

Pigmented Lesions in a Day-to-Day Practice in Dermatopathology: A practical case-based approach

2023 Pennsylvania Association of Pathologists
Saturday, April 15, 10:30 AM – 11:00 AM

Jason B. Lee, MD

Professor

Director of Dermatopathology

Director of Pigmented Lesion Clinic

Department of dermatology and Cutaneous Biology

Thomas Jefferson University

I have no financial conflict to disclose

Table of Contents: Melanocytic Neoplasms

1. Brief Historical Perspective
2. Current Environment of Diagnosis
3. Illustrative Cases



Dysplastic/Atypical/Clark nevus

- Most commonly biopsied melanocytic lesion

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Origin of Familial Malignant Melanomas From Heritable Melanocytic Lesions

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Clark et al. Arch Dermatol, 1978

Clark WH, Reimer RR, Greene M, Ainsworth AM, Mastrangelo MJ. Origin of Familial Malignant Melanomas From Heritable Melanocytic Lesions: The B-K Mole Syndrome. Archives of dermatology (1960). 1978;114(5):732-738. doi:10.1001/archderm.1978.01640170032006



Fig 2

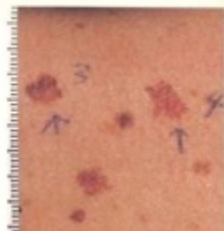


Fig 2



Fig 4, Left



Fig 4, Right



Fig 5



Fig 5

Fig 2.—Back of 27-year-old woman who had four primary malignant melanomas. Pattern and appearance of moles in patient with numerous lesions. Compare with Fig 6 for appearance of B-K moles sparse in number. Proband, family M.

Fig 3.—Constellation of moles from right posterior shoulder of patient shown in Fig 2. Variability in form from lesion to lesion is shown.

Fig 4.—Left and Right. Backs of two brothers, both of whom had malignant melanoma. Two sisters also had mole pattern almost identical to pattern illustrated in right figure.

Fig 5.—Back of 27-year-old woman in April 1972. Note lesion in black circle. Compare with lesion No. 3 in Fig 6 and with Fig 6, inset, which show lesion 4½ years later. Proband, family G.

Fig 6 and Inset.—Same patient as in Fig 5. Photograph taken November 1976. Transformation of B-K mole into malignant melanoma. Lesion indicated as No. 3 and, in closer view, in inset, is malignant melanoma of superficial spreading type. Histology of transformed lesion is shown in Fig 12, 13, and 14. Proband, family G.

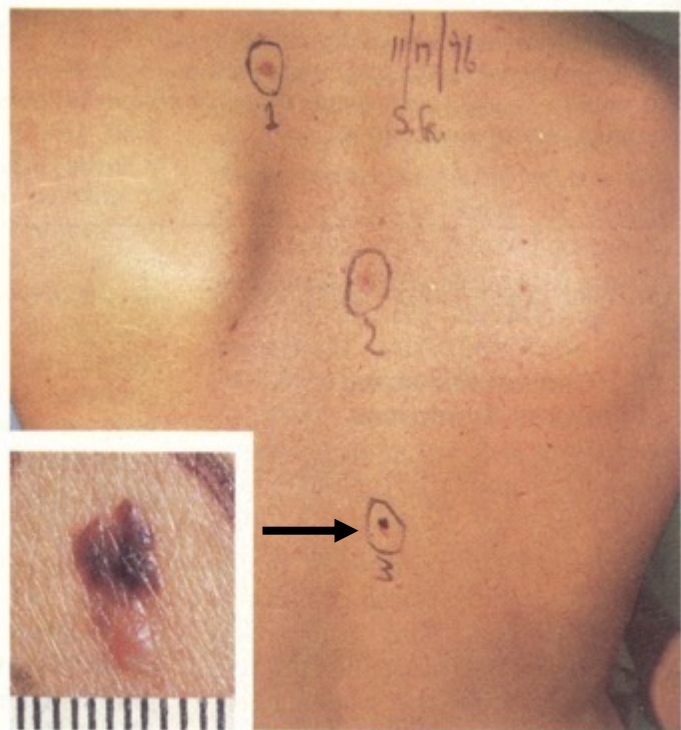


Fig 6

Their Conclusion

“It is proposed that the inherited nevic component of the B-K mole is more susceptible to neoplastic transformation than common acquired melanocytic nevi.” (page 737)



JAMA

The Journal of the American Medical Association

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JAMA, The Journal of the American Medical Association (ISSN 0360-5310), is published four times per month by the American Medical Association, 535 N Dearborn St, Chicago, IL 60610. Phone (312)462-5000. Cable address: "MedChi, Chicago."
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THE COVER

George Stein (active late 19th to early 20th century).
La Place de l'Opéra et le Café de la Paix
 French. Gouache. 47x69 cm.
 Courtesy of the Galleries Maurice Strebler, Paris

MEDICAL NEWS

Attempts to Vanquish Alzheimer's Carious Links Reported Settle . . . Steps Toward Staging, Therapies

LEADS FROM THE MMWR

INSTRUCTIONS FOR AUTHORS

REFERENCE DIRECTORIES

Foreign Meetings 1827
 US Meetings, April 6; Organizations of Medical Interest, Jan 27; State Associations and Exams and Licenses, Jan 20; AMA Officials, April 6

LETTERS

Reliability of Measurements of Tricyclic Levels R. L. Bank, MD, Columbia, SC, LCDR D. A. Johnson, MD, MC, USNR, LCDR T. V. Whelan, MD, MC, USNR, Portsmouth, Va . . . **Generalists and Specialists** R. K. Williams, MD, Providence, RI, T. J. Ruane, MD, East Lansing, Mich, R. A. Davidson, MD, MPH, Chapel Hill, NC . . . **Cystitis Among Medical Students** D. Olan, MD, Philadelphia, L. Kugelmann, PhD, Greenville, NC . . . **The Prader-Willi Syndrome** H. Zuberger, MD, Iowa City . . . **A Severe Response to Substances Released From Cortisol S. S. Lefkowitz, PhD, D. L. Lefkowitz, MD, Lubbock, Tex . . . Septicemia Caused by Penicillinase-Producing Gonococci** P. Ruus, MD, R. Rajala, MD, H. Papp, MD, P. Voronov, MD, J. Lähdevirta, MD, Helsinki

ORIGINAL CONTRIBUTIONS

Obstetric Complications as Risk Factors for Cerebral Palsy or Seizure Disorder 1843
 K. S. Nelson, MD, J. H. Emsberg, PhD, Bethesda, Md
'Benign' Monoclonal Gammopathy 1849
 R. A. Kohn, MD, Rochester, Minn
Marital and Family Therapy for Troubled Physicians and Their Families 1855
 I. G. Gluck, MD, New York, J. P. Soria, MD, Boston

BRIEF REPORT

Late Recurrence (Beyond Ten Years) of Cutaneous Malignant Melanoma 1809
 H. K. Riv, MD; A. J. Sotter, MD; T. B. Fitzpatrick, MD, Boston

CASE REPORT

Migration of Schragel From Lung to Bronchus 1862
 M. Sogomonian, MD, Salisbury, Md

CONSENSUS CONFERENCE

Precursors to Malignant Melanoma 1864

EDITORIALS

Three Major Challenges: Quality, Cost, and Balance 1867
 F. J. Ales, Jr, MD, Chicago

Perinatal Risk and Cerebral Palsy 1865
 R. J. Sokol, MD, Detroit

100 Years of Continuous Publication
 April 13, 1984
 Vol 251, No. 14

CONSENSUS CONFERENCE

Precursors to Malignant Melanoma

1864

1984

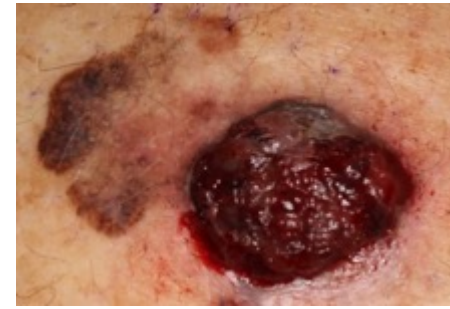
Precursors to Malignant Melanoma. JAMA: the journal of the American Medical Association. 1984;251(14):1864-1866. doi:10.1001/jama.1984.03340380046022

NIH Consensus Conference: Oct. 24-26, 1983

Identifying individuals with higher risk of developing melanoma

“The panel also agreed that the **dysplastic nevus**, a distinctive lesion both clinically and histologically, has been identified in this context, particularly in melanoma families. Dysplastic nevi are both markers and precursors for melanoma. Melanoma may develop also in congenital nevi, especially when the lesion is larger than 20 cm.” (page 1864)

Stepwise Multi-Step Progression of Cancer



“typical” or
“normal” nevus

“dysplastic” nevus

melanoma in situ

invasive melanoma

1. Initiation

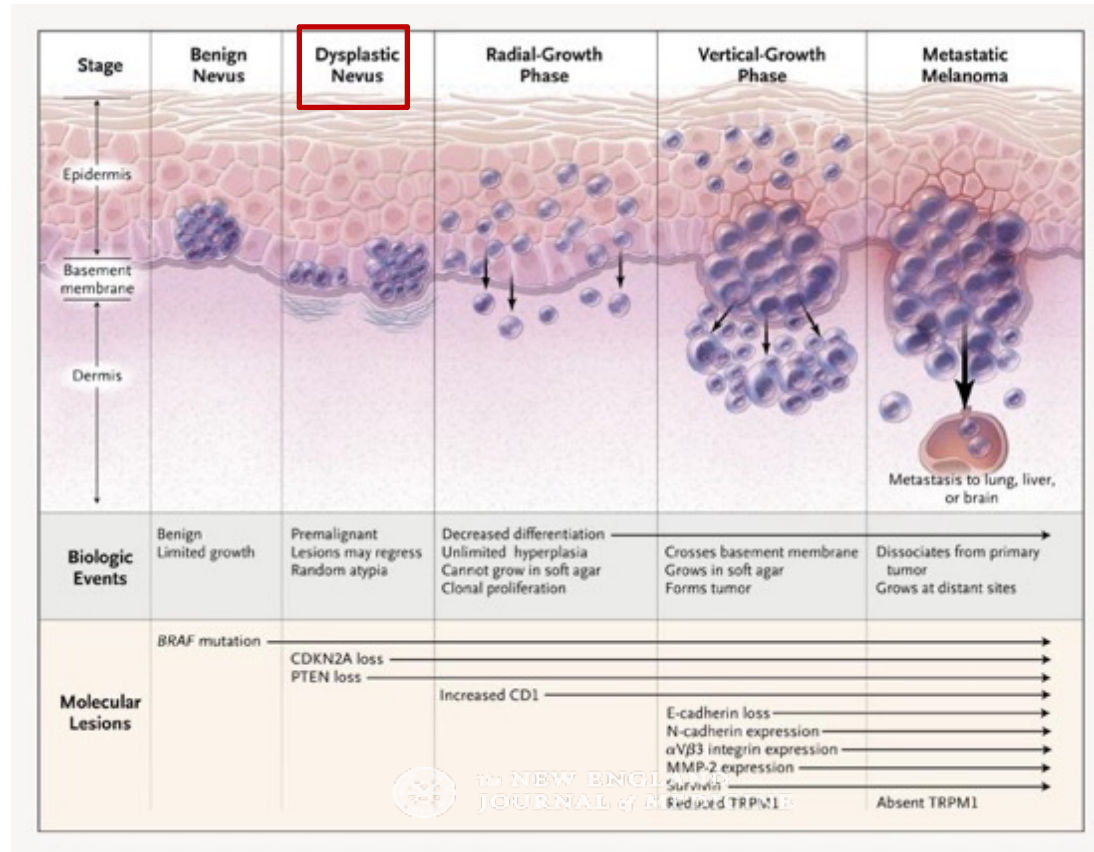
2. Latent

3. Promotion

4. Malignant transformation

The continual accumulation of DNA mutations results in step-wise progression of neoplasia, the steps of which may be recognizable morphologically—e.g. metaplasia and dysplasia

Biologic Events and Molecular Changes in the Progression of Melanoma. Miller AJ, Mihm MC Jr. N Engl J Med 2006;355:51-65.

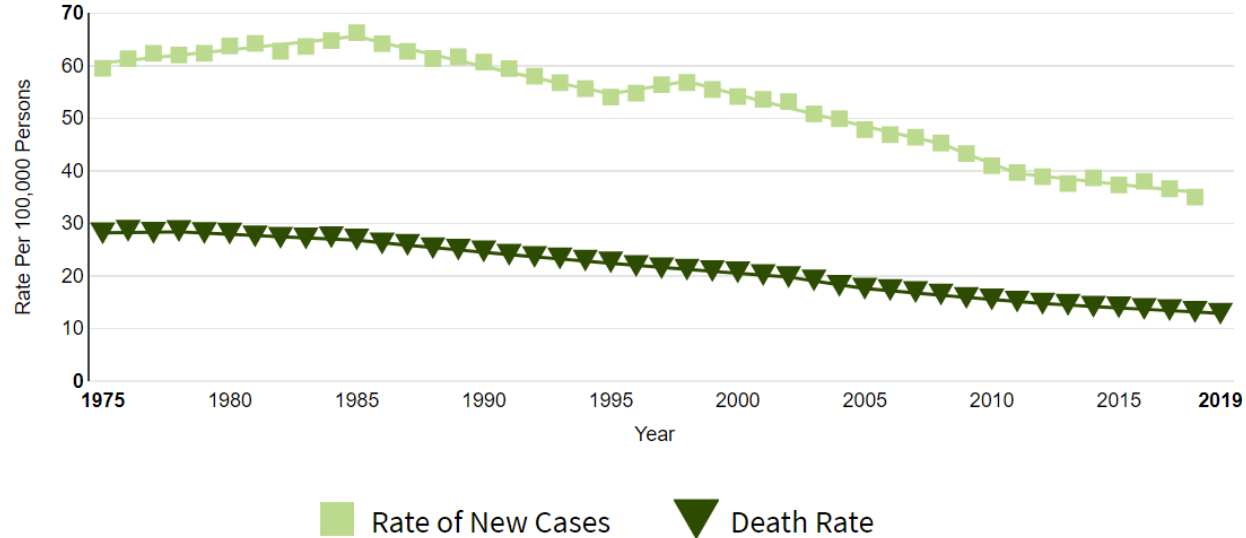


the NEW ENGLAND JOURNAL of Medicine

Reduced TRPM1

Colorectal Cancer Incidence & Mortality

- Reliable *precursor lesion*
 - polyps
- Effective screening program
 - early detection
 - effective treatment
- Reduction in mortality
- Reduction in incidence



Model for Precursor Detection & Cancer Prevention

<https://seer.cancer.gov/statfacts/html/colorect.html>

**Screen Precursor Lesions of Cancer to
Decrease Morbidity & Mortality**



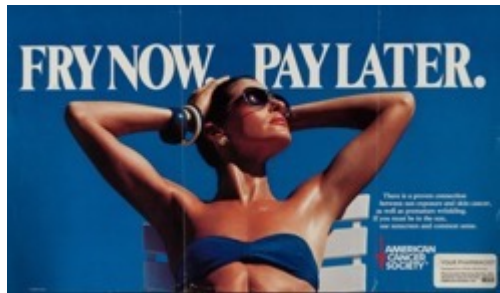
“Malignant melanoma can be diagnosed clinically and histologically when it is small, flat, and confined to the epidermis.”

A. B. Ackerman, 1983

Ackerman AB. Macular and patch lesions of malignant melanoma: malignant melanoma in situ. *J Dermatol Surg Oncol* 1983;9:615-8.

Skin Cancer Awareness Campaigns

- Slip Slop Slap
- Skin Awareness For Everyone (SAFE)
- Fry Now Pay Later
- SunSmart
- Play Sun Smart
- ABCDs of Melanoma
- Melanoma Monday



Benign	Malignant	
		Asymmetry
Symmetrical	Asymmetrical	
		Border
Even edges	Uneven edges	
		Color
One shade	Two or more shades	
		Diameter
Smaller than 1/4 inch	Larger than 1/4 inch	



Introduction of Dermatoscopy USA

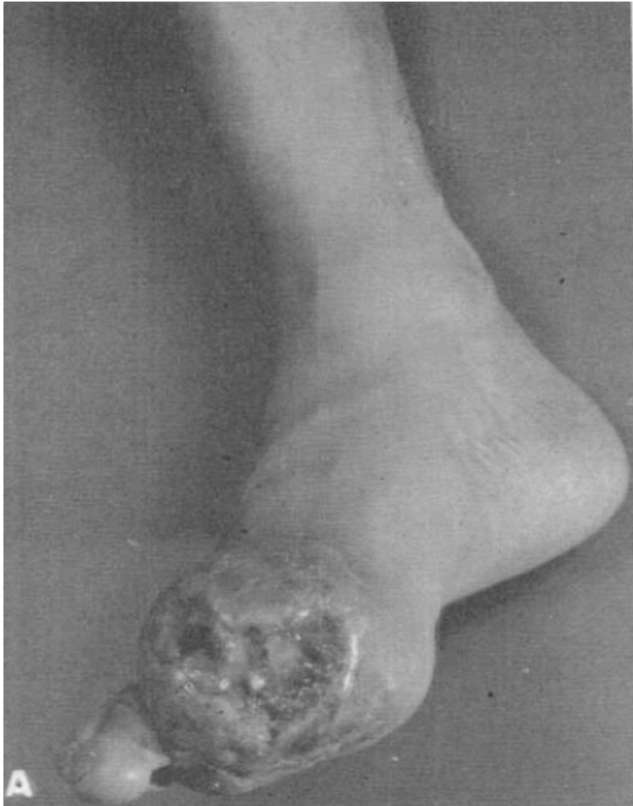


Objectives of Dermatoscopy

1. Increase the diagnostic accuracy of melanoma, especially early melanomas
2. Decrease unnecessary harvesting of benign skin lesions

Improve the diagnostic
SENSITIVITY and ***SPECIFICITY***
of melanoma

Melanoma Then & Now



Cancer Jan-Feb 1960



JAAD Mar 2007

When dermatologists diagnose melanomas

- Stage 0: Melanoma in-situ
- Stage 1A: 0.16mm to 0.80 mm in depth

(earlier stage than when patients or non-dermatologists detects melanomas)

Carli P, De Giorgi V, Palli D, et al. Arch Dermatol. 2003;139:607-612.

Pennie ML, Soon SL, Risser JB, et al. Arch Dermatol. 2007;143: 488-494.

Kantor J, Kantor DE. Arch Dermatol. 2009;145: 873-876.

Table of Contents: Melanocytic Nevi & Melanoma

1. Brief Historical Perspective
2. Current Environment of Diagnosis
3. Illustrative Cases

Incidence

(2023 estimate)

	<u># cases</u>	<u># deaths</u>
Melanoma	97,610	7,990
Melanoma in-situ	90,000	
Breast	300,590	43,700
Lung	238,340	127,070
Prostate	288,300	34,700

5-year survival rate by stage

Year	Overall	Localized	Regional	Distant
2015	91%	98%	62%	15%
2018	92%	99%	63%	20%
2023	94%	99%	71%	32%

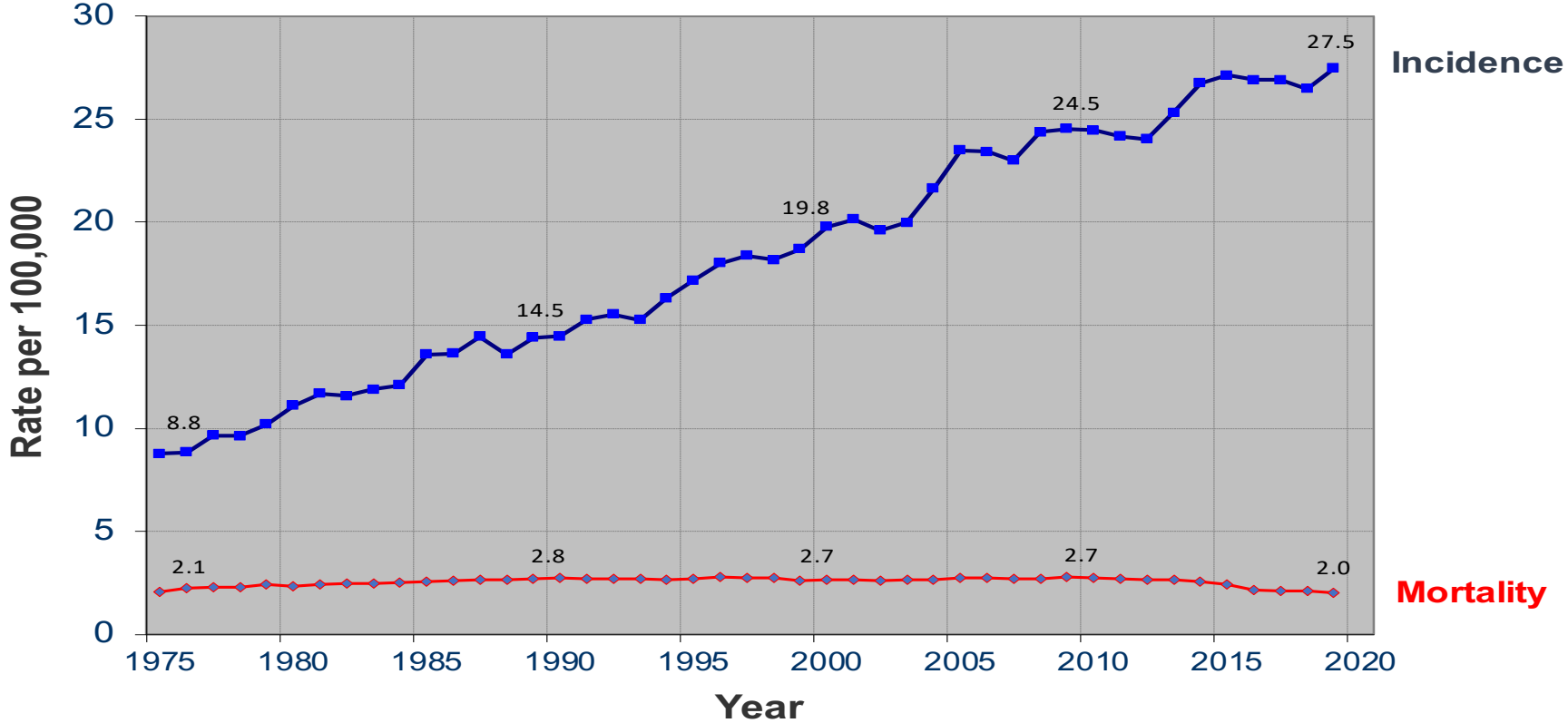


✓ Localized (Stage I & II) disease make up 82%

5-year survival rate of cancers

Cancers	%
Thyroid	98%
Prostate	97%
Testis	95%
Melanoma	94%
Breast	91%
Merkel cell carcinoma	65%
Lung	23%
Esophagus	21%
Pancreas	12%

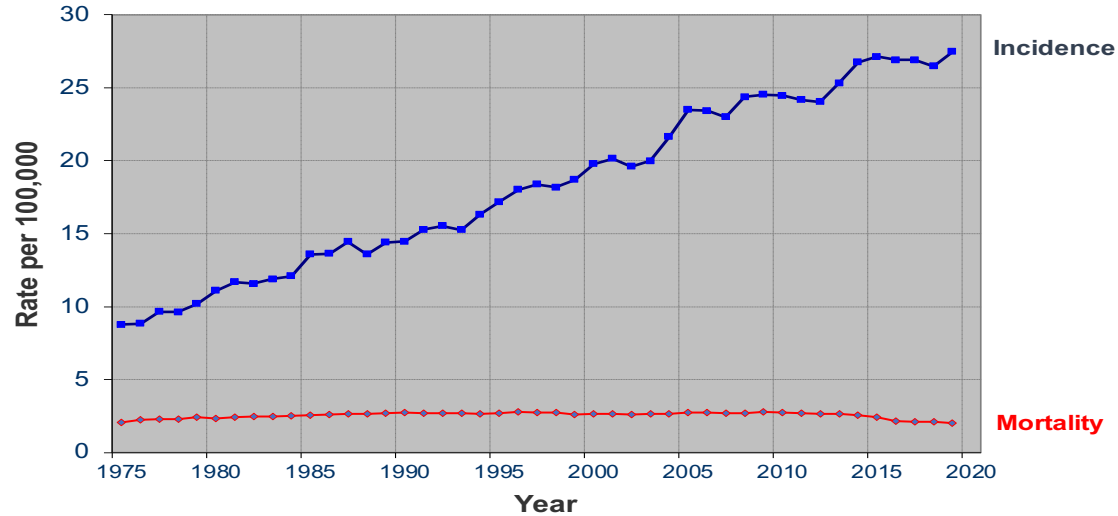
The Melanoma “Epidemic”



