What's New in Barrett's Esophagus: The 2025 Update

Shawn L. Shah, MD

Assistant Professor of Medicine

Division of Digestive and Liver Diseases

University of Texas Southwestern Medical Center

Dallas VA Medical Center – VA North Texas Healthcare System

Disclosures

- None

Learning Objectives

- Discuss the basic tenets of performing a high-quality endoscopic exam for Barrett's esophagus

- Review the indications for screening for Barrett's esophagus and emerging non-endoscopic technologies

- Define and discuss the terms PEEC and PEEN

- Provide an overview of principles, goals and candidates for endoscopic eradication therapy

- Highlight knowledge gaps and future directions within Barrett's esophagus

Barrett's Esophagus
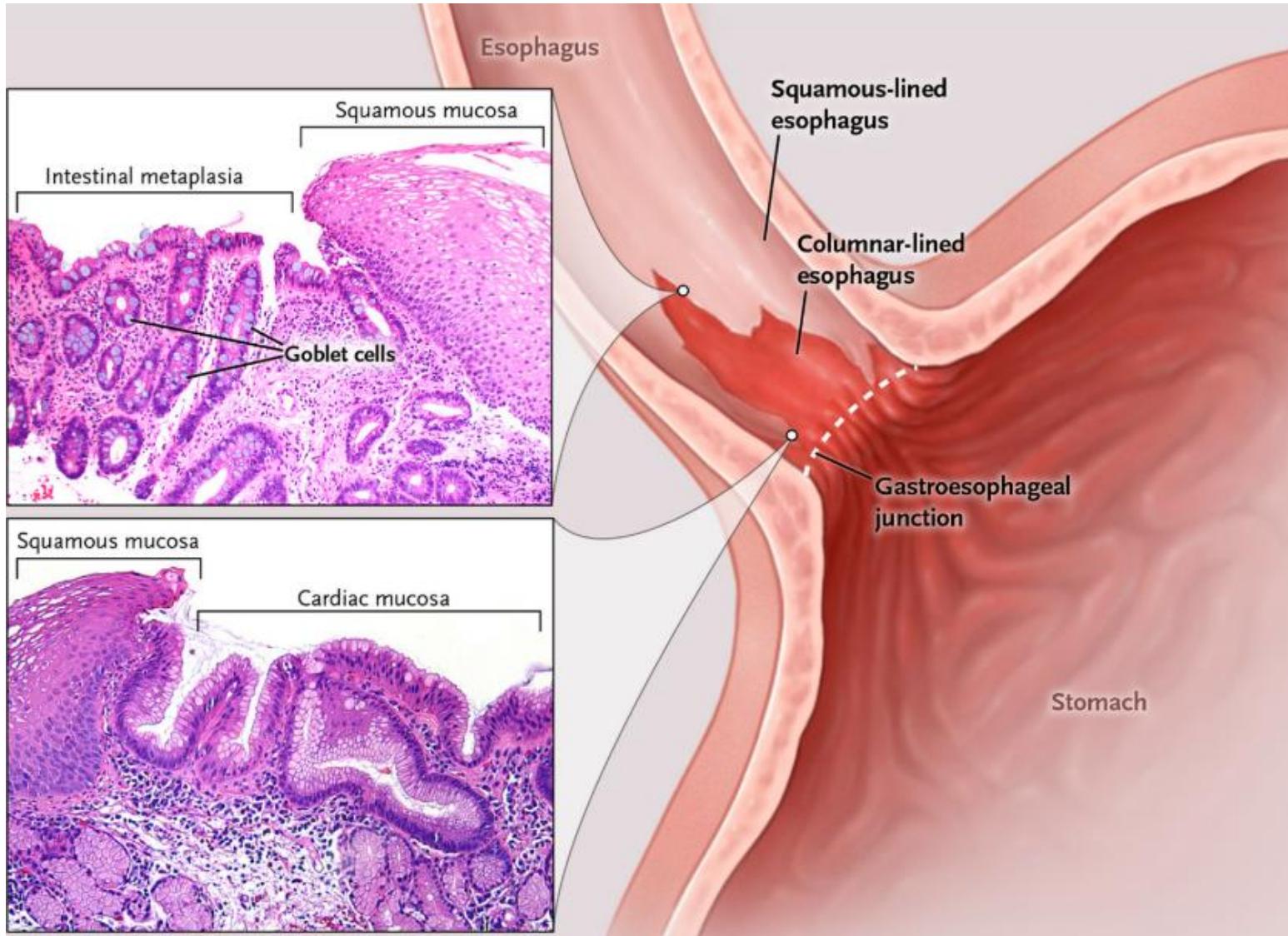
Columnar-lined esophagus + Biopsy confirmation of intestinal metaplasia

Spechler S et al, NEJM 2014

Barrett's Esophagus-Related Dysplasia and Neoplasia
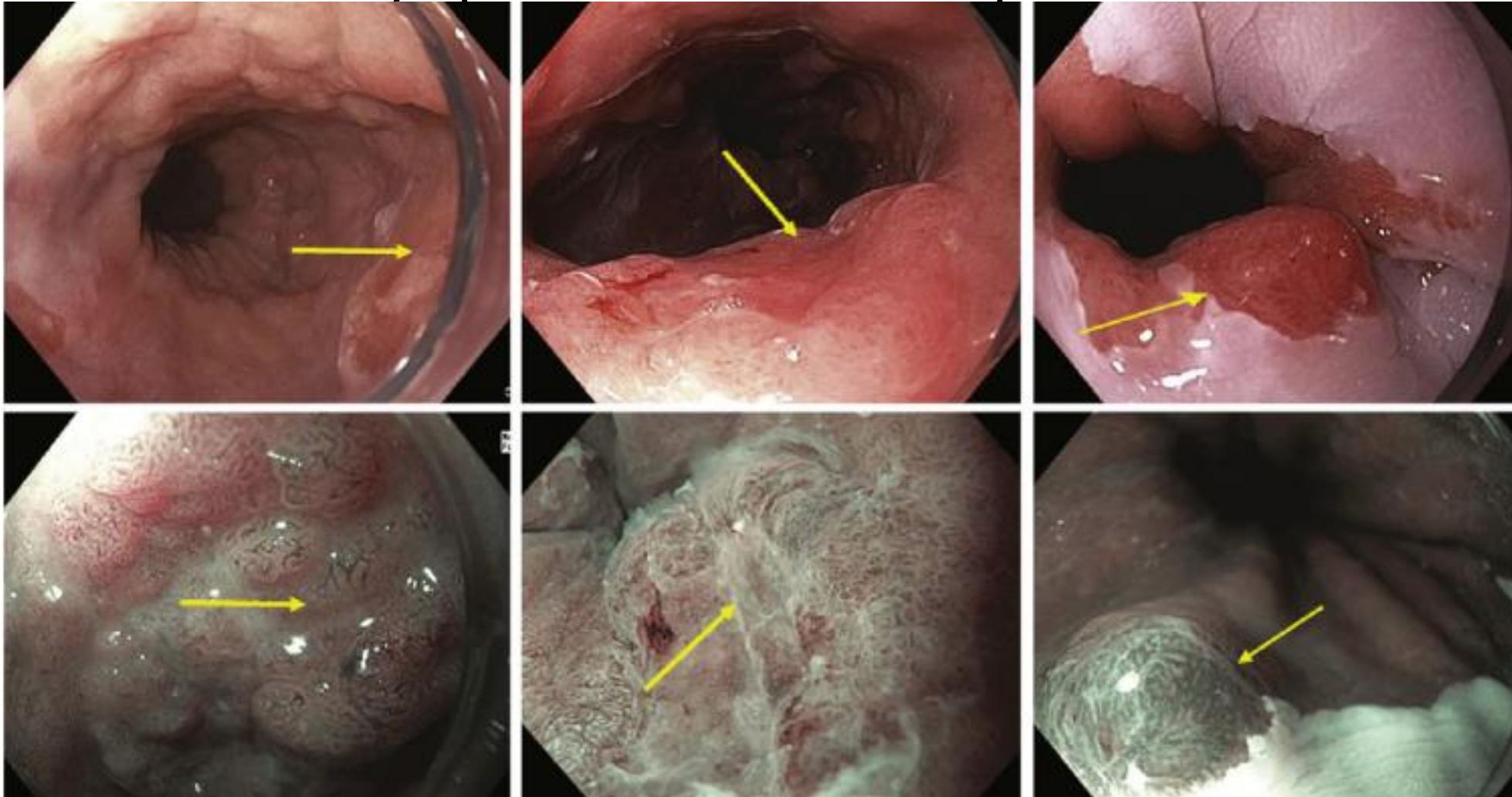
Approach to Performing a High-Quality Endoscopic Exam for BE

