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COLLEGE of AMERICAN  
PATHOLOGISTS

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## Interpretive Diagnostic Error Reduction in Surgical Pathology and Cytology:

Joint Guideline from the College of American  
Pathologists Pathology and Laboratory Quality  
Center and the Association of Directors of  
Anatomic and Surgical Pathology

Corresponding Author:  
Raouf E. Nakhleh, MD

Authors :

Vania Nosé, MD, PhD  
Lisa Fatheree, SCT(ASCP)  
Christina Ventura, MT(ASCP)  
Douglas McCrory, MD  
Carol Colasacco SCT(ASCP), MLIS, AHIP

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College of American Pathologists | 325 Waukegan Rd. | Northfield, IL 60093 | 800-323-4040 | cap.org

### 3 METHODS USED TO PRODUCE THE GUIDELINE

#### 5 Panel Composition

6 The College of American Pathologists (CAP) Pathology and Laboratory Quality Center (the Center) and  
7 Association of Directors of Anatomic and Surgical Pathology (ADASP) convened an expert and advisory  
8 panel consisting of practicing pathologists with expertise in surgical pathology and cytology. CAP and  
9 ADASP approved the appointment of the project co-chairs (RN and VN) and panel members. These  
10 panel members and the methodologist served as the Expert Panel (EP) for the systematic evidence  
11 review.

#### 13 Conflict of Interest (COI) Policy

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

21 Nominees who have the following conflicts may be excused from the panel:

- 22 a. Stock or equity interest in a commercial entity that would likely be affected by the guideline or white  
23 paper
- 24 b. Royalties or licensing fees from products that would likely be affected by the guideline or white paper
- 25 c. Employee of a commercial entity that would likely be affected by the guideline or white paper

27 Nominees who have the following potentially manageable direct conflicts may be appointed to the panel:

- 28 a. Patents for products covered by the guideline or white paper
- 29 b. Member of an advisory board of a commercial entity that would be affected by the guideline or white  
30 paper
- 31 c. Payments to cover costs of clinical trials, including travel expenses associated directly with the trial
- 32 d. Reimbursement from commercial entity for travel to scientific or educational meetings

34 Everyone was required to disclose conflicts prior to beginning and continuously throughout the project's  
35 timeline. Expert panel members' disclosed conflicts are listed in the appendix of the manuscript. The CAP  
36 and ADASP provided funding for the administration of the project; no industry funds were used in the  
37 development of the guideline. All panel members volunteered their time and were not compensated for  
38 their involvement.

## 51 CAP/ADASP Expert Panel Literature Review and Analysis

52 The expert panel met 26 times through teleconference webinars from December 2011 through June 12,  
53 2014. Additional work was completed via electronic mail and the panel met in person October 12, 2013 to  
54 review evidence to date and draft recommendations.

55  
56 All expert panelists participated in the systematic evidence review (SER) level of title-abstract, full-text  
57 review, and data extraction. The co-chairs (RN and VN) and methodologist (DM) performed the audit of  
58 data extraction. All articles were available as discussion or background references. All members of the  
59 expert panel participated in developing draft recommendations, reviewing open comment feedback,  
60 finalizing and approving recommendations and writing/editing of the manuscript.

## 61 62 Peer Review

63 An open comment period was held from December 2, 2013 through January 21, 2014. Five draft  
64 recommendations and three methodology questions were posted online on the CAP Web site  
65 [www.cap.org](http://www.cap.org). An announcement was sent to the following societies deemed to have interest:

66  
67 CAP Board of Governors, Councils, Committees and Membership  
68 Association of Directors of Anatomic and Surgical Pathology (ADASP)  
69 American Society for Clinical Pathology (ASCP)  
70 American Society of Cytopathology (ASC)  
71 Papanicolaou Society of Cytology (PSC)  
72 Arthur Purdy Stout Society (APSS)  
73 Association of Pathology Chairs (APC)  
74 Canadian Association of Pathologists (CAP-APC)  
75 United States & Canadian Academy of Pathology (USCAP)  
76 Quality Initiative in Interpretive Pathology (QIIP) Canadian Partnership Against Cancer  
77 Society to Improve Diagnoses in Medicine (SIDM)  
78 American Society of Clinical Oncologists (ASCO)  
79 Veteran's Affairs (VA) and Department of Defense (DOD)  
80 Centers for Disease Control and Prevention (CDC)  
81 Centers for Medicare and Medicaid Services (CMS)

82  
83 The website received 303 comments in total (Agree and Disagree responses were also captured). All the  
84 recommendations achieved between 87% to 93% agreement. Pairs of expert panel members were  
85 assigned 1 draft recommendation for which to review all comments received and provide an overall  
86 summary to the rest of the panel. Following panel discussion, and the final quality of evidence  
87 assessment, the panel members determined whether to maintain the original draft recommendation as is,  
88 revise it with minor language change, or consider it as a major recommendation change. Resolution of all  
89 changes was obtained by majority consensus of the panel using nominal group technique (rounds of  
90 email discussion and multiple edited recommendations) amongst the panel members. The final  
91 recommendations were approved by the expert panel with a formal vote. The panel considered the risks  
92 and benefits throughout the whole process in their considered judgment process.<sup>1</sup> Formal cost analysis or  
93 cost effectiveness was not performed.

