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Journal
Journal of Cutaneous Pathology, 49(2)

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Publication Date
2022-02-01

DOI
10.1111/cup.14126

Peer reviewed

HHS Public Access

Author manuscript

J Cutan Pathol. Author manuscript; available in PMC 2023 July 25.

Published in final edited form as:

J Cutan Pathol. 2022 February ; 49(2): 153–162. doi:10.1111/cup.14126.

Characterization of multiple diagnostic terms in melanocytic skin lesion pathology reports

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Abstract

Background: Histopathologically ambiguous melanocytic lesions lead some pathologists to list multiple diagnostic considerations in the pathology report. The frequency and circumstance of multiple diagnostic considerations remain poorly characterized.

Methods: Two hundred and forty skin biopsy samples were interpreted by 187 pathologists (8976 independent diagnoses) and classified according to a diagnostic/treatment stratification (MPATH-Dx).

Results: Multiple diagnoses in different MPATH-Dx classes were used in n = 1320 (14.7%) interpretations, with 97% of pathologists and 91% of cases having at least one such interpretation.

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CONFLICT OF INTEREST

Dr. Elmore serves as Editor-in-Chief of Primary Care (Adult) topics at UpToDate. Dr. Elder serves as a consultant for Myriad Genetics.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Multiple diagnoses were more common for intermediate risk lesions and are associated with greater subjective difficulty and lower confidence. We estimate that 6% of pathology reports for melanocytic lesions in the United States contain two diagnoses of different MPATH-Dx prognostic classes, and 2% of cases are given two diagnoses with significant treatment implications.

Conclusions: Difficult melanocytic diagnoses in skin may necessitate multiple diagnostic considerations; however, as patients increasingly access their health records and retrieve pathology reports (as mandated by US law), uncertainty should be expressed unambiguously.

Keywords

borderline diagnosis; dermatopathologists; dermatopathology; diagnostic dilemma; melanoma; MELTUMP

1 | INTRODUCTION

Pathology reports provide critical information to guide treatment and patient care. However, biopsy specimens do not always fit into classification criteria for a single diagnosis. Pathologists may convey uncertainty by invoking more than one diagnostic consideration in the pathology report.[1–3] Cases that exhibit histopathologic and/or prognostic ambiguity are sometimes referred to as “borderline” between diagnosis x and diagnosis y. Multiple diagnostic considerations carry the potential to affect management. For example, diagnostic uncertainty could exist between a desmoplastic nevus and a desmoplastic melanoma, but these are two very different entities with differing prognoses and management.[4] On the other hand, severely dysplastic nevi may exist on a biologic continuum between a nevus and melanoma, and the management recommendation of a severely dysplastic nevus may be the same as for a melanoma in situ or even a T1a melanoma.[5]

While cases that elicit multiple diagnoses are often discussed between pathologists and clinicians, the usage of multiple diagnostic considerations on a pathology report has not been well-characterized. Because clinical management of melanocytic lesions relies on the pathology report, multiple diagnoses can present challenges in patient care and may generate confusion regarding a melanocytic lesion’s biologic potential. We assessed how often and under what circumstances pathologists use multiple diagnoses when interpreting melanocytic lesions, focusing on instances where multiple diagnoses result in significantly divergent treatment considerations.

2 | MATERIALS AND METHODS

Our study uses data from the Melanoma Pathology (M-Path) study, which examined the accuracy and reproducibility of pathologists’ interpretations of melanocytic skin lesions.[6–9] Pathologists completed a baseline survey and provided independent interpretations of melanocytic biopsy samples using a standardized histopathology classification schema, the Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis (MPATH-Dx).[7] Participants provided written informed consent, and study activities were approved by the Fred Hutchinson Cancer Research Center (#9551) and the University of California, Los Angeles (#17–001881) Institutional Review Boards.

2.1 | Skin biopsy specimen case and reference diagnosis development

Cutaneous melanocytic biopsy specimens were obtained from patients ≥20 years of age at Dermatopathology Northwest in Washington state. Consultative cases and re-excisions were excluded. Three experienced dermatopathologists independently reviewed the same glass slide of each biopsy specimen and developed a consensus reference diagnosis for all 240 cases using a modified Delphi approach.[8] The MPATH-Dx classification tool was used to categorize interpretations into five diagnostic classes ranging from class I (eg, benign nevi where no further treatment is usually suggested), to class V (eg, invasive melanoma ≥pT1b where treatment with a wide excision and sentinel lymph node sampling and/or adjuvant therapy is considered) (Table S1).[7] "Variable diagnoses" (eg, *superficial atypical melanocytic proliferations of uncertain significance* [SAMPUS] and *melanocytic tumors of uncertain malignant potential* [MELTUMP]) were classified from MPATH-Dx class II to IV based on the suggested treatment consideration. Two hundred and forty cases were divided into five slide sets of 48 cases. To enrich the study set for potentially challenging cases, the final 240 cases had intentionally higher proportions of classes II to V than are typically encountered in practice: 10.4% (n = 25) in class I, 15.0% (n = 36) in class II, 25.0% (n = 60) in class III, 24.2% (n = 58) in class IV, and 25.4% (n = 61) in class V.

