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## **STATEMENT**

by the

**College of American Pathologists**

**On Public Health Issues Related to the Use of Whole Slide Digital  
Imaging for Diagnostic Surgical Pathology**

**Before the FDA's Hematology and Pathology Devices Advisory  
Committee**

**October 2009**

The College of American Pathologists (CAP) appreciates the opportunity to address the FDA's Hematology and Pathology Devices Advisory Committee on public health issues related to the use of whole slide digital imaging systems in diagnostic surgical pathology. The CAP is a national medical specialty society representing more than 17,000 physicians who practice pathology. CAP members practice medicine in community hospitals, academic medical centers, clinical laboratories, and federal and state health facilities. CAP members and professional staff who contributed to this statement have no financial interest in the matter being addressed.

### State of Digital Pathology Today and Its Potential

Use of whole slide digital imaging systems has important implications for the delivery of health care, and is nearing an inflection point, as it moves from educational and research applications to primary clinical diagnosis. Whole slide digital imaging systems have the potential to expand access to specialist consultations, provide access to underserved areas, and promote sharing of images when only a small amount of diagnostic material exists.

### Guiding Principle

The guiding principles in evaluating the use of whole slide digital imaging systems as a tool should be ensuring quality and safety. The College is supportive of any new medical

technology that has been credibly shown to demonstrate equivalence or superiority to existing technologies in the delivery of care to patients.

### Recommended Scope of Review

Whole slide digital imaging systems are proposed as tools used in the process of establishing a clinical diagnosis. Establishing a clinical diagnosis is a comprehensive process that involves gross examination and specimen dissection, tissue selection for histological processing, review of one or more slides, determining which low-power fields of view require examination at higher magnifications, correlation with clinical history and the findings of radiological and other studies, and performance of ancillary pathological studies as required. The Agency's examination of whole slide digital imaging systems should focus on use of the tool in the context of how a diagnosis is rendered in clinical practice to the extent that a whole slide digital imaging device is intended to supplant traditional microscopy.

### Potential Public Health Implications for Not Establishing Proper Validation

Any diagnostic inaccuracy or imprecision introduced by a digital whole slide imaging system has the potential to adversely affect the clinical care of many Americans. Even slight differences between whole slide digital imaging systems and conventional microscopes could result in significant excess mortality and morbidity. For example, there are approximately 600,000 breast biopsies conducted annually in the U.S. If the use of whole slide digital imaging systems increases diagnostic error rates by only 1%, an additional 6,000 patients will be misdiagnosed. Breast cancer misdiagnosis will adversely affect the health of biopsied women and adversely impact cancer research designed to benefit future generations.

### Key Validation Issues and Challenges

CAP recommends the Agency use a non-inferiority model to study whole slide digital imaging systems. The validation protocol should focus on how whole slide digital imaging systems impact *intra-pathologist variability*, rather than the impact on the accuracy of the diagnosis. Specifically, the protocol should focus on measuring whether the diagnosis arrived at using whole slide digital imaging systems is the same as the diagnosis arrived at by the same pathologist using conventional microscopy, and to compare any variability with intra-pathology variability seen with replicate use of a conventional microscope

In determining how to validate whole slide digital imaging systems, the College urges the FDA to consider the factors described below, among others. These criteria are important especially because FDA approval of a digital imaging system for primary diagnosis for a specific tissue application (e.g., examination of single-slide breast specimens) may result in significant off-label use of such systems for specimen types for which the system has not been adequately studied.

*Test conditions:*

Validation of digital whole slide imaging systems is likely to be particularly sensitive to the test conditions under which systems are examined. The research validation environment should be made as similar as possible to a clinical environment. Since multiple slides are typically reviewed as part of the existing diagnostic process using traditional microscopy, all slides from each case using each modality should be compared rather than pre-selected “representative” slides, to simulate the real-world clinical environment. The training of microscopists on whole slide digital imaging systems should be documented, as well as the prior experience with conventional light microscopy, and approval of systems should be limited to the conditions under which validation occurred.

*Sample size:*

An adequate sample size for a validation study is essential to determining whether the use of a digital whole slide imaging system for a particular clinical application is safe. Given the high-diagnostic concordance among experienced pathologists for many types of specimens and diagnoses, a large sample size will be required to provide adequate statistical power to detect small performance differences that could result in significant morbidity and mortality.

*Specimen types:*

Primary diagnosis of different types of specimens requires different capabilities, and validation procedures should be specific for the intended specimen types. For example, the Z-axis (i.e., depth of field) is important for some clinical specimens (e.g., aspirate smears and in cases of suspected amyloid birefringence in tissue), but is not as significant for other specimen types. For some tissue specimens (e.g., breast specimens) polarization microscopy may be required to identify certain types of calcification; for other specimen types, polarization is not required. Approval of whole slide digital imaging systems should be specific for specimen type, not specific diagnoses.

*Diagnostic spectrum:*

Clinical diagnosis involves the assignment of one or more diagnostic labels and an assessment of specimen adequacy. For some diagnoses (such as the diagnosis of invasive breast carcinoma), ancillary (“secondary”) diagnostic attributes must also be assigned (e.g., tumor size and histologic grade). It is important that whole slide digital imaging systems be validated with a challenge set that reflects the spectrum of diagnostic labels and secondary measures that are assigned in practice. CAP is ready to work with the FDA to specify important diagnostic labels and secondary measures pertinent to individual specimen types.

*Additional considerations:*

- Validation protocols should account for the fact that participants may recall histologic images for weeks after reviewing a case. Explicit analytic procedures should be employed to ensure that multiple assessments by the same microscopist are independent (i.e., intra-individual).

- Image compression, focusing protocols, scanning resolution, display screen resolution, bandwidth considerations, and section selection itself (thin and flat vs thick and uneven) impact digital image quality.<sup>1</sup> For some diagnoses, minor changes in image quality may obscure delicate nuclear grooves or weak immunohistochemistry staining and pivotally alter diagnostic interpretation. Technical conditions used to validate whole slide digital imaging systems should be specified and included as minimal conditions for approved use.
- The validation issues listed above are not the only factors that the Agency will need to examine in reviewing whole slide digital imaging products submitted for Agency clearance. For example, the ability of whole slide digital imaging systems to adequately archive and retain data will be necessary to ensure compliance with CLIA-mandated record retention requirements.

### Conclusion

The College looks forward to working with the FDA as the Agency evaluates whole slide digital pathology image systems for primary diagnosis and other applications. In the coming months, we plan to further develop our policy and look forward to sharing our emerging scientific consensus with the Agency.

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<sup>1</sup> Weinstein, SR et al, Overview of Telepathology, Virtual Microscopy, and Whole Slide Imaging: Prospects for the Future. Hum Pathol 2009; 40: 1057-1069