Jefferson
Philadelphia University + Thomas Jefferson University

Pigmented Lesions in a Day-to-Day Practice in Dermatopathology:

A practical case-based approach

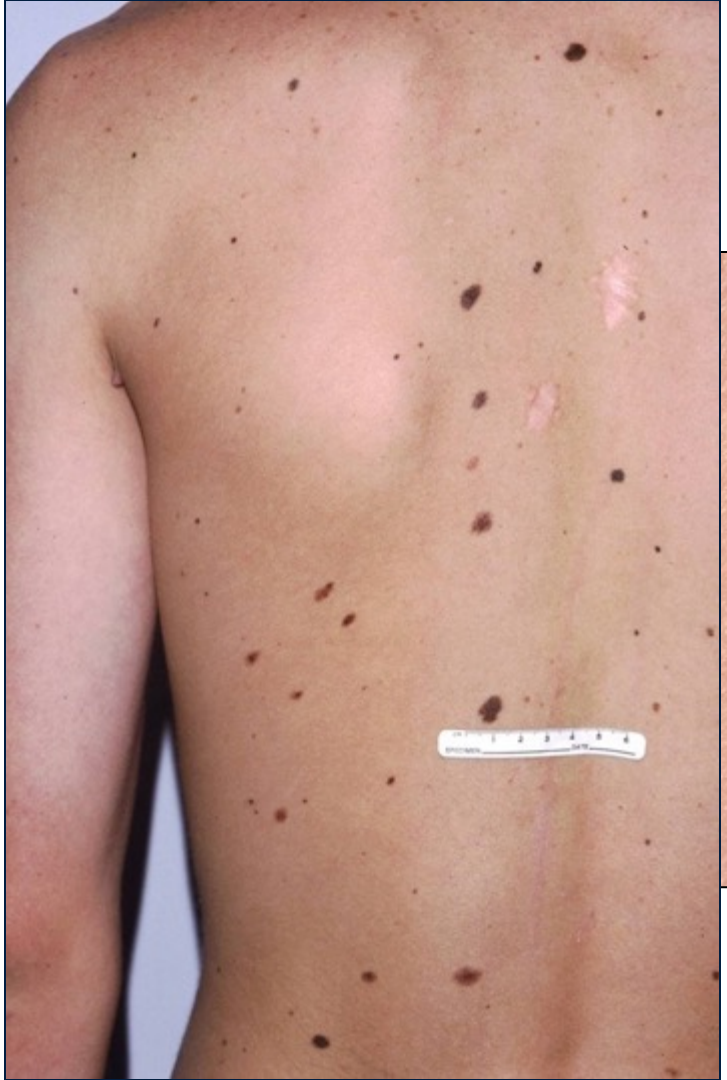
2023 Pennsylvania Association of Pathologists
Saturday, April 15, 10:30 AM — 11:00 AM

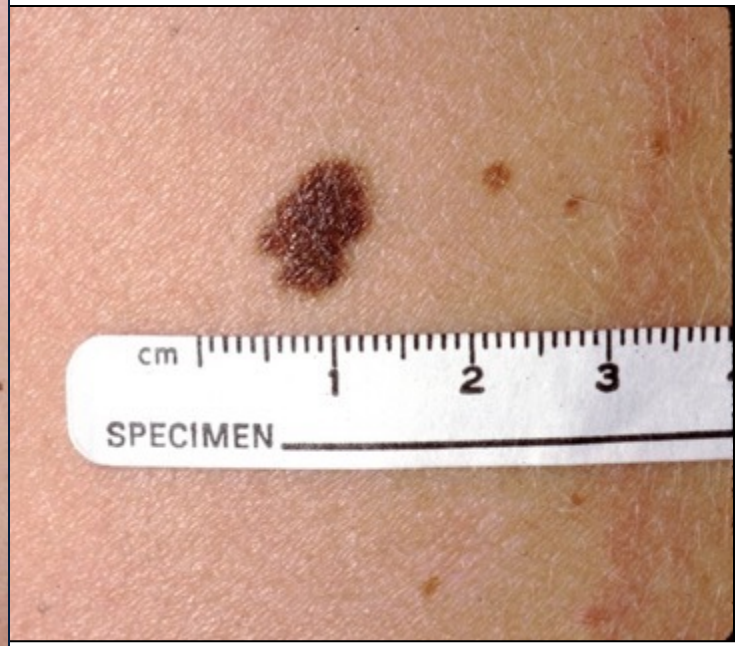
Jason B. Lee, MD
Professor
Director of Dermatopathology
Director of Pigmented Lesion Clinic
Department of dermatology and Cutaneous Biology
Thomas Jefferson University

HOME OF SIDNEY KIMMEL MEDICAL COLLEGE

I have no financial conflict to disclose

Table of Contents: Melanocytic Neoplasms




cm
1
2
3
SPECIMEN

Dysplastic/Atypical/Clark nevus

- Most commonly biopsied melanocytic lesion

Archives of DERMATOLOGY

VOL 114, NO. 5 MAY 1978

ORIGINAL CONTRIBUTIONS

CASE REPORTS

(Continued on page 842)

Origin of Familial Malignant Melanomas From Heritable Melanocytic Lesions

Wallace H. Clark, Jr, MD, Philadelphia;
Ronald R. Reimer, MD; Mark Greene, MD, Bethesda, Md;
Ann M. Ainsworth, MD; Michael J. Mastrangelo, MD, Philadelphia

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

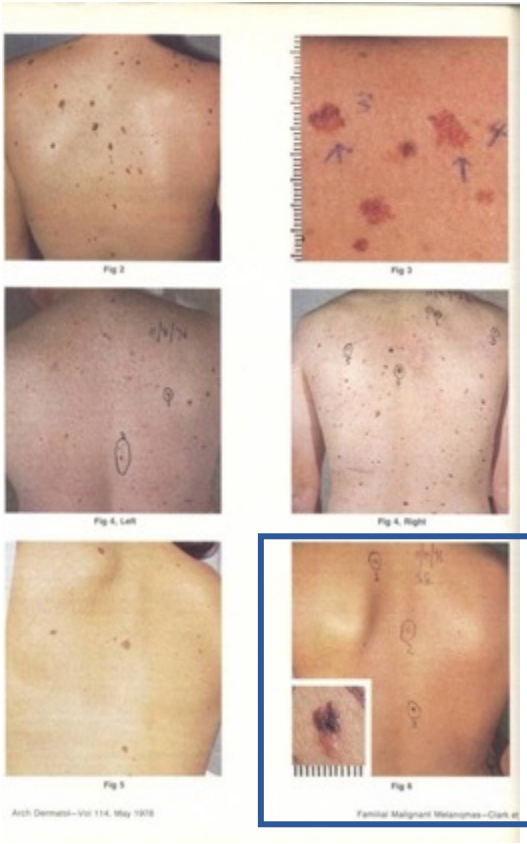


Fig 2.—Back of 27-year-old woman who had four primary malignant melanomas. Pattern and appearance of moles in patient with numerous lesions. Compare with Fig 6 for appearance of B-K moles sparse in number. Proband, family M.

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.

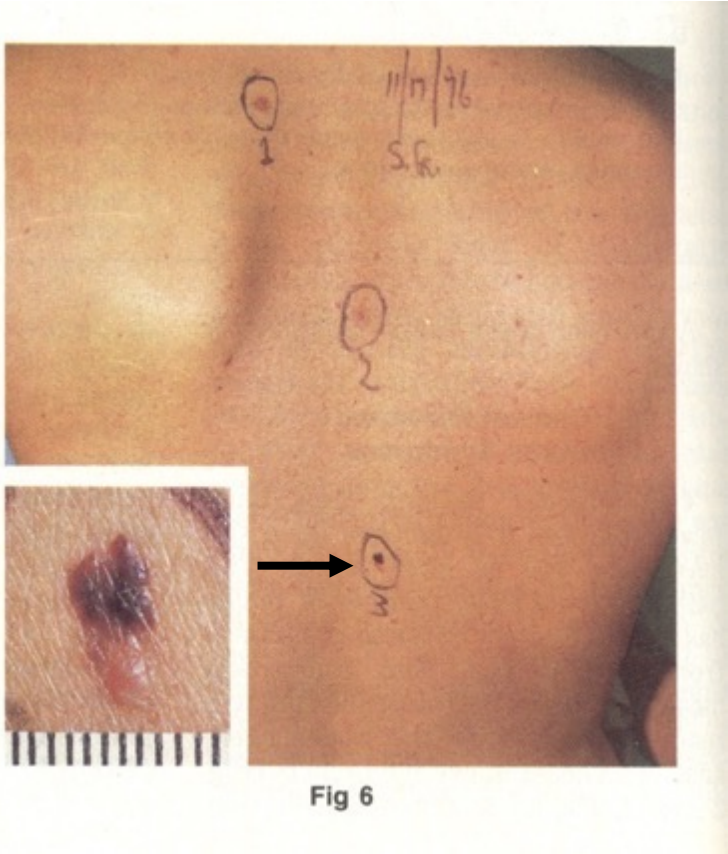
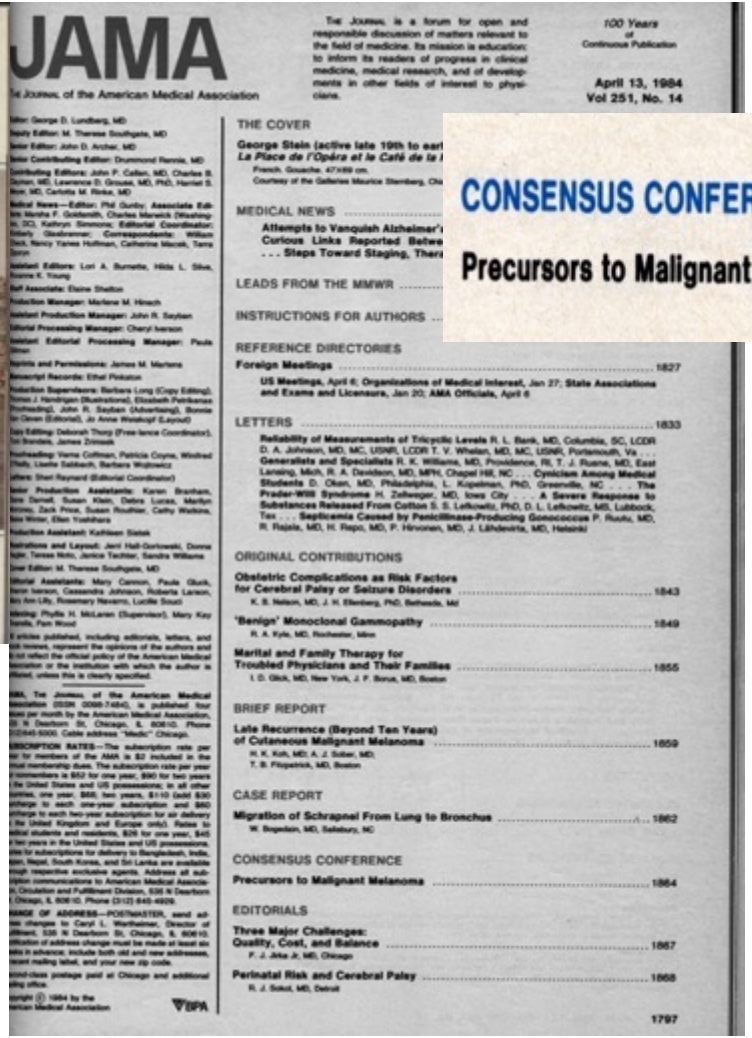


Fig 6

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)



CONSENSUS CONFERENCE

Precursors to Malignant Melanoma 1864

1984

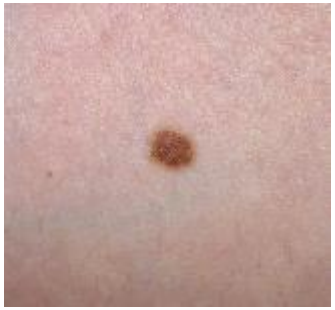
Precursors to Malignant Melanoma. JAMA : the journal of the American Medical Association. 1984;251(14):1864-1866. doi:10.1001/jama.1984.03340380046022

NIH Consensus Conference: Oct. 24-26, 1983

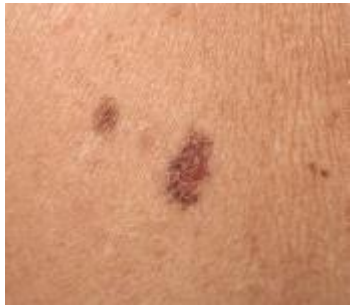
Identifying individuals with higher risk of developing melanoma

"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)

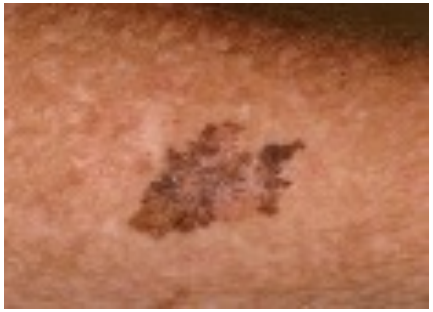
Stepwise Multi-Step Progression of Cancer



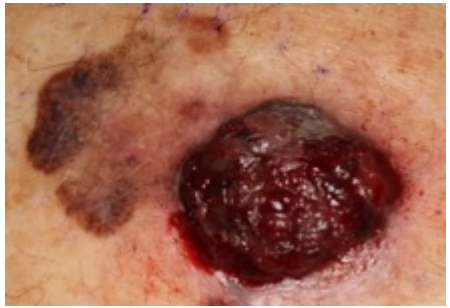
“typical” or “normal” nevus



“dysplastic” nevus



melanoma in situ

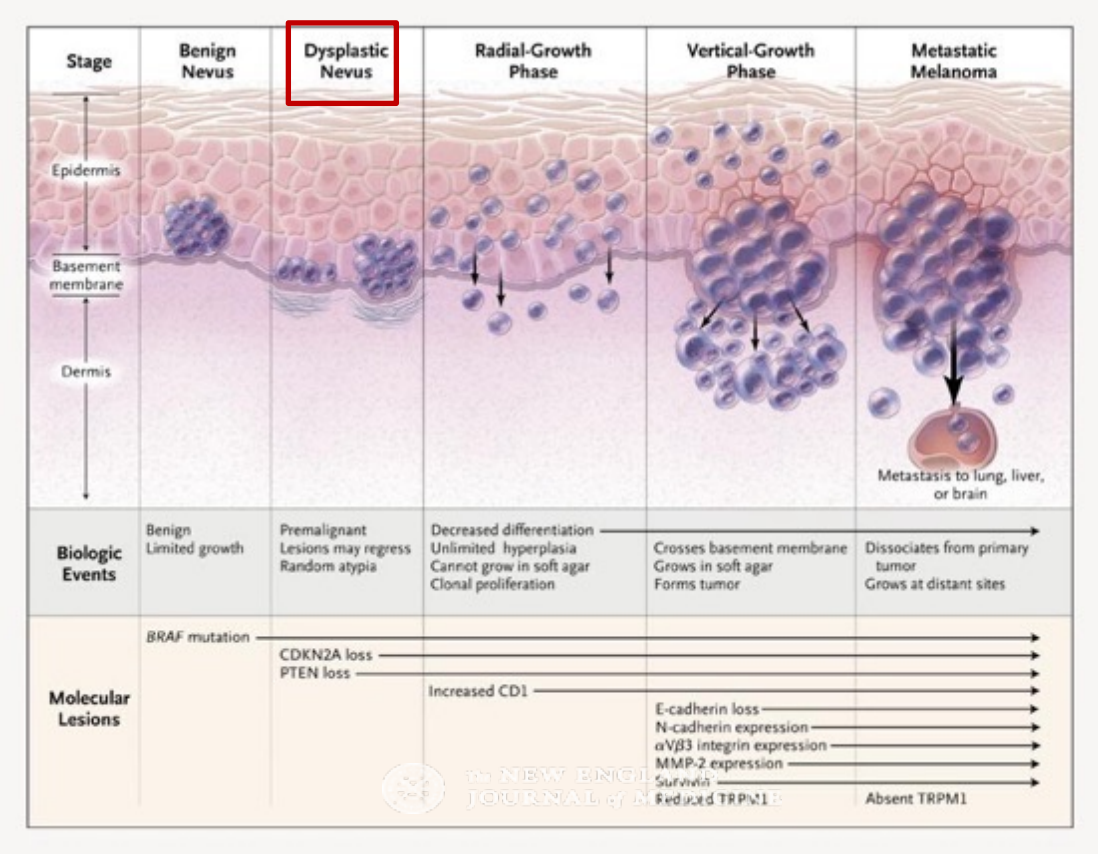


invasive melanoma

1. Initiation 2. Latent 3. Promotion 4. Malignant transformation

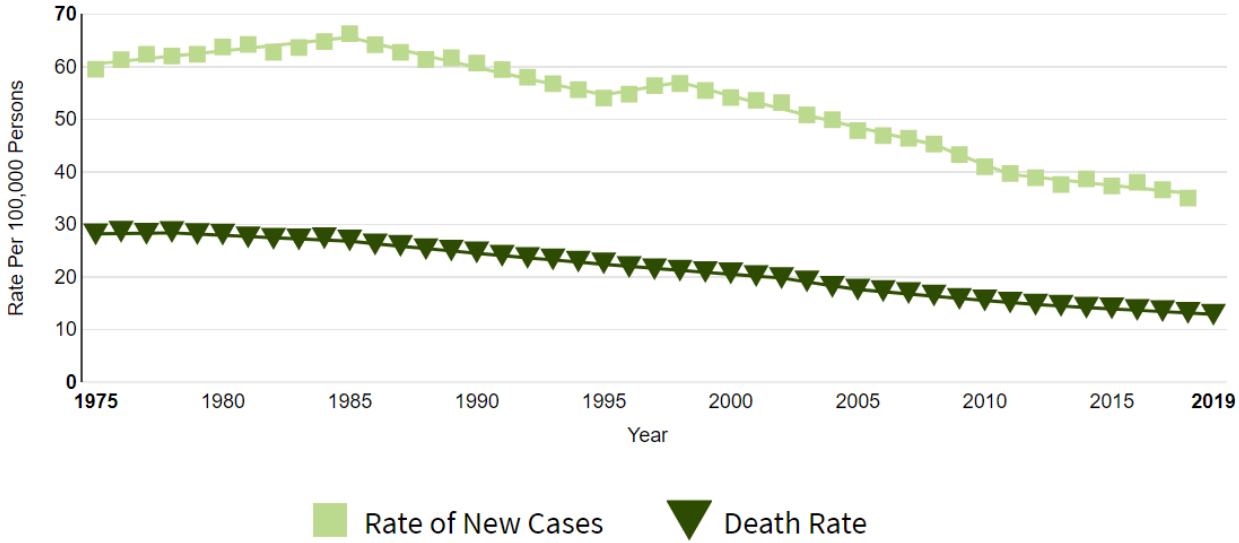
The continual accumulation of DNA mutations results in step-wise progression of neoplasia, the steps of which may be recognizable morphologically—e.g. metaplasia and dysplasia

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



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

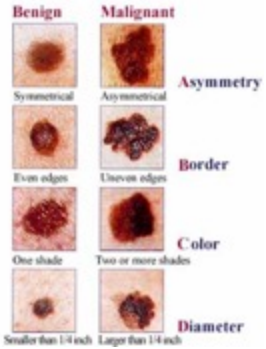
"Malignant melanoma can be diagnosed clinically and histologically when it is small, flat, and confined to the epidermis."

A. B. Ackerman, 1983

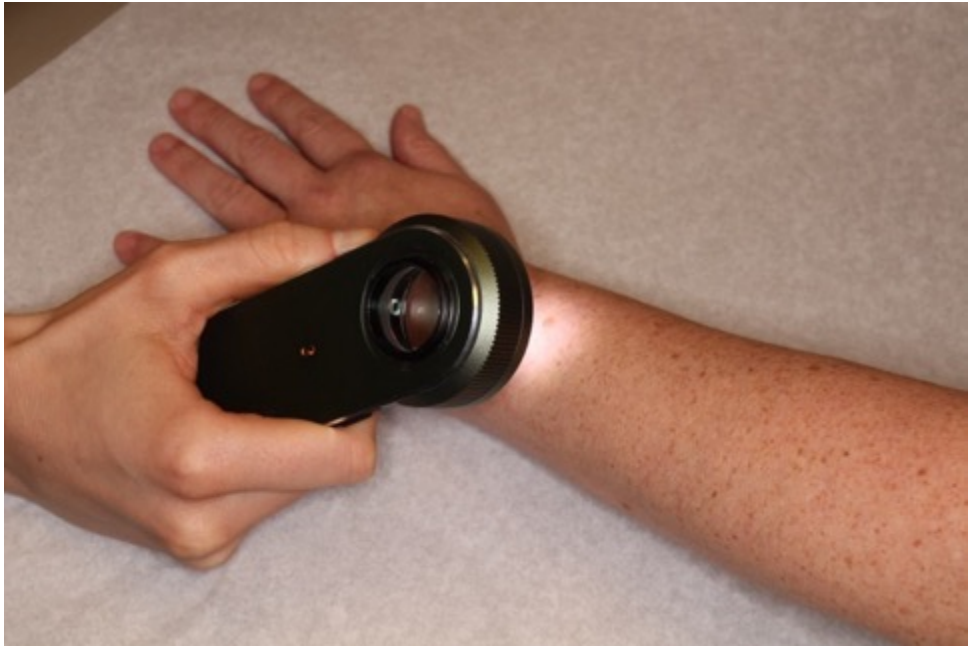
Ackerman AB. Macular and patch lesions of malignant melanoma: malignant melanoma in situ. *J Dermatol Surg Oncol* 1983;9:615-8.

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



Introduction of Dermatoscopy USA



Objectives of Dermatoscopy

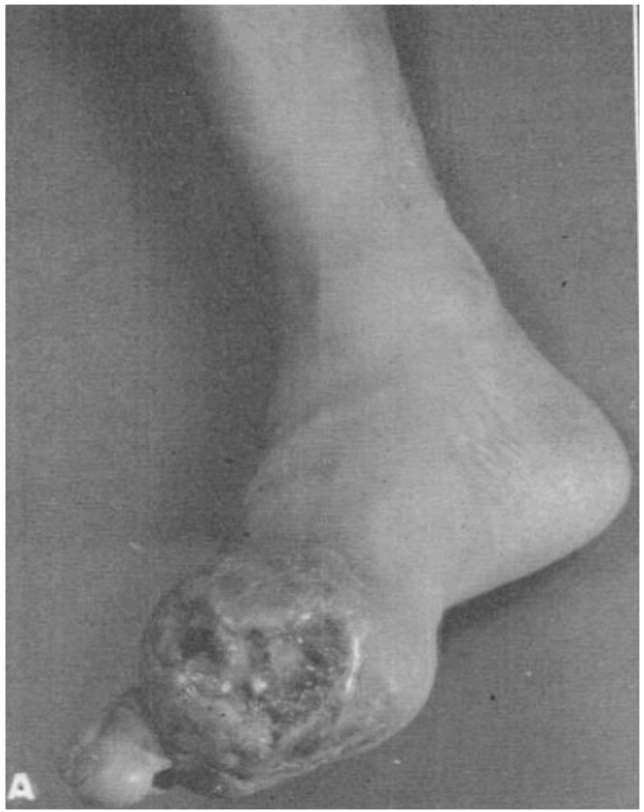
1. Increase the diagnostic accuracy of melanoma, especially early melanomas
2. Decrease unnecessary harvesting of benign skin lesions

Improve the diagnostic

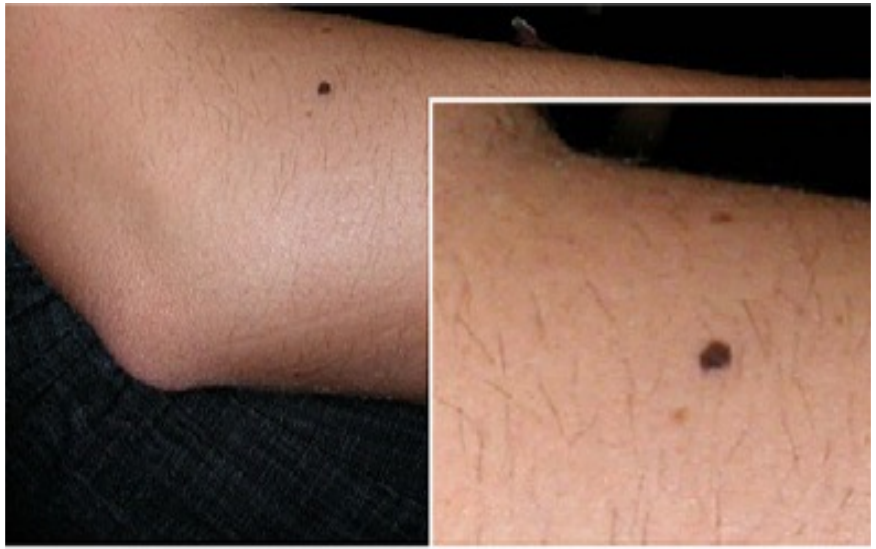
SENSITIVITY and ***SPECIFICITY***

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

Incidence
(2023 estimate)

	# cases	# deaths
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

Data from *Cancer facts and figures 2023, BCC, SCC: 2022 estimate*

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%

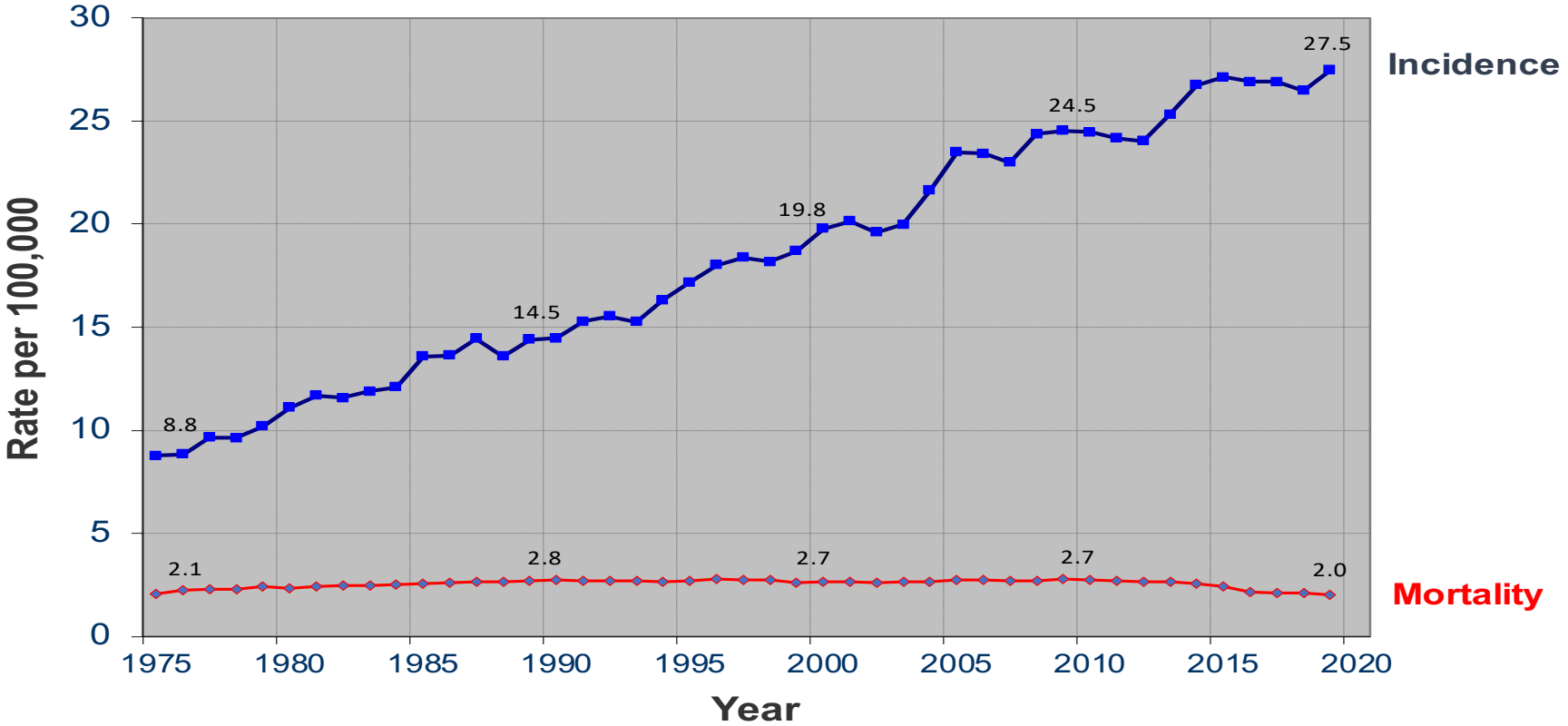
https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/2023-cancer-facts-figures.html

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%

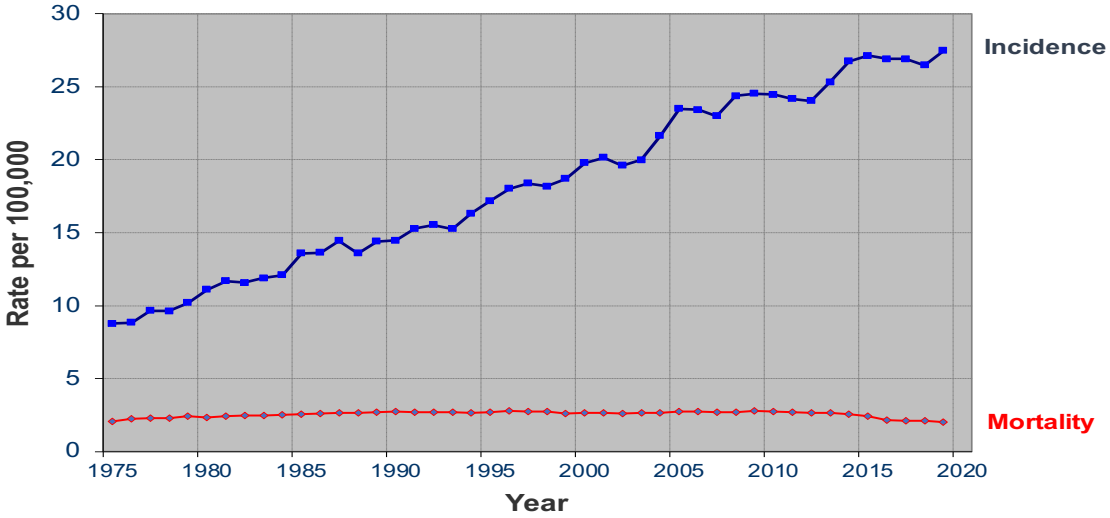
https://www.cancer.org/cancer/merkel-cell-skin-cancer/detection-diagnosis-staging/survival-rates.html 2018
https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures

The Melanoma “Epidemic”



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

The Melanoma "Epidemic"

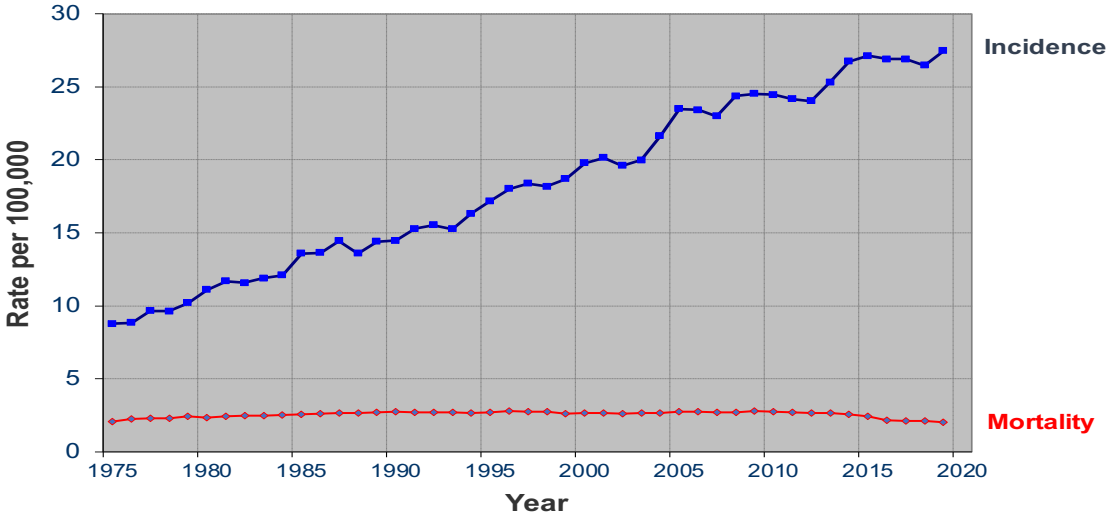


Epidemiologic Signature of Overdiagnosis

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

Welch HG et al. *N Engl J Med*. 2019;381(14):1378-1386.

