

MPath-Dx V2.0

Classification Schema

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CHAPPAPE

MPATH-Dx V2.0 for Optimal Patient Care

- Simplified and standardized diagnostic reporting
- Greater transparency among pathologists, health care providers and patients
- Estimations of risk of recurrence
- Treatment recommendations

MPATH Study Group

- Joann Elmore, Principal Investigator, NIH Grants 2010 – Present
- Expert Reference Panel of Pathologists/Co-Investigators:
 - Michael Piepkorn, Raymond Barnhill, David Elder

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The MPATH-Dx reporting schema for melanocytic proliferations and melanoma

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What Were Our Goals?

- Mapping Tool for standardized classification of a diverse spectrum of melanocytic lesions
- Five categories for mapping based on :
 - degree of atypia
 - perceived risk of progression
 - therapy

MPATH-Dx* Class	Perceived Risk for Progression	Suggested treatment consideration	Examples
0	Incomplete study due to sampling or technical limitations	Repeat biopsy or short-term follow up	N/A
I	Very low risk	No further treatment	-Common melanocytic nevus -Blue nevus -Mildly dysplastic nevus
II	Low risk	Narrow but complete excision (<5 mm)	-Moderately dysplastic nevus -Spitz nevus
III	Slightly higher risk, greater need for intervention.	Complete excision with at least 5 mm but <1 cm margins	-Severely dysplastic nevus -Melanoma in situ -Atypical Spitz tumor
IV	Substantial risk for local or regional progression	Wide local excision with ≥ 1 cm margins	Thin, invasive melanoma (e.g., T1a)
V	Greatest risk for regional and/or distant metastases	Wide local excision with ≥ 1 cm margins. Consideration of staging sentinel lymph node biopsy	Thicker invasive melanomas (e.g., T1b, T2 or greater)

Pathologists' diagnosis of invasive melanoma and melanocytic proliferations: observer accuracy and reproducibility study

Joann G Elmore,¹ Raymond L Barnhill,² David E Elder,³ Gary M Longton,⁴ Margaret S Pepe,⁴ Lisa M Reisch,¹ Patricia A Carney,⁵ Linda J Titus,⁶ Heidi D Nelson,^{7,8} Tracy Onega,^{9,10} Anna N A Tosteson,¹¹ Martin A Weinstock,^{12,13} Stevan R Knezevich,¹⁴ Michael W Piepkorn^{15,16}

ABSTRACT

OBJECTIVE

To quantify the accuracy and reproducibility of pathologists' diagnoses of melanocytic skin lesions.

DESIGN

Observer accuracy and reproducibility study.

SETTING

10 US states.

PARTICIPANTS

Skin biopsy cases (n=240), grouped into sets of 36 or 48. Pathologists from 10 US states were randomized to independently interpret the same set on two occasions

concordance rates were lower, but with similar trends. Accuracy using a consensus diagnosis of experienced pathologists as reference varied by class: I, 92% (95% confidence interval 90% to 94%); II, 25% (22% to 28%); III, 40% (37% to 44%); IV, 43% (39% to 46%); and V, 72% (69% to 75%). It is estimated that at a population level, 82.8% (81.0% to 84.5%) of melanocytic skin biopsy diagnoses would have their diagnosis verified if reviewed by a consensus reference panel of experienced pathologists, with 8.0% (6.2% to 9.9%) of cases overinterpreted by the initial pathologist and 9.2% (8.8% to 9.6%) underinterpreted.

Accuracy: Worse Agreement and Greatest Uncertainty: Intermediate Lesions

MPATH Class		% Inter-observer agreement†
Class I	Nevus, no or mild atypia	92 %
Class II	Nevus, moderate atypia	25 %
Class III	Nevus, severe atypia Melanoma in situ	40 %
Class IV	Melanoma invasive < 0.8 mm	43 %
Class V	Melanoma invasive > 0.8 mm	72 %
†Reference diagnosis was obtained from consensus of three expert dermatopathologists.		

Reproducibility of 118 Pathologists

Intra-observer Agreement

MPATH Class		% Intra-observer agreement after 8 months interval
Class I	Nevus, no or mild atypia	77 %
Class II	Nevus, moderate atypia	35 %
Class III	Nevus, severe atypia Melanoma in situ	60 %
Class IV	Melanoma invasive < 0.8 mm	63 %
Class V	Melanoma invasive > 0.8 mm	83 %

MPath Classification and Mapping Tool: Critical Findings from Our Studies

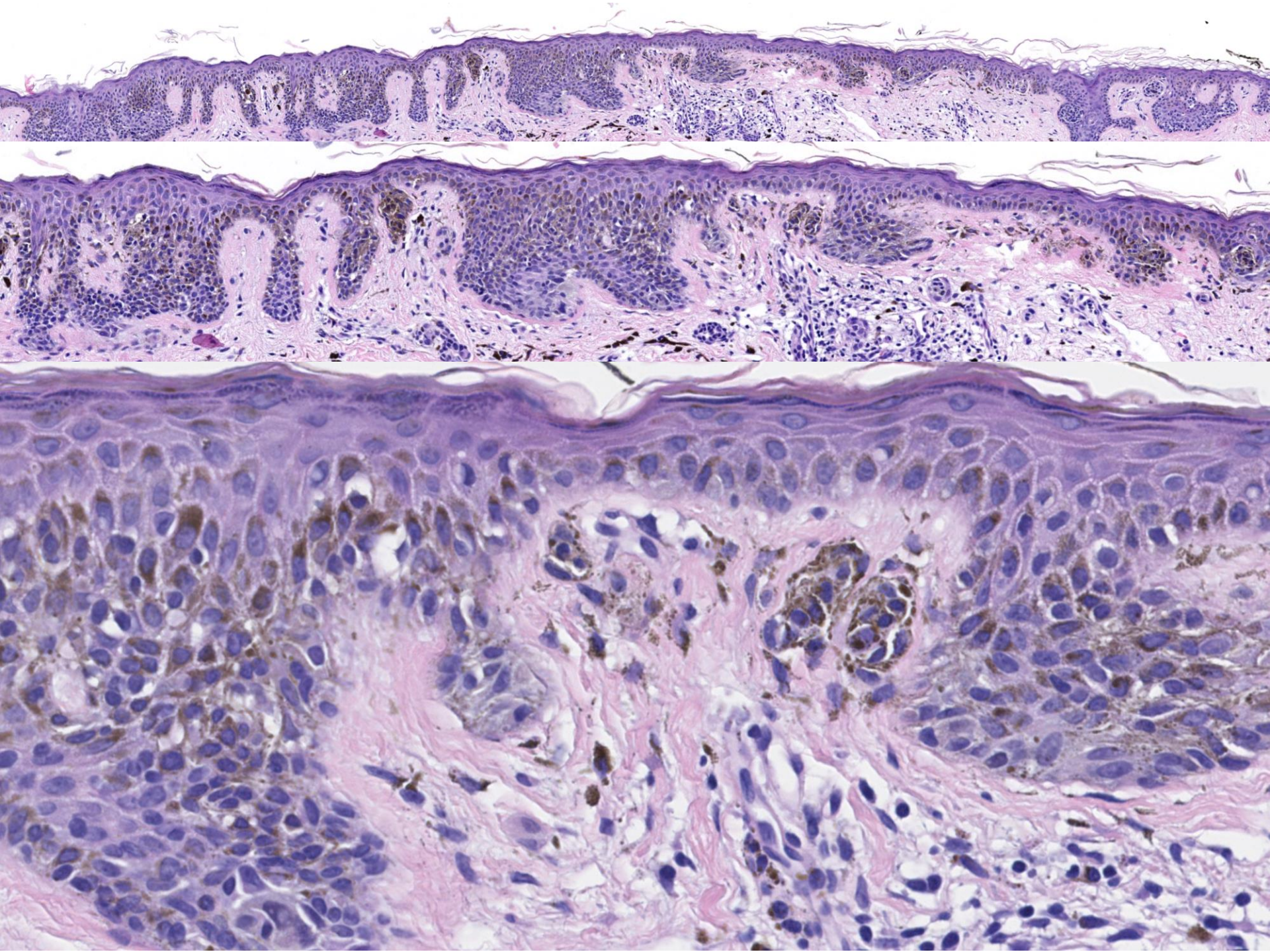
- Poor agreement for intermediate lesions
including melanoma in situ and T1a melanoma
 - Classes II, III, and IV
- The lowest inter- and intra-observer agreement
 - Class II lesions – « Moderate »
atypia/dysplasia

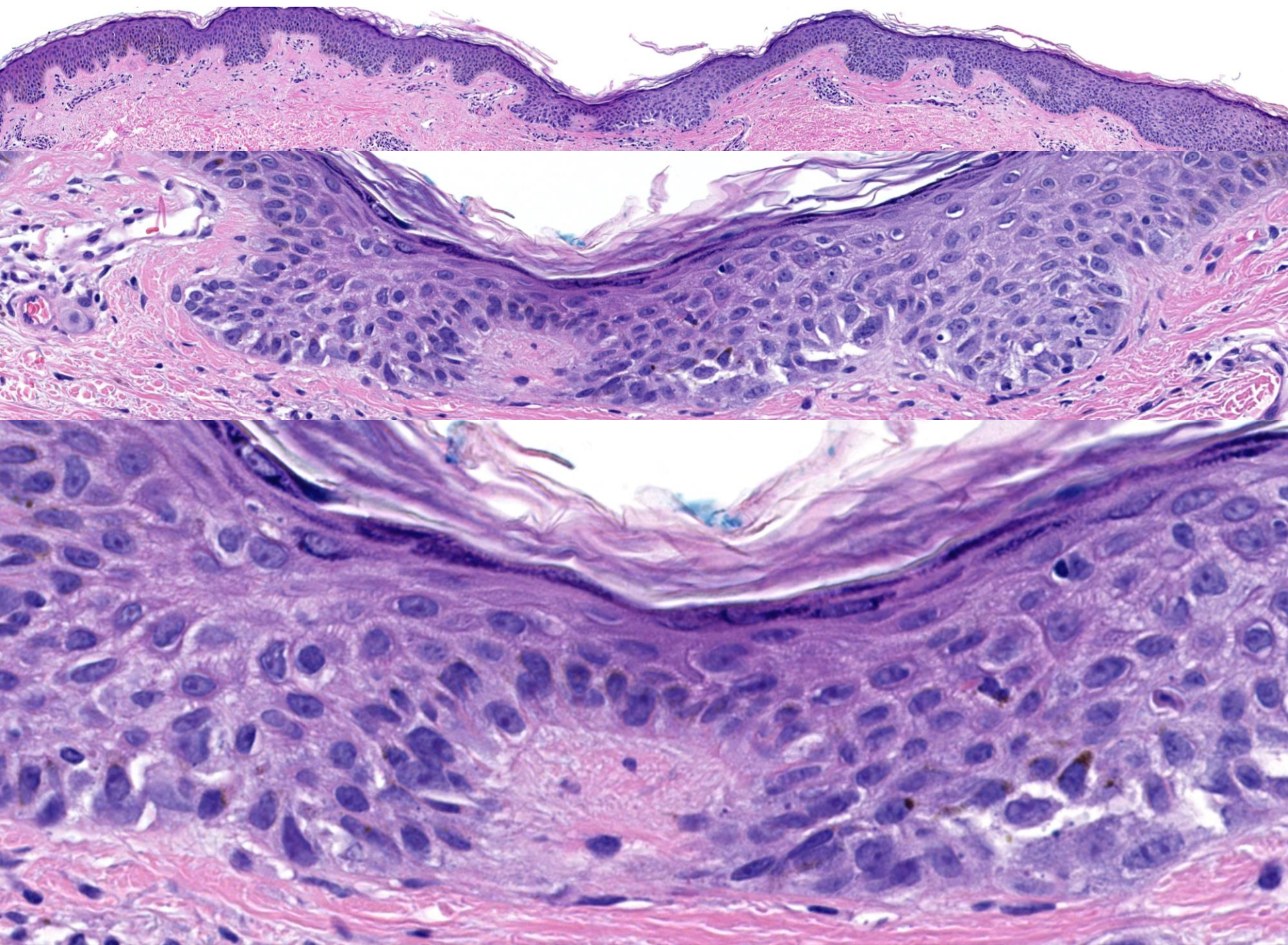
Examples:

Expert Panel Consensus

MPATH-Dx Class II:

Moderate atypia





How to Improve Diagnostic Agreement and Reproducibility

- Sort out intermediate lesions
- Develop better tools, e.g., molecular, AI
- Acknowledge uncertainty
- Implement MPATH-Dx Version 2.0

MPath-Dx Schema V2.0: Rationale for Downgrading Old Class II Moderate

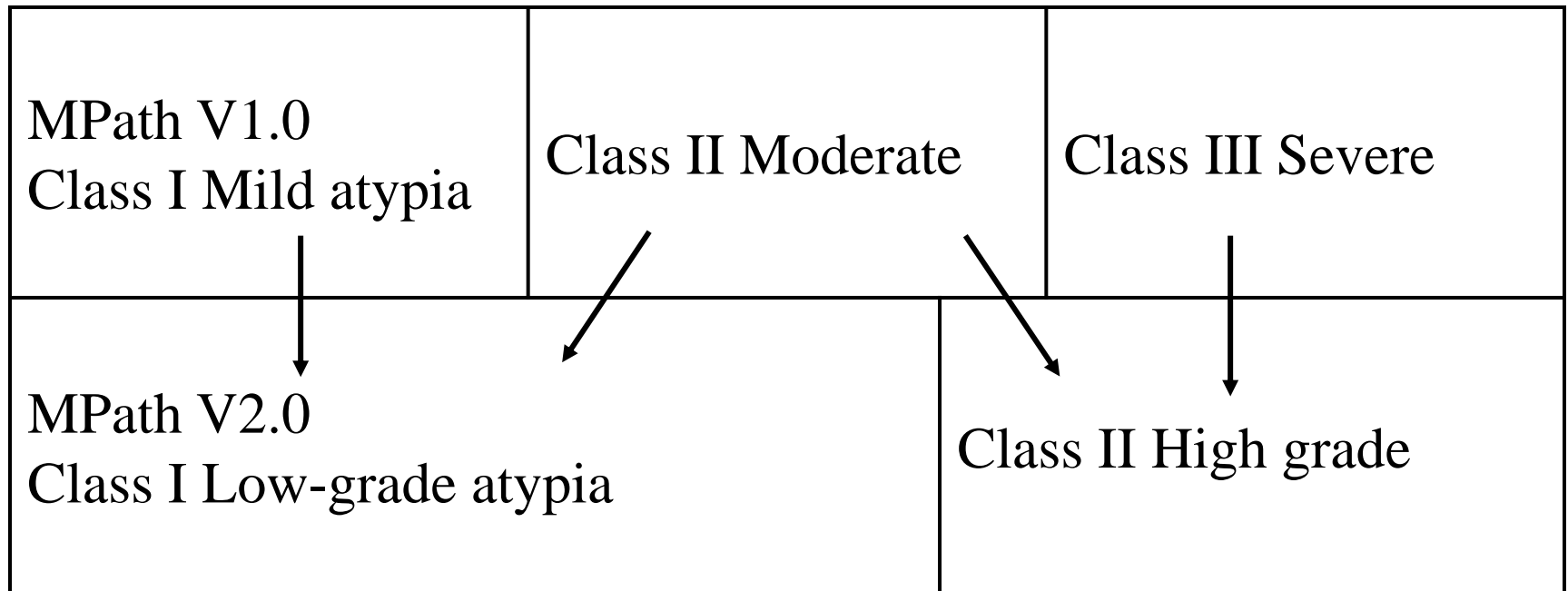
- « Moderate atypia/dysplasia » is increasingly viewed as having very low risk for recurrence as melanoma
- Nevi with « moderate atypia » and positive margins do not systematically need re-excision.
- Greater efforts should be made to diminish excision/reexcision of many such atypical nevi.

