



COLLEGE of AMERICAN
PATHOLOGISTS

Incorporation of In Vivo Microscopy (IVM) into Pathology Practice

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July 10, 2018

Hany Osman, MD

- Completed medical school at Cairo University of Medicine and completed his residency and dermatopathology fellowship at Indiana University School of Medicine
- The first In-Vivo Microscopy fellow at Massachusetts General Hospital, Harvard Medical School, Boston
- Involved in multiple projects that aim to advance in-vivo microscopy



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Disclosure

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Confocal Laser Endomicroscopy

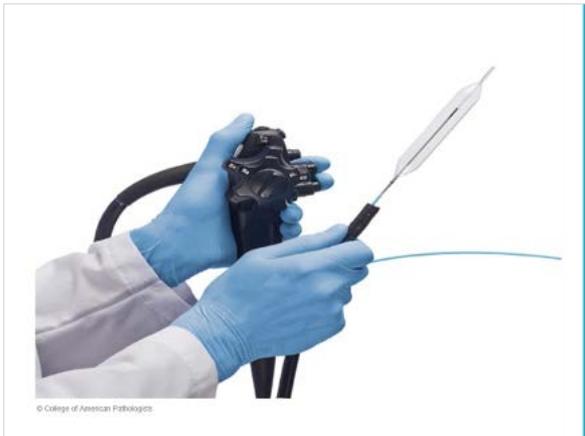


Reflectance Confocal Microscopy



Confocal

Volumetric Laser Endomicroscopy

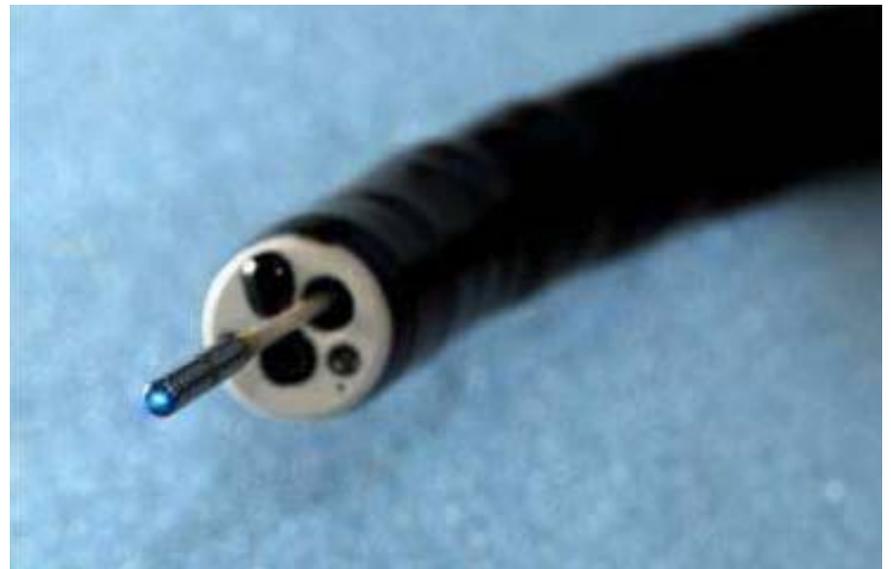


Tethered Capsule endomicroscopy



OCT





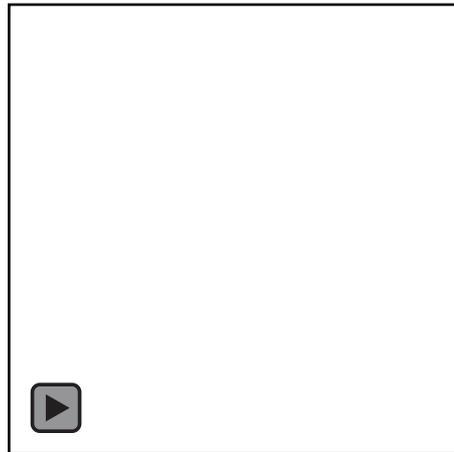
~1 μm axial resolution
Depth ~ 250 μm



En-Face



Injected Fluorescein
Contrast







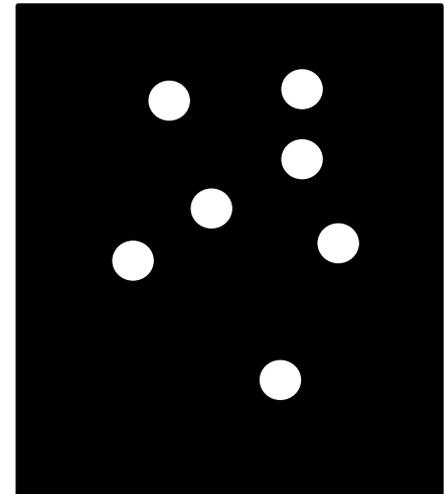
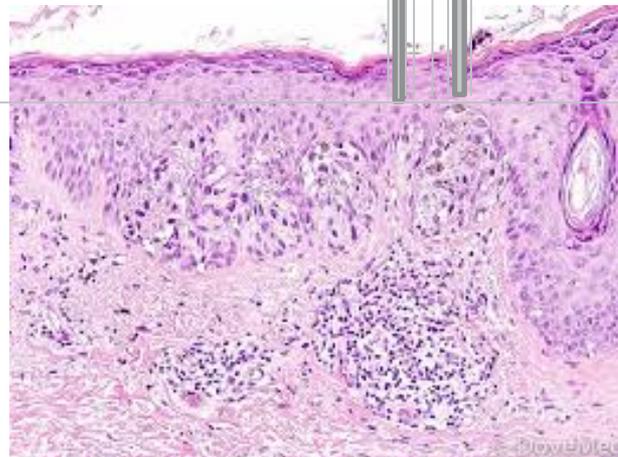
~1 μm axial resolution
Depth ~ 100-200 μm



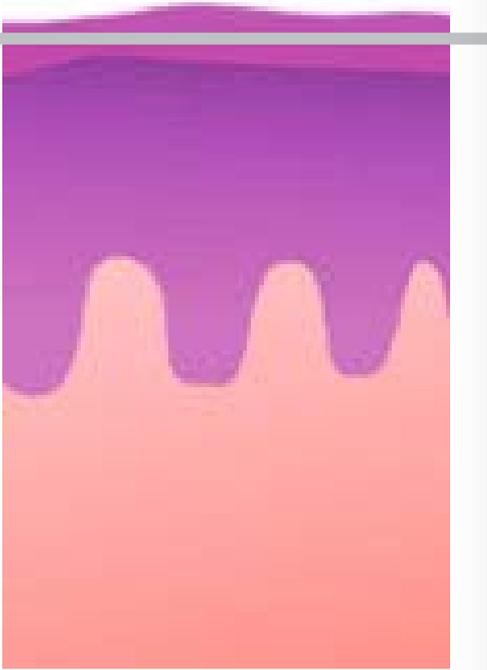
En-Face



No Contrast needed

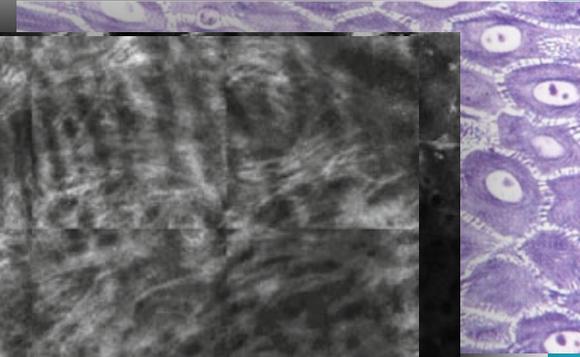
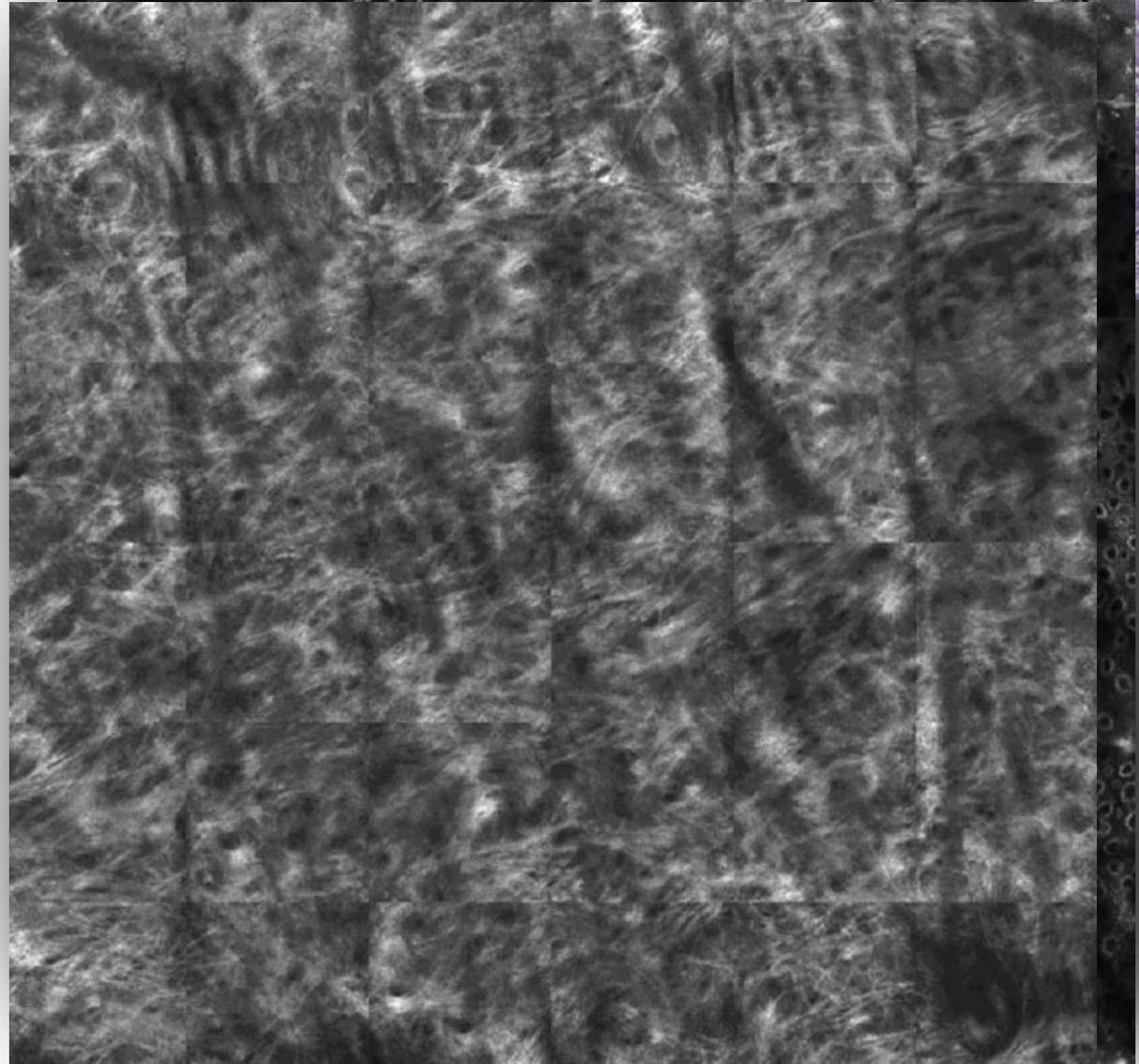


Utility in Dermatopathology



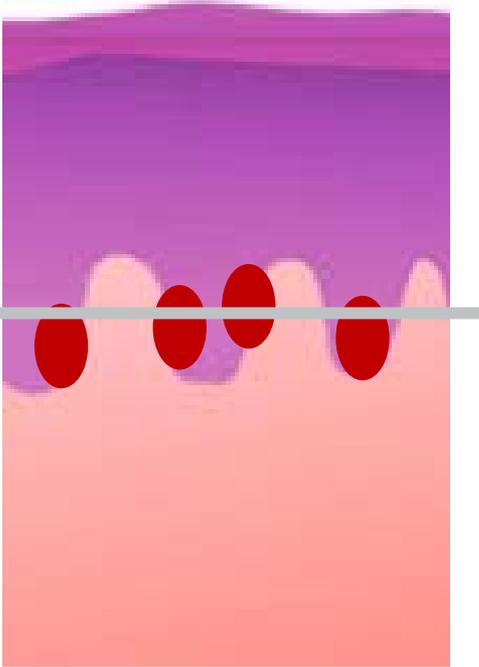
Hofmann-Wellenhof, Rainer, et al., eds. *Reflectance confocal microscopy for skin diseases*. Springer Science & Business Media, 2012.

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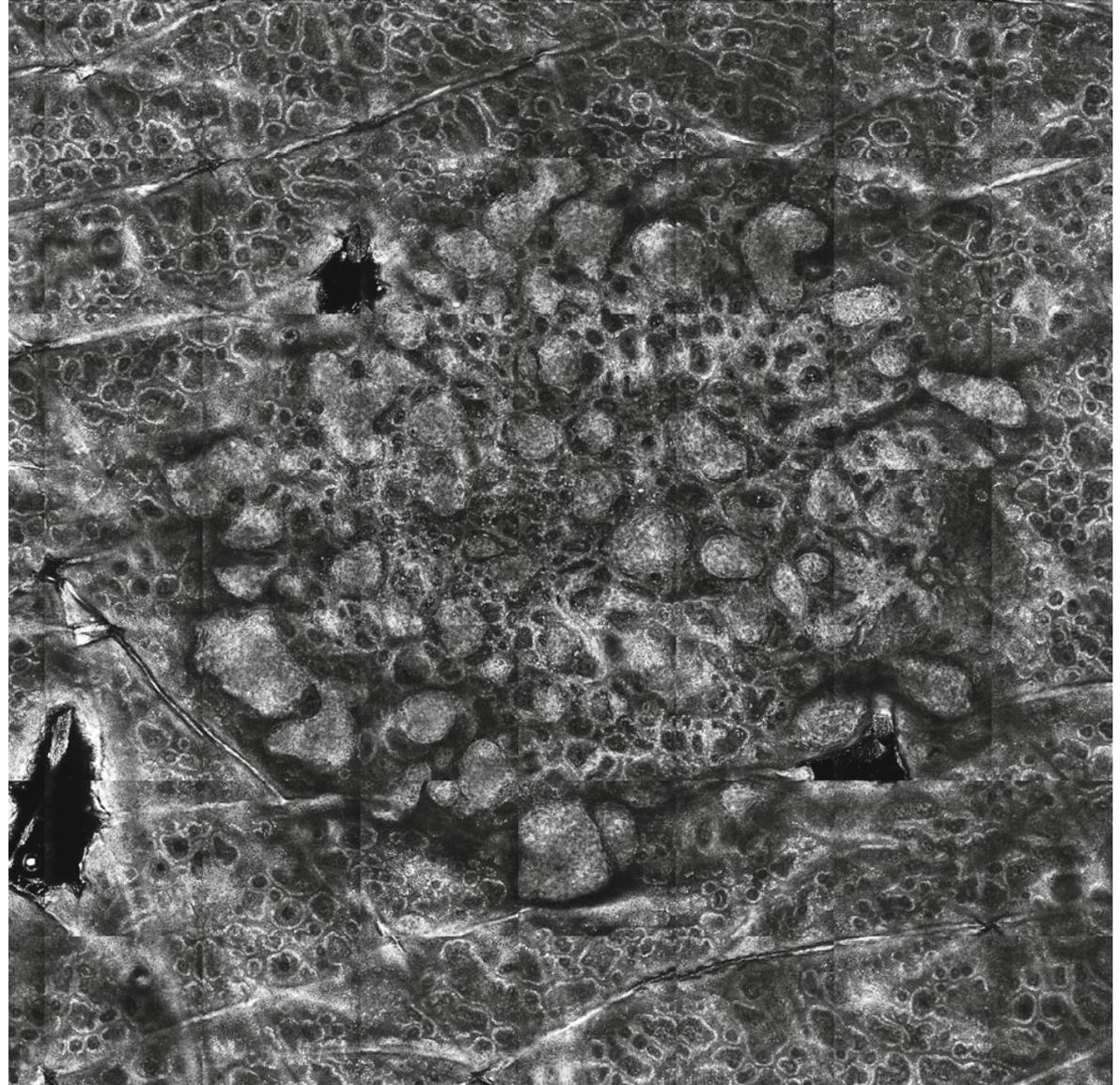


Utility in Dermatopathology

Junctional nevus

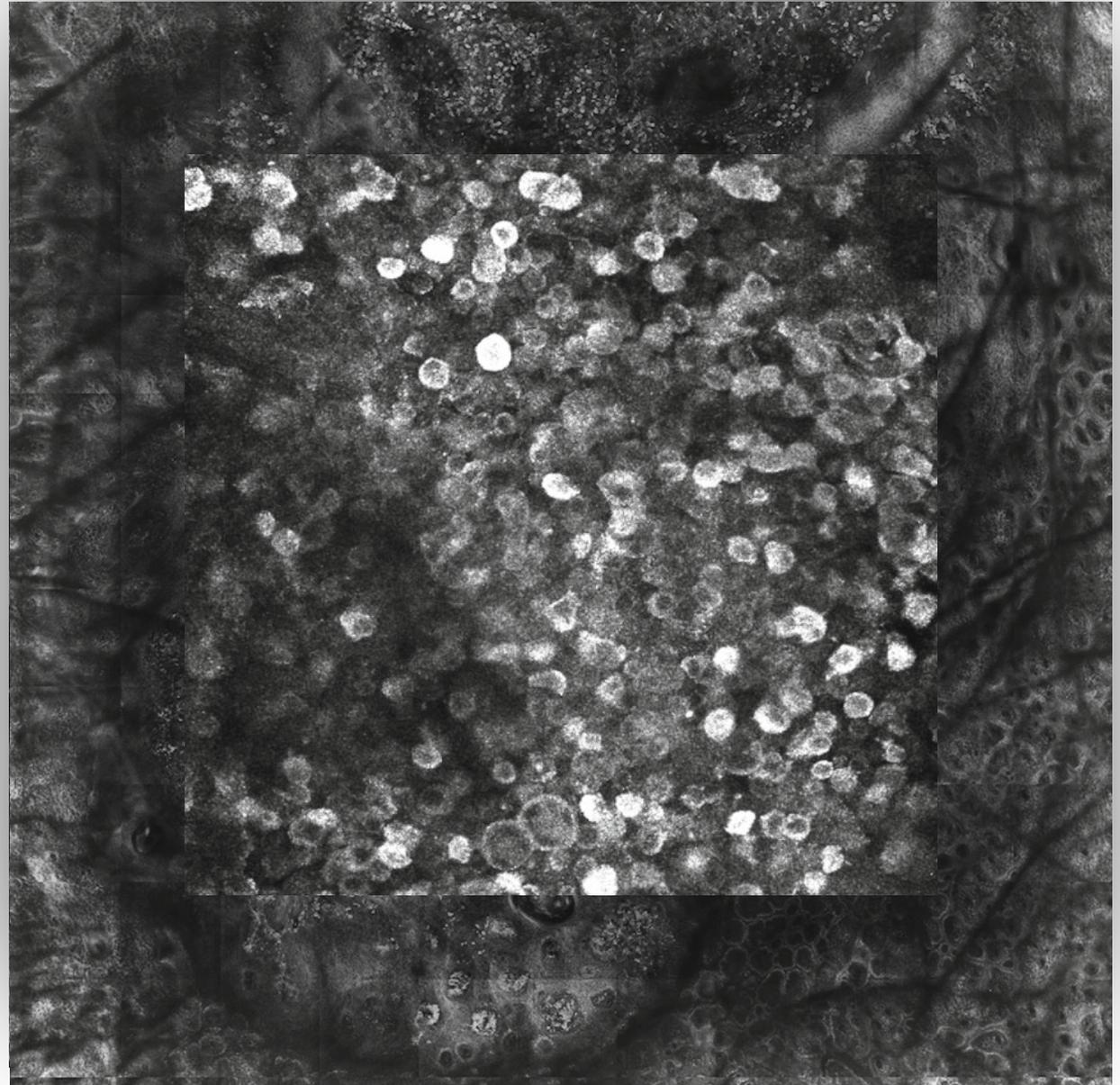


Hofmann-Wellenhof, Rainer, et al., eds. *Reflectance confocal microscopy for skin diseases*. Springer Science & Business Media, 2012.



