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GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

COURTESY DR. SAHIL KHANNA

Dr. Sahil Khanna and coauthors recommend careful monitoring and treatment of *C. difficile* in IBD, as each worsens the other.

AGA Clinical Practice Update: *C. difficile* in IBD

BY AMY KARON
Frontline Medical News

Inflammatory bowel disease (IBD) increases the risk and severity of *Clostridium difficile* infection (CDI) while CDI tends to complicate and worsen the clinical course of IBD, experts note in a Clinical Practice Update.

Thus, it is crucial that clinicians pursue stool testing for toxigenic *C. difficile* infection whenever a patient with IBD presents with a colitis flare, regardless of recent antibiotic history, wrote Sahil Khanna, MBBS, of the Mayo Clinic, Rochester, Minn., and his associates (Clin Gastroenterol Hepatol. 2016 Feb. doi: 10.1016/j.cgh.2016.10.024). Clinicians should also test for recurrent CDI if symptoms of colitis persist or return after antibiotic therapy for CDI, they emphasized.

CDIs are on the rise and now cause about 29,000 deaths annually in the United States, surpassing the combined death count from methicillin-resistant *Staphylococcus aureus* and multidrug resistant gram-negative bacteria. Reasons for this concerning trend include rising antibiotic use, population aging,

See **AGA CPU** · *page 20*

21st Century Cures Act: $500 million for FDA reform

BY GREGORY TWACHTMAN
Frontline Medical News

The 21st Century Cures Act – bipartisan legislation to support medical research, reform the Food and Drug Administration, address the opioid epidemic, and improve access to mental health care – has passed both Houses of Congress and been signed by President Obama last month before leaving office.

"It is wonderful to see how well Democrats and Republicans in the closing days of this Congress came together around a common cause, and I think it indicates the power of this issue and how deeply it touches every family across America," President Obama said when signing the law. "I started the 2016 State of the Union address by saying we might be able to surprise some cynics and deliver bipartisan action on the opioid epidemic. And in that same speech, I put [Vice President] Joe [Biden] in charge of Mission Control on a new cancer moonshot. And today, with the 21st Century Cures Act, we are making good on both of those efforts. We are bringing to reality the possibility of new breakthroughs to some of the greatest health challenges of our time."

A pared-down version of the 21st Century Cures Act passed the House Nov. 30 by an overwhelming

See **Cures Act** · *page 4*

Docs may lose income with ACA repeal

BY GREGORY TWACHTMAN
Frontline Medical News

An expected partial repeal of the Affordable Care Act would hit physicians' bottom line, according to a new analysis from the Urban Institute.

Analysts using the vetoed January 2016 budget reconciliation bill as the basis for their projections estimate that the partial repeal could result in as many as 29.8 million Americans losing coverage through the elimination of the Medicaid expansion, the individual and employer mandates, and the insurance marketplace premium tax credits and cost-sharing reductions. In addition, there would be a surge in uncompensated care.

"The coverage losses would in turn decrease revenues for providers of all

See **ACA repeal** · *page 2*

INSIDE

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Uncompensated care at issue

ACA repeal *from page 1*

types," the report states. "Providers' variable costs would also decrease, but their fixed costs would not."

The Urban Institute estimates that spending by insurers (public and private) and households on health care delivered to the nonelderly would decrease by $145.8 billion in 2019 and $1.7 trillion between 2019 and 2028.

'If federal, state, and local governments do not allocate more funding for [uncompensated] care, the financial burden would fall on health care providers.'

The increase in the uninsured would cause a spike of $88 billion in uncompensated care ($26.4 billion in hospital care, $11.9 billion in physician office care, $33.6 billion in other services, and $18.0 billion in prescription drugs), reaching $1.1 trillion between 2019 and 2028. At the same time, federal funding for uncompensated care would increase no more than $3.2 billion in 2019 and no more than $35 billion from 2019 to 2028, analysts state.

"There is no clear source of funding for the remainder," the report notes. "If federal, state, and local governments do not allocate more funding for this care, the financial burden would fall on health care providers. Large increases in unmet need for the uninsured are likely because the additional costs would require a fourfold increase in provider funding of uncompensated care from current levels."

Congressional Republicans plan to use the budget reconciliation process to partially repeal the revenue-generating aspects of the ACA, a process that allows the repeal to go through with a simple majority in the Senate. However, repeal of the health care reform law's other parts would require at least 60 votes in the Senate, requiring at least eight Democrats to side with the Republican majority, assuming none in the majority go against the party.

The Trump administration has signaled that it plans to maintain certain aspects of the ACA, including the ability for parents to cover children up to age 26 and the ban on denial of coverage for preexisting conditions.

Research for the report was funded by the Robert Wood Johnson Foundation.

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LETTER FROM THE EDITOR:

New President, but GI & Hepatology News' mission stays the same

By the time this issue is published, we will have seen the inauguration of Donald J. Trump as the 45th president of the United States, and we will have begun to understand the process and implications of repealing and replacing the Affordable Care Act. We have provided you with information about potential financial losses under ACA repeal and highlighted the new 21st Century Cures Act.

Our articles span the spectrum of current clinical issues from endoscope cleaning to propofol safety. This month we also feature articles highlighting AGA commentaries and guidelines. AGA has produced a Clinical Practice Update based on the Multi-Society Task Force guideline on scope reprocessing and a guideline concerning management of acute liver failure.

Several articles highlight the importance of recognizing genetic causes for colorectal cancer. In the Practice Management Toolbox, Xavier Llor, MD, PhD, outlines steps to develop a coordinated colorectal cancer genetics program, based on his work at Yale University.

DR. ALLEN

Finally, I hope you again enjoy our latest Flashback column. This month we look back at an important article from 2008, our second year of publication. As this year continues, we will try to keep you abreast of the rapidly changing political and policy landscape, while providing updates on the latest scientific research.

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

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FRONTLINE MEDICAL COMMUNICATIONS

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References: 1. IMS Health, NPA Weekly, July 2016. **2.** Rex DK, Di Palma JA, Rodriguez R, McGowan J, Cleveland M. A randomized clinical study comparing reduced-volume oral sulfate solution with standard 4-liter sulfate-free electrolyte lavage solution as preparation for colonoscopy. *Gastrointest Endosc*. 2010;72(2):328-336. **3.** Rex DK, Schoenfeld PS, Cohen J, et al. Quality indicators for colonoscopy. *Gastrointest Endosc*. 2015;81(1):31-53. **4.** SUPREP Bowel Prep Kit [package insert]. Braintree, MA: Braintree Laboratories, Inc; 2012.

16-00927T August 2016

Funding reduced for approval

Cures Act *from page 1*

392-26 vote, gaining more support on the House floor than did a version of the legislation that passed the House in 2015. For that additional support and for assurance of Senate approval, funding for key biomedical research efforts – the BRAIN Initiative, the Cancer Moonshot, and the Precision Medicine Initiative – was reduced from $9.3 billion to $4.8 billion over a 10-year period. Further, those funds are not guaranteed but will need to be appropriated through the federal budget process. Key provisions of the bill (H.R. 34) include:

- FDA reforms, including expedited review for certain medical devices, streamlined review for drug/device combinations, and increased patient involvement in the drug approval process, with $500 million to implement the reforms.
- $4.8 billion over a 10-year period for key biomedical research efforts including the BRAIN Initiative, the Cancer Moonshot, and the Precision Medicine Initiative.
- $1 billion in grants to states over a 2-year period to help supplement opioid abuse prevention and treatment activities.
- Provisions to improve the interoperability of EHRs.
- Provisions to improve the treatment of serious mental illness.

WHITEHOUSE.GOV

President Obama signs the 21st Century Cures Act.

The FDA funding is designed to help the agency speed up the drug approval process, focusing on identifying biomarkers and developing targeted drugs for rare diseases. It also reauthorizes the pediatric rare disease priority review voucher program, requires drug companies to have a publicly accessible compassionate use policy for drugs treating serious or life-threatening conditions, and provides flexibility to get new antimicrobial drugs to market quickly.

Changes in the drug approval process were contentious during debate on the House floor. "In its attempt to speed up the drug and device approval process, this legislation neglects the very people whom clinical trials are meant to help, that is, the patients," Rep. Rosa DeLauro (D-Conn.) said. "Rather than protect those who rely on the health care system, it reduces the already weak regulation on medical devices, allows drugs with only limited evidence of the drug's safety and efficacy, and rushes the use of new and unproven antibiotics."

Other legislators expressed disappointment at the bill's mental

Continued on following page

Continued from previous page

health care provisions. Rep. Joseph Kennedy III (D-Mass.) said that his "real concerns with the legislation lie with the mental health reform proposals, which don't go nearly far enough. Mental health parity is already the law, thanks to the Mental Health Parity and Addiction Equity Act and the Affordable Care Act, but each study we read, Mr. Speaker, and each story we hear proves that insurance companies are skirting those rules.

"We need enforcement and transparency today," Rep. Kennedy continued. "We need random audits before there have been violations, not after. We need insurers to publicly disclose the rates and reasons for denials in a way that patients and their families can understand, not in a way that mental health advocates can't even obtain. We need to increase Medicaid reimbursements in order to expand access to care, not to reduce them or roll back expansion."

21st Century Cures also contains health IT–related provisions, mostly aimed at improving the interoperability of electronic health records. It also reduces the documentation burden on providers and establishes the authority for the Health & Human Services Office of Inspector General to penalize those engaged in information blocking between EHRs.

The bill also increases the transparency around Medicare local coverage decisions and exempts certain transfers of value from reporting requirements related to continuing education. It sets reimbursement for Medicare Part B drugs infused through durable medical equipment at 106% of the average sales price.

Other provisions include creation of a National Institutes of Health program to support new researchers; funds to accelerate improved methods for prevention, diagnosis, and treatment of tick-borne diseases; the development of a national neurologic condition surveillance system; and the establishment of a task force on research specific to pregnant and breastfeeding women.

"More women with chronic diseases are becoming pregnant, yet safe and effective medications to manage these ongoing conditions throughout their pregnancy and beyond are needed," Mary Norton, MD, president of the Society for Maternal-Fetal Medicine, said in a statement. "This legislation is a great first step toward greater collaboration and communication among federal agencies and public stakeholders."

In the Senate, only five members voted against the legislation: Sens. Elizabeth Warren (D-Mass.), Bernie Sanders (I-Vt.), Ron Wyden (D-Ore.), Jeff Merkley (D-Ore.), and Mike Lee (R-Utah), with most objecting that the legislation did not address key issues in the need to find cures for major diseases.

"The most important prescription drug–related crisis facing our country right now is the skyrocketing price of prescription drugs. This bill does not even deal with that issue," Sen. Sanders said on the Senate floor. "How can we talk about a bill dealing with the pharmaceutical industry without addressing the elephant in the room, which is the fact that we pay the highest prices in the world for medicine?"

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FLASHBACK TO APRIL 2008

2007-**10-Year Anniversary**-2017

The April 2008 issue of *GI & Hepatology News* (*GIHN*) featured an article by Roy M. Soetikno, MD, MS, FASGE and his colleagues from the Palo Alto VA Medical Center in California. They drew our attention to nonpolypoid (flat) colonic lesions in an article from JAMA (2008;299:1027-35).

Coincidentally, the week before this article appeared, I was sitting with Roy in Kyoto at a conference of international experts focused on flat colonic lesions. The Japanese definitions of flat and depressed lesions were markedly different from those used by Western physicians. We now know that most flat lesions seen by U.S.-based endoscopists are sessile serrated adenomas (SSAs). SSAs at that time also were a new and controversial classification.

SSAs were first described by Torlakovic and Snover in 1996 (Gastroenterology. 1996;110:748-55). Dale Snover, MD, was my golfing partner and read pathology slides for our practice in Minneapolis, so we were the first gastroenterologists in the country to grapple with the clinical implications of SSAs. Roy's article was accompanied by an excellent commentary by Jerome D. Waye, MD, FASGE, who emphasized the importance of a slow withdrawal time and meticulous visual technique during colonoscopy. Key points in the JAMA article were a) prevalence of flat lesions was about 9% in a screening population, b) small flat polyps can harbor advanced histologic changes including cancers, and c) many physicians who perform colonoscopy missed these lesions putting patients at risk for interval colon cancers.

