GI07
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3:32am

William Grady, M.D., Fred Hutchinson Cancer Research Center

Epigenetic Alterations in Barretts Esophagus: Novel screening test for Barretts esophagus and cancer

William Grady, MD, AGAF
Ming Yu, PhD
Fred Hutchinson Cancer Research Center
University of Washington School of Medicine

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Early Detection Research Network

BETRNet

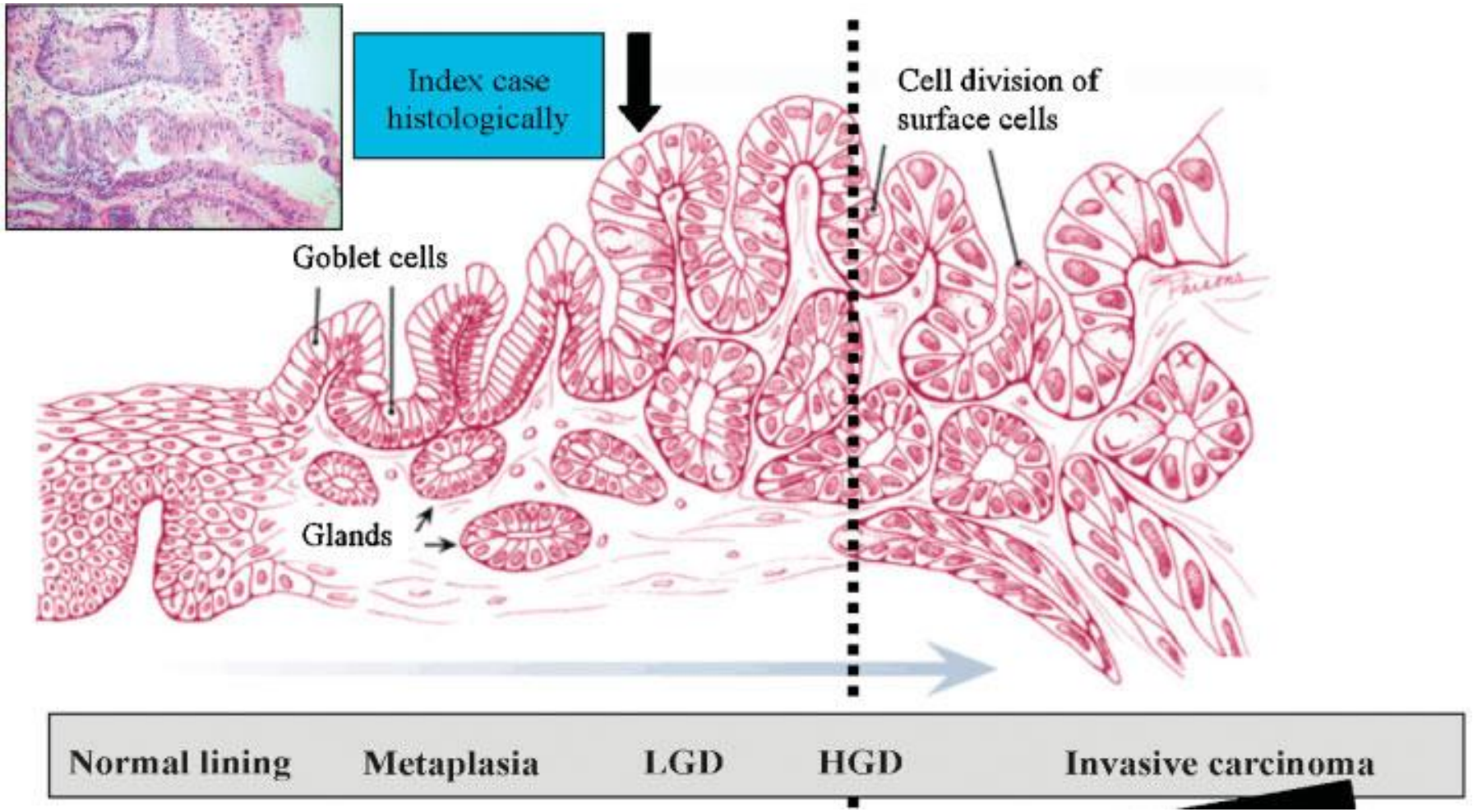
Disclosure Information

William M. Grady

I have the following financial relationships to disclose:

Freenome	Advisory Board Member
SEngine	Advisory Board Member
Guardant Health	Advisory Board Member
Diacarta	Advisory Board Member
Clinical trial support:	Janssen, Tempus, Lucid Technologies

