Classification of melanoma for pathologists

Boris C. Bastian

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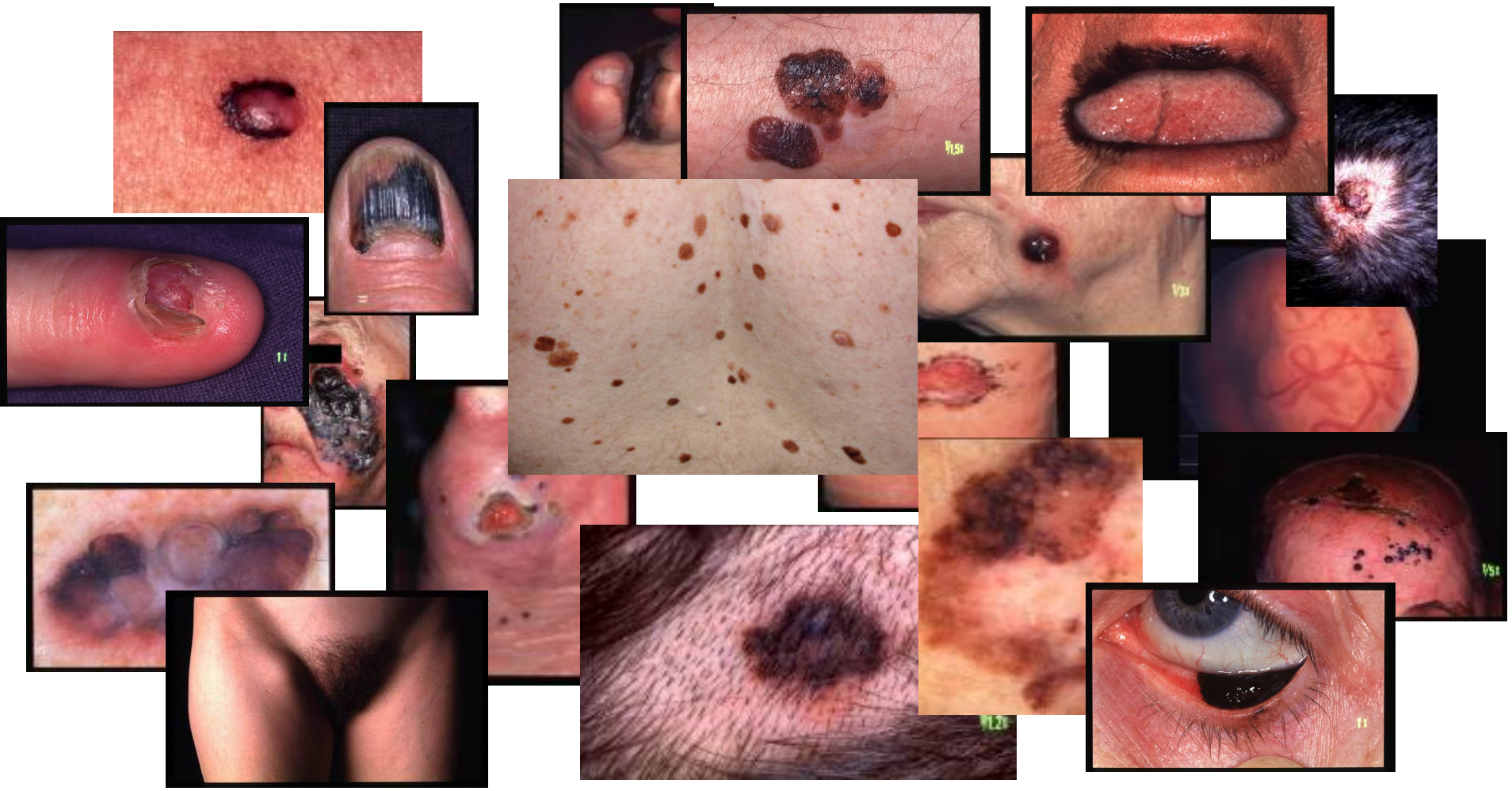
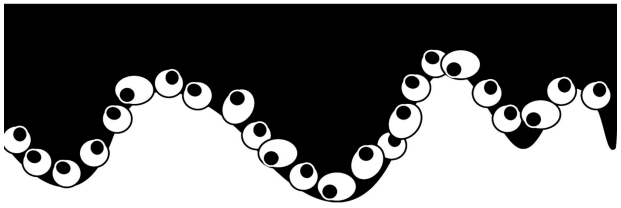
Clinical phenotypes of melanocytic neoplasms

