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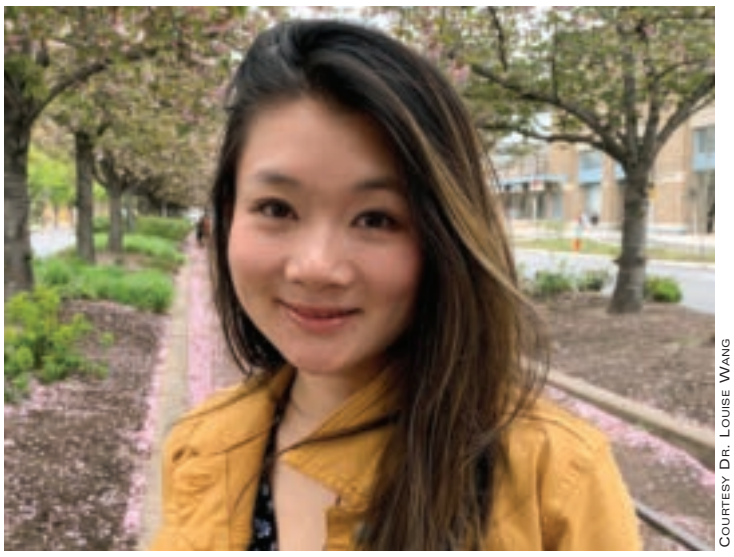
# GI&Hepatology News

September 2022

Volume 16 / Number 9



Courtesy Dr. Louise Wang

Looking for pancreatic cancer among these patients appears cost effective, according to Dr. Louise Wang.

## Screening for cancer in new-onset diabetes

**BY CAROLYN CRIST**
*MDedge News*

A risk-tailored early-detection strategy for pancreatic cancer that targets patients with new-onset diabetes could be cost effective, according to a recent study.

Screening for pancreatic ductal adenocarcinoma in asymptomatic adults is not recommended, but patients with new-onset diabetes have a risk that's eight times higher than expected. Screening these patients could improve diagnosis and survival rates if the cancer can be identified at earlier stages, researchers led by Louise Wang, MD, a gastroenterology fellow at the University of Pennsylvania, Philadelphia, wrote in Clinical Gastroenterology and Hepatology (2021 Nov 1. doi: 10.1016/j.cgh.2021.10.037).

"As we continue to improve therapies for early-stage pancreatic cancers, especially among the local/resectable stage, the case for the targeted early-detection strategy will be stronger," they wrote. "Policy makers should take into consideration these novel findings when formulating [pancreatic ductal adenocarcinoma] screening

*See* **Diabetes** · *page 25*

## 'Reassuring' safety data on PPIs reported

*Jury still out on renal effects*

**BY MEGAN BROOKS**

In a novel analysis accounting for protopathic bias, proton pump inhibitor (PPI) therapy was not associated with increased risk for death due to digestive disease, cancer, cardiovascular disease (CVD), or any cause, although the jury is out on renal disease.

"There have been several studies suggesting that PPIs can cause long-term health problems and may be associated with increased mortality," Andrew T. Chan, MD, MPH, AGAF, gastroenterologist and professor of medicine, Massachusetts General Hospital and Harvard Medical School, both in Boston, told this news organization.

"We conducted this study to examine this issue using data that were better able to account for potential biases in those prior studies. We found that PPIs were generally not associated with an increased risk of mortality," Dr. Chan said.

The study was published online in Gastroenterology (2022 Jun 30. doi: 10.1053/j.gastro.2022.06.067).

### Looking at the data

The findings are based on data collected between 2004 and 2018 from 50,156 women enrolled in the Nurses' Health Study and 21,731 men enrolled from the Health Professionals Follow-Up Study.

During the study period, 10,998 women (21.9%)

*See* **PPIs** · *page 11*

## How well do ADRs capture quality?

**BY JIM KLING**
*MDedge News*

Higher adenoma detection rates (ADRs) during colonoscopies were associated with lower rates of interim colorectal cancer (CRC), and the relationship held true along a broad range of ADR values, according to a retrospective study.

The new study, published online in JAMA (2022;327[21]:2114-22), examined ADRs and rates of interim colorectal cancer among patients in California and Washington State between 2011 and 2017. The authors found a 3% reduction in risk for each additional 1% value of ADR. The reduction in risk held true even at high ADRs.

The study included 735,396 patients with a

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THEN AND NOW

# *Developments in liver disease*

BY JANICE JOU, MD, MHS

Since the first issue of GI & Hepatology News was published 15 years ago, the field of hepatology has undergone a tremendous transformation.

In the late 2000s, we witnessed revolutionary discoveries and advances in our understanding and management of chronic hepatitis C. Who knew that when interleukin-28B was first described in 2009, providing a genetic basis for patients' response to interferon-based therapies, its impact would also be so swiftly supplanted by the introduction of direct-acting antivirals a few years later? The pipeline for HCV treatment was feverish for several years, which resulted in a complete transformation of HCV treatment from a long, exhausting, side effect–filled course to a simple 8- to 12-week regimen. Furthermore, we now have established protocols for organ transplantation for patients without active HCV infection to receive HCV-positive organs because of the effectiveness of treatments for HCV. This kind of progress in our field demonstrates how awe-inspiring medical advances can be and how fortunate we are to have witnessed and lived this progress in such a short period of time.

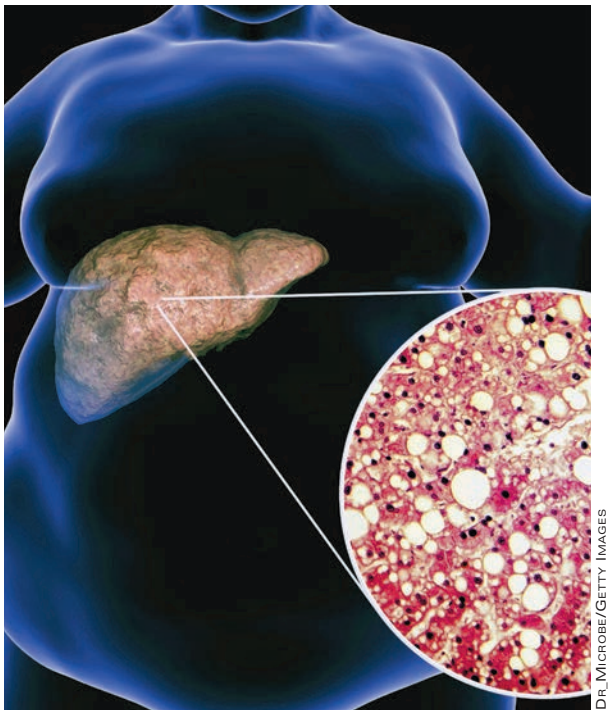
Dr. Jou

In recent years, nonalcoholic fatty liver disease (NAFLD) has supplanted HCV as the most prevalent chronic liver disease seen in GI and hepatology practices across the country.

The sheer number of these patients can be overwhelming for any practice, whether a GI practice or primary care. It has become clear that we have an urgent need for improved and easily accessible noninvasive methods to risk stratify NAFLD to identify patients at greatest risk for developing advanced fibrosis, decompensated cirrhosis, and hepatocellular carcinoma. Furthermore, effective strategies for prevention of these adverse outcomes in the general population still need to be further characterized. For treatment of nonalcoholic steatohepatitis, therapeutic agents being studied for their efficacy are wide ranging with particular interest in weight-loss medications, diabetic medications, and anti-inflammatory medications. Yet, we can all see that there are sizeable gaps in our understanding and management of patients with NAFLD. However, rather than being intimidated, we should look forward to the progress that will surely come in the next 15 years. ■

**We have an urgent need for improved and easily accessible noninvasive methods to risk stratify NAFLD to identify patients at greatest risk for developing advanced fibrosis, decompensated cirrhosis, and hepatocellular carcinoma.**

*Dr. Jou is an associate professor of medicine and the program director of the Gastroenterology Fellowship at Oregon Health & Science University, Portland, as well as section chief of gastroenterology in the VA Portland Healthcare System. She reported no relevant financial conflicts of interest.*



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

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

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# Pre-endoscopy COVID-19 testing may not be needed

**BY CAROLYN CRIST**
*MDedge News*

Pre-endoscopy viral testing may not be necessary to prevent coronavirus transmission from patients to endoscopy staff members, according to a new study published in Gut (2022 Jul 7. doi: 10.1136/gutjnl-2022-327053).

Instead, using personal protective equipment (PPE) and ensuring up-to-date COVID-19 vaccination among the medical team was found to be enough to substantially reduce the risk of spreading SARS-CoV-2, wrote Alexander Hann, MD, gastroenterologist at University Hospital Würzburg, Germany, and colleagues.

Dr. Hann and colleagues analyzed 15,750 endoscopies performed at their institution by 29 staff members during the period between May 2020 and December 2021. The researchers looked at three test approaches: no testing (4,543 patients), rapid antigen testing (682 patients), and real-time polymerase chain reaction testing (10,465 patients). In addition, 60 endoscopies were performed in patients with known COVID-19.

Overall, no staff members became infected with SARS-CoV-2 during the study period. In all three scenarios, staff used PPE, and the vaccination rate of the team was 97%.

All patients were interviewed before admission for COVID-19 symptoms, close contact with infected people, and recent travel to high-risk countries. Moreover, some endoscopies were performed even if a patient had positive markers for COVID-19.

The clinical team wore recommended PPE, including a high-filter FFP2 mask, one pair of gloves, protective eyewear, and disposable gowns. For patients with known COVID-19, staff wore two pairs of gloves, a disposable hairnet, and a water-resistant disposable gown. In addition, endoscopies were performed in negative-pressure intervention rooms.

The hospital's internal policy required medical staff to undergo PCR testing if a rapid antigen test was positive or symptoms developed. Staff were vaccinated with two doses of the Pfizer-BioNTech vaccine in January and February 2021. A single booster dose of the Pfizer or Moderna vaccine was administered in November and December 2021.

The clinical team was not tested routinely, so asymptomatic infections may have existed. Moreover, the relatively low COVID-19 incidence in the local area might have influenced the risk of transmission. "However, even at the end of 2021, when the incidence was increasing, we did not see any higher risk of transmission," the researchers explained.

The authors reported no conflicts of interest. ■

*AGA Clinical Practice Update: Expert Review*

# Barrett's screening update 'goes above and beyond'

**BY MIRIAM E. TUCKER**
*MDedge News*

A new clinical practice update from the American Gastroenterological Association offers practical advice around surveillance and use of new screening technologies for Barrett's esophagus.

The AGA clinical practice update, published in Clinical Gastroenterology and Hepatology (2022 Jul 1. doi: 10.1016/j.cgh.2022.06.003) comes from the AGA's Center for GI Innovation and Technology (https://gastro.org/aga-leadership/centers/aga-center-for-gi-innovation-technology/). It offers 15 best practice advice statements based on expert review of existing literature combined with discussion and expert opinion. The aim is "to provide an update on advances and innovation" but not to replace current guidelines.

