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SPECIAL COLORECTAL CANCER ISSUE

Are they really equal?

Training guidelines for colonoscopy competence vary from **50 procedures** for surgical residents, to upwards of **250 procedures** for training internists.

VIEWPOINTS

Gastroenterologist
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Surgeon
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In this issue

Are they really equal?

A gastroenterologist and a surgeon debate how to define quality in colonoscopy.

ARTICLES CONTRIBUTED BY

Walter J. Coyle, MD, FACG, FASGE, and Robert D. Fanelli, MD, FACS, FASGE

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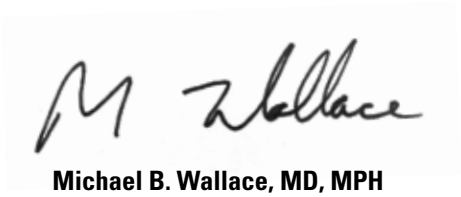
Note From the Editor

March is colorectal cancer awareness month. Thus, we have chosen to focus this issue on many aspects of progress in colon cancer prevention and other colorectal cancer issues. Few if any issues are more important to the day-to-day practice of gastroenterology. In our lead article, we address a hot-button issue of how to train in colonoscopy and whether there should be different standards for surgeons and gastroenterologists. Other topics include a very timely commentary on the emerging stool DNA testing, new payment models including bundled payments which will likely have a significant impact on colon cancer prevention services, and the increasingly critical issue of detecting and completely removing sessile serrated polyps of the colorectum.

Dr. Patrick Lynch guides us through the common scenario of how to manage young patients who have adenomatous polyps and whether to perform genetic testing. Dr. T.R. Levin discusses a highly effective systematic approach to population-based screening. This is further expanded by Dr. Ann Zauber looking at worldwide progress in screening colonoscopy and colon cancer prevention. Lastly, we have a wonderful article on how we can personalize therapy for colorectal cancer based on increasingly available genetic testing of the tumor.

I am sure you will find this issue very exciting and relevant. We welcome any feedback and suggestions for future issues of *AGA Perspectives*.



Michael B. Wallace, MD, MPH
EDITOR

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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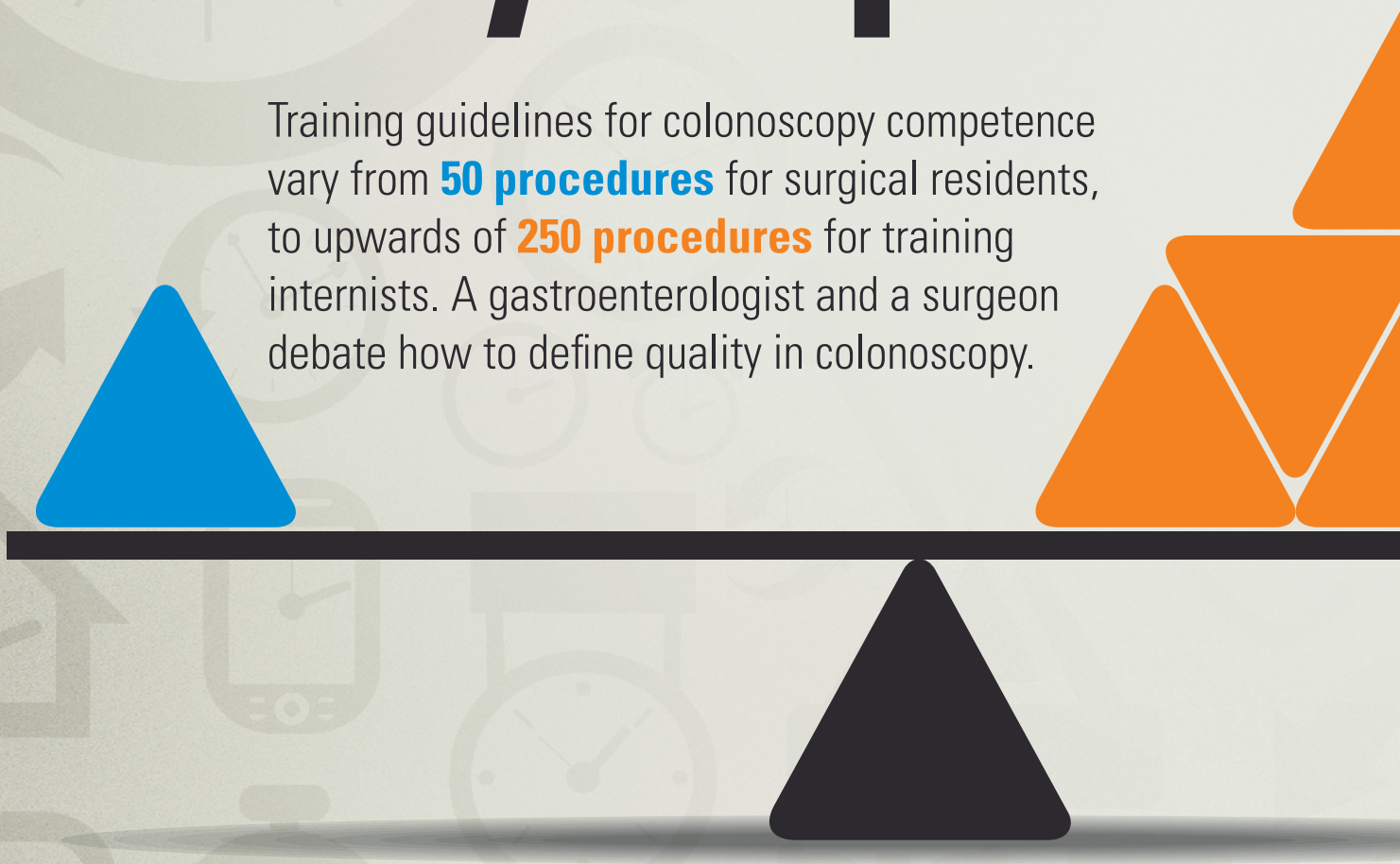

GASTROENTEROLOGIST

Walter J. Coyle,
MD, FACG, FASGE

Gastroenterology Division Head, Division of Gastroenterology and Hepatology, Scripps Clinic Torrey Pines

Dr. Coyle is chair of the ASGE Training Committee.

I have been training fellows in gastroenterology for more than 15 years and welcome the outcomes model for assessing fellow competence. Just like my surgical colleagues, after 15 minutes of observation of a procedure by a trainee, I can tell someone where that trainee is on their learning curve. However, most of that assessment is subjective and is learned from the mentor/apprentice model of training. Recent studies have suggested that this model has significant limitations. The move to outcomes-based training, using milestones as required by the Accreditation Council for Graduate Medical Education (ACGME), is based on the need for superior tools for assessment and documentation of competency.

As we move into the era of increased accountability and quality metrics for procedures, it is the role of professional societies to ensure that all of its members are performing high-quality procedures safely. This is a daunting task and each medical and surgical specialty is developing strategies to implement quality metrics. Screening colonoscopy is such a procedure under scrutiny in the present health-care environment. Metrics have been developed to assess quality colonoscopy such as cecal intubation rate, time to cecal intubation, and polyp or adenoma detection rate. Recent standards, such as a greater than 90 percent cecal intubation rate and adenoma detection rate over 20 percent, have been accepted.

As we implement these quality metrics in colonoscopy, training program directors need to review our training processes to assess whether our present training produces professionals with the prerequisite skills to independently perform screening colonoscopy. In

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SURGEON

Robert D. Fanelli,
MD, FACS, FASGE

Chief, Minimally Invasive Surgery; Chief, Surgical Endoscopy, The Guthrie Clinic, Ltd.

Dr. Fanelli receives royalties from Cook Surgical, Inc and is an owner, member of the board of directors and chairman of the innovation committee for new product development at New Wave Surgical Corporation. He is also a research design consultant for Endogastric Solutions. He is a member of the SAGES Governing Board, SAGES Guidelines Committee, SAGES Enhanced Recovery After Surgery Committee, SAGES Fundamentals of Endoscopic Surgery Task Force, and SAGES Technology and Value Assessment Committee. He is also a member of the ASGE Standards of Practice Committee.

Accepting an invitation to argue that additional training is not necessary in order to perform colonoscopy is difficult for any surgeon, especially for one who has completed two advanced endoscopy fellowships and is involved with the ongoing education of students, residents, fellows and practicing surgeons. The question that really is debated here is whether surgeons are qualified to provide screening colonoscopy. The answer to that question is yes.

Surgeons train to competency in a great number of procedures during their five or six years of residency education, and training in upper endoscopy and colonoscopy are among the core competencies established by the American Board of Surgery (ABS). The endoscopic training provided for surgical residents comes from attending surgical endoscopists, and in many programs, from gastroenterologists. Required procedural competence as set forth in the Surgical Endoscopy Curriculum establishes minimum thresholds for exposure to various techniques important to a career in surgery, but not all surgeons who complete general surgery training will perform endoscopy as a part of their clinical practice. Those who do largely represent two distinct groups: general surgeons practicing in communities where patients have limited or no access to other endoscopists, and surgeons specializing in gastrointestinal surgery, where flexible endoscopy is an increasingly important diagnostic and therapeutic tool. What is common to these surgeons is a focus on continuing education and continuous quality improvement.

Although colonoscopy has emerged as an important fiscal tool for many gastroenterologists, screening colonoscopy in particular is an important public health tool, and

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the U.S., most colonoscopy is performed by gastroenterologists, surgeons and some primary-care practitioners. As gastroenterology has grappled with the issue of quality training in colonoscopy, tension has developed with our surgical colleagues over perceived disparities of training and competency.

Traditionally, gastroenterologists and surgeons focused on procedure numbers as a surrogate for competency. Reliance on numbers alone is an inadequate training model. Outcomes assessment provides a much more robust means to demonstrate competency. Prior gastroenterology curricula set a base number of 140 procedures for assessment of competency. However, newer literature using outcomes-based learning curves suggests that more than 250 procedures may be required for the average colonoscopist to develop competency. Presently, there is a large study underway assessing milestone development in colonoscopy training that should illuminate the training process for colonoscopy. However, until we gain understanding into the training process, it is our duty as medical educators to produce safe and competent colonoscopists by current standards of practice.

The newest surgical training guidelines endorsed by the American Board of Surgery (ABS) require experience with colonoscopy with a procedure minimum of 50. At most institutions, the gastroenterologists have no problem with surgeons having hands-on experience with endoscopy. However, hands-on experience does not equal competency to perform a complete and thorough colonoscopy as required by GI societies for a screening or therapeutic colonoscopy. We cannot have two standards for training for competency. If we choose outcomes assessment as our training method then all trainees performing colonoscopy must be held to the same standards. In a recent surgical study of surgery residents, after a two-month endoscopic rotation surgeons in training only reached the cecum in 47 percent of cases. All of these trainees had more than 50 procedures. Imagine credentialing a provider to perform screening colonoscopy who only reaches the cecum 50 percent of the time. I well understand the difference between training competency and credentialing, but I also know that most hospital credentialing committees are not aware of the discrepancy in training in various procedures.

