GI&Hepatology News

Liquid Biopsy for CRC Appears Promising, But Still Lacks Robust Efficacy
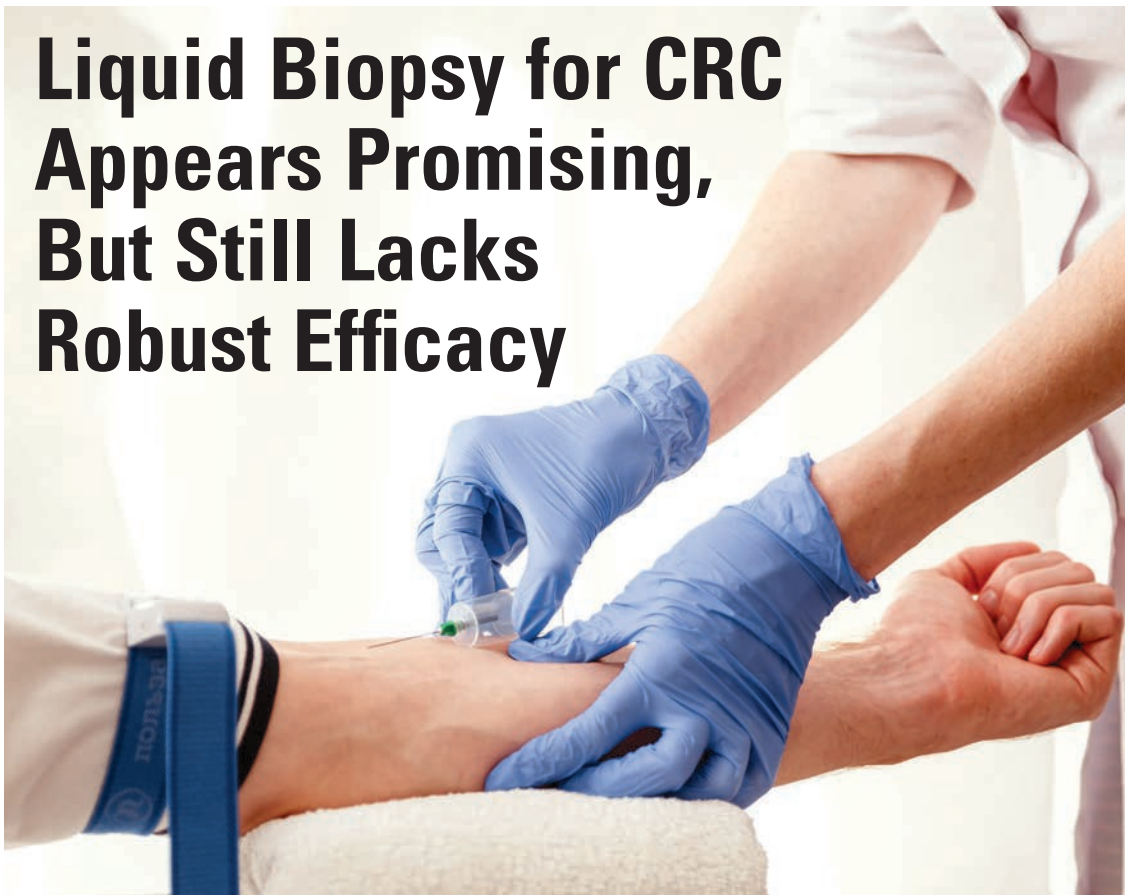
VLADDEEP/ISTOCK/GETTY IMAGES

BY CAROLYN CRIST
MDedge News

Blood-based screening for colorectal cancer (CRC), also known as a "liquid biopsy," may be better than nothing among patients who skip established screening tests, but it can't replace colonoscopy as the gold standard, according to two new modeling studies and an expert consensus commentary.

Although some patients find blood-based tests more convenient, the higher numbers of false positives and false negatives could lead to more CRC cases and deaths.

"Based on their current characteristics, blood tests should not be recommended to replace established colorectal cancer screening tests, since blood tests are neither as effective nor cost-effective and would worsen outcomes," David Lieberman, MD, AGAF, chair of the American Gastroenterological Association's CRC Workshop Panel, and lead author of the expert commentary, said in a statement.

The blood tests detect circulating nucleotides, such as cell-free DNA or metabolic products associated with CRC and its precursors. Current tests are in development by

FDA Approves First Drug for MASH

Oral med is a 'true game-changer'

BY MEGAN BROOKS

The US Food and Drug Administration (FDA) has approved resmetirom (Rezdiffra, Madrigal Pharmaceuticals), the first drug to treat patients with metabolic dysfunction–associated steatohepatitis (MASH) and moderate to advanced liver fibrosis (consistent with stage F2 and F3 disease), along with diet and exercise.

Resmetirom is a once-daily, oral thyroid hormone receptor beta-selective agonist. The FDA granted the drug breakthrough therapy designation and priority review.

The approval is based on the phase 3 MAESTRO-NASH trial, in which resmetirom was superior to placebo at achieving resolution of nonalcoholic steatohepatitis (NASH) and improving liver fibrosis in both 80-mg and 100-mg doses.

The trial used the earlier nomenclature of NASH and nonalcoholic fatty liver disease (NAFLD). An international consensus group has since changed these terms to MASH and metabolic dysfunction–associated steatotic liver disease (MASLD), respectively. (Note that the terms NASH and NAFLD will be used to discuss the trial results in this article to align with the trial's original language.)

The results were published online in *The New England Journal of Medicine* (doi: 10.1056/NEJMoa2309000).

"The approval of the first medication for NASH is a true game-changer for healthcare providers, the research community and, most importantly, patients

For more coverage of CRC screening, see these 2 stories inside:

P. **21** - Cell-Free DNA Blood Test Developed for Detecting Colorectal Cancer

P. **22** - Next-Gen CRC Stool Test Beats FIT for Sensitivity

LETTER FROM THE EDITOR

Converging on Our Nation's Capital

R elease of our May issue coincides with our annual pilgrimage to Digestive Disease Week® (DDW), this year held in our nation's capital of Washington, D.C.

As we peruse the preliminary program in planning our meeting coverage, I am always amazed at the breadth and depth of programming offered as part of a relatively brief, 4-day meeting — this is a testament to the hard work of the AGA Council and DDW organizing committees, who have the gargantuan task of ensuring an engaging, seamless meeting each year.

Dr. Adams

This year's conference features over 400 original scientific sessions and 4,300 oral abstract and poster presentations, in addition to the always well-attended AGA Postgraduate Course. This year's AGA Presidential Plenary, which will feature a series of thought-provoking panel discussions on the future of GI healthcare and innovations in how we treat, disseminate, and teach, also is not to be missed.

Beyond DDW, I hope you will join me in taking advantage of some of D.C.'s amazing cultural offerings, including the Smithsonian museums, National Gallery, Kennedy Center for the Performing Arts, and many others.

In this month's issue of *GIHN*, we highlight an important AGA expert consensus commentary published in *Clinical Gastroenterology and Hepatology* examining the role of blood-based tests ("liquid biopsy") in colorectal cancer screening. This guidance, which recognizes the promise of such tests but also urges caution in their adoption, is particularly important considering recently published data from the ECLIPSE study (also covered in this issue) evaluating the performance of Guardant's ctDNA liquid biopsy compared to a screening colonoscopy. Also relevant to CRC screening, we highlight data on the performance of the "next gen" Cologuard test compared with FIT, which was recently published in the *New England Journal of Medicine*.

In our May Member Spotlight, we feature gastroenterologist Adjoa Anyane-Yeboa, MD, MPH, who shares her passion for addressing barriers to CRC screening for Black patients. Finally, *GIHN* Associate Editor Dr. Avi Ketwaroo introduces our quarterly Perspectives column highlighting emerging applications of AI in GI endoscopy and hepatology. We hope you enjoy all the exciting content featured in this issue and look forward to seeing you in Washington, D.C. (or virtually) for DDW.

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

MJ0007/Thinkstock

GI Doc Aims to Lift Barriers to CRC Screening for Black Patients

BY JENNIFER LUBELL
MDedge News

In gastroenterology, a good bedside manner is a vital attribute. Visiting with an anxious patient before a colonoscopy, Adjoa Anyane-Yeboa, MD, MPH, knew what to say to calm him down.

"I could tell he was really nervous about the procedure, even though he wasn't letting on," said Dr. Anyane-Yeboa, a gastroenterologist with Massachusetts General Hospital in Boston. She put him at ease by cracking jokes and making him smile during the consent process. After it was over, he thanked her for making him feel more comfortable.

"I will have it done again, and I'll come back to you next time," said the patient.

GI doctors perform colonoscopies all day, every day, "so we sometimes forget how nervous people are. But it's nice to be able to connect with people and put them at ease," she said.

Interacting with patients gives her joy. Addressing health disparities is her long-term goal. Dr. Anyane-Yeboa's research has focused on the barriers to colorectal cancer screening in the Black population, as well as disparities in inflammatory bowel disease (IBD).

"I think there's a lot that still needs to be done around colorectal cancer screening," she said.

In an interview, she talks more in depth about her research and ongoing work to increase public knowledge and awareness about colorectal cancer (CRC) screening.

Q: Why did you choose GI?

Dr. Anyane-Yeboa: When I got to residency, GI was the rotation that was the most fun. I was the most excited to read about it, the most excited to go to work the next day.

I remember people saying, "You should look at the people who are in the field and look at their personalities, and then think about which personalities match you best." In residency I considered hematology, cardiology, and GI. The cardiologists were so serious, so intense, talking about research methods all the time. Whereas, the GI folks were joking, laughing, making fart jokes. I felt like these were my

Dr. Adjoa Anyane-Yeboa

people, lighthearted and easy-going. And I genuinely enjoyed going to work every day and learning about the disorders of the GI tract. I still do to this day.

Q: Let's discuss your research with IBD in Black populations and colorectal cancer screening.

Dr. Anyane-Yeboa: My two main areas of work are in IBD and minority populations, predominantly Black populations, and in colorectal cancer screening in minority populations, and again, mostly in historically marginalized populations.

With colon cancer, we know that there are disparities with incidence in mortality. Black individuals have had the second highest incidence in mortality from colorectal cancer. For me, being a Black female physician and seeing people who look like me, time and time again, being diagnosed with colorectal cancer and dying is really what drives me, because in GI, colon cancer screening is our bread and butter.

Some of the work that I'm doing now around colorectal cancer is in predominantly Black community health centers, working on increasing colorectal cancer screening rates in this population, and figuring out what the barriers are to screening and how we can address them, and what are some strategies that will work in a health center setting to get people screened.

Q: One study of yours surveyed unscreened Black individuals age ≥ 45 and found age-specific barriers

to CRC screening in this population, as well as a lack of targeted messaging to incentivize screening.

Dr. Anyane-Yeboa: That mixed method study (Cancer Med. 2023 Sep. doi: 10.1002/cam4.6461) was done in partnership with the National Colorectal Cancer Roundtable and American Cancer Society.

In that study, we found that the most common barrier to screening was self-procrastination or delay of screening, meaning, "I'm going to get screened, just not right now." It's not a priority. What was unique about this is we looked at it from age breakdown, so 45-49, 50-54, 55-plus. With the younger 45-49 group, we don't know as much about how to get them screened. We also saw that healthcare providers weren't starting conversations about screening with these younger newly eligible patients.

We also described effective messages to get people screened in that paper as well.

