HOME OR OFFICE

How Does Cologuard — the New, At-Home CRC Screening Test — Stack Up to Colonoscopy?

Articles by Steven Itzkowitz, MD, FACP, FACG, AGAF, and Uri Ladabaum, MD, MS.

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Vol. 11, No. 1 | February/March 2015

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Funding for AGA Perspectives is provided by Gilead Sciences, Inc.

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Note From the Editor

This issue of *AGA Perspectives* addresses multiple rapidly evolving areas of gastroenterology clinical practice. The recent approval of the COLOGUARD test has introduced another weapon in our battle against colon cancer. However, the role of this test in current screening algorithms remains to be determined. To address this issue, Drs. Steven Itzkowitz and Uri Ladabaum provide a provocative point-counterpoint debate on COLOGUARD.

On the theme of colon cancer screening, one of gastroenterology’s wise sages, Dr. Robert Sandler, addresses the issue of when to stop screening in our older patients, something that the GI community needs to address more actively in coming years.

This issue also provides clinical updates on prioritization of treatment for HCV patients, as well as updates on a variety of emerging clinical issues including “treat to target” in IBD and a practical approach to screening for pancreatic cancer in individuals with a first attack of acute pancreatitis. From a policy perspective, Dr. Joel Brill provides insights into the evolving role of GI practice in treatment of obesity and Dr. Naresh T. Gunaratnam proposes a “peace treaty” with electronic health records. Finally, we provide a brief update on AGA international activities at the 2014 Pan American Digestive Disease Week.

Gary W. Falk, MD, MS, AGAF
EDITOR
HOME
How Does Cologuard — the New, At-Home CRC Screening Test — Stack Up to Colonoscopy?

COLOGUARD

Ideally, a cancer screening test should be non-invasive, safe, easy to perform, operator-independent and inexpensive. And, it should be accurate enough to detect early stage cancers and important precancerous lesions. While we have come to accept colonoscopy as the most sensitive screening test for colorectal neoplasia, colonoscopy does not meet many of these criteria. Colonoscopy has an alleged 95 percent sensitivity for detecting CRC. But how does this reconcile with studies from the U.S., Canada and Germany showing a minimal impact of colonoscopy in reducing right-sided colon cancer incidence and mortality? And how does the interval of 10 years accommodate the variable natural history of CRC, such as interval CRCs?

I am a staunch advocate of colonoscopy as a screening test — after all, I do it for a living! I’ve spent the last decade developing and implementing novel patient navigation approaches to get traditionally underserved patients to complete screening colonoscopy. I have been involved in the ongoing efforts of the New York Citywide Colon Cancer Control Coalition (C5), which helped transform screening colonoscopy rates of 42 percent in 2003 to 61 percent in 2007, while eliminating ethnic disparities.1

COLONOSCOPY

Should Cologuard be recommended instead of screening colonoscopy? Not today. But answering where Cologuard fits now in clinical practice is more nuanced.

The principal goal of colorectal neoplasia screening is to decrease CRC-associated mortality. I believe that CRC prevention should also be a primary goal of screening. In determining where Cologuard fits in the current landscape, we must consider evidence on test performance characteristics, one-time versus programmatic performance, clinical outcomes, participation rates, and the balance between benefits and risks. The context for screening (e.g., an organized program versus opportunistic screening) affects the perspective on these variables and also another important factor: cost.

If we focus narrowly on one-time Cologuard versus one-time screening colonoscopy test performance, we have solid evidence for this comparison with colonoscopy as the gold standard.1 In a large prospective study, Cologuard had sensitivities of 92.3 percent (83–97.5 percent) for CRC, and 42.4 percent (38.9–46 percent) for “advanced precancerous lesions,” defined as advanced adenomas and sessile serrated polyps ≥1 cm. Thus, as a one-time test, Cologuard found almost...
In the Deep-C study, Cologuard demonstrated impressive point sensitivities of 92 percent for CRC and 69 percent for adenomas with high-grade dysplasia. For essentially all parameters, Cologuard outperformed a commonly used commercial FIT, with the exception that Cologuard specificity was lower. The specificity of Cologuard for individuals with normal colonoscopies was 90 percent; i.e., 10 percent false-positives. Of note, because DNA undergoes methylation with normal aging, there are more false positives in older age groups. Actually, only 6 percent of individuals 50 to 65 years old had a false positive Cologuard. In the Deep-C study, Cologuard demonstrated impressive point sensitivities of 92 percent for CRC and 69 percent for adenomas with high-grade dysplasia. And, as a polyp grows, the ability to detect it by Cologuard increases substantially. Third, sessile serrated polyps (important precursors of CRC that are frequently located in the proximal colon and overlooked due to their subtle colonoscopic appearance) essentially never bleed but often express hypermethylated DNA. Cologuard detected 45 percent of sessile serrated polyps ≥1 cm compared to 5 percent detection by FIT. Fourth, FIT and guaiac FOBTs are poor at detecting proximal CRC. Cologuard, however, detects cancers equally well in the proximal and distal colon. For the first time, we now have a noninvasive test that works well in the proximal colon. This can be a useful adjunct to sigmoidoscopy and colonoscopy.

Cologuard, the multitarget stool DNA test used in the Deep-C study, now offers a very viable screening alternative.

potential findings, use of sedation, medical mistrust, fatalism or inconvenience. Most medical societies have embraced the ambitious goal of the American Cancer Society and CDC to reach "80 percent by 2018" for CRC screening by any available method. So, given how prevalent and treatable CRC is if found early, how can we reach these people?

