Minimally Invasive and Novel Therapeutics (M.I.N.T.) in Foregut Disease
September 29th -October 1st 2022

Keynote Address: Current Status of Diagnostic Testing for Barrett's Esophagus and Dysplasia

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David Geffen School of Medicine at UCLA

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The Barrett's Conundrum

- In medicine, we have many diseases we can effectively diagnose but lament the fact that we have no good treatments for them
- In Barrett's esophagus, we have developed excellent and durable treatments that can eradicate the disease, but have difficulty in finding patients with the condition.
- Furthermore, in those we have identified with the condition, we face many challenges in detecting dysplasia in those under surveillance!
- Finally, many patients are incorrectly diagnosed with the disease, leading to variability in risk estimates

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Objectives

- Identify the challenges regarding screening for Barrett's Esophagus (BE)
- Recognize common errors in the diagnosis of BE and recognition of focal lesions arising within BE

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Outline

- Screening
- Correctly identifying Barrett's esophagus
- Detecting Dysplasia
  - Performing a Good Endoscopic Exam
  - NBI-BING
  - CLE/VLE
  - Wide Area Trans-epithelial Sampling
  - Molecular Prediction
  - Improved Training in Lesion Identification/AI
- Summary and Best Practices

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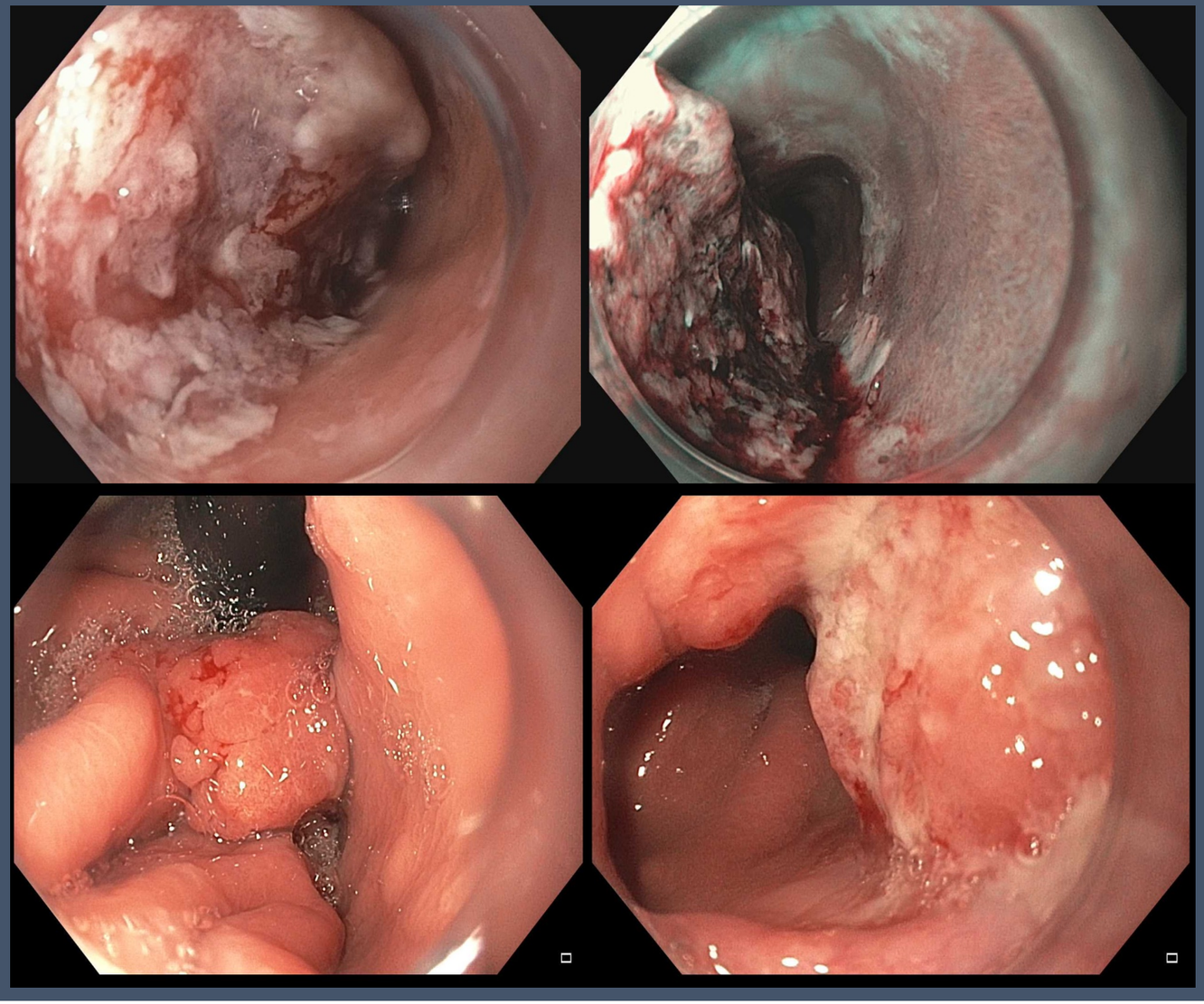
What We are Trying to Prevent: ESOPHAGEAL ADENOCARCINOMA!



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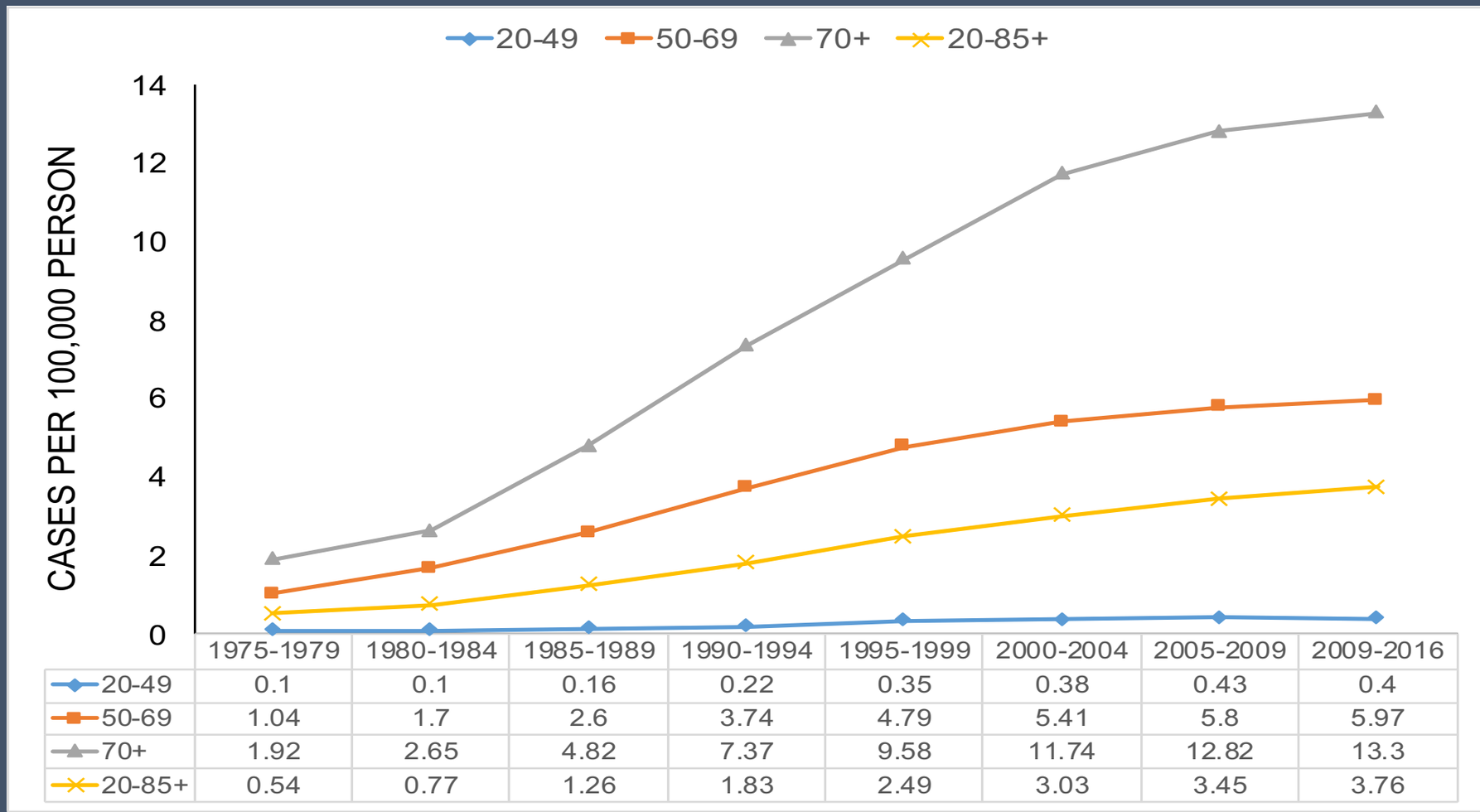
RISING INCIDENCE OF ESOPHAGEAL ADENOCARCINOMA



	1975-1979	1980-1984	1985-1989	1990-1994	1995-1999	2000-2004	2005-2009	2009-2016
20-49	0.1	0.1	0.16	0.22	0.35	0.38	0.43	0.4
50-69	1.04	1.7	2.6	3.74	4.79	5.41	5.8	5.97
70+	1.92	2.65	4.82	7.37	9.58	11.74	12.82	13.3
20-85+	0.54	0.77	1.26	1.83	2.49	3.03	3.45	3.76

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Kolb J, Han S, Wani S. Gastroenterology 2020

Key Questions Regarding Screening

- Should We Screen?
- Who Should We Screen?
- How Should We Screen?

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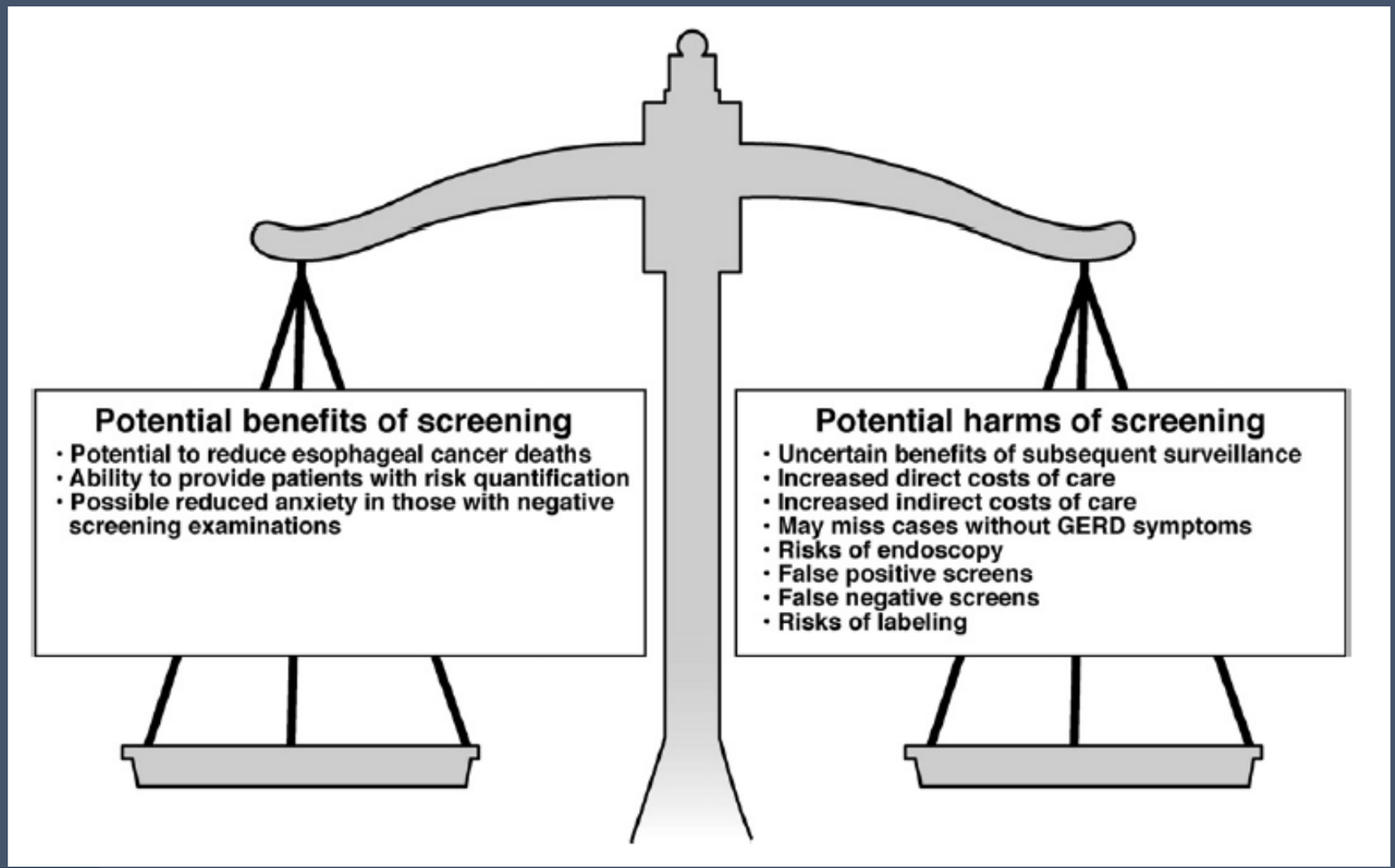
Should We Screen?



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Crockett SD et al, CGH, 2010, 8:7, 565-71.

SCREENING FOR BARRETT'S ESOPHAGUS - LIMITATIONS

- Enormous burden to medical resources (costs with sedated endoscopy) – high prevalence of GERD
- Barrett's esophagus in asymptomatic individuals (6-25%)
- 20-50% of EAC patients have no symptoms
- <10% of EAC – prior diagnosis of BE (suggesting that current clinical referral practices fail to identify majority of high-risk patients)

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Rex DK et al, Gastro 2003; Gerson LB et al, Gastro 2002
Farrow DC et al, Cancer Causes Control 2000; Lagergren J et al, NEJM 1999
Inadomi J et al, Ann Intern Med 2003

Key Questions Regarding Screening

- Should We Screen?
- Who Should We Screen?
- How Should We Screen?

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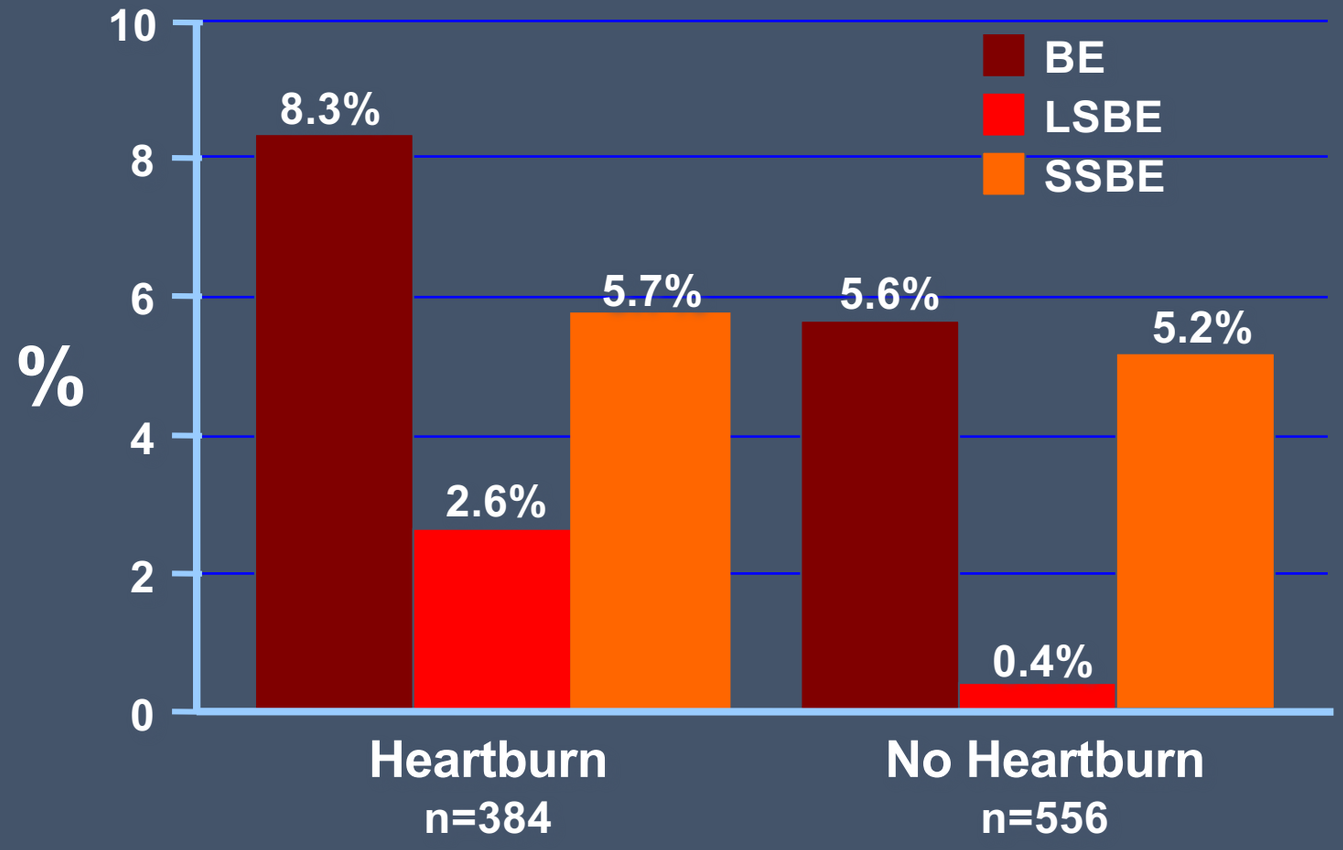
Who should be screened?

- Barrett's is present in at least 1-2% of the US population
- BE occurs in 6-18% of GERD patients
- But many patients with GERD have atypical or no GERD symptoms
- Should all GERD patients be screened or only some?
  - If so, which ones?
  - Should GERD even be a pre-requisite?

Prevalence of Barrett's in Subjects Undergoing Colonoscopy



Rex, et al. Gastroenterology 2003; 125:1670

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GERD and Barrett's

Table 1. Prospective Studies Comparing Prevalence of BE In GERD and Non GERD Patients Demonstrating Substantial Prevalence of BE In Subjects Who Do Not Have Typical GERD Symptoms

Study	Year	Prevalence of BE in GERD patients (%)	Prevalence of BE in non GERD patients (%)	Prevalence of BE in the overall study cohort (%)
Gerson et al[33,a]	2002	n/a	25	25
Rex et al[31]	2003	8	6	7
Ronkainen et al[3]	2005	2	1	2
Ward et al[34]	2006	20	15	17
Zagari et al[35]	2008	2	1	2
Gerson et al[32,b]	2009	n/a	6	6

[a]Asymptomatic veterans only.
[b]Asymptomatic women only.

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Crockett SD et al, CGH, 2010, 8:7, 565-71.

Which GERD Patients to Screen?

- Men > 50 years
- Caucasian race
- GERD symptoms for > 5 years
- Nocturnal Reflux
- Hiatal Hernia
- Elevated BMI
- Tobacco use
- Intra-abdominal distribution of body fat

Screen patients with ***multiple*** risk factors: Weak rec., low-moderate quality evidence

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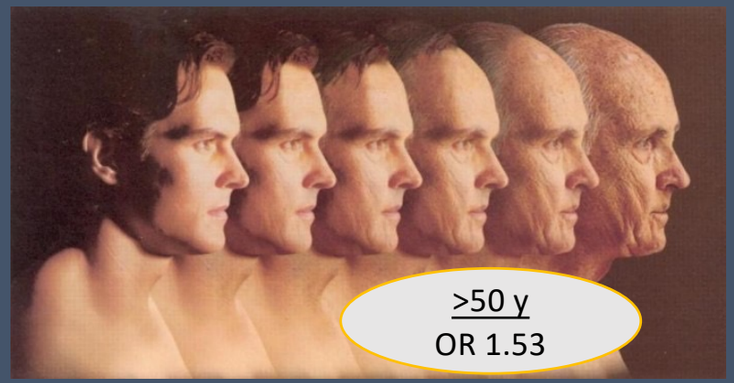
AGA Medical Positional Statement on Management of BE, Gastroenterology 2011; 140:1084-1091

ASGE Guideline on BE and Other Premalignant Conditions of the Esophagus: GIE 2012; 76:6, 1087-94

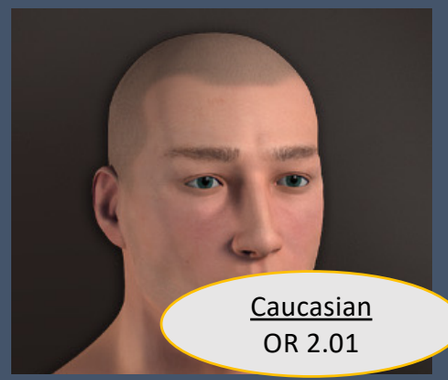
Upper Endoscopy for GERD: Best Practice Advice from CGC of the ACP: Ann Int Med 2012; 157: 808-816.