Q: What changes would you like to see going forward with screening? What still needs to happen?

Dr. Anyane-Yeboa: In some of the other work that I've done, particularly with the health centers and younger populations interviewed in focus groups, I'm seeing that those who are younger don't really know much about colorectal cancer screening. Those who do know about it have seen commercials about popular stool-based testing

brands, and that's how they've learned about screening.

What I would like to see is ways to increase the knowledge and awareness about colorectal cancer screening and colorectal cancer on a broad scale, on a more national, public-facing scale. Because I'm realizing that if they're healthy young folks who aren't going to the physician, who don't have a primary care provider, then they might not even really hear about colorectal cancer screening. We need ways to educate the general public so individuals can advocate for themselves around screening.

I also want to see more providers discussing screening with all patients, starting from those 45-49, and younger if they have a family history. Providers should screen every single patient that they see. We know that every single person should be screened at 45 and older, and not all providers, surprisingly, are discussing it with their patients.

Q: When you're not being a GI, how do you spend your free weekend afternoons?

Dr. Anyane-Yeboa: Saturday morning is my favorite time of the week. I'm either catching up on my TV shows, or I might be on a walk with my dog, particularly in the afternoon. I live near an arboretum, so I usually walk through there on the weekend afternoons. I also might be trying out a new restaurant with my friends. I love traveling, so I might also be sightseeing in another country. ∎

LIGHTNING ROUND

Texting or talking?
Texting

Favorite junk food?
Cookies

Cat or dog person?
Both; love cats, have a dog

If you weren't a gastroenterologist, what would you be?
Fashion boutique owner

Best place you've traveled to?
Morocco

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

Favorite ice cream?
Don't eat ice cream, only cookies

Favorite sport?
Tennis

Optimist or pessimist?
Optimist (glass half full)

Power-Washing Moves Beyond Home Improvement, Into Gastroenterology

BY WILL PASS

MDedge News

FROM TECHNIQUES AND INNOVATIONS IN GASTROINTESTINAL ENDOSCOPY

Power-washing is no longer just for blasting grimy driveways and stripping flaky paint. It's good for work inside the gut, too.

In a proof-of-concept study, a "novel systematically directed high-pressure liquid spray," delivered via the ERBEJET flexible probe, showed promise for collecting cytology specimens from the stomachs of patients undergoing endoscopy for gastric cancer screening or surveillance, reported lead author Charles J. Lightdale, MD, of Columbia University Irving Medical Center, New York City, and colleagues.

"Systematic random biopsies (updated Sydney protocol) have been recommended to increase detection of gastric intestinal metaplasia (GIM) and dysplasia," the investigators wrote in *Techniques and Innovations in Gastrointestinal Endoscopy* (2024 Jan 8. doi: 10.1016/j.tige.2023.12.009). "However, random biopsies can be laborious, time consuming, costly, and susceptible to sampling error owing to the large surface area of the stomach."

Dr. Lightdale

Power-washing, in contrast, with the pressure dial turned to 10 bar, involves spraying the gut in a systematic fashion "using sweeping and painting motions" to dislodge cells from the mucosa. These specimens are then suctioned from the resultant pools of liquid, mixed 1:1 with 10% formalin, and shipped to the lab.

Boom! Cytology!

Just to be sure, however, the nine patients involved in the study also underwent standard-of-care biopsy collection from areas of interest, followed by random sampling according to the updated Sydney protocol. Two of the patients were power-washed again 12 months later for endoscopic surveillance.

Power-washing added 7-10 minutes to standard endoscopy time and generated 60-100 mL of liquid for collection. Post suction, a closer look at the gastric mucosa revealed "scattered superficial erosions," while blood loss was deemed "minimal." The procedure appeared well tolerated, with no aspiration or esophageal reflux during endoscopy, or adverse events reported by patients after 1 week of follow-up.

Cytopathology samples were deemed satisfactory and yielded "multiple strips and large clusters of cells." These were sufficient to diagnose GIM in three patients and reactive glandular changes with inflammation in one patient, with findings confirmed on biopsy. In contrast, the power-washed cells from one patient were "highly suspicious" for dysplasia, but biopsies were negative.

Although the study was too small for a reliable comparison with the Sydney protocol, Dr. Lightdale and colleagues concluded that the power-wash approach deserves further investigation.

"Use of power-wash to obtain cytology has the potential to improve endoscopic screening and surveillance protocols for detecting GIM and dysplasia and to reduce morbidity and mortality from gastric cancer," they wrote.

The investigators predicted that power-washing is likely safe in most patients, although it may be unsuitable for those with non-correctable coagulopathies or in patients who cannot stop anticoagulants. Postsurgical patients, on the other hand, should tolerate the procedure just fine.

Patients with risk of gastric cancer "might be an important group" for evaluating the power-wash procedure, the investigators wrote,

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Impact of the AGA Research Foundation

The AGA Research Foundation, the charitable arm of the American Gastroenterological Association (AGA), plays an important role in medical research by providing grants to young scientists at a critical time in their career. The AGA Research Foundation's mission is to raise funds to support young researchers in gastroenterology and hepatology.

The research program of the AGA has had an important impact on digestive disease research for the last 30 years. Ninety percent of investigators who received an AGA Research Scholar Award over the past 10 years have stayed in gastroenterology and hepatology research.

AGA grants have led to discoveries, including new approaches to down-regulate intestinal inflammation, a test for genetic predisposition to colon cancer, and autoimmune liver disease treatments. The importance of these awards is evidenced by the fact that virtually every major advance leading to the understanding, prevention, treatment, and cure of digestive diseases has been made in the research laboratory of a talented young investigator.

At a time when funds from the National Institutes of Health and other traditional sources of support are in decline, the AGA Research Foundation is committed and ready to support young investigators and fund discoveries that will continue to improve GI practice and better patient care.

The AGA Research Foundation provides a key source of funding at a critical juncture in a young researcher's career. By joining AGA members and donors in donating to the AGA Research Foundation, you will ensure that researchers have opportunities to continue their life-saving work. ∎

See how the AGA Research Foundation has helped make significant strides in advancing the treatment and cure of digestive diseases. Visit www.foundation.gastro.org.

IBD: Histologic Inflammation Linked With Lower Female Fertility

BY WILL PASS

MDedge News

FROM GASTROENTEROLOGY

Histologic inflammation in women with inflammatory bowel disease (IBD) may lead to reduced fertility, according to a Swedish nationwide cohort study.

Reduced fertility was linked with histologic inflammation even in the absence of clinical disease activity, highlighting the importance of achieving deep remission in women planning pregnancy, reported lead author Karl Mårild, MD, PhD, of Sahlgrenska Academy, Gothenburg, Sweden, and colleagues.

Dr. Mårild

"Reduced female fertility (ie, number of live births) is believed to be primarily confined to women with clinically active IBD, especially in Crohn's disease (CD), where symptoms may inhibit sexual activity, and inflammation may affect the fallopian tubes and ovaries," the investigators wrote in *Gastroenterology* (2024 Feb 6. doi: 10.1053/j.gastro.2024.01.018). "Despite the increasing appreciation of histologic activity in IBD, its association with female fertility has not been clarified, including whether histologic activity in the absence of clinical disease activity impairs fertility."

Dr. Mårild and colleagues aimed to address this knowledge gap by analyzing fertility rates and histologic inflammation or IBD activity in two cohorts of women with IBD aged 15-44 years. The first group included approximately 21,000 women with and without histologic inflammation from 1990 to 2016. The second group included approximately 25,000 women with or without IBD clinical activity from 2006 to 2020. In each group, the relationship between fertility and IBD was compared with fertility in matched general population comparator individuals.

The importance of controlling inflammation to ensure a healthy pregnancy cannot be overstated. With regard to fertility, the literature has emphasized that surgery has been the major risk factor for decreasing fertility in both ulcerative colitis and Crohn's disease. Disease activity has been more influential on Crohn's disease versus ulcerative colitis. Other factors such as voluntary childlessness, premature ovarian failure, and malnutrition can also play a role. There have been data to show that anti–tumor necrosis factor use increases the chances of successful implantation for women with sub-fertility who do not have concomitant IBD, perhaps by decreasing inflammation in the pelvis.

Histologic activity has recently become the ultimate therapeutic goal. Up until now this has not been studied in the context of fertility. We know that clinical disease indices do not necessarily correlate with endoscopic appearance, and when trying to optimize pregnancy outcomes it might behoove us to know what our goal is — absence of clinical, endoscopic, or histologic inflammation. However, perfection might be the enemy of good: One fewer child per 14 women with 10 years of histologic inflammation is hard to put into clinical context. I think these results are important to again emphasize that we should not stop therapy in the preconception period, with a goal of controlling as much inflammation as possible. Perhaps the best way to use these data are to counsel women with unsuccessful attempts at pregnancy and, in the absence of any other factors, that more aggressive treatment of inflammation is appropriate.

Dr. Kane

Sunanda Kane, MD, MSPH, AGAF, is based in the Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota. She reports serving as a consultant to Boehringer Ingelheim, Bristol Myers Squibb, Fresenius Kabi, Gilead, Janssen, and Takeda. She is also Section Editor for IBD for UptoDate.

This approach showed that clinical IBD activity was associated with an adjusted fertility rate ratio (aFRR) of 0.76 (95% CI, 0.72-0.79), which equates to one fewer child per six women with 10 years of clinical activity. Impacts on fertility were similar for ulcerative colitis (UC) (aFRR, 0.75) and CD (aFRR, 0.76).

"Fertility rates were notably reduced during

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noting that combining the approach with artificial intelligence could one day yield even better results.

In the meantime, Dr. Lightdale and colleagues — like so many weekend warriors wielding a power-washer — are going to see if a different nozzle will take their work to the next level.

"We are actively studying a catheter with a broader stream and the potential to increase efficiency and decrease procedure time," they wrote. "Another catheter design might allow for simultaneous spray and suction, so that cytology samples from specific regions of the stomach could be separately analyzed."

This study was funded by Dalio Philanthropies, the Price Family Foundation, and the Frederic and Patricia Salerno Foundation. The investigators disclosed relationships with Boston Scientific, Interscope, Medtronic, and others. ∎

The optimal surveillance endoscopic modality for gastric intestinal metaplasia (GIM) is yet to be determined. Although the updated Sydney System, a comprehensive endoscopic biopsy protocol, has been advocated for GIM mapping, challenges are the heterogeneous distribution of GIM, suboptimal diagnostic accuracy of endoscopy to detect GIM, and the cost burden of multiple biopsies.

This study by Lightdale et al. demonstrated the technical feasibility and safety of obtaining cytology for the detection of gastric intestinal metaplasia by using a systemic endoscopy-guided high-pressure spray "power-wash" method. In this study, all cytophathology samples in nine subjects were deemed satisfactory for evaluation. All three subjects who were cytology positive for GIM on H&E stain and confirmed with positive immunohistochemistry showed GIM on biopsy, and one subject had cells highly suspicious for dysplasia on cytology but biopsy was negative. Although all patients showed multiple superficial erosions after power-wash, bleeding

Dr. Tomizawa

was minimal and no adverse events related to power-wash were observed.

