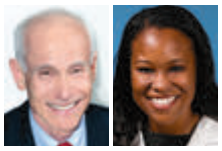

9 • EXPERT ROUNDTABLE
Implications of the First Blood-Based Test for CRC Screening.

12 • FROM THE JOURNALS
A PPI Alternative for Heartburn With Nonerosive Reflux.

18 • PERSPECTIVES
Screening Options for Rare Malignancies in the Pancreas and Bile Ducts.

aga American Gastroenterological Association

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GI&Hepatology News

November 2024

Volume 18 / Number 11

Dr. Ke-You (Yoyo) Zhang

Stanford Medicine

Giving the Smallest GI Transplant Patients a New Lease on Life

BY JENNIFER LUBELL

MDedge News

The best part about working with kids is that "I get to laugh every day," said Ke-You (Yoyo) Zhang, MD, clinical assistant professor for pediatrics–gastroenterology and hepatology at Stanford Medicine in California.

As medical director of intestinal transplant at Stanford Children's Health, Dr. Zhang sees children with critical illnesses like intestinal failure or chronic liver disease. Everyday life for them is a challenge.

Dealing with sick children is difficult. "But I think the difference between pediatrics and adults is, despite how hard things get, children are the single most resilient people you're ever going to meet," she said.

Kids don't always know they're sick and they don't act sick, even when they are. "Every day, I literally get on the floor. I get to play. I get to run around. And truly, I have fun every single day. I get excited to go to work. And I think that's what makes work not feel like work," said Dr. Zhang.

In an interview, she discussed the satisfaction of following patients throughout their care continuum and her research to reduce the likelihood of transplant rejection.

See **Smallest Patients** · *page 23*

In Crohn's Disease, Early Anti-TNF Levels May Be Crucial

BY JIM KLING

Among patients with Crohn's disease, a multicenter prospective cohort study found that anti–tumor necrosis factor (TNF) therapy failed to achieve remission at 3 years in about two-thirds of cases, and that high drug concentrations early in treatment are linked to greater probability of sustained remission.

"The relationship between drug concentrations, immunogenicity, and clinical response is likely to be multidirectional; as an observational study, we cannot definitively show the low drug levels are causative. However, our data are consistent with those from elsewhere and confirm the importance of achieving good drug levels to maximize the chances of success with anti-TNF therapy," said Nicholas Kennedy, MBBS, PhD, a consultant gastroenterologist at Royal Devon University Healthcare NHS Foundation Trust, Exeter, United Kingdom, and coauthor of the study published in *The Lancet Gastroenterology & Hepatology* (2024 April. doi: 10.1016/S2468-1253[24]00044-X).

"We also showed that adequate dosing of thiopurines was needed to prevent immunogenicity, along the lines typically used to treat Crohn's disease rather than the lower doses sometimes proposed," he added.

The findings come from the Personalized Anti-TNF Therapy in Crohn's Disease (PANTS) study conducted in the UK, which included 955 patients treated with

See **Crohn's Disease** · *page 21*

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LETTER FROM THE EDITOR

Treating Digestive Disease Across the Lifespan

Pediatric gastroenterologists are a vital, yet often overlooked, segment of the GI workforce and an important part of AGA's diverse membership. Per the American Board of Pediatrics, 2232 pediatricians have been board certified in pediatric gastroenterology since formal certification was first offered in 1990, and AGA Institute Council's Pediatric Gastroenterology and Developmental Biology Section has nearly 1900 members.


Dr. Adams

According to a recently published study in the journal *Pediatrics* (2024 Feb. doi: 10.1542/peds.2023-063678T), the pediatric GI workforce is expected to double by 2040, growing at a rate faster than that of most other pediatric subspecialties. This is largely due to the increased scope and complexity of the field driven by scientific advances and the increasing prevalence of digestive and liver diseases in children, including inflammatory bowel and other diseases.

In this month's Member Spotlight, we highlight Dr. Yoyo Zhang, a pediatric gastroenterologist at Stanford Children's Health specializing in intestinal and liver transplantation. Her passion for her profession and for improving the lives of her patients shines brightly, and her interview provides fascinating insights into the complexities and rewards of the rapidly expanding field of pediatric gastroenterology.

Also in our November issue, we update you on the FDA's recent approval of the "next-gen" Cologuard test and query a panel of primary care and GI experts on their thoughts regarding the role that newly FDA-approved (but not yet guideline-recommended) Guardant blood-based CRC screening test should play in CRC screening moving forward.

The pediatric GI workforce is expected to double by 2040, growing at a rate faster than that of most other pediatric subspecialties. This is largely due to the increased scope and complexity of the field and the increasing prevalence of digestive and liver diseases in children.

In our Perspectives feature, we offer expert insights on how to appropriately screen patients for certain rare malignancies. Is it worthwhile screening for pancreatic cancer, and if so, how should it be done? Likewise, diagnosing cholangiocarcinoma is challenging; how best should one evaluate for this in higher-risk populations?

We hope you enjoy all the content in our November issue — as always, thanks for reading! ∎

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

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A CRC Blood Test Is Here. What Does It Mean for Screening?

BY CAROLYN CRIST


Dr. Marshall


Dr. Lieberman


Dr. May


Dr. Venook


Dr. Lin


Dr. Golden

In July, the US Food and Drug Administration (FDA) approved the first blood-based test to screen for colorectal cancer (CRC).

The FDA's approval of Shield (Guardant Health) marks a notable achievement, as individuals at average risk now have the option to receive a simple blood test for CRC screening, starting at age 45.

"No one has an excuse anymore not to be screened," said John Marshall, MD, director of The Ruesch Center for the Cure of Gastrointestinal Cancers and chief medical officer of the Lombardi Comprehensive Cancer Center at Georgetown University Medical Center in Washington, DC.

The approval was based on findings from the ECLIPSE study, which reported that Shield had 83% sensitivity for CRC and 90% specificity for advanced neoplasia, though only 13% sensitivity for advanced precancerous lesions.

While an exciting option, the test has its pros and cons.

A major plus for Shield is it provides a noninvasive, convenient way for patients to be screened for CRC, especially among the approximately 30% of Americans who are either not being screened or not up to date with their screening.

The bad news, however, is that it does a poor job of detecting precancerous lesions. This could snowball if patients decide to replace a colonoscopy — which helps both detect and prevent CRC — with the blood test.

This news organization spoke to experts across three core specialties involved in the screening and treatment of CRC — primary care, gastroenterology, and oncology — to better understand both the potential value and potential pitfalls of this new option.

The interview responses have been condensed and edited for clarity.

What does this FDA approval mean for CRC screening?

David Lieberman, MD, AGAF, gastroenterologist and professor emeritus at Oregon Health & Science University: Detecting circulating free DNA associated with CRC in blood is a major scientific breakthrough. The ease of blood testing will appeal to patients and providers.

Folasade May, MD, AGAF, director of the gastroenterology quality improvement program at the University of California, Los Angeles: The FDA approval means that we continue to broaden the scope of available tools to help reduce the impact of this largely preventable disease.

Dr. Marshall: Colonoscopy is still the gold standard, but we have to recognize that not everyone does it. And that not everyone wants to send their poop in the mail (with a stool-based test). Now there are no more excuses.

Alan Venook, MD, gastrointestinal medical oncologist at the University of California, San Francisco: Although it's good to have a blood test that's approved for CRC screening, I don't think it moves the bar much in terms of screening. I worry about it overpromising and underdelivering. If it could find polyps or premalignant lesions, that would make a big difference; however, at 13%, that doesn't really register, so this doesn't really change anything.

Kenny Lin, MD, a family physician at Penn Medicine Lancaster General Health: I see this test as a good option for the 30% people of CRC screening age who are either not being screened or out of date for screening. I'm a little concerned about the people who are already getting recommended screening and may try to switch to this option.

William Golden, MD, internist and professor of medicine and public health at the University of Arkansas for Medical Sciences, Little Rock: On a scale of 1-10, I give it a 2. It's expensive ($900 per test without insurance). It's also not sensitive for early cancers, which would be its main value. Frankly, there are better strategies to get patients engaged.

