Dysplastic naevi (DN) WHO 2018 (Ed 4)

Skin Cancer Annual General Meeting

03 December 2021

S Al-Habba

DN Concept

The concept of dysplastic nevus was introduced in 1978 to identify an indicator of melanoma risk and potential melanoma precursor.

In a series of melanoma families, family members were noted to have increased numbers of acquired nevi that were unusually large, often exceeding 10 mms, and showed irregular pigmentation.

The nevi observed in patients with this syndrome were proposed to have specific histopathological features such as nuclear pleomorphism, bridging of rete ridges, and lamellar fibrosis of the papillary dermis.

It later became clear that the histopathological features are very common in acquired nevi in general and are not specifically associated with the syndrome or with the size of the nevi

Origin of Familial Malignant Melanomas From Heritable Melanocytic Lesions

'The B-K Mole Syndrome'

Wallace H. Clark, Jr, MD; Ronald R. Reimer, MD; Mark Greene, MD; Ann M. Ainsworth, MD; Michael J. Mastrangelo, MD

• **Distinctive melanocytic moles are described in 37 patients from six melanoma families. Among the family members examined by the authors, 15 of 17 patients with melanoma and 22 of 41 nonmelanoma relatives had the unique moles. The clinical and histological features of these moles have been designated the "B-K mole syndrome." The clinical features of the syndrome include the presence of < 10 to > 100 moles prominent on the upper trunk and extremities, and variability of mole size (5 mm to 15 mm), outline, and color combination. Histologically, B-K moles show atypical melanocytic hyperplasia, lymphocytic infiltration, delicate fibroplasia, and new blood vessels that occur within a compound nevus or de novo. The transformation of two B-K moles into malignant melanomas was documented photographically.**

(*Arch Dermatol* 114:732-738, 1978)

Atypical nevus is a clinical term, **Dysplastic Naevus** is a histologic term

- Melanoma prone families

1. B-K Mole syndrome" (B and K were the first letters of the names of two "unusually helpful" patients) - Clark
2. Familial Atypical Multiple-Mole Melanoma (FAMMM) syndrome - Lynch
3. Dysplastic Nevus Syndrome' (DNS) - Elder
4. Atypical mole syndrome -UK

Revised (British group) dysplastic nevus syndrome score

- ≥ 100 nevi of size >2 mm (≥50 if 50 years of age)—1 point
- ≥ 2 atypical nevi—1 point
- ≥1 nevus on buttocks—1 point
- ≥2 nevi on the dorsa feet—1 point
- If total score is >2, the patient has dysplastic nevus syndrome

DNS - Dysplastic Naevus Syndrome

Histologically, the nevi were defined as atypical melanocytic hyperplasias, with mesenchymal changes in the papillary dermis, and a lymphocytic infiltrate.

30–40% of these families harbour a mutation in the CDKN2A locus, which encodes the p16 and ARF tumour suppressor proteins

Dysplastic nevi

how special are they?

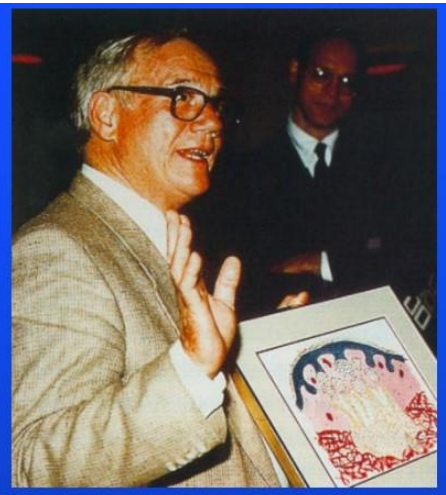
Founder

Convert

Skeptic

Agnostic

Atheist



Wallace H. Clark Jr MD
(1924-1997)

A. Bernard Ackerman MD
(1936-2008)

WHO Melanoma Programme → Dysplastic N.
Hum Pathol 1991;22:313-19

- WHO enumerated major and minor criteria for the histologic diagnosis of DN.
  - The major criteria are:
    - 1) basilar proliferation of atypical melanocytes which must extend at least three rete ridges or "pegs" beyond the dermal component i.e. "shoulder "
    - 2) organization of this proliferation in a lentiginous or epithelioid-cell pattern
  - The minor criteria include:
    - 1) lamellar fibrosis or concentric eosinophilic fibrosis,
    - 2) neovascularization,
    - 3) inflammatory response, and
    - 4) fusion of rete ridges.

Using these criteria, a diagnosis of DN requires both major criteria and at least two minor criteria.

Is DN a real entity?

Ackerman maintained that all benign nevi could be classified as one of four types:

1) Unna's nevus, with polyploid morphology and thickened papillary dermis,

2) Meisher's nevus, dome-shaped with nevus cells arranged in a wedge configuration,

3) Spitz's nevus, characterized by a benign silhouette of epithelioid or spindled cells having large nuclei with abundant cytoplasm, and

4) Clark's (or dysplastic) nevus , 'nevus with architectural disorder.'

