Professor Peter Soyer

Academic Dermatologist

Brisbane, Australia

What's New in Melanoma - Main Session (Workshop options scheduled)

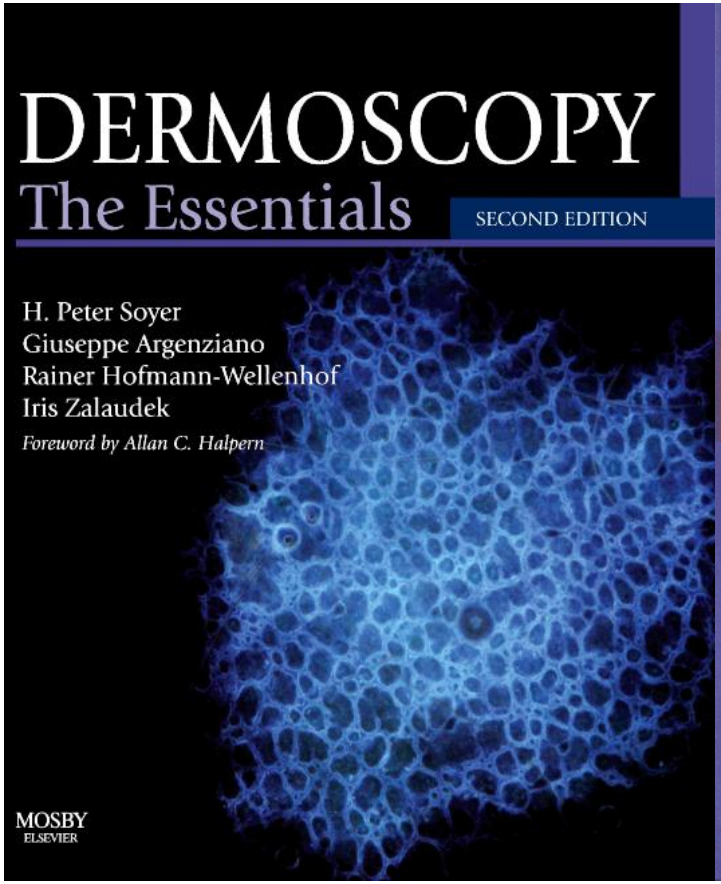
Friday, 21 June 2013 Start 2:00pm Duration: 25mins Baytrust

