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Histopathological Diagnosis of Cutaneous Melanocytic Lesions: Blinded and Non-Blinded Second Opinions Offer Similar Improvement in Diagnostic Accuracy

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Abstract

Background: Previous studies of second opinions in the diagnosis of melanocytic skin lesions examined blinded second opinions, which do not reflect usual clinical practice.

Objectives: To study the diagnostic accuracy of non-blinded and blinded second opinions.

Methods: 100 melanocytic skin biopsy cases, ranging from benign to invasive melanoma, were interpreted by 74 dermatopathologists. Subsequently, 151 dermatopathologists performed non-blinded second and third reviews. We compared the accuracy of single reviewers; second opinions obtained via independent, blinded reviewers; and second opinions obtained via sequential, non-blinded reviewers. Accuracy is defined with respect to a consensus reference diagnosis.

Results: Average case-level diagnostic accuracy of single reviewers was 65.3% (95% CI: 63.4–67.2%). Second opinions arising from sequential, non-blinded reviewers significantly improved

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Ethics Statement: Procedures were HIPAA-compliant and approved by Institutional Review Boards of the Fred Hutchinson Cancer Research Center and UCLA David Geffen School of Medicine.

accuracy to 69.9% (95% CI: 68.0–71.7%; $P=0.0002$). Similarly, second opinions arising from blinded reviewers improved upon the accuracy of single reviewers (69.2%; 95% CI: 68.0–71.7%). Non-blinded reviewers gave diagnoses in the same diagnostic classes as the first diagnosis more often than blinded reviewers. Non-blinded reviewers tended to be more confident when they agreed with prior reviewers, even with inaccurate diagnoses.

Conclusions: Non-blinded or blinded second reviewers offer a similar improvement in diagnostic accuracy compared to single reviewers. Obtaining second opinions with knowledge of prior reviews tends to generate agreement among reviews, and may generate unwarranted confidence in an inaccurate diagnosis. Combining aspects of both blinded and non-blinded review in practice may leverage the advantages while mitigating the disadvantage of each approach.

INTRODUCTION

The purpose of second opinions in clinical care is to improve diagnostic accuracy and, ultimately, patient outcomes. A study of breast cancer found that a second review by a multidisciplinary tumor board changed the diagnosis for 43% of the 70 patients.¹ Similarly, second opinions for prostate consultations more often resulted in discordant rather than concordant diagnoses.²

There is high diagnostic variability for certain skin biopsy specimens, particularly for melanocytic proliferations³, leading to proposals for mandatory second opinions⁴. A prior study of second opinions for diagnosing melanocytic skin lesions found modest improvements in diagnostic accuracy using second opinion strategies⁵. In that study, all case reviews were conducted independently – reviewers were blinded to the diagnostic results of all prior reviewers. This was noted as a study limitation because it deviates from typical clinical practice.

The present investigation into second opinions for diagnosing melanocytic skin lesions incorporates more realistic circumstances, namely that subsequent reviewers were *not blinded* to prior reviews. We are not aware of existing research on the impact of blinding on diagnostic results in pathology. In contrast, blinded vs. non-blinded double-reading has been studied in radiology, especially mammography.^{6,7}

We designed a study to estimate the accuracy of diagnoses obtained from (i) single reviewers; (ii) three independent, blinded reviewers; and (iii) three sequential, non-blinded reviewers (Figure 1). We gathered diagnoses from three rather than two reviewers in order to have a “tie-breaker” when first and second reviewers gave disparate diagnoses, which is a common approach in practice⁸ and previously used to study second opinions in pathology.^{9,10} We compared diagnostic accuracy using 100 cutaneous melanocytic lesions that cover the full range from benign to invasive melanoma. In this study, all interpretations are from pathologists who are board-certified and/or fellowship-trained in dermatopathology (“experienced dermatopathologists” for brevity).

