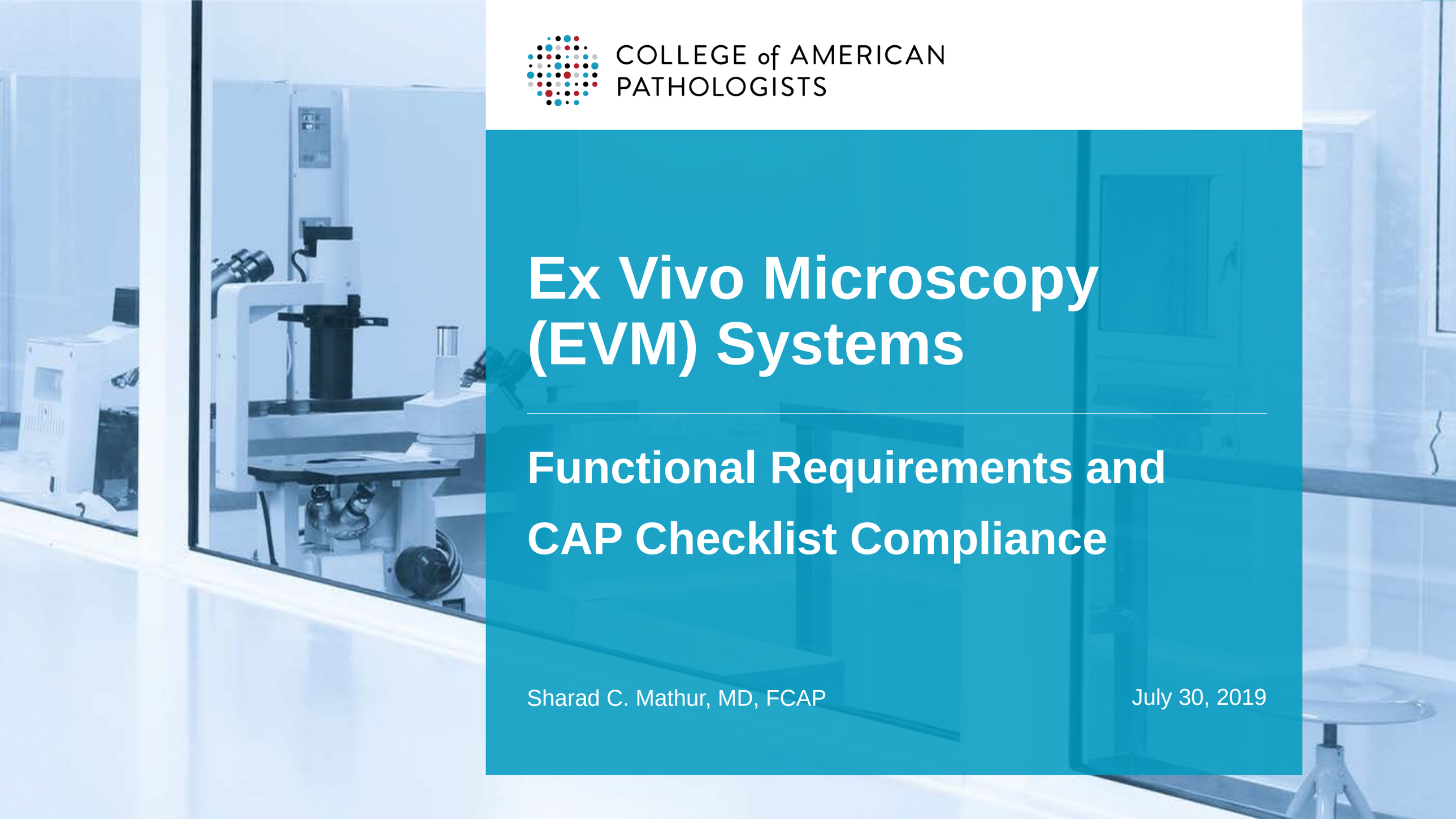

COLLEGE of AMERICAN PATHOLOGISTS

Ex Vivo Microscopy (EVM) Systems

Functional Requirements and CAP Checklist Compliance

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July 30, 2019

Sharad Mathur, MD, FCAP

- Chief of Pathology and Laboratory Medicine at the Kansas City VA Medical Center
- Professor of Pathology at the University of Kansas
- Chaired the subcommittee for development of accreditation checklist requirements for IVM
- Member of the CAP In Vivo Microscopy Committee

