

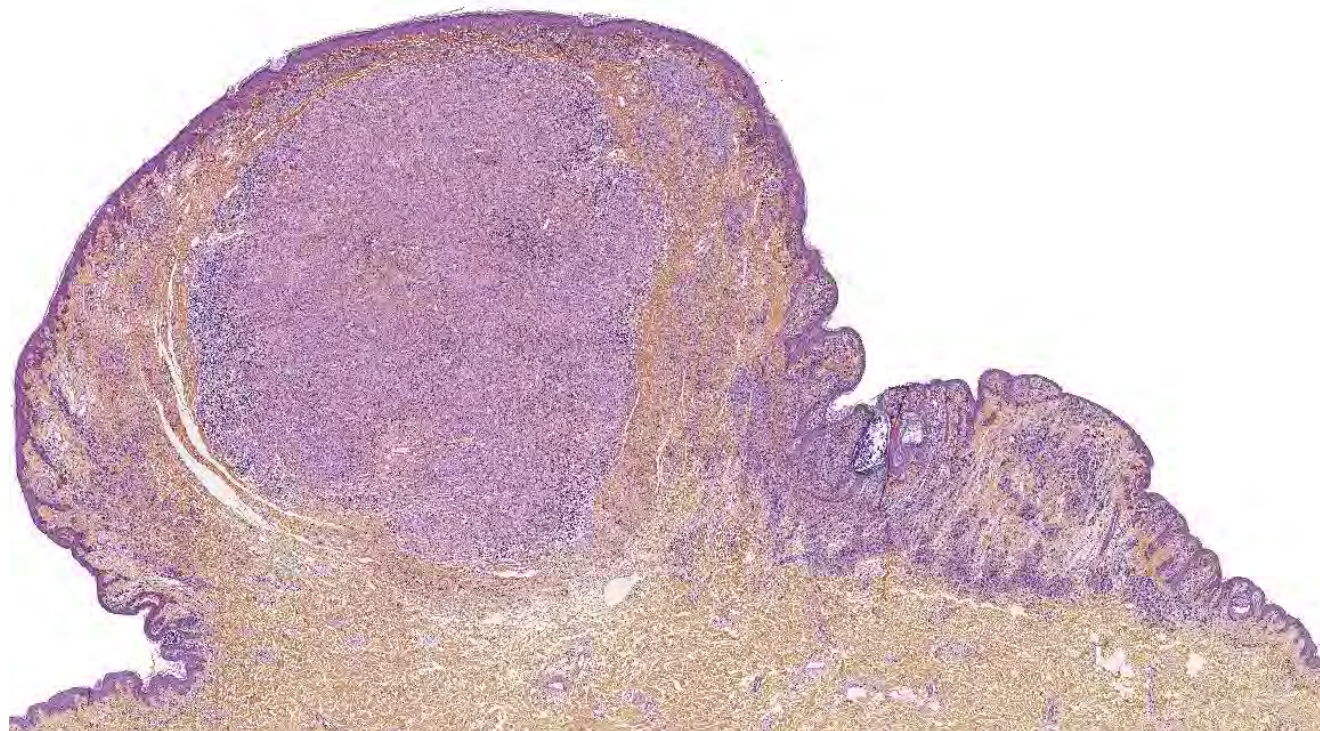
Combined melanocytic nevi BIM, WAM, PEM etc

Arnaud de la Fouchardière MD, PhD
Lyon, France

Combined nevus

Definition

- Combination of 2 or more morphological components within a nevus



Combined nevus

Definition

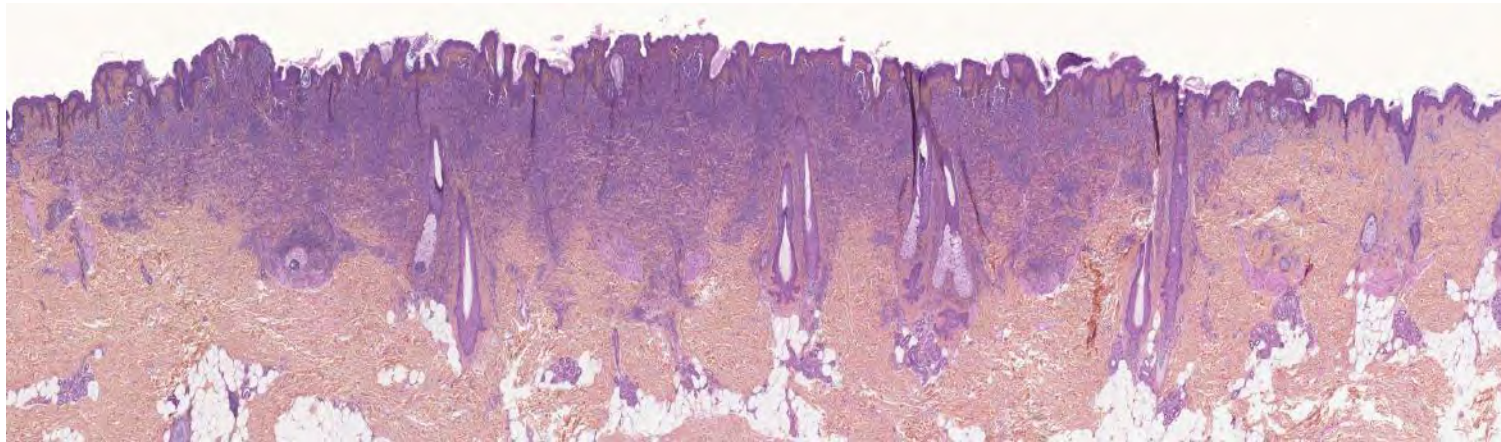
- Combination of 2 or more morphological components within a nevus

Common group	Spitz group	Blue group
<i>BRAF, NRAS, MAP2K1</i>	<i>HRAS, kinase fusions</i>	<i>GNAQ, GNA11, PLCB4, CYSLTR2 PKC-fusion GRM1-fusion</i>
Common nevus, Congenital nevus	Dendritic Mosaism	Blue nevus, uveal nevus
Combined/clonal nevus	Spitz Nevus	Cellular blue nevus
Atypical nevus	Spitz melanocytoma	Atypical blue nevus
<i>NRAS, BRAF</i> mutated melanoma (SSM)	Spitz Melanoma	Blue-type melanoma, Uveal melanoma

Intermediate low-grade intra-dermal clonal tumors arising from common nevi

BRAF, NRAS, MAP2K1

Common nevus,
Congenital nevus



Small *BRAF*-mutated congenital-like nevus



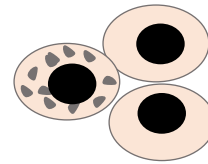
Dr Longueville

Intermediate grade intra-dermal clonal tumors arising from common nevi

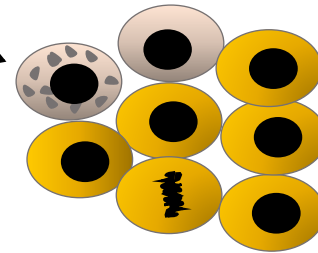
BRAF, NRAS, MAP2K1

Common nevus,
Congenital nevus

Clonal/combined nevus



Nevus



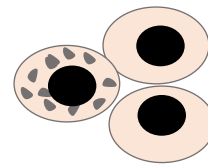
Clonal
nodule

Intermediate grade intra-dermal clonal tumors arising from common nevi

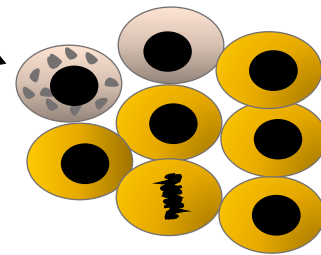
BRAF, NRAS, MAP2K1

Common nevus,
Congenital nevus

Clonal/combined nevus



Nevus



Clonal
nodule

- Secondary genetic events lead to specific morphological features

Intermediate grade clonal melanocytic tumours (WHO 2018)

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 <i>TERT;</i> <i>CDKN2A;</i> <i>TP53;</i> <i>PTEN</i>	BRAF or NRAS + <i>BAP1</i>	BRAF; MAP2K1; or NRAS + CTNNB1 or APC	BRAF + PRKAR1A or PRKCA	NRAS; BRAF (non-p.V600E); KIT; NF1 <i>TERT;</i> <i>CDKN2A;</i> <i>TP53;</i> <i>PTEN;</i> <i>RAC1</i>	NF1; ERBB2; MAP2K1; MAP3K1; BRAF; EGFR; MET <i>TERT;</i> <i>NFKBIE;</i> NRAS; PIK3CA; PTPN11

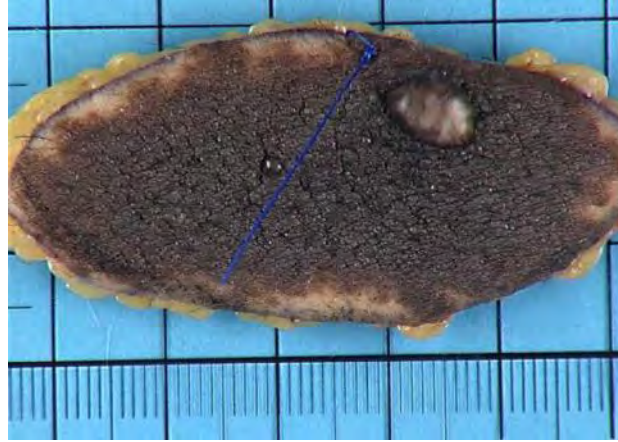
BIN, BAP1-inactivated naevus; BN, blue naevus; CBN, cellular blue naevus; CN, congenital naevus; CSD, cumulative sun damage; DPN, deep penetrating naevus; IAMP, intraepidermal atypical melanocytic proliferation; IAMPUS, intraepidermal atypical melanocytic proliferation of uncertain significance; IMP, 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).

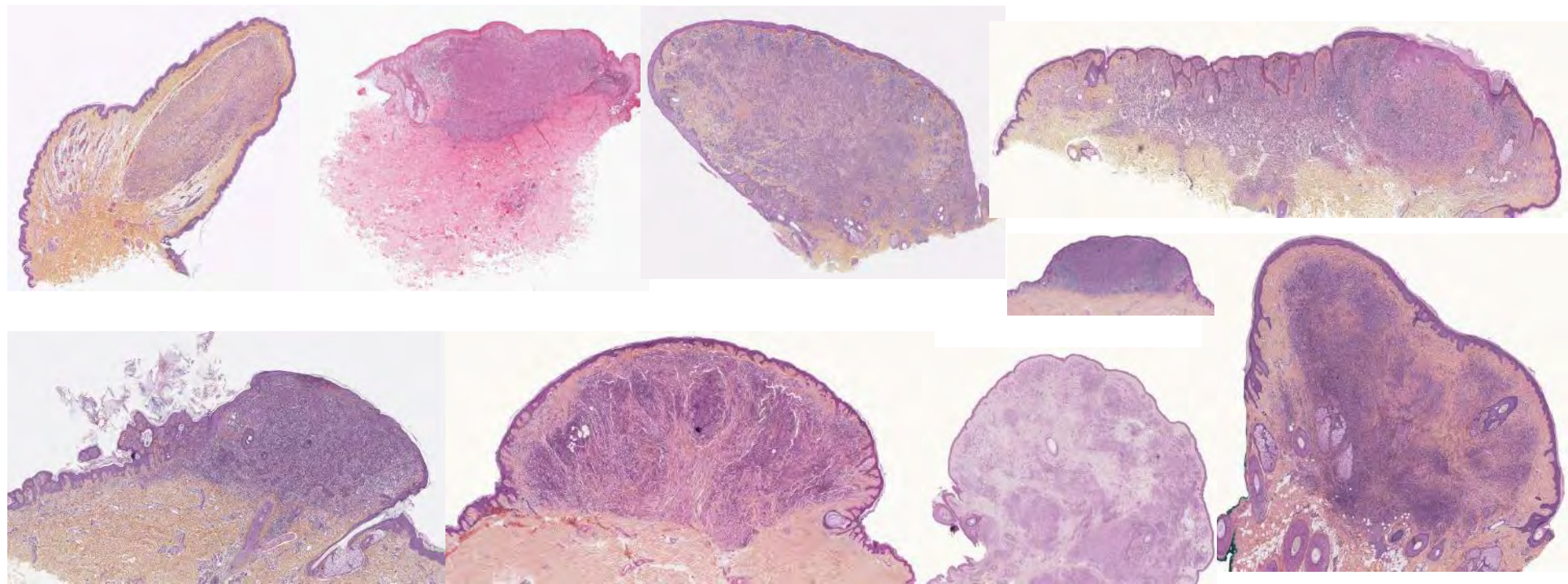
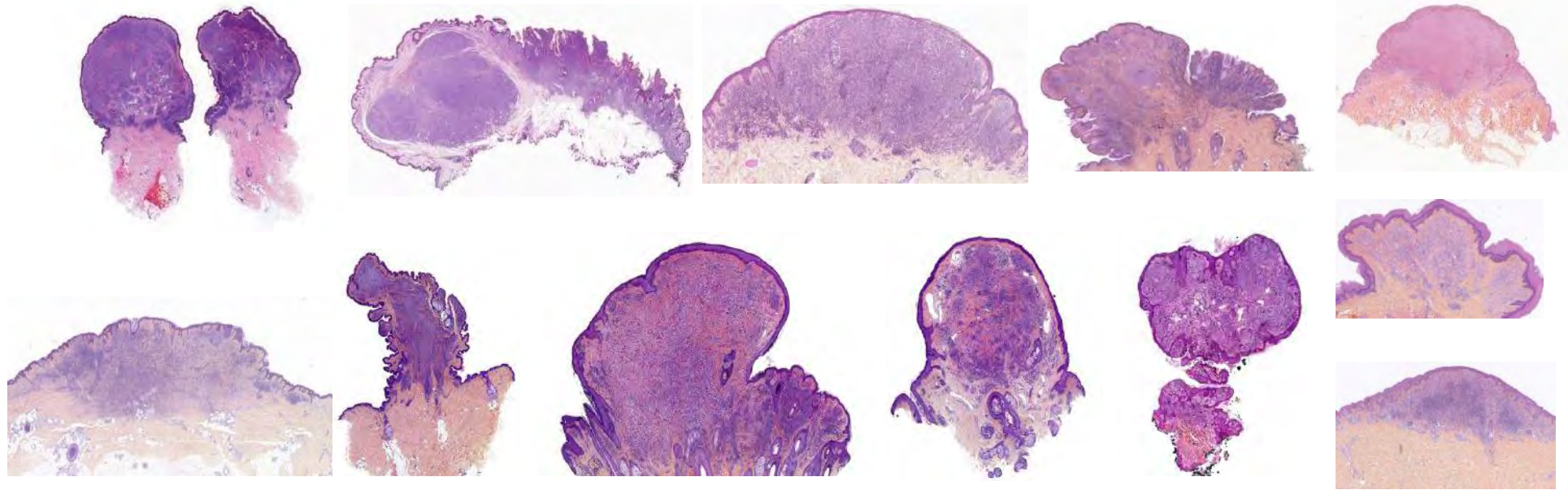
Combined *BAP1*-inactivated melanocytic tumors

BAP1-inactivated melanocytic tumors

Somatic > germline mutation of *BAP1*

- Children or young adults
- Female>Male
- Sun-exposed areas
- Modification of a nevus
- Growing unpigmented nodule <1cm
- Inflammatory features
- Multiple lesions: germline

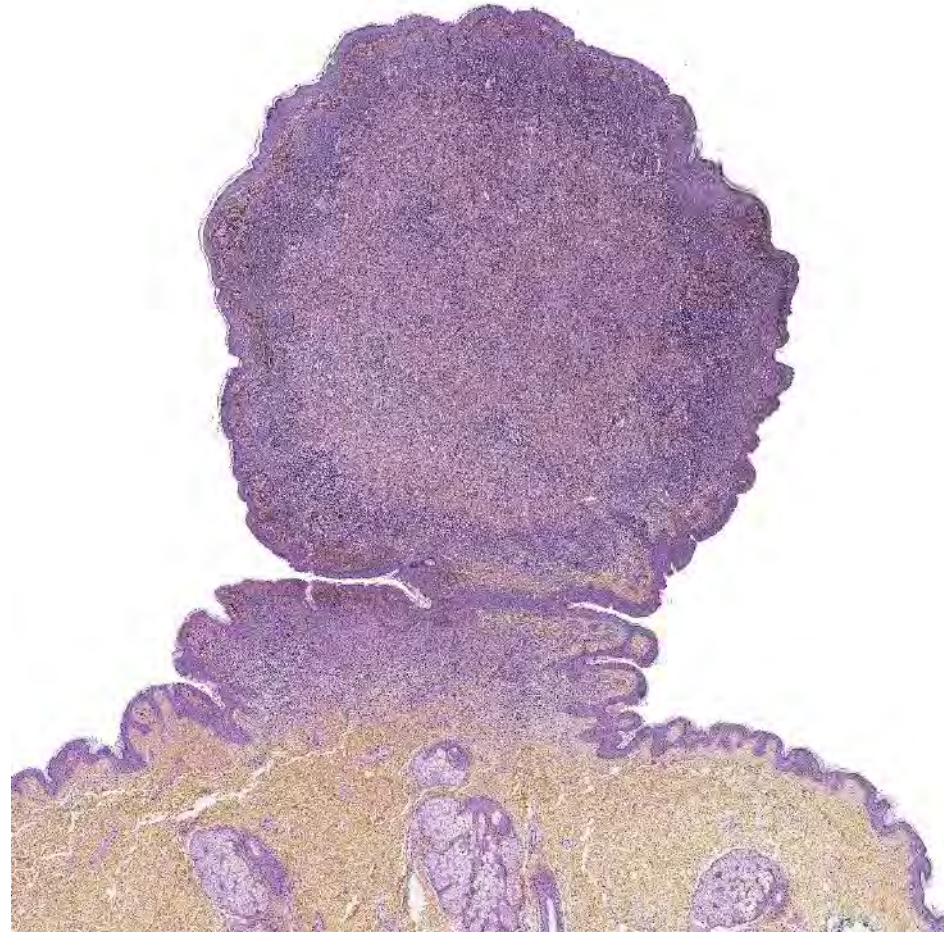




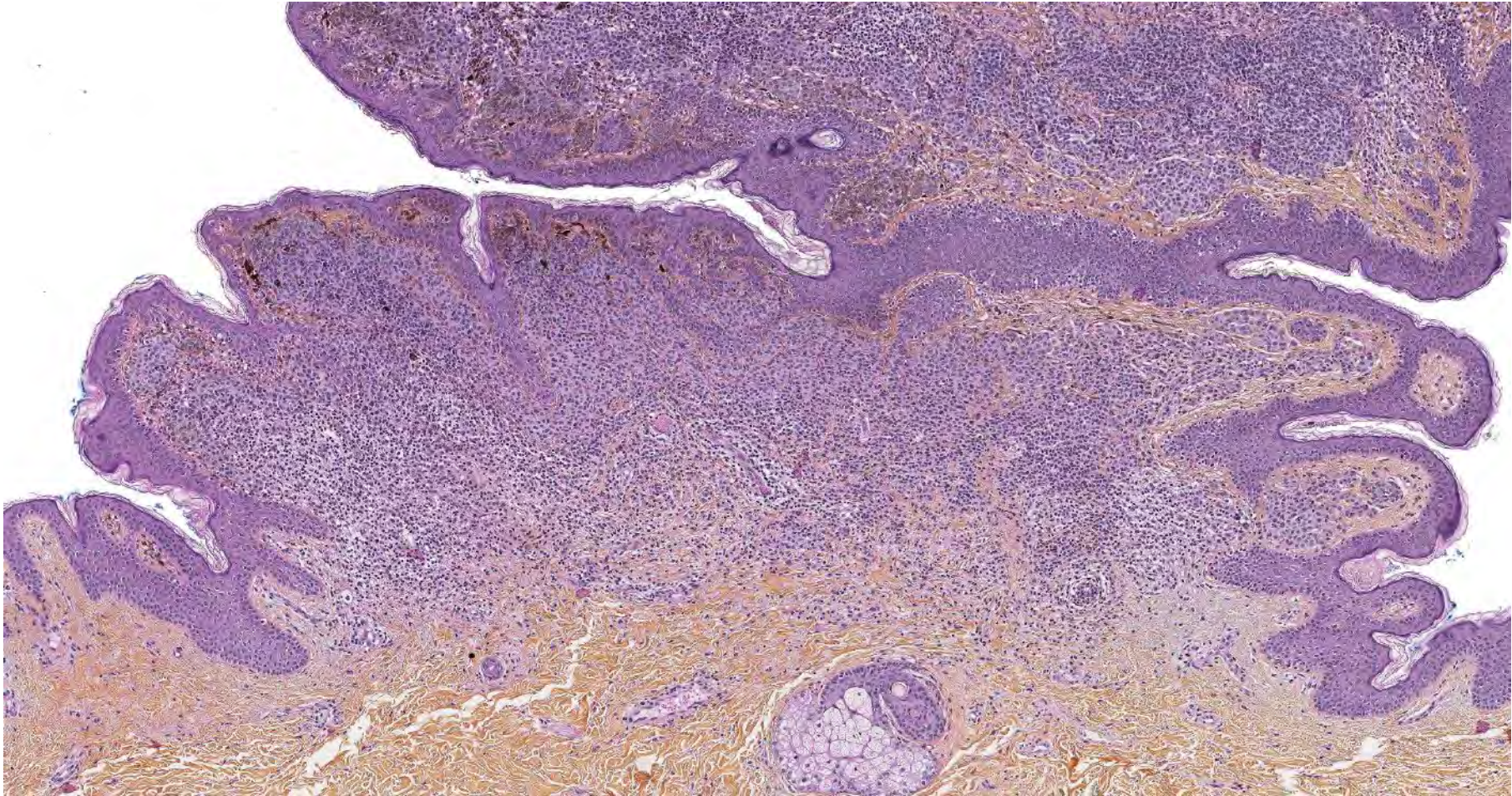
BAP1-inactivated melanocytic nevus (*BRAF V600E*+ *BAP1* mutation)



Dr de Carrère



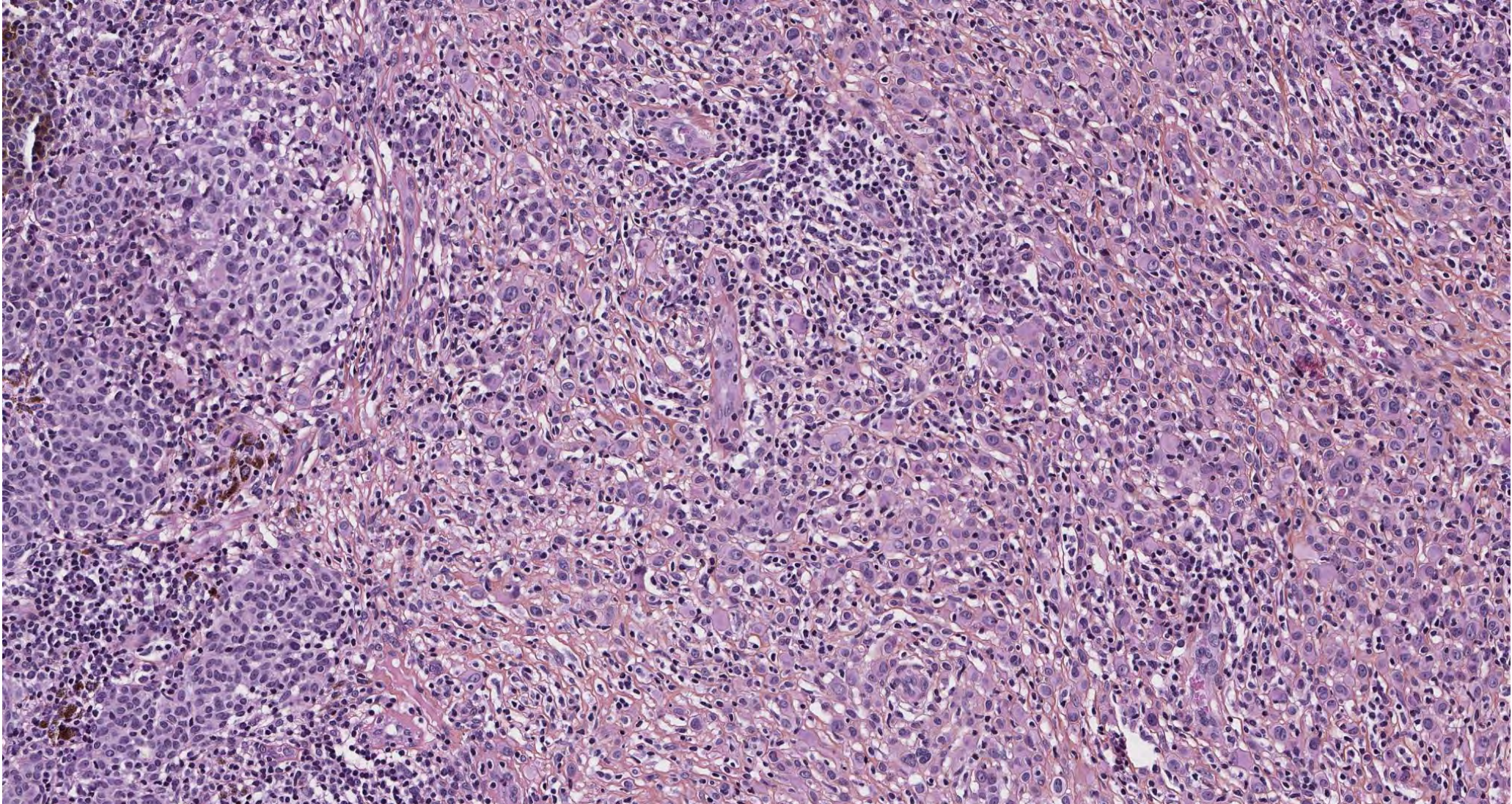
Combined lesion: lateral compound common nevus
usually *BRAF* V600E mutated



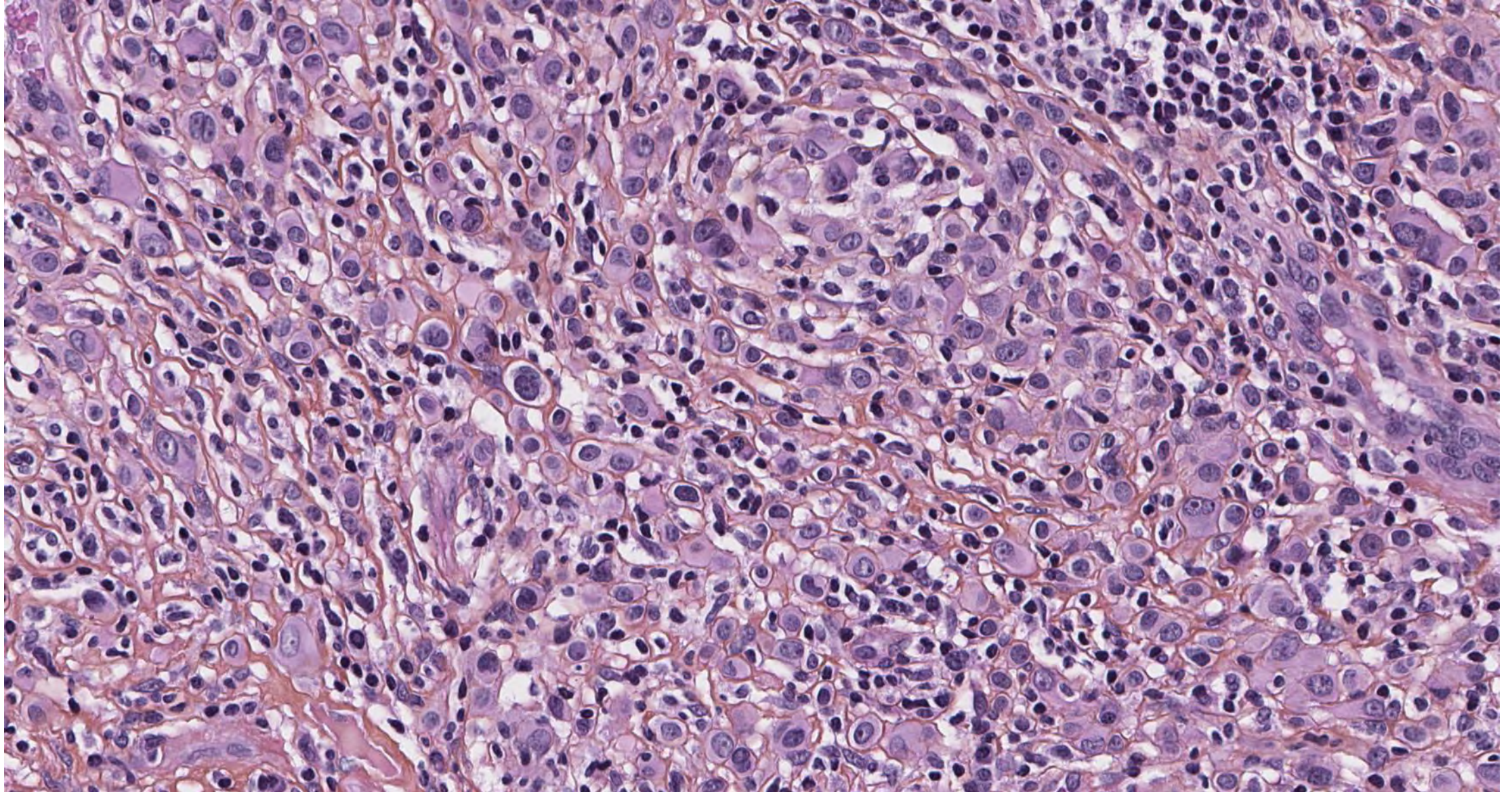
Intradermal clonal expansion



Unpigmented clone with « loose » density

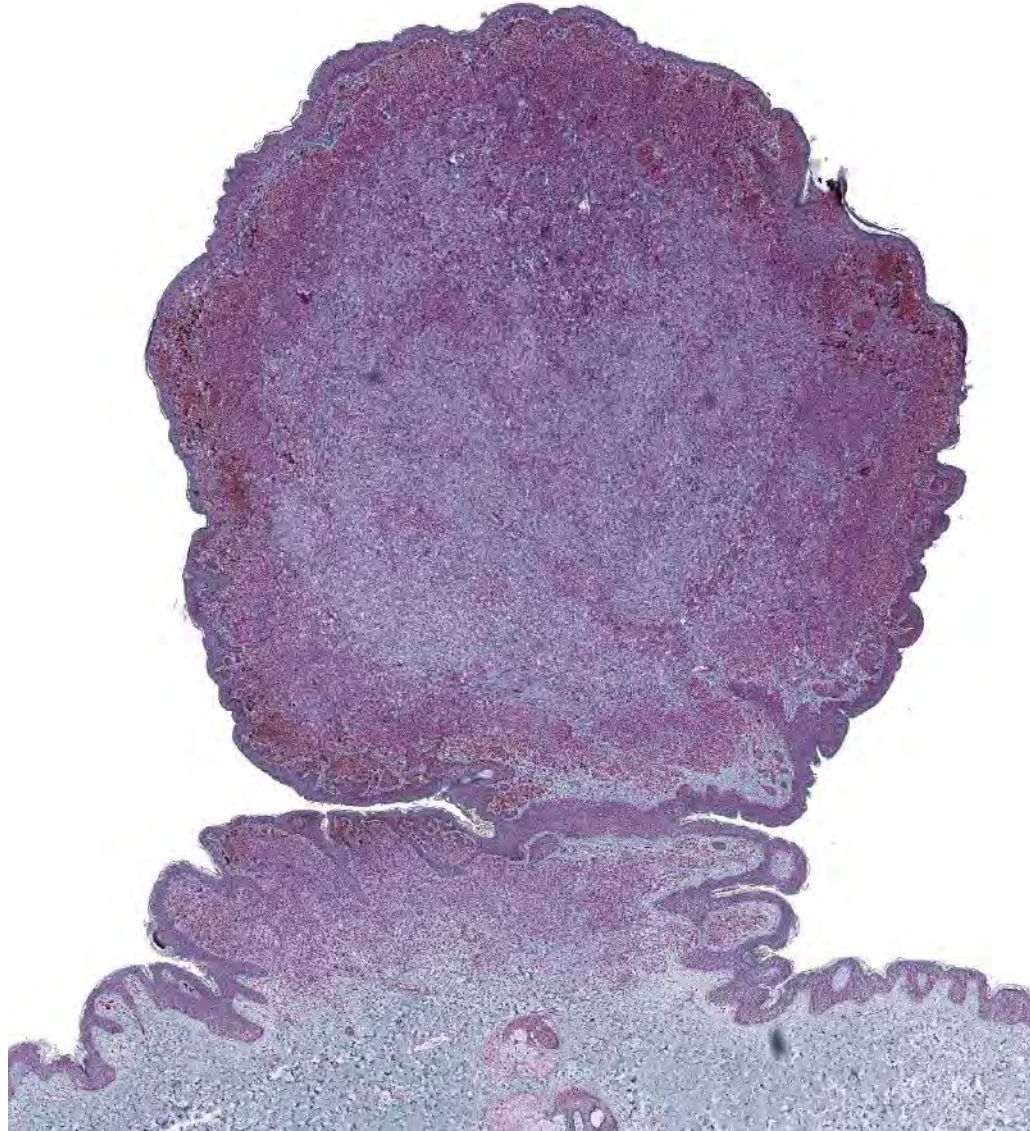


Lymphoid infiltrate with «kissing figures»

