Trento, May 9, 2024

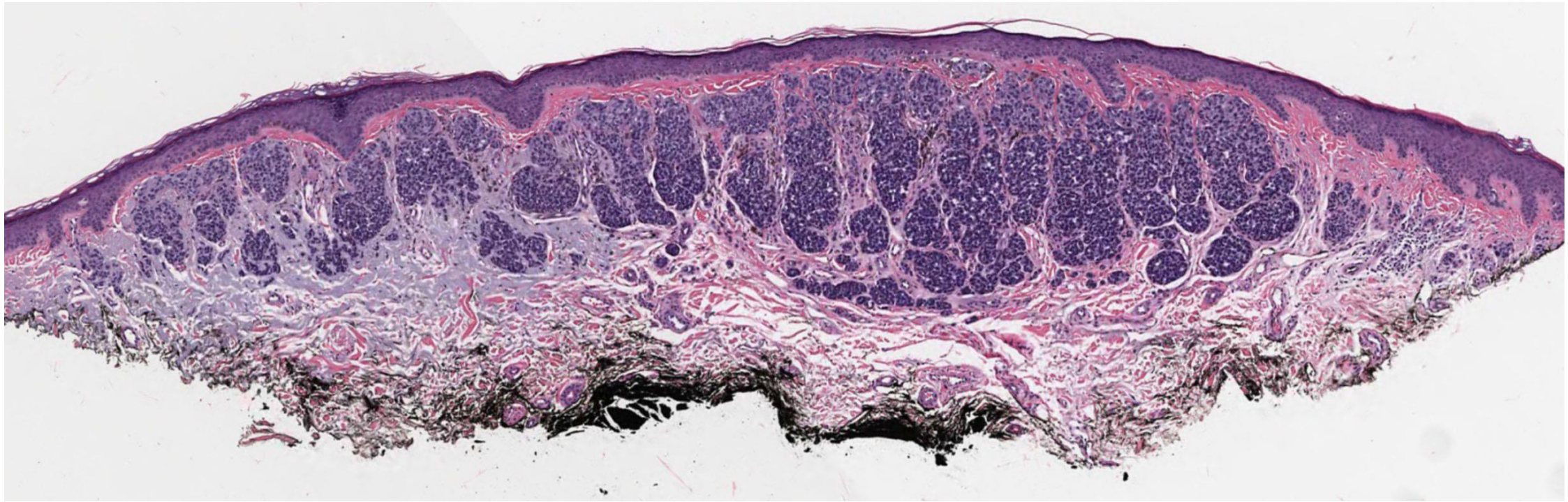
Ancillary Tests for Melanoma Diagnosis

- Immunohistochemistry
- Molecular Tests

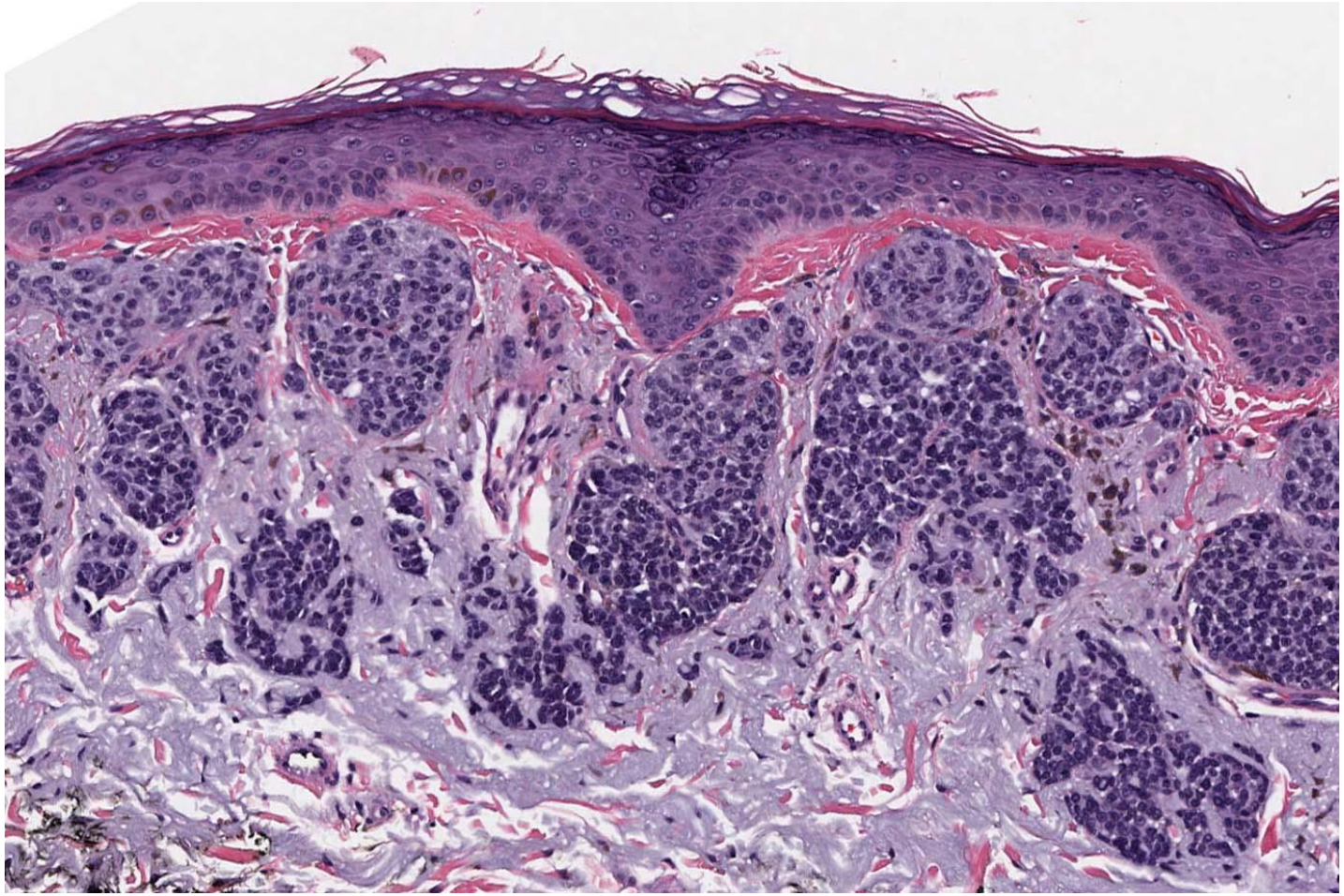
II. Immunohistochemistry

- Melanocytic or Not
  - Amelanotic melanocytic tumor vs other
  - Densely inflamed melanocytic tumor
  - SLN analysis
- Surrogate for molecular pathway (e.g., Spitz; BAP1, beta-catenin)
- Targeted therapy (e.g., BRAFV600E)
- Biomarker to help distinguish benign from malignant

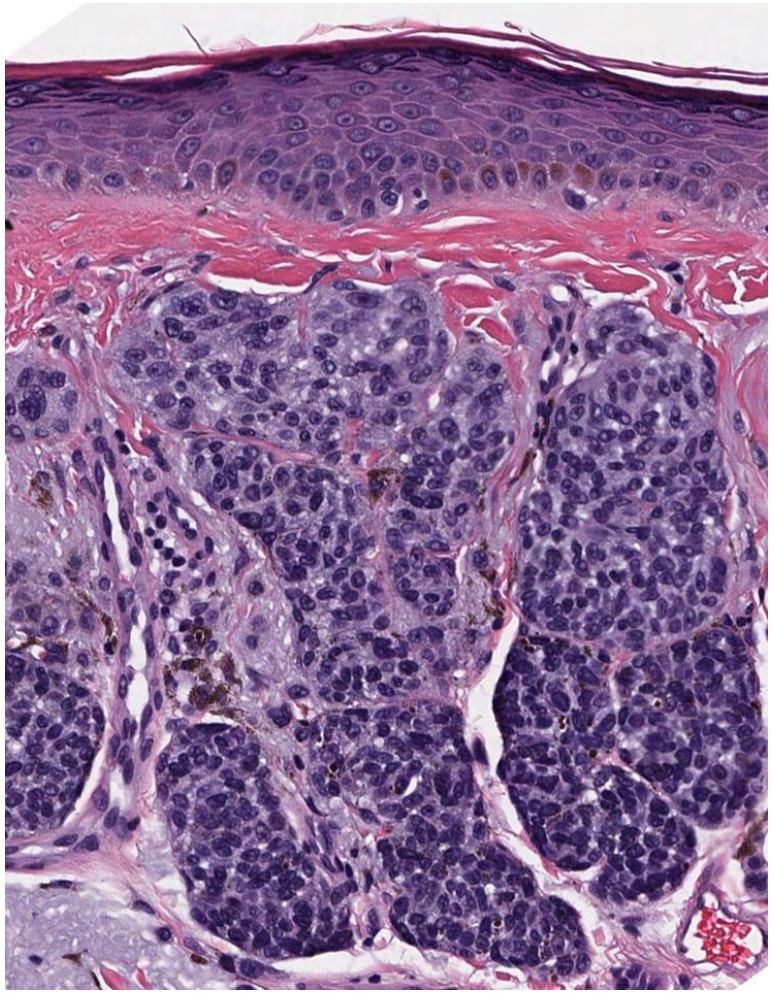
What is Your Diagnosis?

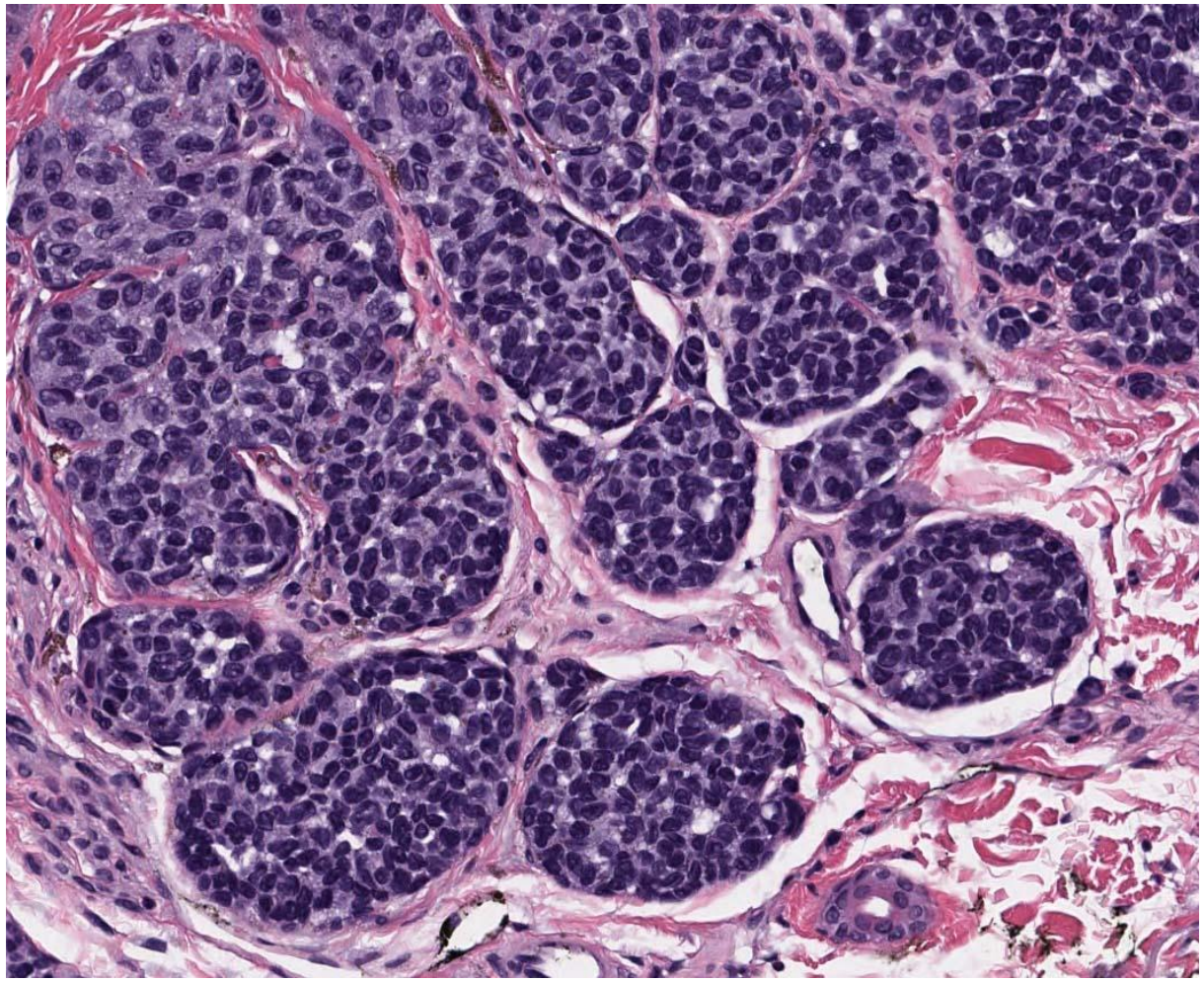


What is Your Diagnosis?

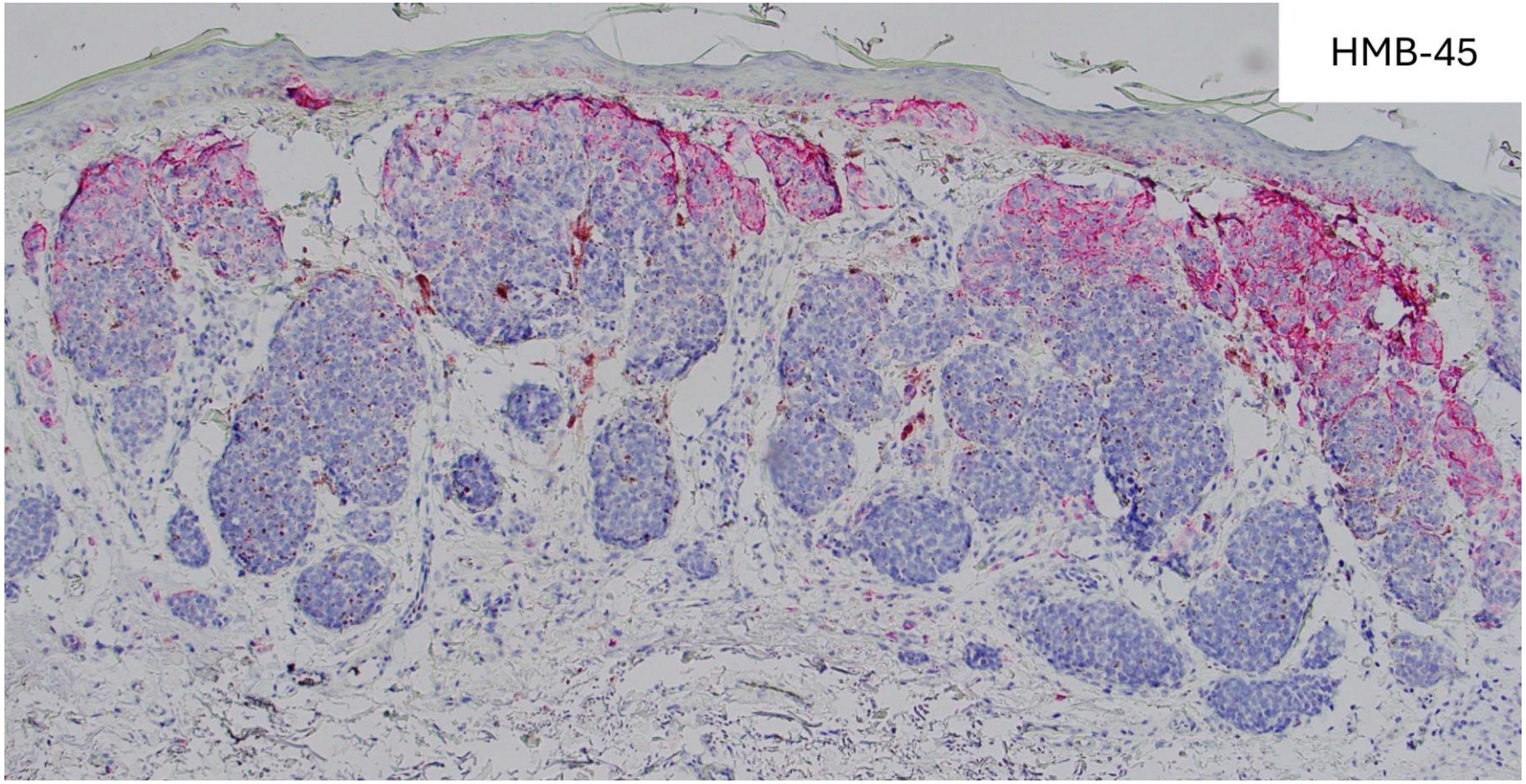


What is Your Diagnosis?





Submitted IHC slide



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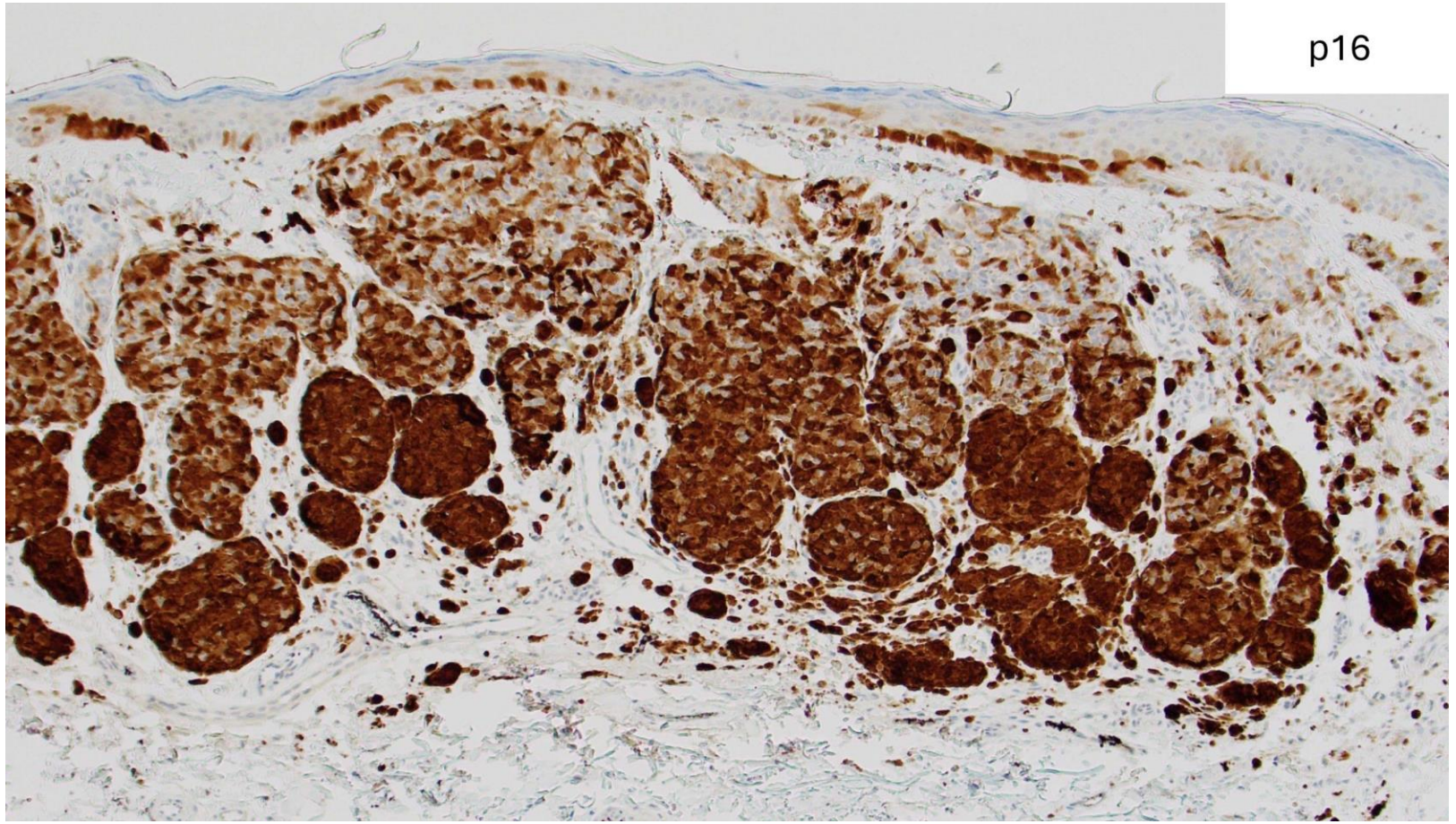
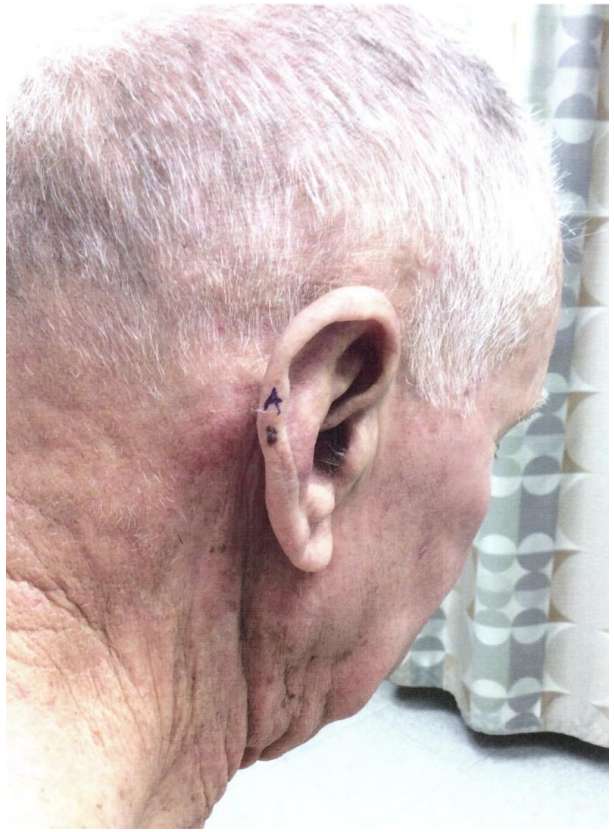
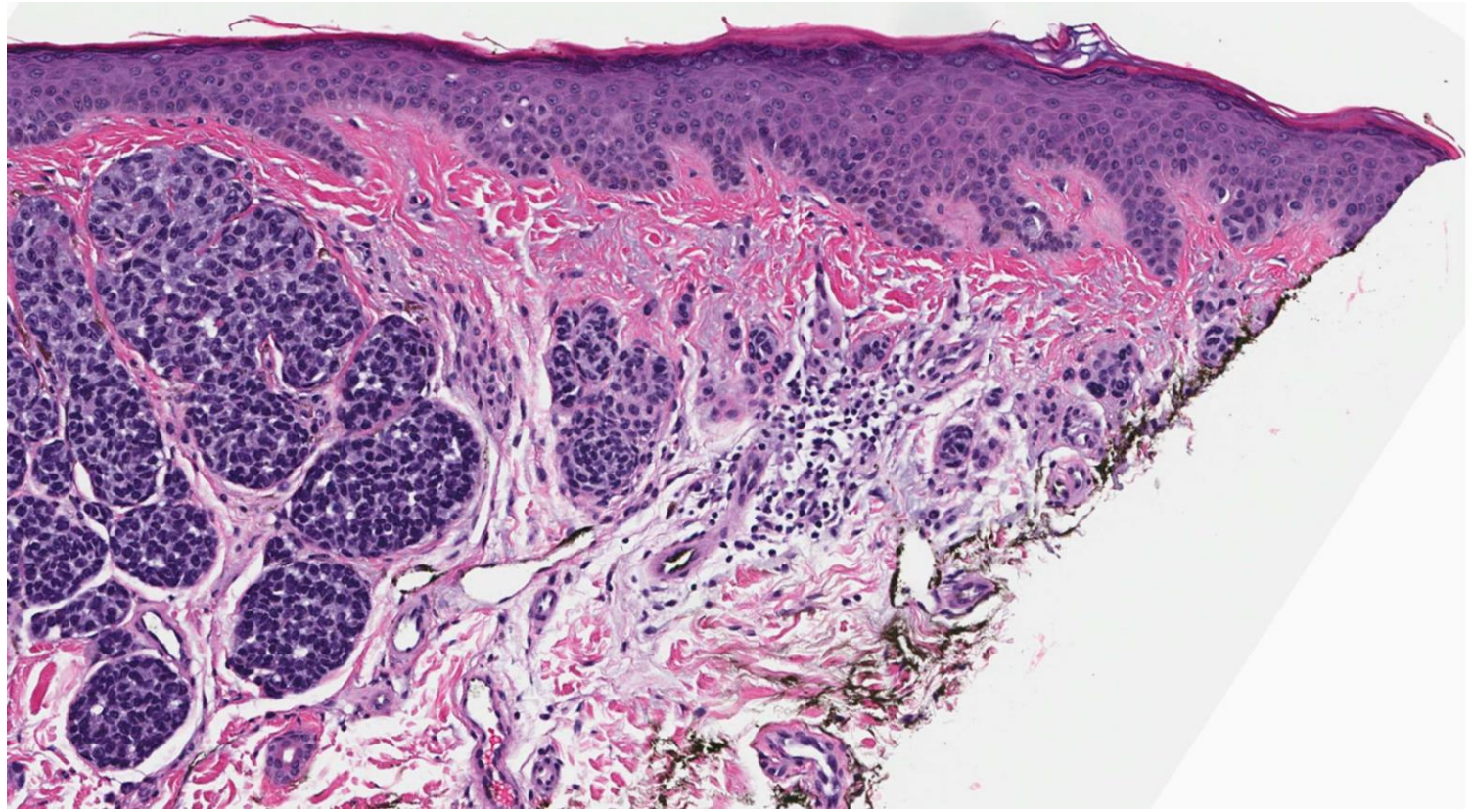
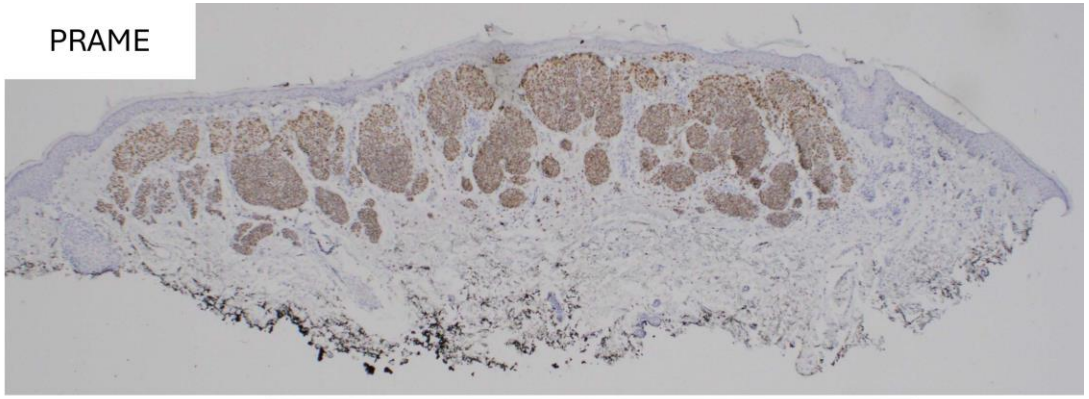


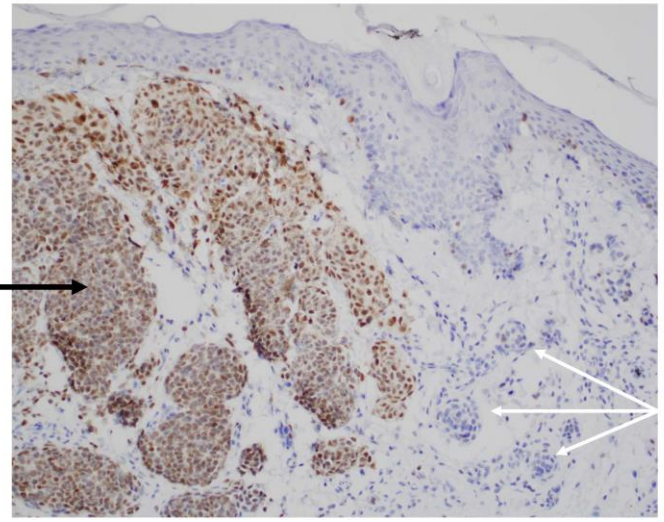
Changing Lesion; Dual Population of Melanocytes

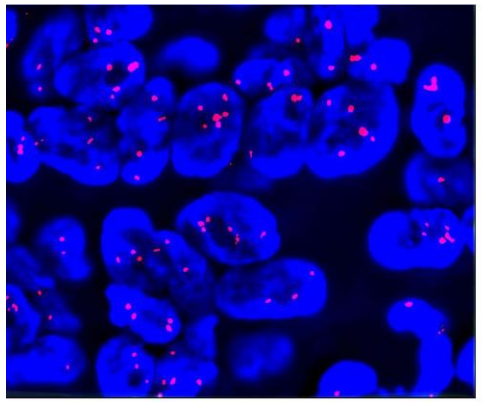




Diagnostic Support from Ancillary Studies







FISH TEST POSITIVE

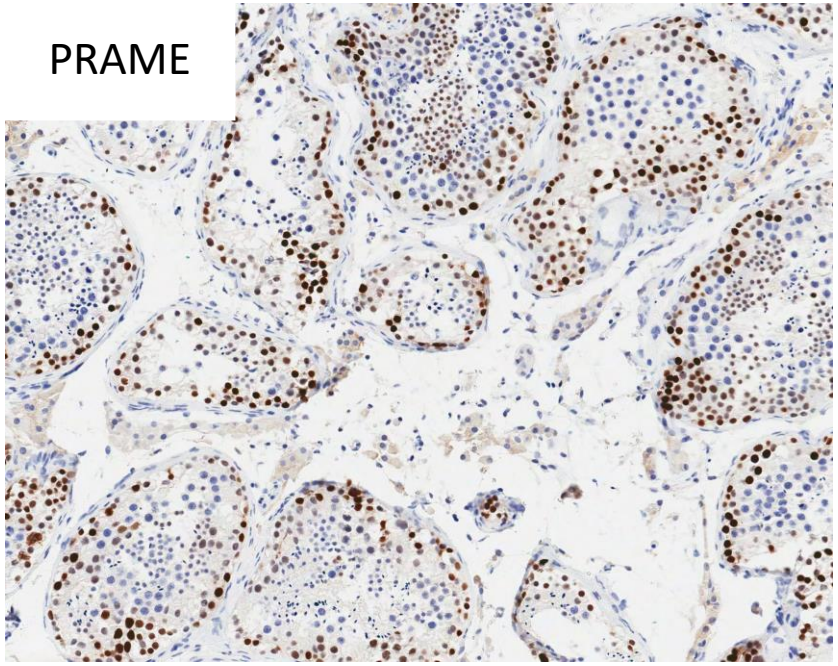
-Gain of 6p
-Loss of 6q
-Gain of 11q

FISH TEST NORMAL
In adjacent nevus

Final Diagnosis **Date Signed Out:**
FISH evaluation following hybridization revealed RREB1 (6p25)gain in 93%, relative gain of RREB1 (6p25)/CEP 6 in 50%, relative loss of MYB (6q23)/CEP 6 in 23%, CCND1 (11q13) gain in 56% and homozygous deletion of CDKN2A (p16, 9p21) in 0%

PRAME

- **PR**eferentially expressed **A**ntigen in **Me**lanoma
- Cancer Testis Antigen

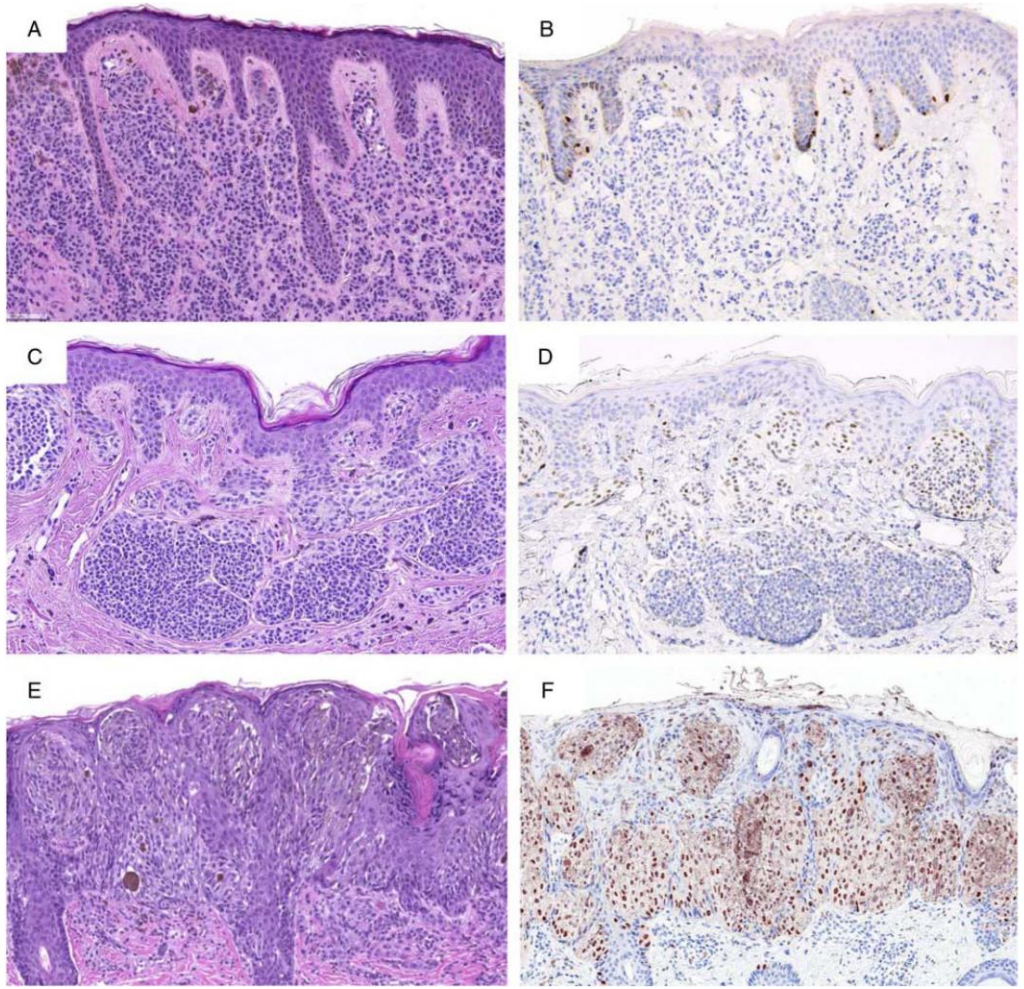


PRAME Expression by IHC

- Metastatic Melanoma (n=100) 87% POS
- Primary Melanoma (n= 155) 83% POS
  - Conventional: 88 – 94%
  - Desmoplastic: 35%
- Melanocytic Nevi (n= 145) 14% POS

Am J Surg Pathol 2018;42: 1456 - 1465

PRAME in Melanocytic Nevi

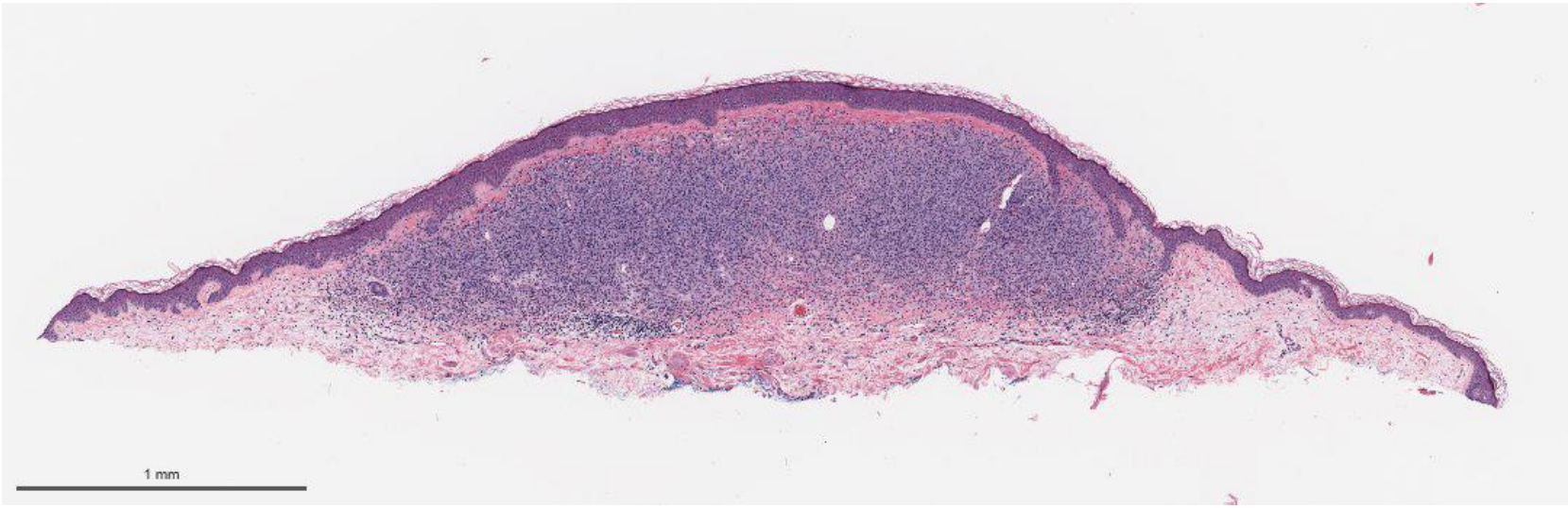


4/40
(1+)

11/60
(1 – 2+)

1/145
(4+)

Nevus or Melanoma?

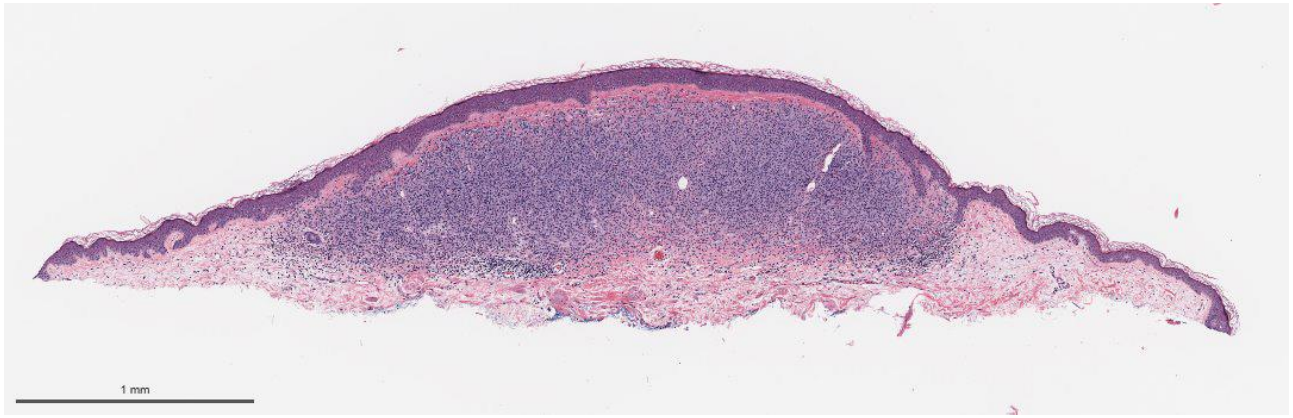


FINAL DIAGNOSIS

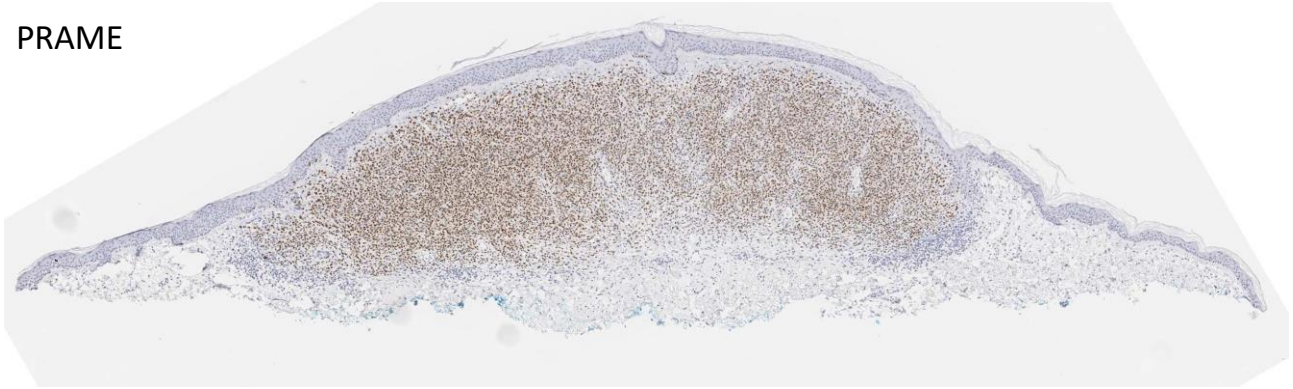
Right Lateral Inferior Chest, Shave Biopsy:

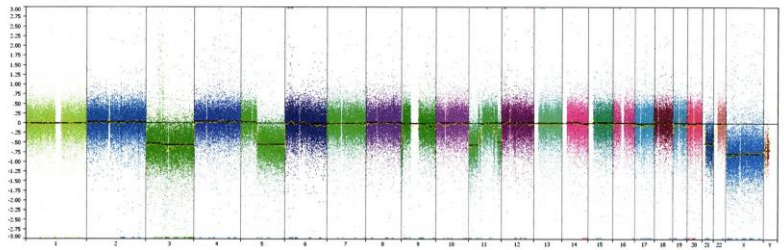
ATYPICAL INTRADERMAL MELANOCYTIC PROLIFERATION
Note: This is a difficult biopsy to interpret. There are sheets of melanocytes with variable nuclear size and few mitotic figures. For these reasons I am concern this may represent dermal melanoma with a thickness of 1.3mm, Clark's IV.

