Uniform Labeling of Blocks and Slides in Surgical Pathology:

Guideline from the College of American Pathologists Pathology and Laboratory Quality Center and the National Society for Histotechnology

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Panel Composition

The College of American Pathologists (CAP) Pathology and Laboratory Quality Center (the Center) convened an expert and advisory panel consisting of pathologists and histotechnologists. Both the CAP and National Society for Histotechnology (NSH) approved the appointment of the project co-chairs and panel members. These panel members served as the Expert Panel (EP) for the systematic evidence review.

Conflict of Interest (COI) Policy

Prior to acceptance on the expert or advisory panel, potential members completed the CAP conflict of interest (COI) disclosure process, whose policy and form (in effect April 2010) requires disclosure of material financial interest in, or potential for benefit of significant value from, the guideline's development or its recommendations 12 months prior through the time of publication. The potential members completed the COI disclosure form, listing any relationship that could be interpreted as constituting an actual, potential, or apparent conflict. The CAP Center uses the following criteria:

Nominees who have the following conflicts may be excused from the panel:
a. Stock or equity interest in a commercial entity that would likely be affected by the guideline or white paper
b. Royalties or licensing fees from products that would likely be affected by the guideline or white paper
c. Employee of a commercial entity that would likely be affected by the guideline or white paper

Nominees who have the following potentially manageable direct conflicts may be appointed to the panel:
a. Patents for products covered by the guideline or white paper
b. Member of an advisory board of a commercial entity that would be affected by the guideline or white paper
c. Payments to cover costs of clinical trials, including travel expenses associated directly with the trial
d. Reimbursement from commercial entity for travel to scientific or educational meetings

Everyone was required to disclose conflicts prior to beginning and continuously throughout the project's timeline. Expert panel members' disclosed conflicts are listed in the appendix of the manuscript. The CAP and NSH provided funding for the administration of the project; no industry funds were used in the development of the guideline. All panel members volunteered their time and were not compensated for their involvement. The CAP contracted a methodologist to assist in the systematic review, perform a quality assessment on the included literature, and to grade the evidence.

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Expert Panel Literature Review and Analysis

The expert panel met 12 times through teleconference webinars from April 2012 through March 2014. Additional work was completed via electronic mail. The panel met in person August 17, 2013 to review evidence to date and draft recommendations and March 22, 2014 to draft the manuscript.

Prior to the first in-person meeting, the expert panel formed the following key questions for which to base the literature search:

1. What are the unique patient identifiers required for the unambiguous labeling of blocks and slides?
2. What elements are required for the unambiguous labeling of blocks and slides with site of origin (specimen and, within the specimen, correlation with gross description)?
3. When additional studies (deeper sections, histochemical stains, immunohistochemistry) are requested, what information should be included on the resulting slides?
    a. How should you identify the different types of slides that have been cut? (i.e., step sections have different meanings across labs)
    b. How would one determine the appending of numbers of subsequent slides?
    c. What standards should apply for the unique labeling of slides that have been stained with histochemical or immunohistochemical techniques?
4. What is the value of standardizing the abbreviations and conventions used in key question #3?
5. In what order should the "essential" elements appear on the slide and, if space precludes inclusion of all, what is the priority?
6. How should you label blocks and slides received in consultation?

All expert panelists participated in the systematic evidence review (SER) level of title-abstract and full-text review, which was performed in duplicate by two members. The co-chairs performed adjudication of all conflicts. Data extraction was performed by the co-chairs. Articles meeting the inclusion criteria were assessed for strength of evidence, methodological rigor, and confirmation of validity by a contracted methodologist. All articles were available as discussion or background references. All members of the expert panel participated in developing draft recommendations, reviewing open comment feedback, finalizing and approving final recommendations and writing/editing of the manuscript.

