The State of the Dysplastic Nevus in the 21st Century

Keith Duffy, MD
Associate professor
Department of Dermatology
University of Utah

Disclosures

- Myriad Genetics
  - Advisory board; honorarium
- Castle Biosciences
  - Advisory board; honorarium

What do I do?

- Clinical
  - 60% Mohs micrographic and reconstructive surgery and high risk skin cancer
  - 40% Dermatopathology sign-out
  - Multidisciplinary cutaneous oncology program – Huntsman Cancer Institute
- Administrative
  - Residency Program Director, Dermatology


UNITED STATES of AMERICA
Arctic Ocean
Greenland (Denmark)
ARCTIC CIRCLE
Alaska
Canada
NORTH AMERICA
Utah
Pacific Ocean
Atlantic Ocean
Bermuda (UK)
Gulf of Mexico
TROPIC OF CANCER
23°5'N
Hawaii
Mexico
CARIBBEAN
Caribbean Sea
1300 mi
1300 km
CENTRAL AMERICA
SOUTH AMERICA
EQUATOR
0°
Pacific Ocean
90°W
©GraphicMaps.com


UTAH
LOW / HILLS / MOUNTAINS
worldatlas
CLICK HERE FOR LARGER MAP
Idaho
Wyoming
100 mi
100 km
Logan
Ogden
Great Salt Lake
Wasatch Mts.
Kings Peak
Flaming Gorge
Bonneville Salt Flats
Wendover
Salt Lake City
Park City
Uinta Mts.
Orem
Provo
Utah Lake
Dinosaur N.M.
White River
Green River
Nevada
Rocky Mts.
Price
Utah
Fillmore
Richfield
Capital Reef N.P.
Goblin Valley
Moab
Colorado
COLORADO PLATEA
Cedar City
Bryce Canyon N.P.
Colorado River
St. George
Zion N.P.
Monument Valley
Lake Powell
Four Corners
Arizona
Grand Staircase-Escalante N.M.
New Mexico
Grand Canyon
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ORIGINAL ARTICLE

The Genetic Evolution of Melanoma from Precursor Lesions

A. Hunter Shain, Ph.D., Iwei Yeh, M.D., Ph.D., Ivanka Kovalyshyn, D.O., Aravindhan Sriharan, M.D., Eric Talevich, Ph.D., Alexander Gagnon, B.A., Reinhard Dummer, M.D., Jeffrey North, M.D., Laura Pincus, M.D., Beth Ruben, M.D., William Rickaby, M.B., Ch.B., Corrado D'Arrigo, M.B., Ch.B., Ph.D., Alistair Robson, F.R.C.Path., and Boris C. Bastian, M.D.

From the Departments of Dermatology and Pathology (A.H.S., I.Y., E.T., A.G., J.N., L.P., B.R., B.C.B.) and the Helen Diller Family Comprehensive Cancer Center (A.H.S., I.Y., E.T., A.G., B.C.B.), University of California, San Francisco (UCSF), San Francisco; the Departments of Dermatology and Pathology, Cleveland Clinic, Cleveland (I.K.); the Department of Pathology, Orlando Health, Orlando, FL (A.S.); the Department of Dermatology, University Hospital of Zurich, Zurich, Switzerland (R.D.); and the Department of Dermatology, Dorset County Hospital, Dorchester (C.D.), and the Department of Dermatology, St. John's Institute of Dermatology, London (W.R., A.R.) — both in the United Kingdom. Address reprint requests to Dr. Bastian at the UCSF Dermatopathology Service, 1701 Divisadero St., Suite 280, San Francisco, CA 94115, or at boris.bastian@ucsf.edu.

N Engl J Med 2015;373:1926-36.
DOI: 10.1056/NEJMoa1502583

ABSTRACT

BACKGROUND

The pathogenic mutations in melanoma have been largely catalogued; however, the order of their occurrence is not known.

METHODS

We sequenced 293 cancer-relevant genes in 150 areas of 37 primary melanomas and their adjacent precursor lesions. The histopathological spectrum of these areas included unequivocally benign lesions, intermediate lesions, and intraepidermal or invasive melanomas.

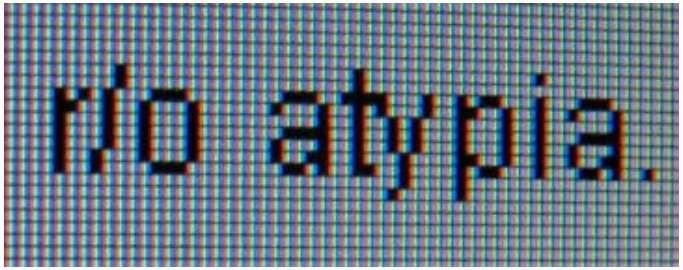
RESULTS

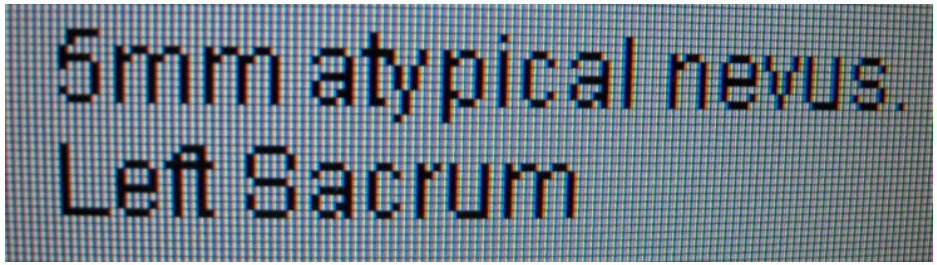
Precursor lesions were initiated by mutations of genes that are known to activate the mitogen-activated protein kinase pathway. Unequivocally benign lesions harbored *BRAF* V600E mutations exclusively, whereas those categorized as intermediate were enriched for *NRAS* mutations and additional driver mutations. A total of 77% of areas of intermediate lesions and melanomas in situ harbored *TERT* promoter mutations, a finding that indicates that these mutations are selected at an unexpectedly early stage of the neoplastic progression. Biallelic inactivation of *CDKN2A* emerged exclusively in invasive melanomas. *PTEN* and *TP53* mutations were found only in advanced primary melanomas. The point-mutation burden increased from benign through intermediate lesions to melanoma, with a strong signature of the effects of ultraviolet radiation detectable at all evolutionary stages. Copy-number alterations became prevalent only in invasive melanomas. Tumor heterogeneity became apparent in the form of genetically distinct subpopulations as melanomas progressed.

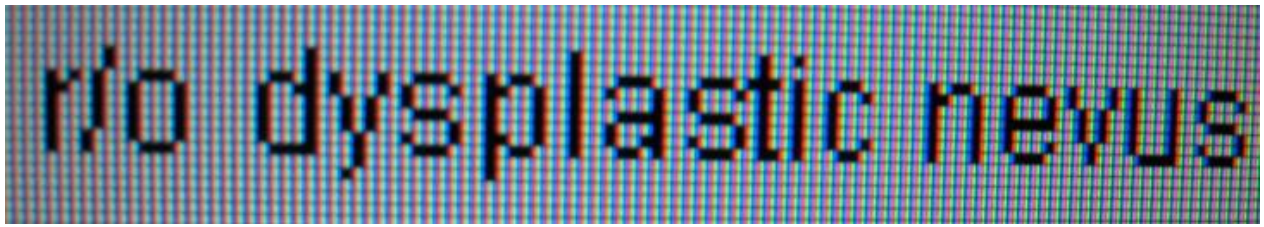
CONCLUSIONS

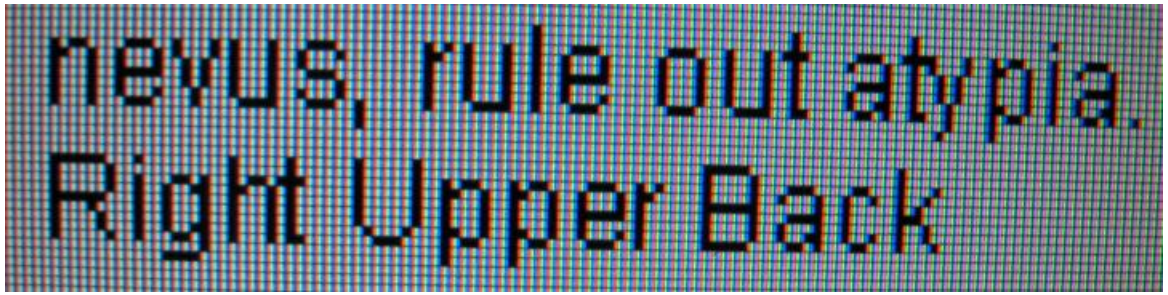
Our study defined the succession of genetic alterations during melanoma progression, showing distinct evolutionary trajectories for different melanoma subtypes. It identified an intermediate category of melanocytic neoplasia, characterized by the presence of more than one pathogenic genetic alteration and distinctive histopathological features. Finally, our study implicated ultraviolet radiation as a major factor in both the initiation and progression of melanoma. (Funded by the National Institutes of Health and others.)

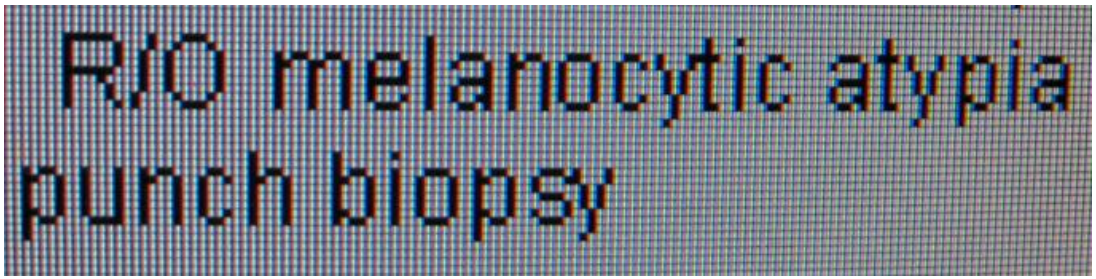
r/o atypia.


r/o atypia.


5mm atypical nevus.
Left Sacrum


r/o dysplastic nevus


nevus, rule out atypia.
Right Upper Back


R/O melanocytic atypia
punch biopsy

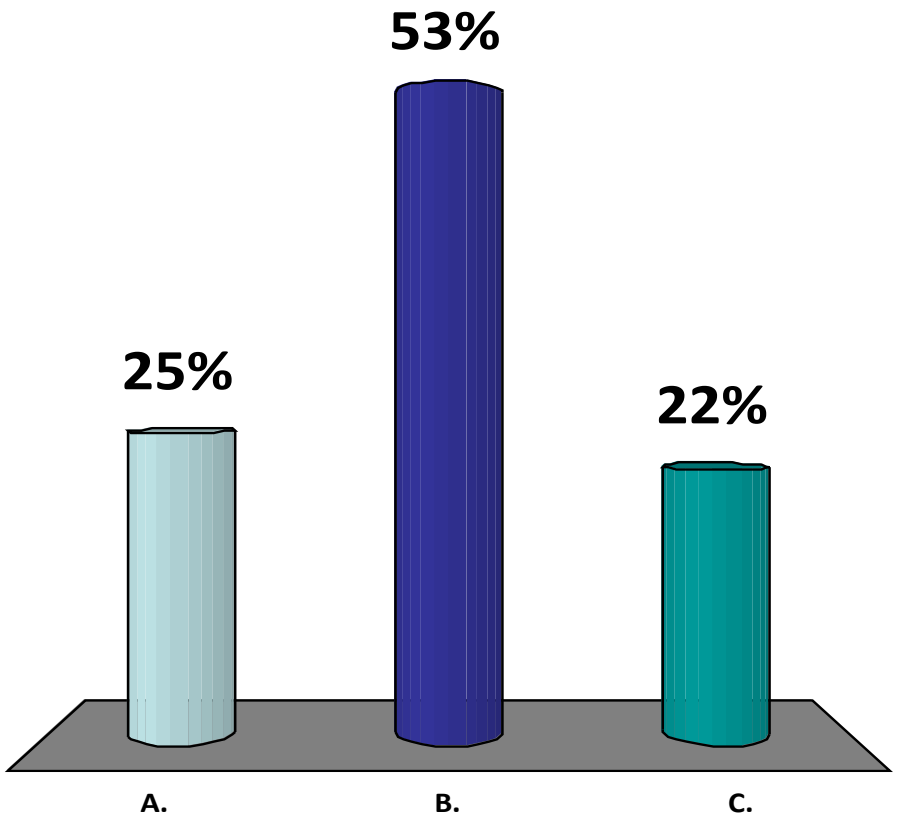
The current(ish) state of affairs…

Do you believe dysplastic (Clark) nevi are truly premalignant lesions?

