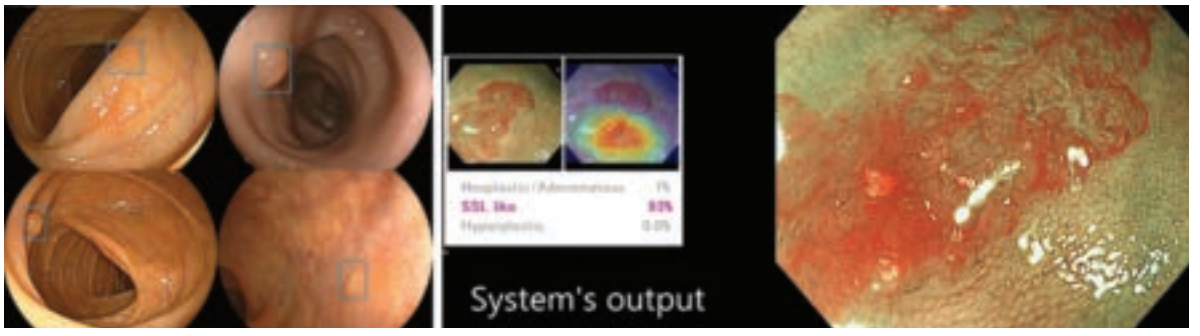

Figure 1. CADe colonic polyp detection is shown at left (source: Wision AI), and CADx real-time characterization of a colonic polyp is shown at right (source: Y. Mori and M. Misawa).

See references online at MDedge.com/gihepnews/new-gastroenterologist.

Non–heavy alcohol use tied to liver fibrosis, NASH

BY CAROLYN CRIST

Non–heavy alcohol use – fewer than 14 drinks per week for women and fewer than 21 drinks per week for men – is associated with liver fibrosis and nonalcoholic steatohepatitis (NASH), according to a new report.

An analysis of current drinkers in the Framingham Heart Study found that a higher number of drinks per week and a higher frequency of drinking were associated with increased odds of fibrosis among patients whose consumption fell below the threshold for heavy alcohol use.

"Although the detrimental effects of heavy alcohol use are well accepted, there is no consensus guideline on how to counsel patients about how non–heavy alcohol use may affect liver health," Brooke Rice, MD, an internal medicine resident at Boston University, said in an interview.

"Current terminology classifies fatty liver disease as either alcoholic or nonalcoholic," she said. "Our results call this strict categorization into question, suggesting that even non–heavy alcohol use should be considered as a factor contributing to more advanced nonalcoholic fatty liver disease [NAFLD] phenotypes."

The study was published online in Clinical Gastroenterology and Hepatology (2022 Dec 7. doi: 10.1016/j.cgh.2022.10.039).

Analyzing associations

NAFLD and alcohol-related liver disease, which are the most common causes of chronic liver disease worldwide, are histologically identical but distinguished by the presence of significant alcohol use, the study authors wrote.

Heavy alcohol use, based on guidelines from the American Association for the Study of Liver Diseases, is defined as more than 14 drinks per week for women or more than 21 drinks per week for men.

Although heavy alcohol use is consistently associated with cirrhosis and steatohepatitis, studies of non–heavy alcohol use have shown conflicting results, the authors wrote. However, evidence suggests that the pattern of alcohol consumption – particularly increased weekly drinking and binge drinking – may be an important predictor.

Dr. Rice and colleagues conducted a cross-sectional study of 2,629 current drinkers in the Framingham Heart Study who completed alcohol-use questionnaires and vibration-controlled transient elastography between April 2016 and April 2019. They analyzed the association between fibrosis and several alcohol-use measures, including total consumption and drinking patterns, among non–heavy alcohol users whose liver disease would be classified as "nonalcoholic" by current nomenclature.

MARIA EKLIND/WIKIMEDIA

The research team defined clinically significant fibrosis as a liver stiffness measurement of 8.2 kPa or higher. For at-risk NASH, the researchers used two FibroScan-AST (FAST) score thresholds – greater than 0.35 or 0.67 and higher. They also considered additional metabolic factors such as physical activity, body mass index, blood pressure, glucose measures, and metabolic syndrome.

