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GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

GREGORY TWACHTMAN/ FRONTLINE MEDICAL MEDIA

Biosimilar drugs are used for gastroenterological indications as well as for rheumatologic and dermatologic treatments.

Supreme Court rules to speed biosimilar drugs to market

BY ALICIA GALLEGOS
Frontline Medical News

The U.S. Supreme Court has ruled that biosimilar companies can take their versions of biological drugs to the market 6 months sooner in a precedential ruling that could mean quicker access to less expensive medications.

The unanimous ruling overturns an appeals court ruling in favor of California-based Amgen that had barred competitor Sandoz from marketing its biosimilar of Neupogen (filgrastim) until 6 months after Food and Drug Administration approval. Justices held that the Biologics Price Competition and Innovation Act of 2009 (BPCIA) allows biosimilar applicants to provide notice of commercial marketing prior to obtaining licensure by the FDA.

Carol Lynch, global head of Biopharmaceuticals at Sandoz, said the ruling helps to eliminate unnecessary barriers so that patients can access more affordable medicine in a more timely manner.

"Biosimilars offer significant value to patients, providers, and payers, increasing the number of

See **Biosimilar** · *page 4*

Upadacitinib advances to phase III for Crohn's

JAK1 inhibitor induced remission.

BY MICHELE G. SULLIVAN
Frontline Medical News

AT DDW

CHICAGO – An investigational inhibitor of the Janus-1 kinase receptor induced clinical and endoscopic remission at several doses in patients with long-standing, treatment-resistant Crohn's disease.

The two highest doses of upadacitinib (ABT-494; AbbVie) also allowed about 30% of patients to rapidly withdraw systemic steroids and stay in remission during the 16-week dose-finding induction trial, William Sandborn, MD, AGAF, said at the annual Digestive Disease Week®.

"This rapid steroid tapering was a unique feature of the trial," said Dr. Sandborn of the University of California, San Diego. "Usually, during induction trials, steroids are held fixed at 20 mg–30 mg throughout the trial and then withdrawn to maintenance levels."

The placebo-controlled study, dubbed CELEST, investigated upadacitinib in four doses. None of the doses tested achieved both of the coprimary endpoints of clinical and endoscopic remission. Additionally, clinical remission relative to placebo didn't achieve statistical significance in any group until the results were analyzed with a revised stool frequency cut point of less than 3 per day, rather

See **Crohn's** · *page 21*

Cirrhosis linked to higher stroke risk

BY MARY ANN MOON
Frontline Medical News

Cirrhosis of any kind was associated with an increased risk of stroke, especially hemorrhagic stroke, in a large nationally representative cohort study reported online June 5 in JAMA Neurology.

Cirrhosis is known to be associated with "extrahepatic hemorrhagic and thrombotic processes, such as GI bleeding and venous thromboembolism. [But] the cerebrovascular complications of cirrhosis are comparatively less well understood." Previous studies of the association with stroke have been small and have yielded conflicting results, with some finding a reduced incidence of stroke and others finding an increase among cirrhosis patients, said Neal S. Parikh, MD, of the Fell Family Brain

See **Cirrhosis** · *page 13*

News from DDW2017 Digestive Disease Week®
in this issue

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CLINICAL CHALLENGES AND IMAGES

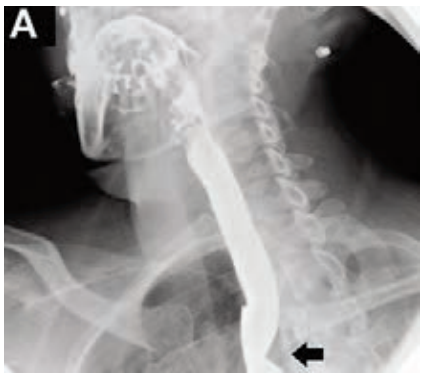
What's your diagnosis?

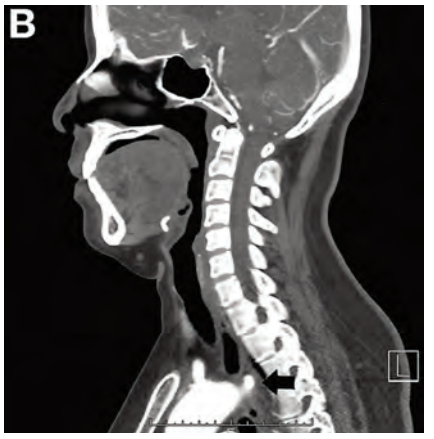
By Eric Wee, MD, and Ma Clarissa Buenaseda, MD. Published previously in Gastroenterology (2013;144:273,467,468).

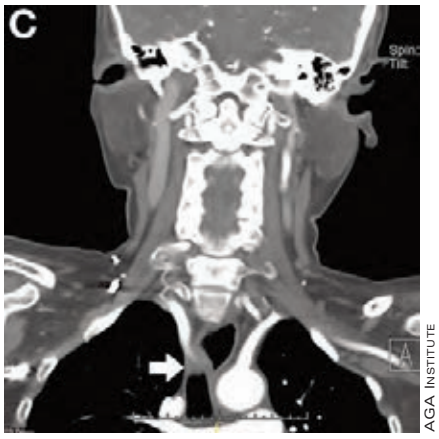
A 51-year-old woman was admitted to our hospital for a myocardial infarction. During the admission, she complained of chronic dysphagia lasting more than 1 year.

Her medical history included a stroke with good functional recovery and no documented oropharyngeal dysphagia during that admission. Her complaint of dysphagia was worse with solid foods. She localized her symptoms to the level of the suprasternal notch.

A neurologic examination did not reveal any new focal deficits and there was no alarming feature such as weight loss or anemia.







AGA Institute

In view of her myocardial infarction, a barium swallow study was performed, which showed a persistent smooth extrinsic indentation on the posterior aspect of the esophagus at the level of T4–T5. There was no retention of contrast in this area (Figure A, arrow). Incidentally, she had a prior computed tomography four-vessel angiogram study of the circle of Willis, performed during her previous admission. The CTA showed a vessel compressing on the esophagus posteriorly causing proximal dilatation. This corresponded to the level of indentation noted on the barium swallow (Figures B and C, arrows).

The diagnosis appears on page 20.

LETTER FROM THE EDITOR: Brace yourself, but have a nice summer

By the time this column appears in print we will know whether the U.S. Senate passed a version of the GOP health care bill. If so, millions of our patients will be at risk of losing insurance coverage in the name of tax and deficit reduction. I refer you to an article I wrote for the June issue of Clinical Gastroenterology and Hepatology about the potential transition from Obamacare to Trumpcare.

Our "Flashback" article this month concerns another long-running Congressional issue: repeal of the Sustainable Growth Rate and implementation of value-based reimbursement. We thank Dr. Larry Kosinski for his commentary and for successfully creating the first GI-specific alternative payment model to be endorsed by CMS.

Elsewhere in this issue you will read quite a bit about biosimilars and their place in IBD therapy. Several new biologic therapies are emerging rapidly for patients with IBD refractory to current regimens. We find out that cirrhosis is associated with increased risk of stroke and are reminded about the importance of adenoma detection rates in reducing the risk of interval colon cancers. Finally, in the practice management section you can find out how to use social media in conducting population research.

Have a restful summer and brace yourself for what might come.

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

DR. ALLEN

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References: 1. IMS Health, NPA Weekly, May 2017. **2.** Rex DK, DiPalma 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.** SUPREP Bowel Prep Kit [package insert]. Braintree, MA: Braintree Laboratories, Inc; 2012. **4.** Rex DK, Schoenfeld PS, Cohen J, et al. Quality indicators for colonoscopy. *Gastrointest Endosc.* 2015;81(1):31-53.

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Cost was not part of the ruling

Biosimilar *from page 1*

treatment options available to patients across many disease areas at a reduced cost to the health care system," Ms. Lynch said in a statement. "The justices' unanimous ruling on the notice of commercial marketing will help expedite patient access to life-enhancing treatments. We also appreciate the clarity provided on the patent dance, which will help the biosimilars industry move forward."

In a statement, an Amgen spokeswoman said the company was "disappointed in the court's decision on the notice of commercial marketing," but that it will "continue to seek to enforce our intellectual property against those parties that infringe upon our rights."

The "patent dance" referred to by Ms. Lynch is the often lengthy process by which companies marketing brand name and biosimilar medications spar and undergo legal proceedings before the biosimilar can enter the market.

In this case, Sandoz filed an application with the FDA in May 2014 seeking approval to market Zarxio (filgrastim-sndz). Amgen, the manufacturer of the reference product, has marketed Neupogen since 1991 and holds patents on methods of manufacturing and using filgrastim. In July 2014, the FDA accepted Sandoz' application for review. In October 2014, Amgen sued for patent infringement, alleging that Sandoz failed to adhere to the BPCIA by unlawfully providing its notice of commercial marketing before FDA licensure, among other arguments.

The U.S. Court of Appeals for the Federal Circuit in Washington ruled in favor of Amgen, holding that Sandoz must wait for an FDA license before marketing its biosimilar, which meant another 6-month waiting period. The Supreme Court disagreed. Justices based their decision on the plain language of the BPCIA, ruling that the statute allows for applicants to provide marketing notice either before or after receiving FDA approval.

In a statement, the Pharmaceutical Care Management Association said the Supreme Court's ruling on biosimilars will help create more competition among costly biologic medications, "which is the key to reducing overall prescription drug costs for consumers, employers, government programs, and others."

See page 10 for AGA's letter to the FDA about biosimilar interchangeability.