94  
95 An independent review panel (IRP) was assembled to review the guideline and recommend approval to  
96 the CAP. The IRP was masked to the expert panel and vetted through the COI process. Final approval  
97 was done by CAP Council on Scientific Affairs and ADASP Executive Board.

## 98 99 Assessing the Strength of Recommendations

100 Strength of recommendation is determined by the balance between desirable and undesirable  
101 consequences of alternative management strategies, quality of evidence, variability in values and  
102 preferences, resource use.<sup>2</sup>

103



- 104 The central question that the panel addressed in developing the guideline was “*What are the most*  
105 *effective ways to reduce interpretive diagnostic errors in Anatomic Pathology?*”
- 106 Development of recommendations requires that the panel review the identified evidence and make a  
107 series of key judgments:
- 108 1) What are the significant findings related to each KQ or outcome?
- 109 2) What is the overall quality of evidence supporting each KQ or outcome? Quality of evidence was  
110 assessed according to the GRADE framework as described below.<sup>2</sup> Summary of Findings tables or when  
111 sufficient information was not available, an alternative short evidence table format, were prepared for  
112 each question. To maintain consistency with previous CAP guideline language, quality of evidence is  
113 described as Convincing, Adequate or Inadequate as shown in Table 1.
- 114 3) What is the net balance of benefits and harms? The consideration of net balance of benefits and harms  
115 will focus on the laboratory redundancy, efficiency and feasibility in comparison to the reduction of errors  
116 or potential errors and their impact on patient outcomes.
- 117 4) What is the strength of each recommendation? The implications of a strong recommendation for  
118 clinicians is that most patients should receive the recommended course of action; while the implications of  
119 a weak recommendation are that different choices may be appropriate for different patients or that  
120 different management options may be preferred by different stakeholders. We used the current CAP  
121 designations for strength of recommendations of *strong recommendation*, *recommendation* and *expert*  
122 *consensus opinion* (Table 2), as determined by a considered judgment process in which the guideline  
123 panel weighs the quality of evidence, balance of benefits and harms, variability in values preference and  
124 data on costs or resource use.<sup>1</sup>

### 125 Dissemination Plans

126 CAP will host an Interpretive Diagnostic Error Reduction Through Targeted Case Reviews In Surgical  
127 Pathology And Cytology Resource web page which will include a link to the [manuscript](#) and supplemental  
128 digital content; summary of recommendations, teaching PowerPoint, and a frequently asked question  
129 (FAQ) document. The ADASP webpage will include a link to the CAP guideline resource page. The  
130 guideline will be promoted and presented at various professional society meetings including the College  
131 of American Pathologists, the United States and Canadian Academy of Pathology (USCAP), and the  
132 American Society of Clinical Pathology (ASCP).

### 134 SYSTEMATIC EVIDENCE REVIEW (SER)

136 The objectives of the SER were to investigate the most effective ways to reduce interpretive diagnostic  
137 errors in surgical pathology and cytology. If of sufficient quality, findings from this review could provide an  
138 evidence base to support development of the laboratory practice guideline. The scope of the SER and the  
139 key questions (KQs) were established by the EP in consultation with a methodologist.

#### 141 Key Questions:

- 142 1. Does targeted review (either done at analytic or post-analytic phase) of surgical pathology or cytology  
143 cases (slides and/or reports) reduce the error rate (often measured as amended reports) or increase the  
144 rate of interpretive error detection compared to no review, random review or usual review procedures?
- 145 2. What methods of selecting cases for review have been shown to increase the rate of interpretive error  
146 detection compared to no review, random review or usual review procedures?

#### 148 Detailed Scope Questions:

- 149 • Can a targeted review of cases lead to increased detection of errors?
- 150 • Is there a particular method (eg, prospective vs. retrospective, random reviews, etc.) that results in  
151 lower error rates? Or amended report rates? If yes, what is the method?
- 152 • Is there a particular type of diagnosis(es) (eg, malignant, benign, borderline) more prone to error? If  
153 yes, what?