A. Yes

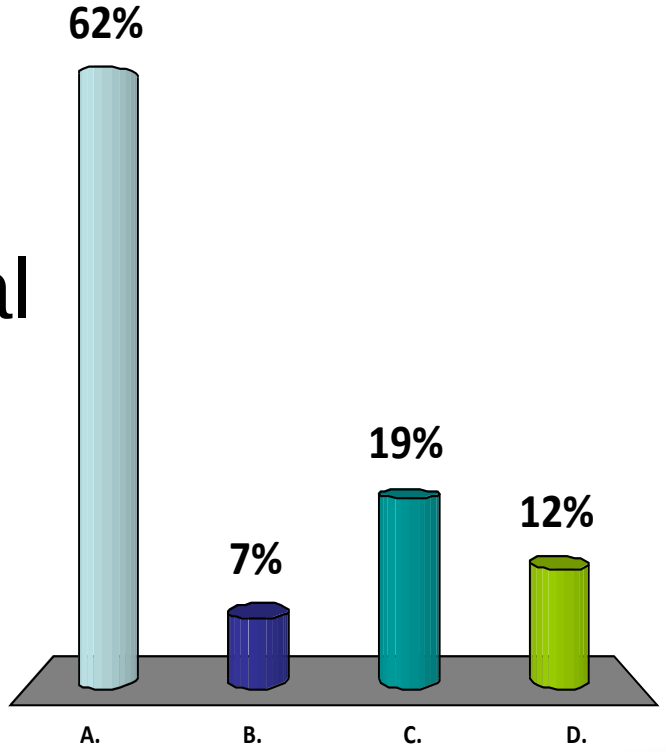
B. No

C. Unsure



How do you report “dysplastic nevi”?

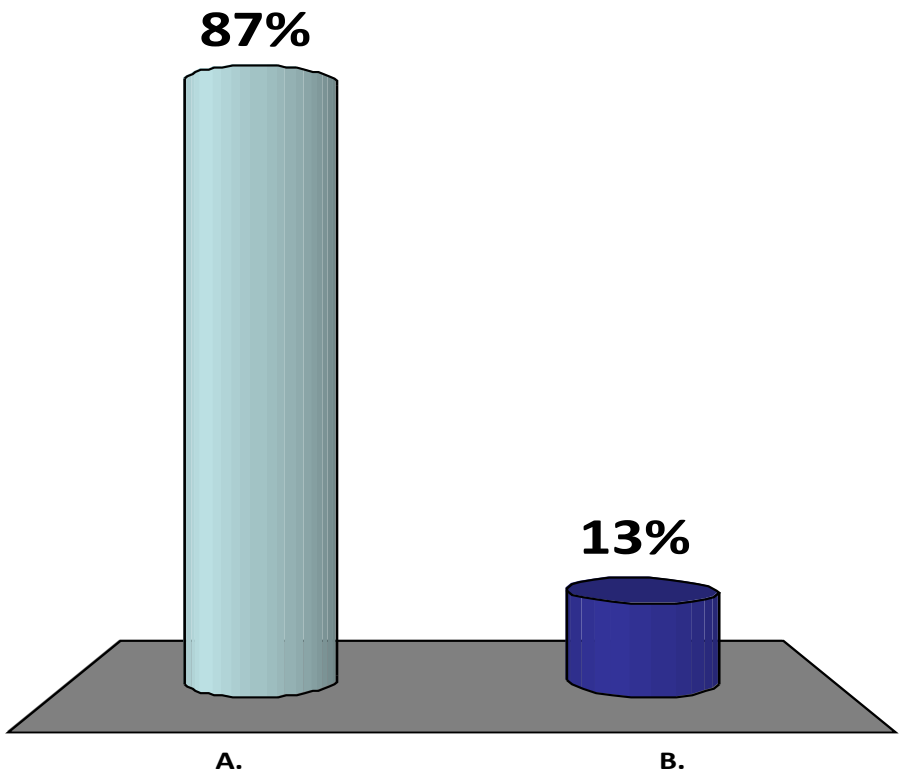
A. Dysplastic nevus
B. Clark nevus
C. Nevus with architectural disorder
D. Other



Do you assign a histologic "grade" to these nevi?

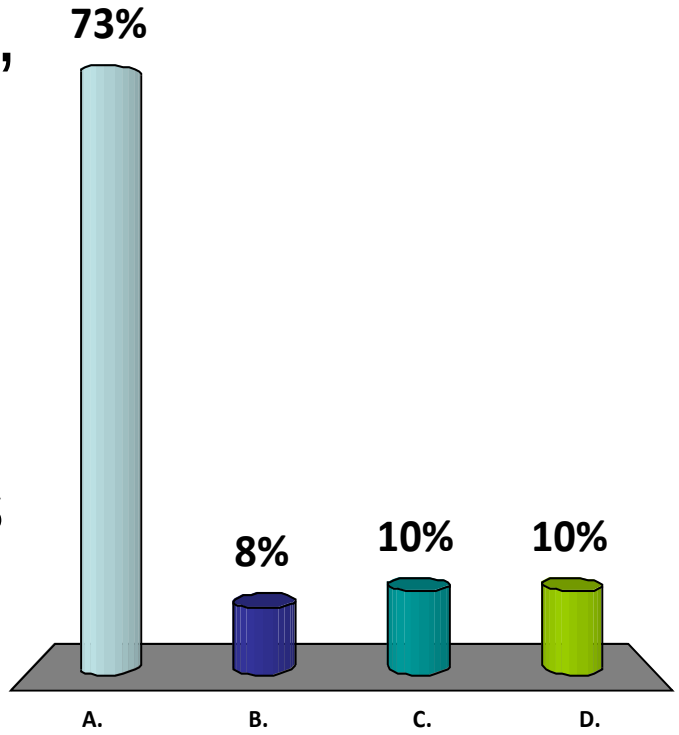
A. Yes

B. No



If yes, what grading system do you use?

A. Cytology as three grades (mild, moderate, severe)
B. Cytology and architecture as two separate grades
C. Cytology as two grades only
D. Other grading system



Origin of Familial Malignant Melanomas From Heritable Melanocytic Lesions

'The B-K Mole Syndrome'

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

(*Arch Dermatol* 114:732-738, 1978)

Journal of Medical Genetics, 1978, **15**, 352-356

Familial atypical multiple mole-melanoma syndrome

HENRY T. LYNCH, BERT C. FRICHOT, III, AND JANE F. LYNCH

From the Department of Preventive Medicine/Public Health, Creighton University, Omaha, Nebraska; and the Departments of Dermatology and Preventive Medicine/Public Health, Creighton and Nebraska University Health Foundation, Omaha Veterans Administration Hospital, Omaha, Nebraska, USA

SUMMARY A family is described showing concordance for malignant melanoma and a cutaneous phenotype characterised by multiple large moles of variable size and colour (reddish-brown to bright red) with pigmentary leakage. Transmission of the cutaneous phenotype in the subject family, and in several others currently under investigation, shows an inheritance pattern consistent with a simple autosomal dominant factor. This cutaneous phenotype signifying melanoma risk may now be added to an increasing body of knowledge dealing with cancer-related genodermatoses.

Brief history

- 1978 – Dr. Clark describes nevi associated with melanoma prone families
  - The B-K mole syndrome
- 1978 – Dr. Lynch describes a single multi-generational family with melanoma and nevi

Brief history

- 1980 – Dr. Elder and Clark describe ‘dysplastic nevi’ in a non-familial setting
  - Introduction of the term ‘dysplastic nevus syndrome’
    - Familial and sporadic variants
    - **Formally postulated that ‘dysplastic nevi’ are precursors of melanoma**

Dr. Wallace H. Clark, Jr.

The concept evolved…

Dr. David Elder

When you are frustrated by the pathology report and management of these lesions please send all complaints to…

REVIEW

Dysplastic nevus: Fact and fiction

Cliff O. Rosendahl, MBBS, PhD,[a] Jane M. Grant-Kels, MD,[b] and Syril Keena T. Que, MD[b]
Brisbane, Queensland, Australia, and Farmington, Connecticut

The term "dysplastic nevus" (DN) implies that this nevus exists as a distinct and defined entity of potential detriment to its host. We examine the current data, which suggest that this entity exists as histologically and possibly genetically different from common nevus, with some overlapping features. Studies show that a melanoma associated with a nevus is just as likely to arise in a common nevus as in DN. Furthermore, there is no evidence that a histologically defined DN evolves into a melanoma or that the presence of 1 or more DN on an individual patient confers any increased melanoma risk. We suggest that the term "dysplastic nevus" be abandoned so that the focus can shift to confirmed and relevant indicators of melanoma risk, including high nevus counts and large nevus size. (J Am Acad Dermatol 2015;73:507-12.)

Key words: B-K mole syndrome; *BRAF*; common nevus; congenital melanocytic nevus; cyclin-dependent kinase inhibitor 2A *(CDKN2A)*; dysplastic nevus; familial atypical multiple-mole melanoma; melanoma; *p16, p53*.

- Recommend abandoning the term "dysplastic nevus."
- Highlights melanoma risk is linked to high nevus counts and large nevus size

POINT/COUNTERPOINT

Point: What's in a name?

David E. Elder, MB, ChB, FRCPA
Philadelphia, Pennsylvania

Key words: diagnosis; dysplastic nevus; epidemiology; melanoma; nevus; risk.

J Am Acad Dermatol 2015;73:513-4

Counterpoint: The "dysplastic" nevus

What I do and do not believe

Clay J. Cockerell, MD
Dallas, Texas

Key word: dysplastic nevus.

J Am Acad Dermatol 2015;73:514-5

POINT/COUNTERPOINT

Point: What's in a name?

David E. Elder, MB, ChB, FRCPA
Philadelphia, Pennsylvania

- "Dysplastic nevi are benign neoplasms of melanocytes that are significant in relation to melanoma in 3 ways: as potential precursors, markers of increased risk, and simulants."
- "Dysplastic nevi are intermediate between common nevi and melanoma – clinically, microscopically and genomically."
- …in my opinion the term "mild dysplasia" should be abandoned."