Peer Review

An open comment period was held from November 4 through December 6, 2013 on the NSH Web site. Thirteen draft recommendations and five methodology questions were posted for peer review. An announcement was sent to the following societies deemed to have interest:

- CAP Board of Governors, Councils, Committees and Membership
- National Society for Histotechnology
- American Association of Pathology Assistants (AAPA)
- American Society for Clinical Pathology (ASCP)
- Association of Directors of Anatomic and Surgical Pathology (ADASP)
- Association of Pathology Chairs (APC)
- Clinical Laboratory Management Association (CLMA)
- Centers for Medicare and Medicaid Services (CMS)
- Canadian Association of Pathologists (CAP-APC)
- United States & Canadian Academy of Pathology (USCAP)
- Canadian Society of Laboratory Medical Scientists (CSLMS)
- International Association of Pathology (IAP)

In addition to the SER, a questionnaire was sent to various slide/block labeling companies to gauge instrument capability (listed below). The EP used this data to inform the recommendations, as understanding the capabilities and limitations of labeling instruments would impact the feasibility of

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implementing the recommendations. The vendors were also sent the open comment announcement to either participate themselves or share with their clients.

- Primera Technology, Inc., Plymouth, MN
- General Data Healthcare, Cincinnati, OH
- ThermoFisher Scientific, Waltham, MA
- Leica Biosystems, Buffalo Grove, IL
- Sakura Finetek, Torrance, CA
- Triangle Biomedical, Durham, NC
- Brady, Milwaukee, WI
- Ventana Medical Systems, Tucson, AZ
- Zebra Technology, (formerly Meditech), Lincolnshire, IL
- Johns Hopkins Pathology Data Systems, Baltimore, MD
- DakoCytomation, (formally Cytologix), Cambridge, MA
- Biocare Medical, Concord, CA
- BioGenex, Fremont, CA
- Dako, Burlington, Ontario
- Thermo Scientific Lab Vision, Fremont, CA
- Milestone Medical North America, Kalamazoo, MI
- Thermo Scientific Shandon, Waltham, MA
- Hacker Instruments and Industries, Inc., Winnsboro, SC
- RMS Omega Technologies, Baltimore, MD

"Agree" and "Disagree" responses were captured for every proposed recommendation. The website also received 539 written comments. Ten of 13 recommendations achieved more than 80% agreement; the other 3 achieved 78-79% agreement. Each expert panel member was assigned 3-4 draft recommendations for which to review all comments received and provide an overall summary to the rest of the panel. One draft recommendation was maintained with the original language, ten were modified with minor changes and/or additions for clarification, and two of the draft recommendations were combined for a total of 12 final recommendations. Resolution of all changes was obtained by majority consensus of the panel using nominal group technique (rounds of teleconference webinars, email discussion and multiple edited recommendations) among the panel members. The final recommendations were approved by the expert panel with a formal vote. The panel considered laboratory efficiency and feasibility throughout the entire process. A formal analysis of cost and cost effectiveness was not performed.

An independent review panel (IRP) was assembled to review the guideline and recommend approval to the CAP and NSH. The IRP was masked to the expert panel and vetted through the COI process.

Dissemination Plans
CAP plans to host a Uniform Labeling resource page which will include a link to manuscript and supplement; a summary of the recommendations, a teaching PowerPoint and a frequently asked question (FAQ) document. The guideline will be promoted and presented at various society meetings.

Discussion of Benefits and Risks of Implementing the Recommendations
Benefits:
The Panel believes that the use of two identifiers on tissue blocks and slides affords a greater opportunity to avoid error and a greater opportunity to discover an error if one occurs. The use of two identifiers provides an opportunity to correlate and check two data points against each other, providing a greater degree of assurance. For those facilities that use barcodes, the inclusion of human readable identifiers provides a safeguard against printer failures which can yield barcodes that will not scan, system downtime occurrences, and the occurrence of barcodes from one institution that may be unreadable at a second institution where a consultation is sought.

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The panel further believes that implementation of a uniform labeling standard with regard to the specific elements needed to unambiguously link each tissue block and the slides derived from it with a specific patient and tissue source will decrease the likelihood that these preparations will be misinterpreted within an institution or in other facilities to which they may be referred.