Risk factors for BE (≈EAC)

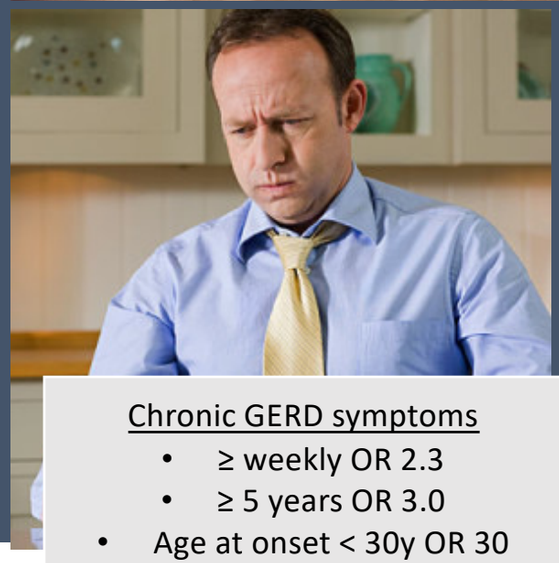


>50 y
OR 1.53

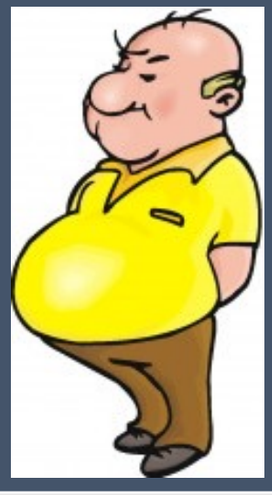
Male gender
OR 1.96



Caucasian
OR 2.01

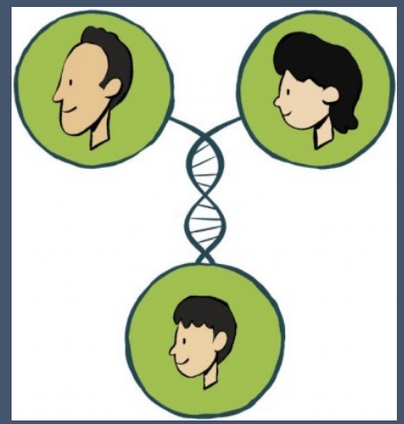


Chronic GERD symptoms
- ≥ weekly OR 2.3
- ≥ 5 years OR 3.0
- Age at onset < 30y OR 30



Central Obesity
OR 2.03

Smoking
OR 1.4



Family history
OR 12.3

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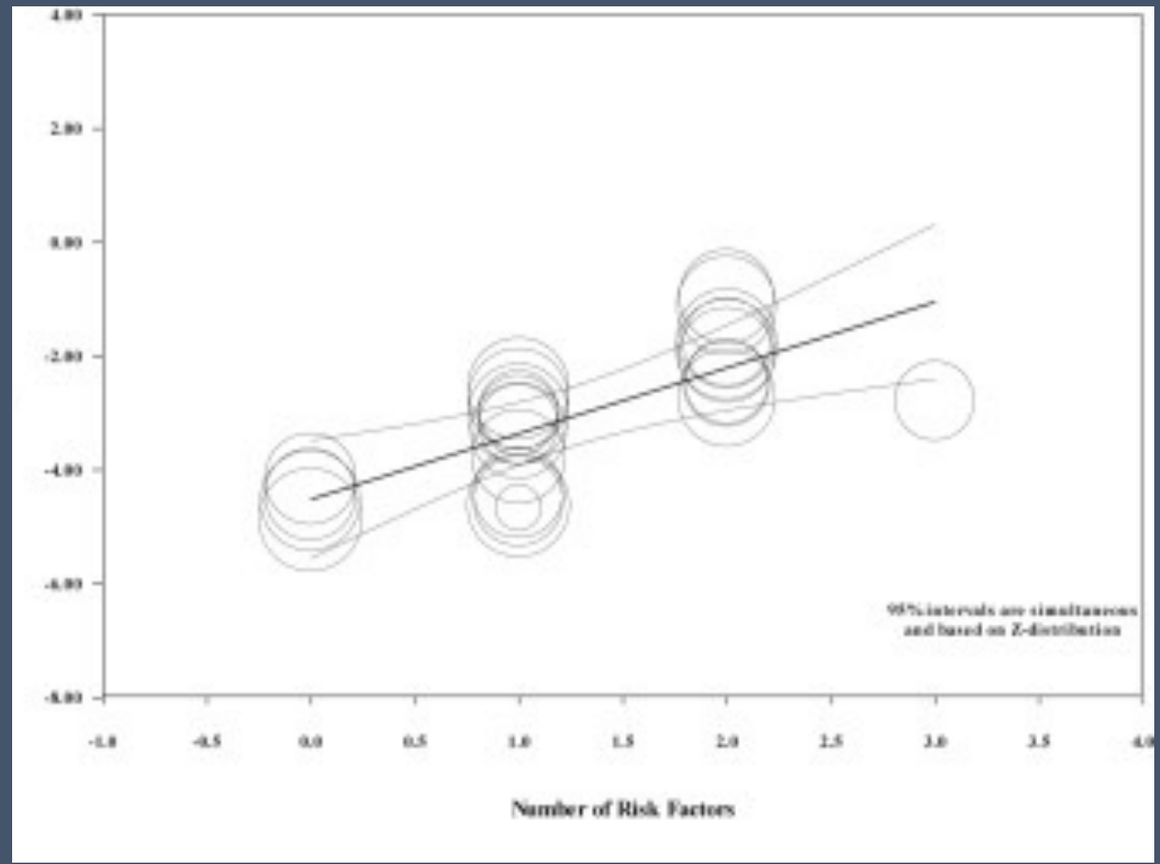
Number of Risk Factors : BE prevalence



Risk of BE increased by 1.2% for every additional risk factor

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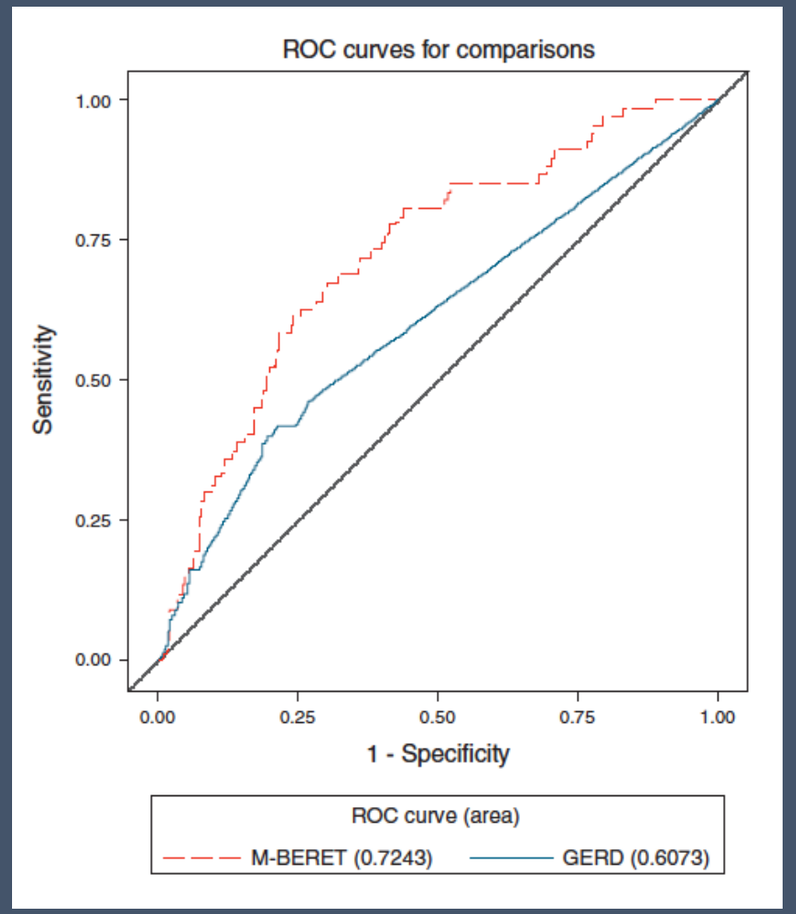
Qumseya, Iyer, Wani GI Endoscopy 2019

Predicting BE: M-BERET

Table 3. Final model for the Michigan Barrett's Esophagus pREdiction Tool (M-BERET)

	OR (95% CI) mutually adjusted for each variable
Intercept	
GERD (weekly vs. not weekly)	2.33 (1.34, 4.05)
Age (per 10 year increments)	1.53 (1.05, 2.25)
Waist-to-hip ratio (WHR) (per 0.10 increments)	1.44 (0.898, 2.32)
Pack-years cigarette use (per increments of 10 pack-years)	1.09 (1.04, 1.14)



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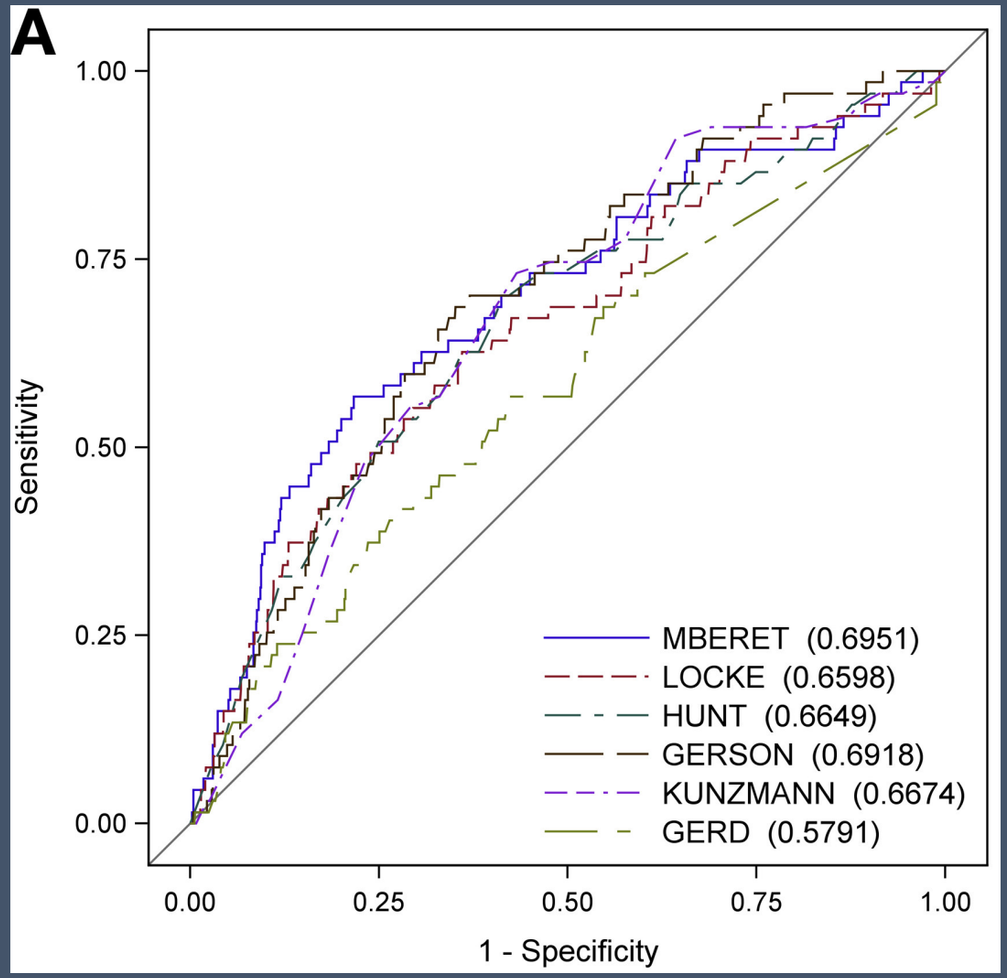
Rubenstein JH et al, AJG, Vol 108, 2013

Prediction Models for Detection of Barrett's Esophagus



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Rubenstein J et al, Gastroenterology 2020

Predicting BE: Summary of Models

- The HUNT (Nord-Trondelag Health Study), MBERET (Michigan BE pREdiction Tool), and Kunzmann tools were found to be more sensitive for predicting BE than GERD symptoms alone.
- Optimal number of risk factors needed yet to be determined
- Models utilizing readily available information from EMR to automatically alert PCPs and Gis are desirable
- Need validation among a diverse population

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Muthusamy VR et al, AGA Clinical Practice Update 2022, CGH, online

Key Questions Regarding Screening

- Should We Screen?
- Who Should We Screen?
- How Should We Screen?

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How Should We Screen?

- Standard Endoscopy
- Unsedated Transnasal Endoscopy
- Tethered Cell Collection Devices?
- Something else? (Blood/Saliva/exhaled breath (VOC))

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Potential Advantages of Minimally Invasive Screening Tools

DETECTION
=
SENSITIVITY *X*
PARTICIPATION *X*
ACCESS

<u>Accurate</u>

Greater PARTICIPATION ?

Non- physician administration : ↑ ACCESS

↑ eligible population screened ?

Lower Cost : Cost effective

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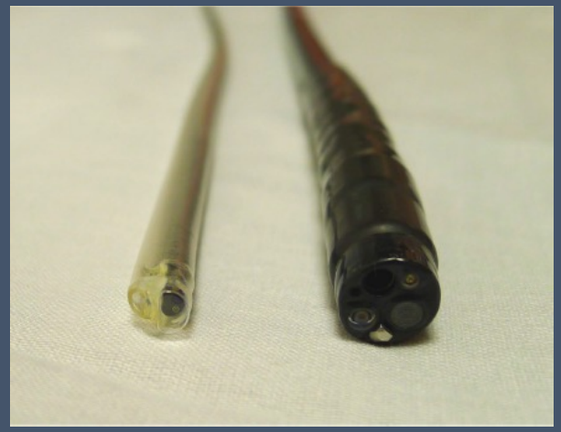
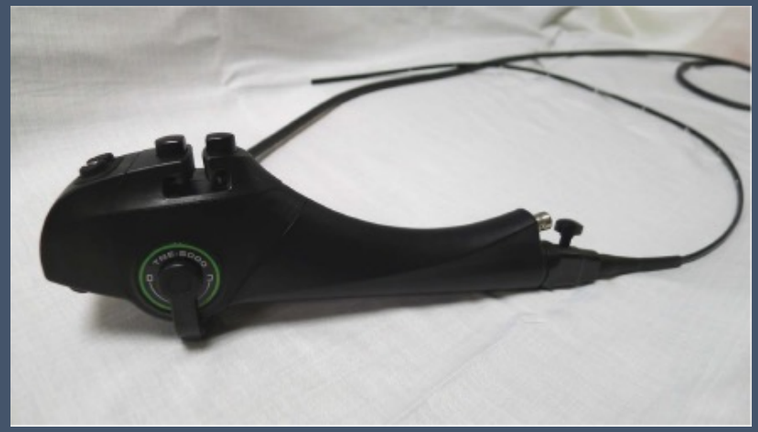
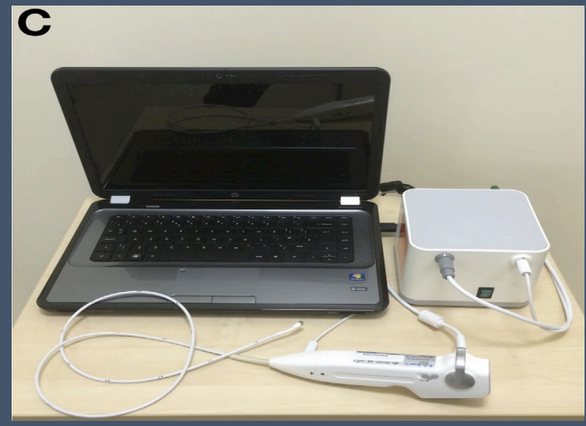
Transnasal Endoscopy







- Accurate **(Sens and Spec > 90%)**
- Well tolerated, Safe, Comparable patient preference
- Less expensive, cost effective
- Can be done by non-physicians
- **Not widely utilized**

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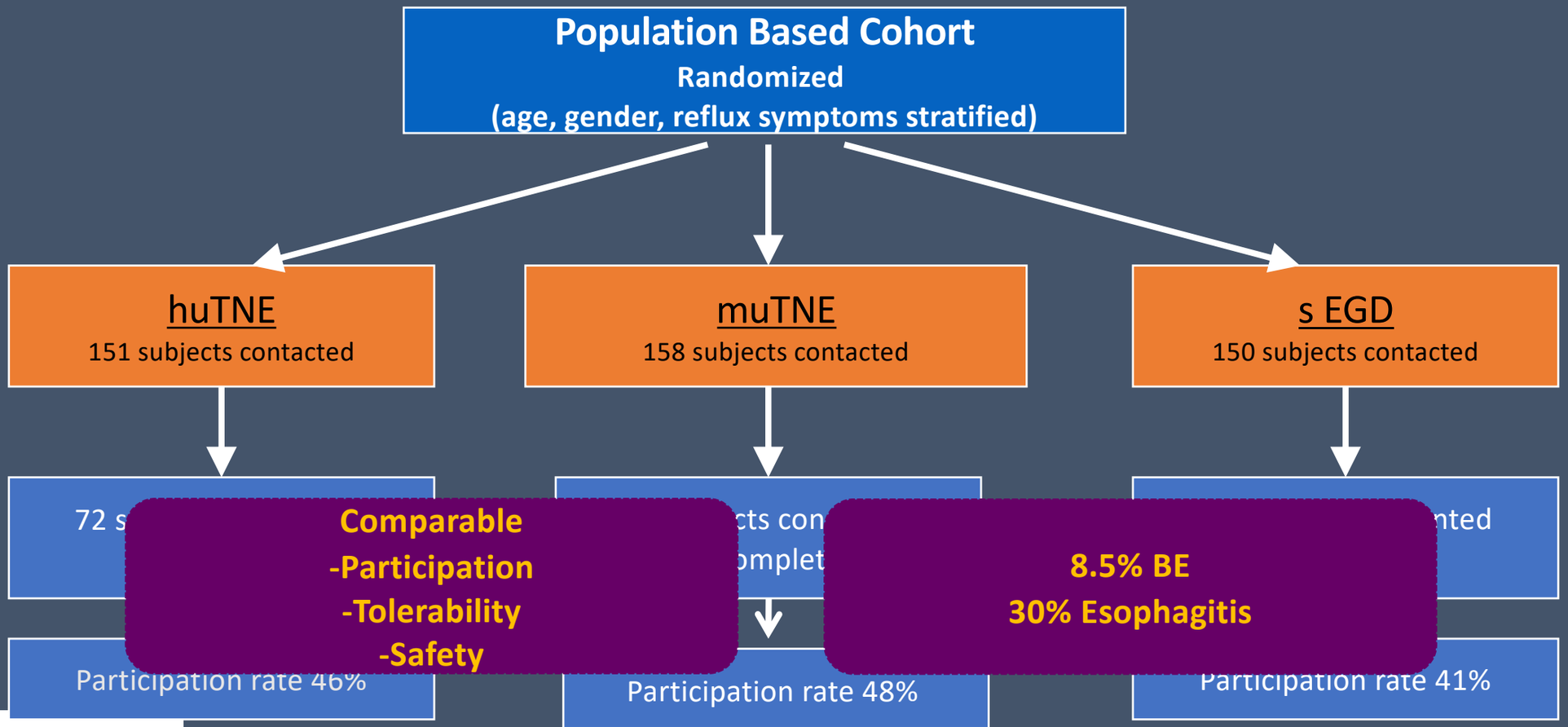
Sami AJG 2015, Mortiarty GIE 2017, Blevins JCG 2017, Chak GIE [illegible], Chak CGH 2015, Peery AJG 2014, Sami CGH 2018

A Randomized Comparative Effectiveness Trial of Novel Endoscopic Techniques and Approaches for Barrett's Esophagus Screening in the Community

Sarmed S. Sami, MBChB, MRCP[1], Kelly T. Dunagan, RN[2], Michele L. Johnson, BS[2], Cathy D. Schleck, BS[3], Nilay D. Shah, PhD[4], Alan R. Zinsmeister, PhD[3], Louis-Michel Wongkeesong, MD[2], Kenneth K. Wang, MD[2], David A. Katzka, MD[2], Krish Ragunath, MD, MPhil, FRCP[1] and Prasad G. Iyer, MD, MS[2]