Melanoma Risk

- Very few studies have attempted to correlate the presence of DN, as defined histologically, with melanoma risk.
- Arumi-Uria et al*. retrospectively reviewed 6275 cases of “nevus with architectural disorder”, which were then grouped based on presence of mild (40%), moderate (26%), and severe (5%) cytologic atypia.
  - A history of melanoma diagnosis in these patients with nevi showing mild, moderate, and severe atypia was 5.7%, 8.1% and 19.7%, respectively.
  - **The authors concluded that melanoma risk is higher for persons with DN having higher grades of histologic atypia.**

  - *Mod Pathol 2003;16(8):764–771

Table 1. Criteria for NAD Grading

Characteristic	CMN-Not Atypical	NAD-Mild	NAD-Mod	NAD-Severe	Melanoma
Lateral circumscription	Sharp	Slightly diminished	Moderate	Moderate	Poor
Symmetry	Good	Good	Good	Often broken	Rare
Junctional extension	Unusual	Usual	Usual	Usual	Extensive
Rete ridge distortion	Occasional	Occasional	Usual	Always	Occasional
Fibrosis	Regressive	Often	Always	Always	Occasional
Melanocyte distribution	Nests dispersed	Nests dispersed	Nests dispersed	Nests dispersed	Dispersed nests
Upward migration	Occasionally centrally	Rarely	Occasionally centrally	Occasional centrally	Often central and peripheral
Suprapapillary plates	Spared	Spared	Usually spared	Often involved	Involved
Nuclear size	Age-related	Small	Medium	Large	Medium/large
Nucleoli	Age-related	Small	Medium	Large	Large
Chromatin	Uniform	Condensed	Partially expanded	Expanded, coarse in some cells	Expanded, hyperchromatic and coarse
Mitoses/dermal	Few superficial	Few superficial	Few superficial	Few superficial	Superficial and deep mitoses

- Although studies are few in number, it appears that patients who develop more severe cytologically atypical nevi may have a higher likelihood of developing subsequent melanoma.

Significance of Nevi

- **Nevi are important almost exclusively in relation to melanoma**

- **Significance as**

Simulants of melanoma	Markers of individuals at increased risk for melanoma	Potential precursors of melanoma

Dx Challenges

- The main **difficulty** with the DN does not necessarily seem to be its histologic diagnosis per se, but rather the ***stratification of melanocytic dysplasia***.
- Interobserver variation: DN grading

  35-58% concordance among experienced dermpaths

Duncan LM, et al. Histopathologic recognition and grading of dysplastic melanocytic nevi: an interobserver agreement study. J Invest Dermatol 1993;133:953-958.

- 2014 " There is no gold standard for the diagnosis of a dysplastic nevus." Massi G, LeBoit PE. Clark nevus and dysplastic nevus. In Histological Diagnosis of Nevi and Melanoma. 2014 Springer: Heidelberg, p. 273

DN Evolution in to Melanoma – No Evidence

- DN as a melanoma precursor "It is highly unusual that DN themselves eventuate into melanoma."

Farber MJ, Heilman ER, Friedman RJ. Dysplastic nevi. Dermatologic Clinics 2012;30:389-404

- "Melanoma in situ does arise in 'dysplastic' nevi but, in our view, only occasionally."

Massi G, LeBoit PE. Clark nevus and dysplastic nevus. In Histological Diagnosis of Nevi and Melanoma. 2014 Springer:Heidelberg, p. 278

- Studies have shown that there is difficulty in distinguishing 'severe cytologic dysplasia' in the junctional component of melanocytic proliferations from melanoma-in-situ and superficial dermal invasion.

For example, Cook et al upon review by a panel of 8 pathologists found that

- 17% of previously diagnosed melanomas were re-classified as benign with atypia
- 2% of lesions previously diagnosed as benign were reclassified as melanoma,.

DN - On going never ending Controversy

- Dysplasia' literally is translated from the Greek dys- (bad or malfunction) and -plasia (growth, development or change), thus connoting a change in cytology towards neoplasia or malignancy.
- Evidence that DN are true precursor lesions of melanoma is not convincing from the published literature
- There is no evidence that individual DN will inevitably progress through sequentially higher grades of dysplasia.
- There is substantial clinical evidence indicating that melanoma most commonly develops de novo, i.e. from isolated melanocytes rather than from nevi.
- Less commonly, melanoma arises from pre-existing nevi which may be either CN or DN.

Dysplastic Nevi as Potential Precursors of Melanoma

About one third of melanomas arise in association with a nevus, usually a dysplastic nevus

But most dysplastic nevi, like other nevi, are stable and will not progress to melanoma

Reason: Dysplastic nevi are much more numerous in the community than melanomas

Tsao H, Bevona C, Goggins W, Quinn T. The transformation rate of moles (melanocytic nevi) into cutaneous melanoma: a population-based estimate. Arch Dermatol. 2003;139(3):282-8. "The annual transformation rate of any single mole into melanoma ranges from 0.0005% or less (ie, </=1 in 200,000) for both men and women younger than 40 years to 0.003% (about 1 in 33,000) for men older than 60 years. "

Overlapping cytology with CN:
Histologic dysplasia occurs in clinically benign naevi.

Klein et al. prospectively analysed 58 clinically benign lesions

- <5 mm in diameter, symmetric,
- uniformly pigmented,
- with distinct margins and
- no erythema

and found that

- 88% had at least one histologic feature of DN, while
- 69% had two features and
- 29% had three features.

- *Klein LJ, Barr RJ. Histologic atypia in clinically benign nevi. A prospective study. J Am Acad Dermatol 1990;22:275-82.*

Grading Dysplasia

D. Elder, R. Barnhill, B Bastian, L Duncan, D Massi, M Mihm, M Piepkorn, M Rabkin, R Scolyer. Dysplastic Nevi.
In Elder DE, Massi D, Scolyer RA, Willemze R. WHO Classification of Skin Tumours. 4th ed. Lyon: IARC; 2018.

Junctional/compound nevus	• Includes former mild dysplasia and "Clark's nevus"
Low Grade Dysplasia (LGD)	• Former moderate dysplasia
High Grade Dysplasia (HGD)	• Former severe dysplasia

Grading Dysplasia (WHO, 2018)

Lesions formerly known as mildly dysplastic nevi

are not associated with increased melanoma risk,

are very common in the community,

have a very low probability of progression to melanoma,

and poor diagnostic reproducibility.