The *GIHN* piece, referencing Soetikno's article, helped inform us about an important (and confusing) problem in our colon cancer prevention efforts. As numerous authors subsequently highlighted (see Gastroenterology. 2016;151:870-8) most cancers, missed at initial colonoscopy, are proximal and frequently develop from SSAs. We continue to work to reduce missed cancers and thanks to this seminal article, we have better insights about how to achieve this goal.


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"What you don't know or don't believe in, you don't seek," said Dr. Roy M. Soetikno, lead investigator in the Flat Lesion Study.

Do Nonpolypoid Lesions Predict Colorectal Ca?

Telaprevir Regimen Reduced Viral Load In Chronic Hep C

Therapy included ribavirin, pegginterferon.

Early Data: Aspirin Looks Safe for Barrett's

INSIDE

Upper GI Tract
Are PET Scans Reliable?
A negative scan after esophageal dysmotilization does not mean surgery is unnecessary. • 4

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Systemic Therapies
Sorafenib extended survival of hepatocellular carcinoma patients in two studies. • 12

From the AGA Institute
New Consensus Guidelines
The AGA Institute supports the CRC screening guidelines that make cancer prevention the new primary goal. • 15

Lower GI Tract
Pain Perception Differs in IBS
Brain responses to anticipated pain and pain itself were altered in irritable bowel syndrome patients. • 16

John I. Allen, MD, MBA, AGAF, is professor of medicine in the division of gastroenterology and hepatology at the University of Michigan, Ann Arbor, and the Editor in Chief of GI & Hepatology News.

Prominent clinical guideline falls short of COI standards

BY JENNIE SMITH
Frontline Medical News

A recent clinical practice guideline for treatment of chronic hepatitis C did not meet the Institute of Medicine's standards for limiting commercial conflicts of interest, according to results of a new analysis.

In research published online Jan. 17, Akilah A. Jefferson, MD, and Steven D. Pearson, MD, both of the National Institutes of Health in Bethesda, Md., re-examined conflict of interest disclosures for the American Association for the Study of Liver Diseases and Infectious Diseases Society of America's joint 2014 guideline related to novel drug treatments for chronic hepatitis C virus (HCV) infection.

The IOM standards for conflicts of interest in guidelines, introduced in 2011, require that less than half the members of any guideline writing committee have a commercial conflict, which can include consultancies, board memberships, and stock in manufacturers of devices or treatments. Guideline writing committee chairs and cochairs should have no commercial conflicts of interest, according to the IOM.

For the HCV guidelines, 72% of the committee members reported commercial conflicts, along with four out of six committee cochairs. An analysis of concurrent publications revealed incomplete disclosure of conflicts among authors of the guideline (JAMA Intern Med.

Continued on following page

CLINICAL CHALLENGES AND IMAGES

What's your diagnosis?

By Kensuke Adachi, MD, PhD, and Kazuaki Enatsu, MD. Published previously in Gastroenterology (2013;144[1]:32, 251).

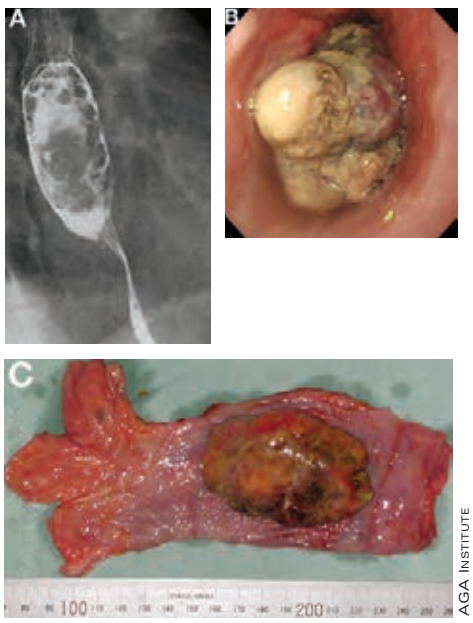
A previously healthy, 56-year-old man visited our hospital with a 2-month history of dysphagia. The patient's past medical history was unremarkable. He denied a recent history of weight loss, reflux symptoms, or food impaction. Laboratory and physical test results revealed no abnormalities.

Barium swallow esophagogram showed dilatation of the esophagus with a filling defect, approximately 7 cm long, in the intrathoracic esophagus (Figure A). Endoscopy also revealed an elastic and large polypoid tumor occupying the almost whole lumen in the mid-esophagus (Figure B). Despite such a bulky appearance, the lesion allowed easy passage of the endoscope into the stomach. Endoscopic biopsy specimens suggested a malignant tumor of the esophagus.

There were no suspicious lymph nodes or distant metastases on preoperative computed tomography. The patient underwent an esophagectomy and standard three-field lymphadenectomy with gastric replacement via the posterior mediastinal route and intrathoracic anastomosis.

He had an uneventful recovery and was discharged on postoperative day 11. The operative specimen is shown in Figure C. According to the TMN classification, the postoperative diagnosis was T2N0M0, equivalent to stage IIA. Fortunately, the patient was alive and free of recurrence after 7 years of follow-up.

The diagnosis appears on page 26.



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Quick quiz

Q1. A 40-year-old man presents with melena and a significant drop in hemoglobin. He is hypotensive and tachycardic. He is resuscitated with intravenous fluids and undergoes urgent endoscopy. A 2-cm gastric ulcer is seen in the antrum with a large adherent clot that resists vigorous washing for 2 minutes.

In addition to an IV proton pump inhibitor, what is the most appropriate method for treating this ulcer?
A. No further therapy is indicated
B. Epinephrine injection, shaving down the clot with a cold snare, and coaptive coagulation of the underlying vessel
C. Combination therapy with epinephrine injection and hemoclip placement over the clot
D. Epinephrine injection around the base of the ulcer

Q2. A 34-year-old woman presents with a 3-year history of watery, nonbloody diarrhea with associated weight loss, and recurrent bacterial bronchitis and pneumonias. Laboratory studies show iron deficiency anemia, low 25-OH vitamin D, and a slightly elevated INR. Celiac serologies were negative, and small bowel biopsies revealed near total villous atrophy, increased intraepithelial lymphocytes, and crypt hyperplasia with absent plasma cells.

What is the most appropriate initial treatment strategy?
A. Gamma globulin
B. Prednisone
C. Infliximab
D. Gluten-free diet
E. Rifaximin

The answers are on page 25.

CORRECTION

In the January 2017 Flashback feature on page 6, in the last paragraph the last sentence should have read "in the 2007 June issue of *GI & Hepatology News* ..."

Continued from previous page

2017 Jan 17. doi: 10.1001/jamainternmed.2016.8439).

"Management of levels of commercial [conflict of interest] among guideline committees remains an important problem 5 years after the IOM standards were published," the investigators wrote. They recommended "broader and more explicit adoption" of the IOM's framework for conflict of interest.

The study notes that the HCV guideline met all nine of the additional IOM guideline development and evidence standards.

The study was funded by an NIH grant. Dr. Pearson reported receiving research funding from foundations and membership dues paid by insurance and pharmaceutical companies. No other disclosures were reported.

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FROM THE AGA JOURNALS

Protein-rich diet helps manage type 2 diabetes, NAFLD

BY DEEPAK CHITNIS
Frontline Medical News

Patients with type 2 diabetes should be put on diets rich in either animal or plant protein to reduce not only liver fat, but insulin resistance and hepatic necroinflammation as well, according to a study published in the February issue of Gastroenterology (doi: 10.1053/j.gastro.2016.10.007).

"High-protein diets have shown variable and sometimes even favorable effects on glucose metabolism and insulin sensitivity in people with type 2 diabetes," wrote the authors of the study, led by Mariya Markova, MD, of the German Institute of Human Nutrition Potsdam-Rehbrücke in Nuthetal, Germany.

Obesity and insulin resistance have long been linked to liver fat, with excessive amounts causing nonalcoholic fatty liver disease (NAFLD). The "hypercaloric Western style diet," as the authors call it, exacerbates the accumulation of fat deposits in the liver and complicates the health of many, regardless of weight.

"Remarkably, diets restricted in methionine were shown to prevent the development of insulin resistance and of the metabolic syndrome in animal models [so] the type of protein may elicit different metabolic responses depending on the amino acid composition," Dr. Markova and her coinvestigators noted. "It is therefore hypothesized that high-plant-protein diets exert favorable effects on hepatic fat content and metabolic responses as compared to high intake of animal protein rich in BCAA [branched-chain amino acids] and methionine."

Dr. Markova and her team devised a prospective, randomized, open-label clinical trial involving 44 patients with type 2 diabetes and NAFLD recruited at the German Institute of Human Nutrition Potsdam-Rehbrücke between June 2013 and March 2015. Subjects were randomized into one of two cohorts, each of which were assigned a diet rich in either animal protein (AP) or plant protein (PP) for a period of 6 weeks. Median body mass index in the AP cohort was 31.0 ± 0.8 kg/m^2, and was 29.4 ± 1.0 kg/m^2 in the PP cohort.

The AP diet consisted mainly of meat and dairy products, while legumes constituted the bulk of the PP diet. The diets were isocaloric and had the same macronutrient makeup: 30% protein, 40% carbohydrate, and 30% fat. Seven subjects dropped out prior to completion of the study; of the 37 that remained all the way through – 19 in the AP cohort, 18 in the PP cohort – the age range was 49-78 years. Subjects maintained the same physical exercise regimens throughout the study that they had beforehand, and were asked not to alter them. Hemoglobin A_{1c} levels ranged from 5.8% to 8.8% at baseline, and evaluations were carried out fasting for each subject.

Patients in both cohorts had significant decreases in intrahepatic fat content by the end of the trial period. Those in the AP cohort saw decreases of 48.0% (P = .0002), while those in the PP cohort saw a decrease of 35.7% (P = .001). Perhaps most importantly, the reductions in both cohorts were not correlated to body weight. In addition, levels of fibroblast growth factor 21 (FGF21), which has been shown to be a predictive marker of NAFLD, decreased by nearly 50% for both AP and PP cohorts (P less than .0002 for both).

"Despite the elevated intake and postprandial uptake of methionine and BCAA in the AP group, there was no indication of negative effects of these components," the authors stated in the study. "The origin of protein – animal or plant – did not play a major role. Both high-protein diets unexpectedly induced strong reductions of FGF21, which was associated with metabolic improvements and the decrease of intrahepatic lipids [IHL]."

However, the 6-week time span used here is not sufficient to determine just how viable this diet may be in the long term, according to the authors. Further studies will be needed to "show the durability of the responses and eventual adverse effects of the diets."

The study was funded by grants from German Federal Ministry of Food and Agriculture and German Center for Diabetes Research. Dr. Markova and her coauthors did not report any financial disclosures.

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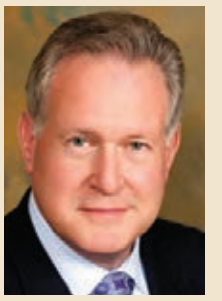
Human studies to assess the effects of isocaloric macronutrient substitution are fraught with difficulty. If one macronutrient is increased, what happens to the others? If you observe an effect, is it the phenomenon you were seeking, or an epiphenomenon caused by changes in the others?