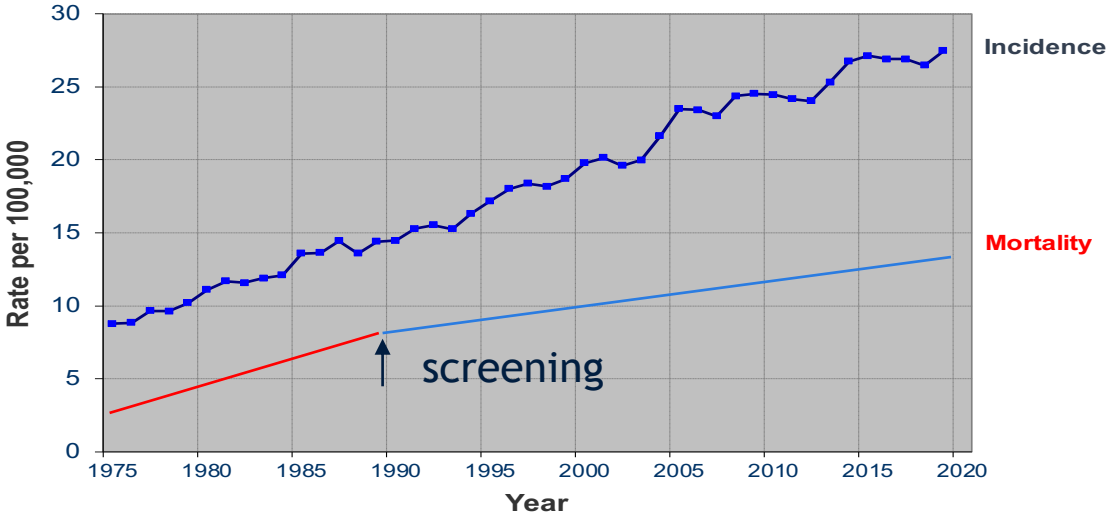
The Melanoma “Epidemic”



- 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 ≈50% mortality at most

Welch HG, Robertson DJ. Colorectal Cancer on the Decline — Why Screening Can’t Explain It All. The New England journal of medicine. 2016;374(17):1605-1607. doi:10.1056/NEJMp1600448

The Melanoma “Epidemic”

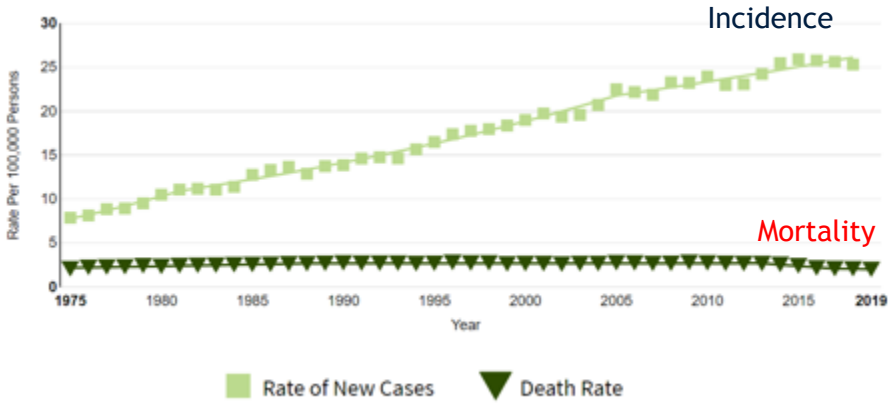


- NO screening captures 100% of the lethal cancer, providing a cure for each one with NO change in mortality
- <10% screened
- Effective screening may prevent ≈50% mortality at most
- Mortality should rise with blunting of the slope with effective screening

Welch HG, Robertson DJ. Colorectal Cancer on the Decline — Why Screening Can’t Explain It All. The New England journal of medicine. 2016;374(17):1605-1607. doi:10.1056/NEJMp1600448

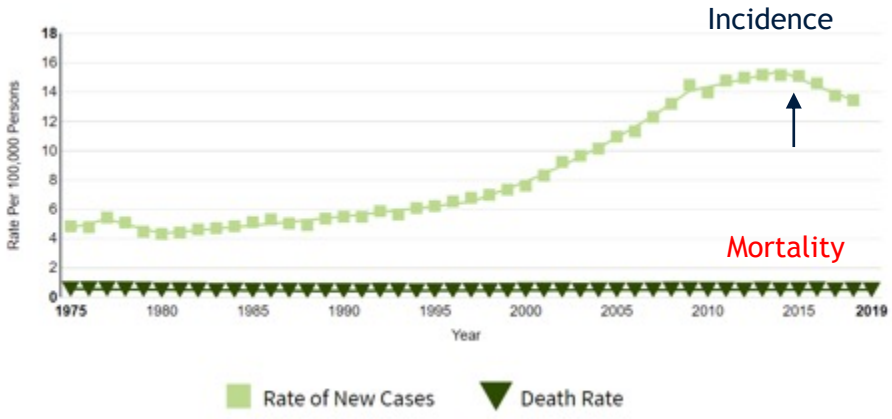
Epidemiologic Signature of Overdiagnosis

Melanoma Incidence and Mortality



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

Thyroid Cancer Incidence & Mortality

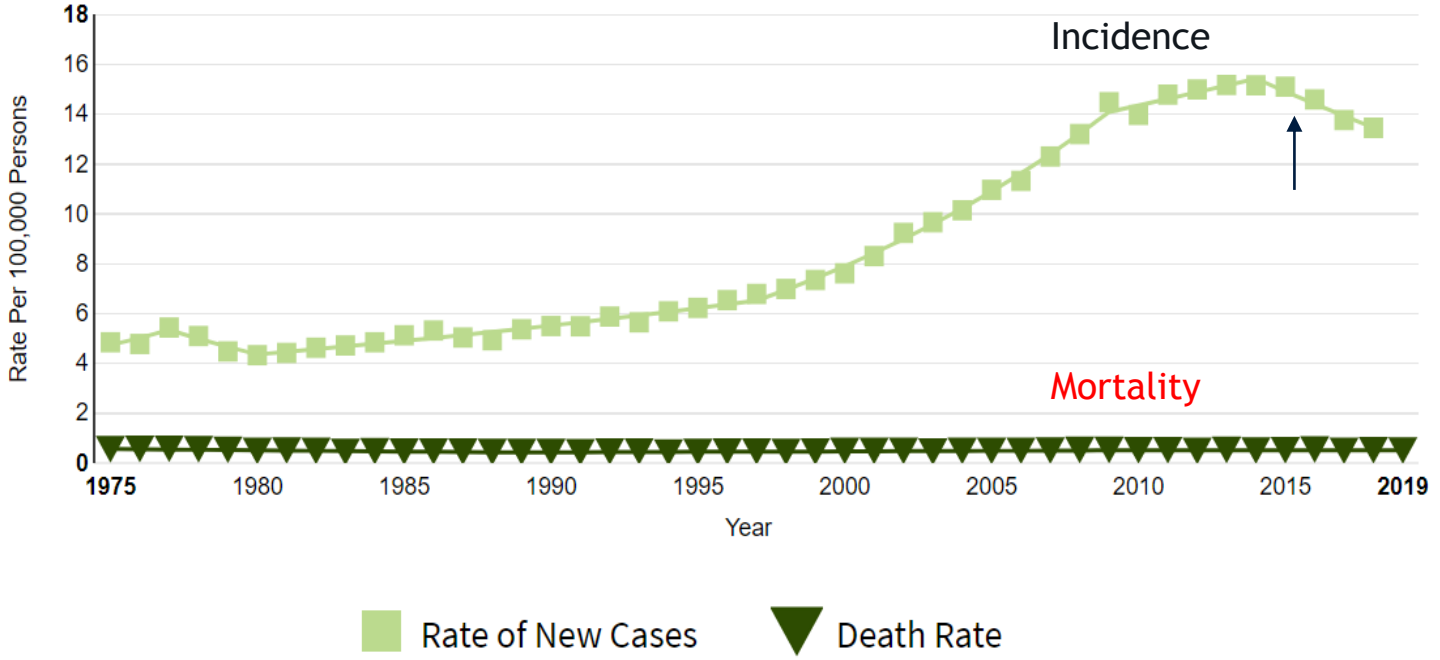


https://seer.cancer.gov/statfacts/html/thyro.html

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 … er, M. … P.

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

EPIDEMIOLOGY

2022 BJD British Journal of Dermatology

The effect of screening on melanoma incidence and biopsy rates*

MELANOCYTIC TUMOUR PATHOLOGY

Diagnostic error, uncertainty, and overdiagnosis in melanoma

Pathology 2023

The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

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"

Welch HG et al. *N Engl J Med*. 2019;381(14):1378-1386.

The NEW ENGLAND JOURNAL of MEDICINE

SOUNDING BOARD

The Rapid Rise in Cutaneous Melanoma Diagnoses

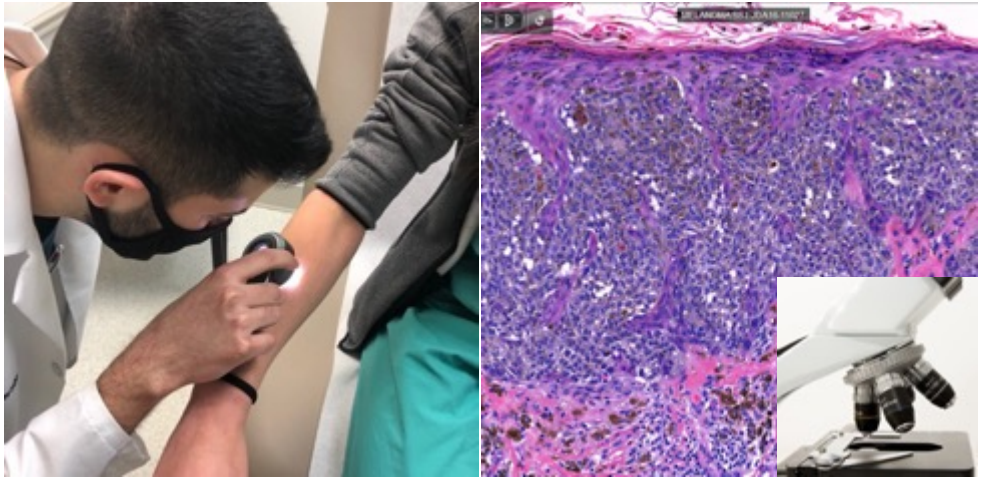
H. Gilbert Welch, M.D., M.P.H., Benjamin L. Mazer, M.D., M.B.A.,
and Adewole S. Adamson, M.D., M.P.P.

"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."

Welch HG et al. *N Engl J Med*. 2019;381(14):1378-1386.

Overdiagnosis is Not discernable at the patient level

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

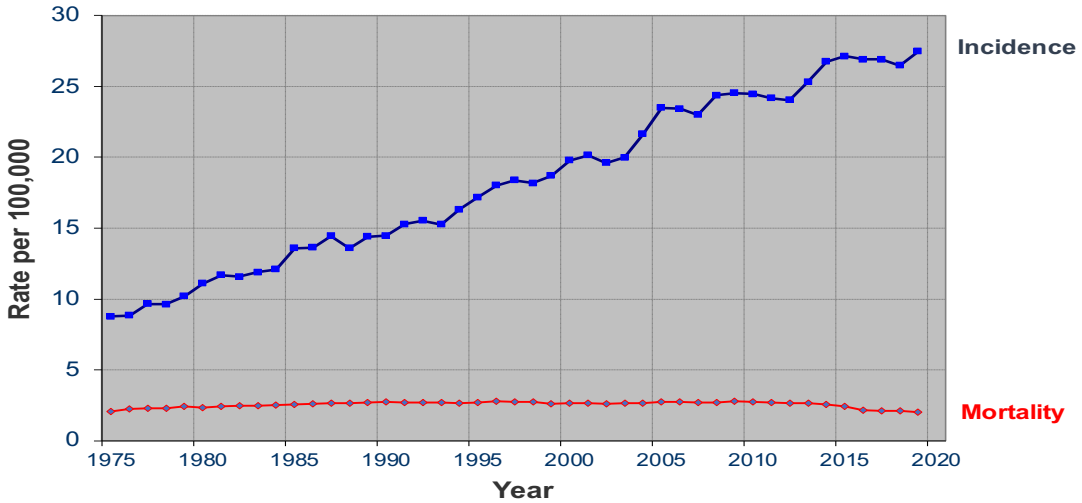


Which will progress?

Robra BP. (2021) Harms and Benefits of Cancer Screening. In: Bauer A.W., Hofheinz RD., Utikal J.S. (eds) Ethical Challenges in Cancer Diagnosis and Therapy. Recent Results in Cancer Research, vol 218. Springer, Cham. https://doi.org/10.1007/978-3-030-63749-1_7

Environment of overdiagnosis

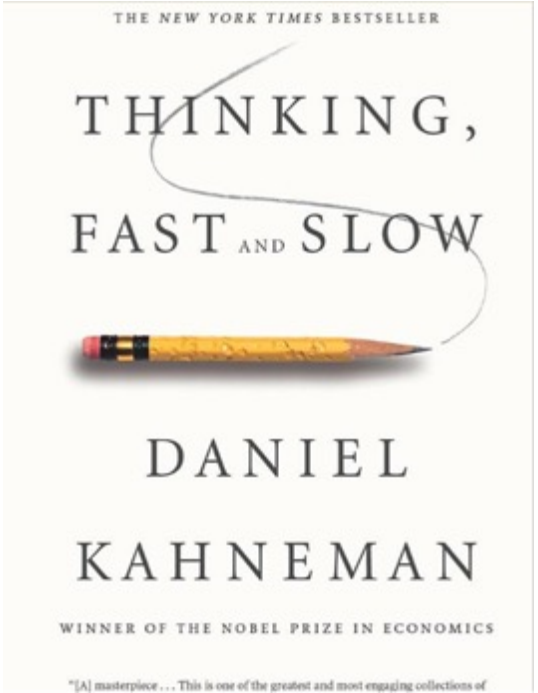
- Heightened awareness by patients and clinicians
- Pressure to diagnose melanomas early
- Fear of missing melanoma—“loss aversion”



Brodersen J, Schwartz LM, Woloshin S. Overdiagnosis: how cancer screening can turn indolent pathology into illness. APMIS. 2014;122(8):683-689. doi:10.1111/apm.12278

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

Brodersen J, Schwartz LM, Woloshin S. Overdiagnosis: how cancer screening can turn indolent pathology into illness. APMIS. 2014;122(8):683-689. doi:10.1111/apm.12278

Gold Standard

Pathologic Diagnosis

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."

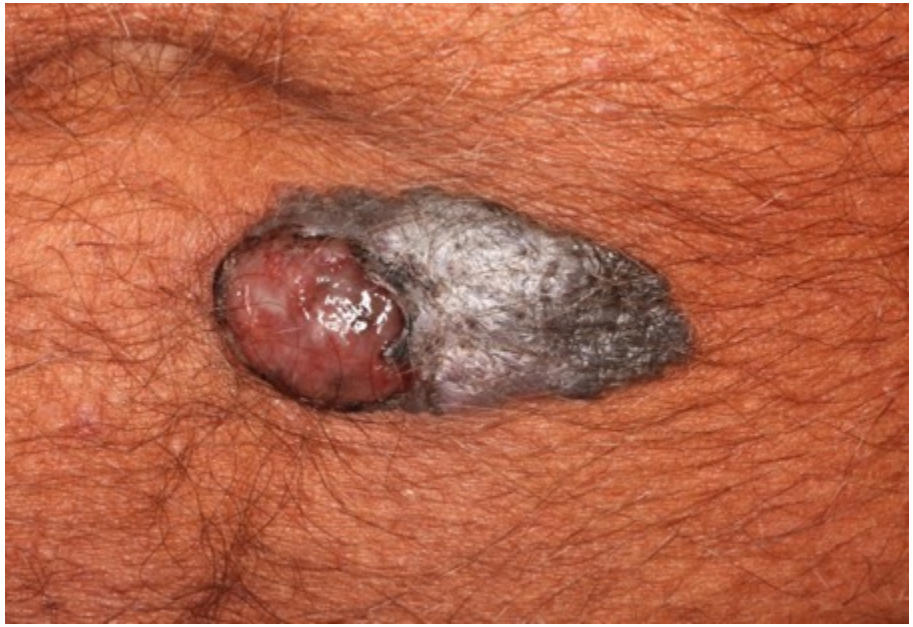
Pathology: Diagnostic Gold Standard

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

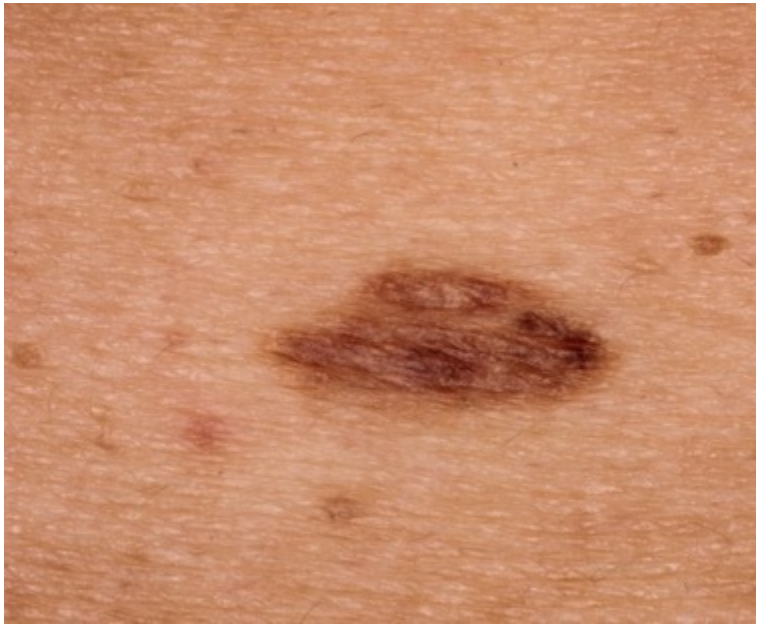
Elmore JG, Barnhill RL, Elder DE, et al. Pathologists' diagnosis of invasive melanoma and melanocytic proliferations: observer accuracy and reproducibility study [published correction appears in BMJ. 2017 Aug 8;358:j3798]. BMJ. 2017;357:j2813.

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.
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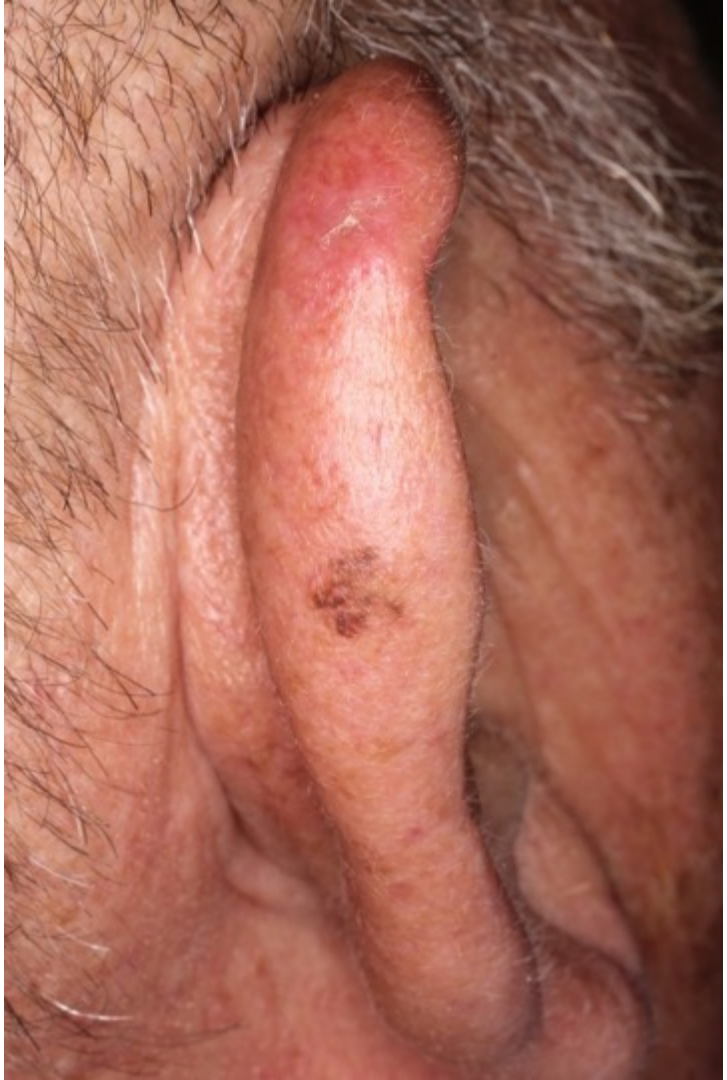
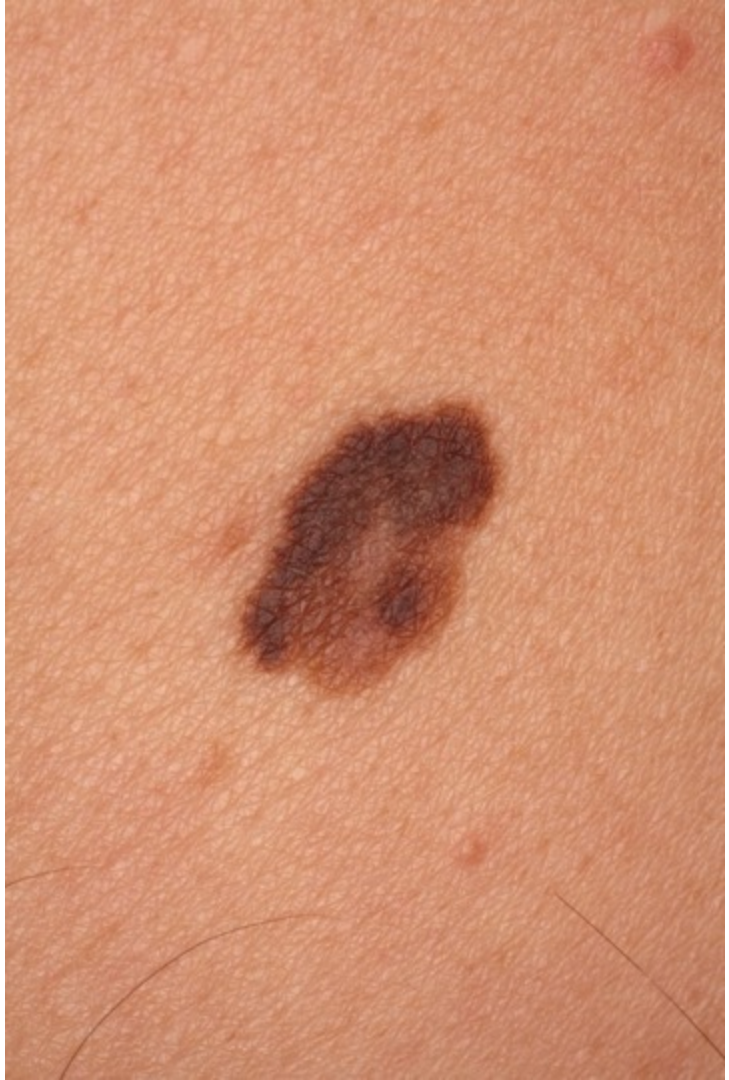


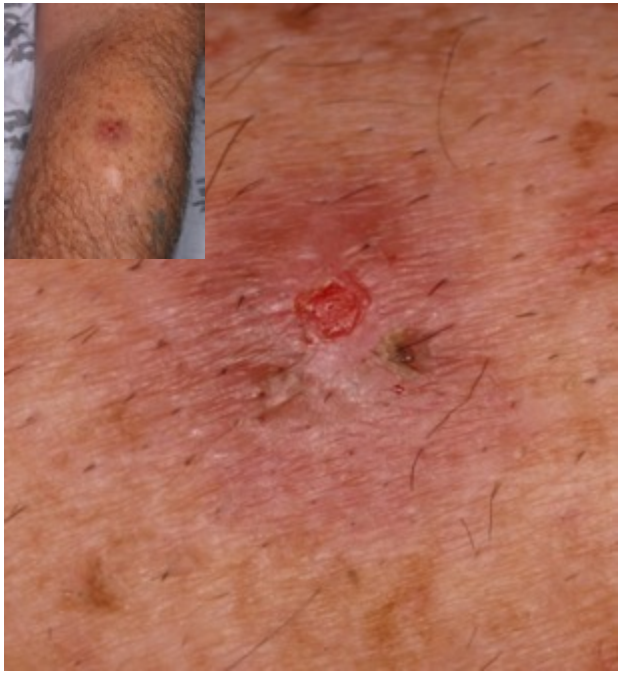


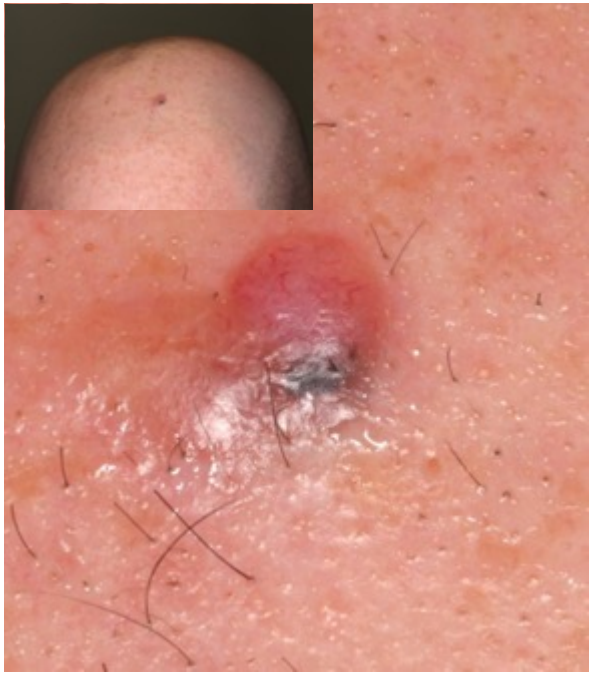
Fast growing + Unrecognizable melanomas

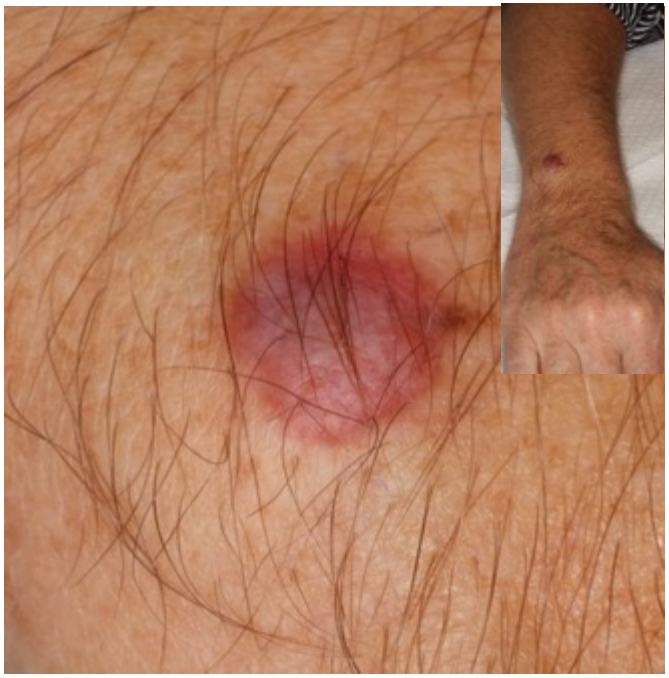
- More common in older men
- Lacks the ABCD signs of slow growing melanoma
- Nonspecific appearance
  - Misdiagnosed as BCC, seborrheic keratosis, scar, hemangioma, dermatofibroma, skin tag & inflammatory diseases
- Not amenable to screening—grows too fast + not recognizable

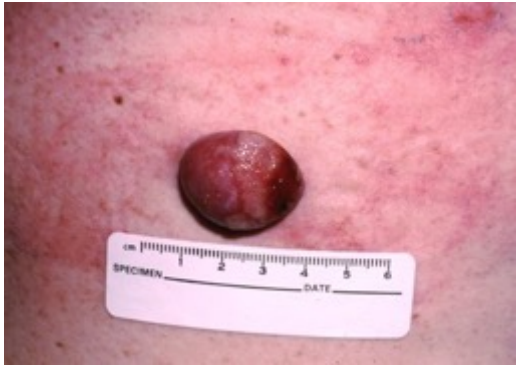
Liu W, Dowling JP, Murray WK, et al. Rate of growth in melanomas: characteristics and associations of rapidly growing melanomas. Arch Dermatol. 2006;142:1551-1558.

