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Revision of the Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis Classification Schema for Melanocytic Lesions:

A Consensus Statement

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Disclaimer: The content of this report is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

SUPPLEMENT.

eTable. MPATH-Dx V2.0 Diagnostic Mapping Tool

eFigure. MPATH-Dx V2.0 Class III: Melanoma <0.8 mm pT1a-lr

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Abstract

IMPORTANCE—A standardized pathology classification system for melanocytic lesions is needed to aid both pathologists and clinicians in cataloging currently existing diverse terminologies and in the diagnosis and treatment of patients. The Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis (MPATH-Dx) has been developed for this purpose.

OBJECTIVE—To revise the MPATH-Dx version 1.0 classification tool, using feedback from dermatopathologists participating in the National Institutes of Health–funded Reducing Errors in Melanocytic Interpretations (REMI) Study and from members of the International Melanoma Pathology Study Group (IMPSG).

EVIDENCE REVIEW—Practicing dermatopathologists recruited from 40 US states participated in the 2-year REMI study and provided feedback on the MPATH-Dx version 1.0 tool. Independently, member dermatopathologists participating in an IMPSG workshop dedicated to the MPATH-Dx schema provided additional input for refining the MPATH-Dx tool. A reference panel of 3 dermatopathologists, the original authors of the MPATH-Dx version 1.0 tool, integrated all feedback into an updated and refined MPATH-Dx version 2.0.

FINDINGS—The new MPATH-Dx version 2.0 schema simplifies the original 5-class hierarchy into 4 classes to improve diagnostic concordance and to provide more explicit guidance in the treatment of patients. This new version also has clearly defined histopathological criteria for classification of classes I and II lesions; has specific provisions for the most frequently encountered low–cumulative sun damage pathway of melanoma progression, as well as other, less common World Health Organization pathways to melanoma; provides guidance for classifying intermediate class II tumors vs melanoma; and recognizes a subset of pT1a melanomas with very low risk and possible eventual reclassification as neoplasms lacking criteria for melanoma.

CONCLUSIONS AND RELEVANCE—The implementation of the newly revised MPATH-Dx version 2.0 schema into clinical practice is anticipated to provide a robust tool and adjunct for standardized diagnostic reporting of melanocytic lesions and management of patients to the benefit of both health care practitioners and patients.

Introduction

The mission of the pathologist interpreting melanoma and related melanocytic lesions is to provide an accurate and reproducible diagnosis to health care practitioners and their patients. This diagnostic report should be accessible, transparent, and understandable and should transmit relevant information regarding diagnosis and prognosis, thereby facilitating optimal treatment of patients.[1] Of note, a 2021 survey of practicing pathologists in the US has suggested that communication of such diagnostic information would be improved with less confusion via a more standardized reporting system.[2]

Although for decades histopathology has functioned as the gold standard for diagnosis of cutaneous melanocytic lesions, many reports over the years have called attention to a striking discordance in the interpretation of some lesions.[3–10] A 2017 study by Elmore et al,[11] the largest and most comprehensive of its kind, to our knowledge, has confirmed that histopathological diagnosis across the spectrum of atypical and dysplastic nevi, including thin melanoma, is neither accurate nor reproducible. These findings have significant implications for patient care. However, it is important to emphasize that a major factor accounting for such poor diagnostic concordance is the lack of established, agreed on, objective, and reproducible histopathological criteria along this continuum of lesions. Until more objective histopathologic breakpoints are delineated by precise correlation with genetic alterations and patient outcomes, diagnostic agreement will remain suboptimal.

In 2014, the Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis (MPATH-Dx)[12] version (V) 1.0 was introduced to provide a standardized classification system to aid both pathologists and clinicians in the diagnosis and treatment of patients with melanocytic lesions. This classification schema was envisioned to function in the same manner as the Breast Imaging Reporting and Data System,[13] a system previously developed for the standardized reporting of radiological images for breast lesions. The MPATH-Dx taxonomy has provided a mechanism for the mapping of a diverse and generally unwieldy range of diagnostic terms, some or many of which are confusing or incomprehensible, into 5 distinct classes to simplify and make transparent communication among pathologists, health care practitioners, and patients. Accordingly, this schema also may function to alleviate the anxiety that may accompany diagnostic reporting. Importantly, this system also provides information as to the probabilistic risk for tumor progression (as much as this is possible based on currently available data) and recommendations for treatment of patients along the spectrum of the MPATH-Dx categories.

We have directly witnessed how the implementation of the MPATH-Dx schema may facilitate agreement and more standardized reporting of melanocytic lesions, foster greater communication and rapport with clinicians, and improve care delivered to patients at

specific institutions.[2] It is evident that there is a substantial need for such a classification system that provides standardization and management guidelines.

Although the introduction of the MPATH-Dx schema was envisioned as a system for standardized diagnostic reporting as related to patient care, it has also served as an important platform for research and study of the classification, accuracy, and reproducibility in diagnosis of melanocytic lesions. The results from the study by Elmore et al,[11] and from current ongoing studies[14] have clearly helped to identify more precisely where the greatest diagnostic discordance lies. Although we established that agreement is poor among pathologists across the entire spectrum of atypical nevi and early melanoma, the lowest concordance rates, as low as 25% for interobserver agreement and 35% for intraobserver agreement, were recorded for moderately atypical or dysplastic lesions (the MPATH-Dx V1.0 class II category).[11] In particular, due to lack of credible criteria, pathologists are frequently prone to reclassify such lesions as being less (mild) or more (severe) atypical or even as melanoma. This finding is consistent across multiple analyses and in other independent studies.[15,16] These observations have prompted discussion about the need for changes in the MPATH-Dx V1.0 classification hierarchy.

