Samir Al Hyassat
HMC , Qatar

Dr. Samir Al-Hyassat is a highly regarded senior consultant pathologist with a wealth of experience and expertise in the field. He earned his MBBS degree from The University of Jordan in 1999 and subsequently pursued advanced training and qualifications in the United Kingdom. He obtained the prestigious FRCPath (Fellow of the Royal College of Pathologists) in 2010, as well as the CCT-UK (Certificate of Completion of Training) in the same year.

Dr. Al-Hyassat's passion lies in various subspecialties, including dermatopathology, urological pathology, and gynaecological pathology. His extensive knowledge and keen eye for detail allow him to provide accurate diagnoses and contribute to effective treatment strategies for patients with complex conditions in these areas.

Notably, Dr. Al-Hyassat has embraced the advancements in digital pathology and artificial intelligence, recognizing their potential to revolutionize clinical diagnostic pathology. He has gained significant experience in utilizing digital pathology tools and AI applications in his daily practice, particularly in the analysis of prostate biopsies. Actively engaged in international multicentric AI research projects, he is at the forefront of cutting-edge developments in the field, seeking to enhance diagnostic accuracy and patient outcomes.

Dr. Al-Hyassat's contributions extend beyond his clinical work. He is committed to sharing his expertise through research, academic pursuits, and collaborations with colleagues worldwide. His dedication to advancing the field of pathology and improving patient care is evident in his active involvement in scientific conferences and publications.

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In partnership with

Melanocytic Tumours with molecular perspective

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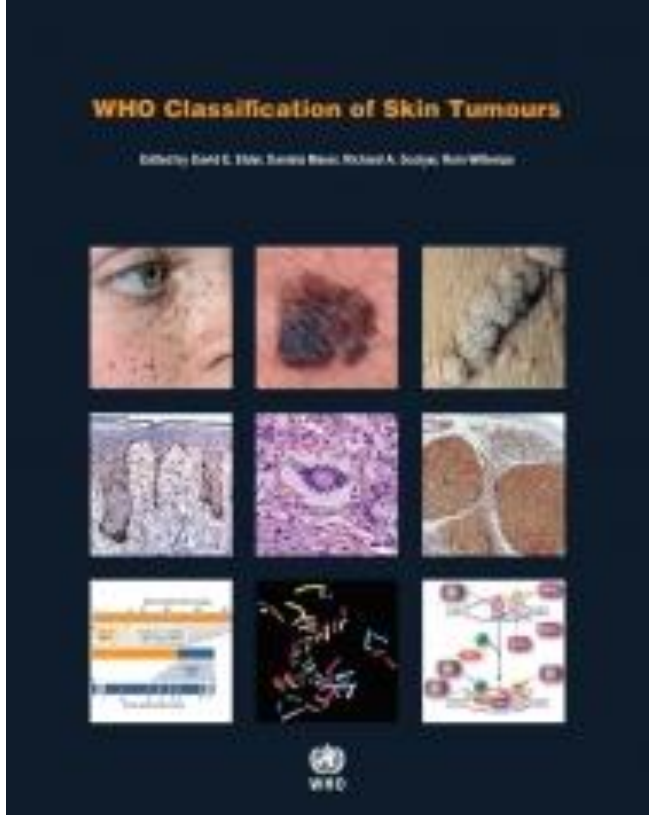
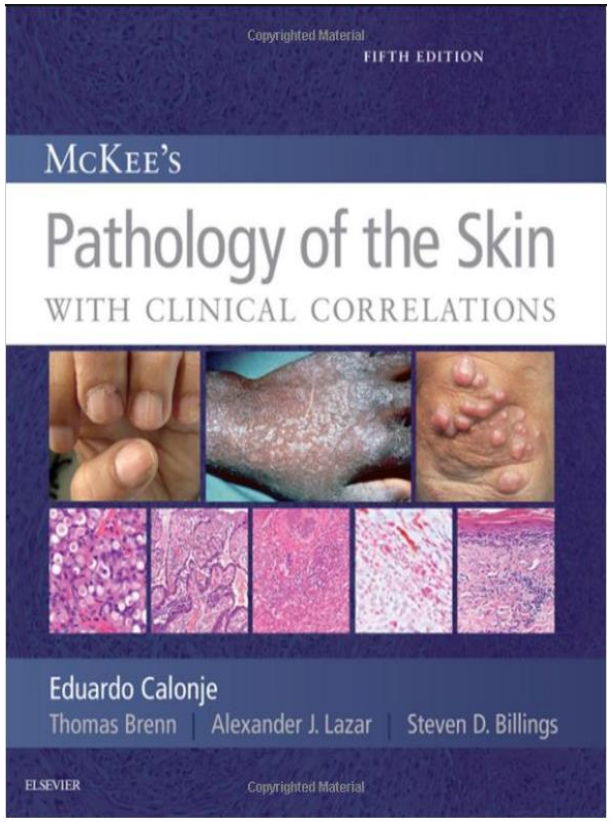
Senior consultant histopathologist
MBBS, FRCPath, CCT
HMC-Qatar

Declaration of Conflict of Interest

- I have no conflict of interest in relation to this presentation

References





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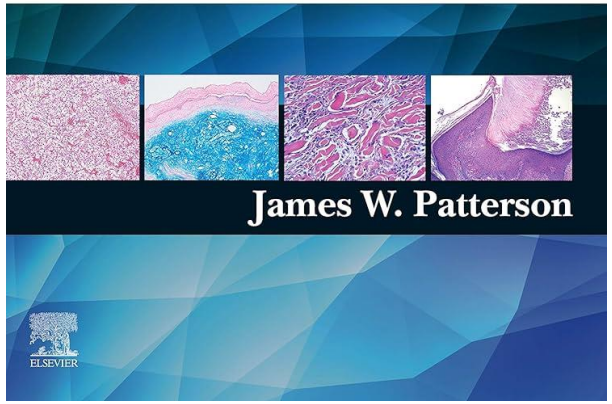
SKIN PATHOLOGY



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https://doi.org/10.1007/s00428-020-03005-1

ORIGINAL ARTICLE

Check for updates

ESP, EORTC, and EURACAN Expert Opinion: practical recommendations for the pathological diagnosis and clinical management of intermediate melanocytic tumors and rare related melanoma variants

Arnaud de la Fouchardiere[1] · Willeke Blokx[2] · Léon C. van Kempen[3] · Boštjan Luzar[4] · Sophie Piperno-Neumann[5,6] · Susana Puig[7,8,9] · Llucia Alos[8,10] · Eduardo Calonje[11] · Daniela Massi[12] · on behalf of the ESP Dermatopathology Working Group · EORTC Melanoma Group · EURACAN

Received: 25 May 2020 / Revised: 17 November 2020 / Accepted: 21 December 2020

Questions

- A: Why and when to do BRAF testing in melanomas
- B: Do you know which subgroups of tumors are related to ALK fusions or GNAQ mutations
- C: When to use Beta catenin, BAP1 and PRKAR1A immunohistochemistry

Teaching points

- Melanocytic proliferations represent different diseases (WHO 2018 & WHO 2022)
- Nevi progress to melanoma with intermediate clonal stages.
- When and what tools to perform in borderline melanocytic neoplasms.
- Suggest a practical approach to the management of atypical melanocytic lesions including Spitzoid melanocytic lesions and dysplastic nevi.

History

- Three major categories of melanoma were initially recognized, based on the presence or absence of the RGP and its variants: nodular melanoma is defined as a VGP melanoma without an identifiable RGP the initially recognized RGP variants were superficial spreading melanoma (also called pagetoid melanoma) and lentigo maligna melanoma.

History

- The distinctions between these categories were later supplemented by epidemiological and genomic observations, leading to the concept of alternative pathways in the development of melanoma.
- Of the two major pathways, which account for the majority of melanomas in populations with skin that is susceptible to solar damage:
  1. One (leading to superficial spreading melanoma and a subset of nodular melanoma) is associated with a low degree of cumulative sun damage (CSD) as assessed by the degree of solar elastosis on biopsy
  2. The other pathway (leading to lentigo maligna melanoma and another subset of nodular melanoma) is associated with a high degree of CSD.
  3. Other melanomas (e.g. melanoma in acral skin or mucosa) arise via pathways in which solar damage does not appear to play any role.

Genomic pathogenesis

- Crucial observations related to genomic pathogenesis followed the seminal discovery of *BRAF* as a commonly mutated oncogene in melanoma.
- *BRAF* p.V600 mutations (in particular p.V600E mutations) are the most frequently found oncogenic alterations in melanomas in skin with a low degree of CSD (low-CSD melanomas).
- Whereas *NF1*, *NRAS*, other *BRAF* (non-p.V600E), and perhaps *KIT* mutations (all mutually exclusive…. Do not happen simultaneously) predominate in melanomas in skin with a high degree of CSD (high- CSD melanomas).

- Tumour suppressor genes such as *CDKN2A* (encoding p16) are also implicated in melanoma pathogenesis.

- Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, Teague J, Woffendin H, Garnett MJ, Bottomley W, Davis N, Dicks E, Ewing R, Floyd Y, Gray K, Hall S, Hawes R, Hughes J, Kosmidou V, Menzies A, Mould C, Parker A, Stevens C, Watt S, Hooper S, Wilson R, Jayatilake H, Gusterson BA, Cooper C, Shipley J, Hargrave D, Pritchard-Jones K, Maitland N, Chenevix-Trench G, Riggins GJ, Bigner DD, Palmieri G, Cossu A, Flanagan A, Nicholson A, Ho JW, Leung SY, Yuen ST, Weber BL, Seigler HF, Darrow TL, Paterson H, Marais R, Marshall CJ, Wooster R, Stratton MR, Futreal PA. Mutations of the BRAF gene in human cancer. Nature. 2002 Jun 27;417(6892):949-54. doi: 10.1038/nature00766. Epub 2002 Jun 9. PMID: 12068308.

- Bastian BC. The molecular pathology of melanoma: an integrated taxonomy of melanocytic neoplasia. Annu Rev Pathol. 2014;9:239-71. doi: 10.1146/annurev-pathol-012513-104658. PMID: 24460190; PMCID: PMC4831647.

Genomic pathogenesis

- One group recently linked the concepts of tumour progression and evolutionary pathways by demonstrating that progression from benign lesions to advanced melanomas depends on sequential acquisition of abnormalities involving oncogenes and tumour suppressors, as well as other classes of genes.
- **The study also provided a genomic definition of so-called intermediate lesions (such as dysplastic naevus), which had more than one genomic abnormality.**

- Shain AH, Yeh I, Kovalyshyn I, Sriharan A, Talevich E, Gagnon A, Dummer R, North J, Pincus L, Ruben B, Rickaby W, D'Arrigo C, Robson A, Bastian BC. The Genetic Evolution of Melanoma from Precursor Lesions. N Engl J Med. 2015 Nov 12;373(20):1926-36. doi: 10.1056/NEJMoa1502583. PMID: 26559571.

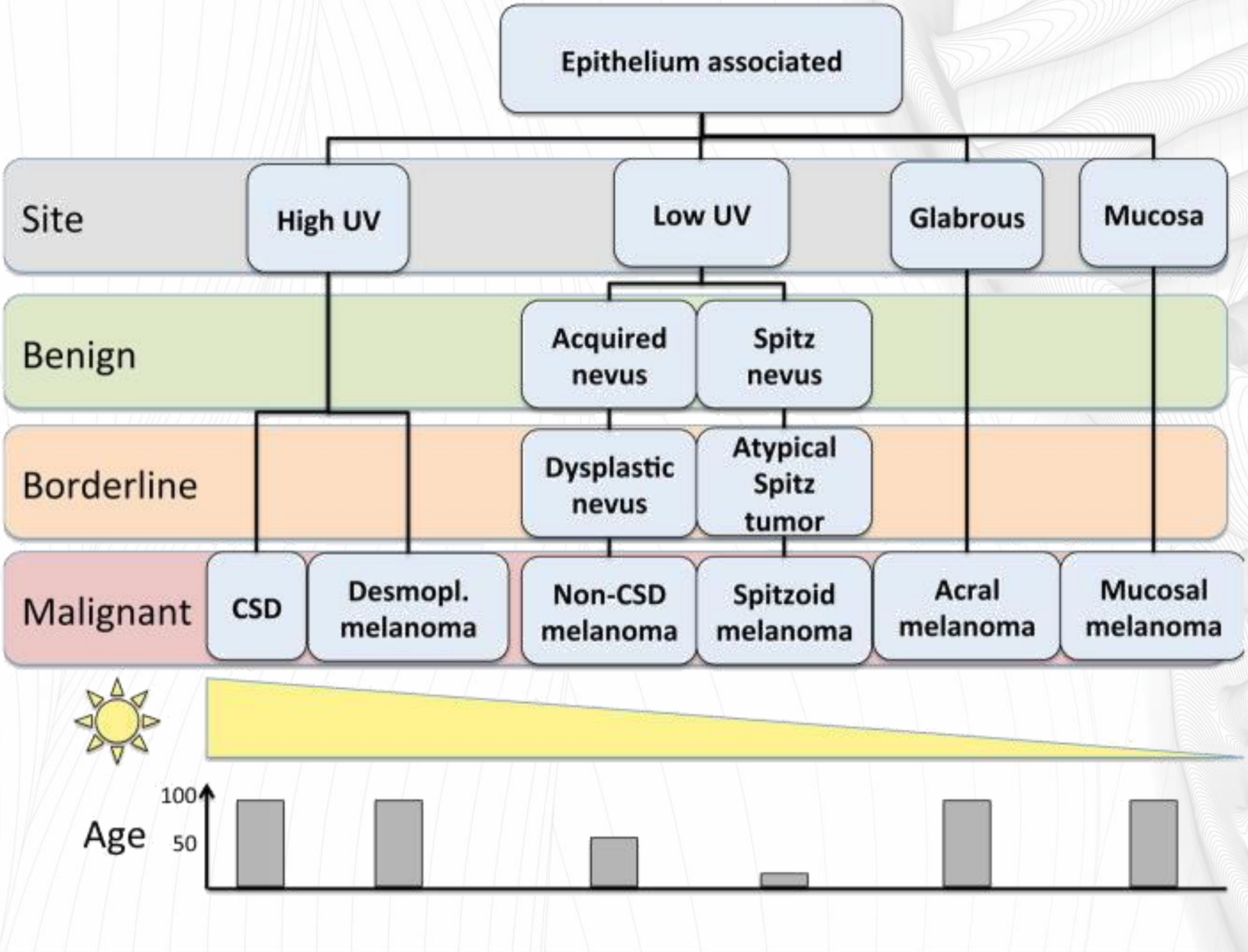
- Dysplastic naevus is characterized by cytological and architectural atypia, and is a potential precursor of melanoma, albeit with a very low individual lesion risk. Other lesions in this category include:
  - Deep penetrating naevus
  - Pigmented epithelioid melanocytoma
  - *BAP1*-inactivated tumours.
- **All of which can present as components of combined naevi and for which the consensus meeting Working Group proposes the general term 'melanocytomas'.**

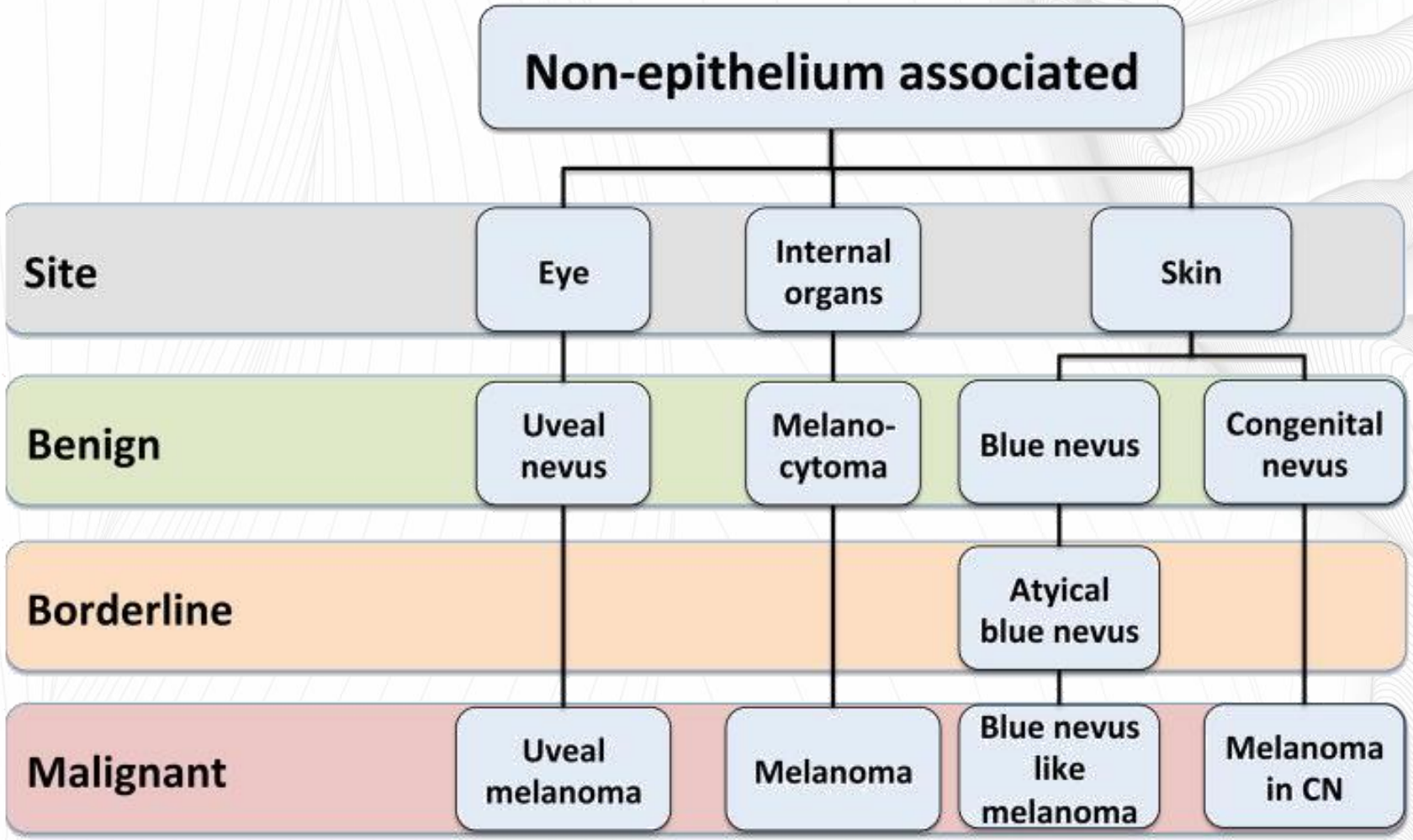
The gold standard for melanoma diagnosis continues to be histopathology, which also remains the primary tool for classification,
in conjunction with clinical characteristics,
despite the advent of large-scale and high-resolution genomics,

Multidimensional pathway classification

- Bastian has proposed a multidimensional classification for melanocytic lesions based on the role of ultraviolet (UV) radiation, the cell (or tissue) of origin, and characteristic recurrent genomic alterations.
- - Bastian BC. The molecular pathology of melanoma: an integrated taxonomy of melanocytic neoplasia. Annu Rev Pathol. 2014;9:239-71. doi: 10.1146/annurev-pathol-012513-104658. PMID: 24460190; PMCID: PMC4831647.

- Most melanomas in Northern Hemisphere populations occur in skin with either a low or high degree of CSD.
- But some types of melanoma occur in skin or mucous membranes either with no CSD or with variable CSD that is not considered to be etiologically relevant (e.g. due to the absence of UV radiation signature mutations), and these tumours account for the majority of melanomas in non-White populations, at a much lower absolute incidence rate.


Epithelium associated
Site
High UV
Low UV
Glabrous
Mucosa
Benign
Acquired nevus
Spitz nevus
Borderline
Dysplastic nevus
Atypical Spitz tumor
Malignant
CSD
Desmopl. melanoma
Non-CSD melanoma
Spitzoid melanoma
Acral melanoma
Mucosal melanoma
Age
100
50


Non-epithelium associated
Site
Eye
Internal organs
Skin
Benign
Uveal nevus
Melano-cytoma
Blue nevus
Congenital nevus
Borderline
Atyical blue nevus
Malignant
Uveal melanoma
Melanoma
Blue nevus like melanoma
Melanoma in CN

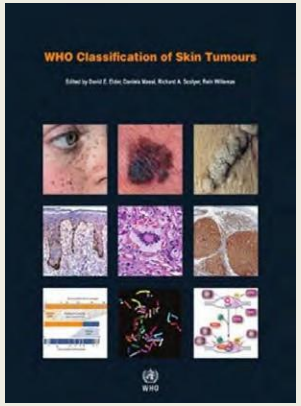
Current classification of melanoma- WHO

Melanomas arising in sun-exposed skin	**Pathway I**: Low-CSD melanoma/superficial spreading melanoma
	Pathway II: High-CSD melanoma/lentigo maligna melanoma
	Pathway III: Desmoplastic melanoma
Melanomas arising at sun-shielded sites or without known etiological associations with UV radiation exposure	**Pathway IV**: Malignant Spitz tumour (Spitz melanoma)
	Pathway V: Acral melanoma
	Pathway VI: Mucosal melanoma
	Pathway VII: Melanoma arising in congenital naevus
	Pathway VIII: Melanoma arising in blue naevus
	Pathway IX: Uveal melanoma

Management-based classification

- The specific diagnosis is particularly important for melanomas, but also guides the management of intermediate lesions that have been incompletely excised; in general, these lesions should be completely removed to enable full histological evaluation and to minimize the potential for local persistence, recurrence, and progression.
- In terms of accuracy and reproducibility, the diagnosis of intermediate lesions is improved by the use of molecular markers but remains challenging using current criteria, and there is considerable variation in the use of terminology across institutions

4 step progression scheme of melanocytic tumors



Nevus

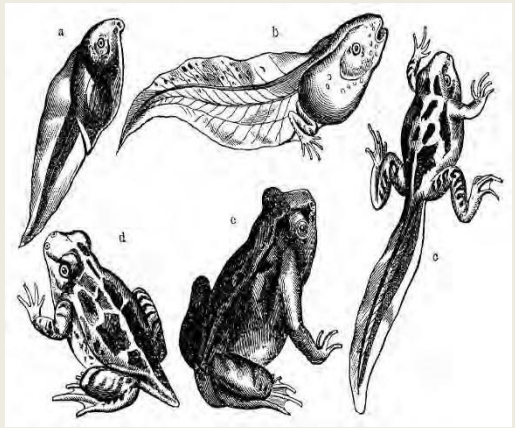
Single driver anomaly

Low grade «melanocytoma»

High grade «melanocytoma»

Melanoma

Multiple genomic alterations



Molecular pathology is part of an integrative analysis

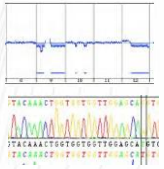
Embryogenesis

Clinical features

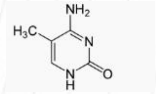
Microscopy/morphology

Immunophenotype

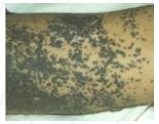
Genomic profile



Mutation status



Methylation profiles



Clinical evolution

9 classes of melanocytic tumours

Table 2.06 Classification of melanomas and precursor lesions on the basis of epidemiological, clinical, pathological, and genomic attributes

	Low UV radiation exposure / CSD				High UV radiation exposure / CS	
Pathway	I				II	III
Endpoint of pathway	Low-CSD melanoma / SSM				High-CSD melanoma / LMM	Desmoplastic melanoma
Benign neoplasms (naevi)	Naevus				? IMP	? IMP
Intermediate / low-grade dysplasias and melanocytomas	Low-grade dysplasia	BIN	DPN		? IAMP/dysplasia	? IAMP/dysplasia
Intermediate / high-grade dysplasias and melanocytomas	High-grade dysplasia / MIS	*BAP1*-inactivated melanocytoma / MELTUMP	Deep penetrating melanocytoma / MELTUMP	PEM / MELTUMP	Lentigo maligna (MIS)	MIS
Malignant neoplasms	Low-CSD melanoma / SSM (VGP)	Melanoma in BIN (rare)	Melanoma in DPN (rare)	Melanoma in PEM (rare)	LMM (VGP)	Desmoplastic melanoma
Common mutations[a,b]	***BRAF* p.V600E**; ***NRAS*** *TERT*; *CDKN2A*; *TP53*; *PTEN*	***BRAF*** or ***NRAS*** + *BAP1*	***BRAF***, ***MAP2K1***, or ***NRAS*** + ***CTNNB1*** or *APC*	***BRAF*** + *PRKAR1A* or ***PRKCA***	***NRAS***; ***BRAF* (non-p.V600E)**; ***KIT***; *NF1* *TERT*; *CDKN2A*; *TP53*; *PTEN*; *RAC1*	***NF1***; *ERBB2*; *MAP2K1*; *MAP3K1*; *BRAF*; *EGFR*; *MET* *TERT*; *NFKBIE*; ***NRAS***; *PIK3CA*; *PTPN11*

BIN, *BAP1*-inactivated naevus; **BN**, blue naevus; **CBN**, cellular blue naevus; **CN**, congenital naevus; **CSD**, cumulative sun damage; **DPN**, deep penetrating naevus; **IAMP**, intraepidermal atypical melanocytic proliferation; **IAMPUS**, intraepidermal atypical melanocytic proliferation of uncertain significance; **IMP**, intraepidermal melanocytic proliferation without atypia; **LMM**, lentigo maligna melanoma; low / high-CSD melanoma, melanoma in skin with a low / high degree of cumulative sun damage; **MELTUMP**, melanocytic tumour of uncertain malignant potential; **MIS**, melanoma in situ; **PEM**, pigmented epithelioid melanocytoma; **SSM**, superficial spreading melanoma; **STUMP**, spitzoid tumour of uncertain malignant potential; **UV**, ultraviolet; **VGP**, vertical growth phase (tumorigenic and/or mitogenic melanoma).