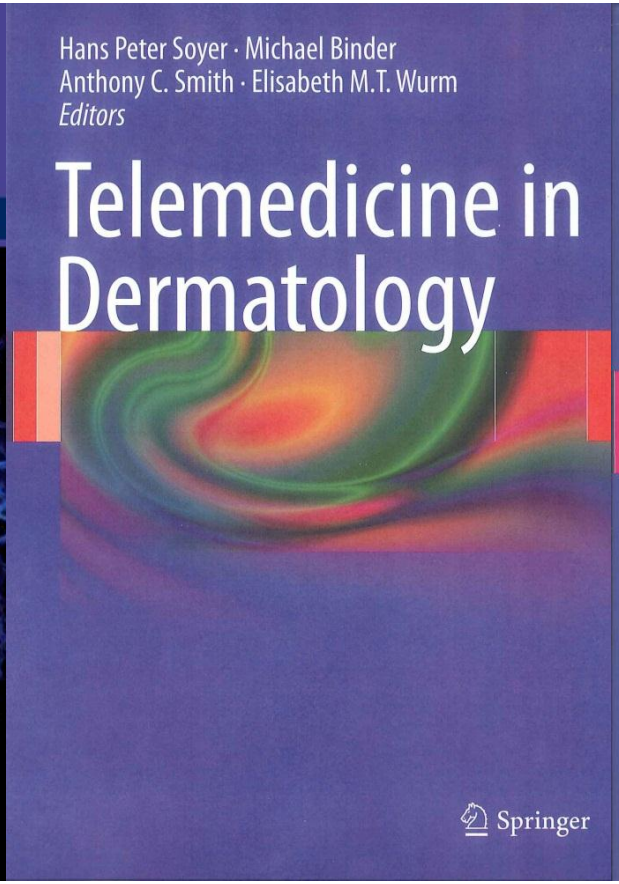
What's New in Melanoma

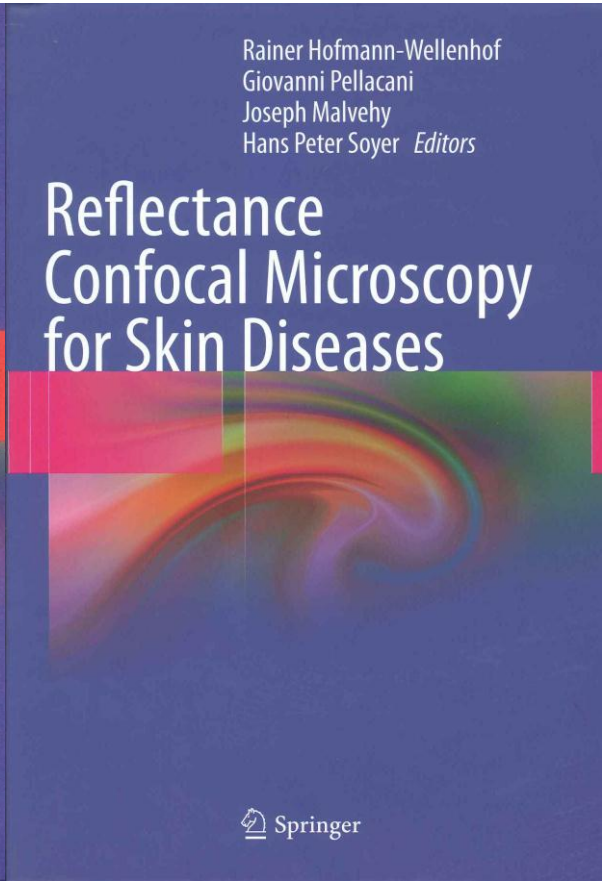
Dermatology Research Centre, The University of Queensland,
School of Medicine, Translational Research Institute
&
Dermatology Department, Princess Alexandra Hospital
Brisbane, Queensland, Australien

p.soyer@uq.edu.au

Conflicts of Interests







e-derm-consult

MoleMap by Dermatologists

SkinbyDerms

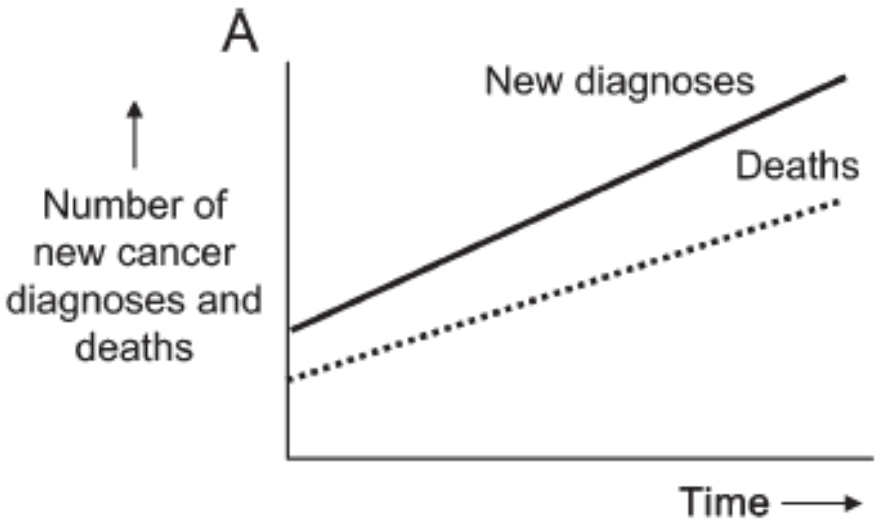
Melanoma Incidence

In 2009, melanoma of the skin was the 4th most commonly diagnosed cancer in Australia accounting for 10.1 per cent of all new cancers.

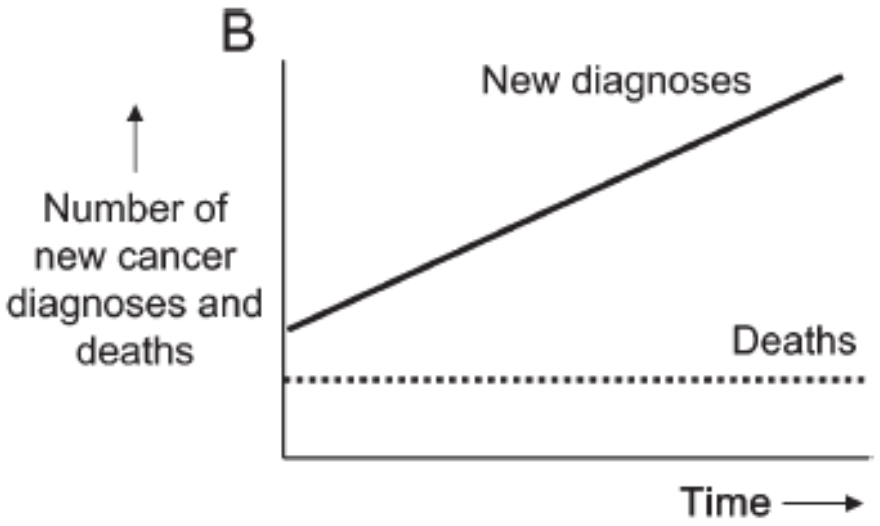
Between 1982 and 2009, the age-standardised incidence rate for melanoma of the skin increased from 26.8 to 49.8 cases per 100,000 people.

