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Dermoscopy of “dysplastic nevi”: A beacon in diagnostic darkness

The sequential progression model for melanocytic tumours from common nevus to malignant melanoma was proposed by Clark almost 30 years ago. The “dysplastic nevus” has frequently been considered a logical offspring of this concept and as a direct precursor of melanoma, analogous to the epithelial dysplasia-carcinoma sequence. Despite the use of modern molecular methods, there is no consensus as to if the dysplastic nevus represents a true precursor lesion of melanoma, a separate distinct type of nevus, or a diagnostic dilemma. Currently, the concept of melanocytic dysplasia remains subject to confusing definitions at all levels of the diagnostic process, *i.e.* clinical appearance, dermatohistopathology, and molecular biology. In this review, we collect evidence that nevi fulfilling Clark and Elder’s classic histological criteria mostly represent “endpoints” of nevocytic evolution, whereas a minority of “dysplastic nevi” represent true melanoma precursors. The unsolved dilemma is that neither clinical, histopathological nor molecular criteria exist to make a distinction between dysplastic nevi and early melanomas. Our analysis of the current knowledge on dysplastic nevi shows that dermoscopy remains the only quantifiable, easily applicable and reproducible diagnostic tool to approach the problem. Due to a “quantum leap” in optical resolution, objective scores can be established, *e.g.* the total dermoscopy score (TDS) according to the ABCD rule, and documentation of changes over time are possible by digital image storage devices. Although dermoscopy does not solve the dilemma of discriminating early, basically feature-less melanomas from dysplastic nevi, and it does not prove that dysplastic nevus is a distinct entity, it helps make melanocytic tumours with unclear malignant potential a manageable disease.

Key words: dysplastic nevus, malignant melanoma, dermoscopy, melanocyte 479

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The first report on an increased incidence of malignant melanomas (MM) in families with multiple melanocytic nevi was published by Wallace H. Clark, Jr., in 1978. He introduced a pathogenetic model for the stepwise development of MM from dysplastic melanocytic nevi (DN), originally using the term B-K mole syndrome (B and K were the initials of the last names of the first individuals reported) [1]. This model remains controversial a quarter-century later. When David Elder extended the nevus-melanoma sequence hypothesis to sporadic DN as a precursor for sporadic MM, he launched an even more heated debate that still continues [2]. Attempts to deal with Clark’s intellectually attractive concept are hampered by the confusing nomenclature. While the term “familial atypical multiple mole melanoma (FAMMM)” syndrome is mainly used in the English-speaking world, the term “dysplastic nevus syndrome (DNS)” is more commonly used in German-speaking countries. “B-K mole syndrome” is now rarely used. The recommendation of the consensus conference held by the US National Institutes of Health to replace

dysplastic nevus with the term “nevus with architectural disorder and cytologic atypia (ARCD)” has not been broadly accepted [3].

The existence of the DNS with increased risk for MM is a fact. Everyone has struggled with patients with many large unusual nevi and a personal or family history of MM. Problems arise if single or few “dysplastic” lesions not associated with DNS are observed in a patient. Both clinical and histological definitions are not uniformly employed and, therefore, the diagnosis “dysplastic nevus” remains non-reproducible. In daily practice physicians are left with a serious dilemma. Since neither clinical morphology, dermatopathology nor modern molecular methods have solved this problem, some authors completely reject the term “dysplastic nevus” except in the familial setting. Others still firmly believe that this nevus subtype represents a transitional lesion between common nevus and MM.

The aim of this review is to devise a clear and practicable approach to the management of suspicious melanocytic lesions based on a critical analysis of current knowledge on

“dysplastic nevi”. For practical purposes we will use the term “dysplastic nevus” in this review for any lesion that does not clearly represent a common nevus and does not fulfil the criteria of MM. So, any lesion in between the well defined endpoints is a “dysplastic nevus” (DN).

Clinical morphology: The daily diagnostic dilemma

Sporadic, common melanocytic nevi are usually smaller than 6 mm and symmetric, they present with an almost homogenous pigmentation and a regular smooth border. They usually occur in limited numbers and reach a maximum number in the second to third decade of life. Later, they show a tendency to regress, often with neuroid or fatty-fibrous degeneration. With the exception of DNS, clinically suspicious lesions most often occur as singular lesions. Originally, Clark and co-workers described the clinical features of such lesions as flat, larger than 10 mm in diameter and haphazardly coloured black, blue, pink and sometimes depigmented [4]. However, because of its low reproducibility, this definition has not been well accepted. Therefore, for detection of clinically suspicious pigmented lesions, one can apply the more structured ABCD(E) rule, which is also used for detection of MM. Lesions are judged as atypical if they have an asymmetrical form (Asymmetry), irregular (polycyclic) borders (Border), composite multicolour pigmentation (Colour), and/or have a diameter of more than 6 mm (Diameter) [5]. The elevation of the lesion (Elevation), i.e. the simultaneous presentation of macular and papular components is a further criterion [6]. However, this approach also presents problems. Although, it is well suited to distinguish between the antipodes of melanocytic tumours – common nevi and MM – it fails to reproducibly describe borderline lesions, which pile up to a considerable fraction in daily routine. This lack of reproducibility is mainly due to a lack of quantitation or use of defined scores [7, 8].

After recognition of a suspicious lesion, the next question is what does the clinical morphology imply and what consequences have to be drawn. Such clinical borderline lesions may represent (1) true MM precursors with a “dysplastic” abnormal histologic appearance (2) early MM with clear histologic indicators of MM (3) clinically suspicious benign lesions with completely innocuous histology, and (4) clinically suspicious lesions fulfilling Clark and Elder’s histological features of dysplasia. In our opinion, the latter mostly represent an endpoint of nevocytic development and never progress into a malignant tumour. But, which one will? A history of rapid growth can be helpful to recognize early MM or precursors, since dysplastic benign nevi are characteristically stable in size [3, 9, 10]. However, patients’ histories are often vague. *Figure 1* displays a number of examples. Five (histologic) MM are hidden among the benign nevi. They are hard to find with the naked eye.

Dermatopathology: Not really a gold-standard

The accuracy of our daily clinical assessment is often judged on the basis of pathologic findings in excised lesions. The microscopic evaluation is still considered as a gold standard for diagnosing melanocytic tumours. How-

ever, limitations in recognition of early MM and distinction of DN exist. It is surprising that these limitations are often not considered even by experts and it is still assumed that a distinction between benign and malignant ought to be possible in all instances. Here we collect evidence that this is not the case, and certainty is an illusion in the DN field [11]. When evaluating epithelial neoplasms, dysplasia is defined as the architectural and cytological deviation from the normal configuration of the epithelium. In epithelial carcinogenesis, a continuous progression from minor dysplasia to severe dysplasia and finally to epithelial carcinoma can often be observed in one single specimen. This applies to the epidermis and other epithelia as well, e.g. the best-known example being the adenoma-carcinoma sequence in colon cancer [12]. For melanocytic proliferations, the situation is not as straightforward as it is in epithelial skin cancer [13]. The main problem with the histological diagnosis of melanocytic “dysplasia” is – very similar to the clinical situation – its lack of commonly accepted and reproducibly measurable criteria.

