Participating in the Webinar

All attendees will be muted and will remain in Listen Only Mode.

Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.

How to Receive CME and MOC Points

LIVE VIRTUAL GRAND ROUNDS WEBINAR
ACG will send a link to a CME & MOC evaluation to all attendees on the live webinar.

ABIM Board Certified physicians need to complete their MOC activities by December 31, 2022 in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after March 1, 2023 for this activity.
MOC QUESTION

If you plan to claim MOC Points for this activity, you will be asked to: Please list specific changes you will make in your practice as a result of the information you received from this activity.

Include specific strategies or changes that you plan to implement. THESE ANSWERS WILL BE REVIEWED.

ACG Virtual Grand Rounds

Join us for upcoming Virtual Grand Rounds!

Week 31 – Thursday, August 4, 2022
Noon Eastern and 8pm Eastern!
* Cadriometabolic Syndrome in Patients with IBD: Complications and Implications*
Faculty: Parakkal Deepak, MD, FACG
Moderator: Andres J. Yarur, MD, FACG

Career Edition - Wednesday, August 10, 2022
8:30pm Eastern
*Leadership Roles: Where To Start*
Faculty: Jami Kinnucan, MD, FACG
Panelists: Aline Charaby, MD, FACG, Uzma Siddiqui, MD, FACG
Moderator: Naemat Sandu, MD, FACG

Visit gi.org/ACGVGR to Register
Disclosures

Nicholas J. Shaheen, MD, MPH, MACG
Medtronic: Research Funding; Steris: Research funding; Pentax: Research funding; CDx Diagnostics: Research funding; Interpace Diagnostics: Research funding; GIE Medical: Research funding; Lucid Medical: Research funding; Cernostics: Consultant; Phathom Pharmaceuticals: Consultant; Aqua Medical: Consultant; Exact Sciences: Consultant; Cook Medical: Consultant

George B. Smallfield, III, MD, MSPH
Steris: Research funding; Lucid: Research funding; Pentax: Research funding

*All of the relevant financial relationships listed for these individuals have been mitigated
Outline

• What Stayed the Same
  – Medical Management
  – Surgical Management
  – Endoscopic Management

• What Changed
  – Medical Management
  – Surgical Management
  – Endoscopic Management
14. We suggest at least once-a-day PPI therapy in patients with BE without allergy or other contraindication to PPI use

Quality of Evidence: Very low
Strength of Evidence: Conditional
Should Patients have Further Chemopreventive Agents?

- Multiple agents have been suggested as chemopreventives in native BE based on epidemiological data
  - ASA, statins, metformin
- AspECT trial in UK demonstrated improved outcomes with high dose PPI + ASA 300 mg compared to low dose PPI and no ASA
  - All cause mortality difference, not EAC difference
  - Hard to know if this is applicable to the post-EET patient
- Recommendation: Give ASA when you have another reason to, o/w just PPI

16. We suggest against the use of antireflux surgery as an antineoplastic measure in patients with BE

Quality of Evidence: Low
Strength of Evidence: Conditional
Indications for EET

17. We recommend endoscopic eradication therapy in patients with BE with HGD or IMC.

18. We suggest endoscopic eradication therapy in patients with BE with LGD to reduce the risk of progression to HGD or EAC vs close endoscopic surveillance.
### What Do Guidelines Say?

<table>
<thead>
<tr>
<th></th>
<th>IMC</th>
<th>HGD</th>
<th>LGD</th>
<th>NDBE</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGA</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>ACG</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>ASGE</td>
<td>X</td>
<td>X</td>
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<tr>
<td>BSG</td>
<td>X</td>
<td>X</td>
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</tbody>
</table>

What is Rate of Progression of LGD?

Is LGD an Indication for Endoscopic Intervention?

**SURF study**

RCT, n=140, surveillance EGD vs. ablation with RFA

- Primary outcome: occurrence of HGD/EAC

Phoa KN et al. JAMA 2014

---

Surveillance versus Endoscopic Therapy for BE with LGD: SURVENT Trial

**Biomarkers:** p53 IHC, TissueCypher, WATS, & BAD-GAS

Opportunity to prospectively evaluate the predictive performance of these biomarkers
Is Non-Dysplastic BE an Indication for Ablation?

