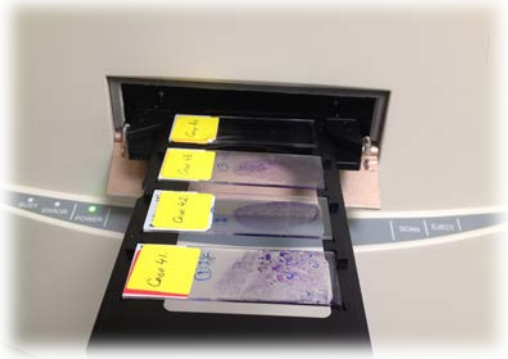
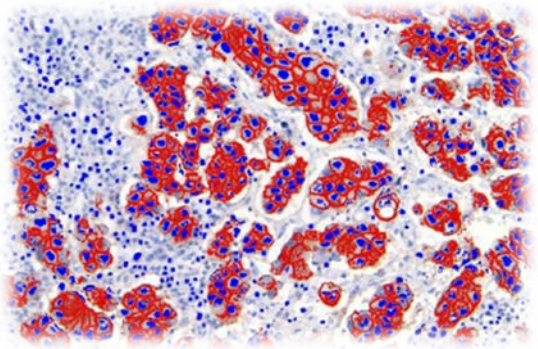
Digital Pathology:
Imaging Systems, Practice & Guidelines





Liron Pantanowitz, MD

Pathology Informatics Division
University of Pittsburgh Medical Center, USA
Email: pantanowitzl@upmc.edu

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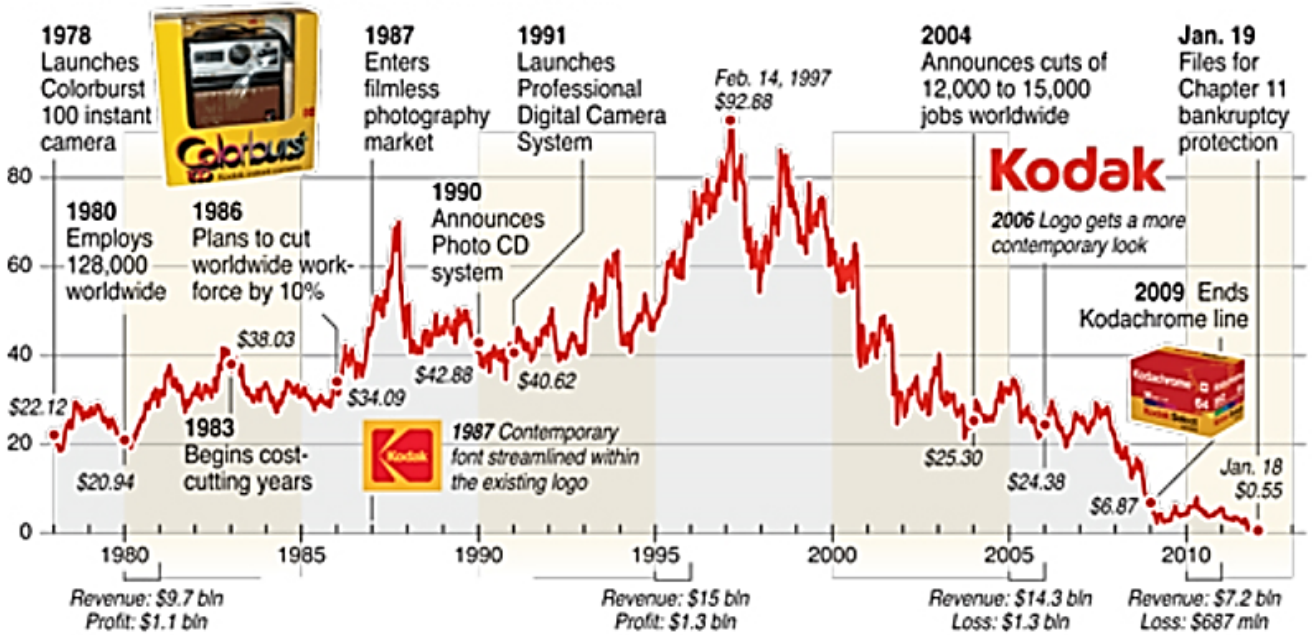
Liron Pantanowitz, MD

KODAK FILES FOR BANKRUPTCY

Eastman Kodak Co, a 130-year-old photographic film pioneer, has filed for bankruptcy protection. It said it had also obtained a $950 million, 18-month credit facility from Citigroup to keep it going

SHARE PRICE HISTORY — WEEKLY CLOSE IN US$



Sources: Eastman Kodak Co., Thomson Reuters, news reports

REUTERS

Why did KODAK go BANKRUPT?

- They did not go digital
- Thought it was just a fad
- Failed to consider the benefits (e.g. applications)
- Stuck with what they always did

Digital Pathology Market

- **Poised to explode!**
  - **$ 205.23 million in 2019**

DARK Daily
Clinical Laboratory and Pathology News/Trends

Financial Experts Predict Sales of Digital Pathology Systems Will Nearly Triple in the United States by 2019

Overview

1. Imaging Basics
2. Imaging Systems
3. Digital Pathology Practice
4. Guidelines

Overview

1. Imaging Basics
   What is essential for pathologists?
2. Imaging Systems

3. Digital Pathology Practice

4. Guidelines

Overview

1. Imaging Basics
   What is essential for pathologists?
2. Imaging Systems
   What is available for pathology use?
3. Digital Pathology Practice

4. Guidelines

Overview

1. **Imaging Basics**
   What is essential for pathologists?
2. **Imaging Systems**
   What is available for pathology use?
3. **Digital Pathology Practice**
   What applications are being used?
4. **Guidelines**

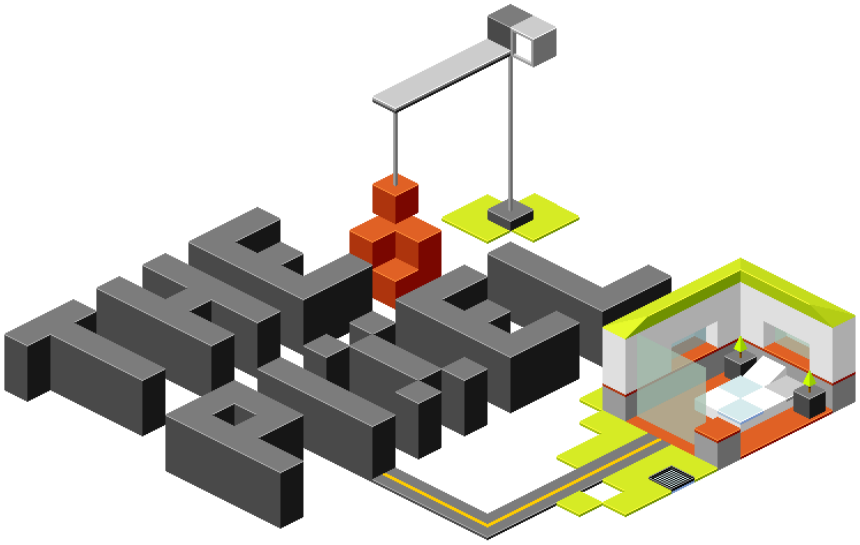
Overview

1. **Imaging Basics**
   What is essential for pathologists?
2. **Imaging Systems**
   What is available for pathology use?
3. **Digital Pathology Practice**
   What applications are being used?
4. **Guidelines**
   Which are important in practice?

Imaging Basics

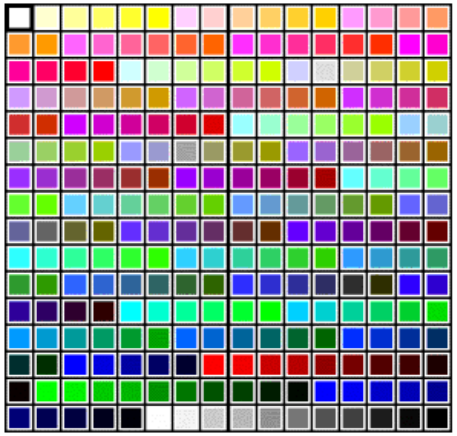
- Images
- Imaging Process
- Image management
- Image analysis

Images

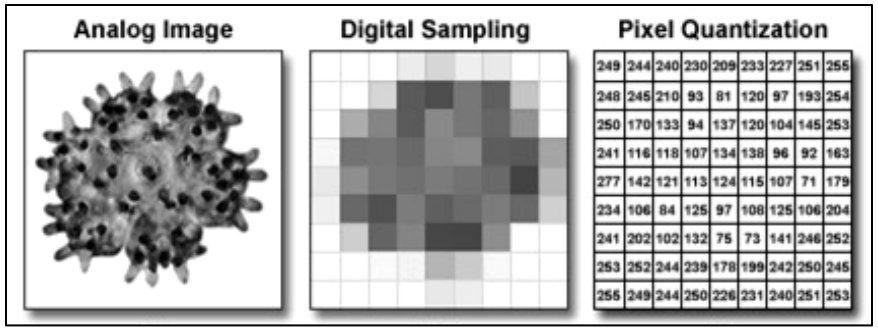


Digital Imaging Basics

- Pixel = Picture element
- RGB are additive primary colors
- Bit (color depth) = # color choices/pixel
- B&W is represented by 0 and 1 (1 bit)
- 256 indexed color values
- File size = number of pixels (W x H) x bit depth (i.e. number of bytes used for each pixel)
- Pixel *density* refers to the output of images:
  - Printed - dpi (dots per inch)
  - Displayed on a screen - ppi (pixels per inch)



24 bit = 8 bit + 8 bit + 8 bit
red green blue



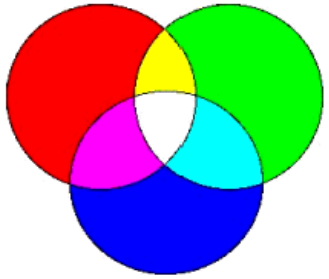


Image Quality

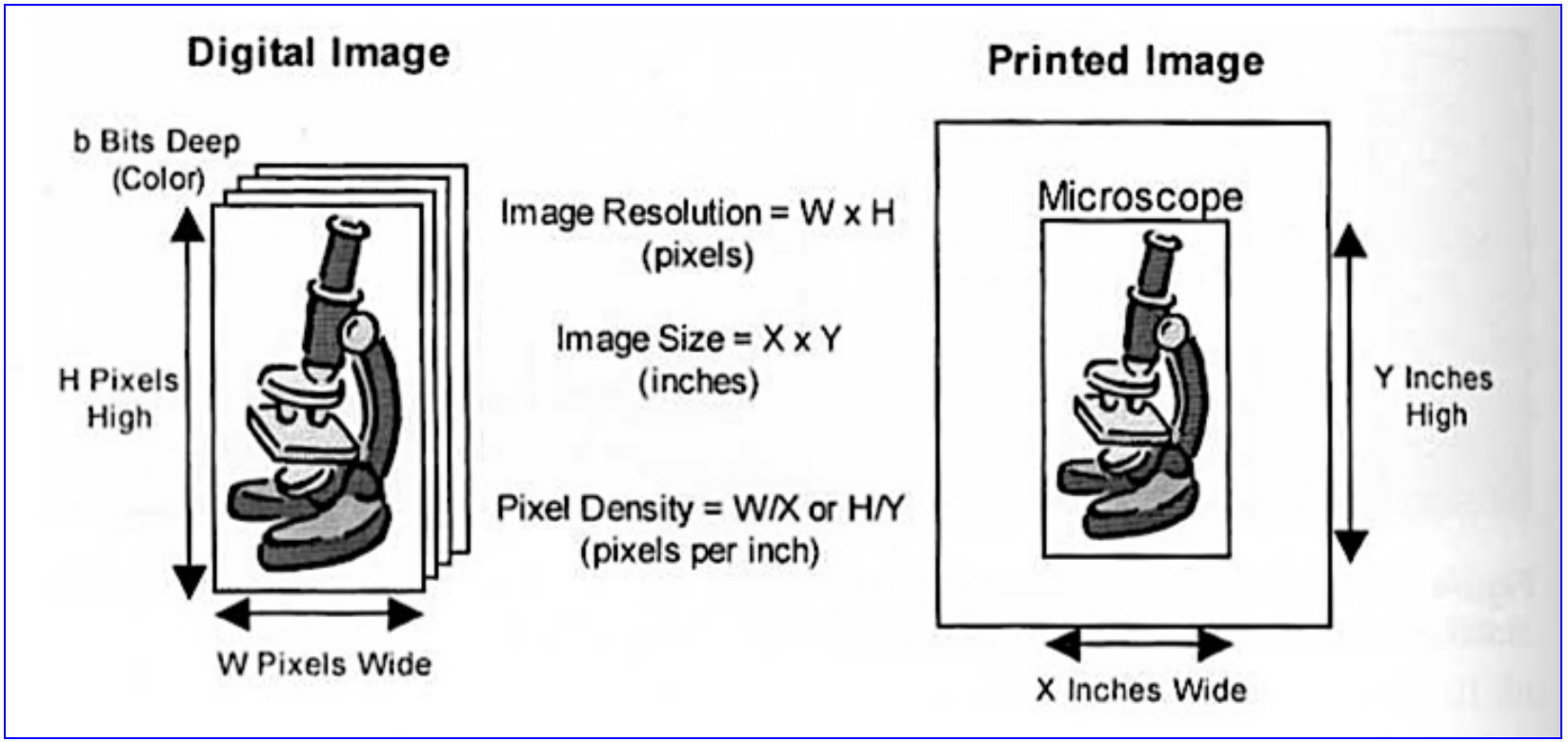
Digital files

- Resolution
  - Pixel (pixel count)
  - Temporal (frames per second)
  - Spatial (pixel size on sensor)
- Aberrations (noise, distortion)
- Contrast
- Color accuracy

Equipment

- Optics (lenses, NA of objectives)
- Dynamic (exposure) range
- Sensor (CCD)
- Artifacts (compression)
- Computer (graphics card)
- Display resolution

Pixel Resolution & Density



from Sinard. Practical Pathology Informatics. 2008.

Compression

- Compacting an image by removing redundant information
  (e.g. pixels of the same color)
- Reduced image size helps image processing, storage & transmission
- File size vs. image quality
- Types of compression algorithms:

  1. Lossless compression (e.g. TIFF)

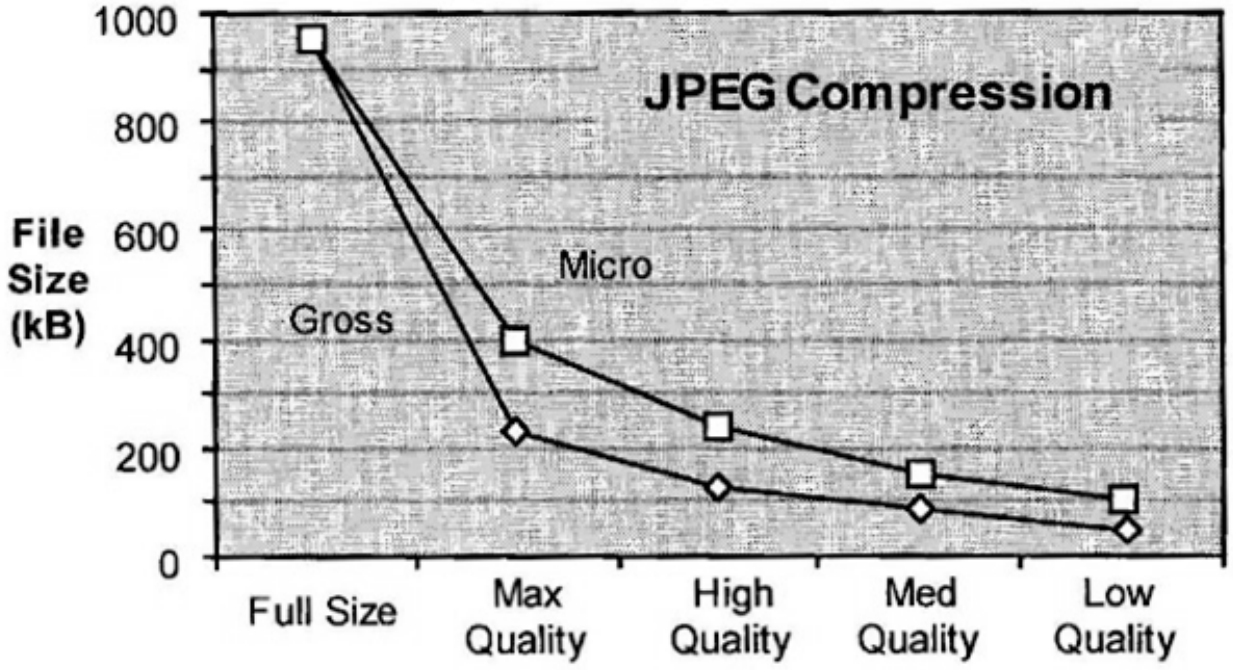
     Reduced storage space without loss of data (e.g. AAABBBCCC→3A3B3C)

     On decompression the original is restored with EXACTLY the same detail

  2. Lossy compression (e.g. gif & jpeg)

     Unnecessary detail is lost with compression

     Decompressed image differs (but usually not to the human eye)



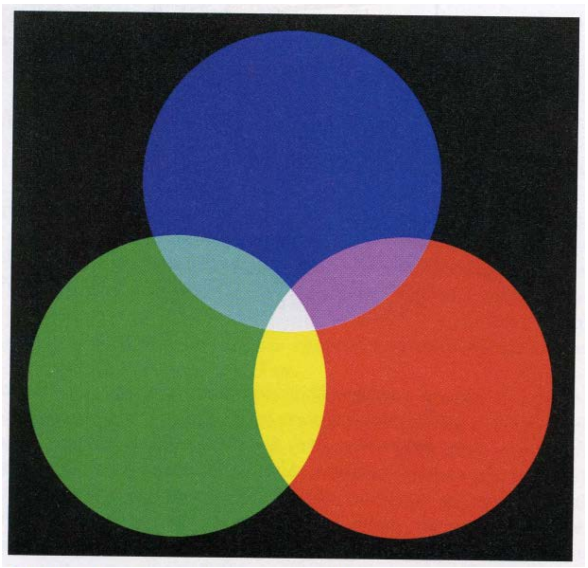
from Sinard. Practical Pathology Informatics. 2008.

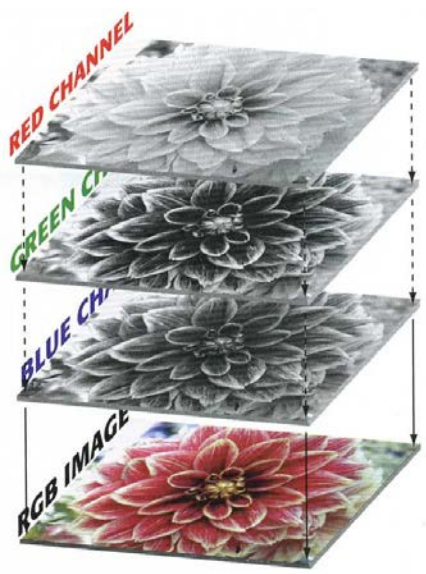
Impact of Compression

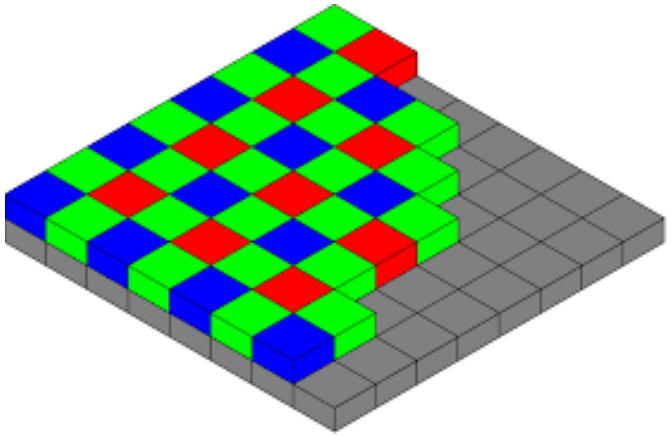
- JPG image compression does not negatively affect the accuracy of telepathology diagnosis (Marcelo et al. APLM 2000; 124:1653-6)
- Compressed images for high speed transfer improves telepathology (Pantanowitz et al. JPI 2015; 6:17)
- WSI can be compressed to high levels (up to 32:1) before impacting interpretation performance (Krupinski et al. JPI 2012; 3:17)

Color

A color image has three values per pixel

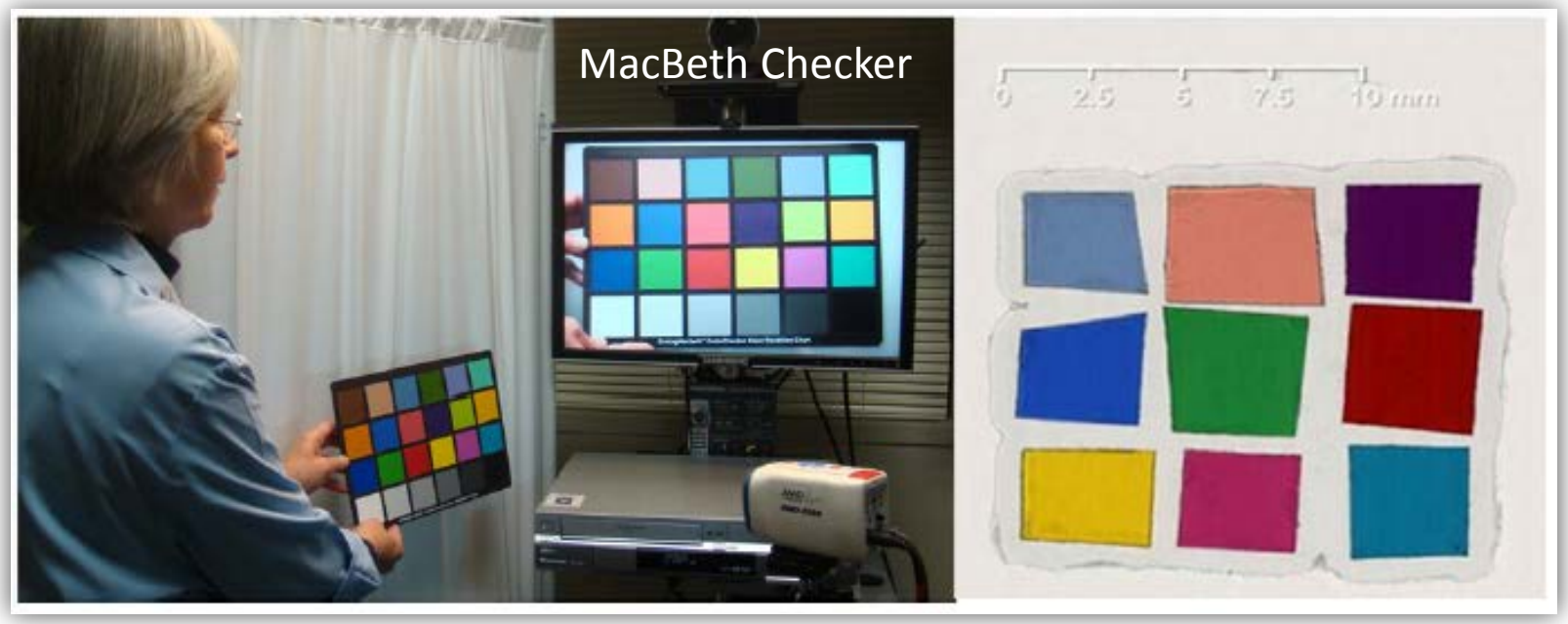






Color in Digital Pathology

- Pre-imaging (stains)
- Imaging process
- Displays (monitor)
- Analysis (multispectral)

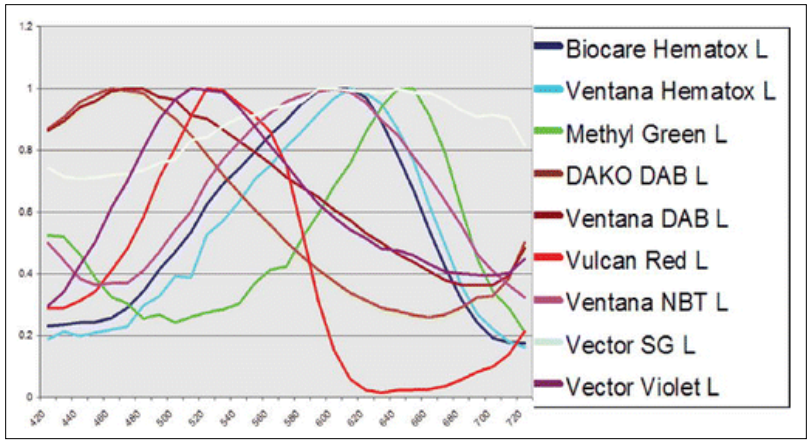


Weinstein RS et al. Human Pathology 2009; 40:1057–1069.