Applying cytology for detection of GIM appears promising as the way of collecting samples from the large surface area of the stomach. As clinicians, however, we are still left with some challenges. Even if cells collected are suspicious for dysplasia/neoplasia by this power-wash method, it would not be useful unless we precisely localize the area as we can not provide a focal curative endoscopic treatment. It is critical to increase the yield of localization of cytology sampling. Further research is also needed to standardize the cytopathologic diagnostic criteria of GIM and cost-effectiveness of the cytology-based approach compared to the current gold-standard biopsy protocol for the diagnosis of GIM.

Yutaka Tomizawa, MD, MSc, is a therapeutic endoscopist and clinical associate professor of medicine, Division of Gastroenterology, University of Washington, Seattle. He has no conflicts related to this report.

TRAIL-Targeting Therapies Still Hold Promise in Cholangiocarcinoma

BY WILL PASS

MDedge News

FROM CELLULAR AND MOLECULAR
GASTROENTEROLOGY AND HEPATOLOGY

Tumor necrosis factor–related apoptosis-inducing ligand (TRAIL)–targeting therapies still hold promise for treating cholangiocarcinoma (CCA) despite disappointing results in previous preclinical research, primarily due to the adaptive resistance and unexpected immune modulation, according to investigators.

Those prior studies evaluated a combination of immunotherapy and TRAIL agonism, but selective TRAIL antagonism shows greater potential via dual ligand/receptor (TRAIL/TRAIL-R) targeting to block immunosuppression, reported lead author Emilien J. Loeuillard, PhD, of Mayo Clinic, Rochester, Minnesota, and colleagues.

Dr. Loeuillard

"The TRAIL/TRAIL-R system has garnered considerable interest in cancer biology, especially as a potential anticancer therapy," the investigators wrote in *Cellular and Molecular Gastroenterology and Hepatology* (2024 Jan 14. doi: 10.1016/j.jcmgh.2024.01.006). "However, TRAIL-R agonists have had very limited anticancer activity in human beings, challenging this concept of TRAIL as an anticancer agent."

This may be because they were working in the wrong direction, Dr. Loeuillard and colleagues suggested, citing recent work linking TRAIL with tumor proliferation and invasion, possibly via modification of the tumor immune microenvironment.

Exact mechanisms of modification, however, remain unclear. While TRAIL has been associated with tumor-promoting effects like induction of a promyeloid secretome in adenocarcinoma, it has also been linked with anticancer effects like activation of natural killer cells and cytotoxic T lymphocytes.

"Thus, the potency and hierarchy of TRAIL anticancer vs procancer processes in cancer biology has yet to be defined," the

The dismal response of cholangiocarcinoma to immune checkpoint inhibitors (ICI) is particularly concerning, as it impedes the adoption of combination regimens, now standard in most solid tumors. Strategies modulating selective genes involved in the tumor inflammatory environment and tumor cell viability, including those within the tumor necrosis factor superfamily, parallel the mechanism of action of ICI and present a double-edged sword due to the context-dependent pro- and/or anticancer effects of their canonical and/or phantom roles.

Recent investigations suggest that selectively antagonizing TRAIL

Dr. Ko

via (TRAIL/TRAIL-R) targeting may be more effective than agonism. The group from the Mayo Clinic delved into the potential of TRAIL in cancer biology, particularly in CCA, shedding light on the complexities of TRAIL's role in cancer, where both procancer and anticancer effects are observed.

Importantly, they unveiled that noncanonical TRAIL signaling contributes to suppressing the tumor microenvironment by promoting the accumulation of myeloid-derived suppressor cells which can be further mitigated by a novel strategy targeting FLICE inhibitory protein to increase cancer cell sensitivity to proapoptotic TRAIL signaling, presenting a potential avenue for therapeutic

investigators wrote.

While TRAIL ligation of cognate receptors has been previously investigated and shown to trigger proapoptotic signaling pathways, noncanonical TRAIL-mediated signaling remains largely unexplored, particularly in CCA.

The present study evaluated TRAIL biology in CCA using immunocompetent mouse models.

These experiments showed that noncanonical TRAIL signaling immunosuppresses the tumor microenvironment by increasing quantity and activity of myeloid-derived suppressor cells (MDSCs). Blocking noncanonical TRAIL signaling by selective deletion of TRAIL-R

intervention as well as biomarkers predictive of TRAIL response for CCA.

Further investigation is warranted to explore how TRAIL/TRAIL-R therapy can be effectively combined with other broad-spectrum and/or targeted therapies to maximize selective toxicity to CCA cells, sparing the nonmalignant tissue, thereby extending the lifespan of CCA patients as well as assessing its preventive potential in predisposed premalignant stages, including cholestasis patients.

Sungjin Ko, DVM, PhD, is assistant professor in the Division of Experimental Pathology at the University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania. He is also a member of the Pittsburgh Liver Research Center. He reported no conflicts of interest.

in immune cells had significantly reduced tumor volumes alongside fewer MDSCs, driven by FLICE inhibitory protein (cFLIP)-dependent nuclear factor kappa-B activation (NF-kappa-B) in MDSCs, which has antiapoptotic activity.

While MDSCs present one possible target in this chain of immunosuppression, "therapeutic strategies for targeting MDSCs are limited," the investigators wrote, noting that available myeloid modulators have fallen short in clinical trials.

Instead, cFLIP may be a convincing option, they suggested, as targeting cFLIP can sensitize cancer cells to proapoptotic TRAIL

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periods of clinical IBD activity and, contrary to a generally accepted belief, equally reduced in clinically active UC and CD," the investigators wrote. "Besides inflammation, clinically active IBD may reduce fertility through psychological mechanisms (eg, depression), dyspareunia (especially in perianal CD), bowel pain, urgency, and other symptoms that hinder sexual activity."

Compared with histologic remission, histologic inflammation was also associated with reduced fertility (aFRR, 0.90). This means that in periods of histologic inflammation, 6.35 live births occurred per 100 person-years of follow-up, compared with 7.09 lives births for periods of histologic remission. This amounts to one fewer

child per 14 women with 10 years of histologic inflammation.

Finally, the study revealed that, in women with clinically quiescent IBD, those with histologic inflammation had significantly reduced fertility, compared with those in histologic remission (aFRR, 0.85). This association persisted after controlling for contraceptive use.

"Even if histologic inflammation was associated with an overall modest fertility reduction … its impact on the individual might be substantial, with potential ramifications beyond reproductive health, given that reduced female fertility is linked to poor quality of life and mental health," Dr. Mårild and colleagues wrote. "At a societal level, involuntary childlessness causes high and

increasing costs, highlighting the need to focus on preventable causes of reduced fertility."

The investigators suggested that inflammation may be driving infertility by reducing ovulation and fertilization, or by reducing endometrial receptivity, which increases risk of pregnancy loss.

"This is the first study, to our knowledge, to show reduced fertility during histologic inflammation in IBD compared to histologic remission," the investigators wrote. "Our findings suggest that achieving histologic remission may improve the fertility of women with IBD, even in the absence of clinically defined disease activity."

The investigators disclosed relationships with AbbVie, Pfizer, Janssen, and others. ■

Computer-Aided Colonoscopy Falls Short in Real-World Practice

BY WILL PASS
MDedge News

FROM CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Colonoscopy with computer-aided detection (CADe) fails to improve adenoma detection rate (ADR) in real-world, nonrandomized trials, according to investigators.

Although CADe did not increase burden of colonoscopy in the real-world, these real-world detection rates cast doubt on the generalizability of positive findings from randomized trials, reported lead author Harsh K. Patel, MD, of the University of Kansas Medical Center, Kansas City, Kansas, and colleagues.

CADe-assisted colonoscopy has gained increasing attention for its potential to improve ADR, particularly with the recent publication of a meta-analysis (Ann Intern Med. 2023 Sep. doi: 10.7326/M22-3678) involving 20 randomized controlled trials (RCTs), Dr. Patel and colleagues wrote in *Clinical Gastroenterology and Hepatology* (2023 Dec 3. doi: 10.1016/j.cgh.2023.11.029). "However, results of RCTs are not necessarily reproducible in clinical practice."

Dr. Patel

RCTs evaluating this technology are susceptible to various issues with validity, they noted, such as psychological bias stemming from lack of blinding to the possibility that CADe could reduce operator attention, paradoxically "deskilling" endoscopists.

The present meta-analysis aimed to overcome these potential shortfalls by analyzing nonrandomized data from eight studies involving 9,782 patients.

"The lack of a highly controlled setting reduces the psychological pressure of the endoscopists to demonstrate a possible benefit of CADe (i.e., the operator bias) and allows endoscopists to use CADe according to their preferences and attitudes which we usually experience in a real-world clinical practice," the investigators wrote. "On the other hand, noncontrolled factors may affect the outcome of the study, especially when considering that an equivalent distribution of prevalence of disease is required for a fair assessment of the effectiveness of the intervention."

The advent of artificial intelligence (AI) in colonoscopy through computer-aided detection (CADe) systems has been promising, with over 20 randomized controlled trials (RCTs) affirming its benefits. However, this enthusiasm has been tempered by several recent nonrandomized studies indicating no real-world advantage, as discussed in Patel et al.'s systematic review and meta-analysis in *Clinical Gastroenterology and Hepatology*.

The stark differences in the results of RCTs and nonrandomized studies with CADe are interesting and thought-provoking, highlighting issues like potential RCT bias (due to lack of blinding) and the critical role of the human-AI interaction. It may be that some endoscopists derive a benefit from CADe while others do not, and further studies looking into the performance of individual endoscopists with and without CADe may be helpful. The meta-analysis also reveals varying outcomes based on study design — prospective or retrospective

Dr. Mansour

— and the nature of the control arm, be it concurrent or historical.

In addition, a critical consideration with evaluating any AI/CADe system is they often undergo frequent updates, each promising improved accuracy, sensitivity, and specificity. This is an interesting dilemma and raises questions about the enduring relevance of studies conducted using outdated versions of CADe.

In my opinion, the jury is still out on the effectiveness of CADe for colonoscopy in a real-world setting. The definitive assessment of CADe's real-world value necessitates larger, well-structured trials that mirror actual clinical environments and span extended periods of time, taking care to minimize biases that may have influenced the results of current published studies.

Nabil M. Mansour, MD, is assistant professor of medicine in the Section of Gastroenterology, Baylor College of Medicine, Houston. He has served as a consultant for Iterative Health.

This approach revealed less favorable outcomes than those reported by RCTs.

CADe-assisted ADR was not significantly different from ADR for standard colonoscopy (44% vs 38%; risk ratio, 1.11; 95% CI, 0.97-1.28), nor was mean number of adenomas detected per colonoscopy (0.93 vs 0.79; mean difference, 0.14; 95% CI, -0.04-0.32).

"Our study provides a contrasting perspective to those results previously known from the randomized studies," the investigators wrote.

While detection benefits were not identified, burden of CADe-assisted colonoscopy was not elevated either.

Mean nonneoplastic lesions per colonoscopy was similar between modalities (0.52 vs 0.47; mean difference, 0.14; 95% CI, -0.07-0.34), as was withdrawal time (14.3 vs 13.4 minutes; mean difference, 0.8 minutes; 95% CI, -0.18-1.90).

Dr. Patel and colleagues described "a high level of heterogeneity that was qualitatively and quantitatively distinct from the heterogeneity discovered in the prior meta-analysis of RCTs." Unlike the RCT meta-analysis, which had no studies with an ADR outcome favoring the control arm,

the present meta-analysis found that one third of the included studies favored the control arm.

