Whole Slide Imaging Systems for Diagnostic Purposes in Pathology
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On behalf of the CAP Digital Pathology Validation Work Group

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www.cap.org
Participant in a Research Agreement with University of Pittsburgh and Omnyx
Increasing interest in using whole slide imaging (WSI) for diagnostic purposes in pathology.

**Question:** Can WSI replace conventional light microscopy as the method by which pathologists review histologic sections and/or cytology 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. [Validation requires checking that a system fulfills its intended purpose]

**What needs to be done to ‘validate’ a WSI system before it is placed in clinical service?**

No current standardized guidelines regarding validation of WSI for diagnostic use & limited validation studies have been published using WSI.

**FDA convened a panel hearing in October 2009 that focused on regulating WSI systems used for primary pathologic diagnosis. Vendors are continuing to work with FDA for regulatory discussions.**
INTRODUCTION

• CAP developed the Pathology and Laboratory Quality Center ("the CAP Center") as a Work Group forum to author and maintain evidence-based guidelines and consensus statements.

• In Spring 2010, the CAP Center convened a non-vendor panel from North America with expertise in digital pathology.

OBJECTIVE:

• To develop recommendations for validating WSI systems used for diagnostic use in Pathology.

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METHODS

- **Data sources** for recommendations derived from:
  - Panel consensus
  - Extensive literature review:
    - 611 international studies (2001-2011).
    - Publications from USA (54%) & Europe (42%).
    - 24 reviewed in detail & graded.
- **13 STATEMENTS** developed to assist the pathology community with validating WSI for clinical diagnostic use.

**Public Comment:**
- Statements were made publically available online from July 22, 2011 through August 21, 2011.
- An announcement was sent to the CAP, ASCP, ADASP, API, DPA, IADP, APC, CAP-APC & FDA.
- Website received 508 visits with 531 comments in total.
- Most respondents agreed with these statements.
STATEMENT #1

• All institutions or practices considering the implementation of WSI technology for clinical diagnostic purposes must carry out their own validation study.
Statement 1: All institutions or practices considering the implementation of WSI technology for clinical diagnostic purposes must carry out their own validation study.

BACKGROUND

• Will WSI systems work as intended in all laboratories, permitting true (valid) primary diagnoses to be made using digitized slides?

• Variables between institutions can affect performance.

• If each institution/practice considering the implementation of WSI technology performs its own validation of a WSI system prior to clinical use, this should provide reasonable assurance that these systems are performing as anticipated in its setting.
Statement 1: All institutions or practices considering the implementation of WSI technology for clinical diagnostic purposes must carry out their own validation study.

Number Respondents

124

Agreement

87%

Working Group Recommendation

Revise with minor language
Statement 1: All institutions or practices considering the implementation of WSI technology for clinical diagnostic purposes must carry out their own validation study.

DISCUSSION

• Change “institutions or practices” to “pathology laboratories”.
• Manufacturer device validation (i.e. verification) alone is insufficient.
• Simple guidelines that were provided for cytology screening devices (which were FDA approved) will not suffice.
STATEMENT #2

• Validation for each diagnostic application is necessary (e.g. reading frozen section slides, reviewing immunohistochemistry slides, etc.).

• WSI should not be used for clinical purposes other than the one validated, unless separate validation for that purpose is undertaken.
Statement 2: Validation for each diagnostic application is necessary. WSI should not be used for clinical purposes other than the one validated, unless separate validation for that purpose is undertaken.

BACKGROUND

• Validation should be appropriate for & applicable to the intended clinical use & clinical setting of the application in which WSI will be employed.

• Foreexample:
  o A validation study used to support the diagnostic use of digitized slides for routine surgical pathology may not necessarily apply to the use of frozen section digitized slides (e.g., with tissue folds, more pale staining, more mounting medium, etc.).
Statement 2: Validation for each diagnostic application is necessary. WSI should not be used for clinical purposes other than the one validated, unless separate validation for that purpose is undertaken.

**Number Respondents**

139

**Agreement**

81%

**Working Group Recommendation**

Revise with minor language
Statement 2: Validation for each diagnostic application is necessary. WSI should not be used for clinical purposes other than the one validated, unless separate validation for that purpose is undertaken.

**DISCUSSION**

- Unclear which “diagnostic application” requires separate validation & concern that these would be onerous to perform.

- A validation process may broadly cover a group/subtypes as long as the overall process of preparation and interpretation is the same.

- For example:
  - For IHC validate digital image captures expected chromophobe colors, intensity & localization adequately
  - Each & every single IHC stain does not have to be individually validated as long as it falls under the same diagnostic application

- If a new intended use for WSI is contemplated, & this new use differs materially from the previously validated use, a separate validation for the new use should be performed.
STATEMENT #3

- The validation study should closely emulate the real-world clinical environment (e.g. include the same workflow process, equipment, etc.)
Statement 3: The validation study should closely emulate the real-world clinical environment.