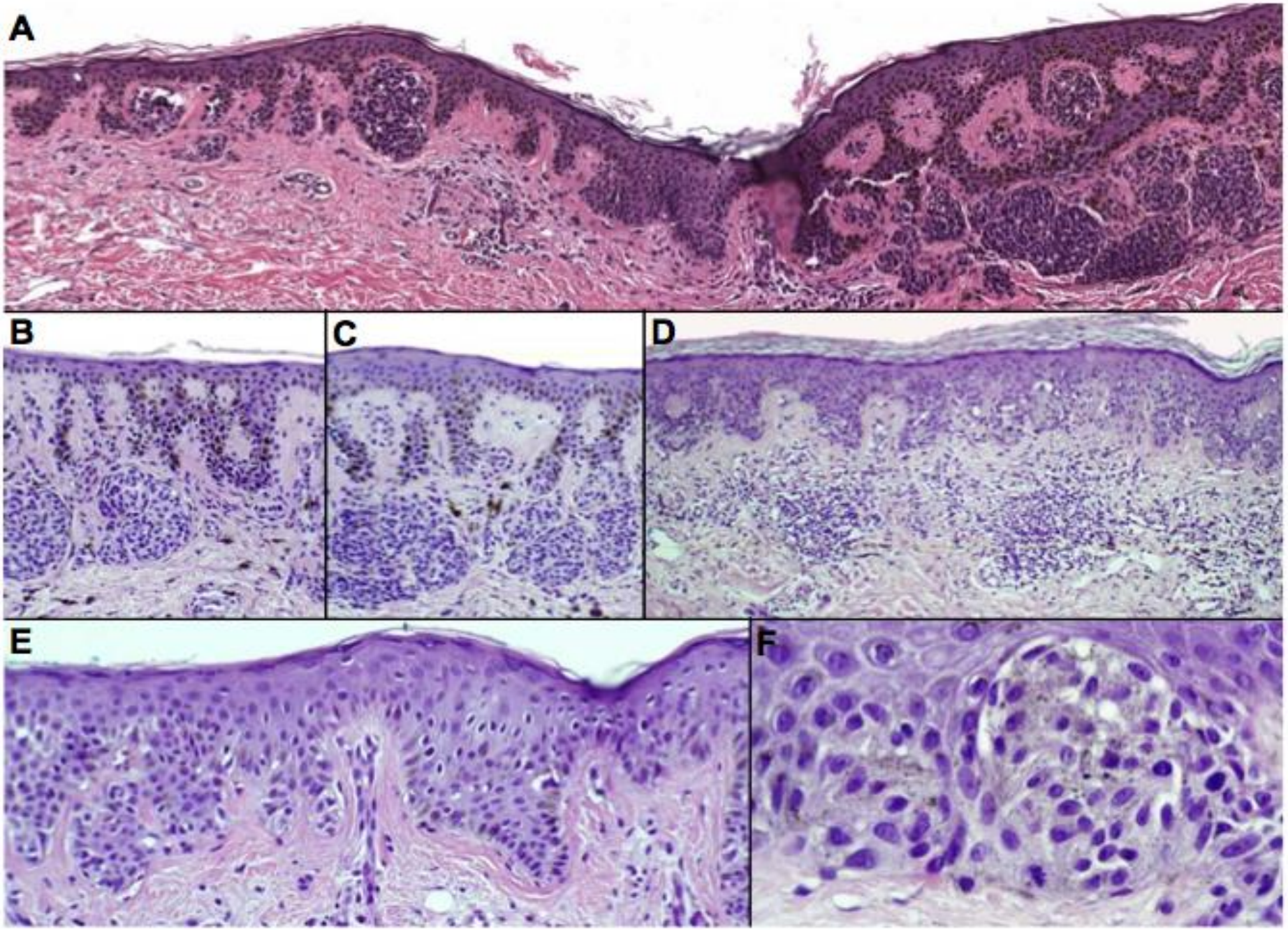
Counterpoint: The "dysplastic" nevus

What I do and do not believe

Clay J. Cockerell, MD
Dallas, Texas

- "I believe that most so-called 'severely dysplastic' are either melanoma or melanoma in situ arising in a nevus."
- "I believe it would be reasonable to change the name 'dysplastic' nevus."
- "I do not believe the name 'dysplastic' nevus will change anytime soon."

What is a dysplastic nevus?



Duffy K, Grossman D, J Am Acad Dermatol. 2012 Jul;67(1):1-16

Table II. Histologic criteria proposed by Clark et al[41]

Architecture	Nests bridge rete
	Nests at the side of rete
	Single cells between nests, nests predominating
	Lentiginous elongation of rete
	Anastomosis of rete
	Little or no pagetoid spread
Host response	Patchy lymphocytic infiltrate
	Eosinophilic fibroplasia
	Lamellar fibroplasia
	Prominent vessels
Cytology	Variable slight to moderate atypia
	Few (if any) mitoses
	Occasional macronuclei
	Scattered epithelioid nevus cells
	Scattered cells with finely granular melanin

Table III. World Health Organization criteria for the diagnosis of dysplastic nevi[42]

Major criteria*	Basilar proliferation of atypical melanocytes, extending at least three rete ridges beyond dermal component
	Organization of proliferation in lentiginous or epithelioid cell pattern
Minor criteria*	Lamellar or concentric eosinophilic fibrosis
	Neovascularization
	Inflammatory response
	Fusion of rete ridges

*The diagnosis of dysplastic nevi requires fulfillment of both major criteria and 2 minor criteria.

Table IV. European Organisation for Research and Treatment of Cancer Cooperative Group criteria[43]

Common nevus	<2 features noted below for dysplastic nevi
Dysplastic nevus	≥ 3 of the following features: marked junctional proliferation, irregular nevus nests, large nuclei, and lymphohistiocytic infiltrate
Melanoma in situ	Pagetoid growth Continuous junctional proliferation

TABLE 7. Duke Grading System for Clark Nevi

Architectural Disorder:	0	1
Junctional component nested at both edges	Yes	No
Good overall symmetry	Yes	No
More than 5% of nests cohesive	Yes	No
Suprabasal spread prominent, or present at edge	No	Yes
Confluence of >50% of proliferation	No	Yes
Single-cell proliferation absent or focal	Yes	No
Sum total:	____	
Key: (0-1) = Mild; (2-3) = Moderate; (4-6) = Severe		
Cytologic Atypia:	0	1
Nuclei round or oval, and euchromatic	Yes	No
Nuclei > basal-layer keratinocyte nuclei	No	Yes
Nucleoli prominent	No	Yes
Cell diameter > 2× basal-layer keratinocyte nuclei	No	Yes
Sum total:	____	
Key: (0-1) = Mild; (2) = Moderate; (3-4) = Severe		

NOTE. A separate score is obtained for architecture and cytology by assigning a value of 0 or 1 for each criterion and summing.

Shea CR, Vollmer RT, Prieto VG, Correlating architectural disorder and cytologic atypia in Clark (dysplastic) melanocytic nevi, Hum Pathol 1999, 30:500-5

“I know one when I see one.”

Duncan et. al., *J Invest Dermatol* 1993 100:318S-321S
Piepkorn et. al., *J Am Acad Dermatol* 1994,30:707-714
Weinstock et. al., *Arch Dermatol* 1997,133:953-958
Clemente et.al., 1991 *Hum Pathol* 22:313-319