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.





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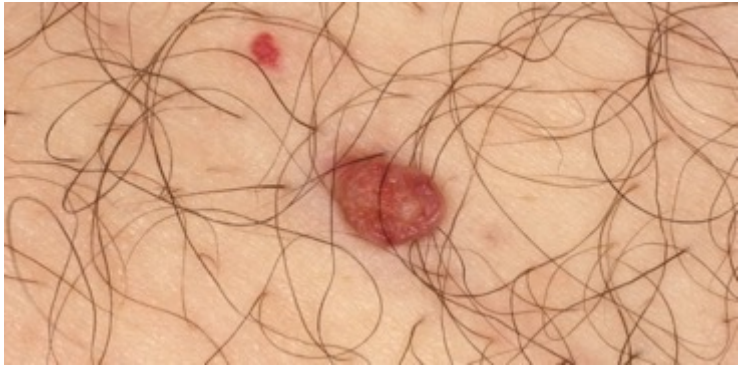
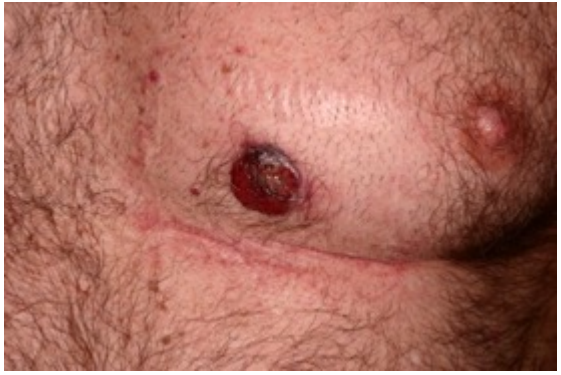
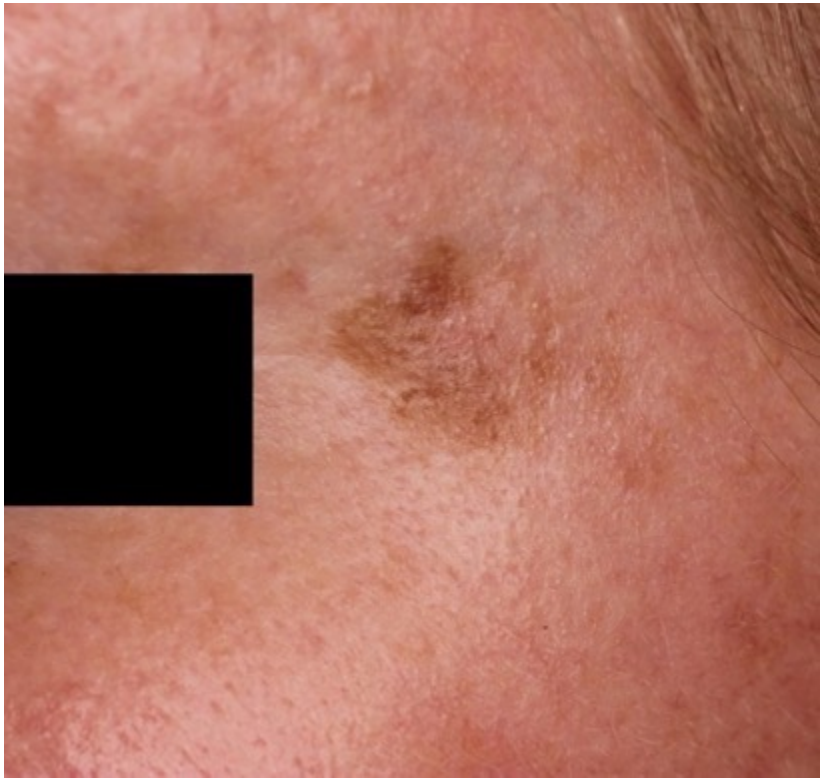
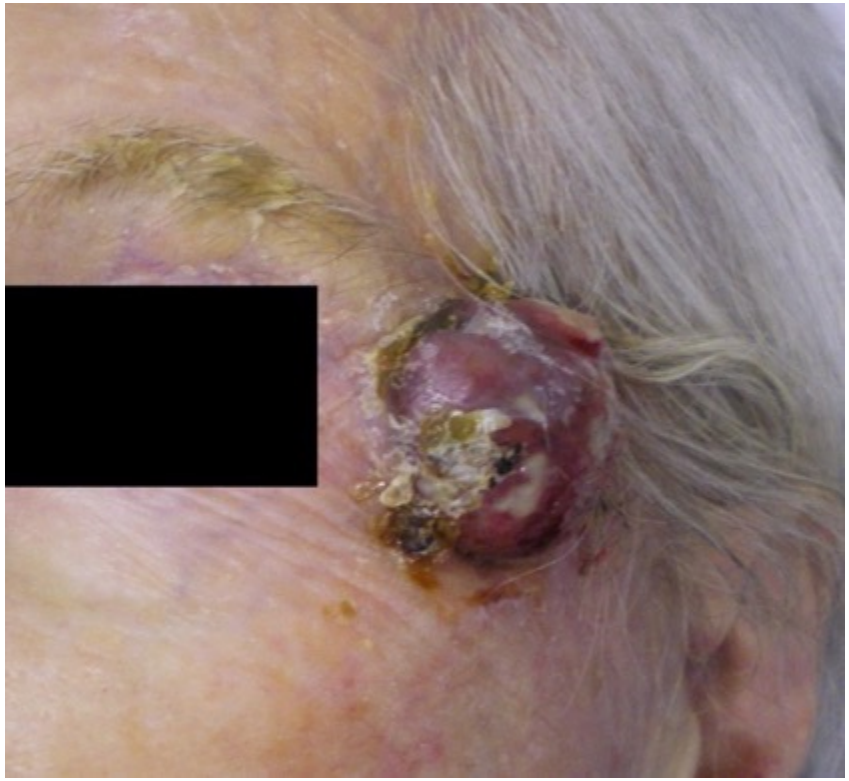




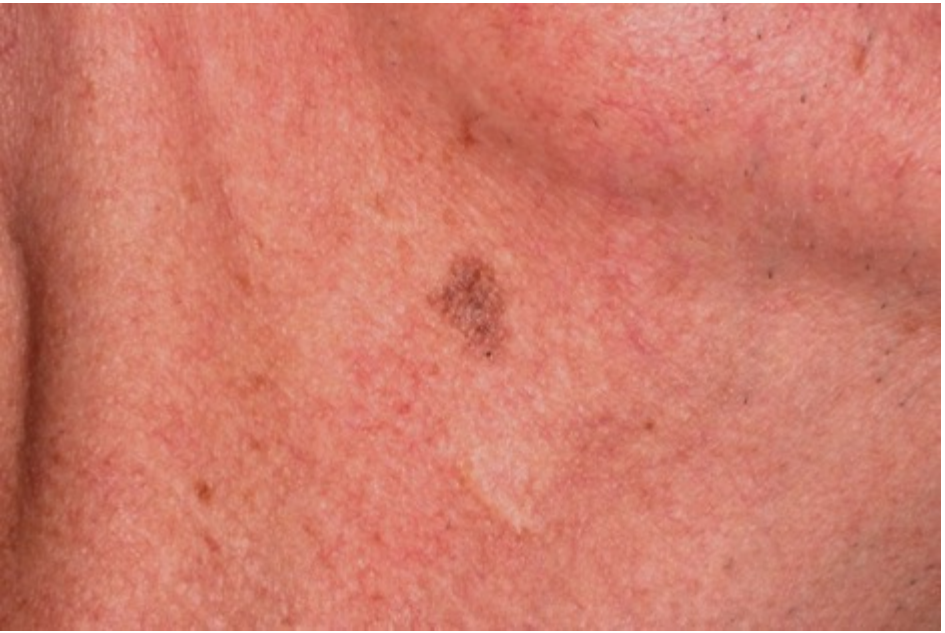
Not the obligate precursor

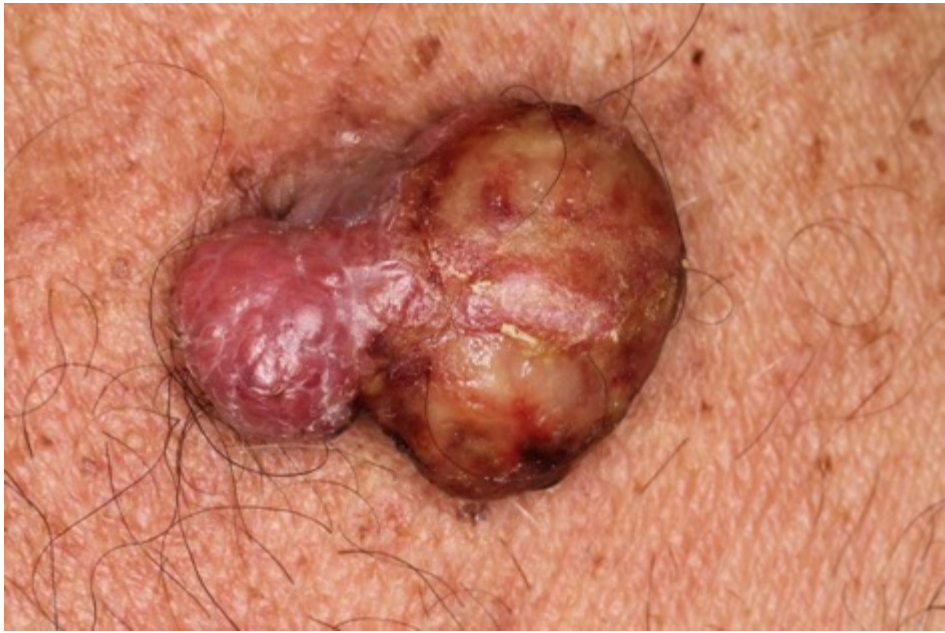




Melanoma in-situ

Not the obligate precursor





Melanoma in-situ

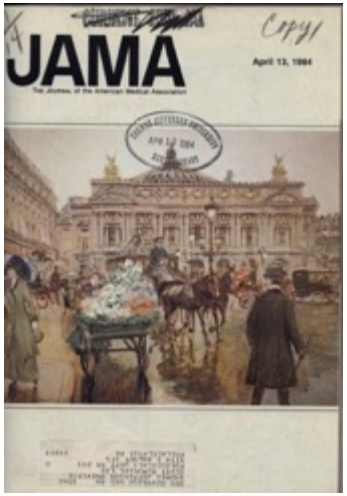
Incidence of in Situ vs Invasive Melanoma: Testing the "Obligate Precursor" Hypothesis

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

Olsen CM,Pandeya N,RosenbergPS,Whiteman DC.Incidence of in-situ vs invasive melanoma: testing the "obligate precursor" hypothesis. J Natl Cancer Inst. 2022;114(10):1364-1370.



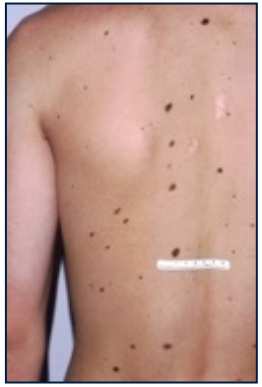
CONSENSUS CONFERENCE **1984**

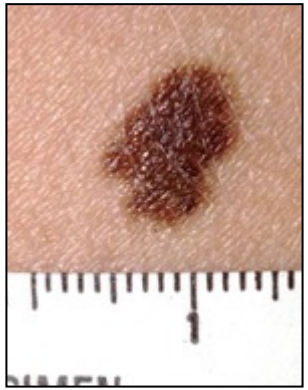
Precursors to Malignant Melanoma 1864

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)

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





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

Duffy K, Grossman D. The dysplastic nevus: from historical perspective to management in the modern era: part II. Molecular aspects and clinical management. *J Am Acad Dermatol*. 2012;67(1):19.e1-32. doi:10.1016/j.jaad.2012.03.013

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)

Tsao et al. Arch Dermatol 2003;139:282-8

Efforts to minimize re-excision of dysplastic nevi

AAD Effort

https://www.aad.org/member/practice/mips/measures/2022/aad13 (not 2023)

WHO

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

[a]Architectural 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

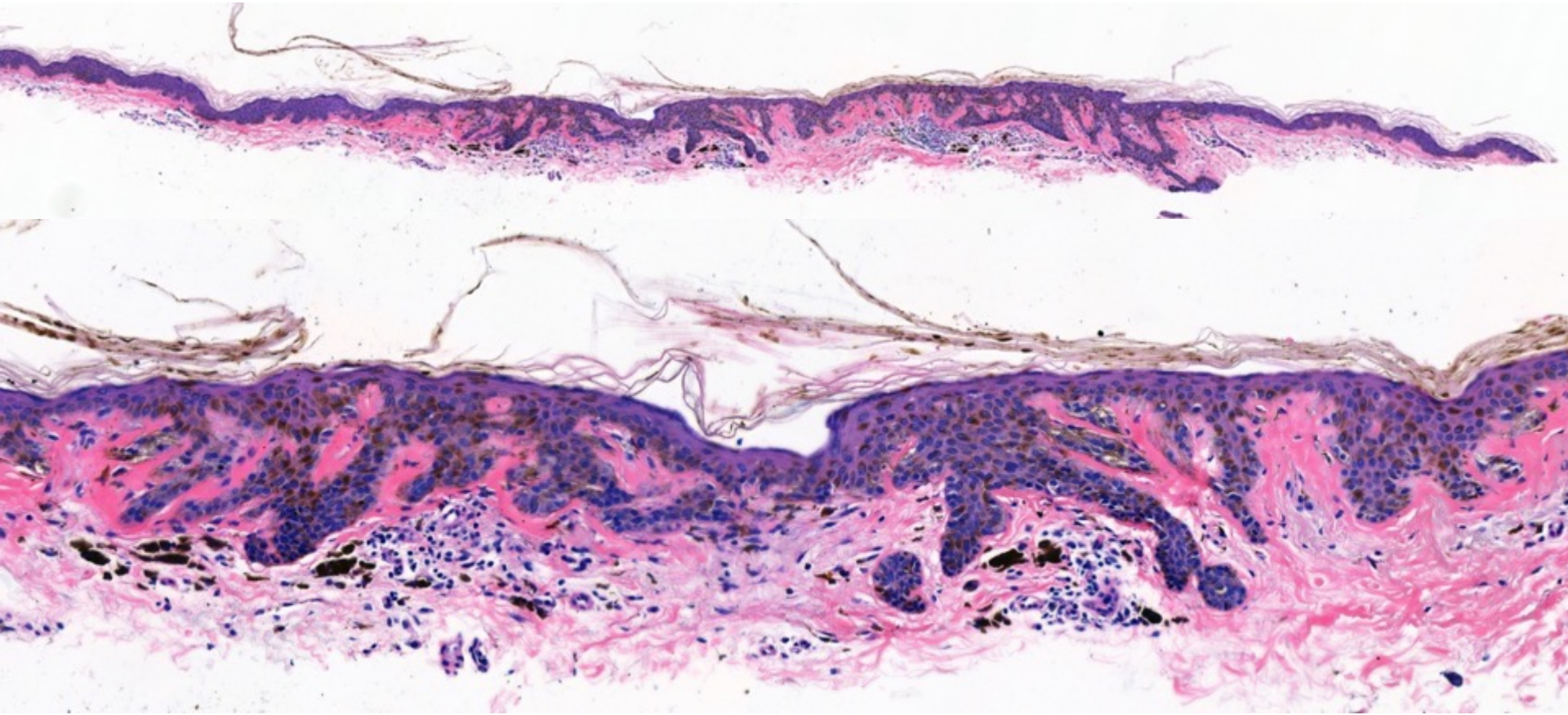
Elder DE, Massi D, Scolyer RA, Willemze R, editors (2018). WHO classification of skin tumours. 4th Ed. Lyon: IARC

Table of Contents: Melanocytic Nevi & Melanoma

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

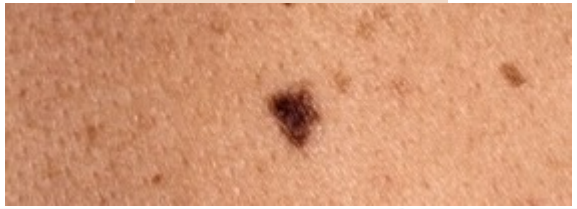
2017 *BMJ*

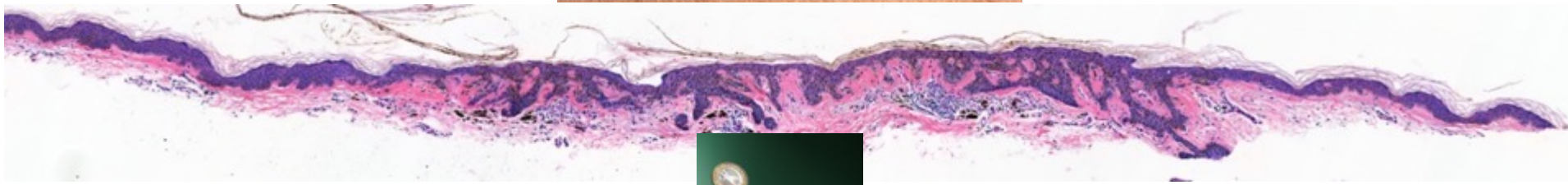
Pathologists' diagnosis of invasive melanoma and melanocytic proliferations: observer accuracy and reproducibility study

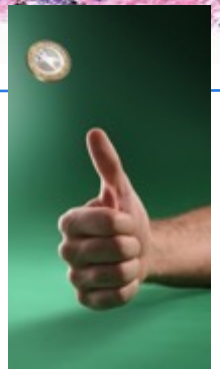
Joann G Elmore,[1] Raymond L Barnhill,[2] David E Elder,[3] Gary M Longton,[4] Margaret S Pepe,[4] Lisa M Reisch,[1] Patricia A Carney,[5] Linda J Titus,[6] Heidi D Nelson,[7,8] Tracy Onega,[9,10] Anna N A Tosteson,[11] Martin A Weinstock,[12,13] Stevan R Knezevich,[14] Michael W Piepkorn[15,16]

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."







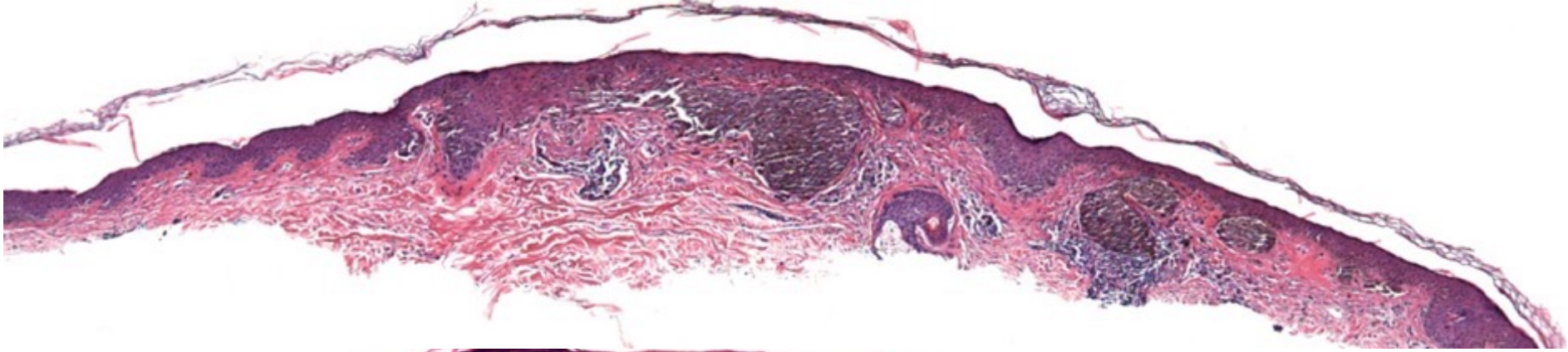
Nevus

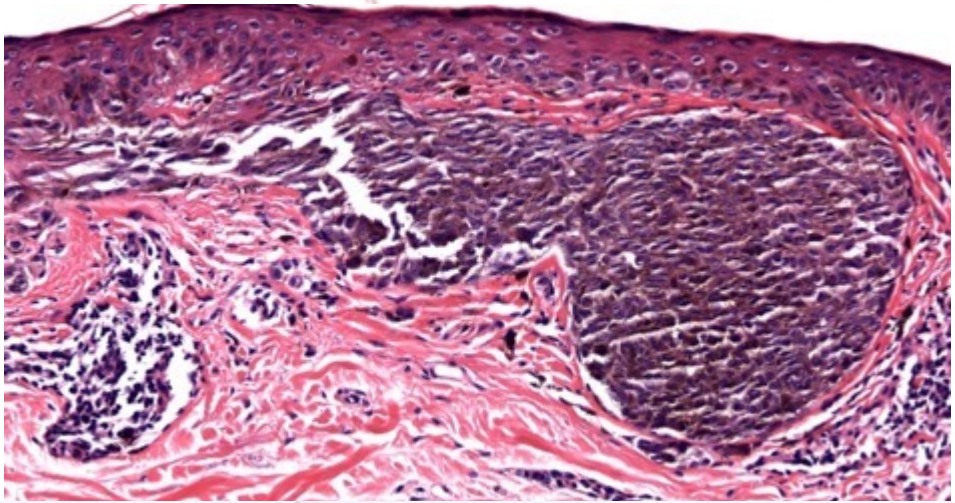
Nevus Moderate Atypia

Nevus Severe Atypia

Melanoma in-situ

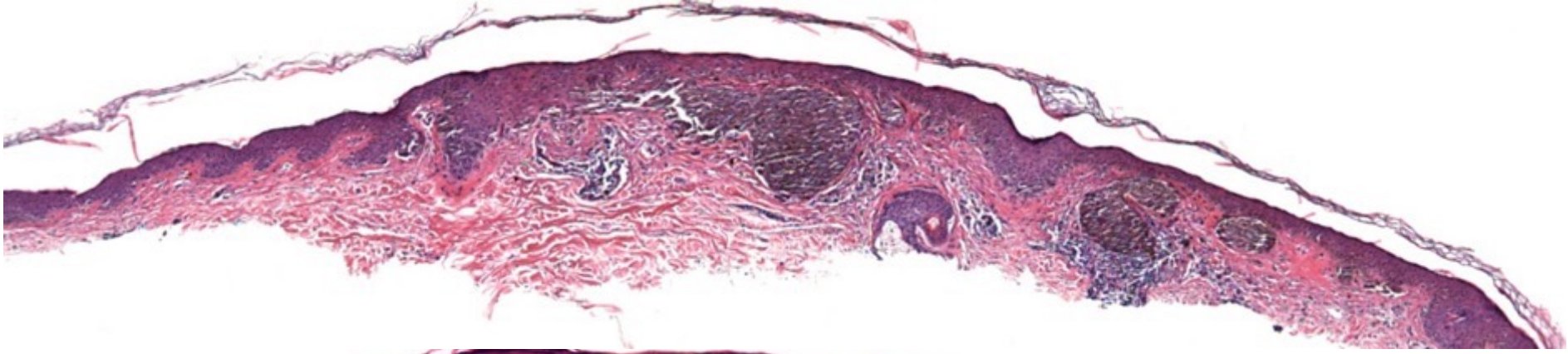
Biopsies of small FLAT melanocytic lesions (<5mm) is subject to a diagnostic gold standard that has questionable reliability

