The State of the Dysplastic Nevus in the 21st Century

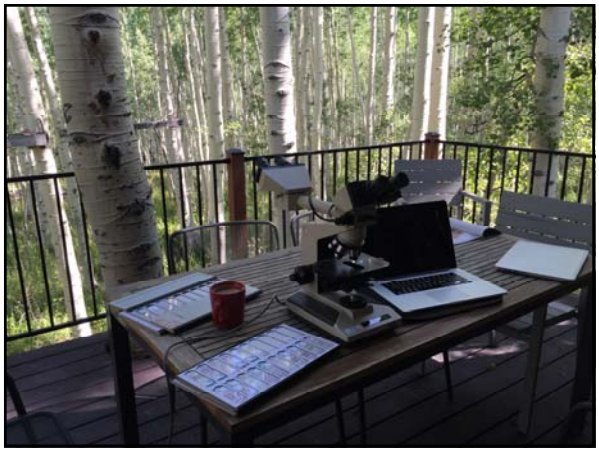
Keith Duffy, MD
Associate professor
Department of Dermatology
University of Utah

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



The NEW ENGLAND JOURNAL of MEDICINE

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., Erin 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.

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…

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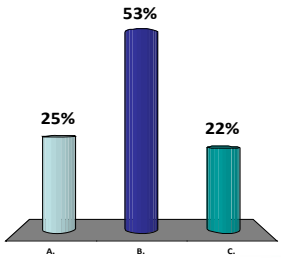
Do you believe dysplastic (Clark) nevi are truly premalignant lesions?

A. Yes
B. No
C. Unsure



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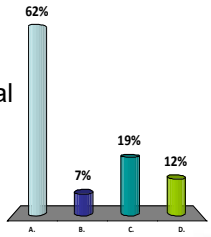
How do you report “dysplastic nevi”?

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



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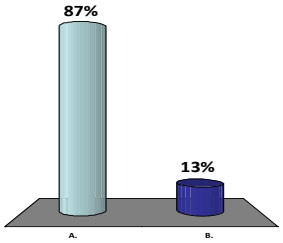
Do you assign a histologic “grade” to these nevi?

A. Yes
B. No



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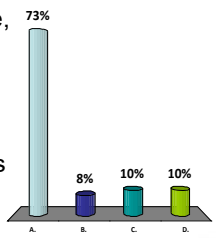
If yes, what grading system do you use?

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



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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)

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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 cutaneods 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.

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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

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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…

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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

Department of Dermatology

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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."

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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."

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What is a dysplastic nevus?

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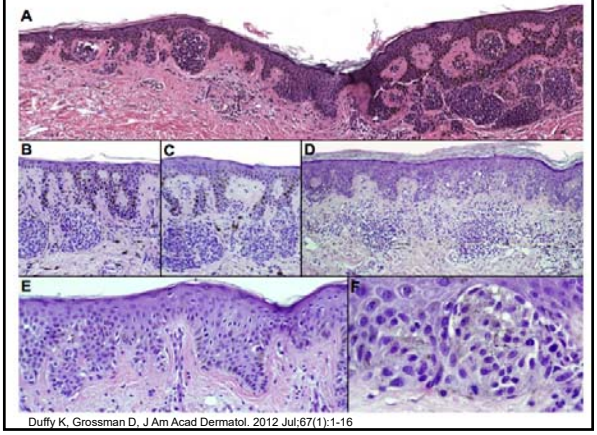

Duffy K, Grossman D, J Am Acad Dermatol. 2012 Jul;67(1):1-16

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

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

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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.

