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# Diagnosis and Reporting of Dysplastic (Atypical, Clarks) Nevi – a Reassessment

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## ABSTRACT

This article on dysplastic nevi was compiled and written in August 2004 but never published in a print journal. It is our opinion that now, 15 years later, the same conclusions documented in the initial article still exist. In fact, the further studies and reports strongly support the lack of malignancy (nor evidence of pre-cursors of malignancy) in correctly histologically diagnosed junctional or compound dysplastic nevi and the lack of need of re-excision of these nevi in almost all cases. [1,2,3,4]

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It is now over 25 years since Clark described the BK mole syndrome 1, and over 20 years since the first NIH consensus development conference, on potential precursors of malignant melanoma, in October 1983, attempted to define and recommend the terms of dysplastic nevus and dysplastic nevus syndrome. [2] Although criteria have been developed and modified for this definition, the individual observers (clinical and histological) have not interpreted and applied these criteria consistently.

Salopek in a recent interview article [3] has stated that “it is clear from the literature that most clinicians are capable (clinically) of recognizing a dysplastic nevus”. Regardless of whether they are capable of this, my own experience and observation over this greater than 20 year period, in a large combined clinical and dermatopathologic practice, is that most non-dermatologic physicians and even our own dermatologic colleagues vary considerably in their understanding and use of terminology such as dysplastic nevus: and particularly and most importantly when submitting biopsies of pigmented lesions for diagnosis.

The clinical features of 100 dysplastic nevi were tabulated and reported by McBride, Rivers, Knopf, Cockerell et al in 1991.[4] The visual changes usually described such as variable color, irregular margins, tan macular shoulder, pebbly (mamillated) surface and larger size (often greater than 5 mm diameter) were observed, but inconsistently apart from almost all having a variegated color, tan macular shoulders and a slight degree of elevation. Importantly 11% were considered difficult to distinguish clinically from malignant melanoma. Others have subsequently used other refinements of criteria for definition, but a large question remains whether the clinician (particularly the non-dermatologist from whom a large number of specimens were submitted for biopsy) can clinically reliably distinguish a dysplastic nevus from a melanoma in most cases. This is of major practical importance, as the purpose of biopsy and histologic diagnosis in this setting is to rule out malignant melanoma: not to confirm a gnosis of dysplastic nevus (nor to diagnose dysplastic nevus syndrome).[3]

On the other hand if one can confidently clinically visually diagnose a dysplastic nevus, or at least be reasonably certain it is not a melanoma, there is no particularly useful purpose in biopsy, just as there is no purpose in biopsying a common congenital Unna or Mieschers nevus (apart from removal for cosmetic or irritation reasons). This would also be particularly true because over the 20 to 25 year period, the data strongly indicate individual dysplastic nevi rarely eventuate in malignant melanoma [3,7,8] even in familial dysplastic nevus syndrome, and do not support the initial concept of dysplastic nevi as common precursors to malignant melanoma. [9,10,11,12]

Our own experience, and we believe that of most dermatologists is that, after an initial few years of marked increased numbers of routinely biopsied clinical dysplastic nevi following the 1983 NIH consensus conference, the number of biopsies routinely taken has dropped over the years, as close follow-up and monitoring leads to more appropriate selection of suspicious clinical lesions for biopsy.

Studies for prophylactic removal of dysplastic nevi, even in patients with familial dysplastic nevus syndrome, have shown it to be an unsatisfactory and unrewarding alternative to adequate clinical follow-up, particularly with use of dermoscopy and photographic monitoring. [3,5,13] A more recent study by Tucker, Fraser and Goldstein et al [14] in melanoma-prone families also showed that most dysplastic nevi in this higher risk group remained stable or static (or even regressed) and very few progressed to malignant melanoma. A reviewer of this article (J.C.Maize) raised the valid question that as the follow-up yield was very low in finding new melanomas in these melanoma-prone families with dysplastic nevi, what would be the yield in monitoring sporadic dysplastic nevi in patients without personal or family history of melanoma? – presumable even far lower.