9 classes of melanocytic tumours

Low to no (or variable/incidental) UV radiation exposure / CSD					
IV	**V**	**VI**	**VII**	**VIII**	**IX**
Malignant Spitz tumour / Spitz melanoma	Acral melanoma	Mucosal melanoma	Melanoma in CN	Melanoma in BN	Uveal melanoma
Spitz naevus	? Acral naevus	? Melanosis	CN	Blue naevus	? Naevus?
Atypical Spitz tumour (melanocytoma)	IAMP / dysplasia	Atypical melanosis / dysplasia / IAMPUS	Nodule in CN (melanocytoma)	(Atypical) CBN (melanocytoma)	?
STUMP / MELTUMP	Acral MIS	Mucosal MIS	MIS in CN	Atypical CBN	?
Malignant Spitz tumour/ Spitz melanoma (tumorigenic)	Acral melanoma (VGP)	Mucosal lentiginous melanoma (VGP)	Melanoma in CN (tumorigenic)	Melanoma in blue naevus (tumorigenic)	Uveal melanoma
HRAS*; ALK; *ROS1*; *RET*; *NTRK1*; *NTRK3*; *BRAF*; *MET	***KIT*; *NRAS*; *BRAF*; *HRAS*; *KRAS*; *NTRK3*; *ALK*; *NF1***	***KIT*, *NRAS*, *KRAS*** or ***BRAF***	***NRAS*; *BRAF p.V600E*** (small lesions); ***BRAF***	***GNAQ*; *GNA11*; *CYSLTR2***	***GNAQ*, *GNA11*, *CYSLTR2*,** or ***PLCB4***
CDKN2A	*CDKN2A*; *TERT*; *CCND1*; *GAB2*	***NF1***; *CDKN2A*; *SF3B1*; *CCND1*; *CDK4*; *MDM2*		*BAP1*; *EIF1AX*; *SF3B1*	*SF3B1*; *EIF1AX*; *BAP1*

Definitions: *Melanocytoma* is a tumorigenic neoplasm of melanocytes that generally has increased cellularity and/or atypia (compared with a common naevus) and an increased (although generally still low) probability of neoplastic progression; *tumorigenic* means forming a mass of neoplastic cells.

[a] Common mutations in each pathway are listed. Mutations already identified in benign or borderline low lesions are shown in bold.

[b] Blue, loss-of-function mutation; red, gain-of-function mutation; green, change-of-function mutation; orange, amplification; purple, rearrangement; grey, promoter mutation.

Multi-dimensional classification

- Sun exposure
- Topography
- Morphological
- Genetics

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	Low UV radiation exposure/CSD				High UV radiation exposure/CS	
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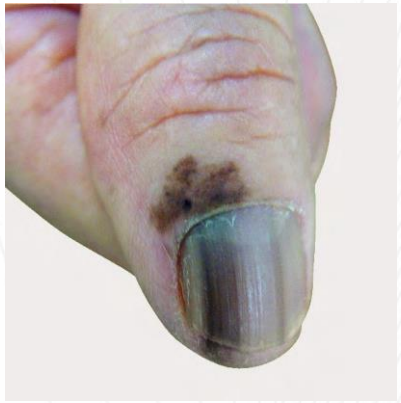
- Morphological
- Genetics



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Atypical Spitz tumour (melanocytoma)	IAMP / dysplasia	Atypical melanosis / dysplasia / IAMPUS	Nodule in CN (melanocytoma)	(Atypical) CBN (melanocytoma)	?
STUMP / MELTUMP	Acral MIS	Mucosal MIS	MIS in CN	Atypical CBN	?
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CDKN2A	*CDKN2A*; *TERT*; *CCND1*; *GAB2*	***NF1*; *CDKN2A*; *SF3B1*; *CCND1*; *CDK4*; *MDM2***		*BAP1*; *EIF1AX*; *SF3B1*	*SF3B1*; *EIF1AX*; *BAP1*

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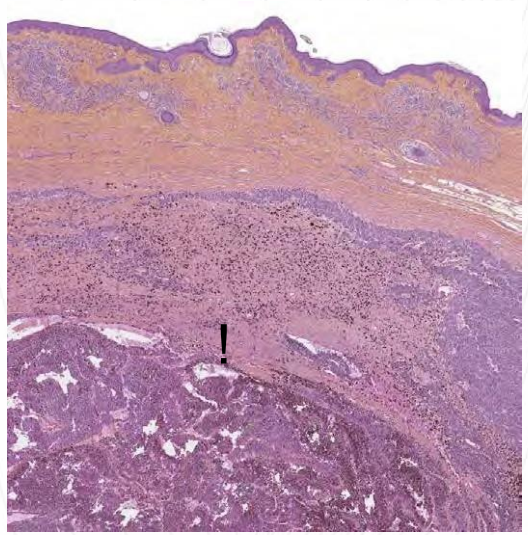
Multi-dimensional classification

- Sun exposure
- **Context**



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CDKN2A	*CDKN2A*; *TERT*; *CCND1*; *GAB2*	*NF1*; *CDKN2A*; *SF3B1*; *CCND1*; *CDK4*; *MDM2*		*BAP1*; *EIF1AX*; *SF3B1*	*SF3B1*; *EIF1AX*; *BAP1*

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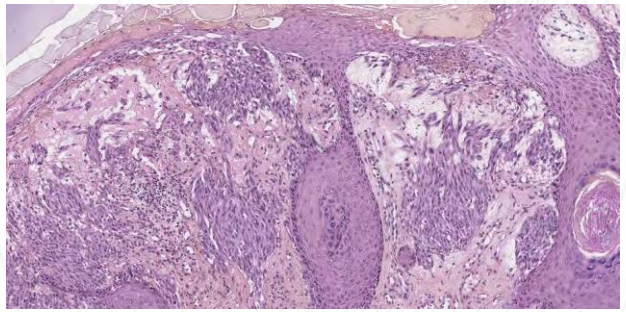
- Genetics



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Atypical Spitz tumour (melanocytoma)	IAMP / dysplasia	Atypical melanosis / dysplasia / IAMPUS	Nodule in CN (melanocytoma)	(Atypical) CBN (melanocytoma)	?
STUMP / MELTUMP	Acral MIS	Mucosal MIS	MIS in CN	Atypical CBN	?
Malignant Spitz tumour/ Spitz melanoma (tumorigenic)	Acral melanoma (VGP)	Mucosal lentiginous melanoma (VGP)	Melanoma in CN (tumorigenic)	Melanoma in blue naevus (tumorigenic)	Uveal melanoma
HRAS; ***ALK***; ***ROS1***; ***RET***; ***NTRK1***; ***NTRK3***; ***BRAF***; ***MET***	***KIT***; ***NRAS***; ***BRAF***; ***HRAS***; ***KRAS***; ***NTRK3***; ***ALK***; ***NF1***	***KIT***, ***NRAS***, ***KRAS*** or ***BRAF***	***NRAS***; ***BRAF p.V600E*** (small lesions); ***BRAF***	***GNAQ***; ***GNA11***; ***CYSLTR2***	***GNAQ***, ***GNA11***, ***CYSLTR2***, or ***PLCB4***
CDKN2A	*CDKN2A*; *TERT*; *CCND1*; *GAB2*	***NF1***; *CDKN2A*; *SF3B1*; *CCND1*; *CDK4*; *MDM2*		*BAP1*; ***EIF1AX***; ***SF3B1***	*SF3B1*; *EIF1AX*; *BAP1*

Definitions: *Melanocytoma* is a tumorigenic neoplasm of melanocytes that generally has increased cellularity and/or atypia (compared with a common naevus) and an increased (although generally still low) probability of neoplastic progression; *tumorigenic* means forming a mass of neoplastic cells.

[a] Common mutations in each pathway are listed. Mutations already identified in benign or borderline low lesions are shown in bold.
[b] Blue, loss-of-function mutation; red, gain-of-function mutation; green, change-of-function mutation; orange, amplification; purple, rearrangement; grey, promoter mutation.

Multi-dimensional classification

- Sun exposure
- Topography
- Morphological
- **Genetics**

Low to no (or variable/incidental) UV radiation exposure / CSD					
IV	**V**	**VI**	**VII**	**VIII**	**IX**
Malignant Spitz tumour / Spitz melanoma	Acral melanoma	Mucosal melanoma	Melanoma in CN	Melanoma in BN	Uveal melanoma
Spitz naevus	? Acral naevus	? Melanosis	CN	Blue naevus	? Naevus?
Atypical Spitz tumour (melanocytoma)	IAMP / dysplasia	Atypical melanosis / dysplasia / IAMPUS	Nodule in CN (melanocytoma)	(Atypical) CBN (melanocytoma)	?
STUMP / MELTUMP	Acral MIS	Mucosal MIS	MIS in CN	Atypical CBN	?
Malignant Spitz tumour / Spitz melanoma (tumorigenic)	Acral melanoma (VGP)	Mucosal lentiginous melanoma (VGP)	Melanoma in CN (tumorigenic)	Melanoma in blue naevus (tumorigenic)	Uveal melanoma
HRAS*; *ALK*; *ROS1*; *RET*; *NTRK1*; *NTRK3*; *BRAF*; *MET *CDKN2A*	***KIT*; *NRAS*; *BRAF*; *HRAS*; *KRAS*; *NTRK3*; *ALK*; *NF1*** *CDKN2A*; *TERT*; *CCND1*; *GAB2*	***KIT*, *NRAS*, *KRAS* or *BRAF*** ***NF1***; *CDKN2A*; *SF3B1*; *CCND1*; *CDK4*; *MDM2*	***NRAS*; *BRAF p.V600E* (small lesions); *BRAF***	***GNAQ*; *GNA11*; *CYSLTR2*** *BAP1*; *EIF1AX*; *SF3B1*	***GNAQ*, *GNA11*, *CYSLTR2*, or *PLCB4*** *SF3B1*; *EIF1AX*; *BAP1*

Definitions: *Melanocytoma* is a tumorigenic neoplasm of melanocytes that generally has increased cellularity and/or atypia (compared with a common naevus) and an increased (although generally still low) probability of neoplastic progression; *tumorigenic* means forming a mass of neoplastic cells.

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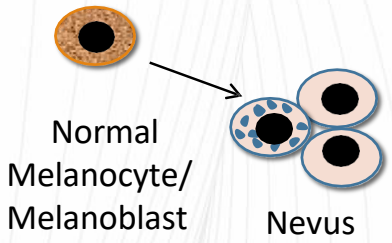
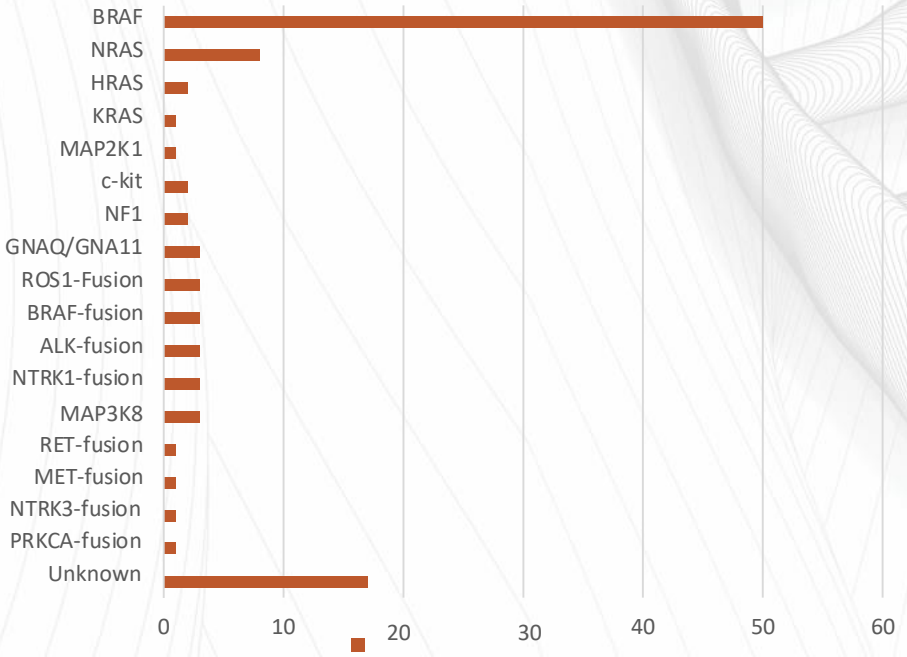
Genetic melanocytic tumours
Driver mutations





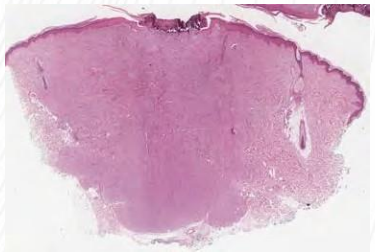
Molecular anomalies of Spitz tumours

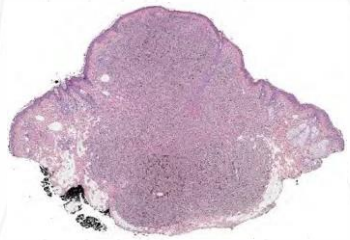
- HRAS mutations (11p)
- Tyrosine kinase fusions
  - ALK
  - ROS1
  - NTRK1
  - NTRK3
  - RET
  - MET
  - MERTK
  - LCK
- Serine kinase fusions
  - BRAF
  - MAP3K8
  - MAP3K3

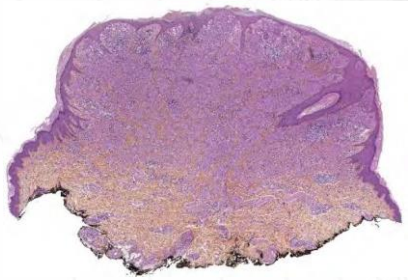
Integrative classification of melanocytic tumors

GNAQ, GNA11, PLCB4, CYSLTR2	*BRAF, NRAS*	*HRAS*, kinase fusions
Blue nevus	Common nevus, Congenital nevus	Nevus Spilus "Field effect"
Cellular blue nevus	Clonal nevus	Spitz Nevus
Atypical blue nevus	Atypical nevus	Atypical Spitz tumor

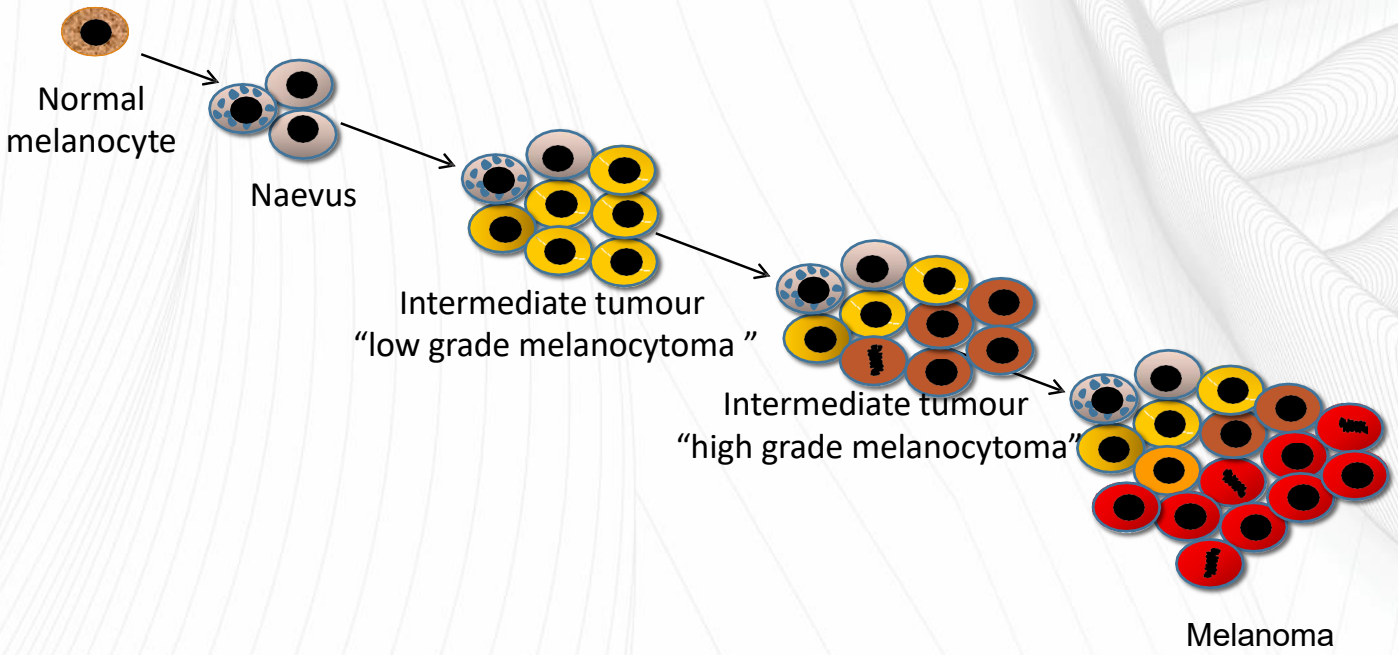
additionnal molecular anomalies



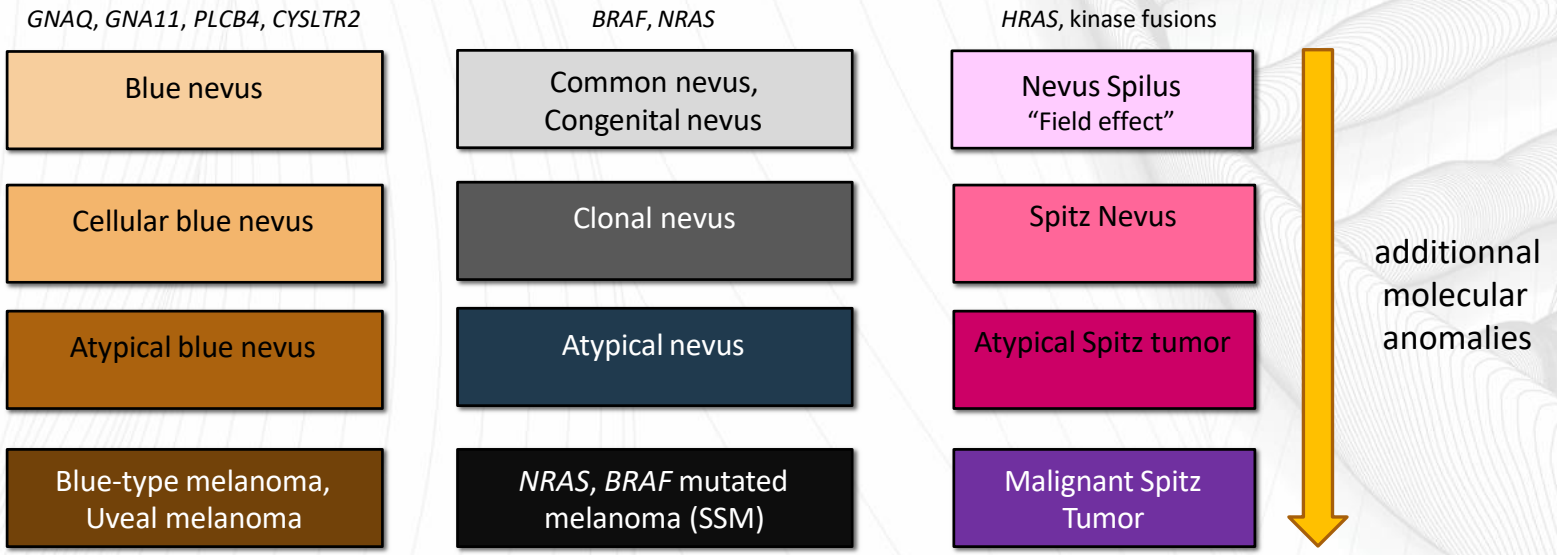




Genetic evolution of melanocytic tumours

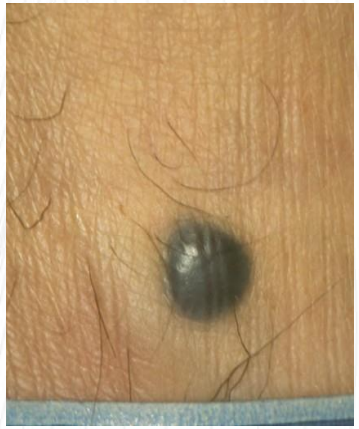


Integrative classification of melanocytic tumors

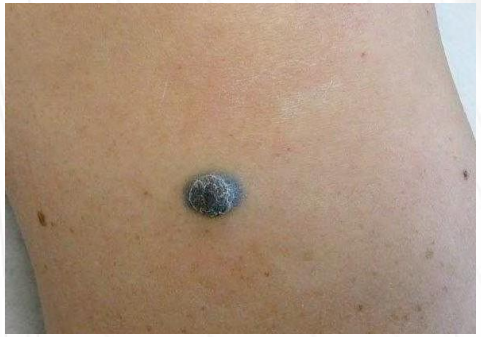


Progression of blue lesions

Blue nevus



Cellular blue nevus



Atypical cellular blue nevus

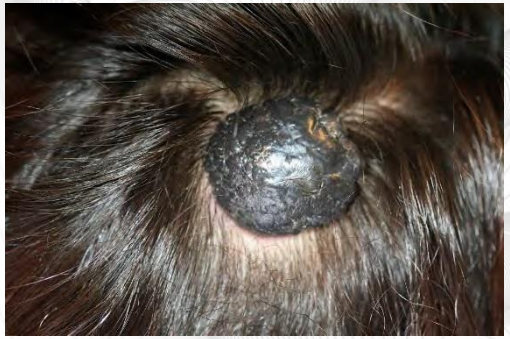
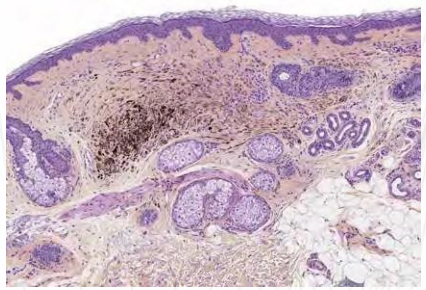


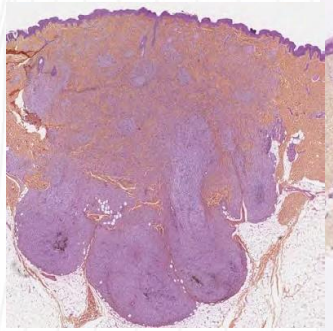
Photo: Pr L. Thomas

Melanoma ex-blue nevus

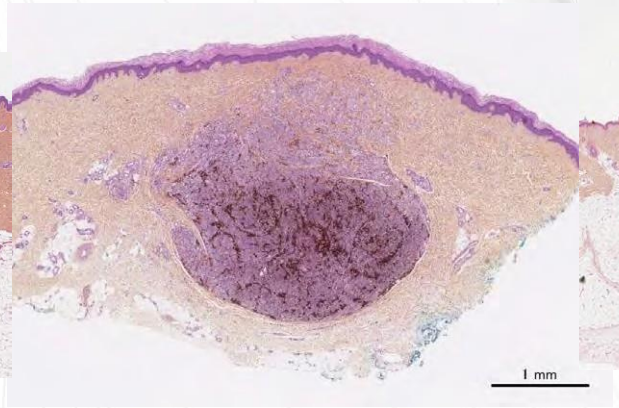
Progression of blue lesions



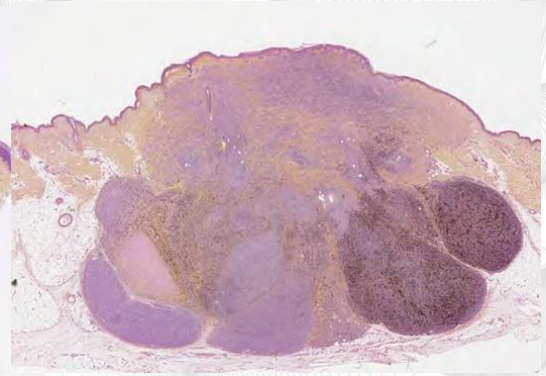
Blue nevus



Cellular blue nevus

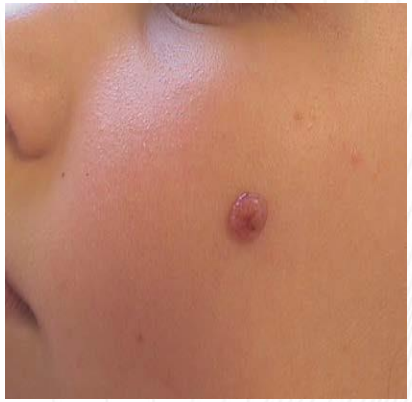


Atypical cellular blue nevus

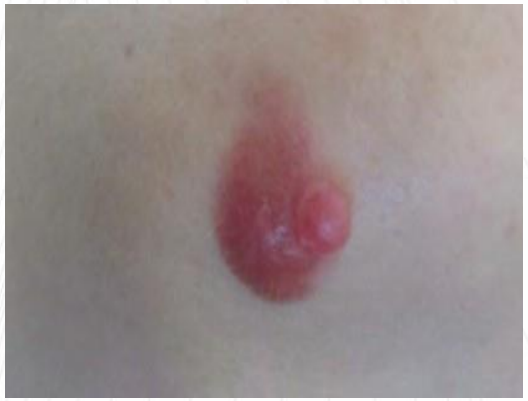


Melanoma ex-blue nevus

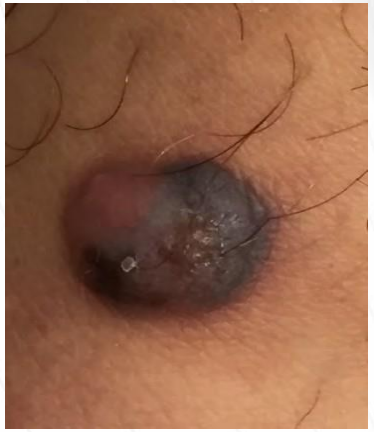
Progression of Spitz lesions



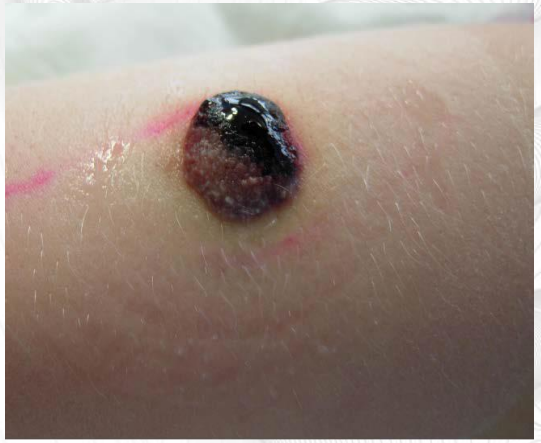
Spitz nevus



Atypical Spitz nevus (melanocytoma)



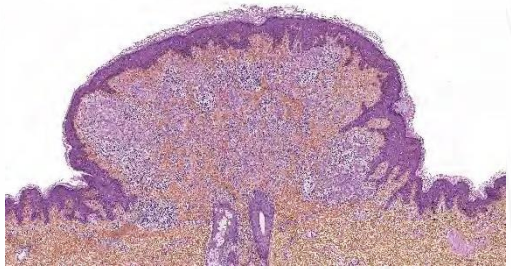
Atypical Spitz nevus (melTUMP)