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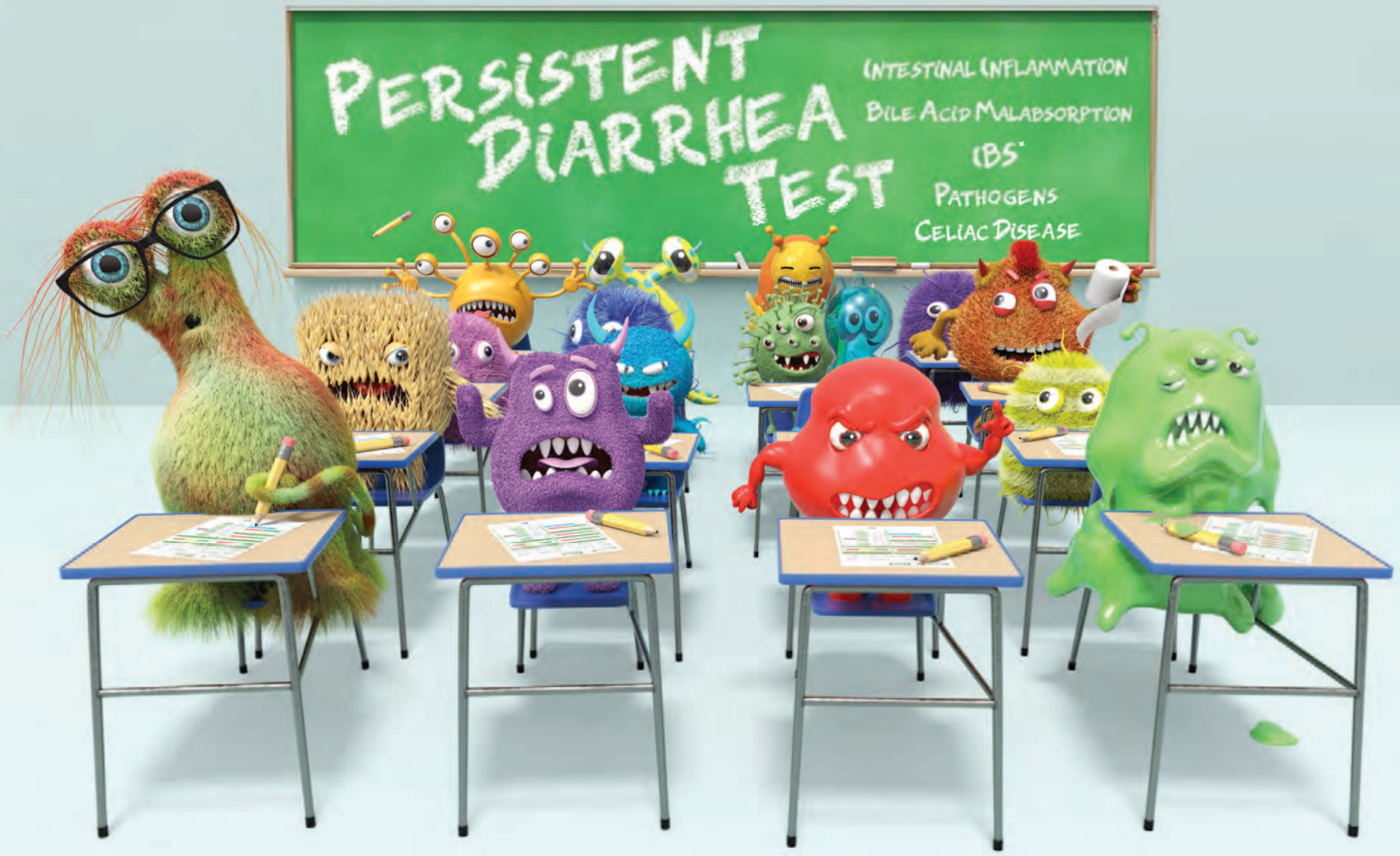
AGA Resource

AGA offers education materials for health care professionals and patients at www.gastro.org/biosimilars.



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References: 1. DuPont HL. Persistent diarrhea: a clinical review. *JAMA.* 2016;315(24):2712-2723. **2.** Juckett G, Trivedi R. Evaluation of chronic diarrhea. *Am Fam Physician.* 2011;84(10):1119-1126. **3.** Gujral N, Freeman HJ, Thomson AB. Celiac disease: prevalence, diagnosis, pathogenesis and treatment. *World J Gastroenterol.* 2012;18(42):6036-6059. **4.** Hodges K, Gill R. Infectious diarrhea: cellular and molecular mechanisms. *Gut Microbes.* 2010;1(1):4-21. **5.** Spiller R, Lam C. An update on post-infectious irritable bowel syndrome: role of genetics, immune activation, serotonin and altered microbiome. *J Neurogastroenterol Motil.* 2012;18(3):258-268. **6.** Barkun AN, Love J, Gould M, Pluta H, Steinhart H. Bile acid malabsorption in chronic diarrhea: pathophysiology and treatment. *Can J Gastroenterol.* 2013;27(11):653-659.

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FLASHBACK TO 2013

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

This month, our "Flashback" article highlights Congress's long-term attempt to repeal the Sustainable Growth Rate formula for physician reimbursement and base our payments on patient health outcomes. Although the Medicare Access and Quality Improvement Act of 2013 (highlighted in our 2013 article) sponsored by Rep. Michael Burgess (Tex.) and passed unanimously in the House of Representatives did not become law, it did set the stage for the passage of H.R.2 – the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA). Also sponsored by Rep. Burgess and passed with bipartisan support, MACRA has now become the foundation for our transition from fee-for-service reimbursement to value-based care.

In just 2 short years, we have all become familiar with terms like MIPS (Merit-based Incentive Payment System) and APMs (Alternative Payment Models). These two methods of reimbursement will become the backbone of a growing percentage of our revenue going forward. Gastroenterologists should embrace these programs and work to find our unique position in the health care value chain.

A less well-known component of the MACRA, the Physician Focused Payment Model (PFPM), allows physicians to develop unique value-based payment models that can then be deployed by the Centers for Medicare & Medicaid as APMs. Project Sonar, an intensive medical home for patients with inflammatory bowel disease, was recently approved as the first PFPM, which may represent an opportunity for gastroenterologists to participate in APMs in 2018.

Do not reject the transition to value. Medicine is no different from most other industries in which value for the consumer is the major driver of business model change. Although physicians pride themselves on practicing quality medicine, quality cannot be our only focus. The cost of the services we provide must also be considered. Together, higher quality and lower cost drive value.

Our focus on cost should be not only directed at the specific services we ourselves provide, but should also be aimed at the total cost of care for the population of patients we are serving. We must be able to demonstrate to those who are taking the risk for payment that the real value of our services lies in improving the health and lowering the overall cost of care for a population of patients.


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GI & HEPATOLOGY NEWS

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Dr. Nicholas J. Talley of the Mayo Clinic in Rochester, Minn., reported at Digestive Disease Week® that patients with normal gastric emptying had significantly better relief with amitriptyline than did patients with delayed gastric emptying.

Amitriptyline eases functional dyspepsia

BY NEIL OSTERWEIL

Supreme Court: Human genes cannot be patented

DNA is a 'product of nature.'

BY MARY ELLEN SCHNEIDER

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Gastric bypass helps type 2 diabetes

BY MARY ANN MOON

Coming Soon DDW2013 Digestive Disease Week

The AGA Report to gihepnews.com and your e-mail inbox

Larry R. Kosinski, MD, MBA, AGAF, is a managing partner of Illinois Gastroenterology Group. He is president and chief medical officer of Project Sonar and an Associate Editor of GI & Hepatology News.

FROM THE AGA JOURNALS

Steatosis linked to persistent ALT increase in hepatitis B

BY AMY KARON
Frontline Medical News

About one in five patients with chronic hepatitis B virus (HBV) infection had persistently elevated alanine aminotransferase (ALT) levels despite long-term treatment with tenofovir disoproxil fumarate, according to data from two phase III trials reported in the July issue of Clinical Gastroenterology and Hepatology (doi: 10.1016/j.cgh.2017.01.032).

"Both host and viral factors, particularly hepatic steatosis and hepatitis B e antigen [HBeAg] seropositivity, are important contributors to this phenomenon," Ira M. Jacobson, MD, AGAF, of Mount Sinai Beth Israel Medical Center, New York, wrote with his associates. "Although serum ALT may indicate significant liver injury, this association is inconsistent, suggesting that relying on serum ALT alone is not sufficient to gauge either the extent of liver injury or the impact of antiviral therapy."

Long-term treatment with newer antivirals such as tenofovir disoproxil fumarate (TDF) achieves complete viral suppression and improves liver histology in most cases of HBV infection. Transaminase levels are used to track long-term clinical response but sometimes remain elevated in the face of complete virologic response and regression of fibrosis. To explore predictors of this outcome, the researchers analyzed data from 471 chronic HBV patients receiving TDF 300 mg once daily for 5 years as part of two ongoing phase III trials (NCT00117676 and NCT00116805). At baseline, about 25% of patients were cirrhotic (Ishak fibrosis score greater than or equal to 5) and none had decompensated cirrhosis.

Continued on page 8

Antiviral therapy for chronic hepatitis B virus in most treated patients suppresses rather than eradicates infection. Despite this, long-term treatment results in substantial histologic improvement – including regression of fibrosis and reduction in complications.


DR. MARTIN

However, as Jacobson et al. report in a histologic follow-up of 471 HBV patients treated long term, aminotransferase elevation persisted in 18%. Factors implicated on multivariate analysis in unresolved biochemical dysfunction included HBeAg seropositivity, age less than 40 years, and steatosis at entry, in addition to steatosis at 5-year follow-up. The only association with hepatic dysfunction that persisted was steatosis when modified normal ranges for aminotransferases proposed by Prati were applied, namely 30 U for men and 19 U for women. This suggests that metabolic rather than viral factors are implicated in persistent biochemical dysfunction in patients with chronic HBV infection. Steatosis is also a frequent finding on liver biopsy in patients with chronic HCV infection.

Importantly, HCV-specific mechanisms have been implicated in the accumulation of steatosis in infected patients, as the virus may interfere with host lipid metabolism. HCV genotype 3 has a marked propensity to cause fat accumulation in hepatocytes, which appears to regress with successful antiviral therapy. In the interferon era, hepatic steatosis had been identified as a predictor of nonresponse to therapy for HCV. In patients with chronic viral hepatitis, attention needs to be paid to cofactors in liver disease – notably the metabolic syndrome – particularly because successfully treated patients are now discharged from the care of specialists.

Paul S. Martin, MD, is chief, division of hepatology, professor of medicine, University of Miami Health System. He has been a consultant and investigator for Gilead, BMS, and Merck.

FROM THE AGA JOURNALS

For chronic abdominal pain, THC resembled placebo

BY AMY KARON
Frontline Medical News

Seven weeks of treatment with delta-9-tetrahydrocannabinol (THC) did not improve chronic abdominal pain in a placebo-controlled trial of 65 adults.

Treatment "was safe and well tolerated," but did not significantly reduce pain scores or secondary efficacy outcomes, Marjan de Vries, MSc, and her associates wrote in the July issue of Clinical Gastroenterology and Hepatology (doi: 10.1016/j.cgh.2016.09.147). Studies have not clearly shown that THC improves central pain sensitization, a key mechanism in chronic abdominal pain, they noted. Future studies of THC and central sensitization include quantitative sensory testing or electroencephalography, they added.

Treatment-refractory chronic abdominal pain is common after abdominal surgery or in chronic pancreatitis, wrote Ms. de Vries of Radboud University Medical Center, Nijmegen, the Netherlands.

Affected patients tend to chronic pain. Some evidence suggests that the shift from acute to chronic pain entails a transition from nociceptive to cognitive, affective, and autonomic sensitization, the researchers noted.

When this happens, pain no longer couples reliably with peripheral stimuli, and therapy targeting central nociceptive pathways is indicated.

The main psychoactive compound of *Cannabis sativa* is THC, which interacts with CB1 receptors in the central nervous system, including in areas of the brain that help regulate emotions. Emotion-processing circuits are often overactive in chronic pain, and disrupting them might help modify pain perception, the investigators hypothesized.

Therefore, they randomly assigned 65 adults with at least 3 months of abdominal pain related to chronic pancreatitis or abdominal surgery to receive oral placebo or THC tablets three times daily for 50-52 days. The 31 patients in the THC group received step-up dosing (3-mg doses for 5 days, followed by 5-mg doses for 5 days) followed by stable dosing at 8 mg.

Both groups continued other prescribed analgesics as usual, including oxycontin, fentanyl, morphine, codeine, tramadol, paracetamol, antiepileptics, and nonsteroidal anti-inflammatories. All but two study participants were white, 25 were male, and 24 were female.