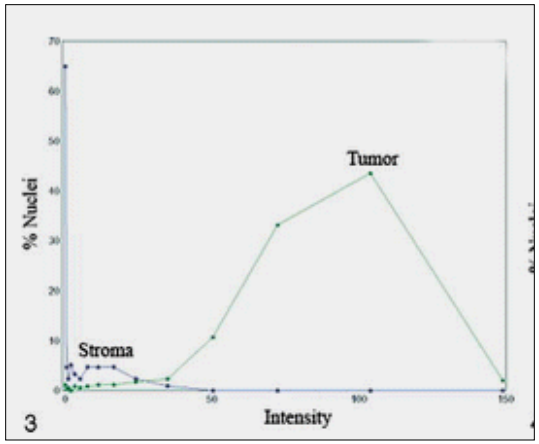
Slide-Based "Histocytometry"

Feldman MD. Arch Path Lab Med 2008; 132:758-763

Immunohistochemistry Spectral Curves



Staining Intensity



Multiplexing of biomarkers

Image Files

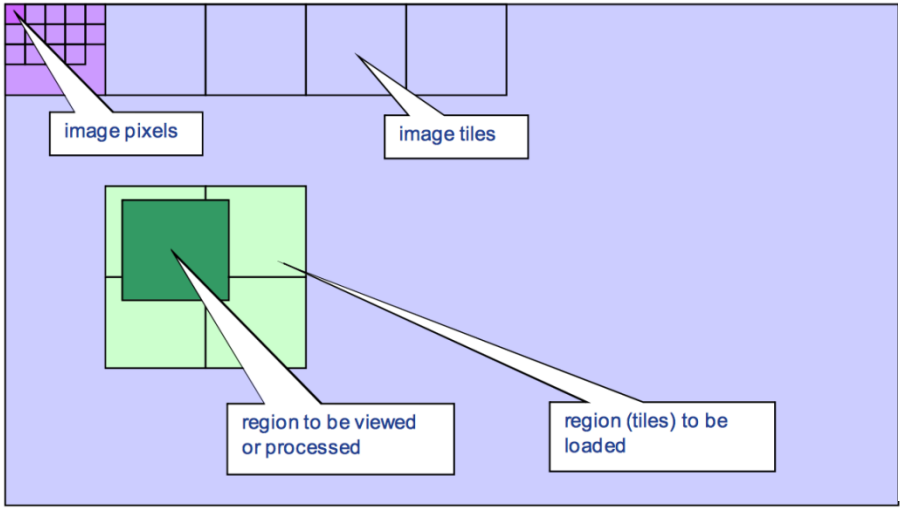
Format

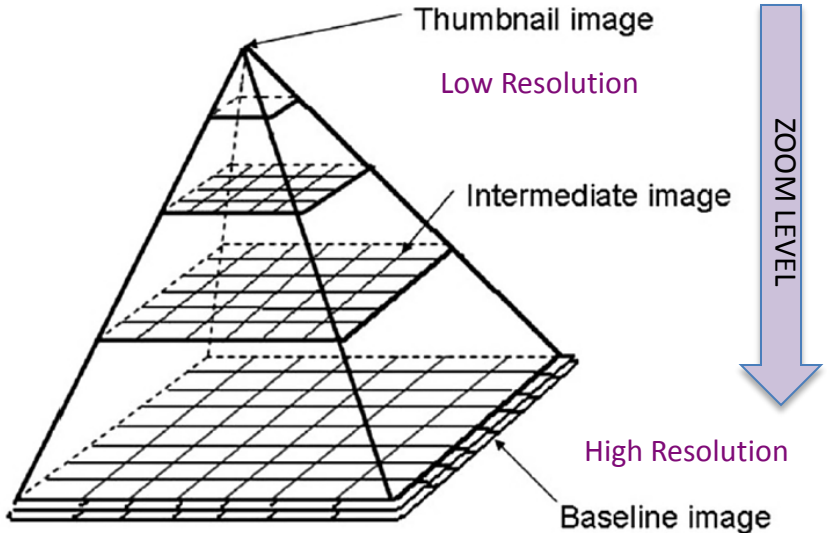
.jpg or JPEG
.JPEG 2000 (JP2)
.TIF (Generic tiles TIFF)
.bif (Ventana)
.svs (Aperio)
.svslide (Sakura)
.ndpi (Hamamtsu)
.DICOM
.etc

Viewers

- Interface to WSI
- Proprietary
  (e.g. ImageScope, DigitalScope)
- OpenSlide
- Mobile viewers
  (e.g. ePathViewer)

Tiled Images

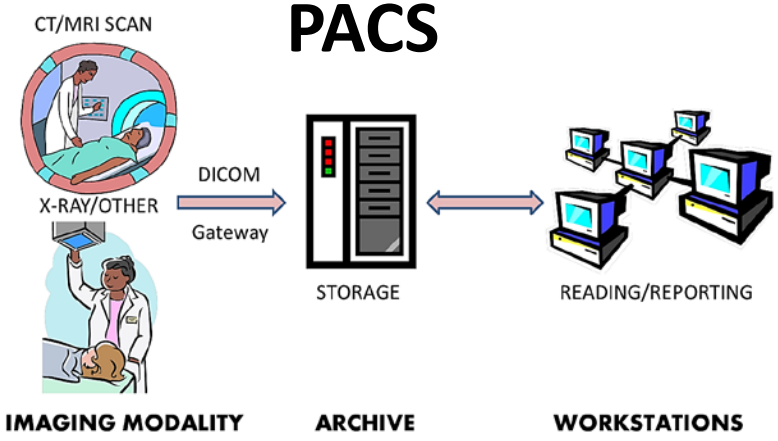


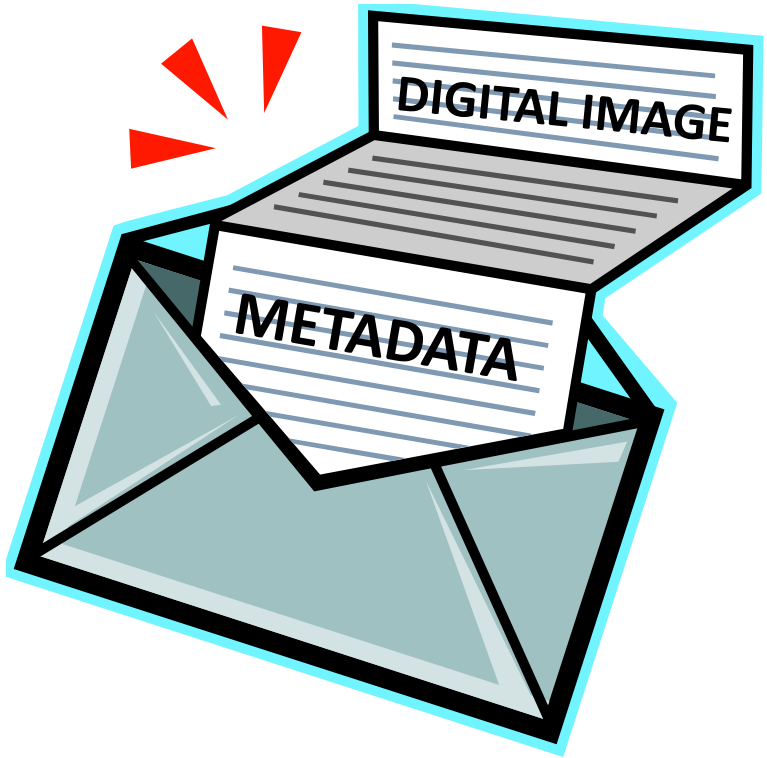


DICOM supplement 145

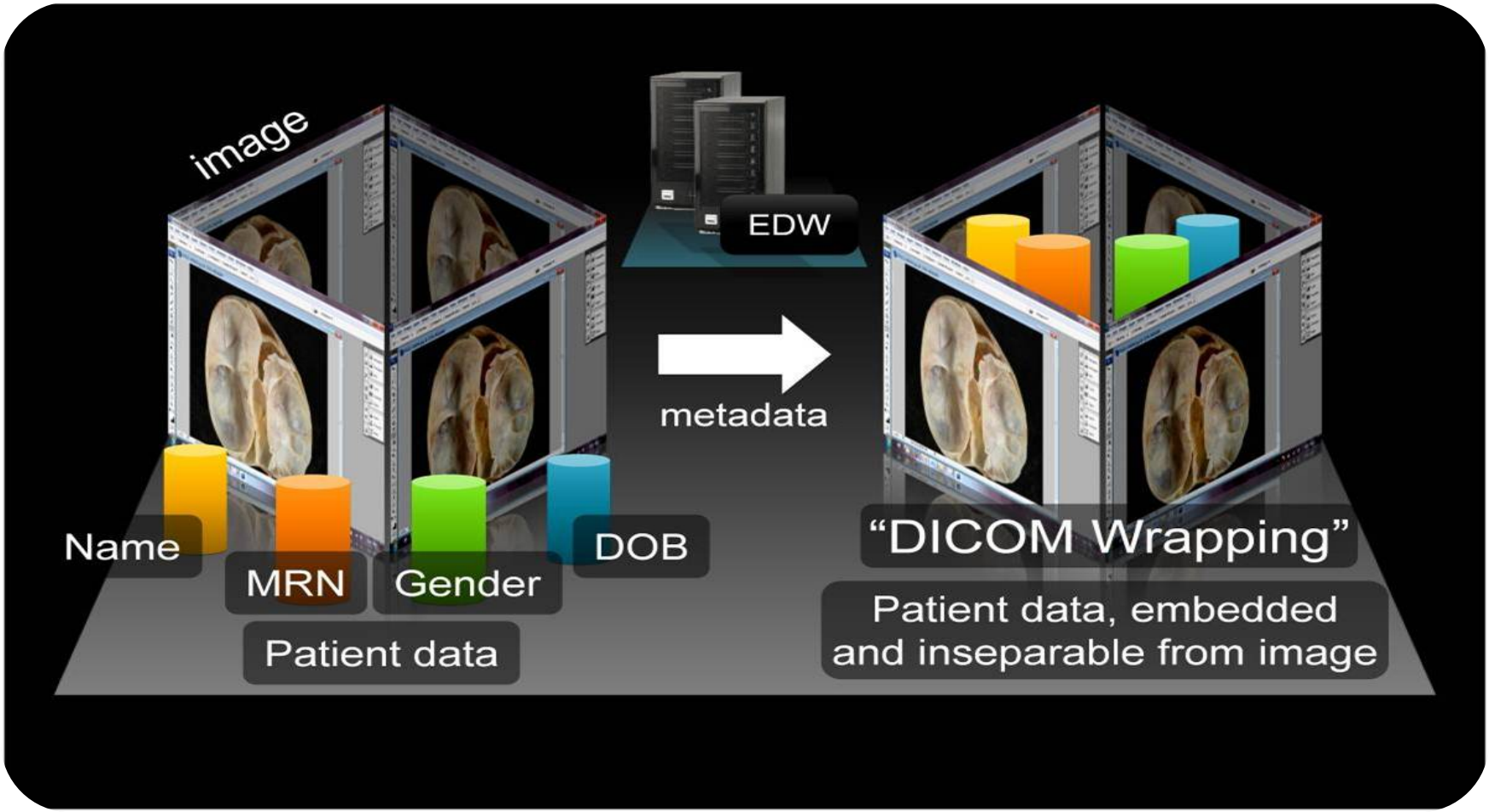
DICOM

- Digital Imaging & Communications in Medicine
- Radiology imaging standard
- Includes file format & network communications protocol





DICOM Compliant Images



Amin M et al. J Pathol Inform 2012; 3:10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MRN:
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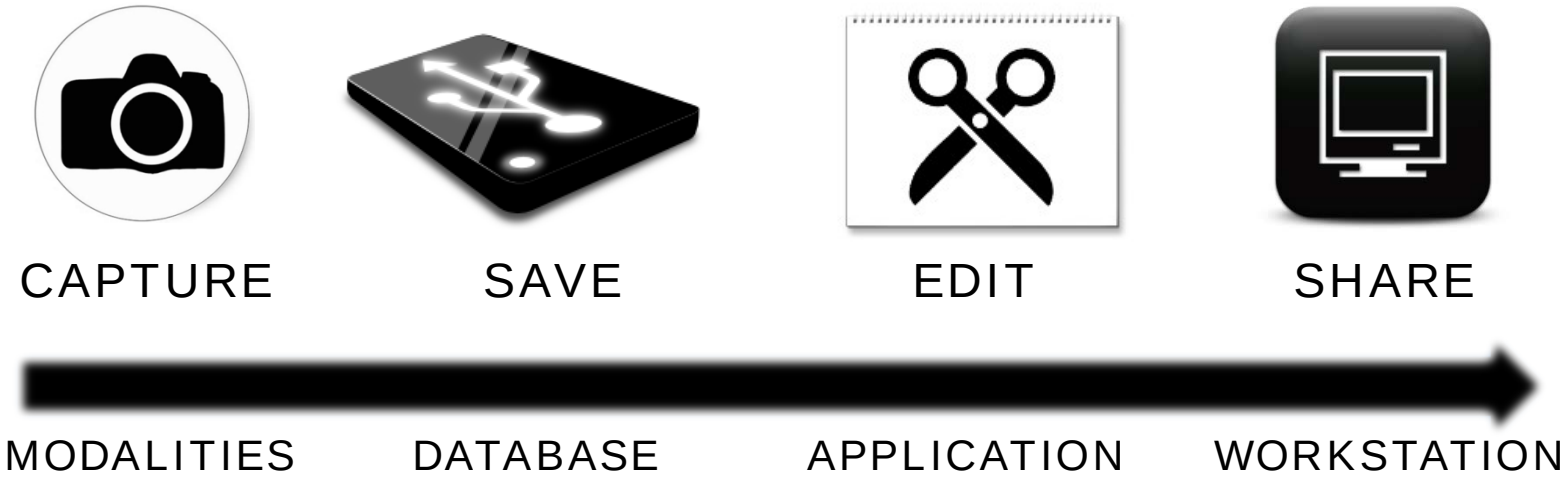
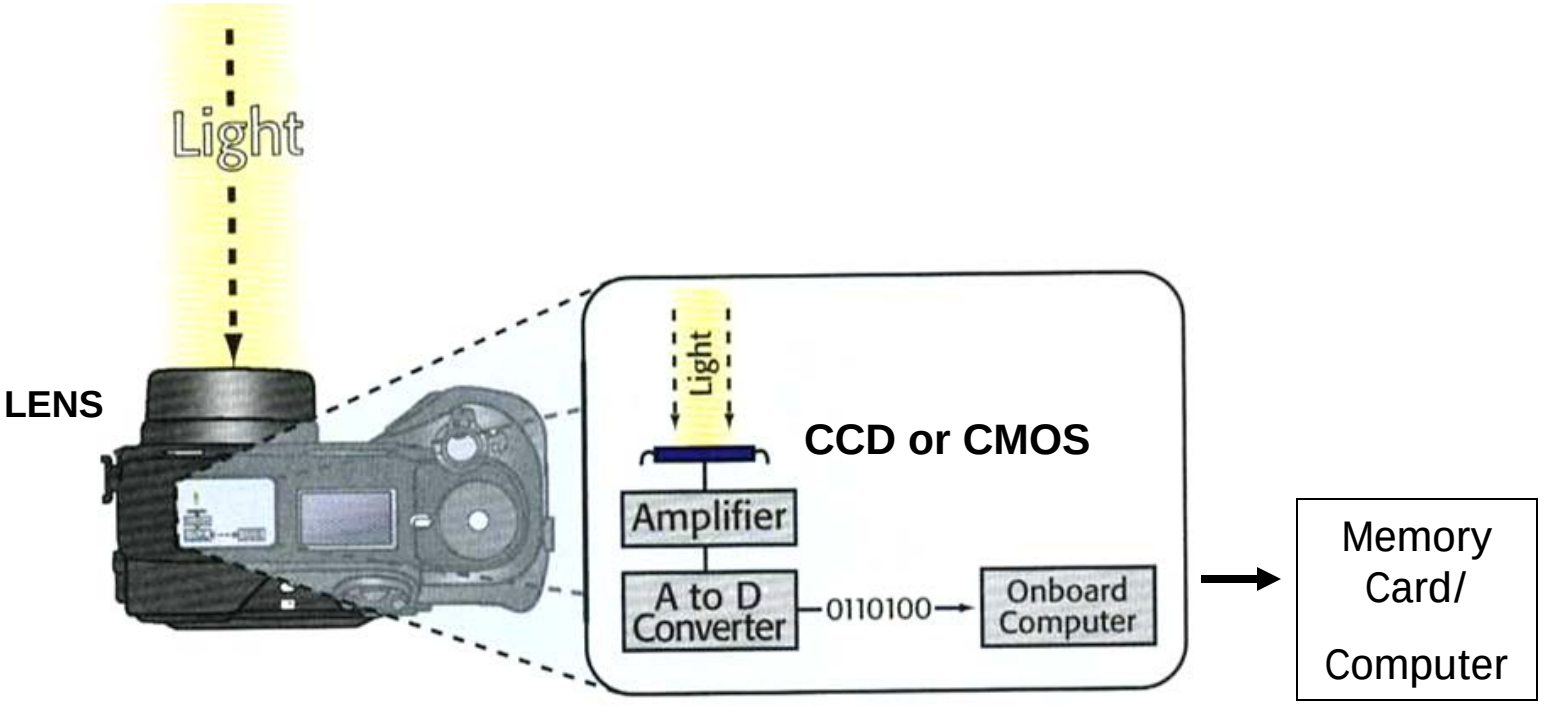
Back
CR CT DS DX MA MG
MR NM OT PT RF RG
US XA
Help
Videos
Feedback
SingleView
Show Relevant Exams
Patient History Timeline
Show Exams Without Images
Most Recent: 11/7/2011 8:45:00 AM
Least Recent: 1/5/2000 9:21:00 AM
METRIC
JPEG Lossy
Acc#
NECK W/O
NECK W/O
Series #2
BONE 2.5S
Series #3
PUH Pathology
Series #4
Monitor Calibration
Brightness / Contrast
SMPTE | Aspect Ratio

Imaging Process

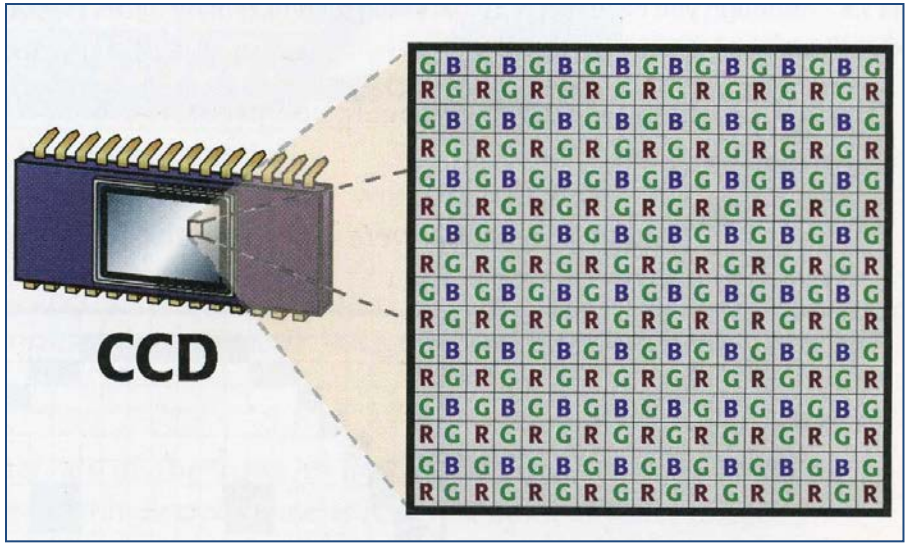


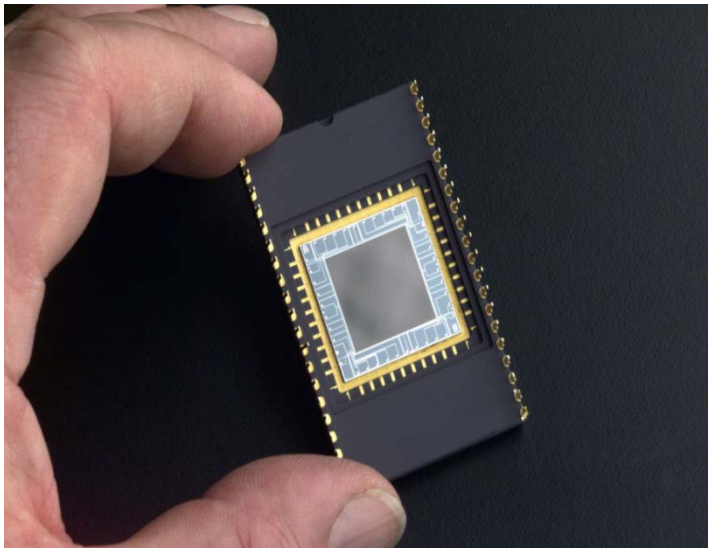
Digital Camera



Sensors

CCD = Charge-Coupled Device converts light into electrical signals
CMOS = Complimentary Metal Oxide Semiconductor functions





