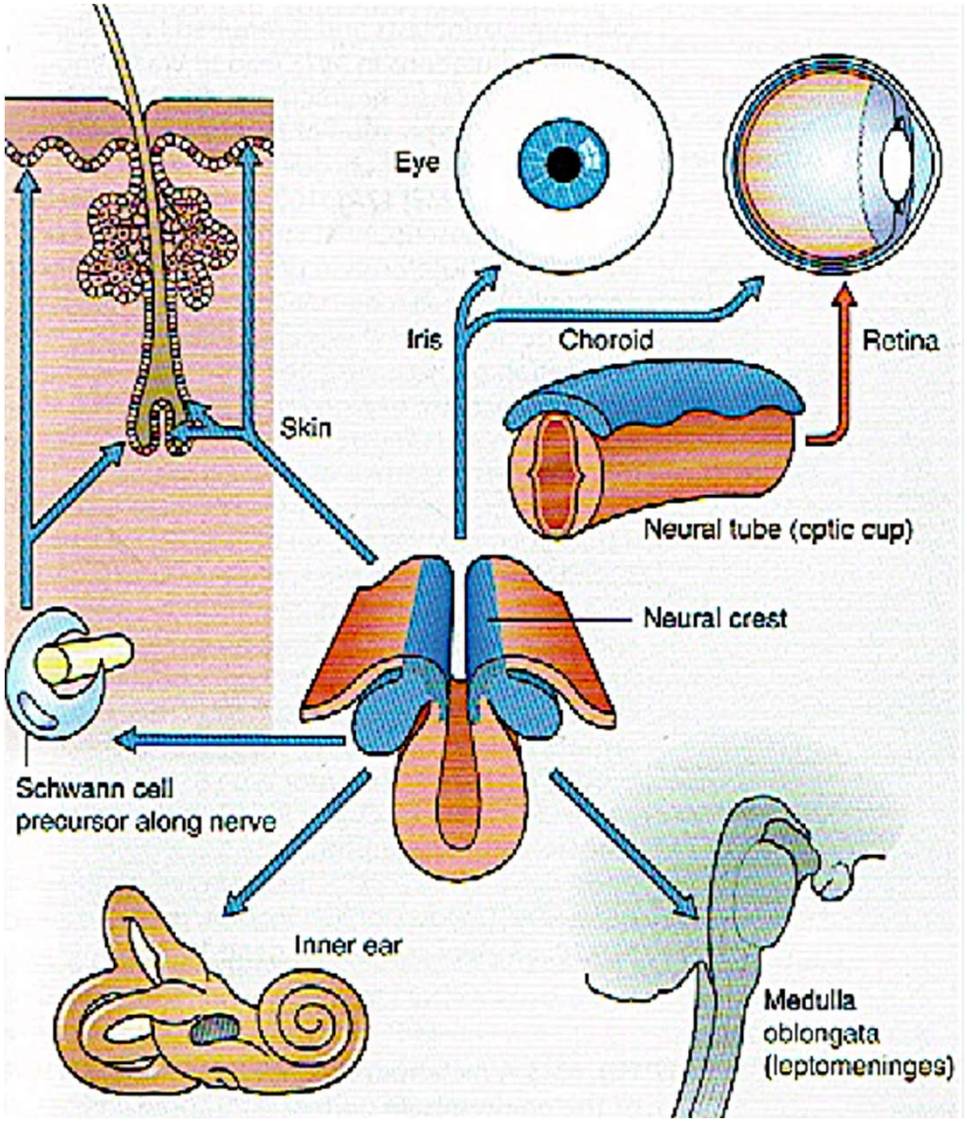
Pathology of

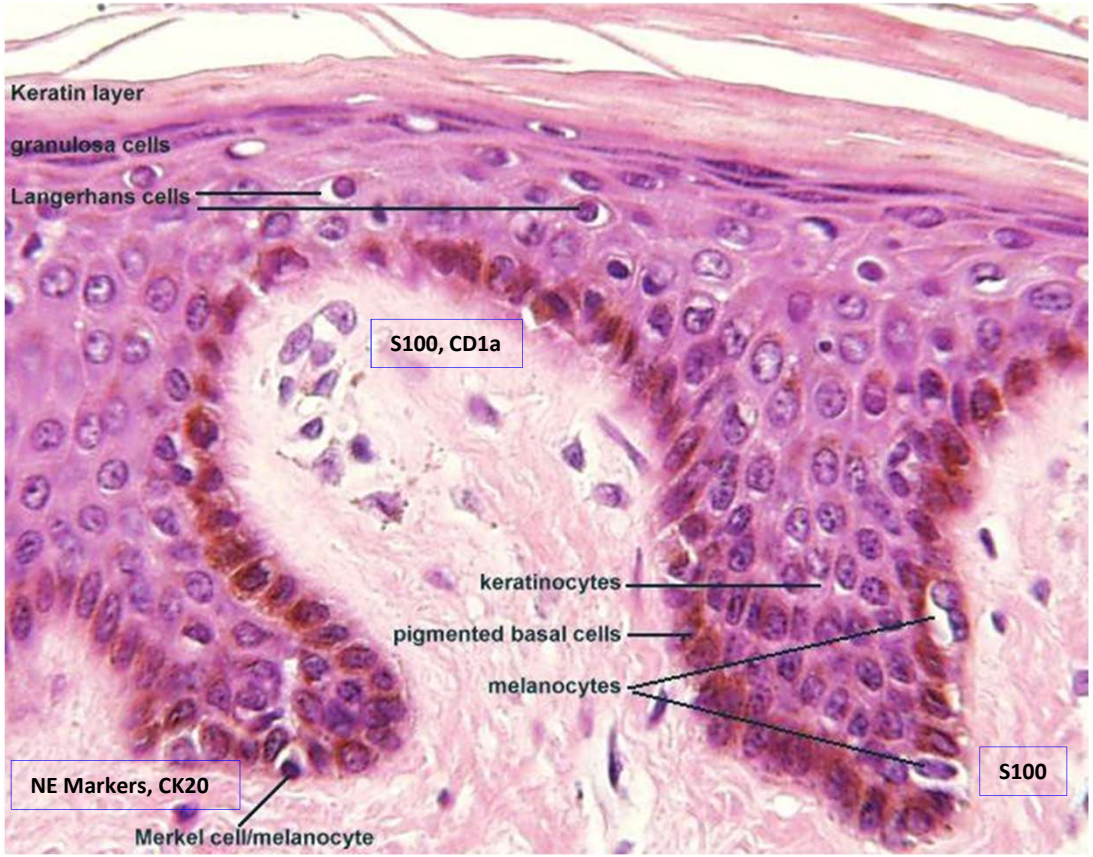
Pigmented skin lesions

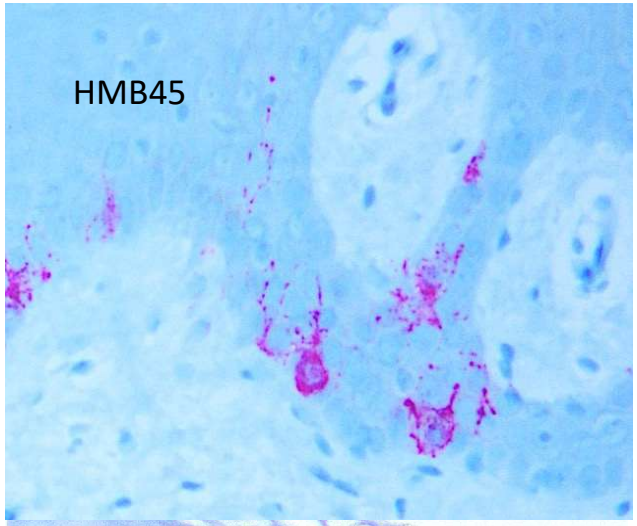
Areas of diagnostic variability and practical considerations