Surgical residency is very demanding and there is no additional time for endoscopic training in most surgical residency curricula. Therefore, we need to look at other means to develop surgeons to meet the societal and professional standards for competency in colonoscopy. Simulation immediately comes to mind. However, the models for simulation in colonoscopy have limitations and prior studies have shown that aggressive simulation practice before starting colonoscopy in actual patients only provides benefit for the first 30 colonoscopies. However, as learned from our colleagues in aerospace, high-

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an underutilized one given the 2013 American Cancer Society estimate that just 53.2 percent of persons appropriate for screening for colorectal cancer had undergone colonoscopy or FOBT.[1] A 2013 University of Connecticut study highlighted waiting times for screening colonoscopy, especially for members of Medicaid insurance programs, in an area of the country replete with gastroenterologists.[2] Even if rural limitations to screening access were resolved and urban gastroenterologists were able to accommodate all patients meeting screening criteria, significant numbers of patients referred to general surgeons for other issues were found to not yet have been screened for colorectal cancer.[3] Surgical endoscopists provide valuable screening access to several segments of society that historically have been underserved by the gastroenterological community.

Surgeons train continuously for five or six years in techniques that uniformly emphasize hand-eye coordination, including endoscopy, whereas most gastroenterology fellowships limit endoscopic training to one-half to two days per week.

So who should perform screening colonoscopy? My answer is simple: surgeons and gastroenterologists capable of providing high-quality colonic screening examinations. Recent efforts to define quality have identified three measures that serve as proxies for quality colonoscopic examinations: the completeness of bowel preparation, the cecal intubation rate and the adenoma detection rate. Surgeons prepare patients for major and minor procedures throughout their training and practice, and are no strangers to instructing patients on the performance of a quality bowel preparation, or to having frank discussions about risks, benefits and alternatives. Cecal intubation should be achieved in at least 90 percent of colonoscopies in general, and in at least 95 percent for screening procedures. This important measure is critical to ensure that the majority of patients screened have their entire colon examined, and may impact utilization and cost.

During a review of 13,580 colonoscopies performed by surgeons, Wexner *et al.* demonstrated a completion rate of 92 percent among all cases performed.[4] Furthermore, this group demonstrated that surgeon performance was reproducible and cecal intubation reliable after just 50 colonoscopic procedures; performance improved additionally with greater and continued experience. To be fair, this study has among its shortcomings that participants were self-selected, data were self-reported and a minority of participants were novice endoscopists. Limitations notwithstanding, this important study validates that surgeons perform safe, efficient colonoscopy, and that novice endoscopists climb the learning curve toward basic

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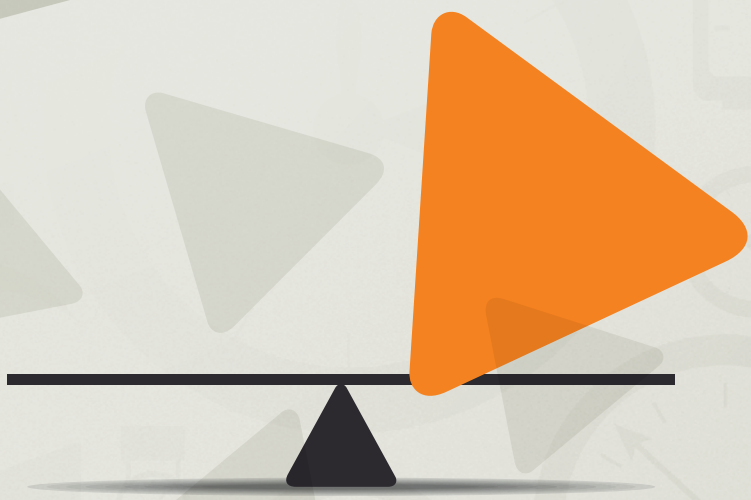
In a recent study of surgery residents, after a two-month endoscopic rotation surgeons in training only reached the cecum in **47 percent of cases**.



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quality simulation has a role in training. The other option for the ABS is to define minimal standards for all surgeons in endoscopic exposure but define rigorous outcomes standards for training to competency in endoscopy. The ABS could define an endoscopic track for their trainees. Surgeons do not train in cholecystectomy where only 47 percent of the procedure can be done. Surgeons must train to the outcomes standards that have been accepted for screening colonoscopy if they want their trainees to provide that service to our patients.

From my experience teaching endoscopy, surgical residents do not have superior hands-on skills for colonoscopy compared to gastroenterology fellows.

From my experience teaching endoscopy, surgical residents do not have superior hands-on skills for colonoscopy compared to gastroenterology fellows. It does not take a leap of faith then to suggest that surgical residents will have similar learning curves as GI fellows. Even if we do develop excellent virtual colonoscopy models, we will still need to do an outcomes-based assessment of all trainees in colonoscopy that, at a minimum, includes a high cecal intubation rate and a high polyp or adenoma detection rate. For some surgical residents, this may be as few as 140 procedures, but I suggest that the literature supports numbers greater than 250 procedures to obtain competence to perform high-quality colonoscopy independently. Unfortunately, there are no prospective studies addressing the learning curves of surgical residents in colonoscopy.

I propose the following for all of us who train residents or fellows in colonoscopy. There is a need to improve present simulators and demonstrate that such tools improve the learning curve for colonoscopy. There is a critical need to develop and validate outcomes-based endoscopic evaluation tools such as those proposed by the ASGE this year.[6] Both surgeons and gastroenterologists should be evaluated using the identical assessment tools for colonoscopy. If graduating gastroenterologists and surgeons want to perform screening colonoscopies, they should demonstrate competency to fulfill the accepted standards of cecal intubation and lesion detection. I also propose that ABS define an endoscopic pathway for those surgical residents who want to perform colonoscopy independently. To graduate trainees that are not competent to perform a procedure independently to established standards as assessed by outcomes measurements is a great disservice to our patients and our profession. ■

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skills fairly quickly. The gastroenterological literature recommends a much higher threshold for training internists learning colonoscopy, nearing 500 procedures in some publications.[5] Surgeons train continuously for five or six years in techniques that uniformly emphasize hand-eye coordination, including endoscopy, whereas most gastroenterology fellowships limit endoscopic training to one-half to two days per week. During surgical training, transferable skills are conferred through practical and simulator-based training, perhaps shortening the learning curve for those immersed in procedural training as compared with those who rarely perform procedures prior to beginning their gastroenterology fellowship.

The third quality measure for screening colonoscopy is adenoma detection rate (ADR), targeting 20 percent in mixed gender populations. Numerous studies reveal widely varying ADR even within individual gastroenterology group practices.[6] A 2009 study revealed a 26 percent ADR and 97 percent completion rate for colonoscopy performed by surgeons in the VA Health System, and a 2012 analysis found surgeons to have a slightly higher ADR than non-surgeon endoscopists.[7,8] Training techniques shown to increase ADR, like manipulating the colonoscope to examine behind folds, liberal irrigation to improve mucosal inspection and coaching to enhance recognition of flat high-risk polyps, are effective in increasing the ADR of experienced endoscopists. These techniques should be shared widely, regardless of provider specialization, in order to improve the quality of patient care and further our collective goal to reduce deaths from colon and rectal cancer.

The Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) has worked in concert with ABS to create a standardized curriculum in flexible endoscopy to ensure more uniform training for surgeons; incorporated are validated measures of competence, like the SAGES Fundamentals of Endoscopic Surgery (FES) Program. FES couples didactic materials with high-stakes cognitive and manual skills examinations, providing objective documentation of endoscopic competency.[9] First-year surgical residents began enrolling in this program in 2013, and it is anticipated that FES will be taken by all surgical residents. SAGES has offered this tool to gastroenterology programs as well, inviting data collection that could result in the first head-to-head comparison of learning curve performance for gastroenterology fellows and surgical residents acquiring endoscopic skills.

A career in surgery is based in large part upon a commitment to lifelong learning. Quality is our goal in all that we do as surgeons, but quality is defined by process and outcomes measures, not by the specialty of the provider or the number of procedures gathered while training. It is my view that surgeons and gastroenterologists committed to providing high-quality endoscopy both are qualified to perform screening colonoscopy, and that excellence shown through quality metrics is far more meaningful than is provider specialty. ■

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"I look through a half-opened door into the future, full of interest, intriguing beyond my power to describe, but with a full understanding that it is for each generation to solve its own problems . . . "

— DR. WILLIAM MAYO,
MAYO CLINIC CO-FOUNDER, 1931

Stool DNA Testing for Colorectal Cancer COMES OF AGE

David A. Ahlquist, MD

Carol Gatton Professor of Digestive Disease Research honoring Dr. Peter Carryer, Mayo Clinic, Rochester, MN

Dr. Ahlquist shares royalties from Exact Sciences as inventor on licensed technologies. He also receives research support from Exact Sciences and serves as scientific advisor.

Stool DNA testing has evolved into what is now a high-performance and robustly validated approach to the screen-detection of colorectal neoplasia and opens exciting new doors for improved effectiveness. Grounded in the biology of exfoliation and enabled by key technical advances,[1] a new generation multi-target stool DNA test (MT-sDNA) comprising two methylated DNA markers, mutant KRAS and fecal hemoglobin, has been optimized and automated.[2]

High-Performance Validated

Case-Control Studies. In a recent study,[2] MT-sDNA detected 98 percent of colorectal cancer (CRC), 83 percent of high-grade dysplasia (nearly all found in polyps larger than 2 cm) and 57 percent of adenomas equal to or greater than 1cm at specificity of 91 percent. CRC detection was unaffected by stage (Fig. 1A) or site; adenoma detection increased with size (Fig. 1B). In another study,[3] MT-sDNA detected 55 percent of sessile serrated polyps (SSP) equal to or greater than 1cm compared to 10 percent by fecal immunochemical testing for blood (FIT) at matched specificities of 91 percent.

Pivotal Screen-Setting Study. A multicenter cross-sectional study comprising more than 10,000 average risk persons is concluded.[4] Published details will soon be available. Based on publicly released top-line results, MT-sDNA detected 92 percent of CRC, 66 percent of adenomas equal to or greater than 2cm, and 42 percent of advanced adenomas (equal to or greater than 1cm or with *villous* features) plus SSP equal to or greater than 1cm. Specificity was 87 percent (non-advanced polyps are included with negative colons in calculation). MT-sDNA superiority over FIT was statistically significant for all lesion categories.

Program Implications. Given its high accuracy, MT-sDNA could compare favorably with conventional methods in a program. MT-sDNA achieves high point-sensitivity for CRC, similar to that of colonoscopy. However, because it is practical to perform more frequently, MT-sDNA (followed by colonoscopy if positive) could improve program sensitivity by catching aggressive metachronous lesions missed by colonoscopy alone done at typical 10-year intervals. Point sensitivities of MT-sDNA for the most critical precancers could translate into very high cumulative program sensitivity with repeated screening rounds, as we have estimated,[1] and, therefore, into effective CRC prevention. Finally, the conservatively estimated MT-sDNA point-specificity of 87 percent, while lower than the average 95 percent reported for FIT, bodes well within a screening program as cumulative false-positives are most relevant. For example, MT-sDNA applied every three years (frequency supported by our early modeling) would yield roughly 4 percent false-positives/year, fewer than the 5 percent rate by FIT applied annually.

Entering Prime Time

MT-sDNA has potential to improve the effectiveness of CRC screening through impacts of its high accuracy on neoplasm detection, user-friendly features on patient compliance and easy mail-out distribution on test access. Implementation systems are being engineered to incorporate high through-put testing into practice. This will require productive medical-industry relationships, large-scale education, coordinated materials distribution, efficient ordering and result reporting, and unencumbered pathways to colonoscopy.