The MPATH-Dx classification was developed with the idea of being applicable to all types of melanocytic lesions, or “one size fits all.”[12] In fact, the 5 classes in the original schema were constructed around the most common progression pathway to melanoma: common acquired nevi, atypical or dysplastic nevi, and superficial spreading melanoma, ie, melanoma developing in intermittently sun-exposed skin (low–cumulative sun damage [CSD]). While this common pathway probably accounts for 80% to 85% of melanocytic lesions encountered in routine clinical and skin pathology practice in White populations[17] and is thus clinically the most relevant, 7 other less common or rare World Health Organization (WHO) pathways to melanoma have been described and must be accommodated (excluding uveal and central nervous system melanomas).[18,19] Although the MPATH-Dx V1.0 schema did make provisions for other types of melanocytic lesions, increasing knowledge in recent years about other pathways to melanoma and the appearance of the 4th edition of the *WHO Classification of Skin Tumours* have highlighted the need to modify the original MPATH-Dx system.[20]

An important related goal of the MPATH-Dx schema was not to supplant existing nomenclatures or classifications of (primarily) benign melanocytic lesions but rather to make them more understandable and transparent by the standardized mapping of diverse terminologies into distinct MPATH-Dx classes. Thus, the MPATH-Dx schema is meant to function as an adjunct classification system to simplify diagnostic reporting and treatment recommendations.

Accordingly, following lengthy discussions and review with many colleagues and with the final consensus of the Reducing Errors in Melanocytic Interpretations (REMI) and International Melanoma Pathology Study Group (IMPSG) investigators, we have effectively implemented perceived changes that were needed. The improved MPATH-Dx V2.0 schema is described in this consensus statement.

Methods

M-Path and REMI Studies Design

The background and development of the Melanoma Pathology (M-Path) Study, including details of a 240 case-study set, and MPATH-Dx Reporting Schema for Melanocytic Proliferations and Melanoma V1.0, have been previously described.[11,12] The methods and results of the M-Path Study concerning interobserver and intraobserver agreement in diagnosis of cutaneous melanocytic lesions and melanoma have also been reported in detail.[11] All procedures were adherent with the Health Insurance Portability and Accountability Act (HIPAA), and approval was obtained from the institutional review board at the University of Washington. All participating pathologists provided written informed consent.

The more recent REMI study procedures also have been described in detail elsewhere.[21] In brief, potential study participants were identified in 40 geographically diverse US states, using a list of board-certified dermatopathologists from Direct Medical Data databases. Eligible participants met the following criteria: board certified and/or fellowship trained in dermatopathology, currently practicing in the US, had interpreted melanocytic skin biopsies within the previous year, and expected to continue interpreting melanocytic skin lesions for the next 2 years. Dermatopathologists verified as eligible were invited to enroll in the REMI study between July 2018 and July 2019, and study procedures continued through May 2021. All procedures were adherent with HIPAA, and approval was obtained from the institutional review boards of the Fred Hutchinson Cancer Research Center in Seattle, Washington and the David Geffen School of Medicine at University of California, Los Angeles. All participating pathologists provided written informed consent.

REMI participants were mailed a phase I glass slide set of 28 melanocytic lesions. Immediately after completing an MPATH-Dx V1.0 tutorial, participants reviewed each lesion and entered diagnostic interpretations and MPATH-Dx V1.0 classifications for each into the online histology reporting form, using the MPATH-Dx V1.0 diagnostic-treatment mapping tool (eTable in the Supplement). Approximately 12 to 24 months (mean, 16 months) after their phase I interpretations, participants interpreted a phase II slide set of 28 images using identical methods to document their interpretations within the histology reporting form and classified their diagnoses using the MPATH-Dx V1.0 diagnostic-treatment mapping tool. A total of 143 REMI study participants completed all study procedures and were given the option to provide feedback in a poststudy survey. Participants were provided 2 open-ended comment boxes with a 1000-word limit for their responses to the following 2 questions: “As the field progresses, the MPATH-Dx classification scheme needs continued updating. Do you have any suggestions for changes or improvements to the MPATH-Dx concept?” and “In general, what changes or improvements need to be made in the field of Dermatopathology related to melanocytic tumor diagnosis?”

Expert Reference Panel Review of REMI Feedback

REMI participant feedback was reviewed by the original MPATH-Dx reference panel of 3 internationally recognized dermatopathologists (R.L.B., D.E.E., and M.W.P.). The reference

panel met periodically on 4 occasions via video conferences during 2020 to 2021 to synthesize feedback from REMI study participants along with antecedent data from the North American Melanoma Pathology Study Group, IMPSG, American Joint Commission for Cancer (AJCC) 8th edition melanoma guidelines, WHO diagnostic criteria, and others, in an effort to iteratively revise and refine the classification tool for presentation at the November 2021 IMPSG Workshop.

International Melanoma Pathology Study Group 2021 Workshop

The annual Workshop of the IMPSG, an international society and network of expert pathologists for the advancement of clinical and basic research on melanoma, was convened with approximately 25 members and guests in attendance in November 2021 to formally discuss and revise as necessary the new version of the MPATH-Dx classification tool. Based on an iterative process of discussion and the incorporation of suggestions from the participants, a revised final version was drafted and is presented in Table 1, with the full version presented in the eTable in the Supplement.