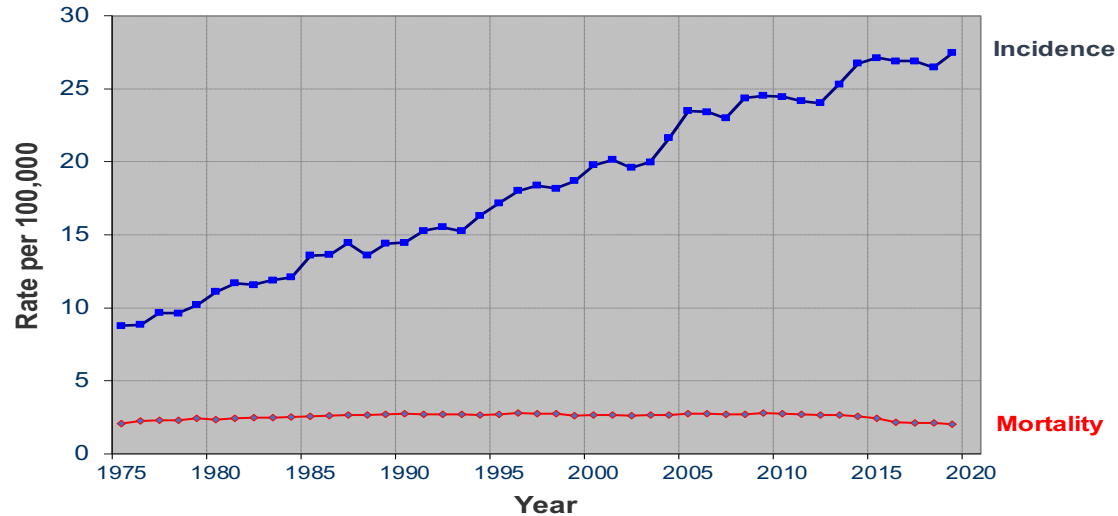
The Melanoma “Epidemic”

Epidemiologic Signature of Overdiagnosis

- Rise in incidence of mostly localized disease
- No change in mortality

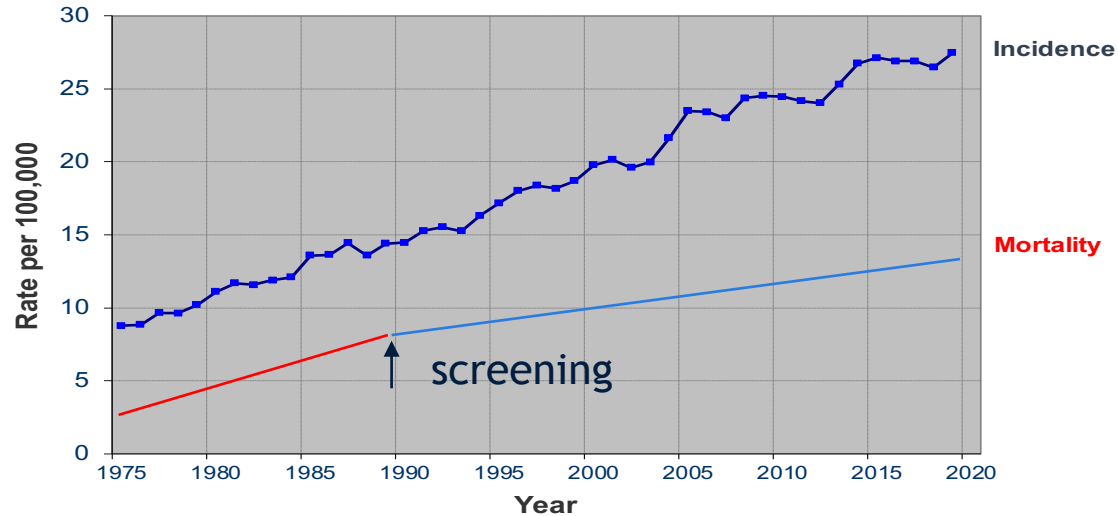


The Melanoma “Epidemic”



- NO screening captures 100% of the lethal cancer, providing a cure for each one with NO change in mortality
- <10% screened
- Effective screening may prevent $\approx 50\%$ mortality at most

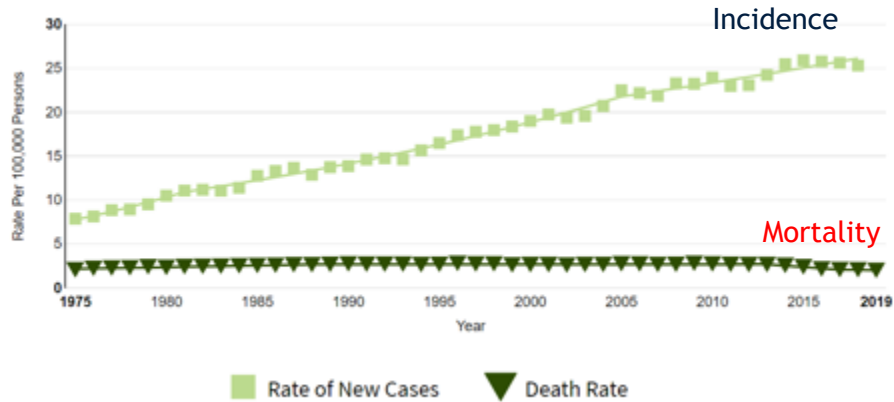
The Melanoma “Epidemic”



- NO screening captures 100% of the lethal cancer, providing a cure for each one with NO change in mortality
- <10% screened
- Effective screening may prevent $\approx 50\%$ mortality at most
- Mortality should rise with blunting of the slope with effective screening

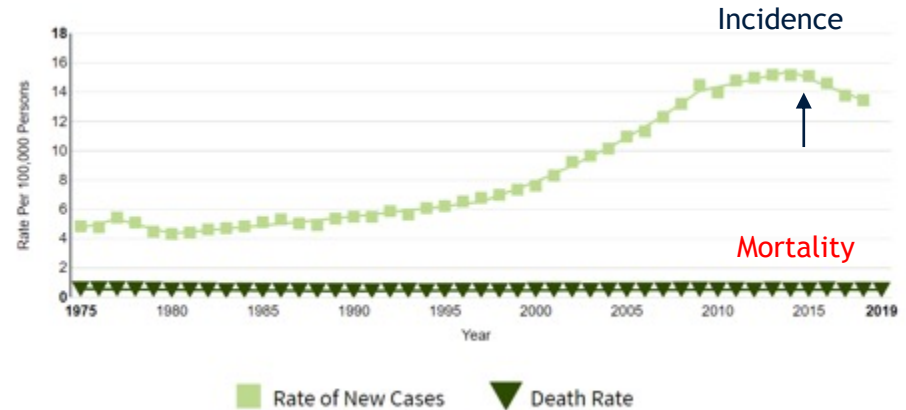
Epidemiologic Signature of Overdiagnosis

Melanoma Incidence and Mortality



<https://seer.cancer.gov/statfacts/html/melan.html>

Thyroid Cancer Incidence & Mortality

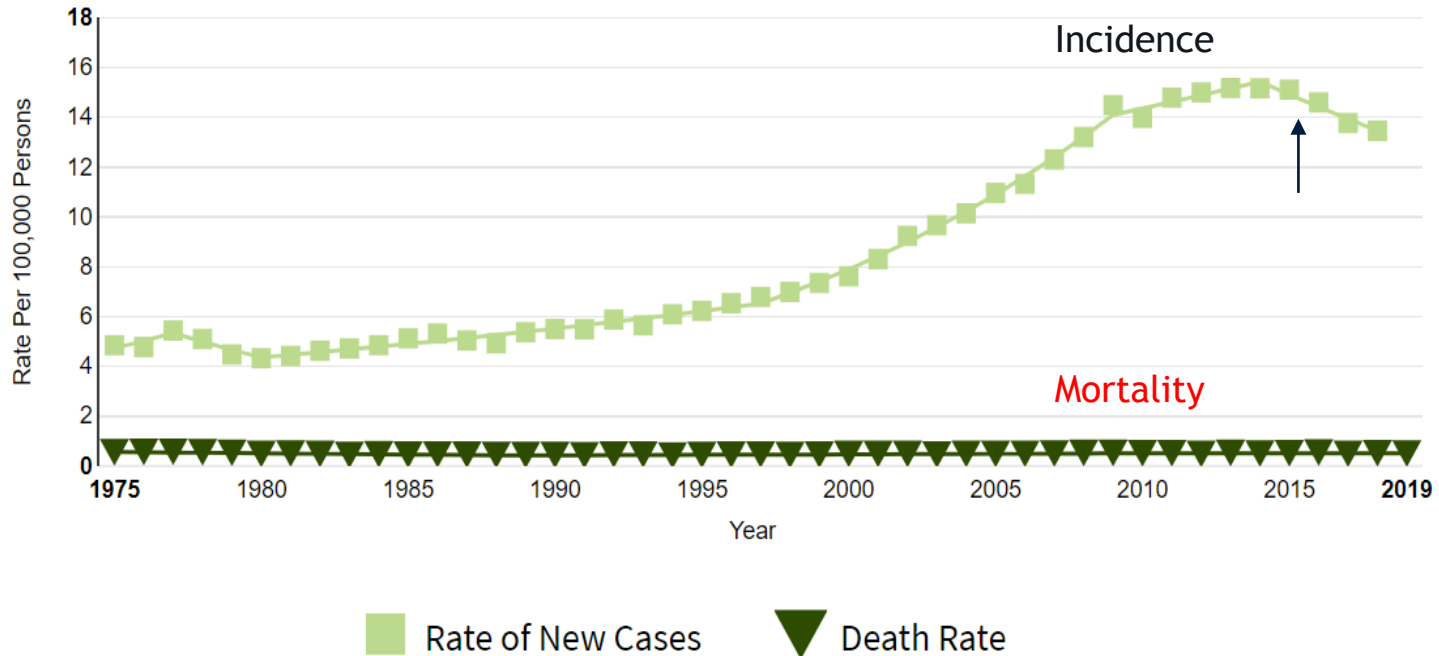


<https://seer.cancer.gov/statfacts/html/thyro.html>

USPSTF Thyroid Cancer Screening Guideline 2017

Recommendation Summary

Population	Recommendation	Grade
Adults	The USPSTF recommends against screening for thyroid cancer in asymptomatic adults.	D



Epidemiologic evidence of melanoma overdiagnosis is mounting

The Rapid Rise in Cutaneous Melanoma Diagnoses




H. Gilbert Welch, MD, MPH
The NEW ENGLAND JOURNAL of MEDICINE
2021

Cancer 2022

Prognostic modeling of cutaneous melanoma stage I patients using cancer registry data identifies subsets with very-low melanoma mortality

Incidence of in Situ vs Invasive Melanoma: Testing the “Obligate Precursor” Hypothesis

JNCI 2022

Catherine M. Olsen, PhD ^{1,2} Nirmala Pandeya, PhD ^{1,2} Philip S. Rosenberg, PhD ³

JAMA Internal Medicine | Original Investigation 2022

Association of UV Radiation Exposure, Diagnostic Scrutiny, and Melanoma Incidence in US Counties

Adewole S. Adamson, MD, MPP; Heather Welch, MSc; H. Gilbert Welch, MD, MPH

JAMA Dermatology | Original Investigation 2022

Estimating Overdiagnosis of Melanoma Using Trends Among Black and White Patients in the US

MELANOCYTIC TUMOUR PATHOLOGY

Diagnostic error, uncertainty, and overdiagnosis in melanoma

Pathology 2023

EPIDEMIOLOGY

The effect of screening on melanoma incidence and biopsy rates*

2022 BJD
British Journal of Dermatology

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The Rapid Rise in Cutaneous Melanoma Diagnoses

H. Gilbert Welch, M.D., M.P.H., Benjamin L. Mazer, M.D., M.B.A.,
and Adewole S. Adamson, M.D., M.P.P.

Recommendations to stop the cycle of overdiagnosis

- Stop population screening
- Curtail self-referral of skin-biopsy specimens
- Clinicians: raise the threshold to biopsy— don't bx lesions <6mm
- Pathologists
 - Increase the thresholds for labeling melanoma
 - Linguistic de-escalation: diagnose as “melanocytic neoplasm”

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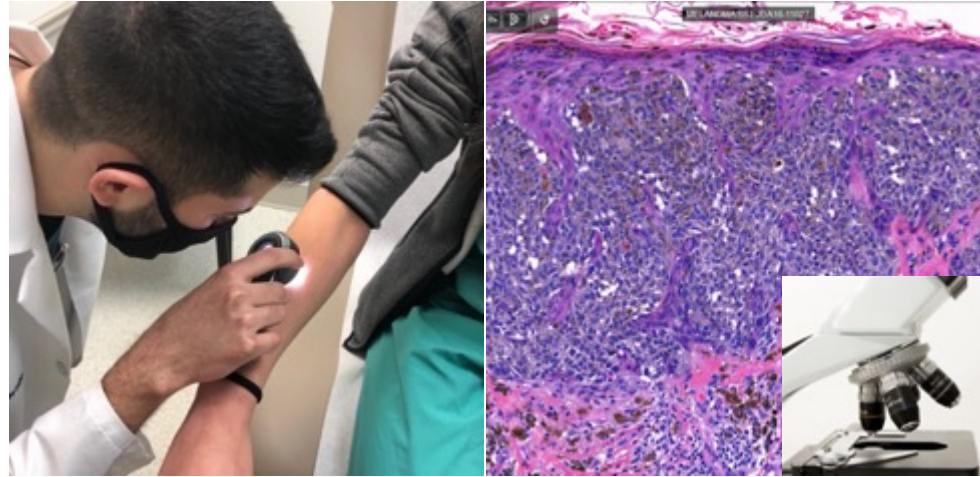
The Rapid Rise in Cutaneous Melanoma Diagnoses

H. Gilbert Welch, M.D., M.P.H., Benjamin L. Mazer, M.D., M.B.A.,
and Adewole S. Adamson, M.D., M.P.P.

“Pathologists could also pursue linguistic deescalation, specifically for melanoma in situ. A diagnosis of “melanocytic neoplasm” would be less distressing for patients and could reduce continued surveillance and overtreatment.”

Overdiagnosis is Not discernable at the patient level

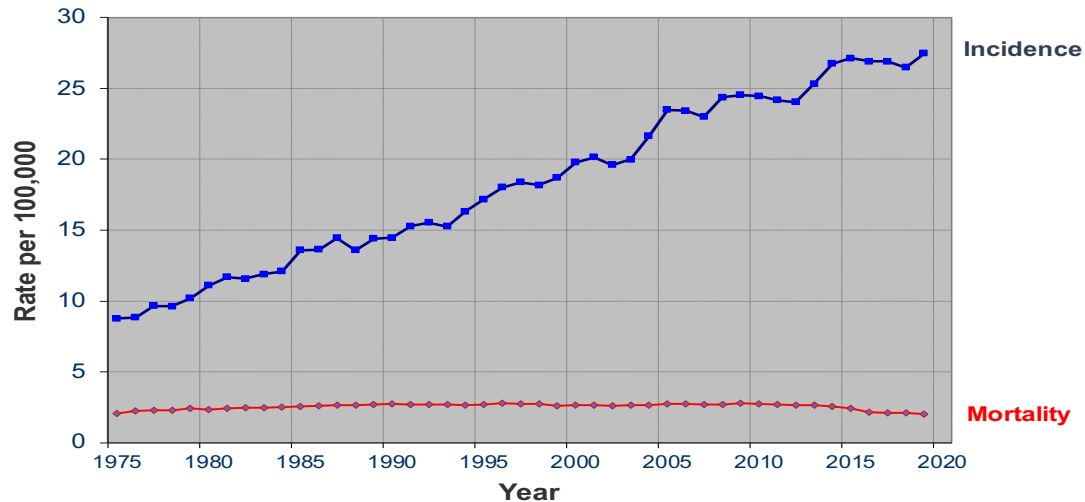
- Overdiagnosis is an epidemiological phenomenon
- Clinicians and pathologists cannot see overdiagnosis



Which will progress?

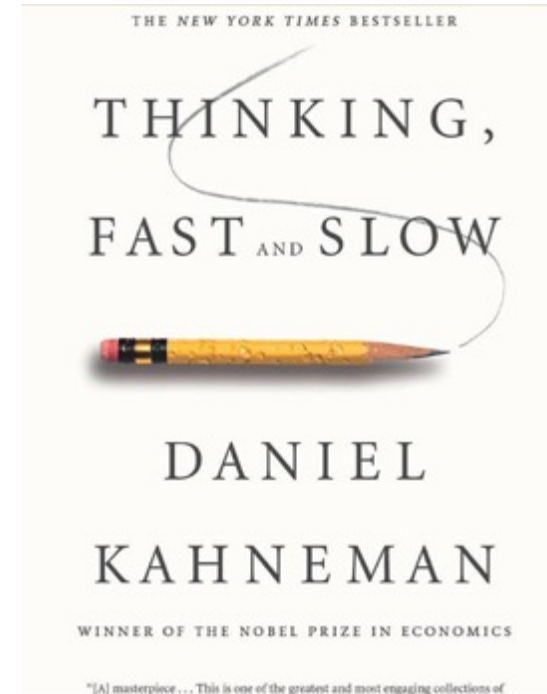
Environment of overdiagnosis

- Heightened awareness by patients and clinicians
- Pressure to diagnose melanomas early
- Fear of missing melanoma—“loss aversion”



Cognitive process also contributes to overdiagnosis

- Everyone is subject to “loss aversion”
- Fear drives our decision making
- Clinician:
 - “When in doubt, cut it out”
- Dermatopathologist:
 - When in doubt, low threshold to label lesions atypical or melanoma
- Everyone errs on the side of caution



Environment of overdiagnosis

- Screening
- Sensitive to detecting small irregularities
- Large reservoir of indolent disease
- Diagnostic test: questionable reliability

Gold Standard

Pathologic Diagnosis



OPEN ACCESS

2017 *BMJ*

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}

25%: Concordance rate for Spitz nevi and atypical nevi

45%: Concordance rate for atypical spitz tumor, severely atypical nevi, MIS

“Diagnoses spanning moderately dysplastic nevi to early stage invasive melanoma [Stage 1] were **neither reproducible nor accurate** in this large study of pathologists in the USA.”

Pathology: Diagnostic Gold Standard

- 100% subjective
- Discordance abound (particularly for thin small melanocytic lesions)

Histopathologic Diagnosis

reliable



unreliable



Categories of Melanomas

1. slow-growing melanomas

- \propto chronic sun exposure occurring on the head and neck

2. slow-growing melanomas

- \propto intermittent sun exposure and melanocytic nevi

3. fast-growing aggressive melanomas

- NOT associated with sun exposure and melanocytic nevi

4. unrecognizable melanomas

Screening usually detects slow-growing indolent cancers

Lipsker D, Engel F, Cribier B, Velten M, Hedelin G. Trends in melanoma epidemiology suggest three different types of melanoma. *British journal of dermatology* (1951). 2007;157(2):338-343.

Pampena R, Lai M, Lombardi M, et al. Clinical and Dermoscopic Features Associated With Difficult-to-Recognize Variants of Cutaneous Melanoma: A Systematic Review. *JAMA Dermatol*. 2020;156(4):430-439.

When dermatologists diagnose melanomas

- Stage 0: Melanoma in-situ
- Stage 1A: 0.16mm to 0.80 mm in depth

(earlier stage than when patients or non-dermatologists detects melanomas)

Carli P, De Giorgi V, Palli D, et al. Arch Dermatol. 2003;139:607-612.

Pennie ML, Soon SL, Risser JB, et al. Arch Dermatol. 2007;143: 488-494.

Kantor J, Kantor DE. Arch Dermatol. 2009;145: 873-876.



Fast growing + Unrecognizable melanomas

- More common in older men
- Lacks the ABCD signs of slow growing melanoma
- Nonspecific appearance
 - Misdiagnosed as BCC, seborrheic keratosis, scar, hemangioma, dermatofibroma, skin tag & inflammatory diseases
- Not amenable to screening—grows too fast + not recognizable

Liu W, Dowling JP, Murray WK, et al. Rate of growth in melanomas: characteristics and associations of rapidly growing melanomas. Arch Dermatol. 2006;142:1551-1558.

Demierre MF, Chung C, Miller DR, Geller AC. Early detection of thick melanomas in the United States: beware of the nodular subtype. Arch Dermatol. 2005;141:745-750.



Not the obligate precursor



Melanoma in-situ



Not the obligate precursor






Melanoma in-situ

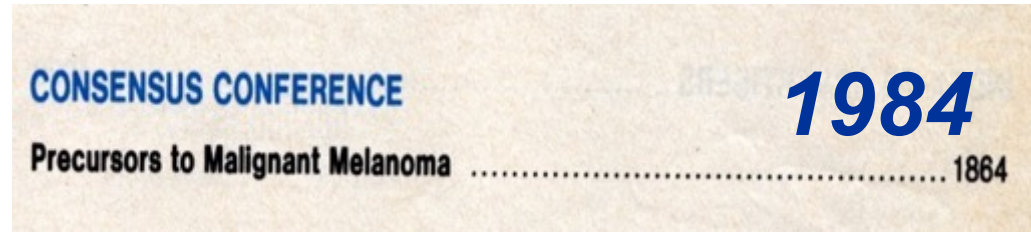


Incidence of in Situ vs Invasive Melanoma: Testing the “Obligate Precursor” Hypothesis

J Natl Cancer Inst. 2022

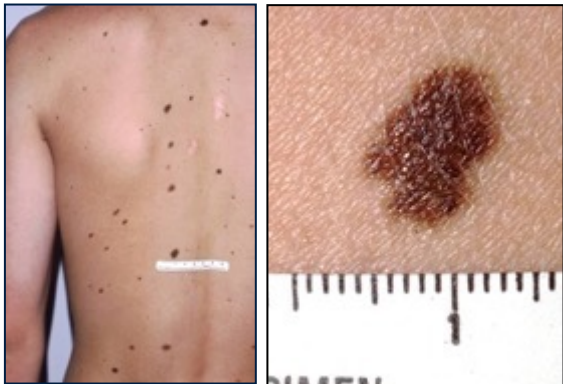
Catherine M. Olsen, PhD ^{1,2} Nirmala Pandeya, PhD ^{1,2} Philip S. Rosenberg, PhD ³

- Analyzed incidence trend in-situ and invasive melanomas 3 decades
- MIS as an obligate precursor model
 - Increase MIS should be detected earlier age than invasive melanoma
 - Decrease in thick deadly melanomas should be observed
- Findings
 - Increased MIS detection at older age than invasive melanoma
 - No decrease in thick deadly melanomas
- Conclusion
 - Questions MIS being the obligate precursor to invasive melanoma



NIH Consensus Conference: Oct. 24-26, 1983

“The panel also agreed that the **dysplastic nevus**, a distinctive lesion both clinically and histologically, has been identified in this context, particularly in melanoma families. Dysplastic nevi are both markers and precursors for melanoma. Melanoma may develop also in congenital nevi, especially when the lesion is larger than 20 cm.” (page 1864)



Jul 2012

CONTINUING MEDICAL EDUCATION

The dysplastic nevus: From historical perspective to management in the modern era

Part I. Historical, histologic, and clinical aspects

Conclusion

- ✓ Marker for high-risk individual
- ✓ Not a precursor



Histologic Outcomes of Excised Moderate and Severe Dysplastic Nevi

Derm Surg 2014

MARIA V. ABELLO-POBLETE, MD, LILIA M. CORREA-SELM, MD, DANIELLE GIAMBRONE, BS, FRANK VICTOR, MD, FAAD, AND BABAR K. RAO, MD, FAAD*

Outcomes of Biopsies and Excisions of Dysplastic Acral Nevi: A Study of 187 Lesions

Derm Surg 2014

TARA BRONSNICK, BA,* NADEEM KAZI,[†] A. YASMINE KIRKORIAN, MD,* AND BABAR K. RAO, MD*

A nongrading histologic approach to Clark (dysplastic) nevi: A potential to decrease the excision rate

Daniel F. Lozeau, MD, Michele J. Farber, MD, and Jason B. Lee, MD
Philadelphia, Pennsylvania

JAAD 2016

JAMA Dermatology | [Original Investigation](#)

Reexamining the Threshold for Reexcision of Histologically Transected Dysplastic Nevi

JAMA Derm 2016

JAMA Dermatology | [Original Investigation](#)

Risk of Subsequent Cutaneous Melanoma in Moderately Dysplastic Nevi Excisionally Biopsied but With Positive Histologic Margins

JAMA Derm 2018

Re-excision studies

- These studies showed none to very low association with melanoma when dysplastic nevi are re-excised
- Recommendation is to monitor and not re-excise

Annual Transformation Rate of Nevus to Melanoma

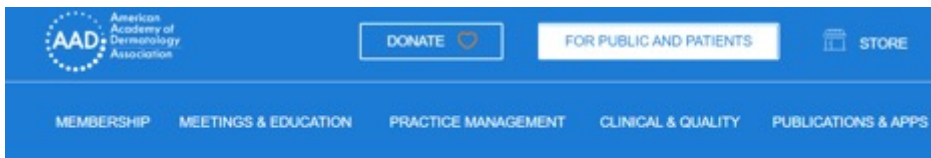
Too low to remove or monitor

- <1 in 200,000 (age less than 40)
- 1 in 33,000 (age greater than 60)

Efforts to minimize re-excision of dysplastic nevi

AAD Effort

WHO



Mildly Atypical Dysplastic Nevi – Appropriate Non-Excision

Description: Percentage of procedures with histologically proven dysplastic nevus/mild atypia that are NOT excised by the biopsying physician and are NOT referred to others for excision.