Nevoid Melanoma

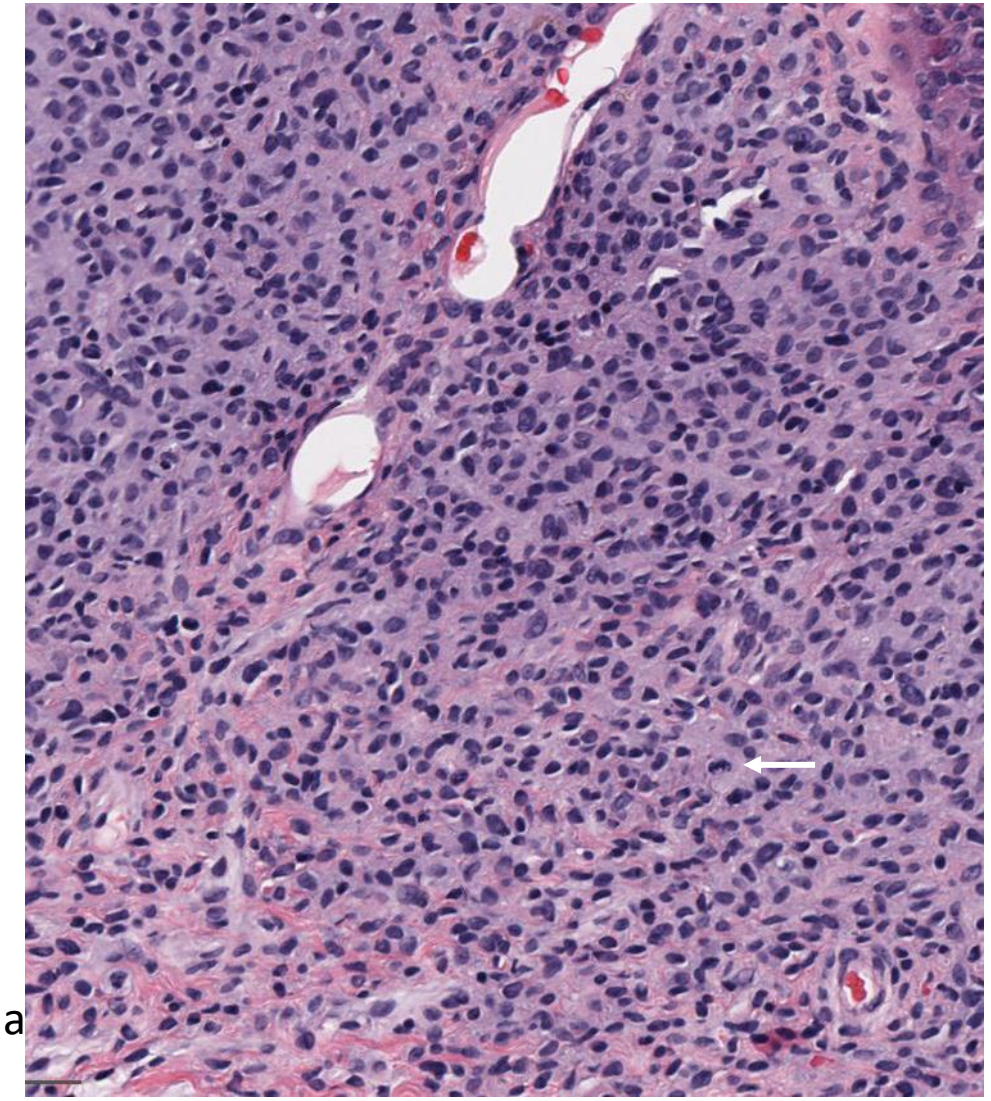


PRAME





SNP Array:
supportive of melanoma



Immunohistochemistry for PRAME

Probably **R**ight, **A**lso **M**akes **E**rrors

Phil LeBoit

Pitfalls in Using PRAME IHC

- PRAME is not melanoma-specific
- Not all melanomas express PRAME
- Some nevi or non-neoplastic melanocytes express PRAME
- Suboptimal assays
- False interpretation of the results

Utility of PRAME IHC in Clinical Practice

- Nodal Nevus vs metastatic melanoma
- Melanoma in situ vs melanocyte hyperplasia, margins of MIS
- Nevus vs melanoma
- Other

Immunohistochemistry for PRAME in the Distinction of Nodal Nevi From Metastatic Melanoma

Cecilia Lezcano, MD, Melissa Pulitzer, MD, Andrea P. Moy, MD, Travis J. Hollmann, MD, PhD, Achim A. Jungbluth, MD, and Klaus J. Busam, MD

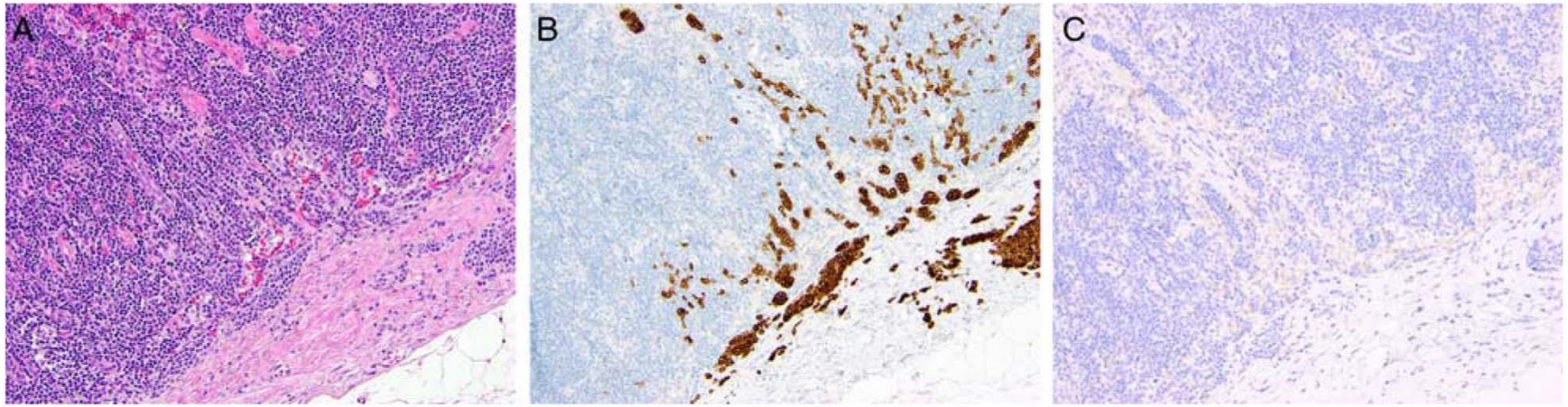
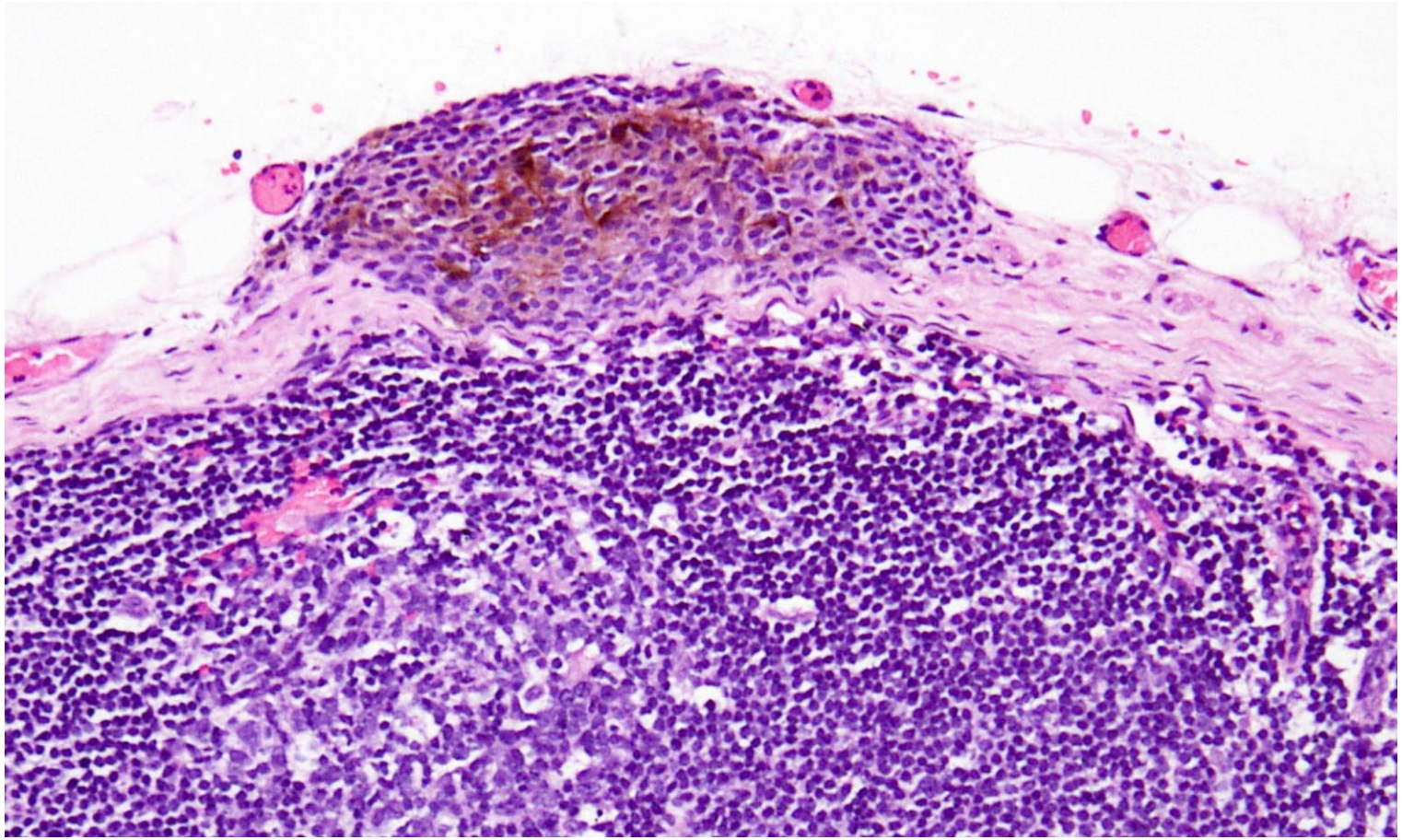


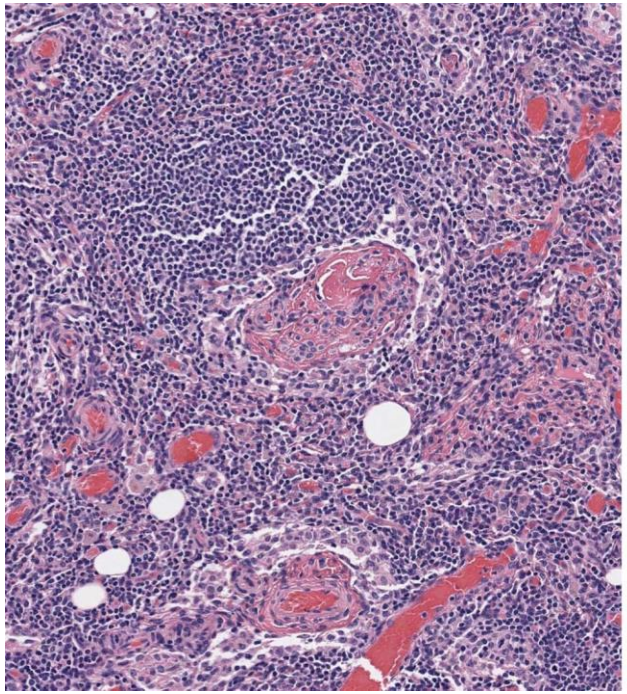
FIGURE 2. Nodal nevus. Capsular, subcapsular, and intraparenchymal nevus (A, H&E; B, Melan A; C, PRAME) showing no immunoreactivity for PRAME.

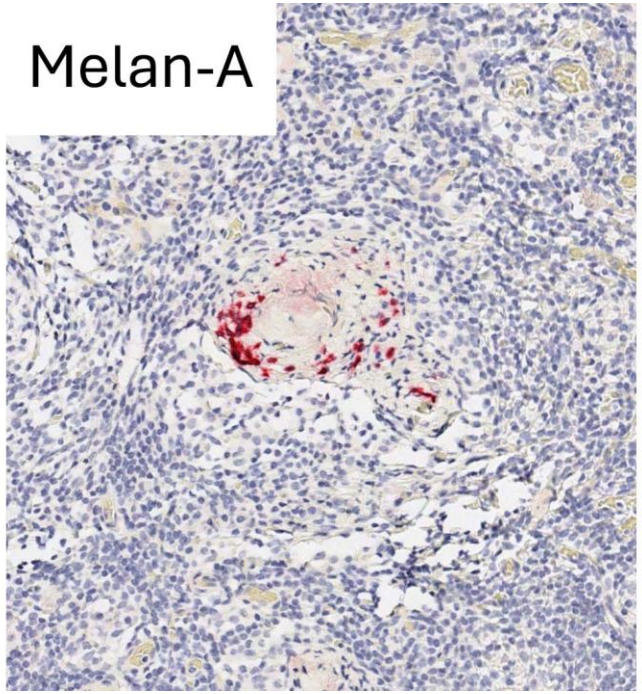
Am J Surg Pathol. 2020;44:503-508.

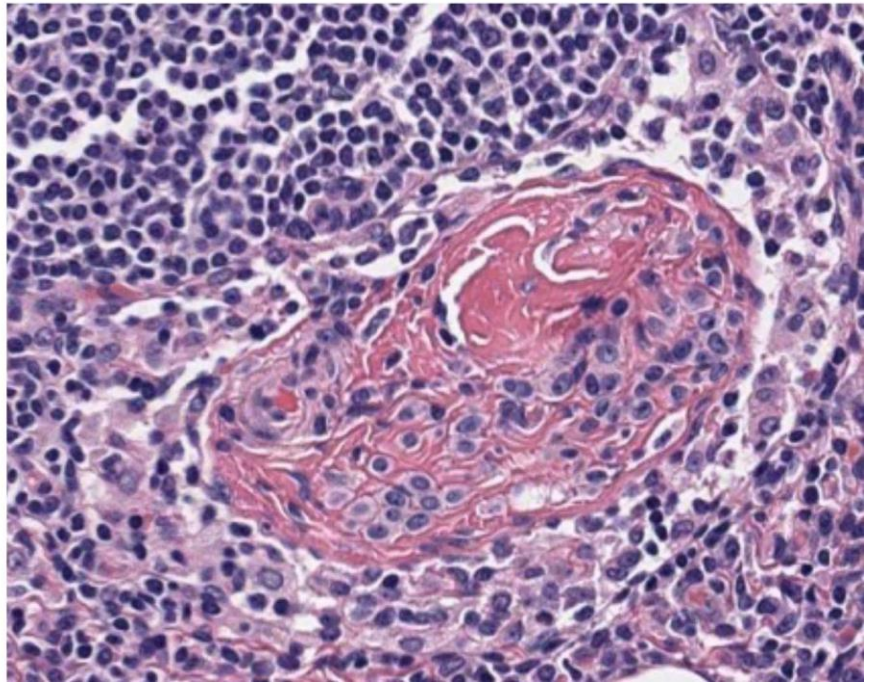
Capsular Nodal Melanocytic Nevus



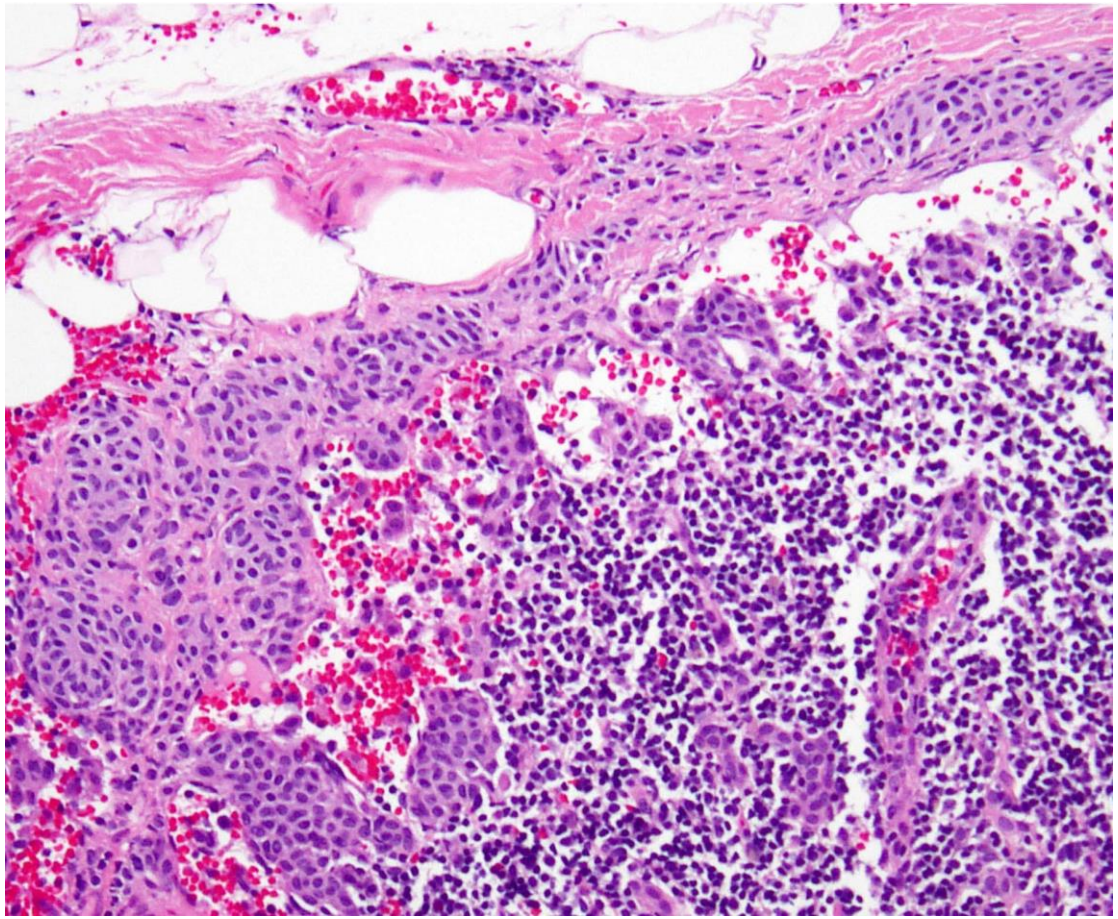
Trabecular Melanocytic Nevus



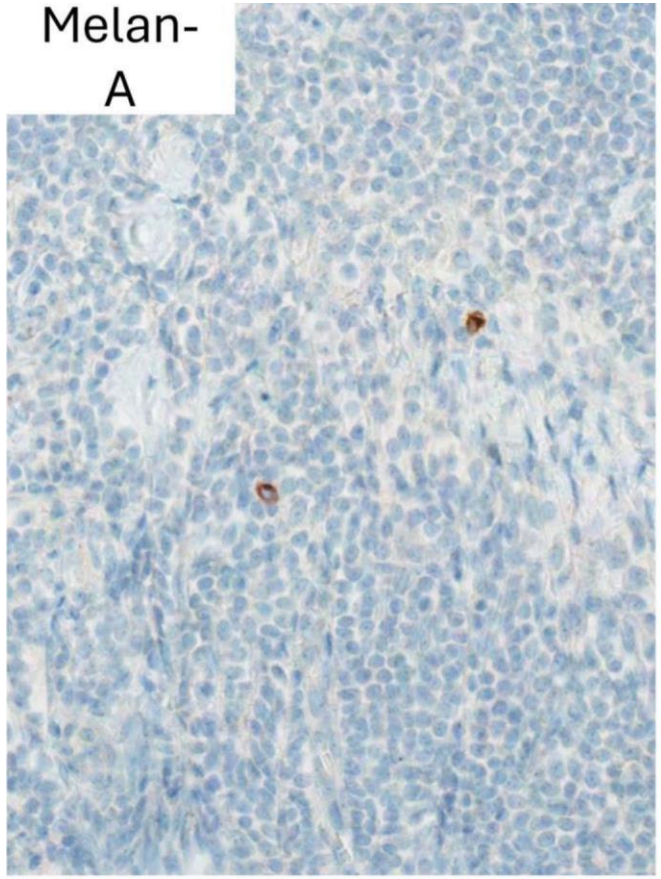


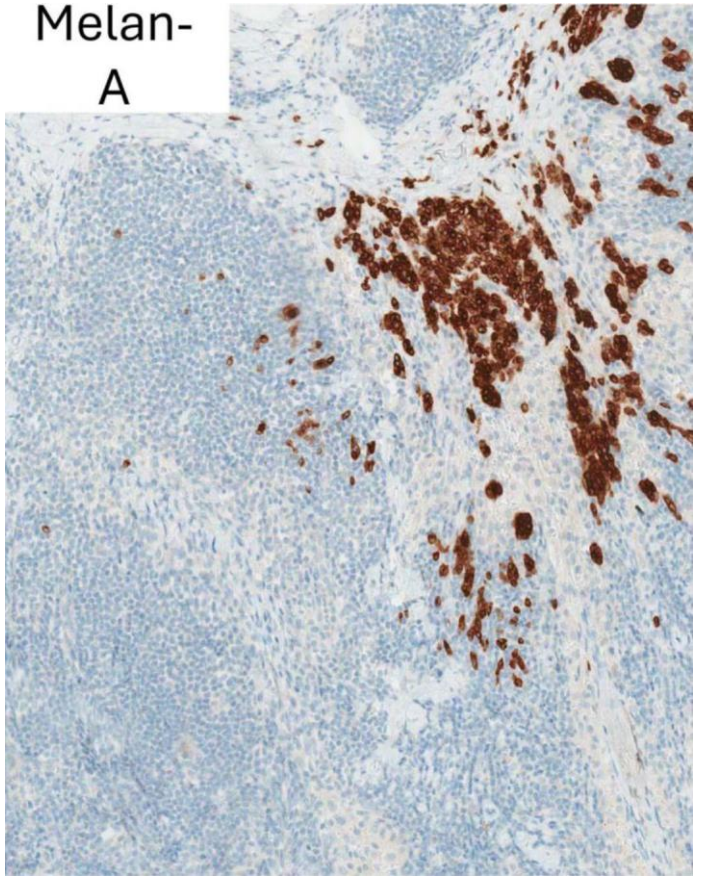


Capsular and Subcapsular Melanocytic Nevus

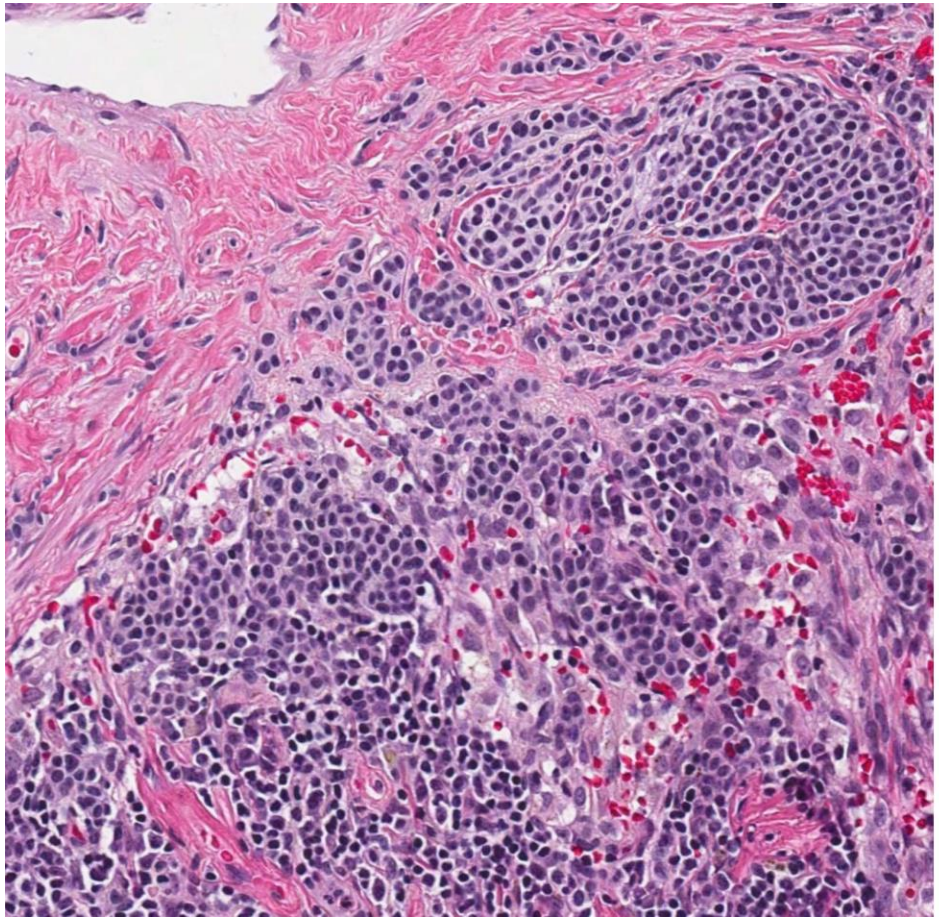


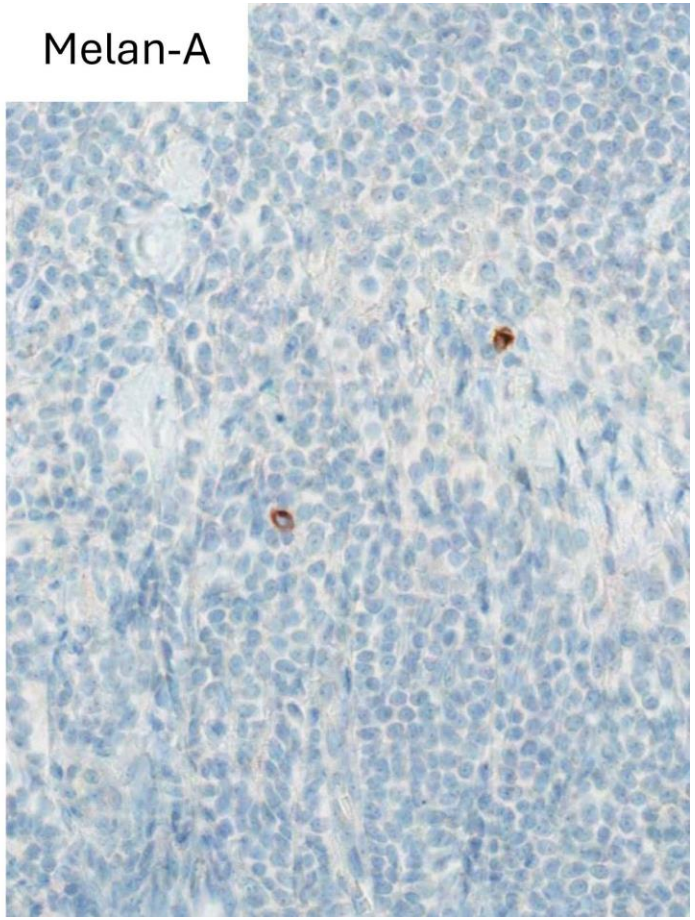
Capsular and Intranodal Melanocytic Nevus



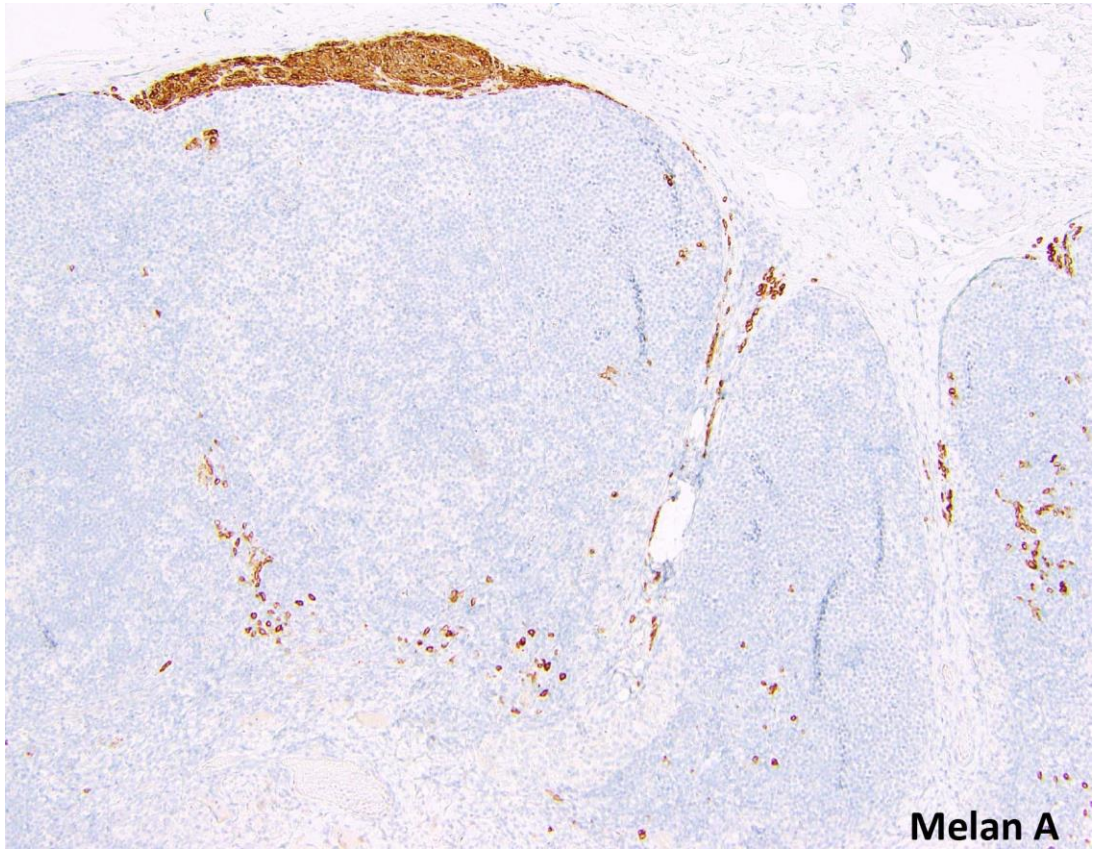


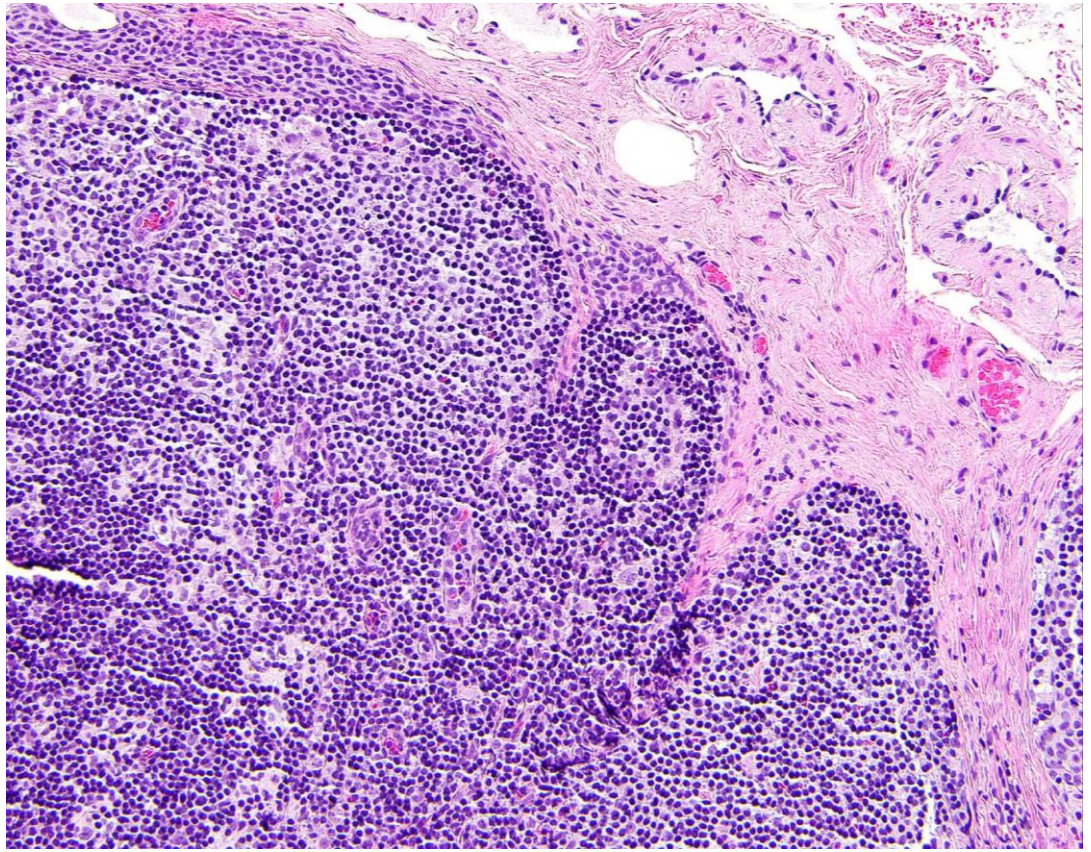
Capsular and Intranodal Melanocytic Nevus