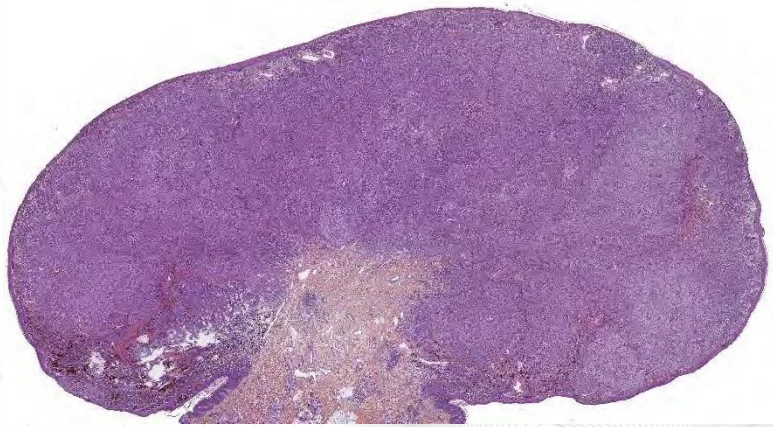
F, 6 ans (photo Dr Dadban)

Malignant Spitz tumour

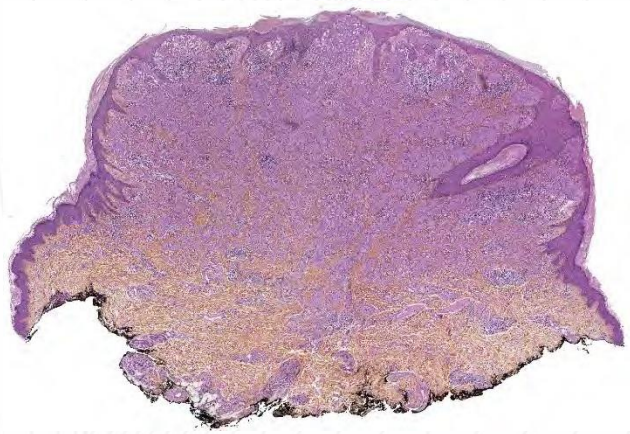
Progression of Spitz lesions



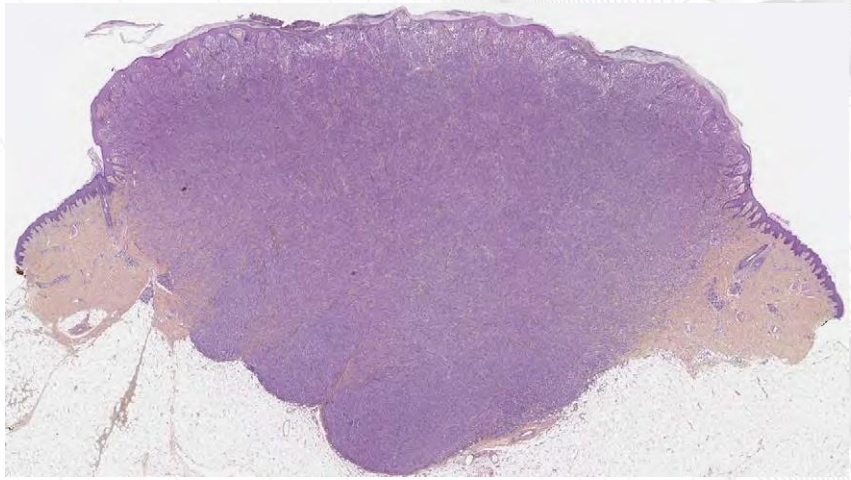
Spitz Nevus



AST High-grade



Atypical Spitz Tumor (AST)



Malignant Spitz Tumor

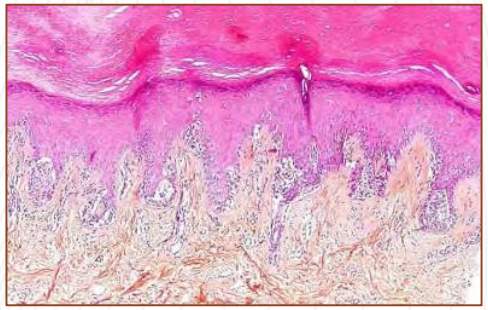
Genetic evolution of melanocytic tumours

In situ melanoma

Normal melanocyte

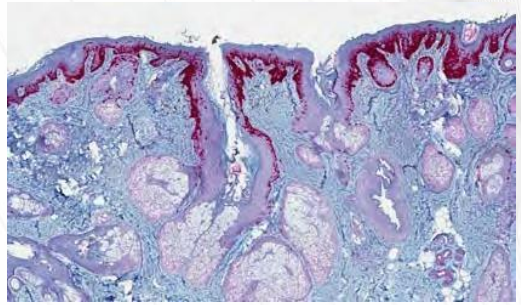
Ckit, NRAS, BRAF,…

ALM *in situ*



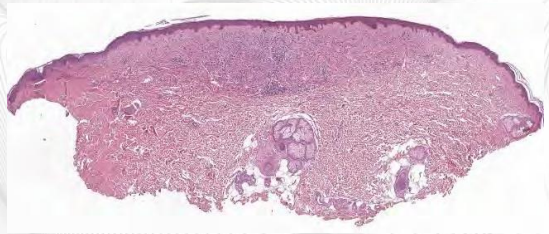
BRAF V600K,…

Lentigo Maligna



NF1, NFKBIεR,…

Desmoplastic Melanoma



Adapted from Yeh /Bastian

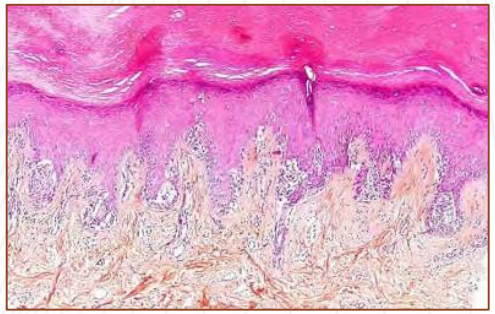
Genetic evolution of melanocytic tumours

In situ melanoma

Normal melanocyte

Ckit, NRAS, BRAF,…

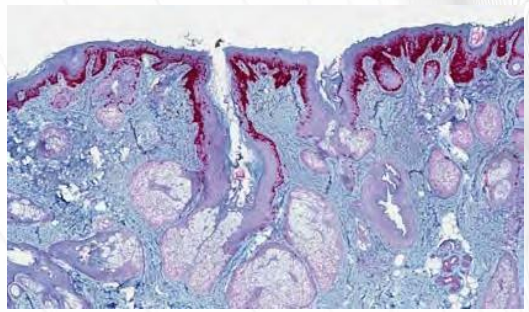
ALM *in situ*



Unexposed skin

BRAF V600K,…

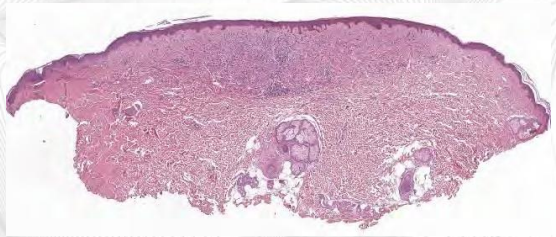
Lentigo Maligna



Chronic sun damage

NF1, NFKBIεR,…

Desmoplastic Melanoma

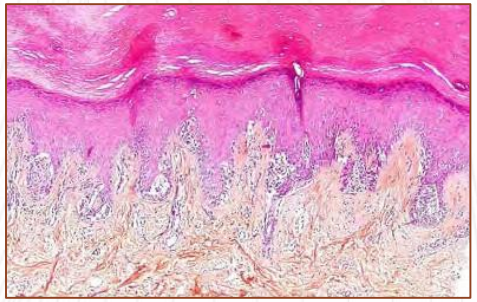


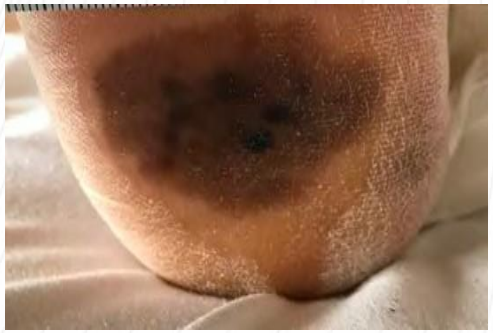
Chronic sun damage

Genetic evolution of melanocytic tumours

Ckit, NRAS, BRAF,…

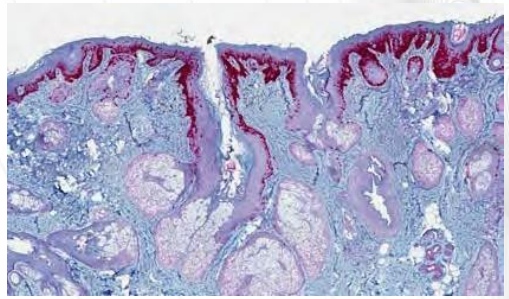
ALM *in situ*

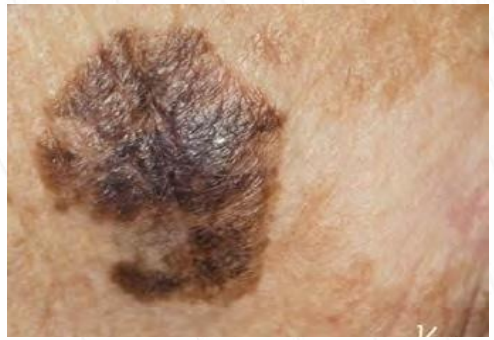




BRAF V600K,…

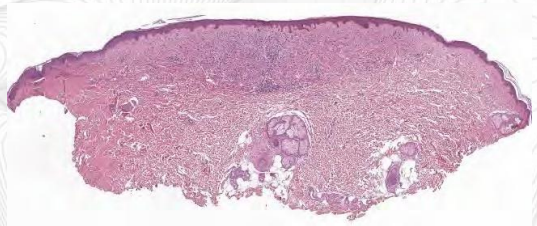
Lentigo Maligna

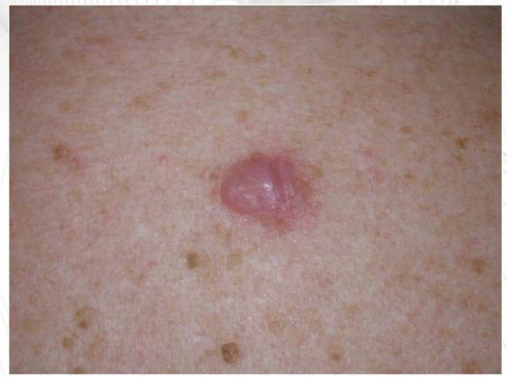




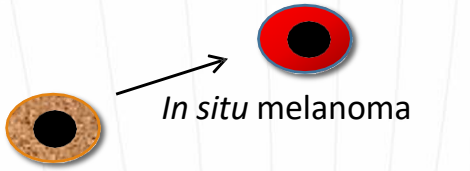
NF1, NFKBIεR,…

Desmoplastic Melanoma



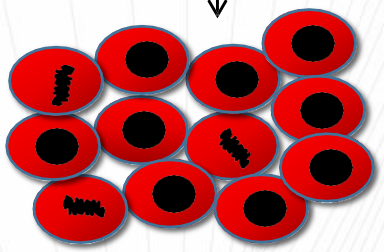


Genetic evolution of melanocytic tumours



In situ melanoma

Normal melanocyte

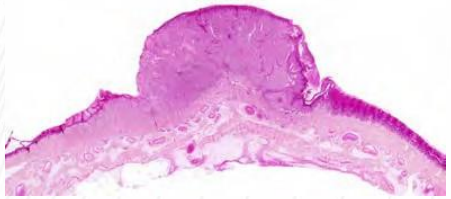


Melanoma

Ckit, NRAS, BRAF,…

ALM *in situ*

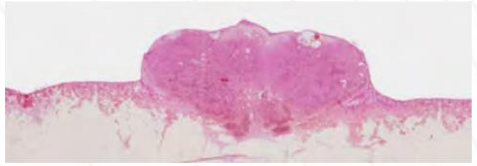
Invasive ALM



BRAF V600K,…

Lentigo Maligna

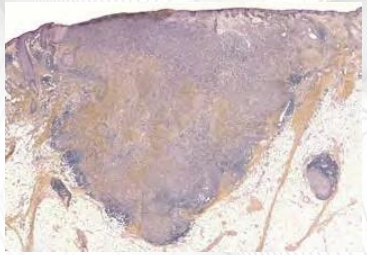
Lentigo Maligna Melanoma



NF1, NFKBIεR, …

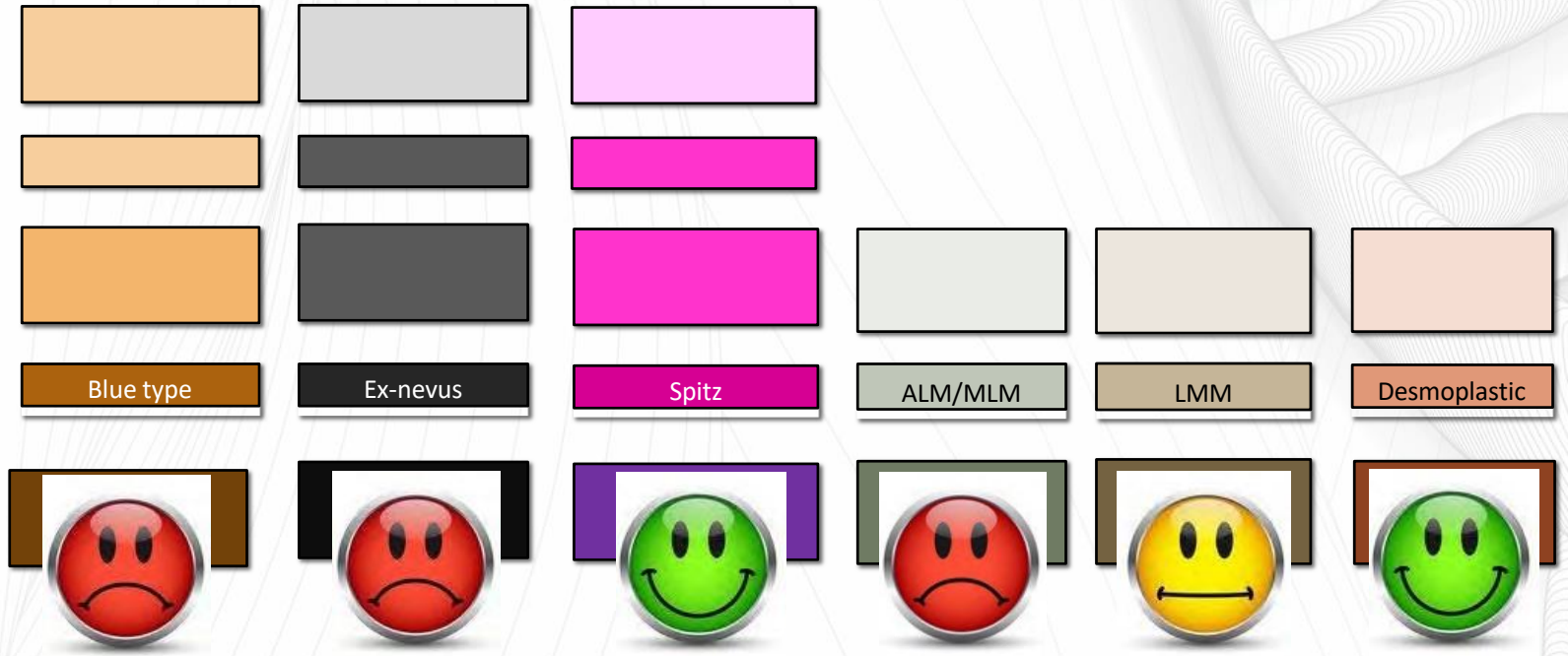
Desmoplastic Melanoma

Desmoplastic Melanoma



Adapted from Yeh /Bastian

Molecular pathology of melanocytic tumors Also perceiving the prognosis of the “color”



Large panel of tools with specific functions:

- Histology H&E stain
- IHC
- Array-CGH
- FISH technique
- DNA studies by NGS
- RNA-sequencing
- Understand what you are looking for to choose them wisely

Large panel of tools with specific functions:

- IHC
- Chromosomal microarray-CGH
- FISH technique
- DNA studies by NGS
- RNA-sequencing
- Understand what you are looking for to choose them wisely

Diagnostic tools

- IHC: screening tool for molecular driver/passengers' alteration
- Potential enticement to use other confirmation tools
- aCGH: whole genome screen of gains and losses on chromosomes
- Analysis of specific gene exons for mutations/deletions (panel)

Screening of atypical lesions >1mm thickness

- MelanA
- HMB45
- P16
- Ki67
- BRAF V600E
- RAS Q61R
- ALK
- ROS1
- Pan-TRK
- BAP1
- Betacatenin
- PRKAR1A
- New specific antibodies

Screening of atypical lesions >1mm thickness

- MelanA
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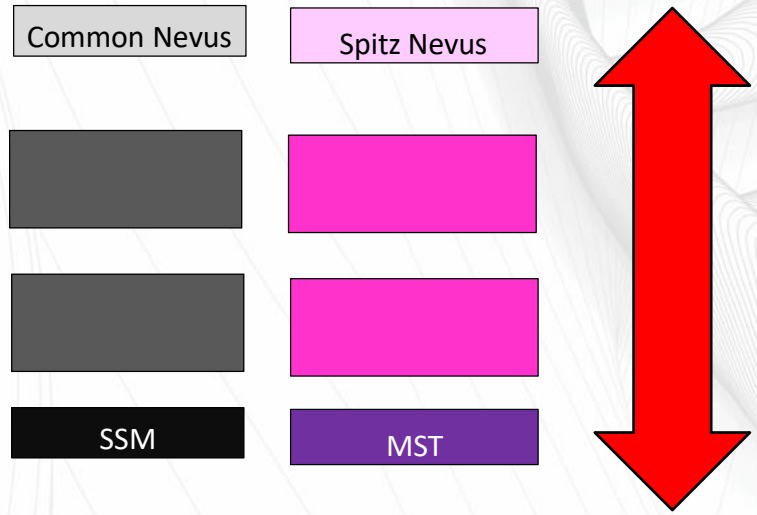
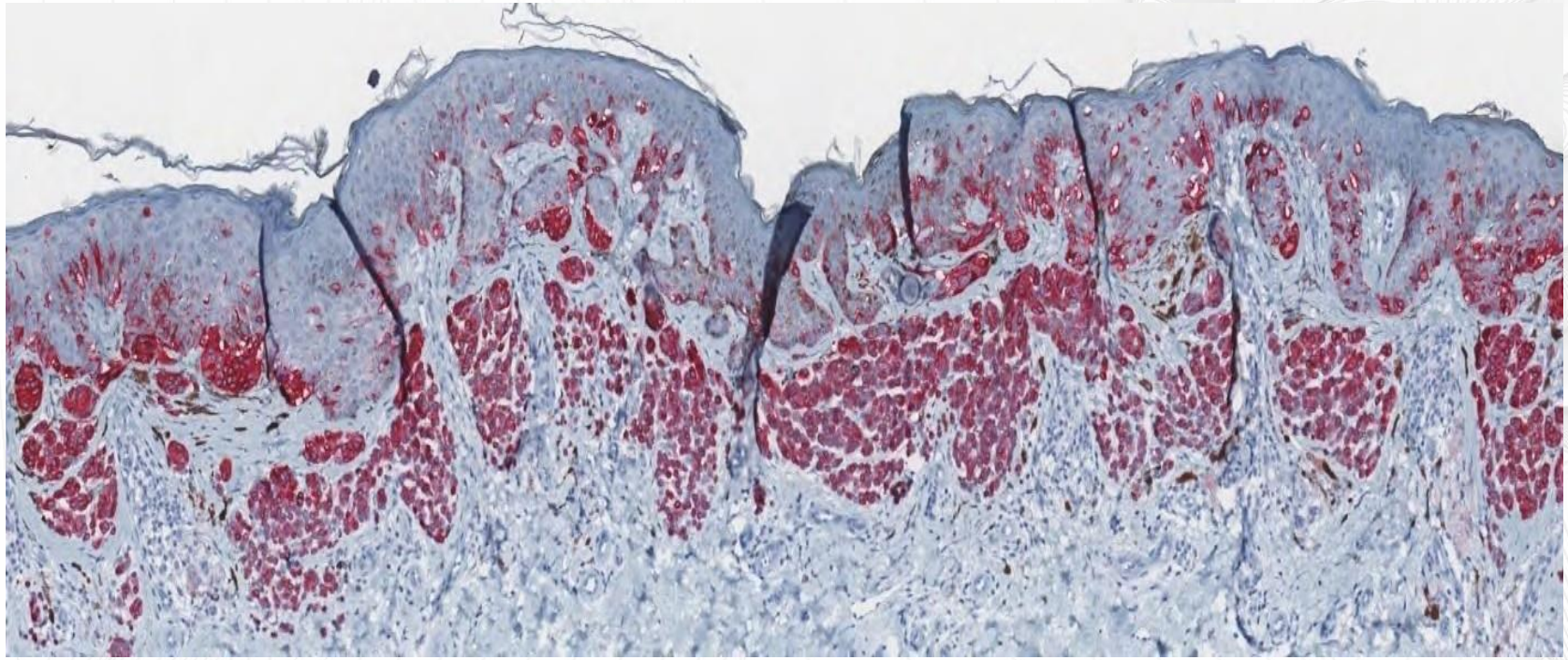
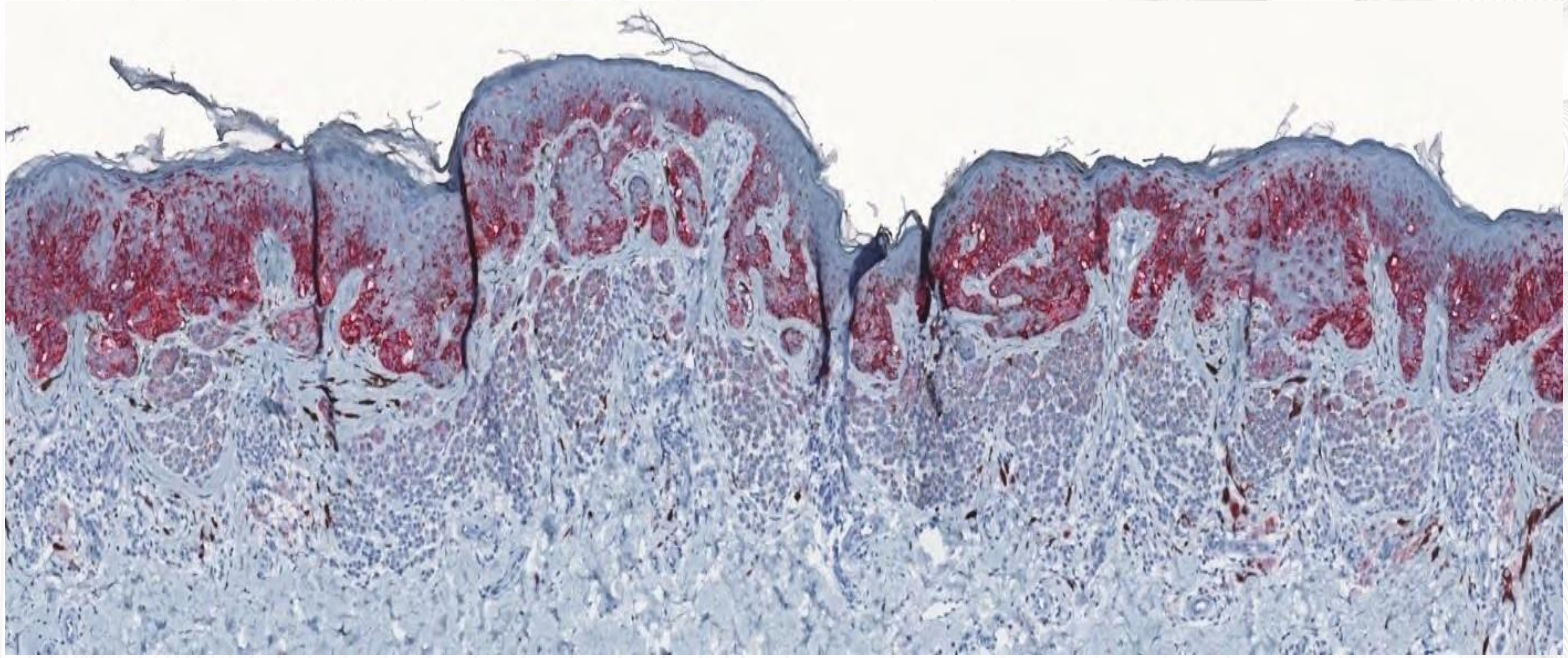