BE→EAC progression sequence



Driven by genetic and epigenetic alterations=candidate biomarkers

Kopert, 2005

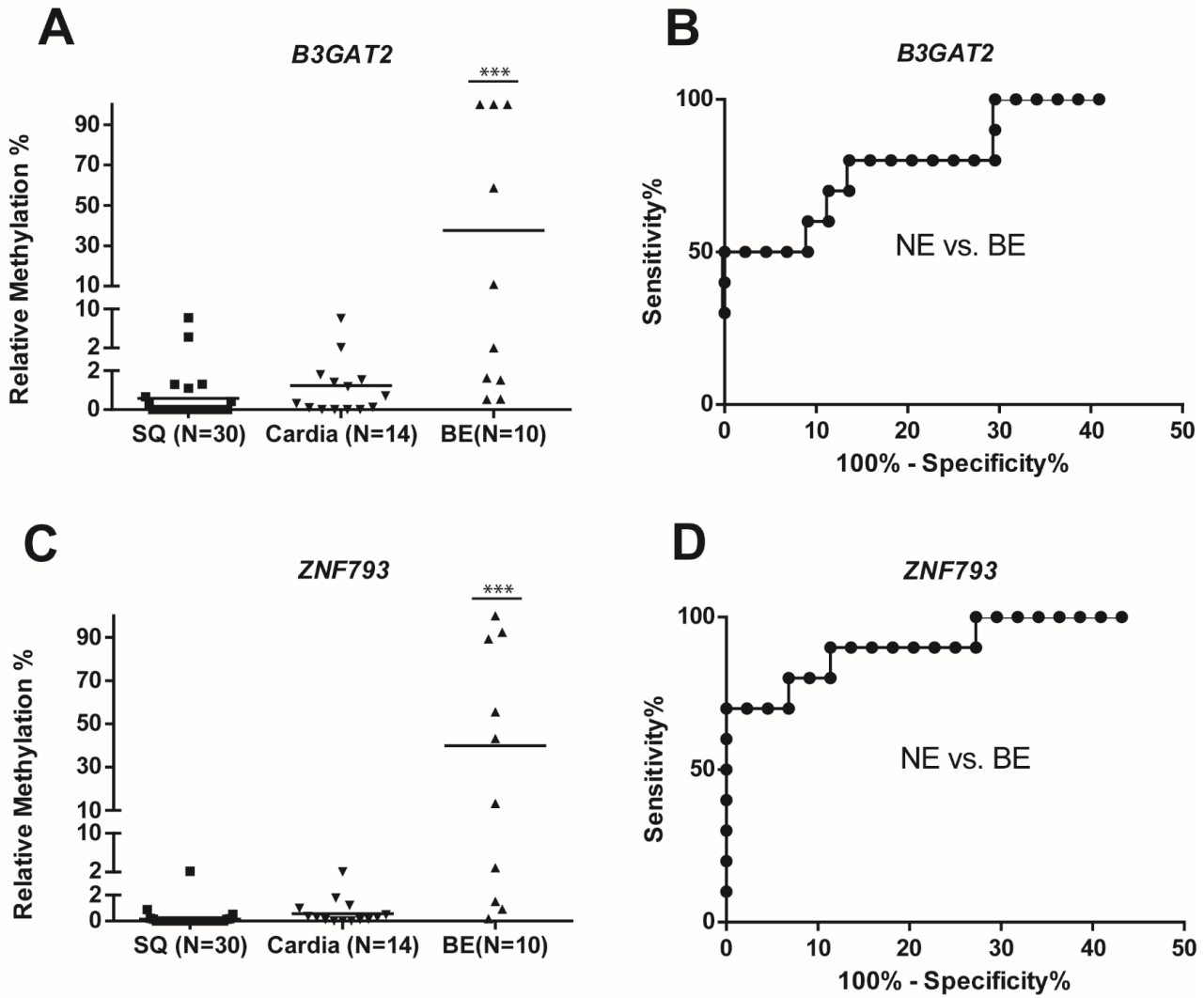
Methylated genes:
High potential for screening and surveillance biomarkers

- Aberrant methylation is common in both BE and EAC and more common in EAC

- Assay technology optimal for clinical assays

- Feasibility demonstrated for colon cancer screening
  - -Cologuard assay
  - -Epi proColon assay