Cologuard, the multitarget stool DNA test used in the Deep-C study, now offers a very viable screening alternative. Unlike other stool-based CRC screening tests that detect only occult blood in the stool, Cologuard detects abnormal DNA and fecal hemoglobin. This is an important advance for several reasons. First, DNA is amplifiable, so even the very small amounts of human DNA in stool can be detected using sensitive PCR techniques. Second, many cancers, and most adenomas, do not bleed sufficiently/consistently to be detected by hemoglobin alone. By contrast, DNA is continuously shed from neoplasms into the lumen due to aberrant cell death. Also, DNA comes from epithelial cells. Since the epithelial layer of adenomas is thrown into extensive invaginations (tubules), the effective surface area of a 2 cm adenoma is actually 200 times larger than it appears through the scope. And, as a polyp grows, the ability to detect it by Cologuard increases substantially. Third, sessile serrated polyps (important precursors of CRC that are frequently located in the proximal colon and overlooked due to their subtle colonoscopic appearance) essentially never bleed but often express hypermethylated DNA. Cologuard detected 45 percent of sessile serrated polyps ≥1 cm compared to 5 percent detection by FIT. Fourth, FIT and guaiac FOBTs are poor at detecting proximal CRC. Cologuard, however, detects cancers equally well in the proximal and distal colon. For the first time, we now have a noninvasive test that works well in the proximal colon. This can be a useful adjunct to sigmoidoscopy and colonoscopy.
all (but not all) the CRCs and a reasonable fraction (but still a minority) of the advanced precancerous lesions detected by colonoscopy. If we take this as the principal basis for comparison, then we must conclude that Cologuard cannot be recommended instead of colonoscopy.

However, things are more complicated than that. Although one-time screening has substantial impact on CRC incidence and mortality, screening usually consists of a program of repeated testing over time. CMS decided to cover Cologuard every three years. This seems like a reasonable interval, but there is no direct evidence to support it. While a 10-year interval for screening colonoscopy was a similar “educated guess” initially, subsequent evidence has accumulated that a high-quality normal screening colonoscopy predicts a low risk of interval CRC for 10 years. How does Cologuard every three years perform versus colonoscopy every 10 years? We don’t know yet.

Regarding clinical outcomes, the evidence supporting screening colonoscopy’s benefits consists of extrapolating data from randomized controlled trials of sigmoidoscopy and observational studies. Randomized controlled trials of colonoscopy versus fecal immunochemical testing (FIT) are ongoing. As would be expected for a new test, comparable data are not yet available for Cologuard. Must we have comparative randomized controlled trials assessing CRC incidence and mortality to make clinical and policy decisions today? I don’t think so. However, the requirements regarding levels of evidence are probably different when making decisions for a single patient versus an organized national or regional screening program.

Test performance characteristics (and the clinical outcomes that follow based on them) do not matter if a test is not used in the first place. For both one-time screening and a program of repeated
The proposed 3-year interval may be preferred over annual FIT testing by primary care providers.

Easy to order

Office does not have to deal with the kits

FROM THE PUBLIC HEALTH PERSPECTIVE:

Likely to enhance overall CRC screening uptake

Table: Benefits of Cologuard

FROM THE PATIENT’S PERSPECTIVE:

Convenient (done at home; mailed directly to lab)

Patient privacy preserved

Safe

No bowel prep necessary

No need to take off from work or caretaking

No need to arrange escort

No need for sedation

No need to do annually

Covered by CMS

FROM THE PHYSICIAN’S PERSPECTIVE:

HOME - CONTINUED FROM PAGE 6

every three years, the programmatic specificity and sensitivity should be even higher. Cancers of the upper GI tract rarely cause a false positive Cologuard, based on preliminary studies (www.fda.gov).

Perhaps the greatest benefit of Cologuard comes from the patient's perspective (Table). The provider orders the test directly with the lab. The collection kit is mailed from the lab to the patient's home. The patient collects the stool in a container conveniently mounted on the toilet and mails it back to the lab using a prepaid air-bill. Parenthetically, this makes Cologuard easy to administer in remote or low-resource parts of the country. It is safe, and the patient does not have to deal with bowel prep, dietary/medication restrictions, work absence, escort or returning the test to the clinic. The three-year interval recommended by CMS, informed by a review of screening effectiveness from an unpublished modeling exercise, may be preferred to the annual FIT interval. Compared to not screening, the $600 cost, modeled at three-year intervals, is cost-effective (unpublished data).

We do not yet know how Cologuard compares to colonoscopy as a primary screening tool. In the Deep-C study, all patients who performed the Cologuard test also underwent colonoscopy, regardless of whether the Cologuard was positive or negative. Will patients with a negative Cologuard avoid doing colonoscopy? Of note, if Cologuard is negative, there is only a 0.06 percent chance that there is cancer.

Will Cologuard be used by patients previously unwilling to undergo any CRC screening, as seen with earlier sDNA based tests? Will endoscopists faced with a positive Cologuard be more careful when performing a screening colonoscopy, especially in seeking proximal neoplasia?

Now that Cologuard has been approved by FDA and CMS, I am greatly looking forward to seeing how it will add to our important fight against what is arguably the most preventable cancer. As Yogi Berra said: "The future ain’t what it used to be."
screening over time, participation is a key determinant of yield (detection of early CRCs and advanced precancerous lesions) and outcomes (reduction in CRC incidence and mortality). While it is clear that one-time colonoscopy detects more CRCs and advanced precancerous lesions than one-time FIT, the first interim analysis of the COLONPREV study reported higher participation in the first FIT round versus uptake of colonoscopy (34.2 percent compared with 24.6 percent, p<0.001), and this was associated with comparable overall CRC detection rates (0.1 percent in each arm). Although advanced adenomas were found in 1.9 percent versus 0.9 percent and nonadvanced adenomas in 4.2 percent versus 0.4 percent of subjects in the colonoscopy versus FIT arms, biennial FITs are continuing in this study, which is expected to improve the programmatic performance of the FIT arm. What will be the rates of initial uptake and adherence over time for Cologuard? What will be the impact of the Cologuard “compliance program,” which offers support for patients and physicians? We don’t know yet.

