Validation of Whole Slide Imaging For Routine Practice

Dr. Andrew. J. Evans MD PhD FRCPC
Director of Computational Pathology
University Health Network
Toronto, ON, CANADA

Disclosures

- None

Overview

- Definitions and barriers to adoption of WSI for routine practice
- Why validate?
- Options for study design and endpoints
- Evidence from validation studies to date
- Regulatory approval for primary diagnosis - USFDA
- Guidelines

Definitions

- **Telepathology**
  - transmission of pathology images and patient information for various clinical applications.
- **Whole-slide imaging (WSI)**
  - high-resolution digitized replica of glass slide created by a scanner
  - manipulated by software to simulate microscope review (virtual slide)

Whole Slide Imaging: Value Proposition

- Growing emphasis (and expectation)on improving quality in pathology by creating healthcare networks
- WSI enables:
  - ❑ enhanced access to sub-specialty expertise
  - ❑ decreased need to transport glass slides
    - reduce cost
    - avoid lost or broken slides
    - improved turnaround times for consultations
    - work load levelling across sites
  - ❑ remote/under-serviced regions
    - support for solo pathologists
    - enhanced recruitment and retention of local surgeons
  - ❑ **next-generation pathology based on machine learning/AI**

Historical Barriers to Adoption of Digital Pathology

- Lack of regulatory approval - FDA
- Lack of standards/best practice guidelines
- Cost, IT infrastructure - business case, system-wide efficiencies, savings and return on investment (ROI)
- Pathologist mindset
  - disruptive technology with different workflow – *"It's too slow"*
  - learning curve – "*I am too busy to learn this*"
  - fear of medicolegal liability - *"I don't trust these images"*
  - professional billing/new practice models - *"I will be replaced"*

Getting Pathologists Comfortable Making Diagnoses with WSI

- Abundance of literature showing excellent correlation between WSI and glass diagnoses
- Less stressful uses - tumour boards, research, teaching
- Proper training with WSI systems
- Provide a “safety valve” - defer to glass slides when required
- **Perform internal validation of WSI for intended uses**
  - **prove it to yourself!**

Validation:

- A process to demonstrate:
  - A new method (WSI) performs as expected for its intended use and environment prior to using it for patient care
    - ➢ SAFE IMPLEMENTATION
  - Pathologists can make accurate diagnoses to at least the same level as with light microscopy
  - There are no interfering artifacts or technological risks to patient safety

Verification:

- Objective evidence confirming that specified performance requirements have been satisfied
  - Acceptable diagnostic concordance between WSI and glass slides
  - Scanning completeness and accuracy
  - Timely and efficient workflow (frozen sections with TAT requirements)

- Appropriate use of laboratory “test” as intended by a manufacturer.

Why Validate WSI?

- Diagnostic pathology is interpretive and is not a “laboratory test”- how can it be validated?
- WSI depends on complex hardware and software components as well as external variables
  - histology
  - pathologists and technologists
- Use of such a system for diagnostic result merits performance verification

- Consensus: perform WSI validation for clinical uses

Study Endpoints: Diagnostic Discrepancy (and Concordance) for WSI vs Glass Slides

- None
- Minor - no/minimal harm/impact on patient care
- Major - definite impact/harm on patient care
  - ❑ unnecessary repeat invasive procedures
  - ❑ delay diagnosis/treatment $\geq$ 6 months
  - ❑ major morbidity
  - ❑ loss of life/limb, unnecessary major surgery
- **Assessment of harm is arbitrary and unstandardized**

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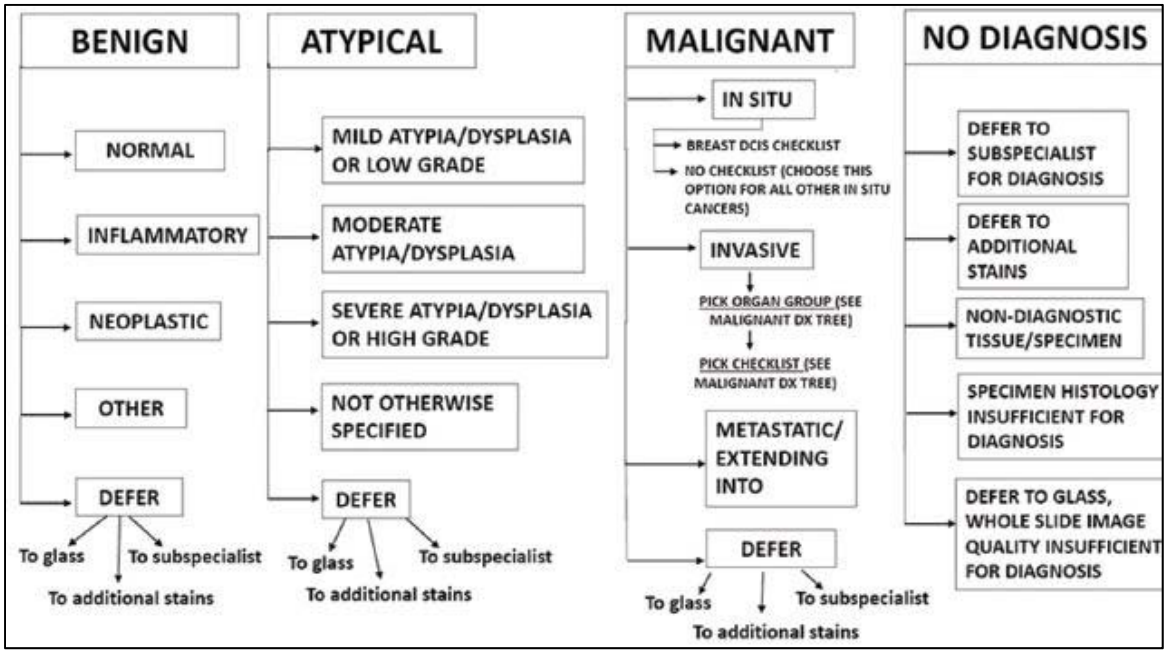
Original Article

A multisite validation of whole slide imaging for primary diagnosis using standardized data collection and analysis

Katy Wack[1,2], Laura Drogowski[2], Murray Treloar[3], Andrew Evans[4], Jonhan Ho[5], Anil Parwani[6], Michael C. Montalto[2,7]

J Pathol Inform 2016, 1:49



- standardized checklists (CAP protocols)
- identify hypothetical pairwise discordances
- assign level of harm based on published definitions

- discordance matrices for WSI validation

Validation Study Designs

- Retrospective (using old cases)
  - Intraobserver
  - Interobserver
  - Non-inferiority
- Prospective (using new cases)
  - Intraobserver
  - Interobserver

Retrospective: Intraobserver

- Same pathologist reviews old cases - glass and WSI
- Should not be cases reported by the pathologist reviewing them for the study
- Washout period between modalities

- Does the same pathologist make the same diagnosis regardless of modality?
  - Not necessarily the correct diagnosis
  - Isolate the effect of WSI on the diagnosis

Rationale for “Intraobserver” Study Design

- Expertise/experience affect “correctness” of diagnosis
- Lessens the impact of variable diagnostic “thresholds”
- Isolate the impact of WSI on diagnostic interpretation

- **Consensus: intraobserver more important for clinical purposes**

Retrospective: Interobserver

- Requires at least 2 pathologists/groups of pathologists
  - One reads cases as glass slides
  - One reads cases by WSI
- Will the 2 pathologists make same diagnosis?

- Problems with this approach:
  - Does not isolate the effect of WSI from the pathologist with respect to making diagnoses
  - Could expose a weak pathologist as opposed to an inferior diagnostic modality

Retrospective: Non-Inferiority

- Cases previously reported by glass slides (GDx1)
- Review them a second time as glass slides after a washout period (GDx2)
  - 1 year or more
- Review the cases a third time by WSI after a suitable washout period following GDx2.
- Assess glass to glass concordance - GDx1 vs GDx2
- Assess glass to WSI concordance
- Compare % discrepancy (GDx1 vs GDx2) to (WSI vs GDx2) using a non-inferiority margin

Prospective Self-Validation Study

Work flow:

UHN Pathologist

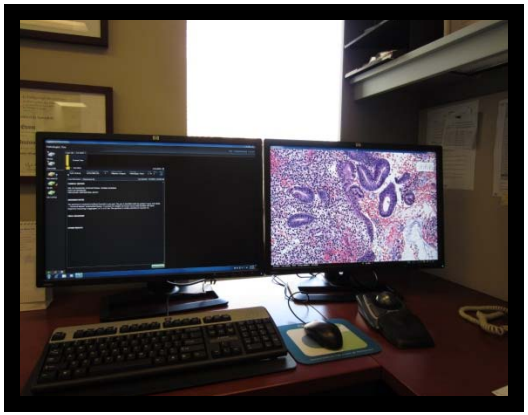
- Select representative **new** cases each day when on service.
- 2 phases:
  1. scanner at UHN (present)
  2. 2'nd scanner in Timmins