Markova et al. attempted to study a 6-week "isocaloric" increase of animal vs. plant protein (from 17% to 30% of calories as protein). However, a decrease of percent fat from 41% to 30%, and a reduction in carbohydrate from 42% to 40% occurred commensurately. This brings up three concerns. First, despite the diets being "isocaloric," weight and body mass index decreased by 2 kg and 0.8 kg/m^2, respectively. Reductions in intrahepatic, visceral, and subcutaneous fat, and an increase in lean body mass were noted. So was the diet isocaloric? Protein reduces plasma ghrelin levels and is more satiating. Furthermore, metabolism of protein to ATP is inefficient compared to that of carbohydrate or fat. The authors say only that calories were "unrestricted." These issues do not engender "isocaloric" confidence. Second, animal protein (high branched-chain amino acid and methionine) consists of meat and dairy, but their fatty acid compositions are quite different. Dairy has odd-chain fatty acids, which are protective against type 2 diabetes, while meat has even-chain fatty acids, which may be more predisposing to disease. Did the change in fatty acids play a role, rather than the change in amino acids? Lastly, the type of carbohydrate was not controlled for. Fructose is significantly more lipogenic than glucose. Yet they were lumped together as "carbohydrate," and were uncontrolled. So what macronutrient really caused the reduction in liver fat? These methodologic issues detract from the author's message, and this study must be considered preliminary.


DR. LUSTIG

Robert H. Lustig, MD, MSL, is in the division of pediatric endocrinology, UCSF Benioff Children's Hospital, San Francisco; member, UCSF Institute for Health Policy Studies. Dr. Lustig declared no conflicts of interest.

Endoscopy during pregnancy risks preterm birth

BY DEEPAK CHITNIS
Frontline Medical News

Women who undergo an endoscopy during pregnancy are increasing the chances that their baby will be born preterm, or be small for gestational age (SGA), according to research published in the February issue of Gastroenterology (doi: 10.1053/j.gastro.2016.10.016).

"Research in pregnancy outcome in women undergoing endoscopy during pregnancy is scarce," wrote the authors, led by Jonas F. Ludvigsson, MD, of the Karolinska Institutet in Stockholm, adding that there are nine studies with original data on a total of 379 pregnant women undergoing endoscopy; two of these studies examined pregnancy outcome in upper endoscopy (n = 143), two examined pregnancy outcome in sigmoidoscopy or colonoscopy (n = 116), and four examined pregnancy outcome in endoscopic retrograde cholangiopancreatography (n = 120).

Continued on following page

FROM THE AGA JOURNALS

Vedolizumab effective for UC in range of patients

BY DEEPAK CHITNIS
Frontline Medical News

When treating patients for ulcerative colitis (UC), clinicians should consider using vedolizumab, because the drug has been found to be both safe and highly effective in patients who have never received tumor necrosis factor (TNF)–antagonist treatment and in those who have but did not benefit from it, according to a study published in the February issue of Clinical Gastroenterology and Hepatology (doi: 10.1016/j.cgh.2016.08.044).

"Approximately 50% of patients with UC do not respond to induction therapy with TNF antagonists or lose response over time such that, after 1 year of treatment, clinical remission is observed in only 17%-34% of patients," explained the authors of the report, led by Brian G. Feagan, MD, of the University of Western Ontario in London. "Furthermore, the risk of serious infection (with immunosuppressants in general, and TNF antagonists specifically) is an important concern [so] alternative approaches to treatment are needed."

For this study, Dr. Feagan and his colleagues turned to the GEMINI 1 trial, which evaluated vedolizumab in patients with moderate and severe UC via a multicenter, phase III, randomized, placebo-controlled trial. This study produced data on 374 subjects who had been randomized into cohorts receiving either vedolizumab intravenously or a placebo. However, this number was deemed too low, so a further 521 patients were enrolled for an open-label study and randomized in the same 3:2 ratio as the previous study. The former study was called Cohort 1 and the latter called Cohort 2.

"Eligible patients had UC for [at least] 6 months before enrollment, MCS [Mayo Clinic scores for disease activity] from 6 to 12, and endoscopic subscores of [at least] 2 within 7 days before the first dose of study drug, and evidence of disease extending [at least] 15 cm proximal to the rectum," the authors explained.

Vedolizumab was administered at baseline, with follow-up evaluations at 2, 4, and 6 weeks. Subjects who experienced a clinical response – defined as an MCS reduction of at least 3 points and 30%, along with at least a 1-point reduction in rectal bleeding and an absolute rectal bleeding subscore of either 0 or 1 – were re-randomized into cohorts that received the drug every 4 weeks or every 8 weeks, for a period of up to 46 weeks. The total length of the study was, therefore, 52 weeks; for patients that were re-randomized, follow-up evaluations took place every 4 weeks.

A total of 464 patients who were enrolled and completed the study were naive to TNF antagonists, while 367 had previously been treated with TNF antagonists unsuccessfully. At 6-week follow-up, 53.1% of naive subjects receiving vedolizumab had achieved clinical response, vs. 26.3% of naive subjects on placebo (absolute difference, 26.4%; 95% confidence interval, 12.4-40.4). Similarly, those with previous TNF antagonist exposure who were given vedolizumab had a 39.0% clinical response rate, versus 20.6% of those on placebo (AD, 18.1%; 95% CI, 2.8-33.5).

At week 52, TNF antagonist–naive subjects on vedolizumab continued to have far higher rates of clinical response than did those on placebo.

At week 52, naive subjects on vedolizumab continued to have far higher rates of clinical response than did those on placebo, with 46.9% and 19.0%, respectively (AD, 28.0%; 95% CI, 14.9-41.1). For those with previous TNF antagonist exposure, the disparity between vedolizumab and placebo was similarly profound: 36.1% versus 5.3%, respectively (AD, 29.5%; 95% CI, 12.8-46.1).

Adverse event rates between naive and previously exposed patients were not significantly different, according to the findings. In naive patients, 74% of those on vedolizumab experienced an adverse event, and 9% experienced a serious adverse event. For those on placebo, those rates were 75% and 16%, respectively. For patients who had previously been on a TNF antagonist, subjects on vedolizumab had an 88% rate of adverse events and a 17% rate of serious adverse events, compared with 84% and 11%, respectively, for those on placebo.

The study was funded by Millennium Pharmaceuticals. Dr. Feagan disclosed serving as a consultant and receiving financial support for research from Millennium and other companies. No other coauthors reported relevant financial disclosures.

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Continued from previous page

Additionally, the authors noted that, to their knowledge, there are no studies that offer data on the relative risk of endoscopy during pregnancy, and none that followed up subjects after birth. Of the few studies that do exist, a handful conclude that endoscopy during pregnancy is actually safe, but do not include data on stillbirths and neonatal deaths that did not occur immediately after patients underwent endoscopy, which could compromise that data.

To address the lack of reliable research on the effect of endoscopy on pregnancy, Dr. Ludvigsson and his coinvestigators launched a nationwide study of pregnancies in Sweden that occurred between 1992 and 2011, all of which were registered in the Swedish Medical Birth Registry and the Swedish Patient Registry. The databases revealed 2,025 upper endoscopies, 1,109 lower endoscopies, and 58 endoscopic retrograde cholangiopancreatographies, for a total of 3,052 pregnancies exposed to endoscopy over that time period.

The primary endpoint of the study was the frequency of preterm birth and stillbirth in this population. To measure this, the investigators used adjusted relative risk (ARR), calculated via Poisson regression by using data on 1,589,173 pregnancies that were not exposed to endoscopy as reference.

"Stillbirth is recorded from 22 completed gestational weeks since mid-2008, and before that from gestational week 28. Gestational age was determined using ultrasound, and when ultrasound data were missing, the first day of the last menstrual period was used for pregnancy start," the authors wrote.

The results showed that mothers who had any kind of endoscopy during pregnancy were more likely to experience a preterm birth or give birth to a baby who was SGA, with the ARR being 1.54 (95% confidence interval, 1.36-1.75) and 1.30 (95% CI, 1.07-1.57), respectively. However, the risk of other adverse effects, such as stillbirth or congenital malformation, was not significant: Stillbirth ARR was 1.45 (95% CI, 0.87-2.40) and congenital malformation ARR was 1.00 (95% CI, 0.83-1.20).

Women who were exposed to endoscopy during pregnancy were more likely to have a preterm birth, compared with women who had endoscopy 1 year before or after pregnancy, but were not more highly predisposed to SGA, stillbirth, or congenital malformations. Additionally, when data on multiple pregnancies carried by the same mother were compared, no correlation was found between endoscopy and gestational age or birth weight, if the mother was exposed to endoscopy during only one of the pregnancies.

"Earlier recommendations suggest that endoscopy should only be performed during pregnancy if there are strong indications, and if so, not during the second trimester, [but] our study shows that endoscopy is unlikely to have a more than marginal influence on pregnancy outcome independently of trimester," the authors concluded. "Neither does it seem that sigmoidoscopy is preferable to a full colonoscopy in the pregnant woman."

Regarding the latter conclusion, the authors clarified that "it is possible that in women with particularly severe gastrointestinal disease where endoscopy is inevitable, the physician will prefer a sigmoidoscopy rather than a full colonoscopy, and under such circumstances the sigmoidoscopy will signal a more severe disease."

The investigators also noted that their study had several limitations, including not knowing the length of time each endoscopy took, the sedatives and bowel preparations used, the patient's position during the procedure, and the indication that prompted the endoscopy in the first place.

The study was funded by grants from the Swedish Society of Medicine and the Stockholm County Council, and the Swedish Research Council. Dr. Ludvigsson and his coauthors did not report any relevant financial disclosures.

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FROM THE AGA JOURNALS

Propofol safety similar to that of traditional sedatives

BY DEEPAK CHITNIS
Frontline Medical News

For doctors performing gastrointestinal endoscopic procedures, use of propofol as a sedative instead of the combination of opioid and benzodiazepine carries about the same risk of causing cardiopulmonary adverse events, according to a study published in the February issue of Clinical Gastroenterology and Hepatology (doi: 10.1016/j.cgh.2016.07.013).

"Because of its popularity, propofol is being used for both simple endoscopic procedures such as esophagogastroduodenoscopy and colonoscopy, and advanced endoscopic procedures, [but] despite the widespread use of propofol, significant concerns remain regarding its safety profile," according to the authors of the study, led by Vaibhav Wadhwa, MD, of Fairview Hospital in Cleveland.

While still used today, the opioid/benzodiazepine combination has seen a dramatic decline in usage because of its longer recovery time and lower rates of satisfaction among both patients and doctors, according to the authors. Combinations including midazolam, meperidine, pethidine, remifentanil, and fentanyl.

To compare the safety of propofol with the more traditional sedative combination, Dr. Wadhwa and his coauthors conducted a meta-analysis of published studies in the Medline (Ovid), EMBASE, and the Cochrane controlled trials registry databases. All searches were for research conducted through September of 2014, with the Medline database search starting in 1960, and the EMBASE and Cochrane searches starting in 1980, yielding a total of 2,117 studies eligible for inclusion.

Of those, 1,568 remained after duplicates were removed, then 136 were screened after removal of those deemed irrelevant or otherwise unsuitable. From those 136, 83 were excluded for various reasons – because they featured either ineligible populations, or were retrospective studies, single-arm studies, or conference abstracts – leaving 53 full-text articles to be evaluated for inclusion in the study. Of those, 27 were deemed eligible and were ultimately included.

"The primary outcomes measured were cardiopulmonary complications such as hypoxia, if oxygen saturation decreased to less than 90%; hypotension, if systolic blood pressure decreased to less than 90 mm Hg; arrhythmias, including bradycardia, supraventricular and ventricular arrhythmias, and ectopy," Dr. Wadhwa and his coauthors wrote. "A subgroup analysis also was performed to assess studies in which sedation was directed by gastroenterologists and was compared with nongastroenterologists."

'Our results showed that propofol sedation for gastrointestinal endoscopic procedures, whether simple or advanced, did not increase the cardiopulmonary adverse event rate when compared with traditional sedative agents.'

Pooled odds ratios were used to measure and compare results. The 27 included studies featured data on a total of 2,518 patients. Traditional sedatives were used on 1,194 of these subjects, while the remaining 1,324 received propofol. Regarding hypoxia, 26 of the 27 studies addressed this, of which 13 concluded that propofol was safer and 9 found that traditional sedatives were safer, with a pooled OR for propofol of 0.82 (95% confidence interval, 0.63-1.07).