Photomicroscopy Camera

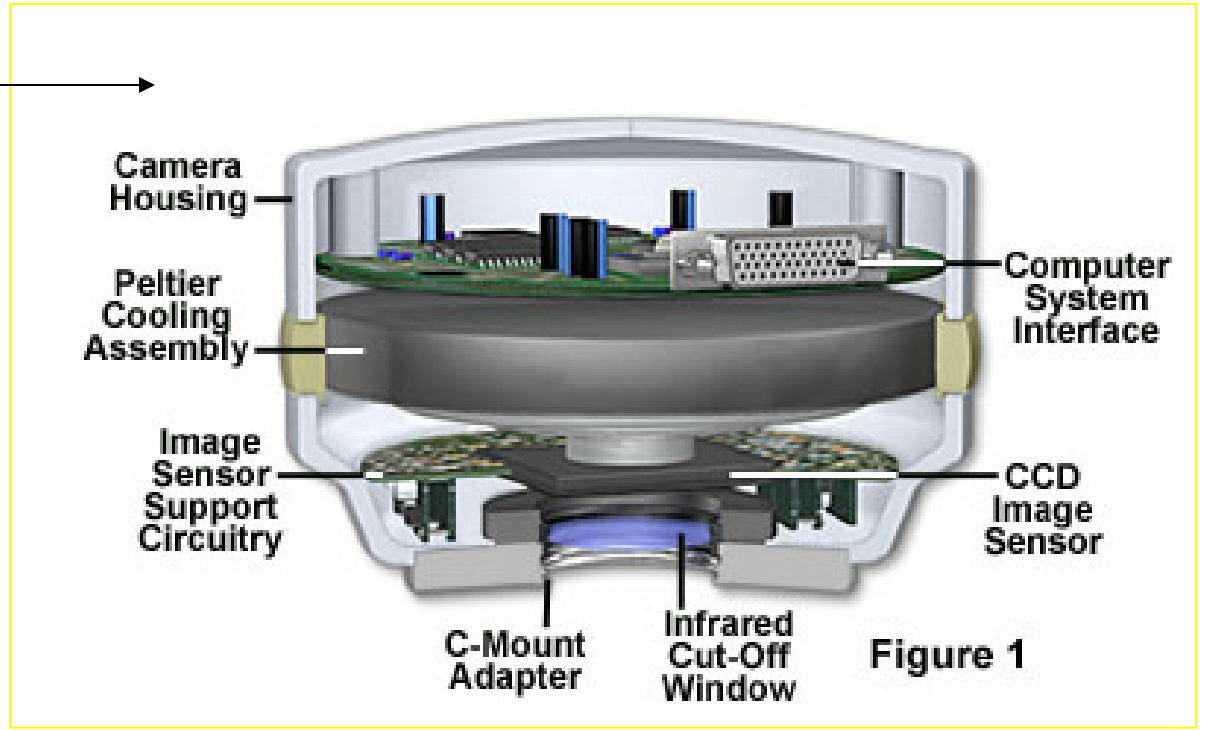


Figure 1

Image Management

1. File sizes & storage
2. LIS integration

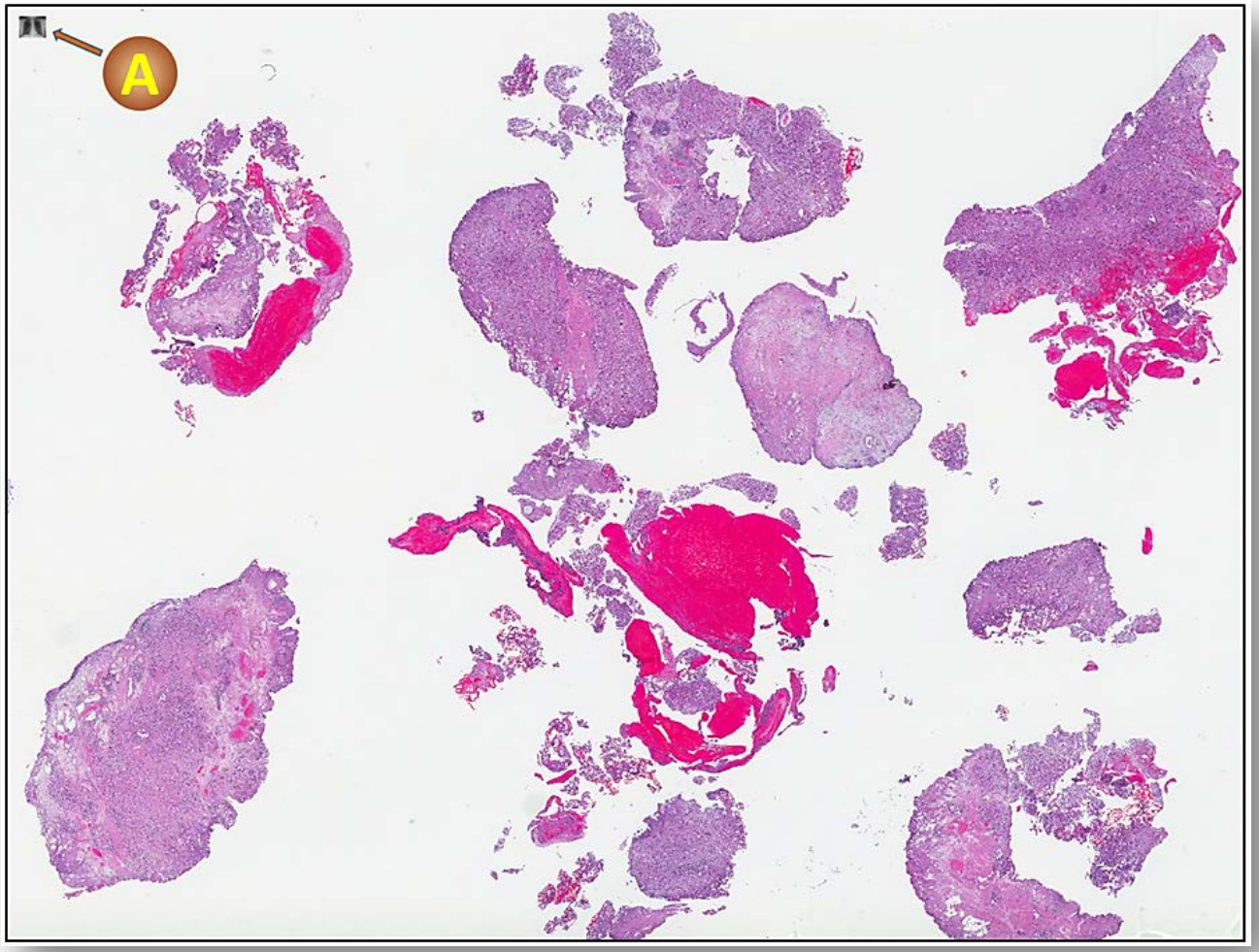
Image File Sizes

Image	Avg. Size (MB)
Endoscopy image	7
MRI	100
CT scan	150
PET	370
WSI (core biopsy 20x compressed)	300
WSI (core biopsy 40x compressed)	750

Romero Lauro G et al. J Digital Imaging. 2013

Magnitude of WSI dataset size

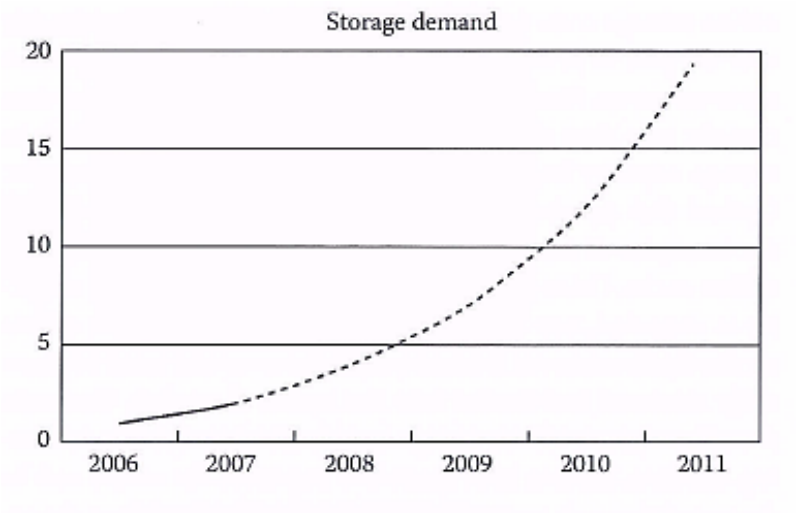
Pixel-normalized display of a chest X-ray image vs. 40x scan of 2.5 x 2.0cm biopsy



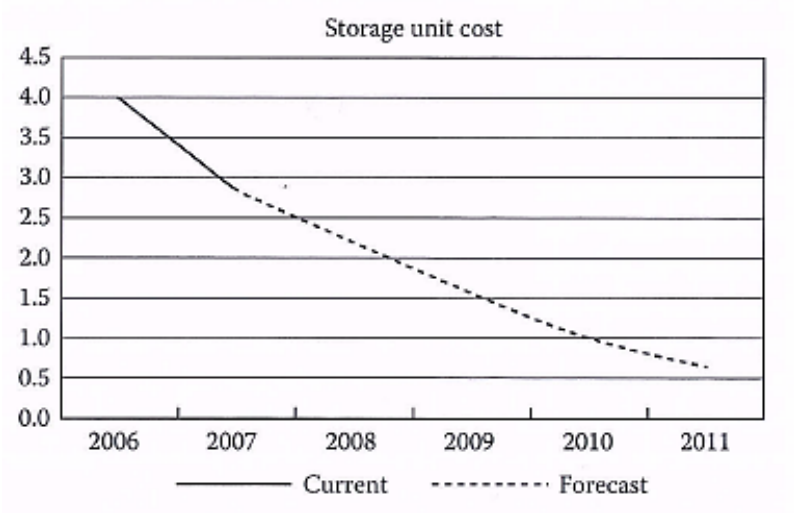
Pantanowitz et al. Pathology Informatics: Theory & Practice. ASCP Press. 2012.

Demand for Storage

Kagdadis & Langer. Informatics in Medical Imaging. CRC Press. 2012



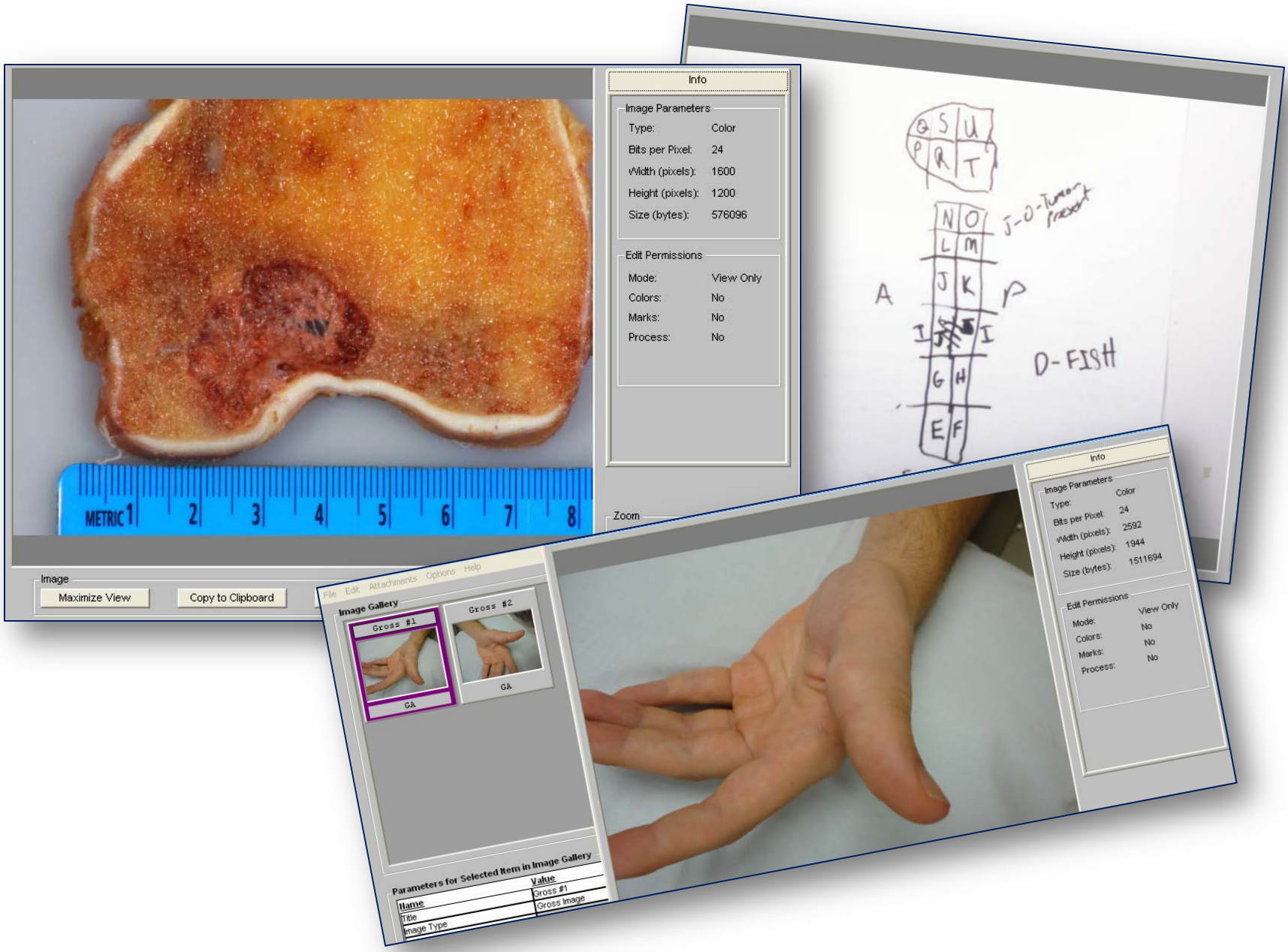
Per 1000's of petabytes



Per gigabyte in $

1 GB = 10^9 bytes

1 PB = 10^{15} bytes (or 1 million gigabytes)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Maximize View
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Q S U
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N O
L M
J K
A P
I I
G H
E F
J-O-Tumor present
D-FISH
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GA
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Parameters for Selected Item in Image Gallery
Name
Value
Title
Gross #1
Image Type
Gross Image

LIS-Related Image Management

Integral

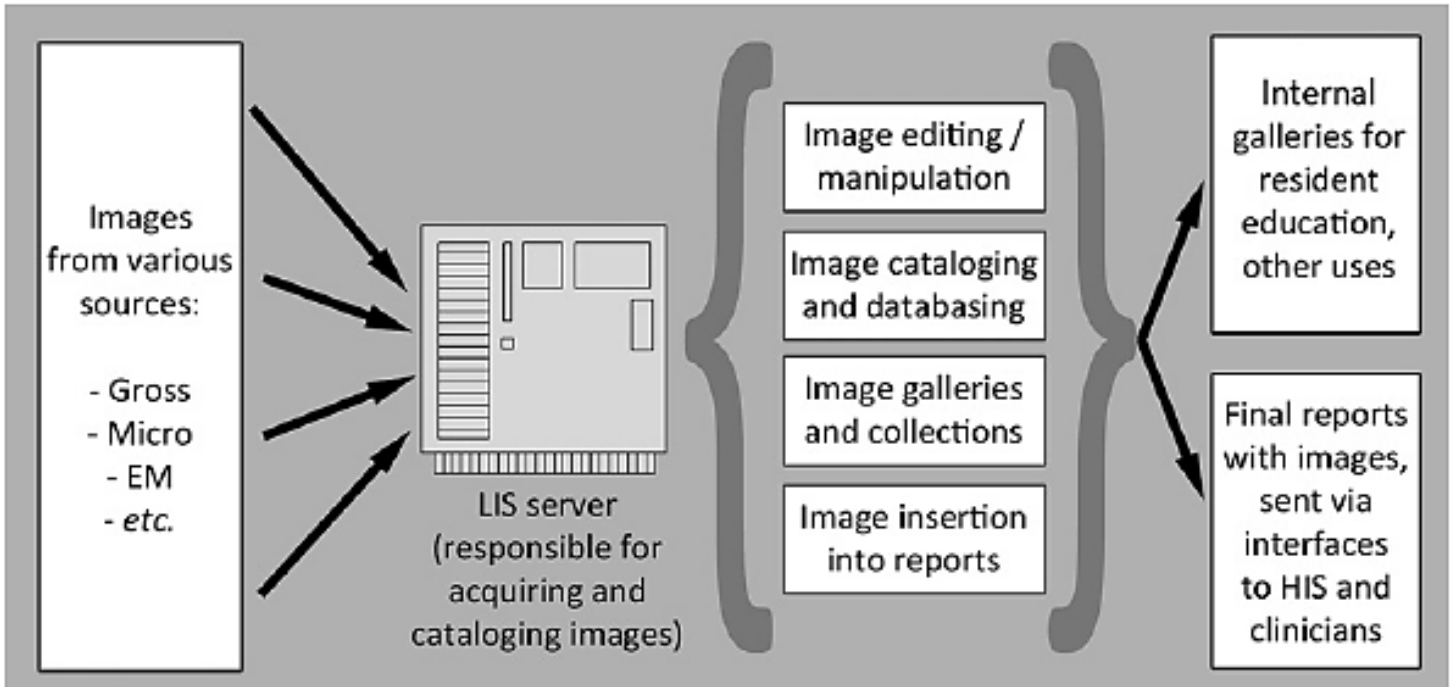
- Within the LIS (gallery)
- Not all devices are interfaced
- Image metadata automatically stored in the LIS database
- Users need access to the LIS
- Restricted editing & sharing tools
- Difficult to access raw image data
- Image format may be proprietary

Modular

- Separate from the LIS
- Requires central image repository
- Images need to be fed (manual, automatic) into the LIS
- Any imaging modality supported
- Greater user flexibility to share & manipulate images
- Middleware

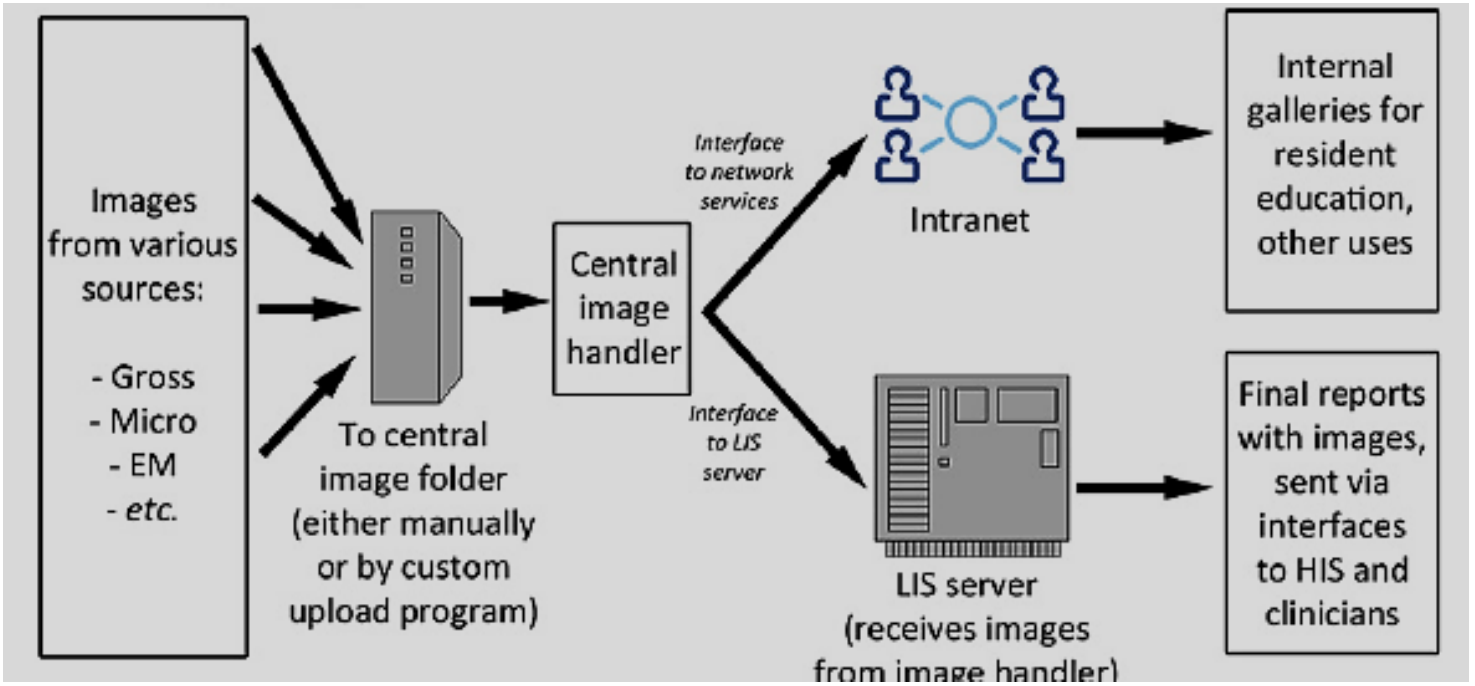
Integral Image Management

Park et al. Digital imaging in Pathology. Clin Lab Med 2012; 32:557-84

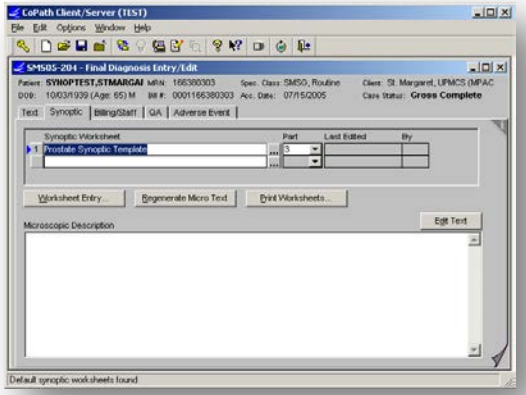


Modular Image Management

Park et al. Digital imaging in Pathology. Clin Lab Med 2012; 32:557-84



AP-LIS Integration



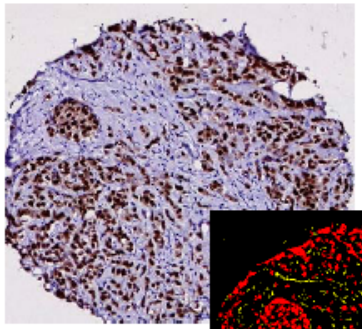
AP-LIS ⟷ Digital Workstation

Image Analysis

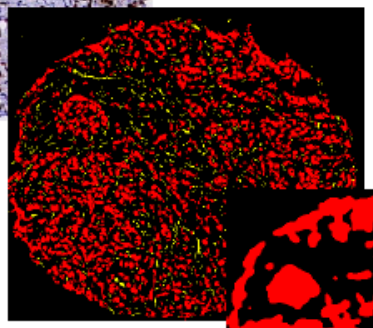
- Image pre-processing (e.g. color normalization)
- Automated detection (identification)
- Segmentation (global, nuclear)
- Feature extraction (object level, spatially related)
- Dimensionality reduction (focuses on few features)
- Classification
- Quantification

Digital Algorithms

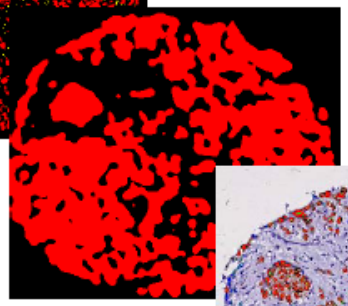
How the algorithms work…



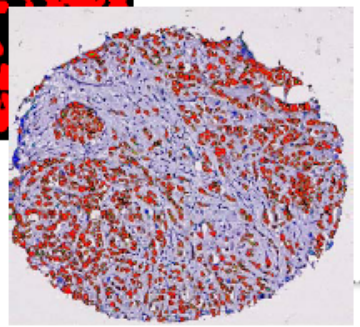
Step 1: Background corrected tissue image



Step 2: Morphology-based classification of objects (epithelial Vs stromal cells)