"This qualitative difference generates a much higher degree of ambiguity, as it does not apply only to the magnitude of the effect of CADe, but it puts in question the actual existence of any CADe-related benefit," they wrote. "An important point to make is that the analysis of adenoma and serrated lesions per colonoscopy supported the qualitative heterogeneity, favoring the control arm over the CADe arm, in the direction of the effect."

Dr. Patel and colleagues suggested that the concurrent lack of benefit and lack of harm associated with CADe in the present meta-analysis is "interesting," and may point to underutilization or a lack of effect of CADe.

"To address the uncertainties in the current literature, we recommend conducting additional randomized studies in a more pragmatic setting," they concluded.

This meta-analysis was supported by the European Commission and AIRC. The investigators disclosed relationships with NEC, Satisfy, Odin, and others. ∎

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signaling. What's more, cFLIP appears to protect MDSCs from TRAIL-mediated apoptosis, so taking out this barrier could render MDSCs susceptible to therapy.

"Our studies suggest that switching prosurvival/proliferation TRAIL signaling to canonical proapoptotic TRAIL signaling will promote MDSC apoptosis, which in turn has therapeutic implications for CCA suppression," the investigators wrote.

Hope therefore remains for targeting TRAIL in patients with CCA, but with selective antagonism instead of agonism, as previously attempted.

"In summary, our findings support the role of selective therapeutic targeting of TRAIL-positive cancer cells in an effort to block TRAIL/TRAIL-R–mediated tumor immunosuppression," Dr. Loeuillard and colleagues concluded.

This study was funded by the Cholangiocarcinoma Foundation

and the Mayo Clinic Eagles 5th District Cancer Telethon Funds for Research Fellowship Program, the CTSA/National Center for Advancing Translational Science, the National Institutes of Health/National Cancer Institute, and others. The investigators disclosed no conflicts of interest. ∎

Endoscopic Management of Barrett's Esophagus

In Focus
Brought To You By The New Gastroenterologist

BY SACHIN SRINIVASAN, MD, AND PRATEEK SHARMA, MD

Introduction

Barrett's esophagus (BE) is characterized by the replacement of squamous epithelium by columnar metaplasia of the distal esophagus (> 1 cm length). It is a precancerous condition, with 3%-5% of patients with BE developing esophageal adenocarcinoma (EAC) in their lifetime. EAC is one of the cancers with high morbidity and mortality (5-year survival < 20%), and its incidence has been on the rise. Studies examining the natural history of BE have demonstrated that the progression happens through a metaplasia-dysplasia-neoplasia sequence. Therefore, early detection of BE and timely management to prevent progression to EAC is crucial.

Grades of Dysplasia

The current gold standard for the diagnosis of BE neoplasia includes a high-quality endoscopic evaluation and biopsies. Biopsies should be obtained from any visible lesions (nodules, ulcers) followed by a random 4-quadrant fashion (Seattle protocol) interval of the entire length of the BE segment. It is essential to pay attention to the results of the biopsy that have been obtained since it will not only determine the surveillance interval but is crucial in planning any necessary endoscopic therapy. The possible results of the biopsy and its implications are:

- *No intestinal metaplasia (IM)*: This would rule out Barrett's esophagus and no further surveillance would be necessary. A recent population-based study of over 1 million patients showed a 55% and 61% reduced risk of upper gastrointestinal (UGI) cancer and deaths respectively after a negative endoscopy.[1]

- *Intestinal metaplasia with no dysplasia (NDBE)*: Biopsies confirm presence of intestinal metaplasia in the biopsies without any evidence of dysplasia. While the rate of progression to EAC is low (0.07%-0.25%), it is not absent and thus surveillance would be indicated. Current guidelines suggest repeating an endoscopy with biopsy in 5 years if the length of BE is < 3 cm or 3 years if length of BE ≥ 3 cm.[2]

- *Indeterminate for dysplasia (BE-IND)*: Biopsies confirm IM but are not able to definitively rule out dysplasia. This can be seen in about 4%-8% of the biopsies obtained. The progression rates to EAC are reported to be comparable or lower to low-grade dysplasia (LGD), so the current recommendation is to intensify acid reduction therapy and repeat endoscopy in 6 months. If repeat endoscopy downgrades to non-dysplastic, then can follow surveillance according to NDBE protocol; otherwise recommend continuing surveillance every 12 months.

- *Low-grade dysplasia (BE-LGD)*: Biopsies confirm IM but also show tightly packed overlapping basal nuclei with hyperchromasia and irregular contours, basal stratification of nuclei, and diminished goblet and columnar cell mucus. There is significant inter-observer variability reported,[3] and thus the slides must be reviewed by a second pathologist with experience in BE to confirm the findings. Once confirmed, based on risk factors such as presence of multifocal LGD, persistence of LGD, presence of visible lesions, etc., the patient can be offered Barrett's endoscopic therapy (BET) or undergo continued surveillance. The decision of pursuing one or the other would be dependent on patient preference and shared decision-making between the patient and the provider.

- *High-grade dysplasia (BE-HGD)*: Biopsies confirm IM with cells showing greater degree of cytologic and architectural alterations of dysplasia than LGD but without overt neoplastic features. Over 40% of the patients would progress to EAC and thus the current recommendations would be to recommend BET in these patients.[4]

- *Esophageal adenocarcinoma*: Biopsies demonstrate neoplasia. If the neoplastic changes are limited to the mucosa (T1a) on endoscopic ultrasound or cross-sectional imaging, then BET is suggested. If there is involvement of submucosa, then depending on the depth of invasion, absence of high-risk features (poor differentiation, lymphovascular invasion), BET can be considered as an alternative to esophagectomy.

Lesion Detection on Endoscopy

Data from large population-based studies with at least 3 years of follow-up reported that 58%-66% of EAC detected during endoscopy was diagnosed within 1 year of an index Barrett's esophagus screening endoscopy, or post-endoscopy Barrett's neoplasia, and was considered likely to have been missed during index endoscopy.[5] This underscores the importance of careful and systematic endoscopic examination during an upper endoscopy.

Studies have also demonstrated that longer examination time was associated with significantly higher detection of HGD/EAC.[6,7] Careful examination of the tubular esophagus and gastroesophageal junction (GEJ) should be performed in forward and retroflexed views looking for any subtle areas of nodularity, loop distortion, variability in

Dr. Srinivasan and Dr. Sharma are based at the University of Kansas Medical Center, Kansas City, Kansas, and the Kansas City Veterans Affairs Medical Center, Kansas City, Missouri. Dr. Srinivasan has no relevant disclosures. Dr. Sharma disclosed research grants from ERBE, Ironwood Pharmaceuticals, Olympus, and Medtronic. He has served as a consultant for Takeda, Samsung Bioepis, Olympus, and Lumendi, and reports other funding from Medtronic, Fujifilm Medical Systems USA, and Salix.

Photos courtesy University of Kansas Health System

Barrett's esophagus (BE) is prevalent in clinical gastroenterology practices and the majority of patients can be managed by non-tertiary care centers. However, it is important to recognize when to refer to BE specialists for endoscopic management. Barrett's endoscopic therapy (BET) reduces the risk of advanced malignancy, if not curative, in early neoplasia.

Dr. Sachin Srinivasan and Dr. Prateek Sharma highlight the importance of understanding dysplasia grading of BE and lesion detection. They also review modalities of BET, including endoscopic resection with endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), as well as ablative therapies, such as radiofrequency ablation (RFA), cryotherapy, and hybrid argon plasma coagulation (APC). Lastly, they describe outcomes and current recommendations for surveillance after BET.

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vascular patterns, mucosal changes concerning for dysplasia or neoplasia. Use of high-definition white light endoscopy (HD-WLE) and virtual chromoendoscopy techniques such as narrow banding imaging (NBI) or blue laser imaging (BLI) are currently recommended in the guidelines.[2] Spray chromoendoscopy using acetic acid can also be utilized. Another exciting development is the use of artificial intelligence (AI) in detecting and diagnosing BE-associated lesions and neoplasia.

Barrett's Endoscopic Therapy (BET)

Patients with visible lesions, dysplasia, or early EAC are candidates for BET **(Table 1)**. BET involves resective and ablative modalities. The resective modalities include endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) and are the modalities of choice for nodular or raised lesions.

Currently there are no guideline recommendations regarding the preference of one endoscopic modality over another or consideration of potential endoscopic or surgical fundoplication.

EMR involves endoscopic resection of abnormal mucosa using either lift-assisted technique or multi-band ligation **(Figure 1)**. ESD, on the other hand, involves submucosal dissection and perimeter resection of the lesion, thus providing the advantage of an en-bloc resection. In a recent randomized controlled trial (RCT) of 40 patients undergoing ESD vs EMR for HGD/EAC, ESD was better for curative resection (R0) (58%) compared with EMR (12%); however, the remission rates at 3 months were comparable with two perforations reported in the ESD group while there were no complications in the EMR group.[8]

There is an apparent learning curve when it comes to these advanced techniques, and with more experience, we are seeing comparable results for both these modalities. However, given the complexity and time required for the procedure, current practices typically involve preserving ESD for lesions > 2 cm, those having a likelihood of cancer in the superficial submucosa, or those that EMR cannot remove due to underlying fibrosis or post-EMR recurrence.

Table 1. Patients suitable for BET

1. BE with HGD
2. T1a EAC (Intramucosal EAC)
3. T1b EAC (Submucosal EAC) with low-risk features (sm1 [<500-μm invasion in the submucosa] cancer, good to moderate differentiation, and no lymphatic invasion)
4. BE with LGD with high-risk features (confirmed by 2 histopathologists with repeat EGD confirmation in 6 months, visible lesions, multifocal)

Note: Any visible lesion should first be resected prior to application of ablative therapy
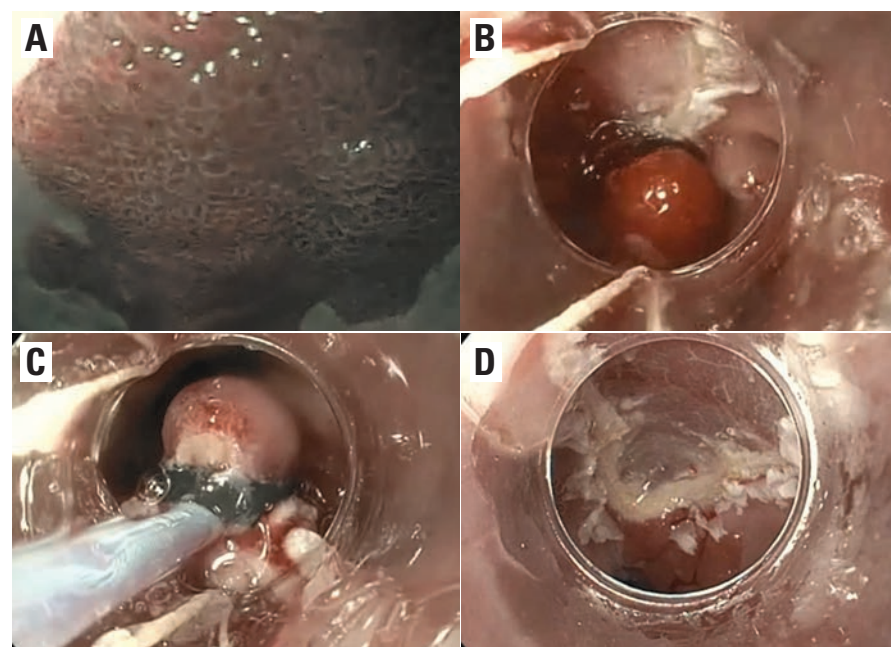**Source:** Dr. Sachin Srinivasan and Dr. Prateek Sharma