Results

The New MPATH-Dx V2.0 4-Class System

Our prior studies[11,14] have confirmed strikingly poor rates of interobserver (as low as 25%) and intraobserver (as low as 35%) agreement of moderately atypical lesions in class II of the MPATH-Dx V1.0.[11,14] In effect, because of this inability to reliably recognize the limits of so-called *moderate* atypia, pathologists inadvertently interpret many such moderately atypical lesions in routine practice as mildly (or mildly to moderately) atypical, on the one hand, or, alternatively, as severely (or moderately to severely) atypical (even including melanoma on occasion) on the other.[11,14] In fact, many pathologists have resorted to this practical use of a 2-tiered system of mild to moderate and moderate to severe because of the difficulties in reliable grading. To address this problem, we have devised a new 2-tiered classification schema that takes the place of the old 3-tiered system: class I, defined as mild atypia; class II, moderate atypia; and class III, severe atypia. Thus, the prior MPATH-Dx V1.0 class II has been replaced by 2 newly expanded classes: MPATH-Dx V2.0 class I, indicating low grade (no atypia and mild to moderate atypia) (Figure 1) and MPATH-Dx V2.0 class II, high grade (severe atypia, including some high-end, formerly *moderately atypical lesions* and *melanoma in situ*) (Figure 2, Table 1, and Table 2). In effect, we have introduced a histopathological break point that permits classification of lesions into these new classes I and II (Table 1 and Table 2; eTable in the Supplement). In addition to the practical need for the institution of these 2 new classes I and II, there is also an objective basis for introducing this histopathological threshold criterion. We have proposed, as the principal threshold criterion, the size of nuclei in 5 or more junctional or intraepidermal melanocytes (nevus cells) in the most atypical high-power field in melanocytic nevi and related lesions relative to (1.5 times) the size of nuclei in nearby resting basal keratinocytes (Table 2), coupled with other nuclear and cytoplasmic features, disordered architecture, host response, and other morphological attributes (Figure 1, Figure 2, and Table 2). These criteria using nuclear size and architecture have been validated in previous studies[15,22,23] and have a general association with cytometric nuclear area,[24] DNA aneuploidy,[25] and

increased melanoma risk.[26] Computerized image cytometrical analysis and DNA image cytometry have provided objective evidence for classes I and II.[24,25] These morphological criteria using nuclear size and architecture were validated in a previous study with 7 observers.[15] Conclusions from that study were "Agreement was substantial to excellent for the histopathologic diagnosis of 112 melanocytic tumors by dermatopathologists. Using predetermined criteria, melanocytic dysplasia can be reproducibly graded among diverse general dermatopathologists." We expect that the synergy of eliminating 1 MPATH-Dx V1.0 class that had low accuracy and reproducibility and the introduction of clearly stated cytological criteria for the new MPATH-Dx V2.0 classes I and II should improve rates of diagnostic agreement.

The inability to distinguish a dysplastic nevus, severe (or high grade), from melanoma in situ and very thin melanoma is well established.[4,11,14,25,27] This issue with dysplastic nevus severe or high grade and melanoma in situ has already been addressed by placing both entities into the same MPATH-Dx class. These 2 entities are thus considered equivalent. A similar reasoning may apply to very thin invasive (radial growth phase) T1a melanomas. The real reason that these 3 entities cannot be easily distinguished morphologically may be that they are very closely related genetically, and morphological criteria simply do not exist to permit their subcategorization. With additional study and stringent criteria, very low–risk T1a melanoma may eventually be reclassified into new MPATH-Dx class II.

Particular entities in both the common low CSD pathway[20] and in other WHO pathways to melanoma are exceptions to the histopathological criteria outlined in Table 2 for the junctional components of nevi in this common pathway. In brief, in this WHO pathway I, these exceptions include some site-specific nevi, deep-penetrating/plexiform nevi, or melanocytomas; pigmented epithelioid melanocytomas; and *BAP1*-inactivated tumors or melanocytomas, in which atypia of the dermal component merits greater attention (as is also true in most advanced [beyond T1a] melanomas). Exceptions in other pathways include Spitz tumors, acral and mucosal nevi, proliferative nodules in congenital nevi, and cellular and other blue nevi. In particular, the baseline melanocytes in the various latter entities may be larger and have larger nuclei that surpass the nuclear size breakpoint of the 1.5 times criterion (Table 2). Thus, reliance on other criteria, such as increasing nuclear to cytoplasmic ratios, prominent pleomorphism, nuclei at least 2 times the size of those in nearby basal layer keratinocytes, thickened nuclear membranes, increasingly coarse nuclear chromatin, strikingly prominent nucleoli, and multiple nucleoli, must be used in grading and classification of the lesion (Table 3).

New MPATH-Dx V2.0 Recommendations for Treatment of Patients

Implicit in the development of the new MPATH-Dx V2.0 classes I and II is the goal of providing more clearly defined guidelines for pathologists and clinicians in the treatment of patients with these melanocytic lesions. First of all, with respect to surgical intervention for atypical nevi, we are striving to reduce the overall number of surgical procedures, in line with increasing information, eg, that many lesions with lesser degrees of atypia (ie, mild to moderate atypia; low grade in the WHO 2018 Classification) need not, in general, be re-excised because of very low risk for recurrence as bona fide melanoma.[28–32] In particular,

new class I lesions with positive margins, if adequately sampled, should not require any further therapy (especially if patients are to be followed up), whereas class II lesions with positive margins, in general, would require re-excision. Because of the lack of validated standardized criteria and imperfect knowledge concerning the biology and natural history of many atypical melanocytic lesions and melanoma, exceptions to these guidelines exist and must always be considered.[33] The provisions about exceptions are outlined in the detailed version of the new MPATH-Dx V2.0 schema (eTable in the Supplement).