Utility in Dermatopathology

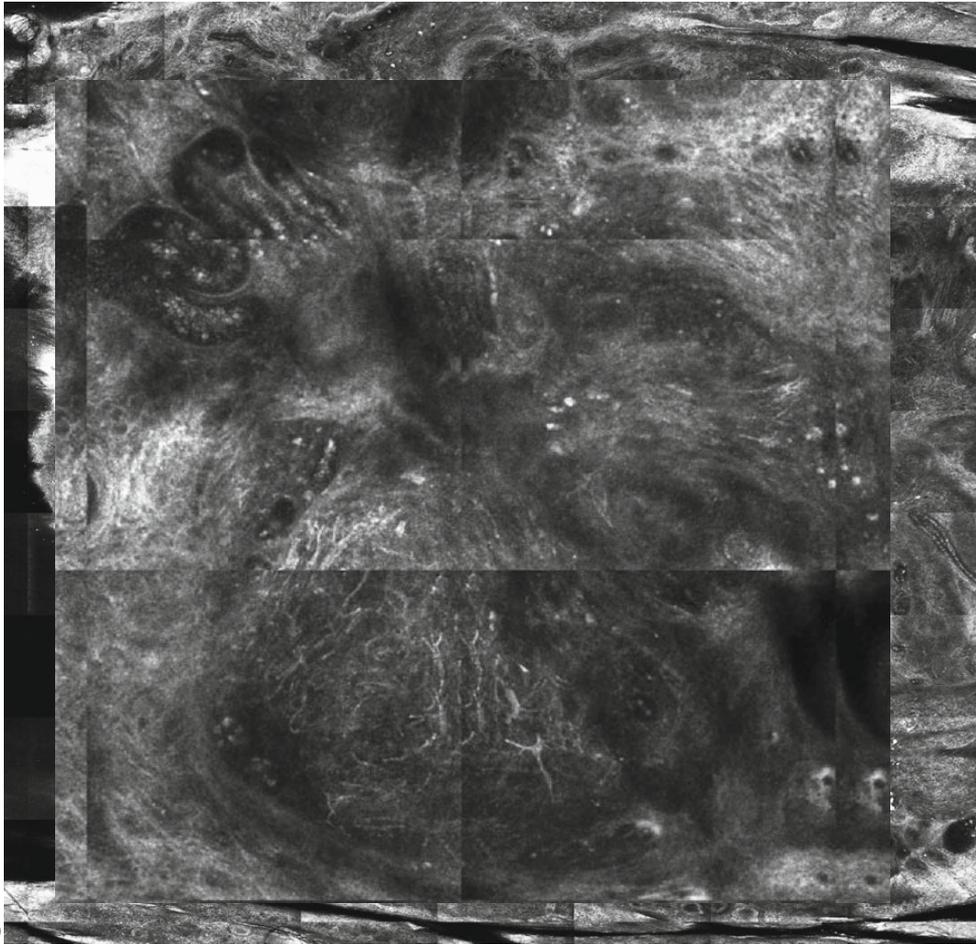
Melanoma



Hofmann-Wellenhof, Rainer, et al., eds. *Reflectance confocal microscopy for skin diseases*. Springer Science & Business Media, 2012.

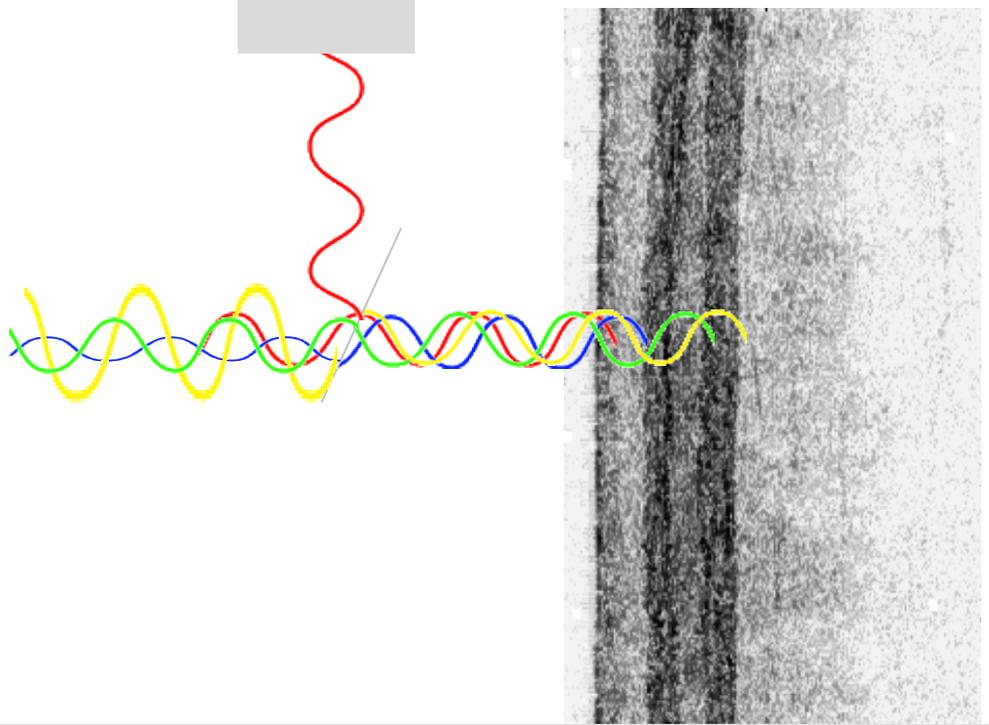
Utility in Dermatopathology

Basal cell carcinoma



Hofmann-Wellenhof, Rainer, et al., eds. *Reflectance confocal microscopy for skin diseases*. Springer Science & Business Media, 2012.





~10 μm axial resolution
Depth ~ 2-3mm



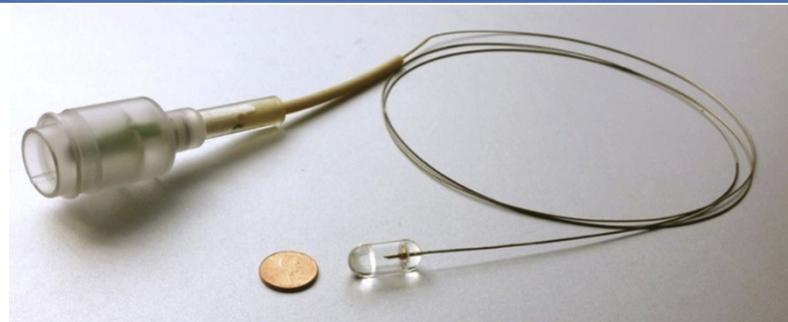
Cross-sectional

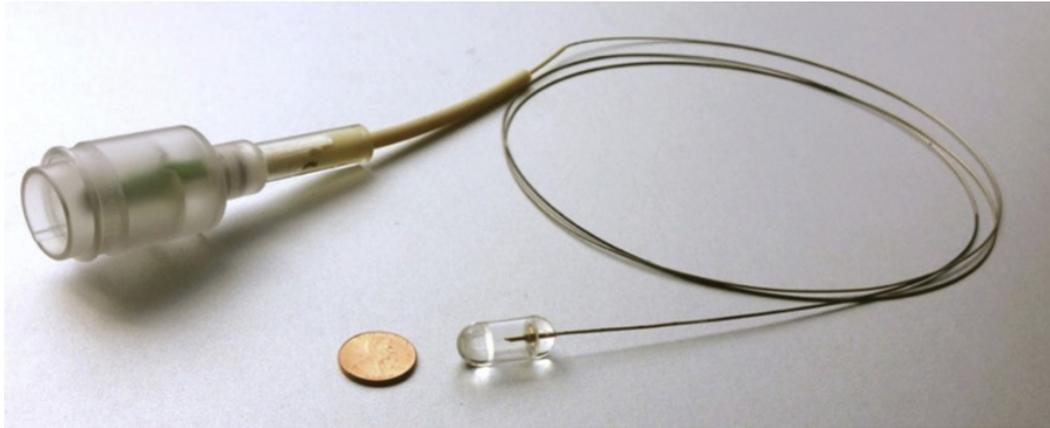


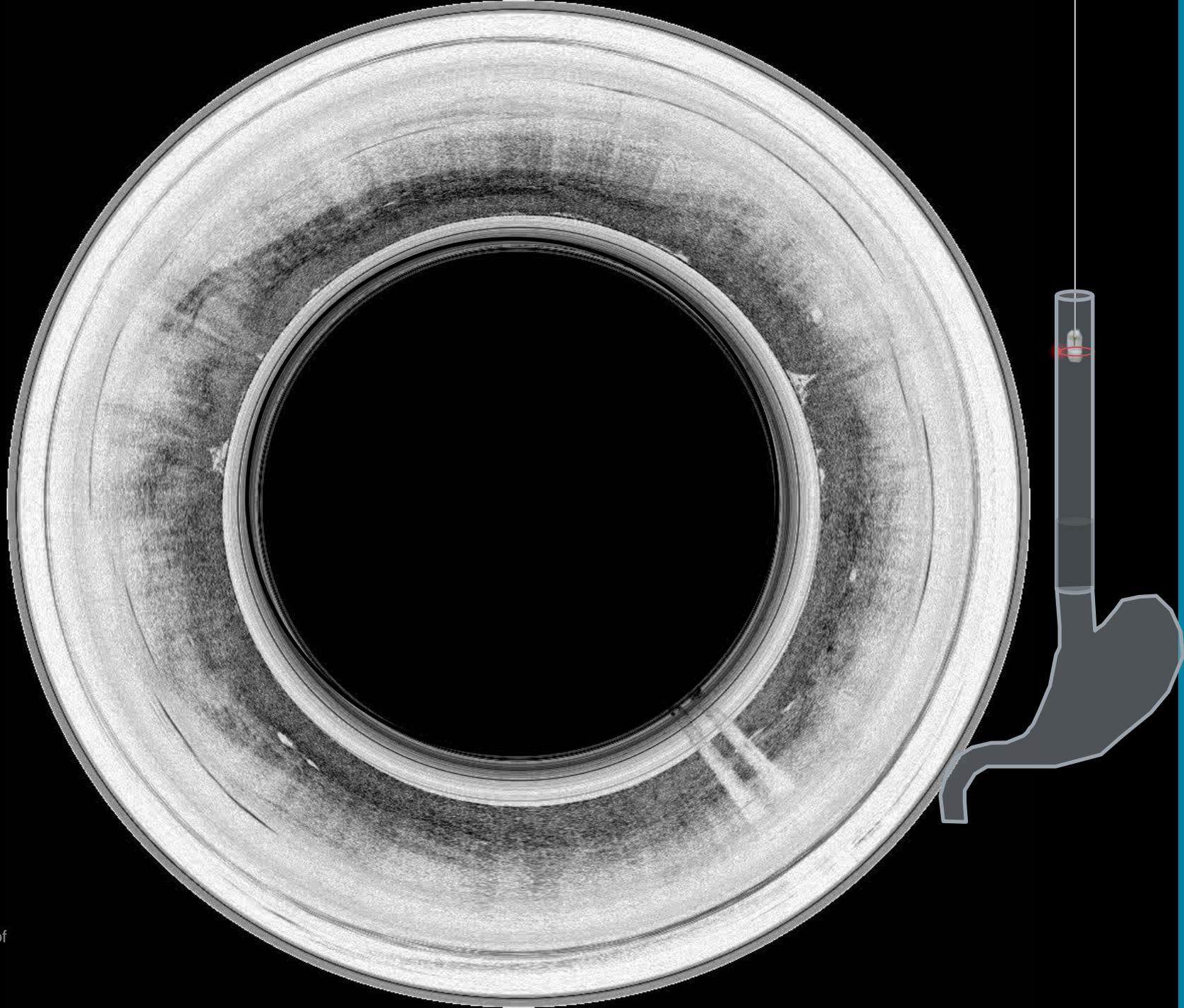
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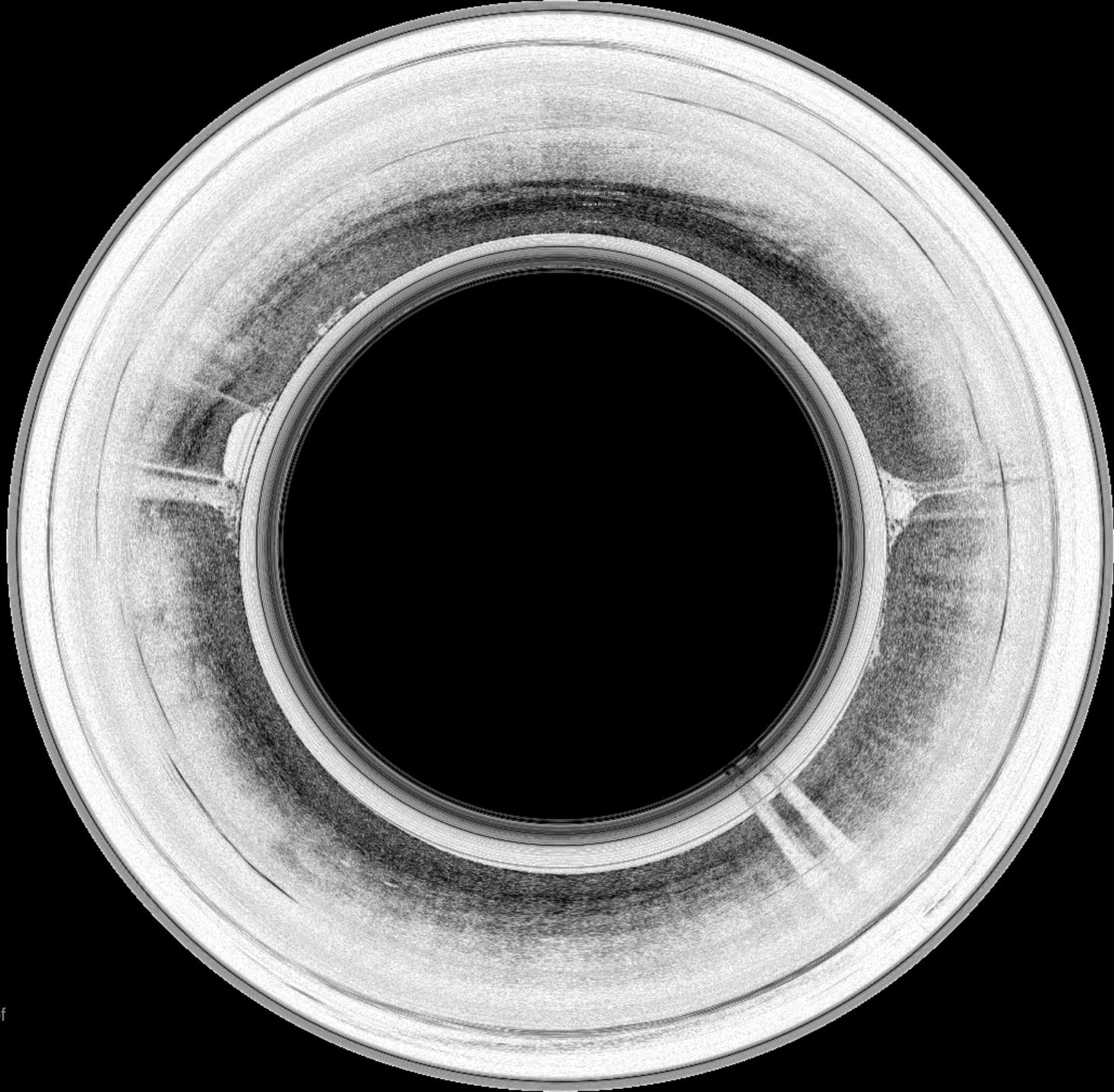