Moderate and severe dysplasia are risk markers and severe dysplasia may also be a precursor

Therefore, the committee recommends against the continued use of mild dysplasia, and recommends using only two grades of dysplasia:

Low Grade and High Grade Dysplasia.

D. Elder, R. Barnhill, B Bastian, L Duncan, D Massi, M Mihm, M Piepkorn, M Rabkin, R Scolyer. Dysplastic Nevi. In Elder DE, Massi D, Scolyer RA, Willemze R. WHO Classification of Skin Tumours. 4th ed. Lyon: IARC; 2018.

Mild Dysplasia → changed to 'Lentiginous' Junctional/Compound Nevus

Poorly reproducible diagnosis (vs. nevus)

Not associated with melanoma risk

Not a high-risk precursor

Not a strong simulant of melanoma

UNCERTAINTY vs. Moderate dysplasia, No dysplasia

spectrum of banal nevi (junctional or compound nevus, e.g. lentiginous junctional nevus)

Complete excision is not necessary even when margins are positive

- TERM "MILD DYSPLASIA" SHOULD NO LONGER BE USED

Moderate Dysplasia

- Controversial
- Poorly reproducible diagnosis (vs mild, severe)
- UNCERTAINTY vs. Mild dysplasia, MIS
- Associated with melanoma risk
- Probably not a high risk precursor
- A weak simulant of melanoma (at least histologically)
- Complete excision is a consideration; observation is an option

- *Kim CC, Berry EG, Marchetti MA, Swetter SM, Lim G, Grossman D, Curiel-Lewandowski C, Chu EY, Ming ME, Zhu K, Brahmbhatt M, Balakrishnan V, Davis MJ, Wolner Z, Fleming N, Ferris LK, Nguyen J, Trofymenko O, Liu Y, Chen SC; Pigmented Lesion Subcommittee, Melanoma Prevention Working Group. Risk of Subsequent Cutaneous Melanoma in Moderately Dysplastic Nevi Excisionally Biopsied but With Positive Histologic Margins. JAMA Dermatol. 2018 Dec 1;154(12):1401-1408.*

Mild-moderate DN

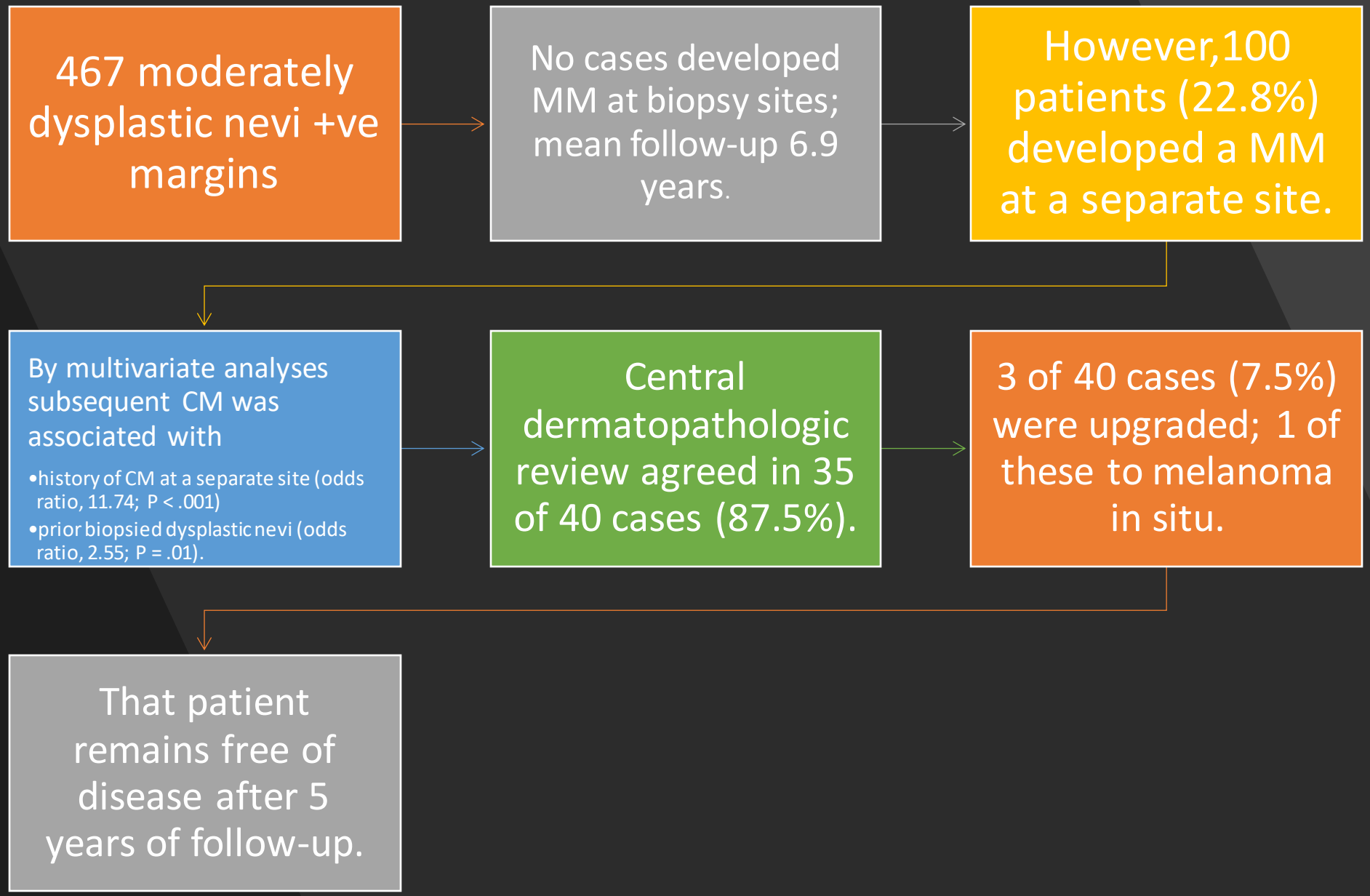
- N=115 HDN (histologically DN) extending within 0.2 mm of border and not re-excised
- 17.4 years avg F/U; no melanomas
- Routine re-excision of mild-mod DN not necessary

Hocker TL, Alikhan A, Comfere NI, Peters MS. Favorable long-term outcomes in patients with histologically dysplastic nevi that approach a specimen border. *J Am Acad Dermatol* 2013;68:545--51.