Imaging Technologist

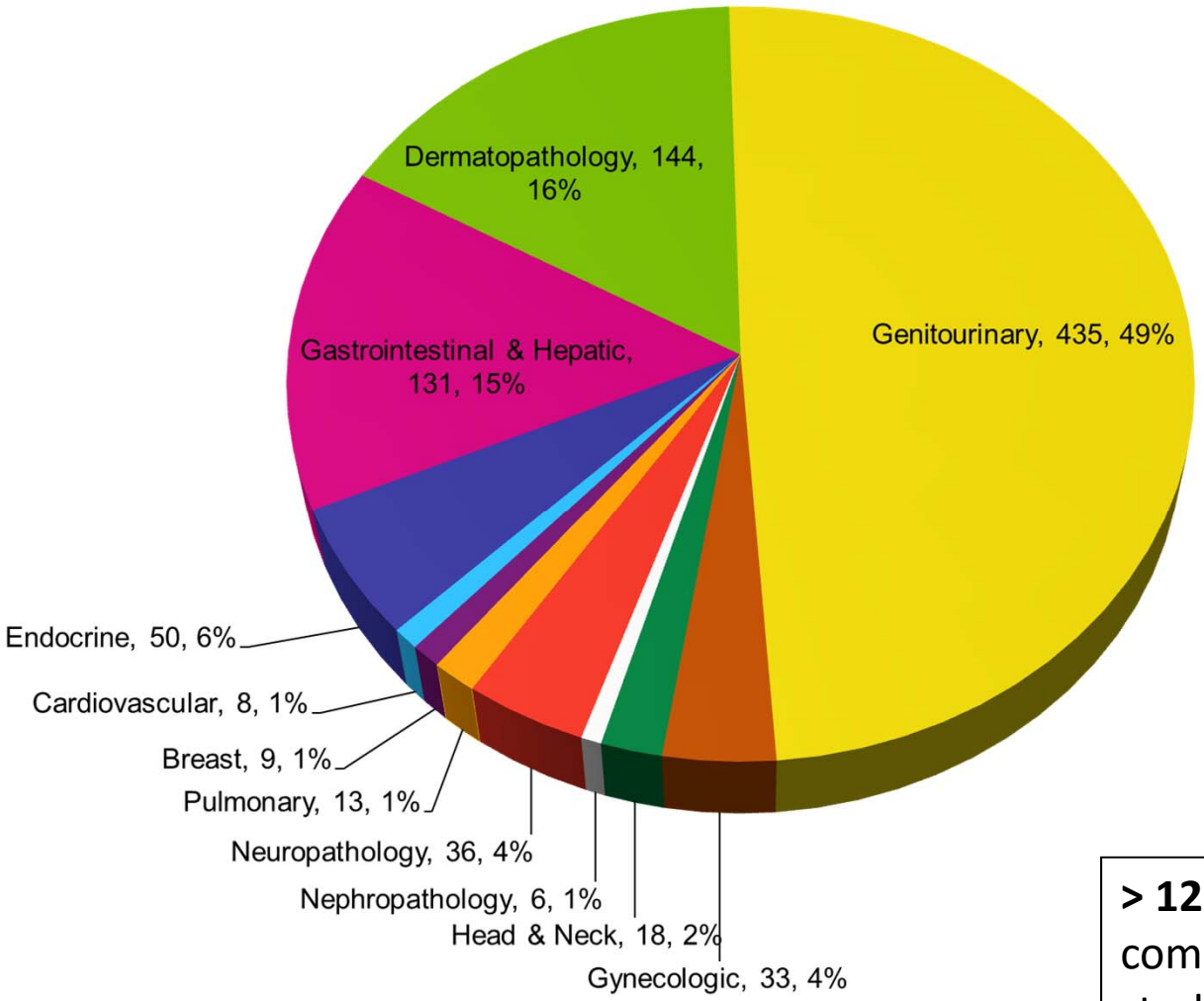
- Scans slides and prepares digital cases
- Basic QA for image quality

UHN Pathologist

- Review digital slides first
- Preliminary digital Dx in CoPath (or order additional sections/stains).
- Review slides with light microscope and sign out
- Fill in study worksheet in CoPath



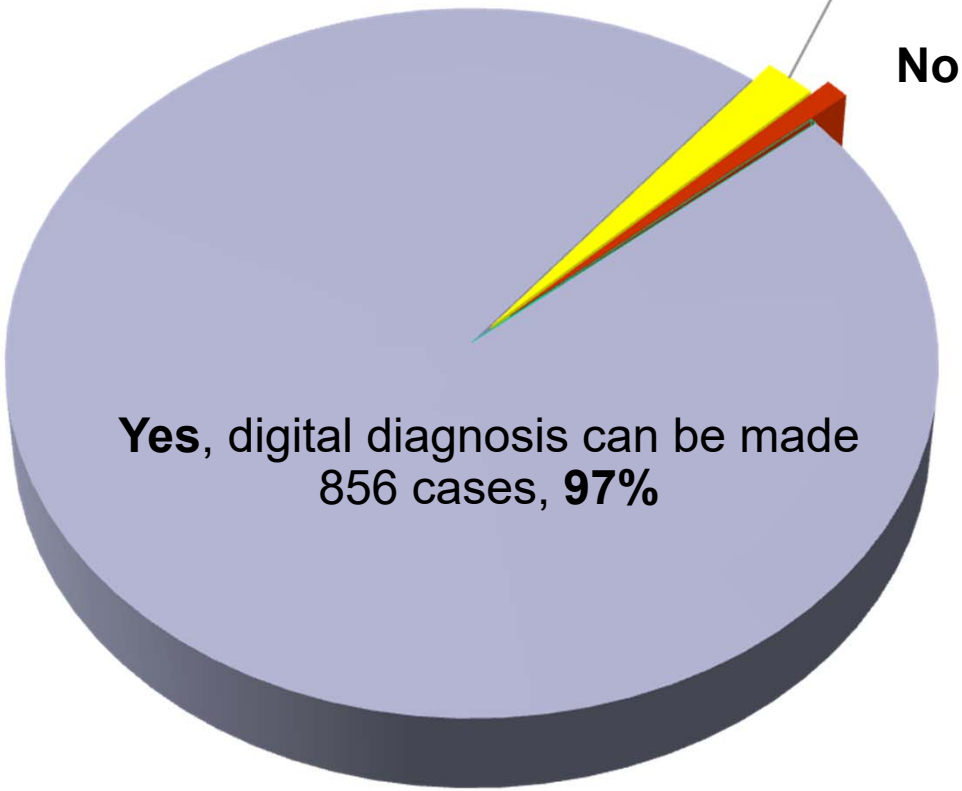
Distribution of Cases



- 11 sub-specialties
- 29 pathologists
- Cases range from small biopsies (1 slide, multiple levels) to large resection specimens (84 slides)

> 1200 cases with all slides completely reviewed according to study protocol.

Can a Digital Diagnosis Be Made ?



Yes diagnosis can be made but areas of suboptimal focus are noted
17 cases, **2%**

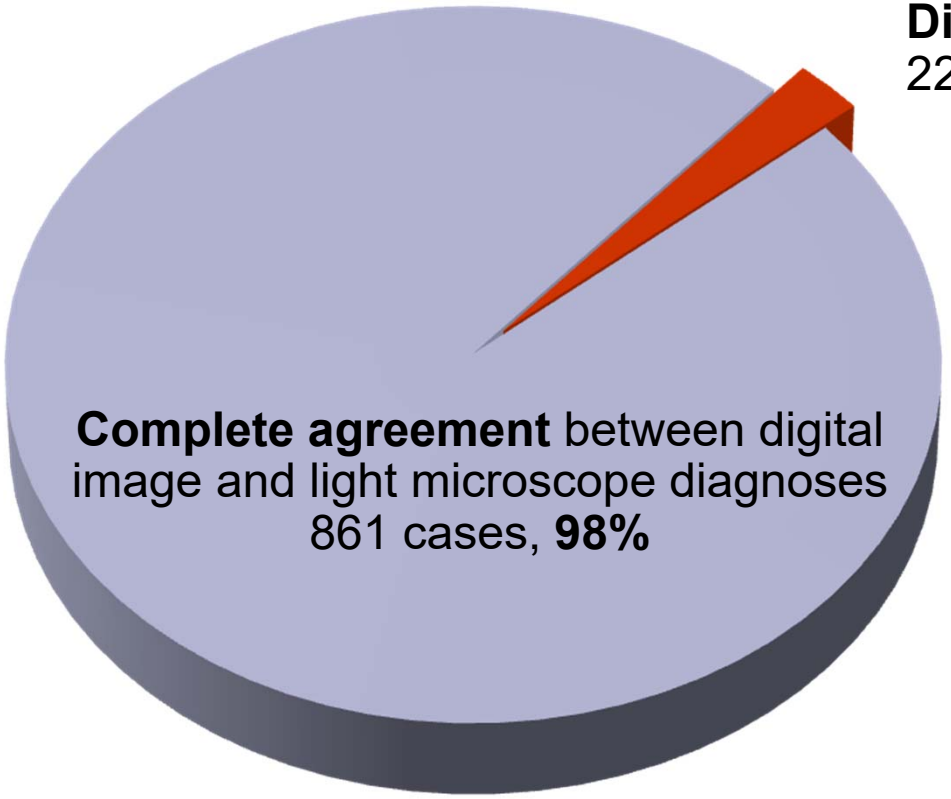
No digital diagnosis could not be made
8 cases, **1%**

Reasons :

3 tissue too low on the slide, out of scan area
2 poor focus in area of clinical significance
1 small area with benign fatty tissue not captured

✓ **99% Digital Diagnosis Can Be Made**

Agreement Between Digital and Glass Slides/Light Microscopy



Discrepancy
22 cases, **2%**

Minor discrepancies:
7 small pieces of tissue/floaters not captured
2 breast biopsies - polarized light required to identify microcalcifications
1 atypical meningioma – quantification of mitotic figures

Major discrepancies (Technical):
2 gastric biopsies – *H. Pylori* not confidently seen on digital image

Major discrepancies (Non-technical):
1 prostate biopsy - high-grade PIN found on glass slide, but initially overlooked on digital slide (intra-observer variability).