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

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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

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

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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

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"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

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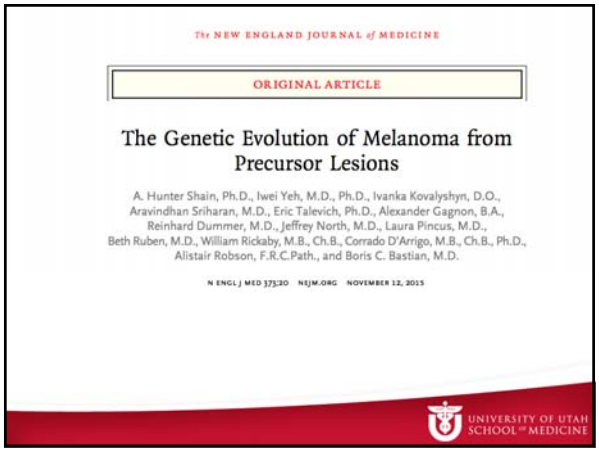
The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE
The Genetic Evolution of Melanoma from Precursor Lesions
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N ENGL J MED 373;20 NEJM.ORG NOVEMBER 12, 2015
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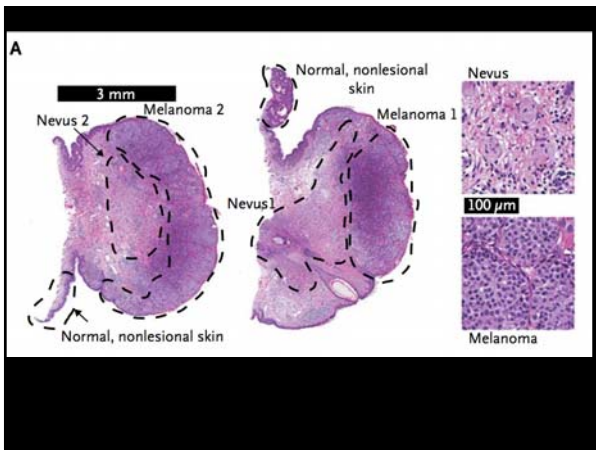
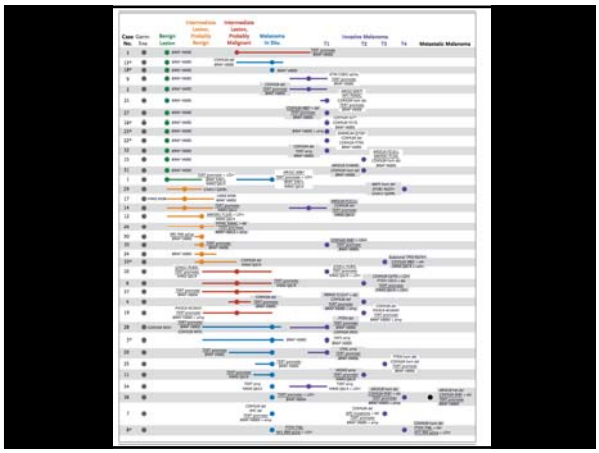
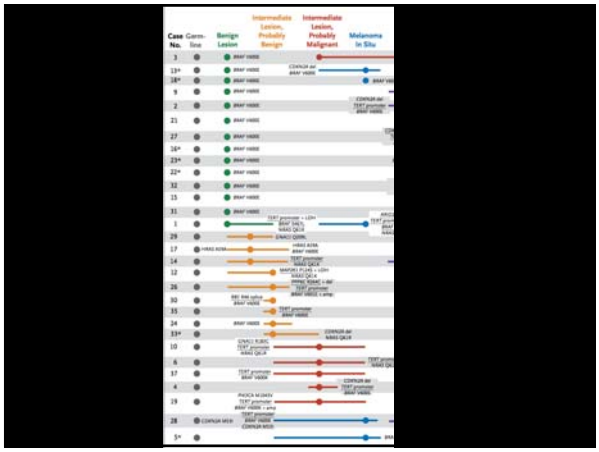
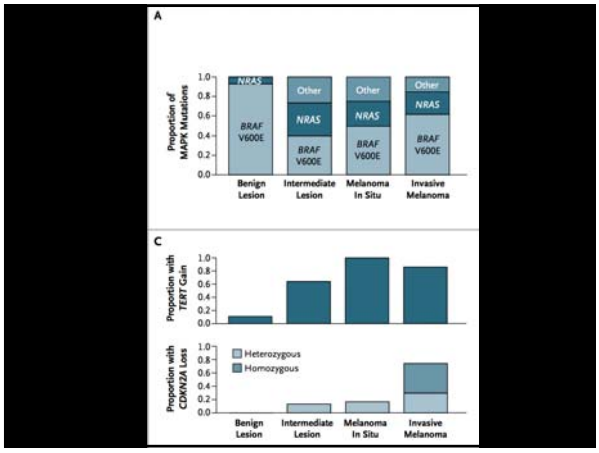