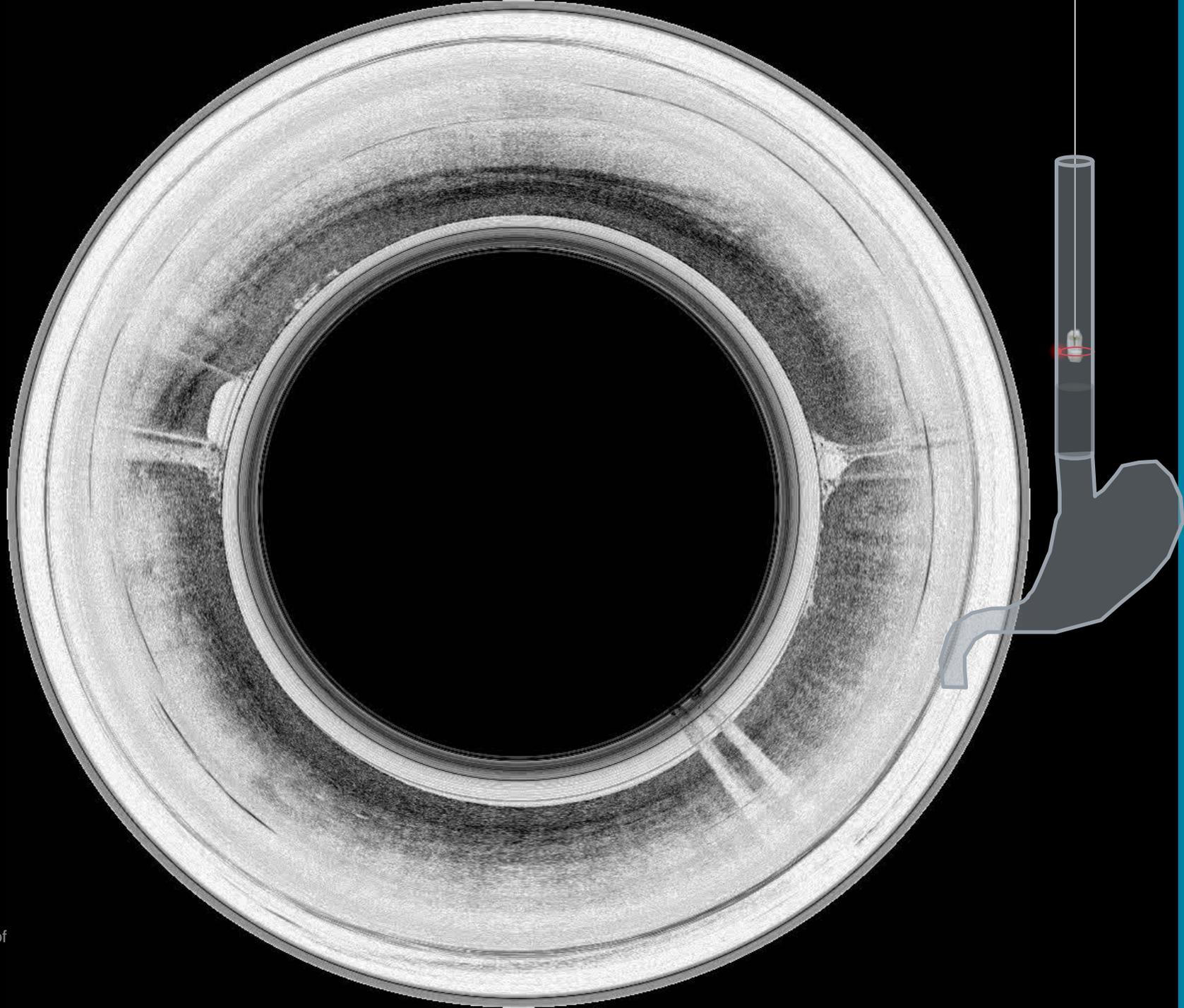


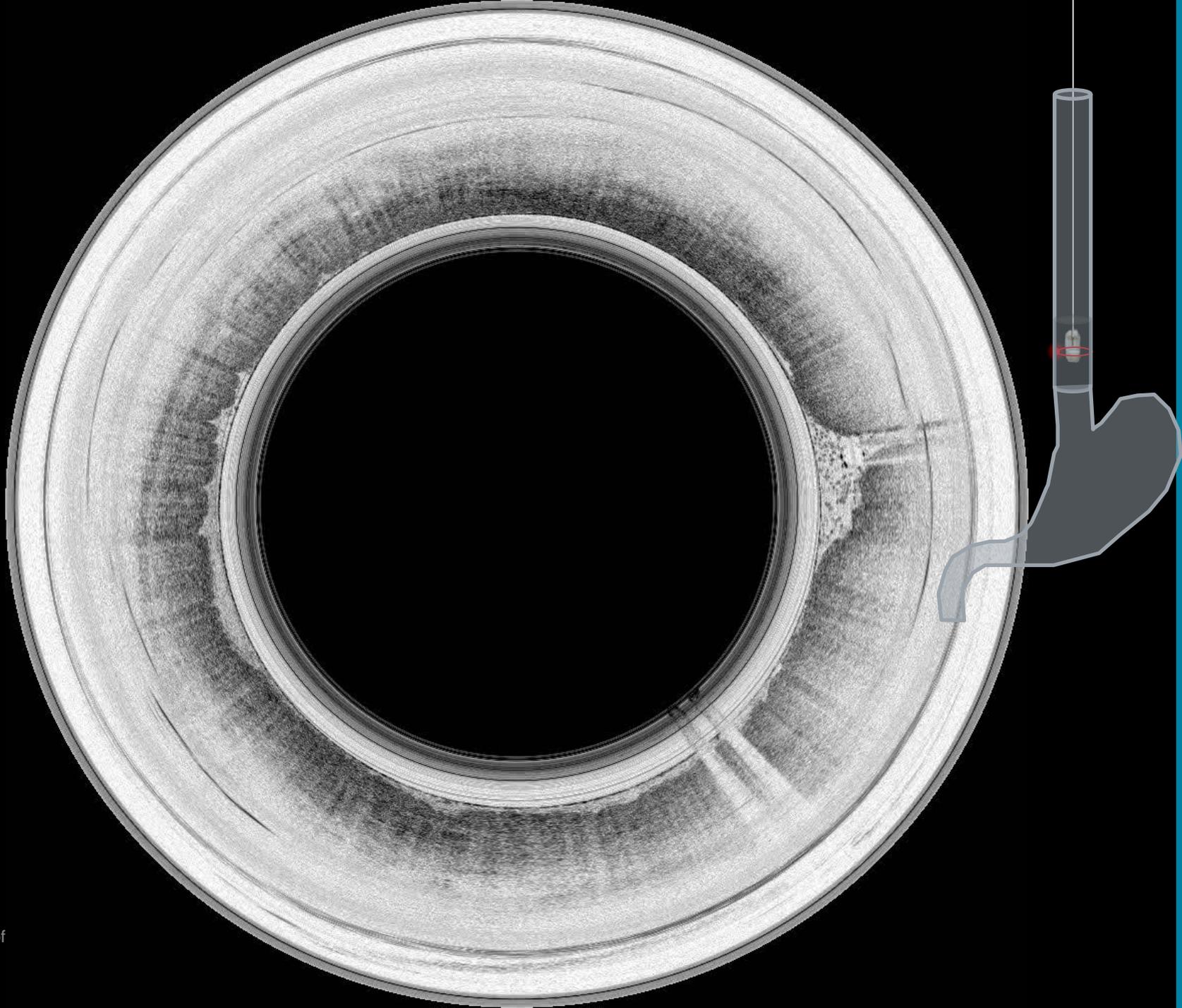


Muscularis Interna

Submucosa
Muscularis
mucosa
Lamina Propria

Epithelium





Spectrally Encoded Confocal Microscopy (SECM)