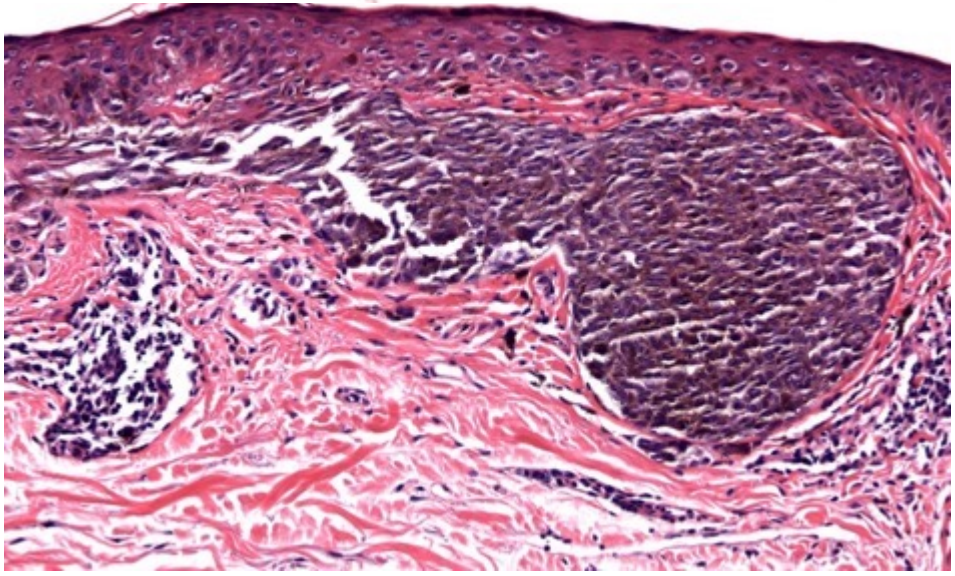




DIAGNOSIS: - RIGHT SHOULDER

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

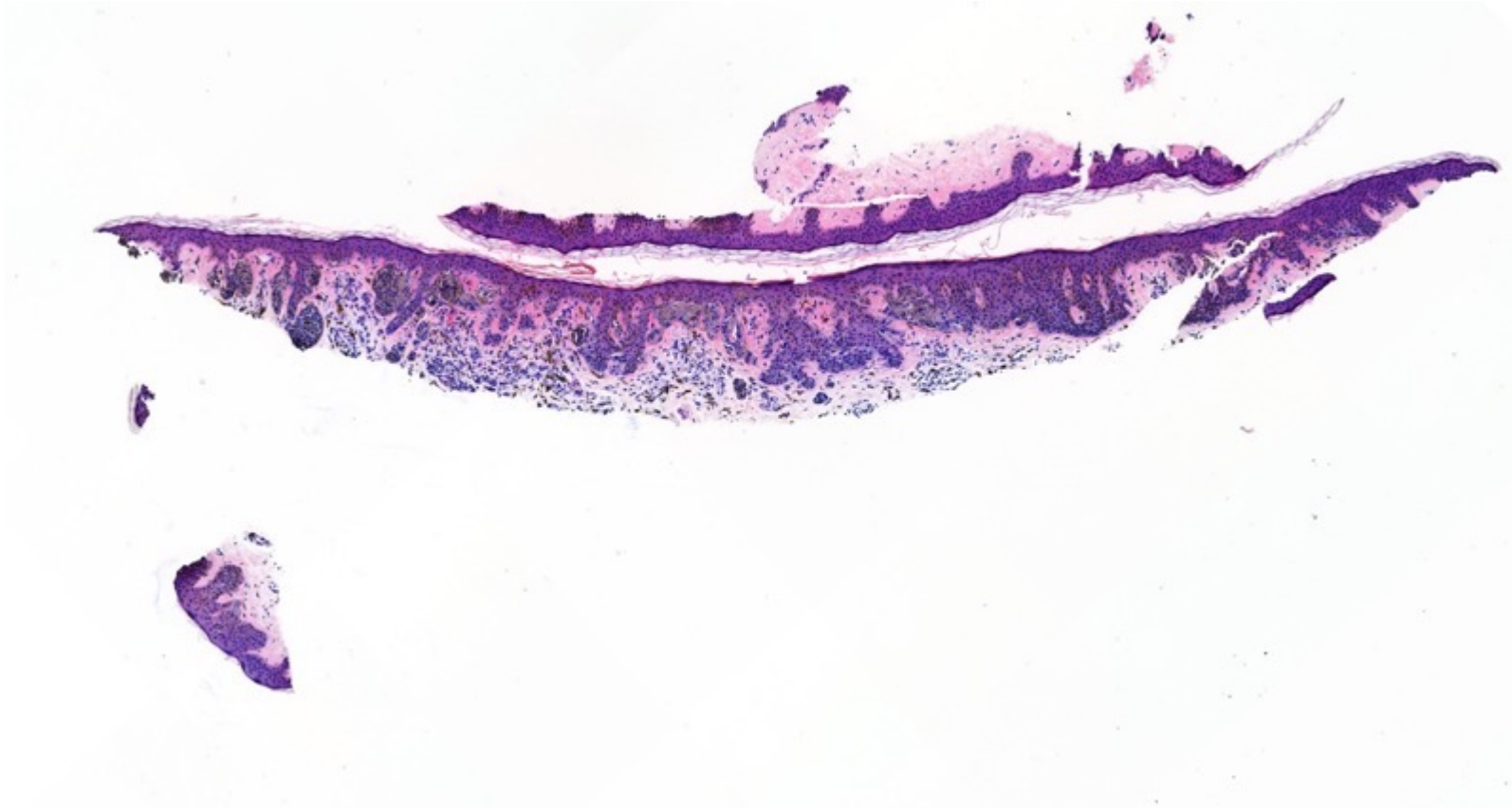


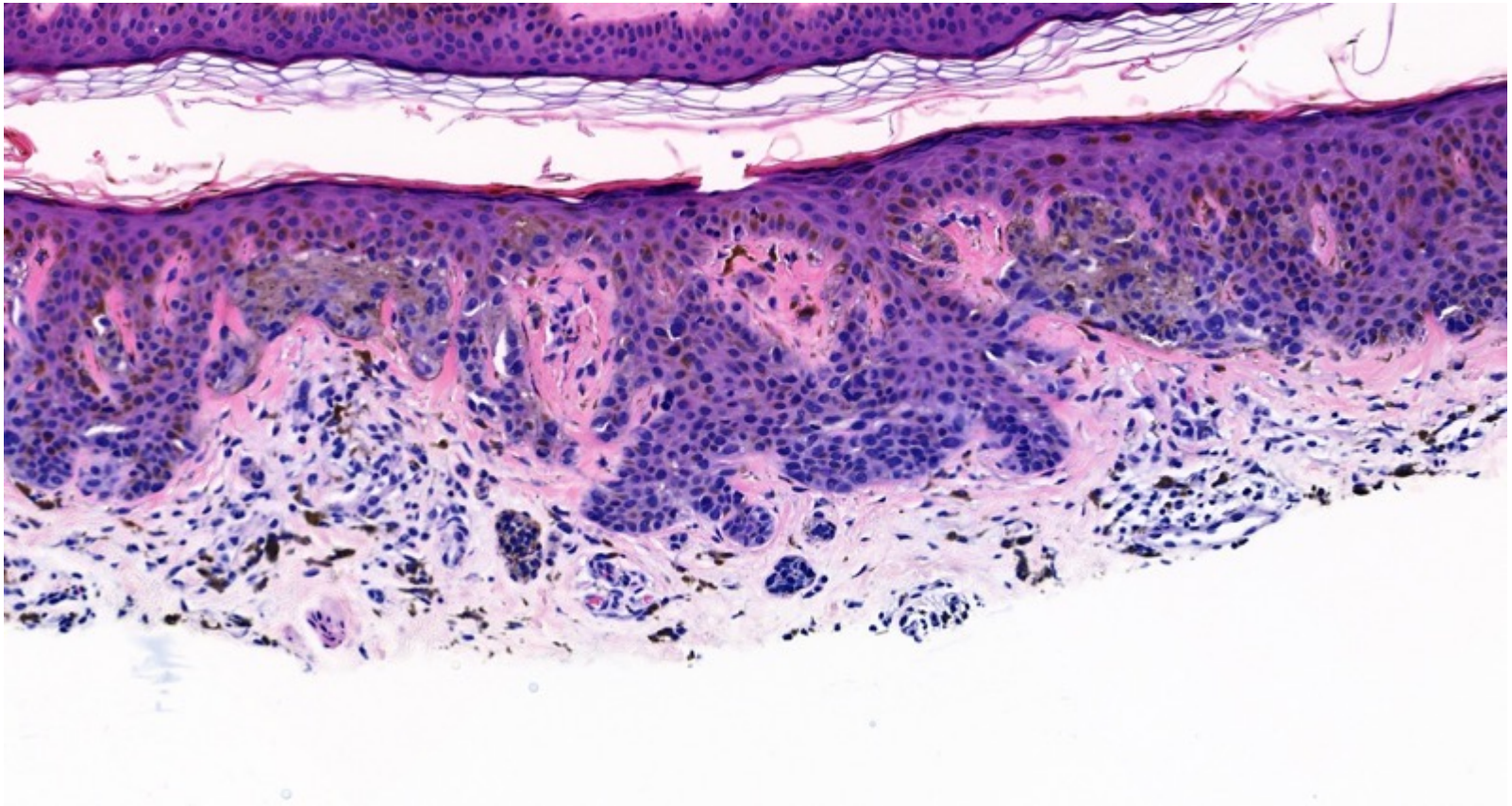


Compound Melanocytic Nevus, Clark

Case 2

51 yo woman, back

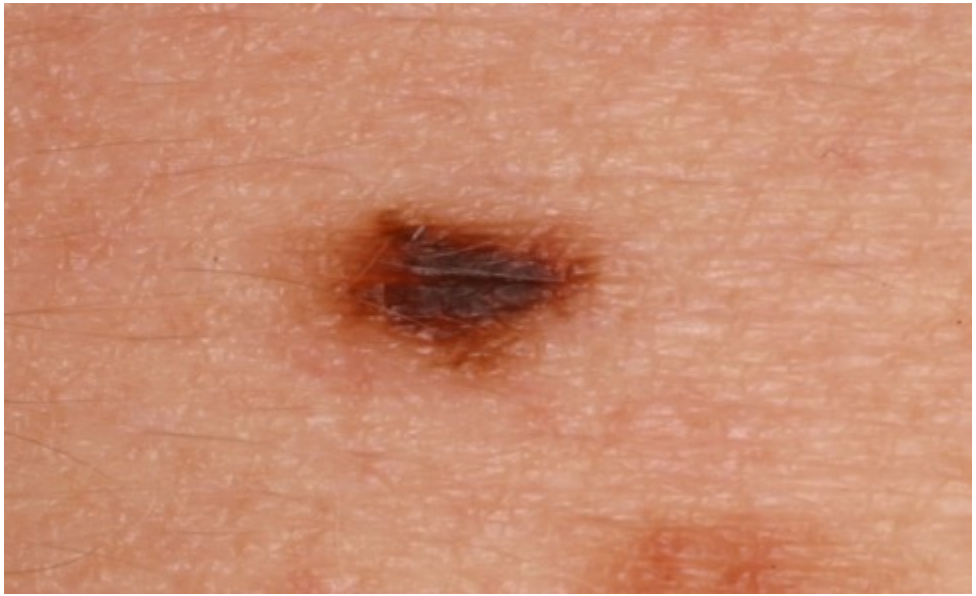




Part B: SKIN BIOPSY, MID BACK:
COMPOUND MELANOCYTIC NEVUS OF THE SKIN WITH ARCHITECTURAL DISORDER AND SEVERE CYTOLOGIC ATYPISM OF THE MELANOCYTES. (DYSPLASTIC NEVUS, SEVERE).
MARGINS ARE INVOLVED. A COMPLETE LOCAL EXCISION IS ADVISED WITH 5 MM LESION FREE MARGINS.

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

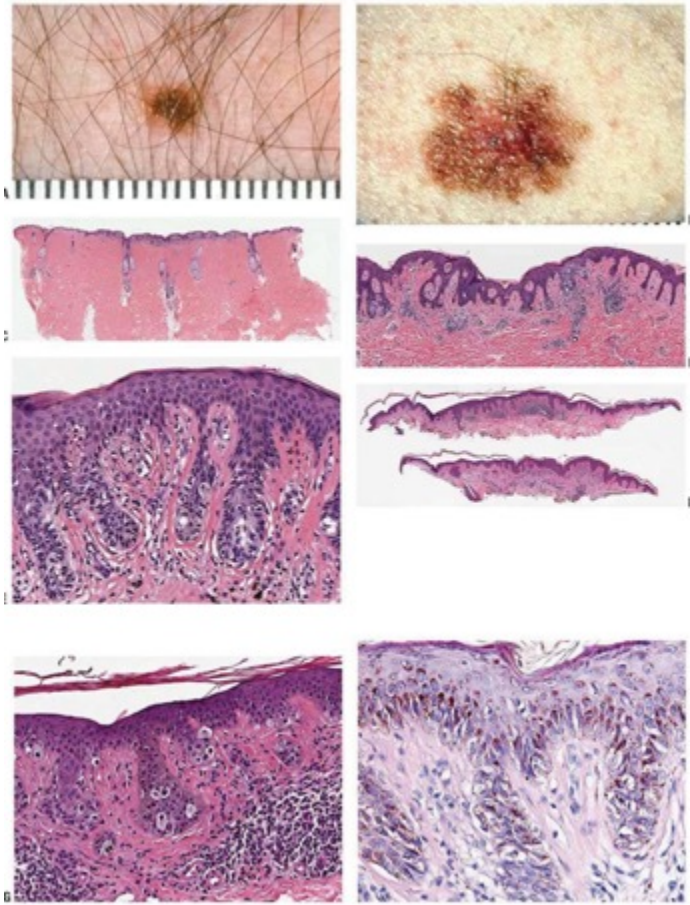
Dysplastic/Atypical/Clark Melanocytic nevus



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



Lever's Histopathology of Skin, Elder DE, Murphy GF, Xiaowei X editors, in Chap 28 p Benign Pigmented Lesions and Malignant Melanoma. p1916-28

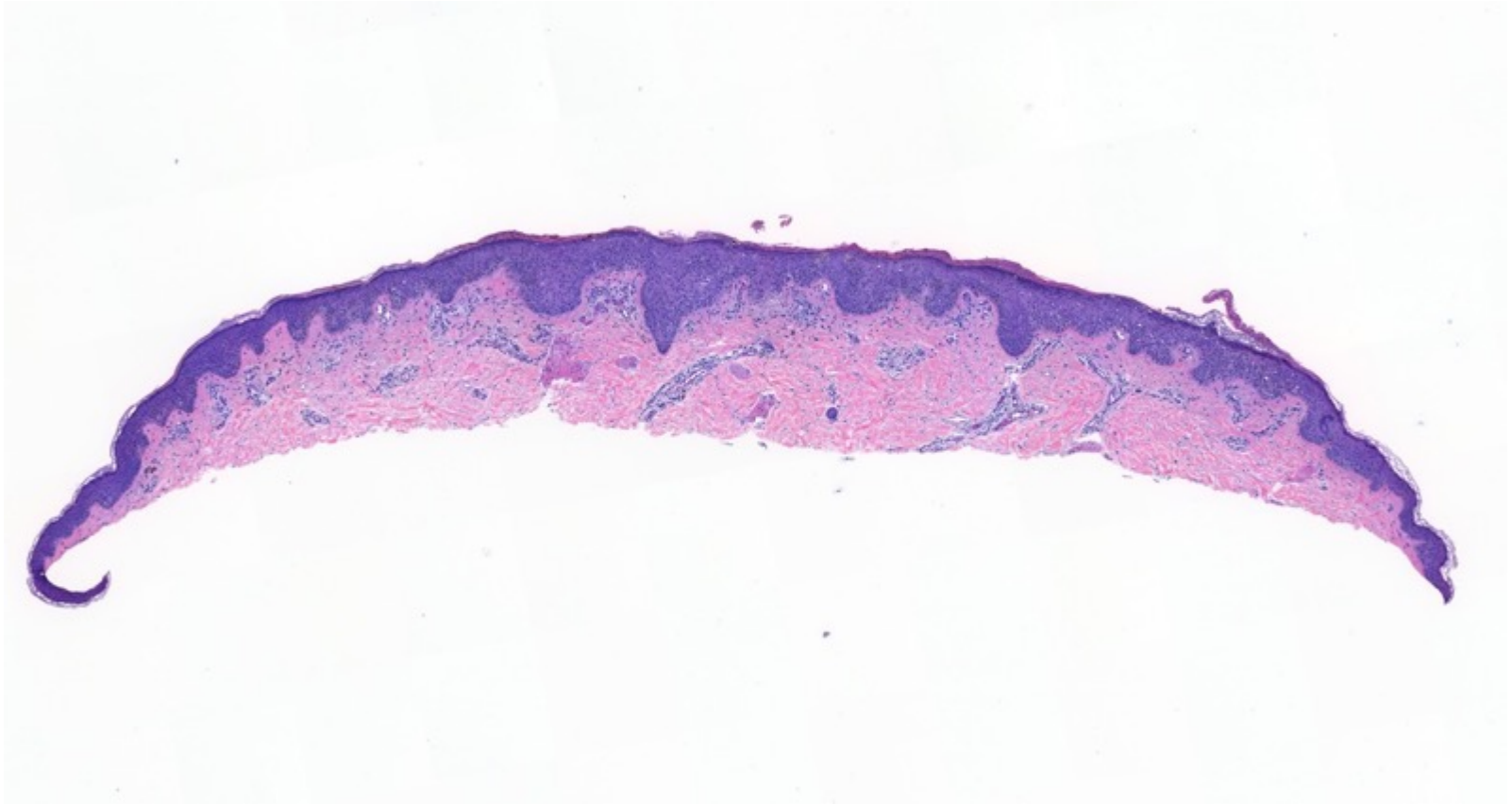
Dysplastic/Atypical/Nevus

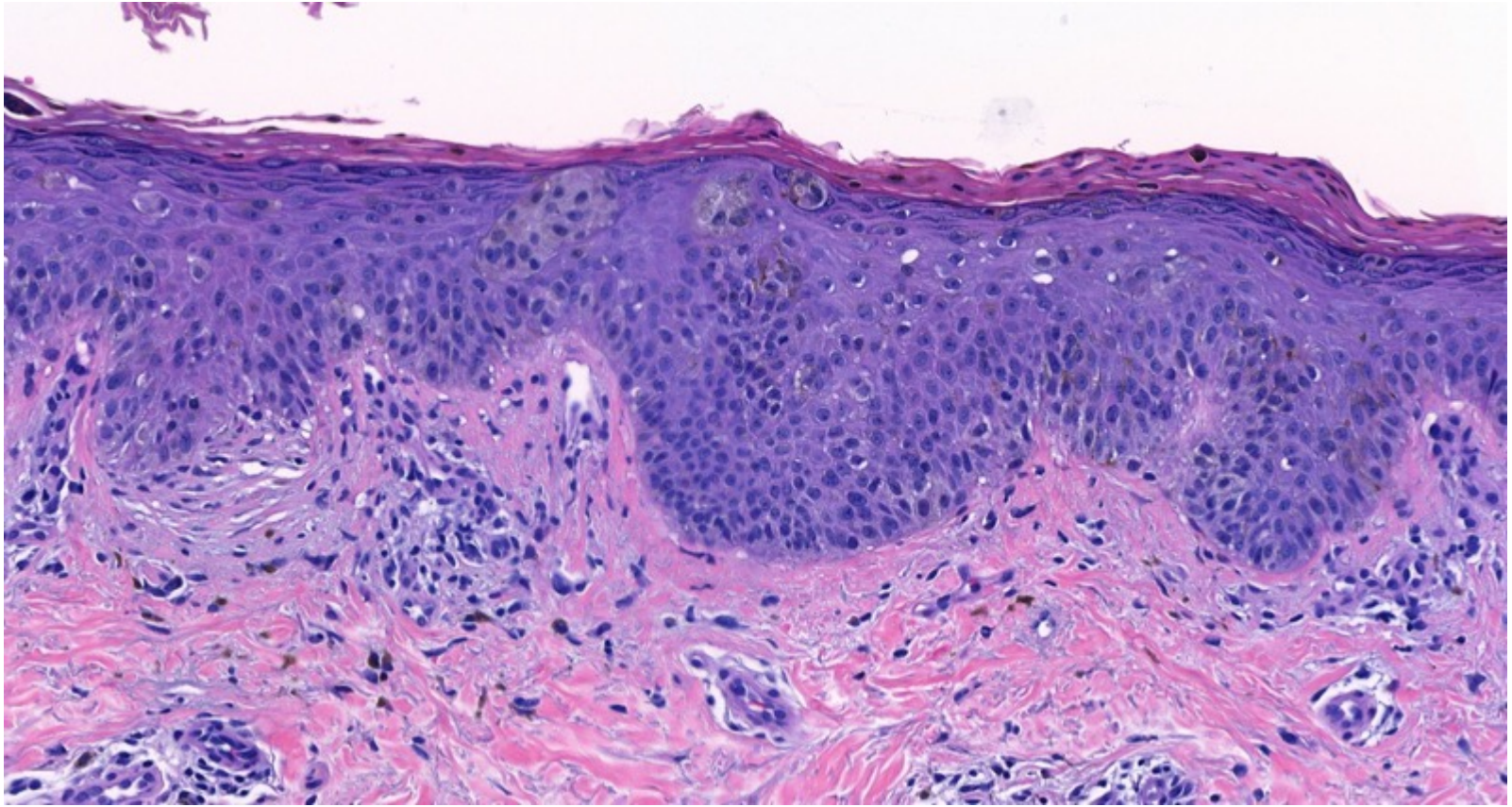
- None to minimal association with melanoma
- Most common type of nevus on Caucasian skin
- Pivoting away from aggressive diagnosis and management

- 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:	[redacted]	Ordering Provider:	
Ordering Location:	Jefferson Dermatology Center City	Collected:	05/17/2021 05:46 PM
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

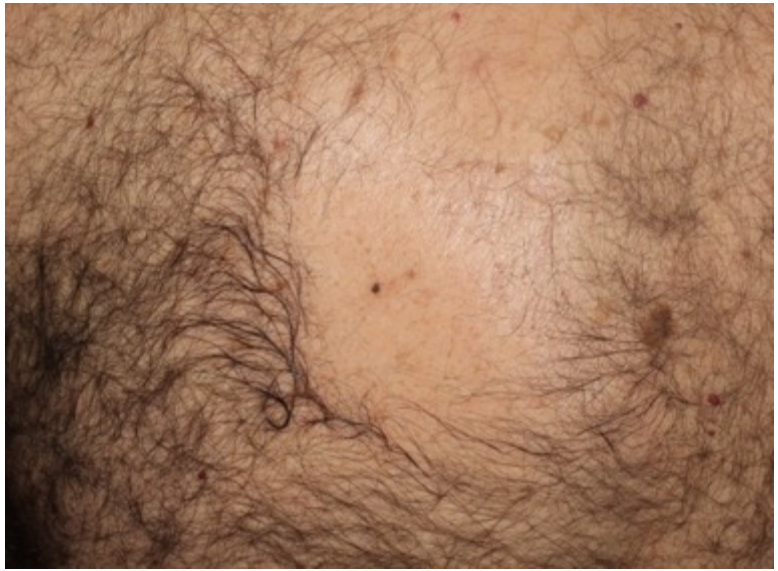
FINAL REPORT (08/11/22)

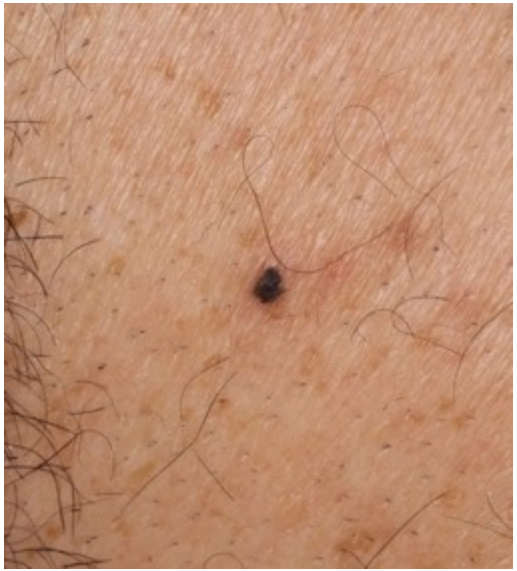
Diagnosis:
Right forearm - RESIDUAL MELANOMA IN-SITU, FOCALLY SPITZOID (SEE NOTE)

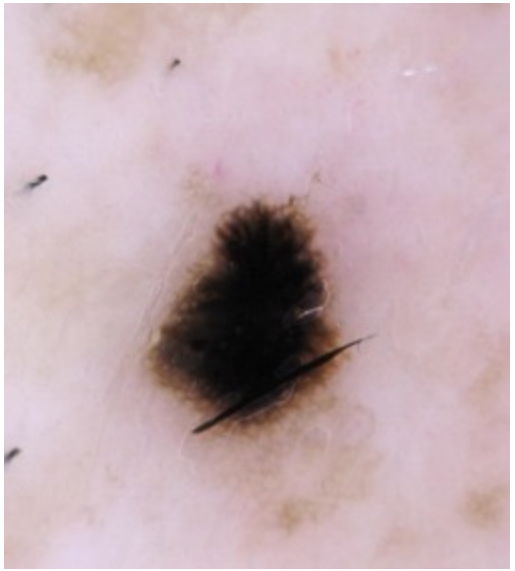
Note:
Prior to reviewing the original sections, the differential diagnosis was between pseudo-melanoma in-situ (residual atypical Spitz nevus with the melanomatous features secondary to previous procedure) and melanoma in-situ. In the context of the re-excision, the previous outside sections (DP21-08415 Jefferson Dermatopathology) 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

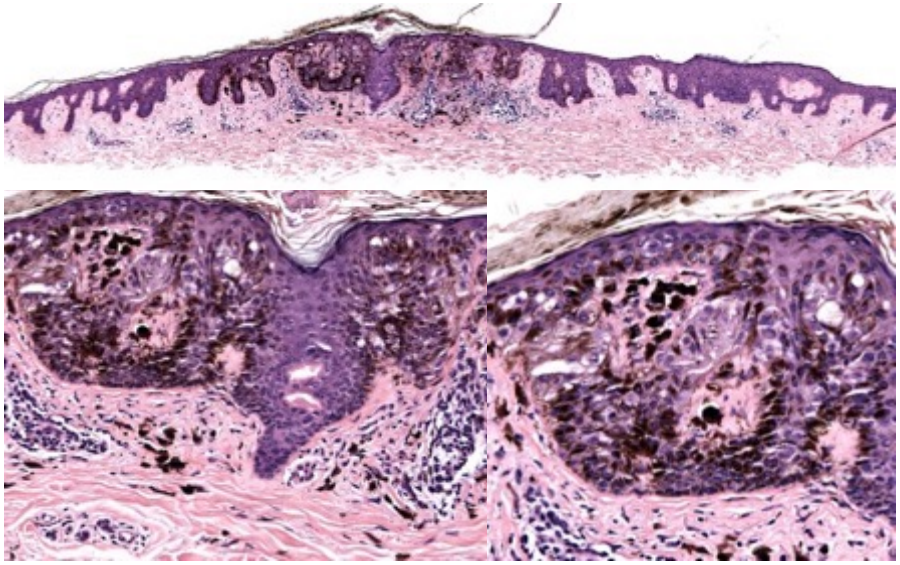
What is the diagnosis?



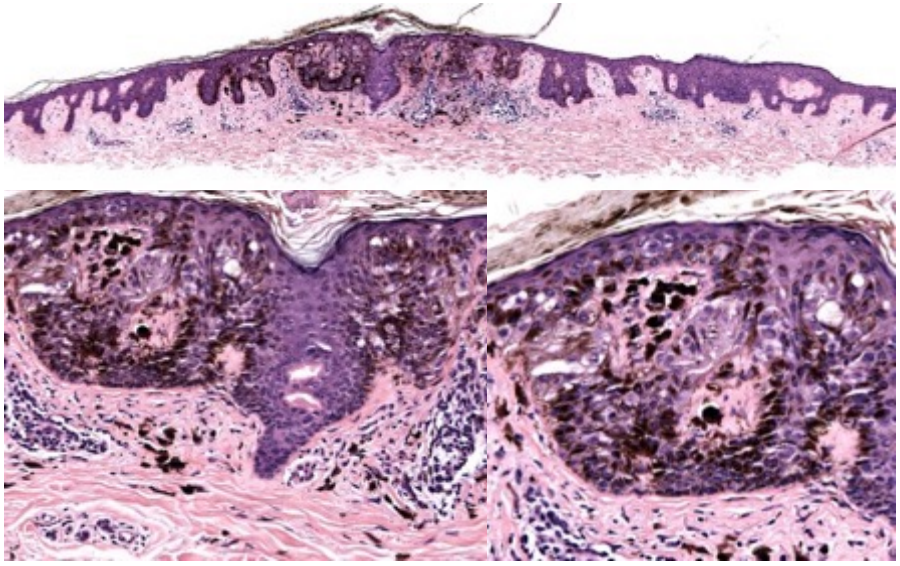




68 yo man



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

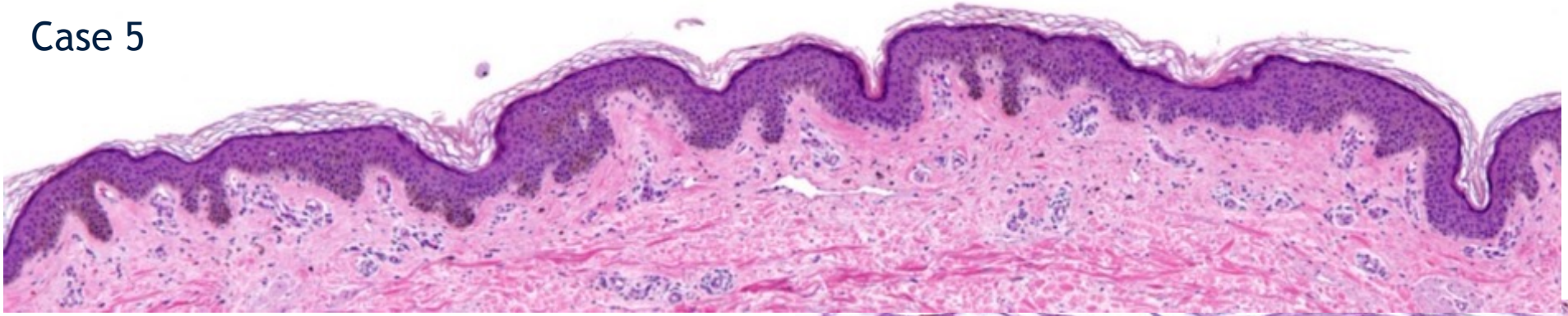
atypical or melanoma

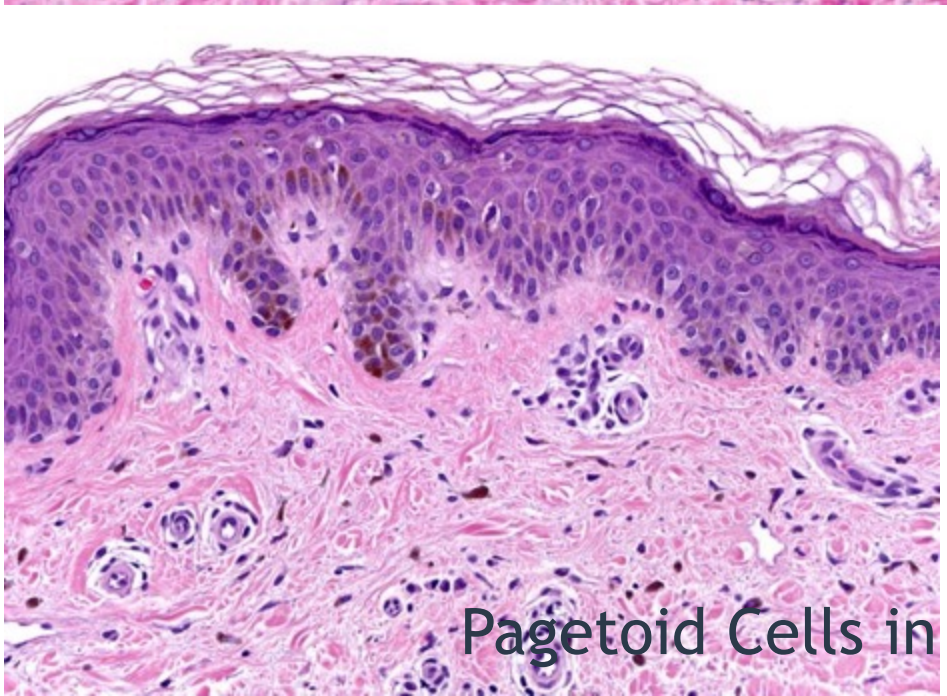
Body sites at risk of misdiagnosis as melanoma—"special site"

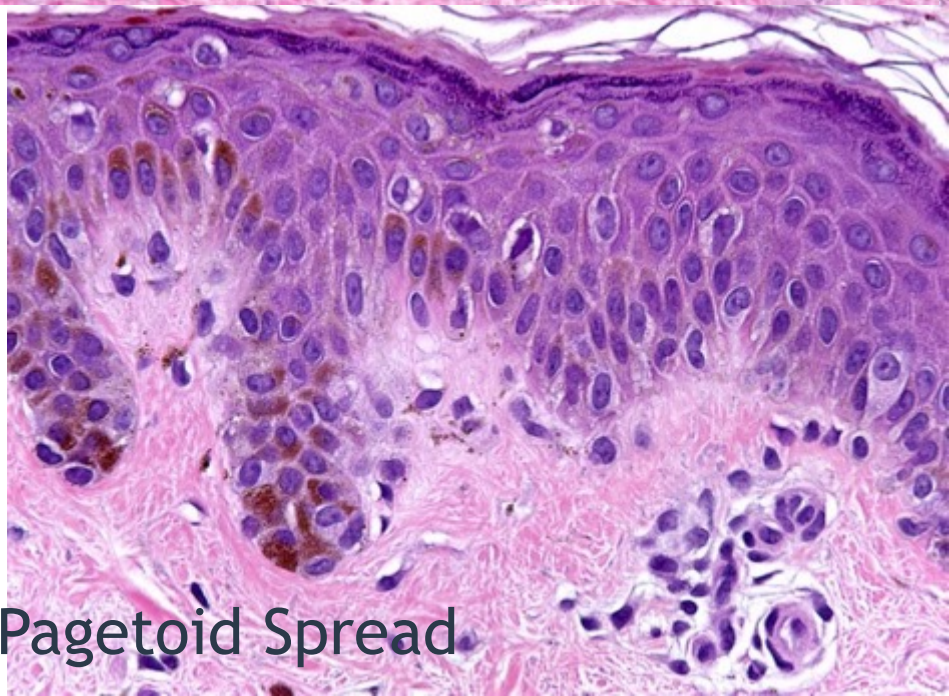
- Volar(Acral) skin
- Thigh
- Shin/Ankle
- Ear
- Breast/Milk line
- Genitalia
- Umbilicus
- Shoulder
- Scalp