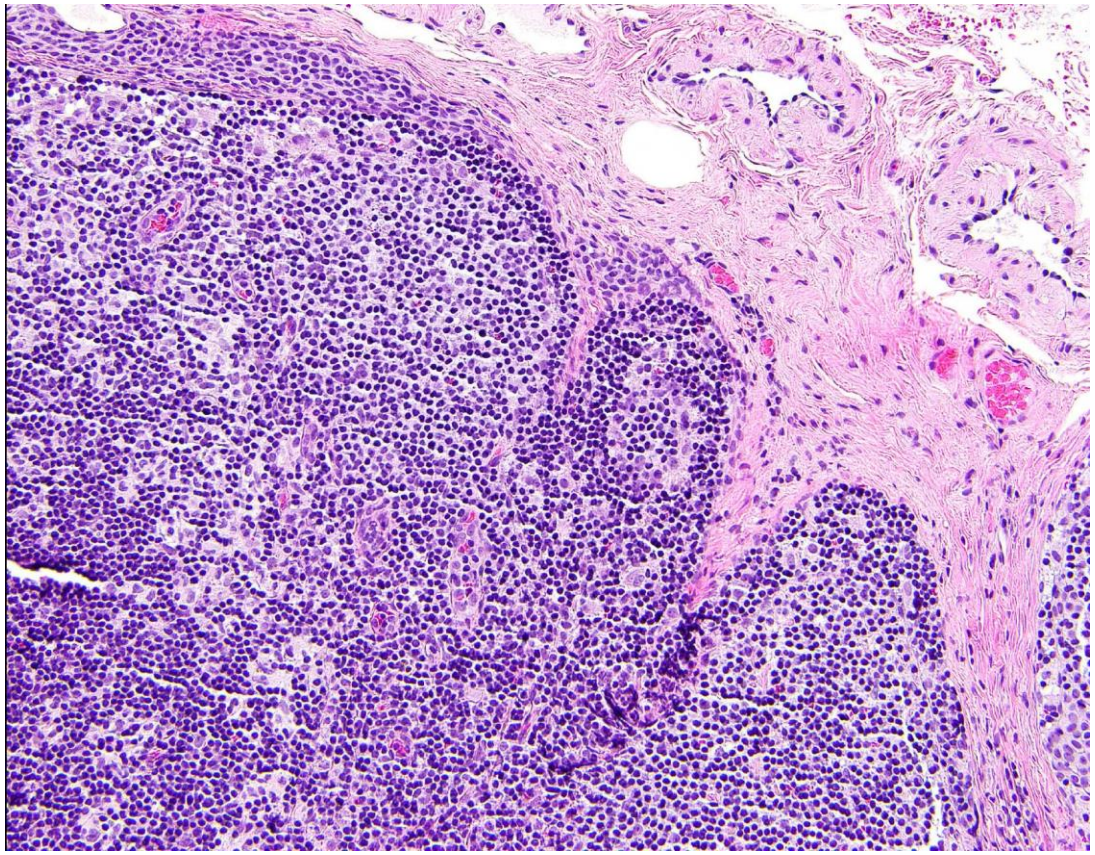


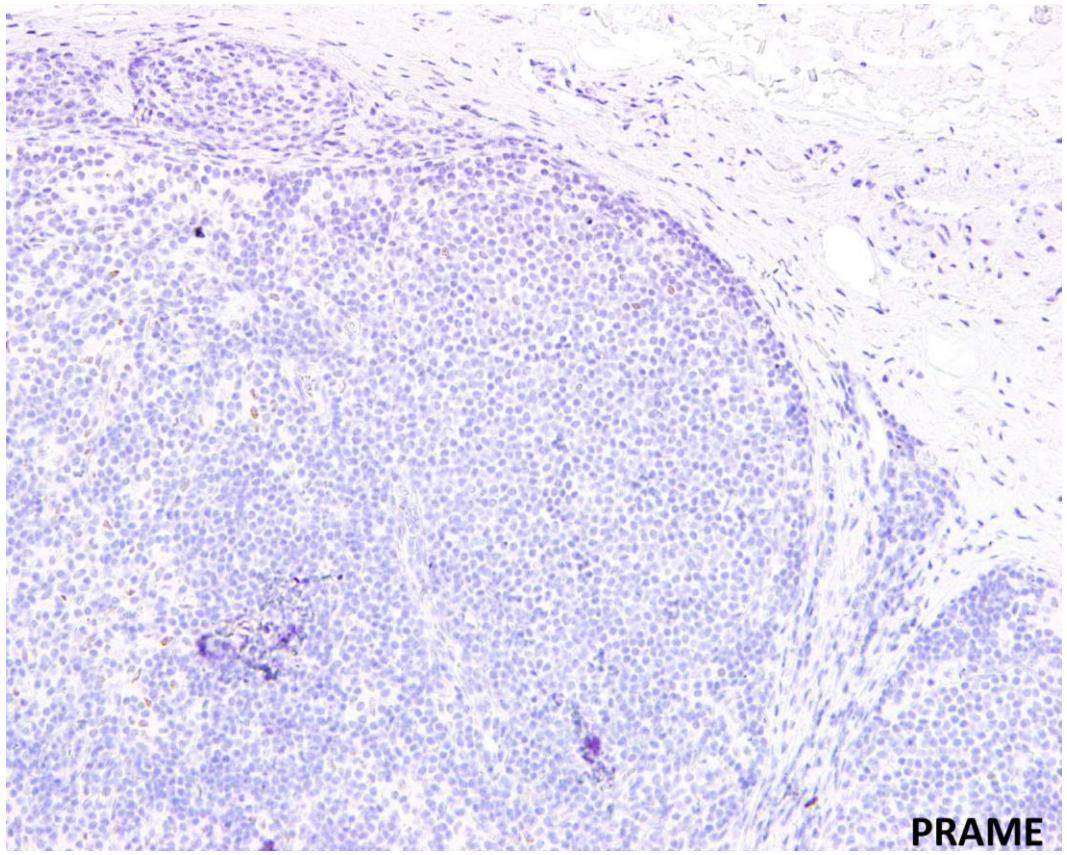
Capsular and parenchymal nodal nevus





Capsular and parenchymal nodal nevus

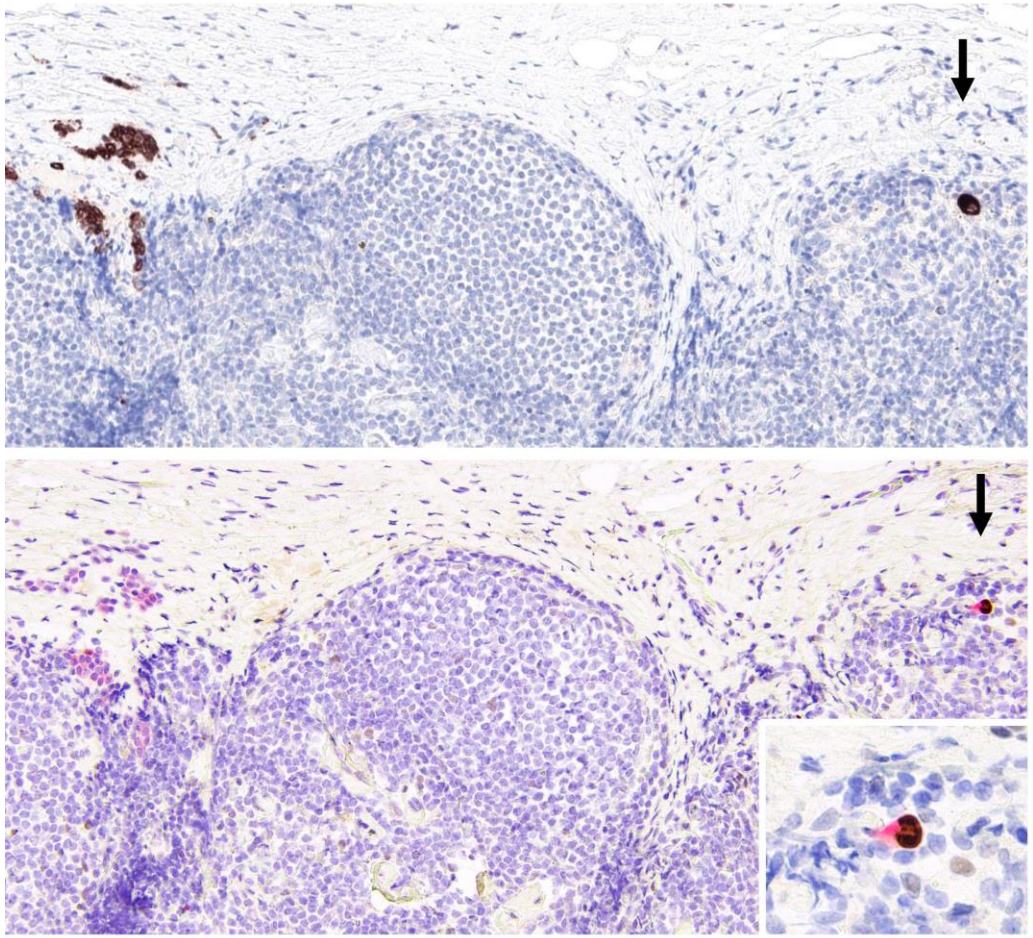




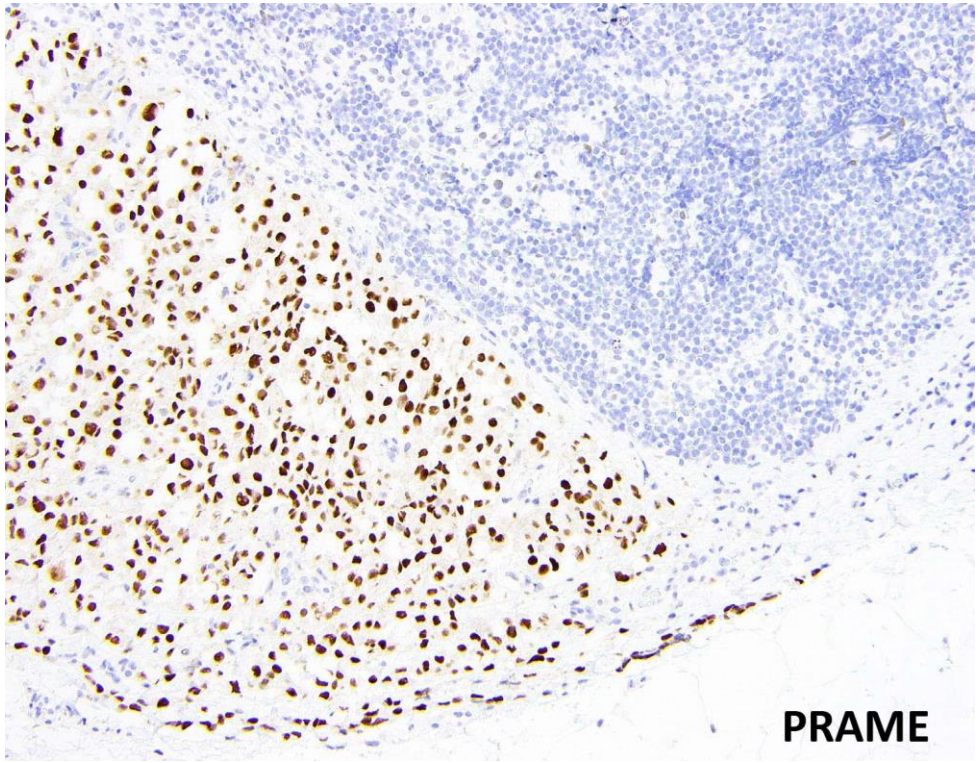
PRAME IHC for SLN Analysis

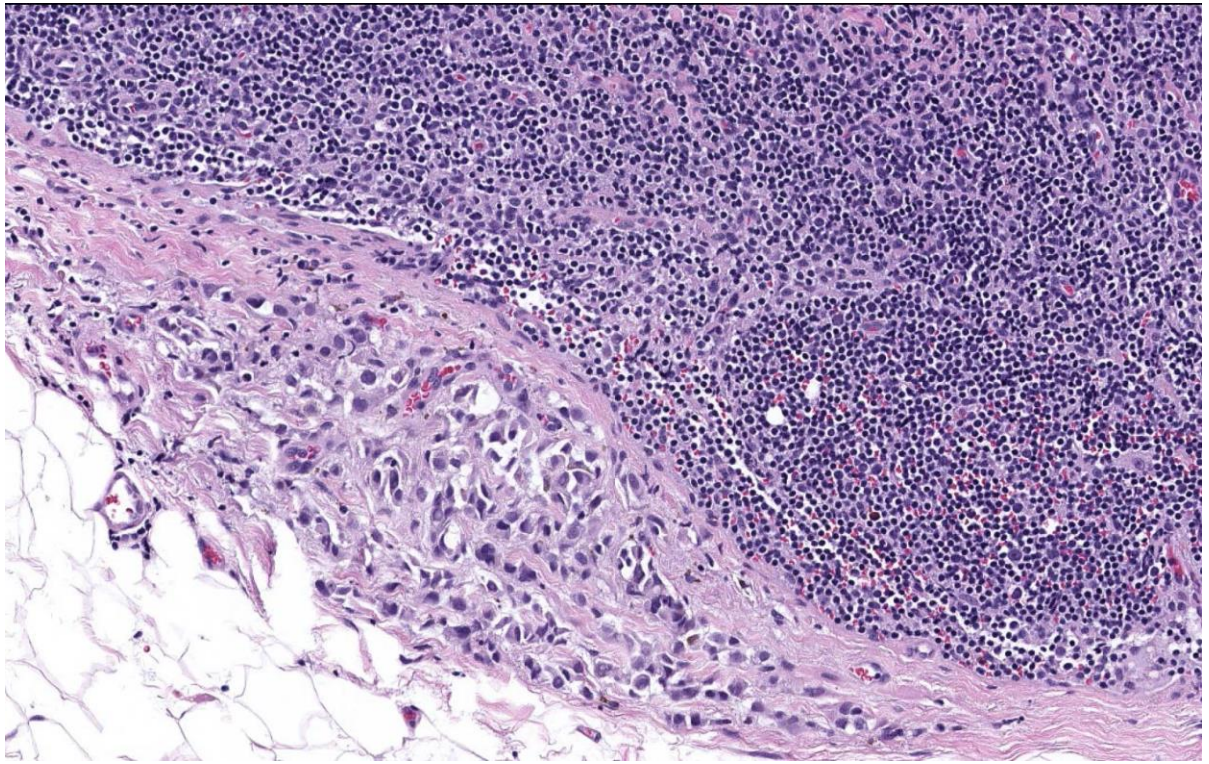
Melan-A

PRAME/
Melan-A



Capsular Metastatic Melanoma



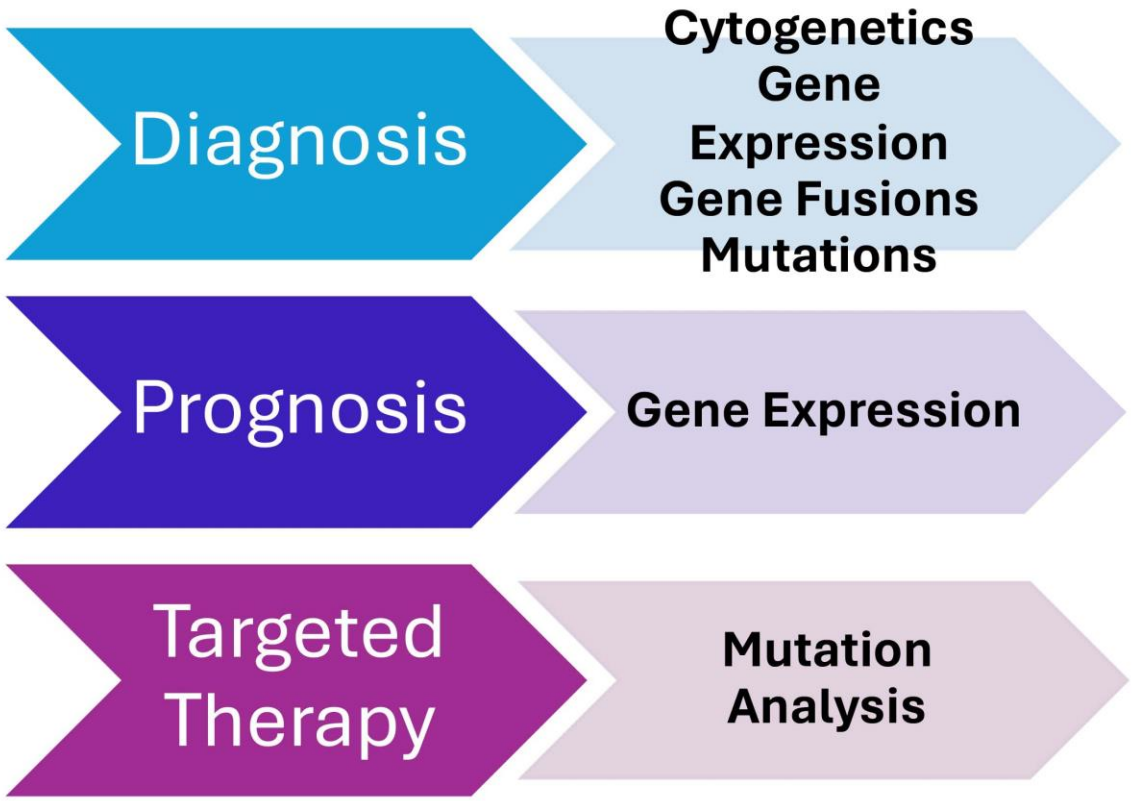


Nodal Nevus vs Metastatic Melanoma

- Features typical of nodal nevus
  - Located in fibrous tissue, but may also be surrounded by lymphocytes
  - Cytologically bland
  - Negative for HMB-45 and PRAME

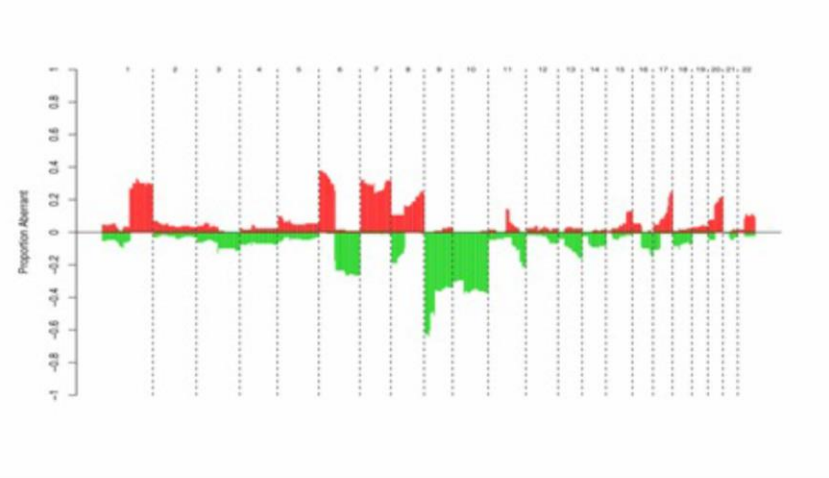
- Features typical of metastatic melanoma
  - Located in nodal parenchyma, but may also involve the fibrous tissue
  - Cytologically atypical
  - Positive for PRAME and/or HMB-45

III. Molecular Tests

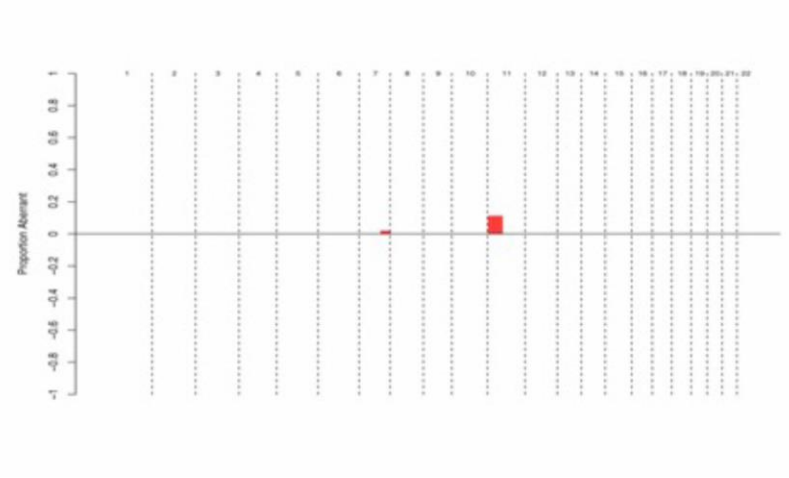


Nevus vs Melanoma – Cytogenetic Tests

Melanoma *n=133*

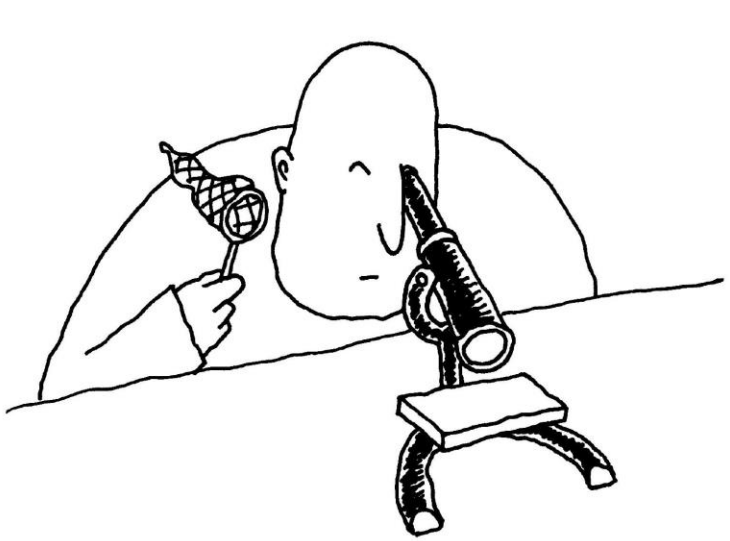


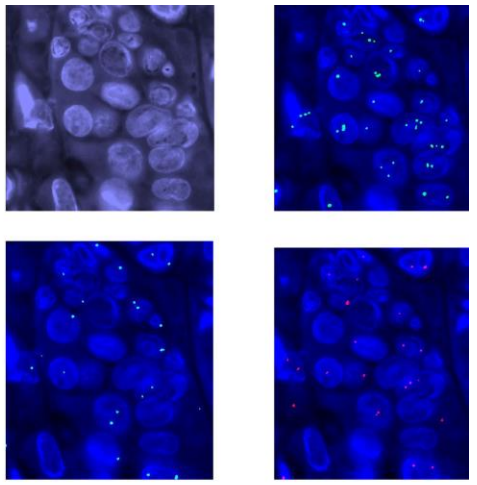
Nevi *n=54*



Bastian et al Am J Pathol 2003

FISHING for Melanoma Diagnosis





Fluorescence In Situ Hybridization (FISH) as an Ancillary Diagnostic Tool in the Diagnosis of Melanoma

Pedram Gerami, MD, Susan S. Jewell, PhD,† Larry E. Morrison, PhD,†*
Beth Blondin, BSc,† John Schulz, BSc,† Teresa Ruffalo, BSc,† Paul Matushek, IV, MS,†
Mona Legator, BSc,† Kristine Jacobson, MS, MAJ,† Scott R. Dalton, MC,‡
*Susan Charzan, MS,§ Nicholas A. Kolaitis, BS,§ Joan Guitart, MD,**
Terakeith Lertsbarapa, MD, Susan Boone, MD,**
Philip E. LeBoit, MD,§ and Boris C. Bastian, MD§

Am J Surg Pathol 2009;33:1146-56

Melanoma FISH test

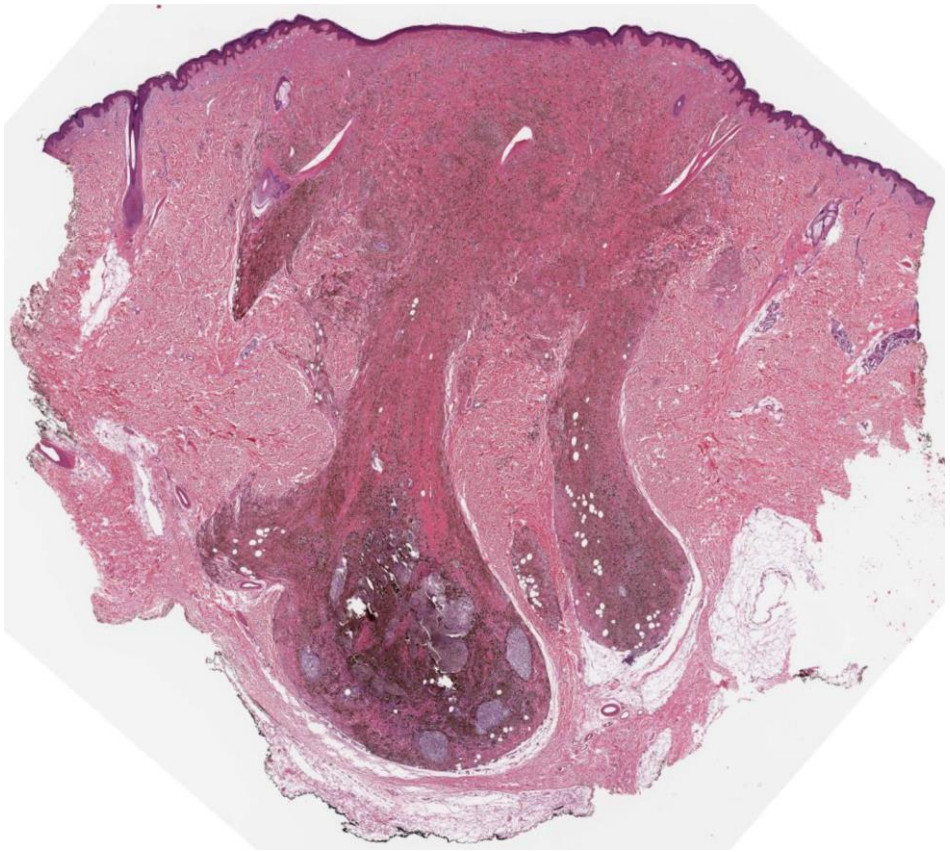
- Advantages
  - Suitable for small biopsies and mixed tumor cell populations
  - FISH technology fairly widely available

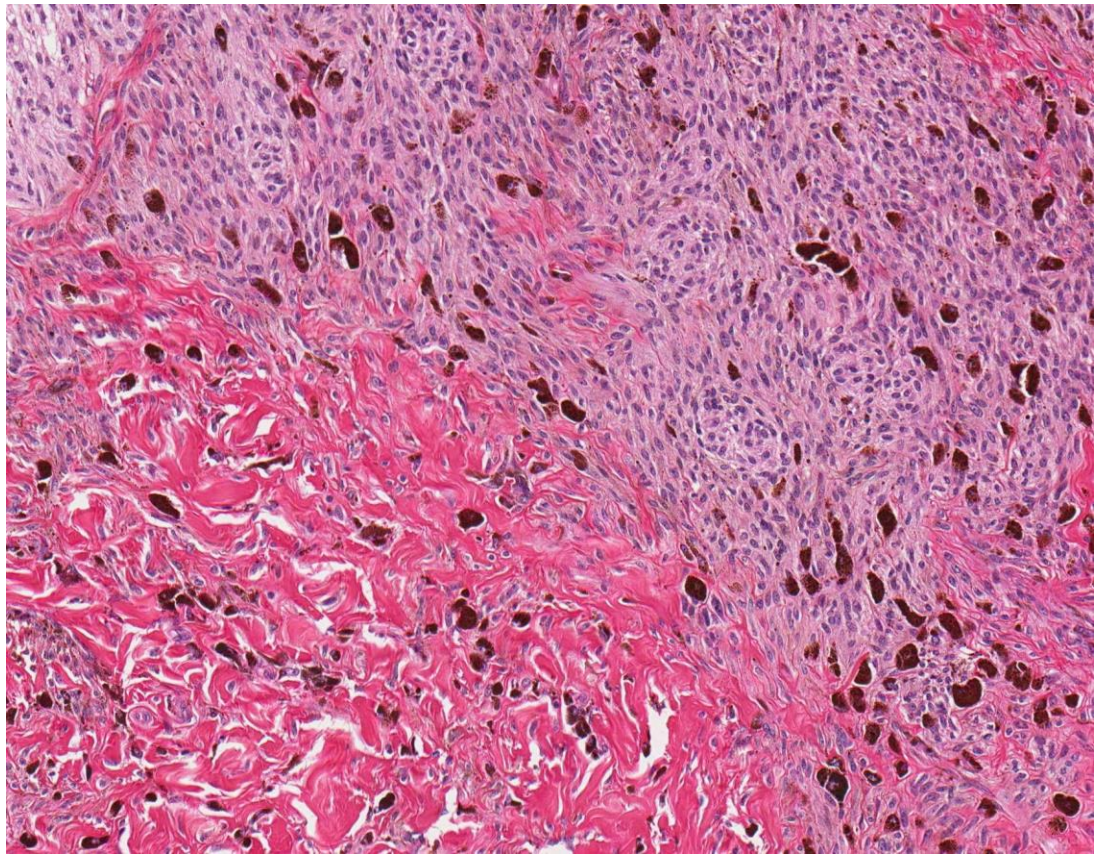
- Disadvantages
  - Limitations in test sensitivity and specificity
  - Added cost and time

Spectrum of Blue Tumors

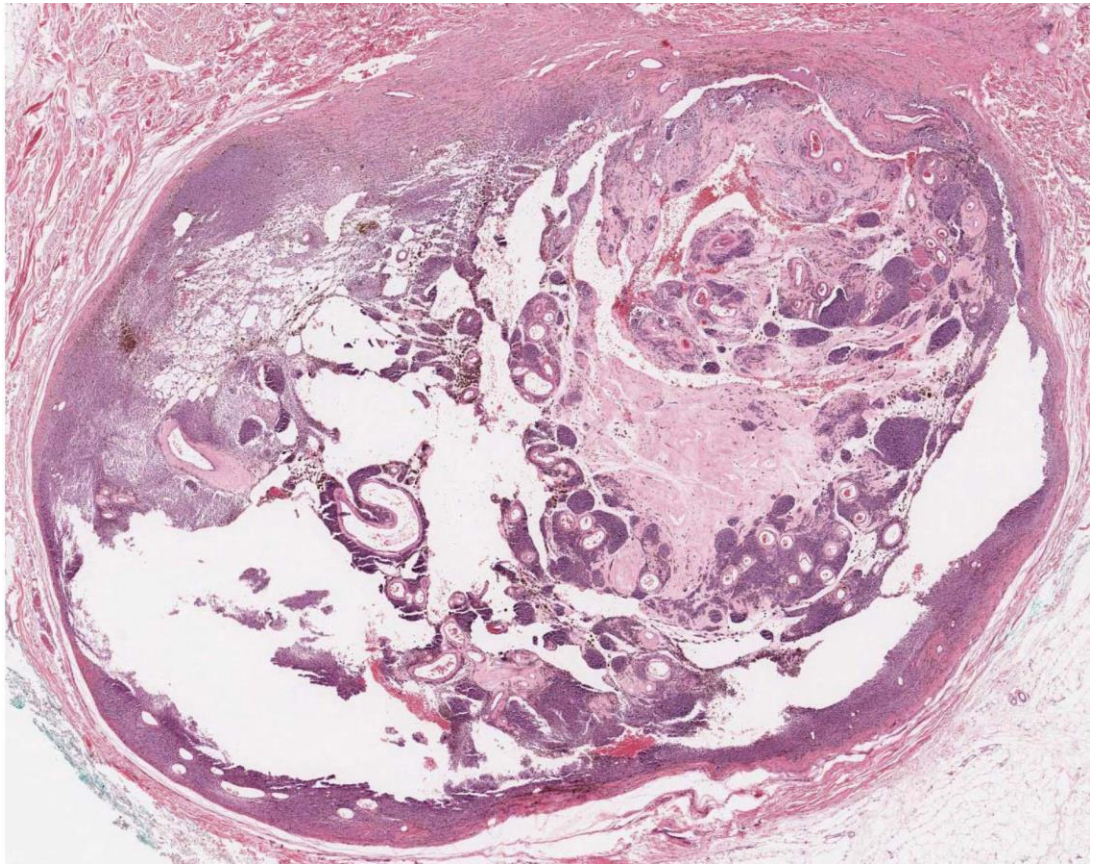
- Blue nevi (e.g., common, sclerosing, cellular)
- Blue nevus-related melanomas
- Metastatic melanoma simulating a blue nevus
- Blue tumors with uncertain diagnosis

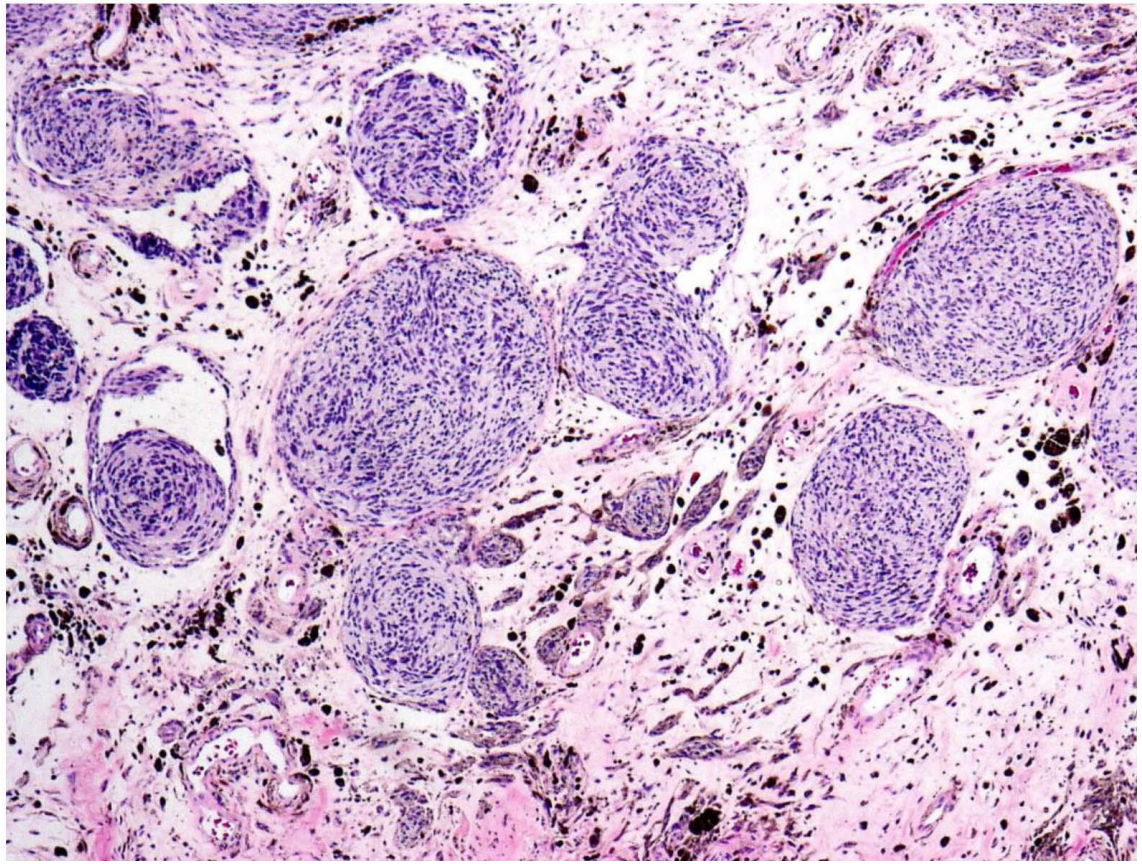
Cellular Blue Nevus



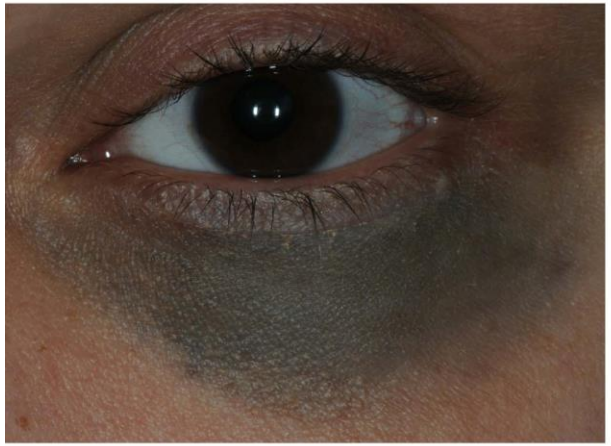


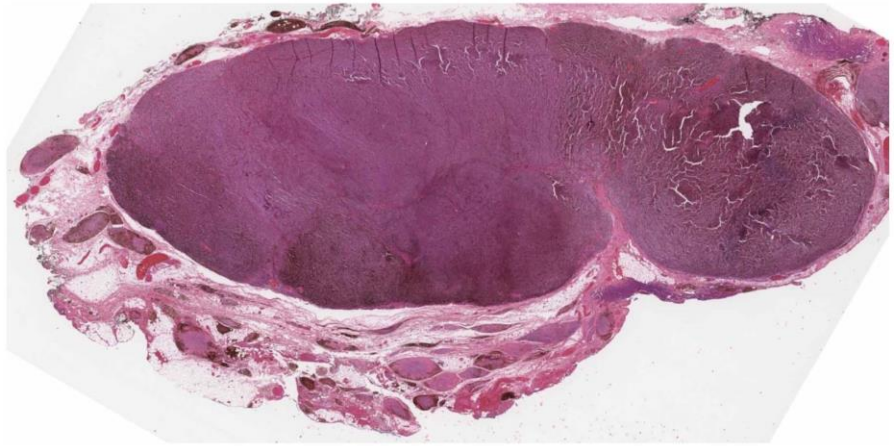
Cellular Blue Nevus

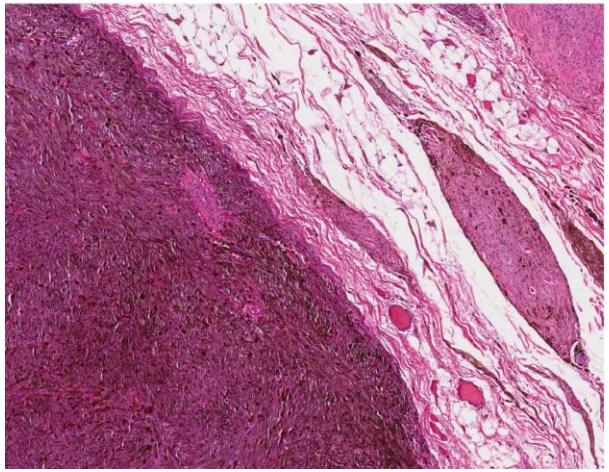


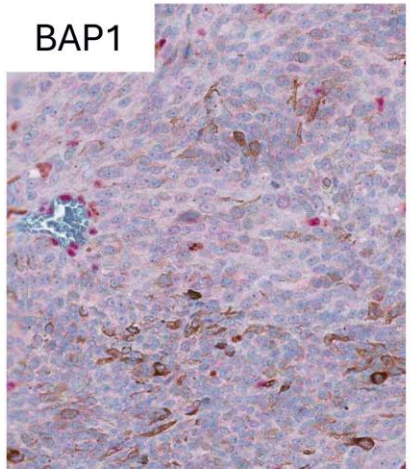


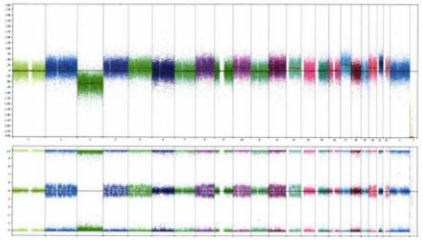
Melanoma ex BN vs Atypical Cellular BN











Numerical aberrations
of chromosomes 2,3,4
5,6,10,12,13,20,22

Blue Tumors: Features worrisome for melanoma

- Tumor cell overgrowth (loss of background fibrotic dendritic BN)
- Expansile growth of cytologically atypical cells with mitoses
- Tumor necrosis
- Ancillary test results:
  - Loss of BAP1 expression
  - Genomic aberrations

Chromosomal CNA – common in Blue Melanomas

ORIGINAL ARTICLE

Melanomas Associated With Blue Nevi or Mimicking Cellular Blue Nevi

Clinical, Pathologic, and Molecular Study of 11 Cases Displaying a High Frequency of GNA11 Mutations, BAP1 Expression Loss, and a Predilection for the Scalp

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Abstract: Melanomas associated with blue nevi (MABN) or mimicking cellular blue nevi (MMCBN) represent exceptional variants of malignant cutaneous melanocytic tumors. Uveal and leptomeningeal melanomas frequently have somatic mutations of *GNAQ* or *GNA11*, which are believed to be early driver

large dermal atypical melanocytes, in some cases lying adjacent to a blue nevus. Four patients developed metastatic disease, and 2 died from their disease. A *GNA11* mutation was found in 8/11 cases and a *GNAQ* mutation in 1 case. Seven of 11 cases showed loss of nuclear BAP1 immunohistochemical (IHC) expression in the malignant component, sparing the adjacent nevus. Array

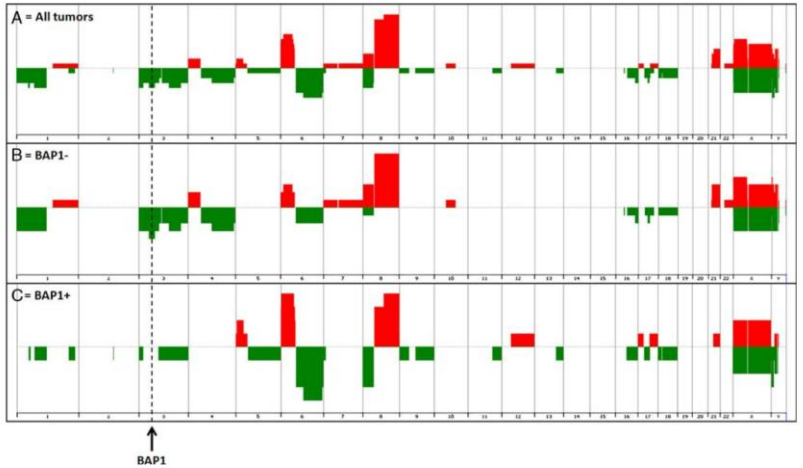
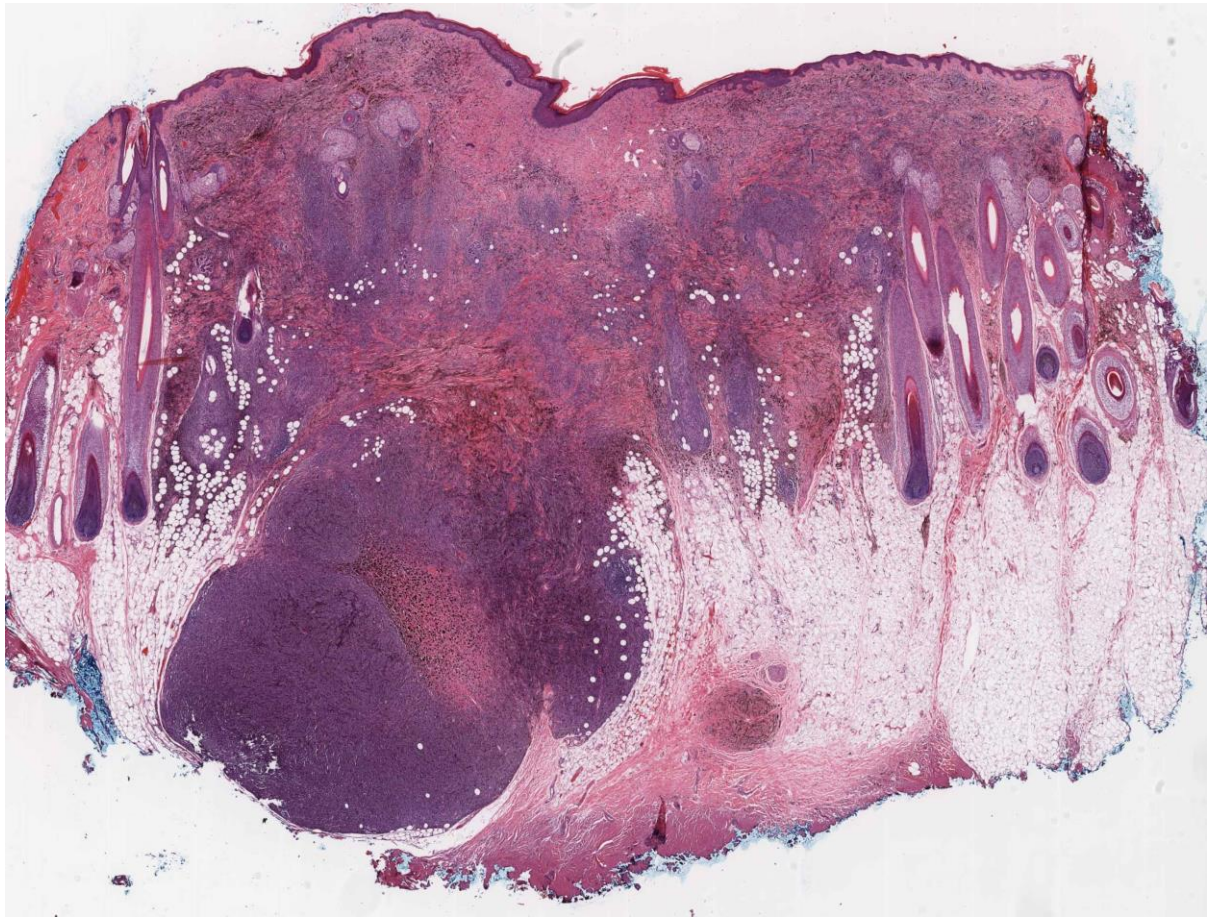
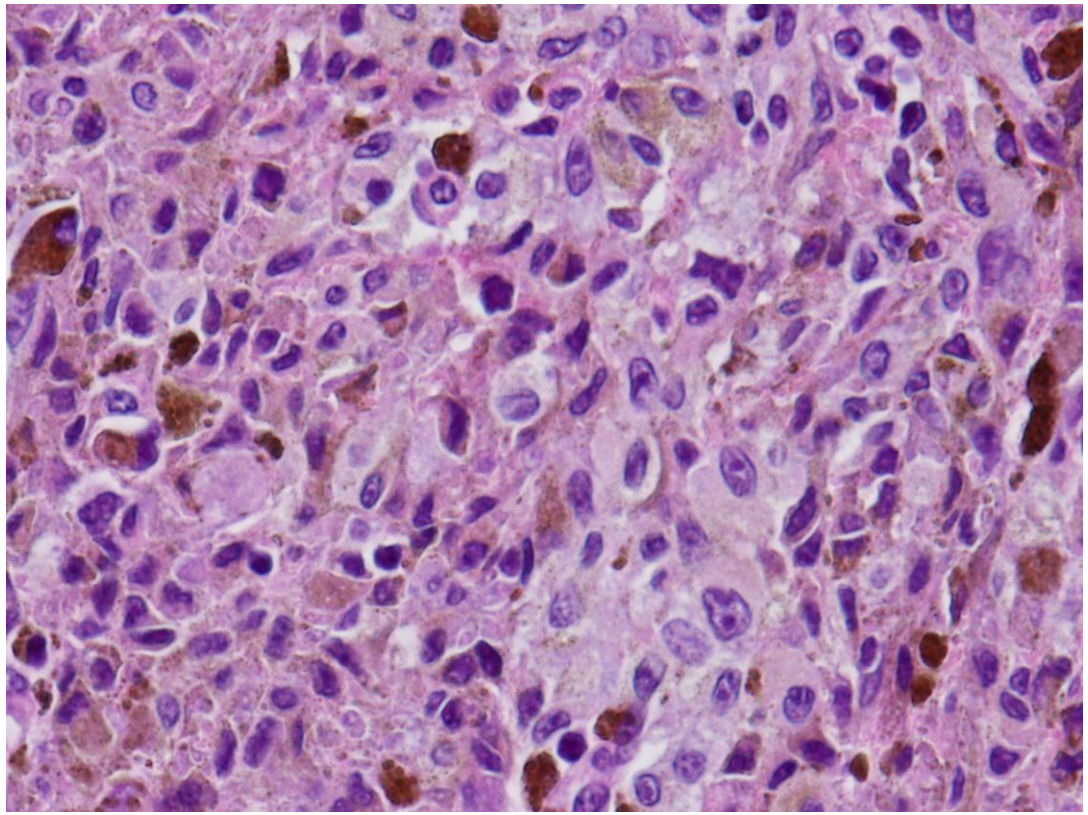


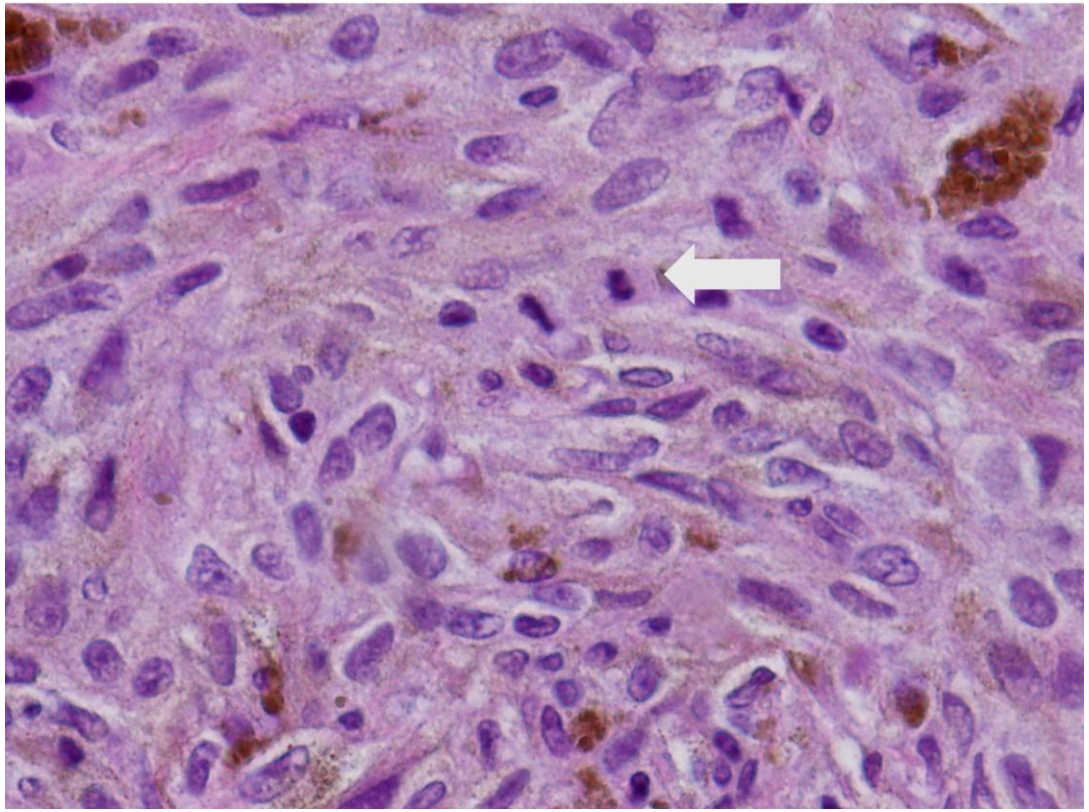
FIGURE 4. Penetrance plots showing recurrent chromosomal alterations in MABN/MMCBN. Red blocks represent chromosome gains; green blocks represent chromosome losses. The amplitude of each abnormality corresponds to its prevalence. A, Penetrance plot summarizing the copy number imbalances per chromosome in all patients. B, Penetrance plot summarizing the copy number imbalances per chromosome in the group of 7 patients with BAP1 IHC loss (BAP1-negative tumors). C, Penetrance plot summarizing the copy number imbalances per chromosome in the group of 4 patients without BAP1 loss (BAP1-positive tumors).