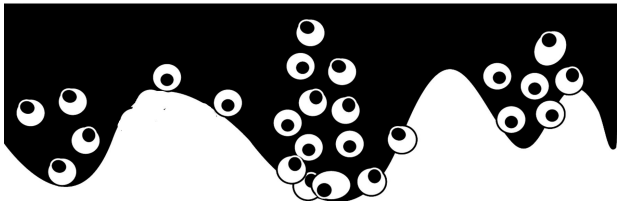


Histopathological phenotypes

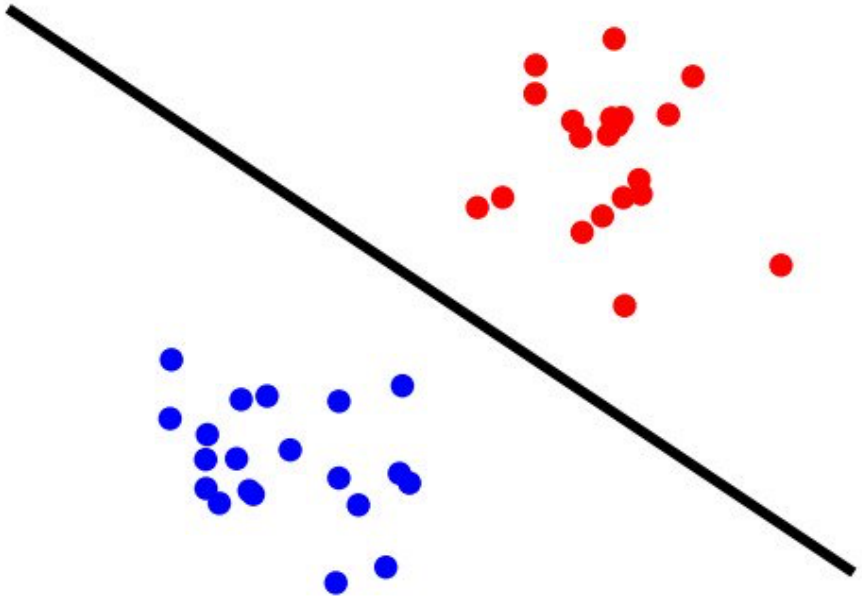
Lentiginous



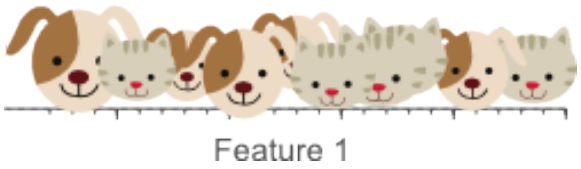
Pagetoid



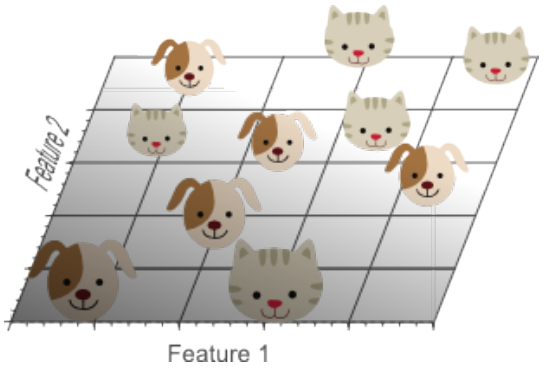
Classification



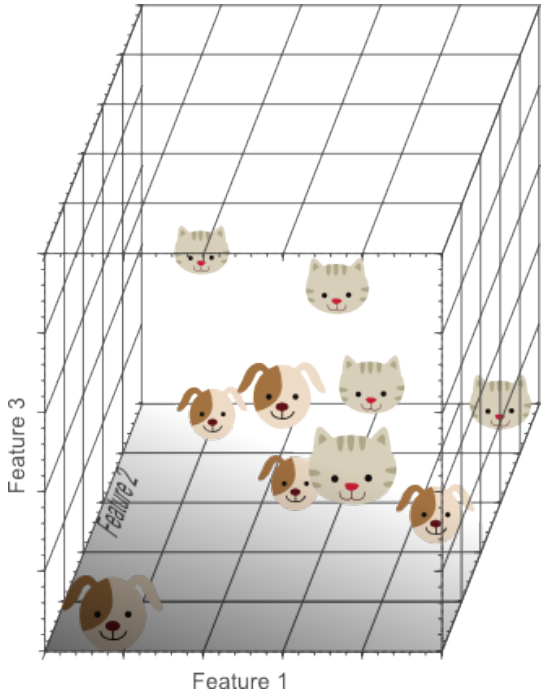
Dimensionality and classification



1 Dimension



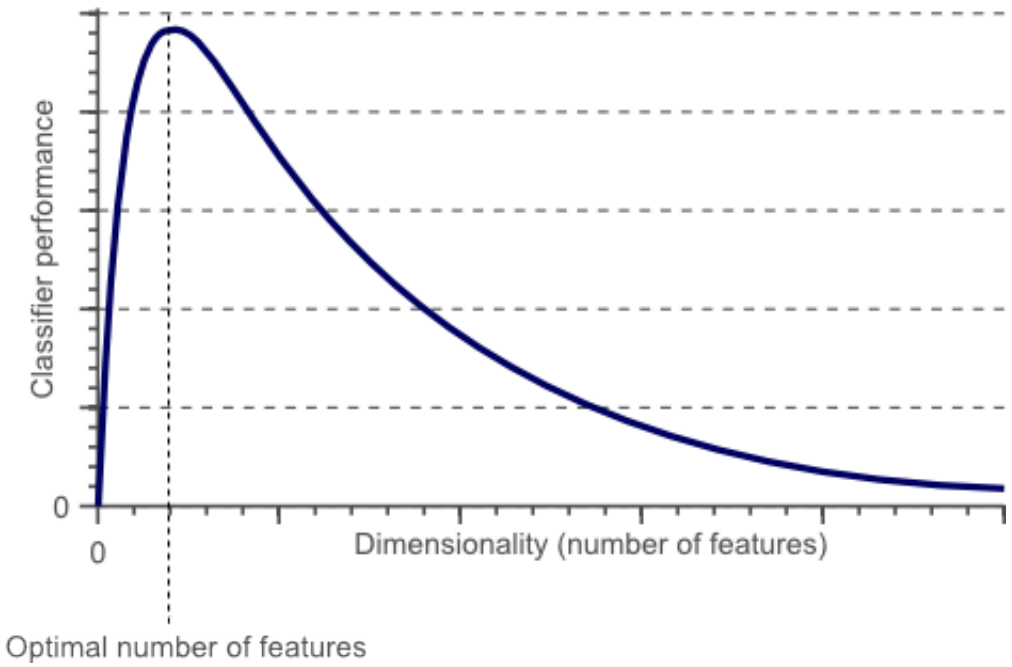
2 Dimensions



3 Dimensions

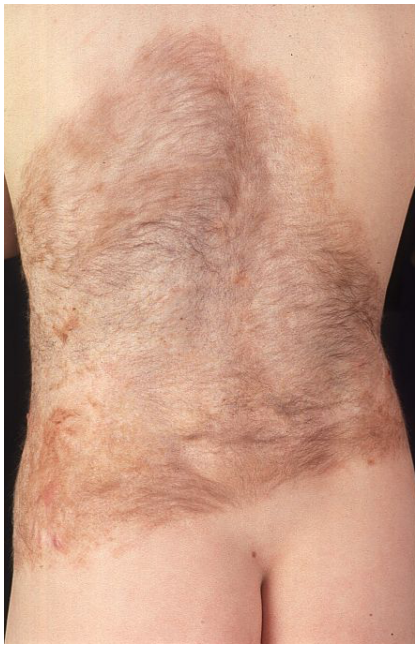
Vincent Spruyt

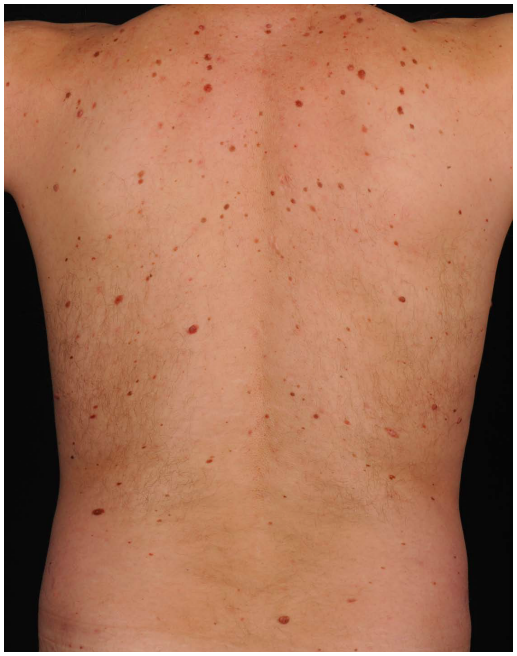
