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PATHOLOGISTS



IVM-Guided Biopsy

Advances in Barrett's Esophagus Surveillance

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- **Chair of the In Vivo Microscopy Committee**



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- **Dr. Tearney has the following financial relationships with commercial interests to disclose:**
- **Consulting**
 - NinePoint Medical, Spectrawave
- **Sponsored research**
 - Canon, iLumen, CN USA Biotech Holdings, Vivolight, Boston Scientific, Vertex, Astra Zeneca, Hamamatsu
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 - Spectrawave
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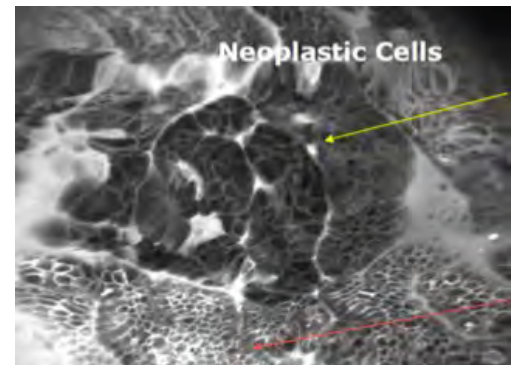
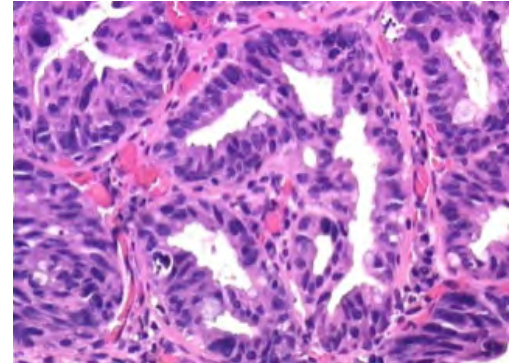
Barrett's Esophagus by Standard Endoscopy View

Seattle
Protocol



In Vivo Microscopy (IVM)

- Emerging field in which microscopic images are obtained in real time from living patients
- Technologies use reflected light
- Images may be rapidly constructed in 2D and 3D
- Both static images and video are captured



Kiesslich R et al. *Clin Gastroenterol Hepatol.* 2006; 8:979-987.

In Vivo Microscopy (IVM)



- IVM dataset consists of static images as well as video
- Images obtained via instruments that can be inserted into **endoscope** accessory ports or used as standalone imaging tools

Image courtesy of Eric F. Glassy, MD: Affiliated Pathologists Medical Group Inc

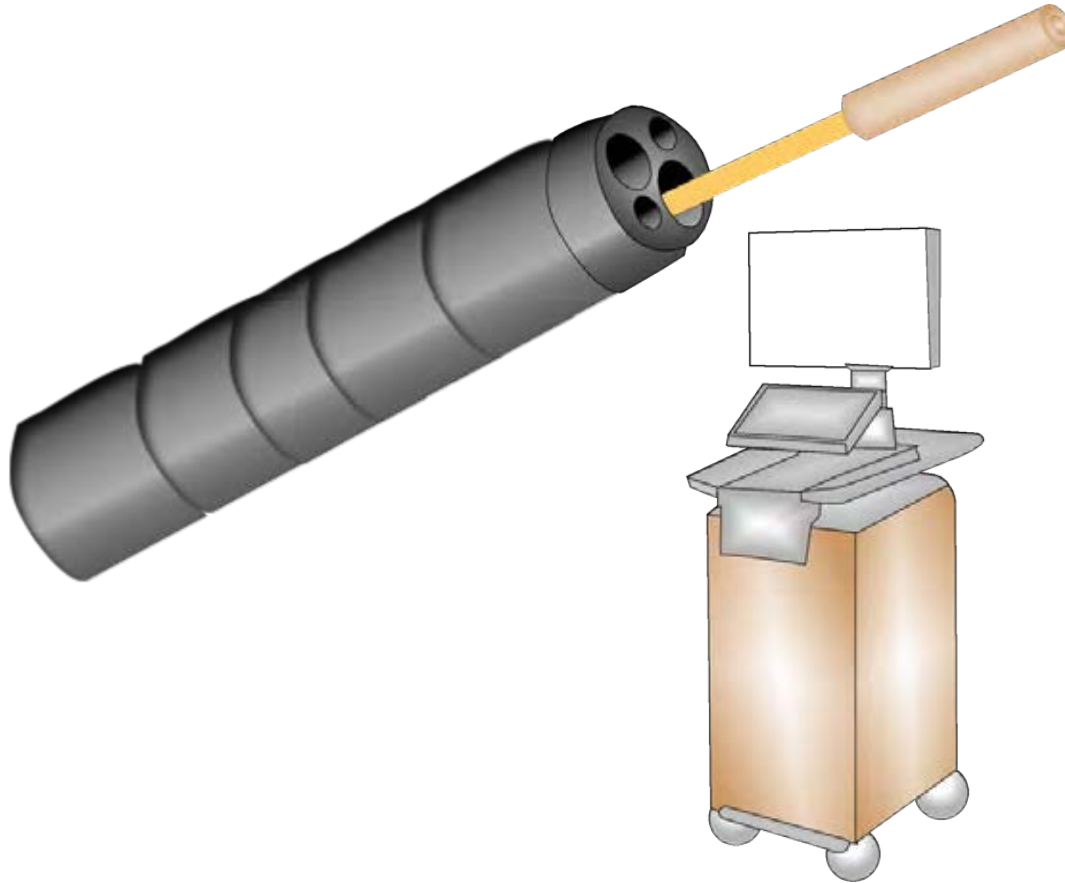
Endomicroscopy Technologies

- **Commercially available and FDA-approved**
 - Confocal microscopy
 - Confocal laser endomicroscopy (CLE)
 - Optical coherence tomography (OCT)
 - Volumetric laser endomicroscopy (VLE)
- **Many other technologies used in research**
- **Material costs (estimates)**
 - Equipment: ~\$50K-\$250K
 - Endoluminal probes: ~\$100-\$1000/use

Confocal Laser Endomicroscopy (CLE)

- Endoscopic microscopy – microscopy through an endoscope
- Multiple variants:
 - Probe-based CLE (pCLE)
 - Endoscope-based CLE (eCLE)
 - Needle-based CLE (nCLE)
 - Probe inserted through the bore of a biopsy needle

Confocal Laser Endomicroscopy (pCLE)

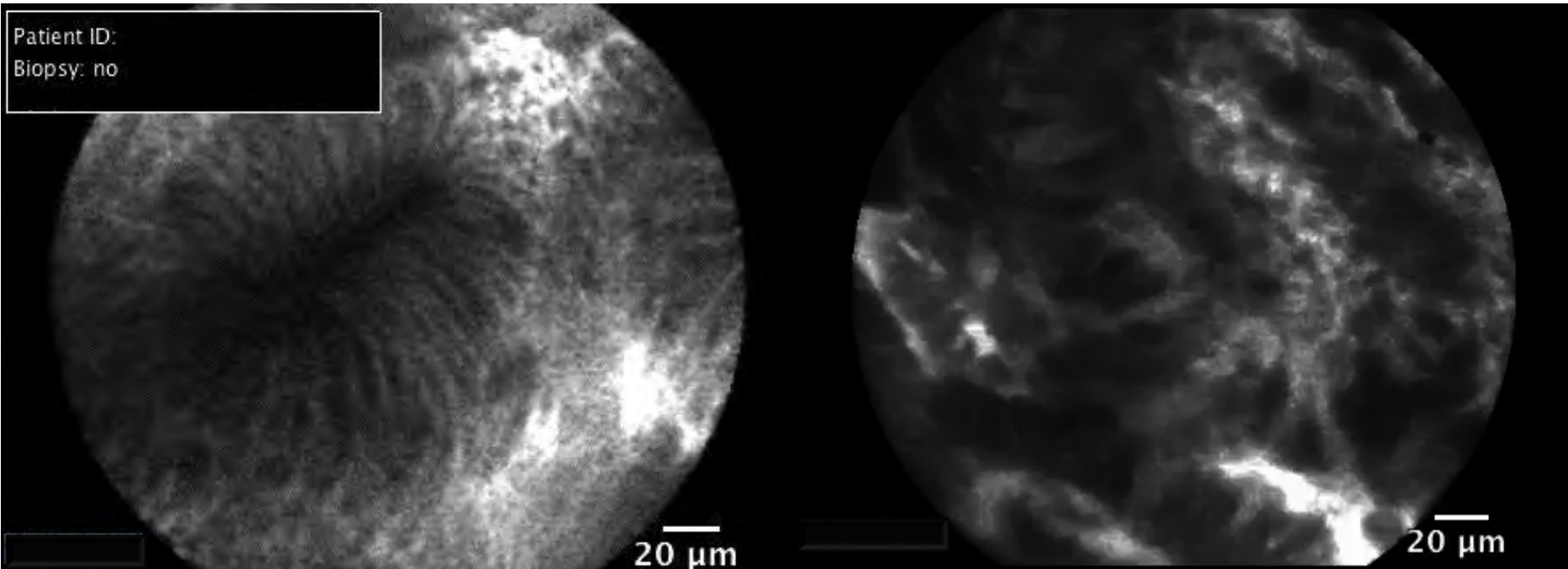


Images courtesy of Eric F. Glassy, MD: Affiliated Pathologists Medical Group Inc

Confocal Laser Endomicroscopy (CLE)

- Enables visualization of microscopic tissue architectural and cellular morphology
- Provides 2D images in plane parallel to tissue surface (en face)
- 1-2 μm resolution
- 10 μm resolution in depth
- Contrast arises from scattering within tissue or from fluorescein injected i.v.

pCLE of Barrett's: Normal vs. High Grade Dysplasia/Intra-Mucosal Carcinoma



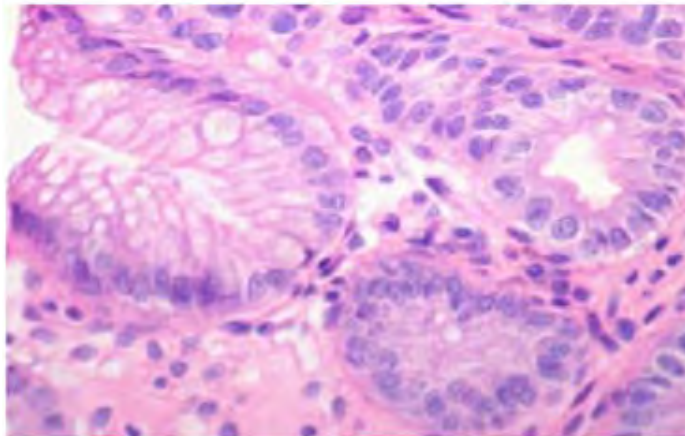
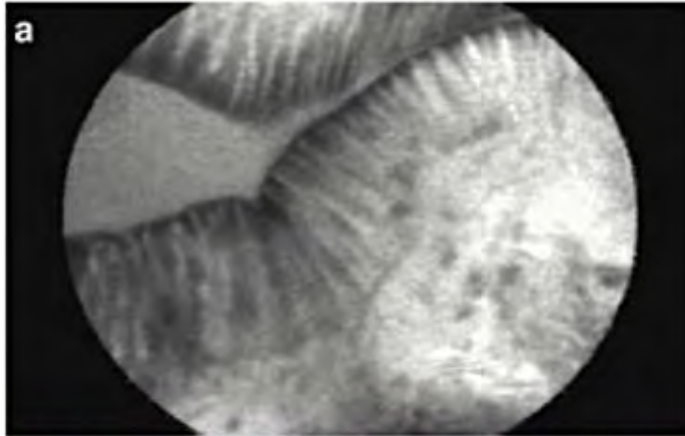
No Dysplasia

High Grade Dysplasia /
Intra-Mucosal Carcinoma

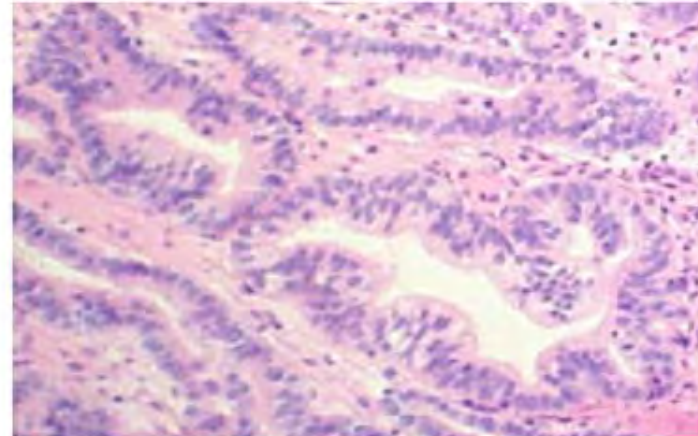
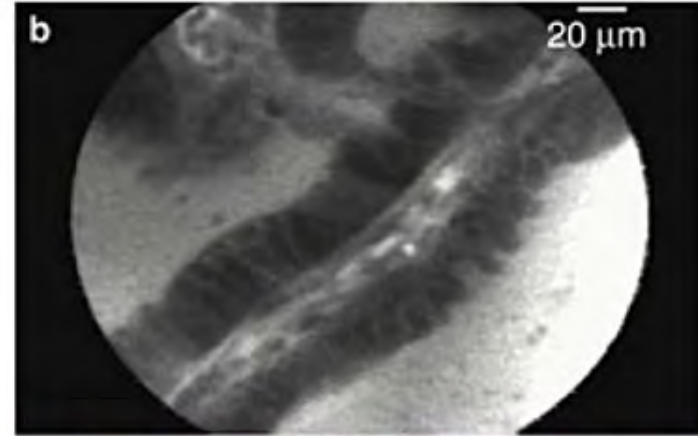
Images courtesy of Dr. Emmanuel Coron, Université de Nantes, France