"Guidelines operate on rigorous methodology which requires the use of [Grading of Recommendations, Assessment, Development and Evaluation] methodology and a higher level of evidence. In gastroenterology especially, innovation is moving quickly and there's no way for patients to reap their benefits if clinical practice was dictated by guidelines alone. That said, we do need documents that support and drive innovation in clinical practice," corresponding author Srinadh Komanduri, MD, professor of medicine and surgery in the division of gastroenterology and hepatology at Northwestern University, Chicago, told this news publication.

Asked to comment, Vivek Kaul, MD, AGAF, the Segal-Watson Professor of Medicine in the Center for Advanced Therapeutic Endoscopy in the division of gastroenterology and hepatology at the University of Rochester (N.Y.) Medical Center, said that the document is "an important attempt to not only present the available scientific literature in a very concise and understandable manner, but it goes above and beyond that in terms of diving into some novel paradigms and technologies and procedures that are either emerging or will be emerging in the near future."

## Improving detection by dropping GERD requirement

The first of the 15 statements may also be the most paradigm shifting: The panel suggests screening via standard upper endoscopy of people with at least three risk factors for Barrett's esophagus and esophageal adenocarcinoma, including those who are male, are non-Hispanic White, are aged above 50 years, and have a history of smoking, chronic gastroesophageal reflux disease (GERD), or obesity, or a family history of Barrett's esophagus or esophageal adenocarcinoma.

This represents a departure from all current guidelines, which stipulate GERD as a necessary prerequisite for screening. But the reason is simple, according to the authors: A majority of patients diagnosed with esophageal cancer never experience classic GERD symptoms.

"There is growing evidence in high-level publications over the last couple of years that reflux is not the ideal predictor, based on odds, for development of Barrett's esophagus. So the consensus among the experts was that we need to remove GERD as an absolute prerequisite or we're never going to make progress. In order to make an impact on the rise of esophageal adenocarcinoma we have to increase the denominator of patients we are seeing," Dr. Komanduri explained.

**"There is growing evidence in high-level publications over the last couple of years that reflux is not the ideal predictor, based on odds, for development of Barrett's esophagus."**

While it might be difficult to screen every White male over 50 years of age, the data do suggest screening those who also have obesity and/or are current smokers. "That's a perfect subset you might want to start with. There are permutations that have greater value that don't occupy unnecessary resource utilization. Most critical are the family history of esophageal cancer or Barrett's esophagus," he noted.

Dr. Kaul said that a one-time Barrett's esophagus screening of all White males over 50 years old "is not unreasonable, especially given the rising rates of esophageal cancer."

However, he also noted, "The feasibility, preferred screening modality, incremental costs, and yield of this new strategy will need to be studied further. Access to GI endoscopy in the postpandemic world is already a concern and will need to be factored into execution of this [advice statement] and will likely impact adoption in some way."

For his part, Dr. Komanduri said that more investigation will be needed to validate which patients most benefit from screening and that the AGA is planning educational programs for clinicians about interpreting this new paradigm.

## New technology could make screening easier and cheaper

The availability of nonendoscopic cell collection devices, including the swallowable Cytosponge (Medtronic), EsoCheck (Lucid), and EsoCap (Capnostics) could help make screening for Barrett's esophagus easier and more cost effective. They are designed for in-office use and don't require sedation. Each one is currently in various stages of development and clinical trials. As of now they are approved in the United States only for cell collection but not for Barrett's esophagus screening, but their use is endorsed by some guidelines (Am J Gastroenterol. 2022 Apr;117(4):559-87). The Cytosponge in particular is widely available and has been used extensively in the United Kingdom.

While the current lack of reimbursement in the United States limits use of these devices now, the document was written in anticipation of future approval and coverage. "We wanted to let people know we need to pay attention to these less-invasive devices that allow for greater access to screening. Once you start to increase the screening pool you obviously want something less invasive," Dr. Komanduri noted.

Dr. Kaul commented, "While there is a need for nonendoscopic screening devices, the ideal patient population and practice setting for administration of these devices has not been clearly defined. Also, who will be delivering these tests: primary care or gastroenterology providers? These devices ... represent a major step forward and a novel paradigm for Barrett's esophagus screening, and the only platform that non-GI providers could use."

## Virtual chromoendoscopy: A must have in 2022

A third best practice advice statement shouldn't be controversial because it's in other guidelines already, but data show clinicians aren't always doing it: performing screening and surveillance endoscopic examinations using virtual chromoendoscopy in addition to high-definition white-light endoscopy, with adequate time spent inspecting the Barrett's segment. The majority of data supporting this is for narrow-band imaging only.

"The blue light lets you pick up early mucosal and vascular changes which might represent dysplastic lesions. It's not a question of should. It's a medicolegal slam dunk; you must do it. It's been a guideline recommendation in the last few years, and it's just a switch on the scope. It doesn't require separate equipment, yet people are often still skipping it," Dr. Komanduri said.

Indeed, Dr. Kaul concurred, "The importance of a high-quality, meticulous endoscopic examination for screening and surveillance in Barrett's esophagus cannot be overemphasized."

## Continue to use the Seattle protocol ... for now

The update continues to advise the long-established Seattle protocol for sampling and surveillance during endoscopic examinations, namely, four quadrant biopsies every 1-2 centimeters and targeted biopsies from any visible lesion. That's been the standard of care for over 20 years.

However, the update also suggests wide area transepithelial sampling (WATS-3D, CDx Diagnostics) as an adjunctive technique to the Seattle protocol. This is important, Dr. Komanduri said, because random Seattle protocol sampling misses a significant portion of the total surface area.

*Continued on following page*

*AGA Clinical Practice Update: Expert Review*

# Best practices for NAFLD in lean persons

**BY LIAM DAVENPORT**

Ongoing follow-up and lifestyle interventions are needed in lean patients with nonalcoholic fatty liver disease (NAFLD), suggests a panel of experts in a recent review.

They also urge screening for NAFLD in individuals who are older than 40 years with type 2 diabetes, even if they are not overweight.

NAFLD is a leading cause of chronic liver disease that affects more than 25% of the United States and worldwide populations, note lead author Michelle T. Long, MD, Boston Medical Center, Boston University, and colleagues.

Dr. Long

They add that around one-quarter of those affected have nonalcoholic steatohepatitis, which is associated with significant morbidity and mortality due to complications of liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma.

Although NAFLD occurs primarily in individuals with obesity or type 2 diabetes, between 7% and 20% have a lean body habitus, they write.

There are differences in rates of disease progression, associated conditions, and diagnostic and management approaches between lean and nonlean patients, the authors note, but there is limited guidance on the appropriate clinical evaluation of the former group.

The American Gastroenterological Association therefore commissioned an expert review to provide best practice advice on key clinical issues relating to the diagnosis, risk stratification, and treatment of NAFLD in lean individuals.

Their review was published online in Gastroenterology (2022 Jul 13. doi: 10.1053/j.gastro.2022.06.023).

## Evidence-based approaches

The 15 best practice advice statements covered a wide range of clinical areas, first defining lean as a body mass index less than 25 in non-Asian persons and less than 23 in Asian persons.

The authors go on to stipulate, for example, that lean individuals in the general population should not be screened for NAFLD but that screening should be considered for individuals older than 40 years with type 2 diabetes.

More broadly, they write that the condition should be considered in lean individuals with metabolic diseases, such as type 2 diabetes, dyslipidemia, and hypertension, as well as elevated values on liver biochemical tests or incidentally noted hepatic steatosis.

After other causes of liver diseases are ruled out, the authors note that clinicians should consider liver biopsy as the reference test if uncertainties remain about liver injury causes and/or liver fibrosis staging.

**There are differences in rates of disease progression, associated conditions, and diagnostic and management approaches between lean and nonlean patients.**

They also write that the NAFLD fibrosis score and Fibrosis-4 score, along with imaging techniques, may be used as alternatives to biopsy for staging and during follow-up.

The authors, who provide a diagnosis and management algorithm to aid clinicians, suggest that lean patients with NAFLD follow lifestyle interventions, such as exercise, diet modification, and avoidance of fructose- and sugar-sweetened drinks, to achieve weight loss of 3%-5%.

Vitamin E may be considered, they continue, in patients with biopsy-confirmed nonalcoholic steatohepatitis but without type 2 diabetes or cirrhosis. Additionally, oral pioglitazone may be considered in lean persons with biopsy-confirmed nonalcoholic steatohepatitis without cirrhosis.

In contrast, they write that the role of glucagonlike peptide–1 agonists and sodium-glucose cotransporter 2 inhibitors requires further investigation.

The advice also says that lean patients with NAFLD should be routinely evaluated for comorbid conditions, such as type 2 diabetes, dyslipidemia, and hypertension, and risk-stratified for hepatic fibrosis to identify those with advanced fibrosis or cirrhosis.

For lean patients with NAFLD and clinical markers compatible with liver cirrhosis, twice-yearly surveillance for hepatocellular carcinoma is also advised.

## Fatty liver disease in lean persons with metabolic conditions

Approached for comment, Liyun Yuan, MD, PhD, assistant professor of clinical medicine, University of Southern California, Los Angeles, said it is very important to have uniform guidelines for general practitioners and other specialties on NAFLD in lean individuals.

Dr. Yuan, who was not involved in the review, told this news organization that it is crucial to raise awareness of NAFLD, just like awareness of breast cancer screening among women of a certain age was increased, so that individuals are screened for metabolic conditions regardless of whether they have obesity or overweight.

Zobair Younossi, MD, MPH, professor of medicine, Virginia Commonwealth University, Inova Campus, Falls Church, added that there is a lack of awareness that NAFLD occurs in lean individuals, especially in those who have diabetes.

He said in an interview that, although it is accurate to define individuals as being lean in terms of their BMI, the best way is to look not only at BMI but also at waist circumference.

Dr. Younossi said that he and his colleagues have shown that, when BMI is combined with waist circumference, the prediction of mortality risk in NAFLD is affected, such that lean individuals with an obese waist circumference have a higher risk for all-cause mortality.

Dr. Long is supported in part by the National Institute of Diabetes and Digestive and Kidney Diseases, Doris Duke Charitable Foundation, Gilead Sciences Research Scholars Award, Boston University School of Medicine Department of Medicine Career Investment Award, and Boston University Clinical Translational Science Institute. Dr. Long declares relationships with Novo Nordisk, Echosens Corporation, and Gilead Sciences. Dr. Yuan declares relationships with Genfit, Intercept, and Gilead Sciences. Dr. Younossi declares no relevant relationships. ■

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*Continued from previous page*

This new technology allows you to circularly brush the entire area, in contrast to random biopsies.