Risks:
For those using automated instrumentation to label cassettes and slides, the use of two identifiers, the alphanumeric designations needed, and the specific recommendations stated regarding the sequential numbering of slides and stain identification may result in increased cost if existing equipment does not have this capability.

For laboratories that label cassettes and slides by hand, incorporation of additional information in fields that have limited space will be challenging and force individuals to write more carefully and deliberately. Rushed labeling may lead to illegible notations and increased identification errors. The use of two identifiers will therefore force individuals to slow down, which may negatively impact workflow in busy laboratories, affecting sample turnaround times.

The goal of the SER was to identify scholarly literature pertaining to the labeling of microscopic glass slides and paraffin blocks. If of sufficient quality, findings from the review would provide an evidence base to support development of recommendations. The scope of the SER and the key questions (KQs) were established by the EP in consultation with a methodologist prior to beginning the literature search.

Search and Selection
The literature search strategy involved searching the following electronic databases from January 2002 through January 2013: Ovid MEDLINE, Ovid MEDLINE In-Process & Other Non-indexed Citations, PubMed, and Web of Science. Pathology-specific (e.g., Pathology, Surgical; Pathology, Clinical; Laboratories) *and* labeling-specific (e.g., Staining and Labeling, Patient Identification Systems, Clinical Laboratory Techniques) *and* quality-specific (e.g., Quality Improvement, Quality Assurance, Health Care, Quality Control) medical subject headings (MeSH) terms were combined with related keywords (e.g., pathology, histology, histopathology *and* patient identifier, slide labeling, block labeling, cassette labeling *and* quality control, quality improvement, quality assurance). See Supplemental Table 1 for the complete Ovid search strategy. The Ovid search strategy was modified for the parallel searches run in PubMed and Web of Science. The Ovid search was rerun on October 26, 2013, to capture any articles published since January 2013.

Abstracts (2011-2013) from the United States & Canadian Academy of Pathology (USCAP), College of American Pathologists (CAP), National Society for Histotechnology (NSH), International Academy of Pathology (IAP), and American Society for Clinical Pathology (ASCP) annual meetings were searched as were the tables of contents (2011-2013) from identified pathology journals (*Archives of Pathology and Laboratory Medicine, American Journal of Surgical Pathology, Journal of Histotechnology, Modern Pathology, American Journal of Clinical Pathology, Human Pathology, CAP Today, and Laboratory Medicine*)

Monographs (2002-2012) were searched utilizing Online Computer Library Center (OCLC) WorldCat, Google Books, and National Library of Medicine LocatorPlus.

Bibliographies of identified articles were reviewed for relevant reports, and citation reports (Scopus, Web of Science) for included articles were also reviewed.

Selection at all levels of the review was based on predetermined inclusion/exclusion criteria.

Inclusion criteria:
- Surgical pathology studies

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- Original research addressing the labeling of microscopic slides and/or paraffin blocks
- English language articles
- All study types were initially included
- Animal and human studies

Exclusion criteria:
- Autopsy or cytopathology studies
- Non-English studies
- Studies focused exclusively on specimen container labeling
- Studies did not include original data regarding the labeling of microscopic slides or paraffin blocks

An environmental scan for regulatory evidence was also performed (January, 2013) and involved a targeted search of known organization web sites (e.g., College of American Pathologists, Royal College of Pathologists, New York State Department of Health, Clinical Laboratory Standards Institute (CLSI), The Joint Commission, American Association of Veterinary Laboratory Diagnosticians, Inc., Health and Human Services, Medicare and Medicaid Services, HL7 Anatomic Pathology Work Group, International Organization for Standardization) as well as an untargeted search of general guideline websites (TRIP Database, Guidelines International Network, Agency for Healthcare Research and Quality) using the keyword search terms "pathology or laboratory" and "guidelines or regulations."

Outcomes of Interest
Due to the nature of the scope of this project, the outcomes of interest to the EP were not those typically associated with clinical guidelines (e.g., disease free survival, prognosis, overall survival, etc.). Instead, reducing misidentification of paraffin blocks and microscopic glass slides, incorrect diagnosis, therapy, or procedure to the patient due to mislabeling, reducing histotechnologist error of cutting the wrong paraffin block or mixing cases, and reducing misidentification of glass slides and paraffin blocks sent for consultative interpretation were outcomes of interest.