Perceptions by multiple stakeholders that MT-sDNA brings added value should incent its adoption. Patients, particularly those who remain unscreened, may find MT-sDNA appealing because it avoids the unpleasant bowel preparation, medication restrictions and uncovered personal expenses from lost work time and travel with invasive approaches. In the emerging accountable-care environment, health organizations would seem increasingly attracted by its potential for improved outcomes and resource savings. And, with the substantial improvements in MT-sDNA performance over earlier generation tests, third-party payors will look at gains in cost effectiveness; updated models incorporating new data are currently being evaluated and will help guide MT-sDNA testing frequencies and reimbursement levels.

MT-sDNA is currently undergoing an unprecedented parallel review by the U.S. Food and Drug Administration and Center for Medicare and Medicaid Services for regulatory and reimbursement approvals. Such approvals represent two of the final hurdles for widespread use.

The Future: Expanded Applications

Within the Colon. In addition to first-line CRC screening, MT-sDNA could supplement screening or surveillance colonoscopy as an interval test and as backup in patients with incomplete colonoscopy or at risk for sedation. In high-risk groups, like IBD, stool DNA testing may complement colonoscopy to improve surveillance detection and compliance rates. In a feasibility study,[5] accurate detection of both CRC and HGD in IBD patients was observed by stool assay of methylated DNA.

Supra-Colonic Cancers. There remains an enormous unmet need for early detection of cancers above the colon, which collectively exact a death toll twice that of CRC. Based on early studies,[6] stool DNA testing represents a potentially feasible strategy to fill this void. If combined with CRC screening, it would be ideal to differentiate upper from lower GI lesions, and preliminary data suggest that site-specific DNA tumor markers can be identified.[7] Clearly, more studies are needed and warranted.

As stool DNA testing moves from historical promise into primetime, efficient implementation systems and essential linkages with endoscopy will need to be established to achieve highest impact. Logical extensions of this powerful molecular technology open intriguing new doors that expand its value and lead to central roles for the gastroenterologist. ■

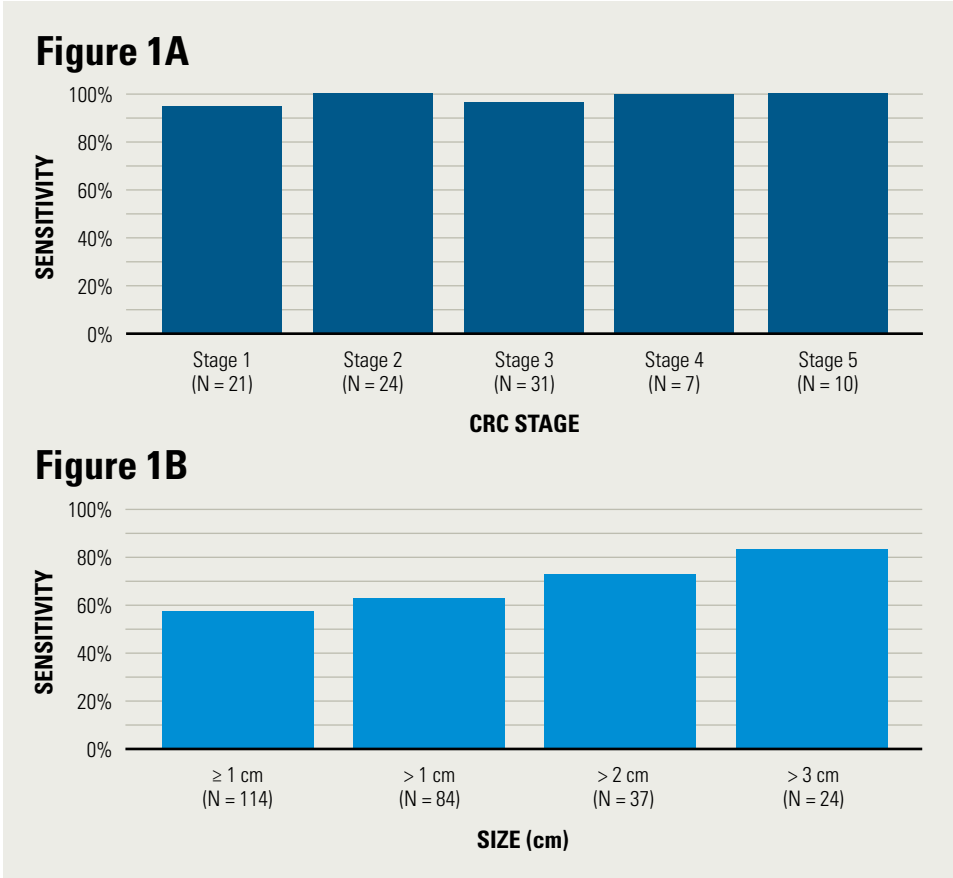

Figure 1: Detection of colorectal neoplasia by an optimized & automated multi-target stool DNA test in case-control study. A. Sensitivity for colorectal cancer by stage. Sensitivity for curable stages I-III was 97 percent. Detection of proximal cancers was 100 percent and distal cancers 94 percent. B. Sensitivity for advanced precursor lesions (adenomas plus sessile serrated polyps) by lesion size. Detection rates increased directly with lesion size. In this study, 94 percent of high-grade dysplasia occurred in lesions greater than 2cm and sensitivity was 83 percent. (From Lidgard *et al.*, *Clin Gastroenterol Hepatol* 2013; 11:1313-8. With permission.)

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BUNDLED PAYMENTS WHY NOW?

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Dr. Brill possesses personal shares/warrants for Early Bird Alert, Inc., EndoChoice and Given Imaging Ltd. He also serves on the Early Bird Alert, Inc. governing board and on the advisory boards for Humana Inc., United Healthcare and Blue Shield of California. Dr. Brill is also the AGA liaison to the ASGE Practice Management Committee and serves on the board of directors at the American Board of Quality Assurance and Utilization Review Physicians, Inc.

Over the years, physicians have faced external challenges when attempting to control the provision of care for their patients. Many have developed ambulatory surgery centers (ASCs) and incorporated pathology labs, pharmacies and/or imaging into their practices, in part because of a belief that the ability to provide all services to the patient improves care coordination and quality.[2] Utilization review, specialty benefit management, narrow networks and exclusive contracts are some of the reasons why your ASC or path lab isn't an in-network option for some patients. This can be frustrating to patients who may be forced to have procedures at a hospital that wants to keep the money within their system, rather than paying for services at an outside entity.

Many physicians have experience with payments for an episode of physician services, such as global payments for surgical services. Lump sum payments for obstetrical care can include ultrasounds in addition to the pre-natal, delivery and post-natal care. But the structure of global payments often fails to allow physicians to demonstrate their true value in this era of cost consciousness, and to allow your patients to use your ASC or path lab.

The logical next step for physicians to consider is a "bundled payment," a method in which payments to health-care providers are based on the expected costs of a predetermined grouping.

So what can you do to demonstrate quality to patients, high value and cost efficiency to purchasers and payors, and improve productivity of ancillary services under our control?

The logical next step for physicians to consider is a "bundled payment," a method in which payments to health-care providers are based on the expected costs of a predetermined grouping, or "bundle," of related health-care services. The intent of a bundled payment is to decrease health-care spending while improving the quality of care.[3] While still a form of fee-for-service care, bundled payments aim to facilitate financial

"I swear by Apollo … to prescribe regimens for the good of my patients according to my ability and my judgment and never do harm to anyone …. In every house where I come I will enter only for the good of my patients, keeping myself far from all intentional ill-doing and all seduction.[1]"

OATH OF HIPPOCRATES

alignment and coordination among providers. Instead of being paid in piecemeal for each service provided — and being rewarded for the quantity of services billed — providers are rewarded for identifying efficiency gains, effectively coordinating patient care and improving the quality of care provided.

In gastroenterology, conditions such as IBD, GERD, Barrett's esophagus, diverticulitis, IBS and viral hepatitis might appear to lend themselves to a bundled payment. Similar to other chronic conditions such as heart failure, diabetes mellitus and chronic obstructive pulmonary disease, the management of these conditions can be complex and require the coordination of care with primary care, specialists, surgeons, behavioral health, hospitals, ASCs, emergency departments, laboratory, pharmacy and other services all involved in an episode of care. What happens if there is a complication? Who is financially responsible if the patient is seen by an out-of-network provider? Starting with a bundled payment for a complex chronic condition could be a prescription for disaster.

What we do — and do very well — is colonoscopy for colorectal cancer screening and surveillance, which is a defined episode with a clear "beginning" and "end" point. In a colonoscopy bundle, the gastroenterologist controls what gets done and where. Controlling the episode of care presents physicians with an incentive for improving quality and the opportunity to demonstrate their value to purchasers, patients and payors. A bundled payment for colonoscopy that covers a multiple-day episode of care, tied to data collection around surveillance intervals in accordance with the multi-society recommendations,[4] may meet the criteria as an alternative payment model and trigger a bonus payment under the SGR Repeal and Medicare Beneficiary Access Improvement Act of 2013.[5] Negotiating a bundled payment for colonoscopy provides physicians with the potential to secure favorable reimbursement in advance of reimbursement cuts looming in the future.

The coming years promise to be interesting. Would you rather control your destiny, or have it dictated to you? ■

BUNDLED PAYMENTS
What You Need to Know and Why

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DEXILANT WORKS A SECOND SHIFT TO HELP SHUT DOWN ACID PUMPS

Conclusions of comparative efficacy cannot be drawn from this information.

96% OF 24-HOUR PERIODS REMAINED HEARTBURN FREE IN A 6-MONTH STUDY[1]

Overall treatment Median percentage of 24-hour heartburn-free periods of the maintenance of healed EE study vs 29% with placebo. Secondary efficacy endpoint, $p<0.0025$.[1,2]

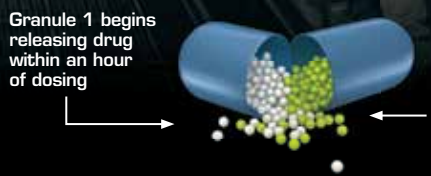
DEXILANT 30 mg (n=132); Placebo (n=141)

DEXILANT 30 mg provides effective maintenance of EE healing

- 66% of patients remained healed over 6 months with DEXILANT 30 mg (n=125) vs 14% with placebo (n=119; $p<0.00001$). Study primary endpoint.[1,2]

Results of a 6-month, multicenter, double-blind, placebo-controlled, randomized study of patients who had successfully completed an EE study and showed endoscopically confirmed healed EE. Based on crude-rate estimates, patients who did not have endoscopically documented relapse and prematurely discontinued were considered to have relapsed.

DDR DEXILANT WORKS WITH A DUAL DELAYED RELEASE FORMULATION



Artistic rendition of granules.

