How far do we need to evolve as pathologists focusing on melanocytic tumors?

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Melanoma

- 76,000 new cases in 2014 in the US & 9,700 deaths
- UV light
- Lightly pigmented individual: higher risk
- >10mm
- Other site: oral & anogenital mucosa, pharynx, GI & GU tract, esophagus, meninges, uvea of the eye

Contents

- 2018 WHO Classification, which lets us assume a molecular pathway through which melanoma develops.
- Melanoma simulants
- Histopathology of melanoma
- What will be our role in the future? How can we prepare for it?

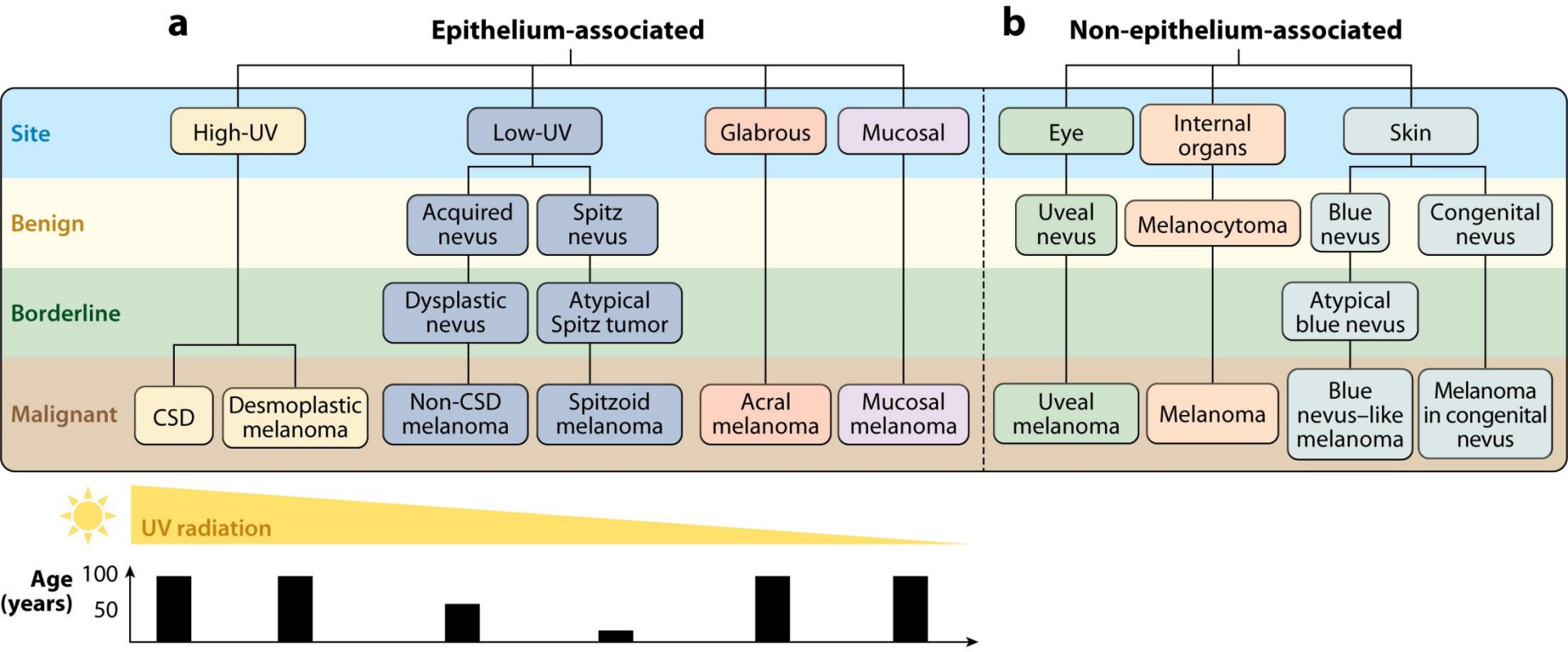
2018 WHO CLASSIFICATION

WHO, 2006

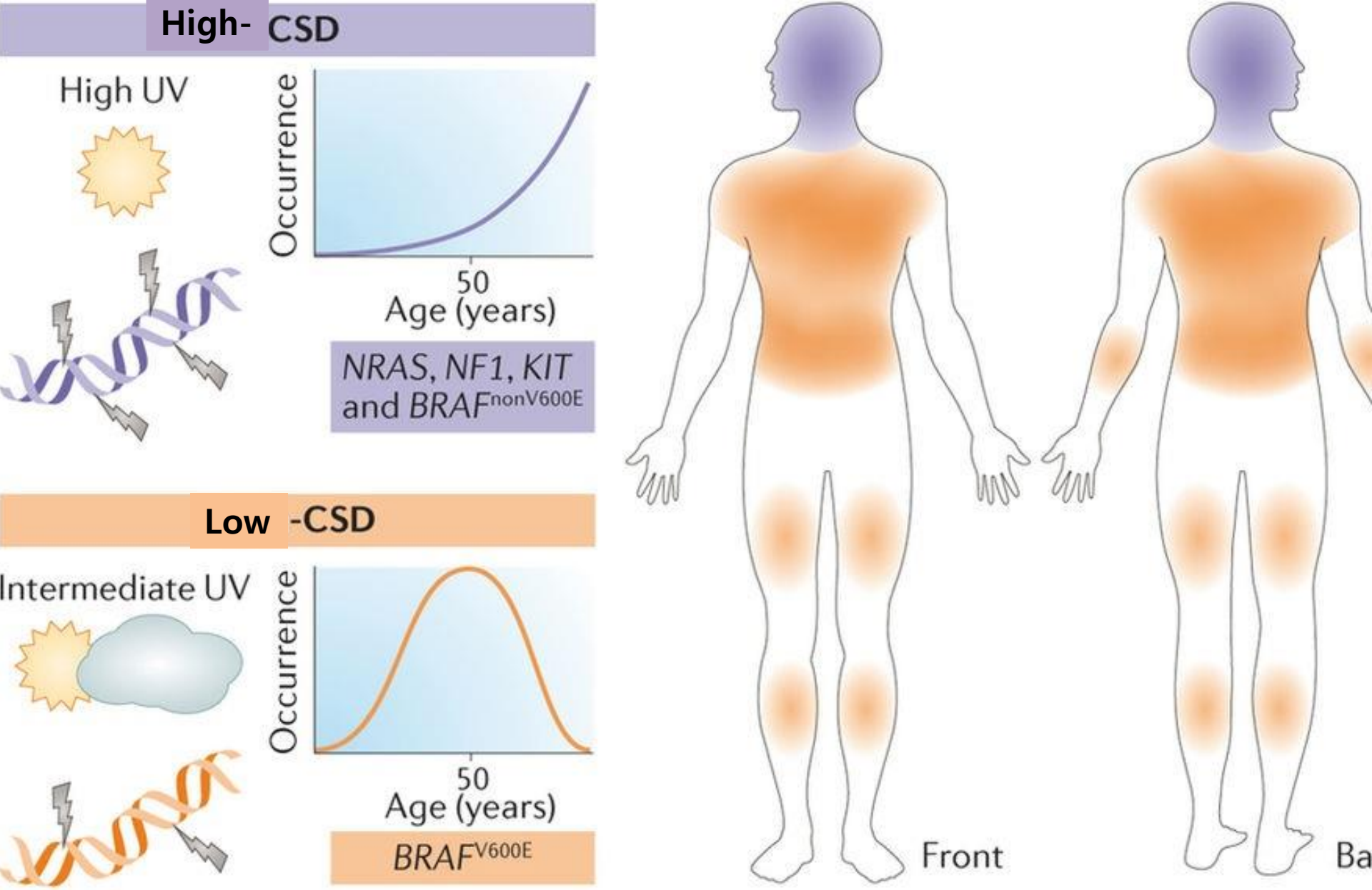
WHO histological classification of melanocytic tumours

Malignant melanoma	8720/3
Superficial spreading melanoma	8743/3
Nodular melanoma	8721/3
Lentigo maligna	8742/2
Acral-lentiginous melanoma	8744/3
Desmoplastic melanoma	8745/3
Melanoma arising from blue naevus	8780/3
Melanoma arising in a giant congenital naevus	8761/3
Melanoma of childhood	
Naevoid melanoma	8720/3
Persistent melanoma	8720/3
Benign melanocytic tumours	
Congenital melanocytic naevi	
Superficial type	8761/0
Proliferative nodules in congenital melanocytic naevi	8762/1
Dermal melanocytic lesions	
Mongolian spot	
Naevus of Ito and Ota	
Blue naevus	8780/0
Cellular blue naevus	8790/0
Combined naevus	
Melanotic macules, simple lentigo and lentiginous naevus	
Dysplastic naevus	8727/0
Site-specific naevi	
Acral	
Genital	
Meyerson naevus	
Persistent (recurrent) melanocytic naevus	
Spitz naevus	8770/0
Pigmented spindle cell naevus (Reed)	8770/0
Halo naevus	8723/0

[1] Morphology code of the International Classification of Diseases for Oncology (ICD-O) {786} and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, /2 for non-invasive tumours, and /1 for borderline or uncertain behaviour.



Bastian BC. 2014.
Annu. Rev. Pathol. Mech. Dis. 9:239–71



Shain et al, NATURE REVIEWS/CANCER 2016

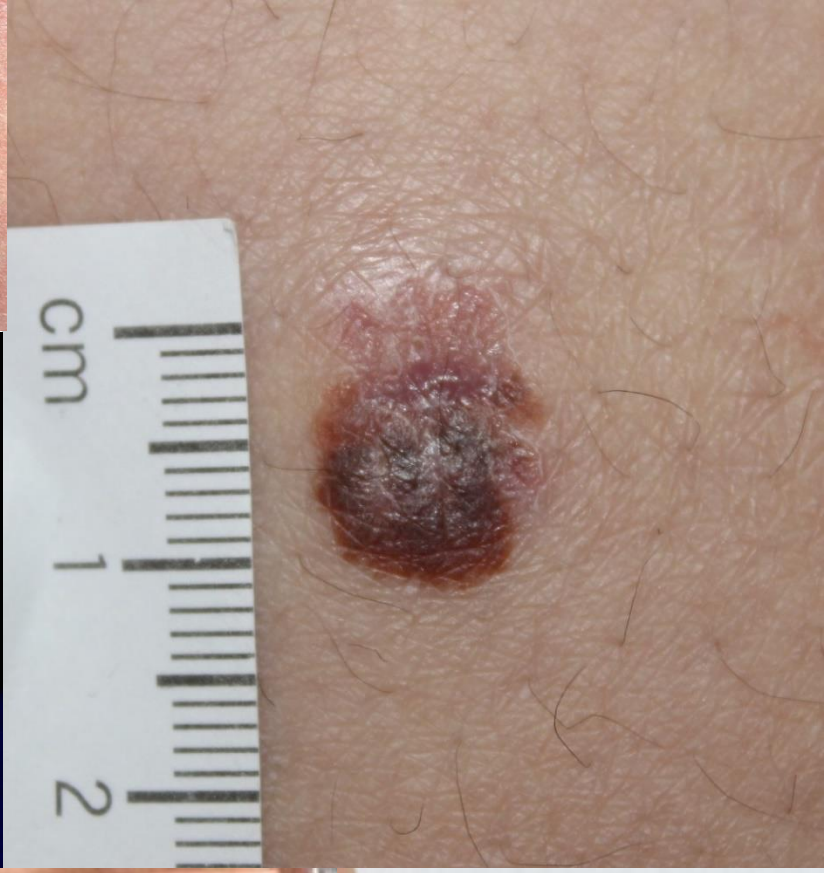
Classification of Melanoma

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 association with UV radiation exposure	Pathway IV	Malignant Spitz tumor (Spitz melanoma)
	Pathway V	Acral melanoma
	Pathway VI	Mucosal melanoma
	Pathway VII	Melanoma arising in congenital nevus
	Pathway VIII	Melanoma arising in blue nevus
	Pathway IX	Uveal melanoma
Low/high-CSD melanoma, melanoma in skin with a low/high degree of cumulative sun damage. Various: Nodular, naevoid, and metastatic melanomas.		

Genomic attribution

Melanomas arising in sun-exposed skin	Pathway I	***BRAF(pV600E) or NRAS*** *TERT;CDKN3A;TP53;PTEN*
	Pathway II	***NRAS;BRAF;KIT:*** *or NF1* *TERT;CDKN2A;TP53;PTEN;RAC*
	Pathway III	***NF1****;MAP2K1;MAP3K1;BRAF;EGFR;MET* *TERT;NFKBIE;NRAS;PIK3CA;PTPN11*
Melanomas arising at sun-shielded sites or without known etiological association with UV radiation exposure	Pathway IV	***HRAS;ALK;ROS1;RET;NTRK1;BRAF or MET*** *CDKN2A*
	Pathway V	***KIT;NRAS;BRAF;HRAS;KRAS;NTRK3;ALK; or NF1*** *CDKN2A;TERT;CCDN1;GAB2*
	Pathway VI	***KIT;NRAS;KRAS or BRAF*** ***NF1;****CDKN2A;SF2B1;CCDN1;CDK4;MDM2*
	Pathway VII	***NRAS; BRAF(pV600E) or BRAF***
	Pathway VIII	***GNAQ;GNA11; or CYSLTR2*** *BAP1;EIF1AX;SF3B1*
	Pathway IX	***GNAQ;GNA11; CYSLTR2; or PLCB4*** *BAP1;SF3B1;EIF1AX*