pCLE

Non-dysplastic Barrett's

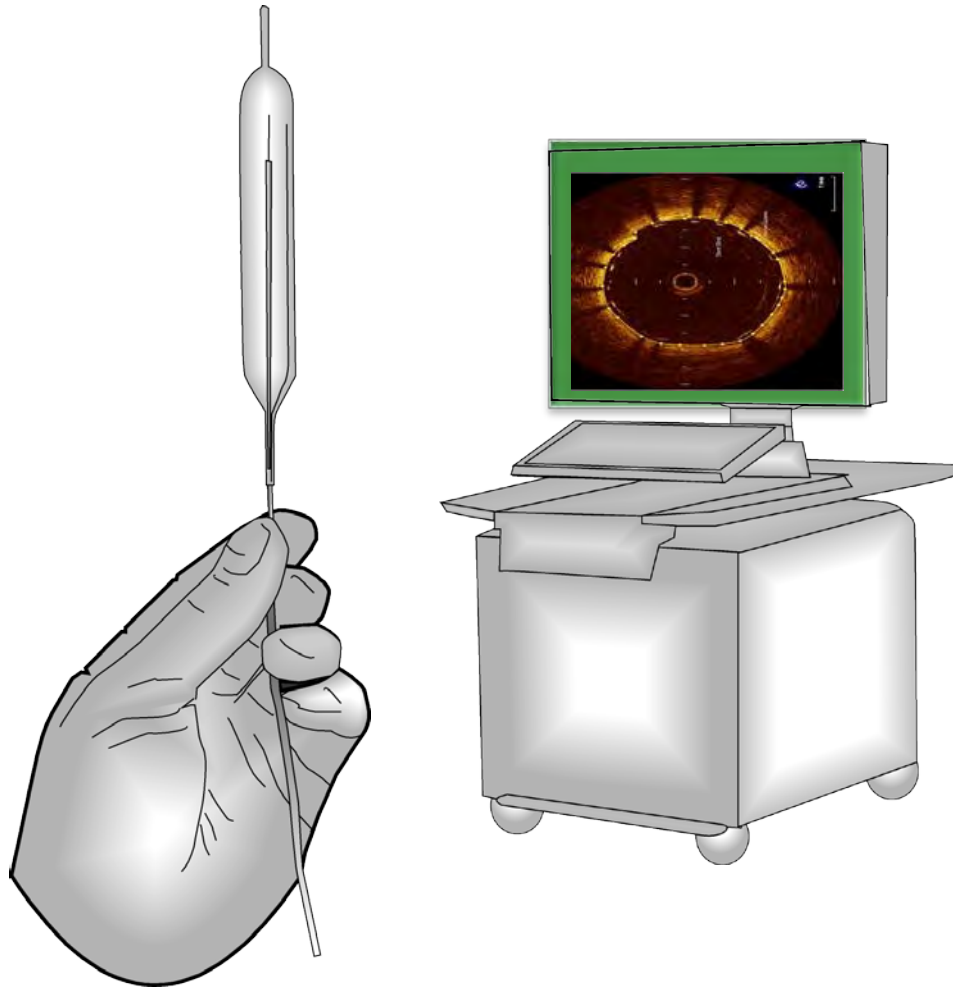


Dysplastic Barrett's



Gaddam S et al. *Am J Gastroenterol.* 2011; 106(11):1961-9.

Optical Coherence Tomography (OCT)



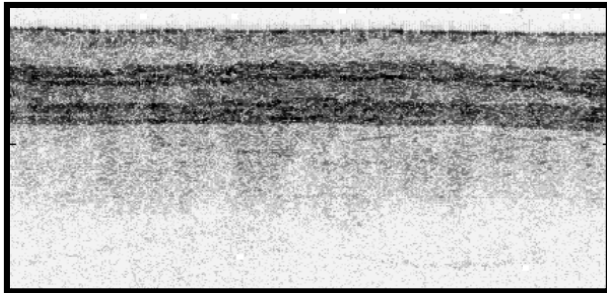
Images courtesy of Eric F. Glassy, MD: Affiliated Pathologists Medical Group Inc

Optical Coherence Tomography

- Enables visualization of microscopic tissue architectural morphology
- Analogous to ultrasound, but uses light to achieve higher resolution
- Provides cross-sectional and 3D images
- 10 μm resolution in depth
- 30-40 μm resolution in plane parallel to surface of tissue
- Contrast arises from scattering within tissue

OCT

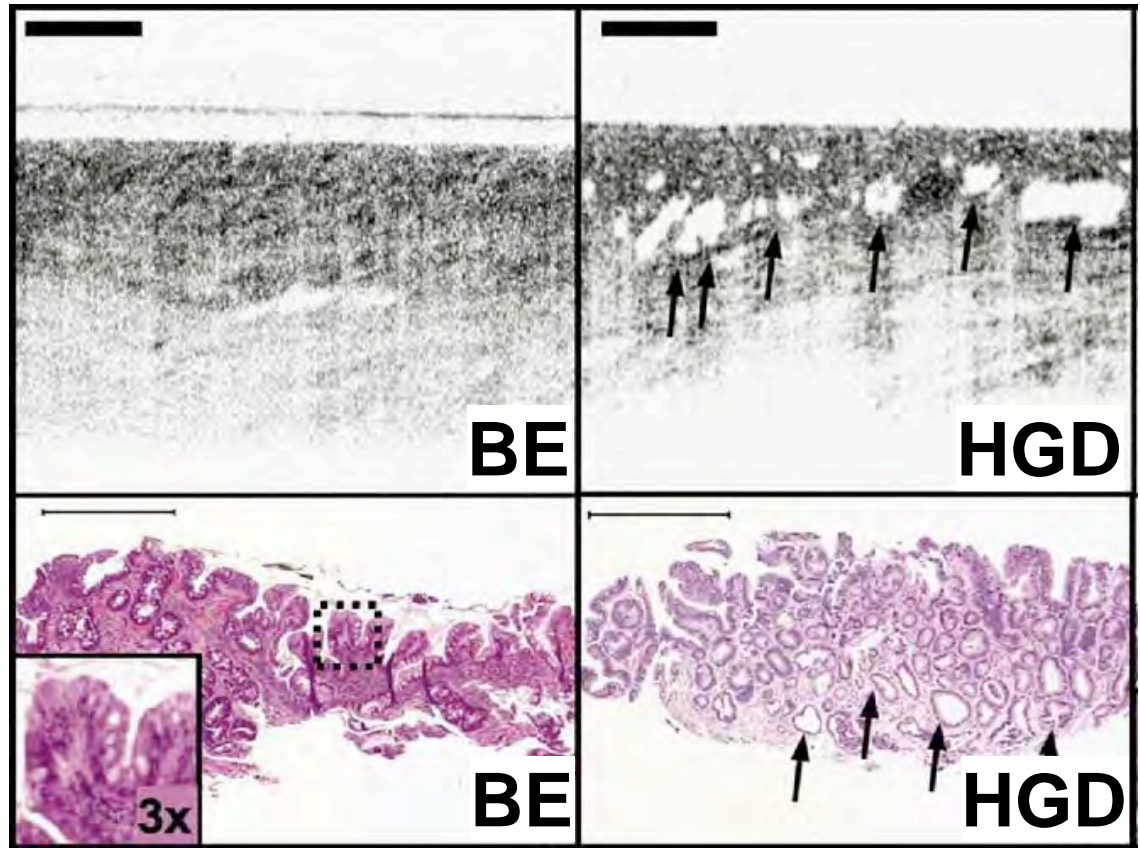
Examples: OCT images of Barrett's esophagus with and without high grade dysplasia (HGD)



Normal Esophagus

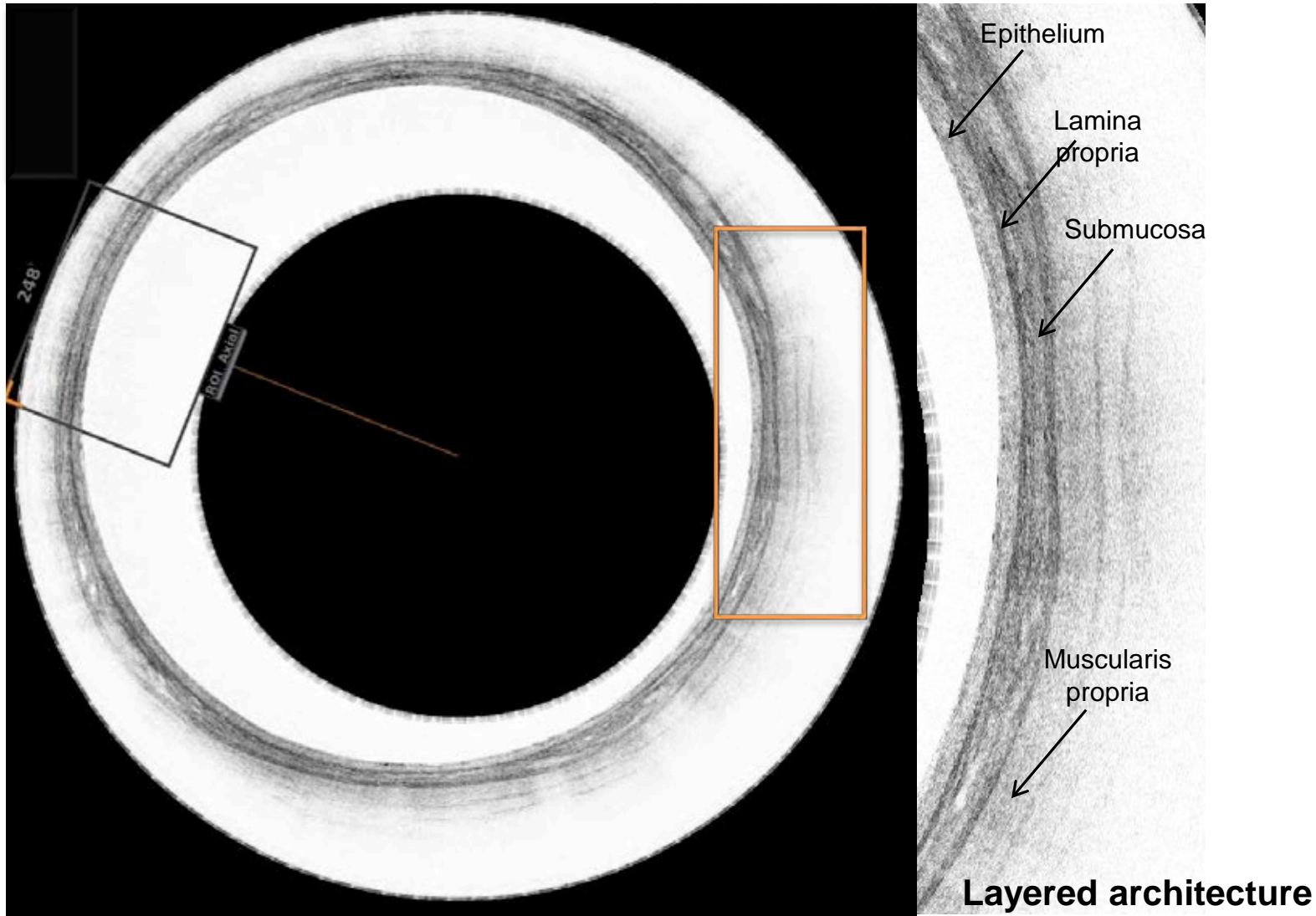
Image courtesy of Tearney Labs

OCT (in vivo)

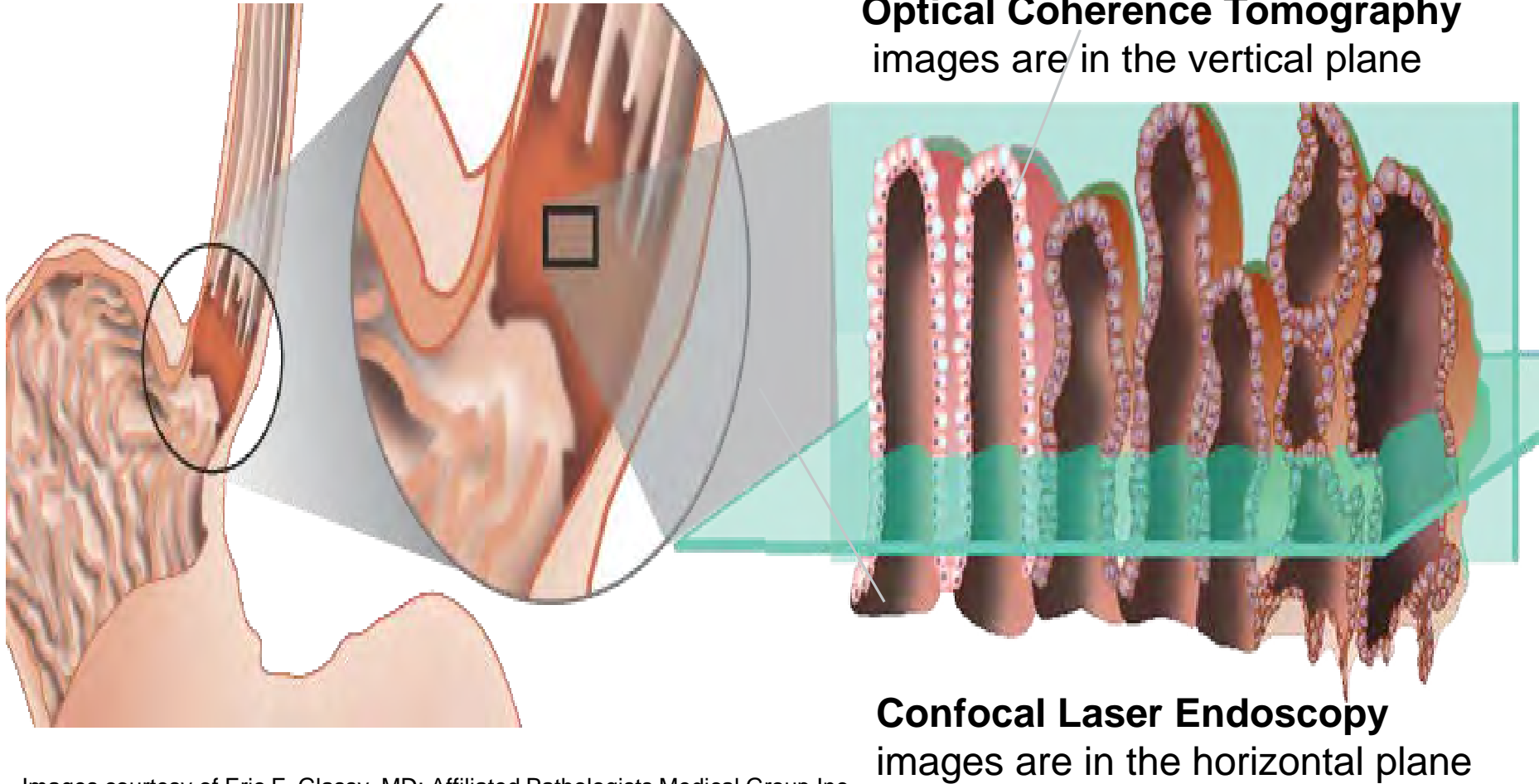


Arrows point to atypical glands in the mucosa

OCT Cross Section of Normal Squamous-Lined Esophagus



Barrett's Esophagus: OCT vs. CLE



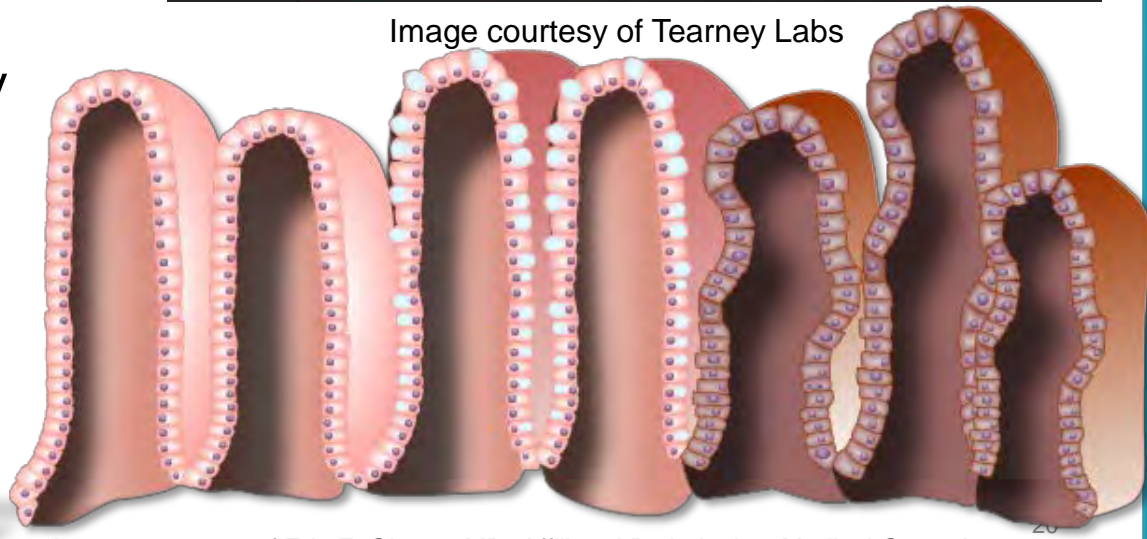
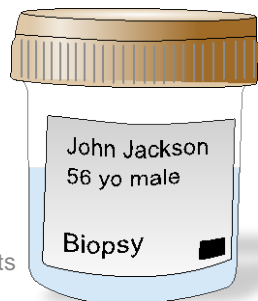
Images courtesy of Eric F. Glassy, MD: Affiliated Pathologists Medical Group Inc