BACKGROUND

- Goal of validation:
  - Conducted in a manner that mimics how WSI will be used in the specific lab’s work environment
  - Institution-specific workflow should be employed
  - Mimic how the system is to actually be used after “go live”
Statement 3: The validation study should closely emulate the real-world clinical environment.

Number Respondents
136

Agreement
91%

Working Group Recommendation
Revise with minor language
Statement 3: The validation study should closely emulate the real-world clinical environment.

DISCUSSION

• Take into account the system’s intended use at the institution doing the validation.

• Foreexample:
  o If rapid digitization of glass slides is required for clinical use (e.g. frozen sections), then timely preparation & reading of WSI should be included in the validation process.
  o Validation of multi-part specimens may be required if this reflects true clinical practice.
STATEMENT #4

• Validation of the entire WSI system should be performed. It is not necessary to separately validate each individual component (e.g., computer hardware, monitor, network, scanner) of the system nor the individual steps of the digital imaging process.
Statement 4: Validation of the entire WSI system should be performed. It is not necessary to separately validate each individual component of the system nor the individual steps of the digital imaging process.

BACKGROUND

• WSI system is made up of different components: scanner, hardware, software, network & viewing monitor (+pathologist).

• Parameters of each of component may impact digital image quality and therefore interpretation:
  o Workstation display (e.g. monitor size, settings, resolution, luminance, etc.)
  o Computer (e.g. processing speed, video card, memory, etc.)
  o Network (e.g. bandwidth, firewalls, etc.)

• Imaging process involves several steps including image acquisition, storage, sharing & viewing.

• Recommend the entire WSI system & imaging process be validated.
Statement 4: Validation of the entire WSI system should be performed. It is not necessary to separately validate each individual component of the system nor the individual steps of the digital imaging process.

Number Respondents

136

Agreement

89%

Working Group Recommendation

Revise with minor language
Statement 4: Validation of the entire WSI system should be performed. It is not necessary to separately validate each individual component of the system nor the individual steps of the digital imaging process.

DISCUSSION

• The validation study should encompass the entire WSI system.

• All components are important & should not be separated, including:
  o Technical system (“tool”)
  o Observer (“pathologist”)
STATEMENT #5

- A pathologist adequately trained to use the WSI system must be involved in the validation process.
Statement 5: A pathologist adequately trained to use the WSI system must be involved in the validation process.

**BACKGROUND**

- Validation process should include individual(s) who will actually be using the system to make diagnoses.
- Published validation studies: Average # evaluators = 8 individuals/study (range, 3 - 26 persons).
- Validation team may include other pathology staff (e.g. image technician, histotechnologists, PA), IT personnel and/or consultants.
Statement 5: A pathologist adequately trained to use the WSI system must be involved in the validation process.

Number Respondents

129

Agreement

91%

Working Group Recommendation

Revise with minor language
Statement 5: A pathologist adequately trained to use the WSI system must be involved in the validation process.

DISCUSSION

• Essential that validation include one or more pathologists.
• Validation need not involve all pathologists that use the WSI system.
• User training is important, but not part of validation.
• Training methods are outside of the scope of this document.
STATEMENT #6

- Validation of WSI systems should involve specific types of specimens and their preparations (e.g., fixed versus frozen tissue, cytology slides, hematology blood smears), but not specific tissues, diseases, microscopic changes or diagnoses.
**Statement 6:** Validation of WSI systems should involve specific types of specimens and their preparations, but not specific tissues, diseases, microscopic changes or diagnoses.

**BACKGROUND**

- Different specimen types (e.g., tissue biopsy, cytology smear) & their slide preparation (e.g., fixed vs. frozen tissue) may require different WSI capabilities in order for a pathologist to make a primary diagnosis.
  - For example, FS slides need to be validated separately from routine surgical pathology slides as the slide/tissue/staining quality is often very different.

- We do not recommend that specific tissue types, diseases, microscopic changes or diagnoses be individually validated.
Statement 6: Validation of WSI systems should involve specific types of specimens and their preparations, but not specific tissues, diseases, microscopic changes or diagnoses.

Number Respondents

126

Agreement

84%

Working Group Recommendation

Revise with minor language
Statement 6: Validation of WSI systems should involve specific types of specimens and their preparations, but not specific tissues, diseases, microscopic changes or diagnoses.