According to Clark and Elder, histologic melanocytic dysplasia is characterized by the following features [1, 2, 4]:

- (1) lentiginous melanocytic hyperplasia (confluence of melanocytic cells in the junctional zone; melanocytic cells bridging across papillary tips (*figure 2G*); shoulder phenomenon, i.e., peripheral extension of the junctional component beyond the dermal component (*figure 2H*);
- (2) epithelioid melanocytic atypia (large melanocytic cells with raised quantities of cytoplasm and finely distributed pigmentation resulting in “dusty” or “milky” appearance; (*figure 2G, H*);
- (3) lamellar fibrosis, i.e., elongated fibroblasts positioned next to each other, separated by layers of condensed extracellular matrix, and/or concentric eosinophilic fibrosis around the rete ridges (*figure 2G*);
- (4) perivascular lymphocytic infiltrate in the papillary dermis (*figure 2H*).

However, Ackermann pointed out that the nevus subtype defined by these criteria represents the most common subtype at all, because some of Clark and Elder’s criteria are found in almost any excised melanocytic nevus [14]. Most nevi which are excised have been found clinically suspicious. In this dilemma, some dermatopathologists generously use the diagnosis “dysplastic nevus”, often just to indicate “I have seen the problem, don’t blame me if it is already an early MM”. Sometimes even re-excision of “dysplastic” nevi with larger safety margins is recommended by pathologists, which is inconsequential and means “I don’t know”. Others, including our group, raise the threshold of melanocytic “dysplasia”, restricting the diagnosis to lesions that already partially fulfil MM criteria, in particular those showing a certain asymmetry. This latter approach is more likely to identify MM precursors, but it will also miss a few early MM. *Figure 2* displays examples of clear MM (*I-M*), common nevi (*A-D*) and questionable “DN” (*E-H*).

The degeneration of melanocytic nevi is one point that may have not received enough attention as a factor contributing to “dysplastic” cytological appearance. In other neuroectodermal tumours such as schwannomas, it is well accepted that degenerative changes may lead to impressive cytological atypia with the occasional formation of bizarre, hyperchromatic giant nuclei, sometimes denoted as ancient schwannoma [13]. Some of the cellular features interpreted



Figure 1. Displays a number of examples of suspicious melanocytic tumors, suspicious on the basis of the clinical ABCD rule. Five (histologic) malignant melanomas are hidden among the (histologic) benign nevi. They are hard to find with the naked eye.