The definition of the dysplastic nevus syndrome remains contentious and has been variously defined [2,3,10,12,16] However dermatologists know close clinical follow-up and monitoring is required in patients with a personal or family history of malignant melanoma and those with increased number of nevi, often including larger or clinically dysplastic nevi, as there are higher risks of development of malignant melanoma with time. The clinical observance of dysplastic nevi in these patients is only one marker of risk and this type of clinical phenotype has correlated with risk of melanoma in many case control studies. [17,18] A biopsy finding of a dysplastic nevus however does not confirm or define the syndrome. [3]

The histologic criteria for diagnosis of a dysplastic nevus have varied with lack of consensus. The initial NIH conference in 1983[2] stressed the architectural pattern: most commonly including junctional melanocytic hyperplasia with lentiginous epidermal pattern, junctional nests, (often more transversely oriented) bridging of rete ridges and “shoulders”, plus lamellar or concentric fibroplasia around rete ridges. Upper dermal changes commonly include variable lymphocytic infiltration, increased vascularity or telangiectases, some degree of mild fibrosis, and melanin pigment incontinence. For a compound dysplastic nevus the dermal nevus component invariably should show no significant abnormality. Ackerman 19 also stressed the superficial nature of dysplastic nevi.

This is important as in our own opinion many superficial congenital nevi may be falsely reported as dysplastic nevi and can show similar architectural epidermal and dermal-epidermal junction changes (although not usually showing prominent lamellar or concentric fibrosis or as much upper dermal inflammatory changes). Initially cytologic atypia was not retained or required as a criterion 2 largely because the pathologists at the first NIH consensus conference in 1983 showed poor concordance on deciding if there was cytologic atypia or not in sections, and even if present whether this was of any significance, particularly if there were no diagnostic criteria of melanoma. However, many observers since then have unfortunately stressed the importance of cytologic atypia as a necessary criterion for diagnosis. [20,21] They have particularly included random focal cytologic nuclear changes including variation of nuclear shape and size or hyperchromatism, usually with sparse cytoplasm, but occasionally appearing as “epithelioid” nuclei with more abundant cytoplasm containing finely dispersed melanin pigment. [17]

Interobserver studies however have shown a great deal of variability in concordance and reproducibility in cytologic atypia. Some more recent studies have purported to show more concordance on diagnosis with strict histologic criteria, but the validity of criteria remain unproven. [20,21]

Some have also stressed the importance of using both architectural pattern and cytologic atypia criteria in the diagnosis. [23] The histologic criteria however have not permitted the differentiation of common sporadically occurring dysplastic nevi from those present in patients with dysplastic nevus syndrome, [3] and therefore the diagnosis of the latter remains a clinicopathologic one, with necessary essential clinical features such as large numbers of nevi and a family or personal history of melanoma.

The prevalence of dysplastic nevi, regardless of the strictness of criteria for histologic diagnosis has been shown to be reasonably common and may correlate poorly with clinical phenotype. [22,25,26,27]

Other studies had also suggested dysplastic histologic changes were not uncommon in clinically banal nevi, [28] (although they were not usually correlated with the degree of cytologic atypia) and some have regarded it as a common nevus pattern developing as a progression from lentigo to nevus. [7]

Those of us who have used the basic criteria from the first NIH Consensus Conference in 1983 [2]

over the past 20 years can attest to the extremely common histologic finding of

dysplastic nevi regardless of the degree of cytologic “atypia” and regardless of the clinical appearance as the information provided with the biopsy is very often scant and unreliable. As Seab stated, ”most busy dermatopathologists (and dermatologists I would add) can attest that they see no strong association of isolated dysplastic nevi and malignant melanoma in their practice”. [7] This is also our strong opinion as both a dermatopathologist and clinic dermatologist.

The high prevalence of dysplastic nevi supports the strong doubts about their specificity as a risk marker for melanoma, particularly in the patient with isolated sporadic dysplastic nevi and without a clinical melanoma-prone phenotype, and there is strong data to show that the histologic diagnosis of a dysplastic nevus cannot be shown to predict or help stratify risk factors for melanoma, just as it cannot by itself diagnose or predict dysplastic nevus syndrome. [3,7,17]

It has also been advocated to classify or grade the severity of cytologic atypia in dysplastic nevi into mild, moderate, and severe. However, Piepkorn was unable to confirm a significant correlation between histologic criteria and risk of melanoma in a large Utah database study. [17,29]

The NIH consensus development conference in 1992 also suggested using these criteria in reporting [15] however, to our knowledge, no study has consistently shown that this grading helps in any meaningful way, such as predicting risk of melanoma. Our contention is actually that the recommendations of this 1992 conference have led to an increase in unnecessary re-excision surgery, as many pathologists began to report lesions as atypical (or dysplastic) nevi with architectural disorder and cytologic atypia (mild, moderate and severe), which clinicians often take as a recommendation that follow-up excision is required as a precaution, even if not explicitly stated. The additional reporting of uncertain margins has also reinforced this interpretation.

