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Mitchel L. Zoler/MDedge News

Dr. Juliana Henrique reported that people with a history of obesity and bariatric surgery had lower rates of obesity-related cancer.

Evidence builds for bariatric surgery tie to lower cancer risk

BY MITCHEL L. ZOLER
MDedge News

LAS VEGAS – The ability of bariatric surgery and substantial subsequent weight loss to cut the incidence of a variety of obesity-related cancers and other malignancies received further confirmation in results from two studies reported at a meeting presented by the Obesity Society and the American Society for Metabolic and Bariatric Surgery.

In one study, 2,107 adults enrolled in the Longitudinal Assessment of Bariatric Surgery (LABS-2) study showed a statistically significant halving of the cancer incidence during 7 years of follow-up in patients who underwent bariatric surgery and had a reduction of at least 20% in their presurgical body mass index, compared with patients in the study who underwent bariatric surgery but lost less weight, reported Andrea M. Stroud, MD, a bariatric surgeon at the Oregon Health & Science University, Portland.

In the second study, anal-

See **Bariatric** · *page 21*

AGA releases update on endoscopic treatment of Barrett's

Emphasis is on risk stratification

BY WILL PASS
MDedge News

The American Gastroenterological Association recently released a clinical practice update on endoscopic treatment of Barrett's esophagus with dysplasia and/or early esophageal adenocarcinoma.

The update offers best practice advice for a range of clinical scenarios based on published evidence, including guidelines and recent systematic reviews, reported lead author Prateek Sharma, MD, of the University of Kansas, Kansas City. Dr. Sharma was accompanied on the authoring review team by three other expert gastroenterologists from the United States and the Netherlands.

Beyond practice advice, the investigators highlighted a research focus for the future.

"Given the expense and time required for careful and continual surveillance after Barrett's endoscopic therapy, the future must define improved means of risk-stratifying patients for therapy who are at

See **Barrett's** · *page 17*

Eradicating *H. pylori* may cut risk of gastric cancer

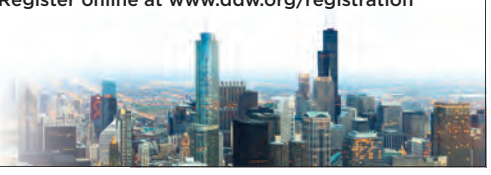
BY AMY KARON
MDedge News

Eradication of *Helicobacter pylori* infection was associated with a more than 75% decrease in the hazard of subsequent stomach cancer in a large retrospective cohort study.

Simply being treated for *H. pylori* infection did not mitigate the risk of gastric adenocarcinoma, and patients whose *H. pylori* was not eradicated were at increased risk, said Shria Kumar, MD, of the Perelman Center for Advanced Medicine in Philadelphia, and her associates. "This speaks to the ability of *H. pylori* eradication to modify future risks of gastric adenocarcinoma, and the need to not only treat

See **Gastric cancer** · *page 7*

INSIDE



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LETTER FROM THE EDITOR

Hope springs eternal

As practicing clinicians, we all want to do what is best for patients. We hope our treatments will improve actual health outcomes (and not intermediate process metrics), so we make decisions based on "evidence" that lies on a continuum from "I hope" on one end to "I'm sure" on the other. This month, our three lead articles represent differing points along that continuum.


Dr. Allen

First, we consider *H. pylori* and gastric cancer. We know *H. pylori* eradication reduces ulcer risk and that *H. pylori* is a risk for gastric cancer. We did not know whether eradication reduces cancer risk. In a large retrospective study from the VA, Kumar et al. demonstrated that eradication (not just treatment) substantially reduced subsequent gastric cancers. These data are not definitive, but they nudge us towards the "I'm sure" end of the continuum.

A second group of studies (both retrospective and prospective) suggests that successful weight loss after bariatric surgery was associated with a substantial reduction of risk for 13 cancer types related to obesity. Moderate evidence but again nudging us away from "I hope."

A third article highlights the recent Clinical Practice Update on Barrett's esophagus published by the AGA Clinical Practice Update Committee in Gastroenterology's February 2020 issue. This practice update helps us understand the impact we will make on cancer reduction with surveillance and treatment of Barrett's. Despite this publication, Barrett's management remains closer to "hope" than "sure."

As practicing clinicians, we all want to do what is best for patients. We hope our treatments will improve actual health outcomes (and not intermediate process metrics).

The difficulty we face, as clinician or patient, is what to do when outcomes are really serious but evidence remains close to the "I hope" end. Take a reasonably healthy 68-year-old man with asymptomatic coronary disease, but a very high (and increasing) coronary artery calcium score, despite maximum statins and appropriate lifestyle practices. Should he initiate a PCSK9 inhibitor ($14,000 per year) absent evidence that it would alter cardiac risk? Recently, a retrospective study nudged us along the continuum (Peng et al. JACC Cardiovascular Imaging. 2020 Jan;13[1 Pt 1]:83-93). A serious outcome, suggestive but not definitive evidence, and no time for an RCT. Will such aggressive therapy help? I sure hope so.

John I. Allen, MD, MBA, AGAF
Editor in Chief

DDSEP 9
Digestive Diseases Self-Education Program

Quick Quiz

Q1. You recently diagnosed a 66-year-old man with cirrhosis due to nonalcoholic steatohepatitis. The patient presents to your clinic now inquiring about his long-term prognosis.

Which of the following is the most common cause of long-term mortality among patients with nonalcoholic steatohepatitis (NASH) cirrhosis?
A. Colon cancer
B. Cardiovascular disease
C. Hepatic failure
D. Infection

Q2. What is the maximal dose of carvedilol recommended in the management of esophageal varices?
A. 6.25 mg daily
B. Carvedilol is not recommended
C. 12.5 mg daily
D. 12.5 mg twice a day
E. 3.25 mg daily

The answers are on page 18.

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Trial of epicutaneous immunotherapy in EoE

BY AMY KARON
MDedge News

For children with milk-induced eosinophilic esophagitis (EoE), 9 months of epicutaneous immunotherapy (EPIT) with Viaskin Milk did not significantly improve eosinophil counts or symptoms, compared with placebo, according to the results of an intention-to-treat analysis of a randomized, double blinded pilot study.

Average maximum eosinophil counts were 50.1 per high-power field in the Viaskin Milk group versus 48.2 in the placebo group, said Jonathan M. Spergel, MD, of the Children's Hospital of Philadelphia and associates. However, in the per-protocol analysis, the seven patients who received Viaskin Milk had mean eosinophil counts of 25.6 per high-power field, compared with 95.0 for the two children who received placebo (P = .038). Moreover, 47% of patients had fewer than 15 eosinophils per high-power field after an additional 11 months of open-label treatment with Viaskin Milk. Taken together, the findings justify larger, multicenter studies to evaluate EPIT for treating EoE and other non-IgE mediated food diseases, Dr. Spergel and associates wrote in Clinical Gastroenterology and Hepatology.

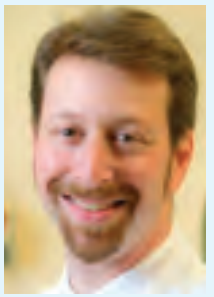
EoE results from an immune response to specific food allergens, including milk. Classic symptoms include difficulty feeding and failure to thrive in infants, abdominal pain in young children, and dysphagia in older children and adults. Definitive diagnosis requires an esophageal biopsy with an eosinophil count of 15 or more cells per high-power field. "There are no approved therapies [for eosinophilic esophagitis] beyond avoidance of the allergen(s) or treatment of inflammation," the investigators wrote.

In prior studies, exposure to EPIT was found to mitigate eosinophilic gastrointestinal disease in mice and pigs. In humans, milk is the most common dietary cause of eosinophilic esophagitis. Accordingly, Viaskin Milk is an EPIT containing an allergen extract of milk that is administered epicutaneously using a specialized delivery system. To evaluate its use for the treatment of pediatric milk-induced EoE (at least 15 eosinophils per high-power frame despite at least 2 months of high-dose proton pump–inhibitor therapy at 1-2 mg/kg twice daily), the researchers randomly assigned 20 children on a 3:1 basis to receive either Viaskin Milk or placebo for 9 months. Patients and investigators were double-blinded for this phase of the study, during most of which patients abstained from milk. Toward the end of the 9 months, patients resumed consuming milk and continued doing so if their upper endoscopy biopsy showed resolution of EoE (eosinophil count less than 15 per high-power field).

In the intention-to-treat analysis, Viaskin Milk did not meet the primary endpoint of the difference in least squares mean, compared with placebo (8.6; 95% confidence interval, –35.36 to 52.56). Symptom scores also were similar between groups. In contrast, at the end of

Continued on following page

Eosinophilic esophagitis (EoE) is a chronic immune mediated disease that is primarily triggered by food antigens. Though many patients can be treated with dietary elimination or pharmacologic therapies, when foods are added back, elimination diets are not followed, or medications stopped, the disease will flare. Further, unlike some other atopic conditions, patients with EoE do not "grow out of it." A true cure for EoE has been elusive. In this study by Dr. Spergel and colleagues, they build on intriguing data from animal models showing induction of immune tolerance to food antigens with epicutaneous immunotherapy (EPIT).


Dr. Dellon

The investigators conducted a proof-of-concept, double-blind, placebo-controlled randomized trial of epicutaneous desensitization with a milk patch in children with EoE who had milk as a confirmed dietary trigger. The primary intention-to-treat results showed that there was no difference between placebo and active patches for decreasing esophageal eosinophil counts. However, in the small set of patients who were able to adhere fully to the protocol, the per-protocol analysis suggested that there was a lower eosinophil count with active treatment. Additionally, in an 11-month, open-label extension, there were patients who maintained histologic response (less than 15 eosinophils/hpf) after reintroducing milk.

These data suggest that EPIT potentially can desensitize milk-triggered EoE patients and that this treatment method should be pursued in future studies, with protocol alterations based on lessons learned regarding adherence in this study. Should this line of investigation be successful, then EoE patients who have milk as their EoE trigger, and who undergo successful desensitization with mild reintroduction while maintaining disease remission, may be able to be deemed cured.

Evan S. Dellon, MD, MPH, AGAF, is professor of medicine and epidemiology, division of gastroenterology and hepatology, University of North Carolina at Chapel Hill. He has received research funding from and consulted for Adare, Allakos, Celgene/Receptos, GSK, and Shire/Takeda among other pharmaceutical companies. He has received educational grants from Allakos, Banner, and Holoclara.