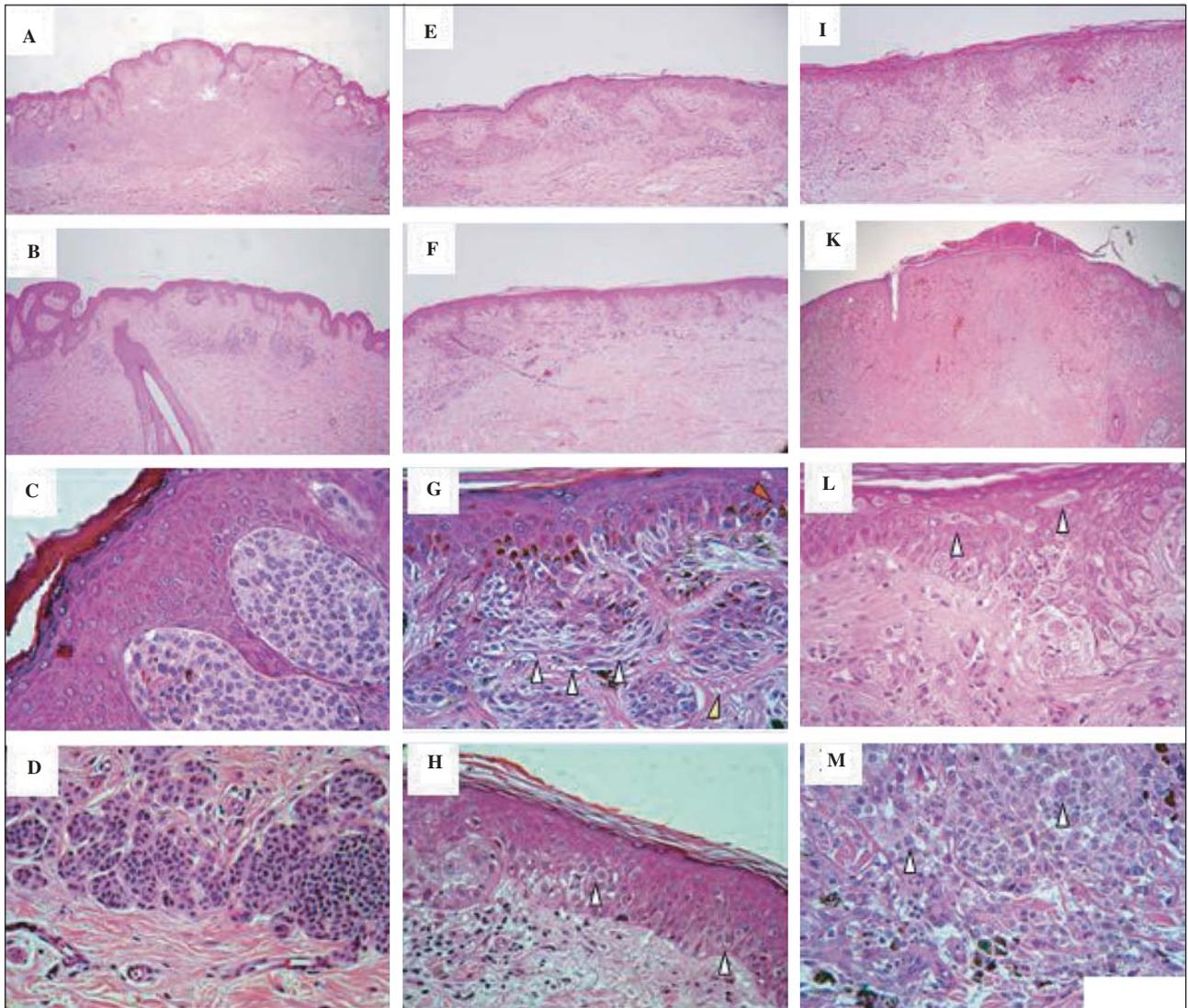


Figure 2. Displays a few examples of histopathologic features of common nevi (A-D), questionable dysplastic nevi (E-H), and clear malignant melanoma (I-M). Criteria for dysplastic nevi are: lentiginous melanocytic hyperplasia, *i.e.* confluence of melanocytic cells in the junctional zone, melanocytic cells bridging across papillary tips (arrows in G); furthermore a shoulder phenomenon, *i.e.* peripheral extension of the junctional component beyond the dermal component (arrows in H), epithelioid melanocytic atypia, *i.e.* large melanocytic cells with raised quantities of cytoplasm and finely distributed pigmentation resulting in “dusty” or “milky” appearance (arrows in G and H), lamellar fibrosis, *i.e.* elongated fibroblasts positioned next to each other, separated by layers of condensed extracellular matrix, and/or concentric eosinophilic fibrosis around the rete ridges (H), and perivascular lymphocytic infiltrate in the papillary dermis. Asymmetrical growth (I, K), pagetoid scattering (L), and lack of maturation at the lower rim (M *versus* D) are significant markers of malignant melanoma.

as melanocytic “dysplasia” may also be the result of homologous degenerative processes. Accordingly, an “ancient nevus” subtype has been described by Kerl *et al.* as one possible end point of nevocytic development [15]. The impressive cellular atypia of these cases was regarded as a degenerative change; the histological findings suggesting malignancy were contrary to the benign clinical behaviour confirmed by long-time follow-up.

In contrast to the definition of DN, for MM there are more commonly accepted histological criteria [16, 17]:

(1) asymmetry of the tumour architecture, pagetoid scattering (suprabasal infiltration of the epidermis by melanocytic cells; *figure 2L*);

(2) nuclear pleomorphism, heterogeneous chromatin distribution with relative hyperchromasia, prominent nucleoli, mitoses, lack of maturation at the base (*figure 2M*);

(3) fibrosis and regression;

(4) asymmetric lymphocytic infiltration.

Some authors emphasize cyto-morphologic deviations in the diagnosis of DN. For instance Barnhill suggested that discontinuous nuclear atypia and abnormal, intraepidermal proliferation of melanocytic cells (lentiginous or junctional) should be regarded as a prerequisite for the diagnosis of intermediary melanocytic lesions, *i.e.*, true MM precursors [3, 18, 19]. Previously, Mihm and Barnhill tried to distinguish six grades of melanocytic dysplasia: (i) com-

mon melanocytic nevi, (ii) melanocytic nevi with features of DN, (iii) DN with slight cytologic atypia, (iv) DN with moderate cytologic atypia, (v) DN with severe cytologic atypia, and (vi) primary MM. However, as with all schemes for melanocytic dysplasia, this concept also lacked interobserver reproducibility. In this study, experienced dermatopathologists had a concordance in grading DN ranging from 35% to 58% (kappa value 0.38-0.47), while that of less experienced dermatopathologists ranged from 16% to 65% (kappa value 0.05-0.24) [20]. Regardless of how refined the histological criteria become, the distinction between DN and true initial MM remains blurred and a gold standard remains elusive. The bad thing about it is not only the imponderability from the perspective of the patient, it also challenges any research effort on DN, also the molecular analyses. The question is always what did researchers investigate, if they say DN were included [21]?

In summary, similarly to the clinical dilemma, histopathology has problems in discriminating the dysplastic portion of tumors from the true malignant ones and the true benign ones. And, histopathology also does not solve the question whether the DN is an end point or a precursor lesion of MM. The histopathological detection of DN (according to Clark and Elder's criteria) within MM biopsies was taken as a proof for Clark's model of melanoma progression. However, current data suggest that a considerable proportion – around 60–75% – of MM develop *de novo* without any precursor lesion [14, 22]. It became clear that only a relatively small proportion of melanomas as a whole are associated with preexisting nevi. The size of this subset has been studied extensively [23]. In one larger study Harley and Walsh found, for instance, that only 23% of the melanomas arose in association with preexisting nevi of which 55% were acquired, 28% were congenital (small) and in 17% a distinction could not confidently be made. Of the acquired nevi, the majority were of the dysplastic type according to

Clark's definition along with common nevi. They concluded, similarly to other authors, that only a small subset of melanomas suggests a DN to MM sequence, and a similar role of small congenital nevi and common nevi should not be underrecognized [24]. The reported proportions again challenge the true role of DN as a precursor. For the clinician this means that the high incidence of both small congenital and common acquired nevi, and DN *versus* the incidence of melanomas should be kept in perspective in devising strategies for early detection and prevention.

Epidemiology: Limited predictive value of dysplastic melanocytic nevi

In the given dilemma with DN definitions it is a particularly hard task to prove the existence of DN and its relation to MM by epidemiologic analysis. The rationale of the epidemiological approach seems clear; if DN exist as precursors of MM, then logic tells us that DN must be a significant risk marker and DN and MM should occur at the same sites. Both assumptions have not been proven. Instead, the highly varying results of studies concerning the correlation between relative risks of MM and the number of DN again document the difficulties with DN definitions (*figure 3*). For instance, Tucker *et al.* tried to add more details to the concept described by Clark and Elder. They showed that the presence of only one clinically suspicious nevus, according to the clinical ABCD rule, doubles the risk for the development of MM. Individuals with ten or more nevi filtered by the ABCD rule had a twelve-fold increased risk of MM in their study [35]. From this point of view, the postulate that MM develops from pre-existing DN and the conclusion that there is a nevus-melanoma sequence with DN as interme-