A
3 mm
Nevus 2
Melanoma 2
Normal, nonlesional skin
Nevus1
Normal, nonlesional skin
Melanoma 1
Nevus
100 μm
Melanoma




Case No.
Germline
Benign Lesion
Intermediate Lesion, Probably Benign
Intermediate Lesion, Probably Malignant
Melanoma In Situ


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

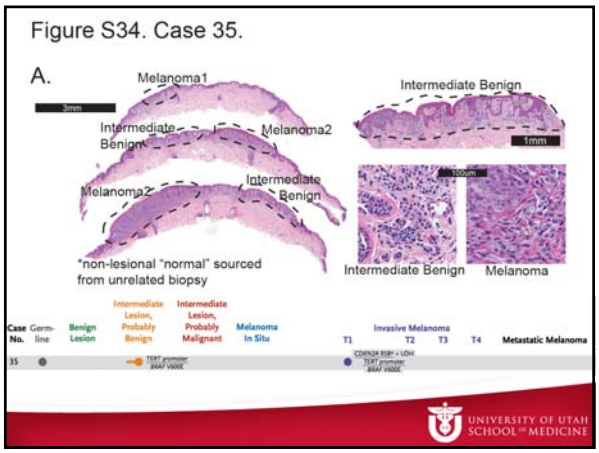


Figure S34. Case 35.
A.
Melanoma1
3mm
Intermediate Benign
Melanoma2
Intermediate Benign
1mm
Melanoma2
Intermediate Benign
100um
*non-lesional "normal" sourced from unrelated biopsy
Intermediate Benign
Melanoma
Case No.
Germ-line
Benign Lesion
Intermediate Lesion, Probably Benign
Intermediate Lesion, Probably Malignant
Melanoma In Situ
Invasive Melanoma
T1
T2
T3
T4
Metastatic Melanoma
35
TERT promoter
BRAF V600E
CDKN2A 9bp + LOH
TERT promoter
BRAF V600E
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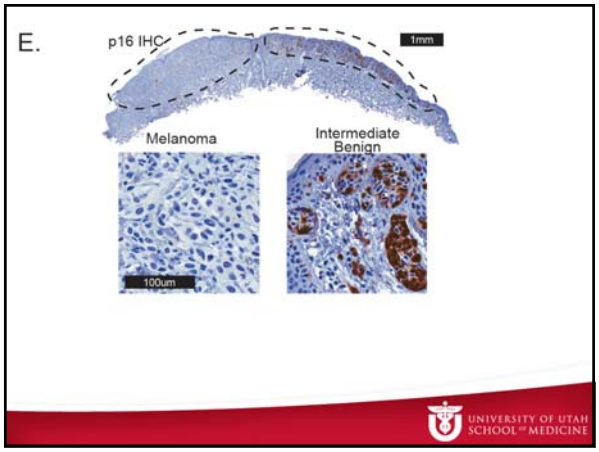
E.
p16 IHC
1mm
Melanoma
Intermediate Benign
100um
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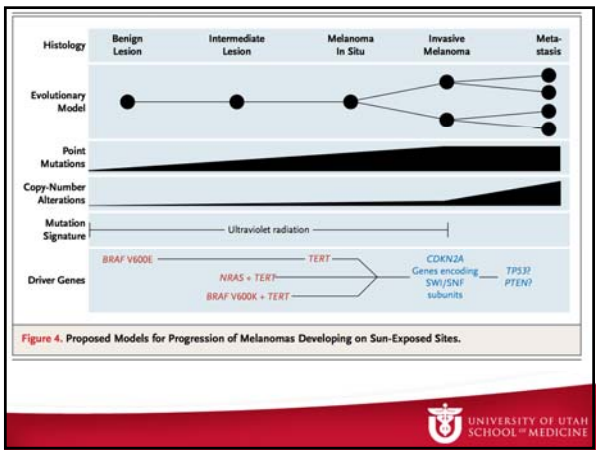
Histology
Benign Lesion
Intermediate Lesion
Melanoma In Situ
Invasive Melanoma
Meta-stasis
Evolutionary Model
Point Mutations
Copy-Number Alterations
Mutation Signature
Ultraviolet radiation
Driver Genes
BRAF V600E
TERT
NRAS + TERT
BRAF V600K + TERT
CDKN2A
Genes encoding SWI/SNF subunits
TP53?
PTEN?
Figure 4. Proposed Models for Progression of Melanomas Developing on Sun-Exposed Sites.
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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[1,2], B.M. Warf[1,2], 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