Methylated *ZNF793* and *B3GAT2*: BE Detection Markers



Yu, 2014

Promising candidate BE screening markers

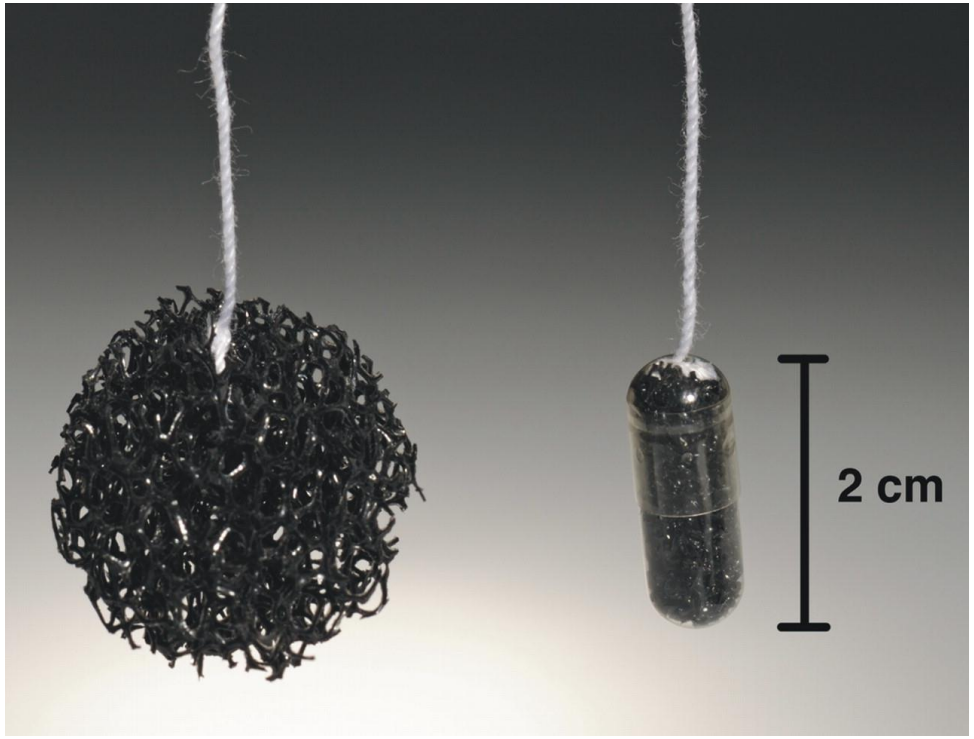
EDRN Phase 2/3 Biomarkers

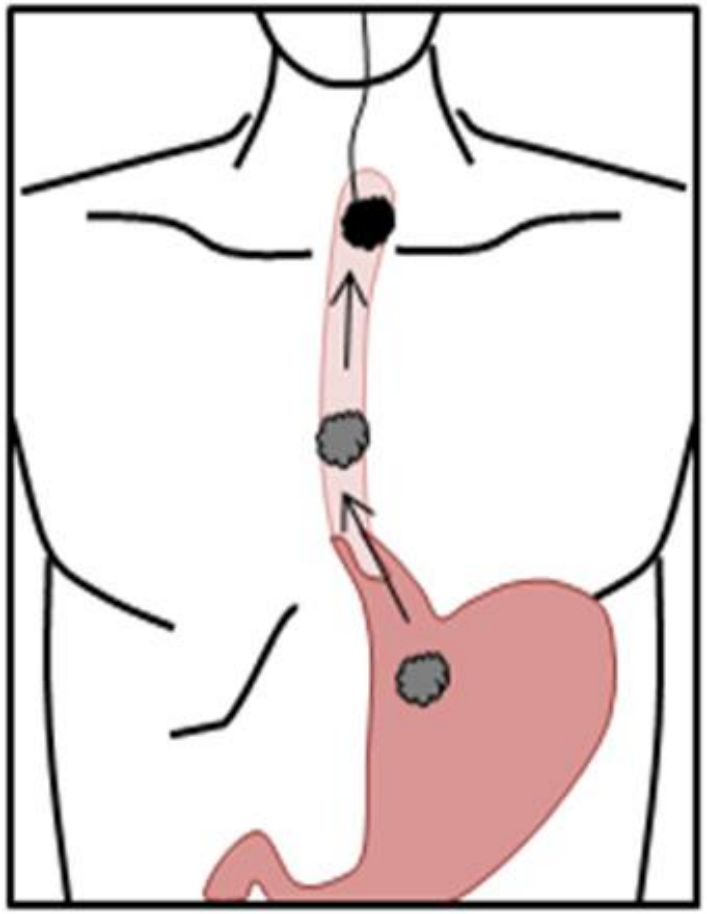
- TFF3
- Methylated *VIM* and *CCNA1*
- Methylated *B3GAT2* and *ZNF793*

- Clinical trials-EDRN and BETRNET sponsored

1st generation non-endoscopic tests for BE screening

Cytosponge





Kadri 2010

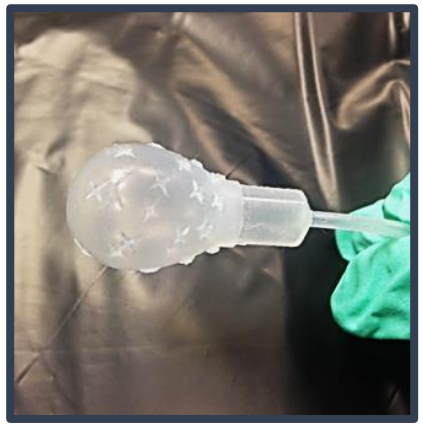
2nd generation device: Esocheck balloon

- ***Esochek*** combines a swallowed balloon to sample the esophagus with a DNA based biomarker test for diagnosing BE: **Esoguard** (FDA approved)

- Additional biomarkers to catch progression of BE to EAC in development → potential to create a panel for BE detection and continued monitoring

" Esophageal Pap Smear to detect BE / EAC "

Tethered, capsule sized balloon is swallowed



Balloon with structured surface is inflated in the stomach and withdrawn to resistance at distal esophagus to retrieve sample