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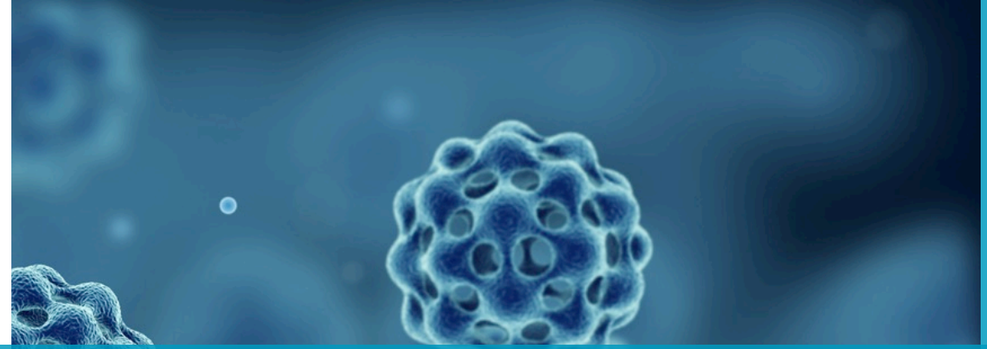
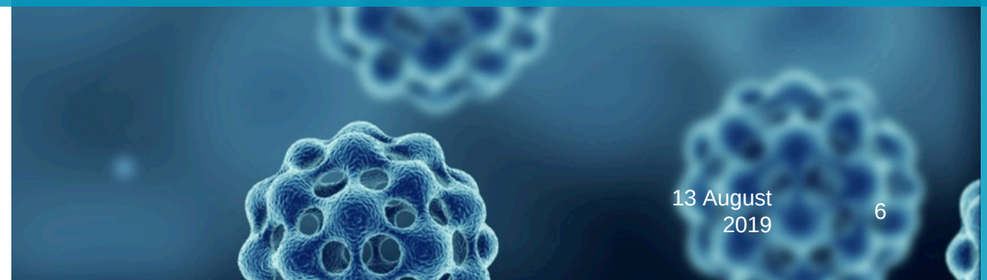
- **Opinions expressed by the speaker are the speaker's own and do not necessarily reflect an endorsement by the CAP of any organizations, equipment, reagents, materials, or services used by participating laboratories.**

Disclosures

- None



- In vivo and Ex vivo microscopy – technology and scope
- EVM applications
- Functional requirements for EVM
- CAP checklist compliance



In Vivo Microscopy (IVM)
Ex Vivo Microscopy (EVM)

IVM Technology

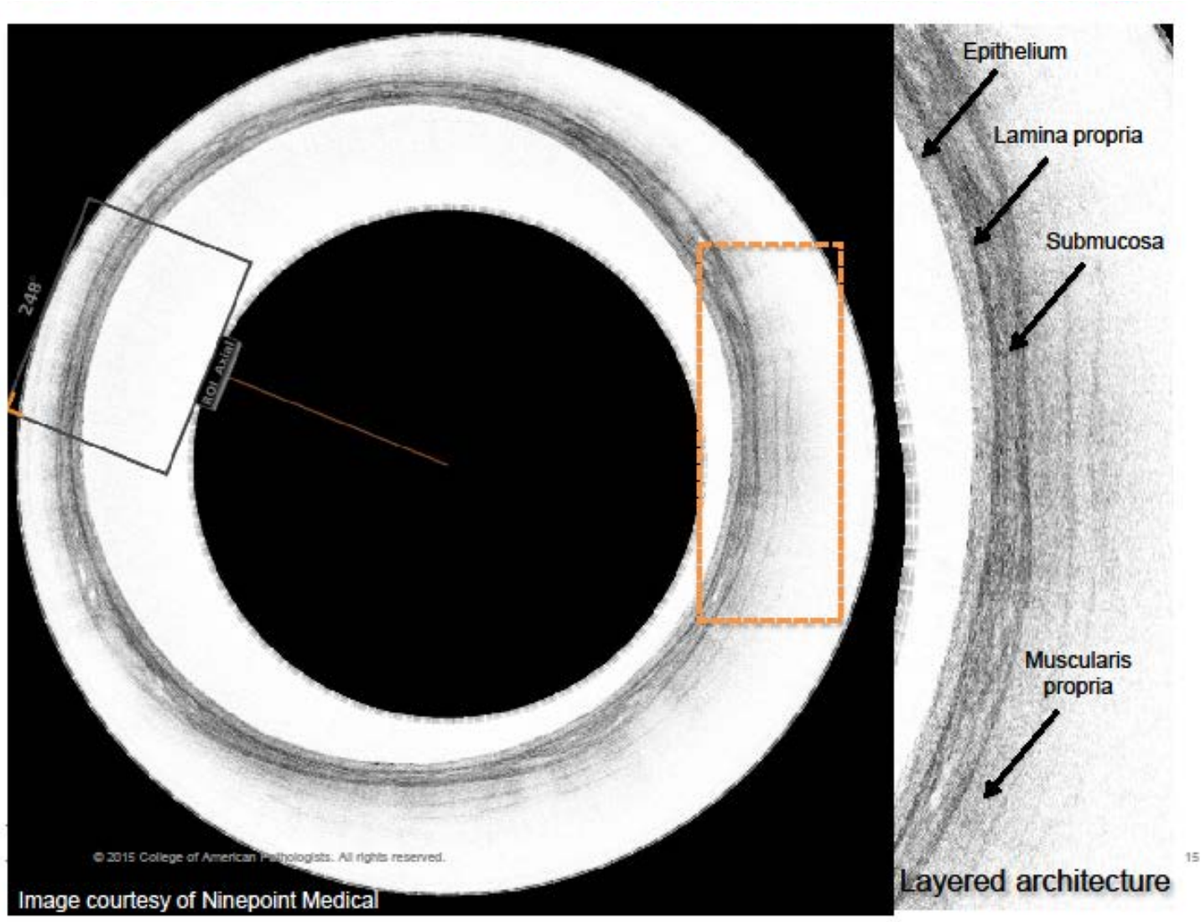
- **Optical imaging techniques suitable for direct visualization of tissue at the microscopic level in vivo**
  - **Generate “optical” sections at various depths through fresh tissue**
  - **Video or static images suitable for real-time interpretation or evaluation at a later time by trained personnel**
- **IVM technologies**
  - **Confocal microscopy***
  - **Optical coherence tomography***
  - **Multiphoton microscopy**
  - **Photoacoustic imaging**
  - **Optical spectroscopy and spectroscopic imaging**