A summary of the literature review results are found in Supplemental Table 1.

Data Extraction and Management

The data elements from an included article/document were extracted by one reviewer into standard data formats and tables developed using systematic review database software (DistillerSR, Evidence Partners Inc., Ottawa, Canada); a second reviewer confirmed accuracy and completeness. Any discrepancies in data extraction were resolved by discussion with the methodologist. A bibliographic database was established in EndNote (Thomson Reuters, Carlsbad, CA) to track all literature identified and reviewed during the study.

Quality Assessment Methods
Articles meeting the inclusion criteria were assessed for strength of evidence and methodological rigor, and were graded by a methodology consultant. The hierarchy of data sources and criteria for grading studies were based on published methods [1-3]. The other components of evidence such as generalizability and applicability to labeling of blocks and slides in surgical pathology were also considered when determining the strength of evidence.

For *strength* of the evidence, we considered the level of evidence, its quantity, and quality of included studies. The *level* of evidence (Supplemental Table 2) was based on the study design as follows: Level I was evidence from systematic reviews of appropriate level II studies; level II was evidence from good quality randomized controlled trials; level III was evidence from low quality comparative studies; level IV was evidence from studies without a comparator. In general, level I and II evidence is considered most appropriate to answer clinical questions, but in the absence of such high quality evidence, the panel considered data from lower quality studies. The *quantity* of evidence refers to the number of studies and number of cases included for each outcome in the recommendation. The *quality of studies* reflected how well the studies were designed to eliminate bias and threats to validity.

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Methodological rigor was then assessed by establishing both internal and external validity criteria and the risk of bias. Specifically, the methodological quality of pre-post implementation studies was assessed using four elements of the Ramsay et al Quality Criteria for Interrupted Time Series (ITS) Designs.[1] These included an evaluation of whether the interventions occurred independent of other changes over time and were unlikely to affect data collection, the reliability of the primary outcome measure, and appropriateness of data analysis. Scientific quality assessment of case series were informed by Centre of Reviews and Dissemination's Guidance for Reviews.[2] The elements considered here included whether the series were prospective or retrospective, the representativeness of the sample, sufficiency of follow-up period, and the application of objective criteria to assess study outcomes. Finally, the qualitative study was assessed for methodological quality using five components of the National Institute for Health and Clinical Excellence (NICE) 2009 Methodology checklist for qualitative studies.[3] The appropriateness of the study design and data collected, relevance and clarity of findings, and adequacy of conclusions were evaluated.

Each study was assessed individually, and then summarized by study type. Finally, a summary of the overall quality of the evidence was given considering the evidence in totality. Quantitative studies were rated: Good (no features that suggest flaws or bias); Fair (susceptible to some bias, but flaws not sufficient to invalidate results); or Poor (significant flaws suggesting bias of various types that might invalidate results). Qualitative documents were rated: Good (*e.g.,* published/peer-reviewed, from an informed consensus process or professional/advisory committee report); Fair (*e.g.*, from credible source with unknown level of peer review, report/guideline from known expert(s) with no observed bias, otherwise good documents with a flaw or bias); or Poor (*e.g.,* document lacking information on source, peer review, potential bias, referencing, or updating; or having multiple flaws or possible biases).

Quality Assessment Results

The available literature on uniform labeling of slides and blocks is comprised exclusively of low level evidence. Nine studies and one report met the inclusion criteria and are included in this review. This level IV evidence was comprised of five pre- and post implementation studies,[4-8] three case series,[9-11] and one qualitative data analysis.[12] One report of a single institution's labeling policy also met inclusion criteria.[13] Included studies were assessed for quality and these results appear in Supplemental Table 3.

In all pre- and post studies included,[4-8] data was appropriately collected, assessed and analyzed. Three such studies[4, 7, 8] were deemed to have a low risk of bias. In two pre- and post studies,[5, 6] however, it was unclear if the intervention occurred independently of other changes over time and, consequently, the risk of bias was downgraded to low-moderate.