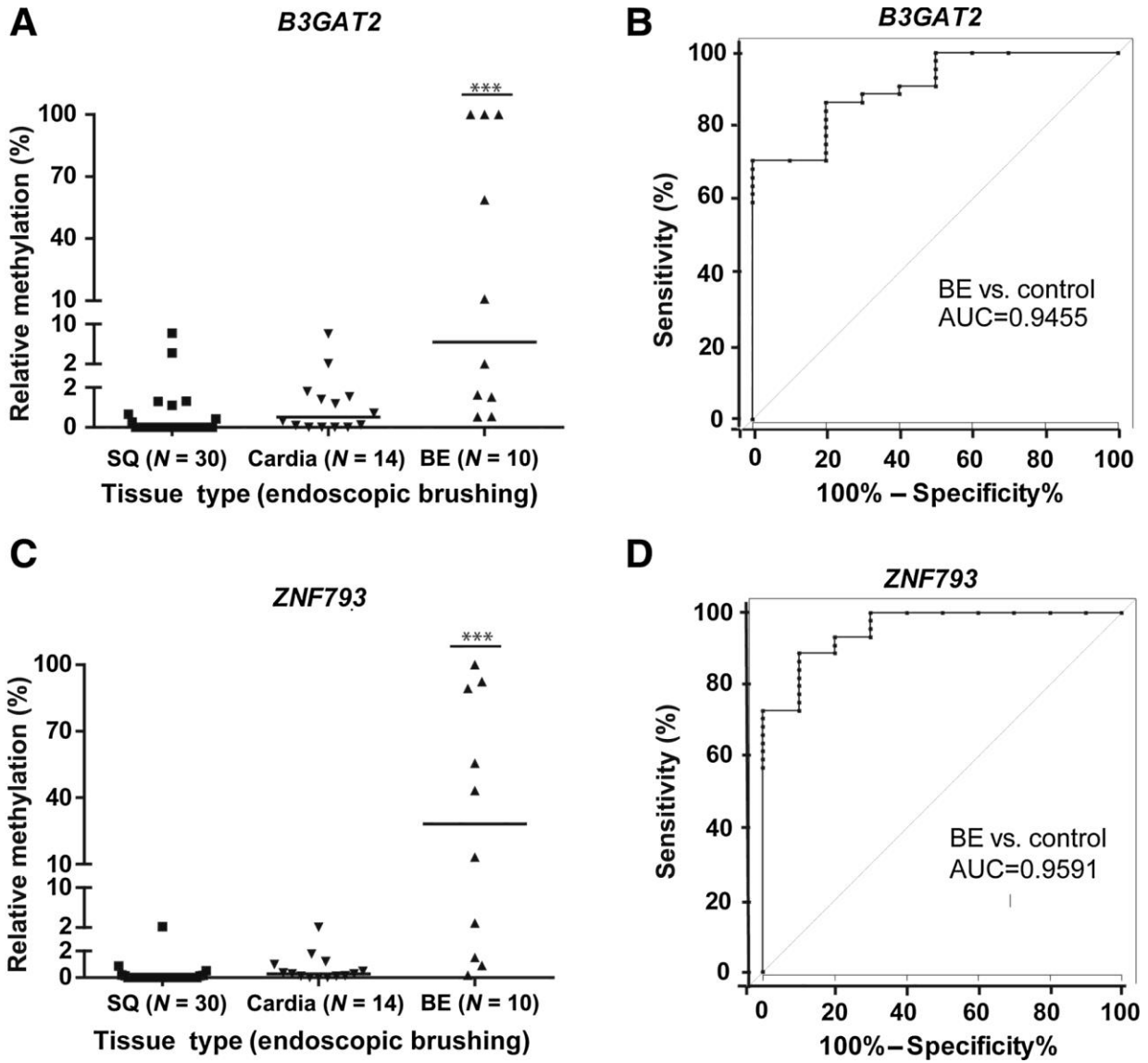
Inverted to protect sample on retrieval

Sample sent to lab for DNA assay

Courtesy: A Chak, Case Western Reserve University

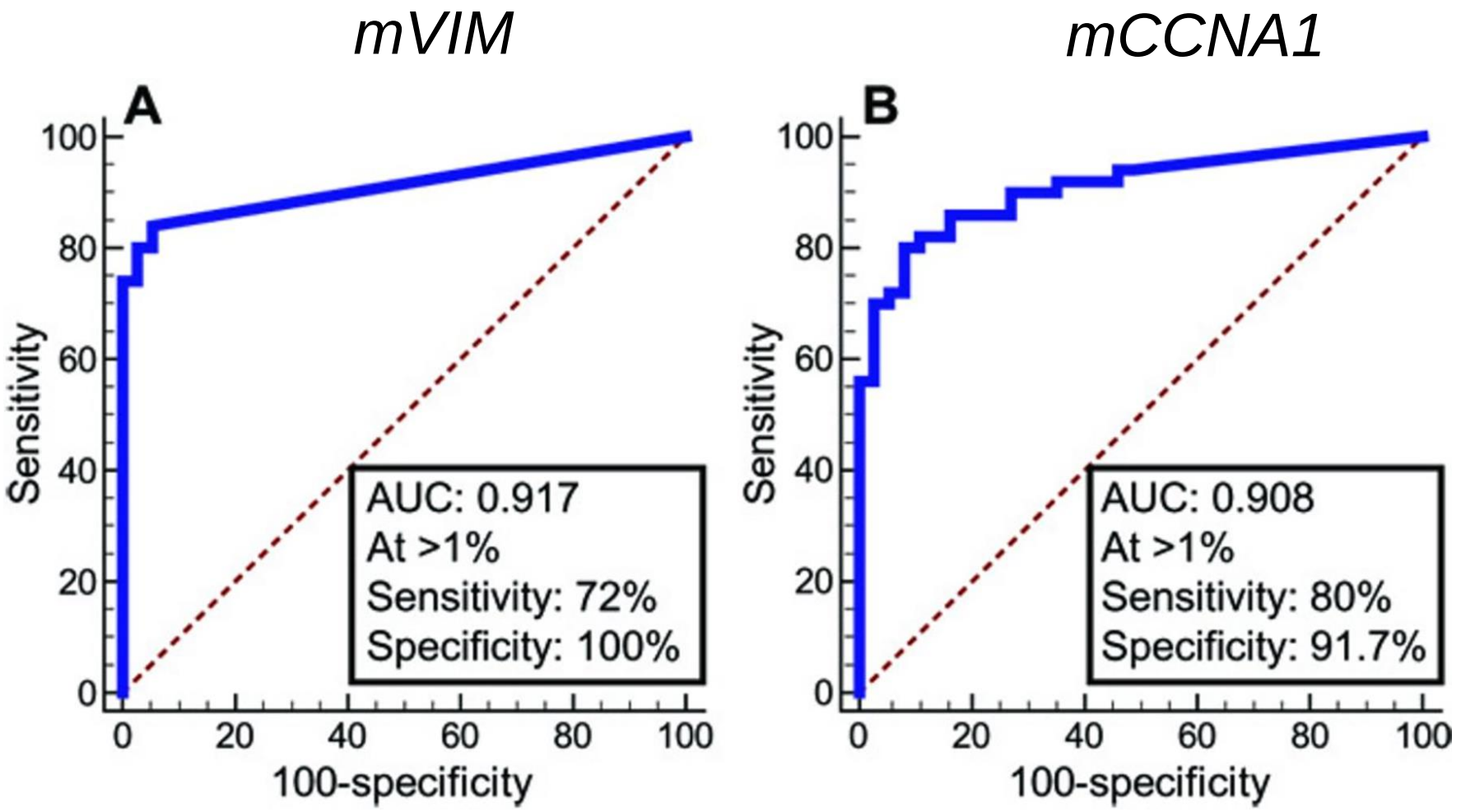
Methylated *ZNF793* and *B3GAT2*: Accurate BE markers in esophageal brushings

