Case Western Reserve University | Case Comprehensive Cancer Center

NCI CCC
A Comprehensive Cancer Center Designated by the National Cancer Institute

Biomarker Based Non-Endoscopic Detection Of Barrett's Esophagus (BE) And Esophageal Adenocarcinoma (EAC)

Sanford Markowitz
Helen Moinova
Joseph E. Willis
Amitabh Chak

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COI DISCLOSURE

- **Sanford Markowitz receives royalties on methylated DNA technology licensed to Exact Sciences and is a founder, board member, consultant, and inventor on patents licensed to Lucid Diagnostics.**

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The Case Esophagus Team

Helen Moinova

Amitabh Chak

Joe Willis

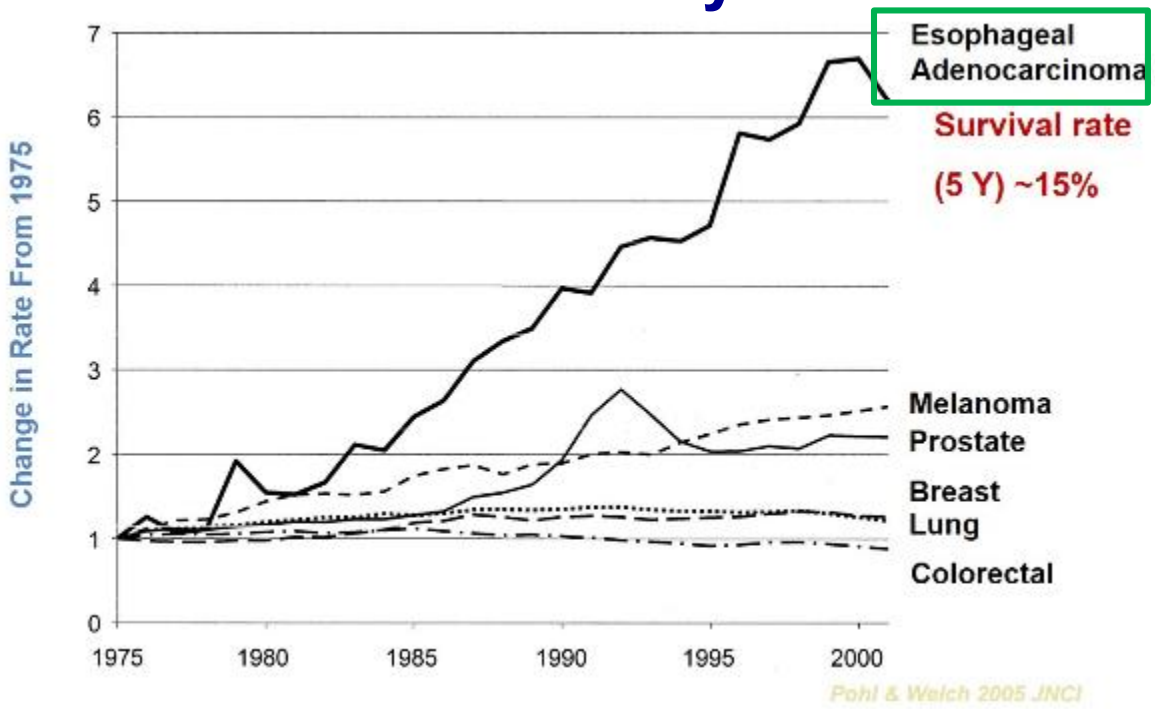
Tom LaFramboise

Kishore Guda

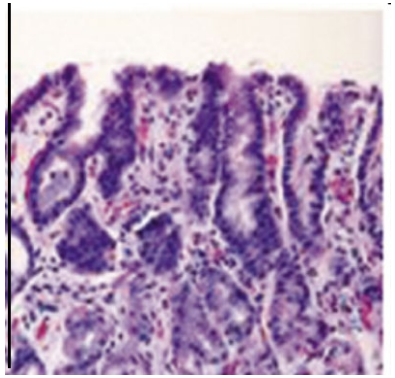
The EAC Challenge

Esophageal Cancer (EAC):

- Fastest growing cancer in U.S.
- 5-year survival < 20%
- Death toll now exceeds ovarian cancer
- Seldom detected early



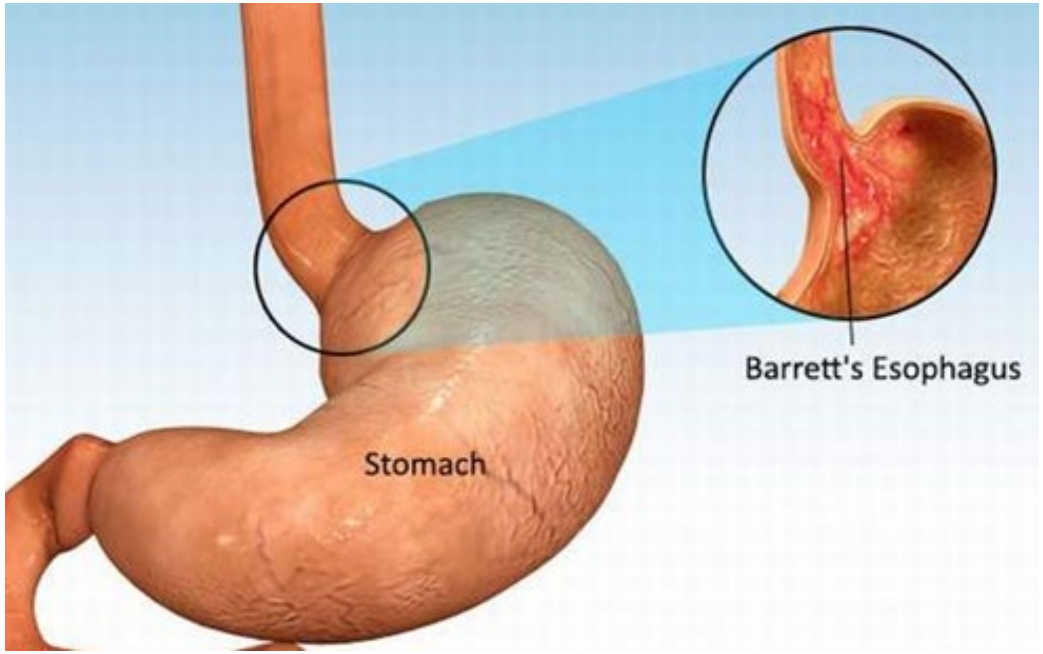
Cancer (EAC)



The EAC Opportunity

Barrett's esophagus (BE)

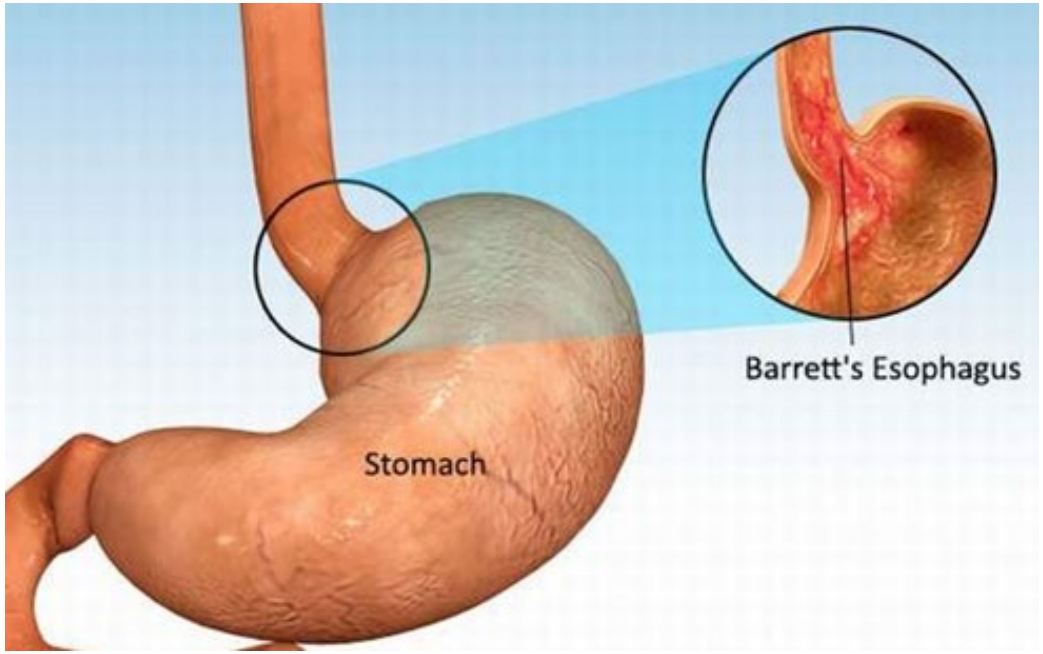
- Only known precursor to EAC
- Occurs in distal esophagus in patients with GERD