Approach	Rationale
1. Consider use of a distal attachment cap	1. Facilitate visualization
2. Utilize CO_2 insufflation and desufflation	2. Fine adjustments to luminal insufflation can help with detection of subtle abnormalities
3. Clean mucosa well using water jet channel and carefully suction the fluid	3. Remove any distracting mucus or debris and minimize mucosal trauma
4. Identify esophageal landmarks, including the location of the diaphragmatic hiatus, gastroesophageal junction, and squamocolumnar junction	4. Critical for future exams
5. Examine the Barrett's segment using high definition white light endoscopy	5. Standard of care
6. Examine the Barrett's segment using chromoendoscopy (including virtual chromoendoscopy)	6. Enhances mucosa pattern and surface vasculature
7. Spend adequate time inspecting (consider 1 minute per cm)	7. Careful examination increases dysplasia detection
8. Use the Prague classification to describe the circumferential and maximal Barrett's segment length	8. Standardized reporting system
9. Use the Paris Classification to describe superficial neoplasia	9. Standardized reporting system
10. Use the Seattle Protocol (in conjunction with advanced imaging modalities) to sample the Barrett's segment	10. Increases dysplasia detection

Muthuswamy VR et al, Clin Gastroenterol Hepatol 2022, Kolb JM et al, TGH 2021
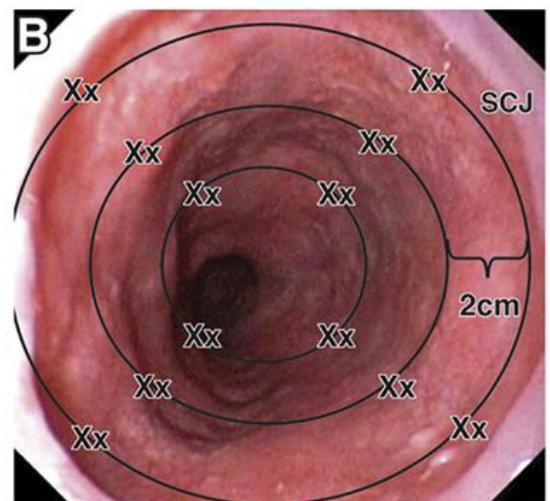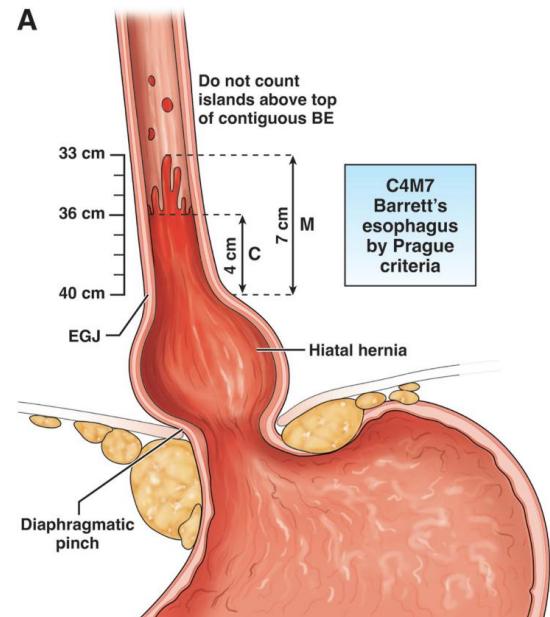
Guidelines for Screening for Barrett's Esophagus

AGA 2011	BSG 2014	ASGE 2019	ESGE 2020	ACG 2022
Suggest	Consider	Risk stratify	Consider	Consider
Multiple risk factors: - Age > 50 years - Male - White race - Chronic GERD - Elevated BMI with central distribution	Selected patients with multiple risk factors (> 3): - Age > 50 years - White race - Male	High risk group (recommended) - FH of EAC or BE Moderate risk group (may benefit) - Smoking Low risk group (screening not recommended) - No risk factors	Longstanding GERD symptoms (> 5 years) + multiple risk factors - Age > 50 years - White race	Chronic GERD (OR 3 if > 5y) + > 3 risk factors: - Male (OR 1.96) - Age > 50 years (OR 1.53) - Caucasian (OR 2.01) - Central obesity (OR 2.03) - Current or past smoking (OR 1.4) - 1st degree relative with BE or EAC (OR 12.3)

Risk of Barrett's esophagus increases by 1.2% for every additional risk factor

Spechler S et al, Gastroenterology 2011, Fitzgerald R et al, Gut 2014, Qumseya B et al, Gastrointestinal Endoscopy 2019, Saftoiu A et al, Endoscopy 2020, Shaheen N et al, Am J Gastroenterology 2022

Screening Fraught with Limitations

- Approximately ~3-6M Americans have BE
  - Up to 18% have GERD and 25% are asymptomatic
- Screening associated with improved outcomes from EAC
  - 20-50% of EAC have no symptoms
  - **< 10% with prior diagnosis of BE and identified through screening**
- Enormous financial burden with > 2 million EGDs performed annually for GERD with non-negligible risks