Loss of function;gain of function;promotor;change of funcion;amplification;rearrangement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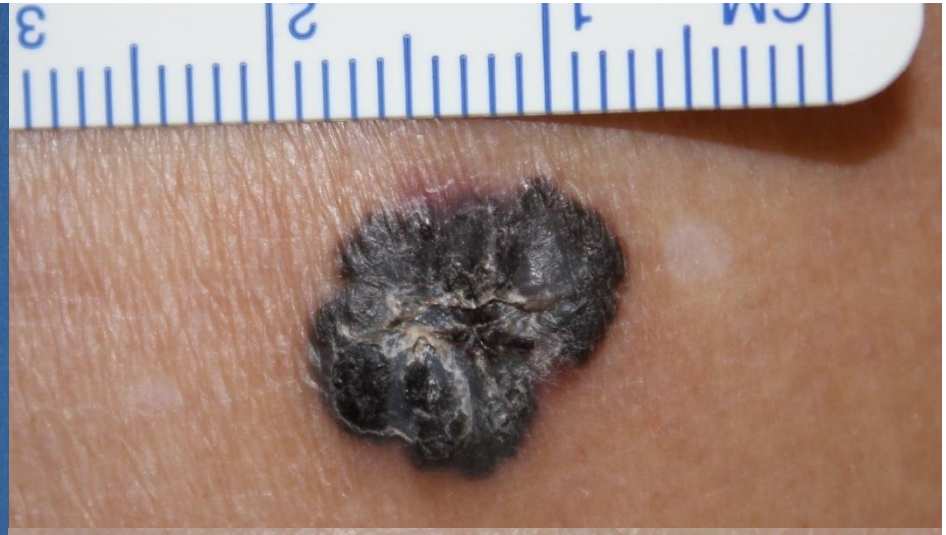
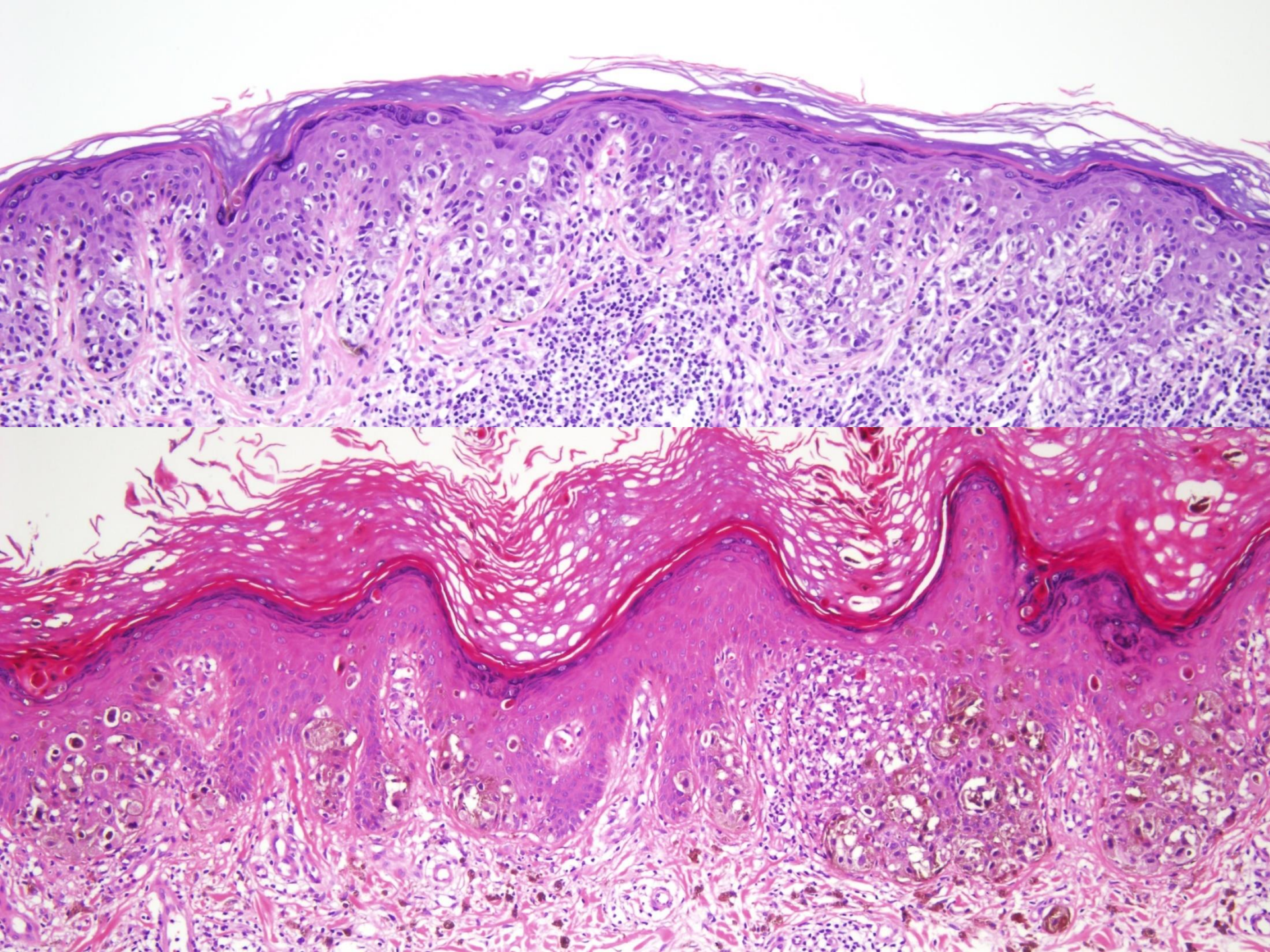
Melanocytic Tumors in Intermittently Sun-exposed skin

Low-CSD melanoma	8743/3
Simple lentigo and lentiginous melanocytic nevus	8742/0
Junctional nevus	8740/0
Compound nevus	8760/0
Dermal nevus	8750/0
Dysplastic nevus	8727/0
Nevus spilus	8720/0
Special site nevus	
Halo nevus	8723/0
Meyerson nevus	8720/0
Recurrent nevus	
Deep penetrating Nevus	8720/0
Pigmented epithelioid melanocytoma	8780/1
Combined nevus, including combined BAP1-inactivated nevus/melanocytoma	8720/0

Pathway I: Low-CSD melanoma/superficial spreading melanoma



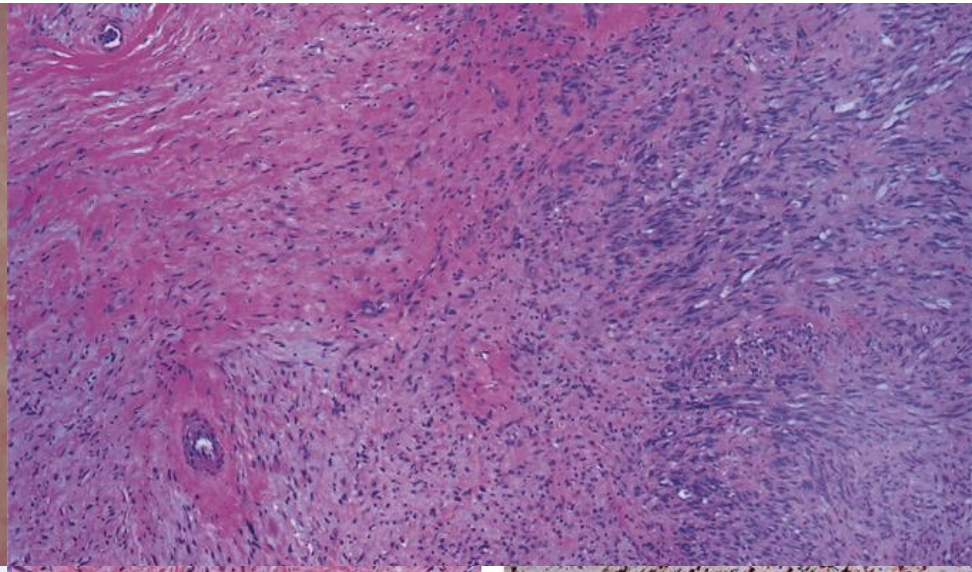


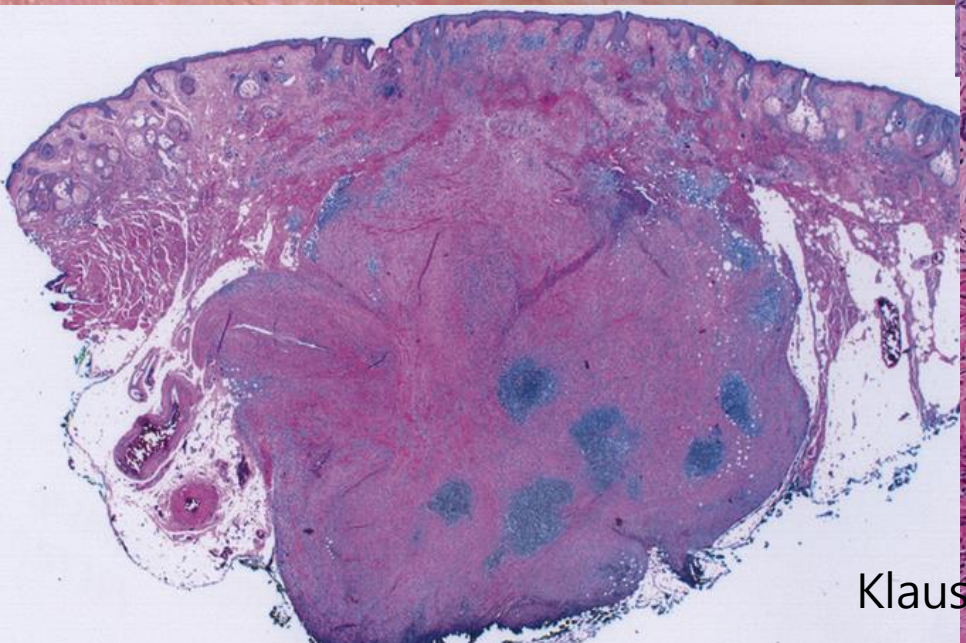
Melanocytic Tumors in Chronic Sun-exposed skin

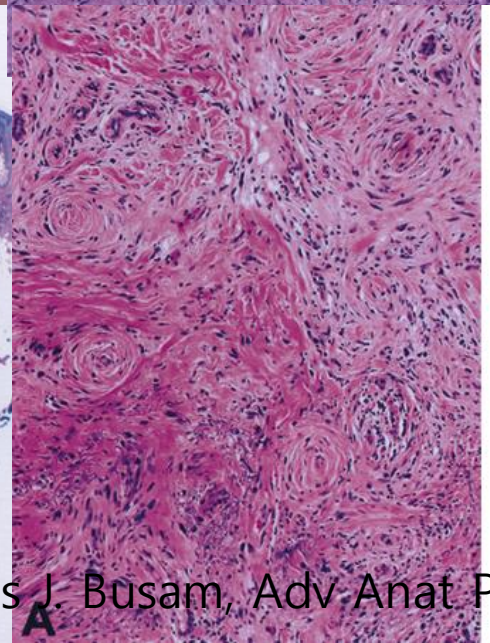
Lentigo maligna melanoma	8742/3
Desmoplastic melanoma	8745/3

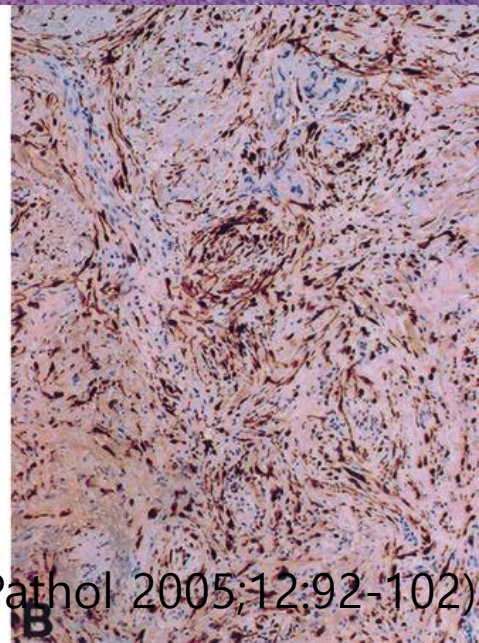
Pathway II

Pathway III: Desmoplastic melanoma









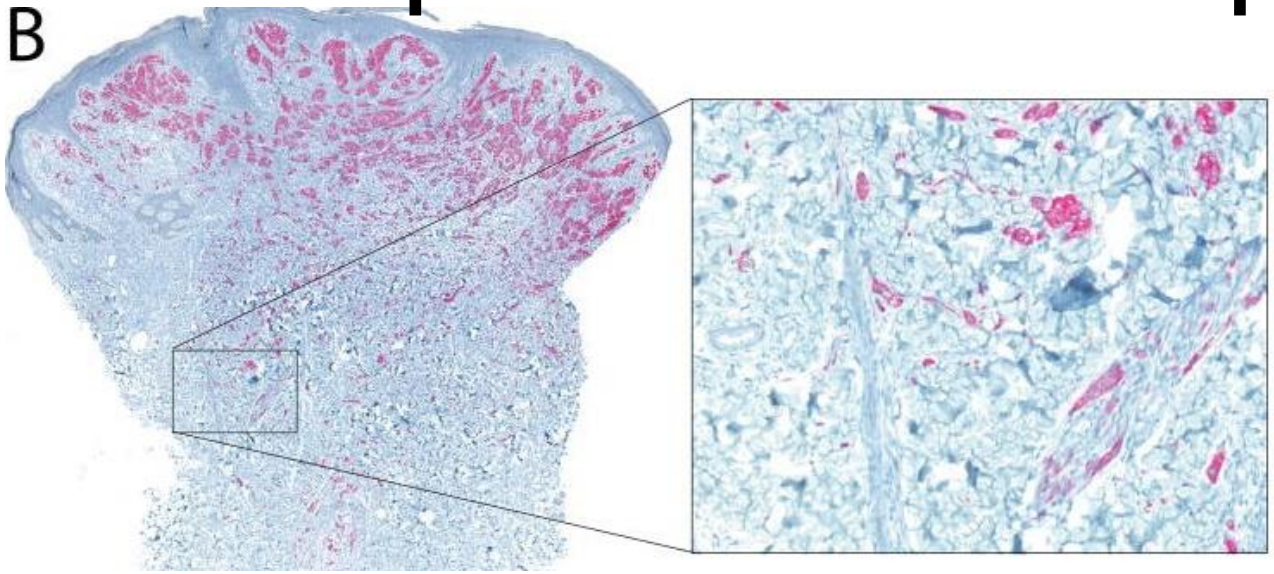
Klaus J. Busam, Adv Anat Pathol 2005;12:92-102)

Spitz tumors

Malignant Spitz Tumor	8770/3
Spitz Nevus	8770/0
Pigmented spindle cell nevus	8770/0

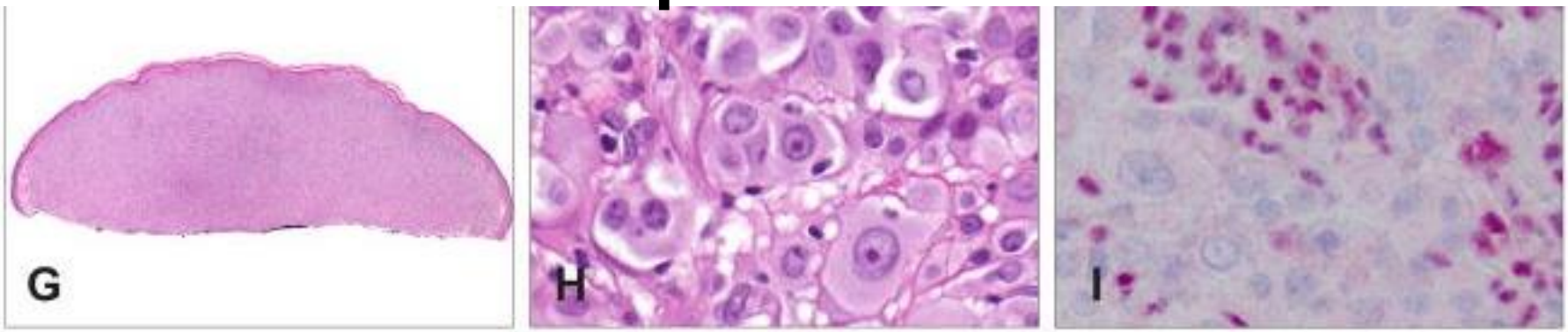
Pathway IV : Malignant Spitz tumor

ALK fusion protein associated Spitz melanoma



Iwei Yeh et al. Am J Surg Pathol. 39, 2015

BAP-1 inactivated Spitz melanoma



THOMAS WIESNER et al. Pathology 48, 2016

Spitz Nevus

Histopathologic criteria for conventional Spitz nevi, atypical Spitz tumors, and melanoma

	Conventional Spitz tumors	Atypical Spitz tumors	Melanoma
Architecture			
Diameter	<5 to 6 mm	≥5 to 6 mm	≥10 mm
Outline	Symmetric (wedge-shaped)	Asymmetric	Asymmetric
Circumscription	Sharp lateral circumscription	Often poor circumscription	Poor circumscription
Epidermal hyperplasia	Present	Effacement of the epidermis may be present	Absent, or effacement of the epidermis may be present
Maturation with dermal depth	Present	Possibly diminished or lack of zonation and maturation	Lack of zonation and maturation often present
Eosinophilic hyaline globules (Kamino bodies)	Present	Absent or few	Typically absent
Cellular density	Orderly nondisruptive infiltration of collagen by melanocytes	High cellular density	High cellular density
Cytology			
Cellular population	Uniform spindle and/or epithelioid	Spindle and/or epithelioid cells showing increasing cytologic atypia	Spindle and/or epithelioid cells showing increasing cytologic atypia and pleomorphism
Cytoplasm	Opaque or ground glass cytoplasm	Granular versus ground glass cytoplasm	Granular or mixed cytoplasm
Nuclear to cytoplasmic ratio	Low nuclear to cytoplasmic ratio	Increasingly high nuclear to cytoplasmic ratio	High nuclear to cytoplasmic ratio
Chromatin pattern	Nuclei with open, delicate chromatin pattern	Loss of delicate or dispersed chromatin pattern	Loss of delicate or dispersed chromatin pattern
Nucleoli	Uniform nucleoli	Increasingly prominent nucleoli	Large nucleoli
Pleomorphism	Rare	May be present	Usually present
Hyperchromatism	Absent	May be present	Present
Proliferation			
Mitotic rate	<2/mm^2 Absent or rare mitoses in deep dermis Lack of atypical mitoses	2 to 6/mm^2 (particularly >6/mm^2) Deep or marginal dermal mitoses may be present	2 to 6/mm^2 (particularly >6/mm^2) Deep or marginal dermal mitoses frequently present
Proliferative index (Ki-67 expression)	<2%	2 to >10%	Often >15 to 30%

Adapted from: Barnhill RL. The Spitzoid lesion: rethinking Spitz tumors, atypical variants, 'Spitzoid melanoma' and risk

Barnhill RL. The Spitzoid lesion: rethinking Spitz tumors, atypical variants, 'Spitzoid melanoma' and risk assessment. Mod Pathol 2006; 19 Suppl 2:S21.

