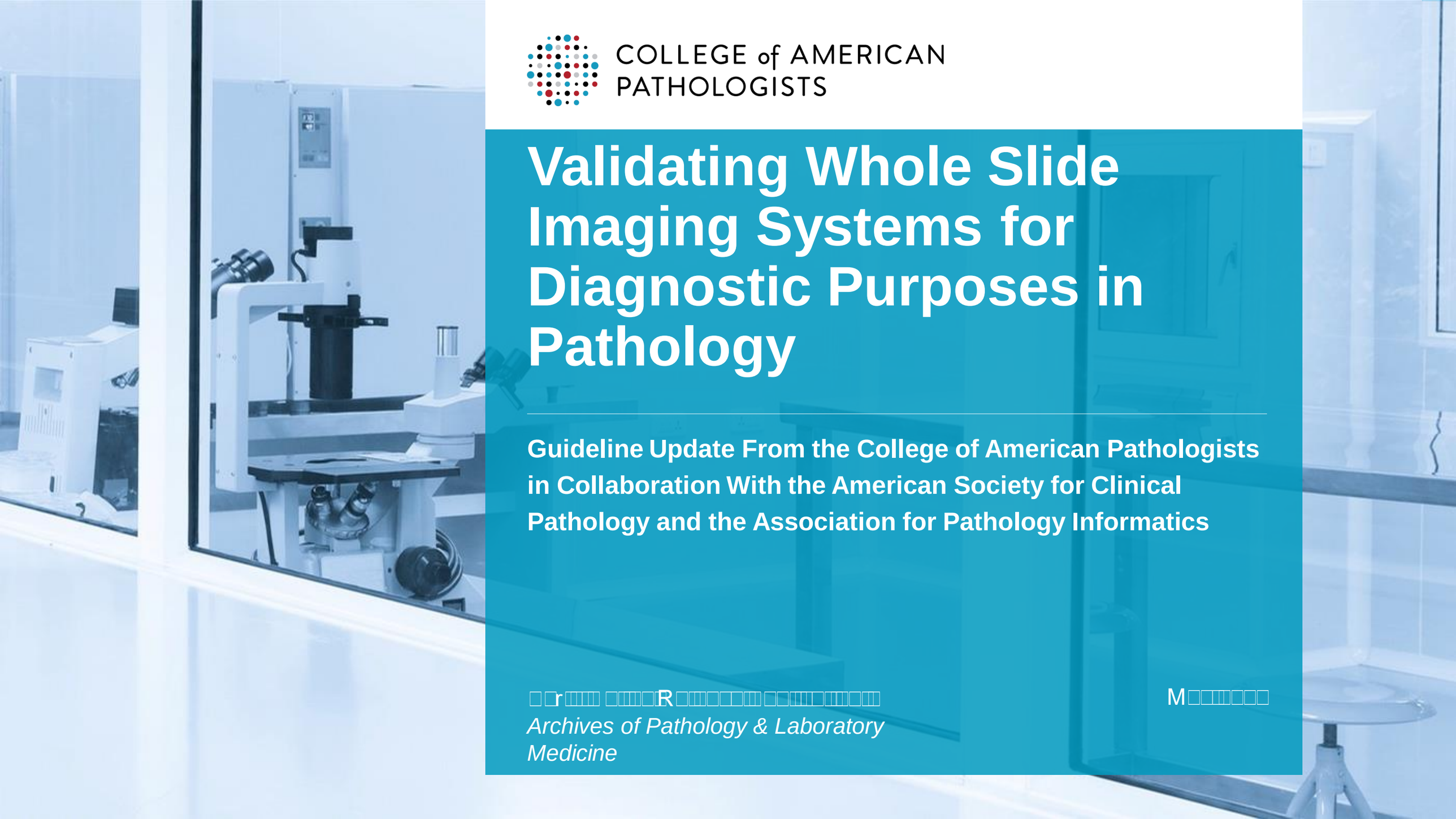


COLLEGE of AMERICAN PATHOLOGISTS

Validating Whole Slide Imaging Systems for Diagnostic Purposes in Pathology

Guideline Update From the College of American Pathologists in Collaboration With the American Society for Clinical Pathology and the Association for Pathology Informatics