MPath-Dx Schema V2.0: Rationale for Downgrading Old Class II Moderate

- A two-class system of Low Grade and High Grade in place of three classes should:
 - simplify classification
 - improve diagnostic concordance
 - correspond to systems in other organs

MPath-Dx V1.0 to V2.0

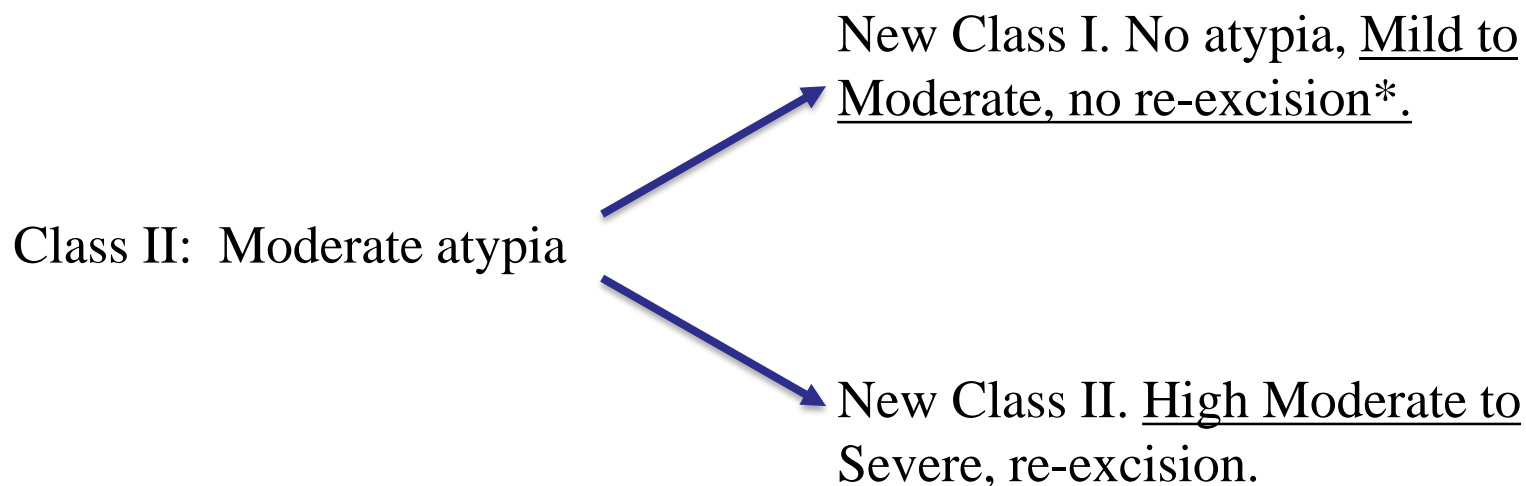
Restructuring of Old Class II. Moderate



MPath-Dx Schema V2.0 :

Reassignment of Old Class II.

- Reassignment of Old Class II. « Moderate » atypia,
- Re-classify as Mild to Moderate or Severe (including high moderate) as a four-tiered rather a five-tiered system



MPATH-Dx Schema V2.0

Cytomorphologic Criteria*

for Distinguishing

Classes I and II

*Acknowledgements: Martin Weinstock, Arthur Rhodes, Martin Mihm, Raymond Barnhill

Size of Melanocytic Nuclei* – 1.5 x

Table 2. Cytological, Architectural, and Genetic Criteria for Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis Version 2.0 Classes I and II

Feature	Class I: low-grade atypia ^a	Class II: high-grade atypia ^b
Cytological feature		
Size of nucleus in ≥ 5 junctional melanocytes in most atypical high power field	<1.5 Times the size of resting basal keratinocyte nuclei	Ranging from ≥ 1.5 times to >2 times the size of resting basal keratinocyte nuclei
Variability in shape and size of nucleus	Minimal to moderate	Marked (some nuclei ≥ 2 times larger than others)
Chromatin	Homogenous or condensed	Ranging from condensed or dispersed up to dense hyperchromatism or dispersed with thickened nuclear membranes
Nucleolus	Not visible, or visible but not prominent	Ranging from visible but not prominent up to prominent, often lavender, unless obscured by hyperchromatism
Cytoplasm	Not visible, scant, or abundant	Scant or abundant

*Grading of cytological atypia in Version 2. based on criteria outlined in Arch Dermatol. 1997

Architectural feature	Class I: Low grade	Class II: High grade
Diameter (mm)	Ranging from <4 mm to >4 mm	>5 mm
Symmetry (vertically-bisected mirror image)	Symmetrical	Often asymmetrical
Circumscription	Sharply circumscribed	Often poorly circumscribed
Junctional nesting	Ranging from regular junctional nests to progressively irregular junctional nesting, horizontal confluence of nests, bridging of nests	Irregular junctional nests, horizontal confluence of nests, bridging of nests
Lentiginous melanocytic proliferation	Absent, slight, or focal	Contiguous melanocytes, proliferation of melanocytes between epidermal retia
Effacement of epidermis	Absent	Often present
Density of intraepidermal melanocytes	Usually lower density	Usually higher density
Pagetoid spread	Absent, low level, or focal	Focally full thickness or full thickness epidermal involvement (at least 1 HPF indicates melanoma in situ)
Lymphocytic infiltrates	Absent or present	Often dense infiltrate
Papillary dermal (concentric or lamellar) fibroplasia	Absent or present	Often lamellar fibroplasia
Mitoses, intraepidermal	Absent or few	Often present
Mitoses, dermal	Usually absent	Absent or few
Dermal atypia	Usually absent	Absent or present
Dermal confluence	Usually absent	Absent or present
Dermal maturation	Usually present	Present, diminished, or absent
Genetic feature		
DNA aneuploidy	Usually diploid	Often DNA aneuploidy
Genetic alterations	Single alteration (eg, <i>BRAF</i> , <i>NRAS</i>)	Usually 2 alterations

MPATH-Dx V2.0:

The Melanocytic Pathology Assessment Tool
and Hierarchy for Diagnosis



Consensus Statement | Pathology and Laboratory Medicine

Revision of the Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis Classification Schema for Melanocytic Lesions

A Consensus Statement

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JAMA Netw Open. 2023 Jan 3;6(1):e2250613.

MPATH-Dx V2.0 Class	Risk of tumor progression (probability of progression, No. per population)	Treatment recommendation	Examples ^a
Class I Low Grade	Very low risk for continued proliferation and progression to invasive melanoma, (1 in 10 ⁴ to 1 in 10 ⁵)	No further treatment ^b	Common acquired nevi, no atypia
			Congenital nevi, no atypia
			Atypical and dysplastic nevi, low-grade atypia ^c
			Common blue nevus
Class II High Grade	Low risk for progression to invasive melanoma, (1 in 10 ² to 1 in 10 ³)	Re-excision with margins < 1 cm ^b	Atypical and dysplastic nevi, high-grade atypia ^c
			Spitz nevus, tumor/melanocytoma and atypical variants
			Cellular blue nevus/melanocytoma and atypical variants
			Plexiform or deep penetrating nevus/melanocytoma
			Lentigo maligna
			Melanoma in situ
Class III Melanoma pT1a	Relatively low risk for local and regional metastasis, (1 in 10 to 1 in 10 ²)	Follow National Guidelines, e.g., excision with 1 cm margins ^b	Melanoma AJCC ^d stage pT1a < 0.8 mm Breslow thickness: <ul style="list-style-type: none"> • Melanoma pT1a _{lr} (low risk)^e • - Melanoma pT1a^f
Class IV Melanoma ≥ pT1b	Moderate to increased risk for regional and/or distant metastasis, (1 in 2 to 1 in 10)	Follow National Guidelines, e.g. excision with 1 to 2 cm margins ^b , consider sentinel lymph node staging and therapies	Melanoma AJCC ^d stage pT1b or greater ≥ 0.8 mm Breslow thickness

MPATH-Dx V2.0 Schema

Treatment Considerations

MPATH-Dx V2.0 Class	Diagnosis	Treatment Considerations* (margins positive)
Class I. Low grade	Common nevi, no atypia to low grade	No further treatment.
Class II. High grade	Nevi, high grade atypia, melanoma in situ, intermediate lesions, melanocytomas	Re-excision, margins up to 1 cm.
Class III. Melanoma	Melanoma pT1a, pT1a-lr (< 0.8 mm)	Re-excision 1 cm margins, National guidelines
Class IV. Melanoma	Melanoma pT1b and above (\geq 0.8 mm)	Re-excision 1 to 2 cm margins. National guidelines, additional measures.

*There are exceptions and flexibility in all treatment considerations.

MPATH-Dx V2.0 Therapeutic Guidelines (*eTable 1*)

- One may consider not to re-excise lesions on a case-by-case basis based on the following:
- Patient age (e.g. age < 10 to 20 years)
- Anatomic site
- Adequate sampling
- Absence of particular concerning clinical and histopathological features
- Other pertinent clinical considerations

MPATH-Dx V2.0

Diagnostic Mapping Tool

eTable. MPATH-Dx V2.0 Diagnostic Mapping Tool

The surgical margins are considered positive and the lesion adequately sampled for the purposes of these recommendations.

MPATH-Dx V2.0 Class ^a	Management	Diagnosis Terms
Lesions have very low risk for tumor progression	No further treatment. (Note: There are exceptions to all clinical management guidelines, and clinical judgement and common sense are fundamental to clinical management. In the decision process about re-excision or not, it is necessary to consider whether a specimen with positive margins is representative of the entire clinical lesion or not, and whether sampling error may	<u>Common Low UV Radiation (Cumulative Sun Damage (CSD)) WHO Pathway I</u> <u>Lentigo and related entities</u> Ephelis, freckle Lentigo simplex <u>Common acquired nevus without atypia</u> Common nevus: junctional, compound, intradermal, congenital pattern Lentiginous nevus: junctional, compound Nevus with architectural disorder ^b : junctional, compound Halo nevus Nevus spilus, speckled lentiginous nevus

MPATH-Dx V2.0

Diagnostic Mapping Tool

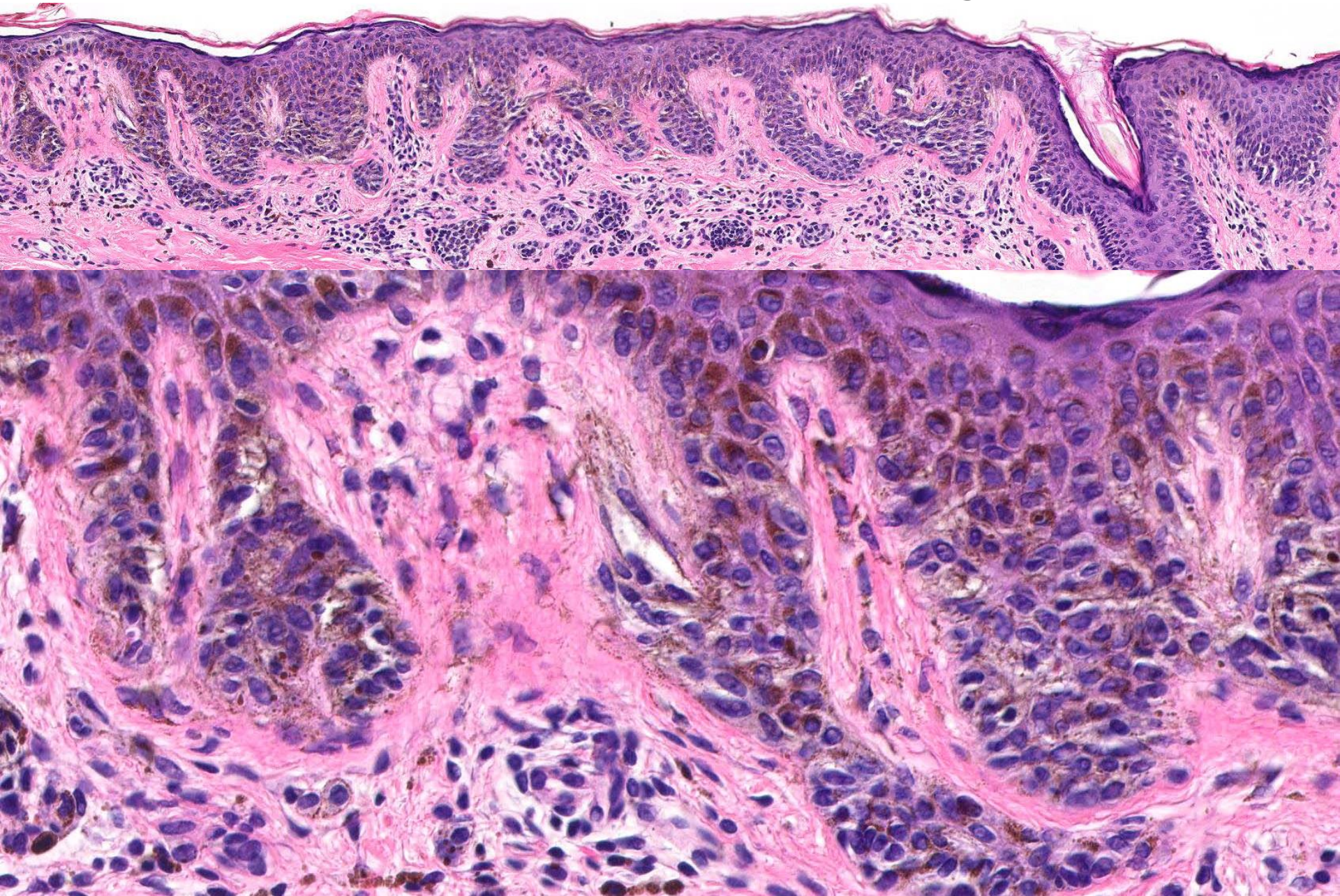
- Virtually any melanocytic lesion may be mapped into the four MPATH Classes.
- Pathologists may continue to use their own terminologies with MPATH mapping and treatment recommendations.
- Lesions in the WHO Classification pathways to melanoma are included in this mapping.

WHO Pathways to Melanoma

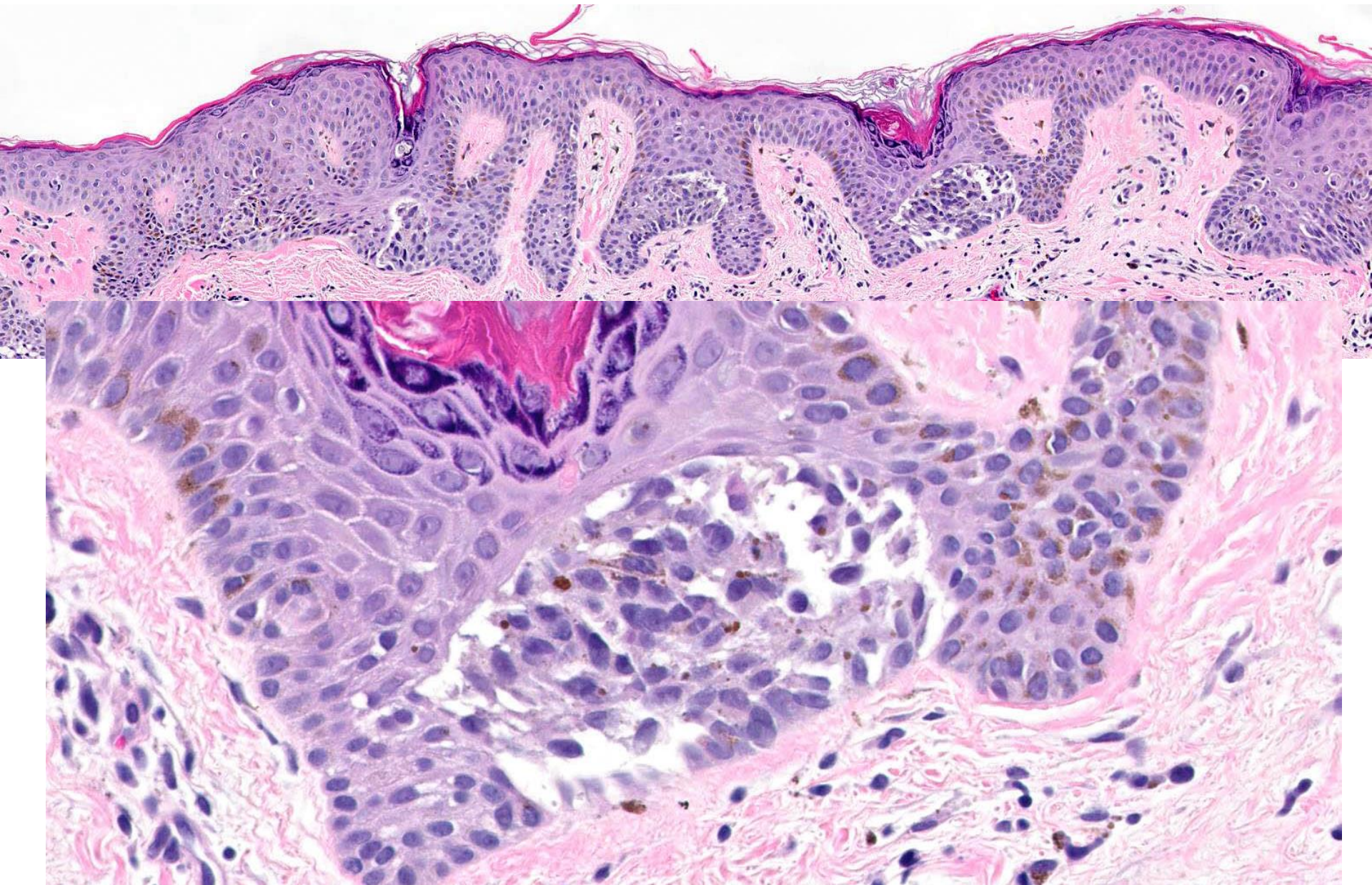
- ~85%:
 - Common acquired nevi→ atypical/dysplastic nevi→ melanoma (low CSD; intermittently sun-exposed skin)
- ~15%:
 - Lentigo maligna→ LM melanoma (high CSD)
 - Acral lentiginous lesion→ acral melanoma
 - Mucosal lentiginous lesion→ mucosal melanoma
 - Congenital nevi→ melanoma
 - Spitz nevus→ atypical Spitz→ melanoma
 - Blue nevus→ atypical blue nevus→ melanoma