At baseline, all patients reported pain of at least 3 on an 11-point visual analogue scale (VAS). By days 50-52, average VAS scores decreased by 1.6 points (40%) in the THC group and by 1.9 points (37%) in the placebo group ($P = .9$). Although a strong placebo effect is common in studies of visceral pain, that did not prevent pregabalin from significantly outperforming placebo in another similarly designed randomized clinical trial of patients from this study group with chronic pancreatitis, the investigators noted.

The THC and placebo groups also resembled each other on various secondary outcome measures, including patient global impression of change, pain catastrophizing, pain-related anxiety, measures of depression and generalized anxiety, and subjective impressions of alertness, mood, feeling "high," drowsiness, and difficulties in controlling thoughts. The only exception was that the THC group showed a trend toward improvement on the Short Form 36, compared with the placebo group ($P = .051$).

Pharmacokinetic analysis showed good oral absorption of THC. Dizziness, somnolence, and headache were common in both groups, but were more frequent with THC than placebo, as was nausea, dry mouth, and visual impairment. There were no serious treatment-related adverse events, although seven patients stopped THC because they could not tolerate the maximum dose.

The trial was supported by a grant from the European Union, the European Fund for Regional Development, and the Province of Gelderland. The THC was provided by Echo Pharmaceuticals, Nijmegen. The investigators reported having no conflicts of interest.

ginews@gastro.org

Continued from page 6

A central laboratory analyzed ALT levels, which were up to 10 times the upper limit of normal in both HBeAg-positive and -negative patients and were at least twice the upper limit of normal in all HBeAg-positive patients.

After 5 years of TDF, ALT levels remained elevated in 87 (18%) of patients. Patients with at least 5% (grade 1) steatosis at baseline were significantly more likely to have persistent ALT elevation than were those with less or no steatosis (odds ratio, 2.2; 95% confidence interval, 1.03-4.9; $P = .04$).

At least grade 1 steatosis at year 5 also was associated with persistent ALT elevation (OR, 3.4; 95% CI, 1.6-7.4; $P = .002$). Other significant correlates included HBeAg seropositivity (OR, 3.3; 95% CI, 1.7-6.6; P less than .001) and age 40 years or younger (OR, 2.1; 95% CI, 1.01-4.3; $P = .046$). Strikingly, half of HBeAg-positive patients with steatosis at baseline had elevated ALT at year 5, said the investigators.

Because many patients whose ALT values fall within commercial laboratory reference ranges have chronic necroinflammation or fibrogenesis, the researchers performed a sensitivity analysis of patients who achieved a stricter definition of ALT normalization of no more than 30 U/L for men and 19 U/L for women that has been recommended (Ann Intern Med. 2002;137:1-10).

In this analysis, 47% of patients had persistently elevated ALT despite effective virologic suppression, and the only significant predictor of persistent ALT elevation was grade 1 or more steatosis at year 5 (OR, 6.2; 95% CI, 2.3-16.4; P less than .001). Younger age and HBeAg positivity plus age were no longer significant.

Hepatic steatosis is common overall and in chronic HBV infection and often leads to increased serum transaminases, the researchers noted. Although past work has linked a PNPLA3 single nucleotide polymorphism to obesity, metabolic syndrome, and hepatic steatosis, the presence of this SNP was not significant in their study, possibly because many patients lacked genotype data, they added. "Larger longitudinal studies are warranted to further explore this factor and its potential effect on the biochemical response to antiviral treatment in [chronic HBV] patients," they concluded.

Gilead Sciences sponsored the study. Dr. Jacobson disclosed consultancy, honoraria, and research ties to Gilead and several other pharmaceutical companies.

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Study supports expanded definition of SPS

BY AMY KARON
Frontline Medical News

Patients with more than 10 colonic polyps, of which at least half were serrated, and their first-degree relatives had a risk of colorectal cancer (CRC) similar to that of patients who met formal diagnostic criteria for serrated polyposis syndrome (SPS), according to a retrospective multicenter study published in the July issue of Gastroenterology (doi: 10.1053/j.gastro.2017.04.003).

Such patients "should be treated with the same follow-up procedures as those proposed for patients with SPS, and possibly the definition of SPS should be broadened to include this phenotype," wrote Cecilia M. Egoavil, MD, Miriam Juárez, and their associates.

SPS increases the risk of CRC and is considered a heritable disease, which mandates "strict surveillance" of first-degree relatives, the researchers noted. The World Health Organization defines SPS as having at least five histologically diagnosed serrated lesions proximal to the sigmoid colon, of which two are at least 10 mm in diameter, or serrated polyps proximal to the sigmoid colon and a first-degree relative with SPS, or more than 20 serrated polyps throughout the colon. This "arbitrary" definition is "somewhat restrictive, and possibly leads to underdiagnosis of this disease," the researchers wrote. Patients with multiple serrated polyps who do not meet WHO SPS criteria might have a

Continued on following page

FROM THE AGA JOURNALS

Improved adenoma detection rate found protective

BY AMY KARON
Frontline Medical News

An improved annual adenoma detection rate (ADR) was associated with a significantly decreased risk of interval colorectal cancer (ICRC) and subsequent death in a national prospective cohort study published in the July issue of Gastroenterology (doi: 10.1053/j.gastro.2017.04.006).

This is the first study to show a significant inverse relationship between an improved annual ADR and ICRC or subsequent death, Michal F. Kaminski MD, PhD, of the Institute of Oncology, Warsaw, wrote with his associates.

The rates of these outcomes were lowest when endoscopists achieved and maintained ADRs above 24.6%, which supports the currently recommended performance target of 25% for a mixed male-female population, they reported (Am J Gastroenterol. 2015;110:72-90).

This study included 294 endoscopists and 146,860 individuals who underwent screening colonoscopy as part of a national cancer prevention program in Poland between 2004 and 2008. Endoscopists received annual feedback based on quality benchmarks to spur improvements in colonoscopy performance, and all participated for at least 2 years. For each endoscopist, investigators categorized annual ADRs based on quintiles for the entire data set. "Improved ADR" was defined as keeping annual ADR within the highest quintile (above 24.6%) or as increasing annual ADR by at least one quintile, compared with baseline.

Based on this definition, 219 endoscopists (75%) improved their ADR during a median of 5.8 years of follow-up (interquartile range, 5-7.2 years). In all, 168 interval CRCs were diagnosed, of which 44 cases led to death. After age, sex, and family history of CRC were controlled for, patients whose endoscopists improved their ADRs were significantly less likely to develop (adjusted hazard ratio, 0.6; 95% confidence interval, 0.5-0.9; $P = .006$) or to die of interval CRC (95% CI, 0.3-0.95; $P = .04$) than were patients whose endoscopists did not improve their ADRs.

Maintaining ADR in the highest quintile (above 24.6%) throughout follow-up led to an even lower risk of interval CRC (HR, 0.3; 95% CI, 0.1-0.6; $P = .003$) and death (HR, 0.2; 95% CI, 0.1-0.6; $P = .003$), the researchers reported. In absolute numbers, that translated to a decrease from 25.3 interval CRCs per 100,000 person-years of follow-up to 7.1 cases when endoscopists eventually reached the highest ADR quintile or to 4.5 cases when they were in the highest quintile throughout follow-up. Rates of colonic perforation remained stable even though most endoscopists upped their ADRs.

Together, these findings "prove the causal relationship between endoscopists' ADRs and the likelihood of being diagnosed with, or dying from, interval CRC," the investigators concluded. The national cancer registry in Poland is thought to miss about 10% of cases, but the rate of missing cases was not thought to change over time, they noted. However, they also lacked data on colonoscope withdrawal times, and had no control group to definitively show that feedback based on benchmarking was responsible for improved ADRs.

Funders included the Foundation of Polish Science, the Innovative Economy Operational Programme, the Polish Foundation of Gastroenterology, the Polish Ministry of Health, and the Polish Ministry of Science and Higher Education. The investigators reported no conflicts of interest.

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The U.S. Multi-Society Task Force on Colorectal Cancer proposed the adenoma detection rate (ADR) as a colonoscopy quality measure in 2002. The rationale for a new measure was emerging evidence of highly variable adenoma detection and cancer prevention among colonoscopists. Highly variable performance, consistently verified in subsequent studies, casts a pall of severe operator dependence over colonoscopy. In landmark studies from Kaminski et al. and Corley et al. in 2010 and 2014, respectively, it was shown that doctors with higher ADRs provide patients with much greater protection against interval colorectal cancer (CRC).


DR. REX

A huge body of work investigated whether colonoscopists can improve ADRs. After initial setbacks, methods of ADR improvement have been convincingly demonstrated.

Now Kaminski and colleagues from Poland have delivered a second landmark study, demonstrating for the first time that improving ADR prevents CRCs. We now have strong evidence that ADR predicts the level of cancer prevention, that ADR improvement is achievable, and that improving ADR further prevents CRCs and CRC deaths. Thanks to this study, ADR has come full circle. Measurement of and improvement in detection is now a fully validated concept that is essential to modern colonoscopy. In 2017, ADR measurement is mandatory for all practicing colonoscopists who are serious about CRC prevention. The tools to improve ADR that are widely accepted include ADR measurement and reporting, split or same-day preparations, lesion recognition and optimal technique, high-definition imaging, double examination (particularly for the right colon), patient rotation during withdrawal, chromoendoscopy, mucosal exposure devices (caps, cuffs, balloons, etc.), and water exchange. Tools for ADR improvement that are emerging or under study are brighter forms of electronic chromoendoscopy, and videorecording.

Douglas K. Rex, MD, AGAF is professor of medicine, division of gastroenterology/hepatology, at Indiana University, Indianapolis. He has no relevant conflicts of interest.

Continued from previous page

phenotypically attenuated form of SPS.

For the study, the researchers compared 53 patients meeting WHO SPS criteria with 145 patients who did not meet these criteria but had more than 10 polyps throughout the colon, of which at least 50% were serrated. For both groups, number of polyps was obtained by adding polyp counts from subsequent colonoscopies. The data source was EPIPOLIP, a multicenter study of patients recruited from 24 hospitals in Spain in 2008 and 2009. At baseline, all patients had more than 10 adenomatous or serrated colonic polyps but did not have familial adenomatous polyposis, Lynch syndrome, hamartomatous polyposis, inflammatory bowel disease, or only hyperplastic rectosigmoid polyps.

The prevalence of CRC was statistically similar between groups ($P = .4$). There were 12 (22.6%) cases among SPS patients (mean age at diagnosis, 50 years), and 41 (28.3%) cases (mean age, 59 years) among patients with multiple serrated polyps who did not meet SPS criteria. During a mean follow-up of 4.2 years, one (1.9%) SPS patient developed incident CRC, as did four (2.8%) patients with multiple serrated polyps without SPS. Thus, standardized incidence ratios were 0.51 (95% confidence interval, 0.01-2.82) and 0.74 (95% CI, 0.20-1.90), respectively ($P = .7$). Standardized incidence ratios for CRC also did not significantly differ between first-degree relatives of patients with SPS (3.28, 95% CI, 2.16-4.77) and those with multiple serrated polyps (2.79, 95% CI, 2.10-3.63; $P = .5$).