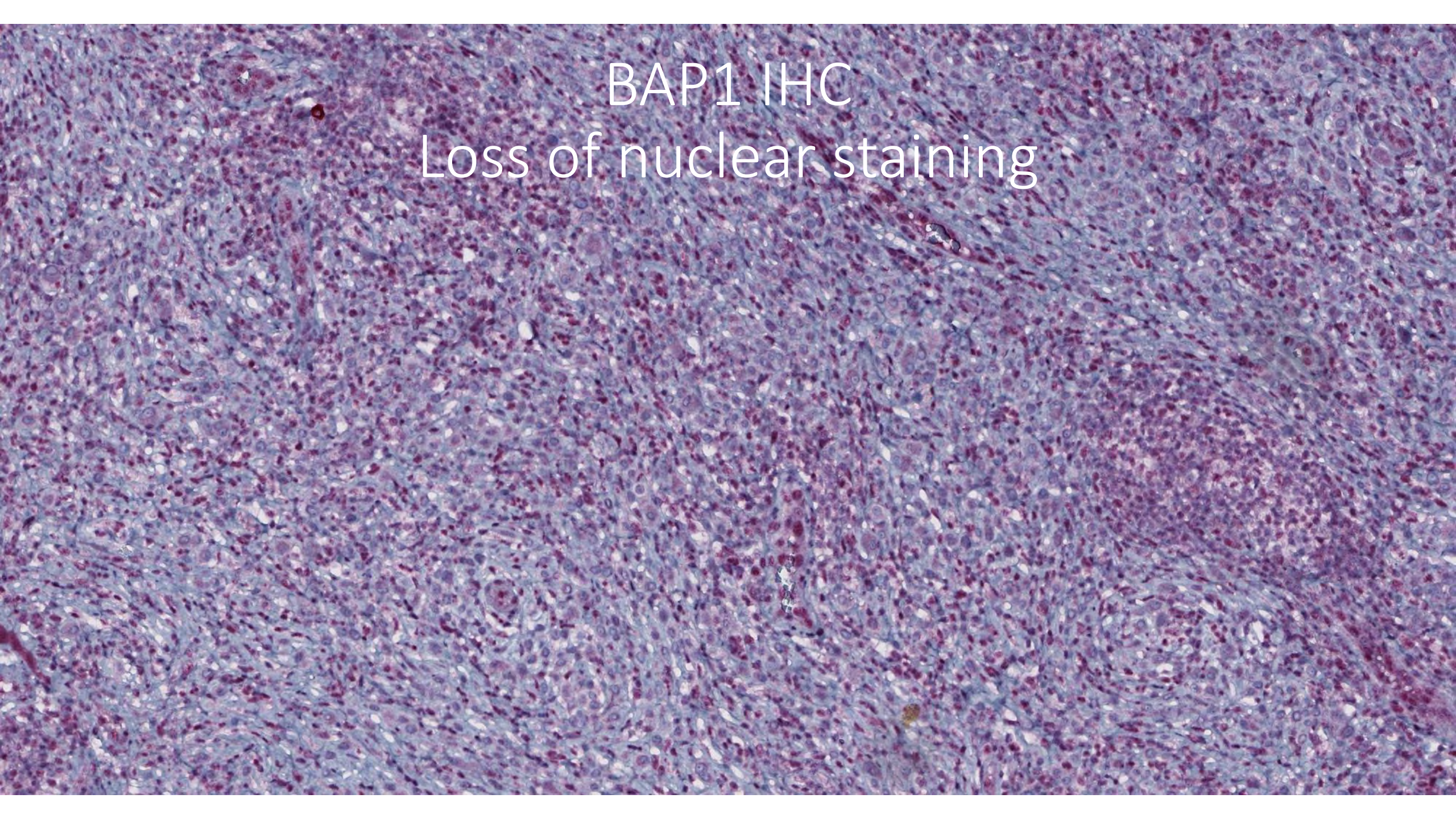


BAP1 IHC

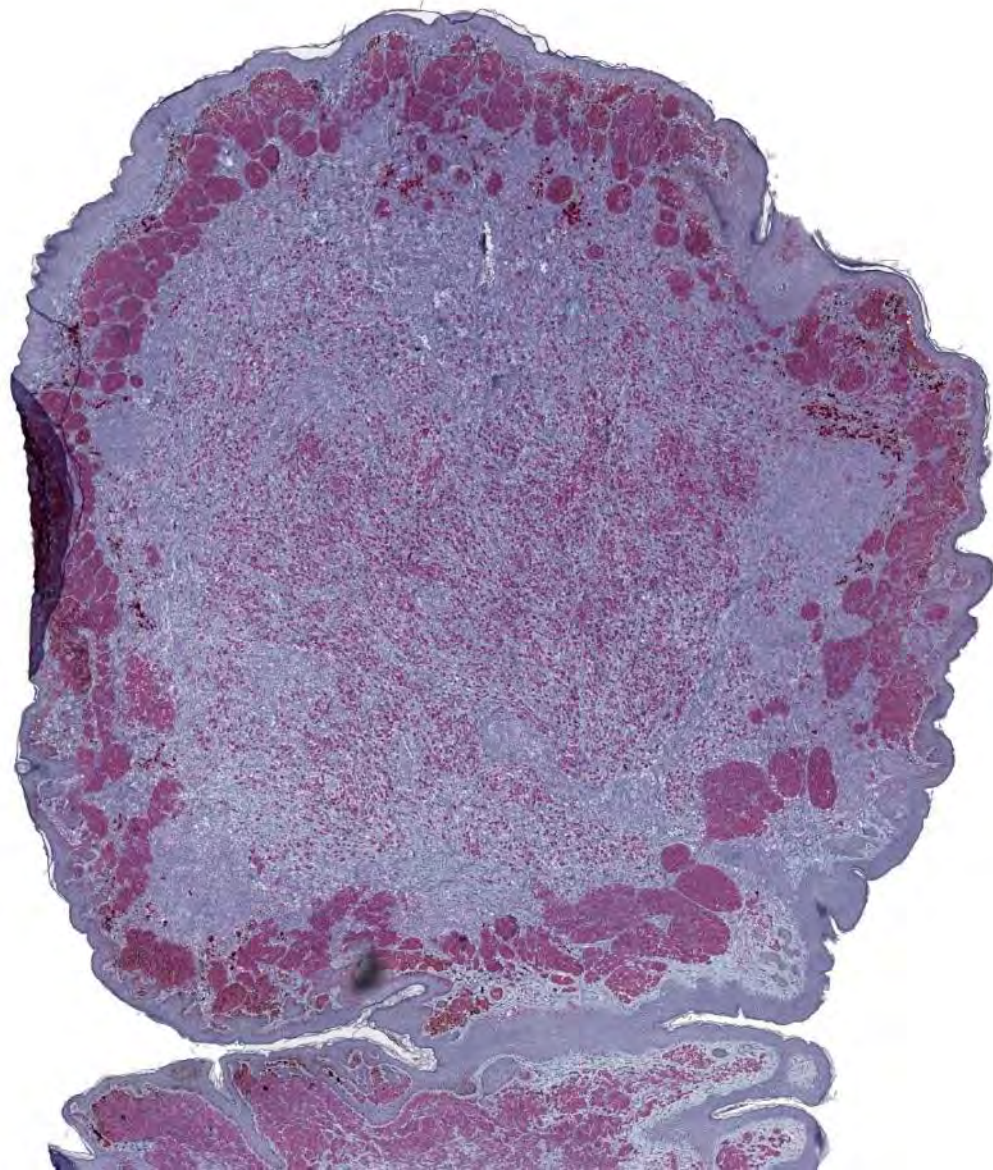
Loss of nuclear staining



BAP1 IHC
Loss of nuclear staining



BRAF V600E mutation >80% of cases

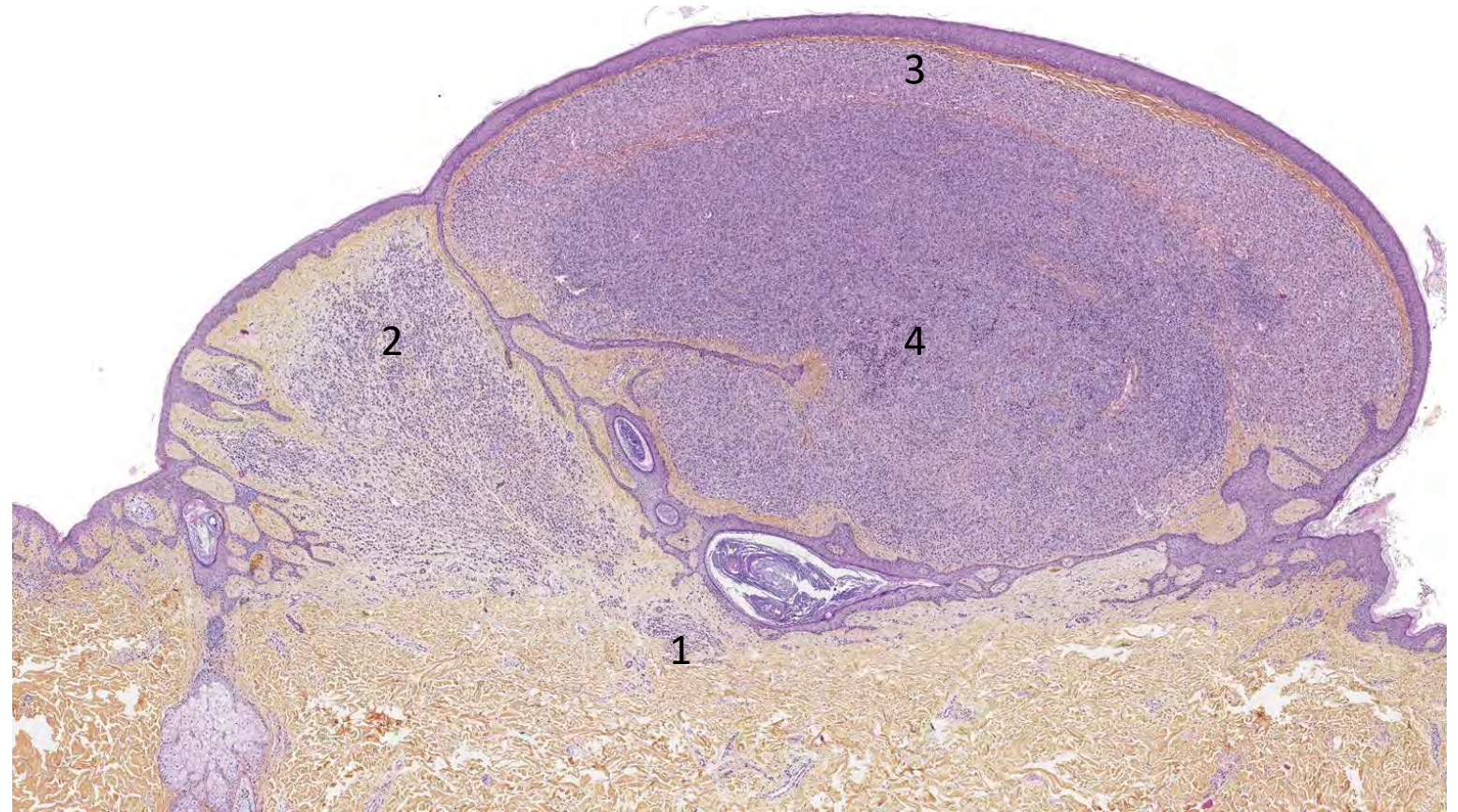


BAP1-inactivated melanocytic tumors

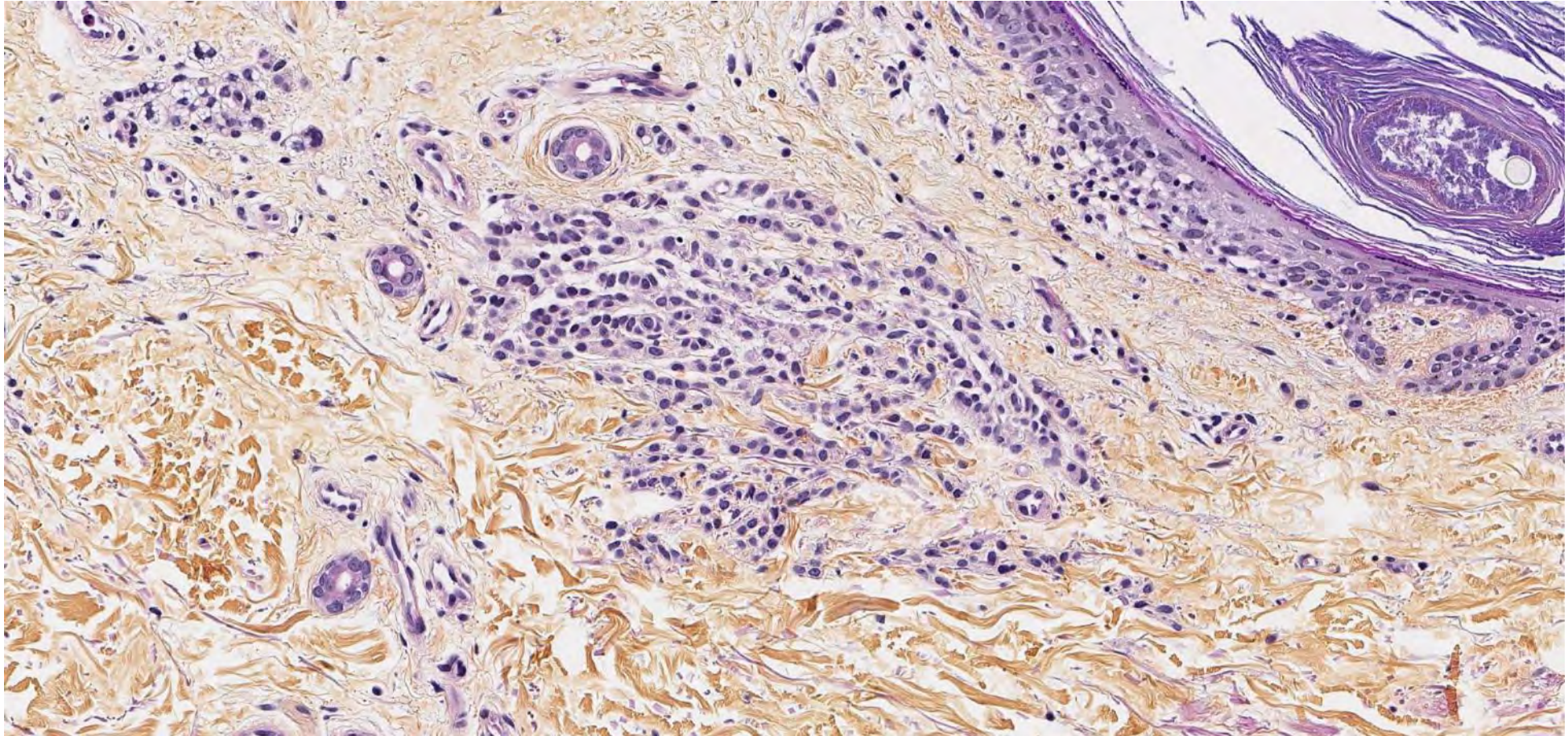
- Evaluate degree of atypia (rare malignant cases)
- Complete surgical removal with adapted margins
- Follow-up

4 step progression scheme of *BAP1*-Inactivated Melanocytic Tumors

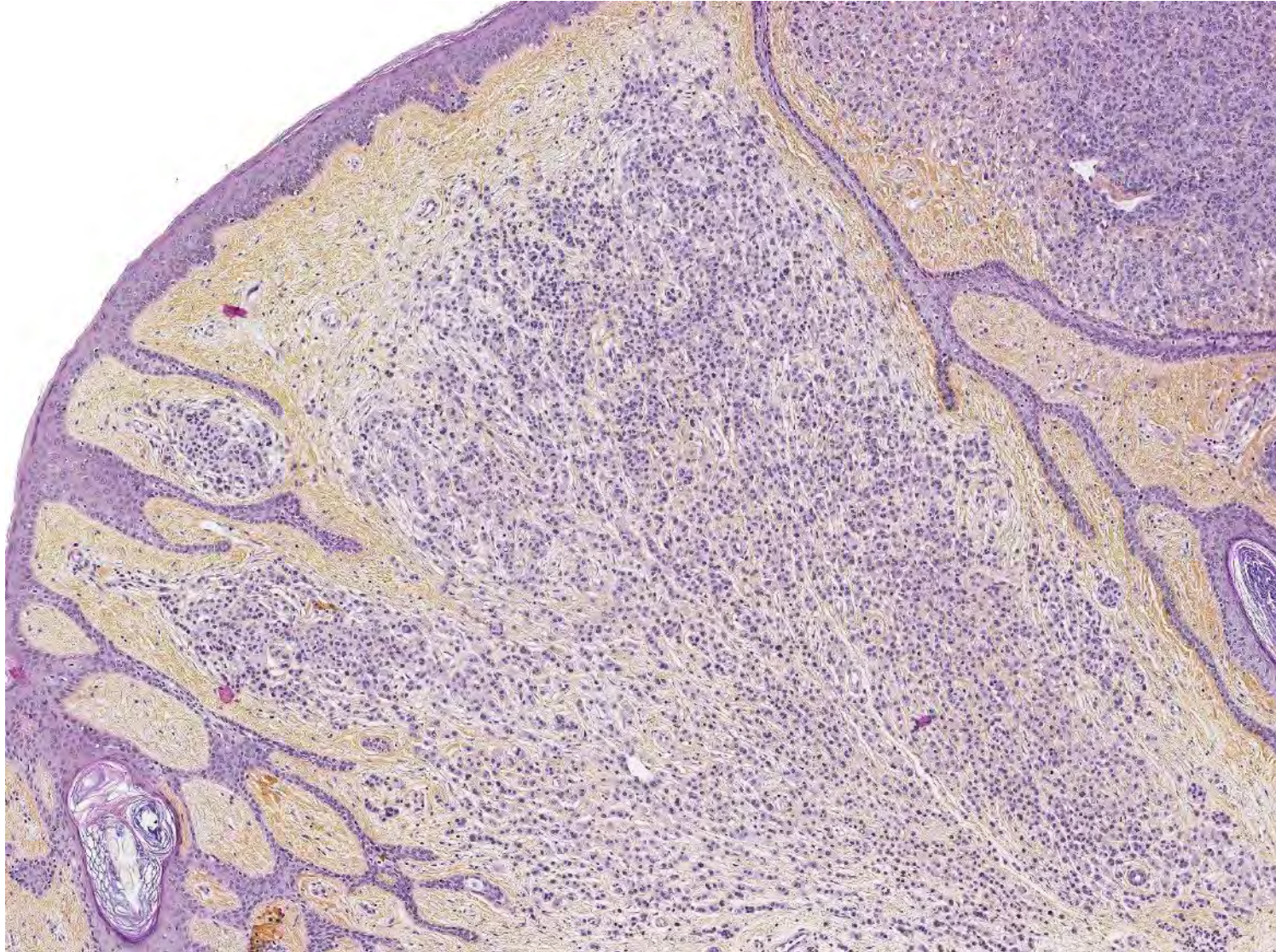
- BRAF* > *NRAS*
- 1 Common nevus
 - 2 *BAP1*-inactivated nevus
 - 3 *BAP1*-inactivated tumor
 - 4 Melanoma ex-*BAP1*-inactivated nevus