MATERIALS AND METHODS

Pathologist Eligibility, Recruitment, and Data Collection

The current investigation uses diagnostic interpretations of melanocytic skin lesions by dermatopathologists who participated in one of two studies: the Melanoma Pathology Study (M-Path) and the Reducing Errors in Melanocytic Interpretations Study (REMI). For both studies, pathologists were eligible if they had completed residency and/or fellowship training, and had interpreted melanocytic lesions in clinical practice within the previous year with plans to continue for 2 years. The REMI study additionally specified board certification and/or fellowship training in dermatopathology for eligibility, and this investigation only uses data from the subset of M-Path participants meeting this criterion. Altogether, the current investigation uses data from 74 experienced dermatopathologists who participated in M-Path (Phase I) and all 151 experienced dermatopathologists who participated in REMI.

The design and conduct of both the M-Path and REMI studies have been previously described.^{3,11} Both studies had high response and retention rates. In both studies participants interpreted H&E glass slides of melanocytic skin biopsies and provided their diagnostic results and confidence using an online histology form. The cases used in the REMI study were a subset of the cases used in the M-Path study. Procedures were HIPAA-compliant and approved by Institutional Review Boards of the Fred Hutchinson Cancer Research Center and UCLA David Geffen School of Medicine.

Test Case Development and MPATH-Dx Classification

Development of study cases has been previously described.³ Briefly, a consensus panel of three dermatopathologists with recognized expertise in cutaneous melanocytic lesions (RLB, DEE, and MWP) independently reviewed 240 melanocytic skin cases, followed by identifying a consensus diagnosis¹² for each case. Diagnoses were mapped to one of five classes using the Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis (MPATH-Dx) scheme.^{3,13,14} The MPATH-Dx classes range from benign or mildly dysplastic nevi (Class I) to fully malignant invasive melanoma (Class V), with each class associated with suggested treatments. The MPATH-Dx classes and example diagnostic terms are as follows: class I, nevus or mild atypia; class II, moderate atypia; class III, severe atypia or melanoma in situ; class IV, pT1a invasive melanoma; class V, pT1b invasive melanoma. The consensus panel identified 3 sequentially-cut glass slides for each case that matched the consensus diagnosis, and one of the three was included in study test sets. Due to fading, glass slides were replaced with sequential cuts mid-way through REMI Phase I.

This investigation uses 100 of the 240 cases described above, selected by randomly drawing 20 cases from each MPATH-Dx class. Using stratified randomization, we arranged the 100 cases into 10 test sets of 10 cases each (two supp

Non-blinded second opinions

For this investigation, first opinions were interpretations by experienced dermatopathologists in the M-Path study on the 100 cases. Each REMI participant provided second opinion

interpretations for 10 cases in REMI Phase 1. After 12 months, each REMI participant provided third opinions for a different 10 cases in REMI Phase 2 (see Appendix 2 for details). A scheme of randomization and Latin Square designs ensured that second opinions received for each of the 10 cases interpreted by a participant in REMI Phase 2 were from different REMI Phase 1 pathologists, and that each Phase 1 interpretation of a case was used only once as a 2nd opinion in Phase 2 (Appendix 2).

When giving non-blinded second opinions, participants received the following message in the online histology form: “*First reviewer’s diagnosis: An experienced board-certified and/or fellowship-trained U.S. dermatopathologist previously diagnosed this case, using the same glass slide (or a sequential cut if the original had faded), as follows [diagnosis inserted].*” When giving non-blinded third opinions, participants received information in the same way about the first and second opinions.

Study Endpoints and Data Analysis

The primary study endpoint is the average diagnostic accuracy of the 100 cases. We compared this endpoint for three strategies: single readers; blinded second opinions; and sequential, non-blinded second opinions (Figure 1). An interpretation is deemed accurate if it maps to the same MPATH-Dx class as the consensus reference diagnosis.

For the second opinion strategies, we defined the composite diagnosis as the majority opinion if at least 2 of the 3 interpretations map to the same MPATH-Dx class, or the median MPATH-Dx class otherwise.^{9,10} See Appendix 3.

In a pre-specified secondary analysis, we repeated the primary analysis on 45 of the 100 cases where at least 30% of experienced dermatopathologists giving first opinions indicated that they would want a second opinion. We also pre-specified a secondary analysis collapsing MPATH-Dx classes of diagnoses with similar associated risks and treatment suggestions. Specifically, we collapsed MPATH-Dx classes I & II and III & IV, keeping class V separate. We refer to this as 3-category accuracy, in contrast to the primary analysis of 5-category accuracy.