Measure ID: AAD13

Type: Process/Overuse

CMS Derm Specialty Set: N/A

High priority: Yes

Topped out: No

Telehealth Eligible: No

Reporting methods: Registry/QCDD

Maximum points: 7

Measure purpose: This measure aims to reduce the excision of mildly dysplastic nevus/mild atypia.

Table 1. Nuclear features in the varying grades of dysplasia^a

WHO Classification	Former grade	Nuclear size vs resting basal cells	Chromatin	Variation in nuclear size and shape	Nucleoli
Not a dysplastic naevus	0 (Mild dysplasia)	1x	May be hyperchromatic	Minimal	Small or absent
Low grade dysplasia	1 (Moderate dysplasia ^a)	1-1.5x	Hyperchromatic or dispersed chromatin	Prominent in a small minority of cells (random atypia)	Small or absent
High grade dysplasia	2 (Severe dysplasia ^a)	≥ 1.5x	Hyperchromatic, coarse granular chromatin, or peripheral condensation	Prominent in a larger minority of cells	Prominent, often lavender

^aArchitectural features are required for the diagnosis of dysplasia (see Table 2) and also contribute to grade; attributes that indicate a diagnosis of high grade (severe) dysplasia, even when cytological atypia is low grade, include pagetoid scatter above the basal layer (but to a lesser degree than in melanoma, usually not above the middle third, and focal, i.e. contained within an area <0.5mm²), focal continuous basal proliferation, and intraepidermal mitoses (any dermal mitosis or anything more than a rare mitosis should raise concern for melanoma).

Low & High grade only classification of dysplastic nevi

<https://www.aad.org/member/practice/mips/measures/2022/aa d13> (not 2023)

Elder DE, Massi D, Scolyer RA, Willemze R, editors (2018). WHO classification of skin tumours. 4th Ed. Lyon: IARC

Table of Contents: Melanocytic Nevi & Melanoma

1. Brief Historical Perspective
2. Current Environment of Diagnosis
3. Illustrative Cases

Case 1

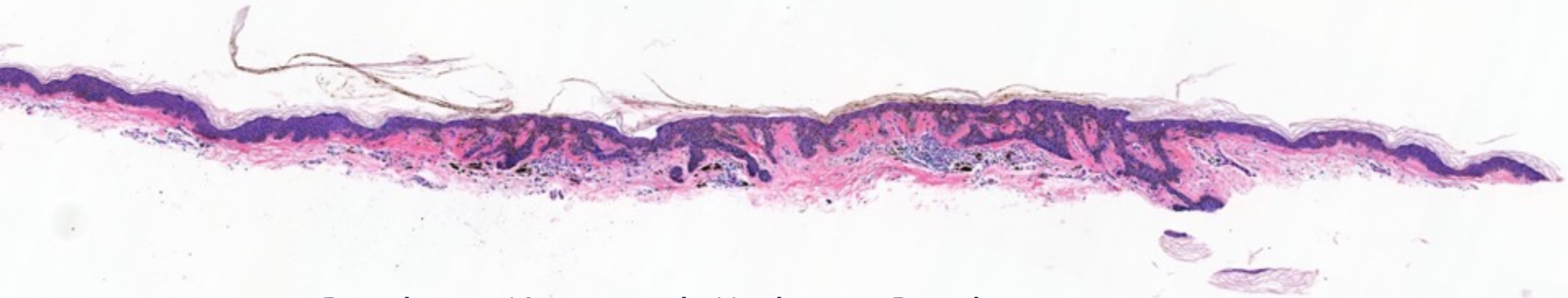
Hip, left (Skin)

Clinical Diagnosis: MELANOCYTIC NEVUS R/O ATYPIA

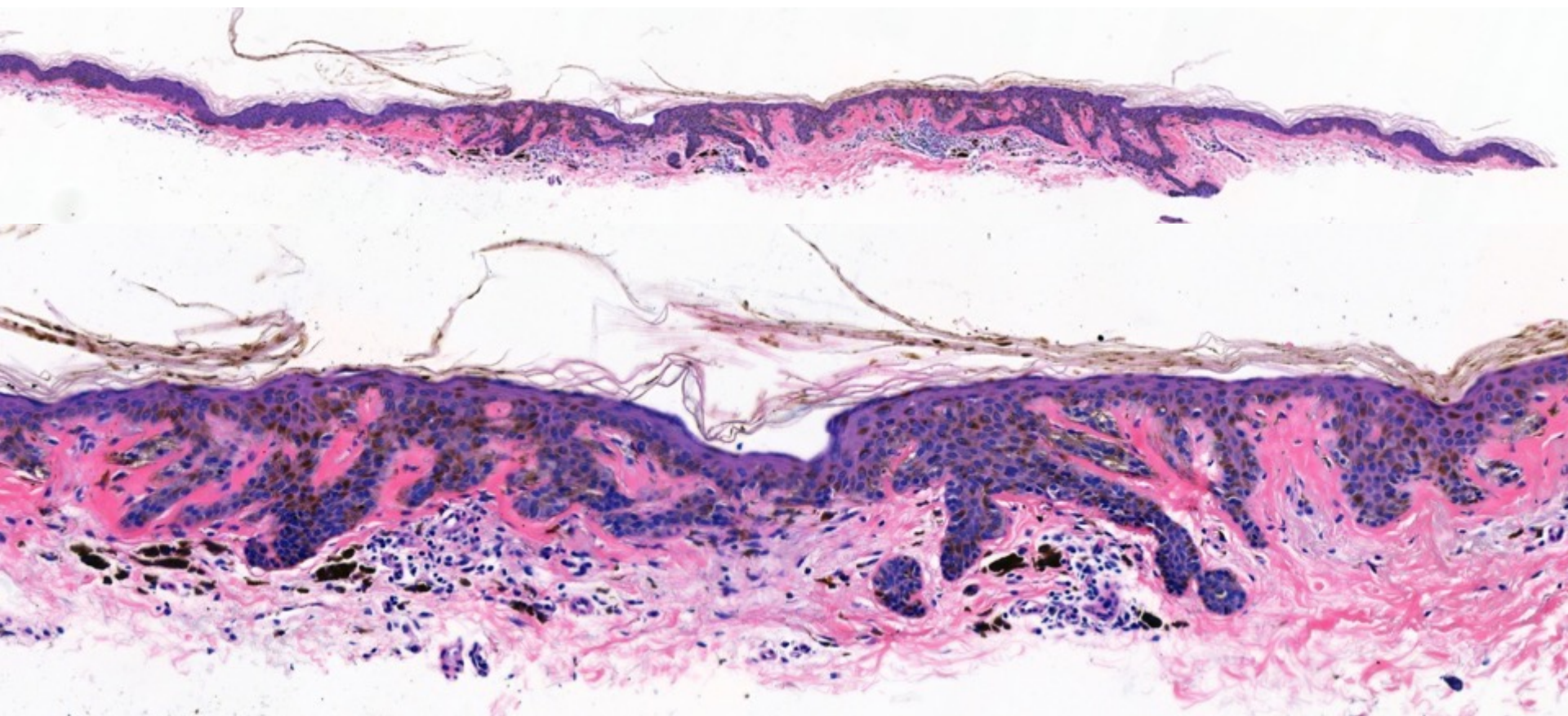
Clinical Description:

Gross Description: Received in a formalin-containing bottle is a cylindrical piece of skin and adipose tissue measuring 0.4 by 0.4 by 0.2 cm. The specimen is submitted entirely in a single cassette. Due to shrinkage, measurements may be different than those at time of procedure.

ICD-10: D48.5



Dysplastic Nevus with Moderate Dysplasia
Excision Recommended



Junctional Clark Nevus



OPEN ACCESS

2017 *BMJ*

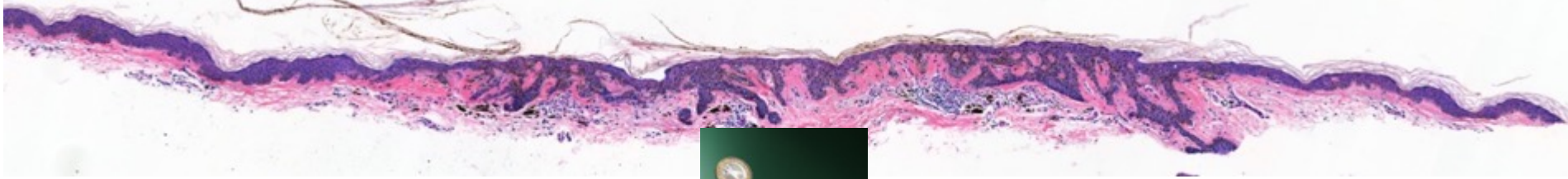
Pathologists' diagnosis of invasive melanoma and melanocytic proliferations: observer accuracy and reproducibility study

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}

25%: Concordance rate for Spitz nevi and atypical nevi

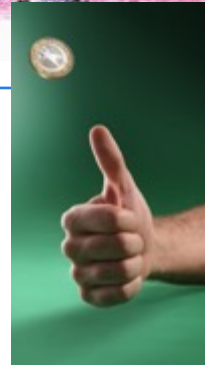
45%: Concordance rate for atypical spitz tumor, severely atypical nevi, MIS

“Diagnoses spanning moderately dysplastic nevi to early stage invasive melanoma [Stage 1] were **neither reproducible nor accurate** in this large study of pathologists in the USA.”



Nevus

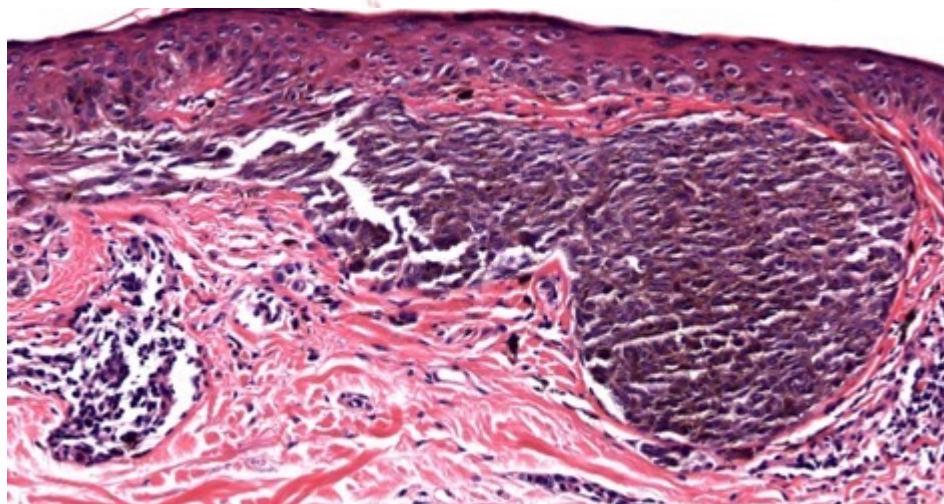
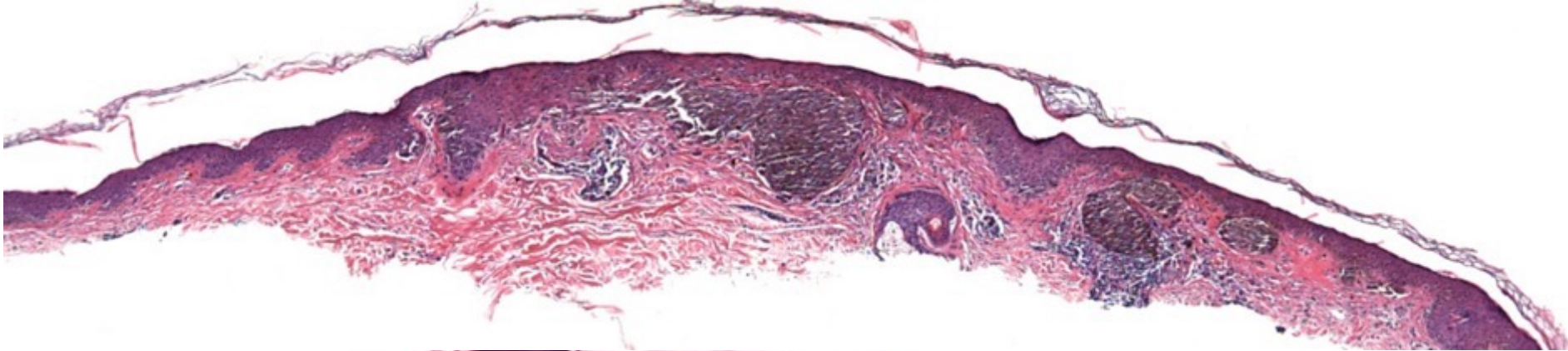
Nevus
Moderate
Atypia



Nevus
Severe
Atypia

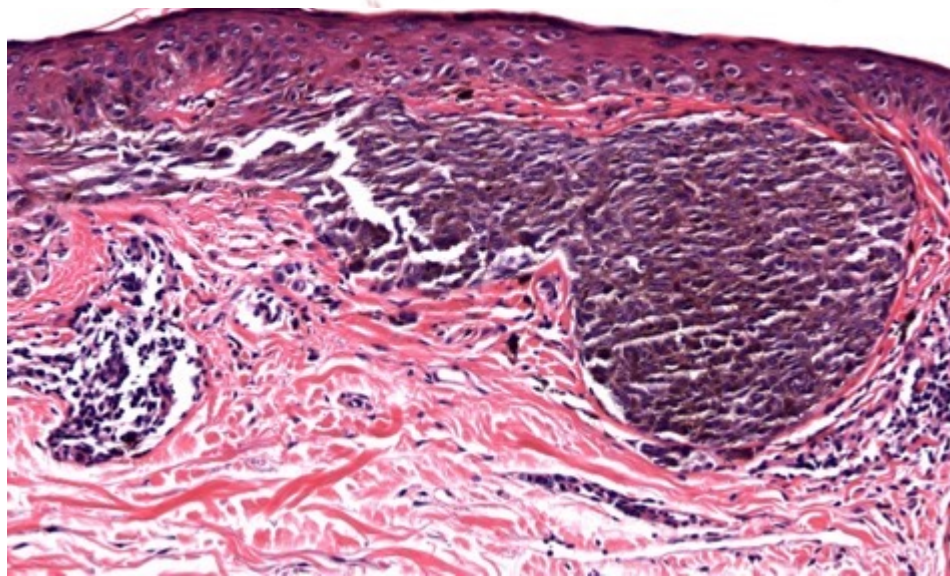
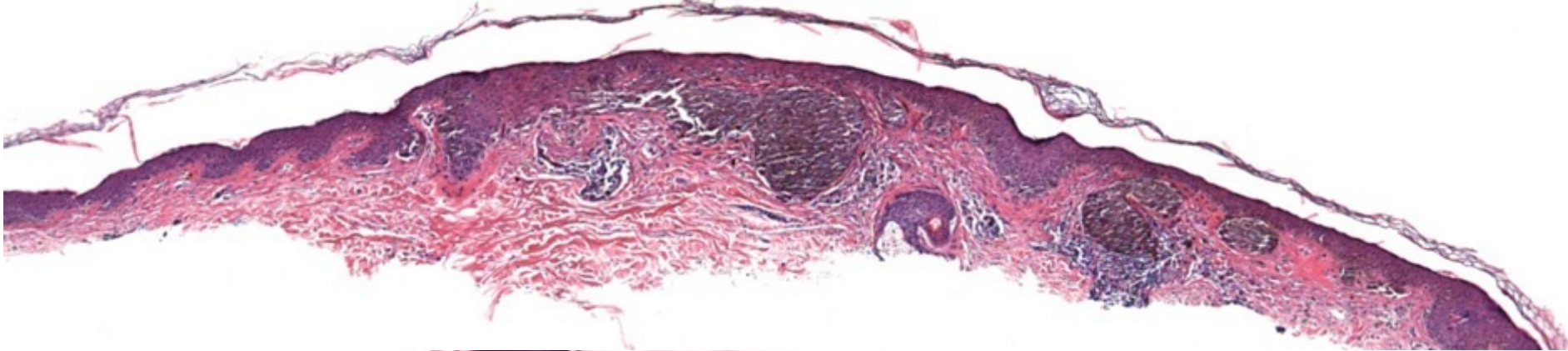
Melanoma in-situ

Biopsies of small FLAT melanocytic lesions (<5mm) is subject to a diagnostic gold standard that has questionable reliability



DIAGNOSIS: - RIGHT SHOULDER

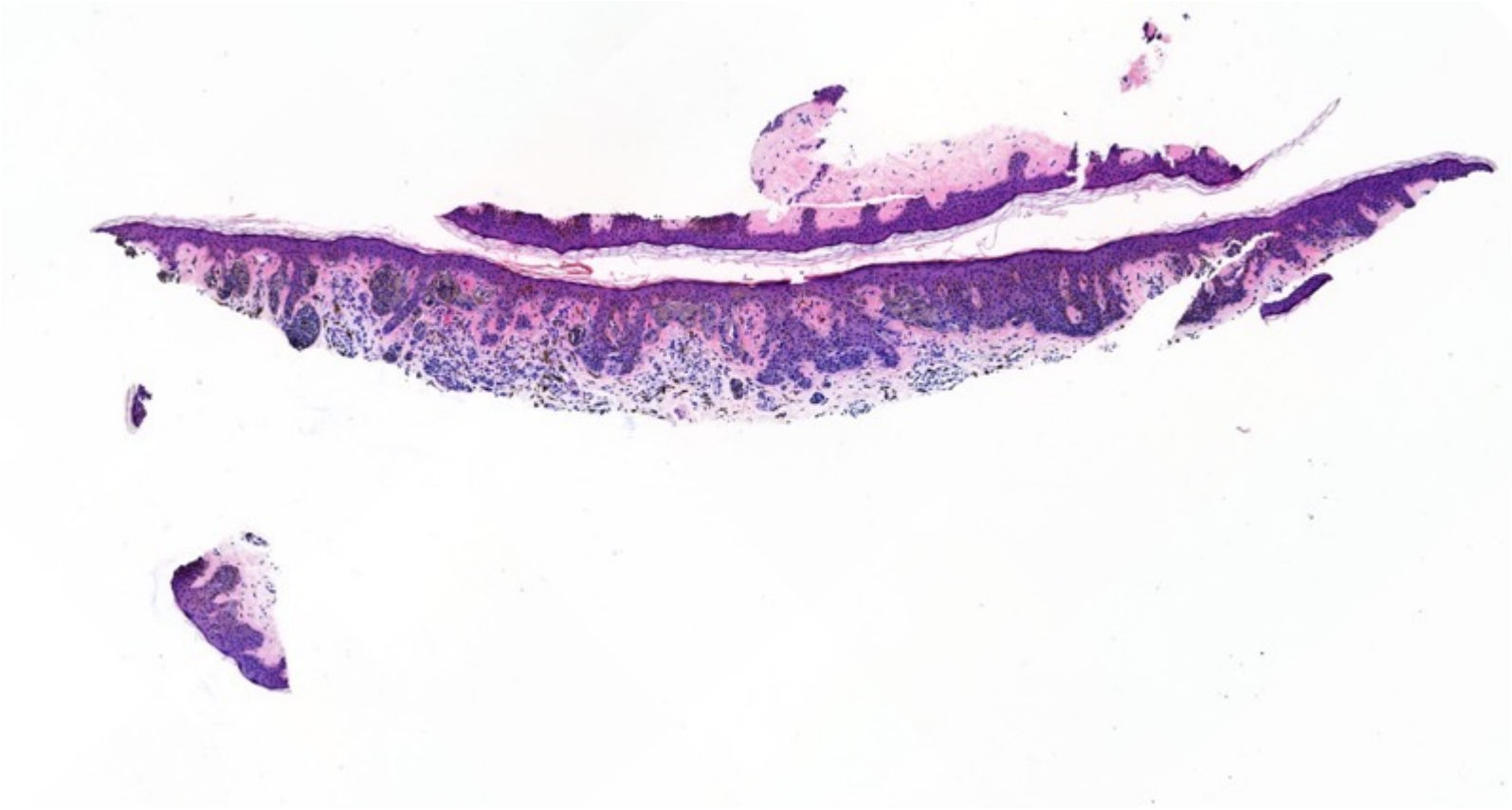
MELANOCYTIC NEVUS, COMPOUND TYPE WITH ARCHITECTURAL AND CYTOLOGIC ATYPIA, SEVERE (DYSPLASTIC NEVUS), WITH REGRESSION, SEE DESCRIPTION

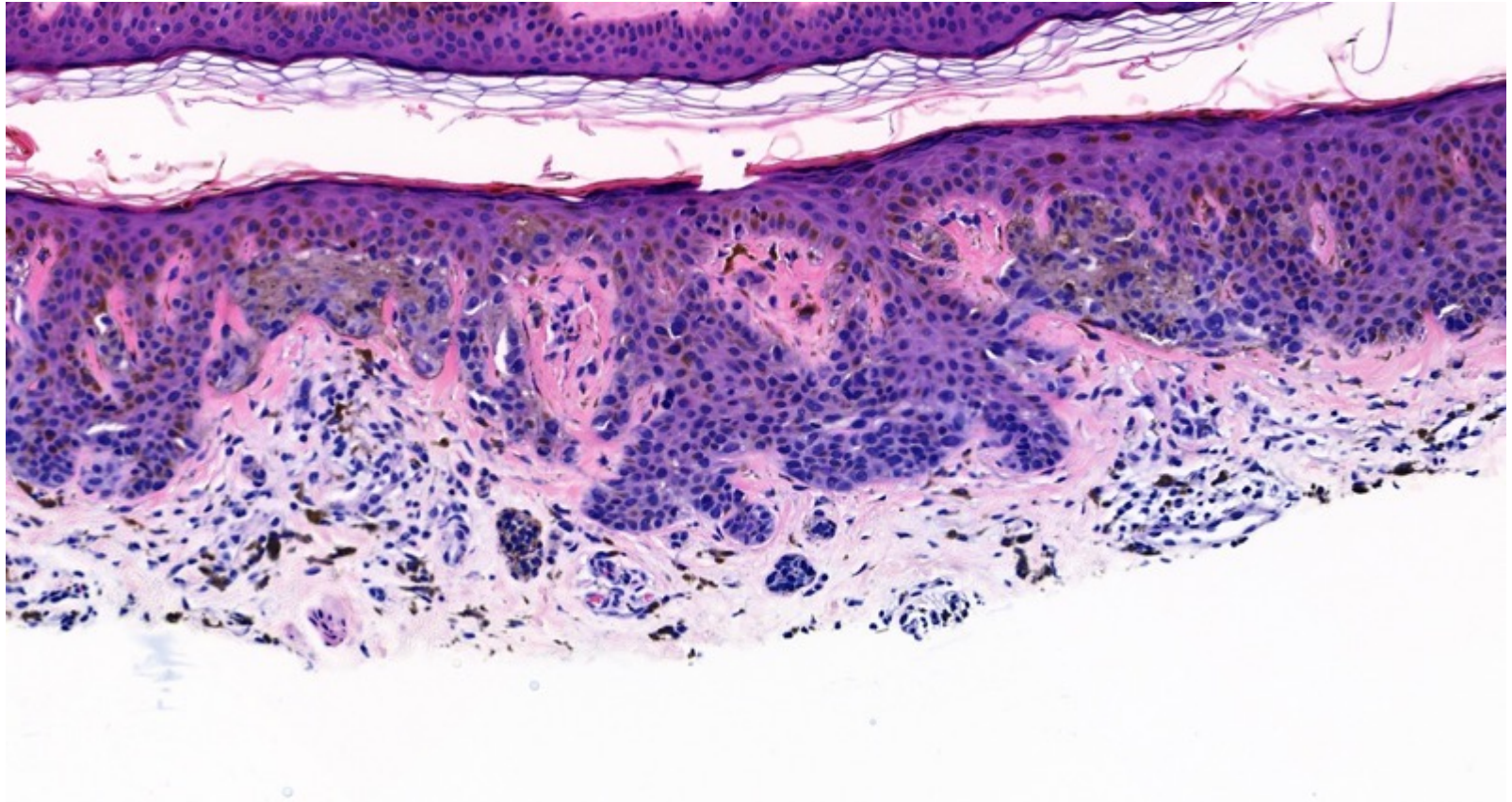


Compound Melanocytic Nevus, Clark

Case 2

51 yo woman, back





Part B: SKIN BIOPSY, MID BACK:

COMPOUND MELANOCYTIC NEVUS OF THE SKIN WITH ARCHITECTURAL DISORDER AND SEVERE CYTOLOGIC ATYPISM OF THE MELANOCYTES. (DYSPLASTIC NEVUS, SEVERE).