Melanoma Mortality

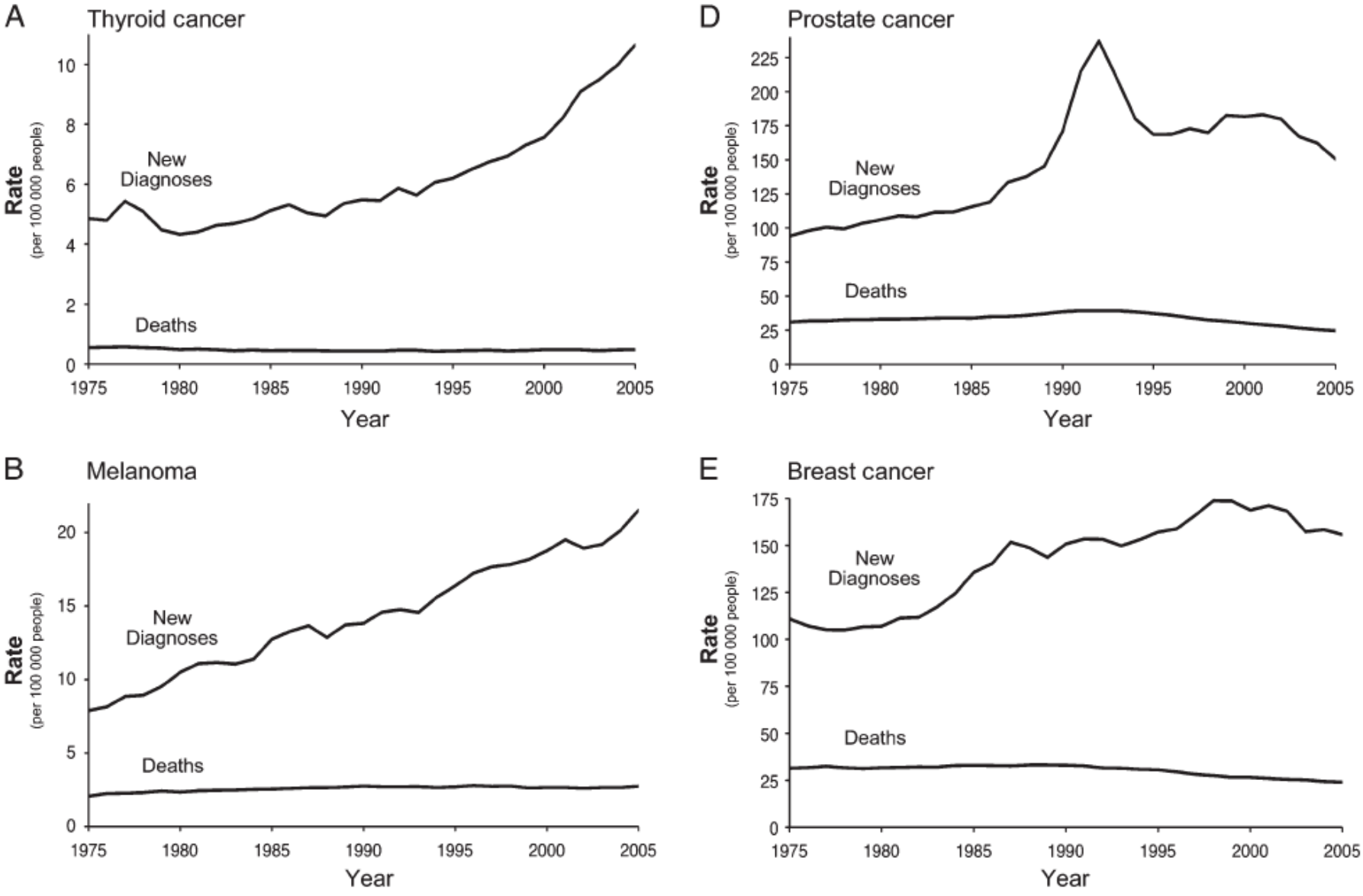
Between 1982 and 2010, the age-standardised mortality rate for melanoma of the skin increased from 4.7 to 5.9 deaths per 100,000 people.