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

The Genetic Evolution of Melanoma from Precursor Lesions

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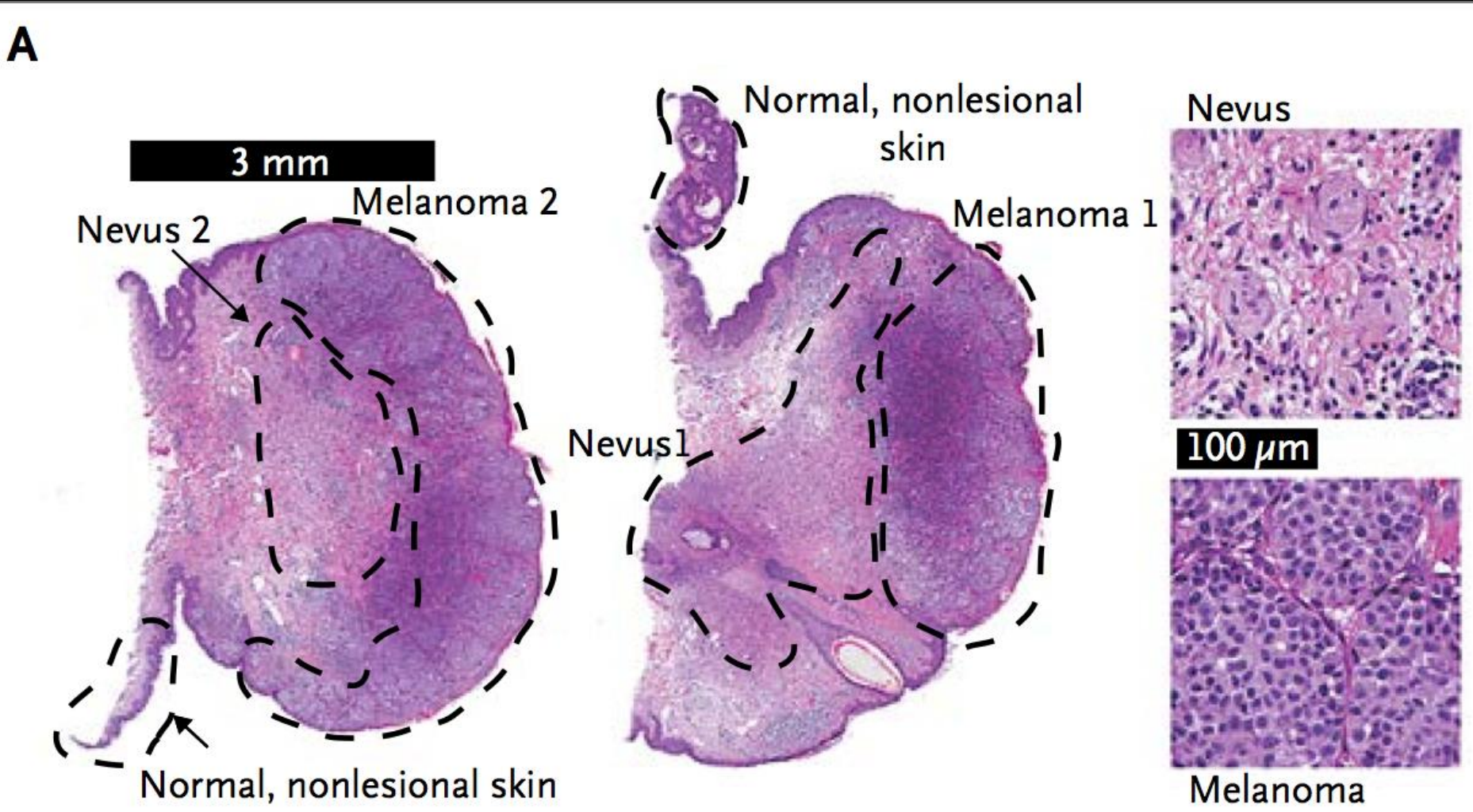
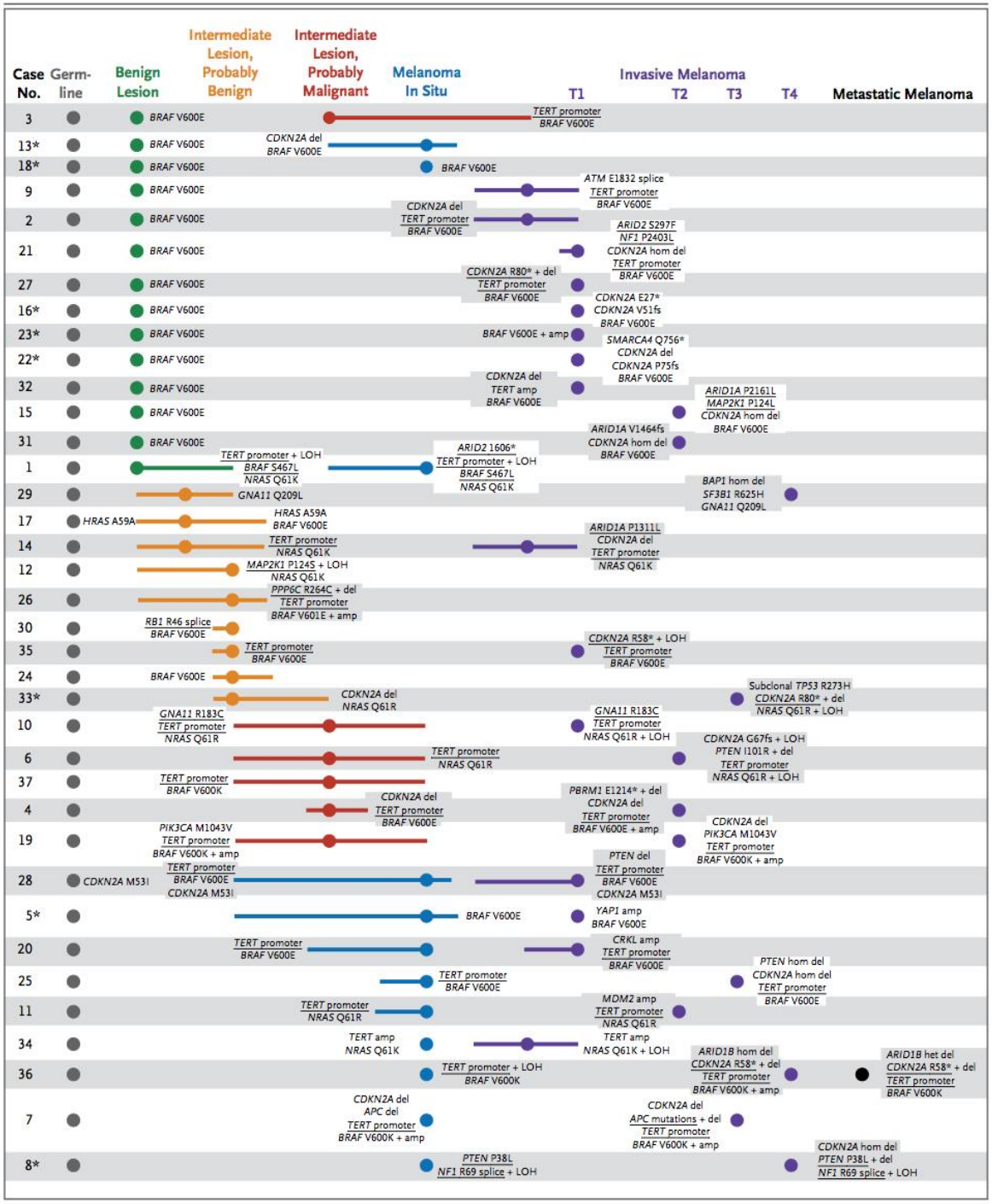
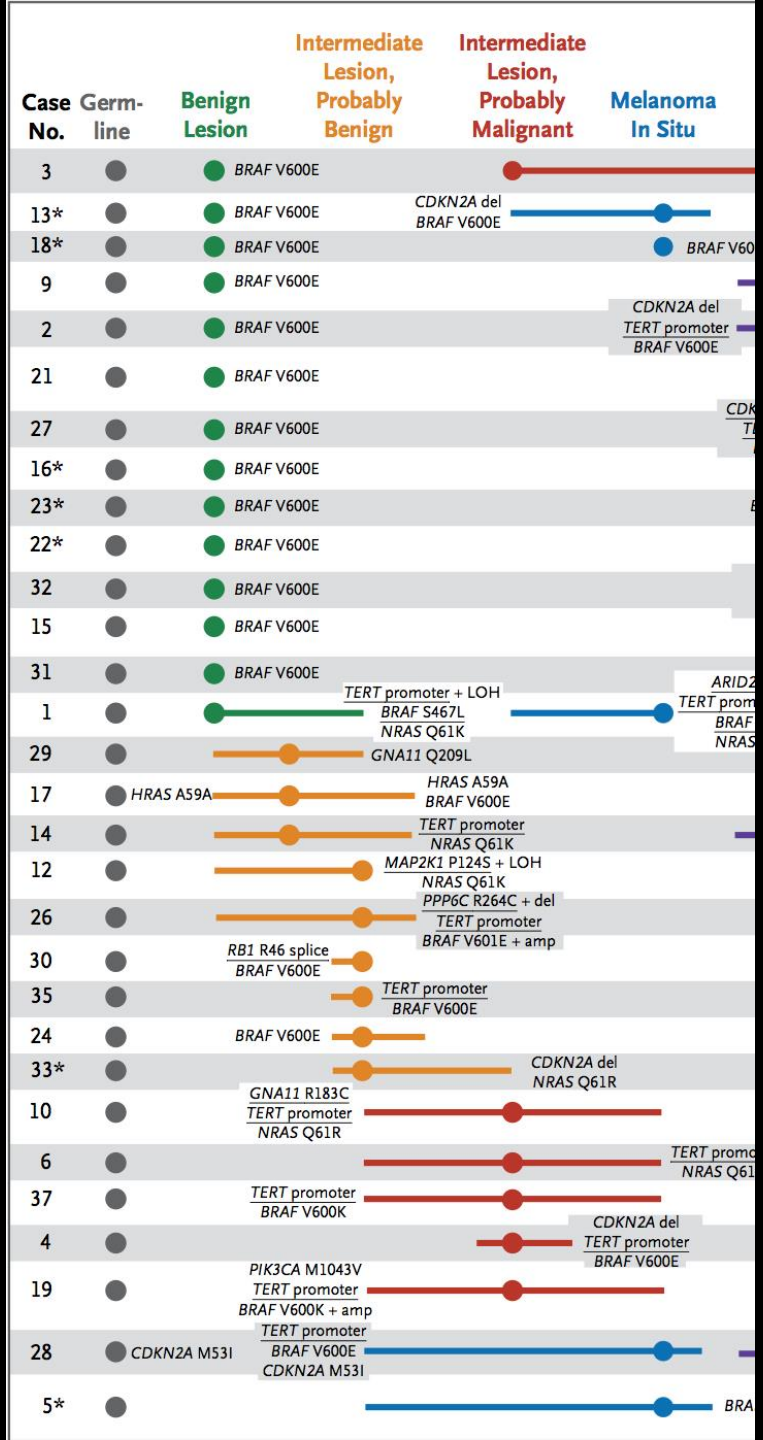
N ENGL J MED 373;20 NEJM.ORG NOVEMBER 12, 2015


A
3 mm
Melanoma 2
Nevus 2
Normal, nonlesional skin
Normal, nonlesional skin
Melanoma 1
Nevus1
Nevus
100 μm
Melanoma


Case No.
Germ-line
Benign Lesion
Intermediate Lesion, Probably Benign
Intermediate Lesion, Probably Malignant
Melanoma In Situ
Invasive Melanoma
T1
T2
T3
T4
Metastatic Melanoma
3
BRAF V600E
TERT promoter
BRAF V600E
13*
BRAF V600E
CDKN2A del
BRAF V600E
18*
BRAF V600E
BRAF V600E
9
BRAF V600E
ATM E1832 splice
TERT promoter
BRAF V600E
2
BRAF V600E
CDKN2A del
TERT promoter
BRAF V600E
21
BRAF V600E
ARID2 S297F
NF1 P2403L
CDKN2A hom del
TERT promoter
BRAF V600E
27
BRAF V600E
CDKN2A R80* + del
TERT promoter
BRAF V600E
16*
BRAF V600E
CDKN2A E27*
CDKN2A V51fs
BRAF V600E
23*
BRAF V600E
BRAF V600E + amp
22*
BRAF V600E
SMARCA4 Q756*
CDKN2A del
CDKN2A P75fs
BRAF V600E
32
BRAF V600E
CDKN2A del
TERT amp
BRAF V600E
15
BRAF V600E
ARID1A P2161L
MAP2K1 P124L
CDKN2A hom del
BRAF V600E
31
BRAF V600E
ARID1A V1464fs
CDKN2A hom del
BRAF V600E
1
TERT promoter + LOH
BRAF S467L
NRAS Q61K
ARID2 1606*
TERT promoter + LOH
BRAF S467L
NRAS Q61K
29
GNA11 Q209L
BAP1 hom del
SF3B1 R625H
GNA11 Q209L
17
HRAS A59A
HRAS A59A
BRAF V600E
14
TERT promoter
NRAS Q61K
ARID1A P1311L
CDKN2A del
TERT promoter
NRAS Q61K
12
MAP2K1 P124S + LOH
NRAS Q61K
26
PPP6C R264C + del
TERT promoter
BRAF V601E + amp
30
RB1 R46 splice
BRAF V600E
35
TERT promoter
BRAF V600E
CDKN2A R58* + LOH
TERT promoter
BRAF V600E
24
BRAF V600E
33*
CDKN2A del
NRAS Q61R
Subclonal TP53 R273H
CDKN2A R80* + del
NRAS Q61R + LOH
10
GNA11 R183C
TERT promoter
NRAS Q61R
GNA11 R183C
TERT promoter
NRAS Q61R + LOH
6
TERT promoter
NRAS Q61R
CDKN2A G67fs + LOH
PTEN I101R + del
TERT promoter
NRAS Q61R + LOH
37
TERT promoter
BRAF V600K
4
CDKN2A del
TERT promoter
BRAF V600E
PBRM1 E1214* + del
CDKN2A del
TERT promoter
BRAF V600E + amp
19
PIK3CA M1043V
TERT promoter
BRAF V600K + amp
CDKN2A del
PIK3CA M1043V
TERT promoter
BRAF V600K + amp
28
CDKN2A M53I
TERT promoter
BRAF V600E
CDKN2A M53I
PTEN del
TERT promoter
BRAF V600E
CDKN2A M53I
5*
BRAF V600E
YAP1 amp
BRAF V600E
20
TERT promoter
BRAF V600E
CRKL amp
TERT promoter
BRAF V600E
25
TERT promoter
BRAF V600E
PTEN hom del
CDKN2A hom del
TERT promoter
BRAF V600E
11
TERT promoter
NRAS Q61R
MDM2 amp
TERT promoter
NRAS Q61R
34
TERT amp
NRAS Q61K
TERT amp
NRAS Q61K + LOH
36
TERT promoter + LOH
BRAF V600K
ARID1B hom del
CDKN2A R58* + del
TERT promoter
BRAF V600K + amp
ARID1B het del
CDKN2A R58* + del
TERT promoter
BRAF V600K
7
CDKN2A del
APC del
TERT promoter
BRAF V600K + amp
CDKN2A del
APC mutations + del
TERT promoter
BRAF V600K + amp
8*
PTEN P38L
NF1 R69 splice + LOH
CDKN2A hom del
PTEN P38L + del
NF1 R69 splice + LOH


Case No.
Germ-line
Benign Lesion
Intermediate Lesion, Probably Benign
Intermediate Lesion, Probably Malignant
Melanoma In Situ
3
BRAF V600E
13*
BRAF V600E
CDKN2A del
BRAF V600E
18*
BRAF V600E
BRAF V60
9
BRAF V600E
2
BRAF V600E
CDKN2A del
TERT promoter
BRAF V600E
21
BRAF V600E
27
BRAF V600E
16*
BRAF V600E
23*
BRAF V600E
22*
BRAF V600E
32
BRAF V600E
15
BRAF V600E
31
BRAF V600E
1
TERT promoter + LOH
BRAF S467L
NRAS Q61K
29
GNA11 Q209L
17
HRAS A59A
HRAS A59A
BRAF V600E
14
TERT promoter
NRAS Q61K
12
MAP2K1 P124S + LOH
NRAS Q61K
26
PPP6C R264C + del
TERT promoter
BRAF V601E + amp
30
RB1 R46 splice
BRAF V600E
35
TERT promoter
BRAF V600E
24
BRAF V600E
33*
CDKN2A del
NRAS Q61R
10
GNA11 R183C
TERT promoter
NRAS Q61R
6
37
TERT promoter
BRAF V600K
4
CDKN2A del
TERT promoter
BRAF V600E
19
PIK3CA M1043V
TERT promoter
BRAF V600K + amp
28
CDKN2A M53I
TERT promoter
BRAF V600E
CDKN2A M53I
5*

