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COVERING THE SPECTRUM?

Is elastography the way to go for patients with HCV?

Articles by Stuart Gordon, MD; and Keyur Patel, MD

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In this issue

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Note From the Editor

One of the goals of *AGA Perspectives* is to provide the readership with expert updates on rapidly evolving areas of research and clinical practice in digestive diseases. It is clearly a challenge to keep up with the rapid advances in the field, and importantly, how best to decide when to add new approaches into clinical practice given the economic realities of medicine in 2016. This issue addresses a variety of those themes.

In the area of technology advances, Drs. Stuart Gordon and Keyur Patel provide a point-counterpoint discussion on the promise and pitfalls of transient elastography in patients with hepatitis C infection. Another area flush with new technology is advanced imaging in Barrett's esophagus. Gastroenterologists need to ask if, and when, to add new techniques such as confocal laser endomicroscopy and volumetric laser endomicroscopy to their armamentarium, which is a topic addressed by Drs. Stuart Thomas and Prateek Sharma.

The gut microbiome is another emerging area in the field of digestive health with clear clinical implications in *Clostridium difficile* infection, but less clear implications beyond that. Drs. Ece Mutlu and Purna Kashyap provide the readership with an overview of both the promises and limitations of the microbiome today. Practice measures are moving from theory to clinical practice and Drs. Jason Reich, Sharmeel Wasan and Francis Farraye provide insights into the utilization of these measures in inflammatory bowel disease.

Extraesophageal manifestations of gastroesophageal reflux disease are one of the more frustrating areas for both patients and gastroenterologists. This area has been the subject of Dr. Michael Vaezi's research for many years and he and Dr. David Francis provide their views on the vexing problem of chronic cough.

Other topics discussed in this edition, which are of special importance to trainees and early-career gastroenterologists, include microvolunteerism [and what it means!], the unique perspectives of an international trainee in the U.S. and a look at the involvement of young gastroenterologists in health-care policy curriculum development.

After reading through these articles, make sure to share your thoughts on the themes and topics covered in this issue of *AGA Perspectives* in our new online networking and collaboration forum, AGA Community. AGA Community provides a fantastic outlet for contributors and readers alike to dive further into these important clinical practice topics. Visit community.gastro.org to get started.

Best,

Gary W. Falk, MD, MS, AGAF
EDITOR
@DrGaryFalk

We welcome member feedback on all of the perspectives presented in this issue. Send your letters and comments to communications@gastro.org and include "*AGA Perspectives*" in the subject line.

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COVERING THE SPECTRUM?

Is elastography the way to go for patients with HCV?

Elastography: Paving a New Pathway in HCV Testing

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Dr. Gordon receives grant/research support from AbbVie, Bristol-Myers Squibb, Conatus, CymaBay, Exalenz, Gilead, Intercept and Merck. He also consults for Abbie, Bristol-Myers Squibb, Intercept, CVS Caremark, Gilead and Merck, and has spoken on behalf of Gilead and Intercept.

Given the option of a diagnostic procedure that is invasive, even with a small risk of death, over a noninvasive equivalent, the choice seems obvious. As an analogy, why in 2016 would a patient with ulcerative colitis, a raised alkaline phosphatase level and suspected primary sclerosing cholangitis

undergo ERCP first and not magnetic resonance cholangiopancreatography?

Now two decades after subjecting our hepatitis C (HCV) patients to liver biopsy (because it is the gold standard) before starting treatment, gastroenterologists are realizing that biopsy may not always be "the way to go."

In 1958, Menghini's "one-second liver biopsy" ushered in a new era;[1] at one point 30,000 liver biopsies were done in the U.S. annually. It is worth recalling that in order for the first oral hepatitis B (HBV) drugs to gain FDA approval, there was an insistence on tangible evidence of "liver improvement," (i.e., histological evidence of reduction in hepatic inflammation. Viral levels were relatively immaterial). Later, the initial hepatitis C therapies also required both pre- and post-treatment liver biopsies in order for these agents to gain approval. But lately, the numbers of HCV-staging biopsies have plummeted and many centers are reporting steep declines in the use of this procedure.

The use of biopsy in order to stage liver disease, in retrospect, probably contributed to a vast underdiagnosis of HCV-related cirrhosis in the U.S. Physicians were reluctant to order or perform the test, and patients were even more reluctant to proceed. Often pathologists could not visualize complete nodules and render the diagnosis, and cirrhosis was frequently diagnosed only once decompensation occurred, when it was too late. Up to 25 percent of HCV patients today have cirrhosis but most are still not aware of their diagnosis. Several very useful and validated noninvasive biomarkers are available (FibroTest, aspartate aminotransferase/platelet ratio index, Fibrosis-4 and others) but are relatively underutilized. Finally, U.S. clinicians are catching up with their European and Asian counterparts and can instantly, cheaply and noninvasively utilize elastography to assess their

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Elastography: Proceed With Caution

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Dr. Patel has served as a consultant, advisor or has conducted data monitoring for Gilead, Nitto-Denko, Bristol-Myers Squibb, Benitec and Merck.

Histologic assessment of liver disease has been a cornerstone of therapeutic decisions and predicting prognosis in chronic liver disease for much of modern hepatology. Although we still regard liver biopsy as the gold standard for assessment of injury, inflammation and fibrosis stage, its clinical application for chronic hepatitis C (HCV) has significantly decreased over the past decade. Non-invasive approaches for assessment of liver fibrosis have been under development over the same period, and now include various "biochemical" serum marker panels, or imaging modalities, which provide a "physical" measure of liver stiffness.[1] These non-invasive tests certainly overcome the risks, and perhaps some of the limitations, associated with liver biopsy, but have diagnostic limitations that need to be considered when interpreting results.

From a historical perspective, the initial development of serum fibrosis marker panels in chronic HCV, (such as the proprietary FibroTest, BioPredictive, Paris, FR [HCV FibroSURE, LabCorp, Burlington, NC, in the U.S.], or the easily calculated nonproprietary AST-to-Platelet Ratio [APRI]), were based upon differentiating a broad fibrosis range (e.g. METAVIR F0-1 vs. F2-4).

The subsequent development of vibration-controlled transient elastography (FibroScan®, Echosens®, Paris, FR) provided a viable alternative method for differentiating these broad categories of fibrosis. Early studies showed us that biopsies could be avoided in most patients, if the presence of F2-F4 was the only information required to guide the decision to initiate 48 weeks of interferon-based therapy. The rapid evolution of simplified noninterferon direct acting antiviral therapeutic regimens, with high efficacy and tolerability among all HCV genotypes, suggests that the role of liver biopsy for accurate staging of disease prior to antiviral therapy is even more limited. There has been a steady decline in the use of diagnostic liver biopsy in chronic hepatitis C, as can be judged by the experience of any recent graduate from a gastroenterology fellowship. This has been paralleled by the increased availability, use and subsequent incorporation of noninvasive tests in chronic HCV clinical practice and society guidelines.[2] The requirement for fibrosis staging prior to antiviral therapy approval by third-party payors, means that our routine narrative in everyday clinical practice now includes results from vibration-controlled transient elastography or serum fibrosis marker panel.

Following regulatory approval of transient elastography in the U.S. in 2013, there is increasing but not universal availability of this device.[3] At our tertiary medical center in North Carolina, patients still travel significant distances for vibration-controlled transient elastography assessment. Other practical limitations that prevent point-of-care testing for all chronic HCV patients at their initial visit includes significant facility fees that often require prior authorization, and/or the absence of a dedicated technician or experienced provider. Quality measures are established for transient elastography, and require at least 10 validated measurements, a success rate (the ratio of valid measurements to the total number of measurements) of greater than 60 percent, and an interquartile range that reflects variations among liver stiffness measurements of less than 30 percent of the median value (interquartile range/liver stiffness measurement (IQR/LSM) less than or equal to 30 percent). Interpretation of the liver stiffness measurement must be in the context of these quality metrics.

In fact, prior studies have shown that the highest accuracy for fibrosis staging is obtained with the more stringent interquartile range/liver stiffness measurement less than or equal to 10 percent. Around 15 percent of results may be unreliable, and failure to obtain any liver stiffness measurement occurs in 3 percent of chronic HCV patients, mostly due to obesity or operator inexperience (less than 500 examinations). Transient elastography results indicating IQR/LSM greater than 30 percent in conjunction with liver stiffness measurement greater than or equal to 7.1 kPa are particularly unreliable.

In clinical practice, liver stiffness measurement readings can still be obtained in most patients, so quality measures are often overlooked. This important limitation is perhaps not always appreciated by the requesting provider, and is rarely documented clearly in the main narrative. By obtaining liver stiffness measurements at a greater skinfold depth than the M probe, the relatively newer XL probe now overcomes some of the difficulties with obtaining successful vibration-controlled transient elastography readings in obese patients. However, liver stiffness measurement with the XL probe is around 2 kPa lower than with the M probe, and validated thresholds for fibrosis stage in chronic hepatitis C (or other chronic liver disease) have not yet been established. Transient elastography reliability decreases with a body mass index greater than 30, and significant steatosis (for example in chronic hepatitis C genotype 3 or concurrent non-alcoholic fatty liver disease) may underestimate fibrosis stage, with failure rates of up to 25 percent even with the XL probe.

Apart from obesity and operator inexperience, other important liver stiffness measurement confounders

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patients' "liver stiffness" to help gauge if cirrhosis is likely, and if present, determine how to proceed.

In many ways the advent of transient elastography has paved a new pathway in HCV diagnostic testing. Stiffness scores are visualized, and it represents a simplistic and understandable concept both for physicians and patients. In addition to the most popular transient (vibration-controlled) elastography, there are ultrasound-based, acoustic radiation force impulse and magnetic-resonance-based elastography platforms. Each has their respective strengths and weaknesses, but each is also noninvasive. Moreover, the ability to provide a numerical "degree" of liver stiffness that correlates both with diagnosis of cirrhosis and with translation to clinical outcomes (hepatocellular carcinoma and hepatic decompensation) offers a giant leap forward in staging liver fibrosis measurement. Thus the potential ability to provide a tangible parameter of "how much" cirrhosis is present, not just that it exists.

Therefore, transient elastography not only obviates the need for invasive and often inaccurate liver biopsies, but the actual stiffness score provides us with our first glimpse of "staging" cirrhosis on a continuum: the higher the score, the stiffer the liver, the worse the prognosis. On the other hand, even the most successful percutaneous liver biopsy, no matter how large a specimen, that actually rendered the diagnosis of cirrhosis could provide a "METAVIR IV" score or an "Ishak 6" score, but no additional assessment of degree of fibrosis.