DISCUSSION

- Validation of WSI systems should:
  - Involve specimen preparation types relevant to intended use
  - Not specific organ systems, diseases, microscopic changes or diagnoses.
STATEMENT #7

- The validation process should include a sample set of approximately 100 cases that reflects the spectrum & complexity of specimen types and diagnoses likely to be encountered during routine operation.
Statement 7: The validation process should include a sample set of approximately 100 cases that reflects the spectrum and complexity of specimen types and diagnoses likely to be encountered during routine operation.

**BACKGROUND**

- Important that an adequate sample size be used.
  - Allow pathologists to negotiate any technology learning curve.
    - [Learning curve = time for pathologist to become facile with WSI]
- Literature: Average 92 cases/ study (range 10 to 633 cases).
- Number of cases chosen not based on statistical calculation
- Test sample must include case mix that reflects both the spectrum of diagnoses & complexities encountered during routine operation.
**Statement 7:** The validation process should include a sample set of approximately 100 cases that reflects the spectrum and complexity of specimen types and diagnoses likely to be encountered during routine operation.

**Number Respondents**

129

**Agreement**

73%

**Working Group Recommendation**

Discussion in Progress
Statement 7: The validation process should include a sample set of approximately 100 cases that reflects the spectrum and complexity of specimen types and diagnoses likely to be encountered during routine operation.

**DISCUSSION**

- **Number based on published data & consensus (not statistical rigor).**
  - Biostatistician consulted

- **Considering differentiating # cases needed by factoring in the breadth of what is being done (e.g. organ system & slide preparation type).**
  - *Foreexample:* $\#$ organ systems x single (20)/multiple (30) preparation types = $\#$ cases to validate (in no case should this be $>$ 100)

<table>
<thead>
<tr>
<th># Organ Systems</th>
<th>Single Preparation Type (e.g. frozen only, smears only, liquid cytology only, etc.)</th>
<th>Multiple preparation types</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>60</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>5 or more</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Special stains only</td>
<td>20</td>
<td>N/A</td>
</tr>
<tr>
<td>IHC stains only</td>
<td>20</td>
<td>N/A</td>
</tr>
</tbody>
</table>

- **Multiple scanners will likely have to be validated (e.g. 3 scanners + X cases).**
STATEMENT #8

- Digital and glass slides should be evaluated in random order to minimize order effect.
Statement 8: Digital and glass slides should be evaluated in random order to minimize order effect.

BACKGROUND

• Some believe that digital slides should be viewed before glass slides - considered the gold standard for making diagnoses.

• Order of viewing virtual vs. glass slides has been shown not to affect interpretation (Koch LH et al. Human Pathol 2009; 40:662–7).

• Nevertheless, if the order of case evaluation is randomized it may help minimize order effect (i.e. confounding of validation results).

• To accomplish this, both the order in which the cases are presented and the order of the modalities (glass vs. digital) utilized should be randomized.
Statement 8: Digital and glass slides should be evaluated in random order to minimize order effect.

Number Respondents

136

Agreement

81%

Working Group Recommendation

Discussion in Progress
Statement 8: Digital and glass slides should be evaluated in random order to minimize order effect.

DISCUSSION

• For clarification, randomization should occur during validation.
STATEMENT #9

• A washout period of approximately 3 weeks should occur between viewing digital and glass slides.
Statement 9: A washout period of approximately 3 weeks should occur between viewing digital and glass slides.

BACKGROUND

• **Washout period** = time interval between viewing the same case/slide using a different (glass or digital) modality.

• **Important to take into consideration:**
  o Pathologists may recall pathologic images for lengthy periods after reviewing a case
  o With very long washout periods a pathologist’s experience and/or diagnostic criteria could change over time
Statement 9: A washout period of approximately 3 weeks should occur between viewing digital and glass slides.

Number Respondents

128

Agreement

68%

Working Group Recommendation

Discussion in Progress
**Statement 9:** A washout period of approximately 3 weeks should occur between viewing digital and glass slides.

**DISCUSSION**

- Varied responses (too short/too long/not necessary/provide range)

- Insufficient evidence to support exactly 3-week period (only 1 paper by Jukic et al Arch Pathol Lab Med 2011; 135:372-8).

- Until further published evidence, pathologists involved in validating WSI technology should decide on a washout period practical for their purposes.
STATEMENT #10

• The validation process should ensure that all of the material present on a glass slide, or purposefully selected area(s) on a slide to be scanned, are included in the digital image.
**Statement 10:** The validation process should ensure that all of the material present on a glass slide, or purposefully selected area(s) on a slide to be scanned, are included in the digital image.

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**BACKGROUND**

- WSI is produced by scanning an entire area of a glass slide.
- Accurate digital reproductions of scanned glass slides is required if they are to be used for diagnostic use.
- Therefore, it is important that the validation process make sure that all material on a glass slide needed to make a diagnosis is present in the digital image to be used for this diagnostic purpose.
**Statement 10:** The validation process should ensure that all of the material present on a glass slide, or purposefully selected area(s) on a slide to be scanned, are included in the digital image.