The EAC Opportunity

Barrett's esophagus (BE)

- Only known precursor to EAC
- Occurs in distal esophagus in patients with GERD
- Detection of BE and ablation of dysplastic BE can prevent cancer



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Challenges to BE Screening by EGD

Challenges to BE Screening by EGD

- EGD is costly, requires sedation, day off work.
- EGD Screening only recommended by AGA, and only in those with chronic GERD + additional risk factors.
- EGD screening, even in GERD, not generally accepted by primary care physicians or patients.
- Challenge: Antecedent BE recognized beforehand in <10% of EAC cases.

The Need

- **Needed: Non-EGD Biomarker Driven approaches that can detect BE more easily and at less expense than EGD.**

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Biomarker Approach

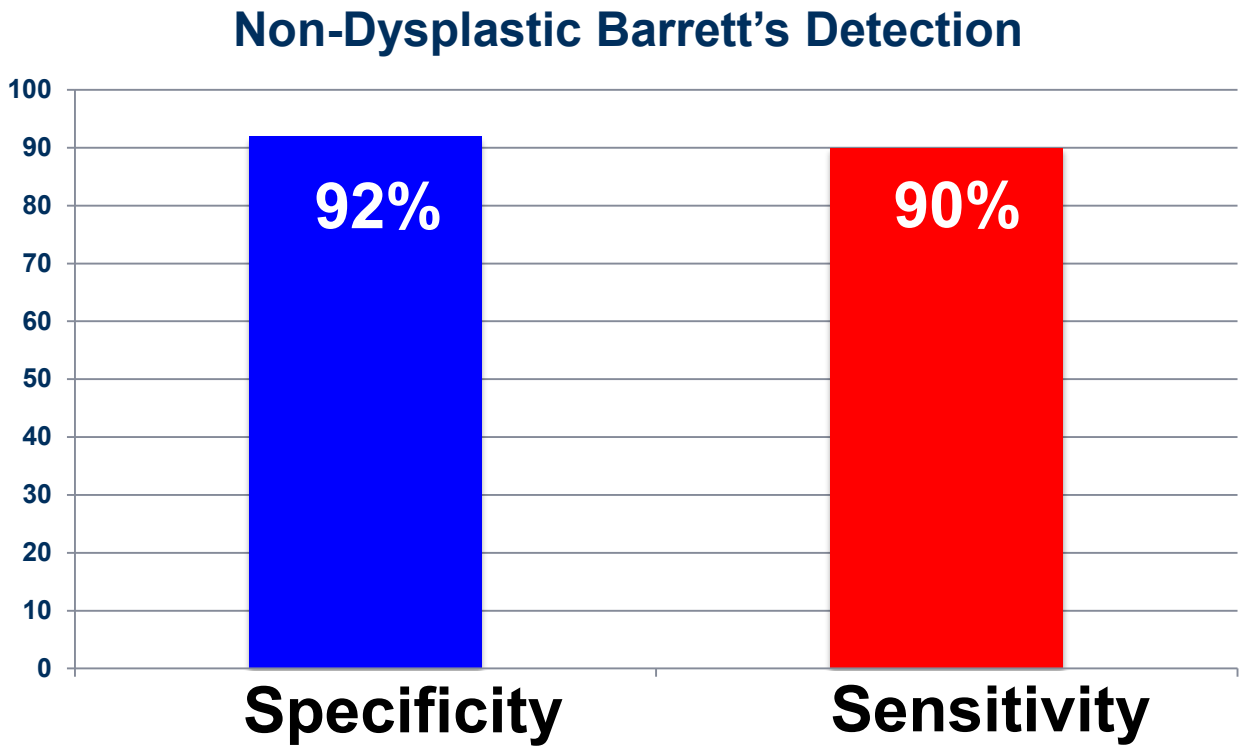
SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

Identifying DNA methylation biomarkers for non-endoscopic detection of Barrett's esophagus

Helen R. Moinova,[1] Thomas LaFramboise,[2,3] James D. Lutterbaugh,[1] Apoorva Krishna Chandar,[1] John Dumot,[1] Ashley Faulx,[1] Wendy Brock,[1] Omar De la Cruz Cabrera,[4] Kishore Guda,[2] Jill S. Barnholtz-Sloan,[2] Prasad G. Iyer,[5] Marcia I. Canto,[6] Jean S. Wang,[7] Nicholas J. Shaheen,[8] Prashanti N. Thota,[9] Joseph E. Willis,[2,10,11*†] Amitabh Chak,[1,2,11*†] Sanford D. Markowitz[1,2,3,11*†]

Moinova *et al.*, *Sci. Transl. Med.* **10**, eaao5848 (2018) 17 January 2018



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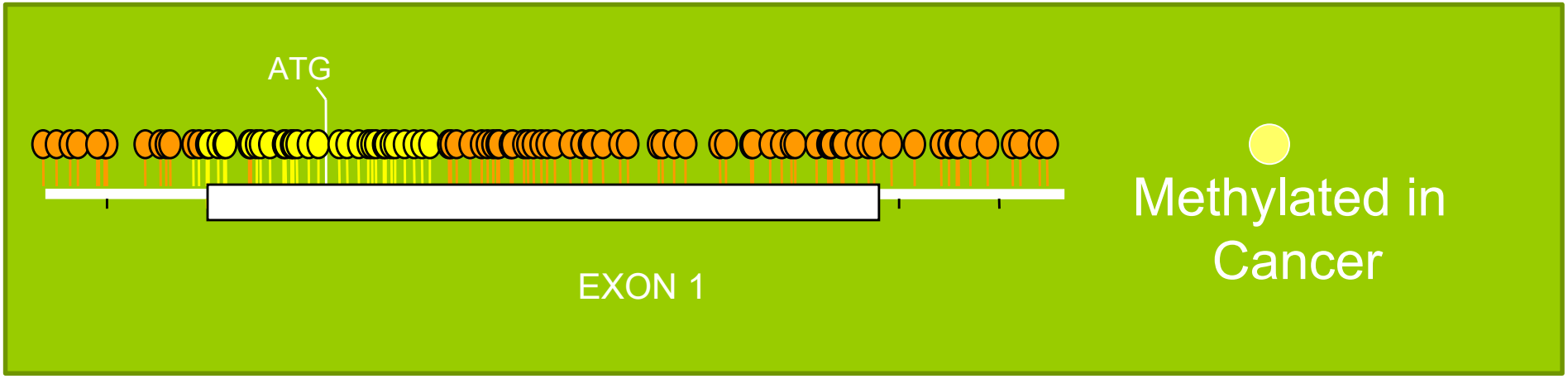
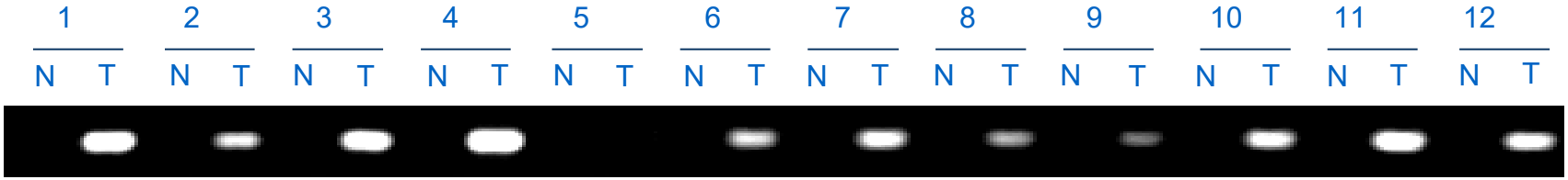
Biomarker Approach

i) Methylated DNA Biomarker Panel

ii) Swallowable Esophageal Sampling Device

Vimentin Gene Methylation (mVim) is a Colon Cancer Biomarker





Methylated in 80% of Colon Cancer Cases

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Vimentin Gene Methylation (mVim) is a Colon Cancer Biomarker