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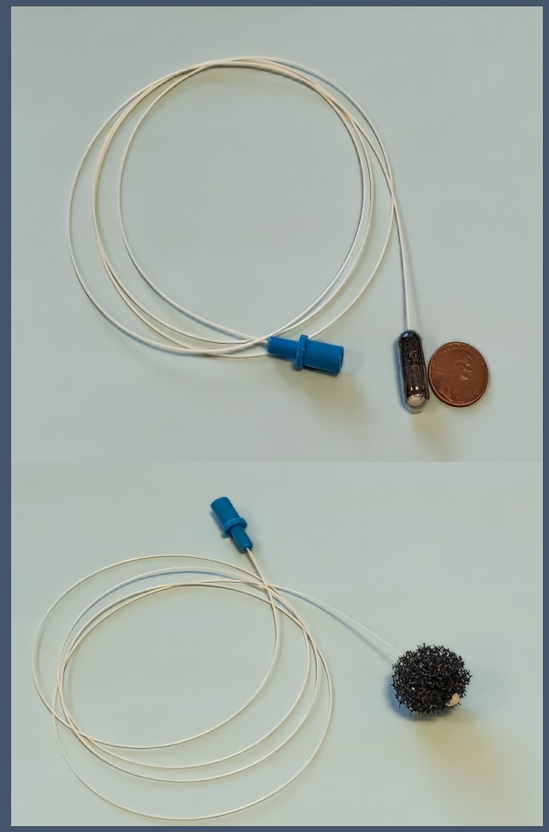
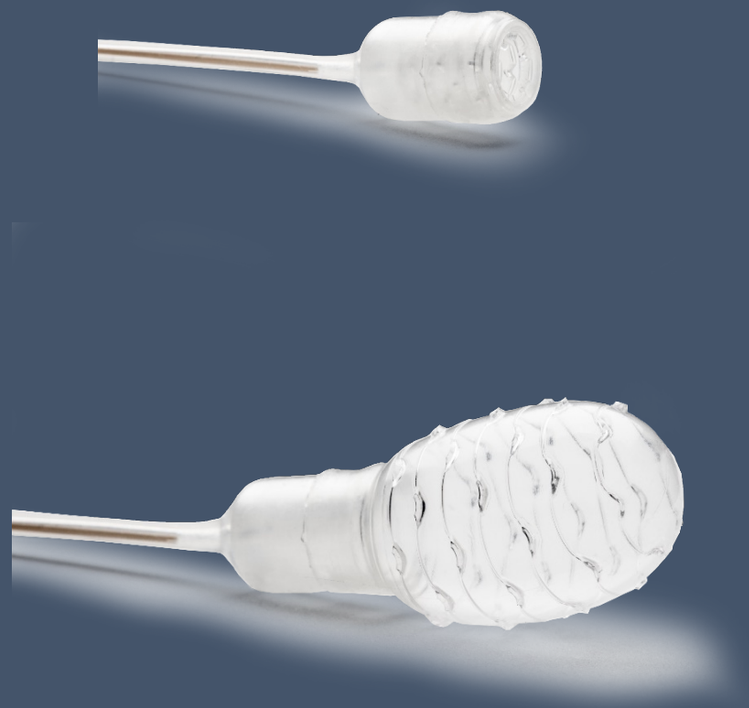
Am J Gastroenterology 2015

POPULATION-BASED SCREENING FOR BARRETT'S ESOPHAGUS

Cytosponge



EsophaCap



EsoCheck

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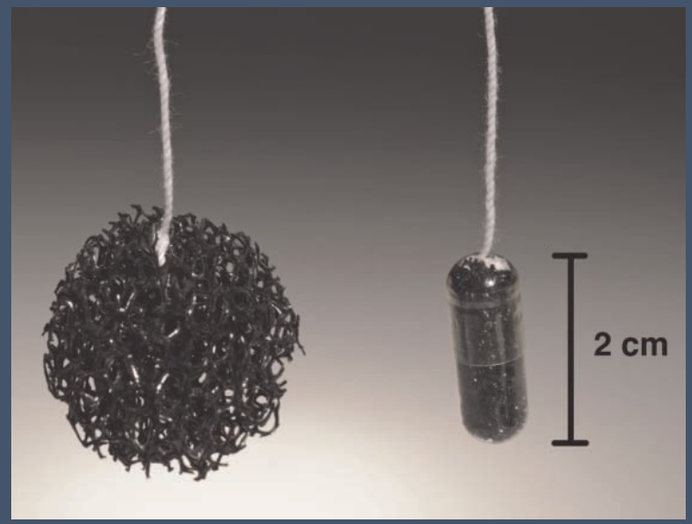
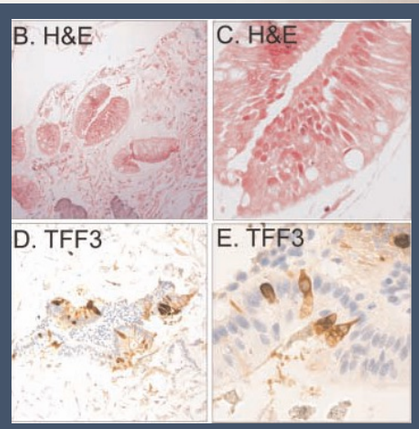
Shaheen NJ, et al. Am J Gastroenterol 2022

Cytosponge for BE Screening





- Office-based, < 10 min
- Can be done by PCPs
- Tests for trefoil factor 3
- Study of 504 pts
  - 99% swallowed sponge
  - 3% diagnosed with BE
  - 73% Se and 94% Sp for >=1 cm of BE
  - 90% Se and 93.5% Sp for >=2 cm of BE

Kadri et al, BMJ 2010; 341

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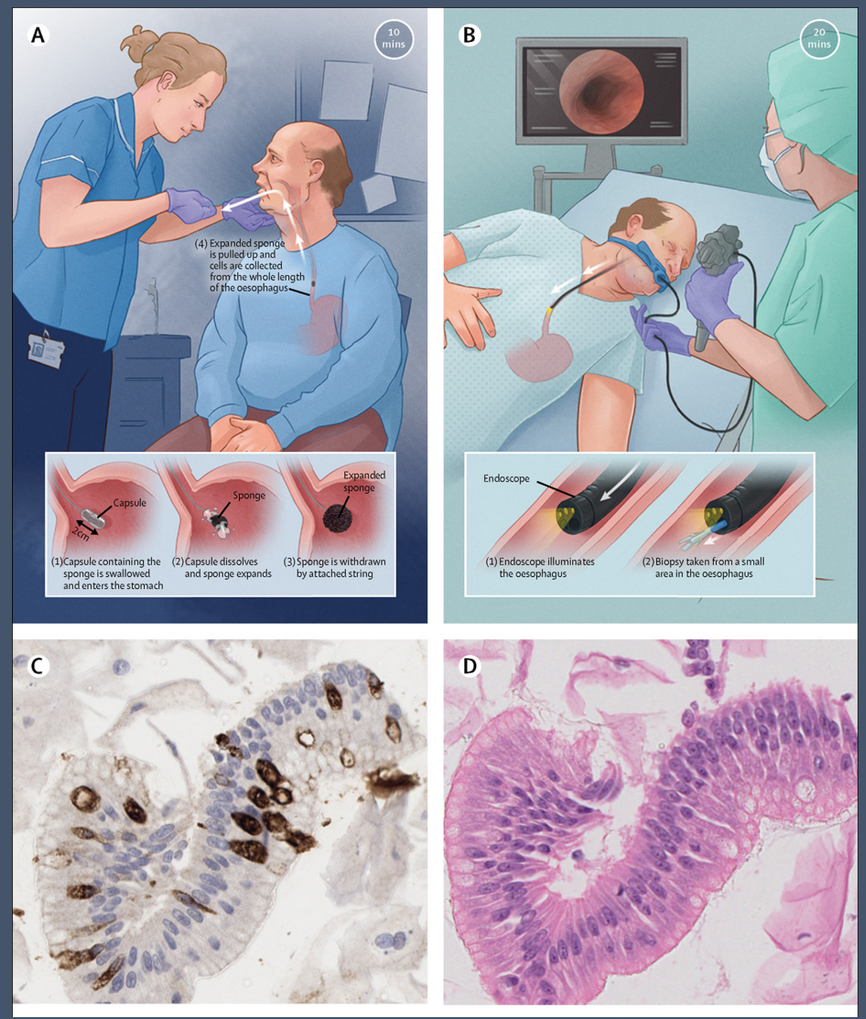
Cytosponge-trefoil factor 3 vs. Usual Care BEST3 Trial

- Pragmatic RCT across 109 GP clinics across England
- 13,222 patients (Cytosponge 6834, usual care 6388)
- BE diagnosis (primary outcome)
  - 2% (intervention group)
  - 0.2% (usual care)
- Absolute difference:18.3/1000 pyrs (95% CI 14.8-21.8)
- Rate ratio 10.6 (95% CI 6-18.8)



Fitzgerald R et al, The Lancet 2020

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Cell Collection Device Performance Summary

Device Biomarker used Country of Origin	Design Sample size	Sensitivity	Specificity
30 mm capsule sponge (Cytosponge™) TFF3 UK	Case Control Cases: 647 Controls: 463	80%*	92%
30 mm capsule sponge (Medtronic) TFF3 USA	Case Control Cases: 129 Controls: 62	76%	77%
25 mm capsule sponge (EsophaCap™) MDMs USA	Case Control Cases: 112 Controls: 89	92%	94%
25 mm capsule sponge (EsophaCap™) MDMs USA	Case Control Training set: Cases: 110, Controls: 89 Test set: Cases: 60, Controls: 29	93%	93%
18 mm swallowable and inflatable balloon (EsoChek™) MDMs USA	Case Control Cases: 50 Controls: 36	92%	88%
20 mm capsule sponge (EsophaCap™) MDMs USA	Case Control Training set: Cases 18, Controls 34 Test set: Cases 14, Controls 14	94%	62%

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BE Defined as > 2 cm in length

Shaheen NJ, et al. Am J Gastroenterol 2022

Recommendations Regarding Cell-Collection Devices for BE

- ACG Guideline 2022
  - We suggest that a swallowable, non-endoscopic 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
- AGA Clinical Practice Update 2022
  - Best Practice Advice Statement 2: Nonendoscopic cell-collection devices can be considered as an option to screen for BE.

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Shaheen NJ, et al. Am J Gastroenterol 2022

GUIDELINES FOR SCREENING

AGA 2011	BSG 2014	ACG 2022	ASGE 2019	ESGE 2020
Suggest	***Consider***	***Consider***	***Risk Stratify***	***Consider***
Multiple risk factors: •Age > 50 yrs. •Male •White race •Chronic GERD •Elevated BMI with central distribution	***Selected*** patients with multiple risk factors (≥3): •Age > 50 yrs. •White race •Male •Obesity Lower threshold if first degree relative with BE or EAC	Chronic GERD + 3 or more risks: •Males •Age > 50 yrs •Caucasian •Central obesity •Current or past smoking •First degree relative with BE or EAC	***High risk group (recommend)*** + FH EAC/BE ***Moderate risk group (May benefit):*** GERD + > 1 risk •Age > 50 yrs. •Male •Obesity/central adiposity •Smoking ***Low risk group (screening not recommended)*** No risk factors	•Long standing GER symptoms (≥ 5 yrs) + multiple risk factors •Age ≥ 50 yrs •White race •Male •Obesity •First degree relative BE/EAC

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Fitzgerald R et al, Gut 2014, Shaheen N et al, Am J Gastroenterol 2022, Spechler S et al, Gastroenterology 2011, Qumseya B et al Gastrointest Endosc 2019

AGA Clinical Practice Update

- Best Practice Advice 1: Screening with standard upper endoscopy may be considered in individuals with at least 3 established risk factors for BE and EAC, including individuals who are male, non-Hispanic white, age >50 years, have a history of smoking, chronic gastroesophageal reflux disease (GERD), obesity, or a family history of BE or EAC.

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Muthusamy VR et al, AGA Clinical Practice Update 2022, CGH, online

Outline

- Screening
- Correctly identifying Barrett's esophagus
- Detecting Dysplasia
  - Performing a Good Exam using HD-WLE
  - NBI-BING
  - CLE/VLE
  - Wide Area Trans-epithelial Sampling
  - Molecular Prediction
  - New Approaches: Video training and AI
- Summary and Best Practices

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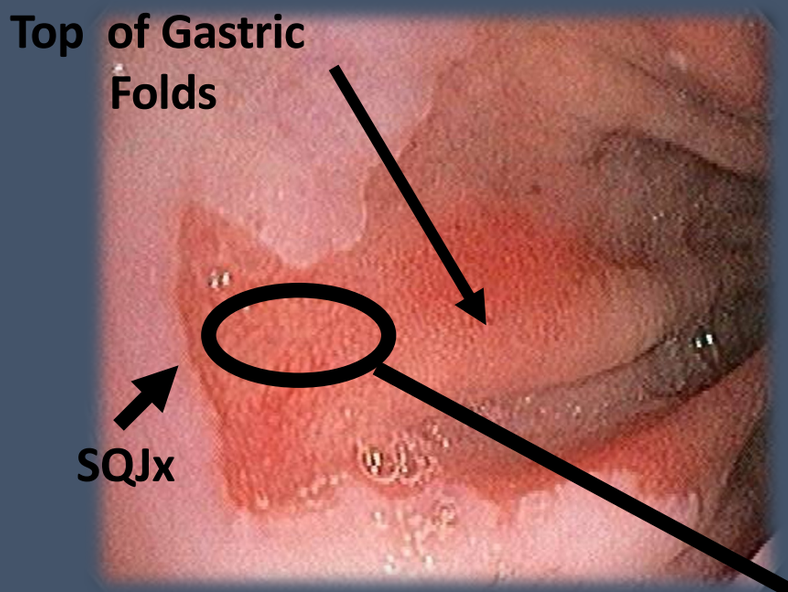
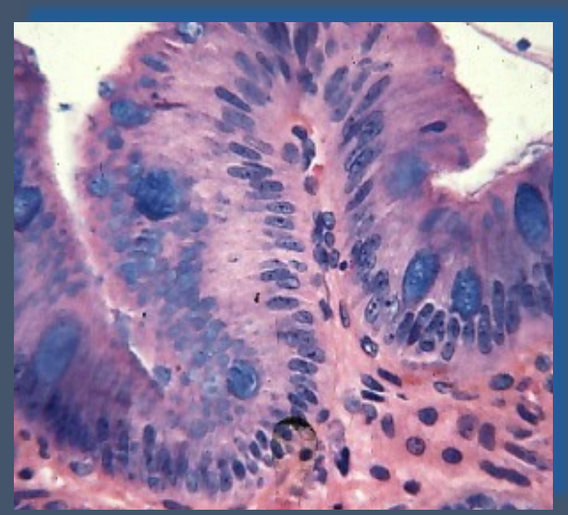
Current Definition of Barrett's Esophagus



Barrett's esophagus (BE) implies replacement of a portion **(typically 1 cm)** of the squamous epithelium of distal esophagus by specialized intestinal epithelium (IM).

Endoscopically

Histologically



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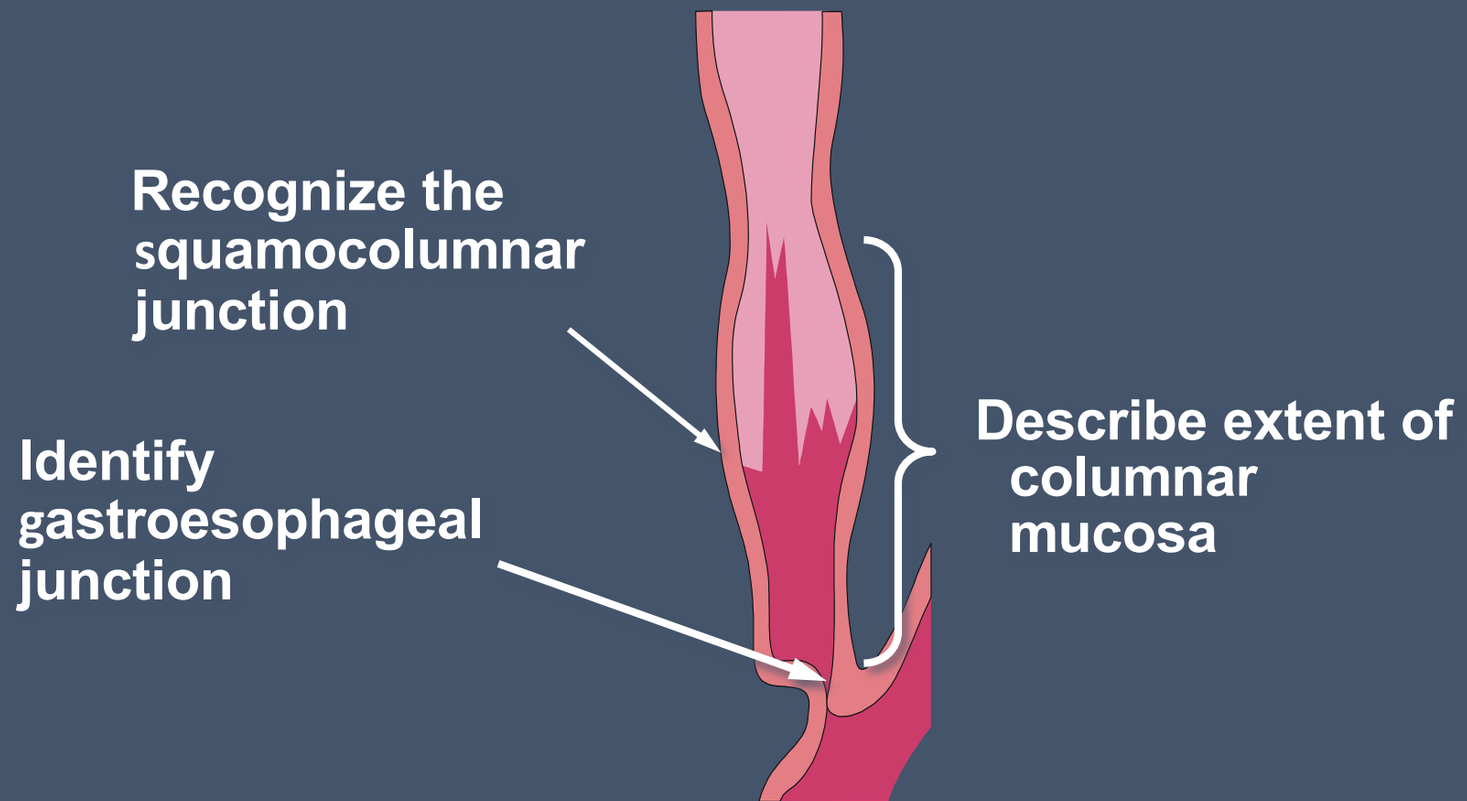
AGA Barrett's Workshop, 2003

Three Essential Steps for Endoscopic Diagnosis and Description



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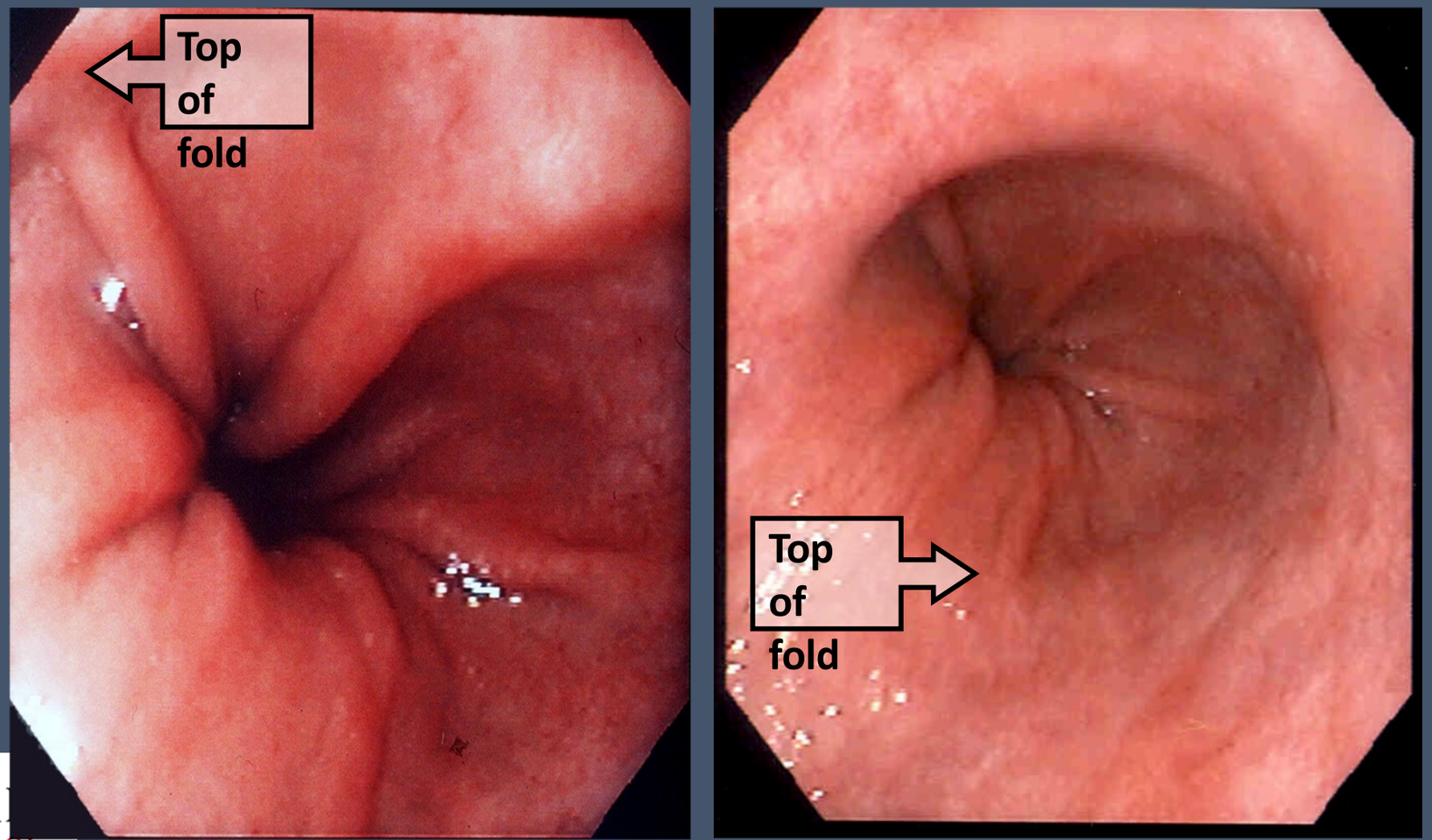
Tytgat GN, et al. Gastroenterol Clin North Am 1997; 26:507