- 154 • Is there a particular organ/system associated with a higher rate of error/disagreements revealed as
- 155 problematic in the literature (eg, thyroid FNA, lymphoma, brain biopsy)? If yes, what?
- 156 • How does the error rate for multi-organ reviews compare with single organ reviews? (eg, internal
- 157 and/or external)
- 158 • Do blinded reviews find more or less errors than non-blinded reviews?
- 159 • Can we learn anything from external review studies that can be applied to internal reviews (or vice-
- 160 versa)?
- 161 • Can we establish an external error rate (benchmark) for surgical pathology or cytology?
- 162 • Can we establish an internal error rate (benchmark) for surgical pathology or cytology?
- 163 • What are the costs of conducting internal or external reviews?
- 164 • What is the effect on turn-around times (efficacy) for internal or external reviews?
- 165 • What is the effect on patient care when conducting internal or external reviews?
- 166 • Has there been improvement in reducing error reduction over time?
- 167 • What other factors (eg, standard criteria, clinical correlation, ancillary testing) are emphasized most
- 168 frequently and with which organ system or diagnosis?

### 169 Search and Selection

170 The systematic literature search for relevant studies included a search of MEDLINE using the Ovid SP  
 171 interface on November 12, 2013, with the date parameters of January 1992 through October 2012.  
 172 Medical subject headings (MeSH) for the concept *pathology* (eg, Pathology, Surgical/ Pathology, Clinical;  
 173 Pathology) were combined with MeSH terms for the concept *quality* (eg, Quality Assurance, Health Care;  
 174 Quality Control; Quality Improvement; Reproducibility of Results; Diagnostic Errors). MeSH terms were  
 175 supplemented with keywords (eg, histopathology, cytopathology, histology, or cytology; and second  
 176 opinion, misinterpretation, or interpretation errors). A targeted concept of slide/case review included  
 177 keywords such as targeted review, peer review, or random review and the keywords slide, case, or report.  
 178 Limits were set for human studies published in English. The search was not limited by study design in  
 179 order to capture editorials, letters, or commentaries that might be relevant and useful for discussion  
 180 purposes. A literature refresh of the OvidSP search strategy was run on November 21, 2013, to identify  
 181 relevant studies published since October 2012. The full Ovid search strategy is included in the appendix.  
 182

183 The Ovid search strategy was modified for PubMed (1/1/92-12/31/12), and Google Scholar (1/1/12 –  
 184 1/26/13). In addition, a handsearch of relevant journals (*American Journal of Clinical Pathology, American*  
 185 *Journal of Surgical Pathology, Archives in Pathology and Laboratory Medicine, Cancer, Cancer*  
 186 *Cytopathology, Diagnostic Cytopathology, Histopathology, Modern Pathology*) was completed for issues  
 187 published from January 2008, through December 2012. A search for meeting abstracts was completed  
 188 utilizing Biosis Previews (Web of Science) (1/1/2008-12/31/2012) and by handsearching published  
 189 abstracts from relevant meetings (American Society of Cytopathology, American Society for Clinical  
 190 Pathology, British Society for Clinical Cytology, College of American Pathologists, European Congress of  
 191 Cytopathology, International Academy of Pathology, United States and Canadian Academy of Pathology)  
 192 held from January 2008 through December 2012. Reference lists from included articles were scanned for  
 193 additional relevant studies.  
 194

195 Two reviewers were used at all levels of review (eg, title/abstract, full article) and for data/information  
 196 extraction. Conflicts were resolved by discussion or referral to the panel co-chairs for a decision. When  
 197 article abstracts or document summaries were not available or a conflict was not resolved, full articles  
 198 were reviewed.  
 199

200 Selection at all levels of the review was based on predetermined inclusion/exclusion criteria.  
 201

#### 202 Inclusion criteria:

- 203 • Surgical pathology or cytology studies
- 204 • Original research addressing targeted review
- 205 • English language articles
- 206 • All study types were initially included
- 207



- 208  
209 Exclusion criteria:
- 210 • Clinical pathology studies
  - 211 • Additional diagnostic techniques, issues related to competency, use of checklists, standardized language, taxonomy or formatting
  - 212 • Studies focused on pre-analytic specimen processes
  - 213 • Post-analytic typographic errors
  - 215 • Non-English studies
  - 216 • Animal studies

### 217 **Outcomes of Interest**

218 We are interested in identifying discrepancies in interpretation between a primary pathologist review and  
219 a second pathologist review as a way of estimating the error rate. To the extent that erroneous readings  
220 can be identified in excess of an expected degree of disagreement, then a method of targeted review  
221 would be said to be effective. Thus, studies with a control group are desirable; as a practical matter,  
222 however, it is necessary to examine uncontrolled series, too. Studies had to report numbers of discrepant  
223 diagnoses among a defined population of specimens examined to allow calculation of a discrepancy rate.  
224

225 We are not interested in discrepancies from the pre-analytic specimen process (ie, related to tissue  
226 collection and processing) or post-analytic errors (eg, typographic or transcription errors, amended  
227 reports), additional diagnostic techniques (eg, immunomarkers), issues related to competency, or the use  
228 of checklists, standardized language, taxonomy or formatting.  
229