Indications for DEXILANT (dexlansoprazole)

- Healing all grades of erosive esophagitis (EE) for up to 8 weeks
- Maintaining healing of EE and relief of heartburn for up to 6 months
- Treating heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD) for 4 weeks

Important Safety Information

- DEXILANT is contraindicated in patients with known hypersensitivity to any component of the formulation. Hypersensitivity and anaphylaxis have been reported with DEXILANT use.
- Symptomatic response with DEXILANT does not preclude the presence of gastric malignancy.
- PPI therapy may be associated with increased risk of *Clostridium difficile* associated diarrhea.
- Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.
- Hypomagnesemia has been reported rarely with prolonged treatment with PPIs.
- Most commonly reported adverse reactions were diarrhea (4.8%), abdominal pain (4.0%), nausea (2.9%), upper respiratory tract infection (1.9%), vomiting (1.6%), and flatulence (1.6%).
- Do not co-administer atazanavir with DEXILANT because atazanavir systemic concentrations may be substantially decreased. DEXILANT may interfere with absorption of drugs for which gastric pH is important for bioavailability (e.g., ampicillin esters, digoxin, iron salts, ketoconazole). Patients taking concomitant warfarin may require monitoring for increases in international normalized ratio (INR) and prothrombin time. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Concomitant tacrolimus use may increase tacrolimus whole blood concentrations. DEXILANT may increase serum levels of methotrexate.

Please see adjacent brief summary of prescribing information for DEXILANT.

References: 1. DEXILANT (dexlansoprazole) package insert, Takeda Pharmaceuticals America, Inc. **2.** Metz DC, Howden CW, Perez MC, et al. *Aliment Pharmacol Ther.* 2009;29:742-754.

DEXILANT
dexlansoprazole
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BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION
DEXILANT (dexlansoprazole) delayed-release capsules for oral use

INDICATIONS AND USAGE

DEXILANT is indicated for:

- healing of all grades of erosive esophagitis (EE) for up to 8 weeks
- maintaining healing of EE and relief of heartburn for up to 6 months
- the treatment of heartburn associated with symptomatic non-erosive gastroesophageal reflux disease (GERD) for 4 weeks

CONTRAINDICATIONS

DEXILANT is contraindicated in patients with known hypersensitivity to any component of the formulation. Hypersensitivity and anaphylaxis have been reported with DEXILANT use *[see Adverse Reactions]*.

WARNINGS AND PRECAUTIONS

Gastric Malignancy
Symptomatic response with DEXILANT does not preclude the presence of gastric malignancy.

***Clostridium Difficile* Associated Diarrhea**
Published observational studies suggest that PPI therapy like DEXILANT may be associated with an increased risk of *Clostridium difficile* associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve *[see Adverse Reactions]*.

Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

Bone Fracture
Several published observational studies suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the conditions being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines *[see Adverse Reactions]*.

Hypomagnesemia
Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically *[see Adverse Reactions]*.

Concomitant use of DEXILANT with Methotrexate
Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration, a temporary withdrawal of the PPI may be considered in some patients *[see Drug Interactions]*.

ADVERSE REACTIONS

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of DEXILANT was evaluated in 4548 patients in controlled and uncontrolled clinical studies, including 863 patients treated for at least 6 months and 203 patients treated for one year. Patients ranged in age from 18 to 90 years (median age 48 years), with 54% female, 85% Caucasian, 8% Black, 4% Asian, and 3% other races. Six randomized controlled clinical trials were conducted for the treatment of EE, maintenance of healed EE, and symptomatic GERD, which included 896 patients on placebo, 455 patients on DEXILANT 30 mg, 2218 patients on DEXILANT 60 mg, and 1363 patients on lansoprazole 30 mg once daily.

Most Commonly Reported Adverse Reactions
The most common adverse reactions (≥2%) that occurred at a higher incidence for DEXILANT than placebo in the controlled studies are presented in Table 2.

Table 2: Incidence of Adverse Reactions in Controlled Studies

Adverse Reaction	Placebo (N=896) %	DEXILANT 30 mg (N=455) %	DEXILANT 60 mg (N=2218) %	DEXILANT Total (N=2621) %	Lansoprazole 30 mg (N=1363) %
Diarrhea	2.9	5.1	4.7	4.8	3.2
Abdominal Pain	3.5	3.5	4.0	4.0	2.6
Nausea	2.6	3.3	2.8	2.9	1.8
Upper Respiratory Tract Infection	0.8	2.9	1.7	1.9	0.8
Vomiting	0.8	2.2	1.4	1.6	1.1
Flatulence	0.6	2.6	1.4	1.6	1.2

Adverse Reactions Resulting in Discontinuation
In controlled clinical studies, the most common adverse reaction leading to discontinuation from DEXILANT therapy was diarrhea (0.7%).

Other Adverse Reactions
Other adverse reactions that were reported in controlled studies at an incidence of less than 2% are listed below by body system:
Blood and Lymphatic System Disorders: anemia, lymphadenopathy
Cardiac Disorders: angina, arrhythmia, bradycardia, chest pain, edema, myocardial infarction, palpitation, tachycardia
Ear and Labyrinth Disorders: ear pain, tinnitus, vertigo
Endocrine Disorders: goiter
Eye Disorders: eye irritation, eye swelling
Gastrointestinal Disorders: abdominal discomfort, abdominal tenderness, abnormal feces, anal discomfort, Barrett's esophagus, bezoar, bowel sounds abnormal, breath odor, colitis microscopic, colonic polyp, constipation, dry mouth, duodenitis, dyspepsia, dysphagia, enteritis, eructation, esophagitis, gastric polyp, gastritis, gastroenteritis, gastrointestinal disorders, gastrointestinal hypermotility disorders, GERD, GI ulcers and perforation, hematemesis, hematochezia, hemorrhoids, impaired gastric emptying, irritable bowel syndrome, mucus stools, oral mucosal blistering, painful defecation, proctitis, paresthesia oral, rectal hemorrhage, retching
General Disorders and Administration Site Conditions: adverse drug reaction, asthenia, chest pain, chills, feeling abnormal, inflammation, mucosal inflammation, nodule, pain, pyrexia
Hepatobiliary Disorders: biliary colic, cholelithiasis, hepatomegaly
Immune System Disorders: hypersensitivity
Infections and Infestations: candida infections, influenza, nasopharyngitis, oral herpes, pharyngitis, sinusitis, viral infection, vulvo-vaginal infection
Injury, Poisoning and Procedural Complications: falls, fractures, joint sprains, overdose, procedural pain, sunburn
Laboratory Investigations: ALP increased, ALT increased, AST increased, bilirubin decreased/increased, blood creatinine increased, blood gastrin increased, blood glucose increased, blood potassium increased, liver function test abnormal, platelet count decreased, total protein increased, weight increase
Metabolism and Nutrition Disorders: appetite changes, hypercalcemia, hypokalemia
Musculoskeletal and Connective Tissue Disorders: arthralgia, arthritis, muscle cramps, musculoskeletal pain, myalgia
Nervous System Disorders: altered taste, convulsion, dizziness, headaches, migraine, memory impairment, paresthesia, psychomotor hyperactivity, tremor, trigeminal neuralgia
Psychiatric Disorders: abnormal dreams, anxiety, depression, insomnia, libido changes
Renal and Urinary Disorders: dysuria, micturition urgency
Reproductive System and Breast Disorders: dysmenorrhea, dyspareunia, menorrhagia, menstrual disorder
Respiratory, Thoracic and Mediastinal Disorders: aspiration, asthma, bronchitis, cough, dyspnoea, hiccups, hyperventilation, respiratory tract congestion, sore throat
Skin and Subcutaneous Tissue Disorders: acne, dermatitis, erythema, pruritis, rash, skin lesion, urticaria
Vascular Disorders: deep vein thrombosis, hot flush, hypertension

Additional adverse reactions that were reported in a long-term uncontrolled study and were considered related to DEXILANT by the treating physician included: anaphylaxis, auditory hallucination, B-cell lymphoma, bursitis, central obesity, cholecystitis acute, dehydration, diabetes mellitus, dysphonia, epistaxis, folliculitis, gout, herpes zoster, hyperlipidemia, hypothyroidism, increased neutrophils, MCHC decrease, neutropenia, rectal tenesmus, restless legs syndrome, somnolence, tonsillitis.

Other adverse reactions not observed with DEXILANT, but occurring with the racemate lansoprazole can be found in the lansoprazole prescribing information, ADVERSE REACTIONS section.

Postmarketing Experience
The following adverse reactions have been identified during post-approval of DEXILANT. As these 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.

Blood and Lymphatic System Disorders: autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura
Ear and Labyrinth Disorders: deafness
Eye Disorders: blurred vision
Gastrointestinal Disorders: oral edema, pancreatitis
General Disorders and Administration Site Conditions: facial edema
Hepatobiliary Disorders: drug-induced hepatitis
Immune System Disorders: anaphylactic shock (requiring emergency intervention), exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis (some fatal)
Infections and Infestations: Clostridium difficile associated diarrhea
Metabolism and Nutrition Disorders: hypomagnesemia, hyponatremia
Musculoskeletal System Disorders: bone fracture
Nervous System Disorders: cerebrovascular accident, transient ischemic attack
Renal and Urinary Disorders: acute renal failure
Respiratory, Thoracic and Mediastinal Disorders: pharyngeal edema, throat tightness
Skin and Subcutaneous Tissue Disorders: generalized rash, leukocytoclastic vasculitis

DRUG INTERACTIONS

Drugs with pH-Dependent Absorption Pharmacokinetics

DEXILANT causes inhibition of gastric acid secretion. DEXILANT is likely to substantially decrease the systemic concentrations of the HIV protease inhibitor atazanavir, which is dependent upon the presence of gastric acid for absorption, and may result in a loss of therapeutic effect of atazanavir and the development of HIV resistance. Therefore, DEXILANT should not be co-administered with atazanavir.

DEXILANT may interfere with the absorption of other drugs where gastric pH is an important determinant of oral bioavailability (e.g., ampicillin esters, digoxin, iron salts, ketoconazole).

Warfarin

Co-administration of DEXILANT 90 mg and warfarin 25 mg did not affect the pharmacokinetics of warfarin or INR. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with DEXILANT and warfarin concomitantly may need to be monitored for increases in INR and prothrombin time.

Tacrolimus

Concomitant administration of dexlansoprazole and tacrolimus may increase whole blood levels of tacrolimus, especially in transplant patients who are intermediate or poor metabolizers of CYP2C19.

Clopidogrel

Concomitant administration of dexlansoprazole and clopidogrel in healthy subjects had no clinically important effect on exposure to the active metabolite of clopidogrel or clopidogrel-induced platelet inhibition. No dose adjustment of clopidogrel is necessary when administered with an approved dose of DEXILANT.

Methotrexate

Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of high-dose methotrexate with PPIs have been conducted *[see Warnings and Precautions]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects

Pregnancy Category B. There are no adequate and well-controlled studies with dexlansoprazole in pregnant women. There were no adverse fetal effects in animal reproduction studies of dexlansoprazole in rabbits. Because animal reproduction studies are not always predictive of human response, DEXILANT should be used during pregnancy only if clearly needed.

A reproduction study conducted in rabbits at oral dexlansoprazole doses up to approximately 9 times the maximum recommended human dexlansoprazole dose (60 mg per day) revealed no evidence of impaired fertility or harm to the fetus due to dexlansoprazole. In addition, reproduction studies performed in pregnant rats with oral lansoprazole at doses up to 40 times the recommended human lansoprazole dose and in pregnant rabbits at oral lansoprazole doses up to 16 times the recommended human lansoprazole dose revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole.

Nursing Mothers

It is not known whether dexlansoprazole is excreted in human milk. However, lansoprazole and its metabolites are present in rat milk following the administration of lansoprazole. As many drugs are excreted in human milk, and because of the potential for tumorigenicity shown for lansoprazole in rat carcinogenicity studies *[see Nonclinical Toxicology]*, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness of DEXILANT in pediatric patients (less than 18 years of age) have not been established.