The principal risks of a colorectal neoplasia screening program are procedure-related complications. Cologuard’s specificity of 86.6 percent (85.9–87.2 percent) among participants with nonadvanced or negative findings suggests that most people tested once with Cologuard might avoid the small but non-negligible risk of colonoscopy. However, here too it gets more complicated. What happens over time? How many people with normal colons eventually end up with a colonoscopy anyway? We don’t know this yet either.

Before turning to cost, I would ask: is “Cologuard versus colonoscopy” the right question? If we focus instead on screen-eligible, average-risk persons who are unwilling or unable to undergo screening colonoscopy, then the question becomes, “what about Cologuard versus FIT or other alternatives?” The major prospective Cologuard study also assessed FIT (OC FIT-CHEK, Polymedco, at a threshold of 100 ng/mL). In that study, the sensitivities of one-time FIT were not as good as those of one-time Cologuard (73.8 percent [61.5–84 percent] for CRC; 23.8 percent [20.8–27 percent] for advanced precancerous lesions; and 5.1 percent for sessile serrated polyps ≥1 cm versus 42.4 percent [32.6–52.8 percent] with Cologuard), but the specificity of FIT was superior (94.9 percent [94.4–95.3 percent]). For Cologuard versus FIT or other alternatives, the questions discussed above also apply — as does the question of cost.

CMS will pay $492.72 for Cologuard, and the self-pay list price is $599. The total payment for colonoscopy can range from approximately $700 to several thousand dollars, depending on site of service, use of anesthesia and other factors, with commercial payments averaging approximately 1.7-fold those of CMS. Payments for FIT are $20 to $40. How is the “screening dollar” best spent? There is no straightforward answer.

In conclusion, Cologuard is a welcome addition to the menu of options for colorectal neoplasia screening. Today, I don’t think it can replace colonoscopy for those willing and able to be screened by colonoscopy. I look forward to the emergence of data that will refine our understanding of the merits of a Cologuard screening program compared with the alternatives.

Cologuard cannot be recommended instead of colonoscopy.

REFERENCES
The mortality from colorectal cancer has decreased substantially in the U.S. during the past decade. While some of the improvement is due to better cancer treatment and reduced risk factors, the largest proportion is thought due to screening. The concept that early detection saves lives has now become well-recognized. The harms of screening — particularly among individuals with limited life expectancy — are less well-appreciated.

Royce et al recently examined self-reported cancer screening in the five years prior to interview among individuals aged 65 years and older using data from the National Health Interview Survey from 2000-2010. They used a validated mortality index based on age, sex, smoking, body mass index, comorbidities, hospitalization and functional measures. Among individuals with very high (greater than 75 percent) risk of dying within nine years, the colorectal cancer screening rate was 40.8 percent. For those with a greater than 50 percent chance of dying in five years, the colorectal cancer screening rate was the same.

There have been other reports of potential overscreening among the elderly. In a 5 percent sample of Medicare patients with a prior negative colonoscopy, Goodwin et al found repeat colonoscopies within seven years in 45.6 percent of individuals aged 75-79; among those over age 80 repeat colonoscopies were performed in 32.9 percent. High rates of screening in patients with limited life expectancy will become a greater problem as the population ages.

While there is general agreement about when to start colorectal cancer screening — age 50 — there is less certainty about...
when to stop. Authoritative guidelines from the U.S. Preventive Services Task Force recommend against screening for colorectal cancer in adults older than age 85 and against routine screening in adults age 76-85 years of age. The American College of Physicians does not recommend continued screening in adults over the age of 75 or when the life expectancy is less than 10 years. Life expectancy can be tricky to estimate, although there are ‘apps’ and websites available (www.eprognosis.org).

How can we explain high rates of screening in groups with limited life expectancy? Public health campaigns have done such a good job promoting screening that the idea of stopping may be new to some patients. Interviews with the elderly have found that they perceived screening tests as morally obligatory and continued screening a habit or custom. We have created such momentum for screening that recommendations to stop screening may threaten trust. Patients are skeptical about statistics used by government panels to limit screening (rationing). The situation may be even more difficult for colonoscopy screening by gastroenterologists because many of us work in open-access procedure units where we do not meet patients until they are already prepped and gowned awaiting their procedure. Having a discussion about the need for screening with a prepped patient in the endoscopy room is the wrong place and the wrong time.

There are some positive steps that gastroenterologists could take to limit inappropriate screening. First, we could do a better job managing expectations. There are harms as well as benefits to colonoscopy. For patients with limited life expectancy the benefits are likely to be negligible, and patients need to be educated that screening is not always an undisputed good. Gastroenterologists need to turn off automatic ‘call back letters’ for elderly patients. The decision to screen after age 75 should be a shared one between the patient and the primary care physician. Life expectancy is not simply a function of age, and decisions about screening must include comorbidities and functional status. A request for a screening colonoscopy in an elderly patient ought to prompt a conversation with the referring physician and not an automatic appointment. We might wish to qualify the language we use with younger patients. When we tell the patient that we have removed a ‘precancerous’ polyp, they conclude that we have saved their life even though the chance of eventual cancer from a tiny precancerous polyp is remote. It will be hard to tell the patient to stop screening when they are older because they believe their life was spared by removing a polyp before it turned into cancer. Finally, the government, through Medicare, could alter payment policies making it unattractive to perform screening colonoscopies in elderly patients. If gastroenterologists don’t take steps to limit procedures with little benefit, payors may step in.