IVM Can Deliver Better Diagnoses

- Guide the acquisition of more meaningful, targeted biopsies
- Help screen entire organs for occult microscopic disease
- Obtain microscopic diagnoses when tissues cannot be easily or safely excised
- Assess the efficacy of therapy

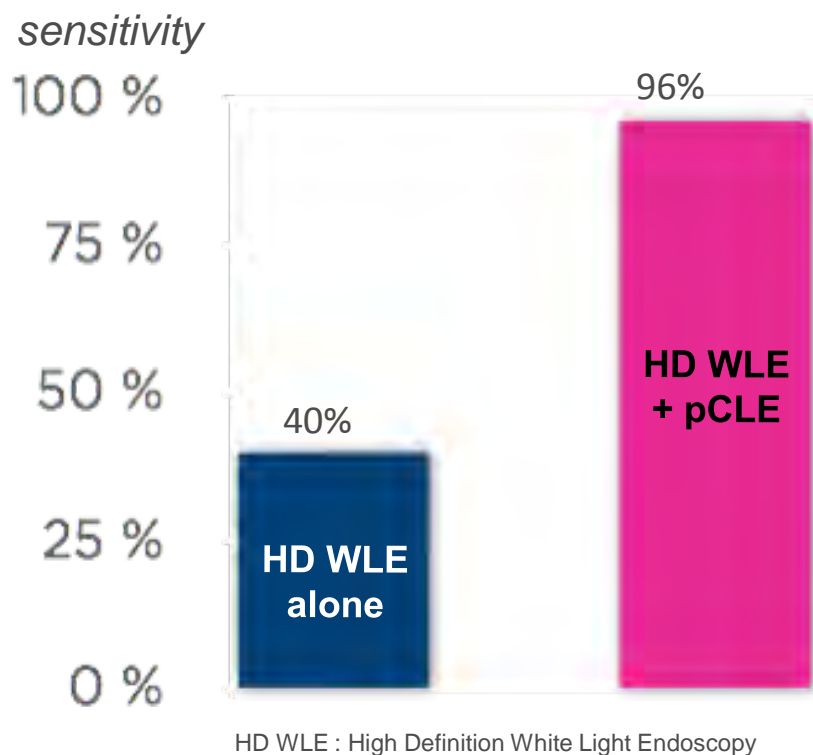


Image courtesy of Tearney Labs



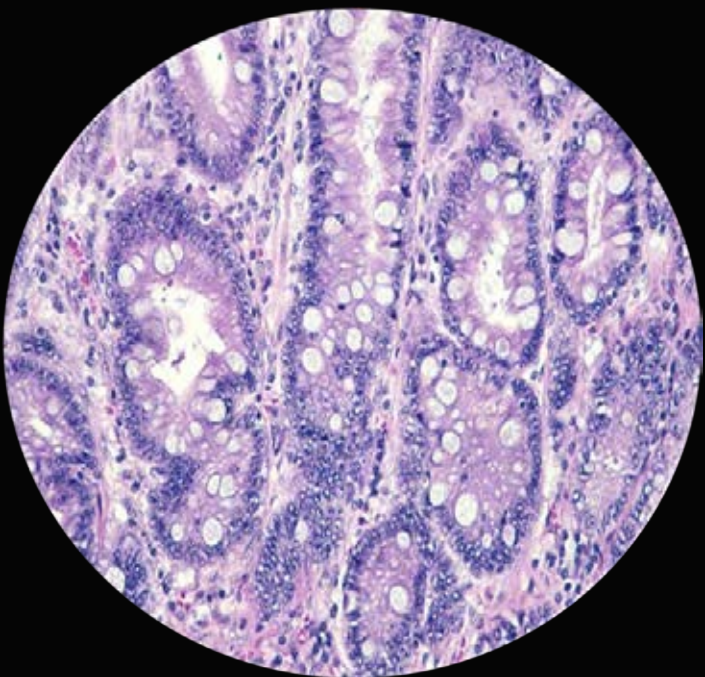
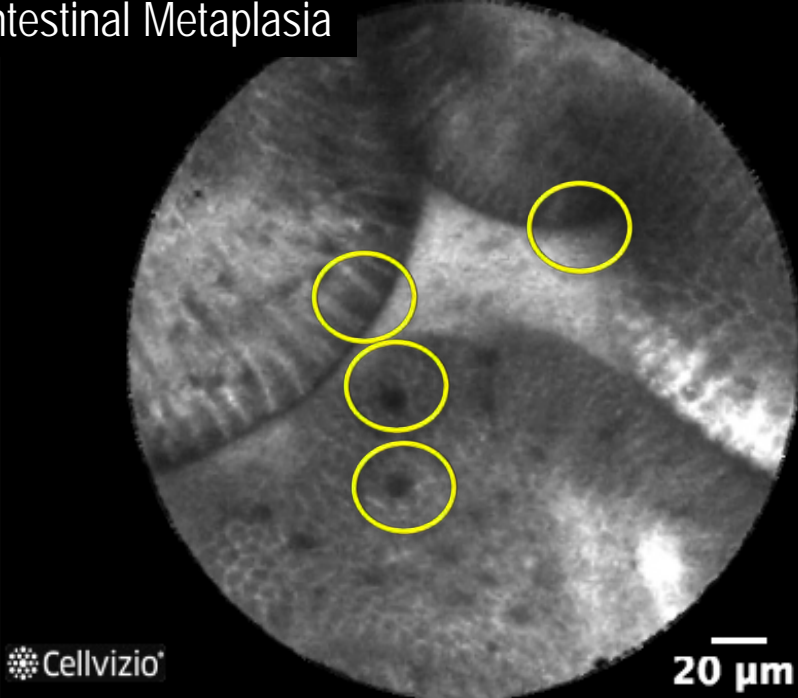
Sensitivity for neoplastic detection during BE surveillance pCLE

multi-center, randomized controlled trial, 192 patients, 2 arms



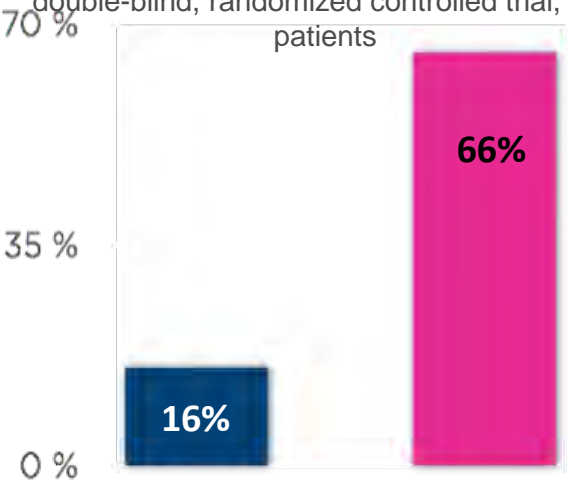
- Improved the treatment plan in 36% of patients
- **TRIPLE** the diagnostic yield of physical biopsies for neoplasia

Intestinal Metaplasia



Diagnostic yield* of GIM

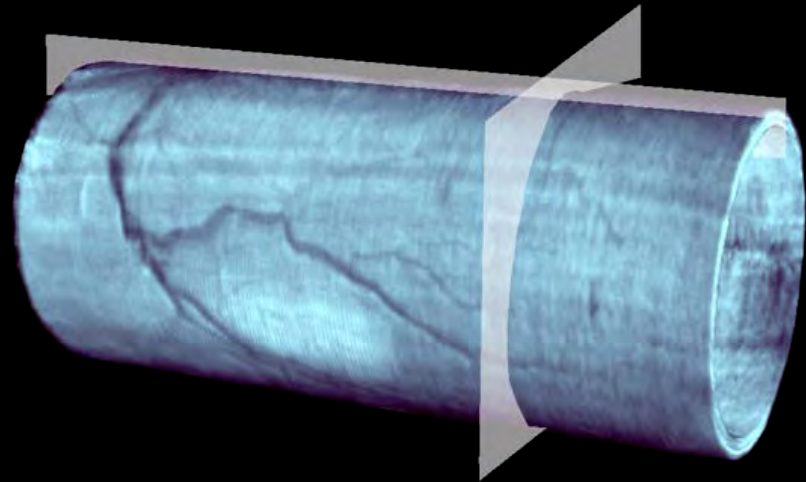
double-blind, randomized controlled trial, 168 patients



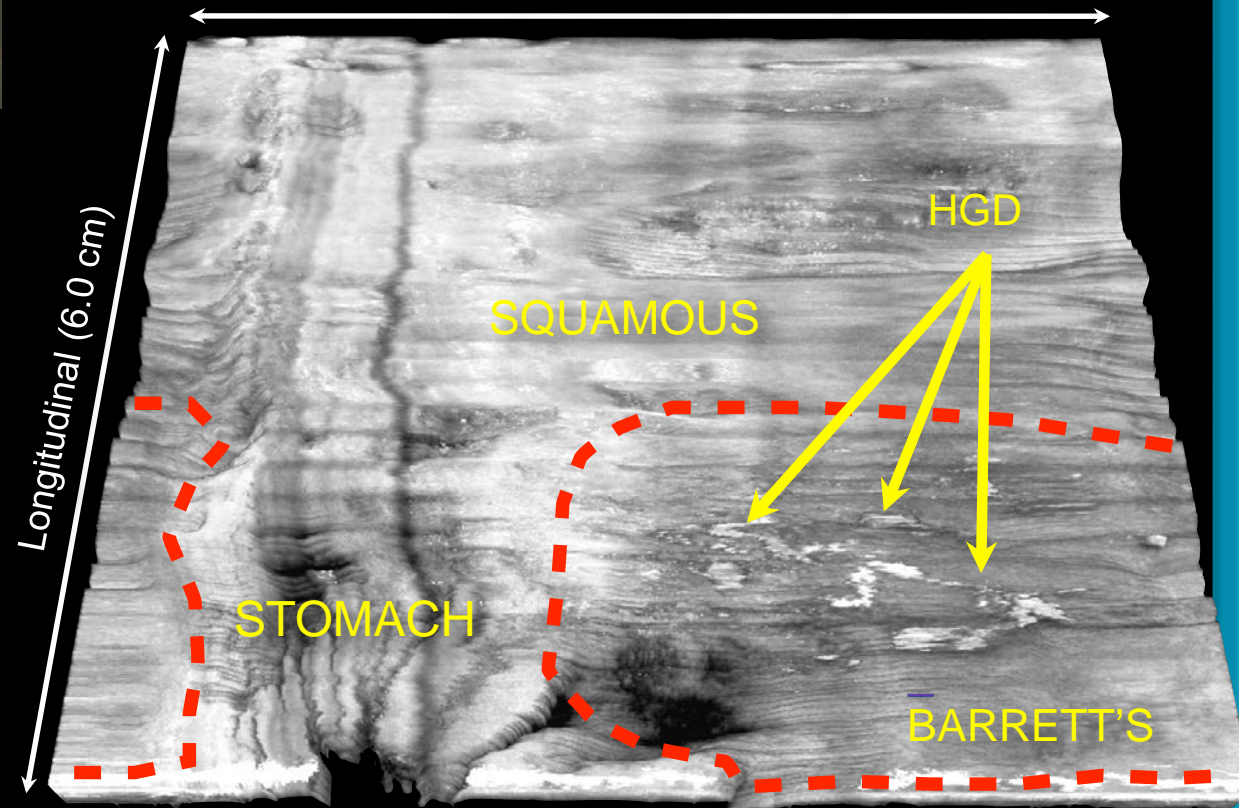
CLE-guided biopsy decreased by 68% the mean number of biopsies required per patient

Li Z.. CLE for in vivo detection of GIM: a randomized controlled trial, Endoscopy, 2014.