One qualitative data analysis[12] reported on all quality indicators and was deemed to have an appropriate design, data collection, relevance, conclusions and a clear presentation. This analysis represents evidence with a low risk of bias.

All three case series[9-11] were based on a representative sample, each with adequate follow-up and objective assessment. Two of these series were prospective[10, 11] and one retrospective,[9] representing a low to a low-moderate risk of bias, respectively.

One final report[13] did not collect or analyze data. It was merely a narrative of a single institution's labeling policy and, as such, was not assessed for methodological rigor.

Overall, the majority of studies received a rating of good,[4, 7, 8, 10-12] suggesting appropriate conduct. Three studies[5, 6, 9] were rated as fair with some methodological shortcomings. The final narrative report was rated as poor.[13]

Despite the largely favorable ratings overall, this body of evidence is comprised exclusively of low level study designs. Such study designs are inherently more susceptible to bias and difficult to compare and interpret. Accordingly, the overall strength of the evidence is graded to be inadequate to base recommendations upon.

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Assessing the Strength of Recommendations

The central question that the panel addressed in developing the guideline was "What are the essential elements for the proper labeling of paraffin blocks and microscopic slides in the routine practice of surgical pathology?"

Development of recommendations required that the panel review the identified evidence and make a series of key judgments:

1) What are the significant findings related to each KQ or outcome? Determine any regulatory requirements and/or evidence that support a specific action.

2) What is the overall strength of evidence supporting each KQ or outcome? Strength of evidence is graded as Convincing, Adequate or Inadequate, based on four published criteria (Supplemental Table 4). Strength of evidence is a key element in determining the strength of a recommendation.

3) What is the strength of each recommendation? There are many methods for determining the strength of a recommendation based on the strength of evidence and the magnitude of net benefit or harm. However, such methods have rarely (if ever) been applied to the area of slide/block labeling. Therefore, the method for determining strength of recommendation has been modified for this application (Supplemental Table 5), and is based on the strength of evidence and the likelihood that further studies will change the conclusions. Recommendations not supported by evidence (*i.e.,* evidence was missing or insufficient to permit a conclusion to be reached) were made based on consensus expert opinion. Another potential consideration is the likelihood that additional studies will be conducted that fill gaps in knowledge.

4) What is the net balance of benefits and harms? The consideration of net balance of benefits and harms will focus on the core recommendation to unambiguously identify blocks and slides in surgical pathology.

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Supplemental Table 1: Ovid Search Strategy
1   Pathology, Surgical/mt, st
2   Pathology, Clinical/mt, st
3   exp Laboratories/mt, st
4   exp Biopsy, Fine-Needle/mt, st
5   Biopsy/mt, st
6   (patholog$ or histolog$ or histopatholog$).tw.
7   or/1-6
8   *quality control/
9   *total quality management/
10   *quality improvement/
11   exp *quality assurance, health care/
12   *medical errors/
13   exp *"Outcome and Process Assessment (Health Care)"/
14   *liability, legal/
15   *risk management/
16   misidentif$.tw.
17   (near adj miss).tw.
18   (quality or amended or error$).ab. /freq=3
19   (error adj2 reduc$).tw.
20   or/8-19
21   "Staining and Labeling"/
22   workflow/
23   Automatic Data Processing/
24   Patient Identification Systems/
25   Clinical Laboratory Techniques/
26   Histocytological Preparation Techniques/
27   Specimen handling/
28   (data adj2 transcription).tw.
29   (patient adj2 identif$).tw.
30   ((slide$ or block$ or cassette$ or consult$ or deeper$ or recut$) and (label$ or mislabel$)).tw.
31   or/21-30
32   7 and 20 and 31