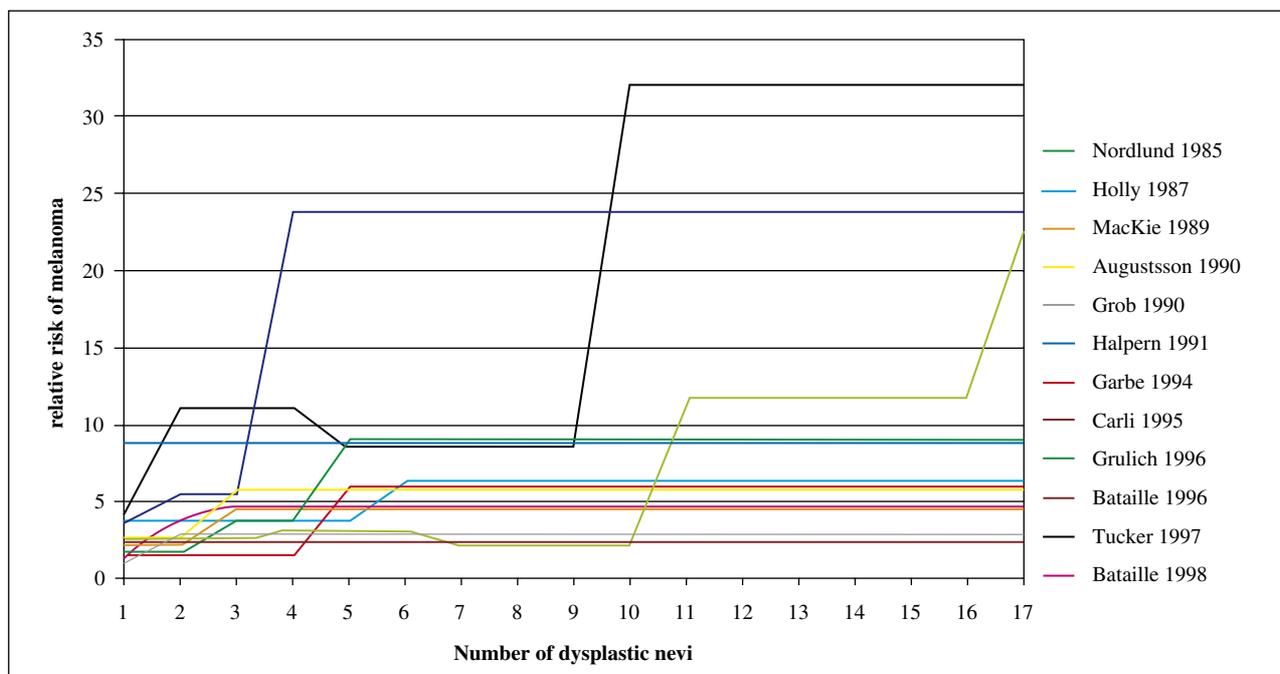


Figure 3. Highly varying results were obtained in studies concerning the relative risk for melanoma and the number of dysplastic nevi (DN). The curves document the difficulties with DN definitions, an inherent dilemma of all studies on DN.

diate lesions seems logical. However, contradictory data were published by Grob *et al.* [29], who found a significant increase in MM risk in patients with an increased total number of melanocytic skin lesions, including clinically innocuous nevi. In their study, the presence of DN was not linked to an increased MM risk. Instead, the presence of more than 120 pigmented nevi with a diameter of less than 5 mm indicates a 19.6- fold increase in risk, as compared to subjects with less than ten nevi. They assigned particular importance to the frequency of lesions with diameters > 5 mm, independently from other morphological criteria. Five nevi with a diameter > 5 mm increased the risk of MM by a factor of 10. A further current large evaluation of more than 20,000 patients with MM in the German Central Malignant Melanoma Registry points into the same direction, showing that the total number of clinically inconspicuous nevi on the lower extremities is a good predictor for the development of MM in both males and females [37]. Weiss, Bertz and Jing also found a correlation between the total number of pigmented skin tumors including small common nevi and the development of MM [38]. In their study, the number of benign nevi turned out to be the best predictive parameter, with a relative MM risk of 14.9 for patients with fifty nevi or more. Bataille *et al.* added that the presence of common nevi in atypical locations (back of the foot, buttocks, dorsal

capillitium) might also indicate an increased risk of MM development [34].

Kanzler and Mraz-Gernhard have suggested three theoretical possibilities to explain these epidemiological circumstances [39]: (i) subjects with multiple pigmented nevi, whether typical or not, have more melanocytic cells than other individuals. This increases the probability of a deleterious genetic defect per melanocytic cell; (ii) the formation of multiple benign tumors may already be the result of a genetic predisposition for proliferative changes, and consequently also for the occurrence of malignant cells in the pigment cell system, and (iii) previous exposure to environmental factors, such as sunlight in childhood, may generally foster the development of melanocytic tumors, benign and malignant. This concept implies that nevus and MM development are independent without an obligate stepwise transition. Furthermore, it should be noted that there is a weak correlation between the topographic distribution of MM and DN which also contradicts the paradigm of DN as MM precursors [40].

Taken together, it becomes obvious that any melanocytic tumour has a certain propensity to progress to MM. In this regard, the DN are not different from other pigmented tumors such as common benign nevi, developing (growing) melanocytic nevi in children/adults, irritated melanocytic