A Kaplan-Meier analysis confirmed that there were no differences in the incidence of CRC between groups during follow-up. The findings "confirm that a special surveillance strategy is needed for patients with multiple serrated polyps and their relatives, probably similar to the strategy currently recommended for SPS patients," the researchers concluded.

Funders included Instituto de Salud Carlos III, Fundación de Investigación Biomédica de la Comunidad Valenciana-Instituto de Investigación Sanitaria y Biomédica de Alicante, Asociación Española Contra el Cáncer, and Conselleria d'Educació de la Generalitat Valenciana. The investigators had no conflicts of interest.

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DDSEP eight
Digestive Diseases Self-Education Program

Quick quiz

Q1. A 46-year-old man with a history of alcoholic cirrhosis presents to the ED with new-onset melena and hematemesis. On examination, he appears weak, but his mental status is stable with no signs of encephalopathy. His abdomen is soft, with no clinical ascites. Vitals include temperature 97.9˚, BP of 83/42 mm Hg, HR 112. Labs reveal hemoglobin 6.3 g/dL, hematocrit 18%, creatinine 1.3 mg/dL, total bilirubin 1.2 mg/dL, INR 1.0, platelet count of 63 x 10^3/microL. You suspect that this is an esophageal variceal bleed.

What is the initial best next step in the management of this patient?
A. Endoscopy with potential variceal band ligation
B. Placement of a Blakemore tube
C. Send patient for TIPS
D. Transfuse PRBC to a goal hemoglobin of 7-8 g/dL
E. Endoscopy with potential sclerotherapy

Q2. A 36-year-old woman presented to clinic with complaints of constipation. She reported daily bowel movements, but with a sensation of rectal fullness and incomplete evacuation. She strained with bowel movements at least 50% of the time. Her symptoms have been present for most of her adult life. She denied diarrhea or blood in her stools, and has had no recent unintentional weight loss. She was sent for anorectal manometry, which revealed adequate propulsive forces, but less than 20% relaxation of the basal resting sphincter pressure. Balloon expulsion is abnormal.

Which of the following is the next best step in management for this patient?
A. Lubiprostone 25 mcg twice daily
B. Biofeedback therapy
C. Amitriptyline 25 mg daily
D. Surgical referral for rectal biopsy
E. Trial of fiber supplementation

The answers are on page 23.

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New research grant will support pediatric genomics research

The AGA Research Foundation has partnered with the Rady Children's Institute of Genomic Medicine to establish the AGA-Rady Children's Institute of Genomic Medicine Research Scholar Award in Pediatric Genomics. This award will support one promising young investigator conducting research that utilizes genomics to enhance our fundamental understanding of childhood digestive diseases.

This newly established award will provide $90,000 per year for 3 years to one investigator. The funded research must be conducted at Rady Children's Institute for Genomic Medicine in San Diego starting July 2018.

Complete eligibility requirements and application information for this award are available on AGA's website and on the Rady Children's Hospital website.

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AGA makes six recommendations to FDA on biosimilars

Gastroenterologists and patients rely on biologics to manage Crohn's disease and ulcerative colitis. Biosimilar products, which are "highly similar" to the biologic, have begun to be approved by the U.S. Food and Drug Administration for such indications. The FDA is now developing a pathway for interchangeable products, which are biosimilars that "may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product" according to Section 351(i) of the Public Health Service Act. AGA provided the FDA six recommendations in response to the agency's draft guidance on demonstrating interchangeability focused on measures to enhance patient safety and ensure that physicians, not insurance companies, drive decisions about switching products. Here is a summary of our comments.

1. Extrapolation of data should not be allowed for any indication where the pathophysiology is known to be different or is yet to be elucidated.

Post-marketing evidence on interchangeability of biosimilar products would alleviate concerns as testing specific products in individual diseases is an important step in determining whether the product is effective and safe for that particular disease. AGA recommends that manufacturers should be required to seek licensure for all the same indications as the reference product to appropriately track adverse events should they arise.

2. The agency should use caution when allowing extrapolation for pediatric indications.

Pediatric patients are recognized as a vulnerable population for which a disease may differ from those of adult patients. In the absence of data specifically ensuring safety and efficacy in children, AGA recommends an exemption of pediatric patients from current FDA positions and guidance documents related to interchangeable products.

3. Sponsors should exclusively use U.S.-licensed reference products in switching studies.

Currently, the FDA's draft guidance has wording that seems to signal that the agency is willing to entertain use of non-U.S.-licensed products in some cases, casting doubt on the true "interchangeability" of the product. AGA recommends that the guidance be amended to include specific scenarios where this may be acceptable or remove the clause altogether.

4. "Real world" data on biosimilar and interchangeable products must be collected through formal post-marketing observational studies to ensure the longitudinal safety and efficacy for all patient populations being treated with these products.

A central observational registry, like the AGA Fecal Microbiome Transplant National Registry, would ensure the capture of data on the safety and efficacy of interchangeable products for all manufacturers and their adverse effects on patients, if any. Such a registry would also allow the study of outcomes in patients who are switched among multiple products.

5. Gastroenterologists with appropriate disease expertise should be engaged by the FDA when interchangeable products are reviewed for approval.

AGA is part of the FDA's Network of Experts and hopes that this relationship will continue to be proactively utilized when a proposed product is seeking a gastrointestinal indication.

6. Prescribing physicians must be empowered with the ability to prevent nonmedical switching from a reference product to an interchangeable product.

AGA has concerns over the section of the Public Health Service Act that states that an interchangeable product "may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product." Health care providers must be empowered to be aware of and prevent nonmedical switching if they believe that the patient's safety and health is at risk. AGA encourages the FDA to consider making a statement encouraging states to protect physician discretion as it applies to interchangeable biosimilars.

AGA will continue to work with the FDA to ensure that the voice of gastroenterology is heard in relation to biosimilars and interchangeable products.

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GI & HEPATOLOGY NEWS

THE OFFICIAL NEWSPAPER OF THE AGA INSTITUTE

Mixed coagulopathy of disease adds to risk

Cirrhosis *from page 1*

and Mind Research Institute and Weill Cornell Medicine, both in New York, and his associates.

They examined a possible association in a retrospective study involving 1,618,059 Medicare beneficiaries hospitalized during a 6-year period. This included 15,586 patients (1%) who had cirrhosis at baseline. A total of 77,268 developed stroke during a mean of 4.3 years of follow-up. The overall incidence of stroke was 2.17% per year among patients with cirrhosis, compared with only 1.11% per year among those without cirrhosis.

After the data were adjusted to account for stroke risk factors, relevant comorbidities, and demographic traits, the annual incidence of any type of stroke was significantly higher with cirrhosis than without cirrhosis (hazard ratio, 1.4). The association was stronger for intracranial hemorrhage (HR, 1.9) and subarachnoid hemorrhage (HR, 2.4) than for ischemic stroke (HR, 1.3).

The results of several secondary and sensitivity analyses were consistent with those of the primary analysis, regardless of whether the cirrhosis was alcohol-related or the stroke was fatal. The association was strongest among patients who had decompensated cirrhosis and was not evident at all among patients who had mild liver disease, Dr. Parikh and his associates said (JAMA Neurol. 2017 Jun 5. doi: 10.1001/jamaneurol.2017.0923).

This study was not designed to explore the reasons for an association between cirrhosis and stroke, but the investigators noted many possible explanations. First, "cirrhosis is accompanied by a mixed coagulopathy, with potential implications for hemorrhagic and thrombotic processes." It has been linked to many bleeding complications, including, most recently, cerebral microhemorrhages detectable on brain MRI. In addition, the underlying causes of cirrhosis, including alcohol abuse, hepatitis infection, and metabolic disease, may also contribute to stroke risk.

Alternatively, clinicians caring for patients with cirrhosis "may limit the aggressiveness of stroke prevention" – for example, by limiting antithrombotic medications or statins – because they are mindful of the patient's increased risk of bleeding and hepatic toxicity, the investigators said.

This study was supported by the National Institute of Neurological Disorders and Stroke and the Florence Gould Endowment for Discovery in Stroke. Dr. Parikh and his associates reported having no relevant financial disclosures.

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Few states fully support HCV prevention, treatment

BY RICHARD FRANKI
Frontline Medical News

The prevalence of hepatitis C virus (HCV) varies considerably by state, and the same can be said for the state laws and policies attempting to decrease that prevalence, according to an assessment by the Centers for Disease Control and Prevention.

'The costs of HCV treatment have declined in recent years, increasing the cost-effectiveness of treatment, particularly among persons who inject drugs and who might serve as an ongoing source of transmission to others.'

In 2015, incidence of acute HCV infection exceeded the national average of 0.8 per 100,000 population in 17 states, including 7 with rates that at least doubled it, the report noted. New HCV infections have increased in recent years despite curative therapies "and known preventive measures to interrupt transmission."

The U.S. incidence of HCV jumped by 294% from 2010 to 2015, and "this increase in acute cases of HCV is largely attributed to injection drug use," the CDC investigators said. Since state laws and policies affect access to HCV preventive and treatment measures, the researchers reviewed laws related to access to clean needles and policies on Medicaid fee-for-service treatment.

The "most comprehensive" laws on prevention through clean needle access as of 2016 were found in Maine, Nevada, and Utah, with laws in 12 other states categorized as "more comprehensive" and 18 states falling into the "least comprehensive" category. On the Medicaid side of the equation, 16 states had permissive policies that did not require sobriety or required only screening and counseling before treatment, 24 states had restrictive policies that required sobriety, and 10 states had no policy available, the report showed (MMWR. 2017 May 12:66[18]:465-9).

Only three states – Massachusetts, New Mexico, and Washington – had a comprehensive (all three were considered "more comprehensive") set of prevention laws and a permissive treatment policy, the investigators said, while also noting that two of the three – Massachusetts and New Mexico – were among the states with acute HCV rates that were at least twice the national average.

"Although the costs of HCV therapies have raised budgetary issues for state Medicaid programs in the past, the costs of HCV treatment have declined in recent years, increasing the cost-effectiveness of treatment, particularly among persons who inject drugs and who might serve as an ongoing source of transmission to others," the report concluded.

The analysis examined three types of laws on access to clean needles and syringes: authorization of exchange programs, the scope of drug paraphernalia laws, and retail sale of needles and syringes. Each law was assessed for five elements, including authorization of syringe exchange statewide or in selected jurisdictions and exemption of needles or syringes from the definition of drug paraphernalia.

For the accompanying map (see "Acute hepatitis C infection incidence rates, 2015: State vs. national"), each state's acute HCV incidence rate for 2015 was divided by the national rate to determine the incidence rate ratio, with data unavailable for 10 states.