2.2 | Population estimates

Because the sample of test cases was enriched for MPATH-Dx classes II to V, we extrapolated the observed use of multiple diagnoses to a US population-based distribution of melanocytic skin lesions using previously described methods.[6,10] In clinical practice, a population-based analysis of a large health-care delivery system found a distribution of 83.1% class I, 8.3% class II, 4.5% class III, 2.2% class IV, and 1.9% class V among all melanocytic skin lesions.[11] To obtain population estimates of the frequency of pathology reports listing multiple diagnoses, we applied the class-specific percentage of multiple diagnoses found in this study to the population-based class distribution.

2.3 | Study pathologists

Pathologists in 10 US states were selected from the College of American Pathologists and American Society of Dermatopathology membership lists and invited to participate through email, postal mail, and telephone contact. Eligibility criteria included self-reported interpretation of melanocytic skin lesions over the past year and an expectation to continue interpreting melanocytic skin lesions over the next 2 years. Residents and fellows in training were excluded. Three hundred and one pathologists met eligibility criteria, and 187 (62%) completed the study. An online baseline survey queried participants' demographics and perceptions of topics clinically relevant to the field. The survey also included a question asking pathologists "For what percentage of melanocytic skin lesions is your final assessment that the diagnosis is borderline or uncertain?" without defining "borderline or uncertain."

2.4 | Case interpretation by participants

Pathologists were randomized to receive one of five slide sets of 48 cases. For each case, pathologists were given the patient's age, biopsy type, and anatomic location. Pathologists

were told to assume the glass slide was representative of the lesion, and that the lesion extended to the edge of the sample.[6]

2.5 | Utilization of multiple diagnoses

Using an online histopathology form (Table S2), pathologists reported their primary diagnosis from a list of >50 diagnoses. A secondary diagnosis was allowed for cases they thought were “borderline” or indeterminate for a single diagnosis (Figure S1). Interpretations where the multiple diagnoses fell within the same MPATH-Dx class were excluded from population estimates. Cases with multiple diagnoses in different MPATH-Dx classes were classified as *adjacent* or *nonadjacent* (Table 1). Six interpretations with incomplete borderline selections were dropped from all analyses, leaving 8970 interpretations.

2.6 | Analysis

Pathologists’ use of multiple diagnoses was represented as dichotomous variables. We investigated associations between this outcome and participant, case, and other diagnostic characteristics using logistic regression. We controlled for slide set and used robust SE estimates that treated data points from the same participant as clusters to account for nonindependence. Ordered categorical variables were included in models as ordinal variables; therefore, *P*-values represent tests for trend. Nonordered categorical variables were included using indicator variable coding, so that a *P*-value for a variable with k categories is from a k-1 degree-of-freedom test. We considered results statistically significant when $P < 0.05$. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, North Carolina).

3 | RESULTS

3.1 | Case characteristics and use of multiple diagnoses

Each of the 240 cases was interpreted by a median of 38 pathologists (range 35–39). Across all 240 cases, the median percentage of interpretations per case where multiple diagnoses from different MPATH-Dx classes were given was 13% (range 0%–66%) (Figure 1A, Table S3). A total of 90.8% of cases received different-class multiple diagnoses from at least one participant and 70.4% received at least one non-adjacent second diagnosis.

3.2 | Pathologists’ characteristics and use of multiple diagnoses

A total of 96.8% of pathologists included different-class multiple diagnoses for at least one case in their test set, and 83.4% selected at least one nonadjacent second diagnosis. Figure 1B shows the variability in use of multiple diagnoses across pathologists. The median pathologist used different-class multiple diagnoses for 13% of their interpretations (range 0%–48%) and nonadjacent multiple diagnoses for 4% of interpretations (range 0%–31%). When pathologists were asked on the baseline survey about their use of borderline diagnoses in melanocytic skin lesions in their own clinical practice, the median response was 3% of interpretations (range 0%–50%).

Table 2 describes pathologists' characteristics and their rates of multiple diagnoses by these characteristics. The median age was 51 years (range 33–79) and 61% were male. Forty percent were either fellowship-trained/board-certified in dermatopathology. Seventy-two percent were not affiliated with an academic medical center. Pathologists with fewer years of experience interpreting melanocytic skin lesions were more likely to use multiple diagnoses although the association fell short of statistical significance (*P*-value = 0.0540). Agreement with the statement "interpreting melanocytic skin lesions makes me more nervous than other types of pathology" positively associates with use of multiple diagnoses (*P*-value = 0.0010).