Salopek [3] has indicated that re-excision of these lesions is probably unnecessary “unless there is substantial cytologic architectural atypia” however even the latter situation is unnecessary in our opinion if there are no criteria for malignant melanoma in the initial biopsy. Our own experience is that the re-excision specimen usually shows no residual nevi (even when marginal extension is reported) and we have not seen a single re-excision specimen showing melanoma. Our findings are basically in accordance with the documented study of Cohen 30 who evaluated the usefulness of re-excision in 189 dysplastic nevi and the strong majority had no residual nevi and in only 1 of the 189 cases was a melanoma diagnosed on re-excision. A review of the initial biopsy was not reported but may well have showed a missed diagnosis of malignant melanoma.

In over twenty years of personally reporting dysplastic nevi (of a minimum estimated number of 15 to 20,000) but additionally always stating ”no evidence of malignancy” in the report, and also not reporting the degree of cytologic atypia (or uncertain marginal extension), I can recall only a relatively small number of re-excision specimens being submitted and no evidence of a malignant melanoma developing at a previously biopsied dysplastic nevus site. However, an initial review of more recently reported cases by pathologists using the reporting recommendations of the 1992 NIH conference, has indicated, in our experience, a very marked and startling increase in submitted re-excision specimens with the vast majority, as indicated above, showing no residual nevi and no case showing malignant melanoma.

The essential question on a submitted biopsy however is whether it is or is not a malignant melanoma (and not if it is a dysplastic nevus). Well developed histologic criteria for the diagnosis of malignant melanoma have been developed and have proven reliable and reproducible over the past 25 to 30 years. Criteria, mainly developed by Ackerman, and stressing architectural pattern, such as symmetry, circumscription, predominance and uniformity of nesting at a dermal-epidermal junction plus maturation of the dermal component and symmetry of inflammation and

melanin incontinence in the dermis, define the benignity in the vast majority of lesions. [31]

Le Boit in his edited book – Malignant Melanoma and Melanocytic Neoplasms (1994) wrote a well-described review of potential simulants of malignant melanoma [32] recognizing the atypical features in nevi in special sites such as the genital region, acral lesions , Spitz nevi, irritated nevi, recurrent nevi (at prior excision sites), some congenital nevi; and included dysplastic nevi. In the latter case he pointed out histologic features which can be of concern in ruling out melanoma, and also described features of the very uncommon case of development of melanoma in situ developing at the site of dysplastic nevus. These features included the presence of confluent aggregates of atypical melanocytes and upward epidermal spread of atypical melanocytes singly and in groups. Other criteria could include loss of definition of the basal layer, a broader extent of atypical melanocytic proliferation, particularly beyond the margin of the main lesion, increased skip areas of involvement, a focal increased dermal distribution of melanocytic proliferation without regard to rete ridges, and asymmetric or focal increased upper dermal lymphocytic infiltration plus asymmetric melanin pigment incontinence.

The 1992 NIH consensus conference, 15 recommended changing the terminology to atypical nevus with architectural disorder, which does not appear helpful as it introduced a term that can have differing connotations and which does not clarify the problem of conveying the appropriate clear biopsy report information to the ordering clinician. The term atypical is also commonly used by reporting pathologists for changes in many other nevi such as Spitz nevi and nevi on the genital region or as a commonly used descriptive adjective. One may reasonably point out that as the lesion is extremely common with very low documented malignant potential, it might just as well be termed a typical nevus rather than atypical, or at most a typically atypical nevus.