Standard immunophenotype



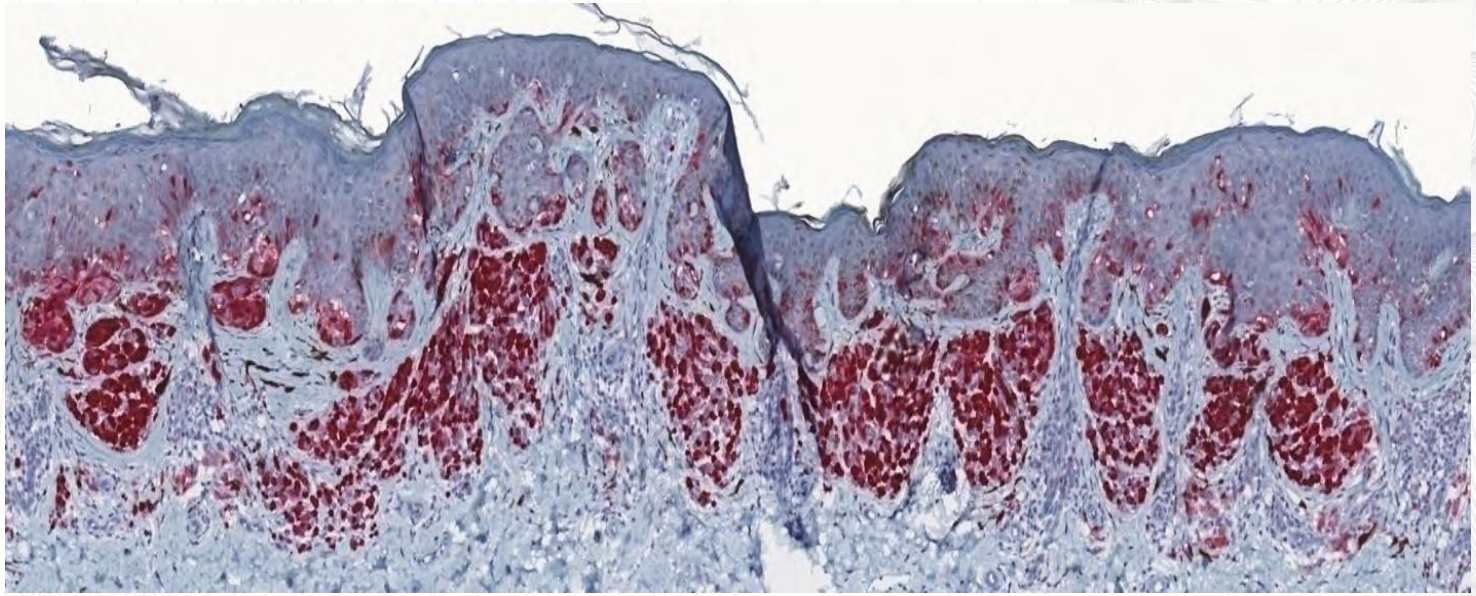
Diffuse MelanA staining

Standard immunophenotype



Top heavy HMB45 staining

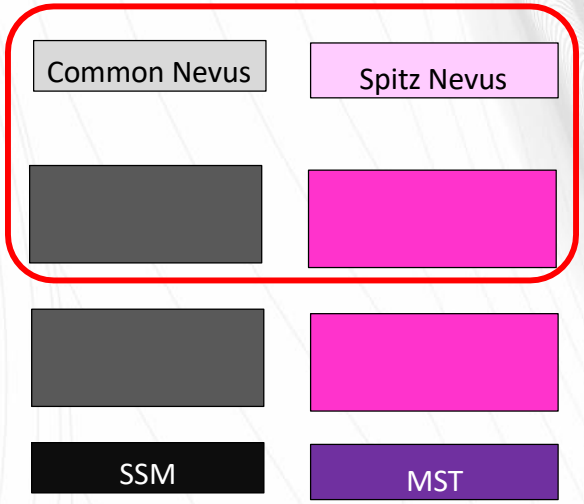
Standard immunophenotype



P16: mosaic pattern staining

Standard immunophenotype

- MelanA
- HMB45
- P16
- Ki67
- BRAF V600E
- RAS Q61R
- ALK
- ROS1
- Pan-TRK
- BAP1
- Betacatenin
- PRKAR1A
- New specific antibodies



Abnormal immunophenotype

- MelanA
- HMB45
- P16
- Ki67
- BRAF V600E
- RAS Q61R
- ALK
- ROS1
- Pan-TRK
- BAP1
- Betacatenin
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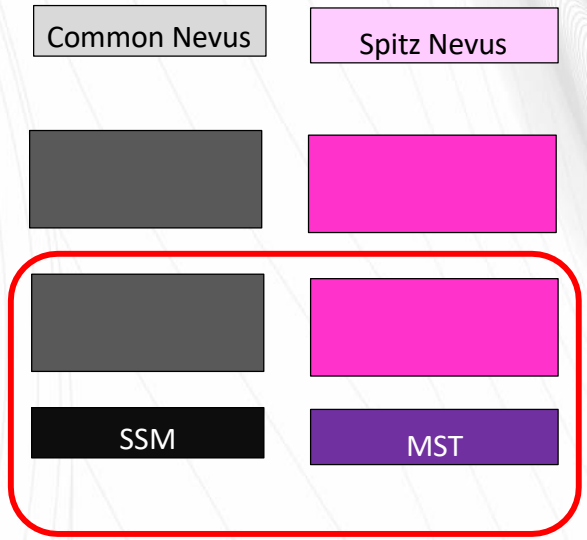
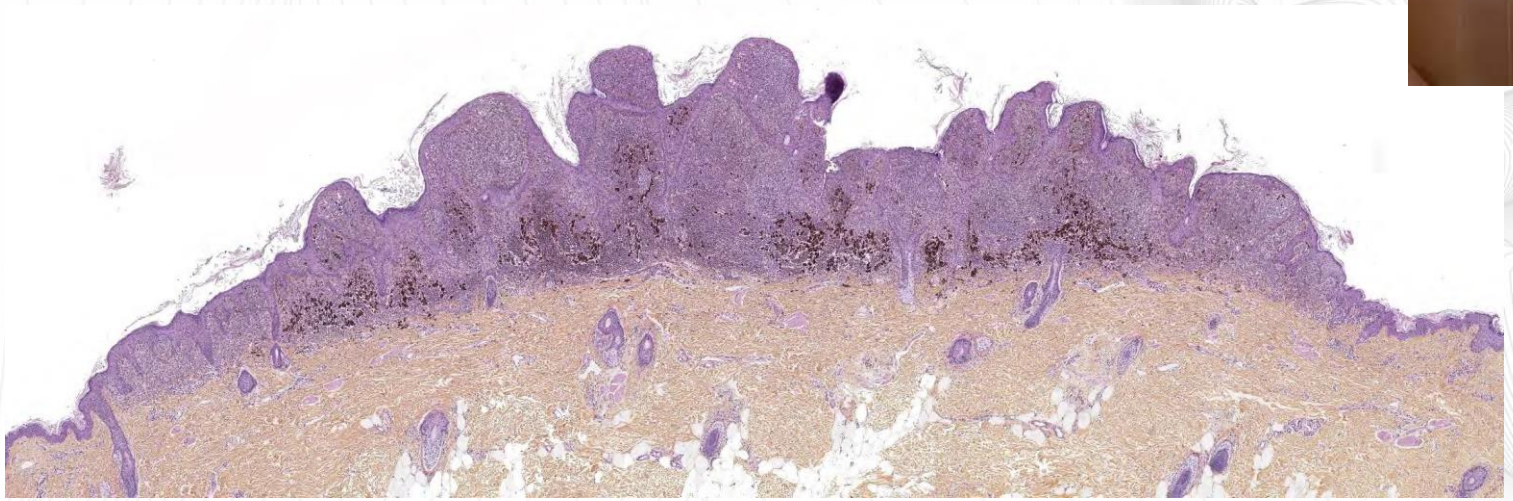


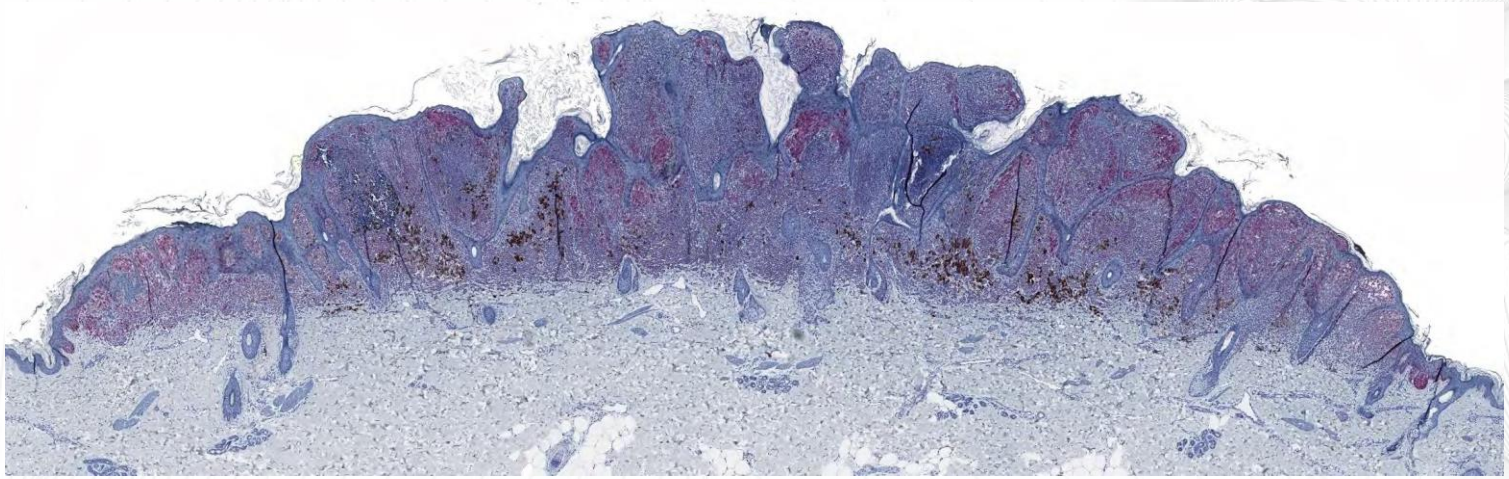
60-year-old male with lesion on back



Puffy shirt appearance PMID: 31237702

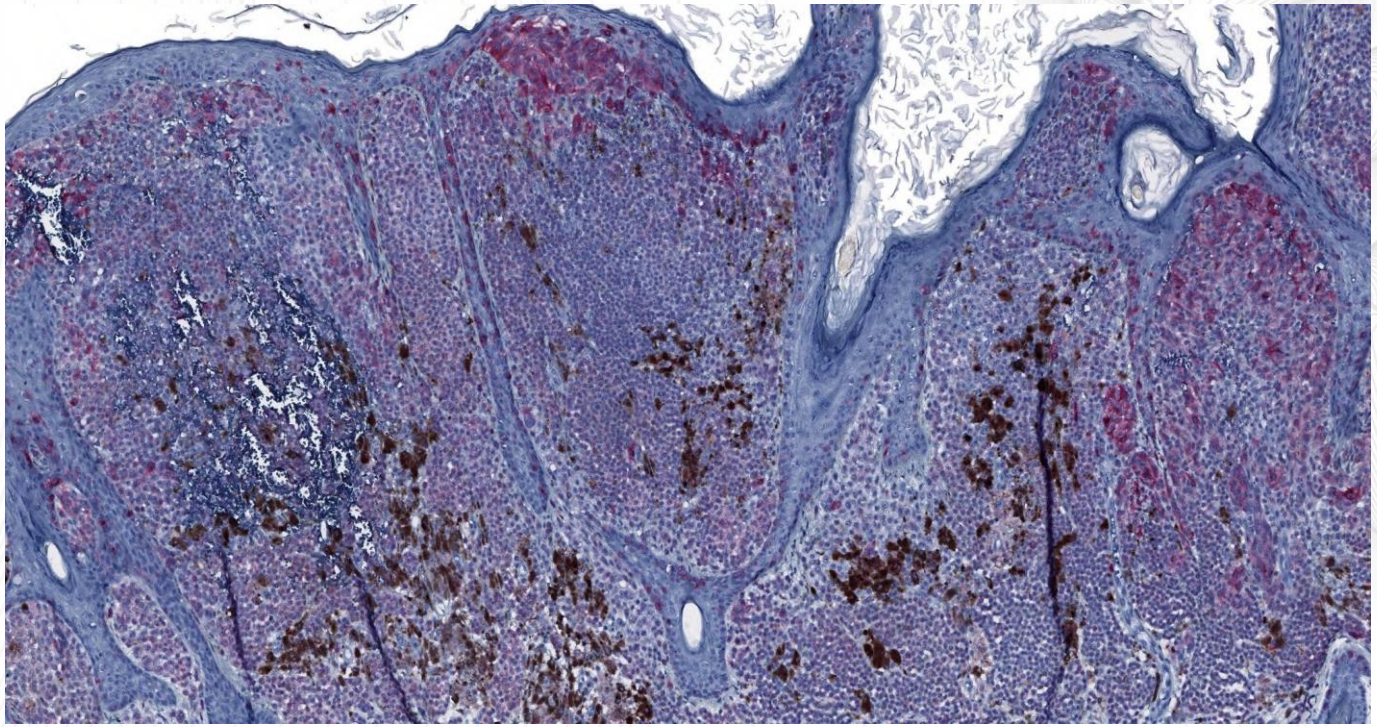
IHC panel anomalies

MelanA

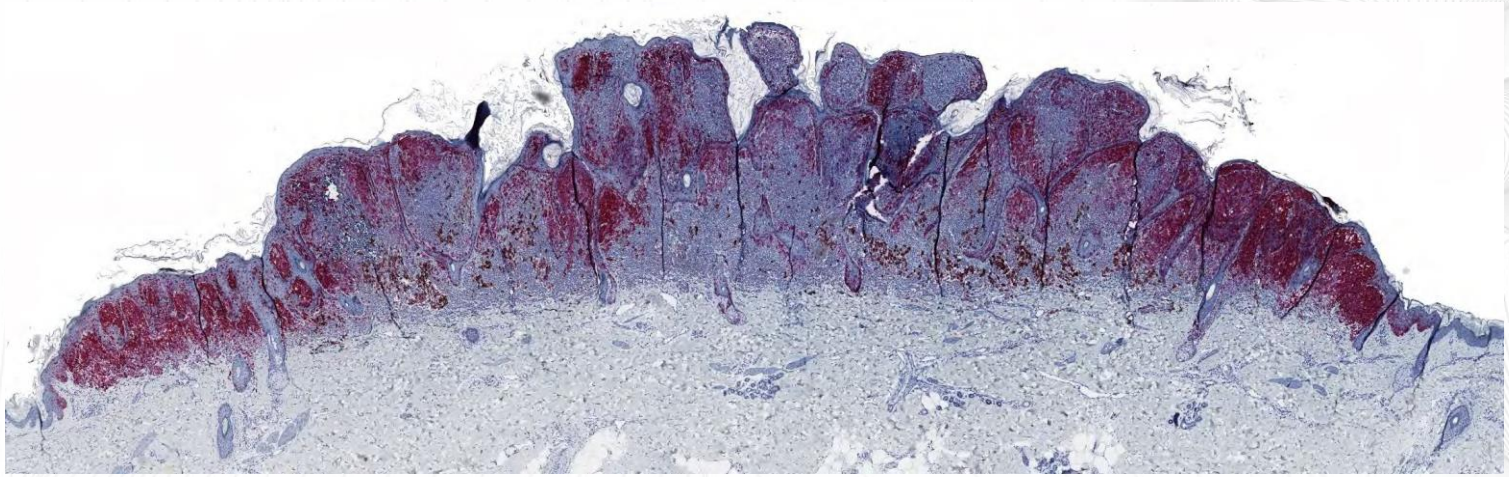


IHC panel anomalies

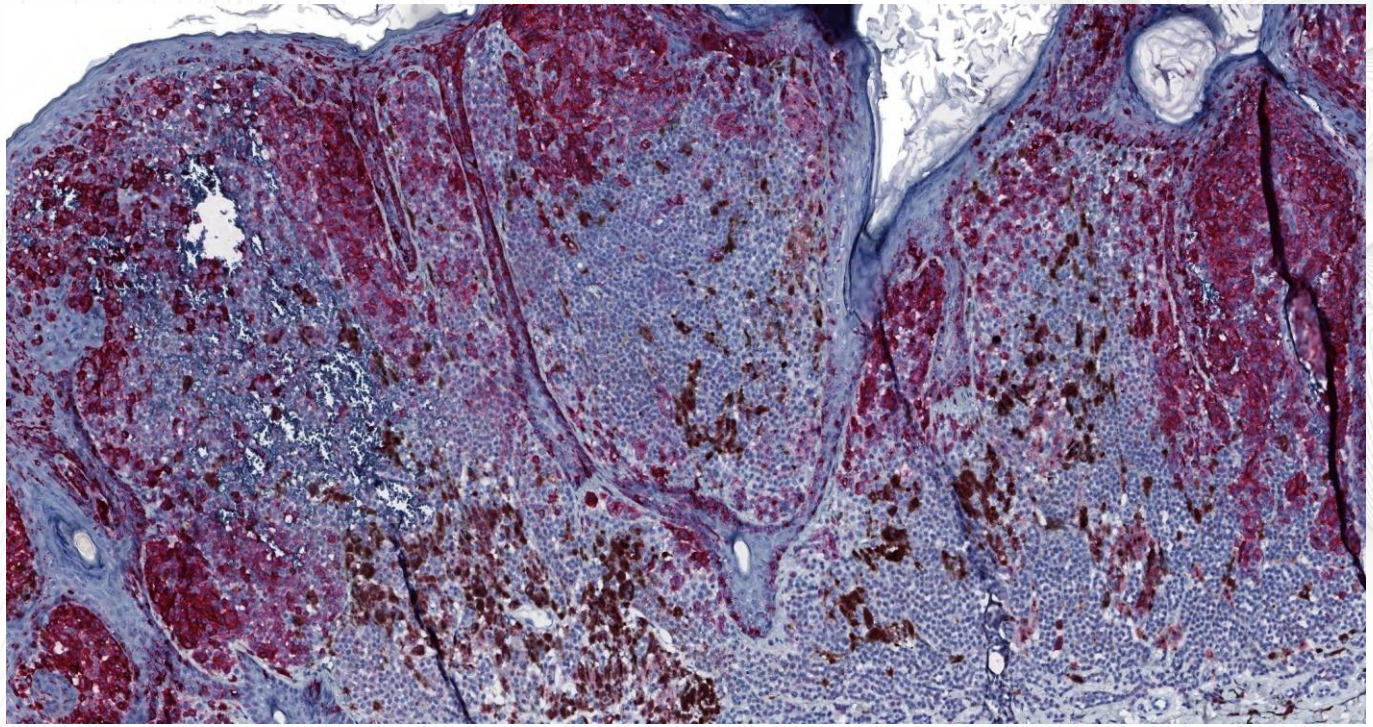
MelanA



HMB45



HMB45



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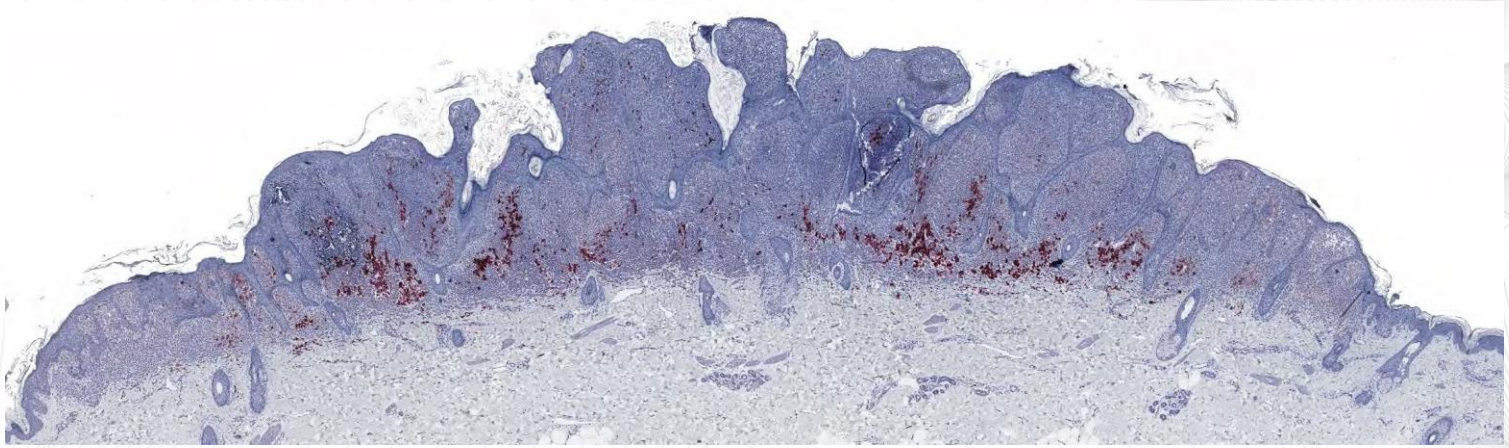

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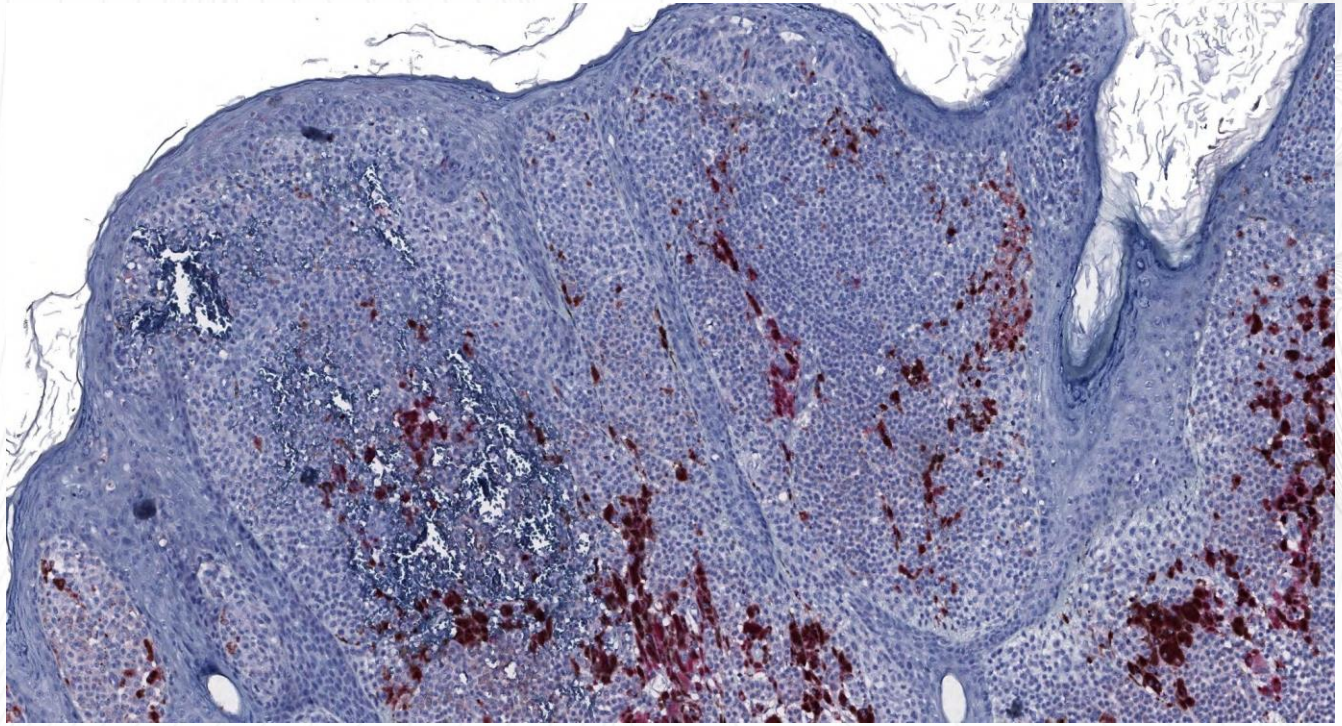
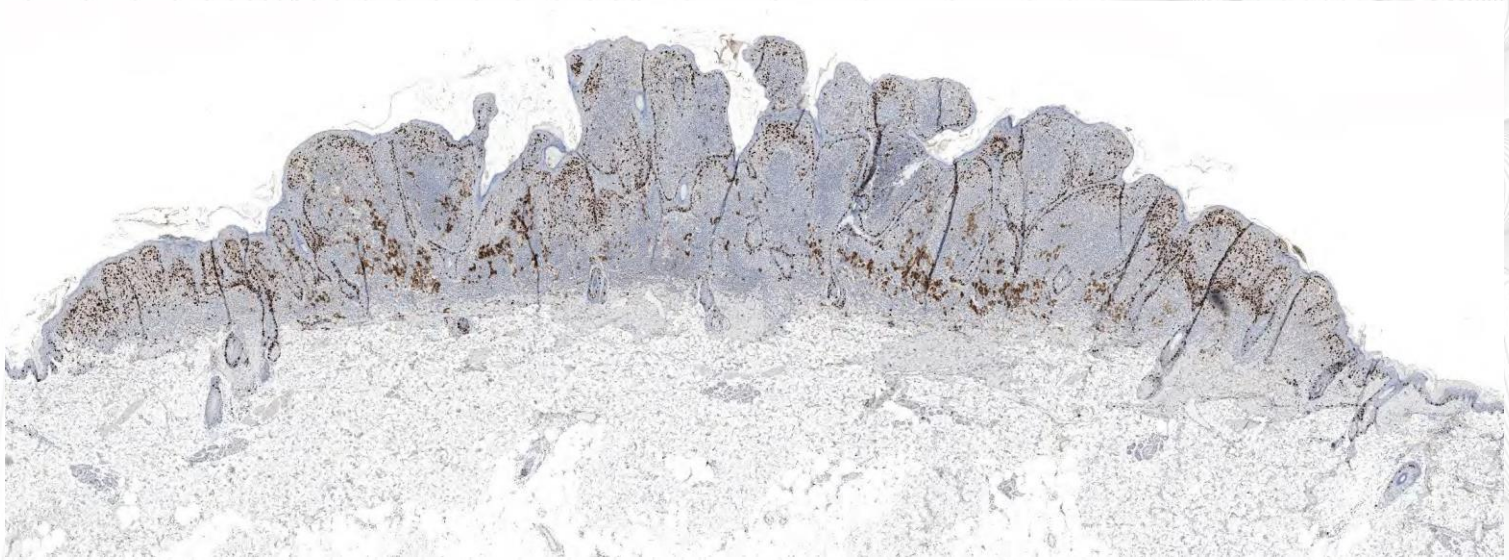
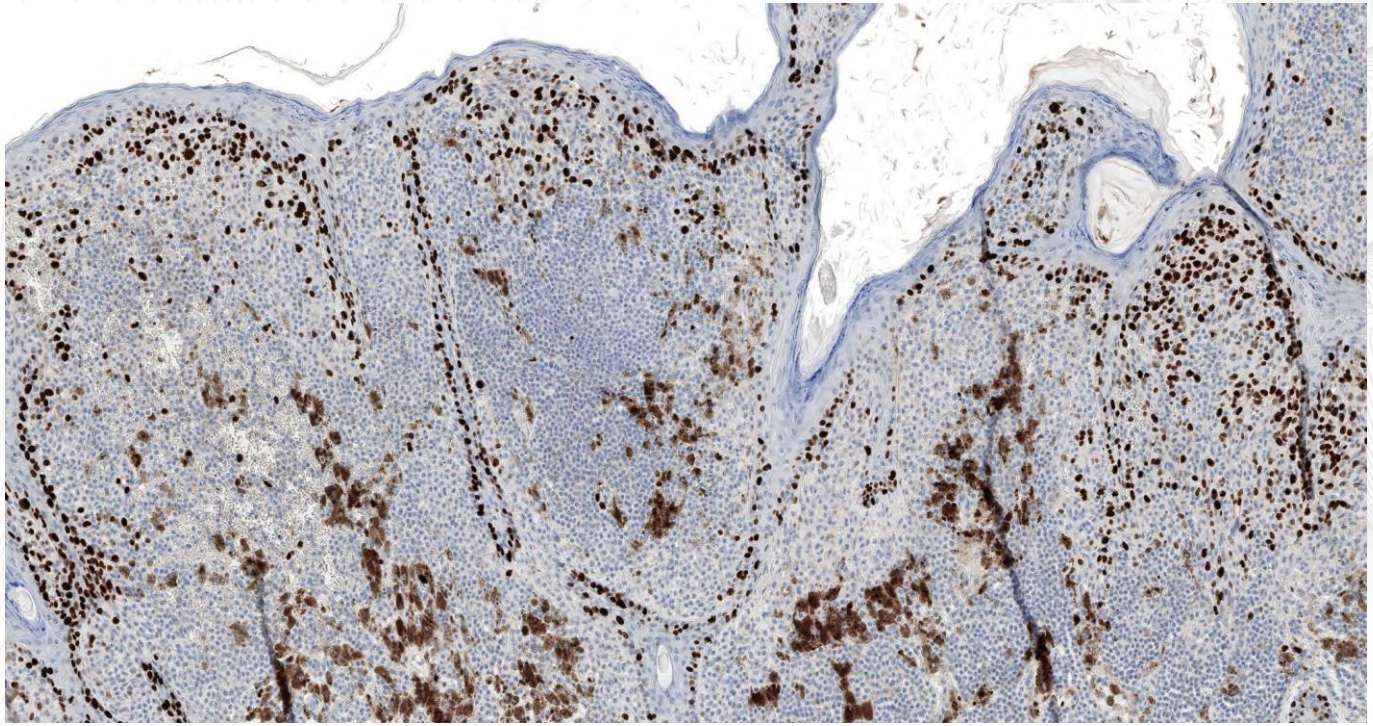