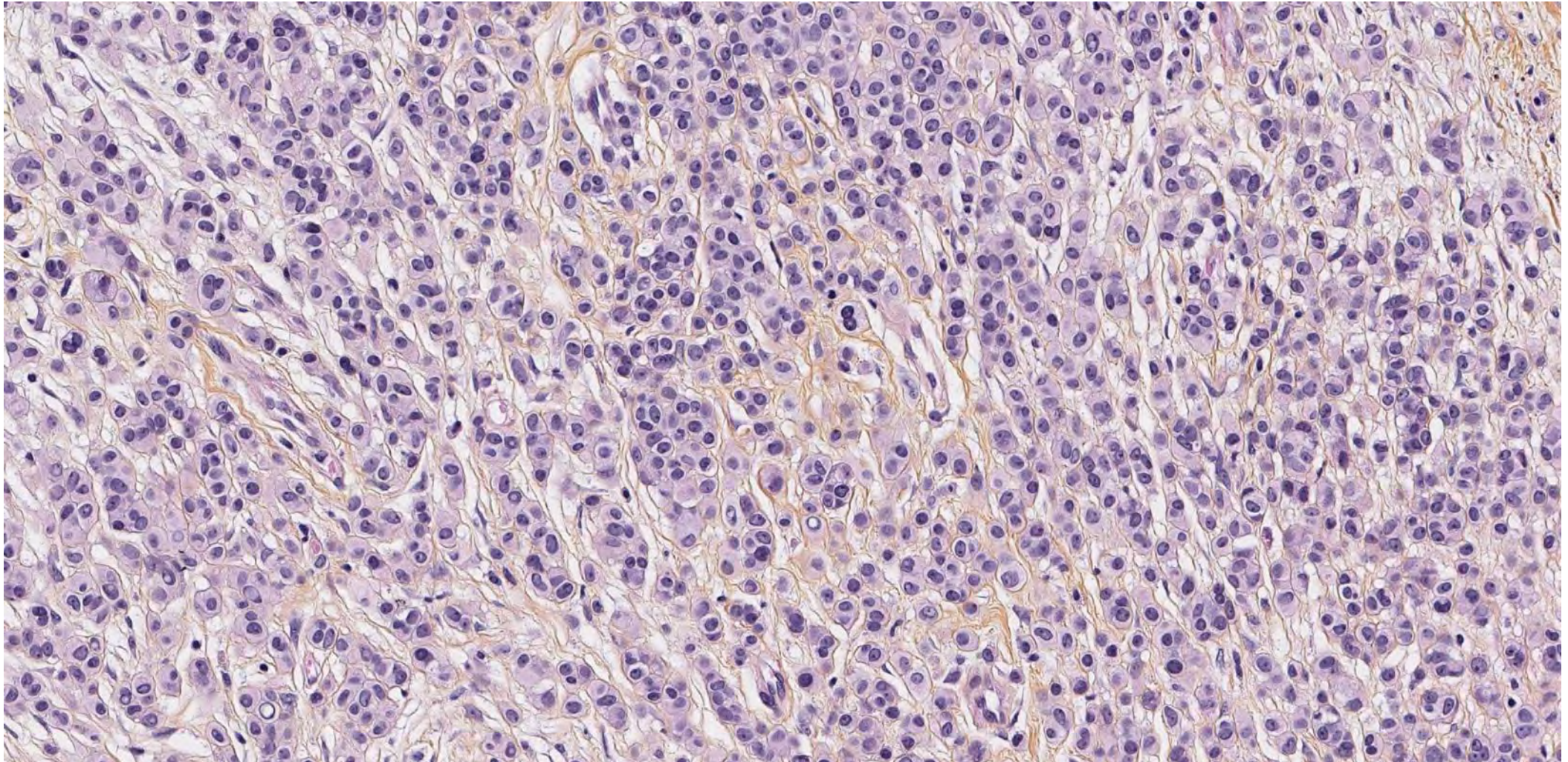
Area 1



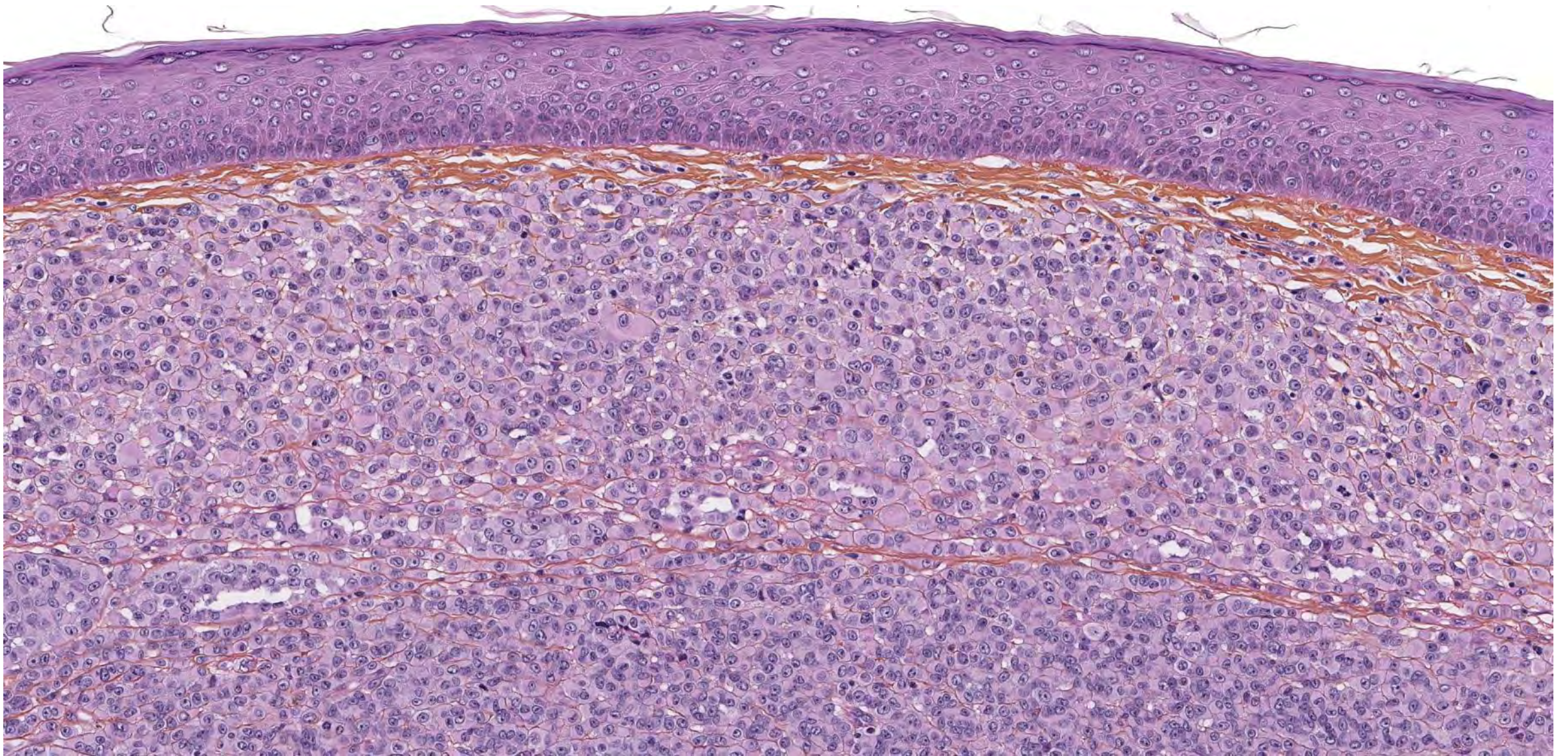
Area 2



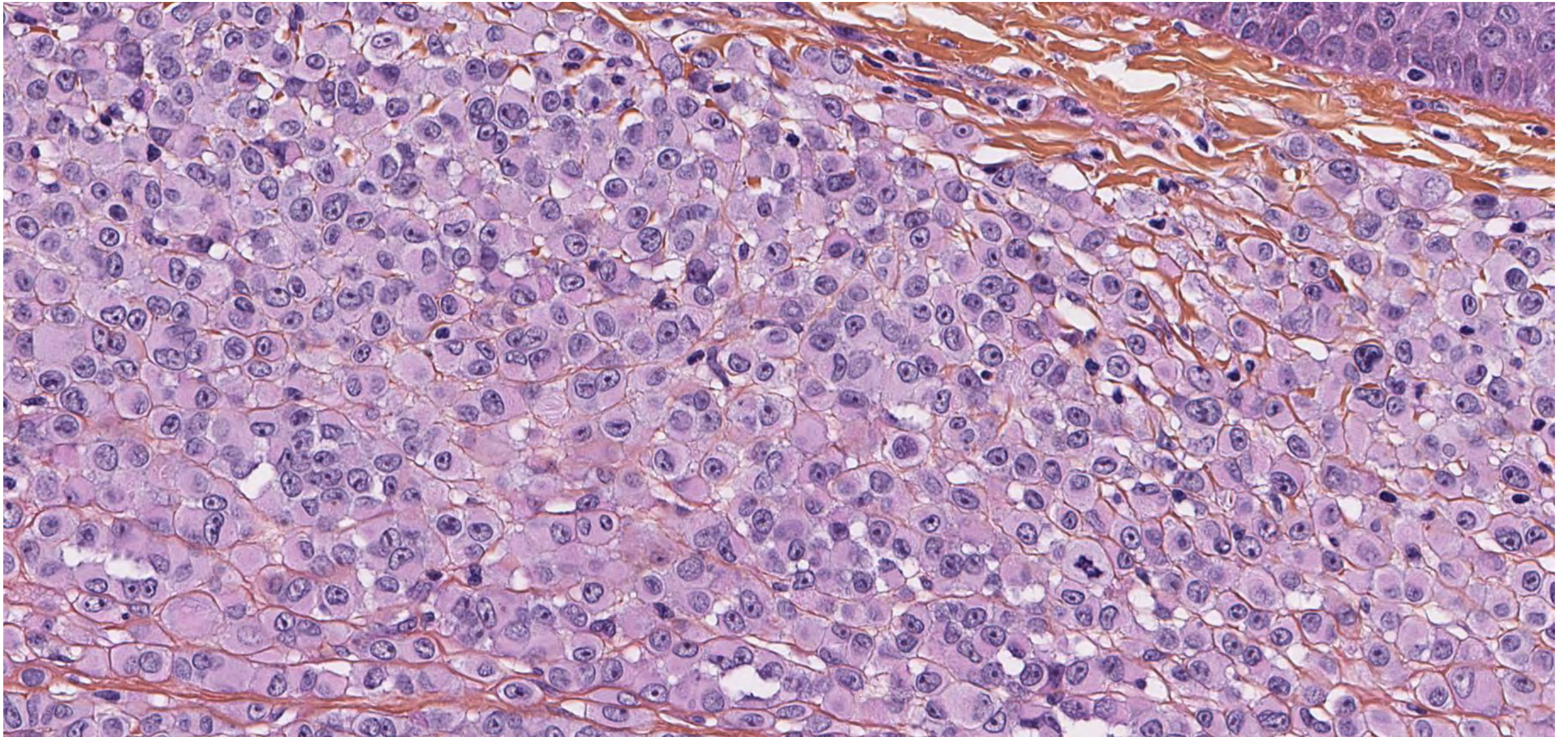
Area 2



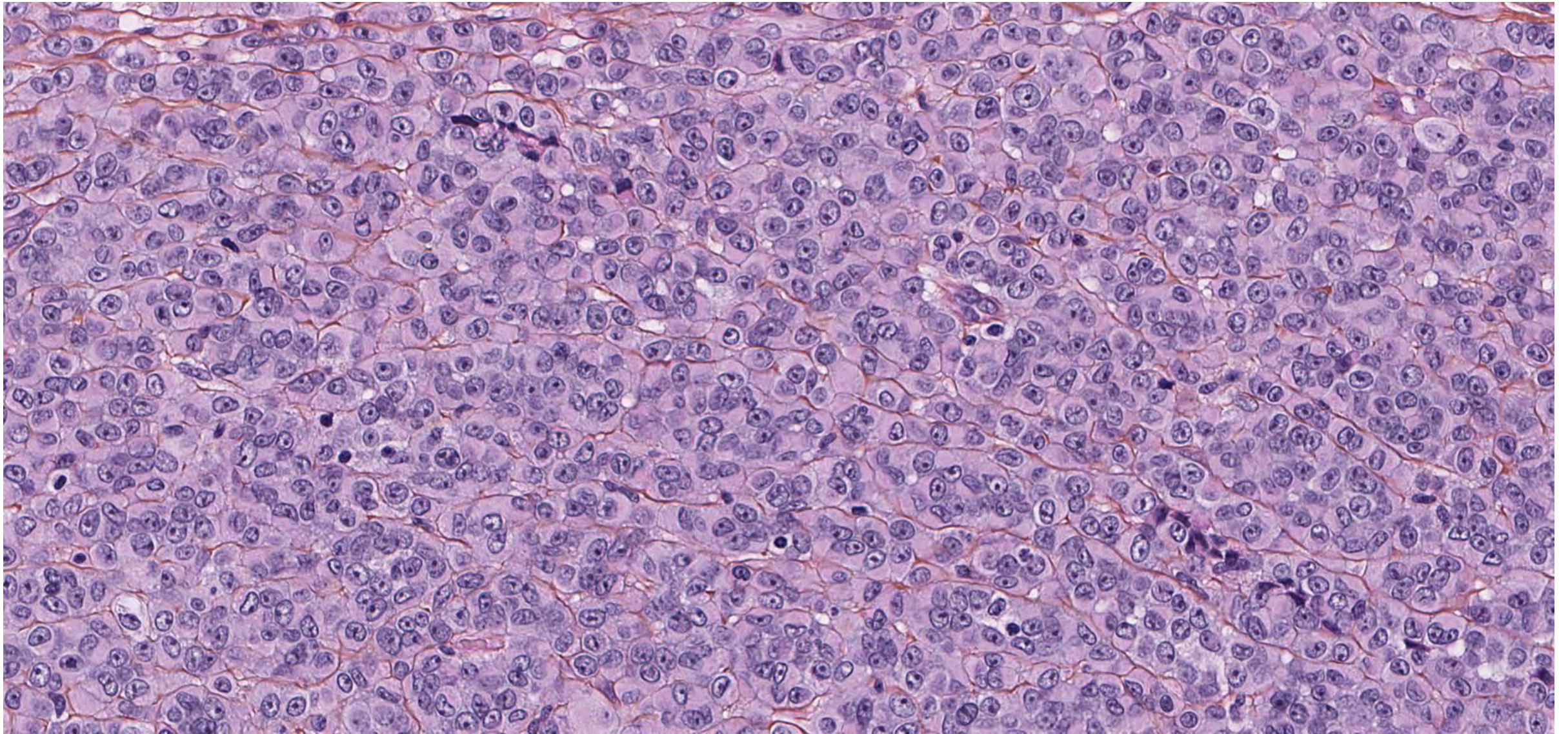
Area 3



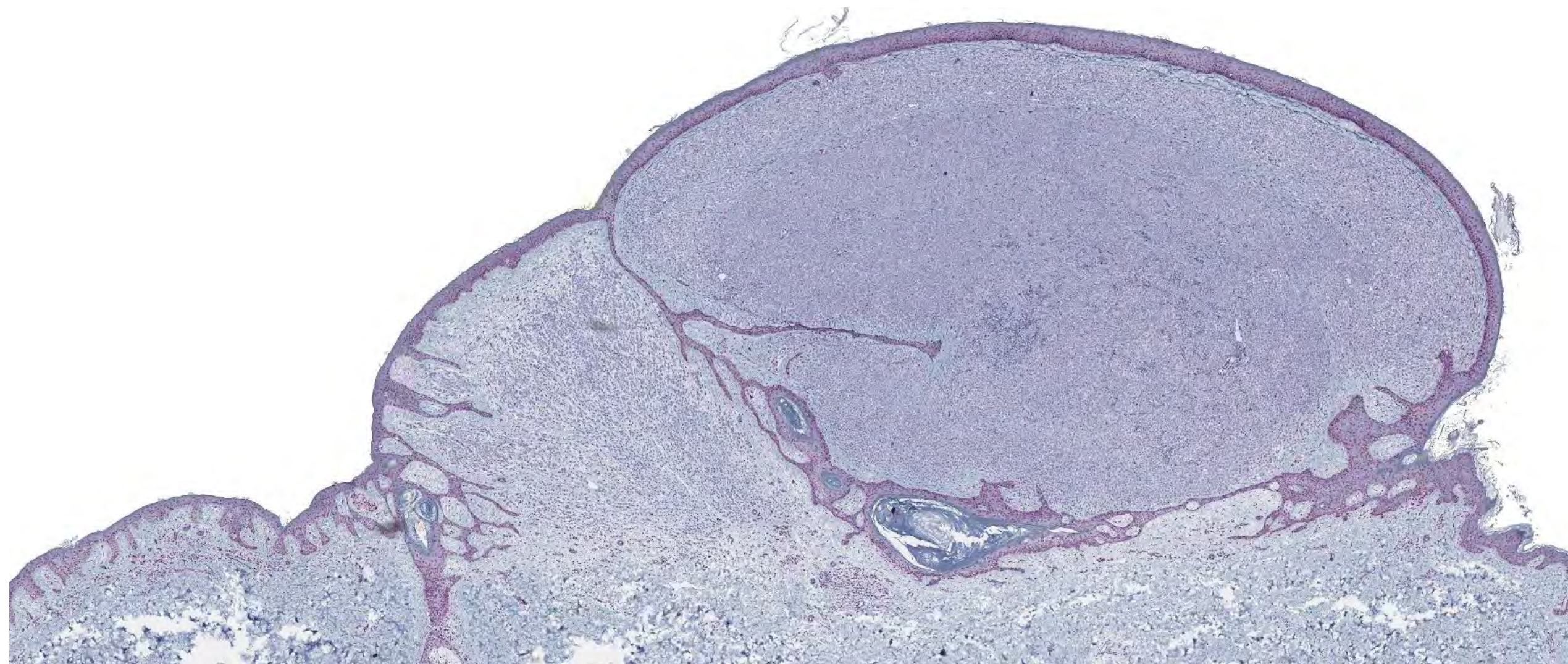
Area 3



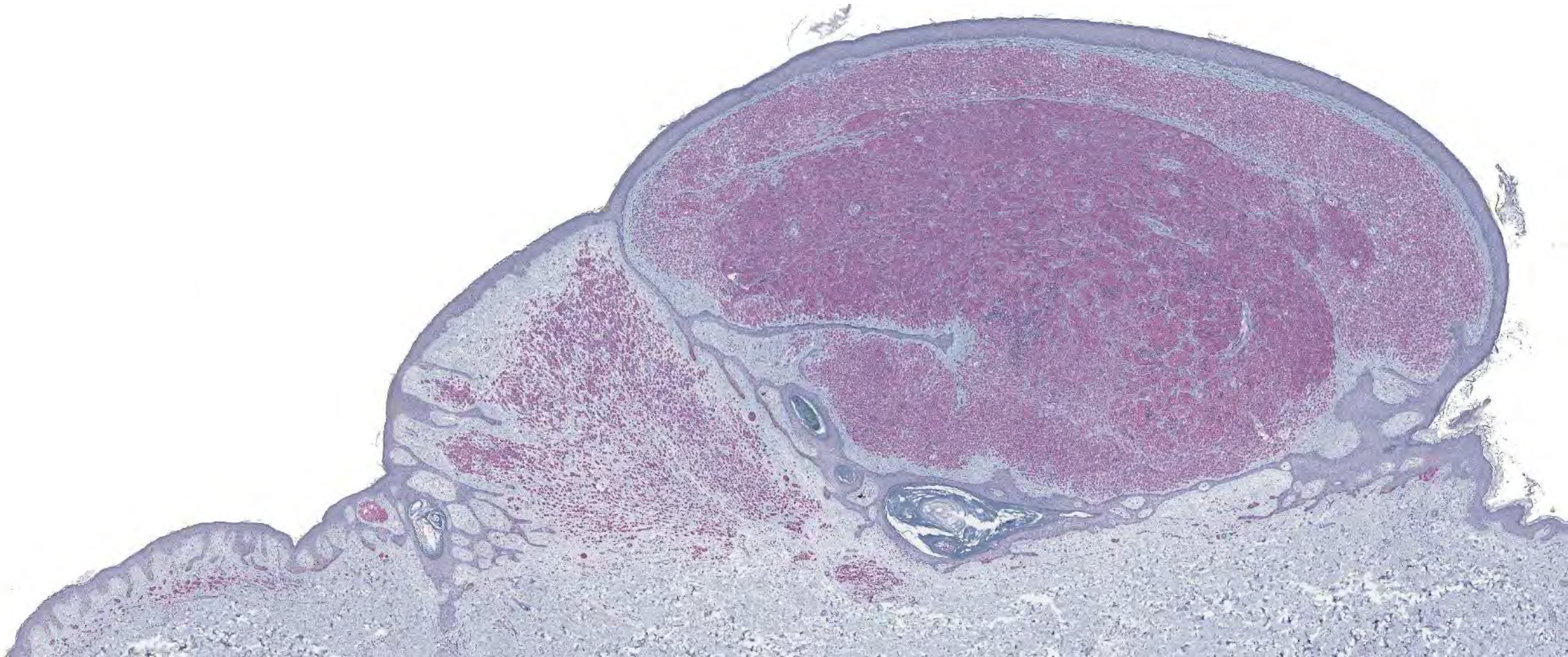
Area 4



BAP1 IHC



BRAF V600E IHC



BAP1-inactivated melanocytic tumors

- Evaluate degree of atypia (rare malignant cases)
- Complete surgical removal with adapted margins
- Follow-up
- Identify patients needing oncogenetic counseling (history/IHC)

M27 with uveal melanoma



Tumors associated with a *BAP1* germline mutation

- Atypical cutaneous melanocytic tumors (BAPimts)
- Uveal melanoma
- Cutaneous melanoma
- Leptomeningeal melanoma
- Mesothelioma (pleural and abdominal)
- Clear cell renal cancer
- Meningiomas
- Multiple basal cell carcinomas
- Hepatocellular carcinoma
- Cholangiocarcinoma
- Arise at a younger age

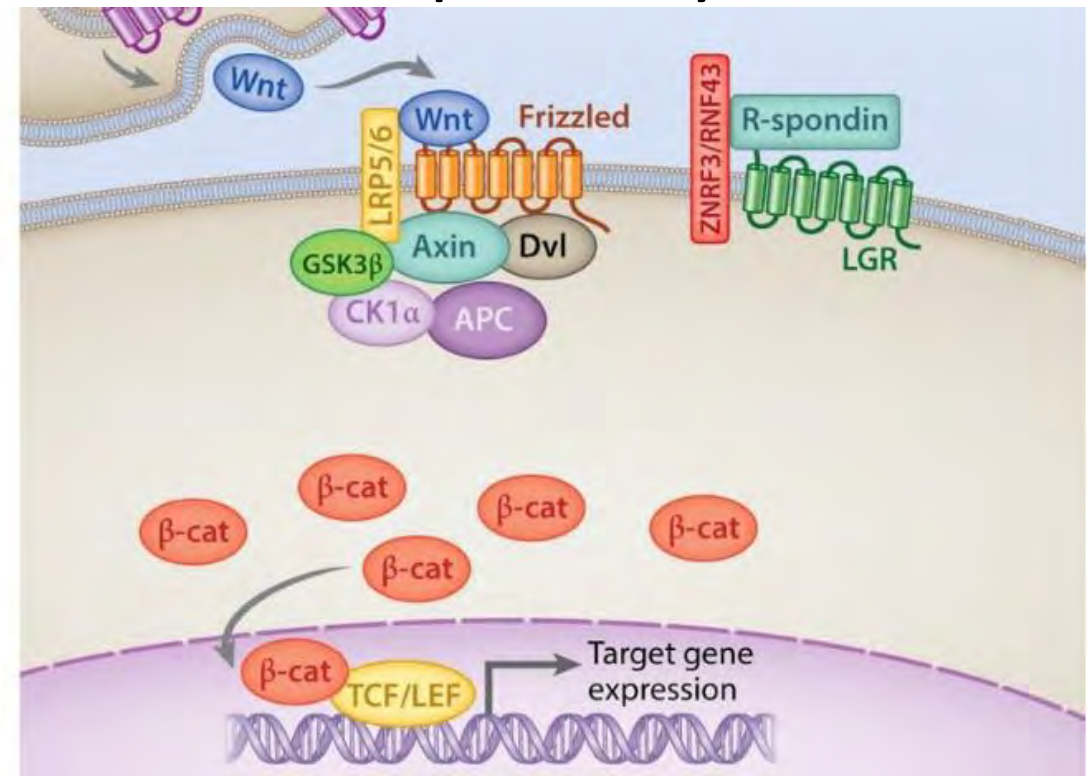
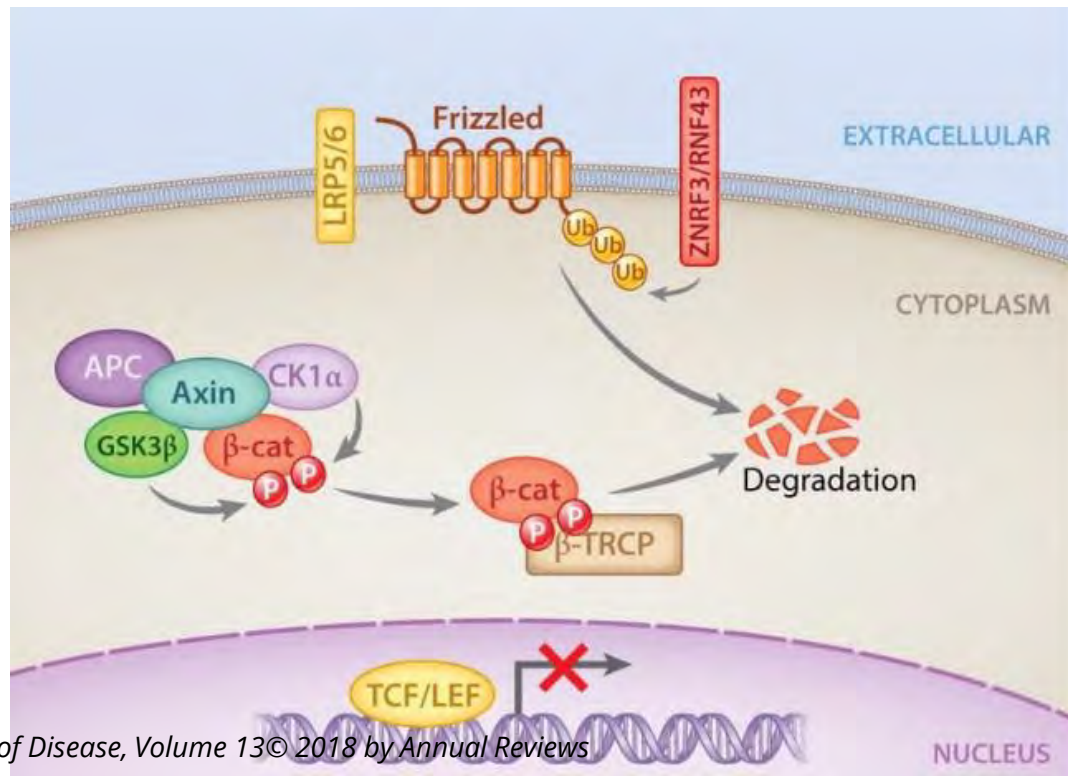
BAP1-inactivated melanocytoma take home messages

- Melanocytic tumors with loss of BAP1 expression can identify carriers of a germline syndrome with cancer-predisposition.
- Isolated cases with somatic mutations prevail.
- Exophytic combined architecture
- Large unpigmented epithelioid and nevoid dermal melanocytes +/- lymphocytes.
- IHC is an excellent technique to identify loss of function.

Combined WNT-Activated Melanocytoma (WAM)
ex-combined Deep Penetrating Nevus (DPN)

WNT-activated deep penetrating/plexiform melanocytoma

- Class I: *BRAF*, *NRAS* or *MAP2K1* ie “common” genetic background
- + either *CTNNB1* or *APC* mutations ie WNT pathway activation



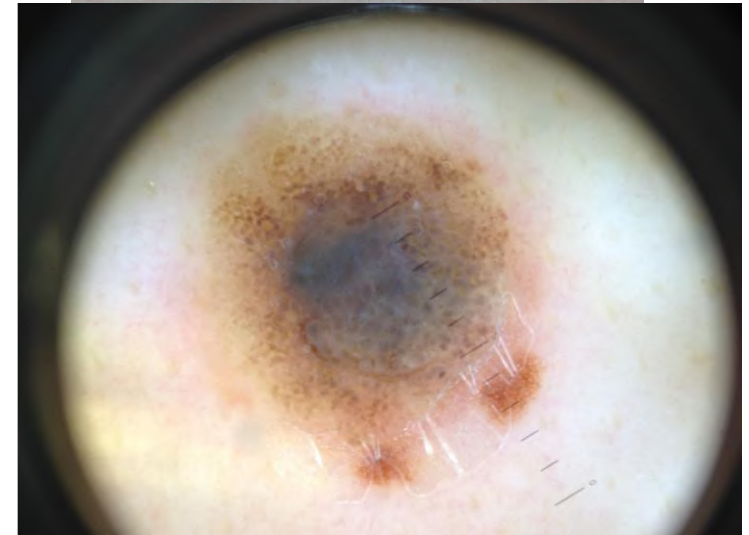
WNT-activated deep penetrating/plexiform melanocytoma

- Young adults
- Upper body
- Small pigmented lesion



WNT-activated deep penetrating/plexiform melanocytoma

- Young adults
- Upper body
- Small pigmented lesion
- Clinically worrysome
- Asymmetrical pigmentation
- Modified pigmentation





ARTICLE

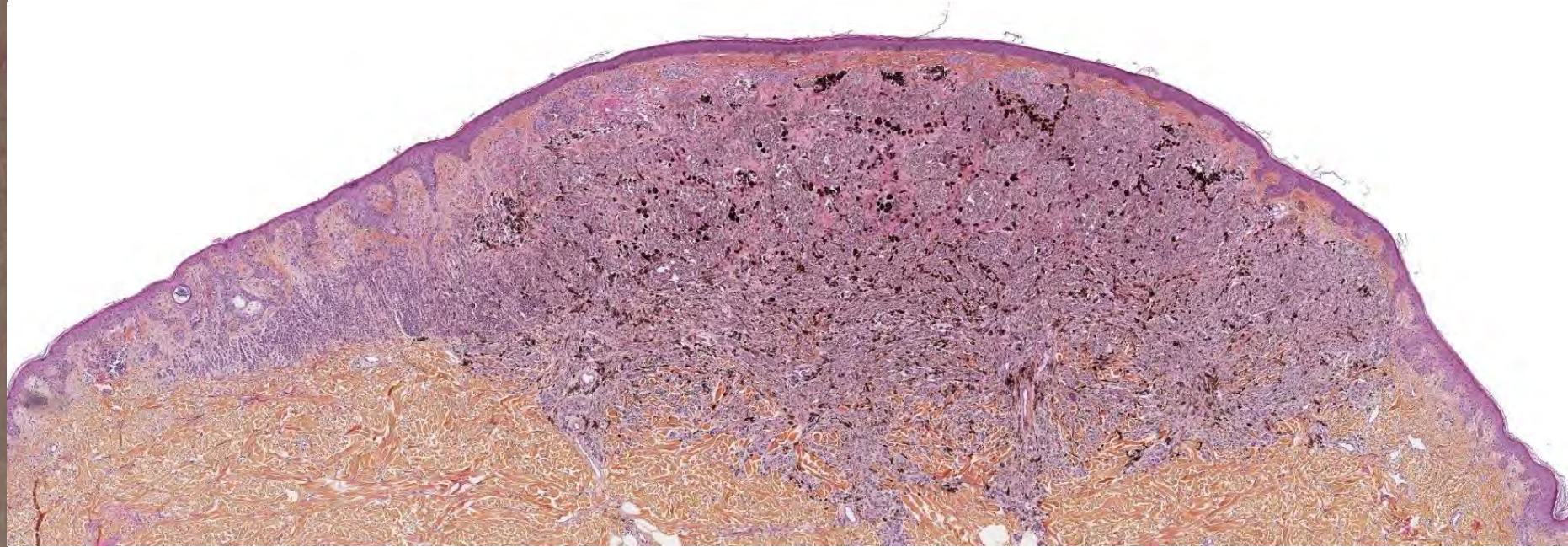
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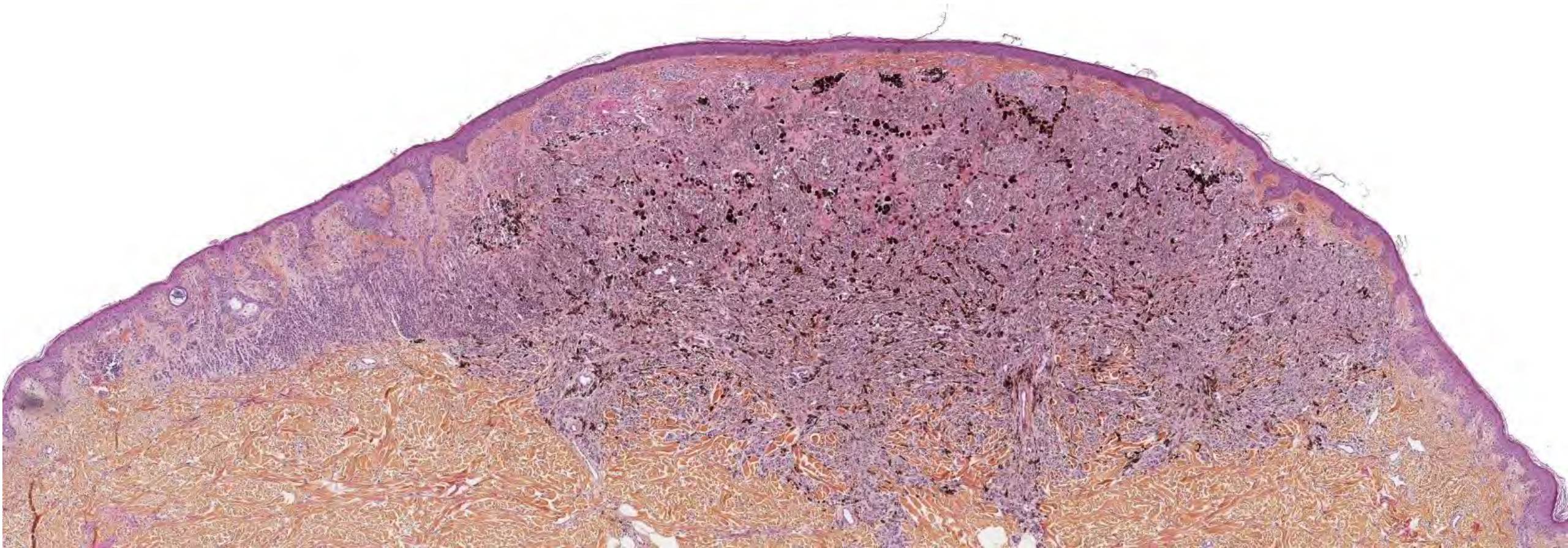
Combined activation of MAP kinase pathway and β -catenin signaling cause deep penetrating nevi

Iwei Yeh^{1,2}, Ursula E. Lang², Emeline Durieux³, Meng Kian Tee¹, Aparna Jorapur¹, A. Hunter Shain¹, Veronique Haddad⁴, Daniel Pissaloux⁴, Xu Chen¹, Lorenzo Cerroni⁵, Robert L. Judson ¹, Philip E. LeBoit^{1,2}, Timothy H. McCalmont^{1,2}, Boris C. Bastian^{1,2} & Arnaud de la Fouchardière ⁴

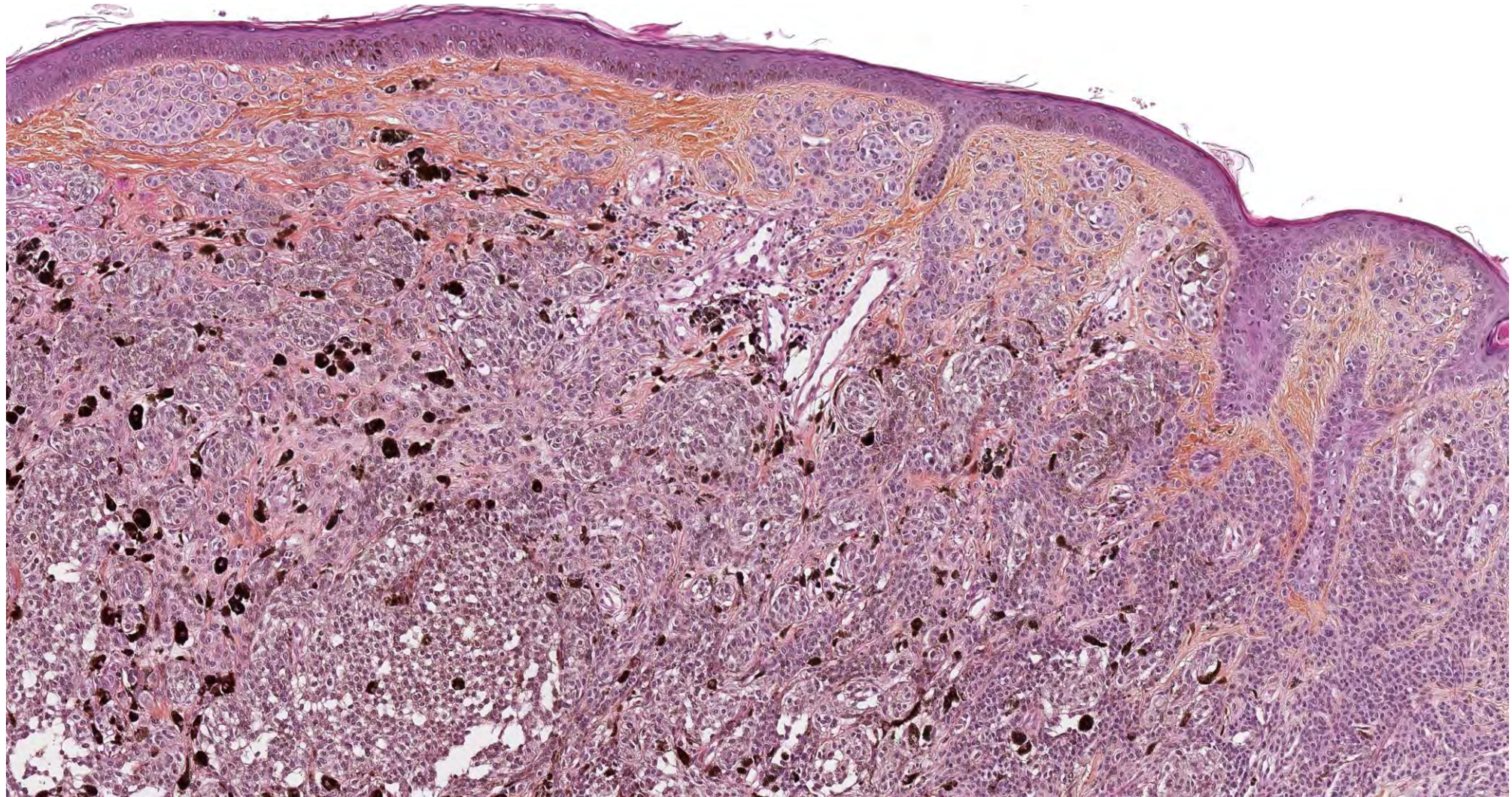
Combined WNT-activated deep penetrating melanocytoma