Melanocytic Tumors in Acral Skin

Acral melanoma	8744/3
Acral nevus	8744/0

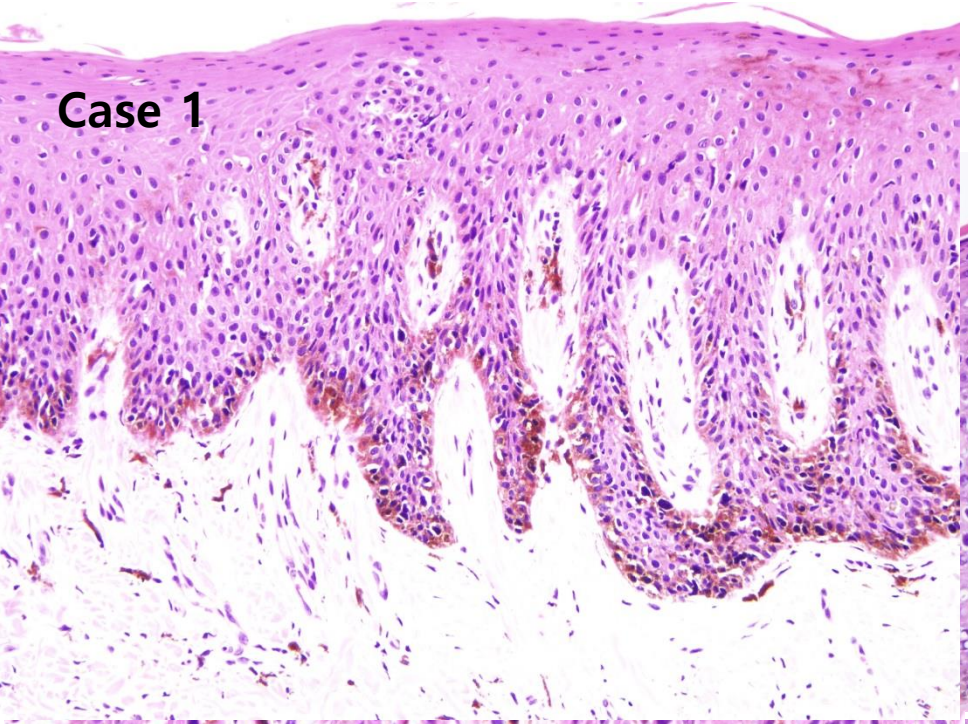
Pathway V: Acral melanoma

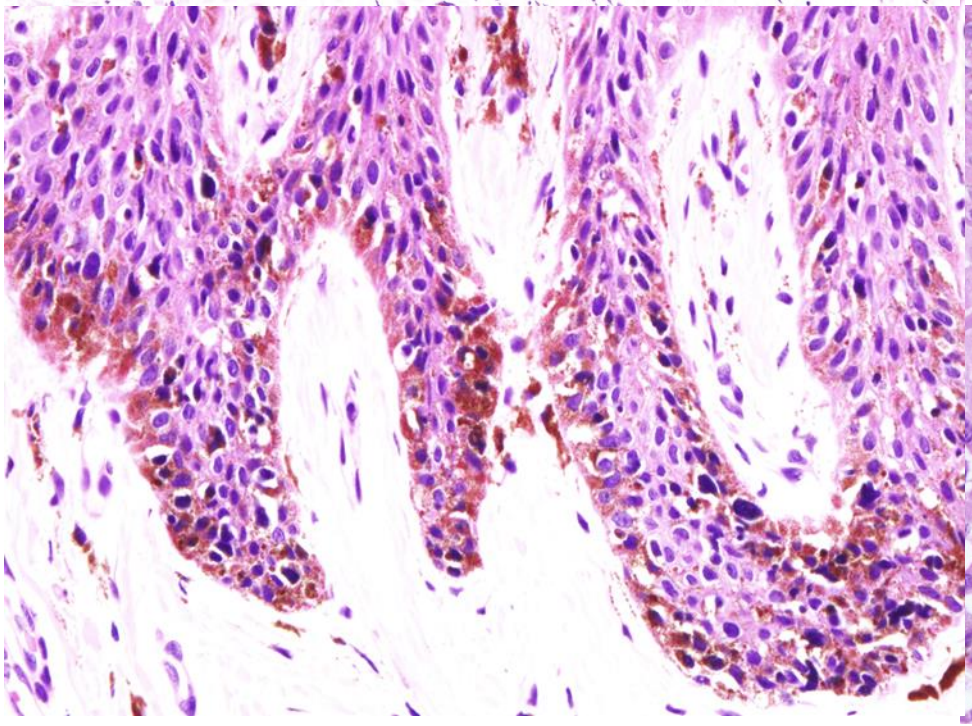
Genital and Mucosal melanocytic tumors

Mucosal melanomas(genital, oral, sinonasal)	8720/3
Mucosal lentiginous melanoma	8746/3
Mucosal nodular melanoma	8721/3
Genital nevus	8720/0