CBN or Melanoma?

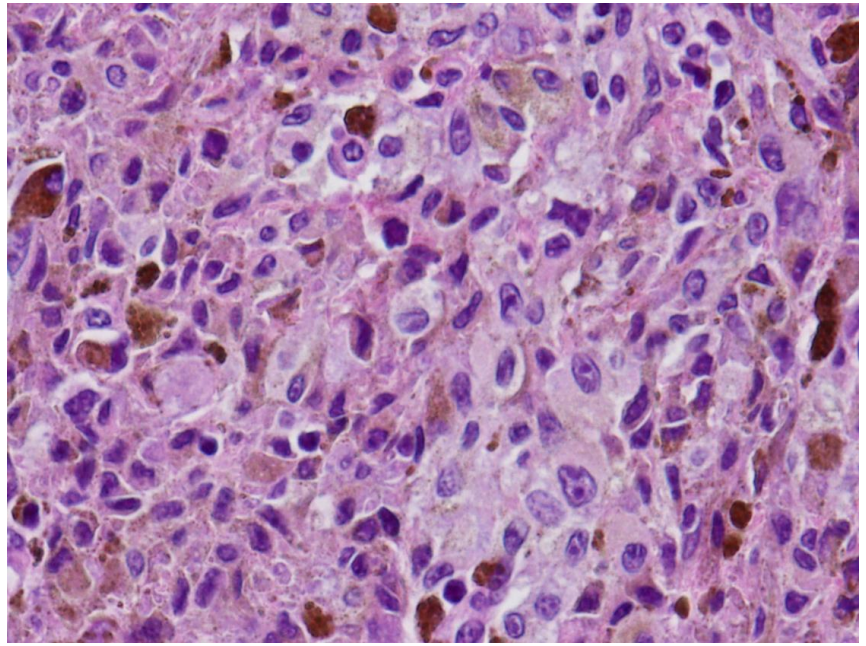


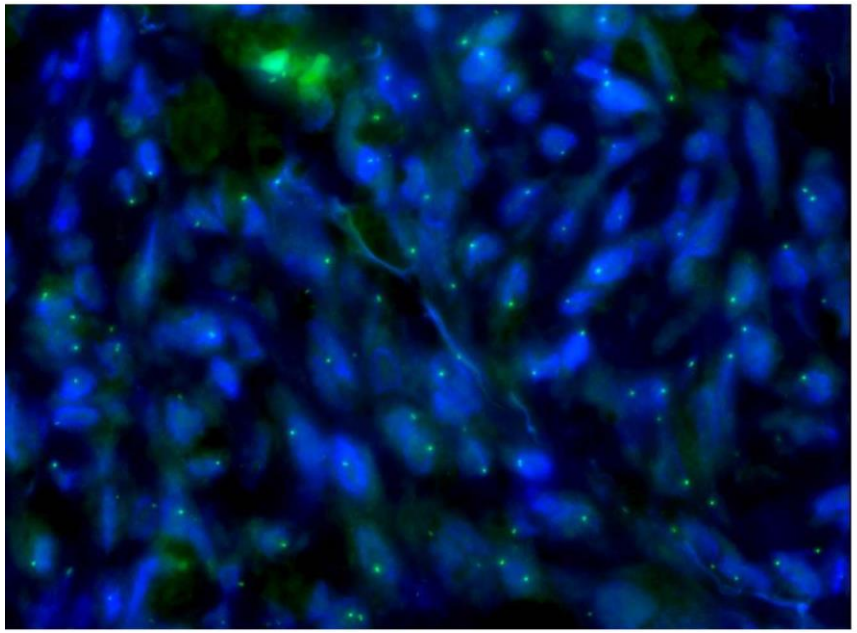
Epithelioid Atypia and Mitoses

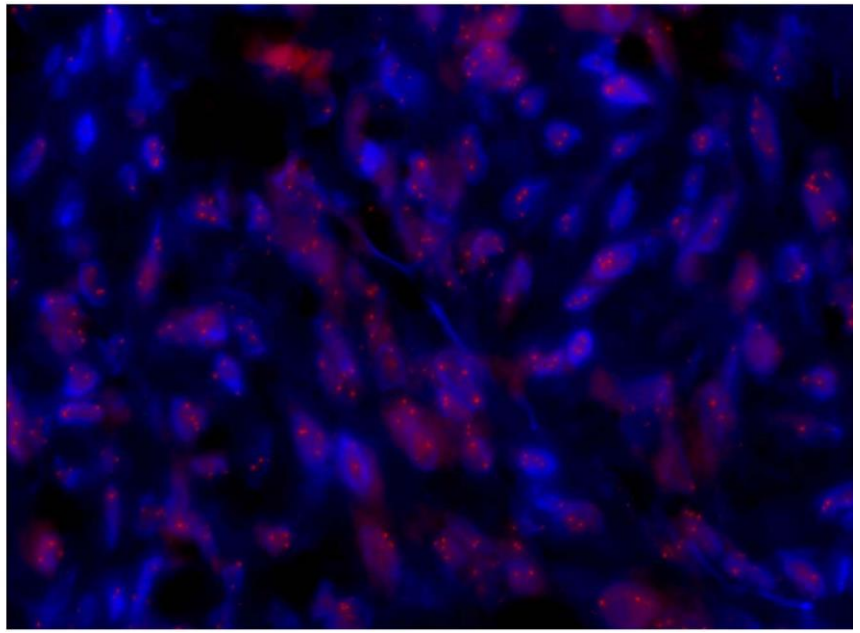




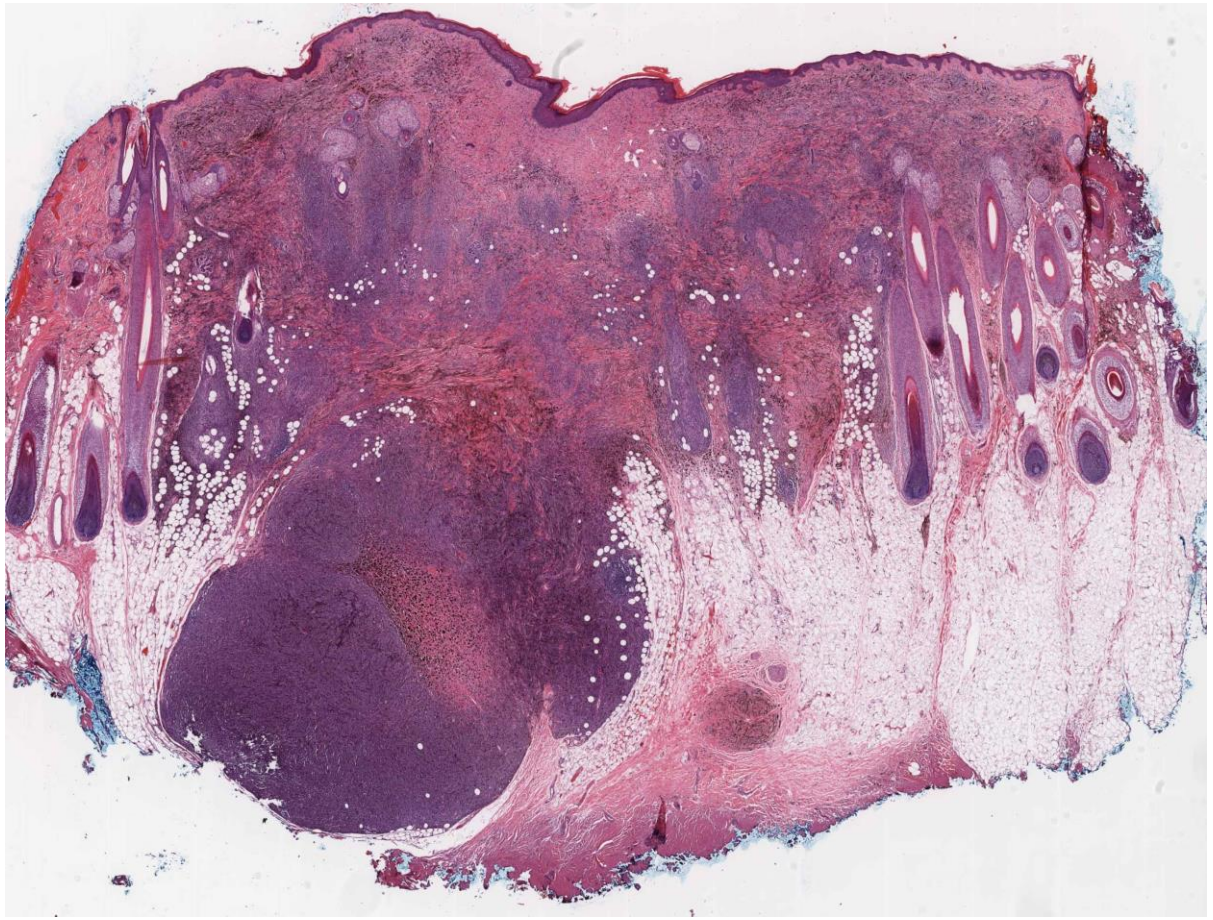
Positive FISH test







Melanoma ex plaque-type blue nevus



Spitz Tumors

- Spitz nevi
- Spitz melanocytoma
- Atypical Spitz tumor with uncertain diagnosis
- Spitz melanoma

Sophie Spitz

"Melanomas of Childhood"; Am J Pathol 1948

1910 - 1956

- 13 children (18 mo - 12 yrs)
- 12/13 had a benign clinical course

JUVENILE MELANOMA -
different from adult melanomas

Sophie Spitz

Sophie Spitz's Melanomas

- Heterogeneous Group of Tumors

Am J Pathol 1948

1910 - 1956

- 13 children (18 mo -12 yrs)

- All benign except for one:
  - 12 yo girl
  - Tumor on foot
  - Deeply located: plantar fascia

Probable correct diagnosis: **Clear cell sarcoma**

Juvenile Melanoma

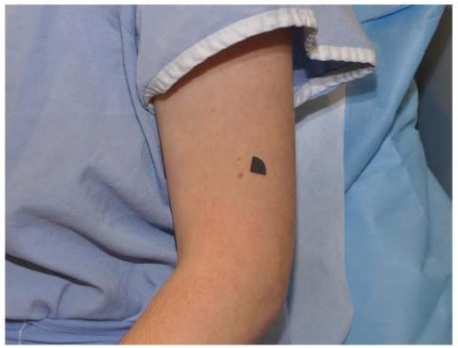
Spitz Nevus

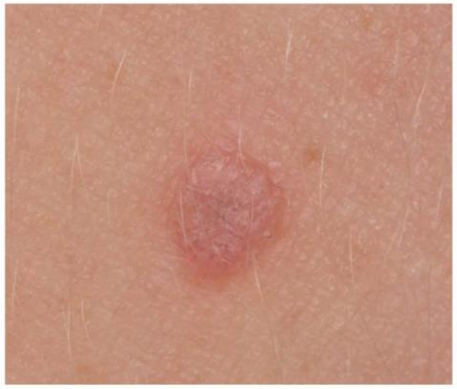
- Kernan JA, Ackerman LV. Spindle cell nevi and epithelioid cell nevi (so-called juvenile melanomas) in children and adults: a clinicopathological study of 27 cases. Cancer. 1960;13:612-25.

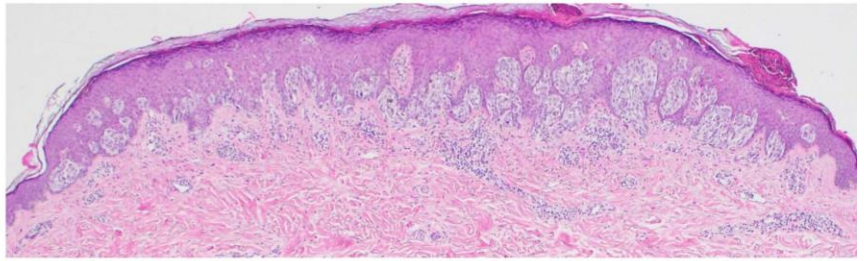
- Weedon D, Little J. Spindle and epithelioid cell nevi in children and adults. A review of 211 cases of Spitz nevi. Cancer 1977; 40: 217-25.

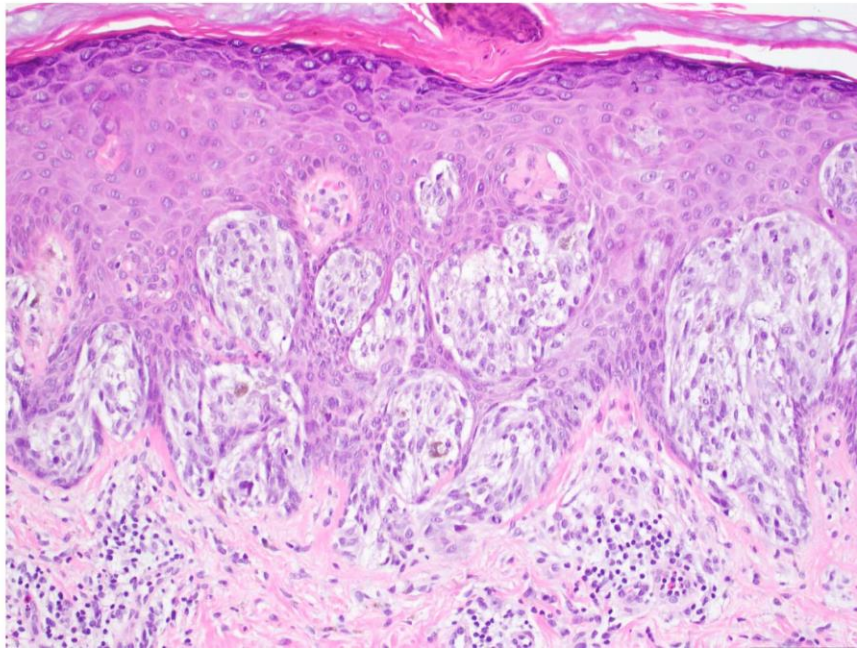
- Paniago-Pereira C, Maize JC, Ackerman AB. Nevus of large spindle and/or epithelioid cells (Spitz's nevus). Arch Dermatol. 1978; 114: 1811-23

Spitz Nevus









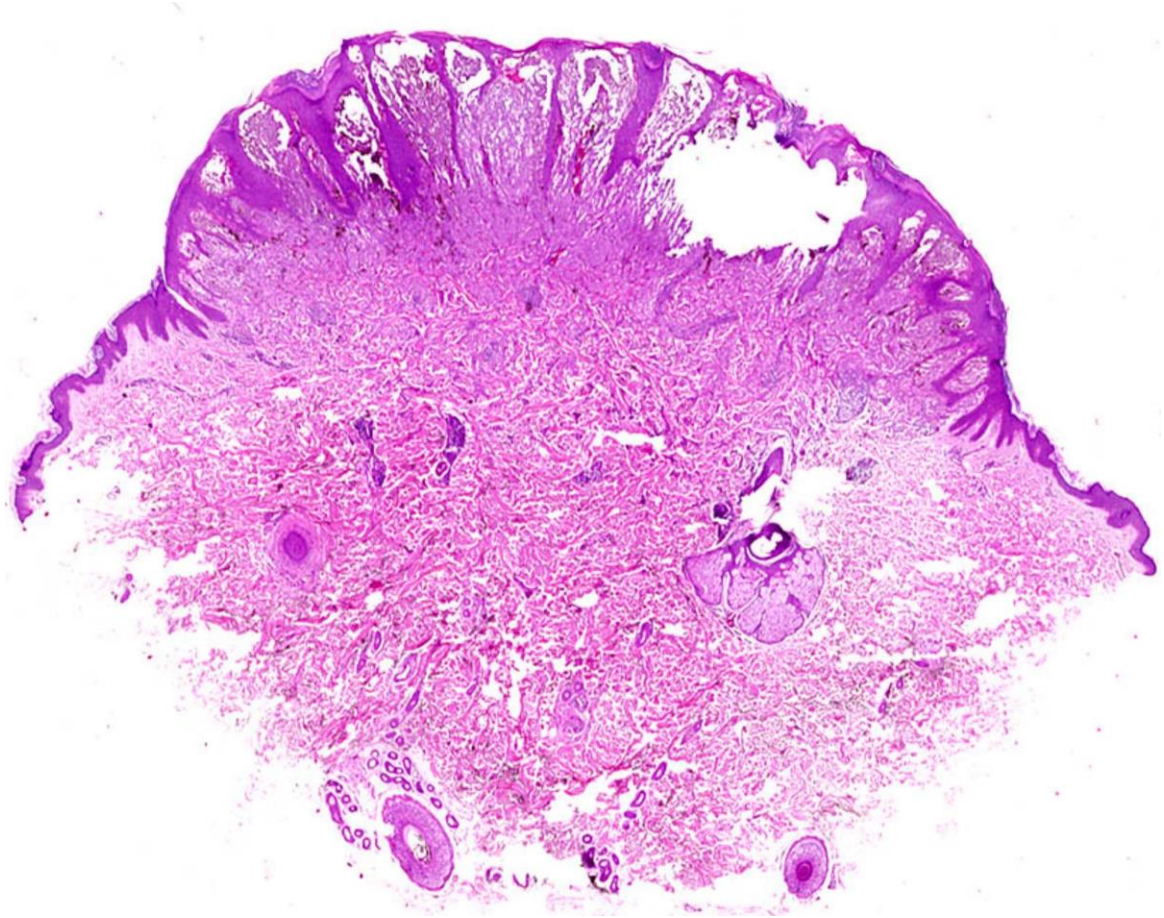
The Spitz Family Grows

Polypoid Spitz naevus
Agminated Spitz naevus
Pagetoid Spitz naevus
Dysplastic Spitz tumour
Desmoplastic Spitz naevus
Angiomatous Spitz naevus
Hyalinized Spitz naevus
Plexiform Spitz naevus
Halo Spitz naevus
Pseudogranulomatous Spitz naevus
Tubular Spitz naevus
Myxoid Spitz naevus
Pigmented spindle cell Spitz naevus
Pigmented epithelioid cell Spitz naevus
Combined Spitz naevus
Recurrent/persistent Spitz naevus

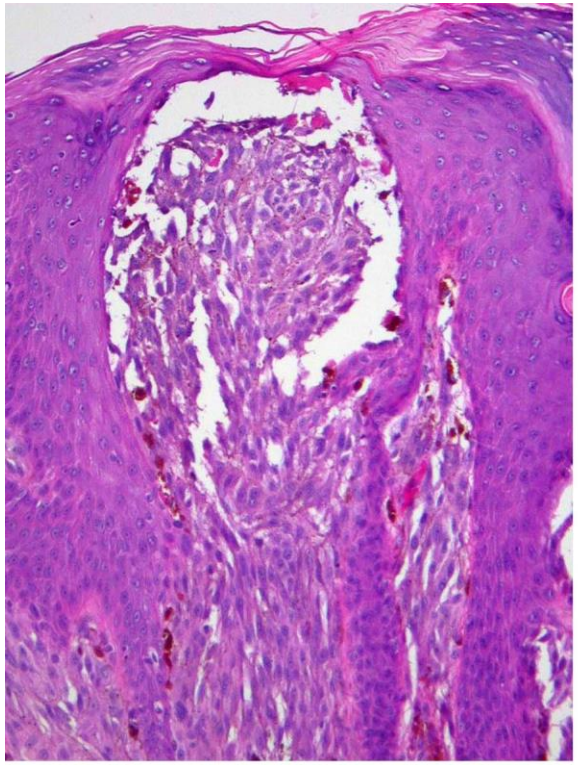
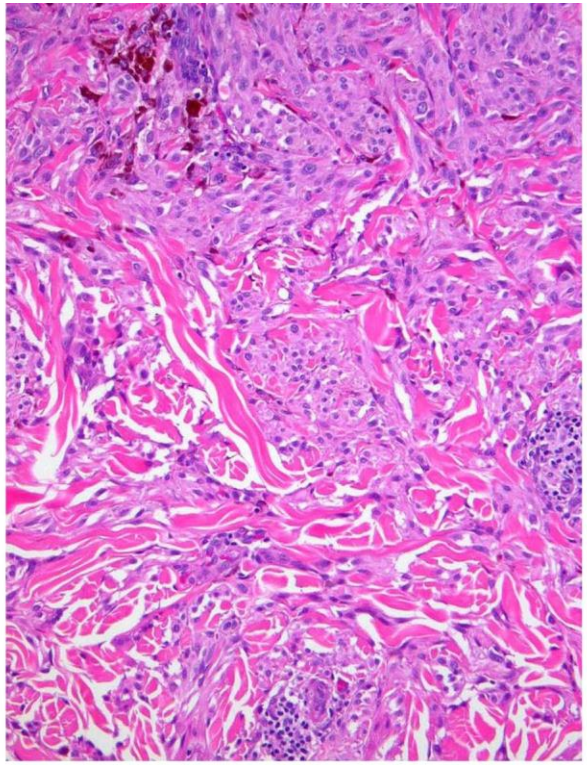
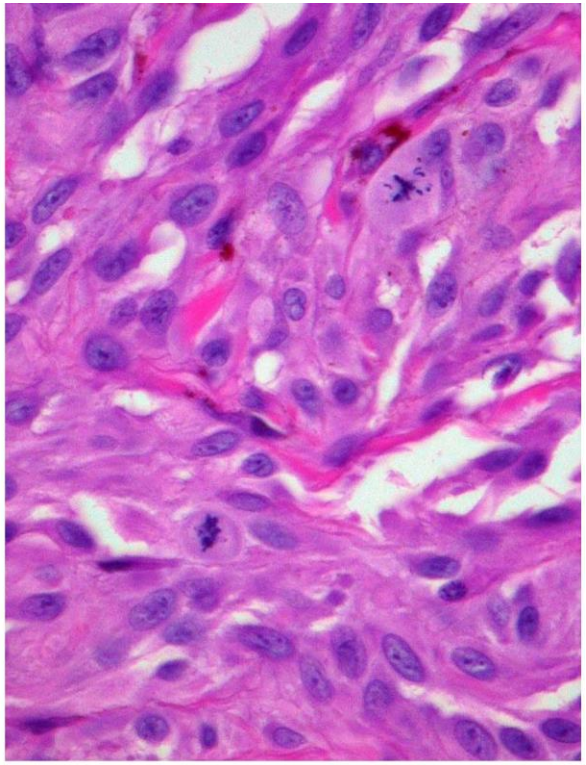
WHO Classification of Skin Tumours. 2018. Chapter 2. Spitz Naevus, p111.

Darth Spitz

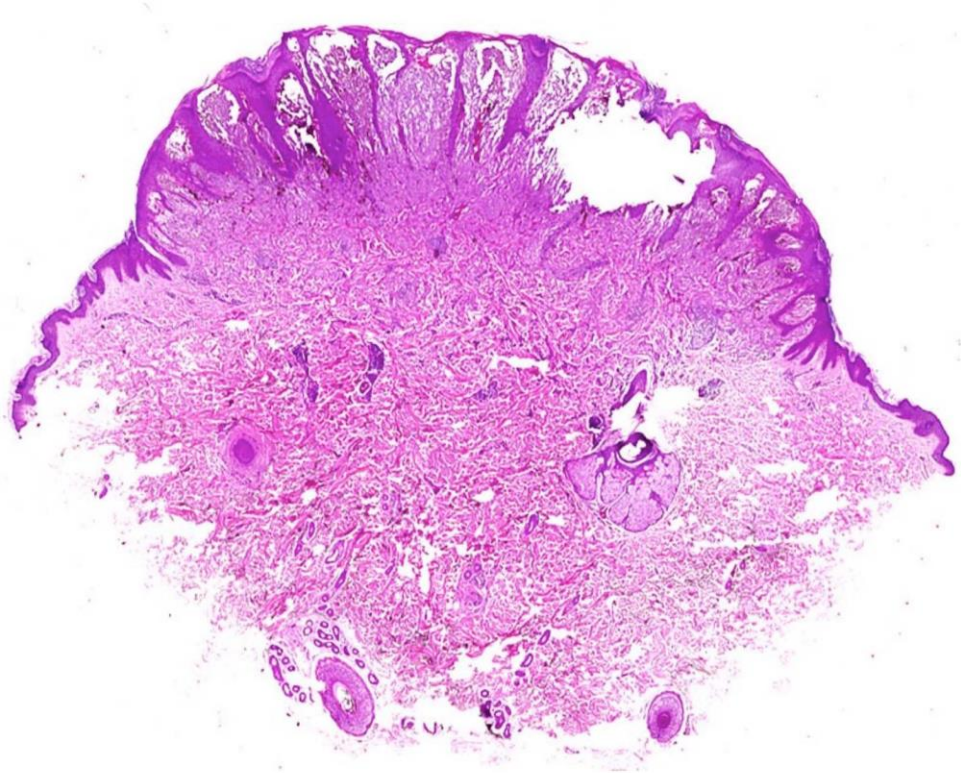
Report as “Spitz Nevus”

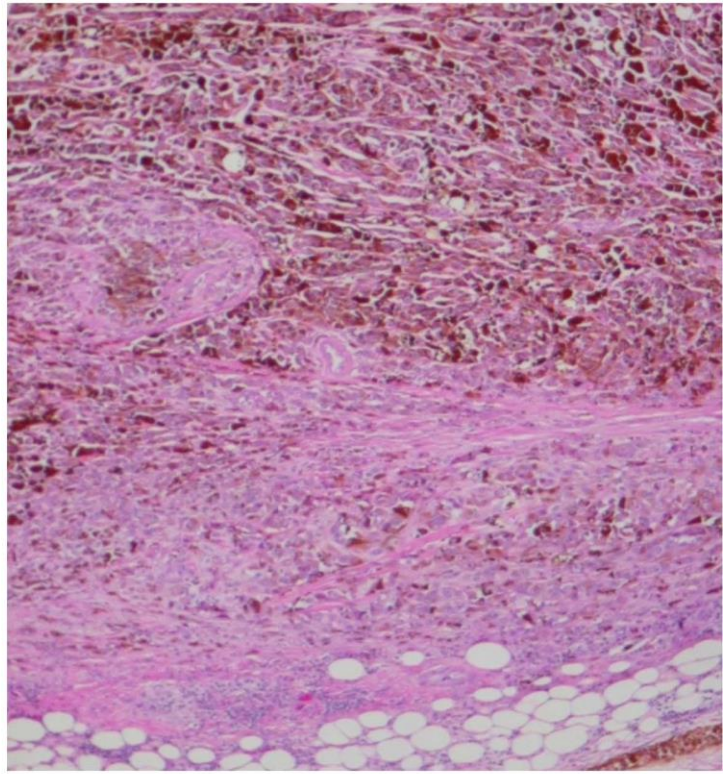


Report as “Spitz Nevus”

Correct diagnosis: Melanoma





6 yrs later: LN Metastasis

The Fog of Spitz

The Fog of Spitz

Atypical Spitz Nevi/Tumors: Lack of Consensus for Diagnosis, Discrimination From Melanoma, and Prediction of Outcome

RAYMOND L. BARNHILL, MD, ZSOLT B. ARGENYI, MD, LYNN FROM, MD, L. FRANK GLASS, MD, JOHN C. MAIZE, MD, MARTIN C. MIHM, JR., MD, MICHAEL S. RABKIN, MD, PHD, SALVE G. RONAN, MD, WAIN L. WHITE, MD, AND MICHAEL PIEPKORN, MD, PHD

Hum Pathol 1999; 30: 513

Modern Pathology (2006) 19, S21–S33

www.modernpathology.org

The Spitzoid lesion: rethinking Spitz tumors, atypical variants, 'Spitzoid melanoma' and risk assessment

Raymond L Barnhill

MALIGNANT SPITZ NEVUS

CDR HENRY G. SKELTON III, MC USN,

LTC KATHLEEN J. SMITH, MC USA, CDR THERESA T. HOLLAND, MC USN,

COL MARIA-MAGDALENA TOMASZEWSKI, MC USA, AND COL GEORGE P. LUPTON, MC USA

The patient is a 22-year-old white woman, who was 16 years of age at the time of initial presentation. At that time, a lesion was removed from her left cheek, which was diagnosed as dermatofibrosarcoma protuberans. Four years later, a physical examination of the patient revealed an enlarged lymph node in the lower midline neck area. The lymph node was biopsied and both lesions were sent for further histopathologic examination.

Histopathology: The original lesion was composed of densely cellular fascicles of plump spindle-shaped cells extending into the subcutaneous fat with a pushing not infiltrating margin (Fig. 1). Examination at higher power showed regular fascicles of plump spindle-shaped cells with prominent nucleoli. Occasional mitotic figures were seen, some present deep within the lesion (Fig. 2). The lymph node biopsy showed similar fascicles of spindled cells within the parenchyma surrounded by normal lymphoid tissue (Figs. 3 and 4). Mitotic figures were not found. Between the fascicles were areas of fibrosis. Both the skin and lymph node biopsies showed positive staining with S-100 protein (Chemicon 1:2000, ABC method).

The patient has had no evidence of recurrence or further spread now 5.5 years after excision of the original lesion.

Figure 1. "Malignant Spitz nevus" of this case showing sharp lateral demarcation and a deep pushing margin extending into the subcutaneous fat. (hematoxylin and eosin, original magnification × 75)

DISCUSSION

Before Dr. Sophie Spitz established criteria for the diagnosis of spindle cell and epithelioid cell nevi (S&E nevi) in 1948, these lesions were considered histologically indistinguishable from malignant melanomas (MM).[1,2] McWhorter and Woolner confirmed the benign clinical behavior of these lesions after reviewing similar lesions reported by Allen and Spitz, which could be used to differentiate S&E nevi from MM, included (1) features of a compound nevus, (2) edema and telangiectasia in the upper portion of the dermis, (3) nests of cells sharply

Atypical Spitz tumors in patients younger than 18 years

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Florence, Turin, Naples, Milan, Genoa, Rome, and Padua, Italy

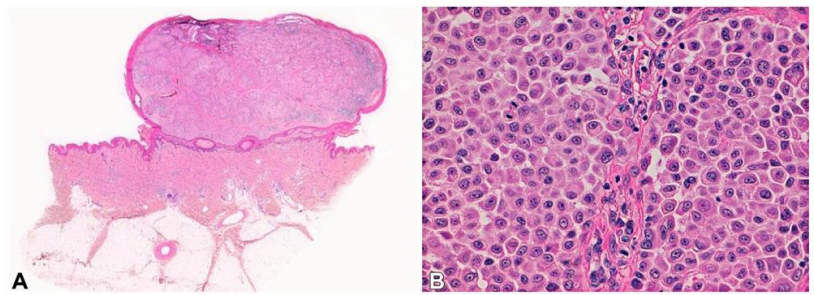

Fig 1. Atypical Spitz tumor in the lower limb of 8-year-old boy. The lesion measures 6 mm in thickness. The child is alive, no further evidence of disease after 127 months follow-up. (**A** and **B**, Hematoxylin and eosin stain; original magnifications: **A**, ×2.5; **B**, ×40.)

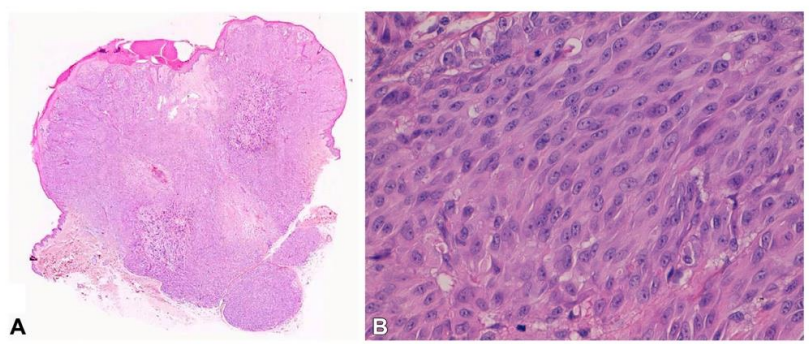

Fig 2. Atypical Spitz tumor in the upper limb of a 3-year-old girl. The lesion is 7.5 mm in thickness. Sentinel lymph node was negative. Patient was alive with no evidence of disease at 16 months follow-up. (**A** and **B**, Hematoxylin and eosin stain; original magnifications: **A**, ×2.5; **B**, ×40.)

Risk Assessment of Spitz Tumors

STUDY

Spitz Tumors in Children

A Grading System for Risk Stratification

Alain Spatz, MD; Eduardo Calonje, MD; Susan Handfield-Jones, MD; Raymond L. Barnhill, MD

Objective: To describe a grading system for risk stratification of atypical Spitz tumors in children and adolescents. In some circumstances, unequivocal distinction between Spitz nevus and melanoma is practically impossible. It is likely that these lesions for which we lack specific diagnostic criteria represent a broad histological continuum extending from benign to malignant tumors. Therefore, we propose that Spitz tumors be categorized into low-, intermediate-, or high-risk categories based on the accumulation of abnormal features.

Design: Retrospective study.

Settings: Institutional practice.

Patients: We present 30 cases of atypical Spitz tumors in patients younger than 18 years evaluated for at least 3 years or in whom a metastatic event developed during this period.

Intervention: None.

Main Outcome Measure: The grading system was formulated after data collection.

Results: Among the parameters studied, only diagnosis at age greater than 10 years, diameter of the lesion greater than 10 mm, presence of ulceration, involvement of the subcutaneous fat (level V), and mitotic activity of at least 6/mm² carried a likelihood ratio greater than 1.50 and were therefore used for the grading system.

Conclusion: The application of an objective grading system, such as the one described herein for the first time, is the first step in providing useful information for the management of atypical Spitz tumors.

Arch Dermatol. 1999;135:282-285

	Score 0	Score 1	Score 2
Age	0-10	11-17	
Diameter	0 to 10mm	>10mm	
Fat Involvment	Absent		Present
Ulceration	Absent		Present
Mitotic activity/mm2	0 to 5	6 to 8	>8
	Low Risk	**Intermediate**	**High Risk**
Total Score	0 to 2	3 to 4	5 to 11

	Metastasis	No Metastasis	Total	% Metastasis
Low	1	14	15	7%
Intermediate	3	3	6	50%
High	7	2	9	78%
Total	11	19	30	37%

FOR DISCUSSION

Sentinel lymph node biopsy as an adjunct to management of histologically difficult to diagnose melanocytic lesions: A proposal

Scott W. Kelley, MD, and Clay J. Cockerell, MD *Dallas, Texas*

J Am Acad Dermatol 2000;42:527-30

Surgery to the Rescue

Pediatric Melanoma: Confirming the Diagnosis With Sentinel Node Biopsy

Randall Zuckerman, MD
Joel P. Maier, MD
William B. Guiney, Jr, MD
W. Thomas Huntsman, MD
Eric K. Mooney, MD

Many pediatric melanoma lesions present at a more advanced stage than those in the adult population. Clinical and histological melanoma mimics, including a subset of Spitz nevi, are difficult to discriminate from melanoma. When dealing with a childhood melanoma, the clinician is likely to be faced with a thick lesion, and one in which the actual diagnosis may even be in doubt. There is a paucity of data to guide the physician in his management of melanoma in this age group, particularly with respect to node status and adjuvant therapy. The authors present two cases of pediatric melanoma in which the novel use of sentinel node biopsy helped confirm the diagnosis of melanoma, determined the need for full lymph node dissection, and guided the use of adjuvant interferon therapy.