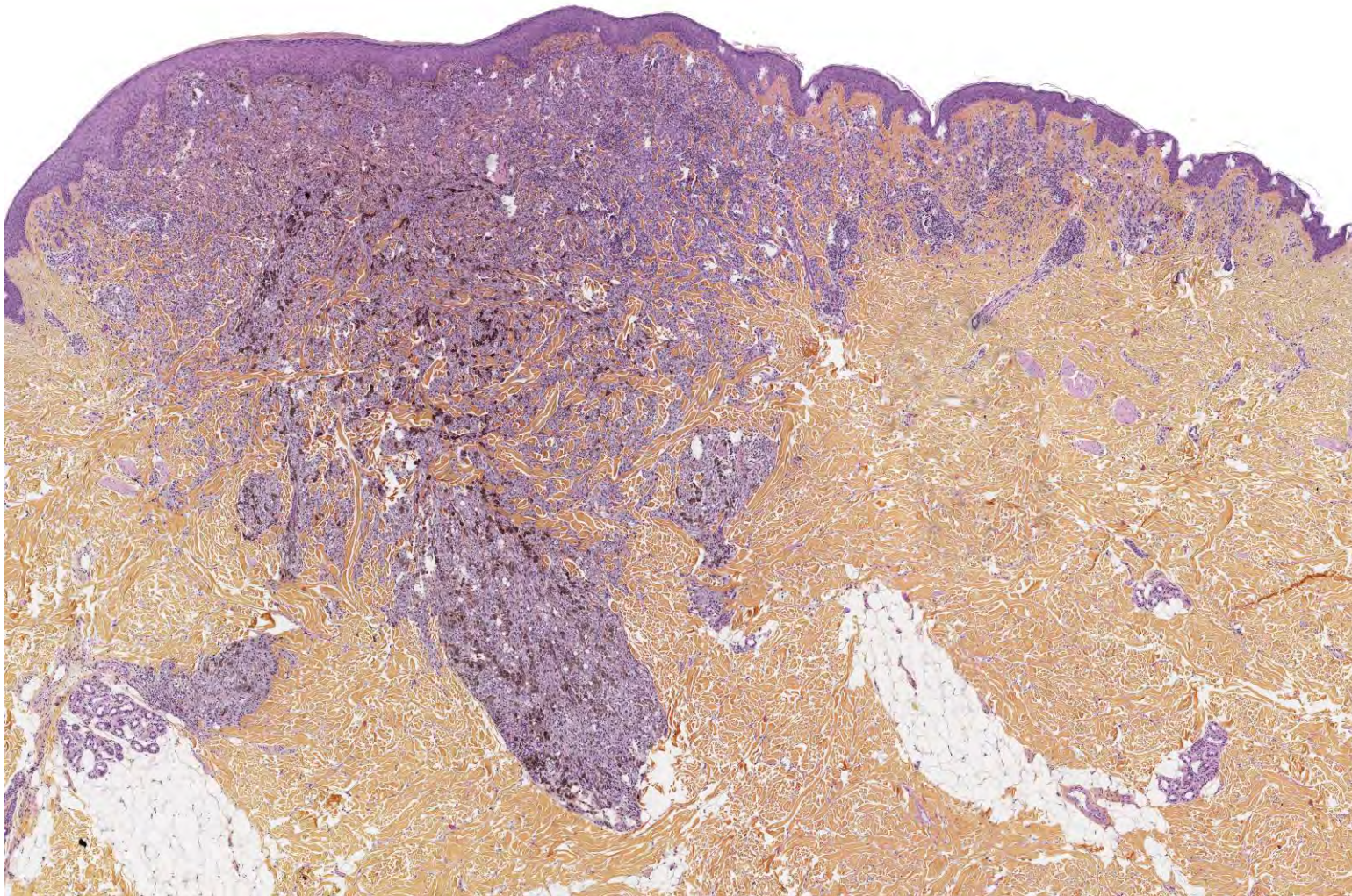
Dermal pigmented clone intricated with a
«**grid**» of melanophages



Peaceful transition between
common and pigmented clones

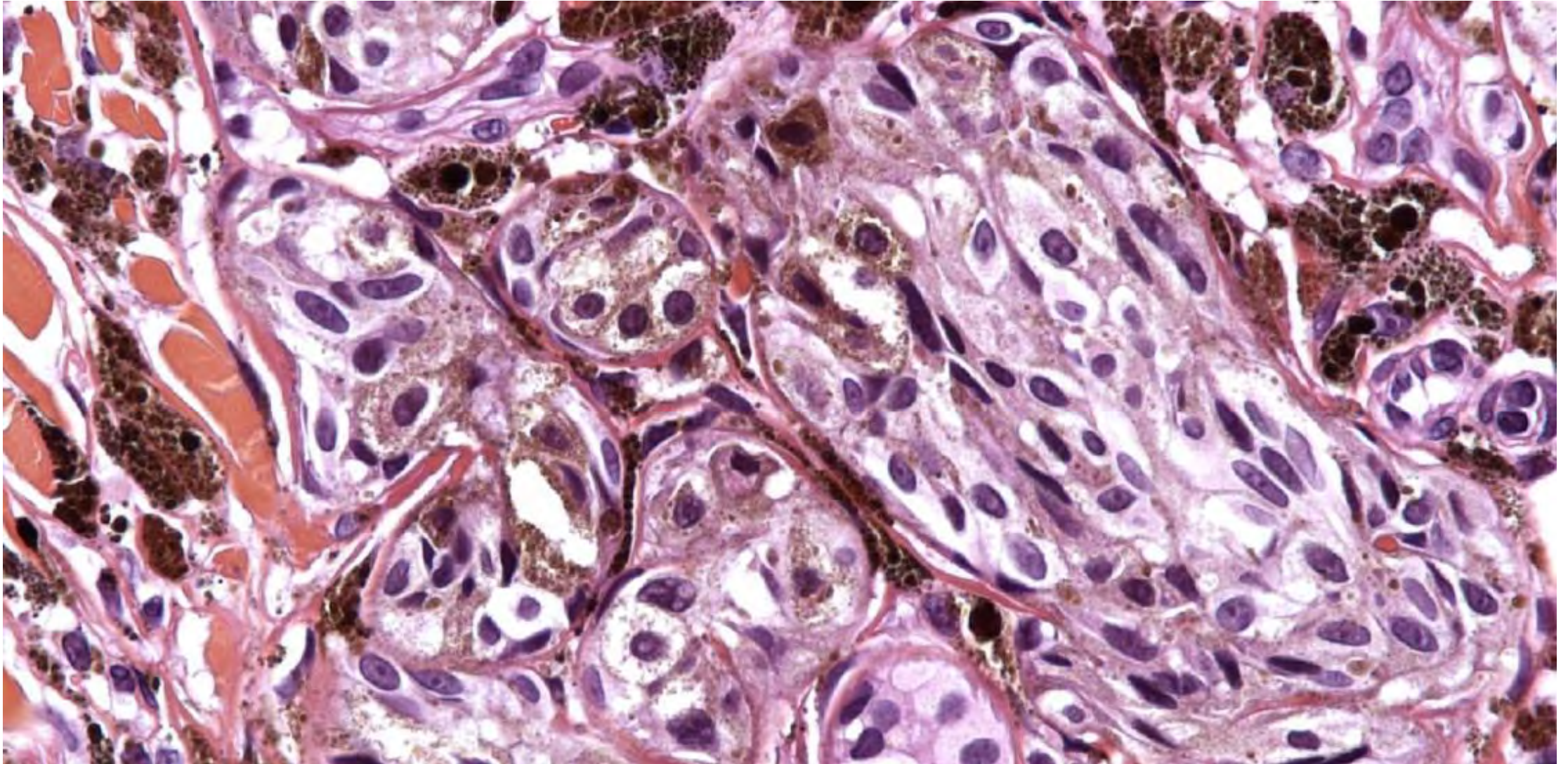


Deep **vertical expansions** into the subcutis

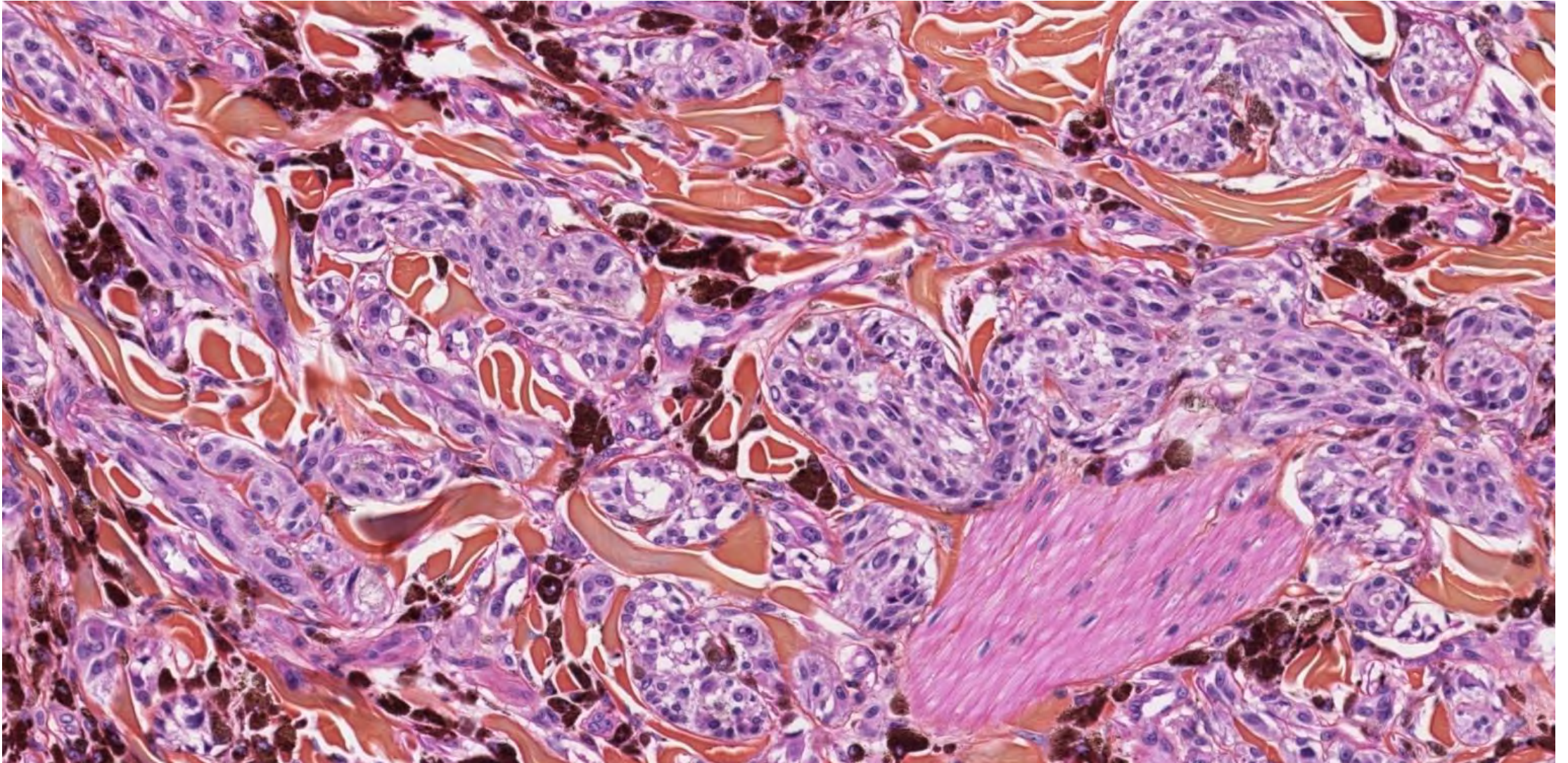


Spatula

Large melanocytes with a foamy pigmented cytoplasm and mild nuclear atypia



Occasional spindled (spitzoid) cytology
Mild dermal fibrosis and vertical maturation





β -Catenin nuclear expression discriminates deep penetrating nevi from other cutaneous melanocytic tumors

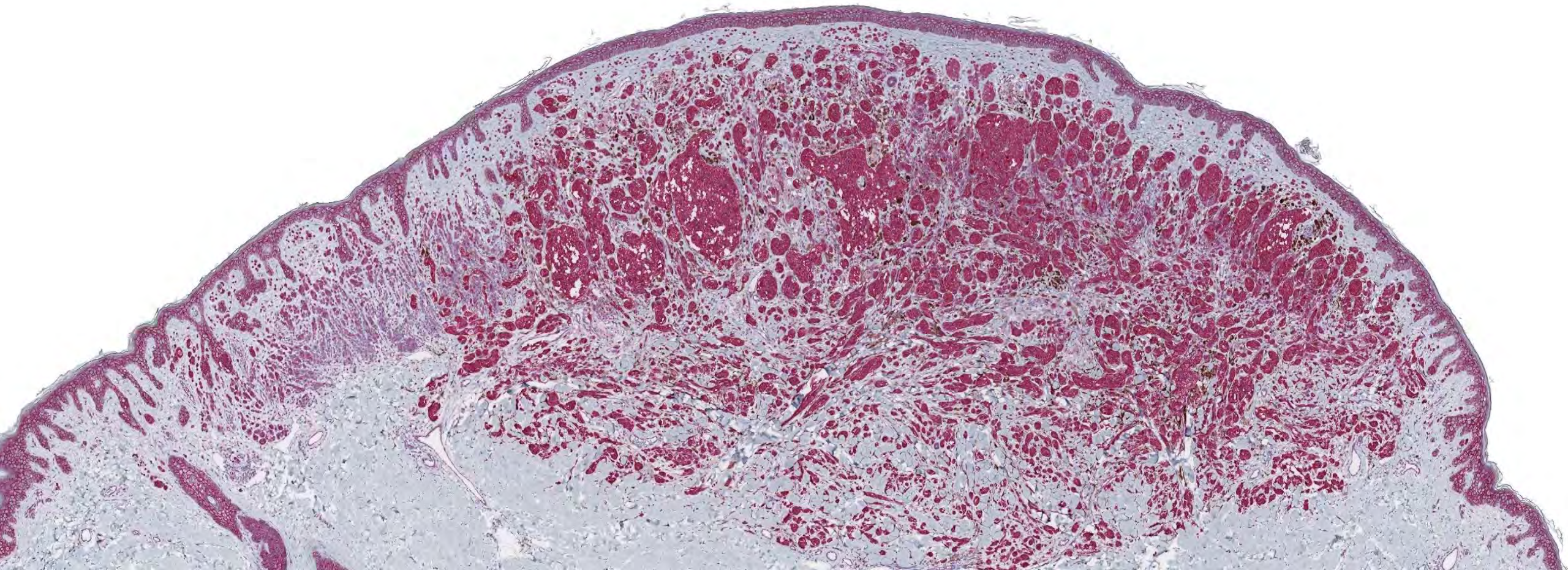
Arnaud de la Fouchardière^{1,2}  • Claire Caillot¹ • Julien Jacquemus¹ • Emeline Durieux³ • Aurélie Houlier^{1,2} • Véronique Haddad¹ • Daniel Pissaloux^{1,2}

Received: 15 November 2018 / Revised: 21 January 2019 / Accepted: 25 January 2019

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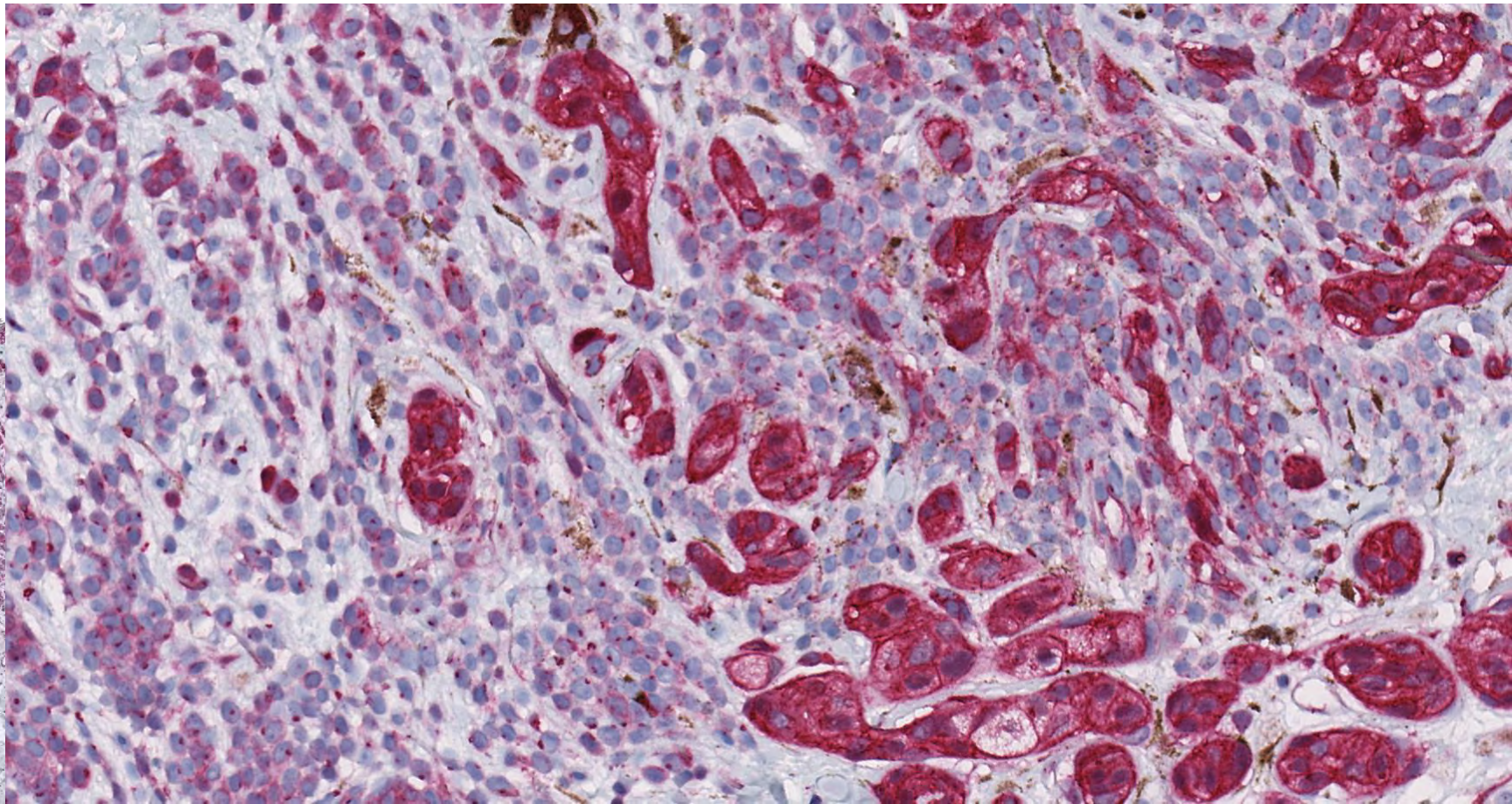
Combined WNT-activated deep penetrating/plexiform melanocytoma

Beta-CATENIN Immunohistochemistry



Combined WNT-activated deep penetrating/plexiform melanocytoma

Beta-CATENIN Immunohistochemistry
Nuclear and cytoplasmic positivity



WNT-activated deep penetrating/plexiform melanocytoma

LEF1: Nuclear positivity (**adjuct** help)

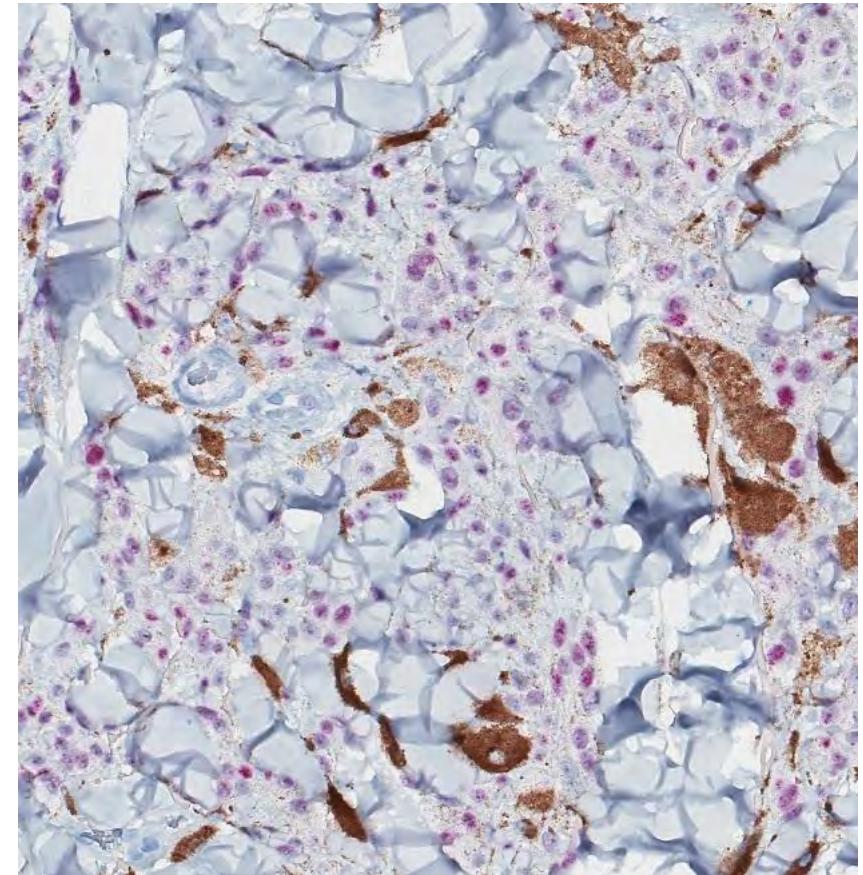
> [Am J Surg Pathol.](#) 2020 Oct;44(10):1413-1418. doi: 10.1097/PAS.0000000000001513.

Diagnostic Utility of LEF1 Immunohistochemistry in Differentiating Deep Penetrating Nevi From Histologic Mimics

Shyam S Raghavan¹, Atif Saleem¹, Jennifer Y Wang^{1 2}, Kerri E Rieger^{1 2}, Ryanne A Brown^{1 2}, Roberto A Novoa^{1 2}

Affiliations + expand

PMID: 32520758 DOI: [10.1097/PAS.0000000000001513](#)



PRAME and LEF1 in Combined Deep Penetrating Nevus and Combined Blue Nevus: Utility and Pitfalls

Kaitlin Vanderbeck ¹, Aimi T Rothrock ¹, Woo Cheal Cho ¹, Priyadharsini Nagarajan ¹, Phyu P Aung ¹, Courtney Hudgens ², Roland L Bassett ³, Doina Ivan ¹, Victor G Prieto ^{1 4}, Jonathan L Curry ^{1 2}, Carlos A Torres-Cabala ^{1 4}

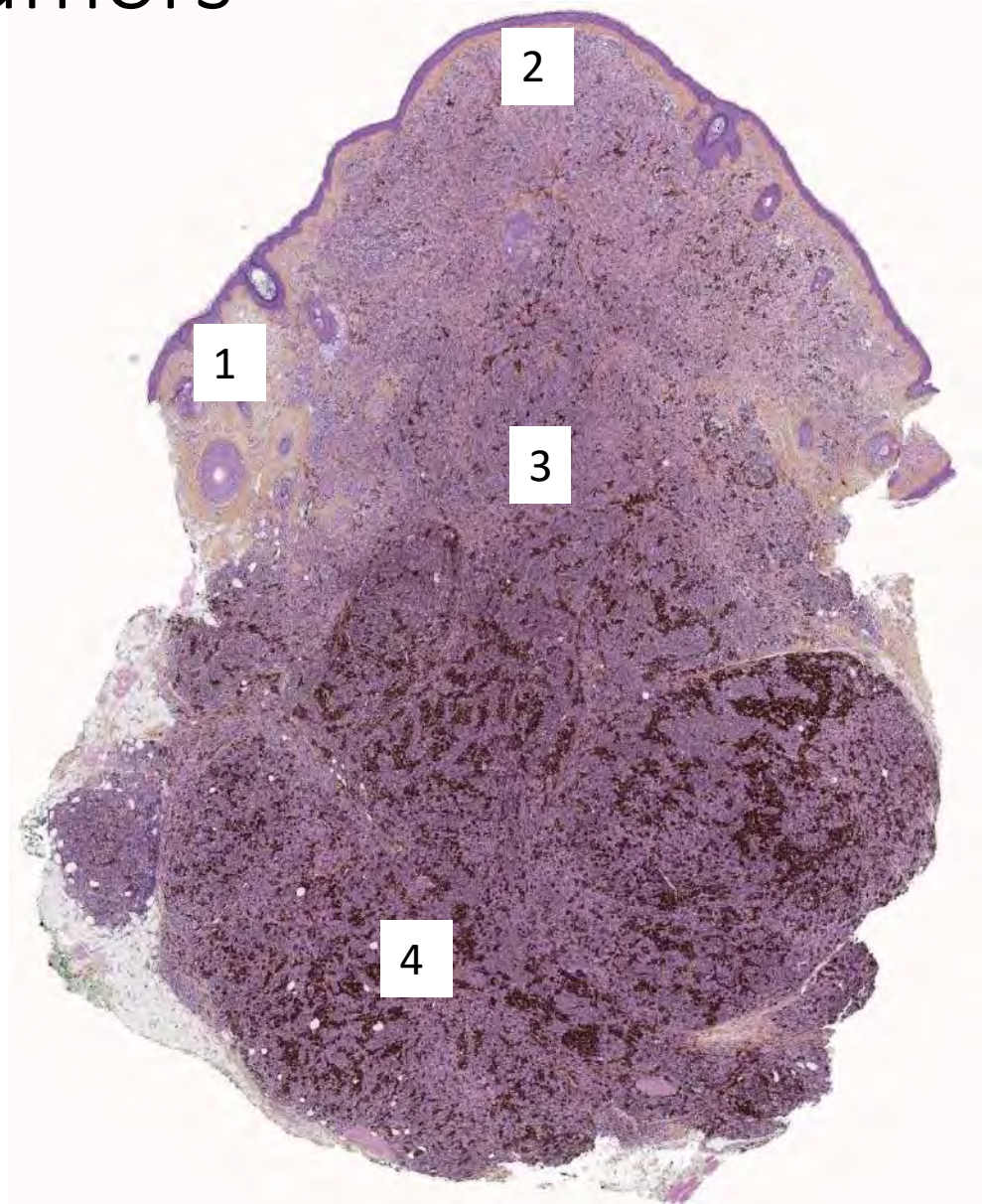
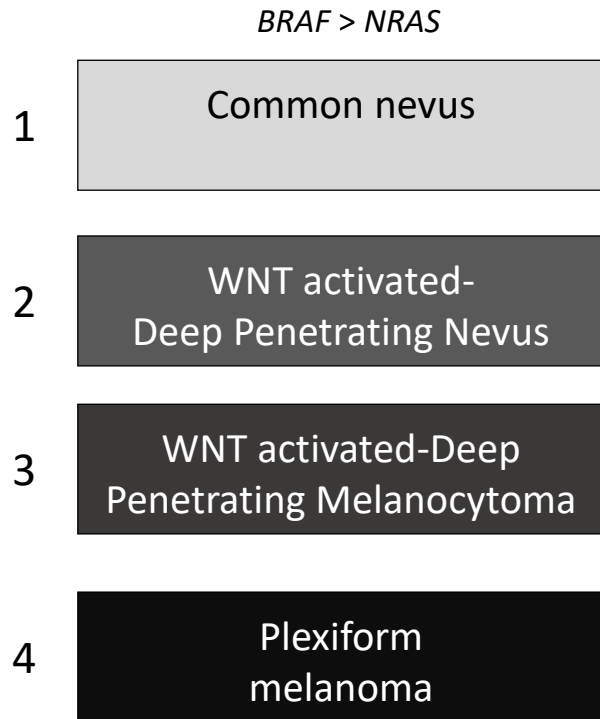
Affiliations + expand

PMID: 37462205 DOI: [10.1097/DAD.0000000000002488](#)

Abstract

Deep penetrating nevi (DPN), particularly those showing combined features, or combined deep penetrating nevi (CDPN), may show histopathological resemblance to blue nevus (BN) and melanoma. Preferentially Expressed Antigen in MELanoma (PRAME) is a marker that helps distinguish melanoma from benign melanocytic lesions. Lymphoid enhancer-binding factor 1 (LEF1) has been proposed to be used in conjunction with β -catenin for diagnosis of DPN. The immunohistochemical expression of PRAME and LEF1 was evaluated in 10 DPN (including 6 CDPN and 2 DPN-like proliferations with atypical features), 16 BN (including combined and cellular BN), and 2 melanomas with features of DPN or BN. PRAME was negative in most DPN (n = 10/10, n = 9/10, one case with discrepancy between readers) and all BN (n = 16/16), while the 2 melanomas included were positive (n = 2/2). All DPN were positive for LEF1 (n = 9/9) while only a subset of BN were positive (n = 6/16, P = 0.0028; n = 5/16, P = 0.001, per both readers). LEF1 seemed to be easier to interpret than β -catenin because of its nuclear pattern of expression. The expression of LEF1 in the regular nevus component of combined BN presents a potential pitfall in practice because it may lead to misinterpretation of LEF1 as positive in the BN component of the lesion. However, a subset (approximately one-third) of combined BN seemed to show true LEF1 expression. Taking into account pitfalls in interpretation, the combinatorial panel of PRAME and LEF1, in addition to conventional histopathological features, may be useful to distinguish CDPN from combined BN and other benign and malignant mimics.