Non-Endoscopic Barrett's Esophagus Cell Collection Devices

Cytosponge

EsophaCap
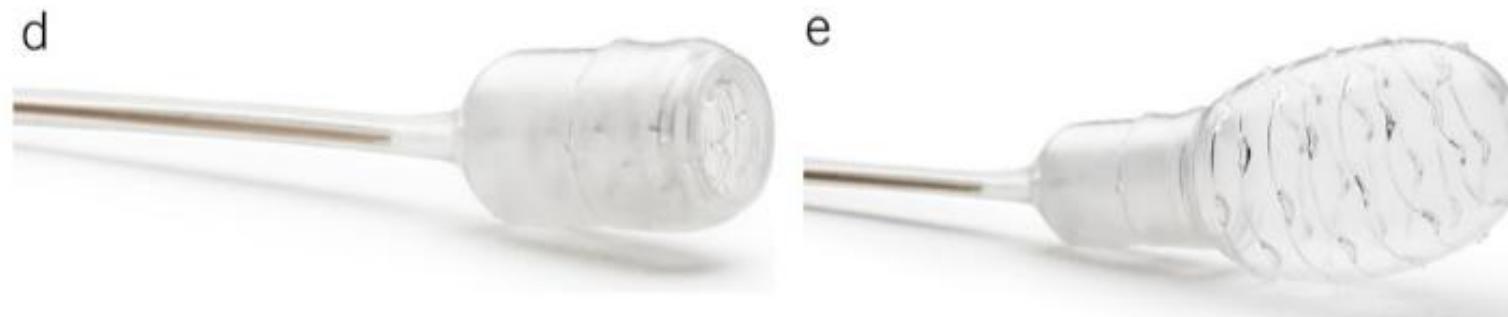
EsoCheck

Table 4. Summary of performance characteristics of minimally invasive nonendoscopic swallowable cell collection devices combined with biomarkers for the nonendoscopic detection of BE

| Device Biomarker used Country of origin	Design Sample size	Sensitivity (%)	Specificity (%)
30-mm capsule sponge (Cytosponge) (226) TFF3 United Kingdom	Case-control Cases: 647 Controls: 463	80[a]	92
30-mm capsule sponge (Medtronic) (227) TFF3 United States	Case-control Cases: 129 Controls: 62	76	77
25-mm capsule sponge (EsophaCap) (228) MDMs United States	Case-control Cases: 112 Controls: 89	92	94
25-mm capsule sponge (EsophaCap) (229) MDMs United States	Case-control Training set: cases 110, controls 89 Test set: cases 60, controls 29	93	93
18-mm swallowable and inflatable balloon (EsoChek) (230) MDMs United States	Case-control Cases: 50 Controls: 36	92	88
20-mm capsule sponge (EsophaCap) (231) MDMs United States	Case-control Training set: cases 18, controls 34 Test set: cases 14, controls 14	94	62

2022 ACG Guidelines on Recommendations for Swallowable Nonendoscopic Devices

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**

Shaheen N et al, Am J Gastroenterology 2022

Post-Endoscopy Esophageal Neoplasia (PEEN) and Post-Endoscopy Adenocarcinoma (PEEC)

- PEEN → BE-HGD or EAC detected prior to next surveillance endoscopy

- PEEC → EAC detected prior to next surveillance endoscopy

- Multitude of causes but most common due to missed lesions

  - Nonadherence to Seattle biopsy protocol
  - Limited mucosal sampling
  - Limited time inspecting BE segment
 - Inability to recognize high-risk lesions

Hall M et al, Gastro 2021, Wani S et al, Gastro 2020
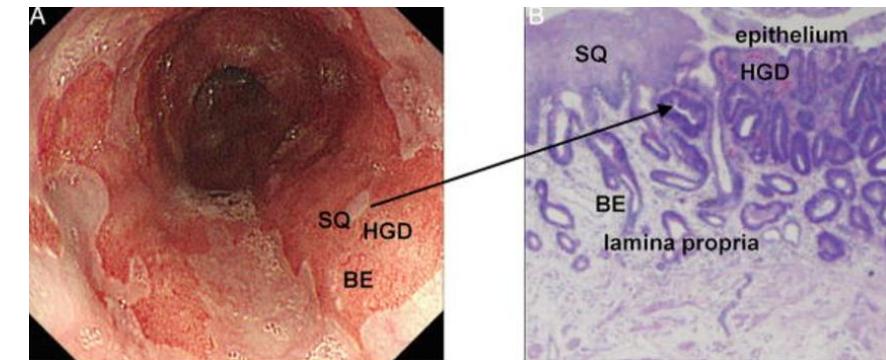
Rising Incidence Rates of PEEC and PEEN

Nordic Barrett's Esophagus Study (NordBEST)

Population-based cohort study: Denmark, Finland, Sweden

Missed lesion

Rapidly developing cancer

Newly Diagnosed Barrett's Esophagus (n=20,588)

PEEC/PEEN (possible explanations)

Outcomes

Patients diagnosed with EAC (overall database) n=293

Post-Endoscopy esophageal adenocarcinoma (PEEC) EAC diagnosed 30 – 365 days from BE diagnosis **n= 69 (23.5%)**

Patients diagnosed with HGD/EAC [Swedish database] n=279

Post-endoscopy esophageal neoplasm (PEEN) High-grade dysplasia/EAC diagnosed 30 – 365 days from BE diagnosis. **n= 48 (17.2%)**

Time Trend Analysis (2006 – 2020) → Rising incidence rates of PEEC/PEEN.

Gastroenterology

Wani S et al, Gastro 2023

Wide-Area Transepithelial Sampling (WATS)

- Brush biopsy with abrasive bristles to acquire deep mucosal tissue

- High-speed neural network identifies abnormal cells, followed by pathologist review