***FDA approved**

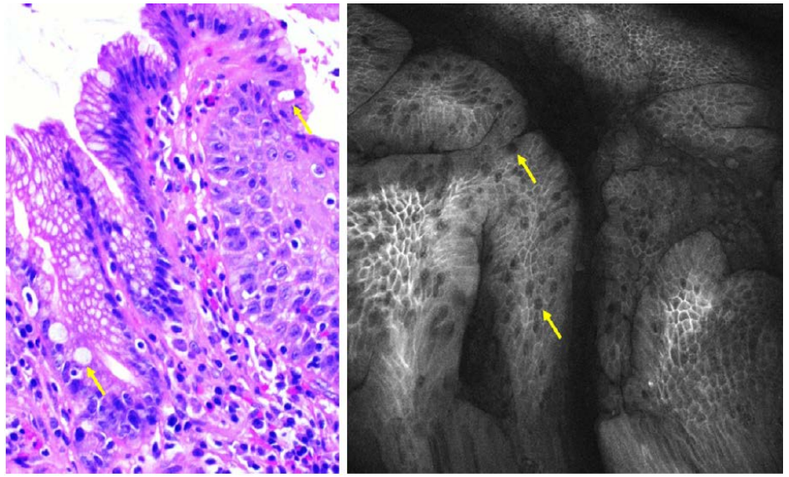
IVM Applications

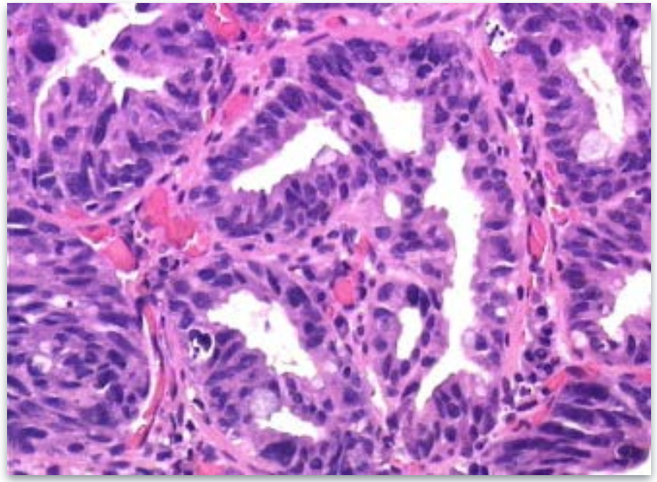
- **Commercially available systems in clinical use**
  - Ophthalmologic imaging for retinal diseases
  - Cardiovascular (coronary) imaging
  - Endoscopic imaging in gastroenterology for biopsy guidance and identification of pathology
  - Dermatologic diagnosis of pigmented and non-pigmented tumors
- **Applications in development**
  - Pulmonary disease – tumors and interstitial lung disease
  - Head and neck disease – flat lesions of pharynx and larynx
  - Breast surgery – intraoperative assessment of margins and lymph nodes

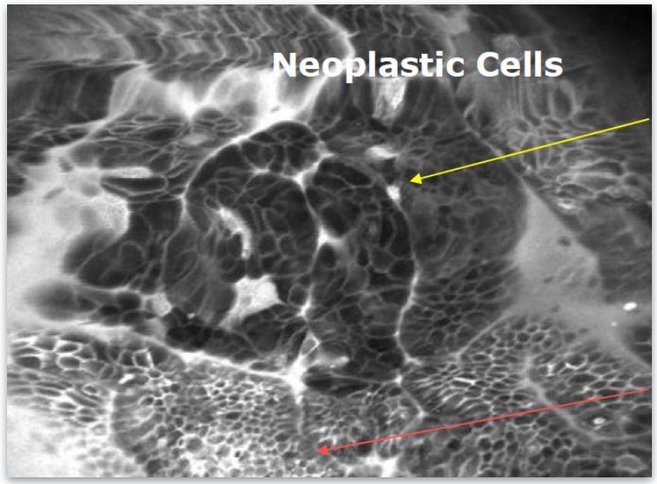
Normal Esophagus (optical coherence tomography)