The ablative modalities include radiofrequency ablation (RFA), cryotherapy, and hybrid argon plasma coagulation (hybrid APC). These modalities are used for flat lesions, and as therapy following endoscopic resection of nodular lesions to treat residual flat segment of BE. RFA, one of the earliest introduced endoscopic modalities, involves applying directed and controlled heat energy to ablate lesions. Current devices allow circumferential or focal application of RFA. It is a safe and effective modality with good complete eradication of IM (CE-IM) (71%-93%) and complete eradication of dysplasia (CE-D) (91%-100%) rates. These results have been sustained even at 2 years, with the most recent long-term data from a registry study showing a relapse rate of 6% for dysplasia and 19% for IM after 8 years, suggesting durability of this treatment.[9]

Cryotherapy involves the application of liquid nitrogen or rapidly expanding CO_2 to the abnormal mucosa, leading to the rapid freezing and thawing that leads to the death of the cells. Cryogen can be applied as a spray or using a balloon with the spray nozzle in the center. This modality can be used to treat focal lesions and/or larger segments. While it has not been systematically compared with RFA, rates of CE-IM up to 81% and CE-D up to 97% are reported. Hybrid APC involves the use of submucosal saline injection to provide a protective cushion before APC is applied. It has CE-IM rate of 69% and CE-D rate of 67%-86%.[10] In a recent RCT of 101 patients randomized to RFA or hybrid APC, CE-IM rates were similar (RFA:74.2% vs hAPC: 82.9%).[11]

Recently, another technique called radiofrequency vapor ablation (RFVA) is being evaluated, which involves ablating BE segment using vapor at 100° C generated with an RF electrode. A proof-of-concept study of 15 patients showed median squamous conversion of 55% (IQR 33-74) and 98% (IQR 56-99) for 1- and 3-second applications, respectively, with no reported adverse events.[12]

Figure 1: Endoscopic mucosal resection of a nodular BE lesion

A: Careful examination under NBI; **B:** Application of suction and band ligation;
C: Resection using hot snare; **D:** Post EMR visualization of the resection site.
Source: Dr. Sachin Srinivasan and Dr. Prateek Sharma

Barrett's Refractory to Endoscopic Therapy

Failure of BET is defined as persistent columnar lined epithelium (intestinal metaplasia) with inadequate response, after adequate attempts at endoscopic ablation therapy (after resection) with at least four ablation sessions.[13] If encountered, special attention must be given to check compliance with proton pump inhibitors (PPIs), previous incomplete resection, and presence of large hiatal hernia. If CE-IM is not achieved after multiple sessions, change of ablative modality is typically considered. In addition, careful examination for visible lesions should be performed and even if a small one is noted, this should be first resected prior to application of any ablative therapy.

Currently there are no guideline recommendations regarding the preference of one endoscopic modality over another or consideration of potential endoscopic or surgical fundoplication. These modalities primarily rely on technologies available at an institution and the preference of a provider based on their training and experience. Most studies indicate 1-3 sessions (~ 3 months apart) of ablative treatment before achieving CE-IM.

Success and Adverse Events of BET

In a recent real-world study of over 27,000 patients with dysplastic BE, 5295 underwent BET. Analysis showed that patients with HGD/EAC who had BET had a significantly lower 3-year mortality (HGD: RR, 0.59; 95% CI, 0.49-0.71; EAC: RR, 0.53; 95% CI, 0.44-0.65) compared with those who did not undergo BET. Esophageal strictures were the most common adverse event and were noted in 6.5%, followed by chest pain (1.8%), upper GI bleeding (0.47%), and esophageal perforation (0.2%).[14]

In general, adverse events can be divided into immediate and delayed adverse events. Immediate adverse events typically involve bleeding and perforation that can occur during or shortly after the procedure. These are reported at higher rates with resective modalities compared with ablative therapies. Standard endoscopic techniques involving coagulation grasper or clips can be used to achieve hemostasis. Endoscopic suturing devices offer the ability to contain any perforation. The need for surgical intervention is small and limited to adverse events not detected during the procedure.

Continued on following page

Let's Mingle at DDW

We are looking forward to seeing you in our hometown for Digestive Disease Week® (DDW) 2024!

As you plan your schedule, here's a listing of AGA's free networking events. For more details and featured programming, visit www.gastro.org/DDW.

Meetups at AGA Central (L Street Bridge)
Network with like-minded attendees, build your #AGAGastroSquad and enjoy refreshments at our meetups.
Saturday, May 18
- 3 p.m.: *Advocacy champions meetup* – A "thank you" for everyone who supported our grassroots advocacy efforts this year!
Sunday, May 19
- 11 a.m.: *NPPA meetup*
- 1 p.m.: *Dietitian meetup*
- 3 p.m.: *IBD meetup* – Happy World IBD Day!
Monday, May 20
- 11 a.m.: *Trainee meetup* – Mingle with AGA journal editors!
- 1 p.m.: *Psychologists meetup*
- 3 p.m.: *Clinician meetup*
Tuesday, May 21
- 11 a.m.: *Innovator meetup*

RSVP and add to your calendar: www.signupgenius.com/go/10C0E4E-A4AE2DA2F5C43-48529281-aga-central#/

Additional events for trainees
We have more opportunities for you to network at DDW! The following events all take place on **Sunday, May 19**
- 10 a.m.: *Live recording: Small Talk, Big Topics* – Mingle with fellow trainees and early career GIs during a live recording of AGA's podcast. Our hosts will interview fellowship program director Dr. Janice Jou.
[Location: AGA Central (L Street Bridge)]
- 1 p.m.: *Meet-the-Experts: AGA Leadership* – Held in the DDW Trainee and Early Career Lounge, these sessions are an opportunity for early career attendees to get tips from those further along in their career.
[Location: DDW Trainee and Early Career Lounge]
- 2 p.m.: *AGA/DHPA Networking Event* – Join us for guided networking and 4-way Jeopardy!
[Location: DDW Trainee and Early Career Lounge] ∎

We Have a New Congressional Champion in the Fight Against CRC!

Rep. Yadira Caraveo, MD (D-CO), recently introduced the Colorectal Cancer Early Detection Act along with Reps. Donald Payne Jr. (D-NJ), Haley Stevens (D-MI), and Terri Sewell (D-AL).

The Colorectal Cancer Early Detection Act would award grants to states to promote colorectal cancer prevention and early detection efforts to individuals under age 45.
Grants would be used to:
- Screen increased risk and high-risk individuals under age 45 for colorectal cancer (CRC).
- Provide appropriate referrals for medical treatment.
- Develop and carry out a public education and awareness campaign for the detection and control of CRC.
- Improve the education and training of health providers in detecting and controlling CRC.
- Establish mechanisms through which states can monitor the quality of CRC screening procedures.
- Develop strategies to assess family history and genetic predispositions to CRC.
- Design patient and clinician decision support tools for CRC.
- Conduct surveillance to determine other risk factors for CRC in this population.

Dr. Jung

"Colorectal cancer is the second-leading cause of cancer death in the US and is increasing at an alarming rate in younger people. AGA celebrates Rep. Caraveo's work to address this trend through education and awareness" said Barbara Jung, MD, AGA President.

We look forward to working with our congressional champions to increase screening rates and reverse the trend of early onset colorectal cancer! ∎

Delayed adverse events such as stricture and stenosis are higher for resective modalities (up to 30%), especially when involving more significant than 75% of the esophageal circumference. Post-procedural pain/dysphagia is most common after ablative therapies. Dysphagia reported after any endoscopic therapy should be promptly evaluated, and sequential dilation until the goal esophageal lumen is achieved should be performed every 2-4 weeks.

Recurrences and Surveillance After BET
What is established is that recurrences can occur and may be subtle, therefore detailed endoscopic surveillance is required. In a prospective study, recurrence rates of 15%-16% for IM and 3%-5% for any dysplasia were reported, with the majority being in the first 2 years after achieving CE-IM.[15] A systematic review of 21 studies looking at the location of recurrences suggested that the majority (56%) occur in the distal esophagus. Of those that occur in the esophagus, about 80% of them were in the distal 2 cm of the esophagus and only 50% of the recurrences were visible recurrences, thus reiterating the importance of meticulous examination and systematic biopsies.[16]

BE patients with visible lesions and/or dysplastic changes in the biopsy who would require BET should be considered for referral to high-volume centers.

On the contrary, a recent single-center study of 217 patients who had achieved CE-IM with 5.5 years of follow-up demonstrated a 26% and 8% recurrence of IM and dysplasia, respectively. One hundred percent of the recurrence in the esophagus was reported as visible.[17] Therefore, follow-up endoscopy surveillance protocol after CE-IM should still involve meticulous examination, biopsy of visible lesions, and systematic biopsies for non-visible lesions from the original BE segment, similar to those patients who have not needed BET.

Current guidelines based on expert consensus and evidence recommend surveillance after CE-IM based on original most advanced histology:[2]
1. LGD: 1 year, 3 years, and every 2 years after that.
2. HGD/EAC: 3 months, 6 months, 12 months, and annually after that.
There is no clear guideline on when to stop surveillance since the longest available follow-up is around 10 years, and recurrences are still detected. A potential surveillance endpoint may be based on age and comorbidities, especially those that would preclude a patient from being a candidate for BET.

When Should a Patient Be Referred?
BE patients with visible lesions and/or dysplastic changes in the biopsy who would require BET should be considered for referral to high-volume centers. Studies have shown higher success for CE-IM and lower rates of adverse events and recurrences in these patients managed at expert centers. The presence of a multidisciplinary team involving pathologists, surgeons, and oncologists is critical and offers a timely opportunity in case of need for a high-risk patient.

Conclusion
BE is a precursor to EAC, with rising incidence and poor 5-year survival. Endoscopic diagnosis is the gold standard and requires a high-quality examination and biopsies. Based on histopathology, a systematic surveillance and BET plan should be performed to achieve CE-IM in patients with dysplasia. Once CE-IM is achieved, regular surveillance should be performed with careful attention to recurrences and complications from the BET modalities. ∎

For a complete list of references, please see the online version of this article at www.mdedge.com/gihepnews.

A 'game-changer' for providers

MASH *from page 1*

living with this serious liver condition," lead MAESTRO-NASH investigator Stephen Harrison, MD, gastroenterologist, hepatologist, and chairman of Pinnacle Clinical Research and Summit Clinical Research, San Antonio, Texas, said in a news release.

"Based on the robust efficacy and safety data generated in two large Phase 3 MAESTRO studies, I believe Rezdiffra will become the foundational therapy for patients

Dr. Harrison

with NASH with moderate to advanced liver fibrosis. Importantly, we continue to study Rezdiffra to determine if the positive results observed in the MAESTRO studies will lead to reduced risk of progression to cirrhosis, liver failure, need for liver transplant and premature mortality," Dr. Harrison added.

Addressing an Unmet Need

MASH is a progressive liver disease and the leading cause of liver-related mortality. The disease affects an estimated 1.5 million adults in the United States, of which, roughly 525,000 have MASH with significant fibrosis. Until now, there was no FDA-approved medication.

In the ongoing MAESTRO-NASH, 996 adults with biopsy-confirmed NASH and significant stage 2-3 fibrosis were randomly assigned to receive oral once-daily resmetirom (80 mg or 100 mg) or placebo.