- SWAT-BE study – multicenter RCT underway

- Incremental dysplasia yield of 44.6% in prospective registry study

Shaheen NJ et al, AJG 2024
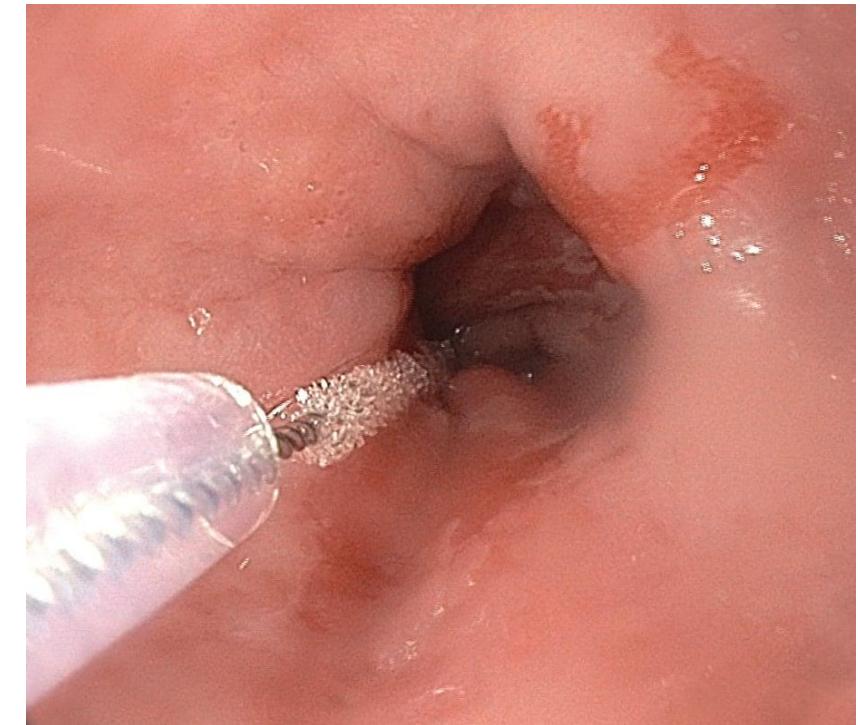
2022 AGA Clinical Practice Update on Recommendations for WATS

Wide-area transepithelial sampling **may be used** as an adjunctive technique to sample the suspected or established Barrett's segment (in addition to the Seattle biopsy protocol)

Muthuswamy VR et al, CGH 2022

TissueCypher is a Promising Risk Stratification Tool

- AI-powered tissue biomarker test that predicts 5-year risk of developing HGD/EAC in patients with NDBE
  - Biomarkers ➔ p53, p16, AMACR, HER-2, CD68, COX2, HIF1 alpha, CD45RO

Critchley-Thorne RJ et al, Cancer Epidemiol Biomarkers Prev 2018
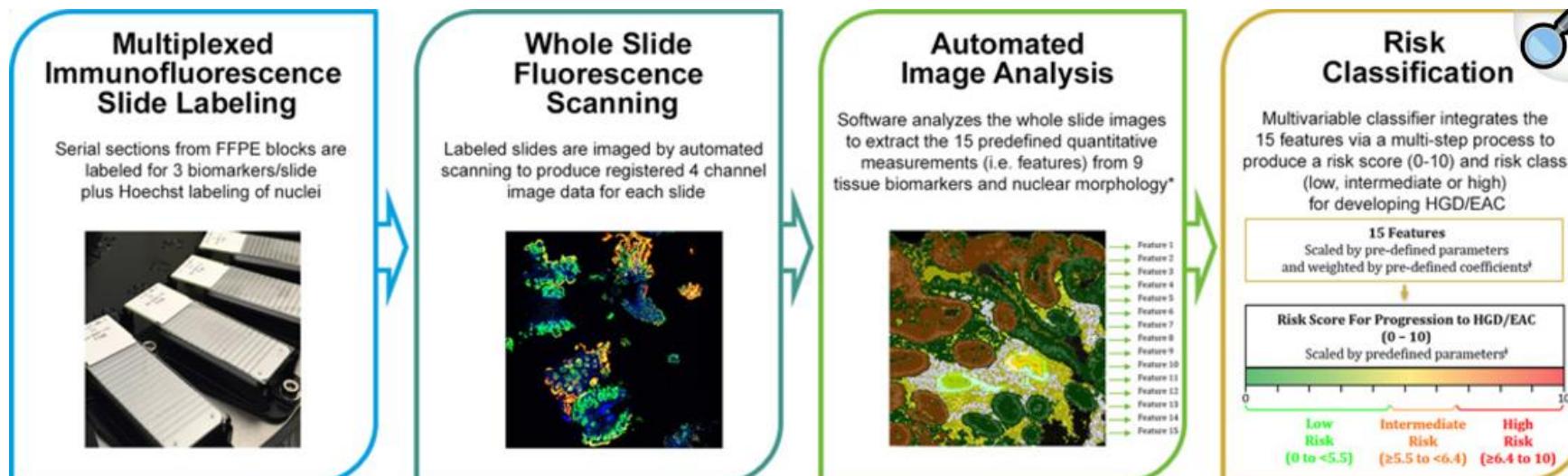
2022 AGA Clinical Practice Update on Recommendations for Tissue Based Systems

Tissue systems pathology-based prediction assay **may be utilized** for risk stratification of patients with nondysplastic BE

Muthuswamy VR et al, CGH 2022

GUIDELINES

AGA Clinical Practice Guideline on Endoscopic Eradication Therapy of Barrett's Esophagus and Related Neoplasia

**Joel H. Rubenstein,**[1,2,3,*] **Tarek Sawas,**[4,*] **Sachin Wani,**[5,*] Swathi Eluri,[6] Shailendra Singh,[7,8] Apoorva K. Chandar,[9] Ryan B. Perumpail,[10] John M. Inadomi,[11] Aaron P. Thrift,[12] Alejandro Piscoya,[13] Shahnaz Sultan,[14,15] Siddharth Singh,[16] David Katzka,[17] and Perica Davitkov[18,19]