Geriatric Use

In clinical studies of DEXILANT, 11% of patients were aged 65 years and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified significant differences in responses between geriatric and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Renal Impairment

No dosage adjustment of DEXILANT is necessary in patients with renal impairment. The pharmacokinetics of dexlansoprazole in patients with renal impairment are not expected to be altered since dexlansoprazole is extensively metabolized in the liver to inactive metabolites, and no parent drug is recovered in the urine following an oral dose of dexlansoprazole.

Hepatic Impairment

No dosage adjustment for DEXILANT is necessary for patients with mild hepatic impairment (Child-Pugh Class A). DEXILANT 30 mg should be considered for patients with moderate hepatic impairment (Child-Pugh Class B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C).

OVERDOSAGE

There have been no reports of significant overdose of DEXILANT. Multiple doses of DEXILANT 120 mg and a single dose of DEXILANT 300 mg did not result in death or other severe adverse events. However, serious adverse events of hypertension have been reported in association with twice daily doses of DEXILANT 60 mg. Non-serious adverse reactions observed with twice daily doses of DEXILANT 60 mg include hot flashes, contusion, oropharyngeal pain, and weight loss. Dexlansoprazole is not expected to be removed from the circulation by hemodialysis. If an overdose occurs, treatment should be symptomatic and supportive.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Serum Gastrin Effects

The effect of DEXILANT on serum gastrin concentrations was evaluated in approximately 3460 patients in clinical trials up to 8 weeks and in 1023 patients for up to 6 to 12 months. The mean fasting gastrin concentrations increased from baseline during treatment with DEXILANT 30 mg and 60 mg doses. In patients treated for more than 6 months, mean serum gastrin levels increased during approximately the first 3 months of treatment and were stable for the remainder of treatment. Mean serum gastrin levels returned to pre-treatment levels within one month of discontinuation of treatment.

Enterochromaffin-Like Cell (ECL) Effects

There were no reports of ECL cell hyperplasia in gastric biopsy specimens obtained from 653 patients treated with DEXILANT 30 mg, 60 mg or 90 mg for up to 12 months.

During lifetime exposure of rats dosed daily with up to 150 mg per kg per day of lansoprazole, marked hypergastrinemia was observed followed by ECL cell proliferation and formation of carcinoid tumors, especially in female rats *[see Nonclinical Toxicology]*.

Effect on Cardiac Repolarization

A study was conducted to assess the potential of DEXILANT to prolong the QT/QT_c interval in healthy adult subjects. DEXILANT doses of 90 mg or 300 mg did not delay cardiac repolarization compared to placebo. The positive control (moxifloxacin) produced statistically significantly greater mean maximum and time-averaged QT/QT_c intervals compared to placebo.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of dexlansoprazole was assessed using lansoprazole studies. In two 24-month carcinogenicity studies, Sprague-Dawley rats were treated orally with lansoprazole at doses of 5 to 150 mg per kg per day, about 1 to 40 times the exposure on a body surface (mg/m^2) basis of a 50 kg person of average height [1.46 m^2 body surface area (BSA)] given the recommended human dose of lansoprazole 30 mg per day.

Lansoprazole produced dose-related gastric ECL cell hyperplasia and ECL cell carcinoids in both male and female rats *[see Clinical Pharmacology]*.

In rats, lansoprazole also increased the incidence of intestinal metaplasia of the gastric epithelium in both sexes. In male rats, lansoprazole produced a dose-related increase of testicular interstitial cell adenomas. The incidence of these adenomas in rats receiving doses of 15 to 150 mg per kg per day

(4 to 40 times the recommended human lansoprazole dose based on BSA) exceeded the low background incidence (range = 1.4 to 10%) for this strain of rat.

In a 24-month carcinogenicity study, CD-1 mice were treated orally with lansoprazole doses of 15 to 600 mg per kg per day, 2 to 80 times the recommended human lansoprazole dose based on BSA. Lansoprazole produced a dose-related increased incidence of gastric ECL cell hyperplasia. It also produced an increased incidence of liver tumors (hepatocellular adenoma plus carcinoma). The tumor incidences in male mice treated with 300 and 600 mg lansoprazole per kg per day (40 to 80 times the recommended human lansoprazole dose based on BSA) and female mice treated with 150 to 600 mg lansoprazole per kg per day (20 to 80 times the recommended human lansoprazole dose based on BSA) exceeded the ranges of background incidences in historical controls for this strain of mice. Lansoprazole treatment produced adenoma of rete testis in male mice receiving 75 to 600 mg per kg per day (10 to 80 times the recommended human lansoprazole dose based on BSA).

A 26-week p53 (+/-) transgenic mouse carcinogenicity study of lansoprazole was not positive.

Lansoprazole was positive in the Ames test and the *in vitro* human lymphocyte chromosomal aberration assay. Lansoprazole was not genotoxic in the *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) test, the *in vivo* mouse micronucleus test or the rat bone marrow cell chromosomal aberration test.

Dexlansoprazole was positive in the Ames test and in the *in vitro* chromosome aberration test using Chinese hamster lung cells. Dexlansoprazole was negative in the *in vivo* mouse micronucleus test.

The potential effects of dexlansoprazole on fertility and reproductive performance were assessed using lansoprazole studies. Lansoprazole at oral doses up to 150 mg per kg per day (40 times the recommended human lansoprazole dose based on BSA) was found to have no effect on fertility and reproductive performance of male and female rats.

PATIENT COUNSELING INFORMATION

See FDA-Approved Medication Guide

To ensure the safe and effective use of DEXILANT, this information and instructions provided in the FDA-approved Medication Guide should be discussed with the patient.

Inform the patient to watch for signs of an allergic reaction as these could be serious and may require that DEXILANT be discontinued.

Advise patients to immediately report and seek care for diarrhea that does not improve. This may be a sign of *Clostridium difficile* associated diarrhea *[see Warnings and Precautions]*.

Advise the patient to immediately report and seek care for any cardiovascular or neurological symptoms including palpitations, dizziness, seizures, and tetany as these may be signs of hypomagnesemia *[see Warnings and Precautions]*.

Advise the patient to tell their health care provider if they take atazanavir, tacrolimus, warfarin and drugs that are affected by gastric pH changes *[see Drug Interactions]*.

Advise the patient to follow the dosing instructions in the Medication Guide and inform the patient that:

- DEXILANT is available as a delayed-release capsule.
- DEXILANT may be taken without regard to food.
- DEXILANT should be swallowed whole.
- Alternatively, DEXILANT capsules can be administered as follows:
  - Open capsule;
  - Sprinkle intact granules on one tablespoon of applesauce;
  - Swallow immediately. Granules should not be chewed.
  - Do not store for later use.

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Revised: September 2012

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Classifieds

CALIFORNIA

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Avoid the stress of large intercity systems and come and be a part of a close community of patients and staff. It is one of the most beautiful regions in New England. The surrounding communities boast some of the best public and private schools in the country. It is hard to beat this area to build a family and a practice.

Package includes 401K with match, health and disability insurance, CME allowance, full malpractice including tail, six weeks of vacation, half day off per week, and one week off for CME.

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Kaua'i's premier multi-specialty group is seeking a BC/BE, fellowship-trained gastroenterologist with excellent clinical and patient relation skills. ERCP experience preferred. Call is 1:3. Kauai Medical Clinic is a 71-physician multispecialty group affiliated with a 71-bed community hospital and Hawaii Pacific Health.

Combine the advantages of an integrated group practice in a spectacularly beautiful, safe, family-oriented, rural community with the cultural diversity, superb lifestyle, excellent climate and year-round recreational activities of the islands. Competitive salary, benefits and relocation package.

Send/fax CV to:

Helene Oyama
Mail: Kauai Medical Clinic, 3-3420 Kuhio Highway, Suite B, Lihue, HI, 96766-1098
Fax: (808) 246-1645
Phone: (808) 246-2951
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GI hospitalist needed to join 16 member single-specialty GI group in Southwest Ohio. PA help available to do consults and follow ups. Generous guaranteed salary. Full benefits including malpractice insurance. University town with great suburbs and nationally ranked public as well as private schools, plus affordable housing.

Candidate will perform both outpatient and inpatient procedures in state of the art endoscopy unit. ERCP required and EUS a plus. If interested, contact **Marilyn Robinson** at mrobinson@digestivespecialists.com or call: 937-396-2767.

RHODE ISLAND

The Center for Women's Gastrointestinal Medicine at The Miriam Hospital d.b.a. Women's Medicine Collaborative is seeking a gastroenterologist to join the department of medicine. The successful candidate must qualify for a full-time medical faculty position at the rank of instructor/assistant professor level at Alpert Medical School of Brown University. Minimum requirements include: board eligibility or certification in gastroenterology, strong clinical background in gastroenterology, excellence in patient care and teaching, and a commitment to scholarly participation in the clinical programs of gastroenterology. Experience in women's health and/or pregnancy related disorders are highly desirable. It is preferred that the candidate's research focus on translational research or a closely related field. ERCP and/or endoscopic ultrasound training is preferred but not required. The Miriam Hospital is an EEO/AA employer and encourages applications from minorities and women. Review of applications will begin immediately and will continue until the position is filled or the search is closed. Interested applicants may apply through Interfolio at http://apply.interfolio.com/24170.

Serrated Lesions of the Colorectum

Douglas K. Rex, MD, AGAF

Distinguished Professor of Medicine, Indiana University

Dr. Rex is on the speaker's bureau for Olympus, Braintree and Boston Scientific and serves on the scientific advisory board for Given Imaging, American BioOptics, CheckCap, Epigenomics AG and Exact Sciences. He also receives research support from Given Imaging, Olympus and Braintree.

The serrated class of colorectal lesions are the precursors of about 30 percent of colorectal cancers. These tumors are hypermethylated and account for a disproportionate percentage of cancers arising after colonoscopy. In this article, I will review key aspects of the clinical management of the serrated class of lesions by colonoscopists.

Use Correct Terminology

There are two major classes of precancerous colorectal lesions including the conventional adenomas (tubular, tubulovillous, villous) and the serrated polyps.[1] Serrated as a class has three subclasses: hyperplastic polyp (HP), sessile serrated polyp (synonymous with sessile serrated adenoma) (SSA/P), and the traditional serrated adenoma (TSA) (Table 1).

The terms "sessile serrated adenoma" and "serrated adenoma" for SSA/P create enormous confusion because physicians often assume such a lesion must be dysplastic (all conventional adenomas are dysplastic). Actually, more than 90 percent of SSA/Ps have no dysplastic component. Less than 10 percent of SSA/Ps do contain a dysplastic region that does look just like a conventional adenoma, while the remainder of the lesion looks like a typical SSA/P. In the past, such lesions were often termed "mixed hyperplastic-adenomatous polyps," but now are designated "SSA/P with cytological dysplasia" (Figure 1) (Table 1).

Know Characteristic Features and Location

HPs are typically small and predominantly in the left colon. Pathologically, they are classified as goblet cell HP, microvesicular HP and mucin-free HP. In clinical practice this subclassification is almost never made. HPs are considered to have almost no malignant potential.

TSAs are rare, predominantly left-sided, often bulky, and thus easy to detect endoscopically. TSAs are dysplastic and precancerous, and have an unpredictable molecular profile. Many clinicians never see TSA on a pathology report because their pathologists confuse them with conventional tubulovillous adenomas.