MARGINS ARE INVOLVED. A COMPLETE LOCAL EXCISION IS ADVISED WITH 5 MM LESION FREE MARGINS.

B. Back, Mid, : ***Compound Melanocytic Nevus, Clark***
There was no atypia noted within the specimen.

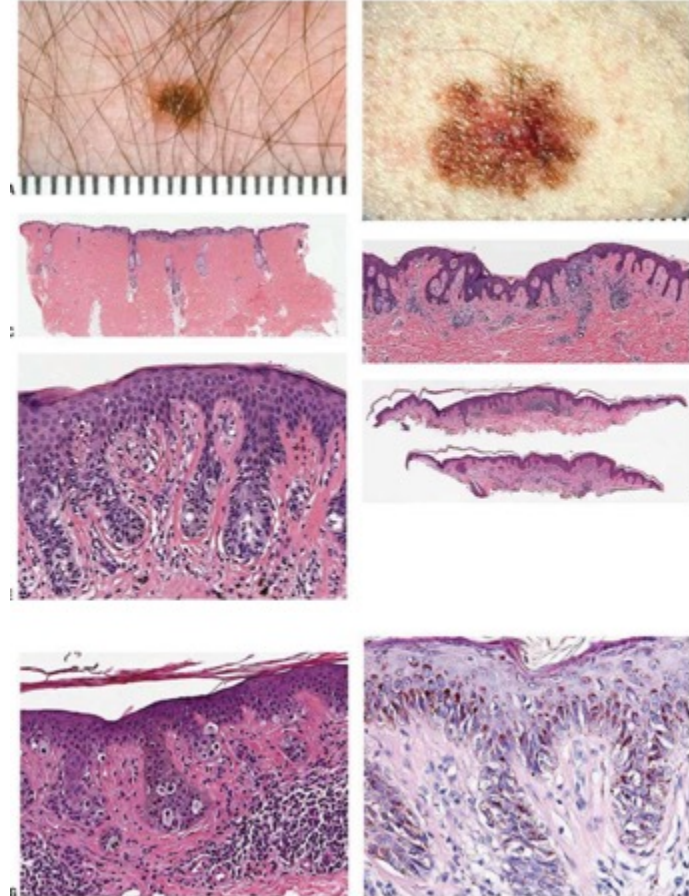
Dysplastic/Atypical/Clark Melanocytic nevus



Histopathologic Criteria for *Dysplastic Nevus*

1. Lentiginous hyperplasia
2. Bridging of rete-ridges
3. Lamellar and concentric fibroplasia
4. Lymphocytic infiltrate
5. Intradermal component, when present confined to the expanded papillary dermis in the center of the lesion
6. Random cytologic atypia greater than 10%

- **Grading of cytology:** mild, moderate, severe
- **Grading of architecture:** mild, moderate, severe

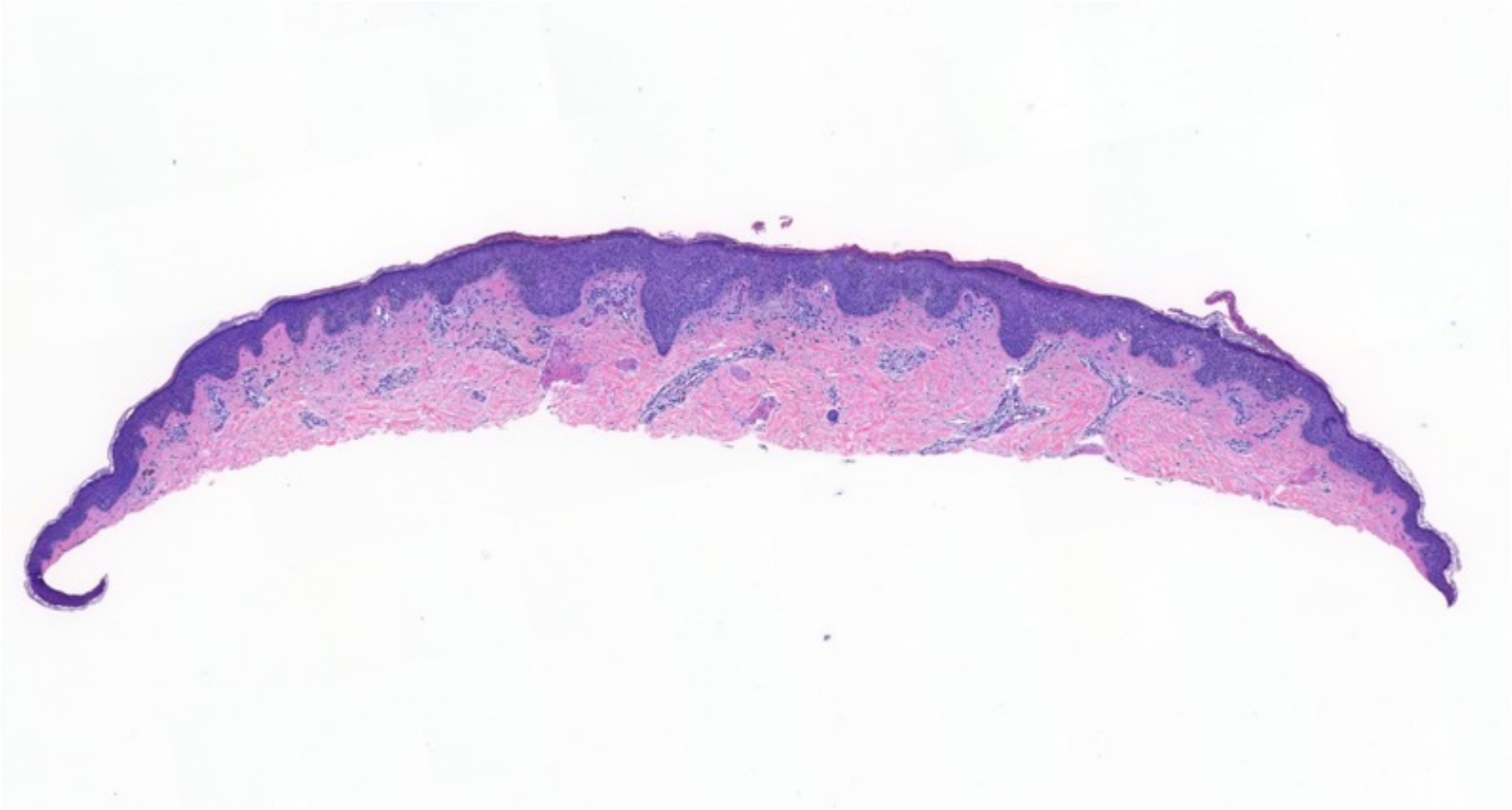


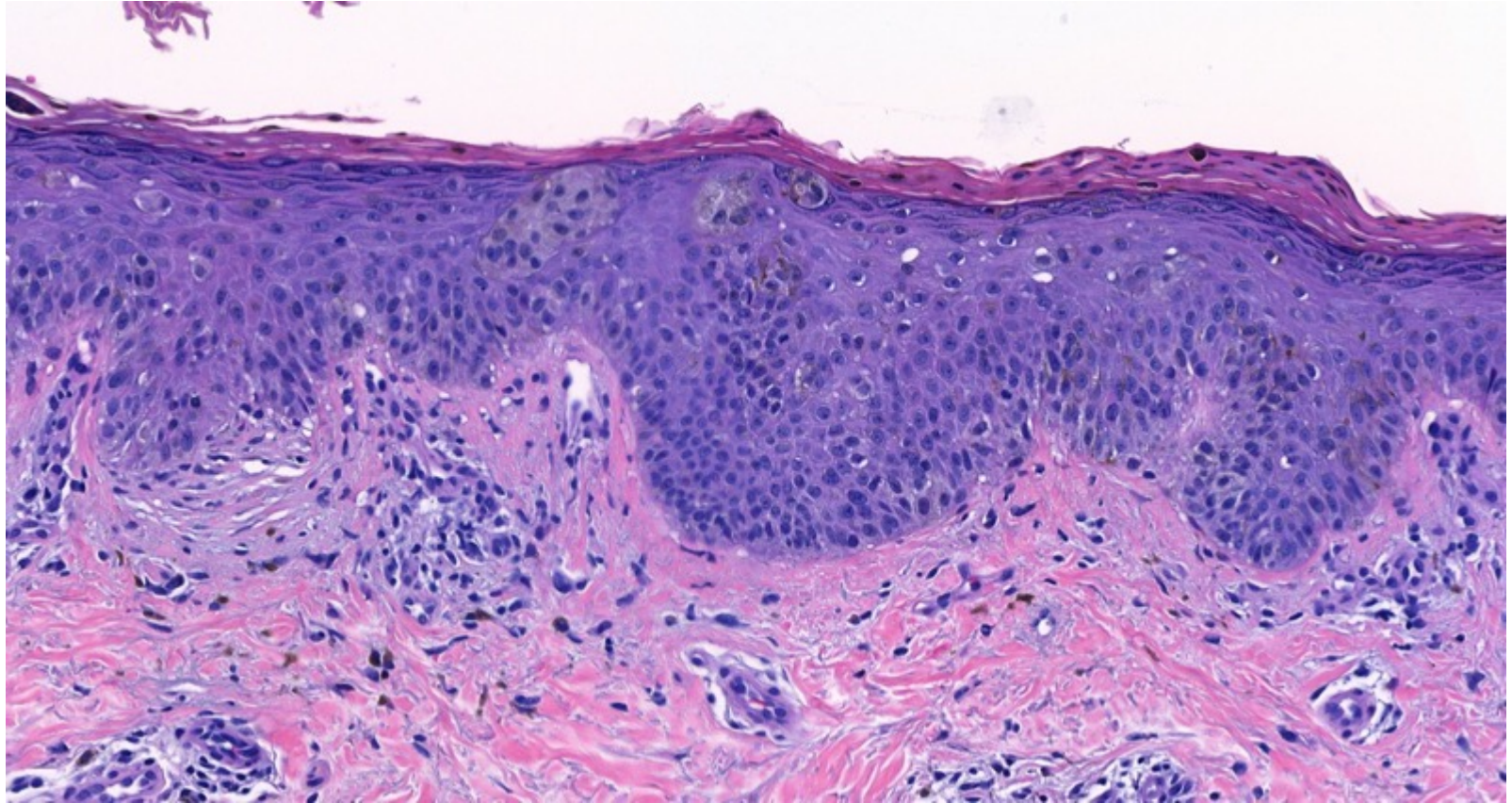
Dysplastic/Atypical/Nevus

- None to minimal association with melanoma
- Most common type of nevus on Caucasian skin
- Pivoting away from aggressive diagnosis and management
- Histopathology
 - Nested and solitary melanocytes at the DE junction
 - Allow for
 - some uneven distribution melanocytes
 - site specific variation
 - cytology varies widely and is usually larger than the background melanocytes

Case 3

28 yo woman, forearm lesion





DERMATOPATHOLOGY REPORT

Dermatopathology (Final result)

DP21-08415

Authorizing Provider:	████████████████████	Ordering Provider:	
Ordering Location:	Jefferson Dermatology Center	Collected:	05/17/2021 05:46 PM
	City		
Pathologist:	Jason B Lee, MD	Received:	05/19/2021 06:06 PM

Diagnosis

Right forearm: **Junctional Melanocytic Nevus, Spitz, Pigmented (Reed Nevus) with Atypical Features**

Melan A immunohistochemical stain revealed the scatter of melanocytes associated with foci of prominent parakeratosis and serous crust. The marked scatter is most likely due to trauma at this site. Because of the significant scatter, excision of the lesion margins that include normal unscarred skin is recommended. The proliferation EXTENDS to peripheral margins.

Electronically signed by Jason B Lee, MD on 5/21/2021 at 5:16 PM

FINAL REPORT (08/11/22)

Diagnosis:

Right forearm - RESIDUAL MELANOMA IN-SITU, FOCALLY SPITZOID (SEE NOTE)

Note:

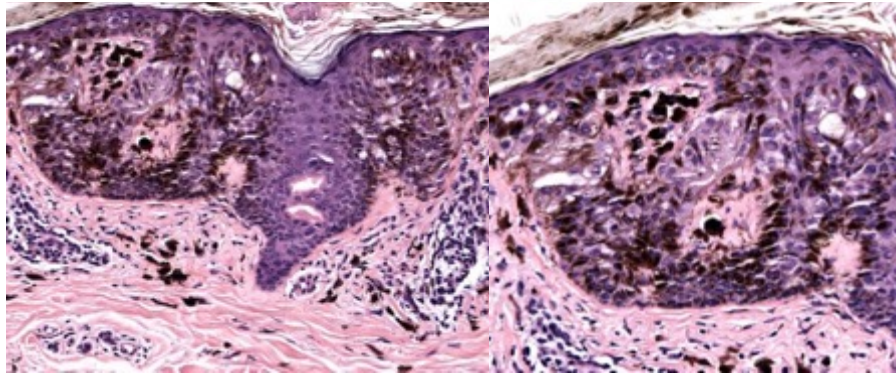
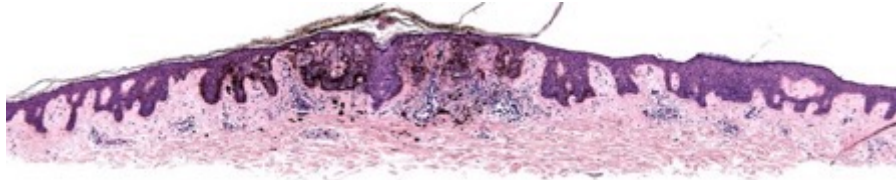
Prior to reviewing the original sections, the differential diagnosis was between pseudo-melanoma in-situ (residual atypical Spitz nevus with the melanomatous features secondary to previous procedure) and melanoma in-situ. In the context of the re-excision, the previous outside sections (DP21-08415 Jefferson Dermatology) are most consonant with melanoma in-situ with spitzoid features rather than an atypical Spitz nevus. A few neoplastic melanocytes on the re-excision appear to be in the dermis, however, those changes are interpreted as being secondary to tangential sectioning of melanocytes involving epithelial structures of adnexa rather than authentic neoplasm in the dermis. The lesion is completely excised in this multiply-sectioned specimen, although it extends to within just over 2 mm of one lateral margin from approximately 9:00 to 10:00 (suture marks 12:00).

Case 4

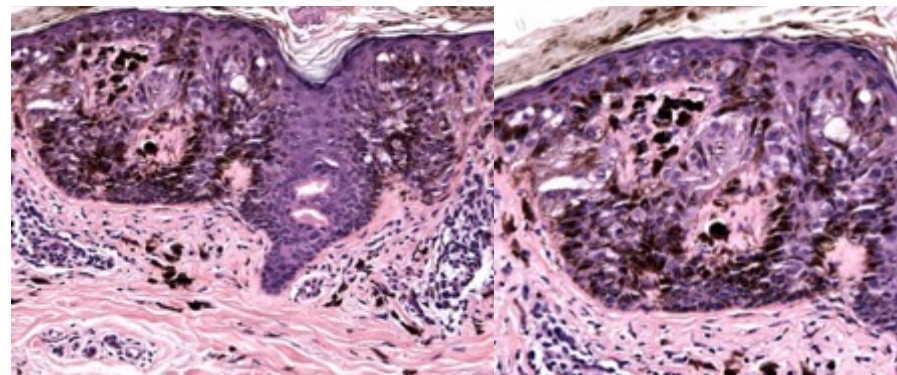
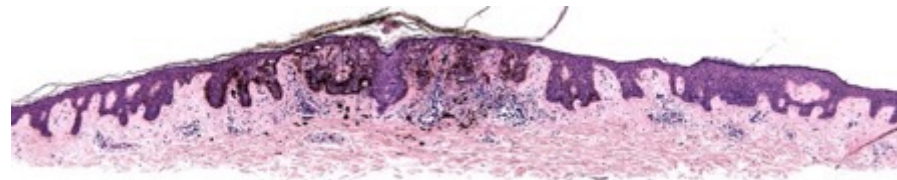
What is the diagnosis?



68 yo man



Melanoma In-Situ
(opinion of one dermatopathologist)



Pigmented Spitz Nevus
(opinion of another dermatopathologist)

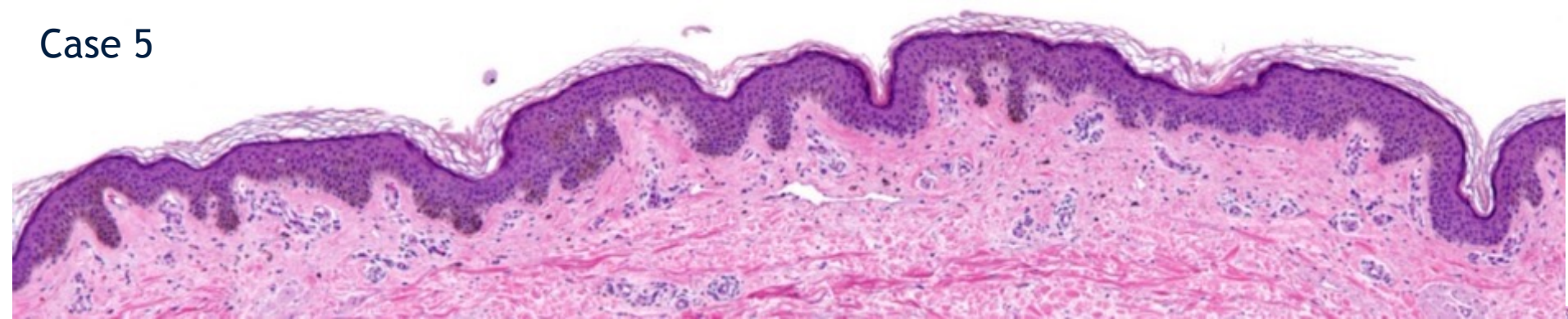
Expected site specific variation on architecture and cytology that are frequently interpreted as

atypical or melanoma

Body sites at risk of misdiagnosis as melanoma—“special site”

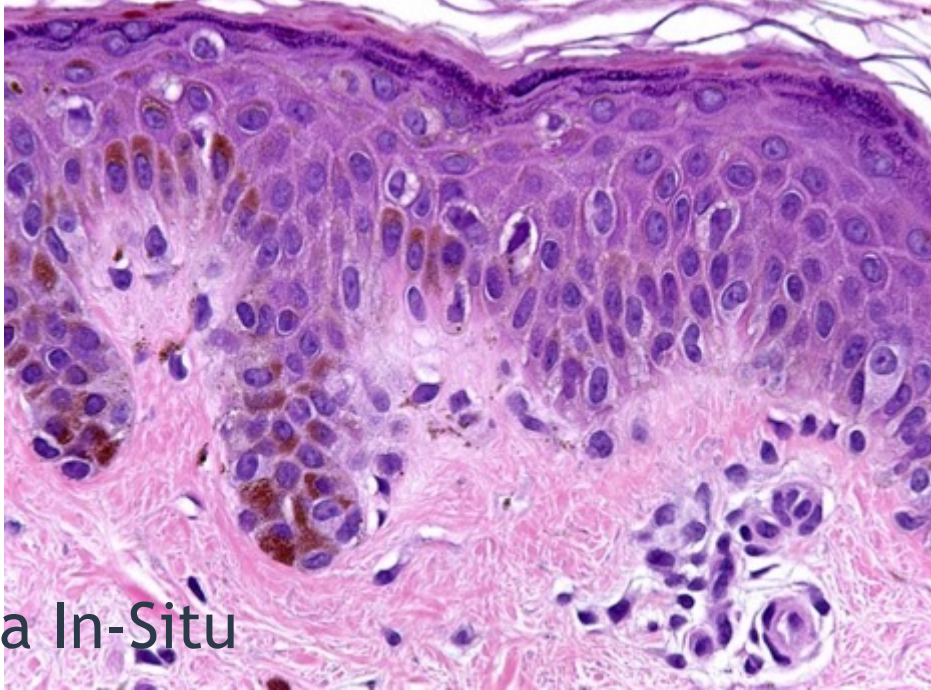
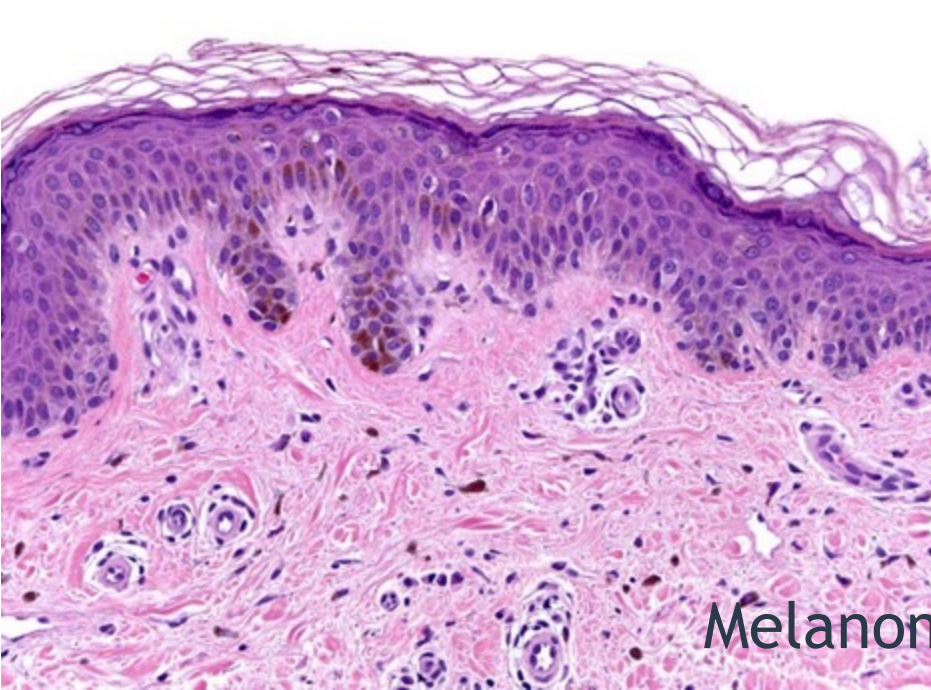
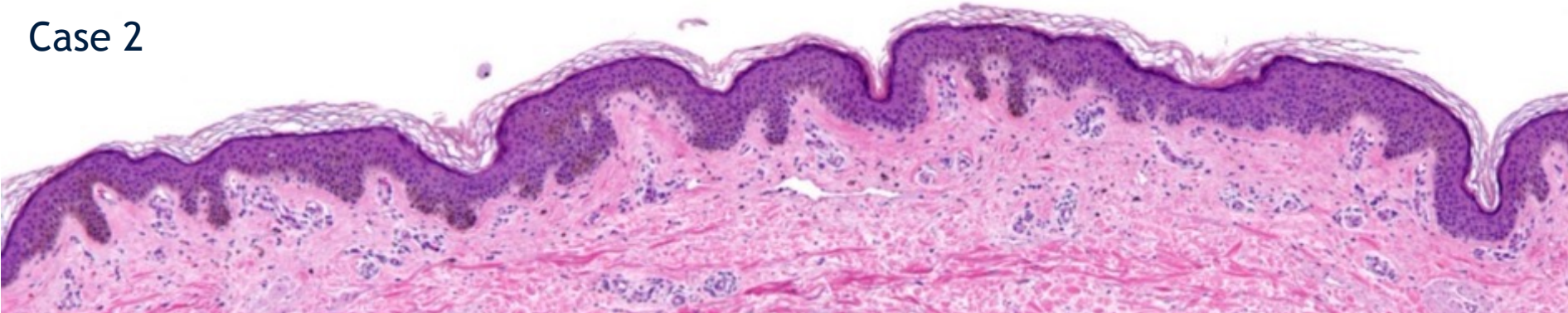
- Volar(Acral) skin
- Thigh
- Shin/Ankle
- Ear
- Breast/Milk line
- Genitalia
- Umbilicus
- Shoulder
- Scalp