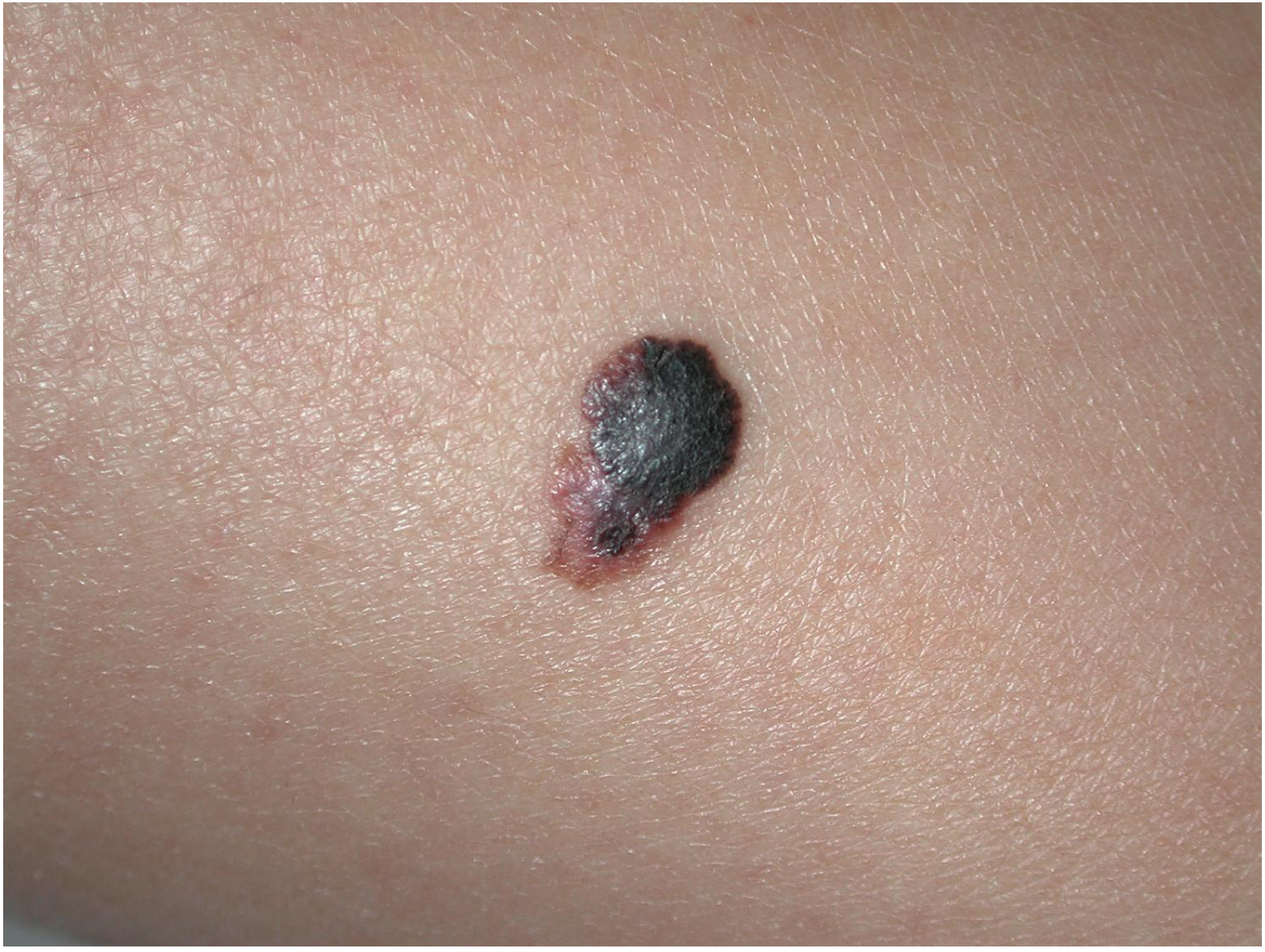
Suggests a true increase in the amount of cancer