As with any diagnostic medical test, caveat emptor, or "let the buyer beware." For elastography, caveats abound. The stiffness score represents a risk stratification; it does not stage fibrosis and this fact bears repeating. State Medicaid groups and third-party insurance companies dangerously use these scores as a means by which to deny curative antiviral HCV therapy. We have seen the patient with a non-cirrhotic stiffness score who subsequently, one year later, was found to have hepatocellular carcinoma and, alas, a cirrhotic liver. Stiffness scores correlate very well with fibrosis, but confounders can affect results. Scores depend upon user experience and competence, comorbid conditions, obesity and a host of other factors. Although very low and very high scores are helpful, in-between scores are by definition ambiguous.

Elastography not only obviates the need for invasive and often inaccurate liver biopsies, but the actual stiffness score provides us with our first glimpse of "staging" cirrhosis on a continuum

There is also now the exciting option of longitudinal follow up and assessment of fibrosis progression over time. Previously, serial liver biopsy studies were few and far between, fraught with confounders and low patient numbers. As the elastography field is refined, one can envision a "delta score" over time as a means by which to assess fibrosis progression or regression. This truly represents a refinement in liver disease assessment that was not heretofore possible.

In many ways, the archaic days of mandated liver biopsies, are alive and well: the new NAFLD drugs in development, like HBV and HCV in the past, still require pre- and post-treatment liver biopsies, including the stipulation for large liver sample size, length and width, to document changes in fibrosis as the pathway toward drug registration.

For nonalcoholic fatty liver disease, biopsy remains king, with noninvasive elastography not yet ready for prime time for fibrosis staging. Nevertheless, the reality is that gastroenterologists and hepatologists are largely abandoning doing the procedure themselves (too much risk, too little reimbursement). Radiologists rarely use the 16-gauge cutting needle that allows for adequate sampling. So where does that leave us — and is liver biopsy becoming a dying art?

The revelations at liver biopsy can help establish many unexpected diagnoses including infiltrative disorders, neoplasms, unusual infections, vascular conditions and cellular rejection. For those hepatologists and liver pathologists who appreciate the clinical and academic value of each liver biopsy specimen, the advent of elastography will serve to augment but never replace biopsies. Yet for simply staging fibrosis in patients with chronic hepatitis C, the era of liver biopsy is fading fast, because primum non nocere, or "first, do no harm." ■

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CAUTION - CONTINUED FROM PAGE 5

that are independent of fibrosis include inflammation, cholestasis, congestion and food intake.4 Based on liver stiffness measurements, elevation in alanine aminotransferase greater than 100 IU/L may place chronic HCV patients with F0-2 fibrosis into the cirrhotic range. Fortunately, chronic HCV is not associated with significant hepatic transaminase flares, which can lead to three-fold elevations in liver stiffness measurement as seen in chronic hepatitis B (HBV) infection. Also, transient elastography assessments are scheduled throughout the entire day, so a strict requirement for a two-to-three hour fasting period is often not feasible and is overlooked for point-of-care testing, particularly if there is no requirement for prior authorization and a return visit. A 600 Kcal meal will increase liver stiffness measurement for one-to-two hours, and could easily place a patient with moderate-advanced disease into the cirrhotic range.[4] Alcohol excess, or other co-morbid conditions that lead to hepatic congestion (right heart failure) or cholestasis, will also significantly elevate liver stiffness measurement. Thus, transient elastography should be performed by an experienced operator in fasting patients (for at least two to three hours), taking into account alanine aminotransferase levels, body mass index, alcohol intake and other co-morbid states.

Apart from obesity and operator inexperience, other important liver stiffness measurement confounders that are independent of fibrosis, include inflammation, cholestasis, congestion and food intake.

Liver stiffness measurement thresholds have been validated for chronic HCV but vary in HIV-HCV co-infection or other chronic liver diseases. Vibration-controlled transient elastography is useful for the exclusion of cirrhosis, but has similar accuracy for significant fibrosis (greater than or equal to F2) as serum fibrosis markers that are readily available, and also provide an alternative for discordant findings (between transient elastography and other clinical/radiological/biochemical assessments). Transient elastography and other noninvasive tests cannot differentiate between adjacent stages of fibrosis. Repeating alanine aminotransferase at relatively short intervals (three-to-six months) as is often done in clinical practice, will not provide any meaningful assessment in terms of changes in disease severity and is more likely to be influenced by observer error. It is important to remember that liver stiffness measurement readings will likely be lower in chronic HCV patients following sustained virologic response. This is due to reduced necroinflammation and normalization of liver transaminases, and not regression of fibrosis. Of clinical relevance, patients with persistent chronic HCV cirrhosis on biopsy following sustained virologic response may have early reductions in liver stiffness measurement and could be placed in lower fibrosis stage categories that could be falsely reassuring to both the clinician and patient. Actual changes in liver stiffness measurement that reflect fibrosis remodeling may take two-to-three years following sustained virologic response.[5]

The ease of use and familiarity with transient elastography often results in application to disease states without established thresholds. I have seen requests for transient elastography by experienced clinicians for fibrosis assessment in patients with potential methotrexate-induced liver injury or autoimmune disease, with non-validated chronic HCV thresholds subsequently used to report an estimated fibrosis stage. Vibration-controlled transient elastography may be useful for predicting complications from portal hypertension. However, liver stiffness measurement readings for hepatic vein portal pressure gradient greater than or equal to 10 to 12 are influenced by significant changes in hemodynamics rather than fibrosis, and at this time, transient elastography cannot be used to follow changes in hepatic vein portal pressure gradient in decompensated disease, or replace GI endoscopy for varices surveillance.[6]

Transient elastography (along with other imaging methods and blood tests) certainly represents a significant advance in our field. With appropriate use, and cautious interpretation in the context of quality metrics and understanding of device limitations, transient elastography now provides complementary and clinically relevant information, to the health-care provider for the assessment of liver-disease severity. ■

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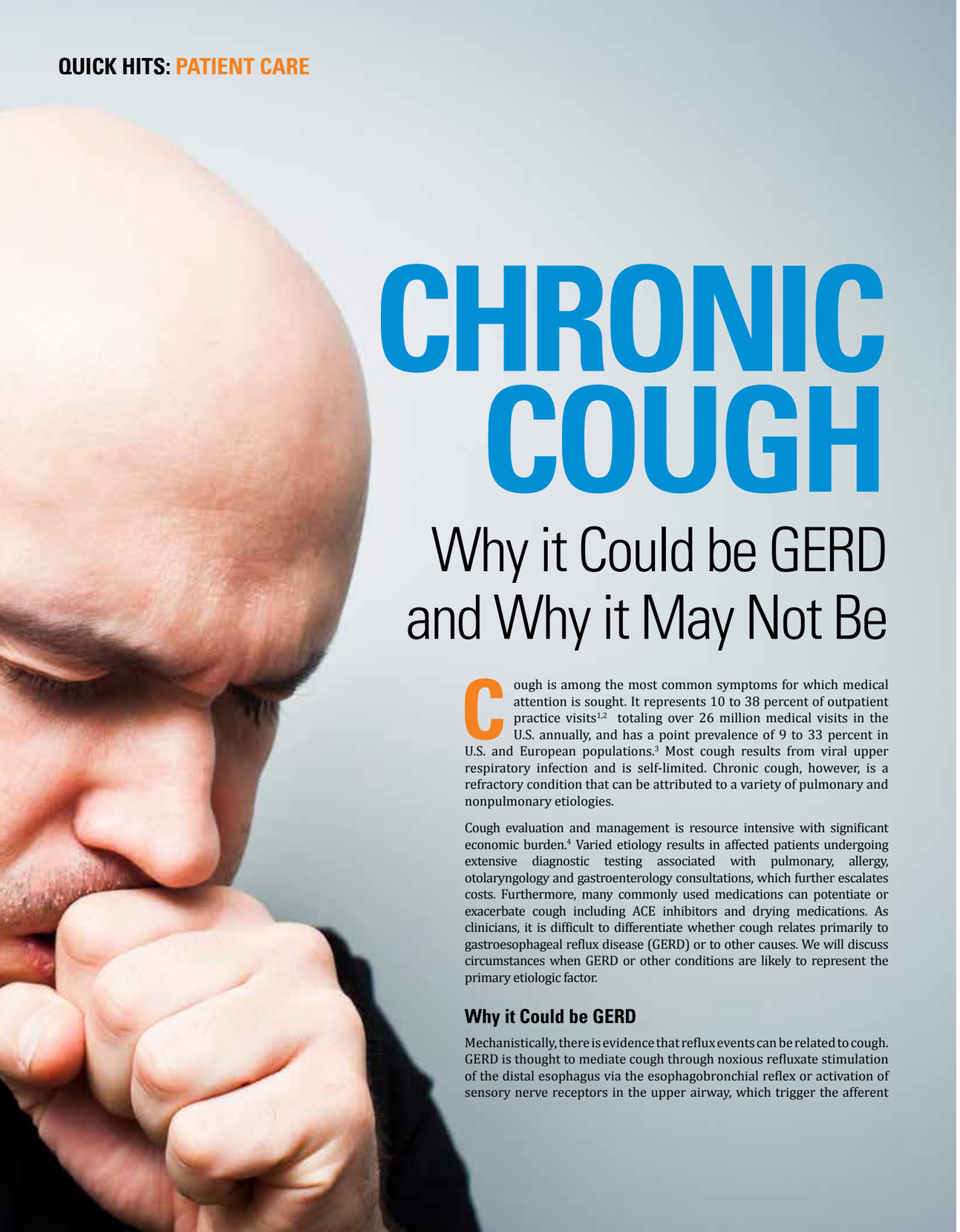

CHRONIC COUGH

Why it Could be GERD and Why it May Not Be

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Cough is among the most common symptoms for which medical attention is sought. It represents 10 to 38 percent of outpatient practice visits[1,2] totaling over 26 million medical visits in the U.S. annually, and has a point prevalence of 9 to 33 percent in U.S. and European populations.[3] Most cough results from viral upper respiratory infection and is self-limited. Chronic cough, however, is a refractory condition that can be attributed to a variety of pulmonary and nonpulmonary etiologies.