Volume Esophageal Surveillance with OCT



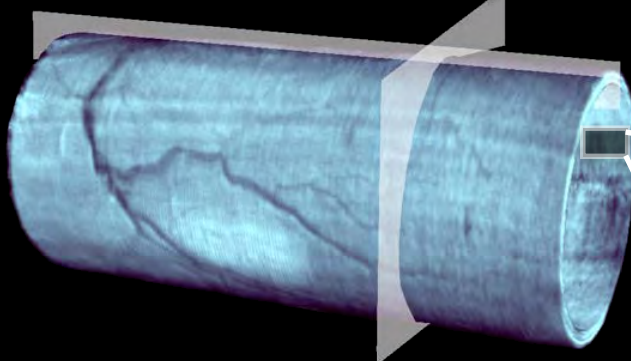
Circumferential (7.5 cm)



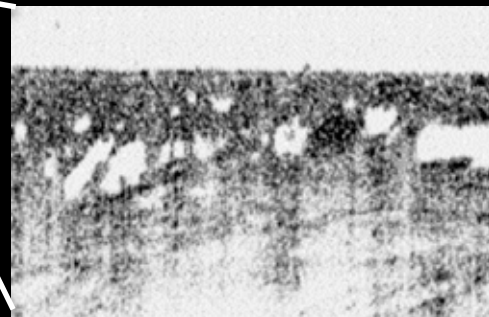
Balloon Insertion



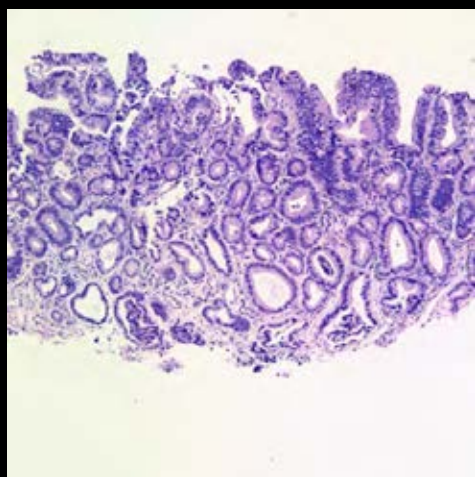
Volume Microscopy



Identify Suspect Areas



VLE Targeted Biopsy Paradigm



Histopathology

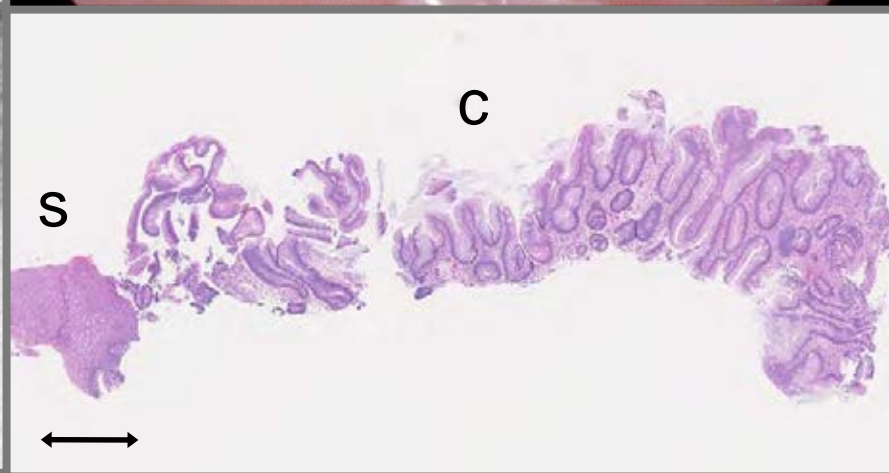
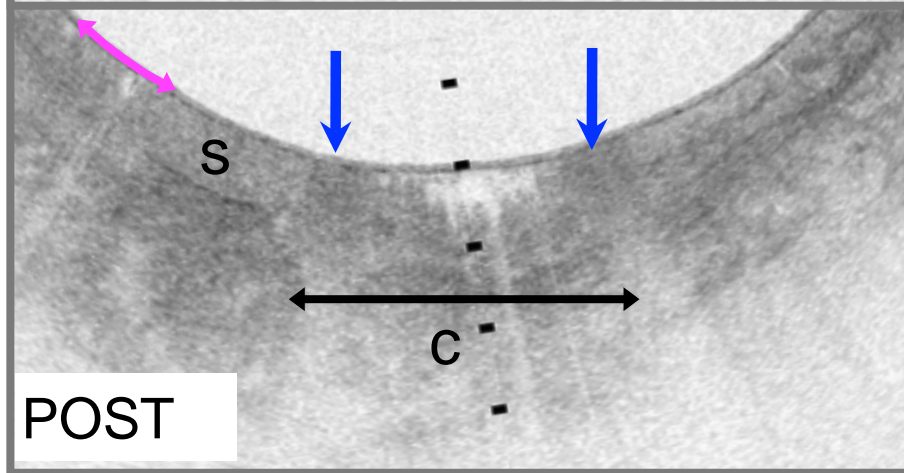
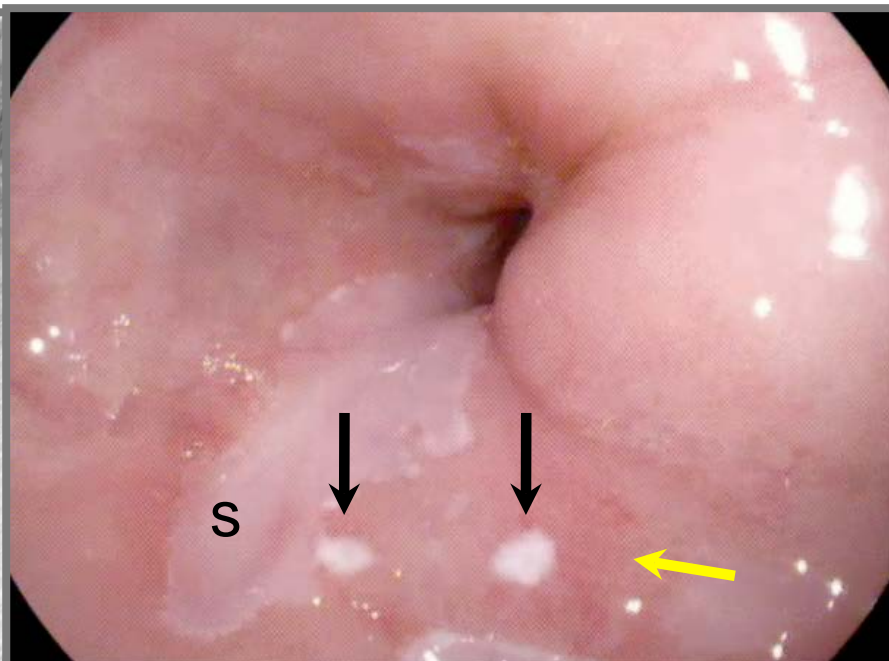
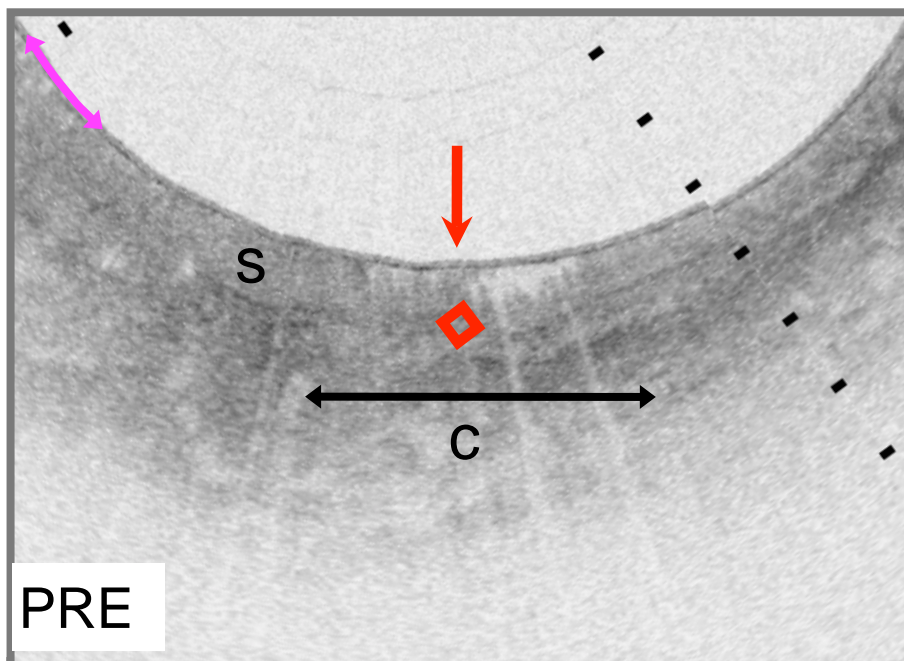


Biopsy at Marks



Mark Suspect Areas

OCT Guided Biopsy



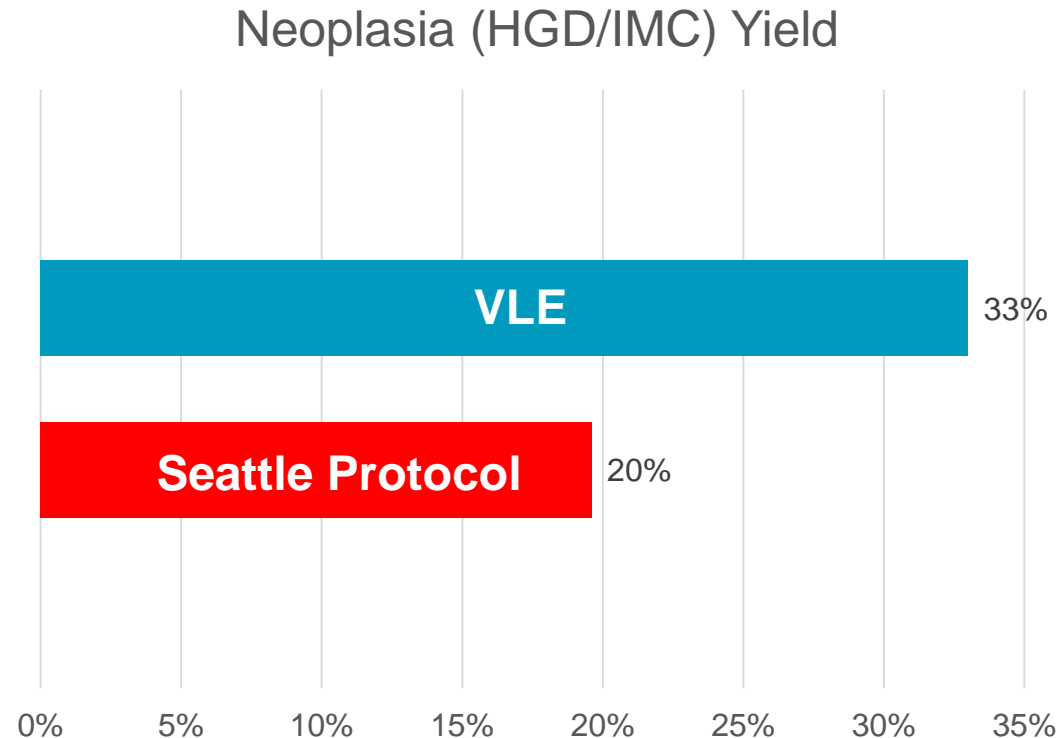
Incremental yield of dysplasia detection in Barrett's esophagus using volumetric laser endomicroscopy with and without laser marking compared with a standardized random biopsy protocol

Mohammad Alshelleh, MD, Sumant Inamdar, MD, Matthew McKinley, MD, Molly Stewart, BS, Jeffrey S. Novak, MD, Ronald E. Greenberg, MD, Keith Sultan, MD, Bethany Devito, MD, Mary Cheung, MD, Maurice A. Cerulli, MD, Larry S. Miller, MD, Divyesh V. Sejpal, MD, Anil K. Vegesna, MD, Arvind J. Trindade, MD