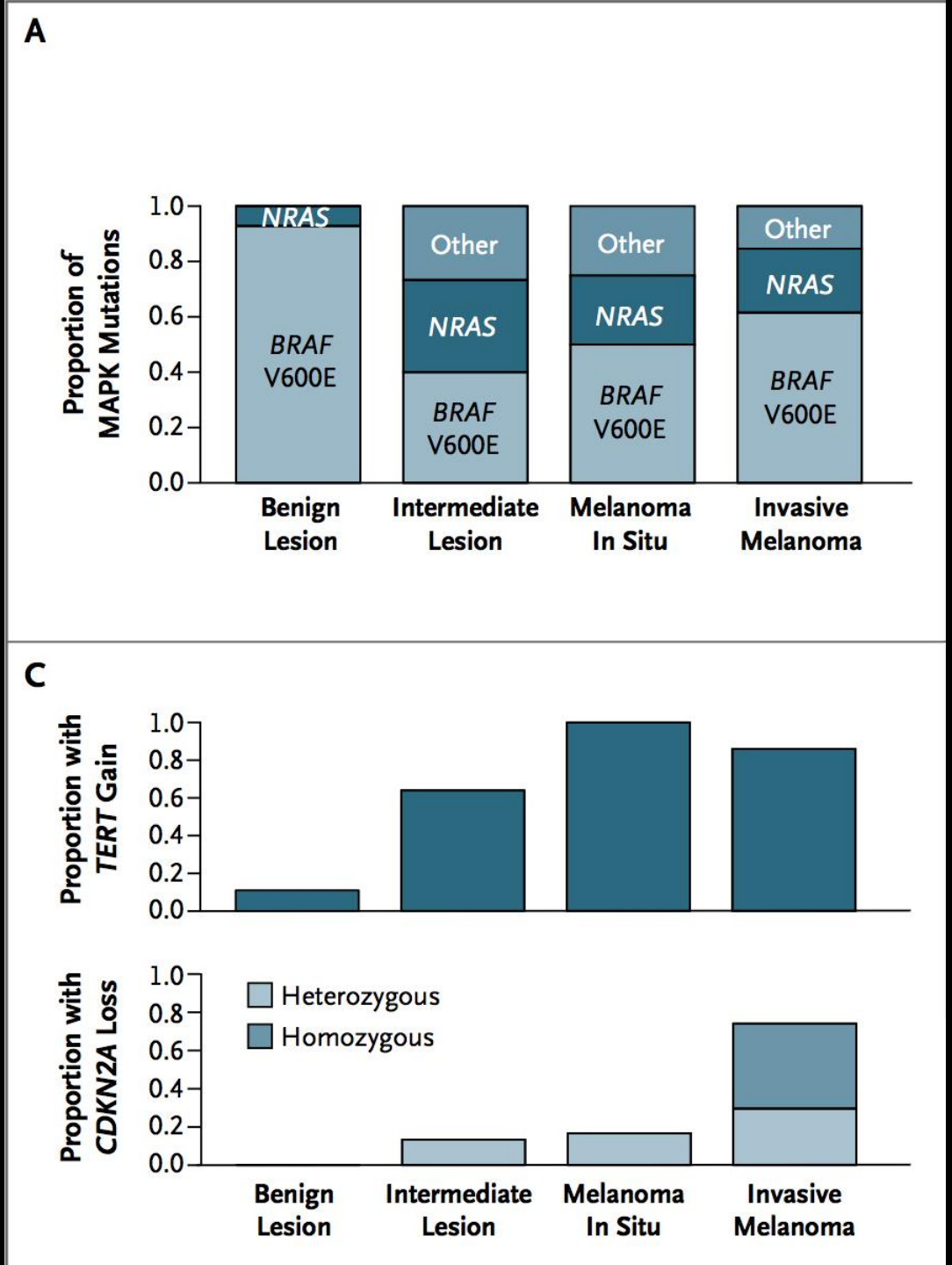
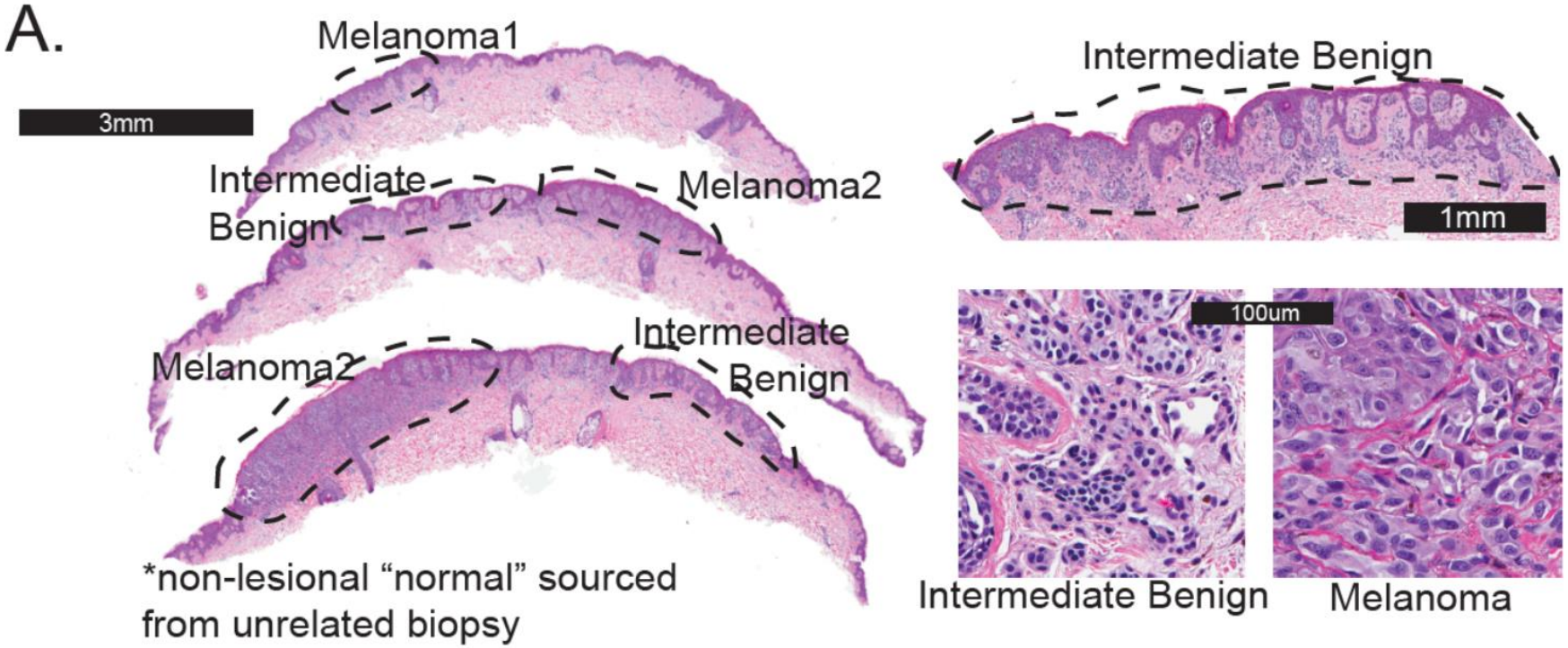
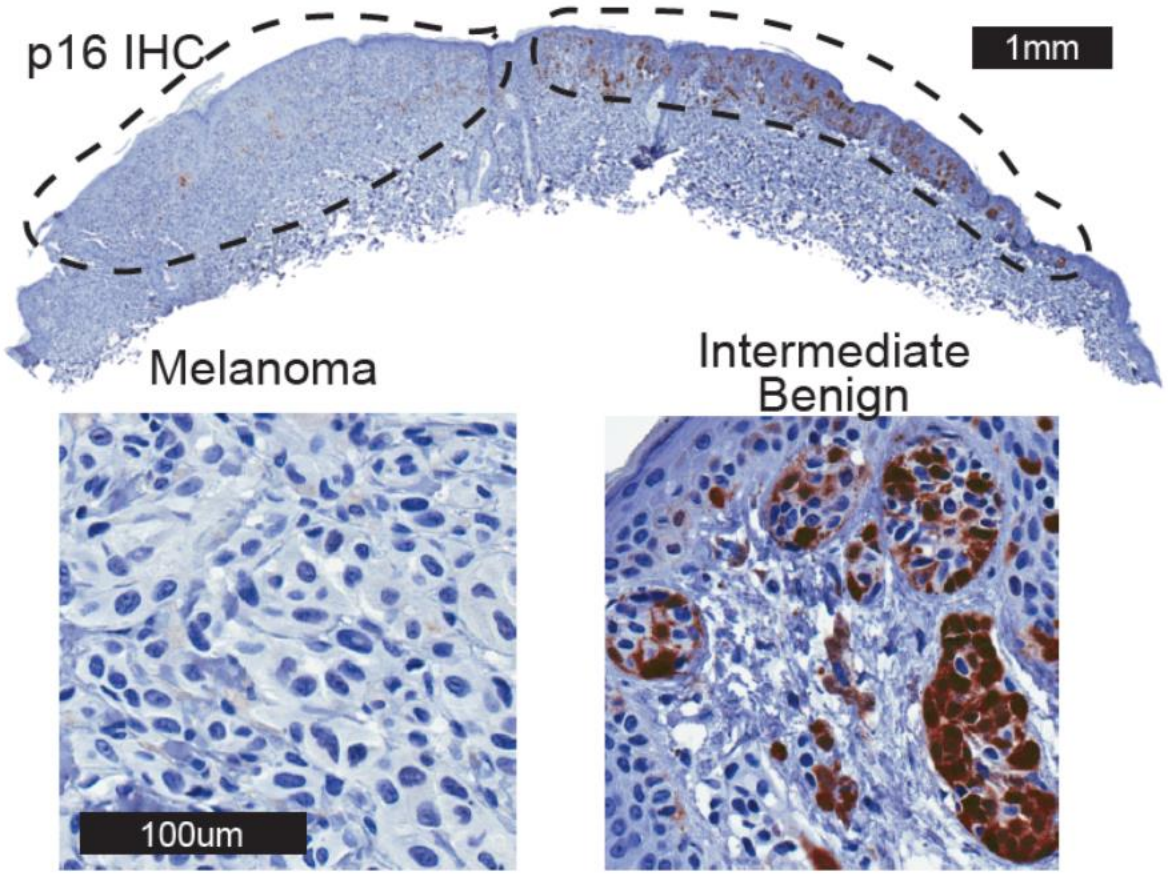

A
Proportion of MAPK Mutations
1.0
0.8
0.6
0.4
0.2
0.0
NRAS
BRAF V600E
Other
NRAS
BRAF V600E
Other
NRAS
BRAF V600E
Other
NRAS
BRAF V600E
Benign Lesion
Intermediate Lesion
Melanoma In Situ
Invasive Melanoma
C
Proportion with TERT Gain
Proportion with CDKN2A Loss
Heterozygous
Homozygous
Benign Lesion
Intermediate Lesion
Melanoma In Situ
Invasive Melanoma

Figure S34. Case 35.



Case No.	Germ-line	Benign Lesion	Intermediate Lesion, Probably Benign	Intermediate Lesion, Probably Malignant	Melanoma In Situ	Invasive Melanoma T1	T2	T3	T4	Metastatic Melanoma
35	●		— *TERT* promoter / *BRAF* V600E			● *CDKN2A* R58* + LOH / *TERT* promoter / *BRAF* V600E				

E.