Cough evaluation and management is resource intensive with significant economic burden.[4] Varied etiology results in affected patients undergoing extensive diagnostic testing associated with pulmonary, allergy, otolaryngology and gastroenterology consultations, which further escalates costs. Furthermore, many commonly used medications can potentiate or exacerbate cough including ACE inhibitors and drying medications. As clinicians, it is difficult to differentiate whether cough relates primarily to gastroesophageal reflux disease (GERD) or to other causes. We will discuss circumstances when GERD or other conditions are likely to represent the primary etiologic factor.

Why it Could be GERD

Mechanistically, there is evidence that reflux events can be related to cough. GERD is thought to mediate cough through noxious refluxate stimulation of the distal esophagus via the esophagobronchial reflex or activation of sensory nerve receptors in the upper airway, which trigger the afferent loop of the cough reflex. Evaluating clinicians rarely have a simple approach to differentiate the particular etiology of reflux-related cough or even to determine if reflux is the culprit. While it is plausible that reflux is the primary cause of idiopathic chronic cough, it is less common than previously presumed.

Cough is more likely to be triggered by reflux if associated with classic GERD symptoms. In a recent study of patients with laryngopharyngeal reflux symptoms post fundoplication, we found that chronic cough response to surgery is more likely in those with concomitant typical GERD symptomatology — heartburn ± reflux.[5] Those who improved also had pathological reflux on pH monitoring and endoscopic presence of hiatal hernia. This highlights the importance of volume regurgitation as a trigger for cough. Thus, presence of concomitant classic GERD symptoms and a moderate degree of reflux by pH monitoring off therapy may guide whose chronic cough symptoms may be reflux related. Another recent study, employing a novel cough monitor device synchronized with 24-hour pH-impedance testing, showed that even physiologic reflux events may be temporally associated with cough events.[6] This suggests that in patients with chronic cough, irritation from physiological reflux can also initiate coughing spells. It also indicates that once someone has chronic cough, it can be perpetuated by normal physiologic reflux events into the esophagus. In the context of these studies, it is important to recognize that the associated therapeutic benefit of acid suppression is modest compared to the effects on classic GERD symptoms (i.e., heartburn, regurgitation). Although commonly practiced, acid-suppression therapy is not a sensitive test, thus caution should be exercised when attributing the cough to reflux even among responders.[7]

Why it May Not be GERD

One must not be too simplistic when considering the etiology of chronic cough. It is easy to attribute cough to allergies, asthma, GERD or other sources without demonstrable evidence. Empiric treatment of these conditions may be effective. However, in many situations, particularly in patients with chronic cough, it is a disservice to overly simplify their disease. Each specialty approaches chronic cough differently from within the lens of their experience, training and biases. It is important to carefully listen to the patient's triggers, and to be open minded and approach this process with a degree of humility to avoid the tendency toward furor medicus (or misdirected medical activity). There is a reason that nearly half of patients with chronic cough have etiologies deemed idiopathic.

In many patients, chronic cough is multifactorial in etiology and that cough's precipitating inciting event is distant history. Additionally, it might no longer have management-related relevance at the patient's presentation. For example, patients often state that the inciting event was an upper respiratory infection, but as other associated symptoms resolved, the cough persisted. They did not have pathological cough prior to the upper respiratory infection, so is it fair to attribute the cough to asthma, allergies or even GERD? Some argue that the act of coughing may have caused some damage to the esophagus or diaphragm that resulted in a predisposition to GERD. It is difficult to conceptualize how the vast number of patients with this condition would all suffer this fate. In this scenario, it is also difficult to understand how anyone with this degree of damage could have symptom resolution.

Thus, it is important to recognize that other etiologies for chronic cough exist beyond those routinely espoused, including adult-onset asthma, allergies and GERD. The same study mentioned previously that synchronized the cough monitor to pH-impedance also was illustrative of what other etiologies may be contributing to the chronic cough.[6] The strongest predictor of cough in this study was the occurrence of a prior cough. While this may seem intuitive, it is a critically important point. Chronic coughing involves repeated trauma to the vocal folds as they close, as manifested by the cough sound. Its chronicity can result in what is termed laryngeal sensory neuropathy or irritable larynx syndrome. The proposed pathophysiology is abnormal, repeated stimulation of sensory receptors causing neuroplastic changes in brainstem laryngeal controlling networks, inducing them into a perpetually hyperexcitable state, which increases the epithelial sensitivity to sensory stimuli. Depending on the coughing frequency and severity, it can stimulate further cough with lesser and typically nonstimulating inciting factors (e.g., breathing, laughing, talking, certain smells, throat mucus). Thus, we found that cough strongly begets cough, thereby explaining the paroxysmal nature of cough in these patients. Furthermore, this study found that phonation was a trigger for cough, providing more evidence that typically physiologic activities can act as an effector of cough in patients who are hypersensitive.

These findings underscore the importance of a careful history and understanding what the triggers are for these patients. If chronic cough patients complain of concomitant typical GERD symptoms or show evidence of pathologic reflux on pH testing, then the probability is higher that GERD is playing a role in their cough. In the absence of these findings, it is incumbent on the physician to have an understanding of the complex differential diagnosis, including careful consideration of whether this could be a hypersensitivity phenomenon triggered by typically non-noxious physiological processes. Idiopathic chronic cough remains a difficult condition for patients and providers. Patients recognize how debilitating it is for their quality of life, and it is important that we as providers are sympathetic and not dismissive of its severity. It's also important that we continue to better understand specific underpinnings as we move toward a cogent understanding of its complex pathophysiology and development of effective treatment approaches. ■

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NEW HORIZONS

The Perspective of an International Trainee in the U.S.

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Imagine that you are born in a country where English is not the primary language and that an interest in biological sciences, a passion for healing and the lure of a prestigious career catapults you into medical school. What follows is a whirlwind of events. In order to prove that Newton was correct you continue to be in motion, scaling new heights of academic excellence. The search for the next frontier and the desire to be at the leading edge of medical science brings you to the U.S. Writing this article gives me an opportunity to reflect upon what happens next and possibly provide helpful insight to international trainees who are at different stages of this journey.

Let me start by talking about the upside. If you are an international trainee in the U.S., you have already overcome the most difficult step of getting accepted into an accredited medical training program in this country. Now, as long as you have a clear career objective and the motivation to work hard, the U.S. graduate medical education system will help you advance your career. When I started as an internal medicine resident and a new international trainee I was pleasantly surprised at the ease with which I could access medical information electronically both for patient care and educational purposes. This facilitated case-based learning and laid the foundation for an evidence-based practice of medicine. I soon realized that there were other components of care delivery that were as important as medical knowledge. My subsequent years of training taught me the importance of quality, safety, multi-disciplinary teamwork, care transitions and, above all, the ability to assess and prioritize the needs of my patient. If you are a trainee reading this article, I would encourage you to pay close attention to these components of training not only as simple terms but as learning objectives.

The journey is beautiful and the hardships endured along the way provide the contrast. Several training programs do not consider applications from international medical graduates when selecting a residency class. This can be frustrating and it is during these difficult stages that one learns to persevere and not lose hope. The hours of a trainee are long, the learning curve is steep and financial strain is almost unavoidable. If that sounds difficult, add to it the social challenges of adapting to a new culture, a change in food and eating habits, linguistic barriers at the patient-physician interface, and the fear of isolation among peers. This makes the transition from medical school to a trainee physician extremely challenging for even the most outstanding international trainee. If I were to identify one skill that helps overcome some of these hurdles, I would pick effective communication skills. Some individuals are naturally gifted communicators; most however need to learn and practice. Participating in teaching skills workshops and using validated online resources is helpful. Soliciting feedback from 'role models' often identifies areas for improvement and can be quite helpful as well. Identifying mentors, not only among faculty but also among peers, especially those who have traveled this path, is also invaluable.

Transitioning to subspecialty training poses additional unique challenges for the international trainee. You should focus your attention on identifying a career path early during residency, excelling in all aspects of clinical training, seeking out opportunities to engage in scholarly activities, developing a credible relationship with peers and an impeccable reputation among mentors that would eventually translate into strong letters of recommendation. I distinctly remember something that a fellowship program director once told me when I was a resident, "The best residents make the best fellows, and that's who you want to be, a top-notch resident in the eyes of your patients, peers and faculty members."

The transition to your first job is another critical and high-stress phase in the life of an international trainee. The conflict between staying in the U.S. and going back to one's home country is coupled with anticipating needs from a social, academic, professional and immigration standpoint. Planning ahead of time is pivotal to a successful transition.

In summary, I have always felt that as an international trainee, you cannot accurately plan for all the eventualities of life. But you can observe the people around you and imbibe the traits that you find admirable. Learn to listen to your inner voice and let it guide you when you are at crossroads in your career. Failure is disappointing, but it is also universal. Success has different measures and it is important to know what it means to you and your loved ones. May the force be with you! ■

If I were to identify one skill that helps overcome some of these hurdles, I would pick effective communication skills.

PROMISES AND LIMITATIONS

Translating Microbiome Research to Practice

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The advent of affordable, next-generation sequencing technology has democratized the study of the microbiome, the vast collection of microbial life both within and on us, and has enabled the discovery of hundreds of host-microbiome interactions. This has brought with it a wave of optimism, leading scientists and the public alike to seek new avenues for health and a panacea in the microbiome for many diseases. As with all new areas of research, once the initial wave of optimism subsides, we realize that targeting the microbiome will not cure all. However, it is also clear that there are areas where it will be a key strategy. In this article, we will highlight a few of these key areas: infections, host metabolism, cardiovascular disease and pharmacotherapy.

1. Infections

The best-studied example of resistance to pathogen invasion is in C. difficile infection. The disruption of gut microbial community by antibiotics and other factors alters the gut metabolic milieu allowing C. difficile to colonize. Restoration of the microbial community by fecal microbiota transplant or defined microbial communities can drive C. difficile out, effectively restoring colonization resistance. A similar paradigm likely holds true for other infections like Salmonella.

2. Host Metabolism

The role of gut microbiota in regulating host metabolism, including weight gain and impairment of glucose tolerance, is another key area. An example of this is seen with improvement in glucose tolerance by transplanting gut microbiota from lean to obese individuals.

3. Cardiovascular Disease

Gut microbiota was noted to be a driver of atherosclerotic plaques by facilitating the conversion of dietary L- carnitine found in red meat to Trimethylamine N-oxide (TMAO), further confirmed by a complimentary finding that plasma L-carnitine levels with concurrently high TMAO were predictive of increased risk of cardiovascular disease in humans. The recent study on small molecule inhibitors of microbial trimethylamine lyases holds promise as a strategy to curb the epidemic of cardiovascular disease.