230 Various studies classify errors in different ways (eg, major versus minor). Recognizing that all errors are  
231 not alike, we assessed the severity of interpretive errors according to the clinical impact on a patient.<sup>3</sup> We  
232 considered the clinical impact of errors as follows: 1) diagnostic thinking (error results in a change in  
233 diagnosis or diagnostic category); 2) therapeutic efficacy (error results in a change in therapeutic choice);  
234 or 3) patient outcome efficacy (error results in a change in outcome (eg, procedure avoided);  
235 demonstrating this unequivocally may require long-term follow-up). We also considered the efficiency or  
236 cost (in terms of effort or dollars) that a targeted review strategy entails.  
237

### 238 **Data Extraction and Management**

239 The data elements from an included article/document were extracted by one reviewer into standard data  
240 formats and tables developed using systematic review database software (DistillerSR, Evidence Partners  
241 Inc., Ottawa, Canada); a second reviewer confirmed accuracy and completeness. In all cases, the  
242 methodologist acted as either the primary or secondary reviewer. Any discrepancies in data extraction  
243 were resolved by discussion with the methodologist. A bibliographic database was established in  
244 EndNote (Thomson Reuters, Carlsbad, CA) to track all literature identified and reviewed during the study.  
245

### 246 **Environmental Scan**

247 An environmental scan for established guidelines was performed including a targeted search of pathology  
248 organizations' web sites and a search of guideline clearinghouse websites (TRIP Database, Guidelines  
249 International Network, Agency for Healthcare Research and Quality) using the search terms "pathology or  
250 laboratory" and "guidelines or regulations."  
251

### 252 **Quality Assessment**

253 Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach provides a  
254 system for rating quality of evidence and strength of recommendations that is explicit, comprehensive,  
255 transparent, and pragmatic and is increasingly being adopted by organizations worldwide.<sup>2</sup> The GRADE  
256 approach examines the quality of evidence as the level of individual studies and also at the review level.  
257 GRADE was used for rating the quality of evidence.  
258

259 At the individual study level, we assessed studies according to three criteria: 1) study design rating; 2)  
260 risk of bias rating; and 3) applicability concerns. Study design was assessed according to the following  
261 hierarchy:



- 262 1) noncomparative studies (where a single method of targeted review is considered, in determining a  
263 single error rate)  
264 2) comparative studies (where two or more methods of targeted review are independently applied and  
265 compared in one group of patients)  
266 3) comparative studies (where two or more methods of targeted review are compared in different groups  
267 of patients  
268 a. historical (eg, a before-after series )  
269 b. concurrent (eg, comparison of two different institution's targeted review programs)  
270 c. quasi-randomized (concurrent, similar or identical sites, allocated with attempt to reduce bias  
271 beyond that provided by 3.a. or 3.b.)  
272 d. randomized

273  
274 Risk of bias ratings were based on the following three criteria, rated as yes, no, or unclear:

- 275 1) Were review diagnoses independent, blinded from the primary diagnosis?  
276 2) Was case selection done using explicit, objective and reproducible criteria?  
277 3) Was interpretive error ascertained without confounding by pre- or post-analytic error?  
278

279 Applicability concerns were assessed for three areas, rated as yes, no, or unclear:

- 280 1) Is study limited to particular organ systems, specimen types or diagnoses?  
281 2) Is the inter-rater performance examined and acceptable?  
282 3) Is there a distinction between major and minor errors based on impact on patient treatment or  
283 outcome?  
284

285 At the review level, we examined the collection of studies according to the following domains:

- 286 1) Consistency  
287 2) Directness  
288 3) Precision  
289 4) Magnitude of effect  
290 5) Number of studies/patients

291 We developed a GRADE evidence table, and mapped the quality of evidence ratings to the CAP rating  
292 scheme according to table 1.  
293

### 294 Data Analysis

295 Rates of discrepancy and major discrepancy were described for all studies, and subgroups based on type  
296 of specimen (surgical pathology, cytopathology or both), focusing on one organ or organ system (single-  
297 organ) versus multi-organ studies, and whether conducted within a single institution (internal) or reviews  
298 of cases diagnosed at a different institution (external). Studies were tested for homogeneity using  
299 Comprehensive Meta Analysis version 2.2.064. Nonparametric descriptive statistics including median,  
300 and 1<sup>st</sup> and 3<sup>rd</sup> quartiles were calculated using Excel.  
301

### 302 Results

303 Among the 823 citations identified by electronic and hand searches, 141 were selected for inclusion.  
304 These included 130 published peer-reviewed articles, and 11 grey literature documents (Appendix 1).  
305 Among the extracted documents, 4 articles/documents did not meet minimum quality standards,  
306 presented incomplete data or data that were not in useable formats, or included only information based  
307 on expert opinion. These articles were not included in analyses or narrative summaries.  
308

309 Of 137 studies included, 128 (91.4%) were single arm clinical case series. Of 12 comparative studies, 2  
310 reported a comparison of 2 or more methods of targeted review in one group of patients; 6 compared  
311 targeted review methods in different historical cohorts (eg a before-after study), and 4 compare 2 or more  
312 targeted review methods in concurrent groups of patients. No studies used random allocation or other  
313 robust measures to control for potential bias.