To further compare blinded and non-blinded second opinions, we examined how often triple-reads yielded diagnoses in 1, 2, or 3 different MPATH-Dx classes. For the non-blinded strategy, we examined the self-reported diagnostic confidence of third reviewers, and whether confidence was associated with concordance among reviewers.

RESULTS

Characteristics of participants in the M-Path and REMI studies are very similar (Table 1). REMI participants (N=151) have slightly more years of experience interpreting melanocytic skin lesions than M-Path participants (N=74). When serving as a consultant on a case in clinical practice, most report that they read a first opinion after viewing the slides but before finalizing their own diagnoses (Table 1).

Figure 1 summarizes the diagnostic strategies of single-reads, blinded second opinions, and non-blinded second opinions. All single-read interpretations were blinded to all other

interpretations. These interpretations provided the data to study single-read and blinded second opinions. To study non-blinded second opinions, dermatopathologists gave second opinions, with knowledge of first opinions, in Phase 1 of the REMI study; they gave third opinions, with knowledge of first and second opinions, in Phase 2 of the REMI study.

In total, 225 experienced dermatopathologists contributed 4,510 case interpretations to this investigation. For the 100 cases, the average case accuracy of the composite diagnosis from sequential, non-blinded reviewers was 69.9% (95% CI: 68.0–71.7%). This is nearly identical to accuracy of composite diagnoses from independent, blinded reviewers at 69.2% (95% CI: 66.3–72.1%) and modestly higher ($P=0.0002$) than single reviewer accuracy at 65.3% (95% CI: 63.4–67.2%). Appendix 4 shows results stratified by the MPATH-Dx class of the reference diagnosis. For each MPATH-Dx class, accuracy is higher with second opinions compared to single reviewers, but blinded second opinions were not consistently more or less accurate than non-blinded second opinions.

Figure 2 summarizes results for the primary analysis (summarized above), analyses of the subset of 45 challenging cases, and analyses using the simplified 3-category classification. As expected, average case-level accuracy was lower for the subset of 45 challenging cases, and higher for the simplified 3-category classification. In all analyses, blinded and non-blinded second opinions were similarly accurate, and modestly more accurate than single reviewers. Supplementary Figure 1 gives results for individual cases. Second opinions consistently improved accuracy over single interpretations, but there was no consistent trend for better results with or without blinding.

Somewhat greater differences between blinded and non-blinded diagnoses were seen in examining the concordance among three reviewers. Across all cases and participants, 49.9% of blinded triples-reads were internally concordant for MPATH-Dx class; when opinions were non-blinded the proportion was higher at 59.8% (Appendix 5A). The comparison is similar when conditioned on whether the final diagnostic result is accurate (Appendix 5B) or inaccurate (Appendix 5C). In particular, when the composite diagnosis from three reviewers is inaccurate, 19.0% of blinded triple-reads contain three diagnoses within the same MPATH-Dx class, compared to 29.9% when non-blinded. A different framing of the same data is that blinded reviewers were more likely to generate diagnoses in different diagnostic classes compared to non-blinded reviewers. For example, 9.4% of blinded triple-reads yielded three distinct diagnoses compared to 4.6% of non-blinded triple-reads (Appendix 5A).

Participants rated their confidence for each case interpretation using a 6-point confidence scale (1: Not at all confident - 6: Very confident; 5-point range). Participants mostly used a small portion of the scale: 89.6% of confidence ratings were 4, 5, or 6 (2-point range). Third reviewers were significantly more confident when their diagnoses matched both of the first two opinions than when any discordance existed (confidence ratings higher by mean 0.56 points (95% CI: 0.46, 0.65)). See also Appendix 6.

DISCUSSION

Many patients seek second opinions when diagnosed with cancer, yet second opinions receive little research attention. Prior research on second opinions in the diagnosis of melanocytic skin lesions exclusively studied blinded second opinions, but most experienced dermatopathologists report in our study that they are not blinded when giving second opinions in practice. The current investigation examined the impact of blinded vs. non-blinded second opinions for melanocytic skin lesions, finding that blinded and non-blinded second opinions yielded similar improvements in accuracy over single reviews.