Dimensionality and classification

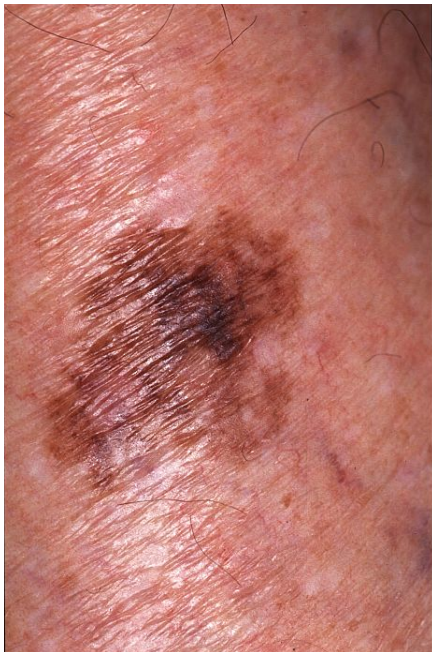


Vincent Spruyt

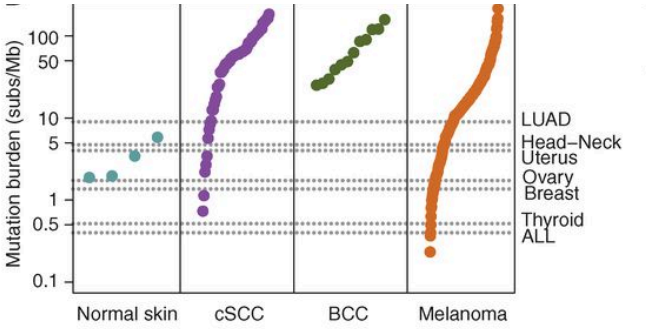
Age of onset



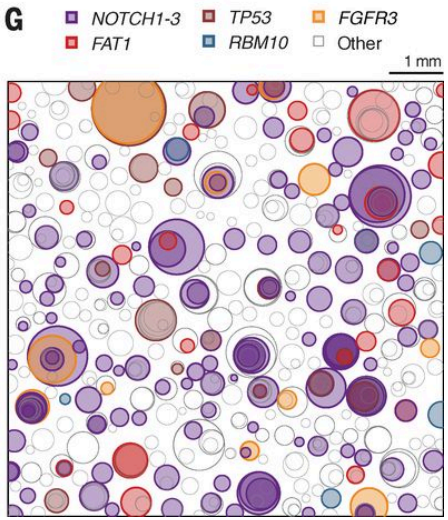


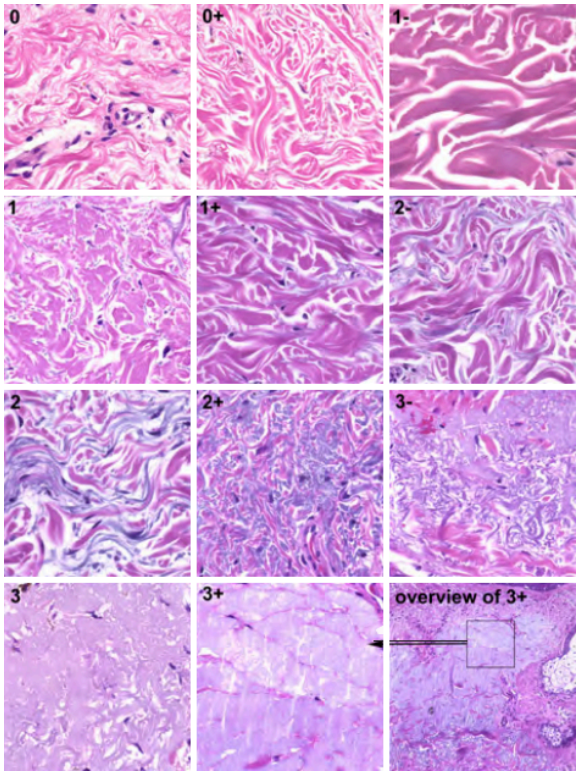


Degree of sun exposure



Martincorena et al. Science 2015

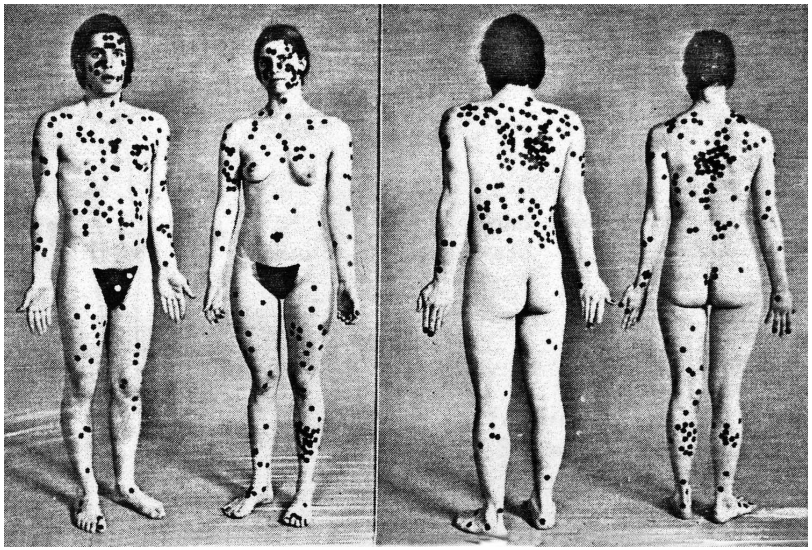




Landi, Bauer et al. Science 2015

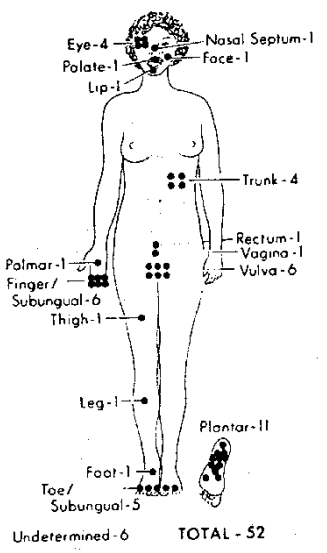
Host characteristics influence melanoma phenotypes