What do you see as the pros and cons of this test?

Dr. Lin: The pros are that it's very convenient for patients, and it's especially easy for physicians if they have a lab in their office and can avoid a referral where patients may never get the test. However, the data I saw were disappointing, with sensitivity and specificity falling short of the stool-based Cologuard test, which is also not invasive and less likely to miss early cancers, precancerous lesions, and polyps.

Dr. Lieberman: A major con is the detection rate of only 13% for advanced precancerous lesions, which means that this test is not likely to result in much cancer prevention. There is good evidence that if advanced precancerous lesions are detected and removed, many — if not most — CRCs can be prevented.

Dr. Marshall: Another issue is the potential for a false-positive result (which occurs for 1 in every 10 tests). With this result, you would do a scope but can't find what's going on. This is a big deal. It's the first of the blood tests that will be used for cancer screening, and it could be scary for a patient to receive a positive result but not be able to figure out where it's coming from.

Will you be recommending this test or relying on its results?

Dr. Lieberman: Patients need to understand that the blood test is inferior to every other screening test and, if selected, would result in less protection against developing CRC or dying from CRC than other screening tests. But models suggest that this test will perform better than no screening. Therefore, it is reasonable to offer the test to individuals who decline any other form of screening.

Dr. May: I will do what I've always done — after the FDA approval, I wait for the US Preventive Services Task Force (USPSTF) to endorse it. If it does, then I feel it's my responsibility to tell my patients about all the options they have and stay up to date on how the tests perform, what the pros and cons are, and what reliable information will help patients make the best decision.

Dr. Venook: No, but I could potentially see us moving it into surveillance mode, where CRC survivors or patients undergoing therapy could take it, which might give us a unique second bite of the apple. The test could potentially be of value in identifying early relapse or recurrence, which might give us a heads-up or jump start on follow-up.

Are you concerned that patients won't return for a colonoscopy after a positive result?

Dr. Golden: This concern is relevant for all tests, including fecal immunochemical test (FIT), but I've found that if the patient is willing to do the initial test and it comes back positive, most are willing to do the follow-up. Of course, some folks have issues with this, but now we'll have a marker in their medical records and can re-engage them through outreach.

Dr. Lieberman: I am concerned that a patient who previously declined to have a colonoscopy may not follow up an abnormal blood test with a colonoscopy. If this occurs, it will render a blood test program ineffective for those patients. Patients should be told upfront that if the test is abnormal, a colonoscopy would be recommended.

Dr. May: This is a big concern that I have. We already have two-step screening processes with FIT, Cologuard, and CT colonography, and strong data show there is attrition. All doctors and companies will need to make it clear that if patients have an abnormal test result, they

Continued on following page

New Biologic Tulisokibart Beats Placebo in UC Trial

BY DIANA SWIFT

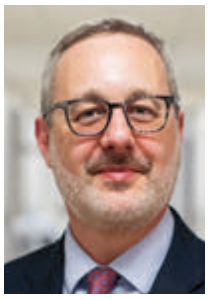
The experimental monoclonal antibody tulisokibart safely induced clinical remission in a phase 2 randomized trial of moderately to severely active ulcerative colitis (UC).

In one cohort of 135 patients, the primary endpoint of clinical remission occurred in 26% of those given the novel antibody to tumor necrosis factor–like cytokine 1A (TL1A) vs 1% given placebo (95% CI, 14-37, $P < .001$). In a smaller cohort of 43 patients genetically pretested for likely response to the new biologic, remission after treatment was only slightly higher at 32% vs 11% (95% CI, 2-38, $P = .02$).

The incidence of adverse events was similar in both arms, and most events were mild.

The 12-week induction trial, conducted in 14 countries by the ARTEMIS-UC Study Group and led by Bruce E. Sands, MD, MS, AGAF, a professor of medicine at Icahn School of Medicine at Mount Sinai and system chief in the Division of Gastroenterology at Mount Sinai Health System in New York City, was published in *The New England Journal of Medicine* (2024 Sep 25. doi: 10.1056/NEJMoa2314076).

"Our results suggest that important clinical benefit may be achieved through TL1A blockade in patients with UC," Dr. Sands said in an interview with *GI & Hepatology News*, adding that this is the first rigorous study of a drug class with an entirely new mechanism of action that may be beneficial in other immune-mediated and fibrotic diseases.


Dr. Sands

"And it is also the first prospective randomized controlled trial in IBD [inflammatory bowel disease] to incorporate a precision-medicine approach using a predictive biomarker for response in a drug development program," he added.

Dr. Sands stressed the urgent need for new therapies since, despite the approval of multiple new classes of agents, both small molecules and biologics, "there is still a plateau of efficacy in that less than 50% of patients achieve remission at a year."

Continued on following page

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must undergo a colonoscopy. We must have activated and involved systems of patient follow-up and navigation.

Dr. Lin: I already have some concerns, given that some patients with positive FIT tests don't get timely follow-up. I see it in my own practice where we call patients to get a colonoscopy, but they don't take it seriously or their initial counseling wasn't clear about the possibility of needing a follow-up colonoscopy. If people aren't being screened for whatever reason in the first place and they get a positive result on the Shield blood test, they might be even less likely to get the necessary follow-up testing afterward.

What might this mean for insurance coverage and costs for patients?

Dr. May: This is an important question because if we don't have equal access, we create or widen disparities. For insurers to cover Shield, it'll need to be endorsed by major medical societies, including USPSTF. But what will happen in the beginning is that wealthy patients who can pay out of pocket will use it, while lower-income individuals won't have access until insurers cover it.

Dr. Golden: I could do 70 (or more) FIT tests for the cost of this one blood test. A FIT test should be offered first. We're advising the Medicaid program that physicians should be required to explain why a patient doesn't want a FIT test, prior to covering this blood test.

Dr. Venook: It's too early to say. Although it's approved, we now have to look at the monetization factor. At the end of the day, we still need a colonoscopy. The science is impressive, but it doesn't mean we need to spend $900 doing a blood test.

Dr. Lin: I could see the coverage trajectory being similar to that for Cologuard, which had little coverage when it came out 10 years ago, but eventually, Medicare and commercial coverage happened. With Shield, initially, there will be some coverage gaps, especially with commercial insurance, and I can see insurance companies having concerns, especially because the test is expensive compared with other tests and the return isn't well known. It could also be a waste of money if people with positive tests don't receive follow-up colonoscopies.

What else would you like to share that people may not have considered?

Dr. Marshall: These tests could pick up other genes from other cancers. My worry is that people could have another cancer detected but not find it on a colonoscopy and think the blood test must be wrong. Or they'll do a scan, which could lead to more scans and tests.

Dr. Golden: This test has received a lot of attention and coverage that didn't discuss other screening options, limitations, or nuances. Let's face it — we'll see lots of TV ads about it, but once we start dealing with the total cost of care and alternative payment models, it's going to be hard for this test to find a niche.

Dr. Venook: This test has only been validated in a population of ages 45 years or older, which is the conventional screening population. We desperately need something that can work in younger people, where CRC rates are increasing. I'd like to see the research move in that direction.

Dr. Lin: I thought it was unique that the FDA Advisory Panel clearly stated this was better than nothing but also should be used as second-line screening. The agency took pains to say this is not a colonoscopy or even equivalent to the fecal tests in use. But they appropriately did approve it because a lot of people aren't getting anything at all, which is the biggest problem with CRC screening. ■

Continued from previous page

He added that UC may progress over time owing to fibrosis of the bowel, a condition not directly or safely addressed by any existing therapies. "Identifying novel targets such as TL1A may allow us to address a different subpopulation of patients who may not respond to the targets addressed by existing therapies," he said.

In agreement is Jason K. Hou, MD, MS, AGAF, an associate professor of medicine at Baylor College of Medicine and section chief of gastroenterology at Michael E. DeBakey VA Medical Center, both in Houston, Texas. "Although it's a very exciting time with more options in the last few years for treating UC, even inhibitors with new agents such as JAK [Janus kinase] inhibitors and interleukin 23 antagonists, many patients have no or only a partial response," he said in an interview. "Targeting molecules, which has been studied for decades, may offer more than a shot in the dark."