Methylated Vimentin DNA: Commercialized by Exact Sciences For Stool DNA Detection of Colon Cancer (ColoSure™, LabCorp)

Cancer Epidemiology, Biomarkers & Prevention, April 2012

Vimentin Methylation as a Gastrointestinal Cancer Biomarker Moinova *et al.*

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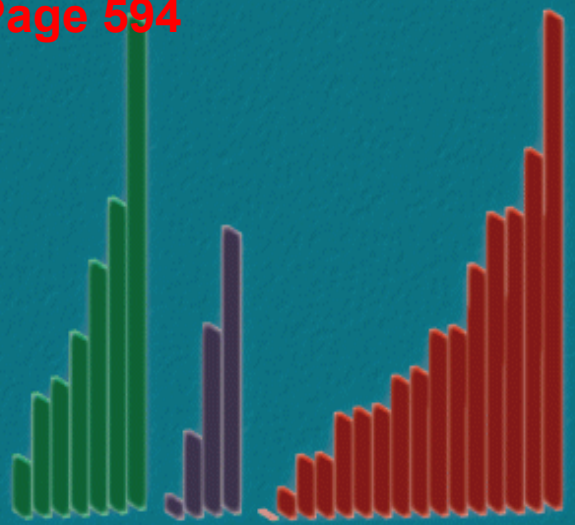
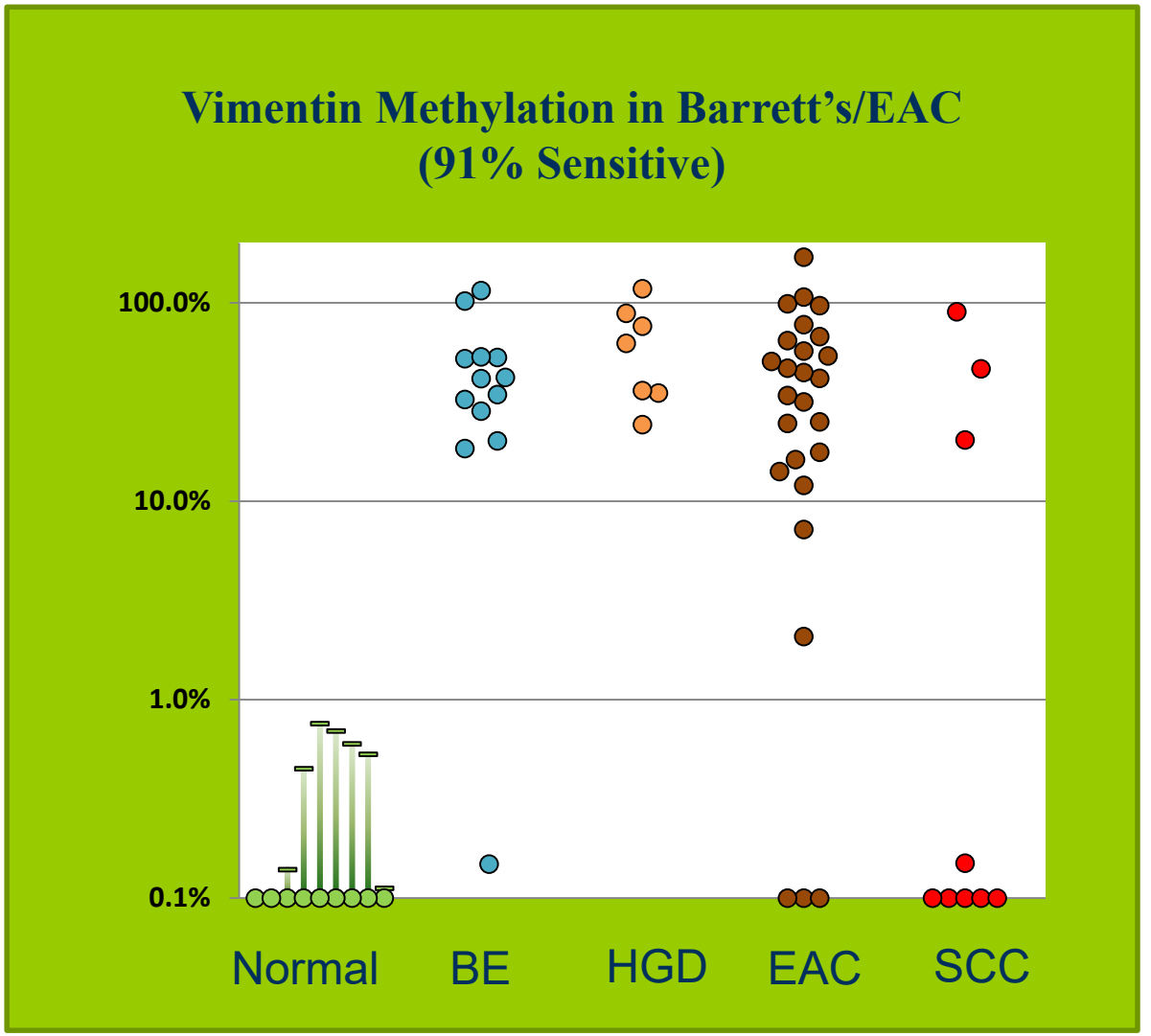
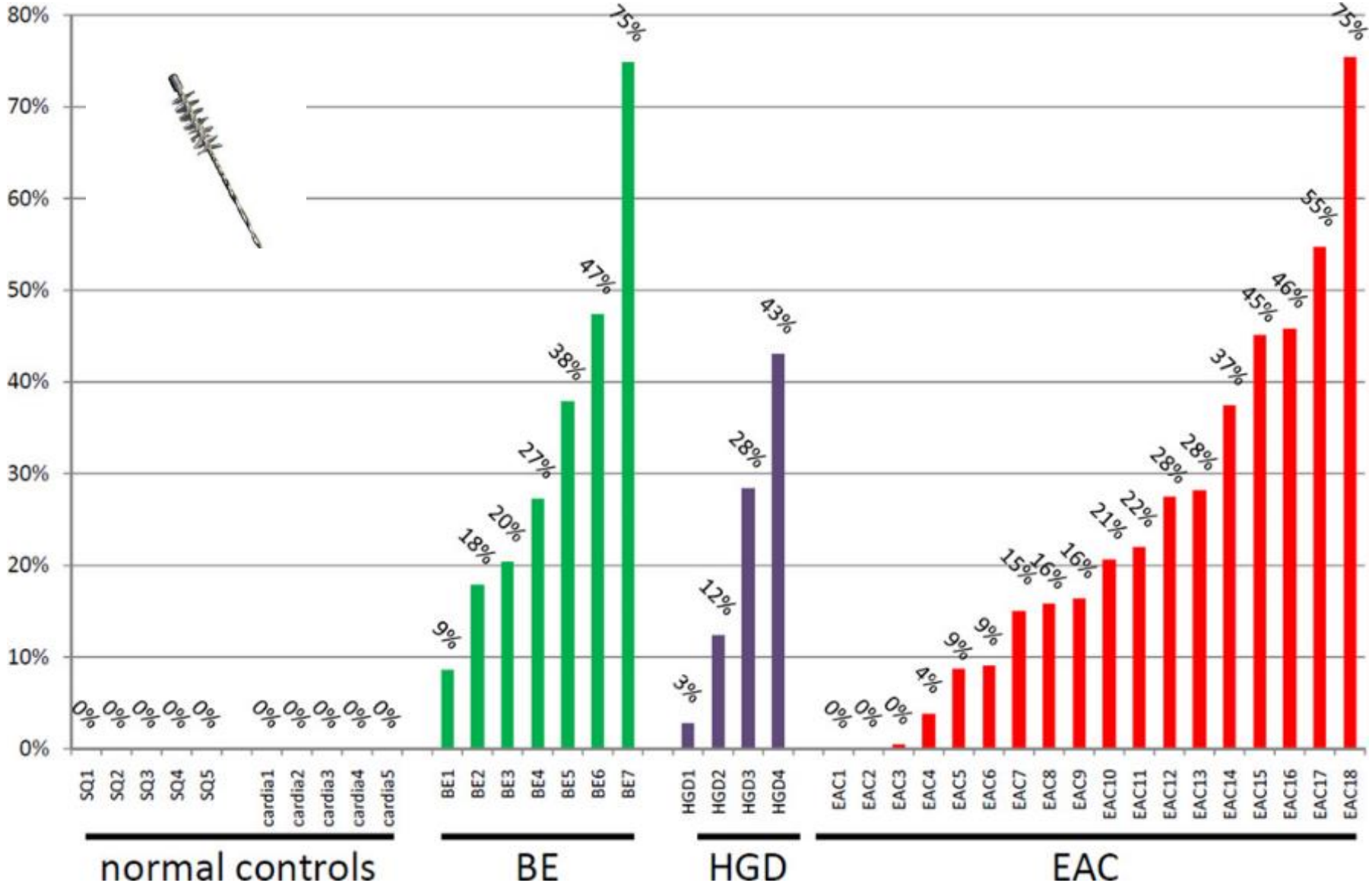