4. Pharmacotherapy

The role of gut microbiome in mediating side effects of drugs such as irinotecan for colorectal cancer is yet another example where targeting the microbiome can potentially improve outcomes.

While the majority of other findings implicating the microbiome have not yet been translated to impact human health, the above few examples underscore the rapidity with which we are getting there.

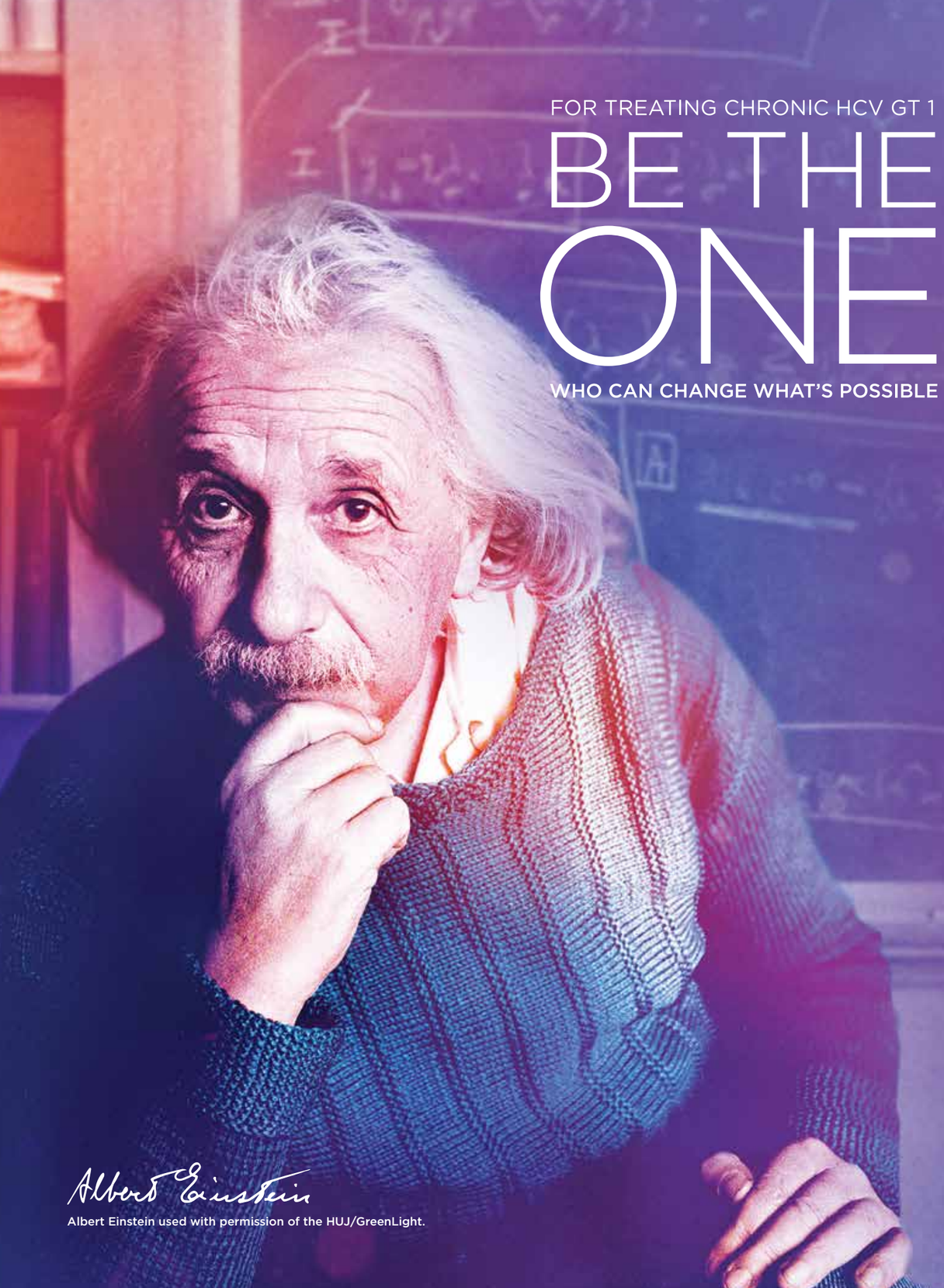
There are also significant limitations to understanding the microbiome and related research. The most important of these is lack of a mechanistic approach in studying the microbiome and its effects on the host. To date, the majority of the studies have focused on disease association with changes in microbial composition, with little attention to microbial function, which is much more relevant. But identifying functions within the microbiome is no simple task. In the gut microbiome, at least, it appears that function depends on individual genes carried by organisms at the species/strain level, complicating our search to hundreds of slightly different organisms (as opposed to being able to study a handful of related organisms within the same phylogenetic lineage, i.e. a family). Furthermore, unlike eukaryotic organisms where single genes are translated to single functional proteins, bacteria can utilize multiple gene segments to synthesize a single protein and can switch the synthesis of such proteins, responding to stimuli within the environment, either from the host or from other bacteria or non-bacterial organisms such as viruses and fungi. Efforts characterizing these nonbacterial members of the microbiome are still at their early stages, with limited availability of databases of information on them. Some functions in the microbiome can also be highly specialized, limiting them to certain members of the microbial community, which compose less than 1 percent of the total, complicating the search for them and making them similar to searching for a needle in a haystack.

Learn more from the AGA Center for Microbiome Research and Education on **gastro.org**

Lastly, research about environmental factors affecting the function of the microbiome also needs development to make a significant impact on health. One example is diet: research suggests that one factor in the diet that affects the microbiome can no longer be operational when another dietary component is added, and additives in the diet that make up less than 1 to 2 percent of food can have effects on both function and colonization in the gut. Characterizing such interactions and effects of minor components are still difficult, especially on a large scale.

Not only we are just scratching the surface when it comes to determining function, but we are also in our infancy in understanding the variation in the microbiome from one person to another, in our quest for the "healthy/normal microbiome." Common demographic factors such as age, race/ethnicity and BMI have little impact on an individual person's gut bacterial fingerprint, implying that we will need to look for singletime events, either in childhood or adulthood, which can have long lasting consequences on microbiome composition and function. Such legacy events can be in individual organisms (i.e., in their appearance or disappearance from the gut microbiome) or in individual gene elements within organisms. These can be passed on from one bacteria to another or through shared genetic elements via viruses, especially bacteriophages. We also now know that the gut microbiome has a luminal and a mucosal component, which differ in terms of their composition, and much work needs to be done to understand the dynamics within these compartments.

It is clear that gut microbiota plays a key role in several functions that are vital for our health, and we have made huge leaps over the past decade in terms of accelerating microbiome research and translating the early findings. We are at a point, however, that this long-neglected organ needs further inquiry. Studying the microbiome in health and disease will likely need long-term and larger scale investigations, collaboration between researchers not only in medicine but also in ecology, epidemiology, nutrition, statistics and computing. Looking for the needles in our large microbial haystacks requires persistence, invention and dedication to finding new animal models, new high throughput experimental and analysis techniques, and the embrace of this multi-dimensional science into clinical research. ■



FOR TREATING CHRONIC HCV GT 1

BE THE ONE

WHO CAN CHANGE WHAT'S POSSIBLE

Albert Einstein used with permission of the HUJ/GreenLight.

HARVONI IS NOW APPROVED FOR MORE CHRONIC HCV PATIENT TYPES: HCV/HIV-1 CO-INFECTED AND GT 4, 5, OR 6 PATIENTS

HARVONI DELIVERED HIGH CURE (SVR) RATES IN SUBJECTS WITH HCV/HIV-1 CO-INFECTION[1,a]

96%

OVERALL CURE RATE IN GT 1 OR 4 HCV/HIV-1 CO-INFECTED SUBJECTS[1,a]

ION-4 (n=321/335)

- HARVONI delivered consistently high cure rates regardless of prior HCV treatment experience or cirrhosis status (94% in subjects with cirrhosis and 98% in treatment-experienced subjects with cirrhosis)[1]
- The safety profile in HCV/HIV-1 co-infected subjects was similar to that observed in HCV mono-infected subjects. See the Drug Interactions section of the HARVONI Prescribing Information for potentially significant drug interactions with HIV antiretrovirals[1]
- For patients with HCV/HIV-1 co-infection, follow the dosage recommendations listed on the next page[1]

[a]Sustained virologic response (SVR12) was the primary endpoint and was defined as HCV RNA <25 IU/mL at 12 weeks after the cessation of treatment.[1] Achieving SVR is considered a virologic cure.[2]

Study Design[1]

ION-4: an open-label trial that included GT 1 and 4 treatment-naïve and treatment-experienced subjects (N=335) with HCV/HIV-1 co-infection with or without cirrhosis. Subjects received HARVONI for 12 weeks. Treatment-experienced subjects had failed prior treatment with Peg-IFN + RBV, Peg-IFN + RBV + an HCV protease inhibitor, or sofosbuvir + RBV. None of the 8 GT 4 subjects had cirrhosis. Subjects were on a stable HIV-1 antiretroviral therapy that included emtricitabine + tenofovir disoproxil fumarate, administered with efavirenz, rilpivirine, or raltegravir.

INDICATION

HARVONI is indicated for the treatment of patients with chronic hepatitis C virus (HCV) genotype (GT) 1, 4, 5, or 6 infection.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

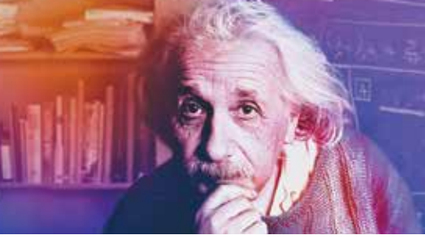
- If HARVONI is used in combination with ribavirin (RBV), all contraindications, warnings and precautions, in particular pregnancy avoidance, and adverse reactions to RBV also apply. Refer to RBV prescribing information.

WARNINGS AND PRECAUTIONS

- **Risk of Serious Symptomatic Bradycardia When Coadministered with Amiodarone:** Amiodarone is not recommended for use with HARVONI due to the risk of symptomatic bradycardia, particularly in patients also taking beta blockers or with underlying cardiac comorbidities and/or with advanced liver disease. In patients without alternative, viable treatment options, cardiac monitoring is recommended. Patients should seek immediate medical evaluation if they develop signs or symptoms of bradycardia.

Please see Brief Summary of full Prescribing Information on the following pages.