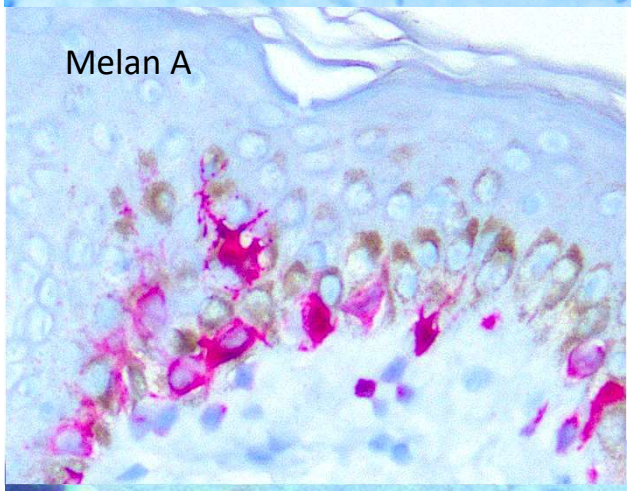
Francesco Feoli MD

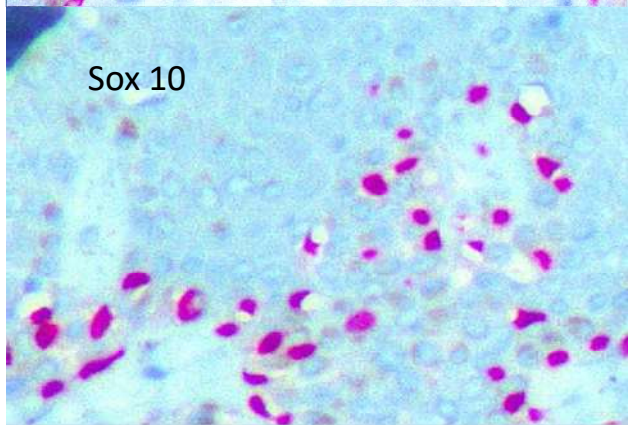


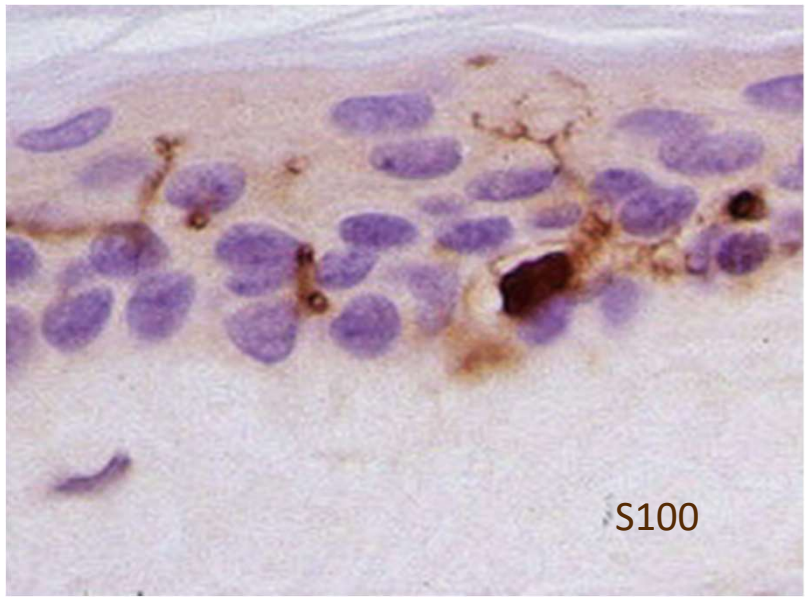
Bolognia JL, Schaffer JV and Cerroni L
Dermatology 2018


Keratin layer
granulosa cells
Langerhans cells
S100, CD1a
keratinocytes
pigmented basal cells
melanocytes
S100
NE Markers, CK20
Merkel cell/melanocyte