The SSA/P is the most important lesion in the serrated class because it is both common (relative to TSA) and premalignant (unlike the HP). About 80 percent of SSA/Ps are located proximal to the sigmoid colon. When serrated lesions in the proximal colon are seen endoscopically, larger size predicts SSA/P over HP. However, endoscopic differentiation of HP from SSA/P is very challenging.[2,3] The pathological distinction between HP and SSA/P is also not reliable, even among pathology experts.[4] The critical distinction between SSA/P and the microvesicular HP is that the SSA/P has distorted crypts at the base, with dilation and lateral growth. For some expert pathologists, even one unequivocally distorted crypt changes a microvesicular HP to an SSA/P. Since deciding whether these changes are present is subject to substantial

Table 1: World Health Organization terminology for colorectal lesions in the serrated class

Hyperplastic polyps

Sessile serrated polyp (also sessile serrated adenoma)
- without cytological dysplasia
- with cytological dysplasia

Traditional serrated adenoma

Table 2: Endoscopic features of sessile serrated polyp (also known as sessile serrated adenoma)

- Pale color
- Flat or sessile shape
- Indistinct edges
- Mucus cap
- Debris on edges or center
- No surface vessels or few lacy vessels that course past pits
- Surface texture ("cloud-like" pattern) and pits vary from normal
- Type "O" pits

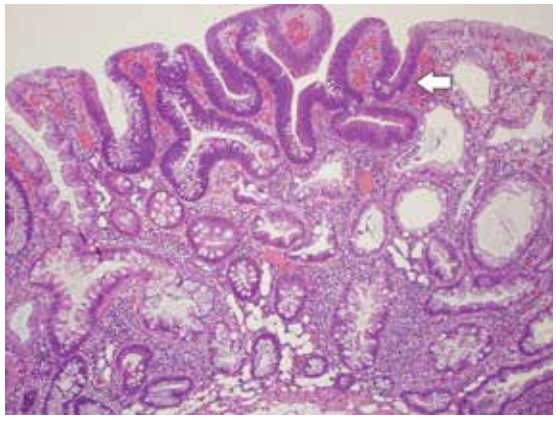

Figure 1. A sessile serrated polyp/adenoma with cytological dysplasia. The upper central area (to the left of the arrow) with darker blue epithelium is a focus of cytological dysplasia. This portion of a sessile serrated polyp with cytological dysplasia has the appearance of a conventional adenoma.

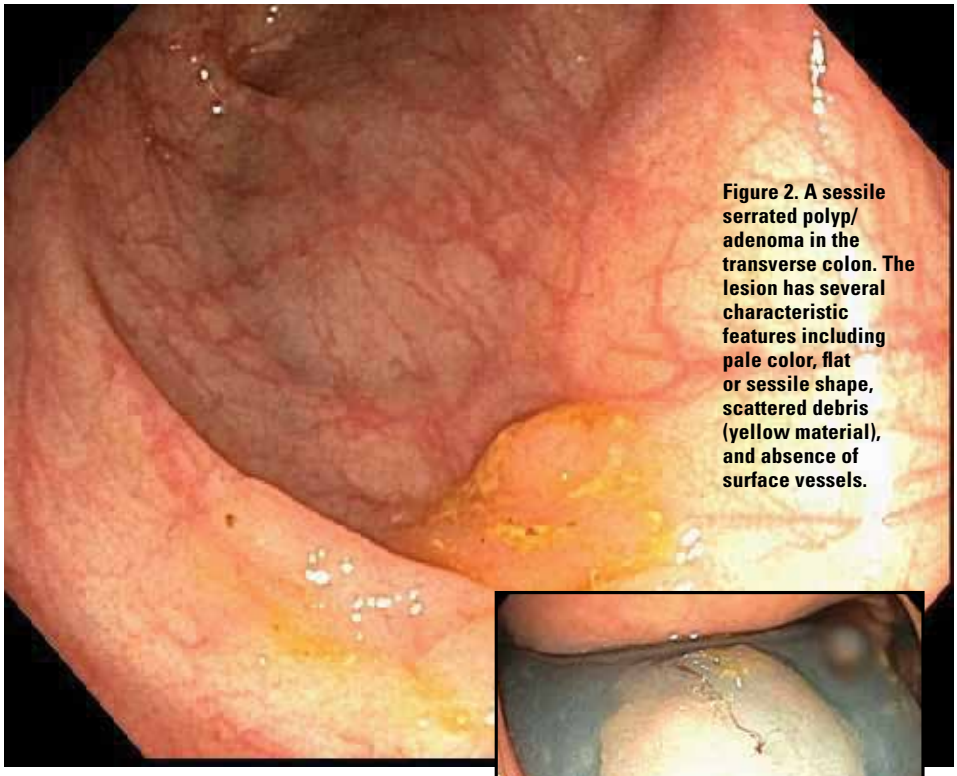

Figure 2. A sessile serrated polyp/ adenoma in the transverse colon. The lesion has several characteristic features including pale color, flat or sessile shape, scattered debris (yellow material), and absence of surface vessels.

Figure 3. (Right) A sessile serrated polyp after submucosal injection with hydroxyethyl starch containing indigo carmine. Note the sharp delineation of the polyp edges by the contrast agent.

interobserver variation, many expert clinicians treat a proximal colon serrated lesion greater than or equal to 10 mm as an SSA/P even when the pathology report says HP.

Detect SSA/P Effectively

Since HPs lack importance, and TSAs are easy to detect, the focus here is on SSA/P. Detection of these lesions can be extremely challenging and has been shown to vary dramatically among gastroenterologists.[5,6] Table 2 lists characteristic endoscopic features of the SSA/Ps. A uniformly flat or sessile shape and color similar to the surrounding mucosa create the detection difficulty (Figure 2). In very subtle lesions, the distinction from normal mucosa is made by recognizing an altered pit pattern and surface texture pattern that is consistently present.

Remove SSA/P Completely

The C.A.R.E. study[7] found that serrated lesions were five times more likely to be incompletely resected by polypectomy compared to conventional adenomas. The problem surely lies in the indistinct edges (Table 2), so that the endoscopist does not gather the entire lesion in the snare, and does not recognize this failure.

I use electrocautery for most proximal colon lesions in the serrated class, and try intentionally to gather a margin of normal tissue of 1-3 mm around the polyp. A high-definition colonoscope is essential in precisely defining the edges. For any serrated lesion above 15 mm in size I prefer to inject submucosally, preferably with hydroxyethyl starch (e.g. Voluven) containing indigo carmine. The contrast agent sharply delineates the polyp edges. If the injection is made through the proximal half of the polyp and allowed to spread 1-2 cm beyond the border of the entire lesion, it will typically turn the lesion more en face to the operator. Using a stiff snare (e.g. the Olympus spiral snare), lesions even 2 to 3 cm in size can often be snared in one piece (including a margin of 1 to 3 mm of normal tissue). For extremely flat lesions, a short hood on the end of the colonoscope (e.g. the Olympus distal attachment) will facilitate grasping the lesion. After resection, inspect the defect margin carefully to identify altered pits or texture change that signal residual lesion.

Table 3: World Health Organization criteria for serrated polyposis

1. 20 or more lesions in the serrated class (HP, SSA/P or TSA) located through the colon
2. Five lesions in the serrated class (HP, SSA/P or TSA) proximal to the sigmoid, of which two are > 10 mm in size
3. Any serrated lesions proximal to the sigmoid in a first degree relative of a patient with serrated polyposis

HP: hyperplastic polyp
SSA/P: sessile serrated polyp/adenoma
TSA: traditional serrated adenoma

Follow-Up

Post-resection surveillance intervals have been recommended[1,8]. In general, the interval shortens with SSA/P (versus HP) histology, and increasing size, number and proximal location of serrated lesions. In our experience, serrated polyposis is frequently unrecognized,[9] and I suspect it is by far the most common polyp syndrome. Remember to count the number, size and location of lesions over time to identify serrated polyposis, an important marker of colorectal cancer risk (Table 3). ■

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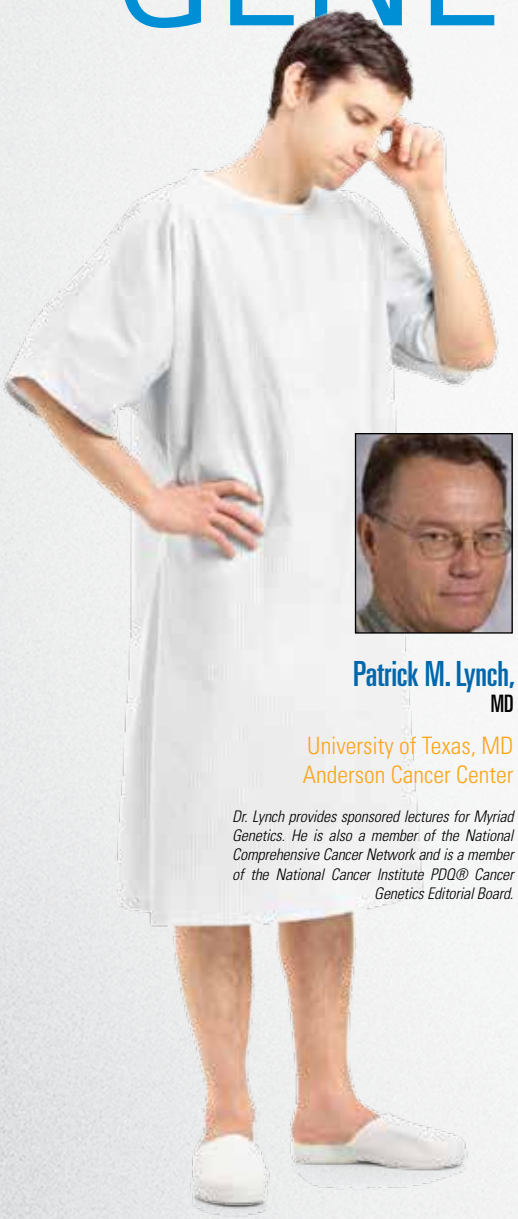
MEDICAL MANAGEMENT OF YOUNG PATIENTS WITH ADENOMAS

WHO SHOULD GET GENETIC TESTING?



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Adenomas in patients under age 50 are uncommon, and distinctly uncommon before age 40. One colonoscopic screening series[1] found that just under 9 percent of subjects had adenomas and only 3.5 percent were advanced (large, multiple and/or severely dysplastic). Rather, adenomas in young people are detected either through symptom evaluation or because of a colonoscopy performed for an underlying risk factor, most commonly a family history of colorectal cancer (CRC).

A key question always is the polyp burden. If more than 100 adenomas are seen below age 40, familial adenomatous polyposis (FAP) is pretty certain; but, we commonly see "oligopolyposis" or an attenuated FAP (AFAP) in which there are far fewer than 100 polyps, perhaps only 10 to 20. A similar picture will be seen with the recessively inherited MYH-associated polyposis or "MAP," with adenomas seen in screening when there is a sibling that carries biallelic mutations. One needs to make sure the polyps are really adenomas, so as to distinguish hamartomatous, inflammatory, lymphoid or "sessile serrated" polyposis. Examination with indigo carmine dye is an ideal way to identify micro-adenomas and thus identify the full adenoma count. I do typically perform an upper endoscopy, since duodenal adenoma and fundic gland polyps (with low-grade dysplasia, as distinct from FGPs in PPI users which lack dysplasia) will help confirm a genetic etiology even when mutation testing is uninformative.