Cecinaro AM et al. Am J Dermatopathol 2016;38:867–881
Hosler GA, J Cutan Pathol 2008; 35: 889–898

Case 5

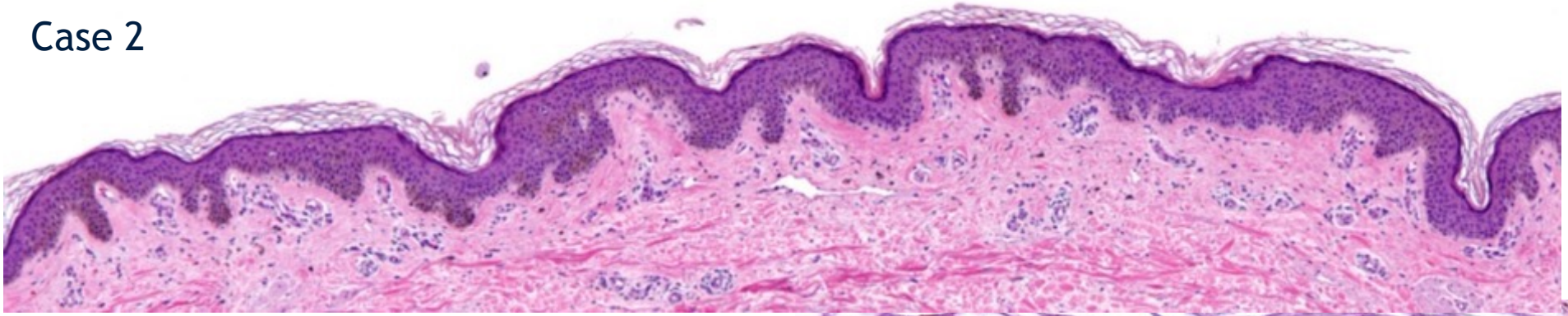


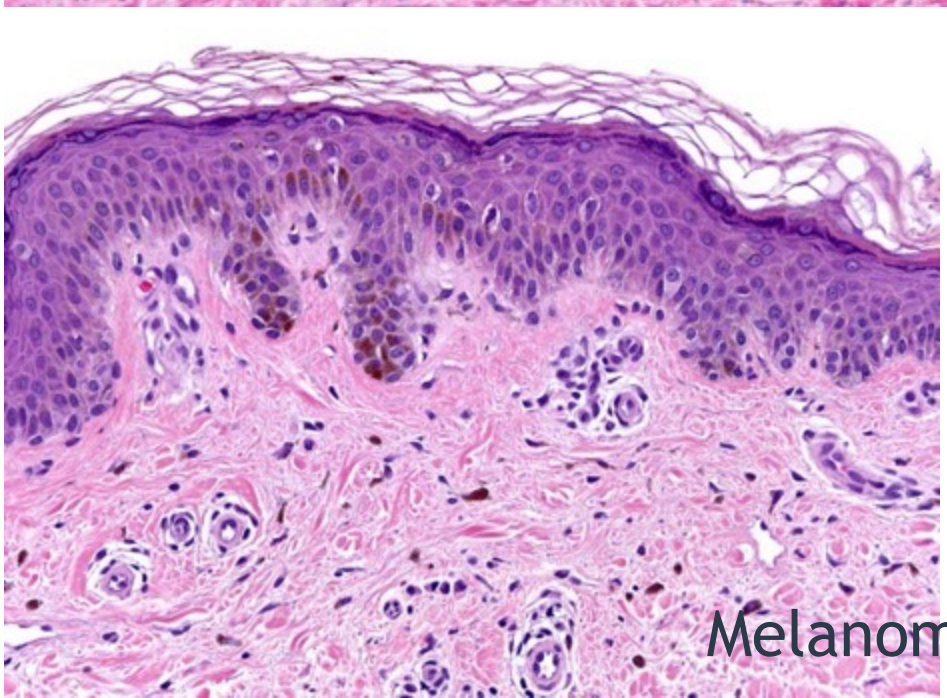


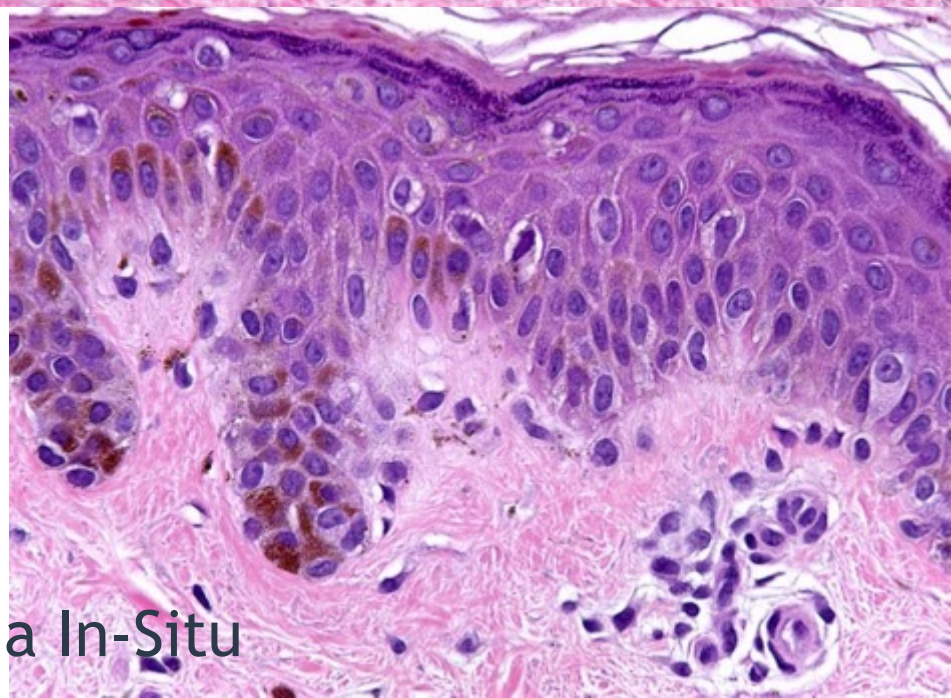


Pagetoid Cells in Pagetoid Spread

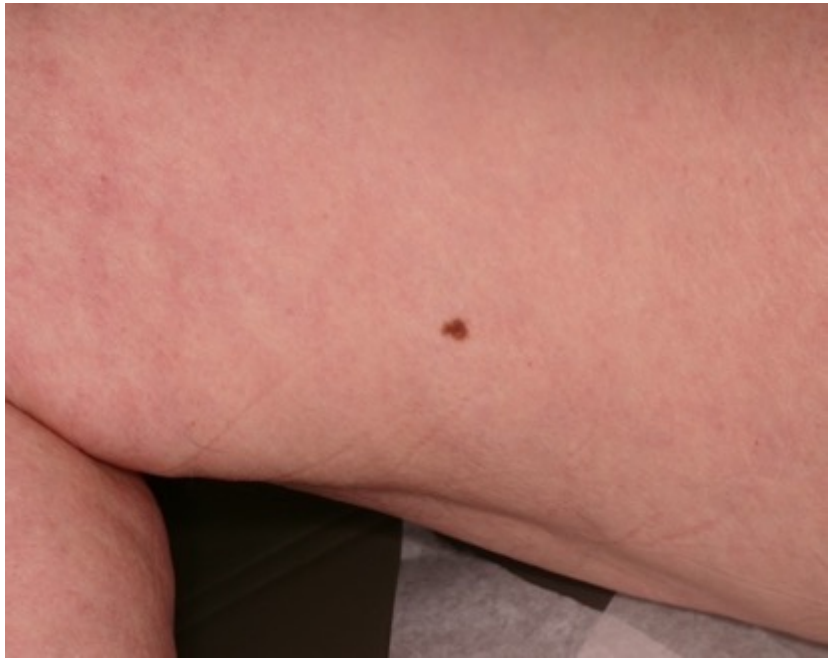
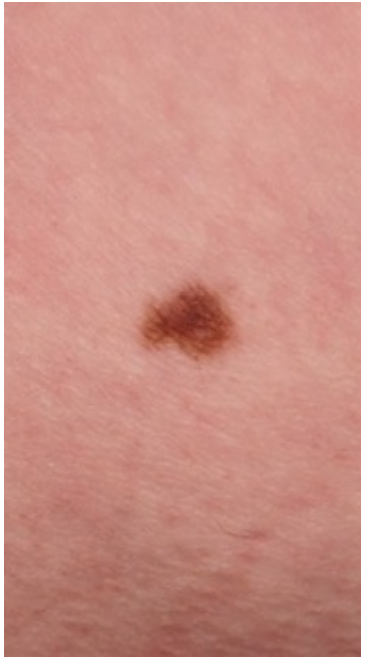
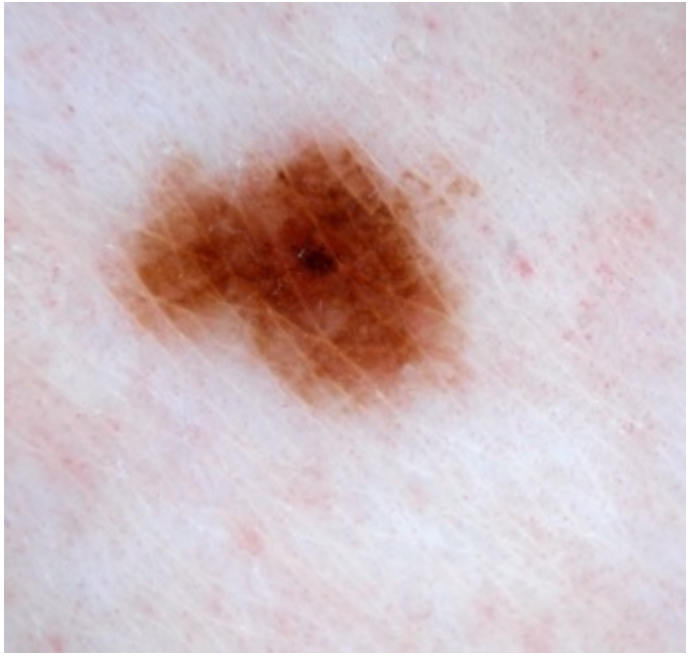
Case 2



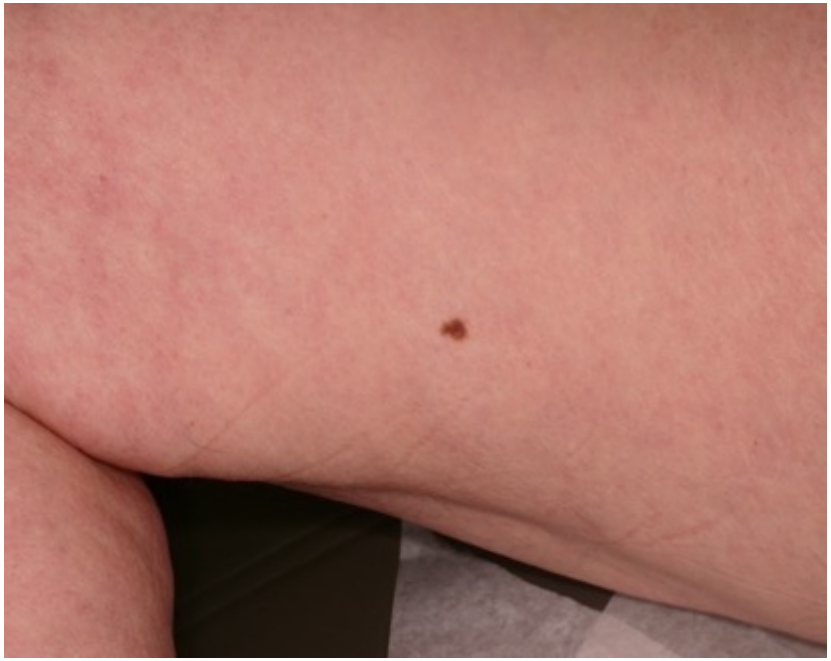
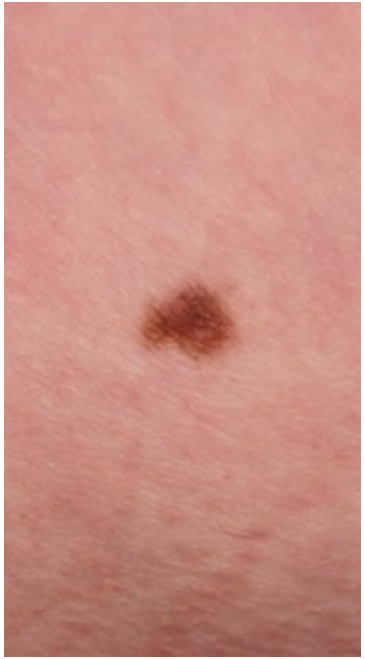
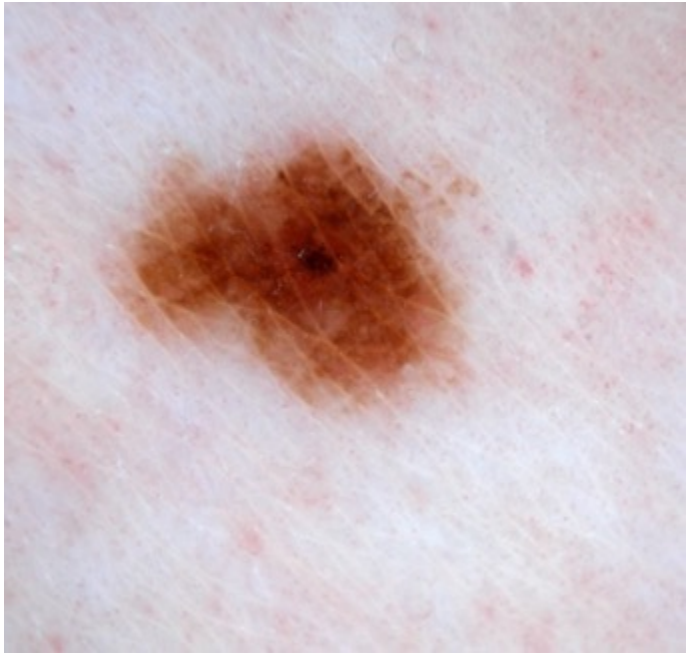




Melanoma In-Situ

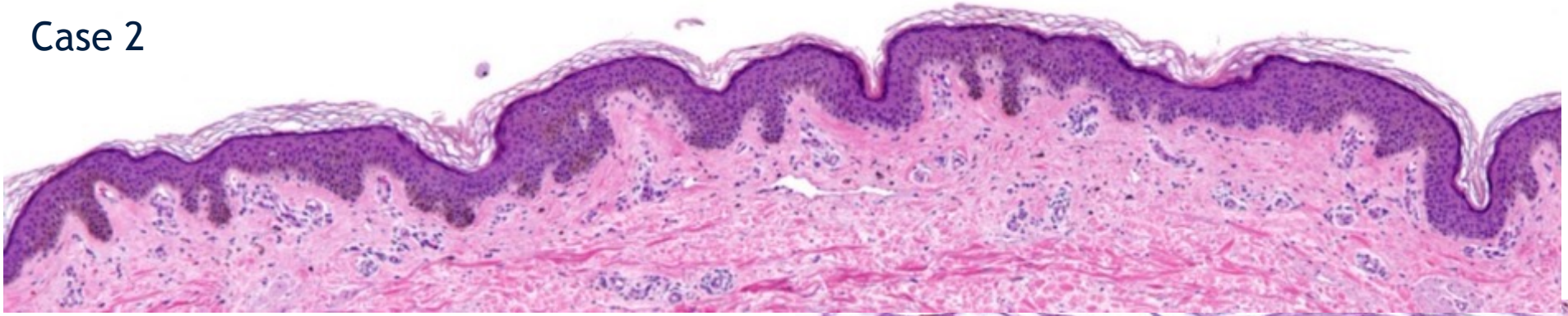




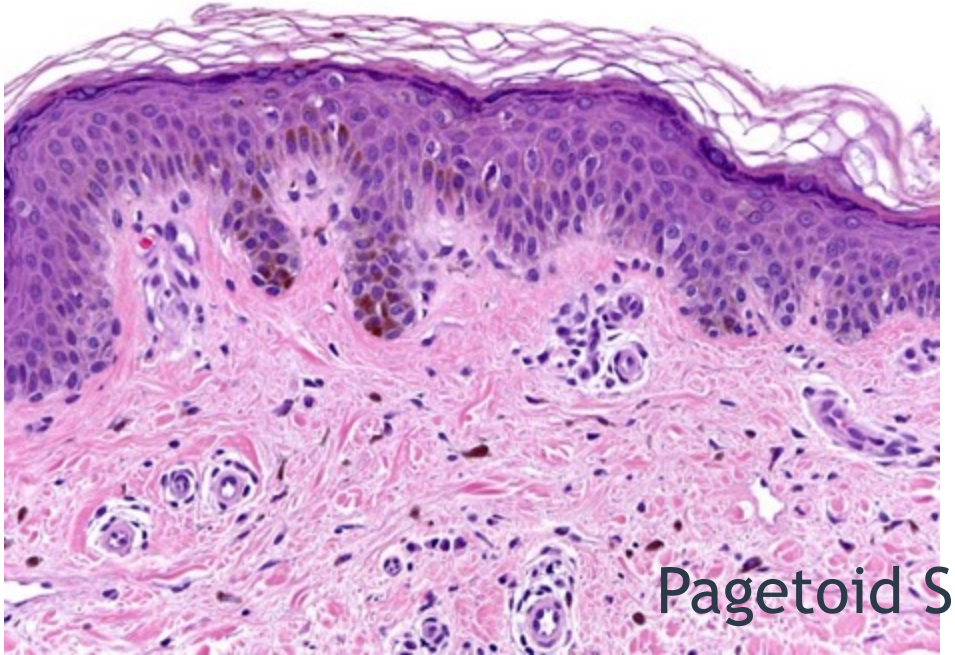
61 yo woman

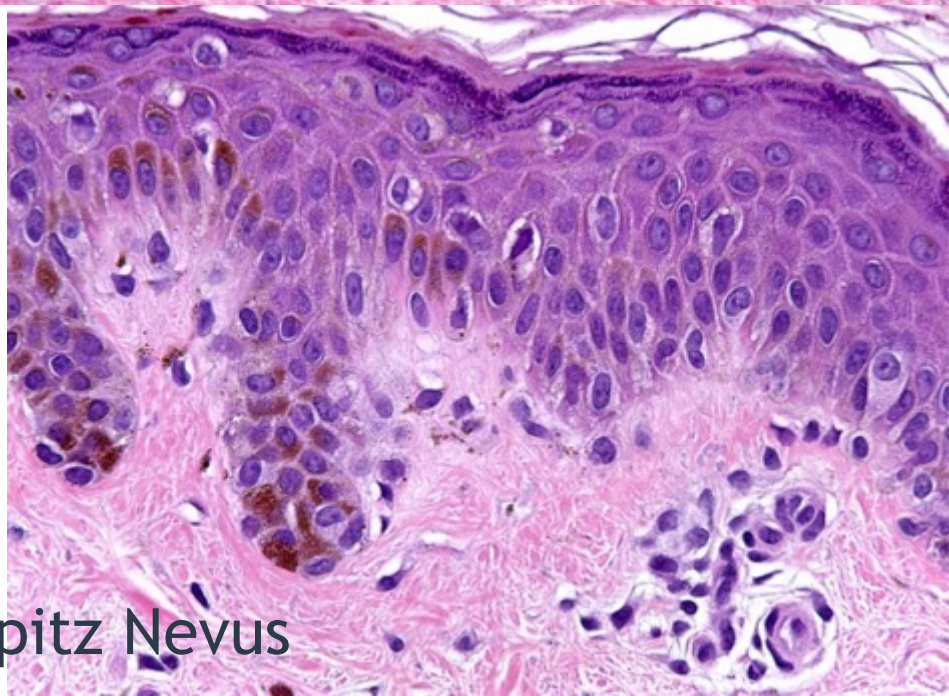




Pagetoid Spitz nevus

Case 2







Pagetoid Spitz Nevus

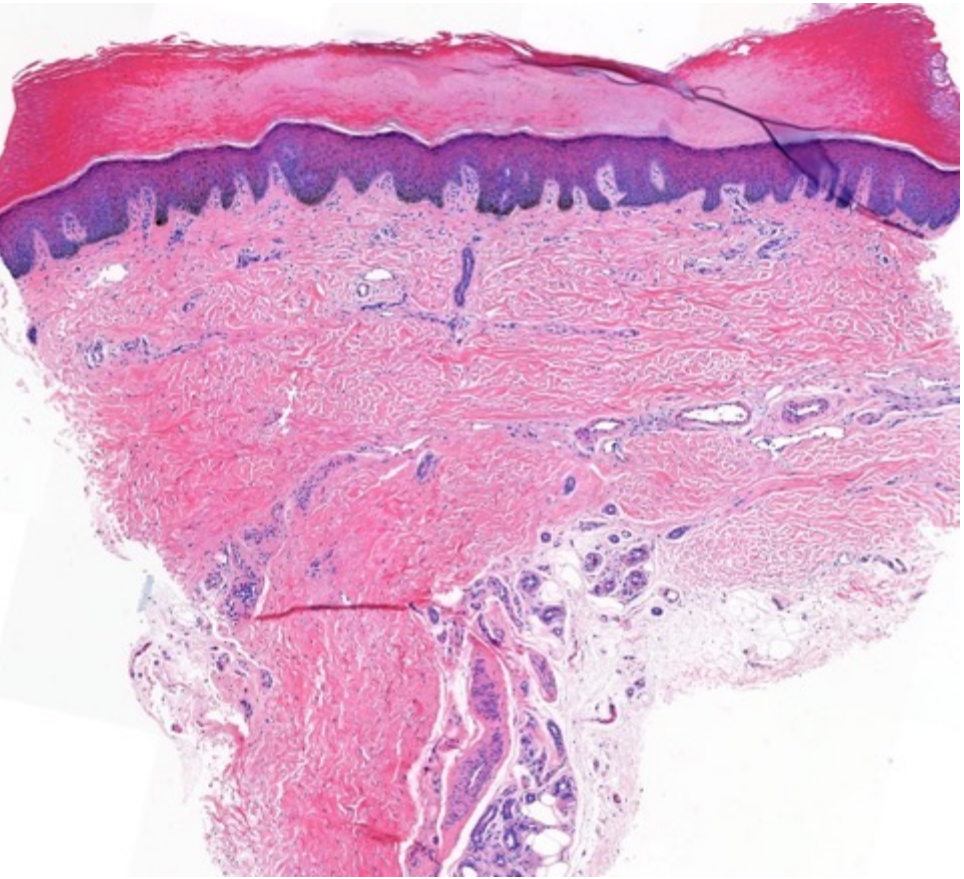
Thigh nevi

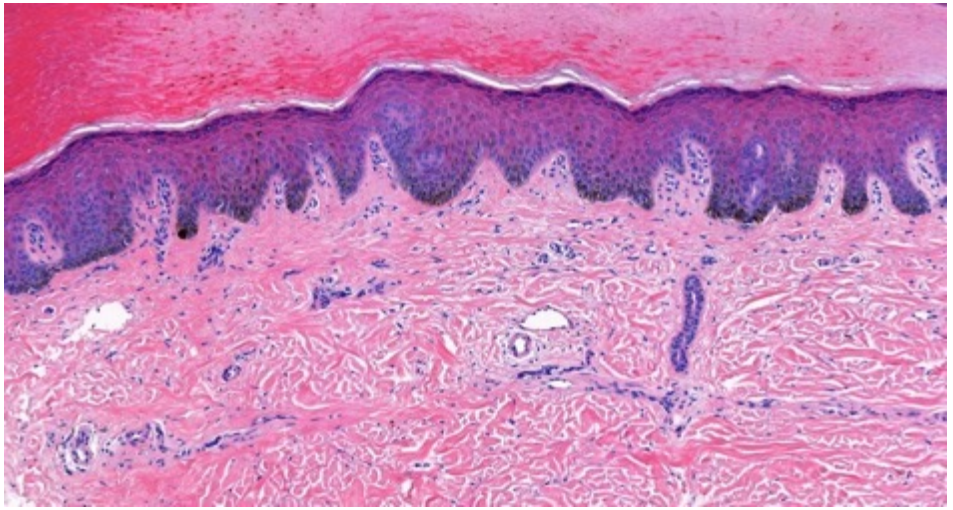
Frequent spitzoid features with some scatter

- “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

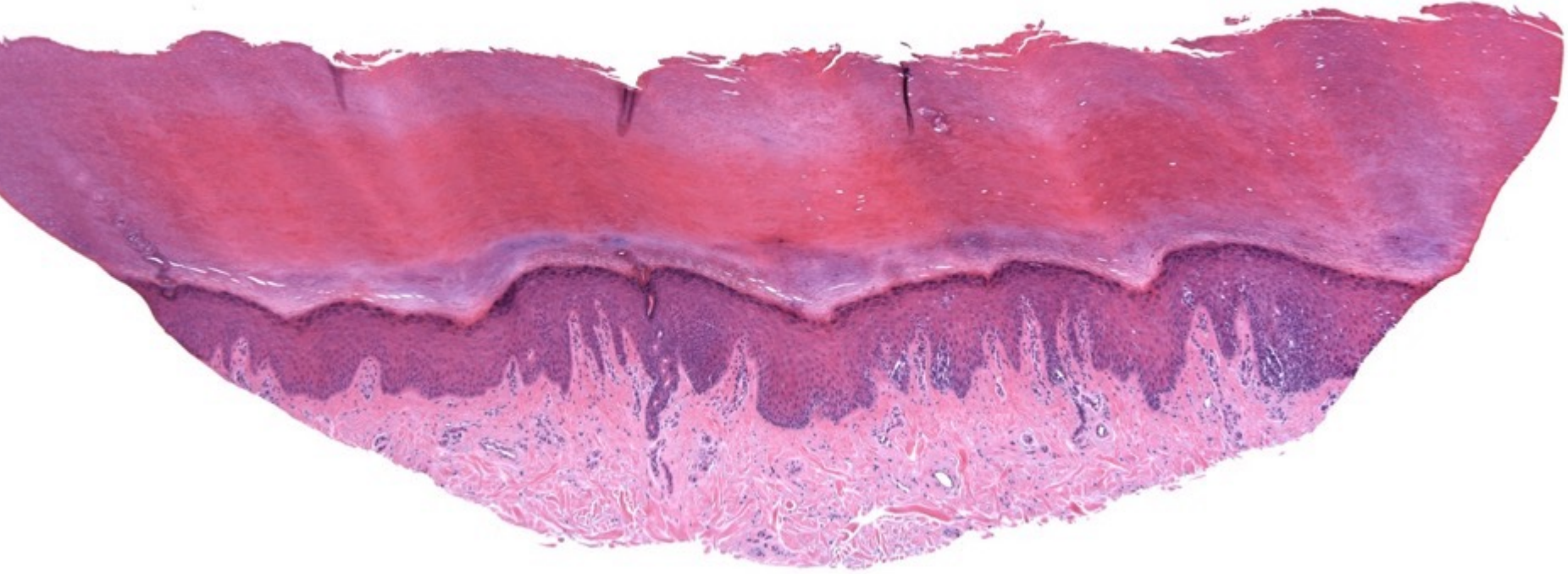
Chung J, Yuan ZM, Lee JB. Clinical and histopathological features of pagetoid Spitz nevi of the thigh. J Cutan Pathol. 2020;47(12):1143–1149
Donati, Pietro et al. *Am J Dermatopathol* 34.8 (2012): 853–855