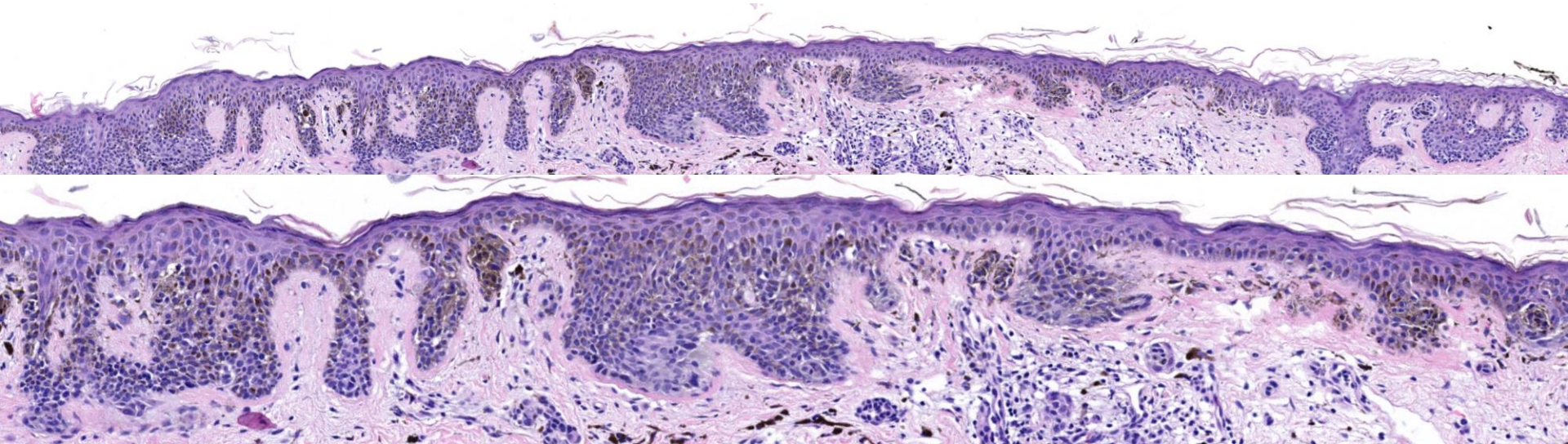
**MPATH-Dx V2.0:
Class I. Low Grade**


MPATH Class I. Low grade

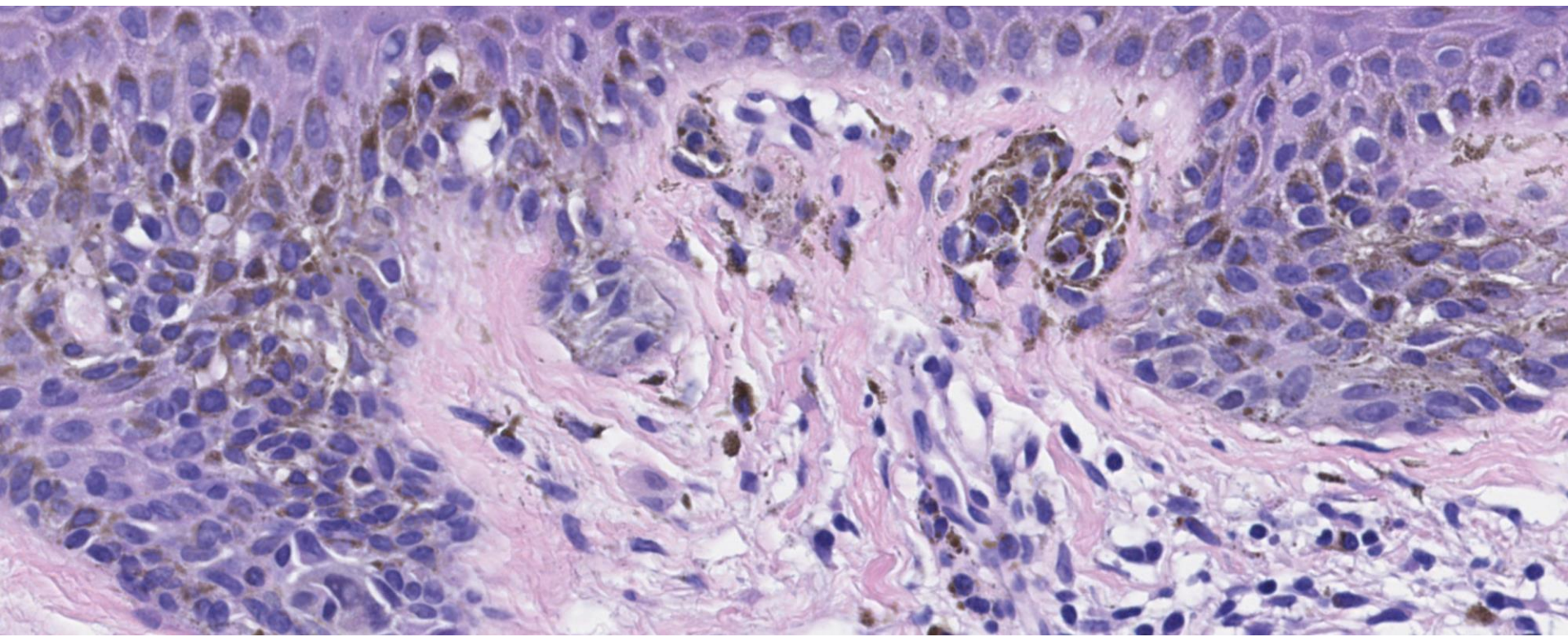


MPATH Class I. Low grade



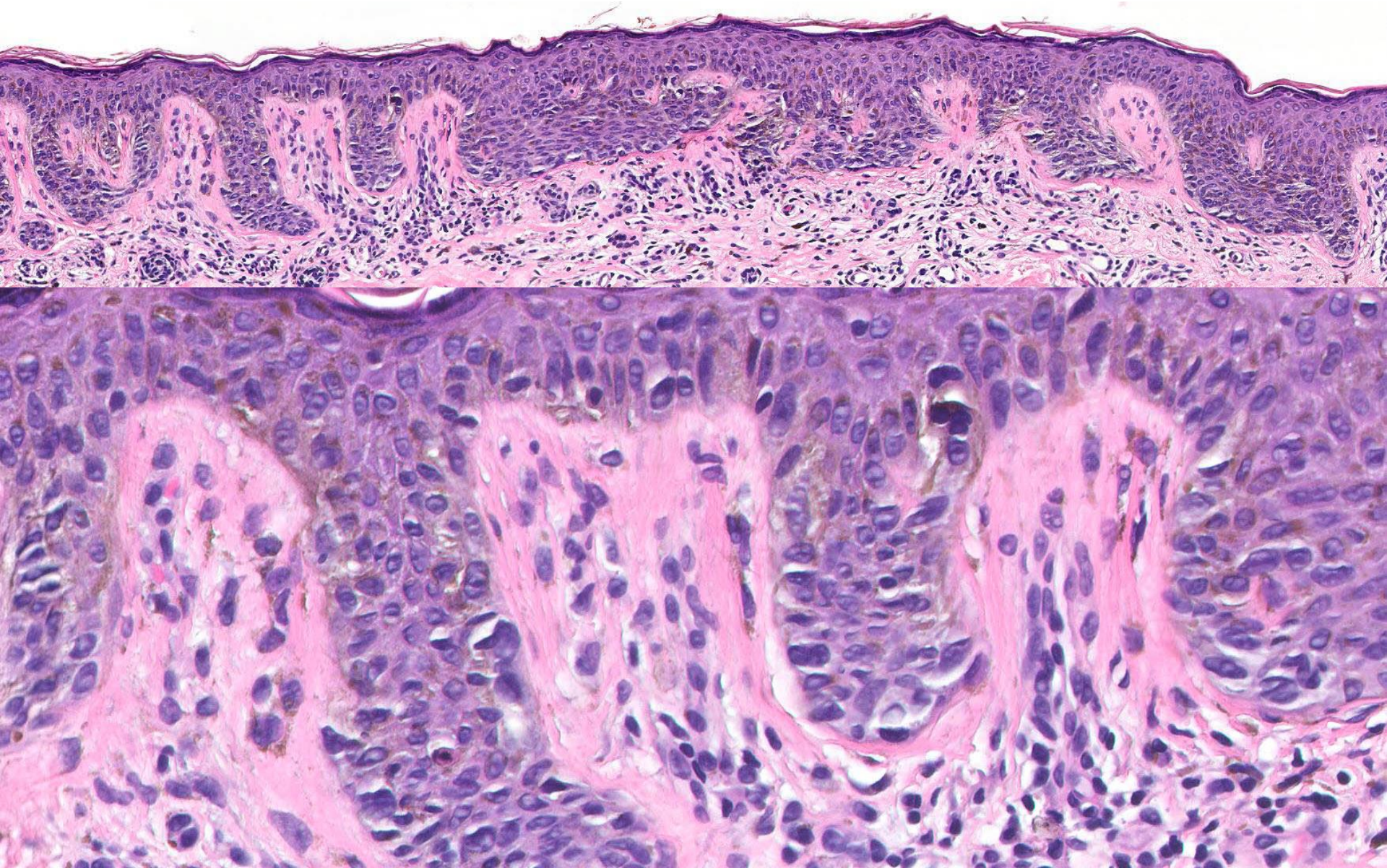


MPATH V1.0 Class II  V2.0 Class I. Low grade

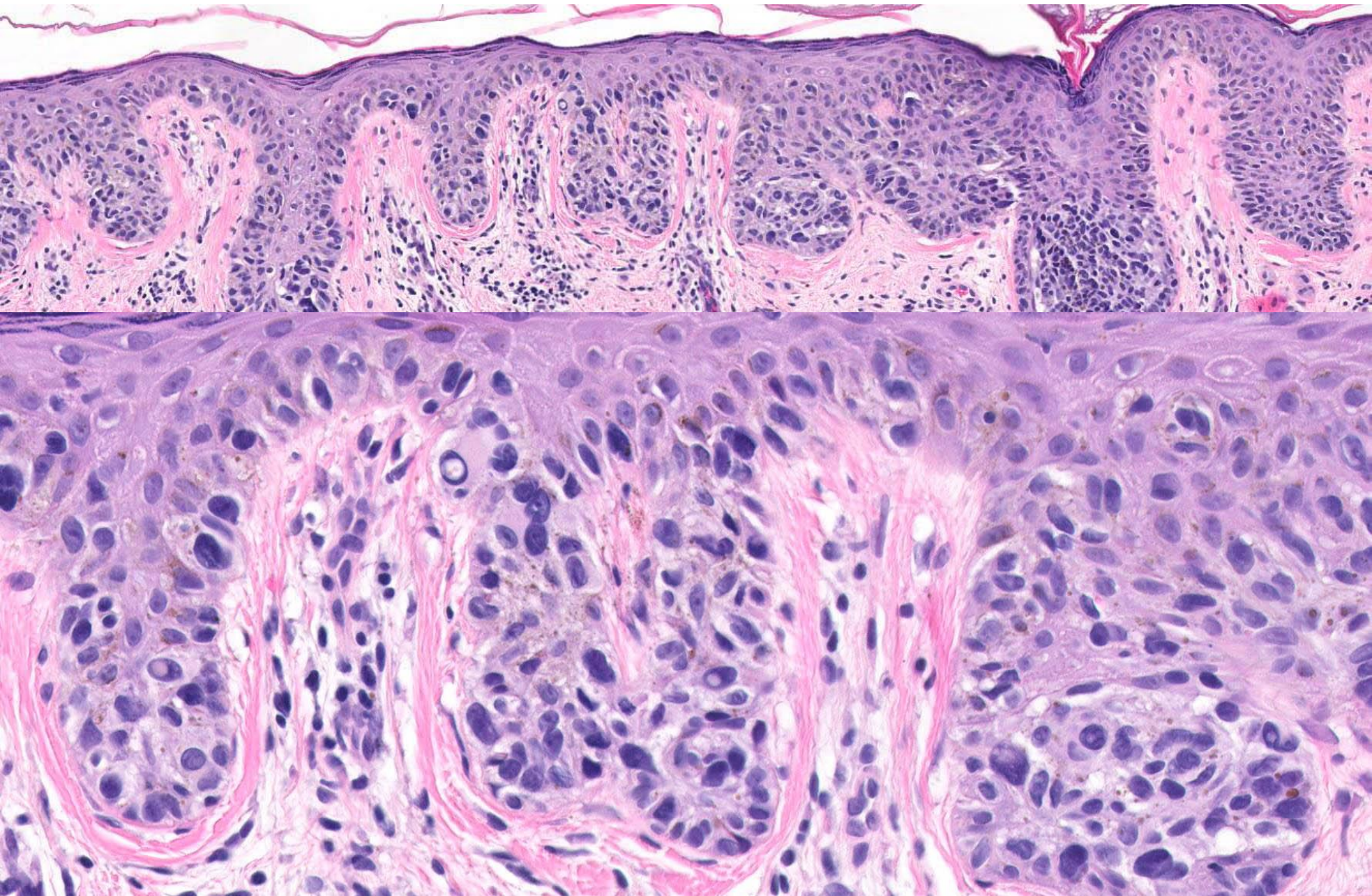


**MPATH-Dx V2.0:
Class II. High Grade**

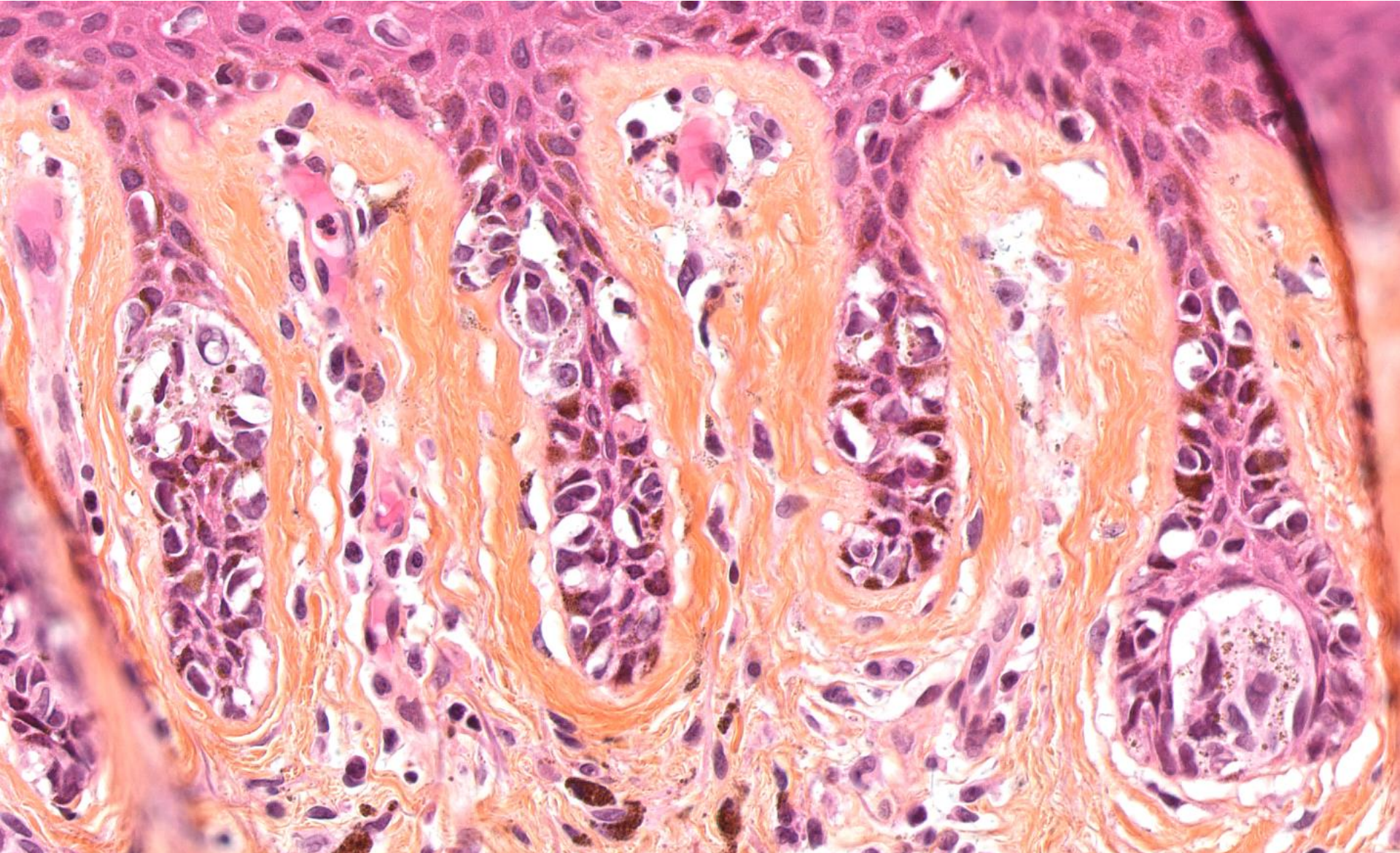
MPATH Class II. High grade

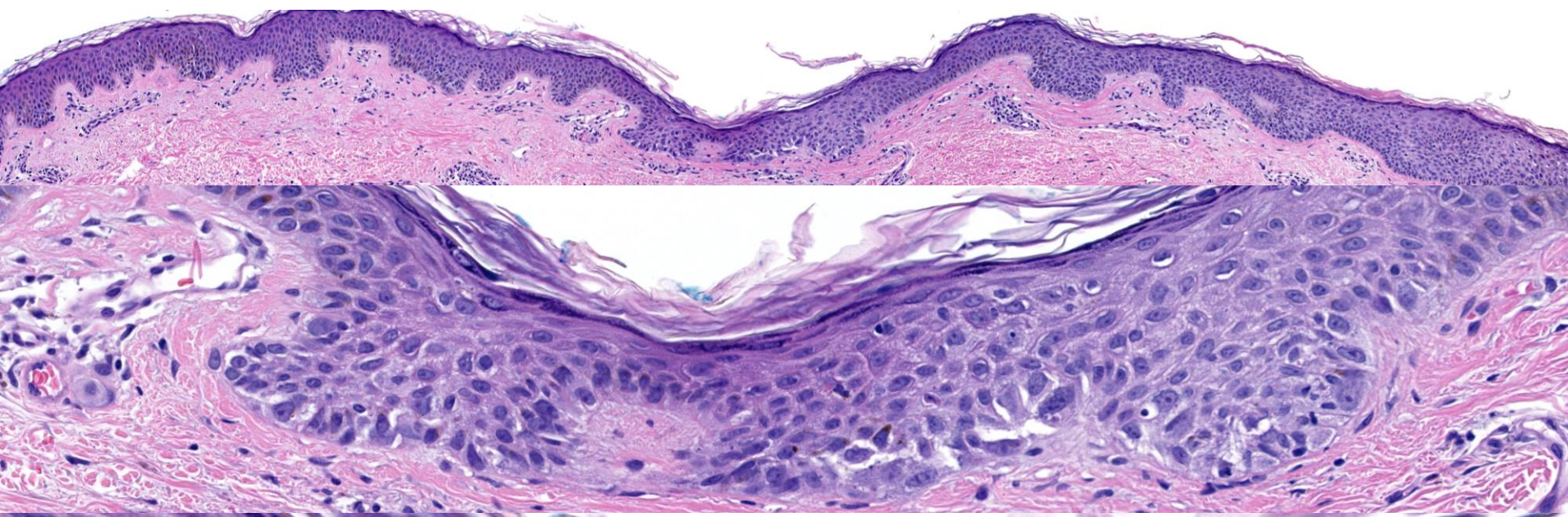


MPATH Class II. High grade

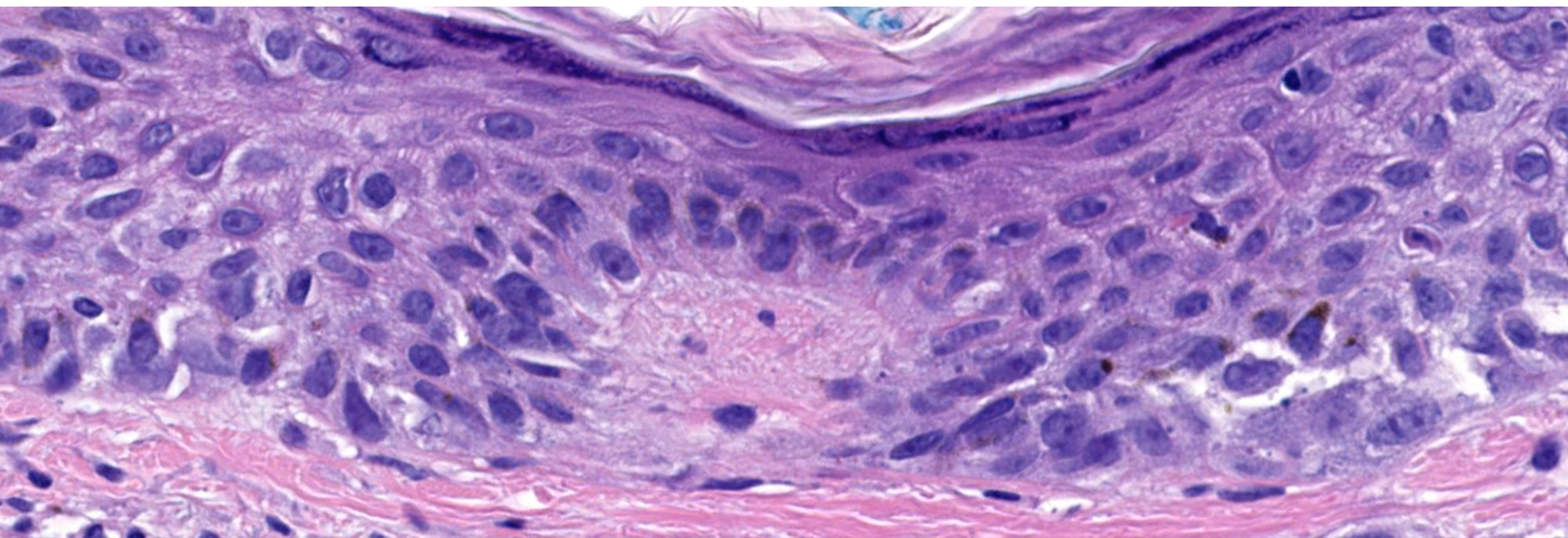


MPATH Class II. High grade





MPATH V1.0 Class II → V2.0 Class II High grade



Class II: Intermediate Lesions

Class II High Grade	Low risk for progression to invasive melanoma, (1 in 10 ² to 1 in 10 ³)	Re-excision with margins < 1 cm ^b	Atypical and dysplastic nevi, high-grade <u>atypia</u> ^c
			Spitz nevus, tumor/melanocytoma and atypical variants
			Cellular blue nevus/melanocytoma and atypical variants
			Plexiform or deep penetrating nevus/melanocytoma
			Lentigo maligna
			Melanoma in situ

What is a Melanocytoma?

- Ocular melanocytoma – probably heavily pigmented nevus
- CNS melanocytoma – “benign to intermediate” lesions
- Benign dermal melanocytoma (blue nevus. Lund and Kraus, 1962)
- Pigmented epithelioid melanocytoma in the skin (Zembowicz and Mihm)

Melanocytoma: An Intermediate Lesion, WHO Skin4/5 [2024]

- Morphological definition: *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
- Genetic definition at least two genetic alterations (mutations)

Melanocytoma: Intermediate Lesions

Often biphasic (combined)

- ❖ Conventional nevus with second genetic « hit » and second component:
 - Deep-penetrating/plexiform nevus/melanocytoma
 - BAP1-inactivated tumor/melanocytoma
 - Pigmented Epithelioid Melanocytoma
 - Cellular blue nevus/atypical CBN

Melanocytoma: An Intermediate Lesion

- Often raise concern for melanoma but can usually be distinguished from melanoma by light microscopy (and with IHC)
- Melanocytomas may elicit varying degrees of uncertainty (from little to great)
- Relatively rare melanocytomas prove difficult to distinguish from melanoma and require comprehensive evaluation

Melanocytoma: An Intermediate Lesion

- True biological melanoma in this context is quite rare
- High-risk morphological criteria correlating with metastases and death should be applied for diagnostic purposes

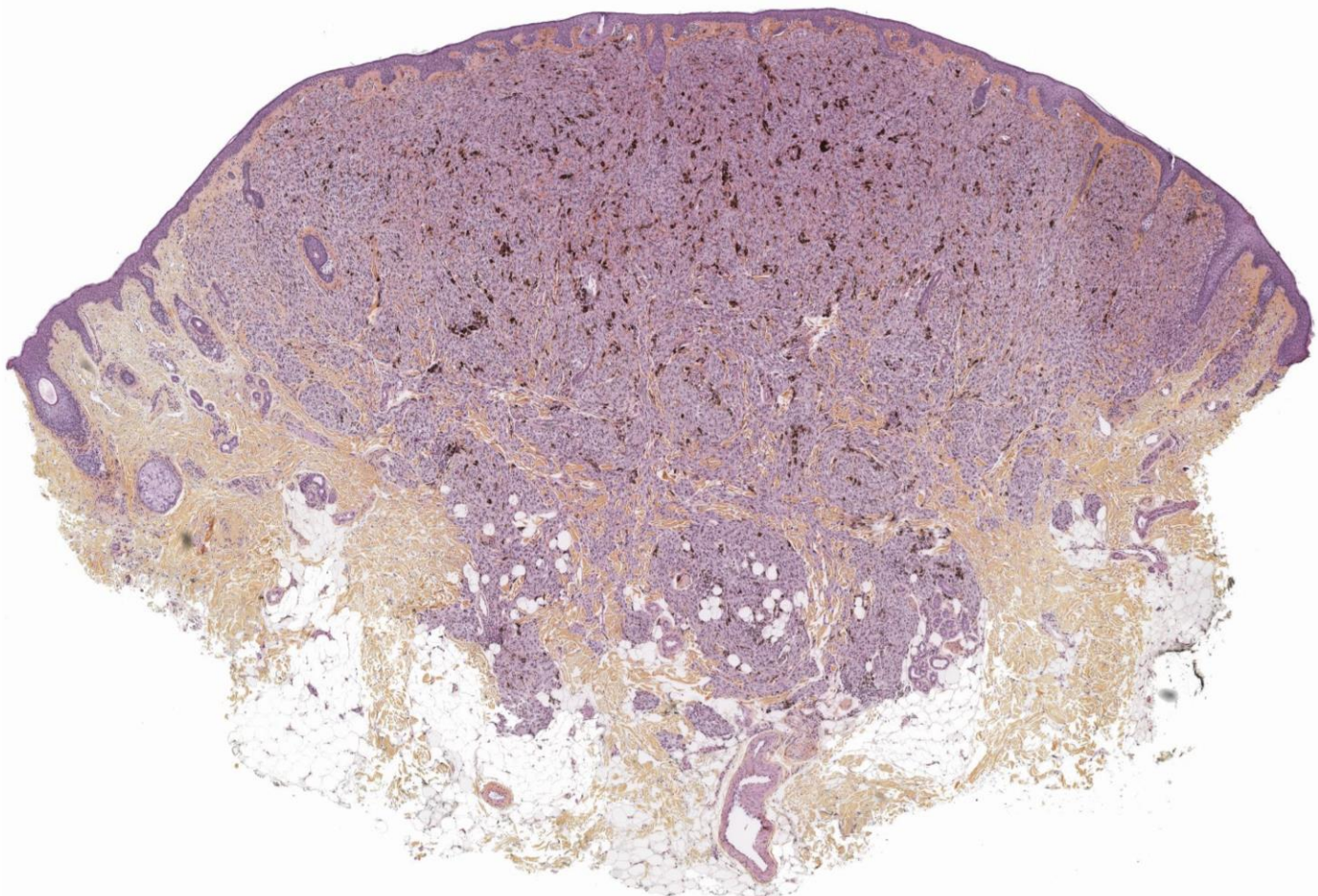
Table 3. Guidelines for the Classification of Various Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis Version 2.0 Class II and III or IV Lesions With Emphasis on the Dermal Component

Feature	Class II	Class III or IV
WHO Pathway		