- Is it effective?
  - Most studies document high rates of reversion to squamous tissue
  - Data from U.S. RFA Registry shows a markedly decreased rate of cancer in NDBE after RFA compared to historical controls (0.5/1000 p-y)

- Can we afford it?
  - Cost-effectiveness is questionable
  - Will treat 20 or more for one to benefit
  - Effective intervention is still available if they progress to dysplasia

- Bottom line: Until better risk stratification is available, highly unlikely we will be recommending RFA for all NDBE
When Is Endoscopic Rx Inadequate?

- Lesion too deep
  - Anything SM1 or deeper deserves consideration of esophagectomy
  - SM1 may be managed endoscopically if the patient is a poor surgical cancer

- Lesion too aggressive
  - Poor differentiation
  - Lymphovascular invasion

- Lesion not amenable to endoscopic Rx
  - Won’t raise, too large

Invasion depth and risk of LNM

0-3% m1
0 – 22% sm1
36 – 54% sm3

Courtesy of Jacques Bergman
What Is the Best Weapon(s) for EET?

Choices for Endoscopic Ablation, 2022
The short answer is that no one knows for sure the best treatment modality for dysplastic BE.

However, the most extensively studied, and only modality with level one evidence of cancer prevention, is radiofrequency ablation.

What Changed?
### Current Society Guidelines for BE Screening

<table>
<thead>
<tr>
<th>Society</th>
<th>Year</th>
<th>Screening Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACG</td>
<td>2022</td>
<td>Chronic GERD symptoms and 3 or more additional risk factors for BE, including male sex, age ≥50 yr, White race, tobacco smoking, obesity, and family history of BE or EAC in a first-degree relative</td>
</tr>
<tr>
<td>ESGE</td>
<td>2020</td>
<td>Long-standing GERD symptoms (i.e., &gt;5 years) and multiple risk factors (age≥50 years, white race, male sex, obesity, first-degree relative with BE or esophageal adenocarcinoma)</td>
</tr>
<tr>
<td>ASGE</td>
<td>2019</td>
<td>A family history of EAC or BE (high risk) or patients with GERD plus at least 1 other risk factor (moderate risk). RFs reviewed incl male, obesity, central adiposity, smoking.</td>
</tr>
<tr>
<td>BSG</td>
<td>2014</td>
<td>GERD with ≥3 risk factors: &gt;50 yrs, Caucasian, male, obesity +/‐ (+)FHx</td>
</tr>
<tr>
<td>AGA</td>
<td>2011</td>
<td>Multiple risk factors: &gt;50 yrs, caucasian, male, chronic GERD, hiatal hernia, obesity</td>
</tr>
</tbody>
</table>

### As One Adds Risk Factors, the Yield of Screening EGD Increases

- Meta-analysis of 49 studies suggests that the prevalence of BE in GERD populations is ≈3%
- Add one RF, ≈12%
- Each increase by 1 RF, BE prevalence increases ≈1.2%
- Family history has an esp high risk, 23.4%

*Qumseya BJ et al. GIE, 2019.*
6. We suggest that a swallowable, nonendoscopic capsule device combined with a biomarker is an acceptable alternative to endoscopy for screening.

Quality of Evidence: Very low
Strength of Evidence: Conditional

Is there a better way to screen patients with heartburn for BE?
Current management strategies for EAC detection are not successful

In Many Ways, Allegiance to Endoscopy has Fenced Us In

- The costs, availability, and need for expert pathology services all argue for honing screening down to only the highest risk patients
- While rising dramatically in the last several decades, esophageal adenocarcinoma is still a relatively low incidence cancer even in those with GERD
  - The window of opportunity for successful intervention after the development of neoplasia but before metastasis is lower than in many cancers
- Our risk stratification abilities are weak
- SO…. We have a screening tool which needs great risk stratification to have any shot at cost-effectiveness, but a poor ability to risk stratify
How Good in the Sponge?