"We advocate it can be used as an adjunct, but we need further prospective data to bear out whether it can be used as a standalone," he noted.

Dr. Kaul said, "Debate persists regarding what to do with WATS-positive/forceps-negative cases. It has also not been clearly defined which patients should undergo WATS-3D sampling along with Seattle protocol–forceps biopsies."

## 'Finally pushing the needle in the right direction'

The overall goals, Dr. Komanduri said, are "increasing the denominator, using less invasive screening, but finding more patients. If we find more patients we'll need to stratify their risk. We hope that all these things eventually tie together in a nice story, all with the aim of preventing an invasive cancer that can't be treated."

He believes the new update "is a pivotal document in this field that's going to be a paradigm changer. A lot of aspects need further validation. It's by no means the end. But I think we're finally pushing the needle in the right direction as things move forward with innovation."

Dr. Kaul agrees. "It's highlighting the principles that may become established paradigms in the future."

Dr. Komanduri and the other authors of the update reported relationships, including consulting and research support, with companies like Boston Scientific, Medtronic, Virgo Video Solutions, and Castle Biosciences. Dr. Kaul serves as a consultant and advisory board member for CDx Diagnostics, an advisory board member for Castle Biosciences, and an investigator for Lucid Diagnostics. ■

# Study designed to minimize bias

**PPIs** *from page 1*

and 2,945 men (13.6%) initiated PPI therapy, and PPI use increased over the study period from 6.1% to 10.0% in women and from 2.5% to 7.0% in men.

The mean age at baseline was 68.9 years for women and 68.0 years for men. During a median follow-up of 13.8 years, a total of 22,125 participants died – 4,592 of cancer, 5,404 of CVD, and 12,129 of other causes.

Unlike other studies, the researchers used a modified lag-time approach to minimize reverse causation (protopathic bias).

"Using this approach, any increased PPI use during the excluded period, which could be due to comorbid conditions prior to death, will not be considered in the quantification of the exposure, and thus, protopathic bias would be avoided," they explain.

In the initial analysis that did not take into account lag times, PPI users had significantly higher risks for all-cause mortality and mortality due to cancer, CVD, respiratory diseases, and digestive diseases, compared with nonusers.

However, when applying lag times of up to 6 years, the associations were largely attenuated and no longer statistically significant, which "highlights the importance of carefully controlling for the influence of protopathic bias," the researchers write.

However, despite applying lag times, PPI users remained at a significantly increased risk for mortality due to renal diseases (hazard ratio, 2.45; 95% confidence interval, 1.59-3.78).

The researchers caution, however, that they did not have reliable data on renal diseases and therefore could not adjust for confounding in the models. They call for further studies examining the risk for mortality due to renal diseases in patients using PPI therapy.

The researchers also looked at duration of PPI use and all-cause and cause-specific mortality.

For all-cause mortality and mortality due to cancer, CVD, respiratory diseases, and digestive diseases, the greatest risks were seen mostly in those who reported PPI use for 1-2 years. Longer duration of PPI use did not confer higher risk for mortality for these endpoints.

In contrast, a potential trend toward greater risk with longer duration of PPI use was observed for mortality due to renal disease. The hazard ratio was 1.68 (95% CI, 1.19-2.38) for 1-2 years of use and gradually increased to 2.42 (95% CI, 1.23-4.77) for 7 or more years of use.

Notably, when mortality risks were compared among PPI users and histamine H2 receptor antagonist (H2RA) users without lag time, PPI users were at increased risk for all-cause mortality and mortality due to causes other than cancer and CVD, compared with H2RA users.

But again, the strength of the associations decreased after lag time was introduced.

"This confirmed our main findings and suggested PPIs might be preferred over H2RAs in sicker patients with comorbid conditions," the researchers write.

### 'Generally safe' when needed

Summing up, Dr. Chan said, "We think our results should be reassuring to clinicians that recommending PPIs to patients with appropriate indications will not increase their risk of death. These are generally safe drugs that when used appropriately can be very beneficial."

Offering perspective on the study, David Johnson, MD, professor of medicine and chief of gastroenterology at the Eastern Virginia School of Medicine, Norfolk, noted that a "major continuing criticism of the allegations of harm by PPIs has been that these most commonly come from retrospective analyses of databases that were not constructed to evaluate these endpoints of harm."

BananaStock/Thinkstock

"Accordingly, these reports have multiple potentials for stratification bias and typically have low odds ratios for supporting the purported causality," Dr. Johnson told this news organization.

"This is a well-done study design with a prospective database analysis that uses a modified lag-time approach to minimize reverse causation, that is, protopathic bias, which can occur when a pharmaceutical agent is inadvertently prescribed for an early manifestation of a disease that has not yet been diagnostically detected," Dr. Johnson explained.

Echoing Dr. Chan, Dr. Johnson said the finding that PPI use was not associated with higher risk for all-cause mortality and mortality due to major causes is "reassuring."

"Recognizably, too many people are taking PPIs chronically when they are not needed. If needed and appropriate, these data on continued use are reassuring," Dr. Johnson added.

This work was supported by the National Institutes of Health and the Crohn's and Colitis Foundation. Dr. Chan has consulted for OM1, Bayer Pharma AG, and Pfizer for topics unrelated to this study, as well as Boehringer Ingelheim for litigation related to ranitidine and cancer. Dr. Johnson reports no relevant financial relationships. ■

DDSEP 9
Digestive Diseases Self-Education Program

## Quick quiz

**Q1.** A 54-year-old male is referred to you for advice on weight-loss management. His body mass index is currently 37 kg/m$^2$; he exercises regularly and is interested in starting medications for weight loss. He is a chronic alcoholic who has a history of pancreatitis in the past and a few admissions for management of alcohol withdrawal, which included seizures. However, he has maintained his job as a cook at the local diner. The only other history is kidney stones as a teenager. He recently visited his primary care physician who "cleared" him. He remembers going for a sonogram of the heart, which was normal. He claims that he has been depressed about his brother's recent diagnosis of thyroid cancer and has vowed to stop drinking and lose weight.

Which of the following medications is the best option for him?

A. Naltrexone/bupropion (Contrave)
B. Liraglutide (Saxenda)
C. Phentermine/topiramate (Qsymia)
D. Lorcaserin (Belviq)

**Q2.** A 65-year-old man undergoes upper endoscopy for epigastric discomfort. The exam results are normal, except for a 3-cm submucosal mass in the body of the stomach. Endoscopic ultrasound shows that the mass arises from the fourth layer of the stomach wall. CT of the abdomen confirms the solid gastric mass with several small lesions in the liver concerning for metastatic disease. Biopsy of the mass shows CD117-positive spindle cells.

Which of the following is true about this tumor?

A. Small intestine is the most common location
B. KIT negative
C. Worse prognosis for tumors located in the stomach
D. Treatment for recurrent or metastatic disease is imatinib

*The answers are on page 24.*

# Procalcitonin algorithm targets antibiotic overuse

**BY WILL PASS**
*MDedge News*

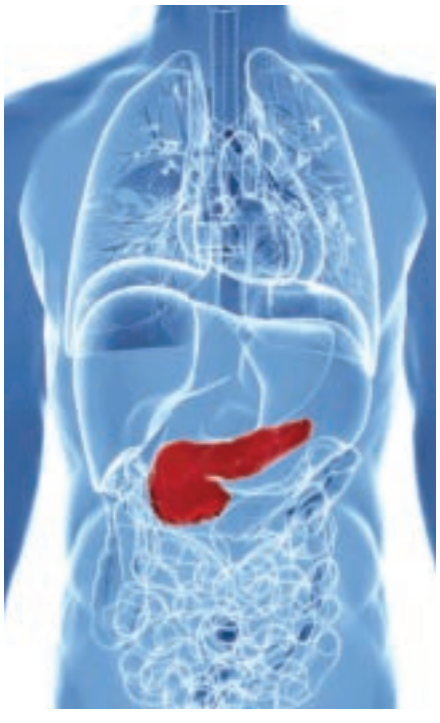
A procalcitonin-based algorithm could safely reduce unnecessary usage of antibiotics in patients with acute pancreatitis, based on results of a randomized controlled trial.

Physicians should consider incorporating the decision-making process into their daily practice, suggested lead author Ajith K. Siriwardena, MD, of Manchester (England) University and colleagues, who also recommended that the algorithm be added to future guidelines.

"Overuse of antibiotics and the resultant emergence of multidrug resistant microorganisms is a potent threat to the welfare of humanity in the 21st century," the investigators wrote in The Lancet Gastroenterology & Hepatology (2022 Jul 18. doi: 10.1016/S2468-1253[22]00212-6).

Antibiotic overuse is common in cases of acute pancreatitis, they noted, because clinical features are typically insufficient to distinguish between inflammation and infection. While measuring procalcitonin can help detect infection, "indiscriminate measurement" of the biomarker is not cost effective, according to the investigators, leading previous reviews and analyses to conclude that further research is needed before widespread usage can be recommended.

Dr. Siriwardena and colleagues aimed to meet this need by conducting a randomized controlled trial involving 260 patients hospitalized for acute pancreatitis at Manchester Royal Infirmary. Patients were randomized in a near 1:1 ratio. Both the intervention group (n = 132) and the control group (n = 128) received guideline-based care (Pancreatology. 2013 Jul-Aug;13[4 Suppl 2]:e1-15); however, in addition to standard of care, procalcitonin was measured in the intervention group at days 0, 4, and 7 then weekly. Among these patients, antibiotics were stopped



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or not started when procalcitonin was below 1.0 ng/mL, but antibiotics were started or continued when procalcitonin was 1.0 ng/mL or more.

The primary outcome was presence or absence of antibiotic use during hospital stay. A range of secondary outcomes were also reported, included all-cause mortality, days of antibiotic use, rates of infection, and endoscopic, radiological, or surgical intervention.

**"Overuse of antibiotics and the resultant emergence of multidrug resistant microorganisms is a potent threat to the welfare of humanity in the 21st century."**

Significantly fewer patients in the procalcitonin group received antibiotics during their stay, compared with the usual-care group (45% vs. 63%), which translated to an adjusted risk difference of –15.6% ($P$ = .0071). Patients in the procalcitonin group who did receive antibiotics received about 1 day less of antibiotic treatment.

Despite the reduced antibiotic usage, length of hospital stay was similar between groups, as were rates of clinical infection, hospitalacquired infection, death, and adverse events, which suggests that the algorithm safely reduced antibiotic usage without negatively impacting clinical outcomes, according to investigators.


Dr. Sasson

"Procalcitonin-based algorithms to guide antibiotic use should be considered in the care of this group of patients and be incorporated into future guidelines on the management of acute pancreatitis," the investigators concluded.

Aaron Sasson, MD, director of the pancreatic cancer center and codirector of the gastrointestinal oncology team at Stony Brook (N.Y.) Medicine, said the study is noteworthy because it addresses an important topic with a large prospective randomized trial; however, he pointed out some limitations.