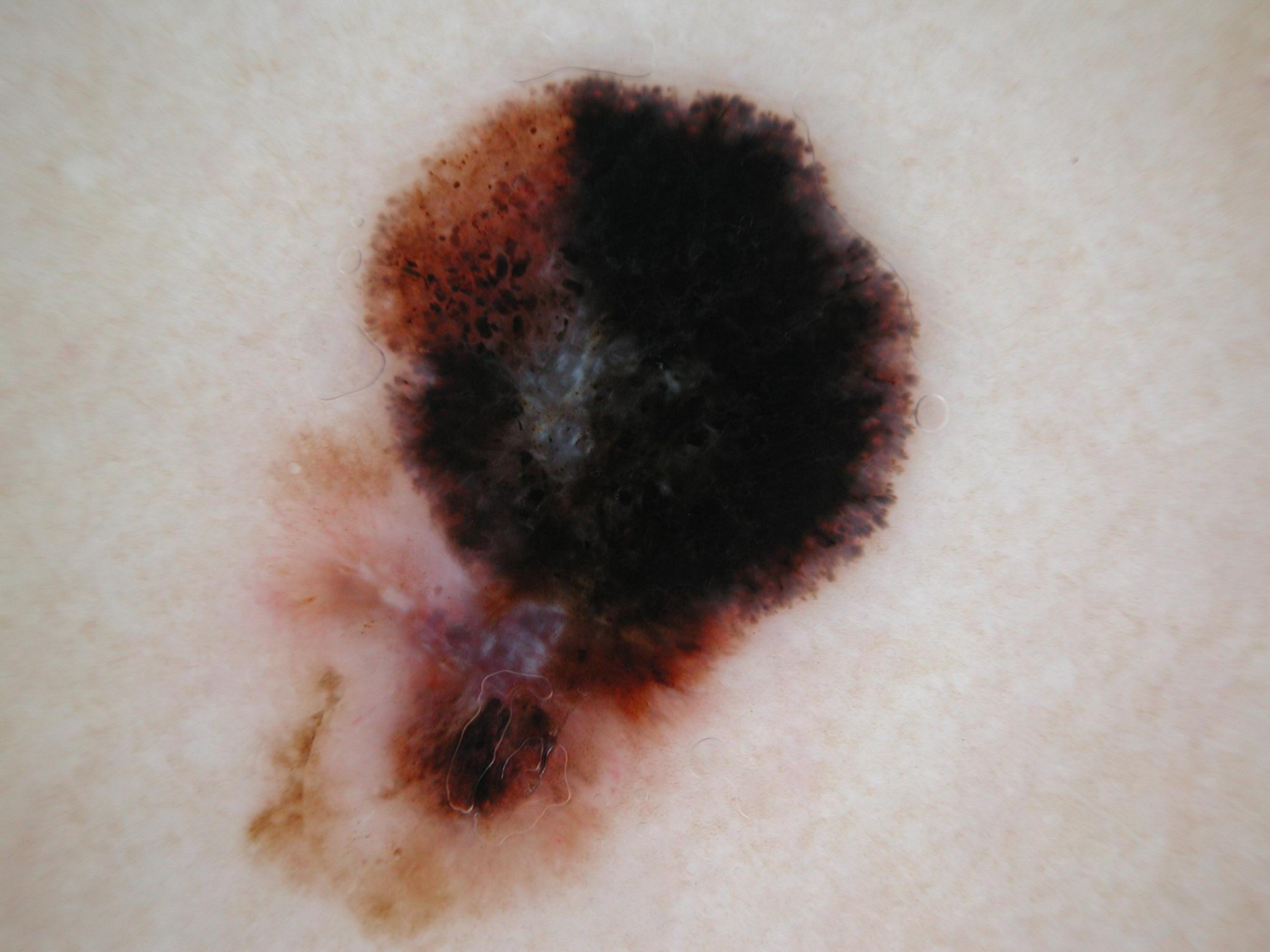


Suggests overdiagnosis of cancer


A
Thyroid cancer
Rate
(per 100 000 people)
New
Diagnoses
Deaths
0
2
4
6
8
10
1975
1980
1985
1990
1995
2000
2005
Year
B
Melanoma
Rate
(per 100 000 people)
New
Diagnoses
Deaths
0
5
10
15
20
1975
1980
1985
1990
1995
2000
2005
Year
D
Prostate cancer
Rate
(per 100 000 people)
New
Diagnoses
Deaths