Finally, in the diagnostic interpretation and management of all melanocytic neoplasms, it is of vital importance to integrate all relevant clinical information in this decision-making process. Essential clinical information should include age, sex, anatomic site, size and clinical features (gross morphology) of the individual lesion, and clinical history. A clinical photograph and the results of dermoscopy are also important considerations.

Characterization of a Low-risk Subset in MPATH-Dx V2.0 Class III pT1a Melanomas to Melanoma pT1a-lr

It has long been known that a subset of thin invasive melanomas (<1.0 mm, especially <0.76 mm) is associated with a very good prognosis, approaching 5-year overall survival rates of approximately 99%.[34–38] In general, accumulating evidence has suggested that this very favorable prognosis is associated with specific low-risk histopathological attributes: Breslow thickness less than 0.8 mm, absence of ulceration, radial growth phase only (absence of the vertical growth phase), Clark level II only (absence of Clark level III or greater; growth phase and Clark levels II and III are very closely related), absence of dermal mitotic activity, and absence of extensive regression (>50% of the melanoma).[39,40] Recent analysis of a Surveillance, Epidemiology, and End Results database has provided additional evidence to support designating such a subset of melanomas as pT1a-lr (low risk) in the new MPATH-Dx V2.0 with the latter criteria (eFigure in the Supplement).[41] With additional study, this subset of melanomas may eventually merit designation as *melanocytic neoplasm with low malignant potential*.

Introduction of WHO Pathways to Melanoma

Dating back to the mid-20th century, it had been understood that there were at least 2 developmental pathways to cutaneous melanoma.[42] Over the past 2 decades or longer, studies by Bastian[19] and Whiteman et al[18] have delineated 9 pathways to melanoma, incorporating clinical, histopathological, environmental, and genetic information.[18,19] These pathways have provided the basis for the classification of melanocytic tumors in the recent 4th edition of the *WHO Classification of Skin Tumours*.[20,43] These other pathways to melanoma have also been specifically introduced into the revised MPATH-Dx V2.0 schema (eTable in the Supplement).

A comprehensive list of cutaneous (and conjunctival) melanocytic lesions in the WHO pathways to melanoma and in the 4 MPATH-Dx V2.0 classes is provided in eTable in the Supplement. Definitions of various entities and explanations regarding the rationale for mapping lesions into these classes are provided as needed. In addition, detailed guidelines for the management of these lesions with important exceptions are included.

Discussion

The revised MPATH-Dx V2.0 schema simplifies the previous 5-class V1.0 to a 4-class hierarchy of melanocytic lesions to improve diagnostic concordance and also provides more explicit guidance in the treatment of patients. MPATH-Dx V2.0 also has clearly defined histopathological criteria for classification of class I and II lesions, specific provisions for entities in the other, much less common WHO pathways to melanoma,[20] provides guidance for classifying intermediate class II tumors (melanocytomas) vs melanoma, and recognizes a subset of pT1a melanomas with very low risk and possible eventual reclassification as a neoplasm falling short of fully evolved melanoma. Importantly, this schema is meant to be a flexible adjunct to existing nomenclatures or classification systems for benign melanocytic lesions, not a replacement. For example, a pathologist may continue to use his or her own terminology and protocol for the grading of atypical nevi and then place (or map) the individual lesion into the appropriate MPATH-Dx class I or class II based on guidelines and the need for re-excision or not.

In developing a revised 2-tiered classification system for atypical nevi (and related lesions), our goal is to define histopathologically and as precisely as possible at what point melanocytic nevi develop increased probabilistic risk for progression to melanoma[44] and when optimal surgical removal may effectively interrupt this progression. Ideally, this involves the identification of a precise genetic alteration and test with precise histopathological correlation.[45,46] To this end, we have introduced cytological criteria using nuclear size of junctional melanocytes along with other features of the junctional component of nevi as an approximate breakpoint for distinguishing MPATH-Dx V2.0 class I and II lesions. We believe that both the reduction in the number of classes and the introduction of these criteria should improve rates of concordance. However, we fully realize that low rates of diagnostic agreement cannot be eliminated overnight and that additional studies are needed to confirm improved concordance.

Pertinent to the development of the new MPATH-Dx V2.0 schema are strategies to diminish the number of, or extent of, surgical interventions and re-excisions for melanocytic lesions with low or very low risk for progression to melanoma. A number of studies have suggested that so-called *moderately atypical or dysplastic or even severely atypical or dysplastic* nevi with positive margins do not need to be systematically re-excised.[28–32] However, in view of the inability to reliably recognize moderate atypia and the recurrence of such nevi as melanoma,[31] we do not believe that sufficient evidence is currently available to support such an initiative without some refinement of criteria. Accordingly, with the introduction of the new MPATH-Dx V2.0 classes I and II, we provide criteria and guidelines for reducing the number of re-excisions for many nevi currently classified as moderately atypical.