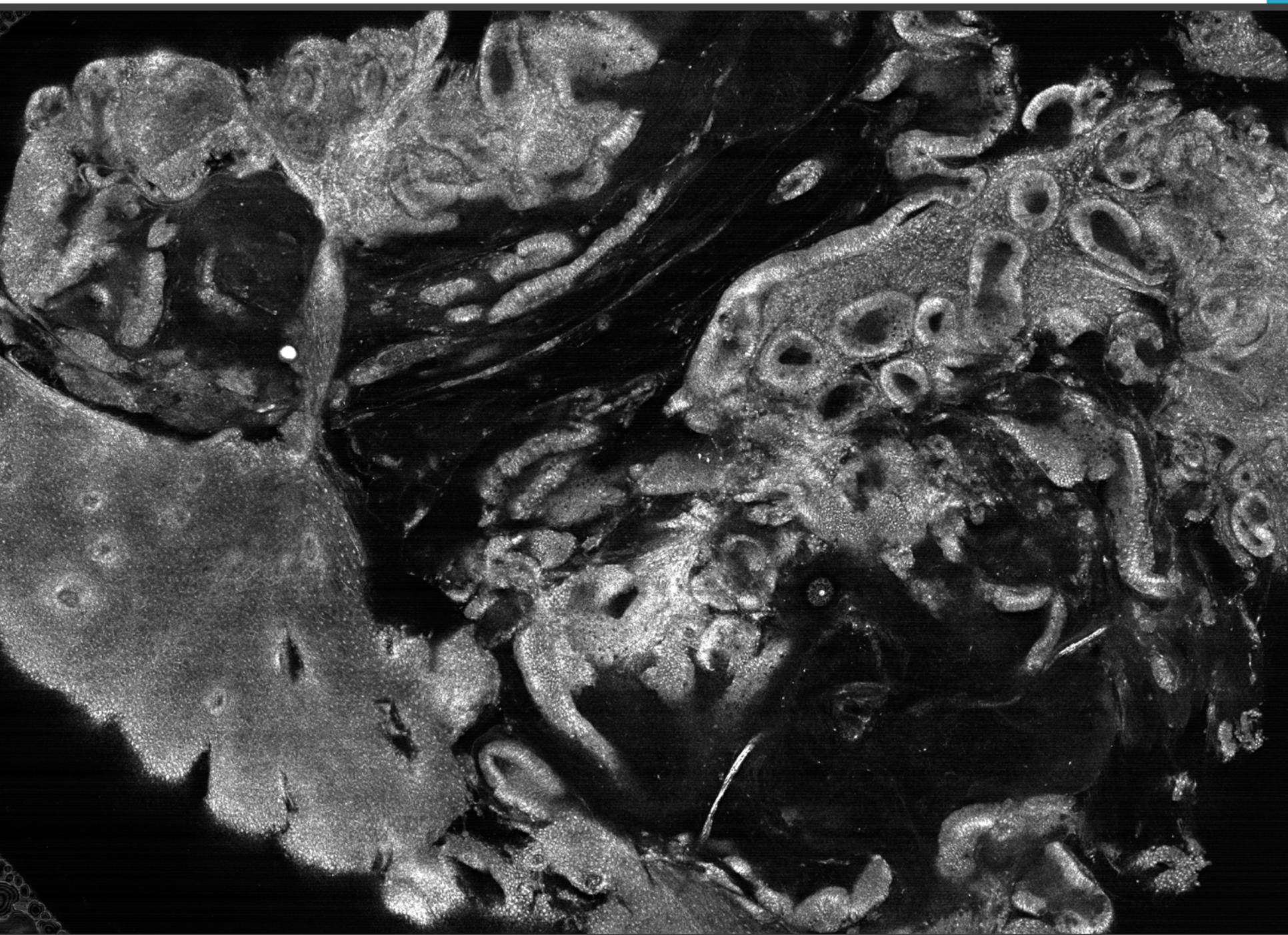
<5 μm axial resolution
Depth ~ 2-3mm



En-face

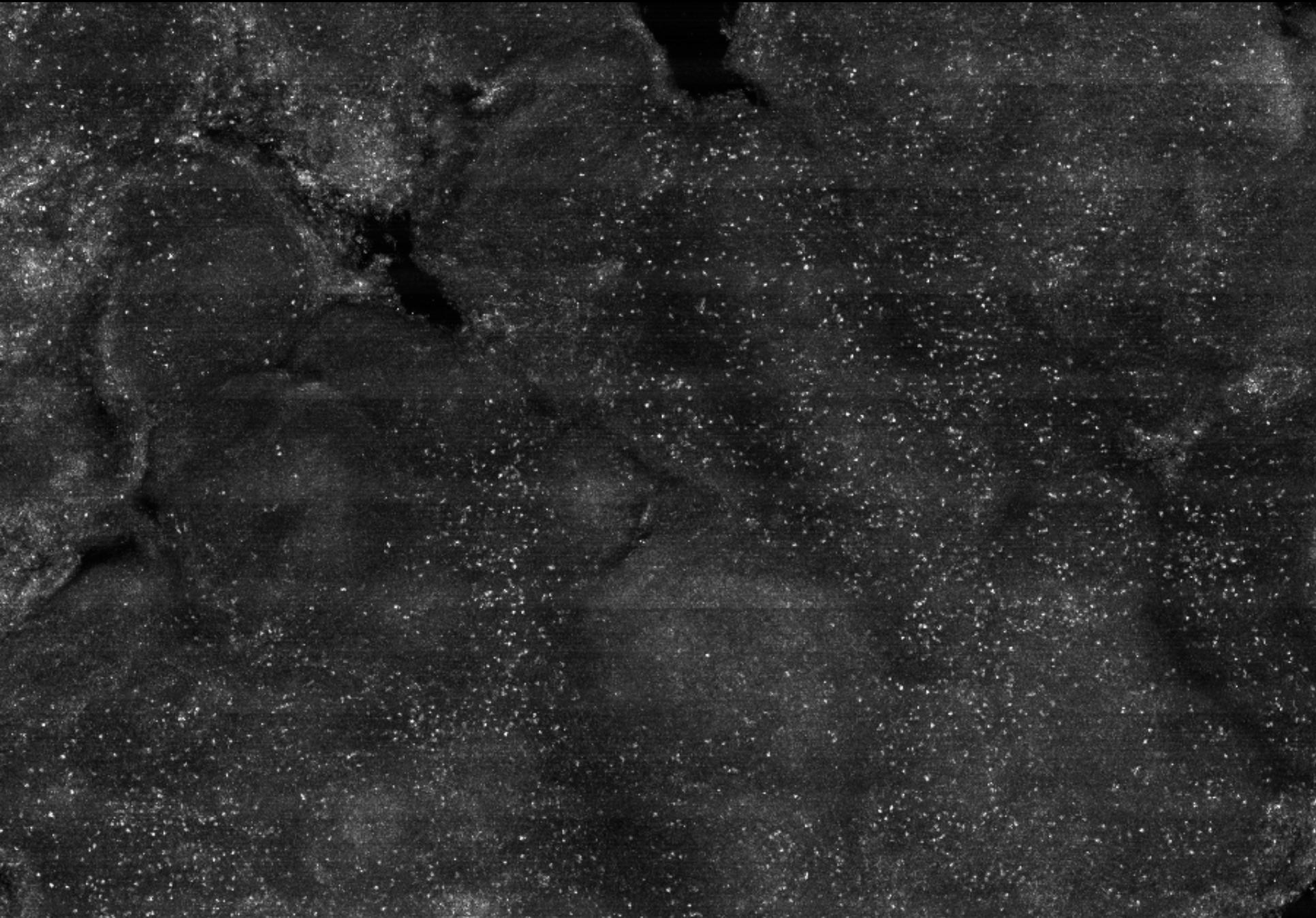


No Contrast needed

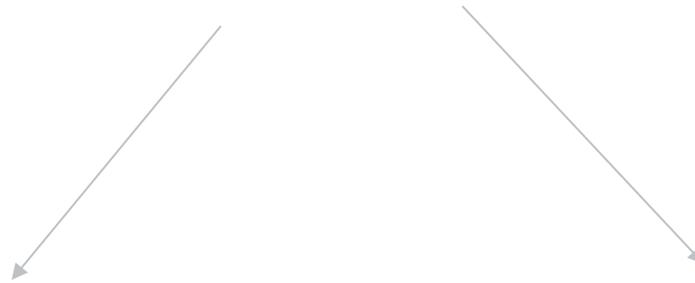




Imaging of Eosinophilic Esophagitis with SECM: Biopsy, No AA



Transition to Clinical Practice



Adoption

Incorporation

Adoption

Adoption

Resolution

Orientation/artefacts

Magnification

Color Map

**Ancillary
studies**

In-vivo based contrast

Adoption

Resolution

Orientation/artefacts

Magnification

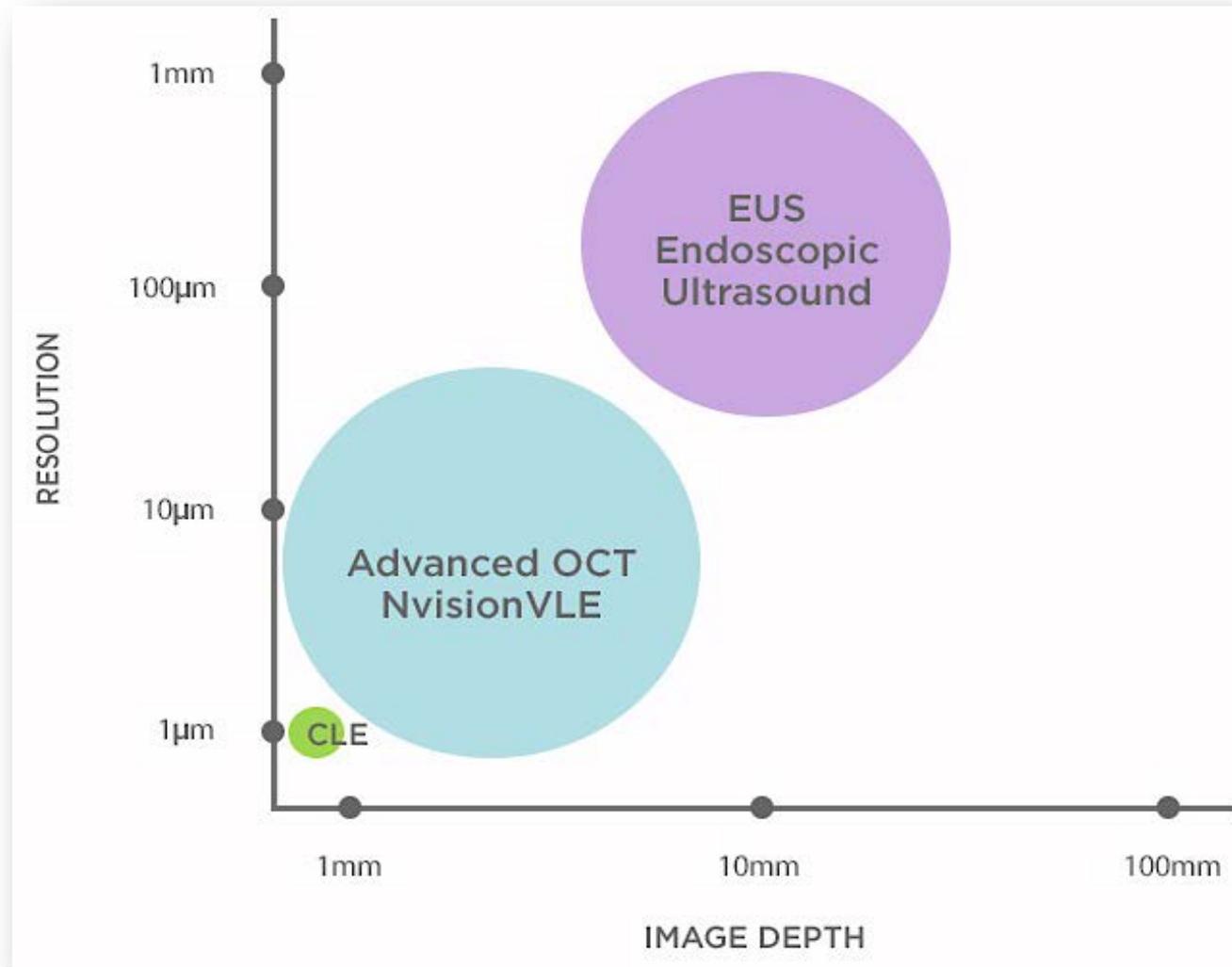
Color Map

**Ancillary
studies**

In-vivo based contrast

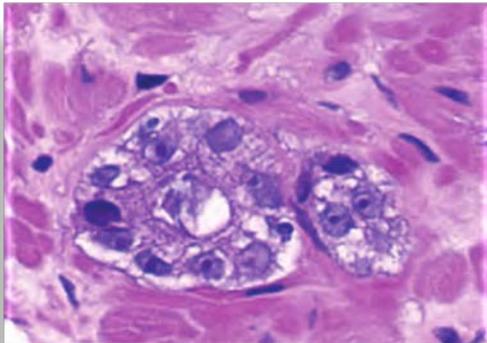
Adoption

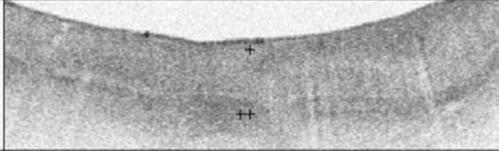
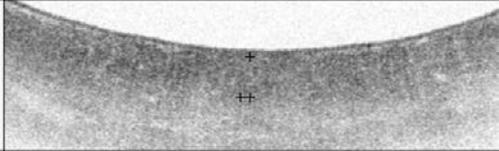
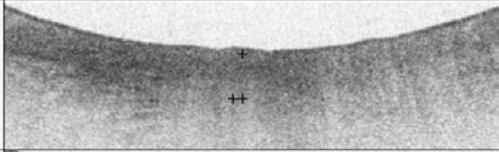
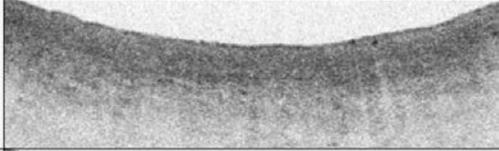
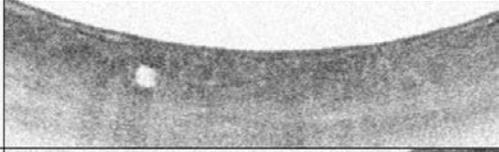
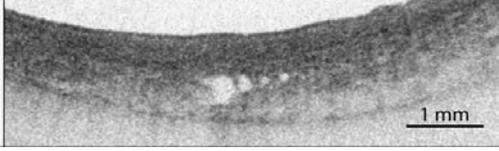
Resolution



Adoption

Resolution



Signal Intensity Score	surface intensity < subsurface intensity = 0	
	surface intensity = subsurface intensity = 1	
	surface intensity > subsurface intensity = 2	
Glandular Architecture Score	no mucosal glands = 0	
	glands or ducts without atypia* = 1	
	glands or ducts with atypia* = 2	

A score of >2 associated with a sensitivity of 83% and a specificity of 75% for BE Neoplasia

Evans, J.A., Poneros, J.M., Bouma, B.E., Bressner, J., Halpern, E.F., Shishkov, M., Lauwers, G.Y., Mino-Kenudson, M., Nishioka, N.S. and Tearney, G.J., 2006. Optical coherence tomography to identify intramucosal carcinoma and high-grade dysplasia in Barrett's esophagus. *Clinical Gastroenterology and Hepatology*, 4(1), pp.38-43.

Leggett, C.L., Gorospe, E.C., Chan, D.K., Muppa, P., Owens, V., Smyrk, T.C., Anderson, M., Lutzke, L.S., Tearney, G. and Wang, K.K., 2016. Comparative diagnostic performance of volumetric laser endomicroscopy and confocal laser endomicroscopy in the detection of dysplasia associated with Barrett's esophagus. *Gastrointestinal endoscopy*, 83(5), pp.880-888.

Adoption

Resolution

Orientation/artefacts

Magnification

Color Map

**Ancillary
studies**

In-vivo based contrast

Adoption

Resolution

Orientation/artefacts

Magnification

Color Map

**Ancillary
studies**

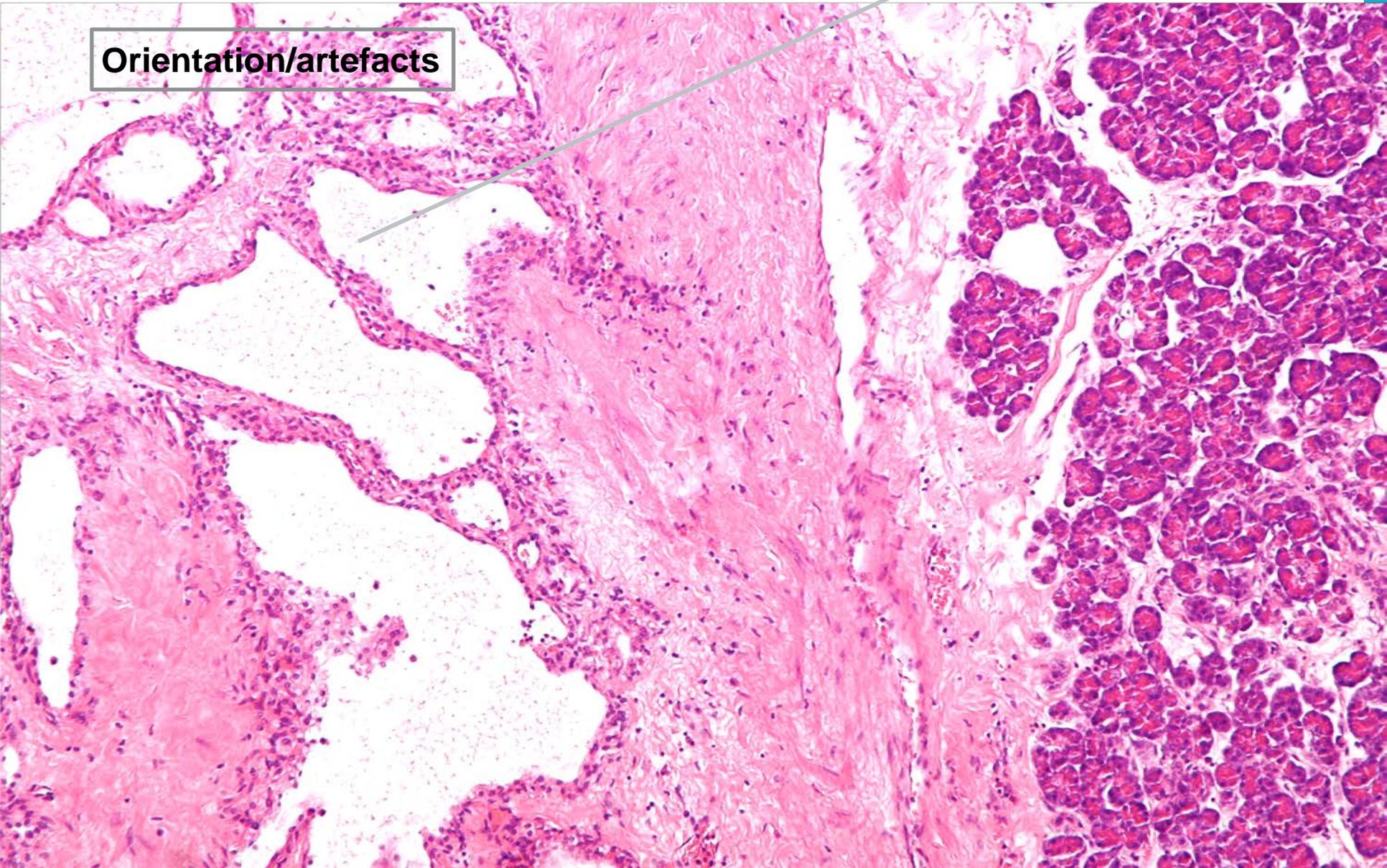
In-vivo based contrast

Adoption

Orientation/artefacts

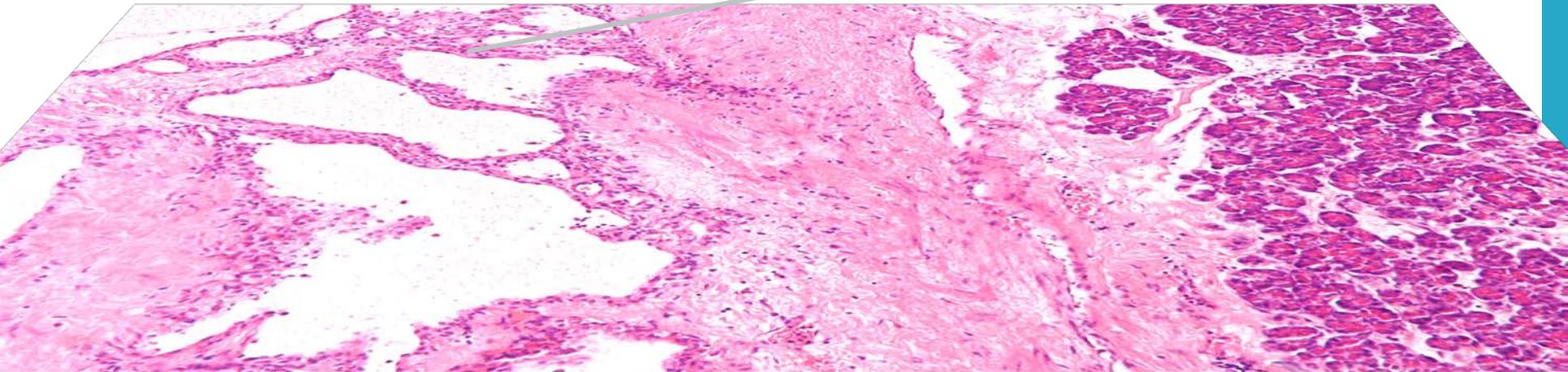
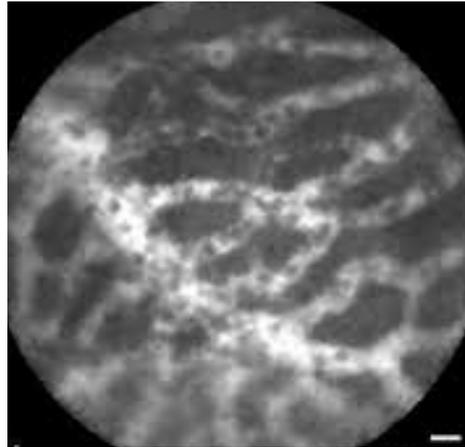
Adoption

Orientation/artefacts



Adoption

Orientation/artefacts

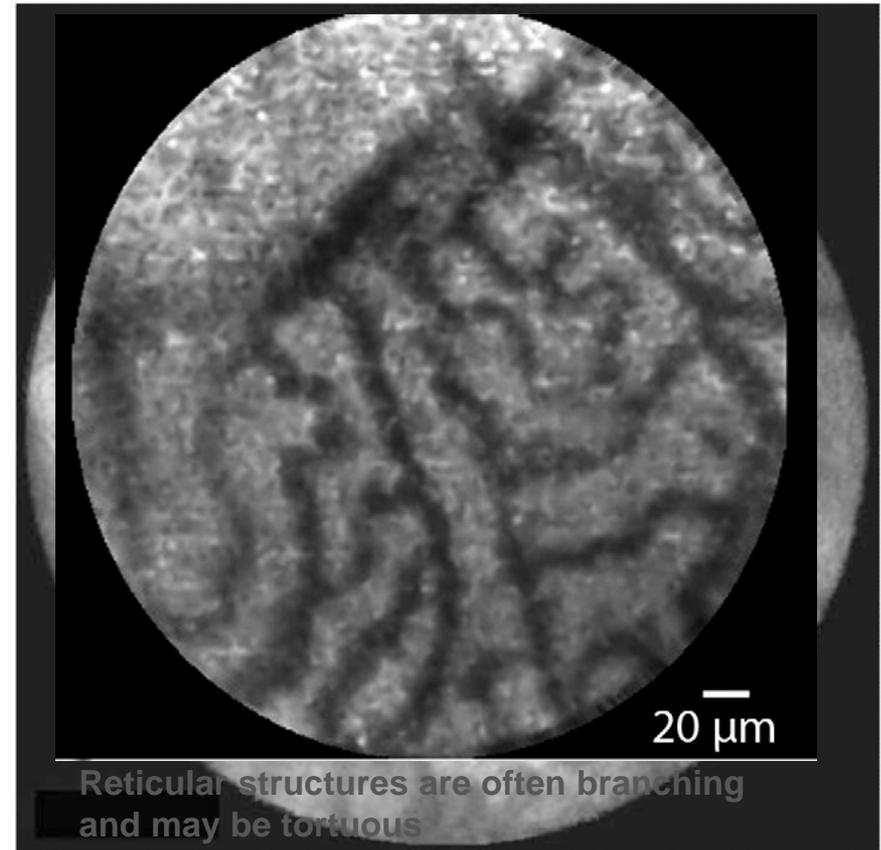


Adoption

Orientation/artefacts

- **Normal Bile duct – Miami and Paris Classifications**
 - Thin Reticular dark bands
 - less than 20
 - Fluorescein filled vessels
 - Less than 20 microns
 - Light gray background
 - Epithelium is usually not seen, may be seen if probe not in contact with duct

In-Vivo pCLE of Bile duct



Fluorescein containing vessels are often seen with gray background

Loeser, C.S., Robert, M.E., Mennone, A., Nathanson, M.H., and Jamidar, P. 2011. First assessment of probe-based confocal laser endomicroscopy (pCLE) in the biliary system. *Gastrointestinal Endoscopy*, 74(3), p.1039-1040.