Mutational testing for FAP (including AFAP) and MYH can be readily performed on peripheral blood samples sent to reference laboratories. A positive test will confirm the diagnosis and may influence one's threshold for considering surgical resection. It is essential to appreciate the limitations of mutational testing. Grover and colleagues reported a large series in which patients having fewer than 10 polyps had only a 4 percent likelihood of APC and 2 percent chance of (biallelic) MYH mutation, while those with 10 to 19 polyps had APC and MYH probabilities of 5 percent and 4 percent, respectively.[2] Taking age into account, those below age 20 and having 10 to 19 adenomas were predicted to carry a 38 percent likelihood of APC mutation and a 6 percent likelihood of MYH mutations. At age 50, predicted risk of APC mutation dropped to 7 percent and MYH risk was 6 percent for those with 10 to 19 polyps.

As adenoma burden drops below 10 or so, the chance that one is in fact dealing with hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome) increases, as compared with FAP or MYH. Key differences in thinking about the possibility of HNPCC/LS are the characteristic family history and the potential informativeness of doing focused evaluation of the adenoma itself. The family history will rarely involve relatives with multiple polyps

but may show CRC and a spectrum of tumors such as endometrium, upper gastrointestinal, uroepithelial or sebaceous skin tumors. Such a family history will commonly be the reason for doing colonoscopy in young, asymptomatic patients. It is often difficult, however, to obtain a family history that is detailed and accurate enough to clearly implicate HNPCC/LS.

Ideally, workup of suspected HNPCC/LS starts with evaluation of malignant tissue for evidence of microsatellite instability (MSI) either by PCR-based techniques or, more commonly, by immunohistochemistry (IHC) for detection of loss of mismatch repair (MMR) protein expression. The current National Comprehensive Cancer Network (NCCN) guidelines (www.nccn.org) recommend just such an approach, and provide helpful algorithms for both the tumor and germline testing process. When informative, MSI/IHC testing of tumor is followed by testing of germline DNA for underlying MMR gene mutation. In the case of CRC, virtually all cases of HNPCC will show changes on MSI/IHC. The main confounder is the fact that in older patients abnormal MSI/IHC can occur with no underlying germline mutation, and involves methylation of the promoter of one of the MMR genes, MLH1. Sorting this out can be accomplished by means of an additional assay for hypermethylation or testing for BRAF mutation. In the younger patient this is not commonly a sporadic event.

Since our focus here is on the young patient with an adenoma, it can be stated that benign adenoma tissue can be tested in the same fashion as malignant tumors. In known MMR mutation carriers, about 40 to 50 percent of adenomas larger than 8mm have MSI or loss of MMR protein staining,[3] compared to 95 percent or more when an HNPCC/LS cancer is tested. So testing of adenomas is helpful when it is informative, but not when it's not. Typically, when a young person is diagnosed with only one or very few adenomas, we do attempt to more aggressively evaluate family history for an HNPCC/LS pattern, so that if a cancer-affected close relative is identified, an attempt to perform MSI/MMR IHC of that person's tumor is proposed. Evaluation of the adenoma is only undertaken when potentially informative cancer tissue from a near relative is unavailable for testing.

Alternatively, use of a priori risk models to estimate likelihood of an MMR mutation may be employed. If the prior probability of a MMR gene mutation is 5 to 10 percent or greater, based on strength of family history of (early onset) CRC and related HNPCC/LS tumors, mutation testing may be appropriate if tumor (including benign adenoma) testing is uninformative or is not done.

A host of considerations enter the decision-making surrounding genetic testing. Does the clinician have suitable genetic counselor support? Clinical testing laboratories can provide excellent molecular diagnostics, but such facilities, even when supported by their own genetic counselors, cannot properly decide whether testing will be beneficial for a particular patient. Real tension exists between the clinical need for careful genetic counseling on the one hand, and the ready availability of very sophisticated genetic testing that can be ordered without any real understanding of its limitations. Indeed, direct-to-consumer marketing of genetic testing and even performance of testing are available. The gastroenterologist uncomfortable with his or her ability to properly counsel the young patient with one or more adenomas can find a wealth of information to enable more informed approaches, or can simply identify and refer to centers with suitable expertise.

To summarize: a genetic workup has three goals: a) to confirm the suspected diagnosis of one of the conditions discussed (HNPCC/LS, AFAP, MAP); b) to potentially change the patient's clinical management (frequency of colonoscopy, threshold for considering surgical resection, appropriate extracolonic surveillance; c) provide a foundation for predictive genetic testing in other family members, so as to pinpoint those at high risk of similar adenoma involvement, while excluding from further consideration those who are not mutation carriers. ■

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A Systematic Approach to Colorectal Cancer Screening

Gastroenterologists play an essential role in promoting CRC screening, by providing expert guidance and in smoothing the path for referral of patients for colonoscopy.

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Dr. Levin has no conflicts to disclose.

Colorectal cancer (CRC) screening is underused. More than one-third of the eligible U.S. population remains unscreened for CRC. Accountable-care organizations (ACOs) are being formed across the country as a result of the Affordable Care Act. ACOs are groups of doctors, hospitals and other health-care providers who come together to give coordinated care to a group of patients. The ACO is accountable financially for the quality results of its patient population. CRC screening is a common target for quality programs, including the National Committee on Quality Assurance (NCQA) Healthcare Effectiveness Data and Information Set (HEDIS) measure, a common quality measure for health plans and medical groups. ACOs are likely to need to measure and optimize CRC screening rates just as commercial insurers have under HEDIS. This change in the way health systems are organized offers an opportunity for implementing systematic population-oriented CRC screening programs. Gastroenterologists play an essential role in promoting CRC screening, by providing expert guidance and in smoothing the path for referral of patients for colonoscopy.

A systematic approach to CRC screening has been an effective approach for improving CRC screening participation in our medical group and elsewhere. We employ a combined screening model with fecal immunochemical test (FIT) outreach and colonoscopy available by primary-care physician referral. It has been demonstrated that a program that offers patients a fecal screening option is likely to have higher participation than a program that offers only colonoscopy, and randomized trial evidence suggests similar outcomes between FIT and colonoscopy screening.[1,2] Our successful systematic approach involves four components:

1. Measure CRC screening performance.
2. Perform outreach to patients sending a screening invitation directly to their home.
3. Leverage support staff to help physicians deliver the screening message.
4. Employ a systematic reminder system to prompt physicians and support staff to encourage patients due for CRC screening.

Measuring Performance

CRC screening rates can be measured through systematic review of electronic records, telephone or mailed survey of patients, or a review of sample paper charts. However it is done, measurement is essential for evaluating the impact of any screening intervention. It allows identification of which patients are up to date with CRC screening, who is coming due and who is overdue for screening. Documentation of screening requires the recording of screening done in the practice, but also screening performed by outside providers.

Outreach

Outreach refers to contacting a patient outside of a regular office visit. This can be done by mail, phone or secure electronic communication. This allows the screening message to be delivered to patients who do not come into the office often enough to be invited to screen. FIT outreach allows the test kit to be mailed to a patient's home, and saves them from having to travel to the office to pick up the test or to miss any time from work to complete their screening.

Leverage Support Staff

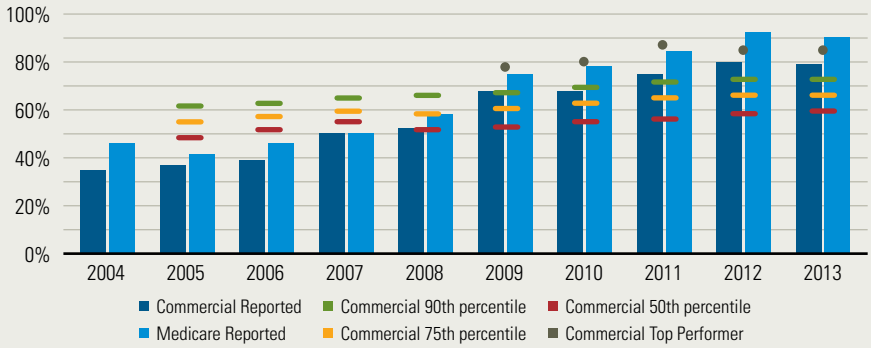
Successful systematic screening programs use office support staff to remind patients about the need for CRC screening. Support staff can give FIT kits to overdue patients and document outside screening if it has occurred. This allows the primary-care physician to spend time with the patient discussing the patient's concerns, and not having to redirect the conversation to the need for CRC screening. It also helps ensure that the screening invitation is made.

Systematic Reminders

Systematic reminding can be done with stickers placed on paper charts or prompts in electronic medical records. This helps ensure that everyone caring for the patient at the time of a visit can reinforce the messages delivered by mailed outreach. Some patients will respond to mailed outreach alone, but many reluctant patients need to hear about the importance of CRC screening to their individual health from a physician they trust or from the office staff of that physician.

Kaiser Permanente, Northern California CRC HEDIS Performance 2004-2013

The dark blue boxes represent the HEDIS commercial insurance population CRC screening rate and the light blue represents the Medicare population CRC screening rate. The red hash mark is the commercial 50th percentile, the yellow the 75th percentile and the green the 90th percentile.



The Kaiser Permanente, Northern California Experience

In 2012, more than 80 percent of eligible patients at Kaiser Permanente, Northern California, were screened for CRC (Figure). This is a significant improvement over our performance in 2005, when less than 40 percent of Kaiser Permanente members were up to date with CRC screening. This improvement was accomplished through a systematic approach to our screening population, using a combination of organized mailed outreach and electronic medical record assisted opportunistic screening. We leveraged our support staff to take advantage of electronic reminders. A key to our success, however, was organizational and leadership alignment around the goal of improving our CRC screening rates. This signaled to all members of our organization that CRC screening is a priority, and all departments in our multispecialty medical group are pursuing the goal of getting our members screened for CRC.

A key challenge of implementing our program was meeting the new demand for colonoscopy generated by the increase in CRC screening. We increased our production of colonoscopy by 200 percent (from 25,000 per year to more than 80,000), with the attendant hiring of additional staff and need for additional equipment. We increased the number of gastroenterologists in our group by 75 percent (from 60 to 105). An additional challenge has been getting patients with positive FIT to follow up with colonoscopy. We use an electronic reminding system to remind physicians to refer patients for colonoscopy, and often have to repeatedly attempt contacting patients who may not be initially willing to have a colonoscopy. ■

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SHOULD WE INDIVIDUALIZE THERAPY BASED ON GENETICS OF COLORECTAL TUMORS?