4 step progression scheme of WNT-activated melanocytic tumors



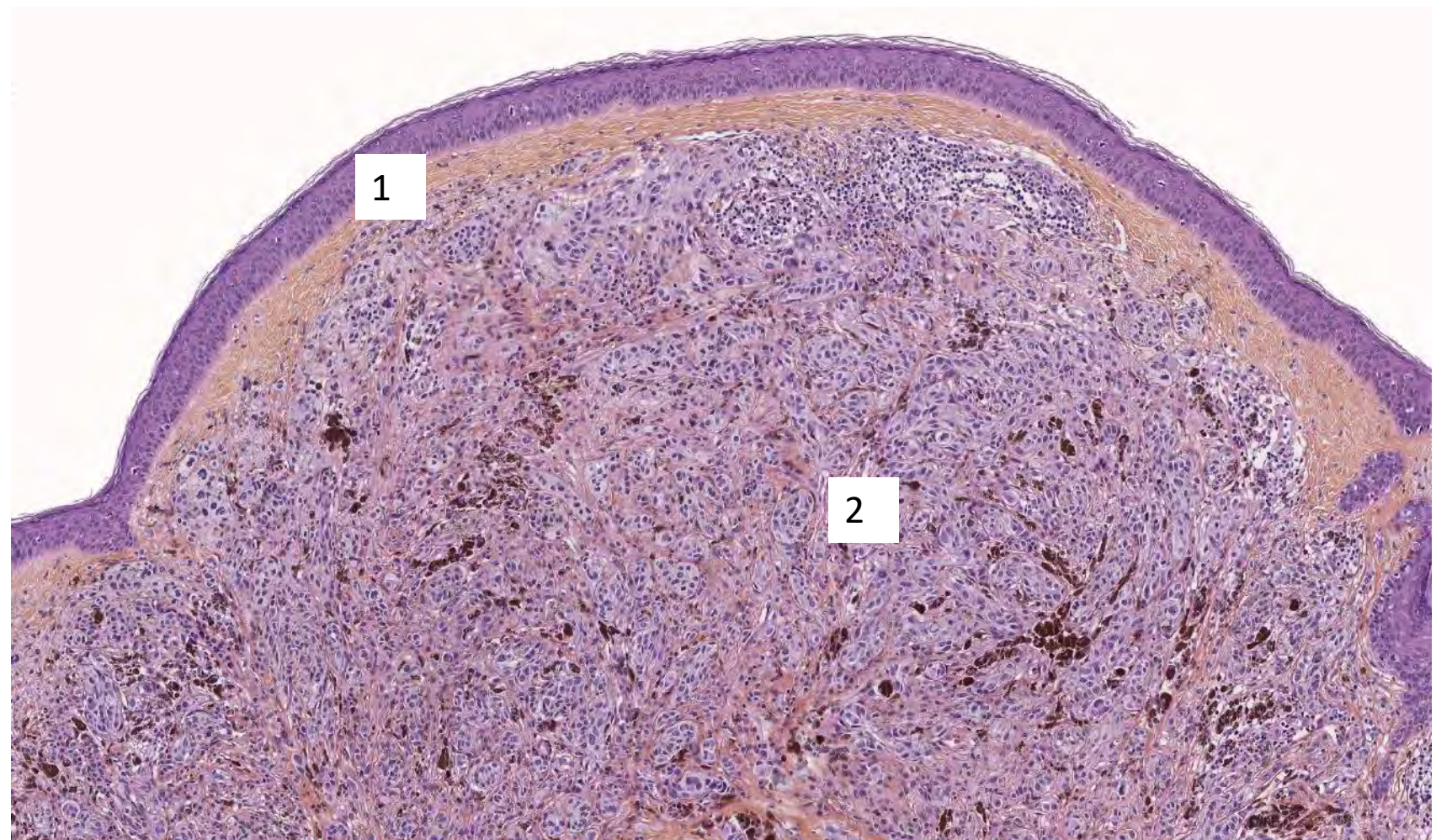
BRAF > NRAS

1

Commun nevus

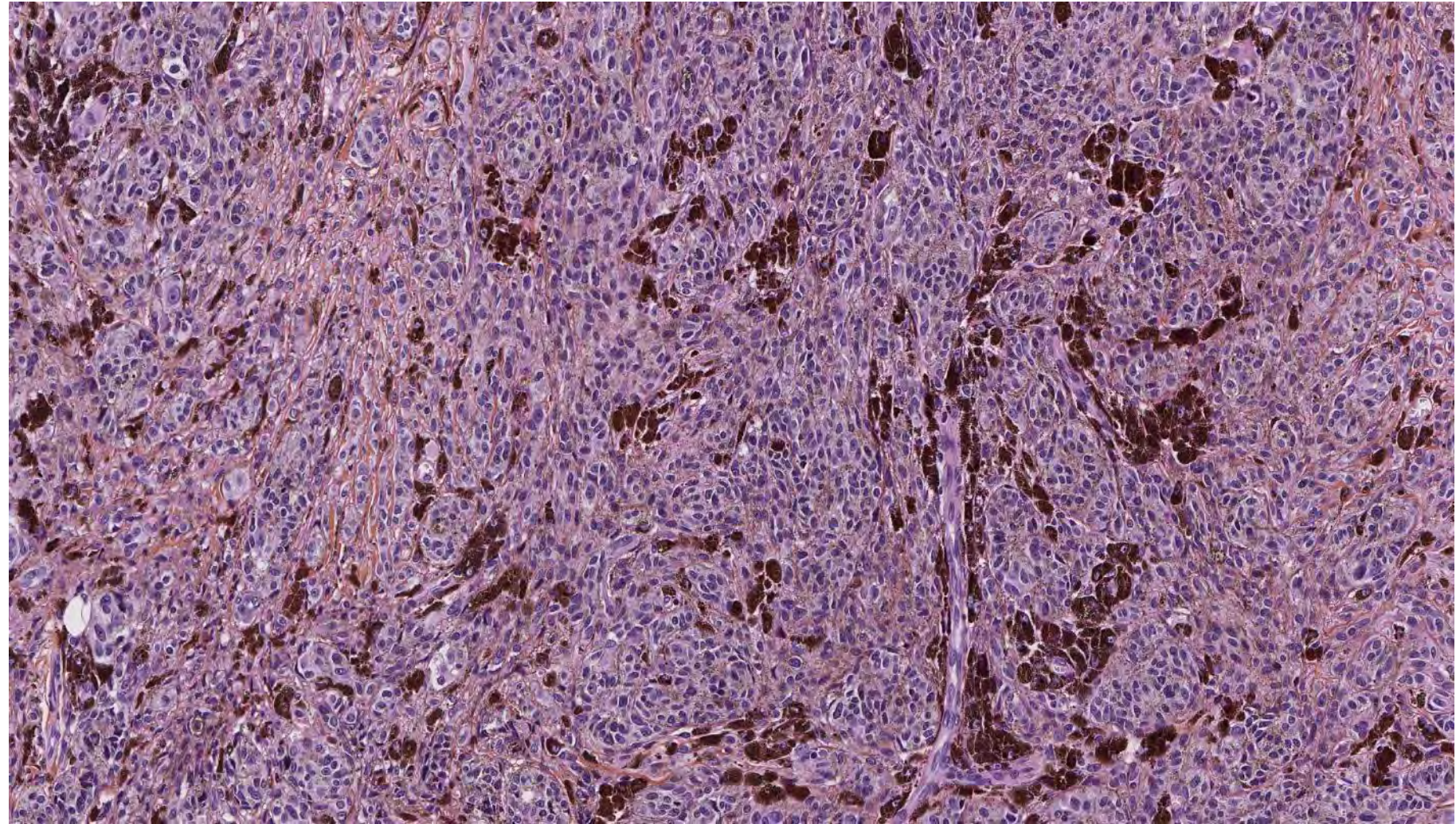
2

WNT activated-
Deep Penetrating Nevus



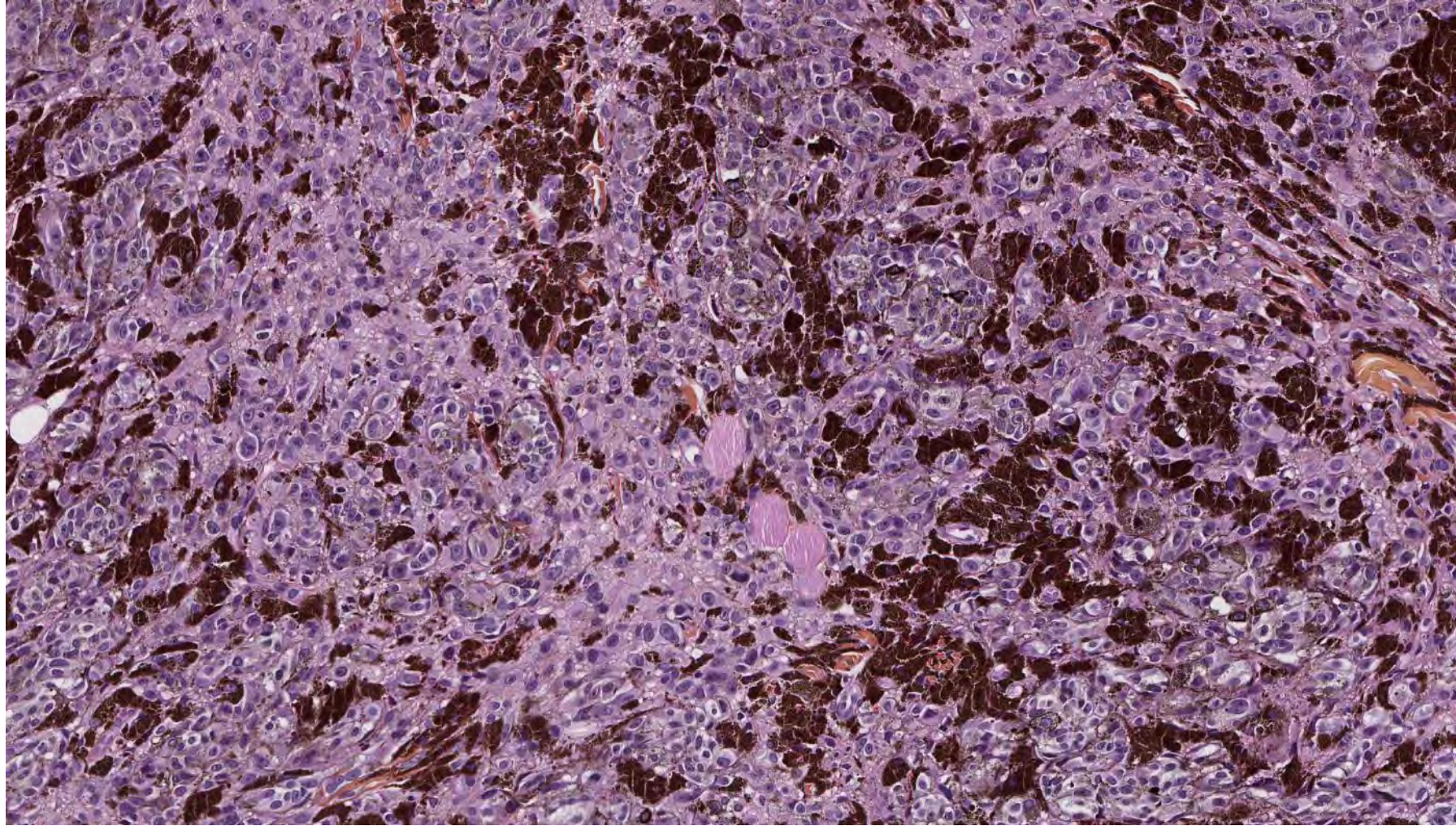
2

WNT activated-
Deep Penetrating Nevus



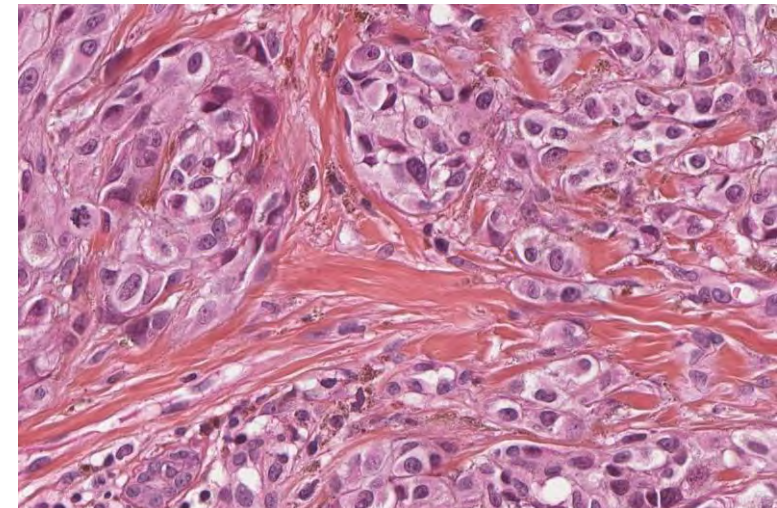
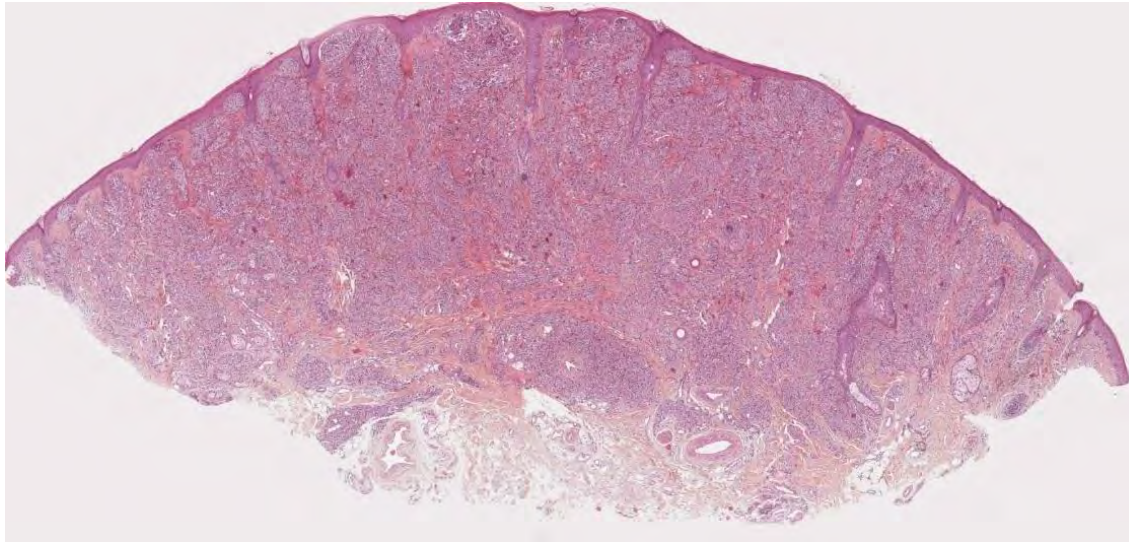
3

WNT activated-Deep
Penetrating Melanocytoma



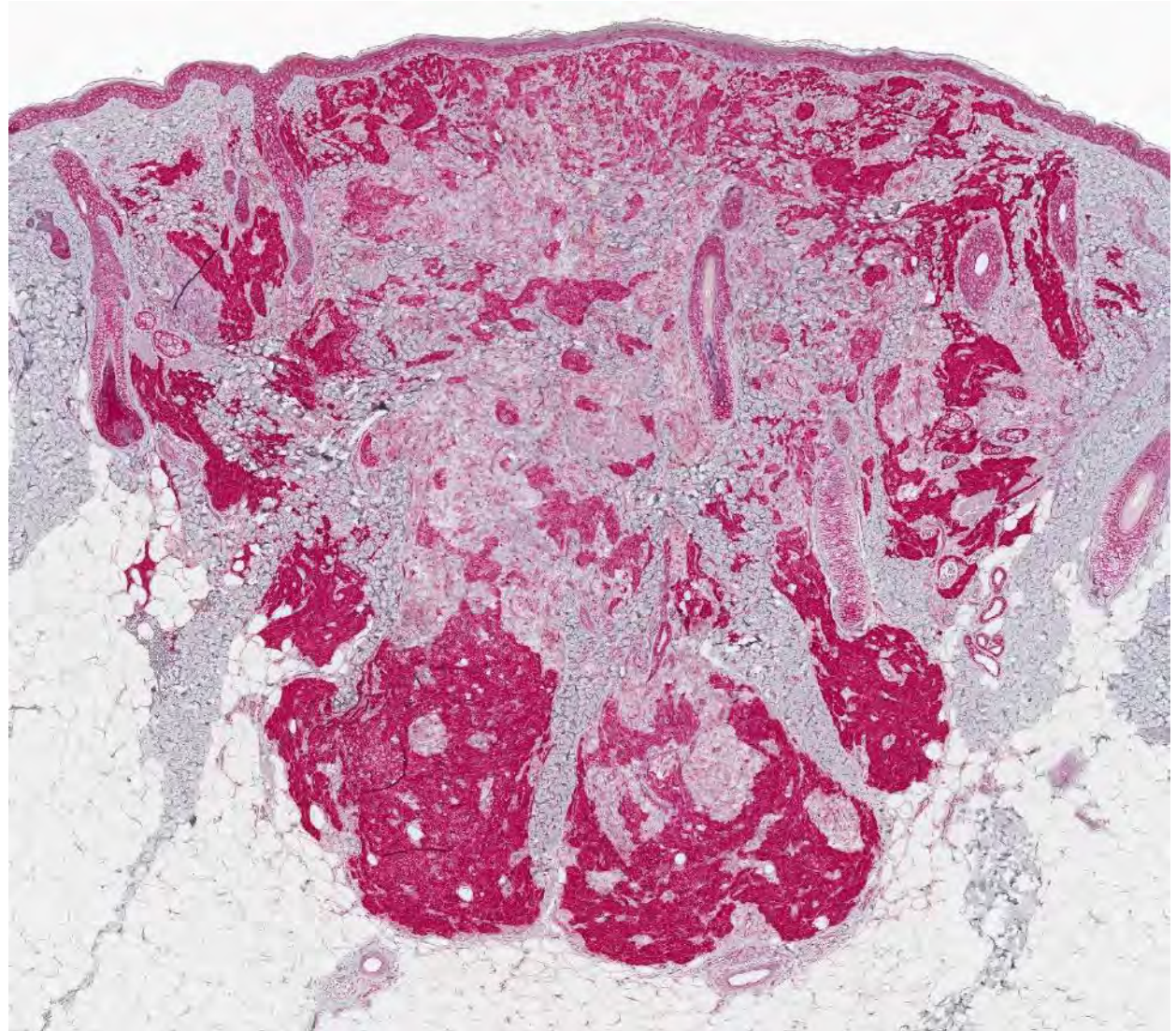
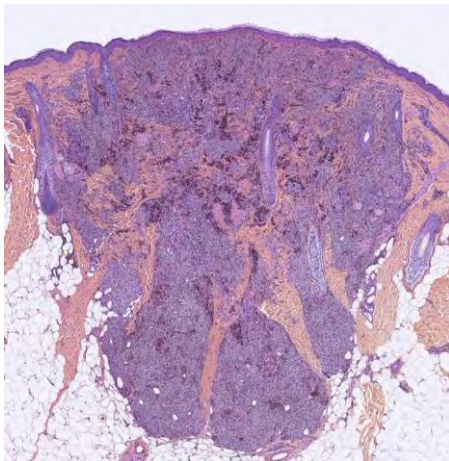
High grade WNT activated- Deep Penetrating Melanocytoma

- Large size
- Cellular density
- Mitotic activity



High grade WNT activated- Deep Penetrating Melanocytoma

- Large size
- Cellular density
- Mitotic activity
- «Bulky» β -catenin stain



WNT activated-Deep Penetrating Melanocytoma

“Stacking” of known secondary anomalies
is the progression model

- Class I: *BRAF* or *NRAS* *ie* “common” genetic background
- + either *CTNNB1* or *APC* mutations *ie* WNT pathway activation
- +/- *IDH1 R132C* mutation
- +/- *tert* promoter mutation

PMID: 34205480; 35184152; 32526042

NGS-Based Analysis of Atypical Deep Penetrating Nevi

Antonella Manca ¹, Maria Cristina Sini ², Anna Maria Cesinaro ³, Francesca Portelli ⁴, Carmelo Urso ⁵, Maria Lentini ⁶, Roberta Cardia ⁶, Lluvia Alos ⁷, Martin Cook ⁸, Sara Simi ⁴, Panagiotis Paliogiannis ⁹, Vincenzo De Giorgi ¹⁰, Antonio Cossu ¹¹, Giuseppe Palmieri ¹², Daniela Massi ⁴

Affiliations [+](#) expand

PMID: 34205480 PMCID: [PMC8234376](#) DOI: [10.3390/cancers13123066](#)

[Free PMC article](#)

Abstract

Deep penetrating nevi (DPNs) are rare melanocytic neoplasms consisting of pigmented spindled or epithelioid melanocytes with a distinctive wedge-shaped configuration showing activation of the WNT pathway, with unusual cyto-architectural features. It is unclear whether they show a distinct genomic profile associated with a diverse metastatic potential. We describe herein a cohort of 21 atypical DPNs analyzed by next-generation sequencing using the Ion AmpliSeq™ Comprehensive Cancer Panel. We found that β -catenin exon 3 was mutated in 95% and MAP kinase pathway genes in 71% of the cases. Less frequent mutations were observed in HRAS (19%) and MAP2K1 (24%). Isocitrate dehydrogenases 1 (IDH1) mutations, including R132C, V178I, and S278L, were identified in 38% of cases and co-existed with BRAF/HRAS mutations. The only case with progressive nodal disease carried alterations in the β -catenin pathway and mutations in IDH1 and NRAS (codon 61). By a comprehensive mutation analysis, we found low genetic heterogeneity and a lack of significant associations between specific gene mutations and histopathological features, despite atypical features. Whether the acquisition of an NRAS or IDH1 mutation in an atypical DPN may represent a molecular evolution implying a pathway to melanoma progression should be confirmed in a larger series.

EXTRAORDINARY CASE REPORT

An Atypical Deep Penetrating Nevus With Mutations in *Beta Catenin*, *BRAF*^{V600E}, and *IDH1*^{R132C} in an 8-Year-Old Boy

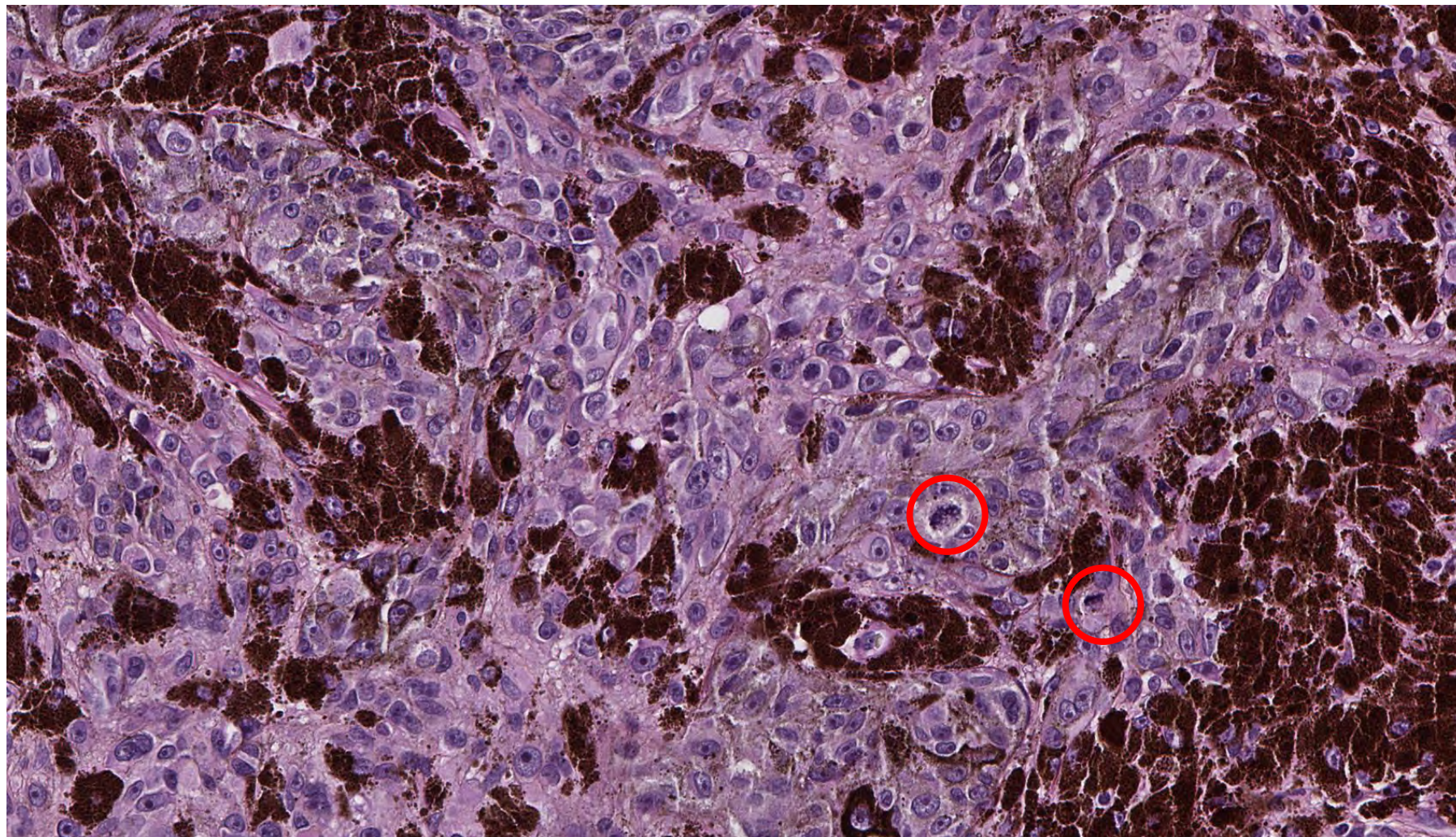
Ireland, Amanda M. FRCPA^{*}; Wood, Benjamin A. FRCPA^{*,†}; Whitfield, Joseph FRCPA[‡]; Amanuel, Benhur FRCPA^{*}; Harvey, Nathan T. FRCPA^{*,†}; Mesbah Ardakani, Nima FRCPA^{*}

[Author Information](#) 

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4

Plexiform
melanoma



BRAF > NRAS

1

Common nevus

2

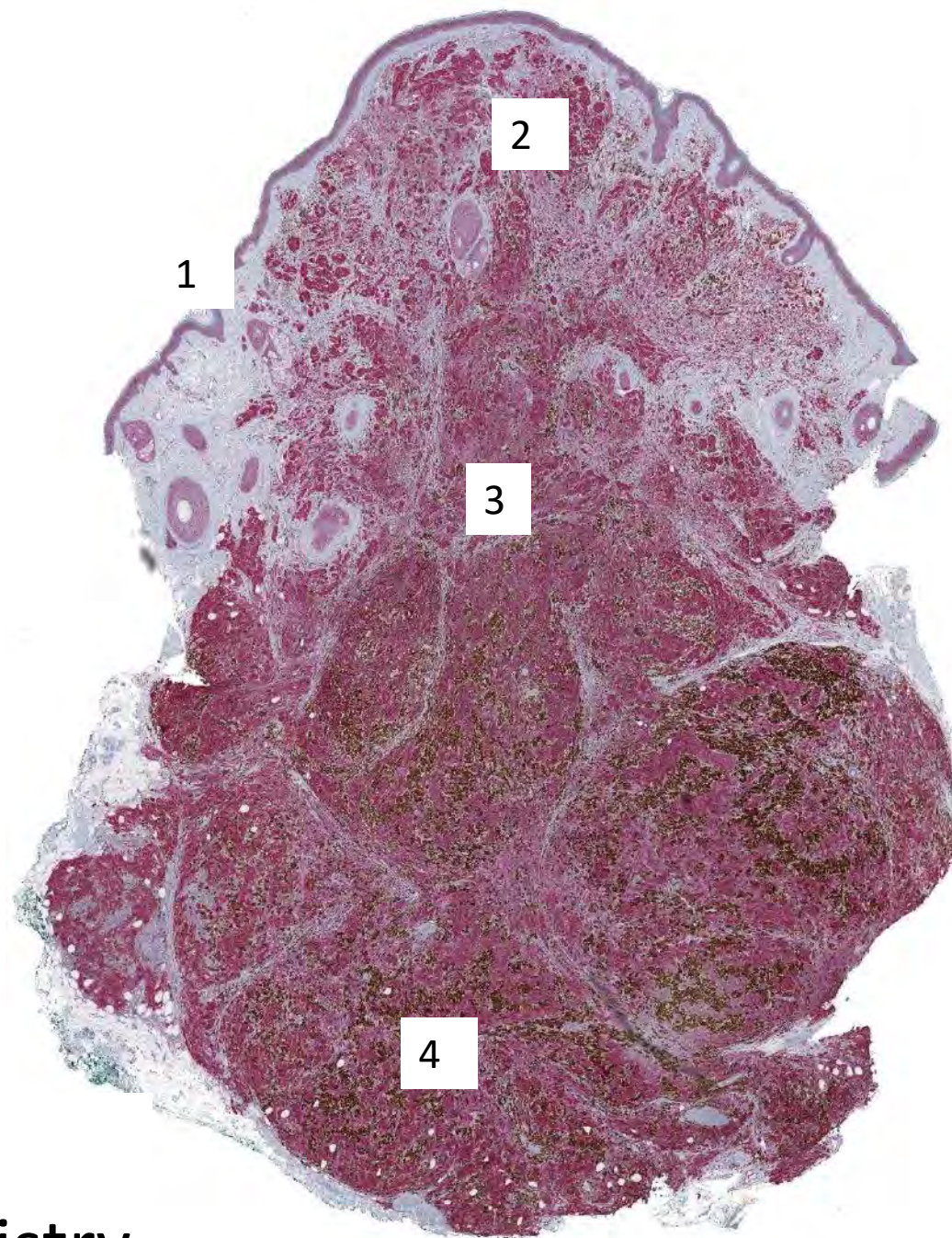
DPN

3

Atypical DPN

4

Plexiform
melanoma



Beta-CATENIN
Immunohistochemistry

Extra-cutaneous WNT-activated melanocytoma



Pathology

Available online 25 July 2023

In Press, Corrected Proof [?](#) What's this? [↗](#)