0
25
50
75
100
125
150
175
200
225
1975
1980
1985
1990
1995
2000
2005
Year
E
Breast cancer
Rate
(per 100 000 people)
New
Diagnoses
Deaths
0
25
50
75
100
125
150
175
1975
1980
1985
1990
1995
2000
2005
Year

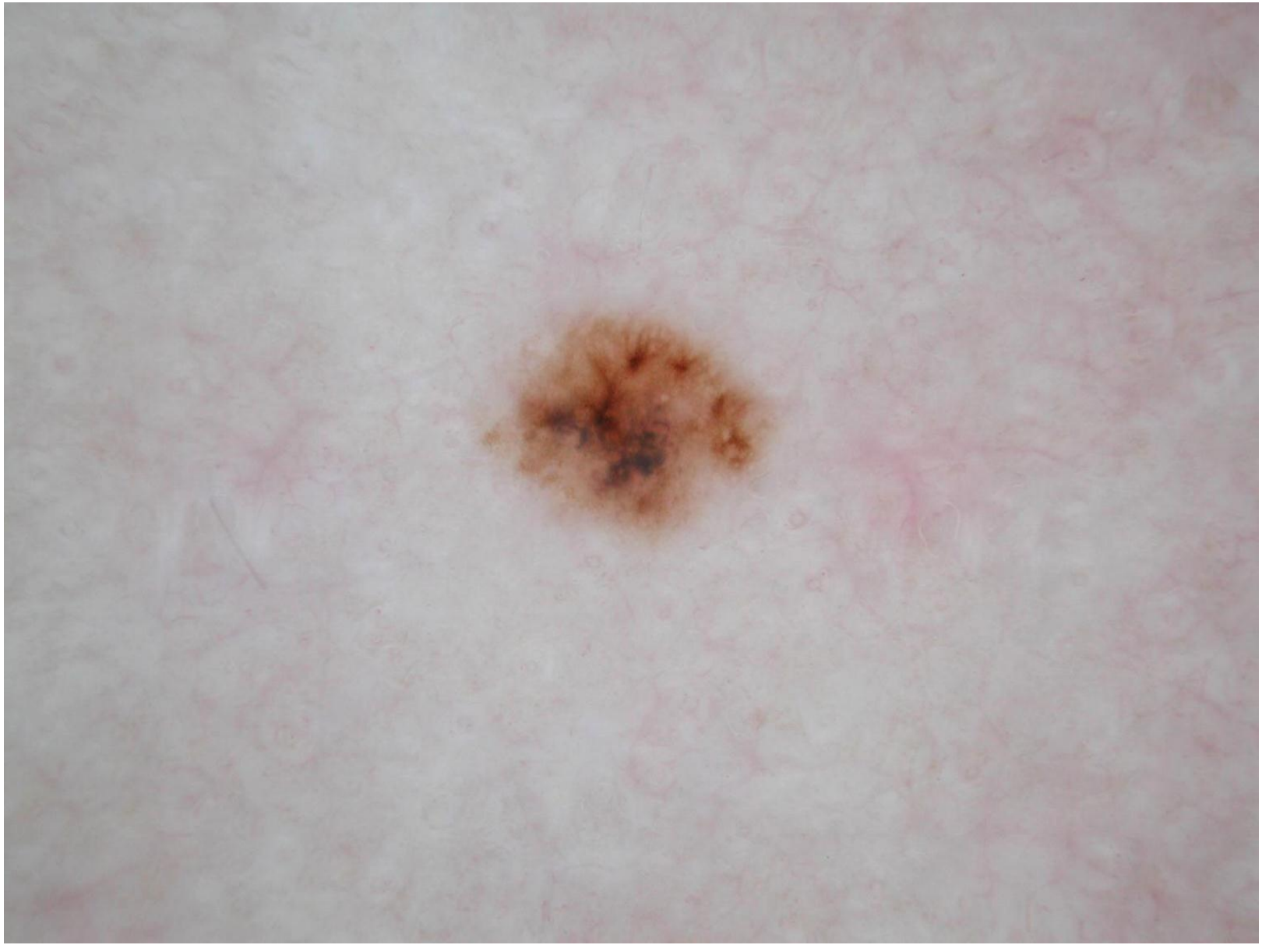
The five-year relative survival from melanoma of the skin for 2006-2010 was 88.5 % for men and 93.6 % for women