I: low-CSD	<ul style="list-style-type: none"> Atypical dermal melanocytic proliferation in common acquired nevus Dysplastic nevi Plexiform or deep-penetrating nevus or melanocytoma^a <i>BAP1</i> inactivated nevus or melanocytoma^a Pigmented epithelioid melanocytoma 	Melanoma
II-III: high-CSD	Atypical dermal melanocytic proliferation, NOS	<ul style="list-style-type: none"> Melanoma Desmoplastic melanoma
IV: Spitz	Spitz melanocytoma (atypical Spitz tumor)	Spitz melanoma
V-VI: acral and mucosal	Atypical dermal or submucosal melanocytic proliferation, NOS	Melanoma
VII: congenital	Atypical proliferative nodule or melanocytoma in congenital nevus	Melanoma
VIII: blue nevus	<ul style="list-style-type: none"> Cellular blue nevus or melanocytoma Atypical cellular blue nevus or melanocytoma Atypical blue nevus, NOS 	Melanoma arising in blue nevus
Cytology	Variable, increasing nuclear size >1.5 times that of resting basal keratinocyte nuclei, nuclear pleomorphism, chromatin condensed or dispersed, prominence of nucleoli	Nuclear size often ≥2 times that of keratinocyte nuclei and other melanocytes, increased nuclear to cytoplasmic ratios, thickened nuclear membranes, hyperchromatism, coarse chromatin or dispersed, strikingly prominent nucleoli, multiple nucleoli
Diameter (mm)	Variable, 4-10 mm, or greater	Variable, often >1 cm
Architecture	<ul style="list-style-type: none"> Ulceration, usually absent Increasing depth, may involve subcutaneous fat (level V) Symmetrical or asymmetrical May be biphasic (ie, combined, 2 components) Nodule formation, absent or present Maturation with depth, present or absent Infiltrative at peripheries, absent or present Cellularity, normal or increased Usually no necrosis 	<ul style="list-style-type: none"> Ulceration, absent or present Involvement of subcutaneous fat, absent or present Often asymmetrical Melanoma in 1 component Nodule often present Maturation often absent Infiltrative, often present Prominent cellularity, sheet-like appearance Necrosis, absent or present
Mitotic rate	Variable, mitotic rates: 0-2 per mm ² , uncommonly 2 to 5 per mm ²	Often 2-6 per mm ² or greater, deeply located mitoses, atypical mitoses
Immunohistochemistry	Often PRAME negative, p16 positive, Ki67 < 5% to 10%	Often PRAME positive, p16 negative, Ki67 > 10% to 20%
Alterations or gene fusions	Usually 2: <i>BRAF</i> , <i>NRAS</i> , <i>GNAQ</i> , <i>GNA11</i> , <i>MAPK</i> , plus β-catenin, <i>APC</i> , <i>BAP1</i> , or <i>PRKAR1A</i> ; various gene fusions of <i>ALK</i> , <i>NTRK</i> , <i>ROS1</i> , <i>PRKCA</i>	Often <i>CDKN2A</i> -/-, <i>TP53</i> , <i>TERT</i> promoter, or <i>BAP1</i> (blue nevoid tumors)
Copy number variations	Usually 2	>3