With the introduction of the new MPATH-Dx V2.0, it is important to emphasize that clinical judgment should be exercised and that exceptions to the guidelines exist. In addition to commonly acquired nevi and related lesions in the common low-CSD pathway, other uncommon to rare entities remain controversial as to their biological nature, classification, and management.[20] These include deep-penetrating/plexiform nevi or tumors; *BAP1*-inactivated tumors; pigmented epithelioid melanocytoma; cellular blue nevi; and

proliferative nodules and atypical variants. These entities are noteworthy because of a frequent biphasic configuration comprising a common nevus and a distinctive atypical second component, often 2 genetic alterations, and a greater risk for neoplastic progression than common nevi. As a result, these lesions, including Spitz tumors, are considered intermediate tumors or melanocytomas, as proposed in the WHO 4th edition classification,[20] and are categorized as MPATH-Dx V2.0 class II. The latter entities represent a spectrum of neoplasia in which true malignancy is difficult to prove, except in rare examples by adverse biological outcome, since convincing clinical, histopathological, and molecular data are not yet available for sufficient numbers of neoplasms with sufficiently long follow-up to draw definitive conclusions. At present, there are no definitive criteria for the distinction of class III or IV lesions from class II. Nonetheless, the progressive increase in number of abnormal features, including increasing age of the patient, tumor diameter greater than 1 cm, asymmetry, ulceration, aberrant nodular or sheet-like growth, severe cytological atypia, necrosis, mitotic rates at least 3 to 6 per mm^2 (depending on patient age), loss of p16 expression, diffuse (ie >75% nuclear, grade 4+) expression of *PRAME*, Ki67 greater than 10% to 20%, 3 or more genetic alterations or copy number variations (as seen in melanoma), *CDKN2A* biallelic deletions, *TERT* promoter alterations, and *BAP1* alterations in blue nevus–derived tumors, are associated with increasing probability for melanoma.[47–50] Thus, because of frequent confusion with melanoma, complete removal of these lesions is considered prudent standard practice in line with class II lesions. However, exceptions to these guidelines may be invoked and re-excision considered unnecessary for some neoplasms.

Another issue pertinent to the development of MPATH-Dx V2.0 is the increasing controversy and debate about a putative epidemic of melanoma. That is, is the incidence of melanoma truly increasing, is it simply an artifact that can be explained away by distinct trends in patient care, or is it a combination of both?[51–54] Evidence suggests that the increased incidence of melanoma can be attributed to a combination of greatly increased screening of individuals for melanoma, increased rates of biopsy of ever smaller clinical lesions, and increased rates of overinterpretation of small and superficial atypical melanocytic nevi and related lesions as melanoma by pathologists. The latter trend by pathologists has been ascribed to so-called *diagnostic drift*, the implementation of diagnostic criteria that are overly sensitive for melanoma, and also to medicolegal concerns.[55–57] Important considerations are that mortality rates of melanoma remain flat over time and that a subset of pT1a melanomas comprises lesions with minimal risk for recurrence or metastasis (as is also the case for melanoma in situ).[41] It is envisioned that the latter subset of melanomas with very low–risk properties, as proposed in the new MPATH-Dx V2.0 class III, may eventually be reclassified as atypical neoplasms rather than melanoma. This could result in not only fewer patients burdened with the diagnosis of melanoma but also diminished intervention for staging and therapy.

Limitations

A limitation of the MPATH-Dx V2.0 schema is the continued use of subjective morphological criteria for the interpretation and classification of melanocytic lesions. However, this cannot be circumvented until a precise genetic alteration or alterations with

histopathological associations has been established for distinguishing melanocytic lesions with substantial risk for progression to melanoma vs those without such risk. However, the threshold criteria used in MPATH-Dx V2.0 provide a reasonably rational basis for classification and decision-making, and studies are underway to confirm increased accuracy and reproducibility.

Conclusions

We expect that the implementation of the new revised MPATH-Dx V2.0 schema into routine practice will provide a robust tool and adjunct for standardized diagnostic reporting of melanocytic lesions and management of patients to the benefit of both health care practitioners and patients. Nonetheless, it is clear that additional study is needed to confirm the positive impact of this tool on clinical practice and health care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Conflict of Interest Disclosures:

Drs Barnhill, Elder, and Piepkorn reported receiving grants from the National Institutes of Health (NIH) during the conduct of the study. Ms Eguchi reported receiving grants from NIH during the conduct of the study. Dr Elenitsas reported receiving personal fees from Wolters Kluwer outside the submitted work. Dr Gerami reported receiving personal fees from Castle Biosciences, Myriad Genetics, and DermTech fee outside the submitted work. Dr Lazar reported receiving personal fees from Bio-AI Health, College of American Pathologists (CAP), Caris, Elsevier, Illumina, Invitae, Nucleai, Paige, SpringerNature, and Tempus outside the submitted work; in addition, Dr Lazar has a patent for a system and method to quantify tumor-infiltrating lymphocytes pending. Dr Shea reported receiving personal fees from Castle Biosciences and Orlucent during the conduct of the study. Dr Scolyer reported receiving grants from National Health and Medical Research Council of Australia (NHMRC) during the conduct of the study and personal fees from F. Hoffmann-La Roche, Evaxion, Provectus Biopharmaceuticals Australia, Qbiotics, Novartis, Merck Sharp & Dohme, from NeraCare, Amgen, Bristol Myers Squibb, Myriad Genetics, GlaxoSmithKline, and MetaOptima Technology outside the submitted work. Dr Elmore reported serving as editor-in-chief for adult primary care topics at UpToDate outside of the submitted work. No other disclosures were reported.

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Key Points

Question

Can a revised Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis (MPATH-Dx) schema provide more standardized classification and diagnostic reporting of melanocytic lesions?

Findings

This consensus statement reports on the simplification of the MPATH-Dx version 1.0 five-class hierarchy into 4 classes to improve diagnostic concordance and to provide more explicit treatment guidance. Version 2.0 also has clearly-defined histopathological criteria for the classification of classes I and II benign lesions with specific provisions for all World Health Organization progression pathways to melanoma, provides guidance for classifying intermediate class II tumors vs melanoma, and recognizes a subset of pT1a melanomas with very low risk.