Twenty-five studies examined hypotension, of which 9 favored propofol and 10 favored traditional sedatives, for an OR of 0.92 (95% CI, 0.64-1.32). Of the 20 studies that included arrhythmia, 8 favored propofol and 7 favored traditional sedatives, for an OR of 1.07 (95% CI, 0.68-1.68).

"Our results showed that propofol sedation for gastrointestinal endoscopic procedures, whether simple or advanced, did not increase the cardiopulmonary adverse event rate when compared with traditional sedative agents," the authors concluded.

In terms of the risk of developing any of the aforementioned complications, of the 20 relevant studies, 9 found propofol to be safer versus 6 that found traditional sedatives to be the better option, yielding an overall OR of 0.77 (95% CI, 0.56-1.07) for propofol. For the subanalysis regarding which type of clinician administered each sedative, 25 studies contained relevant data, of which 9 studies reported gastroenterologists administering sedatives, 5 studies reported endoscopy nurses administering sedatives under the supervision of the gastroenterologist, and 11 studies reported either an anesthesiologist, intensive care unit physician, or critical care physician administering sedatives.

"Gastroenterologist-directed sedation with propofol was noninferior to nongastroenterologist sedation," Dr. Wadhwa and his coinvestigators wrote. "The risk of complications was similar to [that of traditional sedatives] both during simple and advanced endoscopic procedures."

While the authors point to the sheer size of the study population as a strength of these results, they also note that because this is a study-level analysis rather than one conducted on an individual level, there is an inherent limitation to the study. Furthermore, variations from study to study in how propofol was administered to each patient may have caused heterogeneity in the findings of the meta-analysis. A large clinical trial would be the next logical step to affirm what this analysis has found.

However, they wrote, the difference in complications between propofol and other agents might not be clinically relevant owing to the lack of any serious complications such as intubations or deaths in the studies used in this meta-analysis.

Dr. Wadhwa and his coauthors reported no relevant financial disclosures.

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The use of propofol-mediated sedation and, in particular, anesthetist-directed sedation has become a hot-button item in the landscape of gastrointestinal endoscopy by virtue of its overall cost. Some experts place the cost of this at over $1.1 billion annually. Recent studies stemming from a large administrative database question the safety of propofol-mediated sedation when compared to the standard combination of a benzodiazepine and opioid. Still other studies have found that anesthesiologist-directed sedation did not improve the rate of polyp detection or polypectomy. Given these findings, our research group decided to embark upon a meta-analysis to further study the safety profile of propofol when compared to the combination of a benzodiazepine and opioid. We found that when compared with the traditional sedation agents, the pooled odds ratio of propofol-mediated sedation was not associated with a safety benefit in terms of the development of hypoxia or hypotension. We also found that the safety profile of propofol-mediated sedation was equivalent whether it was administered by a gastroenterologist or nongastroenterologist.

DR. VARGO

Does this answer the question? I think it is safe to say that for healthy patients undergoing elective upper endoscopy and colonoscopy, there is no safety benefit of propofol-mediated sedation, compared with traditional agents. Our data also suggest that with appropriate patient selection and training, endoscopist-directed propofol sedation is a viable alternative to the traditional sedation with a combination of a benzodiazepine and an opioid. The benefit of the agent may be its pharmacodynamics, which allow for a rapid targeting of the appropriate level of sedation and enhanced recovery, which lead to both augmented throughput and patient satisfaction. This has been well studied for endoscopist-directed propofol sedation when compared to traditional sedation regimens and may be true for anesthesiologist-directed sedation, although I know of no comparative data. Propofol sedation is a much more expensive alternative for healthy patients undergoing elective ambulatory endoscopy.

John Vargo, MD, MPH, AGAF, is the department chair of gastroenterology and hepatology at Cleveland Clinic and vice chairman of Cleveland Clinic's Digestive Disease Institute. He declared no conflicts.

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Join AGA in supporting GI research

Decades of research have revolutionized the care of many digestive disease patients. These patients, as well as everyone in the GI field, clinicians and researchers alike, have benefited from the discoveries of dedicated investigators, past and present. As the charitable arm of the American Gastroenterological Association (AGA), the AGA Research Foundation contributes to this tradition of discovery to combat the continued lower quality of life and suffering brought on by digestive diseases.

The AGA Research Foundation's mission is to raise funds to support young researchers in gastroenterology and hepatology. The foundation provides a key source of funding at a critical juncture in a young investigator's career.

Rani Richardson, 2016 AGA Investing in the Future Student Research Fellowship Award Recipient said, "Using this award, I plan to study the cytoskeletal intermediate filament proteins that are expressed in digestive-type epithelia, allowing me to better understand the molecular basis of GI diseases. My goal is to create a career in medical research and develop more ways to make biomedical research meaningful for clinical health care professionals, and ultimately for patients."

MS. RICHARDSON

By joining others in donating to the AGA Research Foundation, you can help fill the funding gap and protect the next generation of investigators.

Help provide critical funding to young researchers today by making a donation to the AGA Research Foundation on the foundation's website at www.gastro.org/contribute or by mail to 4930 Del Ray Avenue, Bethesda, MD 20814.

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Annual AGA Tech Summit returns to Boston in 2017

AGA is excited to return to Boston for its eighth annual Tech Summit on April 12-14, 2017, at the InterContinental Hotel. We've assembled prominent individuals in the physician, medtech, and regulatory communities to lead attendees through a program that's both informative and inspirational.

This is an ideal opportunity to explore critical elements impacting how GI technology evolves from concept to reality, including what it takes to obtain adoption, coverage, and reimbursement in a continually evolving health care environment.

We hope to see you this spring in Boston for a truly unique experience. Learn more and register at http://techsummit.gastro.org.

Have a novel idea or innovation? Apply for the AGA "Shark Tank"

Calling all companies and entrepreneurs with an innovative technology or Food and Drug Administration–regulated product. If you are looking to get it financed, licensed, or distributed, you are encouraged to submit an application for an opportunity to present during the "Shark Tank" session at the 2017 AGA Tech Summit. A panel of business development leaders, investors, entrepreneurs, and other strategic partners will provide valuable feedback.

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Access our MACRA resource collection

Prepare for 2017 with AGA's Medicare Access and CHIP Reauthorization Act of 2015 (MACRA) resources, which are available in the AGA Community resource library. This includes webinars, a tip sheet, and discussion threads.

The webinars and discussions in the community are available to members only, and contain information on the following topics:

- Intro to MACRA.
- 2016 PQRS Quality Reporting through the AGA Digestive Health Recognition Program.
- Preparing for MIPS.

The materials were collected from a series of webinars and eQ&As in December, when topic experts presented a series of webinars on relevant MACRA protocols to help clinicians prepare for Medicare changes starting this year.

Each webinar preceded an Ask the Expert session in the AGA Community forum. Members brought their wide range of questions to the forum, including discussions about MACRA basics, as well as meticulous situation-based recording scenarios.

This members-only library can be accessed at community.gastro.org/MACRA. For more information, including a timeline, downloadable guides, and the latest MACRA news, visit gastro.org/MACRA.

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Register for DDW® before the early-bird deadline

Registration for AGA members opened Jan. 11, and general registration opened on Jan. 18. Register by March 22 to save at least $80; registration is complimentary up until this date for member trainees, students, and postdoctoral fellows.

Why attend DDW?

Digestive Disease Week is the world's leading educational forum for academicians, clinicians, researchers, students, and trainees working in gastroenterology, hepatology, GI endoscopy, gastrointestinal surgery, and related fields. Whether you work in patient care, research, education, or administration, the DDW program offers something for you. For more information regarding why you should attend DDW, what's included in registration, and more, visit ddw.org.

Registration is also now open for the AGA Postgraduate course on May 6 and 7 at DDW 2017. Visit pgcourse.gastro.org to register.

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AGA comment on ABIM announcement

For more than a year, AGA has pushed the American Board of Internal Medicine (ABIM) to eliminate high-stakes testing and reform the maintenance of certification (MOC) system into one that's personalized and reflective of the realities of practice.

ABIM's listening tour is over. In December 2016, they announced the addition of an option for a 2-year "knowledge check-in." Although ABIM can point to nominal progress by making the assessment available outside its testing centers, they have not addressed cost, personalization, or the impact on patient care of such assessments.

Despite AGA's diligent efforts to co-create a new MOC process – which included creating G-APP, constant communication, and participation in numerous summits – ABIM deemed AGA's approach to be inconsistent with its own philosophy. Nonetheless, we are still in the midst of an evolution. AGA will continue to work with our sister GI and internal medicine societies to bring about change that supports meaningful lifelong learning through the least intrusive means possible.

In the meantime, if your professional situation requires you to maintain certification, please visit ABIM's blog for more information. AGA tools such as the Digestive Diseases Self-Education Program® can help you prepare.

Visit http://www.gastro.org/career-center/maintenance-of-certification for the latest updates and information on MOC.

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Use vancomycin or FMT

AGA CPU *from page 1*

and the emergence of highly virulent *C. difficile* strains. Patients with CDI and underlying IBD are at particular risk of hospitalization, intensification of medical therapies for IBD, and surgery. Rates of CDI have risen among both the ulcerative colitis and Crohn's disease populations, but are higher in the setting of ulcerative colitis, perhaps because these patients are more likely to have colonic dysbiosis.

CDI can present atypically in IBD. Underlying colitis leads to colonic dysbiosis and loss of resistance to bacterial colonization, which permits CDI to develop even when patients have not recently received antibiotics. Patients with IBD also tend to develop CDI starting at younger ages, more often acquire it from community settings, and may lack the typical colonoscopic features of CDI. Simple colonization with *C. difficile* without infection also is more common in patients with IBD than in those without IBD, the experts note.

The authors contradict guidelines from both the American College of Gastroenterology and Infectious Diseases Society of America by recommending consideration of vancomycin over metronidazole for treatment of CDI. Not only are *C. difficile* treatment failures with metronidazole rising, but vancomycin was more effective than metronidazole in a recent post hoc analysis (Clin Infect Dis. 2014;59[3]:345-54) of two large multicenter phase III trials. Another phase III trial (N Engl J Med. 2011;364:422-31) found vancomycin noninferior to fidaxomicin for CDI.

The experts recommend hospitalization for patients with IBD and CDI who present with profuse diarrhea, severe abdominal pain, a markedly increased peripheral blood leukocyte count, or other signs and symptoms of sepsis. Aggressive monitoring and treatment are especially important because it can be difficult to distinguish an IBD flare, which merits immunosuppression, from superimposed CDI, which might exacerbate the underlying infection. Few studies are available to help guide the decision about when to intensify steroids and other immunosuppressives in IBD patients with acute CDI. Thus, the experts suggest delaying this step until after starting therapy for CDI, but note that the decision should be individualized pending more robust data.

The authors emphasized the potential role of fecal microbiota transplantation (FMT), which has been shown to be very effective in both immunocompetent patients with CDI and those who are immunosuppressed, which includes those on IBD therapies. They recommend considering referral for FMT as early as the first recurrence of CDI in patients with IBD, particularly because of the strong safety and efficacy profile of FMT, the risk of complications from CDI in IBD patients, and scarce data on antibiotic therapy for recurrent CDI in the setting of IBD.

Dr. Khanna disclosed consulting relationships with Rebiotix and Summit Pharmaceuticals. Senior author Ciaran P. Kelly, MD, disclosed serving as a consultant to Merck, Seres Therapeutics, Summit Pharmaceuticals, and Takeda Pharmaceuticals. There were no other relevant disclosures.