Colorectal cancer (CRC) is a leading cause of cancer-related mortality worldwide. While CRC is among the best-understood cancers at the molecular level, this knowledge has only recently begun to impact therapeutic decision-making. CRCs typically display chromosomal instability (CIN) and carry frequent mutations in *TP53*, *KRAS* and *SMAD4* genes. Genomic analyses continue to expand the number of genes identified with somatic mutations. A tumor subset (approximately 12 to 15 percent) shows microsatellite instability (MSI) with deficient DNA mismatch repair (MMR).[1] Deficient MMR occurs due to a germline mutation in an MMR gene (*MLH1, MSH2, MSH6, PMS2*) or more frequently by epigenetic inactivation of *MLH1*. Sporadic CRC's that have MSI are often part of another molecular subclass of CRC that has the CpG island methylator phenotype (CIMP). CIMP is associated with $BRAF^{V600E}$ hotspot mutations (approximately 50 percent).[2] Phenotypic features of MSI tumors include earlier stage at diagnosis, right-sided predominance, a robust lymphocytic infiltration in the CRC and better survival.[1]

An increased understanding of the molecular biology and genetics of CRC is beginning to be exploited for therapeutic advantage and is enabling individualized treatment. This advance is most evident in patients with metastatic CRC (mCRC) where molecularly targeted agents in combination with newer cytotoxic chemotherapy combinations have significantly improved patient survival over the last decade. A key example is the mutation status of the *KRAS* gene that has been validated as a predictive biomarker for the efficacy of antibodies against the epidermal growth factor receptor (EGFR) (cetuximab, panitumumab). *KRAS* mutations, found in 30 to 40 percent of CRCs, predict for lack of efficacy of anti-EGFR antibodies whose usage is therefore restricted to patients with wild-type tumors.[3] This finding has led to the routine testing of mCRCs to determine *KRAS* status in clinical practice. *KRAS* encodes a GTPase involved in signal transduction pathways that includes EGFR signaling. While most (approximately 90 percent) *KRAS* mutations occur in exon 2 (codons 12 or 13), recent data suggest that mutations in exons 3 and 4 or in *NRAS* (roughly 2 percent) may also predict for lack response to anti-EGFR antibodies.[4] Evidence suggests that CRCs with a $BRAF^{V600E}$ mutation and wild-type copies of *KRAS* may not respond as favorably as tumors that are wild type for both genes. *BRAF* has not been validated as a predictive biomarker in this setting, and data suggest that $BRAF^{V600E}$ mutations are associated with a poor prognosis in CRCs.[4-5] *BRAF* is a member of the RAF kinase family of serine/threonine kinases and is also involved in EGFR signaling. To date, no predictive biomarkers have been identified for the anti-angiogenic antibody bevacizumab. This agent, given in combination with cytotoxic chemotherapy, is a standard front-line regimen for patients with mCRC.

While the paradigm has been to take effective treatments in mCRC and apply them to earlier stage disease, trials evaluating the combination of bevacizumab or the anti-EGFR antibody therapy with cytotoxic chemotherapy in patients with curatively resected stage II (transmural invasion tumor without lymph node metastasis) or III (with lymph node metastasis) CRC have

not been associated with a survival benefit. More recently, data from large observational studies indicate that aspirin intake following CRC resection was associated with a significant improvement of survival in patients whose tumors carried mutant copies of the *phosphatidylinositol 3-kinase* (*PI3KCA*) gene, which is found in 15 to 20 percent of CRC.[6] A similar result was found in VICTOR clinical trial whereby regular aspirin, in contrast to the selective COX-2 inhibitor rofecoxib, was also found to reduce the tumor recurrence rate after CRC resection in patients with *PIK3CA* mutations.[7] Taken together, these compelling data suggest that aspirin may be beneficial after CRC resection in patients with *PIK3CA* mutant tumors.

Gene expression profiling of CRCs has been performed to identify genomic signatures that can distinguish patients at low- versus high-risk for tumor recurrence.[8-9] To date, such signatures are prognostic but not predictive which, thereby, limits their utility in patient management. While MSI testing of CRCs has known utility for the diagnosis of patients with Lynch syndrome, it is also a biomarker associated with favorable clinical outcome in patients with resected stage II and III CRCs.[1] Furthermore, preclinical data and results from randomized trials indicate that MSI CRC cell lines and human tumors display resistance to 5-fluorouracil, but not to oxaliplatin.[1] Adjuvant chemotherapy is standard of care for stage III, but not for stage II CRC although one-third of stage II patients in the U.S. receive adjuvant chemotherapy. Since MSI cancers are at low risk of recurrence, we and others have recommended that these patients can generally be spared adjuvant chemotherapy.[10] Stage III MSI cancers, however, should continue to receive standard chemotherapy with 5-fluorouracil, leucovin and oxaliplatin (FOLFOX).

> Mutations in genes regulating oncogenic signaling pathways can provide predictive information to enable personalized cancer therapy.

In summary, mutations in genes regulating oncogenic signaling pathways can provide predictive information to enable personalized cancer therapy. A current example is *KRAS* mutation testing that is routinely performed in mCRCs. MSI testing in stage II cancers is commonly used to identify patients unlikely to benefit from adjuvant chemotherapy. Some other molecular markers appear to be predictive, yet additional research and independent validation are needed before these biomarkers can be utilized in clinical practice. One of the challenges for the future is tumor heterogeneity and how to optimally interpret a patient's molecular profile to select the most effective treatment. ■

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WORLDWIDE TRIALS IN SCREENING COLONOSCOPY AND COLORECTAL CANCER

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Dr. Zauber has no conflicts to disclose.

Colorectal cancer (CRC) is the third most common cancer and the fourth most common cause of cancer death in the world. Approximately 1.4 million people are diagnosed with CRC and 700,000 die of CRC annually. CRC incidence and mortality rates are highest in the more developed countries of North America, Western Europe and Oceania (Figure). However, CRC incidence rates are now rising in East Asia and Eastern Europe, in part perhaps due to changes to a more Westernized diet and physical activity level.[1] Also, the estimated case fatality rate (the ratio of CRC deaths to CRC incident cases) is lowest for the developed countries and highest for the developing countries. These findings are of concern and most likely reflect a lack of resources for curative treatment (surgery and chemotherapy) and even less for screening in the developing countries.[2]

Screening is an important tool to reduce CRC incidence and death. Colonoscopy is the primary diagnostic method to evaluate a positive CRC screening test, whether that test is based on evaluating stool, serum (blood), radiological findings, endoscopic findings (such as flexible sigmoidoscopy with limited reach), or other methods that visualize the lumen but cannot remove all lesions. Colonoscopy can be used as a primary screening test as well as an effective intervention for detection or removal of early-stage cancer and adenomas. In prospective studies, colonoscopy provided long-term (20 to 30 years) protection against CRC deaths.[3,4] Retrospective studies also demonstrated that colonoscopy reduced the risk of incident late-stage CRC.[5]

In the February/March 2012 issue of *AGA Perspectives*, investigators reviewed CRC screening programs across the globe. This year (2014) we assess those clinical trials being conducted for colonoscopy and CRC screening across the world. These trials are designed to further improve colonoscopy and its use.

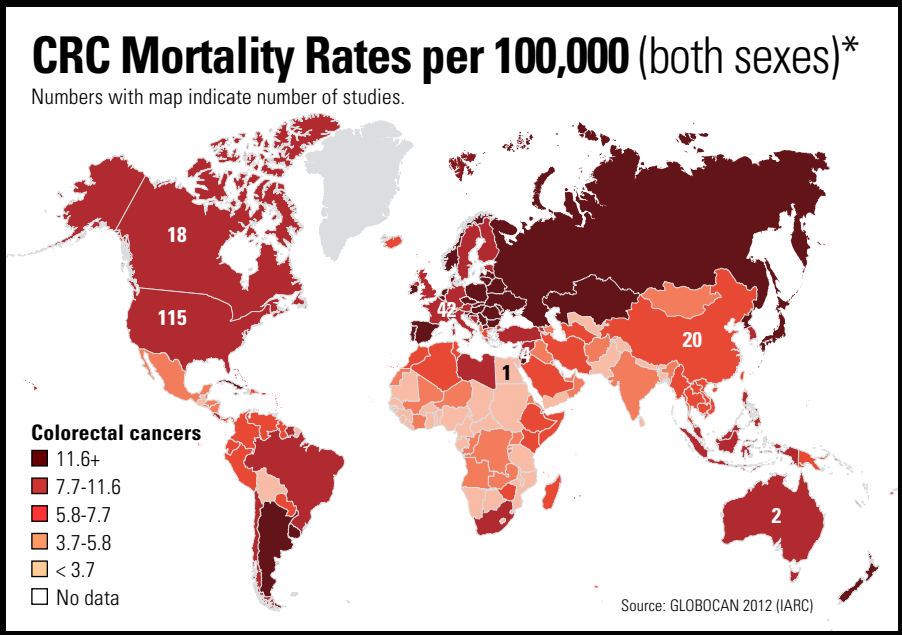
The International Committee of Medical Journal Editors (ICMJE) requests registration of clinical trials in a public trial registry at or before the time of first patient enrollment as a condition for publication in the major clinical journals (http://www.icmje.org/publsihsing_j.html). Therefore, we reviewed the two registries recommended by the ICMJE for clinical trials on colonoscopy or other colorectal cancer screening. The registries reviewed are the WHO International Clinical Trials Registry Platform (WHO ICTRP) (http:/www.who.int/ictrp.html) and the ClinicalTrials.gov of the U.S. National Institutes of Health. There were approximately 200 registered trials across the world as shown on the GLOBOCAN map of level of CRC mortality risk (Figure).[1]

Three of the trials in the registry are large-scale randomized controlled trials of screening colonoscopy with long-term outcomes of incidence and mortality reduction. These include the Northern European Initiative on Colorectal Cancer (NordICC; comparing colonoscopy to usual care in Norway, Sweden, Poland and the Netherlands for ages 55-64); CRC Screening in Average Risk Population: Fecal Immunochemcial Test (FIT) Versus Colonoscopy study (COLONPREV; comparing colonoscopy to biennial FIT in eight regions of Spain for ages 50-69); and the Colonoscopy Versus FIT in Reducing Mortality from CRC study (CONFIRM; comparing colonoscopy versus annual FIT for ages 50-75 in the U.S. veterans population). These studies are currently in accrual and testing. We would anticipate that at least a 10-year interval would be needed before CRC incidence or mortality data would be reported from any of these trials.

The majority of the other registered trials are studies to increase compliance with screening colonoscopy, to improve the quality of colonoscopy as a screening tool, or to compare colonoscopy with other CRC screening tests. Studies to increase compliance include bundling CRC screening with other cancer screening tests, using patient navigators and computerized personalized reminders for screening. Studies for quality improvements include developing new colonoscopy bowel preparations and procedures such as split dosing, reducing conscious sedation, using water infusion and alternative positioning of the patient that might facilitate a higher adenoma detection rate. Other studies are evaluating safety and efficacy of nurses performing colonoscopies under supervision of a physician. Techniques to reduce looping and to evaluate innovative optics and other techniques (such as narrow-band imaging, confocal probes, chromo-colonoscopy) are being assessed as well.

An important area of research is comparative effectiveness studies of colonoscopy versus other screening methods such as FITs, flexible sigmoidoscopy, CT-colonography, improved stool DNA tests, serum markers and imaging capsules. These studies evaluate the acceptance of the tests as measured by compliance, the level of neoplastic findings of advanced adenomas or early stage, and safety of the tests so that risk and benefits can be measured.

Given the major financial and resource investments in these large number of trials now ongoing across the world, improvements in colonoscopy quality should provide an even larger reduction of colorectal cancer deaths worldwide. ■



Age-standardized (world 2000) colorectal cancer mortality rates per 100,000 (both sexes) by quintile of risk with the number of colonoscopy and colon cancer screening studies listed by global region: Canada: 18; United States: 115; Europe: 42; Egypt: 1; Israel: 4; East Asia (China, Korea, Japan Taiwan): 20; Australia: 2.

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