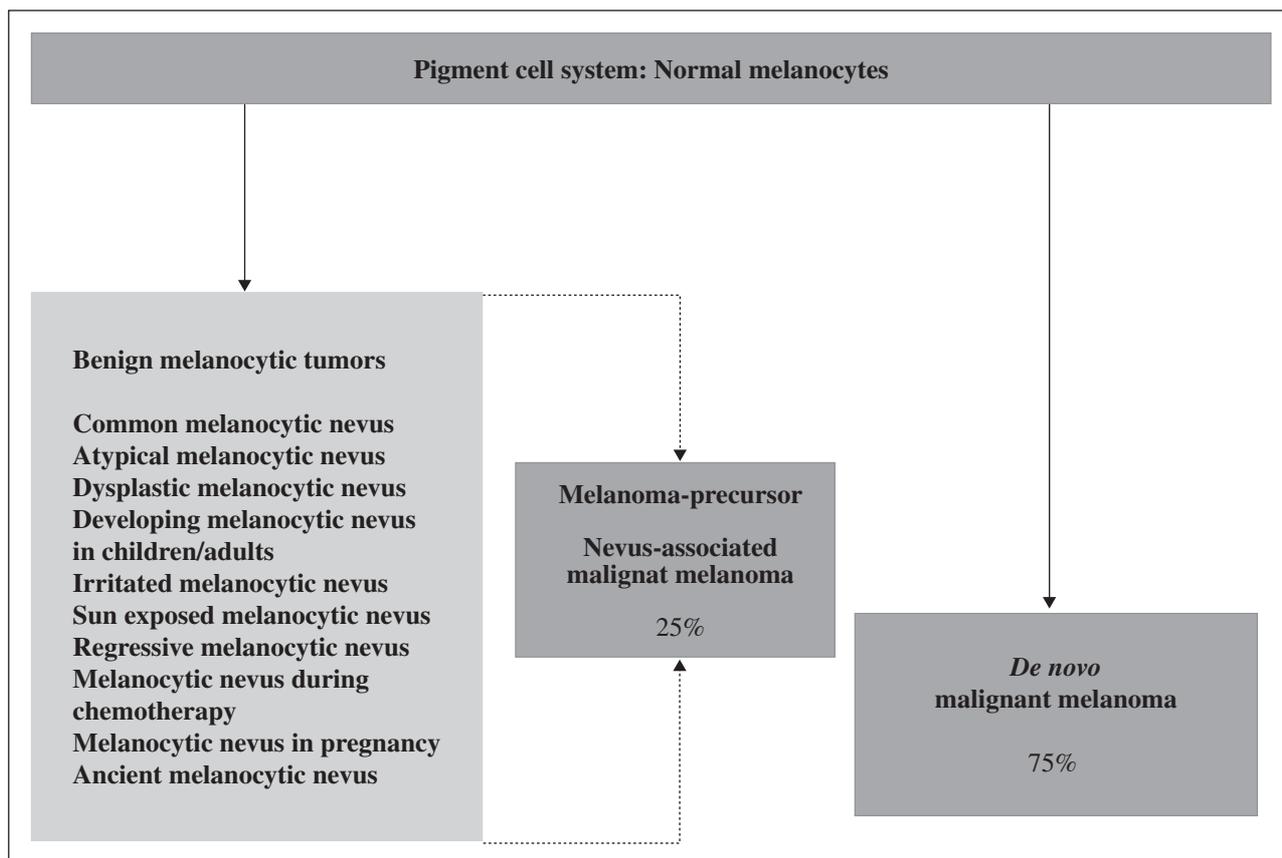


Figure 4. On the basis of this review it becomes obvious that any melanocytic tumor has a certain propensity to progress to malignant melanoma. In this regard, the so-called dysplastic nevi are not different from other pigment tumors such as common benign nevi, developing (growing) melanocytic nevi in children/adults, irritated melanocytic nevi, sun exposed melanocytic nevi, regressive melanocytic nevi, melanocytic nevi under chemotherapy, melanocytic nevi in pregnancy, or ancient melanocytic nevi. They all contribute to the subfraction of nevus-associated MM. Those are outnumbered by *de novo* malignant melanomas that account for about 75% of all cases.

nevi, sun-exposed melanocytic nevi, regressive melanocytic nevi, melanocytic nevi under chemotherapy, melanocytic nevi in pregnancy, or ancient melanocytic nevi. They all contribute to the set of nevus-associated MM (figure 4).

Molecular biology and genetics: A mirror of the dilemma, but no solution

New discoveries in molecular biological research fostered hope of proving the existence of a nevus-melanoma sequence and developing new diagnostic tools for clear separation of clinically suspicious lesions from true MM. Due to the difficult definition of melanocytic dysplasia, however, comparing molecular studies remains a problem. Depending on the diagnostic criteria used for tissue sample selection, study results vary considerably. Nevertheless, the insights gained into the molecular intricacies of “dysplastic” melanocytic tumors are highly informative and valuable. Therefore, we give a short overview about molecular studies. Most molecular biology papers claim “dysplastic nevi were analyzed” after selection by expert dermatopatholo-

gists. Any discussion on the criteria for selection is avoided, for good reasons.

Table 1 provides an orientation and overview over the varying molecular aspects that have been studied in DN. Major issues in molecular DN research have been cell cycle control (loss of suppressor gene functions), genomic instability (mismatch repair deficits), chromosomal aberrations, oncogene activating mutations and telomerase activation, and signal transduction and signalling kinase activation levels [64].

Among the complex and heterogeneous findings listed in table 1, the possible role of p16 tumour suppressor gene deserves a closer look, since it is deleted or mutated in various human tumors including MM, particularly in MM families (inherited MM). Only limited conflicting results have been reported in sporadic DN [48, 49, 54, 55]. The p16-gene, INK4a (CDKN2A), is located on chromosome 9p21 and codes for a 16 kDa protein that inhibits proliferative, cyclin-dependent kinases (CDK 4/6) in the G1 phase of the cell cycle. About 50% of patients from melanoma-prone families have a germline mutation in

Table 1. Molecular biological features of dysplastic nevi

Molecular feature studied	Chromosome/gene affected	References	Comment
Linkage analyses	1p36 MM/DN susceptibility locus based on linkage studies	Bale 1989 [41] Goldstein 1996 [42]	Later studies did not unequivocally confirm this finding.
	9p21 MM/DN susceptibility locus based on linkage studies	Fountain 1991 [43] Cannon-Albright [44]	Linkage to DN is questionable according to Goldstein.
Allelic losses	1p	Lee 1997 [45]	Losses involved in carcinogenesis of various tumors. Similar patterns of losses in MM and DN seem to exist, although the rate is much lower in DN.
	9p	Park 1998 [46]	
	17p	Boni [47]	
Loss/Mutation of tumor suppressor genes	p16/CDKN2	Piepkorn 2000 [48] Healy 1996 [49] Papp 1999 [50]	Deleted and mutated in various tumors. Also in lymphoblastoid cell lines from patients with DNS. Contrasting results were obtained in sporadic DN.
	p53	Levin 1995 [51] Vogt 1997 [52] Cristofolini 1993 [53]	Involved in about 50% of all human malignancies. C:G to T:A (UV induced) transitions can be present in DN, but at much lower rates compared to MM. The role of p53 in MM is still unclear, since overexpression of wild type p53 implies a worse prognosis. Similar accumulation of p53 is found in 5- 15% of DN.
Mismatch repair	hMSH2, hMLH1, hPMS1, hPMS2, GTPB	Hussein 2001 [54]	Defects cause genomic instability, <i>i.e.</i> microsatellite instability and accumulation of mutations. DN postulated to express intermediate levels of repair enzyme activity between common nevi and MM.
Microsatellite instability	1p	Hussein 2001 [55]	Supposed to be increased in DN and correlated with the degree of atypia.
	9q	Birindelli 2000 [56]	
Oncogenes	ras	Shukla 1989 [57]	Only occasionally mutated/activated in DN.
Extracellular matrix	collagen I, III, VI tenascin, fibronectin	Van Duinen 1994 [58]	Frequent changes in the stromal microenvironment in DN related to the known fibroplasia in DN.
Growth factors	bFGF	Reed 1994 [59]	Typically overexpressed in MM, supposed to be differentially expressed in DN.
Signaling molecules	BRAF (kinase)	Pollock 2003 [60]	Typically overexpressed in MM, supposed to be differentially expressed in DN.
Genome maintenance	Telomerase	Glässl 1999 [61] Miraco 2000 [62] Rudolph 2000 [63]	Activity is supposed to be increased in DN. Regulates the theoretical number of possible cell cycles. Increased in many human cancers.

INK4a. 25-40% of sporadic MM also show mutations leading to a failure of INK4a function [65]. Since MM and the tumour suppressor INK4a seem to be causally linked, chromosome analyses of the 9p21 locus have been carried out particularly carefully on individuals with DN. Patients with mutations in INK4a had a significantly higher total number of nevi, but there was no significant correlation with the number of DN [66]. In summary, while the linkage of familial MM and the 9p21 locus seems to be consistent in many studies, the linkage of DN and this locus remains questionable [42].