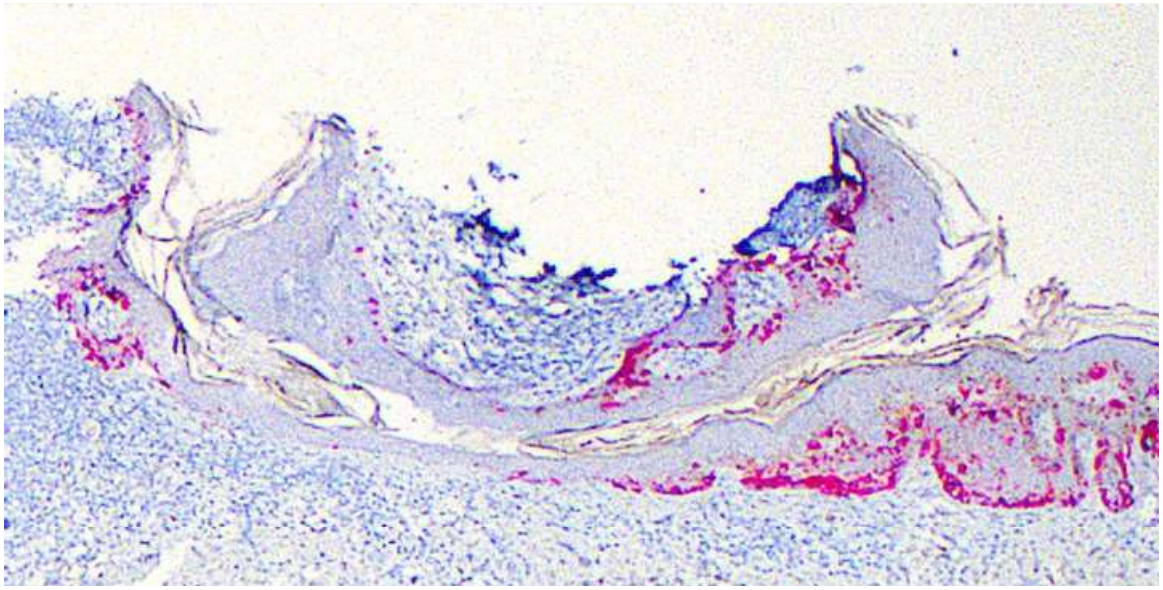




Melanocytic Antibodies

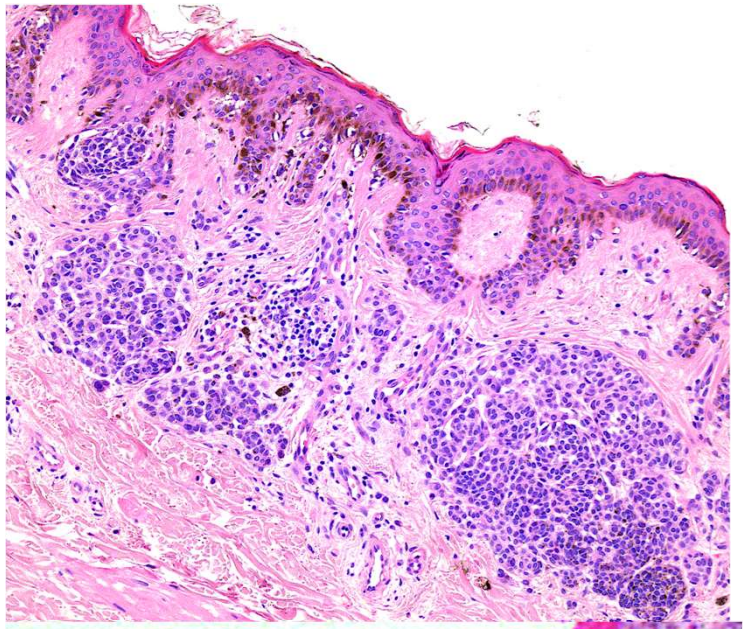
S100
Melan A
HMB45
Sox10

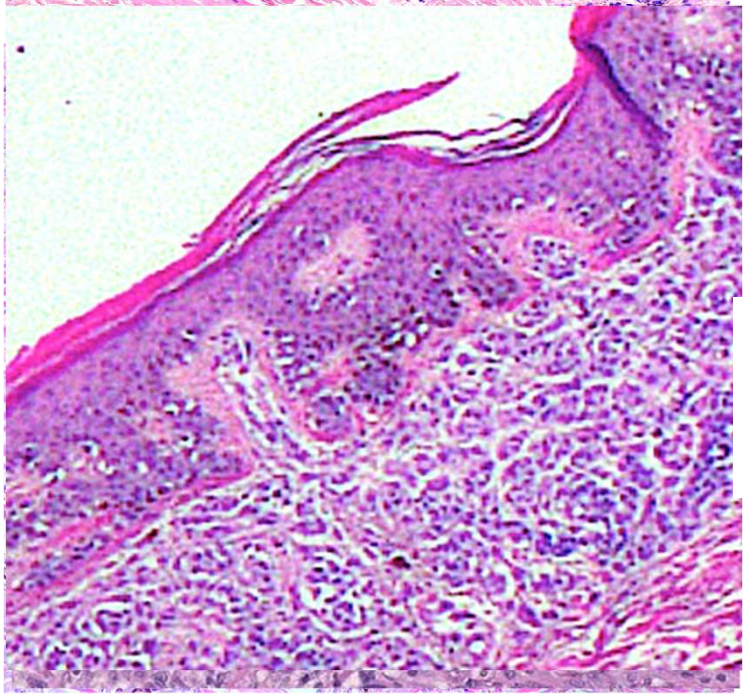
MiTF
PNL2



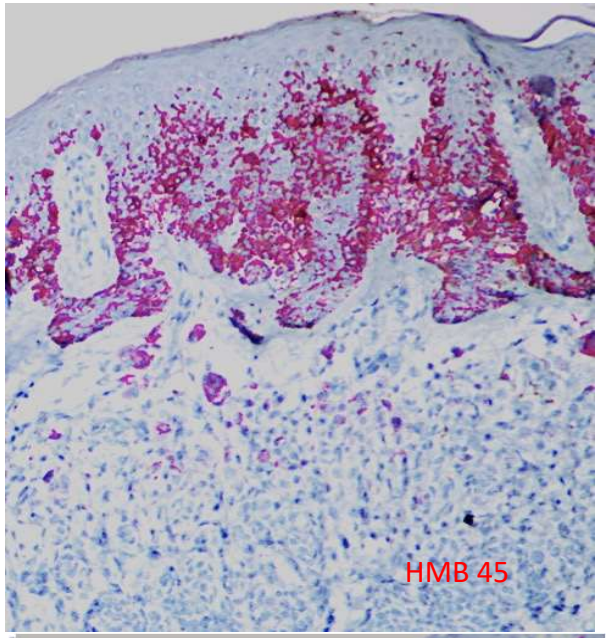
Symmetry, delimitation, regression, lentiginous pattern,
intraepidermal ascent of cells, invasion, margins.

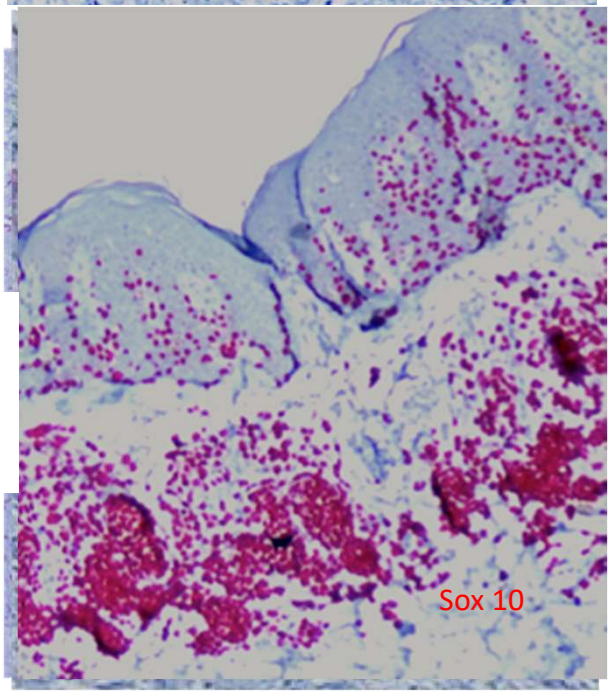
Pitfalls in immunohistochemistry



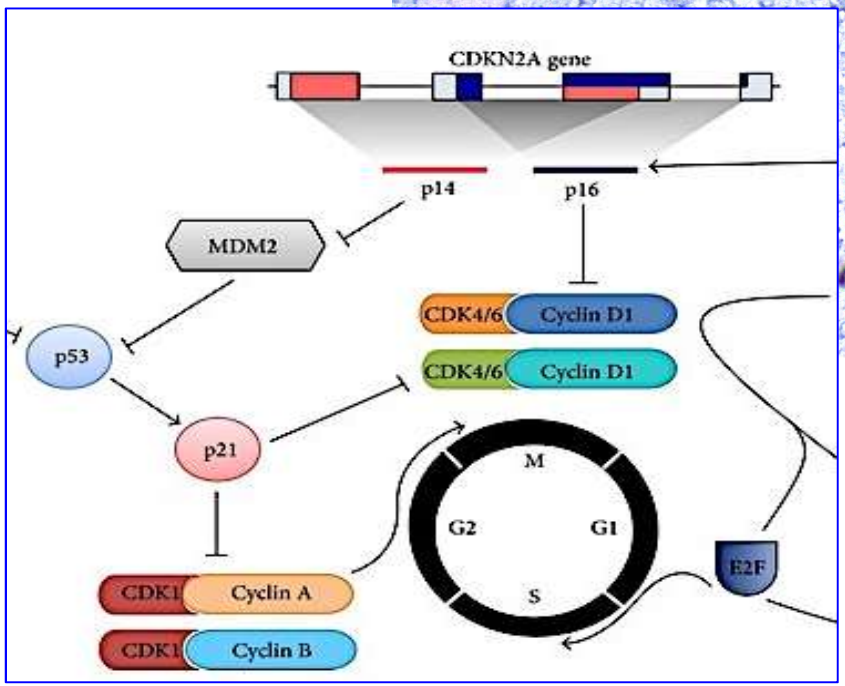


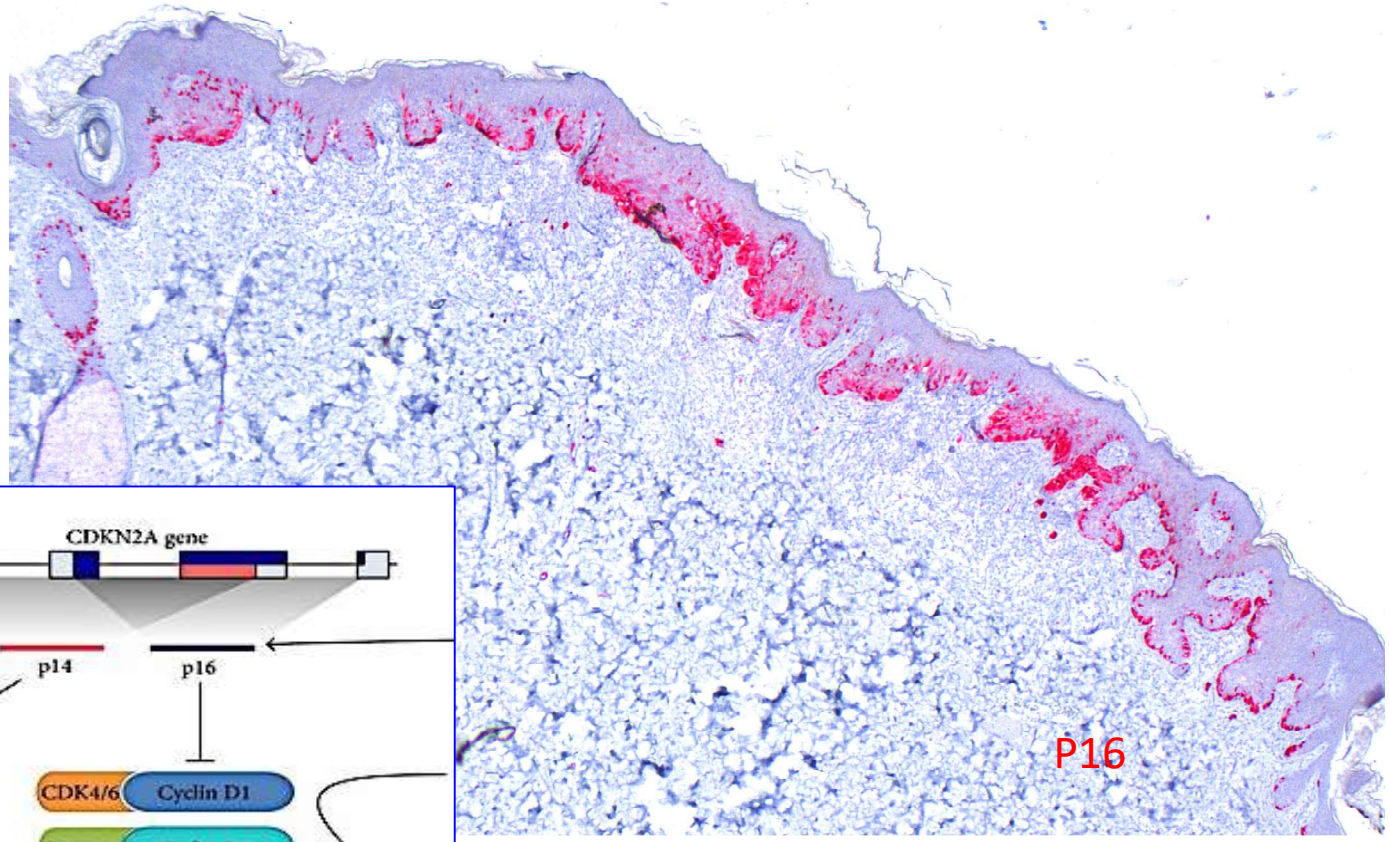
Sox 10
Jonctional
Intraepidermal
Components