Colonoscopy has revolutionized the practice of gastroenterology and saved countless lives. We should work tirelessly to promote colorectal cancer screening in appropriate individuals. When the harms outweigh the benefits, we need to stop.

We have created such momentum for screening that recommendations to stop screening may threaten trust.

REFERENCES
IS GASTROENTEROLOGY READY TO TAKE A BITE OUT OF OBESITY?
What does orthodontia have in common with laser vision correction? Patients have an incentive to shop for services based on price and perceived quality, as these services are elective, and at times, optional. Fees are often negotiable, providers offer payment plans, insurance coverage is limited or non-existent, different techniques abound, and reading the fine print is essential to determine whether the quoted fees include consultation, follow-up visits and care for complications.

It is estimated that more than 1.1 million orthodontia and 800,000 to 1.2 million Lasik surgeries are performed yearly in the U.S., with the volume of procedures related to macroeconomic trends and consumer confidence. Could this be the future for endoscopic obesity procedures?

The American Society for Metabolic & Bariatric Surgery reports that approximately 150,000 to 200,000 bariatric surgeries are performed yearly; this is only 1 percent of the population eligible for weight-loss surgery. At present, there are two FDA-approved devices for treating obesity. In July 2014, ReShape Medical submitted a premarket approval application to FDA for the ReShape Integrated Dual Balloon System for nonsurgical weight loss designed for people with a 30- to 40- body mass index (BMI), anticipated as the first of several devices for obesity to be considered by FDA in the coming years.

FDA states: "However, before medicine is prescribed or surgery is recommended, doctors will probably want their patients to demonstrate a healthy lifestyle that includes healthful eating and increased physical activity. Even with medical or surgical treatments, patients will need to maintain a healthy lifestyle for the rest of their lives." Any gastroenterologist who is considering entering into the obesity market should carefully consider these words. Medical devices or bariatric surgery, by themselves, may not be the 'cure' for obesity. Successful weight-loss programs should include:

1) A plan to keep the weight off long run.
2) Guidance on how to develop healthier eating and physical activity habits.
3) Ongoing feedback, monitoring and support.
4) Slow and steady weight-loss goals.

The Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program (MBSAQIP), a national accreditation standard for bariatric surgery centers from the American College of Surgeons (ACS) and the American Society for Metabolic and Bariatric Surgery (ASMBS), has established recommendations for a bariatric surgery program, including recommendations for pre-, peri- and post-operative care programs and data collection. NIH, ACS and ASMBS also recommend that surgery be performed at a center that has a multidisciplinary team of experts for follow-up care, which may include a nutritionist, an exercise physiologist or specialist, and a mental health professional. As several endoscopic trans-orifice bariatric procedures have been developed to be inserted and removed over a period of months, the gastroenterologist should strongly consider the development of a multidisciplinary program to support the obesity patient.

While we may see FDA approval of nonsurgical weight-loss devices in 2015, there are several other factors for gastroenterologists to consider, including:

- Whether approval or indications for the procedure differ from the 1991 NIH consensus recommendations for surgery for severe obesity.
- Insurance may or may not cover services including the pre-operative evaluation and counseling, the peri-operative procedure including the endoscopist, anesthesiologist, facility and device, and the post-operative follow-up.
- CPT and/or HCPCS codes are unlikely to be established at the time of FDA approval for placement of the device.
- While there may be existing CPT codes for endoscopic removal of the device, insurance might not cover the costs resulting from a prior non-covered procedure.
- Coverage of weight-loss services under a flexible savings account or health reimbursement amount may require a letter of medical necessity from the physician describing the specific medical condition(s) being treated, the need for the program and an outline of treatment options.

Planning ahead, gastroenterologists should begin now to cost out the components of an obesity program in order to consider offering financing options to patients.

The gastroenterology ecosystem is evolving. As Medicare reimbursement for colonoscopy might decrease in 2016, endoscopic obesity programs offer a timely and potentially attractive alternative to GI practices. Establishing high-quality programs for the management of obesity, with data collection and public reporting of results, will be essential to ensure that this opportunity is not lost.

New technologies in obesity will be a hot topic at the AGA Technology Summit, taking place March 19 & 20, 2015, in San Francisco, CA.

Learn more and register at www.gastro.org/tech-summit.

Medical devices or bariatric surgery, by themselves, may not be the ‘cure’ for obesity.
ONE HE’S BEEN WAITING FOR IS HERE

harvoni.com/hcp
HCV QUESTION

The HOT HCV QUESTION

Treat everyone now or only those with advanced fibrosis?

**Chronic hepatitis C virus (HCV)** infection is the leading cause of cirrhosis, hepatocellular carcinoma (HCC) and liver transplantation in the U.S. Of the more than 3 million (and as high as 5.2 million by some estimates) U.S. population estimated to be living with chronic HCV infection, only about half have been identified, and only about 10 percent have been successfully treated and cured. Left untreated, at least 20 percent will progress to cirrhosis over 20 years, with increased risk of progressive liver failure, HCC and death. The only curative treatment at that point is liver transplantation, with initial year and lifetime costs exceeding $500,000 and 1 million, respectively. In fact, over a third of all liver transplantations in the U.S. have been performed among HCV patients.