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Oral, liquid supplement improves lactose intolerance

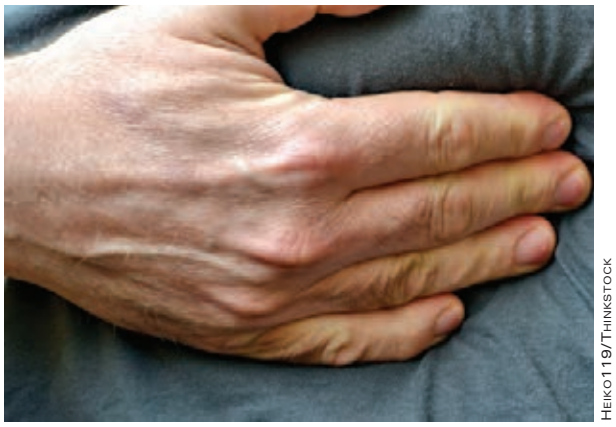
BY WHITNEY MCKNIGHT
Frontline Medical News

Adults with self-reported lactose intolerance were shown to have significant improvement in their clinical outcomes, including abdominal pain, after consuming an oral, liquid supplement intended to increase lactose-fermenting gut bacteria, M. Andrea Azcarate-Peril, PhD, assistant professor of medicine at the University of North Carolina, Chapel Hill, and her colleagues have shown in a small phase IIa study (Proc Nat Acad Sci. doi: 10.1073/pnas.1606722113).

In a placebo-controlled, double-blind trial, randomly assigned in a 2:1 ratio and conducted at two U.S. sites, highly purified (more than 95%) short-chain galactooligosaccharide (GOS) was given to 42 adults with a self-reported history of lactose intolerance, confirmed by a hydrogen breath test administered after a 25-g lactose challenge. The 20 controls were given a corn syrup mixture formulated according to the same sweetness and consistency as the test drug. Each study arm was started on its regimen at 1.5 g daily, with incremental increases in dose every 5 days until reaching 15 g. Beginning with their first dose at day 1, through day 35, all participants avoided consumption of dairy foods. Stool samples were collected from both groups at days 0 and 36. After day 36, all participants were asked to resume eating dairy foods. At day 66, stool samples were once again collected. Changes in the microbiome at all endpoints were measured by testing the stools via polymerase chain reaction.

Of the 30 study arm participants for whom complete stool samples were available, 27 were found to have had a bifidobacterial response at day 36, including a significant increase in the lactose-fermenting *Bifidobacterium*, *Faecalibacterium*, and *Lactobacillus* species. The remaining three participants in the study arm were considered nonresponders.

In an interview, Andrew Ritter, whose company, Ritter Pharmaceuticals, sponsored the trial, reported that of the 36 study arm participants who had reported abdominal pain pretreatment, 18 said they no longer had the pain at either endpoint, day 36 or day 66 ($P = .019$); three of 19 in the placebo group reported they no longer had abdominal pain at either endpoint. The study group was also six times more likely to report lactose tolerance at day 66 compared with their pretreatment levels ($P = .0389$); 28% of the placebo arm reported lactose tolerance at the endpoints. These results were previously published in Nutrition Journal in 2013 [doi:



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10.1186/1475-2891-12-160].

"We're super excited about these results," said Mr. Ritter. "This is really one of the first clinical studies in a lactose-intolerant population that shows changes in the microbiome." As to how long before the treatment will be ready for the Food and Drug Administration approval process, Mr. Ritter said, "We're probably just a couple of years away."

Two coauthors are advisers to Ritter Pharmaceuticals, which provided the highly purified GOS used in the study. The North Carolina Agriculture Foundation also provided funding for the study.

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High red meat consumption linked to diverticulitis

BY DEEPAK CHITNIS
Frontline Medical News

Men who consume higher quantities of red meat are at an increased risk of developing diverticulitis, especially if they're eating unprocessed red meat, according to a new study published in Gut.

"In our prior analysis from a large prospective cohort study, the Health Professionals Follow-Up Study (HPFS), we found that red meat intake, independent of fiber, may be associated with a composite outcome of symptomatic diverticular disease, which included 385 incident cases over 4 years of follow-up," wrote the authors, led by Andrew T. Chan, MD, AGAF, of Massachusetts General Hospital, Boston. Dr. Chan added that "in the present study, we updated this analysis, which allowed us to prospectively examine the association between consumption of meat (total red meat, red unprocessed meat, red processed meat, poultry, and fish) with risk of incident diverticulitis in 764 cases over 26 years of follow-up."

Dr. Chan and his coinvestigators conducted a prospective cohort study using subjects from the ongoing HPFS. Men who already had a diagnosis of diverticulitis, associated complications, inflammatory bowel disease, or a GI-related cancer at baseline were excluded from this analysis, leaving 46,461 eligible subjects. Of those, 764 developed diverticulitis.

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Subjects in the HPFS responded to questionnaires regarding their dietary habits, with questions specifically asking if they consumed red meat and/or unprocessed red meat and at what frequency. Nine responses to each question were possible, with the lowest being "never or less than once per month" to "six or more times per day." These questionnaires were sent out every 2 years during the follow-up period, with more extensive follow-ups – at which investigators would monitor medical history, disease outcomes, and so on – occurring every 4 years during the follow-up period. Red meat consumption was divided in quintiles of 1-5, with 1 being the lowest amount and 5 and being the highest.

The entirety of the follow-up period constituted 651,970 person-years. Average servings of total red meat per week were 1.2 in quintile 1, compared to 5.3 in quintile 3 and 13.5 in quintile 5. Those in the highest quintile had a multivariable risk ratio of 1.58 (95% CI, 1.19-2.11; $P = .01$), indicating a significantly higher risk for developing diverticulitis. In terms of unprocessed red meat, the average number of servings per week were 0.8 for the lower quintile, 3.2 for quintile 3, and 8.6 for quintile 5, yielding a risk ratio of 1.51 (95% CI, 1.12-2.03, $P = .03$) when comparing the highest and lowest cohorts. The increase in risk, however, leveled off after about 6 servings of red meat per week, and was found to be nonlinear ($P = .002$). Those who ate more servings of poultry or fish did not have a higher risk of diverticulitis.

"We also observed that unprocessed red meat, but not processed red meat, was the primary driver for the association between total red meat and risk of diverticulitis," the authors explained. "Compared with processed meat, unprocessed meat (e.g., steak) is usually consumed in larger portions, which could lead to a larger undigested piece in the large bowel and induce different changes in colonic microbiota [and] higher cooking temperatures used in the preparation of unprocessed meat may influence bacterial composition or proinflammatory mediators in the colon."

Although medical information and self-reports were validated, there are inherent possible limitations to self-reported data, such as misremembering the amount of meat consumed or reporting incorrect amounts. Residual confounding may have occurred despite adjustment of the data to account for it.

The National Institutes of Health funded the study. The authors reported no conflicts of interest.

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Mild, moderate hypertriglyceridemia tied to pancreatitis

BY MARY ANN MOON
Frontline Medical News

Mild to moderate hypertriglyceridemia, not just severe hypertriglyceridemia, is associated with increased risk of acute pancreatitis, according to a report published in JAMA Internal Medicine.

Severe hypertriglyceridemia is a recognized risk factor for acute pancreatitis, but "there is no consensus on a clear threshold above which triglycerides" raise that risk. The American College of Gastroenterology and The Endocrine Society state that levels over 1,000 mg/dL should be considered a risk factor, while the European Society of Cardiology and the European Atherosclerosis Society set the cutoff at 885 mg/dL, said Simon B. Pedersen, MD, of the department of clinical biochemistry, Herlev and Gentofte Hospital, Copenhagen University, and his associates.

To examine whether lower triglyceride levels also put patients at risk for acute pancreatitis, the investigators analyzed data from two large prospective longitudinal studies of the general Danish population. They included 116,550 consecutive men and women who provided nonfasting triglyceride measurements and were followed for a median of 6.7 years. During that time, 434 of these participants developed acute pancreatitis.

The risk of developing acute pancreatitis increased with increasing triglyceride levels starting at the mildly elevated level of only 177 mg/dL. Compared with normal triglyceride levels of less than 89 mg/dL, the risk increased with a hazard ratio of 1.6 at 89-176 mg/dL, an HR of 2.3 at 177-265 mg/dL, an HR of 2.9 at 266-353 mg/dL, an HR of 3.9 at 354-442 mg/dL, and an HR of 8.7 at 443 mg/dL or above, Dr. Pedersen and his associates said (JAMA Intern Med. 2016;176:1834-42).

This linear association persisted after the data were adjusted to account for potential confounders such as patient age, sex, body mass index, smoking status, alcohol intake, and education level, as well as the presence or absence of hypertension, diabetes, alcohol use, gallstone disease, and statin therapy.

This study was supported by the Herlev and Gentofte Hospital and Copenhagen University Hospital. Dr. Pedersen reported having no relevant financial disclosures; one of his associates reported ties to AstraZeneca, Merck, Omthera, Ionis, and Kowa.

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Half of new AMAs do not lead to primary biliary cholangitis

BY LORI LAUBACH
Frontline Medical News

Nearly half of newly detected antimitochondrial antibodies (AMAs) in clinical practice do not lead to a diagnosis of primary biliary cholangitis (PBC), according to a prospective study.

Geraldine Dahlqvist, MD, and her associates examined 720 patients whose AMA tests were registered during a 1-year census period. They were divided into groups according to whether they were newly diagnosed (275), were previously diagnosed (216), or had a nonestablished diagnosis (229) of PBC. Results showed the prevalence of AMA-positive patients without evidence of PBC was 16.1 per 100,000 inhabitants. It was four (all AMA-positive patients) to six (PBC patients) times higher in women than in men. Normal serum alkaline phosphatases (ALP) were 74%, and were 1.5 times above the upper limit of normal in 13% of patients, while cirrhosis was found in 6%. Among the patients with normal ALP and no evidence of cirrhosis, the 5-year incidence rate of PBC was 16%. Find the full story in Hepatology (doi: 10.1002/hep.28559).

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AGA Clinical Practice Update

Commentary: Scope guidelines are an improvement

BY DOUG BRUNK
Frontline Medical News

While the 2016 Multi-Society Task Force Endoscope Reprocessing Guidelines are an improvement over the 2011 guidelines, some of the minor changes are unlikely to guarantee against prevention of future outbreaks, according to Susan Hutfless, PhD, and Anthony N. Kalloo, MD.

"The prevention of future outbreaks is left to the manufacturers to modify their protocols and the endoscopy units to adopt the protocols rapidly," the authors, both from Johns Hopkins University, Baltimore, wrote in a commentary about the 2016 guidelines, which contain 41 recommendations and were endorsed by the AGA. "The guidelines will make it possible to better track the source of future outbreaks if the tracking and monitoring suggested is performed." They added that the current cleaning paradigm for duodenoscopes "is ineffective and these guidelines reflect changes to contain, rather than prevent, future outbreaks."

The commentary, which is scheduled to appear in the February 2017 issue of Gastroenterology (doi: 10.1053/j.gastro.2016.12.030), notes that the two major changes to the 2016 guidelines are language to maintain consistency with the 2015 Food and Drug Administration endoscope reprocessing communications, and statements suggesting greater monitoring and tracking of the endoscope throughout the clinical units and cleaning rooms, including timing of events and who performs the key steps. Dr. Hutfless directs the Johns Hopkins Gastrointestinal Epidemiology Research Center, while Dr. Kalloo directs the university's division of gastroenterology and hepatology.


DR. HUTFLESS

A specific change to the 2016 guidelines includes recommendation no. 5, which has been revised to recommend "strict adherence" to manufacturer guidance. "The expectation is that all personnel will remain up to date with the manufacturer guidelines and that there will be documentation of the training," Dr. Hutfless and Dr. Kalloo wrote. The 2016 guidelines specifically state that a "single standard work process within one institution may be insufficient, given differences among manufacturers' instructions and varied instrument designs." However, Dr. Hutfless and Dr. Kalloo point out that "an individual or group of individuals may need to be identified to keep up with the [Food and Drug Administration], [Centers for Disease Control], manufacturer, and professional societies in order to modify and implement the changes to the cleaning and training protocols and update the training of all individuals in the unit."

Recommendation no. 24 is new and includes a suggestion consistent with the 2015 FDA endoscope reprocessing communications. "Beyond the reprocessing steps discussed in these recommendations, no validated methods for additional duodenoscope reprocessing currently exist," the guidelines state. "However, units should review and consider the feasibility and appropriateness for their practice of employing one or more of the additional modalities suggested by the FDA for duodenoscopes: intermittent or per procedure culture surveillance of reprocessing outcomes, sterilization with ethylene oxide gas, repeat application of standard high level disinfection, or use of a liquid chemical germicide."