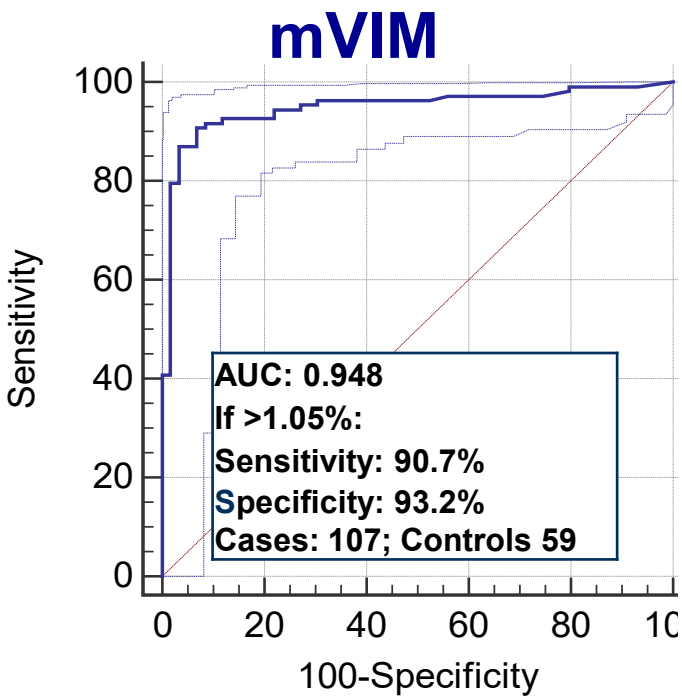


Pilot Study – Molecular Cytology: 90% of BE Detected by mVIM DNA on Esophageal Brushings



Molecular Cytology: mVim in Esophagus Cytology Brushings (N=310)

Training set



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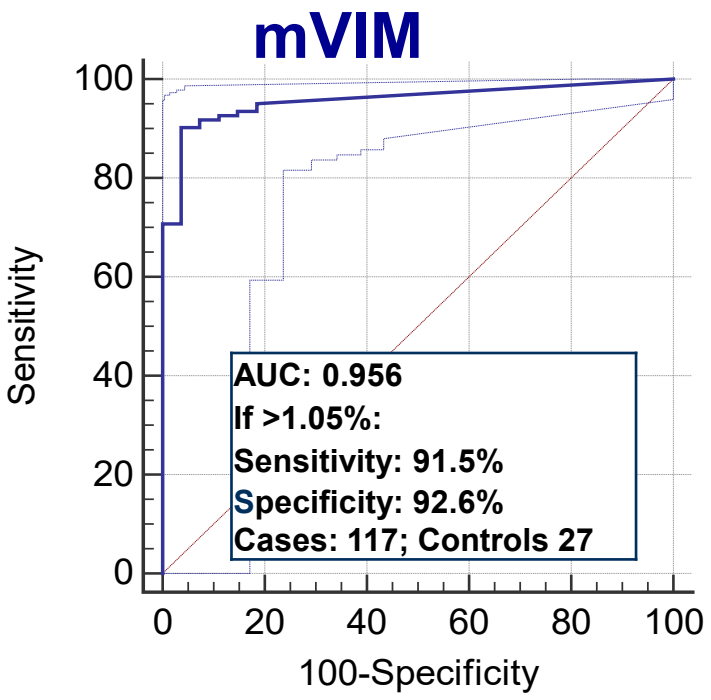