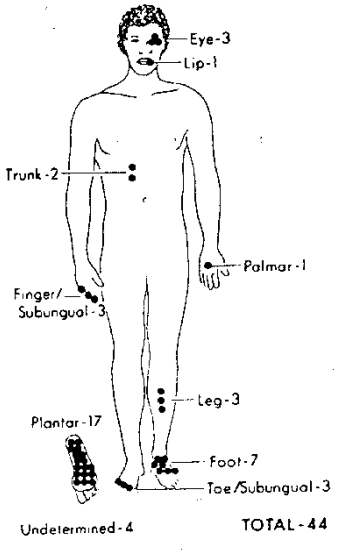
Caucasian



Melanoma Clinical Cooperative Group data

African



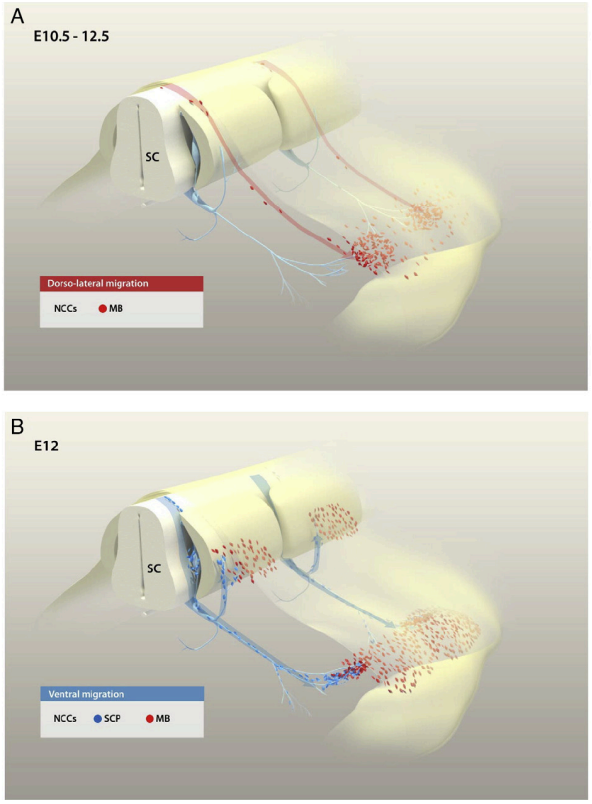


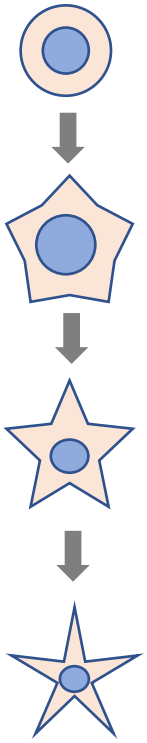
Krementz ET et al. Ann Surg 1976

Cells of origin and their differentiation states

Dorsolateral developmental pathway

Ventral developmental pathway