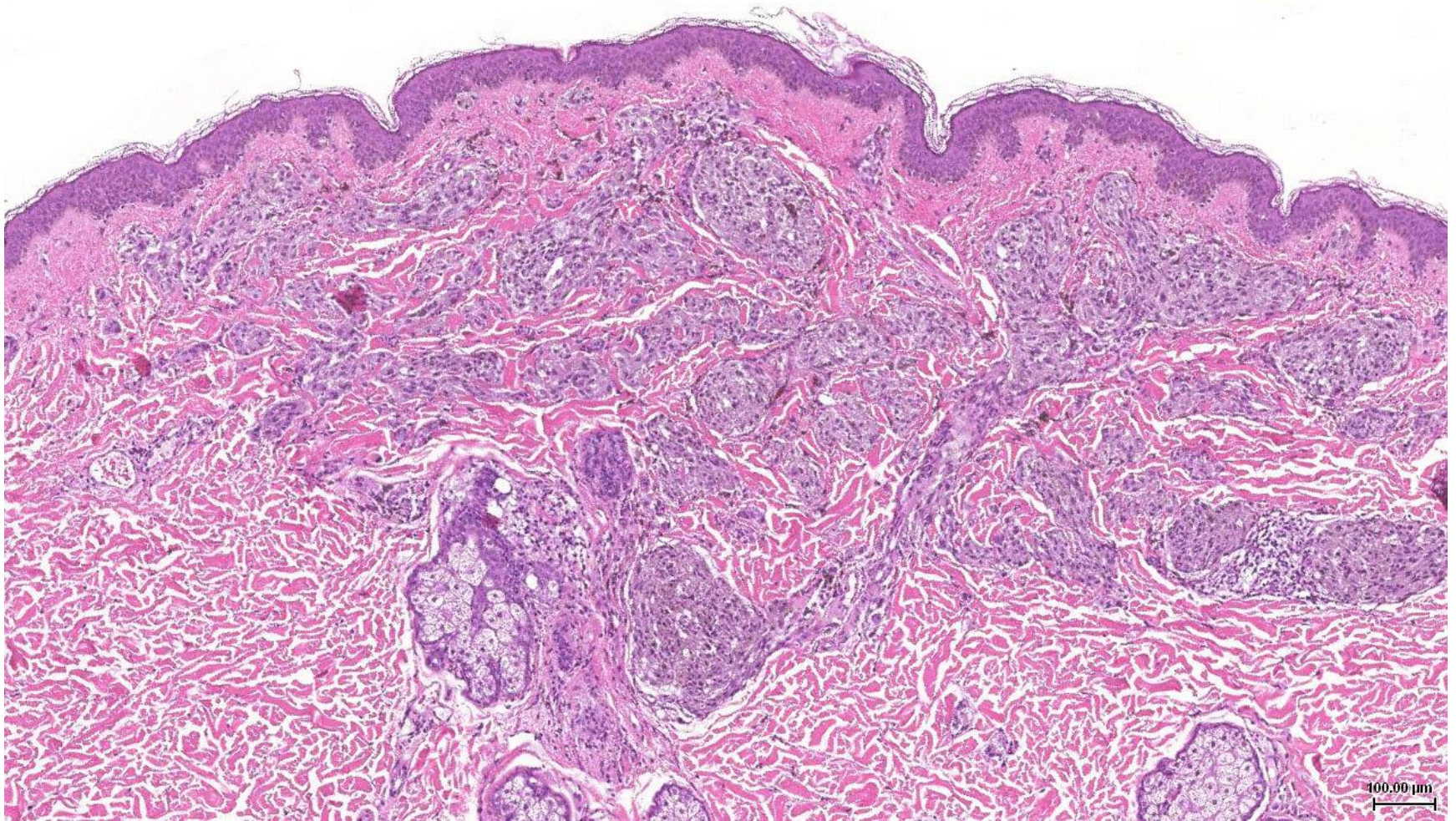
Criteria for Assessing Risk of Possible Melanoma

- Age > 10 years
- Diameter ≥ 1 cm
- Ulceration
- Extension into subcutaneous fat (thickness)
- Dermal mitotic rate ≥ 6 per mm²
- High-grade atypia
- Aberrant nodular growth
- TERT promoter hot spot mutation
- BAP1 mutation in atypical cellular blue nevus

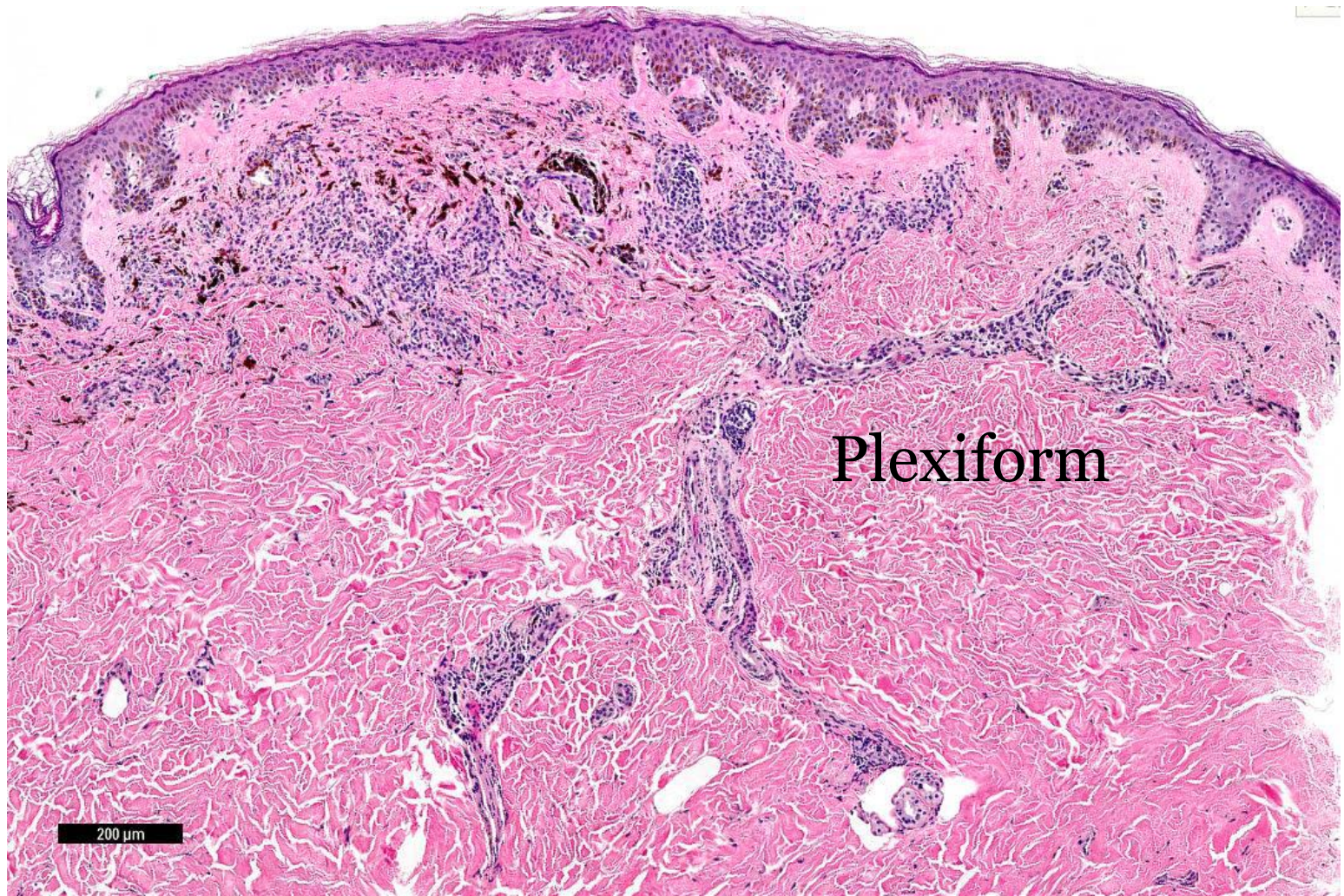
Class II. Wnt-Activated Deep-penetrating/Plexiform Tumor (Melanocytoma)



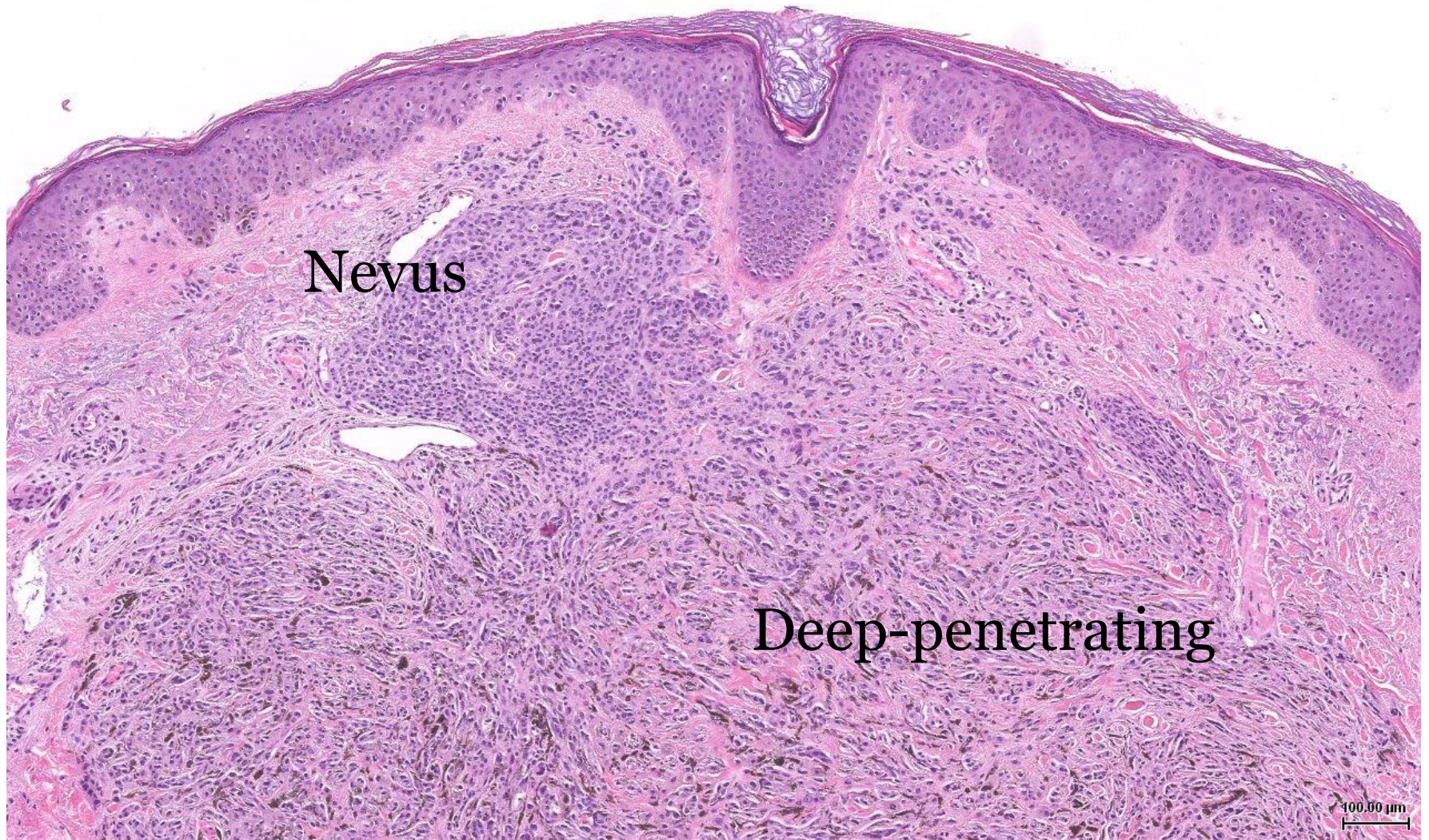
Class II. Wnt-Activated Deep-penetrating/Plexiform Tumor (Melanocytoma)



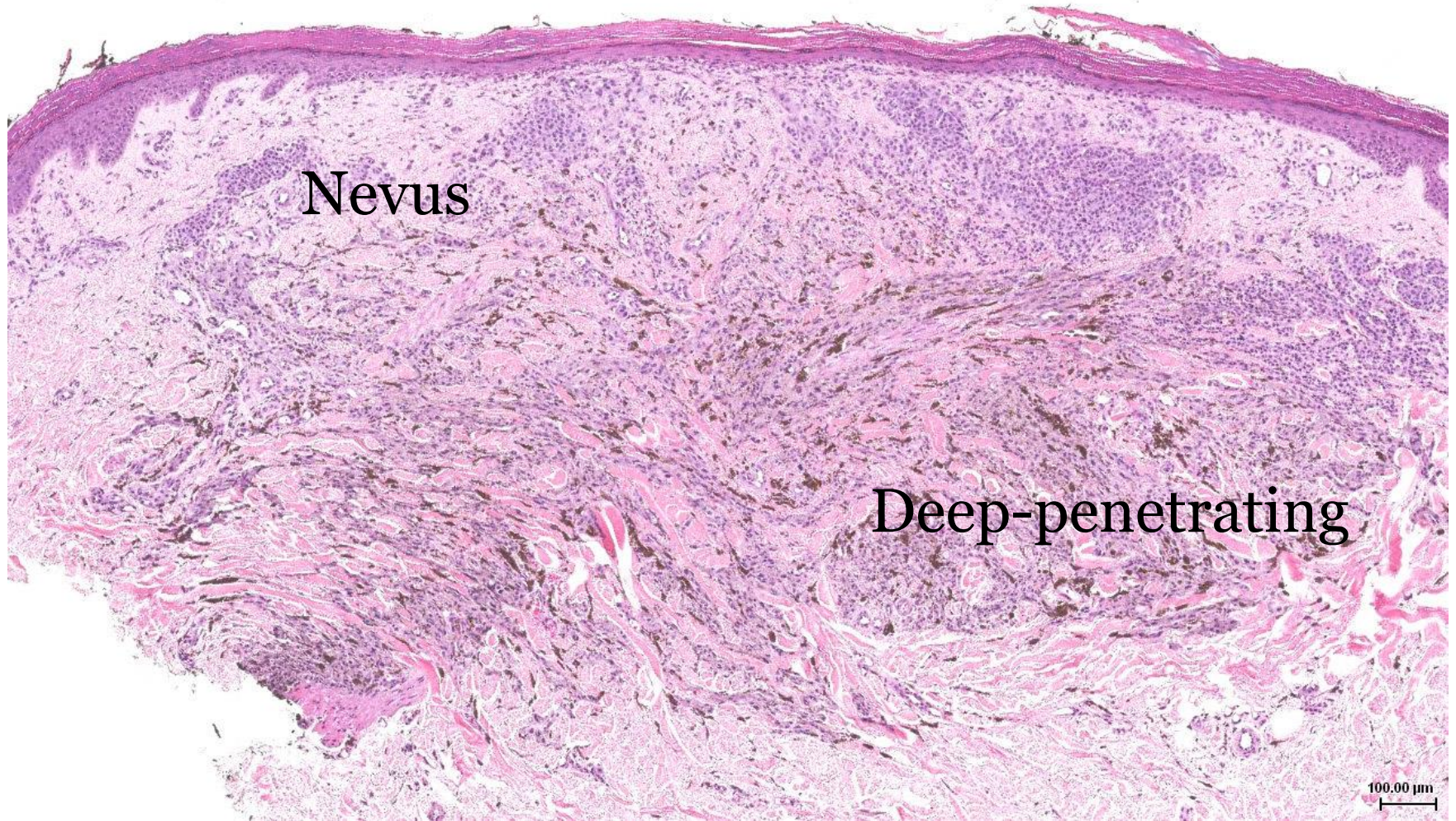
Class II. Wnt-Activated Deep-penetrating/Plexiform Tumor (Melanocytoma)