"There are several issues with this trial," Dr. Sasson said in a written comment. "First, it included a large percentage of patients with mild acute pancreatitis, a group of patients for whom the use of antibiotics is not controversial. Secondly, the rate of infected pancreatic necrosis was 5% in both arms of the study, indicating the lack of severity of the cohort of patients."

Dr. Sasson said that the algorithm "could be useful" to differentiate between inflammation and infection in patients with acute pancreatitis, "but only as an adjunct with other clinical parameters."

He suggested that the algorithm would offer more utility if it could distinguish between pancreatic necrosis and infected pancreatic necrosis. "Unfortunately, this trial did not answer this question," he said, noting that a similar trial involving "only patients with severe pancreatitis" would be needed.

The investigators and Dr. Sasson disclosed no competing interests. ■

# Detection disparities remain

**ADR** *from page 1*

median age of 61.4 years. Among these patients, 852,624 negative colonoscopies were performed by 383 eligible physicians. Participating physicians had to perform at least 25 screening colonoscopies and 100 total colonoscopies per year. After 2.4 million person-years of follow-up, the researchers observed 619 postcolonoscopy colorectal cancers and 36 related deaths over a median follow-up of 3.25 years.

There was an association between each 1% increase in ADR and a reduced probability of postcolonoscopy CRC (hazard ratio], 0.97; 95% confidence interval, 0.96-0.98) and mortality from postcolonoscopy CRC (HR, 0.95; 95% CI, 0.92-0.99).

The median ADR was 28.3%. There was an association between ADR above the median versus below the median and a reduced risk of postcolonoscopy CRC with 1.79 cases versus 3.10 cases per 10,000 person-years, respectively (absolute difference in 7-year risk, –12.2 per 10,000 negative colonoscopies; HR, 0.61; 95% CI, 0.52-0.73). There was a similar reduction in risk of postcolonoscopy CRC-related mortality (0.05 versus 0.22 per 10,000 person-years; absolute difference in 7-year risk, –1.2 per 10,000 negative colonoscopies; HR, 0.26; 95% CI, 0.11-0.65).

These findings may be limited in generalizability to physicians with lower procedure volumes or to populations with different adenoma prevalence.

"Given the strong, consistent associations of higher adenoma detection rates with colonoscopy effectiveness for reducing colorectal cancer incidence and mortality, the current results support more research to identify reliable and readily adoptable methods for increasing adenoma detection rates among physicians with lower values across diverse settings," the researchers wrote.

The improvement over a broad range of ADRs, along with other recent findings, suggests that there may need to be updates to the use of ADRs as a quality metric, according to an accompanying editorial by Douglas K. Rex, MD, of the division of gastroenterology/hepatology at Indiana University, Indianapolis (JAMA. 2022 Jun 7;327[21]:2088-9). For example, it's possible that ADRs could be measured by averaging values from screening, diagnostic, and surveillance colonoscopy. The editorialist suggested that, if improvements in interim cancer rates continue as ADRs approach 50%, the current view of ADRs, as a minimally acceptable standard, may require reconsideration. Instead, it may be appropriate to continue with a minimum threshold, but add a much higher, aspirational target. Dr. Rex also suggested that highly variable detection of sessile serrated lesions could be excluded from ADRs in order to reduce variability.

### Factors to consider

The study is useful, but it doesn't address the disparity in adenoma detection that exists between individual doctors, according to Lawrence Kosinski, MD, MBA, AGAF, founder and chief medical officer of SonarMD and previously director of a large gastroenterology clinic. "Even if you look at doctors who do a minimum of 250 screening colonoscopies in a year, there's still variability. There was even a study published in 2014 showing ADRs anywhere from 7.4% to 52.5%. The bell curve is broad," he said (N Engl J Med. 2014 Apr 3;370[14]:1298-306).

SDI Productions/E+/Getty Images

As patients age, they have a higher frequency of polyps appearing on the right side of the colon, and those polyps are flatter and more easily missed than polyps on the left side. "The variation in ADR is higher on the right side of the colon than it is on the left. Doctors have to really do a very good job of examining that right side of the colon so that they don't miss the flat polyps," said Dr. Kosinski.

If a patient hasn't prepped well enough, it's better to send the patient home without the procedure than to conduct a poor-quality screening. "If you can't see the mucosal surface, you can't tell the patient that they have a negative colonoscopy. If you have to do more cleaning during the procedure, then do more cleaning during the procedure. If you have to cancel the procedure and bring the patient back, it's better to do that than it is to do an incomplete colonoscopy," said Dr. Kosinski.

He also stressed the need to make sure that the patient is properly sedated and comfortable "so that you can do the job you're supposed to do," he said.

Some authors disclosed relationships with Amgen and the National Cancer Institute. Dr. Rex disclosed relationships with Olympus, Boston Scientific, Aries, and others, all outside the submitted work. Dr. Kosinski had no relevant financial disclosures. ■

# Liver cancer risk persists after direct-acting antiviral treatment

**BY CAROLYN CRIST**

Hepatocellular carcinoma risk declines after direct-acting antiviral treatment but remains high enough to justify screening for at least 7 years after hepatitis C cure, according to a new report.

Among patients with cirrhosis and fibrosis-4 (FIB-4) scores of 3.25 or higher, the incidence of hepatocellular carcinoma appeared to decline progressively each year up to 7 years after a sustained virologic response, although the rate remained above the 1% per year threshold that warrants screening.

"The majority of patients with hepatitis C have been treated and cured in the United States," George Ioannou, MD, the senior study author and professor of medicine at the University of Washington, Seattle, said in an interview. "After hepatitis C eradication, these patients generally do very well from the liver standpoint, but the one thing they have to continue worrying about is development of liver cancer."

Dr. Ioannou, who is also director of hepatology at the Veterans Affairs Puget Sound Health Care System, Seattle, noted that patients may be screened "indefinitely," which places a burden on the patients and the health care system.

The study was published online in Gastroenterology (2022 Jun 28. doi: 10.1053/j.gastro.2022.06.057).

The research team analyzed electronic health records from the Veterans Affairs Corporate Data Warehouse, a national repository of VA records developed specifically for research purposes. The researchers included 29,033 patients in the Veterans Affairs health care system who had been infected with hepatitis C virus and were treated with direct-acting antivirals between January 2013 and December 2015. The patients had a sustained virologic response, which is defined as a viral load below the lower limit of detection at least 12 weeks after therapy completion.

The patients were followed for incident hepatocellular carcinoma until December 2021. The researchers then calculated the annual incidence during each year of follow-up after treatment.

About 96.6% of patients were men, and 52.2% were non-Hispanic White persons. The average age was 61 years.

Among the 7,533 patients with pretreatment cirrhosis, 948 (12.6%) developed hepatocellular carcinoma during a mean follow-up period of 4.9 years. Among patients with FIB-4 scores of 3.25 or higher, the annual incidence decreased from 3.8% in the first year to 1.4% in the seventh year but remained substantial up to 7 years after sustained virologic response. Among patients with both cirrhosis and a high FIB-4 score, the annual rate ranged from 0.7% to 1.3% and didn't change significantly over time.

Among the 21,500 patients without pretreatment cirrhosis, 541 (or 2.5%) developed hepatocellular carcinoma during a mean follow-up period of 5.4 years. The incidence rate was significantly higher for patients with high FIB-4 scores. Among patients without cirrhosis but who had a high FIB-4 score, the annual rate remained stable but substantial (from 0.8% to 1.3%) for up to 7 years.

The study was funded by an National Institutes of Health/National Cancer Institute grant and a VA CSR under Dr. Ioannou. ■

# Patients aren't being offered what they want when it comes to CRC screening, study suggests

**BY TARA HAELLE**
*MDedge News*

Patients said they'd prefer fecal immunochemical test (FIT)–fecal DNA tests over any of the other colorectal cancer (CRC) screening modalities currently recommended by the U.S. Multi-Society Task Force, according to a study published in Clinical Gastroenterology and Hepatology (2022 Jul 20. doi: 10.1016/j.cgh.2022.07.012).

Just over a third of American adults aged 40 and older who hadn't yet been screened for CRC preferred the FIT–fecal DNA test every 3 years, whereas just one in seven respondents preferred a colonoscopy – considered the gold standard in colorectal cancer screening – every 10 years.

"When you talk to patients and to your friends and family members, people tend to think colonoscopy is synonymous with colon cancer screening, but we have lots of different tests," senior author Christopher V. Almario, MD, MSHPM, of the department of medicine at the Karsh division of gastroenterology and hepatology, Cedars-Sinai Medical Center, Los Angeles, said in an interview.

"Most people in general tend to prefer noninvasive stool tests, and when we try to predict who would prefer what, we actually couldn't, so this is a very personal decision," Dr. Almario said. "It's important for clinicians to offer multiple choices to their patients, not to mention just colonoscopy. We have data from observing clinician-patient interactions showing that, a lot of times, colonoscopy is the only test that's offered, despite there being multiple options."

At the very least, Dr. Almario said, providers should offer patients a colonoscopy along with a noninvasive test, particularly a stool test, and discuss the two options, getting the patient's input in terms of what they prefer. "The best test is the test that actually gets done," he said.

## Giving patients options

Reid M. Ness, MD, MPH, AGAF, an associate professor of medicine in the division of gastroenterology, hepatology and nutrition at Vanderbilt University Medical Center in Nashville, Tenn., was not involved with the study but wasn't surprised at the findings since "most people wisely prefer to avoid invasive procedures," he said in an interview. He agreed that many patients aren't necessarily informed of all their options for screening.

"Many people who are now being offered colonoscopy as their only screening option may prefer a noninvasive option, such as FIT or multitarget stool DNA testing," Dr. Ness said. "Also, people now refusing colonoscopy for colorectal cancer screening may instead accept FIT or multitarget stool DNA testing. It is difficult to know how many people now refusing colorectal cancer screening may have accepted screening if it had been offered differently."

That's precisely what Dr. Almario and his colleagues wanted to find out. They surveyed 1,000 people aged 40 and older who were at average risk for colorectal cancer to find out their preferences for different screening modalities and what features of different screening types they most valued. The researchers asked about the following screening tests recommended by the U.S. Multi-Society Task Force:

- FIT every year.
- FIT–fecal DNA every 3 years.
- Colon video capsule every 5 years.
- CT colonography every 5 years.
- Colonoscopy every 10 years.

The respondents who completed the online survey were recruited from a sample of more than 20 million people across the United States who have agreed to receive survey invitations. Respondents were excluded if they had a first-degree relative with colorectal cancer, had already undergone colorectal cancer screening or had been diagnosed with colon polyps, Crohn's disease, or ulcerative colitis.