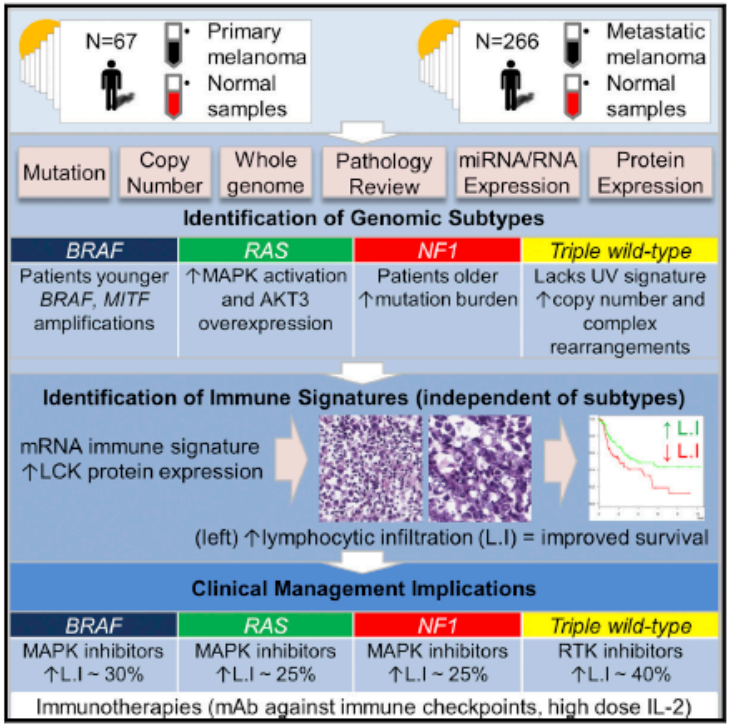


Somatic mutations

Cell

Genomic Classification of Cutaneous Melanoma

Graphical Abstract



Authors

The Cancer Genome Atlas Network

Correspondence

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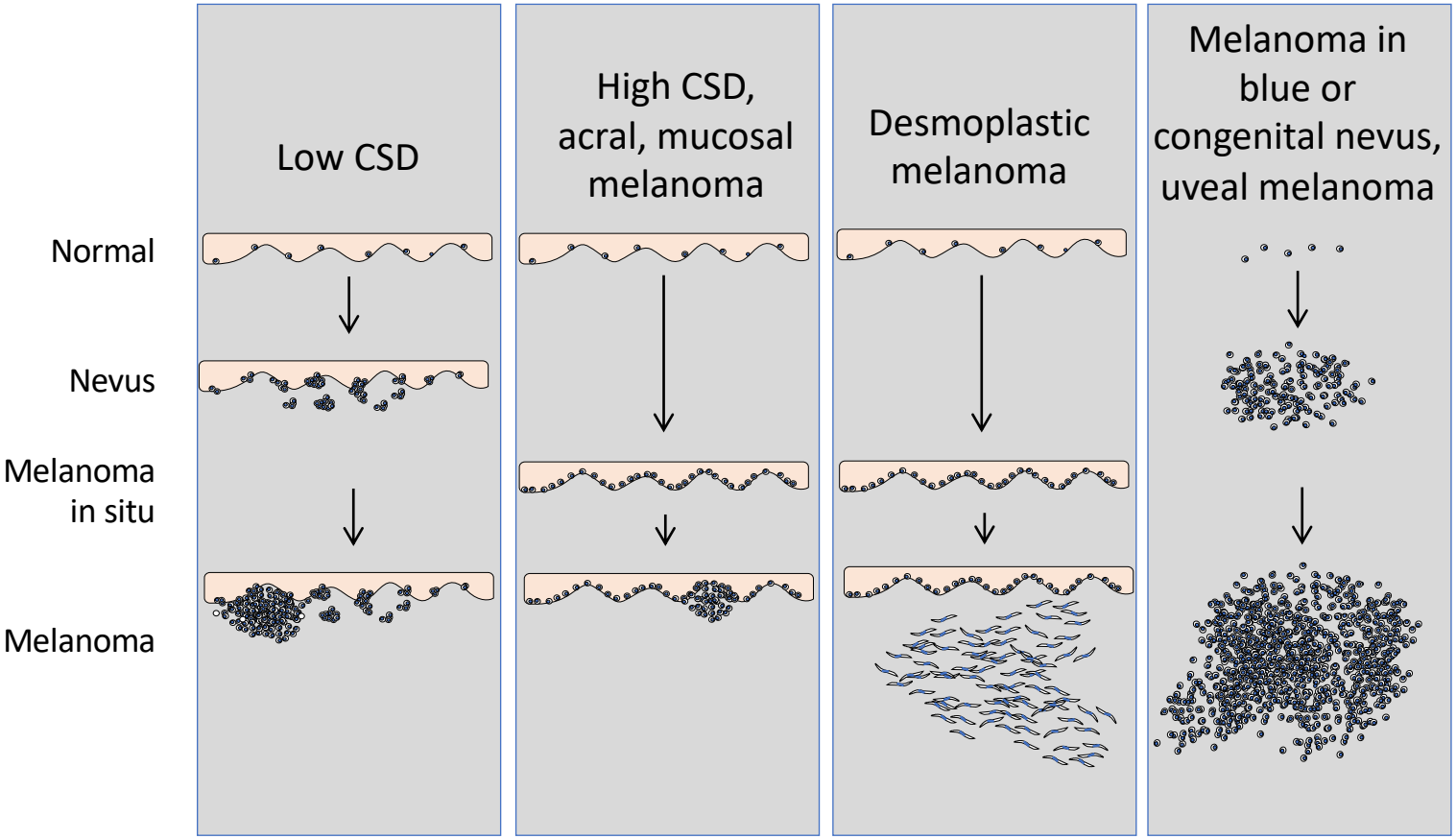
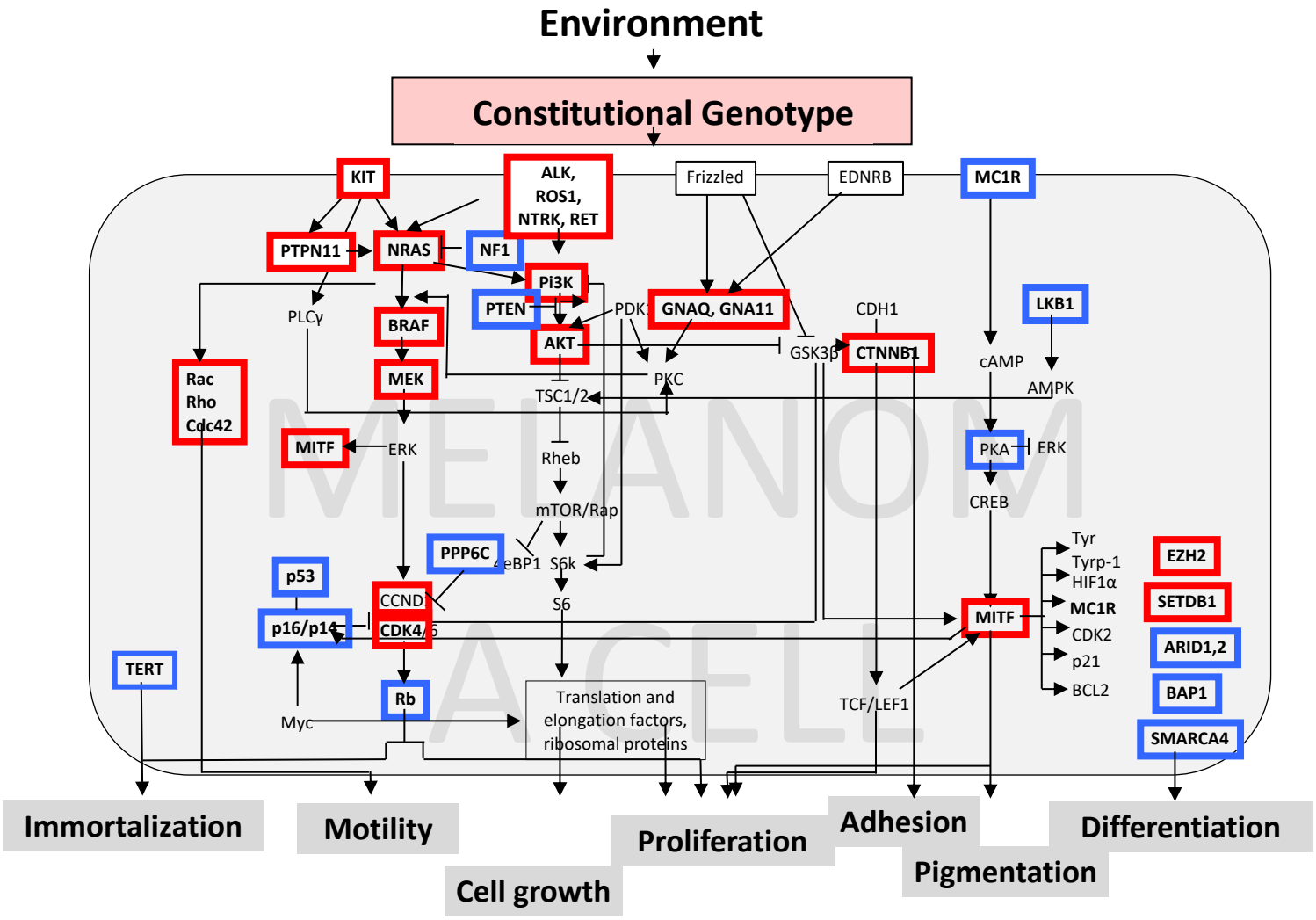
In Brief