Meaning

The new MPATH-Dx version 2.0 schema is anticipated to provide a robust tool and adjunct for standardized diagnostic reporting of melanocytic lesions and patient treatment.

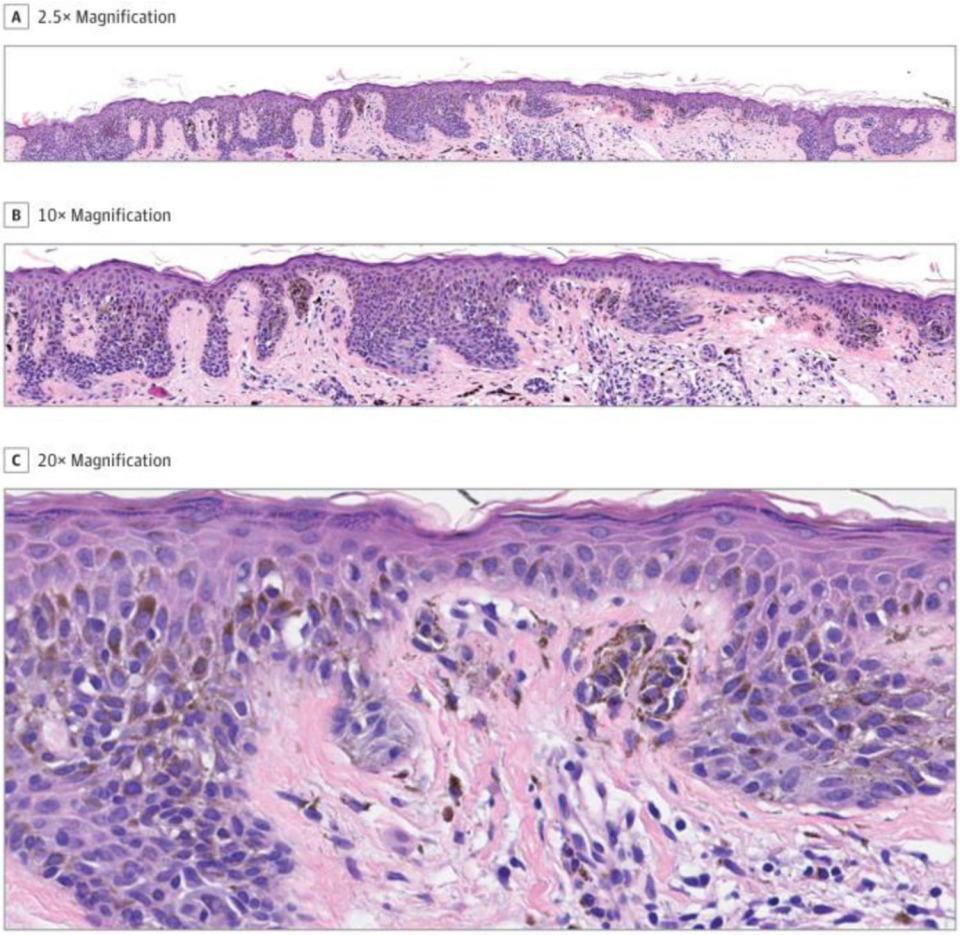

Figure 1.

Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis (MPATH-Dx) Version 2.0 Class I: Compound Nevus With Low-grade Atypia

Note disordered junctional architecture at scanning magnification (A and B). At high magnification, at least 5 melanocytes in junctional nests contain nuclei less than 1.5 times the size of adjacent resting basal keratinocytes (C). This lesion was originally associated with discordant interpretations of mild and moderate atypia by the expert panel and by consensus classified as MPATH-Dx version 1.0 class II: compound nevus with moderate atypia. Based on use of cytological and morphological criteria in Table 2, the lesion is reclassified by consensus as MPATH-Dx version 2.0 class I by the expert consensus panel.