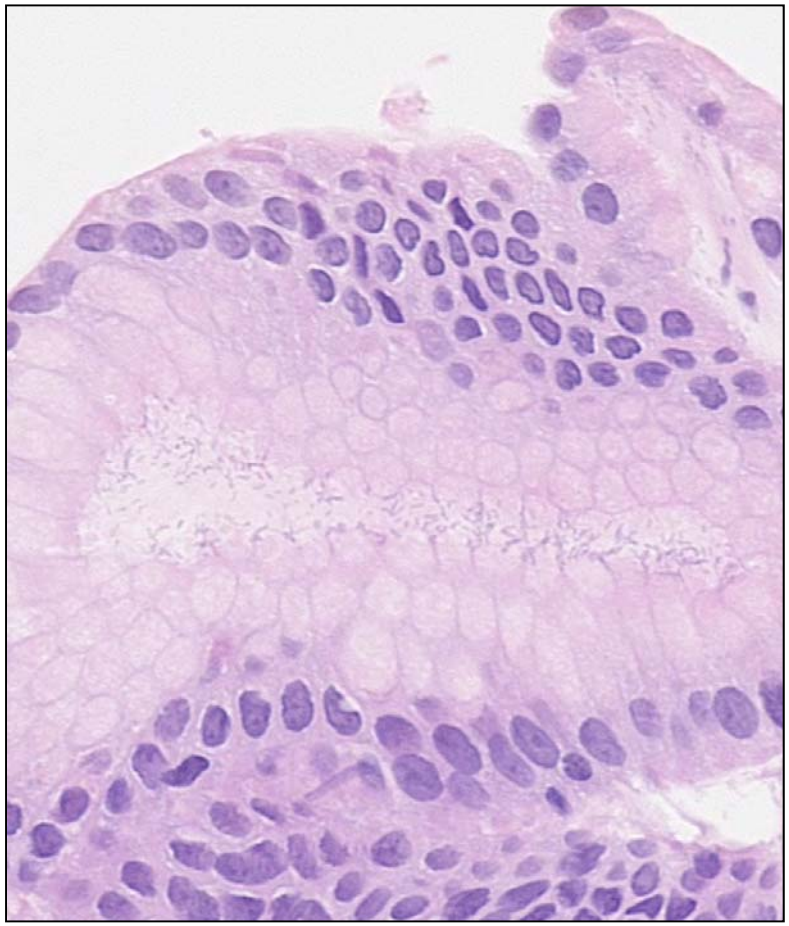
✓ **98% Complete Agreement**

Self-Validation Studies: What is Learned?

- WSI can be used for making accurate and complete diagnoses
- What needs to be optimized to facilitate digital sign out
  - ➢ histopathology laboratory
  - ➢ scanner - important feedback to vendor
- Limitations
  - cases that require re-scanning
  - cases to scan at 40X
  - **cases requiring deferral to glass slide review**

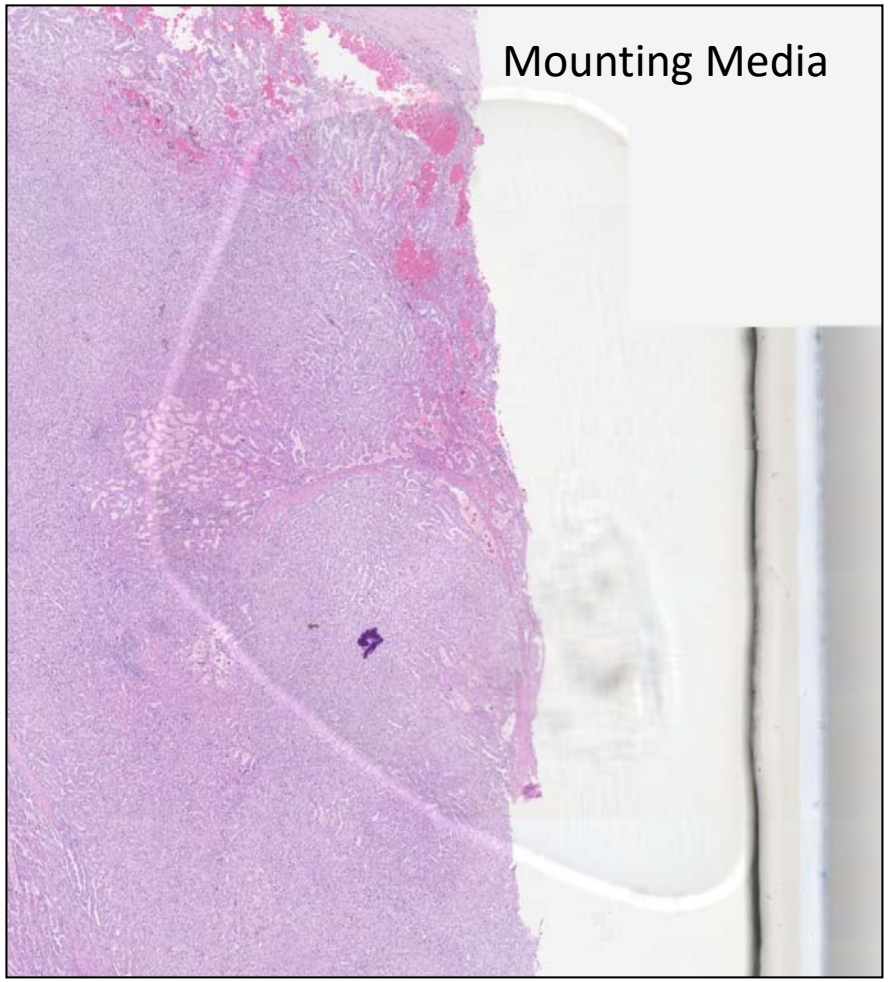
5%

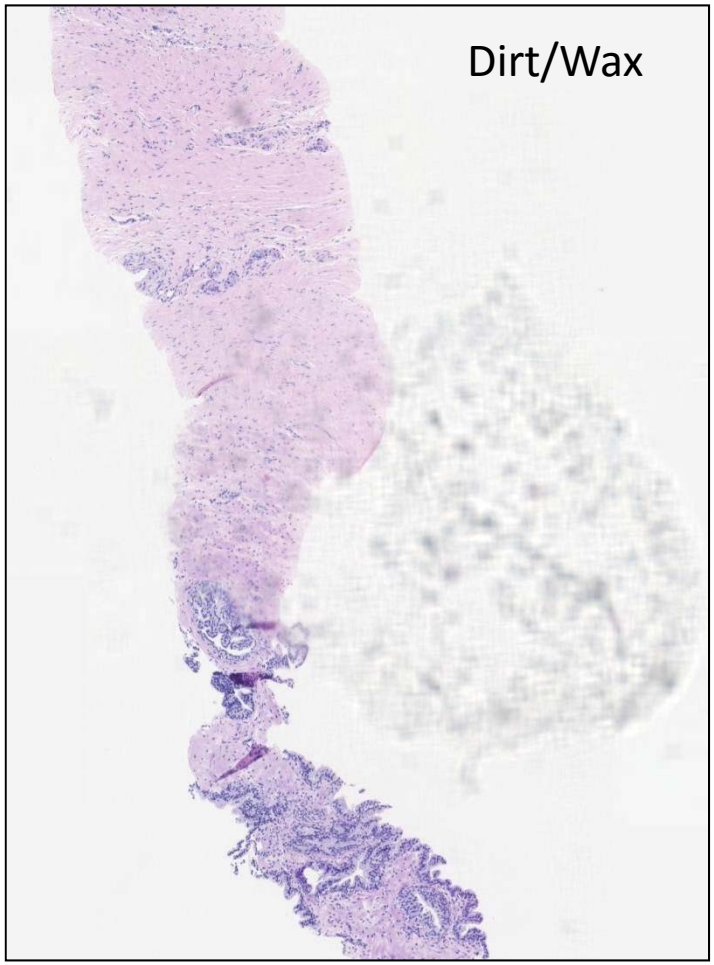
H. pylori Identification on H&E



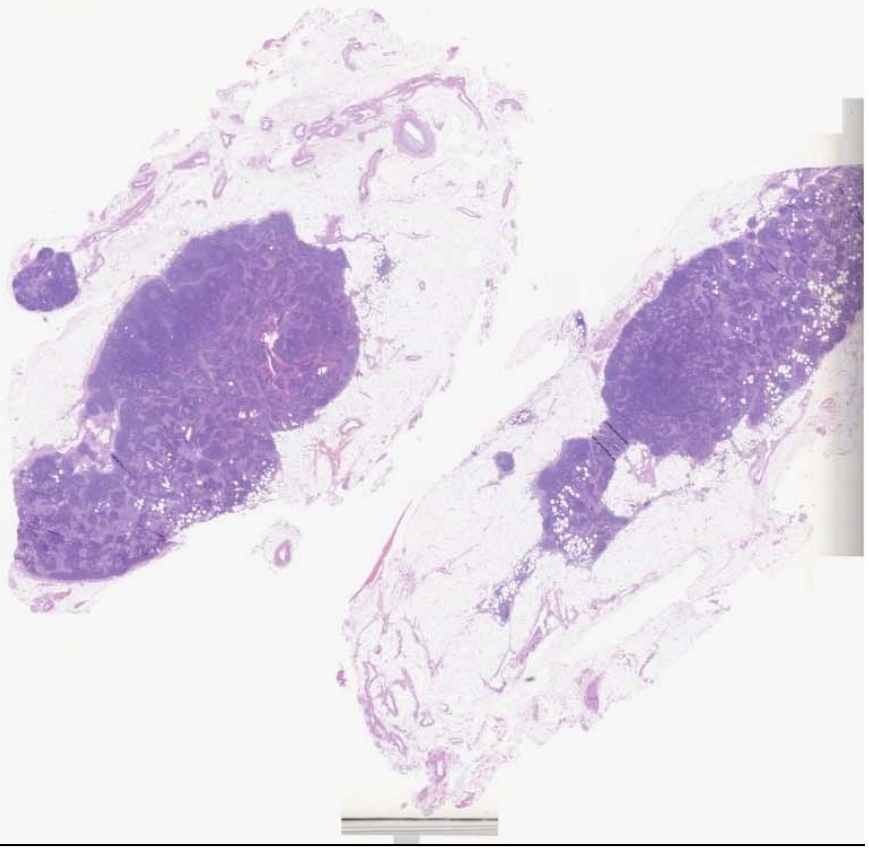
- Differing comfort levels between GI pathologists.
- Dependent on burden of organisms.
- Primary sign-out by WSI would likely result in greater use of special stains.