- 501 subjects screened in a general medicine population, EGD used as gold standard
- For BE of ≥ 1 cm:
  - Sensitivity – 73.3% (44.9-92.2%)
  - Specificity – 93.8% (91.3-95.8%)
- For BE of ≥ 2 cm:
  - Sensitivity – 90.0% (55.5-99.7%)
  - Specificity – 93.5% (90.9-95.5%)

Cytosponge-trefoil factor 3 versus usual care to identify Barrett’s oesophagus in a primary care setting: a multicentre, pragmatic, randomised controlled trial

Rebecca C Fitzgerald, Massimiliano di Pietro, Marie O’Donovan, Roberta Maroni, Beth Muldrew, Irene Debrinam-Beecham, Marcel Gebaur, Judith Offman, Monika Tripathi, Samuel G Smith, Benedikt Alpert, Fiona M Walter, Greg Rubin, on behalf of the BEST 3 Trial team*, Peter Sasieni

Interpretation In patients with gastro-oesophageal reflux, the offer of Cytosponge-TFF3 testing results in improved detection of Barrett’s oesophagus. Cytosponge-TFF3 testing could also lead to the diagnosis of treatable dysplasia and early cancer. This strategy will lead to additional endoscopies with some false positive results.
How Well does EsoCheck Work?

- Detects and characterizes volatile organic compounds (VOCs)
- 5 minute continuous breath sample
- Measures conductance of aggregate exhaled VOCs via a neural network


Electronic Nose Device
Barrett’s Breath Detection: ROC Curve

- 82% Sensitivity
- 80% Specificity
- 81% Accuracy
- AUC 0.79

Recommendations Changed for How Often People with BE Need Endoscopy
There is a Tremendous Over-Use of EGDs in BE

235 patients with NDBE at UNC, Mayo, SAVAMC, with BE for an average of 6.5 years.
There is a Tremendous Over-Use of EGDs in BE

Distribution of Recommended Follow-Up Interval in Procedures with Finding of Nondysplastic Barrett’s Esophagus


How about After Successful Eradication of Dysplastic BE?

Table 7. Recommended endoscopic surveillance intervals following CEIM based on worst pretreatment histology

<table>
<thead>
<tr>
<th>Worst pretreatment histology</th>
<th>Suggested endoscopic surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-grade dysplasia</td>
<td>1 yr following CEIM</td>
</tr>
<tr>
<td></td>
<td>3 yr following CEIM</td>
</tr>
<tr>
<td></td>
<td>Every 2 yr thereafter</td>
</tr>
<tr>
<td>High-grade dysplasia</td>
<td>3 mo following CEIM</td>
</tr>
<tr>
<td></td>
<td>6 mo following CEIM</td>
</tr>
<tr>
<td></td>
<td>12 mo following CEIM</td>
</tr>
<tr>
<td></td>
<td>Annually thereafter</td>
</tr>
<tr>
<td>Intramucosal carcinoma</td>
<td>3 mo following CEIM</td>
</tr>
<tr>
<td></td>
<td>6 mo following CEIM</td>
</tr>
<tr>
<td></td>
<td>12 mo following CEIM</td>
</tr>
<tr>
<td></td>
<td>Annually thereafter</td>
</tr>
<tr>
<td>CEIM, complete eradication of intestinal metaplasia.</td>
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</tbody>
</table>
Should I be Using Biomarkers, and if so, Which Ones?

12. We could not make a recommendation on the use of wide-area transepithelial sampling with computer-assisted 3-dimensional analysis in patients undergoing endoscopic surveillance of BE.

13. We could not make a recommendation on the use of predictive tools (p53 staining and TissueCypher) in addition to standard histopathology in patients undergoing endoscopic surveillance of BE.
Wide Angle Transepithelial Tissue Sample

WATS3D Computer Algorithm Generates a Synthetic Image for Pathologist

150 micron thick sample  
Advanced imaging system makes 50, 3-micron thick optical slices  
Synthesizes images into a single 3D en face view of gland
WATS Computer Synthesized 3D EnFace View