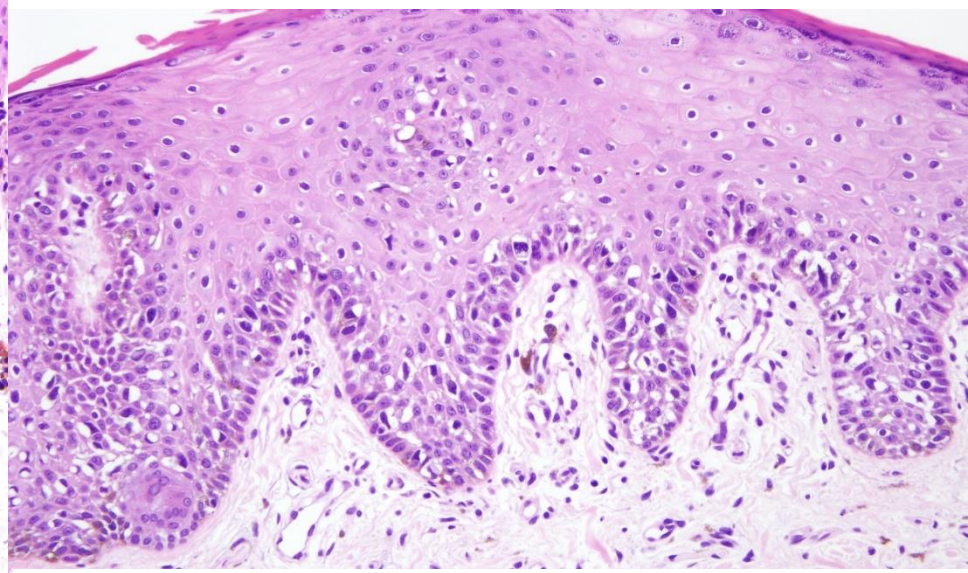
Pathway VI : Mucosal melanoma

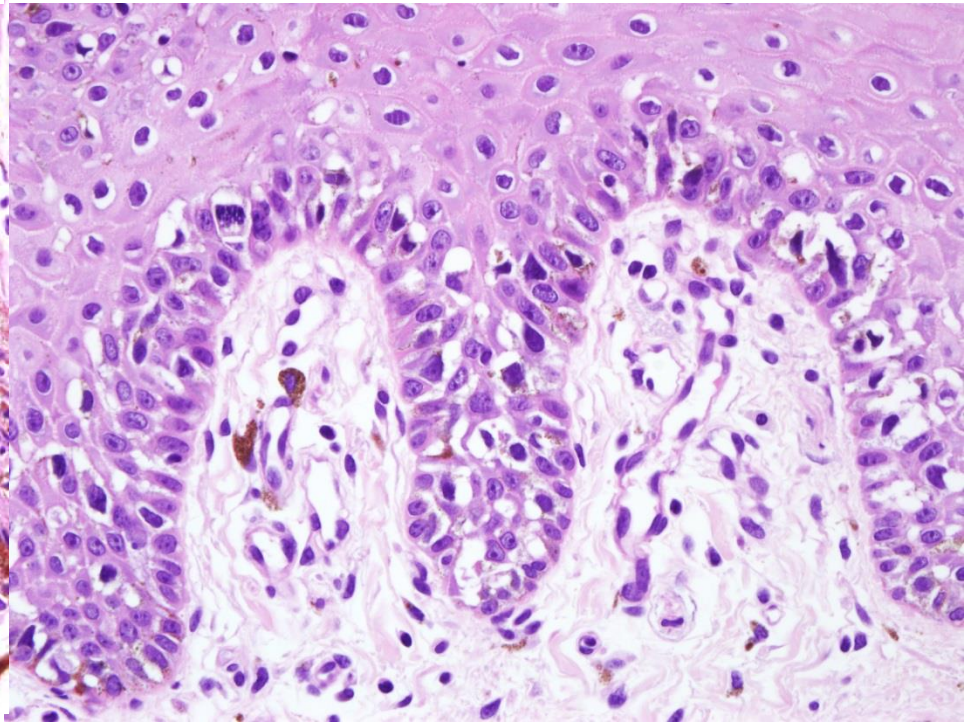
Case 1





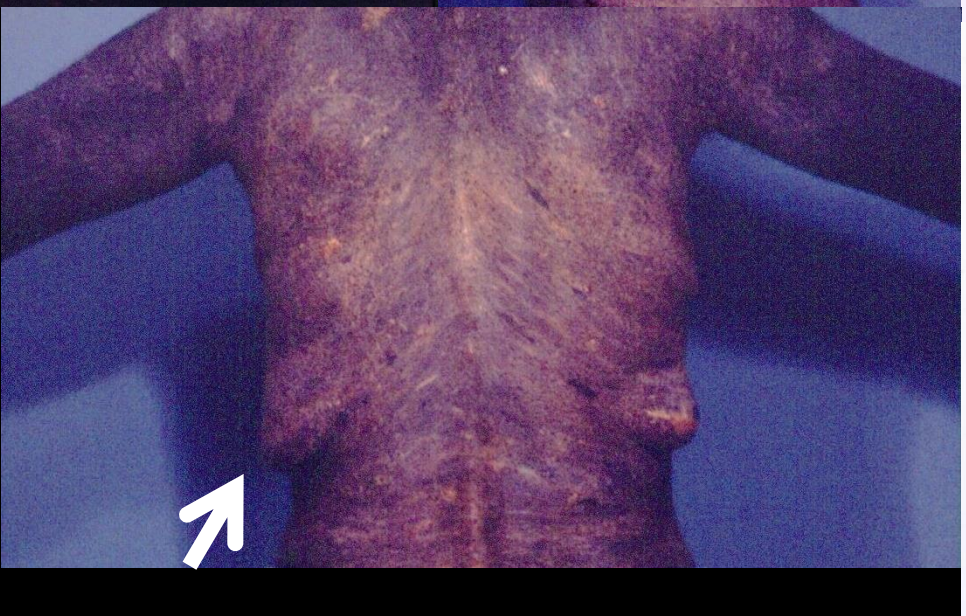
Case 2

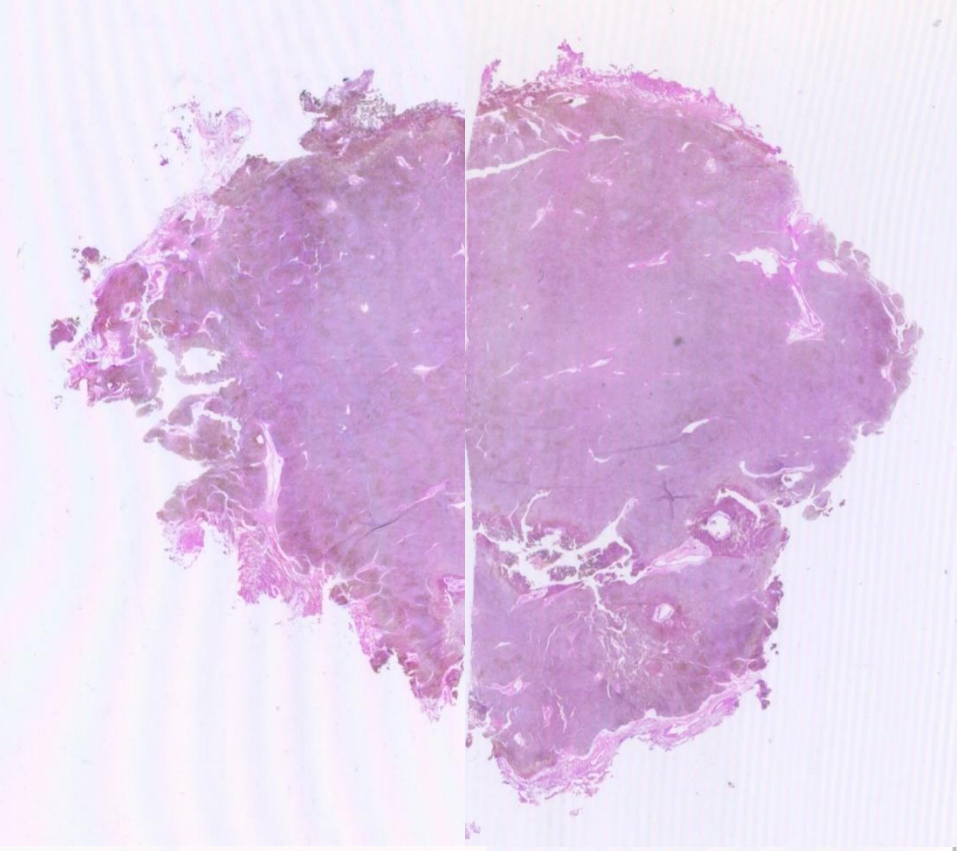


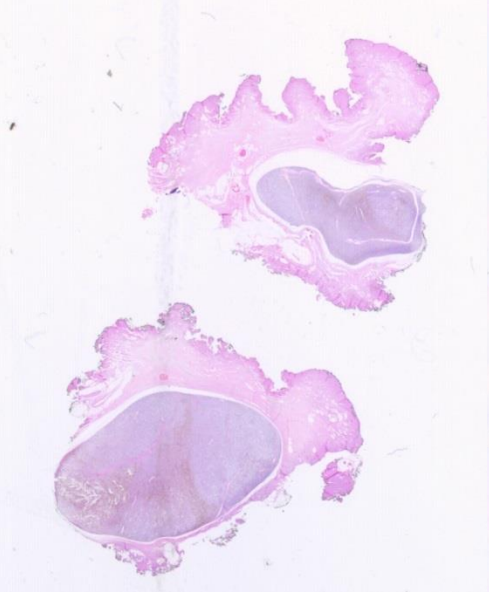


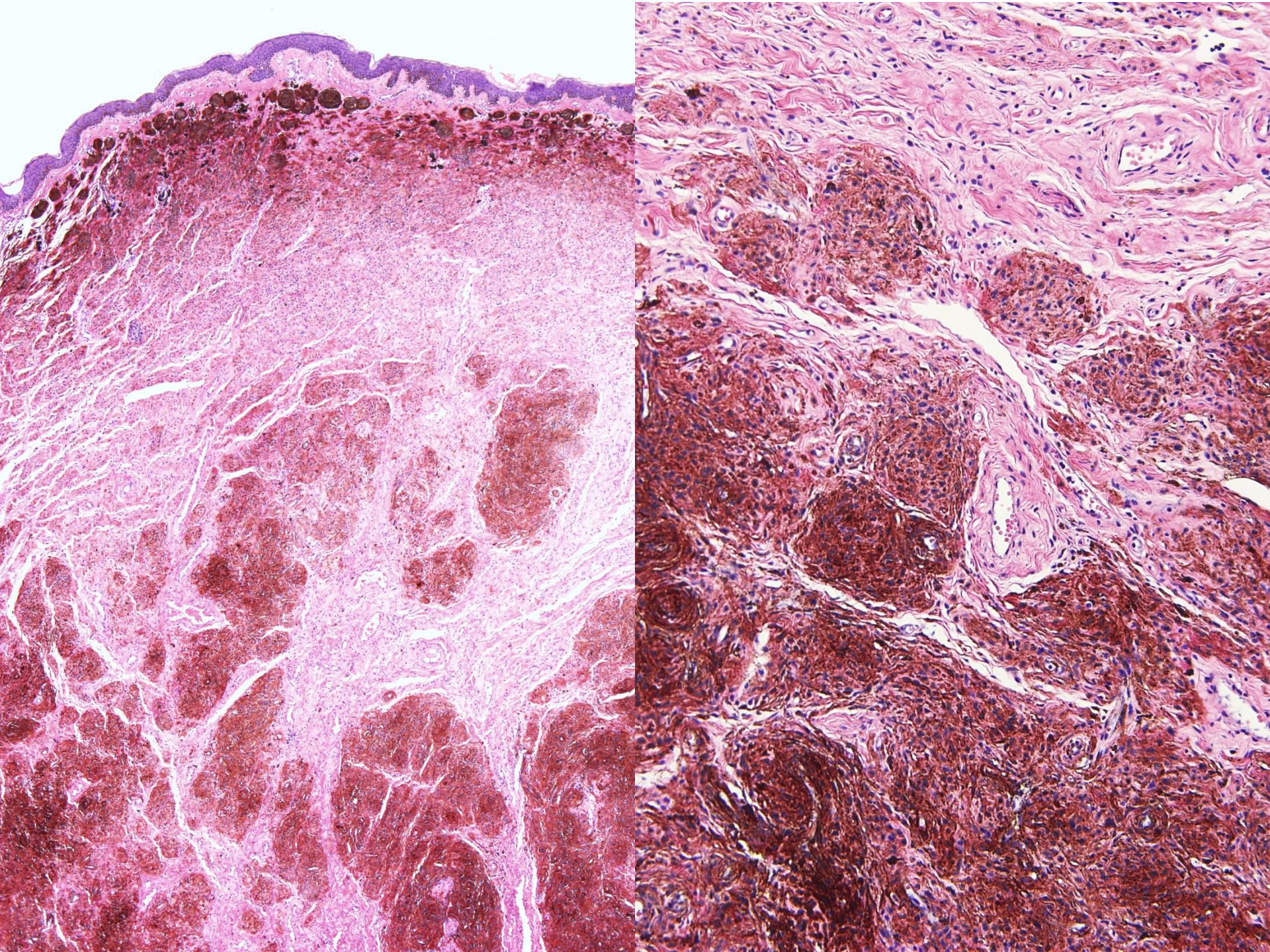
Melanocytic Tumors Arising in Congenital Nevus

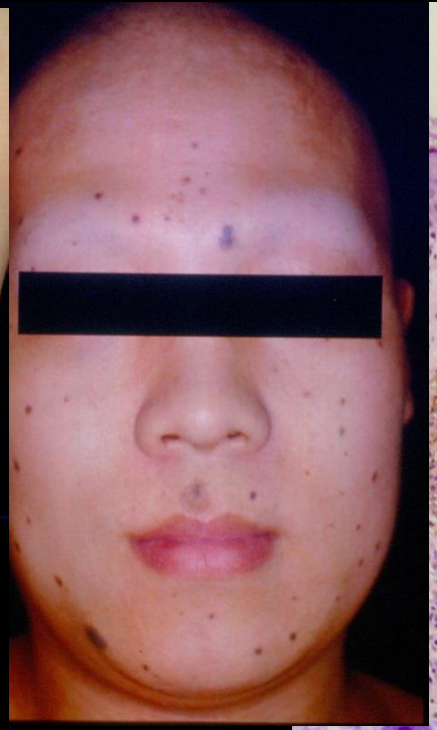
Melanoma arising in giant congenital nevus	8761/3
Congenital melanocytic nevus	8761/0
Proliferative nodules in congenital melanocytic nevus	8762/1

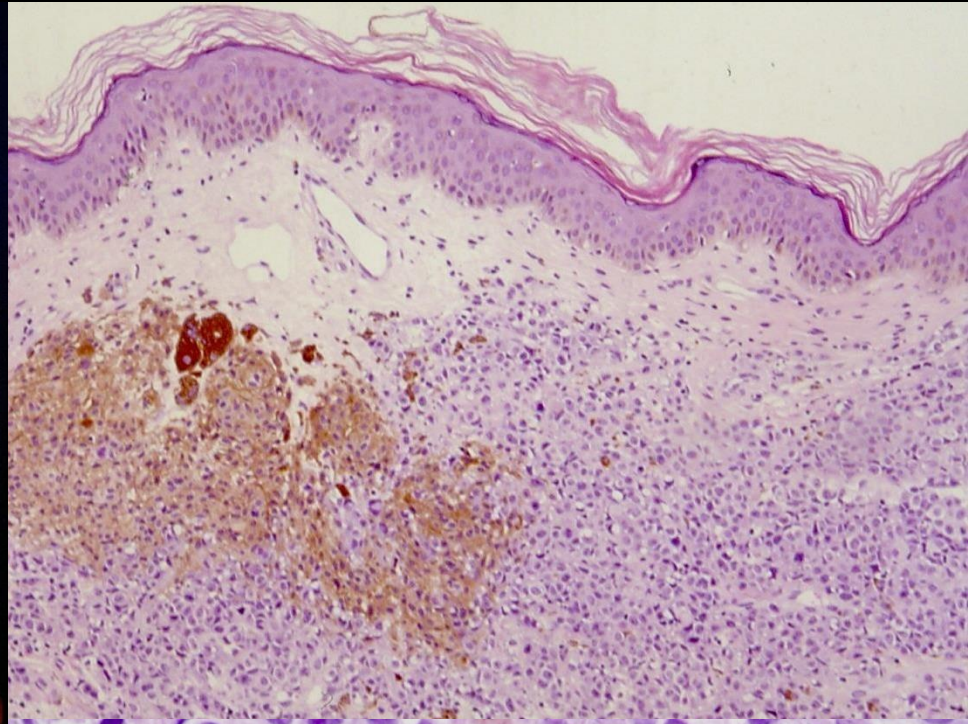


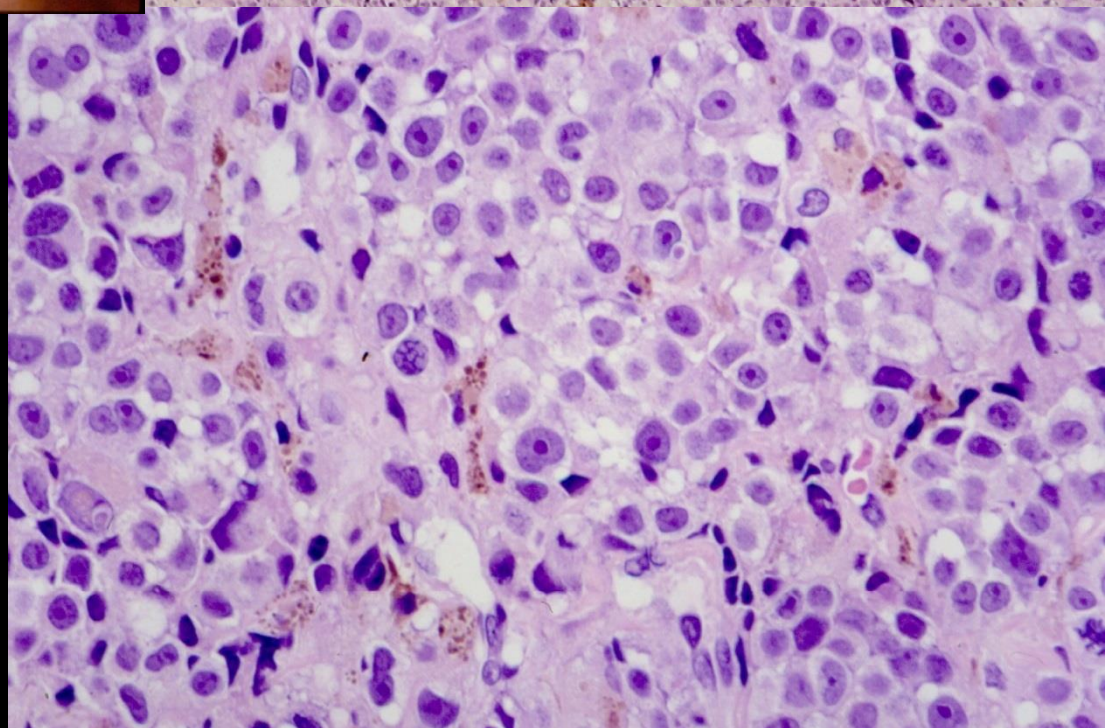








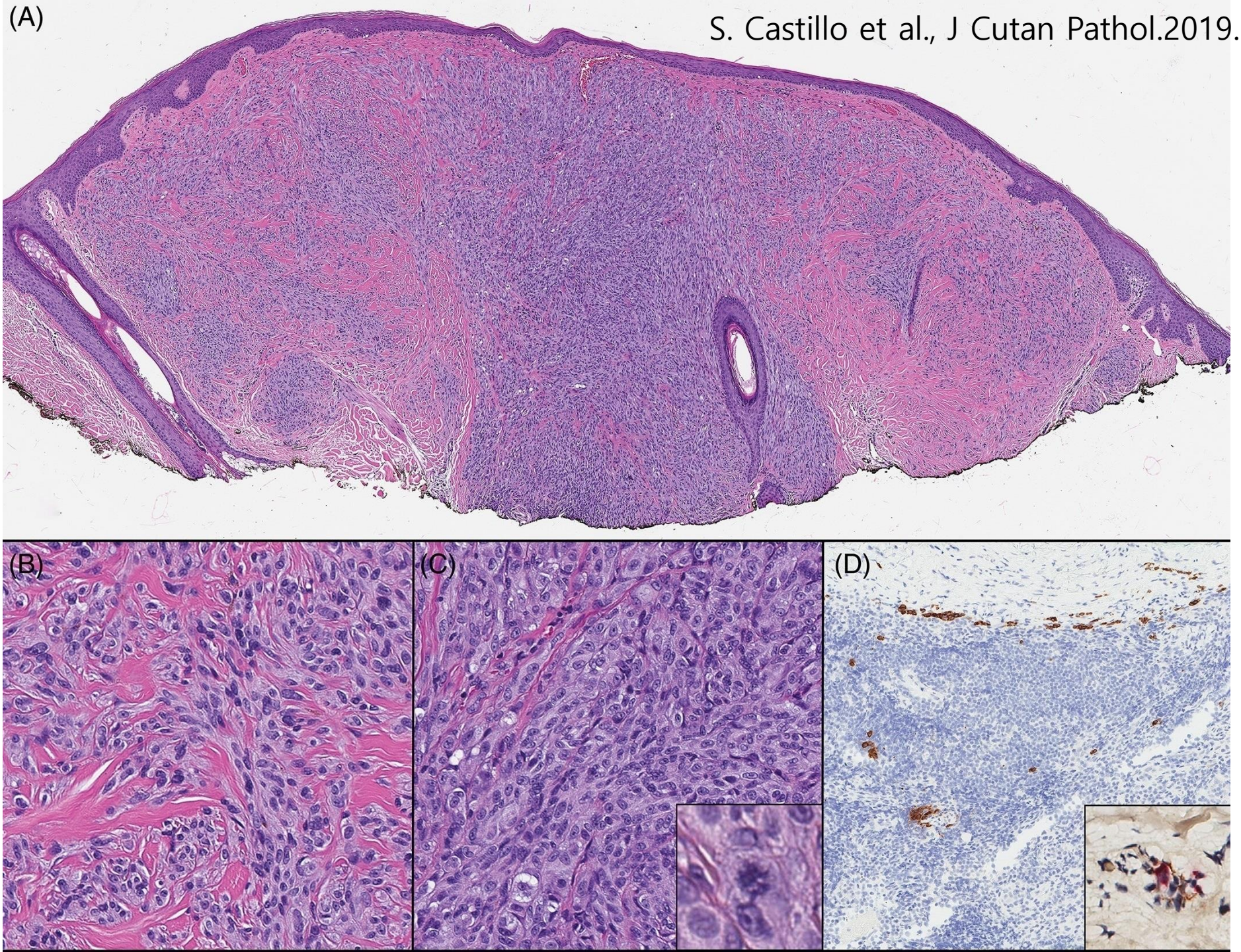




Pathway VII: *Melanocytic Tumors Arising in Blue Nevus*

Melanoma arising in blue nevus	8780/3
Blue nevus NOS	8780/0
Cellular blue nevus	8790/0
Mongolian spot	
Nevus of Ito	
Nevus of Ota	

Pathway VIII: Melanocytic tumors arising in blue nevus


(A)
S. Castillo et al., J Cutan Pathol.2019.
(B)
(C)
(D)

Nodular, Nevoid, metastatic Melanomas

Nodular melanoma	8721/3
Nevoid melanoma	8720/3
Metastatic melanoma	8720/6

HOW CAN WE DIFFERENTIATE MELANOMA FRO ITS SIMULANT?