Histology Issues

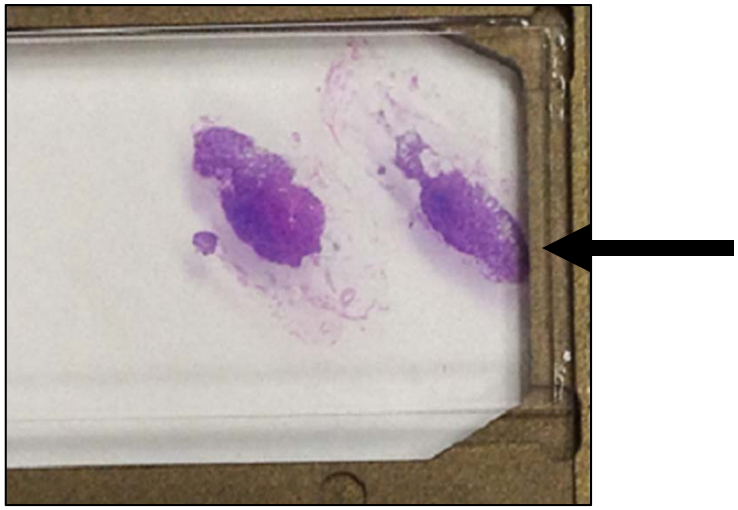




Tissue Placement



Section not centred properly on slide - incomplete capture of tissue



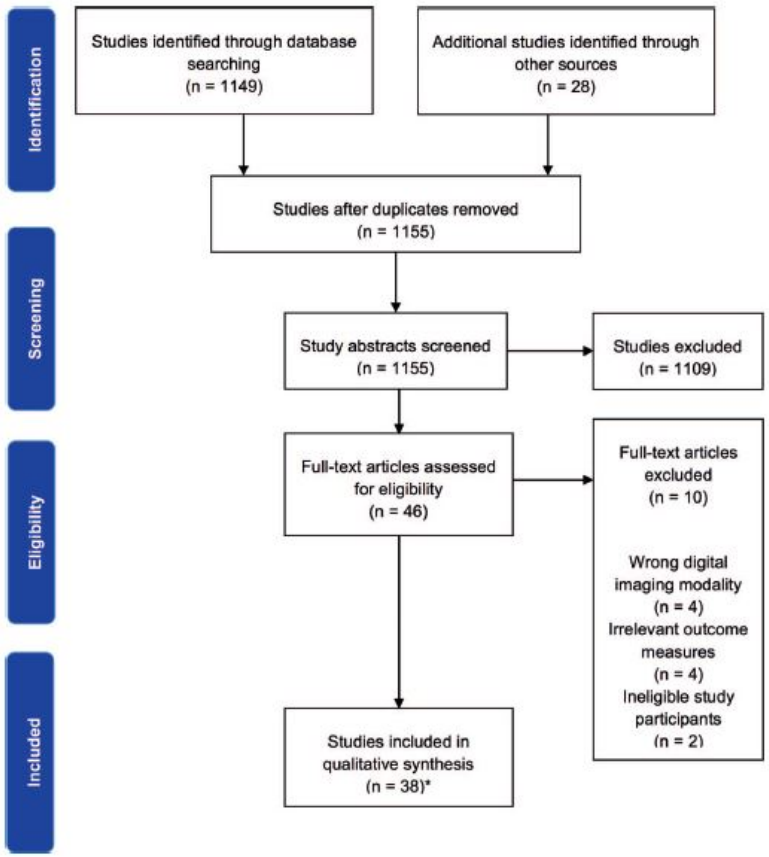
Evidence to Date

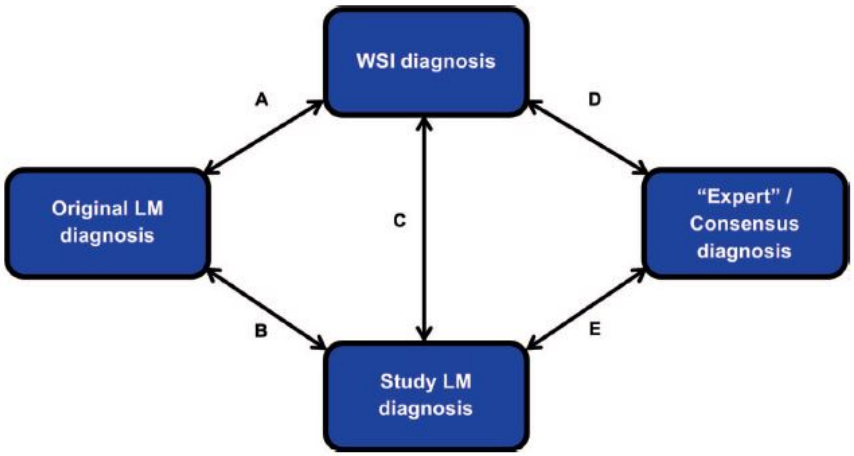
The Diagnostic Concordance of Whole Slide Imaging and Light Microscopy

A Systematic Review

Arch Pathol Lab Med. 2017;141:151–161;

Edward Goacher, BSc; Rebecca Randell, PhD; Bethany Williams, MBBS; Darren Treanor, MB, BSc, PhD, FRCPath





Bias and Applicability

- Patient selection
- Index test (WSI)
- Reference standard (glass slides)
- Flow and timing (washout)

The Diagnostic Concordance of Whole Slide Imaging and Light Microscopy

A Systematic Review

Arch Pathol Lab Med. 2017;141:151–161;

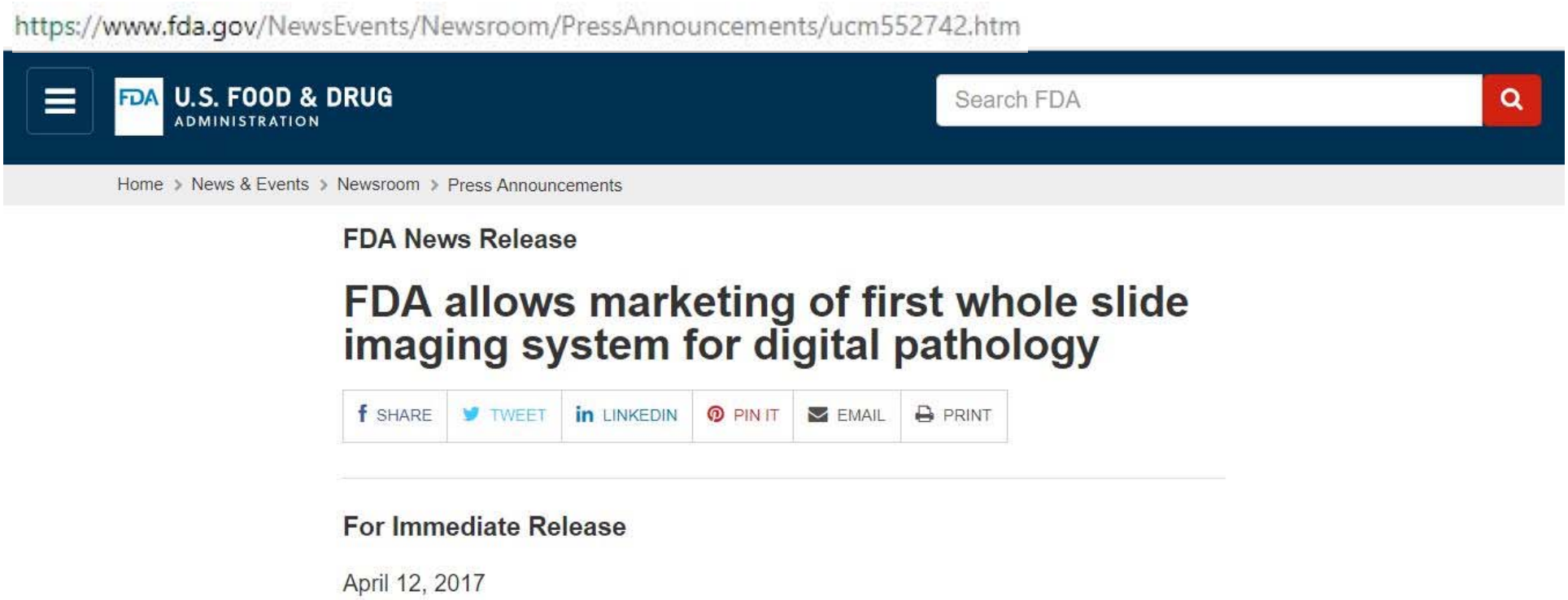
Edward Goacher, BSc; Rebecca Randell, PhD; Bethany Williams, MBBS; Darren Treanor, MB, BSc, PhD, FRCPath