An integrative analysis of cutaneous melanomas establishes a framework for genomic classification into four subtypes that can guide clinical decision-making for targeted therapies. A subset of each of the genomic classes expresses considerable immune infiltration markers that are associated with improved survival, with potential implications for immunotherapy.

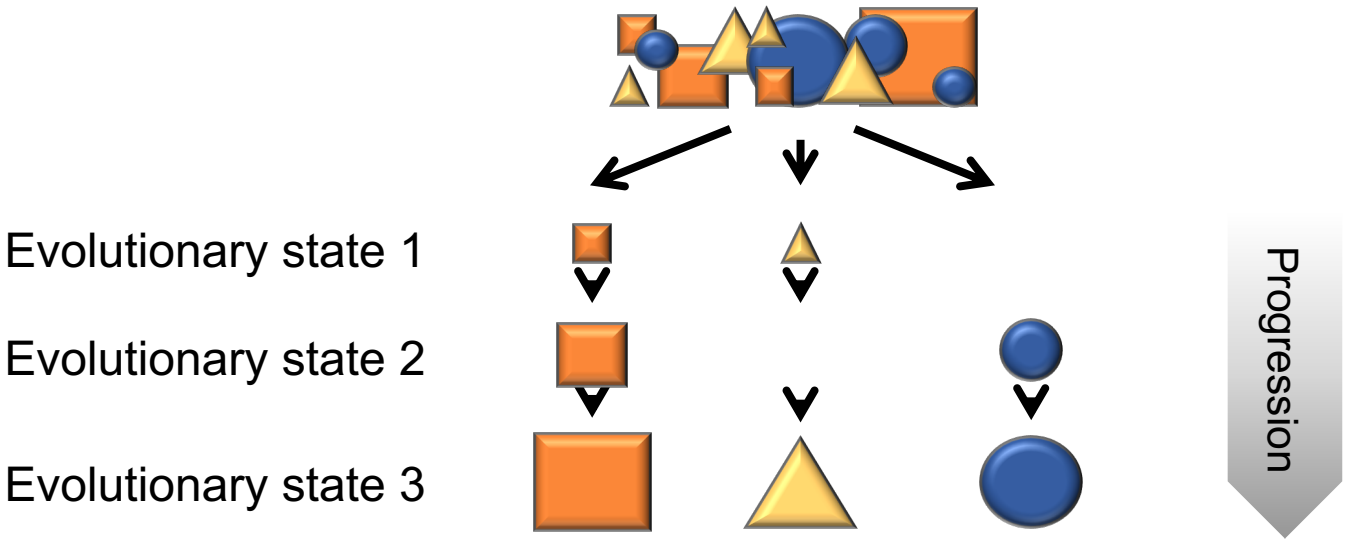
Evolution of primary melanomas



Genotype –> phenotype

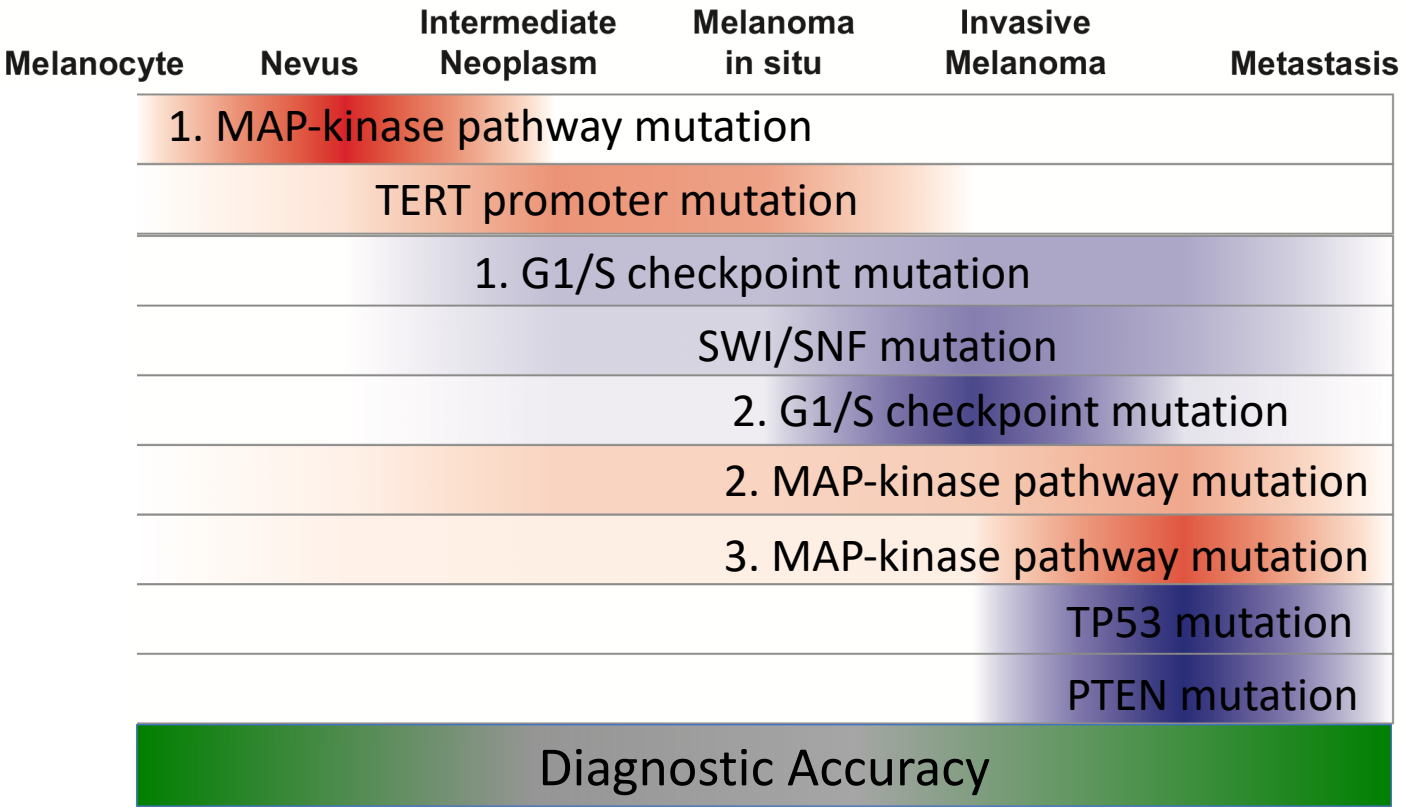


Integrated taxonomy of melanocytic neoplasms



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

Evolution of cutaneous melanoma



Shain et al. NEJM 2015; Shain & Bastian Nature Rev Cancer 2016

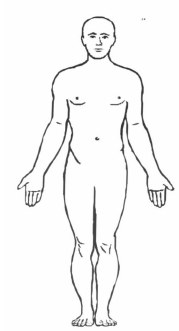
WHO Classification of Melanoma

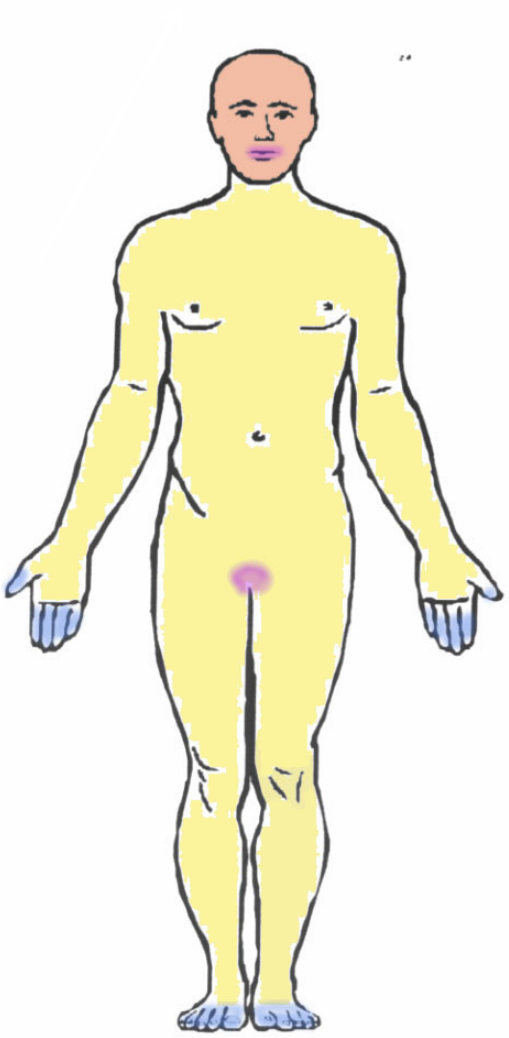
3rd Edition

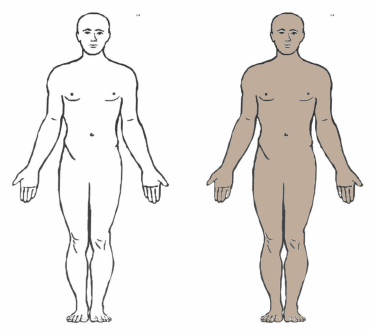
- Superficial spreading melanoma
- Nodular melanoma
- Lentigo maligna melanoma
- Desmoplastic melanoma
- Nevoid melanoma
- Acral-lentiginous melanoma
- Mucosal melanoma
- Uveal melanoma
- Melanoma of childhood
- Melanoma arising from giant congenital nevus
- Melanoma arising from a blue nevus
- Persistent melanoma

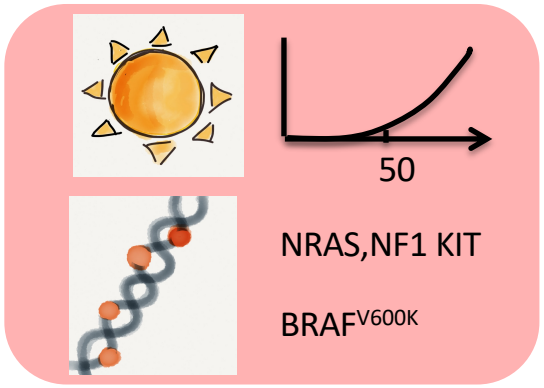
4th Edition

- Low CSD melanoma (SSM)
- High CSD melanoma (LMM)
- Desmoplastic melanoma
- Acral melanoma
- Mucosal melanoma
- Uveal melanoma
- Spitz melanoma
- Melanoma arising from giant congenital nevus
- Melanoma arising from a blue nevus