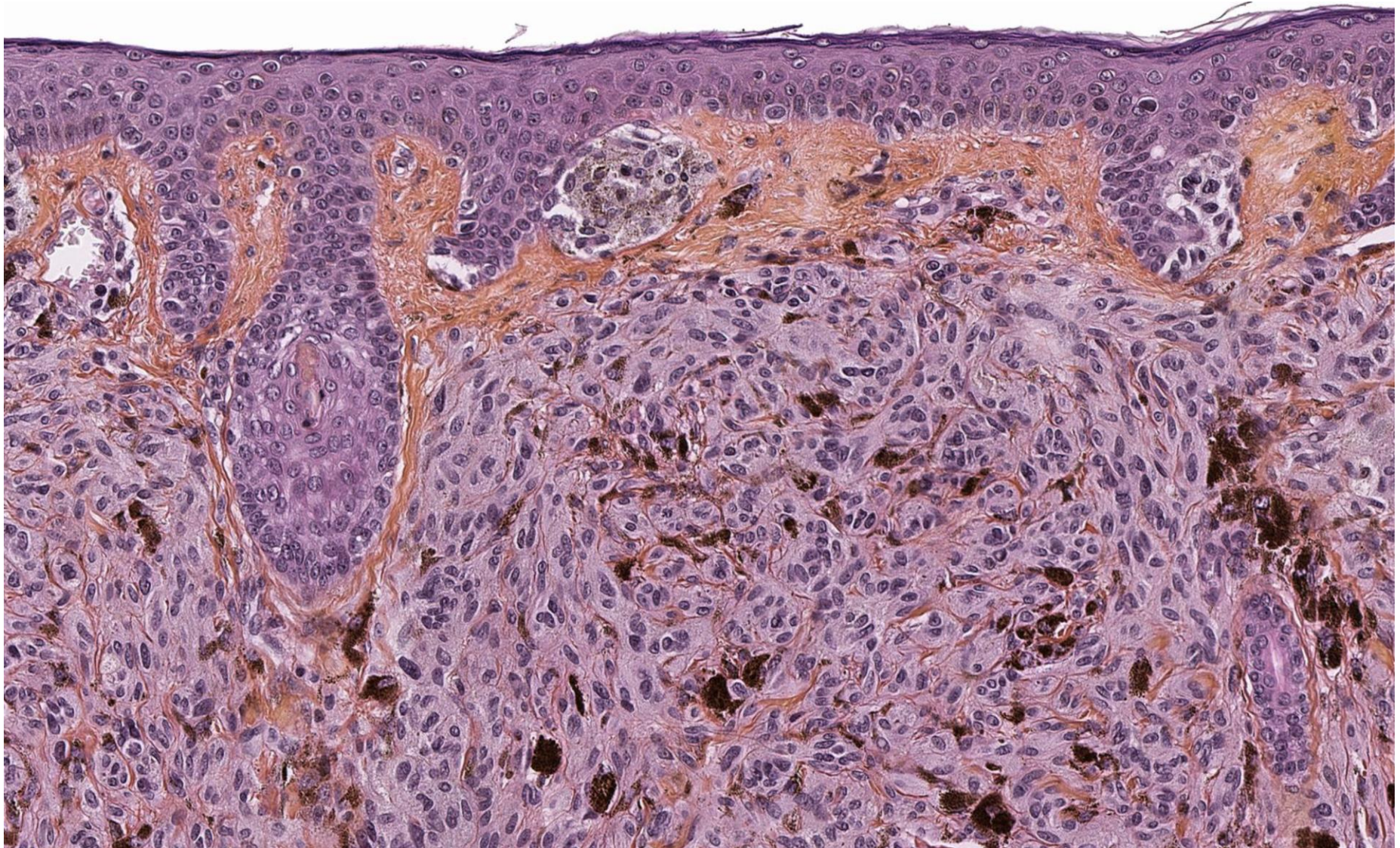
Class II. Wnt-Activated Biphasic Deep-penetrating/Plexiform Tumor



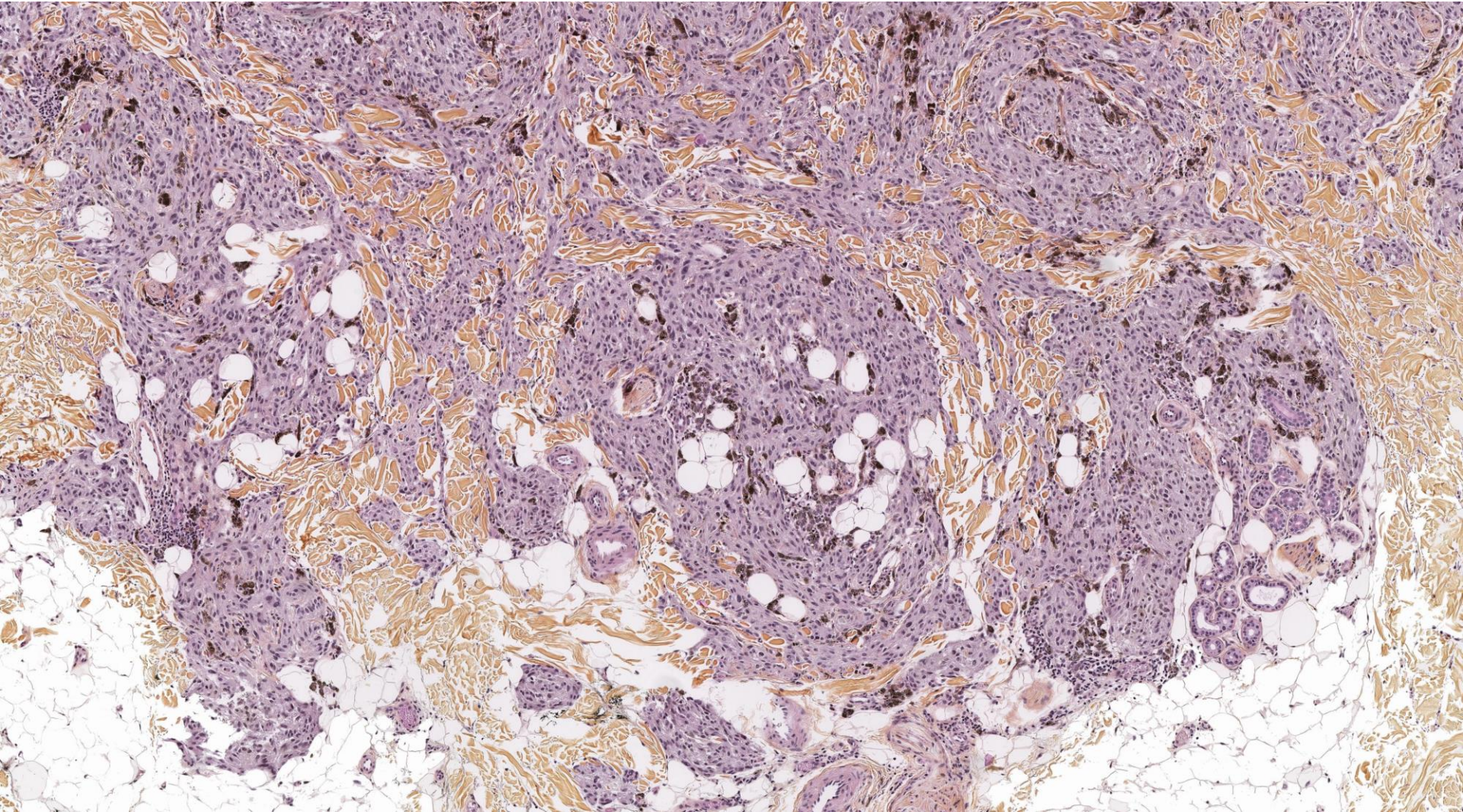
Class II. Wnt-Activated Biphasic Deep-penetrating/Plexiform Tumor



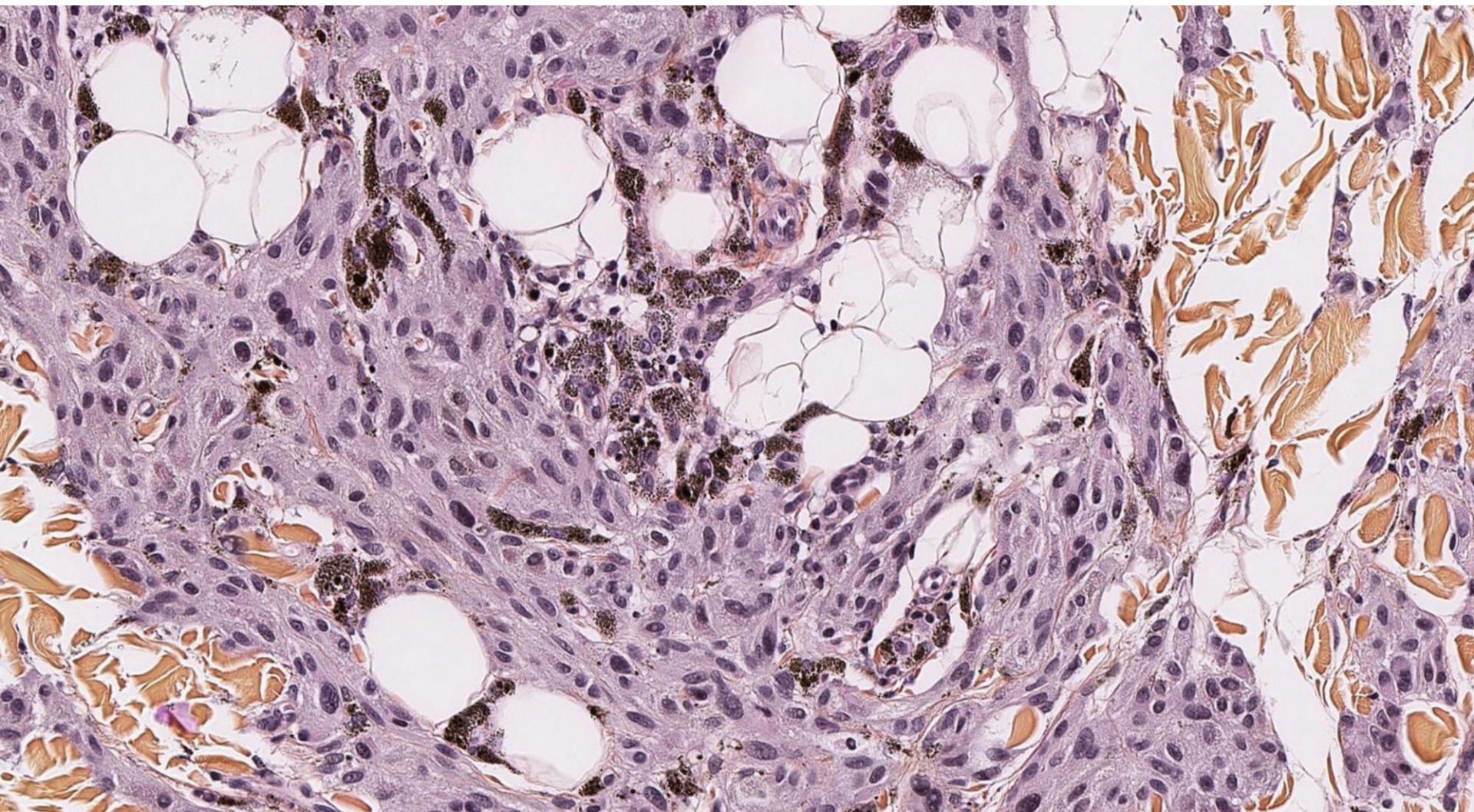
Class II. Deep-penetrating Tumor (Melanocytoma)



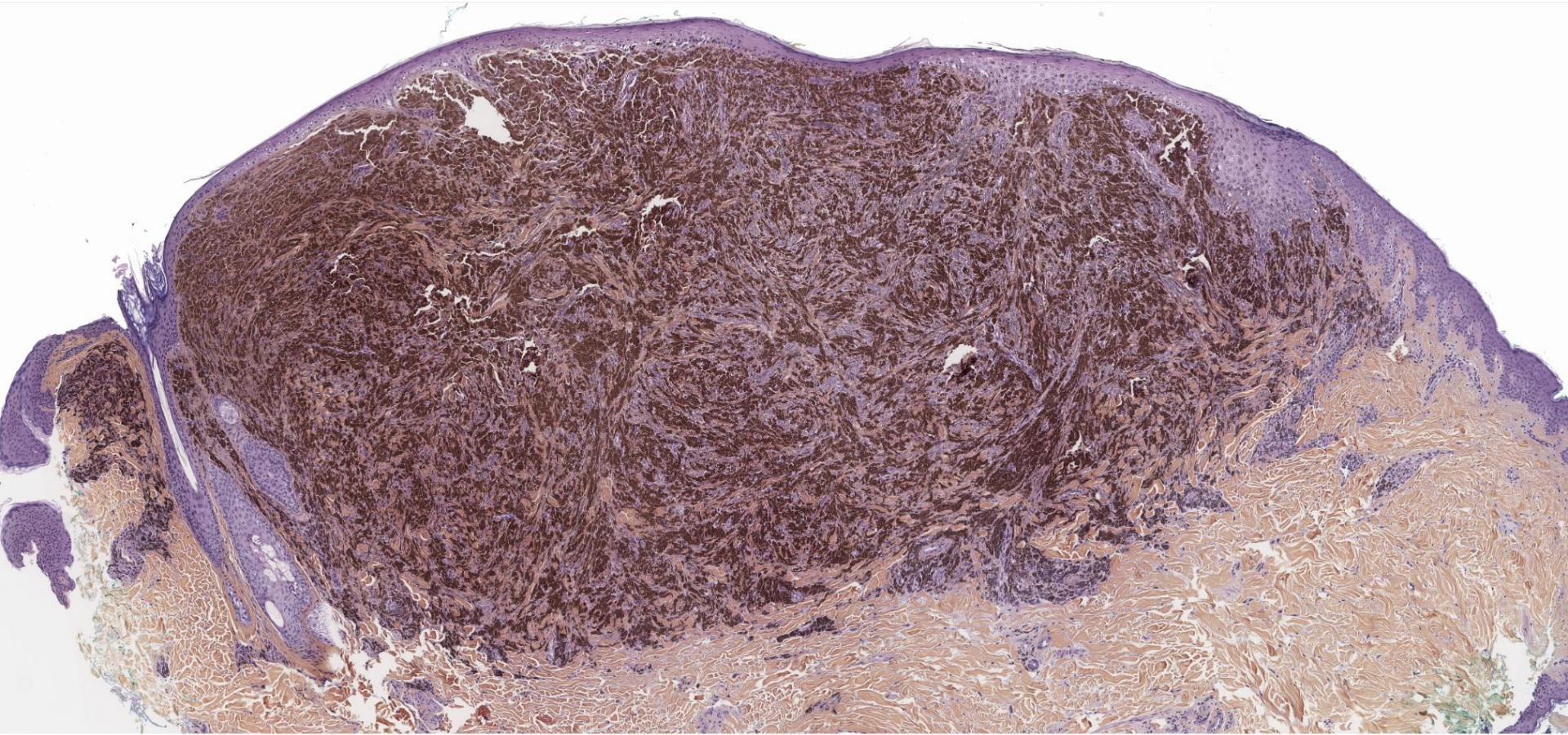
Class II. Deep-penetrating Tumor (Melanocytoma)