The major endoscopic landmark for the gastro-esophageal junction: The top of the gastric mucosal folds



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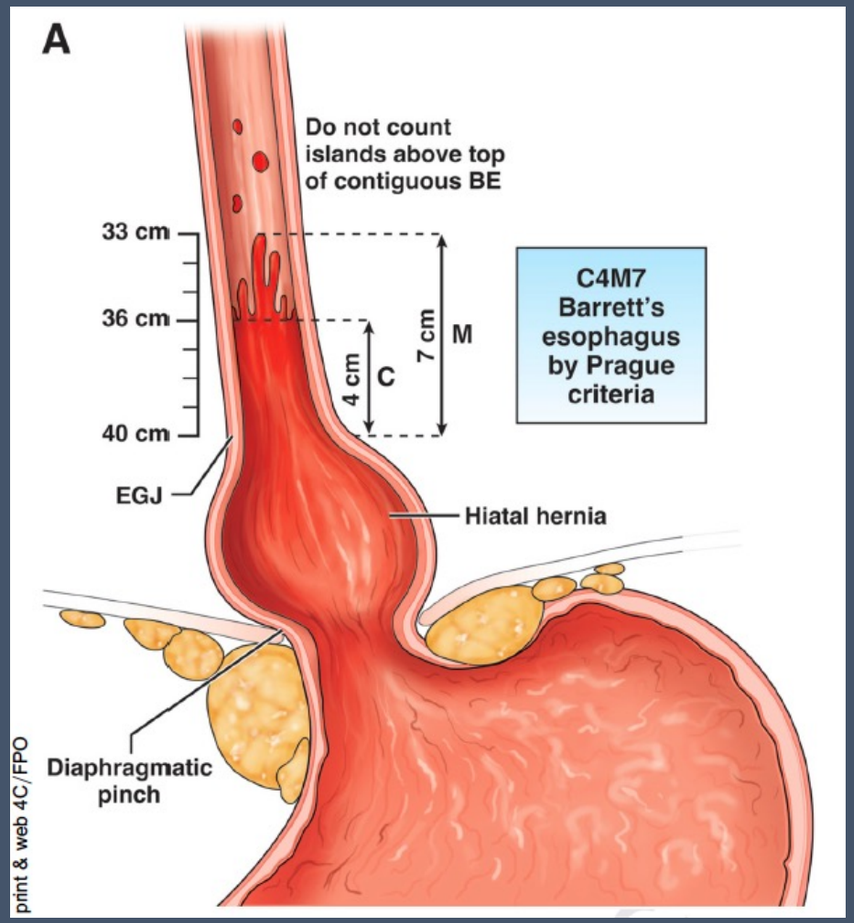
Describing Barrett's Esophagus: The Prague Barrett's C&M Criteria



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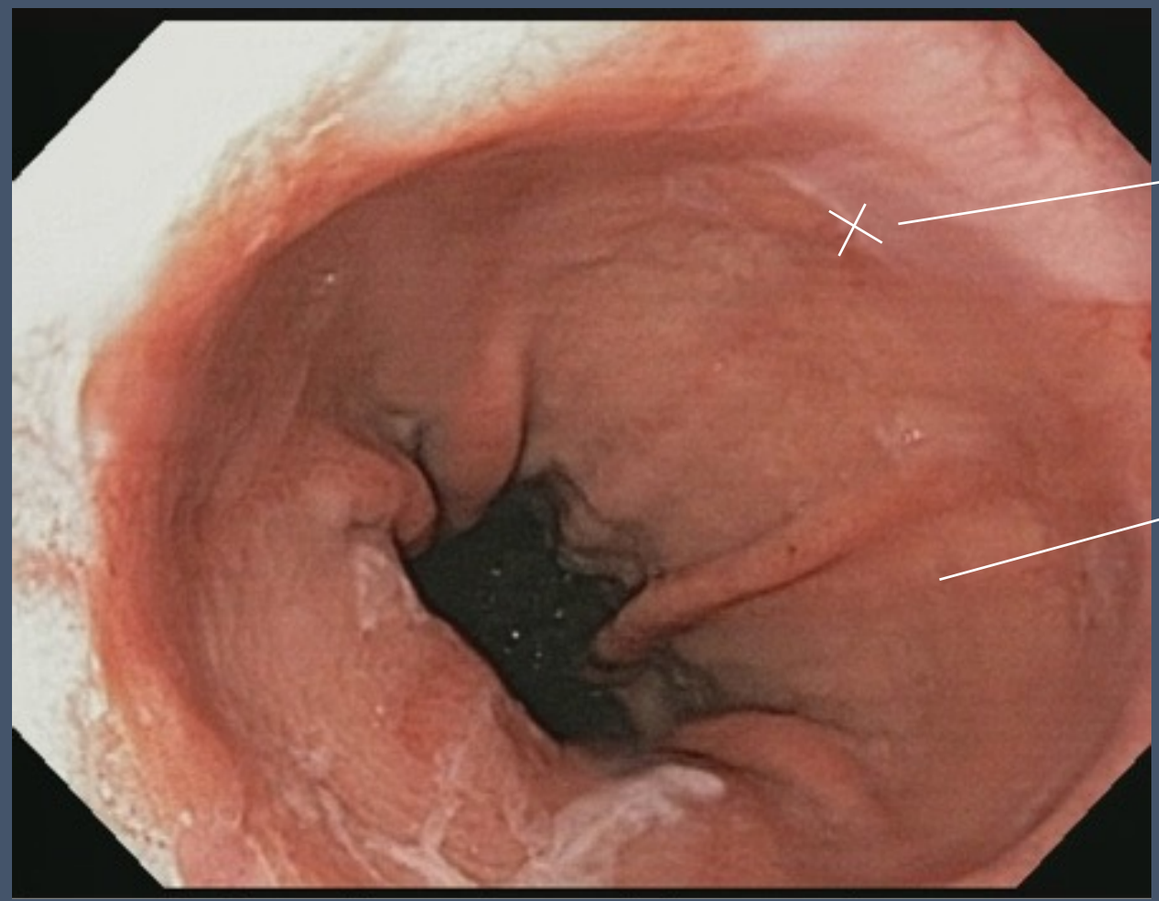
Muthusamy VR et al, AGA Clinical Practice Update 2022, CGH, online

Common Mistakes



Biopsying across the z-line

Calling this BE (it's a hiatal hernia)

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We Are Misclassifying BE!

- 32.3% of those w/ BE were not confirmed (95% CI 24.4-41.1) in a community study
- VA study found 18% of LSBE and 33% of SSBE couldn't be confirmed

Between ¼ and 1/3 of patients diagnosed with Barrett's likely don't have the disease!

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Ganz GIE, 80:5 2014

TEN STEP APPROACH TO HIGH QUALITY EXAMINATION

APPROACH	RATIONALE
1. Identify esophageal landmarks, including location of the diaphragmatic hiatus, GEJ and SCJ	Critical for future exams **QUALITY INDICATOR**
2. Consider use of a distal attachment cap	Facilitate visualization
3. Clean mucosa well using a water jet channel and carefully suction the fluid	Remove any distracting mucus or debris and minimize mucosal trauma
4. Utilize carbon dioxide insufflation and desufflation	Fine adjustments to luminal insufflation can help with detection of subtle lesions
5. Spend adequate time inspecting	Careful examination increases dysplasia detection

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Kolb J, Wani S, Translational Gastro Hepatol 2019
Muthusamy VR et al, AGA Clinical Practice Update 2022, CGH, online

TEN STEP APPROACH TO HIGH QUALITY EXAMINATION

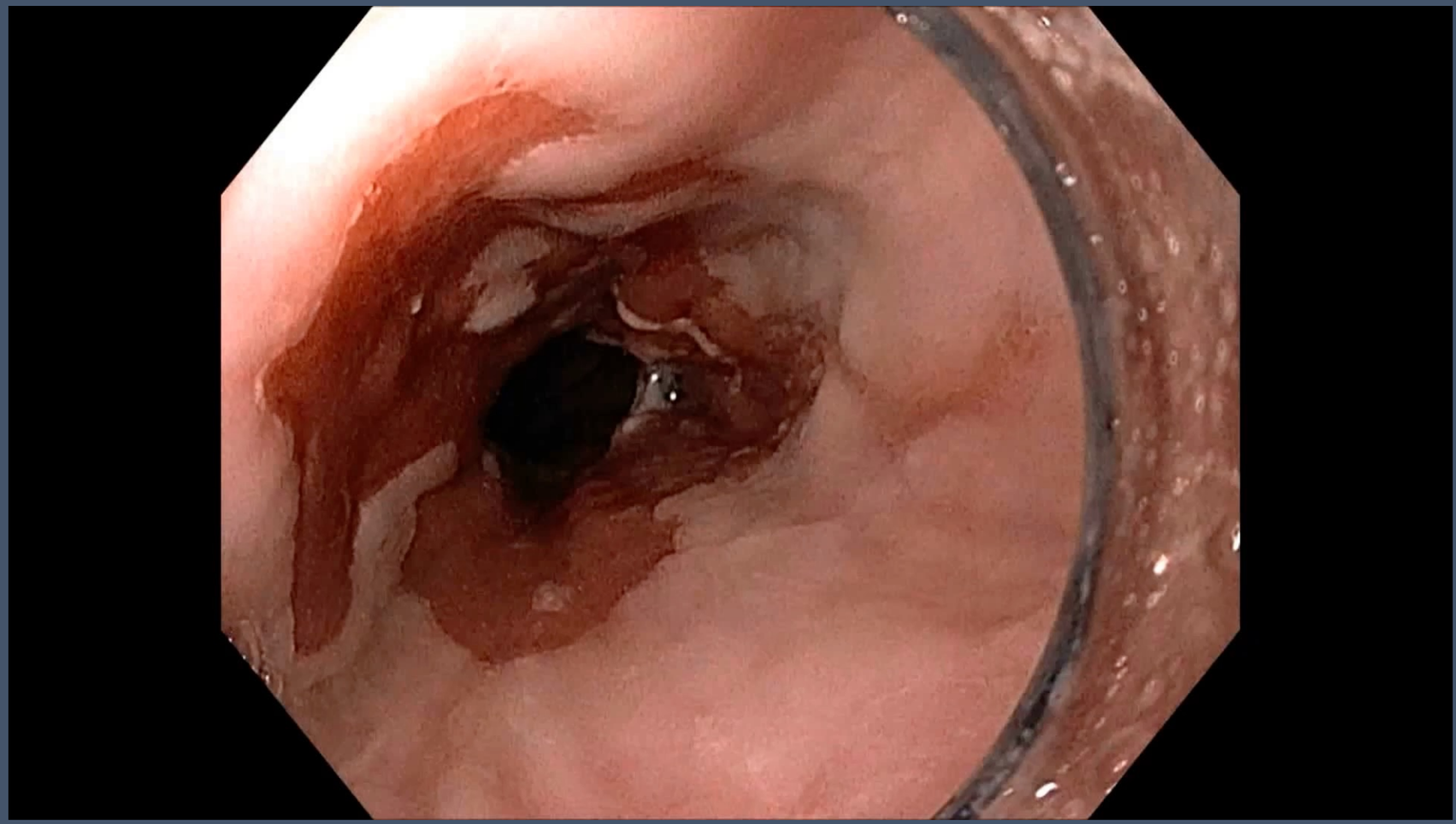
APPROACH	RATIONALE
6. Examine the Barrett's segment using high-definition white light endoscopy	Standard of care **QUALITY INDICATOR**
7. Examine the Barrett's segment using chromoendoscopy (virtual)	Enhances mucosal pattern and surface vasculature
8. Use the Prague classification system to describe circumferential and maximal extent of the Barrett's segment	Standardized reporting system
9. Use the Paris classification to describe superficial neoplasia	Standardized reporting system
10. Use the Seattle protocol (in conjunction with advanced imaging)	Increases dysplasia detection

University of Colorado Anschutz Medical Campus

VARD SCHOOL

Kolb J, Wani S, Translational Gastro Hepatol 2019
Muthusamy VR et al, AGA Clinical Practice Update 2022, CGH, online

How to Perform A High Quality Barrett's Examination



HARVARD
MEDICAL SCHOOL

SLOW DOWN!: The Importance of Barrett's Inspection Time

- BE (n=112) – 38, HGD/Cancer
- HD-WLE, NBI, pCLE

	Inspection time (< 5 min)	Inspection time (> 5 min)	P value
Visible lesion	32.4%	82.9%	<0.001
HGD/Cancer	22.5%	53.7%	0.002
No of visible lesions	0.51	1.95	<0.001
No of areas with HGD/Ca	0.51	2.29	0.004
BE length	3.3	4.4	0.11

Suggestion of 1 min per cm of BE

HARVARD MEDICAL SCHOOL

Gupta et al, GIE 2012

Are We Detecting Visible Lesions?

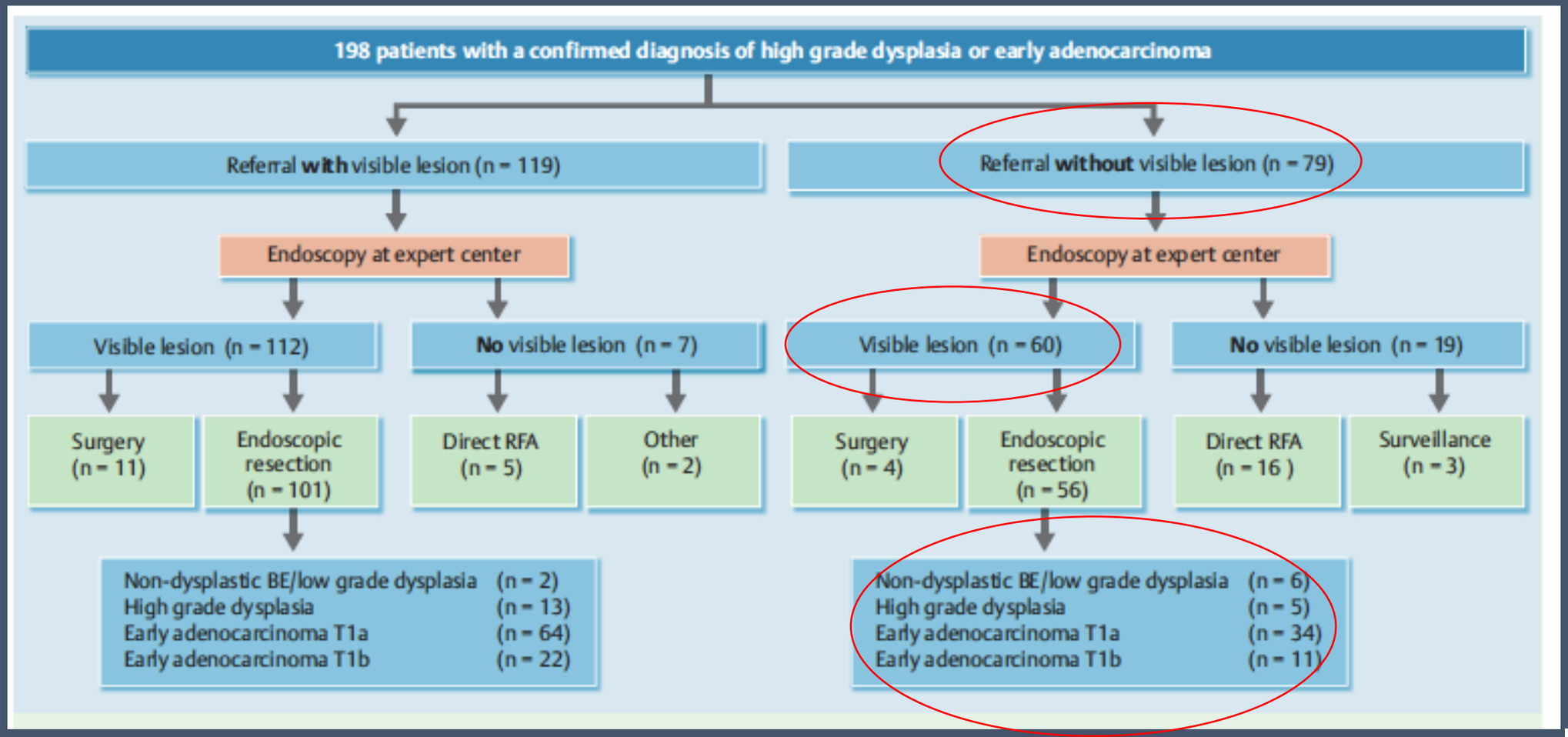
- 198 patients referred from 37 community hospitals
- BE with HGD/IMC
- Review of all Endoscopy reports and images with attention to identification of visible lesions
- Outcome: Endoscopic detection rate of lesions containing histopathologically proven neoplasia (HGD/EAC)
- Results:
  - Community visible lesions: 60%
  - Expert Center: 90%

Conclusion: Nearly 90% of all patients with HGD/IMC have visible lesions and EMR should be strongly considered in all patients undergoing EET

HARVARD MEDICAL SCHOOL

Scholvinck DW et al., Endoscopy 2016

Are we detecting Visible Lesions?



HARVARD MEDICAL SCHOOL

Scholvinck DW et al., Endoscopy 2016

This Can’t Be True! Or Can It?

OUTSIDE EGD FINDINGS: 6/13/18

FINDINGS

Oropharynx	- Normal
Esophagus	- Barrett's Esophagus with C3M4 changes, no nodularity. 4 biopsies taken every 2 cm.
EG-Junction	- 3 cm diaphragmatic hernia without obstruction or gangrene
Cardia	- Normal

B) ESOPHAGUS AT 34 CM (BIOPSY):
PREDOMINANTLY FRAGMENTS OF COLUMNAR MUCOSA

NO EVIDENCE OF GOBLET CELL METAPLASIA, DYSPLASIA OR MALIGNANCY

C) ESOPHAGUS AT 32 CM (BIOPSY):
LOW GRADE GLANDULAR DYSPLASIA ARISING FROM BARRETT'S ESOPHAGUS

PLEASE SEE NOTES

D) ESOPHAGUS AT 30 CM (BIOPSY):
FRAGMENTS OF SQUAMOCOLUMNAR JUNCTIONAL MUCOSA SHOWING LOW GRADE GLANDULAR DYSPLASIA ARISING FROM BARRETT'S ESOPHAGUS

Reason for Referral: Ablation of Barretts

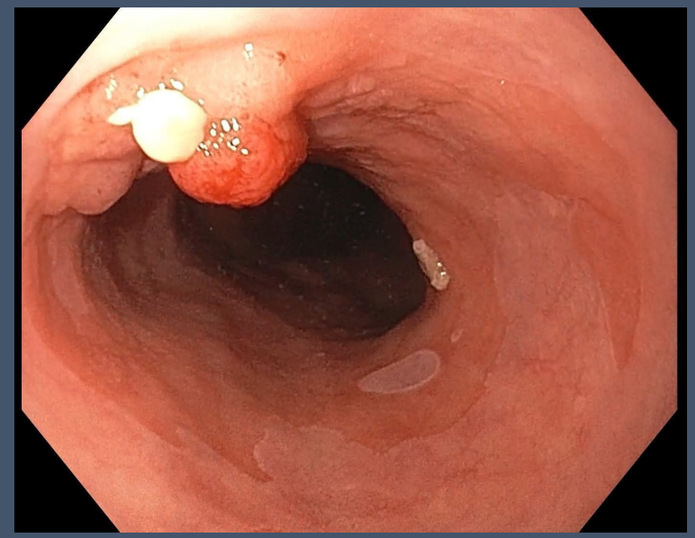
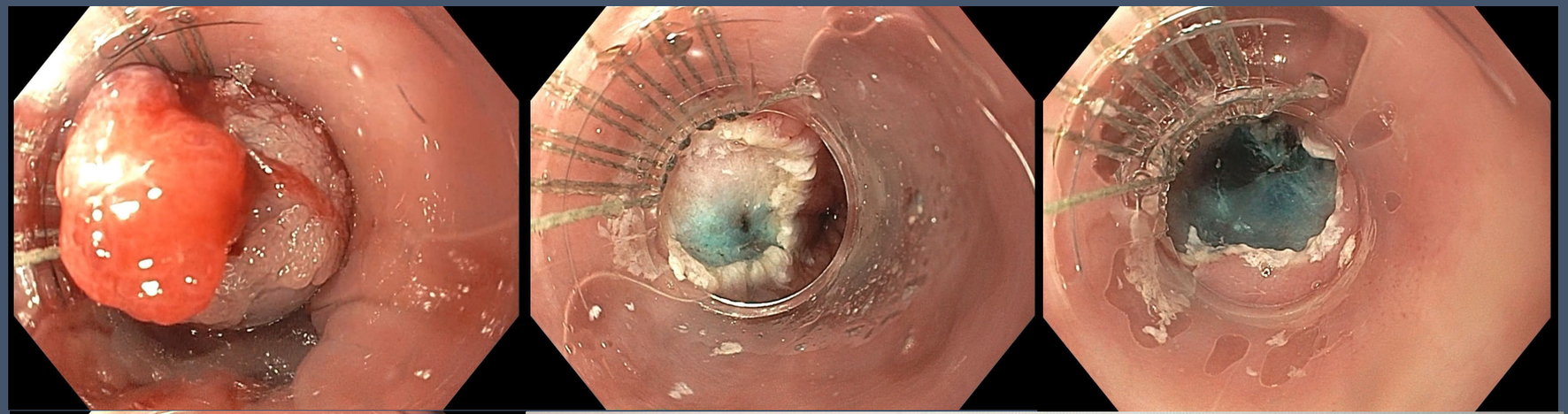
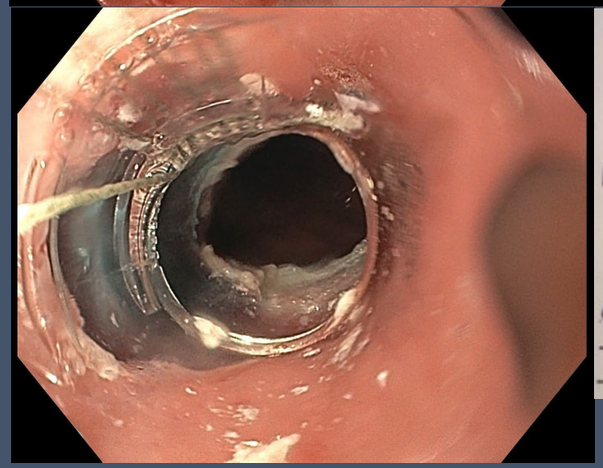


Image from my EGD on 7/9/18

HARVARD MEDICAL SCHOOL

This Can’t Be True! Or Can It?