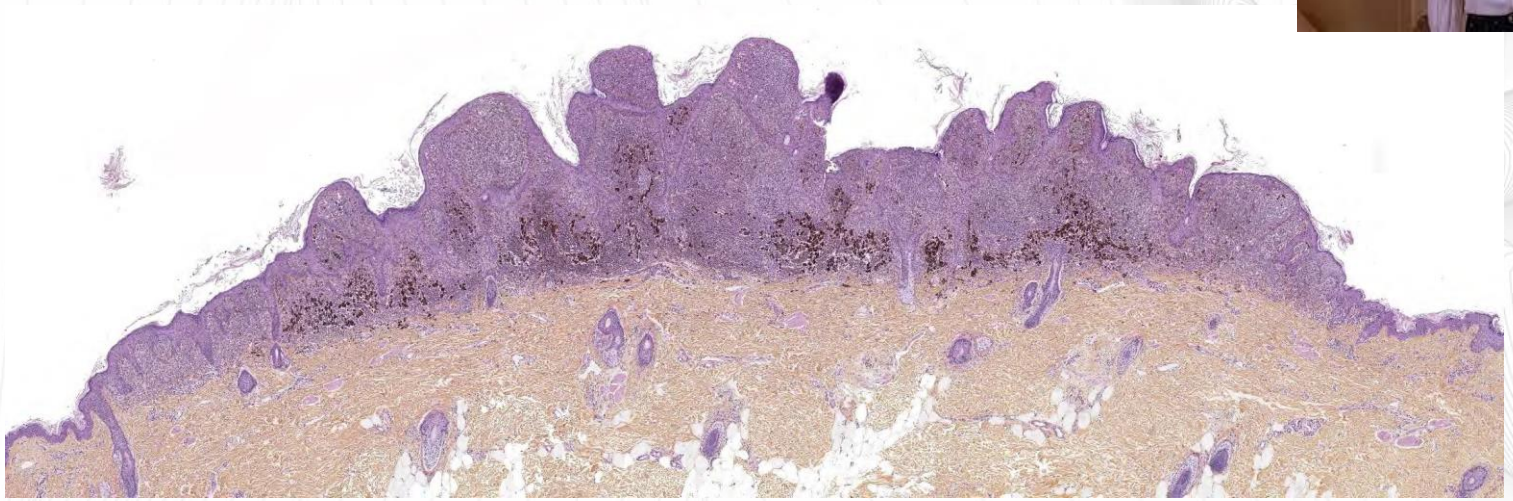
Ki-67 gradient



Ki-67 gradient



Nevoid melanoma



Puffy shirt appearance PMID: 31237702

Genetic drivers of common nevi

- MelanA
- HMB45
- P16
- Ki67
- BRAF V600E specific
- RAS Q61R specific
- ALK
- ROS1
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- Betacatenin
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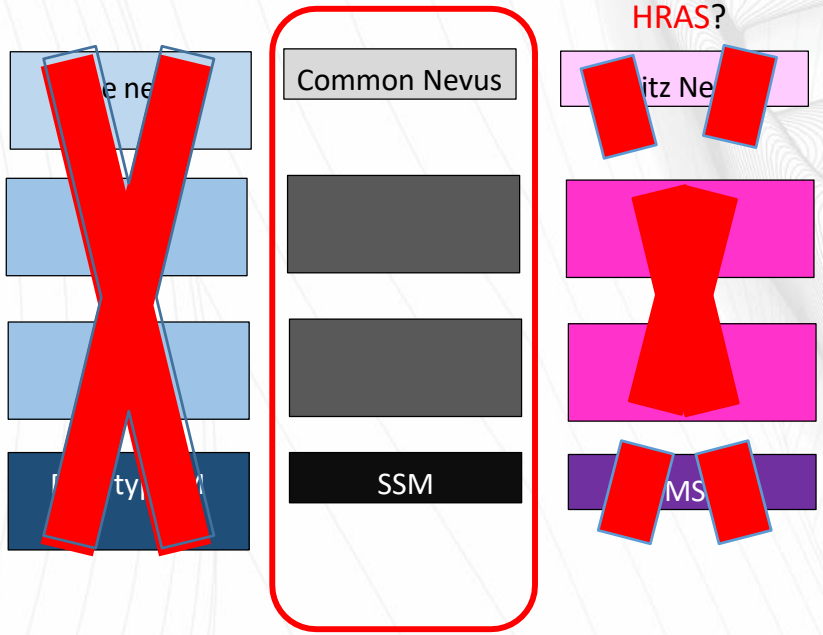

Genetic drivers of common nevi Positivity rules out a Blue or Spitz group tumor (except *HRAS* mutated desmoplastic spitz nevus)

- MelanA
- HMB45
- P16
- Ki67
- BRAF V600E specific
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- ROS1
- Pan-TRK
- BAP1
- Betacatenin
- PRKAR1A
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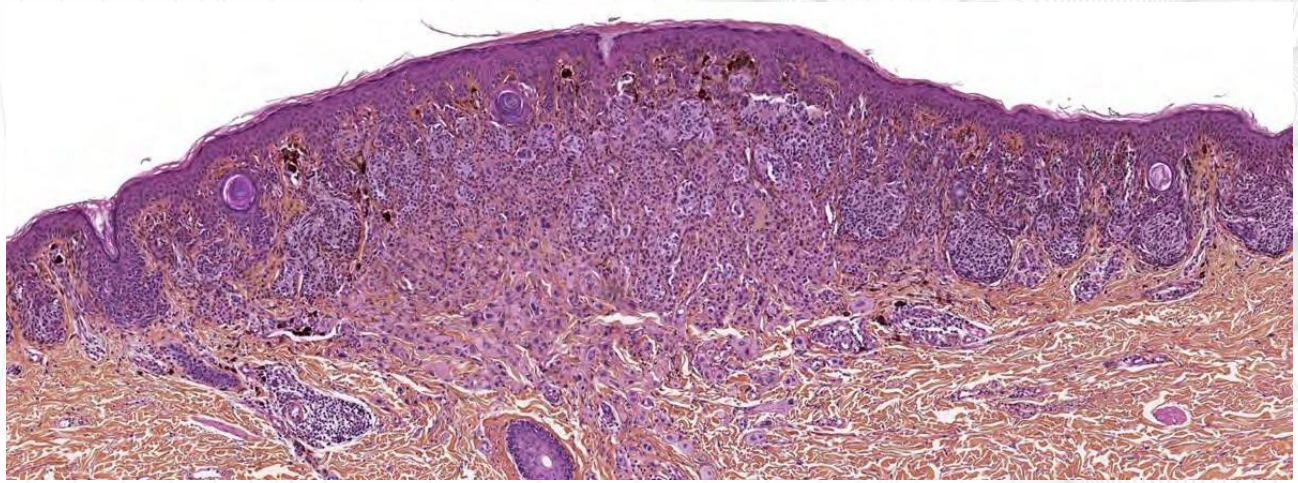

Genetic drivers of common nevi Positivity rules out a Blue or Spitz group tumor (except *HRAS* mutated desmoplastic nevus)

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- HMB45
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- BRAF V600E specific
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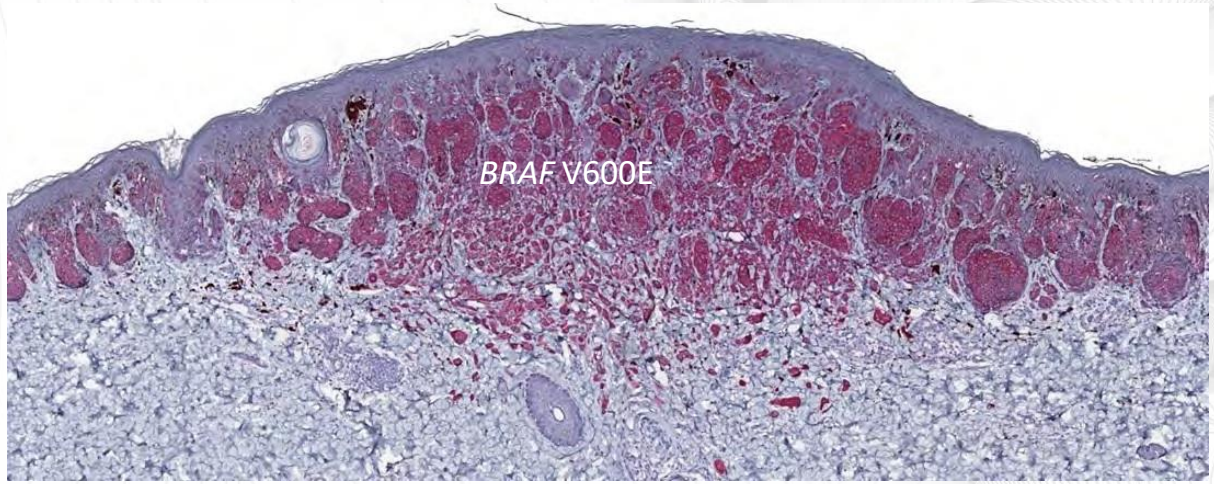
- ROS1
- Pan-TRK
- BAP1
- Betacatenin
- PRKAR1A
- New specific antibodies

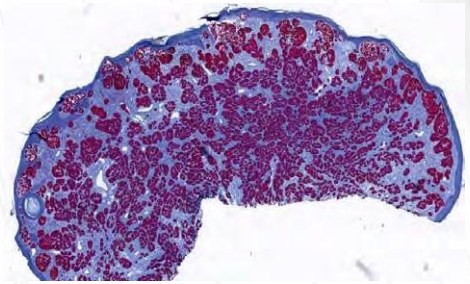


Genetic drivers of Spitz nevi

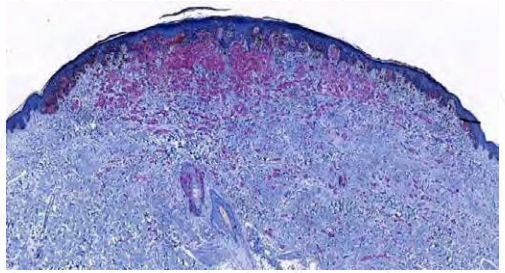
- MelanA
- HMB45
- P16
- Ki67
- BRAFV600E
- NRAS Q61R
- ALK
- ROS1
- Pan-TRK
- BAP1
- Betacatenin
- PRKAR1A
- New specific antibodies

Genetic drivers of Spitz nevi
Positivity rules out a Blue or common group tumor

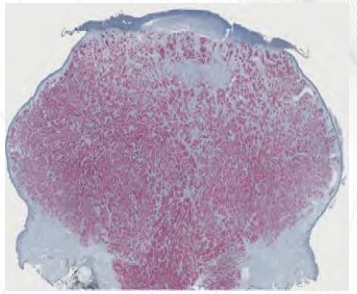
- MelanA
- HMB45
- P16
- Ki67
- BRAFV600E
- NRAS Q61R
- ALK
- ROS1
- Pan-TRK



Pan-TRK (suggesting NTRK1)



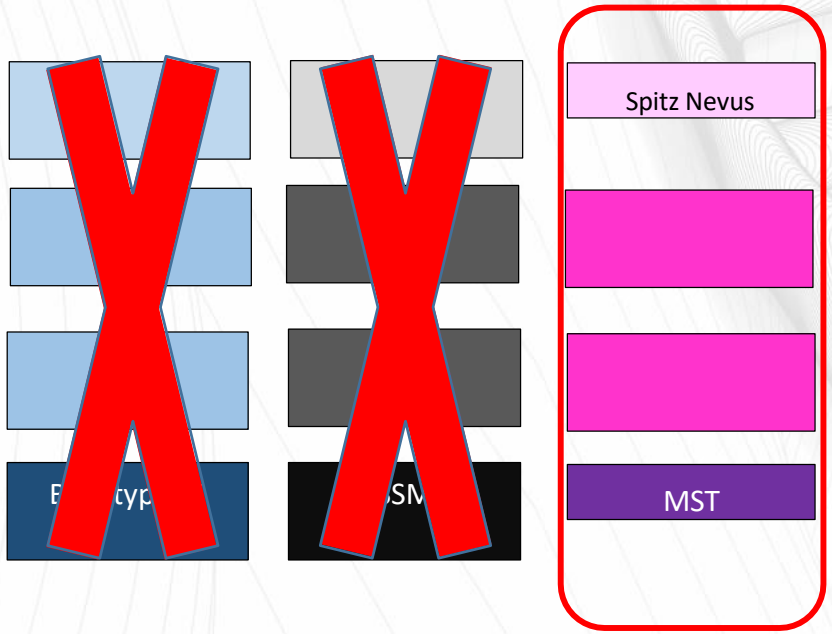
ROS1

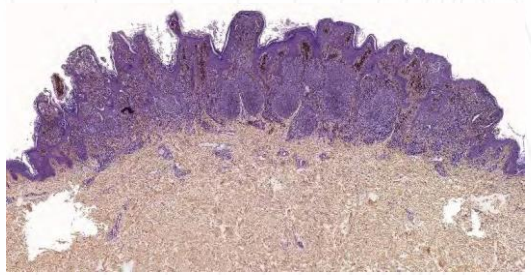


ALK

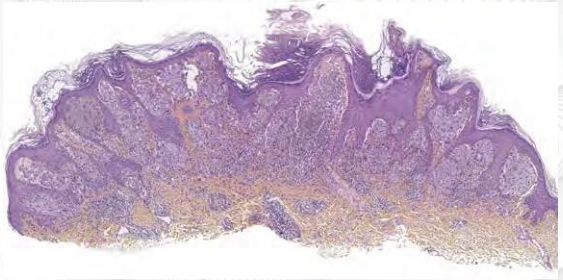
Genetic drivers of Spitz nevi
Positivity rules out a Blue or common group tumor

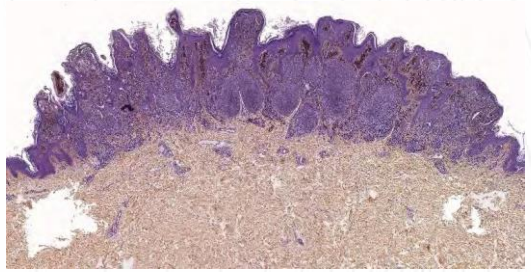
- MelanA
- HMB45
- P16
- Ki67
- BRAFV600E
- NRAS Q61R
- ALK
- ROS1
- Pan-TRK
- BAP1
- Betacatenin
- PRKAR1A
- New specific antibodies

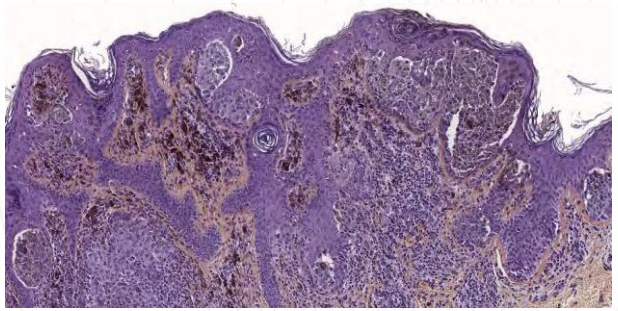




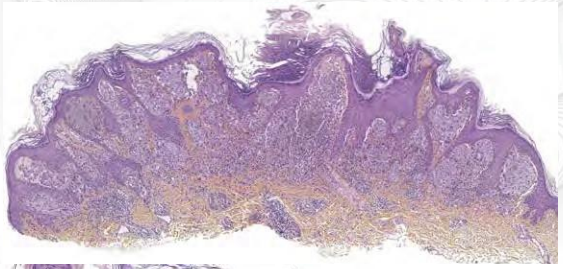

SSM
Spitz
imgflip.com
JAKE-CLARK.TUMBLR

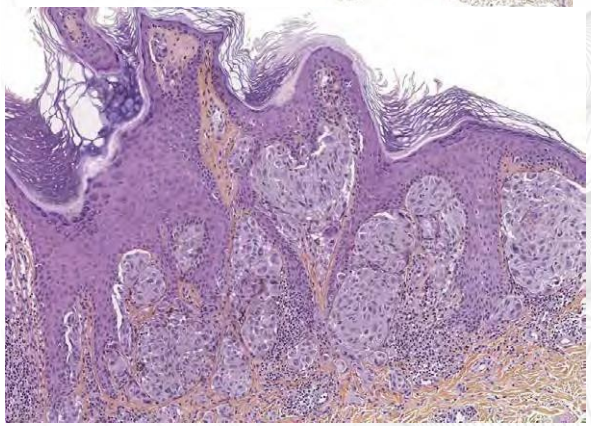


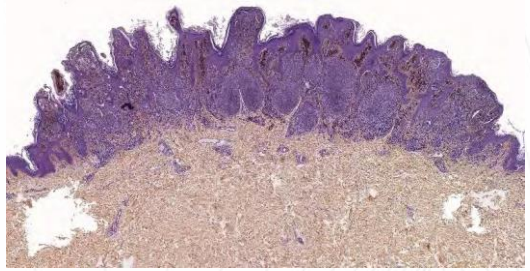


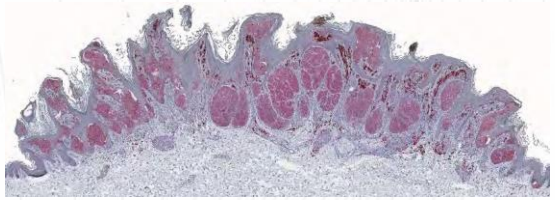



SSM
Spitz
imgflip.com
JAKE-CLARK.TUMBLR

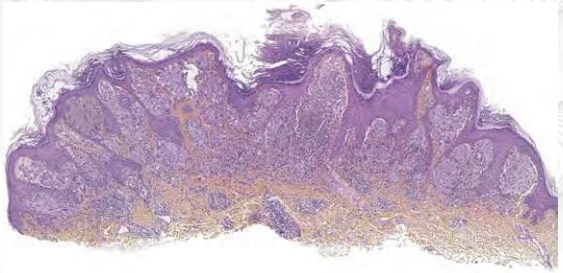


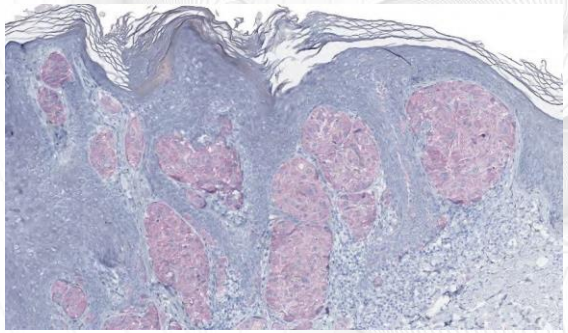




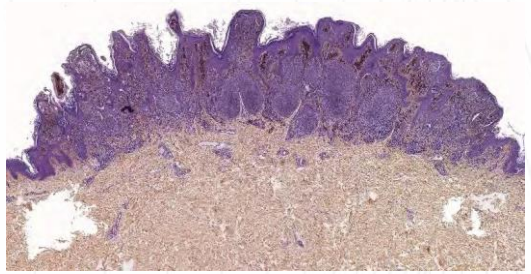


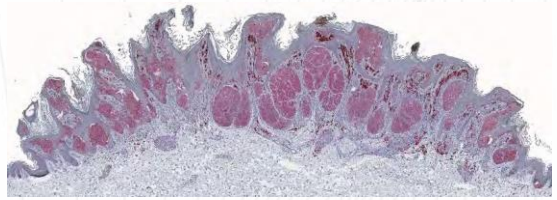
BRAF V600E IHC





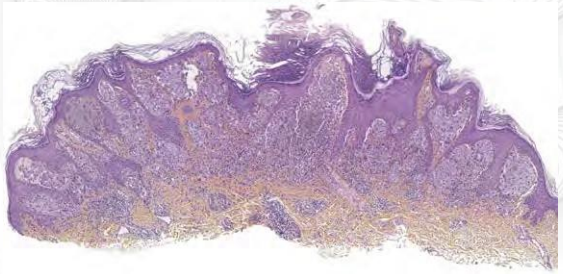
ROS1 IHC

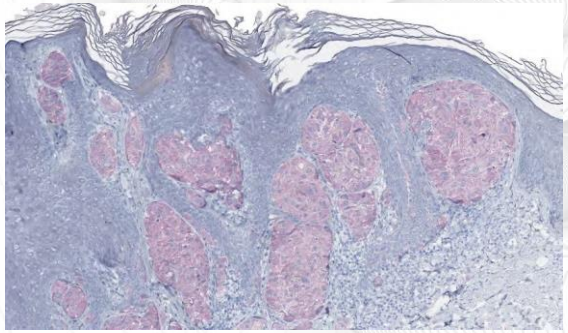




BRAF V600E IHC

SSM





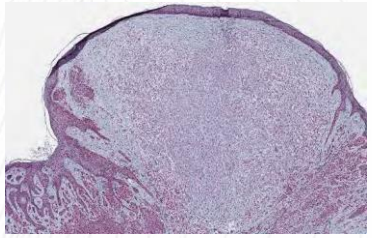
ROS1 IHC

Spitz nevus

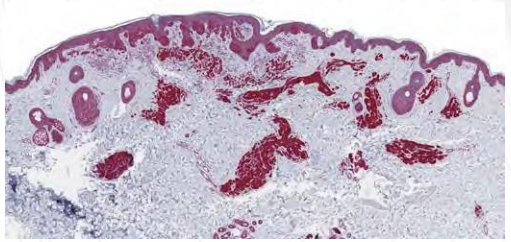
IHC screening for passenger mutations

- MelanA
- HMB45
- P16
- Ki67
- BRAFV600E
- NRAS Q61R
- ALK
- ROS1
- Pan-TRK
- BAP1
- Betacatenin (DPN)
- PRKAR1A (PEM)
- Newer AB PRAME

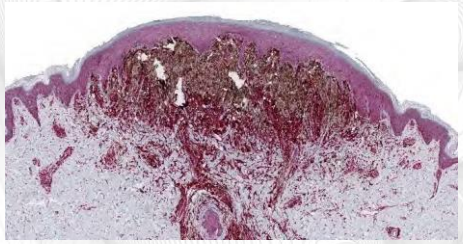
Secondary events, biphenotypic (clonal) morphology



BAP1



Beta-catenin



PRKAR1A

PRAME
Preferentially Expressed Antigen in Melanoma

- Nuclear immunostain
- Frequently diffuse pattern of immunoreactivity in in situ, invasive and metastatic melanoma
- Negative or focal staining seen in nevi and normal background melanocytes

Intermediate grade clonal melanocytic tumours

Table 2.06 Classification of melanomas and precursor lesions on the basis of epidemiological, clinical, pathological, and genomic attributes

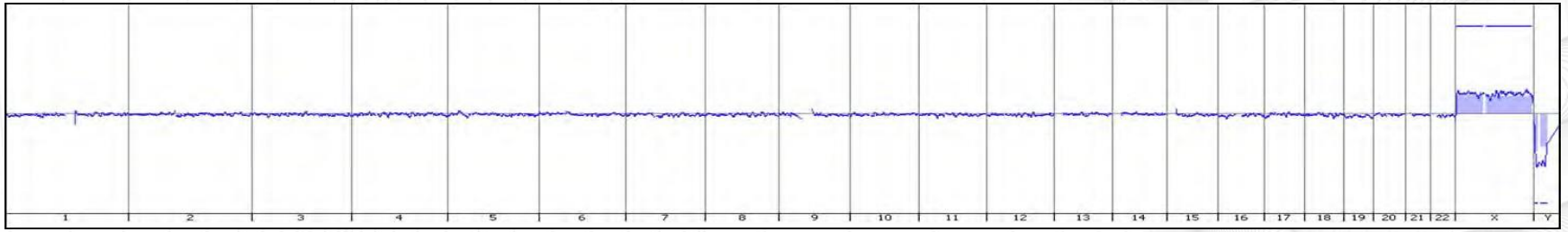
	Low UV radiation exposure/CSD				High UV radiation exposure/CS	
Pathway	I				II	III
Endpoint of pathway	Low-CSD melanoma/SSM				High-CSD melanoma/LMM	Desmoplastic melanoma
Benign neoplasms (naevi)	Naevus				? IMP	? IMP
Intermediate/low-grade dysplasias and melanocytomas	Low-grade dysplasia	BIN	DPN		? IAMP/dysplasia	? IAMP/dysplasia
Intermediate/high-grade dysplasias and melanocytomas	High-grade dysplasia/MIS	*BAP1*-inactivated melanocytoma/MELTUMP	Deep penetrating melanocytoma/MELTUMP	PEM/MELTUMP	Lentigo maligna (MIS)	MIS
Malignant neoplasms	Low-CSD melanoma/SSM (VGP)	Melanoma in BIN (rare)	Melanoma in DPN (rare)	Melanoma in PEM (rare)	LMM (VGP)	Desmoplastic melanoma
Common mutations[a,b]	***BRAF*** **p.V600E**; ***NRAS***	***BRAF*** or ***NRAS*** + ***BAP1***	***BRAF***, ***MAP2K1***, or ***NRAS*** + ***CTNNB1*** or ***APC***	***BRAF*** + ***PRKAR1A*** or ***PRKCA***	***NRAS***; ***BRAF*** ***(non-p.V600E)***; ***KIT***; ***NF1***	***NF1***; ***ERBB2***; ***MAP2K1***; ***MAP3K1***; ***BRAF***; ***EGFR***; ***MET***
	TERT; ***CDKN2A***; ***TP53***; ***PTEN***				***TERT***; ***CDKN2A***; ***TP53***; ***PTEN***; ***RAC1***	***TERT***; ***NFKBIE***; ***NRAS***; ***PIK3CA***; ***PTPN11***

BIN, *BAP1*-inactivated naevus; **BN**, blue naevus; **CBN**, cellular blue naevus; **CN**, congenital naevus; **CSD**, cumulative sun damage; **DPN**, deep penetrating naevus; **IAMP**, intraepidermal atypical melanocytic proliferation; **IAMPUS**, intraepidermal atypical melanocytic proliferation of uncertain significance; **IMP**, intraepidermal melanocytic proliferation without atypia; **LMM**, lentigo maligna melanoma; low/high-CSD melanoma, melanoma in skin with a low/high degree of cumulative sun damage; **MELTUMP**, melanocytic tumour of uncertain malignant potential; **MIS**, melanoma in situ; **PEM**, pigmented epithelioid melanocytoma; **SSM**, superficial spreading melanoma; **STUMP**, spitzoid tumour of uncertain malignant potential; **UV**, ultraviolet; **VGP**, vertical growth phase (tumorigenic and/or mitogenic melanoma).