Participants were asked to estimate the frequency of alcohol use (average number of drinking days per week during the past year) and the usual quantity of alcohol consumed (average number of drinks on a typical drinking day during the past year). Researchers multiplied the figures to estimate the average total number of drinks per week.

Among the 2,629 current drinkers (53% women, 47% men), the average age was 54 years, 7.2% had diabetes, and 26.9% met the criteria for metabolic syndrome. Participants drank about 3 days per week on average with a usual consumption of two drinks per drinking day, averaging a total weekly alcohol consumption of six drinks.

The average liver stiffness measurement was 5.6 kPa, and 8.2% had significant fibrosis.

At the FAST score threshold of 0.67 or greater, 1.9% of participants were likely to have at-risk NASH, with a higher prevalence in those with obesity (4.5%) or diabetes (9.5%). At the FAST score threshold of greater than 0.35, the prevalence of at-risk NASH was 12.4%, which was higher in those with obesity (26.3%) or diabetes (34.4%).

Overall, an increased total number of drinks per week and higher frequency of drinking days were associated with increased odds of fibrosis.

Almost 17.5% of participants engaged in risky weekly drinking, which was defined as 8 or more drinks per week for women and 15 or more drinks per week for men. Risky weekly drinking was also associated with higher odds of fibrosis.

After exclusion of 158 heavy drinkers, the prevalence of fibrosis was unchanged at 8%, and an increased total of drinks per week remained significantly associated with fibrosis.

In addition, multiple alcohol-use measures were positively associated with a FAST score greater than 0.35 and were similar after excluding heavy alcohol users. These measures include the number of drinks per week, the frequency of drinking days, and binge drinking.

"We showed that nonheavy alcohol use is associated with fibrosis and at-risk NASH, which are both predictors of long-term liver-related morbidity and mortality," Dr. Rice said.

Implications for patient care

The findings have important implications for both NAFLD clinical trials and patient care, the study authors wrote. For instance, the U.S. Dietary Guidelines for Americans recommend limiting alcohol use to one drink per day for women and two drinks per day for men.

"Our results reinforce the importance of encouraging all patients to reduce alcohol intake as much as possible and to at least adhere to current U.S. Dietary Guidelines recommended limits," Dr. Rice said. "Almost half of participants in our study consumed in excess of these limits, which strongly associated with at-risk NASH."

Additional long-term studies are needed to determine the benefits of limiting alcohol consumption to reduce liver-related morbidity and mortality, the authors wrote.

The effect of alcohol consumption on liver health "has been controversial, since some studies have suggested that non–heavy alcohol use can even have some beneficial metabolic effects and has been associated with reduced risk of fatty liver disease, while other studies have found that non–heavy alcohol use is associated with increased risk for liver-related clinical outcomes," Fredrik Åberg, MD, PhD, a hepatologist and liver transplant specialist at Helsinki University Hospital, said in an interview.

Dr. Åberg wasn't involved with this study but has researched alcohol consumption and liver disease. Among non–heavy alcohol users, drinking more alcohol per week is associated with increased hospitalization for liver disease, hepatocellular carcinoma, and liver-related death, he and his colleagues have found.

"We concluded that the net effect of non–heavy drinking on the liver is harm," he said. "Overall, this study by Rice and colleagues supports the recommendation that persons with mild liver disease should reduce their drinking, and persons with severe liver disease (cirrhosis and advanced fibrosis) should abstain from alcohol use."

The study authors are supported in part by the National Institute of Diabetes and Digestive and Kidney Diseases, a Doris Duke Charitable Foundation Grant, a Gilead Sciences Research Scholars Award, the Boston University Department of Medicine Career Investment Award, and the Boston University Clinical Translational Science Institute. The Framingham Heart Study is supported in part by the National Heart, Lung, and Blood Institute. The authors and Dr. Åberg reported no relevant financial relationships. ■

A bold national plan to eliminate HCV by 2050

BY NEIL OSTERWEIL

WASHINGTON – "We don't get to use the 'eliminate' word all that often with a disease that's taking thousands or tens of thousands – or worldwide, hundreds of thousands – of lives every year, but we have that opportunity with hepatitis C."