Why Target TL1A?

Genomewide studies have shown elevated TL1A, a member of the tumor necrosis factor superfamily, in patients with inflammatory bowel disease (Curr Drug Targets. 2021;22[7]:760-769).

"The interaction of TL1A and its ligand, death domain receptor 3, contributes to the immune-mediated inflammation and fibrosis seen in IBD through the downstream production of proinflammatory cytokines by multiple different immune cells, and the elaboration of collagen by fibroblasts," Dr. Sands explained.

Dr. Hou

'Although it's a very exciting time with more options in the last few years for treating UC, even inhibitors with new agents such as JAK inhibitors and interleukin 23 antagonists, many patients have no or only a partial response. Targeting molecules, which has been studied for decades, may offer more than a shot in the dark.'

With the intention of targeting TL1A, his group randomly assigned patients with moderate to severe active UC who were glucocorticoid dependent or had not responded to conventional or advanced therapies, with disease extending a minimum of 15 cm from the anal verge. Across arms, the age of the mainly White, non-Hispanic participants ranged from about 37 to about 42, 35%-53% were female, and disease duration was approximately 6-8 years.

The arms received either placebo or intravenous tulisokibart at 1000 mg on day 1 and 500 mg at weeks 2, 6, and 10. Cohort 1 included patients regardless of biomarker status for likelihood of response. Cohort 2 included only patients with a positive test for likelihood of response.

Dr. Hou was surprised that response to tulisokibart vs placebo was not greater in test-identified probable responders. "The biomarker didn't make a huge difference, just a numerical one," he said. "It may be that more genes are involved than the test could identify, and response is more complicated. Or perhaps the placebo response was particularly high in this small group. We need a deeper dive into why."

Earlier Application?

"This was a phase 2 study, so it's too soon to say if tulisokibart could be used as early therapy or in severe disease," Dr. Sands said. "However, the excellent safety profile and efficacy suggest that these populations should be explored in later studies.

Further work is needed to validate the test to predict higher likelihood of response, he added, and recruiting for a phase 3 study is now underway.

The study was supported by Prometheus Biosciences, a subsidiary of Merck. Dr. Sands disclosed multiple ties to private companies, including research support, consulting, data safety monitoring, travel, a gift, and a stock option. Several coauthors reported, variously, research support from and/or consulting for multiple private companies. Others reported employment, variously, with Prometheus and/or Merck, Spyre Therapeutics, and Mirador Therapeutics, or patent holding for IBD drugs. Dr. Hou had no relevant competing interests to disclose but will participate in the phase 3 trial. ■

Vonoprazan Offers PPI Alternative for Heartburn With Nonerosive Reflux

BY WILL PASS
MDedge News

FROM CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

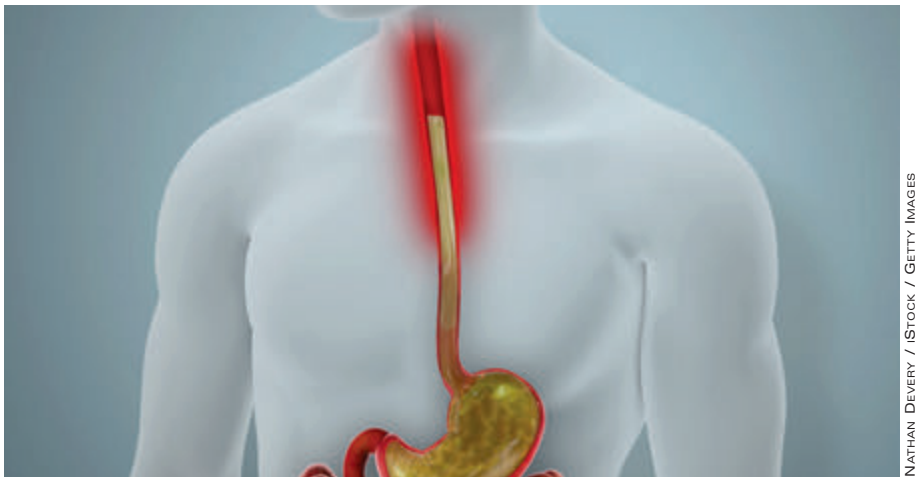
Potassium-competitive acid blocker vonoprazan is safe and effective for patients with heartburn from nonerosive reflux disease (NERD), according to investigators.

Benefits of vonoprazan were seen as soon as the first day of treatment and persisted through the 20-week extension period, lead author Loren Laine, MD, AGAF, of Yale School of Medicine, New Haven, Connecticut, and colleagues reported.

"A potential alternative to PPI [proton pump inhibitor] therapy is a potassium-competitive acid blocker, a new class of antisecretory agents that provide more potent inhibition of gastric acid secretion than PPIs," the investigators wrote in *Clinical Gastroenterology and Hepatology* (2024 May. doi: 10.1016/j.cgh.2024.05.004).


Dr. Laine

While a small observational study found that 18 out of 26 patients (69%) with PPI-resistant NERD had improved symptoms with vonoprazan, subsequent randomized trials in Japan failed to meet their primary endpoints, Dr. Laine and colleagues noted. The present randomized trial was therefore conducted to determine how vonoprazan might help a US patient population.


Nathan Devery / iStock / Getty Images

The study involved 772 patients who reported heartburn at least 4 days per week during screening, but without erosive esophagitis on endoscopy. Participants were randomized into three groups: placebo, vonoprazan 10 mg, or vonoprazan 20 mg. These protocols were administered for 4 weeks, followed by a 20-week extension, in which placebo patients were rerandomized to receive one of the two vonoprazan dose levels.

The primary endpoint was the percentage of days without daytime or nighttime heartburn (24-hour heartburn-free days) during the initial 4-week treatment period. The secondary endpoint, assessed during the same timeframe, was percentage of days without need for a rescue antacid.

In the 4-week placebo-controlled period, patients treated with vonoprazan 10 mg and 20 mg showed a significant improvement in heartburn-free days, compared with placebo. The percentage of 24-hour heartburn-free days was 27.7% in the placebo group vs 44.8% in the 10-mg vonoprazan group (least-squares mean difference 17.1%; $P < .0001$) and 44.4% in the 20-mg vonoprazan group (least-squares mean difference 16.7%; $P < .0001$).

Benefits of vonoprazan were seen as early as the first day of treatment, with 8.3% and 11.6% more patients in the 10-mg and 20-mg groups, respectively, experiencing a heartburn-free day, compared with placebo. By day 2, these differences increased to 18.1% and 23.2%, respectively.

The percentage of days without rescue antacid use was also significantly higher in both vonoprazan groups. Patients in the 10-mg and 20-mg groups had 63.3% and 61.2% of days without antacid use, respectively, compared with 47.6% in the placebo group ($P < .0001$ for both comparisons).

These benefits persisted throughout the 20-week extension period, with similar percentages of heartburn-free days across all groups. Mean percentages of 24-hour heartburn-free days ranged from 61% to 63% in the extension phase, while median percentages spanned 76%-79%.

Adverse events were infrequent and comparable across all groups. The most common adverse event was nausea, occurring slightly more frequently in the vonoprazan groups (2.3% in the 10-mg group and 3.1% in the 20-mg group) vs placebo (0.4%). Serious adverse events were rare and were deemed unrelated to treatment. No new safety signals were identified during the 20-week extension period. Increases in serum gastrin levels, a marker of acid suppression, returned to near baseline after discontinuation of vonoprazan.

"In conclusion, the potassium-competitive acid blocker vonoprazan was efficacious in reducing heartburn symptoms in patients with NERD, with the benefit appearing to begin as early as the first day of therapy," Dr. Laine and colleagues wrote.

In July 2024, the Food and Drug Administration approved vonoprazan for treating heartburn in patients with nonerosive gastroesophageal reflux disease.

This study was funded by Phathom Pharmaceuticals. The investigators disclosed additional relationships with Takeda, Medtronic, Carnot, and others. ■

Proton pump inhibitors (PPIs) have revolutionized the treatment of gastroesophageal reflux disease (GERD). One might ask what the reason would be to challenge this giant of the pharmacopeia with another medication for GERD.