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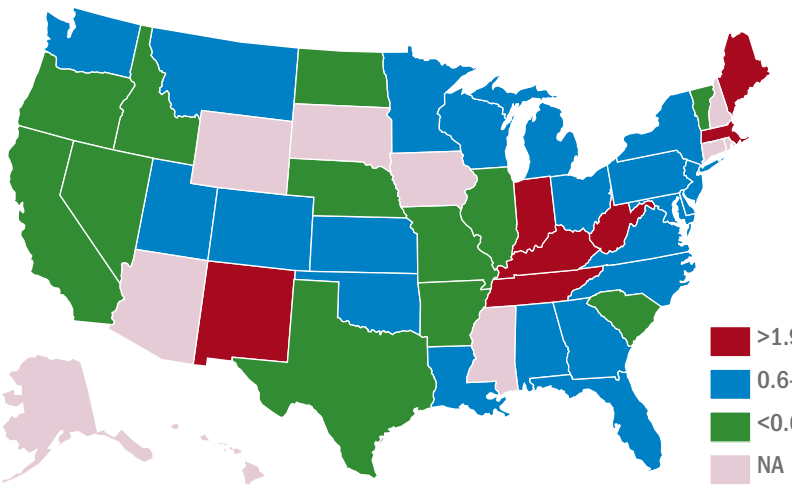
Acute hepatitis C infection incidence rates, 2015: State vs. national



FRONTLINE MEDICAL NEWS

Notes: Incidence rate ratio = state rate/national rate of 0.8 per 100,000 population. Based on data from the National Notifiable Diseases Surveillance System.

Source: MMWR 2017 May 12;66(18):465-9

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GI & HEPATOLOGY NEWS

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Waiving screening copayments could cut CRC deaths

BY ROXANNE NELSON
Frontline Medical News

AT DDW

CHICAGO – Out-of-pocket costs may present a barrier to colorectal screening, and removing those costs could reduce colorectal cancer deaths, according to new data presented at the annual Digestive Disease Week®.

These data imply that removing copayments could result in a 16% decrease in colorectal cancer–related deaths among Medicare beneficiaries, explained lead author Elisabeth Peterse, PhD, of the department of public health, Erasmus Medical Center, Rotterdam, the Netherlands.

The research also demonstrated that waiving copayments is cost effective, she added.

Despite the effectiveness of colorectal cancer screening, only 58% of eligible individuals adhere to current screening recommendations, Dr. Peterse noted. Financial barriers may play a role in the lack of adherence, as studies have found that removing out-of-pocket costs is one of the most effective interventions for increasing screening.

"But despite the fact that the Affordable Care Act has been successful in partially eliminating cost-sharing for colorectal screening, Medicare beneficiaries may still face unexpected out-of-pocket liabilities," said Dr. Peterse.

Out-of-pocket costs can be complicated, given that they can depend largely on how a procedure is coded. A screening colonoscopy or fecal immunochemical test (FIT) is completely covered if it is coded as a screening test, but follow-up colonoscopies come with 20% copayments.

A screening colonoscopy with polypectomy and a follow-up colonoscopy that is done after a positive fecal immunochemical test are coded as diagnostic rather than screening, so the patient has out-of-pocket costs, she explained.

To explore how waiving the cost of screening could impact colorectal cancer–related mortality and cost-effectiveness, the researchers conducted an analysis using a microsimulation model for a cohort composed of 65-year-old individuals.

In the simulation, they estimated colorectal cancer–related mortality, quality-adjusted life-years (QALY), and total cost of screening and treatment using the current Medicare copayment schedule. These were then compared with outcomes for alternative situations.

The study was conducted in two parts, explained Dr. Peterse. In the first part, the researchers looked at five scenarios: one in which the 20% copayment was intact. In the second, the copayment was waived without having any impact on adherence. In the third, the investigators looked at a 5% increase in adherence but only at diagnostic follow-up.

See **Copayments** *on page 19*

PREMM$_5$: Updated Lynch syndrome test available

BY JIM KLING
Frontline Medical News

An updated Lynch syndrome (LS) prediction model improves accuracy and may be used to assess individuals who are currently unaffected by cancer. The model predicts an individual's risk of carrying one of five known gene mutations associated with LS. It could be applied to individuals with a suspicious family history of cancer, as well as to colorectal cancer (CRC) patients who may not have tumor immunohistochemical and microsatellite instability testing results that can spot potential LS patients based on specific tumor characteristics.

LS is linked to a 40%-80% lifetime risk of CRC and heightened risk of gynecologic cancer in women, as well as gastrointestinal, genitourinary, and additional cancers.

The model, called PREMM$_5$, is available online, and produces a result in the form of a percentage chance that the patient carries one of the five LS genes, which include three mismatch repair genes (MLH1, MSH2, and MSH6) and two recently identified LS genes (PMS2 and EPCAM). The development and validation of the model was described in the Journal of Clinical Oncology (2017 May 10. doi: 10.1200/JCO.2016.69.6120). It is the only currently available clinical prediction model to include risk assessment for the PMS2 and EPCAM genes.

Addition of the PMS2 gene is important because there is some evidence that it is the most prevalent gene in LS, although it has a weaker phenotype, with cancer diagnoses at older ages and less striking family histories. Still, its higher frequency makes it an important player. "It's a big deal. We originally thought the majority of LS was caused by MLH1 and MSH2 gene alterations, but that is no longer the case," said lead author Fay Kastrinos, MD, MPH, director of the hereditary GI cancer risk and prevention program at New York–Presbyterian Hospital/Columbia University Medical Center.

The researchers recommend that anyone with a probability over 2.5% should be referred to evaluation for genetic testing, which could include germline genetic testing, microsatellite instability, or immunohistochemistry testing of a CRC tumor.

The new model is a successor to PRMM$_{1,2,6}$, which evaluated a patient's risk of a mutation in MLH1, MLH2, or MLH6. That model was developed from a population predominantly composed of CRC patients.

The researchers expanded the population for the PREMM$_5$ model to include a total of 18,734 subjects who were evaluated for a wide range of clinical characteristics, as well as personal and family cancer history, and were tested for mutations in all five genes.

When the team applied the model to a validation cohort of 1,058 patients with CRC, it achieved a similar level of accuracy (area under the curve, 0.83; 95% CI, 0.75-0.92). For the prediction of each specific gene, the model fared worse in predicting PMS2 mutations (AUC, 0.64; 95% confidence interval, 0.60-0.68) than for other genes.

When applied to the PREMM$_5$ development cohort, PREMM$_{1,2,6}$ over-predicted mutation-positive status. (For MLH1, MSH2, and MSH6, it predicted a prevalence of 8.0%, compared with an observed frequency of 4.5%.)

Dr. Kastrinos reported having no financial disclosures.

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Copayments *from page 17*

In the fourth and fifth scenarios, the investigators looked at 5% and 10% increases in adherence, in both first screening and diagnostic follow-up, she added.

In the study's second part, the researchers also estimated the threshold increase in participation at which copayment removal would be cost effective, using a $50,000 willingness-to-pay threshold.

They found that without screening, the expected mortality would be 25 colorectal deaths per 1,000 people in a population of 65-year-old individuals. With screening, the number was reduced to 12.8 deaths per 1,000 65-year-olds for colonoscopy, and 14.9 deaths per 1,000 for FIT screening. The total associated costs for screening and treatment for the two modalities were $3.02 million and $2.87 million.

If waiving the copayments had no impact in increasing screening levels, the cost of screening was estimated to increase to $3.1 million (2.8% increase) for colonoscopy and $2.9 million (1.6% increase) for FIT.

But if copayments were removed and there were a 5% increase in adherence, colorectal cancer deaths were estimated to decline to 11.7 (–8.3%) and 13.9 (–6.3%) per 1,000 for colonoscopy and FIT, respectively. That would result in cost-effectiveness ratios of $19,288 and $7,894 for no copayment versus having a copayment. Increasing adherence to 10% would result in an even lower ratio, noted Dr. Peterse.

The threshold increase for participating in screening programs – the point where removing a copayment becomes cost effective – was a 1.8% increase in colonoscopy screening and a 0.8% increase for FIT.

The conclusion is that waiving copayments is cost effective, Dr. Peterse said.

Dr. Peterse added that a limitation to the analysis is that the study authors don't know to what extent patients are even aware of the copayments. "So, we don't know if it is a barrier, and we didn't take other insurance scenarios into account," she said. Digestive Disease Week® is jointly sponsored by the American Association for the Study of Liver Diseases (AASLD), the American Gastroenterological Association (AGA) Institute, the American Society for Gastrointestinal Endoscopy (ASGE), and the Society for Surgery of the Alimentary Tract (SSAT).

Dr. Peterse declared no relevant disclosures.

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AGA Resource

Screening colonoscopy is the most cost-effective test for prevention of colorectal cancer. Patients should be incentivized, through the elimination of cost sharing, to use colonoscopy as a colorectal cancer screening mechanism. Additionally, the preventive screening benefit has contributed to the decline in colorectal cancer rates in our country, and AGA believes that this benefit should be preserved in any health care reform legislation. Read more at http://www.gastro.org/take-action/top-issues/patient-cost-sharing-for-screening-colonoscopy.

CLINICAL CHALLENGES AND IMAGES

The diagnosis

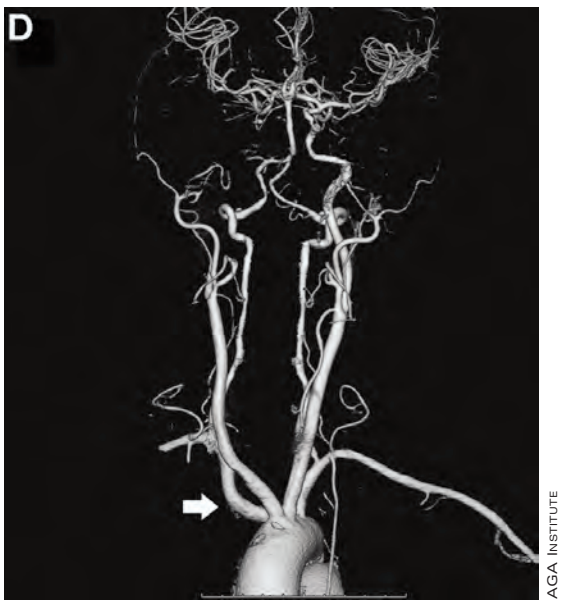
Answer to "What's your diagnosis?" on page 2: Dysphagia lusoria

Dysphagia may be divided into an oropharyngeal cause or an esophageal cause. Esophageal dysphagia may be due to a luminal narrowing or a motility dysfunction. Causes of luminal narrowing include lesions within the lumen such as a foreign body, lesions within the wall of the esophagus such as a mucosal or submucosal tumor, and extrinsic lesions such as an enlarged mediastinal lymph node or mass. Esophageal dysphagia typically presents with difficulty in swallowing solids compared with liquids.

The management of patients with mild to moderate dysphagia is diet modification (minced feeds to well-chewed food; eating slowly and with liquids).

Dysphagia lusoria is a congenital disorder in which an aberrant right subclavian artery (ARSA) causes extrinsic esophageal compression. This woman's CTA confirmed the presence of an ARSA arising directly from the aortic arch (Figure D, arrow). The term dysphagia lusoria was coined by Bayford in 1794 from the Latin phrase lusus naturae (meaning "freak of nature").[1] Of all the congenital aortic anomalies, an isolated ARSA is the most common. This occurs in approximately 0.5% of the population. The ARSA assumes a retroesophageal position; it proceeds out of the thorax into the right arm, compressing the esophagus and causing dysphagia.