CLINICAL INFORMATION

73 y.o. male with a history of GERD, erosive esophagitis, Barrett's esophagus C3M4 with low-grade dysplasia at 30 cm and 32 cm. Findings: C3M4 Barrett's esophagus with nodularity from 32-33 s/p EMR x 3.

FINAL DIAGNOSIS

ESOPHAGUS NODÚLES X3 (ENDOSCOPIC MUCOSAL RESECTION):
- At least focal intramucosal adenocarcinoma arising from extensive high grade and low grade dysplasia in the setting of Barrett esophagus (see comment)
- No dysplasia or carcinoma seen at the inked base margin
- Deeper sections examined

HARVARD MEDICAL SCHOOL

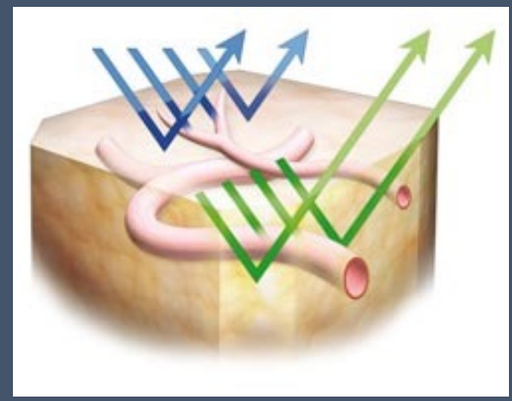
Outline

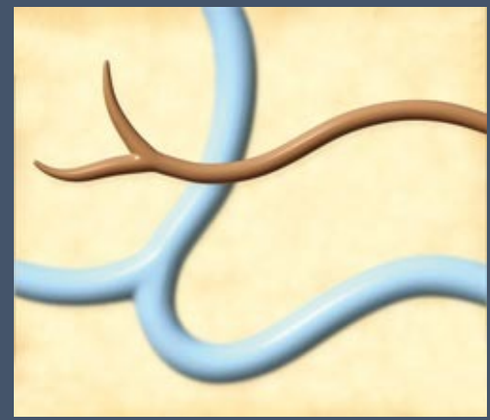
- Screening
- Correctly identifying Barrett's esophagus
- Detecting Dysplasia
  - Performing a Good Exam using HD-WLE
  - NBI-BING
  - CLE/VLE
  - Wide Area Trans-epithelial Sampling
  - Molecular Prediction
  - New Approaches: Video Training and AI
- Summary and Best Practices

HARVARD MEDICAL SCHOOL

Narrow Band Imaging

- Optical Filter technology that improves visibility of vessels
- Optimizes absorbance and scattering characteristics of light
- Two bands of light used
  - Blue (415 nm)
    - Displays surface vessels
  - Green (540 nm)
    - Displays subepithelial vessels

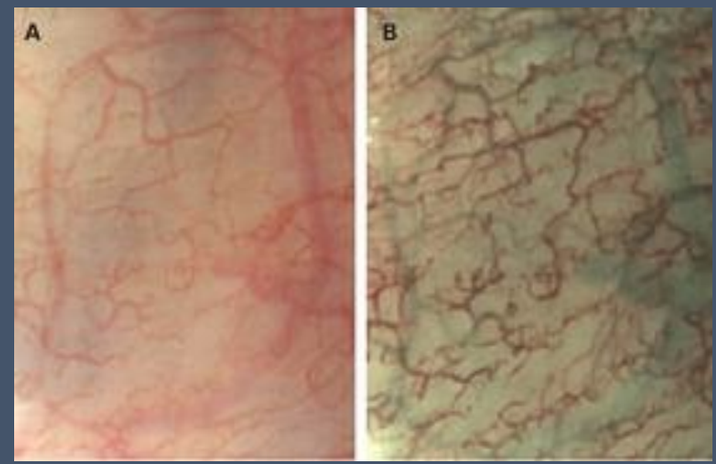


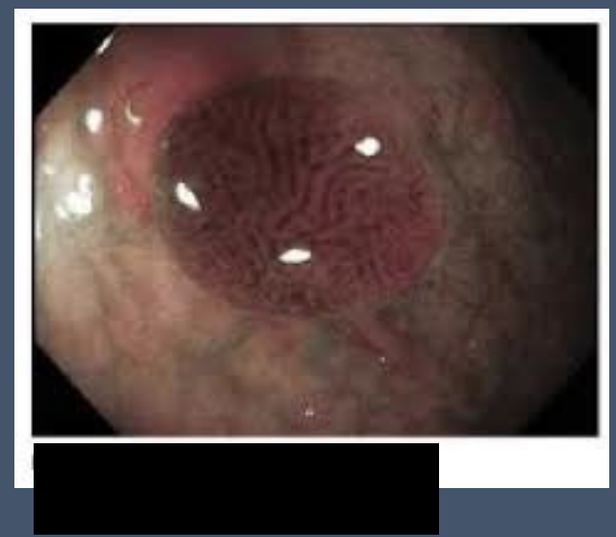


HARVARD MEDICAL SCHOOL

Narrow Band Imaging

- Surface Capillaries
  - brown
- Sub-surface vessels (veins)
  - cyan
- Goals of NBI:
  - Characterize
  - Differentiate
  - Diagnose





HARVARD MEDICAL SCHOOL

NBI for Visible Lesions Prior to EET

"Simplified Optical Chromoendoscopy"

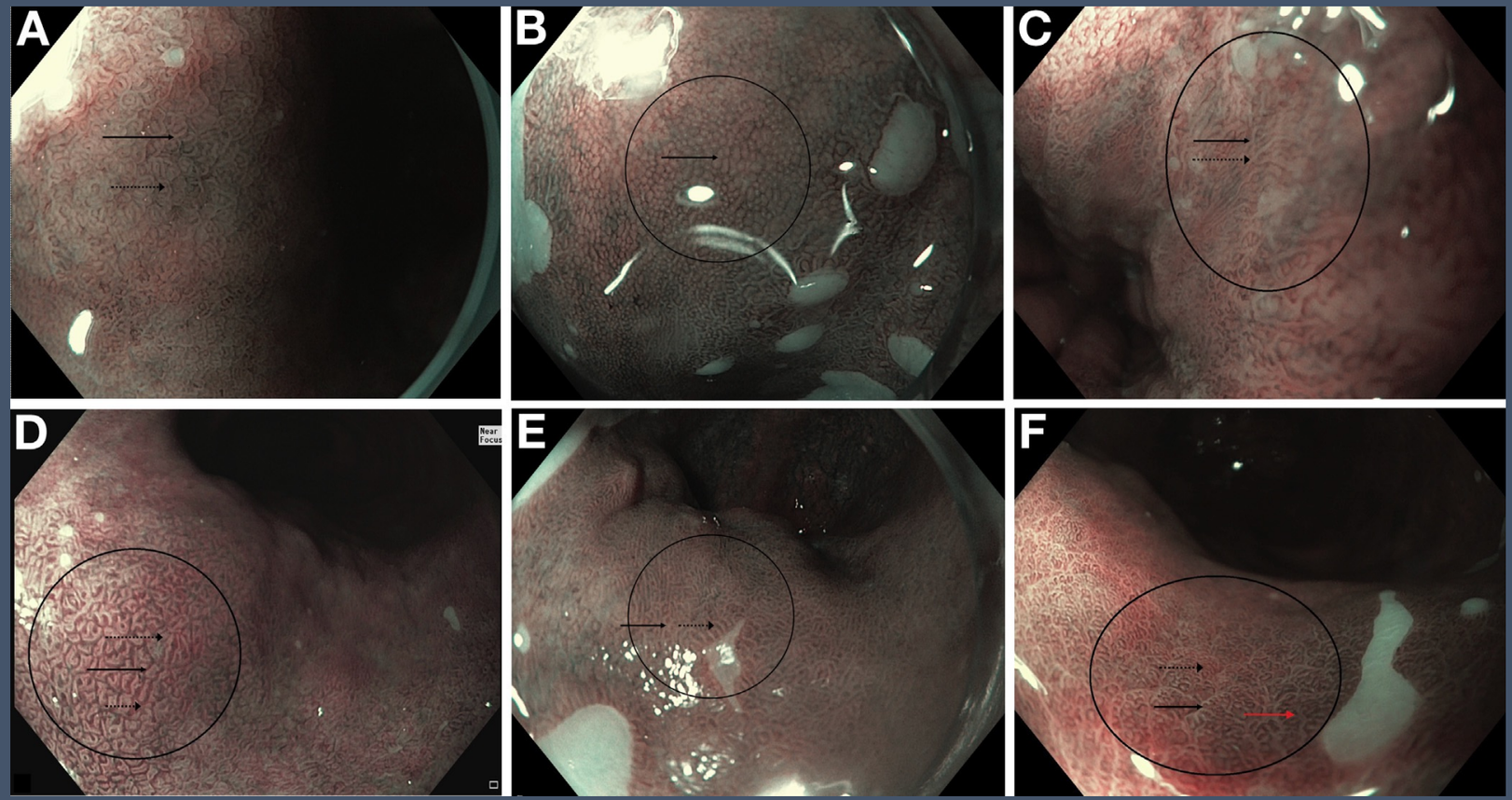
- BING Working Group: Expert review of 60 NBI images of BE and BE associated neoplasia
- Subsequently Prospectively recruited patients
- Reviewed 50 NBI images to validate BING criteria
- Reviewed 120 NBI images to assess if criteria predict histology

Morphologic characteristics	Classification
Mucosal pattern	
Circular, ridged/villous, or tubular patterns	Regular
Absent or irregular patterns	Irregular
Vascular pattern	
Blood vessels situated regularly along or between mucosal ridges and/or those showing normal, long, branching patterns	Regular
Focally or diffusely distributed vessels not following normal architecture of the mucosa	Irregular

HARVARD MEDICAL SCHOOL

Sharma P et al., Gastroenterology 2016

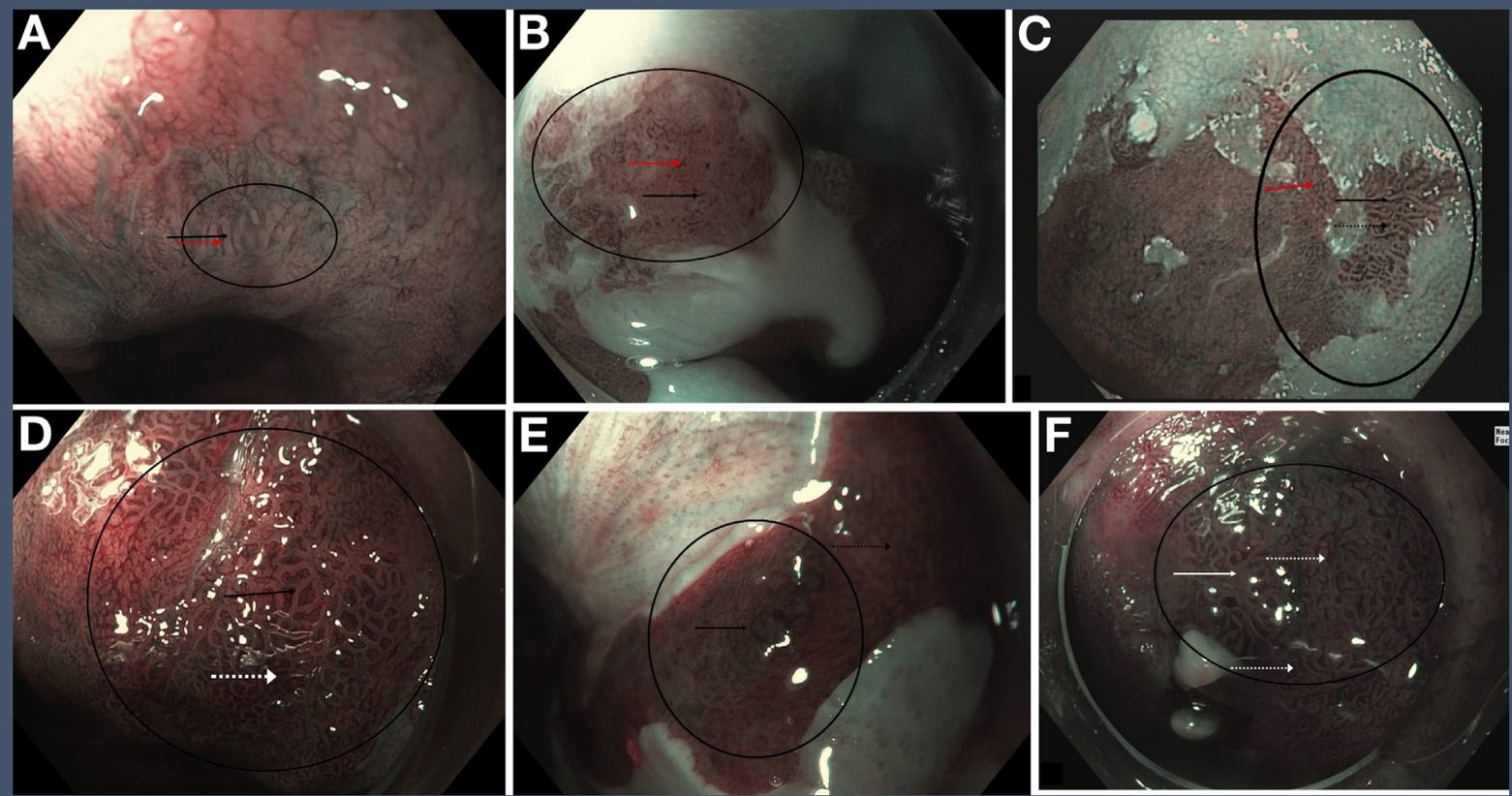
Normal Mucosa on NBI



HARVARD MEDICAL SCHOOL

Sharma P et al., Gastroenterology 2016

Abnormal Mucosa on NBI



HARVARD MEDICAL SCHOOL

Sharma P et al., Gastroenterology 2016

Utility of BING Criteria

Table 4. Accuracy and Sensitivity Analysis of the BING Criteria for the Prediction of Dysplasia in Barrett's Esophagus

Predictions	Accuracy, % (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
Overall	85.4 (82.6–87.9)	80.4 (75.6–85.1)	88.4 (85.4–91.4)	80.7 (75.9–85.4)	88.3 (85.2–91.2)
High-confidence	92.2 (89.3–94.5)	91.1 (86.8–95.4)	92.9 (89.8–95.9)	88.5 (83.7–93.2)	94.6 (91.8–97.2)
Low-confidence	74.1 (68.4–79.2)	62.4 (52.9–71.8)	81.1 (75.1–87.0)	66.3 (56.8–75.8)	78.3 (72.1–84.4)

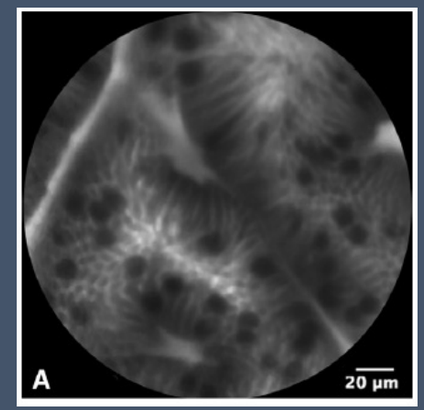
CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.

HARVARD MEDICAL SCHOOL

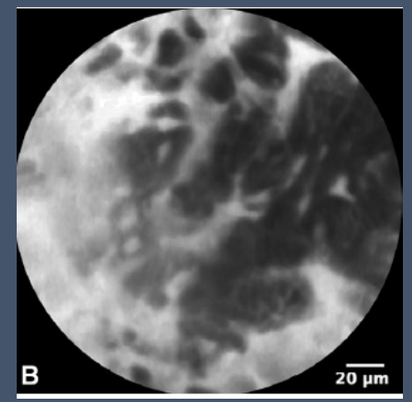
Sharma P et al., Gastroenterology 2016

Confocal Laser Endomicroscopy

- In-vivo histologic imaging
- Probe based and endoscope versions (latter not available at present)
- Expensive capital/probes; requires fluorescein injection



NDBE



Cancer

TABLE 2. Results of the meta-analysis

Technology	Total no. of studies	Sensitivity	95% CI	NPV	95% CI	Specificity	95% CI	Meets ASGE PIVI thresholds
Chromoendoscopy	7	91.9	89.4-93.8	95.5	90.8-97.9	89.9	80.1-95.2	No
Acetic acid	4	96.6	95.2-97.7	98.3	94.8-99.4	84.6	68.5-93.2	Yes
Methylene blue	2	64.2	36.2-84.7	69.8	30.6-92.3	95.9	76.5-99.4	No
NBI	9	94.2	82.6-98.2	97.5	95.1-98.7	94.4	80.5-98.6	Yes
NBI AFI	4	80.6	62.0-91.3	88.7	41.5-98.9	46	31.7-61.0	No
CLE	5	90.4	75.7-96.6	96.2	93.1-97.9	89.9	83.8-93.9	No
eCLE	2	90.4	71.9-97.2	98.3	94.2-99.5	92.7	87.0-96.0	Yes
pCLE	3	90.3	54.1-98.7	95.1	90.7-97.5	77.3	54.3-90.7	No

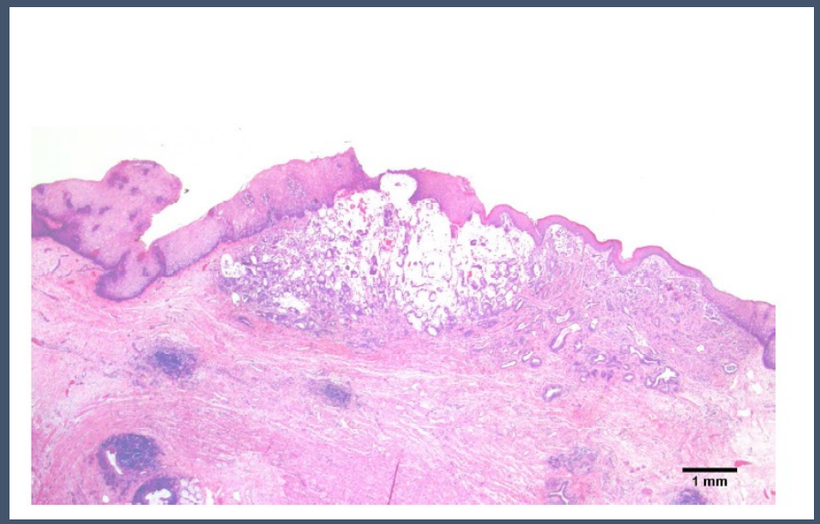
CI, Confidence interval; *NPV*, negative predictive value; *ASGE*, American Society for Gastrointestinal Endoscopy; *PIVI*, ASGE Preservation and Incorporation of Valuable Endoscopic Innovations; *NBI*, narrow-band imaging; *AFI*, autofluorescence imaging; *CLE*, confocal laser endomicroscopy; *eCLE*, endoscope-based CLE; *pCLE*, probe-based CLE.