HARVONI®
ledipasvir/sofosbuvir
90 mg/400 mg tablets



FOR TREATING CHRONIC HCV GT 1

BE THE ONE WHO CAN CHANGE WHAT'S POSSIBLE.
GO TO **HCP.HARVONI.COM/J2**

HARVONI IS THE ONLY SINGLE-TABLET REGIMEN FOR HCV GT 1 PATIENTS BUILT ON A SOFOSBUVIR BACKBONE[1]

1 TABLET ONCE A DAY
WITHOUT IFN OR RBV

Recommended treatment duration for HARVONI[1]

GT 1	8 weeks	Can be considered in TN patients without cirrhosis who have pre-treatment HCV RNA <6 million IU/mL
	12 weeks	TN patients with or without cirrhosis
		TE patients without cirrhosis
	24 weeks	TE patients with cirrhosis[a]
GT 4, 5, 6	12 weeks	TN and TE patients with or without cirrhosis

- Each HARVONI tablet contains 90 mg of ledipasvir and 400 mg of sofosbuvir[1]
- For patients with HCV/HIV-1 co-infection, follow the dosage recommendations listed above. Refer to the Drug Interactions section of the HARVONI Prescribing Information for dosage recommendations for concomitant HIV-1 antiviral drugs[1]

[a]HARVONI + RBV for 12 weeks can be considered in TE GT 1 patients with cirrhosis who are eligible for RBV. The daily dosage of RBV is weight-based (1000 mg for patients <75 kg and 1200 mg for those ≥75 kg) administered orally in 2 divided doses with food. Refer to the RBV prescribing information.

Cirrhosis = compensated cirrhosis, IFN = interferon, RBV = ribavirin, TE = treatment-experienced (patients who have failed a Peg-IFN alfa + RBV–based regimen with or without an HCV protease inhibitor), TN = treatment-naïve

HARVONI DELIVERED HIGH CURE (SVR) RATES IN A BROAD RANGE OF GT 1 SUBJECTS[1,b]

97%

OVERALL CURE RATE ACROSS THREE HARVONI PHASE 3 TRIALS[1,3-5,b]
(n=1042/1079)

- Overall cure rates were 94%-99% across three HARVONI Phase 3 clinical trials[1]
- The HARVONI clinical trial program enrolled the most challenging subjects, regardless of GT 1a or 1b subtype, prior experience with HCV therapy, or presence of cirrhosis[1]

[b]Sustained virologic response (SVR12) was the primary endpoint and was defined as HCV RNA <25 IU/mL at 12 weeks after the cessation of treatment.[1] Achieving SVR is considered a virologic cure.[2]

Study Designs[1]
ION-3: a randomized, open-label trial in GT 1 treatment-naïve subjects (N=647) without cirrhosis. Subjects were randomized in a 1:1:1 ratio to receive HARVONI for 8 weeks, HARVONI + RBV for 8 weeks, or HARVONI for 12 weeks. **ION-1:** a randomized, open-label trial in GT 1 treatment-naïve subjects (N=865) with or without cirrhosis. Subjects were randomized in a 1:1:1:1 ratio to receive HARVONI for 12 weeks, HARVONI + RBV for 12 weeks, HARVONI for 24 weeks, or HARVONI + RBV for 24 weeks. **ION-2:** a randomized, open-label trial in GT 1 treatment-experienced subjects (N=440) with or without cirrhosis. Subjects were randomized in a 1:1:1:1 ratio to receive HARVONI for 12 weeks, HARVONI + RBV for 12 weeks, HARVONI for 24 weeks, or HARVONI + RBV for 24 weeks.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (continued)

- **Risk of Reduced Therapeutic Effect of HARVONI Due to P-gp Inducers:** Rifampin and St. John's wort are not recommended for use with HARVONI as they may significantly decrease ledipasvir and sofosbuvir plasma concentrations.
- **Related Products Not Recommended:** HARVONI is not recommended for use with other products containing sofosbuvir.

HARVONI WAS SAFE WITH LOW RATES OF DISCONTINUATIONS AND ADVERSE EVENTS (AEs) ACROSS CLINICAL TRIALS[1,3-5]

≤1% **DISCONTINUATIONS DUE TO AEs[1]**

- Adverse reactions (all grades) reported in ≥5% of GT 1 subjects receiving 8, 12, or 24 weeks of treatment with HARVONI (in ION-3, ION-1, and ION-2): fatigue (13%-18%), headache (11%-17%), nausea (6%-9%), diarrhea (3%-7%), and insomnia (3%-6%)[1]
- No hematologic monitoring or dose adjustments are required with HARVONI[1]

MORE THAN 200,000 PATIENTS HAVE BEEN PRESCRIBED HARVONI IN THE US[6,c]

#1 **HARVONI IS THE #1 PRESCRIBED TREATMENT FOR HCV GT 1 IN THE US[7,8,d]**

[c]This information is derived from IMS NPA™ Market Dynamics™, IMS NPA Monthly data, IntegriChain® DNA National, and 867 data; data reflect estimated patient starts from October 2014–October 2015.

[d]IMS Weekly NPA Market Dynamics from week-ending 11/14/14–11/6/15.

HELP YOUR PATIENTS GET STARTED ON HARVONI WITH SUPPORT PATH®

Support Path is a suite of resources that assists with benefits investigations and prior authorizations, and identifies potential financial assistance for patients, such as the HARVONI co-pay coupon program

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

Most common (≥10%, all grades) adverse reactions were fatigue, headache and asthenia.

DRUG INTERACTIONS

- In addition to rifampin and St. John's wort, coadministration of HARVONI is also not recommended with carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifapentine, and tipranavir/ritonavir. Such coadministration is expected to decrease the concentration of ledipasvir and sofosbuvir, reducing the therapeutic effect of HARVONI.
- Coadministration of HARVONI is not recommended with simeprevir due to increased concentrations of ledipasvir and simeprevir. Coadministration is also not recommended with rosuvastatin or co-formulated elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate due to increased concentrations of rosuvastatin and tenofovir, respectively.

Consult the full Prescribing Information for HARVONI for more information on potentially significant drug interactions, including clinical comments.

Please see Brief Summary of full Prescribing Information on the following pages.

HARVONI®
ledipasvir/sofosbuvir
90 mg/400 mg tablets

HARVONI® (ledipasvir 90 mg and sofosbuvir 400 mg) tablets, for oral use

Brief Summary of full Prescribing Information. See full Prescribing Information. Rx Only.

INDICATIONS AND USAGE: HARVONI is indicated for the treatment of patients with chronic hepatitis C virus (HCV) genotype (GT) 1, 4, 5, or 6 infection.

CONTRAINDICATIONS
If HARVONI is administered with ribavirin (RBV), the contraindications to RBV also apply to this combination regimen. Refer to RBV prescribing information.

WARNINGS AND PRECAUTIONS:

Serious Symptomatic Bradycardia When Coadministered with Amiodarone: Postmarketing cases of symptomatic bradycardia, as well as fatal cardiac arrest and cases requiring pacemaker intervention, have been reported when amiodarone is coadministered with HARVONI. Bradycardia has generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. Patients also taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with coadministration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this effect is unknown. Coadministration of amiodarone with HARVONI is not recommended. For patients taking amiodarone who will be coadministered HARVONI and patients taking HARVONI who need to start amiodarone, who have no other alternative, viable treatment options; and due to amiodarone's long half-life for patients discontinuing amiodarone just prior to starting HARVONI: Counsel patients about the risk of serious symptomatic bradycardia; and cardiac monitoring in an in-patient setting for the first 48 hours of coadministration is recommended, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment. Patients who develop signs or symptoms of bradycardia should seek medical evaluation immediately. Symptoms may include near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pains, confusion or memory problems.

Risk of Reduced Therapeutic Effect Due to Use With P-gp Inducers: Concomitant use may significantly decrease ledipasvir and sofosbuvir concentrations and may lead to a reduced HARVONI effect. Use of HARVONI with P-gp inducers (e.g., rifampin or St. John's wort) is not recommended.

Risks Associated with RBV Combination Treatment
If HARVONI is administered with RBV, the warnings and precautions for RBV, in particular pregnancy avoidance, apply to this combination regimen. Refer to the RBV prescribing information.

Related Products Not Recommended: Use of HARVONI with products containing sofosbuvir is not recommended.

ADVERSE REACTIONS:

Most common adverse reactions (incidence greater than or equal to 10%, all grades) were fatigue, headache and asthenia.

GT 1 Subjects with Compensated Liver Disease (With and Without Cirrhosis): The safety assessment of HARVONI was based on pooled data from three randomized, open-label Phase 3 clinical trials (ION-1, ION-3 and ION-2) in subjects who received HARVONI once for 8, 12 or 24 weeks. Adverse events led to permanent treatment discontinuation in 0%, less than 1% and 1% of subjects receiving HARVONI for 8, 12 and 24 weeks, respectively. Adverse Reactions (adverse events assessed as causally related by the investigator; all grades; majority Grade 1) observed in at least 5% of subjects receiving HARVONI for 8, 12 or 24 weeks, respectively, were: fatigue (16%, 13%, 18%), headache (11%, 14%, 17%), nausea (6%, 7%, 9%), diarrhea (4%, 3%, 7%), and insomnia (3%, 5%, 6%). Direct comparison across trials should not be made due to differing trial designs.

GT 4, 5 or 6 Subjects with Compensated Liver Disease (With or Without Cirrhosis): The safety assessment of HARVONI was also based on pooled data from three open-label trials (Study 1119, ION-4 and ELECTRON-2) in 118 subjects who received HARVONI once daily for 12 weeks. The safety profile in these subjects was similar to that observed in subjects with chronic HCV GT 1 infection with compensated liver disease. The most common adverse reactions occurring in at least 10% of subjects were asthenia (18%), headache (14%) and fatigue (10%).

GT 1 Treatment-Experienced Subjects with Cirrhosis (SIRIUS): The safety assessment of HARVONI with or without ribavirin (RBV) was based on a randomized, double-blind and placebo-controlled trial. Subjects were randomized to receive HARVONI once daily for 24 weeks without RBV or 12 weeks of placebo followed by 12 weeks of HARVONI + RBV. Adverse reactions (all grades; majority Grade 1 or 2) observed in at least 5% greater frequency reported in subjects receiving HARVONI for 24 weeks or HARVONI + RBV for 12 weeks compared to placebo for 12 weeks, respectively, were: asthenia (31% or 36% vs 23%); headache (29% or 13% vs 16%); fatigue (18% or 4% vs 1%); cough (5% or 11% vs 1%); myalgia (9% or 4% vs 0%); dyspnea (3% or 9% vs 1%); irritability (8% or 7% vs 1%); and dizziness (5% or 1% vs 0%).