- 38 studies met their inclusion criteria
- mean diagnostic concordance WSI vs glass slides 92.4% (63%-100%)
- weighted κ = 0.75 (substantial agreement)

- Relatively small number of studies
- Small sample sizes without sample size calculation/justification
- Single institution (not multi-site clinical trials)
- Incomplete details (displays/monitors)
- Potential publication bias (only successful trials by early adopters)
- VARIABLE QUALITY OF EVIDENCE
  - Supports the use of WSI, but more published validation studies are needed

Regulatory Approval

April 12, 2017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FDA News Release

FDA allows marketing of first whole slide imaging system for digital pathology

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

For Immediate Release

April 12, 2017

- Philips IntelliSite Pathology Solution
- Review and interpretation of digital surgical pathology slides prepared from biopsied tissue - primary diagnosis.
- Risks associated with use of this technology are similar to that of conventional light microscopy
- YOU NEED TO KEEP YOUR MICROSCOPE

Current State of the Regulatory Trajectory for Whole Slide Imaging Devices in the USA

Esther Abels[1], Liron Pantanowitz[2]

[1]Philips, Digital Pathology Solutions, The Netherlands, [2]Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, USA

Received: 06 February 2017 Accepted: 08 March 2017 Published: 15 May 2017

- FDA approval required for devices or processes to be promoted and sold
- FDA regulates vendors and claims made about products

Table 1: Food and Drug Administration medical device regulatory classification system

Medical device class	Risk	Regulatory requirements
I	Low to moderate risk	General controls
II	Moderate to high risk	General and special controls with 510(k) application
III	High risk	General controls and PMA

PMA: Premarket approval

I Bandage

II Da Vinci robot

III Whole slide imaging systems

Regulatory Approval Pathway: 2009-2017

- **October 2009 -** FDA convenes public advisory panel, Gaithersburg, MD

- **October 2011 -** Digital Pathology Association Visions Meeting

CAP TODAY

COLLEGE OF AMERICAN PATHOLOGISTS

January 2012 Pathology/Laboratory Medicine/Laboratory Management Vol. 26 No. 1

Regulators scanning the digital scanners

Karen Titus

A recent panel on whole-slide imaging launched a clear message from the Food and Drug Administration: The agency views WSI systems as Class III medical devices and plans to regulate them as such.

Gentlemen, start your turtles.

While the FDA's decision was clear, the next steps are anything but. Vendors, pathologists, the FDA, and the Centers for Medicare and Medicaid Services could head in any number of directions next, but they won't be moving swiftly. In fact, those who were at the meeting are still dissecting the information presented at the panel, as if Alan Greenspan had delivered one of his famously tortured pronouncements from the Federal Reserve.

Depending on one's views, the news will slow efforts to bring WSI for primary diagnosis into U.S. laboratories, with some vendors looking to Europe for regulatory relief; have virtually no impact on large vendors, who, while not necessarily enamored of the FDA's decision, concede it's one they can live with; kill the market completely; choke innovation among vendors, especially component makers; possibly put laboratories in jeopardy if they try to validate these systems as laboratory-developed tests under CLIA; or encourage laboratories to use WSI for other, already approved purposes, readying themselves for the inevitable day when whole-slide imaging transforms surgical pathology.

What most agree on is that for the first time, the FDA, which regulates the vendor portion of the vendor-laboratory equation, has "put a stake in the sand regarding digital pathology," says David Wilbur, MD, professor of pathology, Harvard Medical School, and chair, CAP Technology Assessment Committee.

Note that the stake is in *sand*. "I suspect there's going to be a whole lot of give-and-take that comes about in the future," says Dr. Wilbur, who was in the audience at the panel dis-

continued on page 56

Of the FDA's decision to regulate whole-slide imaging systems as Class III devices, Aperio president Dirk Soeskens says, "They've made up their mind.... You're talking five years at the *earliest* when someone's going to get approval." How broad will Aperio's submission be? "As broad as FDA allows," he says.

Needlestick patrol: breaking bad habits

Anne Paxton

When Dennis J. Ernst, MT(ASCP), gives lectures to hospital staffs on accidental needlesticks, invariably a few audience members will seem to claim immunity from risk. "They'll say, 'I tear the fingertips off my gloves to find veins, I'm careful, I've never been stuck,'" says Ernst, executive director of the Center for Phlebotomy Education in Corydon, Ind. But these health care workers have a false sense of security, he says. "Legislation has taken us great lengths down the road to reducing needlesticks, but not all the way. You can only reduce accidental needlesticks so far by implementing safer devices."

In his online webinars and other presentations, Ernst targets the be-

continued on page 34

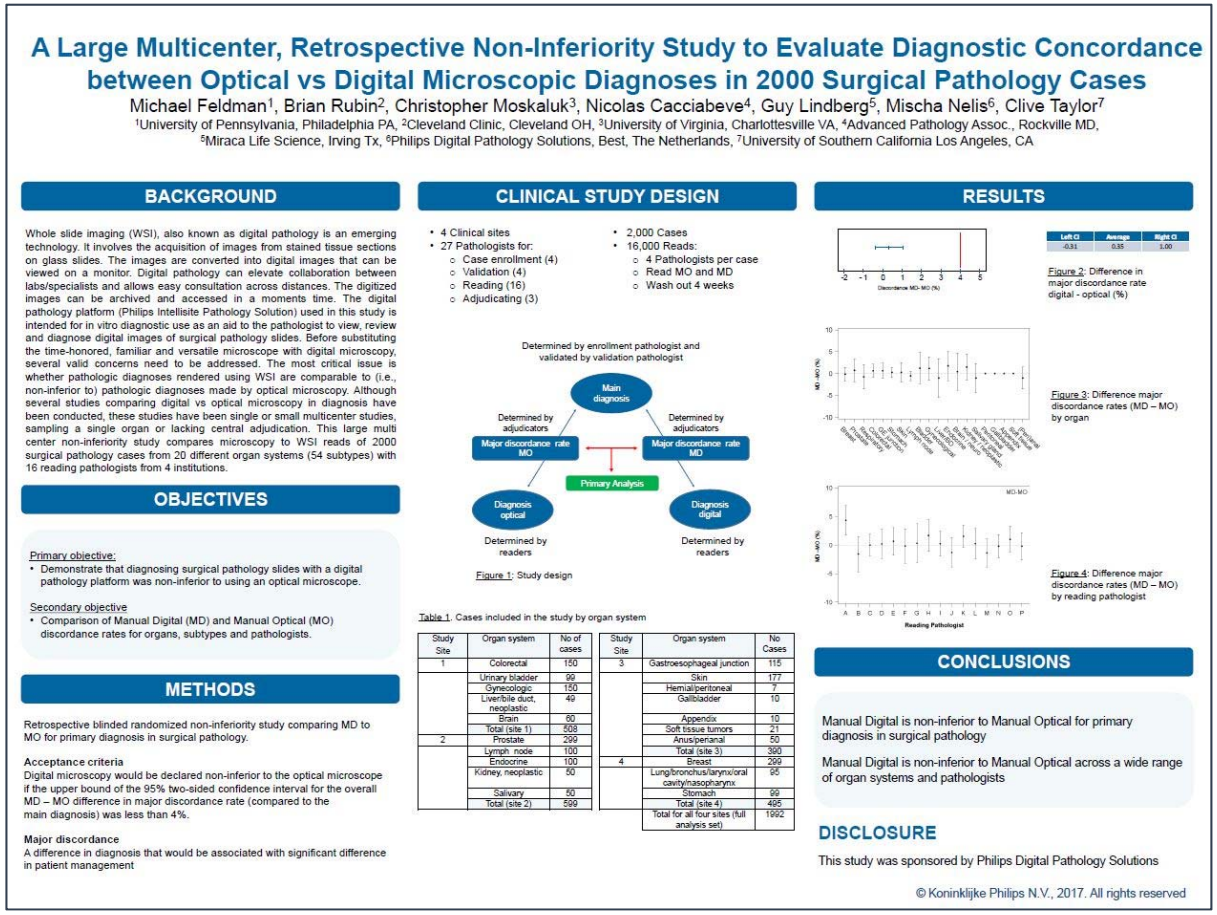
- "Class III"
  - informal designation
- PMA
  - clinical
  - technical

- "It will take five years"

What Happened From 2011-2016?