Step 3: Automatic ROI Identification

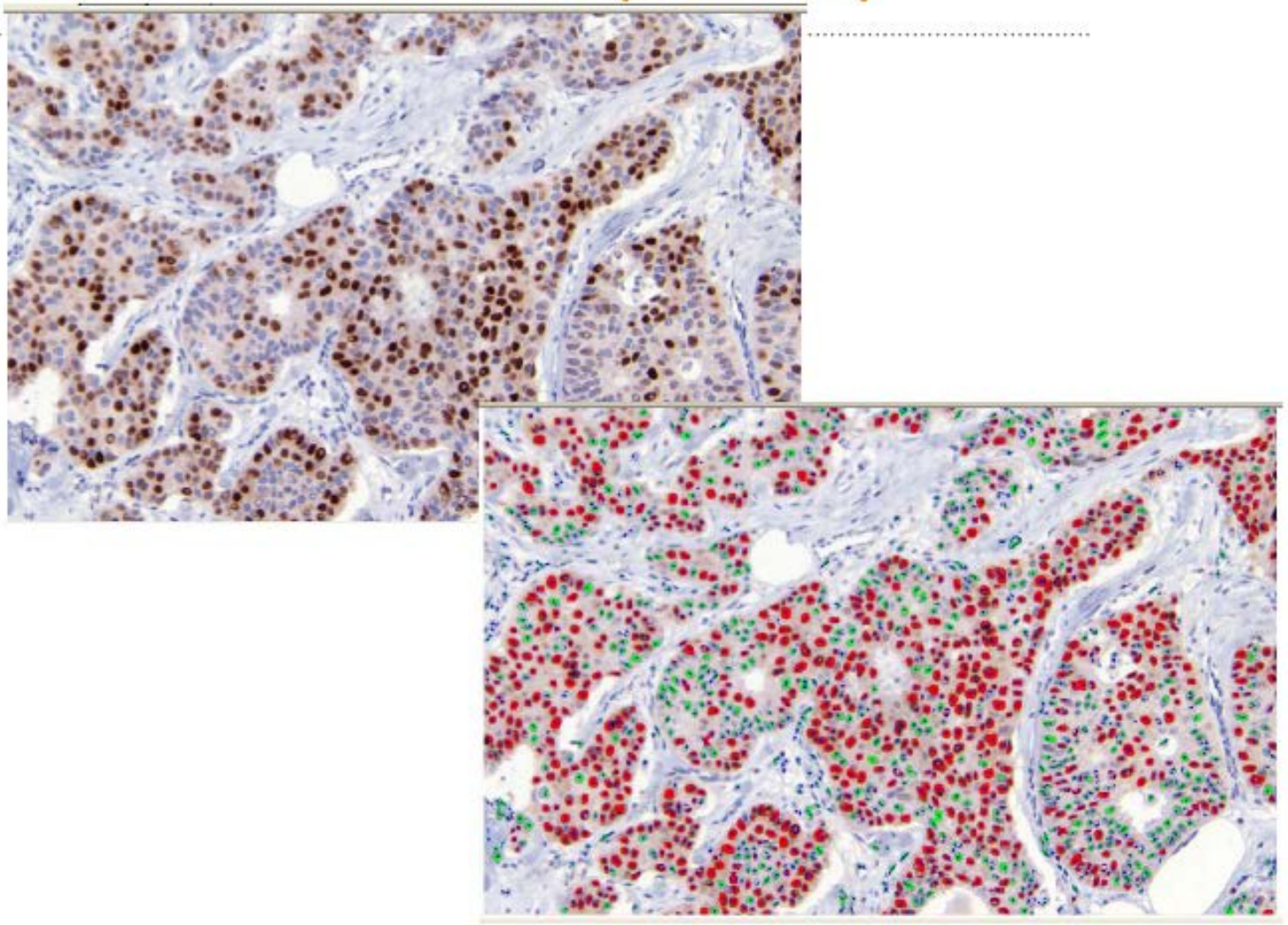


Step 4: (bring in color-metric information) - cell count, measure protein expression

bioimagene

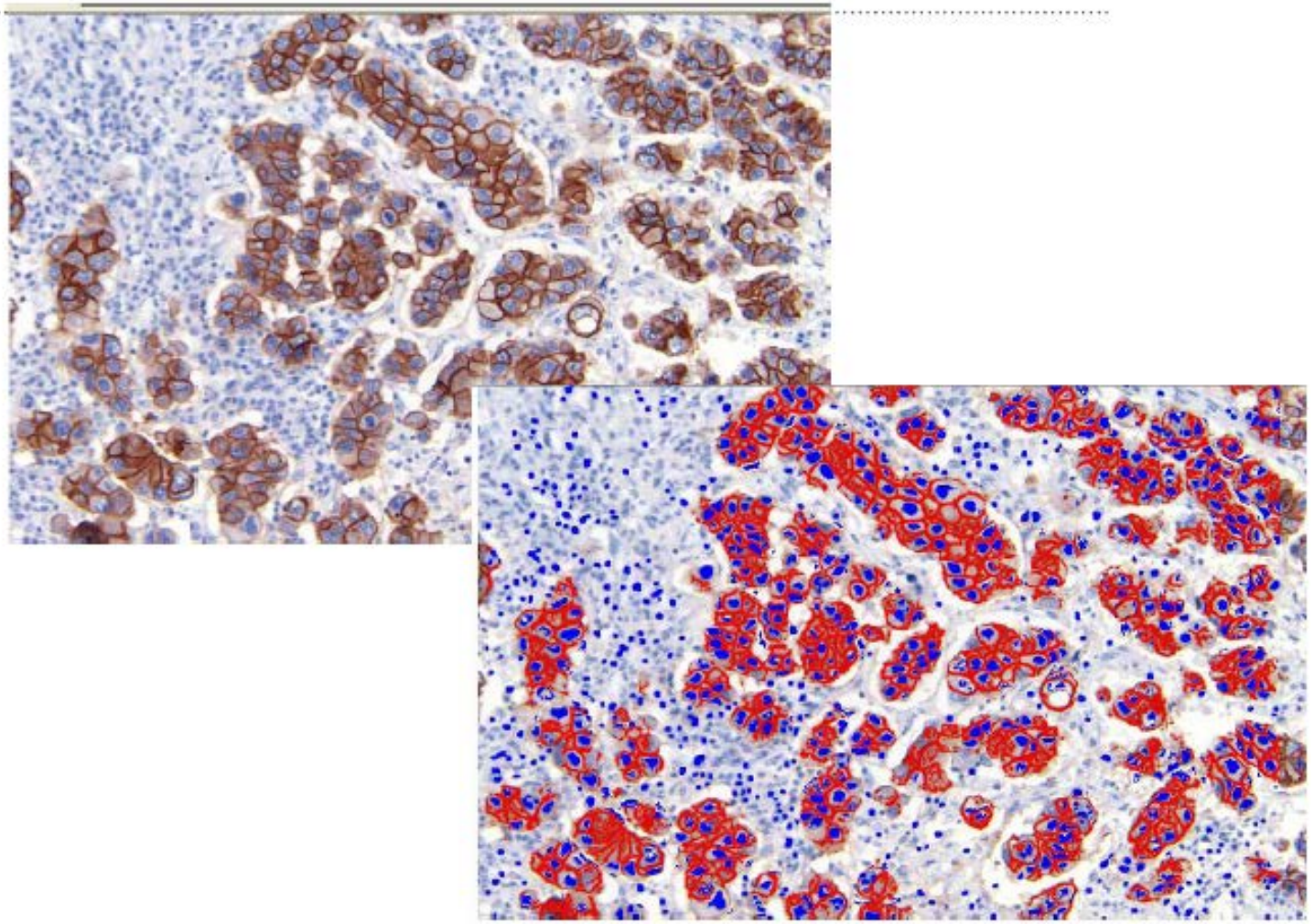
Courtesy of BioImagene

Quantitation of Results (Nuclear)



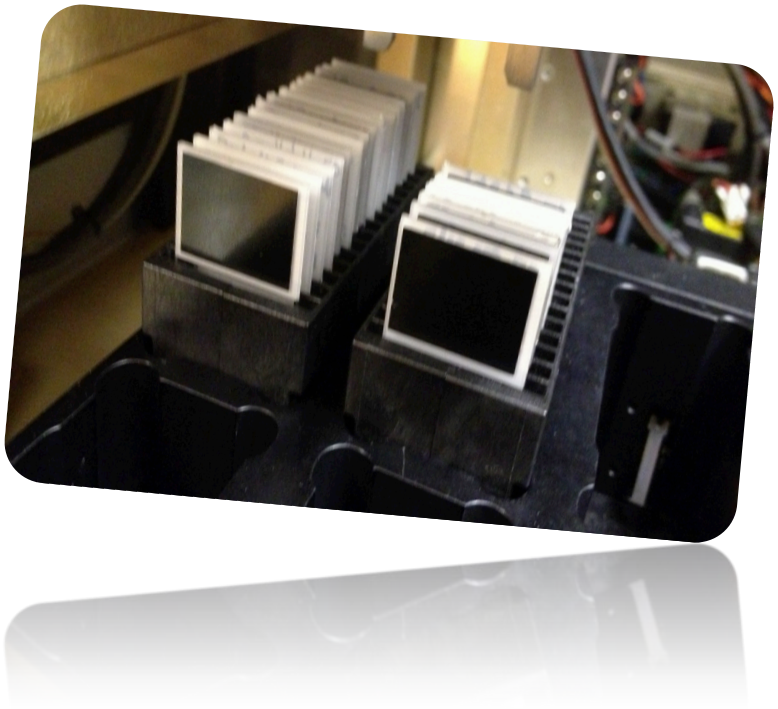
Courtesy of BioImagene

Quantitation of Results (Membrane)



Courtesy of BioImagene

Imaging Systems

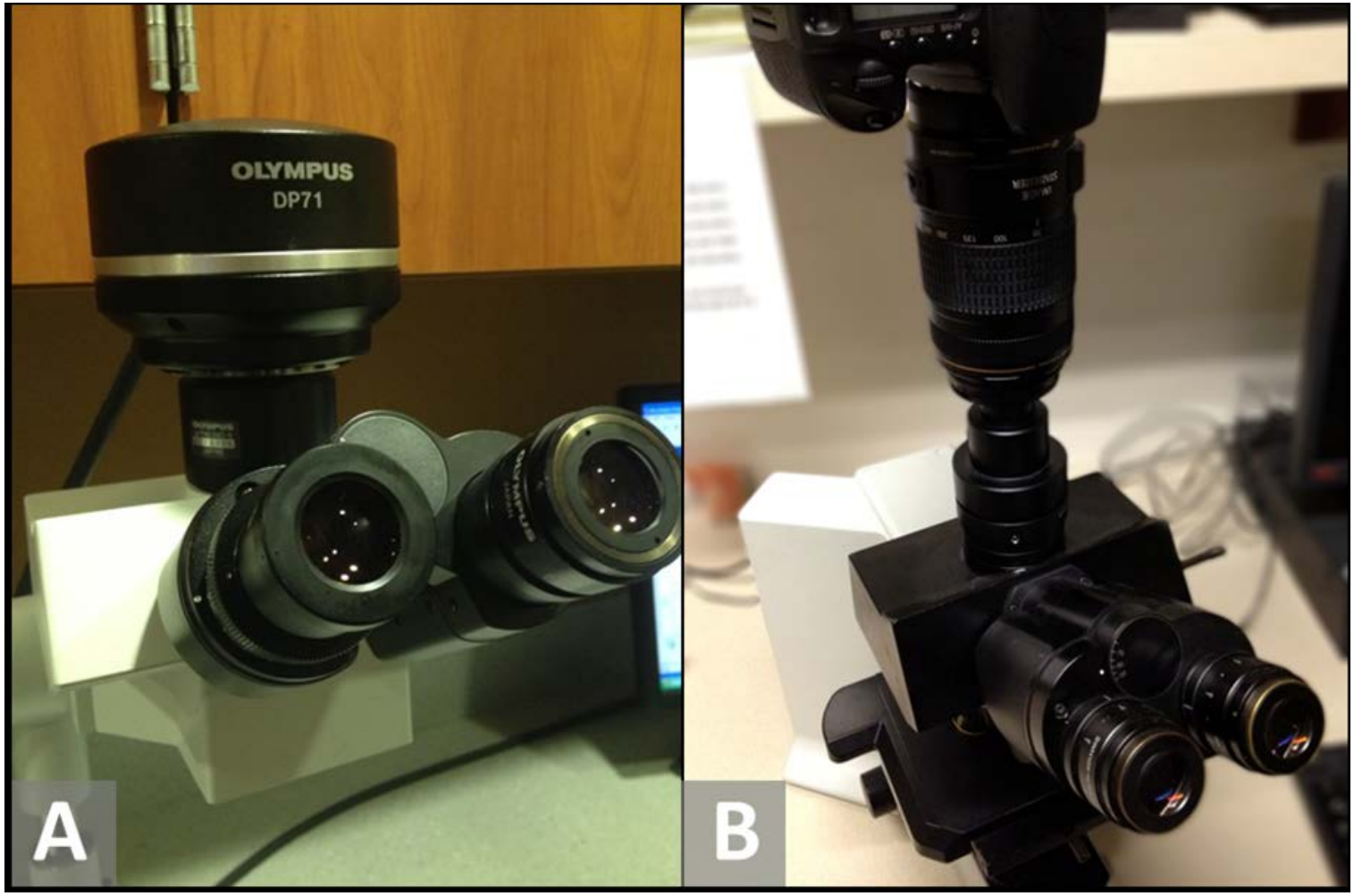


Digital Macro/Gross Photography

Stand-alone

Mounted

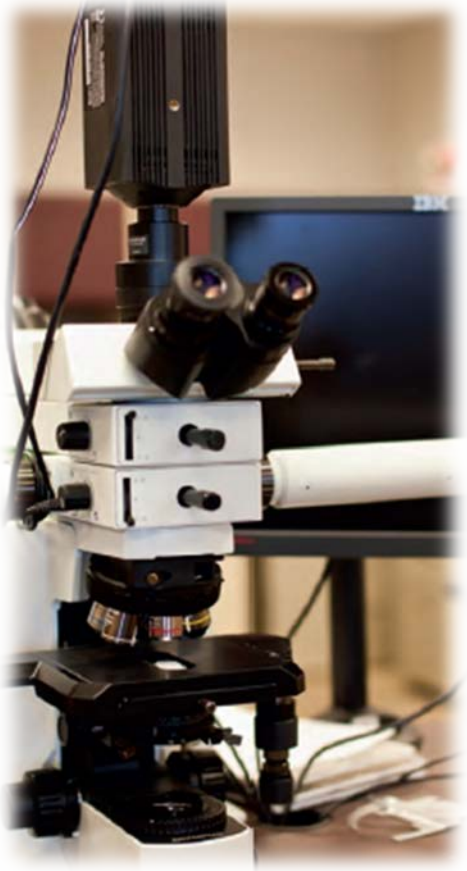
Digital Photomicroscopy



Microscopes & Cameras

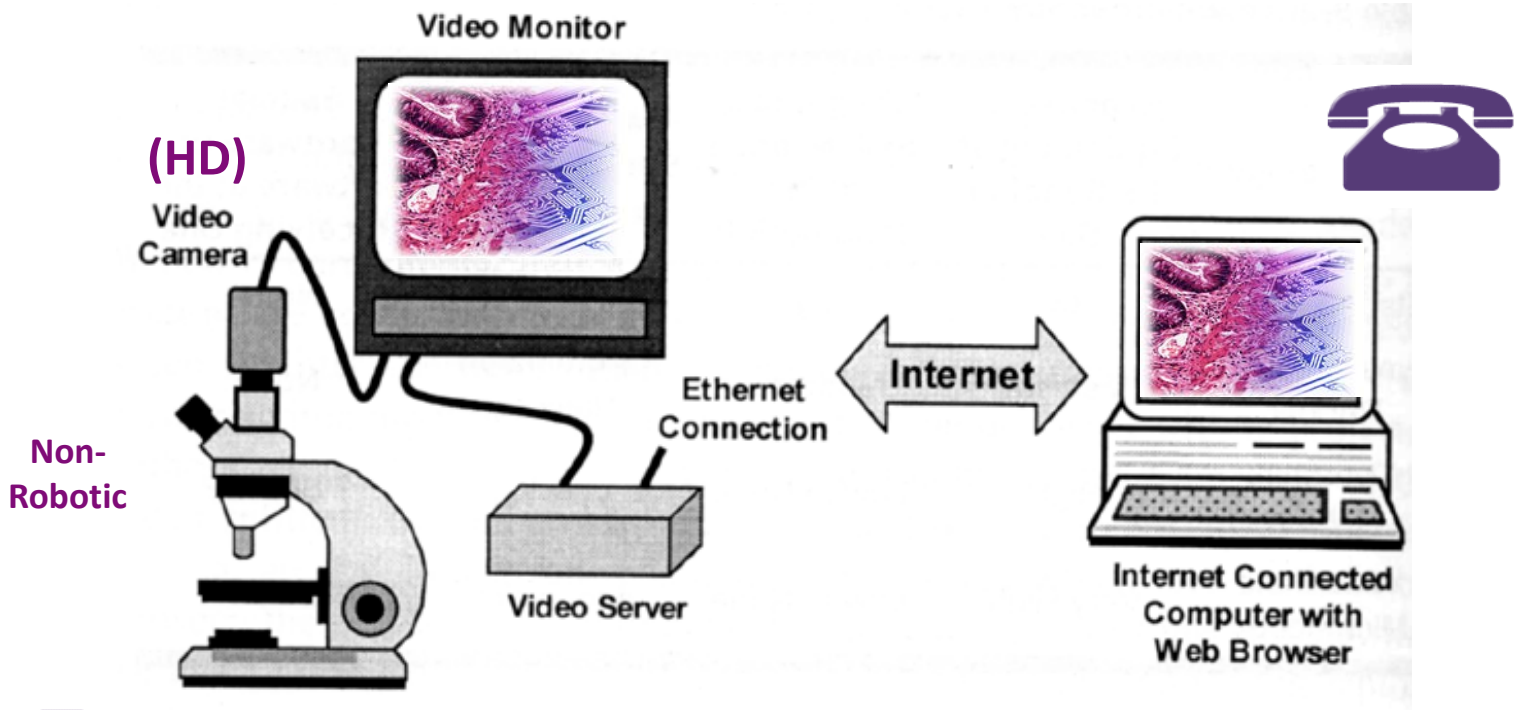
- Telemicroscopy (static telepathology)
  - Microscope + Digital camera
- Video microscopy (dynamic telepathology)
  - Microscope + Video camera
- Teleconferencing
  - Microscope + Digital camera
  - + Web conferencing software

GoToMeeting skype FUZE Meeting webex



Video Microscopy

Dynamic Video Microscopy System

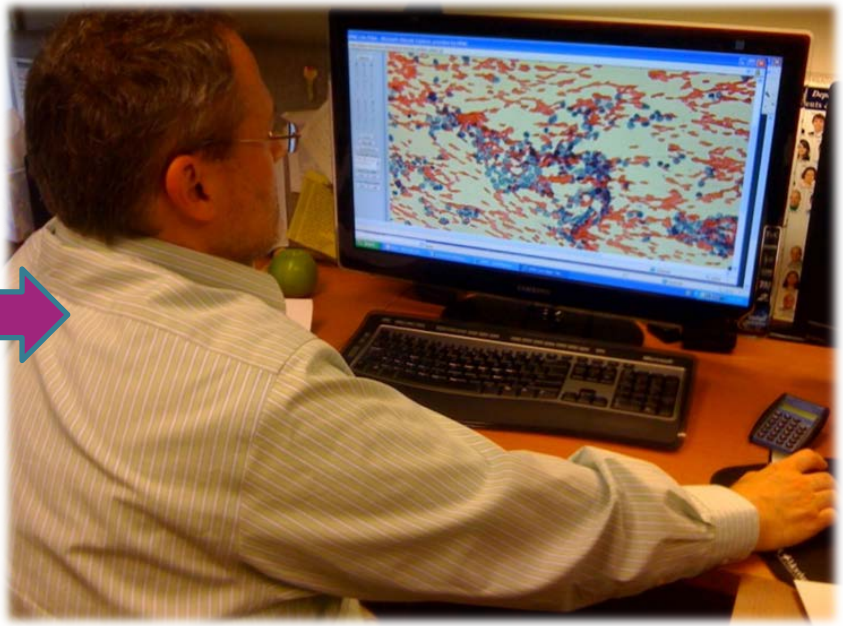


Adapted from Sinard JH. *Practical Pathology Informatics*. Springer 2006.

Telecytology

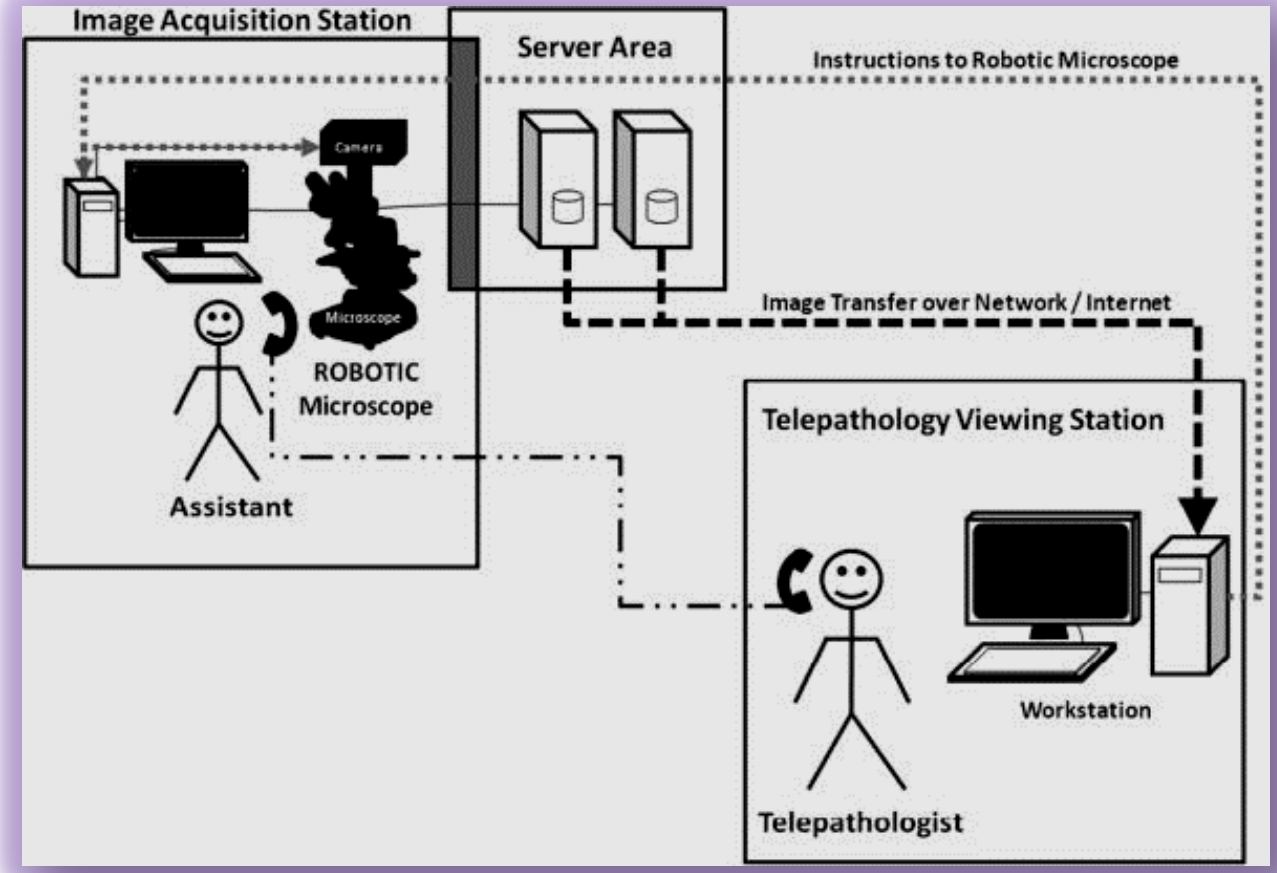
Web-based streaming for FNA rapid on-site evaluation (ROSE)

Fellow streaming slides through NetCam package



Cytopathologist reviewing the same slide on his desktop screen

Robotic Telepathology



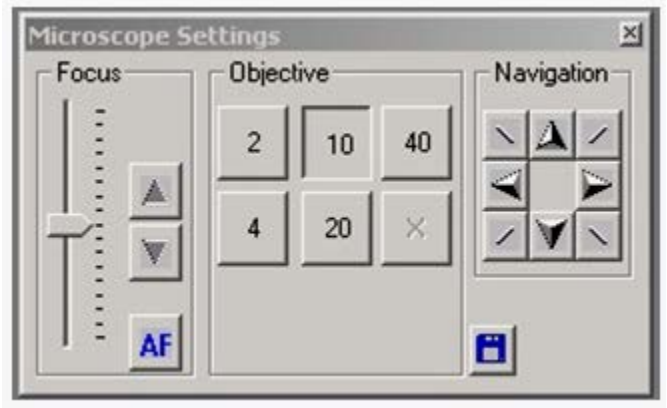
Williams S et al. *Adv Anat Pathol* 2010; 17:130-149.