GT 1 or 4 Subjects with HCV/HIV-1 Co-infection (ION-4): The safety assessment of HARVONI was based on an open-label clinical trial in 335 subjects who were on stable antiretroviral therapy. The safety profile in HCV/HIV-1 co-infected subjects was similar to that observed in HCV mono-infected subjects. The most common adverse reactions occurring in at least 10% of subjects were headache (20%) and fatigue (17%).

Less Common Adverse Reactions Reported in Clinical Trials (less than 5% of subjects receiving HARVONI in any one trial): These events have been included because of their seriousness or assessment of potential causal relationship. *Psychiatric disorders:* depression (including in subjects with pre-existing history of psychiatric illness). Depression, particularly in subjects with pre-existing history of psychiatric illness, occurred in subjects receiving sofosbuvir containing regimens. Suicidal ideation and suicide have occurred in less than 1% of subjects treated with sofosbuvir in combination with ribavirin or pegylated interferon/ribavirin in other clinical trials.

Laboratory Abnormalities: *Bilirubin Elevations:* Elevations of greater than 1.5x ULN were observed in 3%, <1% and 2% of subjects treated with HARVONI for 8, 12 and 24 weeks, respectively and in the SIRIUS trial, 3%, 11% and 3% of subjects with compensated cirrhosis treated with placebo, HARVONI + ribavirin for 12 weeks and HARVONI for 24 weeks, respectively. *Lipase Elevations:* Transient, asymptomatic elevations of greater than 3x ULN were observed in less than 1%, 2% and 3% of subjects treated with HARVONI for 8, 12 and 24 weeks, respectively and in the SIRIUS trial, 1%, 3% and 9% of subjects with compensated cirrhosis treated with placebo, HARVONI + ribavirin for 12 weeks and HARVONI for 24 weeks, respectively. *Creatine Kinase:* was not assessed in Phase 3 trials ION-1, ION-3 or ION-2 of HARVONI but was assessed in the ION-4 trial. Isolated, asymptomatic creatine kinase elevations of greater than or equal to 10xULN was observed in 1% of subjects treated with HARVONI for 12 weeks in ION-4 and has also been previously reported in subjects treated with sofosbuvir in combination with ribavirin or peginterferon/ribavirin in other clinical trials.

Postmarketing Experience: Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. *Cardiac Disorders:* Serious symptomatic bradycardia has been reported in patients taking amiodarone who initiate treatment with HARVONI during post approval use of HARVONI. *Skin and Subcutaneous Tissue Disorders:* Skin rashes, sometimes with blisters or angioedema-like swelling

DRUG INTERACTIONS:

Ledipasvir is an inhibitor of the drug transporters P-gp and breast cancer resistance protein (BCRP) and may increase intestinal absorption of coadministered substrates for these transporters. Ledipasvir and sofosbuvir are substrates of P-gp and BCRP while the inactive sofosbuvir metabolite GS-331007 is not. P-gp inducers (e.g. rifampin or St. John's wort) may decrease ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect; use of HARVONI with P-gp inducers is not recommended.

Established and Potentially Significant Drug Interactions: The drug interactions described are based on studies conducted in healthy adults with either HARVONI, the components of HARVONI as individual agents, or are predicted drug interactions that may occur with HARVONI.

Brief Summary (cont.)

This list includes potentially significant interactions but is not all inclusive. **Alteration in dose or regimen may be recommended for the following drugs when coadministered with HARVONI:**

Acid Reducing Agents: Ledipasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease ledipasvir concentration. *Antacids:* Separate HARVONI and antacid administration by 4 hours. *H_2-receptor antagonists*: Doses comparable to famotidine 40 mg twice daily or lower may be administered simultaneously with or 12 hours apart from HARVONI. *Proton-pump inhibitors:* Doses comparable to omeprazole 20 mg or lower can be administered simultaneously with HARVONI under fasted conditions.

Antiarrhythmics (amiodarone; digoxin) *Amiodarone:* Coadministration of amiodarone with HARVONI may result in serious symptomatic bradycardia and is not recommended. Mechanism of effect is unknown. If coadministration is required, cardiac monitoring is recommended. *Digoxin:* Increased digoxin concentration. Monitor digoxin therapeutic concentration during coadministration with HARVONI.

Anticonvulsants (carbamazepine; phenytoin; phenobarbital; oxcarbazepine): Decreased ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.

Antimycobacterials (rifabutin; rifampin; rifapentine): Decreased ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.

HIV Antiretrovirals

Regimens containing tenofovir disoproxil fumarate (DF) without a HIV protease inhibitor/ritonavir or cobicistat: Due to increased tenofovir concentrations, monitor for tenofovir-associated adverse reactions. Refer to VIREAD or TRUVADA prescribing information for renal monitoring recommendations.

Regimens containing tenofovir DF and a HIV protease inhibitor/ritonavir or cobicistat (e.g., atazanavir/ritonavir or cobicistat + emtricitabine/tenofovir DF, darunavir/ritonavir or cobicistat + emtricitabine/tenofovir DF, lopinavir/ritonavir + emtricitabine/tenofovir DF): The safety of increased tenofovir concentrations has not been established. Consider alternative HCV or antiretroviral therapy to avoid increases in tenofovir exposures. If coadministration is necessary, monitor for tenofovir-associated adverse reactions. Refer to VIREAD or TRUVADA prescribing information for renal monitoring recommendations.

Elvitegravir/cobicistat/emtricitabine/tenofovir DF: The safety of increased tenofovir concentrations has not been established. Coadministration is not recommended.

Tipranavir/ritonavir: Decreased ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.

HCV Products (simeprevir): Increased ledipasvir and simeprevir concentrations. Coadministration is not recommended.

Herbal Supplements (St. John's wort): Decreased ledipasvir and sofosbuvir concentrations. Coadministration is not recommended.

HMG-CoA Reductase Inhibitors (rosuvastatin): Significant increase in rosuvastatin concentrations and risk of rosuvastatin associated myopathy, including rhabdomyolysis. Coadministration is not recommended.

Drugs without Clinically Significant Interactions with HARVONI: Based on drug interaction studies conducted with HARVONI or its components, no clinically significant drug interactions have been observed or are expected when used with the following drugs: abacavir, atazanavir/ritonavir, cyclosporine, darunavir/ritonavir, dolutegravir, efavirenz, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, emtricitabine, lamivudine, methadone, oral contraceptives, pravastatin, raltegravir, rilpivirine, tacrolimus, or verapamil.

Consult the full Prescribing Information prior to and during treatment with HARVONI for potential drug interactions and use with certain HIV antiretroviral regimens; this list is not all inclusive.

USE IN SPECIFIC POPULATIONS:

Pregnancy: There are no adequate and well-controlled studies in pregnant women. Consider the benefits and risks of HARVONI when prescribing to a pregnant woman. If HARVONI is administered with RBV, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. Refer to the RBV prescribing information.

Lactation: It is not known if HARVONI and its metabolites are secreted in human breast milk. Studies in rats have demonstrated that ledipasvir and GS-331007 are secreted in milk without clear effect on nursing pups. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for HARVONI and any potential adverse effects on the breastfed infant from HARVONI or from the underlying maternal condition. If HARVONI is administered with RBV, the lactation information for RBV also applies to this combination regimen. Refer to the RBV prescribing information.

Pediatric Use: Safety and effectiveness of HARVONI have not been established in pediatric patients.

Geriatric Use: Clinical trials of HARVONI included 225 subjects aged 65 and over (9% of total number of subjects in the clinical studies). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment of HARVONI is warranted in geriatric patients.

Renal Impairment: No dosage adjustment of HARVONI is required for patients with mild or moderate renal impairment. The safety and efficacy of HARVONI have not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2) or end stage renal disease (ESRD) requiring hemodialysis. No dosage recommendation can be given for patients with severe renal impairment or ESRD.

Hepatic Impairment: No dosage adjustment of HARVONI is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C). Safety and efficacy of HARVONI have not been established in patients with decompensated cirrhosis.

References: 1. HARVONI US full Prescribing Information. Gilead Sciences, Inc. Foster City, CA. November 2015. **2.** US Department of Health and Human Services, Center for Drug Evaluation and Research. Draft Guidance for Industry. Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment. October 2013. **3.** Afdhal N, Zeuzem S, Kwo P, et al; for the ION-1 Investigators. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med.* 2014;370(20):1889-1898. **4.** Kowdley KV, Gordon SC, Reddy KR, et al; for the ION-3 Investigators. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med.* 2014;370(20):1879-1888. **5.** Afdhal N, Reddy KR, Nelson DR, et al; for the ION-2 Investigators. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med.* 2014;370(16): 1483-1493. **6.** Data on file. HARVONI Patient Starts, October 2014–October 2015. Gilead Sciences, Inc. **7.** Data on file. IMS Weekly National Prescription Audit (NPA) Market Dynamics, 11/14/14–11/6/15. Gilead Sciences, Inc. **8.** Data on file. HCV Weekly Sales Reports, 10/10/14–11/6/15. Gilead Sciences, Inc.

GILEAD

HEALTH MAINTENANCE MEASURES

Best practices for patients dealing with IBD

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Physicians who care for patients with inflammatory bowel disease (IBD) must be aware of the unique health maintenance issues facing these patients in order to deliver appropriate medical care.[1] Studies have shown that patients with IBD do not receive routine preventive care at the same rate as patients with other medical conditions.[2] Recent data also suggests that the quality of care among patients admitted to the hospital with IBD is variable.[3] It is crucial that as gastroenterologists we are familiar with the complex health maintenance issues that our IBD patients face and advise our colleagues in primary care.

In 2011, AGA released the Adult IBD Physician Performance Measures Set. These measures, updated in 2015, were designed to identify core areas for gastroenterologists to focus on to improve the quality of care delivered to patients. Five of the seven measures detailed in AGA's document are specifically geared towards preventative health maintenance care in the IBD patient (Table 1).