Confirm eradication

Gastric cancer *from page 1*

those diagnosed with *H. pylori*, but to confirm eradication, and re-treat those who fail eradication," they wrote in Gastroenterology.

Gastric adenocarcinoma remains a grave diagnosis, with a 5-year survival rate of less than 30%. Although *H. pylori* infection is an established risk factor for gastric cancer (particularly nonproximal disease), most studies have used national cancer databases that do not track *H. pylori* infection. Accordingly, Dr. Kumar and her associates analyzed data for 371,813 patients diagnosed with *H. pylori* infection at U.S. Veterans Health Administration facilities between 1994 and 2018. A total of 92% of patients were men, 58% were white, 24% were black, and approximately 1% each were Native American, Asian, or Native Hawaiian/Pacific Islander. Median age was 62 years.

Patients with *H. pylori* infection who subsequently were diagnosed with nonproximal gastric cancer were significantly (P less than .001) more likely to be older (median age, 65.1 vs. 62.0 years), current or historical smokers, or racial or ethnic minorities (black or African American, Asian, or Hispanic/Latino), compared with patients with *H. pylori* who did not develop cancer. In the multivariable analysis, standardized hazard ratios for these variables remained statistically significant, with point estimates ranging from 1.13 (for each 5-year increase in age at diagnosis of infection) to 2.00 (for black or African American race). Cumulative incidence rates of distal gastric adenocarcinoma following *H. pylori* infection were 0.37% at 5 years, 0.5% at 10 years, and 0.65% at 20 year.

Patients whose infections were confirmed to have been eradicated were at markedly lower risk for subsequent gastric cancer than were patients whose infections were not eradicated (SHR, 0.24; 95% confidence interval, 0.15-0.41; P less than .001). Importantly, simply being treated for *H. pylori* did not significantly affect cancer risk (SHR, 1.16; 95% CI, 0.74-1.83).

Rates in Japan are approximately five times higher, while in sub-Saharan Africa, *H. pylori* infection is prevalent but gastric cancer is uncommon, the researchers noted. These discrepancies support the idea that carcinogenesis depends on additional genetic or environmental variables in addition to *H. pylori* infection alone, they said. They called for future studies of protective factors.

Dr. Kumar is supported by a training grant from the National Institutes of Health. She disclosed travel support from Boston Scientific and Olympus. Her coinvestigators disclosed ties to Takeda, Novartis, Janssen, Gilead, Bayer, and several other companies.

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SOURCE: Kumar S et al. Gastroenterology. 2019 Jul 31. doi: 10.1053/j.gastro.2019.10.019.

Unique T-cell populations pinpointed in hepatocellular carcinoma tissue

BY ANDREW D. BOWSER
MDedge News

Hepatocellular carcinoma (HCC) tissue contains several unique populations of tumor-infiltrating cells, including some exhausted effector T cells that regain normal function when treated with the immunotherapy drug nivolumab, according to researchers.

The unique populations of recently activated CD4+, CD8+, and CD4-CD8 double-negative cells identified in the tumors expressed specific activation markers and inhibitor receptors, according to investigators, who have published the results of their immune profiling analyses in Cellular and Molecular Gastroenterology and Hepatology.

"Importantly, these cells expressed markers of activation and tissue residence, possibly suggesting activation within the tumor," said Daniela Di Blasi, PhD, and associates, of the University of Basel in Switzerland.

A further look at tumor histology revealed an accumulation of those activated T cells in immune-inflamed HCC, according to the investigators, who added that enumeration of specific tumor-infiltrating lymphocytes could represent "a prognostic indicator of therapy responsiveness."

However, they advised caution in interpreting the results to date: "We are aware that the analysis described here is based on a small number of patients and that validation of its prognostic value requires ad hoc prospective studies that include more patients," they said in their report.

The researchers' findings were based on analysis of HCC biopsies before and after treatment with the immune checkpoint inhibitor nivolumab, nontumor liver tissue biopsies, and peripheral blood samples from 36 patients, most of whom were male, and about half of whom had cirrhosis. Investigators used multiparametric flow cytometry to characterize expression of activation markers including CD137, CD150, and ICOS, among others, as well as expression of inhibitory receptors including TIGIT and PD1.

Compared with nonneoplastic liver tissue, tumor tissue was enriched with T cells expressing the activation marker CD137 and the inhibitory receptor ICOS, indicating that HCC tumor-infiltrating lymphocytes "are different from liver-resident T cells and might have immunologic relevance," Dr. Di Blasi and coauthors said in their report.

Immunotherapy with checkpoint inhibitors has been suggested for the treatment of HCC and finding relevant predictors of response to immunotherapy remains one of the most challenging tasks for solid gastrointestinal cancers such as HCC where efficiency of immune therapy suggests only a moderate response so far.

Recently, two randomized phase 3 trials on checkpoint inhibitors in HCC, both first-line against sorafenib (Checkmate 459) as well as second-line against placebo (KEYNOTE-240), have failed to show an overall survival benefit despite clinical benefit in some patients and a manageable side effects profile. The study by Di Blasi et al. therefore provides important insights into the immune cell composition of tumor-infiltrating lymphocytes (TILs) in HCC. In this study it was possible to identify certain cell populations within TILs that resembled recently activated tumor-specific T cells that were in an exhausted state. It was possible to reinvigorate these exhausted cell clusters and to activate IFN-delta–producing T cells with the help of checkpoint inhibitor therapy in these patients.

These data suggest that the enumeration of certain immune cell infiltrates may identify patients responding to checkpoint inhibitor therapy. Another important observation from this study was that not all immune-inflamed tumors identified by immunohistochemistry (or so-called "hot tumors") responded to checkpoint inhibitor therapy and that more sophisticated analysis of the immune infiltrates with, e.g., flow cytometry or mass cytometry seems to be necessary to understand which patients respond. Different immune cell clusters have been suggested by other research groups and further research is needed to confirm this theory and to understand which of the proposed immune cell clusters and phenotypic profiles will prove most valuable in terms of prognosis for checkpoint inhibitor therapy in HCC.

Nico Buettner, MD, and Robert Thimme, MD, are professors in the department of medicine II, Medical Center University of Freiburg (Germany). They have no conflicts of interest.

Further analysis revealed several cell populations unique to HCC samples, the authors said, including CD4+ T cells coexpressing ICOS and TIGIT, which tended to accumulate in tumor tissue, compared with nontumor tissue and peripheral blood mononuclear cells. Those CD4+ tumor-infiltrating T cells were functionally impaired, they added, as shown by a lack of cytokine production.

Activated CD8+ T cells likewise preferentially accumulated in tumor tissue, and most of those tumor-infiltrating cells expressed CD38 and PD1. The presence of these proliferating and functional cells may contribute to local inflammation and antitumor response, according to the investigators, who also identified two unique populations of double-negative T cells, including some that expressed CD137, which they said was a marker of recent T-cell activation.

The investigators also looked at the presence of tumor-infiltrating lymphocytes correlated to the presence of mononuclear cell infiltrate in tumor tissue. They found that immune-inflamed tumors had significantly increased proliferation of unique CD4+, CD8+, and double-negative T cell populations.

Nivolumab treatment appeared to substantially reduce the proportion of impaired CD4+ T cells, while increasing the percentage of interferon gamma–producing CD38+ CD4+ T cells and also promoting enrichment of interferon gamma–producing CD38+ CD8+ cells. Those increases in release of interferon gamma may have a positive influence on antitumor immunity via modulation of immune and tumor cell functions, according to the investigators.

Not all immune-inflamed tumors responded to nivolumab treatment, suggesting that an immune-inflamed profile is "necessary but not sufficient" for clinical response to an anti-PD1 agent, noted Dr. Di Blasi and colleagues.

The study was supported by grants from the European Research Council and the Swiss Initiative in Systems Biology, among others. Dr. Di Blasi and coauthors disclosed no conflicts of interest.

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SOURCE: Di Blasi D et al. Cell Mol Gastroenterol Hepatol. 2019 Aug 22. doi: 10.1016/j.jcmgh.2019.08.004.

Continued from previous page

the 11-month, open-label period, 9 of 19 evaluable patients had eosinophil biopsy counts of fewer than 15 per high-power field, for a response rate of 47%. "The number of adverse events did not differ significantly between the Viaskin Milk and placebo groups," the researchers added.

Protocol violations might explain why EPIT failed to meet the primary endpoint in the intention-to-treat analysis, they wrote. "For example, the patients on the active therapy wanted to ingest more milk, while the patients in the placebo group wanted less milk," they reported. "Three patients in the active therapy went on binge milk diets drinking 4-8 times the amount of milk, compared with baseline." The use of proton pump inhibitors also was inconsistent between groups, they added. "The major limitation in the [per-protocol] population was the small sample size of this pilot study, raising the possibility of false-positive results."

The study was funded by DBV Technologies and by the Children's Hospital of Philadelphia Eosinophilic Esophagitis Family Fund. Dr. Spergel disclosed consulting agreements, grants funding, and stock equity with DBV Technologies. Three coinvestigators also disclosed ties to DBV. The remaining five coinvestigators reported having no conflicts of interest.

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SOURCE: Spergel JM et al. Clin Gastroenterol Hepatol. 2019 May 14. doi: 10.1016/j.cgh.2019.05.014.

Gastric electrical stimulation device may improve refractory vomiting

BY AMY KARON
MDedge News

An implanted gastric electrical stimulation device significantly improved refractory vomiting but not quality of life in a randomized, multicenter, double-blind crossover trial of 172 patients.

After 4 months of electrical stimulation, frequency of vomiting was significantly improved from baseline in the intervention arm, compared with the control arm, in patients with both delayed (*P* less than .01) and normal (*P* = .05) gastric emptying. There was also an improvement in nausea with gastric stimulation. In contrast, there was no significant improvement in the coprimary endpoint of quality of life. Based on these findings, "a limited number of medically resistant patients may benefit from gastroelectric stimulation to relieve nausea and vomiting," wrote Philippe Ducrotté, MD, of Rouen (France) University Hospital and associates in Gastroenterology.

High-frequency gastric electrical stimulation with the surgically implanted Enterra device is regarded as a treatment option for chronic refractory vomiting in patients with or without gastroparesis. However, only moderate evidence supports the use of this therapy, with level 1 evidence limited to a single study, according to the researchers. For the study, they enrolled 172 adults with at least 12 months of nausea or vomiting that was refractory to antiemetic or prokinetic therapy and was either idiopathic or related to type 1 or 2 diabetes mellitus or surgery (partial gastric resection or vagotomy). Symptoms "had to be severe enough to affect the general condition of the patient, including [causing] weight loss, or the need to change dietary intake to control diabetes," said the researchers.