P16 Protein


CDKN2A gene
p14
p16
MDM2
p53
p21
CDK4/6
Cyclin D1
CDK4/6
Cyclin D1
M
G2
G1
S
E2F
CDK1
Cyclin A
CDK1
Cyclin B

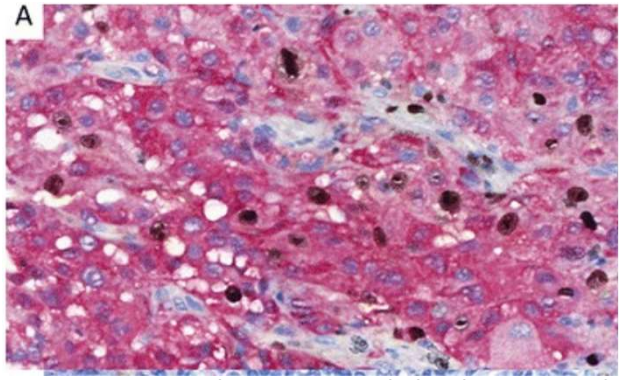

P16

Immunohistochemistry of Melanocytic Proliferations

Victor G. Prieto, MD, PhD. Christopher R. Shea, MD

Arch Pathol Lab Med. 2011;135:853–859

« there is no single marker, or combination, that establishes an unequivocal diagnosis of melanoma or nevus. »



P16 positive melanoma with high Ki67 index

A p16-Ki-67-HMB45 immunohistochemistry scoring system

as an ancillary diagnostic tool in the diagnosis of melanoma

Uguen A et al: Diagn Pathol. 2015; 10: 195.

Belgian Cancer Registry 2016

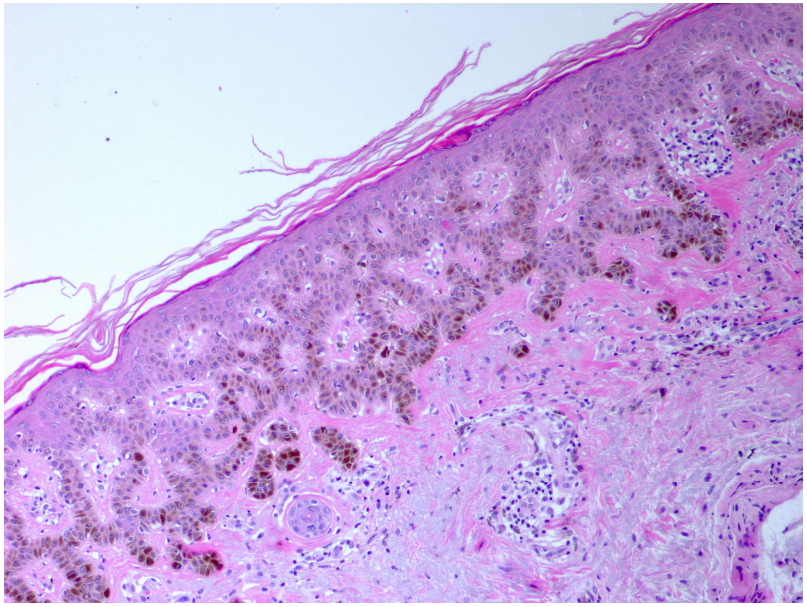
Table 3: Malignant Melanoma: Distribution of combined stage by sex, Belgium 2016

	Stage I	Stage II	Stage III	Stage IV	Stage X	Stage NA	Total
Males							
N	868	210	82	36	42	45	1,283
%	67.7	16.4	6.4	2.8	3.3	3.5	100

2006-2015:US Melanoma incidence rose by 1.5% a year.
Mortality rates declined by 1.2% per year.

Cancer Stat Facts: Melanoma of the skin. National Cancer Institute website. 2018.
Stang A et al: The German skin cancer screening programme. Eur J Cancer. 2016;64:83-88.

Solar Lentigo

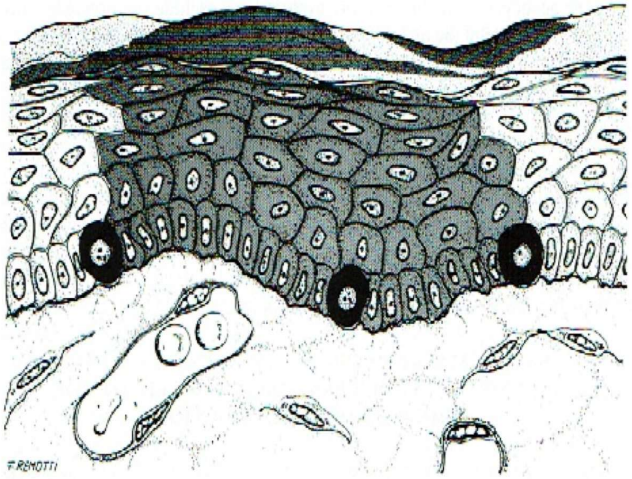


Few mm. to several cm.

Exposure to UV radiation
Face or the back of hands.

Solar Lentigines may evolve to Seborrheic keratoses
or become inflamed
(Lichenoid keratoses)

Ephelide

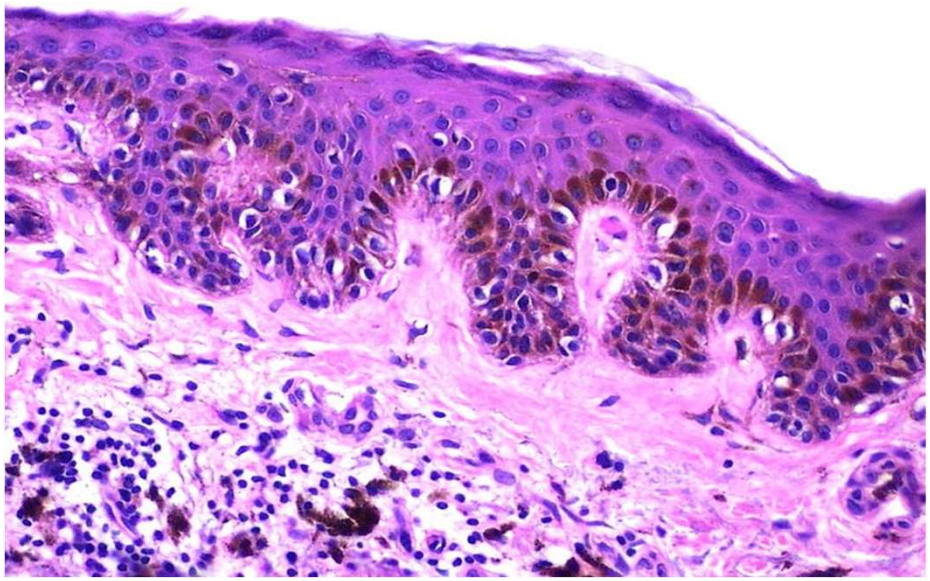


Usually less than 3 mm in diameter

Exposure to UV radiation.
Inherited charcteristic
Common in fair skinned people.
Arises on the mid-face.