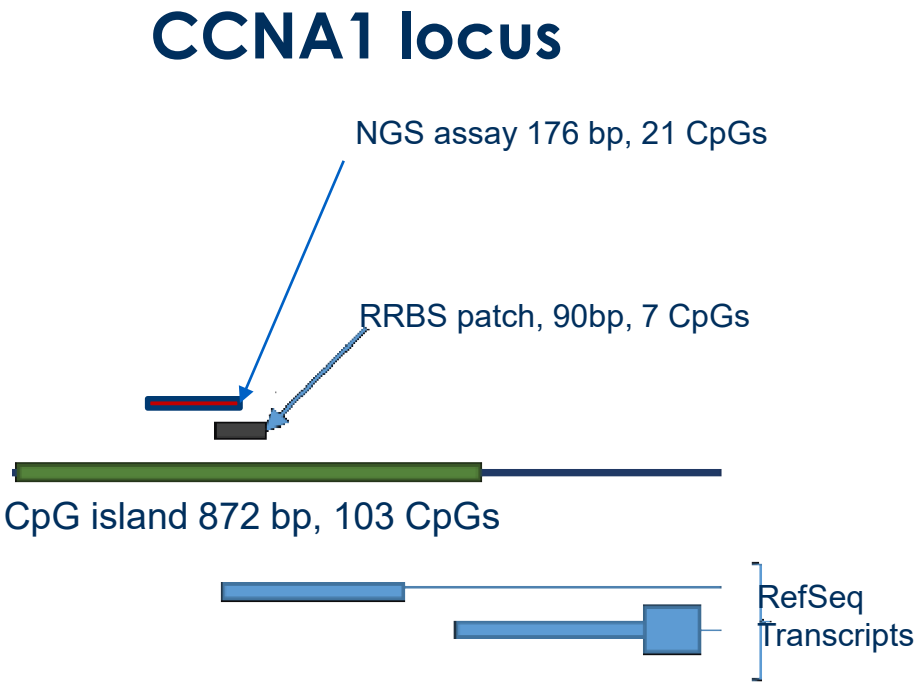
New Complementary Methylation Marker

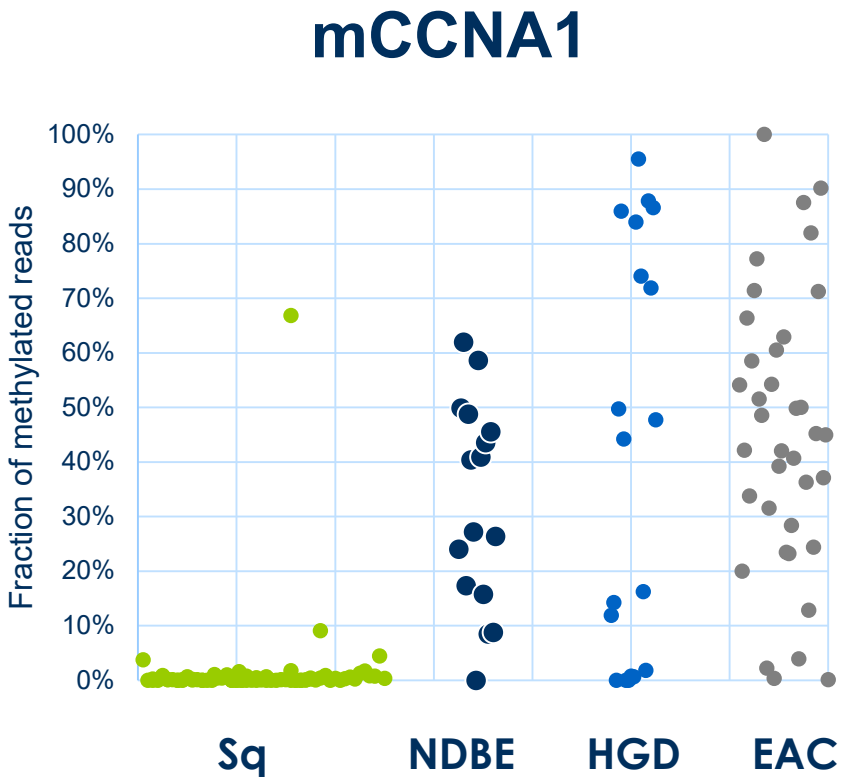
- **If One Marker is Good, Would Two Markers Be Better?**

New Complementary Methylation Marker

- **If One Marker is Good, Would Two Markers Be Better?**
- **Genome Wide RRBS in 72 Biopsies: 26 EAC/Sq pairs; 15 BE; 5 EAC Cell Lines**

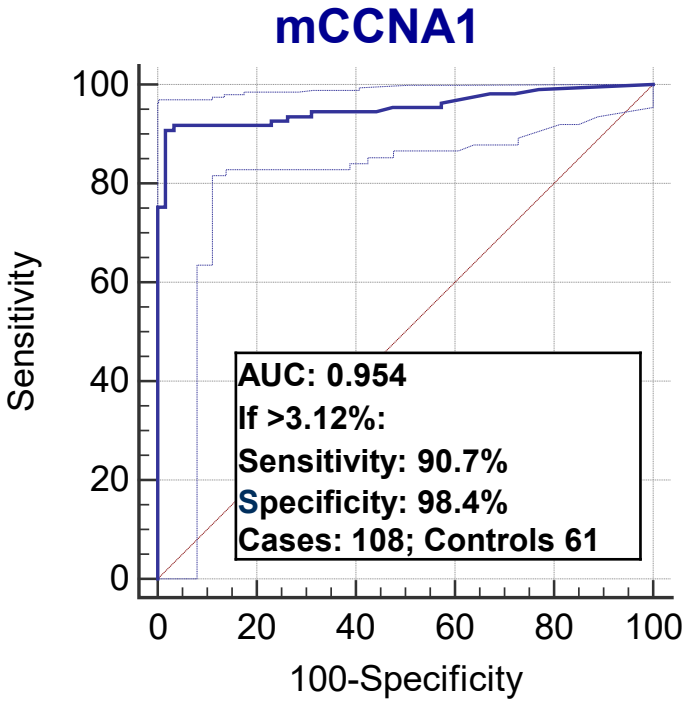
New Complementary Methylation Marker (mCCNA1)





Molecular Cytology: mCCNA1 in Esophagus Cytology Brushings (N=313)

Training set



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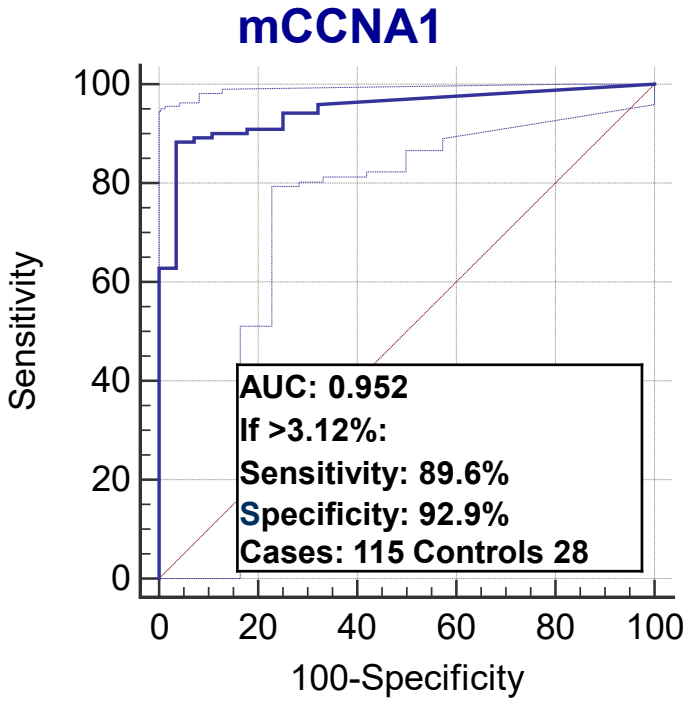

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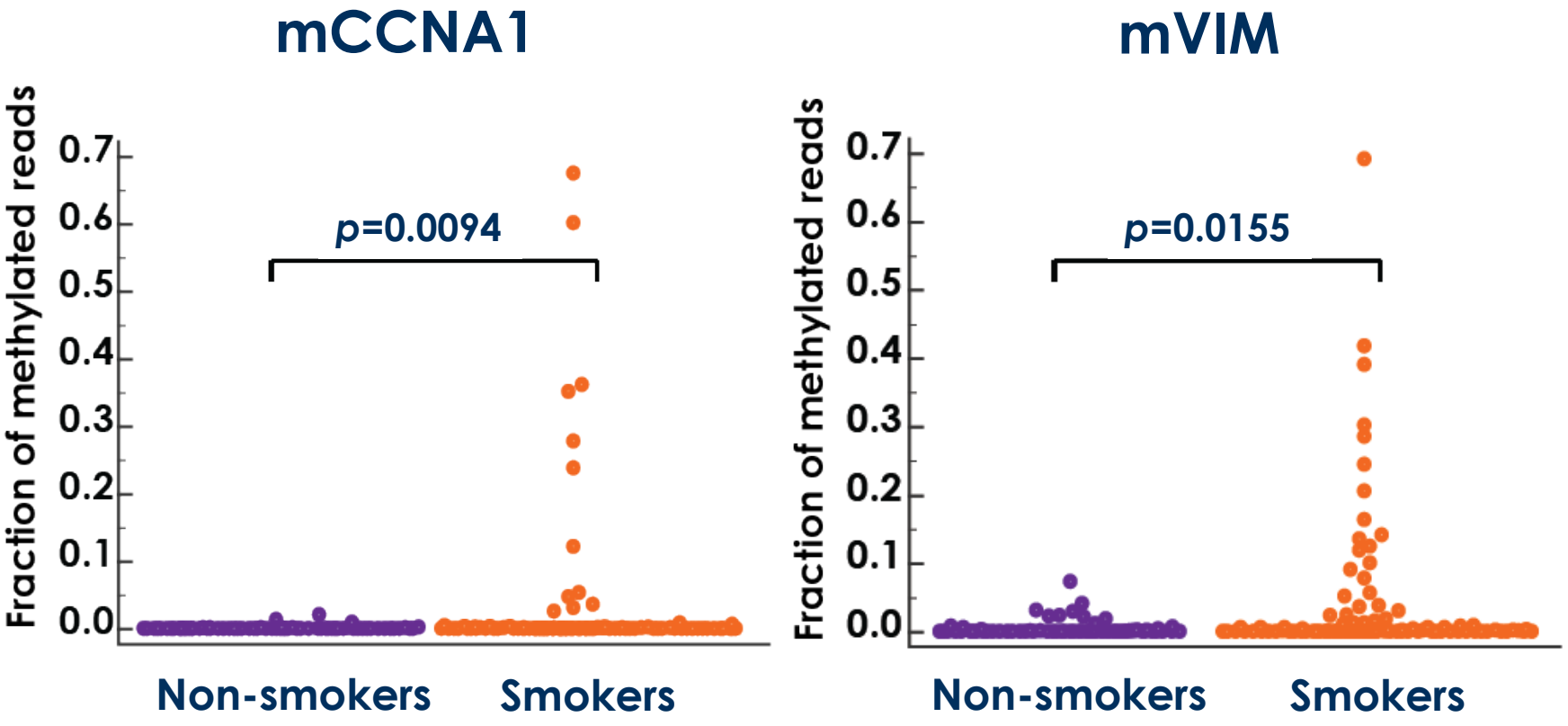
Molecular Cytology: mVIM + mCCNA1 in 313 brushings

	mVIM (Positive if > 1.05%)		*mCCNA1 (Positive if > 3.12%)*		*Either mVIM or mCCNA1 Positive*	
	%	#	%	#	%	#
Specificity Control GEJ (GERD , EE, other)	93%	86	97%	89	91%	84
Sensitivity NDBE	92%	71	80%	69	92%	72
Sensitivity LGD	94%	33	91%	32	94%	34
Sensitivity HGD	87%	23	100%	23	100%	23
Sensitivity Cancer	91%	97	95%	99	96%	100