Zuckerman R, Maier JP, Guiney WB Jr, et al. Pediatric melanoma: confirming the diagnosis with sentinel node biopsy. Ann Plast Surg 2001; 46:394–399

mimic melanoma histologically, particularly the Spitz nevus. Lastly, there is a paucity of data to guide the surgeon in this age group, particularly with respect to node status and adjuvant therapy. No prospective trials exist and even retrospective studies are rare.[4] In a sense, these factors constitute a "triple threat" of pediatric melanoma:

1. Delayed presentation with thicker lesions
2. Histological ambivalence
3. "Terra incognita" with respect to clinical trials of adjuvant therapy and of node management, particularly in the thick lesions of the childhood age group

Human Pathology (2013) **44**, 87–94

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Human PATHOLOGY

www.elsevier.com/locate/humpath

Original contribution

Sentinel lymph node metastasis is not predictive of poor outcome in patients with problematic spitzoid melanocytic tumors☆

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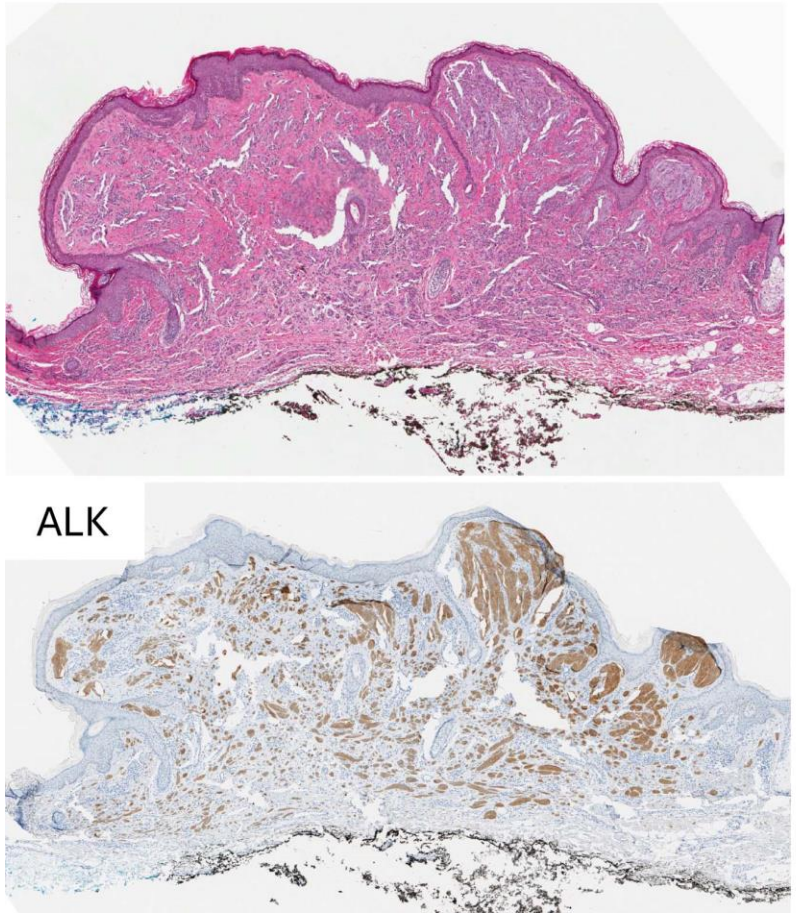
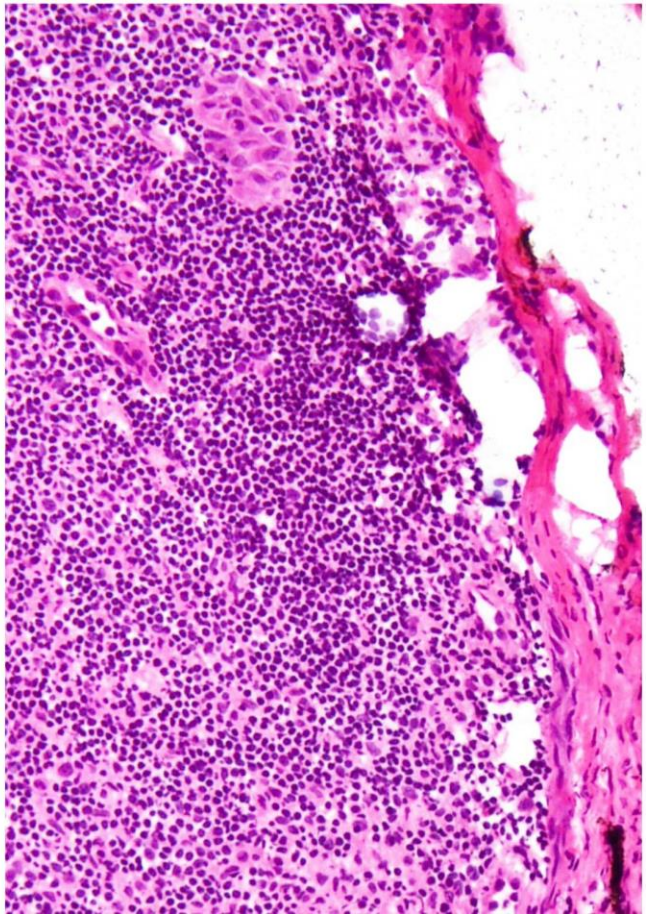
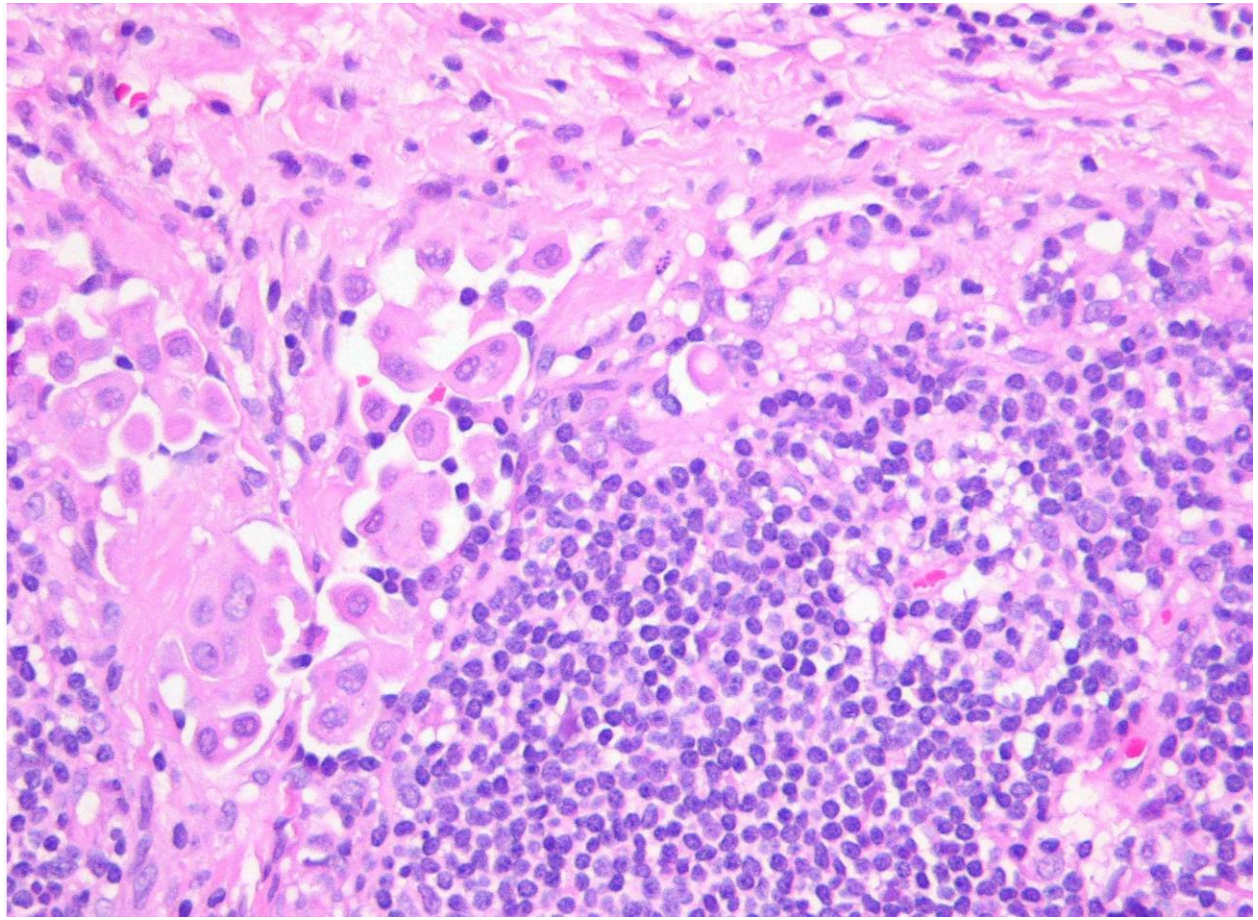
Spitz Nevus with SLN Deposit

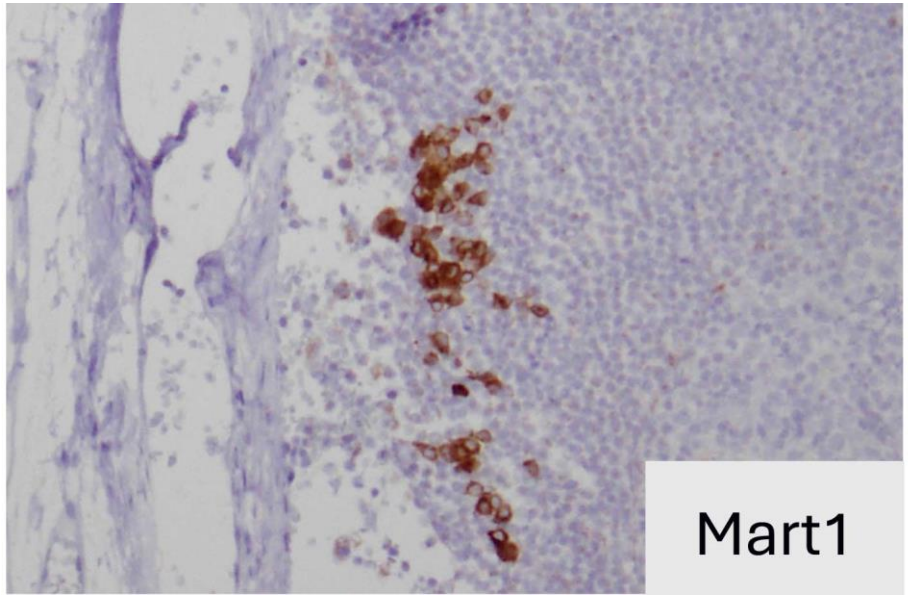


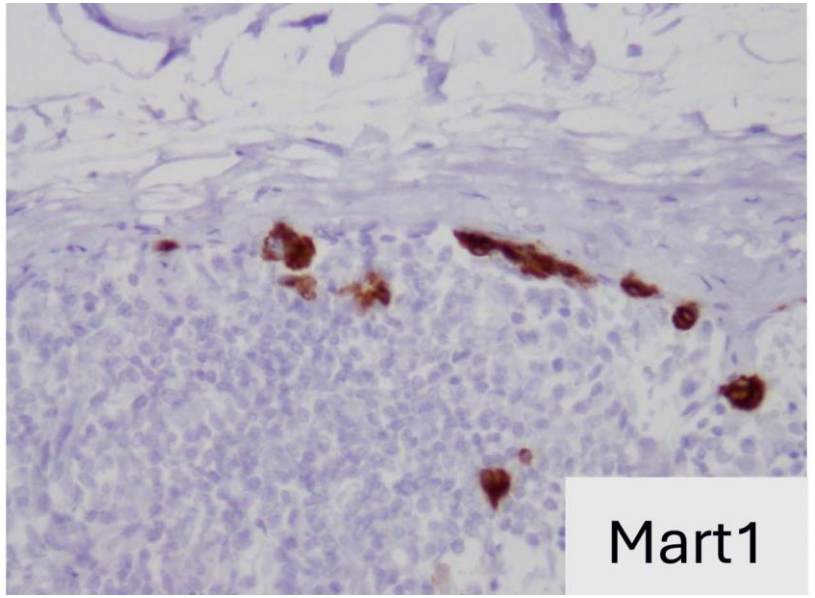


Benign Mesothelial Cells in LN



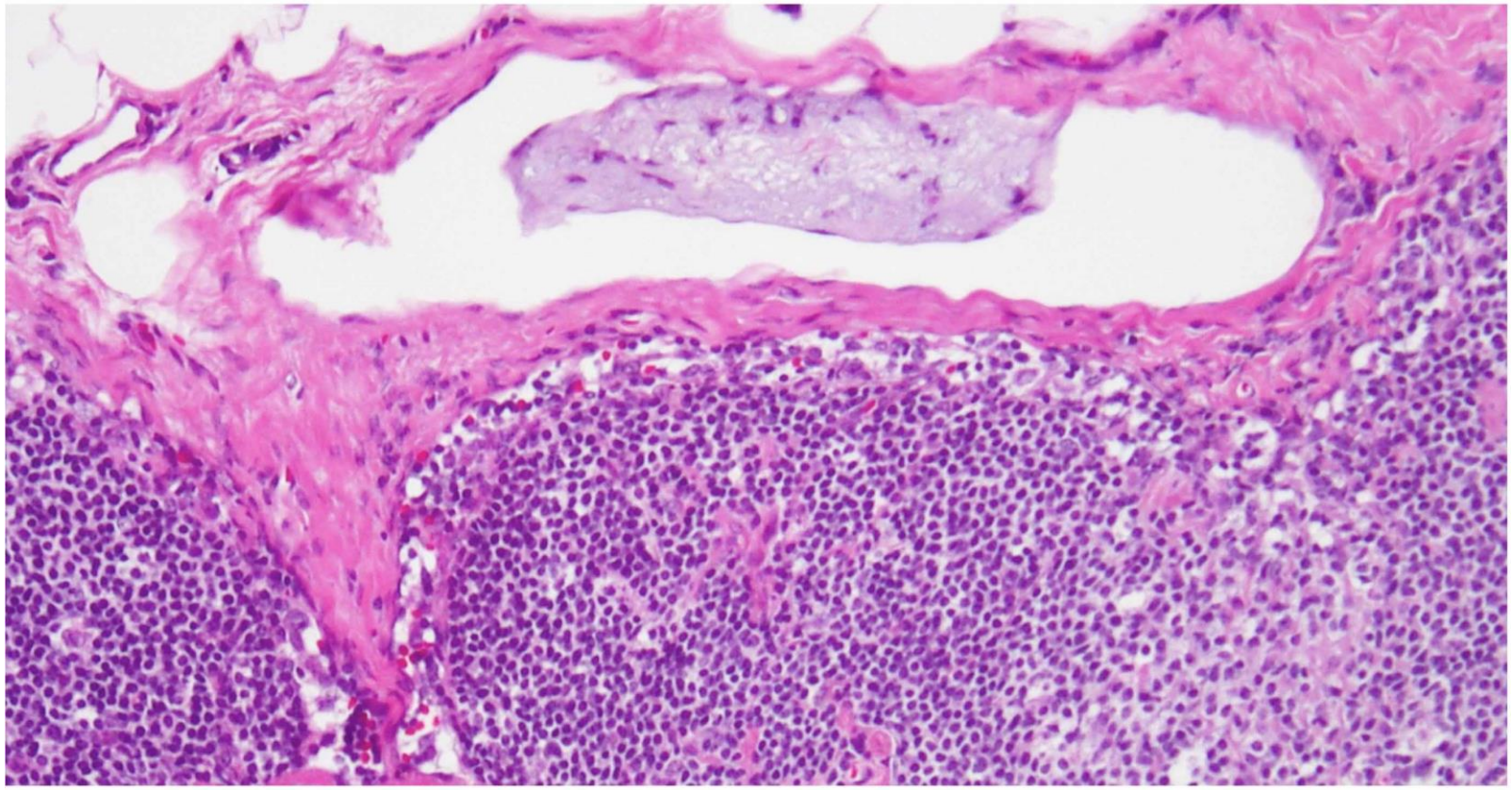
Intranodal Nevus Cells in Lymph node





Incidental finding in an axillary SLN of a patient with breast cancer

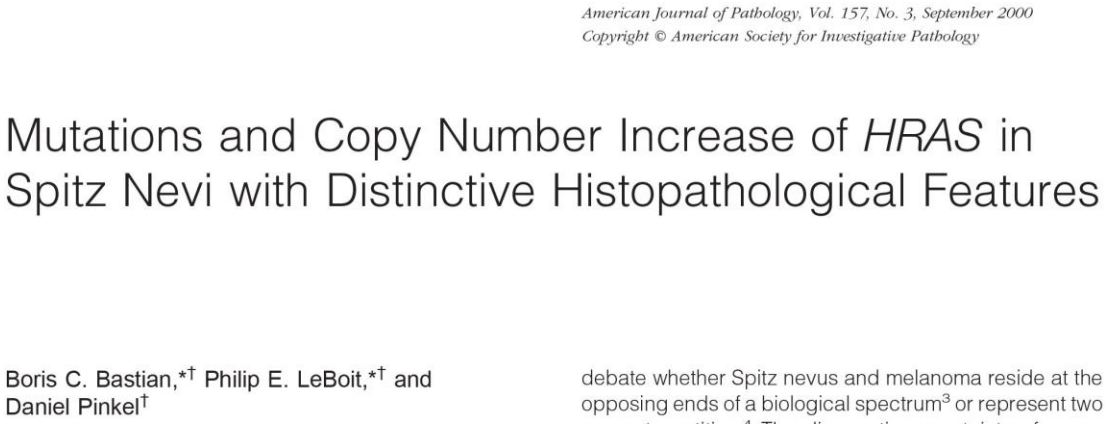
Dermal Stroma in LN



Am J Surg Pathol 2010; 34:1492-7

The Brave New Spitz

The Molecularization of Spitz



American Journal of Pathology, Vol. 157, No. 3, September 2000

Mutations and Copy Number Increase of *HRAS* in Spitz Nevi with Distinctive Histopathological Features

Boris C. Bastian,*† Philip E. LeBoit,*† and Daniel Pinkel†

debate whether Spitz nevus and melanoma reside at the opposing ends of a biological spectrum[3] or represent two

nature COMMUNICATIONS

ARTICLE

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Kinase fusions are frequent in Spitz tumours and spitzoid melanomas

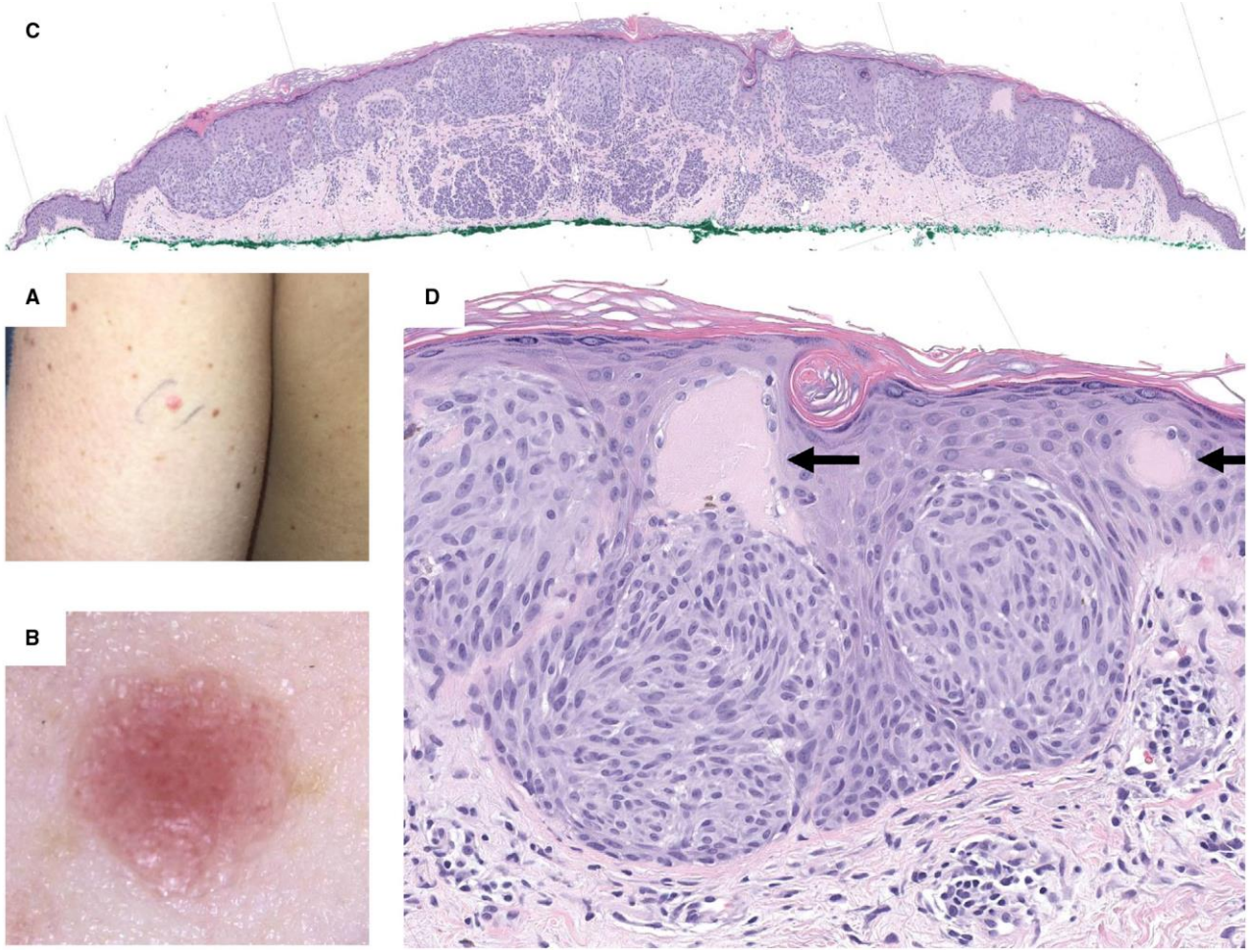
Thomas Wiesner[1,2,*], Jie He[3,*], Roman Yelensky[3,*], Rosaura Esteve-Puig[4], Thomas Botton[4], Iwei Yeh[4], Doron Lipson[3], Geoff Otto[3], Kristina Brennan[3], Rajmohan Murali[5,6], Maria Garrido[4], Vincent A. Miller[3], Jeffrey S. Ross[3], Michael F. Berger[1], Alyssa Sparatta[4], Gabriele Palmedo[7], Lorenzo Cerroni[2], Klaus J. Busam[5], Heinz Kutzner[7], Maureen T. Cronin[3], Philip J. Stephens[3] & Boris C. Bastian[1,4,5]

Molecular Pathology and Spitz

- Definition of “Spitz” by molecular pathway
  - HRAS aberrations
  - Kinase fusions (Ros1, Alk, Ntrk, Ret, Met, MAP3K8, Braf, other)

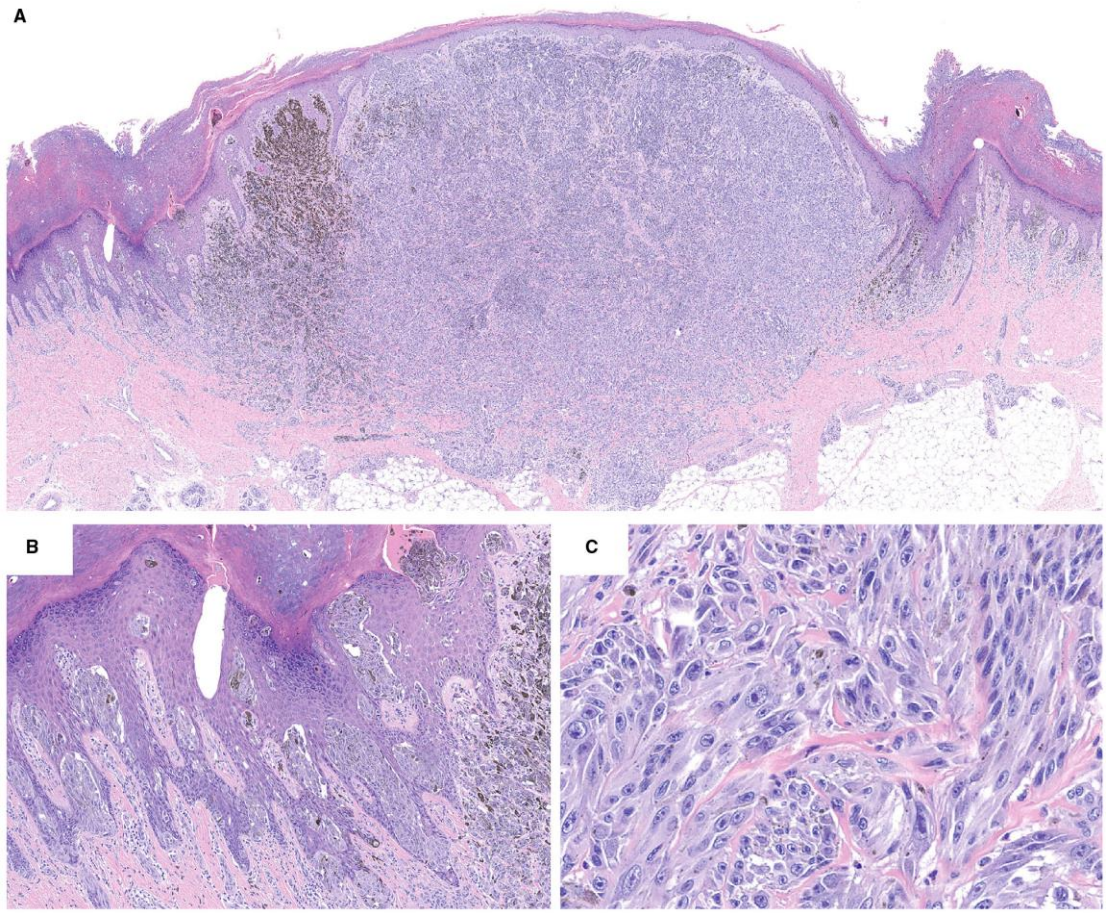
- Molecular findings subclassify Spitz
  - Spitz nevus
  - Spitz melanocytoma
  - Spitz melanoma
  - Atypical Spitz tumor of uncertain biologic potential

Spitz Nevus



- Benign clinical findings
- Benign histopathology
- Single genomic aberration typical of Spitz

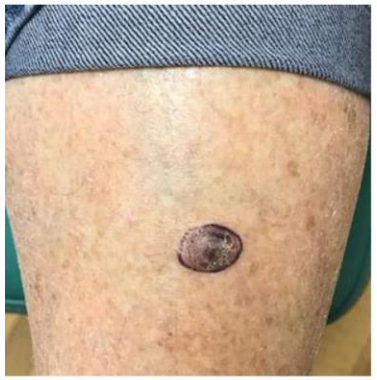
Spitz Melanoma

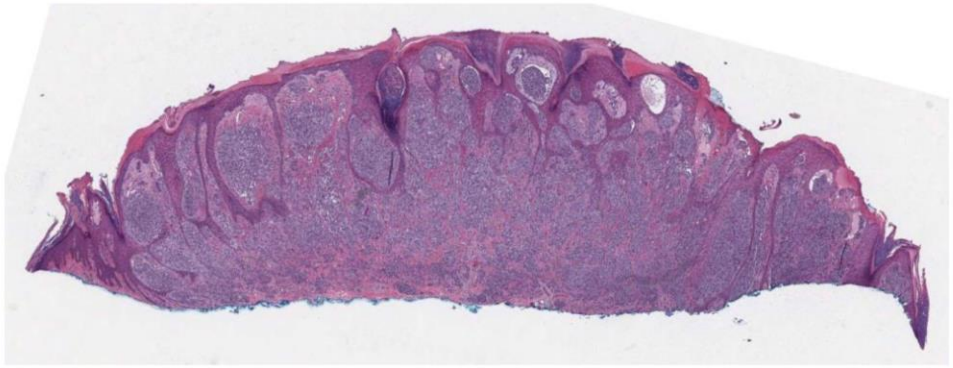


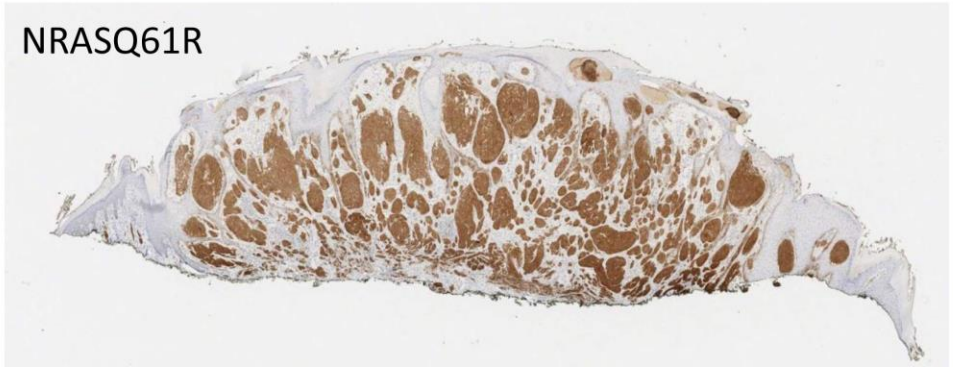
- Atypical/malignant pathology
- Spitz pathway aberration and addtl genetic aberrations typical of melanoma
- Example:MAP3K8-SPECC1 fusion plus numerous segmental gains and/or losses

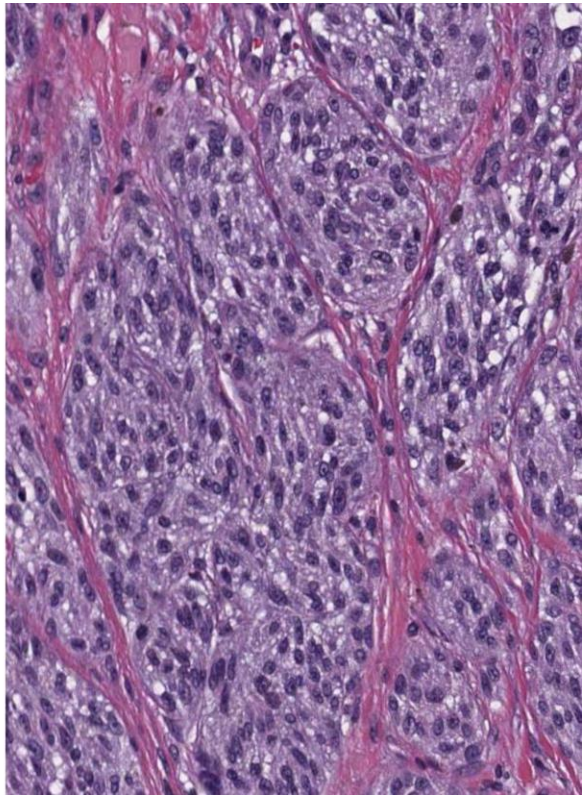
Spitzoid Melanoma

- Melanoma with Spitz-like features
- Non-Spitz pathway (BRAF, NRAS, other)

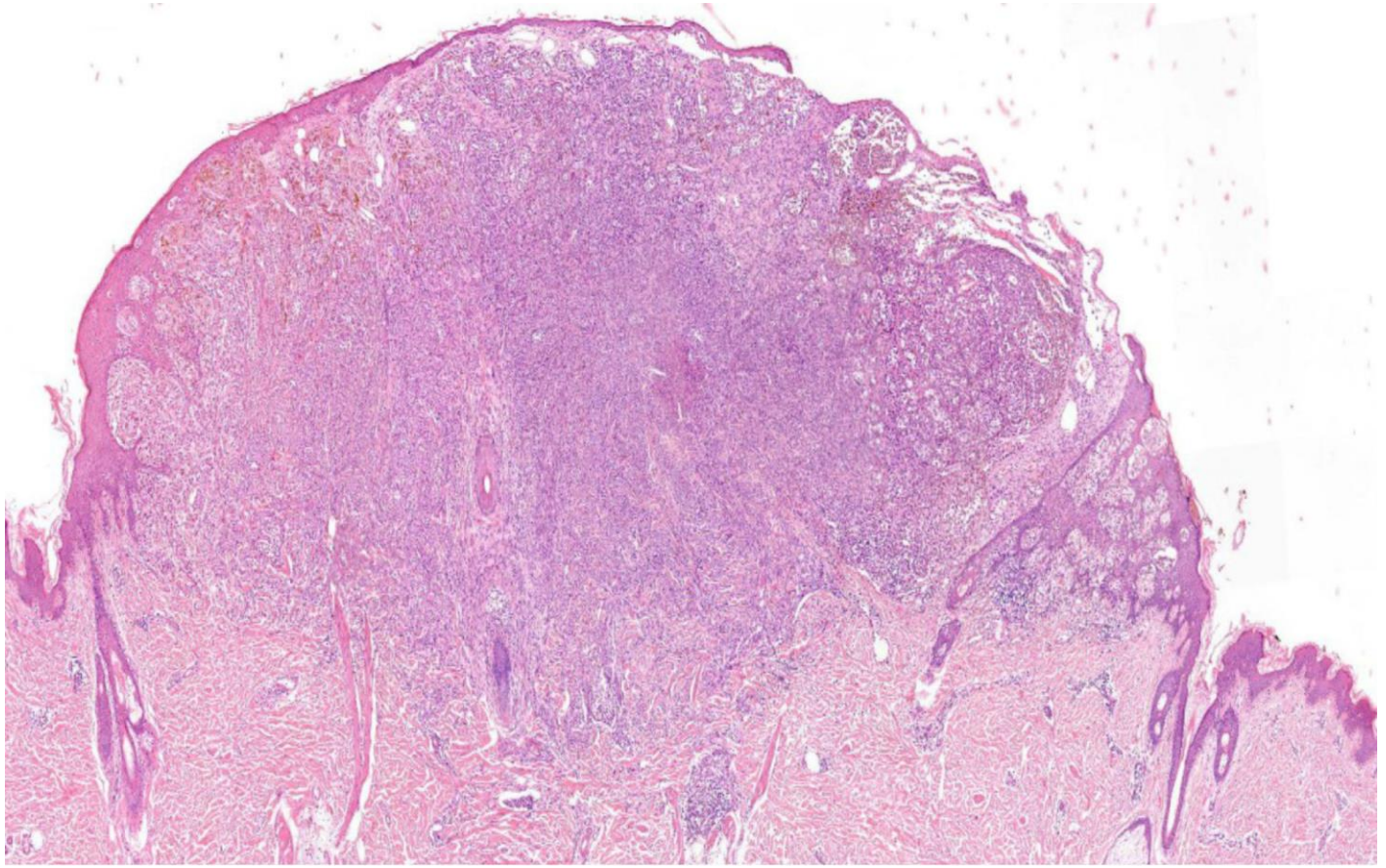


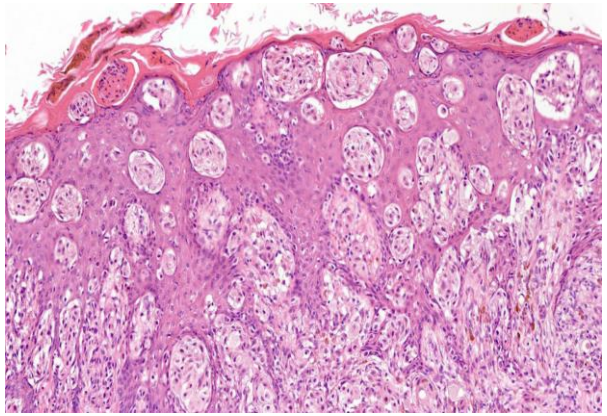


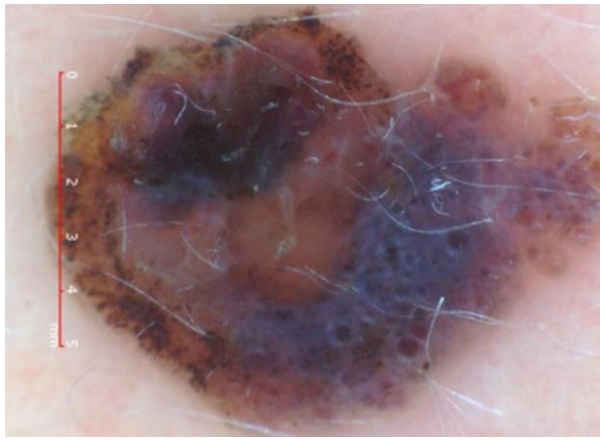




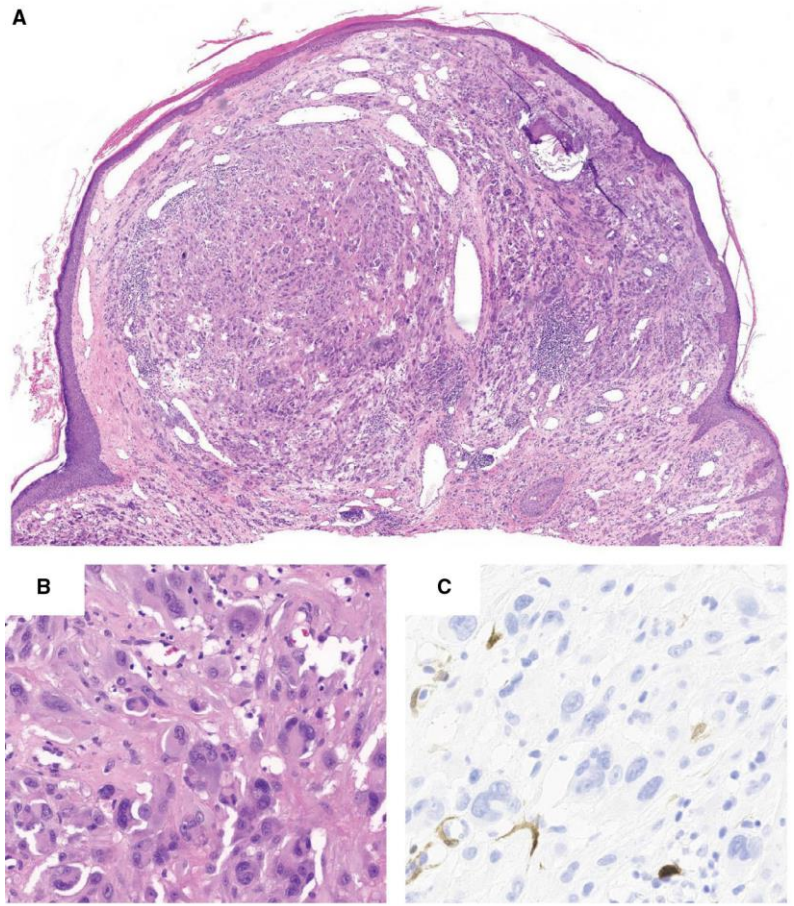
Melanoma (referred as AST)







Spitzoid Melanocytoma



- Atypical histopathology
- Spitz pathway aberration plus select addtl genomic aberration(s) that are not sufficient for melanoma
- Example: MAP3K8-SVIL fusion plus homozygous deletions of p16

Terminology

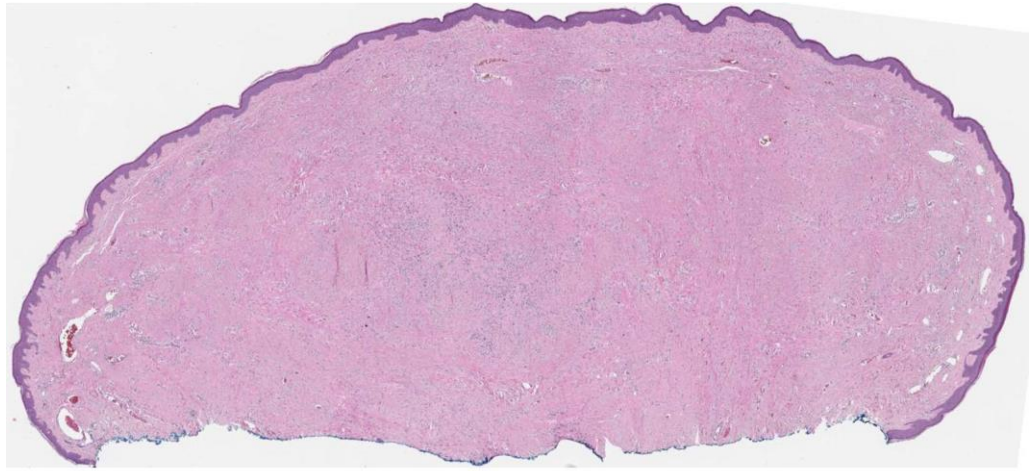
- Atypical Spitz tumor
  - Spitz neoplasm with uncertainty as to whether it is benign or malignant
- Spitz Melanocytoma
  - Benign Spitz neoplasm with genetic/genomic aberrations

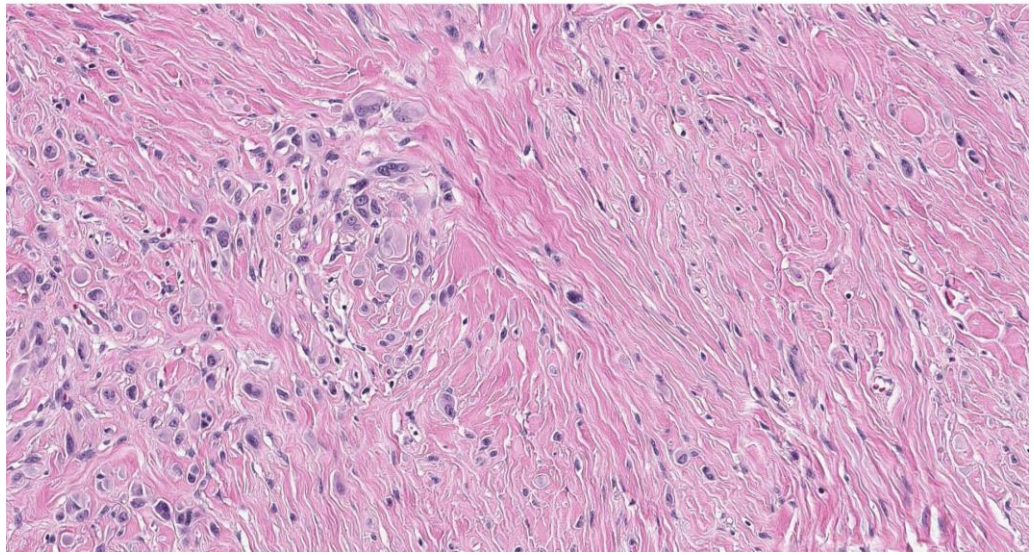
The Spectrum of Spitz

Benign Spitz

Malignant Spitz

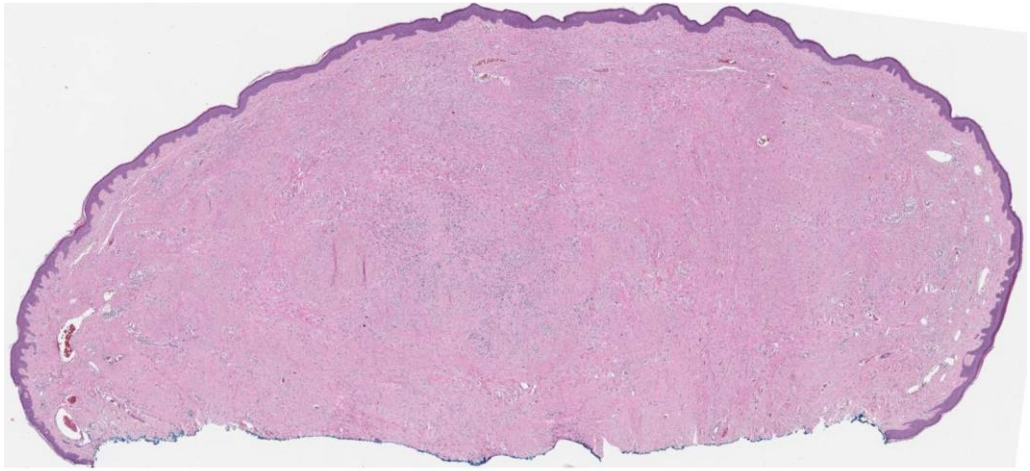
Desmoplastic Melanoma or Not?