No increase in melanocytes.

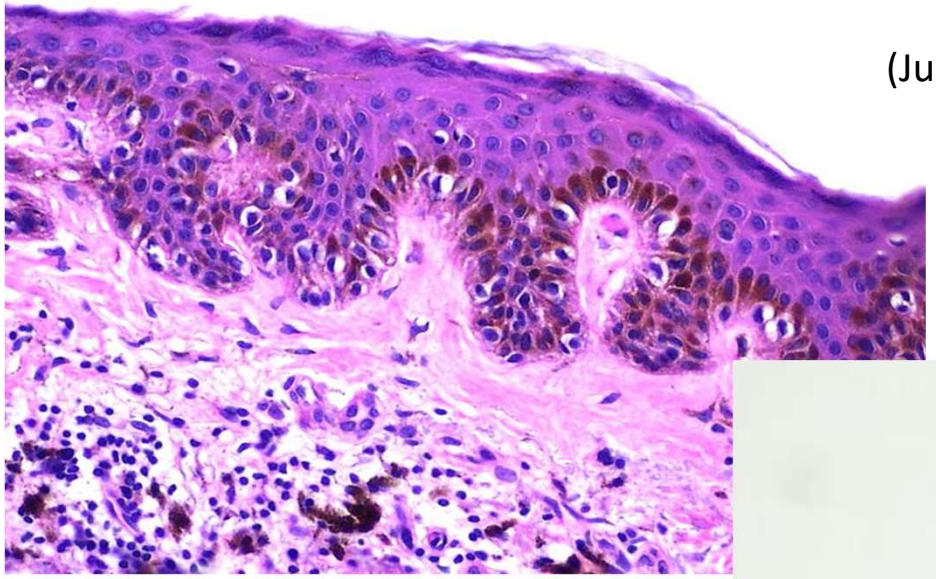
Lentigo simplex

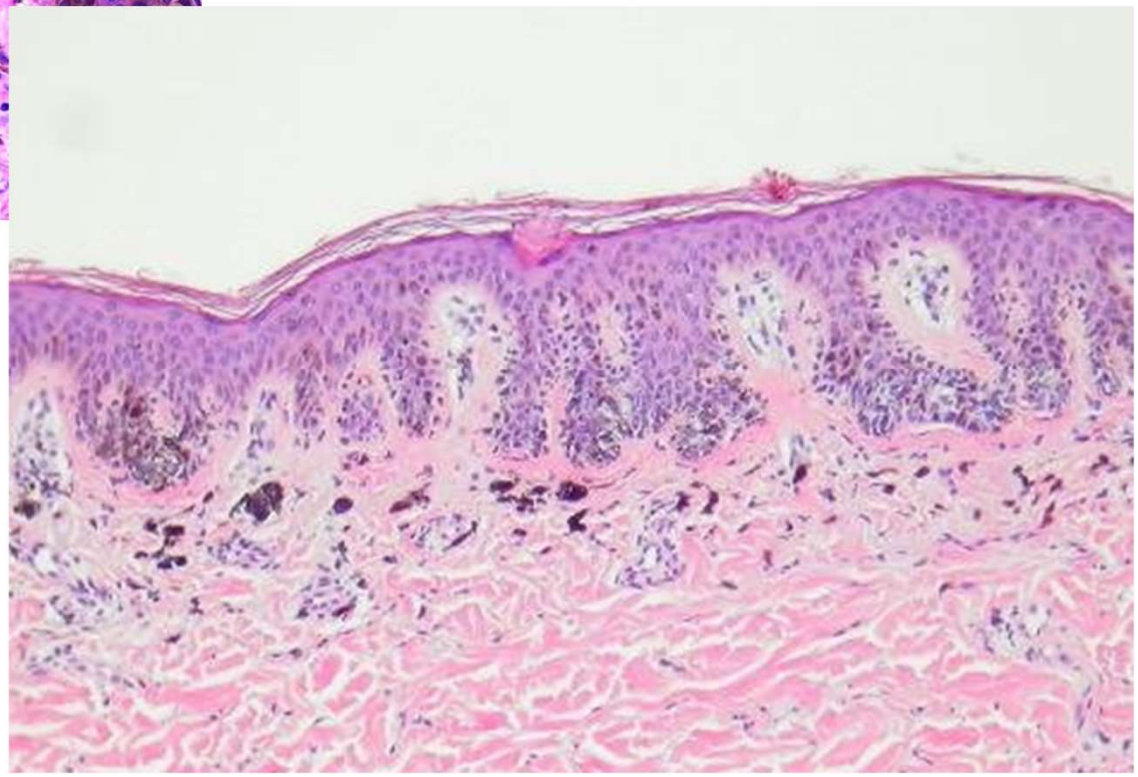


Diameter: 3-15 mm.

Not induced by sun exposure.
Skin or mucousae (anywhere).
More numerous in adult life.

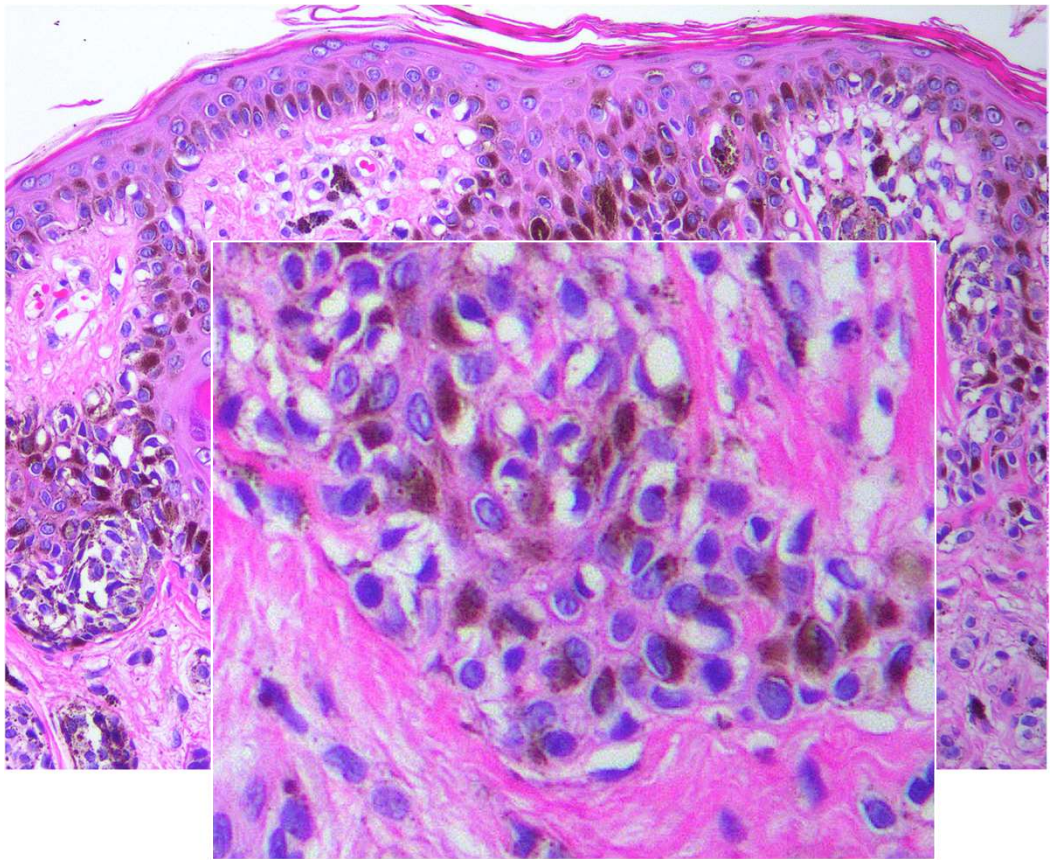
Lentigo simplex can evolve
to Nevi:
(Junctional then compound and finally intradermal) .





Lentiginous jonctional nevus

Nevus with architectural disorder and cellular atypia.



