

# ADVANCES IN GERD

Current Developments in the Management of Acid-Related GI Disorders

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## Novel Screening and DNA Testing for the Detection of Esophageal Precancerous Disease



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### **G&H** Why have screening rates for esophageal cancer historically been low?

**DP** The biggest reason is a lack of awareness and understanding of esophageal cancer, particularly esophageal adenocarcinoma (EAC), the main subtype that has been increasing in incidence in the United States. Esophageal cancer is a highly morbid illness that has poor outcomes and is usually asymptomatic or preceded by very nonspecific symptoms in premalignant stages. Unfortunately, it can be easy for patients to dismiss or self-medicate their symptoms and for physicians to treat the symptoms without looking for the underlying cause. The incidence of esophageal cancer, specifically EAC, has increased more than 700% over the past 4 decades.

### **G&H** What are the main risk factors for esophageal cancer?

**DP** There are a number of factors, some of which are known and others that are still somewhat unclear. The known factors include premalignant conditions associated with EAC, namely intestinal metaplasia or Barrett esophagus. Barrett esophagus represents the body's adaptation to prolonged or excessive acid exposure to the lining of the esophagus. Barrett esophagus is initially protective and asymptomatic, but some patients develop premalignant changes known as dysplasia, and a subset of those patients progress to EAC. One of the most

important risk factors for esophageal cancer is gastroesophageal reflux disease (GERD), which is common in the United States. Also common is obesity, which is an independent risk factor for GERD, particularly excessive weight around the midsection. In addition, several genes have been associated with the premalignant conditions related to EAC. Other risk factors for esophageal cancer include smoking, alcohol use, a family history of esophageal cancer or Barrett esophagus, and certain demographic factors. Typically, disorders on the spectrum from Barrett esophagus to esophageal cancer are more common in men, especially those who are white, older than 50 years, and have had classic reflux symptoms for at least 5 years. The longer the duration of GERD symptoms, the greater the likelihood of acid-related injury as well as the progression of Barrett esophagus to premalignant change (dysplasia) and cancer.

One challenge, however, is that up to 40% of patients with esophageal cancer may have no classic preceding symptoms or may have atypical reflux symptoms. Atypical symptoms associated with reflux disease may include cough, unexplained or unusual chest pain, and excessive throat clearing, and patients may cycle between primary care providers and specialists such as pulmonologists, allergists/immunologists, otolaryngologists, and gastroenterologists for a prolonged period of time. This can be frustrating for patients as well as the physicians involved in their care, and can lead to delays in diagnosis. Aside from symptoms of heartburn or atypical reflux symptoms,

one of the biggest risk factors for esophageal cancer is that patients, sometimes unknown to their physicians but also sometimes with their providers' guidance, treat symptoms without looking for the underlying cause. This is a missed opportunity to potentially screen for premalignant conditions such as Barrett esophagus. This can (and often does) go on for several years or longer.

### **G&H** What methods or tests are currently being used to detect esophageal precancer?

**DP** The gold standard is esophagogastroduodenoscopy (EGD), which is an examination typically performed under sedation in which an endoscope with a camera is used to visually inspect the esophagus and related structures such as the stomach and upper intestine. During the procedure, different light filters can be used to highlight subtle changes in the lining of the esophagus and to obtain biopsies for microscopic examination by a pathologist. Although EGD is a relatively safe procedure, there are still risks (albeit low) of procedure- or sedation-related complications, particularly in older patients who have other medical issues. Because it is typically performed under sedation, and therefore in an endoscopy unit, patients need to have someone take them home afterward, may experience loss of time at work or school, and may have costly expenses for the procedure, the professionals providing their care, and the use of the endoscopy unit. In addition, owing to resource limitations and other constraints, it is simply not feasible to perform endoscopy to screen for Barrett esophagus, dysplasia, and esophageal cancer even in the highest risk group of patients—ie, those with all of the aforementioned risk factors.

Over the years, other endoscopic tools have been developed. One is capsule endoscopy, in which a patient swallows an endoscopic capsule with a high-resolution camera that takes pictures as it traverses the esophagus. However, there are several limitations, primarily that this is only a purely visual examination that cannot be directed toward specific areas of concern or to perform biopsies.

A number of minimally invasive office-based procedures are also used. One is the Cytosponge cell collection device (Medtronic), which is essentially a polyurethane sponge within a gelatin capsule that is tied to a string and swallowed by the patient. The capsule dissolves in the acidic environment of the stomach in approximately 7 minutes, and then the administrator uses the string to pull the sponge across the gastroesophageal junction, where it samples cells that are subsequently analyzed.