Goals of Endoscopic Eradication Therapy for BE-Related Dysplasia and Neoplasia

- EET is safe, effective, and minimally invasive
  - EMR/ESD, thermal ablation, cryotherapy ablation
- Principles
  - Resect all neoplastic lesions and eradicate remaining BE
  - Manage complications
  - Enroll patients in a surveillance program and address recurrence
- Goals
  - Immediate → complete eradication of IM (CE-IM)
  - Intermediate → reduce and manage future neoplastic recurrence
  - Long-term → reduce EAC-associated morbidity and mortality
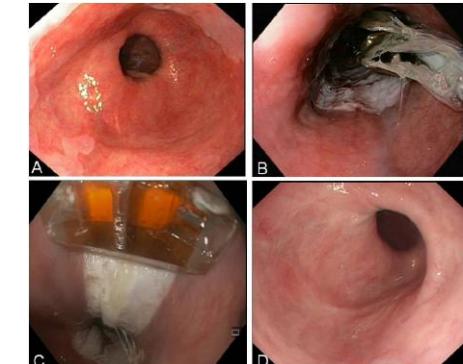
Eligibility for Endoscopic Eradication Therapy
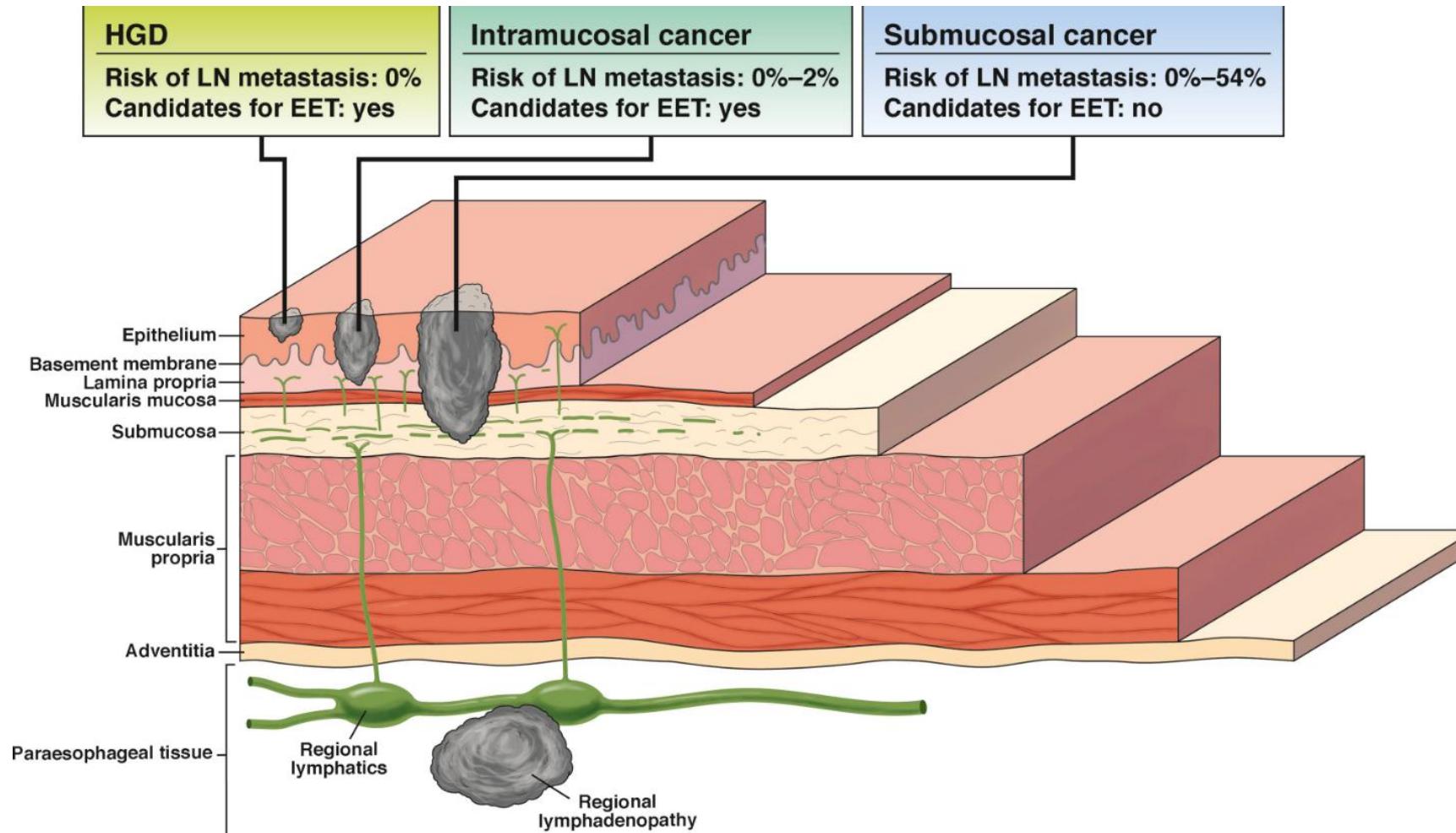
AGA Recommendations for EET for Non-Dysplastic BE

In individuals with NDBE, the AGA **suggests against** the routine use of EET

- Conditional recommendation
- **Very low certainty of evidence** [NNT of ~400-769]

Rubenstein JH et al, Gastroenterology 2024

Challenges in BE with LGD Management

- Variable natural history
  - 1.2%/y to EAC per recent meta-analysis (historically up to 13.6%) vs. .57% for NDBE and 14.16% for HGD
- Interobserver variability among pathologists, even experts
- Phenomenon of regression of LGD
- EET associated with AE rate of 19%
- No difference in mortality between the two arms

AGA Recommendations for EET for BE with LGD

In individuals with BE with LGD, the AGA **suggests for** EET over surveillance. Patients who place a higher value on the well-defined harms and lower value on the benefits (which are uncertain) regarding reduction of esophageal cancer mortality would **reasonably select surveillance** endoscopy

- Conditional recommendation

- **Low certainty of evidence**

*After completion of EET, surveillance EGD at years 1 and 3 after CEIM, then revert to surveillance intervals used in NDBE

Rubenstein JH et al, Gastroenterology 2024

AGA Recommendations for EET for BE with HGD

In individuals with BE with HGD, the AGA **recommends EET** over surveillance

- Strong recommendation

- **Moderate certainty of evidence**

*After completion of EET, surveillance EGD at 3, 6, and 12 months, then annually

Rubenstein JH et al, Gastroenterology 2024

Further Guidance on EET From Guidelines

- Resect visible lesions followed by ablation of remaining BE > resection of the entire BE unless small area
  - Conditional recommendation, **very low certainty of evidence**
- RFA is the preferred ablative modality
- EMR or ESD for visible neoplastic lesions (conditional recommendation, **very low certainty of evidence**)
  - Majority may be managed with EMR
  - ESD > EMR for bulky neoplastic lesions, prior failed EMR lesions or T1b lesions
  - Endoscopic resection > EUS for distinguishing EAC from HGD and for staging depth of invasion in early cancer

AGA Recommendations for Monitoring Quality Metrics

Endoscopists and practices performing EET are encouraged to **monitor key outcomes and quality metrics** including complete eradication of intestinal metaplasia and neoplasia, and adverse events

Rubenstein JH et al, Gastroenterology 2024

Summary

- Barrett's esophagus is the only identifiable precursor for EAC, and use of GERD as a prerequisite for screening is problematic

- Improvements in cell and tissue collection techniques may improve our ability to detect BE and BE-associated neoplasia

- Risk prediction models in the future may allow for early intervention and guide tailored surveillance strategies in high risk BE patients

- Endoscopic eradication therapies are highly effective and reasonably durable for BE-associated dysplasia and neoplasia