Robotic Telepathology System

Digital/video camera

Networked PC

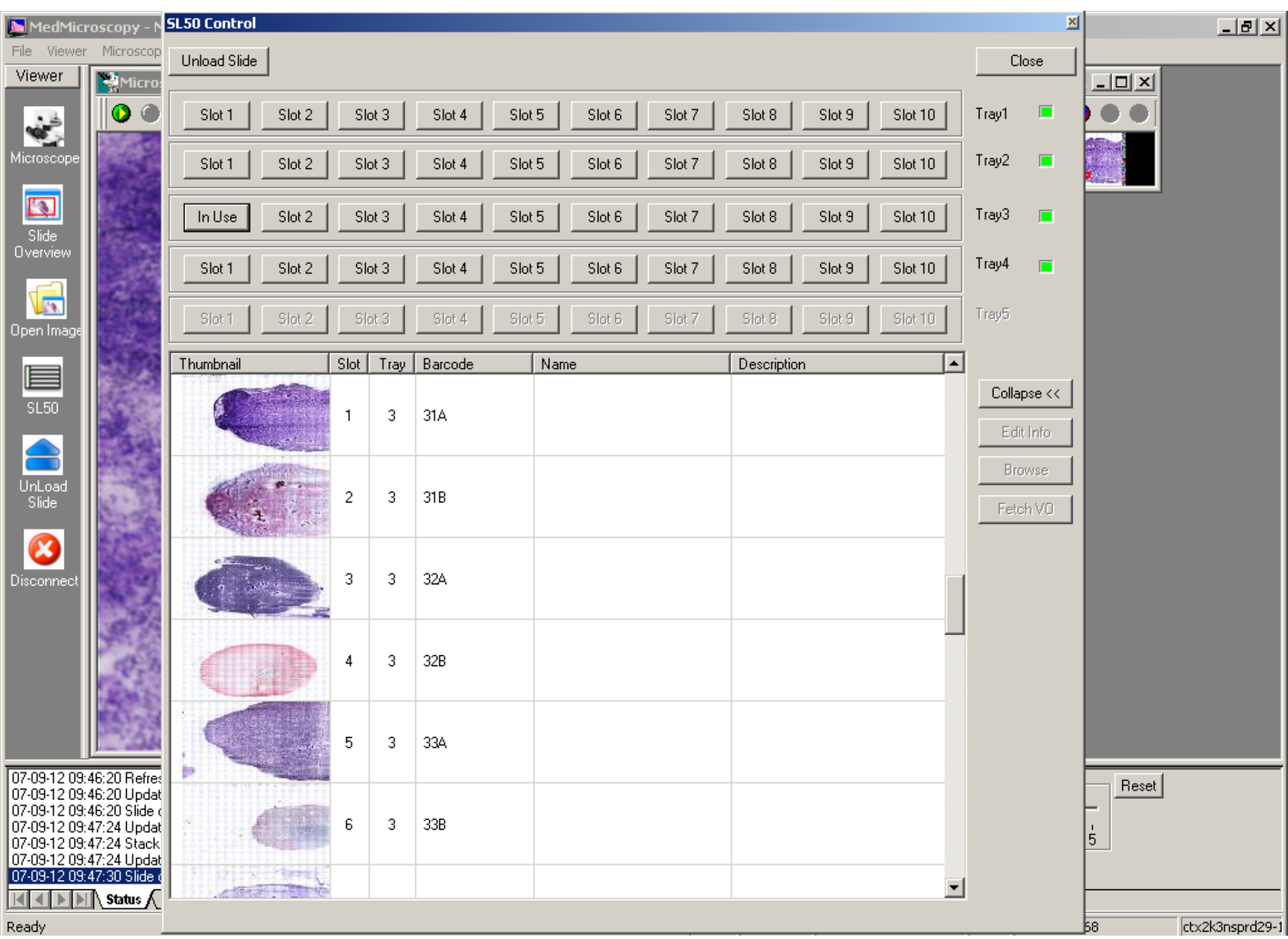
(server software)

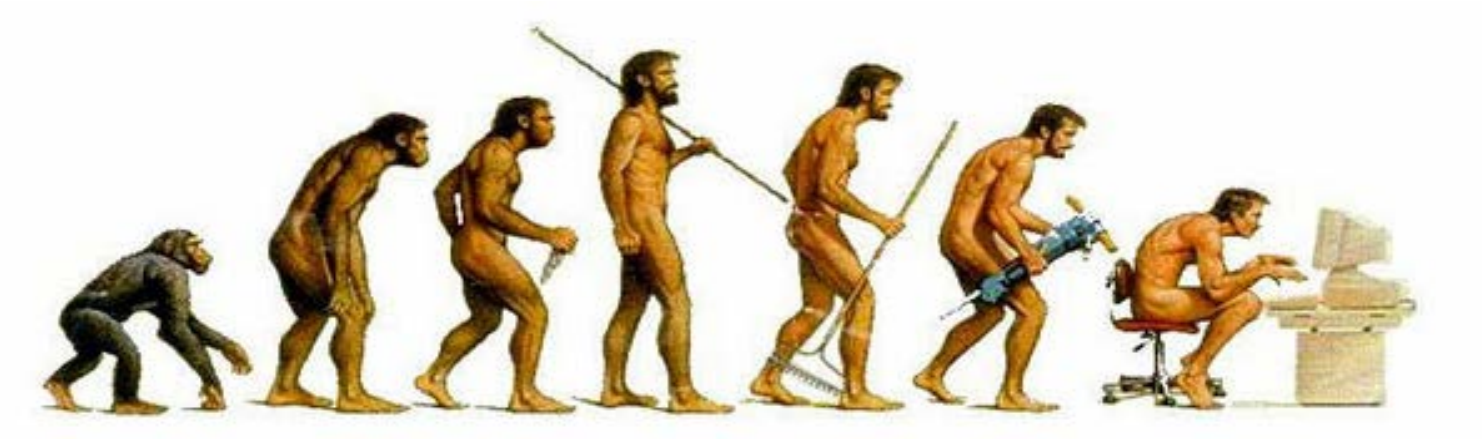


Remote Microscope Controls
(Viewing software required)

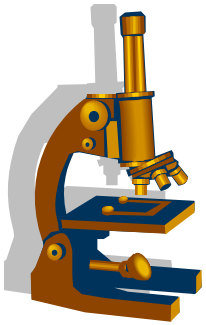
Robotic (motorized) microscope
(1-4 slides)

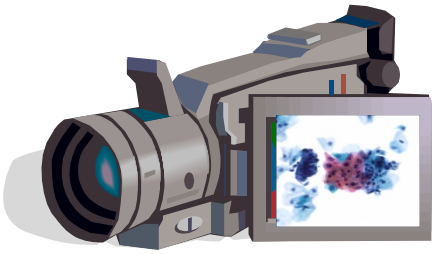

1
2
3
4
DO NOT TURN ANYTHING OFF
Telepathology, UPMC
412-647-9552


MedMicroscopy - N
File Viewer Microscop
Viewer
Microscope
Slide Overview
Open Image
SL50
UnLoad Slide
Disconnect
SL50 Control
Unload Slide
Close
Slot 1 Slot 2 Slot 3 Slot 4 Slot 5 Slot 6 Slot 7 Slot 8 Slot 9 Slot 10
Tray1
Slot 1 Slot 2 Slot 3 Slot 4 Slot 5 Slot 6 Slot 7 Slot 8 Slot 9 Slot 10
Tray2
In Use Slot 2 Slot 3 Slot 4 Slot 5 Slot 6 Slot 7 Slot 8 Slot 9 Slot 10
Tray3
Slot 1 Slot 2 Slot 3 Slot 4 Slot 5 Slot 6 Slot 7 Slot 8 Slot 9 Slot 10
Tray4
Slot 1 Slot 2 Slot 3 Slot 4 Slot 5 Slot 6 Slot 7 Slot 8 Slot 9 Slot 10
Tray5
Thumbnail
Slot
Tray
Barcode
Name
Description
1 3 31A
2 3 31B
3 3 32A
4 3 32B
5 3 33A
6 3 33B
Collapse <<
Edit Info
Browse
Fetch V0
07-09-12 09:46:20 Refres
07-09-12 09:46:20 Updat
07-09-12 09:46:20 Slide
07-09-12 09:47:24 Updat
07-09-12 09:47:24 Stack
07-09-12 09:47:24 Updat
07-09-12 09:47:30 Slide
Status
Reset
Ready
ctx2k3nsprd29-1



DIGITAL IMAGING EVOLUTION





System Classification

Weinstein et al. APMIS 2012; 120:256-75

Imaging System	Year
Real-time Imaging	
Television microscopy	1952
Dynamic-robotic telepathology	1986
Static Image Telepathology	
Store & forward telepathology	1987
WSI (automated)	1991
WSI (operator-directed)	1994
Mutli-modality Telepathology	
WSI dynamic robotic/static imaging	2011

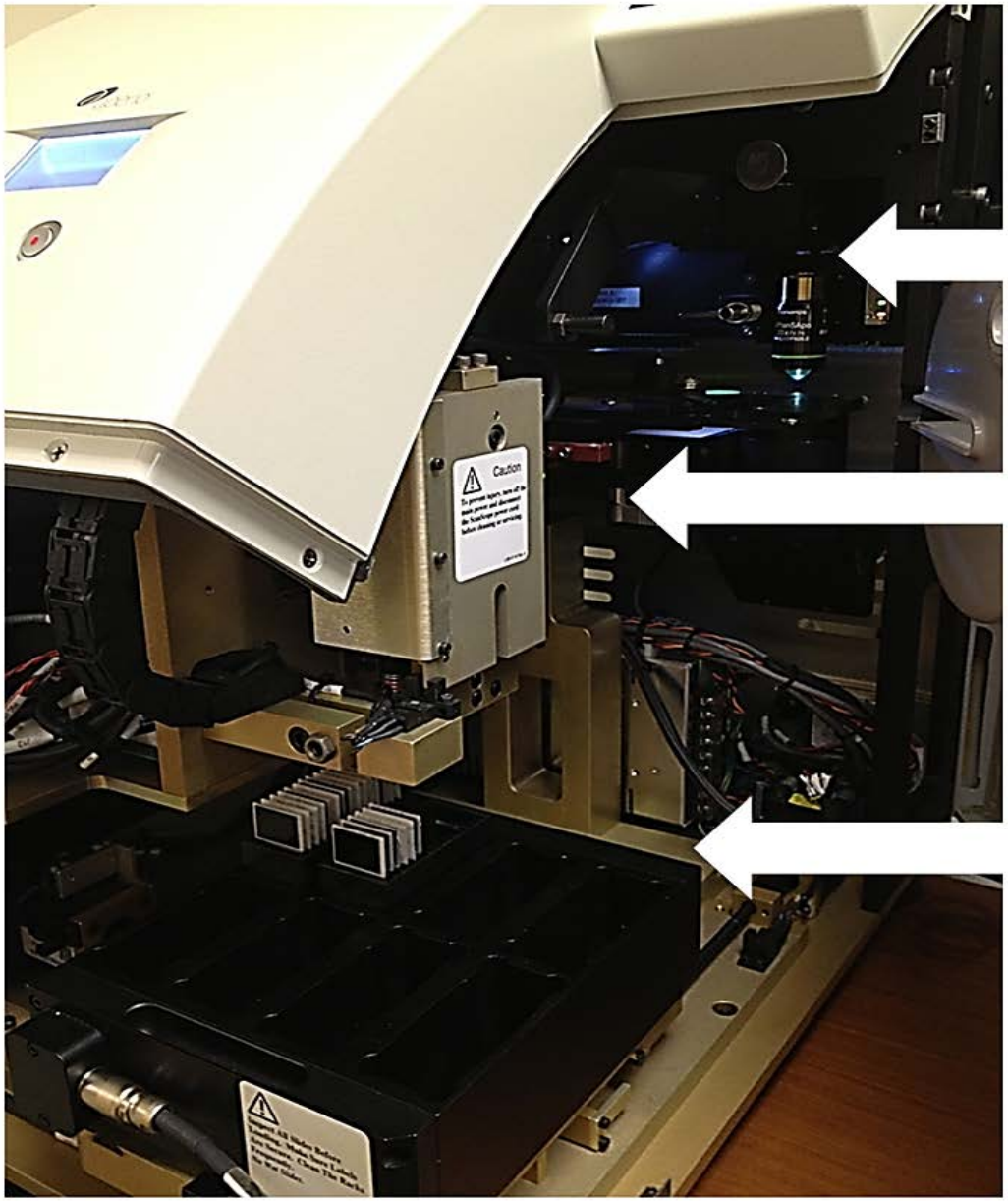
Whole slide imaging

WSI Scanners

- High resolution digital images
- High speed digitization of slides
- Digitization at multiple magnifications
- Scan in multiple focal planes (x,y & z axes)

Some WSI Scanners

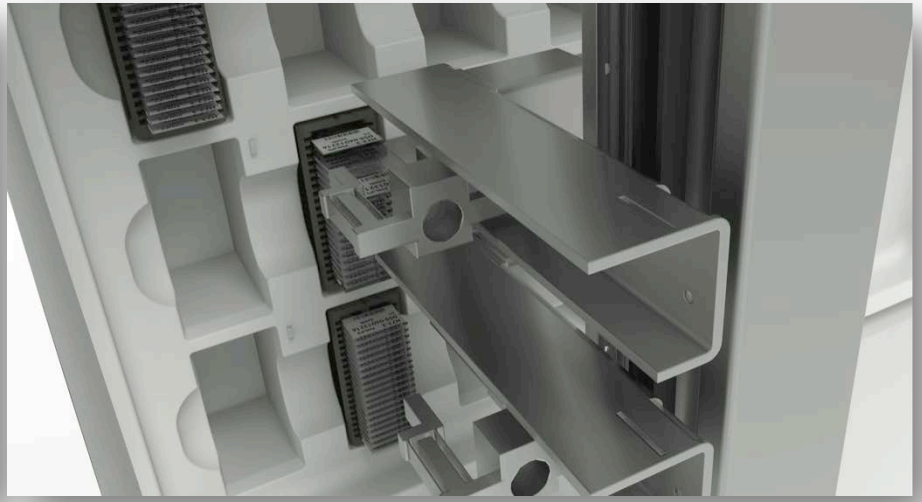
Manufacturer	WSI Scanner Models
3DHISTECH	Pannoramic SCAN II and 250 Flash
DigiPath	PathScope
Hamamatsu	Nanozoomer RS, HT, and XR
Huron Technologies	TISSUEscope 4000, 4000XT, and HS
Leica Biosystems (formerly Aperio)	ScanScope AT, AT2, CS, FL, and SCN 400
Mikroscan Technologies	D2
Olympus	VS120-SL
GE Healthcare	Omnyx VL4 and VL120
PerkinElmer	Lamina
Phillips	Ultra Fast Scanner
Sakura Finetek	VisionTek
Ventana (previously BioImagene)	iScan Coreo and iScan HT
Zeiss	Axio Scan.Z1

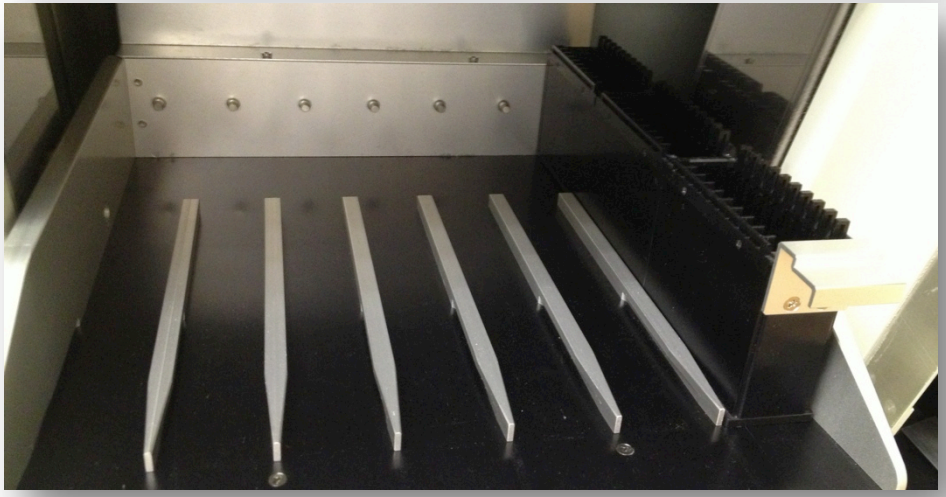


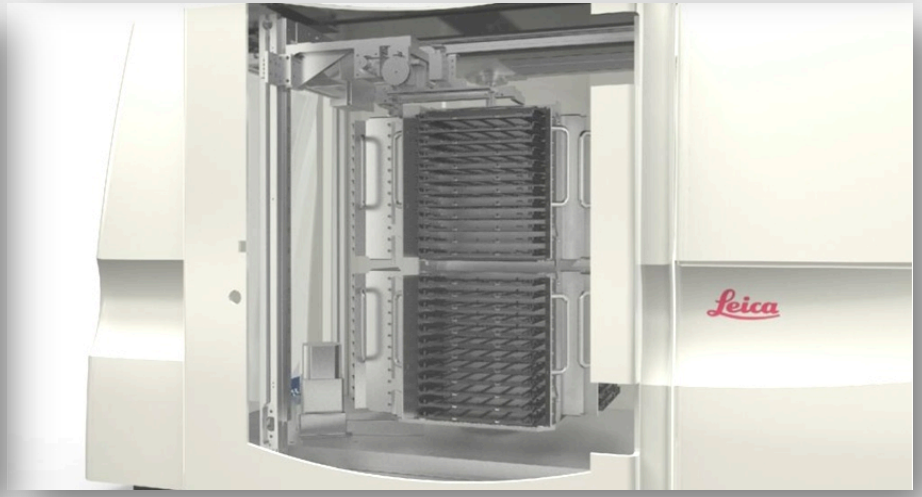
Microscope & Digital camera

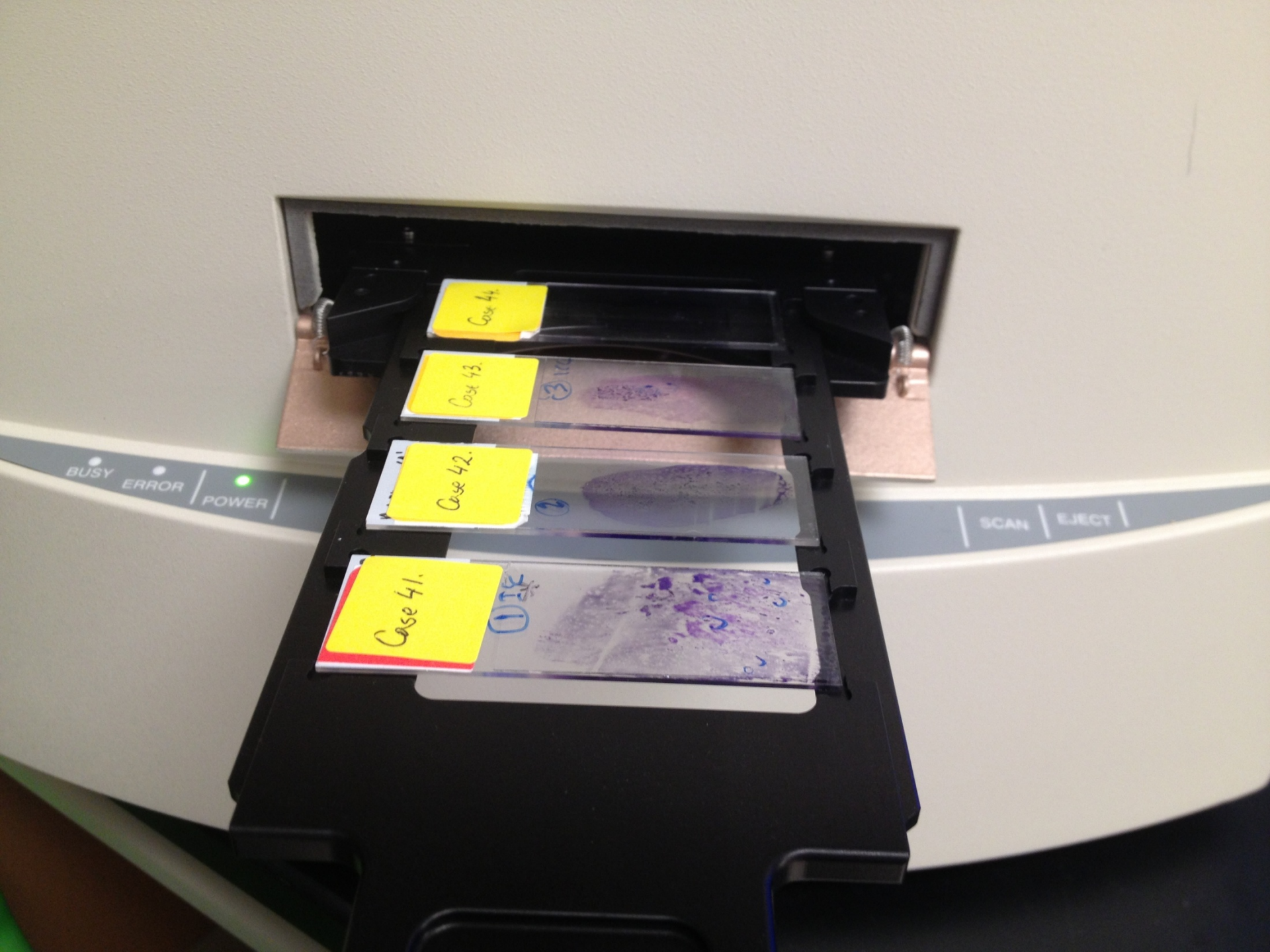
Robotics

Slide tray





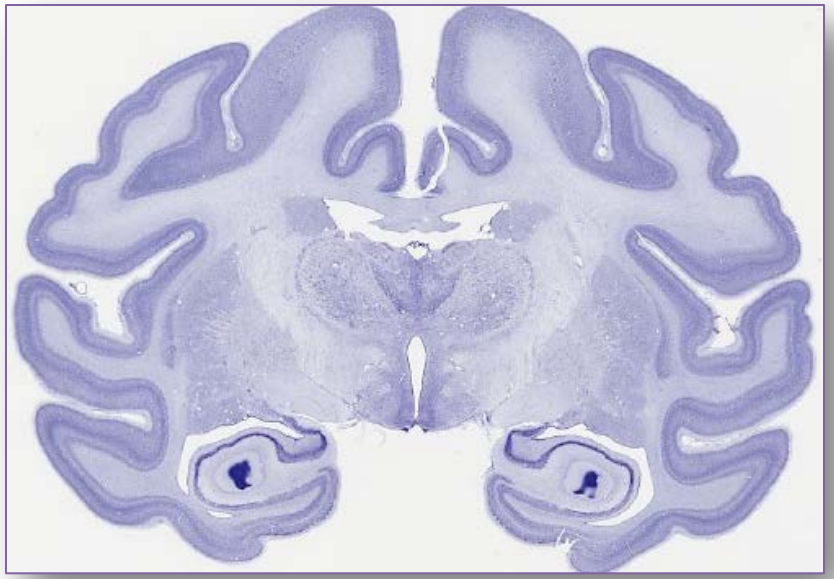

Leica


BUSY
ERROR
POWER
SCAN
EJECT
Case 44.
Case 43.
Case 42.
Case 41.