Sensitivity=100%
Specificity =70-73%



Yu et al. 2015

mVIM and *mCCNA1*: accurate for BE screening



Sensitivity=90% and Specificity =91%

Moinova 2018

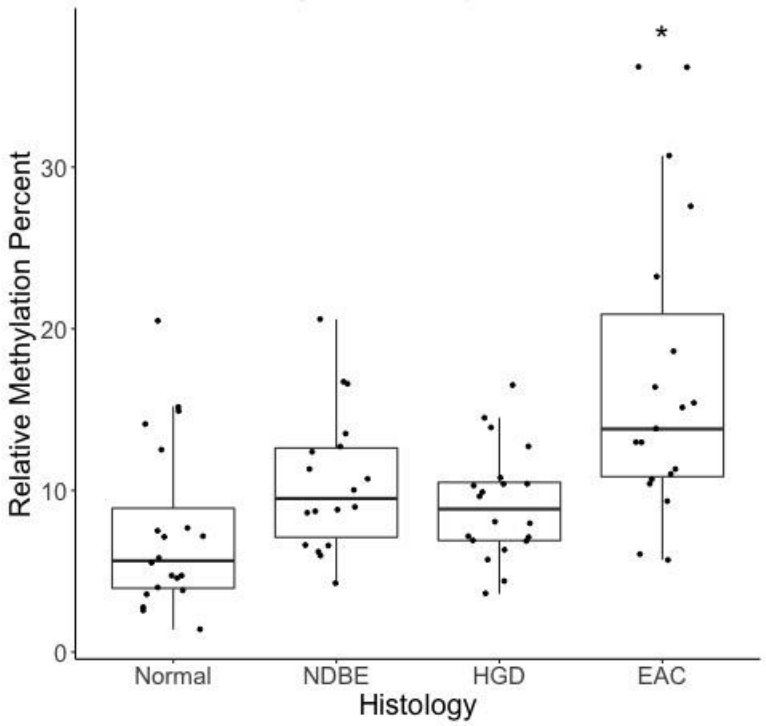
Candidate BE surveillance markers

Detection of high grade dysplasia or cancer

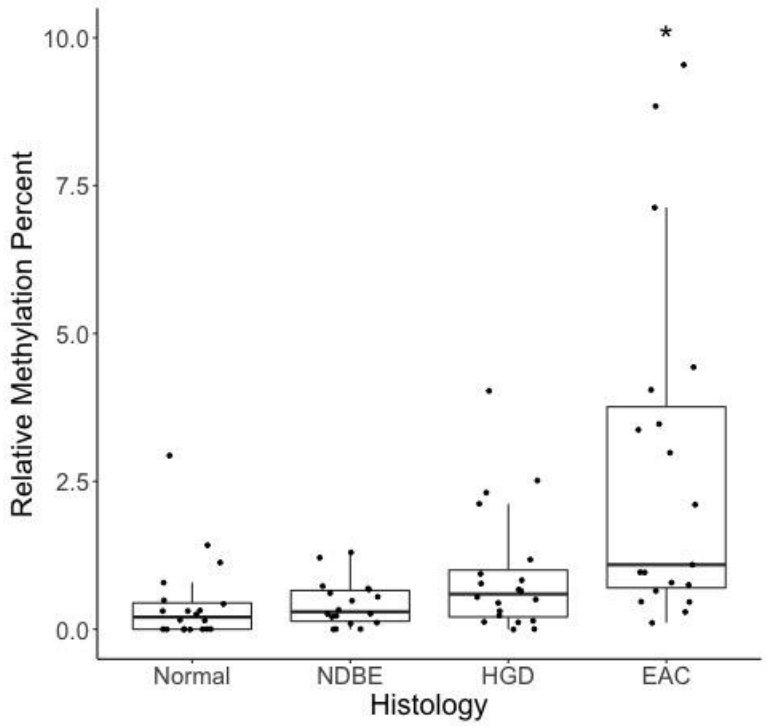
- P53 protein expression-IHC
- *TP53* mutations
- Aneuploidy/tetraploidy
- 17pLOH
- Methylated genes
  - *Cg65-M1*
  - *YP-M2*
  - *PO-M3*