The study started with a 4-month run-in period, after which all patients had the device implanted and left off for 1 month. Patients in the intervention arm then had the device turned on and programmed at standard parameters (5 mA, 14 Hz, 330 micros, cycle on 0.1s, cycle off 5s). Both groups were assessed at 4 months, and 149 patients then crossed over to the other arm and were assessed again at 4 months.

Vomiting was evaluated on a 5-point scale ranging from 0 (most severe) to 5 (symptom absent), while quality of life was assessed by means of the 36-question, self-administered Gastrointestinal Quality of Life Index (GIQLI).

After 4 months of electrical stimulation, frequency of vomiting was significantly improved from baseline in the intervention arm, compared with the control arm, in patients with both delayed (*P* less than .01) and normal (*P* = .05) gastric emptying.

During the intervention, 30.6% of patients reported at least a 1-point improvement on the vomiting frequency scale, while 53% reported no change. With the device turned off, 16.5% of patients reported an improvement in vomiting. During both phases of the trial, median vomiting frequency scores were improved in the intervention arm compared with the control arm (*P* less than .001) in patients with (42%) and without (58%) diabetes. "Gastric emptying was not accelerated during the on period compared with the off period," the investigators wrote.

A total of 133 (77%) patients in the study had gastroparesis. Most patients were women in their 40s who vomited several times per day. Among 45 device-related events, the most common was abdominal pain at the implantation site (62%), followed by "infectious problems" at the abdominal pouch level (36%) and hematoma (2%). Three of these events "were serious enough to prompt device removal," the researchers wrote.

The French government funded the study. The investigators reported having no conflicts of interest. They dedicated the paper to the memory of Dr. Ducrotté, who died during the course of the study.

ginews@gastro.org

SOURCE: Ducrotté P et al. Gastroenterology. 2019 Oct 1. doi: 10.1016/S0016-5085(17)30875-2.

Use of gastric electric stimulation is a controversial therapy for gastroparesis. The Enterra Gastric Electric Stimulator System received FDA approval under a Humanitarian Device Exemption in 2000 considering the device to be safe and of probable benefit. Enterra had been shown to decrease vomiting frequency in patients with medication-refractory gastroparesis. Subsequent studies performed for approval for efficacy did not meet their predefined endpoint. Some physicians use this as treatment for their patients with refractory gastroparesis under the HDE and with institutional review board approval; many physicians do not.


Dr. Parkman

The article by the French group brings support for gastric electric stimulation in a double blind study that showed gastric stimulation significantly reduced nausea and vomiting, both in diabetic and nondiabetic patients and in both those with delayed and normal gastric emptying.

The NIH Gastroparesis Clinical Research Consortium recently reported the symptom response with gastric stimulation for clinical care of patients with gastroparesis, compared with those who did not receive this treatment. In this observational study in multiple practice settings, 15% of patients with symptoms of gastroparesis in the NIH registry underwent gastric stimulation. Patients with more severe overall symptoms were more likely to improve symptomatically over 48 weeks, primarily because of reduction in nausea severity.

In the last 5 years, pyloromyotomy for gastroparesis has reemerged as a treatment for gastroparesis, especially when performed endoscopically (G-POEM or POP). Multiple studies, primarily single-center studies, support this treatment in improving gastroparesis symptoms and gastric emptying, though placebo-controlled studies have not been performed.

When should one perform gastric electric stimulation versus pyloromyotomy? At our center, we perform both stimulator placement and pyloromyotomy procedures in patients with refractory gastroparesis symptoms with delayed gastric emptying. We find that patients with refractory symptoms of gastroparesis undergoing stimulator placement, pyloromyotomy, or combined stimulator with pyloromyotomy each had improvement of their gastroparesis symptoms. Gastric stimulation and combined stimulator with pyloromyotomy improved nausea/vomiting, whereas pyloromyotomy alone tended to improve early satiety and postprandial fullness.

Presently, our clinical protocol for patients with refractory gastroparesis (not responding to metoclopramide, domperidone, granisetron patch, mirtazapine) is the following:

- If nausea and vomiting are particularly severe, we proceed with gastric stimulation.
- If gastric emptying is significantly delayed especially with symptoms of early satiety, patients undergo pyloromyotomy.
- If patients have significant nausea and vomiting with markedly delayed gastric emptying, patients get both stimulator placement and pyloromyotomy.

Studies are currently being performed to evaluate this type of patient-oriented management approach.

Henry P. Parkman, MD, gastroenterologist, gastroenterology section, Temple University, Philadelphia. He has no conflicts of interest.

Long-term entecavir looks safe, effective in HBV

BY AMY KARON
MDedge News

For patients with chronic hepatitis B virus (HBV) infection, up to 10 years of treatment with entecavir was safe and produced a superior rate of sustained virologic response (SVR), compared with other HBV nucleoside or nucleotide analogues in a global randomized clinical trial.

Virologic responses were confirmed and maintained in 80% of entecavir patients and 61% of patients who received other therapies, said Jin-Lin Hou, MD, of Southern Medical University in Guangzhou, China, and associates. Rates of serious treatment-related adverse events were 0.2% in the entecavir arm and 0.8% in the nonentecavir arm. Moreover, the primary outcome of time-to–adjudicated clinical outcome events "showed that entecavir treatment, compared with nonentecavir, was not associated with an increased risk of malignant neoplasms, including hepatocellular carcinoma, nonhepatocellular carcinoma malignancies, and overall malignancies," they wrote in Clinical Gastroenterology and Hepatology.

Entecavir is approved for the treatment of adults with chronic HBV infection, and its long-term use has been linked to the regression of hepatic fibrosis and cirrhosis. In treatment-naive patients, genotypic resistance and virologic breakthrough are rare even after 5 years of entecavir therapy. Although human studies have not linked this treatment duration with an increased risk of adverse events, murine studies have identified tumors of the brain, lung, and liver in entecavir-treated mice and rats. "Rodent tumors occurred only at entecavir exposures [that were] significantly higher than those achieved in human beings with standard approved doses," the researchers wrote.

For the trial, they assigned more than 12,000 patients with chronic HBV infection to receive long-term treatment with entecavir or investigators' choice of another HBV nucleoside or nucleotide analogue. Patients were from 229 centers in Asia, Europe, and North and South America; 6,216 received entecavir, while 6,162 received another therapy.

Compared with other HBV treatments, long-term treatment with entecavir "provided a high margin of safety" and was not tied to higher rates of liver or nonliver malignancies, the researchers found. Furthermore, among 5,305 trial participants in China, an SVR was associated with a clinically and statistically significant reduction in the risk of liver-related HBV disease progression (hazard ratio, 0.09; 95% CI, 0.04-0.22) and hepatocellular carcinoma (HR, 0.03; 95% CI, 0.009-0.113).

The results confirm the appropriateness of long-term entecavir therapy for chronic HBV infection, Dr. Hou and associates concluded.

Bristol-Myers Squibb designed the study, performed statistical analyses, and funded the study and manuscript preparation. The Ministry of Science and Technology of China provided partial support. Dr. Hou disclosed grants and personal fees from Bristol-Myers Squibb, GlaxoSmithKline, and Novartis. Several coinvestigators also disclosed ties to Bristol-Myers Squibb and to several other pharmaceutical companies.

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SOURCE: Hou J-L et al. Clin Gastroenterol Hepatol. 2019 Jul 12. doi: 10.1016/j.cgh.2019.07.010.

Colorectal polyps and cancer – When to refer to genetics

BY JENNIFER K. MARATT, MD, MS, AND ELENA M. STOFFEL, MD, MPH, AGAF

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Introduction

Genetic predisposition to colorectal polyps and colorectal cancer (CRC) is more common than previously recognized. Approximately 5%-10% of all individuals diagnosed with CRC have a known genetic association. However, among those with early-onset CRC (diagnosed at age less than 50 years), recent studies show that up to 20% have an associated genetic mutation.[1,2] In addition, the risk of CRC in patients with certain hereditary syndromes, such as familial adenomatous polyposis (FAP), approaches 80%-90% without timely management.[3] This overall high risk of CRC and extracolonic malignancies in patients with a hereditary syndrome, along with the rising rates of early-onset CRC, underscores the importance of early diagnosis and management of a hereditary condition.

Despite increasing awareness of hereditary polyposis and non-polyposis syndromes, referral rates for genetic counseling and testing remain low.[4] As gastroenterologists we have several unique opportunities, in clinic and in endoscopy, to identify patients at risk for hereditary syndromes. In this article, we highlight key patient and family characteristics that should raise "red flags" for hereditary CRC syndromes and we discuss available tools that may be integrated into practice to help guide the decision of when to refer patients for genetic testing.

Risk stratification

Personal and family history

Reviewing personal medical history and family history in detail should be a routine part of our practice. This is often when initial signs of a potential hereditary syndrome can be detected. For example, if a patient reports a personal or family history of colorectal polyps or CRC, additional information that becomes important includes age at time of diagnosis, polyp burden (number and histologic subtype), presence of inflammatory bowel disease, and history of any extracolonic malignancies. Patients with multiple colorectal polyps (e.g., more than 10-20 adenomas or more than 2 hamartomas) and those with CRC diagnosed at a young age (younger than 50 years) should be considered candidates for genetic evaluation.[5]

Lynch syndrome (LS), an autosomal dominant condition caused by loss of DNA mismatch repair (MMR) genes, is the most common hereditary CRC syndrome, accounting for 2%-4% of all CRCs.[3,6] Extracolonic LS-associated cancers to keep in mind while reviewing personal and family histories include those involving the gastrointestinal (GI) tract such as gastric, pancreatic, biliary tract, and small intestine cancers, and also non-GI tract cancers including endometrial, ovarian, urinary tract, and renal cancers along with brain tumors, and skin lesions including sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas. Notably, after CRC, endometrial cancer is the second most common cancer among women with LS. Prior diagnosis of endometrial cancer should also prompt additional history taking and evaluation for LS.