Wide distribution: as nevi (trunk)
Low degree of chronic sun damage

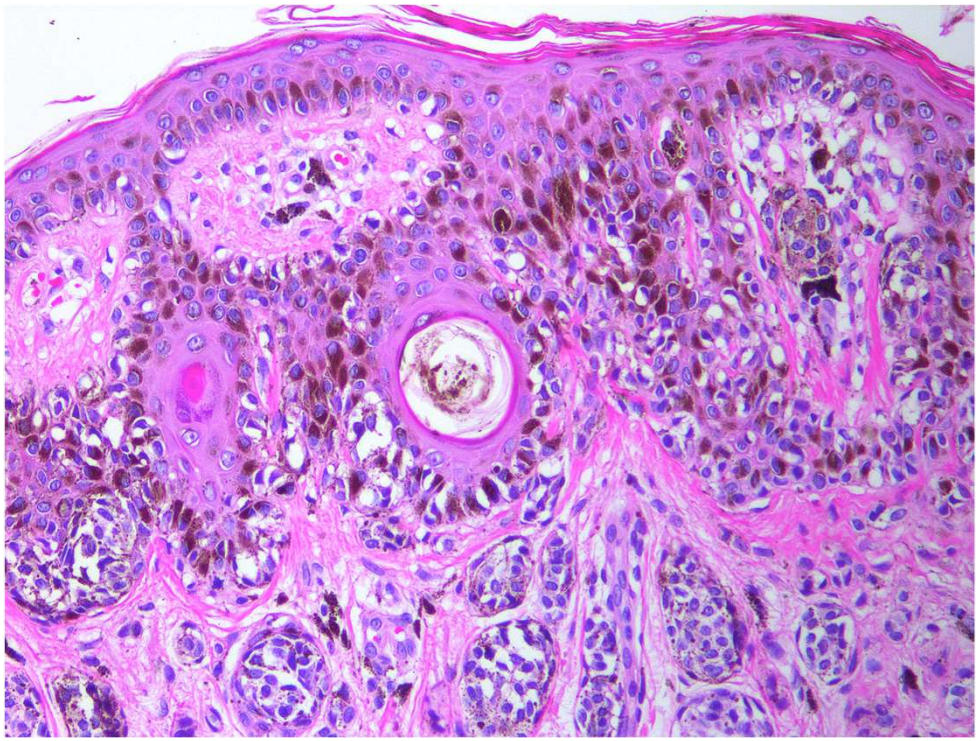
Prominent flat componenent

3/ABCD criteria and erythema
(5 or more mm.)

Tend to be symmetrical (ddx: SSM)

Nevus with architectural disorder and cellular atypia.

WHO 2006: Mild Dysplasia



Risk Factor (familial and sporadic cases)

Potential precursors

Simulators of Melanoma

Grading of Melanocytic Dysplasia
WHO 2018

WHO classification (2018)	Former grade	Nuclear size vs resting basal cells	Chromatism	Variation in nuclear size and shape	Nucleoli
Not a dysplastic naevus	0 (mild dysplasia)	1×	May be hyperchromatic	Minimal	Small or absent
Low-grade dysplasia	1 (moderate dysplasia[a])	1–1.5×	Hyperchromatic, or coarsened chromatin	Prominent in a small minority of cells (random atypia)	Small or absent
High-grade dysplasia	2 (severe dysplasia[a])	≥ 1.5×	Hyperchromatic, coarse granular chromatin, or peripheral condensation	Prominent in a larger minority of cells	Prominent, often lavender

[a] Architectural features are required for the diagnosis of dysplasia (see Table 2.07) and also contribute to grade; attributes that indicate a diagnosis of high-grade (severe) dysplasia even when cytological atypia is low-grade include pagetoid scatter above the basal layer (but to a lesser degree than in melanoma), involving the middle third, and focal, i.e. contained within an area <0.5 mm²), focal continuous basal proliferation, and intraepidermal mitoses (any rare mitosis should raise concern for melanoma).

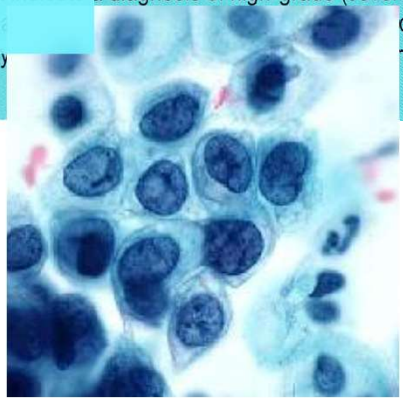
High Grade dysplasia with LG nuclei: Architecture

Pagetoid scatter

usually focal (0,5mm$^{2)}$ and not above the middle third,

Focal continuous basal proliferation,

Intraepidermal mitoses



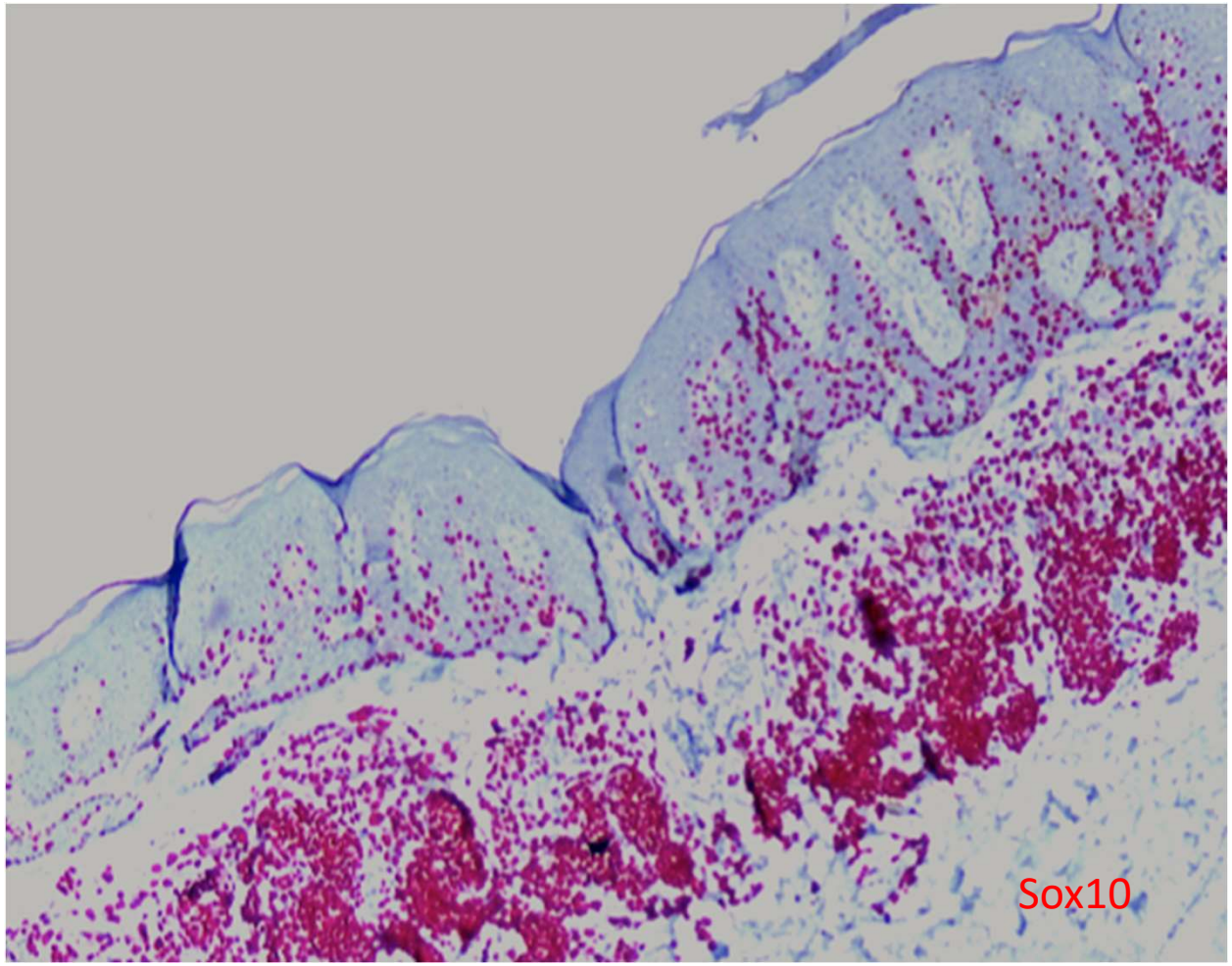
CASE 1

Duke Criteria (Shea CR et al 1999)

Symmetry.
Delimitation.
Bridging: 50%.
Nested vs. single cells.