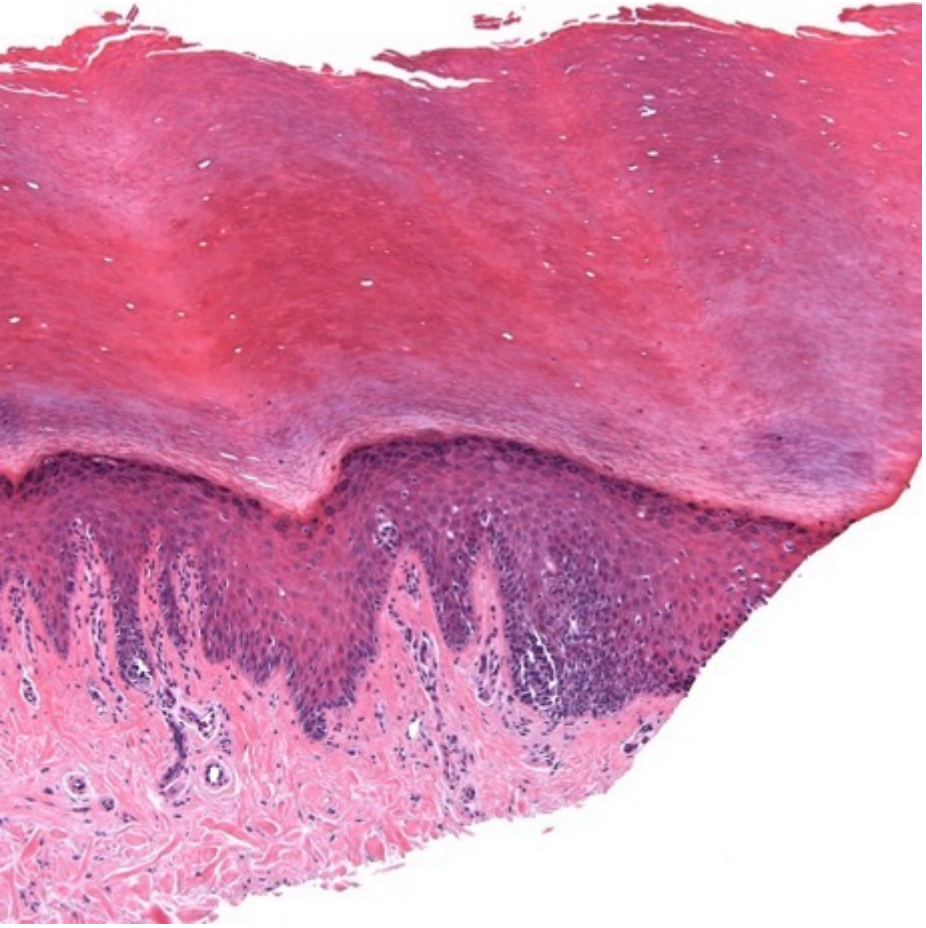
Case 6

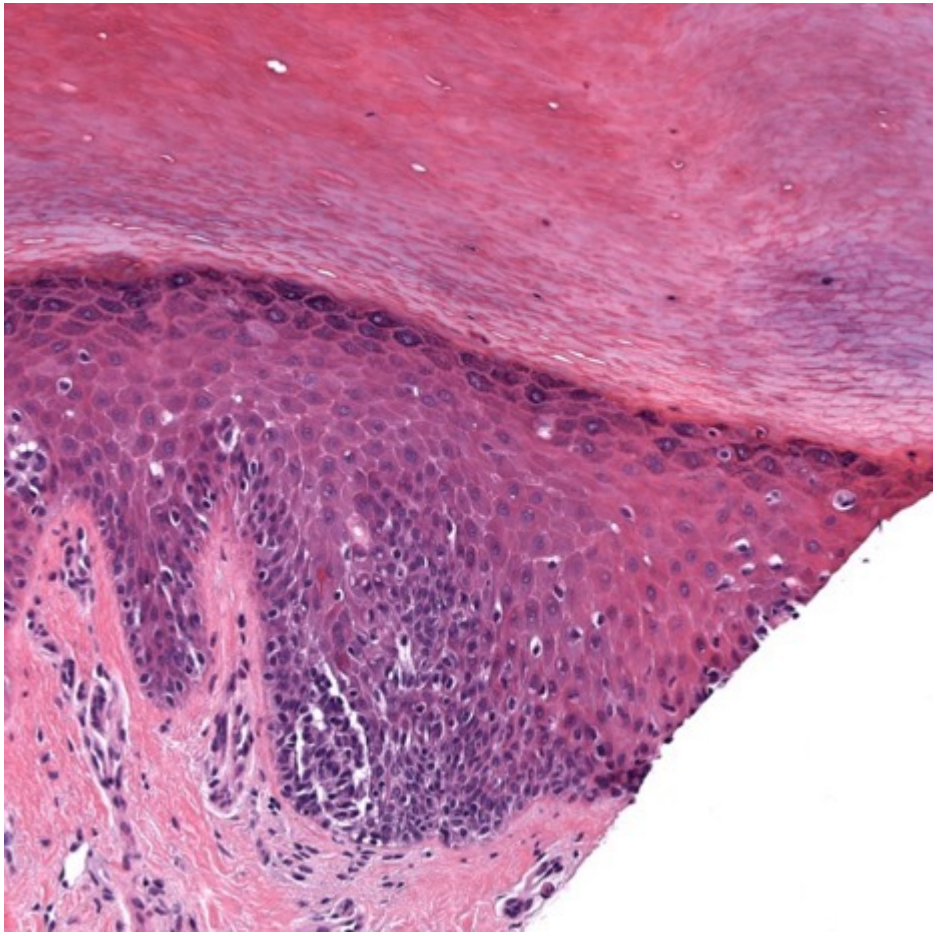


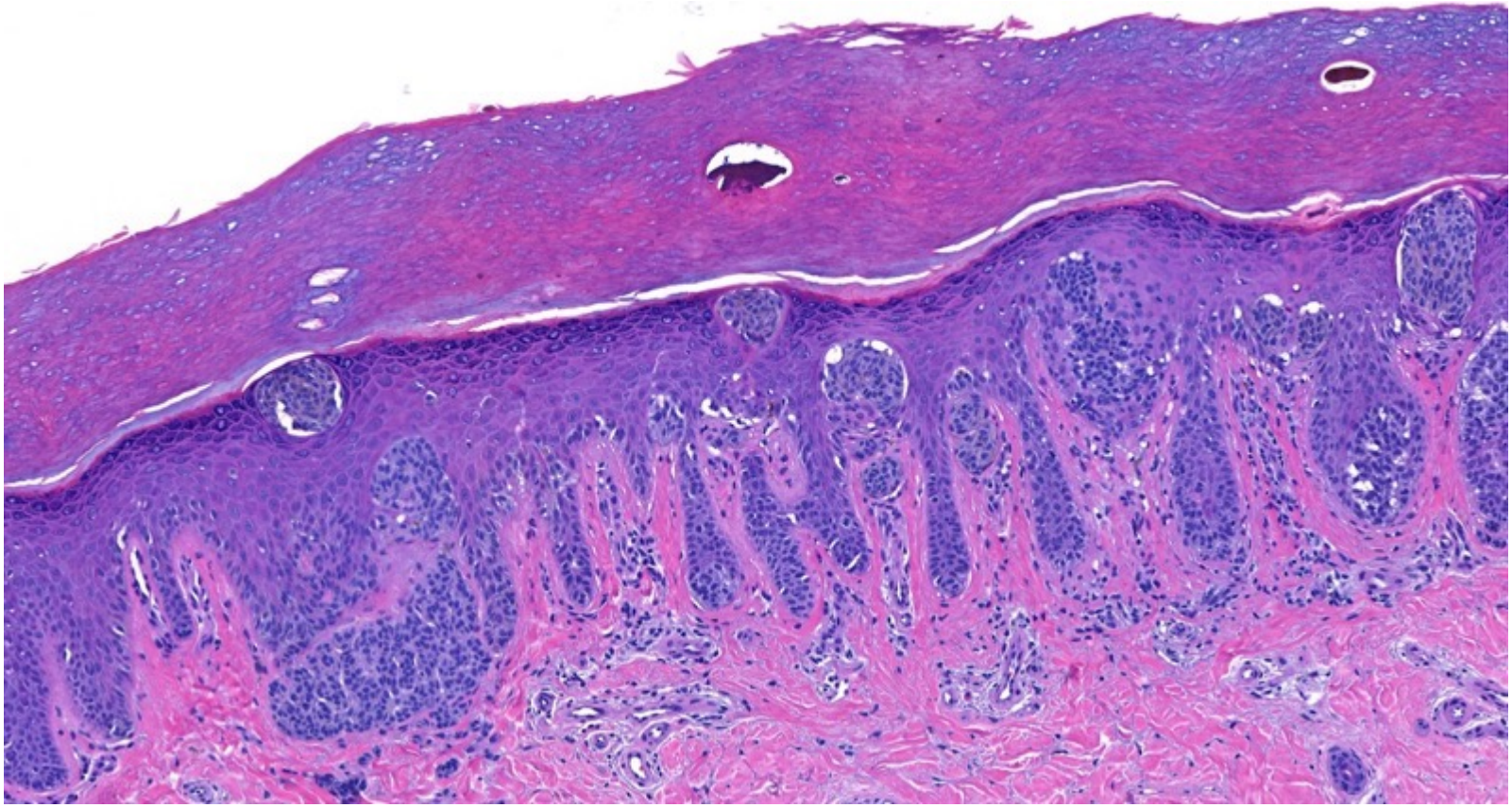


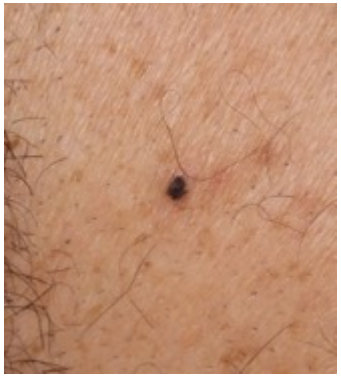
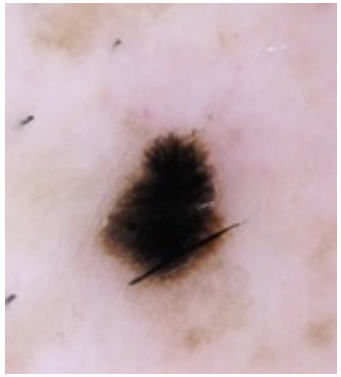
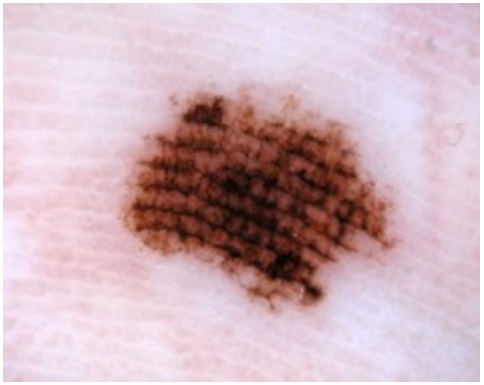
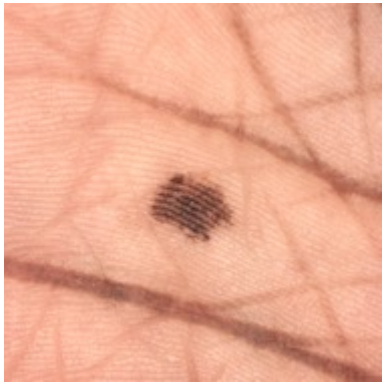
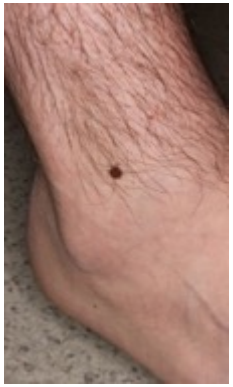
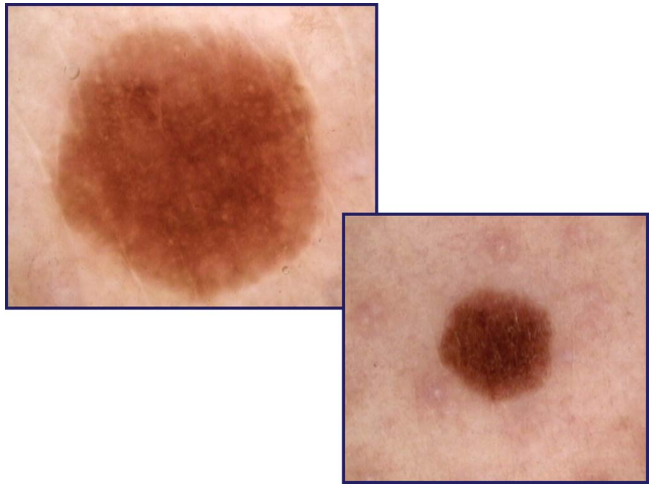
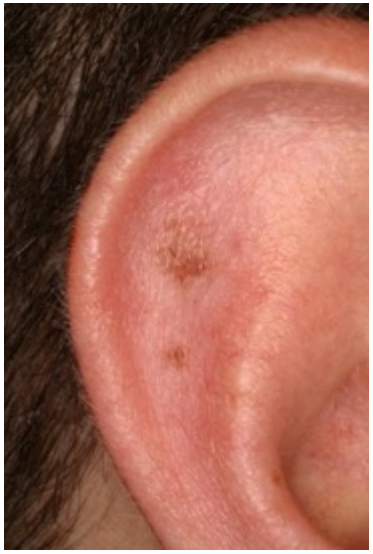
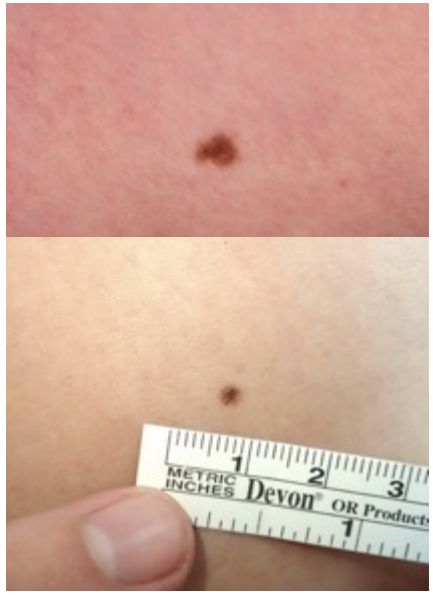
- Volar skin nevi
  - signouts are usually aggressive with excision recommendations
- This lesion is benign
  - small & discrete
  - mostly nested melanocytes are at the DE junction
  - expect mild to moderate degree of scatter of solitary melanocytes and even nests

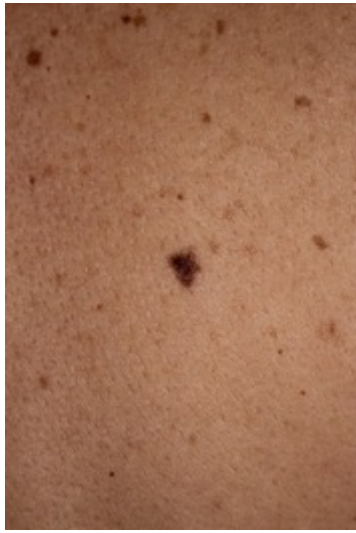










Small discrete lesions
No clinical features of melanoma

Epidemiologic evidence of melanoma overdiagnosis is mounting

The Rapid Rise in Cutaneous Melanoma Diagnoses

H. Gilbert Welch … er, M. … P.

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

EPIDEMIOLOGY

2022 BJD British Journal of Dermatology

The effect of screening on melanoma incidence and biopsy rates*

MELANOCYTIC TUMOUR PATHOLOGY

Diagnostic error, uncertainty, and overdiagnosis in melanoma

Pathology 2023

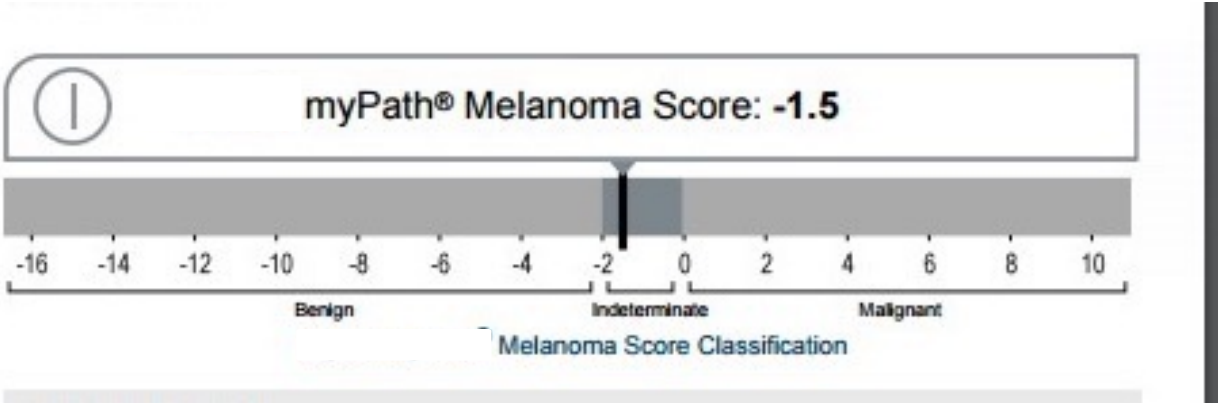
Era of Molecular Testing:

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

myPath ® [GEP (qRT-PCR)]

CASTLE BIOSCIENCES

MyPath Melanoma



+ score: melanoma

- score: nevus

0 to 2: gray zone

23 genes includes PRAME

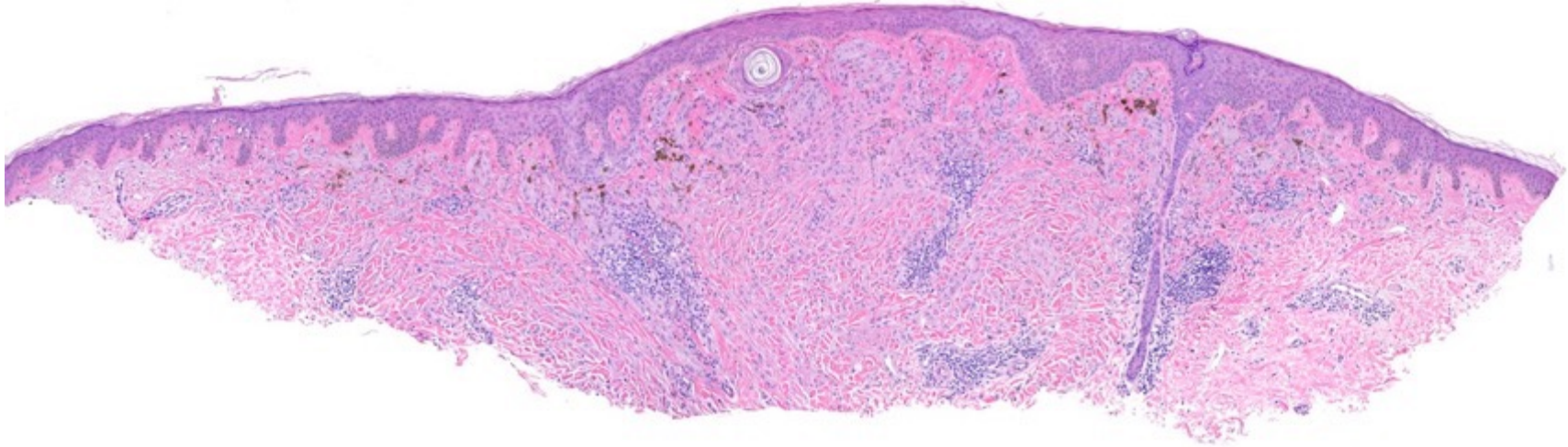
PRAME: Preferentially expressed antigen in melanoma

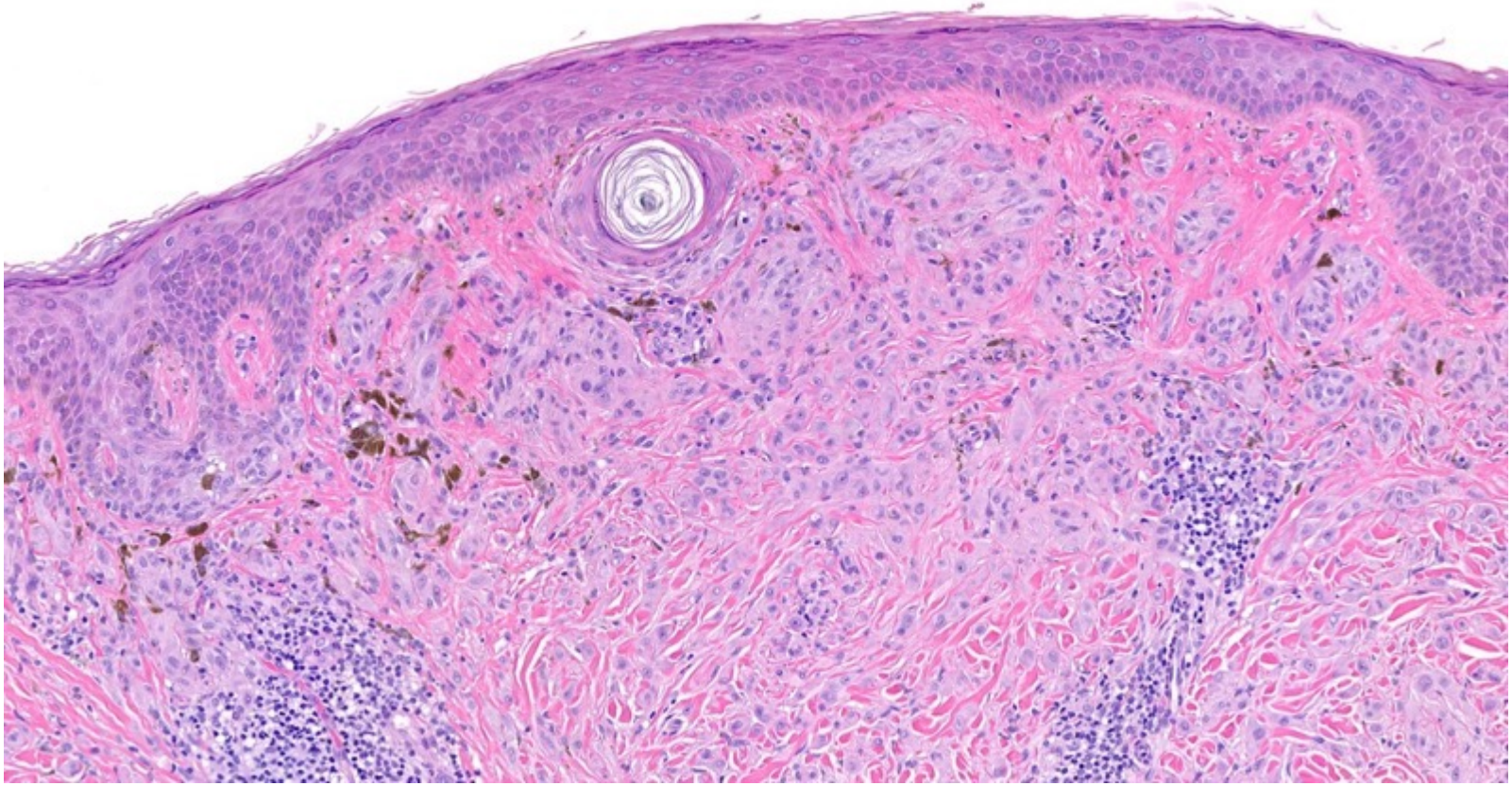
- PRAME used in several gene expression profiling tests
  - DermTech PLA: guidance on the decision to biopsy
  - Decision Dx-UM: uveal melanoma prognosis
  - myPath Melanoma: cutaneous melanocytic lesions
- PRAME IHC
  - Sensitivity: 67%-83%
  - Specificity: 93%-97%

- 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

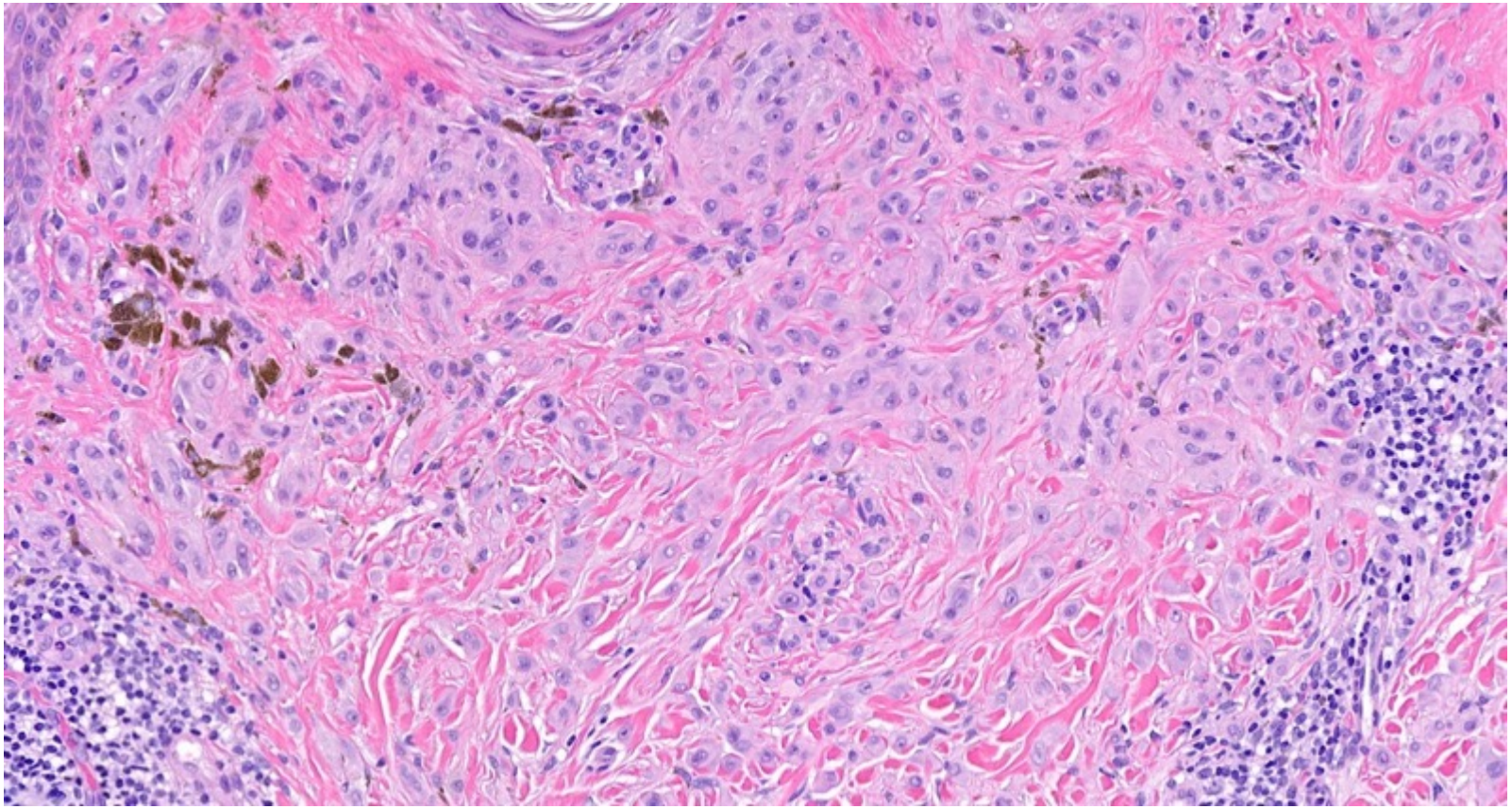
Case 7

52 yo, chest lesion





Spitzoid Lesion



Spitz Nevi

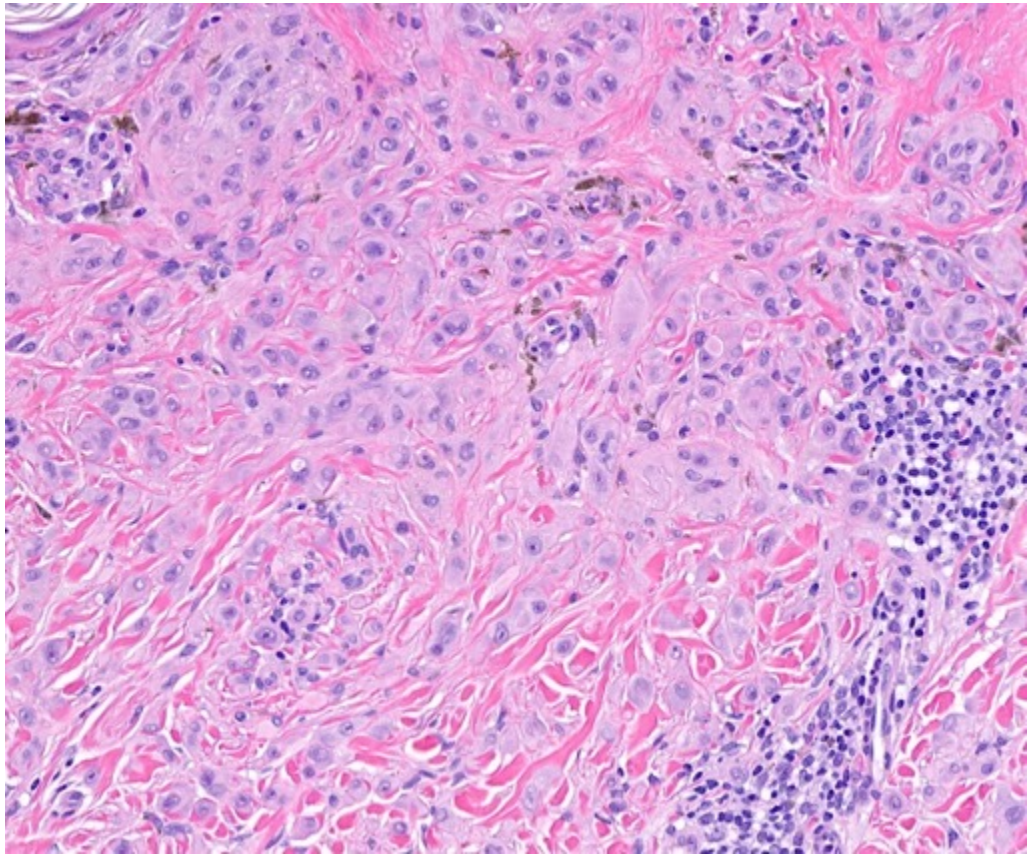
- More common in pediatric population to young adults
- Not as common in older adults

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

Motaparthi K, Kim J, Andea AA, et al. TERT and TERT promoter in melanocytic neoplasms: Current concepts in pathogenesis, diagnosis, and prognosis. Journal of cutaneous pathology. 2020;47(8):710-719. doi:10.1111/cup.13691