As the National Comprehensive Cancer Network (NCCN) highlights in its recent guidelines, several key findings in family history that should prompt referral to genetics for evaluation and testing for LS include: one or more first-degree relatives (FDR) with CRC or endometrial cancer diagnosed at less than 50 years of age, one or more FDR with CRC or endometrial cancer and another synchronous or metachronous LS-related cancer, two or more FDR or second-degree relatives (SDR) with LS-related cancer (including at least one diagnosed at age less than 50 years), and three or more FDR or SDR with LS-related cancers (regardless of age).[5]

Comprehensive assessment of family history should include all cancer diagnoses in first- and second-degree relatives, including age at diagnosis and cancer type, as well as ethnicity, as these inform the likelihood that the patient harbors a germline pathogenic variant associated with cancer predisposition.[5] Given the difficulty of eliciting this level of detail, the family histories elicited in clinical settings are often limited or incomplete. Unknown family history should not be mistaken for unremarkable family history. Alternatively, if family history is unimpressive, this is not necessarily reassuring as there can be variability in disease penetrance, including autosomal recessive syndromes that may skip generations, and de novo mutations do occur. In fact, among individuals with early-onset CRC diagnosed at age less than 50, only

Continued on following page

Dr. Rao

As gastroenterologists, we are uniquely poised to identify patients at risk for malignancies in the gastrointestinal tract. Specific to colorectal cancer, via colonoscopy, we resect and retrieve polyps. Based on the number of polyps removed and their histology, we are able to identify patients who may be at higher risk. In clinic, we discuss a patient's clinical and family history and can recommend an appropriate modality of colorectal cancer screening or surveillance interval accordingly. Within both of these settings, identification of patients who may require referral to a high-risk cancer specialist and undergo a subsequent genetics evaluation is critical. Recognition of key features of hereditary colon cancer or polyposis syndromes can have life-saving implications for both patients and their family members.

This quarter's In Focus article, which is brought to you by *The New Gastroenterologist* and written by Dr. Jennifer Marratt (Indiana University) and Dr. Elena Stoffel (University of Michigan), provides a comprehensive overview of hereditary colorectal cancer and polyposis syndromes. The article is replete with tips on how to readily identify clinical features of these syndromes in the context of a busy clinical practice and guide the next step of management. Given that the identification and prevention of colorectal cancer is one of the cornerstones of our specialty, this article effectively broaches an incredibly important topic.

Vijaya L. Rao, MD
Editor in Chief
The New Gastroenterologist

Continued from previous page

half of mutation carriers reported a family history of CRC in an FDR.[2] Thus, individuals with concerning personal histories should undergo a genetic evaluation even if family history is not concerning.

Polyp phenotype

In addition to personal and family history, colon polyp history (including number, size, and histology) can provide important clues to identifying individuals with genetic predisposition to CRC. Table 1 highlights hereditary syndromes and polyp phenotypes associated with increased CRC risk. Based on consensus guidelines, individuals with a history of greater than 10-20 adenomas, 2 or more hamartomas, or 5 or more sessile serrated polyps should be referred for genetic testing.[5,7] Serrated polyposis syndrome (SPS) is diagnosed based on at least one of the following criteria: 1) 5 or more serrated polyps, all at least 5 mm in size, proximal to the rectum including at least 2 that are 10 mm or larger in size, or 2) more than 20 serrated polyps distributed throughout the colon with at least 5 proximal to the rectum.[8] Pathogenic germline variants in RNF43, a tumor suppressor gene, have been associated with SPS in rare families; however, in most cases genetic testing is uninformative and further genetic and environmental discovery studies are needed to determine the underlying cause.[8,9]

Although they may not be diagnostic, specific histologic characteristics of polyps may also raise red flags for hereditary CRC syndromes. For example, presence of tumor-infiltrating lymphocytes, a Crohn's-like peritumoral inflammatory reaction, or a medullary growth pattern can be markers for hypermutation seen in Lynch-associated neoplasms.[10] In addition, adenomas in FAP are microscopically similar to sporadic adenomas, but histologic evaluation of the intervening normal-appearing mucosa may show microscopic dysplastic crypts or aberrant crypt foci, both of which are characteristic findings in FAP which can also be seen in some cases of MUTYH-associated polyposis.

Risk prediction models

Models have been developed that integrate family history and phenotype data to help identify patients who may be at risk for LS. The Amsterdam criteria (3 or more relatives with LS-associated cancers, 2 or more generations involving LS-associated cancers, and at least 1 cancer diagnosed before the age of 50; "3:2:1" criteria) were initially developed for research purposes to identify individuals who were likely to be carriers of mutations of LS based on CRC and later revised to include extracolonic malignancies (Amsterdam II).[11] However, they have limited sensitivity for identifying high-risk patients. Similarly, the Bethesda guidelines have also been modified and revised to identify patients at risk for LS whose tumors should be tested with microsatellite instability (MSI), but also with limited sensitivity.[12]

Several risk-prediction models have been developed that perform better than the Amsterdam criteria or Bethesda guidelines for determining which patients should be referred for genetic testing for LS. These include MMRPredict, MMRpro, and PREMM5.[13-16] These models use clinical data (personal and family history of cancer and tumor phenotypes) to calculate the probability of a germline mutation in one of the mismatch repair (MMR) genes associated with LS. The current threshold at which to refer a patient for genetic counseling and testing is a predicted probability of 5% or greater using any one of these models, though some have proposed lowering the threshold to 2.5%.[16,17]

Universal tumor testing

Because of the limitations of relying on clinical family history, such as with the Amsterdam criteria and the Bethesda guidelines,[18,19] as of 2014 the NCCN recommended universal tumor screening for DNA MMR deficiency associated with LS. This approach, also known as "universal testing," has been shown to be cost effective and more sensitive in identifying at-risk patients than clinical criteria alone.[20,21] Specifically, the NCCN recommends that tumor specimens of all patients diagnosed with CRC undergo testing for microsatellite instability (MSI) or loss of MMR proteins (MLH1, MSH2, MSH6, PMS2) expression by immunohistochemistry (IHC).[5] Loss of MMR proteins or MSI-high findings should prompt a referral to genetics for counseling and consideration of testing for germline mutations. Universal testing of CRC and endometrial cancers is considered the most reliable way to screen patients for LS.

Universal testing by MSI or IHC may be performed on premalignant or malignant lesions. However, it is important to recognize that DNA MMR deficiency testing may not be as reliable when applied to colorectal polyps. Using data from three cancer registries (Dana-Farber Cancer Institute, University of Michigan, MD Anderson Cancer Center), Yurgelun and colleagues investigated the yield of MSI and IHC in colorectal polyps removed from patients with known LS.[22] Overall, high-level MSI was found in only 41% of Lynch-associated adenomas and loss of MMR protein expression was evident in only 50%. While adenomas 8 mm in size or greater were more likely to have MSI-high or loss of MMR protein expression, compared with those less than 8 mm in size, MMR-deficiency phenotype was less reliable in smaller adenomas. Consequently, results of MSI and/or IHC should therefore be interpreted with caution and in the context of the specimen upon which they are performed.

Considerations for clinical genetic testing

Genetic testing for cancer susceptibility should include informed consent and counseling for patients regarding potential risks and benefits. Clinicians ordering genetic testing should have the expertise necessary to interpret test results, which may be positive (pathogenic or likely pathogenic germline variant identified) or negative (no variants identified), or may yield one or more variants of uncertain clinical significance. Individuals found to carry a pathogenic or likely pathogenic germline variant associated with cancer susceptibility should be referred for additional genetic counseling and may require additional expert consultation for management of extracolonic cancer risks. It is important that individuals diagnosed with a hereditary cancer syndrome be informed that this diagnosis has implications for family members, who may also be at risk for the condition and may benefit from genetic testing.

Practical considerations

Given the difficulty in obtaining a detailed family history while in clinic or in endoscopy, several studies have investigated strategies that may be integrated into practice to identify high-risk patients without

Continued on following page

Table 1. Hereditary colorectal cancer syndromes

Syndrome	Gene mutation	Inheritance pattern	Lifetime risk of colorectal cancer*	Predominant colorectal phenotype
Lynch syndrome	MLH1, MSH2, MSH6, PMS2, EPCAM	Autosomal dominant	10%-74% (varies based on gene mutation involved)	Tumors with DNA mismatch repair deficiency (MSI-high, hypermutated) ≤10 adenomas
Familial adenomatous polyposis	APC	Autosomal dominant	90%-100%	≥100 adenomas
Attenuated FAP	APC	Autosomal dominant	Variable	20-100 adenomas
MUTYH-associated polyposis	MUTYH	Autosomal recessive	Variable	>10 adenomas
Juvenile polyposis syndrome	SMAD4, BMPR1A	Autosomal dominant	38%-68%	>2 hamartomas
Peutz-Jeghers	STK11	Autosomal dominant	39%	>2 hamartomas
Cowden syndrome	PTEN	Autosomal dominant	9%-16%	Mixed polyposis (adenomas, hamartomas, ganglioneuromas, sessile serrated polyps)
Serrated polyposis syndrome	Unknown	Unknown	>50%	Sessile serrated polyps

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*Am J Gastroenterol. 2015 Feb;110(2):223-62

Continued from previous page

substantial burden on providers or patients. Kastrinos and colleagues identified the following three high-yield questions as part of a CRC Risk Assessment Tool that can be used while performing a precolonoscopy assessment: 1) Do you have a first-degree relative with CRC or LS-related cancer diagnosed before age 50?; 2) Have you had CRC or polyps diagnosed prior to age 50?; and 3) Do you have three or more relatives with CRC? The authors found that these three questions alone identified 77% of high-risk individuals.[23] In addition, implementation of family history screening instruments using standardized surveys or self-administered risk prediction models at the time of colonoscopy have been shown to improve ascertainment of high-risk patients.[24,25] Such strategies may become increasingly easier to implement with integration into patients' electronic medical records.

Conclusions

Hereditary CRC syndromes are becoming increasingly important to identify, especially in an era in which we are seeing rising rates of early-onset CRC. Early identification of high-risk features (Table 2) can lead to timely diagnosis with the goal to implement preventive strategies for screening and/or surveillance, ideally prior to development of cancers.

As gastroenterologists, we have several unique opportunities to identify these individuals and must maintain a high level of suspicion with careful attention when obtaining personal and family history details in clinic and in endoscopy.

See references at www.mdedge.com/gihepnews/new-gastroenterologist.

Table 2. High-risk features that should prompt genetic evaluation for cancer susceptibility syndromes

⚠ Colon polyp characteristics: >10-20 adenomas, ≥2 hamartomas, ≥5 serrated polyps.
⚠ Personal history of CRC or Lynch syndrome–associated cancers at age <50 years.
⚠ CRC with microsatellite instability and/or loss of mismatch repair protein expression.
⚠ Known family history of hereditary CRC syndrome or genetic mutation.
⚠ Genetic risk model scores (PREMM5) calculating likelihood of germline mutation of 5% or greater.