Dr. Hutfless and Dr. Kalloo pointed out the limitations of these modalities. They wrote, "the per procedure culture surveillance modality suggested by the FDA is not cost effective unless the unit's transmission probability of carbapenem-resistant Enterobacteriaceae (CRE) is 24% or greater. Sterilization with ethylene oxide is problematic because a unit that used this approach still encountered an endoscope with CRE detected by culture. This unit also incurred extra costs to purchase additional scopes due to the longer reprocessing time for sterilization" (Gastrointest Endosc. 2016 Aug;84:259-62).

In 2016, the FDA approved the first disposable colonoscope, which is expected to be available in the United States in early 2017. Dr. Hutfless and Dr. Kalloo ended their commentary by suggesting that a disposable endoscope with an elevator mechanism, though not currently available, could be a solution to several of the unresolved issues that were present in the 2003, 2011, and 2016 guidelines. "If the outbreaks persist after the use of disposable endoscopes, it is possible that it is some other product or procedure within the endoscopic procedure that is the source of the infectious transmission."

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DDSEPeight Digestive Diseases Self-Education Program

Quick quiz answers

Q1. Answer: B
Critique: The rebleeding rate for ulcers with an adherent clot with medical therapy alone is 30%-35%.

Randomized controlled studies have shown that endoscopic treatment of adherent clots (with combination therapy of epinephrine and coagulation) can decrease the rebleeding rate to less than 5%.

A meta-analysis has found that endoscopic therapy is superior to medical therapy for preventing recurrent bleeding from peptic ulcers with an adherent clot, but no differences in the need for surgery, duration of hospitalization, number of transfusions, or mortality rate are observed.

Epinephrine therapy alone is never recommended as it has been shown to be inferior to combination therapy, or thermal or mechanical therapy alone.

Choice C is not appropriate, as the clot needs to be pared down to expose underlying stigmata. Merely placing a clip over a clot is unlikely to ligate the vessel and lead to hemostasis.

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1. Jensen D.M., Kovacs T.O., Jutabha R., et al. Randomized trial of medical or endoscopic therapy to prevent recurrent ulcer hemorrhage in patients with adherent clots. Gastroenterology. 2002;123:407-13.
2. Kahi C.J., Jensen D.M., Sung J.J., et al. Endoscopic therapy versus medical therapy for bleeding peptic ulcer with adherent clot: A meta-analysis. Gastroenterology. 2005;129:855-62.

Q2. Answer: B
Objective: Recognize the features of common variable immune deficiency (CVID)–associated noninfectious gastrointestinal manifestations.
Explanation: This patient has gastrointestinal manifestations of CVID, which can present similarly to celiac disease or inflammatory bowel disease.

Histologically, intestinal biopsies will reveal villous atrophy, crypt hyperplasia, and intraepithelial lymphocytosis similar to celiac disease. However, while plasma cells are increased in celiac disease, they are absent in CVID.

The initial treatment strategy for CVID typically includes oral corticosteroids, either prednisone or budesonide, with other immunosuppressants such as the thiopurines or anti–tumor necrosis factor agents reserved for steroid-dependent or refractory disease.

Gluten-free diet is ineffective for the treatment of CVID-associated enteropathy. Intravenous immunoglobulin therapy reduces the frequency of infections associated with CVID, but does not affect the noninfectious GI symptoms.

While bacterial overgrowth can occur in CVID, it is typically the consequence of the luminal changes, not the cause.

Reference

1. Agarwal S., Mayer L. Gastrointestinal manifestations in primary immune disorders. Inflamm Bowel Dis. 2010;16:703-11.

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Mutations missed in early-onset colorectal cancer

BY BIANCA NOGRADY
Frontline Medical News

As many as one in six patients with early-onset colorectal cancer (CRC) have a pathogenic genetic mutation, but around one-third of these patients may not have met the criteria for genetic testing for at least one of their mutations under current guidelines, researchers say.

Rachel Pearlman, MS, CGC, of The Ohio State University Comprehensive Cancer Center, and her coauthors reported the results of multigene panel testing of 450 patients aged under 50 years, from 51 institutions, who had been diagnosed with CRC (JAMA Oncol. 2016 Dec 15. doi: 10.1001/jamaoncol.2016.5194).

Overall, 16% of patients were found to have a pathogenic or likely pathogenic cancer susceptibility gene mutations, with 83.3% having at least one gene mutation.

Thirty-seven patients had Lynch syndrome; 13 were MLH1, 16 were LSH2, 1 patient was MSH2/monoallelic MUTYH, 2 were MSH6, and 5 were PMS2.

"While the prevalence of Lynch syndrome reported herein (8.4%) is consistent with previous publications, this is the first study to our knowledge to determine the prevalence and spectrum of other hereditary cancer syndromes (8%) found in an unselected series of patients with early-onset CRC," the authors wrote.

Forty-eight patients (10.7%) had mismatch repair–deficient tumors, nine of which were in high-penetrance genes linked to CRC risk.

But for 145 patients, their genetic variants were of uncertain significance. Thirteen patients had mutations in high- or moderate-penetrance genes not traditionally associated with CRC, including ATM, ATM/ CHEK2, BRCA1, BRCA2, CDKN2A, and PALB2.

The authors pointed out that the multigene panel testing approach enables identification of hereditary cancer syndromes in patients who might not have otherwise met the criteria for testing.

"Importantly, 24 of 72 patients (33.3%) with pathogenic mutations did not meet NCCN Guidelines for at least 1 of the gene(s) in which they were found to have a mutation," the researchers noted. These included three patients with MMR-deficient tumors who had additional mutations in genes that would not have been assessed, one patient with an MMR-proficient tumor who was also found to have Lynch syndrome, and six patients with BRCA1/2 mutations.

"Previous studies have reported early-onset CRC in women with BRCA1 mutations and BRCA2 mutations in families with familial colorectal cancer type X," they noted.

The Ohio Colorectal Cancer Prevention Initiative (OCCPI) is supported by a grant from Pelotonia, and by the National Cancer Institute. Myriad Genetics donated next-generation sequencing testing. Nine authors disclosed ties with private industry, including Myriad Genetics.

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PERSPECTIVE

Multigene testing needed for diagnosis

This study illustrates the shortcomings of current algorithms for diagnosing and managing younger patients with CRC. First, although family history is one of the main components used to stratify an individual's risk for CRC, it is imperfect because only one in five younger patients with CRC reported having a first-degree relative with CRC. Second, although clinical criteria define the phenotypes typically associated with specific gene mutations, variability in penetrance and expressivity can result in overlap among the different hereditary cancer syndromes (e.g., BRCA germline mutations in younger patients with CRC).

The findings of this large population-based study demonstrate that the incorporation of multigene panel genetic testing in the evaluation of patients with CRC will increase the diagnosis of individuals with genetic predisposition to cancer and will expand current knowledge regarding the associated phenotypes, further supporting the cost-effectiveness of testing that can guide management for patients with cancer and their at-risk relatives. The study found germline mutations in one in six patients with CRC and has argued for comprehensive germline genetic testing of patients diagnosed at younger than 50 years.

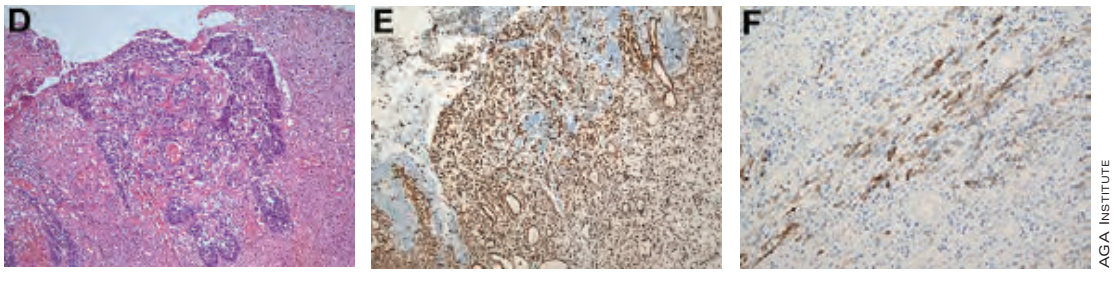
Eduardo Vilar-Sanchez, MD, PhD, is in the department of clinical cancer prevention and clinical cancer genetics program at The University of Texas MD Anderson Cancer Center, Houston. Elena M. Stoffel, MD, is in the department of internal medicine at the University of Michigan, Ann Arbor. These comments are adapted from an editorial (JAMA Oncology. 2016 Dec 15. doi: 10.1001/jamaoncol.2016.5193). No conflicts of interest were declared.

CLINICAL CHALLENGES AND IMAGES

The diagnosis

Answer to the "What's your diagnosis?" on page 6: So-called carcinosarcoma of the esophagus

The operative specimen microscopically harbors moderately differentiated squamous carcinomatous (the central nest) as well as sarcomatous (the remainder of the field) components with a transitional zone (Figure D). This composite feature is compatible with that of carcinosarcoma of the esophagus. Immune staining with vimentin is strongly and diffusely positive only in the mesenchymal element (Figure E), whereas staining with cytokeratin AE1/AE3 is positive not only for the epithelial component, but also for spindle-shaped cells (Figure F), suggesting evidence for gradual dedifferentiation of squamous carcinomatous cells into sarcomatous cells.



AGA INSTITUTE

Carcinosarcoma is a rare malignant entity, representing less than 2% of all esophageal neoplasms. It usually shows a bulky appearance of an intraluminal polypoid lesion owing to predominant sarcomatous development with little stromal proliferation. The exophytic intramurally growing tumors should include this disease in the differential diagnosis. Recent studies have supported the metaplastic theory regarding oncogenesis, whereas the collision concept has fallen out of favor; therefore, most esophageal carcinosarcomas are classified into so-called carcinosarcoma.[1] It has such short doubling time that it can clinically contribute to rapid growth and give early symptoms. This allows for earlier detection and treatment; therefore, this tumor was previously believed to carry a favorable prognosis despite its size, as in the case reported herein. However, current reports have shown the converse result that this earlier detection may not translate to a better outcome.[2] The sarcomatous component may accompany late metastasis targeting the liver as well as peritoneal and pleural surfaces. Treatment of this disease does not differ from that of other malignancies in the esophagus. Early detection and diagnosis, followed by operative resection, remains the mainstay for this entity to produce significant long-term survival.

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Gastric cancer yields to growth hormone antagonist

BY NEIL OSTERWEIL
Frontline Medical News

It sounds counterintuitive, but targeting a neuropeptide hormone produced in the hypothalamus may be an effective strategy for treating gastric cancer, the second most common cause of cancer deaths worldwide, investigators from China and the United States contend.

Growth hormone–releasing hormone (GHRH) and its receptor (GHRH-R) are found primarily in the anterior pituitary gland, but are also present in gastric cancers, other solid tumors, and lymphomas. Increased levels of GHRH-R in tumor samples from patients with gastric cancer are associated with poor outcomes, noted Andrew V. Schally, PhD, MD, DSc, of the University of Miami, and his colleagues at the Shantou (China) University Medical College.

Growth hormone–releasing hormone and its receptor are found primarily in the anterior pituitary gland, but are also present in gastric cancers, other solid tumors, and lymphomas.

Furthermore, an experimental peptide drug labeled MIA-602 that targets GHRH-R inhibited the growth of gastric cancer cell lines and human tumor xenografts in mice, the investigators reported in the journal PNAS.

"The GHRH receptor is both a biomarker that can confirm prognosis and a therapeutic target," Dr. Schally said in a statement.

Elevated GHRH-R expression in tumors

GHRH-R antagonists such as MIA-602 work through downregulation of the p21-activated kinase 1 (PAK1)–mediated signal transducer and activator of transcription 3 (STAT3)/nuclear factor–kappaB (NF-kappaB) inflammatory pathway. This pathway is involved in the interplay between inflammatory processes and intracellular signaling thought to be the cause of gastric cancer tumorigenesis and progression, the investigators explained.