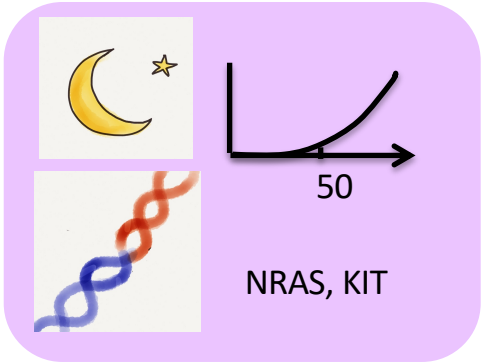




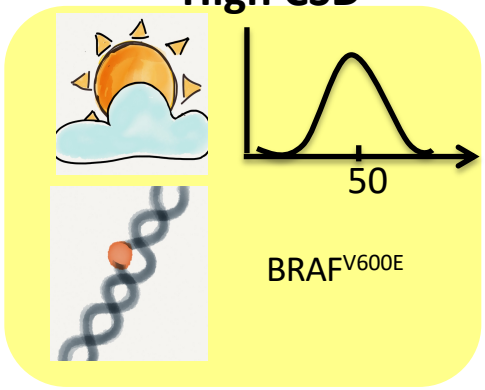




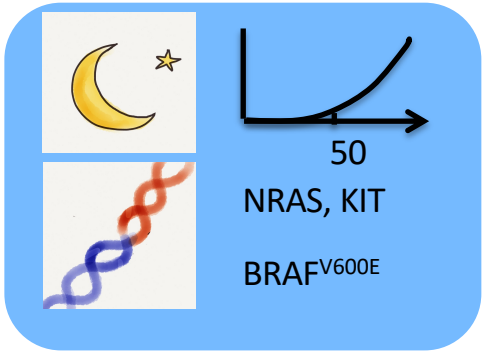
High CSD



Mucosa

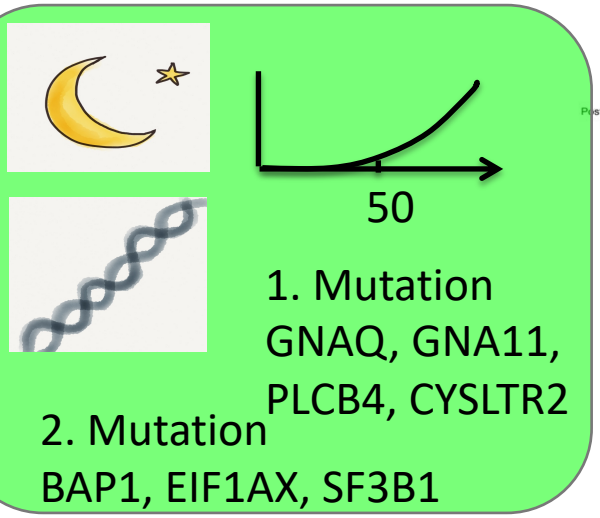


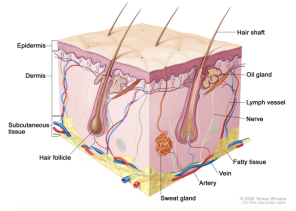
Low CSD



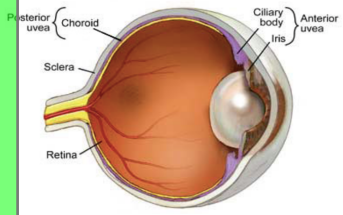
Acral

Neoplasms originating from extraepithelial melanocytes

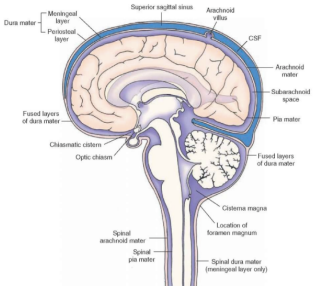




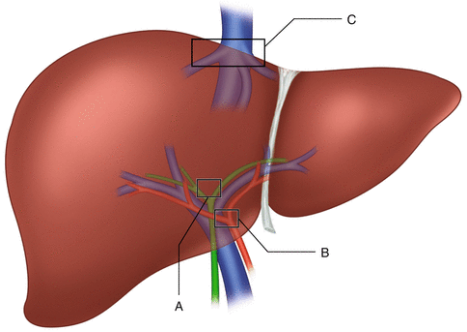
Dermis



Choroid

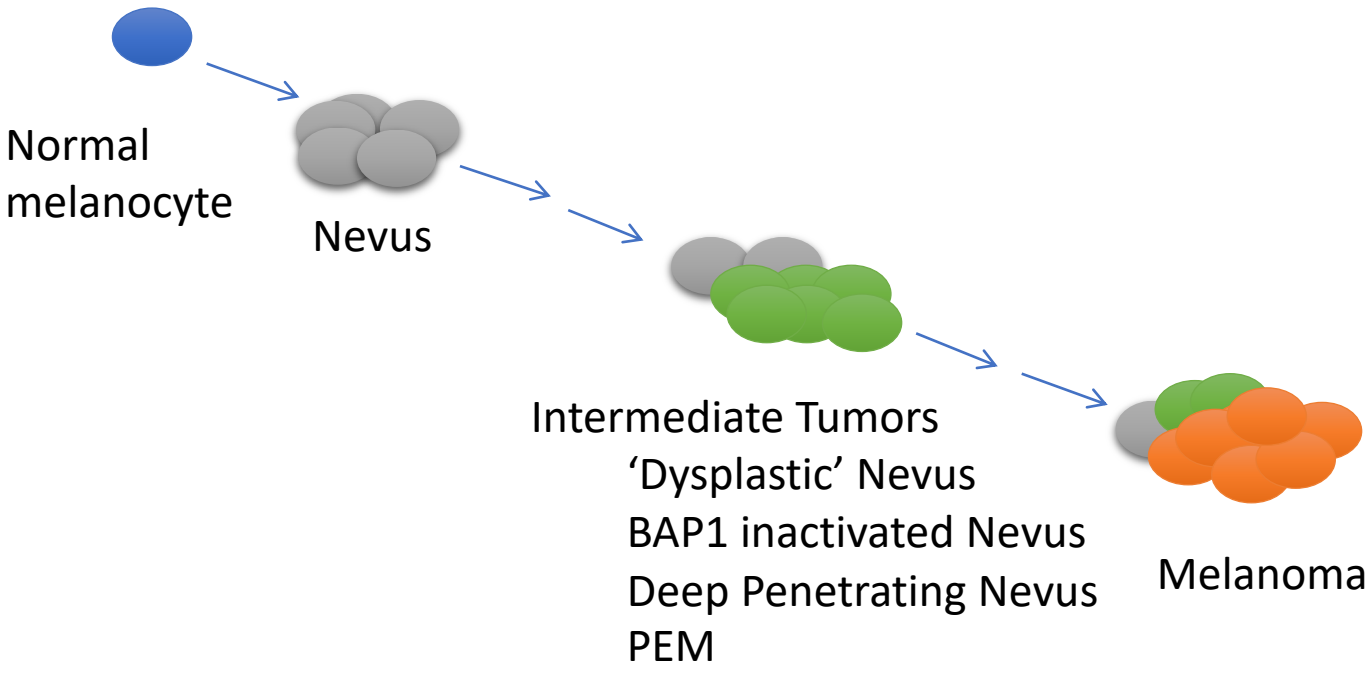


Leptomeninges

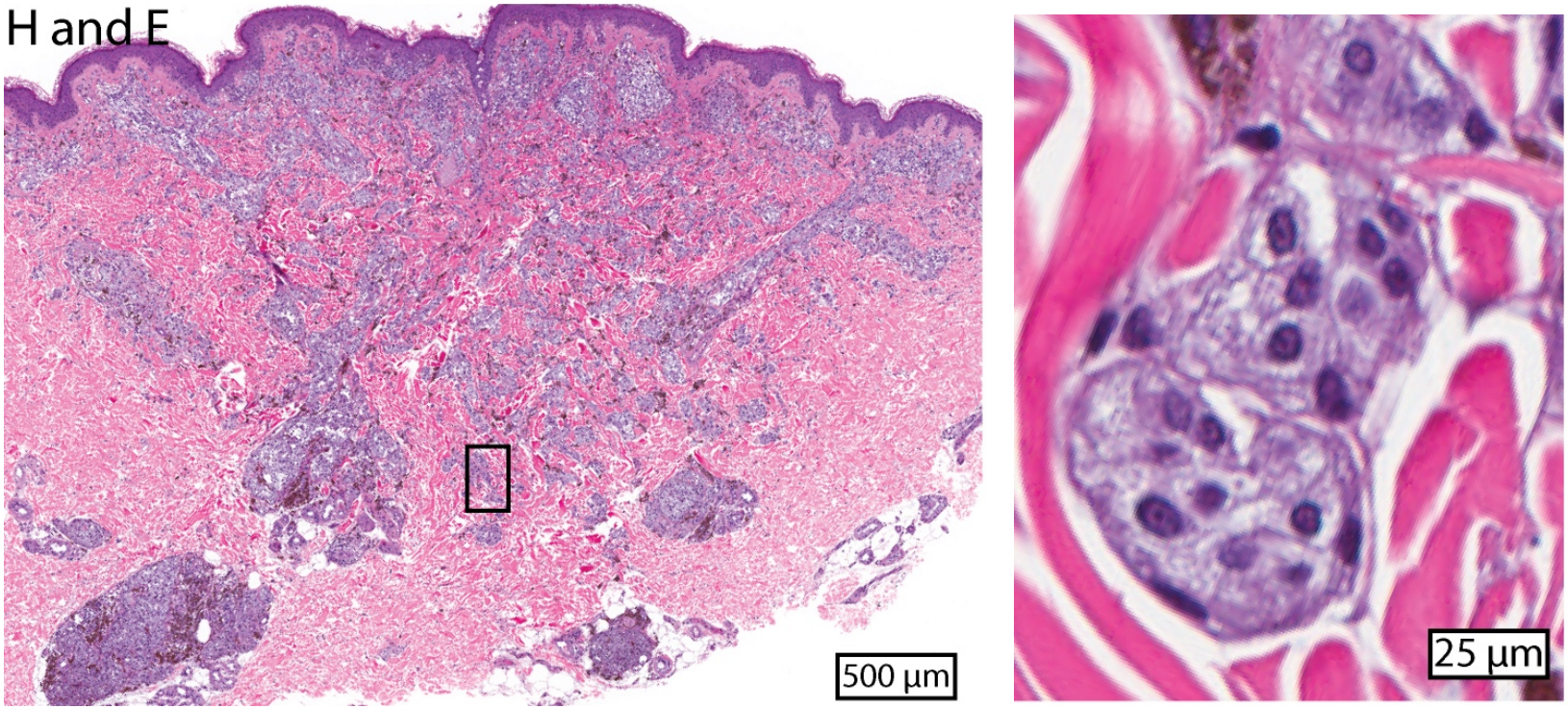


Liver

Genetic evolution of melanocytic neoplasms



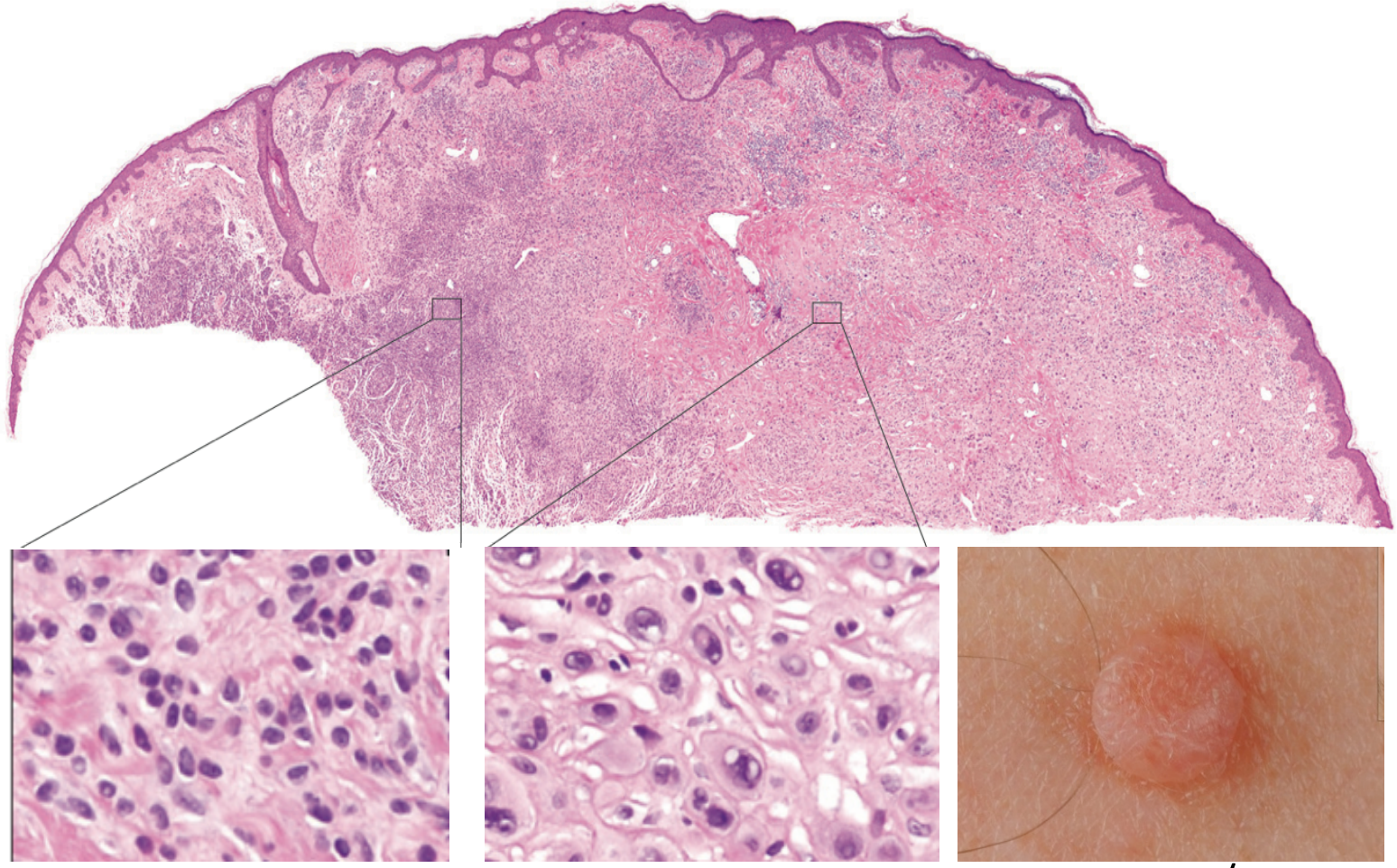
Deep penetrating nevus



DPN = MAP-kinase pathway + WNT pathway