Additional Specificity Studies

Smoking associated DNA methylation in proximal esophagus brushings



The Challenge

- **Comfortable Non-Endoscopic Sampling of the Distal Esophagus / GE Junction**
- **Without Sampling the Proximal Esophagus and Throat**

JASSS Balloon

Joe/Amitabh/Sandy's Swallowable Sampling Balloon

Capsule sized balloon

Tethered balloon is swallowed

Balloon with structured surface:
i) inflated in the stomach
ii) pulled back to sample distal esophagus

Balloon deflated for retrieval

JASSS Balloon – Commercialized as EsoCheck

YouTube Video

32 seconds

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Study Design

- Patients with BE, EAC, or GERD controls were recruited for EsoCheck prior to EGD
- EsoCheck sampling was performed
- Balloons were placed in vials and frozen
- DNA was extracted from balloons, bisulfite converted, and sequenced with NGS
- A software pipeline calculated % DNA reads arising from bisulfite converted methylated versus unmethylated Vim and CCNA1 templates

Results - Tolerance

- Procedure took mean 3.1 minutes (range, 1 – 14 min).
- 72% of the subjects rated overall tolerance as excellent
- 93% preferred EsoCheck to EGD and were willing to repeat it again.
- Scores of 1 or 2 on a 10-point Likert scale, denoting little to no anxiety, pain, or choking, were reported by 75%, 95%, and 82% of subjects, respectively.

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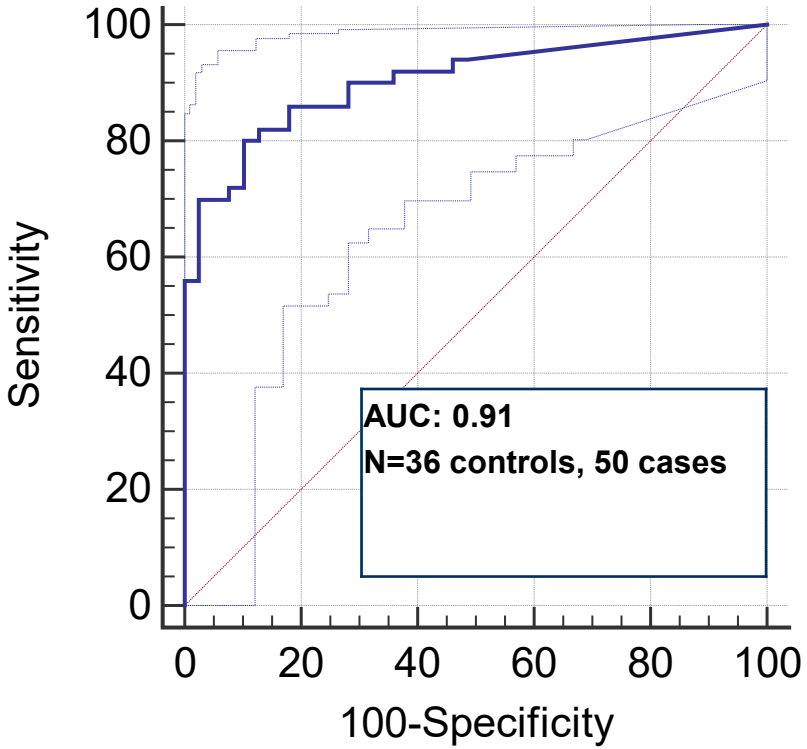
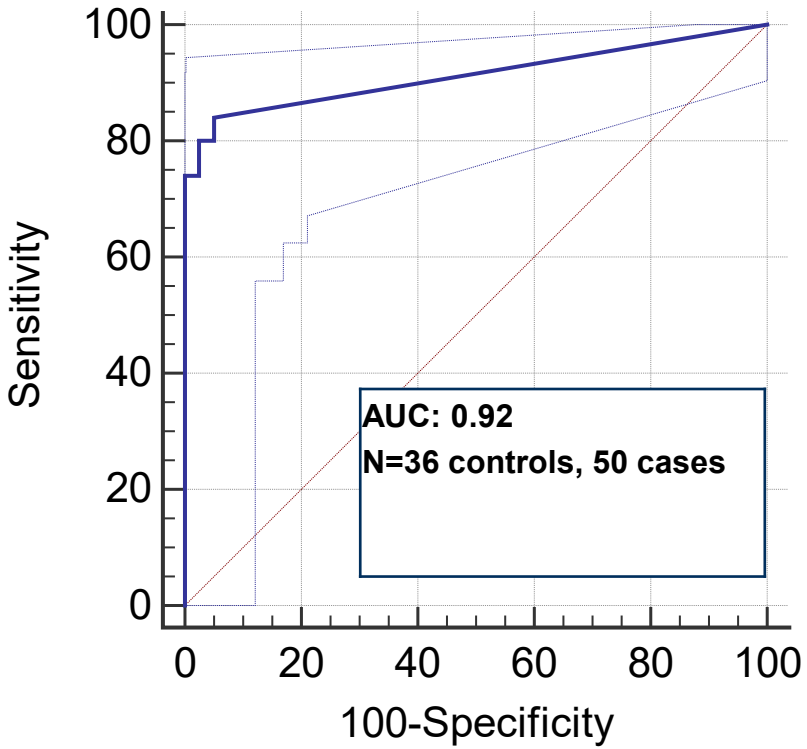
Performance Equals Endoscopic Brushings

mVIM



mCCNA1



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Performance in 86 Subjects

	Sample #	*mVIM (Positive if >1.0%)*	*mCCNA1 (Positive if >1.0%)*	*Either mVIM Or mCCNA1 Positive*
Specificity on Controls	**36**	**92%**	**100%**	**92%**
Sensitivity: Non-Dysplastic BE (>1cm)	**31**	**81%**	**71%**	**90%**
Sensitivity: All Dysplastic BE	**11**	**73%**	**73%**	**82%**
Sensitivity: All Cases	**50**	**80%**	**72%**	**88%**

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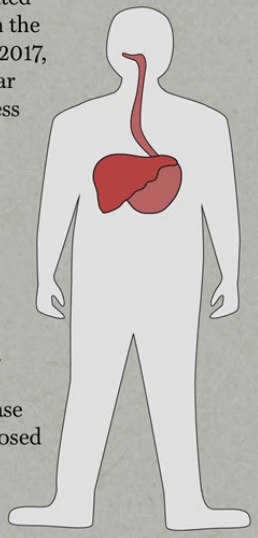
CONCLUSIONS

- **EsoCheck encapsulated balloon can sample the distal esophagus with excellent tolerability and acceptability.**
- **Methylated Vimentin and CCNA1 can be successfully assayed on EsoCheck samples by NGS bisulfite sequencing.**
- **BE and EAC detected with high sensitivity and specificity, demonstrating the feasibility of non-endoscopic unsedated BE screening.**

Summary

Esophageal Carcinoma

Esophageal Carcinoma caused an estimated **15,690 deaths** in the United States in 2017, and has a five-year survival rate of less than **20%**



Esophageal Carcinoma is associated with a poor prognosis because the disease is typically diagnosed at late stages