- **2012** - some vendors begin dialogue with FDA on clinical trial design
  - pre-submission ("pre-sub") process
  - vendor submits possible design - FDA provides feedback
- **2014** - FDA releases draft guidance on technical performance assessment (final version in 2016)
- **2015 - FDA releases details on PMA clinical trial design**
- **2016** - FDA and Digital Pathology Association Regulatory Task Force - de novo process to downgrade WSI from Class III to II

USCAP Meeting, March 4-10, 2017, San Antonio, TX



A Large Multicenter, Retrospective Non-Inferiority Study to Evaluate Diagnostic Concordance between Optical vs Digital Microscopic Diagnoses in 2000 Surgical Pathology Cases

Michael Feldman[1], Brian Rubin[2], Christopher Moskaluk[3], Nicolas Cacciabeve[4], Guy Lindberg[5], Mischa Nelis[6], Clive Taylor[7]
[1]University of Pennsylvania, Philadelphia PA, [2]Cleveland Clinic, Cleveland OH, [3]University of Virginia, Charlottesville VA, [4]Advanced Pathology Assoc., Rockville MD, [5]Miraca Life Science, Irving Tx, [6]Philips Digital Pathology Solutions, Best, The Netherlands, [7]University of Southern California Los Angeles, CA

BACKGROUND

Whole slide imaging (WSI), also known as digital pathology is an emerging technology. It involves the acquisition of images from stained tissue sections on glass slides. The images are converted into digital images that can be viewed on a monitor. Digital pathology can elevate collaboration between labs/specialists and allows easy consultation across distances. The digitized images can be archived and accessed in a moments time. The digital pathology platform (Philips Intellisite Pathology Solution) used in this study is intended for in vitro diagnostic use as an aid to the pathologist to view, review and diagnose digital images of surgical pathology slides. Before substituting the time-honored, familiar and versatile microscope with digital microscopy, several valid concerns need to be addressed. The most critical issue is whether pathologic diagnoses rendered using WSI are comparable to (i.e., non-inferior to) pathologic diagnoses made by optical microscopy. Although several studies comparing digital vs optical microscopy in diagnosis have been conducted, these studies have been single or small multicenter studies, sampling a single organ or lacking central adjudication. This large multi center non-inferiority study compares microscopy to WSI reads of 2000 surgical pathology cases from 20 different organ systems (54 subtypes) with 16 reading pathologists from 4 institutions.

OBJECTIVES

Primary objective:
- Demonstrate that diagnosing surgical pathology slides with a digital pathology platform was non-inferior to using an optical microscope.

Secondary objective
- Comparison of Manual Digital (MD) and Manual Optical (MO) discordance rates for organs, subtypes and pathologists.

METHODS

Retrospective blinded randomized non-inferiority study comparing MD to MO for primary diagnosis in surgical pathology.

Acceptance criteria
Digital microscopy would be declared non-inferior to the optical microscope if the upper bound of the 95% two-sided confidence interval for the overall MD – MO difference in major discordance rate (compared to the main diagnosis) was less than 4%.

Major discordance
A difference in diagnosis that would be associated with significant difference in patient management

CLINICAL STUDY DESIGN

- 4 Clinical sites
- 27 Pathologists for:
  - Case enrollment (4)
  - Validation (4)
  - Reading (16)
  - Adjudicating (3)
- 2,000 Cases
- 16,000 Reads:
  - 4 Pathologists per case
  - Read MO and MD
  - Wash out 4 weeks

Figure 1: Study design

Table 1. Cases included in the study by organ system

Study Site	Organ system	No of cases
1	Colorectal	150
	Urinary bladder	99
	Gynecologic	150
	Liver/bile duct, neoplastic	49
	Brain	60
	Total (site 1)	508
2	Prostate	299
	Lymph node	100
	Endocrine	100
	Kidney, neoplastic	50
	Salivary	50
	Total (site 2)	599

Study Site	Organ system	No Cases
3	Gastroesophageal junction	115
	Skin	177
	Hernia/peritoneal	7
	Gallbladder	10
	Appendix	10
	Soft tissue tumors	21
	Anus/perianal	50
	Total (site 3)	390
4	Breast	299
	Lung/bronchus/larynx/oral cavity/nasopharynx	95
	Stomach	99
	Total (site 4)	495
	Total for all four sites (full analysis set)	1992

RESULTS

Left CI	Average	Right CI
-0.91	0.35	1.00

Figure 2: Difference in major discordance rate digital - optical (%)

Figure 3: Difference major discordance rates (MD – MO) by organ

Figure 4: Difference major discordance rates (MD – MO) by reading pathologist

CONCLUSIONS

Manual Digital is non-inferior to Manual Optical for primary diagnosis in surgical pathology

Manual Digital is non-inferior to Manual Optical across a wide range of organ systems and pathologists

DISCLOSURE

This study was sponsored by Philips Digital Pathology Solutions

- Non-inferiority of WSI to glass slide for the same pathologist.
- Reproducible imaging within and between scanners for the same slide

Whole Slide Imaging Versus Microscopy for Primary Diagnosis in Surgical Pathology

A Multicenter Blinded Randomized Noninferiority Study of 1992 Cases (Pivotal Study)

Sanjay Mukhopadhyay, MD, Michael D. Feldman, MD, PhD,† Esther Abels, MSc,‡ Raheela Ashfaq, MD, MS,§ Senda Beltaifa, MD,‖ Nicolas G. Cacciabeve, MD,‖ Helen P. Cathro, MBChB, MPH,¶ Liang Cheng, MD,# Kumarasen Cooper, MBChB, DPhil, FRCPath,† Glenn E. Dickey, MD,‖ Ryan M. Gill, MD, PhD,** Robert P. Heaton, Jr, MD,‖ René Kerstens, MSc,‡ Guy M. Lindberg, MD,§ Reenu K. Malhotra, MD,§ James W. Mandell, MD, PhD,¶ Ellen D. Manlucu, MD,‖ Anne M. Mills, MD,¶ Stacey E. Mills, MD,¶ Christopher A. Moskaluk, MD, PhD,¶ Mischa Nelis, MSc,‡ Deepa T. Patil, MD,* Christopher G. Przybycin, MD,* Jordan P. Reynolds, MD,* Brian P. Rubin, MD, PhD,* Mohammad H. Saboorian, MD,§ Mauricio Salicru, MD,§ Mark A. Samols, MD, PhD,‖ Charles D. Sturgis, MD,* Kevin O. Turner, DO,§ Mark R. Wick, MD,¶ Ji Y. Yoon, MD,§ Po Zhao, MD, PhD,‖ and Clive R. Taylor, MD, PhD††*

Am J Surg Pathol • Volume 00, Number 00, ■■ 2017

The Philips FDA Clinical Trial in Perspective

- 1992 cases representing 20 organ systems
- Cases read as glass slides and by WSI by the same pathologists
- 4 reading sites with 4 reading pathologists per site
  - systematic errors where 4/4 were wrong with WSI
- 15,925 total reads
- Major discordance rate vs standard reference
  - WSI – 4.9%
  - Microscopy – 4.6%
  - Difference – 0.4% (-0.3-**1.01**%, 95% CI)
  - Non-inferiority cut-off – 4%

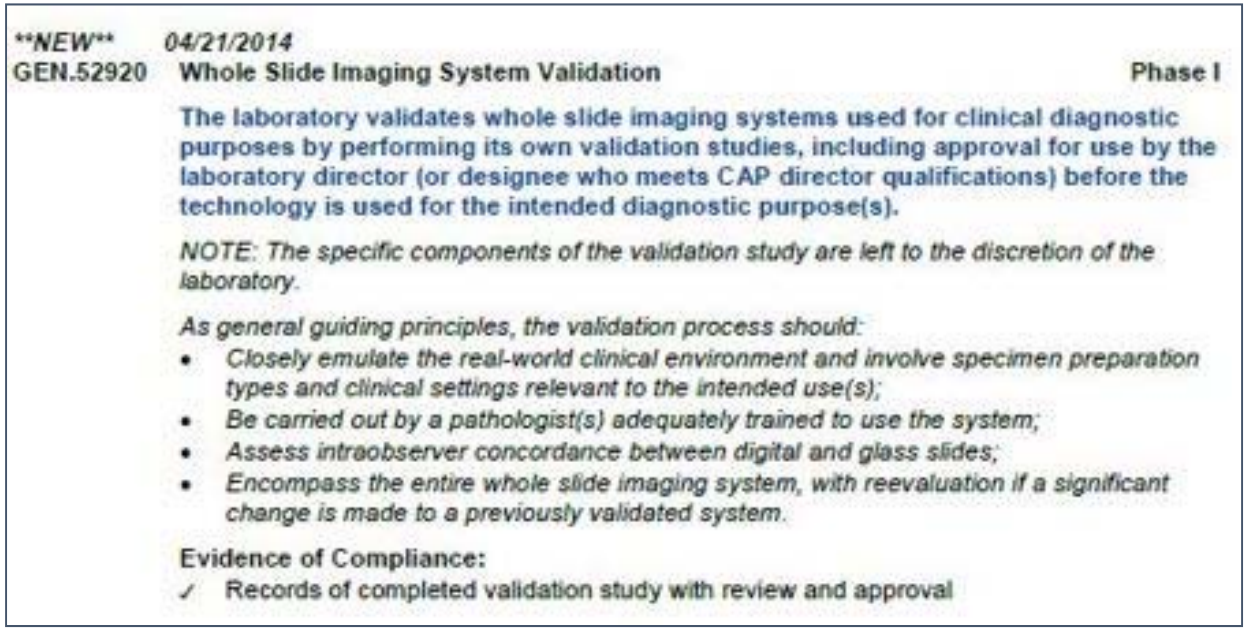
TABLE 3. Major Discordance Rates by Organ System: Microscopy Versus Reference Standard and WSI Versus Reference Standard

Major Discordance Rate	Between Microscopy and Reference Standard (%)	Between WSI and Reference Standard (%)
<1%	Peritoneal (0)	Peritoneal (0)
	Gallbladder (0)	Gallbladder (0)
	Appendix (0)	Appendix (0)
	Soft tissue (0)	Soft tissue (0)
	Stomach (0.5)	Lymph node (0.3)
	Lymph node (0.8)	Stomach (0.8)
1%-4.9%	Colorectal (1)	Peri(anal) (1)
	Kidney neoplastic (1)	Colorectal (1.7)
	Gastroesophageal junction (1.3)	Salivary gland (2)
	Peri(anal) (2)	Gastroesophageal junction (2)
	Salivary gland (3)	Kidney neoplastic (2.5)
	Respiratory (4.2)	Respiratory (3.5)
	Breast (4.3)	Breast (4.2)
	Skin (4.7)	Liver/bile duct (4.6)
	Endocrine (4.7)	Skin (4.9)
≥5%	Gynecologic (5.2)	Brain (6.2)
	Liver/bile duct (5.6)	Gynecologic (6.3)
	Brain (5.8)	Endocrine (6.5)
	Bladder (6.1)	Bladder (7.3)
	Prostate (11.3)	Prostate (12)

No systematic major discrepancies (diagnostic errors) attributable to WSI

Is There Still a Need to Validate WSI?