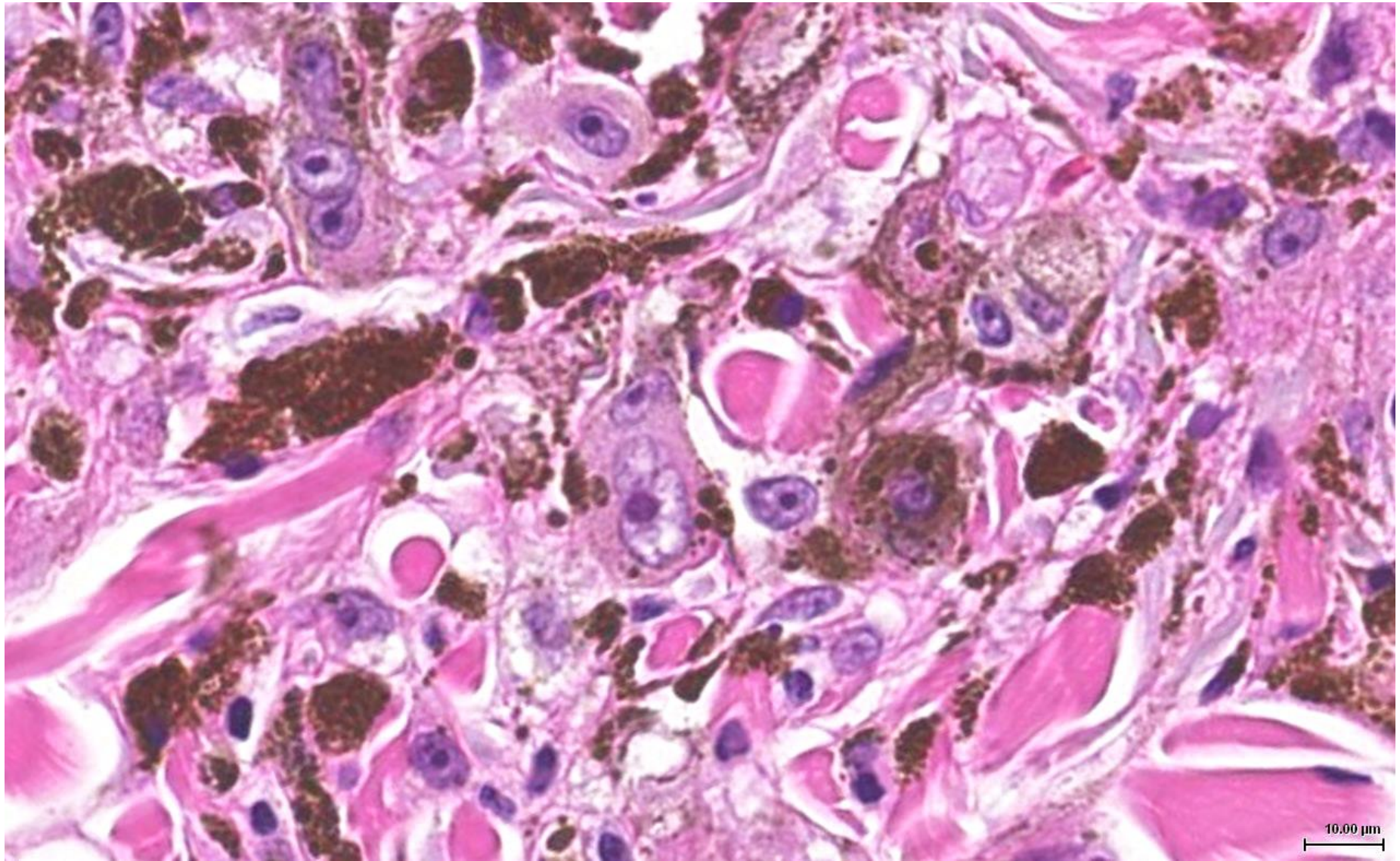
Deep-penetrating Tumor (Melanocytoma)



Class II. Pigmented Epithelioid Melanocytoma



Class II. Pigmented Epithelioid Melanocytoma



MPATH-Dx V2.0:
Class III. pT1a Melanoma

MPATH-Dx Schema V2.0: Class III

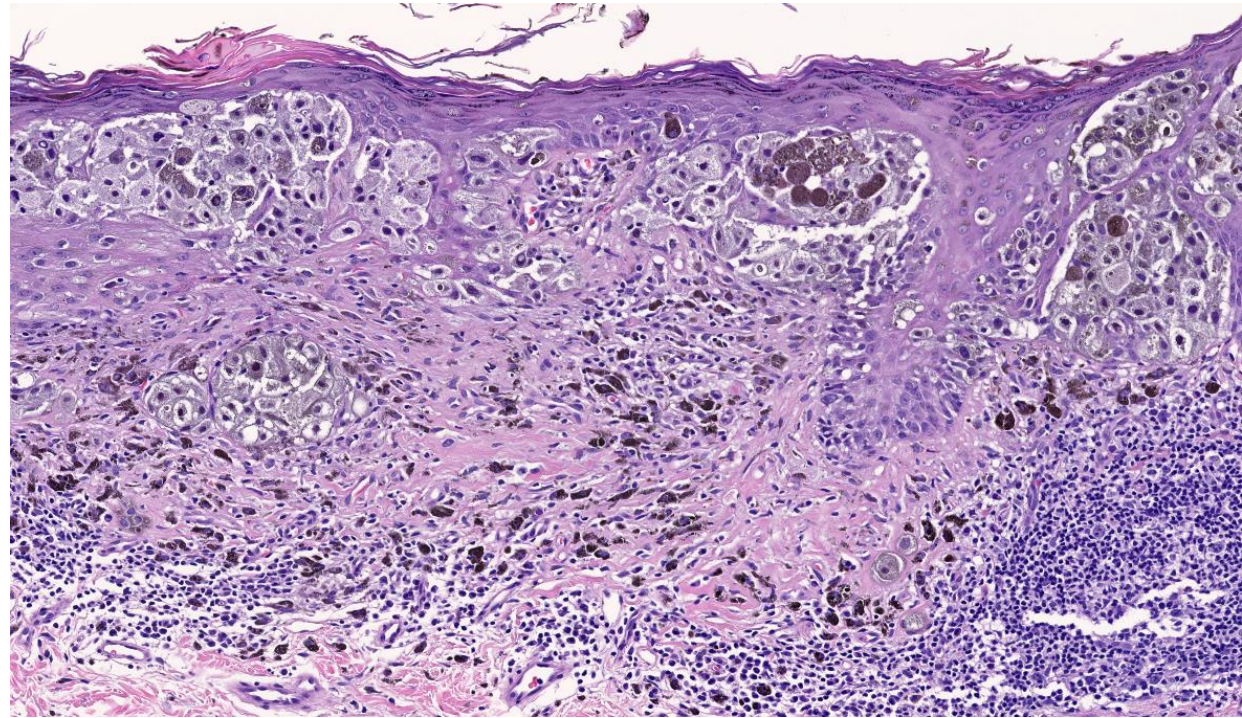
Melanoma pT1a low risk

- Radial growth phase/Level II only
- Negative criteria:
 - NO ulceration
 - NO dermal mitoses
 - NO vertical growth phase
 - NO regression > 50% of tumor

MPATH-Dx Schema V2.0: Class III

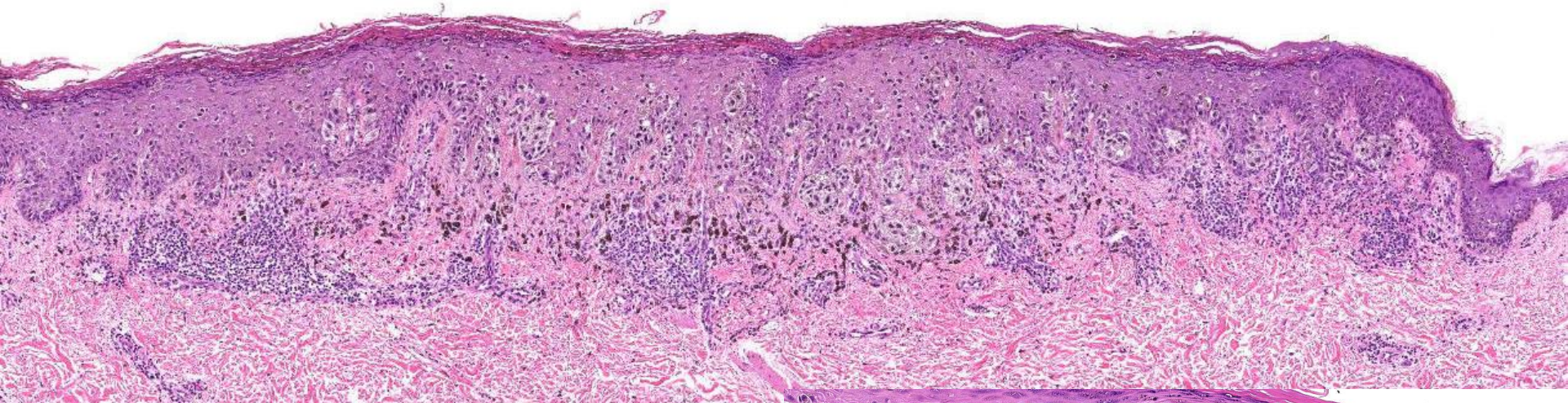
Melanoma pT1a low risk

- Radial growth phase/Level II only
- Negative criteria:
 - No ulceration
 - No dermal mitoses
 - No vertical growth phase
 - No regression

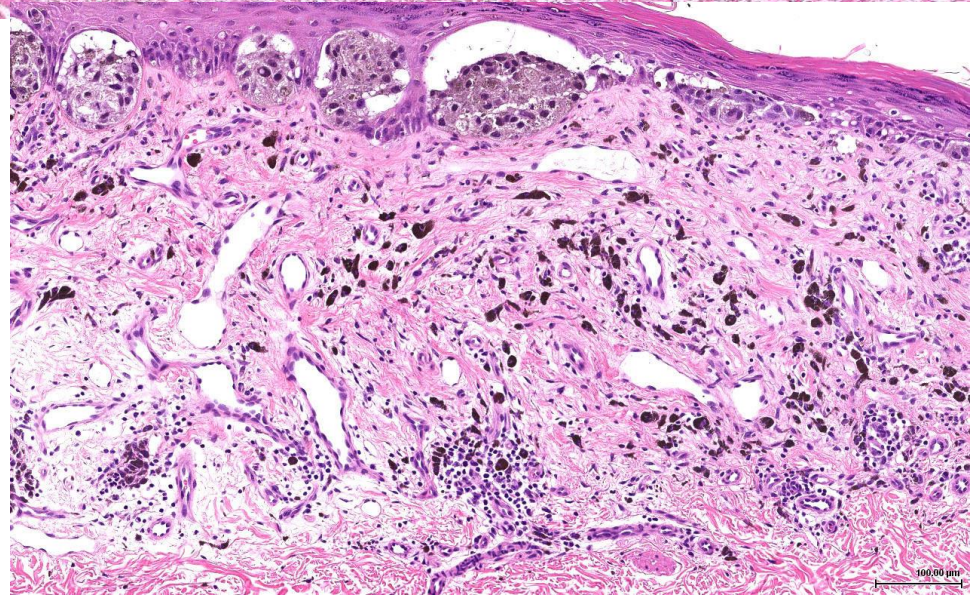


MPATH Class III.

Melanoma pT1a

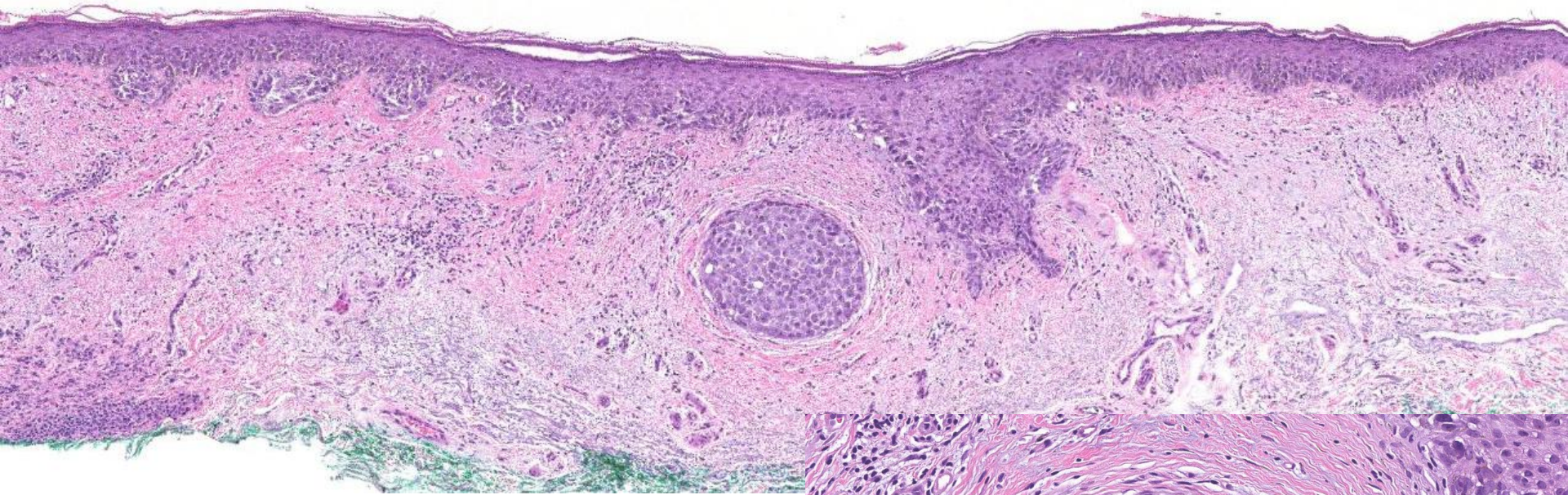


- Breslow: 0.4 mm
- No ulceration
- Mitotic rate 0 per mm²
- No vertical growth phase
- Regression > 50%

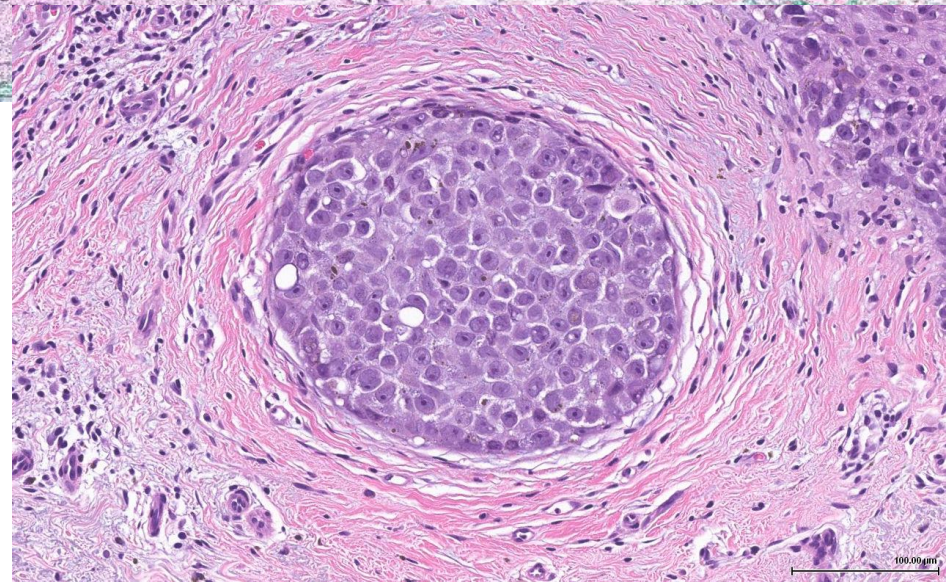


MPATH Class III.