Successful and timely treatment (with sustained virologic response or SVR) can retard or prevent the disease progression and improve survival. With the advent of the highly effective oral-only therapy, the cure for hepatitis C is very close, if it is not already here. The recent approvals of single once-a-day combination pill of sofosbuvir and ledipasvir (Harvoni, Gilead) and the combination from AbbVie (Viekira Pak) are yet another landmark in this regard. With several other regimens expected to be approved in the near future, most, if not all, patients with HCV can be cured. With the spectacular SVR of over 95 percent, minimal to no side effects, and a mere eight to 12 weeks treatment course, these drugs are expected to revolutionize HCV treatment. These mighty pills, however, come with a very hefty price tag that is outrageous for many. So, here is our dilemma: now that we have the cure that we wished for, can we afford to have it?

Until the recent arrival of the direct acting antivirals, peg-interferon/ribavirin was the standard of care for HCV. Although the cost was lower, so was the SVR rate, with daunting side effects and a long list of contraindications. A recent study showed that the cost of telaprevir-based triple regimen (48-week course) was about $189,000 per SVR if management of side effects are included along with the cost of medication, office visits and laboratory testing. In comparison, the cost of sofosbuvir/simeprevir — a regimen that just got approved, for 12 weeks — is about $150,000 with over 85 percent SVR. Therefore, the $94,500 price tag of the 12-week course of Harvoni or $85,000 for Viekira Pak with over 90 percent cure rate may actually be the most cost-effective regimen we have seen thus far. However, owing to excellent safety, tolerability and absence of contraindications, these drugs have wider indications and literally everyone with HCV (e.g., barring those on dialysis) can be eligible for the treatment. This is feared to result in significant overall increased cost burden to the already restrained health-care budget.

With the targeted screening of baby boomers (who constitute three-fourths of all HCV cases in the U.S.), an additional 1 million HCV cases eligible for treatment are expected to be identified in the U.S. In the past, we relied on liver biopsy (with its own risks and added costs) for disease staging and treatment prioritization. Now, we...
HCV QUESTION

Treat everyone now or only those with advanced fibrosis?

have inexpensive serum biomarkers (FIB-4 and APRI) and transient elastography (Fibroscan) available obviating the need of liver biopsy for disease staging in most cases. This may further increase the pool of patients to be treated. About 2 million people with HCV with insurance coverage are expected to be eligible for treatment over the next five years, which will cost payors about $188 billion based on current pricing. This has caused a significant triple among policymakers, and the insurance carriers are imposing additional prior authorization requirements, approving treatment only for those with the most advanced disease, if not denying it outright. On the other hand, patients who have been waiting for the interferon-free treatment for so long are demanding to be treated right away. And as more patients are being identified by targeted screening, this burden will only increase.

While some advocate treating everyone on a first-come, first-served basis, this is not possible in a resource-limited setting, such as our current U.S. health-care system. Therefore, given that HCV is generally a slowly progressive disease taking decades before developing into advanced fibrosis or cirrhosis, and in light of the anticipated approval of more drugs in the near future, which are expected to drive down the cost by competition, the most cost-effective approach at the moment may be to treat those with the more advanced disease, while keeping the rest of the pool in close monitoring so they can be treated down the line.

Certainly, this approach may not be acceptable from the perspective of the individual patients or the treating physicians, the best advocate for these patients. However, given the current high cost, this appears to be the optimal approach from the societal perspective. After all, we in the field of hepatology are not unfamiliar with rationing treatment to the sickest first; we have been doing this for long time for organ allocation to liver transplant recipients. Nonetheless, with more stakeholders in the horizon, we all are looking forward to the day when we can treat and cure every single patient with HCV without having to worry about the cost. So, for now, it appears HCV treatment is so close for some, yet so far for most others.

REFERENCES

Endoscopy should be an ENDPOINT FOR CROHN’S DISEASE

Crohn’s disease is an idiopathic inflammatory bowel disease of the small intestine and colon characterized by mucosal ulceration and transmural inflammation. The clinical course of Crohn’s disease is one of progression from uncomplicated inflammation (ulceration) to disease complications of stricture, fistula and abscess. Once complications occur, most patients require surgical resection, with the most common operations being ileal resection with ileocolonic anastomosis and proctocolectomy with Brooke ileostomy.

A majority of patients who undergo surgical resection will eventually experience disease recurrence. Patients who undergo surgical resection are at risk for other comorbidities resulting from the surgery, including bile acid diarrhea, steatorrhea, small intestinal bacterial overgrowth, and adhesions. Irritable bowel syndrome and Crohn’s disease can occur together in some patients. Finally, patients can experience anxiety and depression as a consequence of their chronic illness.

Historically, patients with Crohn’s disease have been treated in clinical practice according to symptoms (abdominal pain and stool frequency) and in clinical trials according to a composite clinical instrument, the Crohn’s disease activity index (CDAI), which is comprised of measurements of abdominal pain, stool frequency, self-reported patient well-being, body weight, presence of abdominal mass on physical examination, use of anti-diarrhea medications, presence of extra-intestinal manifestations and hematocrit. It is easy to see that the symptoms of inflammatory Crohn’s disease, complications of Crohn’s disease and the comorbid conditions resulting from surgical therapy of Crohn’s disease...
are highly overlapping. Thus, without some objective measure of inflammation, patients and physicians are at risk of over-treating some patients whose symptoms are arising from conditions that are non-inflammatory in nature. In addition, some patients with significant inflammation (ulceration) have no clinical symptoms, and yet these patients have significant risk of progressing on to disease complications that will ultimately require surgical resection. Thus, clinical symptoms in patients with Crohn’s disease are neither sensitive nor specific for the presence of ulceration and inflammation.