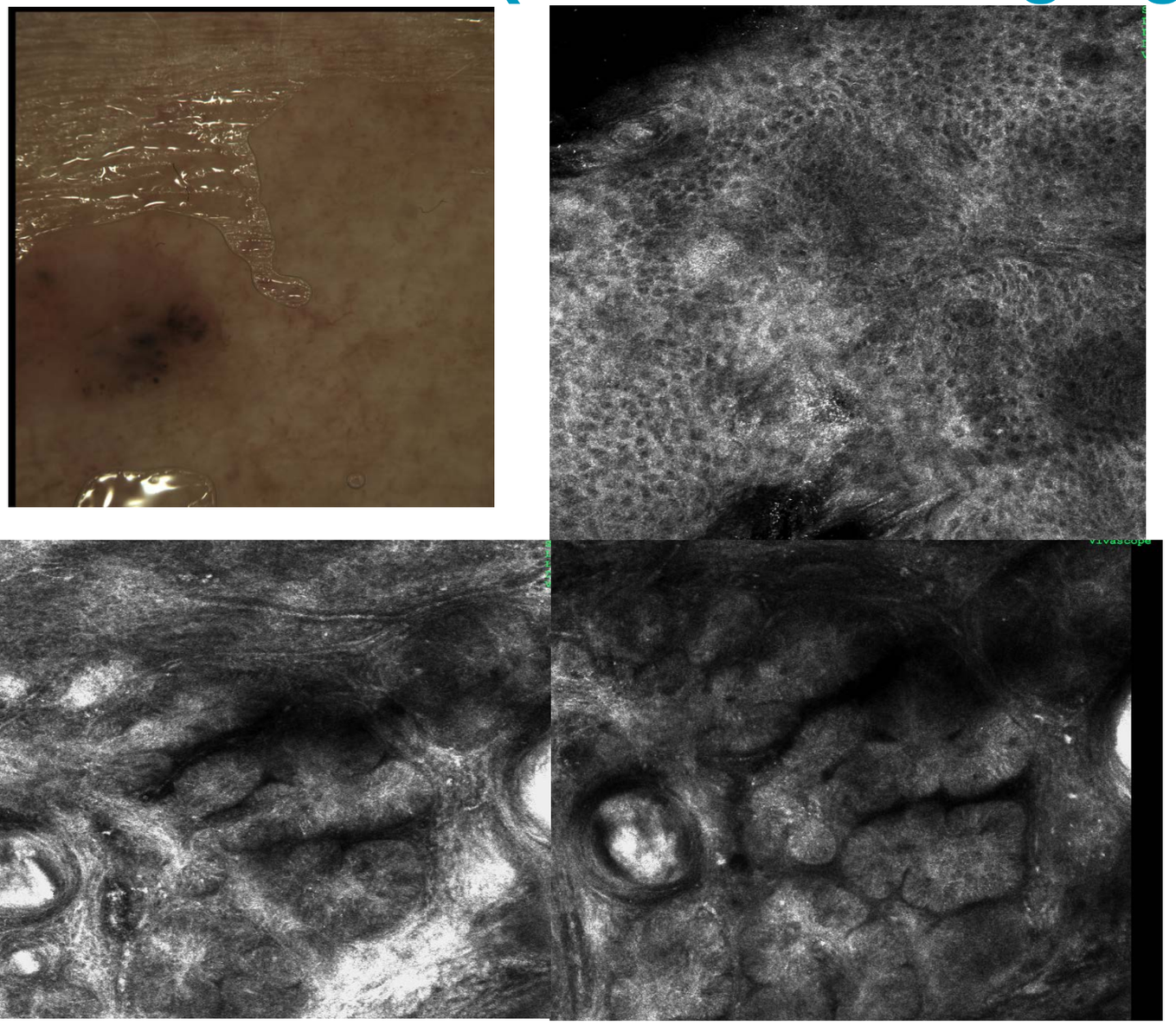
Barrett Esophagus (confocal endomicroscopy)