Thank You

Shawn.Shah@UTSouthwestern.edu
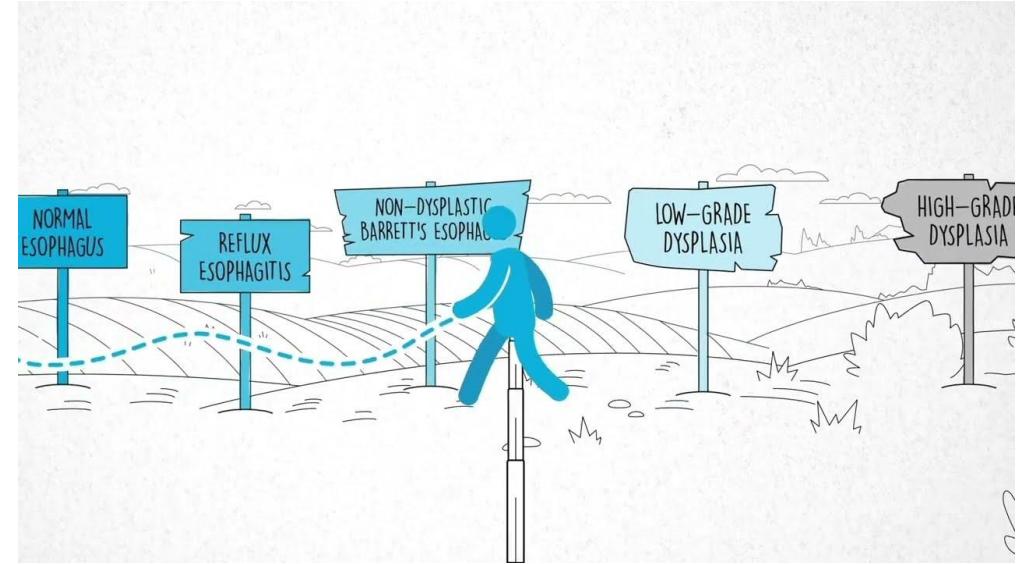
Rising Incidence of Esophageal Adenocarcinoma

9-fold increase in EAC

Esophageal Adenocarcinoma, Melanoma of the Skin, Liver and Intrahepatic Bile Duct, Kidney and Renal Pelvis, Prostate, Breast, Bladder, Pancreas, Lung and Bronchus, Colon and Rectum, Stomach, Esophageal Squamous Cell Carcinoma, Cervix

A Incidence of EC by type

EC, ACE, SCE, Others
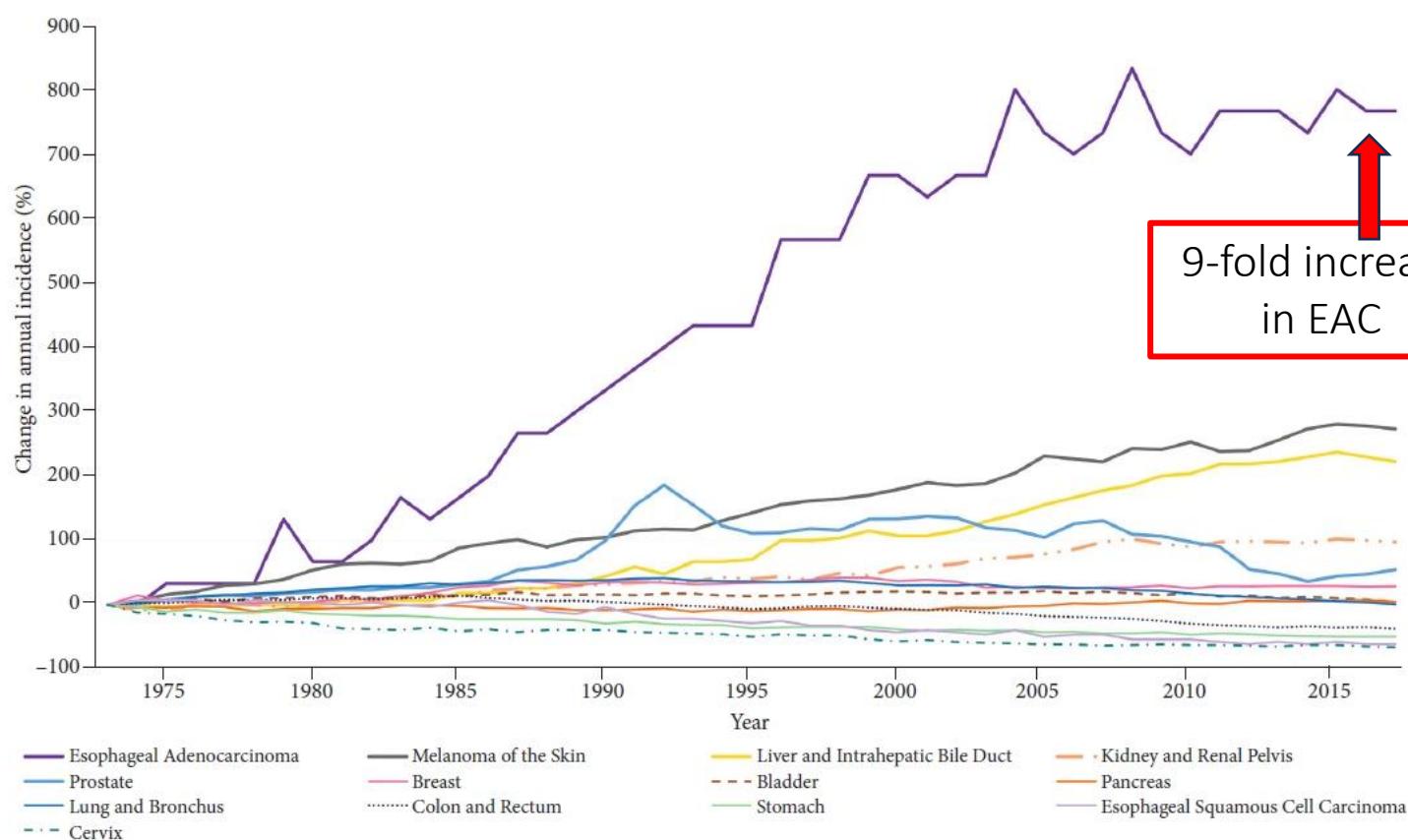
*Esophageal cancer with a 5-year survival < 20%
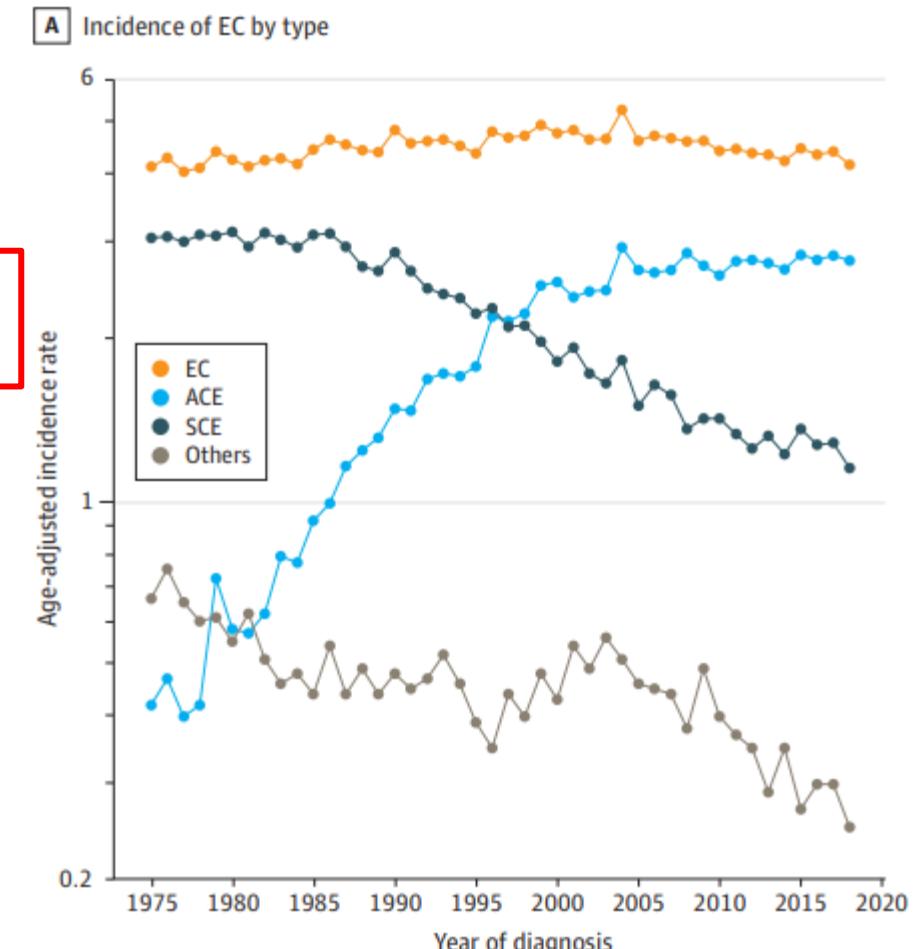
# Cytosponge-Trefoil Factor 3 vs. Usual Care (BEST3 Trial)