The grading of severity of cytologic atypia in these lesions also, in our opinion and experience, as pointed out, has only lead to a marked increase in unnecessary re-excision surgery; and we also believe from our experience in reviewing the initial biopsy specimen that the grade of atypia is overstated by many pathologists in far to many cases. The biopsy report from the pathologist would clearly state benign, or at least no evidence of malignancy, as we believe the NIH recommendations commonly lead to uncertainty in the mind of the clinician receiving the report.

The goal therefore ultimately remains to strive for a consensus as to what is the best most appropriate, and ultimately useful nomenclature for diagnosis in reporting these biopsied lesions.

Ackerman pointed out that the dysplastic nevus is actually an extremely common and benign nevus regardless of the degree of cytologic atypia on histology. [19,20,33] It is also the most common relatively flat nevus on the trunk and limbs and in his opinion is not of great clinical consequence (apart from their role as one of the visual (clinical) markers for dysplastic nevus syndrome). Many dermatologists (dare we say most?) would agree with this, particularly with the 20 year experience with this diagnosis. Many authors (Piepkorn, Saeb, Salopek, Ackerman) have stressed the common prevalence and extremely low incidence of development of malignant melanoma in pre-existing dysplastic nevi. It was considered initially to be the most common nevus associated with a malignant melanoma, possibly simply reflecting the fact that it may be the most common flat nevus and that most melanomas initially develop as relatively flat lesions, however most data support the findings that the majority of malignant melanomas arise de novo and not in pre=existing nevi. [3] There is lack of convincing evidence of the individual dysplastic lesion as a predictive factor for melanoma in many studies over the past 20 years. [3,7,17]

Although a sporadic dysplastic nevus shows no increased risk factor or predictive factor for melanoma, those patients with a clinical phenotype similar to dysplastic nevus syndrome patients, but without family or personal history of

melanoma, and particularly if they have a very large number of nevi, should also be monitored closely although the precise incidence of melanoma in this group is still uncertain. Patients with a fair and freckled complexion and history of severe sunburns as a child are often in this group.

Ackerman proposed replacing the term "dysplastic nevus" with the term Clark's nevus [17,20,33] (named after the initial describer of the BK mole syndrome, WH Clark Jr.). He basically defined this as a common nevus with flat profile in microscopic sections viewed at scanning magnification. According to the NIH consensus conference of 1992, [15] the histologic diagnosis of the dysplastic nevus (which they proposed renaming atypical nevus) depends on this relatively flat profile (or almost gently raised profile) in conjunction with other architectural and cytologic features which they recommended be reported. Thus, as McCalmont has stated, all dysplastic nevi are Clark's nevi but not all Clark's nevi are dysplastic. [34] (Some exceptions for the former are possible however such as raised lesions of combined Spitz and dysplastic nevi, and some genital nevi with histologic dysplastic nevus features).

There of course will be occasional cases which are more difficult to rule out possible malignant melanoma, and we report these as such with full-description and advise close clinical follow-up or advise re-excision as a precaution. Some of these small number of cases may be examples of dysplastic nevi with development of malignant melanoma in situ at the site and can be reported as such, or at least report as suspicious for this, whereas more may be true melanomas from the outset rather than dysplastic nevi. [35] In our opinion the number of these cases should be very small in relation to the total number of dysplastic nevi and biopsy specimens submitted.

In conclusion we would suggest the term atypical only be used as a descriptive adjective as pathologists have always done in some reports of nevi including Spitz, irritated, acral and genital nevi. One could use the term Clark's nevus as suggested by Ackerman; however we chose not to use this term over the years simply because the clinicians we service had become familiar with the term dysplastic nevus, and although not an ideal term, (we believe dermatopathologists should have restricted the term dysplastic as traditional histopathologists mainly do, only in relation to squamous epithelium) we attempted to educate them that the vast majority were benign, and indicated this in our reporting by consistently stating no evidence of malignancy. Piepkorn however suggested that pathologists simply report the lesions as junctional or compound (by definition there should be no such thing as an intradermal dysplastic nevus) as pathologists did prior to 20-25 years ago. The ordering clinician basically wants to know if the lesion is benign or malignant and this should be very clear in the pathology report.

## SUMMARY

Over 20 years of experience and numerous reports and studies have shown no convincing data to support an initial concept that individual dysplastic nevi may be common precursors or predictive factors for malignant melanoma.