The latest iteration of an office-based sampling procedure involves the EsoCheck device (Lucid), which is paired with EsoGuard DNA analysis (Lucid). The patient

swallows the catheter, which has a deflated balloon inside and a cap on the end. Upon reaching the stomach, the balloon is inflated. The balloon, which has ridges, then samples cells at the gastroesophageal junction and up to a distance of approximately 5 to 10 cm above or proximal to the distal esophagus, where Barrett esophagus, dysplasia, and EAC typically arise. After this sampling, the balloon is deflated and the device is removed from the patient.

The balloon is then excised from the device, and the cells that were collected are placed into a solution within a small vial, which is sent to a laboratory for DNA analysis. The analysis of the DNA extracted from these cells looks at changes in 2 markers: vimentin and cyclin A1. Methylation changes to these genes are associated with Barrett esophagus, dysplasia, and EAC. EsoGuard involves polymerase chain reaction at a specialized laboratory, with the final analysis done via next-generation sequencing; therefore, the test is not dependent upon histologic interpretation. Early published reports demonstrate that EsoGuard has a greater than 90% sensitivity and specificity for the spectrum of disorders that lead to EAC. My experience with this procedure over the past year and a half is consistent with these early reports in the ever-growing population of patients who have undergone screening.

### **G&H** How have you incorporated EsoCheck and EsoGuard into your practice?

**DP** Integration has been very smooth. I have incorporated these tools into my general workflow in a large ambulatory outpatient center where I see patients at high risk for Barrett esophagus and esophageal cancer, as well as patients who present with average or unknown risk given the known high incidence of disease, or patients who are asymptomatic or who have nonclassic symptoms for this spectrum of diseases. Whenever I see patients, whether for acid-related disorders or for unrelated gastrointestinal issues, I look at their demographics, dietary and lifestyle factors, and personal and family history to determine whether they have any of the risk factors for esophageal cancer. When asked, many patients admit to having a history of GERD but manage it with over-the-counter medications such as antacids, histamine blockers, or proton pump inhibitors. These medications are very effective for symptomatic control, but typically do not reverse the underlying disease process that can lead to concerning conditions. Therefore, it is important for providers to assess for Barrett esophagus and esophageal cancer risks, even if this may not represent the primary reason for the patient's clinical visit.

In patients for whom it is appropriate—which represents a high percentage of patients who present

to both gastroenterologists and other specialists—I recommend EsoCheck and EsoGuard. In addition to detecting premalignant esophageal conditions, a positive EsoGuard DNA test can guide the timing of endoscopy and expedite more urgent endoscopic procedures. In selected patients, a negative result may obviate the need for endoscopy, especially in patients who do not wish to undergo the procedure or who may be at a higher risk for procedure- or sedation-related complications based on other medical conditions. Even in resource-rich areas, it is not possible to perform endoscopy-based screening on all of the highest-risk patients, let alone for all of those who warrant screening.

For appropriate patients, I discuss the rationale for screening with the EsoCheck device. I demonstrate the balloon-based catheter system and show patients a sample device, which they can examine and manipulate. I provide detailed brochures on the EsoCheck device and the EsoGuard DNA test. When feasible, I recommend performing the procedure at this time (the point of care) if the patient is amenable. The entire process, from discussion to recovery, typically takes under 5 minutes. The procedure does not disrupt workflow in an office setting—once optimized, the procedure does not take long to perform, and the learning curve to become an expert administrator is not steep. The procedure can be performed by a physician, advanced practice practitioner, nurse, medical assistant, or any member of the health care team for whom it is within their scope of practice (which may vary by setting, institution, or regulations).

### G&H What has the patient experience been like?

**DP** In our center, my colleagues and I have performed more than 400 EsoCheck/EsoGuard procedures over the past year and a half. There has been high acceptance by patients, even though the majority of them had not heard of the procedure before. Particularly during the first several months, I was surprised by how quickly patients were amenable to the procedure, including those who may not have come in for GERD-related issues. In these cases, it is even more vital to explain why screening for symptomatic and asymptomatic disease is necessary and the consequences of late recognition of premalignant or malignant disease.

The patient experience has been very positive. Although there is frequently a transient and fairly minimal gag sensation the majority of the time, we have not experienced any complications. Our results show that more than 90% of patients are able to tolerate the procedure successfully. As long as it is performed appropriately, especially making sure that patients have been fasting for

2 hours prior, we have had no issues. Most patients report a better-than-expected tolerance. No sedation is needed, which is an advantage, so patients can immediately return to eating and their usual activities. Because the device is soft and pliable, there has been no esophageal or other trauma.