Clarke et al.

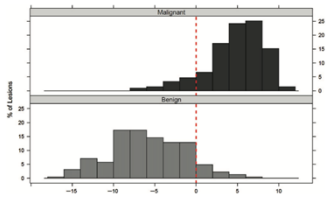

Fig. 3. Distribution of diagnostic scores in the clinical validation cohort.

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.

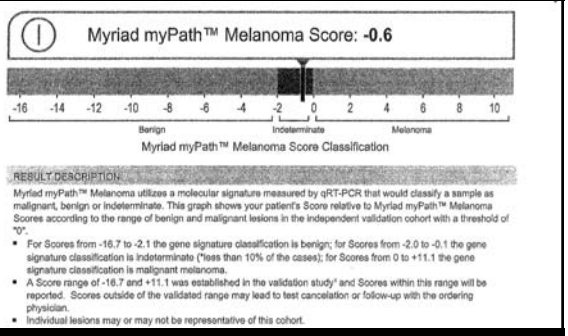

Table 3

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?

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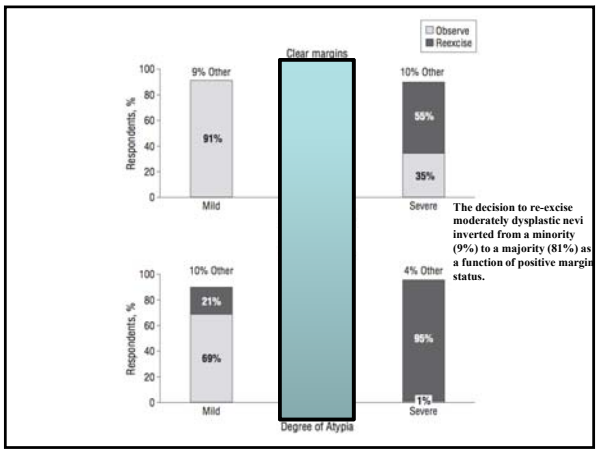
Clinical decision making based on histopathologic grading and margin status of dysplastic nevi

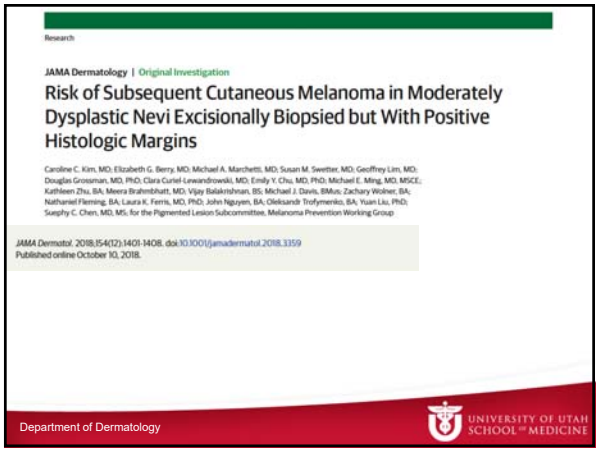
Keith L.Duffy, MD,[a] , David J. Mann, MD,[b] Vesna Petronic-Rosic, MD,[b] and Christopher R. Shea, MD [b]

Salt Lake City, Utah and Chicago, IL

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



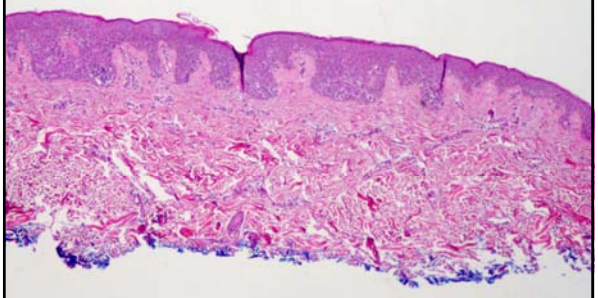
The decision to re-excise moderately dysplastic nevi inverted from a minority (9%) to a majority (81%) as a function of positive margin status.