314  
315 Risk of bias assessments of included studies showed that review diagnoses were made independently  
316 (blinded from the primary diagnosis) in 30 (21.4%) studies, unclear in 2 (1.4%) and without blinding in 108  
317 (77.1%). Case selection was done using explicit, objective and reproducible criteria in 56 (40%), and with  
318 unclear, subjective, non-reproducible or without criteria in 84 (59.3%). Interpretive error was ascertained  
319 without confounding by pre- or post-analytic error in 120 (85.7%), unclear in 2 (1.4%) and not in 18  
320 (12.9%) studies.  
321  
322 Applicability concerns were as follows: Studies were limited to particular organ systems, specimen types  
323 or diagnoses in 111 (79.3%) cases, and not limited in 29 (20.7%) cases. Inter-rater performance was  
324 examined and acceptable in 29 (20.7%), unclear in 6 (4.3%), and not in 105 (75%) of studies. There was  
325 a distinction between major and minor errors based on impact on patient treatment or outcome in 78  
326 (55.7%), unclear in 2 (1.4%), and not in 60 (42.9%) of studies.  
327  
328 Discrepancy rates and major discrepancy rates by study characteristics are provided in the manuscript.  
329  
330 The distribution of discrepancy rates shows that the variability was greater for studies of smaller sample  
331 size. The distribution of discrepancy rates by sample size is shown in figures 1 and 2, both of which show  
332 high variability in discrepancy rates for studies with smaller sample sizes, with larger studies tending to  
333 have lower discrepancy rates.  
334  
335 Evidence on each question was summarized in terms of study quality and effects in Evidence Profile  
336 Tables (Tables 3-5) which were used as the basis for quality of evidence determinations with the panel.  
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**Table 1. Quality of Evidence Ratings: mapping from GRADE categories to CAP**

GRADE	Definition	CAP	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect.	High (Convincing)	High confidence that available evidence reflects true effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	Intermediate (Adequate)	Moderate confidence that available evidence reflects true effect
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.	Low (Inadequate)	Little confidence that available evidence reflects true effect
Very low	Any estimate of effect is very uncertain.	Insufficient	Evidence is insufficient to discern net effect

Adapted from Guyatt et al<sup>2</sup> with permission from BMJ Publishing Group Ltd..342  
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**Table 2. Strength of Recommendations**

<b>CAP Designation</b>	<b>Recommendation</b>	<b>Rationale</b>
<b>Strong Recommendation</b>	Recommend For or Against a particular pathology review practice (Can include must or should)	Supported by high (convincing) or intermediate (adequate) quality of evidence and clear benefit that outweighs any harms
<b>Recommendation</b>	Recommend For or Against a particular pathology review 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.
<b>Expert Consensus Opinion</b>	Recommend For or Against a particular pathology review 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 guideline is necessary.
<b>No Recommendation</b>	No recommendation for or against a particular pathology review practice	Insufficient evidence, confidence, or agreement to provide a recommendation.

Adapted from Teutsch et al<sup>4</sup> with permission from Macmillian Publishers Ltd. Modified by the CAP Pathology and Laboratory Quality Center.

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**Table 3: Evidence profile for Recommendation 1: Should case review be used for diagnostic evaluation of pathology materials?\***

Quality assessment							No. of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Case review	Control	Relative (95% Confidence Interval)	Absolute		
<b>Discrepancy Rate (follow-up 1 years; assessed with case review)</b>												
122	observational studies <sup>a</sup>	no serious risk of bias	no serious inconsistency <sup>b</sup>	no serious indirectness <sup>c</sup>	no serious imprecision	none	27178/513268 (5.3%)	-	-	-	⊕⊕O LOW	IMPORTANT
<b>Major Discrepancy Rate (assessed with: case review)</b>												
79	observational studies <sup>a</sup>	no serious risk of bias	no serious inconsistency <sup>b</sup>	no serious indirectness <sup>d</sup>	no serious imprecision	none	4416/179130 (2.5%)	-	-	-	⊕⊕O LOW	CRITICAL
<b>Inter-observer agreement</b>												
27	observational studies	no serious risk of bias	Serious <sup>d</sup>	Serious <sup>e</sup>	no serious imprecision	reporting bias	-	-	kappa ranged from 0.16 to 0.97	-	⊕OO VERY LOW	IMPORTANT

\*Settings: Pathology laboratories and practices

<sup>a</sup> Studies include single- and multi-institution case series that quantify diagnostic discrepancies or errors according to various definitions

<sup>b</sup> Although the magnitude of discrepancy rates vary considerably from study to study based on sample size, specimen type, single versus multi-organ, review type (internal versus external), and definition of discrepancy, studies are remarkably consistent in finding non-trivial discrepancy rates.