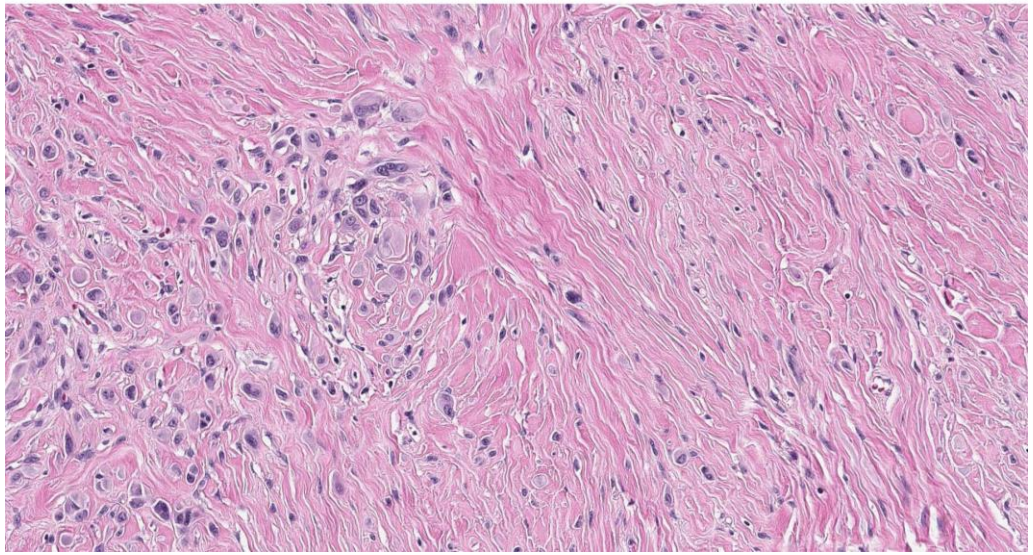




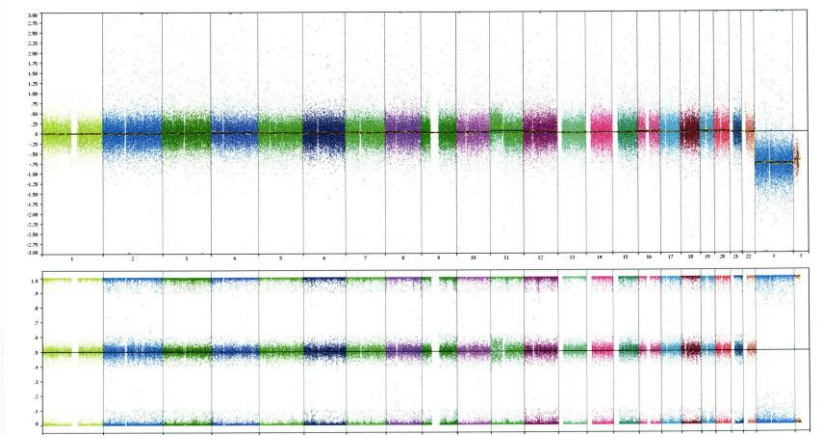
- 41 M with nodule on back
- Referred with a diagnosis of desmoplastic melanoma

Desmoplastic Spitz Nevus

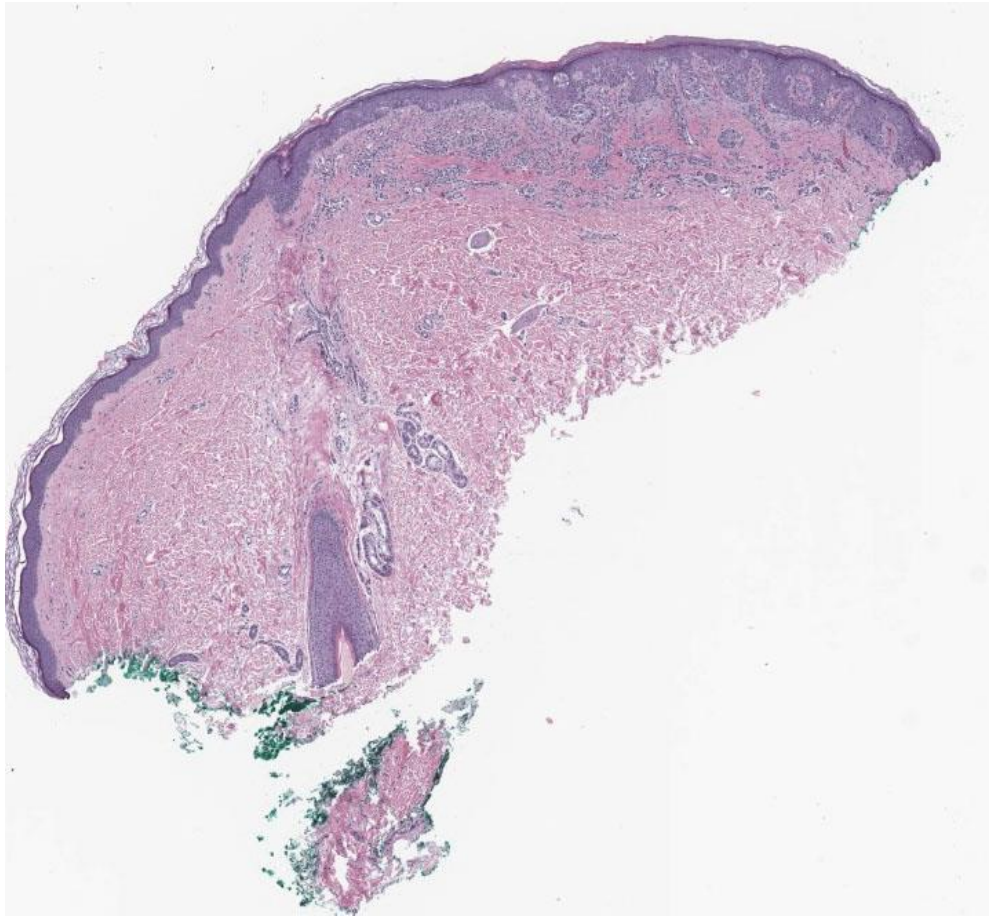


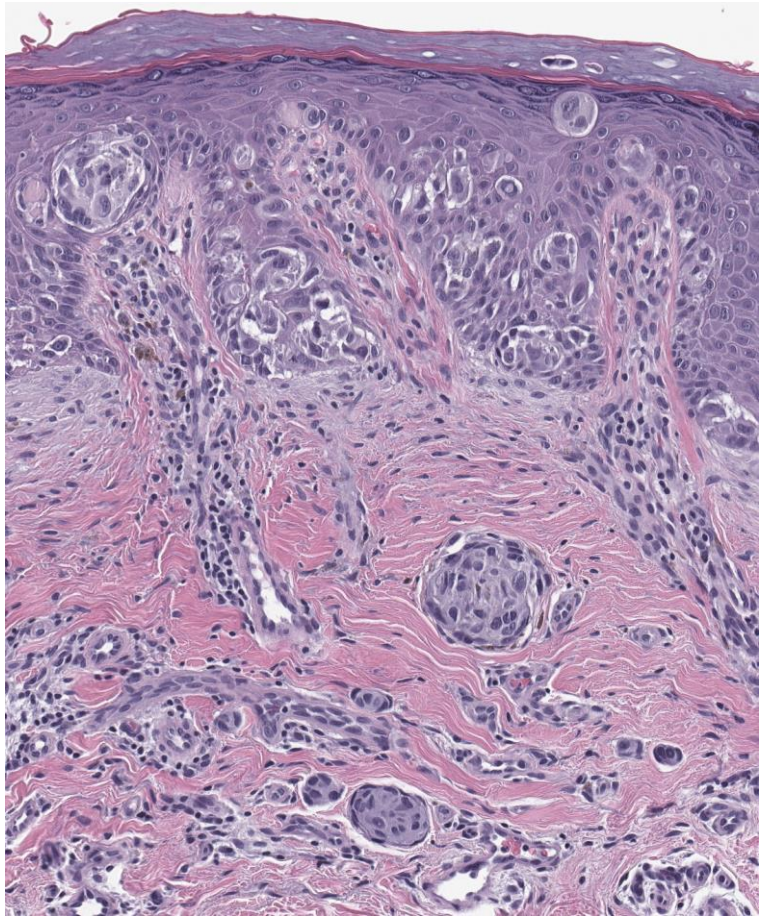


Cytogenetics: Isolated gain of 11p

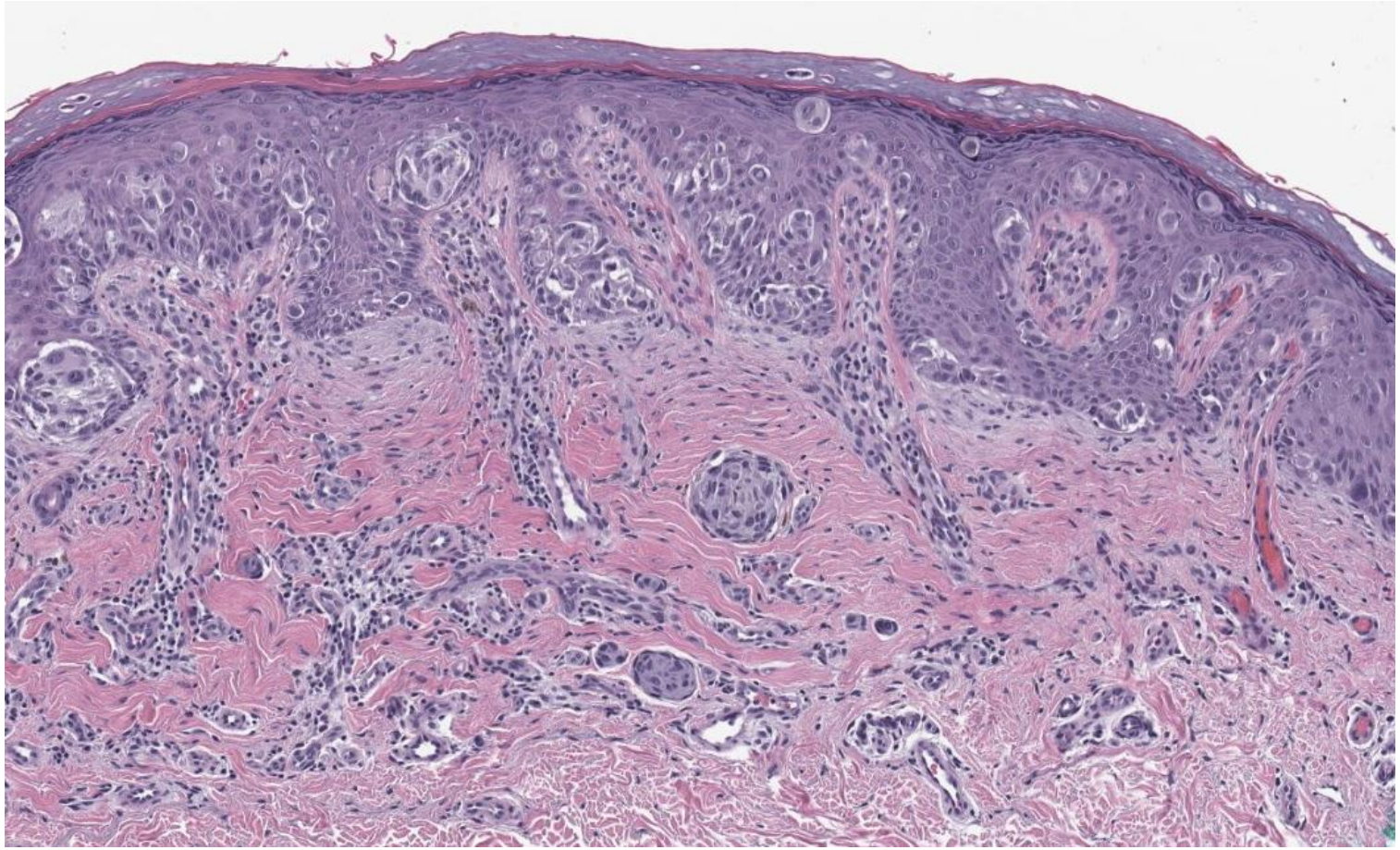


What is Your Diagnosis?



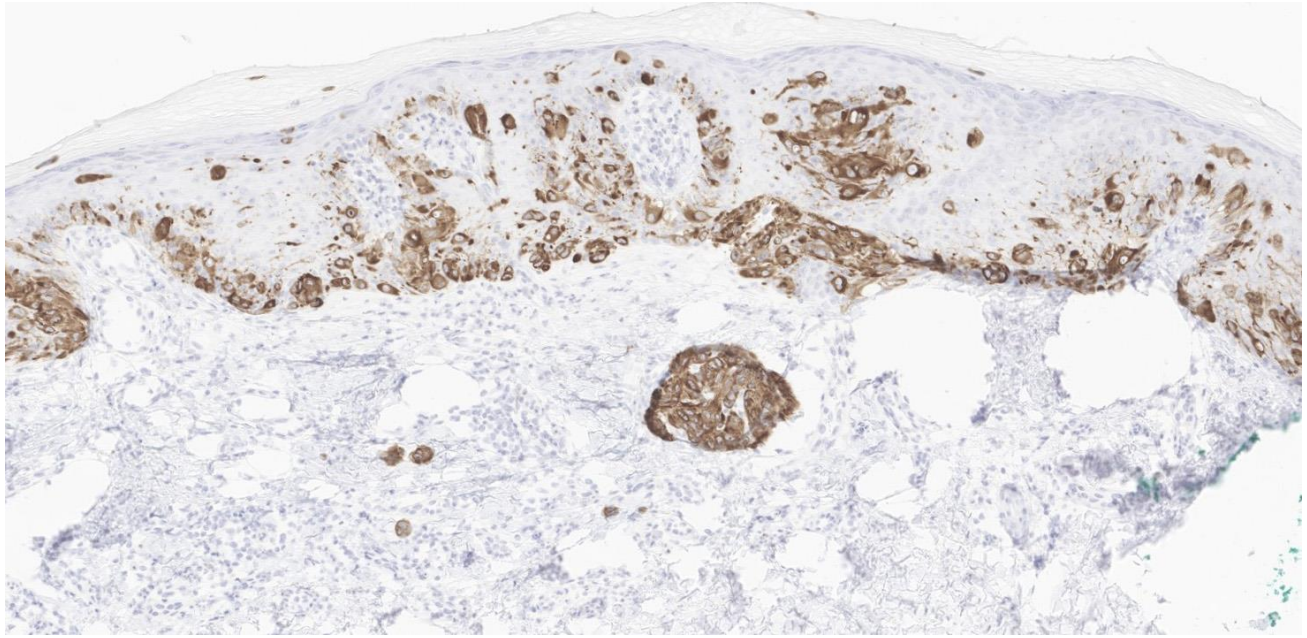


Prelim: “Atypical” Compound Spitzoid Proliferation

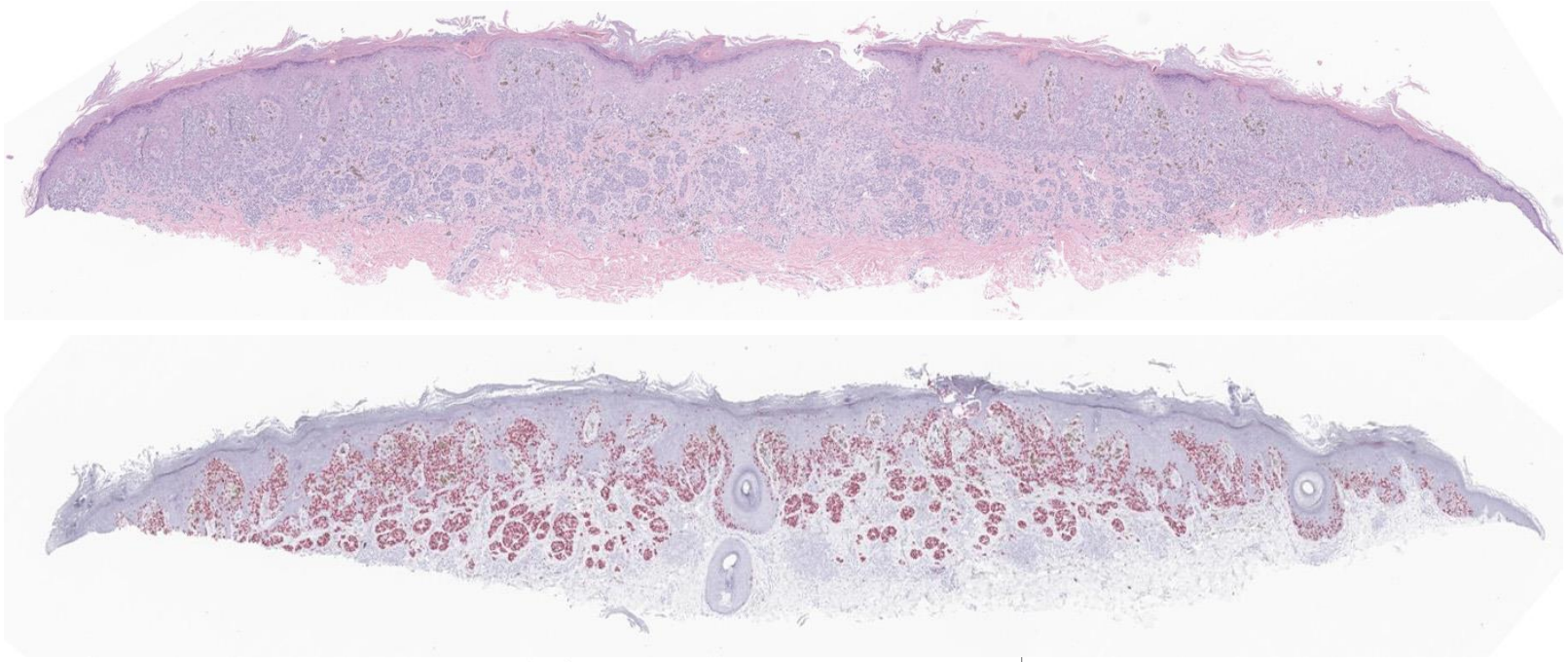


Ancillary Test Results = Spitz Nevus

- Negative for BRAFV600E
- Positive for NTRK



Nevus or Melanoma?

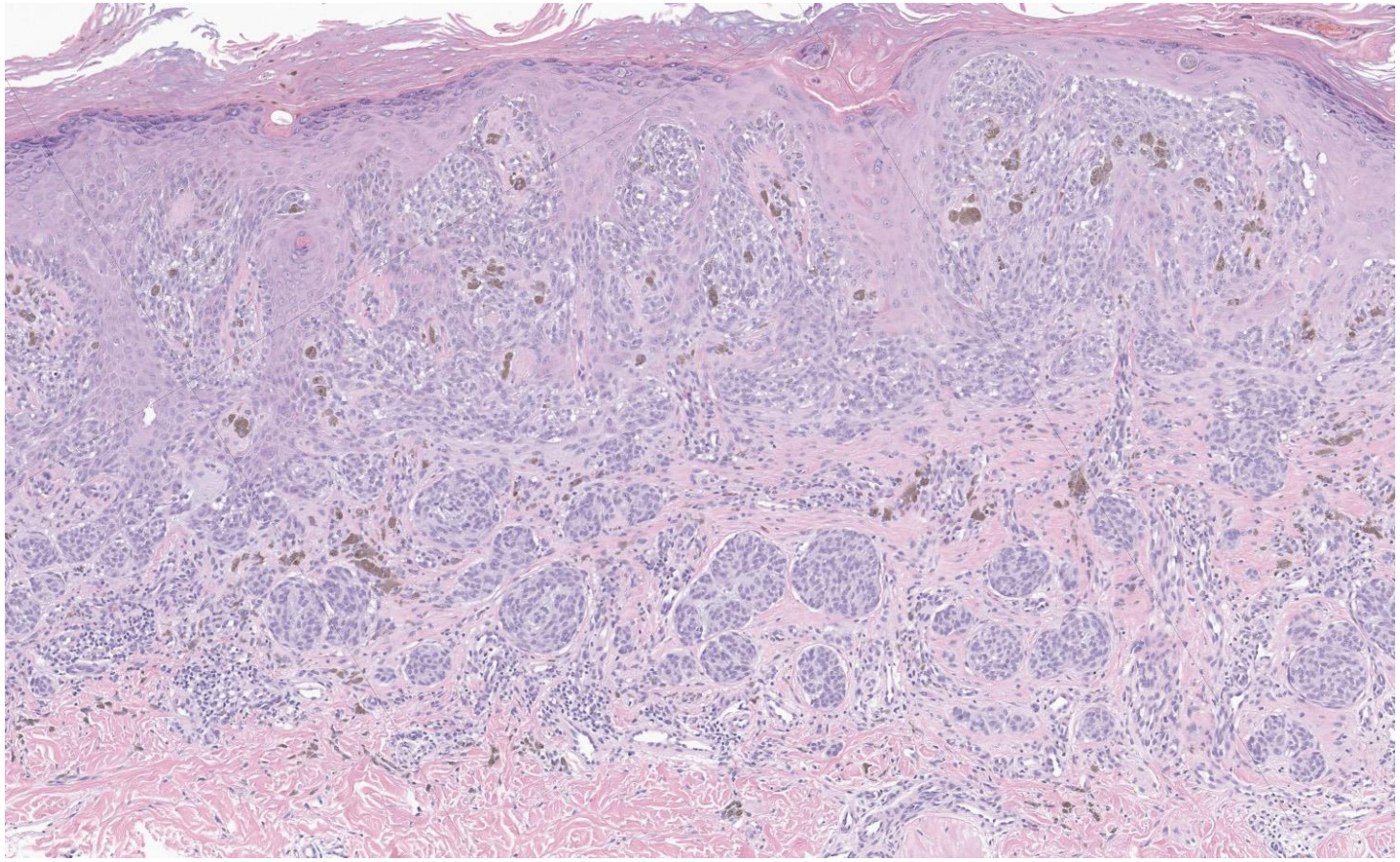


DDX:Neoplasm of Uncertain Behavior vs. Dysplastic Nevus

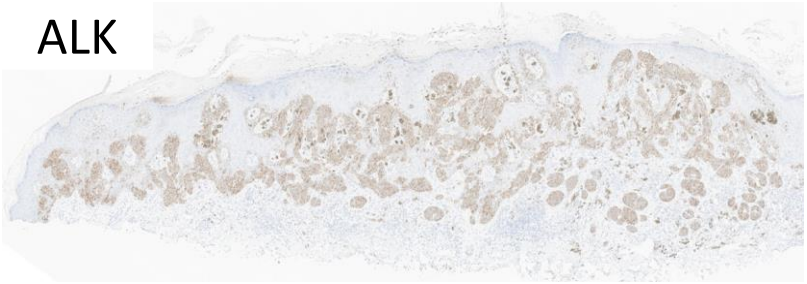
DIAGNOSIS:

Left Anterior Distal Thigh (Shave Biopsy):
MALIGNANT MELANOMA.
GROWTH TYPE: NODULAR
BRESLOW'S ***THICKNESS: ≥ 1.2 MM.***
MITOSIS PER 1MM: 0/MM2.
LYMPHOID INFILTRATE: NON-BRISK INFLAMMATION
ULCERATION: FOCAL
REGRESSION: NOT IDENTIFIED
MARGINS: THE LESION EXTENDS TO THE BASE AND A PERIPHERAL MARGIN.
PATHOLOGIC STAGE: PT2B

Diagnosis: Spitz Nevus



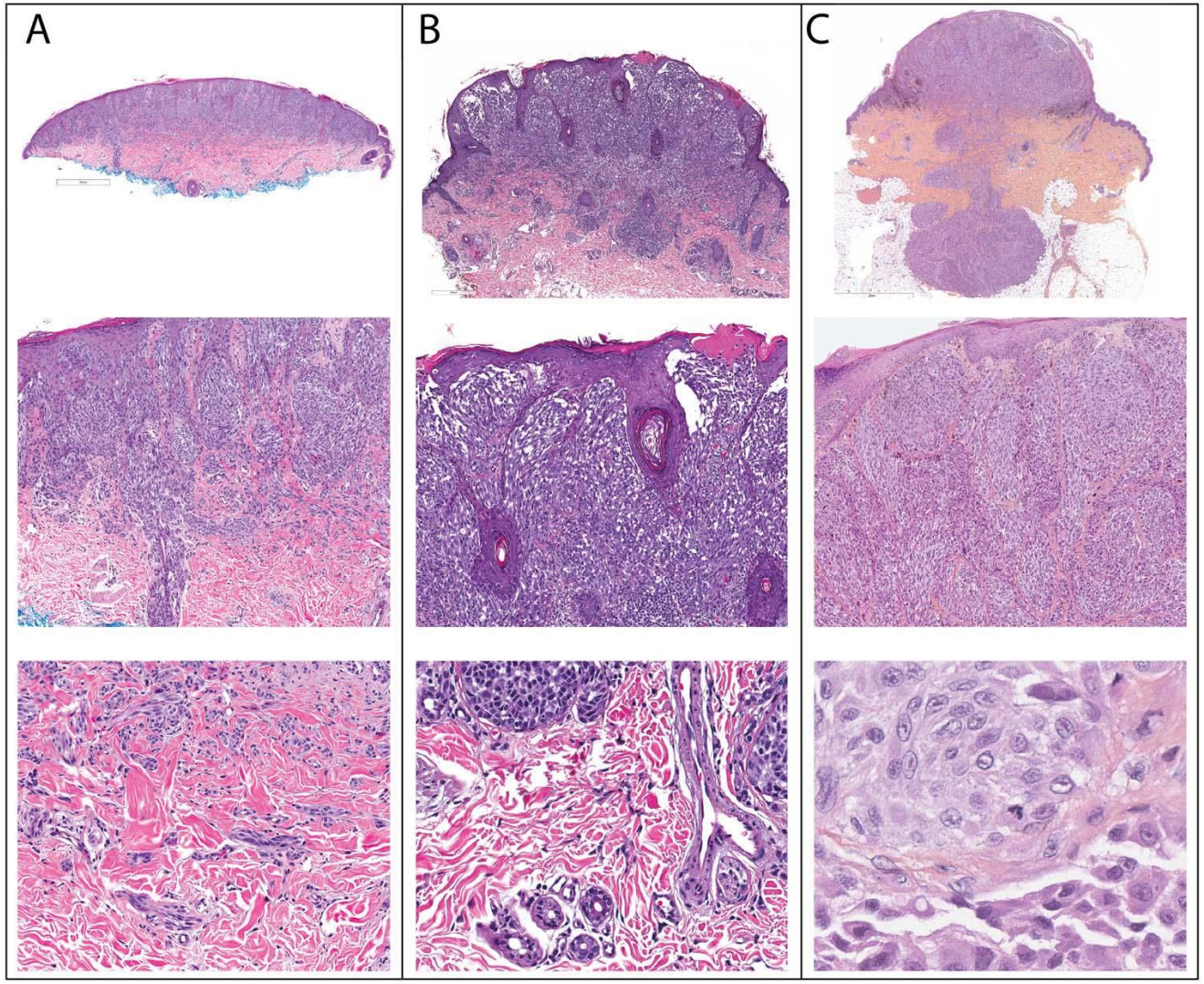
ALK



Sequence analysis: DCTN1-ALK FUSION

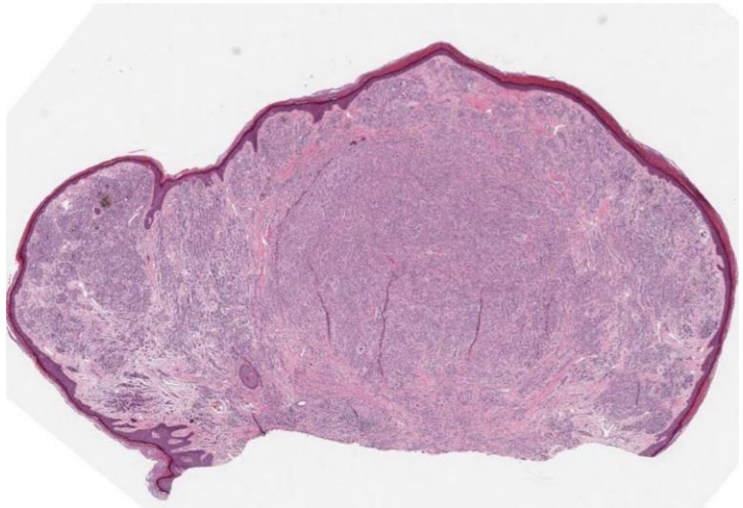
SNP ARRAY:
NO UNBALANCED GENOMIC ABERRATIONS

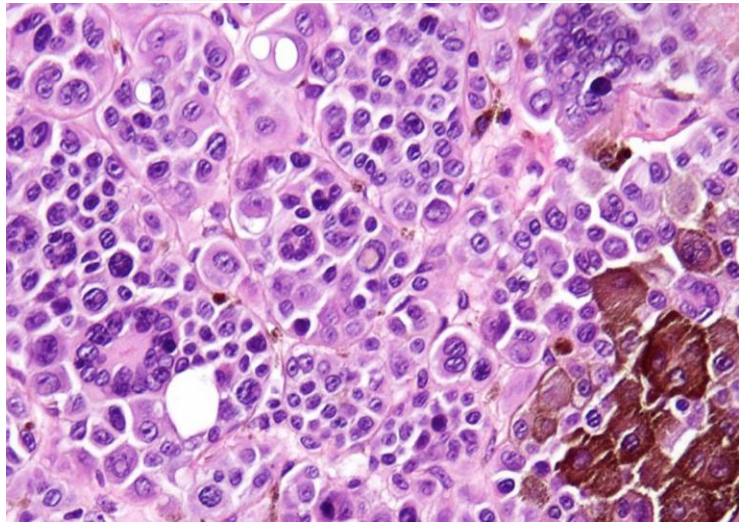
Spitz Tumors with Alk-Fusions

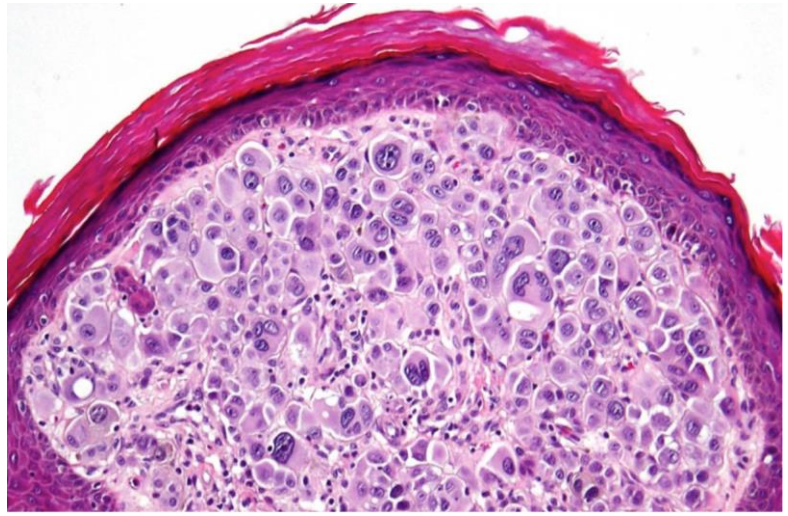


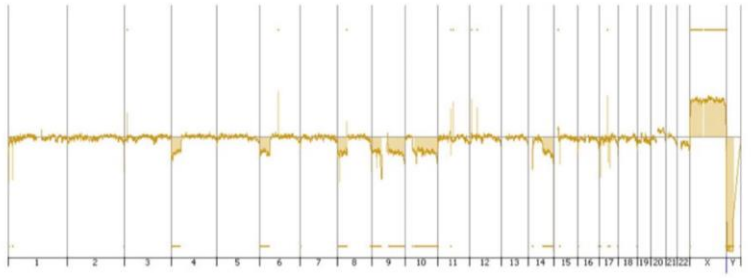
Yeh et al Am J Surg Pathol 2015;39:581-91

Melanoma



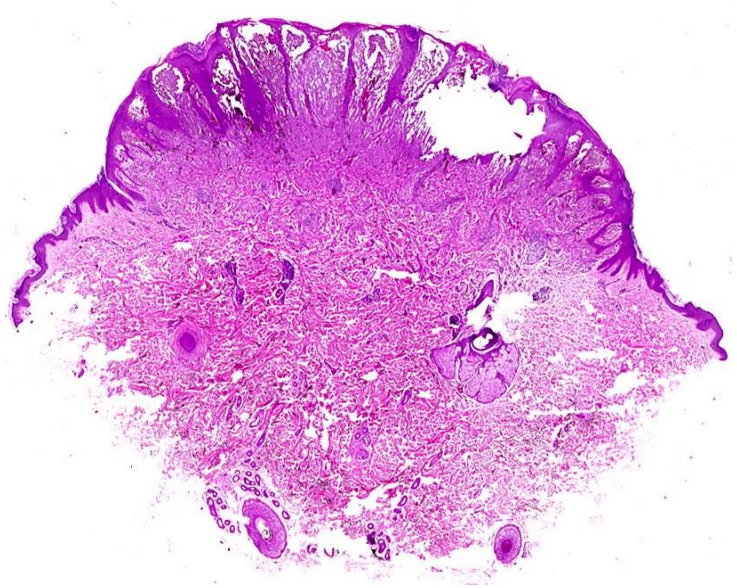




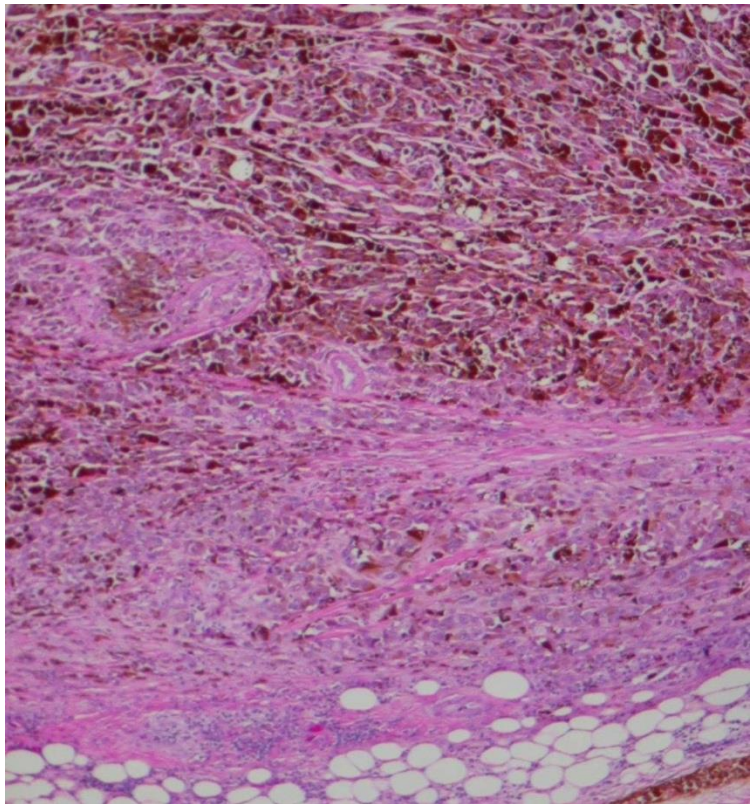


Losses of: 4p, 6p, 8p, 9, 10p, 10q, 14q

Spitzoid Melanoma



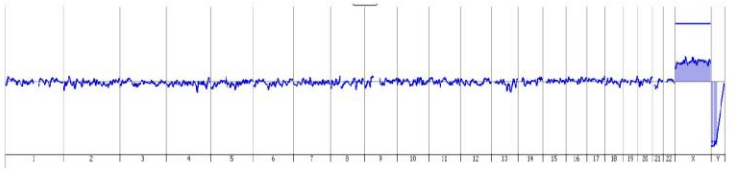
FISH Results:
Gains in CCDN1 (11q13) and
RREB1 (6p25) in > 70% of cells