- Multicenter RCT across 109 GP clinics in England

- 6,834 patients in Cytosponge arm vs. 6,388 in usual care with BE diagnosis as primary outcome

- BE diagnosis - 2% intervention group vs. 0.2% usual care

- Absolute difference 18.3/1,000 person years (95% CI, 14.8-21.8)

Fitzgerald RC et al, Lancet 2020
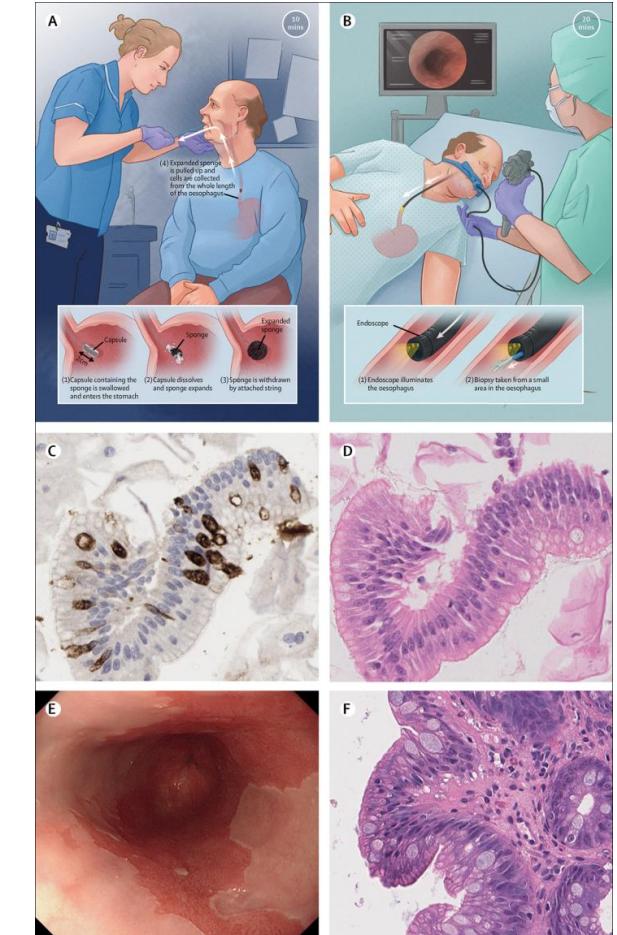
Pooled Analysis of 5 Studies Demonstrates Improved Risk Stratification with TSP-9