Methylation status BE surveillance markers
Training Set Cohort

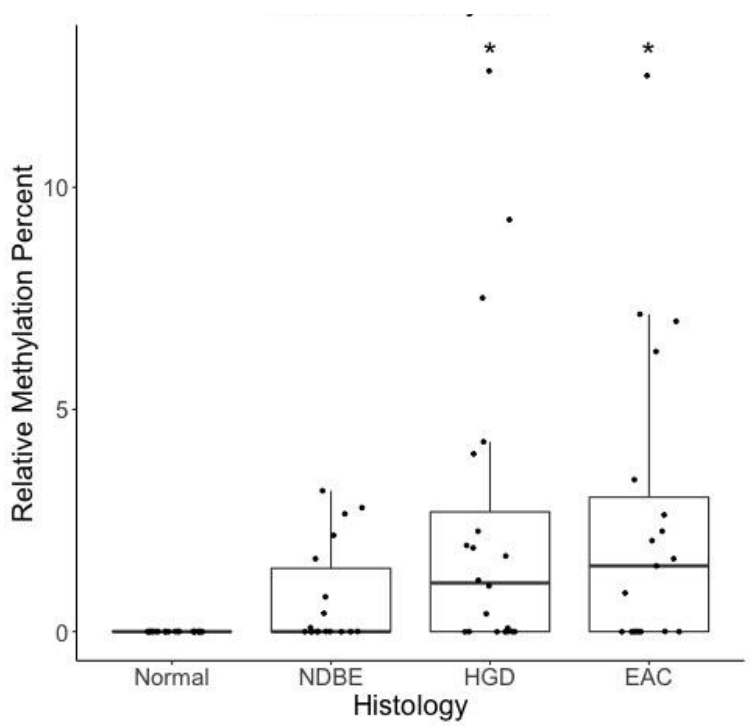
Cg-M1



YP-M2

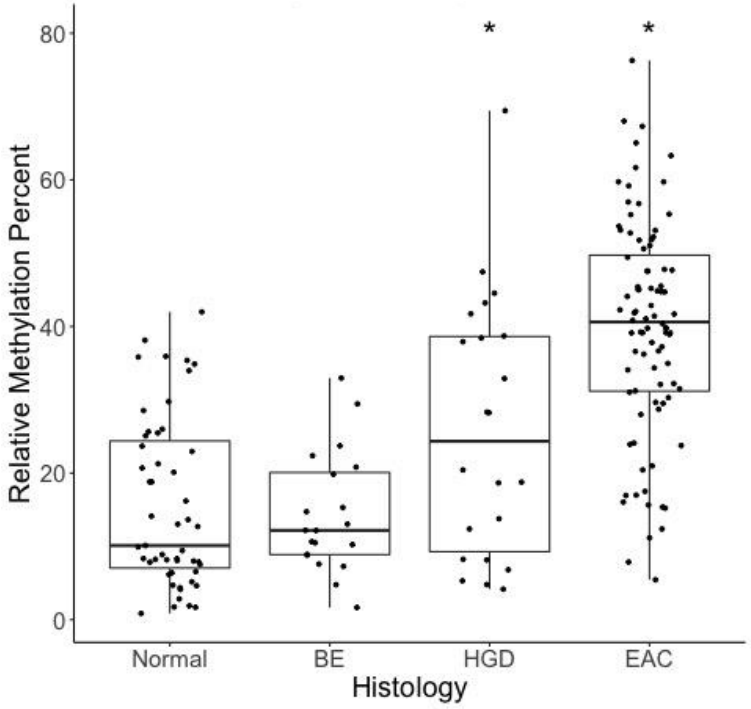


PO-M3

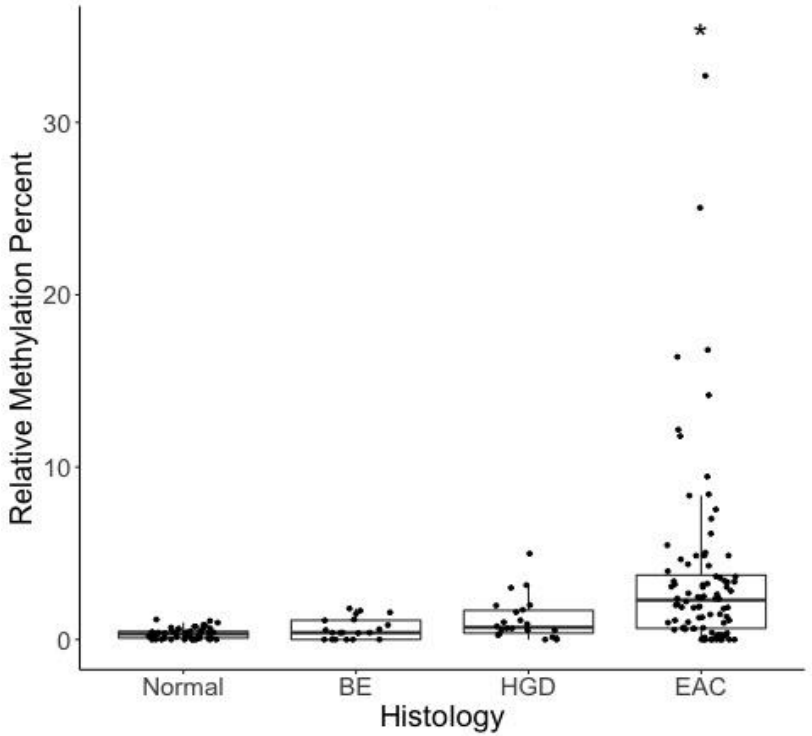


Methylation status BE surveillance markers
Validation Set Cohort

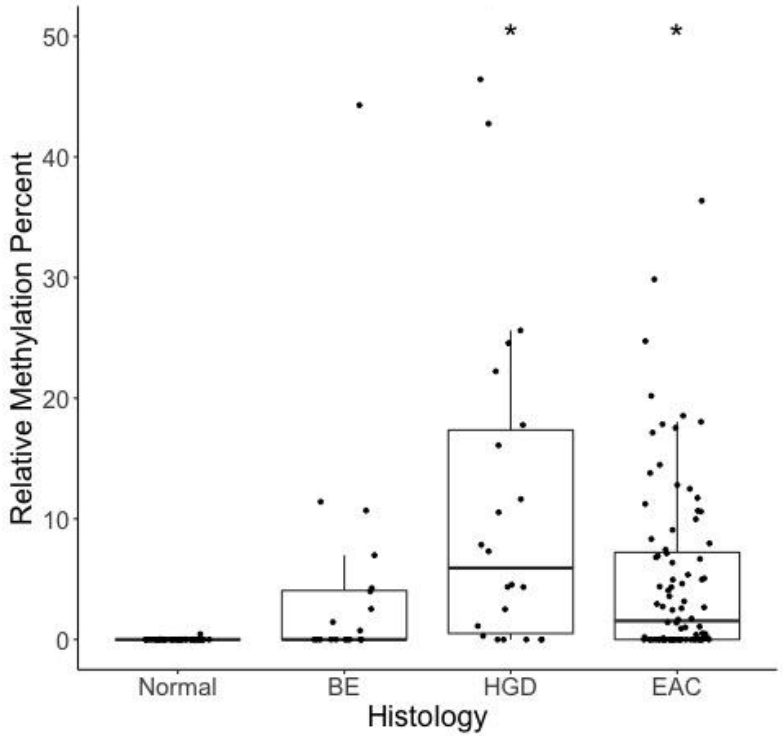