Evaluation of this condition involves a barium swallow study, CTA, or magnetic resonance angiography.[2] Both CTA and MRA have largely supplanted the role of conventional angiography, which is invasive. Both CTA and magnetic resonance angiography may also diagnose any other intrathoracic pathology causing esophageal compression. The management of patients with mild to moderate dysphagia is diet modification (minced feeds to well-chewed food; eating slowly and with liquids). Vascular repair of the aberrant vessel is considered only if the patient has severe symptoms and has failed conservative management.[3] Because our subject did not have significant weight loss or regurgitation, only dietary advice was offered. An interval outpatient upper endoscopy was planned upon discharge, for which she defaulted.



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Steroid-free remission rates notable

Crohn's *from page 1*

than 1.5 per day, as the analysis had specified.

The preplanned analysis used a unique composite outcome of 7-day stool frequency and abdominal pain. At the time of trial design, the scale had been validated only in patients with mild to moderate Crohn's, so the investigators used the validated stool frequency cut point of 1.5 per day as a measure of clinical remission.

That was not an appropriate target for this unique study group, Dr. Sandborn said.

"CELEST was the most refractory patient population ever recruited into a Crohn's disease clinical trial. If we could do this over now, we would use a cut point of less than 3 instead of 1.5 or less. This is a really tough clinical endpoint" that probably isn't a realistic clinical goal for patients in this category. "A number of studies since then now suggest that the right cut point for remission in these patients would be about 3 per day."

CELEST enrolled 220 patients who were randomized to placebo or one of five treatment arms comprising 30-35 patients each: upadacitinib at 24 mg once daily or upadacitinib at 3 mg, 6 mg, 12 mg, or 24 mg b.i.d. The study lasted 16 weeks and was followed by 36 weeks of blinded extension treatment. Dr. Sandborn reported the 16-week induction phase data.

The patients had moderate to severe Crohn's disease, with a mean baseline Crohn's Disease Activity Index (CDAI) score of about 300 and a Simple Endoscopic Score for Crohn's disease (SES-CD) of about 15. About 95% had already failed at least one anti–tumor necrosis factor drug. Half had failed at least two.

DR. SANDBORN

The coprimary endpoints were the proportion of patients who achieved clinical remission (stool frequency of 1.5 or less per day and abdominal pain of 1 or lower) at week 16 and endoscopic remission at weeks 12 or 16. Secondary endpoints included CDAI response, clinical response (at least a 30% reduction from baseline in stool frequency or abdominal pain), and endoscopic response.

In the primary analysis, the rate of endoscopic remission was significant (*P* less than .05) in both the 24-mg b.i.d. and the 24-mg once-daily groups. However, clinical remission with the original stool frequency cut point of 1.5 per day or less wasn't significantly different from that with placebo in any group. Dr. Sandborn pointed out that a 27% rate of clinical remission occurred in those taking 12 mg, which had a *P* value of less than 0.1, relative to placebo.

Among the secondary endpoints, remission as measured by the CDAI score (less than 150) occurred in 39% of those taking 12 mg – the only significant response in that category.

The rate of endoscopic response (at least a 50% improvement in endoscopic findings) was 21% in the 6-mg group and 25% in the 24-mg once-daily group (*P* less than .05) and in about 30% of the 12-mg and 24-mg b.i.d. group (*P* less than .01).

When the clinical remission analysis employed the revised stool frequency cut point of less than 2.8 per day, clinical remission rates improved somewhat. Almost 40% of those taking 24 mg b.i.d. achieved clinical remission (*P* less than .01), and 30% of those taking 6 mg achieved clinical remission, but the significance was marginal (*P* less than .1).

Steroid-free remission rates were significantly better than placebo in the 18-mg group (39%) and the 15-mg group (33%), both with a *P* value less than .05.

Dr. Sandborn also found changes in C-reactive protein and fecal calprotectin levels. These dropped precipitously in all active groups by week 2, in a dose-response manner, and stayed well suppressed in the two highest-dose groups. In the placebo group, C-reactive protein level rose over the 16-week period, and fecal calprotectin remained unchanged from baseline.

The drug was reasonably well tolerated and safe. About 80% of each dosing group reported at least one adverse event. The 12-mg dose appeared particularly troublesome, with 25% stopping because of an adverse event. By comparison, the discontinuation rate was 8% in the 24-mg b.i.d. group and 14% in the 24-mg once-daily group.

Serious adverse events were consistent with what is known about the JAK1-inhibitor safety profile, Dr. Sandborn said. There were nine serious infections, including *Escherichia coli* bacteremia, subcutaneous abscess, and sepsis (3-mg group); anorectal abscess, urinary tract infection, and sepsis (12-mg group); sepsis (24 mg b.i.d.); and peritonitis and sepsis (24 mg once daily). There was one nonmelanoma skin cancer, which Dr. Sandborn said was probably preexisting but not recognized at baseline. Three cases of herpes zoster occurred, all in the 24-mg b.i.d. group.

One patient experienced a gastrointestinal perforation, which sometimes occurs in Crohn's disease. Two patients had a myocardial infarction, a number "too small to understand fully," Dr. Sandborn said.

The drug will move forward into phase III trials, but the final dose hasn't been decided on.

Dr. Sandborn has received consulting fees from AbbVie, which is developing the drug and sponsored CELEST.

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Infliximab biosimilar noninferior to originator – NOR-SWITCH

BY ROXANNE NELSON
Frontline Medical news

AT DDW

CHICAGO – The biosimilar infliximab CT-P13 is not inferior to the originator infliximab in terms of efficacy, safety, and immunogenicity in the treatment of inflammatory bowel disease, a phase IV randomized trial showed.

Patient outcomes were not compromised with the use of the biosimilar, and the cost of treatment was much lower, said lead author Kristin K. Jørgensen, MD, PhD, at Digestive Disease Week®.

"Biologics represent a substantial source of IBD [inflammatory bowel disease] expenditure," said Dr. Jørgensen of Akershus University Hospital, Lørenskog, Norway. "The medication is expensive, patients are treated on a long-term basis, and the incidence of IBD is increasing."

Biosimilars are biotherapeutic products that are similar in terms of quality, safety, and efficacy to the already licensed reference biologic product. "Use of biosimilars can potentially dramatically decrease costs [in the European market] and may lead to better patient care," said Dr. Jørgensen. "The patient gets increased access to biologic therapy, and it is easier to intensify dosing if indicated."

Tumor necrosis factor inhibitors are commonly used to treat Crohn's disease, ulcerative colitis (UC), spondyloarthritis, rheumatoid arthritis, psoriatic arthritis, and chronic plaque psoriasis, and, while they have altered the treatment paradigm, they are expensive products.

The goal of the NOR-SWITCH trial was to evaluate switching from originator infliximab to CT-P13, in terms of efficacy, safety, and immunogenicity.

Dr. Jørgensen and her colleagues conducted a randomized phase IV trial that enrolled 482 patients who were randomly assigned to either infliximab originator (n = 241) or CT-P13 (n = 241). The primary endpoint was disease worsening during follow-up.

Of the group, 155 patients (32%) had Crohn's disease, 93 (19%) had UC, 91 (19%) had spondyloarthritis, 77 (16%) had rheumatoid arthritis, 30 (6%) had psoriatic arthritis, and 35 (7%) had chronic plaque psoriasis.

Disease worsening occurred at a similar rate in both groups. In the infliximab originator group, 53 patients (26%) experienced a worsening of their symptoms, compared with 61 patients (30%) in the CT-P13 group. The 95% confidence interval of the adjusted risk difference (−4.4%) was −12.7% to 3.9%, which fell within the prespecified noninferiority margin of 15%.

Therefore, the findings demonstrated that CT-P13 is not inferior to infliximab originator, and the adjusted relative risk of disease worsening for CT-P13 patients was 1.17 (95% confidence interval, 0.82-1.52), compared with the infliximab originator group.

An almost equal number of patients achieved disease remission, 123 patients (61%) in the infliximab originator group and 126 patients (61%) in the CT-P13 group, and the adjusted rate difference was 0.6% (95% CI, −7.5% to 8.8% per-protocol set).

An explorative subgroup analysis that looked at patients with Crohn's disease and UC showed similar findings between patients treated with either agent.

The study was funded by the Norwegian Ministry of Health and Care Services. Dr. Jorgensen reported receiving personal fees from Tillotts, Intercept, and Celltrion. Several coauthors also reported relationships with industry.

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Risankizumab can effect, maintain Crohn's remission

By week 52, the majority of patients were still in clinical remission.

BY MICHELE G. SULLIVAN
Frontline Medical News

AT DDW

CHICAGO – Subcutaneous risankizumab maintained clinical remission for half a year in 76% of Crohn's disease patients who responded to it during an induction study.

The interleukin-23 antibody (ABBV-066; AbbVie) also maintained endoscopic remission in 52% of patients who entered the open-label maintenance phase of the 52-week study, Brian Feagan, MD, said at the annual Digestive Disease Week®.

The results of the phase II trial are enough to propel the drug into further studies as a Crohn's disease therapy. Both the induction and maintenance doses have yet to be determined for any subsequent studies, said Dr. Feagan of the Robarts Research Institute, University of Western Ontario, London.

The three-phase study enrolled 121 patients with moderate to severe Crohn's disease. The first 12 weeks consisted of intravenous induction therapy; patients were randomized to monthly infusions of risankizumab 200 mg or 600 mg or placebo. The endpoint was deep clinical remission. Patients who achieved remission exited the study. Results of this study were published in April (Lancet. 2017;389[10080]:1699-709).

Phase II included only the patients who did not achieve deep clinical remission. They all received open-label 600 mg risankizumab infusions every 4 weeks from weeks 14 to 26. The endpoints were clinical and endoscopic remission.

Phase III, on which Dr. Feagan reported, included the patients who achieved remission in phase II. These patients continued with subcutaneous risankizumab 180 mg every 8 weeks, from week 26 to 52.

Patients were an average of about 38 years old, with mean disease duration of 16 years. Their median Crohn's Disease Activity Index (CDAI) score was around 300; their mean Crohn's Disease Endoscopic Index score was 12. About a quarter had already taken at least one tumor necrosis factor–alpha inhibitor; half of those had taken at least two of those drugs.

University of Western Ontario, London

Dr. Brian Feagan is at the Robarts Research Institute, University of Western Ontario, London.

At the end of the first induction period, 25 taking the study drug and 6 taking placebo achieved clinical remission (31% vs. 15%). Those taking 600 mg did better than those taking 200 mg (37% vs. 9%).

Patients who didn't achieve deep clinical remission (a CDAI of less than 150 plus endoscopic remission) entered into the open-label reinduction phase; all received monthly 600-mg infusions from weeks 14 to 26. Of these, 62 achieved clinical remission and entered the open-label maintenance phase.

By week 52, the majority of patients were still in clinical remission, although this varied by the original treatment group: 76% of those first randomized to 600 mg, 59% of those randomized to 200 mg, and 79% of those randomized to placebo. Endoscopic remission was maintained in 52% of the 600-mg group, 23% of the 200-mg group, and 32% of the placebo group.