These facts logically lead to the conclusion that treatment goals for patients with Crohn’s disease need to evolve to include some objective measure of inflammation, in addition to clinical symptoms. Potential objective measures of inflammation include biomarkers such as C-reactive protein (CRP) and fecal calprotectin, cross-sectional imaging such as CT enterography (CTE) or MRI enterography (MRE), and ileocolonoscopy. CRP is elevated only in approximately 50 percent of patients who have evidence of inflammation and is therefore not a reliable biomarker. Similarly, fecal calprotectin is frequently not elevated in patients with small intestinal inflammation, and not all patients with elevated fecal calprotectin have evidence of ulceration at ileocolonoscopy. Thus, CRP and fecal calprotectin are not sufficiently accurate to serve as the primary endpoint for treatment of Crohn’s disease.

Cross-sectional imaging studies could potentially be a primary treatment endpoint, but serial CT scans result in an unacceptable level of cumulative radiation exposure, and MRE studies are not ubiquitously available and are relatively more expensive than ileocolonoscopy. This leaves ileocolonoscopy as the preferred objective measure of Crohn’s disease activity at the present time. In the future, we can expect that ileocolonoscopy may be replaced by validated biomarkers that could serve as an accurate surrogate for endoscopic findings.

In clinical trials, the U.S. FDA has moved to require co-primary endpoints comprised of patient reported outcomes, which are comprised of symptoms reported by patients AND improvement in endoscopic inflammation from baseline. Thus, serial ileocolonoscopy is now required in Crohn’s disease clinical trials. A similar evolution is underway in clinical practice. This clinical practice treatment strategy has been dubbed “treat-to-target” and is comprised of performing an ileocolonoscopy approximately four to six months after making a major change in treatment to ensure that the patient has significant improvement or resolution of the ulcers and other inflammatory endoscopic findings observed prior to the change in treatment. If significant endoscopic improvement is not observed, then treatment intensification is undertaken, even if the patient has become clinically asymptomatic. Ultimately, the treatment goal is to achieve deep remission, defined as both the resolution of clinical symptoms AND near- or complete-endoscopic healing.

Recently, AGA published a clinical decision tool for the evaluation and treatment of Crohn’s disease that pulls these concepts together into a practical algorithm. Clinicians should realize that we are in the midst of a paradigm shift, from treating Crohn’s disease based on symptoms, to a treat-to-target paradigm where Crohn’s disease is treated based on both symptoms and endoscopic findings.

REFERENCES
When to suspect pancreatic cancer presenting as a first attack of acute pancreatitis

Five-year survival in pancreatic cancer patients remains dismal and has barely improved in the past several decades. Patients with early stage pancreatic adenocarcinoma with tumor ≤25 mm in size and with ≤1 involved peripancreatic lymph nodes have better survival following R0 resection with median survival of 70.9 months. In the remaining patients with pancreatic cancer, surgery (including R0 resection) and/or chemo-radiation provide marginal benefit. Early diagnosis and timely treatment of pancreatic cancer is potentially the most effective way to improve pancreatic cancer outcomes at the present time.

Despite major advances in imaging — including development of high resolution CT and MRI scans and endoscopic ultrasound — the median size of pancreatic adenocarcinoma at diagnosis has remained largely unchanged at about 3.1 cm since 1970. Less than 10 percent of pancreatic cancers are resectable at the time of diagnosis. At first this seems improbable and counterintuitive, but on careful thought the reasons become obvious. The major problem with pancreatic cancer diagnosis is that, except in a few patients with small tumors who present with obstructive jaundice, most patients with pancreatic cancer remain asymptomatic till late in their course and do not come to medical attention. Symptoms, such as back pain, that often bring these patients to medical...
To try to improve clinical outcomes in patients with pancreatic adenocarcinoma by diagnosing it early, we need to identify new clinical presentations that are associated with earlier-stage pancreatic cancer.

We recently published two separate studies evaluating acute pancreatitis and a new diagnosis of chronic pancreatitis as clinical presentations of pancreatic cancer, in which an underlying pancreatic cancer is usually overlooked with resulting delay in diagnosis and treatment. In patients older than 40 years of age presenting with acute pancreatitis, the risk of an underlying pancreatic cancer was about 1.5 percent, and these patients comprised 10.7 percent of all pancreatic cancers diagnosed during this period. In more than half of these patients with pancreatic cancer, the cancer diagnosis was delayed by two to 24 months. This delay is considered clinically meaningful and adversely influences clinical outcomes.

The appropriate imaging technique to look for an underlying pancreatic cancer in these patients would be EUS performed by an experienced endosonographer. This is because EUS is the most sensitive and accurate technique for diagnosing small early stage tumor and the sensitivity of CT or MRI scans for tumors ≤25 mm is suboptimal. We had earlier reported 99.6 percent accuracy and 100 percent negative predictive value with EUS in diagnosing pancreatic cancer following acute pancreatitis.

In our cohort of veterans, the risk of pancreatic cancer diagnosis within one year after acute pancreatitis was negligible in patients under 40 years of age and increased from 769 to 2,867 per 100,000 patient-years from fifth to eighth decade of life. The risk of pancreatic cancer was 1.29 percent in patients with heavy alcoholism, 2.63 percent in patients with heavy smoking, 0.96 percent in patients with gallstones, and 2.12 percent in patients without gallstones, alcoholism or smoking history. The cancer risk, even in presence of known potential etiologies of acute pancreatitis, was high enough to warrant a search for an underlying pancreatic cancer.

The question then arises — can we identify subset of acute pancreatitis patients with even higher likelihood of underlying pancreatic cancer? We had earlier evaluated factors associated with higher pancreatic cancer risk in patients with NANG-acute pancreatitis. However, several of those criteria are unlikely to be helpful in patients with alcoholic or gallstone pancreatitis. Of these criteria, we suspect that weight loss of greater than 10 pounds prior to the acute pancreatitis episode and CT/MRI findings of a dilated pancreatic duct, mass lesion or distal pancreatic atrophy would likely have a higher likelihood of an underlying pancreatic cancer in a cohort comprising all patients with acute pancreatitis. Selecting patients for further imaging with EUS based on presence of these criteria carries the risk of selecting patients with later stage pancreatic cancer who are more likely to have these associated findings, thereby defeating the purpose.