Archives of Pathology & Laboratory Medicine

Outline

Introduction

- In 2013, the Pathology and Laboratory Quality Center for Evidence-based Guidelines (the Center) of the College of American Pathologists (CAP) released a guideline on the validation of whole slide imaging (WSI) for diagnostic purposes.
- At that time, no guidelines existed to help laboratories understand how to validate WSI.
- Following a systematic review of the literature, 12 guideline statements were offered – this included recommendations and expert consensus opinions.

Introduction, continued

- According to standards set by the National Academy of Medicine, guidelines should be assessed regularly and updated when new evidence suggests the need for modifications.
- In 2018, the Center formed an expert panel to review new literature and evaluate the original recommendations using the Grading of Recommendations Assessment Development and Evaluation (GRADE) approach.

Results

- **In its 2021 update, three recommendations and nine good practice statements were developed to answer the key question “what should be done to validate a whole slide digital imaging system for diagnostic purposes before it is placed in clinical service?”**

Guideline Recommendations

Recommendation 1

The validation process should include a sample set of at least 60 cases for one application, or use case, (e.g., Hematoxylin and Eosin [H&E] stained sections of fixed tissue, frozen sections, hematology) that reflect the spectrum and complexity of specimen types and diagnoses likely to be encountered during routine practice. Note: the validation process should include another 20 cases to cover additional applications such as immunohistochemistry or other special stains if these applications are relevant to an intended use and were not included in the 60 cases mentioned above.

Strong Recommendation

Rationale

- **The expert panel believes that the number of cases being evaluated should:**
  - **Allow pathologists to establish trust in diagnoses made using WSI,**
  - **Identify and mitigate risks associated with the technology,**
  - **Strike a balance in terms of the amount of time and resources required to complete the validation process**

Rationale, continued

- 32 studies from the systematic review informed this recommendation
- 60 cases was determined from a systematic review of published validation studies showing concordance between WSI and glass slide diagnoses is not improved or worsened when sets of more than 60 cases are used.
- See Table 3 and Figure 1 of the WSI guideline update manuscript.
- During the open comment period, 94.6 % (105/111 respondents) either agreed with the recommendation as written or agreed with minor suggested modifications.

Recommendation 2

The validation study should establish diagnostic concordance between digital and glass slides for the same observer (i.e., intraobserver variability). If concordance is less than 95%, laboratories should investigate and attempt to remedy the cause.

Strong Recommendation

Rationale

- **The central question to be addressed is whether the same pathologist makes the same interpretation of a given case regardless of whether it is reviewed by WSI or as glass slides.**
- **Ideally, 100% concordance (or 0% discordance) is desired; however, this does not reflect the subjective nature of pathology as practiced with glass slides where inter- and intraobserver variability is an established reality.**

Rationale, continued

- **The weighted mean percent concordance across the 33 studies that informed this recommendation in our systematic review was 95.2%.**
  - **Discordance between WSI and glass slides was reported in 24 studies, of which five classified the discordance as minor (average rate of 4.2%) and seven classified the discordance as major (average rate of 4.2%)**
- **95% should not be considered a pass/fail mark**
  - **< 95% concordance is below average based on available literature**
  - **All discordances should be reconciled with respect to types of problematic cases, scanner and/or histology issues and pathologist factors**
- **During the open comment period, 94% (104/111 respondents) either agreed with the recommendation as written or agreement with minor suggested modifications.**

Recommendation 3

A washout period of at least two weeks should occur between viewing digital and glass slides.

Strong Recommendation

Rationale

- This recommendation is intended to address the issue of recall bias when cases are reviewed by two different modalities by the same observer.
- A total of 14 studies from the systematic review addressed length of a wash-out period on intraobserver concordance between glass slide and WSI diagnoses. The wash-out period ranged from less than four weeks to greater than eight weeks.
- No influence was found when concordance data from these studies was stratified according to wash-out duration. As such, no new evidence was identified on systematic review to support changing the wash-out period of at least two-weeks recommended in the 2013 guideline.