> **"Our findings suggest that screening programs should strongly consider a sequential-based strategy where FIT is offered first, and if declined then colonoscopy."**

The respondents were split into those aged 40-49 (61% of the sample) who had not yet discussed colorectal cancer screening with their providers and those aged 50 and older, who might have already discussed it and declined. Eighty percent of the respondents were White, 6% were Black, 6% were Hispanic, 4% were Asian, and 3% reported another race/ethnicity. Just over half (52%) had at least two comorbidities. A quarter (25%) reported one comorbidity, and 22% reported none.

One-third of the respondents had a college degree, while 24% had some college, 28% had a high school education or less, and 15% had a graduate degree. Most had health insurance (81%), and most (70%) were currently employed or a student. Nearly half (46%) had a household income below $50,000, with 29% reporting an income of $50,000-$100,000, and 22% reporting an income of $100,001 or higher.

Just over half (52%) of the respondents said they have plans to get screened for colorectal cancer, though the number was higher for the younger group (59%) than the older group (46%). On average, the group perceived themselves as having a low susceptibility to colorectal cancer (2.6 on a scale of 1-5) but did perceive that screening had benefits for them (score of 4) with low barriers (score 2.7).

In thinking about the decision to get screened, respondents ranked the test type as the most important consideration, followed by the reduction in their chance of developing colorectal cancer and then frequency of the test. Lower priority on the list of considerations were their chances of a complication, bowel prep before the test, and required diet changes before the test.

The test preferred by the highest proportion of respondents was the FIT–fecal DNA test every 3 years, preferred by 35% of respondents, followed by the colon capsule video test every 5 years (28%). About one in seven respondents (14%) preferred a colonoscopy every 10 years, followed by the annual FIT (12%) and CT colonography every 5 years (11%). When limited only to the two tier 1–option tests – the annual FIT or a colonoscopy every 10 years – a substantial majority of the younger (69%) and older (77%) groups preferred the annual FIT.

"This finding is discordant with current CRC screening utilization in the United States where colonoscopy is the most commonly performed test, and this may partially explain our suboptimal screening rates," the authors wrote. "Our findings suggest that screening programs should strongly consider a sequential-based strategy where FIT is offered first, and if declined then colonoscopy."

## Understanding underlying factors

Dr. Ness said that many primary care providers might prefer to offer colonoscopies instead of annual FIT tests because it's easier to track a test given every 10 years instead of every year or every 3 years.

"Providers across most of the U.S. are incentivized to recommend colonoscopy as the primary screening modality because the burden of follow-up on them is less," Dr. Ness said. "They are able to justify this choice given colonoscopy remains the most accurate screening modality."

Dr. Ness pointed to the programmatic screening program at Kaiser Permanente of Northern California health care system as a model for a program that utilizes FIT tests more often.

"The only way to accomplish an efficient and equitable colorectal cancer screening program is within the context of a national health service or plan," Dr. Ness added. "Otherwise, the uninsured and underinsured will remain excluded from the benefits of colorectal cancer screening."

**AGA resource**
Help your patients understand colorectal cancer prevention and screening options by sharing AGA's patient education from the GI Patient Center: www.gastro.org/CRC.

Preferences did not differ a great deal between the age groups, with 35% of the younger group and 37% of the older group both preferring the FIT–fecal DNA tests every 3 years. Slightly more people in the 50+ age group preferred an annual FIT (19% vs. 12%) as opposed to the colon capsule video every 5 years (28% of younger group vs. 23%) or colon CT scan every 5 years (11% of

*Continued on page 21*

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# What role does social media have in GI?

Dear colleagues,
Most of us engage with social media, whether actively tweeting, following friends on Facebook, or discussing TikTok videos with family. Many gastroenterologists leverage social media to build their professional brand and to reach a wider audience. Others remain wary of committing a social media faux paux or worry about patient confidentiality. In this Perspectives column, Dr. Stephen Chris Pappas and Dr. Mohammad Bilal discuss the risks and benefits of social media for the practicing gastroenterologist. Dr. Pappas has a unique perspective as a gastroenterologist who is also trained as a lawyer, and Dr. Bilal speaks from a wealth of experience leading educational activities on social media. We look forward to hearing your thoughts on Twitter @AGA_GIHN and by email at ginews@gastro.org. ■


Dr. Ketwaroo

*Gyanprakash A. Ketwaroo, MD, MSc, is an 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.*

## Understand its multifaceted importance

Merriam-Webster's dictionary defines social media as "forms of electronic communication (such as websites for social networking and microblogging) through which users create online communities to share information, ideas, personal messages, and other content." Over the last few years, there has been an increase in use of social media by medical professionals. Whether we like it or not, social media is here to stay. Patients use social media to look up information regarding their doctors, medical practices use it to promote the services they offer, institutions share their programs and initiatives, and doctors use it for education and to engage with like-minded colleagues, collaborate, spread awareness, network, and combat medical misinformation. Social media is now rapidly being used by gastroenterologists and hepatologists, as well as a majority of professional GI organizations, and hashtags such as "#MedTwitter," "#GITwitter," and "#LiverTwitter" have developed into popular academic forums. Therefore, the impact of social media in GI is multifaceted and includes its role in providing medical education, promoting your practice or division, finding collaborations, building your network and establishing mentors and peer-mentors, disseminating your work, and building your brand. ■


Dr. Bilal

*Mohammad Bilal, MD, FACP, is an assistant professor of medicine at the University of Minnesota, Minneapolis, and an advanced endoscopist in the division of gastroenterology at Minneapolis VA Medical Center. He has no relevant conflicts of interest to disclose.*

## Carefully consider the plentiful risks, concerns

Social media for gastroenterologists comes with benefits accompanied by pesky risks. The risks are pesky like a mosquito bite: An itching bite is annoying, but getting malaria is serious. Managing your unprofessional tweet to salvage your reputation is going to be annoying. Disclosing the identity of a patient on social media is going to be serious; you could find yourself fired, fined, reprimanded, and without hospital privileges, as happened recently to a Rhode Island physician. I divide the risks of social media into legal risks (for example, disclosing patient identity or inadvertently creating a doctor-patient relationship), risks of compromising ethical standards (for example, impairing the doctor-patient relationship), and mixed legal/ethics risks (for example, inappropriate Twitter banter disparaging individuals, promotion of "fake news"). Fortunately, these risks are intuitive and can be mitigated by attention to some simple principles.

An initial starting point is pausing to consider, "Would I say/do this in a public venue where everybody could hear/see me?" If there is any concern, don't post. Subsequently, conduct yourself on social media with meticulous attention to protecting confidentiality; avoiding any impression of creating a doctor-patient relationship; avoiding doctor-friend relationships; being aware of key legal, institutional, and professional society guidance; separating personal and professional activities; and maintaining professionalism. ■


Dr. Pappas

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*Continued from page 15*

younger group vs. 8%), but the differences were statistically significant ($P = .019$).

In fact, "sociodemographic, clinical characteristics, and colorectal cancer screening knowledge, attitudes, and beliefs were not predictive of selecting FIT or colonoscopy," the authors found. "This demonstrates the individualized nature of decision making on colorectal cancer screening tests. Moreover, as most individuals preferred FIT, it again emphasizes the importance of sequential or choice-based strategies for colorectal cancer screening."

However, one of the study's notable limitations was its high proportion of White patients relative to other racial/ethnic groups, so additional research may illuminate whether different sociodemographic groups do have slight preferences for one test over another, Dr. Almario said. The advantage to colonoscopies, he noted, is that they occur only every 10 years and if polyps are discovered, they can be taken care of right away.

"You don't have to think about it for a decade, which is certainly a pro for the colonoscopy," Dr. Almario said. "The FIT test is obviously less invasive, but you have to do it every year for it to be an effective screening test." He noted that some data have shown a drop-off in compliance over multiple years. "We certainly need more systems in place to remind patients and providers to do it annually so that we can see the ultimate screening benefit from doing that test specifically."

The participation of 1,000 respondents from the United States may not be generalizable to other countries as well, Dr. Ness said. "The survey was also carried out during the COVID pandemic which might have increased participants' desire for at-home testing," he added.

"The most important point from the clinical perspective is, when we're talking to patients about colon cancer screening, make sure to give them a choice," Dr. Almario said. "We just can't look at someone's chart, their clinical characteristics or demographics, and predict what tests they would prefer. We need to ask them. We need to present them with the options, go over the pros and cons of colonoscopy, the pros and cons of the stool test, and ask the patient what they would prefer to do."

The research was funded by the National Cancer Institute and the National Institutes of Health. One author served on an advisory panel with Exact Sciences. The other authors and Dr. Ness had no disclosures. ■

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### Conclusion

Your gift directly supports talented young researchers working to advance our understanding of digestive diseases. Make a tax-deductible donation to help spur innovation. Donate today at www.gastro.org/donateonline.

# CMS releases proposed payment rule

On July 15, the Centers for Medicare & Medicaid Services released the Medicare Hospital Outpatient Prospective Payment (OPP) and Ambulatory Surgical Center (ASC) Payment Systems Proposed Rule for calendar year 2023.

AGA, along with the American College of Gastroenterology and the American Society for Gastrointestinal Endoscopy, have identified the following top three takeaways:

- **Slight increase in ASC payments –** The proposed ASC conversion factor increases 2.7% to $51.315 for ASCs that meet quality-reporting requirements.
- **Slight increase in facility fees payments –** Hospitals that meet quality-reporting requirements also receive a 2.7% proposed increase, which translates to $86.785 – a stark difference from the ASC payment.
- **18% cuts to some motility and G-tube codes** – Hospital outpatient facility payments for motility codes 91117 and 91122 and G-tube codes 43761-43763 could decrease by 18% because of proposed changes to their Ambulatory Payment Classification (APC) family.



# Vonoprazan-based therapy found superior for resistant *H. pylori*

*Data behind the FDA approval*

**BY CAROLYN CRIST**
*MDedge News*

Vonoprazan, a potassium-competitive acid blocker, appears to be superior to standard proton pump inhibitor–based therapy in clarithromycin-resistant *Helicobacter pylori* strains, as well as noninferior to standard care in nonresistant infections, according to a recent study that supported a Food and Drug Administration approval of vonoprazan dual and triple therapies in May 2022.


Dr. Chey

For decades, *H. pylori* has been mostly treated by proton pump inhibitor–based triple therapy, which includes a proton pump inhibitor, clarithromycin, and amoxicillin or metronidazole. However, eradication rates have dropped below 80% in the United States and Europe, according to the authors, mainly because of rising rates of clarithromycin resistance.

Since *H. pylori* is a leading cause of peptic ulcer, gastric adenocarcinoma, and gastric mucosa–associated lymphoid tissue lymphoma, better eradication methods should be highlighted, researchers led by William Chey, MD, AGAF, chief and professor in the division of gastroenterology and hepatology and director of the GI Physiology Laboratory at Michigan Medicine in Ann Arbor, wrote in Gastroenterology (2022 Jun 6. doi: 10.1053/j.gastro.2022.05.055).