Until more data are available, we recommend that patients older than 40 years of age with acute pancreatitis should undergo EUS exam to look for an underlying pancreatic cancer. The only exception we see is if there are stones in the common bile duct in a patient with acute pancreatitis. A single EUS exam would suffice in most patients and repeat EUS exams for follow-up are not recommended. We believe that the cost of this approach is justifiable based on comparison of cost associated with current screening programs for colon cancer or esophageal adenocarcinoma in patients with Barrett’s where the pre-test risk of cancer is much lower. In expert hands, EUS does not have significantly higher costs or risk of complications than a screening colonoscopy or EGD. More studies are needed to corroborate our data before wide-spread recommendations can be made.

REFERENCES
For most physicians, the mention of electronic health records (EHR) elicits a visceral response akin to scraping your nails across a chalkboard. Most EHRs are good at capturing data at the expense of ease of practice. Most of us long for the day when we could pick up a dictaphone and succinctly summarize a complex medical case, formulate a differential and outline a cogent plan in a few paragraphs. We now are forced to click dozens of boxes while interviewing the patient, which negatively impacts the doctor-patient relationship, increases physician stress and results in a note that most are embarrassed to send. In 10 years of generating thousands of notes, I have learned a few tricks that might help ease your misery. Consistent adherence to these suggestions will give you five more minutes to actually enjoy your time with your patient.

**Naresh T. Gunaratnam, MD, AGAF**

**Huron Gastroenterology**

Dr. Gunaratnam is a speaker for Covidien - Barrx™.

**How to Make Peace With Your EHR**

1. Utilize voice recognition software like Dragon and augment your note.

   You can summarize complex histories and test results easily. You can also develop care plans, differential diagnoses and a work-up of common complaints into predicated paragraphs (called macros) that you can recall by saying a few words (e.g., my diarrhea work-up). You then will have a nice paragraph in your own words that you can edit as needed.

2. Summarize as much of the patient’s history and start to generate a care plan before you see the patient.

   For example, you can summarize testing, the referring doctor’s note and a differential based on the chief complaint. You then can edit this summary when you interview the patient.

3. Dictate pertinent information into your impression in numerical order, then cut and paste this information when you see them again.

   For example, 1. Crohns ileitis with resection of 15 cm of ileum in 2010 with a history of pancreatitis related to azathioprine use, now doing well on ustekinumab. 2. Bone densitometry normal in 2014.
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GA is committed to fostering relationships with gastroenterologists around the world and to contributing to the education of the gastroenterology community worldwide. As continuing education is an increasingly critical need for all gastroenterologists and AGA is the leader in GI education, we are decisively strengthening our educational activities around the globe.

A very ambitious AGA activity has been its partnership with the Inter-American Society of Gastroenterology (AIGE), a scientific organization whose mission is to promote gastroenterology in Latin America. It is a coalition of gastroenterological associations from 18 countries across Latin America, the Caribbean and North America, including the U.S. and Canada.

The AIGE-AGA online educational partnership has previously resulted in the first comprehensive online postgraduate course directed to the Latin American gastroenterologists. This recently completed, year-long course consisted of 50 online modules, half of which were presented by AGA members. Each module was comprised of a didactic presentation followed by a discussion with a question and answer session. This online program was evaluated and endorsed by the AGA Education and Training Committee. After course completion and having passed the corresponding exams, more than 4,000 gastroenterologists were awarded certificates. This online course was complemented by an AIGE-sponsored clinical case-based online course delivered to more than 5,000 additional gastroenterologists throughout the Americas.

Our experience at the Digestive Diseases Pan-American Week 2014

Xavier Llor, MD, PhD
Medical Director, Colorectal Cancer Prevention Program; Co-Director, Cancer Genetics and Prevention Program, Yale School of Medicine
Dr. Llor is chair of the AGA International Committee. He has no conflicts to disclose.

Byron L. Cryer, MD
Associate Dean for Faculty Diversity and Development, Professor, UT Southwestern Medical Center
Dr. Cryer is councillor-at-large on the AGA Institute Governing Board. He receives consultant fees from Ikes Pharmaceuticals, Ritter Pharmaceuticals, Sucampo, Inc., and Sanofi Pharmaceuticals and Sequential Therapeutics.
AGA is decisively strengthening our educational activities around the globe.

with its educational programs to as many gastroenterologists outside of the U.S.

Furtheing the success of the online collaboration with AIGE, AGA has also contributed to live meetings in Latin America by having a significant role and very active participation in the Digestive Diseases Pan-American Week (SPED), which took place Oct. 6–9, 2014, in Buenos Aires, Argentina. This was the most successful SPED event ever, with more than 5,300 attendees who travelled from five continents to attend the meeting. Foremost experts presented the latest information on a wide-range of topics in gastroenterology, hepatology, endoscopy, gastrointestinal surgery, nutrition and other related specialties for a week of impactful educational activities.

The first day of SPED began with a postgraduate course directed by AIGE and a digestive endoscopy workshop organized by the Inter-American Society of Digestive Endoscopy (SIED). Over the course of the next three days, the program encompassed a range of educational activities including plenary sessions, symposiums, discussion forums and oral paper presentations from leading experts in gastrointestinal disease. General sessions explored common causes and current treatment options for a variety of common conditions. Focused, small-group sessions provided direct access to internationally renowned faculty.