Melanoma Simulants

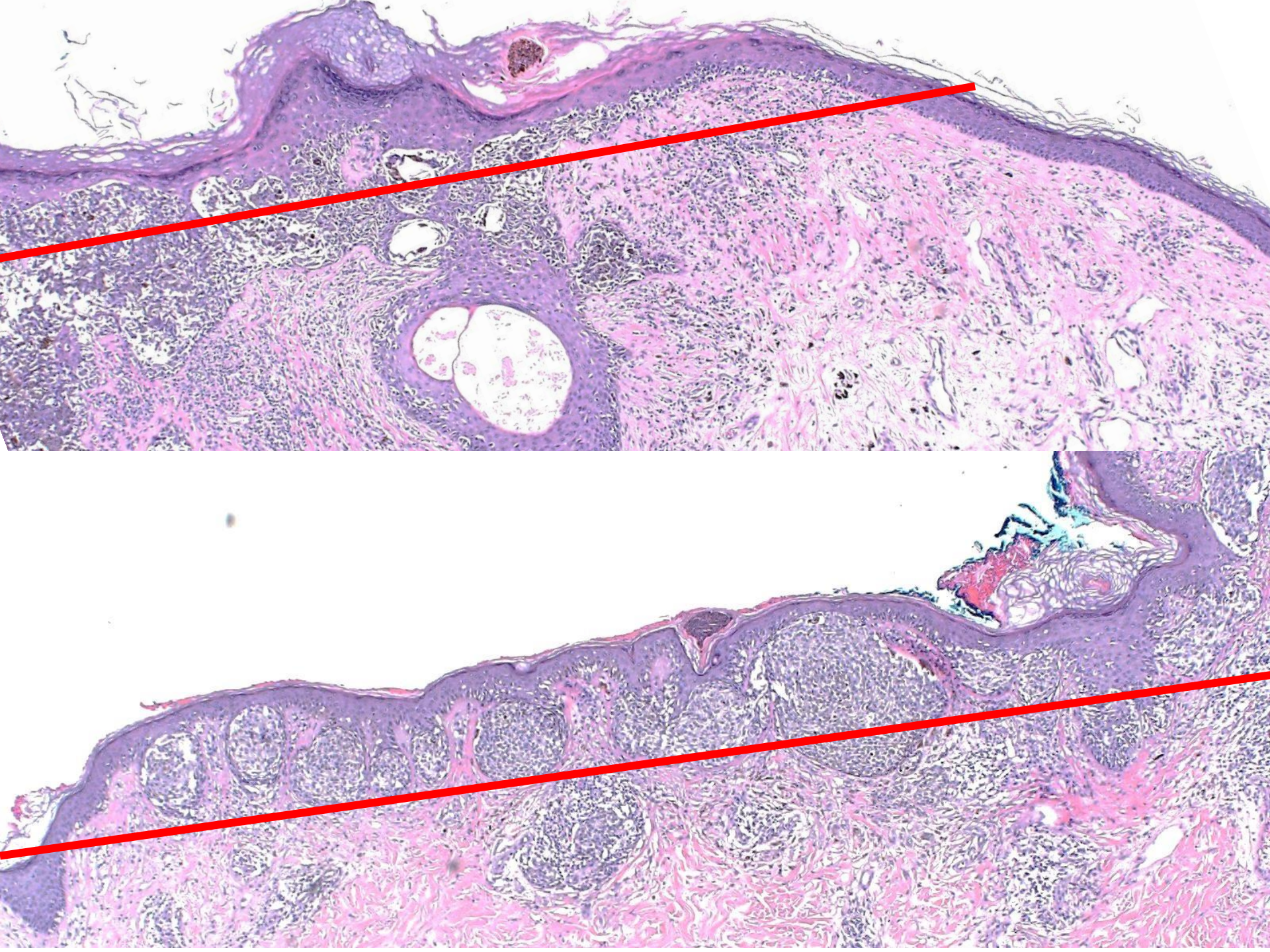
- Deep penetrating nevus
- Spitz nevus vs **spitzoid melanoma**
- Cellular blue nevus vs **melanoma arising in blue nevus**
- Acral nevus vs **acral melanoma**
- Dysplastic nevus vs **melanoma**
- Combined melanocytic nevus vs **melanoma arising in a nevus**
- **Densely inflamed melanoma** vs lichenoid keratosis/ dermatitis (LPLK)
- **Nevoid melanoma**
- **Desmoplastic melanoma vs MPNST**
- Proliferative Nodules within congenital nevi

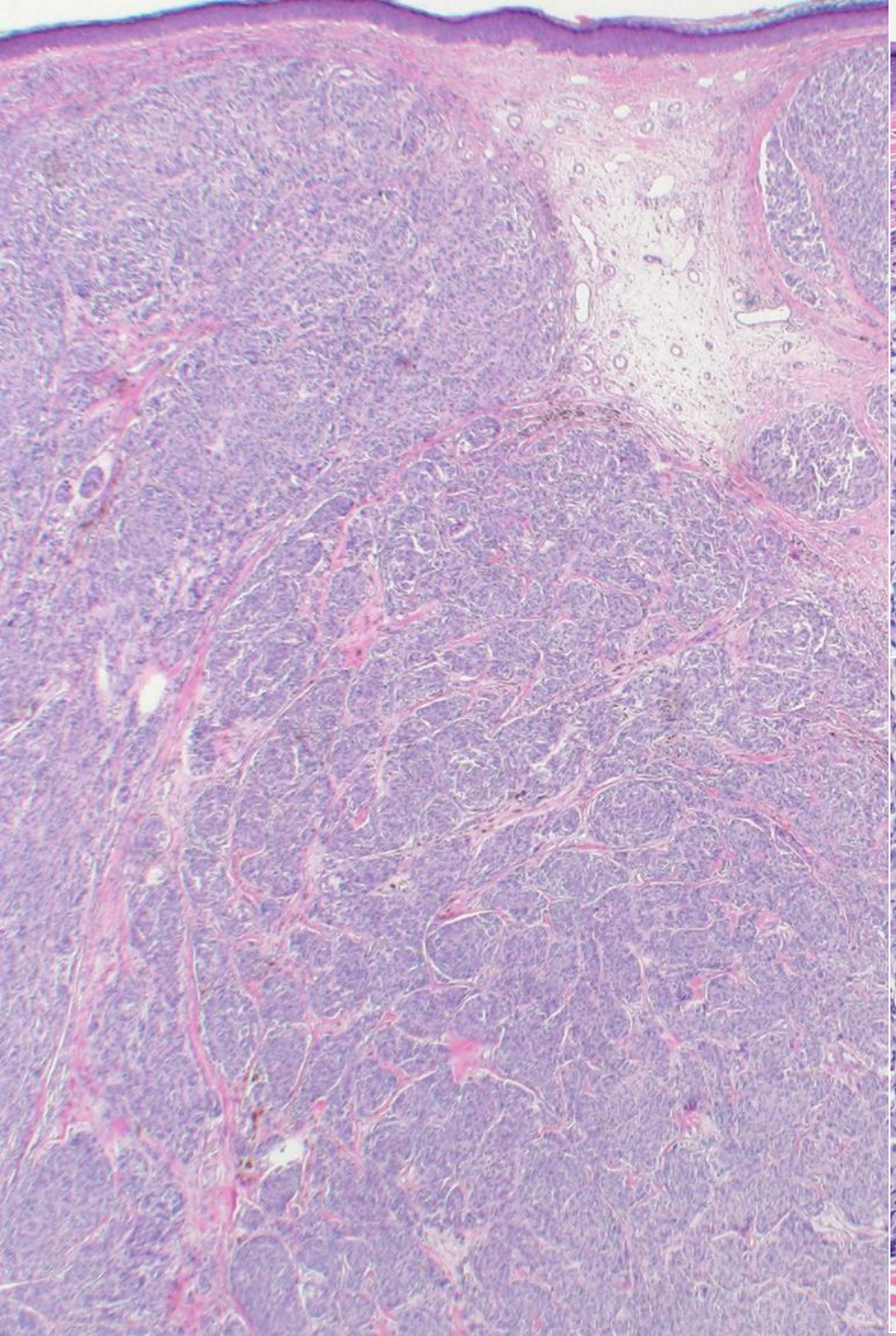
HISTOPATHOLOGY OF MELANOMA

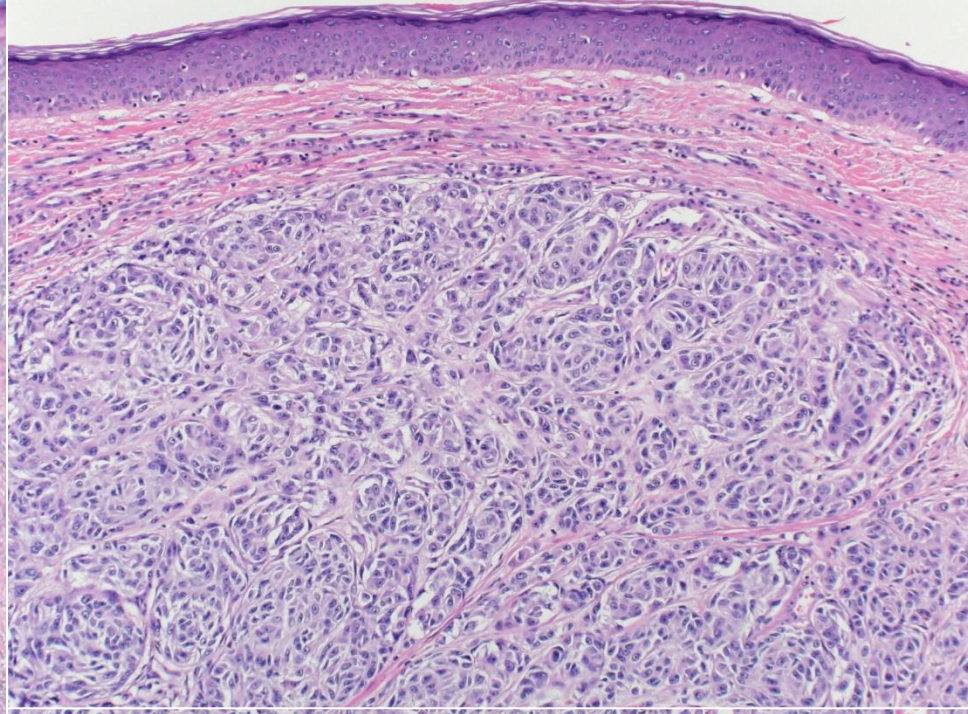
- Lack of symmetry
- Lack of maturation
- Poor circumscription
- Nest vs Single cell predominance
  - Pagetoid scatter of melanocytes, especially at edges
  - lentiginous pattern
- Confluence of nests
- Consumption of the epidermis
- Variable cellular density, cellular pleomorphism, mitosis, necrosis, lymphatic invasion…
- Fibrosis displacing Solar elastosis