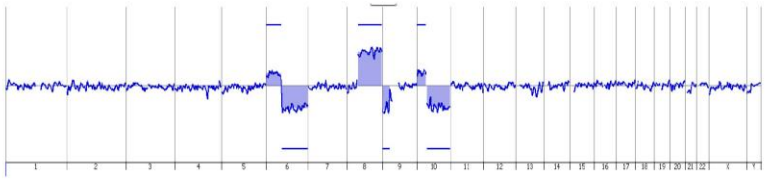
Metastatic melanoma in LN

Nevus vs Melanoma – Cytogenetic Tests

Melanocytic Nevus



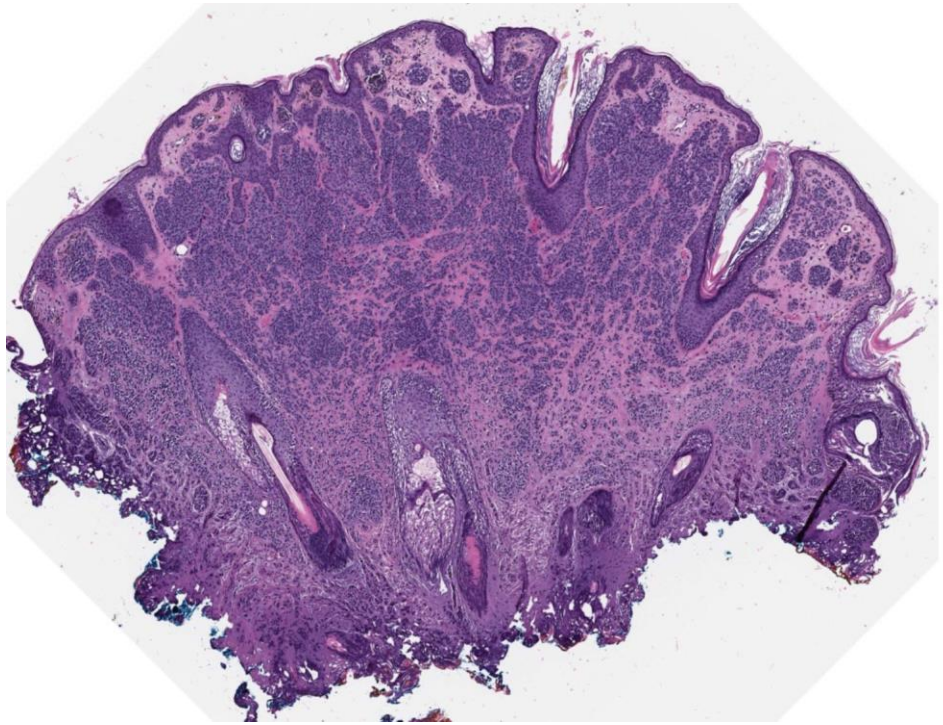
Melanoma

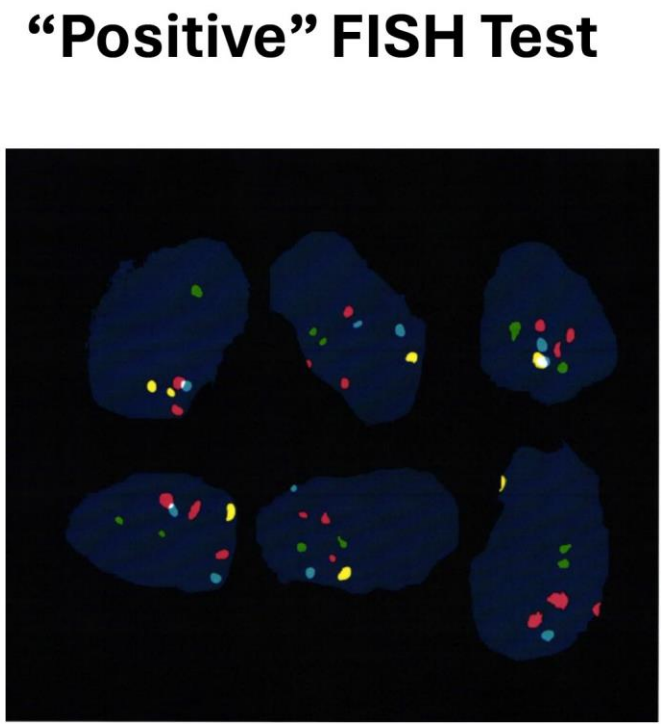


Cytogenetics for Melanocytic Tumors

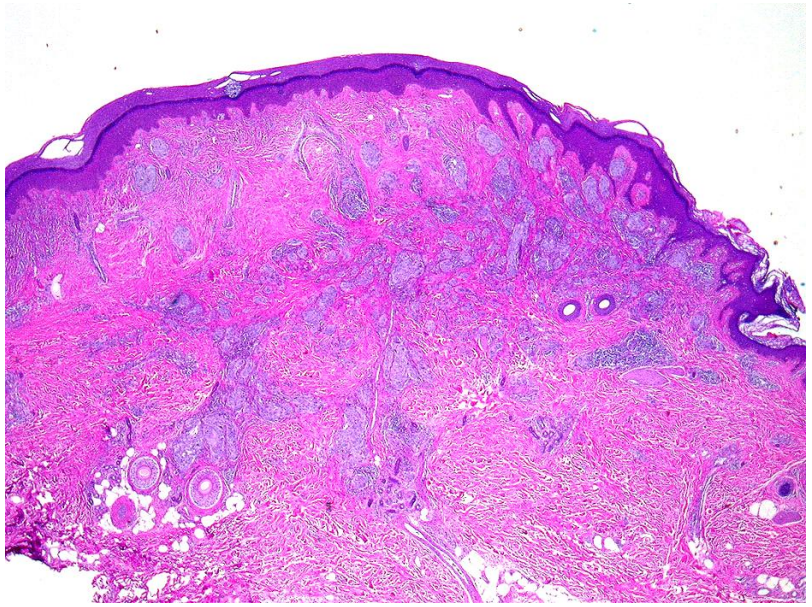
Often right, but also makes errors

Ordinary Nevus with Positive FISH test

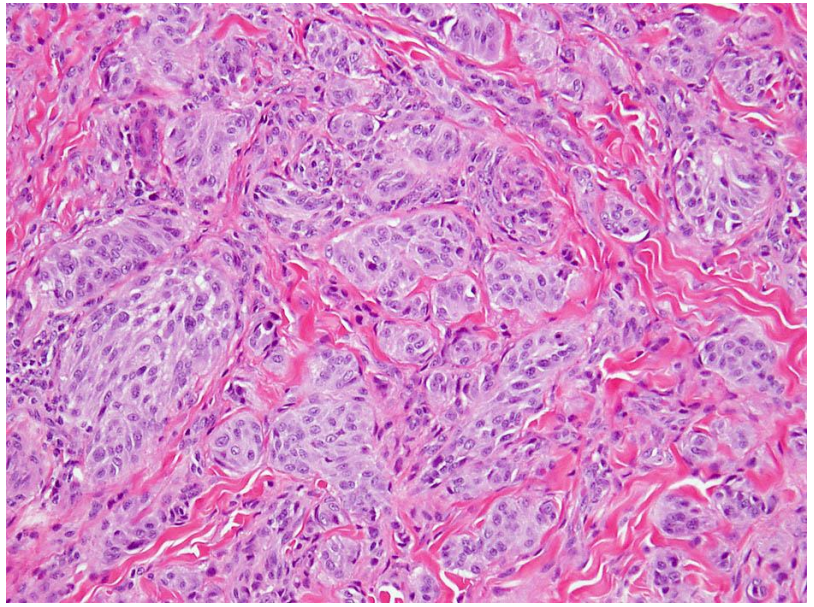




Limitations of Cytogenetic Analysis

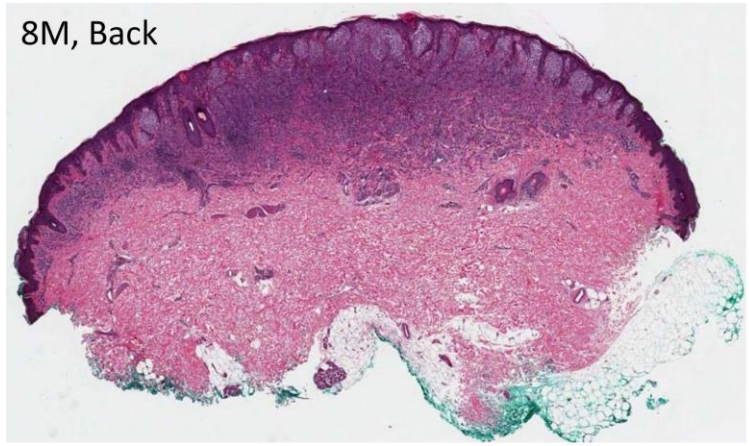


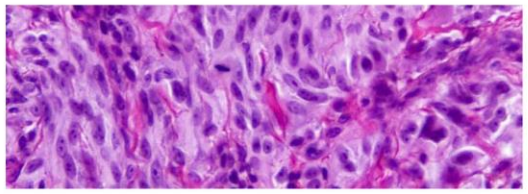
CGH:
-Loss of 1p and 9p

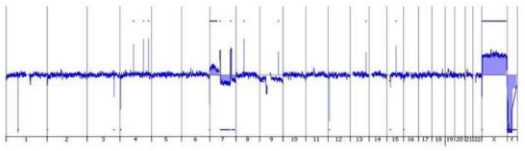


“Spitzoid Melanoma of Childhood” in 2005

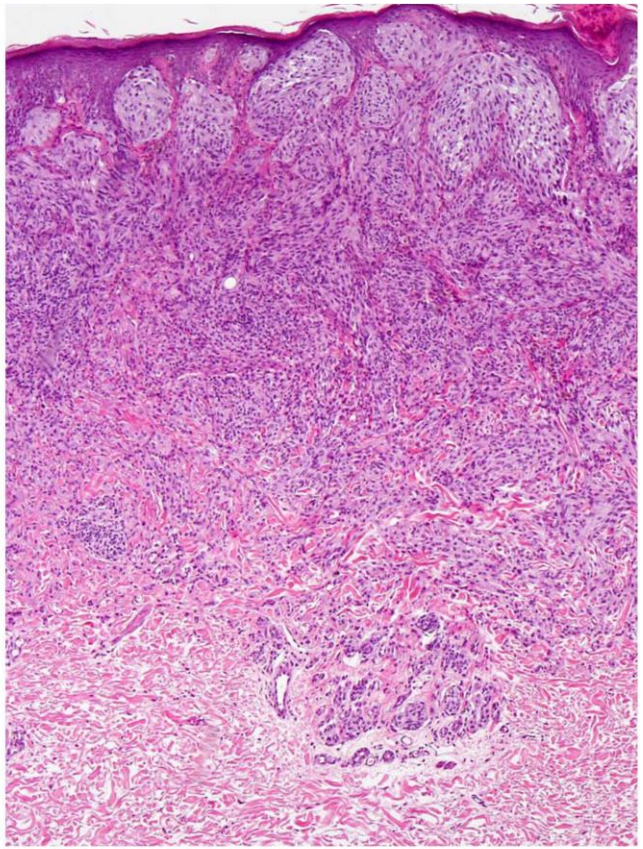
What is Your Diagnosis?







CGH: ↓9p, ↑7q



Fluorescence In Situ Hybridization as an Ancillary Tool in the Diagnosis of Ambiguous Melanocytic Neoplasms

A Review of 804 Cases

Jeffrey P. North, MD,† Maria C. Garrido, MD,‡ Nicholas A. Kolaitis, MD,‡*
Philip E. LeBoit, MD,†‡ Timothy H. McCalmont, MD,*†‡ and Boris C. Bastian, MD*†‡*

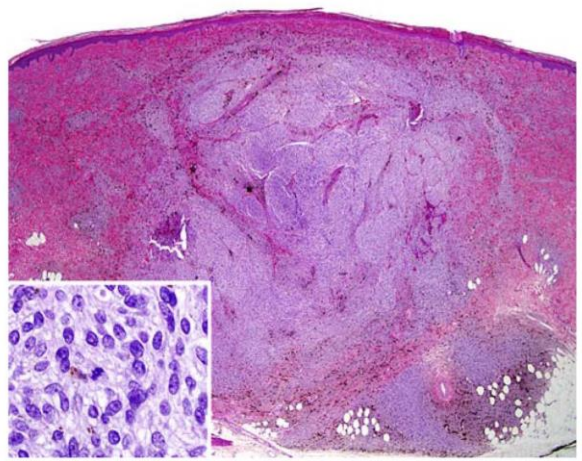


FIGURE 5. Blue nevus or blue nevus-like melanoma. Histopathologic image(s) of a 14-year-old boy with a lesion on the foot. This neoplasm has features of a cellular blue nevus with large nests and fascicles of moderately large, oval, and spindled melanocytes extending into the subcutis. However, scattered mitotic figures were present (inset), and a KI-67 immunostain showed a focus with a mildly elevated proliferation rate. FISH showed no aberrations, and a diagnosis of cellular blue nevus was rendered (hematoxylin and eosin).

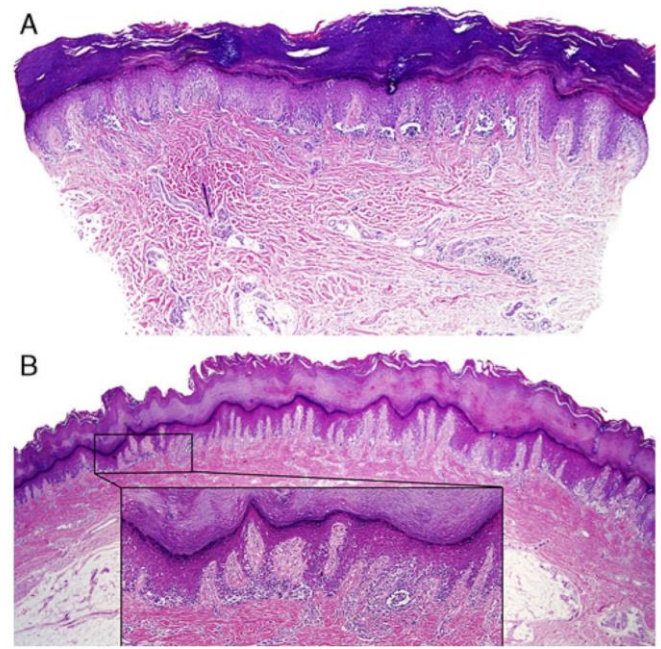


FIGURE 3. Acral neoplasms. Histopathologic image(s) of a 70-

Current trends

- NGS more commonly used as main method
  - Molecular pathway
  - Mutation burden
  - Genomic aberrations

- FISH, CGH will likely become less relevant

TERT Mutations

SCIENTIFIC REPORTS

OPEN

Received: 29 January 2015
Accepted: 30 April 2015
Published: 10 June 2015

TERT Promoter Mutations Are Predictive of Aggressive Clinical Behavior in Patients with Spitzoid Melanocytic Neoplasms

Seungjae Lee[1], Raymond L. Barnhill[2], Reinhard Dummer[3], James Dalton[1], Jianrong Wu[4], Alberto Pappo[5] & Armita Bahrami[1]

TERT Mutations

ORIGINAL STUDY

Utility of *TERT* Promoter Mutations for Cutaneous Primary Melanoma Diagnosis

Nancy E. Thomas, MD, PhD,† Sharon N. Edmiston, BS,*† Yihsuan S. Tsai, PhD,† Joel S. Parker, PhD,†‡ Paul B. Googe, MD,*§ Klaus J. Busam, MD,¶ Glynis A. Scott, MD,‖** Daniel C. Zedek, MD,*§ Eloise A. Parrish, MS,† Honglin Hao,* Nathaniel A. Slater, MD,* Michelle V. Pearlstein, MD,* Jill S. Frank, MS,††† Pei Fen Kuan, PhD,‡‡ David W. Ollila, MD,††† and Kathleen Conway, PhD*†§§*

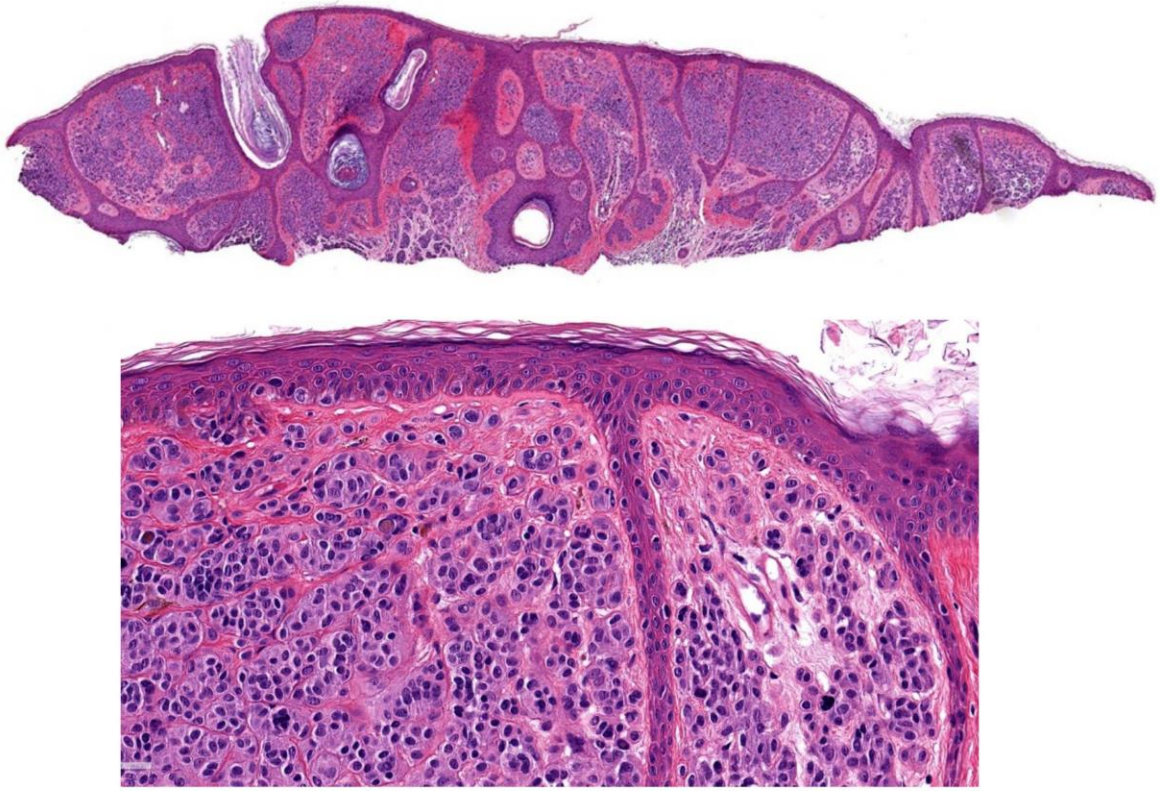
- 86 primary cutaneous melanomas
- 72melanocytic nevi

- Sensitivity for melanoma: 78%
- Specificity for melanoma: 98%

Am J Dermatopathol 2019; 41: 264-72

TERT Mutation in an Ordinary Nevus

Ordinary Melanocytic Nevus with 124C>T *TERT* Mutation

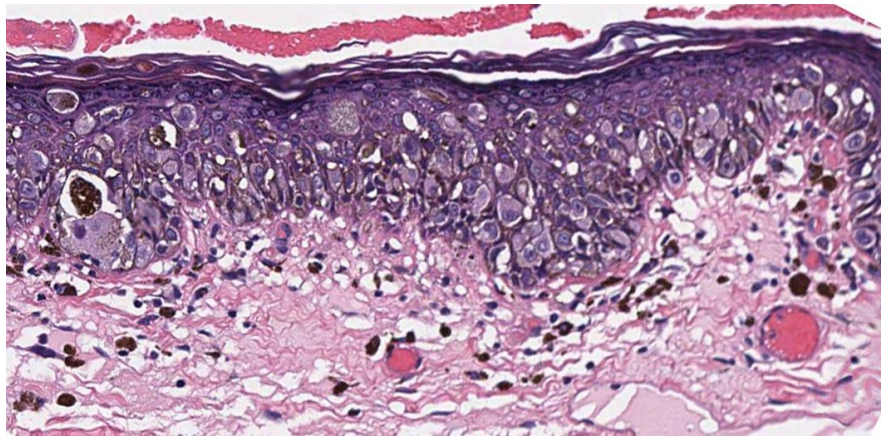


Limitations to Molecular Approach to Spitz

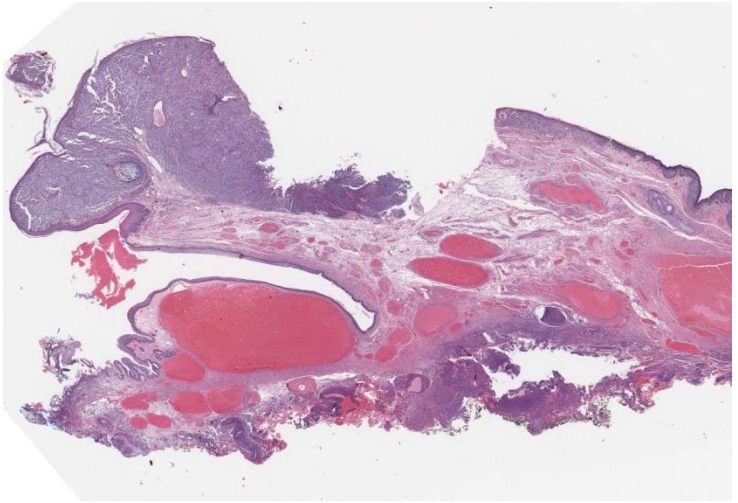
- Overlap in mutation profile and genomic aberrations between nevi, melanocytomas and melanomas

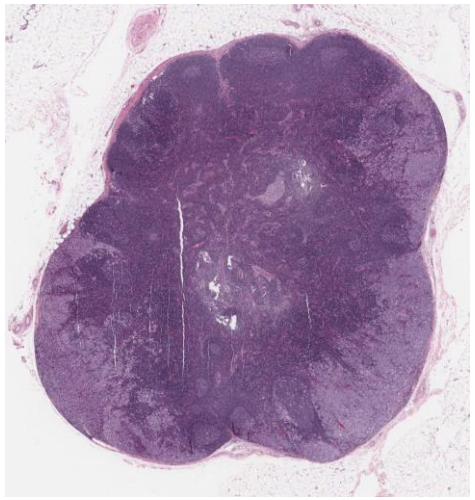
- Overlap in genetic and genomic aberrations between Spitz and non-Spitz melanocytic neoplasms

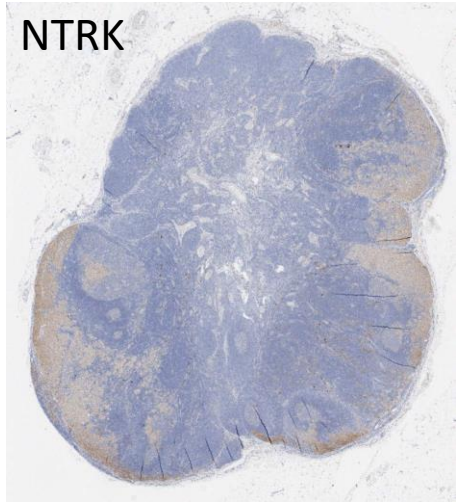
Anal mucosal melanoma with NTRK fusion



NTRK2::TRAF2







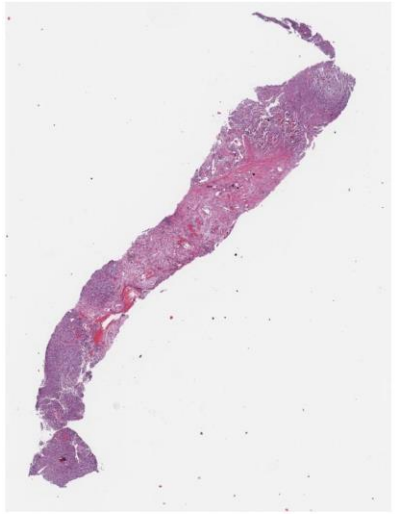
Lezcano et al Am J Surg Pathol 2018

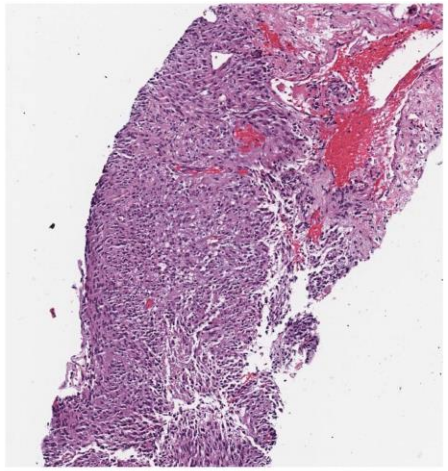
Sequence Analysis for Diagnosis

- Melanoma vs soft tissue tumor
- Staging of melanoma
- Subtyping by pathway (e.g. Spitz vs Blue vs Other)
- Ancillary evidence for assessing benign vs malignant (e.g., TERT)

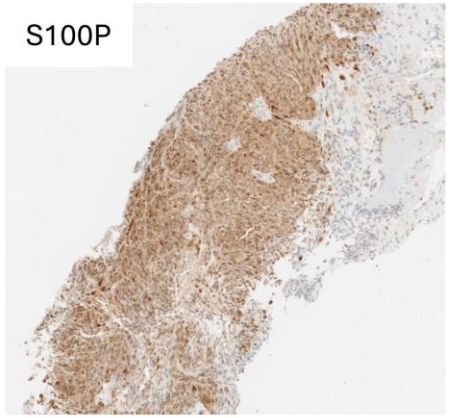
Limitations of Histopathology

41 F with h/o melanoma and nodule in lung





S100P



Reported as
“Metastatic Melanoma”

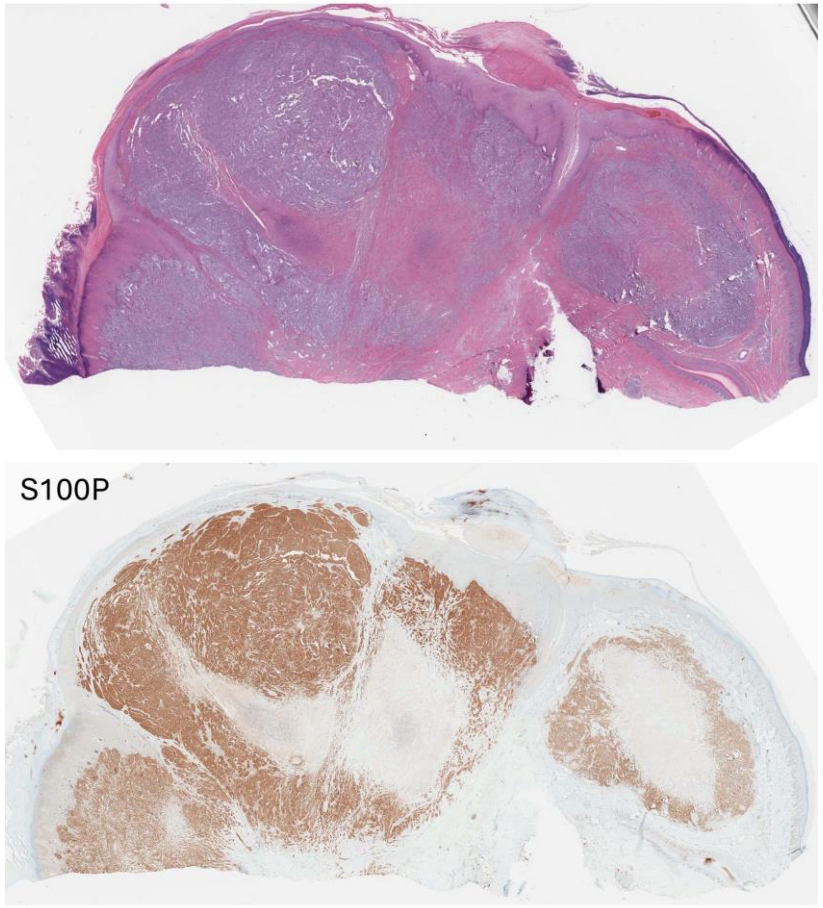
SEQUENCE ANALYSIS

EWSR1- CREM FUSION

Revised Diagnosis”

Clear cell sarcoma

Limitations of Histopathology: Primary Tumor



CLINICAL INFORMATION:
Melanoma of right great toe.

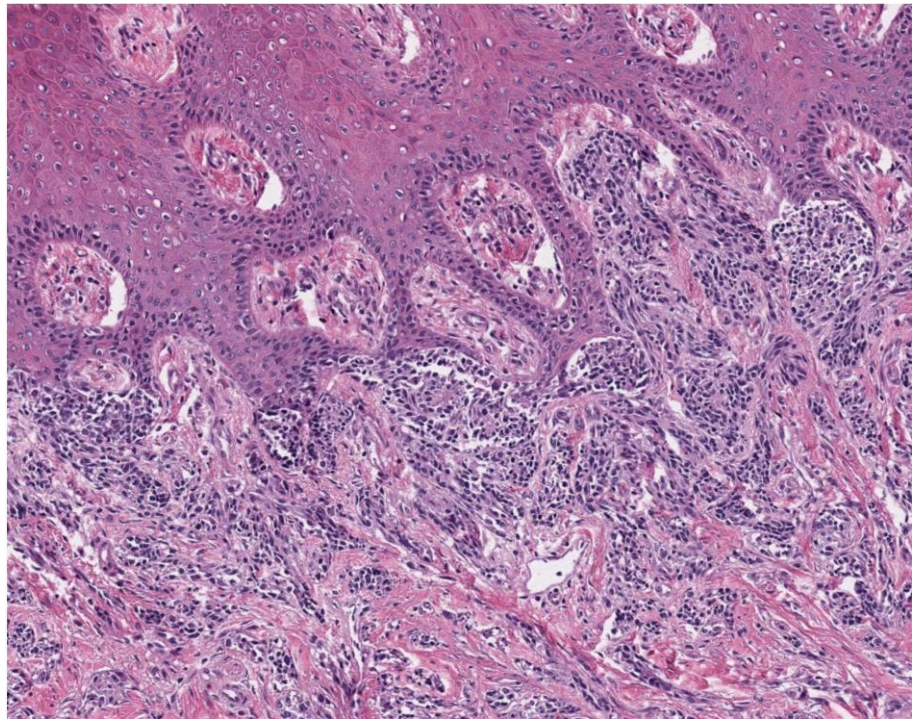
DIAGNOSIS:
A. Great toe, right (resection):

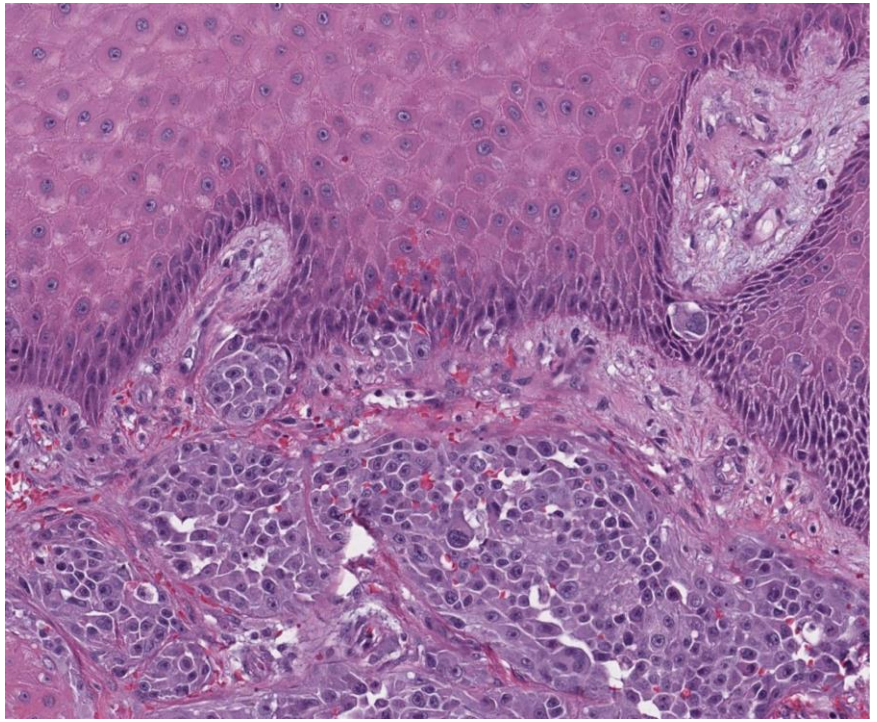
Type:	Acral lentiginous
Breslow Depth:	10 mm
Regression:	Absent
Mitotic count:	3 per 10 high power field
Tumor infiltrating lymphocytes:	Few
Ulceration:	Absent
Satellite nodules:	Absent
Margins:	Negative (skin, soft tissue and bone)

The melanoma involves the bone.

Note: Melanoma is metastatic to a lymph node in a separately submitted specimen

Primary Tumor: Clear Cell Sarcoma





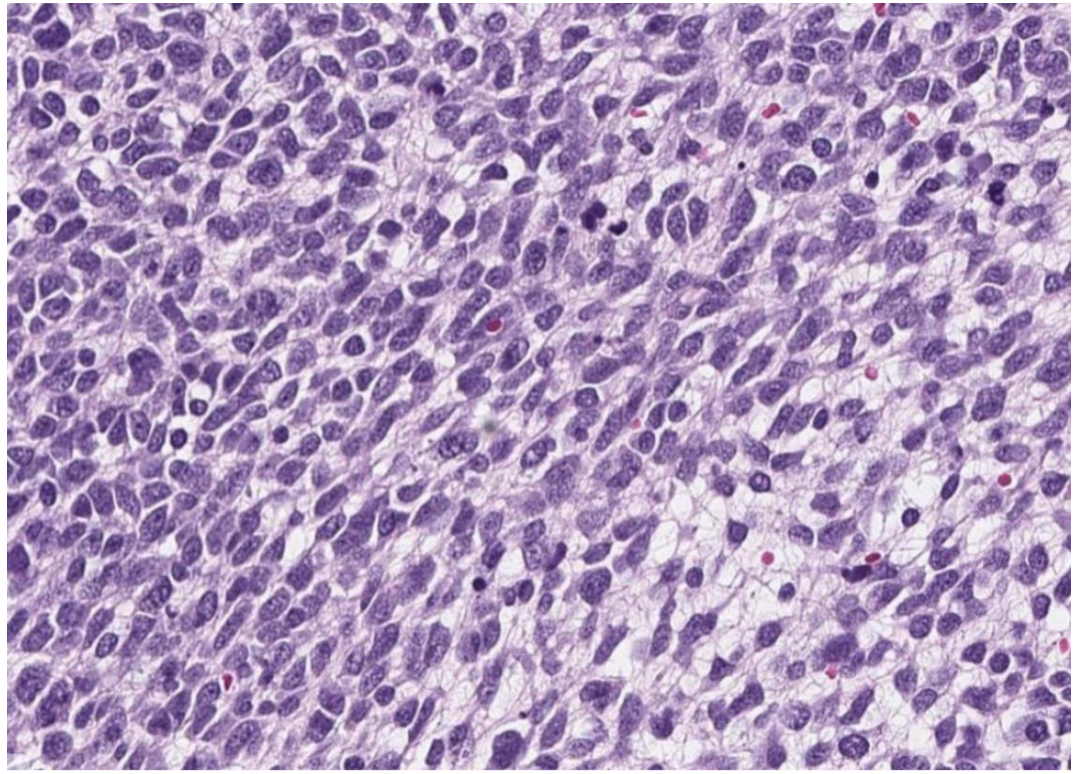
Specimens Submitted:
1: Great toe, right; resection

DIAGNOSTIC INTERPRETATION:

POSITIVE FOR THE FOLLOWING GENE FUSION IN THE CLINICALLY VALIDATED PANEL:

EWSR1-CREM fusion

Undifferentiated Malignant Tumor



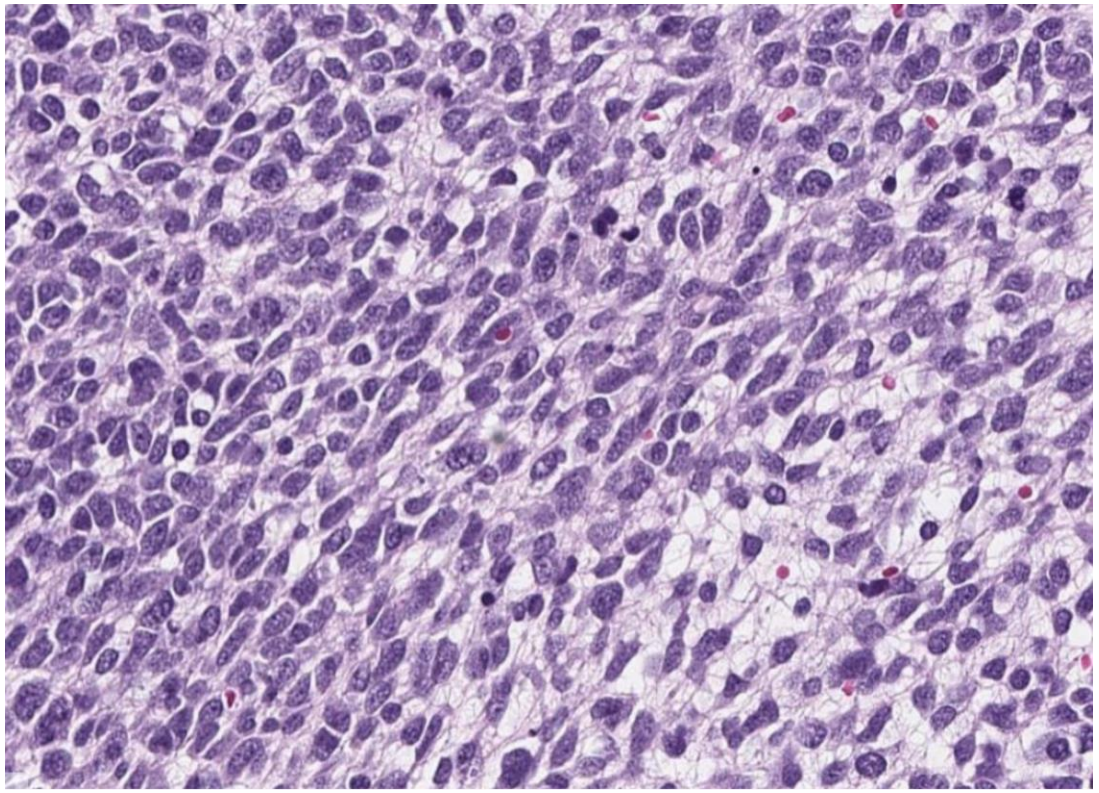
Location: .Bone/Soft tissue **Submitting Physician:**

Service: Gastric & Mixed Tumor **Primary Pathologist:**

Final Diagnosis **Date Signed Out:** 11/14

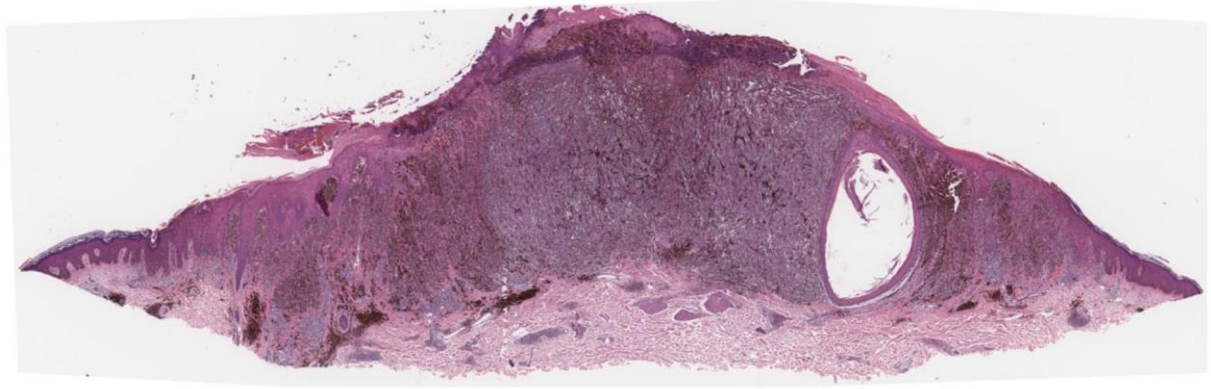
1. Right groin mass, right inguinal lymphadenectomy:
   - High grade primitive sarcoma most consistent with Malignant peripheral nerve sheath tumor. (see Note)
   - Tumor measures 9.0 cm in greatest dimension.
   - Tumor involves superficial soft tissue and shows focal involvement of lymph node.
   - Tumor shows prominent areas of necrosis (50% of tumor).
   - Surgical resection margins are free of tumor.