Elston D, McNIff J, Maize J Sr. Histologically dysplastic nevi that extend to a specimen border. *J Am Acad Dermatol* 2013;68:682-3.

Hocker TL, Alikhan A, Comfere NI, Peters MS. Reply to: Histologically dysplastic nevi that extend to a specimen border. *J Am Acad Dermatol* 2013;68:683-4.

Kim et al: Risk of Subsequent Cutaneous Melanoma in Moderately Dysplastic Nevi Excisionally Biopsied but With Positive Histologic Margins. JAMA Dermatol. 2018 Dec 1;154(12):1401-1408



Severe Dysplasia

Reasonably reproducible diagnosis

UNCERTAINTY vs. MIS

Associated with melanoma risk

Probably a high-risk precursor

A strong simulant of melanoma (histologically)

Should be managed by complete excision and consideration of follow-up, similar to MIS

Dysplastic Nevus Criteria (WHO, 2018)

Must have **both** architectural disorder and cytologic atypia

Architectural disorder requires all of the following:

- **Size > 4 mm wide in fixed sections (> 5 mm clinically)**
- **Nests of intraepidermal melanocytes forming a shoulder adjacent to any dermal component**
- **Increased density of non-nested junctional melanocytes.**

Cytologic atypia is graded on the highest degree of cytologic atypia present in more than a few melanocytes

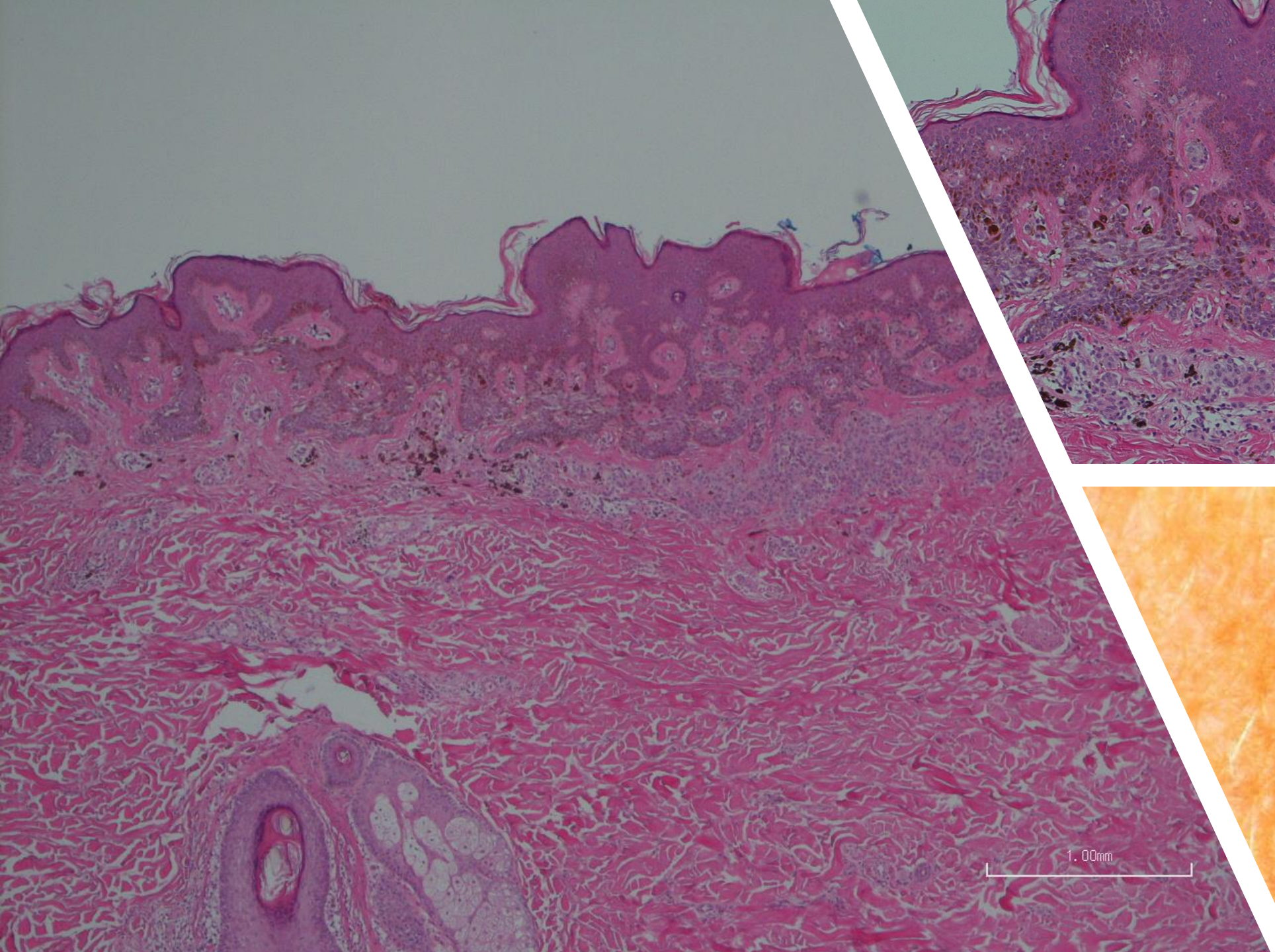
.