In a multicenter, randomized,

*Continued on following page*

Gastric acid inhibition plays a fundamental role for *H. pylori* eradication. Proton pump inhibitors (PPIs) are generally used, combined with antibiotics, in this scenario. More recently, vonoprazan, a potassium-competitive acid blocker, has been suggested to enhance *H. pylori* therapy by optimizing gastric acid suppression. However, clinical experience with vonoprazan has been limited to East Asian countries. The study by Chey et al. reports data from the first clinical trial from the United States and Europe, concluding that vonoprazan triple (together with amoxicillin and clarithromycin) and dual (together with amoxicillin) therapies were superior to PPI-based triple therapy, especially in clarithromycin-resistant strains.


Dr. Gisbert

However, some aspects deserve to be taken into consideration. The first one is that the cure rate with the standard triple therapy (with lansoprazole) was as low as 68%, underlining what has been known for a long time: This regimen should no longer be considered standard treatment in Europe or the United States and that it should not be recommended in areas with high (>15%) clarithromycin resistance, such as the United States and most European countries.

Secondly, the overall efficacy considering all patients (both with clarithromycin-susceptible and -resistant strains) with vonoprazan dual and triple regimens were of only 77% and 81%, not reaching the recommended target (≥ 90%) for first-line treatment. Therefore, the fair conclusion of the present article should have been not only that vonoprazan regimens are more effective than PPI ones, but also that all of them are insufficiently effective.

Finally, eradication rates in clarithromycin-resistant infections with the vonoprazan regimens (≤ 70%), although superior to those with lansoprazole (32%), were still clearly suboptimal, emphasizing that both PPI- and vonoprazan-based treatments would be inadequate if used in high–clarithromycin resistance regions.

*Javier P. Gisbert, MD, PhD, is with the Hospital Universitario de La Princesa and the Universidad Autónoma de Madrid, both in Madrid. Dr. Gisbert has served as speaker, consultant, and advisory member for or has received research funding from Mayoly, Allergan, Diasorin, Gebro Pharma, and Richen.*

*Continued from previous page*

controlled, phase 3 trial, the research team studied 1,046 treatment-naive adults with *H. pylori* infection at 103 sites in the United States, the United Kingdom, Bulgaria, the Czech Republic, Hungary, and Poland between December 2019 and January 2021.

The patients were randomized to receive open-label vonoprazan dual therapy or a double-blind triple therapy twice a day for 14 days. The vonoprazan dual therapy consisted of 20 mg of vonoprazan twice daily and 1 gram of amoxicillin three times per day. The triple therapy consisted of 20 mg of vonoprazan or 30 mg of lansoprazole (standard care), each given with 1 gram of amoxicillin and 500 mg of clarithromycin.

The primary outcome assessed noninferiority in eradication rates in patients without clarithromycin- and amoxicillin-resistant strains, with a noninferiority margin of 10%. Secondary outcomes assessed the superiority in eradication rates in clarithromycin-resistant infections, as well as in all patients.

Eradication rates for nonresistant strains were 84.7% for vonoprazan triple therapy and 78.5% for vonoprazan dual therapy, compared with 78.8% for lansoprazole triple therapy. The rates for both vonoprazan therapies were considered noninferior to standard therapy.

The eradication rates in clarithromycin-resistant infections were 65.8% for vonoprazan triple therapy and 69.6% in vonoprazan dual therapy, compared with 31.9% for lansoprazole triple therapy. The rates for both vonoprazan therapies were considered superior to standard therapy, with a difference of 33.9 percentage points for triple therapy and 37.7 percentage points for dual therapy.

In all patients, the eradication rates were 80.8% for vonoprazan triple therapy and 77.2% for vonoprazan dual therapy, compared with 68.5% for lansoprazole triple therapy. The rates for both vonoprazan therapies were considered superior, with a difference of 12.3 percentage points for triple therapy and 8.7 percentage points for dual therapy.

Treatment-emergent adverse events were reported in 34.1% of patients in the vonoprazan triple-therapy group and 29.9% of patients in the vonoprazan dual-therapy group, compared with 34.5% in the lansoprazole triple-therapy group. Most adverse events were mild to moderate.

Serious adverse events occurred in 1.3% of the overall study population, including 1.7% of the vonoprazan triple-therapy group, 1.4% of the vonoprazan dual-therapy group, and 0.9% of the lansoprazole triple-therapy group. None were considered related to the study drugs.

Vonoprazan was approved for the treatment of *H. pylori* infections by the FDA in May 2022, and had already been approved for treatment of *H. pylori* infections and other acid-related diseases in several other countries. It decreases intragastric pH and maintains it to a greater degree than that of proton pump inhibitors, which has been associated with higher eradication rates, the authors wrote.

"Optimizing current regimens offers the potential to increase eradication rates and reduce additional antibiotic usage, thereby promoting and improving antimicrobial stewardship," the study authors wrote.

The study was funded by Phathom Pharmaceuticals, which contributed to the design and conduct of the trial, collection and interpretation of the data, preparation and review of the manuscript, and the decision to submit the manuscript for publication. The study authors declared various conflicts of interest, including some who have received compensation as a consultant, advisory committee member, or employee for Phathom Pharmaceuticals. ■

# Liver protein may help prevent parenteral nutrition–induced liver injury

**BY CAROLYN CRIST**
*MDedge News*

Hepatic protein PP2A-C-alpha may serve as a protective factor against parenteral nutrition–associated hepatic steatosis by improving liver function, according to a recent study published in Cellular and Molecular Gastroenterology and Hepatology (2022 May 26. doi: 10.1016/j.jcmgh.2022.05.008).

Parenteral nutrition–associated hepatic steatosis likely involves the down-regulation of hepatic PP2A-C-alpha and consequent increased phosphorylation of Akt2; this in turn alters hepatic lipid metabolism, promotes triglyceride accumulation, and leads to liver injury, wrote the researchers, led by Gulisudumu Maitiabula and Feng Tian of the Research Institute of General Surgery at Jinling Hospital, Nanjing, China, and the Medical School of Nanjing University.

"Our study provides a strong rationale that PP2A-C-alpha may be involved in the pathogenesis of [parenteral nutrition–associated hepatic steatosis]," they wrote. "Further research is merited to establish whether interventions to enhance PP2A function might suppress the development of hepatic steatosis in patients receiving long-term [parenteral nutrition]."

Parenteral nutrition can be a lifesaving therapy for patients with intestinal failure caused by insufficient bowel length or function, the authors

*Continued on following page*

Parenteral nutrition is a life saver for children and adults with insufficient absorptive capacity of the gastrointestinal tract. Unfortunately, up to two-thirds of patients requiring parenteral nutrition long term develop liver disease, which can have fatal outcomes. Parenteral nutrition–associated liver disease is characterized by fibrosis and steatosis. While portal inflammation and cholestasis resolve in patients who can be weaned off parenteral nutrition, portal fibrosis and steatosis unfortunately remain in about half of the patients. The development of therapeutic strategies for this condition has thus far been hampered by the fact that the molecular mechanism of parenteral nutrition–associated liver disease was unknown.

Dr. Kaestner

This study by Maitiabula and colleagues from Nanjing University Medical School addresses this problem by performing a proteomic and, importantly, phospho-proteomic analysis of liver biopsies from adults treated with parenteral nutrition compared to normally feeding controls. They discovered that levels of phosphorylated AKT2, the key signaling mediator of insulin in the liver, are increased, while protein levels of the opposing protein phosphatase 2A (PP2A) are decreased in patients receiving parenteral nutrition.

Remarkably, they could reproduce these same pathway changes in a mouse model of parenteral nutrition, which again led to a chronic activation of the insulin signaling pathway, culminating in the phosphorylation of AKT2. They show further that activation of AKT2 inhibits AMPK and alters hepatic lipid metabolism to promote triglyceride accumulation. Using the experimentally tractable mouse model, they demonstrate further that the ablation of a PP2A isoform in the liver is sufficient to cause lipid accumulation and liver injury. Conversely, restoring PP2A expression improved the hepatic phenotype in mice in the parenteral nutrition model. These findings could also be mimicked using pharmacological activation and inhibition of PP2A.

In sum, this experimental study could some day lead the way to novel treatments of parenteral nutrition–induced liver disease through the use of PP2A activators.

*Klaus H. Kaestner, PhD, is with the department of genetics and Center for Molecular Studies in Digestive and Liver Diseases, Perelman School of Medicine, University of Pennsylvania, Philadelphia. He reports no conflicts of interest.*

DDSEP 9
Digestive Diseases Self-Education Program

## Quick quiz answers

*Questions on page 11.*

**Q1.** Correct answer: D. Lorcaserin (Belviq).

### Rationale

Lorcaserin may cause valvulopathy, attention, or memory disturbance. This patient has normal ECHO and does not work with heavy machinery. Given his other history, this may be the best choice for him. Naltrexone/bupropion extended release is contraindicated in patients with seizure disorder, chronic opioid use, anorexia nervosa, bulimia, and abrupt discontinuation of alcohol, benzodiazepines, barbiturates, or antiepileptic drugs because bupropion lowers the seizure threshold. Liraglutide is contraindicated with personal or family history of medullary thyroid carcinoma or MENII. In addition, GLP1 receptor agonists can increase the risk of pancreatitis in patients with a history of pancreatitis. Phentermine/topiramate can increase the risk of nephrolithiasis. All of these medications are contraindicated in pregnancy and in patients with hypersensitivity to the drug and drug class.

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Phentermine HCl/Topiramate Extended Release Prescribing Information (Qsymia). https://qsymia.com/patient/include/media/pdf/prescribing-information.pdf.

**Q2.** Correct answer: D. Treatment for recurrent or metastatic disease is imatinib.

### Rationale

This patient has a gastrointestinal stromal tumor (GIST) of the stomach. GISTs are the most common mesenchymal tumor found in the stomach. Gastric GISTs have a better prognosis than those found in the small intestine. GISTs are often found incidentally but can cause symptoms such as bleeding due to ulceration. Pathology of a GIST shows spindle cells that stain positive for CD117 and harbor KIT mutations. Malignant potential and decreased survival are associated with size more than 2 cm and high mitotic index (more than 5/50 high-power field). Endoscopic ultrasound with tissue sampling is the preferred diagnostic technique. High-risk features include lobulated or irregular borders, invasion into adjacent structures and heterogeneity. Fine-needle aspirate may be suboptimal, and core biopsy is an acceptable alternative. Resection is indicated for lesions that are symptomatic, size more than 2 cm or high-risk EUS features. Lesions less than 2 cm, without high-risk features can be surveyed by EUS annually. Endoscopic resection might be possible for small lesions but should be done in specialized centers. Metastatic or recurrent lesions are treated with imatinib.