Fibroplasia, concentric, lamellar.
Lymphocytic infiltrate.
Vascularity: marked.
Cohesiveness in nests: 50%.
Pagetoid: prominent, at the edge.

Nuclear shape & chromasia.
Nuclear size: 50%.
Cellular size: 50%.
Nucleolar size: 50%.



Compound Nevus. Low grade dysplasia.(WHO 2018)

CASE 2

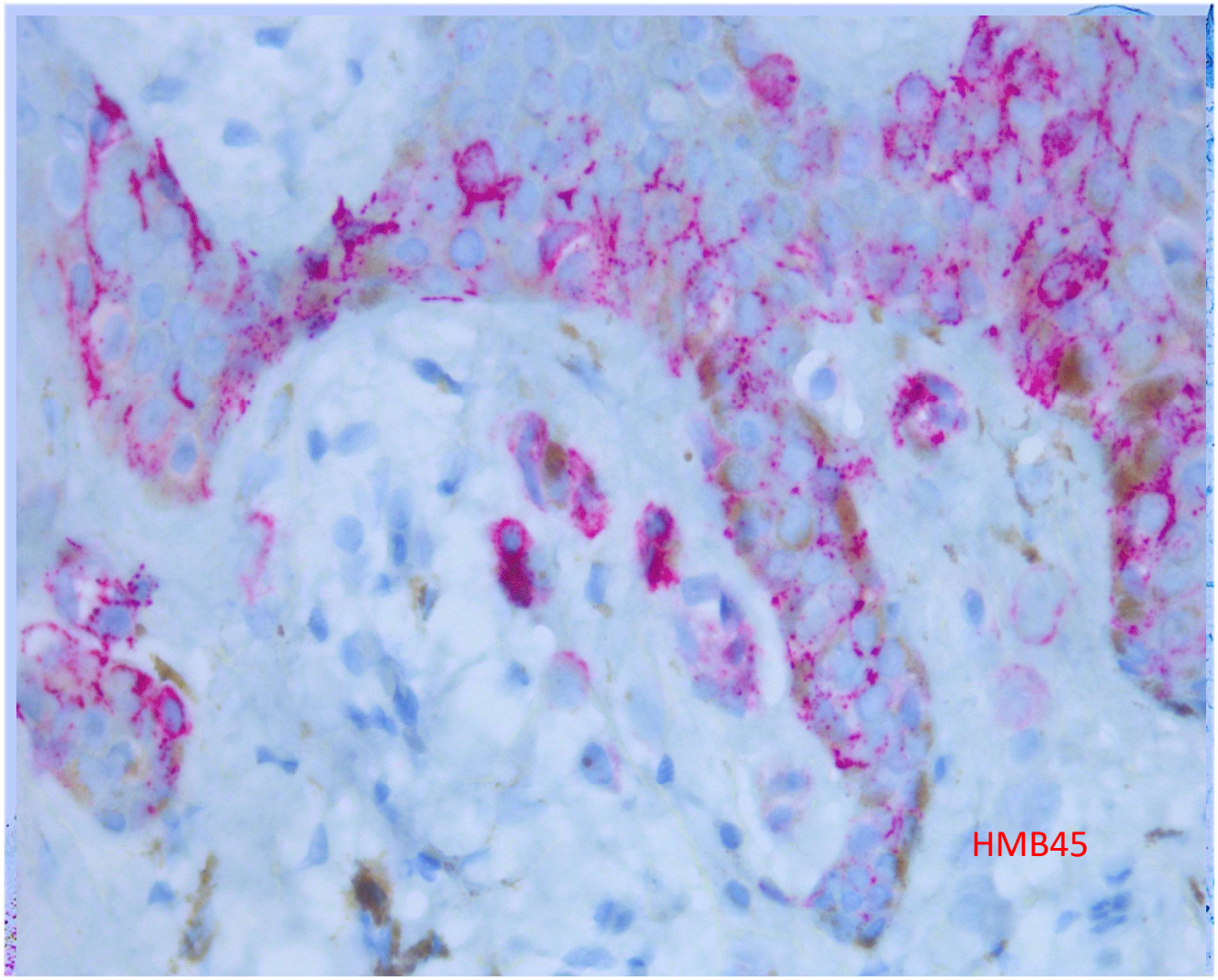
Duke Criteria (Shea CR et al 1999)

Delimitation.

Symmetry.
Fibroplasia, concentric, lamellar.
Lymphocytic infiltrate.
Vascularity: marked.

Nested vs. single cells.
Pagetoid: prominent (shoulder).

Nuclear shape & chromasia.
Nuclear size: 50%.
Cellular size: 50%.
Nucleolar size: 50%.



"SAMPU? or Melanocytic neoplasm of low malignant potential"? (WHO 2018)

CASE 3

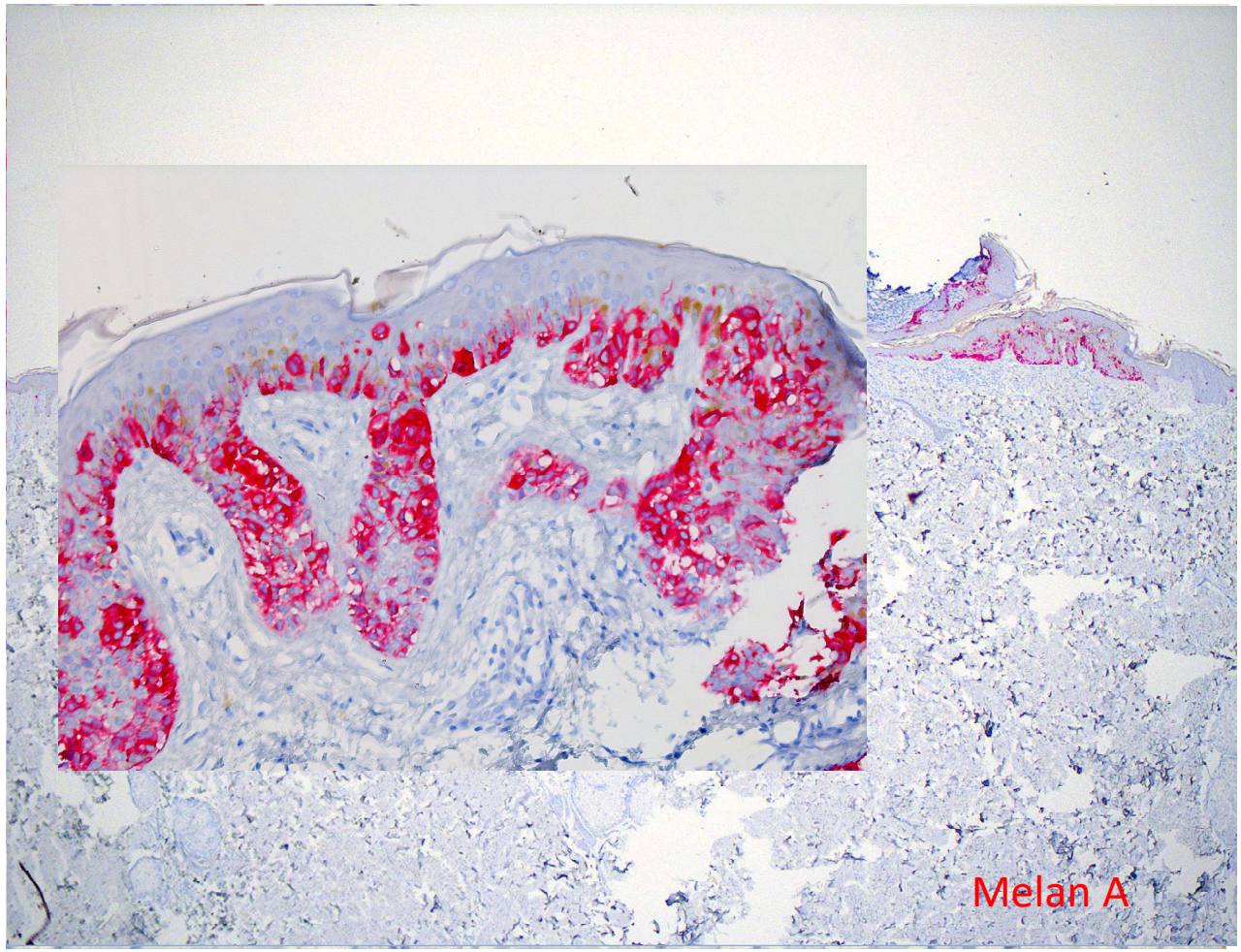
Duke Criteria (Shea CR et al 1999)

Symmetry.
Delimitation.
Lymphocytic infiltrate.