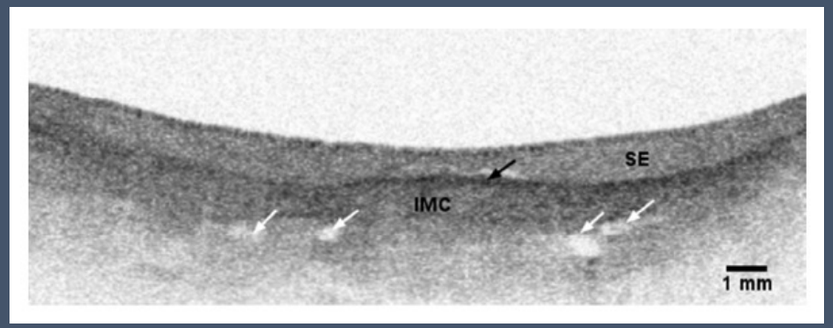
PIVI Targets: per patient sensitivity of >=90% and NPV of >=98% for HGD/EAC & specificity > 80%

Thosani N et al, ASGE Technology Committee SR/MA, GIE 2016

HARVARD MEDICAL SCHOOL

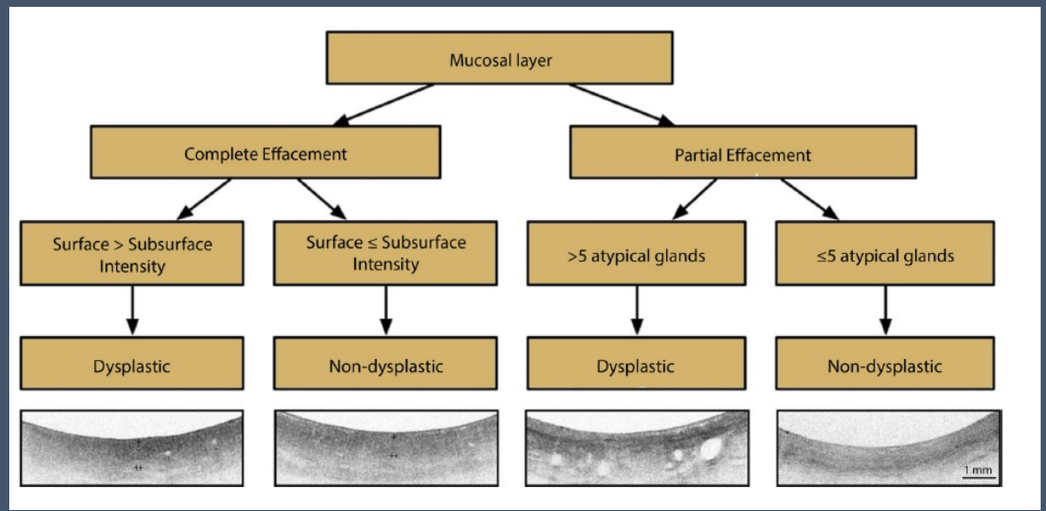
Potential Way to Enhance Dysplasia Detection: VLE

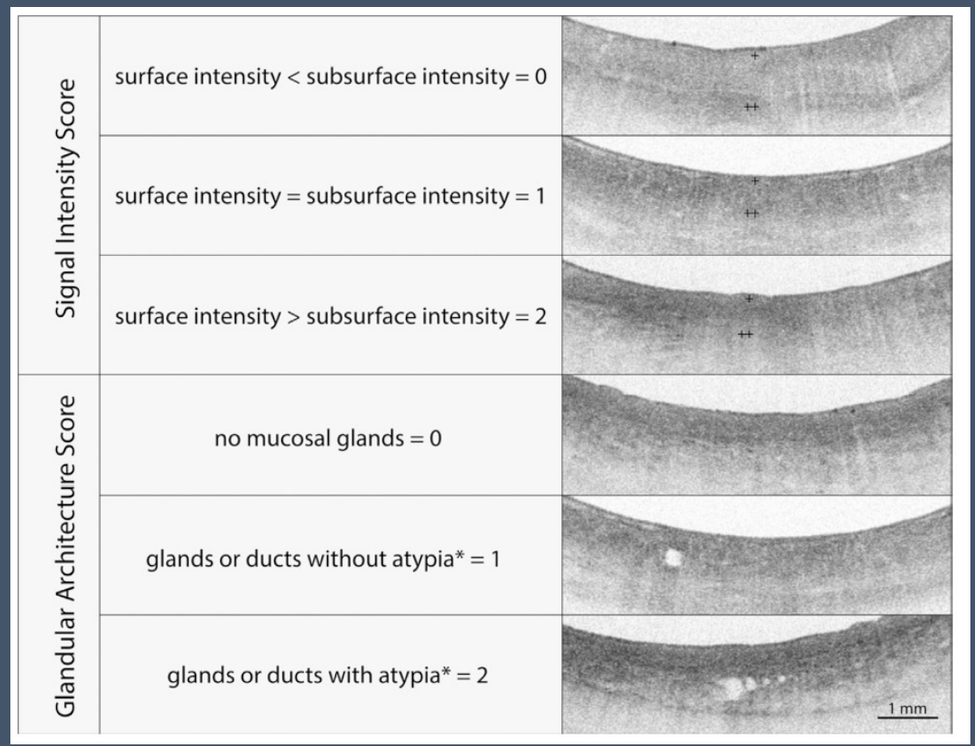




HARVARD MEDICAL SCHOOL

VLE Criteria for Dysplasia





- Important advances in locating identified lesions by Laser Marking
- Among First AI Applications to Barrett's esophagus

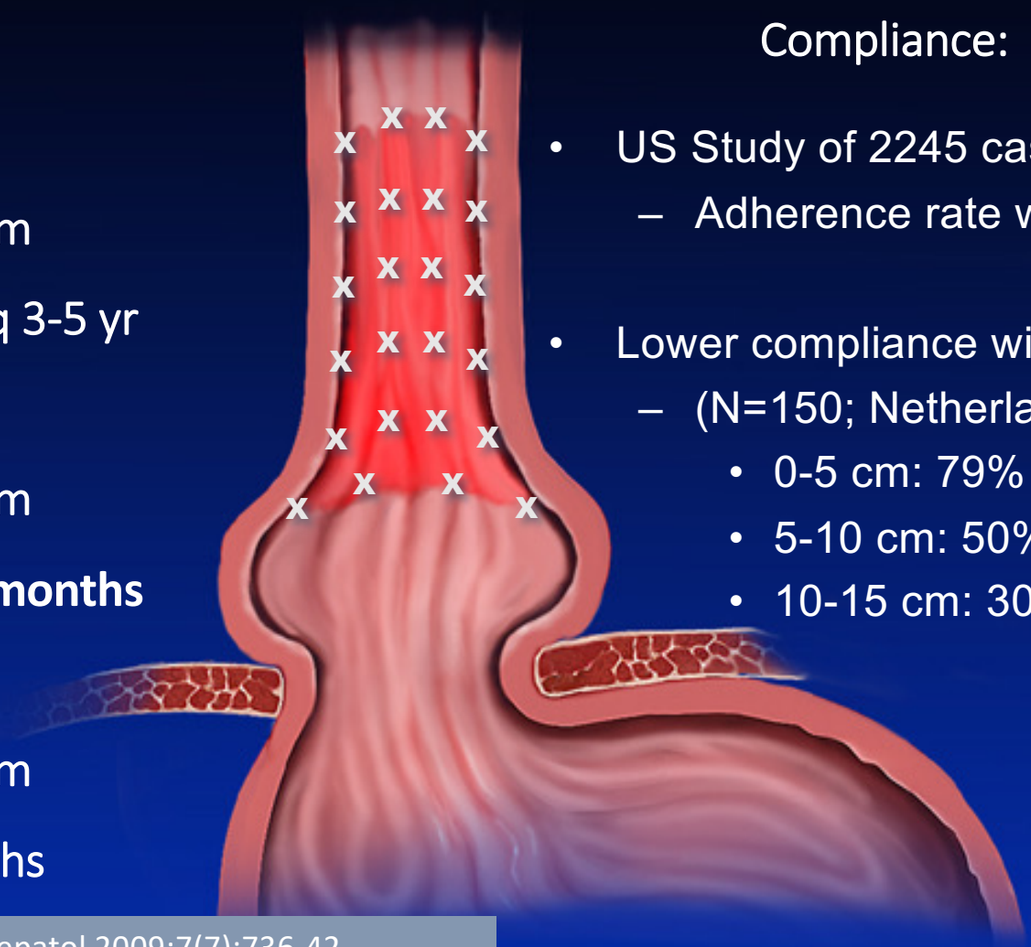
HARVARD MEDICAL SCHOOL

Leggett et al, Gastrointest Endosc , May 2016, 880-888.

Technique of Biopsy in Endoscopic Surveillance

Technique:

- NDBE:
  - 4 quadrant q 2 cm
  - Q 1 yr x 2; then q 3-5 yr
- LGD:
  - 4 quadrant q 1 cm
  - **Repeat: Q 6-12 months**
- HGD:
  - 4 quadrant q 1 cm
  - Repeat q 3 months

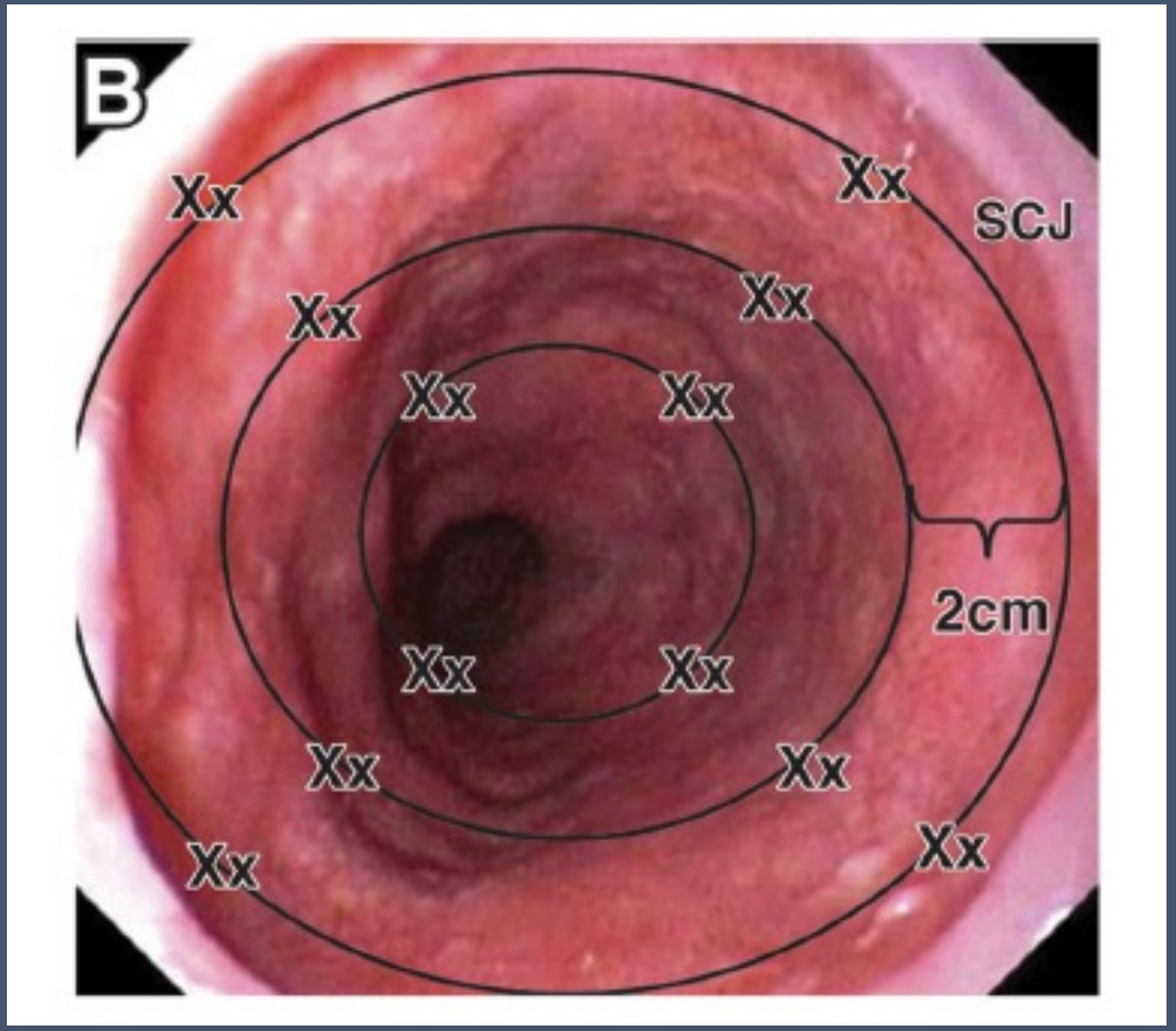


Compliance:

- US Study of 2245 cases
  - Adherence rate was 51.2%
- Lower compliance with longer BE
  - (N=150; Netherlands)
    - 0-5 cm: 79%
    - 5-10 cm: 50%
    - 10-15 cm: 30%

Abrams JA, Clin Gastroenterol Hepatol 2009;7(7):736-42.
Curvers WL Eur J Gastroenterol Hepatol 2008; 20(7):601-7.

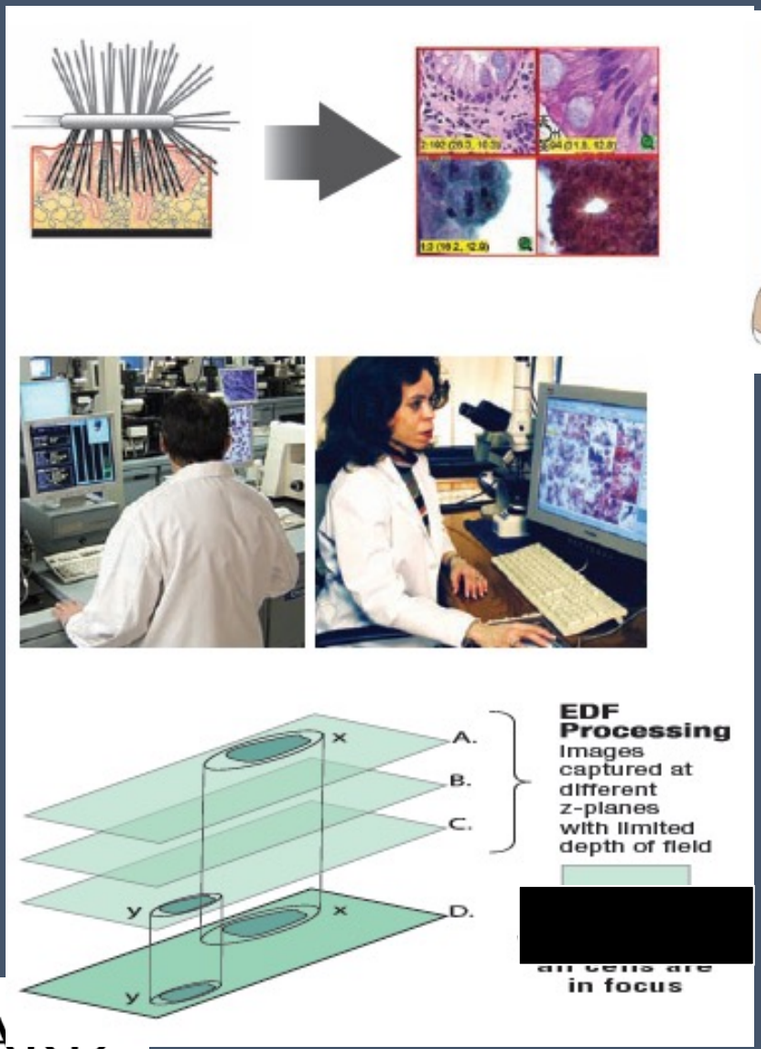
What Does Seattle Protocol Look Like When You Are Done?

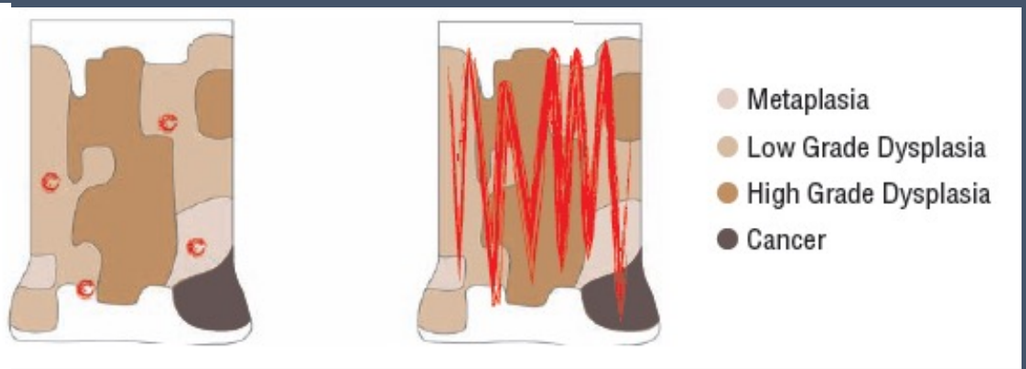


HARVARD MEDICAL SCHOOL

Muthusamy VR et al, AGA Clinical Practice Update 2022, CGH, online

Increased Yield with Specialized Brush





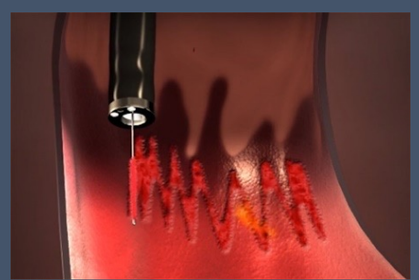
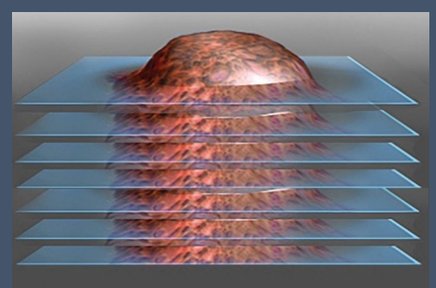
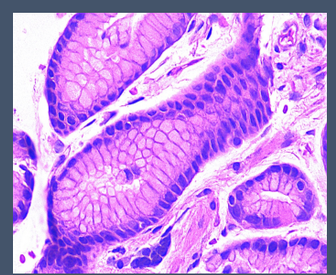
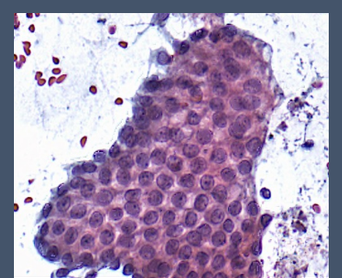
- 39.8% increase in Barrett's esophagus detection in GERD patients
- 42.1% increase in dysplasia detection c/t biopsy in patients w/ dysplasia undergoing surveillance

HARVARD MEDICAL SCHOOL

ADVANCED SAMPLING TECHNIQUES

WIDE-AREA TRANSEPITHELIAL SAMPLING (WATS)

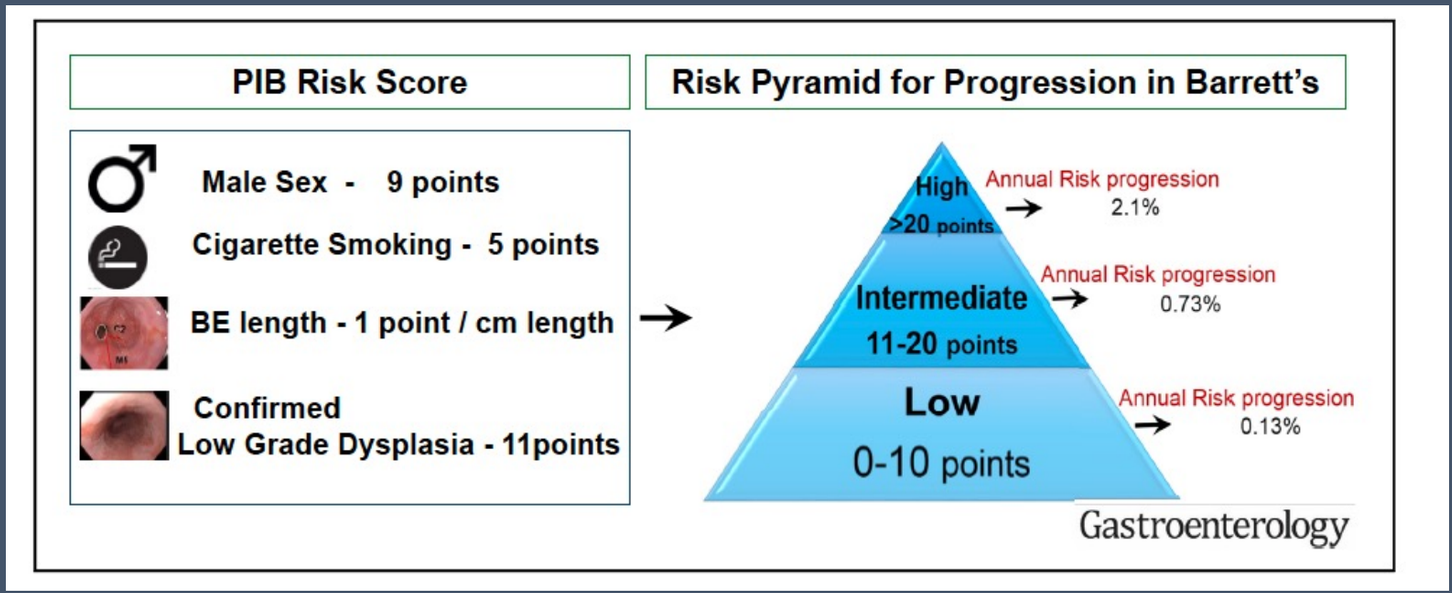
- Provides wide-area tissue sampling using minimally invasive brush biopsy
- Abrasive and sample deeper layers (including muscularis mucosa)
- Sample analyzed – high-speed computer scan that identifies abnormal cells, cell clusters and abnormal glandular cells
- Pathologists review these “suspicious” cells on high-resolution video monitor
- Incremental yield of dysplasia with WATS3D was 7.2% (95% CI 3.9-11.5) from baseline of 15.9%; HGD/EAC was 2.1% (95% CI 0.4-5.3) from baseline of 2.1% – Systematic Review/Meta-analysis of 7 studies Codipilly et al, GIE 2022