MDEDGE NEWS

➤ NEWS FROM THE AGA

Highlights from AGA's FDA engagement

AGA members and staff worked closely with representatives across the FDA on a number of key issues impacting gastroenterologists including duodenoscope reprocessing, fecal microbiota transplantation and new drug approvals for GI indications.

Center for Devices and Radiological Health (CDRH). The issue of duodenoscope reprocessing regained national attention when a safety communication issued by CDRH was covered by the New York Times.

The safety communication had noted that about one in 20 samples collected from reprocessed duodenoscopes tested positive for high-concern organisms such as *E. coli* and *Pseudomonas aeruginosa*.

AGA partnered with ACG, ASGE and SGNA to develop a letter to the editor and provided insights to AGA members in subsequent communications. CDRH issued another safety communication in August recommending a transition to disposable-component duodenoscopes and convened a public advisory committee meeting in November where AGA gave public testimony including several overarching principles for the evolution of clinical practice focusing on patient safety and outcomes. AGA has been at the forefront of this issue since risk of infection transmission during ERCP first came to light in 2015, and we will continue to work closely with FDA and industry to ensure solutions, like the recently approved disposable scopes and parts, meet the needs of our members.

Center for Biologics Evaluation and Research (CBER). Though it is not an approved therapy for *Clostridioides difficile* infection (CDI), FDA permits the use of fecal microbiota transplantation (FMT) for CDI unresponsive to standard antibiotic therapies under a temporary "enforcement policy" that has been in place since 2013. In response to concerns from the physician community that patient access to FMT may be discontinued once manufactured microbiota-based products come to market, AGA reengaged CBER in dialogue about the future of FMT through a meeting with CBER Director Peter Marks and eight senior CBER officials. In response to a June safety alert reporting a patient death from FMT using donor stool that was not screened for extended-spectrum beta-lactamase (ESBL)-producing *E. coli*, AGA requested clarification from CBER on new donor screening requirements announced for those who hold investigational new drug permits for FMT. Most recently, AGA was the only professional society to give public testimony at a November public hearing on the use of FMT to treat CDI. AGA will continue to engage CBER as the agency works to finalize its policy on FMT.

Center for Drug Evaluation and Research (CDER). AGA organized two joint scientific sessions at Digestive Disease Week® 2019 with representatives from CDER's Division of Gastrointestinal and Inborn Errors Products: the inaugural FDA Town Hall and a session on controversies around measuring drug toxicity. The FDA Town Hall, which will continue at DDW 2020, featured four FDA speakers providing the data and rationale behind recent GI drug approvals. The session titled, "Controversies Around Measuring Drug Toxicity" gave FDA and gastroenterologists' perspectives on 5-HT3 antagonists (e.g., alosetron) and 5-HT4 agonists (e.g., prucalopride), as well as proton pump inhibitors. These sessions aimed to promote an interchange of ideas among regulators, clinicians and pharmaceutical manufacturers to advance the development and use of new therapies for GI disorders.

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Watch your step (therapy) – Understanding 'fail first'

Sometimes known as "fail first," step therapy is a tool used by insurance companies that requires patients to fail medications before agreeing to cover a health care provider's initial treatment recommendation.

Largely affecting patients with inflammatory bowel disease (IBD), step therapy focuses on the use of insurer-preferred treatments rather than effective, patient-centric therapies. In addition to causing many patient hardships and health problems, this protocol allows insurance companies to come between the provider-patient relationship and dictate a patient's course of treatment.

To help clinicians navigate this challenging landscape, AGA is pleased to offer a new step therapy webpage, gastro.org/step-therapy, that details the step therapy protocol and opportunities to advocate for patient protections.

Additional education modules — including videos, podcasts and other resources — are also available for several states that have implemented safe step therapy laws, including Illinois, New York, and Texas.

Visit the Navigating State Step Therapy Laws program page to learn more:

- What is the step therapy protocol?
- How does step therapy impact a health care provider's ability to provide patient care?
- Which states have implemented step therapy laws?
- How do state step therapy laws provide physician rights and patient protection?
- Tips to share with your patients.
- What are AGA's advocacy efforts — and how can I help?

Education modules for additional states will be available in early 2020.

AGA's Navigating State Step Therapy Laws program is funded by an unrestricted educational grant from Takeda and Pfizer.

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Not using MBIs on Medicare claims yet? It'll cost you

As of Jan. 1, 2020, Medicare stopped paying claims without the new Medicare Beneficiary Identifier (MBI) regardless of the date of service.

Medicare is rejecting all claims submitted without MBIs, regardless of when the service was provided, with some exceptions. The MBI replaces the social security number–based Health Insurance Claim Numbers (HICNs) from Medicare cards and is now used for Medicare transactions like billing, eligibility status, and claim status.

Not ready yet? Here's what you need to do:

Talk to your office staff today and make a plan to begin reporting MBIs ASAP. Give them Medicare's MBI educational materials. Be prepared to reprocess every claim already submitted without an MBI.

Get MBIs from your patients and through the MAC portals (sign up).

You can also find the MBI on the remittance advice. Medicare returns the MBI on the remittance advice for every claim with a valid and active HICN.

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AGA encourages CMS to provide flexibility to physician practices

AGA and the physician community have long sought to update the Stark self-referral and anti-kickback statute in the era of value-based care that is contingent on shared-savings and care coordination among other physicians and health care providers.

Specifically, CMS has proposed exceptions directed at value-based arrangements and we believe that this will allow providers to participate in value-based arrangement while still protecting the Medicare program from potential abuses. CMS also has defined the financial risk requirements for value-based arrangements and AGA has urged the agency to finalize the full financial risk to the cost of only a defined set of patient care services for a targeted population.

AGA welcomed many of the changes that CMS is seeking and believes these proposed changes will enable physician practices to engage in value-based arrangements that will improve patient care.

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GI societies meet with ABIM

Recently, the leadership of the American Gastroenterological Association, the American Association for the Study of Liver Diseases, the America College of Gastroenterology, and the American Society for Gastrointestinal Endoscopy met with Richard Battaglia, MD, the chief medical officer of the American Board of Internal Medicine, about the status of ABIM's efforts to move toward a longitudinal testing model, which ABIM describes as "a self-paced pathway for physicians to acquire and demonstrate ongoing knowledge."

ABIM anticipates that the new option will be available beginning in 2022, in as many specialties as possible.

In the meantime, all current MOC program policies remain in effect and ABIM directs diplomates to use the current options to maintain certification.

While we would like to see ABIM waive testing requirements while it works with GI to create a new longitudinal model, ABIM has declined to do so. Notwithstanding this fact, the GI societies are committed to advocating for the needs of gastroenterology while working with ABIM to ensure the new model is relevant to gastroenterology and hepatology.

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Endoscopic therapy recommended

Barrett's *from page 1*

highest risk for cancer development and for risk of recurrence after complete eradication of intestinal metaplasia," they wrote in Gastroenterology. "Potentially, we may use a panel of patient characteristics (such as the [Progression in Barrett's] score), preablation tissue characteristics (e.g., baseline grade of dysplasia), and the posttherapy molecular makeup of the epithelium to help risk stratify our patients."

For now, many of the treatment principles in the update depend upon histologic features.

For instance, either endoscopic therapy or continued surveillance are reasonable options for patients with Barrett's esophagus who have confirmed and persistent low-grade dysplasia. In contrast, the update recommends that all patients with high-grade dysplasia or esophageal adenocarcinoma (T1a) undergo endoscopic therapy, highlighting that this method is preferred over esophagectomy for patients with T1a cancer. Along the same lines, the investigators noted that endoscopic therapy is a "reasonable alternative" to esophagectomy in cases of T1b esophageal adenocarcinoma in the presence of minimal invasion and good to moderate differentiation, particularly in patients who are poor candidates for surgery.

During the decision-making process, patients with dysplasia should be advised that not undergoing endoscopic therapy may increase cancer risk, the investigators wrote, adding that patients should also be informed about endoscopic therapy–related risks of bleeding and perforation, which occur in less than 1% of patients, and the risk of postprocedural stricture formation, which occurs in approximately 6% of patients.

If endoscopic therapy is elected, the update suggests that the procedure be done by experts who perform at least 10 new cases per year.

Concerning specifics of therapy, the investigators advised that mucosal ablation be applied to all visible esophageal columnar mucosa, 5-10 mm proximal to the squamocolumnar junction, and 5-10 mm distal to the gastroesophageal junction. Ablation should only be performed in cases of flat Barrett's esophagus in which no visible abnormalities or signs of inflammation are present, the review team wrote.

The investigators went on to lay out some "practical ground rules" for endoscopic therapy, including a potential pitfall.

"Ablation therapy may consist of multiple 2-3 monthly ablation sessions that may extend over a period of more than a year," the investigators wrote. "The worst adverse outcome during the treatment period is failing to recognize and treat an invasive cancer while continuing the ablation sessions. This occurrence may place the patient outside of the window of opportunity for curative endoscopic treatment. Therefore, every ablation session starts with careful endoscopic inspection using [high-definition white-light endoscopy] and preferably optical chromoendoscopy to exclude the presence of visible abnormalities that require an endoscopic resection instead of the scheduled ablation. Routine biopsies of flat Barrett's esophagus are not necessary or recommended prior to ablation at these sessions, as the blood may inhibit optimal energy transfer to the tissue."

Following successfully achieved complete endoscopic and histologic eradication of intestinal metaplasia, the update calls for surveillance endoscopy with biopsies at intervals of 1 and 3 years for cases of low-grade dysplasia and at intervals of 3, 6, and 12 months for high-grade dysplasia or esophageal adenocarcinoma, followed by annual checks thereafter.

The investigators disclosed relationships with Olympus, Ironwood, Erbe, and others.

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SOURCE: Sharma P et al. Gastroenterology. 2019 Nov 12. doi: 10.1053/j.gastro.2019.09.051.

Optimal management of Barrett's esophagus without high-grade dysplasia

BY JAKE REMALY
MDedge News

In patients with Barrett's esophagus and low-grade dysplasia confirmed by repeat endoscopy, endoscopic eradication therapy is the optimal cost-effective management strategy, according to an analysis of population-based models, which was published in Clinical Gastroenterology and Hepatology.

Clinical guidelines recommend surveillance or treatment of patients with Barrett's esophagus, a precursor lesion for esophageal adenocarcinoma, depending on the presence and grade of dysplasia. For high-grade dysplasia, guidelines recommend endoscopic eradication therapy. For low-grade dysplasia, the optimal strategy is unclear, said study author Amir-Houshang Omidvari, MD, MPH, a researcher at Erasmus MC University Medical Center Rotterdam (the Netherlands) and colleagues. In addition, the ideal surveillance interval for patients with nondysplastic Barrett's esophagus is unknown.