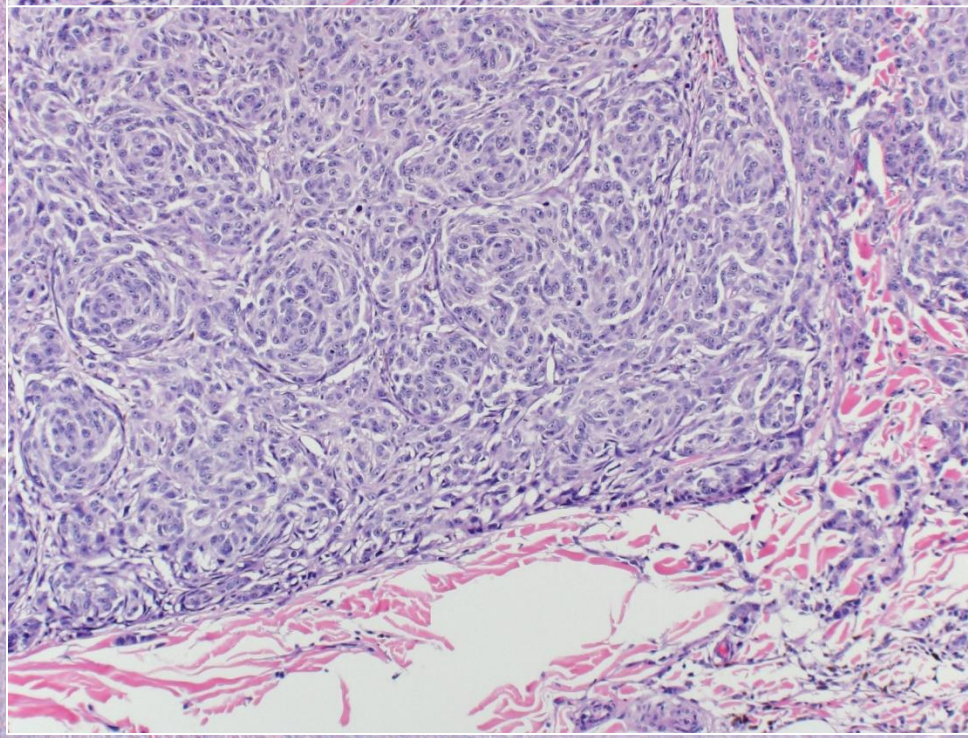
Symmetry

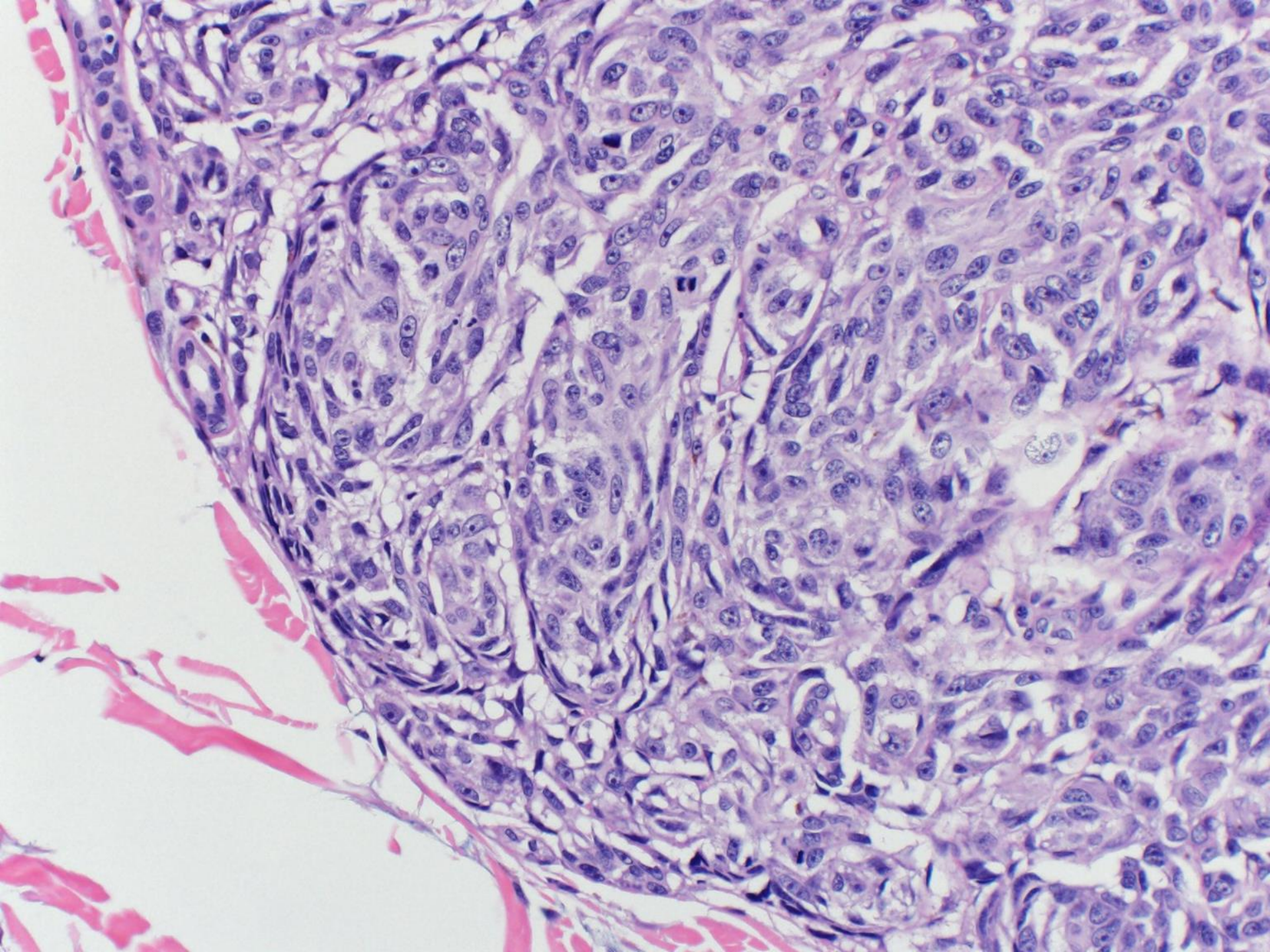
- Silhouette
- Lateral margins
- Horizontal levels of the lesion
- Distribution of the pigment
- Distribution, size, shape of nests
- Epidermal pattern

