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Reassessment of the dysplastic nevus concept in the 21st century: a proposal for a two-tiered system of classification

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"The proposed system is more objective and could be used in future clinical trials more effectively than current schemes that are, at best, subjective and irreproducible and, at worst, inaccurate and controversial."

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The concept and identification of the dysplastic nevus (DN) has been a source of controversy for over three decades, since the landmark paper published by Clark *et al.* in 1978 [1]. There has been an ongoing debate as to whether DN are precursor lesions to melanoma, markers for the development of malignant melanoma (MM), or simply coincidental. In spite of attempts to arrive at consensus, little consensus exists and researchers as well as commercial entities have had to resort to the establishment of their own schemes to study these lesions.

Studies that associate DN with increased melanoma risk reveal that part of the confusion surrounding the clinical and pathologic recognition of these lesions results from the attempts at grading lesions. With the goal of identifying the reproducibility of one current grading system, Piepkorn *et al.* compared readings of six pathologists who did not agree on predetermined criteria [2]. In total, 149 tissue specimens collected from melanoma patients, relatives of melanoma patients and controls were evaluated separately by each pathologist. Interobserver agreement between pathologists was compared in pairs with an average concordance of 56%. The reproducibility of grading was greatest between pathologists who avoided the use of the intermediate category [2]. In an attempt to define histologic features that could identify DN in a reproducible manner, de Wit *et al.* found the least concordance among ten dermatopathologists for the intermediate category between 'benign' and DN (although DN are benign) [3]. Only one case out of a chosen 50 was consistently identified as "common naevocellular neavus with minor abnormal features." Furthermore, concordance was highest when lesions were identified as either benign or malignant ($\kappa = 0.76$), and decreased with the use of six categories ($\kappa = 0.61$). In addition, stratification of DN into grades not only decreases interobserver agreement but also fails to accurately reflect clinical risk [4,5].

Attempts to maximize interobserver concordance with the establishment of defined histologic criteria achieve some success but again question the utility of current grading schemes. In a retrospective study of 123 clinically diagnosed atypical melanocytic nevi, three independent pathologists graded the lesions according to a standard protocol that they developed. Atypical melanocytic nevi were graded according to architectural and cytologic criteria and the number of criteria fulfilled determined whether the nevus was identified as mild, moderate or severe. Using this scheme, the authors were not able to identify nuclear or architectural features

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that consistently distinguished mild DN from moderate DN. In contrast, atypical melanocytic lesions (severe DN and early MM) were easily identified by their prominent nuclear pleomorphism, junctional asymmetry and suprabasal melanocytes [6].

At a cellular level, a recent paper by DeCarlo *et al.* challenges the concept of DN as precursors for MM by establishing the absence of expected mutations and the presence of tumor suppressor genes. Whereas melanocytic neoplasia often displays the *BRAF* mutation in addition to downregulation of the tumor suppressor gene *IGFBP7*, 56% DN from intermittently sun-exposed skin have enhanced expression of IGFBP7. Furthermore, *NRAS* mutations, which are found in the majority of melanoma, were absent in all the DN [7].

The difficulty in distinguishing mild from moderate DN also extends to clinical identification of these lesions. In a prospective study conducted by Kelly *et al.*, 75% of 165 clinically atypical nevi were found to have DN histology, but there was disagreement between the clinical and histologic categorization of the nevi [8]. Both the clinical and histologic characterization of these nevi were separated into categories of mild, moderate and severe; one pathologist was responsible for identifying histologic 'dysplasia' using both architectural and cytologic features. Whereas all clinically diagnosed severe DN were diagnosed as severe DN on histology, only three out of 15 clinically identified moderate DN were identified histologically as such. The remaining 12 were determined to be mild DN on histology. Similarly, seven out of the 72 mild DN were identified by the pathologist as moderate DN. The overlap of mild and moderate nevi on histology echoes their ambiguity clinically. Features such as ill-defined border, irregular pigmentation, erythema and more were found almost equivocally in both clinically mild and moderate DN [8].

In conclusion, the use of 'mild', 'moderate' and 'severe' terminology as applied to DN is confusing, unreliable and unrepeatable among dermatopathologists and should be abandoned in favor of a two-tiered system. In this simpler and clearer methodology, benign appearing DN are classified as 'low grade,' whereas those that have features suggestive of evolving malignancy can be identified as 'high grade.' Some of these criteria include asymmetry, slight pagetoid spread, an occasional mitotic figure and pleomorphism of nuclei, among others. This will afford clinicians precise direction as to how to manage lesions given these diagnoses; 'low-grade' lesions can be treated by selected biopsy and clinical observation alone whereas 'high-grade' lesions must be excised. Furthermore, given that 'high-grade' DN require excision, arguments can be made to payors that the lesion should be reimbursed at the same level as a low grade malignancy such as melanoma *in situ* or lentigo maligna. In addition, there is precedent for its use in the dermatologic literature as numerous papers have been published wherein DN lesions are classified in this fashion. Importantly, the US FDA recently approved a device designed to assist dermatologists in the clinical diagnosis of early MM lesions that used the proposed classification to develop and calibrate the device, further affirming the validity of this nomenclature system [9]. Given that this device will likely gain widespread acceptance and be used world wide, it is timely that the terminology being applied to the very lesions it will be used on be accepted. Furthermore, as newer and more effective pharmaceutical agents have been developed for the treatment of melanoma and the relationship between DN and melanoma continues to be an important line of research, it is anticipated that an ever increasing number of clinical trials will be forthcoming that will require a more precise system of classification of these lesions. The proposed system is more objective and could be used in future clinical trials more effectively than current schemes that are, at best, subjective and irreproducible and, at worst, inaccurate and controversial.

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