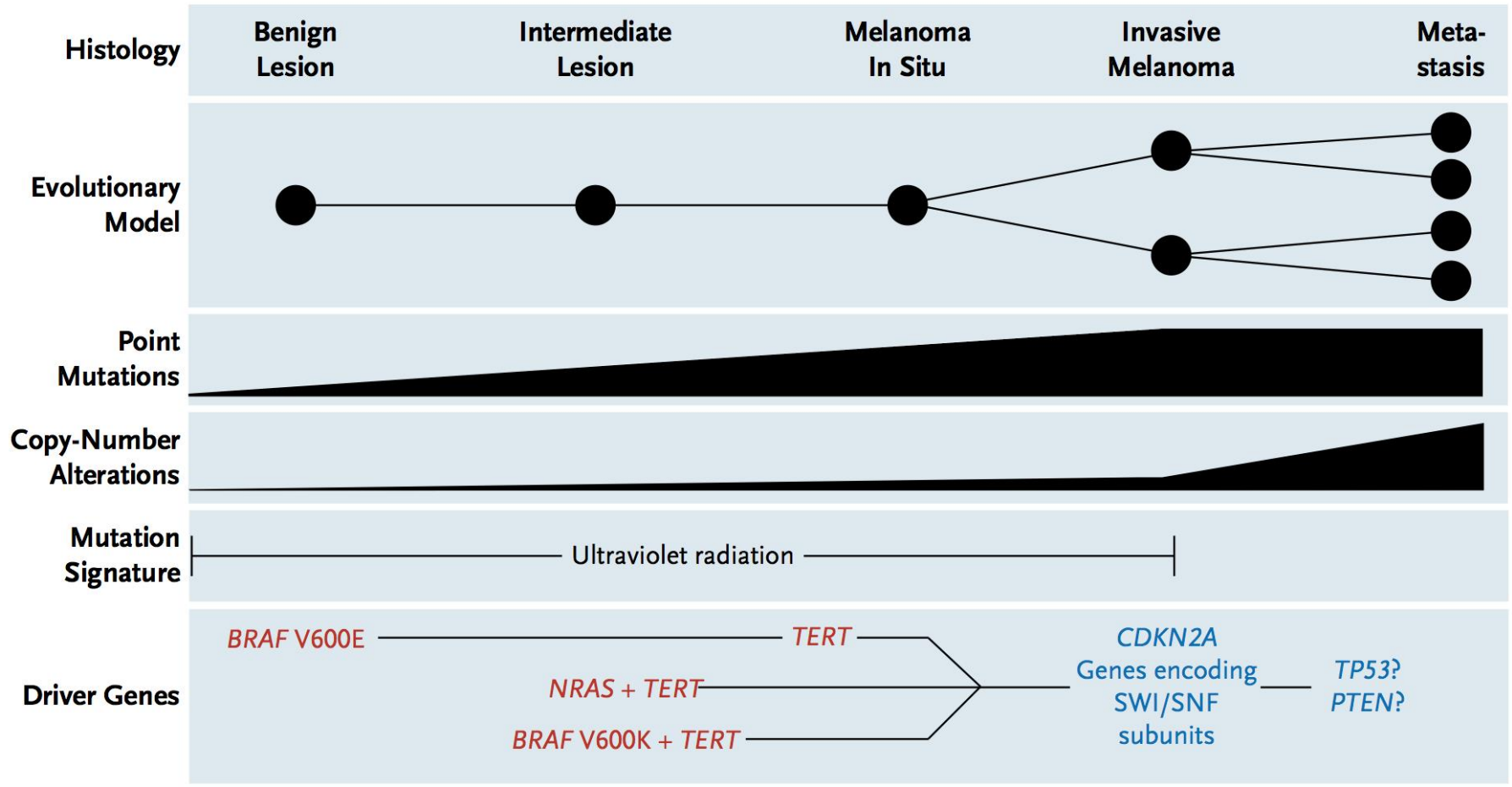


Figure 4. Proposed Models for Progression of Melanomas Developing on Sun-Exposed Sites.

Mutations in nevi

- Common nevi have a high rate of BRAF V600E mutations
- Sporadic dysplastic nevi appear to be enriched for NRAS and BRAF non-V600E mutations
- Recurrent TERT promoter mutations in a significant portion of dysplastic nevi

J Cutan Pathol 2015: 42: 244–252
doi: 10.1111/cup.12475
John Wiley & Sons. Printed in Singapore

Journal of
Cutaneous Pathology

Clinical validation of a gene expression signature that differentiates benign nevi from malignant melanoma

Background: Histopathologic examination is sometimes inadequate for accurate and reproducible diagnosis of certain melanocytic neoplasms. As a result, more sophisticated and objective methods have been sought. The goal of this study was to identify a gene expression signature that reliably differentiated benign and malignant melanocytic lesions and evaluate its potential clinical applicability. Herein, we describe the development of a gene expression signature and its clinical validation using multiple independent cohorts of melanocytic lesions representing a broad spectrum of histopathologic subtypes.

Methods: Using quantitative reverse-transcription polymerase chain reaction (PCR) on a selected set of 23 differentially expressed genes, and by applying a threshold value and weighting algorithm, we developed a gene expression signature that produced a score that differentiated benign nevi from malignant melanomas.

Loren E. Clarke[1,†], B.M. Warf[1,†], Darl D. Flake II[2], Anne-Renee Hartman[1], Steven Tahan[3], Christopher R. Shea[4], Pedram Gerami[5], Jane Messina[6], Scott R. Florell[7], Richard J. Wenstrup[1], Kristen Rushton[1], Kirstin M. Roundy[1], Colleen Rock[1], Benjamin Roa[1], Kathryn A. Kolquist[1], Alexander Gutin[2], Steven Billings[8] and Sancy Leachman[9]

[1]Myriad Genetic Laboratories, Inc., Salt Lake City, UT, USA,
[2]Myriad Genetics, Inc., Salt Lake City, UT, USA,
[3]Harvard Medical School and Beth Israel Deaconess Medical Center, Boston, MA, USA,

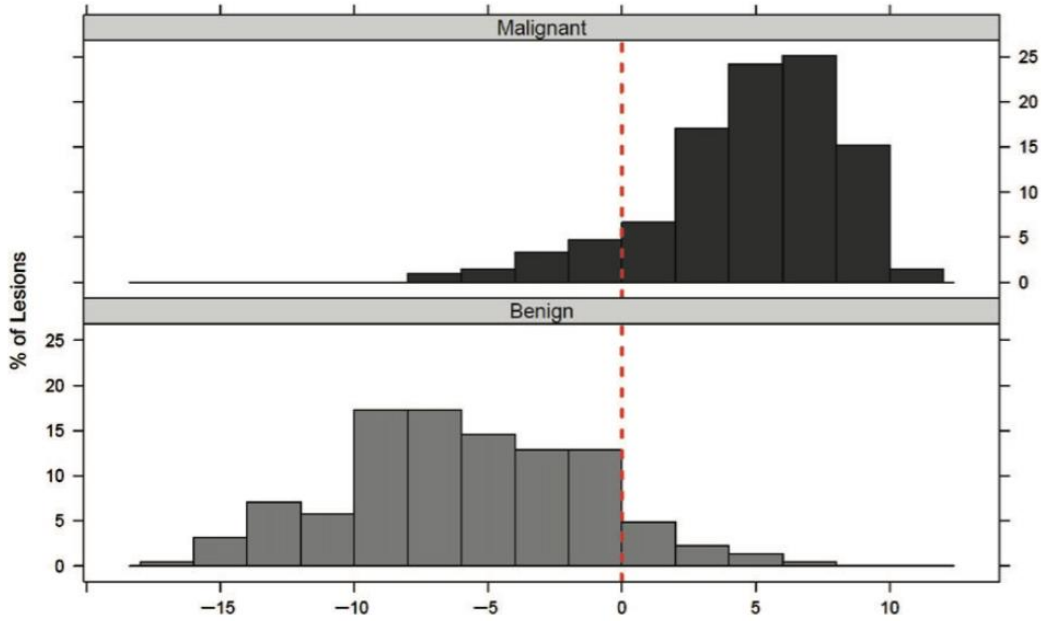


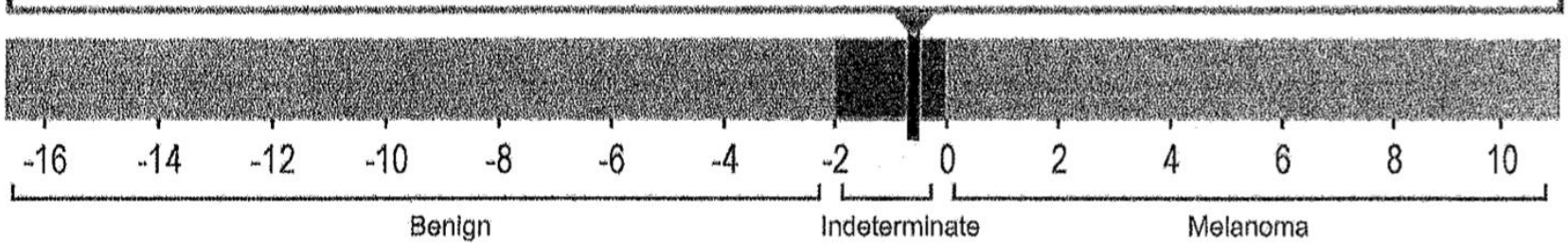
Fig. 3. Distribution of diagnostic scores in the clinical validation cohort.

Table 3. Performance of the signature within individual subtypes*

	Signature classification		Signature performance	
Pathologist classification	Malignant	Benign	Sensitivity	Specificity
All melanomas			90%	
Superficial spreading	90	15	86%	
Nodular	37	1	97%	
Lentigo maligna	28	3	90%	
All nevi†				**91%**
Compound	6	95		94%
Intradermal	1	40		98%

*Results reported only for subtypes with ≥30 samples.
†Compound nevi group contained 52 dysplastic nevi.

Myriad myPath™ Melanoma Score: **-0.6**



Myriad myPath™ Melanoma Score Classification

RESULT DESCRIPTION:

Myriad myPath™ Melanoma utilizes a molecular signature measured by qRT-PCR that would classify a sample as malignant, benign or indeterminate. This graph shows your patient's Score relative to Myriad myPath™ Melanoma Scores according to the range of benign and malignant lesions in the independent validation cohort with a threshold of "0".

- For Scores from -16.7 to -2.1 the gene signature classification is benign; for Scores from -2.0 to -0.1 the gene signature classification is indeterminate (*less than 10% of the cases); for Scores from 0 to +11.1 the gene signature classification is malignant melanoma.
- A Score range of -16.7 and +11.1 was established in the validation study[1] and Scores within this range will be reported. Scores outside of the validated range may lead to test cancelation or follow-up with the ordering physician.
- Individual lesions may or may not be representative of this cohort.

Table 3

Change in pre-test and post-test diagnosis.