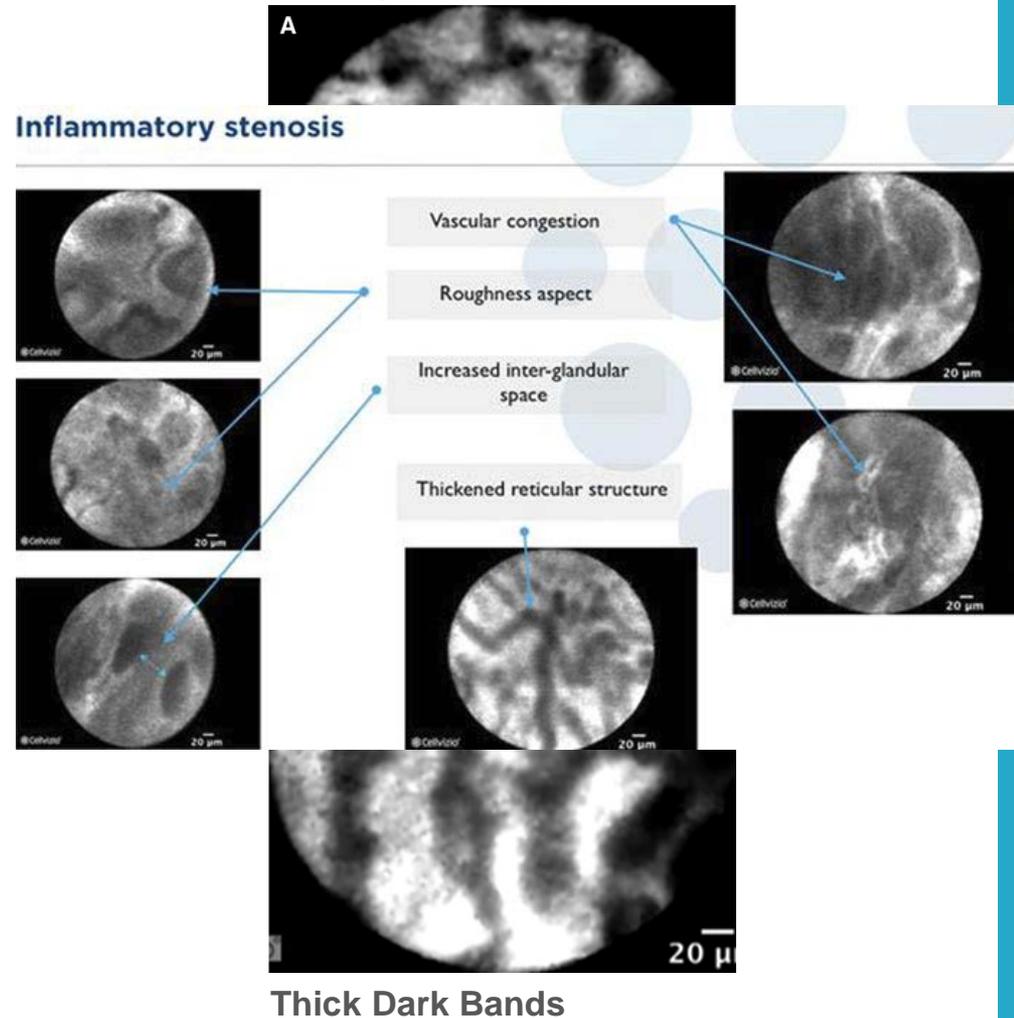
Loeser, C.S., Robert, M.E., Mennone, A., Nathanson, M.H., and Jamidar, P. 2011. Confocal endomicroscopic examination of malignant biliary strictures and histologic correlation with lymphatics. *Journal of clinical gastroenterology*, 45(3), p.246.

Adoption

Orientation/artefacts

- **Inflammatory Bile duct – Paris Classification**
 - Thickened Reticular dark bands
 - More than 20 microns
 - Regular
 - Vascular congestion (thick vessels)
 - Multiple thin white bands (regular)
 - Dark granular patterns with scales
 - Increased inter-glandular space

In-Vivo pCLE of Bile duct

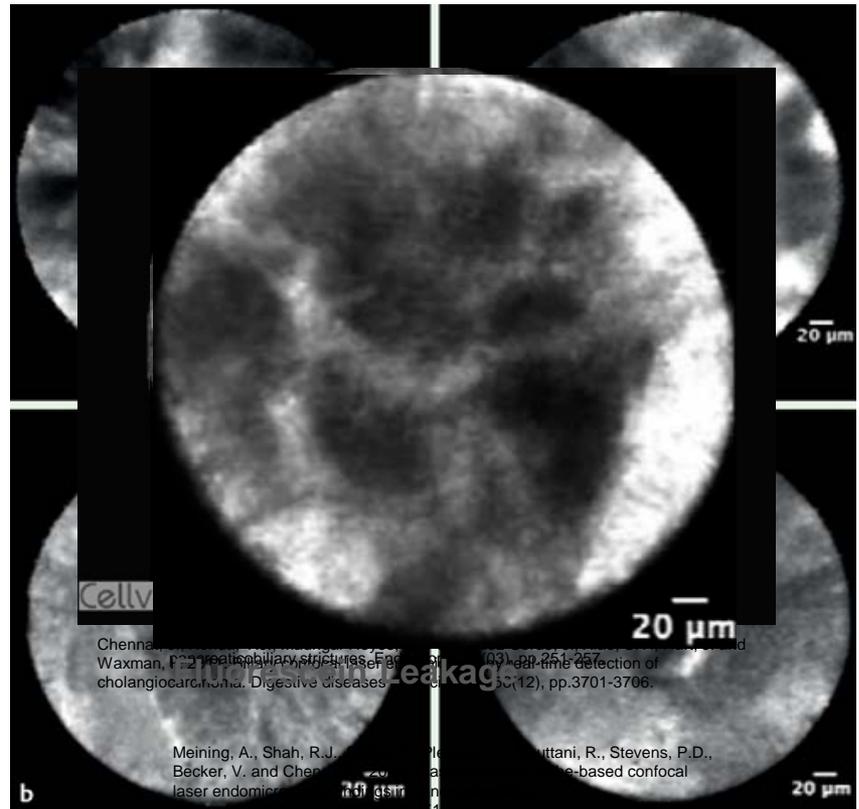


Adoption

Orientation/artefacts

- Cholangiocarcinoma—
Miami classification
 - Thick, dark bands (>40 microns)
 - Thick, white bands (>20 microns)
 - Dark Clumps
 - Epithelium visualized (villi, glands)
 - Fluorescein leakage

In-Vivo pCLE of Bile duct



Wallace, M., Lauwers, G.Y., Chen, Y., Dekker, E., Fockens, P., Sharma, P. and Meining, A., 2011. Miami classification for probe-based confocal laser endomicroscopy.

Adoption

Resolution

Orientation/artefacts

Magnification

Color Map

**Ancillary
studies**

In-vivo based contrast

Adoption

Resolution

Orientation/artefacts

Magnification

Color Map

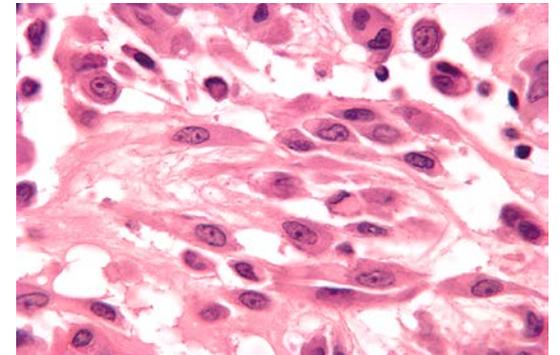
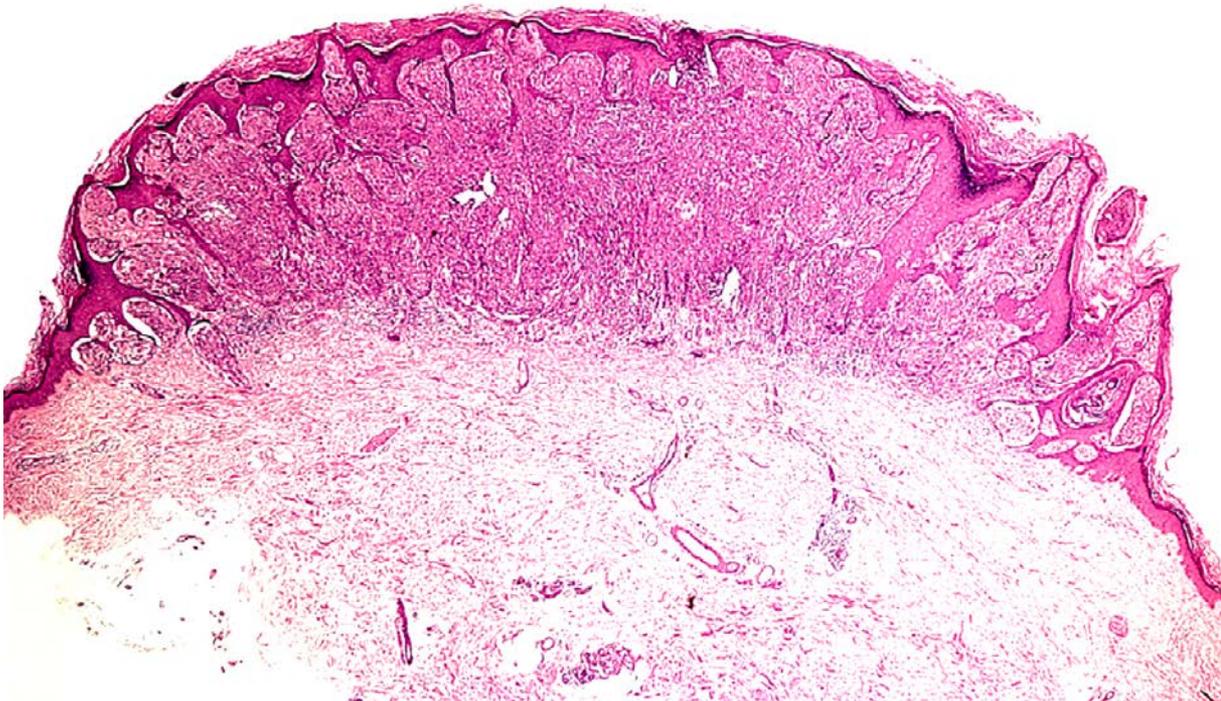
**Ancillary
studies**

In-vivo based contrast

Adoption

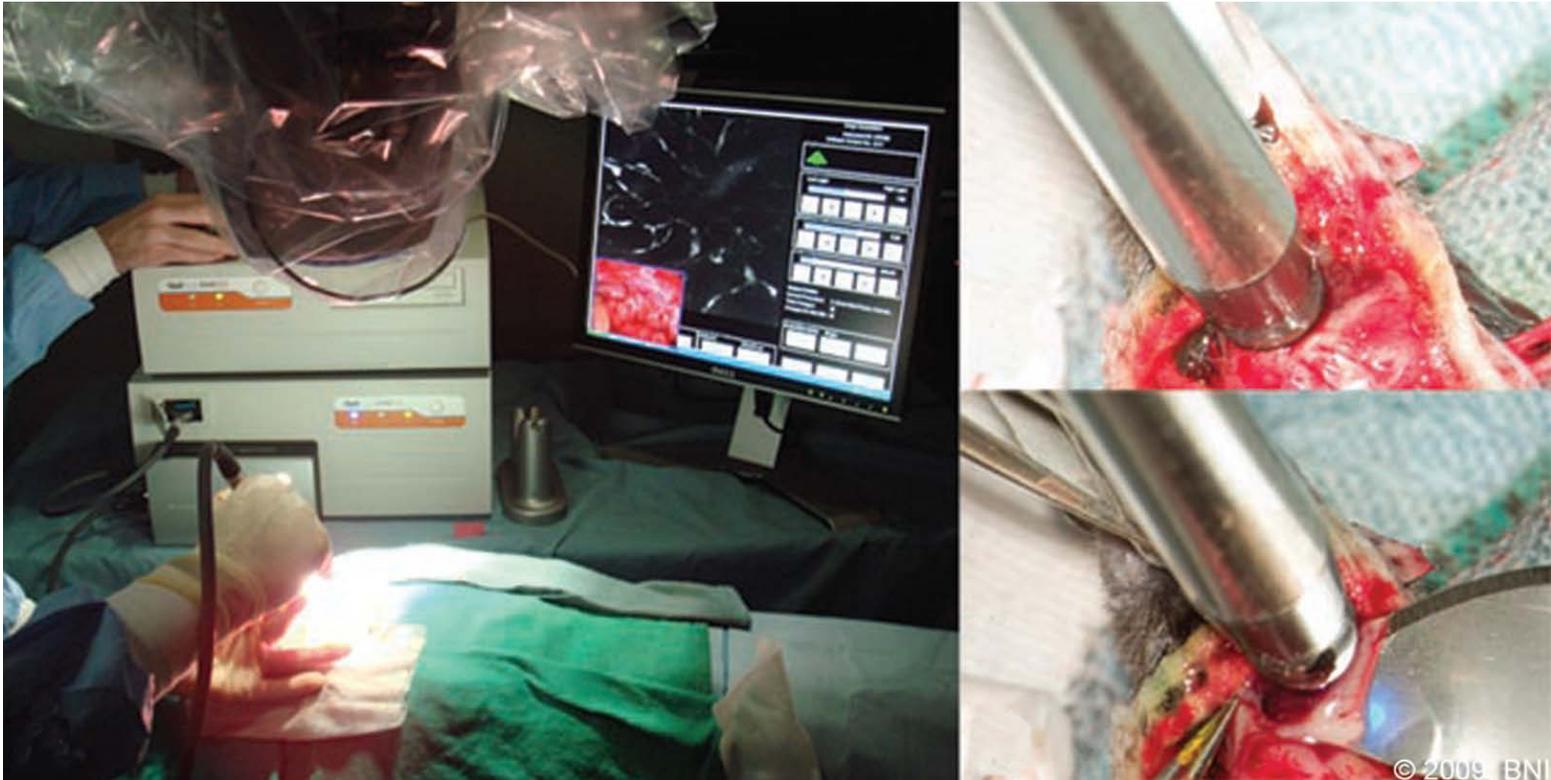
Magnification

The power of low power



Adoption

Magnification



Charalampaki, P., et al., *Confocal Laser Endomicroscopy for Real-time Histomorphological Diagnosis: Our Clinical Experience With 150 Brain and Spinal Tumor Cases*. *Neurosurgery*, 2015. **62 Suppl 1**: p. 171-6