Fellowship-trained/board-certified dermatopathologists chose different-class multiple diagnoses for 13% of interpretations compared with nondermatopathologists at 15% of interpretations (*P*-value = 0.3383); both dermatopathologists and non-dermatopathologists chose nonadjacent diagnoses for 4% of interpretations (*P*-value = 0.1507). Dermatopathologists used different-class multiple diagnoses 18.4% (2.9% nonadjacent) for class IV and 3.6% (3.6% non-adjacent) for class V, compared to 22.1% (5.6% non-adjacent) and 7.0% (7.0% nonadjacent) for nondermatopathologists, respectively (Table S4).

3.3 | Interpretation characteristics and use of multiple diagnoses

Among the 8970 total interpretations, different-class multiple diagnoses were noted for 14.7% of interpretations (858/1320 in adjacent classes and 462/1320 in nonadjacent classes).

Interpretation-level characteristics of multiple diagnoses are shown in Figure 2. Interpretations in MPATH-Dx class II were most likely to be accompanied by another diagnosis in a different class (29%). The most likely primary broad diagnostic term to have a non-adjacent diagnosis was a "Variable Class" diagnosis such as MELTUMP or SAMPUS (40%), followed by "Atypical spitzoid lesion" (13%). Multiple diagnoses were more common for cases with the highest reported diagnostic difficulty, and for cases in which participants reported being "not at all confident" in their interpretation.

3.4 | Population estimates

Although 14.7% of interpretations included different-class multiple diagnoses in the current study, the distribution of cases in the test sets differs from cases seen in usual clinical practice. Application of results from the test sets to a US population-based distribution produces population estimates of 5.9% of pathology reports of melanocytic lesions using multiple diagnostic considerations from different MPATH-Dx classes (3.6% in adjacent classes and 2.3% in the more clinically significant nonadjacent multiple diagnoses).

3.5 | Multiple diagnoses combinations

Figure 3 shows the distribution of secondary MPATH-Dx classes relative to the primary class. Although same-class multiple diagnoses were excluded from most of our analysis, multiple diagnoses with primary classes I and III often had secondary diagnoses in the same class. Class III represented the most common secondary class for primary diagnoses in classes II to V.

The most common class involved with a nonadjacent second diagnosis was class III, with the most common nonadjacent class combination class III with class V and the most common diagnostic combination being atypical spitzoid lesions with invasive melanoma (Table S5). The next most common nonadjacent class combination was class I with class III, with the most common diagnostic combination being mildly dysplastic nevus and melanoma in situ.

3.6 | Further actions by pathologist for cases with multiple diagnoses

Table 3 describes further actions and additional information requested by pathologists for interpretations with and without multiple diagnoses. Participants had a higher probability of requesting a second opinion, additional clinical history, or ordering special stains or ancillary tests for cases when they provided multiple diagnoses compared to when they provided a single diagnosis. The likelihood of pursuing further actions increased as the multiple diagnoses being considered became more discrepant.

4 | DISCUSSION

Pathologists provided multiple diagnoses for the same case in a substantial portion of interpretations of melanocytic lesions in our dataset, and almost no pathologist or case was exempt from this practice. Pathologists appear to be confident in low-to-no risk lesions even when unable to provide a single diagnosis (Figure 3). Higher rates of multiple diagnostic considerations were associated with fewer years' experience interpreting melanocytic skin lesions and agreement with the statement "interpreting melanocytic skin lesions makes me more nervous than other types of pathology." Perhaps less predictably, no statistically significant difference in rates of multiple diagnoses in different MPATH-Dx classes was seen between fellowship-trained, board-certified dermatopathologists and nondermatopathologists (Table 2); however, when considering higher class lesions (class IV/V), dermatopathologists were less likely than nondermatopathologists to render different-class multiple diagnoses (both for adjacent and nonadjacent combinations) (Table S4). Board-certified dermatopathologists have also been shown to request ancillary studies more often in melanocytic skin lesions compared to general pathologists.[12]

Certain lesions outside the conventional melanocytic spectrum were more frequently associated with nonadjacent multiple diagnoses, including persistent/recurrent nevi, blue nevus variants, and melanocytic proliferations with spitzoid features. The lattermost category is a well-known challenge for pathologists, representing the second most common primary term for multiple diagnoses (both adjacent and nonadjacent) after use of variable class diagnoses such as MELTUMP or SAMPUS. Spitzoid features were usually regarded with higher concern, with most diagnosed as a primary class V and secondary class III (Figure 4A). The opposite trend existed with blue nevi variants (Figure 4B) and persistent/recurrent nevi.