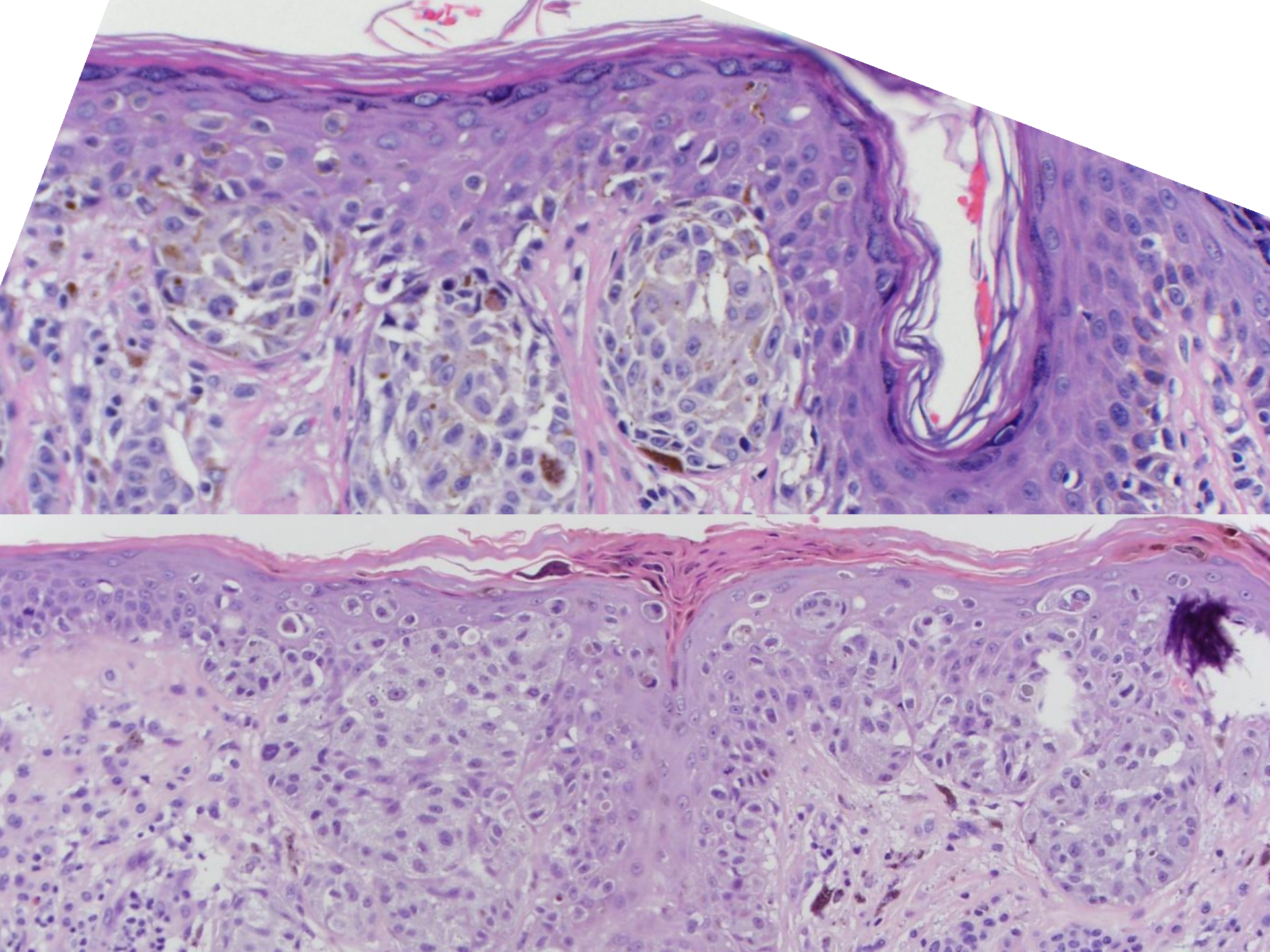


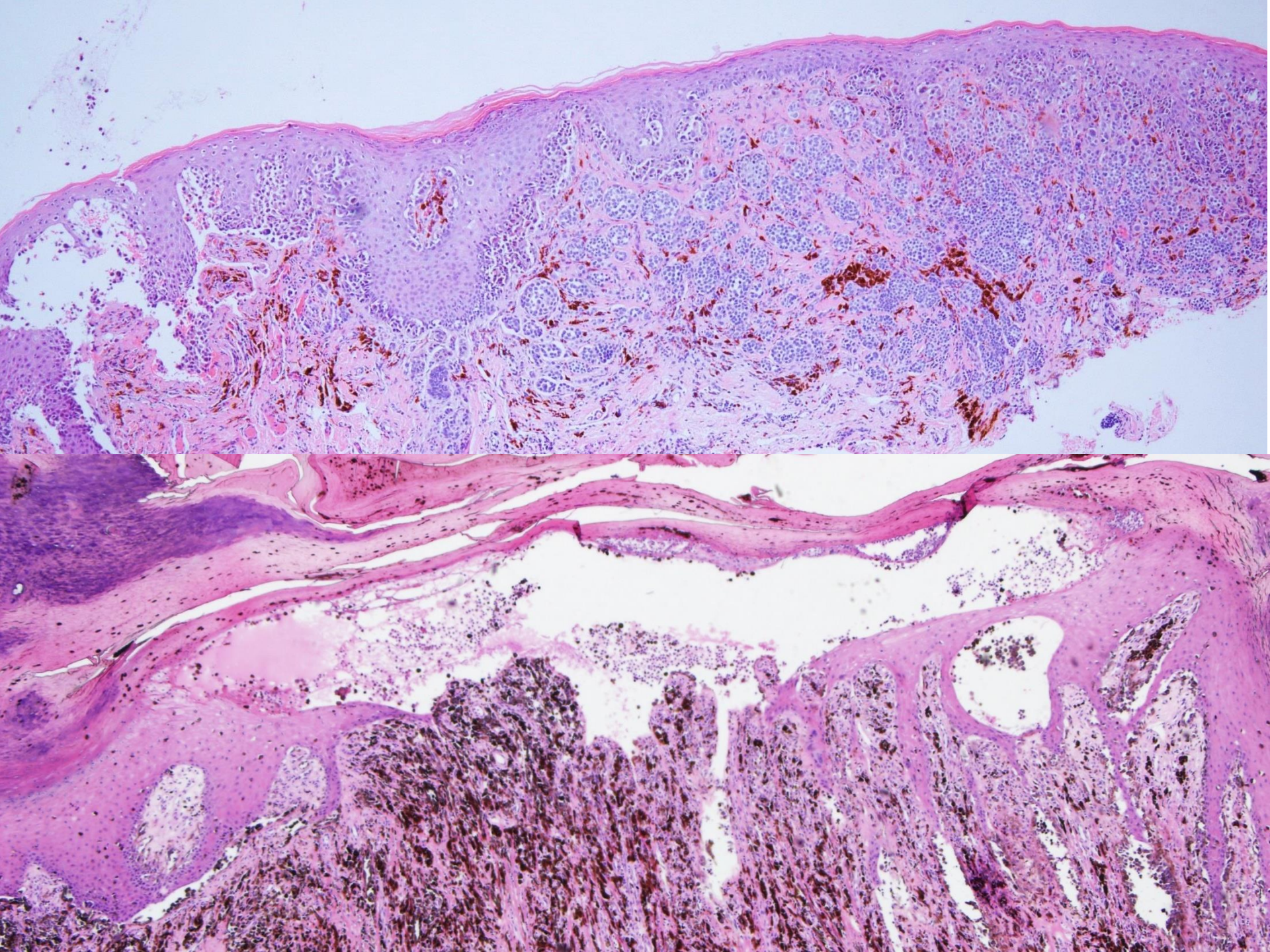


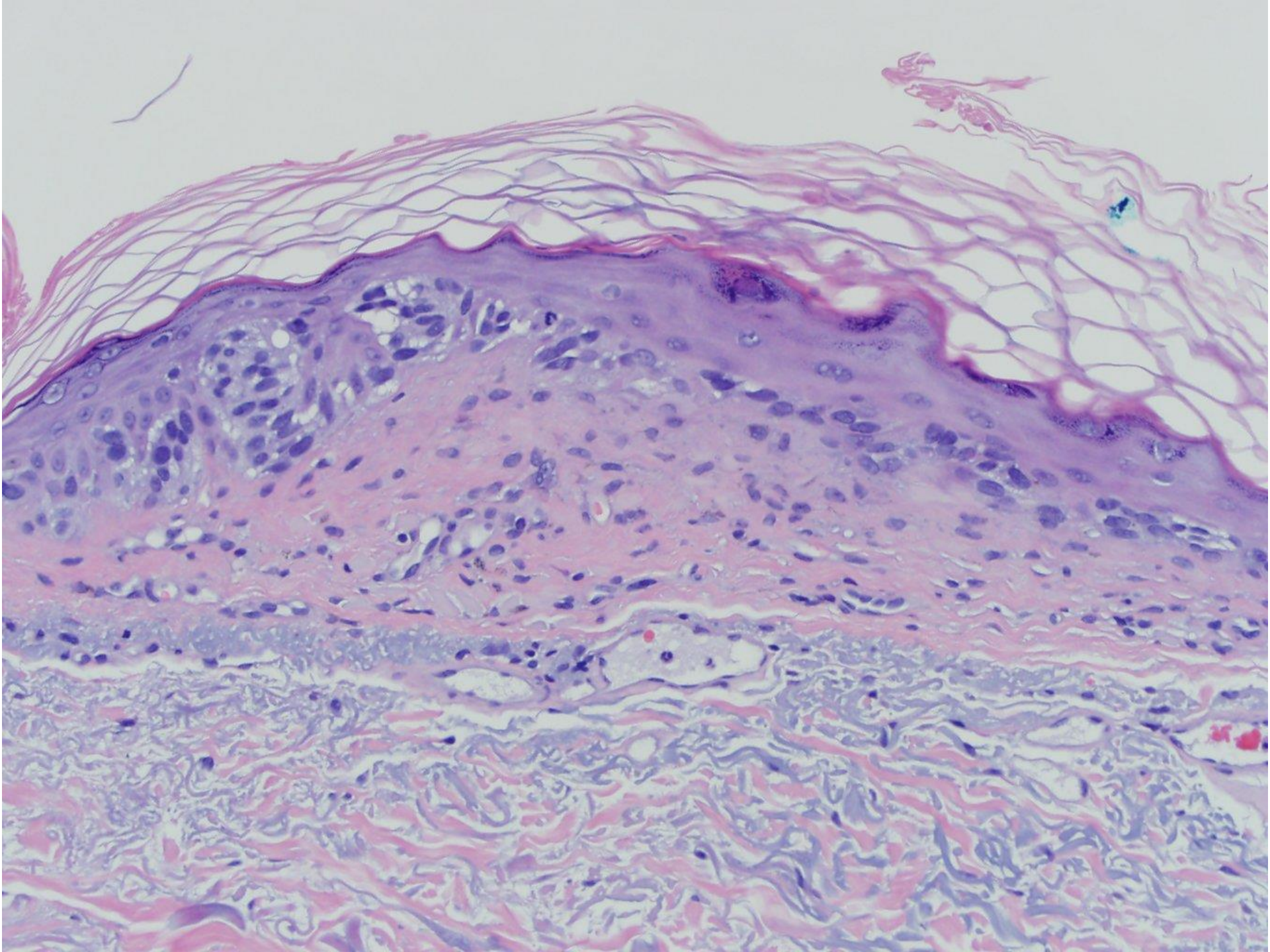


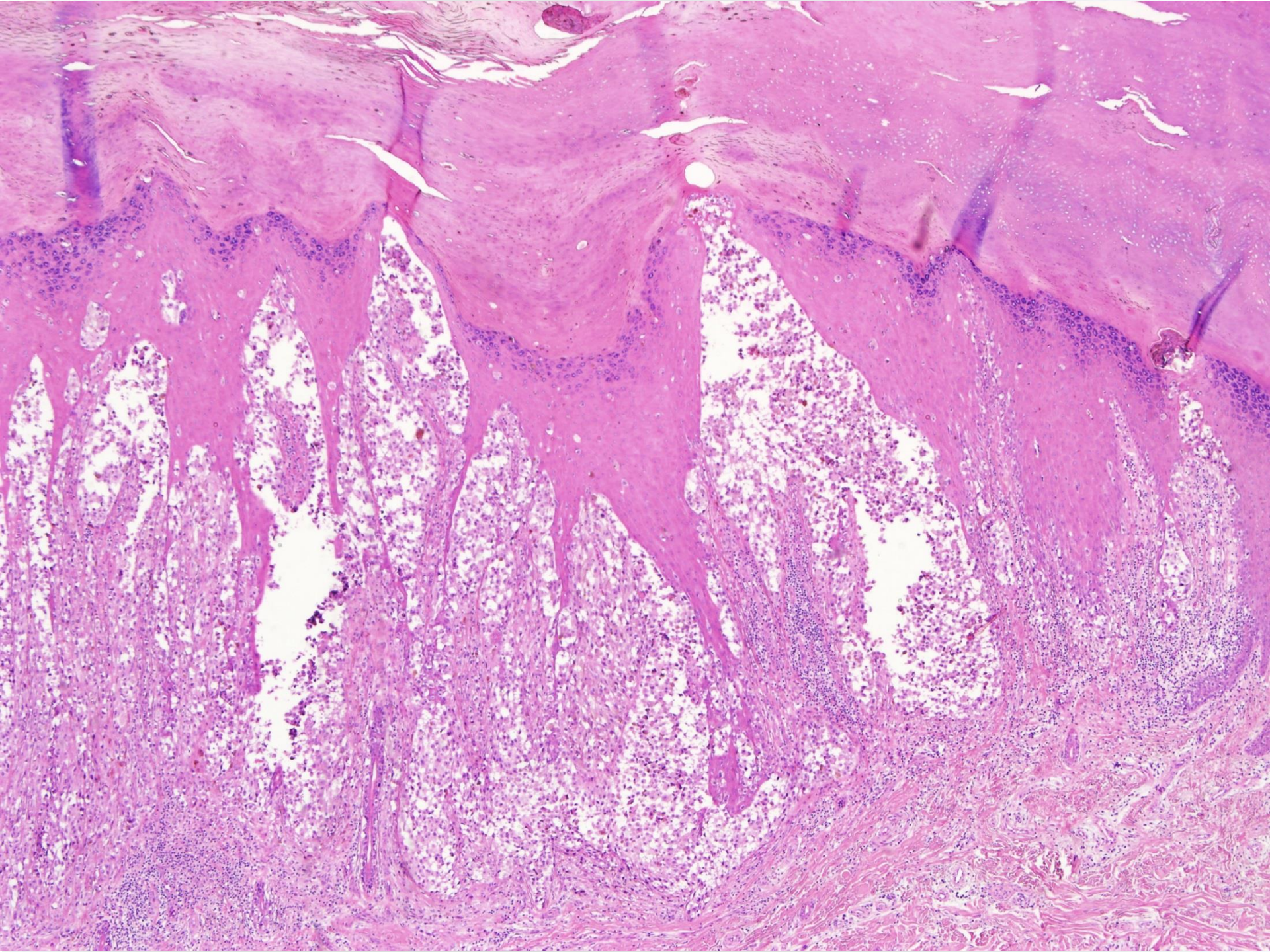












		Benign	w-grade dysplasia	high-grade dysplasia	Malignant
I	Low-CSD melanoma	Nevus	Low-grade Dysplasia	High-grade Dysplasia	Low-CSD melanoma
			BIN	BAP1-inactivated melanocytoma	Melanoma in BIN
			DPN	Deep penetrating melnocytoma	Melanoma in DPN
				Pigmented epithelioid melanocytoma	Melanoma in PEM
III	Desmoplastic M	IMP	IMAP	MIS	Desmoplastic melanoma
IV	Malignant Spitz T/M	Spitz nevus	Atypical Spitz Nevus	STUMP/ MELTUMP	Malignant Spitz T/ melanoma
V	Acral melanoma	Acral nevus	IAMP/dysplasia	Acral MIS	Acral melanoma
VI	Mucosal melanoma	Melanosis	Atypical melanosis /dysplasia	Mucosal MIS	Mucosal lentiginous M
VII	Melanoma in CN	CN	Nodule in CN	MIS in CN	Melanoma in CN
VIII	Melanoma	Blue	Cellular BN	Atypical CBN	Melanoma in BN

IPX 활용

- Lineage : Melan-A
- Junctional: SOX-10
- Architecture: Melan A
- Differentiation: HMB45, Ki67
- Margin: S-100 , SOX-10
- Invasion: Melan A
- Gene fuse or gene loss: ROS1, BAP-1, ALK
- Proliferation: Ki-67, PHH3

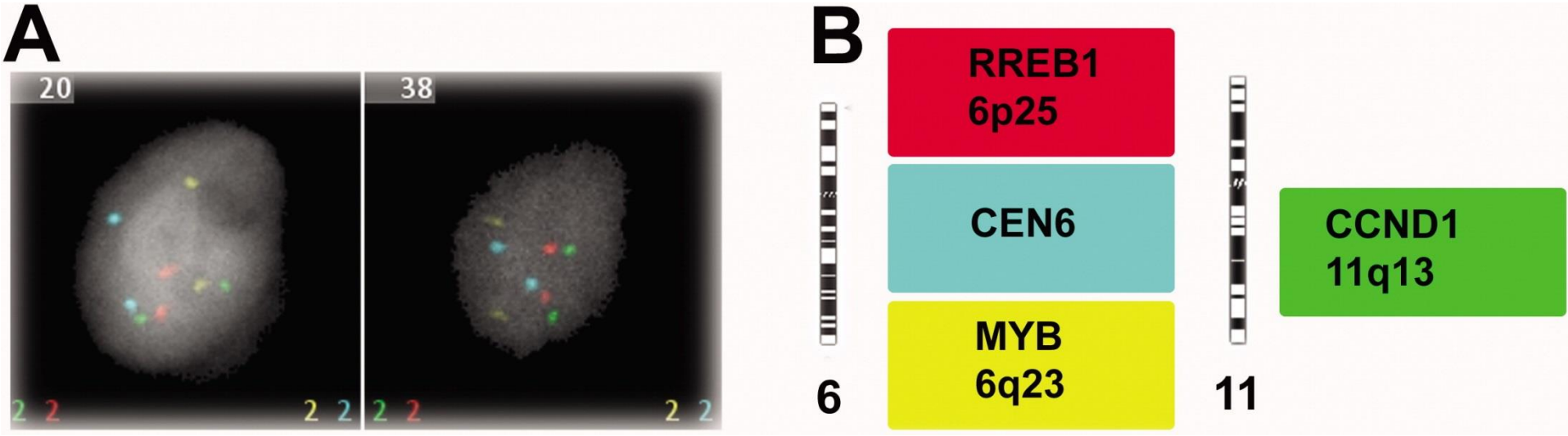
Characteristic attributes

	Mutation Burden	UV Radiation Signature	DNA Copy Number Changes	Types of Aberration
High-CSD	Very high	Strong	Multiple	Typically chromosomal arms or entire chromosomes
Low-CSD	High	Strong	Multiple	Typically chromosomal arms or entire chromosomes
Acral/ Mucosal	Low	Absent	Numerous	Multiple focused amplication and deletions
Uveal	Very low	Absent	Few	Typically chromosomal arms or entire chromosomes
Spitz	Probably low	Variable	Multiple	Typically chromosomal arms or entire chromosomes

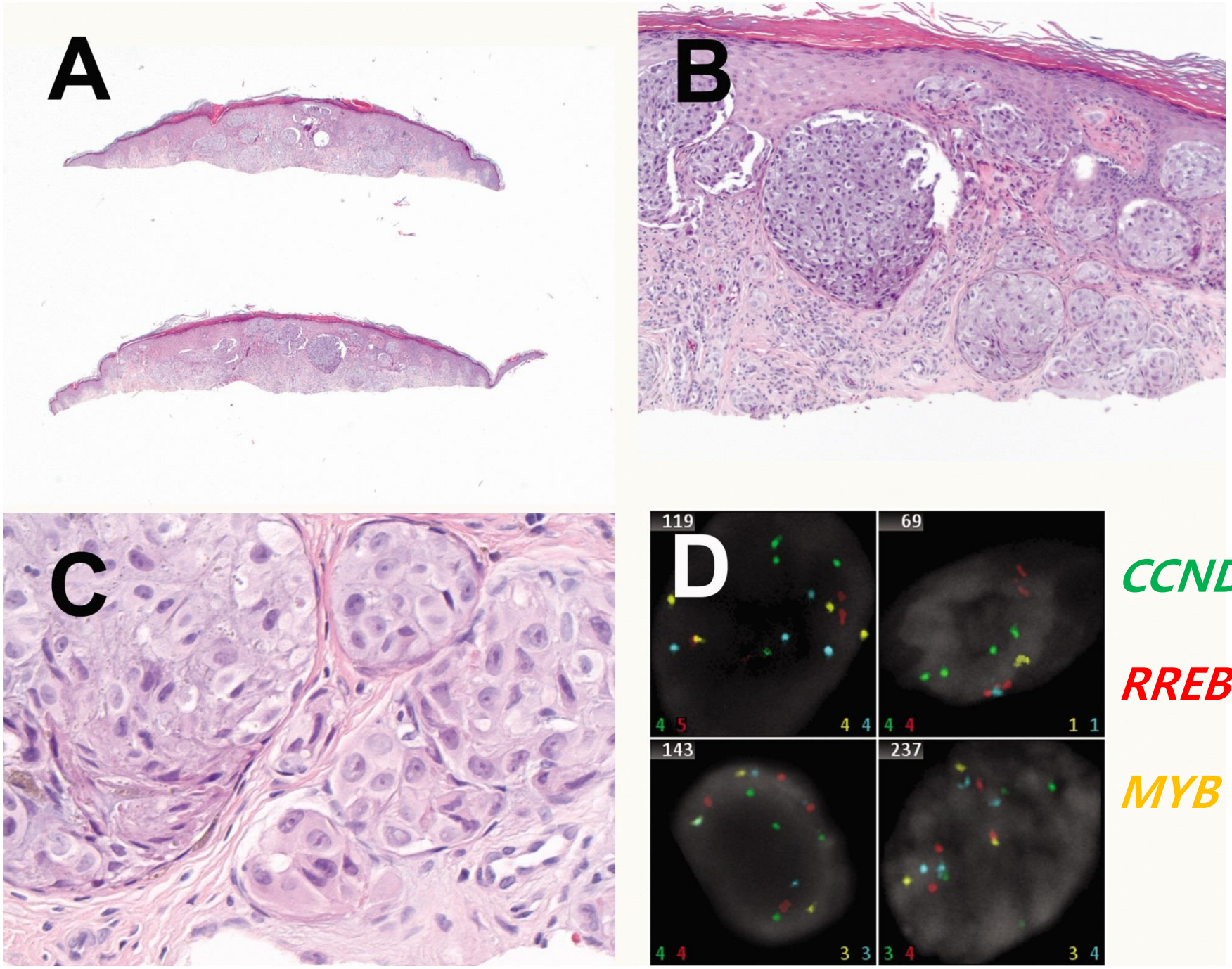
Copy # Variation

- Multiple gain and loss in melanoma
- Lack in gain and loss in conventional and blue nevus
- 9p loss in melanoma
- Amplifications at 11q13(cyclin D1, FGF3, and FGF4) in acral melanoma
- 11p gain in Spitz N(HRAS)
- Proliferative nodule: multiple gain and loss
- Gene fusion→ no gain: FISH

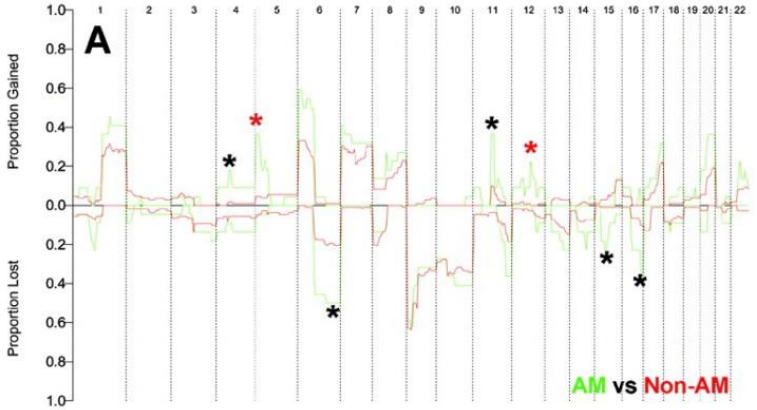
FISH

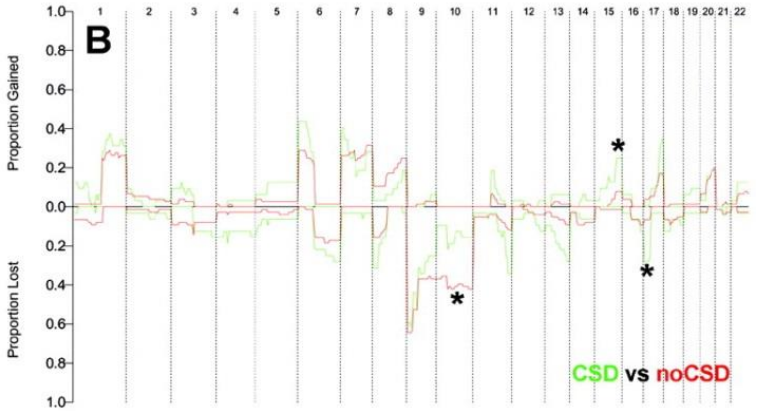


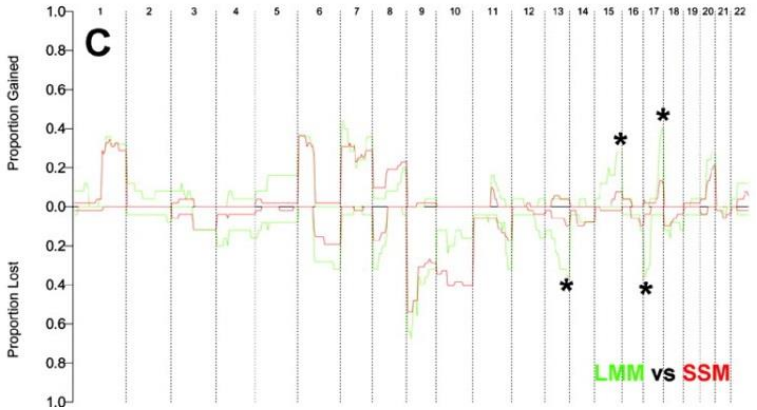
Pedram Gerami and Artur Zembowicz, Arch Pathol Lab Med—Vol 135, July 2011

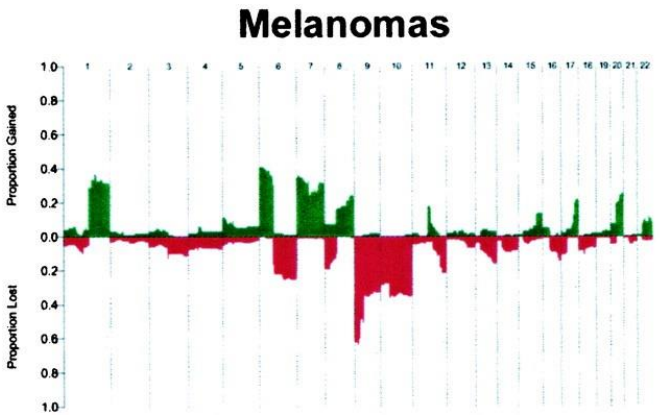


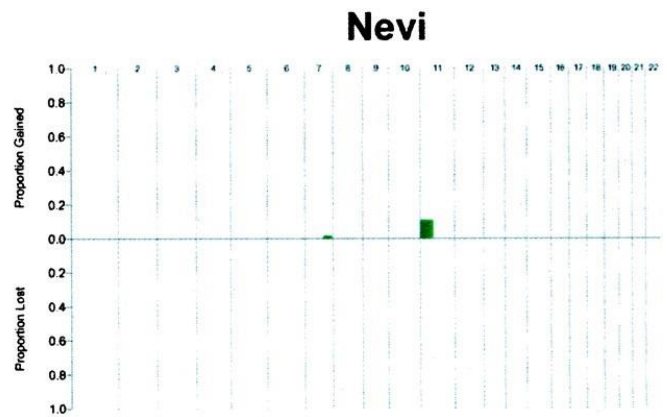
Pedram Gerami and Artur Zembowicz, Arch Pathol Lab Med—Vol 135, July 2011



