based strategy. A recent Veterans Affairs–based prospective study demonstrated the inadequate sensitivity (39%–43%) and modest specificity (67%–76%) of current guidelines requiring the presence of reflux symptoms for screening (65). In addition, as noted above, there are other independent risk factors for BE and EAC, which can be used to stratify risk. However, a challenge of screening those without chronic reflux symptoms is the larger population (120 million adults aged >40 years in the United States vs 30 million adults aged >40 years in the United States with chronic reflux), which will have to be targeted, if reflux symptoms as an essential criterion were to be removed. Hence, a population with a lower incidence of EAC compared with those with chronic reflux symptoms would require screening in this expanded approach. The cost-effectiveness and practical implications (such as costs, personnel issues) of expanding screening to this larger population with an invasive technique such as esophagogastroduodenoscopy are largely unknown. It is, however, conceivable that the availability of a safe, less expensive, minimally invasive screening option may alter this equation. Given the lack of relevant data at this time, the panel did not make specific recommendations on expanding BE screening to those without chronic reflux symptoms.

Recommendation.

6. We suggest that a swallowable, nonendoscopic capsule sponge device combined with a biomarker is an acceptable alternative to endoscopy for screening for BE in those with chronic reflux symptoms and other risk factors (strength of recommendation: conditional; quality of evidence: very low).

Summary of evidence. Over the last decade, substantial progress has been made in developing a minimally invasive, nonphysician and office administered BE detection test. Most data are available on tests which use swallowable esophageal cell collection devices, consisting of dissolvable gelatin or vegetable capsules containing a compressible spherical polyurethane sponge attached to a string/suture which expands to a sphere when the capsule is dissolved [Cytosponge, EsophaCap], or an inflatable silicone balloon [EsoCheck]. These devices are swallowed, then withdrawn orally, obtaining esophageal cytology samples (Figure 3). These samples are then used for the assessment of biomarkers associated with BE: either a protein marker expressed in IM (trefoil factor 3 [TFF3]) or methylated DNA markers (MDMs) associated with BE mucosa to predict the presence of BE. TFF3 staining is performed by immunohistochemistry (IHC) with subsequent interpretation by a pathologist, whereas MDMs are quantitatively analyzed by a polymerase chain reaction–based test.

In addition, these tests can be performed in an office setting, by non–physician-trained providers and do not require the use of sedation. A local anesthetic spray to the oropharynx may be used to reduce discomfort during administration and withdrawal. The safety of this minimally invasive approach has been reported in multiple studies. More than 90% of enrolled participants were able to swallow these esophageal cell collection devices. Adverse events reported with these devices have included mild gagging and throat discomfort. Detachment of the string from the sponge has been reported in an extremely small proportion of patients. If detachment occurs, endoscopic removal of the detached sponge has been performed. In a pooled analysis of 2,672 patients from 5 clinical trials using the Cytosponge, detachment requiring endoscopy was reported in 1 case (66).

Several prospective studies performed in the United States and United Kingdom (summarized in Table 4) have demonstrated the feasibility and accuracy of this approach, with variable performance characteristics. The greatest experience to date and largest available evidence base has been with the Cytosponge device. Of note, all the studies reporting the operating characteristics of these devices are case-control studies performed in populations that have been enriched for BE.

In a landmark pragmatic trial set in primary care clinics and performed in the United Kingdom (67), patients with chronic reflux (defined as those using antireflux medications for at least 6 months), who were randomized to the Cytosponge-TFF3 test, had a 10-fold higher likelihood of being diagnosed with BE by confirmatory endoscopy (2% BE prevalence) compared with those randomized to a usual care arm, where endoscopy was performed only if the provider thought it was indicated (<1% BE prevalence). Of those invited to participate, 39% of patients expressed interest in undergoing the Cytosponge test. The positive predictive value of this test in this screening population was 59%. In addition, more patients in the Cytosponge-TFF3 arm were also diagnosed with dysplastic BE and early-stage EAC (9) compared with the usual care arm (0), suggesting the potential utility of this strategy in identifying those who could benefit from therapeutic intervention. Importantly, this technique was also safe and well tolerated. A previous study has shown this test to be cost-effective (when compared with no screening) (68) when used in a hypothetical sample of 50-year-old White men with chronic reflux. Trials to assess the performance of MDM-based minimally invasive BE detection tests in screening populations are ongoing to determine their performance characteristics in this setting.

Another noninvasive BE screening technology that is being developed is the analysis of exhaled volatile organic compounds by a handheld device (Aeonose; eNose Company, Zutphen, the Netherlands) containing a metal oxide sensor array. Sensor measurements generate a digital signal, which can be analyzed by artificial neural networks for BE detection. In a preliminary study reported from the Netherlands, a sensitivity and specificity of 91% and 74% for BE detection using endoscopy as a gold standard were reported (69).

Recommendation.

7. We suggest against repeat endoscopic screening in patients who have undergone an initial negative screening examination by endoscopy (strength of recommendation: conditional; quality of evidence: low).

Summary of evidence. The yield of a repeat endoscopy for diagnosing BE following an initial negative BE screening endoscopy is low. In a study of the Clinical Outcomes Research Initiative database, which included over 24,000 patients undergoing repeat endoscopy, only 561 (2.3%) patients had suspected BE on repeat endoscopy after an initial negative examination. Esophagitis on the index endoscopy, reflux as an indication for endoscopy (compared with other indications), and male sex were predictors of BE being diagnosed at subsequent endoscopy (70). In patients with esophagitis described at initial endoscopy, 9.9% were found to have suspected BE on repeat examination. However, of note, more than 85% of the repeat examinations were performed within 2 years of the initial examination. Hence, additional data on the detection of BE at endoscopic evaluation performed at longer intervals after an initial negative screening endoscopy would