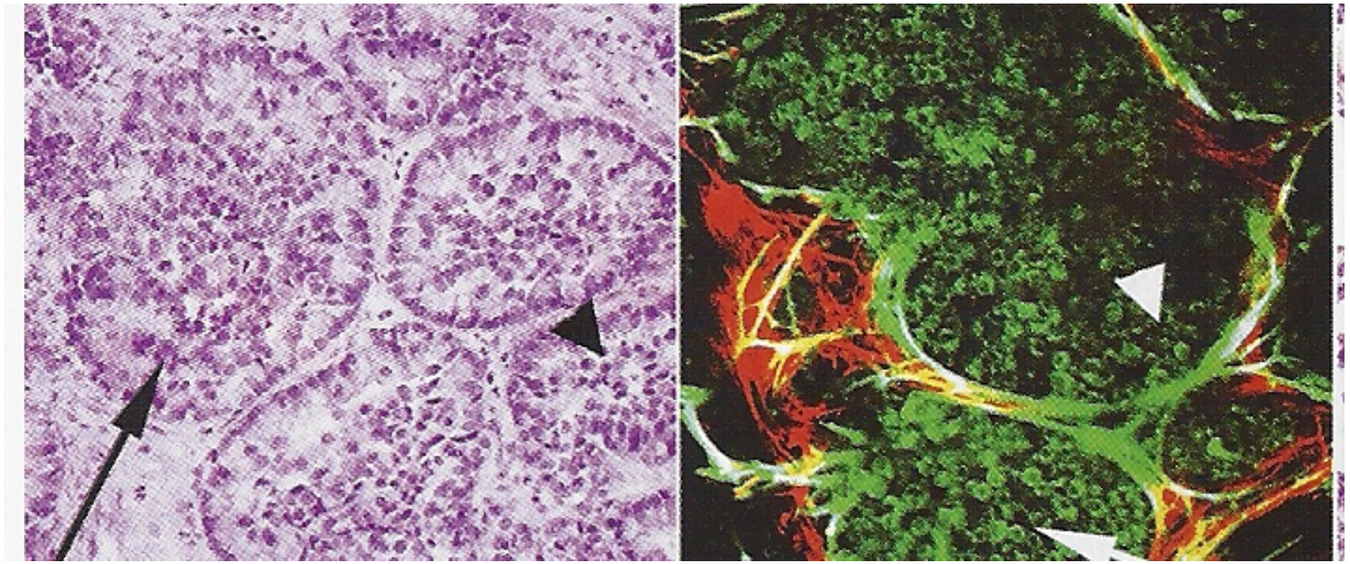


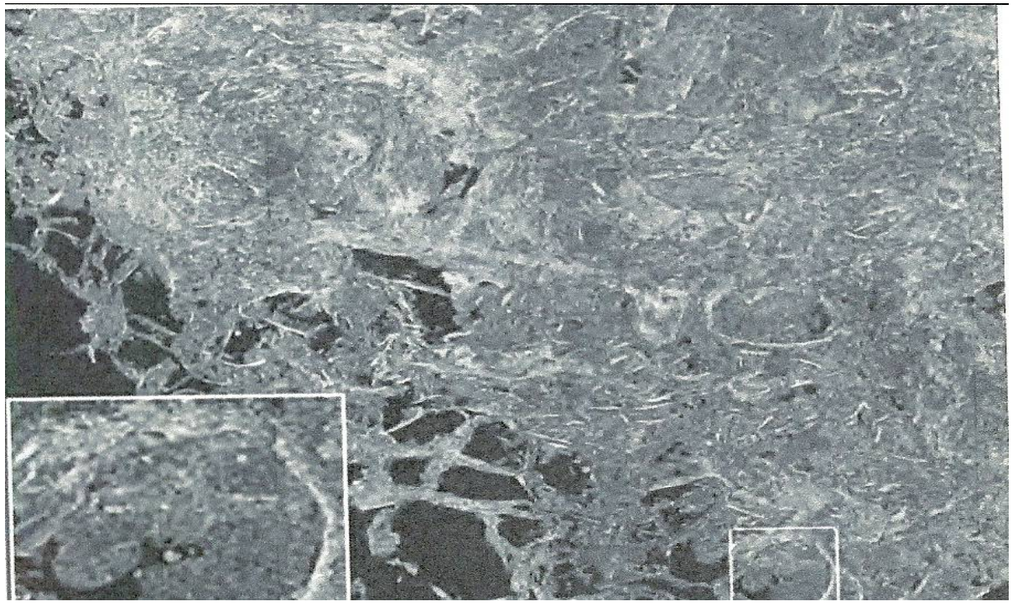
Basal Cell Carcinoma (confocal imaging)



Images courtesy of
Dr. Babar Rao

Adenocarcinoma of the Lung (MPM and OCT)





EVM

- Use of IVM technologies on specimens removed from the patient at the bedside or in the Pathology laboratory
- No commercially available systems at present
- Existing IVM tools used for EVM applications with or without modifications
  - Applications
  - Functional requirements
  - Regulations

EVM Applications

EVM Applications

- Applications are amenable to oversight and ownership by Pathologists
- Many ongoing studies to address feasibility and validation
- Outcomes should match current processes (“gold standard”)
  - Frozen section
  - Touch imprint cytology
  - Crush preps
  - Visual inspection
  - Correlation with imaging data

EVM Applications

- **Intraoperative or intraprocedural (bedside or laboratory)**
  - **Assessment of margins**
  - **Assessment of tissue adequacy**
  - **Assessment of sentinel lymph nodes**
  - **Assessment of organs for transplantation**

EVM Applications

- **Gross examination (laboratory)**
  - **Selection of tissue for histologic evaluation**
  - **Selection of tissue for biorepository**
- **Genomic/molecular testing and biorepository (bedside, laboratory or tissue bank)**
  - **Selection of tissue suitable for genomic or molecular testing**
  - **Non-destructive identification of tissue types in banked tissue**

EVM Applications – Potential Advantages

- Non-destructive histologic evaluation of limited tissue samples
- Reduced need for tissue processing and sectioning (as compared to frozen sections)
- Faster turnaround time
- Histologic imaging at bedside
- Permanent digital image record
- Potential impact on manpower needs

EVM Functional Requirements

EVM Functional Requirements

- **Varied requirements for different applications**
- **Traditional (“gold standard”) technologies have different attributes as compared to IVM/EVM technologies**
  - **Frozen section – can image large or small tissue fragments**
  - **IVM/EVM technologies – equipment needed depends on area to be imaged and resolution/magnification required**
- **Can minimal functional requirements be standardized to allow for greater flexibility in design and use of equipment for EVM?**

EVM Functional Requirements

- Selection of most likely applications

1. Assessment of margins
2. Assessment of tissue adequacy for diagnosis
3. Selection of lesional tissue for biorepository or ancillary studies

EVM Functional Requirements

- **Attributes of EVM technology (functional requirements) (functional requirements)**

1. **Size**
2. **Cost**
3. **Specimen preparation**
4. **Total time to interpretation**
5. **Field of view/resolution**
6. **Diagnostic capability**
7. **Yield**
8. **Accuracy**
9. **Ease of use**
10. **Safety**

Current Standards

- **Assessment of margins**
  - **Location – Pathology suite (laboratory or OR; fixed)**
  - **Modality – Frozen section**
- **Assessment of tissue adequacy for diagnosis**
  - **Location – Pathology suite or site of procedure**
  - **Modality – Frozen section or touch imprint**
- **Selection of lesional tissue for biorepository or ancillary studies**
  - **Location – Pathology suite or site of procedure**
  - **Modality – Frozen section or touch imprint**

Functional Requirements

- **Should meet or exceed current standards**
- **Attempt to standardize across applications, if possible**
  - **Default to minimal requirements; more stringent specifications would be acceptable but not required**