HARVARD MEDICAL SCHOOL

Development and Validation of a Model to Determine Risk of Progression of Barrett's Esophagus to Neoplasia

Sravanthi Parasa,[1] Sreekar Vennalaganti,[2] Srinivas Gaddam,[3] Prashanth Vennalaganti,[2,4] Patrick Young,[5] Neil Gupta,[6] Prashanthi Thota,[7] Brooks Cash,[8] Sharad Mathur,[2] Richard Sampliner,[9] Fouad Moawad,[5] David Lieberman,[10] Ajay Bansal,[2,4] Kevin F. Kennedy,[2] John Vargo,[7] Gary Falk,[11] Manon Spaander,[12] Marco Bruno,[12] and Prateek Sharma[2,4]



HARVARD MEDICAL SCHOOL

Parasa S et al Gastroenterology 2018;154:1282–128

Biomarker Based Risk Stratification

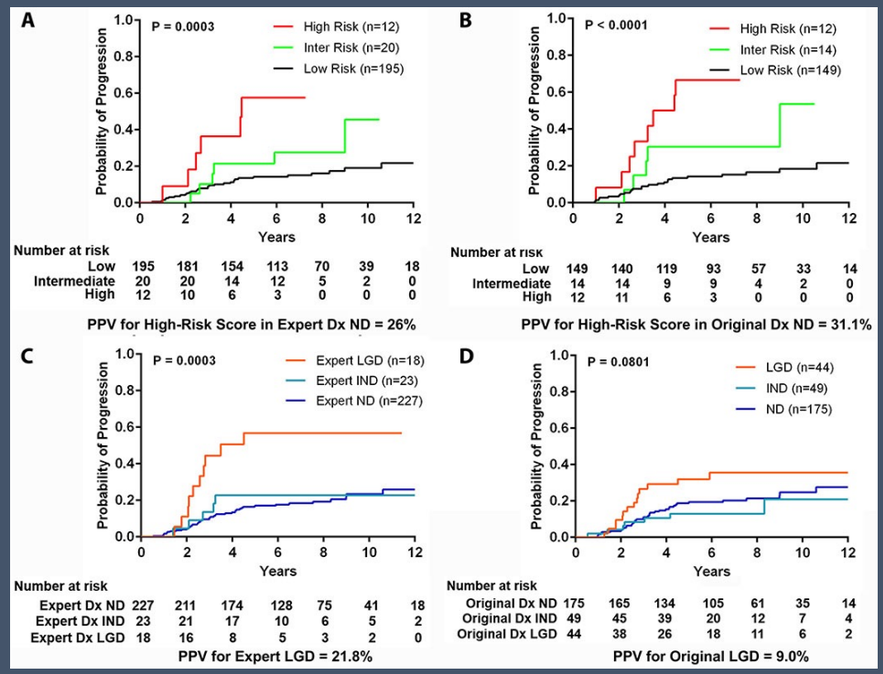
- Multiplexed fluorescence imaging platform that analyzes multiple biomarkers and tissue morphology to predict the risk of progression to HGD and/or EAC
- The assay is performed on formalin-fixed paraffin-embedded (FFPE) tissue obtained via endoscopic biopsies.
- Biomarkers included in the assay measure loss of tumor suppressor genes (p53, p16), alterations in lipid metabolism (AMACR), amplification of oncogenes (HER-2), markers of immune infiltration (CD68, COX2), and angiogenesis (HIF1 alpha, CD45RO).
- In addition morphometric features (nuclear size, shape, and amount of DNA) are also extracted, and make up 3 of the 15 features that a proprietary algorithm integrates to produce the risk score.
- Score classifies patients into high, intermediate, and low risk of progression over 5 years.

HARVARD MEDICAL SCHOOL

Iyer PG et al, Clin Gastro & Hep, 2022 (online)

Biomarker Based Risk Stratification

- 2 centers
- Predict risk to HGD/EAC
- High Risk with OR of 4.7 compared to Low risk for HGD/EAC development
- 5 yr PPV was 23%
- **NDBE patients who scored high-risk progressed at a higher rate (26%) than patients with subspecialist-confirmed LGD (21.8%) at 5 years.**



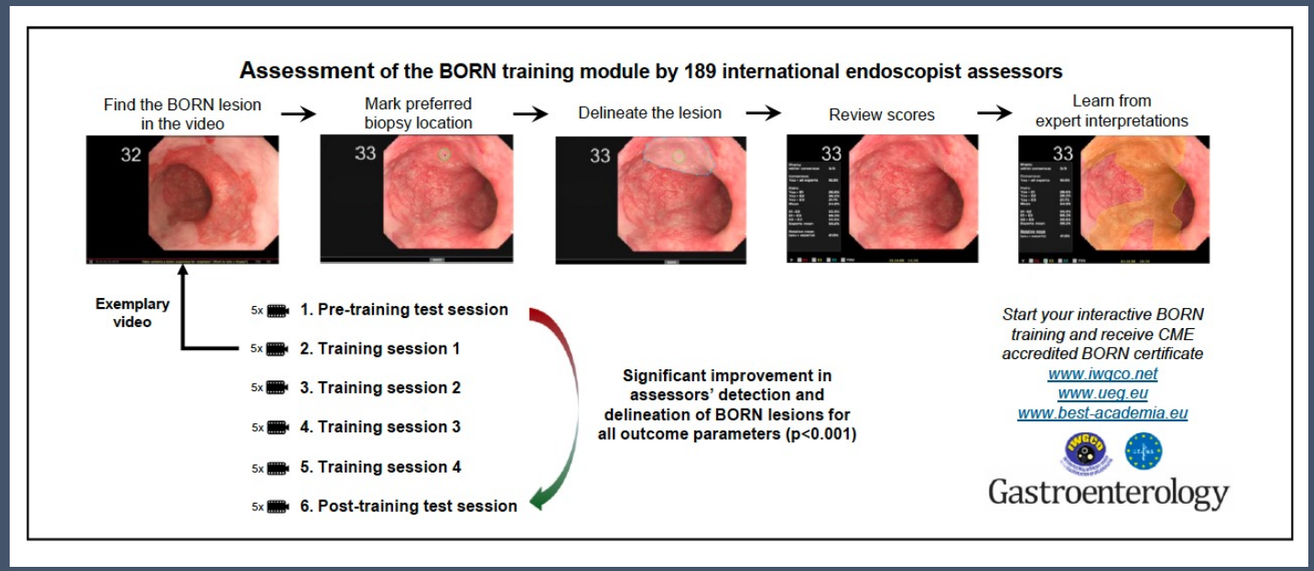
- Pooled Analysis Shows of 552 pts shows **OR of 6.0** [2.9-12.0] for high risk test class, c/w 2.9 [1.2-7.2] for expert confirmed LGD
- All models of progression incorporating this data performed better
- Sensitivity 38%, but specificity was 94%

HARVARD MEDICAL SCHOOL

Davison J et al, Am J Gastroenterol. 2020 June ; 115(6): 843–852.
Iyer PG et al, Clin Gastro & Hep, 2022 (online).

Web Based Video Module to Improve Dysplasia Detection

- Web-based video platform
- 3 experts marked and delineated lesions
- Phase 1: 68 endoscopists assessed 4 batches of 20 videos
- 121 new assessors completed 4 5 video batches after a 5 video run-in session



HARVARD MEDICAL SCHOOL

Bergman JJ et al, Gastroenterology, 2019, 156: 1299-1308

Web Based Video Module to Improve Dysplasia Detection

- Median lesion detection increased by 30%
- Improved delineation of lesions seen as well
- Improvement independent of country of origin or experience level

Table 2. Median Scores of Outcome Parameters per Batch in Phase 1

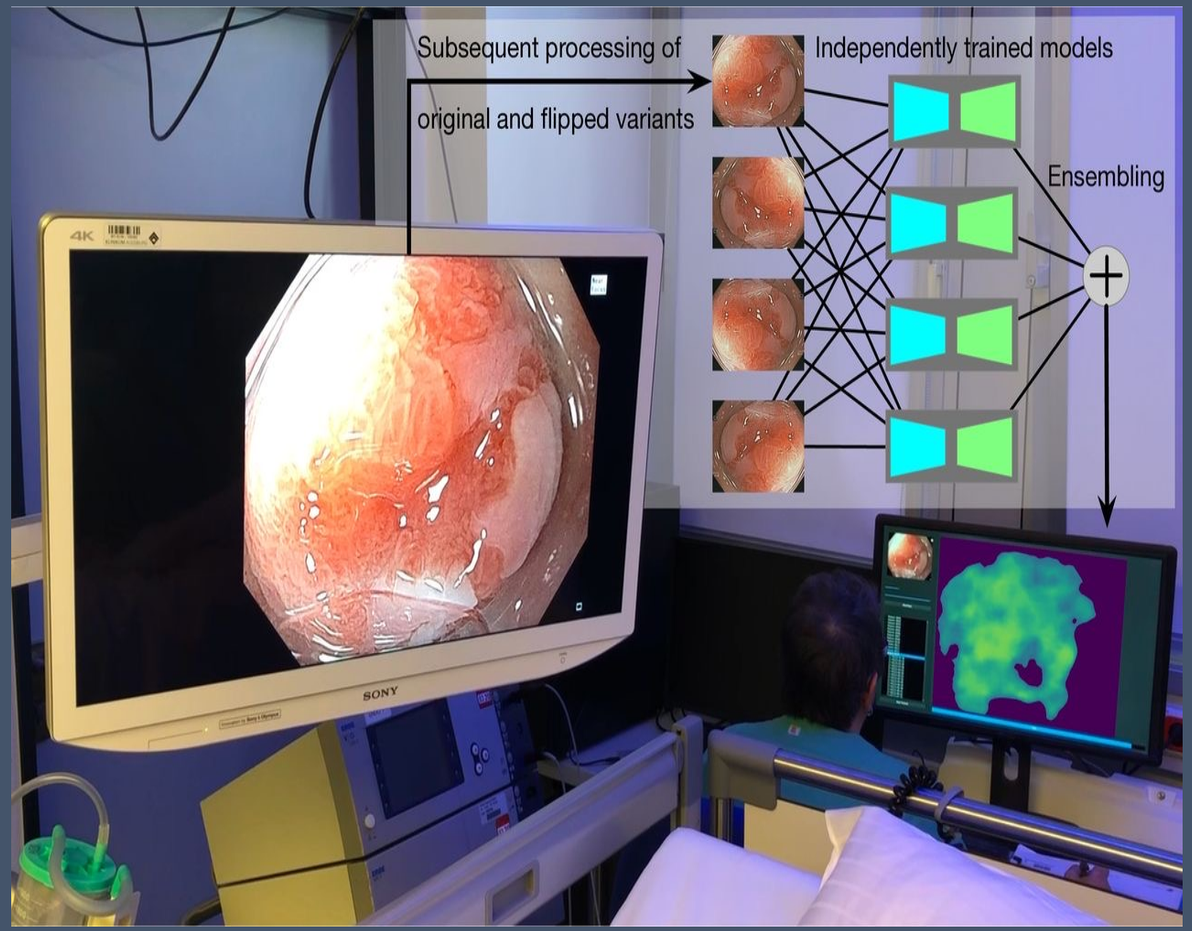
Variable	Training batch 1, % (IQR)	Training batch 2, % (IQR)	Training batch 3, % (IQR)	Training batch 4, % (IQR)	Median absolute increase batch 1–4, % (95% CI)[a]	*P* value	Median relative increase batch 1–4, % (95% CI)[b]	*P* value
Median detection score	64 (54–82)	69 (54–81)	69 (54–82)	73 (54–91)	8 (0–16)	.07	21 (6–40)	.01
Median delineation score	41 (23–56)	52 (38–68)	59 (43–68)	63 (48–78)	22 (14–30)	<.001	64 (36–101)	<.001
Median agreement delineation score	32 (18–41)	39 (27–49)	42 (29–50)	44 (32–52)	13 (8–19)	<.001	55 (27–89)	<.001
Median relative delineation score	45 (25–60)	57 (40–71)	61 (43–72)	65 (47–77)	19 (11–28)	<.001	55 (29–93)	<.001

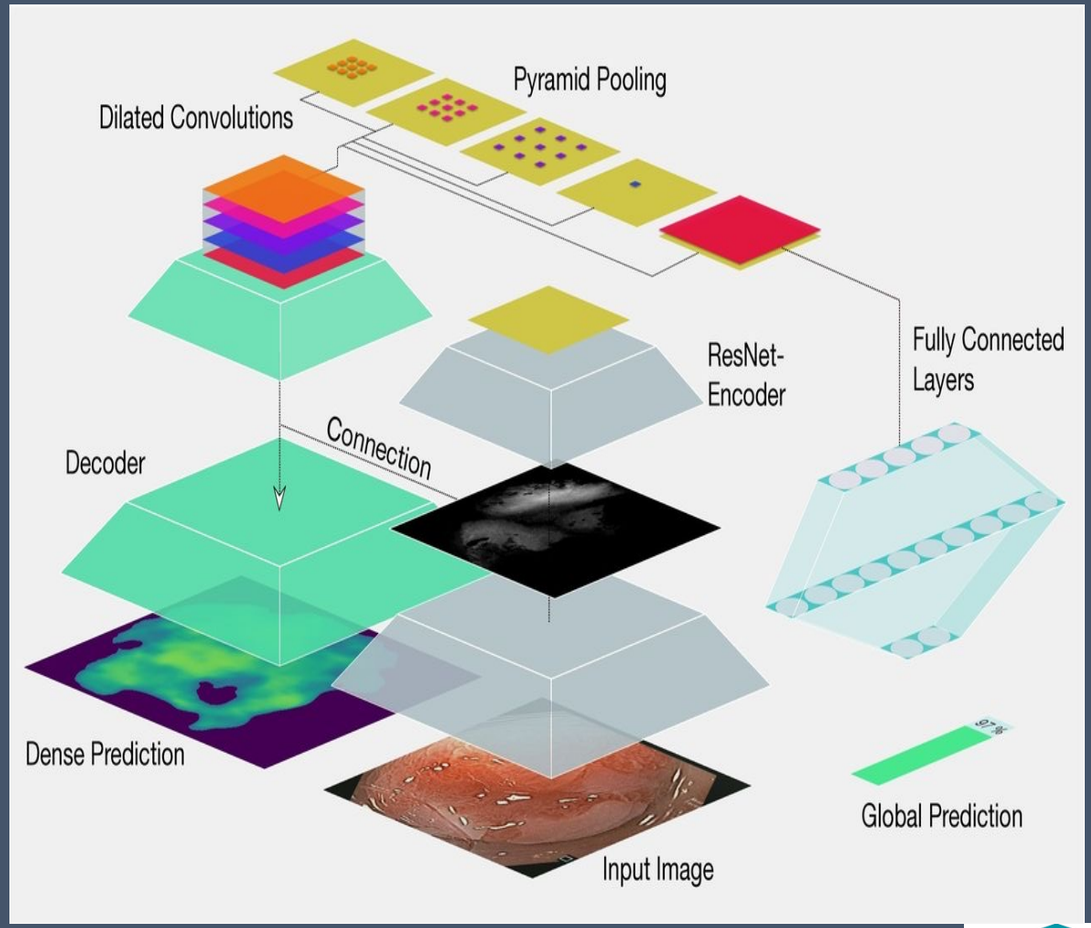
[a]Wilcoxon signed-rank tests.
[b]Wilcoxon tests.

HARVARD MEDICAL SCHOOL

Bergman JJ et al, Gastroenterology, 2019, 156: 1299-1308

ARTIFICIAL INTELLIGENCE – REAL-TIME USE IN BARRETT'S ESOPHAGUS

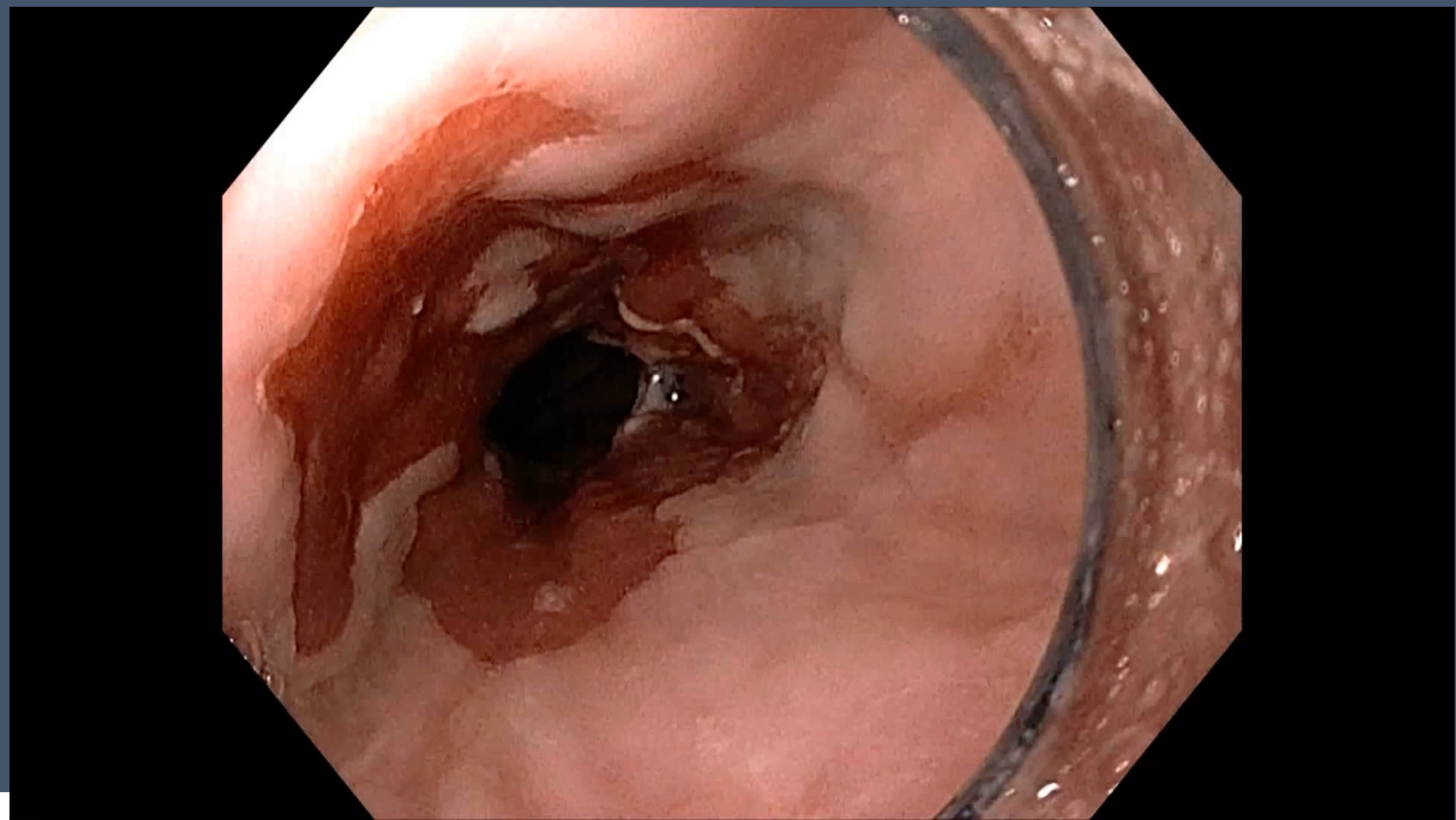




HARVARD MEDICAL SCHOOL

Ebigbo A et al, Gut 2020;
de Groof AJ et al Gastroenterology 2020

Continuous Real Time AI Assisted Barrett's Surveillance Procedure



HARVARD MEDICAL SCHOOL

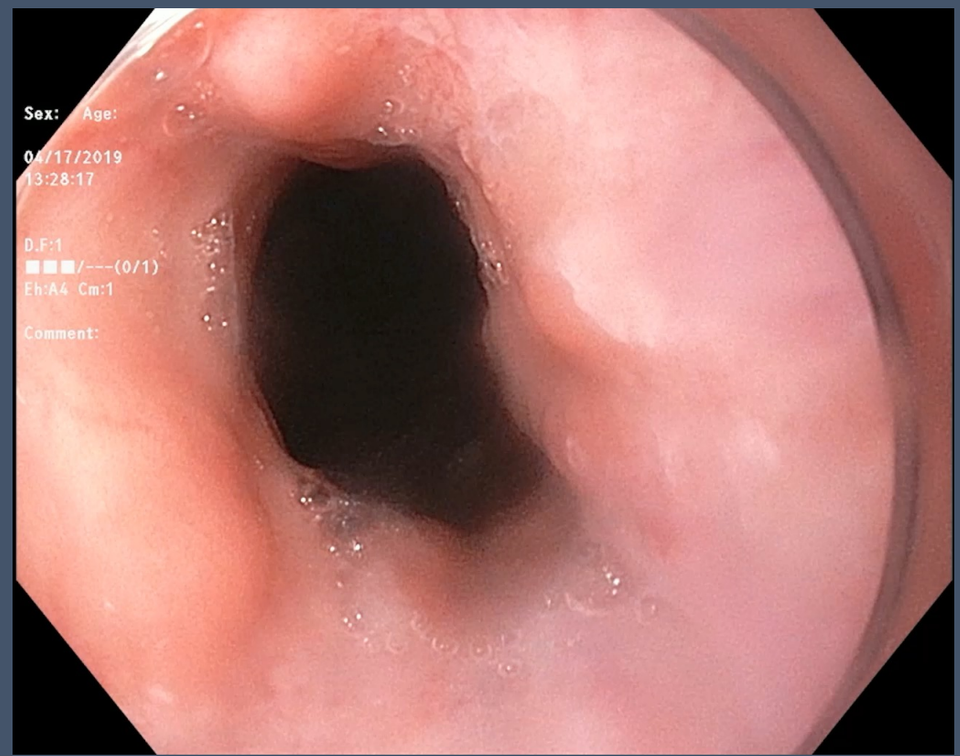
Hashimoto,. Samarasena Gastrointestinal Endoscopy 2020