Case 5



Pagetoid Cells in Pagetoid Spread

Case 2



Melanoma In-Situ

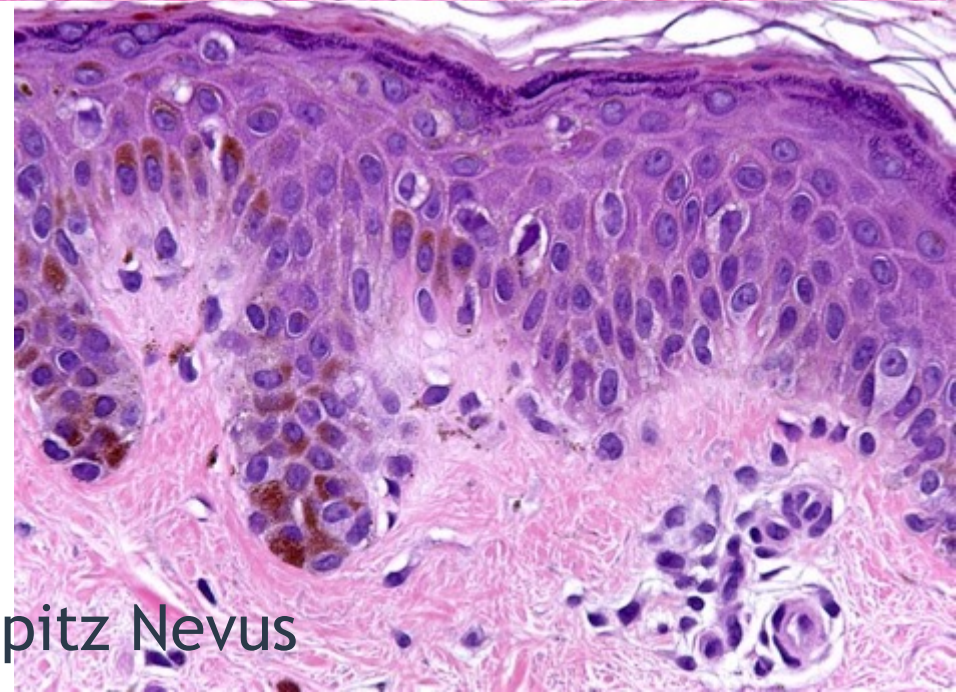
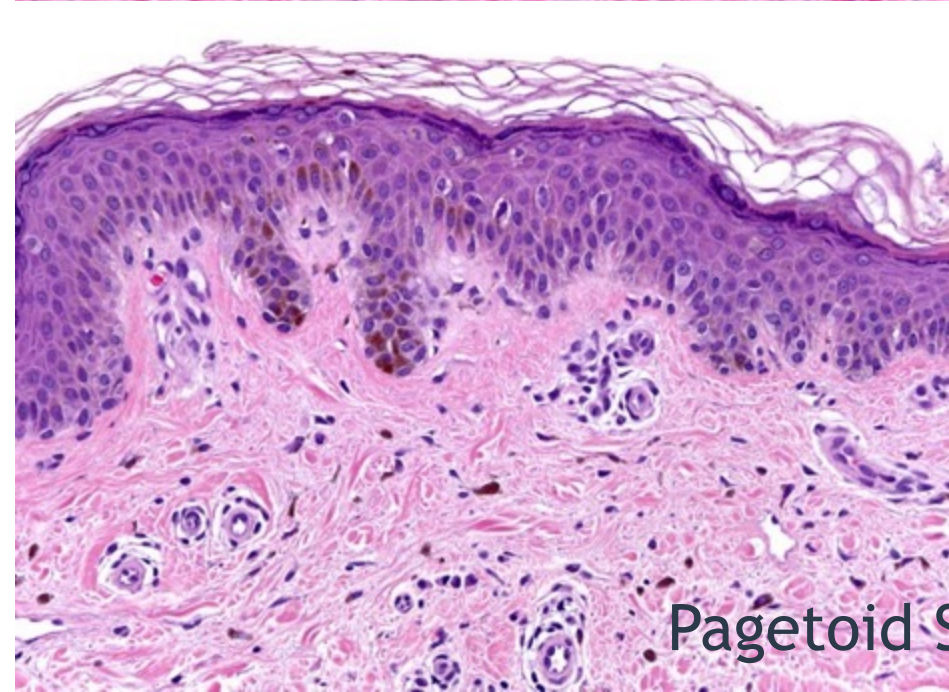
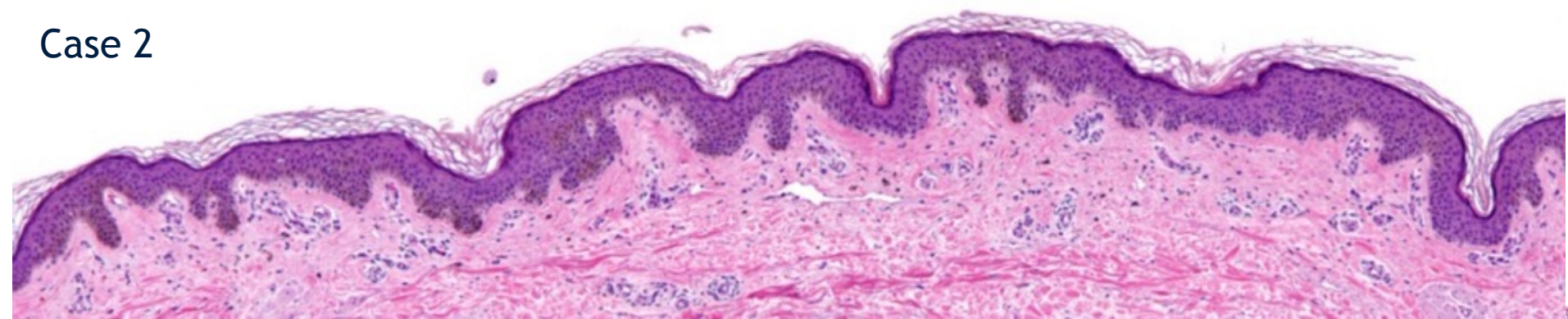


61 yo woman



Pagetoid Spitz nevus

Case 2



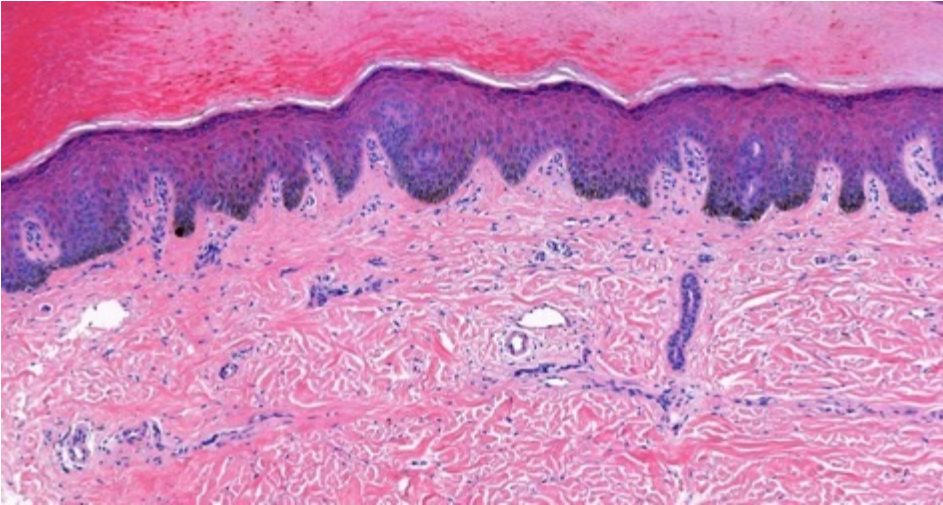
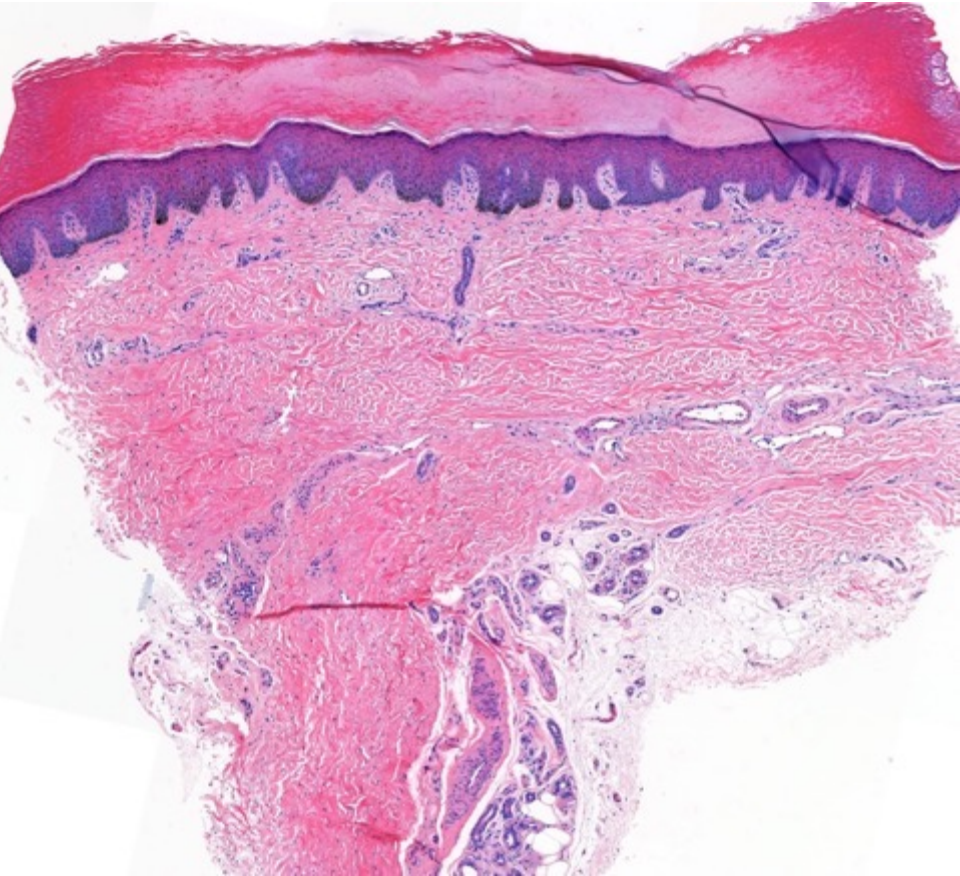
Pagetoid Spitz Nevus

Thigh nevi

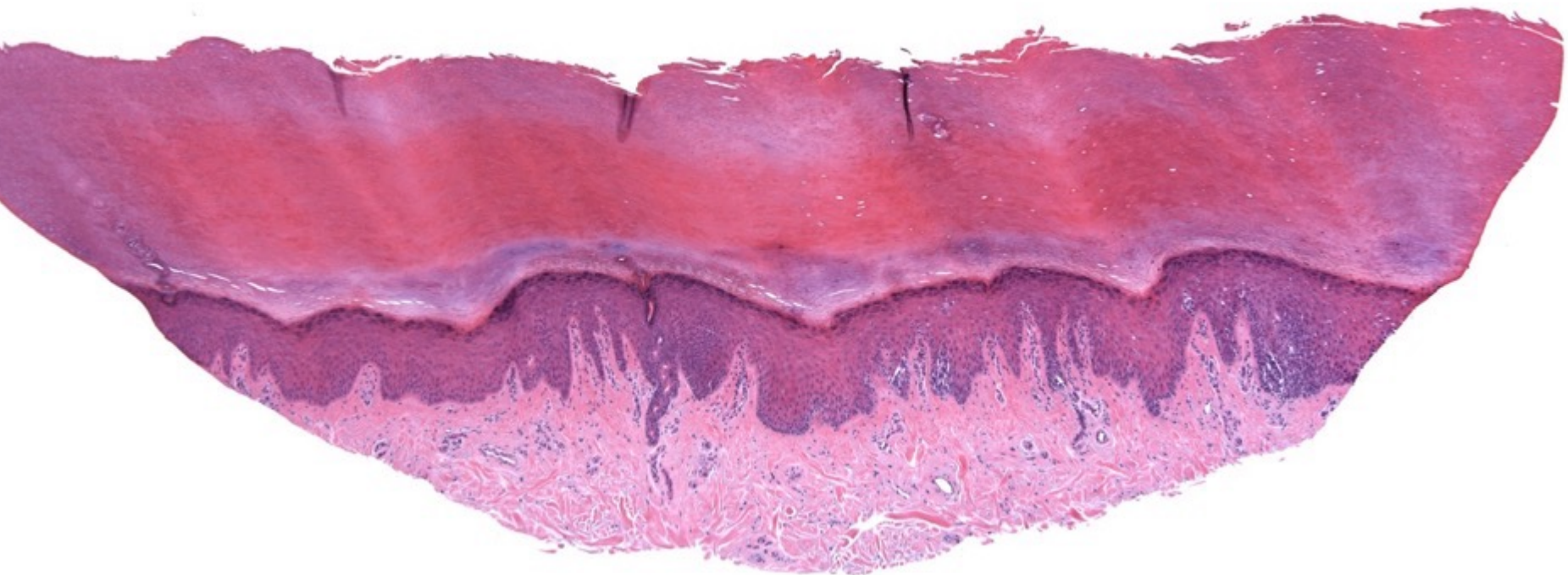
Frequent spitzoid features with some scatter

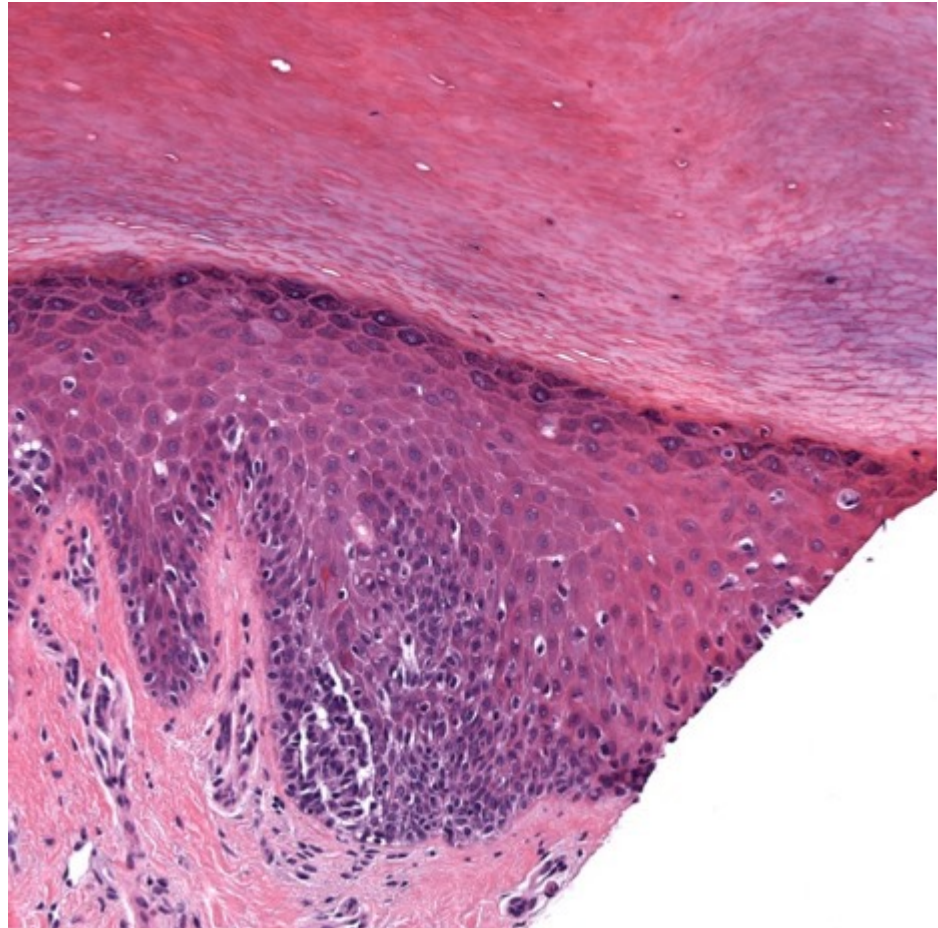
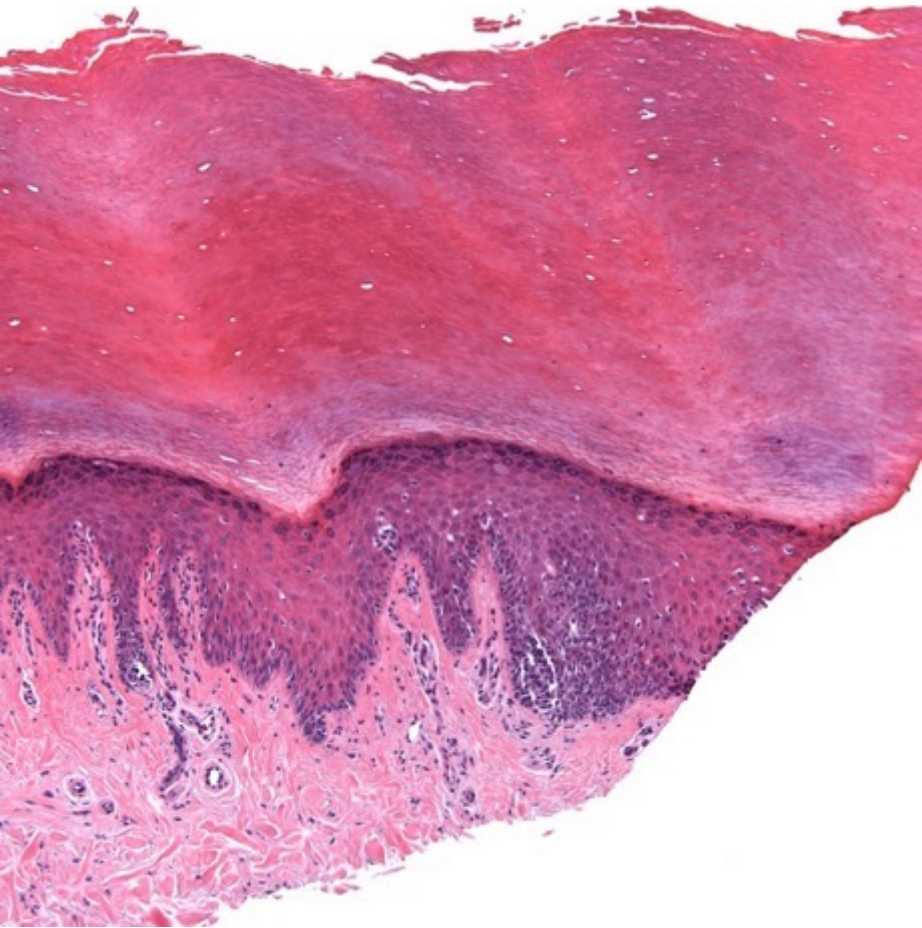
- “Spark” nevi
- Pagetoid Spitz nevi
 - Frequently found on the thigh of young and older adult women
 - Histology: solitary spitzoid melanocytes with significant scatter
 - Frequently misdiagnosed as MIS or thin melanoma
 - Benign: small, discrete, and uniform color

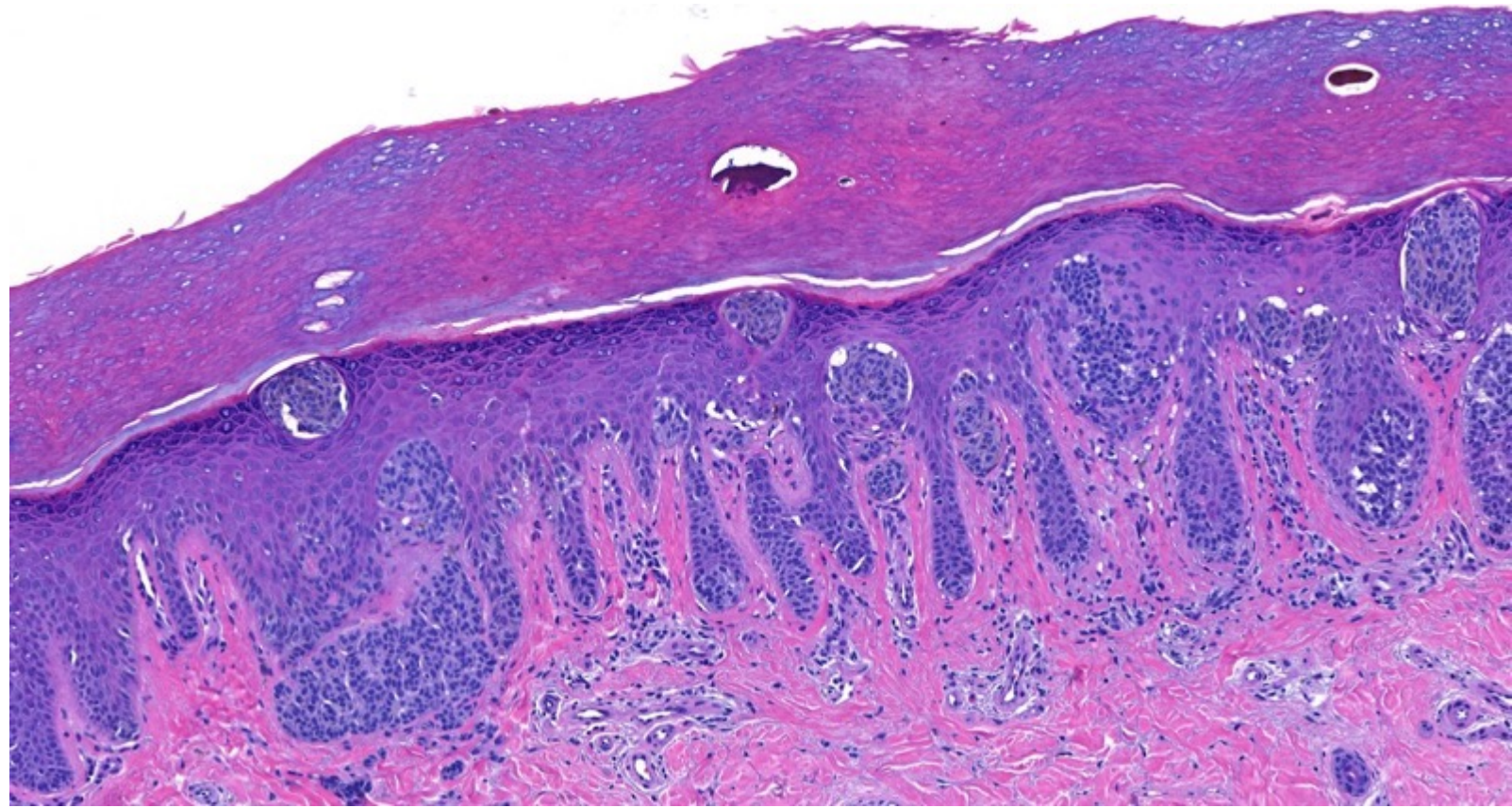
Case 6

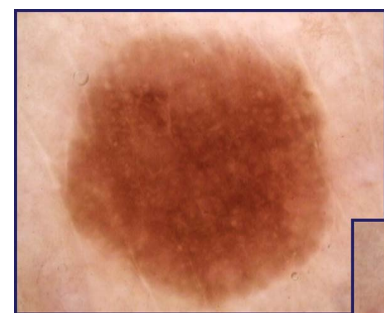
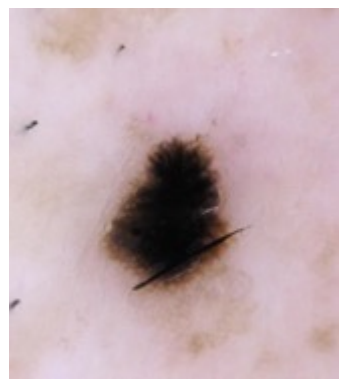


- Volar skin nevi
 - signouts are usually aggressive with excision recommendations
- This lesion is benign
 - small & discrete
 - mostly nested melanocytes are at the DE junction
 - expect mild to moderate degree of scatter of solitary melanocytes and even nests









Small discrete lesions
No clinical features of melanoma

Epidemiologic evidence of melanoma overdiagnosis is mounting

The Rapid Rise in Cutaneous Melanoma Diagnoses




H. Gilbert Welch, MD, MPH
The NEW ENGLAND JOURNAL of MEDICINE
2021

Cancer 2022

Prognostic modeling of cutaneous melanoma stage I patients using cancer registry data identifies subsets with very-low melanoma mortality

Incidence of in Situ vs Invasive Melanoma: Testing the “Obligate Precursor” Hypothesis

JNCI 2022

Catherine M. Olsen, PhD ,^{1,2} Nirmala Pandeya, PhD ,^{1,2} Philip S. Rosenberg, PhD ,³

JAMA Internal Medicine | Original Investigation 2022

Association of UV Radiation Exposure, Diagnostic Scrutiny, and Melanoma Incidence in US Counties

Adewole S. Adamson, MD, MPP; Heather Welch, MSc; H. Gilbert Welch, MD, MPH

JAMA Dermatology | Original Investigation 2022

Estimating Overdiagnosis of Melanoma Using Trends Among Black and White Patients in the US