Functional Requirements

Minimum Functional Requirement	Size		Specimen Preparation	Total Time				Field of View/Resolution	
EVM Application	Footprint	Portability		Specimen Preparation	Image Acquisition	Interpreta-tion	Comment	Area of Tissue to be Imaged	Required Magnifica-tion
Assessment of margins	Up to 3' x 2' (similar to cryostat); countertop or freestanding	Fixed, portable, or handheld	<5 min; simple (1-step), minimal training required, no adverse effects on FFPE histology, IHC, ISH, genomic testing.	1-5 min, maximum	<20 min, preferably <10 min	5-10 min, maximum	Total <20 min for uncomplicated specimens (comparable to frozen section)	100 sq cm, maximum	10-20x
Assessment of aspirate or core biopsy adequacy for diagnosis	Up to 1' x 1' (fit on Cytology or specimen cart)	Portable (handheld preferred)	<5 min; simple (1-step), minimal training required, no adverse effects on FFPE histology, IHC, ISH, genomic testing.	1-5 min, maximum	<5 min	<5 min	Total <10 min (comparable to touch imprints)	1-5 sq cm, maximum	10-20x
Identification of lesional tissue for genomic studies or biobanking	Up to 1' x 1' (fit on Cytology or specimen cart)	Portable (handheld preferred)	<5 min; simple (1-step), minimal training required, no adverse effects on FFPE histology, IHC, ISH, genomic testing.	1-5 min, maximum	<5 min	<5 min	Total <10 min (comparable to touch imprints)	1-5 sq cm, maximum	10-20x

Functional Requirements

Minimum Functional Requirement	Diagnostic Capability	Yield	Accuracy	Ease of Use	Safety	Cost		
EVM Application						Cost of Instrument	Cost per Specimen Analyzed	Cost of Image Storage
Assessment of margins	Able to distinguish normal/benign from malignant (invasive/in-situ)	>90%	>90% NPV (histology/cytology gold standard)	Easy (minimal technical complexity, training requirements); histotech/cytotech should be able to operate	Grounded; laser shielded; all surfaces must be able to be decontaminated between cases	$30,000 - $100,000 depending on types of specimens that can be assessed	<$10	Should be included; data may be compressed for storage or be limited to critical data only
Assessment of aspirate or core biopsy adequacy for diagnosis	Able to distinguish tissue types, identify lesional tissue, and assess cellularity and viability	>90%	>90% PPV (histology/cytology gold standard)	Easy (minimal technical complexity, training requirements); histotech/cytotech should be able to operate	Grounded; laser shielded; all surfaces must be able to be decontaminated between cases	<$25,000	<$10	Should be included; data may be compressed for storage or be limited to critical data only
Identification of lesional tissue for genomic studies or biobanking	Able to distinguish tissue types, identify lesional tissue, and assess cellularity and viability	>90%	>90% PPV (histology/cytology gold standard)	Easy (minimal technical complexity, training requirements); histotech/cytotech should be able to operate	Grounded; laser shielded; all surfaces must be able to be decontaminated between cases	<$25,000	<$10	Should be included; data may be compressed for storage or be limited to critical data only

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Functional Requirements

- **Substantial overlap in functional requirements for the three most likely applications of EVM**
- **Minimal functional requirements for assessment of tissue adequacy for diagnosis and for selection of tissue for biorepository or ancillary studies are essentially identical**
  - **Greater flexibility in the potential application of EVM devices as they become commercially available**

CAP Checklist Compliance

CAP Accreditation Checklists

- **Anatomic Pathology Checklist**
- **Independent sections on IVM and EVM**
- **Some requirements in other sections may also apply**

CAP Anatomic Pathology Checklist – EVM

ANP.23560 EVM - System Validation **Phase I**

The laboratory performs validation studies before the Ex Vivo Microscopy (EVM) technology is used for the intended purpose(s).

NOTE: The specific components of the validation study are left to the discretion of the laboratory. However, studies should be performed using an adequate number of cases, data should be evaluated, and a summary statement provided prior to implementation. Records of how discordant data or unacceptable variations from the expected were resolved are required.

As general guiding principles, the validation process should:

- *Closely emulate the real-world environment and involve tissue types and clinical settings relevant to the intended use(s)*
- *Be carried out by or under the supervision of a pathologist adequately trained to use the EVM system*
- *Encompass the entire EVM system, with reevaluation if a significant change is made to a previously validated system.*

Evidence of Compliance:

✓ Records of completed validation study with supporting validation data, review and approval

CAP Anatomic Pathology Checklist – EVM

ANP.23570 EVM - Function Checks **Phase II**

Regular function checks are performed and records retained on the Ex Vivo Microscopy (EVM) system/instrument.

NOTE: Function checks include confirmation that an instrument or item of equipment operates according to manufacturer's specifications before routine use, at prescribed intervals, or after minor adjustment. Depending on the type of system, function checks may include calibration.

Evidence of Compliance:

✓ Written procedure for function checks and calibration, as required

CAP Anatomic Pathology Checklist – EVM

ANP.23580 EVM - Method Performance Specifications Availability **Phase II**

The current Ex Vivo Microscopy (EVM) methods and all significant changes to analytical methodology, including performance specifications and supporting validation data, are retained by the laboratory.

NOTE: Records should include, but are not limited to, components of EVM equipment, software systems, and image viewing systems.

Evidence of Compliance:

- ✓ Records of changes to analytical methodology

CAP Anatomic Pathology Checklist

***REVISED** 08/21/2017*

ANP.12500 Record Retention **Phase II**

Surgical pathology records and materials are retained for an appropriate period.