Larger differences between blinded vs. non-blinded review emerged when we examined concordance among three reviewers. Non-blinded reviewers were more likely to produce three concordant opinions compared to blinded reviewers (60% compared to 50%). This was true even when interpretations were inaccurate (30% compared to 19%), suggesting anchoring and confirmation biases.^{15,16} Non-blinded second and third reviewers might seek to confirm a prior diagnosis instead of considering the full diagnostic spectrum¹⁷, generating concordance. Moreover, non-blinded third reviewers were significantly more confident in their interpretations when their diagnoses agreed with the first two reviewers. Unanimity could produce misplaced confidence in an inaccurate diagnosis of a biologically significant lesion.

Strengths of this investigation include the innovative study design to examine the challenging and understudied topic of second opinions. This investigation involved 225 U.S. dermatopathologists participating in one of two studies, M-Path and REMI. Participants contributed many hours interpreting cases, reflecting their commitment to patient care. Study cases span the full diagnostic spectrum and the five MPATH-Dx classes are represented equally. While we consider this a strength of this research, study cases are more challenging than cases seen in clinical practice.

Dermatopathologists interpreted cases in this study in a testing situation that is not representative of routine practice in important respects. Consultants in practice can typically access all available clinical, histopathological, and ancillary-testing information, and there is often non-blinded discussion with colleagues. In contrast, study pathologists had no access to additional information beyond patient age and sex, biopsy site, and specimen type, and did not have to issue final reports with the attendant responsibilities.

In prior work, the greatest diagnostic variability occurred for lesions classified in MPATH-Dx Classes II, III, and IV, with <50% inter-observer agreement within these classes.³ These intermediate lesions pose less risk to patients than Class V lesions. Consequently, an “inaccurate” diagnosis of e.g., a Class II lesion as Class I is unlikely to have clinical ramifications. Of course, inaccurate diagnoses sometimes have serious consequences. For example, consider a particular case in this study, which represents MPATH-Dx class V according to the consensus reference diagnosis. In this investigation, non-blinded second opinions yielded 7 out of 16 composite diagnoses in Class III or lower, with two of the 7 triple-reads unanimous for Class III.

We acknowledge that establishing the “ground truth” to assess accuracy is difficult, and likely suboptimal for some subset of lesions. Objective ground truth for uncommon ambiguous lesions could, in principle, only be established with long-term follow-up for metastasis or death, or possibly detailed genetic testing. Nonetheless, such lesions can typically be managed effectively by expert diagnostic consensus, possibly aided by ancillary testing. Finally, some diagnoses deemed inaccurate could simply reflect the challenges of implementing current diagnostic criteria and a degree of uncertainty that is inherent to the field.

We posit that blinded and non-blinded second opinions both have advantages and disadvantages. Blinded review generates independent opinions, with second reviewers who are not biased by anchoring effects.^{18,19} On the other hand, blinded second reviewers cannot consider the observations and opinions of prior reviewers, which could be helpful. Non-blinded review may unduly favor consensus, as seen in our results. A practical solution may be to incorporate aspects of both approaches, e.g., an initial blinded review, followed by a consensus-building discussion between the physicians if there is diagnostic disagreement.

In summary, this investigation found that second opinions improve accuracy, regardless of whether reviewers are blinded or not. When multiple reviewers are non-blinded, they are more likely to give similar diagnoses, and agreement among reviewers is associated with higher diagnostic confidence. An approach that incorporates both mechanisms into practice may leverage the advantages of each while mitigating their disadvantages.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability:

Data available on request from the authors.

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What is already known about this topic?

Second opinions have been shown to modestly improve accuracy for diagnosing challenging melanocytic lesions. In prior research, however, second opinions utilized reviewers who were blinded to the initial diagnosis, which does not reflect clinical practice.

What does this study add?

Non-blinded and blinded second opinions each offer a similar, modest improvement in diagnostic accuracy compared to single reviewers. Non-blinded second opinions increase agreement among reviewers, which is associated with higher diagnostic confidence but not necessarily improved accuracy. The ideal approach for second opinions might include initial blinded review with subsequent unblinded discussion.