### G&H What impact are EsoCheck and EsoGuard having?

**DP** EAC is often diagnosed in advanced or metastatic stages. Overall survival at 5 years is less than 20% across different stages of disease. Although the goal is early detection, even more important is the prevention of EAC, which can be accomplished by detecting Barrett esophagus. Nondysplastic or dysplastic disease can be managed with medical or endoscopic therapy, but once there is malignant disease, the treatment options change and outcomes become quite dismal. Therefore, it is important for screening to be performed as early as possible on as many people as possible for whom it is appropriate.

The impact that EsoCheck and EsoGuard are already having, and can further have in the future, is tremendous. I have a low threshold for recommending EsoCheck/EsoGuard to patients because they are well tolerated and atraumatic, and they can be performed essentially without risk. The esophageal mucosal DNA test can help screen for a malignancy that is often not detected until a more advanced stage. Less than 10% of patients are being screened who meet the highest-risk criteria, as defined by guidelines from the American College of Gastroenterology (ACG) and other professional societies. An even higher percentage of patients is being missed in terms of those who meet some (but not all) of these known risk factors. Having such low screening numbers for a highly morbid and fatal malignancy is unacceptable. A test that can improve screening without excessive costs, risks, and inconvenience that can save lives is warranted. Our experience to date suggests that such a test exists in EsoGuard. With EsoCheck and EsoGuard, screening and detection of both nondysplastic and dysplastic Barrett esophagus are straightforward, effective, and well tolerated. My colleagues and I have performed enough procedures to know that patients who have the highest risk should be screened with these tools, and we have identified Barrett esophagus in patients of more moderate pretest risk.

### G&H What are the main limitations of using EsoCheck and EsoGuard for detecting esophageal precancerous disease?

**DP** These tests, as well as other minimally invasive tests such as Cytosponge, are not visual examinations and

cannot provide directed sampling of specific areas of tissue. In contrast, an endoscopy allows for visualization, and a biopsy forceps can be directed toward abnormal areas found during the procedure to obtain a sample.

### G&H Should EsoCheck and EsoGuard be avoided in any patients?

**DP** Although cleared by the US Food and Drug Administration for approximately 2 and a half years, no clear guidelines or universally agreed-upon indications or contraindications exist to date. Thus, use requires expert clinical decision-making by the provider as well as extrapolation of general endoscopy guidelines from the ACG and other professional societies.

With that being said, both published data and our own extensive experience demonstrate that the EsoCheck collection device is very safe in most patients. However, because this instrument is nonendoscopic and nonvisual and does not involve directed sampling, it may not be ideal for patients with known or suspected cirrhosis, portal hypertension, or esophageal varices. Theoretically, an injury could occur to an esophageal varix or dilated vein that could lead to bleeding and serious complication, although we have not experienced this and I am not aware of any reports of this in the literature. Likewise, this modality should be used judiciously (and avoided in selected patients) in the setting of recent hematemesis and in patients receiving anticoagulation therapy, particularly if it is newly prescribed or with a significant change in dosage.

### G&H What are the key takeaway messages for patients and physicians?

**DP** The key message to patients is not to ignore symptoms. Everyone has (or has had) classic heartburn at some time. However, if patients have symptoms more than occasionally, especially if they require frequent medical therapy (whether prescription or over the counter), or if symptoms are impacting their quality of life, they should

talk to their physician and ask if further evaluation is needed. Medications are effective, but according to the recent ACG guidelines, patients should be screened if they have chronic GERD symptoms and based upon the risk factors previously described. Recognizing the importance of early detection (and indeed prevention), updated guidelines from this year have liberalized the patients who qualify for screening even further. Patients should be aware that atypical symptoms, such as a persistent or atypical cough that does not appear to be related to allergies or postnasal drip, may be a manifestation of GERD, as may frequent throat clearing, nonexertional atypical chest pain, and other symptoms.

As for physicians, both gastroenterologists and providers in other specialties, it is important not to merely treat symptoms, but identify and manage the underlying etiology. At some point, there should be a discussion with patients, especially if they bring up their symptoms, to determine whether they have a high risk of Barrett esophagus or esophageal cancer. If patients do not mention symptoms, I encourage physicians to ask questions because patients do not always bring up what is bothering them. It is important to at least start the conversation so that patients can be evaluated and screened when appropriate, especially now that increasing screening options are available, including effective minimally invasive ones.

### Disclosures

*Dr Poppers is a consultant for Lucid Diagnostics.*

### Suggested Reading

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