CM
1
2
9

Between the periods 1982–1987 and 2006–2010 the five-year relative survival increased from 85.8 % to 90.7 %.

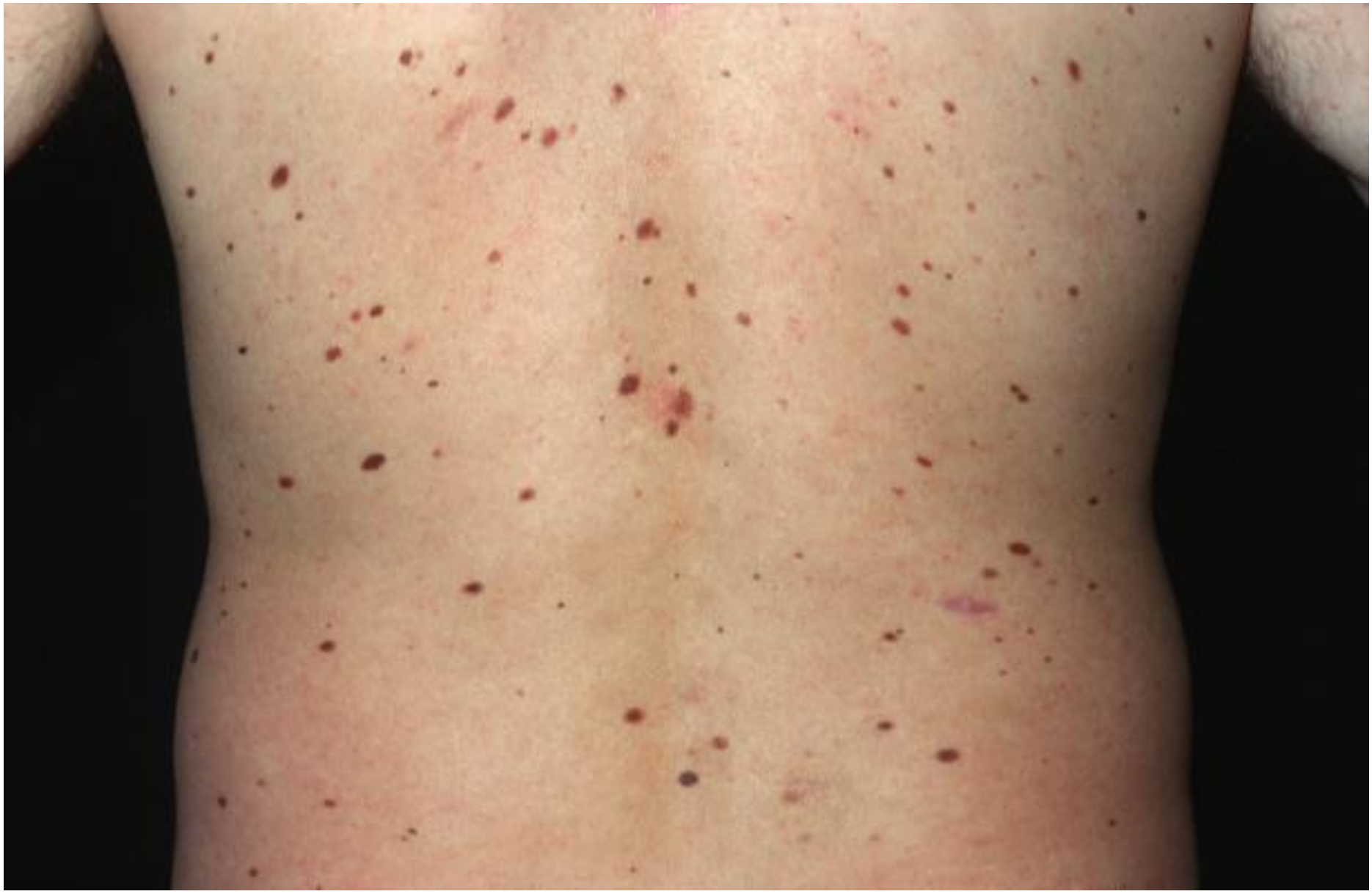


New Melanoma Classification

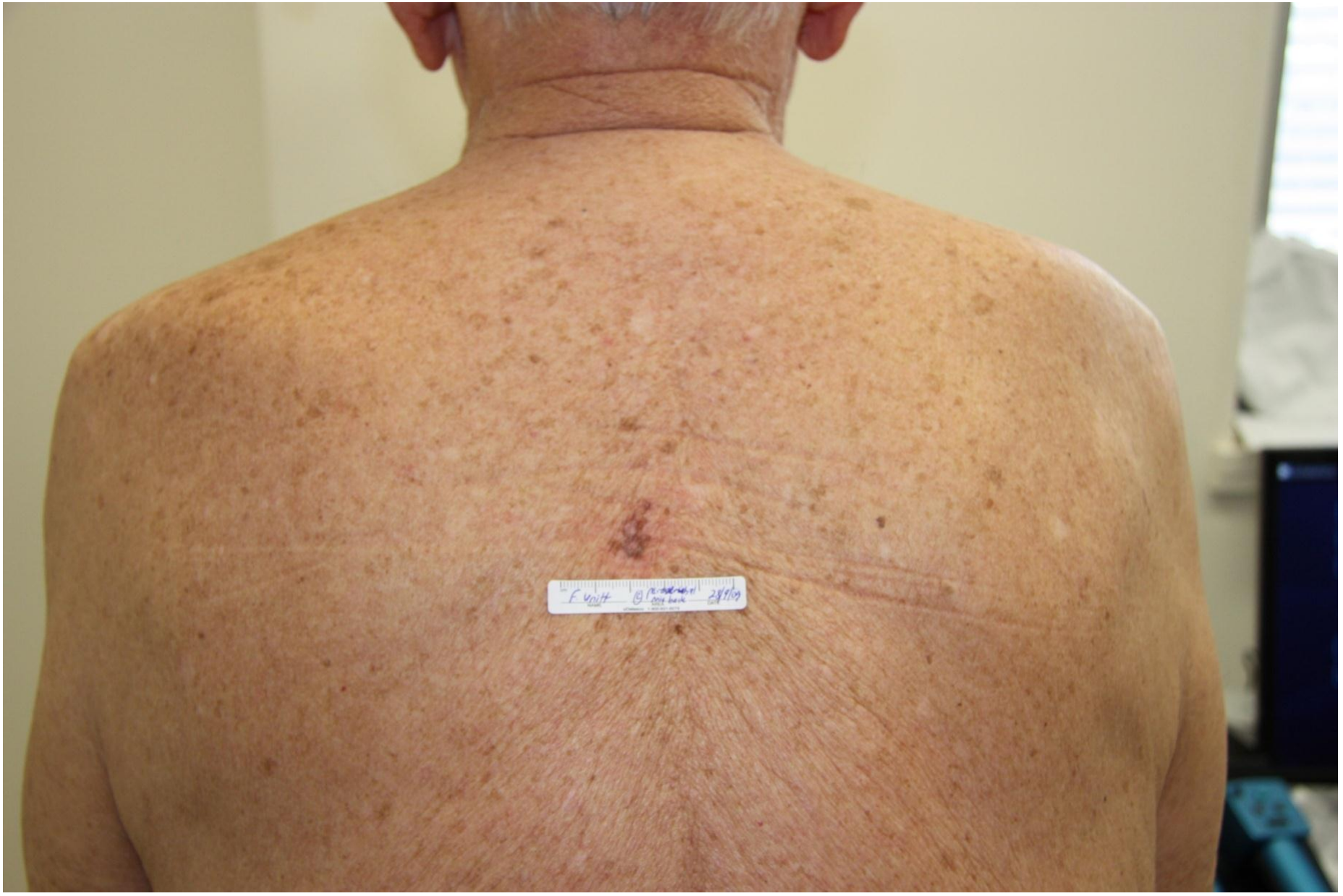
Curtin JA and colleagues 2005

- Melanoma arising on skin with evidence of chronic sun-induced damage (CSD Melanoma)
- Melanoma arising on skin without evidence of chronic sun-induced damage (non-CSD Melanoma)
- Acral Melanoma
- Mucosal Melanoma