MELANOCYTIC TUMOUR PATHOLOGY

Diagnostic error, uncertainty, and overdiagnosis in melanoma

Pathology 2023

EPIDEMIOLOGY

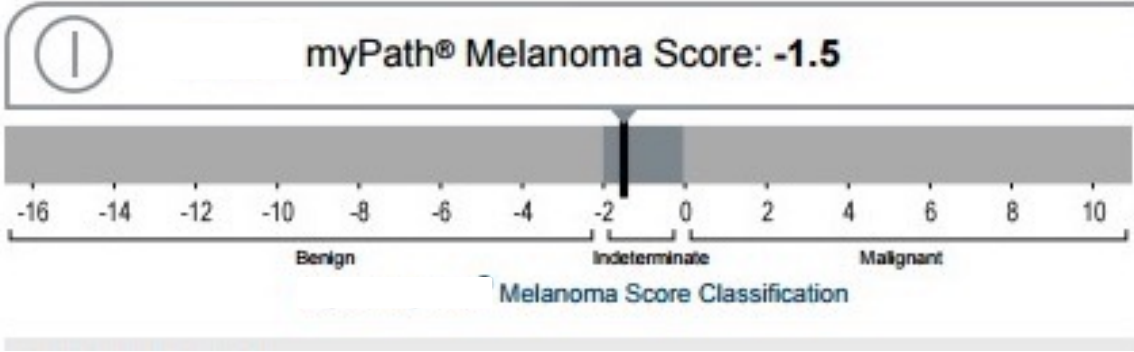
The effect of screening on melanoma incidence and biopsy rates*

2022 BJD
British Journal of Dermatology

Era of Molecular Testing:

1. Derm Tech Pigmented Lesion Assay [Gene Expression Profiling (qRT-PCR)]
2. MyPath ® & Decision Dx DiffDx-Melanoma™ [Gene Expression Profiling (qRT-PCR)] Prognostication
3. Fluorescence In-Situ Hybridization (FISH) Multiprobe Assay
4. Array Comparative Genomic Hybridization (aCGH)
5. Decision Dx-Melanoma™ [Gene Expression Profiling (qRT-PCR)]
6. Caris Lifesciences: NGS mutational analysis for diagnosis & treatment

myPath® [GEP (qRT-PCR)]



+ score: melanoma

- score: nevus

0 to 2: gray zone

23 genes includes PRAME

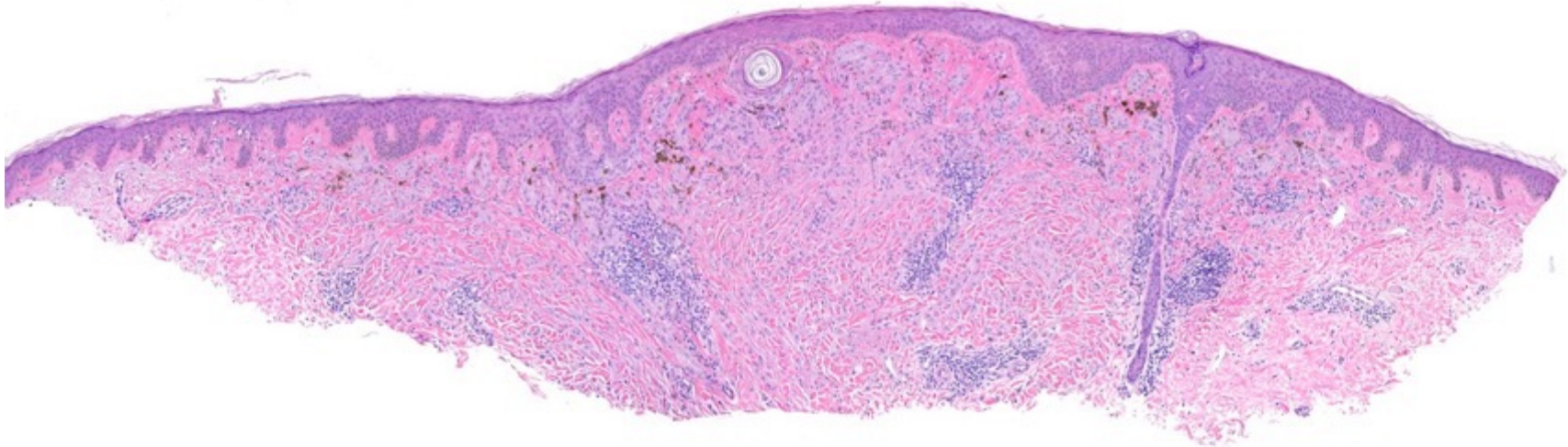
PRAME: Preferentially expressed antigen in melanoma

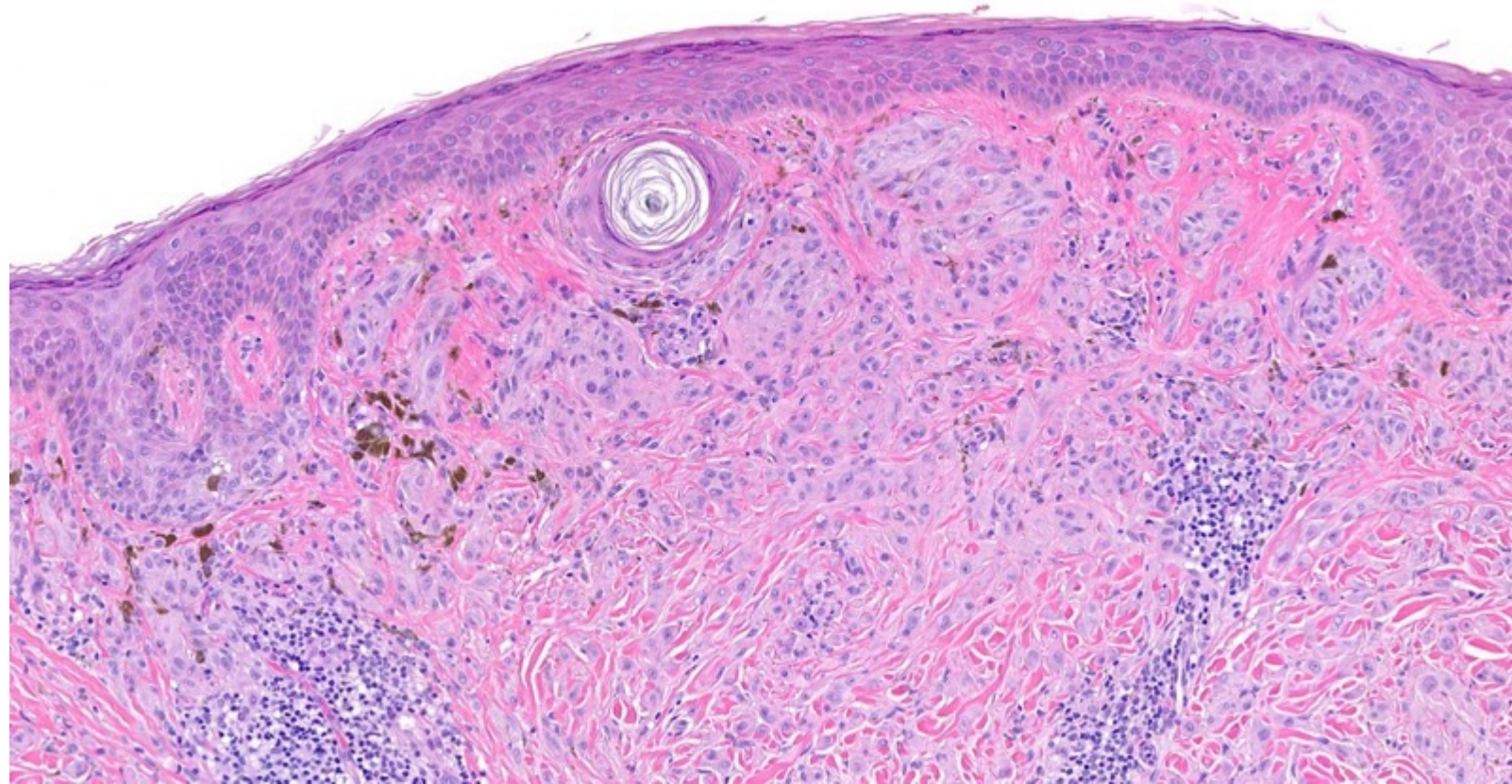
- PRAME used in several gene expression profiling tests
 - DermTech PLA: guidance on the decision to biopsy
 - Decision Dx-UM: uveal melanoma prognosis
 - myPath Melanoma: cutaneous melanocytic lesions
- PRAME IHC
 - Sensitivity: 67%-83%
 - Specificity: 93%-97%

- O'Connor MK, Dai H, Fraga GR. PRAME immunohistochemistry for melanoma diagnosis: A STARD-compliant diagnostic accuracy study. *J Cutan Pathol*. 2022;49(9):780-786. doi:10.1111/cup.14267
- Lezcano C, Jungbluth AA, Nehal KS, Hollmann TJ, Busam KJ. PRAME Expression in Melanocytic Tumors. *The American journal of surgical pathology*. 2018;42(11):1456-1465. doi:10.1097/PAS.0000000000001134

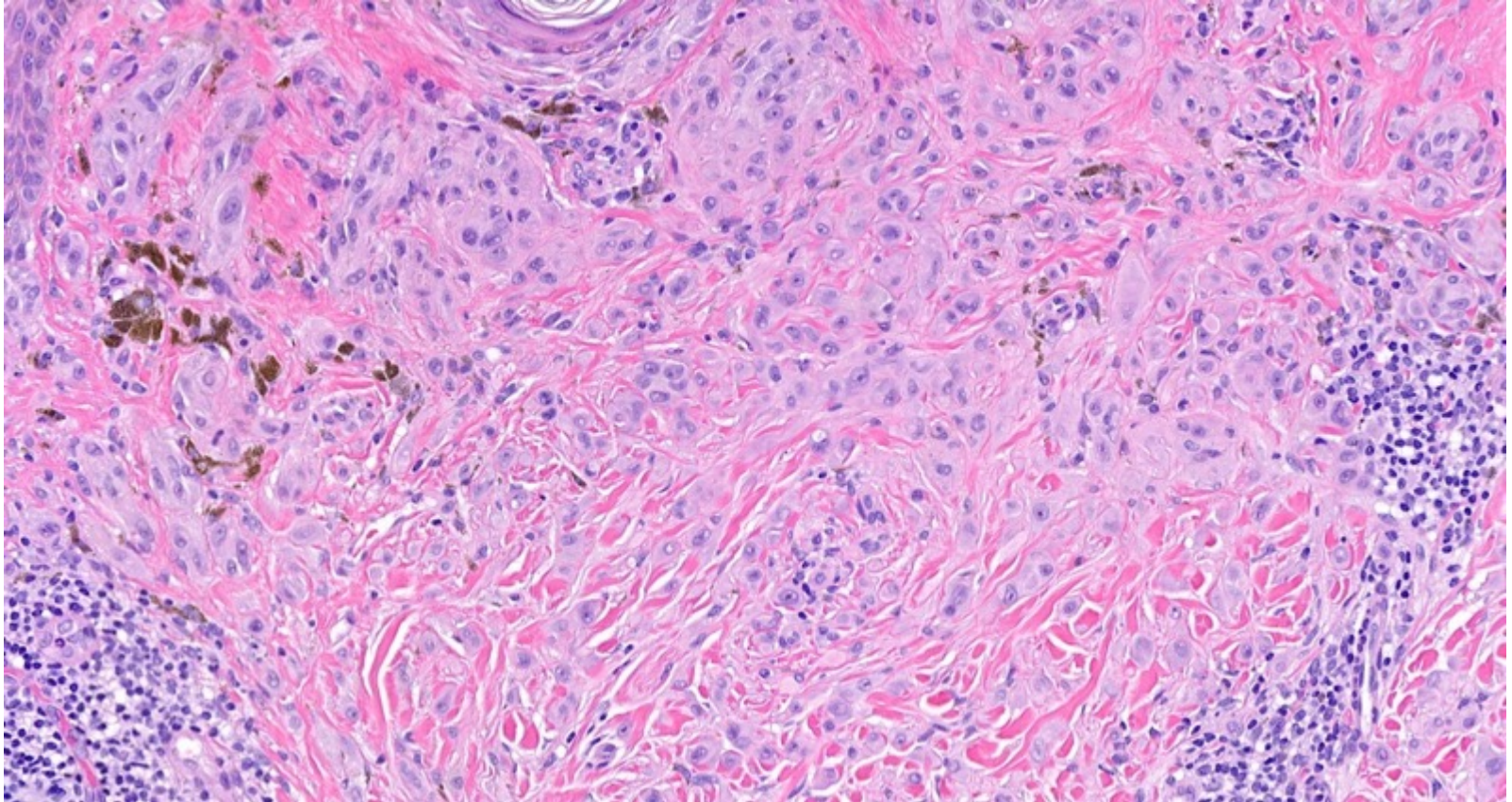
Case 7

52 yo, chest lesion





Spitzoid Lesion

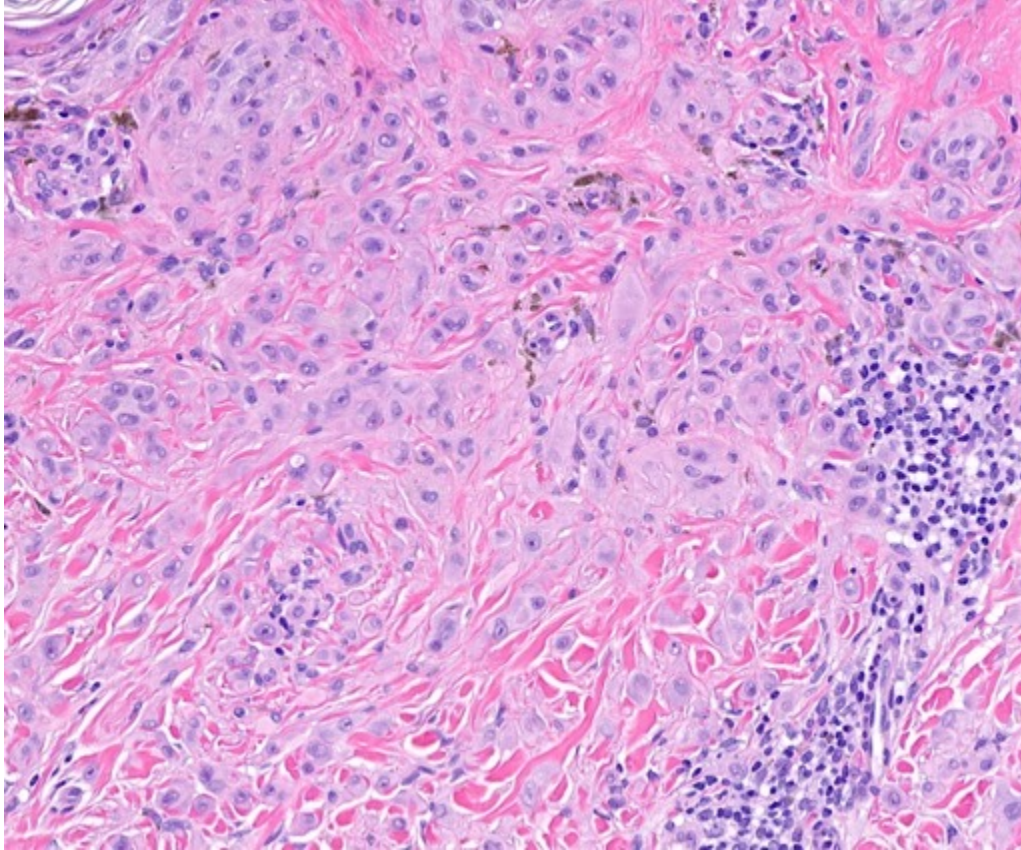


Spitz Nevi

- More common in pediatric population to young adults
- Not as common in older adults

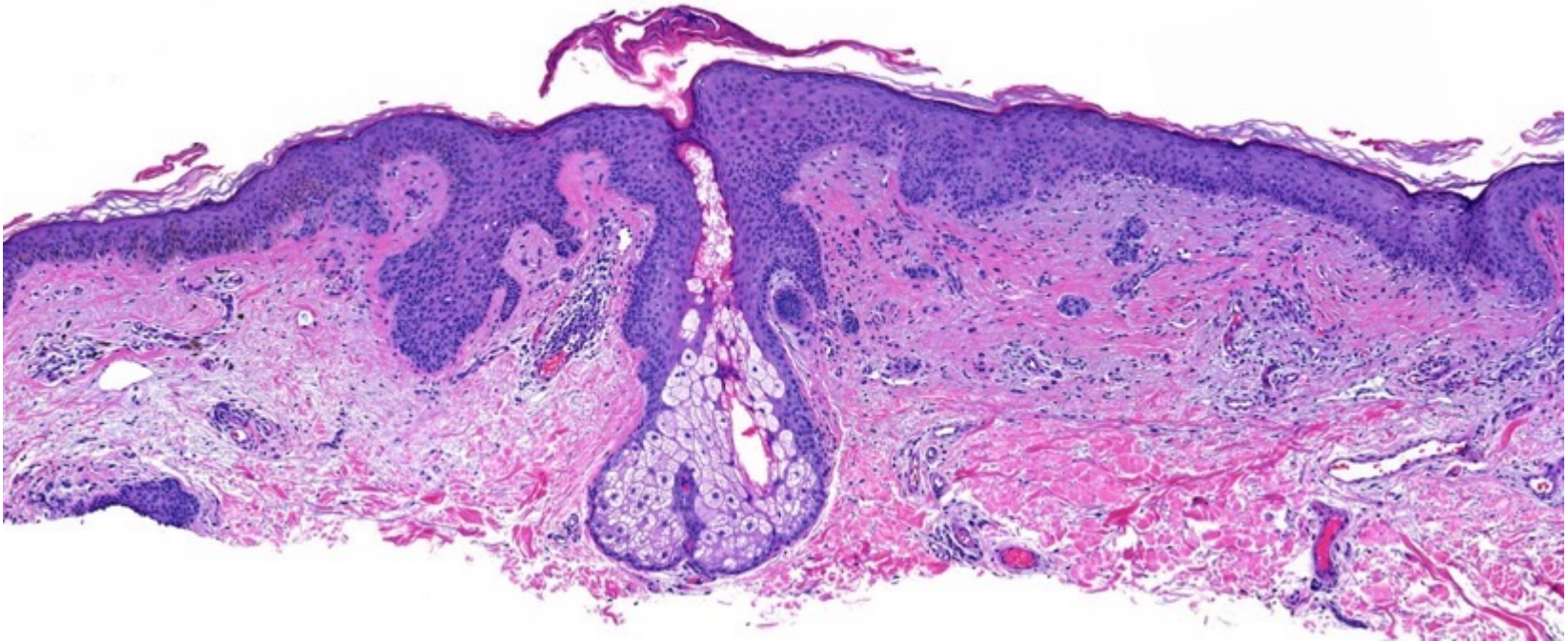
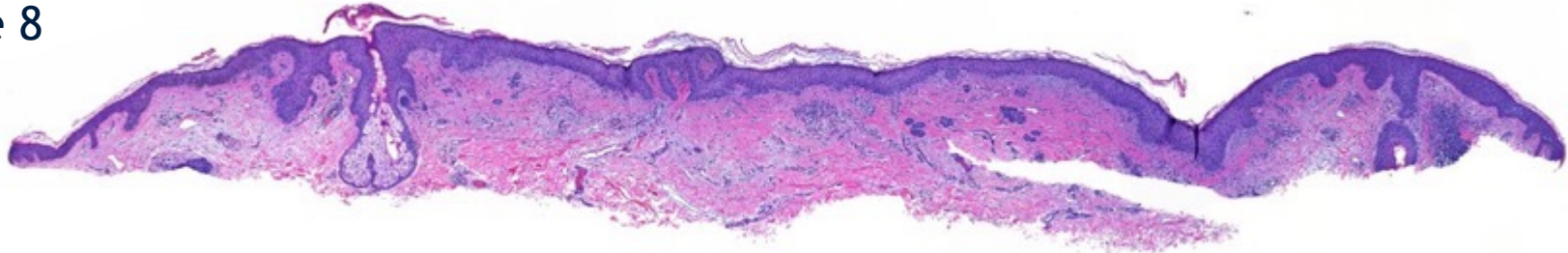
- BRAF: negative
- PRAME: 20%+
- TERT mutation: negative

Spitz nevus in an older adult

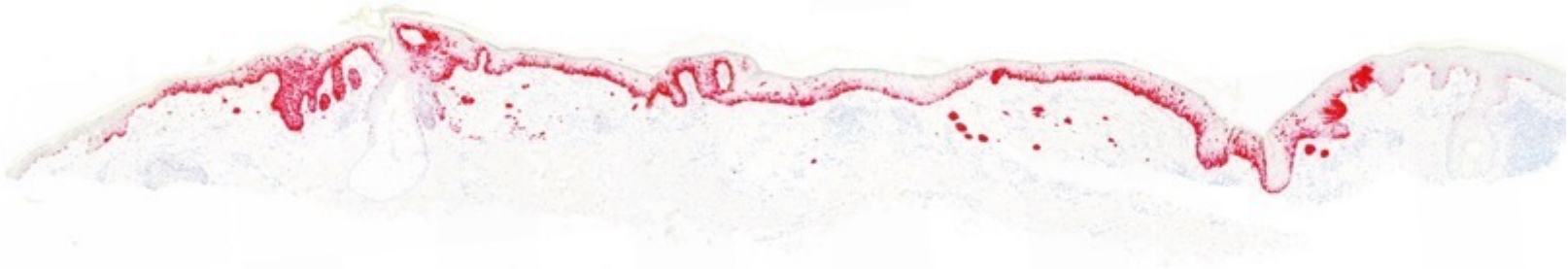
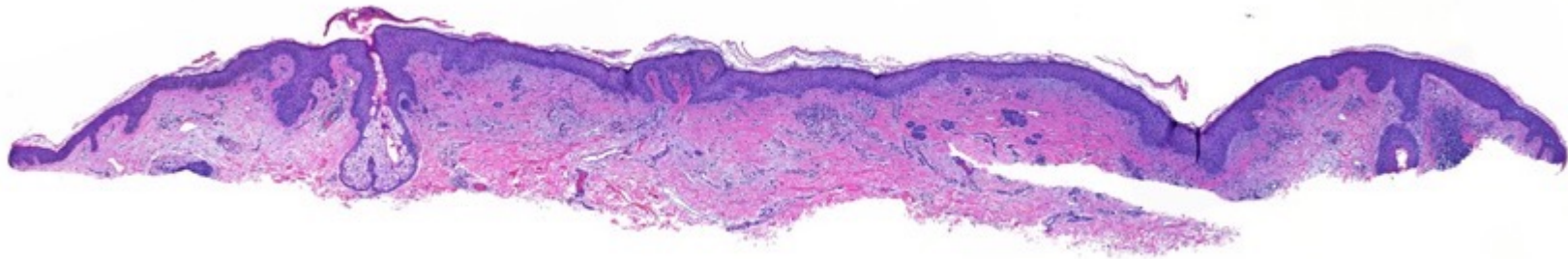