Diagnosis of exclusion, especially of other nevus variants and MIS/Invasive Melanoma

Nuclear Features in Dysplasia

WHO 2018	Former Grade	Nuclear size vs resting basal cell	Chromatin	Variation in Nuclear shape and size	Nucleoli
Not Dysplastic Naevus	0 (mild Dysplasia)	1x	May be hyperchromatic	Minimal	Small or absent
Low Grade Dysplasia	1 (moderate Dysplasia)	1-1.5x	Hyperchromatic or dispersed chromatin	Prominent in a small number of cells (random atypia)	Small or absent
High Grade Dysplasia	2 (severe Dysplasia)	>1.5x	Hyperchromatic, coarse chromatin, or peripheral condensation	Prominent in a larger number of cells	Prominent, often lavender

- Architectural features are required for diagnosis of dysplasia and also contribute to grade;
- Attributes that indicate high grade dysplasia even when cytological atypia is low grade include
    - Pagetoid scatter above the basal layer but not above the middle 1/3 and focal (<0.5 mm2)
    - Focal continuous basal proliferation
    - Intraepidermal mitoses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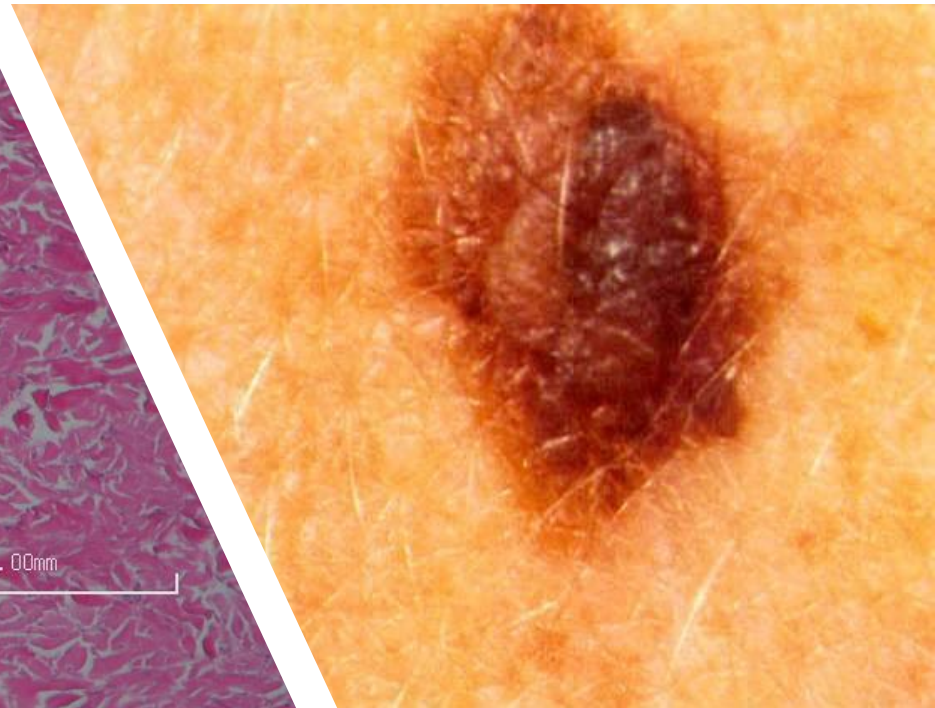
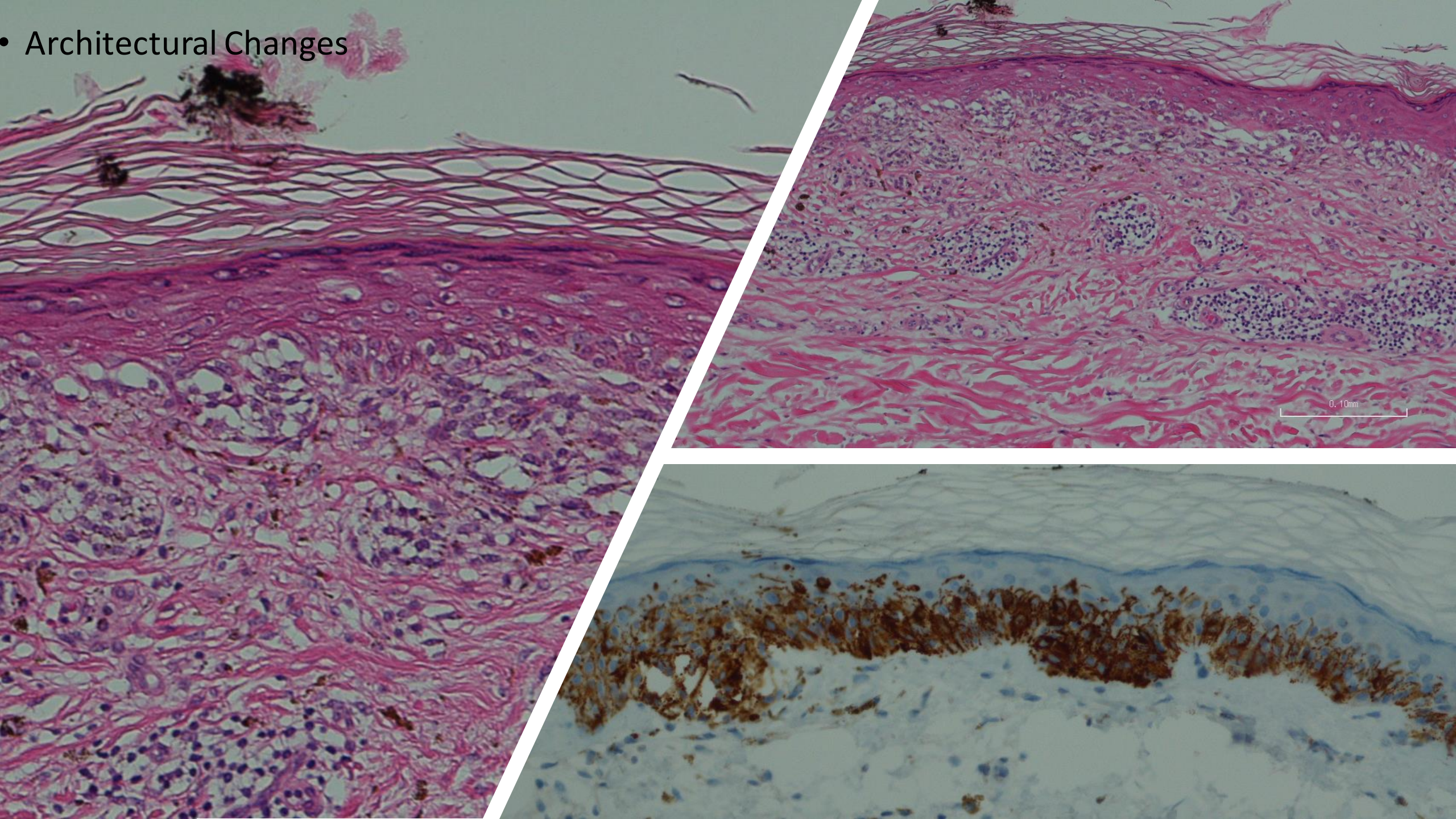