So said Francis S. Collins, MD, PhD, special projects adviser to the Executive Office of the President of the United States, and former director of the National Institutes of Health, speaking at a special session outlining ambitious goals for a national plan to eliminate hepatitis C virus (HCV) infections by the year 2050.

The session was held at the annual meeting of the American Association for the Study of Liver Diseases.

A public health crisis

Dr. Collins labeled HCV a public health crisis, citing statistics from the Centers for Disease Control and Prevention that show that the rate of reported acute HCV infection cases increased 400% between 2010 and 2020, with the highest rates among young adults aged 20-39 years.

In addition, an estimated 2.4 million people in the United States are living with chronic HCV infections, but as many as 40% of these people are unaware of their infection, despite broad recommendations for the screening of all adults aged 18 years and older, he said.

"Our goal is to try to do something to change this," Dr. Collins said. He noted that for the past 8 years we have had highly effective oral agents that don't just treat the disease but cure it – 95%-97% of the time, with only 8-12 weeks of oral therapy and relatively few side effects.

"A wonderful story, one of the most exciting stories that's come out of biomedical research in the last couple of decades," he said.

Yet Dr. Collins also acknowledged that the task of developing a national plan is daunting, despite that pharmaceutical triumph.

National pharmacy claims data show that the number of persons treated for HCV with direct-acting antiviral agents (DAAs) in the United States declined from a high of 164,247 in 2015 to 83,740 in 2020.

Furthermore, CDC data from 2019 and 2020 show that, of persons with a diagnosis of HCV infection, only 23% of those on Medicaid, 28% of those on Medicare, and 35% of those with private insurance were treated for their infections.

"We have a huge gap here between the ability to know you have the disease and to get treatment, and we don't see the numbers here for the uninsured, or people in prisons, but they're probably much worse," he said.

Obstacles abound, as do ways to overcome them

Current barriers to treatment include the aforementioned lack of awareness of infection, a "clunky" two-step diagnosis requiring an antibody test followed by an RNA or core antigen test necessitating three visits often separated by several weeks, and the high cost of treatment (around $90,000 per patient).

In addition, insurers commonly require proof that patients remain sober for extended periods, insist that treatment monitoring be

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performed by specialists only, and often approve treatment only for those patients who have documented evidence of liver damage.

"Does that make sense to you?" Dr. Collins asked. "You've got a cure for a liver disease, and you have to wait and show that the liver's been damaged before you receive it? That just doesn't fit," he said.

Dr. Collins also pointed out that we're dealing with hard-to-reach populations (underserved, uninsured, justice-involved), and people who are in tough times. "Anything that you put in the way as a barrier is going to make this worse in terms of its ability to be implemented," he said.

To demonstrate how a coordinated HCV-elimination program could work, Dr. Collins pointed to a Medicaid cohort study in Louisiana conducted from July 2019 through December 2021, in which 8,867 patients started on therapy, 7,763 (88%) completed therapy, and 5,882 (66%) returned for testing. Of those tested, 5,285 (90%) had sustained virologic responses.

"You've got a cure for a liver disease, and you have to wait and show that the liver's been damaged before you receive it? That just doesn't fit."

Another model of a hepatitis C–elimination program was provided by the Veterans Health Administration. They received funding for an effort for all veterans, and in the space of 7 years were able to reach out even to some of their difficult-to-reach populations and achieve high diagnosis and treatment rates in a way that could be a model for what we would want to do across the nation, Dr. Collins noted.

Doing the math

Also at the session, Jagpreet Chhatwal, PhD, director of the Massachusetts General Hospital Institute for Technology Assessment and associate professor of radiology at Harvard Medical School, Boston, described outcomes projected by a mathematical simulation model of the HCV epidemic that he and his colleagues developed.