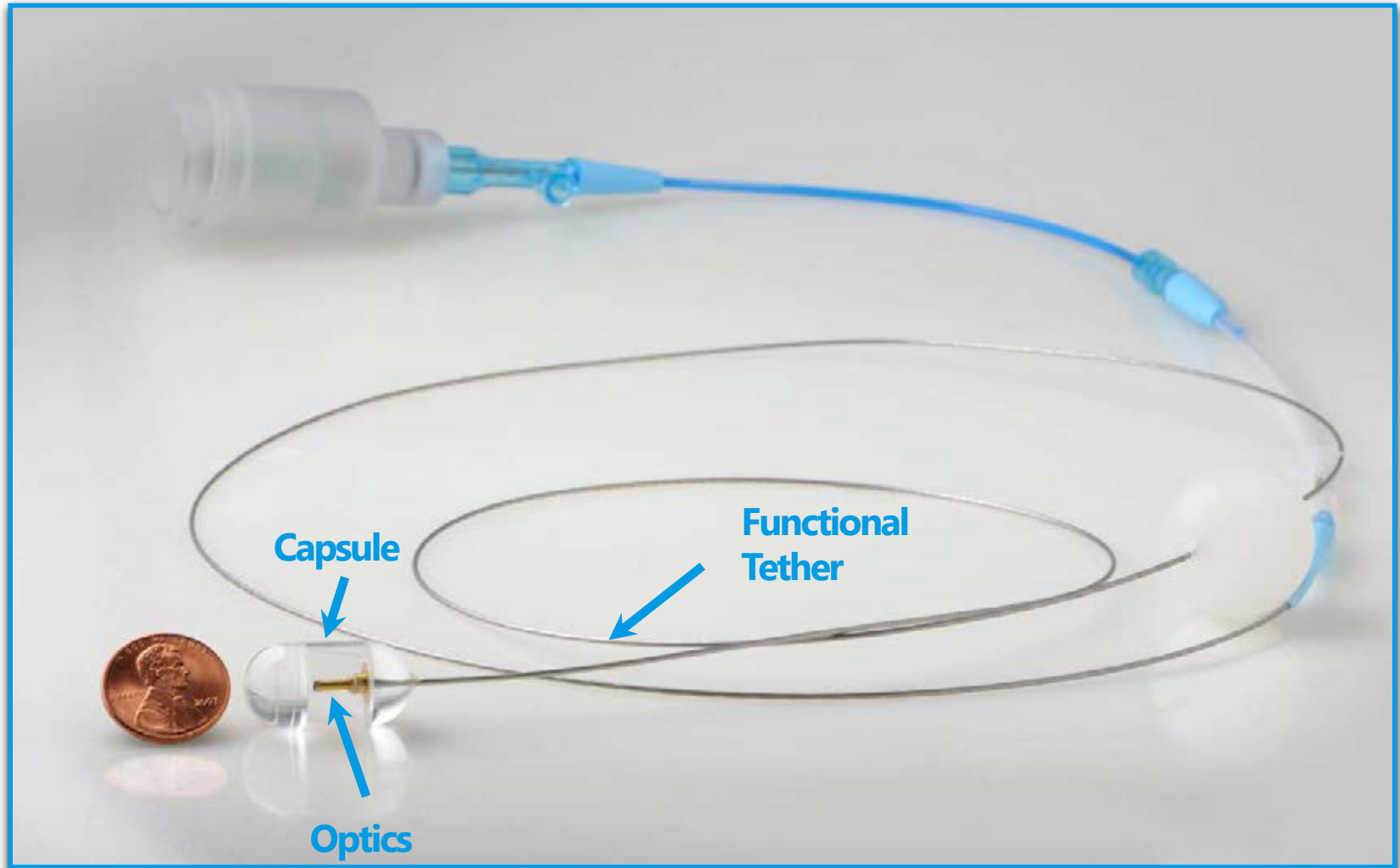
www.gicjournal.org

Volume 88, No. 1 : 2018 GASTROINTESTINAL ENDOSCOPY 35

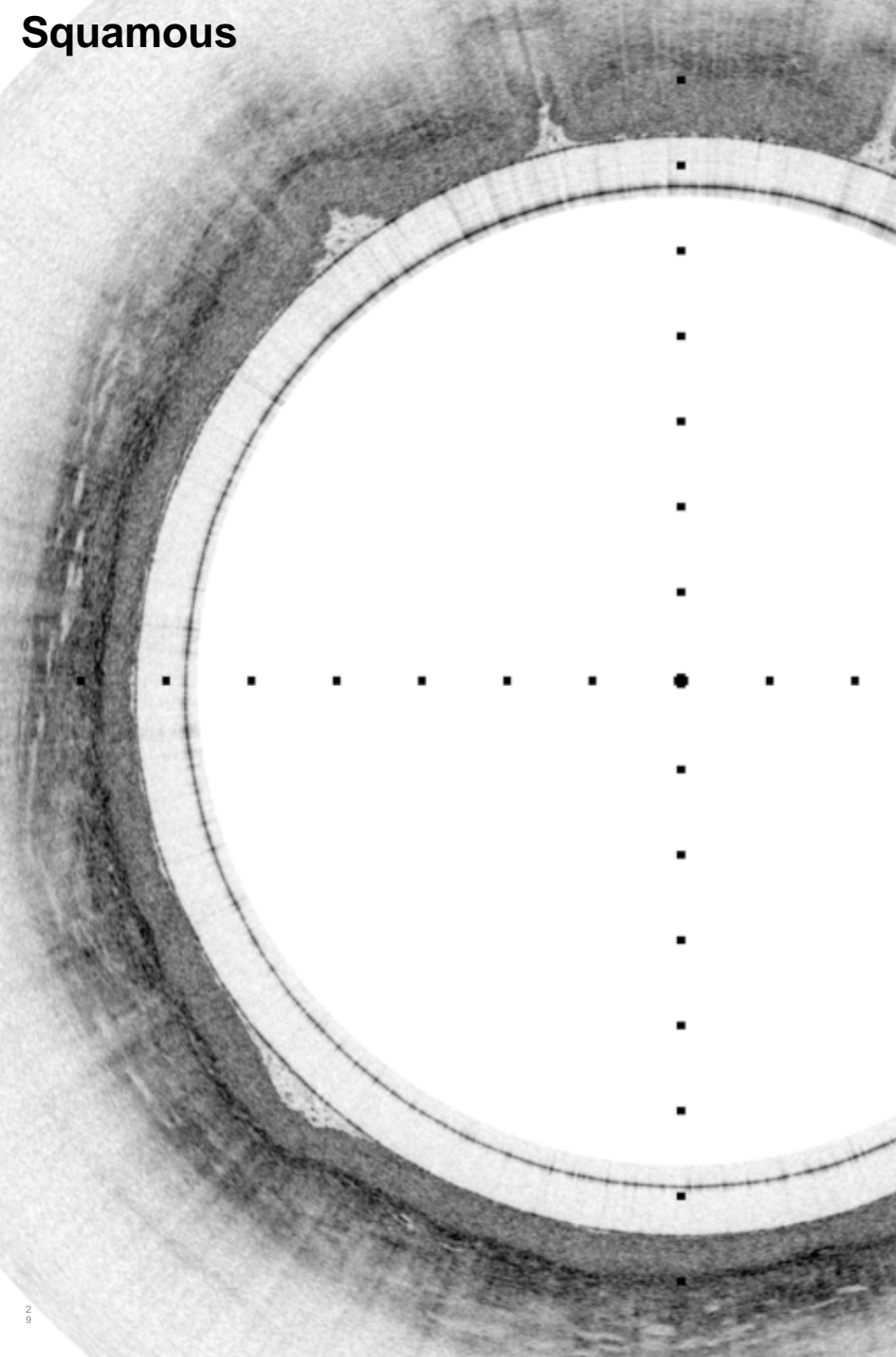
- retrospective study
- VLE (n=168)
- SP (n=95)



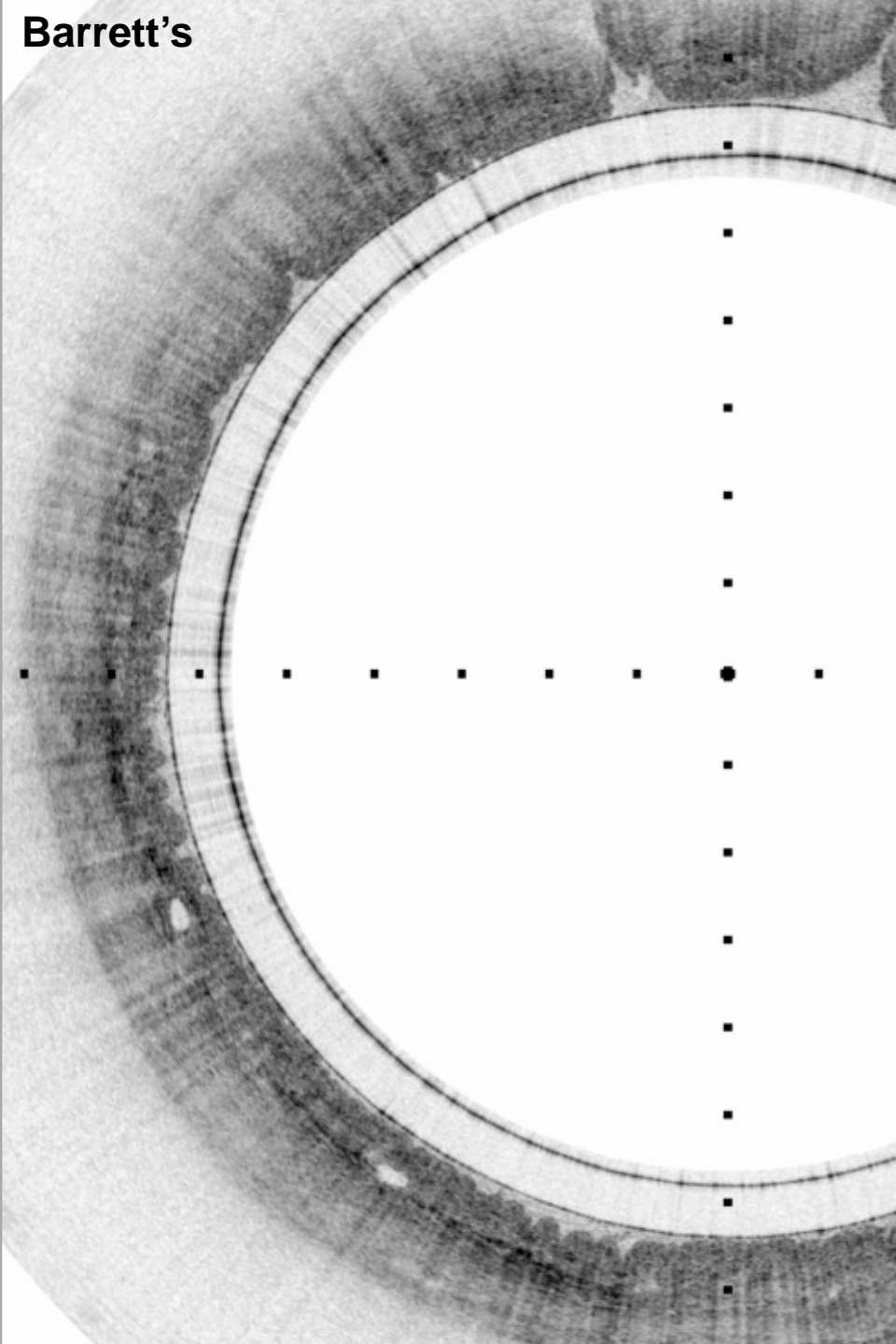
Capsule OCT

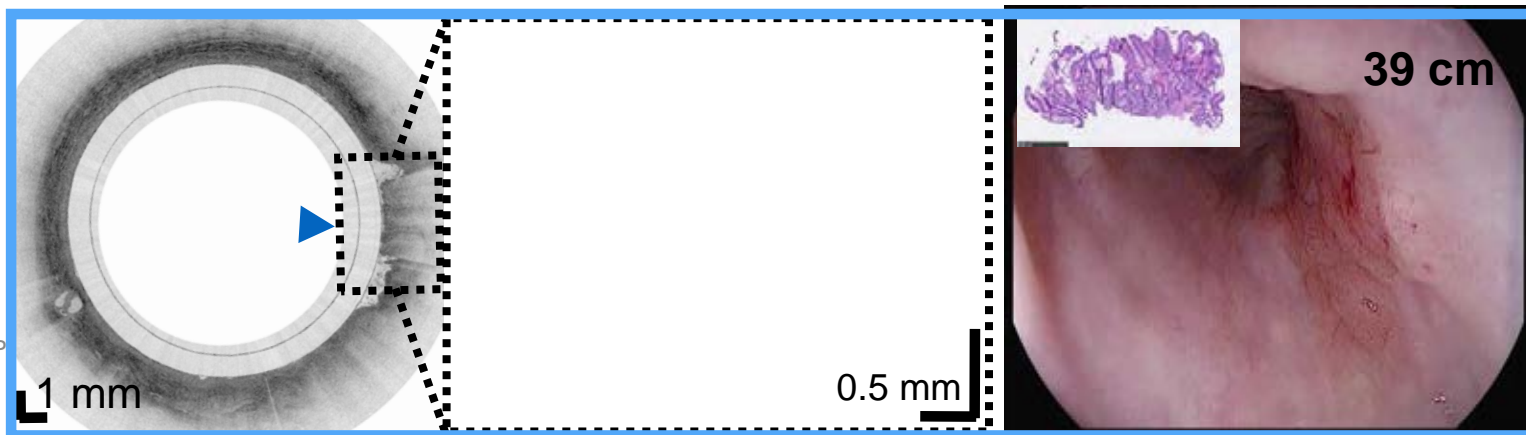
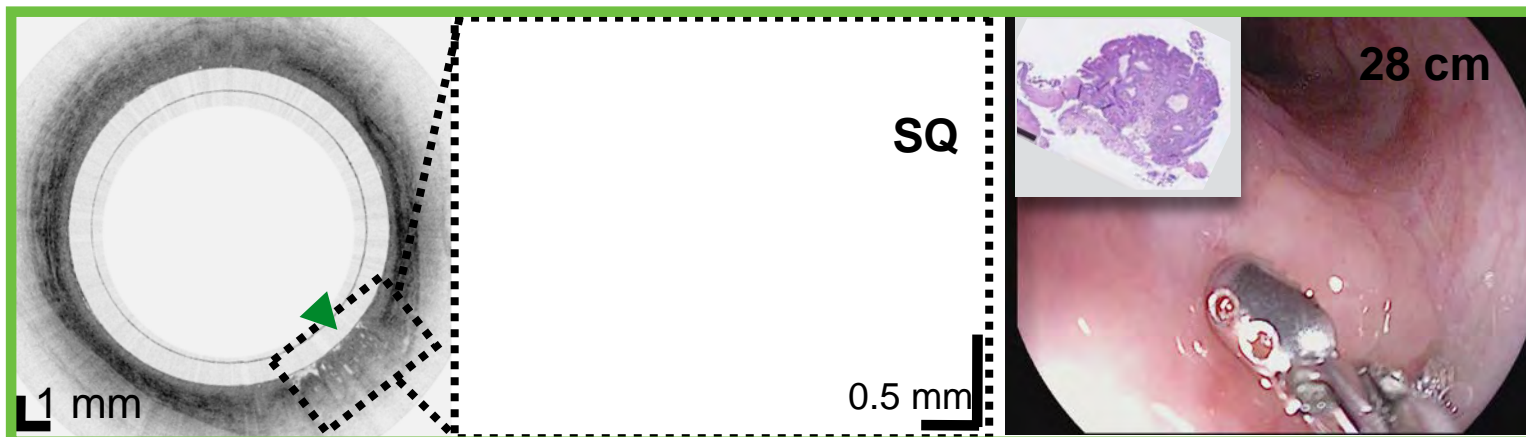
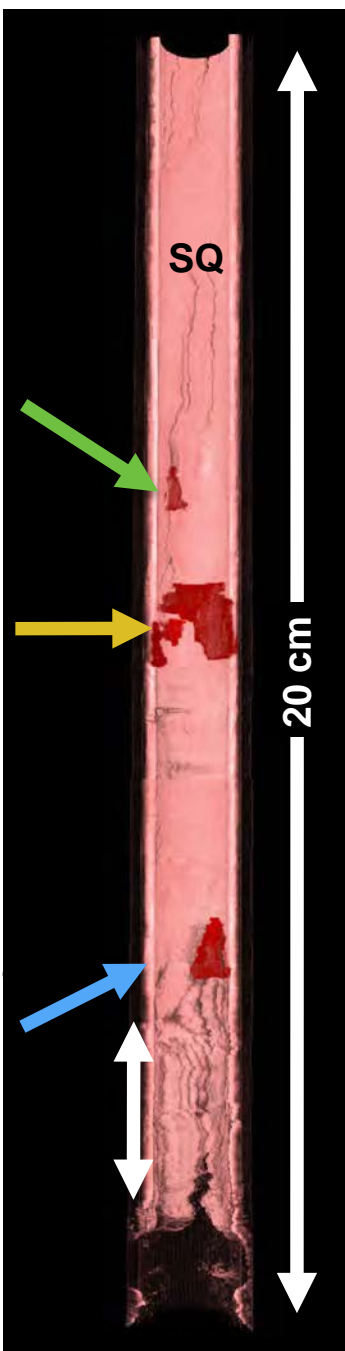