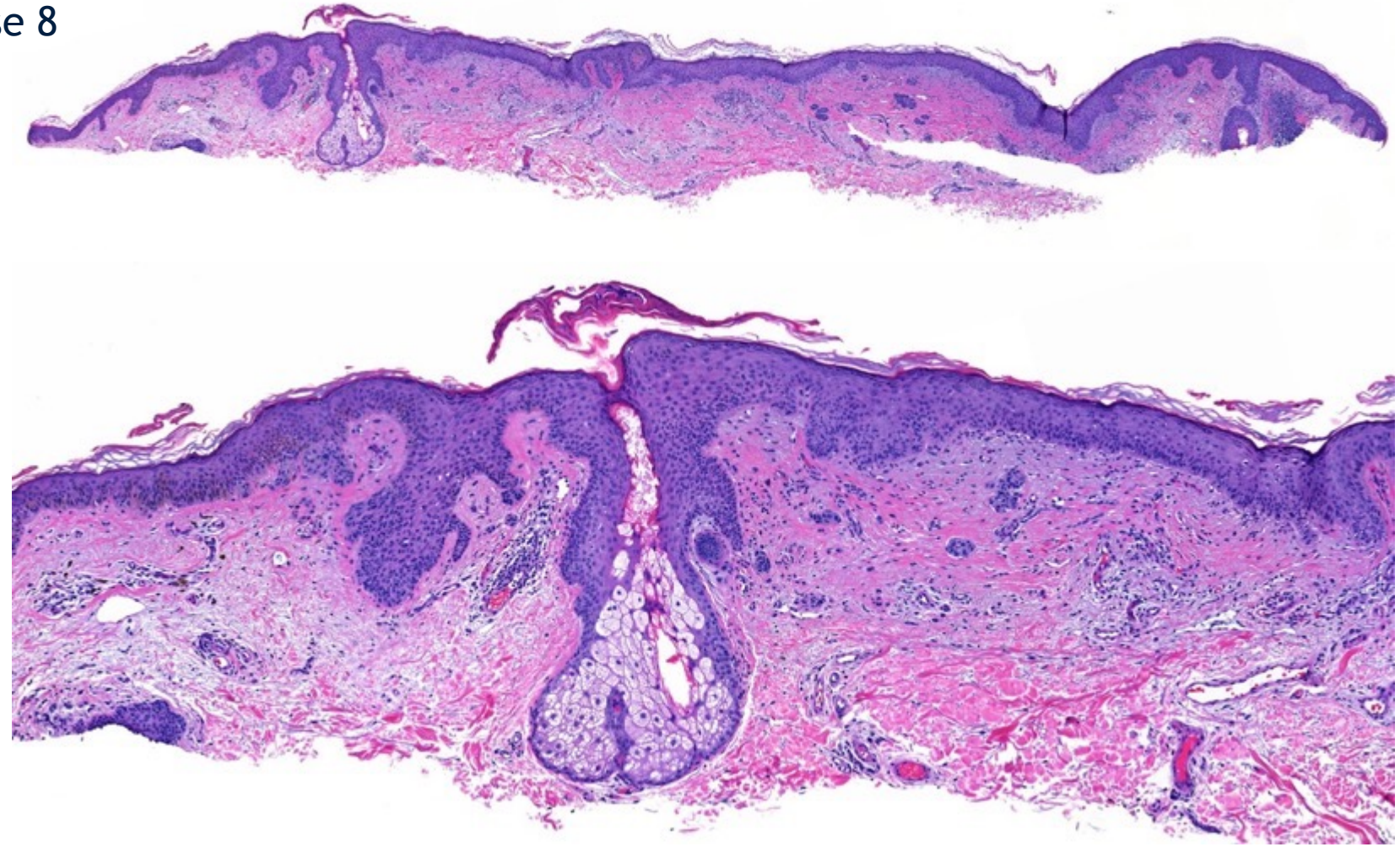
Koh SS, Lau SK, Scapa JV, Cassarino DS. PRAME immunohistochemistry of spitzoid neoplasms. Journal of cutaneous pathology. 2022;49(8):709-716. doi:10.1111/cup.14245