Adoption

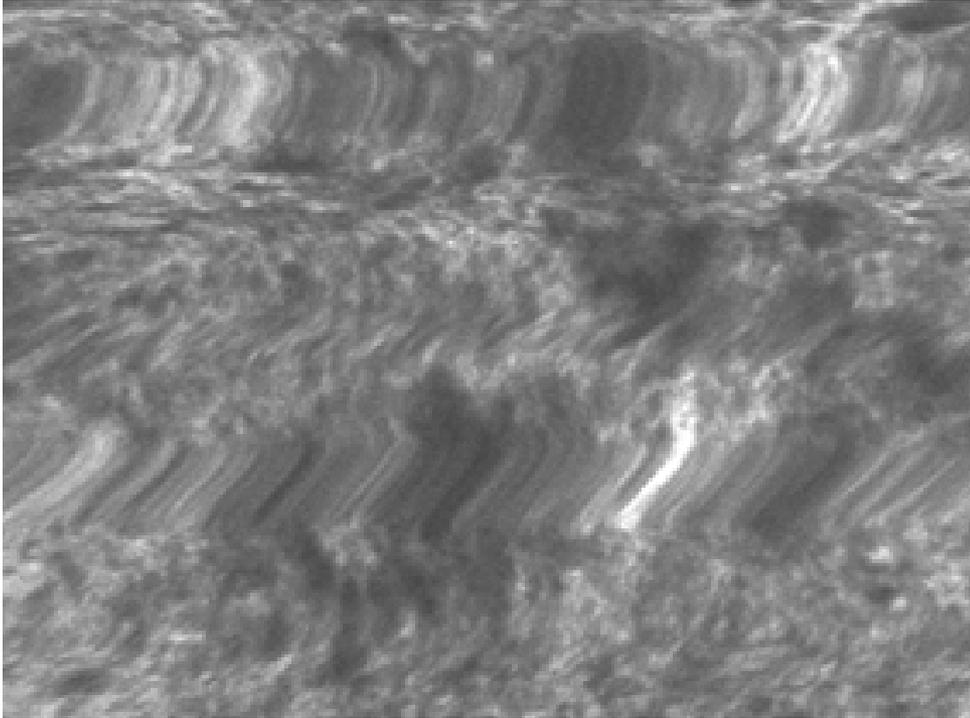
Magnification



Adoption

Magnification

Artefacts



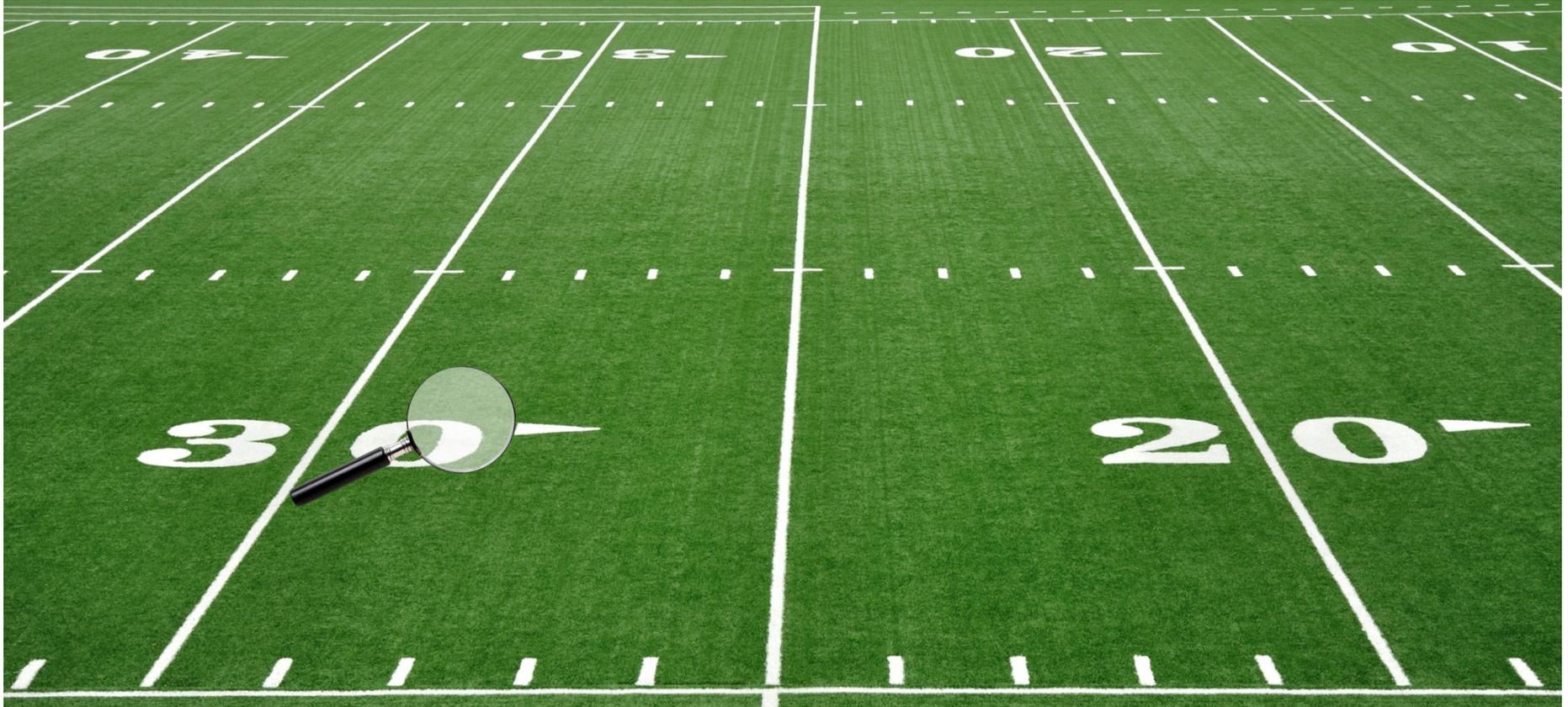
Motion artefact



RBCs

Adoption

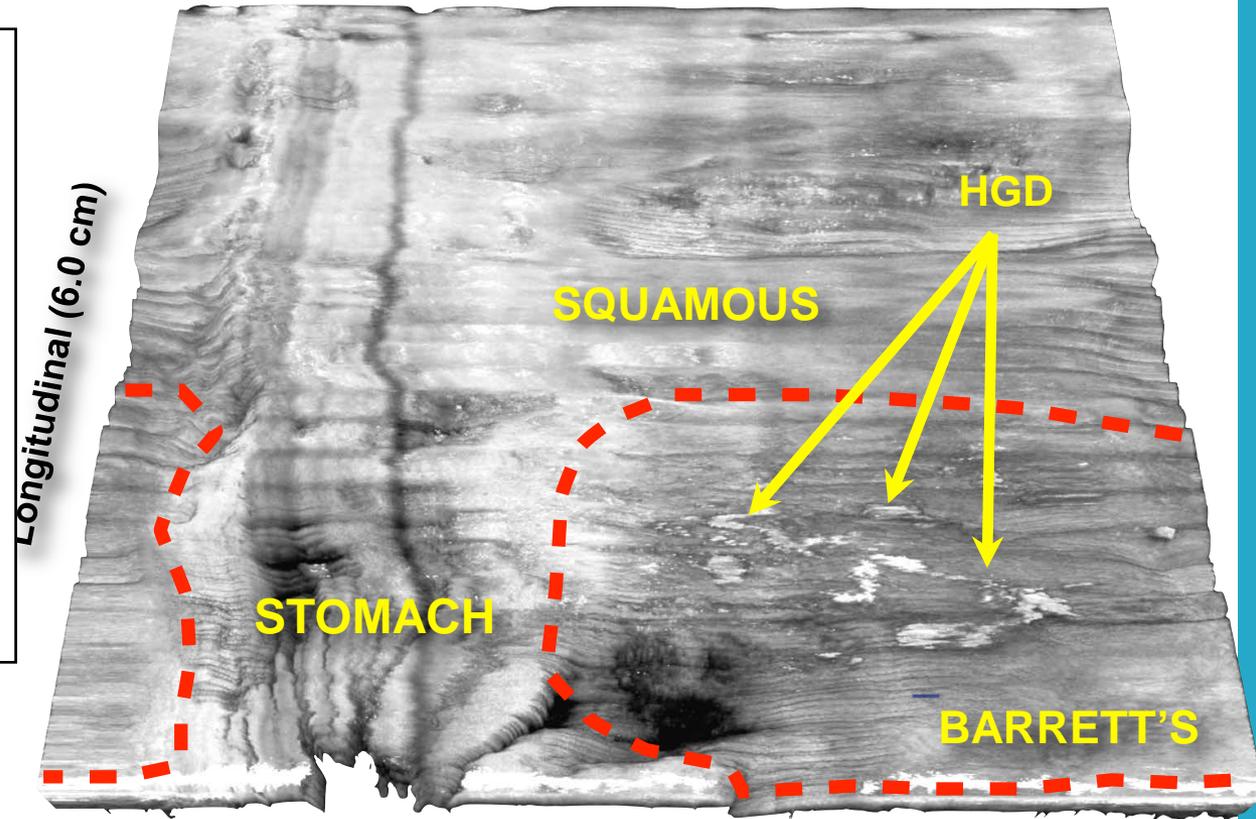
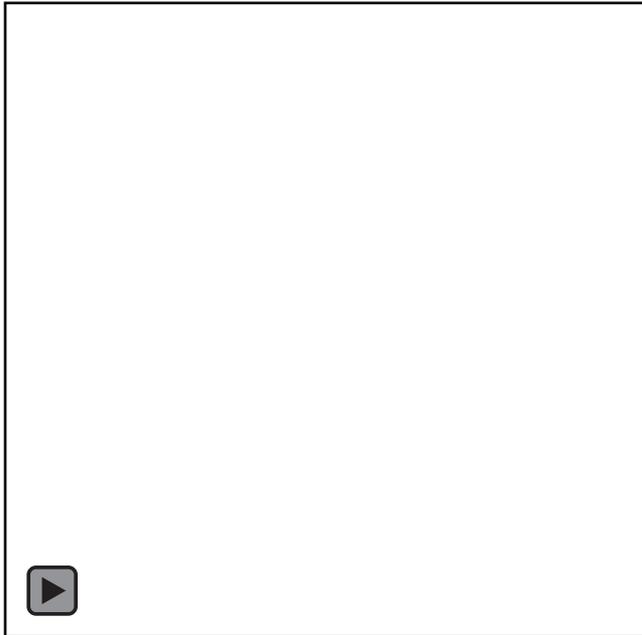
Magnification



Adoption

Magnification

Circumferential (7.5 cm)



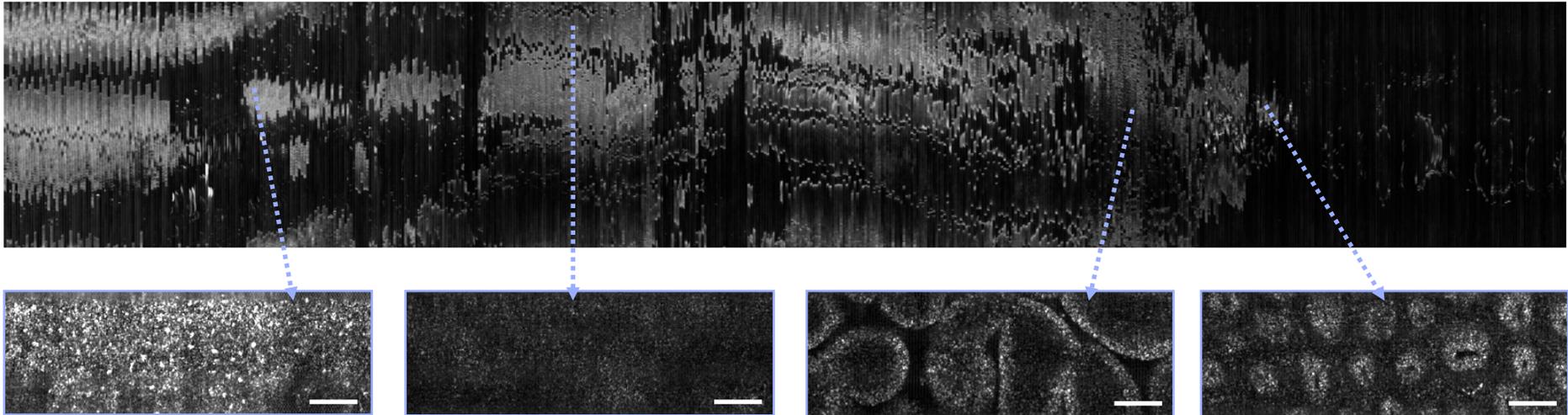


Adoption

Magnification

SECM
Capsule
Microscopy

20 cm



Adoption

Resolution

Orientation/artefacts

Magnification

Color Map

**Ancillary
studies**

In-vivo based contrast

Adoption

Resolution

Orientation/artefacts

Magnification

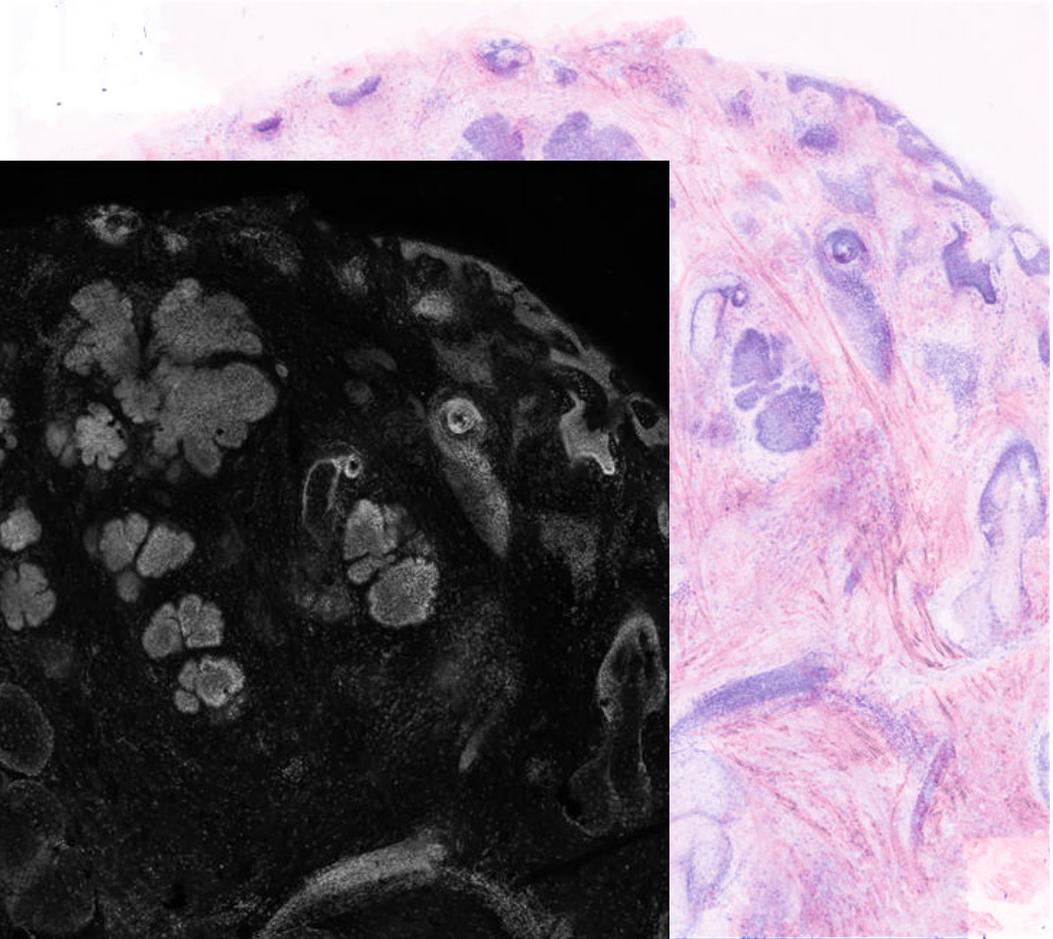
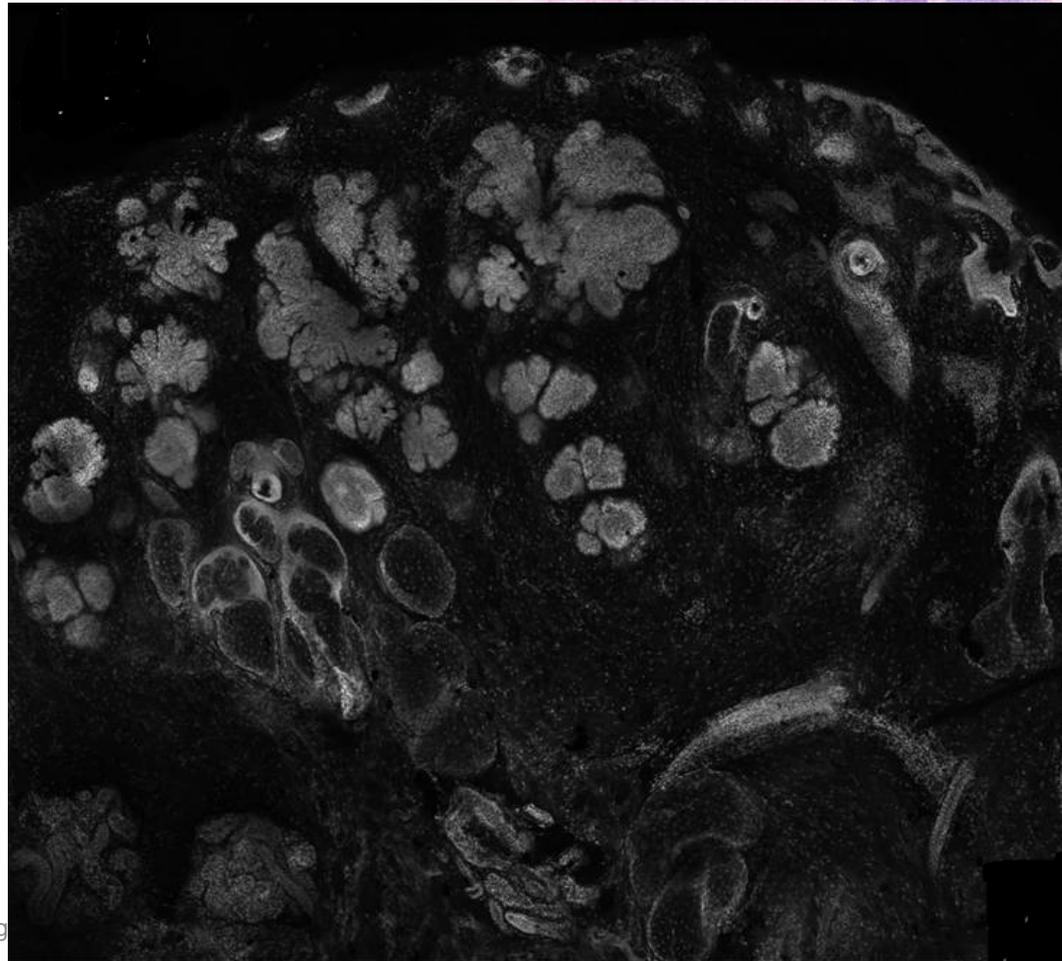
Color Map

**Ancillary
studies**

In-vivo based contrast

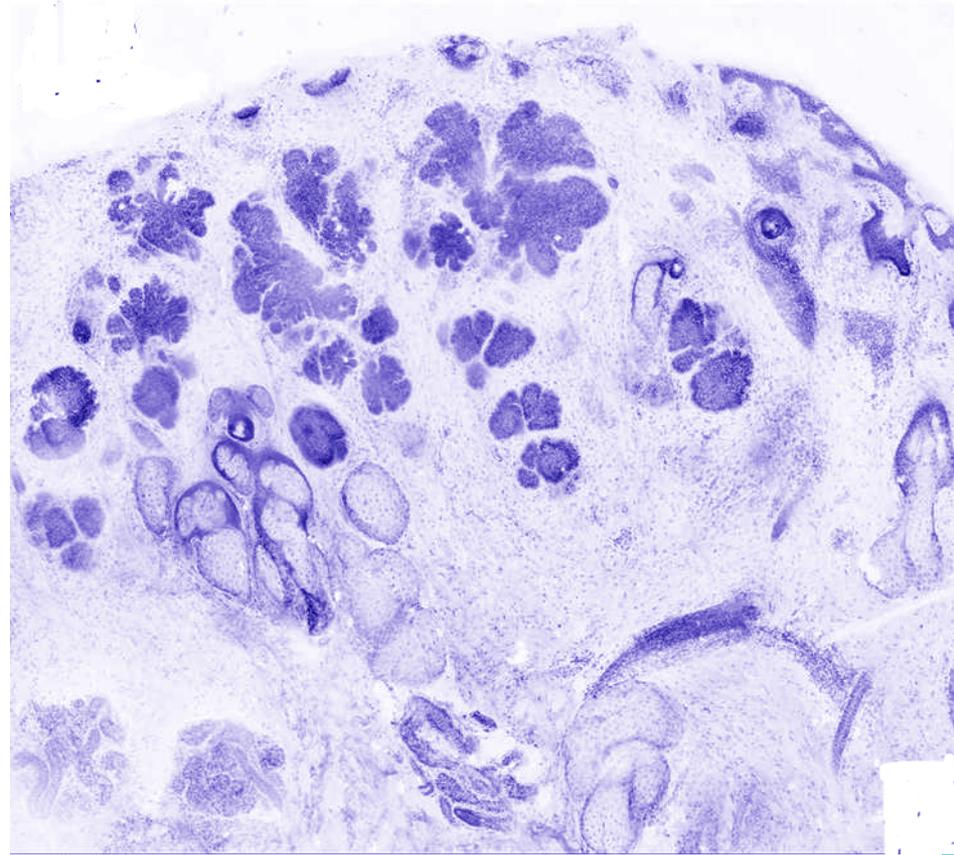
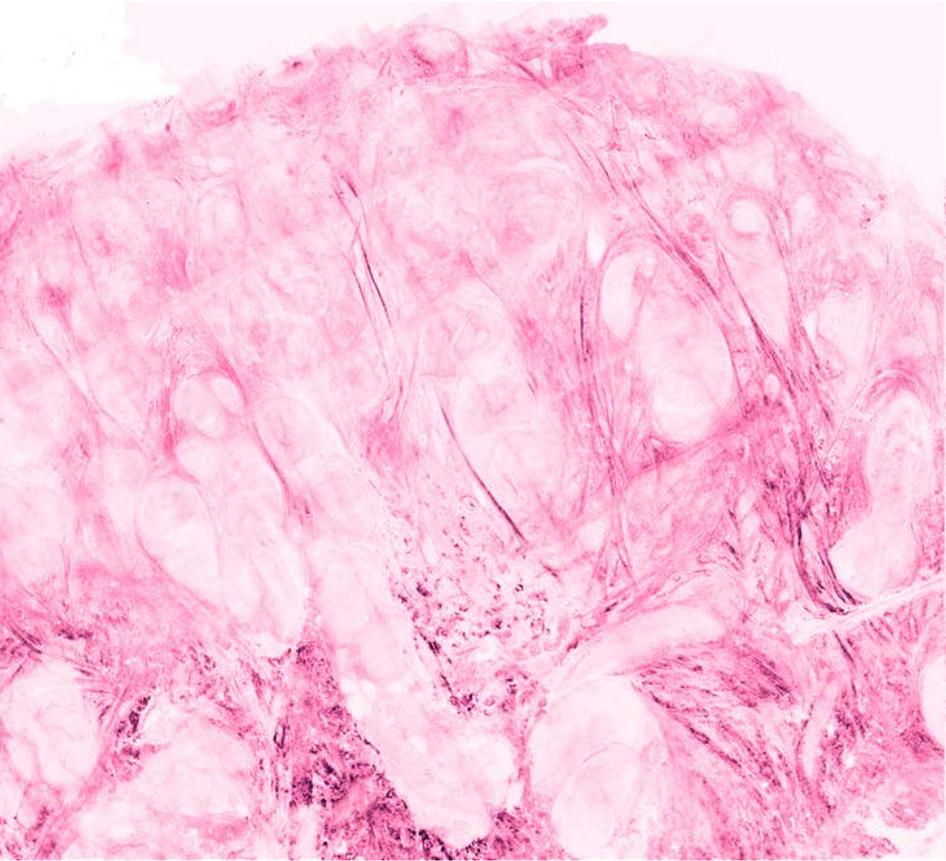
Adoption