Another potential MM susceptibility region with significant linkage scores in DN-families is 1p36 with the PITSLRE gene coding for a p58 protein kinase, which also contributes to the control of the cell cycle. Based on genetic linkage analyses on FAMMM syndrome and familial MM, Goldstein *et al.* suggested that 1p36 is a tumour-susceptibility locus that is not only relevant for MM but also for the formation of DN [42]. But, further studies substantiating a possible role of p58 in the development of DN are not available and later studies did not unequivocally confirm this [64].

According to Knudson's two-hit hypothesis, both alleles of a tumour suppressor gene have to be deactivated for a loss of activity. Loss of the healthy allele (loss of heterozygosity, LOH) is one of the most frequently observed mechanisms for a second hit, with the first hit being a germline mutation in a tumour suppressor gene. Using LOH analyses of tumour tissue, these allelic losses (for example, as a result of chromosomal deletion or unbalanced translocation) can be detected [64]. Allelic losses of 1p, 9p and/or 17p (the coding region for the p53 suppressor gene) could not be found in tissue samples from common nevi, but LOH was present in DN [45-47]. Similar patterns of losses seem to exist in MM and DN, but in DN allelic losses are much less frequent [46].

A further hallmark of cancer genomics is the frequent occurrence of microsatellite instability (MSI) – length variations in non-coding, short, repetitive DNA sections, which flank the coding regions of genes. These regions may act as regulatory DNA sections (for example, as topoisomerase binding sites, sites of recombination). Their sequential uniformity can result in mismatch pairing during chromosome replication and this may also lead to subsequent microsatellite length mutations. Under normal conditions, mismatch repair (MMR) proteins prevent the mismatching of bases during DNA replication. The main human MMRs are hMSH2, hMLH1, hPMS1 and 2 as well as GTBP. MSI has been documented in DN and its incidence seems to increase with the degree of histological atypia in DN [55]. Since no MSI has been reported in normal nevi, DN seem to be intermediate between common nevi and MM, concerning mismatch repair competence. However, MSI is uncommon in both DN and MM. Over 80% of sporadic MM are MSI negative [56, 64, 67-70]. Therefore, both the diagnostic value and the biological significance of MSI and mismatch repair in DN are still doubtful.

Most recently, another new candidate gene has emerged that is linked to MM development, BRAF. As a serine/threonine kinase within the MAPK-modulated signal transduction cascade, BRAF transmits proliferative signals to the nucleus. Since a high mutation rate of BRAF can be found in common nevi, DN and MM [60], BRAF-

analysis is also unsuitable to achieve the desired discriminative power or tell us anything about the MM precursor potential or end point differentiation of a DN.

Finally, telomeres – TTAGG repeats at the end of the chromosomes – represent a promising candidate to elucidate the nature of DN. Telomeres are lost during cell cycling and represent a limiting factor concerning the number of possible cycles. Telomerase is an enzyme that adds TTAGG repeats to the ends of chromosomes. It is suppressed in somatic cells which limits their growth. In contrast, telomerase is active in many cancers including MM. Also during the postulated sequence from normal nevi to MM, a progressive increase of telomerase activity has been postulated by several studies. But strikingly, telomerase activity was only increased in DN when tissue specimens were histologically selected according to cytological and nuclear atypia [61, 62]. If Clark and Elder's criteria were used, no differences in telomerase activity were found between common nevi and DN [63].

Taken together, the molecular studies demonstrate that a few lesions among the DN studied always seem to be transitional between common nevi and MM, but the majority are not. New and yet not fully exploited is the potential of applying "omics"-tools, *i.e.* genome wide analysis of the genome itself, the transcriptome and the proteome by chip-CGH, cDNA array analysis and mass spectrometry of the proteome (*e.g.* by MALDI-TOF MS) [71-73]. There is hope that the growing possibilities of laser catapulted microdissection of DN and chip based "omics"-tools together with the growing possibilities of data mining, cluster and pathway analysis will finally resolve the enigmas of melanocytic dysplasia, too [74-77]. Doubtless, much more work is needed to expand the molecular knowledge of DN. For that purpose however, reproducible definitions of DN would be highly desirable.

Dermoscopy and computer-assisted image analysis: Making melanocytic tumors with uncertain malignant potential a manageable disease

The limitations of dermoscopy in the recognition of early more or less feature-less MM have been highlighted in a very recent study by Kittler and co-workers [78]. Dermoscopy is just as inadequate as other tools in defining DN as an entity and giving clear cut criteria for its distinction [79]. Despite these difficulties, dermoscopy offers an enormous increase in resolution (*figure 5*) and expands the amount of extractable information to a level where objective and reproducible scoring algorithms can be instrumentalized for practical guidance.

Although other systems such as the pattern analysis [80] and the 7-point checklist [81] are available, the ABCD rule of dermoscopy [82, 83] is most often applied. Stolz and co-workers developed the ABCD rule of dermoscopy, an algorithm that also forms the basis for some commercially available computerized systems. Four dermoscopic criteria are analyzed for evaluation of a pigmented lesion: Asymmetry (in no, one or two axes), Border (sharp *versus* blurred demarcation in eight segments), Colour (number of colours: dark brown, light brown, black, red, grey, white), and Differential structures (number of microrichitectural



Figure 5. Dermatoscopy led to a “quantum leap” in visual resolution of melanocytic skin tumors. Due to the enormous increase of the amount of extractable image information, scoring algorithms could be established for practical guidance.