Table 1: AGA Qualified Registry – Inflammatory Bowel Disease (IBD)

PROCEDURE	PQRS MEASURE
Influenza Immunization	110
Pneumonia Vaccination Status for Older Adults	111
Tobacco Screening and Cessation Intervention	226
Corticosteroid Sparing Therapy	270
Corticosteroid Related Iatrogenic Injury — Bone Loss Assessment	271
Testing for Latent Tuberculosis (TB) Before Initiating Anti-TNF (Tumor Necrosis Factor) Therapy	274
Assessment of Hepatitis B Virus (HBV) Status Before Initiating Anti-TNF (Tumor Necrosis Factor) Therapy	275

The key measures include the use of corticosteroid sparing therapies in patients on steroid treatment and screening for osteoporosis in patients who have had a cumulative use of steroid therapy for more than three months. It is well accepted that steroid treatment in IBD patients can have significant health maintenance implications, as steroid use can lead to hypertension, osteoporosis and infectious complications, etc. We also monitor vitamin D status in our IBD patients and refer appropriate patients to their primary care provider for dual energy X-ray absorptiometry (DEXA) bone density scans. While monitoring vitamin D status is not an existing measure, we know that vitamin D sufficiency appears to be associated with better health outcomes in patients with IBD and therefore we consider this a health maintenance issue.

In addition to patients on steroid therapy, patients over the age of 60, post-menopausal patients, and patients with a history of low trauma fractures should be screened for osteoporosis. Patients with T-score of less than 1 should take vitamin D and calcium supplementation, and have these levels checked at regular intervals.

Patients with IBD are at increased risk for vaccine-preventable illnesses. Administering both the influenza and pneumococcal vaccinations to all patients with IBD is a key component to the preventative health care of IBD patients. Lastly, tobacco use should be addressed with patients at each visit and smoking cessation should be strongly encouraged.

The measures proposed by AGA also allow for tracking of practice patterns to facilitate quality improvement interventions, though the challenge of implementing these measures in a busy office practice may be difficult. We have found that the best time to discuss health maintenance issues with patients is during their initial visit. This often allows time for vaccinations to be administered before patients start immunosuppressive therapy. In our practice, we store and administer the hepatitis A and B vaccines as well as pneumococcal vaccines (PCV13 - Prevnar 13© and PRSV 23 - Pneumovax23©) and the injectable flu vaccine. As these are inactivated vaccines, they can be administered to all IBD patients, including those on immunosuppressive therapy. We also recommend the live zoster vaccine for patients who are 50 and older, including those on thiopurines and methotrexate. Ongoing studies are addressing the safety of administering the zoster vaccine to patients on anti-tumor necrosis factor (anti-TNF) drugs. Additionally, patients on vedolizumab may receive the zoster vaccine. Finally, we recommend the HPV vaccine to our eligible male and female patients and refer them to either their primary care provider or, in women, their gynecologist, to receive this vaccine.

Patients with IBD, regardless of medication use, also have an increased risk of developing melanoma. Patients with IBD who are exposed to thiopurines have an increased risk of developing nonmelanoma skin cancer and anti-TNFs increase the risk of melanoma. We have identified several dermatologists in our practice interested in managing patients with IBD-related skin disorders who also see our IBD patients for skin cancer screening. We encourage our female patients, and in particular those on immunosuppressive agents or anti-TNFs, to see their primary care provider or gynecologist for regular Pap tests. Lastly, certain subsets of patients with long-standing and extensive ulcerative colitis and Crohn's disease of the colon are at increased risk for developing colorectal cancer and practices must have processes in place to identify these patients and assure that they undergo appropriate screening tests and procedures.

IBD - CONTINUED ON PAGE 22

IBD - CONTINUED FROM PAGE 21

Recently, studies detailing quality improvement interventions that increase gastroenterologists' adherence to quality measures through systemic education and CME (Continuing Medical Education) have been reported.[4-5] At our practice, we have implemented a quality improvement project to increase the vaccination rate for influenza and pneumococcal pneumonia in our IBD patient population.[6] Our one-page handout assessed a patient's vaccination status, provided educational information on vaccinations, and the opportunity to be vaccinated was offered to our IBD patients during their routine office appointments. We found that we were able to achieve a significant increase in vaccination rates with this simple intervention.

In other chronic diseases, we are beginning to see promising results in studies that look at text messaging as a means to provide patients with reminders to take their medications. However, studies are needed to determine if such modalities have a role in improving the care of patients with IBD. A key tenet of quality improvement is to measure your personal or practice performance. ImproveCareNow is a consortium of multiple pediatric GI practices that share data on the health of their patients. The organization has increased remission rates in pediatric IBD patients through collaborative data-sharing networks across patients, hospitals and providers while lowering costs, and provides a helpful model for other practices interested in forming similar consortiums

Cornerstones Health has developed a valuable health maintenance checklist at www.cornerstoneshealth.org/checklist that allows both providers and patients to keep track of key health maintenance issues such as vaccines, bone health and cancer prevention online. And with the advent of electronic health records, gastroenterologists can embed health-maintenance checklists directly into patients' charts. In our practice, we have developed an IBD outpatient form in our electronic health record software, Epic, which populates the encounter with vaccination dates, important lab data and hepatitis A and B antibody status, allowing easy access to these data. The Crohn's and Colitis Foundation of America is also developing an Epic IBD encounter form that will be available to sites using their software.

> It is crucial that as gastroenterologists we are familiar with the complex health maintenance issues that our IBD patients face and advise our colleagues in primary care.

Despite many of these advancements and new techniques that we have listed above, more research is still needed to see if implementation of such technologies, screenings and informational methods can improve adherences to measures detailed by AGA, and ultimately improve the care we provide to our IBD patients. ■

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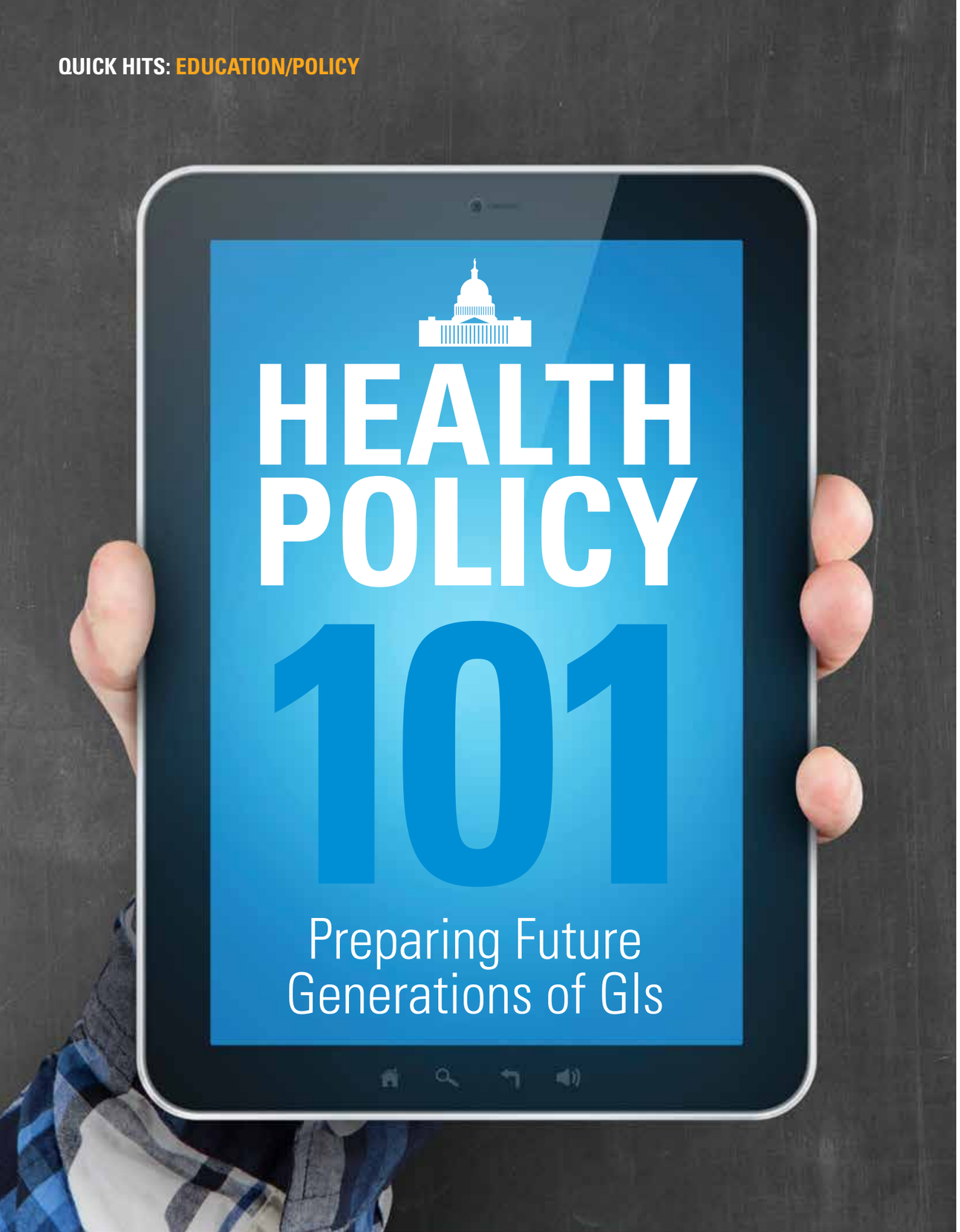

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Dr. Shah has no conflicts to disclose.

This past September, I had the opportunity to participate in AGA Advocacy Day, where I went with a coalition of other New York gastroenterologists to speak with our representatives and senators about two pressing issues that face our profession — payment for colon cancer screening and funding for research from NIH. During the event, we heard from congressional members and health policy professionals to prepare ourselves for our meetings. I consider myself to be in touch with current events and politics, but not until this transformative experience did I have a clear understanding of how policy decisions could impact the day-to-day reality of health-care delivery for me and my patients.

As a GI specializing in GI care for the older adult, I see a diverse range of patients in my practice, from various backgrounds, who are predominantly older. After Advocacy Day, I read current events and articles in health journals with a deeper understanding of how health care is shaped, both locally and nationally. In my geriatrics fellowship, I learned about health-care financing and the forces that impact older adults. This curricula was vital, as most geriatric patients receive some health-care insurance from a public source. I felt better equipped to talk to my geriatric patients, their families and other providers when there are changes in our Medicare and Medicaid programs.

The past few years have been filled with health policy issues directly impacting gastroenterologists and hepatologists. There continues to be a threat to decreasing payment and access to colonoscopy for colon cancer screening. A larger number of patients are being diagnosed with hepatitis C; however a portion cannot afford treatment. There is also a growing number of programs for value-based purchasing and newer care delivery models stemming from the Affordable Care Act. The research budget is at risk of decreasing, limiting the pace of discovery for

Only after learning this important history and background information can the current and future generations of GIs advocate for the best for our patients.

treatment and cures. It is important for our fellows to understand how these events have come to pass and to understand how they can change the course of actions to improve health for our patients, irrespective of their ultimate path.