To identify optimal management strategies, the investigators simulated cohorts of 60-year-old patients with Barrett's esophagus in the United States using three independent population-based models. They followed each cohort until death or age 100 years. The study compared disease progression without surveillance or treatment with 78 management strategies. The cost-effectiveness analyses used a willingness-to-pay threshold of $100,000 per quality-adjusted life-year (QALY).

For low-grade dysplasia, the researchers assessed various surveillance intervals, endoscopic eradication therapy with confirmation of low-grade dysplasia by a repeat endoscopy after 2 months of high-dose acid suppression, and endoscopic eradication therapy without confirmatory testing. For nondysplastic Barrett's esophagus, the researchers evaluated no surveillance and surveillance intervals of 1, 2, 3, 4, 5, or 10 years. The researchers made assumptions based on published data about rates of misdiagnosis, treatment efficacy, recurrence, and complications. They used Centers for Medicare & Medicaid Services reimbursement rates to evaluate costs. For all management strategies, the researchers assumed surveillance would stop at age 80 years.

In a simulated cohort of men with Barrett's esophagus who did not receive surveillance or endoscopic eradication therapy, the models predicted an average esophageal adenocarcinoma cumulative incidence of 111 cases per 1,000 patients and mortality of 77 deaths per 1,000 patients, with a total cost of $5.7 million for their care.

Management strategies "prevented 23%-75% of [esophageal adenocarcinoma] cases and decreased mortality by 31%-88% while increasing costs to $6.2-$17.3 million depending on the management strategy," the authors said. The most cost-effective strategy – endoscopic eradication therapy for patients with low-grade dysplasia after endoscopic confirmation, and surveillance every 3 years for patients with nondysplastic Barrett's esophagus – decreased esophageal adenocarcinoma incidence to 38 cases (–66%) and mortality to 15 deaths (–81%) per 1,000 patients, compared with natural history. This approach increased costs to $9.8 million and gained 358 QALYs.

The models predicted fewer esophageal adenocarcinoma cases in women without surveillance or treatment (75 cases/1,000 patients). The optimal strategy was surveillance every 5 years for nondysplastic Barrett's esophagus the researchers reported.

The National Institutes of Health/National Cancer Institute supported the study and funded the authors.

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SOURCE: Omidvari A-H et al. Clin Gastroenterol Hepatol. 2019 Dec 6. doi: 10.1016/j.cgh.2019.11.058.

DDSEP 9
Digestive Diseases Self-Education Program

Quick Quiz answers

Q1. Correct Answer: B

Rationale

The leading cause of death in patients with NASH is cardiovascular disease. Death from liver-related causes is much more common in NASH than in the general population, but is not the leading cause of death. Cancer-related death is among the top three causes of death in patients with NASH, but is not the most common.

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Q2. Correct Answer: C

Rationale

Carvedilol is a nonselective beta-blocker with vasodilating properties that is used to decrease portal pressure and prevent first variceal hemorrhage. It has more robust effect on the reduction of portal pressure than nadolol or propranolol. A safe and effective dose is 12.5 mg/day. Doses higher than 12.5 mg/day are associated with increased side effects and hypotension in patients with impaired liver function caused alpha$_1$ antagonist action and excessive first pass metabolism.

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Ustekinumab response predictor in Crohn's called 'brilliant'

BY BRUCE JANCIN
MDedge News

SAN ANTONIO – The probability of achieving clinical remission of Crohn's disease in response to ustekinumab can now be readily estimated by using a clinical prediction tool, Parambir S. Dulai, MBBS, announced at the annual meeting of the American College of Gastroenterology.

This new clinical decision support tool also provides individualized stratification of the rapidity with which symptoms will be reduced in response to the anti-interleukin-12/23 biologic, added Dr. Dulai, a gastroenterologist at the University of California, San Diego.

He and his coinvestigators developed the prediction tool through analysis of detailed data on 781 patients with active Crohn's disease treated with ustekinumab (Stelara) during both the induction and maintenance portions of the phase 3 UNITI randomized trials conducted in the biologic's development program. The researchers identified a series of baseline features associated with clinical remission as defined by a Crohn's Disease Activity Index (CDAI) score below 150 by week 16 of treatment. Through statistical manipulation, they transformed the data into a predictive model and then went one step further by turning the model into a decision support tool with points given for the individual predictive variables (see graphic).

Patients with 5 or more total points were categorized as having a high probability of week 16 clinical remission. Patients with 0 or 1 point were deemed low probability, and a score of 2-4 indicated an intermediate likelihood of clinical remission.

Next, the investigators applied

Continued on following page

CROHN'S DISEASE

Clinical decision support tool for ustekinumab

Variable	Points awarded
No prior exposure to TNF antagonists	2
No prior bowel surgery	2
No current or prior smoking	1
No active fistulizing disease at baseline	1
Baseline albumin:	
25 g/L or less	–3
>25 to 32 g/L	–1
>32 to 39 g/L	0
>39 to 43 g/L	1
>43 g/L	3

Probability of response

Low	*0 or 1 point*
Intermediate	*2-4 points*
High	*≥5 points*

Note: Tool development involved analysis of data for 781 patients with active disease.

Source: Dr. Dulai

MDedge News

Continued from previous page

their new clinical decision support tool to the 781 ustekinumab-treated patients included in the derivation analysis. The tool performed well: The high-probability group had a 57% clinical remission rate, significantly better than the 34% rate in the intermediate-probability group, which in turn was significantly better than the 21% rate of clinical remission in the group with a baseline score of 0 or 1.

In addition, onset of treatment benefit was significantly faster in the group having a score of 5 or more. They had a significantly higher clinical remission rate than the intermediate- and low-probability groups at all scheduled assessments, which were conducted at weeks 3, 6, 8, and 16. Indeed, by week 3 the high-probability group experienced a mean 69-point drop from baseline in CDAI and a 94-point drop by week 8, as compared with week 8 reductions of 54 and 40 points in the intermediate- and low-probability groups, respectively.

In an exploratory analysis involving the 122 patients who underwent week 8 endoscopy, endoscopic remission was documented in 12% of patients whose baseline scores placed them in the high-probability group, 10% in the intermediate group, and 8% of those in the low-probability group.

The high-probability group had significantly higher ustekinumab trough concentrations than did the intermediate- and low-probability groups when measured at weeks 3, 6, 8, and 16.

An external validation study conducted in a large cohort of Crohn's disease patients seen in routine clinical practice has recently been completed, with the results now being analyzed, according to Dr. Dulai.

Miguel Requeiro, MD, chairman of gastroenterology and hepatology at the Cleveland Clinic, rose from the audience to declare the creation of the decision support tool to be "brilliant work." He asked if it has changed clinical practice for Dr. Dulai.

"We've begun doing two things differently," Dr. Dulai replied. "First, we've built a similar model for vedolizumab and Crohn's. That means we can use both tools together to discriminate between a patient who should get vedolizumab versus ustekinumab because the variables and their weighting differ between the two. And the other thing we've been able to do is argue with payers for positioning of the treatments when we have evidence to support that we can use them earlier in the treatment course to optimize outcomes."

Bruce Jancin/MDedge News

Dr. Parambir S. Dulai

Another audience member, David T. Rubin, MD, AGAF, professor of medicine and codirector of the Digestive Diseases Center at the University of Chicago, also praised the decision support tool as "brilliant" and "definitely needed."

Dr. Dulai reported receiving a research grant for the project from Janssen, which markets ustekinumab.

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AGA Resource

Help your patients better understand their Crohn's disease treatment options by sharing AGA patient education at https://www.gastro.org/practice-guidance/gi-patient-center/topic/inflammatory-bowel-disease-ibd.

Weight loss cuts cancer

Bariatric *from page 1*

ysis of about 1.7 million hospitalized U.S. patients in the National Inpatient Sample showed that the incidence of obesity-related cancer was 21% higher in more than 1.4 million obese individuals (BMI, 35 kg/m^2 or greater) with no history of bariatric surgery, compared with nearly 247,000 people in the same database with a history of both obesity and bariatric surgery, said Juliana Henrique, MD, a bariatric surgeon at the Cleveland Clinic Florida in Weston.

The study reported by Dr. Henrique focused specifically on the 13 cancer types identified by the Centers for Disease Control and Prevention as having an incidence that links with overweight and obesity (Morb Mortal Wkly Rep. 2017;66[39]:1052-8), whereas the study presented by Dr. Stroud included all incident cancers during follow-up, which were predominantly obesity related, with breast cancer – an obesity-related malignancy – having the highest incidence. Overall, 40% of all U.S. cancers in 2014 were obesity related, according to the CDC's report.

"A number of studies have shown decreases in cancer rates after bariatric surgery, especially female cancers like breast and ovarian," commented John Scott, MD, director of metabolic and bariatric surgery for Prism Health–Upstate in Greenville, S.C. "These two reports build on that."

The evidence for weight loss after bariatric surgery as a means to cut the risk of a first or recurrent cancer has become strong enough for some patients to see cancer prophylaxis as a prime reason to undergo the procedure, said surgeons at the meeting.

Bariatric surgery and subsequent weight loss "is a substantial preventive factor for cancer, especially in patients who have obesity and diabetes," commented Theresa LaMasters, MD, a bariatric surgeon in West Des Moines, Iowa. "It might not just be weight loss. It's likely a multifactorial effect, including reduced inflammation after bariatric surgery, but weight loss is a component" of the effect, Dr. LaMasters said in an interview. It is now common for her to see patients seeking bariatric surgery because of a family or personal history of cancer. "Patients are trying to reduce their future risk" for cancer with bariatric surgery, she added.

Dr. Andrea M. Stroud reported a prospective study that followed patients for 7 years after bariatric surgery for cancer.

Dr. John Scott commented on decreases in cancers like ovarian and breast cancer after bariatric surgery.

Mitchel L. Zoler/MDedge News

The LABS-2 study enrolled 2,458 patients who were part of the first LABS cohort, LABS-1, but followed them longer term. The data Dr. Stroud reported came from 2,107 of the LABS-2 patients without a history of cancer, no cancer diagnosed in the first year after bariatric surgery, and longer-term follow-up of 7 years. About three-quarters of the patients underwent gastric bypass, with the rest undergoing laparoscopic gastric band placement. Nearly half of those included had diabetes. Their average BMI was 45-50 kg/m^2.