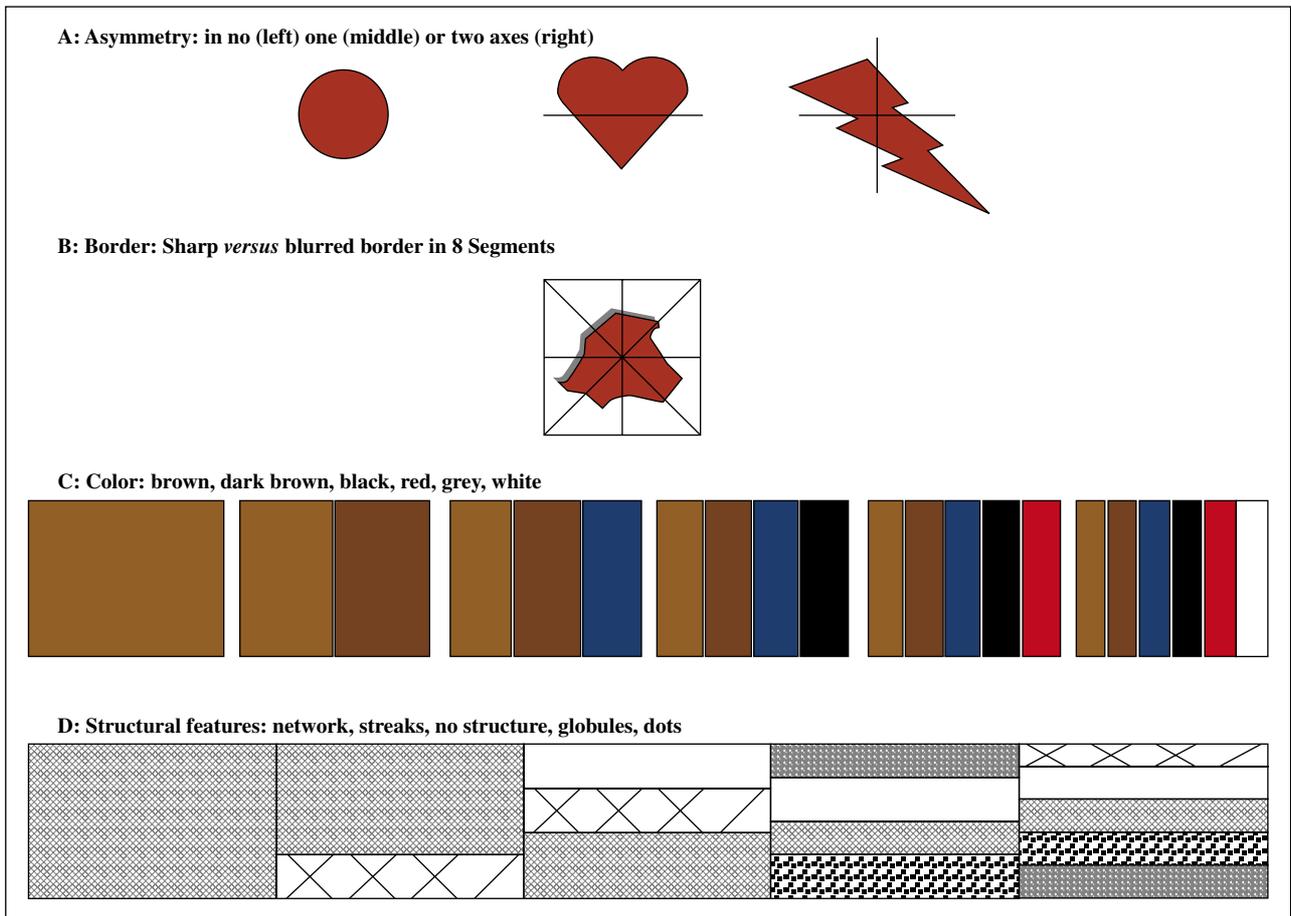


Figure 6. The basic principles of the ABCD rule of dermatoscopy, which is also the basic algorithm for some commercially available computerized systems. For evaluation of a pigmented lesion, four dermatoscopic criteria are analyzed: Asymmetry (in no, one or two axes), Border (sharp *versus* blurred demarcation in eight segments), Colour (number of colours: dark brown, light brown, black, red, grey, white), and Differential structures (number of microrarchitectural features of melanocytic lesions: network, branching streaks, structure-free zones, globules, dots). A total dermatoscopy score (TDS) can be calculated on this basis.

features of melanocytic lesions: network, branching streaks, structure-free zones, globules, and dots). *Figure 6* displays the basic principles of the ABCD rule of dermatoscopy [22, 84].

For example, when analysing *figure 5*, the point value would be calculated as follows: A: 2 points, since one can not find an axis to mirror one half to the other when considering form and structural features. B: 0 points, since the border is blurred all around the eight segments. C: 3 points for colour, since one can discriminate light brown, dark brown and black. D: 4 points for structure-free zones, branching streaks, dots, globules. Based on empirical data the ABCD point values need to be weighted to express the relative power of each of the criteria [22, 84]. Since asymmetry turned out to be a much stronger discriminator between MM and nevus than colours or structural features and the latter are stronger discriminators than the border, asymmetry goes into the total dermatoscopic score (TDS) multiplied with 1.3, colour and structural feature multiplied with 0.5 and border with 0.1. Hence, the TDS for *figure 5* would be:

$$1.3 \times 2 + 0.1 \times 0 + 0.5(3 + 4) = 5.1$$

differential structures, divide the result by two and add 1.3 per axis of asymmetry and then score gradually up 0.1 increments for any of the eight segments with sharp demarcation of the structures. Such TDS scoring certainly needs

practice. However, it turned out to be particularly useful for guidance of less-experienced investigators, and increased the accuracy of MM diagnosis to over 90% in experts [85]. *Figure 7* gives an impression of the leap in resolution by dermatoscopy. The hidden MMs are now more easily to detect if one guides oneself through the images according to the ABCD rule of dermatoscopy.

Another great advantage is that with the advent of digital computer-assisted dermatoscopy, the TDS can be established by computed image analysis. Therefore, objectivity and reproducibility is guaranteed. Next to its reproducibility, the main advantage of computer-aided dermatoscopy is the rapid and exact digitized recording of skin lesions. Even minor structural changes can be followed over time, e.g. the development of small peripheral pseudopods or asymmetrical growth, two criteria that are highly specific for malignant melanocytic progression [86]. Morphological changes such as increase of size, changes in shape and colour, signs of regression, and the appearance of other differential structures can also be sensitively monitored. Binder and colleagues demonstrated by computerized dermatoscopy that typical and dysplastic nevi may undergo a subtle increase in size, but they keep their symmetrical form, and rarely develop new dermatoscopic structures [87]. *Figures 8 and 9* give examples of suspicious melanocytic lesions. One was stable over time, probably representing an end point of



Figure 7. Gives an impression of the leap in resolution by dermatoscopy. The hidden melanomas are now more easily to detect if one guides oneself through the images according to the ABCD rule.

nevocytic evolution (figure 8), whereas the other one showed asymmetrical growth over time, a sign of malignancy (figure 9). Both were histologically “proven”.

In summary, video documentation systems with an integrated, computerized colour image analysis can guide clinicians in the assessment of pigmented skin lesions but do not solve the problem of “dysplastic” lesions [22, 88]. Surprisingly, the practical net effect of such objective scoring systems is a dramatic reduction of doubtful, suspicious cases [22]. Figure 10 shows a Gaussian distribution of the scores of common nevi and MM with no overlap. The problematical lesions, the DN, also distribute in a Gaussian manner in the range between TDS 4.75 to 5.45, with little overlap. To us this proves the existence of indeterminate melanocytic tumors which cannot be further resolved. Therefore, regardless of the nature of DN and irrespective of the current semantic confusion, a practical approach could be to remove lesions with a TDS of over 4.75 or, alternatively, to closely follow-up such lesions by computerized dermatoscopy. Tumors with a TDS of higher than 5.45 have already a 90% probability of being a MM and should in any case be removed with an appropriate safety margin [82].