Deep remission occurred in a subset of patients: 43% of the 600-mg group, 13.6% of the 200-mg group, and 31.6% of the placebo group.

Dr. Feagan also said C-reactive protein levels remained suppressed in the maintenance period. Patients who entered that period had experienced a mean drop of about 9 mg/L in CRP. By week 52, this had risen slightly, but the median decrease was still around 8 mg/L from baseline measures.

There were 11 drug-related adverse events; these were severe in five patients, causing two to withdraw. There were 22 infections during the study, 1 of which was serious, but no cases of tuberculosis, cancer, or fungal or opportunistic infections.

"We did not see any new or unexpected safety signals," Dr. Feagan said. "The drug was well tolerated and appears safe."

This study showed a superior response for the 600-mg induction dose, but Dr. Feagan said the company may explore higher doses before making a final determination. Last November, the Food and Drug Administration granted Orphan Drug Designation to risankizumab for the investigational treatment of Crohn's disease in pediatric patients. The company is also investigating it in psoriasis; it recently outperformed ustekinumab in a small phase II study of patients with moderate to severe psoriasis.

The study was funded by Boehringer Ingelheim. Dr. Feagan reported financial relationships with AbbVie and Boehringer Ingelheim.

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DDSEP eight
Digestive Diseases Self-Education Program

Quick quiz answers

Q1. Answer: D
Objective: Understand the role of the restrictive transfusion strategy during patient stabilization and resuscitation as the initial step in the management of a variceal bleed.

Discussion: The initial therapy for acute variceal hemorrhage is resuscitation in an intensive care unit. Blood volume restitution should be undertaken promptly but with caution, with the goals of maintaining hemodynamic stability and hemoglobin around 7-8 g/dL.

Overtransfusion or volume overexpansion can precipitate variceal re-bleeding. A randomized clinical trial found that a restrictive transfusion strategy (transfusion when the hemoglobin fell below 7 g/dL) in patients with cirrhosis significantly improved survival. Endoscopic evaluation with potential variceal band ligation is appropriate only after initial resuscitation and stabilization of the patient.

Placement of a Blakemore tube and TIPS are not first-line therapy for this patient with Childs class A cirrhosis, and could be considered for recurrent bleeding that fails endoscopic therapy.

Endoscopic variceal ligation is more effective than sclerotherapy and is associated with fewer side effects. However, in patients for whom endoscopic variceal ligation is not feasible, sclerotherapy is a reasonable alternative.

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Q2. Answer: B
Objective: Diagnose dyssynergic defecation and treat with biofeedback therapy.

Rationale: This patient has a functional defecation disorder, or dyssynergic defecation. According to Rome III guidelines, to fulfill this diagnosis, the patient must satisfy criteria for functional constipation.

In addition, they must also have at least 2 of the following: 1) Evidence of impaired evacuation on balloon expulsion test or imaging; 2) inappropriate contraction of the pelvic floor muscles or less than 20% relaxation of basal resting sphincter pressure by manometry, imaging or EEG; and 3) inadequate propulsive forces assessed by manometry or imaging.

The treatment mainstay for functional defecation disorders is pelvic floor retraining and biofeedback. Although lubiprostone and fiber supplementation are used to treat constipation, this is not the treatment of choice for dyssynergic defecation. Amitriptyline is often used for functional gastrointestinal disorders, but is not the primary therapy for dyssynergic defection, and often can worsen constipation and so is not appropriate for this patient.

Finally, rectal biopsy is the gold standard for diagnosis of Hirschsprung's disease or congenital aganglionic megacolon. This is thought to be due to the failure of neural crest cells to migrate during gestation. The manometric findings with Hirschsprung's consist of lack of relaxation of internal anal sphincter with distention of the rectum. This is a diagnosis usually made during childhood. Adults with Hirschsprung's disease usually describe severe constipation since birth. It is therefore not the most likely diagnosis in this patient.

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PRACTICE MANAGEMENT TOOLBOX: Digital cohorts within the social mediome can circumvent conventional research challenges

BY ANAND KULANTHAIVEL, MIS, RACHEL FOGEL, JOSETTE JONES, RN, PHD, AND CRAIG LAMMERT, MD

As health care systems realize that they are changing from direct-to-business to a direct-to-customer model, their ability to connect directly with individuals will become a foundational strategy. This month's column introduces us to social media as a research tool. Information derived from social media sites can be harvested for critical clinical information (the Centers for Disease and Control and Prevention tracks the spread of influenza using social media analytic tools), for research data (patient preferences), and as a recruitment method for clinical studies. Kulanthaivel and colleagues have described their experiences and literature review to help us imagine new ways to collect data at markedly reduced transaction costs compared to a formal clinical trial. While there are many cautions about the use of social media in your practice or research, we are only beginning to understand its potential.

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

Beyond systemic issues, conventional research methods are burdened by minimal patient engagement, inadequate staffing, and geographic limitations to recruitment. Clinical research has failed to keep pace with patient demands, and the limited scope of well-funded, disease-specific investigations has left many patients feeling disenfranchised. Social media venues may represent a viable option to surpass these current and evolving barriers when used as an adjunctive approach to traditional clinical investigation.

The term social media (SM) most commonly refers to relatively public,

Continued on following page

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Internet-based communication platforms that enable users to consume and disseminate information. The most popular SM venues currently include Facebook, Twitter, YouTube, and independent online forums (*see* Table 1 at http:/dx.doi.org/10.106/j.cgh.2017.02.015). These digital platforms support sharing multiple forms of media including text, images, and videos among users who interact within a wide realm of medical groups and genres (e.g., specific diseases, symptoms, and so forth). This collective mediome[1] is a relatively untapped resource for clinical study, but research applications using SM methodology have begun to produce real study benefits in an array of diseases. Effective implementation of this technology by interested investigators will require an in-depth working knowledge of digital venues beyond their own online social presence. A firm grasp of these applications can enable contact with previously out-of-reach study participants, promote patient engagement and disease investment, and cultivate a community of interacting patients and researchers. This data-rich resource already has facilitated various aspects of biomedical studies, including dissemination of epidemiologic surveys,[2] direct recruitment into clinical trials,[3] collection of biologic samples,[4] and extraction of patient-provided data, all within SM platforms.[5]

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MR. KULANTHAIVEL

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Advantages and pitfalls in social media research

SM use is a new frontier containing a wide spectrum of clinical and qualitative data from connected users (patients). Collection and examination of either individuals' or groups' SM information use can provide insight into qualitative life experiences, just as analysis of biologic samples can enable dissection of genetic disease underpinnings.

There are many advantages to scientific interrogation of the social mediome, specifically because applications within SM have no physical bounds, encourage information exchange among stakeholders, and work in real time. SM far exceed the geographic limitations determined by the location of patients and academic systems, thus expanding dramatically the available recruitment population (*see* Table 1 at http:/dx.doi.org/10.106/j.cgh.2017.02.015). Patient-to-patient communication is facilitated by the format of most SM venues (Facebook and other Internet forums), thus creating an enriched collection of disease testimonies, symptom discussions, and treatment effects. In fact, patients frequently use SM to form online support groups to share experiences with similarly afflicted patients and families. These groups and their documented communications are valuable because qualitative patient data can provide a high resolution of variable patient metrics to investigators.[5] Finally, data collection from SM can occur continuously in real time and with little cost. Facebook, Twitter, and YouTube are free to use, although online Internet forums may incur small monetary investments (typically $15–$50 per month).

Because of study heterogeneity, it remains challenging to compare costs between a SM-based research study and a similar traditional clinic-based approach. However, historically, costs incurred to SM research pioneers have been dramatically lower than cost estimates of conventional approaches in the clinic.[6]

Several limitations and potential risks of SM for medical research should be addressed, including the possible compromise of privacy and confidentiality, the use and dissemination of medical advice and information, potential demographic biases, and a required trust of the investigator by patients. Many of these challenges can be similar to traditional methods; however, careful management can drastically reduce unwanted study issues.

The risk of Health Insurance Portability and Accountability Act violations must be considered seriously in the context of patient-researcher interactions on SM. Because of the relatively public nature of these venues, patient confidentiality may be at risk if patients choose to divulge personal medical information. However, if proper protective measures are taken to ensure that the venue is secure (e.g., a private or closed group on Facebook or a by-invitation-only online Internet forum), and the researcher vets all patients who request entrance into the group, this risk may be minimized. To further reduce any legal liability, the researcher should not provide any medical advice to patients who participate in a SM study. Safe approaches to communication could include redirecting patients to consult with their own doctor for advice, unbiased dissemination of disease-specific educational materials, or depiction of only institutional review board–approved study materials.[7,8]

An investigator-driven interactive community (e.g., Facebook group) may bolster patient involvement in SM studies and help facilitate disease-specific research. However, because most SM venues facilitate patient-patient interactions, misleading or incorrect medical information may be spread quickly between patients and could be misconstrued as official medical advice.[9] To mitigate this, a researcher or trusted study personnel must actively moderate the digital venue to prevent the spread of counterproductive information.[7]

The perception that only younger populations use SM may appear to be a significant limitation, but recent studies have shown that the use of SM has become increasingly common among older adults. As of 2014, more than half of the U.S. adult population used Facebook, including 73% and 63% of Internet-using adults ages 30-49 and 50-64 years, respectively.[10]

Finally, it is imperative for researchers to gain the trust of patients on SM to effectively use these venues for research purposes. Because patient-researcher interaction does not occur face-to-face on these platforms, gaining the trust of patients may be more difficult than it would be in a clinical setting. Thus, patient-patient and patient-researcher communications within SM platforms must be cultivated carefully to instill participant confidence in the research being performed on their behalf. One of the authors (C.L.) has established an SM educational model for this exchange.[4] Specifically, he provides patients with a distillation of current field research by posting updates in a research-specific Facebook group and on Twitter. Invested patients return to seek more study involvement.

Studies have shown SM methods to be an effective means of collecting data and improving quality of care for patients. One randomized controlled trial found that the use of SM to disseminate instructional information to patients alongside the traditional educational pamphlet increased patients' quality of bowel preparation for colonoscopies.[11] Another study successfully used the Crohn's and Colitis Foundation of America Partners Internet Cohort of more than 14,000 patients to examine factors associated with fiber consumption in inflammatory bowel disease and whether fiber was associated with disease flares.[2] In addition, several studies have assessed the roles of mobile applications, remote health sensors, and telemedicine in research and patient care and have found that these tools are effective at providing more comprehensive care in real time and with decreased costs.[12] Riaz and Atreja[13] noted that the most significant barrier to the use of these techniques in research and patient care is provider acceptability, in addition to the need for strict HIPAA compliance to ensure patient confidentiality.