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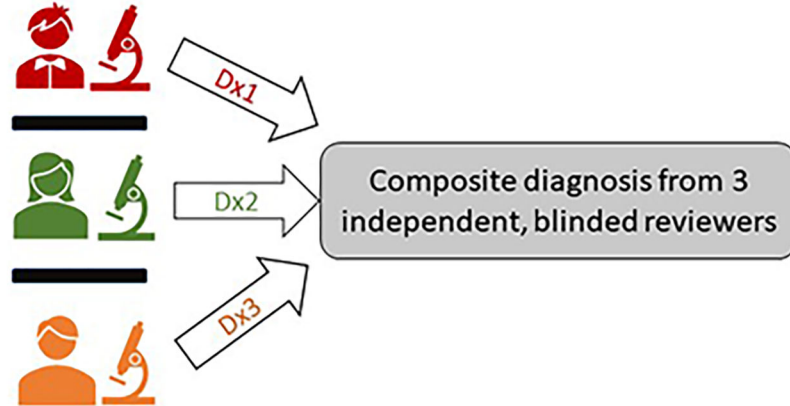
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(1) Single Reviewer



(2) Independent, Blinded Reviewers



(3) Sequential Reviewers, Non-Blinded

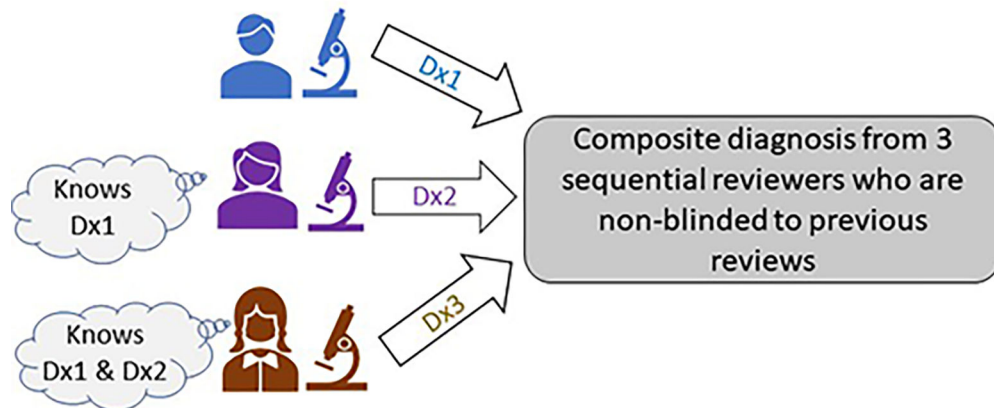


Figure 1. The three diagnostic strategies evaluated in this study.

(1) Single reviewer interprets the case. (2) Three blinded reviewers independently interpret the case, with no knowledge of each other's interpretive results. (3) Three reviewers interpret the case in sequence, non-blinded: the second reviewer knows the diagnosis of the first reviewer, and the third reviewer knows the diagnosis of the first and second reviewers. For both (2) and (3), the three diagnoses produce the composite diagnosis, which is the majority if at least two of the three agree, or the median otherwise.