Studies indicate, regardless of strictness of criteria of histologic definition, a high prevalence of this lesion, and there are no convincing data to show any predictive risk factor of melanoma in biopsy or an individual dysplastic nevus. Studies indicate clinical phenotype (especially in melanoma prone families) with increased number of nevi (many of which may be clinically dysplastic) help define the patient requiring close follow-up and monitoring (preferably with photographic assessment).

Prophylactic excision of dysplastic nevi has proven unproductive and unwarranted (even in patients with true dysplastic nevus syndrome) and many studies indicate the vast majority of dysplastic nevi remain stable (or even regress) and do not progress to malignant melanoma. Biopsy is only required for a clinically suspicious lesion to rule out malignant melanoma and there is no need to biopsy to define or determine the presence of a dysplastic nevus. Biopsy also does not define the dysplastic nevus syndrome,

nor help as a predictive risk factor in these patients with similar clinical phenotype but without personal or family history of melanoma and of course not in the patient with only a sporadic dysplastic nevus.

In our opinion, the recommendations of the 1992 NIH conference suggesting reporting atypical nevi with architectural disorder, grading the degree of cytologic atypia and reporting marginal extensions, has led to a much higher and unnecessary re-excision rate without leading to increased diagnosis of malignant melanoma, nor helping to improve the diagnosis of melanoma. The grading of atypia plus the reporting of suggestive marginal extension without stating whether the lesion is benign or malignant, or at least reporting no evidence of malignancy, leads to confusion in the physician receiving the report, who is often left with the impression that the lesion is suspicious or could be presumably re-malignant or malignant, even if not explicitly stated in the report. The re-excision specimen usually shows no evidence of residual nevi and almost never shows a malignant melanoma. We do not usually re-excise other benign nevi, regardless s of residual clinical pigmentation, apart from occasional cosmetic reasons, and this should also apply to dysplastic nevi.

The use of the term atypical in place of dysplastic has not helped, and in our opinion has served only to confuse many clinicians; and most ordering clinicians are unfamiliar with the term Clarks nevus. Even if the term dysplastic nevus is retained, the clinician submitting the biopsy essentially wants to know whether it is melanoma or not, and this should be conveyed or reported clearly. We contend that the vast number of lesions, regardless of variable cytologic atypia are benign and should be stated as such in the pathology report or at least stated as no evidence of malignancy. The number of more problem cases should be very much smaller if the criteria for diagnosis of malignant melanoma are applied appropriately.

We therefore believe it is necessary to avoid the fog of uncertainty frequently conveyed by the terminology of pathology reports in these lesions, and perhaps it is time to adopt the recommendation of Piepkorn and simply report these lesions as benign compound or junctional nevi.

**UPDATE - AUGUST 2019**

The histologic criteria for dysplastic nevi were essentially based on architectural pattern as outlined and described by Dr. Bernard Ackerman at the initial NIH Consensus conference in October 1983. [5] These criteria and features were given in the above August 2004 article (Page 2). Dr Ackerman had previously provided the essential histologic pattern criteria for defining benignity in these lesions and ruling out melanoma (page 4 of the above report).

If the histologic pattern guidelines for dysplastic nevi and malignant melanoma are consistently applied there should be far less confusion or errors in diagnosis. [6,7,8,9] As indicated in the above August 2004 article a subsequent January 1992 NIH Consensus Development conference in recommending changing the terminology in dysplastic nevi to (atypical) nevi with architectural disorder added confusion to the biopsy report for the ordering physician. This remains as a common problem. There is very poor concordance among pathologists and no accepted uniform definition of cytologic atypia of melanocytes. Therefore, the recommended terminology of the 1992 conference for histologic reporting of these nevi into mild, moderate and severe atypia has continued to lead to frequent unnecessary re-excisions. [10,11]

Updating our own experience of reporting dysplastic nevi, now of almost 36 years, and never using the terminology of mild, moderate or severe atypia, has shown only one instance out of thousands of reported cases in dysplastic nevi, of malignant melanoma in a re-excision specimen. However, a review of that case indicated that the initial biopsy was a true malignant melanoma and should have been reported as such. Thankfully this patient had no further recurrence or spread of the tumour. In addition, far fewer re-excision specimens have been sent in after the initial diagnosis of

dysplastic nevus as we routinely add the diagnostic statement," no evidence of malignancy", to the pathology report.There of course will be an uncommon case (estimated personally at no more than 1%) in which it is more difficult to definitively rule out malignant melanoma (or melanoma insitu) in the histologic specimen. In this situation we report the histology showing "atypical" (used only as an adjective) melanocytic features and advise close follow-up to ensure complete excision and absence of recurrence in the report.