They first looked for GHRH-R expression in gastric cancer samples from 106 patients, using immunohistochemistry staining of primary tumors and adjacent normal tissues. They found that gastric cancer tissues "exhibited robust expression of GHRH-R, compared with normal tissues."

In 50 samples, GHRH-R was determined to be overexpressed, and this overexpression was significantly associated with both greater tumor size (P = .031) and high pathologic tumor stage (P = .001). Increasing expression of GHRH-R was also significantly associated with worse overall survival (P less than .001).

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They confirmed these findings in samples from a multinational cohort of patients, which again showed that the highest levels of GHRH-R expression were associated with poor overall survival (*P* less than .001). The authors also looked at messenger RNA expression and gene copy number in 65 gastric cancer samples and 19 adjacent normal tissue samples, and found that GHRH-R mRNA was significantly higher in tumor tissues than normal control tissues (*P* less than .001).

The cancer suppression effects of MAI-602 work through inhibition of STAT3/NF-kappaB inflammatory signaling. In vitro and in vivo, MAI-602 decreased the expression of both GHRH and GHRH-R.

MAI-602 in vitro and in vivo

To see whether MAI-602 could inhibit the growth of gastric cancer cells, the investigators tried it at various doses in three human gastric cancer cell lines, and found that it inhibited cells in a dose-dependent fashion, compared with vehicle used as a control (*P* less than .001).

In addition, the experimental agent "exhibited remarkable inhibitory effects on tumor growth in vivo" in mice with human tumor xenografts (*P* less than .001).

Finally, they showed that the cancer suppression effects of MAI-602 work through inhibition of STAT3/NF-kappaB inflammatory signaling. In vitro and in vivo, MAI-602 decreased the expression of both GHRH and GHRH-R, whereas as a GHRH-R agonist increased levels of both the hormone and its receptor. They also demonstrated that PAK1 appears to be a critical mediator of STAT3/NF-kappaB activity, and that MAI-602 works primarily by blocking PAK1-mediated inflammatory signaling.

"MIA-602 remarkably inhibits the growth of human in vitro and in vivo through the suppression of PAK1–STAT3/NF-kappaB signaling. Our study strongly highlights the therapeutic potential of GHRH-R antagonists in the treatment of gastric cancer patients. Knowledge gained in our study will shed light on how to select the appropriate patients for personalized cancer therapy using GHRH-R antagonists," Dr. Schally and his coauthors wrote.

The study was supported by the Li Ka Shing Foundation, Chinese foundation, and government grants to individual researchers, as well as support from the the Medical Research Service of the U.S. Department of Veterans Affairs, South Florida Veterans Affairs Foundation for Research and Education, and the University of Miami.

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AGA GUIDELINE

Management of acute liver failure

BY AMY KARON
Frontline Medical News

Physicians should avoid routinely testing patients with acute liver failure (ALF) for Wilson's disease unless there is "high clinical suspicion" for the disorder, according to a new guideline from the AGA Institute.

Wilson's disease so rarely accompanies ALF that a positive test will have low predictive value, Steven L. Flamm, MD, of Northwestern University, Chicago, and his associates wrote in the February issue of Gastroenterology (doi: 10.1053/j.gastro.2016.12.026). Diagnosing Wilson's disease also is unlikely to change treatment "because liver transplantation is the ultimate outcome," they emphasize.

This is 1 of 11 recommendations in the guideline, which attempts to reconcile "many areas of controversy" in diagnosing, predicting outcomes, and managing ALF. Given the relative lack of randomized controlled trials, they make only one strong recommendation – to use N-acetyl cysteine in patients with acetaminophen-associated ALF. This guidance is based on three trials that yielded a "marginally significant mortality benefit with N-acetyl cysteine in conjunction with relatively minor toxicity," they state.

The guideline grades seven recommendations as "conditional" based on "very-low" quality evidence. These include the statement on Wilson's disease testing, plus suggestions to test and treat patients for herpes simplex virus (HSV) infection, to test pregnant patients for hepatitis E virus infection, and to test for autoimmune hepatitis. Case series report only about a 1% prevalence of HSV infection in ALF, and there is little information on diagnostic accuracy or treatment in this setting, the guideline states. Although acyclovir is relatively safe and inexpensive, data on efficacy are limited to "a suggestion on a case-report level that patients with acute hepatitis secondary to HSV do better with treatment than without."


Dr. Steven L. Flamm

The guideline also conditionally recommends against routine testing for varicella zoster virus and routine liver biopsy in ALF. The authors note only about 10 case reports of varicella zoster–associated ALF and few data on how liver biopsy results in ALF alter treatment plan, outcome, or the choice to seek liver transplantation. The experts do recommend prognostic scoring with Model for End-Stage Liver Disease, which analyses have found to be more sensitive than King's College Criteria, they wrote.

The guideline conditionally recommends against empirically treating elevated intracranial pressure in ALF, on the basis of five randomized trials that found no overall mortality benefit of moderate hypothermia, hypertonic saline, L-ornithine, L-aspartate, intravenous mannitol, or hyperventilation.

The experts cite insufficient evidence to recommend using N-acetyl cysteine in patients whose ALF is not associated with acetaminophen exposure. Likewise, they find few data to make any recommendation about using extracorporeal liver support systems outside clinical trials. Although such systems can "potentially" buy time for patients to either spontaneously recover without transplant or survive longer on the transplant list, three systematic reviews found "no clear effect on mortality," and randomized trials reported either null results or a "marginally significant survival benefit" in the face of steep costs and potentially significant toxicities, the authors emphasize.

There were no relevant financial disclosures.

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CMS nixes Part B drug payment demonstration

BY GREGORY TWACHTMAN
Frontline Medical News

A controversial demonstration project that would have tested new methods to pay for the drugs administered in medical offices has been canceled by the Centers for Medicare & Medicaid Services. The agency received considerable backlash from physicians, Congress, and others when the demonstration project was announced in March 2016.

"After considering comments, CMS will not finalize the Medicare Part B Drug Payment Model during this administration," the agency said in a statement. "The proposal was intended to test whether alternative drug payment structures would improve the quality of patient care and the value of Medicare drug spending."

The agency said it received "a great deal of support from some" for the proposed demonstration. However, "a number of stakeholders expressed strong concerns about the model. While CMS was working to address these concerns, the complexity of the issues and the limited time available led to the decision not to finalize the rule at this time."

The demonstration project was designed to test new methods to "improve how Medicare Part B pays for prescription drugs and supports physicians and other clinicians in delivering high quality care," according to a fact sheet published in March.

Under the project, medical practices would have been divided into two groups. A control group would continue to be paid for Part B drugs

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at the current rate of 106% of average sales price (ASP), while the other would have been paid at 102.5% of ASP plus a flat fee of $16.80 per drug payment. Starting in January 2017, each group would have been further subdivided with a portion of each being subjected to value-based purchasing tools.

One key criticism of the demonstration project centered on the proposed randomization of practices, which was based on primary care service areas (clusters of zip codes with similar Part B medical care patterns). That randomization scheme could have caused different payment levels – and patient out-of-pocket spending – for geographically close areas. Further, participation in the demonstration project would have been mandatory, with no mechanism to opt out.

"This is a model for how Washington should, but often doesn't, work," American Medical Association President Andrew W. Gurman, MD, said in a statement. "We are grateful that CMS came to the right decision after listening to stakeholders."

An analysis of the proposed demonstration project by Avalere found that specialists would likely

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see a decrease in their drug payments under the proposal, while primary care doctors would likely see an increase, and that 7 of the 10 drugs most affected by this proposal were drugs used to treat cancer.

The AGA expressed concern that many of the drugs that gastroenterologists administer would be included in this proposed new payment model and that the model would affect the patients treated for the most complex conditions, such as Crohn's disease and ulcerative colitis. Ultimately, this payment model would limit patient access to specialist care. The AGA urged CMS to include all stakeholders in the development of approaches to control Part B costs.

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PRACTICE MANAGEMENT TOOLBOX:

Building a cancer genetics and prevention program

BY XAVIER LLOR, MD, PHD

Gastroenterologists offer more than just high-quality colonoscopy for colon cancer prevention. We often are the specialists who first recognize a genetic cancer syndrome during our endoscopy or clinic sessions. The patient who piqued my interest in colon cancer genetics was a 24-year-old woman who was referred for postoperative nausea after a hysterectomy for early-stage uterine cancer (that alone should have raised alarm bells). Endoscopy revealed (by happenstance) a stomach coated with polyps. This led to a colonoscopy and diagnosis of familial adenomatous polyposis (uterine cancer within FAP is unusual but reported, for those of you studying for boards). In 1991, no coordinated genetics program existed within my practice so I arranged referrals to genetic counselors, surgeons, and pathologists. This led to the discovery of FAP and early stage (and curable) cancers in her two brothers and her father, in addition to extended pedigree analysis that established multi-organ cancer risks in other relatives. Years later, she brought her two adopted children to meet me and told me of lighting candles in my honor during an American Cancer Society walk. This is why we become doctors.

In this month's column, Dr. Xavier Llor describes the cancer genetics program he and others have built at Yale. It provides practical steps that can be taken by health system or community-based gastroenterologists to recognize and manage these complex syndromes. We are the specialists on the front lines and Dr. Llor helps us provide the coordinated care our patients expect from us.

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

Among all common cancers, breast and colon have the highest percentage of cases that are due to hereditary syndromes. Many of the responsible genes have been identified, and the last few years have seen an increase in uptake of genetic testing supported by the refinement of the clinical criteria suggestive of these syndromes as well as the clear improvement in outcomes as a result of the adoption of cancer preventive measures in mutation carriers.[1] In spite of this, genetic testing for colorectal cancer (CRC) syndromes is not ordered as often as it should be according to the prevalence of these syndromes.[2]

In contrast, testing for hereditary breast cancer has become more generalized, and the threshold for ordering genetic testing in the latter is often lower than for CRC. The are several reasons for this: 1) much greater awareness, by both providers and the general public, of hereditary breast cancer conditions; 2) fewer providers with expertise in CRC genetics; 3) lack of a systematic approach to identify patients with potential CRC syndromes; and 4) absence of a clear premorbid phenotype for the most common of all CRC syndromes, Lynch syndrome.[3]

The recent recommendation in practice guidelines to screen all CRC tumors for Lynch syndrome either with immunohistochemistry to evaluate mismatch repair (MMR) protein expression or through tandem repeat analysis to test for microsatellite instability[4] has highlighted that about 10% of all CRCs (a percentage consistently seen in different ethnic groups[5]) need further cancer genetic evaluation, and many will require sequencing of germline DNA. Although data on cost-effectiveness of this approach are somewhat conflicting,[6,7] it is sensible because it is systematic, and studies have shown an increase in diagnostic yield through universal tumor screening.[8] Unfortunately, in practice, often suspicious tumor testing results are not followed up by cancer genetics referrals, and many patients with CRC syndrome remain undiagnosed.

Patients with oligopolyposis (fewer than 100 polyps over time) also present diagnostic challenges. Some have attenuated familial adenomatous polyposis because of an APC mutation or MUTYH-associated polyposis. Recent findings have revealed other less commonly mutated genes that also result in oligopolyposis and a significant CRC risk: polymerases POLE and POLD1,

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GREM1, MCM9, or NTHL1. Because of the relatively low number of polyps in many of these syndromes and the lack of a systematic strategy to add up all polyps diagnosed over time, we not uncommonly fail to suspect some polyposis syndromes. Furthermore, the mixed pattern of polyps that is often associated with some of the mentioned mutated genes adds an extra challenge to diagnosing these cases.

Once individuals with CRC syndromes are identified, the challenge is to provide them with the care that they need, because many gastroenterologists, oncologists, and other health care providers are not extremely familiar with the current options for these patients.

In summary, there is a need to find systematic ways to triage and appropriately refer patients with a potential CRC syndrome to cancer genetics specialists so patients and their families can benefit from proper diagnosis and cancer preventive measures.