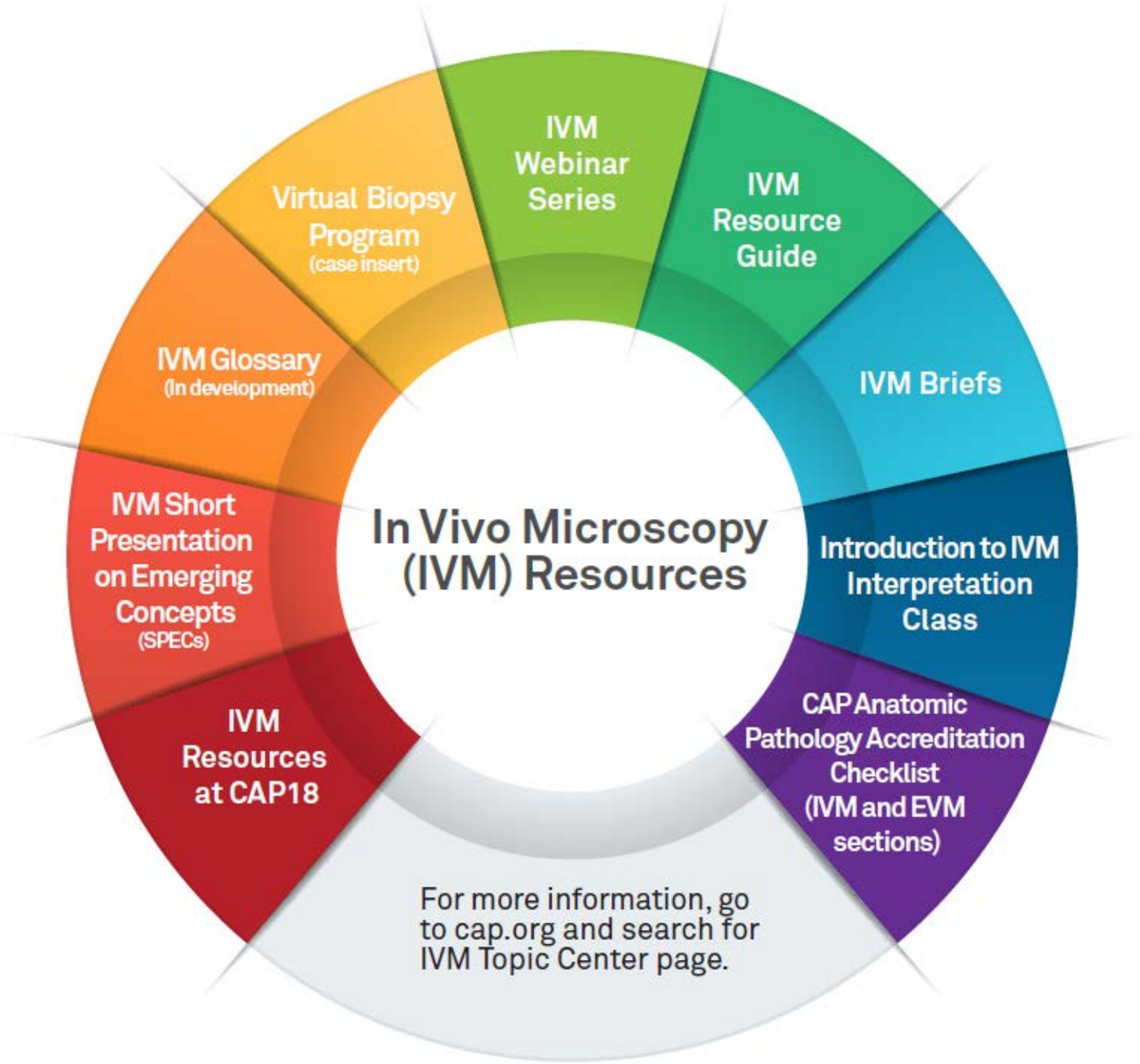
Type of Record/Material	Retention Period
Digital images used for primary diagnosis	10 years if original glass slides are not available
Datasets from In-Vivo Microscopy (IVM) or Ex Vivo Microscopy (EVM) systems used to aid in interpretation or diagnosis	10 years - data must be retrievable for this period (Subject to Note 6 below)

NOTE 6: In Vivo Microscopy (IVM) and Ex Vivo Microscopy (EVM) systems include confocal microscopy, optical coherence tomography, multiphoton microscopy, optical spectroscopy/ spectroscopic imaging, and similar technologies. These systems may be used by physicians during procedures (IVM) or by the laboratory in the evaluation of specimens that have been removed from the patient (EVM). The dataset refers to digitized or analog video or still images or other data (eg, spectroscopic data) generated by an IVM or EVM system. If such data is used to aid in interpretation or diagnosis, record retention requirements apply. Stored data should include, at a minimum, the data used to aid in interpretation or diagnosis.

Evidence of Compliance:

✓ Written record and specimen retention policy(ies)