Melanoma pT1a

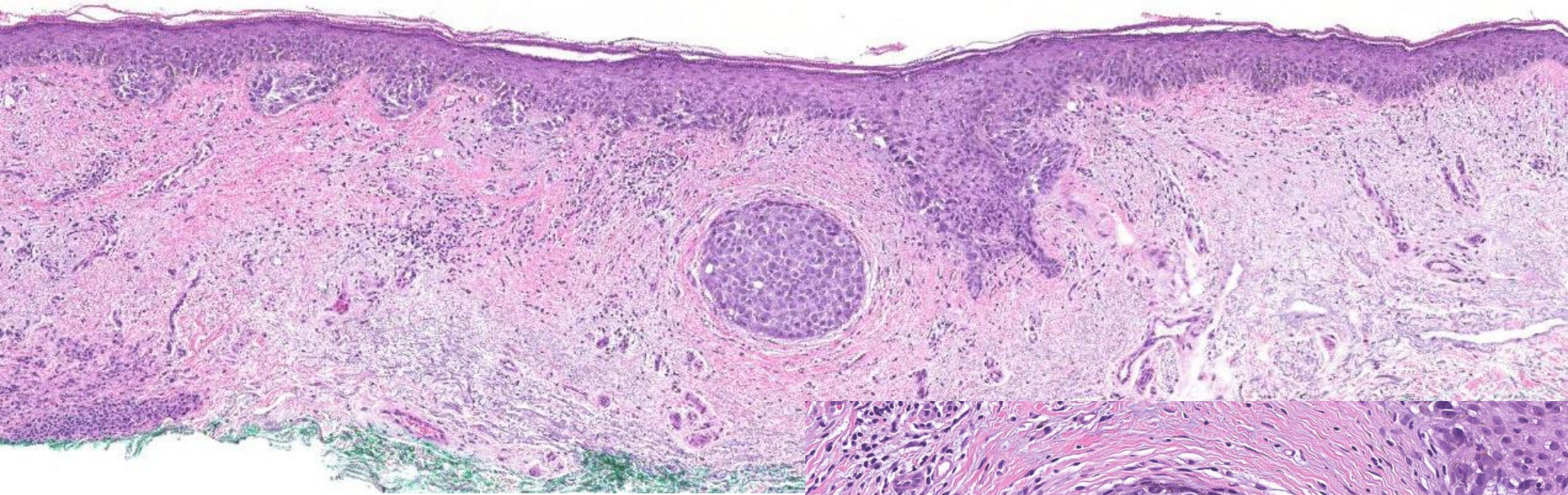


- Breslow: 0.5 mm
- No ulceration
- Mitotic rate 1 per mm²
- Vertical growth phase
- Regression

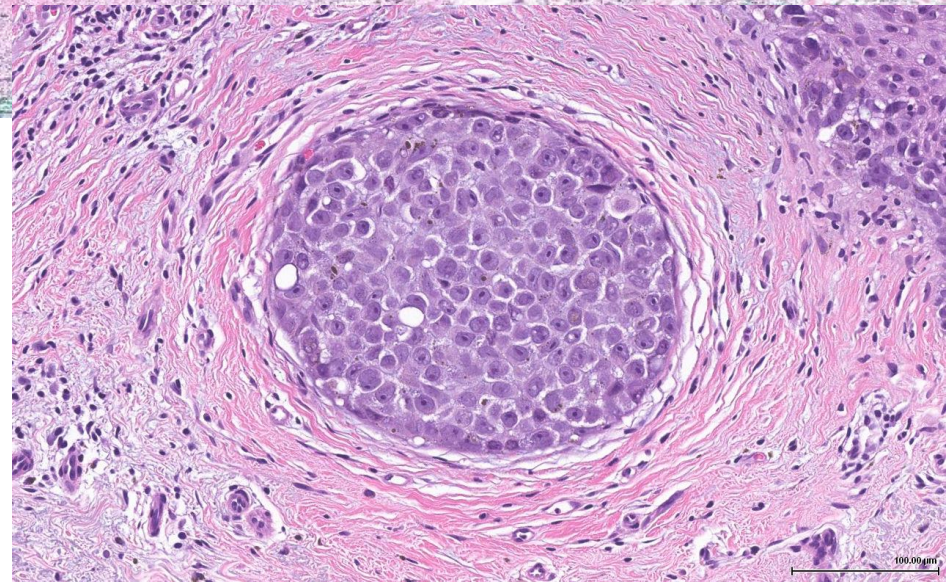


MPATH Class III.

Melanoma pT1a



- Breslow: 0.5 mm
- No ulceration
- Mitotic rate 1 per mm²
- Vertical growth phase
- Regression



Conclusion: Optimal Diagnosis for Patient Care

- Studies are underway to confirm the positive impact of this tool on clinical practice and patient care.
- We anticipate implementation and use the MPATH-Dx Version 2.0

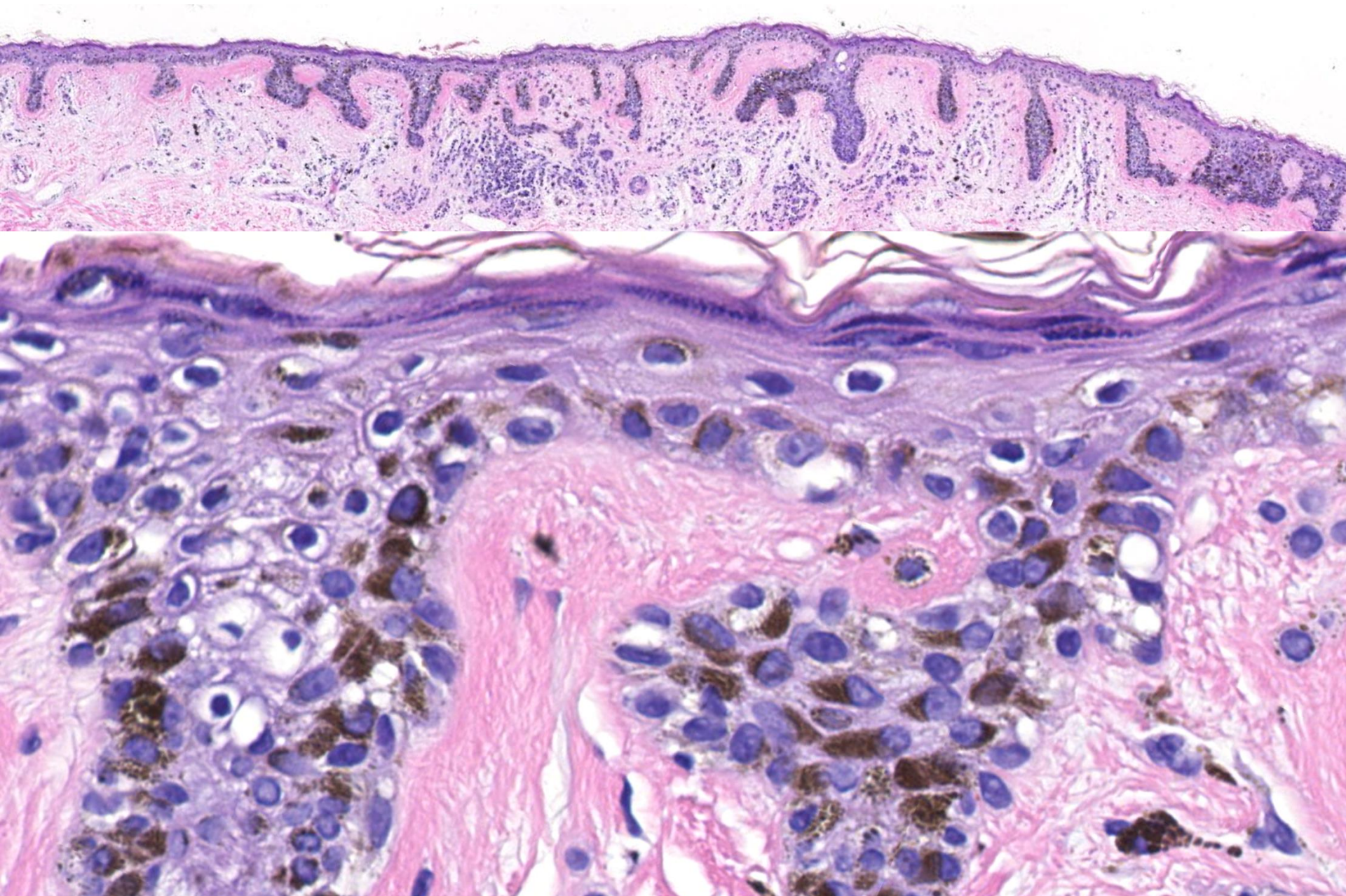


Classification

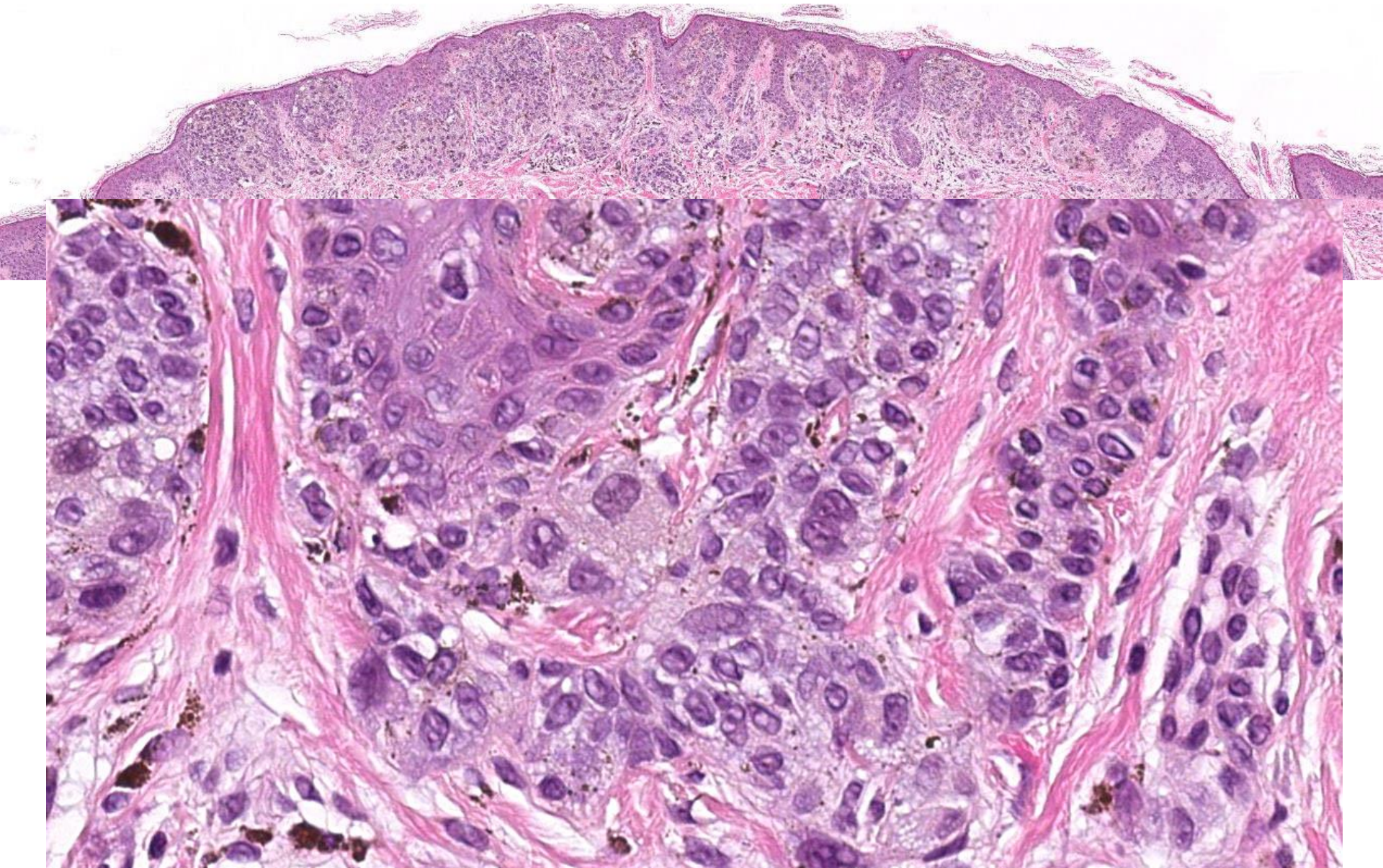
- Overdiagnosis of melanoma
- Underdiagnosis of melanoma and significant lesions



MPATH Class I. Low grade



MPATH Class I. Low grade

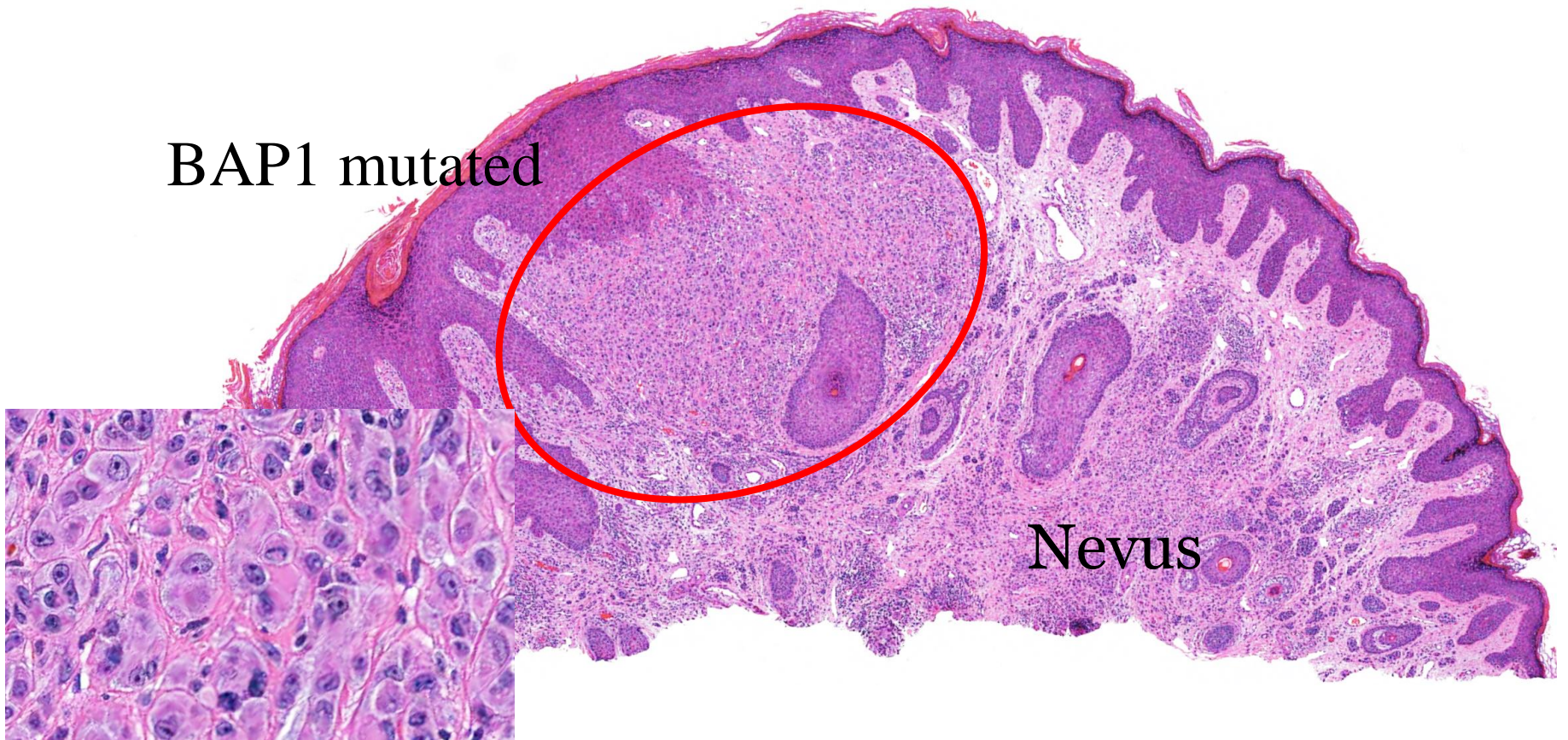


Class II. BAP1-inactivated Tumor (Melanocytoma)

- Conventional nevus (BRAF mutation) + BAP1-

BAP1 mutated

Nevus



BAP1-inactivated Tumor (Melanocytoma)

BAP1 mutated