Attributes that indicate high grade dysplasia even when cytological atypia is low grade include

- Pagetoid scatter above the basal layer but not above the middle 1/3 and focal (<0.5 mm^2)
- Focal continuous basal proliferation
- Intraepidermal mitoses

- Architectural Changes



Exclusions

Moderate or severe atypia in more than a few melanocytes plus severe solar elastosis → indicates high cumulative sun damage (High-CSD) – suggests lentigo maligna and not dysplastic naevus

Moderate or severe atypia in more than a few melanocytes plus irregular and high cellularity with pagetoid scatter in the setting of Low-CSD → indicates suggests early melanoma and not dysplastic naevus

Dysplastic Naevus Management

The most important simulants, risk markers and potential precursors of melanoma

Management should include consideration of surveillance depending on other risk factors

Number of nevi, family history, personal history of melanoma. The higher the count of large nevi, the higher the melanoma risk

Removal of dysplastic nevi to prevent melanoma is futile

In the general population the risk of progression to melanoma is very low.

Remain stable for decades and tend to fade away later in life

Dysplastic Nevus Management

Low Grade Dysplasia

- Consider complete excision if margin is positive
- Physician surveillance may be a reasonable option
- Patent self-observation may be reasonable

High Grade Dysplasia

- Complete excision is important in order to allow for full evaluation and minimize any potential for local recurrence or progression
- Consider surveillance especially if the patient has other clinically atypical nevi and/or a family or personal history of melanoma

David E Elder, MB ChB, FRCPA Hospital of the University of Pennsylvania:

Dermpedia-Orlando 2019

Superficial Spreading MIS

Continuous proliferation of uniformly moderately atypical melanocytes in area of =/> 0.5mm^2

Upward spread of atypical melanocytes involving the superficial spinous and granular layers in an area =/> 0.5mm^2

Large irregular junctional nests of different size, with focal confluence and variable nuclear atypia + lesion asymmetry; so called nested melanoma.

Anything in between is regarded as SAMPUS/Evolving or early melanoma

Genomic Tests for Dysplastic Nevus Diagnosis

Testing not currently directed at identifying "significant" atypia

- Testing for more than one genomic abnormality could identify lesions at truly increased risk of progression (Shain et al)

Tests for melanoma versus nevus:

- Comparative genomic hybridization – sensitivity and specificity not defined; interpretation tends to be subjective, not widely available, expensive
- Fluorescence in situ hybridization (FISH) – Se/Sp 94/98%
- Gene expression profiling - Se/Sp 93/95%
- Both have been evaluated against expert opinion, no prognostic ability

Should only be used as adjunct tests (in addition to H&E, IHC)

Gerami P, Li G, Pouryazdanparast P, Blondin B, Beilfuss B, Slenk C, et al. A highly specific and discriminatory FISH assay for distinguishing between benign and malignant melanocytic neoplasms. Am J Surg Pathol. 2012;36(6):808-17.

Clarke LE, Flake DD, Busam K, Cockerell C, Helm K, McNiff J, et al. An independent validation of a gene expression signature to differentiate malignant melanoma from benign melanocytic nevi. Cancer. 2017;123(4):617-28.