IVM Resources at CAP



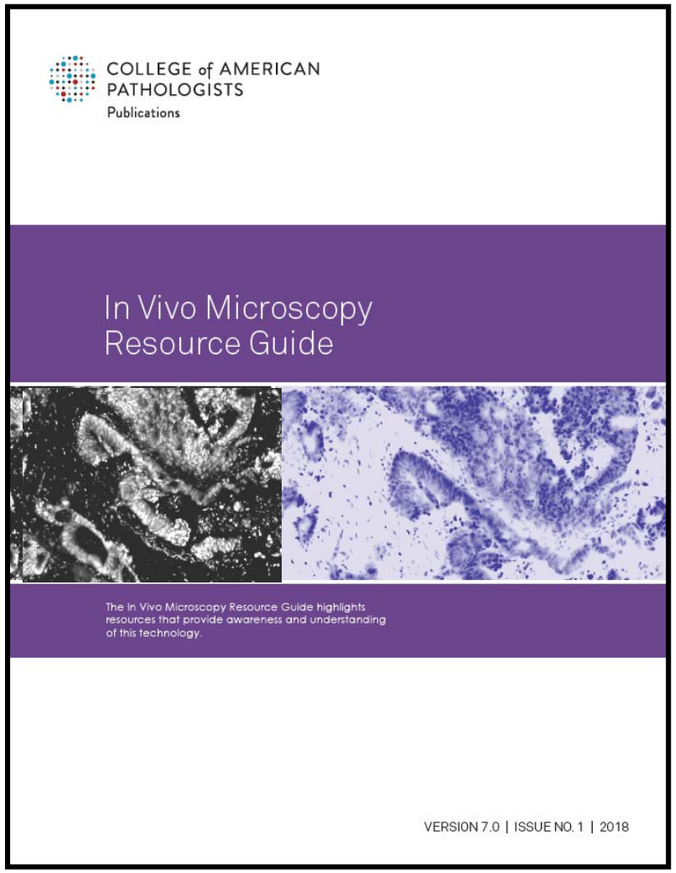
Upcoming IVM Webinars

Date	Topic	Speaker
October 29, 2019	TBD	Sandra Camelo-Piragua, MD

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**



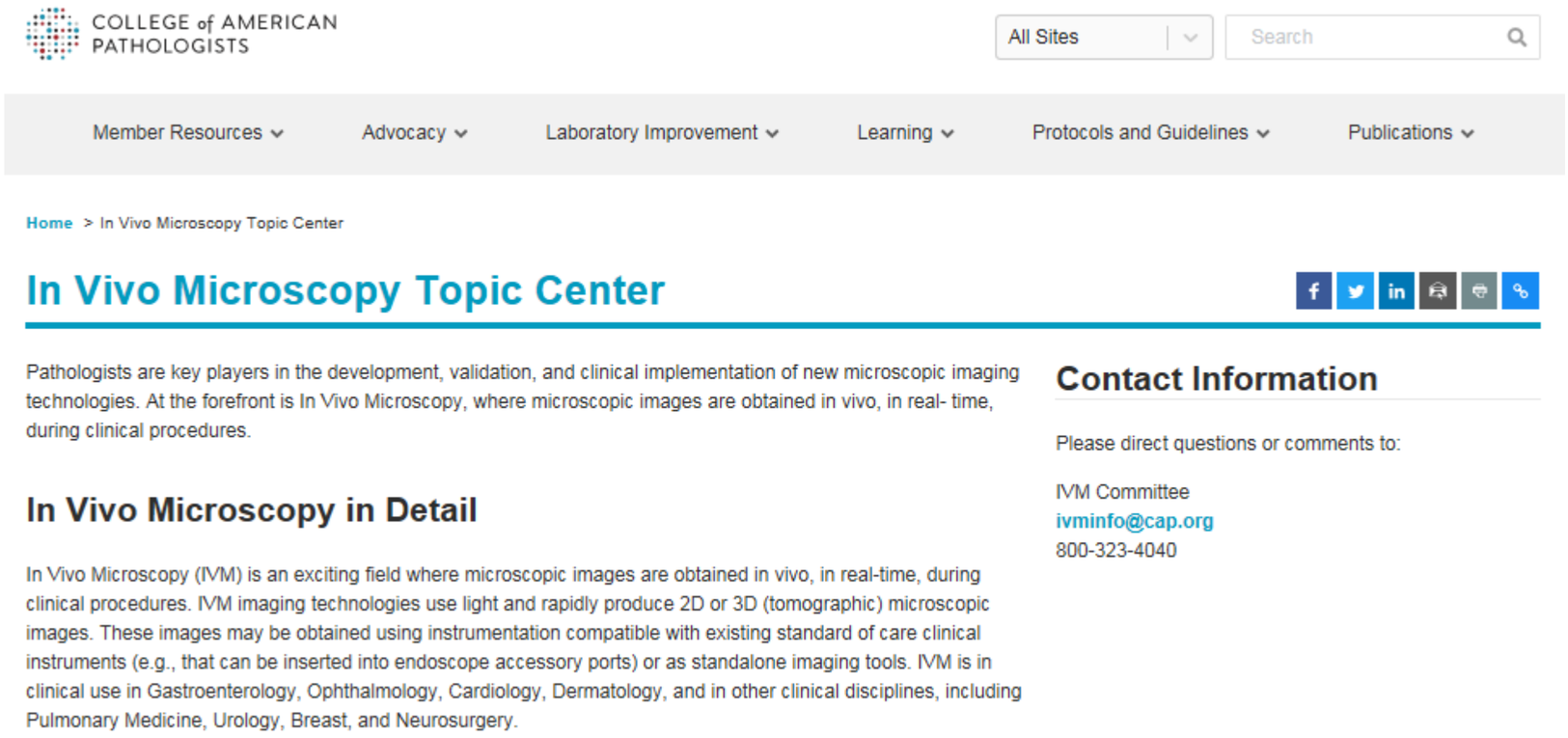
IVM Short Presentations on Emerging Concepts (SPECs) – see handout

- **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 "Ex Vivo Microscopy (EVM) Systems: Functional Requirements and CAP Checklist Compliance" by Sharad Mathur, MD

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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