Large studies have shown only very rare evidence of progression of dysplastic nevi to malignant melanoma. Tsao and colleagues [14] estimated an overall rate of transformation as 1 in 10,000 similar to other studies. [15] They found, for an average atypical nevus, the potential annual dysplastic nevus transformation rate to melanoma to be very low at approximately 1 in 30,089 for males and 1 in 39,809 for females. Elder 4 in his article "Dysplastic Nevi: an update" in 2010 also reported that most malignant melanomas do not arise from dysplastic nevi. Further reports of re-excision of dysplastic nevi revealed no evidence of malignant melanoma in a series of 77 acral nevi and 134 cases which used the reporting terminology of moderate atypia. Reddy et al 15 reported in 201, in a study, no cases of malignant melanoma arising at the site of a previously biopsied dysplastic nevus in accordance with our own experience and that of others. [16,17] Goodson [18] and colleagues reported a recurrence rate of dysplastic nevi after biopsy at 3.6% very similar to 3.3% recurrence rate for other benign nevi. Reddy and Rogers [2] also reported that biopsy margin positivity does not appear to influence the recurrence rate.

The incidence of finding nevi in biopsies of malignant melanoma is variable. Most studies have indicated that the majority of melanomas arise de novo. Pampena and colleagues[19] in a large meta-analysis study found approximately 71% of melanomas arise de novo with 29% associated with a pre-existing nevus. They reported no higher incidence of dysplastic nevi at melanoma sites over non-dysplastic nevi. It can also be argued that the presence of a nevus at a melanoma site does not necessarily prove origin from the nevus. In the past the nevus found at melanoma sites was usually assumed to be a dysplastic nevus but Bevona et al [20] reported that of 1606 nevus associated melanomas, 43% arose from dysplastic nevi and 57% from congenital nevi. A prior report by Sagebiel et al [21] found 79% were associated with congenital nevi and 21% with dysplastic nevi. Goodson et al [22] in 2011 also found more congenital nevi than dysplastic nevi at the melanoma sites. As dysplastic nevi are always superficial, if nevus cells at melanoma sites extend significantly below the upper dermis, they are not dysplastic nevi and may well be congenital.

Variable genomic, chromosomal and other biomarkers have been evaluated in dysplastic nevi and malignant melanoma but have not so far provided reliable diagnostic help in defining or distinguishing dysplastic nevi and malignant melanoma, and the pathologists histologic interpretation remains the standard for diagnosis, (with or without the aid of special stains such as MART1 and HMB45). [23-34]

**CONCLUSIONS**

1.) Dysplastic nevi are very common benign nevi and the most common superficial nevus, with distinctive criteria for histologic diagnosis.

2.) There is extremely limited evidence of dysplastic nevi as precursors for malignant melanoma.

3.) There is no accepted uniform definition of cytologic atypia in dysplastic nevi and very poor concordance among pathologists. Therefore, proper interpretation of histologic pattern criteria for malignant melanoma and dysplastic nevi should markedly reduce the incidence of unnecessary re-excisions.

4.) Most malignant melanomas arise de novo (estimated 71%). In the other 20% to 30%

finding nevi at the melanoma sites, there has not been definitive proof of origin of the melanoma from a pre-
existing nevus, including dysplastic nevi. Recent studies have shown roughly similar or much higher
incidences of congenital nevi rather than dysplastic nevi at these melanoma sites.

5.) There is no evidence of development of malignant melanoma at a skin biopsy re-excision site, apart from the rare case of missed diagnosis of malignant melanoma in the initial biopsy.

6.) Genomic chromosomal and other biomarkers have shown no practical application so far in defining dysplastic nevi or malignant melanoma, and diagnosis is still largely dependent on histologic biopsy pattern and interpretation.

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