Versatile WSI Scanners

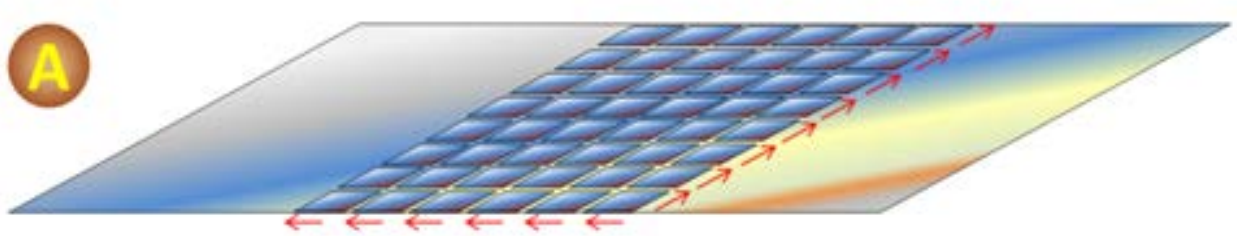
TISSUEscope™ Digital Slide Scanner (Huron Technologies)

- **Images glass slides from 3" x 1" to 8" x 6"**
- **Whole mount specimens**

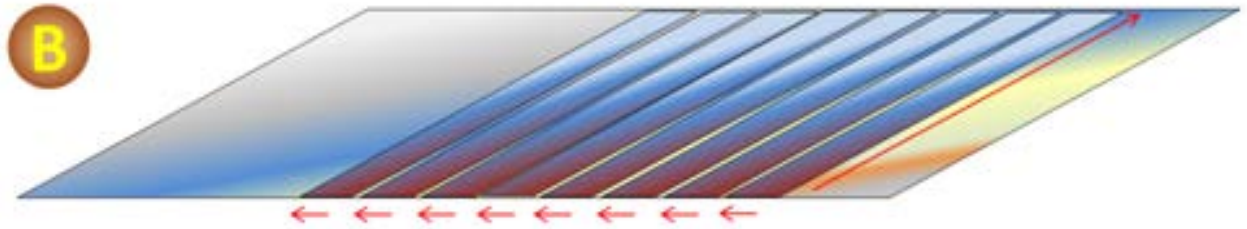


Whole Mount Human Brain Imaging

WSI Scanning Strategies



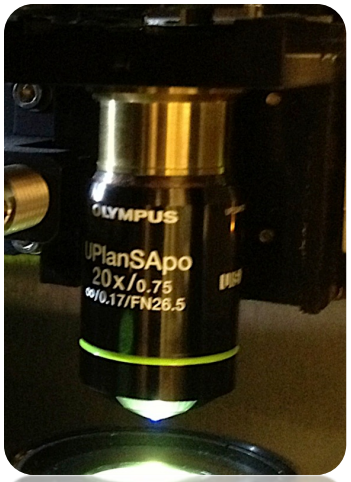
A - Tile-based acquisition mode (grid pattern)



B - Line-scan acquisition mode (linear pattern)

Scan Features

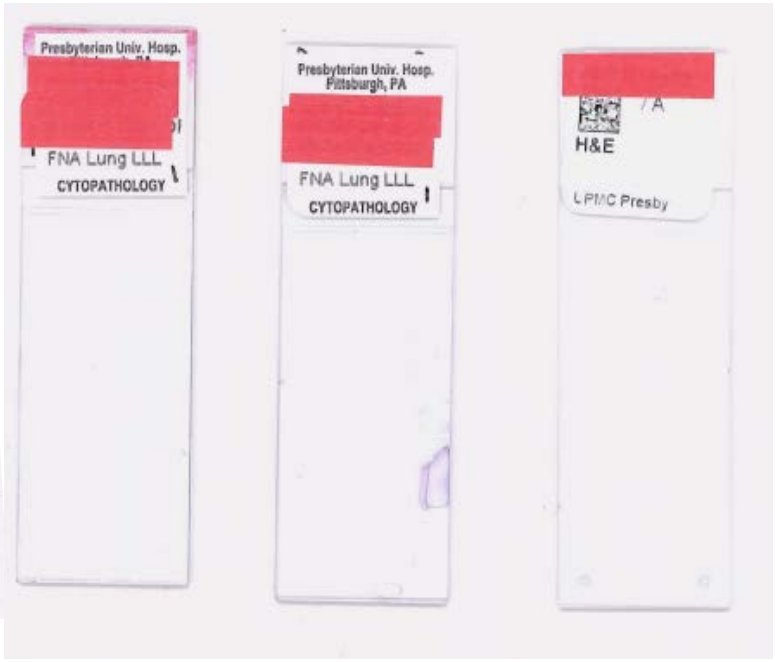
- Scan time (1-8+ minutes, per 15x15 mm^2)
- Brightfield vs. Fluorescent (spectrum range may restrict fluorophores)
- Manual vs. Automated (continuous loading, scan/view slides simultaneously)
- Tissue detection (automatic, manual override, scan user defined areas)
- Color calibration (automatic white balance)
- Scan failure rates (can be as high as 5% for 20x & 20% for 40x)
- Image quality (dependent on sensor & objectives, average NA = 0.75)
- Image resolution (average 0.5 micrometers/pixel at 20x)



Imaging Phase (Acquisition Failures)

Thick Glass Slides

Broken Slide



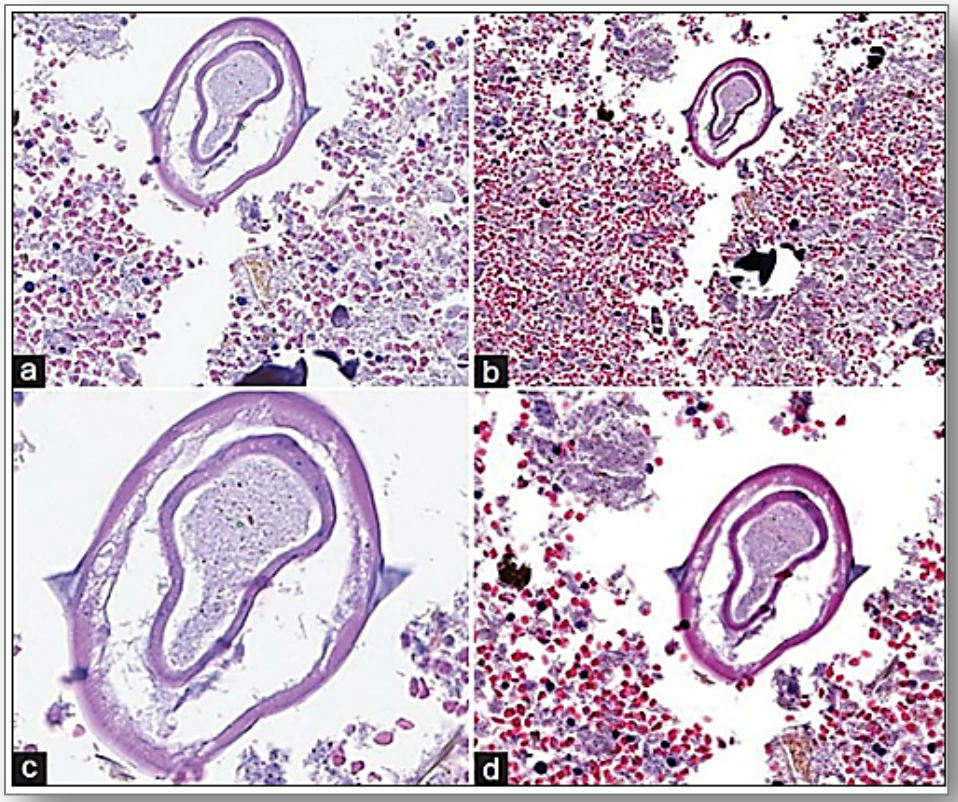
Material too Pale

Digital Magnification & Resolution

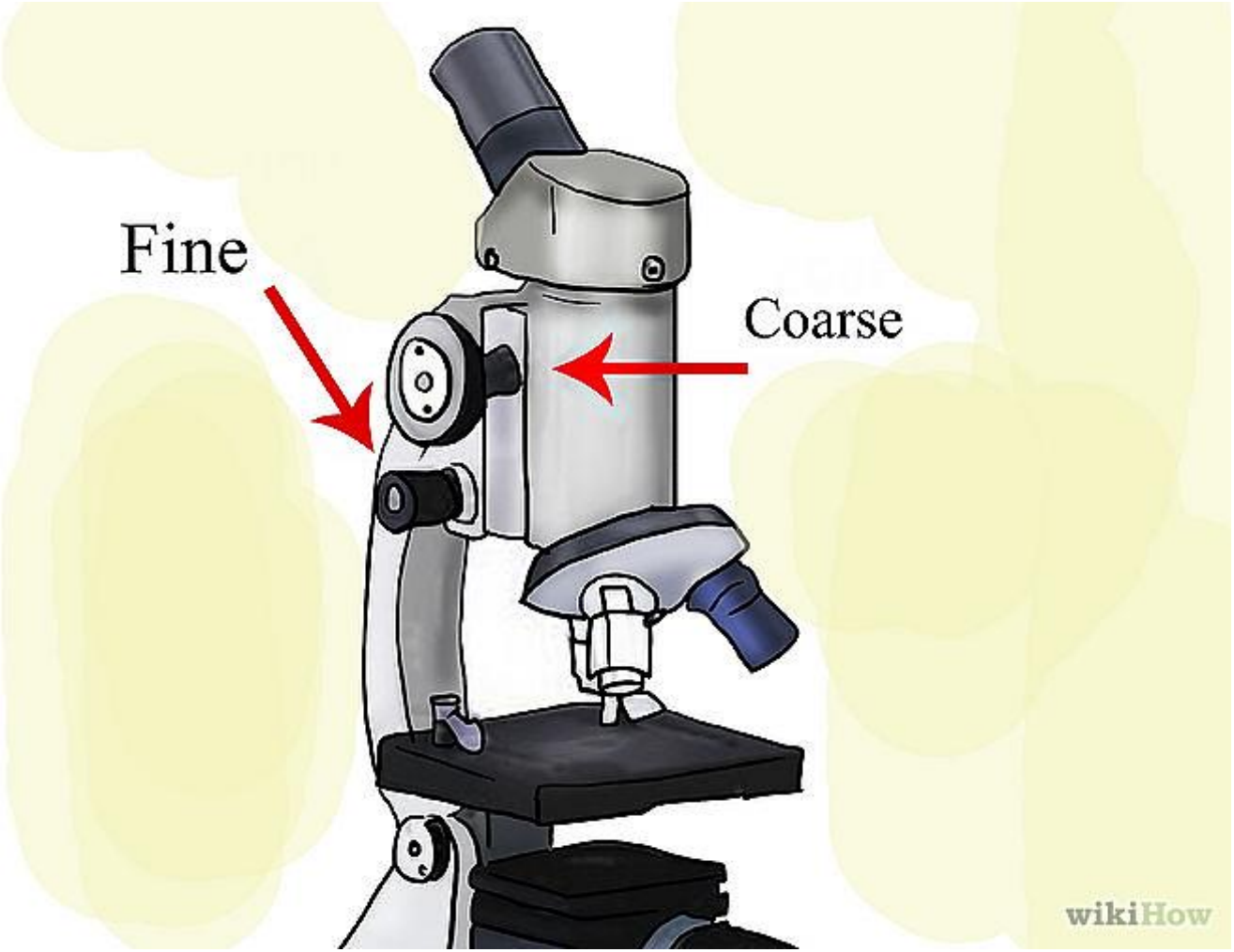
Sellaro TL et al. J Pathol Informatics 2013; 4:21

- Traditional glass microscope image quality monikers (e.g.×40) should be replaced with vendor-neutral descriptors (e.g. microns/pixel)

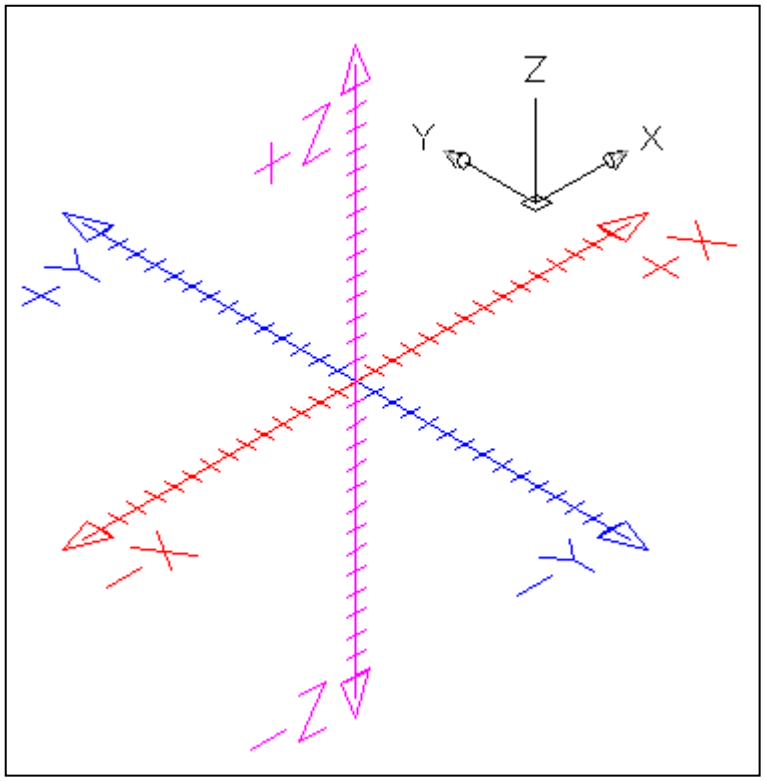
5.5 micron pixel size vs 10 micron pixel size



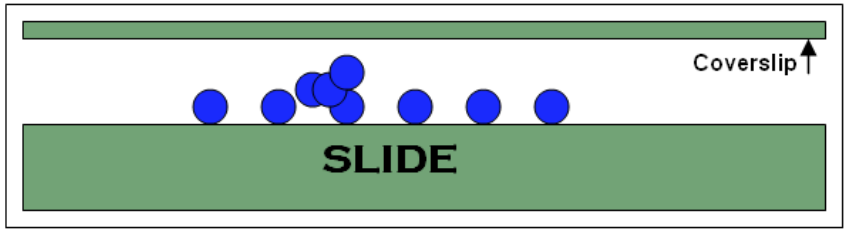
Similar 20x objective, but with different sensor pixel sizes


Fine
Coarse
wikiHow

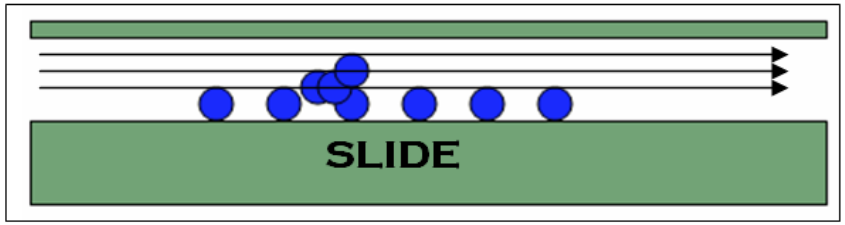
X, Y & Z Axes



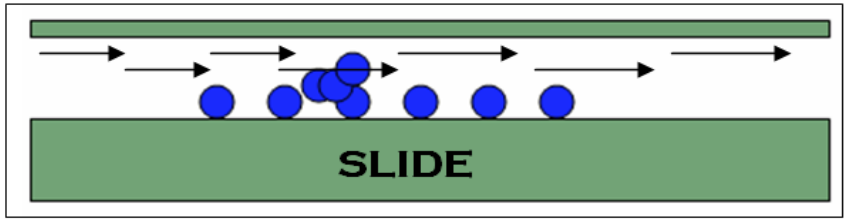
Z-Stacks



3D cell group



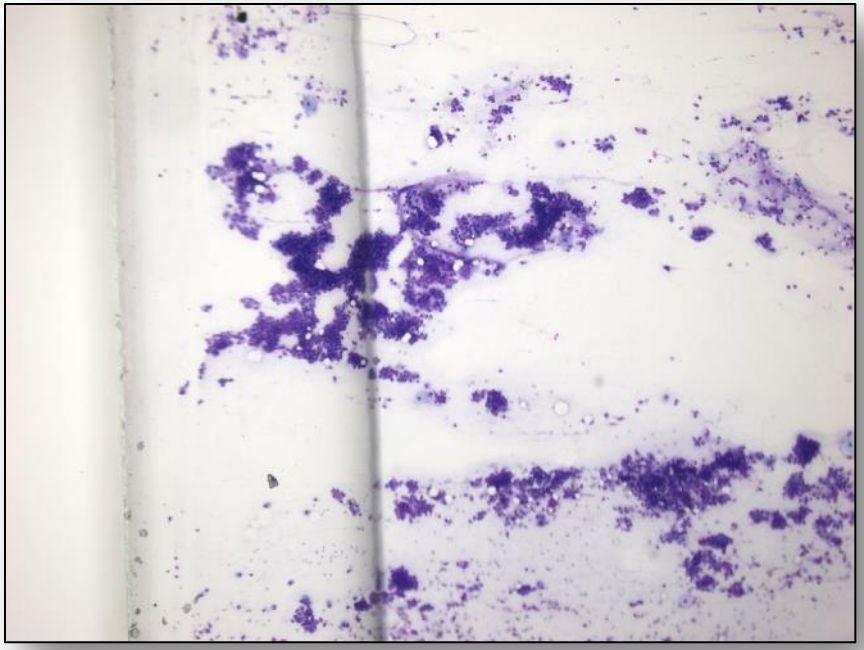
Z stack



Focal point interpolation

Challenging Slides

Coverslips



Air Bubble

Multiplane Images

Take a long time to scan

Produce large files

J Pathol Inform

Editor-in-Chief:
Anil V. Parwani , Pittsburgh, PA, USA
Liron Pantanowitz, Pittsburgh, PA, USA

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HTML format

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Research Article

Optimal z-axis scanning parameters for gynecologic cytology specimens

Amber D. Donnelly, Maheswari S. Mukherjee, Elizabeth R. Lyden[1], Julia A. Bridge[2], Subodh M. Lele[2], Najia Wright[3], Mary F. McGaughey[4], Alicia M. Culberson[5], Adam J. Horn[2], Whitney R. Wedel[2], Stanley J. Radio[2]

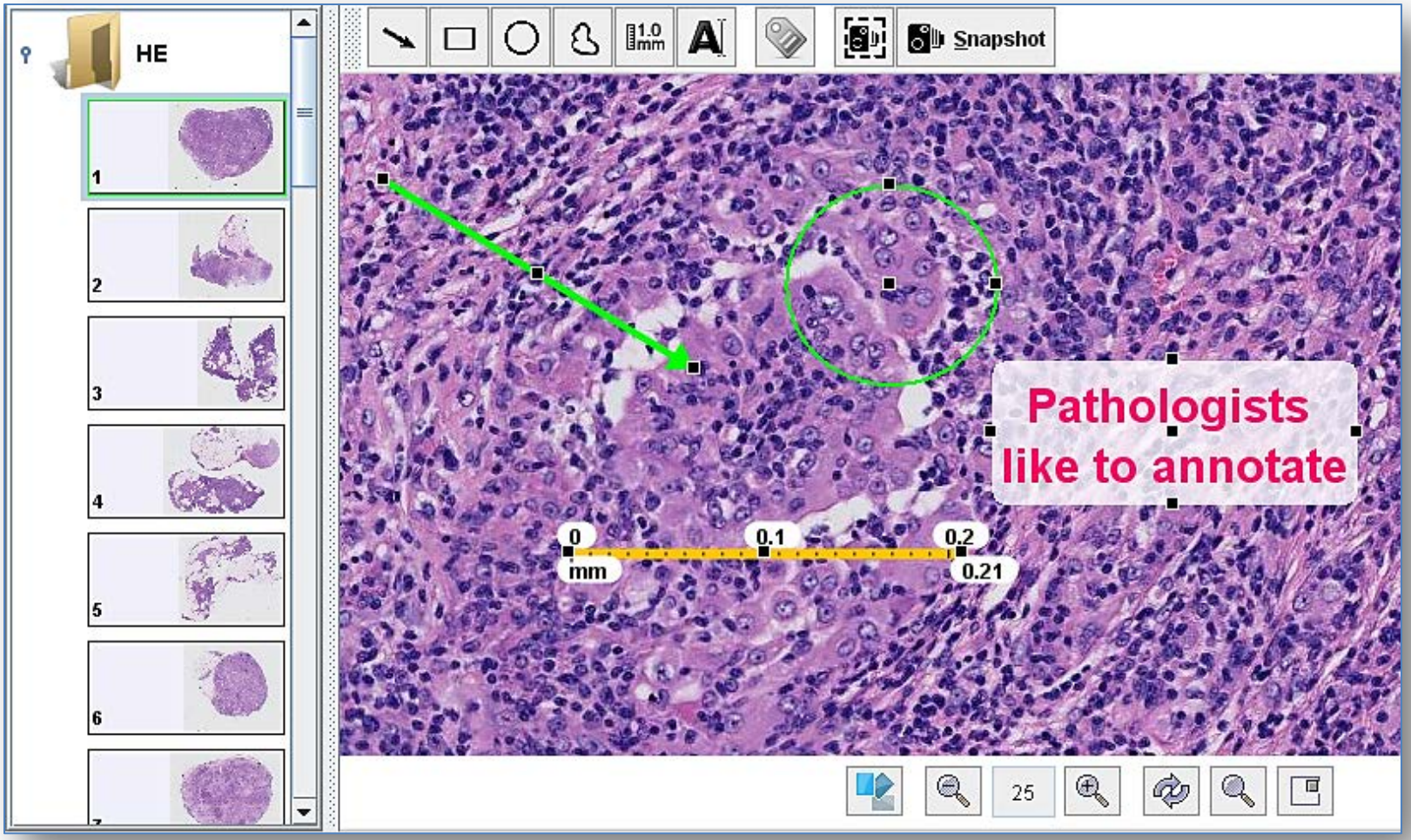
Cytotechnology Education, School of Allied Health Professions, University of Nebraska Medical Center, Omaha, Nebraska, [1]Department of Biostatistics, College of Public Health, University of Nebraska Medical Center, [2]Department of Pathology and Microbiology, College of Medicine, University of Nebraska Medical Center, [3]Department of Cytology, Alegent-Creighton Health, [4]Department of Cytology, The Nebraska Medical Center, Omaha, NE, [5]Texas Health Hugley Hospital, Fort Worth South, Burleson, TX

- This study supports using three focal plane levels and 1µ interval for digital Pap test slides.