Cg-M1



YP-M2

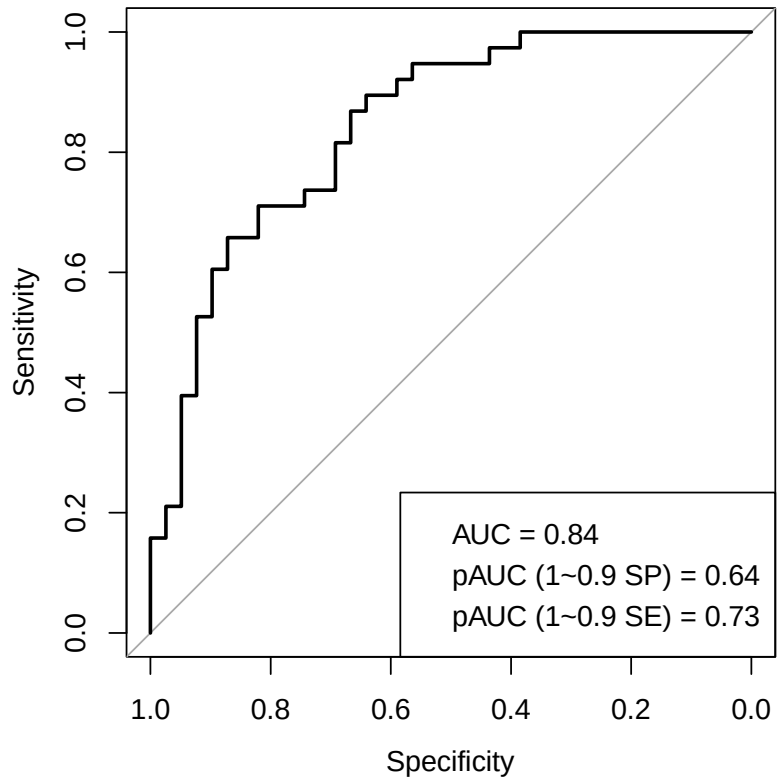


PO-M3



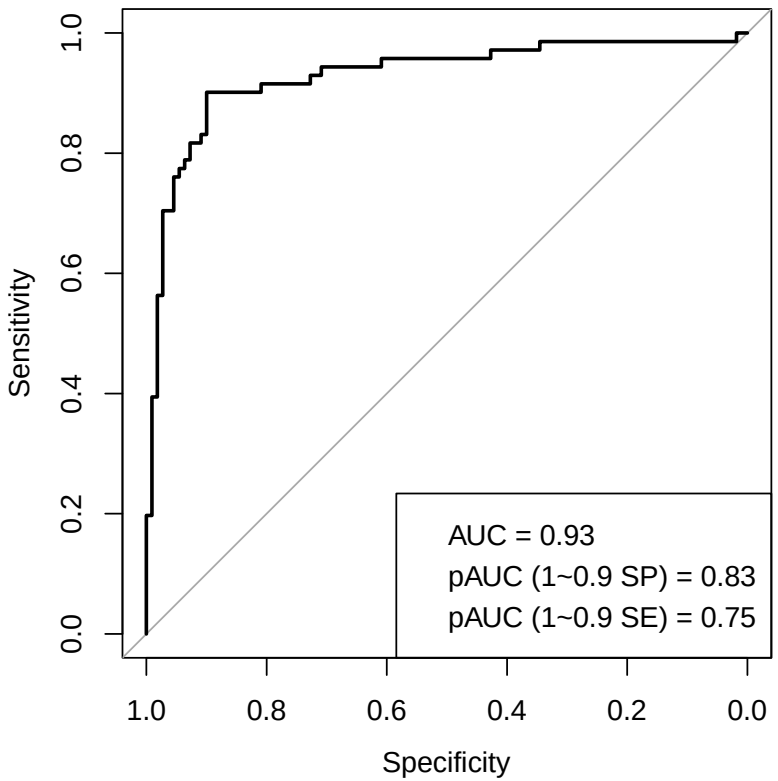
Candidate BE surveillance 3 marker panel

Training Set



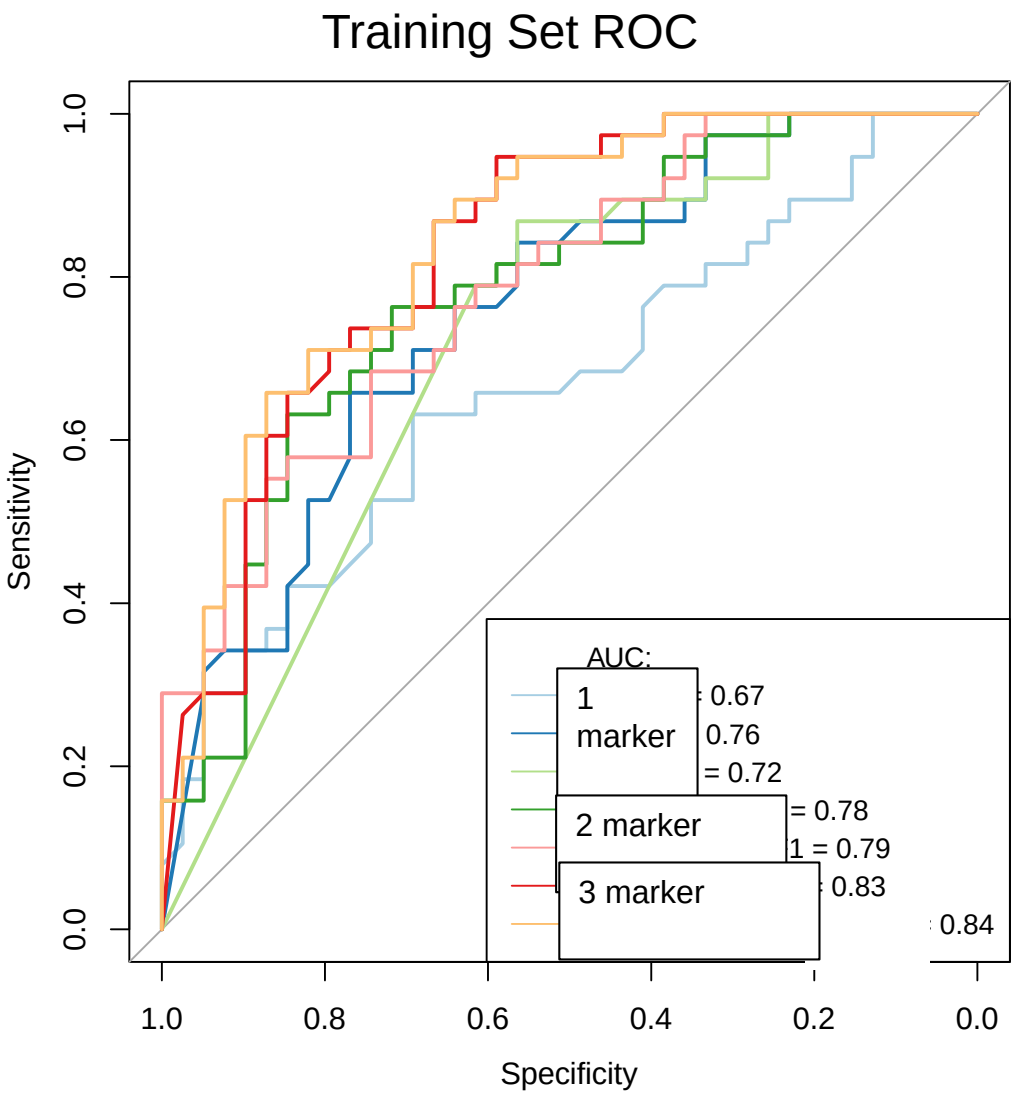
Accuracy = 0.74 Sensitivity = 0.67 Specificity = 0.82		True	
		HGDEAC	SQBE
Predicted	HGD+EAC	26	7
	SQ+BE	13	31