Patients were followed for 52 weeks, at which point, they were assessed for the dual primary endpoints of NASH resolution (including a reduction in the NAFLD activity score by ≥ 2 points) with no worsening of fibrosis and an improvement (reduction) in fibrosis by at least one stage with no worsening of the NAFLD activity score.

Patients receiving resmetirom had a significant improvement across both doses and both primary endpoints.

At 52 weeks, NASH resolution with no worsening of fibrosis was achieved in 25.9% and 29.9% of the patients in the 80-mg and 100-mg groups, respectively, compared with 9.7% on placebo.

Fibrosis improved by at least one stage with no worsening of the NAFLD activity score in 24.2% and 25.9% of patients in the 80-mg and 100-mg groups, respectively, compared with 14.2% on placebo.

The trial also met multiple secondary endpoints, including statistically significant reduction from baseline in liver enzymes (alanine transaminase, aspartate aminotransferase, and gamma-glutamyl transferase) and low-density lipoprotein cholesterol with resmetirom compared with placebo.

Improvement in fibrosis biomarkers and relevant imaging tests were also observed in resmetirom treatment groups compared with placebo.

The most common adverse events included diarrhea and nausea, which typically began early in treatment and were mild to moderate in severity. Pruritus, abdominal pain, vomiting, constipation, and dizziness were also reported.

Resmetirom is expected to be available to patients in the United States in April and will be distributed through a limited specialty pharmacy network.

Full prescribing information is available online (https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/217785s000lbl.pdf). Prescribing information does not include a liver biopsy requirement for diagnosis. ∎

Artificial Intelligence in GI and Hepatology

Dear colleagues,
Since our prior Perspectives piece on artificial intelligence (AI) in GI and Hepatology in 2022 (gastro.org/news/innovation-in-gi-whats-the-next-big-thing/), the field has seen almost exponential growth. Expectations are high that AI will revolutionize our field and significantly improve patient care. But as the global discussion on AI has shown,

there are real challenges with adoption, including issues with accuracy, reliability, and privacy.

In this issue, Dr. Nabil M. Mansour and Dr. Thomas R. McCarty explore the current and future impact of AI on gastroenterology, while Dr. Basile Njei and Yazan A. Al-Ajlouni assess its role in hepatology. We hope these pieces will help your discussions in incorporating or

researching AI for use in your own practices. We welcome your thoughts on this issue on X @AGA_GIHN.

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

Dr. Ketwaroo

Artificial Intelligence in Gastrointestinal Endoscopy

BY THOMAS R. MCCARTY, MD, MPH; NABIL M. MANSOUR, MD

The last few decades have seen an exponential increase and interest in the role of artificial intelligence (AI) and adoption of deep learning algorithms within healthcare and patient care services. The field of gastroenterology and endoscopy has similarly seen a tremendous uptake in acceptance and implementation of AI for a variety of gastrointestinal conditions. The spectrum of AI-based applications includes detection or diagnostic-based as well as therapeutic assistance tools. From the first US Food and Drug Administration (FDA)-approved device that uses machine learning to assist clinicians in detecting lesions during colonoscopy, to other more innovative machine learning techniques for small bowel, esophageal, and hepatobiliary conditions, AI has dramatically changed the landscape of gastrointestinal endoscopy.

Approved applications for colorectal cancer
In an attempt to improve colorectal cancer screening and outcomes related to screening and surveillance, efforts have been focused on procedural performance metrics, quality indicators, and tools to aid in lesion detection and improve quality of care. One such tool has been computer-aided detection (CADe), with early randomized controlled trial (RCT) data showing significantly increased adenoma detection rate (ADR) and adenomas per colonoscopy (APC).[1-3]
Ultimately, this data led to FDA

Dr. McCarty   Dr. Mansour

approval of the CADe system GI Genius (Medtronic, Dublin, Ireland) in 2021.[4] Additional systems have since been FDA approved or 510(k) cleared including Endoscreener (Wision AI, Shanghai, China), SKOUT (Iterative Health, Cambridge, Massachusetts), MAGENTIQ-COLO (MAGENTIQ-EYE, Haifa, Israel), and CAD EYE (Fujifilm, Tokyo), all of which have shown increased ADR and/or increased APC and/or reduced adenoma miss rates in randomized trials.[5]

Yet despite the promise of improved quality and subsequent translation to better patient outcomes, there has been a noticeable disconnect between RCT data and more real-world literature.[6] In a recent study, no improvement was seen in ADR after implementation of a CADe system for colorectal cancer screening — including both higher and lower-ADR performers. As for change over time after implementation, CADe had

The Promise and Challenges of AI in Hepatology

BY BASILE NJEI, MD, MPH, PHD; YAZAN A. AL-AJLOUNI, MD, MPHIL

In the dynamic realm of medicine, artificial intelligence (AI) emerges as a transformative force, notably within hepatology. The discipline of hepatology, dedicated to liver and related organ diseases, is ripe for AI's promise to revolutionize diagnostics and treatment, pushing toward a future of precision medicine. Yet, the path to fully realizing AI's potential in hepatology is laced with data, ethical, and integration challenges.

The application of AI, particularly in histopathology, significantly enhances disease diagnosis and staging in hepatology. AI-driven approaches remedy traditional histopathological challenges, such as interpretative variability, providing more consistent and accurate disease analyses. This is especially evident in conditions like metabolic dysfunction-associated steatohepatitis (MASH) and hepatocellular carcinoma (HCC), where AI aids in identifying critical gene signatures, thereby refining therapy selection.

Similarly, deep learning (DL), a branch of AI, has attracted significant interest globally, particularly in image recognition. AI's incorporation into medical imaging marks a significant advancement, enabling early detection of malignancies like HCC and improving diagnostics in steatotic liver

Dr. Njei   Dr. Al-Ajlouni

disease through enhanced imaging analyses using convolutional neural networks (CNN). The abundance of imaging data alongside clinical outcomes has catalyzed AI's integration into radiology, leading to the swift growth of radiomics as a novel domain in medical research.

AI has also been shown to identify nuanced alterations in electrocardiograms (EKGs) associated with liver conditions, potentially detecting the progression of liver diseases at an earlier stage than currently possible. By leveraging complex algorithms and machine learning, AI can analyze EKG patterns with a precision and depth unattainable through traditional manual interpretation. Given that liver diseases, such as cirrhosis or hepatitis, can induce subtle cardiac changes long before other clinical symptoms manifest, early detection through AI-enhanced EKG analysis could lead to timely interventions, potentially halting or reversing disease progression. This approach further enriches our understanding of the intricate interplay between liver function and cardiac health, highlighting the potential for AI to transform not just liver disease diagnostics but also to

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Read more!

Find more of these debates online at www.mdedge.com/gihepnews/perspectives.

Gastro · *Continued from page 18*

no positive effect in any group over time, divergent from early RCT data. In a more recent multicenter, community-based RCT study, again CADe did not result in a statistically significant difference in the number of adenomas detected.[7] The differences between some of these more recent "real-world" studies vs the majority of data from RCTs raise important questions regarding the potential of bias (due to unblinding) in prospective trials, as well as the role of the human-AI interaction.

Importantly for RCT data, both cohorts in these studies met adequate ADR benchmarks, though it remains unclear whether a truly increased ADR necessitates better patient outcomes — is higher always better? In addition, an important consideration with evaluating any AI/CADe system is that they often undergo frequent updates, each promising improved accuracy, sensitivity, and specificity. This is an interesting dilemma and raises questions about the enduring relevance of studies conducted using an outdated version of a CADe system.

In the end, more widespread adoption in community practice and larger scale real-world clinical outcomes studies are likely to determine the true impact of these exciting technologies.

Additional unanswered questions regarding an ideal ADR for implementation, preferred patient populations for screening (especially for younger individuals), and the role and adoption of computer-aided polyp diagnosis/characterization (CADx) within the United States remain. Furthermore, questions regarding procedural withdrawal time, impact on sessile serrated lesion detection, cost-effectiveness, and preferred adoption strategies have begun to be explored, though require more data to better define a best practice approach. Ultimately, answers to some of these unknowns may explain the discordant results and help guide future implementation measures.

Innovative applications for alternative gastrointestinal conditions

Given the fervor and excitement, as well as the outcomes associated with AI-based colorectal screening, it is not surprising these techniques have been expanded to other gastrointestinal conditions. At this time, all of these are fledgling, mostly single-center tools, not yet ready for widespread adoption. Nonetheless, these represent a potentially important step forward for difficult-to-manage gastrointestinal diseases.

Machine learning CADe systems have been developed to help identify early Barrett's neoplasia, depth and invasion of gastric cancer, as well as lesion detection in small bowel video capsule endoscopy.[8-10] Endoscopic retrograde cholangiopancreatography (ERCP)-based applications for cholangiocarcinoma and indeterminate stricture diagnosis have also been studied.[11] Additional AI-based algorithms have been employed for complex procedures such as endoscopic submucosal dissection (ESD) or peroral endoscopic myotomy (POEM) to delineate vessels, better define tissue planes for dissection, and visualize landmark structures.[12,13] Furthermore, AI-based scope guidance/manipulation, bleeding detection, landmark identification, and lesion detection have the potential to revolutionize endoscopic training and education. The impact that generative AI can potentially have on clinical practice is also an exciting prospect that warrants further investigation.

Artificial intelligence adoption in clinical practice

Clinical practice with regard to AI and colorectal cancer screening largely mirrors the disconnect in the current literature, with "believers" and "non-believers" as well as innovators and early adopters alongside laggards. In our own academic practices, we continue to struggle with the adoption and standardized implementation of AI-based colorectal cancer CADe systems, despite the RCT data showing positive results. It is likely that AI uptake will follow the technology predictions of Amara's Law — i.e., individuals tend to overestimate the short-term impact of new technologies while underestimating long-term effects. In the end, more widespread adoption in community practice and larger scale real-world clinical outcomes studies are likely to determine the true impact of these exciting technologies. For other, less established AI-based tools, more data are currently required.

Conclusions

Ultimately, AI-based algorithms are likely here to stay, with continued improvement and evolution to occur based on provider feedback and patient care needs. Current tools, while not all-encompassing, have the potential to dramatically change the landscape of endoscopic training, diagnostic evaluation, and therapeutic care. It is critically important that relevant stakeholders, both endoscopists and patients, be involved in future applications and design to improve efficiency and quality outcomes overall. ∎

Dr. McCarty is based in the Lynda K. and David M. Underwood Center for Digestive Disorders, Houston Methodist Hospital. Dr. Mansour is based in the section of gastroenterology, Baylor College of Medicine, Houston. Dr. McCarty reports no conflicts of interest. Dr. Mansour reports having been a consultant for Iterative Health.

References

1. Repici A, et al. Efficacy of real-time computer-aided detection of colorectal neoplasia in a randomized trial. Gastroenterology. 2020 Aug. doi: 10.1053/j.gastro.2020.04.062.

2. Repici A, et al. Artificial intelligence and colonoscopy experience: Lessons from two randomised trials. Gut. Apr 2022. doi: 10.1136/gutjnl-2021-324471.

3. Wallace MB, et al. Impact of artificial intelligence on miss rate of colorectal neoplasia. Gastroenterology 2022 Jul. doi: 10.1053/j.gastro.2022.03.007.