The HEP-SIM (Hepatitis C Disease Burden Simulation) model evaluates HCV prevalence trends, the number needed to screen and treat to eliminate HCV, HCV-associated clinical outcomes, the cost of an elimination program, and the cost savings that could be realized from preventing long-term complications.

The model seeks to determine whether the up-front costs of a national HCV-elimination program could be offset by savings down the road. Specifically, it assumes that within the next 5 years 1.31 million individuals would be diagnosed with HCV and projects that within that time frame 1.52 million would need to be treated to meet HCV-elimination goals. The model shows that, compared with the status quo, a concerted campaign of screening and treatment would prevent more than 10,000 HCV-related deaths by 2030, and 91,000 deaths by 2050.

A coordinated screening program is also projected to prevent 17,000 cases of hepatocellular carcinoma by 2030 and 108,000 cases by 2050, as well as avert 29,000 cases of decompensated cirrhosis by 2030 and

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CLINICAL CHALLENGES AND IMAGES

The diagnosis

Answer to 'What's your diagnosis?' on page 7: Blue rubber bleb nevus syndrome

Based on the history of hemangioma resection and vascular lesions in the small intestine, along with typical manifestations of chronic gastrointestinal bleeding, diagnosis of blue rubber bleb nevus syndrome (BRBNS) was made. According to an American College of Gastroenterology Clinical Guideline,[1] for patients with recurrence of small-bowel bleeding, endoscopic management could be considered depending on the patient's clinical course and response to prior therapy. Consequently, injections of lauromacrogol with SBE (single-balloon enteroscopy) were given (Figure D). Lesions that ranged from 1 to 2 cm were injected with 1-2 mL lauromacrogol until the mucosa turned white. Three SBEs had been performed in a 5-month period. A total of 20 lesions were successfully treated with lauromacrogol. The treated hemangiomas became small, and the site healed 5 months after treatment (Figures E and F). The patient has been followed for 1 year, and he remains in good clinical condition with his latest hemoglobin level at 110 g/L. No further blood transfusion is needed.

BRBNS is a rare disorder characterized by discrete venous malformations of varying size and appearance that are present on the skin and within the gastrointestinal tract.[2]

With wider application of video capsule endoscopy and the increase of image resolution, the detection rate and diagnostic accuracy of BRBNS are significantly improved. Treatment of BRBNS varies depending on the site, size, and number of lesions. Medication, surgery, and endoscopic therapy are currently clinically applied. The successful use of sirolimus was recently reported in the treatment of vascular lesions.[3]

Sirolimus has potential adverse effects on renal function, bone marrow, and cholesterol metabolism, however. In consideration of the patient's young age, we did not adopt this method. Surgical resection is more suitable for limited or life-threatening lesions. The lesions in this patient were mild and sporadic. Consequently, in this case, endoscopic injection of lauromacrogol was performed. This was the most complicated case of endoscopic treatment of BRBNS in our center and proved lauromacrogol injection was a feasible approach. According to a literature review, lauromacrogol has been used to treat vascular lesions for decades, but there is still no standard instruction for the dosage of lauromacrogol. We hope that our experience can be a reference for the endoscopic treatment of BRBNS. ■