Dr. Stroud and associates ran an analysis that divided the populations into tertiles based on percentage of baseline body mass lost at 12 months after surgery and cancer-free survival during the 7 years after the 12-month follow-up. The incidence of cancer was 51% lower in patients who lost 20%-34% of their BMI, compared with those who lost less than 20%, a statistically significant difference, and patients who lost 35% or more of their BMI had a 31% reduced cancer rate, compared with those who lost less than 20%, a difference that was not statistically significant, Dr. Stroud reported. The patients who lost less weight after surgery mostly underwent gastric banding, whereas those who lost more mostly underwent gastric bypass.

The analysis reported by Dr. Henrique used data collected in the U.S. National Inpatient Sample during 2010-2014, which totaled more than 7 million patients hospitalized for cancer, including 1,423,367 with a history of obesity and 246,668 with obesity who had undergone bariatric surgery. Those without bariatric surgery had a 21% higher rate of developing obesity-related cancers after adjustment for many baseline demographic and clinical features, Dr. Henrique said. The cancer protection after bariatric surgery was especially notable in the subset of patients in the sample with a genetic predisposition to developing cancer.

LABS-1 and LABS-2 were funded by the National Institute of Diabetes and Digestive and Kidney Diseases. Dr. Stroud and Dr. Henrique had no disclosures.

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SOURCES: Stroud AM et al. Obesity Week, Abstract A107; Henrique J et al. Obesity Week, Abstract A108.

Score predicts surgery's benefits for obesity, diabetes

BY MITCHEL L. ZOLER
MDedge News

LAS VEGAS – Researchers have devised a risk calculator for patients with obesity and type 2 diabetes that can estimate their 10-year risk for death and cardiovascular disease events if their clinical status continues relatively unchanged, or if they opt to undergo bariatric surgery.

The Individualized Diabetes Complications risk score "can provide personalized, evidence-based risk information for patients with type 2 diabetes and obesity about their future cardiovascular disease outcomes and mortality with and without metabolic surgery," Ali Aminian, MD, said at a meeting presented by the Obesity Society and the American Society for Metabolic and Bariatric Surgery.

AGA Resource
The AGA Practice guide on Obesity and Weight management, Education and Resources (POWER) white paper provides physicians with a comprehensive, multidisciplinary process to guide and personalize innovative obesity care for safe and effective weight management. Learn more at www.gastro.org/obesity.

Although the calculator needs validation in a prospective, randomized study to document its impact on practice, it is now available on two separate websites and as a downloadable app, said Dr. Aminian, a surgeon at the Cleveland Clinic.

The calculator inputs data for 26 distinct, "readily available" demographic and clinical entries, and based on that, estimates the patient's 10-year risk for all-cause death, diabetic kidney disease, cerebrovascular disease, heart failure, and coronary artery disease if no surgery occurs or after some type of metabolic or bariatric surgery. The calculator does not currently have the ability to individualize predicted risks based on the specific type of metabolic surgery performed, but that is planned as a future refinement of the score.

"We validated the model in the nonsurgical patients, which showed it was very accurate. The next step is to run a randomized trial to see how useful the calculator is" for assisting in patients' decision making, Dr. Aminian said.

The data for deriving the risk calculator, and for a preliminary validation of it, came from 13,722 patients with obesity (body mass index, 30 kg/m^2 or greater) and type 2 diabetes, who were managed at the Cleveland Clinic during 1998-2017, drawn from more than 287,000 such patients in the clinic's database. The study focused on 2,287 patients who underwent metabolic (bariatric) surgery and 11,435 patients from the same database who did not have surgery and matched by propensity scoring on a 5:1 basis with those who had surgery. The two cohorts this created matched well for age (about 54 years), sex (about two-thirds women), BMI (about 44 kg/m^2), and the prevalence of various comorbidities at baseline.


Mitchel L. Zoler/MDedge News
Dr. Ali Aminian

Dr. Aminian and associates then analyzed the incidence of all-cause mortality and various cardiovascular disease endpoints, as well as nephropathy during follow-up, through December 2018. Patients who had undergone metabolic surgery showed statistically significant reductions in the incidence of each of those events, compared with patients who did not have surgery (JAMA. 2019;322[13]:1271-82).

The investigators used these findings to create their model for calculating a patient's risk score. For example, to calculate an estimate for the 10-year risk from all-cause mortality, the results showed that the most powerful risk factors were age, baseline body mass index, heart failure, need for insulin, and smoking status. For the endpoint of nephropathy, the most important factors were estimated glomerular filtration rate at baseline and age. Identified risk factors could account for about 80% of the 10-year risk for all-cause death and for about 75% of the risk for developing nephropathy during 10 years, based on the area-under-the-curve values the model produced.

The calculator is available at a website maintained by the Cleveland Clinic, at a site of the American Society for Metabolic and Bariatric Surgery, and in app stores, he said.

The work was partially funded by Medtronic. Dr. Aminian has received grants from Medtronic.

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SOURCE: Aminian A et al. Obesity Week 2019, Abstract A101.

Nearly 25% of U.S. adults take an obesogenic prescription

BY MITCHEL L. ZOLER
MDedge News

LAS VEGAS – Nearly a quarter of American adults are on a prescription drug that often produces obesity as a side effect, and use of such obesogenic drugs was significantly higher among patients who already are obese, based on national U.S. data collected during 2013-2016.

The Endocrine Society, the STOP Obesity Alliance, and other medical societies have recommended that clinicians try to minimize use of obesogenic drugs and focus on prescribing weight-neutral agents or ones that trigger weight loss when those options are available. The new findings add further evidence that clinicians need to be more mindful of this issue, Craig M. Hales, MD, said at a meeting presented by the Obesity Society and the American Society for Metabolic and Bariatric Surgery.

Among the adults interviewed for the survey, 40% of those on at least one prescription medication were on at least one drug that is considered obesogenic, said Dr. Hales, a medical epidemiologist at the Centers for Disease Control and Prevention in Hyattsville, Md.

According to practice guidelines published by the Endocrine Society, all drugs in the classes of glucocorticoids, beta-blockers, and antihistamines are obesogenic, as well as selected agents in the classes of antidepressant drugs, antipsychotics, antidiabetics, and contraceptives that are progestin only, said Dr. Hales (J Clin Endocrinol Metab. 2015 Feb;100[2]:342-62).

The data he reported came from the National Health and Nutrition Examination Survey (NHANES) run by the CDC during 2013-2016 that included 11,055 adults who were at least 20 years old. The findings showed that 23% of those adults had taken at least one drug that was considered obesogenic during the 30 days preceding the survey date. By comparison, 35% of the same adults had taken any type of prescription drug during the previous 30 days. That meant that, overall, 40% of surveyed adults who had recently used any prescription medication had taken an obesogenic drug.

The 23% prevalence of recent obesogenic drug use was fairly stable at that level during several preceding NHANES surveys going back to 2001, suggesting that the increasing use of obesogenic drugs during the period since 2001 was not a factor in the recent increased prevalence of obesity among U.S. residents, added Dr. Hales.

The 2013-2016 analysis also showed a strong link between obesogenic drug use and increasing obesity severity. Among survey participants with a body mass index in the normal range (18.5-24 kg/m^2), 16% had recent use of an obesogenic drug. This prevalence increased to 22% among those who were overweight (BMI, 25-29 kg/m^2), 29% among those with class 1 or 2 obesity (BMI, 30-39 kg/m^2), and 33% among those with class 3 obesity (BMI, 40 kg/m^2 or greater). In contrast, use of prescription medications that do not contribute to obesity showed no relationship with BMI.

An example of this relationship for the obesogenic drug class of beta-blockers: Use was about 7% among people with a normal BMI, about 10% among those who were overweight, about 14% among people with class 1 or 2 obesity, and about 17% among people with class 3 obesity, a statistically significant link suggesting that the relationship between use of obesogenic drugs and obesity is "bidirectional," Dr. Hales said.

The authors reported no conflicts.

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SOURCE: Hales CM et al. Obesity Week 2019, Abstr.act T-OR-2037.Volorem nectotas aut ulpa quoditem facimi, solenti

AGA publishes clinical practice guidelines for gastric intestinal metaplasia

BY WILL PASS
MDedge News

The American Gastroenterological Association recently published clinical practice guidelines for managing gastric intestinal metaplasia (GIM).

The guidelines are the first of their kind to be published in the United States, according to lead author Samir Gupta, MD, AGAF, of the University of California, San Diego, and colleagues. The panelists suggested that the guidelines may help standardize decision making in a common clinical scenario.

"GIM has been considered as one specific marker to identify patients who might benefit from surveillance because it has been associated with increased risk for gastric cancer and is routinely encountered in clinical practice," the panelists wrote in (Gastroenterology. 2019 Dec 6. doi: 10.1053/j.gastro.2019.12.003).

The guideline panel was composed of three gastroenterologists, two guideline methodologist trainees, and three GRADE (Grading of Recommendations Assessment, Development and Evaluation) experts. Recommendations were based on the AGA guideline development process, the GRADE methodology, best practices set forth by the Academy of Medicine, and a technical review.

"Given the paucity of robust direct data on GIM in the U.S., evidence from all regions of the world was considered relevant in the evidence-gathering phase," the panelists wrote Based on available evidence, the expert panel developed three clinical recommendations.

First, the panelists recommended that clinicians test all patients with GIM for *Helicobacter pylori*, followed by eradication, over no testing and eradication. This recommendation was strong and based on moderate quality evidence from 22 studies, including 7 randomized, controlled trials. These studies showed that, compared with placebo, eradication of *H. pylori* was associated with a 32% pooled relative risk reduction in gastric cancer and a 33% pooled relative risk reduction in gastric cancer mortality among patients with or without GIM. The pooled relative risk reduction rate was similar in analyses solely composed of individuals with GIM, the panelists noted, whereas mortality data restricted to individuals with GIM were lacking.

"Overall, the known strong association of *H. pylori* with risk for incident gastric cancer and the technical review's findings, which reinforce the evidence of reduced risk for incident gastric cancer after *H. pylori* eradication, supports the AGA recommendation to test for and eradicate *H. pylori*," the panelists wrote.

The second recommendation, which was conditional and based on very-low-quality evidence, advised against routine use of endoscopic surveillance for patients with GIM. Still, surveillance may be considered for patients with higher risk of gastric cancer, including those with incomplete and/or extensive GIM, a family history of gastric cancer, racial/ethnic minorities, and immigrants from high-incidence regions, the panelists wrote.