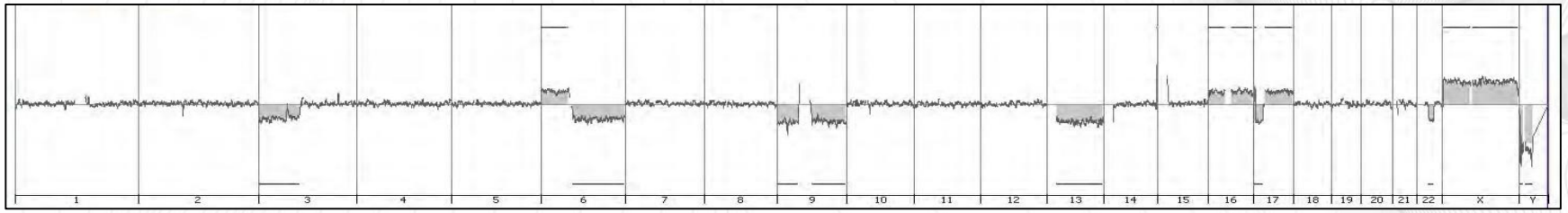
Diagnostic tools

- IHC: screening tool for molecular driver/passengers alteration or immunophenotype aberations
- Potential enticement to use other confirmation tools
- aCGH: whole genome screen of gains and losses on chromosomes
- Analysis of specific gene exons for mutations/deletions (panel)

Chromosomal microrray-
Comparative Genomic Hybridization (CGH)



Compound Nevus



Iso 6p

9 loss

with homozygeous CDKN2A deletion

p16 loss by IHC

Melanoma

Array-Comparative Genomic Hybridization

- Can suggest a transformed status (threshold?)
- In par with the step by step acquisition of anomalies
- Range of anomalies detected (unbalanced breakpoints, amplification, deletion)
- Tumor specific patterns

Diagnostic tools

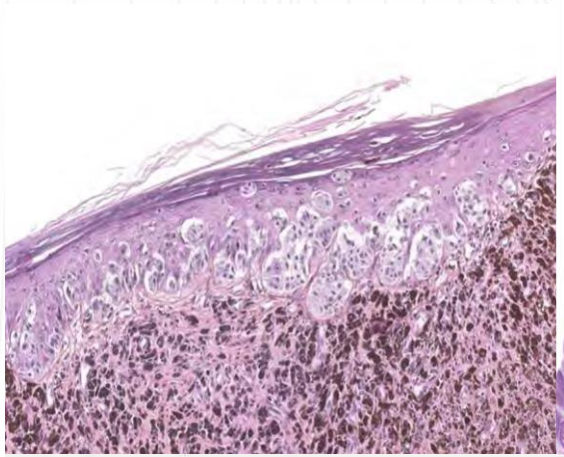
- IHC: screening tool for molecular driver/passengers alteration or immunophenotype aberations
- Potential enticement to use other confirmation tools
- aCGH: whole genome screen of gains and losses on chromosomes
- NGS: Analysis of specific gene exons for mutations/deletions

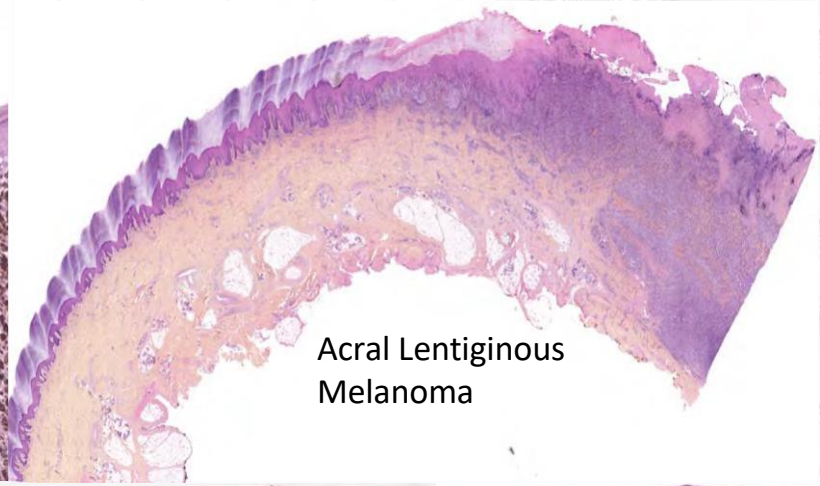
Next Generation Sequencing

- IHC: screening tool for molecular driver/passengers alteration or immunophenotype aberations
- Potential enticement to use other confirmation tools
- aCGH: whole genome screen of gains and losses on chromosomes
- Analysis of specific gene exons for mutations/deletions (panel)

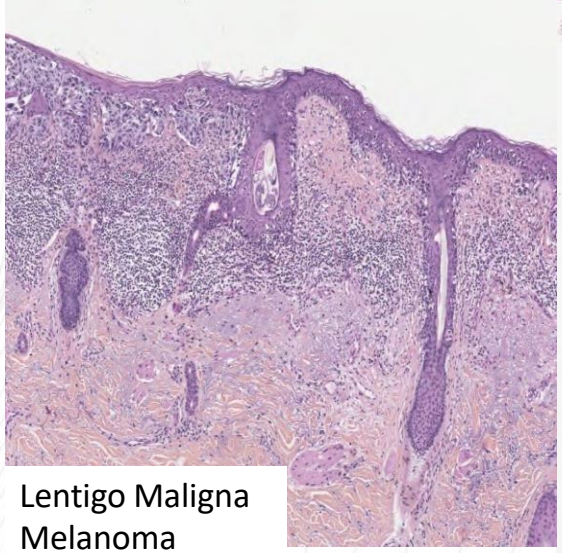
Mutations : AKT1 (3) , ALK (22, 23, 24, 25), AXL (5, 11, 15, 17), BRAF (11, 15) , CTNNB1 (3), CYSLTR2 (6*), DDR2 (17) , EGFR (18, 19, 20, 21), ERBB2 (20), FGFR1 (2, 8, 9, 10, 17), FGFR2 (2, 5, 7, 8, 9, 10), FGFR3 (3, 5, 8, 9, 10), GNA11 (4,5), GNAS (8, 9), GNAQ (4,5), HRAS (2, 3, 4), IDH1 (4), IDH2 (4), KEAP1 (ful), KIT (11, 13, 17), KRAS (2, 3, 4), MAP2K1 (2, 3) , MET (13 à 19), NRAS (2, 3, 4), PIK3CA (9, 20), POLE (9 à 14), RAF1 (4, 5, 6, 7, 9, 10, 11, 12), RET (11, 13, 14, 15, 16), ROS1 (38), STK11 (full), TP53 (full)
Fusion : ALK, AXL, BRAF, CCND1, EGFR, FGFR1, FGFR2, FGFR3, MAP2K1, MET, NRG1, NTRK1, NTRK2, NTRK3, PPARG, RAF1, RET, ROS1
Expression : ALK, CCND1, EGFR, ERBB2, FGFR1, FGFR2, FGFR3, MET, NTRK1, NTRK2, NTRK3, RET, ROS1

Superficial Spreading Melanoma

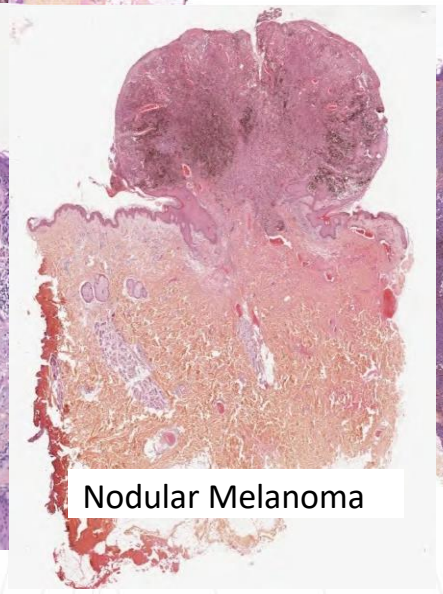




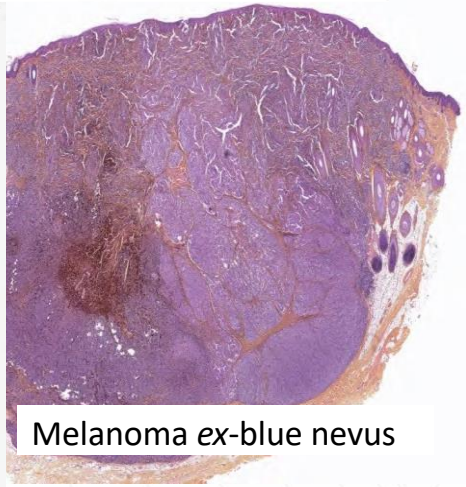
Acral Lentiginous Melanoma



Lentigo Maligna Melanoma

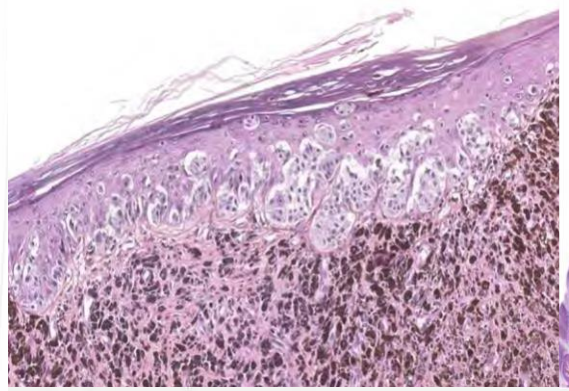


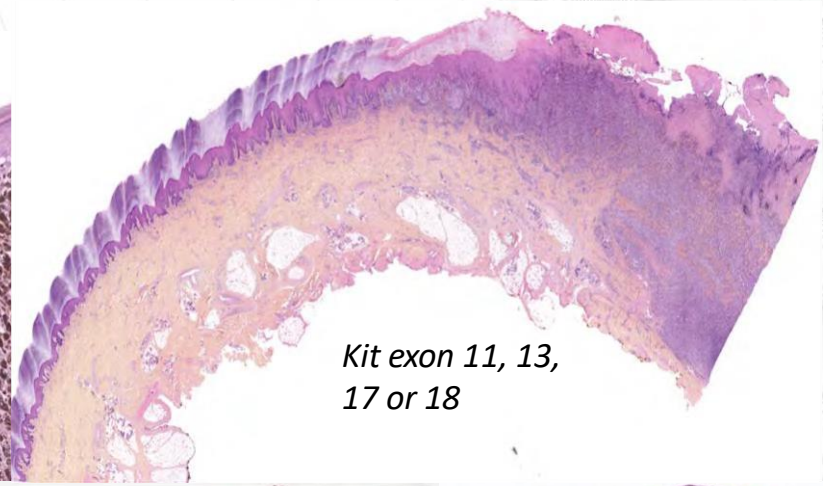
Nodular Melanoma



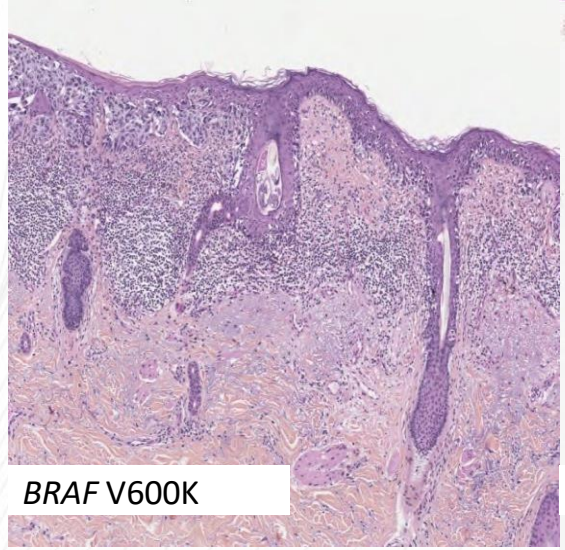
Melanoma *ex*-blue nevus

BRAF V600E

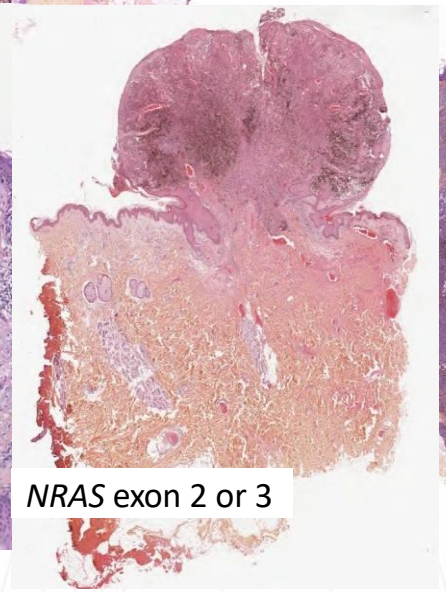




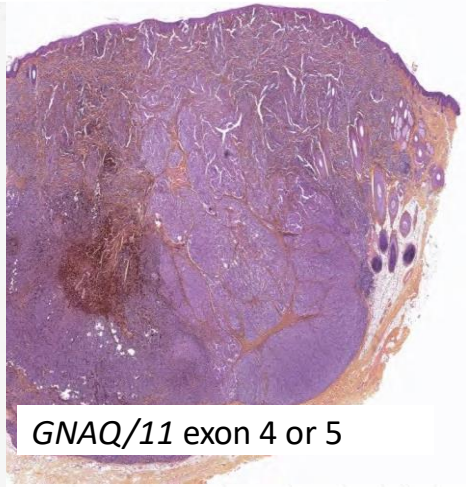
Kit exon 11, 13, 17 or 18



BRAF V600K



NRAS exon 2 or 3



GNAQ/11 exon 4 or 5

Fluorescent *in situ* Hybridization (FISH)

- IHC: screening tool for molecular driver/passengers alteration or immunophenotype aberations
- Potential enticement to use other confirmation tools
- aCGH: whole genome screen of gains and losses on chromosomes
- NGS: analysis of specific gene exons for mutations/deletions (DNA)
- Specific DNA probes confirm the anomaly is present in the tumoral cells (rearrangement, deletion, amplification)

Nevus

4 step progression scheme of melanocytic tumors (WHO 2018)

Single driver anomaly

Low grade «melanocytoma»

High grade «melanocytoma»

Melanoma

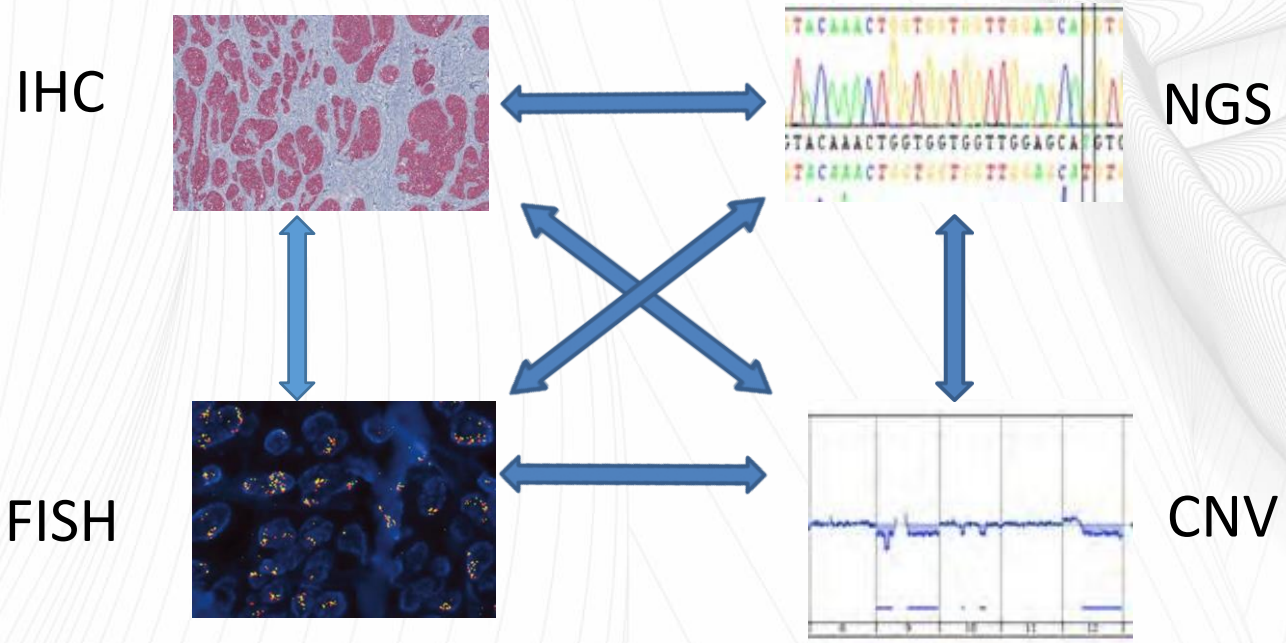
Multiple genomic alterations

Table 2.06 Classification of melanomas and precursor lesions on the basis of epidemiological, clinical, pathological, and genomic attributes

	Low UV radiation exposure / CSD				High UV radiation exposure / CS	
Pathway	I				II	III
Endpoint of pathway	Low-CSD melanoma / SSM				High-CSD melanoma / LMM	Desmoplastic melanoma
Benign neoplasms (naevi)	Naevus				? IMP	? IMP
Intermediate / low-grade dysplasias and melanocytomas	Low-grade Low grade dysplasia	BIN	DPN		? IAMP/dysplasia	? IAMP/dysplasia
Intermediate / high-grade dysplasias and melanocytomas	High grade /MIS	*BAP1*-inactivated melanocytoma / MELTUMP	Deep penetrating melanocytoma / MELTUMP	PEM / MELTUMP	Lentigo maligna (MIS)	MIS
Malignant neoplasms	Low-CSD melanoma / SSM (VGP)	Melanoma in BIN (rare)	Melanoma in DPN (rare)	Melanoma in PEM (rare)	LMM (VGP)	Desmoplastic melanoma
Common mutations[a,b]	***BRAF*** p.V600E; ***NRAS***	***BRAF*** or ***NRAS*** + ***BAP1***	***BRAF***, ***MAP2K1***, or ***NRAS*** + ***CTNNB1*** or ***APC***	***BRAF*** + ***PRKAR1A*** or ***PRKCA***	***NRAS***; ***BRAF*** *(non-p.V600E)*; ***KIT***; ***NF1***	***NF1***; *ERBB2*; *MAP2K1*; *MAP3K1*; *BRAF*; *EGFR*; *MET*
	TERT; *CDKN2A*; *TP53*; *PTEN*				*TERT*; *CDKN2A*; *TP53*; *PTEN*; *RAC1*	*TERT*; *NFKBIE*; ***NRAS***; *PIK3CA*; *PTPN11*

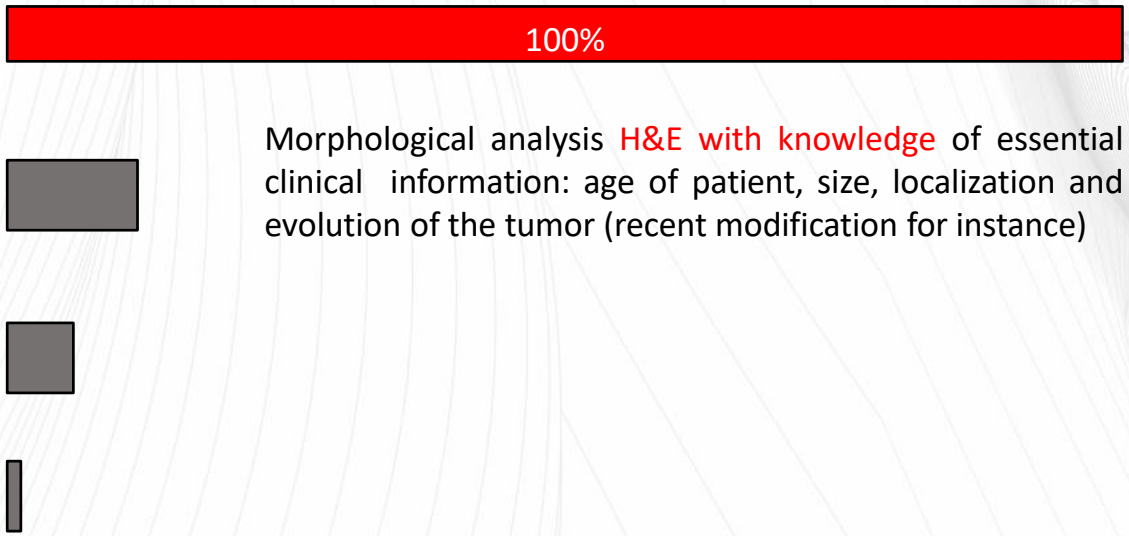
BIN, *BAP1*-inactivated naevus; **BN**, blue naevus; **CBN**, cellular blue naevus; **CN**, congenital naevus; **CSD**, cumulative sun damage; **DPN**, deep penetrating naevus; **IAMP**, intraepidermal atypical melanocytic proliferation; **IAMPUS**, intraepidermal atypical melanocytic proliferation of uncertain significance; **IMP**, intraepidermal melanocytic proliferation without atypia; **LMM**, lentigo maligna melanoma; low/high-CSD melanoma, melanoma in skin with a low/high degree of cumulative sun damage; **MELTUMP**, melanocytic tumour of uncertain malignant potential; **MIS**, melanoma in situ; **PEM**, pigmented epithelioid melanocytoma; **SSM**, superficial spreading melanoma; **STUMP**, spitzoid tumour of uncertain malignant potential; **UV**, ultraviolet; **VGP**, vertical growth phase (tumorigenic and/or mitogenic melanoma).

Molecular Tools: use is guided by clinical morphological features



Usefulness of molecular pathology in cutaneous melanocytic tumors

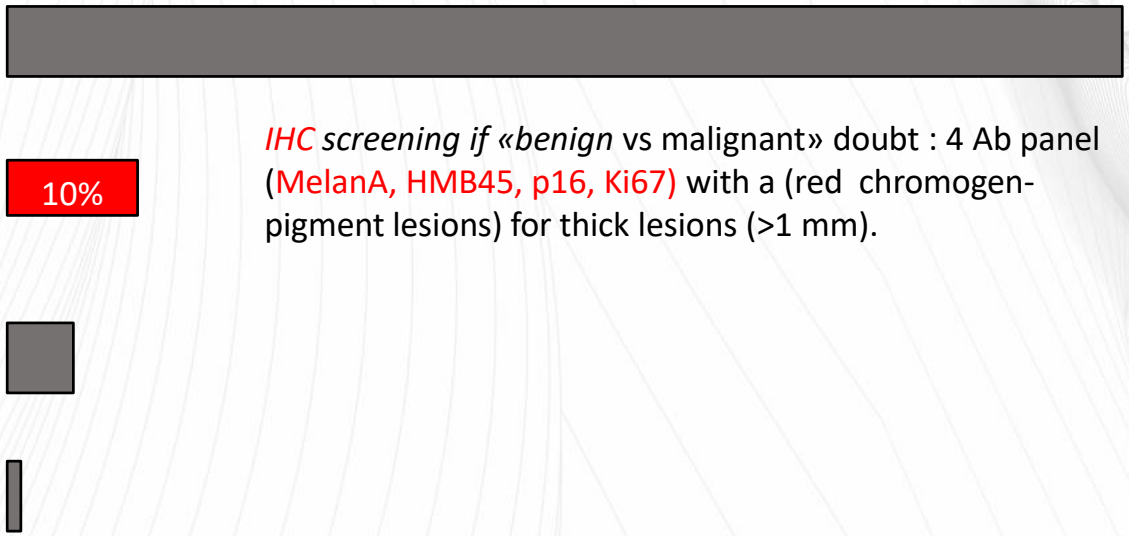
- Level 1



Morphological analysis H&E with knowledge of essential clinical information: age of patient, size, localization and evolution of the tumor (recent modification for instance)

Usefulness of molecular pathology in cutaneous melanocytic tumors

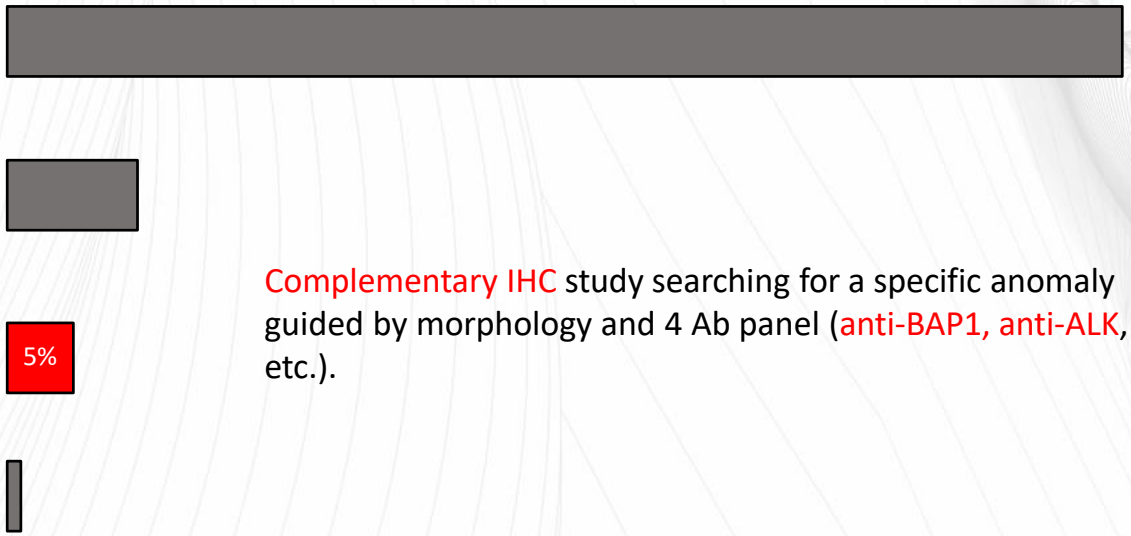
- Level 2



IHC screening if «benign vs malignant» doubt : 4 Ab panel (MelanA, HMB45, p16, Ki67) with a (red chromogen-pigment lesions) for thick lesions (>1 mm).