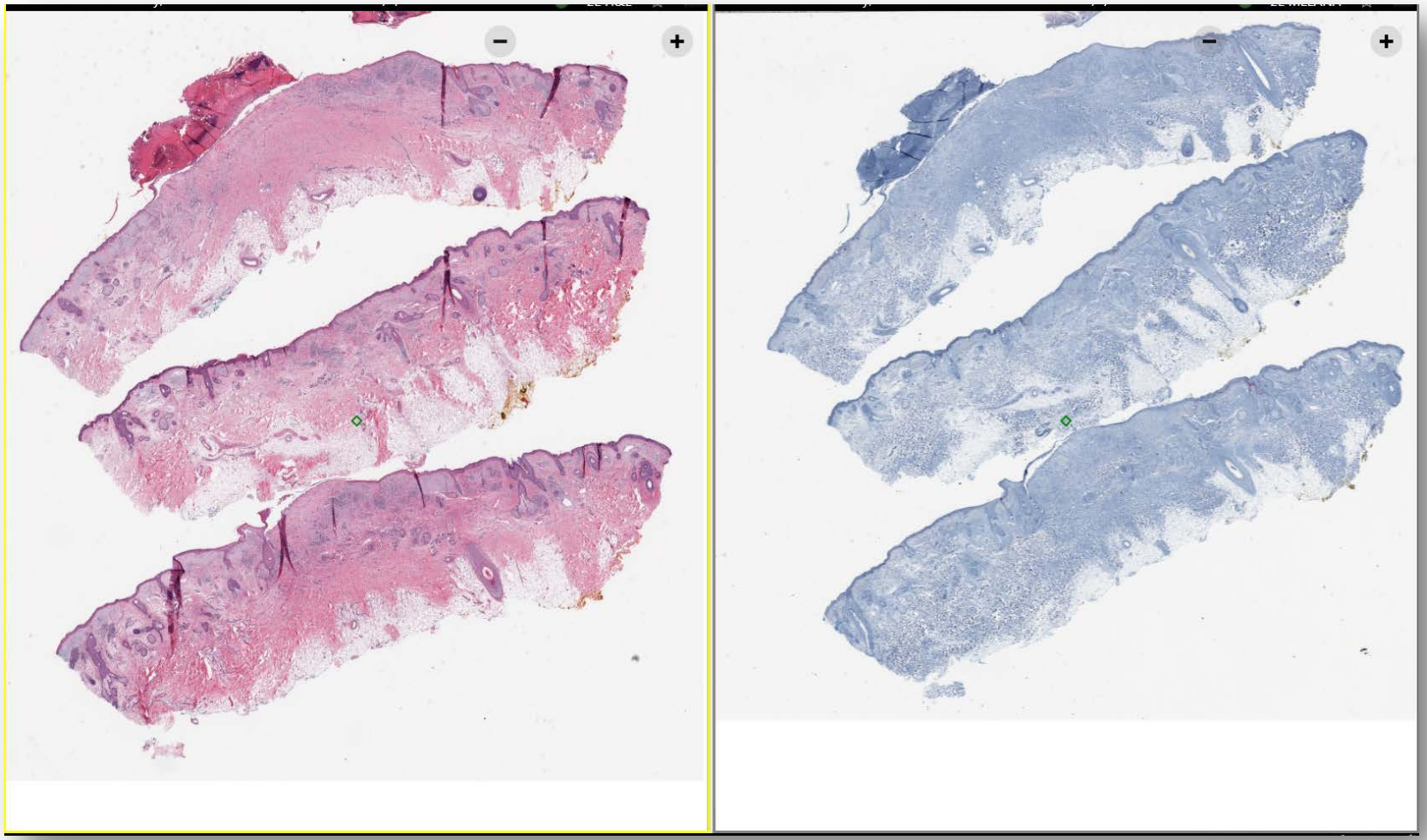
Image Viewing

- Annotations
- Multi image viewing (e.g. side-by-side)
- Co-registration (e.g. overlay of images, 3D)

Image Applications



Split Screen Display



Digital Pathology Practice

Digital Pathology Uses

Pantanowitz. J Pathol Inform. 2010;1: 15

- Primary diagnosis
- 2nd opinion (consultation)
- Telepathology
- Quality Assurance (PT)
- Archiving & Sharing
- Education/Conferencing
- Image analysis
- Research & Publications
- Marketing & Business
- Track (audit) & Training

Education Paradigm Shift

WSI Benefits

- Simulates microscopy
- More interactive than static images
- Easy to share (anywhere at anytime)
- Standardizes training material
- Digital teaching sets (virtual slide box)
  - Don’t fade, break or disappear
  - Broader case range & rare cases
  - Ability to provide annotation

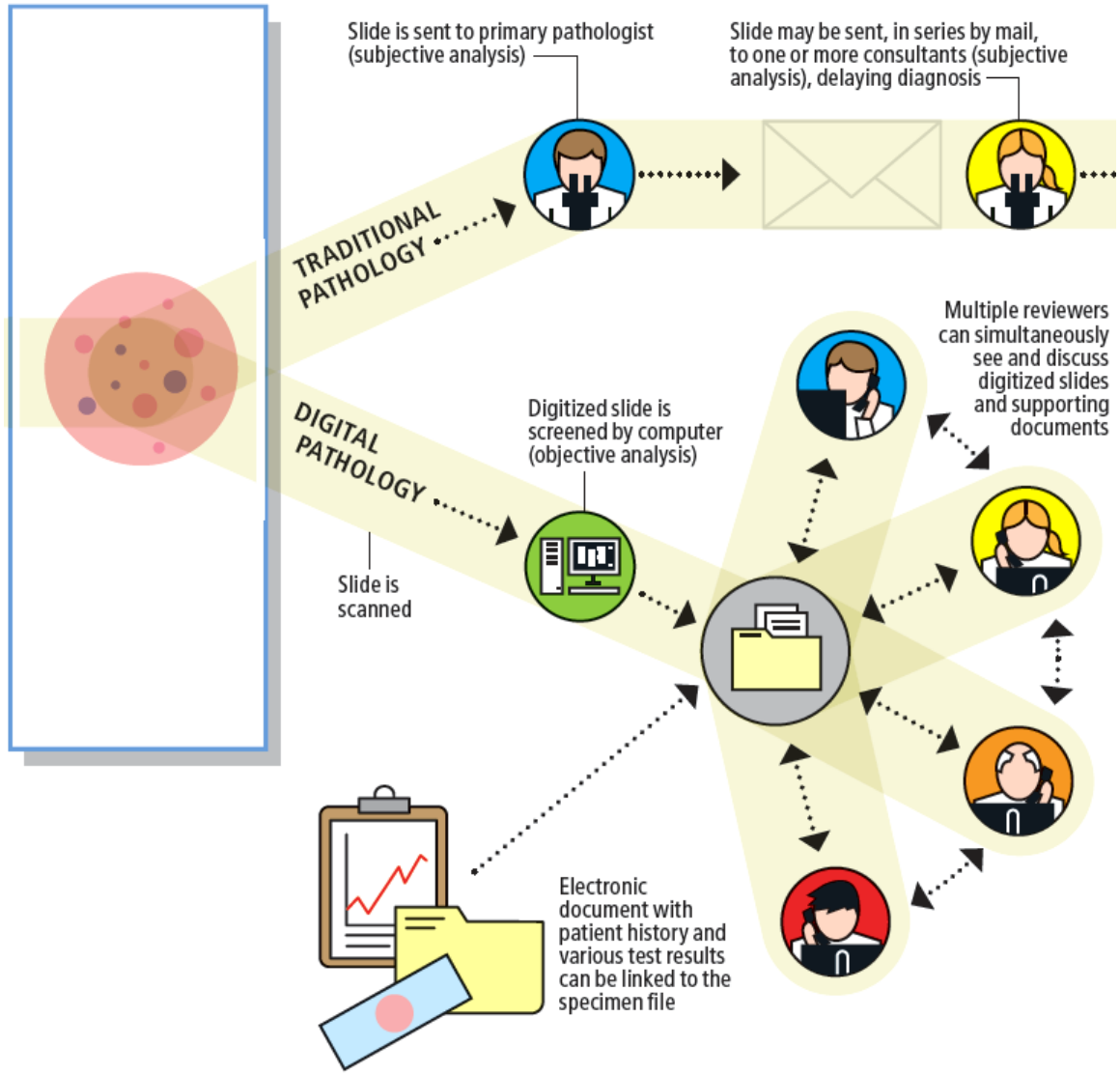
Telepathology Definition

Pantanowitz et al. *Pathology Informatics: Theory & Practice*. ASCP Press 2012.

- The practice of pathology at a distance, transmitting macroscopic &/or microscopic images via telecommunication links for:
  - Remote interpretations (telediagnosis)
  - Second opinions or consultations (teleconsultation)
  - Educational purposes (teleconferencing)

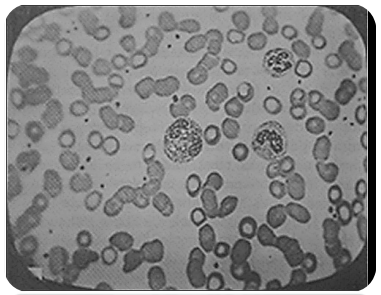
A Better Lens on DISEASE

Computerized pathology slides may help doctors make faster and more accurate diagnoses • BY MIKE MAY



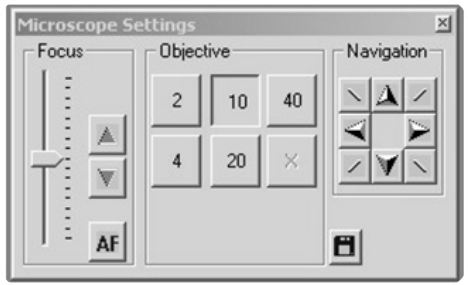
Scientific American May 2010:74-77

Telepathology Timetable



Video

1968



Robotic

1986

WSI

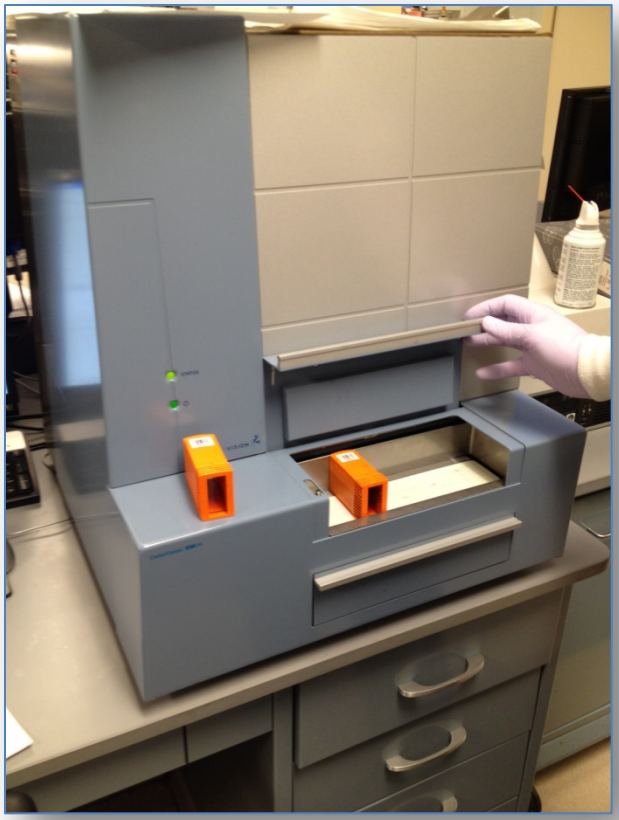
2000+

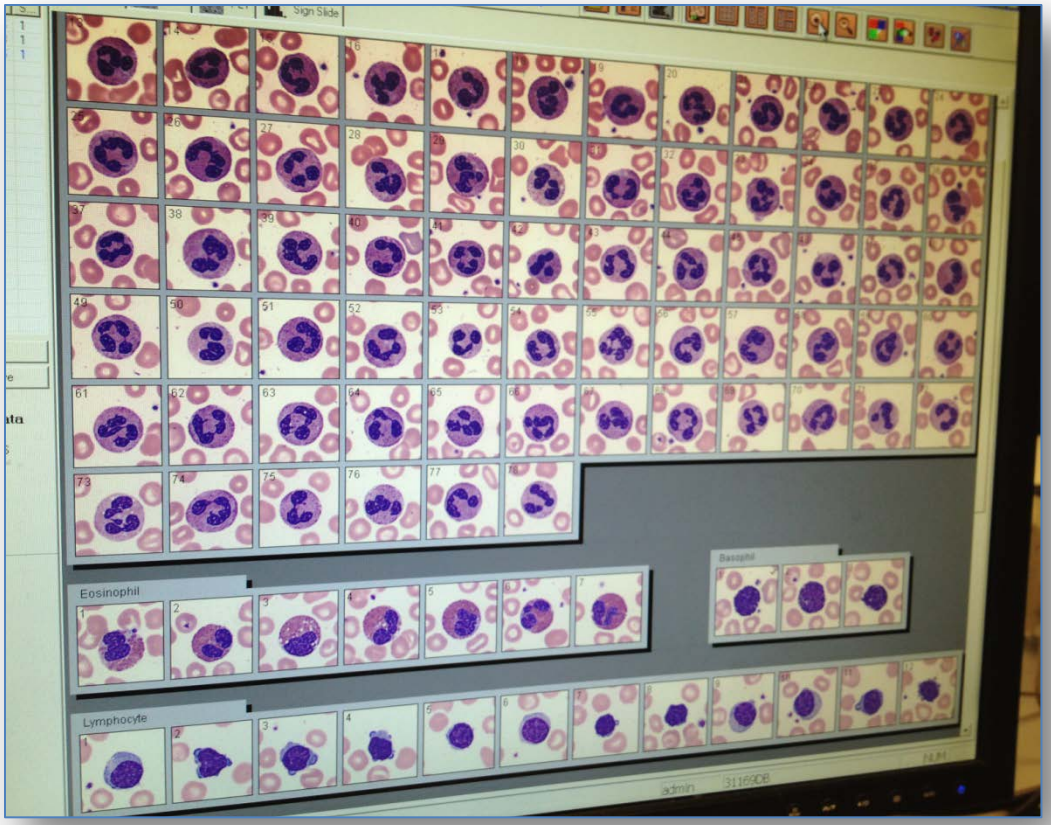
47 Years

Telepathology Applications

- **Anatomical Pathology**
  - Intraoperative consultation (frozen sections)
  - Surgical pathology (2nd opinions, immunostains)
  - Telecytology (eg, on-site evaluation)
  - FISH & Ultrastructural pathology
- **Clinical Pathology**
  - Telehematology (eg, blood smears)
  - Microbiology (eg, parasites)
  - Chemistry (eg, gels)

CellaVision Analyzer & Remote Review System





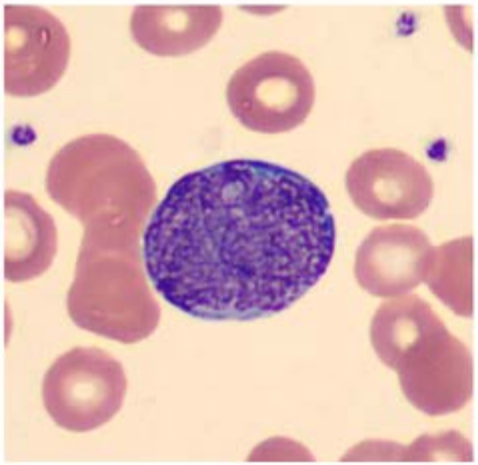
From: CellaVisionBloodDifferentialSoftware
Sent: Thursday, February 03, 2011 2:47 PM
To:
Subject: FOR PEER REVIEW ONLY

Cell images from CellaVision Blood Differential Software

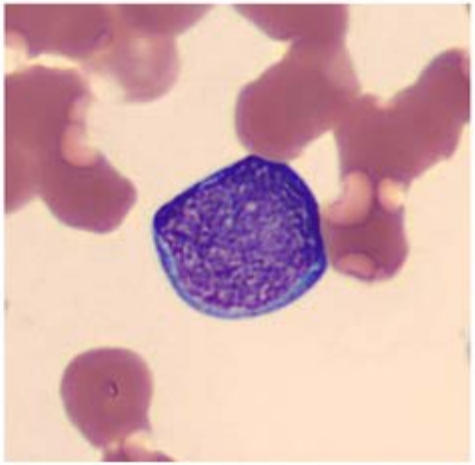
System Serial Nbr:

Message from sender: Possible immature cells, high n/c ratio, nucleoli

Database:
Number of cells included in e-mail: 2
Order ID:
Slide number: 1
Analyzed: 2011-02-03 12:37



Suggested cell class:
Other
Cell comments:



Suggested cell class:
Other
Cell comments:

CELLAVISION

Telepathology Benefits

Clinical advantages

- Access to pathology experts
- Improved patient care

Operational gains

- Easier to move images
- Encourages consultation

Business rewards

- Increased potential revenue

Telepathology Components

Imaging Workstation

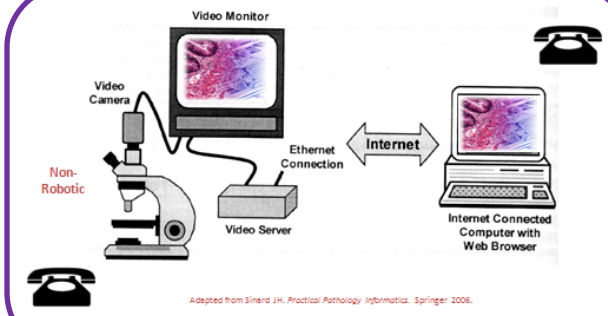
Network

Remote Image Display

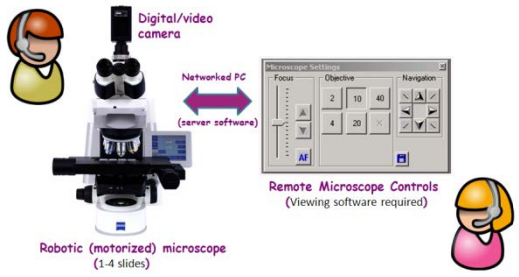
Telepathology Modes

Static

Video



Robotic



WSI

Static Telepathology

Static Telepathology

ADVANTAGES

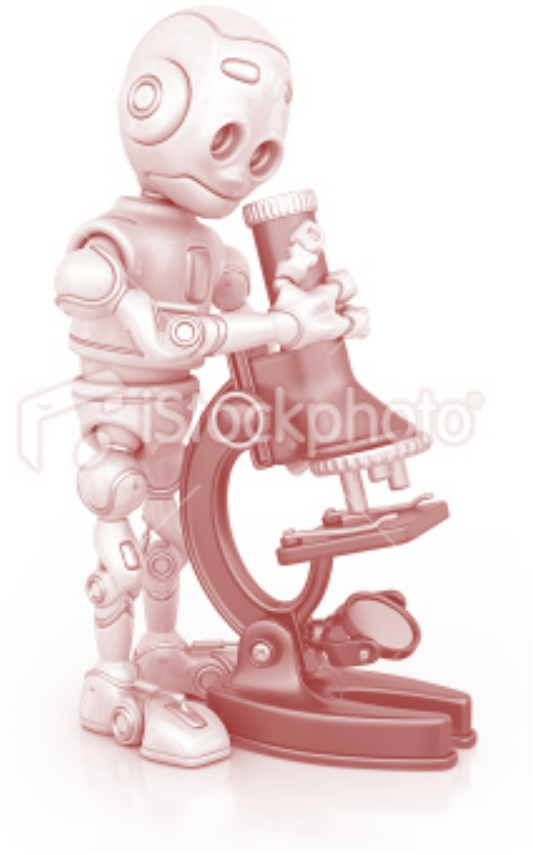
- Low cost (relatively inexpensive cameras)
- Vendor independent
- Technically simple (e.g, e-mail access)
  - Recipient does not require special software to view images
  - Small manageable files (store-&-forward)
- Easy maintenance

Static Telepathology

DISADVANTAGES

- Telepathologist has no remote control
- Host needs to have some expertise
- Acquiring images is labor intensive
- Possibility of sampling error
- Limited FOVs to examine
- Lack of clarity at low power magnification
- Lack of focus in still images

Robotic Telepathology



Robotic Telepathology

ADVANTAGES

- Access to the entire slide
- User controls the microscope & image
  - Fields (panning) & Magnification (zoom)
- Good image quality
- Fast (but not immediate) driving speed
- Viewed areas can be tracked (audit trail)

Frozen section diagnoses by robotic telepathology

Evans AJ et al. *Human Pathology* 2009; 40:1070–1081.

Year	Primary author	Accuracy (%)	Deferral (%)	Time (min/slide)
1991	Nordrum [9]	100	0	15
1995	Oberholzer [10]	90.3	6 [a]	20-40
1997	Steffen [11]	89	4 [a]	NA
1999	Della Mea [12]	100	NA	4.5
2000	Dawson [13]	97	NA	3
2003	Hutarew [17]	99.4	NA	1-36
2003	Terpe [15]	98	NA	15
2005	Sukal [16]	NA [b]	NA	NA
2005	Hitchcock [18]	95.3	NA	NA
2006	Hutarew [14]	97.9	0	10.7
2007	Horbinski [7]	95.5-96.9	12-20	NA

Abbreviation: NA indicates not available.

[a] These reports did not provide deferral rates but rather the percentage of cases during which technical problems were encountered.

[b] This report did not provide diagnostic accuracy data but concluded that TP was a useful adjunct in Mohs surgery.

Robotic Telepathology

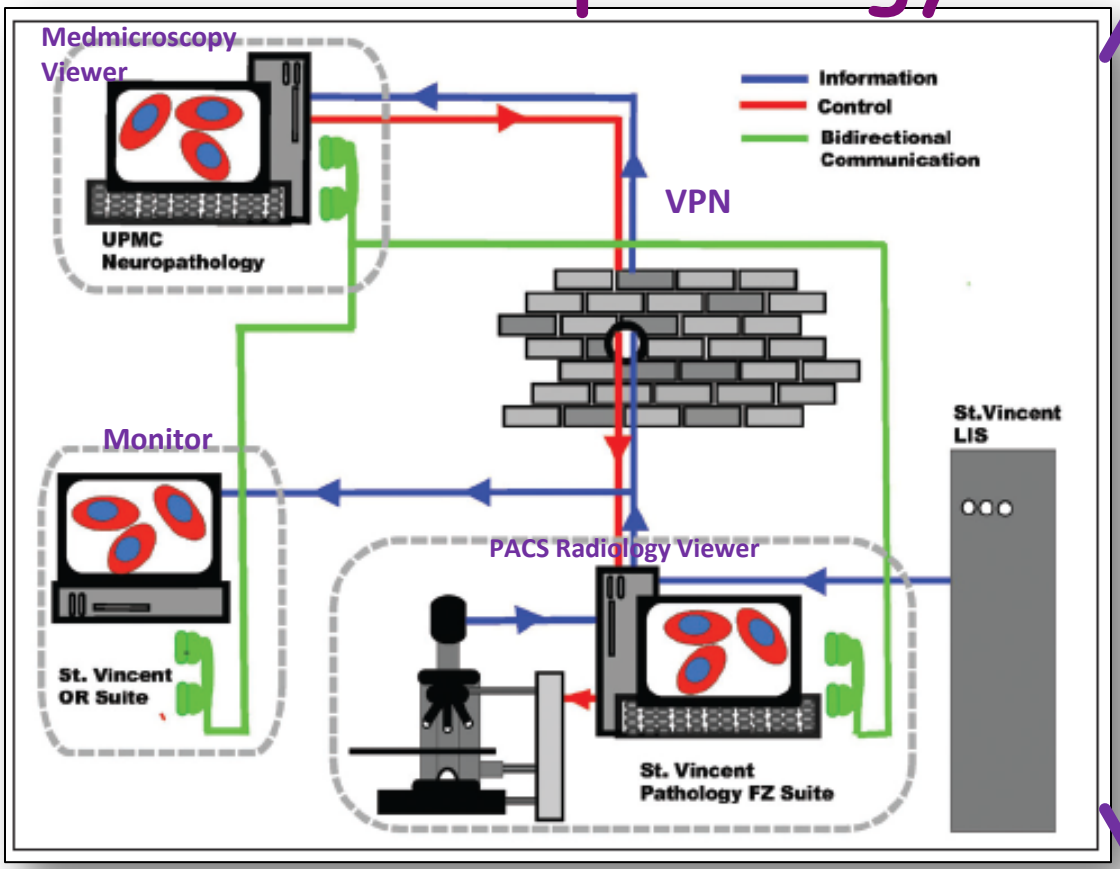
DISADVANTAGES

- Need for a highly experienced host (assistant)
- Expensive
- Slow (approx.10min/slide)
- Both host & recipient require integrated software
- Lack of interoperability between vendors
- High bandwidth requirements

Interinstitutional Teleneuropathology

Wiley et al. J Pathol Inform 2011; 2:21

9 neuropathologists



4-slide Zeiss AxioImager

370 miles

1 neuropathologist

WSI Telepathology

ADVANTAGES

- Access to an entire case (set of slides)
- Automated (or manual) scanning
- High (better) resolution of images
- Added software (e.g. teleconferencing)

Time requirements for single block frozen sections

Evans AJ et al. Human Pathology 2009; 40:1070–1081

TP modality	Slide preparation time (min)	Slide interpretation time (min)	Total TAT (min)
Robotic (range)	10.33 (9-42 [a])	9.65 (<1-25)	19.98 (11-45)
Virtual slide (range)	12.26 * (8-20)	3.42**,[b] (<1-10)	15.68 * (9-35)

FS

N = 350

N = 633

- Robotic microscopy system = *Leica TPS2*
- Hybrid whole slide scanner = *Aperio ScanScope CS*