Squamous



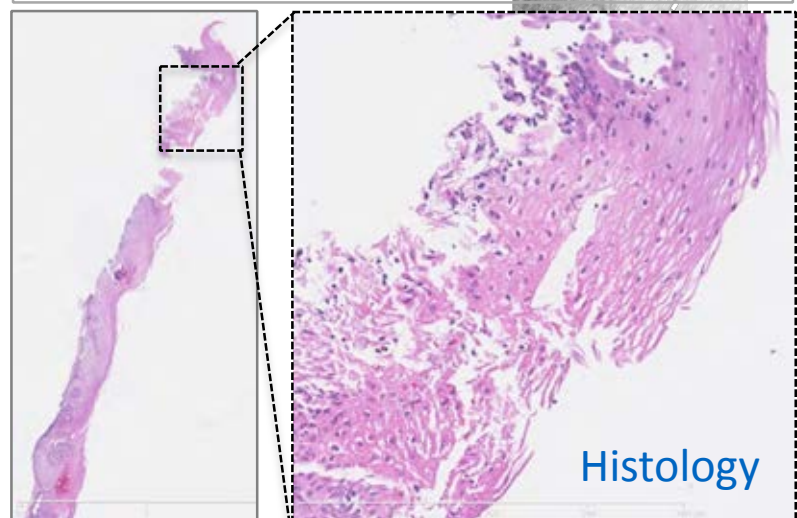
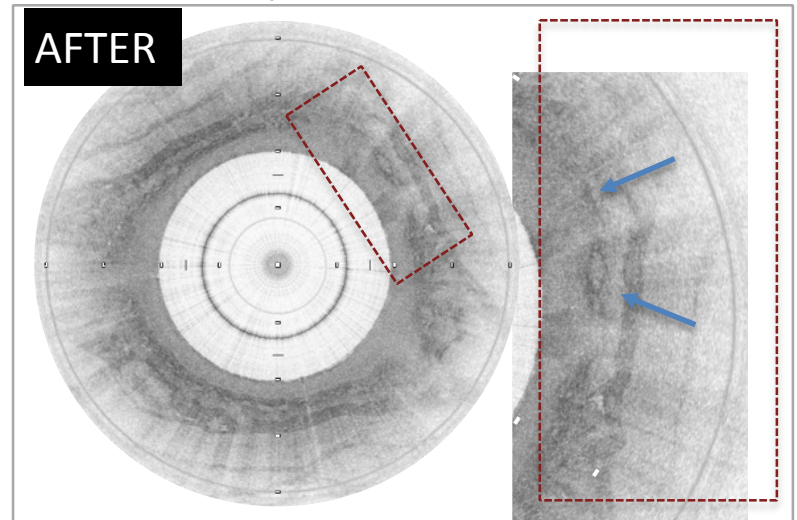
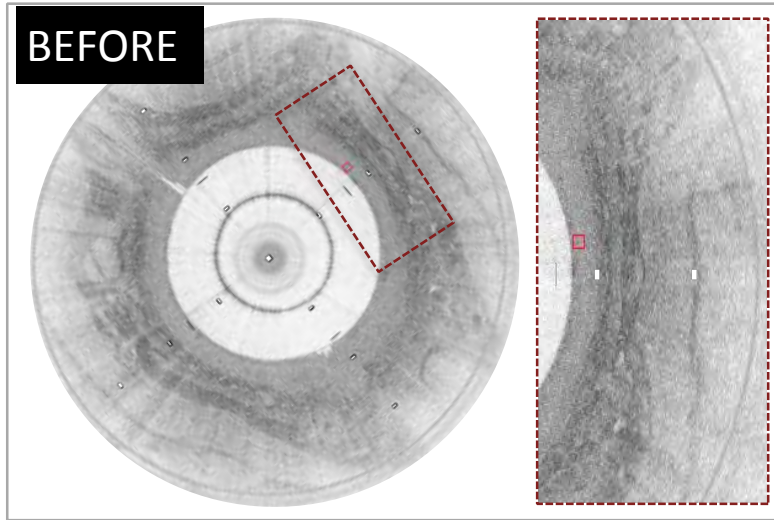
Barrett's



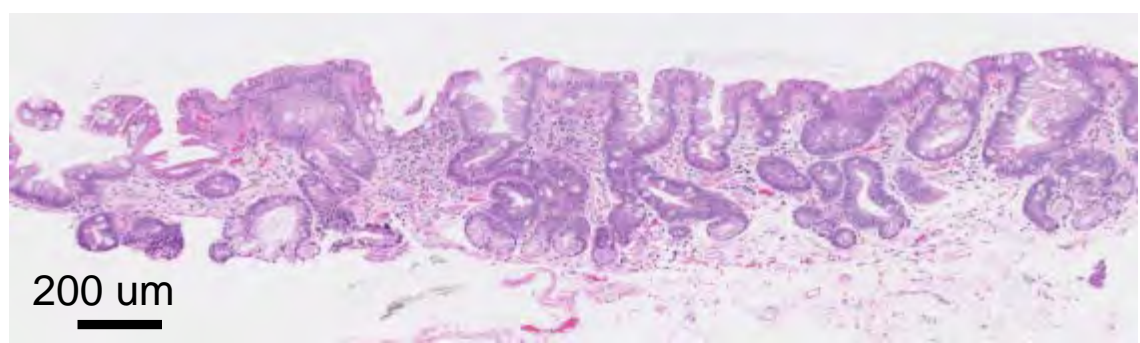
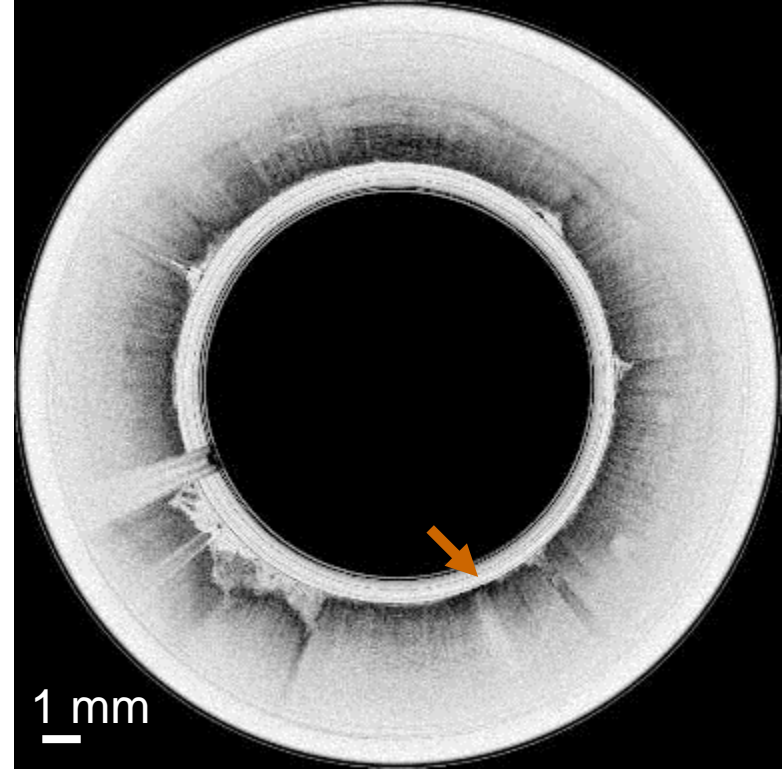
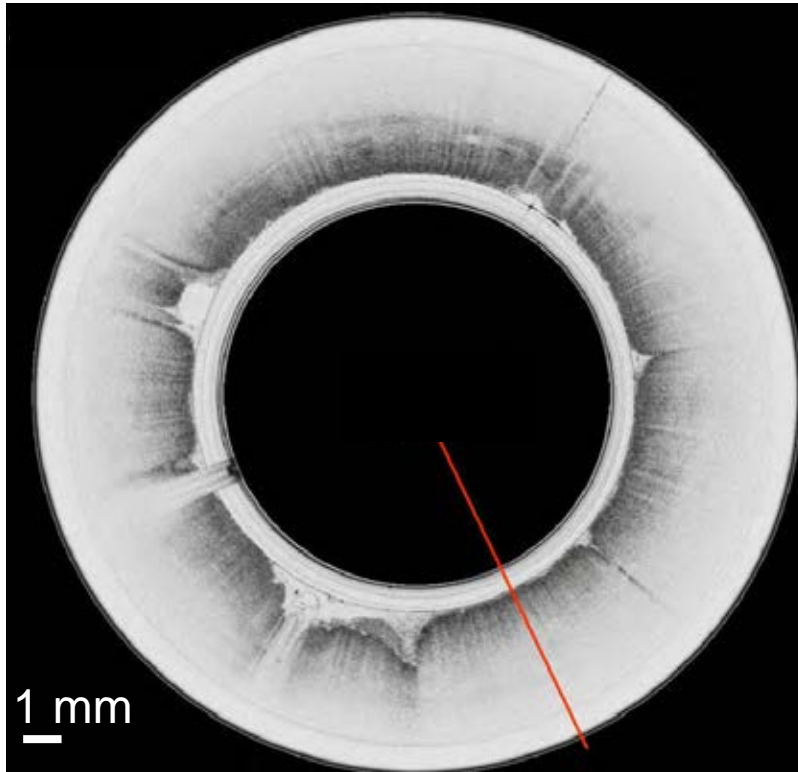


Capsule Guided Biopsy

- Laser cautery marking
- 1 second exposure per mark, 1 second delay between marks

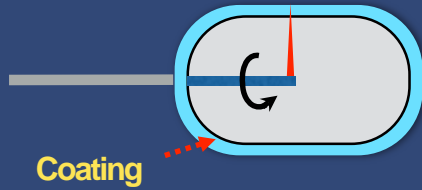


Capsule Guided Biopsy



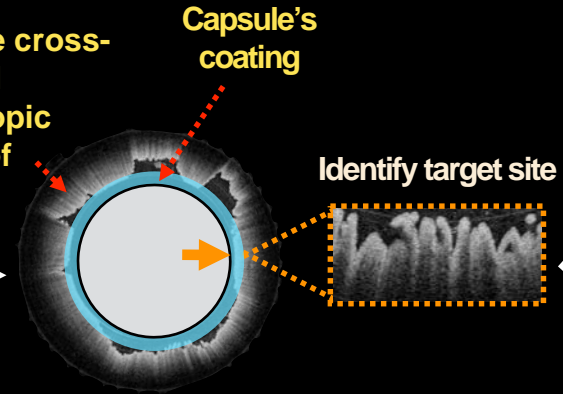
In Vivo Laser Capture Microdissection

- Tethered microscopy capsule with biocompatible coating
- Coating melts when illuminated by capture laser

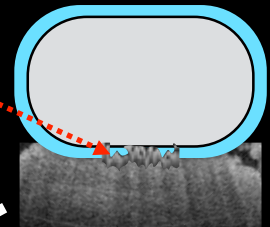


- Swallow or introduce capsule non-invasively
- Capsule goes to intestine

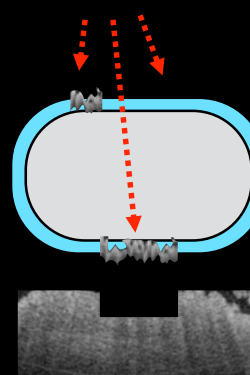
Real time cross-sectional microscopic images of intestine



Illuminate capsule's coating at target site, coating melts



Biopsies remain bound to capsule



Capsule moved off tissue site (repeat for other target sites)

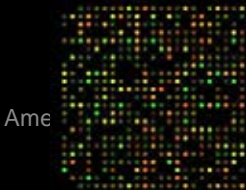
Take capsule out of patient

Extract biopsies from coating

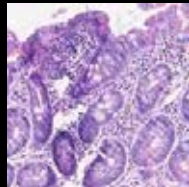
Microbiome



Molecular Analysis
Genome, Proteome

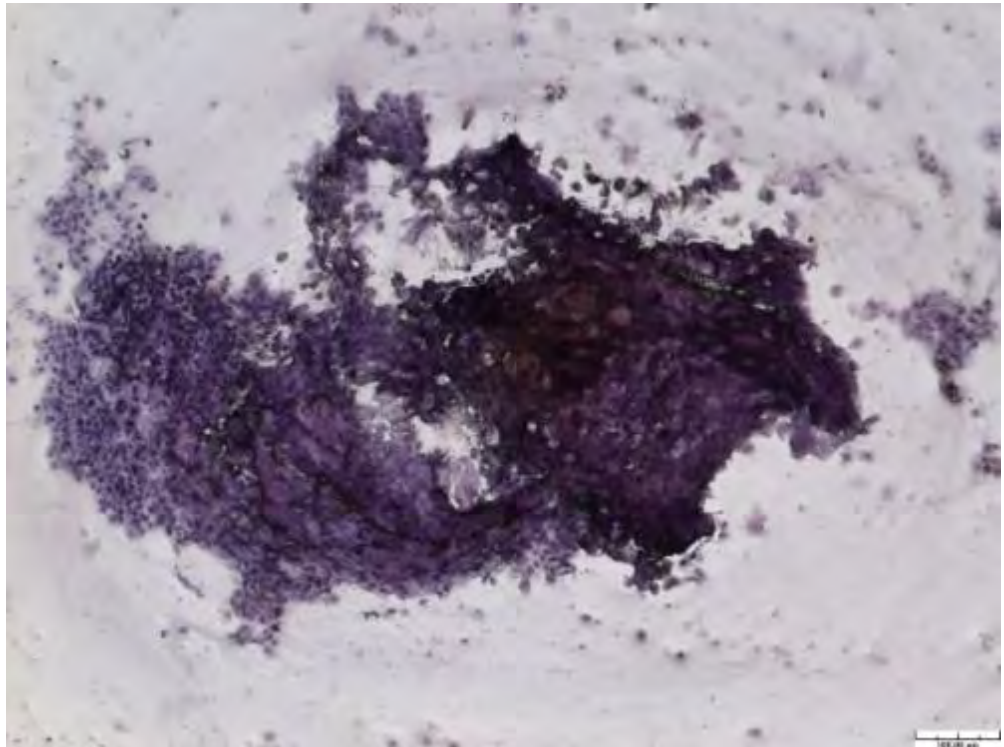


Histology



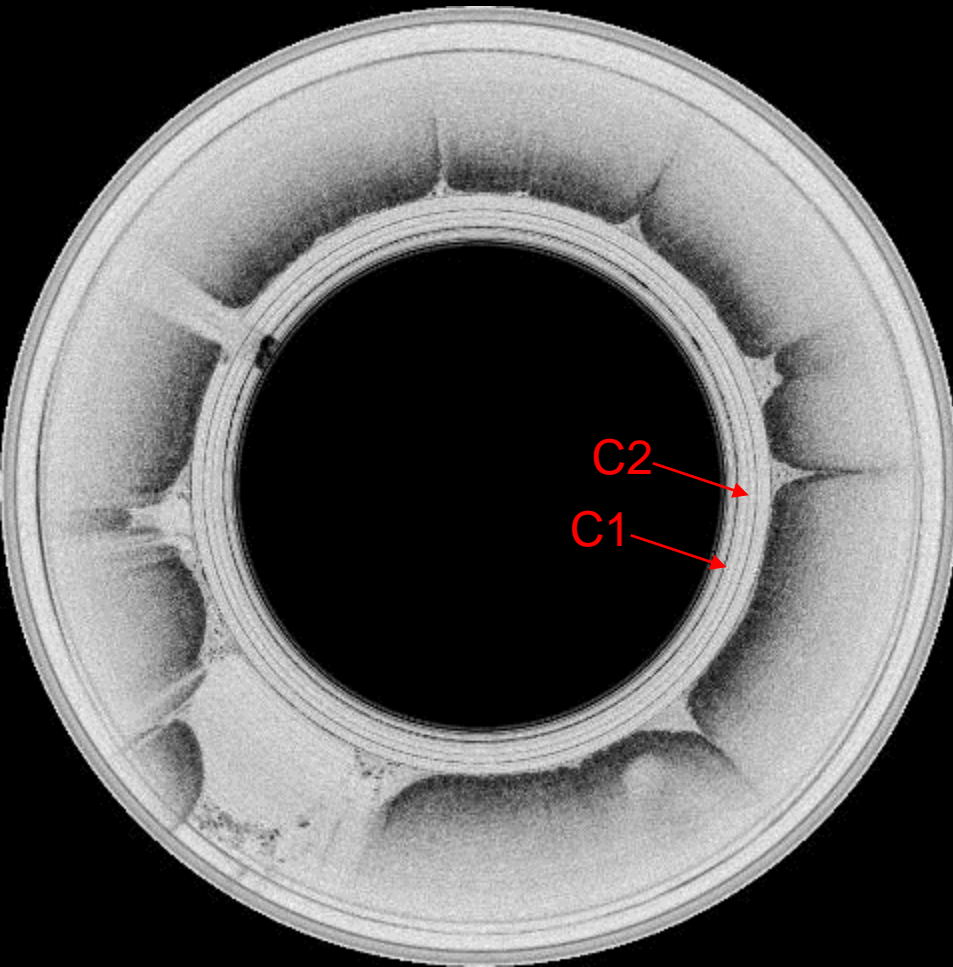
IVLCM: Tissue Expulsion and Incorporation into Device