"Although the technical review did not find evidence supporting increased risk for gastric cancer among racial/ethnic minorities or immigrants with documented GIM, an overall increased risk for gastric cancer (irrespective of presence/absence of GIM) has been established among these groups, and may be considered as part of decision making regarding surveillance," the panelists wrote.

The third recommendation was also conditional and based on very weak evidence; the panelists recommended against routine short-interval repeat endoscopy for the purpose of risk stratification.

"The technical review found no direct evidence to support the impact of short-interval (less than 12 months) repeat upper endoscopy among patients with incidental GIM on patient-important outcomes," the panelists wrote. However, the guidelines note that patients with potentially elevated risk profiles, such as patients with a family history of gastric cancer, "may reasonably elect for repeat endoscopy within 1 year for risk stratification."

Comparing these guidelines with those from other organizations, such as the European Society of Gastrointestinal Endoscopy, the panelists concluded that recommendations across organizations are "generally similar."

Finally, the panelists outlined knowledge gaps and pointed to future research topics. For instance, data are scarce comparing outcomes in relation to surveillance versus no surveillance among patients with GIM; and biomarkers such as pepsinogen levels, which are used in Asian countries for risk stratification of gastric cancer, have been studied minimally in the United States.

Guideline development was funded by the AGA. The panelists disclosed no conflicts of interest.

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SOURCE: Gupta S et al. Gastroenterology. 2019 Dec 6. doi: 10.1053/j.gastro.2019.12.003.

ctDNA outmatches CEA for detection of CRC recurrence

BY WILL PASS
MDedge News

For detection of recurrent colorectal cancer, circulating tumor DNA (ctDNA) may be more reliable than carcinoembryonic antigen (CEA), based on a recent Australian study.

Among 144 patients with a history of colorectal cancer (CRC), ctDNA testing offered a sensitivity of 66.0%, compared with 31.9% for CEA, reported lead author Erin L. Symonds, PhD, of Flinders University, Bedford Park, Australia, and colleagues, who noted that the two tests had comparable specificity.

According to the investigators, many patients with CRC who relapse are incurable because they have multiple unresectable metastases.

"This may be due to the poor sensitivity of the currently applied surveillance tools, with guidelines focused on radiological imaging (mostly yearly computed tomography scans) and regular blood tests for carcinoembryonic antigen (CEA)," the investigators wrote in Cancer. "There is a need to improve the timely detection of metastatic disease while it is still confined to a resectable state."

To this end, the investigators compared ctDNA testing with CEA testing in a real-world setting. Initially, 548 patients were enrolled. The final dataset included 144 of these patients, all of whom were disease negative on CT or MRI after surgical resection or neoadjuvant therapy. Most exclusions were because of unavailability of imaging results. Circulating tumor DNA testing evaluated methylation levels of BCAT1 and IKZF1. The LIAISON CEA test was used to measure CEA plasma concentration.

After a median follow-up of almost 4 years, 50 out of 144 patients had disease recurrence, most of which involved distant metastasis (74%). As described above, the sensitivity of ctDNA was higher than CEA by a wide and significant margin (66.0% vs. 31.9%; *P* less than .001). The superior sensitivity of ctDNA was observed regardless of whether recurrence was locoregional (76.9% vs. 15.4%; *P* = .006) or distant (62.1% vs. 38.2%; *P* = .044). Specificity was not statistically different between ctDNA (97.9%) and CEA (96.4%). Multivariate analysis showed that ctDNA was an independent predictor of recurrence, while CEA was not.

"In conclusion, the methylated BCAT1/IKZF1 ctDNA test is twice as sensitive as CEA for detecting recurrent CRC during the monitoring of patients after their initial treatment," the investigators wrote.

The study was funded by the National Health and Medical Research Council, Clinical Genomics, Cancer Council SA's Beat Cancer Project, and others. The investigators reported additional relationships with Eiken Chemical and the Commonwealth Scientific and Industrial Research Organisation.

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SOURCE: Symonds EL et al. Cancer. 2020 Jan 7. doi: 10.1002/cncr.32695.

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Quality reporting of improvement activities in 2020

BY BRIJEN J. SHAH, MD, AGAF

2020 has begun and therefore so has a new year of quality reporting requirements. Quality reporting under the Centers for Medicare and Medicaid Services (CMS) Merit-based Incentive Payment System (MIPS) may seem like a burden, but it doesn't need to be. You can likely get credit for the things you are already doing in your practice with little to no augmentation needed.

First, there are a few pieces of information to keep in mind when tracking your data and preparing your staff for their 2020 strategy.

1. Group Participation – For 2020 there is an increase in the MIPS participation threshold for those participating as part of a group. At least 50% of the MIPS eligible clinicians in the reporting group must participate in the same continuous 90-day period to receive credit for a quality improvement activity. That's a significant increase from 2019 when only one (1) MIPS eligible clinician in a group was required to participate. Connect with your staff now to make sure your group meets the new 50% participation requirement.


Dr. Shah

2. Improvement Activities for Group Participation – Improvement Activities that are approved for credit by CMS are given a weight based on their requirements. Approved activities are weighted as either medium or high, and this impacts how many activities a practitioner must report on. In 2020, CMS increased the participation threshold for group reporting from a single clinician to 50% of the clinicians in the practice for the Improvement Activities category along with other changes such as modifying the definition of rural area to mean a ZIP code designated as rural by the Federal Office of Rural Health Policy using the most recent file available, updating the improvement activities and removing some criteria for Patient-Centered Medical Home designation. Work with your staff now to make sure at least 50% of the MIPS-eligible clinicians in your group are participating in the same Improvement Activities.

3. Quantity of Improvement Activities Required – CMS requires most individuals or groups report on any of the following options during any continuous 90-day period (or as specified in the activity description) in the same performance year, provided that all participating clinicians are reporting on the same activities:

a. 2 high-weighted activities, or

b. 1 high-weighted and 2 medium-weighted activities, or

c. 4 medium-weighted activities

Be sure to pay attention to the weight of the activity you (if you're reporting as an individual) or your group is reporting so you don't have any surprises at the end of

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the reporting period.

There are a variety of options for activities you can report on and some may be a lower lift than you expect.

Does your practice treat Medicaid patients? If so, do you know their average wait time for an initial visit? If that number is 10 days or less, you can report on this activity. If you aren't quite hitting this benchmark, then consider implementing a scheduling protocol for this population of your patients in the new year.

Engagement of new Medicaid patients and follow-up

Seeing new and follow-up Medicaid patients in a timely manner, including individuals dually eligible for Medicaid and Medicare. A timely manner is defined as within 10 business days for this activity.

Subcategory name: Achieving Health Equity
Activity weighting: High

Are you responsible for onboarding and training new clinicians to your rural practice? If so, you could report on the next activity. Eligible clinicians would be responsible for training of new clinicians including physicians, advanced practice providers and clinical nursing specialists. These clinicians must practice in small, underserved, or rural areas. **What is considered a small, rural, or underserved practice for the purpose of MIPS?**

Small practice

- Defined as a practice with 15 or fewer eligible clinicians-based billing under the same TIN

Rural/underserved practice

- Defined as a practice in a zip code included in the most recent set of Health Professional Shortage Areas (HPSAs), as determined by the Health Resources and Services Administration (HRSA).
- HPSAs are designations that indicate health care provider shortages in primary care, dental health or mental health can be geographic population based or facility based.

Provide education opportunities for new clinicians

- MIPS-eligible clinicians acting as a preceptor for clinicians-in-training (such as medical residents/fellows, medical students, physician assistants, nurse practitioners, or clinical nurse specialists) and accepting such clinicians for clinical rotations in community practices in small, underserved, or rural areas.

  Subcategory name: Achieving Health Equity
  Activity weighting: High

There are also activities you can report on under the beneficiary engagement category that you may already be doing in your practice. First, the collection of patient experience and satisfaction data and the development of an improvement plan as necessary counts as one activity. Second, the engagement of the patient's support team in the development of a plan of care, which needs to include goals and be documented in the electronic health record.

Collection and follow-up on patient experience and satisfaction data on beneficiary engagement

Collection and follow-up on patient experience and satisfaction data on beneficiary engagement, including development of improvement plan.

Subcategory name: Benficiary Engagement
Activity weighting: High

Engagement of Patients, Family, and Caregivers in Developing a Plan of Care

Engage patients, family, and caregivers in developing a plan of care and prioritizing their goals for action, documented in the electronic health record (EHR) technology.

Subcategory name: Beneficiary Engagement
Activity weighting: Medium

Another data collection category is patient access to care. If you collect and use patient data on their satisfaction and experience related to access to care and commit to developing an improvement plan as

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necessary, you can receive credit for this reporting category.

Collection and use of patient experience and satisfaction data on access

Collection of patient experience and satisfaction data on access to care and development of an improvement plan, such as outlining steps for improving communications with patients to help understanding of urgent access needs.

Subcategory name: Expanded Practice Access
Activity weighting: Medium

One of the hallmarks of a medical practice in any specialty is improvement. We are always striving to improve something, whether it be the patient experience, patient outcomes, the bottom line, or the education of clinical staff. You can leverage the practice improvement plans you have put into place for credit.

Leadership engagement in regular guidance and demonstrated commitment for implementing practice improvement changes

Ensure full engagement of clinical and administrative leadership in practice improvement that could include one or more of the following: Make responsibility for guidance of practice change a component of clinical and administrative leadership roles; Allocate time for clinical and administrative leadership for practice improvement efforts, including participation in regular team meetings; and/or Incorporate population health, quality and patient experience metrics in regular reviews of practice performance.

Subcategory name: Patient Safety and Practice Assessment
Activity weighting: Medium

Prescription drug use is a topic on every providers' radar right now. Proper prescribing and monitoring of patients are crucial to their safety and quality of care. In the field of gastroenterology, step-therapy adds a new level of complication to the use of prescription drugs. Ensuring the proper medication protocols allows you to provide appropriate and timely treatment for your patients.

Annual registration in the Prescription Drug Monitoring Program

Annual registration by eligible clinician or group in the prescription drug–monitoring program of the state where they practice. Activities that simply involve registration are not sufficient. MIPS-eligible clinicians and groups must participate for a minimum of 6 months.

Subcategory name: Patient Safety and Practice Assessment
Activity weighting: Medium

As you can see, there are a variety of improvement activities that you can report on for 2020. This article has outlined several of them that you may already be doing in your practice, but many more can be found by visiting https://qpp.cms.gov/mips/improvement-activities?py=2020 along with information on how to report and the necessary forms for submission.

Dr. Shah is associate professor, Mount Sinai Medical Center, New York, member of the AGA Quality Leadership Council. He has no disclosures.

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