As physicians, we serve as advocates within our communities for better health and access to care for the populations we care for. We disseminate what we have learned about GI and liver diseases, frequently to patients and families, so they can understand their health and improve their own lives. Our patients and our societies also expect us to apply our knowledge to better the health of many, advocating for health-care delivery, access and services that we know will improve the lives of as many patients as possible. To do this, we have to educate our fellows about what health-care policy is, how health care is financed and how changes in policy are made. Only after learning this important history and background information can the current and future generations of GIs advocate for the best for our patients.

Health-care policy encompasses a broad category of topics including health-care financing, how policy is designed and implemented, issues in health-care delivery, and programs that assess quality and value. Curricula can include discussion of these issues at the local, national and global levels, which can encompass resource allocation and health-care disparities within populations.

Health-care policy falls with under the Accreditation Council for Graduate Medical Education domain of systems-based practice and the subcompetency of identifying forces that impact the cost of health care and advocates for and practices cost-effective care.[3] In the milestone narrative, the fellow is to learn and demonstrate the forces impacting health-care costs and resource utilization, both at the individual and societal levels. The aspirational goals for the practicing physician include advocacy and teaching about these forces, which are shaped by health policy. With the changes in health-care delivery, our fellows must understand how to work within the systems they practice to measure and improve the health of various populations, understand the disparities and learn how to best advocate for resources. I've included published examples of health-policy curricula in my references.

The rising generation of gastroenterologists and hepatologists are a connected generation. Most of our training programs are situated in health-care facilities, systems and communities that are seeing dramatic changes to the health-care and technology landscapes. As stewards of their professional education, we should find opportunities to teach them about the forces at play, open a dialogue about what this means for our patients, and determine how they can use their education and role as health-care leaders to advocate for what they believe is best. These discussions in training may help to develop a more socially engaged generation of gastroenterologists who may be interested in political action for the well-being of their patients and the profession at all levels. ■

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A NEW 'LOOK' AT BARRETT'S ESOPHAGUS

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Barrett's esophagus, a precursor to esophageal adenocarcinoma, is the focus of current efforts to combat the rapidly rising incidence of this deadly cancer. Barrett's esophagus is thought to progress from nondysplastic Barrett's esophagus through low-grade dysplasia and high-grade dysplasia before becoming adenocarcinoma. The risk of esophageal adenocarcinoma is assessed by sampling the affected mucosa through biopsies for the detection of dysplasia and mucosal cancer. The current recommendation from all major gastrointestinal societies is to survey Barrett's esophagus with random biopsies: four quadrants of the esophagus every one-to-two centimeters for the entire length of Barrett's. This is a tedious, expensive and time-consuming protocol, and there is good evidence to show that endoscopists do not routinely adhere to this.[1]

To address several of these shortcomings, advanced endoscopic imaging technologies have been evaluated and hold the potential to reshape the way we survey Barrett's esophagus.

High-definition white light endoscopy (HD-WLE) has essentially replaced standard-definition white light endoscopy (SD-WLE). For Barrett's esophagus, studies have found that high-definition white light endoscopy increases the yield in targeted biopsies over standard-definition white light endoscopy[2] and that spending one minute per centimeter of Barrett's esophagus on examination of the affected mucosa increases the detection of suspicious lesions for targeted biopsy.[3] Such a 'quality examination' could be easily implemented and should be the minimal standard in surveillance of patients with Barrett's.

Chromoendoscopy is the endoscopic application of a solution (examples include indigo carmine, acetic acid, etc.) to enhance mucosal details. These can be applied by introducing a spray catheter through the channel of an endoscope that allows for the detection of suspicious lesions for targeted biopsies. A recent meta-analysis of 843 patients from 14 studies evaluated chromoendoscopy with targeted biopsies versus white light endoscopy with random biopsies and found chromoendoscopy increases the yield for detecting dysplasia or cancer by 35 percent over white light endoscopy.[4] Chromoendoscopy is easily implemented without having to purchase expensive equipment or new endoscopes, but it can be time consuming to prepare and is limited by the subjective interpretation of mucosal patterns.

Virtual chromoendoscopy is the enhancement of endoscopic images to enhance mucosal details, much like chromoendoscopy. There are several forms of virtual chromoendoscopy: narrow-band imaging, iScan and flexible spectral imaging color enhancement. One study compared narrow-band imaging with targeted biopsies to high-definition white light endoscopy with random biopsies and found narrow-band imaging required fewer biopsies (3.6 compared to 7.6) but maintained the same sensitivity of 92 percent.[5] A system for identifying suspicious mucosal patterns is required to ensure consistent and reliable examinations between different providers. The BING (Barrett's International NBI group) consortium developed a system using expert consensus, which has a sensitivity of 92 percent, a negative predictive value of 95 percent and a specificity of 88 percent for dysplasia when images are interpreted with confidence. This system also had a significant inter-user agreement.[6]

Confocal laser endomicroscopy visualizes a plane of tissue in vivo at the cellular level. This procedure will allow the endoscopist to see the goblet cells as well as features of dysplasia. A multi-center study comparing high-definition white light endoscopy using random biopsies with confocal laser endomicroscopy using targeted biopsies found that confocal laser endomicroscopy increases the yield of biopsies for the diagnosis of neoplasia to 34 percent compared to 7 percent with random biopsies, and allows the endoscopist to avoid biopsies in as much as 65 percent of patients with non-dysplastic Barrett's esophagus.[7] This technique requires specialized endoscopes or probes through the working channel of endoscopes.

Volumetric laser endomicroscopy also visualizes a plane of tissue at the cellular level, but uses a balloon to generate a circumferential image over a 6 centimeter segment of the esophagus and has a greater depth of view than confocal laser endomicroscopy. Preliminary studies have shown this to be safe and effective in patients with Barrett's esophagus.[8,9]

While we are still struggling with random biopsy protocols, the next generation of technology for Barrett's esophagus surveillance is here. How should we apply this to clinical practice? ASGE's Preservation and Incorporation of Valuable Endoscopic Interventions (PIVI) initiative has proposed that if any tool is to replace random biopsies, it must have a sensitivity greater than 90 percent, a negative predictive value greater than 98 percent and specificity greater than 80 percent.[10] Based on published evidence to date, narrow-band imaging and confocal laser endomicroscopy have met the PIVI requirements. And a recent expert consensus whitepaper from the AGA Center for GI Innovation and Technology proposed that those endoscopists with expertise in any of these tools, such that they can meet the standards set by the PIVI initiative, could start applying these technologies in practice.[11] Once the tools and training are available, endoscopists will have to choose between the current protocol for random biopsies or the more efficient targeted biopsies with advanced imaging. We believe the majority will favor this new, advanced way of 'looking' at Barrett's esophagus. ■

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UPDATES FROM THE AGA YOUNG DELEGATES PROGRAM

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The strength of professional associations like AGA depends on the contributions of its volunteer members. Traditionally, membership volunteerism has taken the form of a hierarchical structure consisting of governing boards, committees and task forces. These bodies often require that volunteers have a high level of specialization and make significant time commitments, two things that early-career gastroenterologists may not have. GI fellows and those gastroenterologists who are just out of training face unique challenges when it comes to volunteering their time. Between handling the clinical load, staying up-to-date on the literature and managing young families, early-career GIs often feel like they have little or no time left to meaningfully participate in an organization like AGA.

However, we believe these individuals have both a desire to give back to the GI community and something highly important to contribute. For this reason, in 2015, AGA launched the AGA Young Delegates program with the objective of creating alternate volunteer opportunities that provide short-term assignments, flexible deadlines, project-based work and virtual participation. The program also tries to align these opportunities with a volunteer's interests and experience. We hope this new initiative can solve several of the roadblocks faced by early-career GIs and enhance their participation in AGA.

The crucial question to ask before embarking on a solution like this is whether early-career GIs seek involvement in AGA, and if so, why? Current data shows that a large proportion of GI fellows join AGA as trainee members but

> Micro volunteerism, like the name suggests, involves dividing tasks into small, bite-sized portions that busy volunteers can help complete.

member engagement and retention appears to drop sharply in the years following fellowship training. Despite having a desire to contribute to their profession and to explore their own leadership strengths, these young members face several barriers that prevent them from active engagement in AGA. The main reasons for this appear to be lack of access to volunteering opportunities, requirements for extended time commitments, and an ambiguous path toward leadership within the organization. We believe that by changing the approach to volunteering and involvement within AGA, we can significantly enhance participation in mission-driven projects and tailor projects to fit an individual's competence and expertise.

Traditional volunteer leadership involvement in AGA has been based on the committee model, and service in these committees generally involves attending meetings in person or virtually for at least two years. This, in turn, requires the ability to take time off from paid employment to attend to committee duties and also requires a willingness to sacrifice personal time that could be spent on other pursuits. The traditional model does allow for extended deliberations and strong collaborations, but at the same time can be plagued with volunteer burnout, limited access and a consequent lack of innovation.

We believe that a solution for this is the concept of micro volunteerism, which has become more and more popular in recent years with the explosion of social media. Micro volunteerism, like the name suggests, involves dividing tasks into small, bite-sized portions that busy volunteers can help complete. It often involves crowdsourcing the solution, thus leading to greater engagement and innovation by members. This concept appears to be the ideal solution for engagement of busy, early-career GIs who are usually juggling multiple tasks simultaneously, both at home and at work, and is the basis for the Young Delegates program.

For more information on how to get involved with AGA Young Delegates, visit www.gastro.org/youngdelegates, where you can fill out a brief online form to list your skills, areas of interest and availability. AGA will maintain a list of all currently available volunteer activities where member input is solicited. Each volunteer activity will contain a project summary, time required of volunteers, expertise required and instructions on how to complete the activity. Individual delegates can then choose projects to volunteer for on an ad-hoc basis. AGA will maintain a database of all the members in the Young Delegates program with the goal of aligning an individual member's interests with AGA's unmet needs.

Overall, the program provides an innovative platform that promotes bottom-up, grassroots engagement and invites innovative ideas, and solutions, to problems commonly faced by our members. It also offers opportunities for members to become progressively more involved with AGA. This is an exciting venture with a flexible platform, and we hope that it will help foster a sense of belonging and recognition among early-career GIs. ■

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