Results

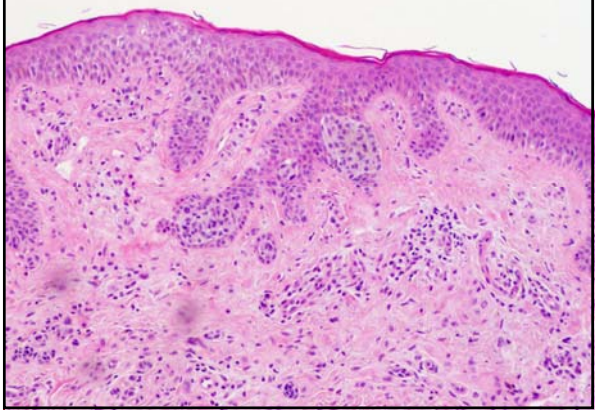
- 467 moderately dysplastic nevi with positive histologic margins observed for >3 years
  - Median f/u 6.9 years
- **NO** cases of cutaneous melanoma developed at those sites
- 100 patients (22.8%) developed a cutaneous melanoma at a separate site

41 year old female left lower back
40x

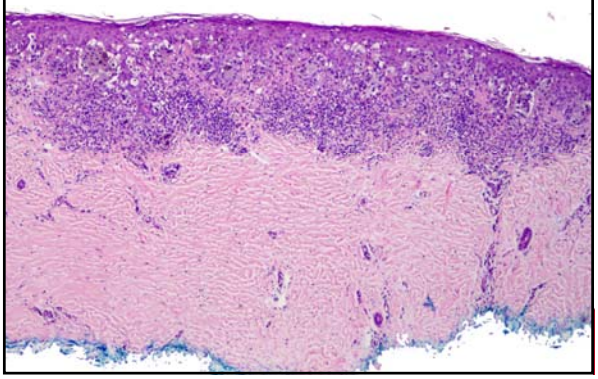


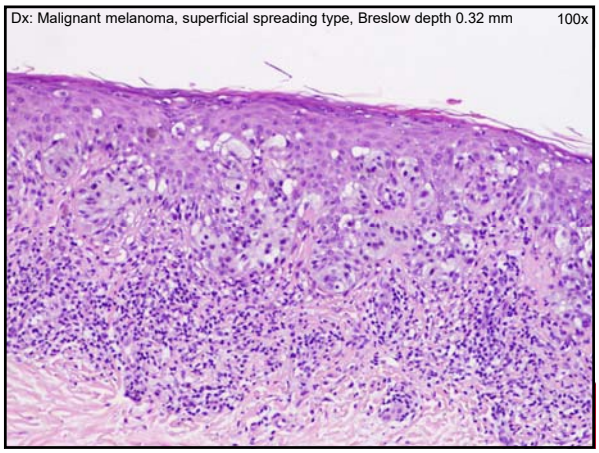
Do you think there is a TERT promoter mutation in this lesion?

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



49 year old, left lower back
40x





Study results

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

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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

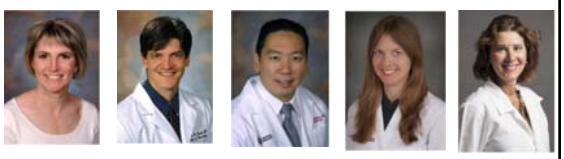
2 - COMPOUND MELANOCYTIC PROLIFERATION WITH ATYPICAL FEATURES (SEE COMMENT)

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?

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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

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Thank you. Questions or comments?
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