Dr. Katzka

Enter vonoprazan, which competitively binds to the H+, K+-ATPase alpha-subunit (PCAB), has a more rapid and sustained onset of gastric acid inhibition, is resistant to degradation by acid and remains active at a neutral pH, has a half-life four times longer than a PPI, and is not metabolized through the CYP2C19 or CYP3A4 enzyme. But do these pharmacokinetic advantages translate to clinical advantages in the treatment of GERD?

In this important study by Laine et al, vonoprazan is expectedly efficacious in treating nonerosive GERD (NERD) but notably less so when compared with the authors' trial for erosive GERD. This is not surprising owing to the multiple and common acid-independent etiologies of NERD, such as esophageal hypersensitivity. The high placebo response supports this. Two notable results, however, merit emphasis in potential advantages over PPIs.

First, vonoprazan is effective at day 1 of therapy by eliminating the need for loading. Second, nocturnal reflux, a purer form of GERD, is better controlled with a morning dose of vonopazan mitigating against nocturnal acid breakthrough and the need for twice-daily dosing with PPIs and/or addition of an H2 antagonist. These results by no means advocate for replacement of PPIs with PCABs, but at least suggest certain populations of GERD patients who may specifically benefit from PCAB use. The study also indirectly emphasizes that careful selection of NERD patients whose GERD symptoms are predominantly caused by increased esophageal acid exposure are the most appropriate candidates. The ultimate answer as to where vonoprazan will be used in our practice is evolving.

David Katzka, MD, is based in the Division of Digestive and Liver Diseases, Columbia University Medical Center, New York City. He has received research support from Takeda, Sanofi, and Regeneron. He is also an associate editor for GI & Hepatology News.

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MASLD Healthcare Costs Climbing Fast in Canada

BY WILL PASS
MDedge News

FROM GASTRO HEP ADVANCES

Metabolic dysfunction–associated steatotic liver disease (MASLD) is expected to bring a wave of added healthcare costs to Canada, with projections indicating an increase of almost C$2 billion (Canadian dollars) by 2050, according to a new study.

The expected surge reflects the growing prevalence of MASLD and its associated conditions, emphasizing the necessity for a comprehensive approach to address this escalating public health issue, reported lead author K. Ally Memedovich, BHSc, of the University of Calgary in Alberta, Canada, and colleagues.

"The costs associated with the management of MASLD in Canada remain unknown but have been estimated as being very high," the investigators wrote in *Gastro Hep Advances* (2024 Jun. doi: 10.1016/j.gastha.2024.05.010). "Specifically, in one study from the United States, the healthcare costs and utilization of those with MASLD was nearly double that of patients without MASLD but with similar health status. This difference was largely due to increases in imaging, hospitalization, liver fibrosis assessment, laboratory tests, and outpatient visits."


Ms. Memedovich

Although projections are available to estimate the future prevalence of MASLD in Canada, no models are available to predict the growing national economic burden, prompting the present study.

Ms. Memedovich and colleagues analyzed healthcare usage data from 6358 patients diagnosed with MASLD disease in Calgary from 2018 to 2020. Using provincial administrative data, they calculated both liver-specific and total healthcare costs associated with different stages of liver fibrosis, ranging from F0/F1 (minimal fibrosis) to F4 (advanced fibrosis or cirrhosis).

The patients' liver fibrosis stages were determined using liver stiffness measurements obtained through shear-wave elastography. Average annual cost per patient was then calculated for each fibrosis stage by analyzing hospitalizations, ambulatory care, and physician claims data.

The annual average liver-specific cost per patient increased with severity of liver fibrosis; costs for patients with fibrosis stages F0/F1, F2, F3, and F4 were C$7.02, C$35.30, C$60.46, and C$72.55, respectively. By 2050, liver-specific healthcare costs are projected to increase by C$51 million, reaching C$136 million Canada-wide.

Total healthcare costs were markedly higher; annual costs for patients with fibrosis stages F0/F1, F2, F3, and F4 were C$397.90, C$781.53, C$2881.84, and C$1598.82, respectively. As a result,

See **MASLD** *on following page*

Celiac Screening in Kids Appears Cost-Effective

BY WILL PASS
MDedge News

FROM GASTROENTEROLOGY

Primary care screening for celiac disease (CD) in kids could improve health outcomes, and it appears cost-effective over time, according to a Dutch analysis.

If these screening strategies are deemed feasible by clinicians and patients, then implementation in routine care is needed, lead author Jan Heijdra Suasnabar, MSc, of Leiden University Medical Centre in the Netherlands, and colleagues reported.

"Cohort studies have shown that CD likely develops early in life and can be easily diagnosed by detection of CD-specific antibodies against the enzyme tissue transglutaminase type 2 (IgA-TG2)," the investigators wrote in *Gastroenterology* (2024 Jul. doi: 10.1053/j.gastro.2024.07.024).


Mr. Suasnabar

Despite the ease of diagnosis, as few as one in five cases of CD are detected using current clinical strategies, meaning many cases are diagnosed years after symptom onset.

"Such high rates of missed/delayed diagnoses have been attributed to CD's varied and nonspecific symptoms, lack of awareness, and the resource-intensive process necessary to establish the diagnosis," Mr. Heijdra Suasnabar and colleagues wrote. "From an economic perspective, the burden of CD translates into substantial excess healthcare and societal costs."

These practice gaps prompted the present study, which explored the long-term cost-effectiveness of mass CD screening and active case finding among pediatric patients.

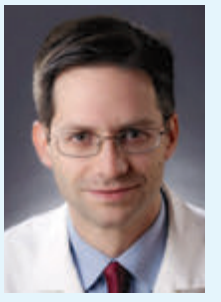
The investigators employed a model-based cost-effectiveness analysis with a hypothetical cohort representing all children with CD in the Netherlands. Iterations of this model evaluated long-term costs as these children moved through the healthcare system along various CD detection strategies.

The first strategy was based on the current

See **Celiac** *on following page*

Celiac disease (CD) is common, affecting about 1% of the population, but it remains underdiagnosed because of its heterogeneous presentation and limited provider awareness. Most cases are detected only after patients develop gastrointestinal symptoms or laboratory abnormalities.


Dr. Doyle


Dr. Lebwohl

While several international guidelines recommend screening high-risk children — such as those with a family history of CD or certain autoimmune conditions — population-based screening of average-risk children is not routine in most countries. There is growing interest in population-based screening, particularly with the increased acceptance of serological-only diagnosis of CD in children, but evidence on its long-term economic feasibility is limited.

In this cost-effectiveness analysis, Mr. Heijdra Suasnabar and colleagues demonstrate that screening children for celiac disease would be highly cost-effective relative to the current practice of clinical detection. They modeled point-of-care testing using tissue transglutaminase IgA in all 3-year-old children in the Netherlands. While both mass screening and case finding (via a standardized questionnaire) would increase healthcare costs relative to current care, both strategies would improve quality of life (QoL), reduce long-term complications (such as osteoporosis and non-Hodgkin lymphoma), and minimize productivity losses in individuals with CD. In sensitivity analyses accounting for uncertainty in QoL inputs and in the utility of diagnosing and treating asymptomatic CD, each screening strategy remained well below accepted willingness-to-pay thresholds.

These results suggest population-based CD screening in children may be a viable policy. As many inputs in this model were specific to the Netherlands, international generalization is not ensured, but extrapolation to other developed countries seems reasonable. Future studies should explore optimal screening intervals for older children and adults.

John B. Doyle, MD, is a gastroenterology fellow in the Division of Digestive and Liver Diseases at Columbia University Medical Center, New York City. Benjamin Lebwohl, MD, MS, AGAF, is professor of medicine and epidemiology at Columbia University Medical Center and director of clinical research at The Celiac Disease Center at Columbia. They have no conflicts of interest to declare.

MASLD *from previous page*

total healthcare costs are expected to rise by nearly C$2 billion, contributing to a Canadian healthcare burden of C$5.81 billion annually by 2050.