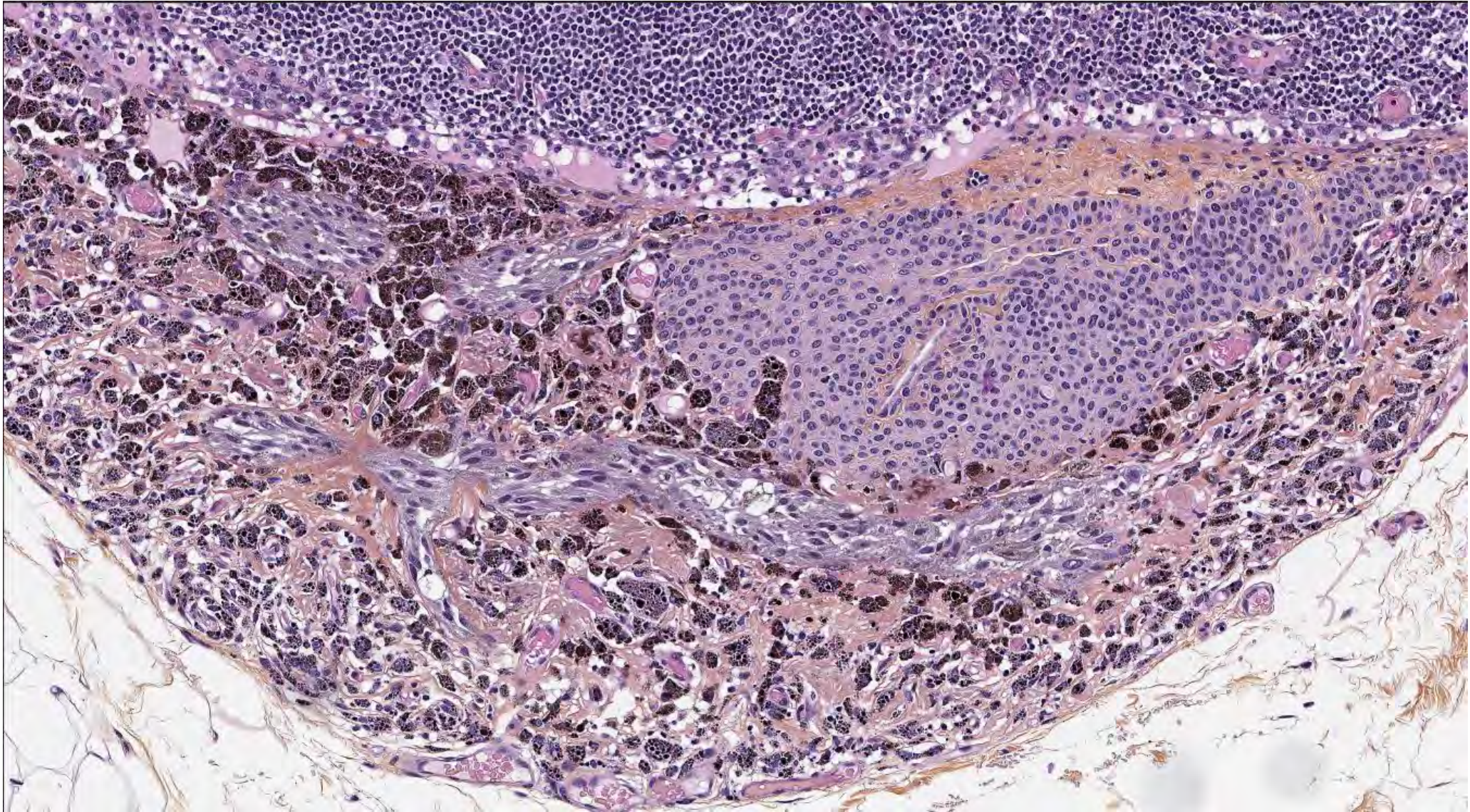


CORRESPONDENCE

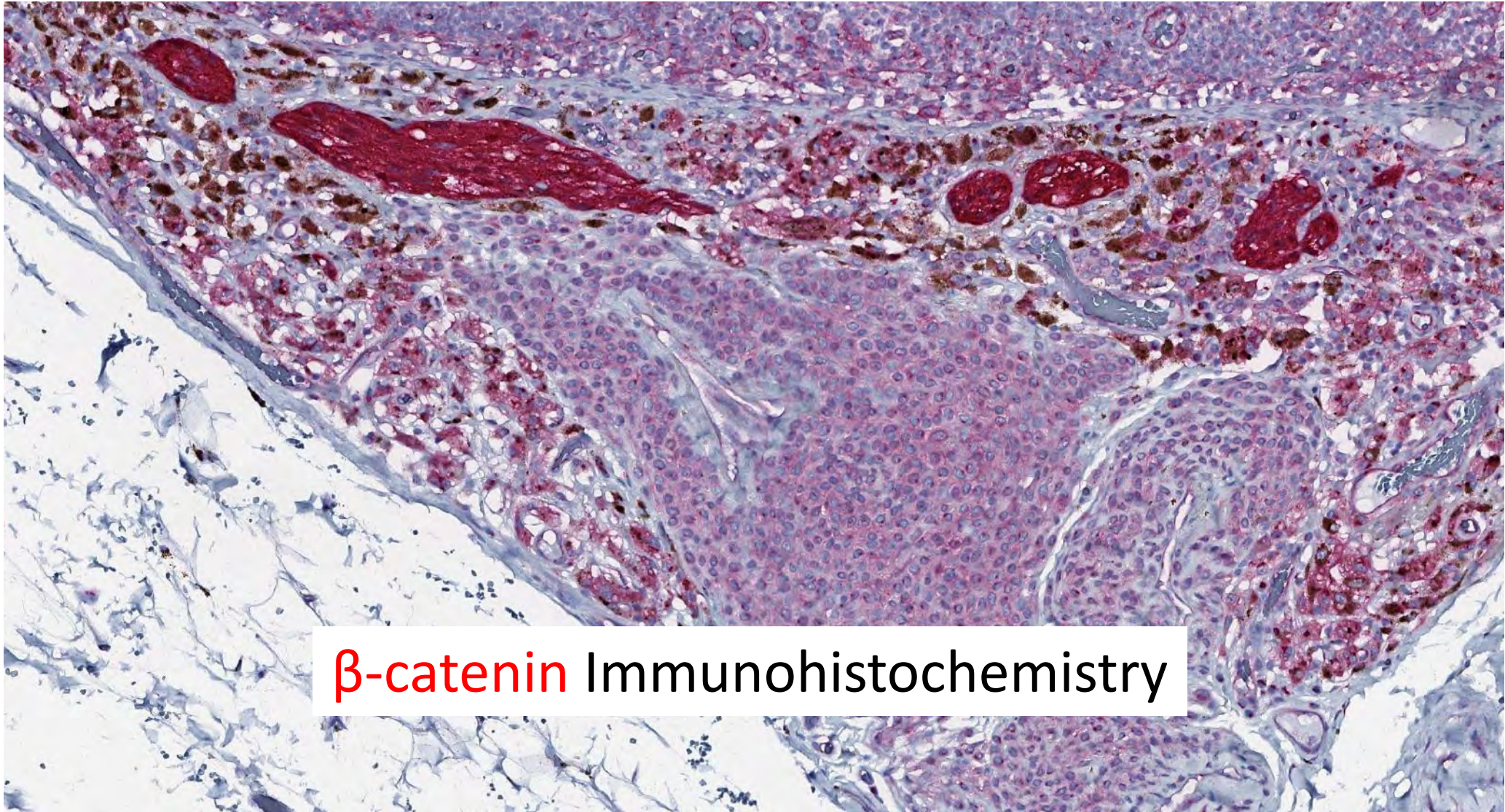
Combined deep penetrating naevus in a capsular nodal naevus

Jérémy Schoelinck¹ [✉](#), Anne Neuhart¹, Mona Amini-Adle², Paul Frobert³, Inès Saizonou¹,
Arnaud de la Fouchardière^{1 4}

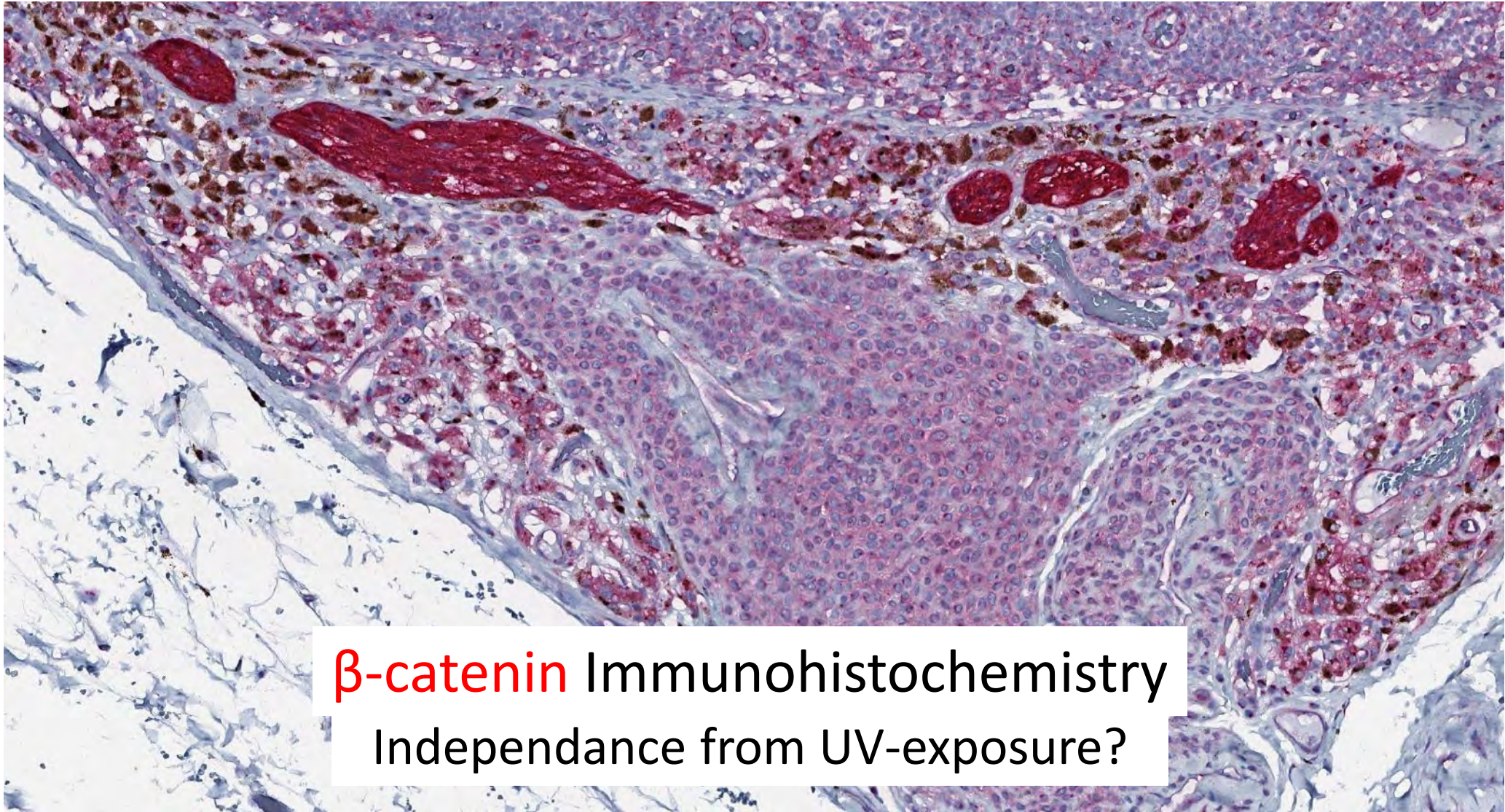
WAM in capsular nevus (SLN)



WAM in capsular nevus (SLN)



WAM in capsular nevus (SLN)



β -catenin Immunohistochemistry
Independence from UV-exposure?

WNT-activated melanocytic tumors

Take home messages

- Terminology change
- «Intermediate tumour» that can progress towards malignancy
- β -catenin IHC is useful +/- LEF1

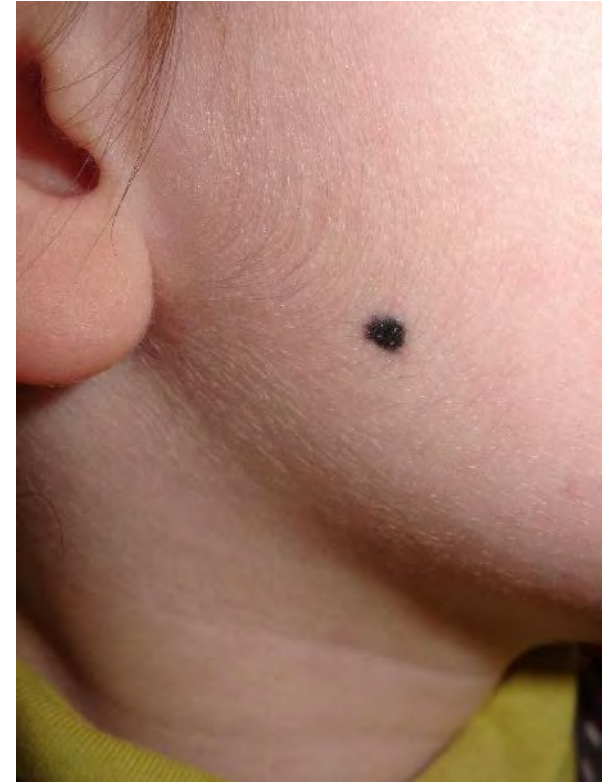
Combined Pigmented Epithelioid Melanocytoma

Pigmented Epithelioid Melanocytoma

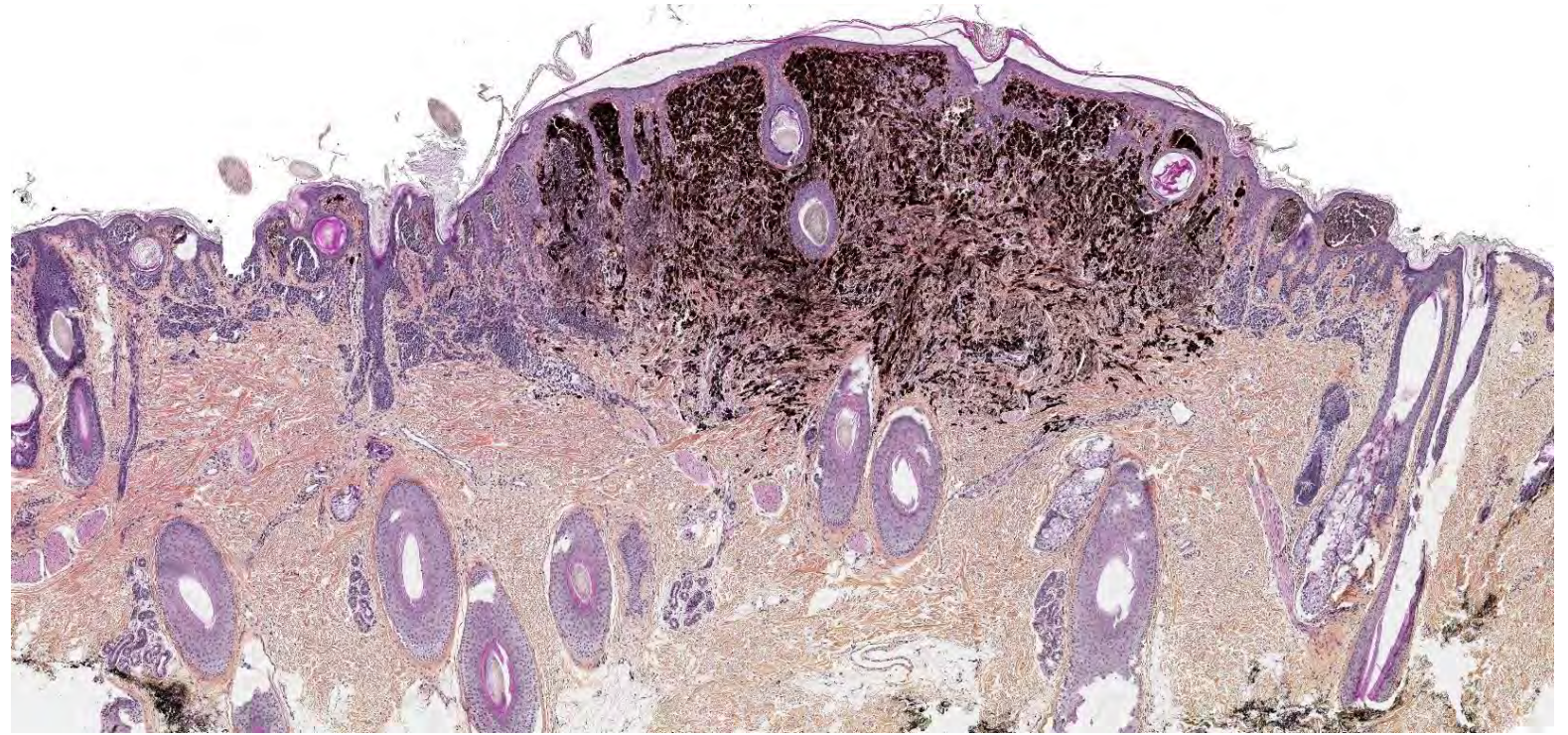
- Child – young adults; All phototypes
- Scalp, genital area



- Multiple lesions : Carney's syndrome



Combined Pigmented Epithelioid Melanocytoma (*BRAF* V600E+ *PRKAR1A* inactivation)



Attempting to Solve the Pigmented Epithelioid Melanocytoma (PEM) Conundrum

PRKAR1A Inactivation Can Occur in Different Genetic Backgrounds (Common, Blue, and Spitz Subgroups) With Variation in Their Clinicopathologic Characteristics

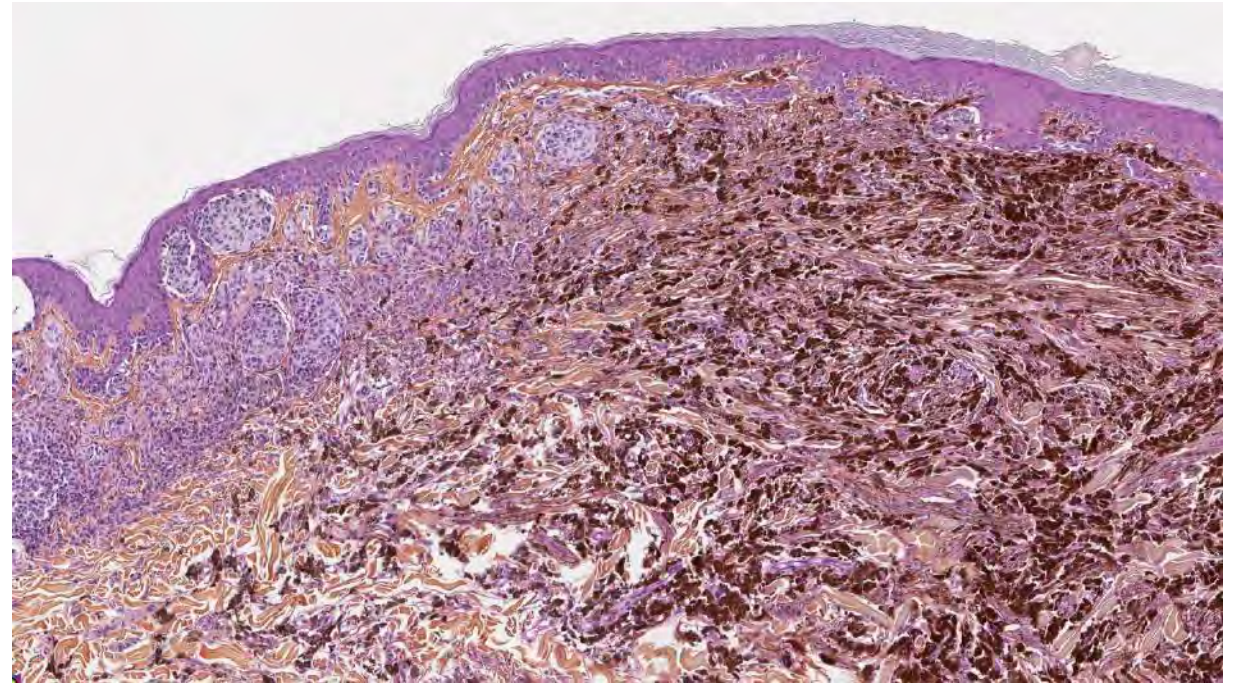
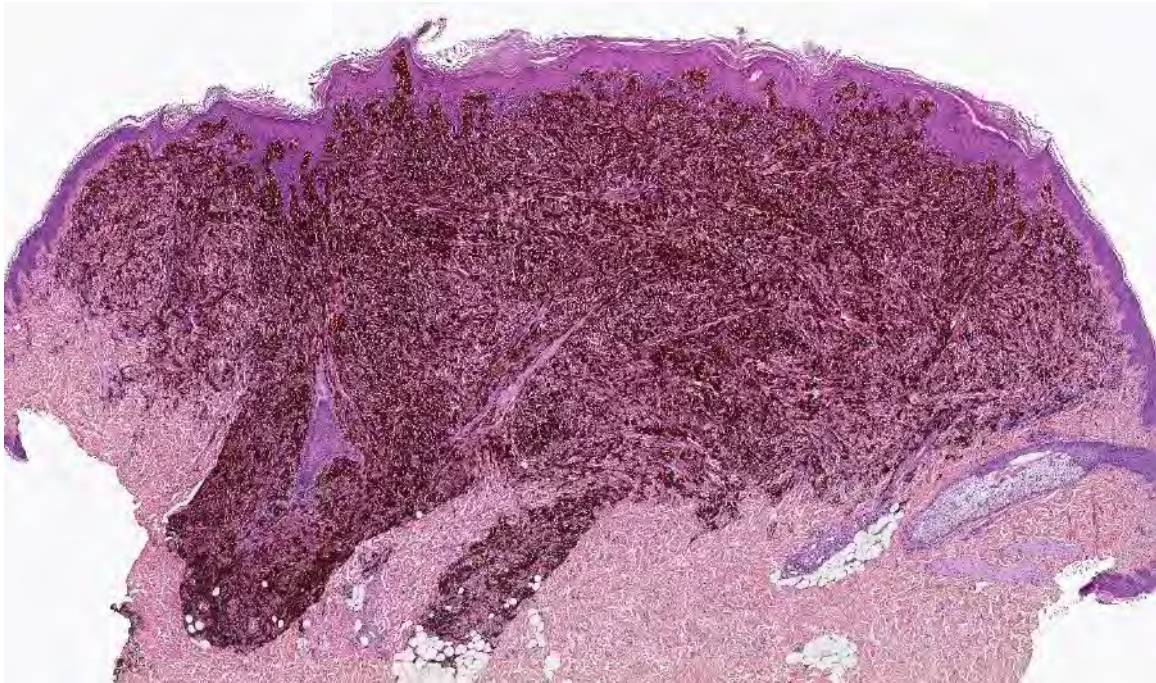
de la Fouchardiere, Arnaud MD, PhD^{*,†}; Tirode, Franck PhD^{*,†}; Castillo, Christine MD[‡]; Buisson, Adrien PharmD[†]; Boivin, Felix MSc^{*}; Macagno, Nicolas MD, PhD^{†,§}; Pissaloux, Daniel PhD^{*,†}

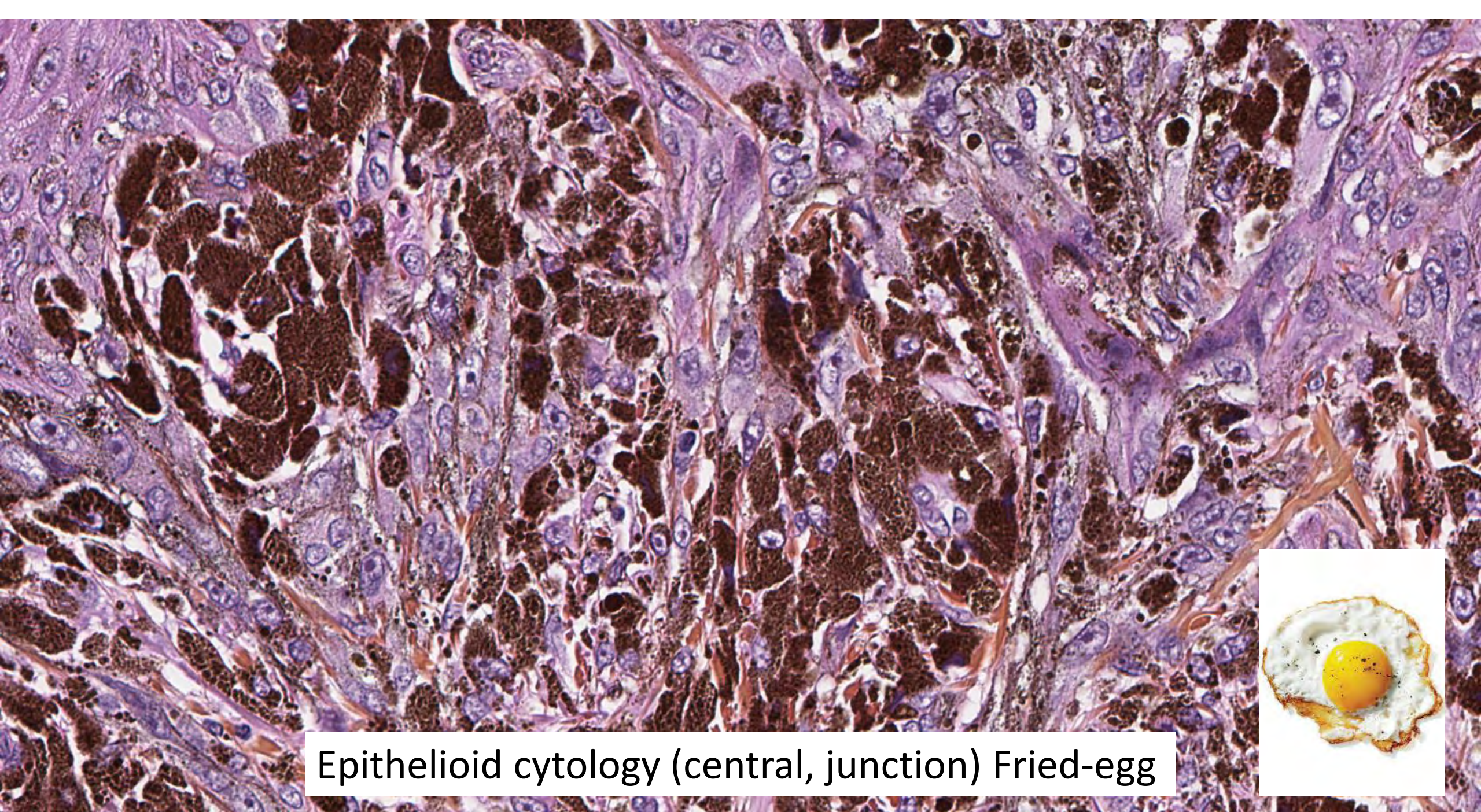
Author Information 

The American Journal of Surgical Pathology: March 22, 2022 - Volume - Issue -
doi: 10.1097/PAS.0000000000001888

PRKAR1A-inactivated melanocytic tumor with a *BRAF* V600E background

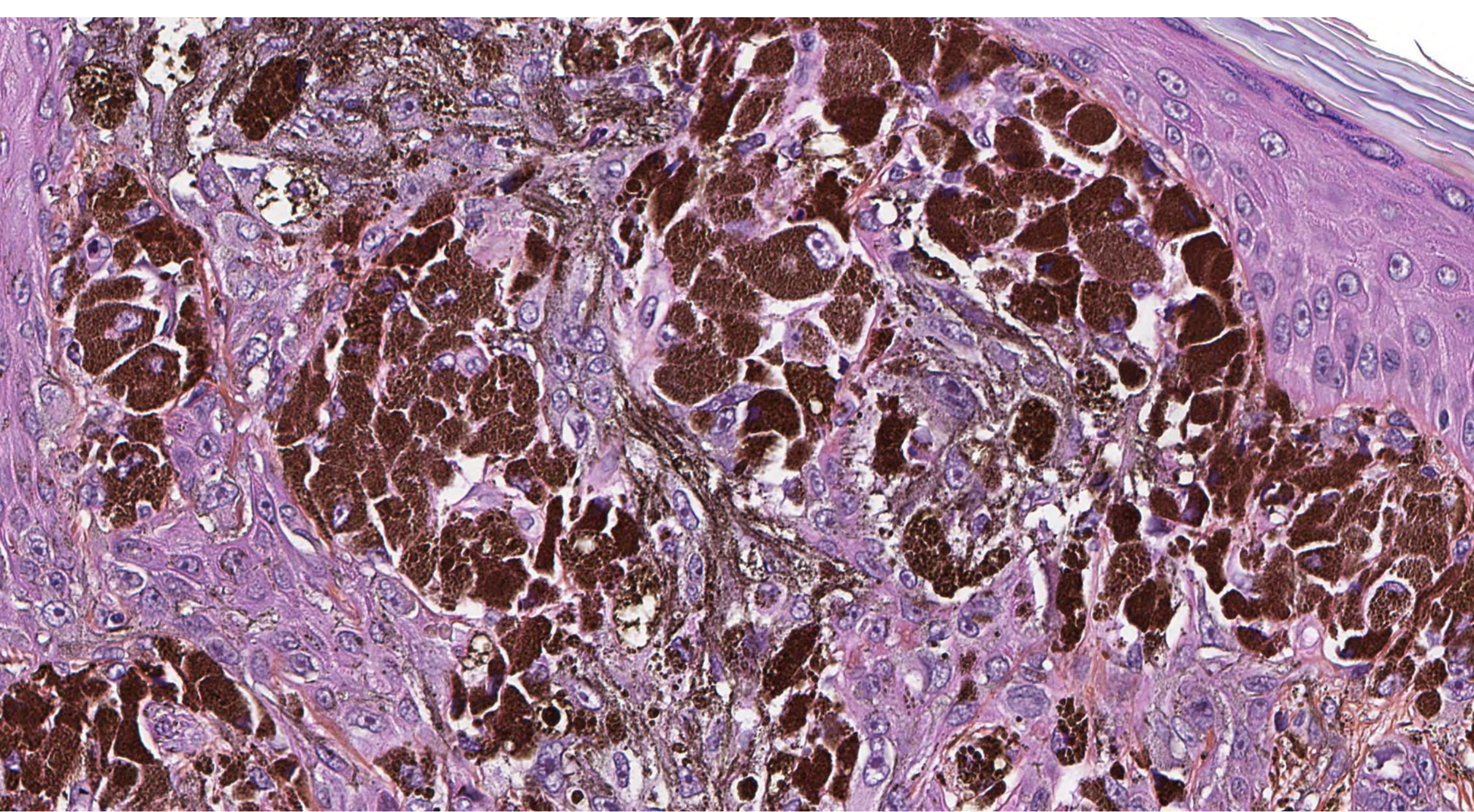
- Young adults
- Pure or biphenotypic with common component
- Mainly dermal with melanophages >> melanocytes