Usefulness of molecular pathology in cutaneous melanocytic tumors

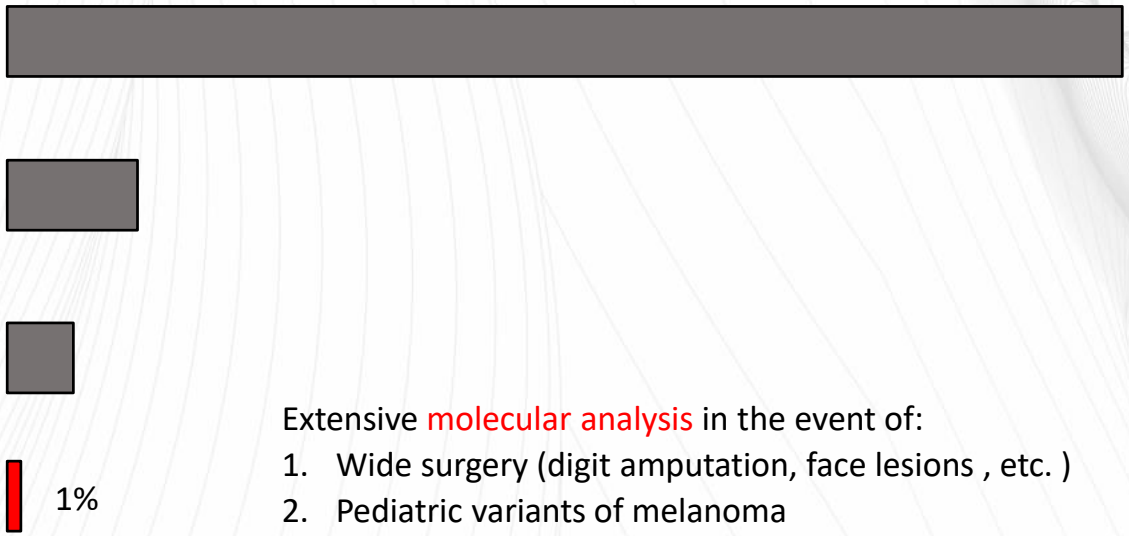
- Level 3



Complementary IHC study searching for a specific anomaly guided by morphology and 4 Ab panel (anti-BAP1, anti-ALK, etc.).

Usefulness of molecular pathology in cutaneous melanocytic tumors

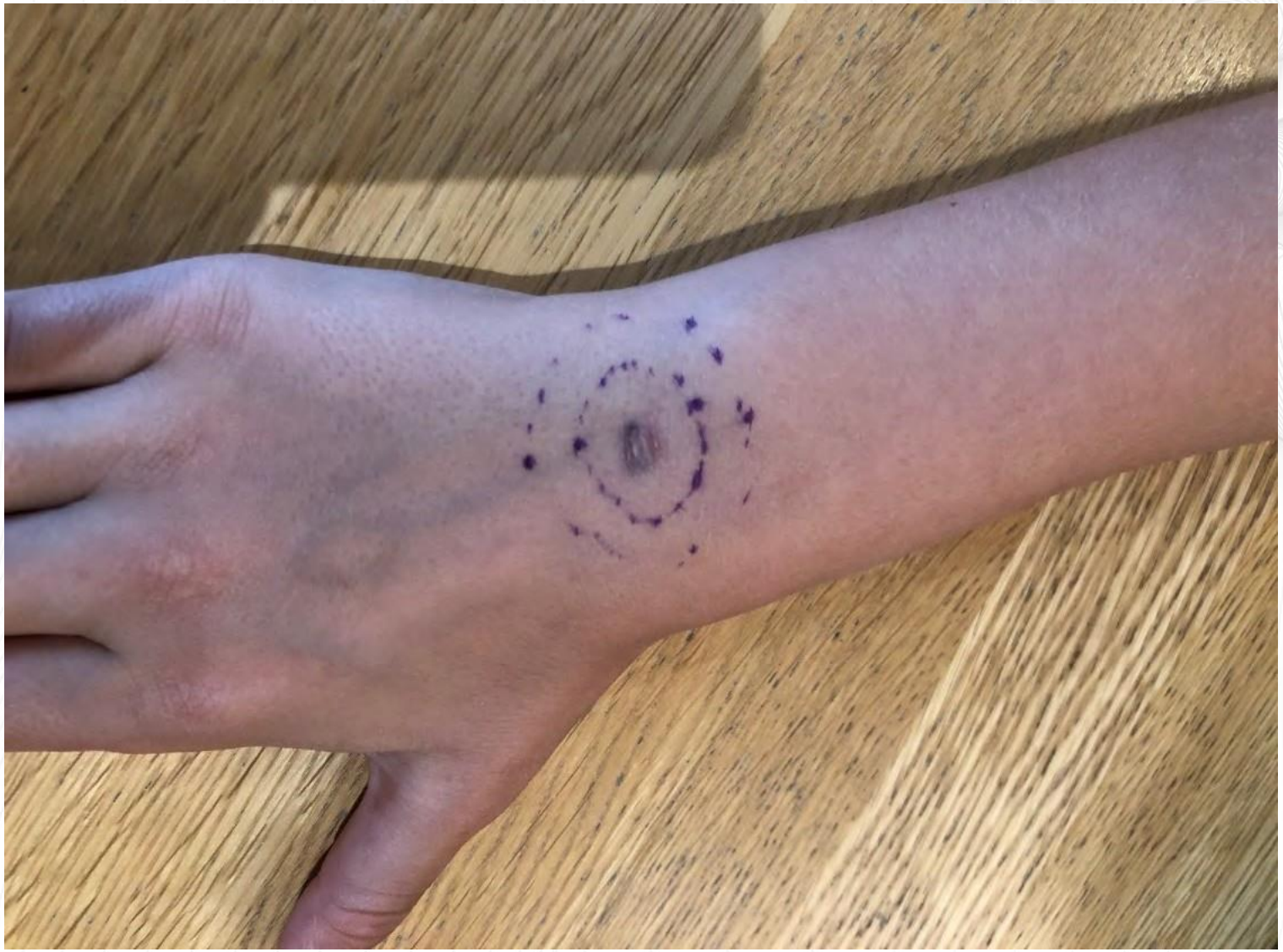
- Level 4



Extensive molecular analysis in the event of:

1. Wide surgery (digit amputation, face lesions , etc.)
2. Pediatric variants of melanoma
3. Rare melanocytic tumors (unclassified)
4. Difficult or borderlie histological pattern.

5mm vs 10mm resection?



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https://doi.org/10.1007/s00428-020-03005-1

ORIGINAL ARTICLE

ESP, EORTC, and EURACAN Expert Opinion: practical recommendations for the pathological diagnosis and clinical management of intermediate melanocytic tumors and rare related melanoma variants

Arnaud de la Fouchardiere[1] · Willeke Blokx[2] · Léon C. van Kempen[3] · Boštjan Luzar[4] · Sophie Piperno-Neumann[5,6] · Susana Puig[7,8,9] · Llucia Alos[8,10] · Eduardo Calonje[11] · Daniela Massi[12] · on behalf of the ESP Dermatopathology Working Group · EORTC Melanoma Group · EURACAN

Received: 25 May 2020 / Revised: 17 November 2020 / Accepted: 21 December 2020

Atypical melanocytic tumors Recommendations

- Expert opinion centers
- Diagnostic confirmation by molecular techniques mainly to rule out melanoma
- Multidisciplinary tumor board
- 2-10mm clinical margins+ follow up according to:

  -Clinical presentation

  -Morphology

  -Molecular anomalies

Shift from the concept of MelTUMP to High grade melanocytoma WHO 2018

- MELTUMP: Melanocytic Tumor of Unknown Malignant Potential
- ie “it could be a melanoma but maybe not”
- Pre-genetic era of uncertainty because no real test available
- ie “time will tell”

Shift from the concept of MelTUMP to High grade melanocytoma WHO 2018

- High grade melanocytoma WHO 2018
- Genetic tests are unable to confirm it is a malignant tumor
- Downscaling in grading and local treatment

Distinguishing Spitzoid from Spitz melanoma terminology

- Any melanoma can be called spitzoid if it displays morphologic features of the Spitz group.
- A Spitz melanoma means you have identified a typical genetic anomaly of the Spitz group…… Prognosis.

PMID: 31900433

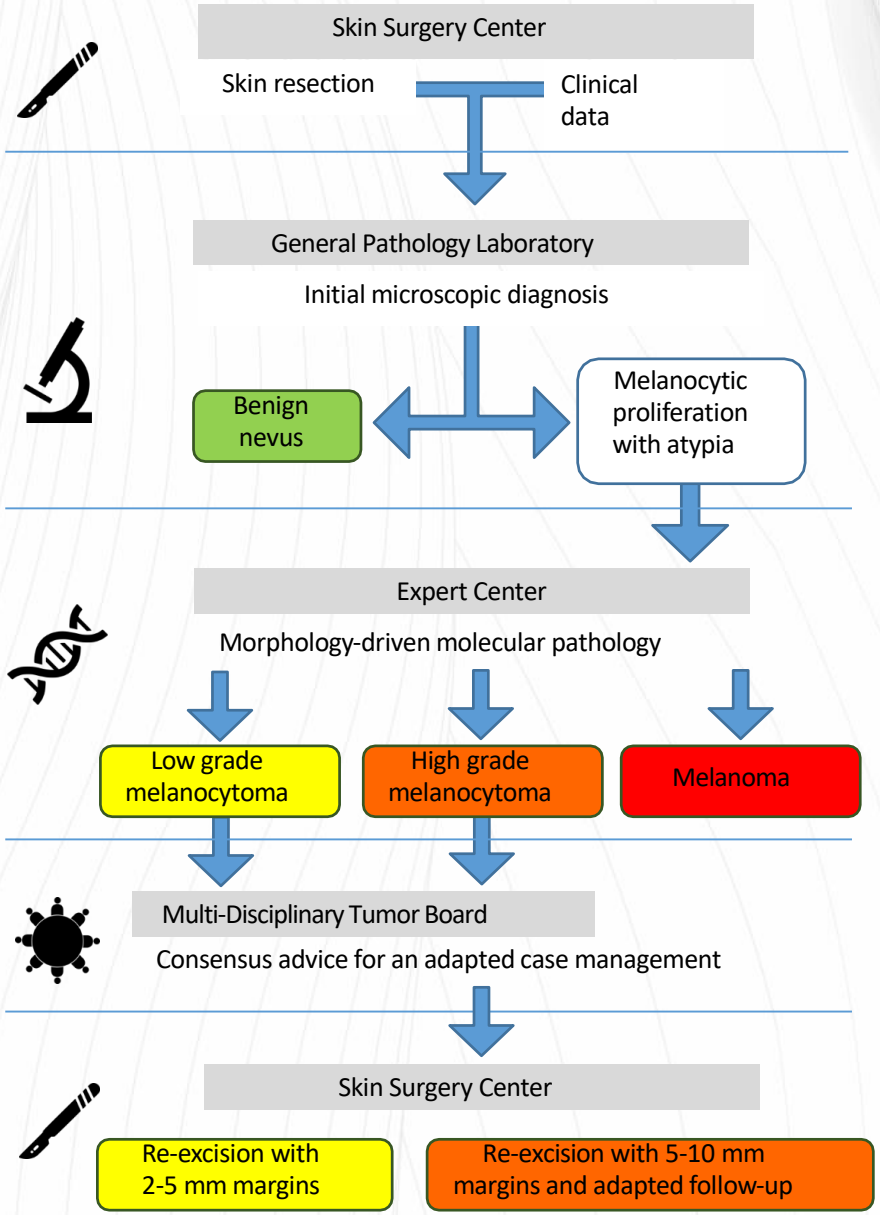

Skin Surgery Center
Skin resection
Clinical data
General Pathology Laboratory
Initial microscopic diagnosis
Benign nevus
Melanocytic proliferation with atypia
Expert Center
Morphology-driven molecular pathology
Low grade melanocytoma
High grade melanocytoma
Melanoma
Multi-Disciplinary Tumor Board
Consensus advice for an adapted case management
Skin Surgery Center
Re-excision with 2-5 mm margins
Re-excision with 5-10 mm margins and adapted follow-up

Table 3 Suggested resection margins for intermediate melanocytic tumors

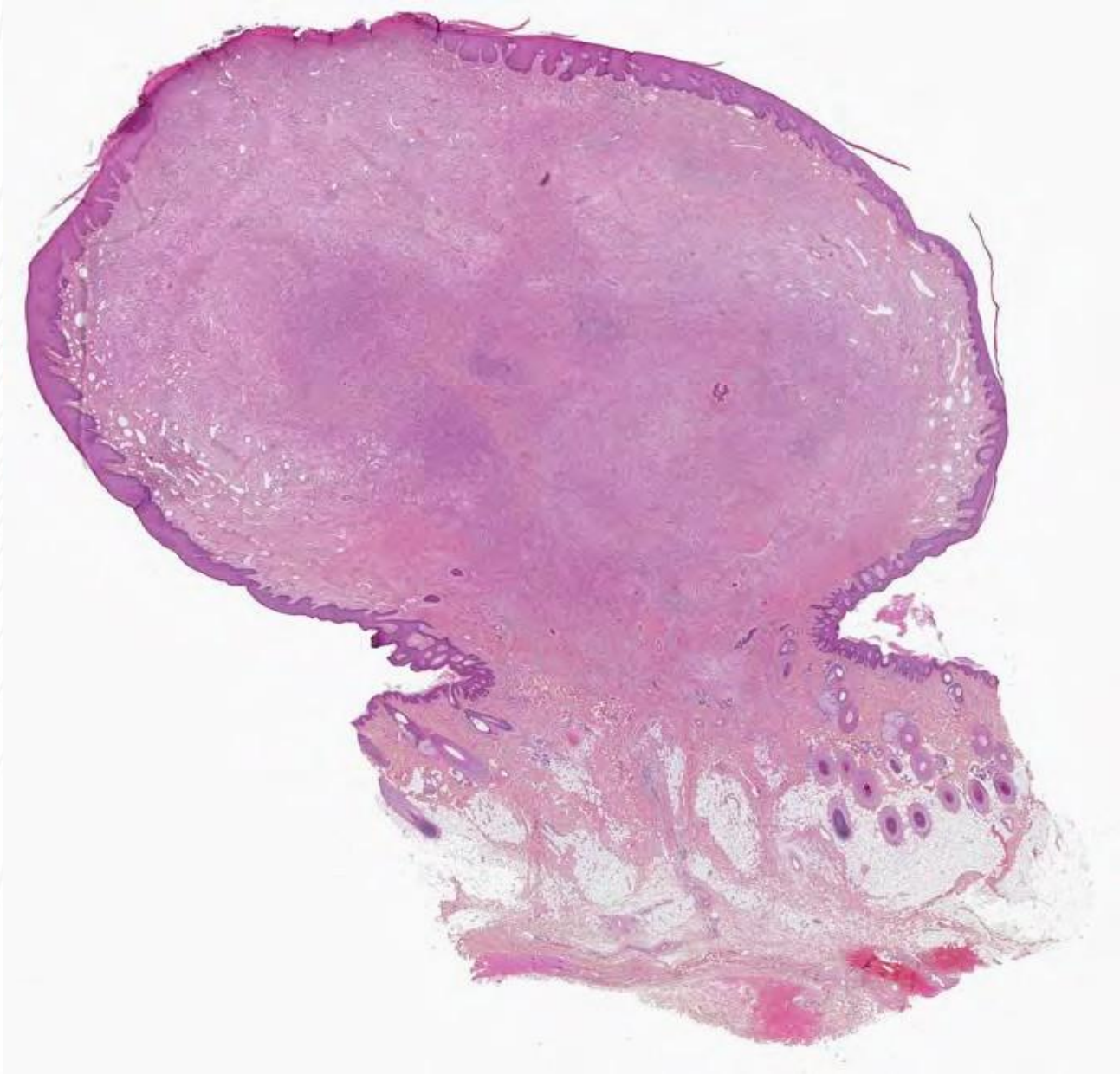
	Pathway 1-BAP1	Pathway 1-DPN	Pathway 1-PEM	Pathway 4 Spitz	Pathway 8 Ex-BN	Unclassified atypical dermal lesions
Low grade	2 mm	2 mm	NA	2 mm	2 mm	2–5 mm
High grade	5–10 mm	5–10 mm	5–10 mm	5–10 mm	5–10 mm	5–10 mm

DPN deep penetrating nevus, *PEM* pigmented epithelioid melanocytoma, *Ex-BN* ex blue nevus, *NA* not applicable

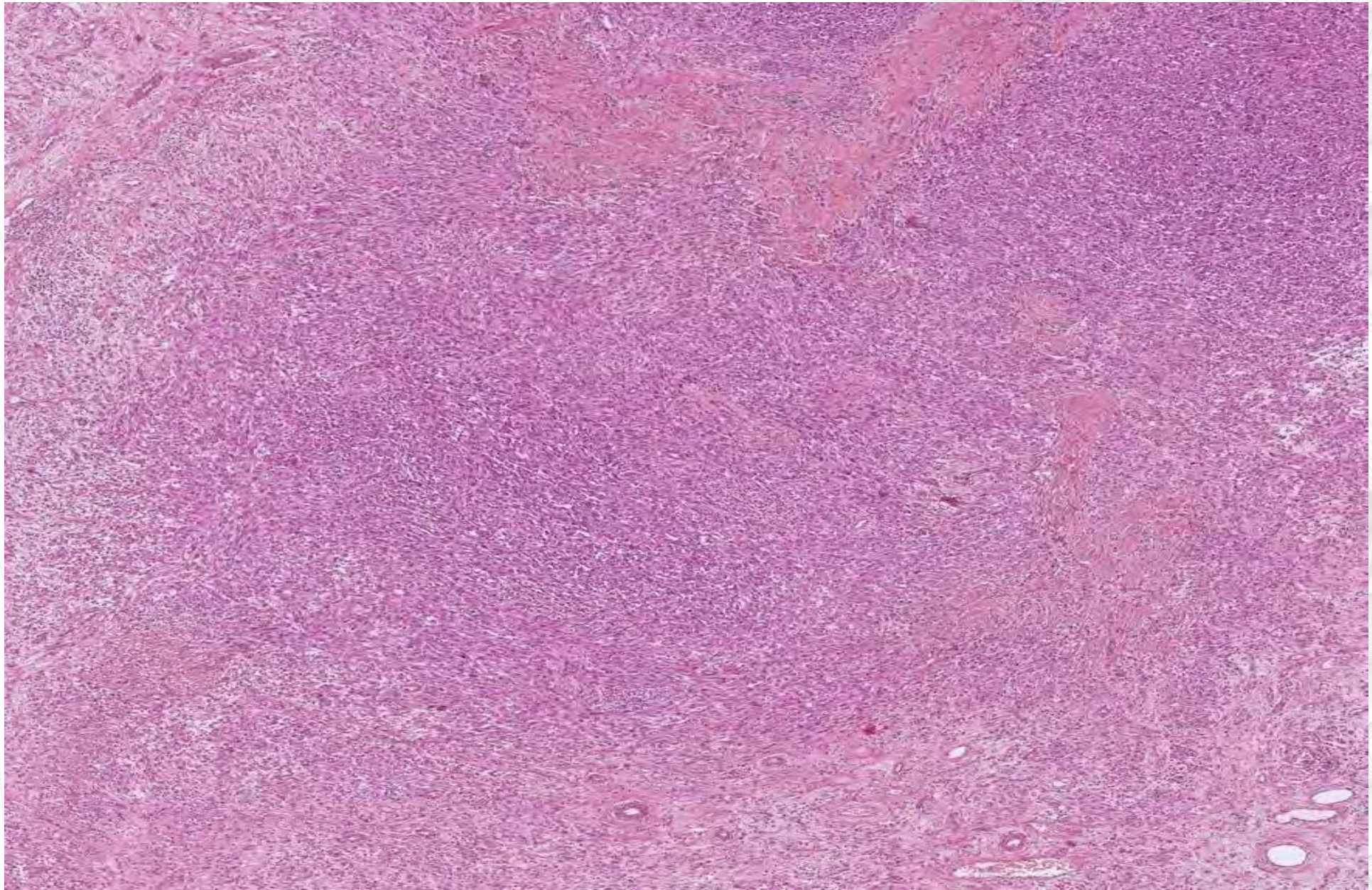
Molecular pathology of melanocytic tumors Take home messages

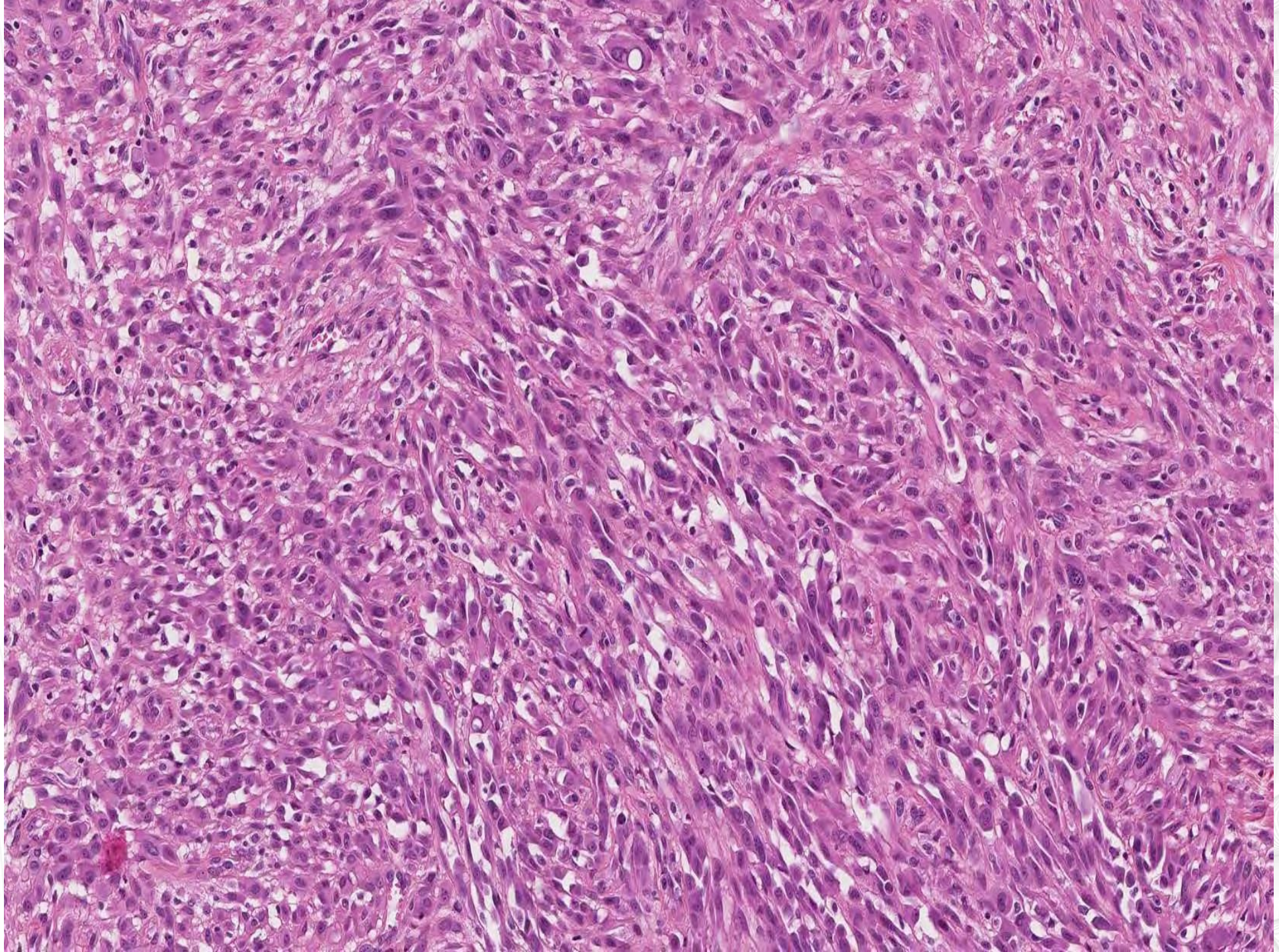
- Adapted to clinical and morphological setting
- Step by step process towards the final results
- Growing number of available techniques