Color Map



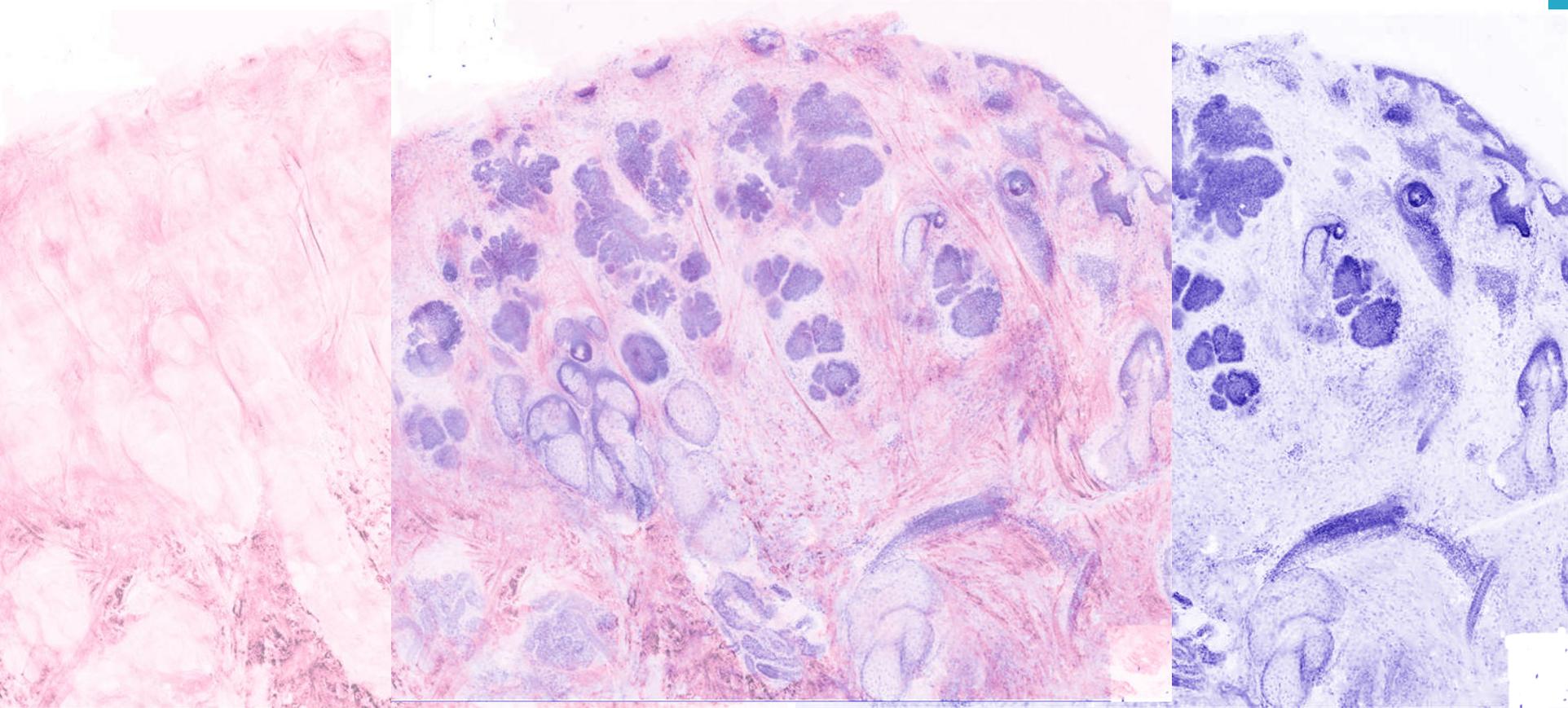
Adoption

Color Map



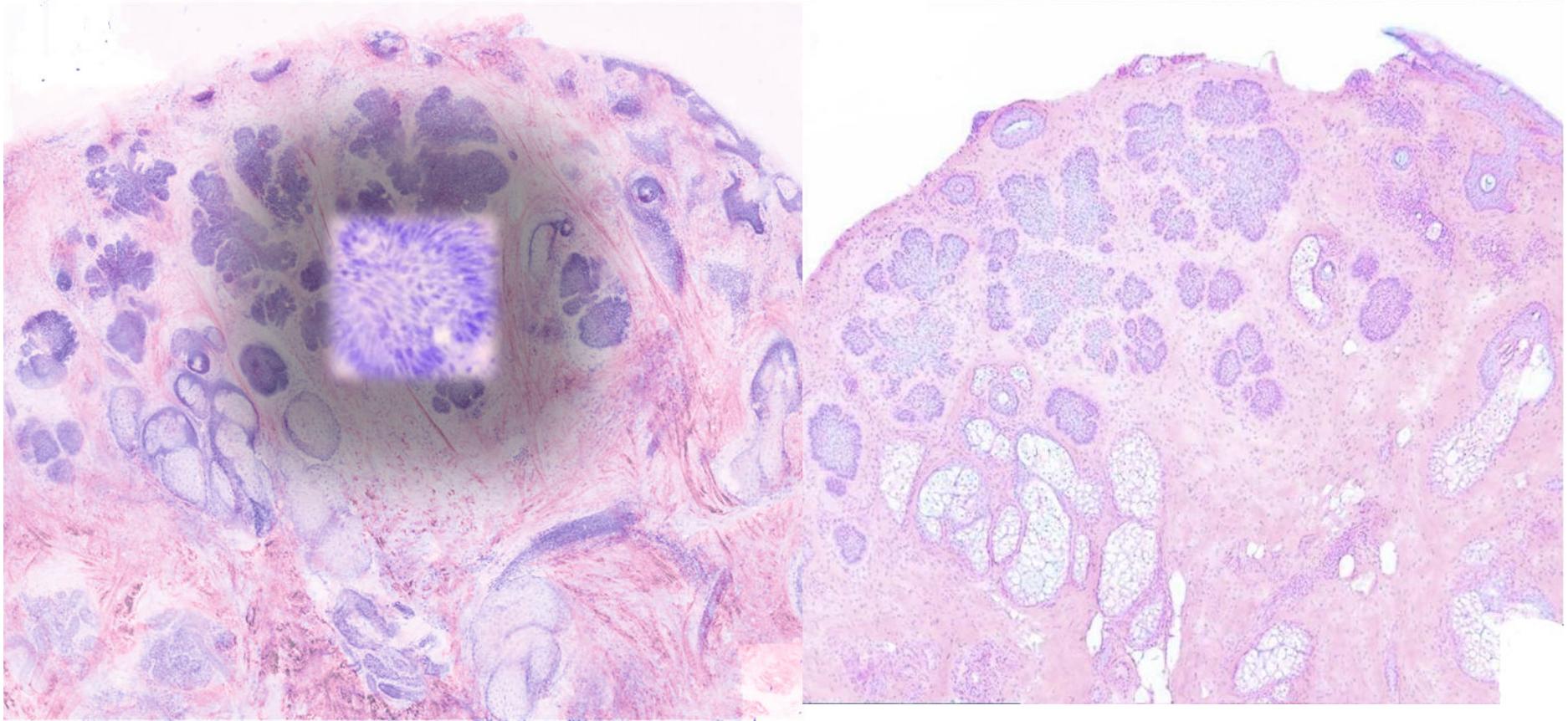
Adoption

Color Map



Adoption

Color Map



Gareau, D.S., *Feasibility of digitally stained multimodal confocal mosaics to simulate histopathology*. J Biomed Opt, 2009. **14**(3): p. 034050.

Adoption

Resolution

Orientation/artefacts

Magnification

Color Map

**Ancillary
studies**

In-vivo based contrast

Adoption

Resolution

Orientation/artefacts

Magnification

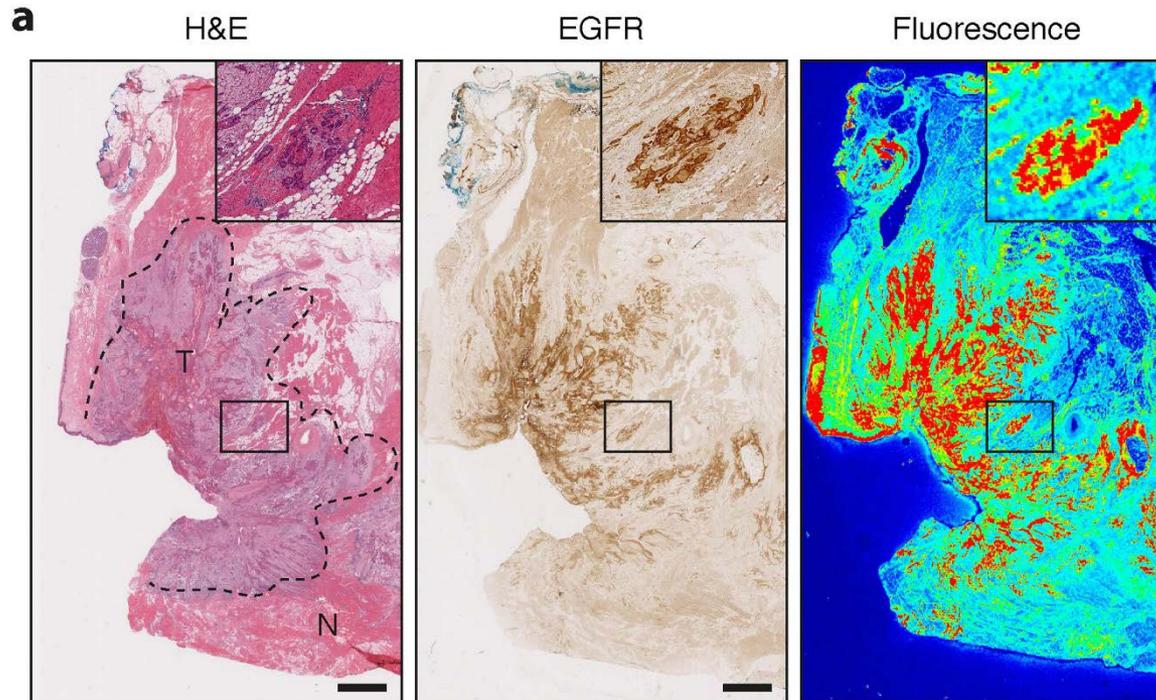
Color Map

**Ancillary
studies**

In-vivo based contrast

Adoption

Ancillary studies



Cetuximab
(EGFR)

Boer, Esther de, Jason M. Warram, Matthew D. Tucker, Yolanda E. Hartman, Lindsay S. Moore, Johannes S. de Jong, Thomas K. Chung, et al. 2015. "In Vivo Fluorescence Immunohistochemistry: Localization of Fluorescently Labeled Cetuximab in Squamous Cell Carcinomas." *Scientific Reports* 5 (June). The Author(s):10169.

Adoption

Resolution

Orientation/artefacts

Magnification

Color Map

**Ancillary
studies**

In-vivo based contrast

Adoption

Resolution

Orientation/artefacts

Magnification

Color Map

**Ancillary
studies**

In-vivo based contrast

Adoption

In-vivo based contrast

Adoption

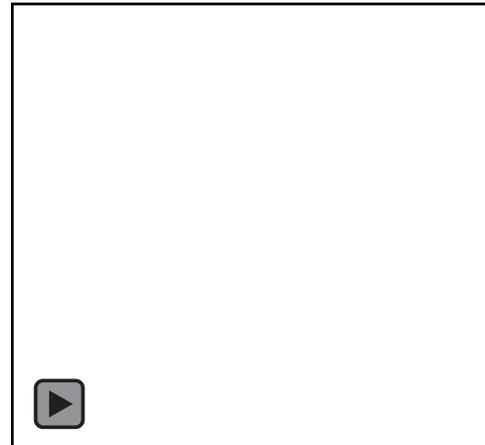
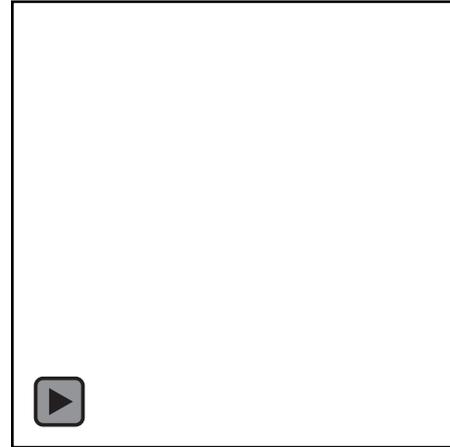
In-vivo based contrast

Esophagus, Normal

- Regular rhomboid squamous cells with clear borders.
- Regularly spaced intraepithelial papillary capillary loops (IPCLs)
- Lack of Fluorescein leakage from intrapapillary capillary loops

Barrett's Esophagus

- Dark goblet cells
- Columnar epithelial layer appearing as dark band with uniform cells.
- bright basal border of epithelium
- dark line outlining apical border of columnar epithelium
- Regular capillaries in deeper mucosa with no fluorescein leakage



Adoption

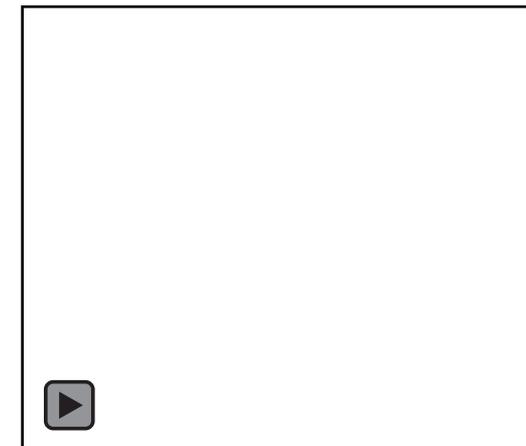
In-vivo based contrast

Barrett's Esophagus, Dysplasia

- Irregular epithelial lining with saw-toothing of luminal border
- Decreased epithelial thickness.
- Gland fusion
- Irregular vascular pattern
- Dark areas

Adenocarcinoma

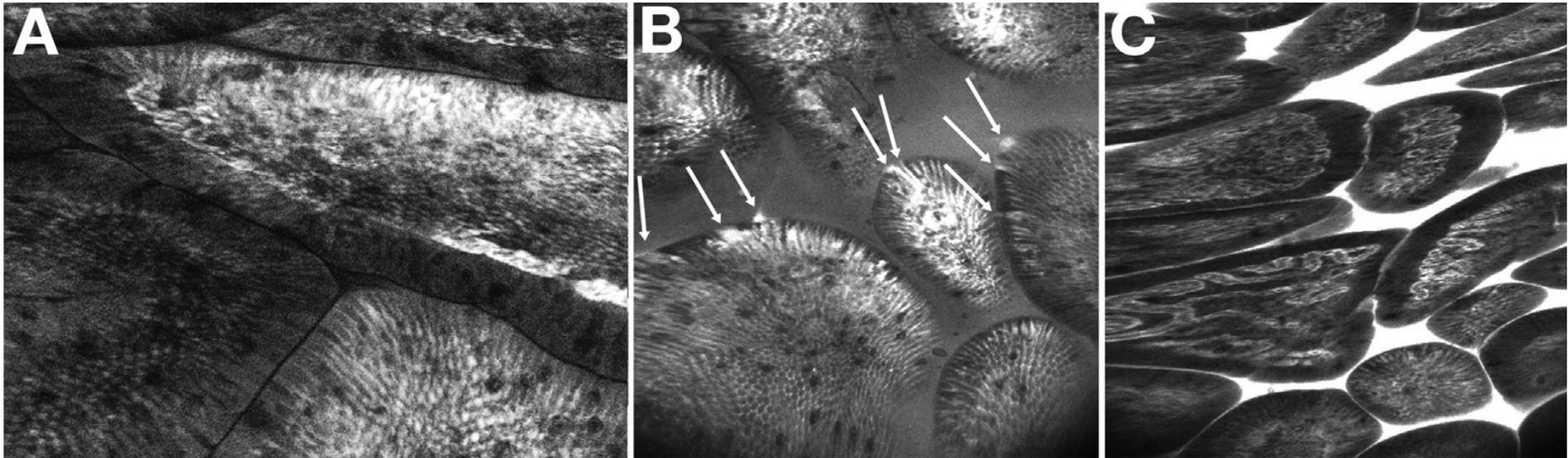
- Cellular and architectural Disarray
- Fluorescein leakage
- Infiltrative dark malignant cells beyond epithelium



Adoption

In-vivo based contrast

Irritable Bowel Syndrome



Fritscher-Ravens, A., Schuppan, D., Ellrichmann, M., Schoch, S., Röcken, C., Brasch, J., Bethge, J., Böttner, M., Klose, J. and Milla, P.J., 2014. Confocal endomicroscopy shows food-associated changes in the intestinal mucosa of patients with irritable bowel syndrome. *Gastroenterology*, 147(5), pp.1012-1020.