Barrett's Esophagus is the precursor for Esophageal Carcinoma, but routine clinical visits do not check patients for this lesion

Detecting Barrett's Esophagus currently requires endoscopic evaluation, but a new DNA biomarker screening method and balloon-based sampling device could allow for quick and non-invasive diagnosis

Endoscope diagnosis	DNA Biomarker
Time-consuming	Samples collected in less than five minutes
Patients must be sedated	Patients fully conscious
Based on tissue characteristics	DNA-sequence based
Expensive	Inexpensive

Science Translational Medicine | AAAS

Moinova *et al.*, *Science Translational Medicine* (2018)

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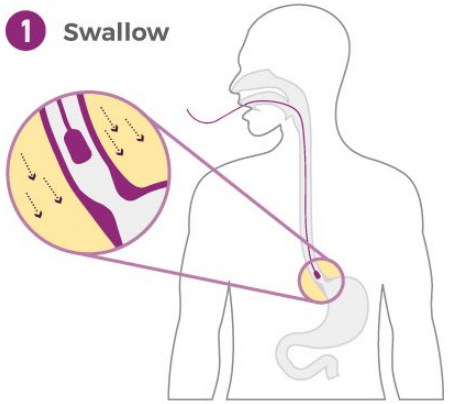
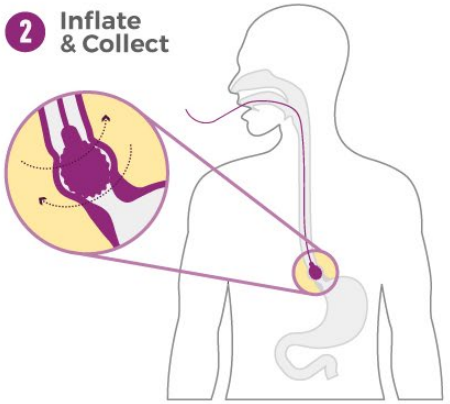
Highlighted in September 2018 NCI Director's Annual Report to Congress

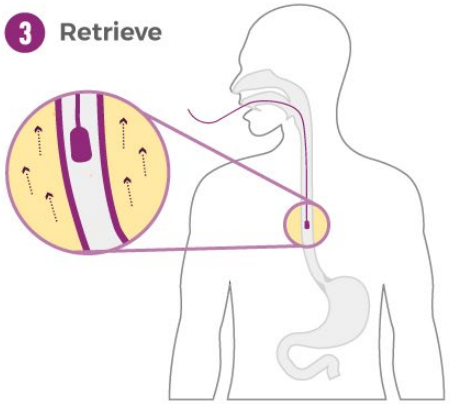
How the Swallowable Balloon Device Helps Detect Barrett Esophagus



Instead of undergoing standard endoscopy, patients can swallow a pill-sized capsule attached to a thin silicone catheter. The capsule passes through the esophagus and stops near the stomach.



Once the capsule nears the stomach, a balloon with a textured surface is inflated and maneuvered to swab the lower esophagus, where Barrett esophagus (BE) typically begins. A sample of the cells lining the lower esophagus is collected.



The balloon is deflated through the catheter and inverted back into the capsule, thus protecting the sample from dilution or contamination. After retrieving the capsule through the mouth, DNA is extracted from the balloon's surface for a DNA methylation test.

Device capsule and catheter in comparison to a vitamin pill and a dime.

The small dimensions of the balloon device allow clinicians to retrieve samples quickly and easily without sedation during an outpatient exam.

Source: Moinova HR et al., Sci. Transl. Med., Vol. 10, Issue 424, eaao5848 (2018). Reprinted with permission from AAAS.

cancer.gov

CLIA Implementation of Biomarker Assay

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

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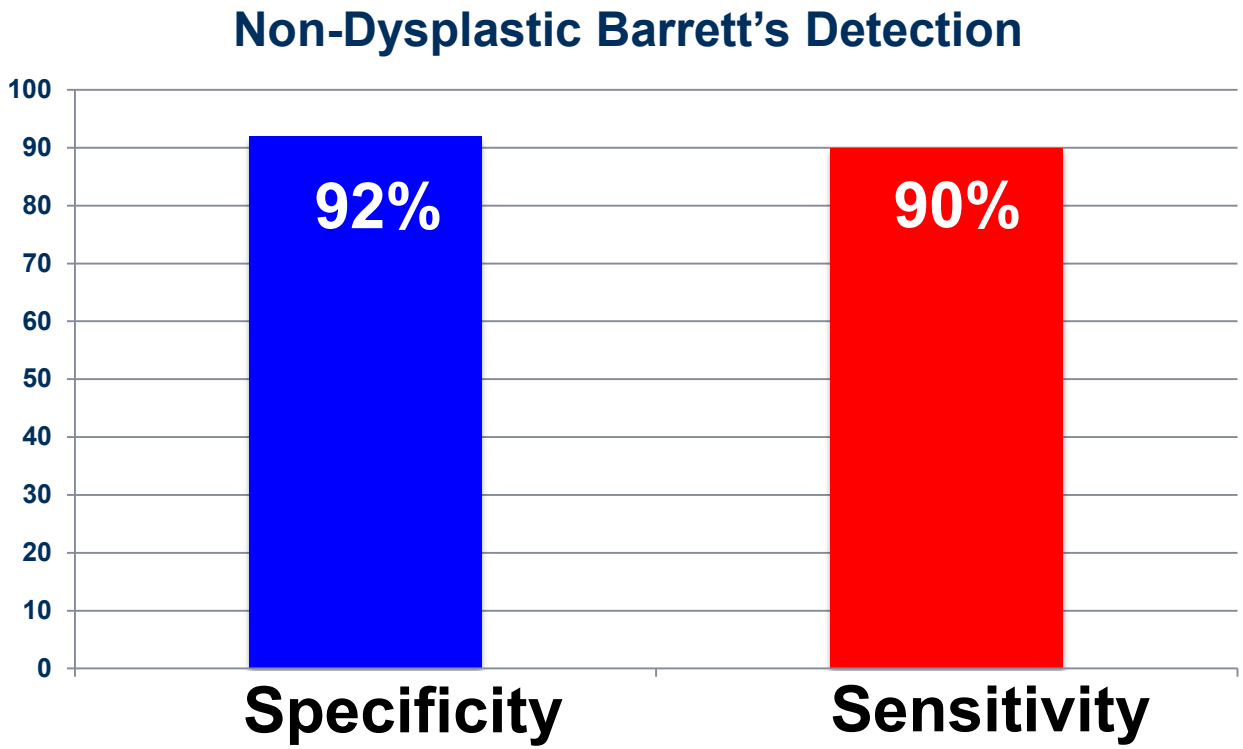

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Technology Commercially Licensed

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Introducing

EsoCheck

a five minute office based procedure to sample cells from the esophagus

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Lucid Diagnostics is developing a revolutionary non-invasive, office based diagnostic test for biomarkers to esophageal cancer.