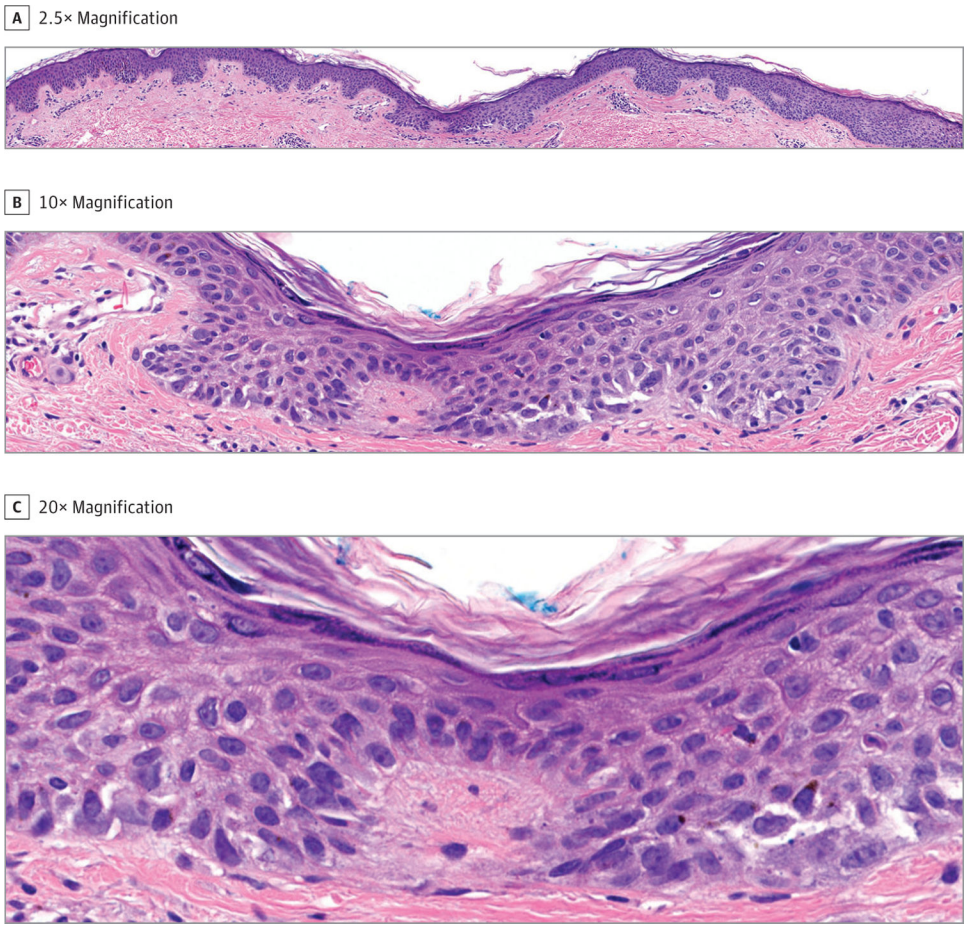

Figure 2.

Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis (MPATH-Dx) Version 2.0 Class II: Compound Melanocytic Lesion, Probable Compound Dysplastic Nevus With High-grade Atypia, Uncertain

The lesion is poorly defined and measures 4 mm in diameter (A). The junctional and dermal components are paucicellular. The junctional component comprises scant basilar single cells and disordered junctional nesting with relatively sparse pagetoid spread of melanocytes mostly confined to the lower half of the epidermis (B). Rare melanocytes (2–3 cells) reach the granular layer. No effacement of the epidermis is noted, and the epidermal rete-oriented pattern of melanocytic proliferation is maintained. Slight solar elastosis is present. At high magnification, at least 5 junctional melanocytes contain nuclei more than 1.5 times the size of surrounding resting basal keratinocytes (C). Because of scant pagetoid spread and conspicuous cytological atypia, there is concern for melanoma in situ in this lesion. Rare single atypical melanocytes in the dermis raise the possibility of focal invasive melanoma. However, a number of findings argue against clear-cut melanoma in situ or invasive melanoma. The lesion was originally associated with discordant interpretations of moderate and severe atypia by the expert panel and by consensus classified as MPATH-Dx version 1.0 class II: compound nevus with moderate atypia, but with some uncertainty about its biological nature (suspicion for melanoma in situ). Based on the use of cytological and morphological criteria in Table 2, this lesion is reclassified by consensus as MPATH-Dx

version 2.0 class II, but again with uncertainty by the expert consensus panel. This lesion illustrates how morphological criteria may not be conclusive for the definitive interpretation of many melanocytic lesions in this intermediate spectrum and particularly for high-grade lesions. Uncertainty about such lesions exists and should be communicated in diagnostic reports.

Table 1.

The Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis Version 2.0

Class	Risk of tumor progression	Probability of progression, No. per population	Treatment recommendation	Examples[a]
0	NA	NA	Consider repeat biopsy	Nondiagnostic or unsatisfactory
I: low grade	Very low risk for continued proliferation and progression to invasive melanoma	1 in 10 000 to 1 in 100 000	No further treatment[b]	Common acquired nevi, no atypia
				Congenital nevi, no atypia
				Atypical and dysplastic nevi, low-grade atypia[c]
				Common blue nevi
II: high grade	Low risk for progression to invasive melanoma	1 in 100 to 1 in 1000	Re-excision with margins <1 cm[b]	Atypical and dysplastic nevi, high-grade atypia[c]
				Spitz nevi, tumors or melanocytomas, and atypical variants
				Cellular blue nevi or melanocytomas and atypical variants
				Plexiform or deep penetrating nevi or melanocytomas
				Lentigo maligna
				Melanoma in situ
III: melanoma pT1a	Relatively low risk for local and regional metastasis	1 in 10 to 1 in 100	Follow national guidelines (eg, wide excision with 1 cm margins)[b]	Melanoma AJCC stage pT1a, <0.8 mm Breslow thickness
				Melanoma pT1a lr (low risk)[d]
				Melanoma pT1a[e]
IV: melanoma ≥pT1b	Moderate to increased risk for regional or distant metastasis	1 in 2 to 1 in 10	Follow national guidelines (eg, wide excision with 1–2 cm margins[b] and consideration of sentinel lymph node staging and other therapies)	Melanoma AJCC stage pT1b or greater, ≥0.8 mm Breslow thickness

Abbreviations: AJCC, American Joint Commission on Cancer; NA, not applicable.

[a]Examples are not a comprehensive list of diagnostic terms. A comprehensive list is provided in eTable in the Supplement.

[b]Margins are considered positive and the lesion adequately sampled.

[c]Low-grade atypia connotes nevi (or other lesions) previously graded as mild and moderate (not all), and high-grade atypia nevi (or other lesions) previously graded as moderate (not all) and severe. Degree of atypia is defined by both architectural disorder and cytological atypia.

[d]pT1a lr (low risk) is defined as radial growth phase (Clark level II) only; absence of ulceration, vertical growth phase, dermal mitotic activity, and extensive regression (>50% of tumor).

[e]Conventional pT1a risk category (does not qualify as low risk pT1a lr).

Table 2.