Adoption

Resolution

Orientation/artefacts

Magnification

Color Map

**Ancillary
studies**

In-vivo based contrast

Incorporation

Incorporation

Education

Utility

Patient

Data

Billing

Regulation

Organ	In Vivo Microscopy		
	Now	3-5 Years	7-10 Years
Eye	Standard of Care	Standard of Care	Standard of Care
Cardiovascular	Clinical Procedures	Standard of Care	Standard of Care
GI	Clinical Procedures	Standard of Care	Standard of Care
Skin	Clinical Procedures	Clinical Procedures	Standard of Care
Lung	Clinical Trials	Clinical Procedures	Standard of Care
Head and Neck	Clinical Trials	Clinical Procedures	Standard of Care
Breast	Clinical Trials	Clinical Trials	Clinical Procedures

Source: CAP's In Vivo Microscopy Committee

Incorporation

Education

Utility

Patient

Data

Billing

Regulation

Incorporation

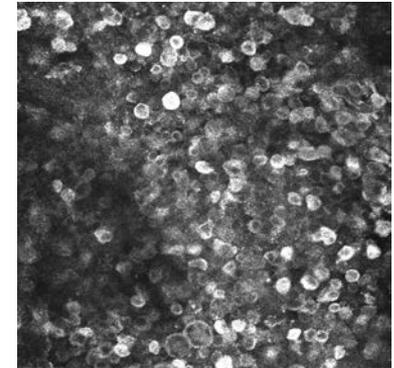
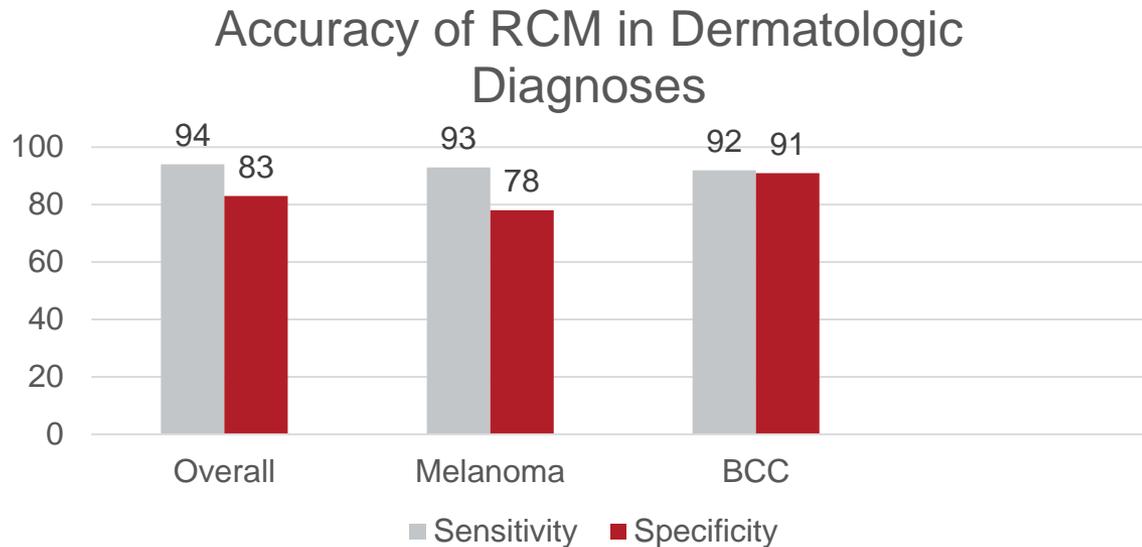
- How is this technology used
 - Screening
 - Guidance

Utility



Incorporation

Utility

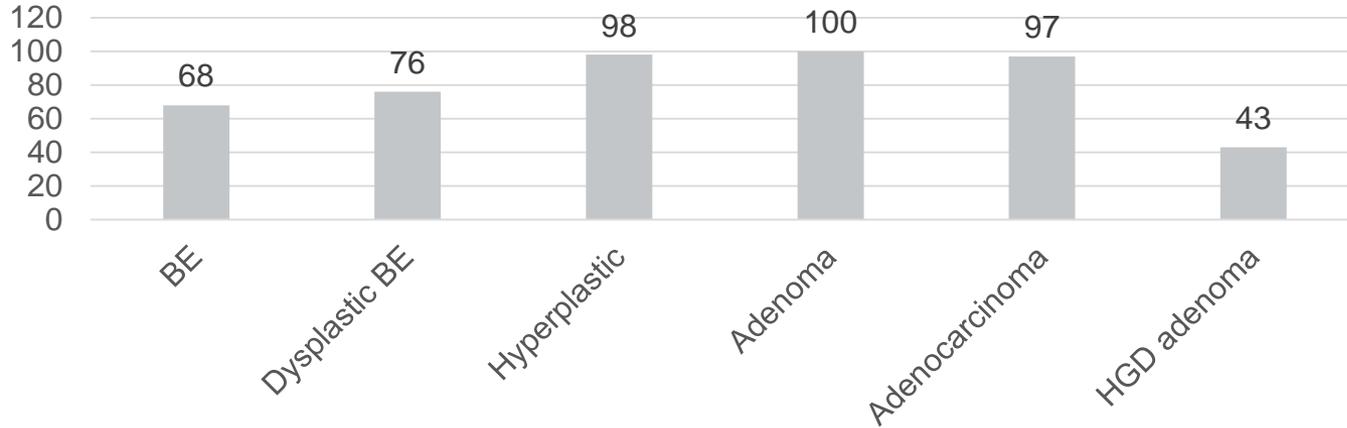


Reduction biopsies of benign lesions, by 50–68%

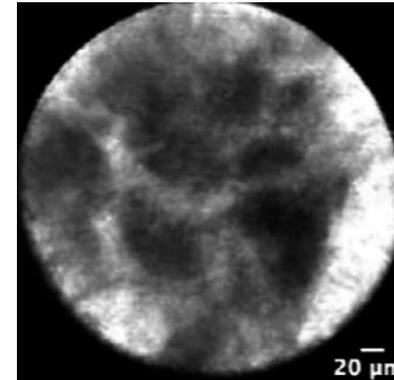
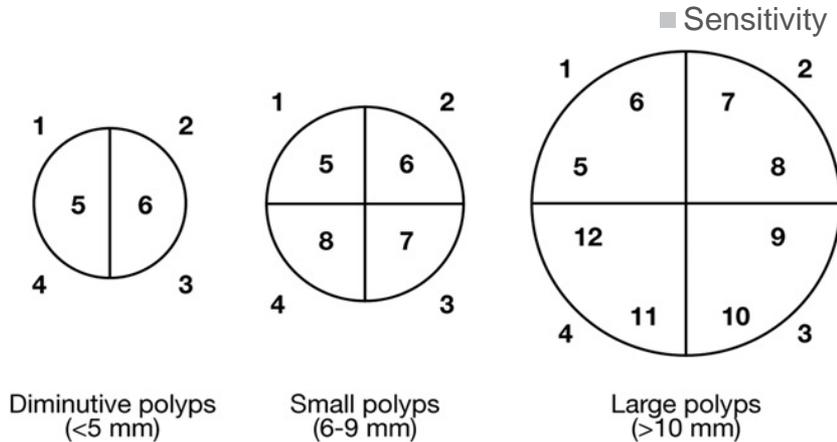
Xiong YD, Ma S, Li X, Zhong X, Duan C, Chen Q. A metaanalysis of reflectance confocal microscopy for the diagnosis of malignant skin tumours. *J Eur Acad Dermatol Venereol* 2016;30:1295–1302.

Incorporation

Accuracy of pCLE in Gastrointestinal diagnoses



Utility



Sanduleanu, S., Driessen, A., Gomez-Garcia, E., Hameeteman, W., de Bruine, A. and Masclee, A., 2010. In vivo diagnosis and classification of colorectal neoplasia by chromoendoscopy-guided confocal laser endomicroscopy. *Clinical Gastroenterology and Hepatology*, 8(4), pp.371-378.

Shahid M.W. et al. Diagnostic Accuracy of probe based Confocal Laser Endomicroscopy in Detecting Residual Colorectal Neoplasia after EMR: A prospective Study. *Gastrointestinal Endoscopy*, 2012.

Sharma P. et al. Real-time Increased Detection of Neoplastic Tissue in Barrett's Esophagus with probe-based Confocal Laser Endomicroscopy: Final Results of a Multi-center Prospective International Randomized Controlled Trial. *Gastrointestinal Endoscopy*, 2011 (DONT BIOPCE).

Incorporation

Education

Utility

Patient

Data

Billing

Regulation

Incorporation

Education

Utility

Patient

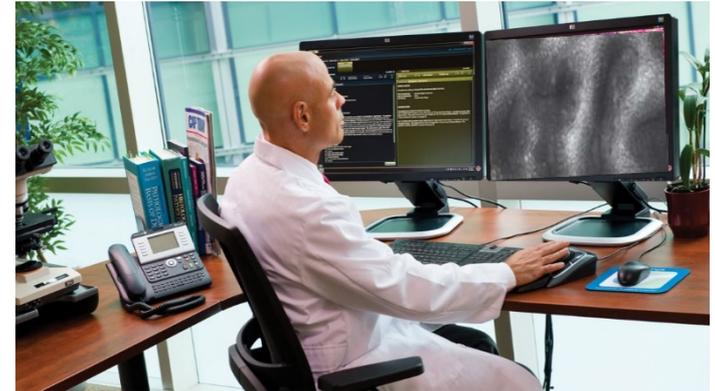
Data

Billing

Regulation

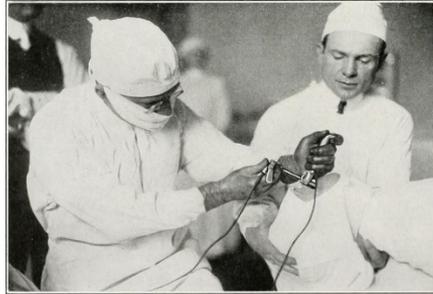
Incorporation

Patient



Incorporation

Patient

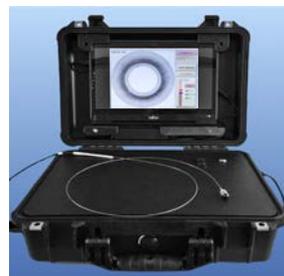
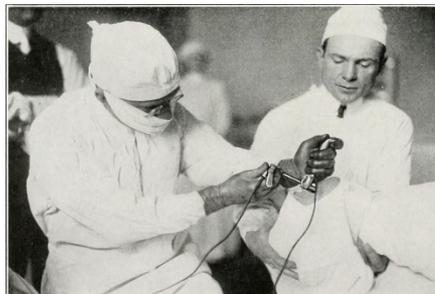


Incorporation

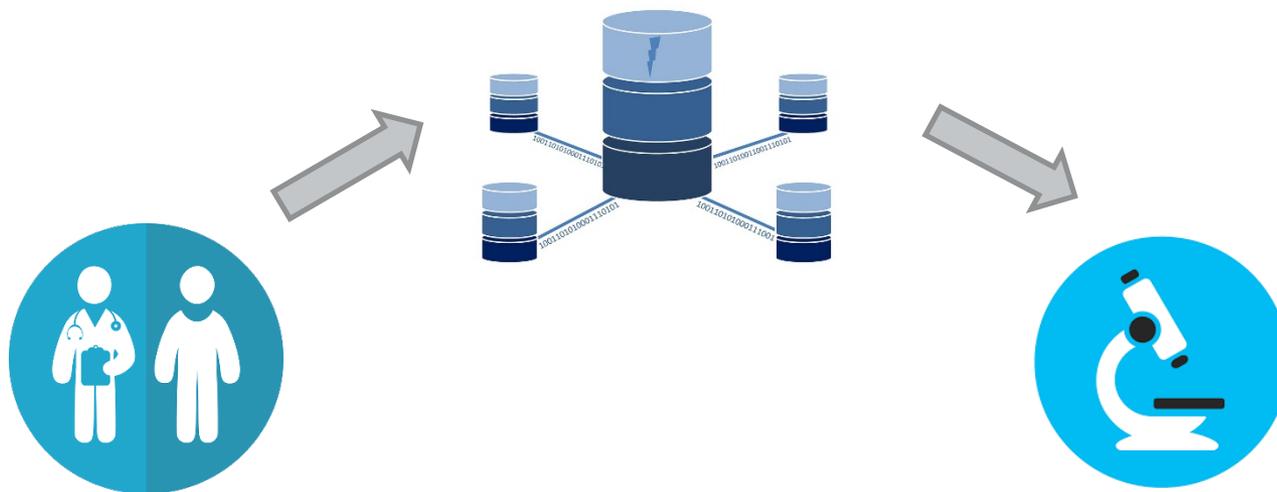
Education

Utility

Patient



Data

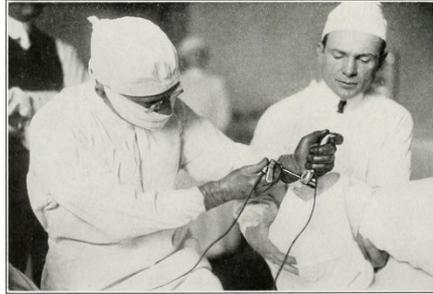


Incorporation

Education

Utility

Patient



New CPT codes for optical endomicroscopy

Two new codes were added to report optical endomicroscopy when performed with esophagoscopy and esophagogastroduodenoscopy (EGD).

Code 43206 was added to the esophagoscopy family to describe real-time therapeutic decisions involved in optical endomicroscopy procedures when performed with esophagoscopy. This procedure includes the diagnostic injection for the administration of the contrast agent, interpretation and report for the service. The supply of the contrast agent itself, however, is not included as part of the procedure. Therefore, a parenthetical note has been included that directs separate report of the agent. Provision of this service includes the interpretation and report for the service; code 88375 should not be reported in conjunction with this code.

▶ **43200** Esophagoscopy, rigid or flexible; diagnostic, with or without collection of specimen(s) by brushing or washing (separate procedure)

• **43206** with optical endomicroscopy

(Report supply of contrast agent separately)

(Do not report 43206 in conjunction with 88375)

Code 43252 was added to the EGD family to describe real-time therapeutic decisions involved in optical endomicroscopy procedures when performed with EGD. The procedure includes diagnostic injection for the administration of the contrast agent and the interpretation and report for the service. The supply of the contrast agent itself, however, is not included as part of the procedure. Therefore, a parenthetical note has been included that directs separate report of the agent. Provision of this service includes the interpretation and report for the service and code 88375 should not be reported in conjunction with this code.

▶ **43235** Upper gastrointestinal endoscopy including esophagus, stomach, and either the duodenum and/or jejunum as appropriate; diagnostic, with or without collection of specimen(s) by brushing or washing (separate procedure)

• **43252** with optical endomicroscopy

(Report supply of contrast agent separately)

(Do not report 43252 in conjunction with 88375)

(For biopsy specimen pathology, use 88305)

Data

Billing

88375

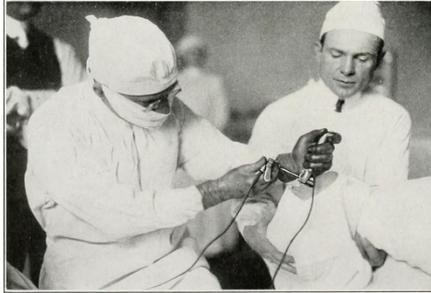
Optical endomicroscopic image(s), interpretation and report, real-time or referred, each endoscopic session

Incorporation

Education

Utility

Patient



Data

Billing

88375

Incorporation

Education

Utility

Patient



Imaging
(Technical)

Interpretation
(Professional)

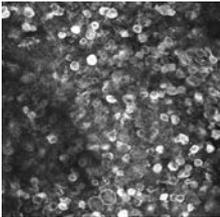
First Lesion

Additional Lesions

Data



+



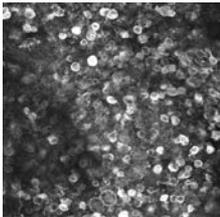
96931

96934



96932

96935



96933

96936

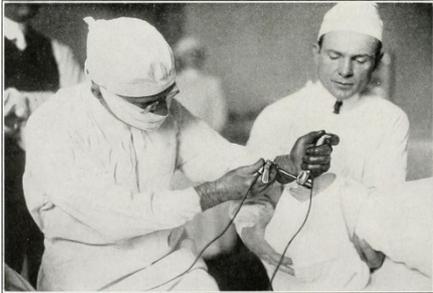
Billing

Incorporation

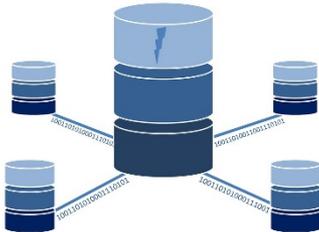
Education

Utility

Patient



Data



Billing

88375

96933

Regulation