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FDA 510K Approval for EsoCheck Balloon Device

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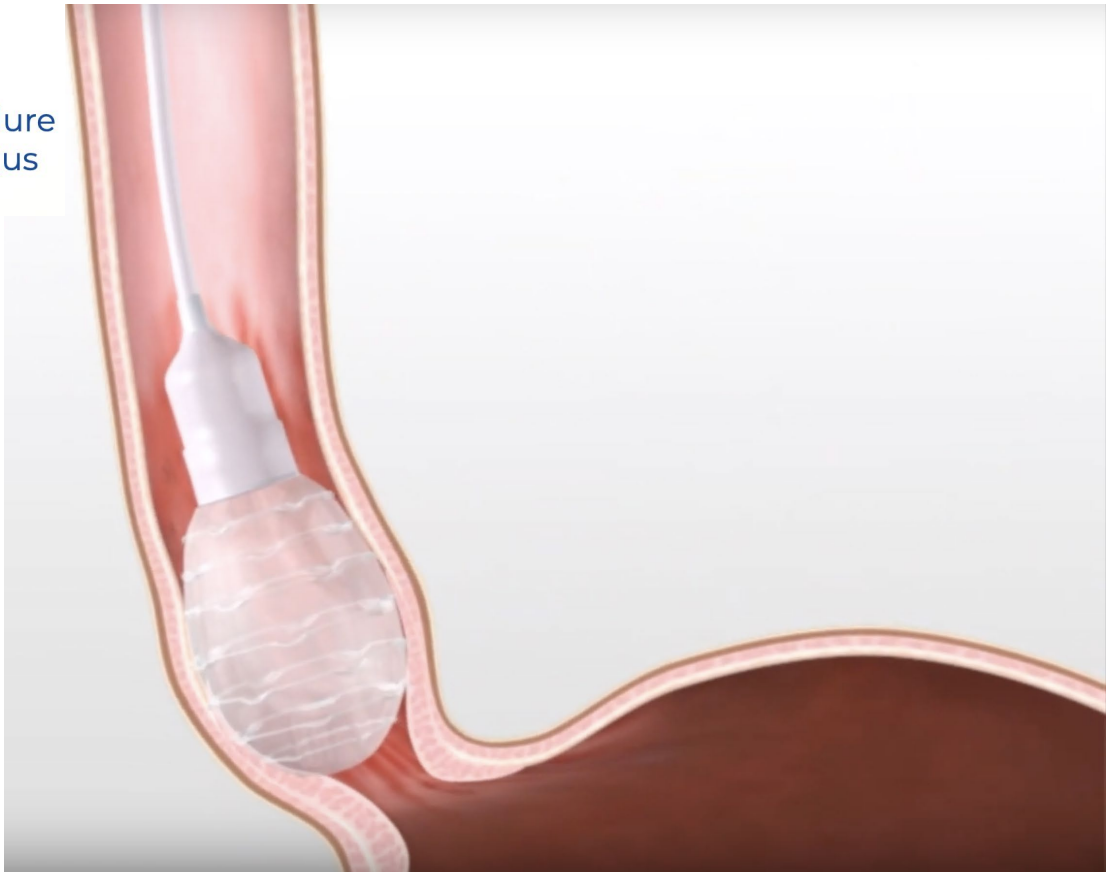

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2020 Silver Edison Award for Innovation in Medical Testing

Lucid diagnostics

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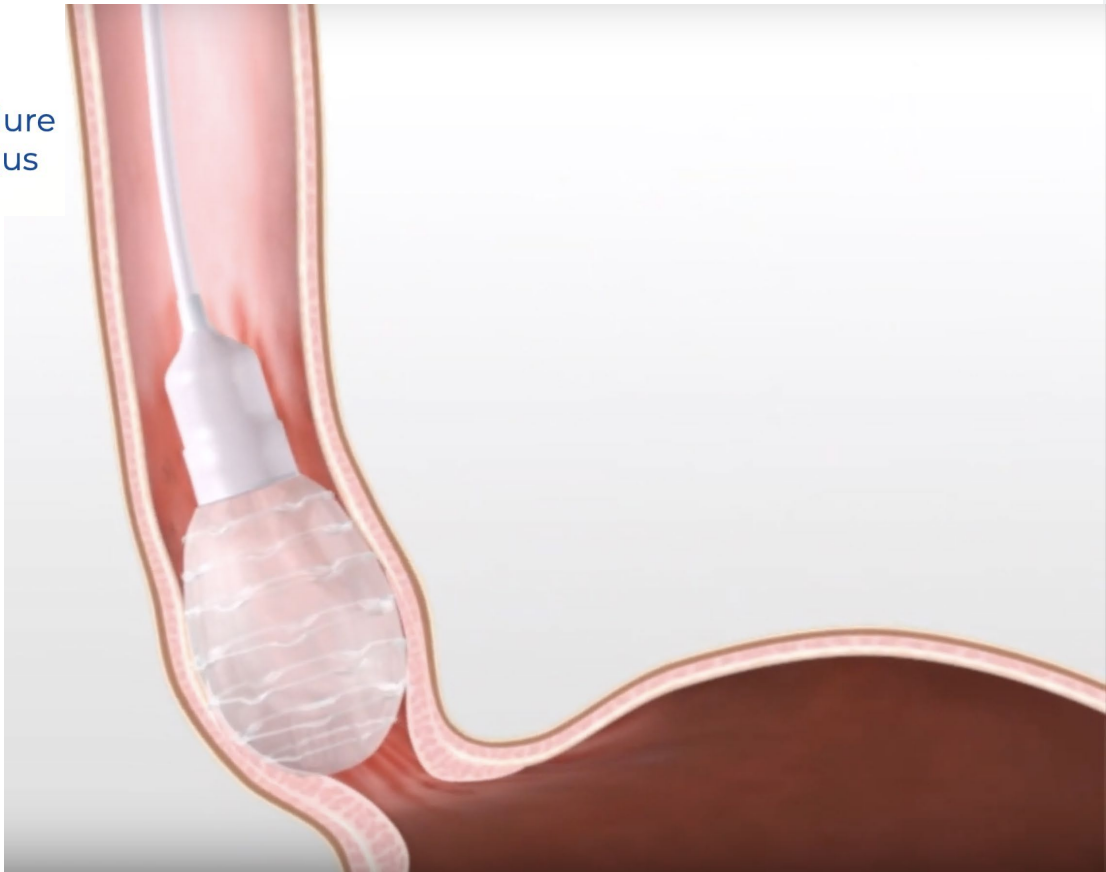

Biomarker Assay (EsoGuard) Awarded FDA Breakthrough Designation

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Lucid Diagnostics is developing a revolutionary non-invasive, office based diagnostic test for biomarkers to esophageal cancer.

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PLA Code for EsoGuard LDT Awarded

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Current Status

- 2nd Generation EsoCheck Balloon with Improved Swallowability and Increased DNA Collection
- Case Control Study to define optimal performance of New Balloon with Marker Panel
- Multi-center BE detection study in at risk screening population.
- Biomarker Discovery to Distinguish BE versus Dysplasias and Cancers to Enable Non-Endoscopic BE Surveillance

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Thank You EDRN!

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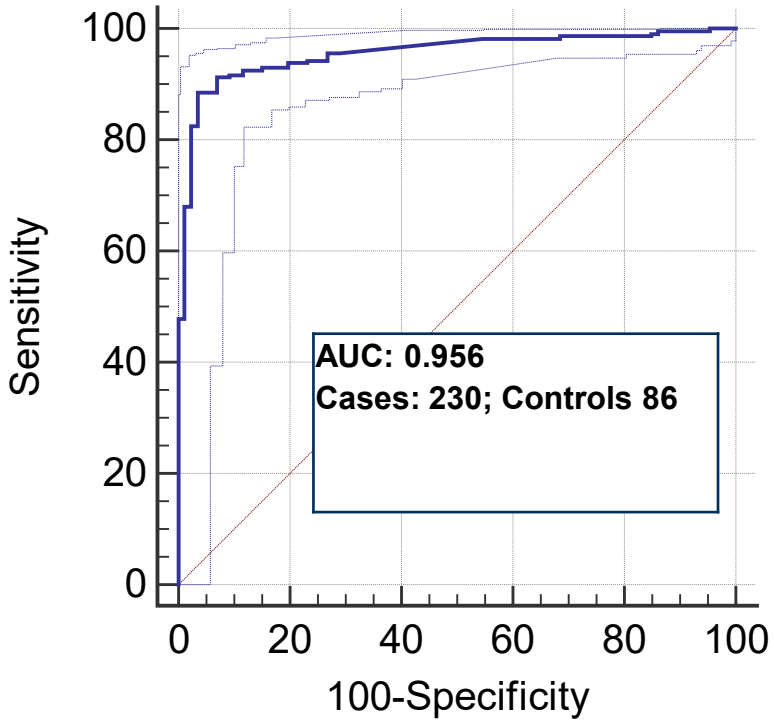
Molecular Cytology: mVIM + mCCNA1 in 313 brushings

mVIM and mCCNA1 in combined esophageal brushings from 229 cases of BE/EAC and 84 controls

mVIM



mCCNA1