4. United States Food and Drug Administration (FDA). GI Genius FDA Approval [April 9, 2021]. Accessed January 5, 2022. Available at: www.accessdata.fda.gov/cdrh_docs/pdf21/K211951.pdf.

5. Maas MHJ, et al. A computer-aided polyp detection system in screening and surveillance colonoscopy: An international, multicentre, randomised, tandem trial. Lancet Digit Health. 2024 Mar. doi: 10.1016/S2589-7500(23)00242-X.

6. Ladabaum U, et al. Computer-aided detection of polyps does not improve colonoscopist performance in a pragmatic implementation trial. Gastroenterology. 2023 Mar. doi: 10.1053/j.gastro.2022.12.004.

7. Wei MT, et al. Evaluation of computer-aided detection during colonoscopy in the community (AI-SEE): A multicenter randomized clinical trial. Am J Gastroenterol. 2023 Oct. doi: 10.14309/ajg.0000000000002239.

8. de Groof J, et al. The Argos project: The development of a computer-aided detection system to improve detection of Barrett's neoplasia on white light endoscopy. United European Gastroenterol J. 2019 May. doi: 10.1177/2050640619837443.

9. Kanesaka T, et al. Computer-aided diagnosis for identifying and delineating early gastric cancers in magnifying narrow-band imaging. Gastrointest Endosc. 2018 May. doi: 10.1016/j.gie.2017.11.029.

10. Sahafi A, et al. Edge artificial intelligence wireless video capsule endoscopy. Sci Rep. 2022 Aug. doi: 10.1038/s41598-022-17502-7.

11. Njei B, et al. Artificial intelligence in endoscopic imaging for detection of malignant biliary strictures and cholangiocarcinoma: A systematic review. Ann Gastroenterol. 2023 Mar-Apr. doi: 10.20524/aog.2023.0779.

12. Ebigbo A, et al. Vessel and tissue recognition during third-space endoscopy using a deep learning algorithm. Gut. 2022 Dec. doi: 10.1136/gutjnl-2021-326470.

13. Cao J, et al. Intelligent surgical workflow recognition for endoscopic submucosal dissection with real-time animal study. Nat Commun. 2023 Oct. doi: 10.1038/s41467-023-42451-8.

foster a more integrated approach to patient care.

Beyond diagnostics, the burgeoning field of generative AI introduces groundbreaking possibilities in treatment planning and patient education, particularly for chronic conditions like cirrhosis. Generative AI produces original content, including text, visuals, and music, by identifying and learning patterns from its training data. When it leverages large language models (LLMs), it entails training on vast collections of textual data and using AI models characterized by many parameters. A notable instance of generative AI employing LLMs is ChatGPT (General Pretrained Transformers). By simulating disease progression and treatment outcomes, generative AI can foster personalized treatment strategies and empower patients with knowledge about their health trajectories. Yet, realizing these potential demands requires overcoming data quality and interpretability challenges, and ensuring AI outputs are accessible and actionable for clinicians and patients.

Despite these advancements, leveraging AI in hepatology is not devoid of hurdles. The development and training of AI models require extensive and diverse datasets, raising concerns about data privacy and ethical use. Addressing these concerns is paramount for successfully integrating AI into clinical hepatology practice, necessitating transparent algorithmic processes and stringent ethical standards. Ethical considerations are central to AI's integration into hepatology. Algorithmic biases, patient privacy, and the impact of AI-driven decisions underscore the need for cautious AI deployment. Developing transparent, understandable algorithms and establishing ethical guidelines for AI use are critical steps towards ethically leveraging AI in patient care.

In conclusion, AI's integration into hepatology holds tremendous promise for advancing patient care through enhanced diagnostics, treatment planning, and patient education. Overcoming the associated challenges, including ethical concerns, data diversity, and algorithm interpretability, is crucial. As the hepatology community navigates this technological evolution, a balanced approach that marries technological advancements with ethical stewardship will be key to harnessing AI's full potential, ensuring it serves the best interests of patients and propels the field of hepatology into the future.

We predict a trajectory of increased use and adoption of AI in hepatology. AI in hepatology is likely to meet the test of pervasiveness, improvement, and innovation. The adoption of AI in routine hepatology diagnosis and management will likely follow Amara's Law and the five stages of the hype cycle. We believe that we are still in the infant stages of adopting AI technology in hepatology, and this phase may last 5 years before there is a peak of inflated expectations. The trough of disillusionment and slopes of enlightenment may only be observed in the next decades. ∎

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Sources

Taylor-Weiner A, et al. A machine learning approach enables quantitative measurement of liver histology and disease monitoring in NASH. Hepatology. 2021 Jul. doi: 10.1002/hep.31750.

Zeng Q, et al. Artificial intelligence predicts immune and inflammatory gene signatures directly from hepatocellular carcinoma histology. J Hepatol. 2022 Jul. doi: 10.1016/j.jhep.2022.01.018.

Ahn JC, et al. Development of the AI-Cirrhosis-ECG Score: An electrocardiogram-based deep learning model in cirrhosis. Am J Gastroenterol. 2022 Mar. doi: 10.14309/ajg.0000000000001617.

Nduma BN, et al. The application of artificial intelligence (AI)-based ultrasound for the diagnosis of fatty liver disease: A systematic review. Cureus. 2023 Dec 15. doi: 10.7759/cureus.50601.

Cell-Free DNA Blood Test Developed for Detecting Colorectal Cancer

BY CAROLYN CRIST

A cell-free DNA (cfDNA) blood test, aimed at detecting abnormal DNA signals in people with an average risk of colorectal cancer (CRC), correctly detected CRC in most people confirmed to have the disease, according to a new study.

The cfDNA blood test had 83% sensitivity for CRC, 90% specificity for advanced neoplasia, and 13% sensitivity for advanced precancerous lesions. Other noninvasive screening methods have sensitivity from 67% to 94% for CRC and 22% to 43% for advanced precancerous lesions.

"The results of the study are a promising step toward developing more convenient tools to detect colorectal cancer early while it is more easily treated," said senior author William M. Grady, MD, AGAF, medical director of the Gastrointestinal Cancer Prevention Program at the Fred Hutchinson Cancer Center in Seattle.

"The test, which has an accuracy rate for colon cancer detection similar to stool tests used for early detection of cancer, could offer an alternative for patients who may otherwise decline current screening options," he said.

The study was published online on March 14 in *The New England Journal of Medicine* (doi: 10.1056/NEJMoa2304714).

Analyzing the Blood Test's Accuracy

Dr. Grady and colleagues conducted a multisite clinical trial called ECLIPSE, which compared the sensitivity and specificity of a cfDNA blood test (Shield, Guardant Health) against that obtained with colonoscopy, the gold standard for CRC screening. Guardant led and funded the study.

Guardant's Shield test is designed to detect CRC through genomic alterations, aberrant methylation status, and fragmentomic patterns, which show up as an "abnormal signal detected" result. Similar blood tests are being developed as "liquid biopsy" tests for other emerging cancer screenings as well.

The study included 7861 people with average CRC risk who underwent routine screening with colonoscopy at 265 sites in the United States, including primary care and endoscopy centers in academic and community-based institutions. Eligible people were aged 45-84 years (average age, 60 years), and 53.7% were women. The race and ethnicity characteristics of the participants closely mirrored the demographic distribution in the 2020 US Census.

Overall, 54 of 65 (83.1%) participants with colonoscopy-detected CRC had a positive cfDNA blood test. However, 11 participants (16.9%) with CRC had a negative test.

The cfDNA blood test identified 42 of 48 stage I, II, or III CRCs, indicating a sensitivity of 87.5%, including 65% for stage I cancers, 100% for stage II cancers, and 100% for stage III cancers. The test also identified all 10 of the stage IV CRC cases. There were no substantial differences in sensitivity for CRC based on primary tumor location, tumor histologic grade, or demographic characteristics.

Dr. Grady

'The test, which has an accuracy rate for colon cancer detection similar to stool tests used for early detection of cancer, could offer an alternative for patients who may otherwise decline current screening options.'

Among participants without advanced colorectal neoplasia on colonoscopy, 89.6% had a negative cfDNA blood test, and 10.4% had a positive test.

Among those with a negative colonoscopy — with no CRC, advanced precancerous lesions, or nonadvanced precancerous lesions — specificity was 89.9%.

Among 1116 participants with advanced precancerous lesions identified as the most advanced lesion on colonoscopy, the cfDNA blood test was positive for 147, indicating a sensitivity for advanced precancerous lesions of 13.2%.

Although the blood test has sensitivity similar to stool-based tests for CRC, the accuracy is lower than it is with colonoscopy, which remains the current gold standard for CRC screening, Dr. Grady said.

"Colorectal cancer is common and very preventable with screening, but only about 50%-60% of people who are eligible for screening actually take those tests," he said. "Getting people to be screened for cancer works best when we offer them screening options and then let them choose what works best for them."

Dr. Melson

Dr. Coronado

Future Research

Colorectal cancer is the second leading cause of cancer-related death among US adults and is now the third most diagnosed cancer for people younger than 50 years.

"When colorectal cancer is found earlier and the cancer has not yet spread throughout the body, patient outcomes are much better, as reflected in 5-year survival being much better. It makes sense that an effective blood-based test could have a potential role, in particular for those not getting screened yet," said Joshua Melson, MD, AGAF, director of the High-Risk Clinic for Gastrointestinal Cancers at the University of Arizona Cancer Center in Tucson.

Dr. Melson, who wasn't involved with this study, noted that blood-based testing shows promise for cancer detection but needs additional support for real-world implementation. For instance, the Shield blood test has difficulty detecting precancerous lesions, and it remains unclear what the optimal intervals for repeat testing would be after a negative test, he said. In addition, screening programs will need to ensure they have capacity to effectively deal with a positive test result.

"For a screening program to actually work, when a noninvasive test (whether blood-based or stool-based) is read as positive, those patients need to have a follow-up colonoscopy," he said.

Proper communication with patients will be important as well, said Gloria Coronado, PhD, of the University of Arizona Cancer Center. Dr. Coronado, who wasn't involved with this study, has developed CRC screening messages for specific patient populations and studied patient reactions to CRC blood tests.

In a study by Dr. Coronado and colleagues, among more than 2000 patients who passively declined fecal testing and had an upcoming clinic visit, CRC screening proportions were 17.5 percentage points higher in the group offered the blood test vs those offered usual care.

"Patients believed that a blood test would be more accurate than a stool-based test. However, for the detection of advanced adenomas, the reverse is true," she said. "It will be important to balance the high acceptance and enthusiasm for the blood test with the lower performance of the blood test compared to other tests already on the market."

In a statement accompanying the study's publication, the American Gastroenterological Association welcomed these results as an exciting development, but cautioned that a blood-based test was not interchangeable with colonoscopy.

"The Centers for Medicare and Medicaid Services (CMS) has determined it will cover a blood test for colorectal cancer screening every three years if the test achieves 74% sensitivity for CRC, 90% specificity, and FDA approval," the statement reads. "However, a blood test that meets only the CMS criteria will be inferior to current recommended tests and should not be recommended to replace current tests. Such a test could be recommended for patients who decline all other recommended tests, since any screening is better than no screening at all."