<sup>c</sup> Few studies reported the impact of discrepant diagnoses on treatment choice, and even fewer on patient outcome.

<sup>d</sup> Inter-rater reliability studies had high variability. Experts agreed better than non-experts.

<sup>e</sup> Inter-rater agreement studies usually used highly selected samples and small numbers of observations

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**Table 4: Evidence profile for Recommendation 2: Should prospective review versus retrospective review be used for diagnostic evaluation of pathology materials?**

Quality assessment							No. of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prospective review	Retrospective review	Relative (95% CI)	Absolute		
<b>Discrepancy Rate</b>												
4	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	510/15515 (3.3%)	0.13%	RD ranged from -2.4 to 1.1	-	⊕⊕⊕⊕ LOW	IMPORTANT
								3.4%		-		
								13%		-		
<b>Major discrepancy</b>												
2	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	32/6129 (0.52%)	0.1%	RD ranged from -0.1 to -0.5	-	⊕⊕⊕⊕ LOW	IMPORTANT
								1.7%		-		

358 CI – confidence interval; RD – risk difference

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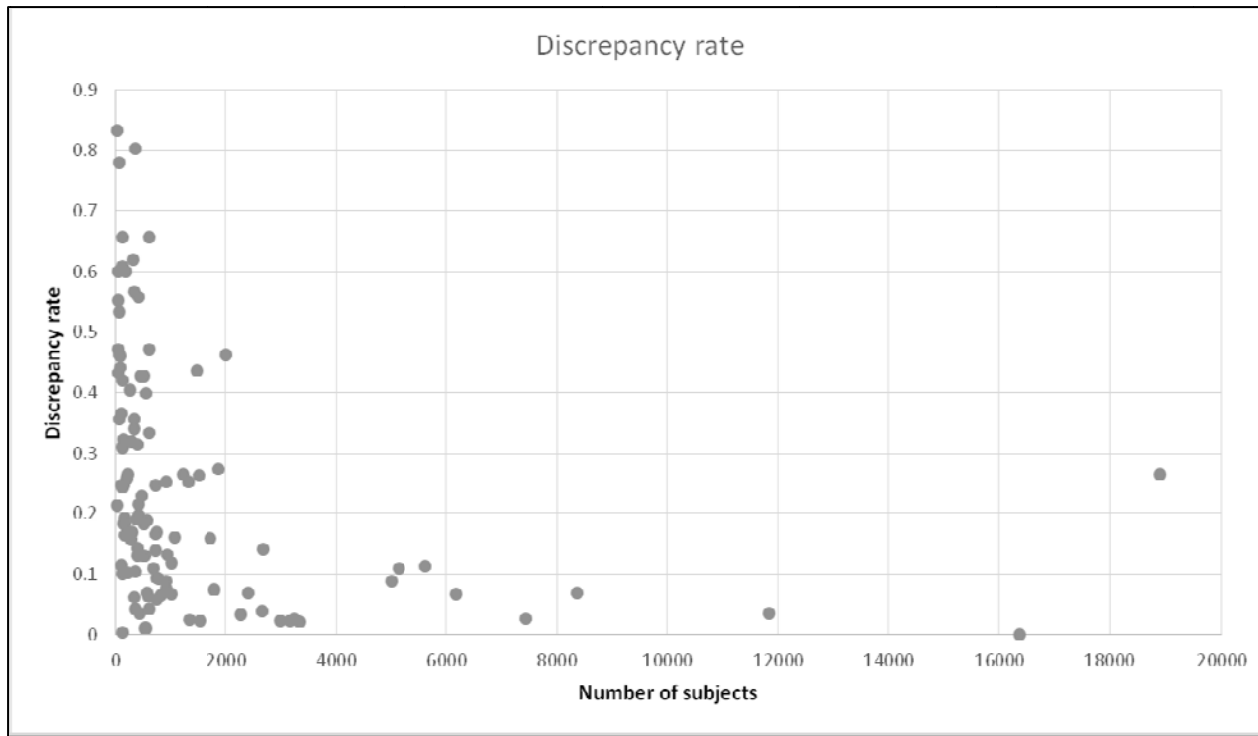
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**Table 5: Evidence Profile for Recommendation 3: Should targeted case review versus random case review be used for diagnostic evaluation of pathology materials?**

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Targeted case review	Random case review	Relative (95% CI)	Absolute		
<b>Discrepancy rate</b>												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	50/380 (13.2%)	195/7444 (2.6%)	OR 5.6 (4.1 to 7.8)	105 more per 1000 (from 73 more to 147 more)	⊕⊕○○ LOW	
<b>Major discrepancy</b>												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/380 (3.2%)	27/7444 (0.36%)	OR 9.0 (4.5 to 18)	28 more per 1000 (from 12 more to 58 more)	⊕⊕○○ LOW	