Cytological, Architectural, and Genetic Criteria for Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis Version 2.0 Classes I and II

Feature	Class I: low-gradeatypia[a]	Class II: high-grade atypia[b]
Cytological feature		
Size of nucleus in ≥5 junctional melanocytes in most atypical high power field	<1.5 Times the size of resting basal keratinocyte nuclei	Ranging from ≥1.5 times to >2 times the size of resting basal keratinocyte nuclei
Variability in shape and size of nucleus	Minimal to moderate	Marked (some nuclei ≥2 times larger than others)
Chromatin	Homogenous or condensed	Ranging from condensed or dispersed up to dense hyperchromatism or dispersed with thickened nuclear membranes
Nucleolus	Not visible, or visible but not prominent	Ranging from visible but not prominent up to prominent, often lavender, unless obscured by hyperchromatism
Cytoplasm	Not visible, scant, or abundant	Scant or abundant
Architectural feature		
Diameter (mm)	Ranging from <4 mm to >4 mm	>5 mm
Symmetry (vertically- bisected mirror image)	Symmetrical	Often asymmetrical
Circumscription	Sharply circumscribed	Often poorly circumscribed
Junctional nesting	Ranging from regular junctional nests to progressively irregular junctional nesting, horizontal confluence of nests, bridging of nests	Irregular junctional nests, horizontal confluence of nests, bridging of nests
Lentiginous melanocytic proliferation	Absent, slight, or focal	Contiguous melanocytes, proliferation of melanocytes between epidermal retia
Effacement of epidermis	Absent	Often present
Density of intraepidermal melanocytes	Usually lower density	Usually higher density
Pagetoid spread	Absent, low level, or focal	Focally full thickness or full thickness epidermal involvement (at least 1 HPF indicates melanoma in situ)
Lymphocytic infiltrates	Absent or present	Often dense infiltrate
Papillary dermal (concentric or lamellar) fibroplasia	Absent or present	Often lamellar fibroplasia
Mitoses, intraepidermal	Absent or few	Often present
Mitoses, dermal	Usually absent	Absent or few
Dermal atypia	Usually absent	Absent or present
Dermal confluence	Usually absent	Absent or present
Dermal maturation	Usually present	Present, diminished, or absent
Genetic feature		
DNA aneuploidy	Usually diploid	Often DNA aneuploidy
Genetic alterations	Single alteration (eg, *BRAF, NRAS*)	Usually 2 alterations

Abbreviation: HPF, high-power field.

[a] Includes nevi previously graded as mild and moderate (not all).

[b] Includes some nevi previously graded as moderate (not all) and severe.

Table 3.

Guidelines for the Classification of Various Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis Version 2.0 Class II and III or IV Lesions With Emphasis on the Dermal Component

Feature	Class II	Class III or IV
WHO Pathway		
I: low-CSD	• Atypicaldermal melanocytic proliferation in common acquired nevus • Dysplastic nevi • Plexiform or deep-penetrating nevus or melanocytoma[a] • *BAP1* inactivated nevus or melanocytoma[a] • Pigmented epithelioid melanocytoma	Melanoma
II-III: high-CSD	Atypical dermal melanocytic proliferation, NOS	• Melanoma • Desmoplastic melanoma
IV: Spitz	Spitz melanocytoma (atypical Spitz tumor)	Spitz melanoma
V-VI: acral and mucosal	Atypical dermal or submucosal melanocytic proliferation, NOS	Melanoma
VII: congenital	Atypical proliferative nodule or melanocytoma in congenital nevus	Melanoma
VIII: blue nevus	• Cellular blue nevus or melanocytoma • Atypical cellular blue nevus or melanocytoma • Atypical blue nevus, NOS	Melanoma arising in blue nevus
Cytology	Variable, increasing nuclear size >1.5 times that of resting basal keratinocyte nuclei, nuclear pleomorphism, chromatin condensed or dispersed, prominence of nucleoli	Nuclear size often ≥2 times that of keratinocyte nuclei and other melanocytes, increased nuclear to cytoplasmic ratios, thickened nuclear membranes, hyperchromatism, coarse chromatin or dispersed, strikingly prominent nucleoli, multiple nucleoli
Diameter (mm)	Variable, 4–10 mm, or greater	Variable, often >1 cm
Architecture	• Ulceration, usually absent • Increasing depth, may involve subcutaneous fat (level V) • Symmetrical or asymmetrical • May be biphasic (ie, combined, 2 components) • Nodule formation, absent or present • Maturation with depth, present or absent • Infiltrative at peripheries, absent or present • Cellularity, normal or increased • Usually no necrosis	• Ulceration, absent or present • Involvement of subcutaneous fat, absent or present • Often asymmetrical • Melanoma in 1 component • Nodule often present • Maturation often absent • Infiltrative, often present • Prominent cellularity, sheet-like appearance • Necrosis, absent or present
Mitotic rate	Variable, mitotic rates: 0–2 per mm^2, uncommonly 2 to 5 per mm^2	Often 2–6 per mm^2 or greater, deeply located mitoses, atypical mitoses
Immunohistochemistry	Often PRAME negative, p16 positive, Ki67 < 5% to 10%	Often PRAME positive, p16 negative, Ki67 > 10% to 20%

Feature	Class II	Class III or IV
Alterations or gene fusions	Usually 2: *BRAF, NRAS, GNAQ, GNA11, MAPK*, plus β-catenin, *APC*, *BAP1*, or *PRKAR1A*; various genefusions of *ALK, NTRK, ROS1, PRKCA*	Often *CDKN2A*−/−, *TP53, TERT* promoter, or *BAP1* (blue nevoid tumors)
Copy number variations	Usually 2	>3

Abbreviations: CSD, cumulative sun damage; NOS, not otherwise specified; WHO, World Health Organization.

[a]And atypical variants.