Dr. Grady is a paid member of Guardant's scientific advisory board and advised on the design and procedure of the clinical trial and data analysis. Dr. Melson previously served as consultant for Guardant. Dr. Coronado reported no relevant disclosures. ■

Next-Gen CRC Stool Test Beats FIT for Sensitivity

BY DIANA SWIFT
MDedge News

A next-generation stool DNA test for colorectal cancer (CRC) screening had higher sensitivity for all screening-relevant lesions but lower specificity than a currently available fecal immunochemical test (FIT), according to the large prospective BLUE-C study.

The multi-target assay by Exact Sciences Corporation, the makers of Cologuard, includes new biomarkers designed to increase specificity without decreasing sensitivity. It showed a sensitivity for CRC of almost 94%, with more than 43% sensitivity for advanced precancerous lesions and nearly 91% specificity for advanced neoplasia, according to the study results, which were published in *The New England Journal of Medicine* (2024 Mar 14. doi: 10.1056/NEJMoa2310336).

Dr. Imperiale

Adherence to CRC screening in the United States is well below the 80% national target, and the quest continues for noninvasive screening assays that might improve screening adherence, noted lead author Thomas F. Imperiale, MD, AGAF, a professor of medicine at Indiana University School of medicine in Indianapolis, and colleagues.

"The test's manufacturer developed a new version of its existing Cologuard FIT/DNA test because it took to heart the feedback from primary care providers and gastroenterologists about the test's low specificity," Dr. Imperiale said in an interview. "The goal of the new test was to improve specificity without losing, and perhaps even gaining, some sensitivity — a goal that is not easily accomplished when you're trying to improve on a sensitivity for colorectal cancer that was already 92.3% in the current version of Cologuard."

Compared with the earlier version of Cologuard, he added, the new generation retained sensitivity for CRC and advanced precancerous lesions or polyps while improving specificity by 30% (90.6% vs 86.6%) for advanced neoplasia — a combination of CRC and advanced precancerous lesions, he said. "This with the caveat, however, that the two versions were not compared head-to-head in this new study," Dr. Imperiale said.

The higher specificity for advanced lesions is expected to translate to a lower false positive rate. Lowering false positive rates is crucial because that reduces the need for costly, invasive, and unnecessary colonoscopies, said Aasma Shaukat, MD, MPH, AGAF, director of outcomes research in NYU Langone Health's division of gastroenterology and hepatology in New York City.

"Many physicians felt there were too many false positives with the existing version, and that is anxiety-provoking in patients and providers," said Dr. Shaukat, who was not involved in the study.

In her view, however, the test's moderate improvements in detecting certain lesions does not make it demonstrably superior to its predecessor, and there is always the possibility of higher cost to consider.

While acknowledging that a higher sensitivity for all advanced precancerous lesions would have been welcome, Dr. Imperiale said the test detected 75% of the most worrisome of such

> 'The test's manufacturer developed a new version of its existing Cologuard FIT/DNA test because it took to heart the feedback from primary care providers and gastroenterologists about the test's low specificity.'

lesions — "the ones containing high-grade dysplastic cells and suggesting near-term conversion to cancer. And its ability to detect other advanced lesions improved as the size of the lesions increased."

Testing Details

Almost 21,000 asymptomatic participants age 40 years and older undergoing screening colonoscopy were evaluated at 186 US sites during the period 2019 to 2023. Of the cohort, 98 had CRC, 2144 had advanced precancerous lesions, 6973 had nonadvanced adenomas, and 10,961 had nonneoplastic findings or negative colonoscopy.

Advanced precancerous lesions included one

Dr. Shaukat

or more adenomas or sessile serrated lesions measuring at least 1 cm in the longest dimension, lesions with villous histologic features, and high-grade dysplasia. The new DNA test identified 92 of 98 participants with CRC and 76 of 82 participants with screening-relevant cancers. Among the findings for the new assay:

- Sensitivity for any-stage CRC was 93.9% (95% CI, 87.1-97.7)
- Sensitivity for advanced precancerous lesions was 43.4% (95% CI, 41.3-45.6)
- Sensitivity for high-grade dysplasia was 74.6% (95% CI, 65.6-82.3)
- Specificity for advanced neoplasia was 90.6% (95% CI, 90.1-91.0).
- Specificity for nonneoplastic findings or negative colonoscopy was 92.7% (95% CI, 92.2-93.1)
- Specificity for negative colonoscopy was 93.3 (95% CI, 92.8-93.9)
- No adverse events occurred.

In the comparator assay, OC-AUTO FIT by Polymedco, sensitivity was 67.3% (95% CI, 57.1-76.5) for CRC, 23.3% (95% CI, 21.5-25.2)

for advanced precancerous lesions, and 47.4% (95% CI, 37.9-56.9) for high-grade dysplasia. In the comparator FIT, however, specificity was better across all age groups — at 94.8% (95% CI, 94.4-95.1) for advanced neoplasia, 95.7% (95% CI, 95.3-96.1) for nonneoplastic findings, and 96.0% (95% CI, 95.5-96.4) for negative colonoscopy.

In another article in the same issue of *NEJM*, Guardant Health's cell-free DNA blood-based test had 83% sensitivity for CRC, 90% specificity for advanced neoplasia, and 13% sensitivity for advanced precancerous lesions in an average-risk population (2024 Mar 14. doi: 10.1056/NEJMoa2304714).

An age-related decrease in specificity was observed with the new Cologuard test, but that did not concern Dr. Imperiale because the same observation was made with the current version. "In fact, the next-gen version appears to have less of an age-related decrease in specificity than the current version, although, again, the two versions were not tested head-to-head," he noted.

The effect of age-related background methylation of DNA is well known, he explained. "Clinicians and older patients in the screening age range do need to be aware of this effect on specificity before ordering or agreeing to do the test. I do not see this as a stumbling block to implementation, but it does require discussion between patient and ordering provider."

The new version of the DNA test is expected to be available in about a year.

According to Dr. Imperiale, further research is needed to ascertain the test's acceptability and adherence rates and to quantify its yield in population-based screening. Determining its cost-effectiveness and making it easier to use are other goals — "and most importantly, the degree of reduction in the incidence and mortality from colorectal cancer," he said.

Cost-effectiveness and the selection of the testing interval may play roles in adherence, particularly in populations with lower rates of screening adherence than the general population, John M. Carethers, MD, AGAF, of the University of California, San Diego, noted in a related editorial (2024 Mar 14. doi: 10.1056/NEJMe2400366).

"Adherence to screening varies according to age group, including persons in the 45- to 49-year age group who are now eligible for average-risk screening," he wrote. "It is hoped that these newer tests will increase use and adherence and elevate the percentage of the population undergoing screening in order to reduce deaths from colorectal cancer."

This study was sponsored by Exact Sciences Corporation, which conducted the stool testing at its laboratories.

Dr. Imperiale had no competing interests to disclose. Several study co-authors reported employment with Exact Sciences, or stock and intellectual property ownership.

Dr. Shaukat disclosed consulting for Freenome. Dr. Carethers reported ties to Avantor Inc. and Geneoscopy. ∎

Blood screens not 'cost-effective'

Guardant Health and Freenome.

The two modeling studies, published in *Gastroenterology* on March 26, analyzed the effectiveness and cost-effectiveness of blood-based CRC screening (2024 Mar 26. doi: 10.1053/j.gastro.2024.02.012) that meets Centers for Medicare & Medicaid Services (CMS) coverage criteria, as well as the comparative effectiveness and cost-effectiveness of CRC screening with blood-based biomarkers versus fecal tests or colonoscopy (2024 Mar 26. doi: 10.1053/j.gastro.2024.03.011).

Also published on March 26 in *Clinical Gastroenterology and Hepatology*, the expert commentary included key conclusions from the AGA CRC Workshop, which analyzed the two modeling studies (2024 Mar 26. doi: 10.1016/j.cgh.2024.01.034).

Comparing CRC Screening Methods

In the first modeling study, an international team of researchers ran three microsimulation models for CRC to estimate the effectiveness and cost-effectiveness of triennial blood-based screening for ages 45-75, compared with no screening, annual fecal immunochemical testing (FIT), triennial stool DNA testing combined with a FIT assay, and colonoscopy screening every 10 years. The researchers used CMS coverage criteria for blood tests, with a sensitivity of at least 74% for detection of CRC and specificity of at least 90%.

Without screening, the models predicted between 77 and 88 CRC cases and between 32 and 36 deaths per 1,000 individuals, costing between $5.3 million and $5.8 million. Compared with no screening, blood-based screening was considered cost-effective, with an additional cost of $25,600-$43,700 per quality-adjusted life-year gained (QALYG).

However, compared with the FIT, stool, and colonoscopy options, blood-based screening was not cost-effective, with both a decrease in QALYG and an increase in costs. FIT was more effective and less costly, with 5-24 QALYG and nearly $3.5 million cheaper than blood-based screening, even when blood-based uptake was 20 percentage points higher than FIT uptake.

In the second modeling study, US researchers compared triennial blood-based screening with established alternatives at the CMS thresholds of 74% sensitivity and 90% specificity.

Overall, a blood-based test at the CMS minimum reduced CRC incidence by 40% and CRC mortality by 52% versus no screening. However, a blood-based test was significantly less effective than triennial stool DNA testing, annual FIT, and colonoscopy every 10 years, which reduced CRC incidence by 68%-79% and CRC mortality by 73%-81%.

Assuming a blood-based test would cost the same as a multi-target stool test, the blood-based test would cost $28,500 per QALYG versus no screening. At the same time, FIT, colonoscopy, and stool DNA testing were less costly and more effective. In general, the blood-based test would match FIT's clinical outcomes if it achieved 1.4- to 1.8-fold the participation rate for FIT.

Even still, the sensitivity for advanced precancerous lesion (APL) was a key determinant. A paradigm-changing blood-based test would need to have higher than 90% sensitivity for CRC and 80% for APL, 90% specificity, and cost less than $120-$140, the study authors wrote.

"High APL sensitivity, which can result in CRC prevention, should be a top priority for screening test developers," the authors wrote. "APL detection should not be penalized by a definition of test specificity that focuses on CRC only."

Additional Considerations

The AGA CRC Workshop Panel met in September 2023 to review the two modeling studies and other data on blood-based tests for CRC. Overall, the group concluded that a triennial blood test that meets minimal CMS criteria would likely result in better outcomes than no screening and provide a simple process to encourage more people to participate in screening.

However, patients who may have declined colonoscopy should understand the need for a colonoscopy if blood-based tests show abnormal results, the commentary authors wrote.

In addition, because blood-based tests for CRC appear to be less effective and more costly than current screening options, they shouldn't be recommended to replace established screening methods. Although these blood-based tests may improve screening rates and outcomes in unscreened people, substituting blood tests for other effective tests would increase costs and worsen patient outcomes.

Beyond that, they wrote, the industry should consider other potential benchmarks for an effective blood test, such as a sensitivity for stage I-III CRC of greater than 90% and sensitivity for advanced adenomas of 40%-50% or higher.

"Unless we have the expectation of high sensitivity and specificity, blood-based colorectal cancer tests could lead to false positive and false negative results, which are both bad for patient outcomes," John M. Carethers, MD, AGAF, vice chancellor for health sciences at UC San Diego, AGA past president, and a member of the AGA CRC Workshop panel, said in a statement.

Several authors reported consultant roles and funding support from numerous companies, including Guardant Health and Freenome. ■

Dr. Lieberman

'Based on their current characteristics, blood tests should not be recommended to replace established colorectal cancer screening tests, since blood tests are neither as effective nor cost-effective and would worsen outcomes.'

Dr. Carethers