The study revealed that over 90% of the healthcare costs for MASLD patients were attributed not to liver disease itself but to the management of associated comorbidities such as diabetes, hypertension, mental illness, and obesity. For instance, diabetes was the most common reason for physician visits among MASLD patients, accounting for 65.2% of cases. One study limitation was exclusion of decompensated cirrhosis, liver cancer, or a liver transplant recipient because of low prevalence in this cohort, potentially contributing to low liver-specific healthcare costs.

Ms. Memedovich and colleagues noted that chronic diseases account for approximately C$68 billion annually in direct healthcare costs in Canada, representing around 58% of total healthcare expenditures. Estimates suggest that 1% annual reduction in chronic disease prevalence could save C$107 billion over the course of 20 years.

"Therefore, an approach that focuses on preventing and managing chronic diseases overall is needed to reduce the burden of MASLD on the healthcare system," they wrote.

This study was funded by LiveRx via an Alberta Innovates grant. The investigators disclosed relationships with Gilead, Abbott, GSK, and others. ■

Metabolic dysfunction–associated steatotic liver disease (MASLD) is the most common chronic liver disease, and its clinical burden is expected to mirror the rising rates of obesity and diabetes over the next couple decades. The cost analysis by Memdovich and colleagues provides a timely report on the healthcare burden of MASLD in Canada. Their results are, nevertheless, generalizable to other healthcare systems.

The authors found that nearly 98% of total healthcare costs of patients with MASLD were not specifically related to liver treatment, but rather linked to the management of patients' cardiometabolic comorbidities. Projection estimates based on this cohort suggests a steep rise in the total healthcare costs over the coming decades reflecting increasing rates of comorbidities, with largest changes expected in the advanced fibrosis patient group. These findings highlight the need for early recognition of MASLD followed by a collaborative effort in management of MASLD in conjunction with its associated cardiometabolic comorbidities.

As rates for obesity, diabetes, and MASLD continue to rise, there is an urgency to create a global strategy for MASLD management that focuses on both prevention and treatment. Public health strategies are needed to increase awareness and focus on the treatment and prevention of cardiometabolic risk factors that appear to be the main drivers of healthcare costs among patients with MASLD. A concerted effort is needed from providers, both primary care and specialists, for early recognition and treatment of MASLD. Such a public health response combined with recent advent in pharmacotherapy for weight loss and metabolic dysfunction–associated steatohepatitis may alter the projected costs and hopefully decrease the disease burden associated advanced MASLD.

Akshay Shetty, MD, is assistant professor of medicine and surgery at the David Geffen School of Medicine, University of California, Los Angeles (UCLA). He has no conflicts of interest to declare. Sammy Saab, MD, MPH, AGAF, is professor of medicine and surgery at the David Geffen School of Medicine at UCLA. He is on the speakers bureau for AbbVie, Gilead, Eisai, Intercept, Ipsen, Salix, Mallinckrodt, and Takeda, and has been a consultant for Gilead, Ipsen, Mallinckrodt, Madrigal, and Orphalan.

Celiac *from previous page*

Dutch approach, which is the same as that in the United States: Patients are evaluated for CD only if they present with symptoms that prompt suspicion of disease. Based on data from population-based studies, the model assumed that approximately one in three cases would be detected using this strategy.

The second strategy involved mass screening using IgA-TG2 point-of-care testing (sensitivity, 0.94; specificity, 0.944) via youth healthcare clinics, regardless of symptoms.

The third strategy, called "active case finding," represented something of an intermediate approach, in which children with at least one CD-related symptom underwent point-of-care antibody testing.

For both mass screening and active case–finding strategies, a positive antibody test was followed with confirmatory diagnostic testing.

Compared with the current clinical approach, mass screening added 7.46 more quality-adjusted life-years (QALYs) per CD patient with an increased cost of €28,635 per CD patient. Active case finding gained 4.33 QALYs per CD patient while incurring an additional cost of €15,585 per CD patient.

Based on a willingness-to-pay threshold of €20,000 per QALY, the investigators deemed both strategies "highly cost-effective," compared with current standard of care. Some of these costs were offset by "substantial" reductions in productivity losses, they noted, including CD-related absences from work and school.

"Our results illustrate how an earlier detection of CD through screening or case finding, although more costly, leads to improved health outcomes and a reduction in disease burden, compared with current care," Mr. Heijdra Suasnabar and colleagues wrote.

Their concluding remarks highlighted the conservative scenarios built into their model, and suggested that their findings offer solid evidence for implementing new CD-testing strategies.

"If found to be feasible and acceptable by clinicians and patients, these strategies should be implemented in the Netherlands," they wrote.

This study was supported by the Netherlands Organization for Health Research and Development. The investigators disclosed no conflicts of interest. ■

Screening Options for Rare Malignancies

Dear colleagues,
As gastroenterologists and endoscopists, we spend significant time preventing and diagnosing GI malignancies. While colorectal and esophageal cancer and their precursor lesions are well known to us, our approach to rarer malignancies is less well defined.

For instance, is it worthwhile screening for pancreatic cancer, and, if so, how should this be done? Likewise, diagnosing cholangiocarcinoma is challenging; how best should one evaluate for this in higher-risk populations, such as primary sclerosing cholangitis? And what about the costs, financial and otherwise, associated with screening?

In this issue of Perspectives, Dr. Darshan Kothari and Dr. Daniel Bernstein discuss their approach to pancreatic cancer screening, including who is eligible, the preferred screening modalities, and the barriers to screening. In the accompanying perspective, Dr. Aparna Goel and Dr. Judah Kupferman focus on cholangiocarcinoma screening, identifying high-risk populations and discussing some of the concerns with screening, necessitating shared decision-making.


Dr. Ketwaroo

We welcome your thoughts on this issue. Share with us on X at @AGA_GIHN.

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

Pancreas: An Approach to Cancer Screening

BY DANIEL A. BERNSTEIN, MD, AND DARSHAN KOTHARI, MD

Pancreatic cancer carries a dismal prognosis, now accounting for the third-most cancer-related mortality in the United States. A small proportion of patients are diagnosed at a local stage of disease, with over half found to have metastatic disease at presentation. Given the low overall incidence and lifetime risk in the general population, population-based screening is not justified.


Dr. Bernstein


Dr. Kothari

About 10% of cases of pancreas cancer are associated with germline mutations and/or with a strong family history of pancreatic cancer. Several academic societies and expert committees now recommend regular screening for pancreatic cancer in patients who are considered high-risk individuals, as they carry a fivefold relative risk for pancreatic cancer. Moreover, studies suggest that screening has the potential to identify early-stage resectable disease and decrease mortality in this patient population.

Patients who benefit from pancreatic cancer screening are those who carry an increased lifetime risk (in excess of 5%) of pancreatic cancer. High-risk individuals include those with germ-line mutations and/or those with a family history of pancreatic cancer in first-degree relatives. Consensus guidelines by the International Cancer of the Pancreas Screening Consortium and the American Society for Gastrointestinal Endoscopy provide medical centers with detailed recommendations on who and when to start screening.

High-risk individuals fall into three categories:

- Patients with high-risk germline mutations including familial atypical multiple mole melanoma syndrome (CDKN2A), hereditary breast and ovarian cancer syndromes (BRCA1, BRCA2, and PALB2), Peutz-Jeghers syndrome (STK11), and hereditary pancreatitis (PRSS1 and SPINK1)
- Patients with low- to moderate-risk germ-line mutations with at least one first-degree relative with pancreatic cancer: Lynch Syndrome (particularly MLH1 mutation), ataxia-telangiectasia (ATM), or Li-Fraumeni syndrome (p53)
- Patients with one first-degree

See **Pancreas** *on following page*

Bile Ducts: Screening for Cholangiocarcinoma

BY JUDAH KUPFERMAN, MD, AND APARNA GOEL, MD

Cholangiocarcinoma is a rare but aggressive cancer of the bile ducts that poses many diagnostic challenges. Approximately 3% of gastrointestinal cancers are attributed to cholangiocarcinoma, and while the annual incidence of disease in the United States is about 1.26 per 100,000 people, the incidence of intrahepatic disease has been rising considerably.[1,2] Screening for cholangiocarcinoma is reserved for high-risk individuals — such as those with primary sclerosing cholangitis (PSC), secondary sclerosing cholangitis (SSC), and biliary tract disorders such as choledochal cysts or Caroli's disease. The goal is to balance the benefits of early diagnosis with the costs and risks associated with screening, particularly given the limitations of available tools like MRI with cholangiopancreatography (MRCP), which has a sensitivity of 70%-85%. In general, we recommend annual cholangiocarcinoma screening for high-risk individuals with MRI and MRCP as well as with cancer antigen (CA) 19-9.