- BRAF negative
- PRAME negative
- Ki67 low mitotic index

Case 8

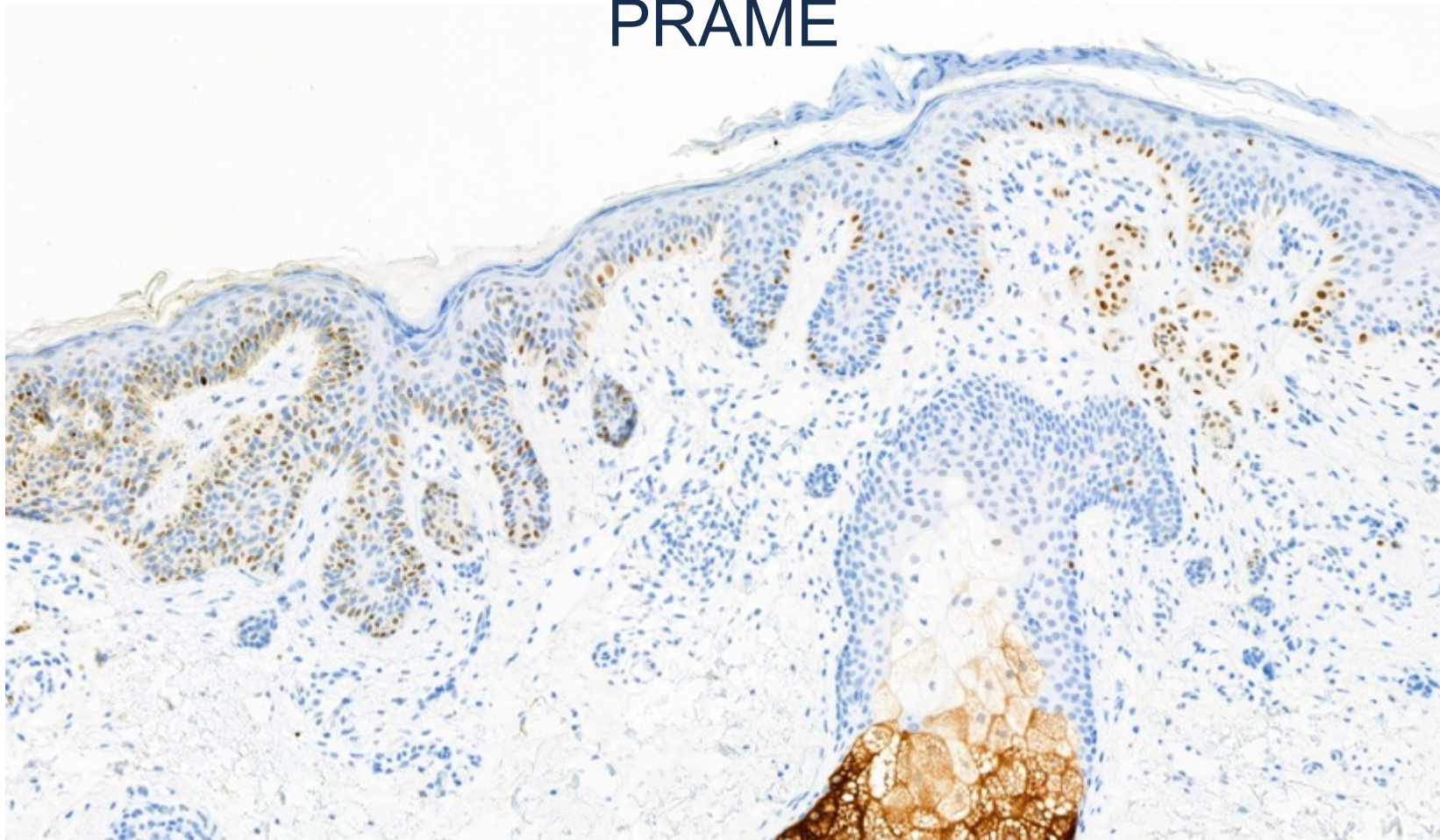


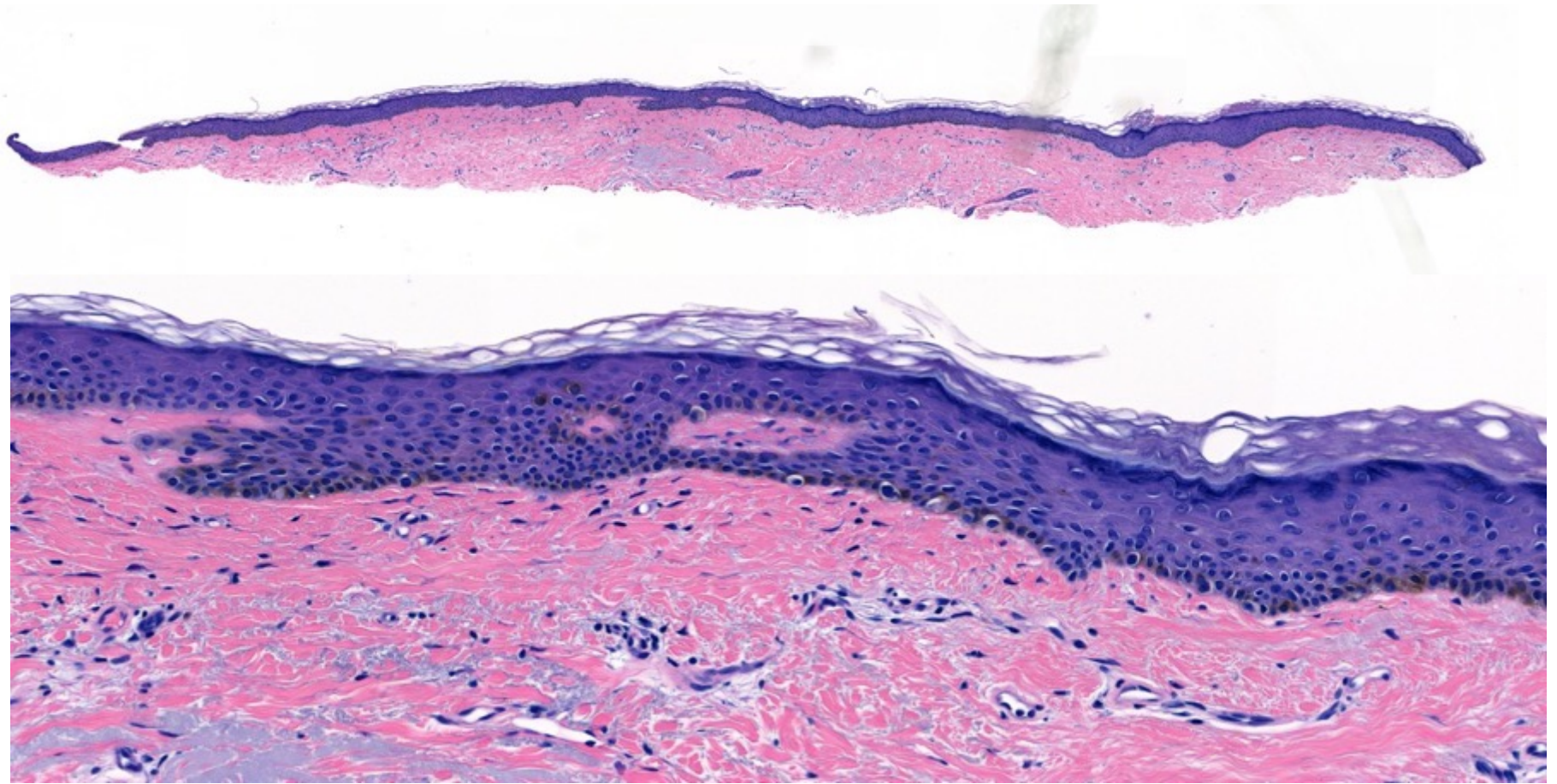
Case 2



Melanoma

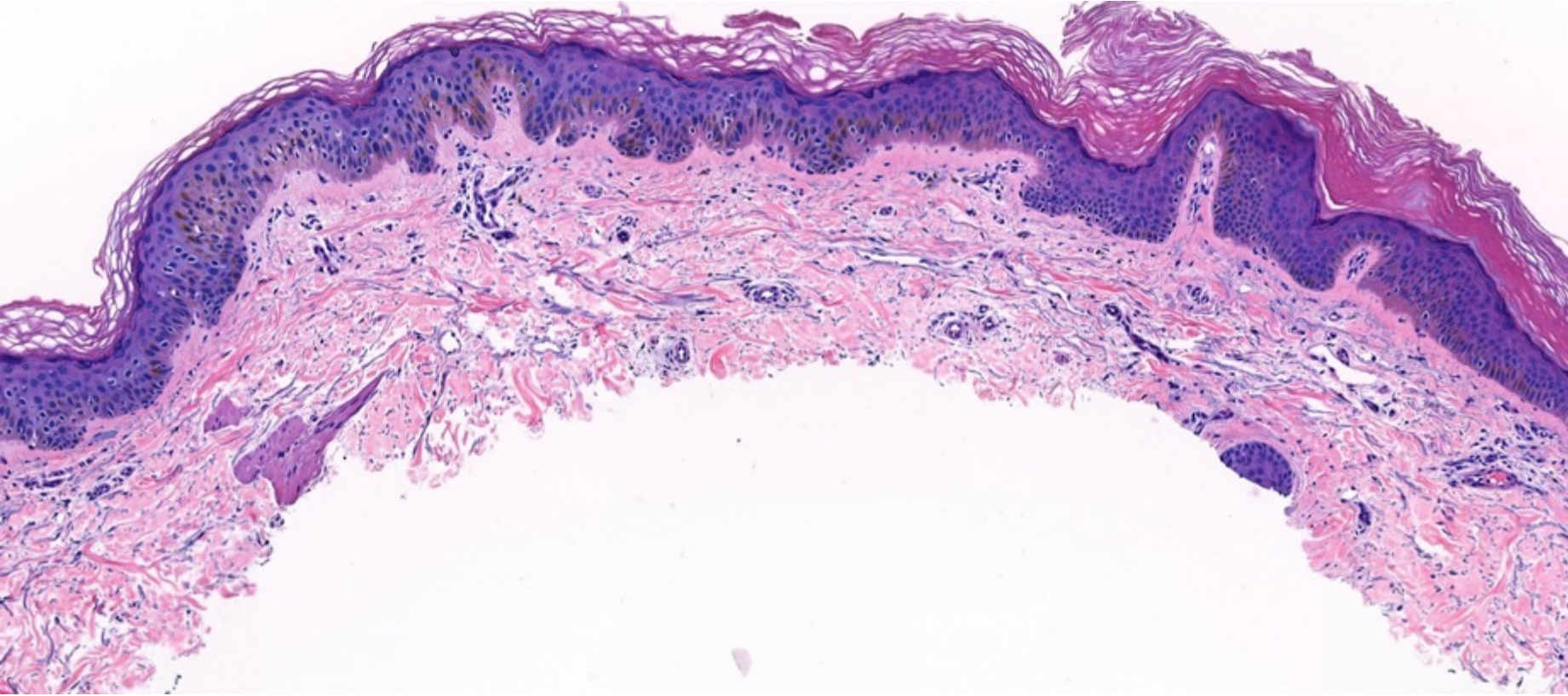
PRAME



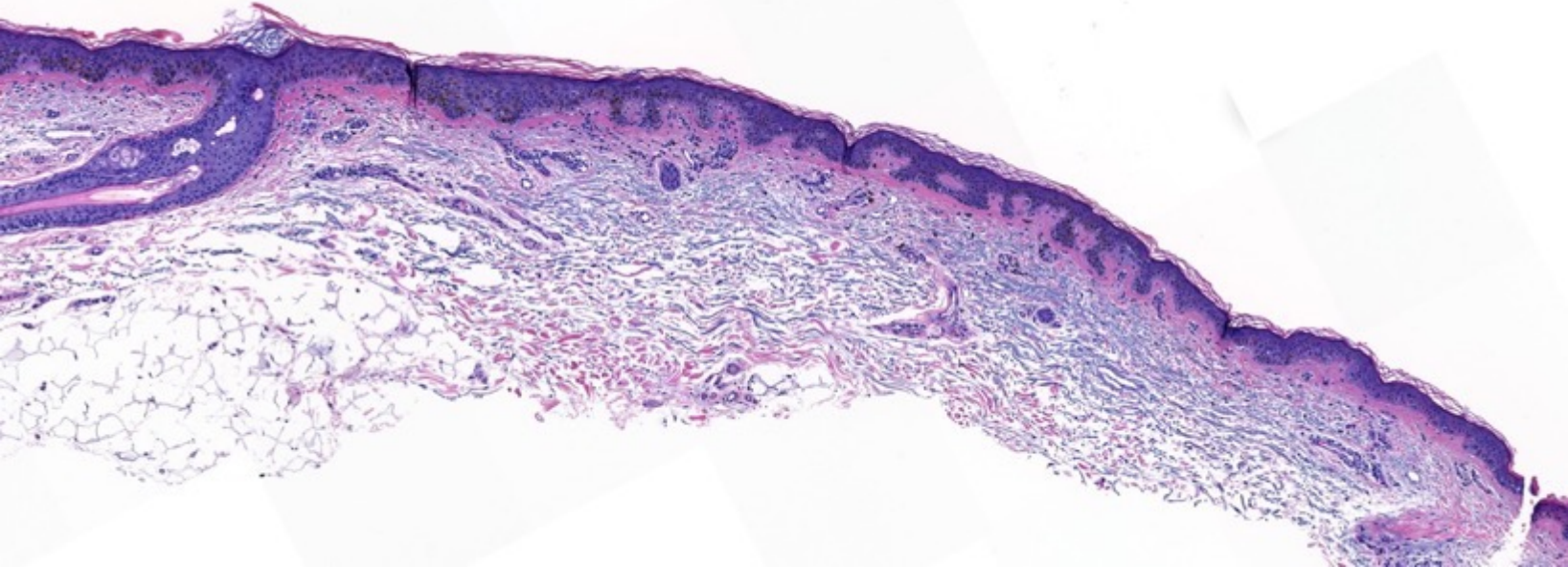
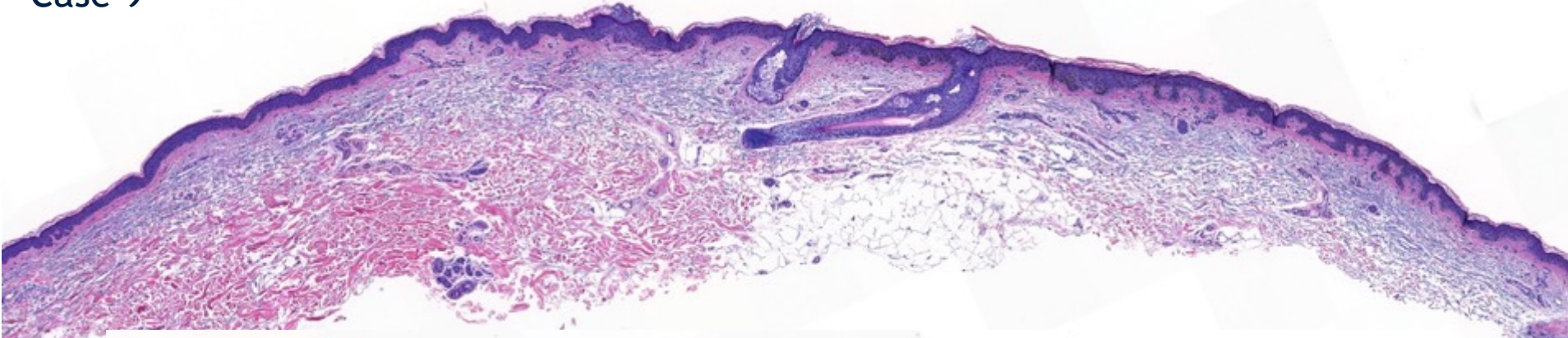


Solar Lentigo

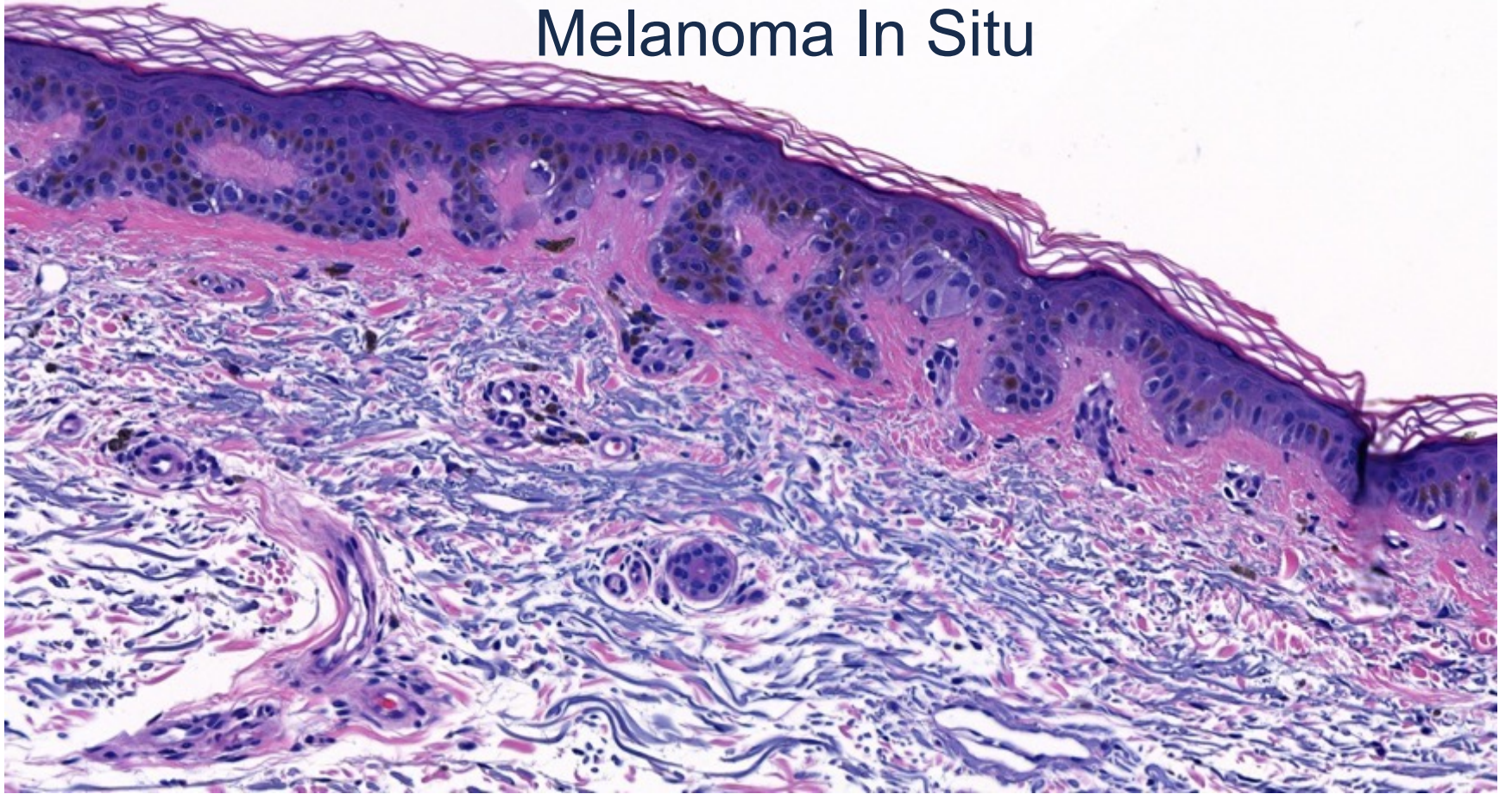
Solar Lentigo with Melanocytic Hyperplasia



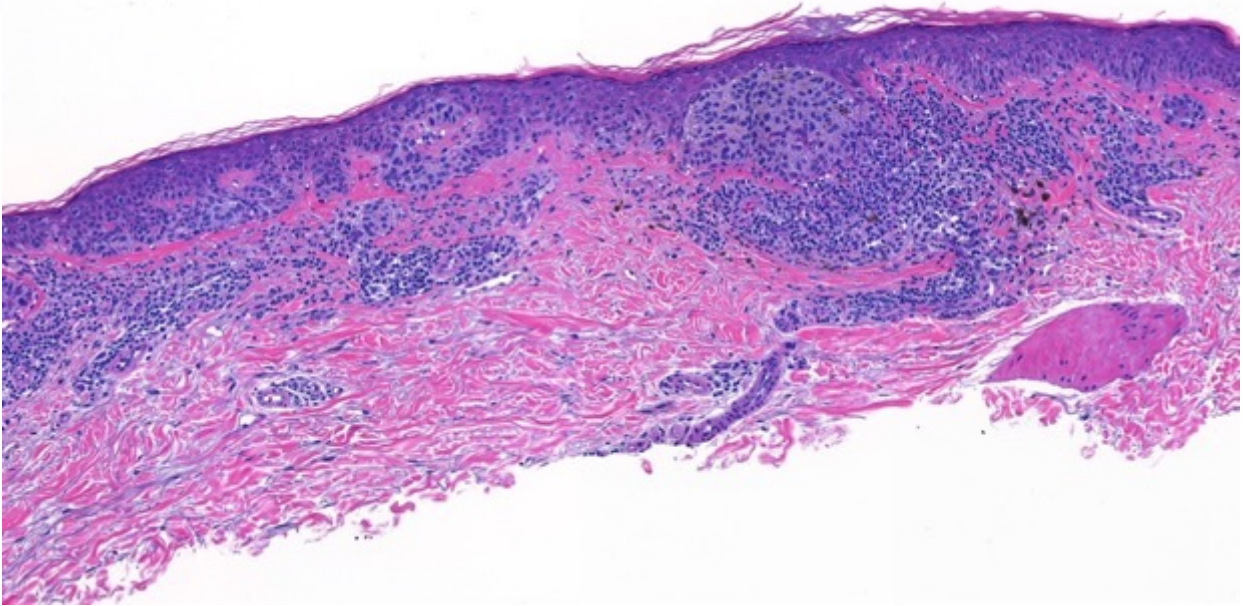
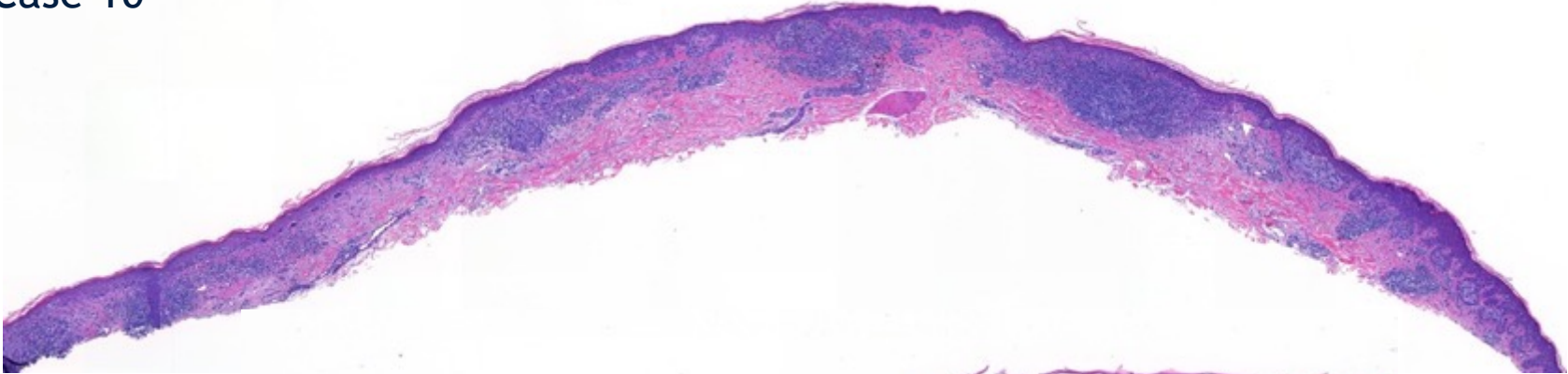
Case 9

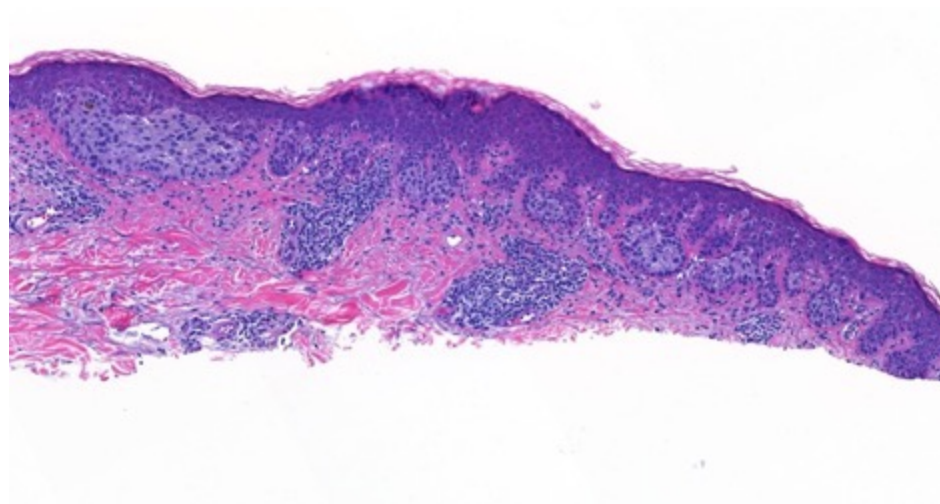
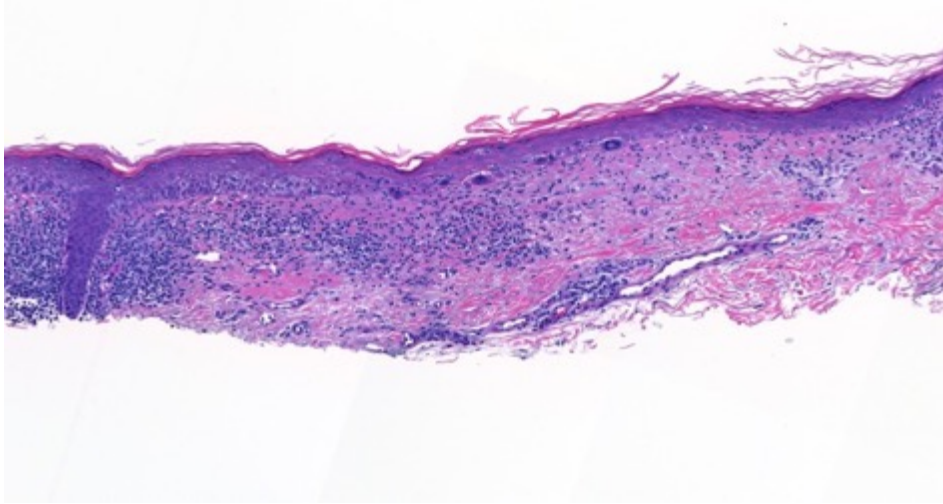