1. FDA trial had small numbers of certain cases (soft tissue tumours)
2. Pathologists will make accurate diagnoses for their intended use in their clinical environment
3. Identify limitations and risks to patient safety
4. It is a CAP LAP requirement



NEW *04/21/2014*

GEN.52920 **Whole Slide Imaging System Validation** **Phase I**

The laboratory validates whole slide imaging systems used for clinical diagnostic purposes by performing its own validation studies, including approval for use by the laboratory director (or designee who meets CAP director qualifications) before the technology is used for the intended diagnostic purpose(s).

NOTE: The specific components of the validation study are left to the discretion of the laboratory.

As general guiding principles, the validation process should:

- *Closely emulate the real-world clinical environment and involve specimen preparation types and clinical settings relevant to the intended use(s);*
- *Be carried out by a pathologist(s) adequately trained to use the system;*
- *Assess intraobserver concordance between digital and glass slides;*
- *Encompass the entire whole slide imaging system, with reevaluation if a significant change is made to a previously validated system.*

Evidence of Compliance:

✓ Records of completed validation study with review and approval

ARCHIVES
of Pathology & Laboratory Medicine

EARLY ONLINE RELEASE

April 30, 2018

US Food and Drug Administration Approval of Whole Slide Imaging for Primary Diagnosis

A Key Milestone Is Reached and New Questions Are Raised

Andrew J. Evans, MD, PhD; Thomas W. Bauer, MD, PhD; Marilyn M. Bui, MD, PhD; Toby C. Cornish, MD, PhD; Helena Duncan, BBA, MJ; Eric F. Glassy, MD; Jason Hipp, MD, PhD; Robert S. McGee, MD, PhD; Doug Murphy, MT (ASCP); Charles Myers, MD; Dennis G. O'Neill, MD; Anil V. Parwani, MD, PhD; B. Alan Rampy, DO, PhD; Mohamed E. Salama, MD; Liron Pantanowitz, MD

COLLEGE of AMERICAN PATHOLOGISTS
DIGITAL PATHOLOGY COMMITTEE

WSI Validation Guidelines

CAP Pathology and Laboratory Quality Center: 2010

- Pathology and Laboratory Quality Center, or “the CAP Center,” developed as a forum to author and maintain evidence-based guidelines and consensus statements.
- Ideas for guideline development are submitted by CAP members and committees

Systematic Review Process: June 2010 - April 2013

- Literature search :
  - 767 studies met search term requirements
  - 27 underwent data extraction for evidence
- Draft recommendations for open comment (July - Aug 2011)
  - 132 respondents; 531 comments
- Final result - 12 guideline statements published in 2013

2013: The 12 Guideline Statements

1. All labs implementing WSI for diagnostic purposes should carry out validation studies.

2. Appropriate for and applicable to the intended clinical use/setting.

3. Closely emulate the real-world clinical environment.

4. Include the entire WSI system (scanner, viewer and monitor).

5. Revalidate when a significant change is made to any component.

6. Pathologists adequately trained to use the WSI system should complete the validation. User training is not validation.

7. Should include a set of at least 60 cases for one specific application
   - *reflect spectrum and complexity of specimen types and diagnoses likely to be encountered*

8. Establish diagnostic concordance between digital and glass slides for the same observer (ie: intraobserver variability).
   - *acceptable pass/fail rate left to medical program directors.*

9. Digital and glass slides can be evaluated in random or nonrandom order.

10. Washout period of at least 2 weeks between digital and glass review.

11. Confirm all tissue present on a glass slide to be scanned is included in the digital image.

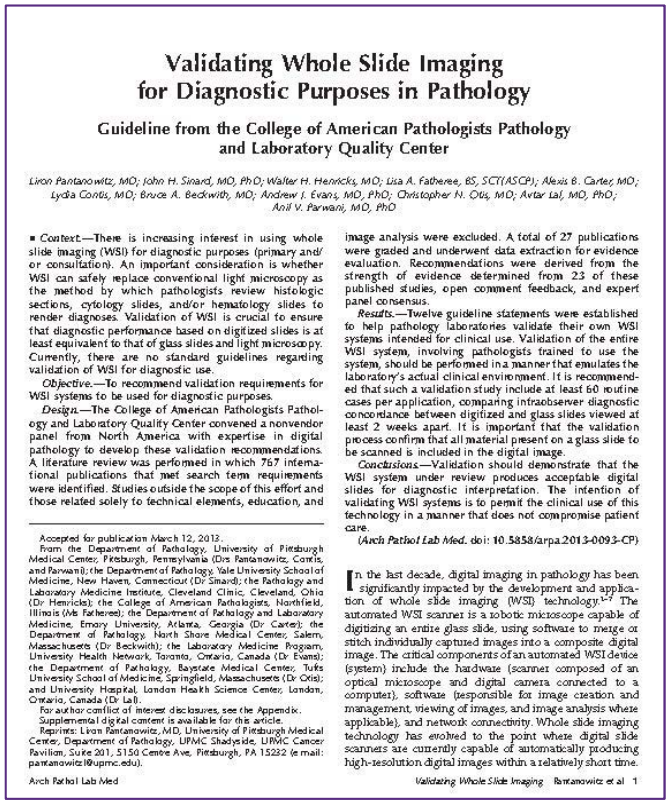
12. Documentation of methods, results and final approval.

2013 Guidelines: Miscellaneous Points

- Validation is NOT required for documenting/archiving cases reported by light microscopy

  - Consults where original slides are returned
  - Cases where a digital copy is created of a slide where tissue is removed for molecular analyses
  - Cases where original slides have been sent out for external review
  - Teaching files

Impact of 2013 Guideline



Validating Whole Slide Imaging for Diagnostic Purposes in Pathology

Guideline from the College of American Pathologists Pathology and Laboratory Quality Center

Liron Pantanowitz, MD; John H. Sinard, MD, PhD; Walter H. Henricks, MD; Lisa A. Fatheree, BS, SCT(ASCP); Alexis B. Carter, MD; Lydia Contis, MD; Bruce A. Beckwith, MD; Andrew J. Evans, MD, PhD; Christopher N. Otis, MD; Avtar Lal, MD, PhD; Anil V. Parwani, MD, PhD

• *Context.*—There is increasing interest in using whole slide imaging (WSI) for diagnostic purposes (primary and/or consultation). An important consideration is whether WSI can safely replace conventional light microscopy as the method by which pathologists review histologic sections, cytology slides, and/or hematology slides to render diagnoses. Validation of WSI is crucial to ensure that diagnostic performance based on digitized slides is at least equivalent to that of glass slides and light microscopy. Currently, there are no standard guidelines regarding validation of WSI for diagnostic use.

Objective.—To recommend validation requirements for WSI systems to be used for diagnostic purposes.

Design.—The College of American Pathologists Pathology and Laboratory Quality Center convened a nonvendor panel from North America with expertise in digital pathology to develop these validation recommendations. A literature review was performed in which 767 international publications that met search term requirements were identified. Studies outside the scope of this effort and those related solely to technical elements, education, and image analysis were excluded. A total of 27 publications were graded and underwent data extraction for evidence evaluation. Recommendations were derived from the strength of evidence determined from 23 of these published studies, open comment feedback, and expert panel consensus.

Results.—Twelve guideline statements were established to help pathology laboratories validate their own WSI systems intended for clinical use. Validation of the entire WSI system, involving pathologists trained to use the system, should be performed in a manner that emulates the laboratory's actual clinical environment. It is recommended that such a validation study include at least 60 routine cases per application, comparing intraobserver diagnostic concordance between digitized and glass slides viewed at least 2 weeks apart. It is important that the validation process confirm that all material present on a glass slide to be scanned is included in the digital image.

Conclusions.—Validation should demonstrate that the WSI system under review produces acceptable digital slides for diagnostic interpretation. The intention of validating WSI systems is to permit the clinical use of this technology in a manner that does not compromise patient care.

(*Arch Pathol Lab Med.* doi: 10.5858/arpa.2013-0093-CP)

In the last decade, digital imaging in pathology has been significantly impacted by the development and application of whole slide imaging (WSI) technology.[1–7] The automated WSI scanner is a robotic microscope capable of digitizing an entire glass slide, using software to merge or stitch individually captured images into a composite digital image. The critical components of an automated WSI device (system) include the hardware (scanner composed of an optical microscope and digital camera connected to a computer), software (responsible for image creation and management, viewing of images, and image analysis where applicable), and network connectivity. Whole slide imaging technology has evolved to the point where digital slide scanners are currently capable of automatically producing high-resolution digital images within a relatively short time.