Diagnosis	Pre-test	Post-test	Change
All diagnostically challenging cases (n = 218)			
Benign	23 (10.6%)	89 (40.8%)	+66 (30.2%)
Malignant	20 (9.2%)	47 (21.6%)	+27 (12.4%)
Indeterminate	175 (80.3%)	82 (37.6%)	−93 (−42.7%)
Atypical junctional melanocytic proliferation (n = 44)			
Benign	1 (2.3%)	12 (27.3%)	+11 (25.0%)
Malignant	1 (2.3%)	9 (20.5%)	+8 (18.2%)
Indeterminate	42 (95.5%)	23 (52.3%)	−19 (−43.2%)
Dysplastic nevus (n = 40)			
Benign	13 (32.5%)	25 (62.5%)	+12 (30.0%)
Malignant	0	6 (15.0%)	+6 (15.0%)
Indeterminate	27 (67.5%)	9 (22.5%)	−18 (−45.0%)
Atypical Spitz tumor (n = 38)			
Benign	0	12 (31.6%)	+12 (31.6%)
Malignant	0	3 (7.9%)	+3 (7.9%)
Indeterminate	38 (100.0%)	23 (60.5%)	−15 (−39.5%)

Cockerell et al. Medicine (2016) 95:40

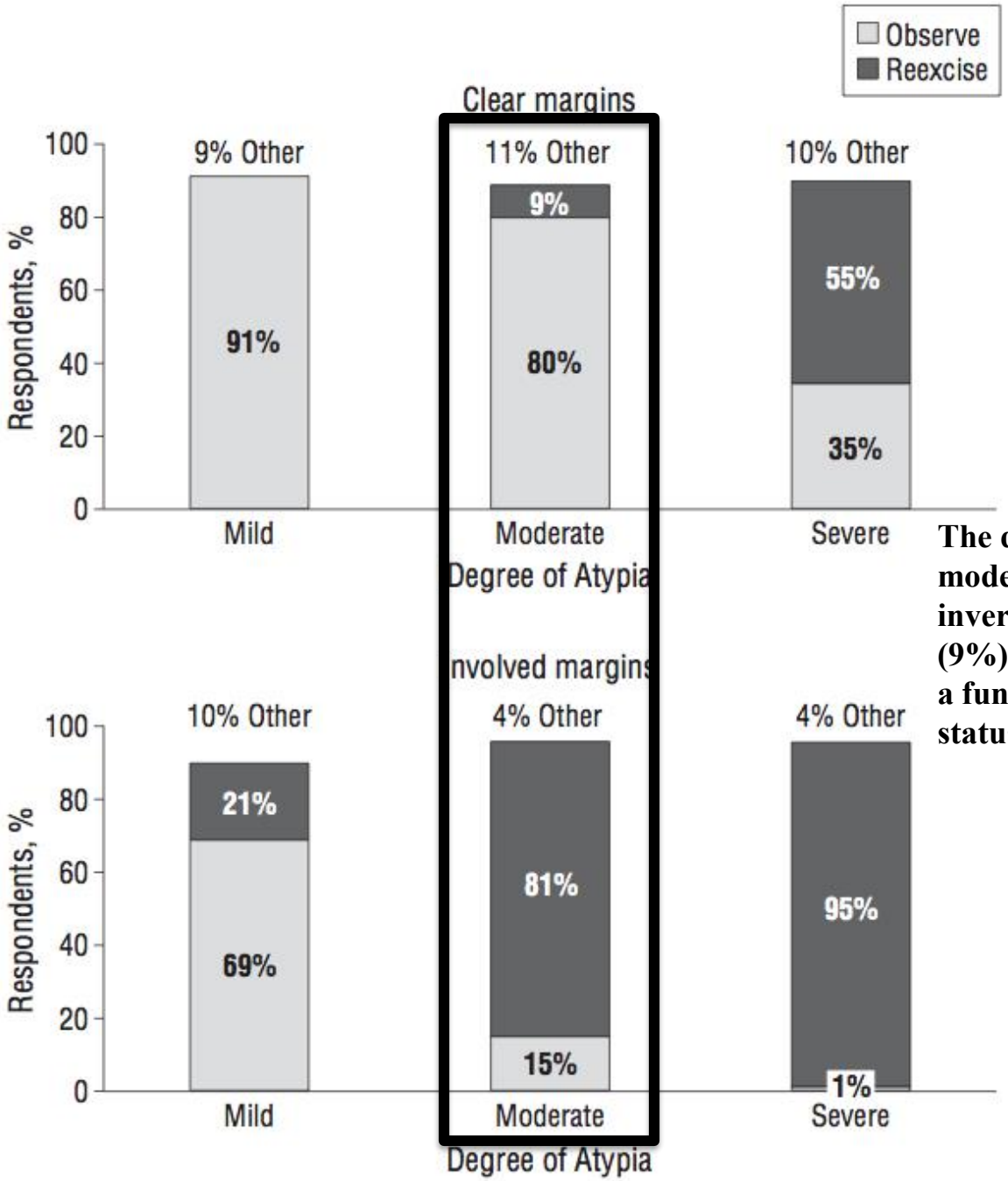
What do we do now?

Clinical decision making based on histopathologic grading and margin status of dysplastic nevi

Keith L.Duffy, MD,[a] , David J. Mann, MD,[b] Vesna Petronic-Rosic, MD,[b] and Christopher R. Shea, MD [b]

Salt Lake City, Utah and Chicago, IL

Arch Dermatol. 2012 Feb;148(2):259-60



The decision to re-excise moderately dysplastic nevi inverted from a minority (9%) to a majority (81%) as a function of positive margin status.

JAMA Dermatology | Original Investigation

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

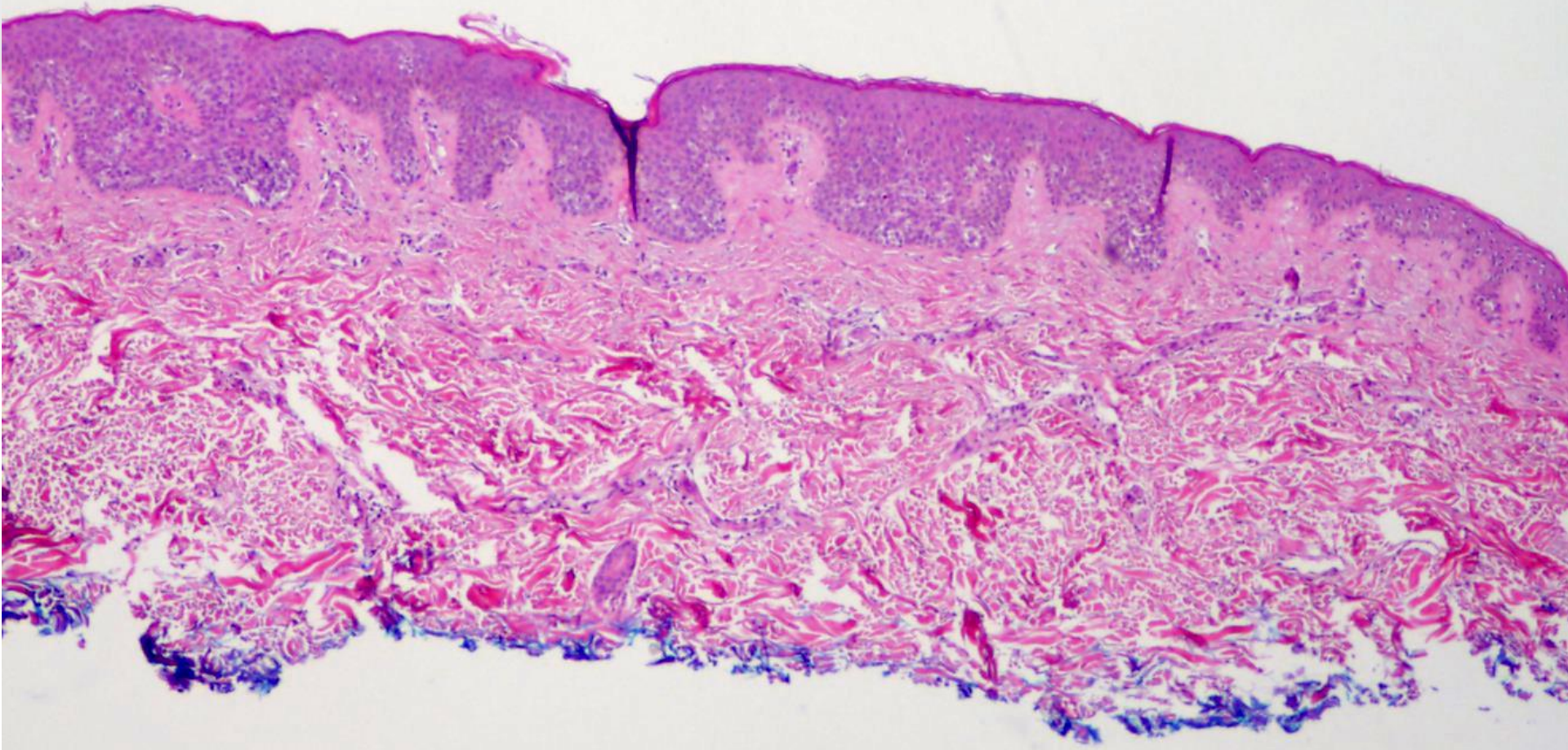
Caroline C. Kim, MD; Elizabeth G. Berry, MD; Michael A. Marchetti, MD; Susan M. Swetter, MD; Geoffrey Lim, MD; Douglas Grossman, MD, PhD; Clara Curiel-Lewandrowski, MD; Emily Y. Chu, MD, PhD; Michael E. Ming, MD, MSCE; Kathleen Zhu, BA; Meera Brahmbhatt, MD; Vijay Balakrishnan, BS; Michael J. Davis, BMus; Zachary Wolner, BA; Nathaniel Fleming, BA; Laura K. Ferris, MD, PhD; John Nguyen, BA; Oleksandr Trofymenko, BA; Yuan Liu, PhD; Suephy C. Chen, MD, MS; for the Pigmented Lesion Subcommittee, Melanoma Prevention Working Group

JAMA Dermatol. 2018;154(12):1401-1408. doi:10.1001/jamadermatol.2018.3359
Published online October 10, 2018.

Results

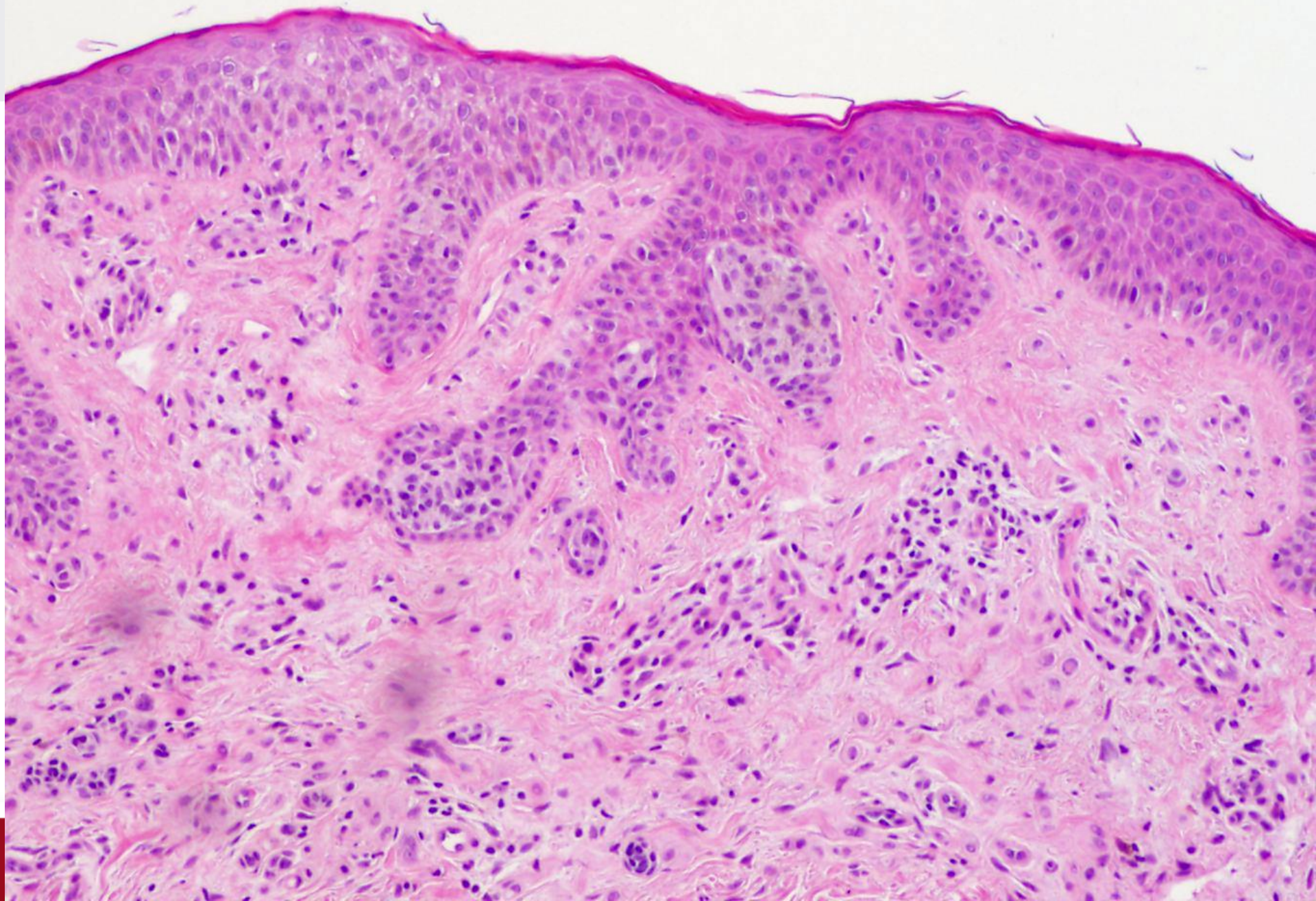
- 467 moderately dysplastic nevi with positive histologic margins observed for >3 years
  - Median f/u 6.9 years
- **NO** cases of cutaneous melanoma developed at those sites
- 100 patients (22.8%) developed a cutaneous melanoma at a separate site