Yeh I, et al. *Nat Commun* 2017

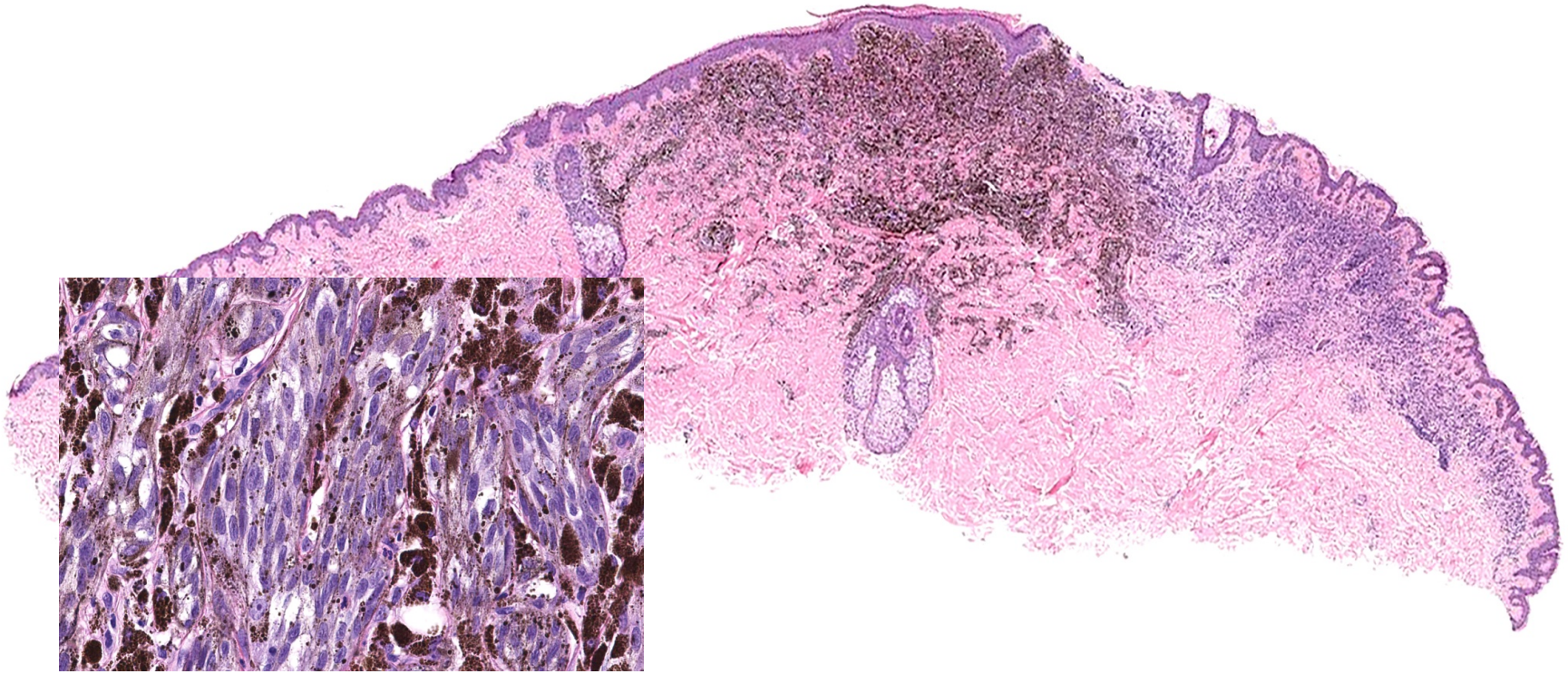
BAP1-inactivated Spitzoid tumor



BAP1oma = MAP-kinase pathway + $BAP1^{-/-}$

Wiesner et. al. Nat Genet 2011

Pigmented epithelioid melanocytoma



PEM = MAP-kinase pathway + PKA pathway

Zembowicz et. al. Am J Surg Pathol. 2007

WHO “Pathways” to melanomas

Pathway I	Low-CSD melanoma/superficial spreading melanoma
Pathway II	High-CSD melanoma/lentigo maligna melanoma
Pathway III	Desmoplastic melanoma
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

Revised WHO classification, 4th Edition

	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).

Revised WHO classification, 4th Edition

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.