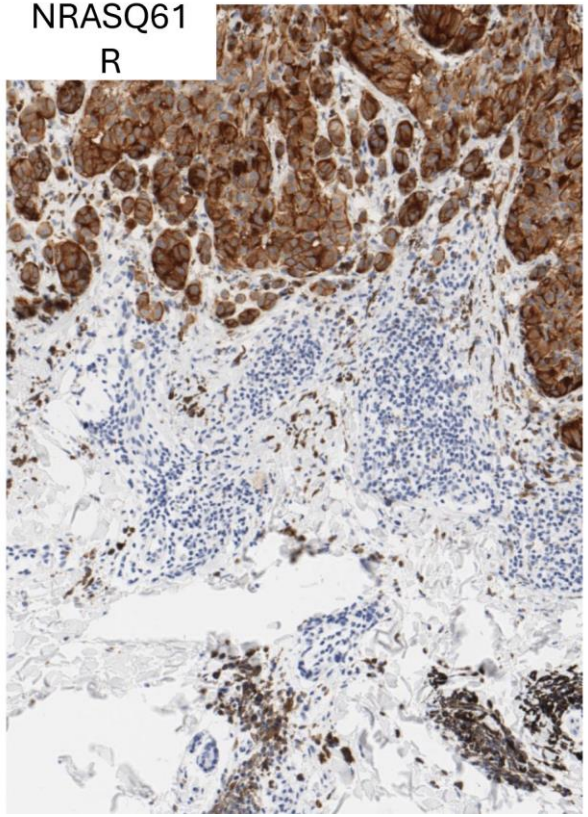
Results from Molecular Studies



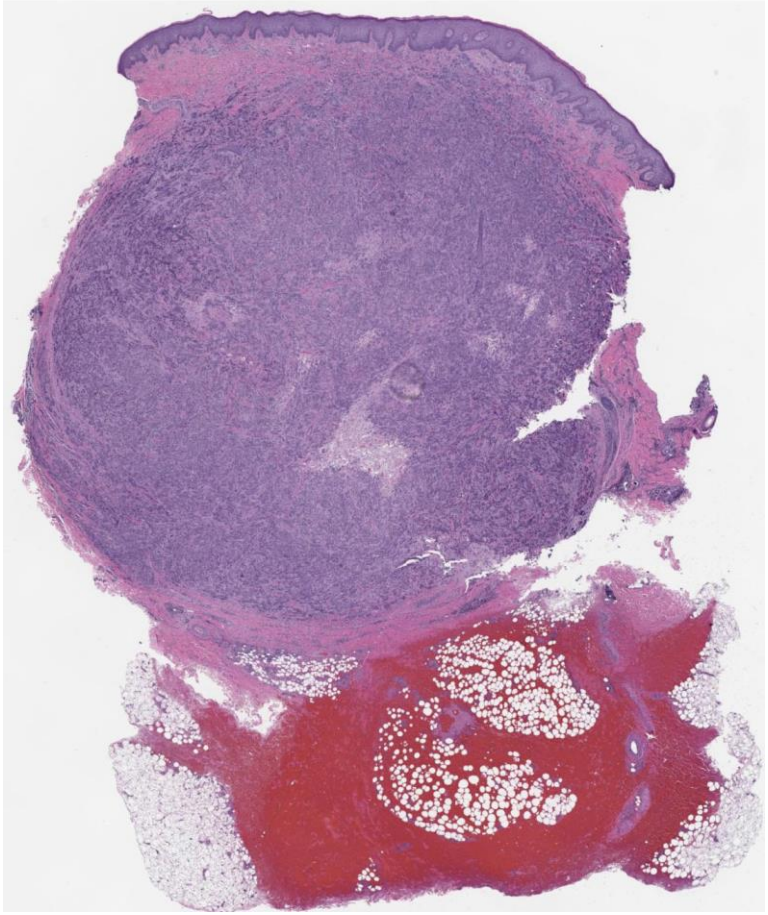
- NRASQ61R mutation
- High TMB
- UV signature mutation

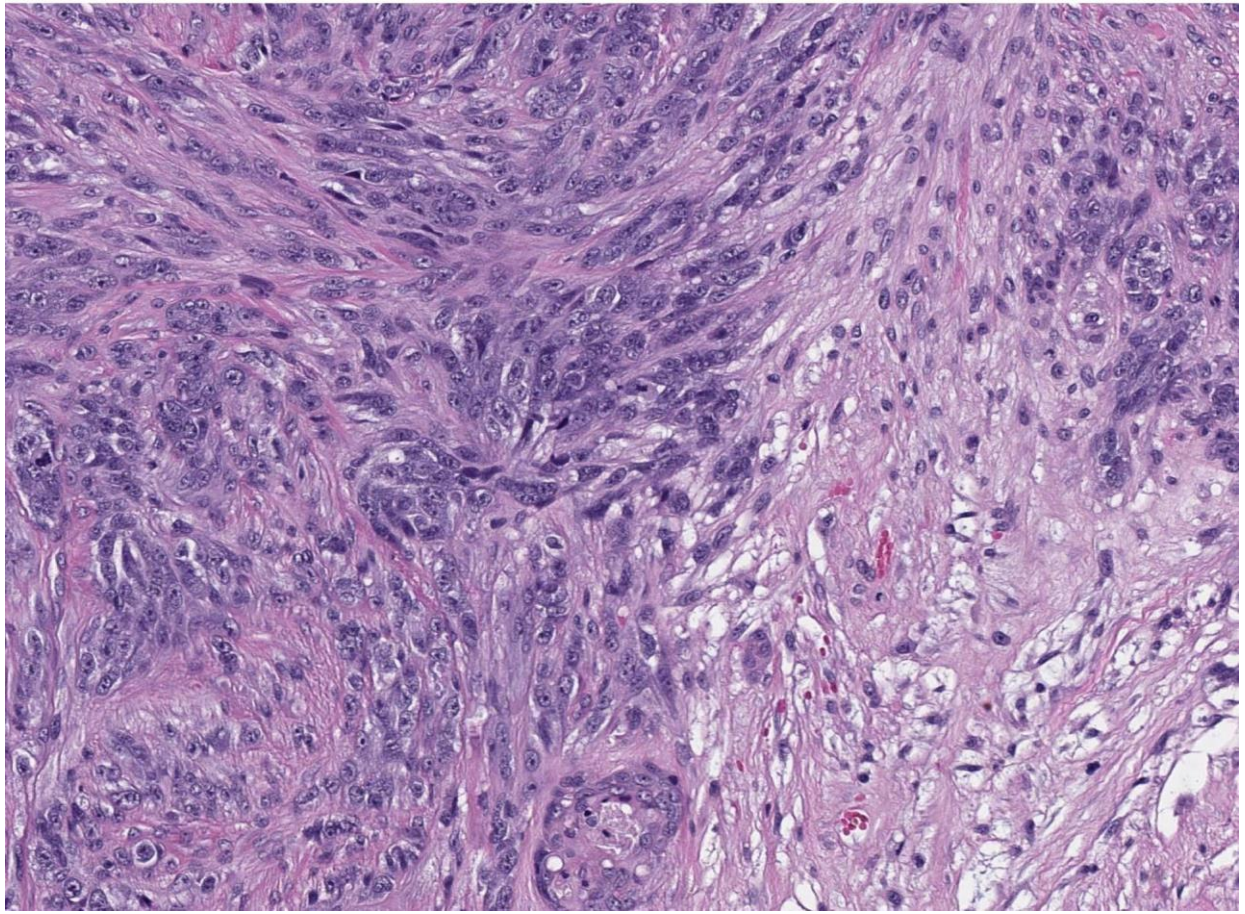
Primary Melanoma with *NRASQ61R* Mutation



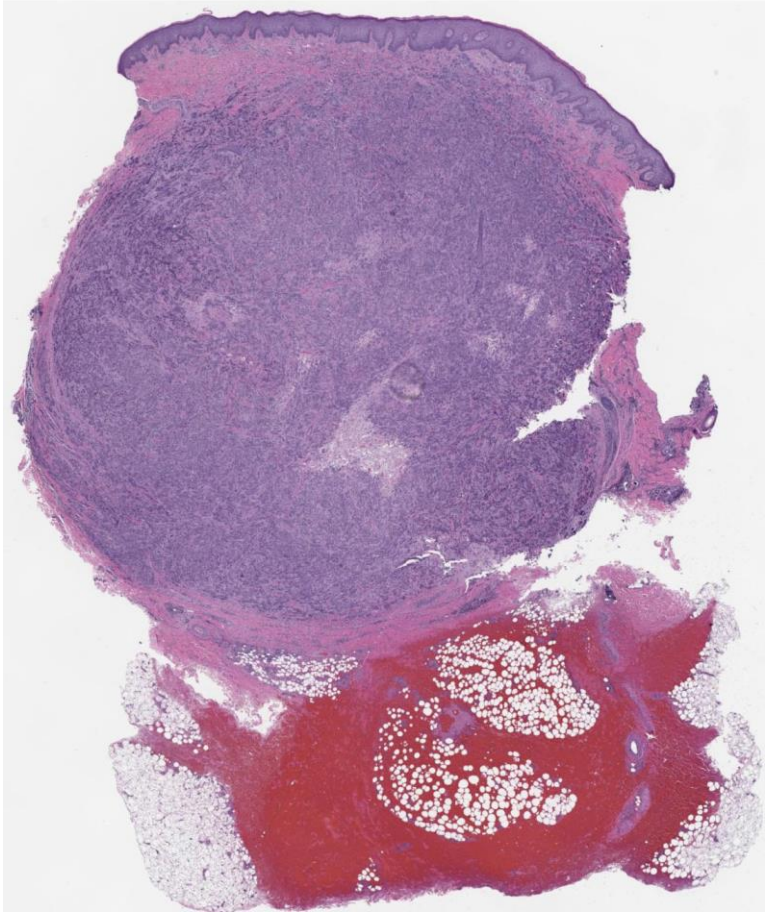


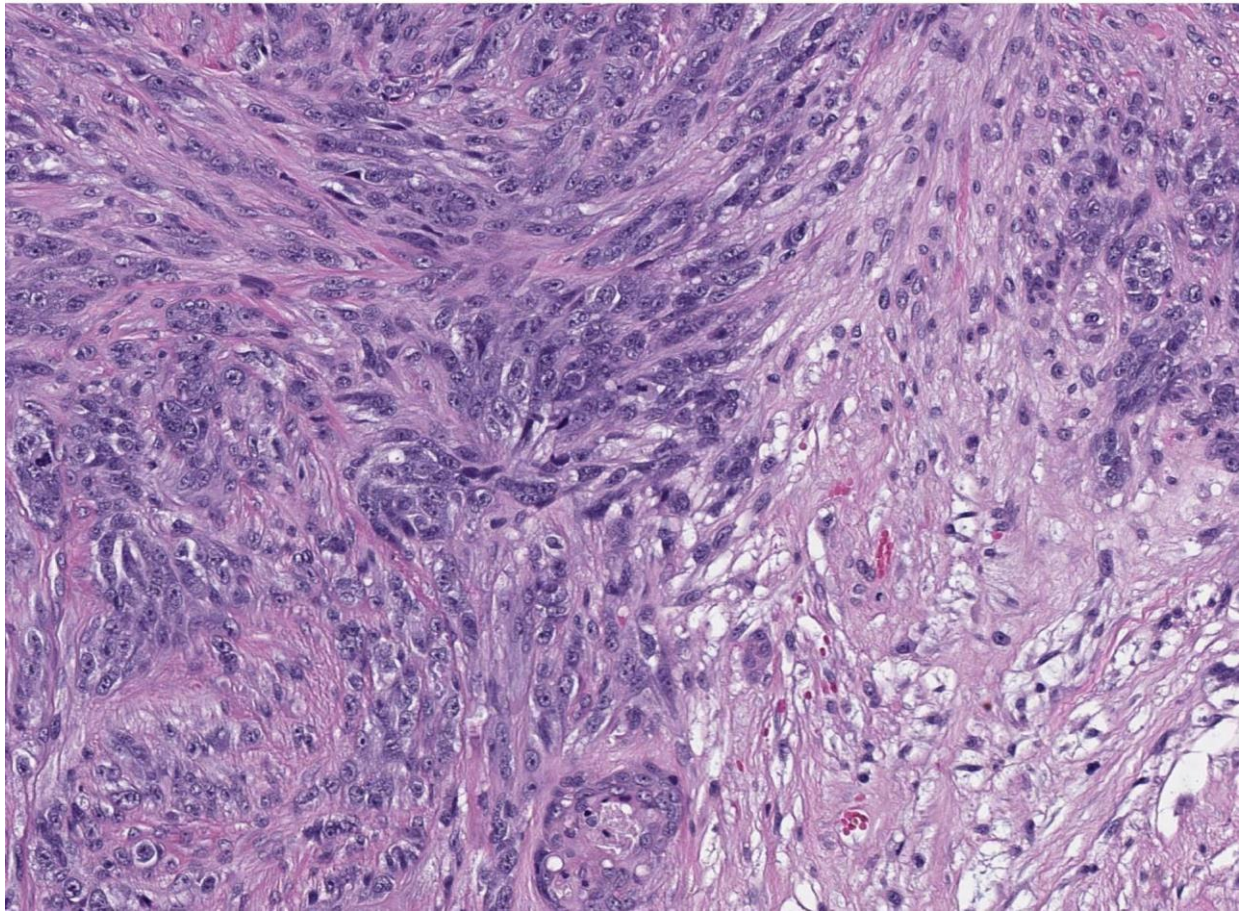
What is Your Diagnosis?





CRTC1::TRIM11 Fusion Tumor





Metastasizing CRTC1:TRIM11 Tumor

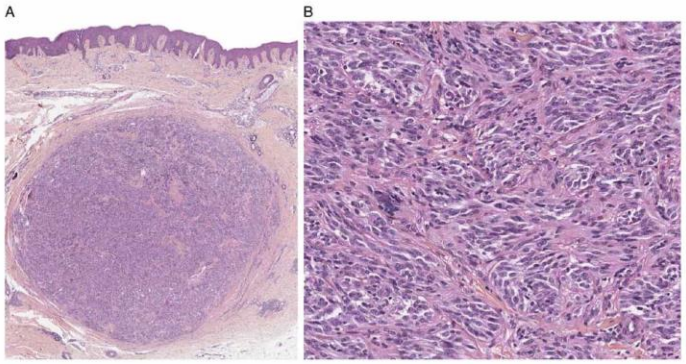
Am J Surg Pathol 2018; 42:382-91

ORIGINAL ARTICLE

Cutaneous Melanocytoma With *CRTC1-TRIM11* Fusion

Report of 5 Cases Resembling Clear Cell Sarcoma

Lucie Cellier, MD, Emilie Perron, MD, MSc,*†‡ Daniel Pissaloux, PhD,* Marie Karanian, MD,* Veronique Haddad, PharmD,* Laurent Alberti, PhD,* and Arnaud de la Fouchardière, MD, PhD**



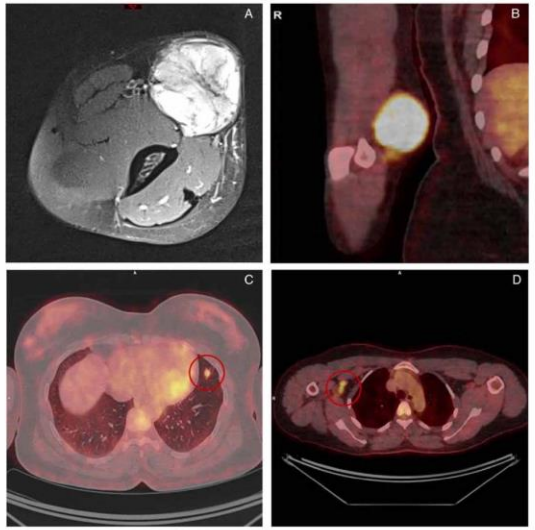
LETTER TO THE EDITOR

CRTC1-TRIM11 Fusion in a Case of Metastatic Clear Cell Sarcoma

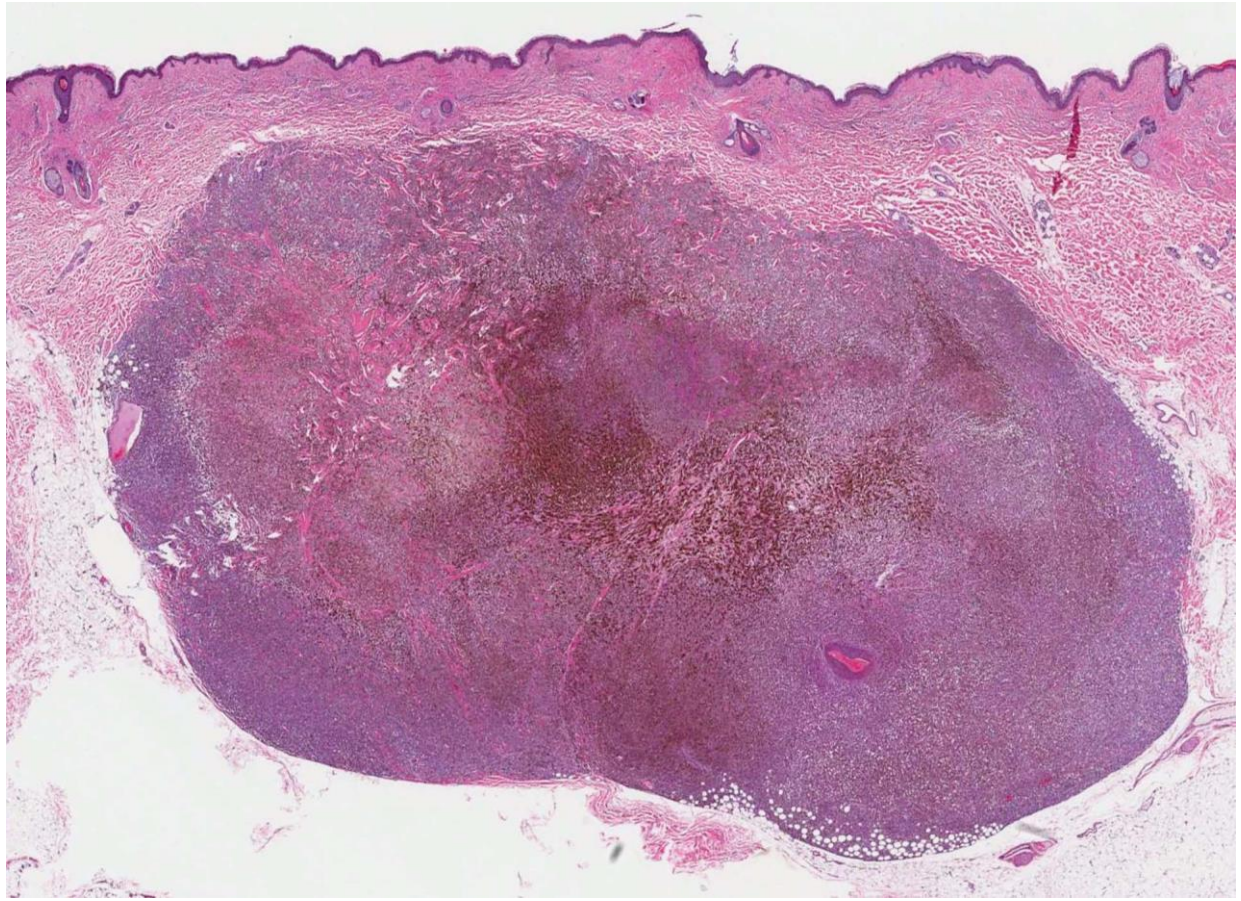
Are CRTC1-TRIM11 *Fusion-bearing Tumors Melanocytomas or Clear Cell Sarcomas?*

To the Editor:

We read with interest the article by Cellier and colleagues in the 2018 March issue of the *American Journal of Surgical Pathology* on the proposal of a new tumor entity named cutaneous melanocytoma with *CRTC1-TRIM11* fusion, which seems to have a favorable prognosis.[1] The authors reported 5 cases of unpigmented nodular dermal tumors, which harbored a previously undescribed invariable *CRTC1-TRIM11* fusion highlighted with RNA sequencing (t(19;1)(p13;q42)). These tumors displayed a unique nodular pattern with dense fascicles and nests of unpigmented cells with medium to large atypical epithelioid and spindle cells, with constant expression of melanocytic markers (SOX10, Melan-A, S100 protein, and HMB45), resembling dermal clear cell sarcoma (CCS). In some cases, necrosis and a high mitotic activity were observed. However, none of the 5 cases recurred during a median follow-up of 14 months (3 to 72 mo). On the basis

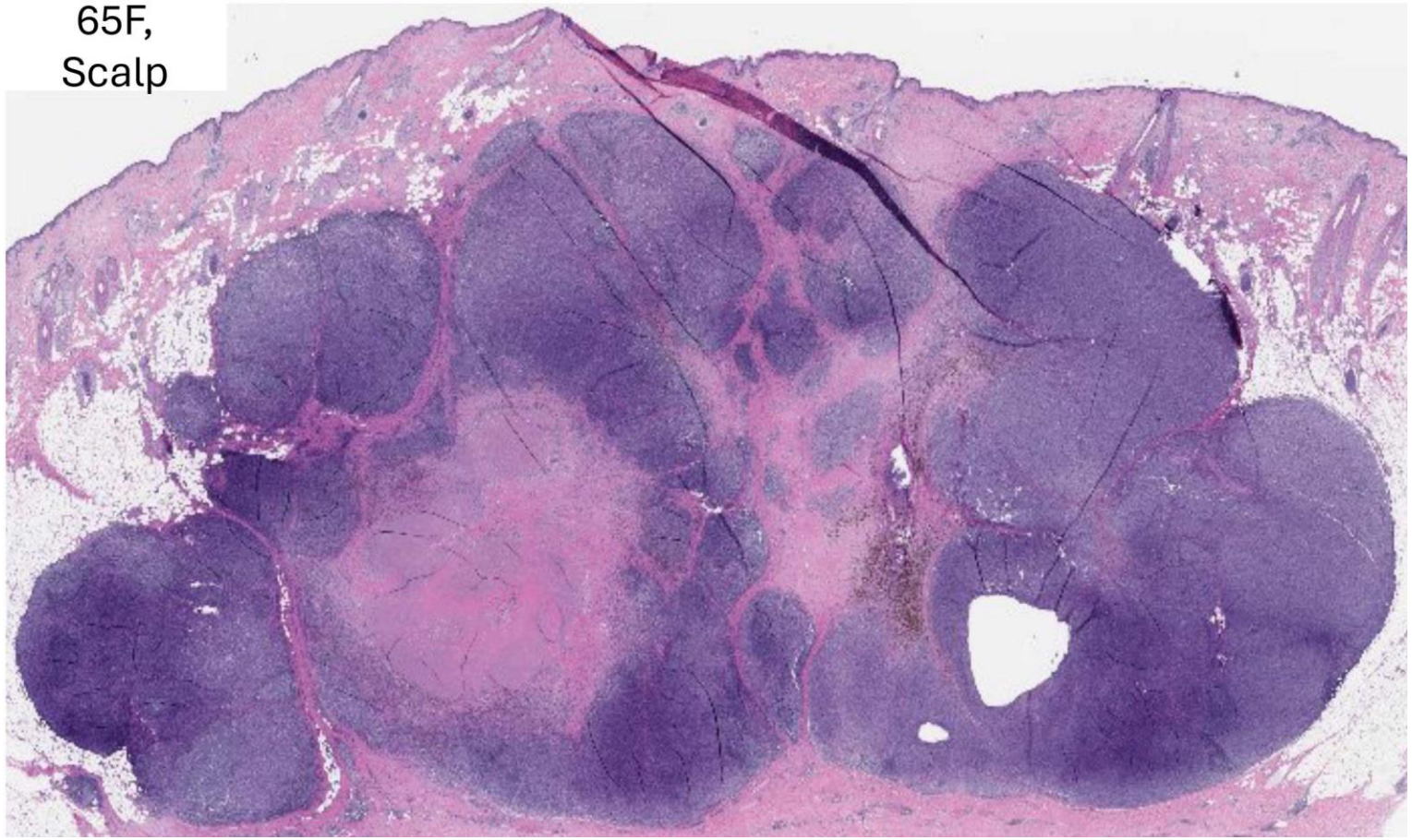


Metastatic melanoma



History of prior invasive melanoma with pos LNs

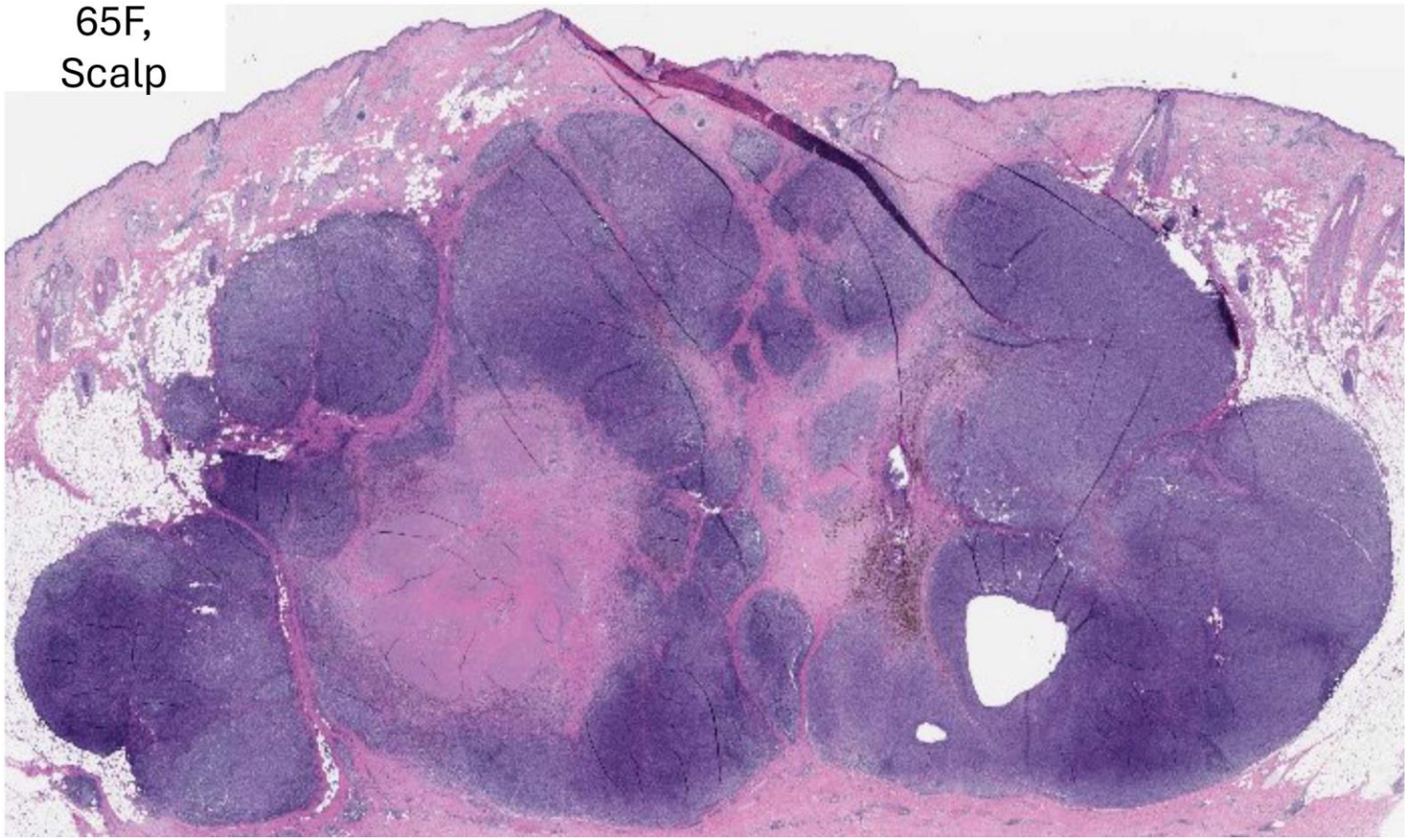
Metastatic Melanoma?



Pathology:

- Mass in subcutis
- Multinodular growth
- Necrosis
- No nevus or melanoma in situ

Primary Melanoma



Clinical History
- Lesion present > 10 yrs
- No evidence of melanoma elsewhere

Molecular Findings
- *GNAQpQ209L*
- Low mutation burden
- No UV signature

Blue Nevus-Related Melanoma

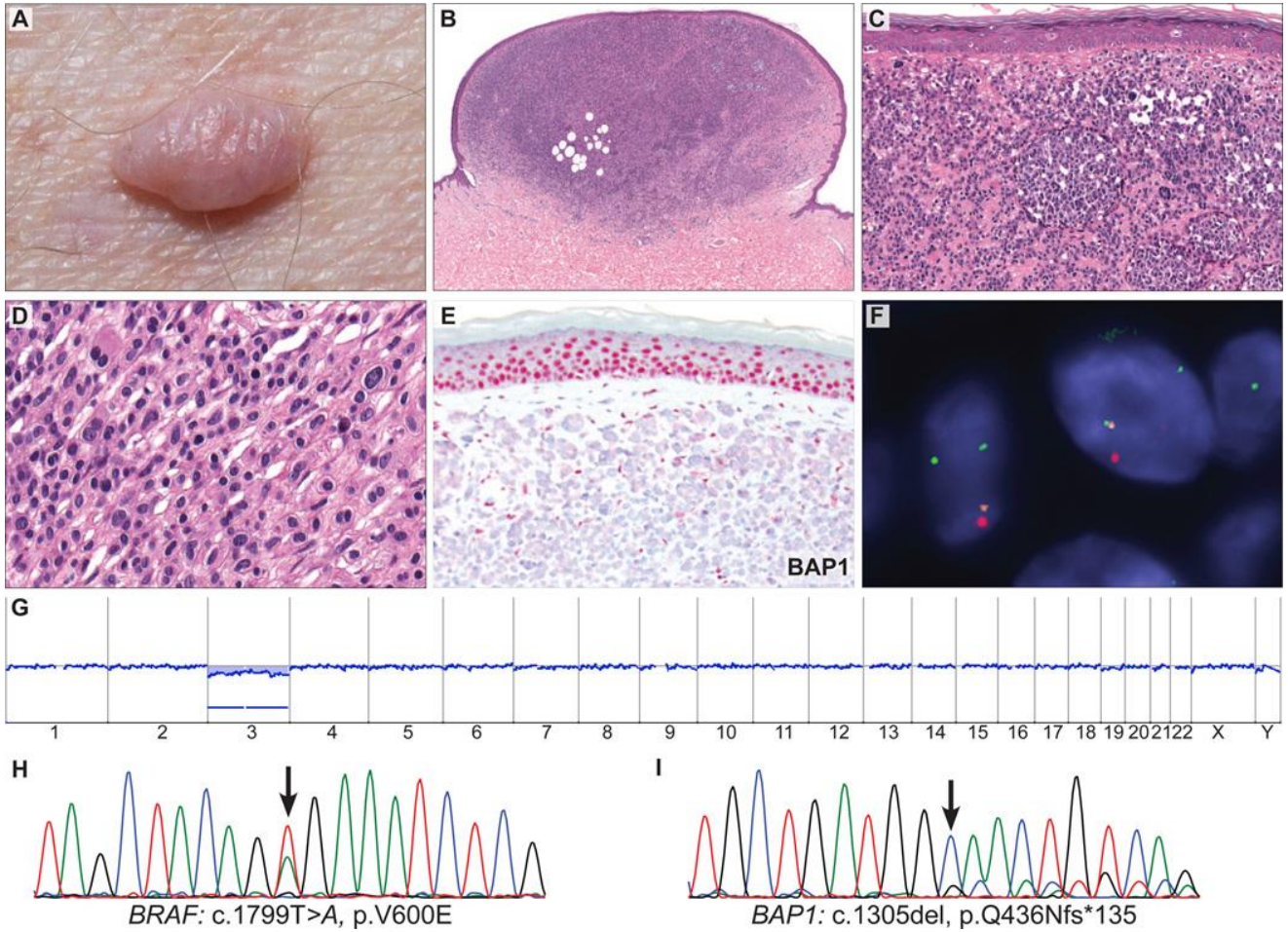
Importance of Clinicopathology Correlation

- Clinicopathologic context important for choice to do NGS
- Clinicopathologic context important to interpret NGS results

The Rise of Melanocytomas

- Pigmented Epithelioid Melanocytoma
- BAP1-Inactivated Melanocytoma
- WNT-Inactivated Melanocytoma
- Spitz Melanocytoma

BAP1-Neg Epithelioid ("Wiesner's") Nevus



Wiesner et al. Am J Surg Path 2012;36:818-30.

Received: 25 February 2019 | Revised: 18 June 2019 | Accepted: 20 June 2019

DOI: 10.1111/cup.13530

REVIEW

JOURNAL OF CUTANEOUS PATHOLOGY WILEY

BRCA1-associated protein (BAP1)-inactivated melanocytic tumors

Arianna J. Zhang[1] | Patrick S. Rush[2] | Hensin Tsao[3,4] | Lyn M. Duncan[1,3]

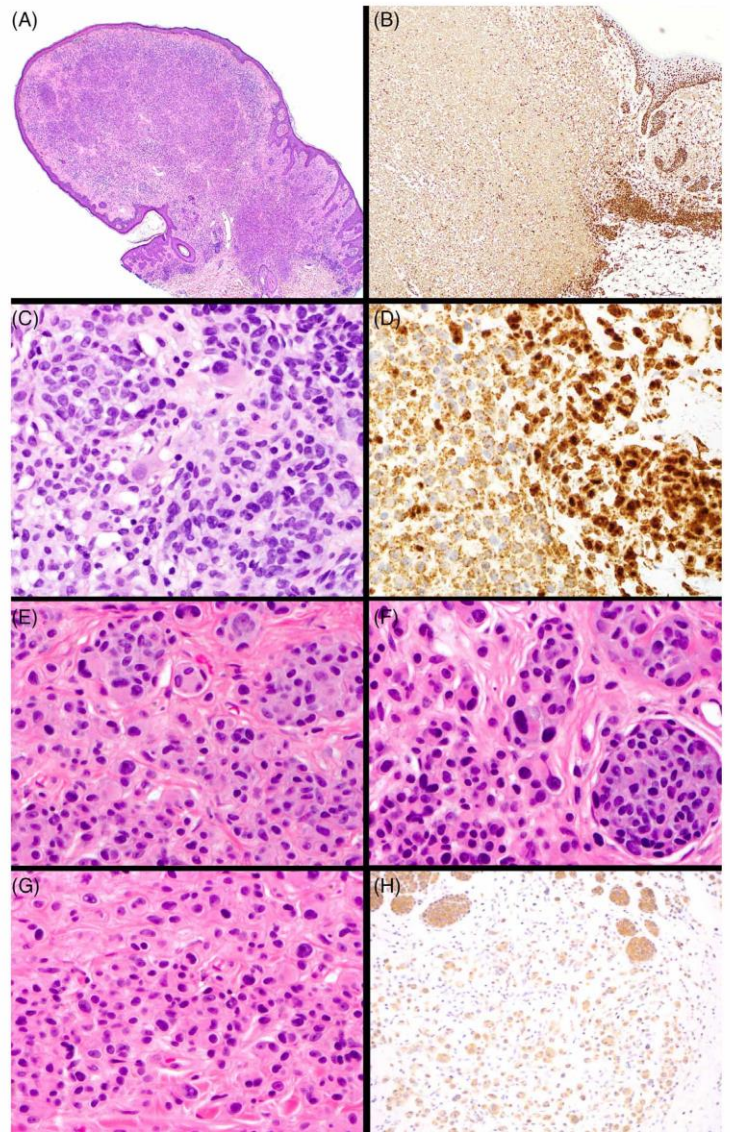


FIGURE 3 Cutaneous *BAP1*-inactivated melanocytic tumor (BIMT). A, This tumor has an overall polypoidal configuration with a biphasic pattern (H&E ×20). B, Positive nuclear BAP1 staining in small peripheral melanocytes and epidermal keratinocytes (×100). C, Biphasic proliferation of melanocytes with large epithelioid cells (left) and smaller melanocytes with less cytoplasm (right) (H&E ×400). D, Absent BAP1 nuclear staining in large melanocytes (left) and retained nuclear BAP1 expression small melanocytes (right) (×400). E, F, G, Examples of variable cytological atypia (H&E ×400, ×630, ×400). H, $BRAF^{V600E}$ staining in both the small nevic population (top) and large epithelioid BAP1-deficient population (bottom) (×200)

MPATH-DX V 2.0

JAMA Network | Open

Consensus Statement | Pathology and Laboratory Medicine

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

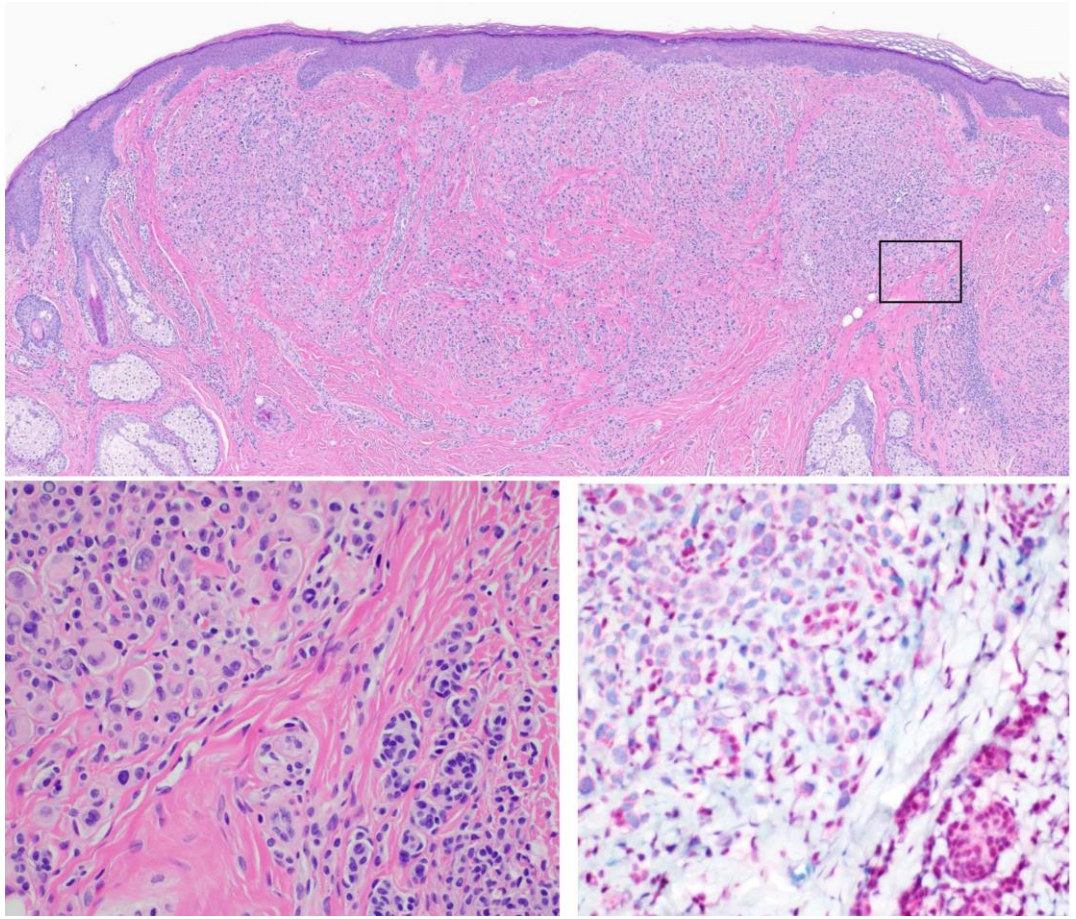
A Consensus Statement

Raymond L. Barnhill, MD; David E. Elder, MBChB; Michael W. Piepkorn, MD, PhD; Stevan R. Knezevich, MD, PhD; Lisa M. Reisch, PhD; Megan M. Eguchi, MPH; Boris C. Bastian, MD, PhD; Willeke Blokx, MD, PhD; Marcus Bosenberg, MD, PhD; Klaus J. Busam, MD; Richard Carr, MBChB; Alistair Cochran, MD; Martin G. Cook, MD; Lyn M. Duncan, MD; Rosalie Elenitsas, MD; Arnaud de la Fouchardière, MD, PhD; Pedram Gerami, MD; Iva Johansson, MD; Jennifer Ko, MD, PhD; Gilles Landman, MD, PhD; Alexander J. Lazar, MD, PhD; Lori Lowe, MD; Daniela Massi, MD, PhD; Jane Messina, MD; Daniela Mihic-Probst, MD; Douglas C. Parker, MD; Birgitta Schmidt, MD; Christopher R. Shea, MD; Richard A. Scolyer, MD; Michael Tetzlaff, MD, PhD; Xiaowei Xu, MD, PhD; Iwei Yeh, MD, PhD; Artur Zembowicz, MD, PhD; Joann G. Elmore, MD

Table 1. The Melanocytic Pathology Assessment Tool and Hierarchy for Diagnosis Version 2.0

Class	Risk of tumor progression	Probability of progression, No. per population	Treatment recommendation	Examples[a]
0	NA	NA	Consider repeat biopsy	Nondiagnostic or unsatisfactory
I: low grade	Very low risk for continued proliferation and progression to invasive melanoma	1 in 10 000 to 1 in 100 000	No further treatment[b]	Common acquired nevi, no atypia
				Congenital nevi, no atypia
				Atypical and dysplastic nevi, low-grade atypia[c]
				Common blue nevi
II: high grade	Low risk for progression to invasive melanoma	1 in 100 to 1 in 1000	Re-excision with margins <1 cm[b]	Atypical and dysplastic nevi, high-grade atypia[c]
				Spitz nevi, tumors or melanocytomas, and atypical variants
				Cellular blue nevi or melanocytomas and atypical variants
				Plexiform or deep penetrating nevi or melanocytomas
				Lentigo maligna
				Melanoma in situ
III: melanoma pT1a	Relatively low risk for local and regional metastasis	1 in 10 to 1 in 100	Follow national guidelines (eg, wide excision with 1 cm margins)[b]	Melanoma AJCC stage pT1a, <0.8 mm Breslow thickness
				Melanoma pT1a lr (low risk)[d]
				Melanoma pT1a[e]
IV: melanoma ≥pT1b	Moderate to increased risk for regional or distant metastasis	1 in 2 to 1 in 10	Follow national guidelines (eg, wide excision with 1-2 cm margins[b] and consideration of sentinel lymph node staging and other therapies)	Melanoma AJCC stage pT1b or greater, ≥0.8 mm Breslow thickness

Combined BAP1-Inactivated Nevus



BAP1-Inactivated Melanocytic Tumors

- Histopathology benign: Nevus
- Atypical histo- or molecular path, but still benign: Melanocytoma
- Atypical, but unsure about biology: “atypical tumor”
- Malignant: Melanoma

Ancillary Tests for Melanoma Diagnosis

- Essential for the diagnosis of fusion tumors
- Can help in select cases to reach the correct diagnosis
- Significant limitations in sensitivity and specificity
- Tendency for over-utilization

Acknowledgements and thank you to:

- Colleagues at MSKCC
- Many collaborators at other institutions
- My family

busamk@mskcc.org

Thank You!