- 1400 nm cw laser - 1s, 0.8 W
- Steam force breaks cellular bonds, expels tissue
- Tissue attaches to overlying thermopolymer

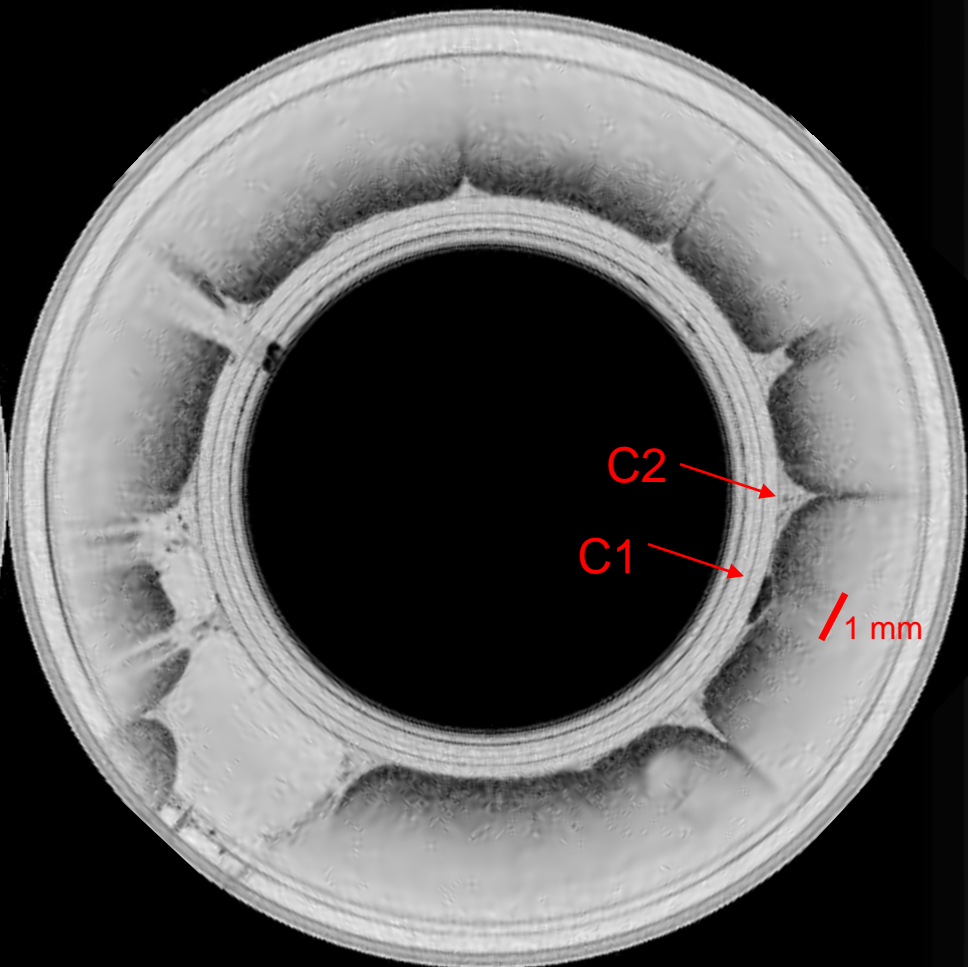


IVLCM: First-in-human

Pre-capture

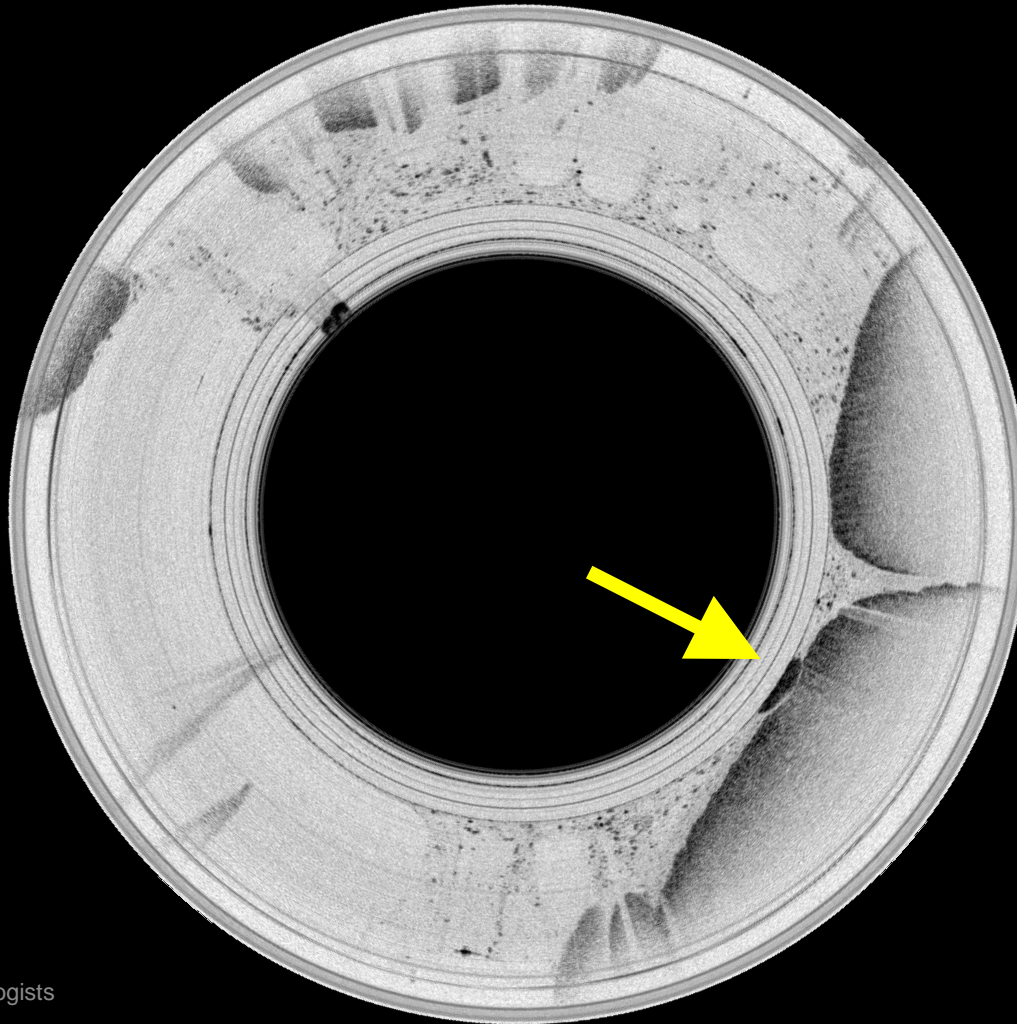


Post-capture

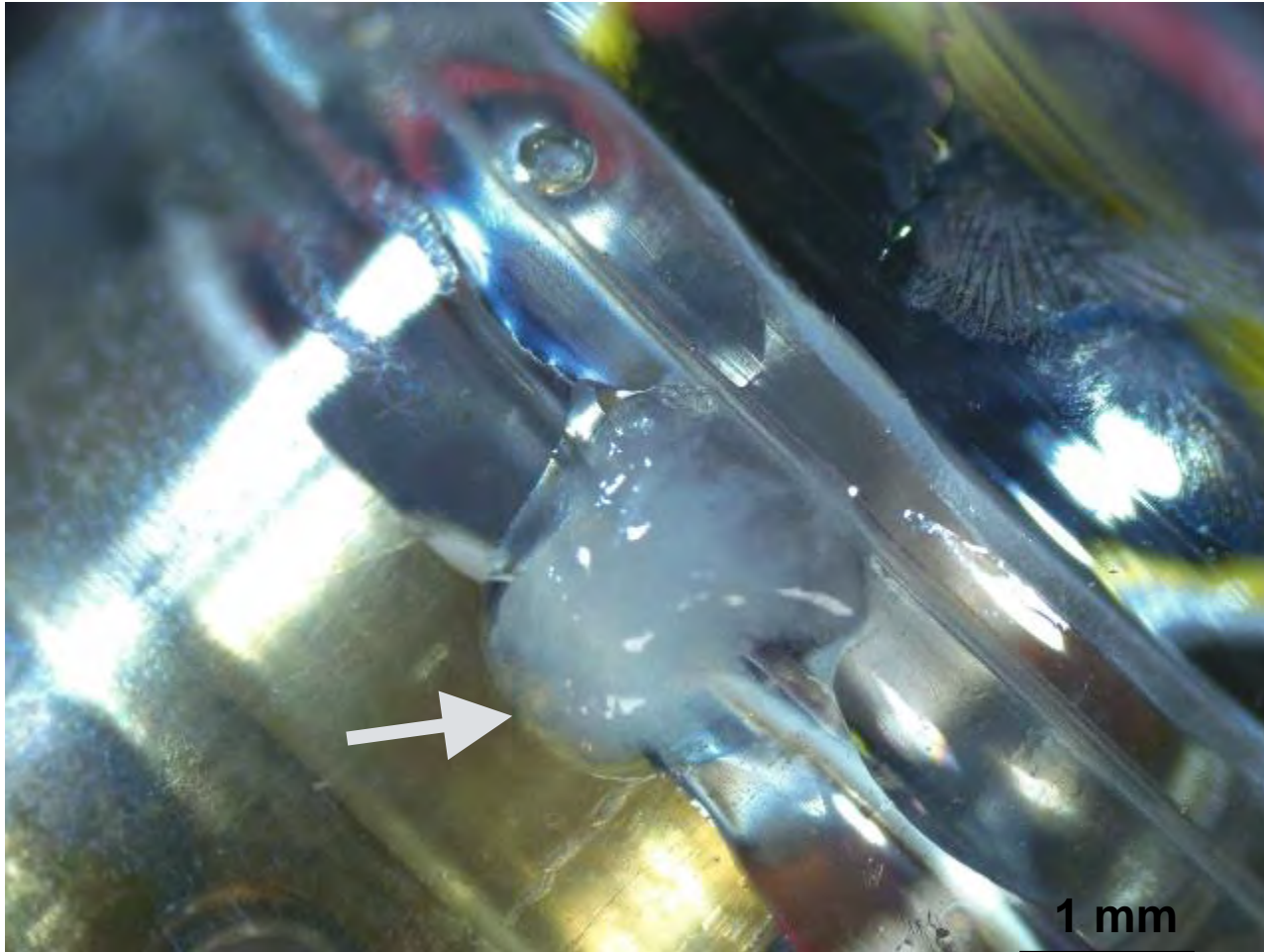


Tissue Retention

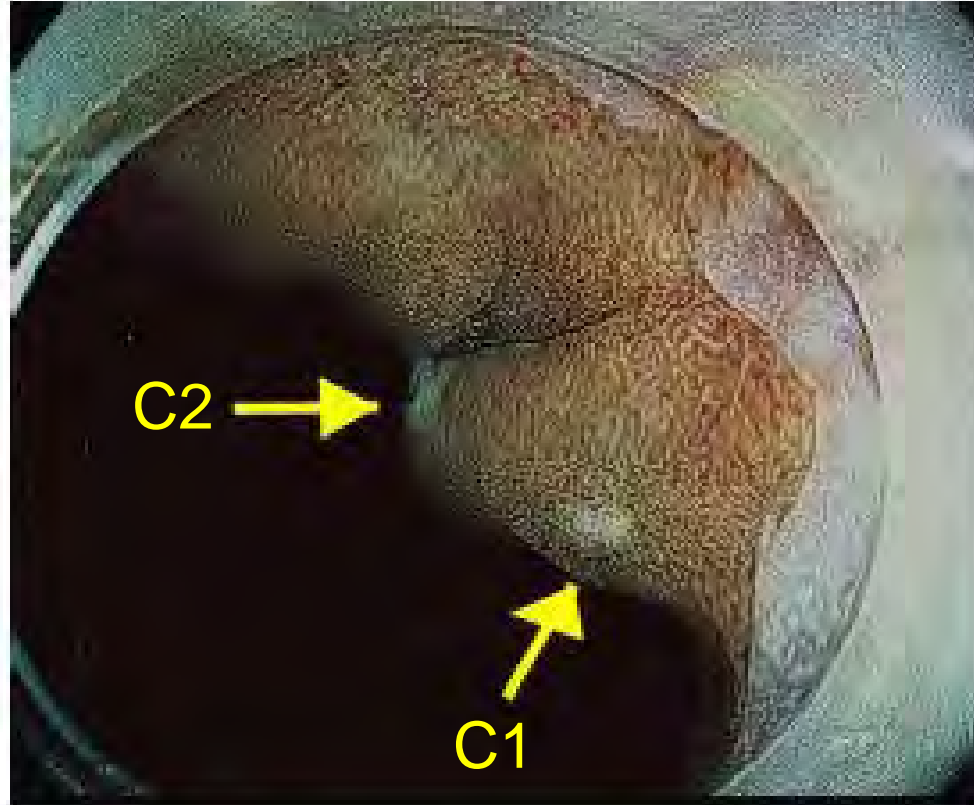
Captured tissue travelled through > 20 cm of esophagus