A more widespread use of this practical approach for research purposes would also contribute to a better comparability of studies dealing with melanocytic tumors. Pigmented tumors would then not fall into variable numbers of ill-defined categories, but would be classified by scores, e.g., a study concept could be the analysis of lesions with TDS 4.75 to 5.45. Concurrent studies would then profit in terms of comparability.

Conclusion and practical approach

Using the diagnostic and investigative equipment available in the 1970s, Clark, Elder and their groups without doubt developed an epoch-making model. With their progression hypothesis, they attempted to find a connection between epidemiological phenomena and the biological nature of melanocytic lesions. In individual cases, the proposed paradigm holds true. However, from today’s point of view, the only objectively assessable feature is a computer-based TDS. Classifications based on TDS would, at the very minimum, ensure homogeneous sampling in future research efforts and perhaps



Figure 8. This lesion was stable over time, probably representing an end point of nevocytic evolution.



Figure 9. This lesion (TDS about 5) showed asymmetrical growth over time, a clear sign of malignancy. MM was proven histologically in this case. Hence, video documentation systems with an integrated computerized colour image analysis can guide clinicians in the assessment of pigmented skin lesions, but can not solve the dilemma of “dysplastic” lesions, *i.e.* discriminate between dysplastic nevi as true melanoma precursors and dysplastic nevi as end point lesions.

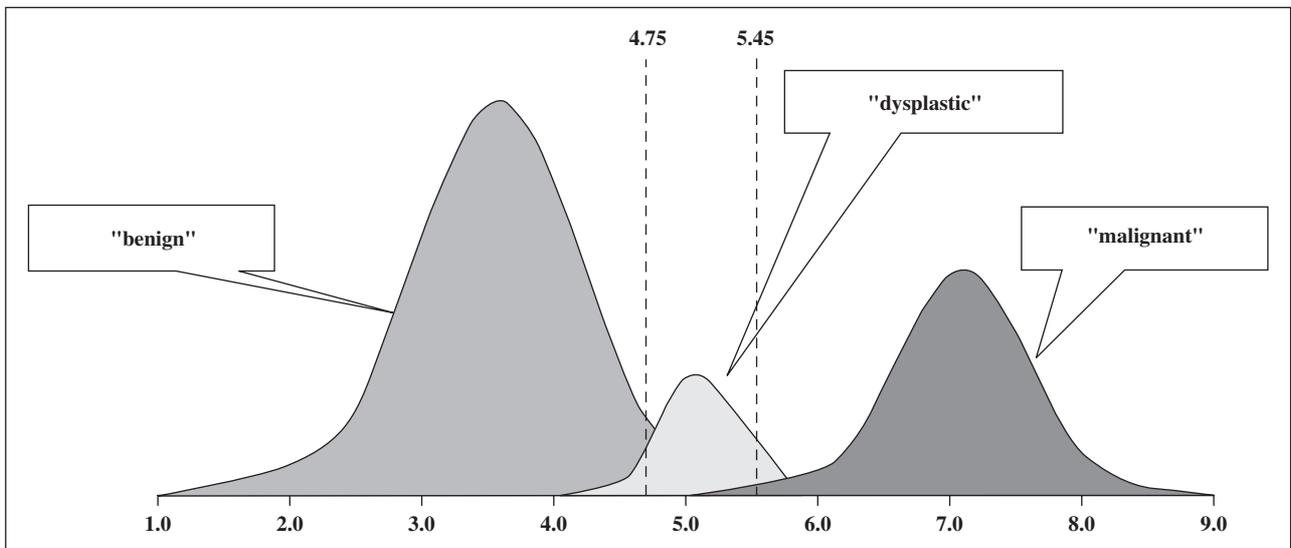


Figure 10. The practical net effect of TDS objective scoring systems is a dramatic reduction of doubtful, suspicious cases. The Figure shows a Gaussian distribution of the scores of common nevi and melanoma with no overlap. The problematical lesions also distribute in a Gaussian manner in the TDS-range between 4.75 and 5.45 with little overlap. It proves the existence of indeterminate melanocytic tumors which can not be further resolved. A practical approach could be to remove lesions with a TDS of over 4.75 or, alternatively, to closely follow-up these lesions. Tumors with a TDS of higher than 5.45 have already a 90% probability of being a melanoma and should in any case be removed with an appropriate safety margin.

also minimize patients' risk. Certainly, TDS systems also need international consensus efforts and need steady adjustments based on enlarging knowledge bases. Currently, on the basis of this review a practical approach to risk minimization could be as follows

(figure 11): Since clinically atypical, suspicious lesions with a TDS > 4.75 and < 5.45 can indicate a true MM precursor as well as an early MM, but also a stable endpoint of melanocytic nevus development, such lesions are removed or, if impossible due to number or location, moni-

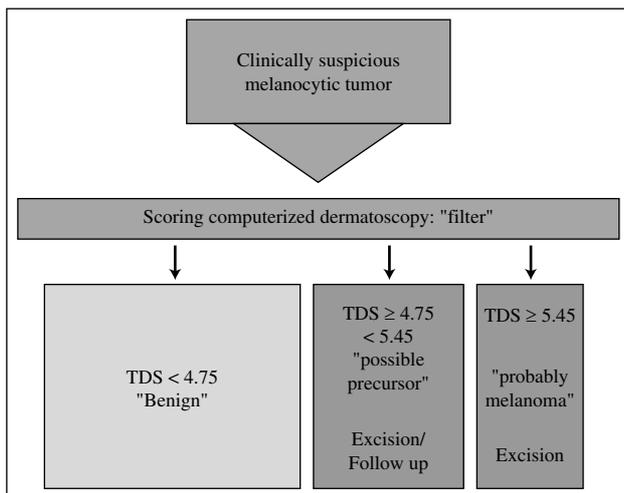


Figure 11. Suggested working concept based on the dermatoscopy scoring. Since the only objectively assessable feature of a given melanocytic lesion is the computer-based total dermatoscopy score (TDS), a classification of indetermined melanocytic tumors based on TDS would, at the very minimum, ensure homogeneous sampling in future research efforts. Practically, on the basis of this review the clinical management of suspicious melanocytic lesions could be "standardized" as follows: Since clinically suspicious lesions with a TDS > 4.75 and < 5.45 can indicate a true MM precursor as well as an early MM, but also a stable endpoint of melanocytic nevus development, such lesions should be removed or, if not possible due to number or location, monitored at six month intervals using computer-aided dermatoscopy systems. A TDS of more than 5.45 indicates a MM with a probability of over 90%. Those tumors should be excised immediately without exception. Patients' and doctors' risk of missing a melanoma seem to be minimal with this approach.

tored at six month intervals using computer-aided dermatoscopy systems. A TDS of more than 5.45 indicates a MM with a probability of over 90%. Those tumors should be excised immediately without exception [22]. ■

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