Bridging: 50%.
Nested vs. single cells.
Cohesiveness in nests: 50%.
Vascularity: marked.
Fibroplasia, concentric, lamellar.

Pagetoid: prominent, at the edge.

Nuclear shape & chromasia.
Nuclear size: 50%.
Cellular size: 50%.
Nucleolar size: 50%.



Superficial Spreading Melanoma & Remnants of DN

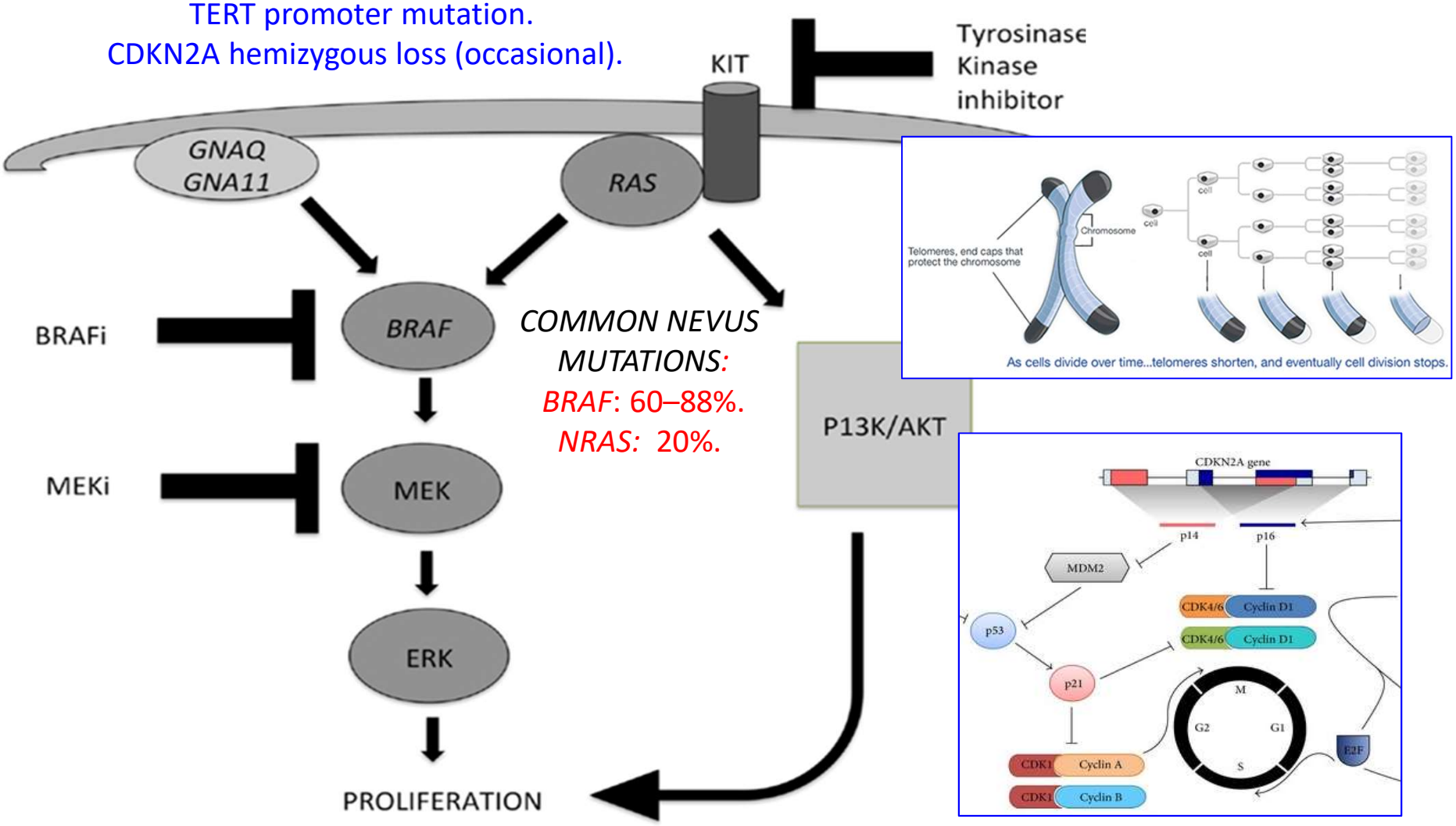
ATYPICAL (DYSPLASTIC) NEVUS:

BRAF or NRAS activating mutations.

>1 genomic abnormality.

TERT promoter mutation.

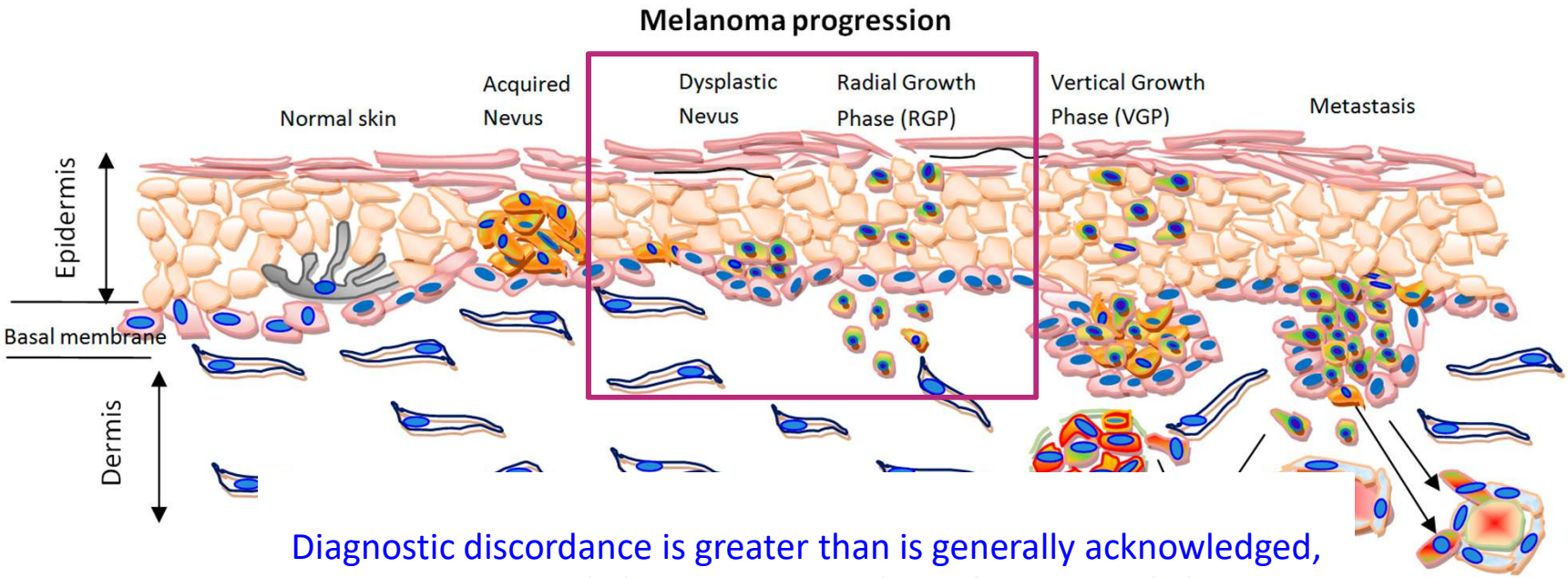
CDKN2A hemizygous loss (occasional).



COMMON NEVUS MUTATIONS:

BRAF: 60–88%.

NRAS: 20%.



Diagnostic discordance is greater than is generally acknowledged,
even among pathologists experienced in melanocytic pathology.

Piepkorn MW et al J Am Acad Dermatol.2014; 70(1): 131-141.