Good Practice Statements

Good Practice Statements (GPSs)

- **High level of certainty that the recommended action will do more good than harm, but has little direct evidence**
- **Are not evidence-based**
- **Expert consensus opinions from the 2013 guideline were largely re-affirmed as GPSs**
  - **Minor, clarifying edits were made to some**

2021 GPSs

- **GPS 1. All pathology laboratories implementing WSI technology for clinical diagnostic purposes should carry out their own validation studies.**
- **GPS 2. Validation should be appropriate for and applicable to the intended clinical use and clinical setting of the application in which WSI will be employed. Validation of WSI systems should involve specimen preparation types relevant to intended use (e.g., formalin-fixed paraffin embedded tissue, frozen tissue, immunohistochemical stains, etc.). If a new application for WSI is contemplated, and it differs materially from the previously validated use, a separate validation for the new application should be performed.**

2021 GPSs, continued

- **GPS 3. The validation study should closely emulate the real-world clinical environment in which the technology will be used.**
- **GPS 4. The validation study should encompass the entire WSI system. 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.**
- **GPS 5. Laboratories should have procedures in place to address changes to the WSI system that could impact clinical results. This statement was revised from the 2013 guideline.**

2021 GPSs, continued

- **GPS 6. Pathologists adequately trained to use the WSI system must be involved in the validation process.**
- **GPS 7. The validation process should confirm all the material present on a glass slide to be scanned is included in the digital image.**
- **GPS 8. Documentation should be maintained recording the method, measurements, and final approval of validation for the WSI system to be used in the anatomical pathology laboratory.**

2021 GPSs, continued

- **GPS 9. Pathologists should review cases/slides in a validation set in random order. This applies to both the review modality (i.e., glass slides or digital) and the order in which slides/cases are reviewed within each modality. This statement was revised from the 2013 guideline.**

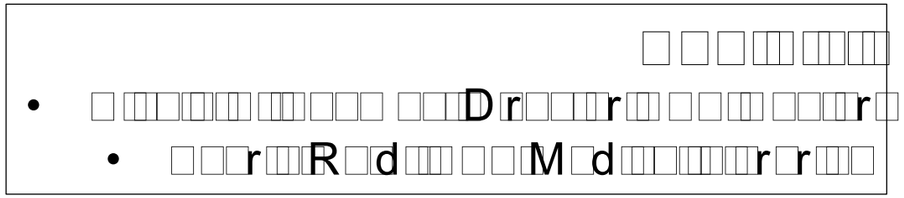
Guideline Development Process

Collaboration

- The CAP collaborated with the American Society for Clinical Pathology (ASCP) and the Association for Pathology Informatics (API)
- ASCP and API provided members to participate on the guideline panels and approved the guideline prior to submission to publication

Expert Panel Members

- Andrew Evans, MD, PhD, Chair, CAP
- Richard Brown, MD, CAP
- Marilyn Bui, MD, PhD, CAP
- Elizabeth Chlipala, BS, HTL(ASCP), CAP
- Christina Lacchetti, MSc, methodology consultant
- Danny A. Milner, Jr., MD, MSc, ASCP
- Liron Pantanowitz, MD, CAP
- Anil V. Parwani, MD, PhD, CAP
- Victor Reuter, MD, CAP
- Michael Riben, MD, API
- Lisa Stephens, MBA, HTLA(ASCP)^{cm}, ASCP
- Rachel Stewart, DO, PhD, CAP



Advisory Panel Members

- Walter H. Henricks, MD, CAP
- Jason Hipp, MD, PhD, CAP
- Dennis O'Neill, MD, CAP
- David McClintock, MD, API
- Paul J. van Diest, MD, PhD, CAP
- Chee Leong Cheng, MBBS, CAP
- Veronica Klepeis, MD, PhD, API

Development Process

COLLEGE of AMERICAN PATHOLOGISTS
Laboratory Quality Solutions

Evidence-based Guideline (EBG) Development and Review Process

The Pathology and Laboratory Quality Center for Evidence-based Guidelines (the Center) develops recommendations related to the practice of pathology and laboratory medicine. Through them, we continually improve the quality of diagnostic medicine and patient outcomes.