Supplemental Table 2: Hierarchy of Level of Evidence

Level	Intervention
I	A systematic review of level II studies
II	Randomized Clinical Trial (RCT) (Good Quality)
III-1	A pseudo- RCT (i.e., alternate allocation or some other method) or RCT (Poor Quality)
III-2	A comparative study with concurrent controls: ▪ Non-randomized, experimental trial ▪ Cohort study, Case-control study, Interrupted time series with a control group (Good Quality)
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Cohort study, Case-control study, Interrupted time series with a control group (Poor quality) ▪ Interrupted time series without a parallel control group ▪ Two or more single arm studies
IV	Case series with either post-test or pre-test/post-test outcomes

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Supplemental Table 3 – Quality Assessment

Pre- and post studies (N=5) (Level IV evidence)

Author, RefID	Year	Intervention occurred independently of other changes over time	Intervention was unlikely to affect data collection	Primary outcome was assessed and measured objectively	The study was analyzed appropriately	Overall risk of bias assessment	Rating
Fabbretti [4]	2010	yes	yes	yes	yes	low	good
Fabbretti [5]	2011	not clear	yes	yes	yes	low-moderate	fair
Zarbo [6]	2009	not clear	yes	yes	yes	low-moderate	fair
Abbuhl [7]	2009	yes	yes	yes	yes	low	good
D'Angelo [8]	2007	yes	yes	yes	yes	low	good

Qualitative data analysis (N=1) (Level IV evidence)

Author, RefID	Year	Is the design appropriate to the research question?	Were the appropriate data collected to address the research Q?	Are the findings clearly presented?	Are the findings relevant to the aims of the study?	Are the conclusions adequate?	Overall risk of bias assessment	Rating
Dunn [12]	2010	yes	yes	yes	yes	yes	low	good

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Supplemental Table 3 continued

Case Series (N=3) (Level IV evidence)

Author, RefID	Year	Prospective/ Retrospective	Is the study based on a representative sample?	Was follow-up long enough for the outcomes to occur?	Were outcomes assessed using objective criteria?	Overall risk of bias assessment	Rating
Nakhleh[10]	2011	prospective	yes	yes	yes	low	good
Layfield[9]	2010	retrospective	yes	yes	yes	low-moderate	fair
Smith[11]	2011	prospective	yes	yes	yes	low	good

Report of single institution labeling policy (N=1) (Level IV evidence)

Author, RefID	Year	Overall risk of bias assessment	Rating
Kay[13]	2011	not applicable	poor

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Supplemental Table 4 - Grades for Strength of Evidence

Convincing

- Two or more Level 1[a] or 2 studies (study design and execution) that had an appropriate number and distribution of challenges[b] and reported consistent[c] and generalizable[d] results.

- One Level 1 or 2 study that had an appropriate number and distribution of challenges and reported generalizable results.

Adequate

- Two or more Level 1 or 2 studies that lacked the appropriate number and distribution of challenges OR were consistent but not generalizable.

Inadequate

- Combinations of Level 1 or 2 studies that show unexplained inconsistencies OR combinations of one or more lower quality studies (Level 3 or 4) OR expert opinion.

Reprinted from Teutsch et al[14] with permission from Macmillan Publishers Ltd: The evaluation of genomic applications in practice and prevention (EGAPP) initiative: methods of the EGAPP working group. *Genet Med.* 11(1):3-14, copyright 2009.

[a] Supplemental Table 1 provides the hierarchy of data sources for analytic validation that define Level 1 through Level 4.

[b] Based on number of possible response categories and required confidence in results.

[c] Consistency can be assessed formally by testing for homogeneity, or, when data are limited, less formally using central estimates and range of values.