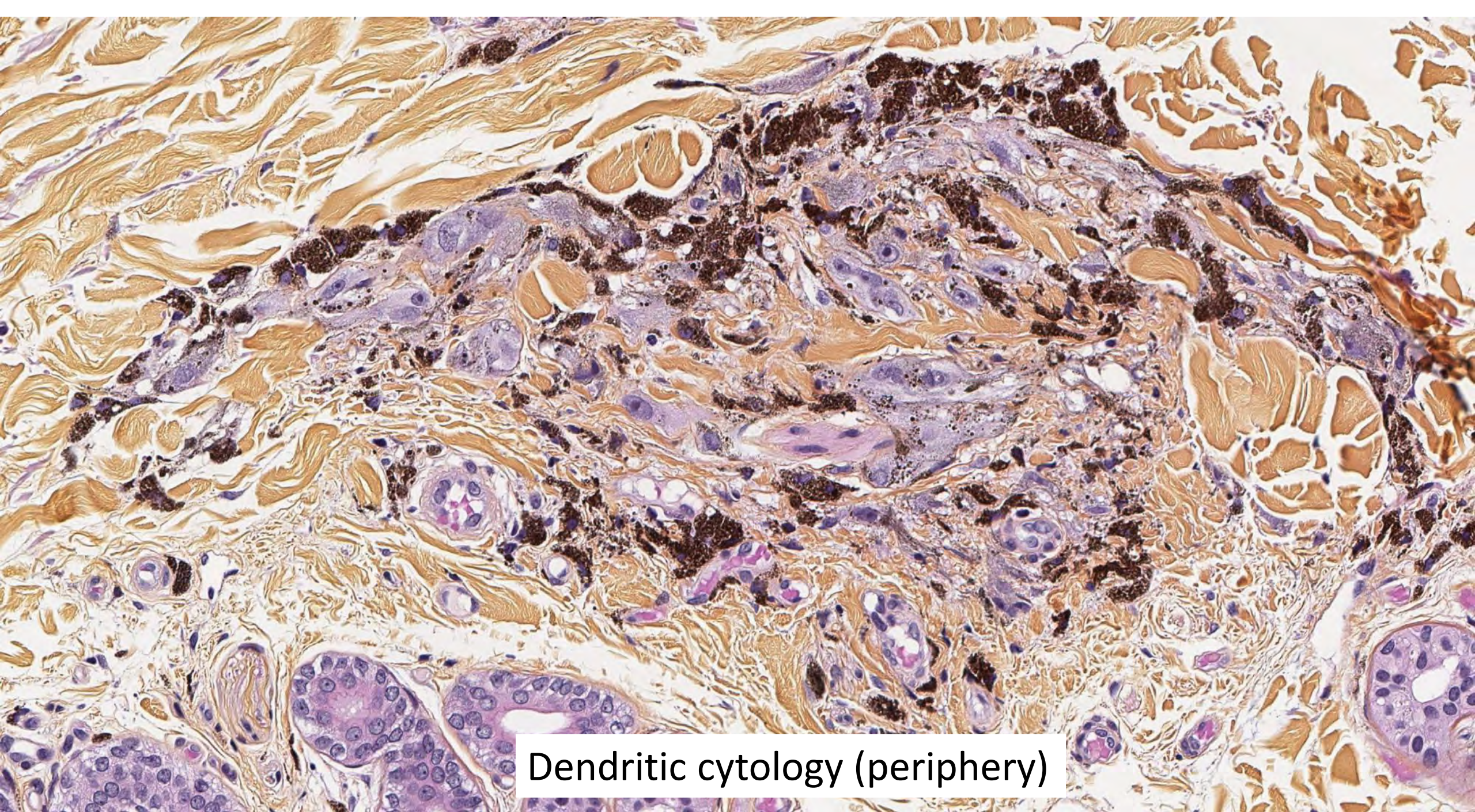




Epithelioid cytology (central, junction) Fried-egg



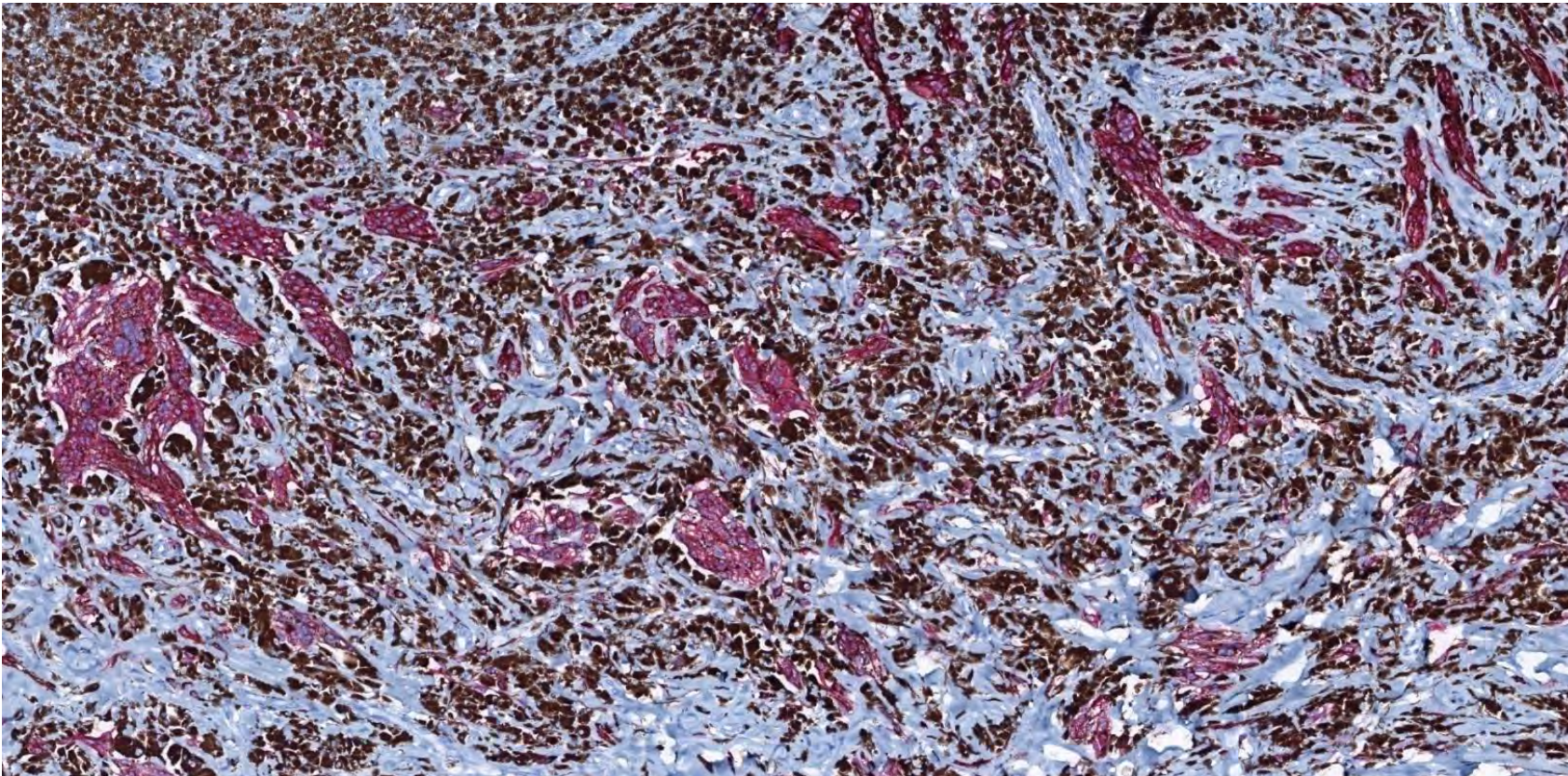




Dendritic cytology (periphery)

PRKAR1A-inactivated melanocytic tumor with a *BRAF* V600E background

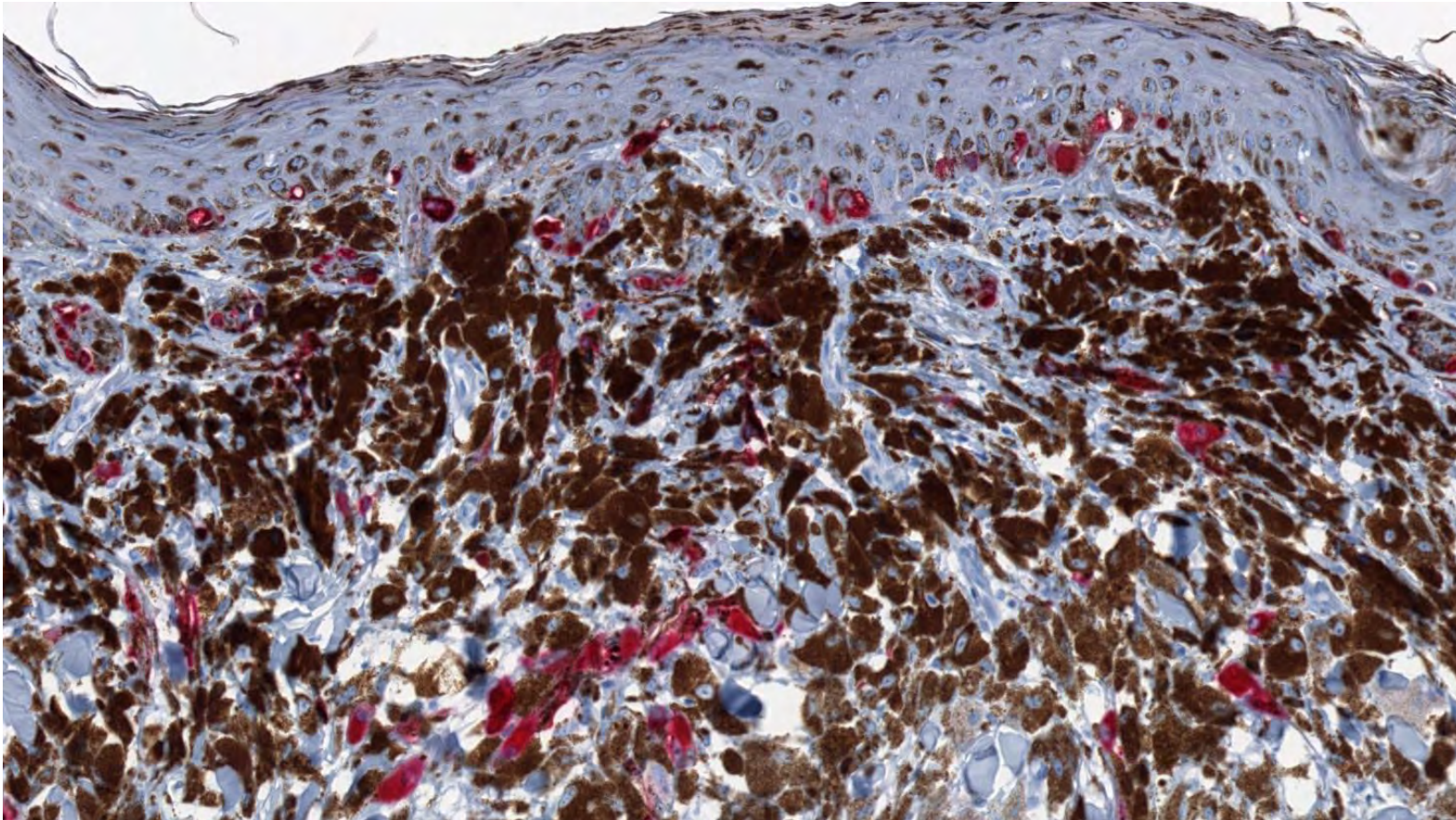
- Low density (no sheets), numerous melanophages



MelanA

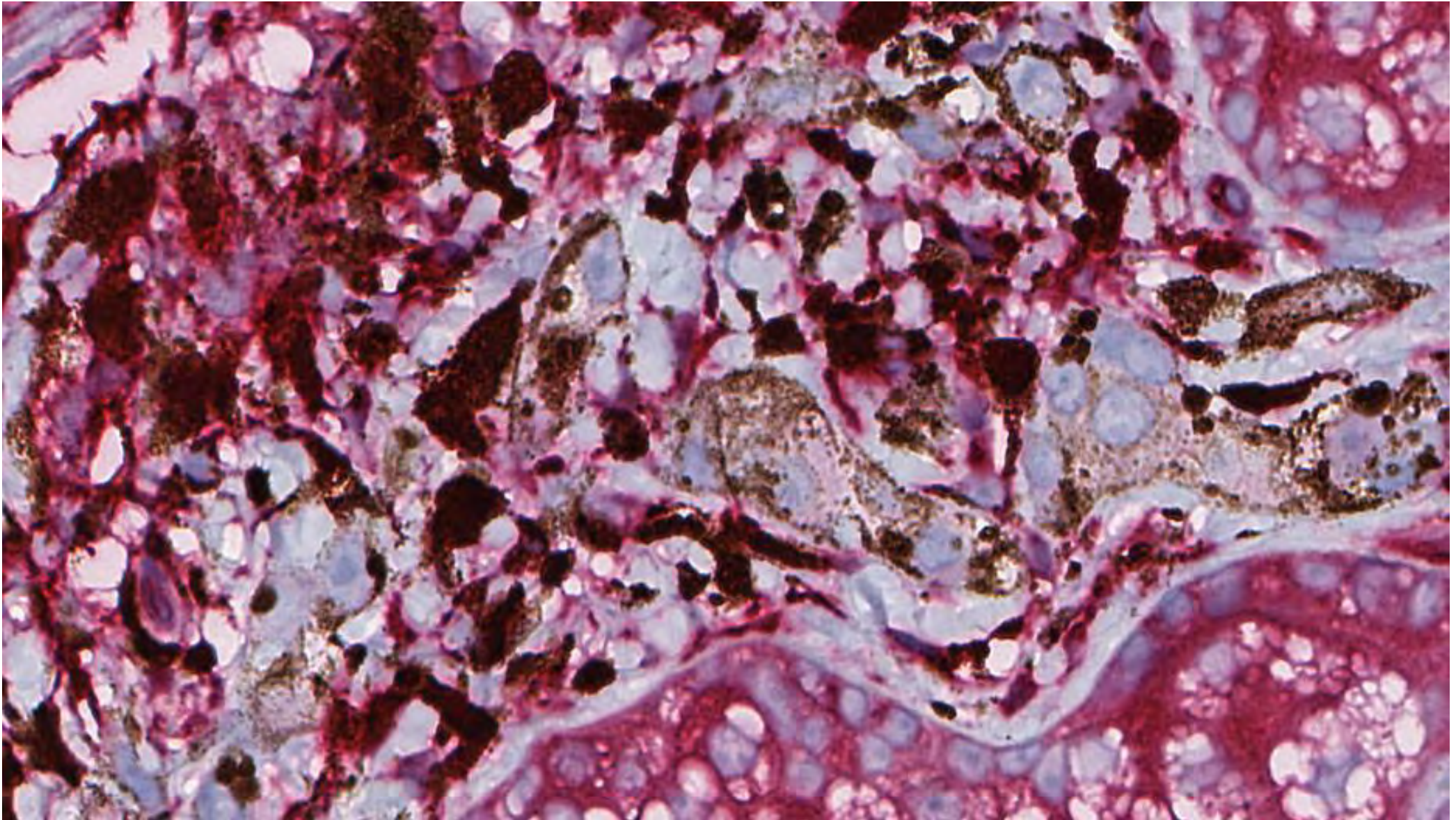
PRKAR1A-inactivated melanocytic tumor with a *BRAF* V600E background

- Low density (no sheets), mainly melanophages

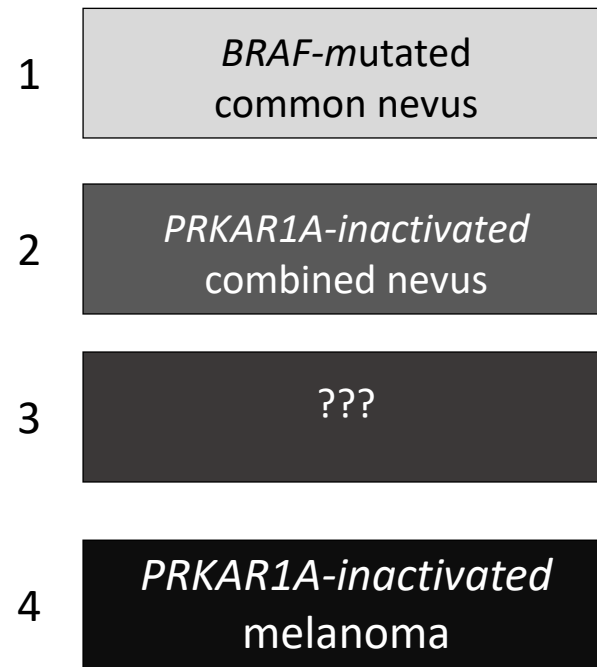


MelanA

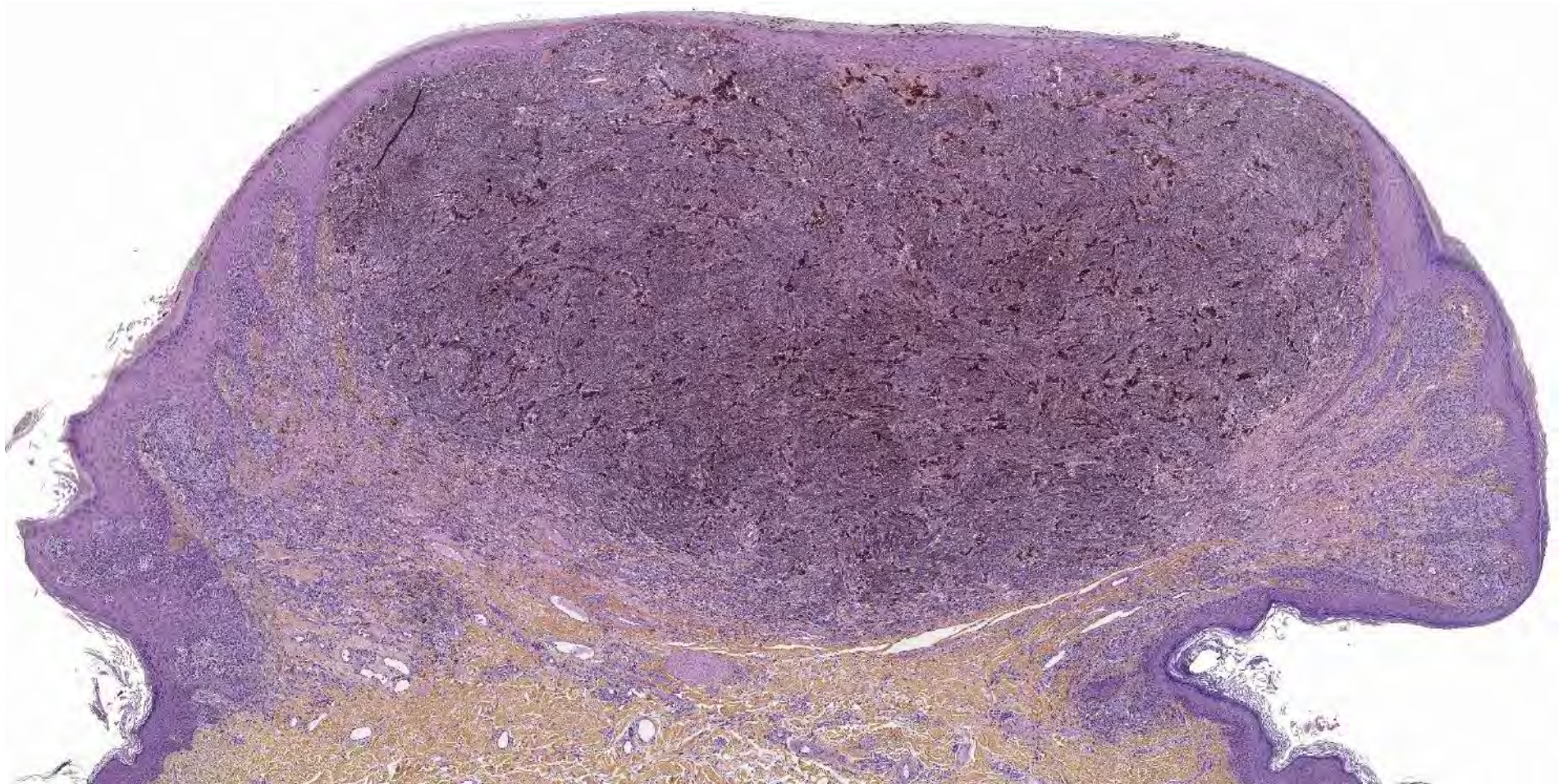
Loss of PRKAR1A cytoplasmic expression by IHC



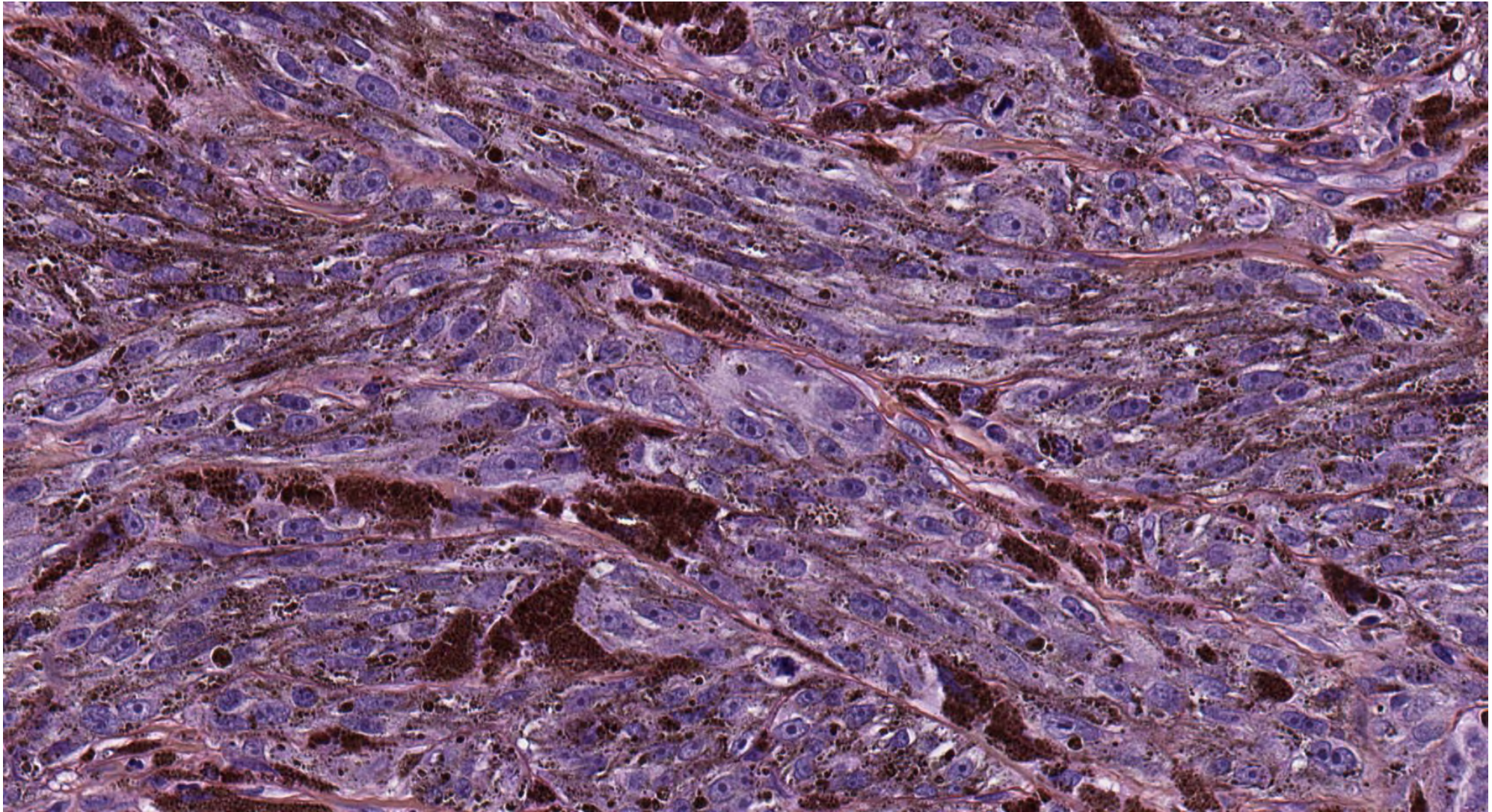
Progression scheme of *PRKAR1A*-inactivated melanocytic tumors in a *BRAF* mutated background?



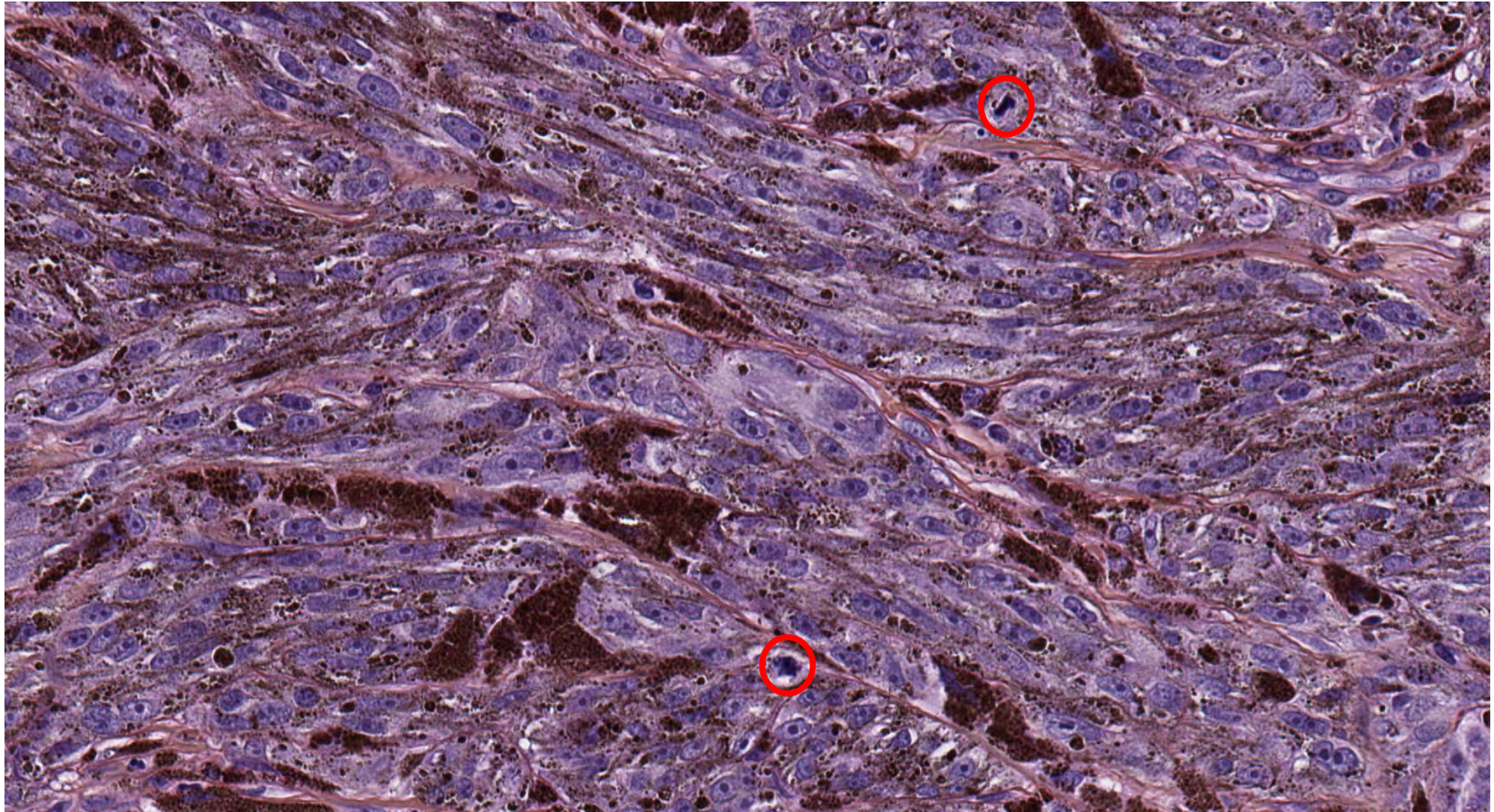
PRKAR1A-inactivated melanoma
with a *BRAF* V600E mutated background



PRKAR1A-inactivated melanoma
with a *BRAF* V600E mutated background



PRKAR1A-inactivated melanoma
with a *BRAF* V600E mutated background



Reconceptualisation of PEM with *PRKAR1A*-inactivation

- *PRKAR1A* inactivation can potentially occur in all known genetic backgrounds that give rise to a nevus , including Spitz and blue

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Reconceptualisation of PEM with *PRKAR1A*-inactivation

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- Specific prognosis could also be related to the various backgrounds

Reconceptualisation of PEM with *PRKAR1A*-inactivation

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- The clinical (age of predilection/ topographies) features are unchanged
- Specific histological features are linked to the various backgrounds
- Specific prognosis could also be related to the various backgrounds
- Terminology remains to be determined (WHO 2024)

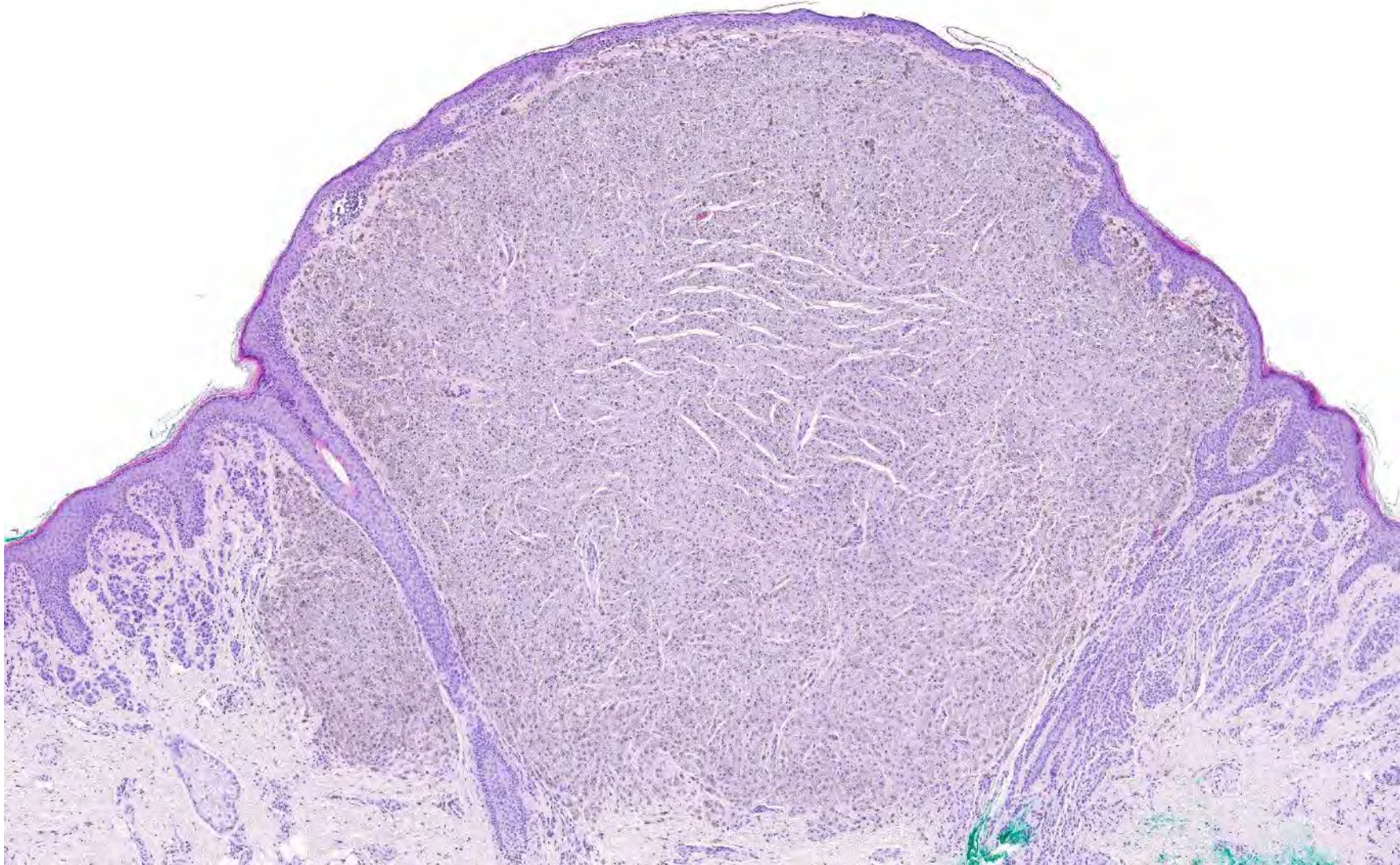
clonal nevus NOS/Rare entities

- Combined/clonal nevus NOS
- *NRAS* mutation/amplification
- *NRAS-IDH1* co-mutation