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# Early detection key

**Diabetes** *from page 1*

policy and making coverage determinations."

The research team compared an early-detection strategy for pancreatic ductal adenocarcinoma that targets new-onset diabetes patients at age 50 years and older with standard of care (no early-detection strategy/no screening). They looked at various minimal predicted cancer risk thresholds versus current standard of care in a Markov state–transition decision model. The analysis assumed a health care sector perspective and a lifetime horizon, with two willingness-to-pay thresholds ($100,000 and $150,000) per quality-adjusted life-year gained.

The researchers used data from one of their previously published studies, which included 89,881 patients with new-onset diabetes diagnosed at age 50 or older. The cumulative incidence of pancreatic cancer was 0.42% during the 3 years after diabetes diagnosis.

In the early-detection strategy, all patients 50 years and older with newly diagnosed diabetes mellitus were placed into low-risk and high-risk cohorts based on their predicted 3-year risk of pancreatic ductal adenocarcinoma under a range of assumed minimum-risk thresholds – 0.5%, 1%, 2%, 3%, 4%, and 5%; these thresholds were based on a previously established prediction model (Gastroenterology. 2017 Mar;152[4]:840-50.e3).

The research team found that an early-detection strategy that targeted patients with a minimum predicted 3-year pancreatic ductal adenocarcinoma risk of 1% was cost effective, based on a willingness-to-pay threshold of $150,000 per quality-adjusted life-year. The incremental cost-effectiveness ratio was $116,911 per quality-adjusted life-year.

At a willingness-to-pay threshold of $100,000 per quality-adjusted life-year, the early detection strategy at the 2% risk threshold was cost effective. The incremental cost-effectiveness ratio was $63,045 per quality-adjusted life-year.

The most influential factors included the proportion of pancreatic ductal adenocarcinomas detected at the local stage, costs of treatment for metastatic cancer, utilities of local and regional cancers, and sensitivity of screening.

The two early-detection strategies were cost effective, capturing 26%-45% of the pancreatic ductal adenocarcinoma cases in patients with new-onset diabetes.

The study authors noted several limitations, including the inability to incorporate out-of-pocket costs for patients, as well as focusing the analysis on the health care perspective.

"We acknowledge that, by incorporating the full consequences of decisions for all stakeholders, a societal perspective would have offered a more complete view on which to base public policy," they wrote.

At the same time, "given the substantial prevalence of [new-onset diabetes] among [pancreatic ductal adenocarcinoma] cases, this strategy could improve the survival of a substantial proportion of sporadic PDAC cases in the general population," they concluded.

The study authors reported various disclosures, including grants and research support from Takeda Pharmaceuticals USA, Janssen Pharmaceuticals, the National Institutes of Health, the Crohn's and Colitis Foundation, Lilly Oncology, GSK, and Clovis Oncology. ■

Earlier detection of pancreatic ductal adenocarcinoma (PDAC) is essential to improving the survival for the group of patients diagnosed with PDAC each year. New-onset diabetes in adults 50 years or older is recognized as a risk factor for being diagnosed with PDAC within the following 3 years.

Dr. Gromski

This study by Wang et al. uses previously described clinical prediction models to stratify the risk of PDAC in patients with new-onset diabetes. These models include age, body mass index, weight change, smoking, diabetic medications, and laboratory values (hemoglobin A1c, cholesterol, creatinine, alkaline phosphatase). They ran simulation models to determine the cost-effectiveness of screening for pancreatic cancer at various risk cut-offs. At the $150,000 willingness-to-pay threshold per quality-adjusted life-year, the 1% risk threshold was cost effective. Stage shifting from a higher-stage cancer to a lower-stage cancer was the driving force behind the cost-effectiveness ratios.

Providers need to have a high index of suspicion when an adult over the age of 50 has had a new diagnosis of diabetes. Abnormalities detected in laboratory data, weight trends, symptoms, a history of underlying smoking or pancreatic disease may appropriately prompt an MRI/magnetic resonance cholangiopancreatography or endoscopic ultrasound. Better and more accessible risk progression calculators for these patients could be used in real time. The current study by Wang et al. will be a helpful tool as well for navigating disputes with payers about the utility of covering screening tests in the subgroup of patients that are higher risk.

*Mark A. Gromski, MD, is assistant professor of medicine at Indiana University School of Medicine and a pancreatobiliary specialist and advanced endoscopist at IU Health. He reports having no relevant disclosures.*

*Continued from previous page*

noted. However, long-term use can lead to potentially fatal complications such as liver disease, but an understanding of the pathological mechanisms behind parenteral nutrition–associated hepatic steatosis is limited.

The research team performed comparative proteomic/phosphoproteomic analyses of liver samples from 10 patients with parenteral nutrition–associated hepatic steatosis, as well as 8 cholelithiasis patients as controls, who were admitted to Jinling Hospital between June 2018 and June 2019. The researchers also assessed the effect of PP2A-C-alpha on liver injury from total parenteral nutrition in mice.

The research team found that PP2A-C-alpha was down-regulated in patients and mice with parenteral nutrition–associated hepatic steatosis. In addition, in patients with parenteral nutrition–associated hepatic steatosis, they found enhanced activation of serine/threonine kinase Akt2 and decreased activation of AMPK.

Mice that were given total parenteral nutrition infusion for 14 days developed hepatic steatosis, down-regulation of PP2A-C-alpha, activation of Akt2, and inhibition of AMPK. Hepatocyte-specific deletion of PP2A-C-alpha in mice given parenteral nutrition exacerbated the Akt2 activation, AMPK inhibition, and hepatic steatosis through an effect on fatty acid degradation.

**Parenteral nutrition can be a lifesaving therapy for patients with intestinal failure; however, long-term use can lead to potentially fatal complications such as liver disease.**

On the other hand, forced expression of PP2A-C-alpha led to reductions in hepatocyte fat deposition and the pathological score for liver steatosis. Overexpression also significantly improved hepatic steatosis, suppressed Akt2, and activated AMPK. In addition, pharmacological activation of Akt2 in mice overexpressing PP2A-C-alpha led to the aggravation of hepatic steatosis.

"Collectively, these observations suggest that [parenteral nutrition] for [more than] 14 days leads to a down-regulation in PP2A-C-alpha expression that activates Akt2-dependent signaling, which would likely lead to hepatic steatosis," the study authors wrote.

Intervention trials of PP2A-C-alpha in humans have not been performed because PP2A-C-alpha activators or effector analogs were unavailable for clinical use, they wrote. Additional clinical studies are needed to investigate the effects of PP2A-C-alpha intervention on the development of hepatic steatosis in patients receiving long-term parenteral nutrition.

The study was supported by the National Natural Science Foundation of China, the Science Foundation of Outstanding Youth in Jiangsu Province, the National Science and Technology Research Funding for Public Welfare Medical Projects, "The 13th Five-Year Plan" Foundation of Jiangsu Province for Medical Key Talents, and the Natural Science Foundation of Jiangsu Province. The study authors disclosed no conflicts of interest. ■

# Barrett's esophagus: Key new concepts

**BY PRASAD G. IYER, MD, MS, AGAF**

Barrett's esophagus (BE) is the only known precursor of esophageal adenocarcinoma (EAC). The rationale for early detection of BE rests on the premise that, after the diagnosis of BE, patients can be placed under endoscopic surveillance to detect prevalent and incident dysplasia and EAC. Randomized controlled trials have demonstrated that endoscopic eradication therapy (EET) of low-grade dysplasia (LGD) and high-grade dysplasia (HGD) can reduce progression to EAC. Guidelines support endoscopic screening for BE in those with multiple (three or more) risk factors.

However, endoscopy is expensive, invasive, and not widely utilized (less than 10% of those eligible are screened). Most patients with BE are unaware of their diagnosis and hence not under surveillance. Non-endoscopic techniques of BE detection – swallowed cell collection devices providing rich esophageal cytology specimens combined with biomarkers – are being developed. Case-control studies have shown promising accuracy and a recent U.K. pragmatic primary care study showed the ability of this technology to increase BE detection safely.

Detection of dysplasia in endoscopic surveillance is critical and the neoplasia detection rate (NDR) has been recently proposed as a quality marker. The NDR is the ratio of HGD+EAC detected to all patients with BE undergoing their first surveillance endoscopy. A recent systematic review and meta-analysis showed an inverse association between NDR and postendoscopy BE neoplasia. Additional and prospective studies are required to further correlate NDR values to clinically relevant outcomes similar to the association between adenoma detection rate and postcolonoscopy colorectal cancer.

Dr. Iyer

**Detection of dysplasia in endoscopic surveillance is critical and the neoplasia detection rate has been recently proposed as a quality marker.**

Detection of dysplasia with endoscopic surveillance is challenging because of sampling error inherent in the Seattle protocol. A recent technology, Wide Area Transepithelial Sampling–3D (WATS), combines the concept of increased sampling of the BE mucosa by using a stiff endoscopic brush followed by use of artificial intelligence neural network–enabled selection of abnormal cells, which are presented to a pathologist. This technology has been shown to increase dysplasia and HGD detection, compared to endoscopic surveillance, in a systematic review and meta-analysis. However, WATS is negative in a substantial proportion of cases in which endoscopic Seattle protocol reveals dysplasia. In addition, only limited data are available on the natural history of WATS LGD or HGD. Confirmation of WATS-only dysplasia (LGD, HGD, or EAC) by endoscopic histology is also recommended before the institution of EET. Finally, assessment of progression risk in those with BE is critical to enable more personalized follow-up recommendations. Clinical risk scores integrating age, sex, smoking history, and LGD have been proposed and validated. A recent tissue systems pathology test has been shown in multiple case-control studies to identify a subset of BE patients who are at higher risk of progression, independent of LGD. This test is highly specific but only modestly sensitive in identifying progressors. ■

*Dr. Iyer is professor of medicine, director of the Esophageal Interest Group, and codirector of the Advanced Esophageal Fellowship at the Mayo Clinic College of Medicine and Science, Rochester, Minn. He reports relationships with Exact Sciences, Pentax Medical, and others.*

# What is new in cirrhosis management?

**BY JENNIFER C. LAI, MD, MBA, AGAF**

There is a rich science around the management of the cirrhotic liver itself – for example, pragmatic prognostic markers such as MELDNa, data-driven strategies to prevent variceal bleeding, and well-utilized algorithms to manage ascites.