Results

- 40 videos from 40 unique pts (WLE, NBI, video 1-6 min)
  - 2 outside facilities; 20 pts w at least 1 dysplastic lesion and 20 with NDBE
- Dysplastic videos:
  - Algorithm detected 19/20 lesions
    - 95% per lesion sensitivity
- Non-dysplastic videos:
  - TN frames: 27559
  - FP frames: 1045

  } FP rate: 3.7%

  - False positive clinical predictions: Zero
  - Per patient negative predictive value: 100%



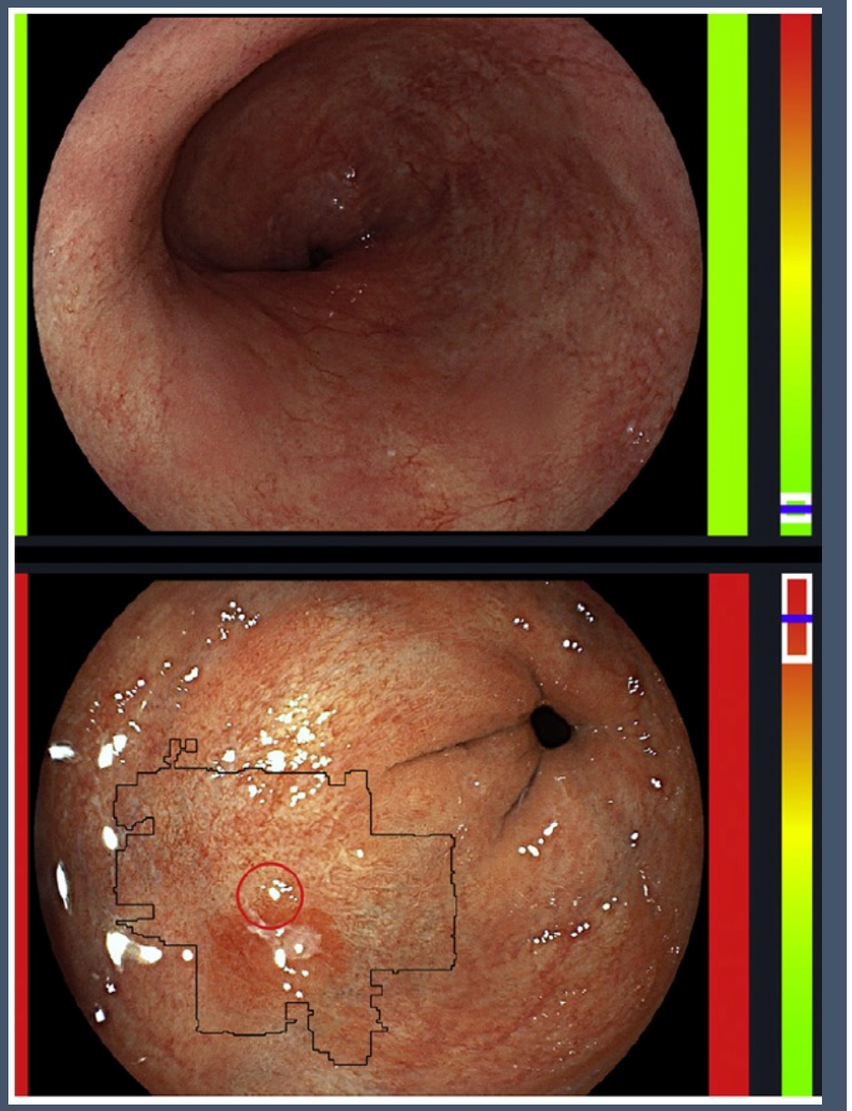
HARVARD MEDICAL SCHOOL

Samarasena J et al, DDW 2021

Deep learning algorithm detection of Barrett's neoplasia with high accuracy during live endoscopic procedures: a pilot study (with video)

Albert J. de Groof, MD,[1] Maarten R. Struyvenberg, MD,[1] Kiki N. Fockens, MD,[1] Joost van der Putten, MSc,[2] Fons van der Sommen, PhD,[2] Tim G. Boers, MSc,[2] Sveta Zinger, PhD,[2] Raf Bisschops, MD, PhD,[3] Peter H. de With, PhD,[2] Roos E. Pouw, MD, PhD,[1] Wouter L. Curvers, MD, PhD,[4] Erik J. Schoon, MD, PhD,[4] Jacques J. G. H. M. Bergman, MD, PhD[1]

- CADe system tested during endoscopic procedures in :
  - 10 patients with NDBE
  - 10 patients with confirmed Barrett's neoplasia
- WLE images were obtained at every 2-cm level of the Barrett's segment → analyzed by the CAD system → feedback to the endoscopist
- At every level, 3 images were evaluated by the CAD system
- Measured - accuracy, sensitivity, & specificity
  - ground truth was established by expert assessment & corresponding histopathology
  - concordance of 3 sequential CAD predictions per level



HARVARD MEDICAL SCHOOL

Deep learning algorithm detection of Barrett's neoplasia with high accuracy during live endoscopic procedures: a pilot study (with video)

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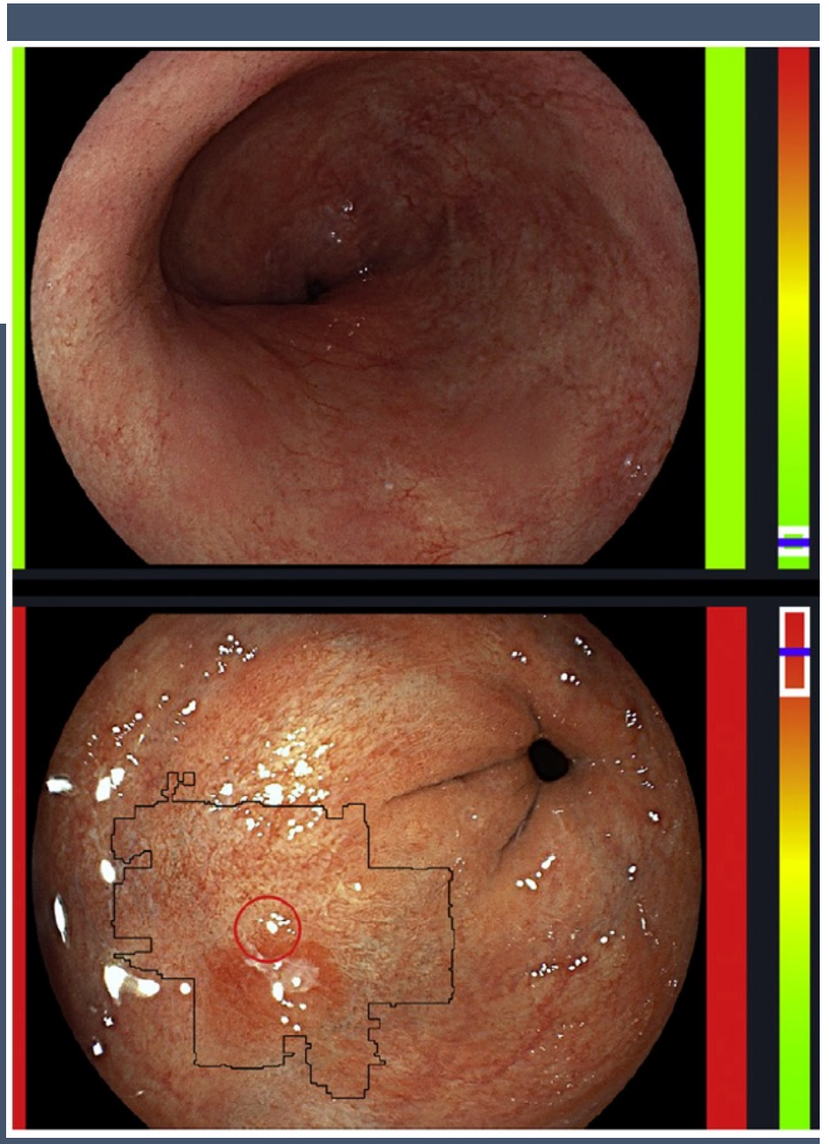
- Per-level analysis of CAD system:
  - Accuracy 90%,
  - Sensitivity 91%
  - Specificity 89 %
- 9/10 neoplastic patients were correctly diagnosed
  - The single lesion not detected by CAD showed NDBE in the endoscopic resection specimen
- CAD system produced false-positive predictions in only 1 NDBE patient
- CAD system produced 3 concordant predictions in 75% of all levels



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Outline

- Screening
- Correctly identifying Barrett's esophagus
- Detecting Dysplasia
  - Performing a Good Exam using HD-WLE
  - NBI-BING
  - CLE/VLE
  - Wide Area Trans-epithelial Sampling
  - Molecular Prediction
  - New Approaches: Video training and AI
- Summary and Best Practices

HARVARD MEDICAL SCHOOL

Putting It All Together……

AGA Clinical Practice Update on New Technology and Innovation for Surveillance and Screening in Barrett's Esophagus: Expert Review

V Raman Muthusamy [1], Sachin Wani [2], C Prakash Gyawali [3], Srinadh Komanduri [4],
CGIT Barrett's Esophagus Consensus Conference Participants

CME

Diagnosis and Management of Barrett's Esophagus: An Updated ACG Guideline

Nicholas J. Shaheen, MD, MPH[1], Gary W. Falk, MD, MS[2], Prasad G. Iyer, MD, MS[3], Rhonda F. Souza, MD[4], Rena H. Yadlapati, MD, MHS (GRADE Methodologist)[5], Bryan G. Sauer, MD, MSc (GRADE Methodologist)[6] and Sachin Wani, MD[7]

HARVARD MEDICAL SCHOOL

Communication from the ASGE Technology Committee

TECHNOLOGY STATUS EVALUATION REPORT

Advances in the diagnosis and surveillance of Barrett's esophagus (with videos)

Prepared by: THE ASGE TECHNOLOGY COMMITTEE

Arvind J. Trindade, MD,[1] Udayakumar Navaneethan, MD,[2] Harry R. Aslanian, MD, FASGE,[3] Manoop S. Bhutani, MD, FASGE,[4] Kumar Krishnan, MD,[5] David R. Lichtenstein, MD, FASGE,[6] Joshua Melson, MD, FASGE,[7] Rahul Pannala, MD, MPH, FASGE,[8] Mansour A. Parsi, MD, MPH, FASGE,[9] Allison R. Schulman, MD, MPH,[10] Amrita Sethi, MD, FASGE,[11] Guru Trikudanathan, MD,[12] Rabindra R. Watson, MD,[13] John T. Maple, DO, FASGE, ASGE technology committee chair[14]

This document was reviewed and approved by the Governing Board of the American Society for Gastrointestinal Endoscopy.

Communication from the ASGE Standards of Practice Committee

GUIDELINE

ASGE guideline on screening and surveillance of Barrett's esophagus

Prepared by: ASGE STANDARDS OF PRACTICE COMMITTEE

Bashar Qumseya, MD, MPH, FASGE,[1,*] Shahnaz Sultan,[2,*] Paul Bain,[3] Laith Jamil, MD, FASGE,[4] Brian Jacobson,[5] Sharmila Anandasabapathy,[6] Deepak Agrawal, MD, MPH, MBA,[7] James L. Buxbaum, MD, FASGE,[8] Douglas S. Fishman, MD, FASGE,[9] Suryakanth R. Gurudu, MD, FASGE,[10] Terry L. Jue, MD, FASGE,[11] Sapna Kripalani, MD,[12] Jeffrey K. Lee, MD,[13] Mouen A. Khashab, MD,[14] Mariam Naveed, MD,[15] Nirav C. Thosani, MD,[16] Julie Yang, MD,[17] John DeWitt,[18] Sachin Wani, MD, FASGE, ASGE Standards of Practice Committee Chair[19]

The final document was approved by the ASGE Governing Board and the Standards of Practice Committee and represents the official guideline of the ASGE on these topics.

HARVARD MEDICAL SCHOOL

AGA Clinical Practice Update 2022

Best Practice Advice (BPA) Statements
Screening for Barrett's Esophagus (BE)
BPA #1. Screening with standard upper endoscopy may be considered in individuals with established risk factors for BE and esophageal adenocarcinoma – presence of at least 3 risk factors (individuals who are male, non-Hispanic white, age >50 years, have a history of smoking, chronic gastrointestinal reflux disease, obesity, or a family history of BE or esophageal adenocarcinoma).
BPA #2. Nonendoscopic cell collection devices can be considered as an option to screen for BE.
Endoscopic Examination of BE
BPA #3. Screening and surveillance exams should be performed using high-definition white light endoscopy and virtual chromoendoscopy, with endoscopists spending adequate time inspecting the Barrett's segment.
BPA #4. Screening and surveillance exams should define the extent of BE using a standardized grading system documenting the circumferential and maximal extent of the columnar lined esophagus (Prague classification) with a clear description of landmarks and the location and characteristics of visible lesions (nodularity, ulceration), when present.
BPA #5. Advanced imaging technologies such as endomicroscopy may be used as adjunctive imaging techniques to identify dysplasia.
BPA #6. Sampling during screening and surveillance exams should be performed using the Seattle biopsy protocol (4-quadrant biopsies every 1–2 cm and target biopsies from any visible lesion).
BPA #7. 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).
BPA #8. Patients with erosive esophagitis may be biopsied when concern of dysplasia or malignancy exists, with the caveat that a repeat endoscopy after 8 weeks of twice a day proton pump inhibitors is performed.

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Muthusamy VR et al, AGA Clinical Practice Update 2022, CGH, online

AGA Clinical Practice Update 2022

Best Practice Advice (BPA) Statements
Risk Stratification of BE
BPA #9. Tissue systems pathology-based prediction assay may be utilized for risk stratification of patients with nondysplastic BE.
BPA #10. Risk stratification models may be utilized to selectively identify individuals at risk for Barrett's associated neoplasia.
Provider Expertise in Managing BE
BPA #11. Given the significant interobserver variability among pathologists, the diagnosis of BE-related neoplasia should be confirmed by an expert pathology review.
BPA #12. Patients with BE-related neoplasia should be referred to endoscopists with expertise in advanced imaging, resection, and ablation.
Follow-up and Surveillance of BE
BPA #13. Patients with BE should be placed on at least daily proton pump inhibitor therapy.
BPA #14. Patients with nondysplastic BE should undergo surveillance endoscopy in 3 to 5 years.
BPA #15. In patients undergoing surveillance after endoscopic eradication therapy, 4-quadrant random biopsies should be taken of the esophagogastric junction, gastric cardia, and the distal 2 cm of the neosquamous epithelium as well as from all visible lesions, independent of the length of the original BE segment.

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Muthusamy VR et al, AGA Clinical Practice Update 2022, CGH, online

Modern BE Care Pathway

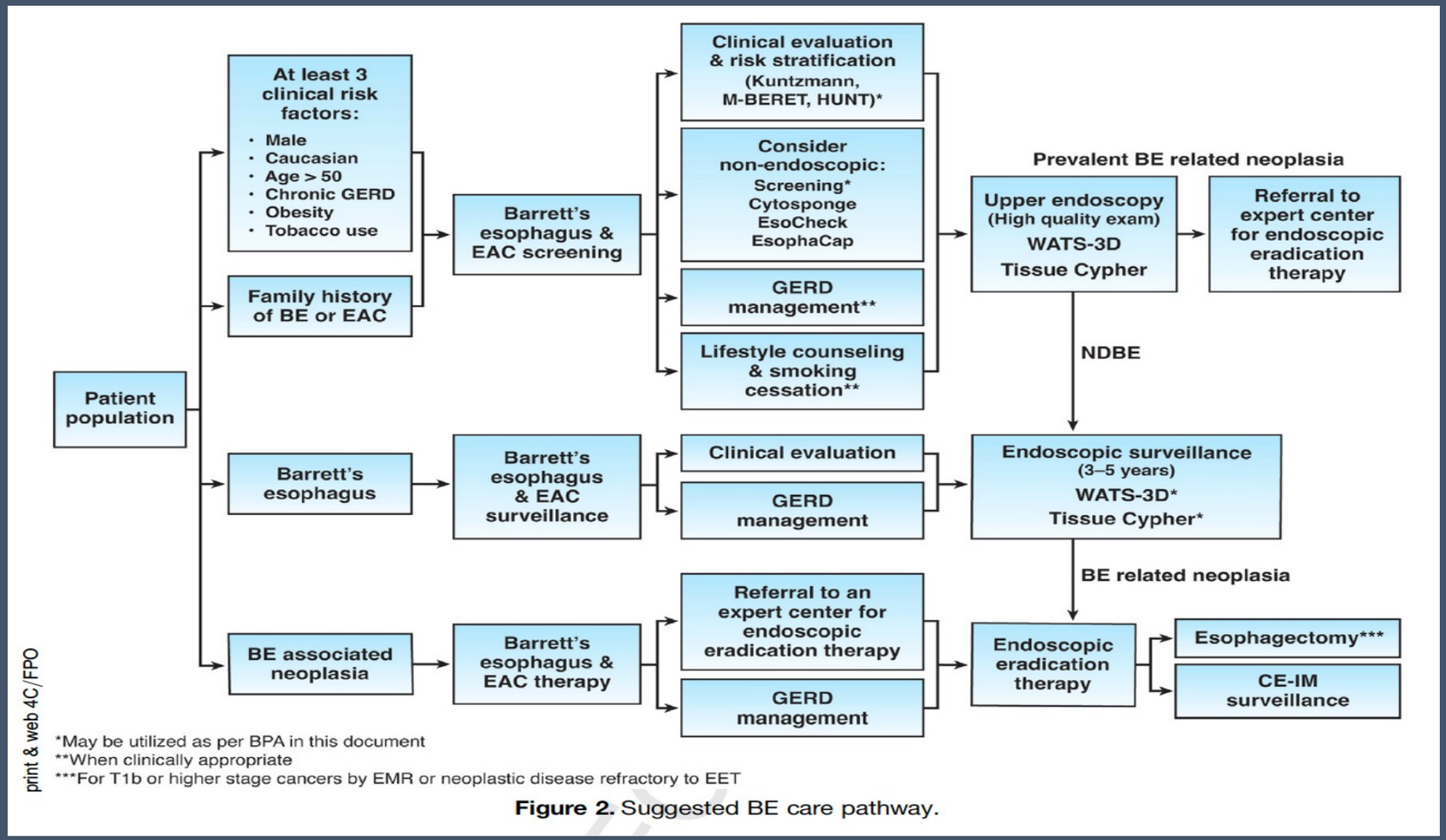

Figure 2. Suggested BE care pathway.

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Muthusamy VR et al, AGA Clinical Practice Update 2022, CGH, online

Conclusions

- The current GERD- based screening strategy for BE has not shown clear benefit
- While the optimal method and timing of screening for BE are uncertain, future approaches may benefit from using a lower-cost initial method and screening a broader population
- Greater attention needs to be paid to training regarding proper endoscopic identification, inspection and documentation of Barrett's esophagus
- Improve cell collection techniques, risk-prediction models and adjunct imaging technologies can improve our ability to detect Barrett's esophagus and associated dysplasia/neoplasia
- Improved training in visual inspection and artificial intelligence hold great promise in our ability to perform better surveillance imaging

HARVARD MEDICAL SCHOOL

We have extremely effective treatments for BE.
We now need for focus our attention on finding those w/ BE and dysplasia!