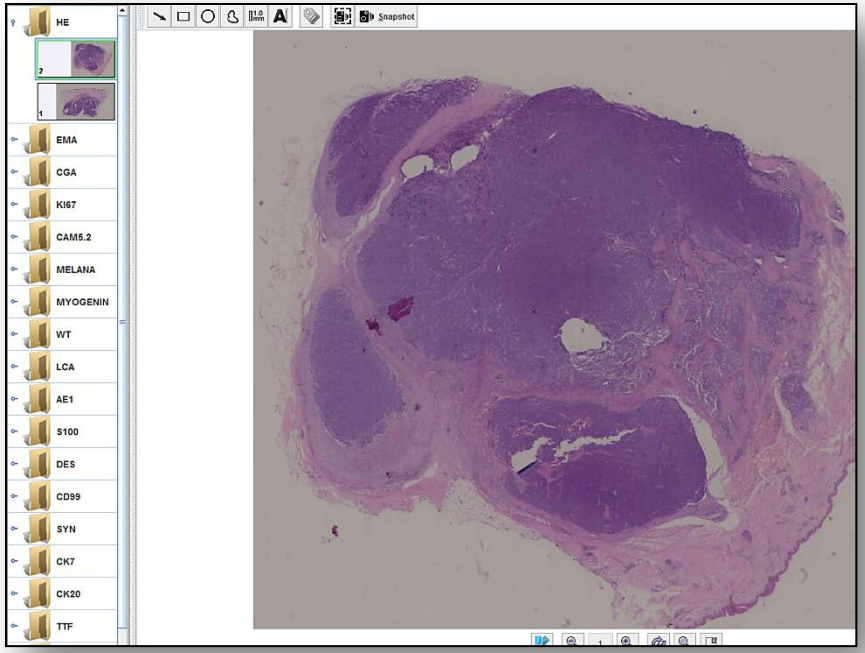
WSI Telepathology

DISADVANTAGES

- Expensive (scanner, server, software license, indirect costs)
- Scanning difficulties (e.g. wet slides, tissue folds)
- Long scan times
- Missed tissue (small fragments, faint tissue, outside coverslip)
- Limited vendor interoperability

Synchronous Telepathology

Referring Pathologist



Consulting Pathologist

Cell Phone Adapters

Magnifi
(Arcturus)

SkyLight
(SkyLightScope)

Mobile cell-phone (M-phone) Telemicroscopy

Bellina & Missoni Diag Pathol 2009; 4:19

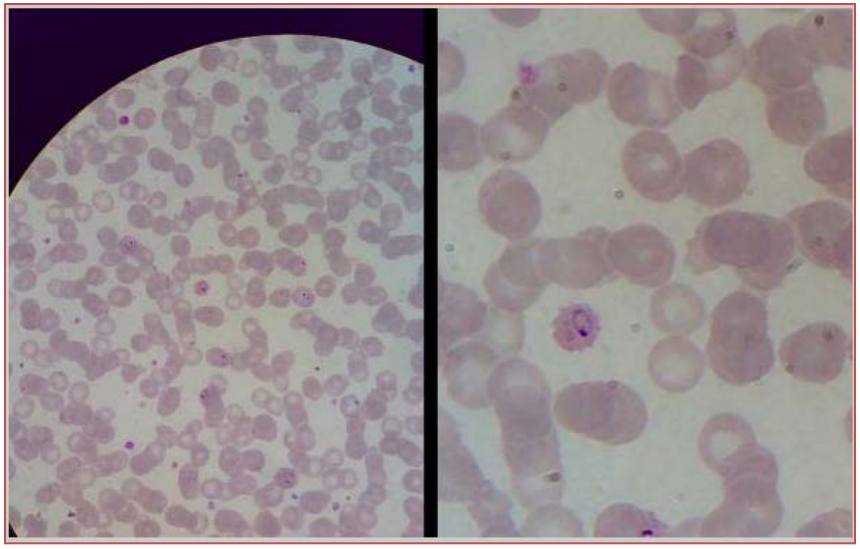
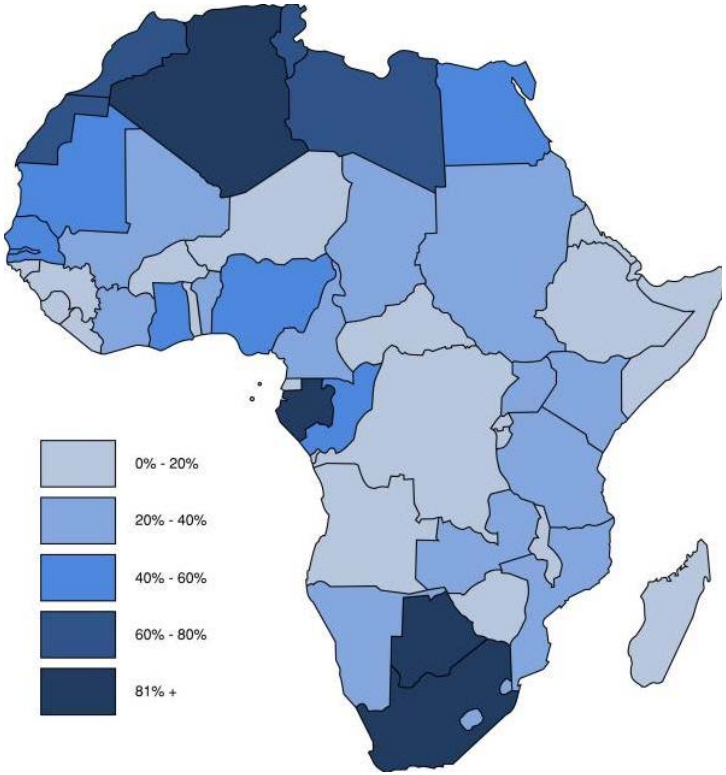


Image captured with m-phone directly from microscope's ocular. *Plasmodium falciparum* rings in erythrocytes, May-Grünwald-Giemsa stain.



M-phone and MMS penetration in Africa. M-phone subscriptions with declared availability of Multimedia Messaging Service (MMS, per 100 inhabitants. Map elaborated by the authors based on last available information (2007–2009).

Image analysis

Identification of Rare Events

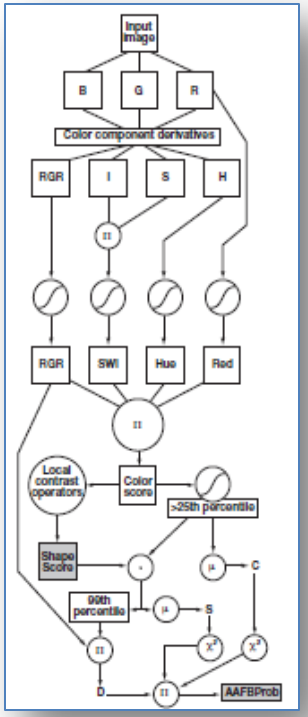
Computer-Assisted Screening of Ziehl-Neelsen–Stained Tissue for Mycobacteria

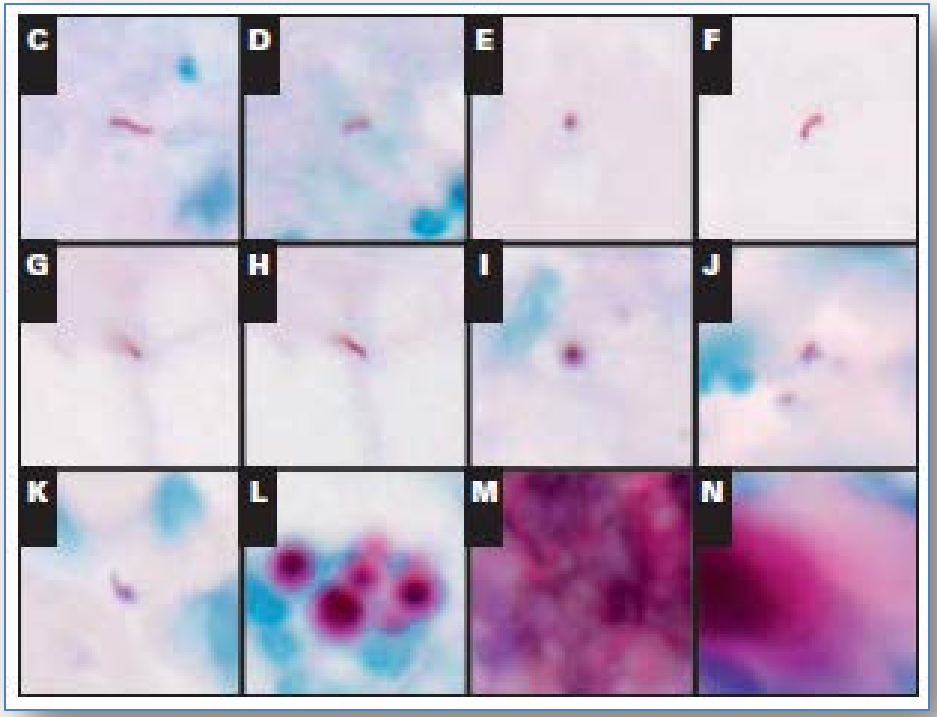
AJCP 2010; 133:849-58.

Algorithm Design and Preliminary Studies on 2,000 Images

Paul J. Tadrous, MBBS, MSc, PhD, FRCPath

Automatic screening algorithm successfully identified AFB despite:
(1) single bacilli occupying 0.0024% of the image & (2) tissue and staining artifacts.





Accurate & Reproducible Quantification

Quantitative Measurements

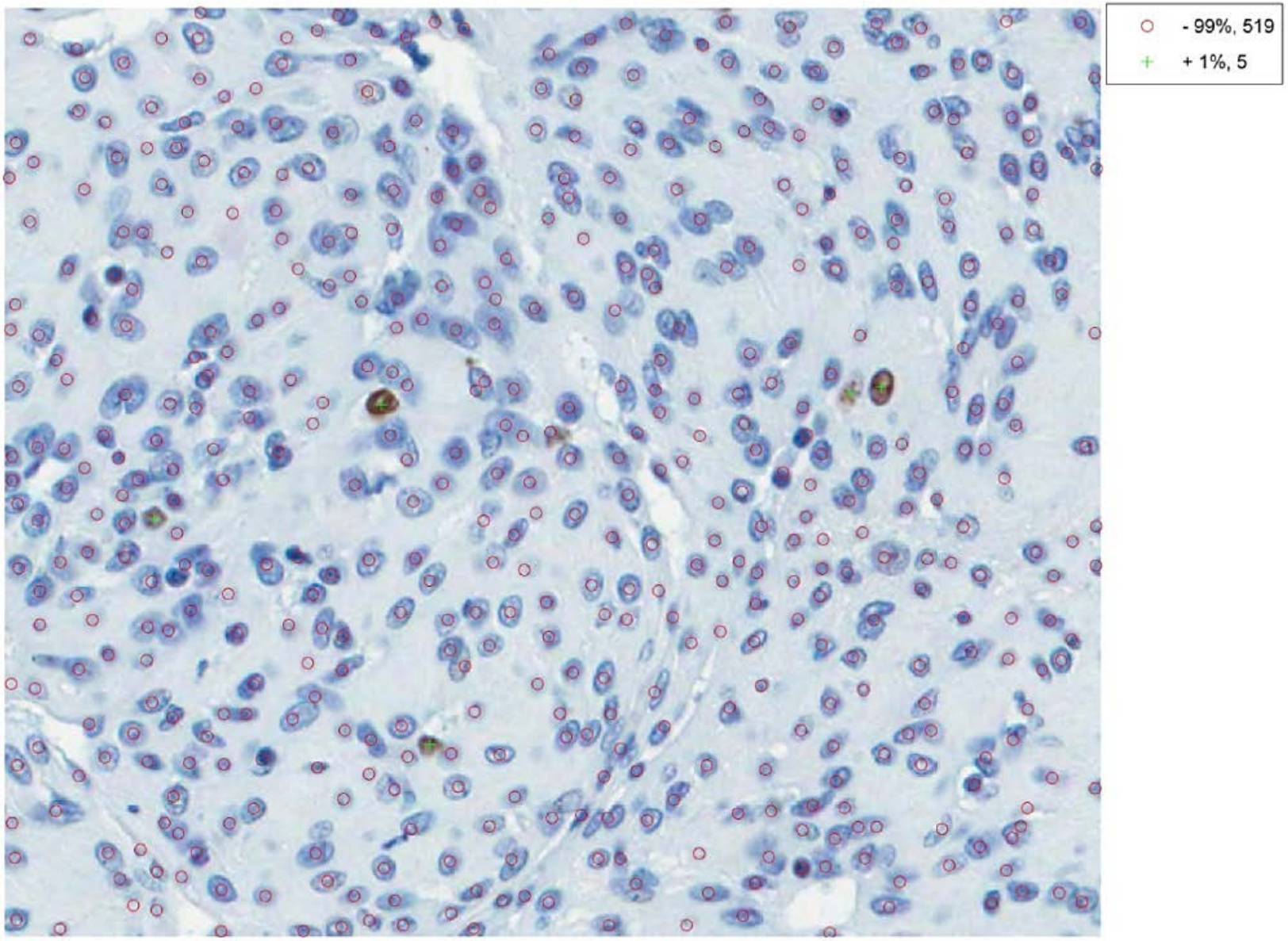
- Structures (e.g. Lewy bodies, Pick bodies, prion protein, etc.)
- IHC (e.g. breast markers, Ki-67)

Spatial Patterns of Features

- Distribution (random, clustered, etc.)

CNS Tumor Ki-67 Labeling Index

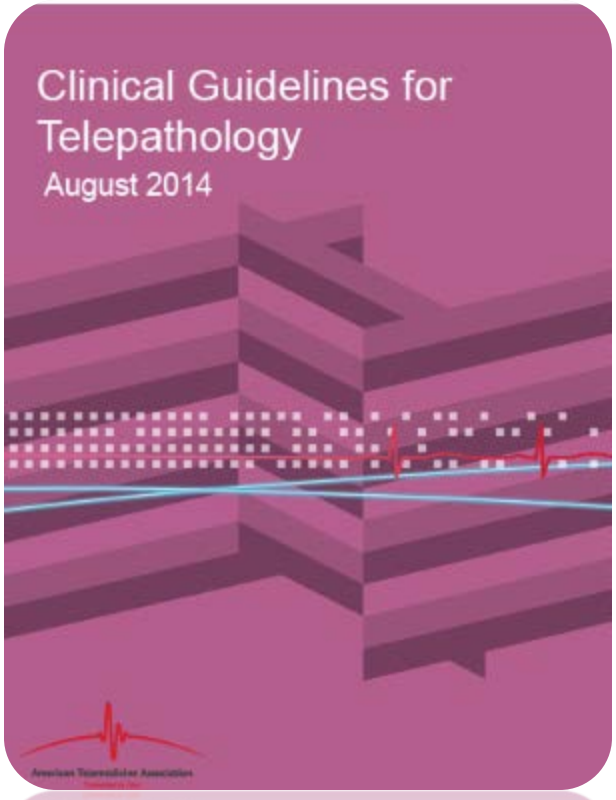
- **Ki-67 labeling index [LI]:**
  - Differentiate better/worse prognostic groups of brain tumors
  - Affected by both staining & counting methods (variability)
- **Manual method (counting):**
  - Interlaboratory & interobserver variability, imprecision & low sensitivity of human visual inspection
- **Image analysis (computer-assisted):**
  - Automated, accurate & more reproducible
- **Problems:**
  - Whole slide vs. Hot Spots, TILs, overlapping cells, crushed cells



Ki-67 LI of 1% corresponds with histologic grade I meningioma

Slodowska et al. *Diag Pathol* 2011; 6 (Suppl 1):S20

Guidelines

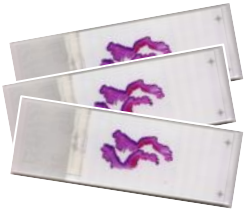


Validation vs. Verification

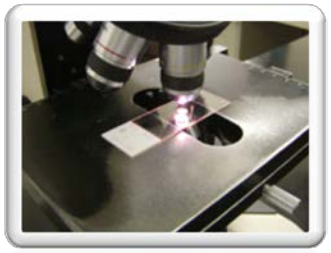
- **Verification** = Checking manufacturer's claims for performance specifications before use (directed by manufacturer's user manual)
- **Validation** = Process of testing an instrument to assess performance & whether it is acceptable (necessary to prove it performs as expected & achieves intended result)

Definition of primary diagnostic use for pathology diagnosis?

- Use of a digital image (and not glass slide) as the primary (final) basis for establishing a pathologic diagnosis



Glass/Microscope



1. Study design
2. Technology
3. Training

Concordance

Whole slide imaging

Accuracy

1. Observer variability
2. Case difficulty
3. User experience

Glass/Microscope

WSI Validation Guidelines

- **College of American Pathologists**

  Pantanowitz L et al. **Validating whole slide imaging for diagnostic purposes in pathology: recommendations of the College of American Pathologists (CAP) pathology and laboratory quality center.** Arch Pathol Lab Med 2013; 137:1710-1722.

- **American Telepathology Association**

  Pantanowitz L et al. **American Telemedicine Association clinical guidelines for telepathology.** J Pathol Inform 2014; 5:39.

- **Digital Pathology Association**

  Lowe A et al. **Validation of Digital Pathology in a Healthcare Environment** White Paper. 2011.

- **Scientific & Regulatory Policy Committee**

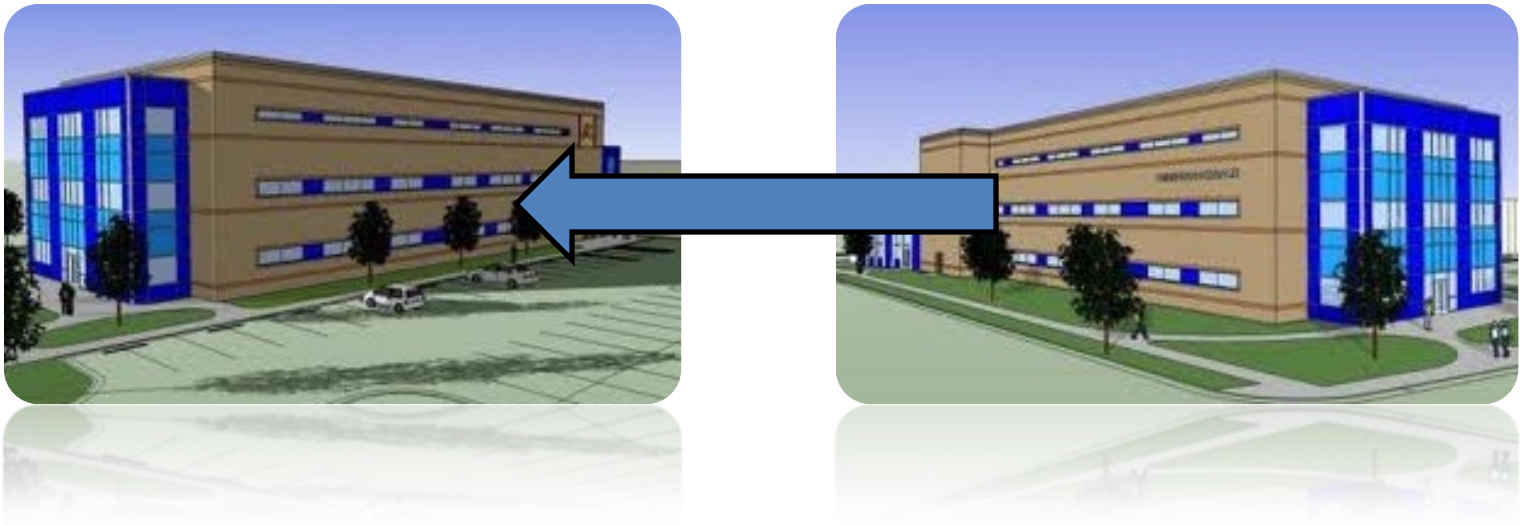
  Long RE et al. **Validation of Digital Pathology Systems in the regulated nonclinical environment.** Toxicol Pathol 2013; 41(1):115-24.

WSI Validation for Diagnosis

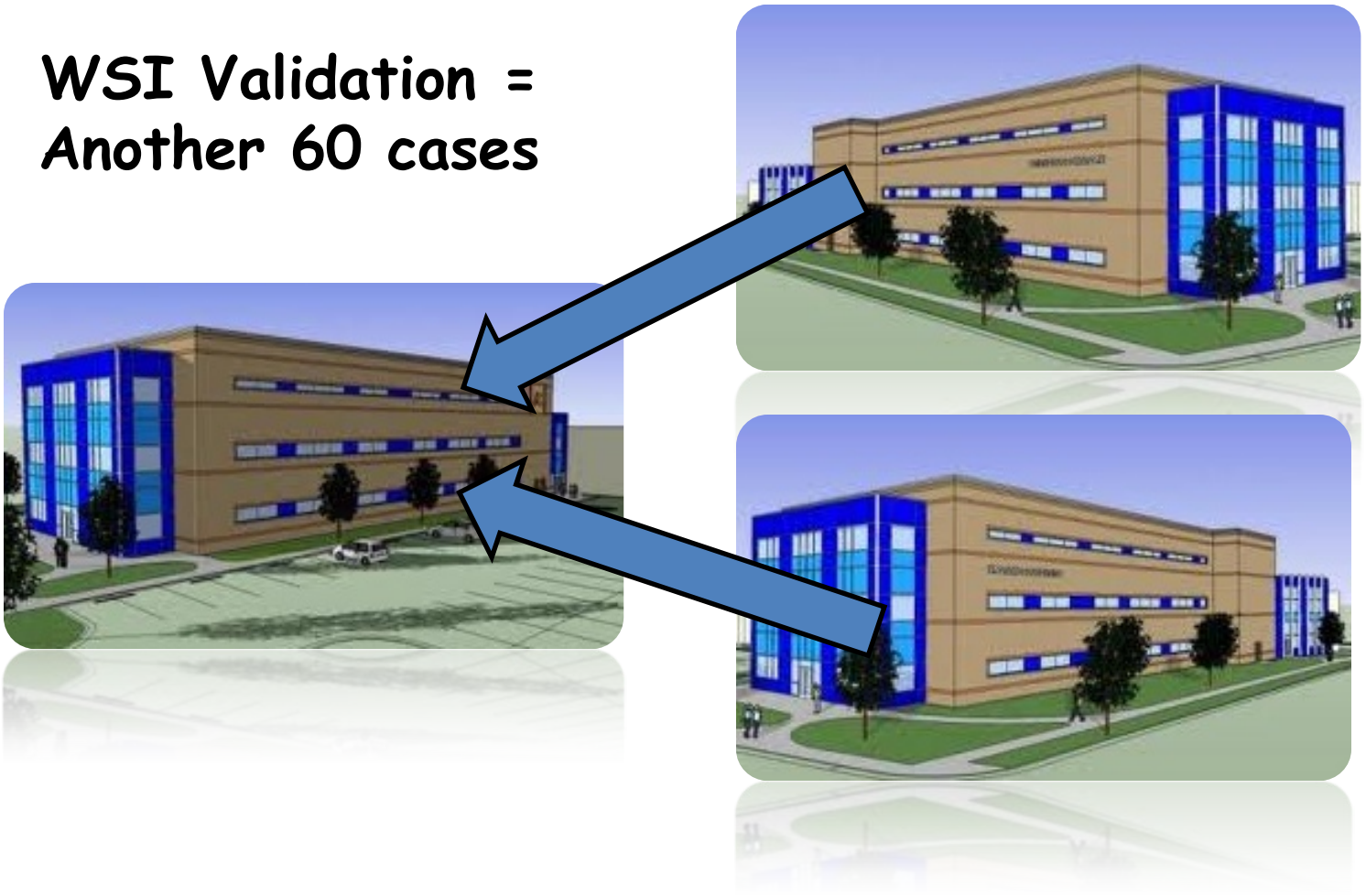
- Validation of the entire WSI system, involving pathologists trained to use the system, should be performed in a manner which emulates the laboratory's actual clinical environment.
- It is recommended that such a validation study include at least 60 routine cases per application, assessing intra-observer diagnostic concordance between digitized and glass slides viewed at least two weeks apart.
- It is important that the validation process confirms that all material present on a glass slide to be scanned is included in the digital image.

WSI Validation = 60 cases

WSI Validation = Another 60 cases



WSI Validation =
Another 60 cases



American Telemedicine Association

Clinical Guidelines for Telepathology

Guideline Outline

- Scope (clinical, not research or education)
- Introduction (e.g. historical background)
- Technology & Modes of Practice
- Clinical Applications
- Facility Responsibilities
- Validation
- Training
- Documentation & Archiving
- Quality Assurance
- Operations & Maintenance
- Security
- Medicolegal & Regulatory Aspects
- Definitions/Abbreviations

Summary

Summary

Pros of Digital Pathology

Cons of Digital Pathology