MELTUMP versus SAMPUS

- **MELTUMP**: melanocytic ***tumour*** of uncertain malignant potential
  - Subgroup: Spitz tumour of uncertain malignant potential

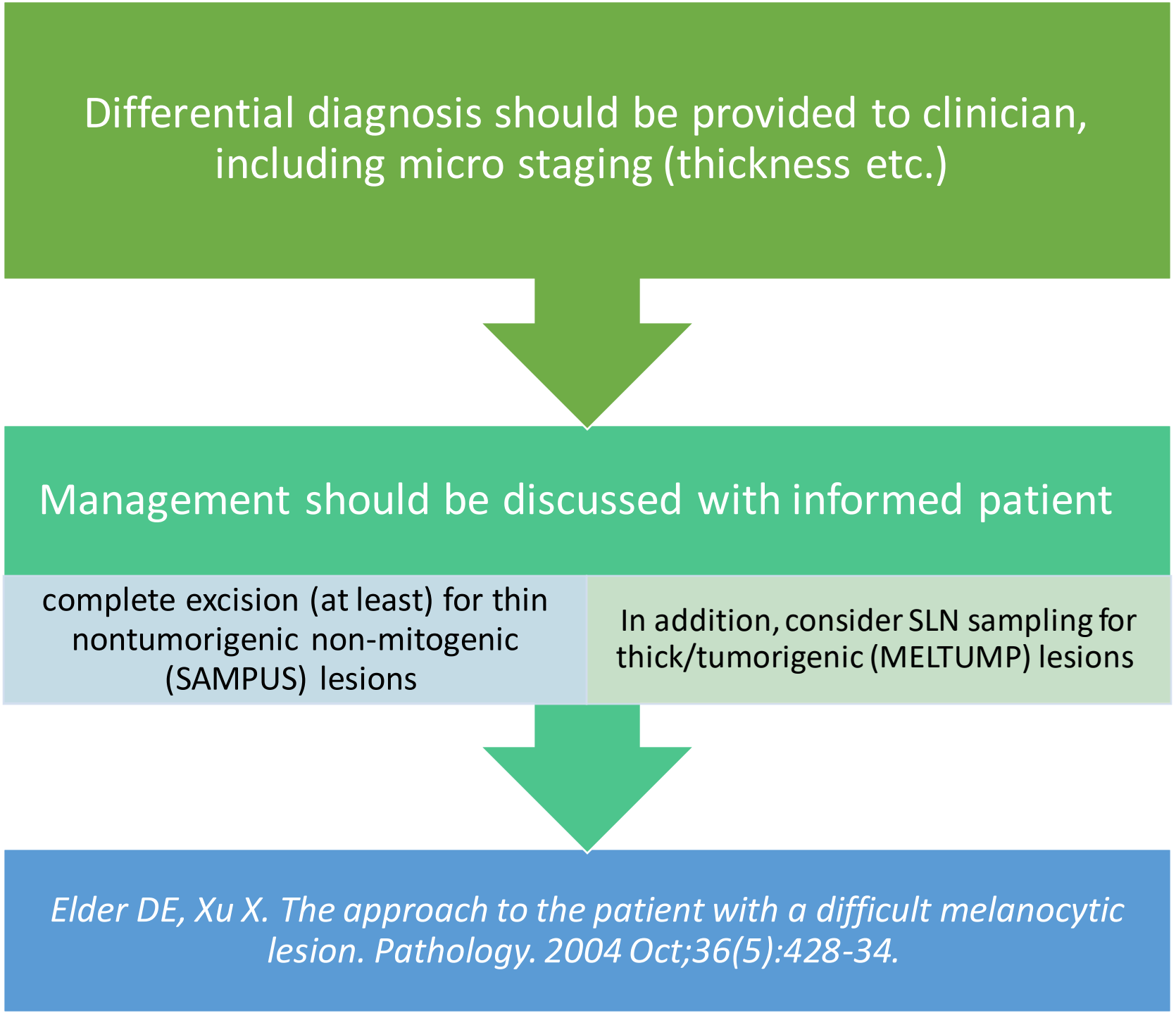
- **SAMPUS**: ***Superficial*** atypical melanocytic proliferation of uncertain significance
  - Proposed minor admendment of criteria: lesion must be < 1 mm in thickness and must lack intradermal mitotic activity, ulceration or obvious regression (the differential diagnosis being: naevus versus T1a melanoma)