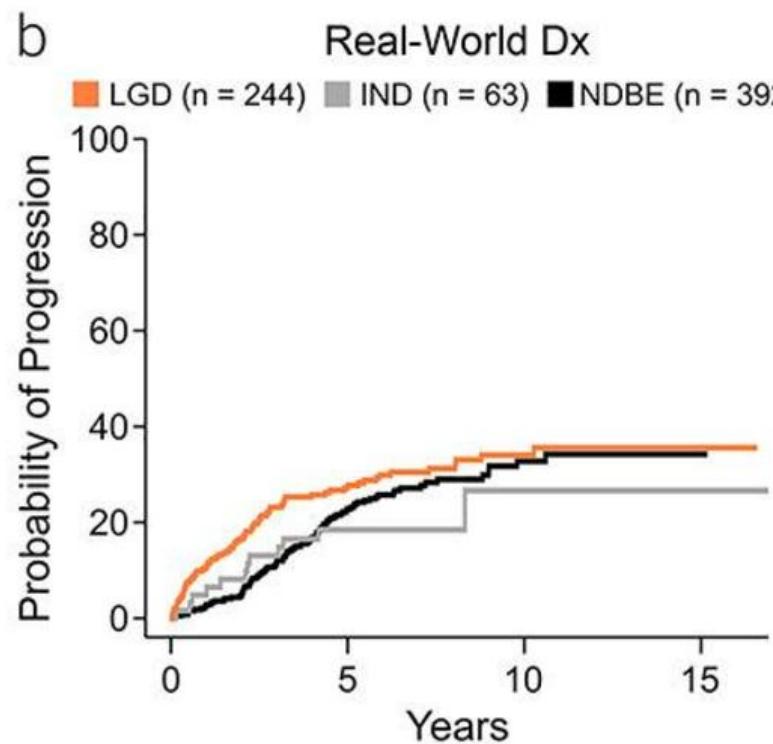
Davison JM et al, Clin & Transl Gastroenetrol 2023
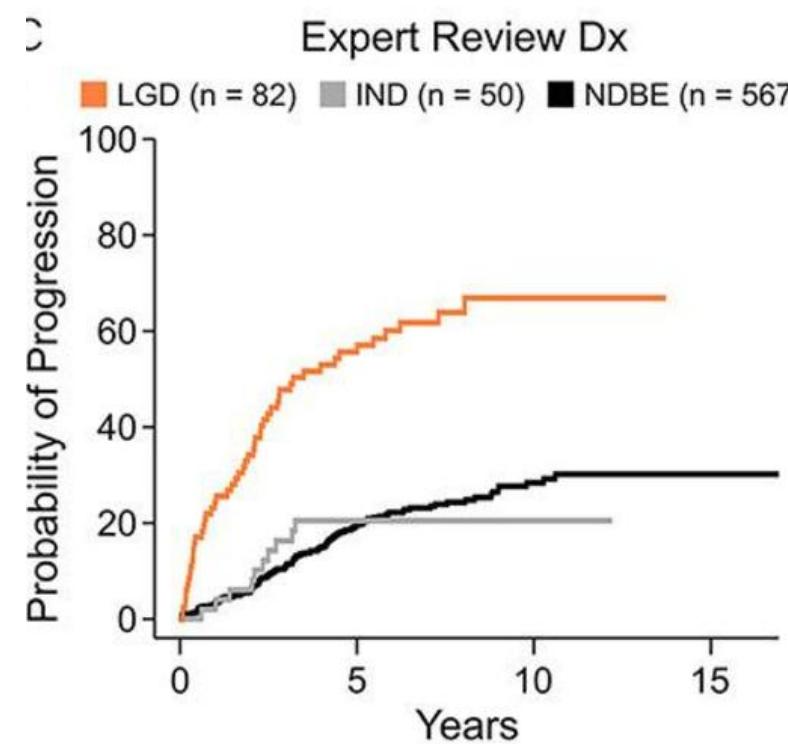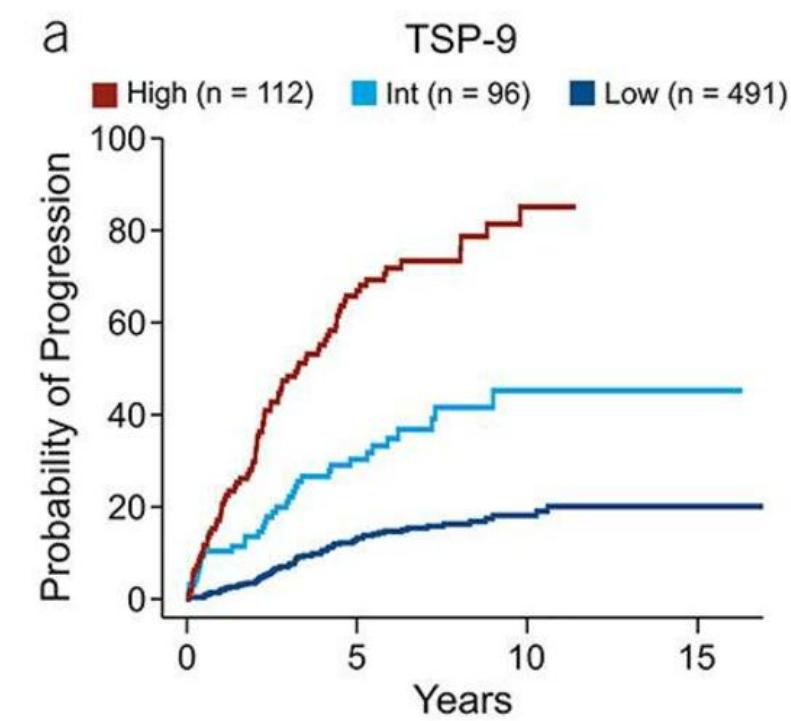
2025 Barrett's Esophagus Pathway
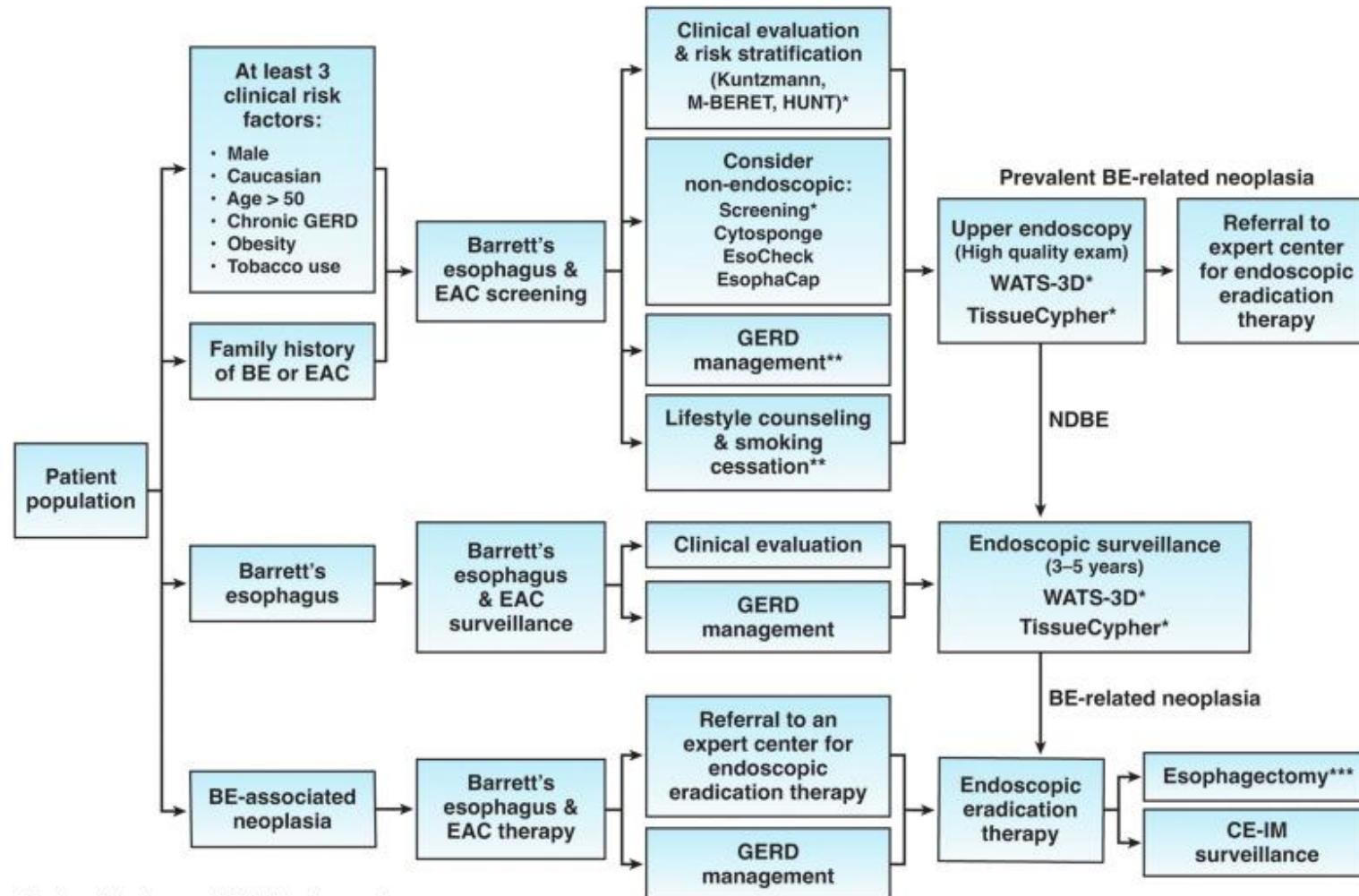
*May be utilized as per BPA in this document
**When clinically appropriate
***For T1b or higher stage cancers by EMR or neoplastic disease refractory to EET

Muthuswamy VR et al, CGH 2022