**Number Respondents**

134

**Agreement**

94%

**Working Group Recommendation**

Discussion in Progress
**Statement 10:** The validation process should ensure that all of the material present on a glass slide, or purposefully selected area(s) on a slide to be scanned, are included in the digital image.

**DISCUSSION**

- Delete “or purposefully selected area(s) on a slide to be scanned”, as several commenters took exception to this phrase.
STATEMENT #11

• Measurable outcomes should establish diagnostic concordance between digital and glass slides for the same observer (i.e., intraobserver variability).
Statement 11: Measurable outcomes should establish diagnostic concordance between digital and glass slides for the same observer (i.e., intraobserver variability).

**BACKGROUND**

- Publications report a good concordance rate for diagnoses made with WSI vs. glass slides – range 63% to 98%.
- **Aim:** Evaluate the technology, not agreement between pathologists.
  - e.g. Breast ADH or Prostate ASAP vs. adenocarcinoma (disagreement)
- Therefore, we recommend:
  - **Measure** intra-pathologist diagnostic reproducibility (i.e. is the pathologist able to reach the same diagnosis with both modalities?)
  - **Do not measure** their diagnosis compared to other pathologists/experts/consensus (i.e. interobserver variability).
Statement 11: Measurable outcomes should establish diagnostic concordance between digital and glass slides for the same observer (i.e., intraobserver variability).

Number Respondents

134

Agreement

86%

Working Group Recommendation

Discussion in Progress
Statement 11: Measurable outcomes should establish diagnostic concordance between digital and glass slides for the same observer (i.e., intraobserver variability).

**DISCUSSION**

- Change “Measurable outcomes..” to “The validation study..”
- Acknowledge baseline intraobserver variability even with glass slides.
STATEMENT #12

- Approval of WSI systems should be limited to the conditions under which validation occurred.
- Revalidation is required whenever a significant change is made to any component of the WSI system.
Statement 12: Approval of WSI systems should be limited to the conditions under which validation occurred. Revalidation is required whenever a significant change is made to any component of the WSI system.

BACKGROUND

• Significant changes to a WSI system may affect the interpretation of digital slides.
  o e.g. new scanner, major hardware or software upgrade

• For major changes the validation process should be repeated:
  o With these new changes incorporated in the WSI system
  o To demonstrate that it can still be employed for the intended use

• Minor changes can be managed through a facilities change management procedure.
Statement 12: Approval of WSI systems should be limited to the conditions under which validation occurred. Revalidation is required whenever a significant change is made to any component of the WSI system.

Number Respondents

127

Agreement

85%

Working Group Recommendation

Discussion in Progress
**Statement 12:** Approval of WSI systems should be limited to the conditions under which validation occurred. Revalidation is required whenever a significant change is made to any component of the WSI system.

**DISCUSSION**

- Revalidation should be flexible & reasonable with the intent of assuring that changes in the system do not negatively impact on the performance of the system & the ability to interpret the image.
STATEMENT #13

• Documentation should be maintained recording the method, measurements and final approval of validation for the WSI system to be used in the clinical laboratory.
**Statement 13:** Documentation should be maintained recording the method, measurements and final approval of validation for the WSI system to be used in the clinical laboratory.

**BACKGROUND**

- **Documentation provides confirmation that a WSI system has been validated for clinical diagnostic use [when operated within established parameters].**
**Statement 13:** Documentation should be maintained recording the method, measurements and final approval of validation for the WSI system to be used in the clinical laboratory.

**Number Respondents**

135

**Agreement**

97%

**Working Group Recommendation**

Discussion in Progress
**Statement 13:** Documentation should be maintained recording the method, measurements and final approval of validation for the WSI system to be used in the clinical laboratory.

**Discussion**

- Include documentation of user training.
- Final approved by lab medical director or designee.
OPEN STATEMENT

• Are there other criteria that should be included in the validation process?
Open Statement: Are there other criteria that should be included in the validation process?

- **Checklists**
  - Independent of LAP

- **Image analysis**
  - Separate CAP project
CONCLUSION

• These practice guidelines & consensus statements reflect the best available evidence & majority expert agreement supported in practice.

• These guidelines are intended to improve the clinical use of WSI by:
  o Provide assurance that these digital tools are used properly
  o That they are used for their intended clinical use (i.e. to make accurate primary diagnoses)
  o Reduce the potential risk of misdiagnosis attributed to this technology

• Final (modified) statements will be published as a manuscript in the Archives of Pathology and Laboratory Medicine.

• As WSI systems & their applications continually evolve so to may validation procedures.