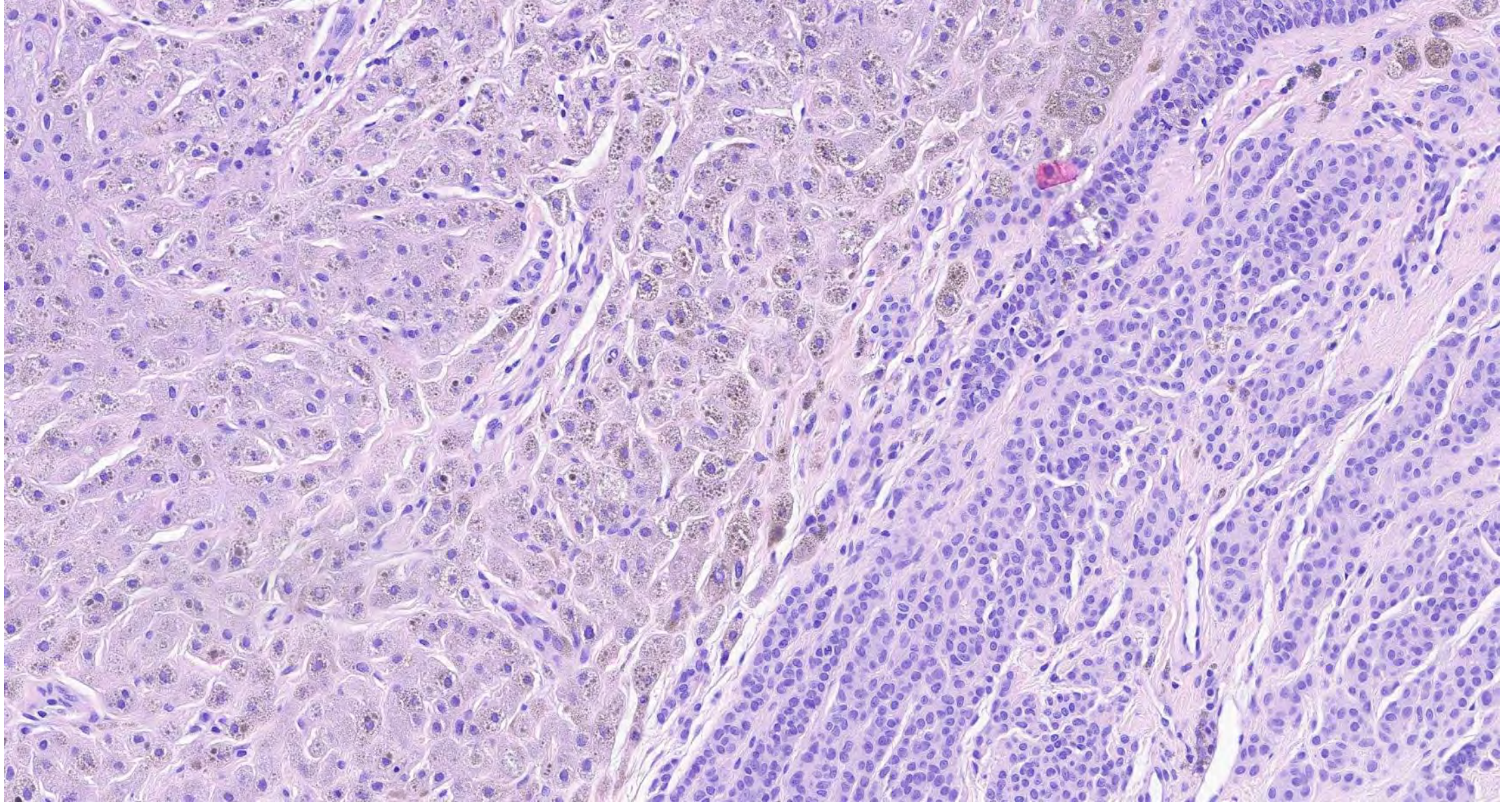
Clonal nevus

- Presence within a compound nevus of a dermal component with different morphological features.
- Absence of known cytomorphological or genetic anomaly
- Clinically the clonal area is visible
 - Nodular
 - Pigmented or achromic

Clonal nevus with BRAF V600E mutation



Clonal nevus with BRAF V600E mutation



NRAS mutation + amplification combined nevus

NRAS mutation + amplification combined nevus

[J Cutan Pathol](#). 2014 Sep 26. doi: 10.1111/cup.12389. [Epub ahead of print]

Mutated and amplified NRAS in a subset of cutaneous melanocytic lesions with dermal spitzoid morphology: report of two pediatric cases located on the ear.

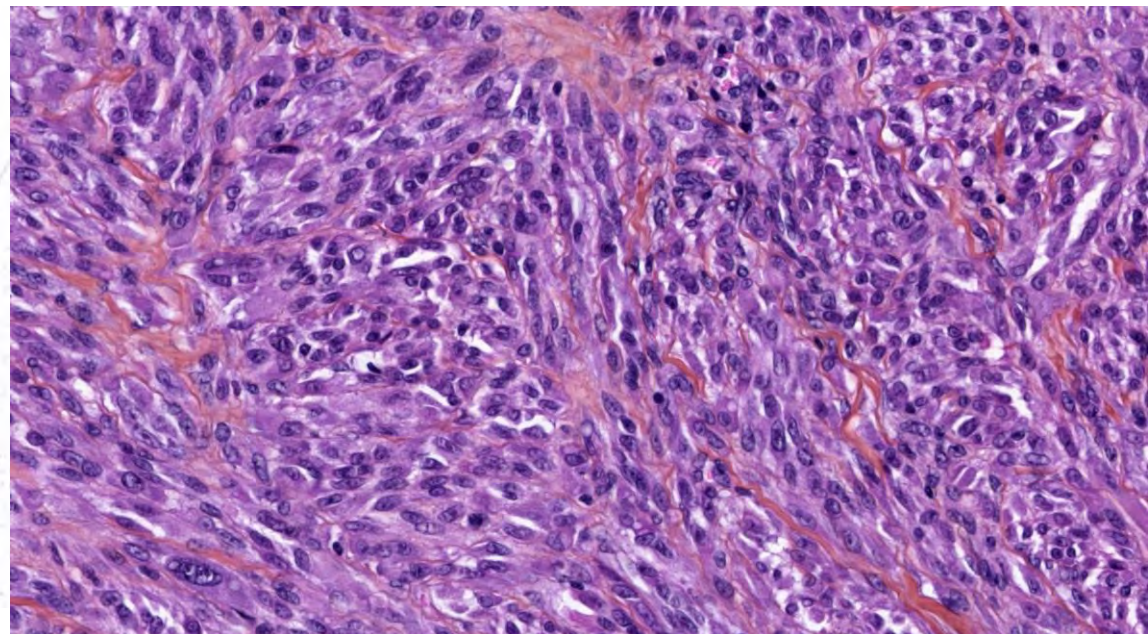
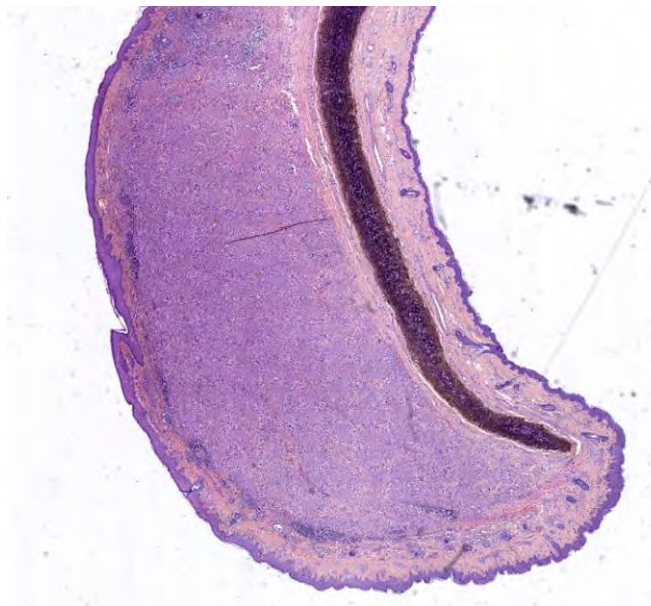
[Dubruc E¹](#), [Balme B](#), [Dijoud F](#), [Disant F](#), [Thomas L](#), [Wang Q](#), [Pissaloux D](#), [de la Fouchardiere A](#).

⊕ Author information

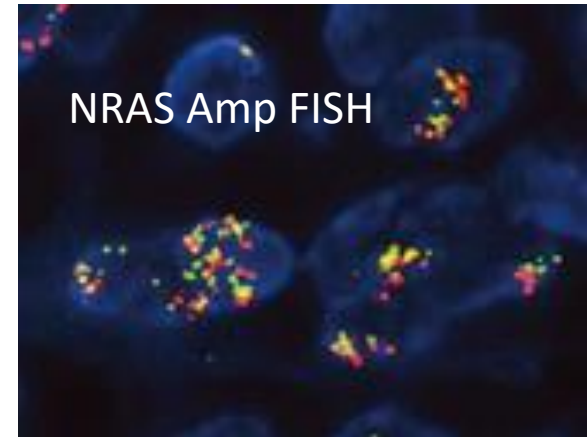
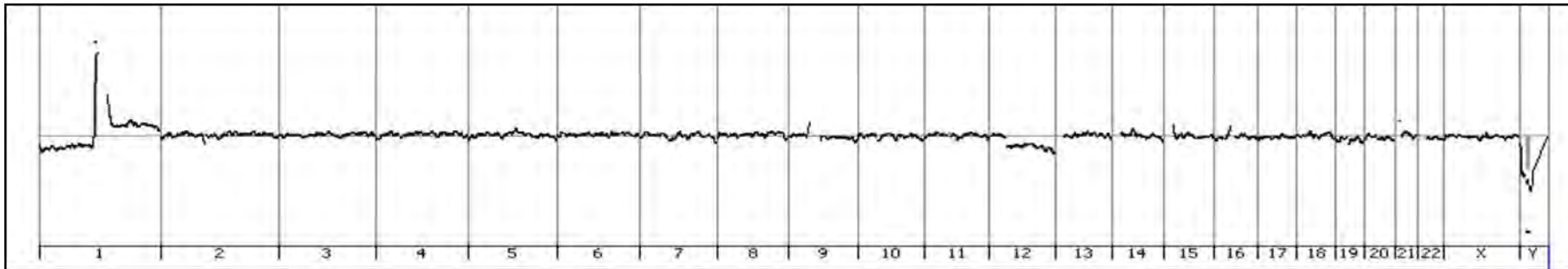
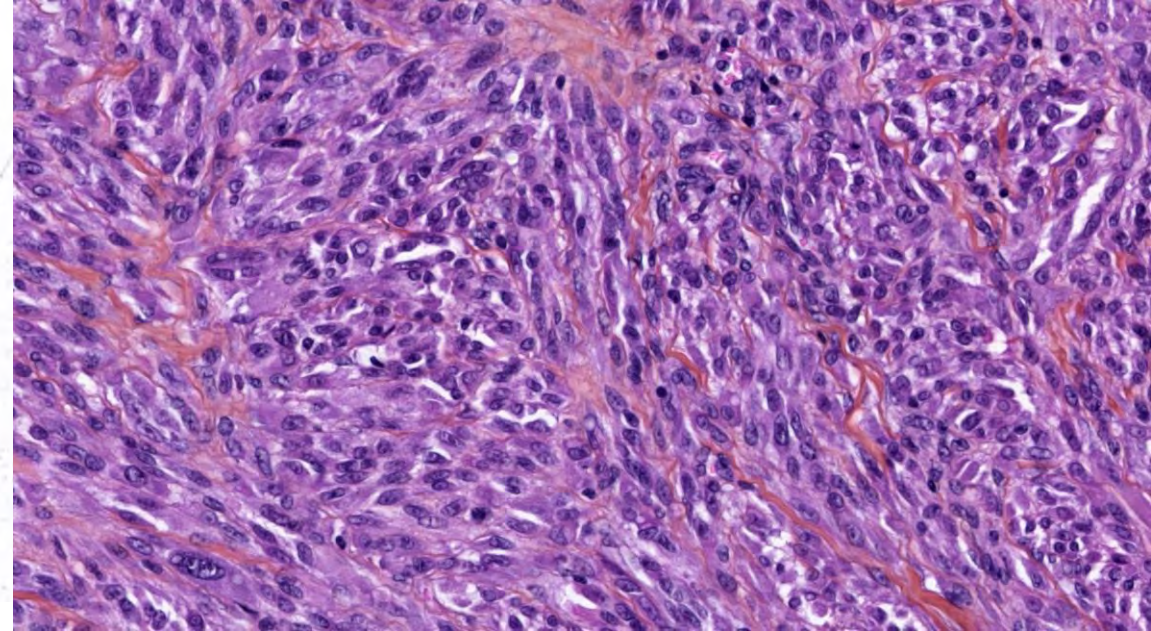
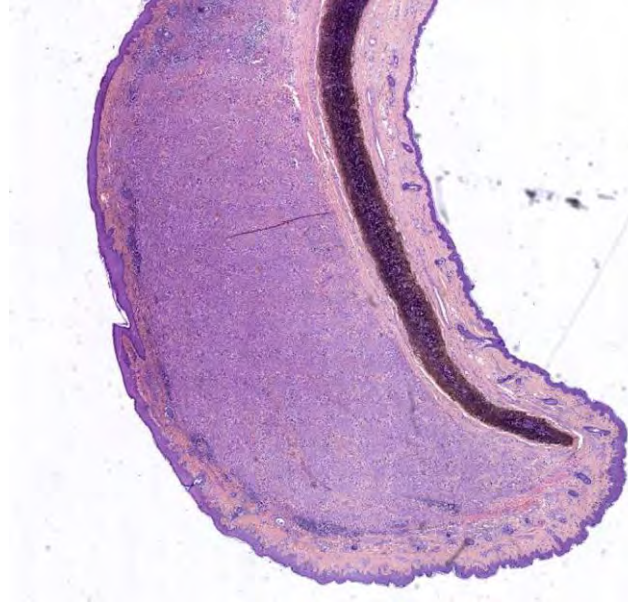
Abstract

Extensive cytogenetic testing is slowly unveiling the complexity of the genomics of melanocytic tumors. NRAS mutations have been the first genetic abnormality described in malignant melanomas. We report the cases of two children, presenting a melanocytic lesion located on the ear. One appeared as a combined dermal clone inside a congenital nevus and the other as a centimetric purely dermal tumor. Both tumors were composed of spindled spitzoid melanocytes with atypical histologic features. aCGH and FISH revealed an amplification of the NRAS gene. Sequencing showed an exon 3 NRAS mutation. In the combined case, the amplification was limited to the spitzoid component, underscoring a possible phenotypic shift induced by the alteration. Similarly an overexpression of CyclinD1 and elevation of ki-67 was found in the spitzoid component confirming a raise in proliferation. Such combination of mutation and copy number increase has been previously reported for the HRAS gene in a subset of Spitz nevi. Further studies must evaluate if mutated NRAS is also amplified in melanomas arising in this clinical setting. These combined alterations could represent an early event ultimately leading to malignancy.

NRAS mutation + amplification combined nevus



NRAS mutation + amplification combined nevus



➤ [Mod Pathol. 2024 Mar 10;37\(5\):100469. doi: 10.1016/j.modpat.2024.100469. Online ahead of print.](#)

Amplification of Mutant NRAS in Melanocytic Tumors With Features of Spitz Tumors

Jeffrey M Cloutier¹, Meng Wang², Swapna S Vemula², Sonia Mirza², Jingly Weier²,
Jamie D Aquino³, Timothy H McCalmont⁴, Philip E LeBoit⁵, Boris C Bastian⁵, Iwei Yeh⁶

Affiliations [+ expand](#)

PMID: 38467248 DOI: [10.1016/j.modpat.2024.100469](#)

IDH1 R132C mutations in *NRAS*-mutated nevi

IDH1 R132C mutations in *NRAS*-mutated nevi

➤ [Am J Surg Pathol](#). 2020 Jul 23. doi: 10.1097/PAS.0000000000001500. Online ahead of print.

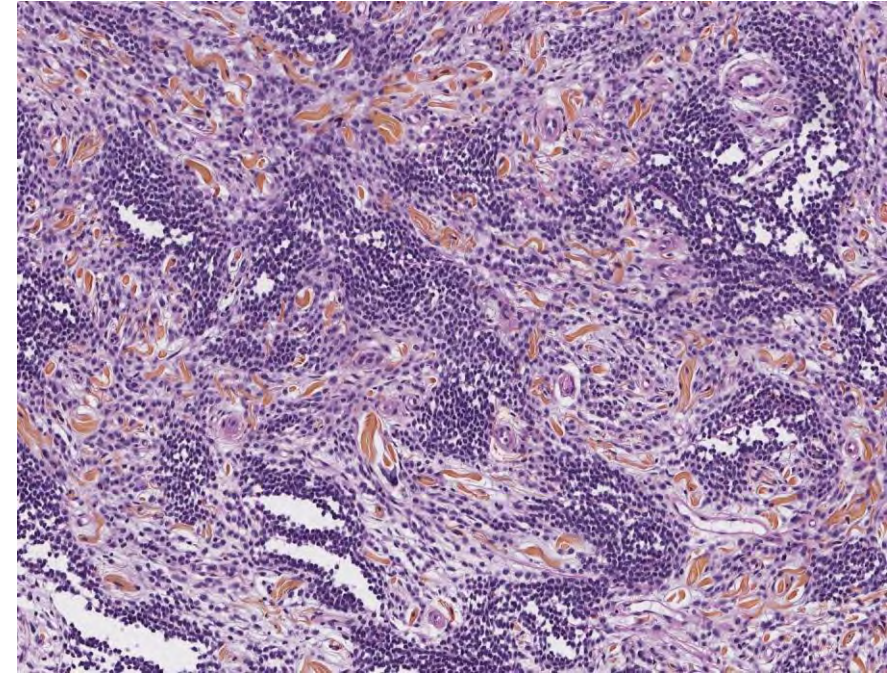
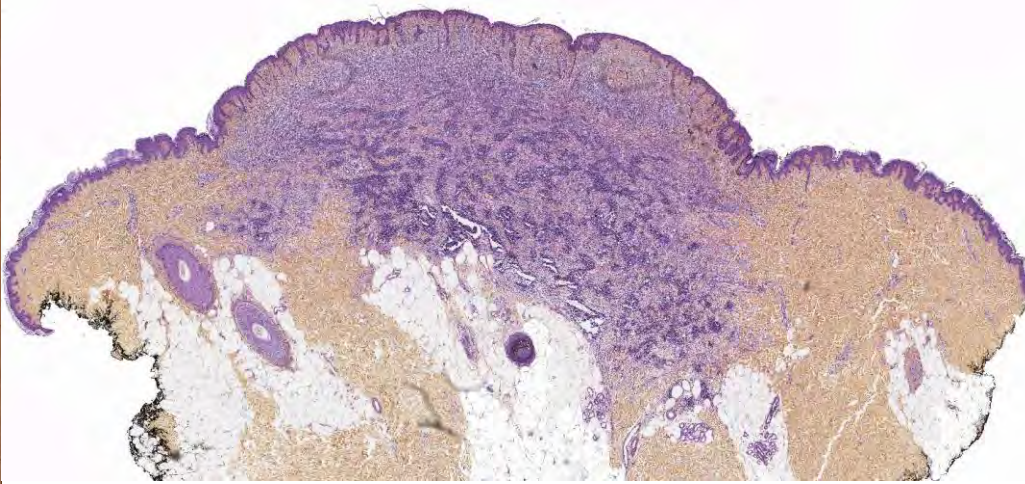
Cutaneous Melanocytic Tumors With Concomitant NRASQ61R and IDH1R132C Mutations: A Report of 6 Cases

Nicolas Macagno ^{1 2}, Daniel Pissaloux ^{3 4}, Heather Etchevers ², Véronique Haddad ³, Beatrice Vergier ⁵, Sandrine Sierra-Fortuny ⁶, Franck Tirode ^{3 4}, Arnaud de la Fouchardière ^{3 4}

Affiliations [+ expand](#)

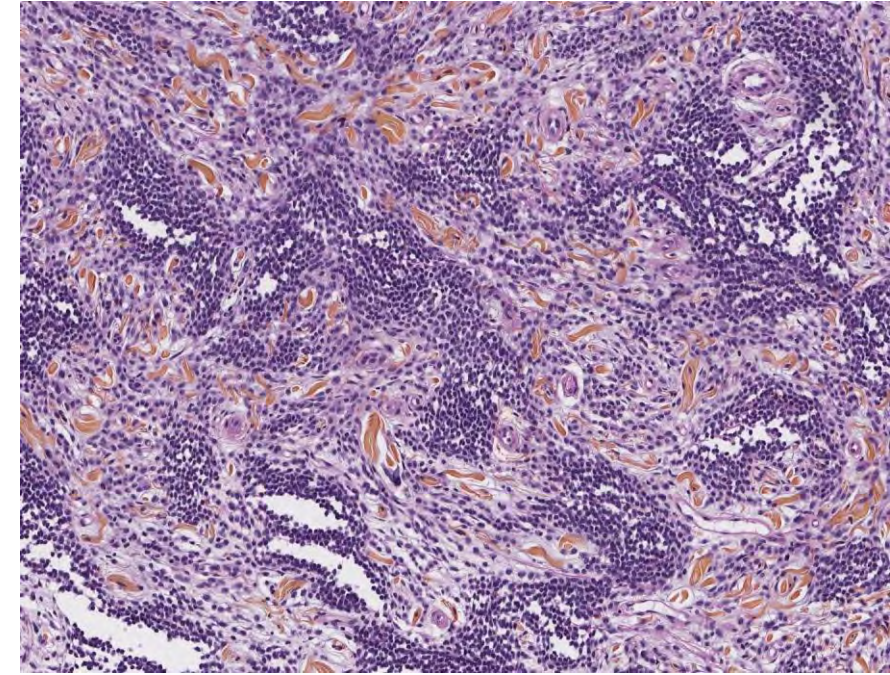
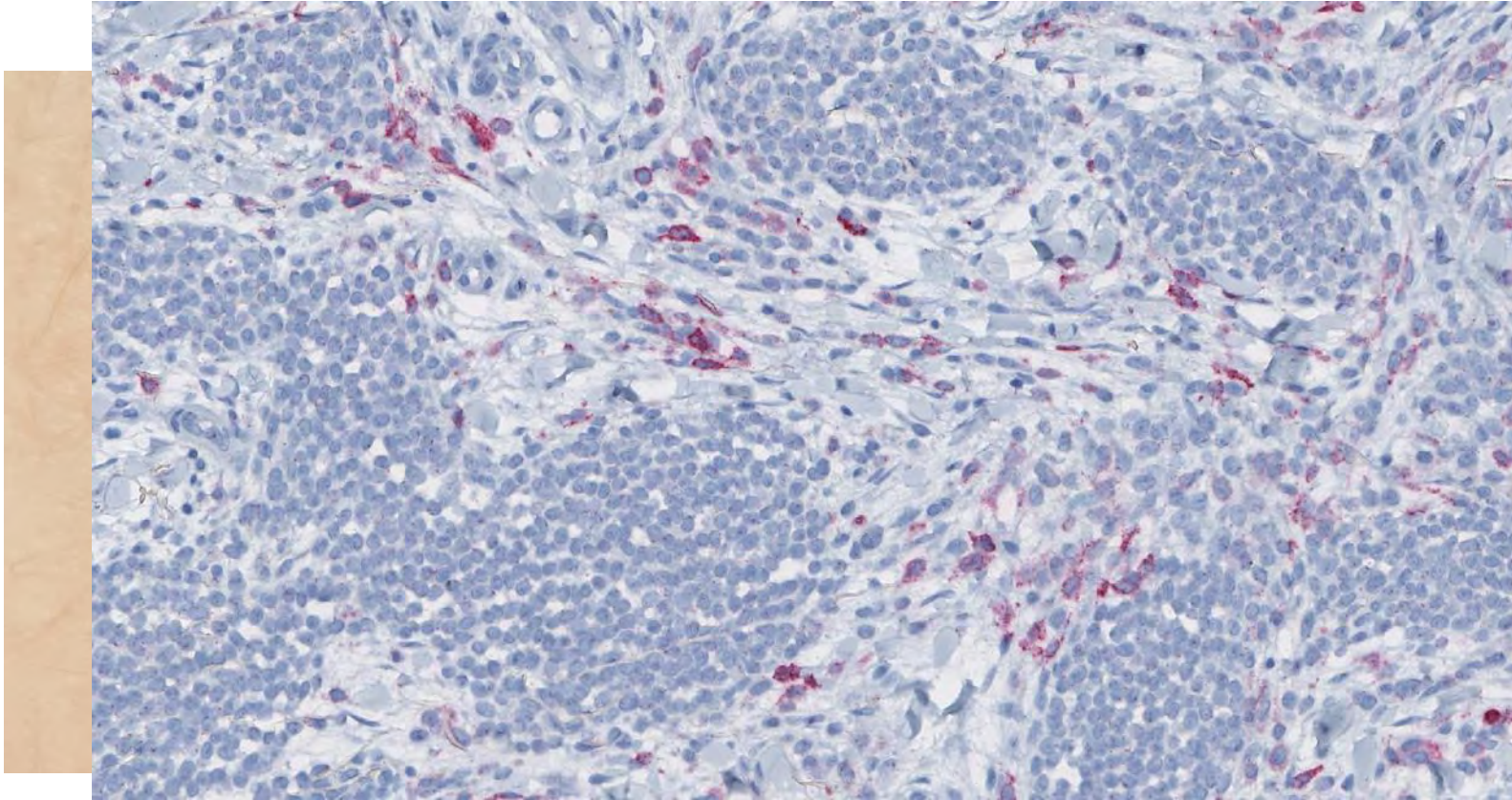
PMID: 32732488 DOI: [10.1097/PAS.0000000000001500](#)

IDH1 R132C mutations in *NRAS*-mutated nevi



Dermal biphasic pattern with islands of bland nevoid and scattered dendritic melanocytes (HMB45+)

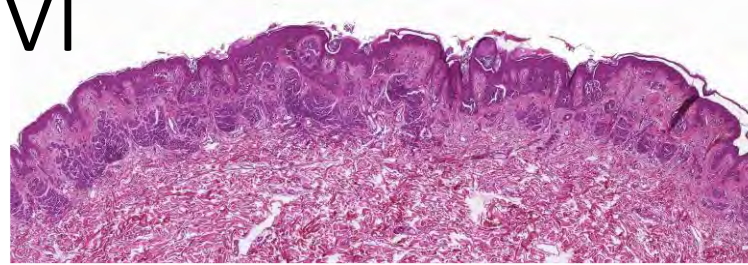
IDH1 R132C mutations in *NRAS*-mutated nevi



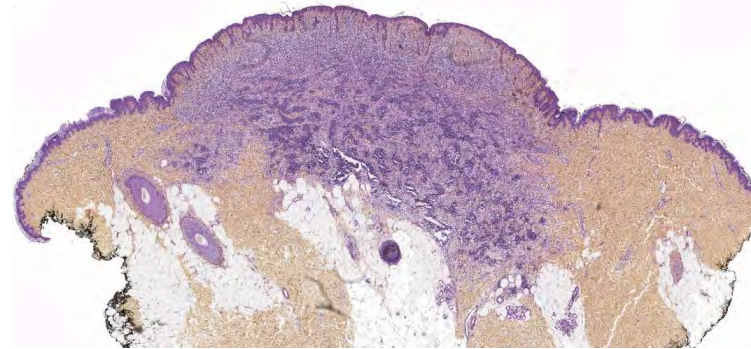
Dermal biphasic pattern with islands of bland nevoid and scattered dendritic melanocytes (HMB45+)

Progression scheme of *IDH1* R132C mutations in *NRAS*-mutated nevi

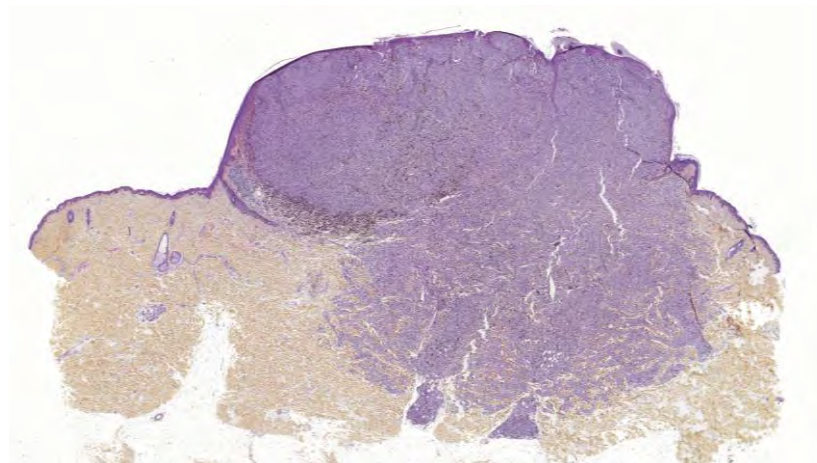
NRAS-mutated
common nevus



NRAS - *IDH1* co-mutated
melanocytic tumor



NRAS + *IDH1* mutated
Melanoma



TCGA melanoma (PMID: 26091043)

Take home messages

- Clonal nevus illustrates the correlation between genetics and morphology
- Entities are more and more defined by activated pathways rather than specific genetic anomalies
- Constant increase in new driver and passenger anomalies discovered
- Growing complexity in the combination of anomalies
- A dermal clone is always a step toward transformation

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Molecular pathology of melanocytic tumors

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