1	Submit & Select Ideas	The Center Guideline Committee vets all topics submitted via the CAP Center website and recommends approval for those meeting the appropriate criteria to the Council on Scientific Affairs (CSA).
2	Determine Scope & Form Panel	A rigorous and transparent screening is conducted, including conflicts of interest, for the volunteer expert panel who defines the scope and key questions and for the advisory panel.
3	Research & Review Evidence	A systematic review of the literature of the literature using the GRADE approach offers a transparent and sensible method to grading the quality (certainty) of the evidence and strength of recommendations.
4	Draft Recommendations	The expert panel develops draft recommendations based upon the extracted data, the strength of evidence, and the considered judgment process including assessment of benefits to harms.
5	Open Comment Period	The draft recommendations undergo a public peer review during which stakeholder feedback is collected.
6	Complete Recommendations & Draft Manuscript	The expert panel finalizes the recommendations and the guideline manuscript based on updated literature and stakeholder feedback.
7	Review & Approve	The independent review panel, comprised of unconflicted individuals with topic expertise, acts on behalf of the CSA as the CAP approval body.
8	Publish & Implement	The guideline manuscript is submitted for publication to the *Archives of Pathology & Laboratory Medicine* (and partner journals if applicable). The Center develops tools and educational activities to support the adoption and implementation of guideline.
9	Maintain & Monitor	Center EBGs are reviewed every four years (or earlier if evidence becomes available that could potentially alter the original guideline recommendations). Upon review, the guideline will either be reaffirmed, updated, or retired.

Reaffirm	Update	Retire
Confirmation complete guideline is accurate and up to date and then place into step 9	Refresh guideline and start at step 2 of process	Guideline inactive (i.e., no updated systematic review)

Email center@cap.org for questions, comments, or to report concerns including conflict of interest issues.

Literature Search

- Ovid MEDLINE and Elsevier Embase were searched
- Search dates
  - 1/1/2012 through 6/26/2018
  - Literature refresh 6/26/2018 to 07/15/2020

Panel Proceedings

- **The expert panel met via conference call/webinar 12 times and met twice in-person to review data and draft the recommendations.**
- **The draft recommendations were released to the public for comments June 24, 2019 through July 15, 2019.**
- **A total of 146 comments were submitted from 154 participants, with all draft recommendation receiving at least 90% outright agreement or agreement with some modification.**

Conclusions

Conclusions

- **Systematic review of literature following release of the 2013 guideline re-affirms the use of a validation set of at least 60 cases, establishing intraobserver diagnostic concordance between WSI and glass slides, and the use of a 2-week washout period between modalities.**
- **While all discordances between WSI and glass slide diagnoses discovered during validation need to be reconciled, laboratories should be particularly concerned if their overall WSI-glass slide concordance is less than 95%.**

References

- Evans A, Brown RW, Bui MM, et al. Validating whole slide imaging systems for diagnostic purposes in pathology: guideline update from the College of American Pathologists in Collaboration with the American Society for Clinical Pathology and the Association for Pathology Informatics. *Arch Pathol Lab Med*. 2021;146(4):440-450. doi: 10.5858/arpa.2020-0723-CP

Disclosure

Practice guidelines and consensus statements are intended to assist physicians and patients in clinical decision-making. New evidence may emerge between the time a practice guideline or consensus statement is developed and when it is published or read. Guidelines and statements cannot account for individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It is the responsibility of the treating physician or other health care provider, relying on independent experience and knowledge, to determine the best course of treatment for a patient. Refer to the guideline manuscript for complete details about the recommendations. The CAP and its collaborators make no warranty, express or implied, regarding guidelines and statements and specifically excludes any warranties of merchantability and fitness for a particular use or purpose. The CAP and its collaborators assume no responsibility for any injury or damage to persons or property arising out of or related to any use of this statement or for any errors or omissions.

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