M12 scalp

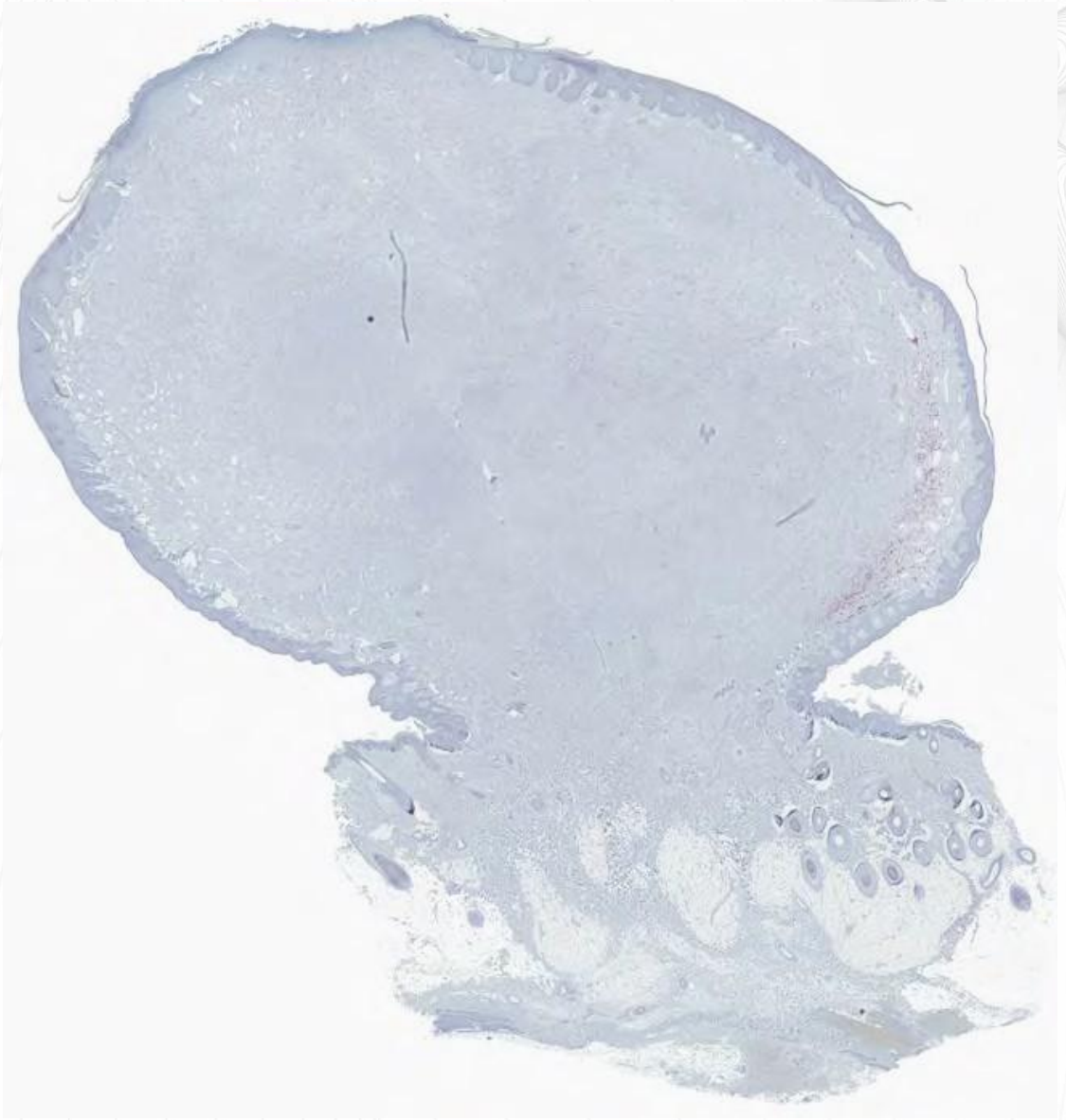


M12 scalp

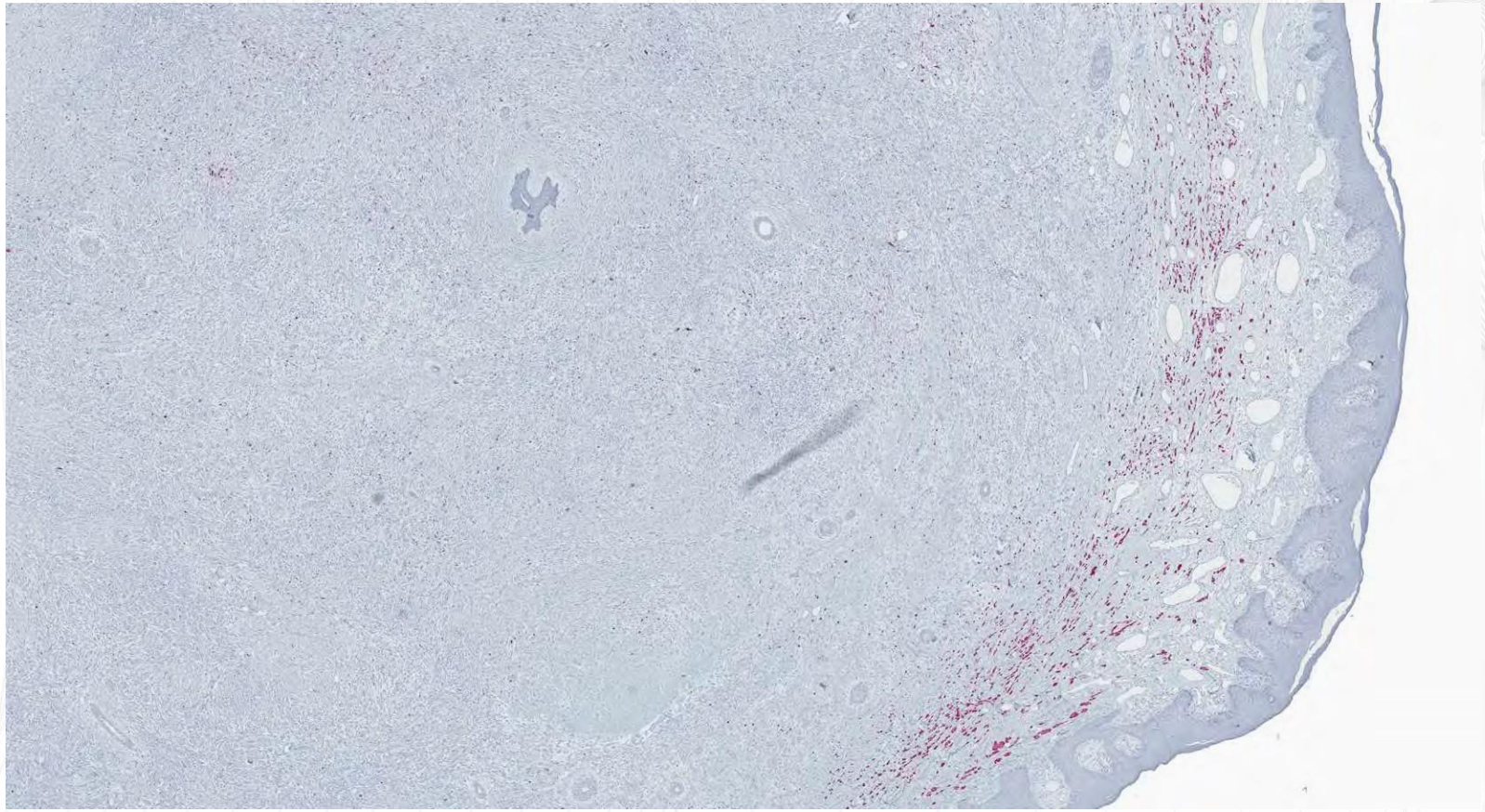




P16 clonal loss

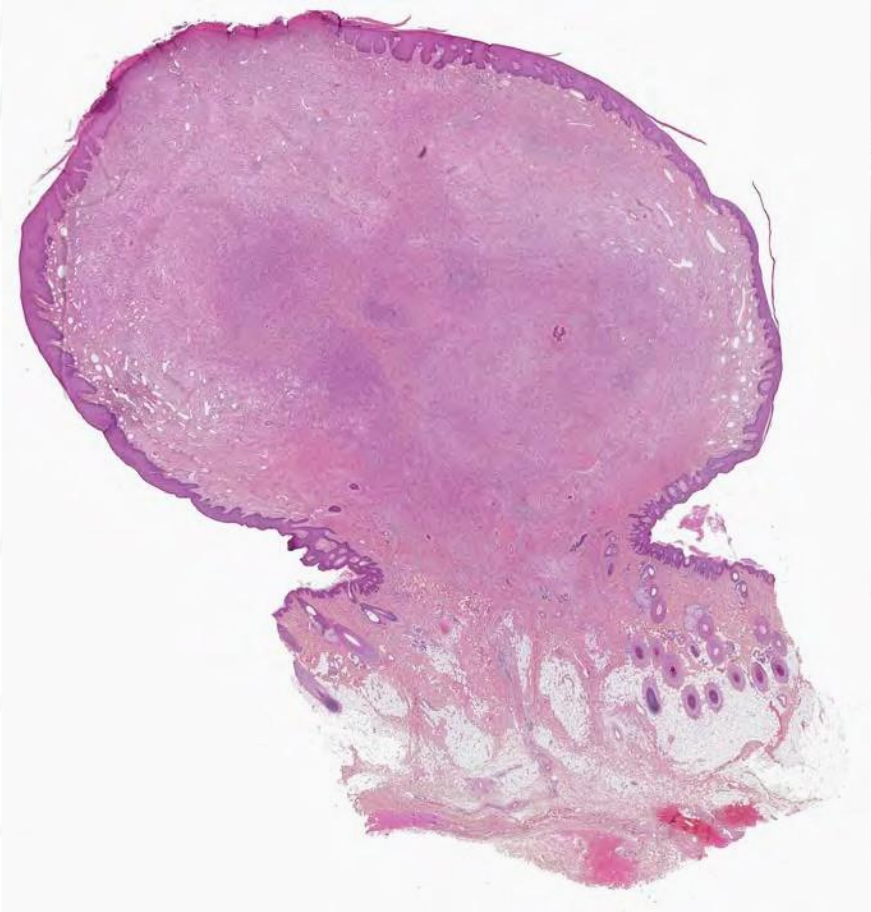


P16 clonal loss



High grade melanocytoma

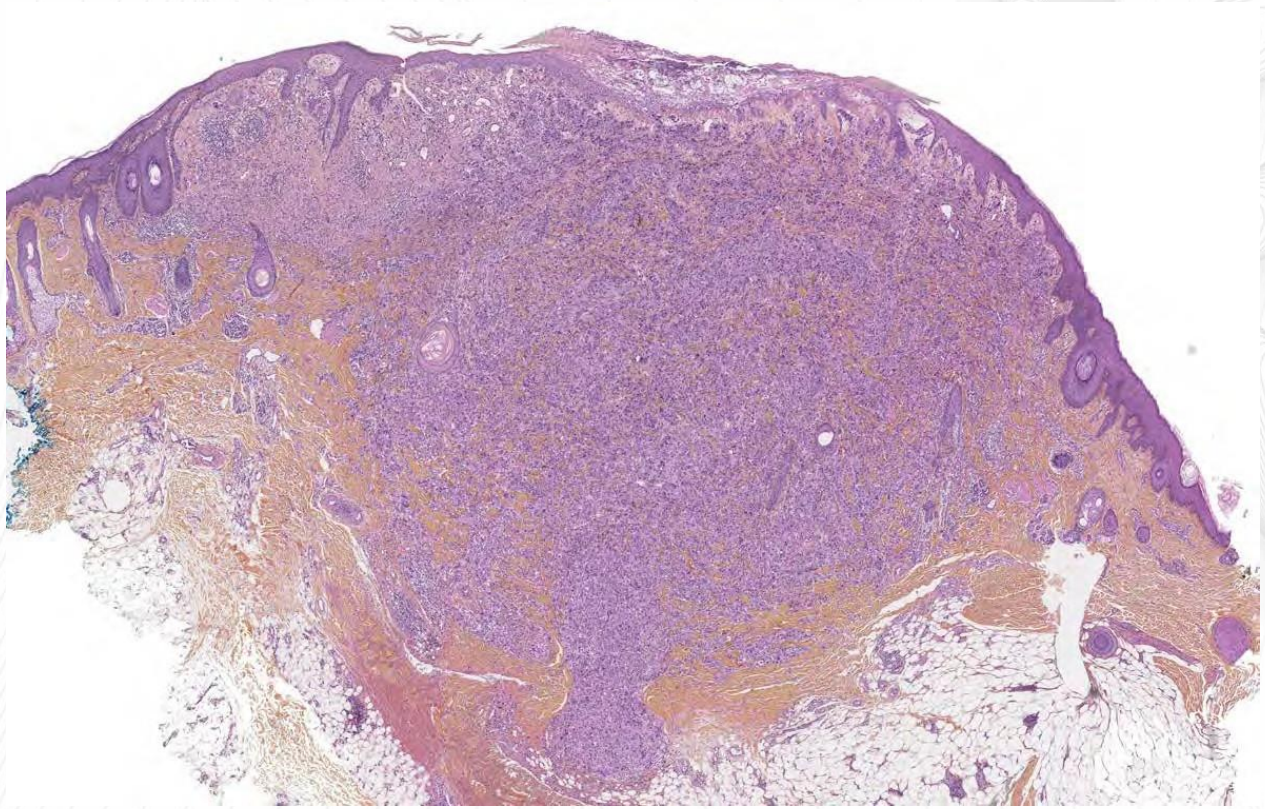
M12 scalp



High grade melanocytoma

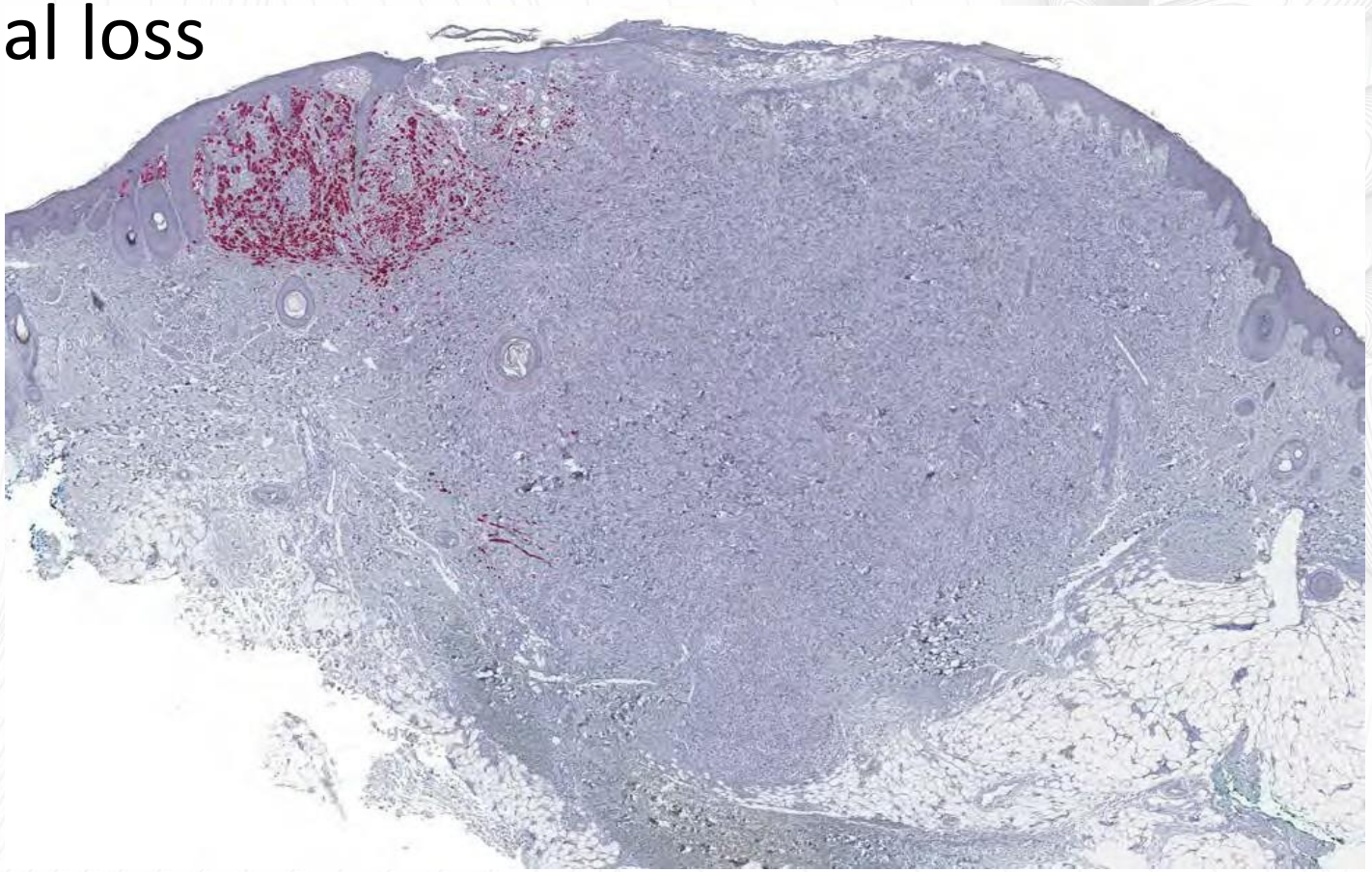
- M12 scalp
- Heterozygeous deletion of CDKN2A (IHC, FISH)
- CLIP2::BRAF fusion (RNA seq)

M8 Face



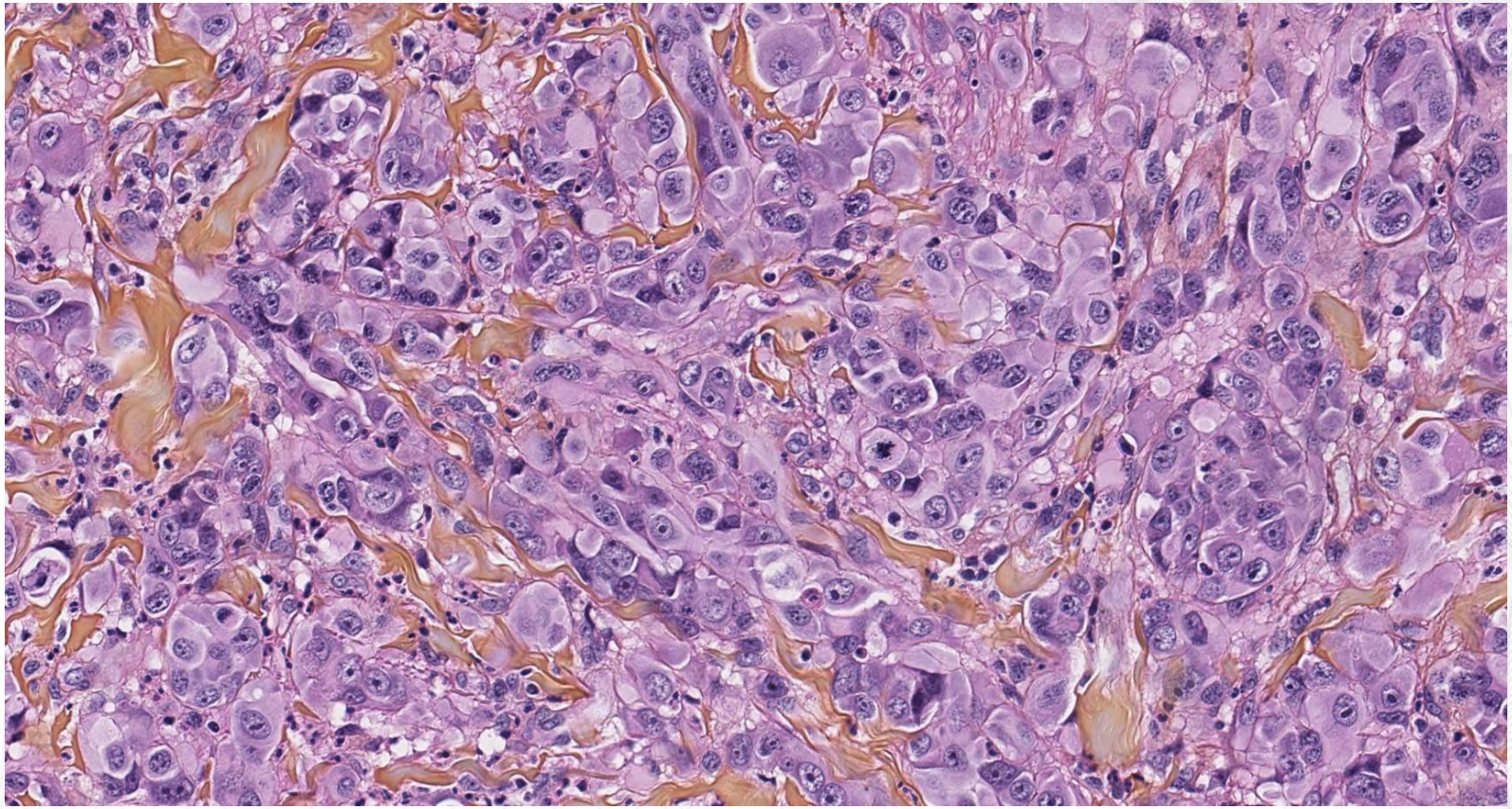
M8 Face

P16 IHC clonal loss



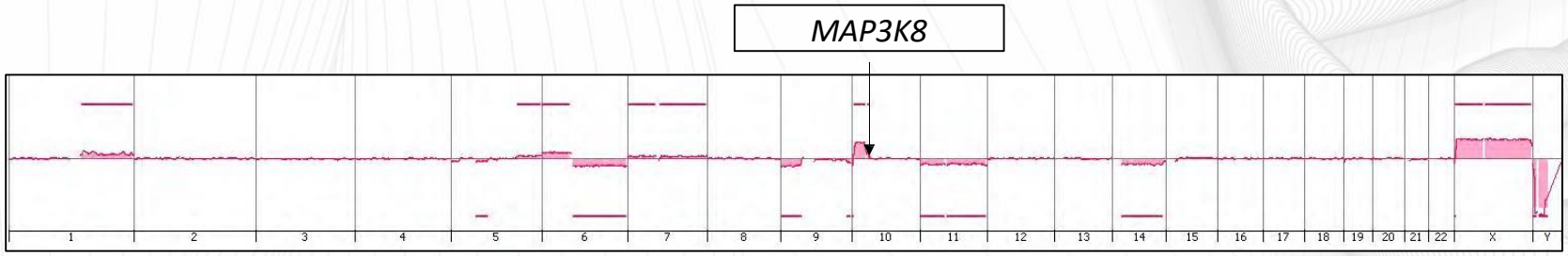
M8 Face

6 Mitoses /mm²



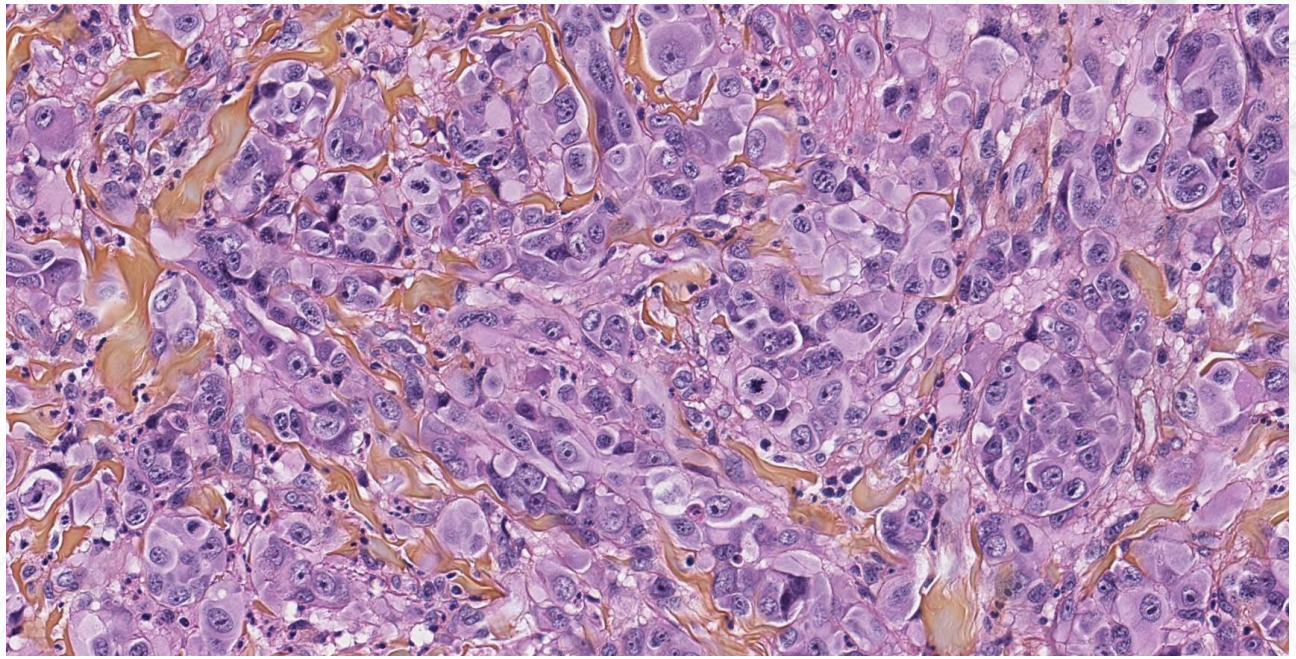
Array CGH: multiple segmental chromosome gains and losses

Array CGH: multiple segmental chromosome gains and losses



M8 Face

6 Mitoses /mm²



Malignant Spitz Tumour with *MAP3K8* fusion

Summary

- Understanding of the classification and prognosis of different melanocyti\ neoplasms is evolving with new developments of molecular findings.
- This would have a significant impact on treatment options available and prognosis.
- We need to be up-to-date with new concepts in melanoma classifications and molecular subtyping.

Why and when to do BRAF testing in melanomas

A. Therapeutic:
   - BRAF V600 is the only biomarker that predicts a therapeutic response in advanced melanoma.
   - It is important to note that the NCCN Clinical Practice Guidelines in Oncology (2017) do not recommend testing the primary cutaneous melanoma for the *BRAF* mutation unless required to guide systemic therapy.
   - BRAF inhibitors are approved only for use in patients with a *BRAF* V600 mutation detected by an FDA-approved test.
   - Patients with *BRAF* WT tumors may experience tumor promotion if treated with a BRAF inhibitor due to the paradoxical activity of the MAPK pathway in WT cells.

B. Diagnostic
   - Can be used to differentiate spitzoid melanomas from Spitz melanoma, together with other Spitz markers.

– Cheng L, Lopez-Beltran A, Massari F, MacLennan GT, Montironi R. Molecular testing for BRAF mutations to inform melanoma treatment decisions: a move toward precision medicine. Mod Pathol. 2018 Jan;31(1):24-38. doi: 10.1038/modpathol.2017.104. Epub 2017 Nov 17. PMID: 29148538; PMCID: PMC5758899.

How to diagnose melanocytic tumours.. Clinical perspective

- If melanoma is suspected, an excisional biopsy is recommended
- If the lesion is too large to excise, an incisional biopsy may be done to include any nodules, dark-black areas and white areas
- <u>Punch biopsy is the last choice.</u>

Thank You!

Any Question?