Validation Set

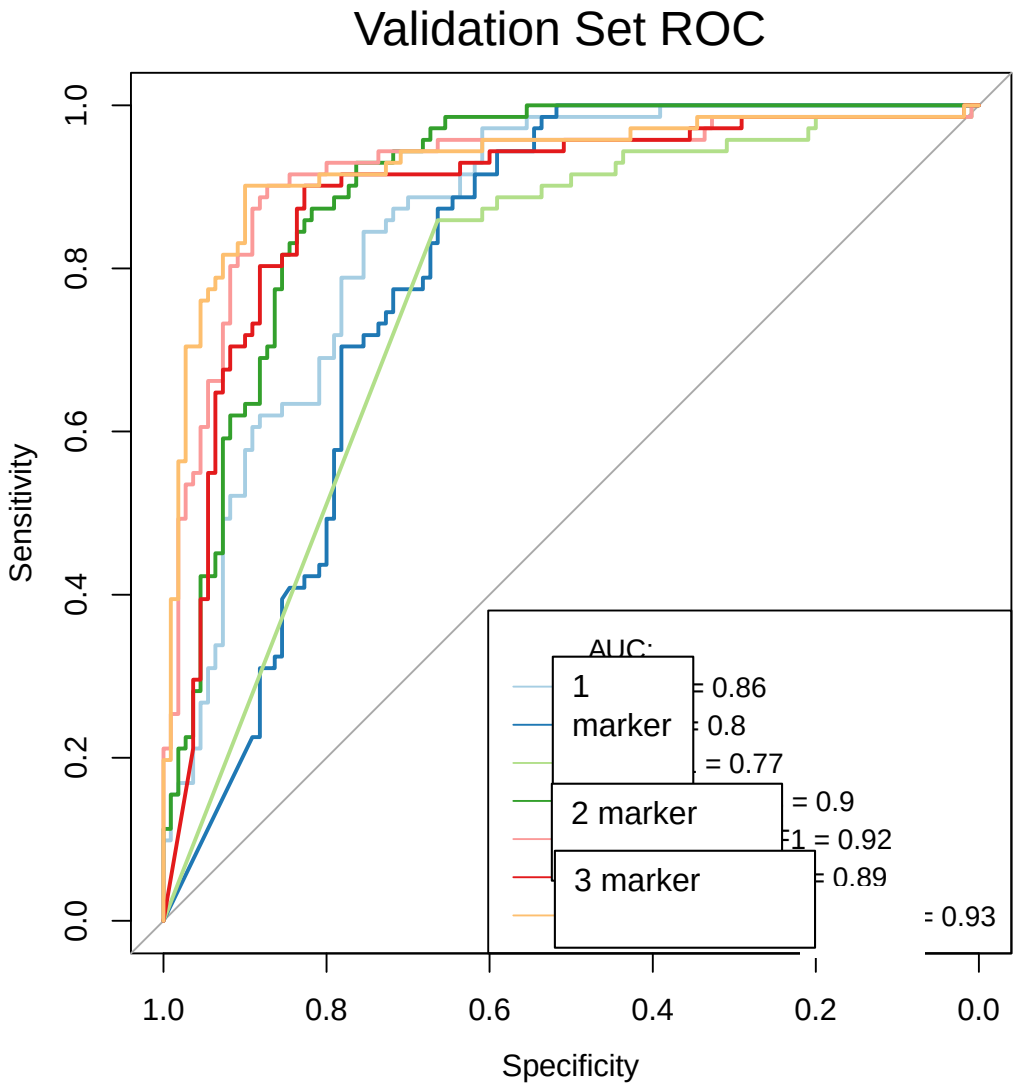


Accuracy = 0.88 Sensitivity = 0.93 Specificity = 0.80		True	
		HGD+EAC	SQ+BE
Predicted	HGD+EAC	102	14
	SQ+BE	8	57

Candidate BE surveillance 3 marker panel ROC



1 marker



Epigenetic alterations in Barretts esophagus: Insights into molecular mechanisms and their potential use in the clinic.

- **BE screening biomarkers**
  - Identify at risk population using safe, cheap test
  - Most promising marker: TFF3 cytology
  - Emerging markers: methylated genes-*VIM, CCNA1,B3GAT2, ZNF793*
- **BE surveillance biomarkers**
  - Identify high-risk BE patients
  - Prevent overtreatment of low-risk BE patients
  - Most promising markers: *TP53* mutations, aneuploidy, LOH events, methylated genes

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Table 1: Patient Demographic Information

Subject Information	Discovery set	Training set	Validation set
Total	167	76	181
Gender			
Female	32	10	55
Male	135	66	126
Age			
Range (Mean)	21-93 (64)	46-82 (64)	23-89 (64)
BMI			
Range (Mean)	21-40 (29)	19-57 (31)	NA
NA	131	3	
Smoking			
Yes (current or former)	36	47	105
Never	15	25	68
NA	116	4	8
NSAID Use			
Yes	NA	39	NA
No		35	
NA		2	
Diabetes (I or II)			
Yes	NA	17	NA
No		59	
NA		0	

- There is no significant difference between HGD/EAC vs SQ/BE for any variable in the three data sets ($p > 0.05$). Chi-Square test for category variables, ANOVA F-test for numerical variables.
- BMI=Body Mass Index; NSAID=nonsteroidal anti-inflammatory drug.

5 minute Q&A

Chair/Co-Chair/NCI
feed Zoom Chat questions to presenter
and Track Time
NCI and Production Team
answer Chat questions not related to presentations
and use Slack

SWOT

Colon & Esophageal
40 Minutes