Describing uncertainty in diagnostic impressions can be performed in several ways, including conveying ambiguity between two diagnostic entities, emphasizing a lack of clinical context, and/or describing inherent limitations with a morphologic diagnosis. Magro et al attempted to characterize "dermal-based borderline melanocytic tumors" with

objective morphologic criteria.[13] Zembowitz has advocated for the nevus-melanocytoma-melanoma paradigm, now adopted by the WHO,[14] characterizing borderline lesions as either of indeterminate malignant potential in nature (ie, uncertainty about the diagnosis), or intermediate malignant potential (ie, between benign and malignant), or both.[15] Foucar has observed that the diagnostic process is an example of complex decision-making that has intrinsic uncertainty, resulting for example, from the large number of variables that can be evaluated (many of which may lack clear definition and/or biological correlation), eventuating in novel combinations of variables that cannot be managed consistently by problem solvers.[16]

Two main principles for dealing with uncertainty have been proposed.[17] First, patients and clinicians deserve to be made aware that their lesion cannot be definitively diagnosed. Uncertainty should not be dismissed in a report because doing so would generate false assurance of confidence in any diagnosis. Second, “uncertain” lesions should be managed by means sufficient to provide adequate therapy for the most clinically significant entity in the differential diagnosis. This may, for example, result in a recommendation for complete excision and consideration of sentinel lymph node staging based on microstaging attributes (ie, ulceration, Breslow thickness) that should be included in the pathology report to facilitate decision making.

This study has several limitations. Testing conditions significantly differed from real-world practice, as pathologists reviewed a single glass slide without access to ancillary immunohistochemical or molecular studies, and they had no ability to consult other pathologists. Slide sets were enriched with a greater percentage of cases representing the middle and higher end of the MPATH-Dx classes than would be seen in typical clinical practice. We attempted to mitigate this by employing US population-based estimates to translate our findings into what would be expected in real-world practice. The absence of clinical photographs and additional clinical information might also affect a pathologist’s ability to reach a definitive diagnosis. The strengths of this study include a wide geographical distribution of pathologists reviewing a diverse variety and volume of cases. To our knowledge, this study represents the largest dataset examining the practice of multiple diagnoses applied to the same case.

Given the considerable variability shown in the reproducibility of diagnosis of pigmented lesions by pathologists—particularly within the “intermediate” category—it seems appropriate that pathologists may report cases as “borderline” or “uncertain” in a high proportion of cases.[6] As ancillary testing progresses and costs decrease, histopathologic ambiguity might be resolved with defined molecular signatures. In practice, descriptive terms are often accompanied by a differential diagnosis and prognostic factors, enough for clinicians to allow for rational planning of therapy. As we enter an era where patients access their electronic health records (as mandated by US law) and retrieve electronic pathology reports, uncertainty must nonetheless be expressed unambiguously. Reliance on appropriate resources and communication between the clinician and pathologist is paramount for these challenging cases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

We thank the study participants for their commitment to improving clinical care in dermatopathology. We also thank Paul Litwin of Fred Hutchinson Cancer Research Center, Collaborative Data Services, for development of the M-Path web platform. A special thank you to the reviewers of this paper for their comments that improved our manuscript.

Funding information

National Cancer Institute, Grant/Award Numbers: R01 CA151306, R01 CA200690, R01 CA201376

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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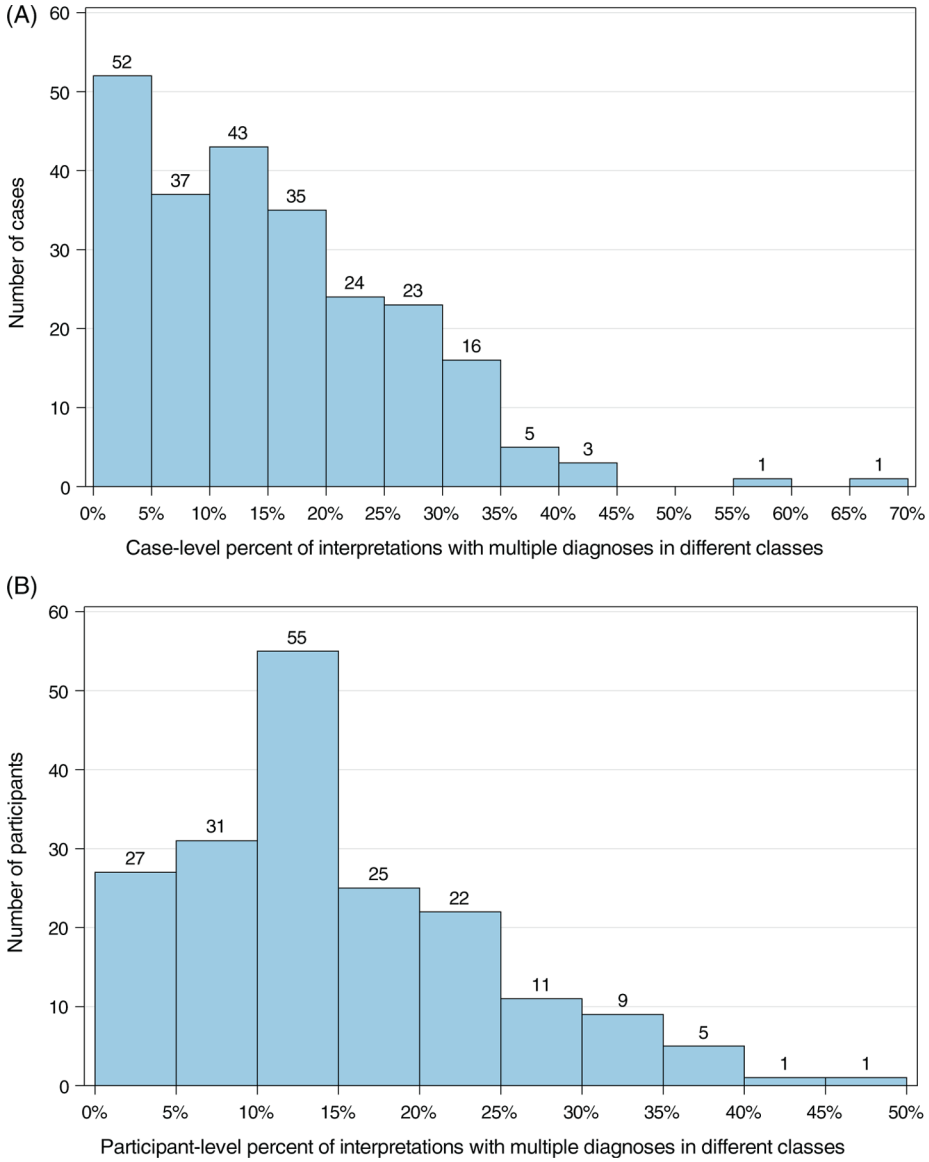