Dr. Kupferman


Dr. Goel

Screening in Patients with Primary Sclerosing Cholangitis

The lifetime risk of cholangiocarcinoma in patients with PSC is 10%-15% with an annual risk of 0.5%-1.5%. In our experience, this is often the most feared complication for PSC patients, even more so than the risk of liver transplantation. We recommend annual MRI with MRCP in addition to CA 19-9 for patients with PSC in the first decade of their diagnosis, as most cancers are diagnosed during this period. If a patient's imaging has remained stable for over a decade and there is minimal hepatic fibrosis, we discuss the option of reducing screening frequency to every 2 years to minimize costs and exposure to MRI contrast risks.

If MRI reveals a concerning new large duct stricture, we will evaluate this with an endoscopic retrograde cholangiopancreatography (ERCP), as differentiating benign and malignant strictures is quite challenging with MRI. We generally recommend ERCP with brush cytology and fluorescence in situ hybridization to improve diagnostic yield. Depending on imaging

See **Bile Ducts** *on following page*

Read more!

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

Pancreas *from previous page*

relative with pancreatic cancer who in turn has one first-degree relative with pancreatic cancer (eg, a patient's mother and maternal aunt or a patient's father and patient's sister)

Consistent with established guidelines, we recommend screening for high-risk patients beginning at age 50, or 10 years before the youngest age at which pancreas cancer was diagnosed in an affected relative. Screening is recommended earlier in patients with particularly high risk: at age 40 for patients with CDKN2A and STKI11 mutations and age 40 for patients with PRSS1 mutation or 20 years after the first attack of acute pancreatitis. For patients with a strong family history of pancreas cancer, we recommend comprehensive evaluation by a certified genetic counselor at a high-volume cancer center.

Several academic societies and expert committees now recommend regular screening for pancreatic cancer in patients who are considered high-risk individuals.

In practice, patients at our institution who are identified as high risk based on the above criteria are referred for an initial consultation at our pancreas center. In most cases, this should occur no sooner than 5 years prior to the recommended starting age for screening. All patients who are identified as high risk should be screened annually for diabetes given the growing evidence base supporting an association between new-onset diabetes and pancreatic cancer.

After an initial visit and discussion of the risks and benefits of screening, most screening protocols start with a baseline endoscopic ultrasound (EUS) and contrast-enhanced magnetic resonance imaging with magnetic resonance cholangiopancreatography (MRI/MRCP), which will be repeated annually or sooner as the clinical condition warrants. A sooner-interval EUS should be considered for patients already undergoing screening who are newly found to have diabetes.

At our institution, we start with an in-person clinic evaluation followed by EUS. Thereafter, patients undergo MRI/MRCP (synchronized with a same-day clinic visit) alternating with EUS every 6 months to ensure patients are seen twice a year, though there are no specific data to support this approach. Non-diabetes patients also undergo yearly diabetes screening which will trigger an EUS if patients become diabetic.

We engage in shared decision-making with our high-risk individuals undergoing pancreatic cancer screening and at each visit we review their concurrent medical conditions and suitability to continue screening. We consider discontinuing screening after age 75, at the onset of any life-limiting illness, or after a discussion of risks and benefits if comorbidities lead to a substantial deterioration in a patient's overall health status.

While a growing body of evidence exists to support the application of pancreatic cancer screening in high-risk individuals, this preventive service remains underutilized. Recent analysis of the screening cohort at our institution showed a demographically homogeneous group of mostly highly educated, high-income White females. These findings are consistent with the patient cohorts described in other pancreatic cancer screening programs and represent only a fraction of people who would qualify for pancreatic cancer screening.

A survey of patients undergoing screening at our institution identified cost, travel, and time associated with pancreatic cancer screening to be frequent challenges to participation. Further studies are needed to fully explore the barriers and psychological burden of pancreas cancer screening in high-risk individuals, and to identify ways to enrich the cohort of patients undergoing screening. This may involve novel methods to identify family members of patients with a new diagnosis of pancreas cancer and increasing health literacy around pancreatic cancer screening among patients and providers.

Pancreatic cancer screening has the potential to identify early-stage disease in patients who are at high risk because of germ-line mutations and/or family history. We recommend that patients engage in pancreatic cancer screening at high-volume centers with well-supported oncology, genetics, and research infrastructure. ■

Dr. Bernstein is a gastroenterology fellow at Duke University School of Medicine, Durham, North Carolina. Dr. Kothari is an associate professor of medicine in gastroenterology and hepatology at Duke University School of Medicine.

Bile Ducts *from previous page*

findings and location of the new large duct stricture, we may consider cholangioscopy during ERCP for direct visualization of the bile duct and directed tissue biopsies. Unfortunately, even in young, asymptomatic patients who undergo regular screening, cholangiocarcinoma is frequently diagnosed at an advanced stage.

Screening in Patients With Secondary Sclerosing Cholangitis

Patients with SSC may develop cholangiocarcinoma because of chronic inflammatory and fibrotic processes, such as IgG4-associated cholangiopathy, sarcoidosis, ischemic cholangiopathy, cystic fibrosis, recurrent pyogenic cholangitis, severe sepsis (as recently seen from SARS-CoV-2), surgical complications, or other etiologies. When the condition is reversible, such as with IgG4-associated cholangiopathy, cancer screening may not be necessary. However, when irreversible damage occurs, the cancer risk increases, though it varies by disease type and severity. In most cases, we recommend routine screening for cholangiocarcinoma with MRI and CA 19-9 in this population.

From our perspective, cholangiocarcinoma screening in high-risk patients is crucial but not without challenges. Our current screening methods, while essential, are far from perfect, often missing early cancers.

Screening in Patients With Biliary Tract Disorders

Biliary tract disorders such as choledochal cysts and Caroli's disease also harbor an increased risk of cholangiocarcinoma. Choledochal cysts are congenital cystic dilations of the bile duct that have a 10%-30% lifetime risk of malignant transformation to cholangiocarcinoma. Surgical intervention to remove the cyst is often recommended because of this high risk. However, some patients may be unable or unwilling to undergo this surgery or they may have residual cysts. We recommend ongoing screening with MRI and CA 19-9 for these patients. Similarly, Caroli's disease is a congenital disease associated with intrahepatic and extrahepatic bile duct cysts and associated with a 5%-15% lifetime risk of cholangiocarcinoma. MRI with MRCP and CA 19-9 should be performed routinely for patients with Caroli's disease and syndrome.

Risks and Challenges in Cholangiocarcinoma Screening

While MRI with MRCP is the gold standard for cholangiocarcinoma screening, its limitations must be carefully considered. One growing concern is the potential for gadolinium retention in the brain, bones, or skin following repeated MRI scans. Though the long-term effects of gadolinium retention are not fully understood, we factor this into screening decisions, particularly for younger patients who may undergo decades of regular imaging.

MRI is not always feasible for certain patients, including those with metal implants, on hemodialysis, or with severe allergic reactions. In such cases, CT or ultrasound may serve as alternatives, though with lower sensitivity for detecting cholangiocarcinoma. Additionally, claustrophobia during MRI can be addressed with sedation, but this underscores the importance of shared decision-making.

From our perspective, cholangiocarcinoma screening in high-risk patients is crucial but not without challenges. Our current screening methods, while essential, are far from perfect, often missing early cancers or leading to unnecessary interventions. Because of these limitations, the window for treatment of localized disease can easily be missed.

In our practice, we tailor screening strategies to each patient's specific needs, weighing the potential benefits against the risks, costs, and the inherent uncertainty of early detection tools. We believe it is essential to involve patients in this decision-making process to provide a balanced, individualized approach that considers both clinical evidence and the personal preferences of each patient. ■

Dr. Kupferman is a hospitalist at Stanford University School of Medicine in California. Dr. Goel is a transplant hepatologist and a clinical associate professor in gastroenterology & hepatology at Stanford.