Cross-Sectional Data - Added Yield of Barrett’s Esophagus and Dysplasia

- Increased Diagnostic Yield with Adjunctive Use of WATS3D

<table>
<thead>
<tr>
<th>Condition</th>
<th>Surveillance</th>
<th>Screening</th>
<th>Meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysplasia</td>
<td>42%</td>
<td>57.10%</td>
<td>68.4%</td>
</tr>
<tr>
<td>Post-Ablation Barrett’s E</td>
<td>39.8%</td>
<td>64.7%</td>
<td></td>
</tr>
<tr>
<td>Barrett’s Esophagus</td>
<td>42%</td>
<td>64.7%</td>
<td></td>
</tr>
<tr>
<td>Dysplasia and</td>
<td></td>
<td></td>
<td>42%</td>
</tr>
<tr>
<td>Barrett’s Esophagus and</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysplasia</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Anandasabapathy et al. Dig Dis Sci, e-pub
- Gerson et al. Digestive Disease Week; May 18-21, 2014; Chicago. Abstract Sa1833.

American College of Gastroenterology
How Useful is p53?

- p53 is a TSG which is inactivated in most cases of BE carcinogenesis
- Mutations may lead to loss of expression or over-expression of abnormal protein
  - Both are associated with increased risk of cancer


A Meta-Analysis of Progression Risk in p53 Positivity

Case-Control Studies

Younes et al., 1993
Kim et al., 1997
Younes et al., 1997
Gimenez et al., 1999
Weston et al., 2001
Devkar et al., 2015
Younes et al., 2017
Total (fixed effects)
Total (random effects)

Cohort Studies

TissueCypher - A multiplexed, Fluorescence Imaging Platform for Risk Prediction in BE

Clinical Report Expresses Risk on 1-10 Scale

 PATIENT RESULTS: TISSUECYpher® RISK SCORE AND RISK CLASS

Risk Score
7.8

Risk Class: HIGH

5 year Probability of Progression: 14% (95% CI 9.1, 19)

Probability of progressing to high grade dysplasia or esophageal adenocarcinoma within 5 years (%)

Risk Score
0 2 4 6 8 10

Low Risk
Intermediate Risk
High Risk

Clinical Report Expresses Risk on 1-10 Scale
A Growing Literature Suggesting this Approach Provides Risk Stratification

- Six studies suggest that TissueCypher selects patients at higher risk for progression, and may improve on current dysplasia categorization
  - Studies use case-control designs
  - Reported sensitivities ranging from 29%-50%
  - Hazard ratios for High+Intermediate group vs Low Risk >5

Phases of Biomarker Development

- **Preclinical Exploratory** (PHASE 1) Promising directions identified
- **Clinical Assay and Validation** (PHASE 2) Clinical assay detects established disease
- **Retrospective Longitudinal** (PHASE 3) Biomarker detects disease early before it becomes clinical and a “screen positive” rule is defined
- **Prospective Screening** (PHASE 4) Extent and characteristics of disease detected by the test and the false referral rate are identified
- **Cancer Control** (PHASE 5) Impact of screening on reducing the burden of disease on the population is quantified

How Good a Biomarker has to be is Ultimately a Clinical Decision!

• I will settle for a relatively poor biomarker to push me over the threshold to do ablation
  – Why? Intervention is low-risk, highly effective and easy to deliver

• I want superb performance in a biomarker to push me over the surgery threshold
  – Why? Intervention is high-risk, costly and difficult to deliver

Conclusions

• Several important changes have occurred in the most recent ACG guidelines
  – Screening is endorsed for both women and men with multiple additional risk factors for BE
  – Non-endoscopic screening was endorsed for the first time
  – The surveillance intervals were changed to allow for a longer interval for very short segment disease
  – Post-EET surveillance intervals were liberalized

• Several issues have remained the same
  – The definition of BE and its diagnosis are unchanged
  – Daily PPI therapy is recommended
  – Indications for EET are unchanged
  – The use of alternative biomarkers awaits further validation
“The Best Day in the Life of any Barrett’s Patient is the Day their Endoscopist Dies.”

-Steve Sontag, MD

Thanks!
Questions and Answers

Nicholas J. Shaheen, MD, MPH, MACG

George B. Smallfield, III, MD, MSPH

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