Spitz nevus in an older adult

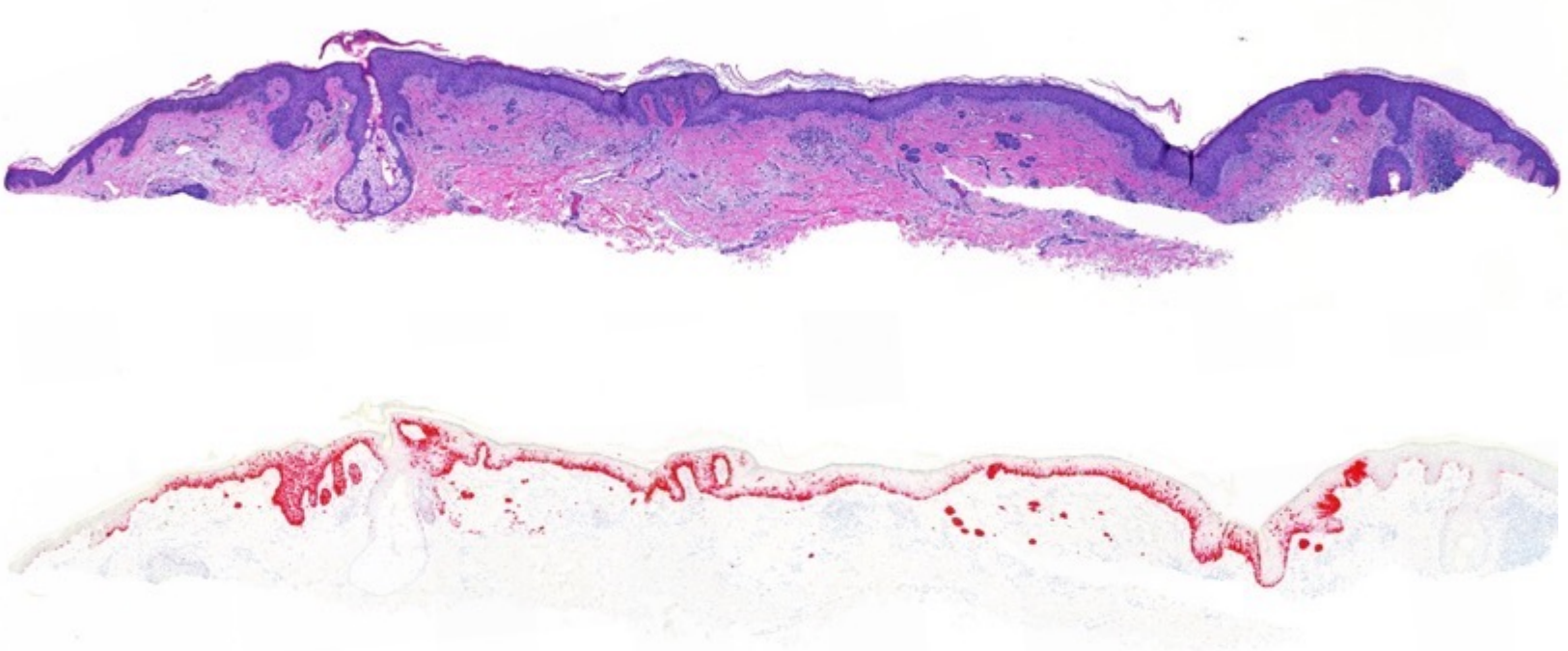


- BRAF negative
- PRAME negative
- Ki67 low mitotic index

Case 8

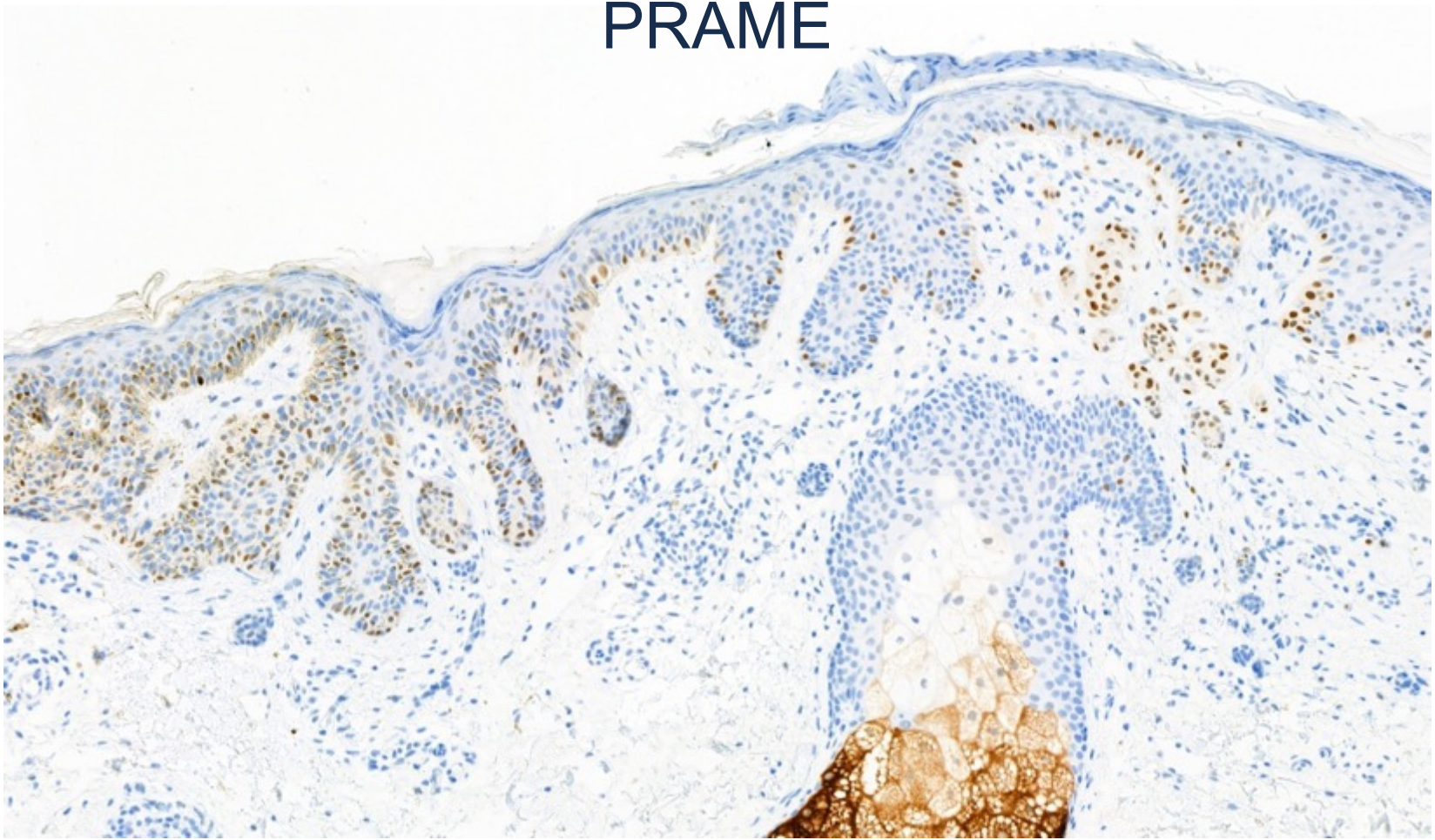


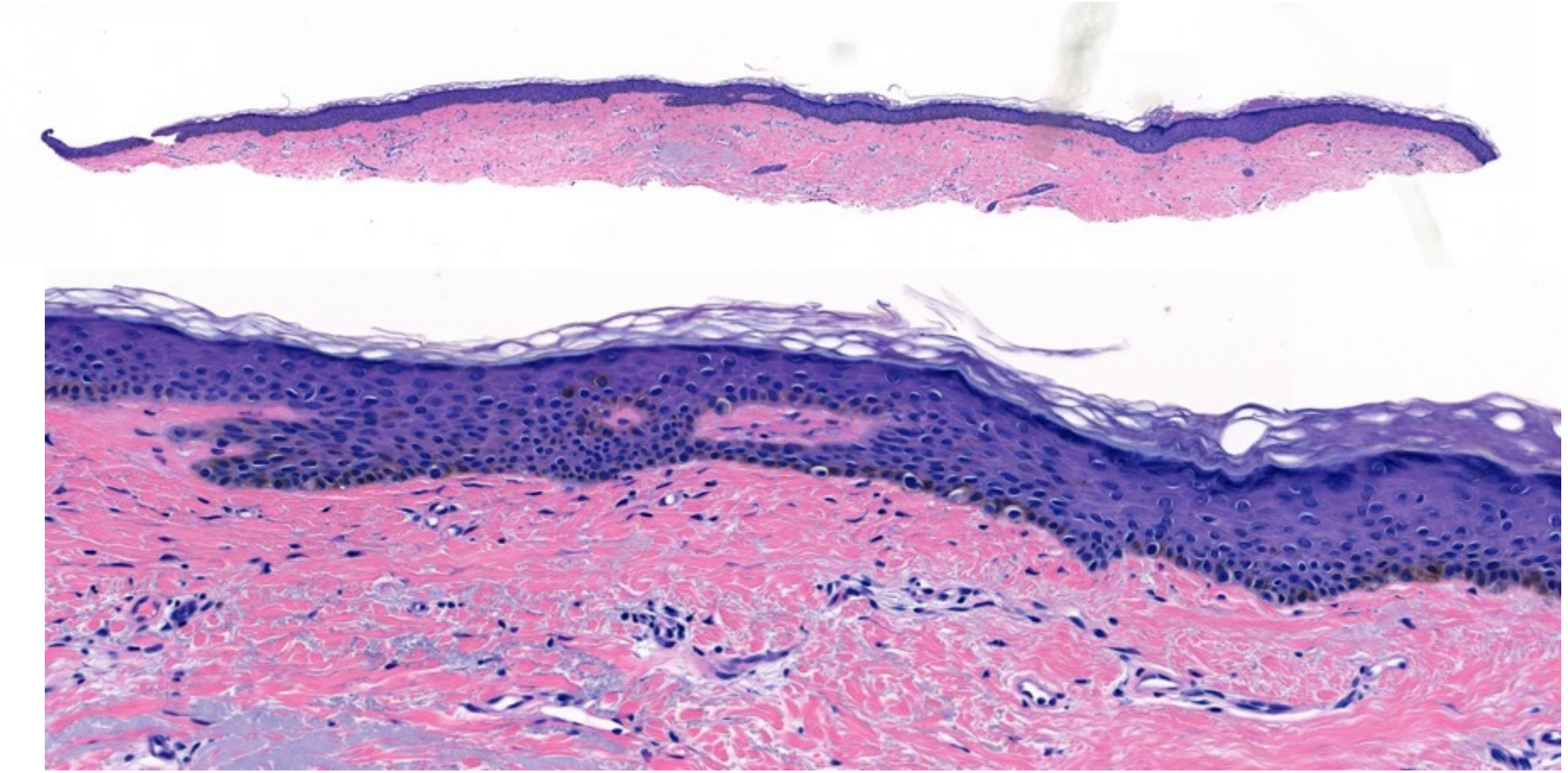
Case 2



Melanoma

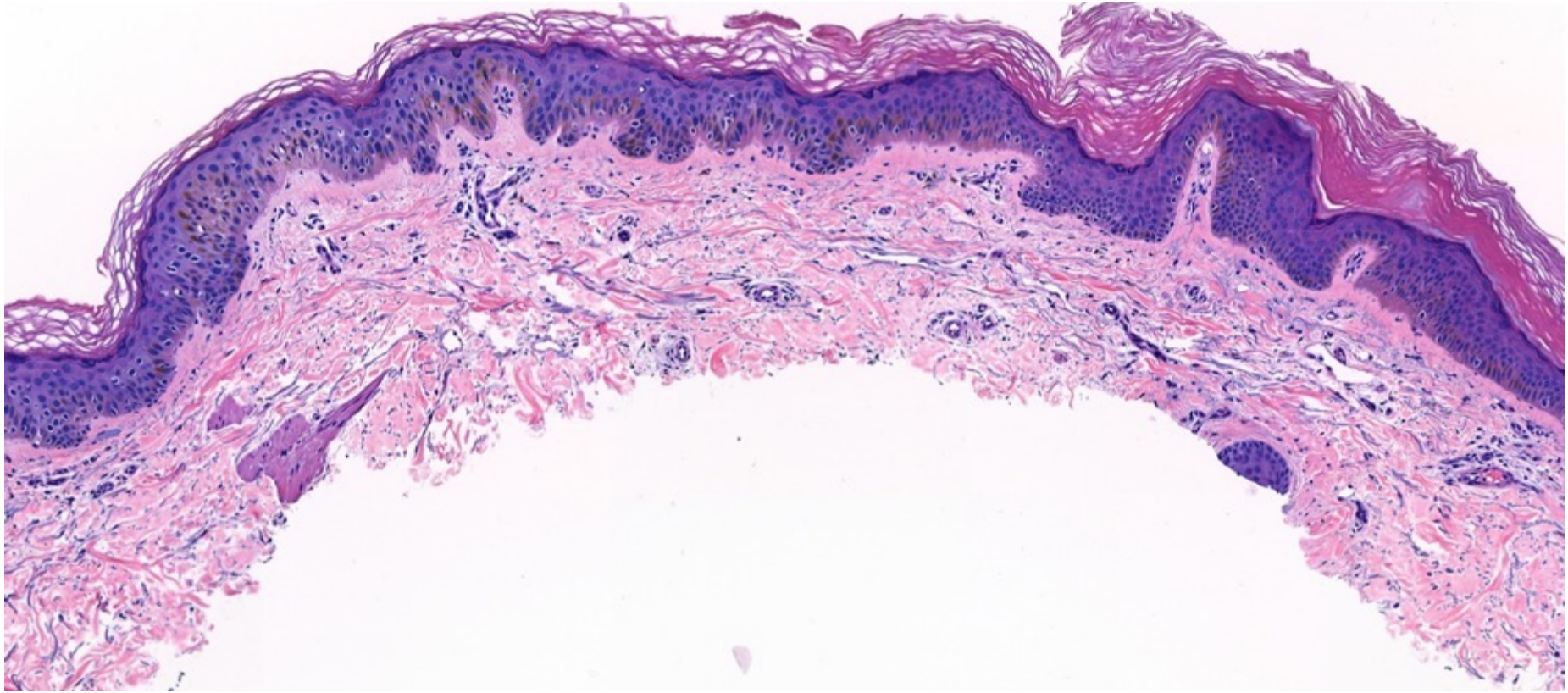
PRAME



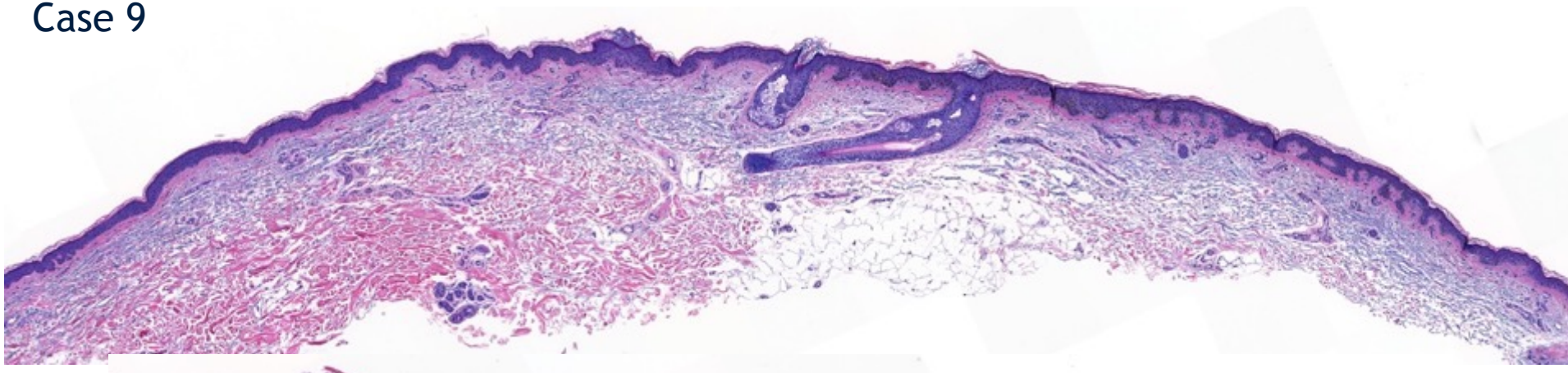


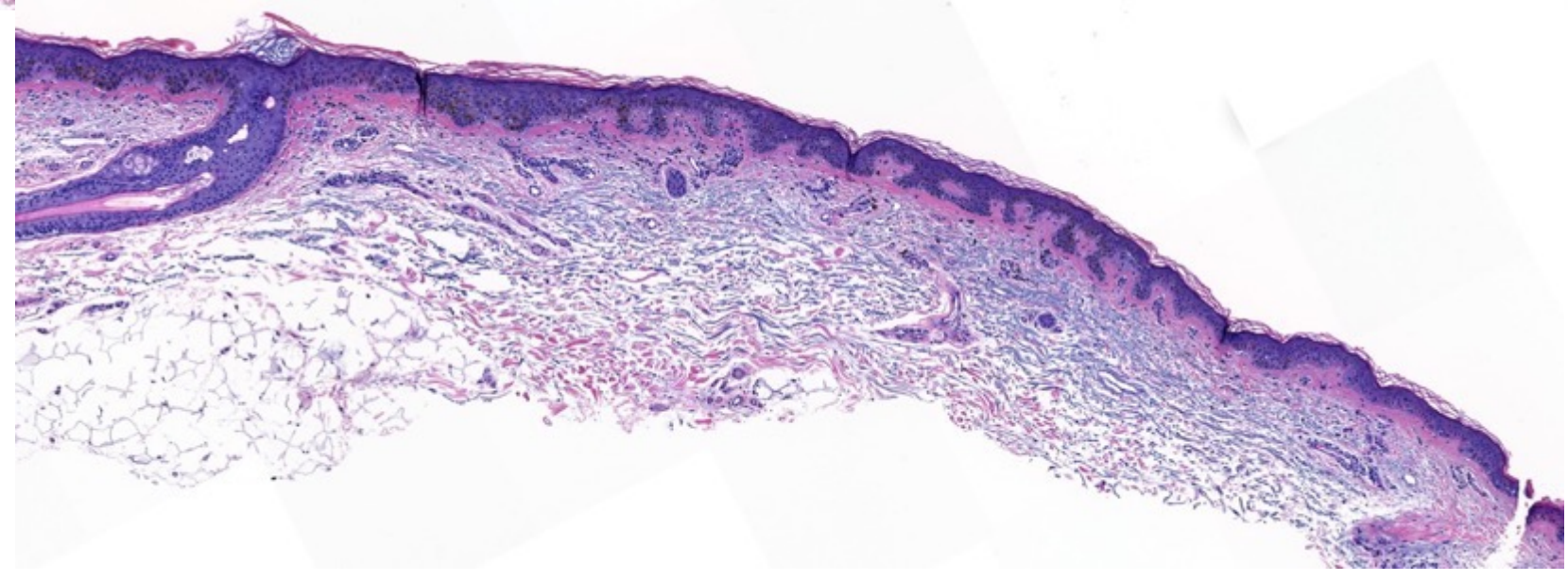
Solar Lentigo

Solar Lentigo with Melanocytic Hyperplasia

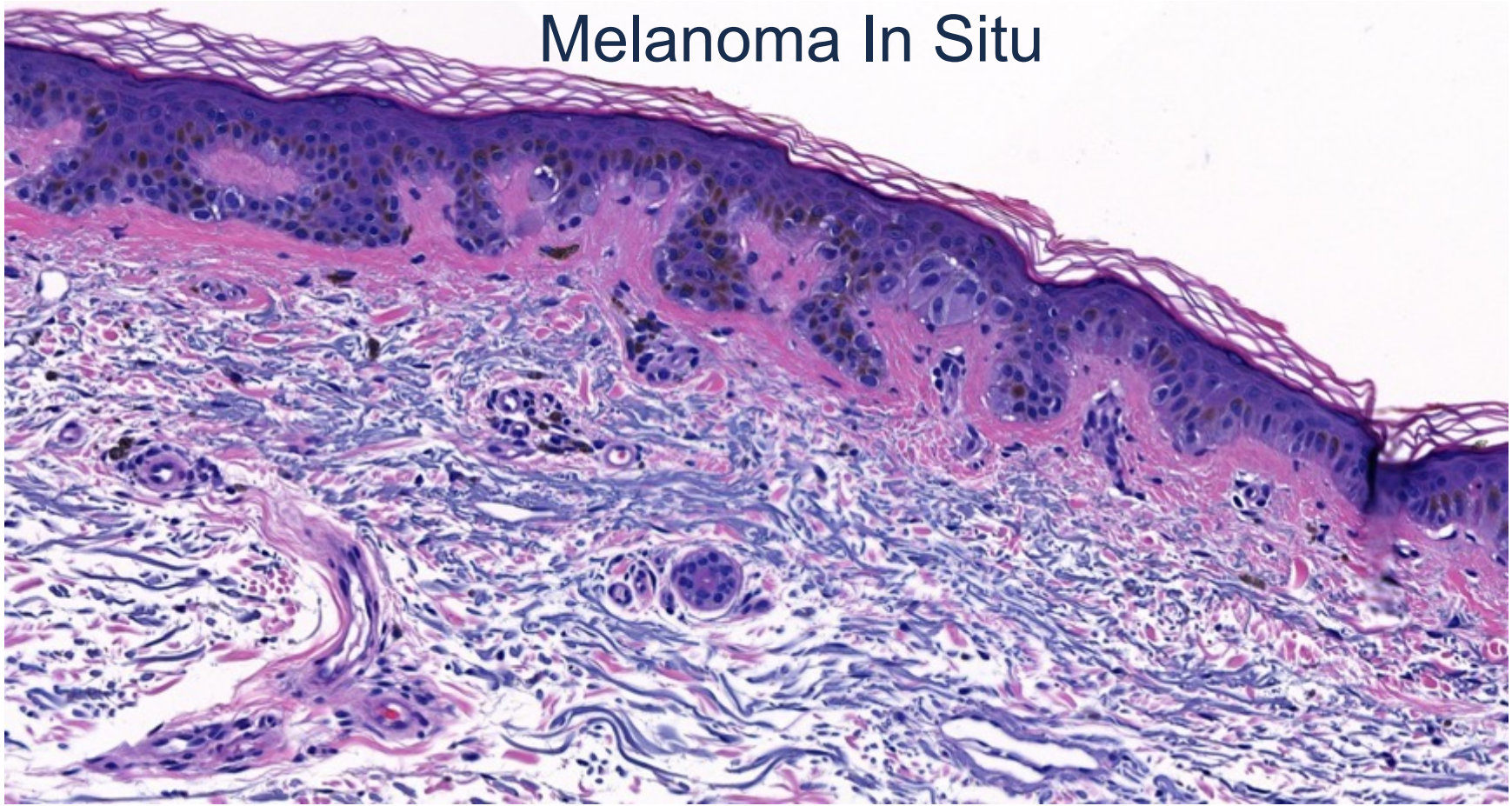


Case 9

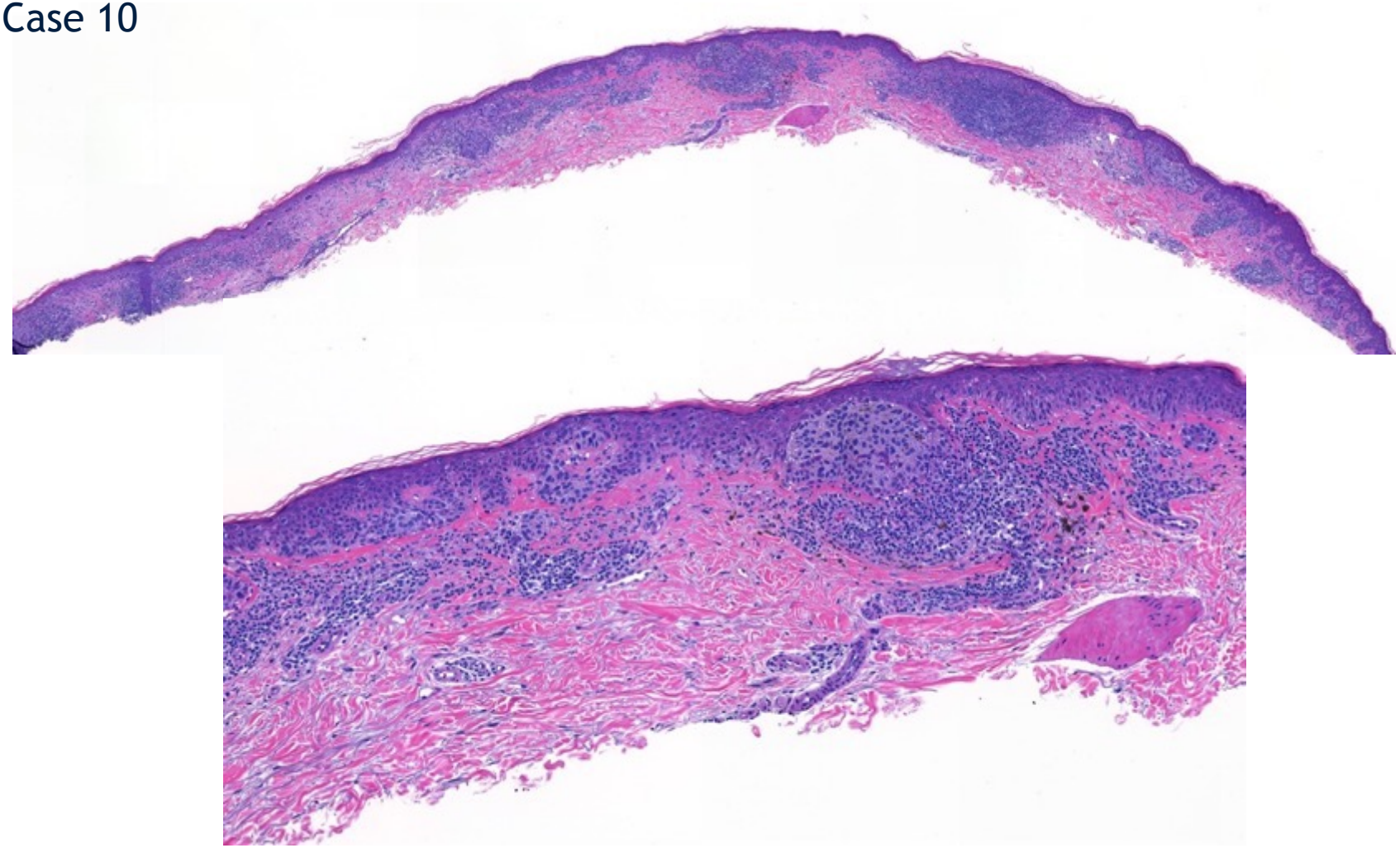


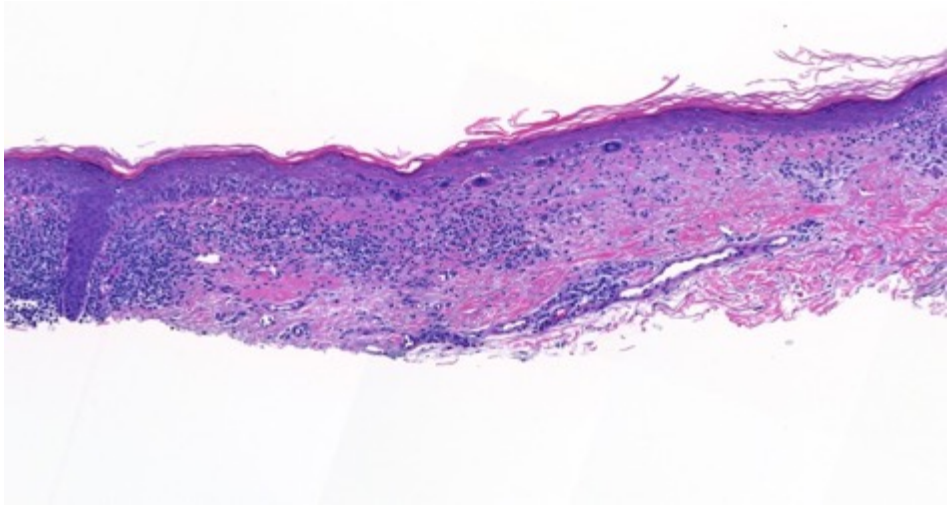


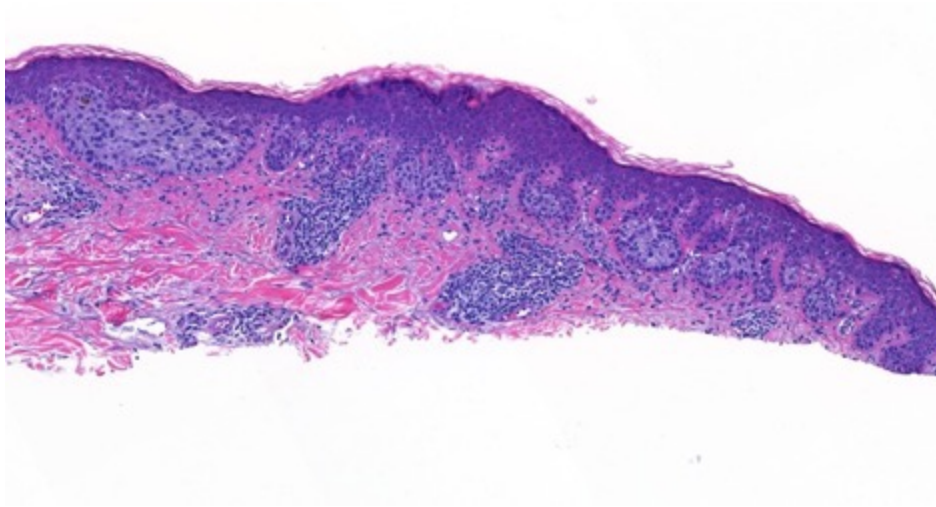
Melanoma In Situ



Case 10

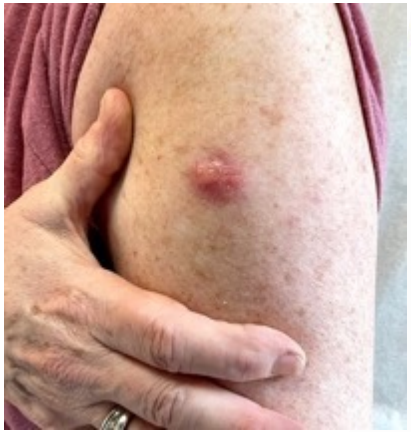


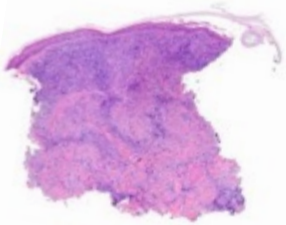


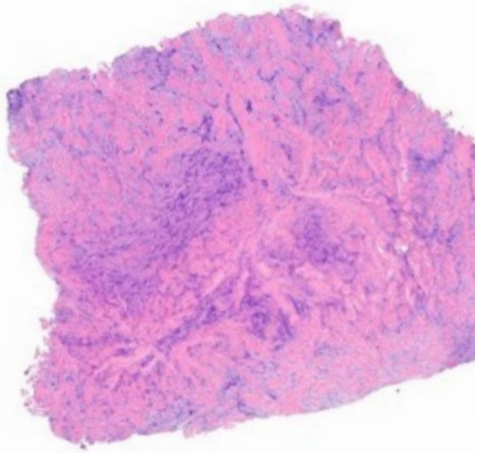


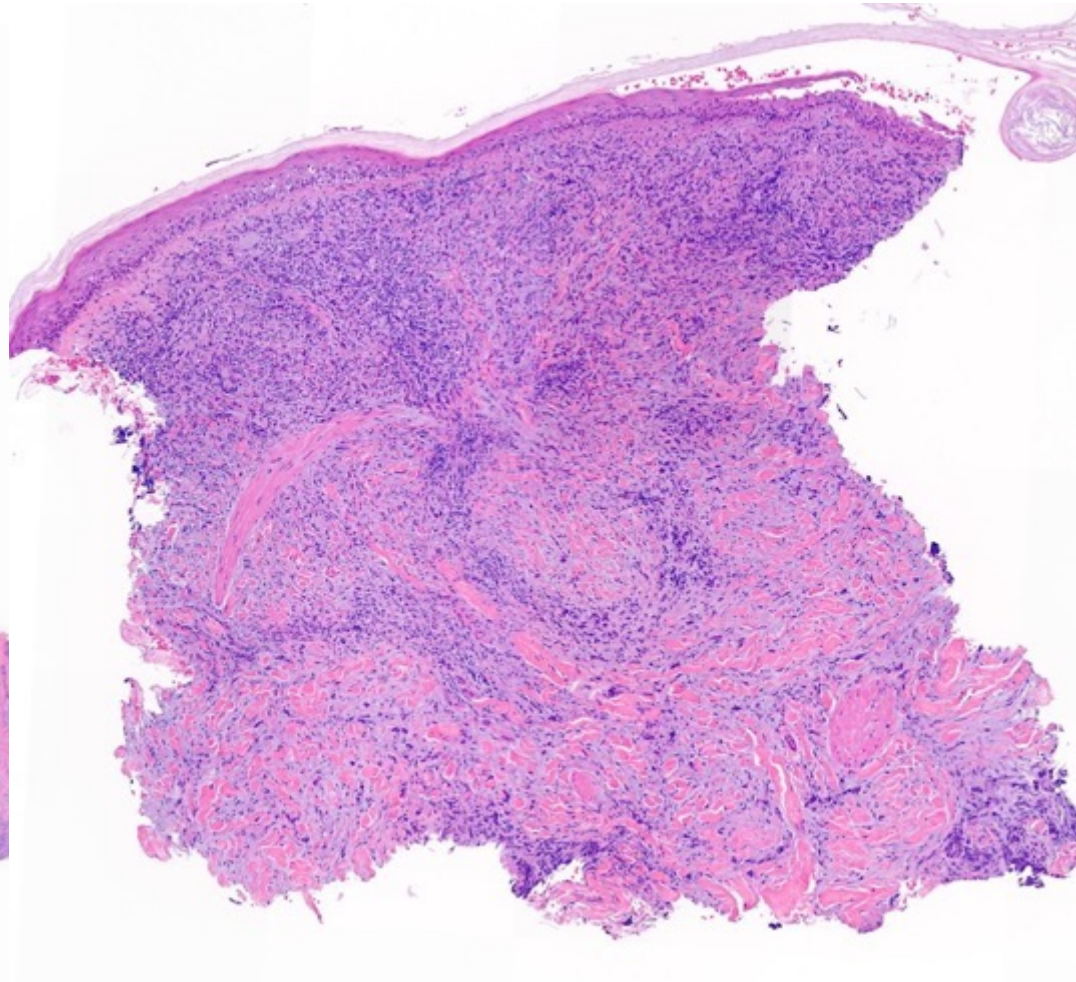
Melanoma

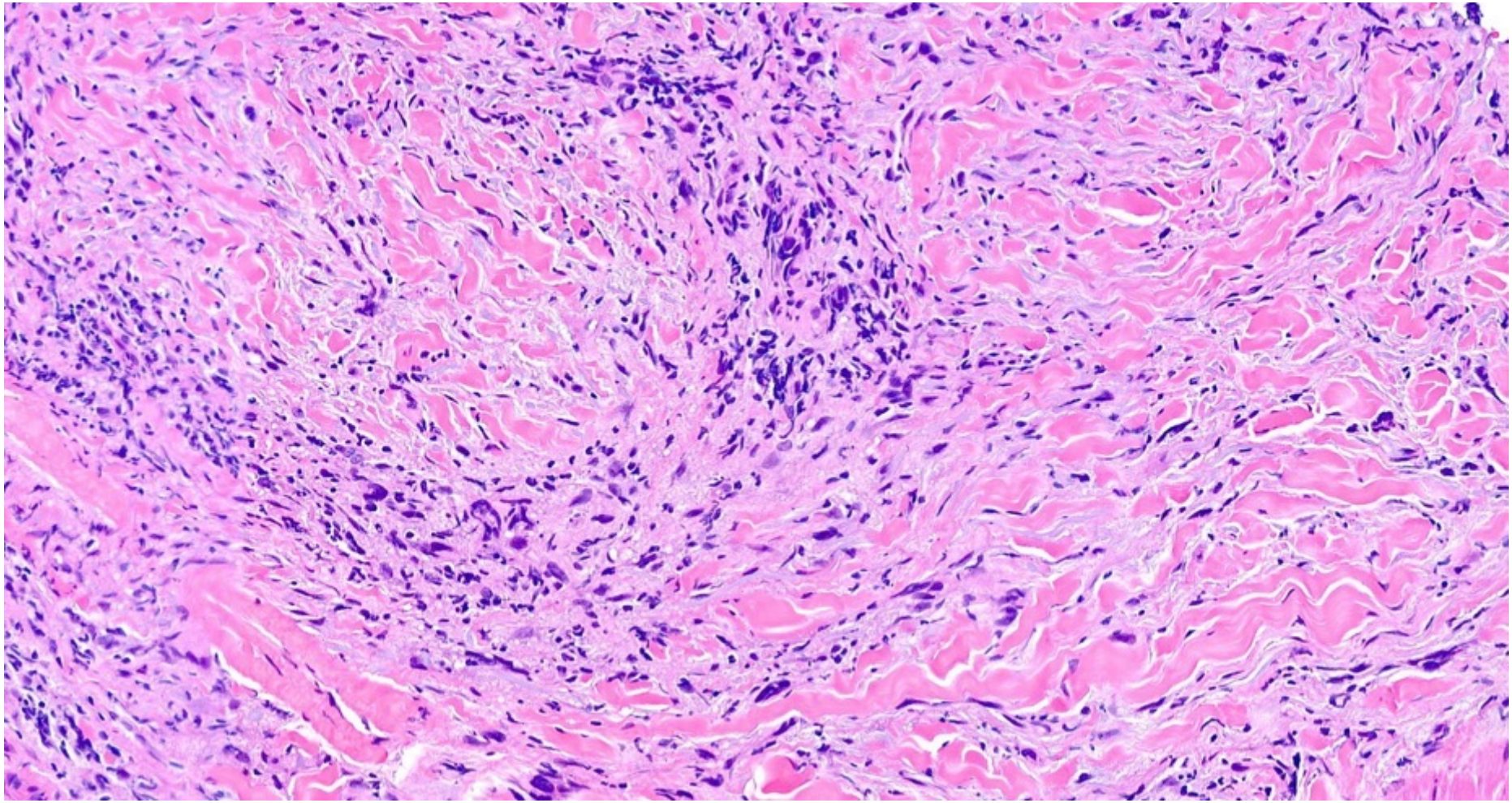
Case 11



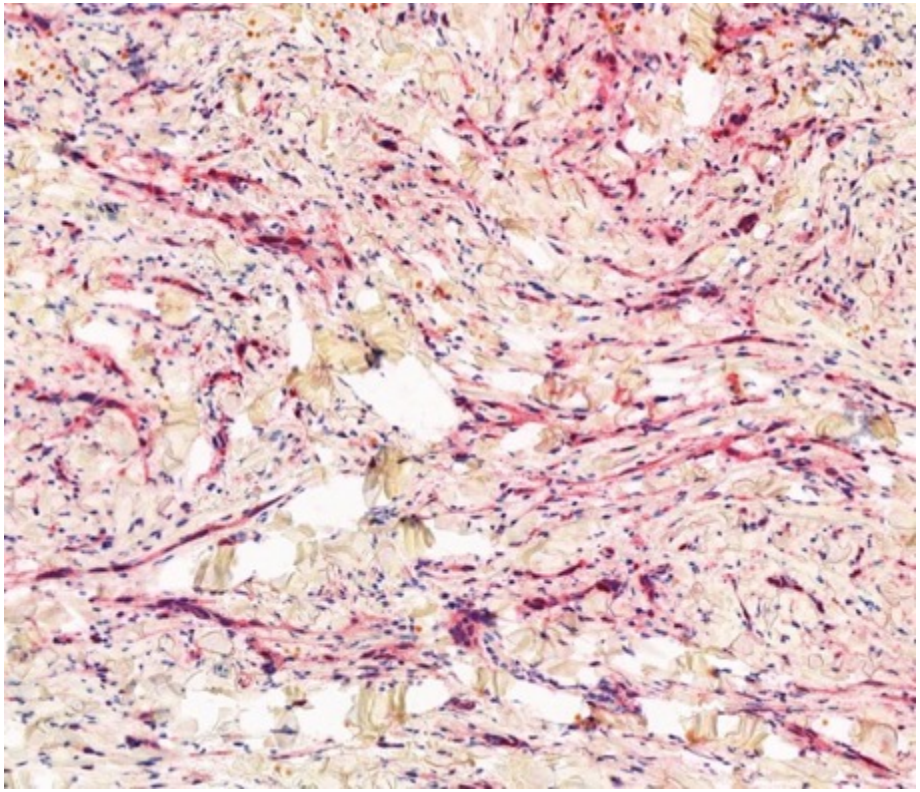




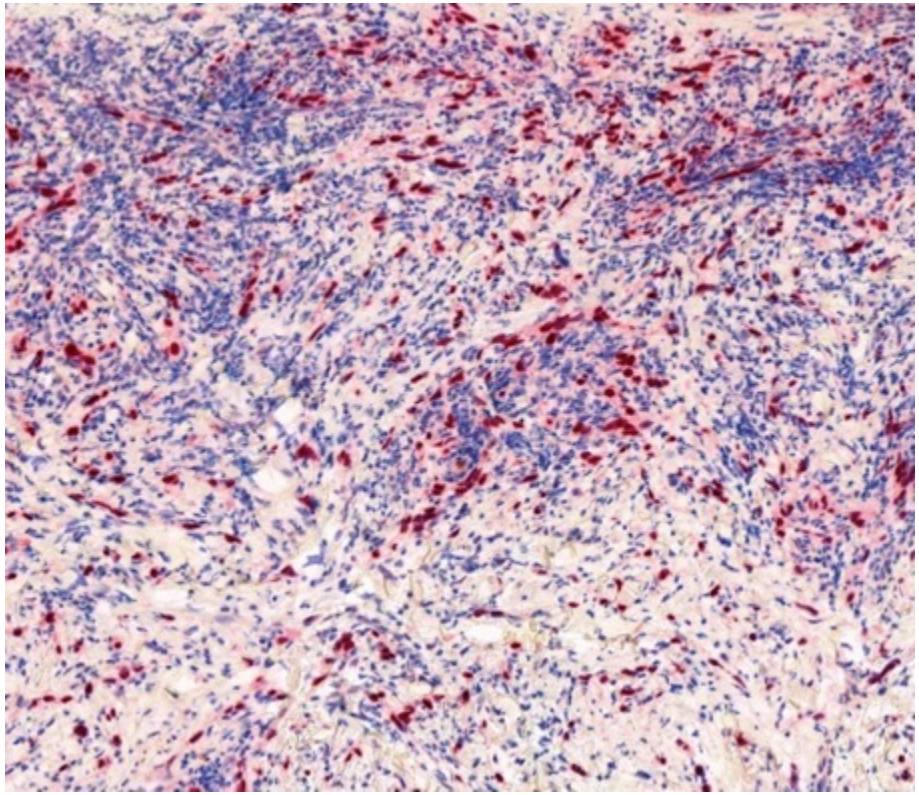




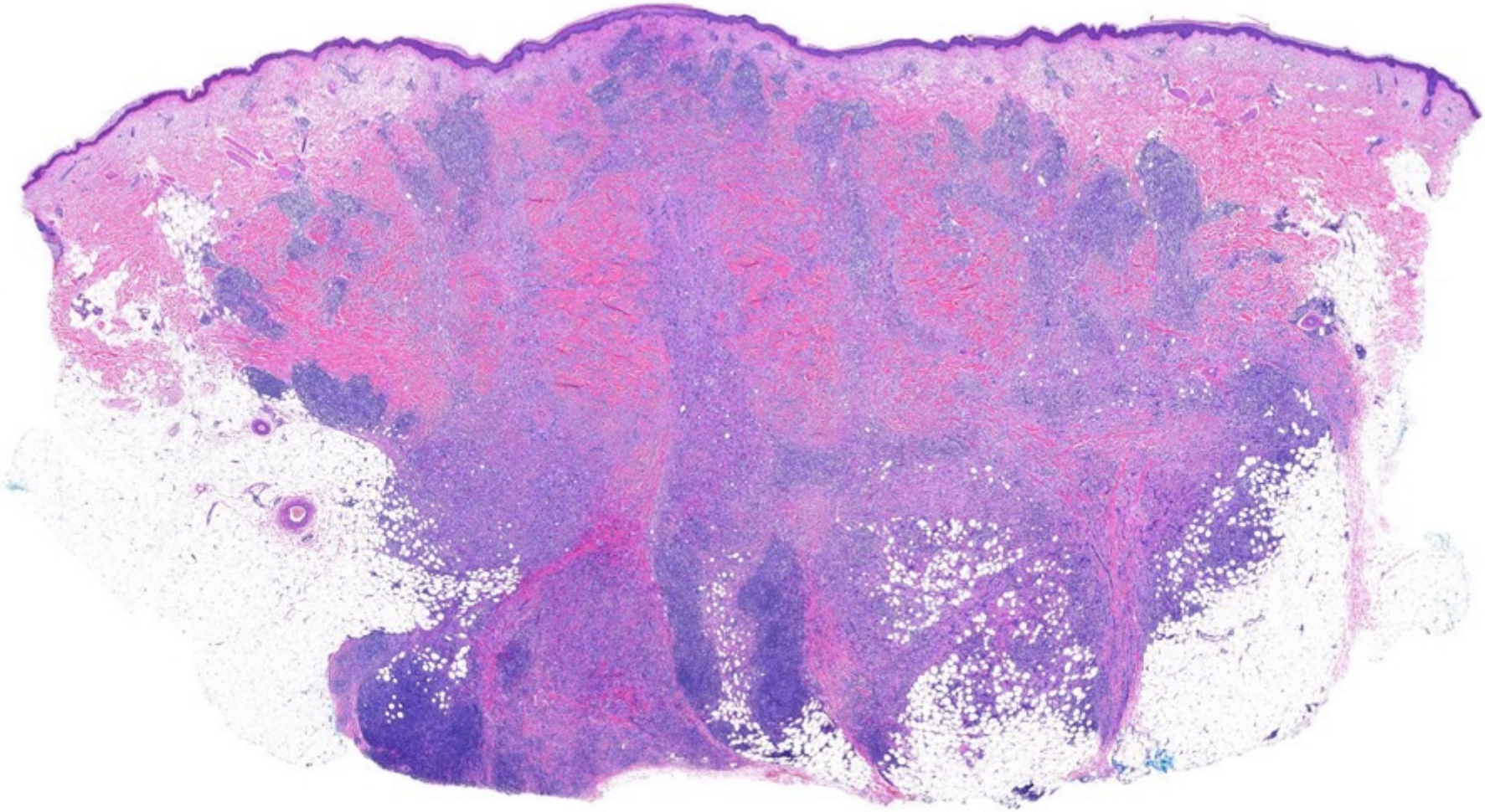
S100



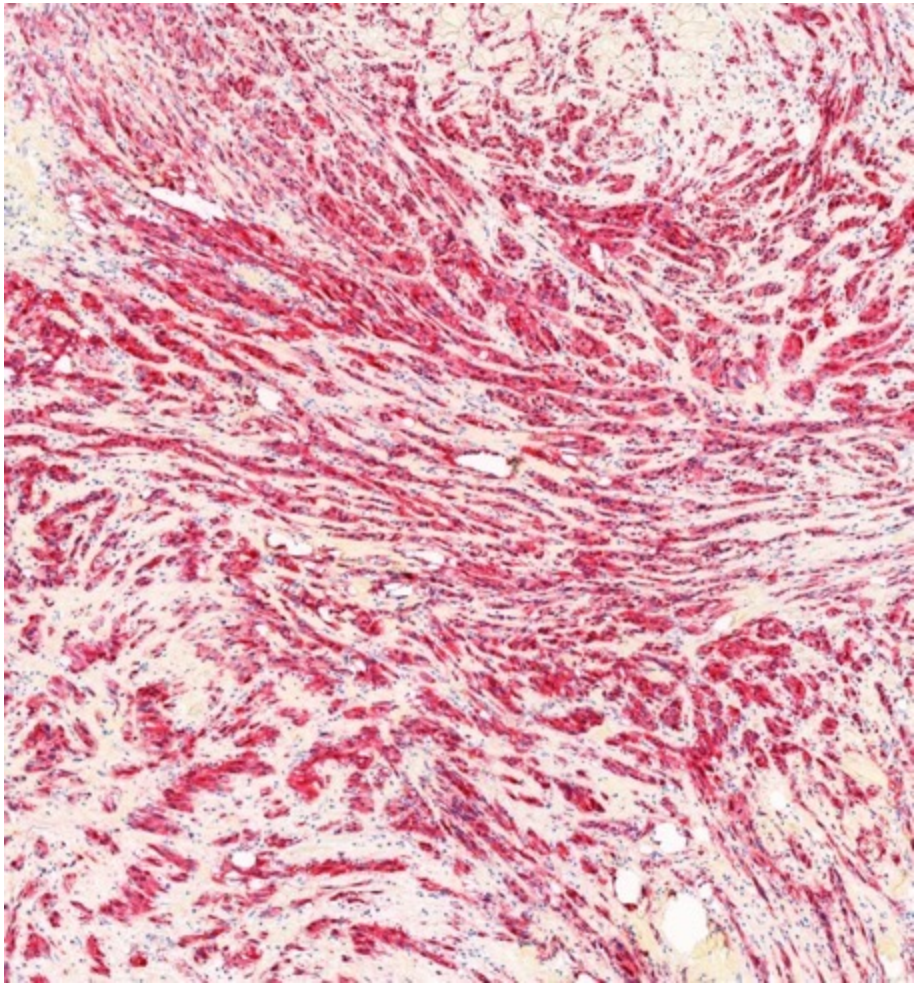
SOX10



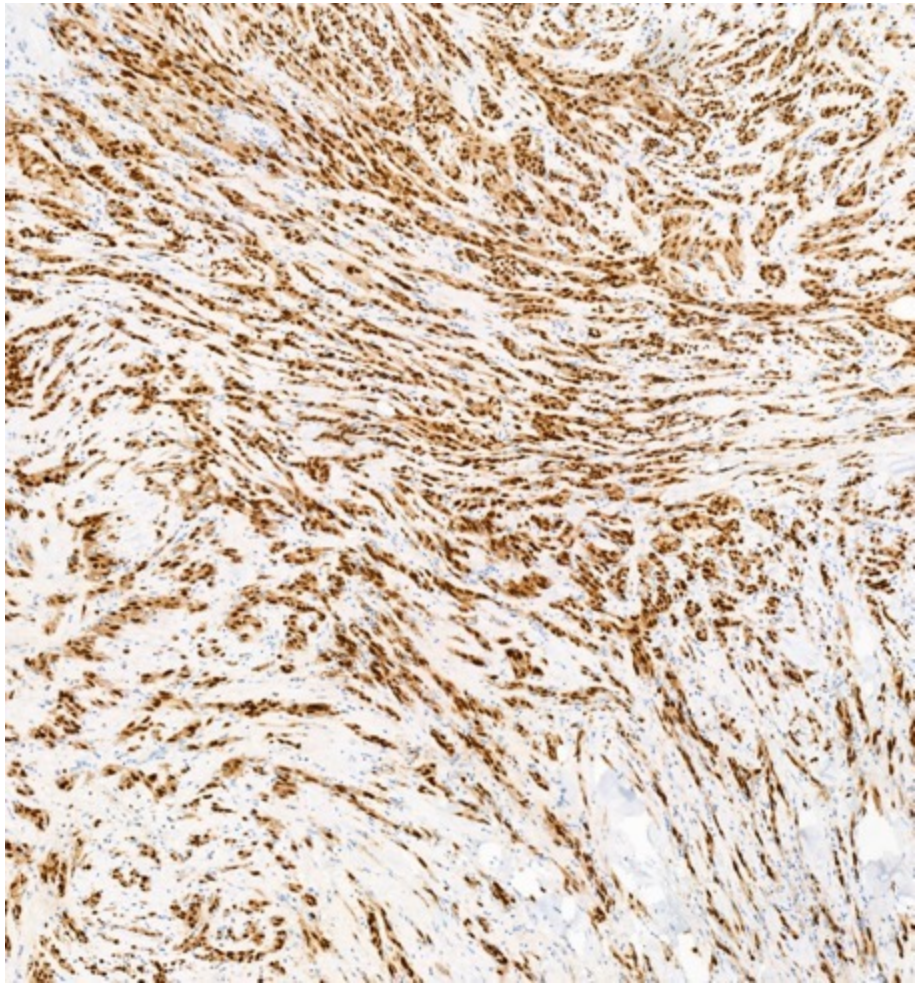
Desmoplastic Melanoma



DP22-09976 S100



DP22-09976 SOX10

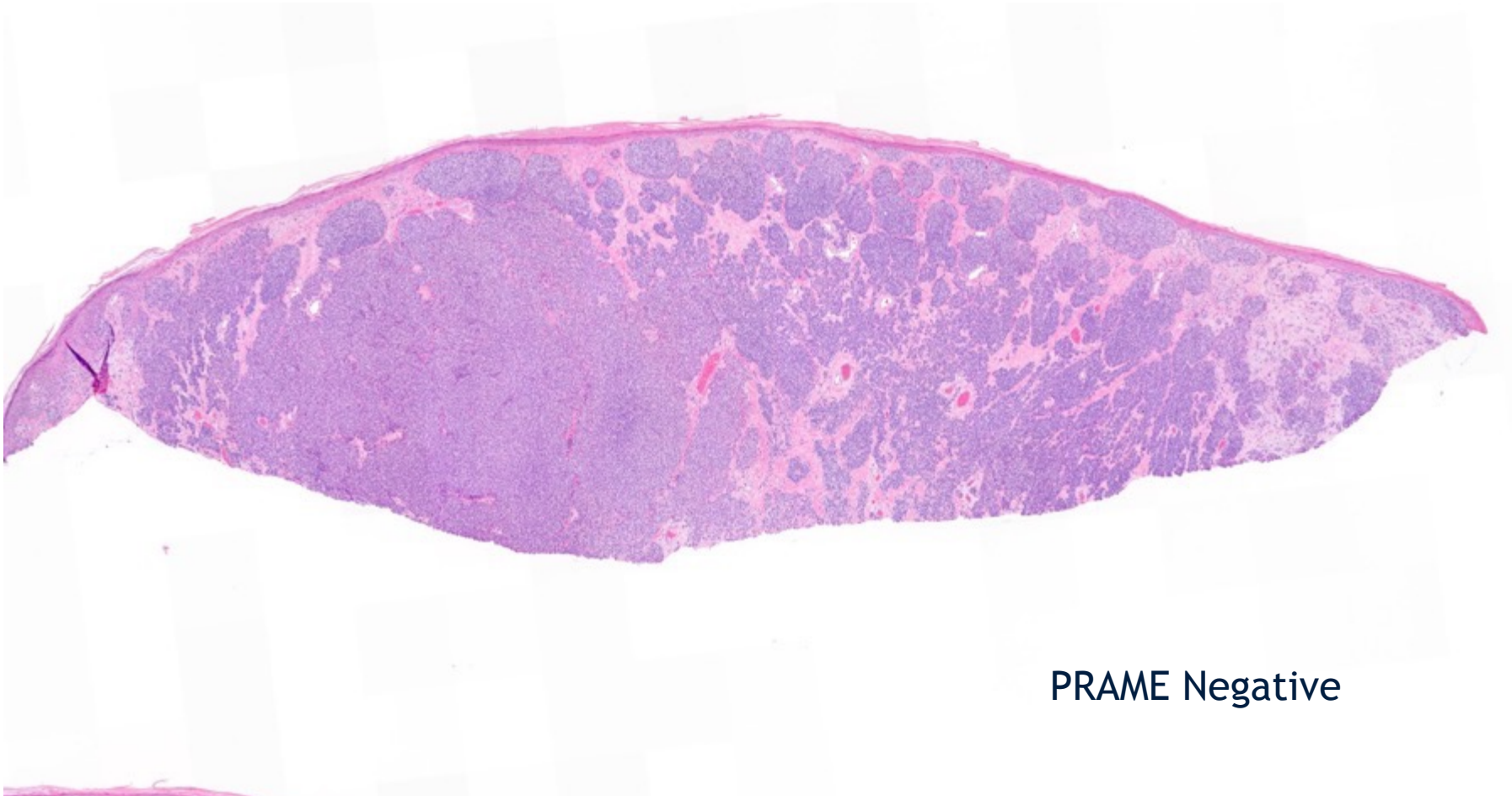


Desmoplastic Melanoma

- 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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