Melanoma In Situ



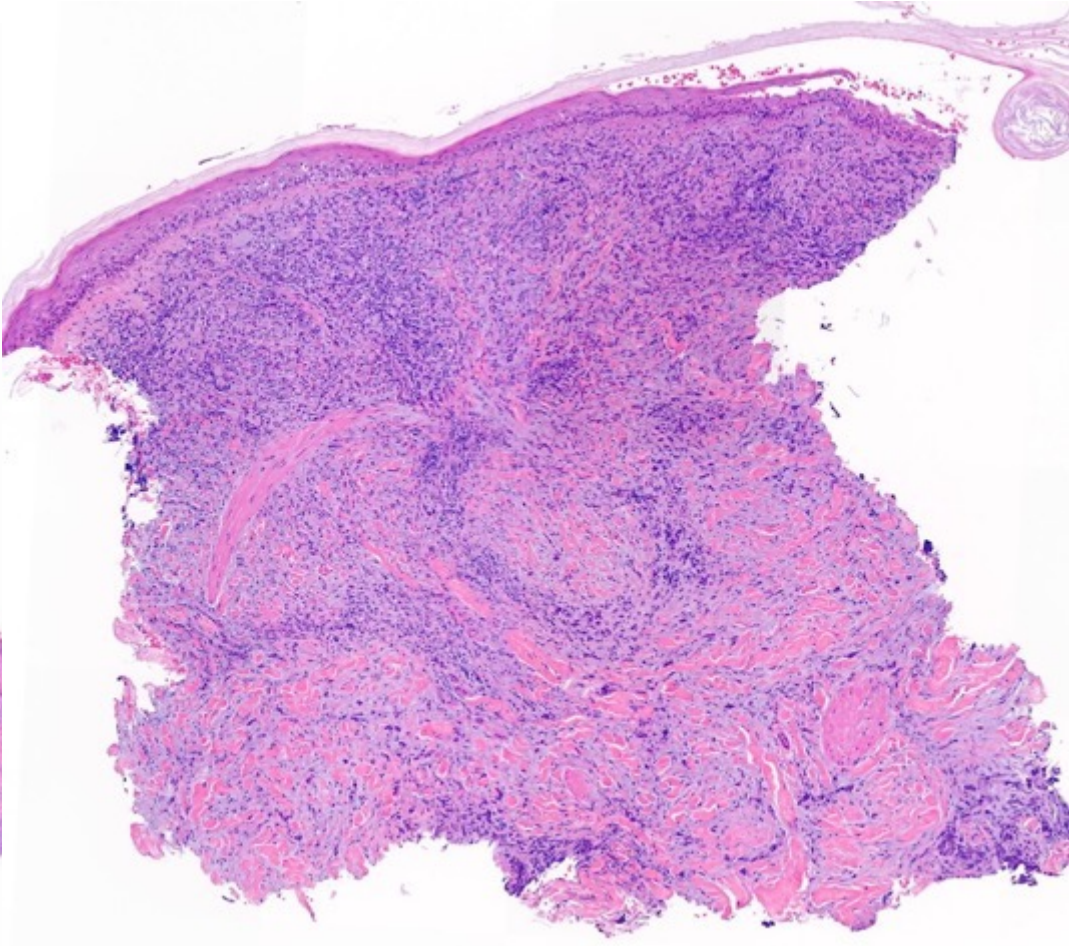
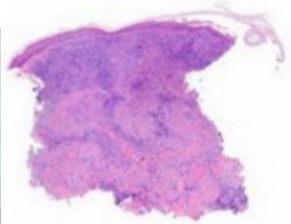
Case 10

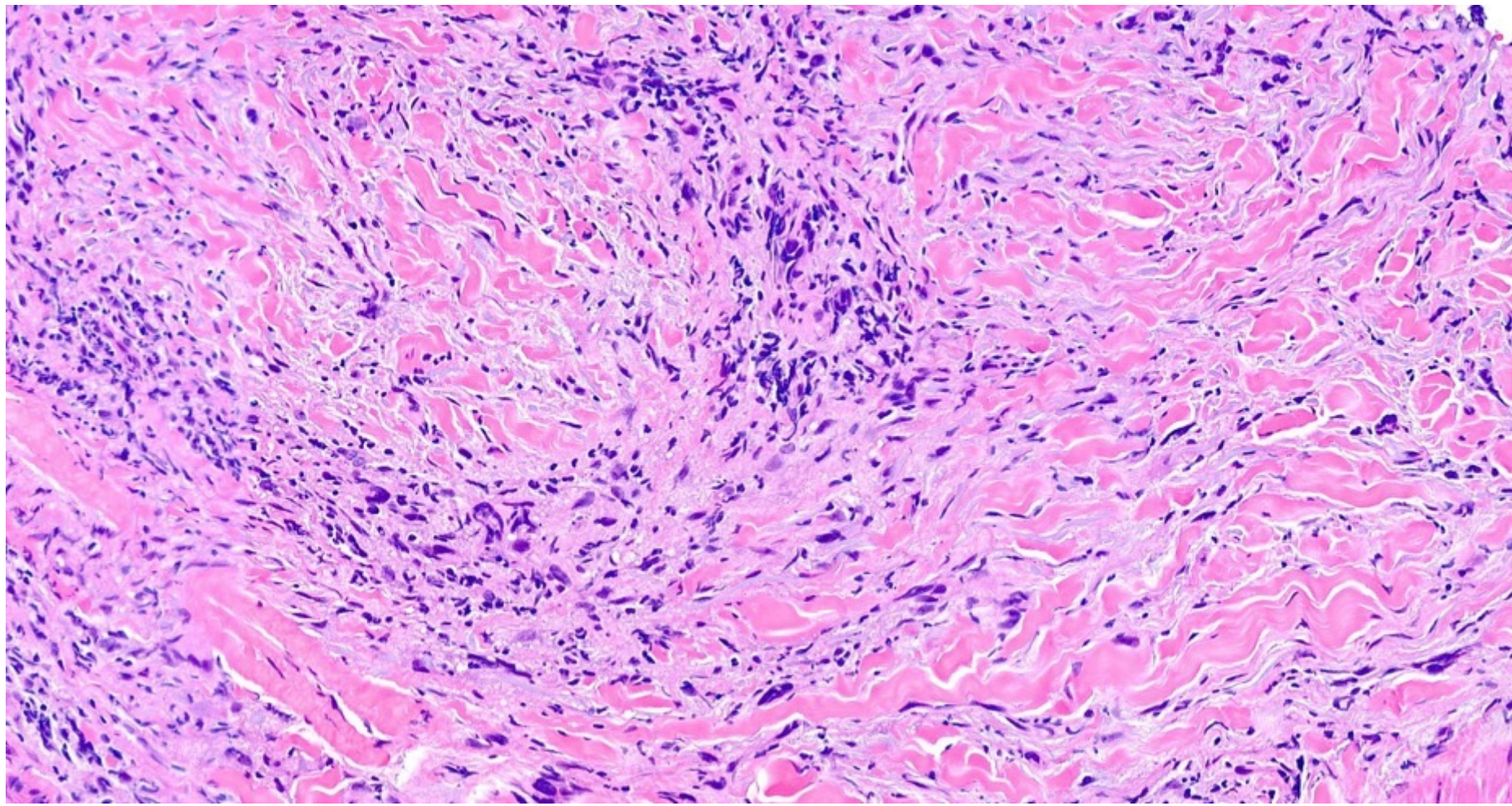




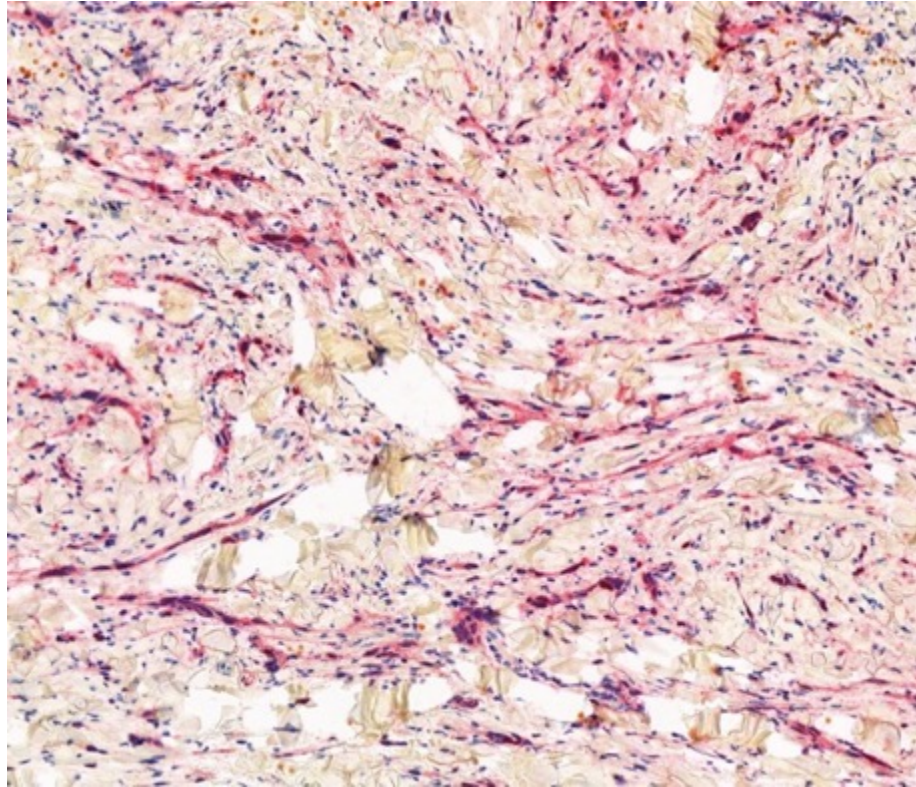
Melanoma

Case 11

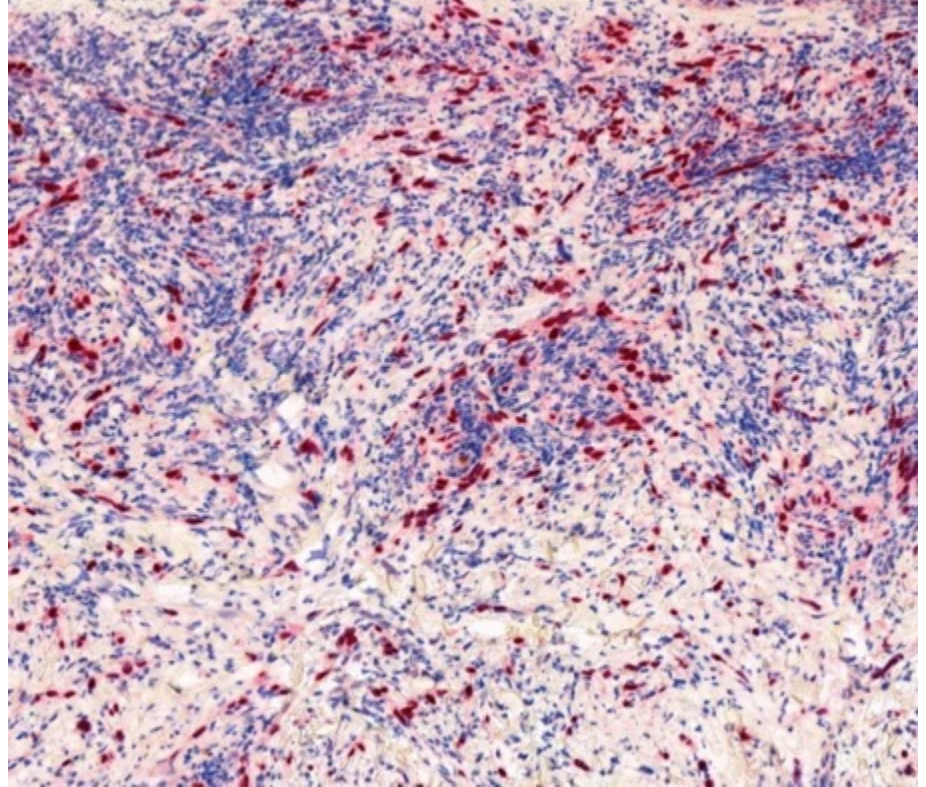




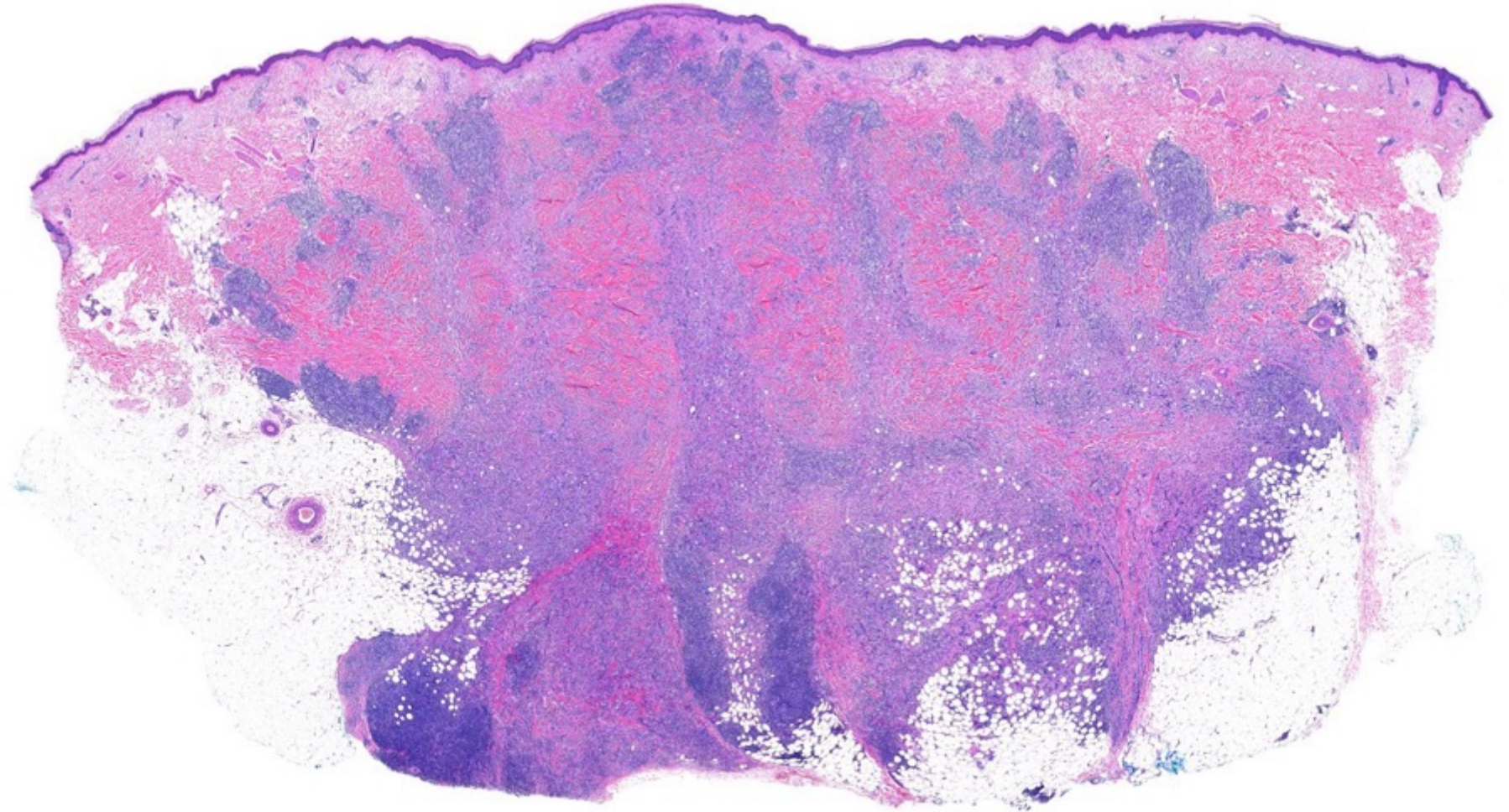
S100



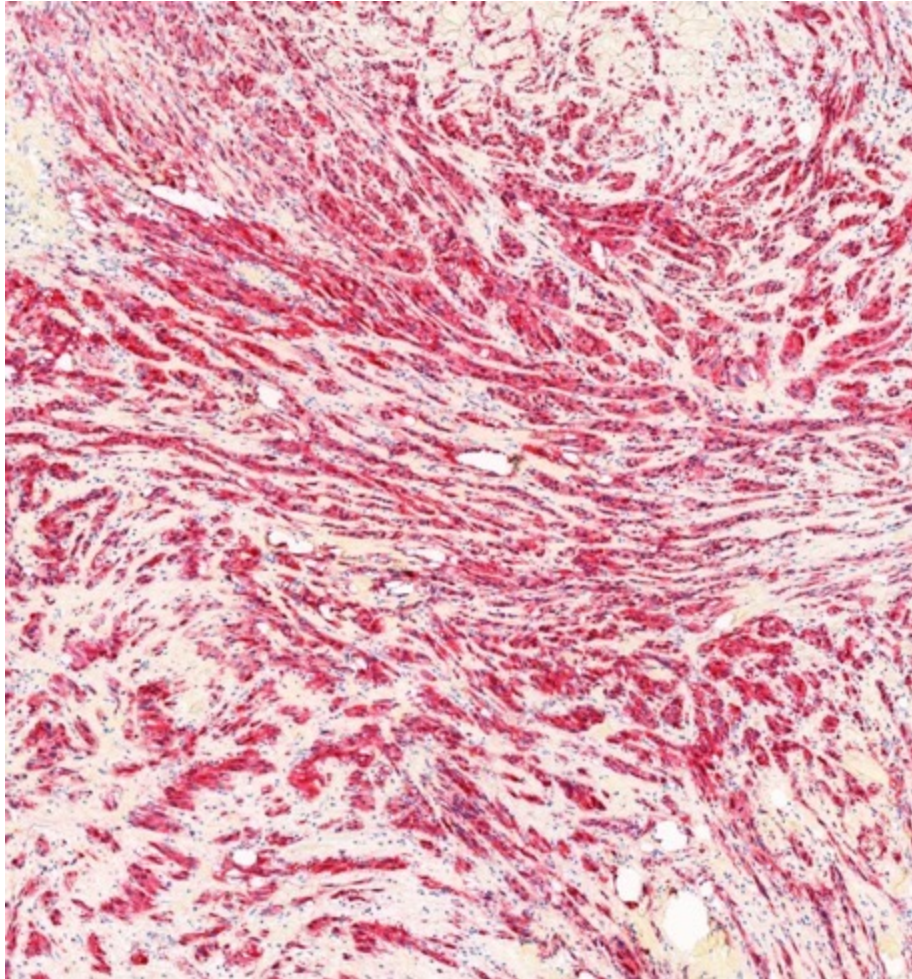
SOX10



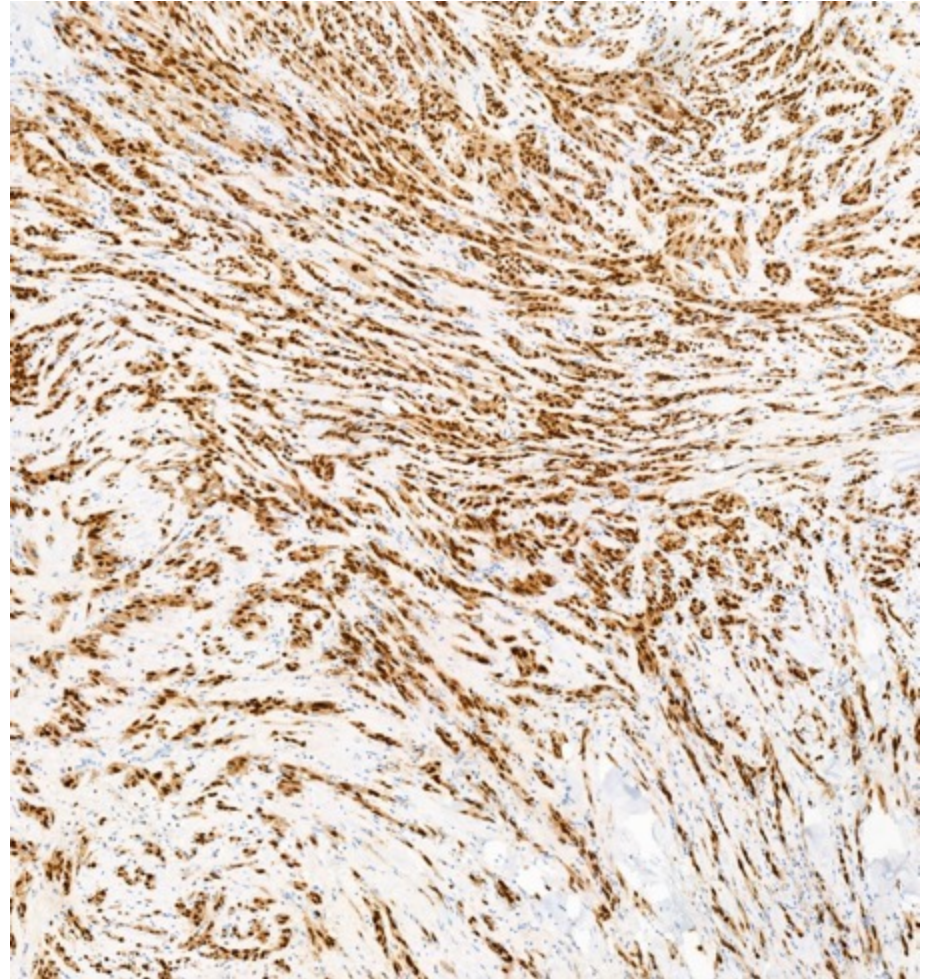
Desmoplastic Melanoma



DP22-09976 S100



DP22-09976 SOX10

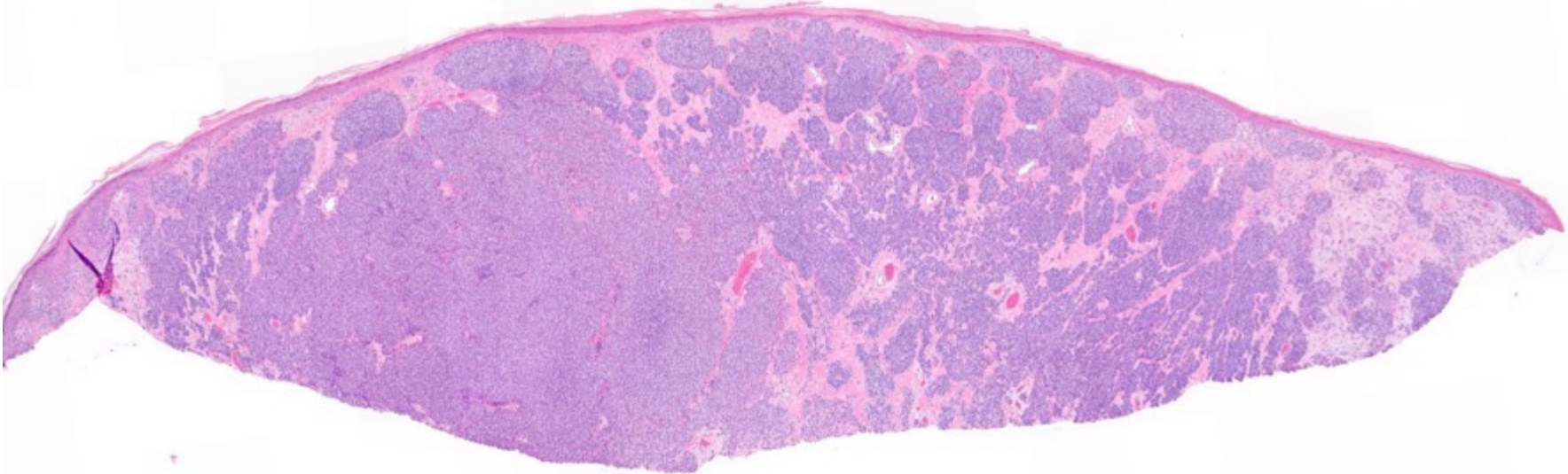


Desmoplastic Melanoma

- Spindle cell melanoma with fibrosis
- Pure vs Mixed
- Neurotropism
- Lymphoid aggregates
- 25% to 50% Melanoma in situ
- S100+, SOX10+, Variable Melan A

Case 12

Nodular Melanoma



PRAME Negative

Conclusive Remarks

- Melanocytic lesions comprise a significant workload of a dermatopathologist
- Epidemiologic evidence suggest substantial overdiagnosis of melanoma in-situ and thin melanomas
- Familiarity with the histopathologic spectrum of benign melanocytic lesions is required to minimize overdiagnosis
- Dysplastic nevus no longer has a precursor status, but continues to be biopsied at a high rate
- Emerging molecular diagnostic tools need further validation

The End

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