[d] Generalizability is the extension of findings and conclusions from one study to other settings.
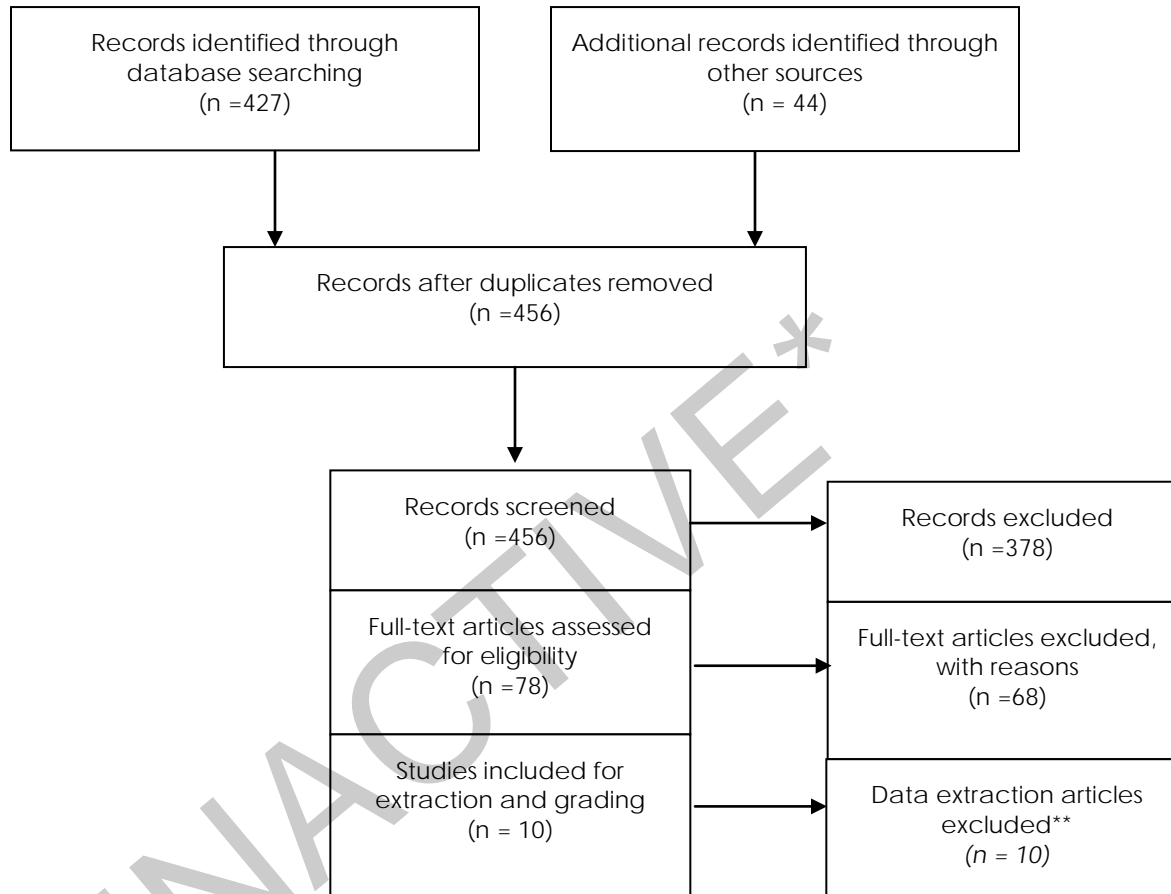
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Supplemental Table 5: Grades for Strength of Recommendations*

Designation	Recommendation	Rationale
Strong Recommendation	Recommend For or Against a particular glass slide or paraffin block labeling practice (Can include must or should)	Supported by high (convincing) or intermediate (adequate) quality of evidence and clear benefit that outweighs any harms
Recommendation	Recommend For or Against a particular glass slide or paraffin block labeling practice (Can include should or may)	Some limitations in quality of evidence (intermediate [adequate] or low [inadequate]), balance of benefits and harms, values, or costs but panel concludes that there is sufficient evidence to inform a recommendation.
Expert Consensus Opinion	Recommend For or Against a particular glass slide or paraffin block labeling practice (Can include should or may)	Serious limitations in quality of evidence (low [inadequate] or insufficient), balance of benefits and harms, values or costs, but panel consensus is that a statement is necessary.
No Recommendation	No recommendation for or against a particular block or slide labeling practice	Insufficient evidence, confidence, or agreement to provide a recommendation

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Supplemental Figure 1: Literature Review Flow Diagram*

*Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6:e1000097.[15]

**Excluded based on expert opinion, did not meet minimum quality standards, presented incomplete data or data that were not in useable formats.

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