FIGURE 1.

A, Case-level utilization of more than one diagnosis per case, with multiple diagnoses in different MPATH-Dx classes (n = 240 cases). Cases ranged from 0% to 66% of participants giving multiple diagnoses. The median case had 13% of participants giving multiple diagnoses. B, Participant-level utilization of more than one diagnosis per case, with multiple diagnoses in different MPATH-Dx classes (n = 187 participants). Participants included multiple diagnoses for a range from 0% to 48% of their cases. The median participant gave multiple diagnoses for 13% of their cases

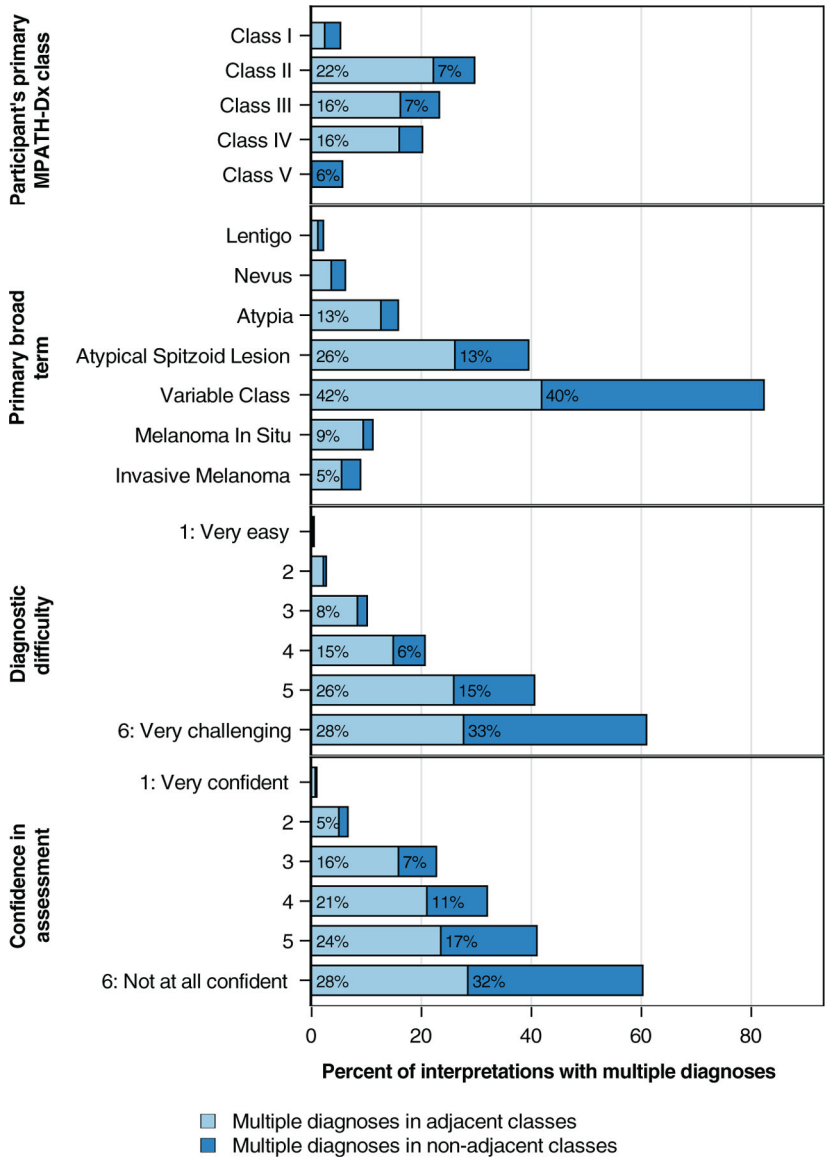

FIGURE 2.