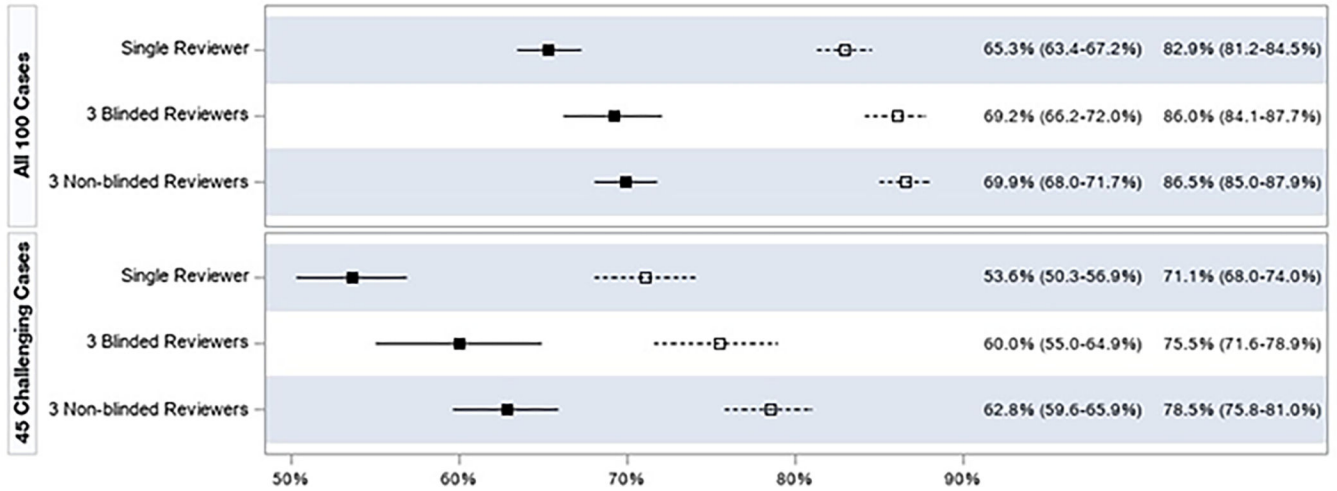


Figure 2. Average case-level diagnostic accuracy for three types of review: single reviewer; 3 blinded reviewers; and 3 sequential, non-blinded reviewers.

Dots represent point estimate and lines are 95% confidence intervals. Solid lines represent accuracy when determined by the 5-category MPATH-Dx classification scheme; dashed lines represent the simplified 3-category scheme. The top panel is all 100 cases, and the bottom panel is the analysis restricted to 45 challenging cases. In all analyses, the 3-reviewer approaches yielded similar diagnostic accuracy, modestly higher than the accuracy of single reviewers.

Table 1.
Characteristics of Study Participants.

All participants are experienced dermatopathologists, i.e. board-certified and/or fellowship-trained in dermatopathology.

Pathologist Characteristic	M-Path Study (N=74), n (%)	REMI Study (N=151), n (%)
Demographics		
Age in years		
< 40	23 (31%)	26 (17%)
40–49	25 (34%)	65 (43%)
50–59	19 (26%)	40 (26%)
60	7 (9%)	20 (13%)
Gender		
Male	49 (66%)	103 (68%)
Training and Experience		
Affiliation with academic medical center		
No	38 (51%)	71 (47%)
Yes, adjunct/affiliated clinical faculty	20 (27%)	46 (30%)
Yes, primary appointment	16 (22%)	34 (23%)
Residency^a		
Anatomic Pathology		27 (18%)
Anatomic/Clinical Pathology	57 (77%)	81 (54%)
Dermatology	19 (26%)	51 (34%)
Fellowship^a		
Surgical Pathology	17 (23%)	29 (19%)
Dermatopathology	72 (97%)	149 (99%)
Board certification^a		
Dermatology	20 (27%)	50 (33%)
Anatomic Pathology	57 (77%)	108 (72%)
Clinical Pathology	43 (58%)	77 (51%)
Dermatopathology	72 (97%)	150 (99%)
Percent of caseload interpreting melanocytic skin lesions		
< 10%	4 (5%)	7 (5%)
10–24%	38 (51%)	73 (48%)
25–49%	24 (32%)	52 (34%)
50%	8 (11%)	19 (13%)
Years interpreting melanocytic skin lesions		
1–4 years	16 (22%)	18 (12%)
5–9 years	25 (34%)	38 (25%)
10–19 years	24 (32%)	64 (42%)
20 years	9 (12%)	31 (21%)

Pathologist Characteristic	M-Path Study (N=74), n (%)	REMI Study (N=151), n (%)
<i>Second Opinions in Clinical Practice</i>		
When providing a second opinion for a melanocytic skin lesion, I prefer to receive the primary pathologist's diagnosis		
Disagree		23 (15%)
Agree		128 (85%)
If you were to serve as a consultant on a case, at what point in the diagnostic process would you typically read the primary pathologist's diagnosis?		
Before I examine the slide(s)		17 (11%)
After I examine the slide(s), but before I finalize my own diagnosis		117 (77%)
After I have finalized my own diagnosis		17 (11%)

^aPathologists could make multiple selections, therefore percentages sum to greater than 100%