David Elder

Uncertainty in Pigmented Lesion Diagnosis

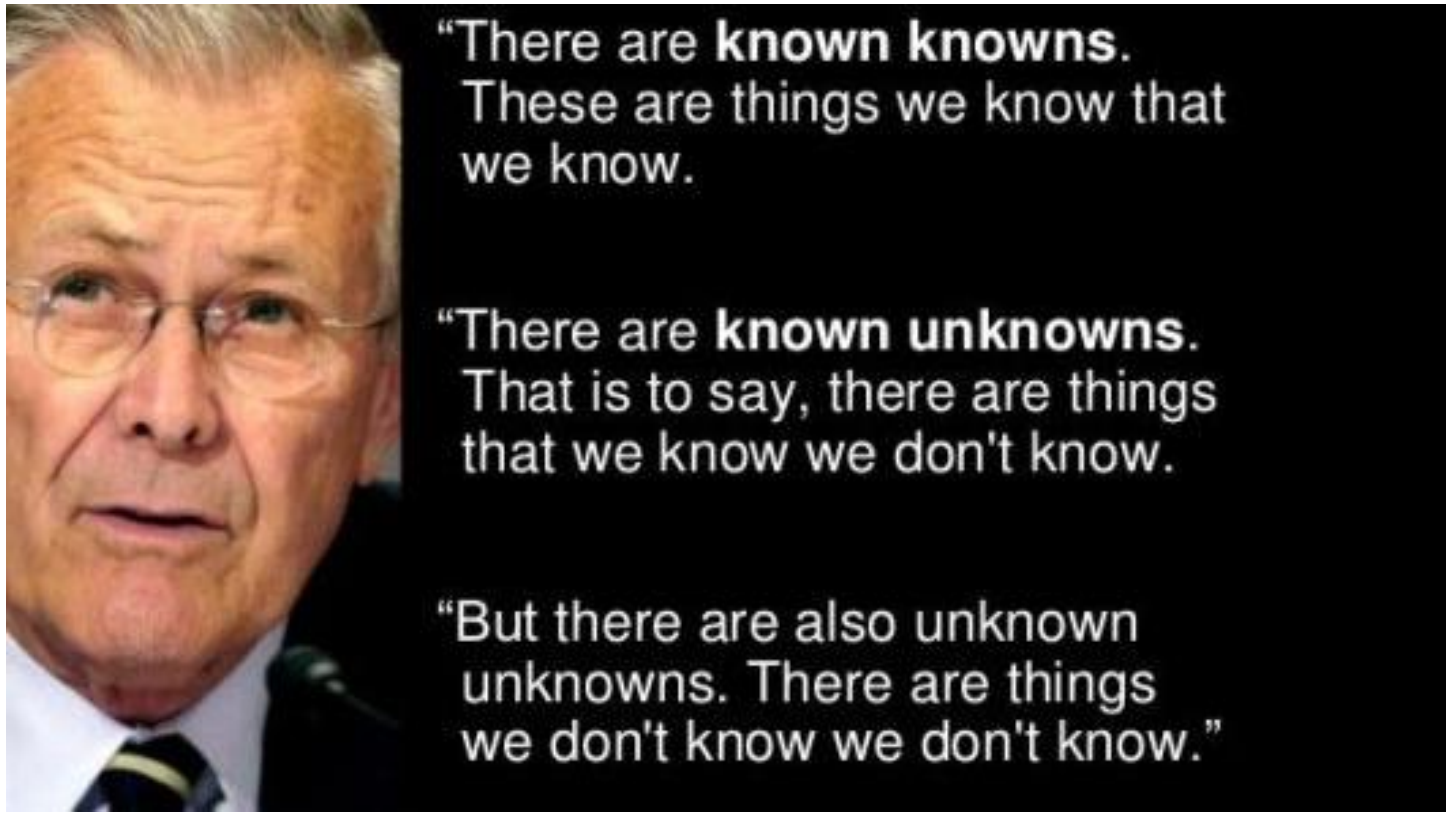
- Uncertainty should be expressed directly with a descriptive diagnosis and a differential diagnosis
- SAMPUS - Superficial atypical melanocytic proliferation of uncertain significance (or STUMP-Spitz Tumour of uncertain significance)
  - Lesions with atypical nontumorigenic components
  - Risk of local persistence/recurrence, not metastasis
- MELTUMP - Melanocytic tumour of uncertain potential
  - Lesions with atypical tumorigenic components
  - Risk of metastasis with or without local recurrence

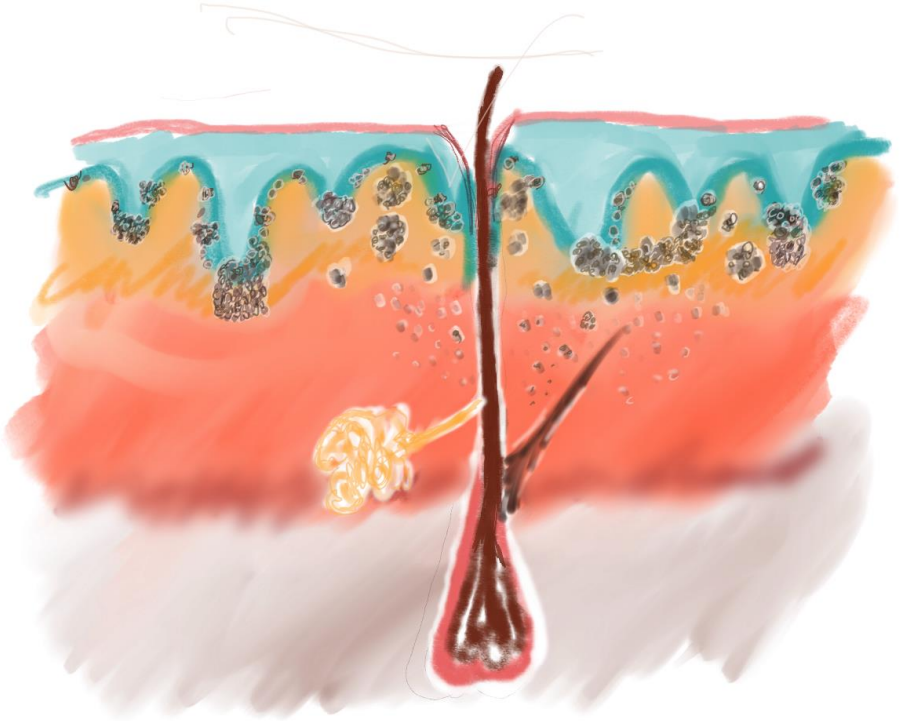
Uncertainty in Pigmented Lesion Diagnosis



Nevi of Special Sites:

- Simulants of melanomas and of dysplastic nevi
- Uncertain whether atypical features are result of neoplastic progression, or reactive (trauma, hormones, etc)
- Not precursors, not risk markers
- The “special sites” include flexures such as axillae and umbilicus, the skin of the breast, genital skin especially in young women, and acral skin.


“There are **known knowns**.
These are things we know that
we know.
“There are **known unknowns**.
That is to say, there are things
that we know we don't know.
“But there are also unknown
unknowns. There are things
we don't know we don't know.”



Dysplastic Naevus

- Width >4 mm in fixed sections (>5mm clinically)
- Presence of Architectural disorder, which requires both the following:
  - Irregular (horizontally oriented, bridging adjacent rete, and/or varying in size and shape) and/or nests on intraepidermal melanocytes
  - Increased density of non-nested junctional melanocytes (e.g. more melanocytes than keratinocytes in an area >/= $1mm^2$)
- Presence of cytological atypia, which is graded on the basis of the highest degree of cytological atypia present in more than a few melanocytes

Architectural features to upgrade