Frequency of subtypes of different-class multiple diagnoses (adjacent MPATH-Dx class, nonadjacent MPATH-Dx class) by participant-reported interpretation characteristics (n = 8970)

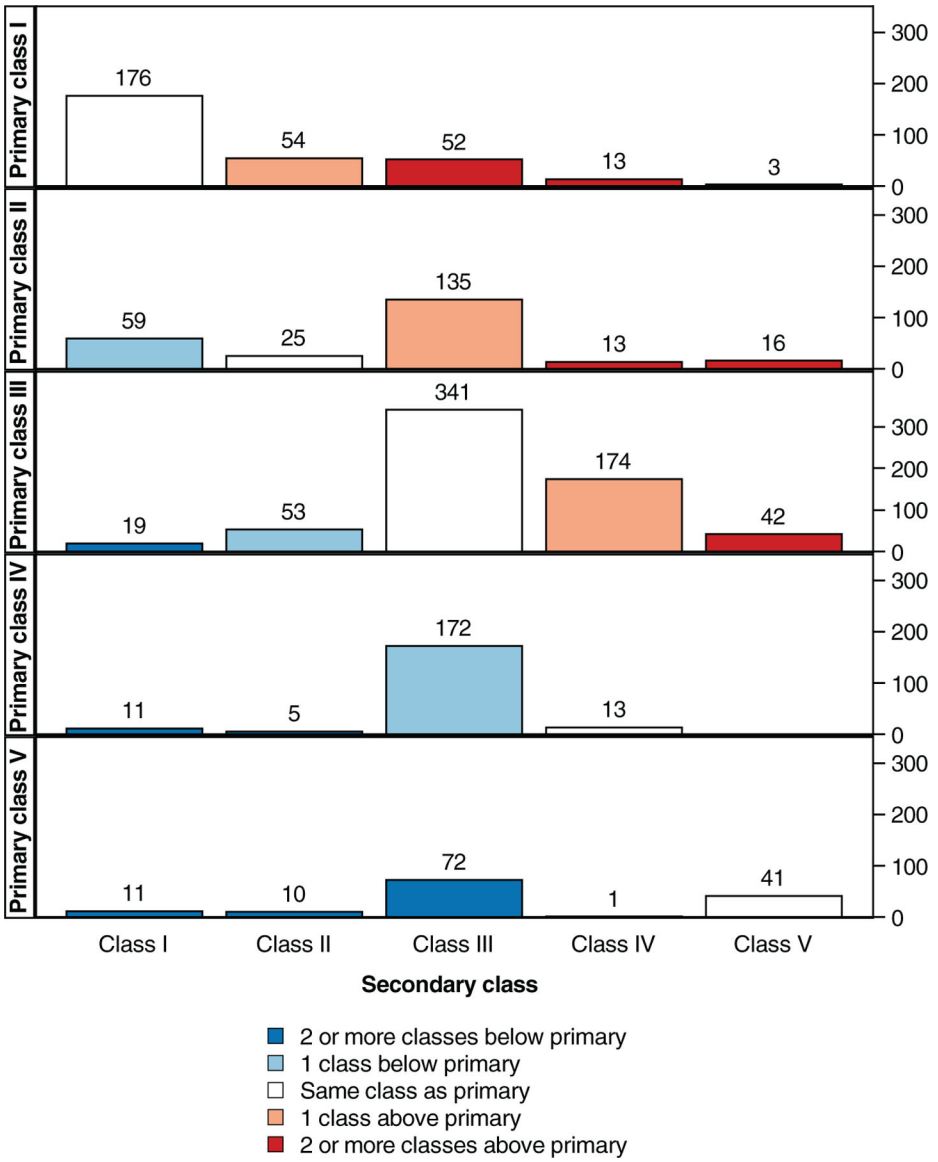

FIGURE 3.