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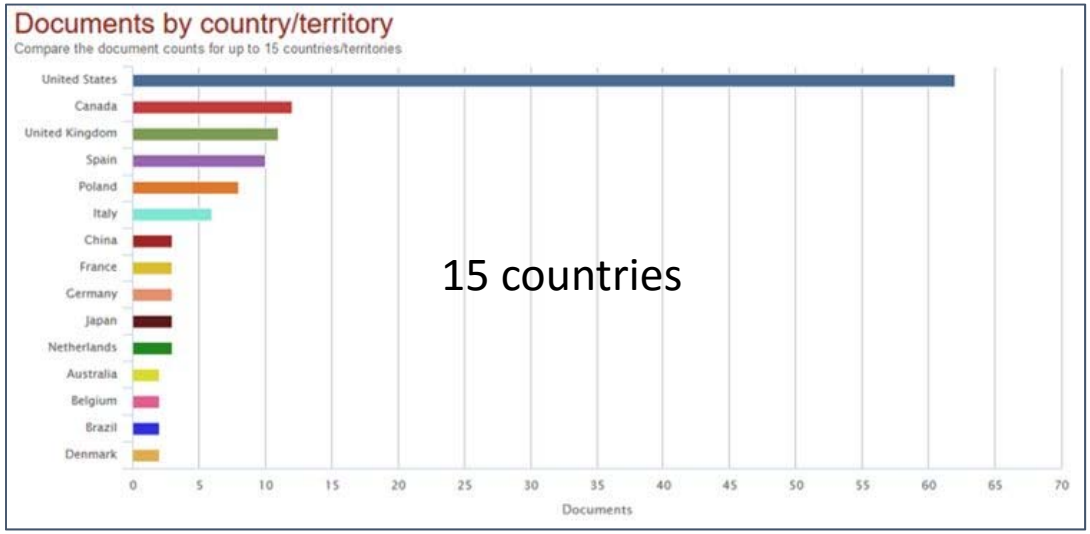
From the Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania (Drs Pantanowitz, Contis, and Parwani); the Department of Pathology, Yale University School of Medicine, New Haven, Connecticut (Dr Sinard); the Pathology and Laboratory Medicine Institute, Cleveland Clinic, Cleveland, Ohio (Dr Henricks); the College of American Pathologists, Northfield, Illinois (Ms Fatheree); the Department of Pathology and Laboratory Medicine, Emory University, Atlanta, Georgia (Dr Carter); the Department of Pathology, North Shore Medical Center, Salem, Massachusetts (Dr Beckwith); the Laboratory Medicine Program, University Health Network, Toronto, Ontario, Canada (Dr Evans); the Department of Pathology, Baystate Medical Center, Tufts University School of Medicine, Springfield, Massachusetts (Dr Otis); and University Hospital, London Health Science Center, London, Ontario, Canada (Dr Lal).

For author conflict of interest disclosures, see the Appendix.

Supplemental digital content is available for this article.

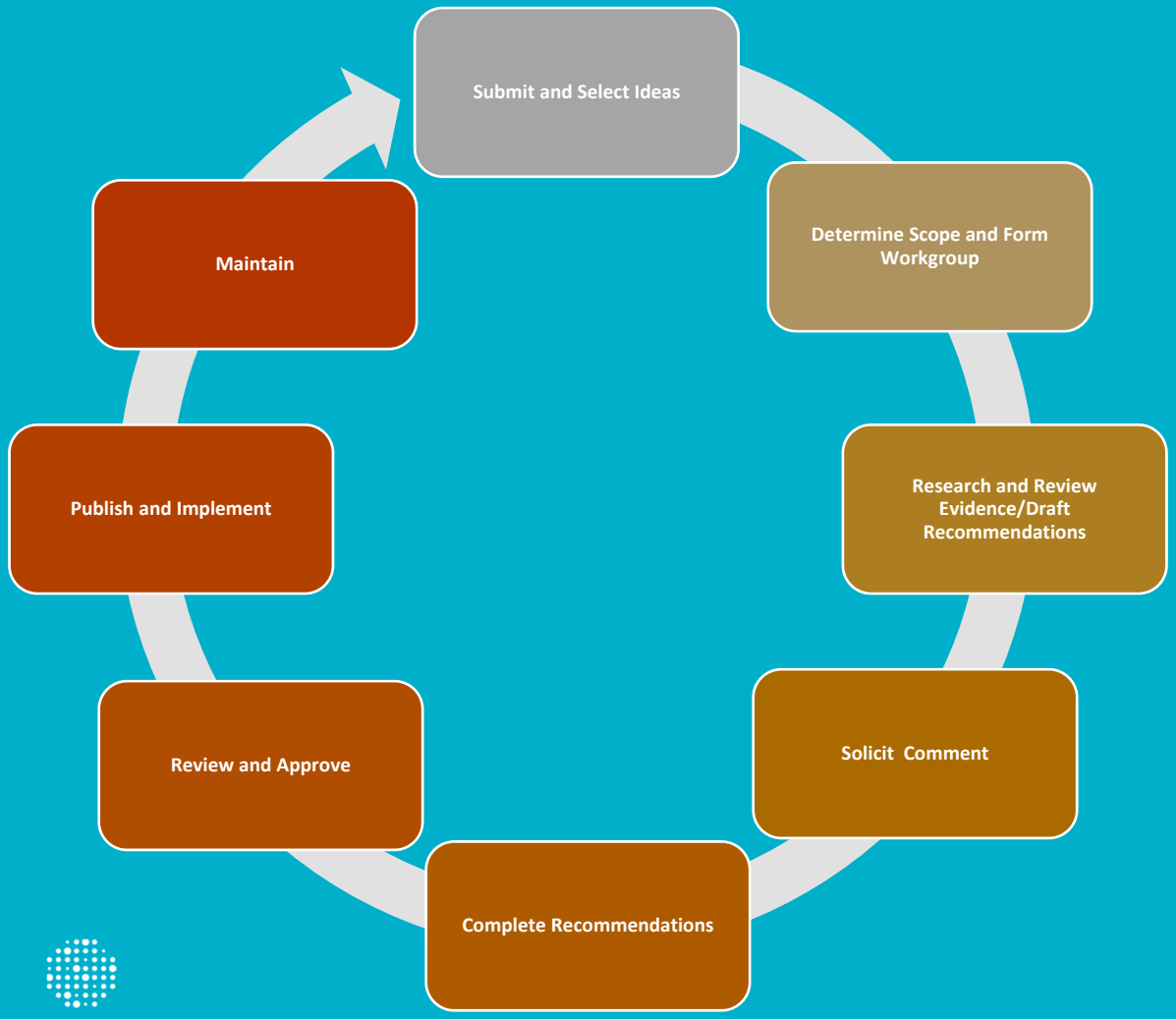
Reprints: Liron Pantanowitz, MD, University of Pittsburgh Medical Center, Department of Pathology, UPMC Shadyside, UPMC Cancer Pavilion, Suite 201, 5150 Centre Ave, Pittsburgh, PA 15232 (e-mail: pantanowitzl@upmc.edu).

- 10,886 pdf downloads
- 113 separate citations as of February 8, 2018
  - ✓ Narrative reviews – 33
  - ✓ Comparative studies – 21
  - ✓ Validation studies – 20
  - ✓ Conference papers – 8
  - ✓ Evaluation studies – 7
  - ✓ Editorials – 4



15 countries

CAP Center Guideline Life Cycle



- revise every 4 years
- revise at 2 years if significant new evidence

CAP

Netherlands: Hengelo and Utrecht

100% digital sign-out

LABPON

- East Netherlands
- 17 pathologists
- 55,000 surgicals/year

CAP WSI Guideline Update: Complete in 2019

- For the update, the panel will:
  - Determine if new questions should be addressed
  - Perform a systematic review of the literature
    - studies using the 2013 guideline
    - what worked, what did not
  - Reaffirm, alter, or sunset original recommendations
  - Develop new recommendations where appropriate

The Royal College of Pathologists
Pathology: the science behind the cure

Best practice recommendations for implementing digital pathology
January 2018

Authors: Simon Cross, Peter Furness, Laszlo Igali, David Snead, Darren Treanor

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Produced by	Simon Cross, Peter Furness, Laszlo Igali, David Snead and Darren Treanor on behalf of the Specialty Advisory Committee on Cellular Pathology.
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Comments	In accordance with the College's pre-publication policy, this document was on The Royal College of Pathologists' website for consultation from 12 May 2017 to 12 June 2017. Responses and authors' comments are available to view on request. **Dr Lorna Williamson** **Director of Publishing and Engagement**

The Royal College of Pathologists
4th Floor, 21 Prescot Street, London. E1 8BB
Tel: 020 7451 6700
Fax: 020 7451 6701
Web: www.rcpath.org

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Pathology: the science behind the cure

January 2018

- Validation is a self-led exercise (independent of regulatory approval (FDA, CE Mark, etc))
- Pragmatic design carried out in stages
  - training with practice and feedback
  - live validation cases - prospectively read by glass and WSI
  - ongoing quality control
- Assessing diagnostic concordance and pathologist confidence in glass vs WSI diagnoses
- Identifying and mitigating risks
- Several examples of validation slide sets by anatomic site

Summary of What We Covered

- Definitions and barriers to adoption of WSI for routine practice
- Why validate?
- Options for study design and endpoints
- Evidence from validation studies to date
- Regulatory approval for primary diagnosis - USFDA
- Guidelines for validation


Thank you!