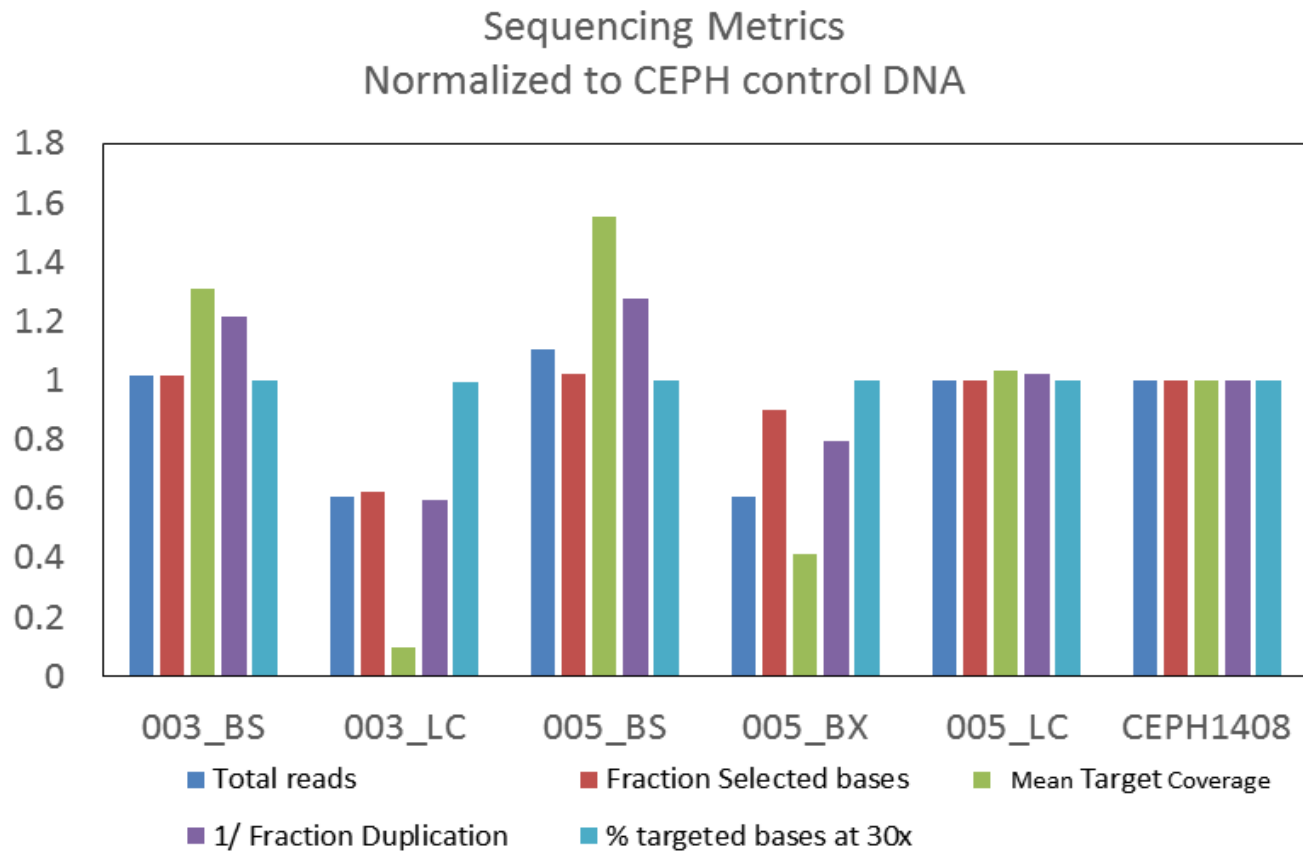
Stereoscope Image of Tissue on Capsule



Endoscopy



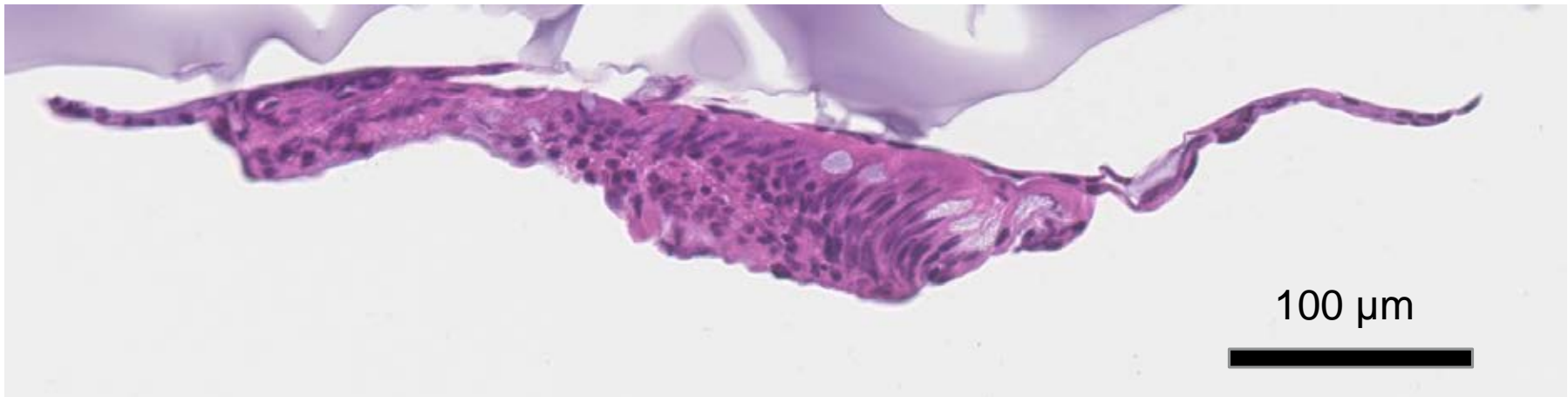
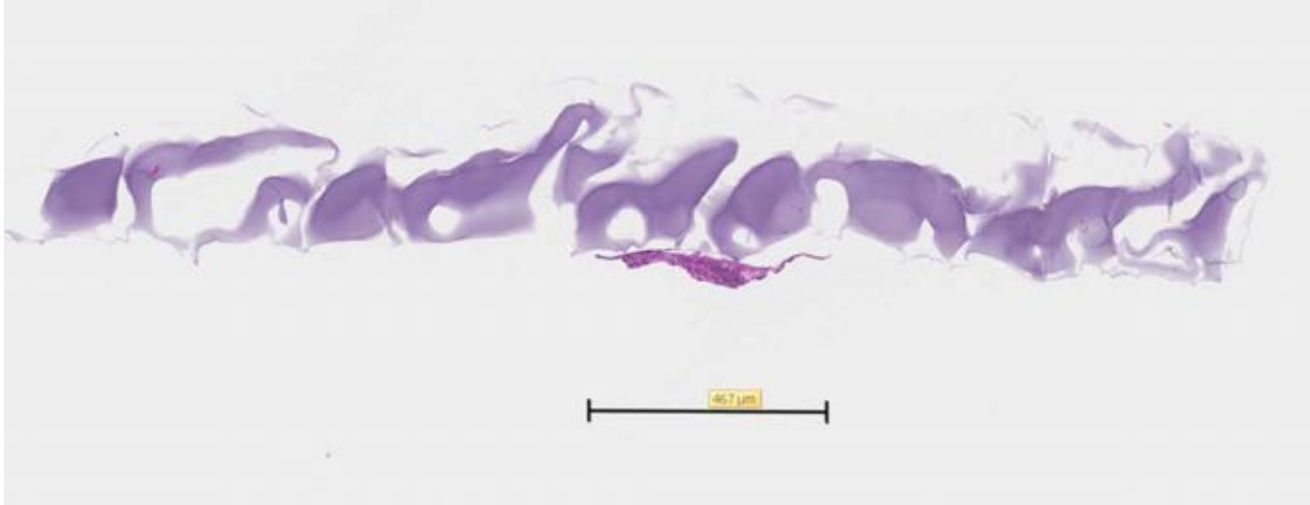
DNA Quality



BS: buccal swab. LC: Laser capture. BX: endoscopic biopsy.

Capture Film Tissue Morphology

- 1 Sec exposure time



Beyond Barrett's Esophagus

- **Similar work has been done throughout the GI tract to demonstrate increased diagnostic yields in stomach and colonic neoplasia**
- **Next phase is lung biopsies where preliminary clinical studies have shown increase in yield**
- **IVM in dermatology**

Conclusions

- Endomicroscopy (CLE & OCT) for conducting microcopy in living patients
- Opens up the possibility of improving the quality and yield of biopsies in the GI tract and other organ systems
- Early studies show that this promise may be realized
- Additional research using technologies such as capsules and IVLCM may provide hybrid devices that take IVM image-guided biopsies in the same instrument
- More work is needed to further develop and validate these technologies to demonstrate superiority over standard of care



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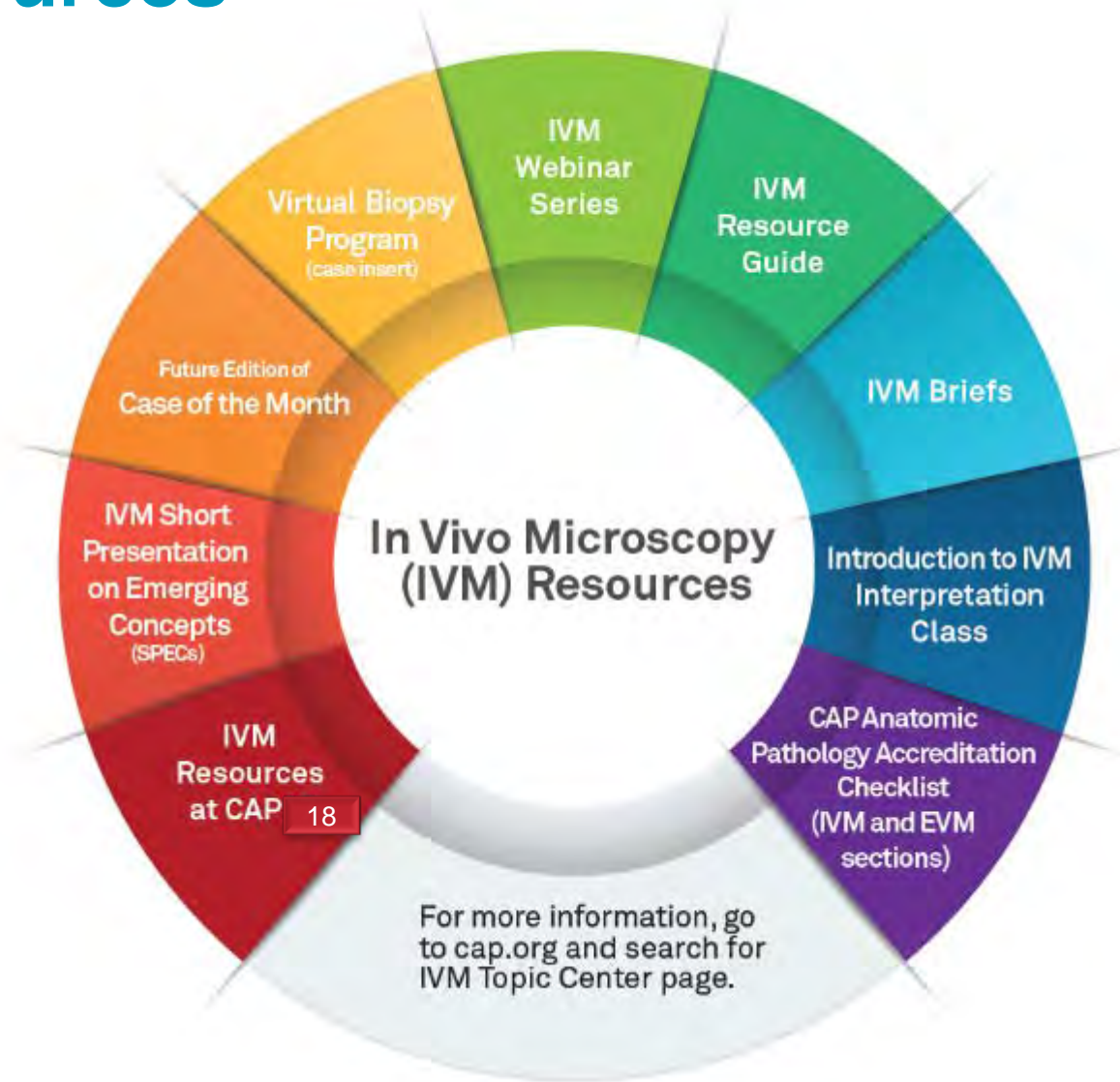
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Jay Rajagopal
Steve Rowe
Michael Strano
Kamran Sadiq
Mike Wallace
Ken Wang
Pratik Sharma
Asad Ali
John Poneris
Charlie Lightdale
DK Kang
Misia Gora

IVM Resources



Upcoming IVM Webinars

Date	Topic	Speaker
April	Introduction to Different EVM Technologies	Savitri Krishnamurthy, MD, FCAP

Register for these upcoming webinars as well as archived webinars:
cap.org > Calendar > Webinars

The CAP In Vivo Microscopy Resource Guide – see handout

- The IVM resource guide highlights current IVM articles and other resources that assist in understanding and potentially adopting IVM and EVM
 - Printed guides are available for members (\$39) and non-members (\$69)
 - The digital copies of all four Resource Guides are a complimentary member benefit
 - Access them www.cap.org > Resources and Publications

IVM Short Presentations on Emerging Concepts (SPECs) – see handout

- IVM SPECs are:
 - Short PowerPoints, created for pathologists
 - Useful for educating colleagues about IVM and GI specialist on the role and value of pathologists in IVM
- IVM SPEC Topics:
 - In Vivo Microscopy (IVM): A New Role for Pathologists
 - IVM of the GI Tract
 - Ex Vivo Microscopy (EVM): A New Tool for Pathologists
 - Access them www.cap.org > Resources and Publications



IVM Topic Center Page on CAP.ORG

- Check the IVM Topic Center for continued updates and for all your IVM resources

www.cap.org > Search for “IVM Topic Center”

THANK YOU!

Thank you for attending our webinar “**IVM Guided Biopsy: Advances in Barrett’s Esophagus Surveillance**” by Guillermo Tearney, MD, PhD, FCAP, FACC, FOSA, FNAI

For comments about this webinar or suggestions for upcoming webinars, contact ivminfo@cap.org

NOTE: There is no CME/CE credit available for today’s complimentary webinar.
The pdf of the presentation will be sent out in about 1 week.



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