41 year old female left lower back
40x

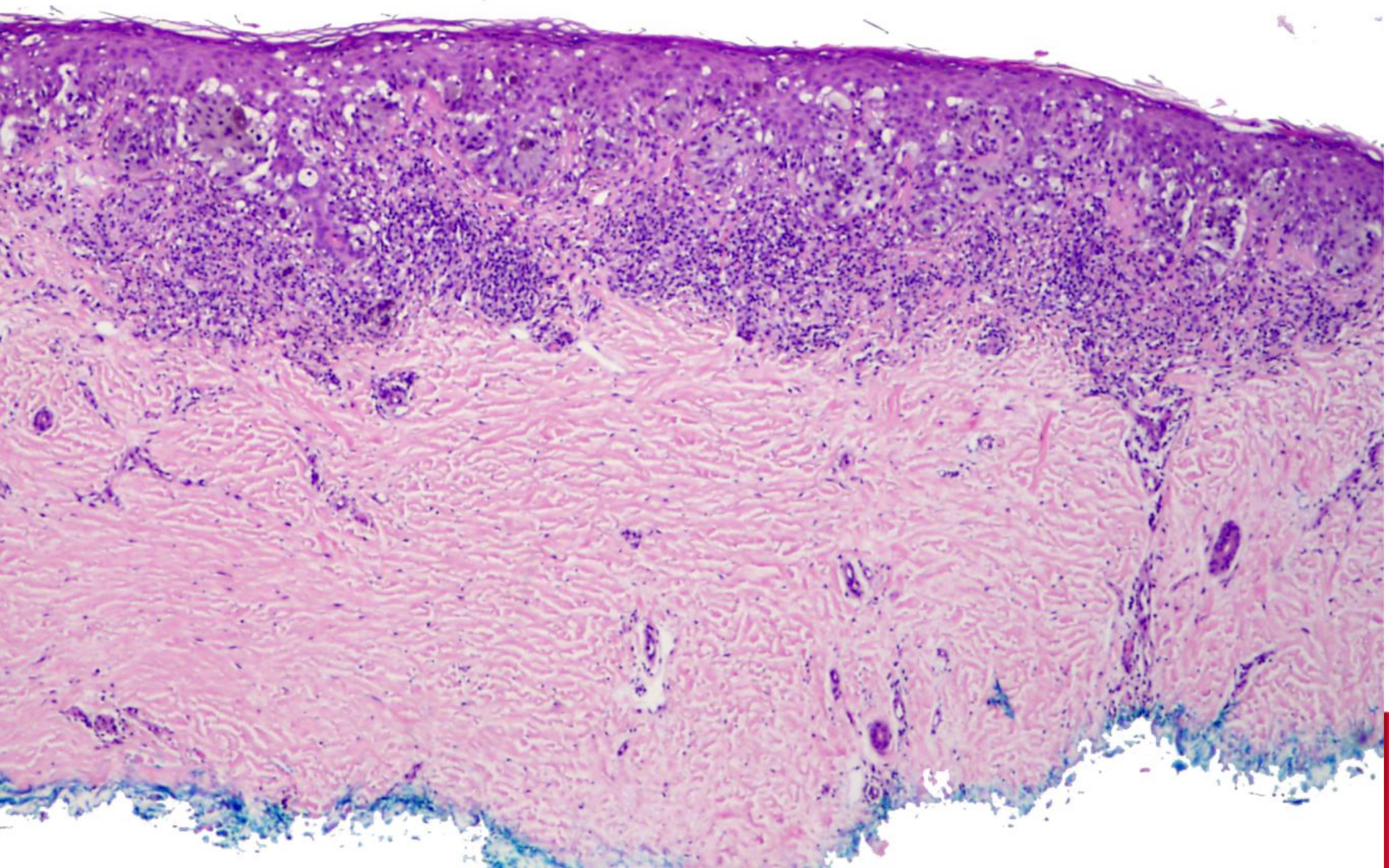


Do you think there is a TERT promoter mutation in this lesion?

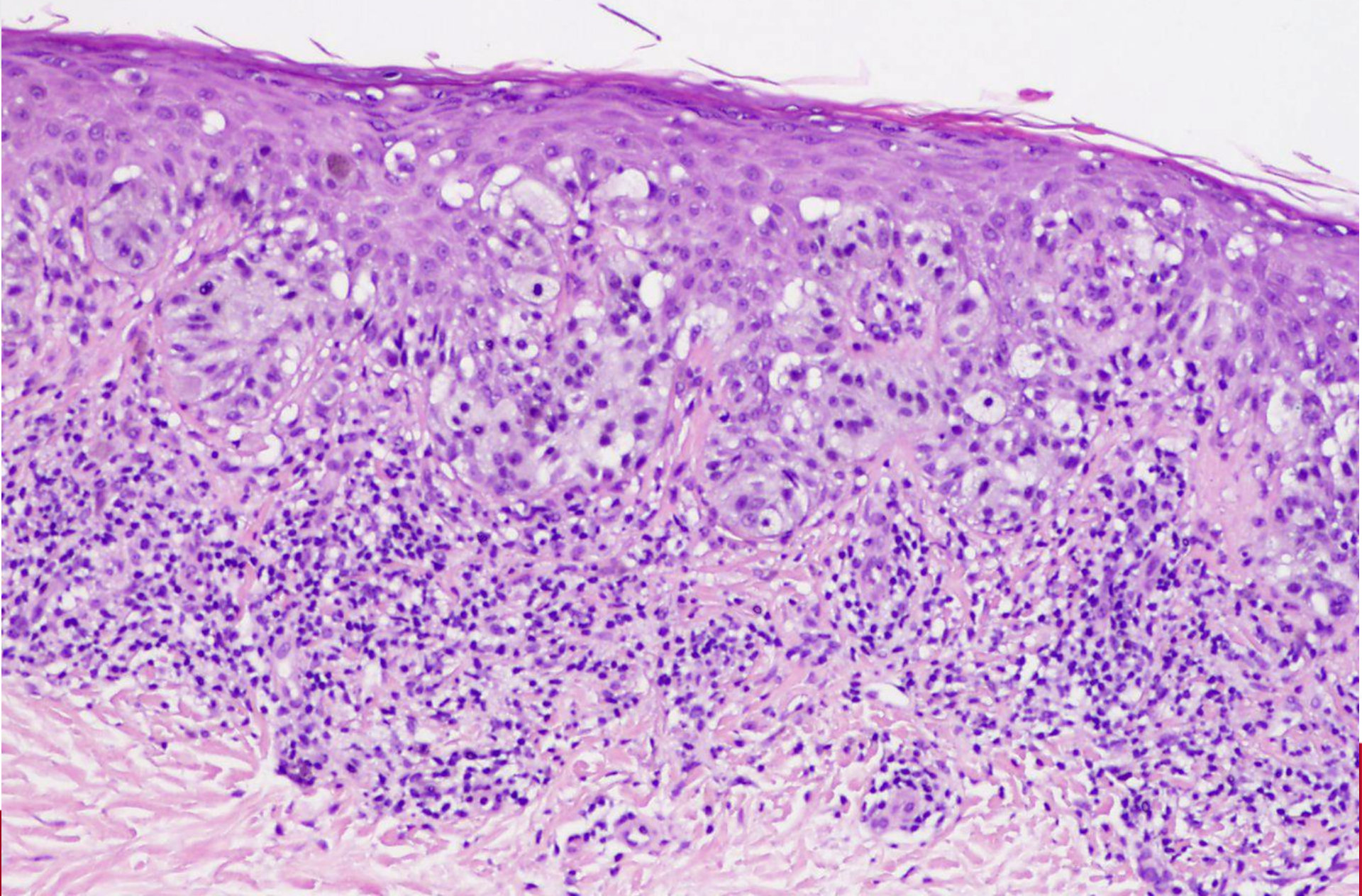
Dx: Compound dysplastic nevus with moderate cytological atypia, narrowly excised 100x



49 year old, left lower back
40x



Dx: Malignant melanoma, superficial spreading type, Breslow depth 0.32 mm 100x



J Am Acad Dermatol
Volume 74, Number 1

J Am Acad Dermatol
January 2016

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

Study results

- 17,024 Total nevi
- 8654 cases Clark nevi (50.8%)
- 959 recommended for re-excision (11.1%)
- 765 re-excised (79.8%)

Study results

- Of those re-excised 765
  - 621 no residual nevus (81.2%)
  - 123 identifiable benign component (16.1%)
  - 6 not classifiable as benign or malignant
  - 15 melanoma (2.0%)
    - 12 MIS
    - 3 superficially invasive

My dermatopathologic approach?

- Less use of the term dysplastic nevus, Clark's nevus or nevus with architectural disorder
  - Use of the terms 'junctional or compound lentiginous nevus'
  - Atypical junctional/compound melanocytic proliferation

How do I practice?

- I **never** diagnose a lesion with moderate or severe dysplasia
- In my estimate this is unfair to the clinician

How do I practice?

- Make specific recommendations to the clinician on management of the lesion

Report example

2 - COMPOUND MELANOCYTIC PROLIFERATION WITH ATYPICAL FEATURES (SEE COMMENT)

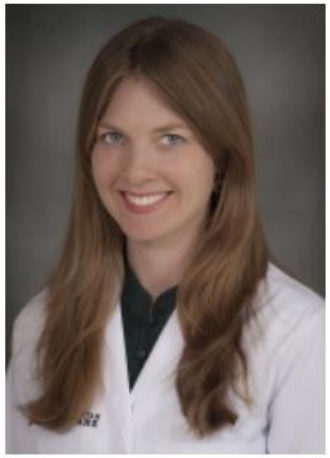
COMMENT: The overall features appear to be most consistent with a compound dysplastic nevus; however the asymmetry of the proliferation, scattered atypical melanocytes and rare melanocytes above the dermal-epidermal junction are unusual features. A complete re-excision is recommended given the lateral margin involvement.

My colleagues in dermatopathology, Drs. Scott Florell and Anneli Bowen, have also reviewed this case and they agree with the above interpretation.

Keith Duffy, MD
Dermatopathologist
Electronically signed 8/31/2012 9:37:54AM

Always another set of eyes…




Conclusions

- Dysplastic nevi appear to be different histologically and genomically
- Still…only a small number progress to melanoma
  - Which ones?
  - Will the genomic and personalized medicine revolution make our job better/easier/more conclusive?

Conclusions

- We are still stuck in The (seemingly) Eternal Debate
- Pigmented lesions are a team sport
  - Clinician concern
  - Concensus dermatopathology opinion
  - Photographs!
- Molecular medicine is coming commercially to a lab near you


Thank you. Questions or comments?
Keith.duffy@hsc.utah.edu