A key session at this meeting was the AGA-sponsored Lo Mejor de DDW® where AGA presented important abstracts previously premiered at the DDW meeting in Chicago in May 2014. The Lo Mejor de DDW program was presented by leading experts in different fields of gastroenterology who discussed in Spanish the most notable and clinically relevant original presentations from DDW. The first iteration of Lo Mejor de DDW was presented at DDW in 2010 and has since been consistently very well received with capacity attendance during the sessions at DDW. Given this program’s previous successes, AGA decided to take this course on the road to Buenos Aires, which was the first time this session was presented outside the U.S. As this program presents the best of DDW in Spanish, AGA felt that it would be a worthwhile endeavor to conduct this program at a large Latin American digestive diseases meeting such as SPED.

Another highlight of AGA’s participation in SPED was that a number of AGA members presented several lectures and participated in a variety of workshops. Michael Camilleri, MD, AGAF, AGA’s president-elect, delivered a state-of-the-art lecture on new therapeutic agents for IBS during the plenary session. In a separate session, he reviewed new guidelines for the management of gastroparesis.

Overall, the congress was a great success, and AGA had a very prominent contribution. Dr Julio C. Bai, president of AIGE and president of the 2014 meeting, comments on AGA’s involvement by stating, “AGA’s involvement in our meeting has been a beneficial contribution to the education of our congress’ attendees and a highly valued relationship between our two societies.”

AGA’s participation in international meetings represents one aspect that furthers the organization’s strategic plan by improving our prominence within the international community. Certainly, AGA’s extensive participation in the recent Digestive Diseases Pan-American Week is strong proof of this commitment.
Classifieds

MICHIGAN

McLaren Northern Michigan, in partnership with Great Lakes Digestive Health Associates, is seeking a full-time gastroenterologist to join an outstanding, well-established practice. Join this respected group of three full-time gastroenterologists and a nurse practitioner.

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Petoskey is a small town, but serves as the referral center for the eastern Upper Peninsula and northern Lower Peninsula. Great Lakes Digestive Health Associates is one of many subspecialty groups of over 120 physicians serving this referral center. As a result, the mix of patients is similar to any larger university center.

Located on the idyllic shores of Lake Michigan’s Little Traverse Bay and surrounded by inland lakes, Petoskey was recently designated as one of America’s “101 Best Outdoor Towns.” Excellent schools, safe and friendly neighborhoods, and community sports programs make it a wonderful place to raise a family. Abundant four-season recreational opportunities include boating, downhill and cross country skiing, road and mountain biking, golf, tennis, hunting, and fishing. The active art and music culture offer diverse opportunities to both to watch and participate in music and theater.

Physician Life at McLaren Northern Michigan: https://www.youtube.com/watch?v=PuL2QrL0kI

For more about McLaren Northern Michigan and this exciting opportunity, please contact:

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Journal Editors’ Picks

CGH FOR FEBRUARY

Microscopic Colitis - Clinical and Pathologic Perspectives
By Andreas Münch, et al.

Update on Biomarkers of Hepatocellular Carcinoma
By Roongruedee Chaiteerakij, et al.

Effects of Antidepressants in Patients With Functional Esophageal Disorders or Gastroesophageal Reflux Disease: a Systematic Review
By Pim W. Weijenborg, et al.

Prevalence of Chronic Narcotic Use Among Children With Inflammatory Bowel Disease
By Jessio P. Buckley, et al.

Performance of Endoscopic Ultrasound in Staging Rectal Adenocarcinoma Appropriate for Primary Surgical Resection
By Nitin K. Ahuja et al.

GASTRO FOR FEBRUARY

Efficacy of Transoral Fundoplication vs. Omeprazole for Treatment of Regurgitation in a Randomized Controlled Trial
By John G. Hunter, et al.

Comparative Effectiveness of Immunosuppressant and Biologics for Inducing and Maintaining Remission in Crohn’s Disease: A Network Meta-Analysis
By Glen S. Hazlewood, et al.

Alisporivir Inhibition of Hepatocyte Cyclophilins Reduces HBV Replication and Hepatitis B Surface Antigen Production
By Sandra Phillips, et al.

HCV Infection Induces Autocrine Interferon Signaling by Human Liver Endothelial Cell and Release of Exosomes, Which Inhibits Viral Replication
By Silvia Giugliano, et al.

CGH FOR MARCH

Psychological Stress Increases Risk for Peptic Ulcer, Regardless of Helicobacter Pylori Infection or Use of Non-Steroidal Anti-Inflammatory Drugs
By Susan Levenstein, et al.

Temporal Trends of Nonalcoholic Fatty Liver Disease-Related Hepatocellular Carcinoma in the Veteran Affairs Population
By Sahil Mittal, et al.

No Association Between Centers for Medicare and Medicaid Services Payments and Volume of Medicare Beneficiaries or per Capita Health-Care Costs for Each State
By Gavin C. Harewood, et al.

GASTRO FOR MARCH

Truncating Mutation in the Nitric Oxide Synthase 1 Gene Is Associated With Infantile Achalasia
By Eyal Shteyer, et al.

Nonalcoholic Steatohepatitis Is the Second Leading Etiology of Liver Disease Among Adults Awaiting Liver Transplantation in the U.S.
By Robert Wong, et al.

Prevalence of Germline Mutations in Cancer Predisposition Genes in Patients With Pancreatic Cancer
By Robert C. Grant, et al.

Blockade of PD1 and TIM3 Restores Innate and Adaptive Immunity in Patients With Acute Alcoholic Hepatitis
By Lee James Lane Markwick, et al.

Quantitative Gastrointestinal and Psychological Traits Associated With Obesity and Response to Weight-Loss Therapy
By Andres Acosta, et al.
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