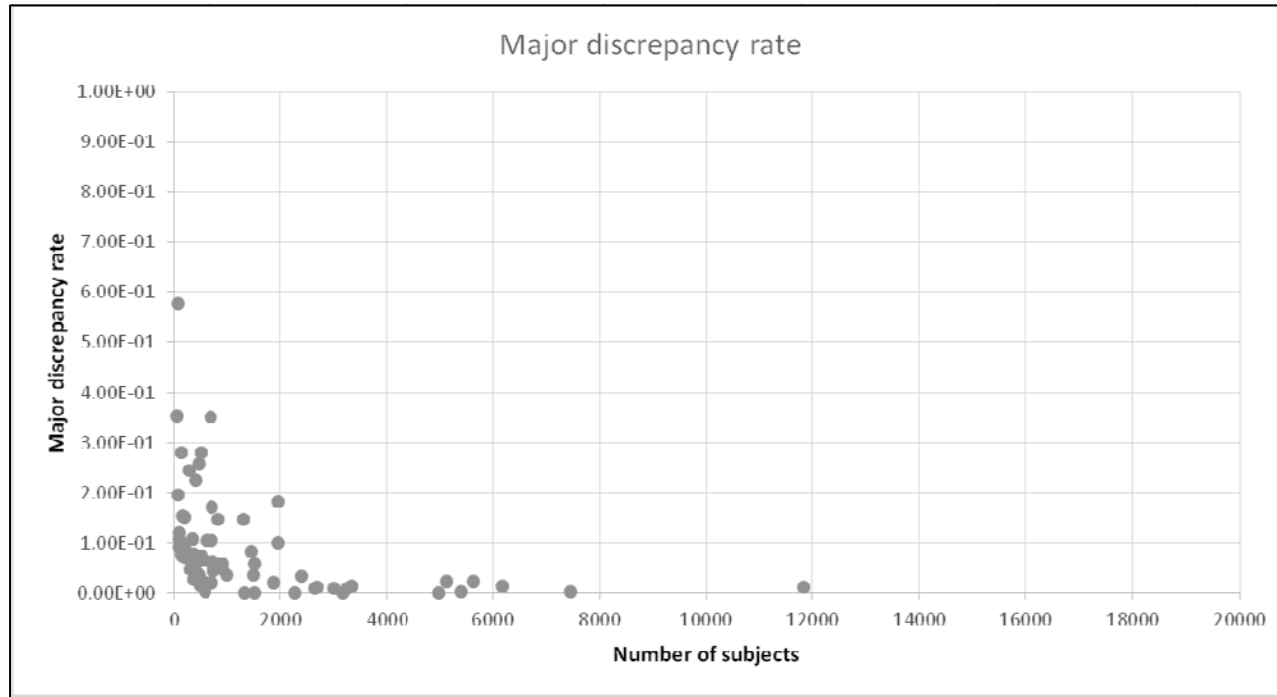
361 CI – confidence interval; OR – Odds ratio