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FDA OKs Next-Gen Cologuard Test for CRC Screening

BY MEGAN BROOKS

The US Food and Drug Administration (FDA) approved Exact Sciences' next-generation multitarget stool DNA (mt-sDNA) test, Cologuard Plus, for use in adults 45 or older who are at average risk for colorectal cancer (CRC).

Developed in collaboration with Mayo Clinic, the company noted in the news release announcing its approval that this noninvasive test "raises the performance bar."

The company says the enhanced sensitivity will help minimize unnecessary follow-up colonoscopy procedures by reducing the odds of a false-positive screening test.

Enhanced sample stability components also will give patients more time to return their sample to the lab.

Cologuard Plus tests for three novel methylated DNA markers and fecal hemoglobin.

The BLUE-C Study

The FDA's approval was based on the results of the BLUE-C study involving more than 20,000 adults at average risk for CRC that compared the next-generation mt-sDNA test with a fecal immunochemical test (FIT) and colonoscopy.

According to the BLUE-C results, the sensitivities of Cologuard Plus were 95% for CRC and 43% for advanced precancerous lesions, at 94% specificity with no findings on colonoscopy.

The BLUE-C results also showed that the test significantly outperformed FIT for sensitivity for CRC overall, CRC stages I-III, high-grade dysplasia, and advanced precancerous lesions.


Dr. Imperiale

"To meaningfully improve outcomes in colorectal cancer, we must catch cancer early — when it is most treatable — and find advanced precancers, which can prevent cases of this cancer," Thomas F. Imperiale, MD, AGAF, professor of medicine at the Indiana University School of Medicine and research scientist at the Regenstrief Institute, both in Indianapolis, said in the news release.

The FDA's approval was based on the results of the BLUE-C study involving more than 20,000 adults at average risk for CRC that compared the next-generation mt-sDNA test with a fecal immunochemical test and colonoscopy.

"The high colorectal cancer sensitivity and specificity of the Cologuard Plus test gives me confidence in the test's ability to do just that while simultaneously maintaining a low risk of false positives. This makes the Cologuard Plus test a strong option for first-line screening of average risk patients," said Dr. Imperiale, who served as principal investigator of the BLUE-C study.

The company plans to launch Cologuard Plus in 2025.

They anticipate that it will be covered by Medicare and included in the United States Preventive Services Task Force guidelines and within quality measures. ■

Anti-TNF Therapy

Crohn's Disease *from page 1*

infliximab and 655 treated with adalimumab between March 2014 and September 2017. The participants were 6 years or older, the median age was 32.5 years, and 51% were female.

The latest findings come from a 2-year extension of the original 1-year PANTS study, published in 2019, which found that low drug concentrations predicted anti-TNF treatment failure — a result likely attributable in part to immunogenicity, since low drug concentrations predicted the presence of anti-drug antibodies, and anti-drug antibodies in turn predicted low drug concentrations, according to Miguel Regueiro, MD, AGAF, chief of the Digestive Diseases Institute and a professor of medicine at the Cleveland Clinic, Ohio.

"This is one of the more important studies looking at the longitudinal care of patients with Crohn's disease on infliximab and adalimumab," said Dr. Regueiro, who was not involved with the study.

The extension study found that anti-drug antibodies and undetectable drug levels were associated with both treatment without an accompanying immunomodulator and carriage of the HLA-DQA1*05 genetic risk factor, though the latter was true only for treatment with infliximab.

Dr. Regueiro noted that the study demonstrates that "getting it right in induction is probably the most important part" of treating Crohn's disease.

"Getting patients in remission early has probably a long-term prediction [of treatment success]. I do think that is practice changing. My practice has changed over the years, largely based on the initial PANTS study. I am measuring infliximab and adalimumab levels after induction, and I am using that number to decide if I dose intensify the drug, or if I've hit that sweet spot," said Dr. Regueiro.

The study highlights a debate among clinicians, about whether higher drug levels are associated with remission because of the effects of higher doses, or because patients who respond have reduced leakiness in the gut, leading to greater retention of protein therapeutics.

"What the study clearly says is that the drug [level] after induction is important. It implies that there are higher remission rates early. The only thing that it didn't really tell you is the total inflammatory burden in the body, and [if] lower inflammation equals higher drug level," said Dr. Regueiro. He did note that the study found that obesity was a negative predictor of long-term remission, which could be attributable to the pro-inflammatory nature of adipose tissue, but he emphasized that the new study doesn't prove causation.

Dr. Regueiro

'Getting patients in remission early has probably a long-term prediction [of treatment success]. I do think that is practice changing. My practice has changed over the years, largely based on the initial PANTS study. I am measuring infliximab and adalimumab levels after induction, and I am using that number to decide if I dose intensify.'

The study also emphasizes the importance of the HLA-DQA1*05 genetic risk factor.

"I think it confirms that if you're a carrier of that HLA-DQA1*05, especially with infliximab, if you're not on an immunomodulator like a thiopurine, you have a very high likelihood of having very high antibodies against infliximab," Dr. Regueiro said. "The long-term rates bear that out, meaning if you have one of those carriers and you're not on a thiopurine, the likelihood of having 3-year success on infliximab — to a lesser degree, adalimumab — is very, very low."

After exclusion of patients who had no initial response, among infliximab patients, the loss of response was 34.4% at 1 year (95% CI, 30.4%-38.2%), 54.5% at 2 years (95% CI, 49.4%-59%), and 60% at 3 years (95% CI, 54.1%-65.2%). For adalimumab, the loss of response rates were 32.1% (95% CI, 26.7%-37.1%), 47.2% (95% CI, 40.2%-53.4%), and 68.4% (95% CI, 50.9%-79.7%), respectively.

Drug concentrations were measured at week 14, and concentration ranges of 6.1-10 mg/L for infliximab and 10.1-12 mg/L for adalimumab were associated with remission at year 2 (infliximab odds ratio [OR], 2.2; 95% CI, 1.38-3.56; adalimumab OR, 3.65; 95% CI, 1.83-8.67) and year 3 (infliximab OR, 1.89; 95% CI, 1.16-3.11; adalimumab OR, 6.15; 95% CI, 2.5-23.19). A multivariate analysis found that each 10-fold increase in drug concentration at week 14 predicted lower odds of loss of response at year 2 or 3, both for infliximab (hazard ratio [HR], 0.45; 95% CI, 0.3-0.67) and adalimumab (HR, 0.39; 95% CI, 0.22-0.7).

SEBASTIAN KAULITZKI / SCIENCE PHOTO LIBRARY / GETTY IMAGES

Among patients taking infliximab, loss of response at year 2 or 3 was associated with female sex (HR, 1.47; 95% CI, 1.11-1.95) and obesity (HR, 1.62; 95% CI, 1.08-2.42). After the researchers controlled for week 14 drug and antibody concentrations, as well as interaction between baseline immunomodulator and HLA-DQA1*05 risk variant, low thiopurine dose was associated with a higher risk of loss of response.

In the adalimumab group, there was an association between presence of the HLA-DQA1*05 risk variant and loss of response (HR, 1.95; 95% CI, 1.17-3.25).

Use of the anti-TNF drug without an immunomodulator was associated with development of anti-drug antibodies for infliximab (HR, 0.4; 95% CI, 0.31-0.52) and adalimumab (HR, 0.42; 95% CI, 0.24-0.75). Development of anti-drug antibodies was also associated with the presence of HLA-DQA1*05 for infliximab (HR, 1.46; 95% CI, 1.13-1.88), but not adalimumab (HR, 1.6; 95% CI, 0.92-2.77). Use of an immunomodulator the day before or day of treatment with infliximab was associated with a delay in development of anti-drug antibodies and undetectable drug concentrations compared to only infliximab (HR, 2.87; 95% CI, 2.2-3.74) and to use of the immunomodulator following infliximab treatment (HR, 1.7; 95% CI, 1.11-2.59).