Social media in rare disease research

Rare diseases (conditions with a prevalence of less than 200,000 patients in North America) are prime for high-yield results and community impact using novel SM approaches. This is the result of established digital support groups, publications with historically low study numbers, and few focused investigators. Several studies of rare diseases have shown considerable advantages of using SM as a study tool. For instance, an existing neuroendocrine cervical cancer Facebook support group recently was used to recruit a geographically widespread cohort of patients with this rare cancer. Through an online survey posted in the Facebook group, patients were able to provide specific information on their treatment, disease, and symptom history, current disease status, and quality of life. Without the use of SM, collecting this information would have been virtually impossible because the patients were treated at 51 cancer centers across the country.[14]

Similarly, a 2014 study investigating Fontan-associated protein-losing enteropathy and plastic bronchitis aimed to compare patient participation in surveys posted on SM with

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Persistent diarrhea:
are there faster diagnostic pathways?*

Persistent diarrhea is a common condition associated with multiple etiologies, which can make it challenging to diagnose the underlying cause.[1,2] A new advancement that streamlines the diagnostic pathway could help healthcare providers consider condition-specific treatment early for their patients.

Current challenges

The differential diagnosis for persistent diarrhea is extensive.[1] It is also not uncommon for patients to have more than 1 potentially causative factor.[3] The etiology of persistent diarrhea can include numerous infectious causes, including parasites (eg, *Giardia* and *Cryptosporidium*) and bacteria (eg, *Escherichia coli*, *Shigella*, and *Campylobacter*), and viruses (eg, norovirus).[4] There are also multiple noninfectious causes, including inflammatory bowel disease (IBD), celiac disease, irritable bowel syndrome (IBS), and bile acid malabsorption (BAM), which may be more prevalent than previously believed.[4,5]

As a result, diagnosis of persistent diarrhea can be a slow process,[1,4] and some patients may suffer longer than necessary. Having to order multiple tests may also be inconvenient for both healthcare providers and patients.

Convenient all-in-one testing is now available

Now there is a stool and serum test that may help healthcare providers diagnose many common causes of persistent diarrhea all at 1 time for added convenience. The PROMETHEUS® IBcause™ Diagnostic Test helps physicians diagnose common causes of persistent diarrhea—including intestinal inflammation, celiac disease, IBS, multiple pathogens, and BAM.[1,4,6-9,**] IBcause can also help clinicians determine if a multifactorial gastrointestinal condition may be irritating the bowel and causing persistent diarrhea, something that could remain unrecognized with sequential testing or empiric treatment.[4]

Combines multiple stool and serum assays***

IBcause evaluates a unique combination of 20 stool and serum measures all at 1 time, which may help clinicians get to a diagnosis faster and a specific treatment plan sooner (compared to sequential testing and empiric treatment). It quickly helps identify both infectious and noninfectious causes of persistent diarrhea in 1 easy-to-order test that is convenient for both clinicians and their patients.

Addition of BAM assay provides a more complete view*

Bile acid diarrhea is common in patients who have ileal-specific Crohn's disease or have undergone ileal resection surgery.[10] Perhaps lesser known is that BAM may affect up to 50% of patients with unexplained persistent diarrhea.[10] BAM is also a condition that is often overlooked or is misdiagnosed as diarrhea-predominant irritable bowel syndrome (IBS-D).[5,11] Some have suggested that IBS-D patients who fail standard therapy should be evaluated for possible BAM. A challenge is that the standard test for measuring bile acid diarrhea (the selenium homocholic acid taurine test, or SeHCAT) is not readily available in the United States, thereby hindering proper diagnosis.[10]

IBcause features a proprietary assay for BAM that is not available elsewhere to test for elevated 7α-hydroxy-4-cholesten-3-one (7C4) plasma levels, which have been associated with BAM.[10]

IBcause represents an important advancement for IBS-D patients who have not had success with standard therapy and can now be evaluated for BAM.[10] In a study where serum 7C4 levels were measured in IBS-D patients (n = 26), IBS with constipation patients (IBS-C, n = 26), and healthy subjects (n = 26), the IBS-D patients had increased hepatic bile acid synthesis, and greater levels of excreted bile acid were detected in stools collected for over 2 days.[12]

Tests for 14 types of pathogens

IBcause allows clinicians to simultaneously test for multiple pathogens that may present concurrently in patients with persistent diarrhea, including 8 types of bacteria, 3 types of parasites, and 3 types of viruses. Due to advanced polymerase chain reaction (PCR)–based amplification, IBcause is faster and more sensitive than conventional culture-based stool-testing methods. Clinicians can use IBcause to rule out > 90% of acute diarrhea-causing agents, including bacterial toxins.[13-15]

Utilizing IBcause can help clinicians streamline the diagnostic pathway for patients who present with persistent diarrhea.* For more information, visit IBcause.com or call Prometheus Customer Services at **888-423-5227**, Option 1, for additional information.

A new way to streamline the diagnostic pathway for persistent diarrhea*

Learn more at IBcause.com

*Compared to sequential testing with standard workup for persistent diarrhea.

**IBcause is recommended for patients with ongoing diarrhea (which may be referred to as persistent or chronic).

***Assays can also be ordered separately and all results should be used in combination with other clinical findings.

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participation in more traditional research modalities. The investigators found that 84% of responses were referred from SM. As of 2014, this cohort was the largest known group of post-Fontan protein-losing enteropathy and plastic bronchitis patients in existence.[15]

Currently, the use of SM in hepatology research is focused specifically on autoimmune hepatitis (AIH) at Indiana University. AIH is a rare autoimmune liver disease that results in immune-mediated destruction of liver cells, possibly resulting in fibrosis, cirrhosis, or liver failure if treatment is unsuccessful. One of the authors (C.L.) used both Facebook and Twitter to construct a large study group of individuals affected with AIH called the Autoimmune Hepatitis Research Network (AHRN; 1,500 members) during the past 2 years.[4] Interested individuals have joined this research group after searching for AIH online support groups or reading shared AHRN posts on other media platforms. Between April 2015 and April 2016, there were posts by more than 750 unique active members.

Preliminary informational analysis on this group has shown that Dr. Lammert and study collaborators have been able to uncover rich clinical and nonclinical information that otherwise would remain unknown. This research was performed by semi-automated download of the Facebook group's content and subsequent semantic analysis. Qualitative analysis also was performed by direct reading of patient narratives. Collected clinical information has included histories of medication side effects, familial autoimmune diseases, and comorbid conditions. The most common factors that patients were unlikely to discuss with a provider (e.g., financial issues, employment, personal relationships, use of supplements, and alcohol use) frequently were discussed in the AHRN group, allowing a view of the complete disease experience.

Take-away points:

1. Carefully constructed social media research approaches have the potential to be a powerful supplement to the traditional research model.
2. Investigators wishing to implement digital methods in research should develop a well-constructed plan to overcome the inherent challenges of privacy requirements.
3. Application of digital cohorts can assist in bridging conventional research barriers fueled by rising study costs, geographically distributed patients, and limited patient awareness of disease-focused research.
4. Patients are overwhelmingly supportive of this means of research engagement, as it provides a functional conduit to report on facets of both clinical and nonclinical information in real time.

Conclusions

SM have the potential to transform health care research as a supplement to traditional research methods. Compared with a conventional research model, this methodology has proven to be cost and time effective, wide reaching, and similarly capable of data collection. Use of SM in research has tremendous potential to direct patient-centered research because invested patient collaborators can take an active role in their own disease and may hone investigatory focus on stakeholder priorities. Limitations to this method are known, but many can be mitigated. Investment in and application of the social mediome by investigators and patients have the potential to support and transform research that otherwise would be impossible.

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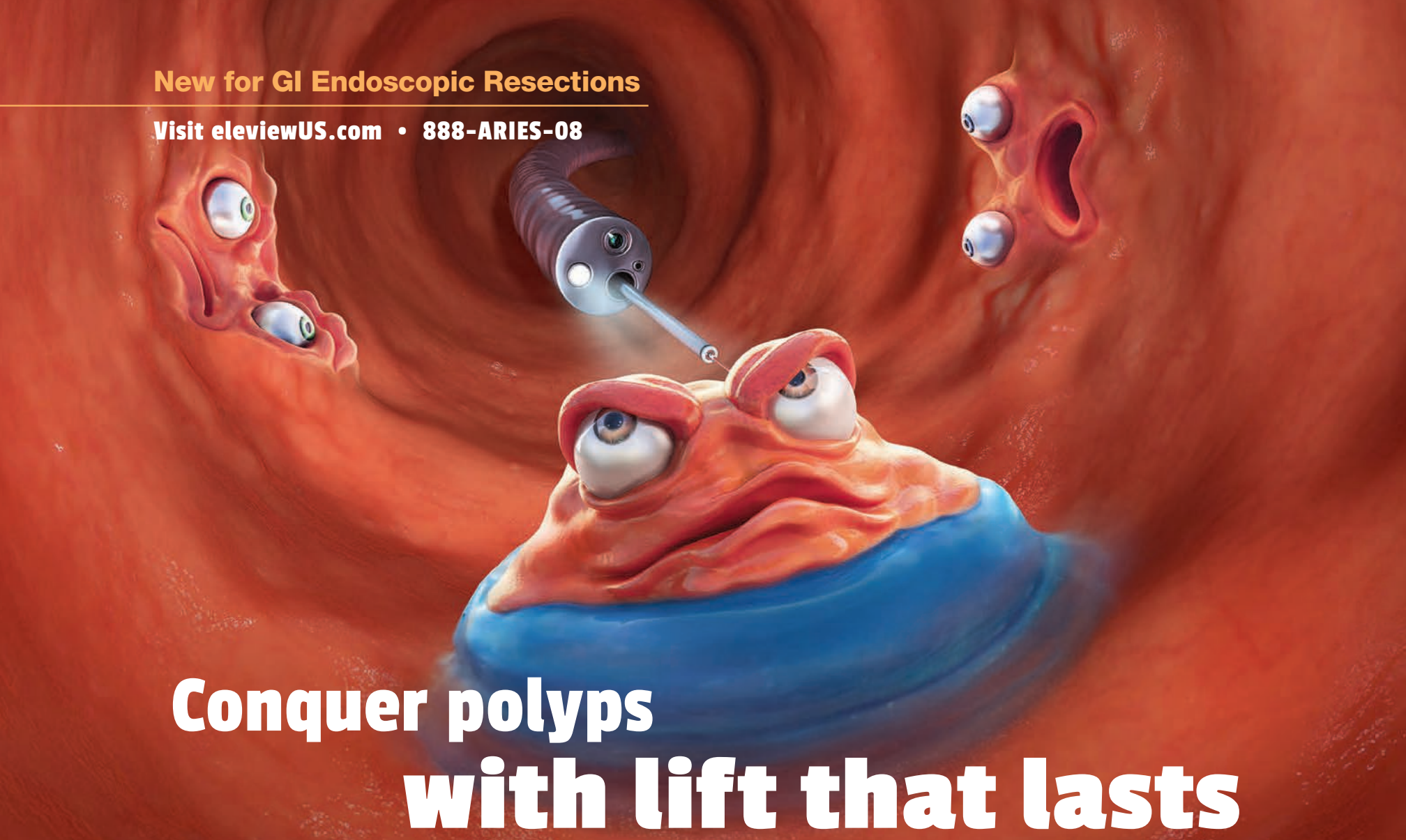

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References: 1. Eleview™ Instructions for Use, Aries Pharmaceuticals, Inc. April 2017. **2.** Data on File, Aries Pharmaceuticals, Inc.

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