**Figure 1: Discrepancy rate distribution by sample size**<sup>5-112</sup>

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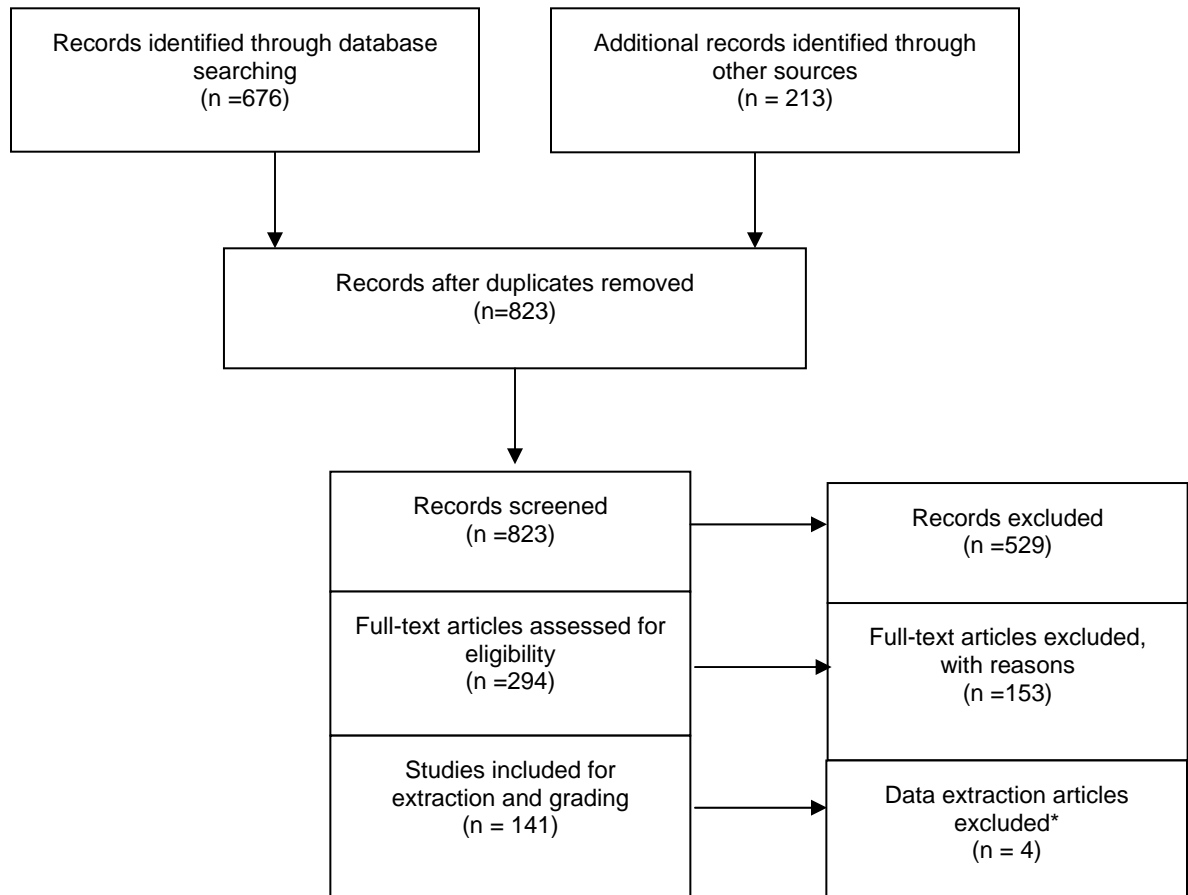


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**Figure 2: Major discrepancy rate distribution by sample size**<sup>5, 6, 8, 10, 11, 13-15, 17-20, 22-24, 31, 33, 36, 40, 42-44, 46, 50, 51, 53-55, 58-61, 64, 67-69, 74, 76, 78, 83, 84, 86-88, 91, 93, 94, 96, 97, 99-101, 106, 108, 110, 113-129</sup>

379 **APPENDIX**

380  
381 Appendix A: Literature Review Results  
382 Adapted with permission from Moher et al.<sup>130</sup>  
383  
384



417 \*Excluded based on expert opinion, did not meet minimum quality standards, presented incomplete data or  
418 data that were not in useable formats  
419

420 Appendix B: Ovid MEDLINE Search Strategy

- 421  
422 1. \*Pathology/  
423 2. \*Pathology, Surgical/  
424 3. Pathology, Clinical/  
425 4. Pathology department, Hospital/  
426 5. Cytodiagnosis/  
427 6. Biopsy/  
428 7. \*"Diagnostic Techniques and Procedures"/  
429 8. (pathology\$ or cytolog\$ or histolog\$ or histopatholog\$ or cytopatholog\$).tw.  
430 9. or/1-8  
431



- 432 AND  
 433  
 434 1. \*Medical Errors/  
 435 2. \*"Referral and Consultation"/  
 436 3. \*Quality Assurance, Health Care/  
 437 4. \*Quality Control/  
 438 5. exp \*Diagnostic Errors/  
 439 6. \*Quality Improvement/  
 440 7. exp \*"Peer Review"/  
 441 8. \*"Root Cause Analysis"/  
 442 9. \*Total Quality Management/  
 443 10. \*"Reproducibility of Results"/  
 444 11. \*"Sensitivity and Specificity"/  
 445 12. \*Medical Audit/  
 446 13. \*"Insurance Claim Review"/  
 447 14. \*Malpractice/lj [Legislation & Jurisprudence]  
 448 15. performance improvement.tw.  
 449 16. ((corrected or amended) adj2 report\$.tw.  
 450 17. (misinterpretation or misdiagnosis or medicolegal or "patient safety" or "second opinion").tw.  
 451 18. ((interpret\$ or diagnostic) adj2 error\$.tw.  
 452 19. (error adj2 (reduction or prevention or rate)).tw.  
 453 20. "diagnostic disagreement\$.tw.  
 454 21. (quality adj3 (improvement or control or assurance or practice\$ or measure\$ or process\$)).tw.  
 455 22. or/1-21  
 456  
 457 AND  
 458  
 459 1. ((routine or target\$ or random\$ or blind\$ or peer\$) adj4 review\$.tw.  
 460 2. ((case\$ or slide\$ or report\$) adj4 review\$.tw.  
 461 3. or/1-2  
 462  
 463 Limits: Humans/English/1/1/1992-10/31/2012. Rerun on 11/21/2013 to include 10/31/2012-11/21/2013.  
 464  
 465  
 466  
 467

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