Building a comprehensive cancer genetics program

Although implementing systematic approaches is key to selecting individuals at risk, the complexity of caring for these patients demands a service that can stand up to the multiple challenges. For instance, most CRC syndromes are in fact multi-cancer syndromes with an increased risk of cancer and other pathologies in different organs beside the colon. Furthermore, the psychological implications of having a heritable cancer condition often take an important toll on affected families, with common feelings of guilt for having passed the mutated genes to the offspring.

Thus, for the best care to be provided to affected families, there is a tremendous need for well-organized and comprehensive cancer genetics services that are capable of responding to the multiple needs of these families so state-of-the-art cancer preventive measures can be carried out and multilevel support can be provided. The mentioned considerations were the guiding force in the creation of the Smilow Cancer Genetics and Prevention Program (SCGPP) at Yale. Thus, we established a comprehensive program that brings together health professionals specializing in different aspects of these patients' care that ensures their proper attention in a longitudinal fashion, making the program their home for health care.

We integrated in the program, among others, physician leaders in gastrointestinal, breast, gynecological, endocrine, and genitourinary high-risk malignancies; genetic counselors; an advanced practice registered nurse specializing in cancer prevention and risk reduction; and a scientific director who leads the Clinical Laboratory Improvement Amendments–certified laboratory at Yale that offers in-house genetic testing, including full-exome sequencing. The SCGPP was started in July 2015, and it currently provides more than 250 new consultations per month.

The following are several key elements that I consider important for a cancer genetics program and how they have been addressed at the SCGPP.

Identification through risk stratification

Because the identification of all individuals who can benefit from cancer genetics consultation is complex yet essential, a comprehensive approach with different strategies is often necessary.[9] Universal tumor testing is an effective tool, but other complementary approaches such as the use of questionnaires can also contribute to identifying patients in need for cancer genetics assessment.

In our program, the pathology department tests for MMR protein expression in all bowel and endometrial tumors. The ones that have loss of expression of an MMR protein are reported to the SCGPP, which contacts the patient's providers to request a referral. In a relatively short implementation time, this has already resulted in a significant increase in the number of patients referred for cancer genetics consultation and new Lynch syndrome diagnosis. On the other hand, two brief and simplified questionnaires have been developed and distributed in clinics, one for health providers and one administered directly to patients. The questionnaires contain questions related to the patient's

DR. LLOR

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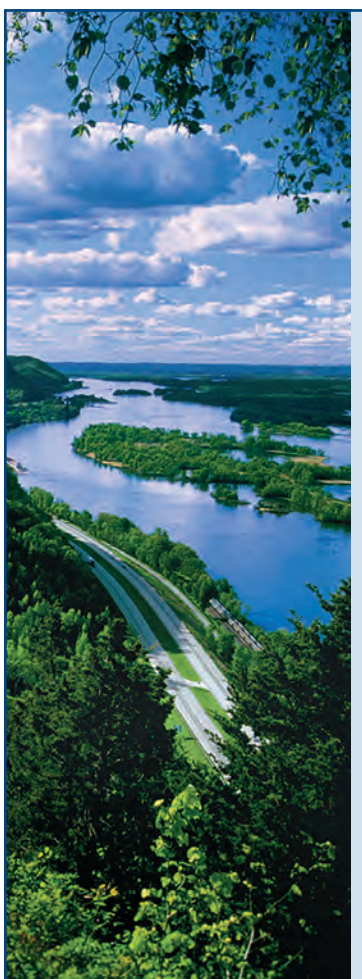

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own cancer history, polyp history, cancer screening tests, and family history. The first one assists health care providers in identifying individuals. The second one is completed by patients, collected, and reviewed by a genetic counselor. Suitable patients are invited to a cancer genetics consultation through their primary health care providers. A third questionnaire directed to endoscopy services will be rolled out soon. This collects information on completed endoscopy procedures, polyps and cancers found, and family history.

The program is currently working with information technology to develop a system to pull from the electronic medical record (EMR) relevant information on the patient's own medical history, family history, and endoscopy findings. A set of criteria has been established so relevant information will generate an alert for prompt referral for the SCGPP.

Because education of health care providers about these conditions is essential to foster collaboration and to help them better understand about cancer risk assessment, genetics, and what the SCGPP can offer to some of their patients, sessions are routinely held with some of them to discuss different aspects on cancer genetics.

We are quickly moving from single gene testing to panels of genes tested at once. This has resulted in unexpected findings such as mutated genes not initially suspected.

In summary, a comprehensive and coordinated approach is key to substantially expand the number of individuals identified and referred for cancer genetics assessment.

Genetic testing

During the last few years we have witnessed changes at different levels around genetic testing that are having a tremendous impact. Some of these changes pose significant new challenges that require rapid adaptation on the providers' side. Thus, we are quickly moving from single gene testing to panels of genes tested at once. This has resulted in unexpected findings such as mutated genes not initially suspected or variants of unknown significance that often should be interpreted in the context of the personal and family history of cancer because of the lack of definite information on their potential pathogenicity.[10]

Adding to that, genome-scale tumor sequencing is becoming more common as it increasingly informs on the types of anti-tumor therapies to be selected for a specific patient (precision medicine). This approach is revealing some unexpected information because in some cases it has helped identify significant mutations in the germline.[11]

Finally, the increasing number of commercial laboratories offering genetic testing has resulted in more competition and lower prices, in some cases to a point that direct-to-consumer charges may be even lower than insurance copayments. This is contributing to a rapid increase in individuals being tested including patients who otherwise would unlikely have been tested in the past because of lack of fulfillment of insurance criteria. The challenge for us is to be ready to help navigate the increasing amount of information obtained as a result of all these changes.

Integration of electronic platforms

In an era of full implementation of EMRs, a cancer genetics program should not simply adapt to the new environment but fully embrace it and explore the possibilities that come with it. Thus, from its inception, the SCGPP has been embracing the electronic plat-

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forms to the maximum extent so the clinical operation is streamlined and documentation is well displayed and accessible in the EMR. The Yale health care system uses EPIC (Epic Systems, Verona, Wisc.) as its EMR, and the SCGPP uses Progeny (Progeny Genetics LLC, Delray Beach, Fla.) to collect data, construct family pedigrees, and build the research registry of the Program. A joint effort by the developers of both systems has resulted in integration at different levels.

Thus, after a referral is received, patients are called, registered, and asked several questions including their own cancer and polyp history as well as their family history of cancer. This assists in triaging patients to the most appropriate SCGPP provider: a genetic counselor, a disease physician leader, or a combined visit according to the established internal protocol.

In all cases, for new patients with GI cancer syndromes, a combined appointment of a genetic counselor and the GI physician leader is scheduled. At the same time, patients are sent an email with a link to the Progeny online questionnaire that includes personal and family history of cancer as well as extensive clinical information. Once the questionnaire is completed, the program generates a preliminary pedigree that patients can print, and the SCGPP gets a message communicating that the patient has completed this questionnaire. Therefore, when patients are seen on consultation, providers already have the provisional data and pedigree. During the visit, information is verified and edited as needed, and the finalized pedigree goes live through a hyperlink in the EMR. Every revision results in an updated pedigree visible through the mentioned hyperlink. This process saves a considerable amount of time to the providers and increases clinic efficiency.

Informed consent for the research registry is also fully electronic, with signatures recorded in tablets that transmit the signed document to a secure server.

The necessary team approach

Another essential component of a cancer genetics program like this is the integrated and comprehensive approach to patients. Thus, in our Program, the combined appointments for GI patients with the genetic counselor and the physician leader cover all different aspects of care, and a complete plan is suggested and discussed. Once the initial assessment is finalized and genetic testing results (if ordered) are completed, patients are followed prospectively to ensure that prophylactic and cancer prevention measures are undertaken according to the updated standards of care. Complex cases are discussed with the entire team in the weekly case conference that is always followed by a scientific conference with alternating topics such as journal club, practice improvement, ongoing research projects, and extensive case reviews.

Take-away points:

1. GI cancer genetics is becoming more complex and there is an increasing need for comprehensive and integrated services to help identify and care for families affected by hereditary GI cancers.
2. A multifaceted approach is needed to increase identification and care for these families.
3. There is an opportunity for electronic platforms to help improve the care of these families.

Network integration

Although the needs for cancer genetics can be found in any corner of the map, it is not realistic to believe that services like this can be provided in a consistent fashion without being part of a bigger program umbrella. In our case, Yale's Smilow Cancer Center charged the SCGPP with the duty to provide high quality and consistent cancer genetics services to the entire network that currently includes a total of 5 affiliated hospitals and 10 care centers.

For this to happen, all cases seen outside the main campus are brought up for discussion in the weekly case conference. Furthermore, counselors distributed throughout the network routinely also see patients in the main office, and when away, they participate in case conference and scientific conference via teleconference or videoconference. All this is considered critical to facilitate a cohesive and state-of-the-art program that extends beyond the main campus.

Recently, telemedicine is used to provide consultations directly to patients so the program's services are brought to the most remote locations. A senior genetic counselor is in charge of the network operations to facilitate all these services and help engage providers in the corresponding facilities. She regularly attends tumor board meetings in the local hospitals to help disseminate knowledge in cancer genetics as well as to assist in the identification of patients who can benefit from referral to the SCGPP.

Surveillance and recall program

Key to the success of a cancer genetics program is successfully coordinating care so preventive tests and measures are performed to decrease cancer risk. The SCGPP aims to be the home for familial and hereditary cancer patients. For these patients, this implies a strong commitment to their needs, with a special emphasis on the appropriate prophylactic and cancer surveillance measures.

The registry database provides an extremely useful tool to track scheduled tests and procedures and to generate reminders. The advanced practice registered nurse meticulously follows them and ensures proper completion and review. She follows up on the scheduling of the specific tests, reviews results once these tests are completed, and brings them back to discussion with the physician leader. She also follows up on incomplete tests and helps to bring down potential barriers in the performance of these tests. Another key aspect of her job consists of facilitating the assistance of psychological support or risk reduction through lifestyle changes, such as smoking cessation or weight reduction, to patients in need of such services.

Cancer genetics research

Key to an academic program in cancer genetics like this one is to facilitate the study of familial and syndromic cancers, including aspects such as phenotype characterization or the efficacy of chemopreventive approaches. To accomplish this, a patient registry is essential. Registries are extremely useful tools that facilitate data accrual and analysis. The SCGPP registry is based on the Progeny suite that incorporates not only clinical and pedigree building components but also the genotype and sample management systems (LAB and LIMS). Thus, a fully searchable and robust database and biological sample repository have been created, and all patients are approached about participating in this institutional review board–approved registry.

Cancer prevention in nonfamilial, nonsyndromic cases

Some nongenetic factors such as diet, physical activity, or toxic exposure seem to underlie the important differences seen in CRC incidence around the world.[12] Thus, interventions at this level can potentially have a very high impact for cancer prevention in all individuals. In fact, even individuals with genetic mutations that carry a high risk for developing malignancies can see their risk modified by addressing lifestyle/environmental factors.[13]

Key to the success of a cancer genetics program is successfully coordinating care so preventive tests and measures are performed to decrease cancer risk.

Therefore, the SCGPP has created tools for assessment and risk stratification that take the mentioned factors into account and create a roadmap for primary prevention. The tools include questionnaires on all environmental exposures, lifestyle factors, and medications the patient is exposed to and that can influence cancer risk. The information is reviewed in a special clinic session, and all services to help modify risk factors are offered to the patient.

Conclusions

There is a clear need for GI cancer genetics services to reach all patients who can benefit from them, and at the same time the field is rapidly growing in complexity. More than ever, these services demand a multidisciplinary approach, with experts leading the care of these patients in a coordinated fashion with the rest of the health care community. However, payers have not fully recognized these complexities, and some

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critical aspects, such as genetic counseling services, are not always properly reimbursed. As we shape up the present and future of health care, which should be fully personalized and patient centered on addition to embracing new ways of delivering it, we need to engage all the players and help them understand what this takes and the rewards in the form of better outcomes that will come with it.

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