Comparison of participants' primary and secondary diagnosis classes for interpretations with multiple diagnoses (n = 1511 total after excluding 480 variable class interpretations and 10 interpretations including class 0[a]). Primary classes are represented by rows, and secondary class frequencies are shown as vertical bars. [a]For variable class interpretations, we evaluated the distance across the range of MPATH-Dx classes of the three diagnoses selected (primary diagnosis and two borderline diagnoses). The participants were not required to select a preference between the two borderline diagnoses, and the treatment recommendation used to determine the primary MPATH-Dx Class did not necessarily align with either of the borderline diagnoses in all cases. Because of the lack of a definite primary class assignment, we do not present the variable class interpretations. Additionally, two interpretations with primary class 0 and 8 observations with secondary class 0 were omitted

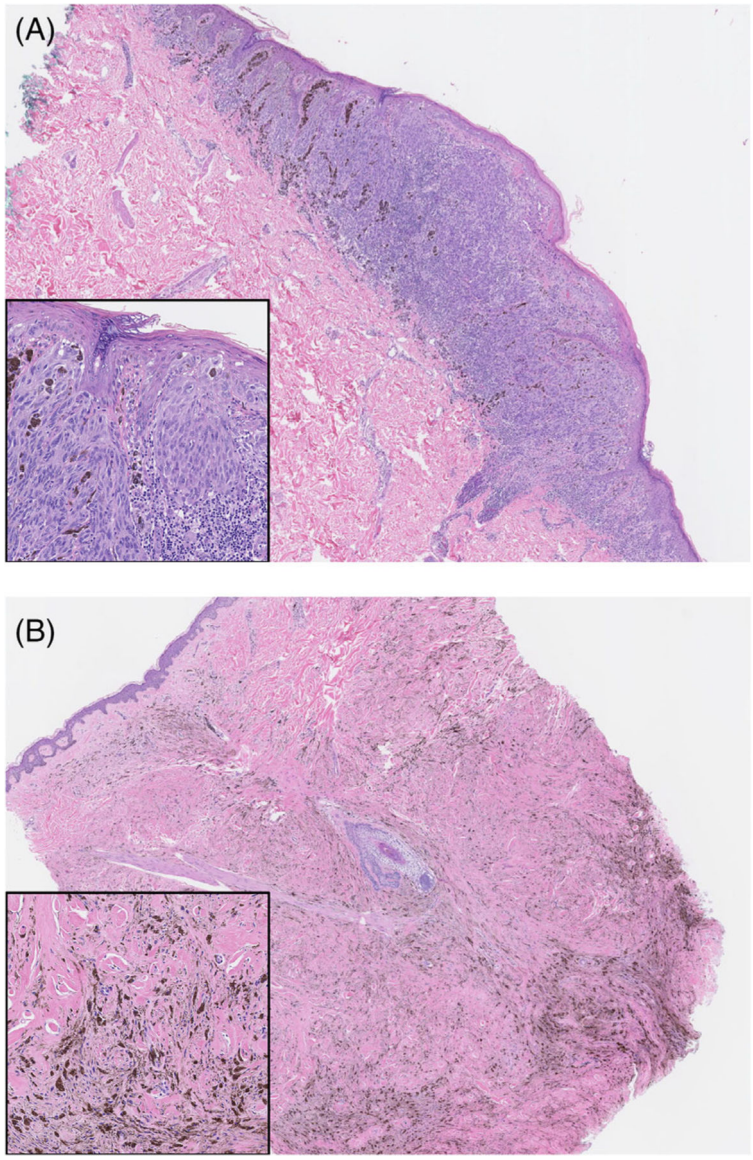

FIGURE 4.

Examples of melanocytic lesions with high rates of multiple diagnoses. A, Malignant expert consensus diagnosis of invasive melanoma with spitzoid features (H&E; ×3.25; inset: ×20). n = 38 participants interpreted this case; 66% of interpretations were different-class multiple diagnoses, of which 80% were nonadjacent (most common class combination was class III/V). B, Benign expert consensus diagnosis of cellular/epithelioid blue nevus (H&E; ×3.25; inset: ×20). n = 36 participants interpreted this case; 33% of interpretations were different-class multiple diagnoses, of which 62% were nonadjacent (most common class combination was class II/V)

TABLE 1

Definitions and clinical examples of multiple diagnoses in different MPATH-Dx classes that occur when two diagnoses are provided in the final pathology report[a]

Multiple diagnoses terms	Definition	Clinical example
Adjacent: MPATH-Dx classes	Borderline diagnoses in which the primary and secondary diagnoses are one class apart according to the MPATH-Dx classification	Melanoma in situ (MPATH-Dx class III) vs superficially invasive melanoma (MPATH-Dx class IV)
Nonadjacent: MPATH-Dx classes	Borderline diagnoses in which the primary and secondary diagnoses are more than one MPATH-Dx class apart	Mildly dysplastic nevus (MPATH-Dx class I) vs melanoma in situ (MPATH-Dx class III)

[a]Variable class diagnoses: MPATH-Dx class used to categorize lesions of uncertain malignant potential. Classified as either MPATH-Dx class II to IV based on the suggested treatment consideration (worst case scenario). Clinical examples include superficial atypical melanocytic proliferations of uncertain significance (SAMPUS), MELTUMP (melanocytic tumors of uncertain malignant potential).