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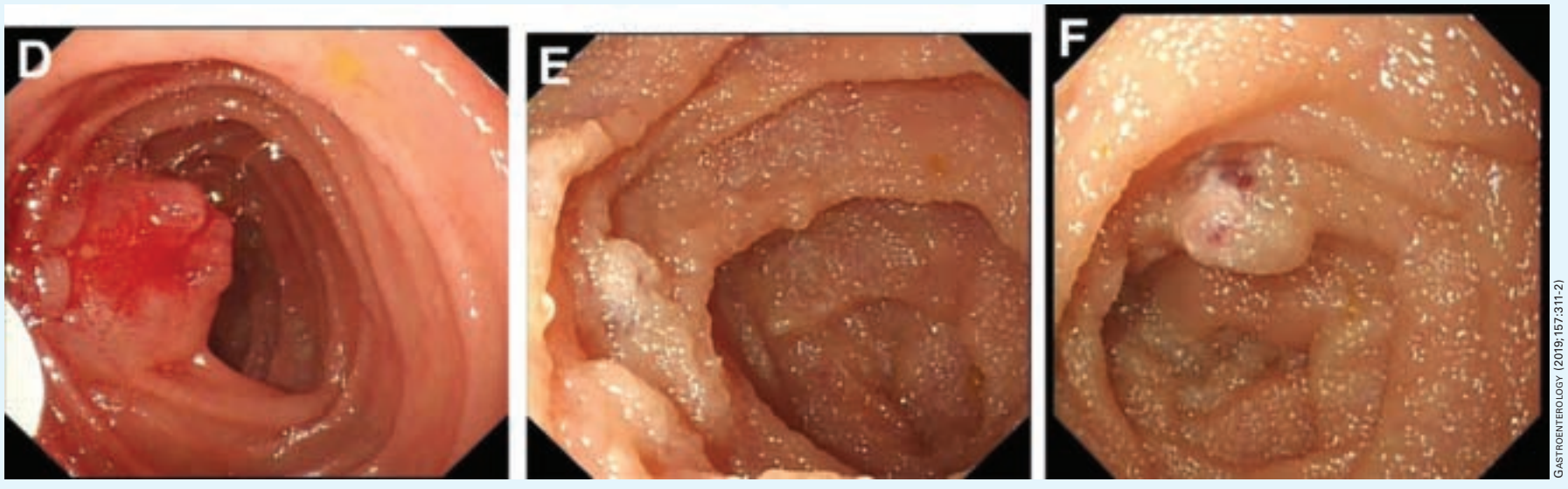

GASTROENTEROLOGY (2019;157:311-2)

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93,000 such cases by 2050.

The cost savings associated with an HCV-elimination plan would also be substantial, Dr. Chhatwal said.

According to the model, over the next decade the cumulative costs associated with HCV would decline by $14.2 billion, compared with the status quo. Nearly 80% of those savings ($11.2 billion) would be in Medicare and Medicaid.

The total projected savings from 2024 through 2050 – in disease management, testing, treatment, and pragmatic costs – are estimated at $59.3 billion, Dr. Chhatwal said.

"This is unprecedented," he said. "We're not just eliminating a disease as a public health threat but also saving money, which is not a common thing. That gives us a lot of impetus to implement such a program."

Getting it done

Rachael L. Fleurence, PhD, MSc, a health economist currently serving as a senior adviser in the Executive Office of the President, summarized efforts to build a national HCV-elimination program with input from federal health care agencies, state health leaders, patients, advocacy groups, drug manufacturers, and insurers.

She noted that a large component and focus of the program will be working on diagnostic test development but also accelerating bringing tests into the United States that are currently unavailable here. "These include point-of-care RNA diagnostic tests, as well as core antigen laboratory tests," she said.

The program will be designed to offer broad access to curative anti-HCV drugs through a national subscription model that would make DAAs available to Medicaid recipients, justice-involved populations, the uninsured, and American Indians and Alaskan Natives who receive care through the Indian Health Service.

"On the Medicare and commercial insurance fronts, we're still exploring different approaches, including potentially a co-pay assistance for Medicare beneficiaries, as well as working with commercial insurers to reduce barriers to access," she said.

The program would also involve screening strategies extending to more settings, especially for high-risk populations, expanding the number of providers allowed to screen and treat HCV infections through telehealth, ensuring incentives for providers, and increasing the number of community health workers and case workers to improve linkage to care.

The next steps for the program would include funding to support the NIH's RADx diagnostics program to accelerate access to testing, planning for the subscription model for DAA purchase, and launching pilot programs with the CDC, the Health Resources & Services Administration, the Substance Abuse and Mental Health Services Administration, and the Indian Health Service.

Dr. Collins ended this portion of the program with an exhortation to AASLD members to do their part.

"We need your help," Dr. Collins said. "This is a bold initiative, but it's an opportunity. It's even a responsibility. If we can actually succeed at this kind of outreach and save lives, and at the same time save money, how can we not do that?"

Dr. Collins, Dr. Chhatwal, and Dr. Fleurence each reported having no financial conflicts. ■

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