"We suggest aiming to start thiopurines alongside infliximab; our data suggest that later introduction is less effective," said Dr. Kennedy, who is currently chair of the British Society of Gastroenterology IBD Clinical Research Group.

Dr. Kennedy reported institutional grants or contracts, personal consulting fees, and personal payments or honoraria from a variety of pharmaceutical companies. See the original article for a complete list.

Dr. Regueiro reported that he has been on advisory boards and consulted for Abbvie, Janssen, UCB, Takeda, Pfizer, BMS, Organon, Amgen, Genentech, Gilead, Salix, Prometheus, Lilly, Celgene, Boehringer Ingelheim Pharmaceuticals, Celltrion, and Roche. ■

Our Biggest Turnout Ever for Advocacy Day!

It's critical to bring the voice of gastroenterology to Capitol Hill to make a real difference in legislation that affects patient care. That's why we gathered our leaders from across the United States in Washington, DC, to meet with congressional offices during our annual Advocacy Day.

GIs from California to Massachusetts and many states in between met with House and Senate offices to educate members of Congress and their staff about the most critical policy issues impacting you and your patients. In total, 28 states were represented and we attended more than 100 meetings in 64 different districts, which was a mix of both Republican and Democratic offices.

For the second year in a row, we were fortunate to be joined by GI patient advocates as well, who shared personal stories about the challenges they encountered in the healthcare system, and the negative effects to their well-being and quality of life because of red tape caused by prior authorization and step therapy.

AGA members and patient advocates pose for a group photo in front of the US Capitol on Advocacy Day 2024 in Washington, DC.

AGA

Dr. Abreu

The in-person advocacy of our members and patient advocates makes a difference. In one of AGA President Maria Abreu's meetings, the congressional staffer remembered that he met with her, Dr. Mel Wilcox, and a patient advocate during 2023's

Continued on following page

Gastro Journal Club: Proximal Cancers in FIT-Positive Patients

For our next installment of the *Gastro* Journal Club, we are honored to host Professor Willemijn de Klaver, MD, PhD, and Professor Evelien Dekker, PhD, from Amsterdam University Medical Centers in the Netherlands. They are joined by fellows from the Icahn School of Medicine at Mount Sinai in New York City for a discussion of the article "Risk of Cancers Proximal to the Colon in Fecal Immunochemical Test–Positive Screenees in a Colorectal Cancer Screening Program," published in the September 2024 issue of *Gastroenterology* (doi: 10.1053/j.gastro.2024.04.028).

Visit our YouTube Channel (youtube.com/@AmerGastroAssn) to watch the session.

The *Gastro* Journal Club is by and for fellows and residents. During these sessions, fellows and residents have the opportunity to ask authors questions about their recently published work in *Gastroenterology*.

If you are interested in arranging a *Gastro* Journal Club session at your institution, please contact mpogachar@gastro.org.

Dr. Yoyo Zhang

Smallest Patients *from page 1*

She also shared an inspirational story of one young patient who spent his life tied to an IV, and how a transplant exposed him to the normal joys of life, like swimming, going to camp, and getting on a plane for the first time.

Q: Why did you choose this subspecialty of pediatric GI?

I think it's the best subspecialty because I think it combines a lot of the things that I enjoy, which is long-term continuity of care. It's about growing up with your patients and seeing them through all the various stages of their life, often meeting patients when they're babies. I get pictures of high school graduations and life milestones and even see some of my patients have families of their own. Becoming a part of their family is very meaningful to me. I also like complexity and acuity, and gastroenterology and hepatology provide those things.

And then lastly, it's great to be able to exercise procedural skills and constantly learn new procedural skills.

Q: How did you become interested in the field of pediatric intestinal and liver transplantation?

I did all my training here at Stanford. We have one of the largest pediatric transplant centers and we also have a very large intestinal rehabilitation population.

Coming through residency and fellowship, I had a lot of exposure to transplant and intestinal failure, intestinal rehabilitation. I really liked the longitudinal relationship I got to form with my patients. Sometimes they're in the neonatal ICU, where you're meeting them in their very first days of life. You follow them through their chronic illness, through transplant and after transplant for many years. You become not just their GI, but the center of their care.

Q: What challenges are unique to this type of transplant work?

Pediatric intestinal failure and intestinal transplant represents an incredibly small subset of children. Oftentimes, they do not get the resources and recognition on a national policy level or even at the hospital level that other gastrointestinal diseases receive. What's difficult is they are such a small subset but their complexity and their needs are probably in the highest percentile. So that's a really challenging combination to start with. And there's only a few centers that specialize in doing intestinal rehabilitation and intestinal transplantation for children in the country.

Developing expertise has been slow. But I think in the last decade or so, our understanding and success with intestinal rehabilitation and intestinal transplantation has really improved, especially at large centers like Stanford. We've had a lot of success stories and have not had any graft loss since 2014.

'I think our understanding of transplant immunology has really progressed, especially recently. That's what part of my research is about — using novel therapies to modulate the immune system of pediatric transplant recipients.'

Q: Are these transplants hard to acquire?

Yes, especially when you're transplanting not just the intestines but the liver as well. You're waiting for two organs, not just one organ. And on top of that, you're waiting for an appropriately sized donor; usually a child who's around the same size or same age who's passed away. Those organs would have to be a good match. Children can wait multiple years for a transplant.

Q: Is there a success story you'd like to share?

One patient I met in the neonatal ICU had congenital short bowel syndrome. He was born with hardly any intestines. He developed complications of being on long-term intravenous nutrition, which included recurrent central line infections and liver disease. He was never able to eat because he really didn't have a digestive system that could adequately absorb anything. He had a central line in one of his large veins, so he couldn't go swimming.

He had to have special adaptive wear to even shower or bathe and couldn't travel. It's these types of patients that benefit so much from transplant. Putting any kid through transplant is a massive undertaking and it certainly has risks. But he underwent a successful transplant at the age of 8 — not just an intestinal transplant, but a multi-visceral transplant of the liver, intestine, and pancreas. He's 9 years old now, and no longer needs intravenous nutrition. He ate by mouth for the very first time after transplant. He's trying all sorts of new foods and he was able to go to a special transplant camp for children. Getting on a plane to Los Angeles, which is where our transplant camp is, was a huge deal.

He was able to swim in the lake. He's never been able to do that. And he wants to start doing sports this fall. This was really a life-changing story for him.

Q: What advancements lie ahead for this field of work? Have you worked on any notable research?

I think our understanding of transplant immunology has really progressed, especially recently. That's what part of my research is about — using novel therapies to modulate the immune system of pediatric transplant recipients. The No. 1 complication that occurs after intestinal transplant is rejection because obviously you're implanting somebody else's organs into a patient.

I am involved in a clinical trial that's looking at the use of extracellular vesicles that are isolated from hematopoietic stem cells. These vesicles contain various growth factors, anti-inflammatory proteins, and tissue repair factors that we are infusing into intestinal transplant patients with the aim to repair the intestinal tissue patients are rejecting.

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

My husband and I have an almost 2-year-old little girl. She keeps us busy and I spend my afternoons chasing after a crazy toddler. ■

Lightning Round

Texting or talking?
Huge texter

Favorite junk food?
French fries

Cat or dog person?
Dog

Favorite ice cream?
Strawberry

If you weren't a gastroenterologist, your dream job?
Florist

Best place you've traveled to?
Thailand

Number of cups of coffee you drink per day?
Too many

Favorite city in the US besides the one you live in?
New York City

Favorite sport?
Tennis

Optimist or pessimist?
Optimist

Continued from previous page

Advocacy Day and recounted the impact of their conversation about delays to timely access to care for inflammatory bowel disease medication.

Numerous GIs had similar experiences on Advocacy Day and recounted the benefits of being able to walk into House and Senate offices and educate congressional staff on the issues they're experiencing in their clinic or lab.

Being able to start these conversations about healthcare and GI and build these relationships showcases the value of Advocacy Day, and demonstrates how AGA works with members to make it easy to advocate for the issues important to them. We were able to have a full day of constructive meetings with lawmakers and their staff thanks to members and patient advocates. Thank you for being engaged and using your voices to protect GI patient care! ■

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