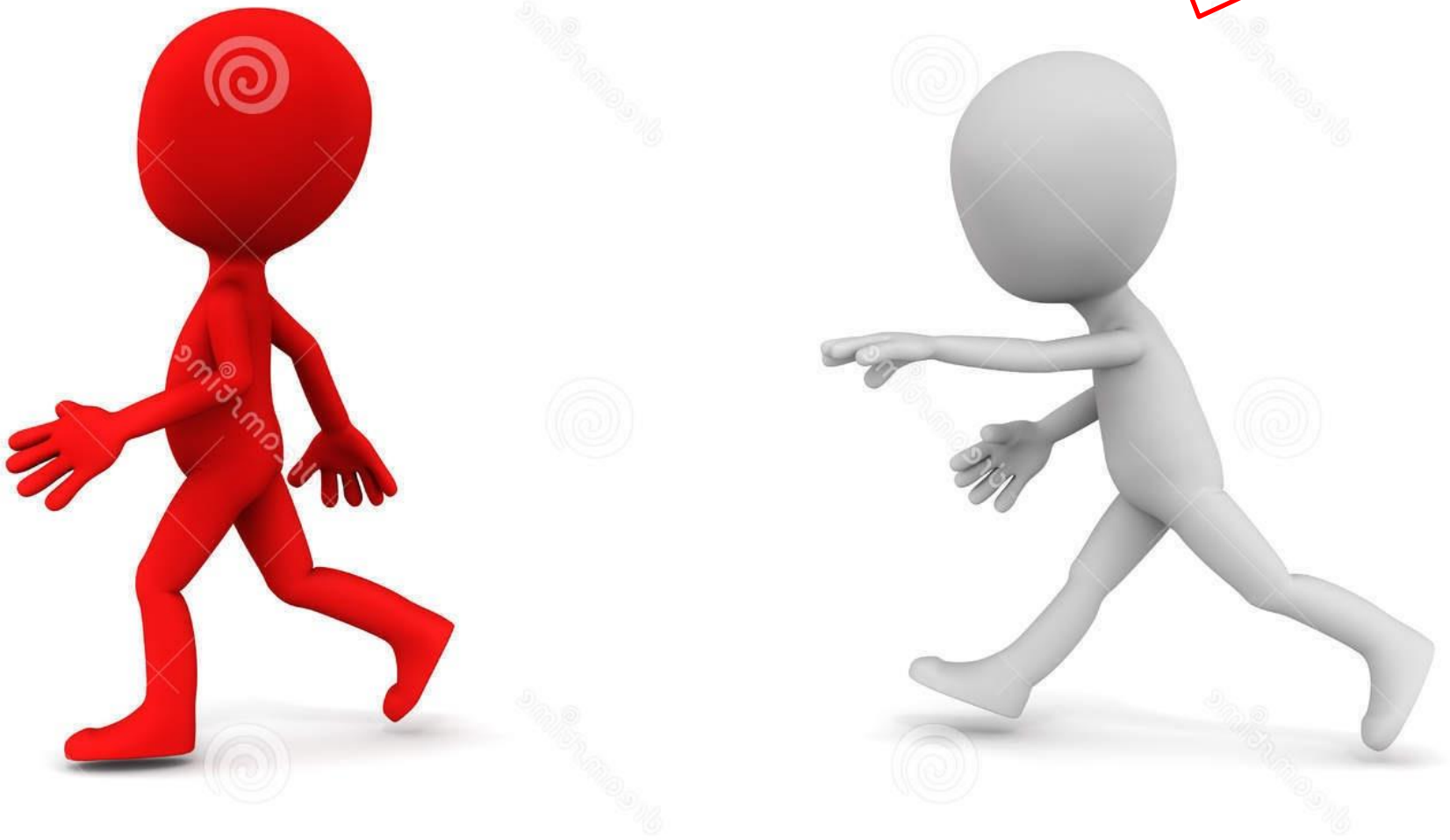








Boris C. Bastian et al, American Journal of Pathology, 2003;163


Morphology
Genomics

New WHO

HOW CAN WE PREPARE FOR THE FUTURE?

Overview

Built on the success of its predecessor, CAMELYON17 is the second grand challenge in pathology organised by the Diagnostic Image Analysis Group (DIAG) and Department of Pathology of the Radboud University Medical Center (Radboudumc) in Nijmegen, The Netherlands.

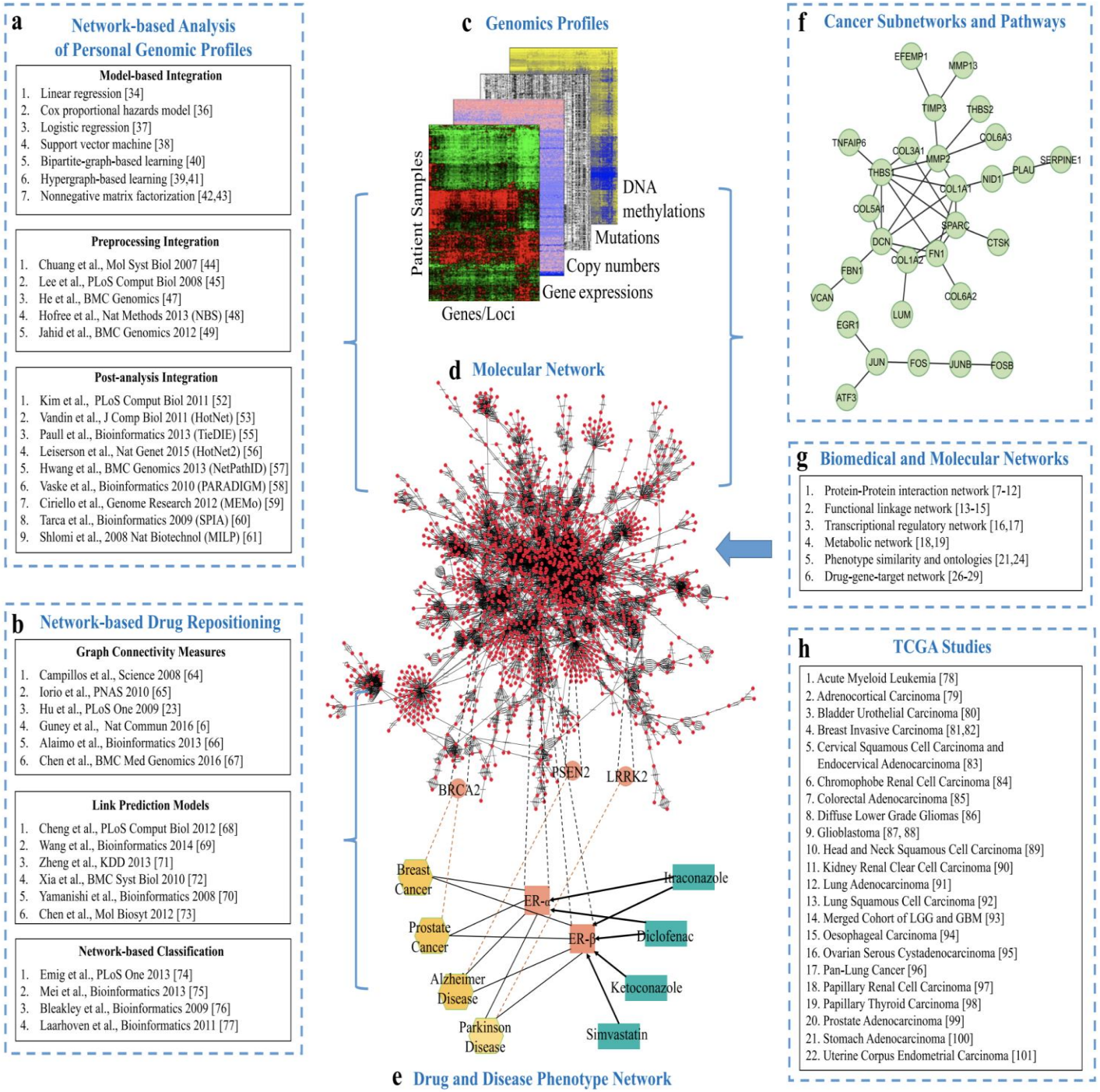
The goal of this challenge is to evaluate new and existing algorithms for automated detection and classification of breast cancer metastases in whole-slide images of histological lymph node sections. This task has high clinical relevance and would normally require extensive microscopic assessment by pathologists. The presence of metastases in lymph nodes has therapeutic implications for breast cancer patients. Therefore, an automated solution would hold great promise to reduce the workload of pathologists while at the same time reduce the subjectivity in diagnosis.

Last year at ISBI, we organised the highly successful CAMELYON16 grand challenge, in which 32 submissions from as many as 23 research groups were received. This was the first challenge ever using whole-slide images, having participants download over 600GB of data. This year, CAMELYON17 will invigorate the challenge by moving from slide level analysis to patient level analysis (i.e. combining the assessment of multiple lymph node slides into one outcome). This will bring the efforts closer to direct usefulness in a clinical setting. Compared to last year, the dataset will be significantly extended and will contain images from five medical centers.

Deep learning model outperforms human pathologists in the diagnosis of metastatic cancer

[1] n=12 [2] Small tumors **Reference: Camelyon16 (JAMA, 2017)**

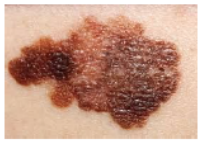
JAMA. 2017;318(22):2199–2210

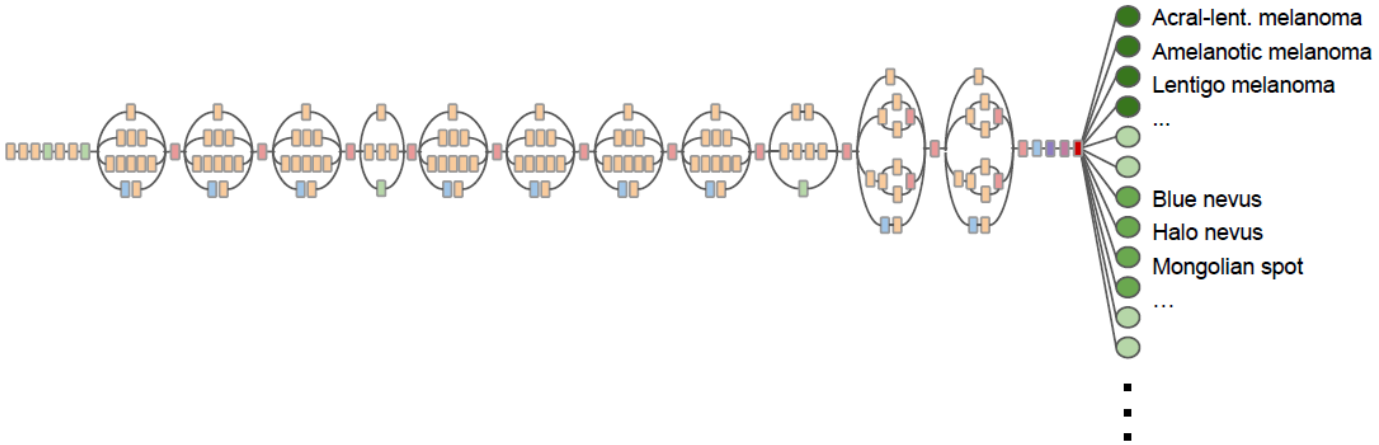


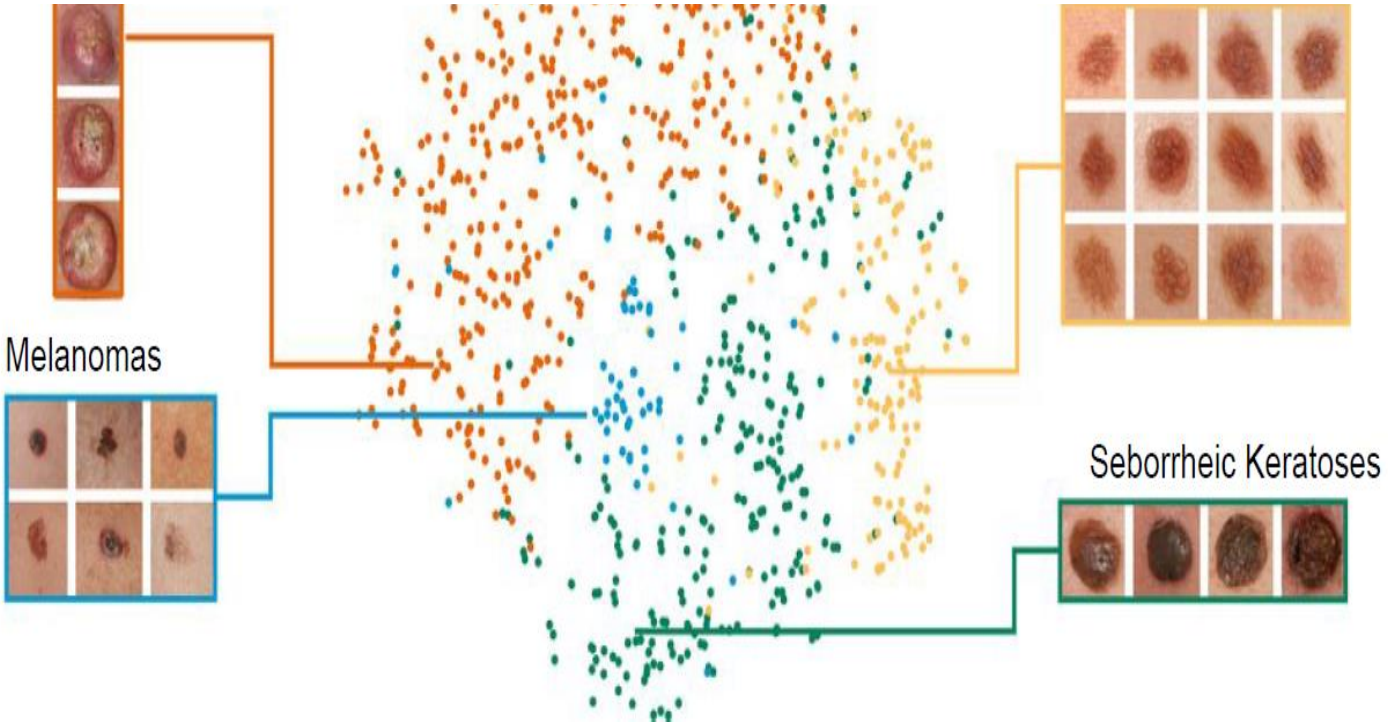
Network-based machine learning and graph theory algorithms for precision oncology

Precision Oncology **volume 1**, Article number: 25 (2017)

Dermatologist-level classification of skin cancer with deep neural networks







“It’s time to jump”