M_A_Y_A/Getty Images

But what is new in cirrhosis management is an emerging science around the management of the person living with cirrhosis – a science that seeks to understand how these individuals function in their day-to-day lives, how they feel, and how they can best prepare for their future. What is so exciting is that the field is moving beyond simply understanding those complex aspects of the patient, which is important in and of itself, toward developing practical tools to help clinicians assess their patients' symptoms and strategies to help improve their patients' lived experience. Although terms such as "frailty," "palliative care," and "advance care planning" are not new in cirrhosis per se, they are now recognized as distinct patient-centered constructs that are highly relevant to the management of patients with cirrhosis. Furthermore, these constructs have been codified through two recent guidance statements sponsored by the American Association for the Study of Liver Diseases.[1,2] Pragmatic tools are emerging to facilitate the integration of these patient-centered constructs into routine clinical practice, tools such as the Liver Frailty Index, the Edmonton Symptom Assessment System adapted for patients with cirrhosis, and structured frameworks for guiding goals-of-care discussions. The incorporation of these tools allows for new management strategies directed toward improving the patient's experience such as timely initiation of nutrition and activity-based interventions, algorithms for pharmacologic and nonpharmacologic strategies for symptom management, and online/video-guided approaches to articulating one's goals of care.

Dr. Lai

So, what is new in cirrhosis management is that we are moving beyond managing the cirrhotic liver itself to considering how cirrhosis and its complications impact the patient as a whole. In doing so, we are turning the art of hepatology care into science that can be applied systematically at the bedside for every patient, with the goal of improving care for all patients living with cirrhosis. ■

*Dr. Lai holds the Endowed Professorship of Liver Health and Transplantation at the University of California, San Francisco. She reports having no conflicts of interest.*

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# An approach to germline genetic testing

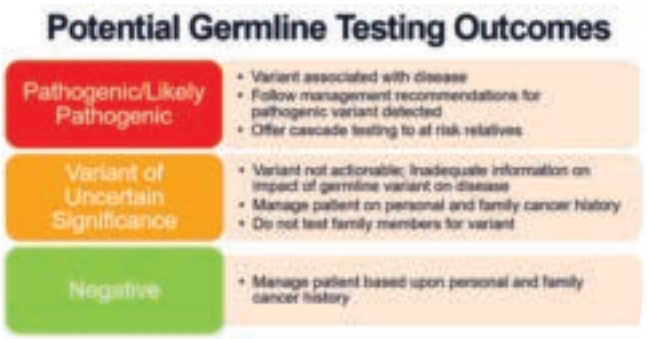
BY CAROL A. BURKE, MD, AGAF

Traditionally, a hereditary colorectal cancer syndrome (HCCS) was suspected in individuals with an obvious personal and/or family cancer phenotype informed by a three-generation family cancer history. Family history is still required to inform cancer risk. Documentation of age at cancer diagnosis, age of relatives' deaths, and key intestinal and extraintestinal features of a HCCS (for example, macrocephaly, café au lait spots, polyp number, size, and histology) are requisite. Historically, Sanger sequencing was used to determine the presence of a suspected single pathogenic germline variant (PGV). If no PGV was detected, another PGV would be sought. This old "single gene/single syndrome" testing was expensive, time consuming, and inefficient, and has been supplanted by multigene cancer panel testing (MGPT). MGPT-driven low-cost, high-throughput testing has widespread insurance coverage in eligible patients. Since considerable clinical phenotypic overlap exists between HCCSs, casting a broader net for determining PGV allows for greater identification of carriers of PGV as well as variants of uncertain significance.

Dr. Burke

The frequency of PGV detection by MGPT in individuals with colorectal cancer (CRC) is dependent on age at diagnosis and presence of DNA mismatch repair (MMR) deficiency in the tumor. According to one review, PGVs on MGPT are detected in approximately 10% and 34% of individuals aged more than 50 and more than 35 years, respectively.[1] Pearlman and colleagues performed MGPT in 450 patients with CRC less than 50 years.[2] PGV were found in 8% and 83.3% of cases with MMR-proficient and -deficient tumors, respectively. Overall, 33.3% of patients did not meet genetic testing criteria for the gene in which a PGV was detected, raising the impetus to consider MGPT in all patients with CRC. The Collaborative Group of the Americas on Inherited Gastrointestinal Cancer and National Comprehensive Cancer Network provide guidance on who warrants PGV testing.[3,4]

HCCS are common and MGPT has broadened the identification of carriers of PGVs. In spite of advances in genetic testing technology, family history remains crucial to deploying risk-mitigation measures, regardless of the results of genetic testing. ■




COURTESY DR. CAROL A. BURKE

*Dr. Burke is in the department of gastroenterology, hepatology, and nutrition at the Cleveland Clinic. She disclosed ties to Janssen Pharma, Emtora Biosciences, Freenome, SLA Pharma, and Ambry Genetics. Dr. Burke is a member of the U.S. Multi-Society Task Force on Colorectal Cancer.*

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# EUS-guided gallbladder drainage for acute cholecystitis

BY SHAYAN IRANI, MBBS, MD

Percutaneous transhepatic gallbladder drainage (PT-GBD) is the most common, nonoperative method for gallbladder decompression in patients unfit for cholecystectomy. However, drain-related complications (20%-75%), including tube changes, dyscosmesis, discomfort, and recurrent cholecystitis (up to 15%), limit its long-term use. Endoscopic transpapillary gallbladder drainage (ET-GBD) and now, endoscopic ultrasound–guided gallbladder drainage (EUS-GBD), have emerged as options.

ET-GBD is performed at endoscopic retrograde cholangiopancreatography (ERCP) by cannulating the cystic duct, allowing placement of a pigtail plastic stent into the gallbladder. However, obstructing pathology (stone, stricture, metal stent, or mass) may result in lower technical and clinical success when compared with EUS-GBD (84% vs. 98% and 91% vs. 97%, respectively). Furthermore, it does not allow for treatment of gallstones, and may require stent exchanges.

EUS-GBD involves placing a stent from the duodenum/stomach into the gallbladder under EUS guidance. Initial use of pigtail plastic stents and biliary self-expandable metal stents were not ideal, because of their risk of leakage, longer

*Continued on following page*



## INDEX OF ADVERTISERS

# Understanding GERD phenotypes

BY RENA YADLAPATI, MD, MSHS

Approximately 30% of U.S. adults experience troublesome reflux symptoms of heartburn, regurgitation, and noncardiac chest pain. Because the mechanisms driving symptoms vary across patients, phenotyping patients via a stepwise diagnostic framework effectively guides personalized management in gastroesophageal reflux disease (GERD).


Dr. Yadlapati

For instance, proton-pump inhibitor (PPI) trials are appropriate when esophageal symptoms are present, whereas up-front reflux monitoring rather than empiric PPI trials are recommended for evaluation of isolated extra-esophageal symptoms. All patients undergoing evaluation for GERD should receive counseling on weight management and lifestyle modifications as well as the brain–gut axis relationship. In the common scenario of inadequate symptom response to PPIs, upper GI endoscopy is recommended to assess for erosive reflux disease (which confirms a diagnosis of GERD) as well as the anti-reflux barrier integrity. For instance, the presence of a large hiatal hernia and/or grade III/IV gastroesophageal flap valve may point to mechanical gastroesophageal reflux as a driver of symptoms and lower the threshold for surgical referral. In the absence of erosive reflux disease the next recommended step is ambulatory reflux monitoring off PPI therapy, either as prolonged wireless telemetry (which can be done concurrently with index endoscopy as long as PPI was discontinued > 7 days) or 24-hour transnasal pH-impedance catheter-based testing. Studies suggest that 96-hour monitoring is optimal for diagnostic accuracy and to guide therapeutic strategies.

**A multitude of treatment options are available to manage GERD. However, not every treatment strategy is appropriate for every patient.**

Patients without evidence of GERD on endoscopy or ambulatory reflux monitoring likely have a functional esophageal disorder for which therapy hinges on pharmacologic neuromodulation or behavioral interventions as well as PPI cessation.

Alternatively, management for GERD (erosive or nonerosive) aims to optimize lifestyle, PPI therapy, and the individualized use of adjunctive therapy which includes H2-receptor antagonists, alginate antacids, GABA agonists, neuromodulation, and/or behavioral interventions. Surgical or endoscopic antireflux interventions are also an option for refractory GERD. Prior to intervention achalasia must be excluded (typically with esophageal manometry) and confirmation of PPI refractory GERD on pH-impedance monitoring on PPI is of value, particularly when the phenotype is unclear. Again, the choice of antireflux intervention (for example, laparoscopic fundoplication, magnetic sphincter augmentation, transoral incisionless fundoplication, Roux-en-Y gastric bypass) should be individualized to the patient's anatomy, physiology, and clinical profile.

A multitude of treatment options are available to manage GERD, including behavioral interventions, lifestyle modifications, pharmacotherapy, and endoscopic/surgical interventions. However, not every treatment strategy is appropriate for every patient. Data gathered from the step-down diagnostic approach, which starts with clinical presentation, then endoscopy, then reflux monitoring, then esophageal physiologic testing, help determine the GERD phenotype and effectively guide therapy. ■

*Dr. Yadlapati is associate professor of clinical medicine, and medical director, UCSD Center for Esophageal Diseases; director, GI Motility Lab, division of gastroenterology, University of California San Diego, La Jolla, Calif. She disclosed ties with Medtronic, Phathom Pharmaceuticals, StatLink-MD, Medscape, Ironwood Pharmaceuticals, and RJS Mediagnostix.*

*Continued from previous page*

length (contralateral wall injury, occlusions) and migration (lack of flanges). Lumen-apposing metal stents (LAMS) overcame these limitations because of their short length and large flanges and their large diameters (up to 20 mm) aid passage of gallstones or cholecystoscopy. Several case series and comparative trials have been published on EUS-GBD including a randomized prospective trial of EUS-GBD vs. PT-GBD demonstrating its superiority. Adverse events are uncommon and include misdeployments, bleeding, perforation, bile leaks, occlusion (commonly with food, prompting some endoscopists to place pigtails stents through the LAMS and avoiding the stomach as a target) and migration.


Dr. Irani

EUS-GBD should be avoided in patients who have a perforated gallbladder, have large volume ascites, or are too sick to tolerate anesthesia. Although there are patients who have subsequently undergone cholecystectomy post EUS-GBD, a discussion with one's surgeon must be had prior to choosing this approach over ET-GBD.

In conclusion, determining the ideal method for endoscopic GBD in high–surgical risk patients requires consideration of comorbidities, anatomy (GB position, cystic duct characteristics), presence of ascites, future surgical candidacy, and local expertise. ET-GBD should be prioritized for patients requiring ERCP for alternative reasons, for large volume ascites, and as a bridge to cholecystectomy. Conversely, EUS-GBD is preferred with indwelling metal biliary stents covering the cystic duct and/or high-volume cholelithiasis. LAMS can be left long term; however, in patients willing to undergo an additional procedure, exchanging the LAMS for plastic stents can be undertaken at 4-6 weeks. Ultimately, more randomized and prospective data are needed to compare ET- and EUS-GBD outcomes, including a formal cost analysis. ■

*Dr. Irani is with Virginia Mason Medical Center, Seattle. He reports being a consultant for Boston Scientific and Gore, as well as remittance to his clinic.*

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