TABLE 2

Pathologist characteristics and utilization of different-class multiple diagnoses (n = 187 pathologists with 43–48 interpretations per pathologist)

Characteristic	n(%)	Percent of interpretations with multiple diagnoses in different classes (adjacent or nonadjacent), per participant–median % across pathologists (range, %)	Percent of interpretations with multiple diagnoses in nonadjacent classes, per participant–median % across pathologists (range, %)
Overall	187 (100)	13 (0–48)	4 (0–31)
Demographics			
Age			
<50 years	87 (47)	15 (0–48)	4 (0–17)
≥50 years	100 (53)	13 (0–42)	4 (0–31)
Gender			
Male	114 (61)	13 (0–48)	4 (0–31)
Female	73 (39)	15 (0–35)	4 (0–17)
Training and experience			
Affiliation with academic medical center			
No	134 (72)	13 (0–42)	4 (0–31)
Yes, adjunct/affiliated clinical faculty	34 (18)	14 (2–48)	4 (0–19)
Yes, primary appointment	19 (10)	15 (2–25)	2 (0–15)
Residency (check all that apply)			
Anatomic/clinical pathology	169 (90)	13 (0–48)	4 (0–31)
Dermatology	19 (10)	10 (2–29)	2 (0–19)
Other	6 (3)	17 (8–33)	4 (2–10)
Fellowship and/or board certified in dermatopathology			
No	113 (60)	13 (0–48)	4 (0–31)
Yes	74 (40)	15 (2–35)	4 (0–19)
Years interpreting melanocytic skin lesions			
<5 years	29 (16)	19 (2–48)	4 (0–15)
5 to 9 years	45 (24)	15 (2–35)	4 (0–17)
10 to 19 years	57 (30)	10 (0–38)	4 (0–17)
≥20 years	56 (30)	13 (0–42)	4 (0–31)
Percentage of caseload interpreting melanocytic skin lesions			
<10%	79 (42)	13 (0–48)	4 (0–31)

Characteristic	n(%)	Percent of interpretations with multiple diagnoses in different classes (adjacent or nonadjacent), per participant–median % across pathologists (range, %)	Percent of interpretations with multiple diagnoses in nonadjacent classes, per participant–median % across pathologists (range, %)
10% to 24%	72 (39)	13 (0–40)	4 (0–19)
≥25%	36 (19)	15 (2–31)	4 (0–15)
Considered an expert in melanocytic skin lesions by colleagues			
No	108 (58)	13 (0–48)	4 (0–31)
Yes	79 (42)	15 (0–35)	4 (0–19)
Attitudes			
Interpreting melanocytic skin lesions makes me more nervous than other types of pathology		*	
Strongly disagree or disagree	31 (17)	10 (0–25)	4 (0–15)
Slightly disagree	27 (14)	13 (0–23)	6 (0–13)
Slightly agree	51 (27)	13 (0–38)	4 (0–19)
Agree	55 (29)	13 (0–48)	4 (0–31)
Strongly agree	23 (12)	19 (2–40)	5 (0–15)
Confidence in assessments of melanocytic skin lesions			
1: very confident	33 (18)	10 (2–33)	4 (0–15)
2	90 (48)	15 (0–42)	4 (0–31)
3	38 (20)	15 (0–48)	4 (0–17)
4/5	26 (14)	13 (2–40)	4 (0–15)
6: not at all confident	0 (0)	–	–

*P-value <0.05 for association with borderline diagnosis.

TABLE 3

Further actions or requested information reported by participants when interpreting melanocytic skin biopsy specimen cases, by multiple diagnoses status of their interpretation (n independent interpretations = 8970)

Characteristic	Single primary diagnosis (no borderline), n (column %)	Multiple diagnoses in same class, n (column %)	Multiple diagnoses in adjacent classes, n (column %)	Multiple diagnoses in nonadjacent[a] classes, n (column %)	*P*-value for trend
Overall	6969 (100)	681 (100)	858 (100)	462 (100)	
Second opinion					
Would you ask for a second opinion for diagnostic reasons?					
No	4706 (68)	180 (26)	139 (16)	47 (10)	
Yes	2263 (32)	501 (74)	719 (84)	415 (90)	**<0.0001**
Additional information					
Would you need additional clinical history to make a definitive diagnosis?					
No	6096 (87)	445 (65)	540 (63)	251 (54)	
Yes	873 (13)	236 (35)	318 (37)	211 (46)	**<0.0001**
Would you order special stains or ancillary tests to make a definitive diagnosis?					
No	6134 (88)	468 (69)	504 (59)	240 (52)	
Yes	835 (12)	213 (31)	354 (41)	222 (48)	**<0.0001**

Note: The *P*-values were generated by tests for trend from using a single diagnosis to using multiple diagnoses of increasing discrepancy. Significant *P*-values <0.05 are bolded.

[a]Nonadjacent MPATH-Dx Classes are more than one MPATH-Dx Class apart, such as class III and class V.