High-Nevus/Low-Sunlight Pathway



Low-Nevus/High-Sunlight Pathway



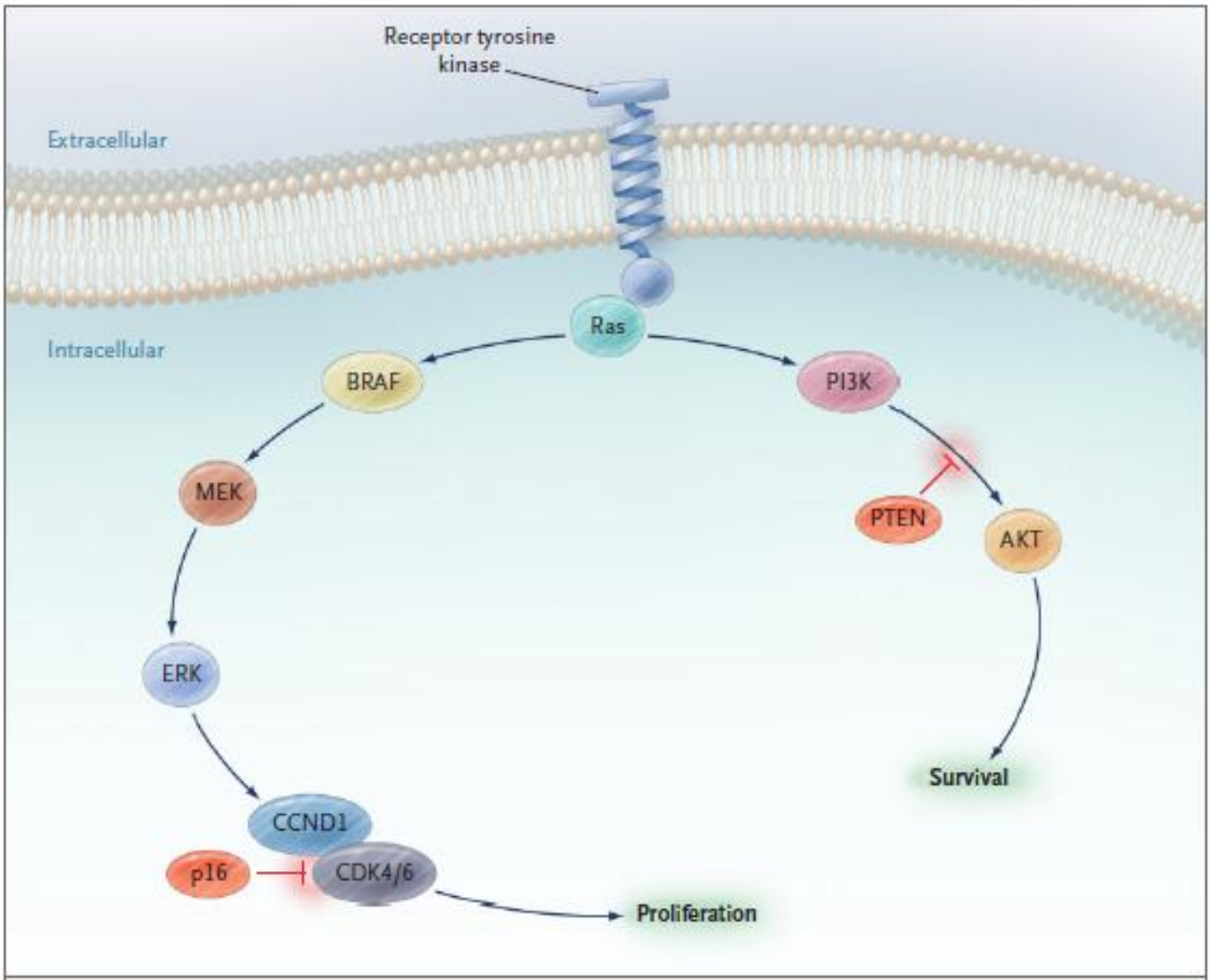
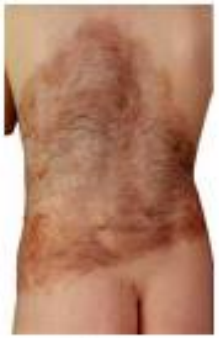
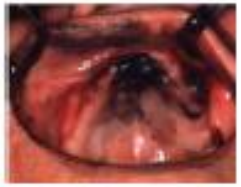
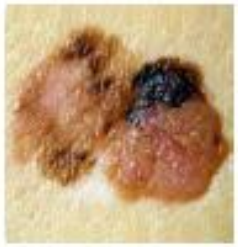
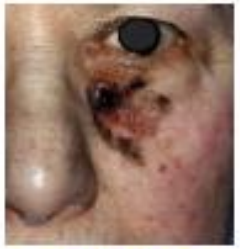
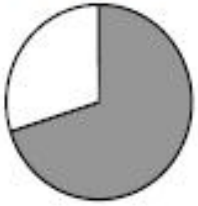


Figure 1. The Mitogen-Activated Protein (MAP) Kinase and Phosphatidylinositol 3' Kinase (PI3K) Pathways.

Signals from receptor tyrosine kinases can promote proliferation through the MAP kinase pathway (left branch) and survival through the PI3 kinase pathway (right branch).

NEJM 2005
Curtin JA et al.

Melanocytic tumors: UV damage and *BRAF* mutations

Cong. Nevi	Mucosal Melanomas	Acral Melanomas	SSM, NM	Acquired nevi	LMM
					
					
BRAF mut 0%	BRAF mut 0-10%	BRAF mut 10-20%	BRAF mut 60-80%	BRAF mut 60-80%	BRAF mut 10%
					

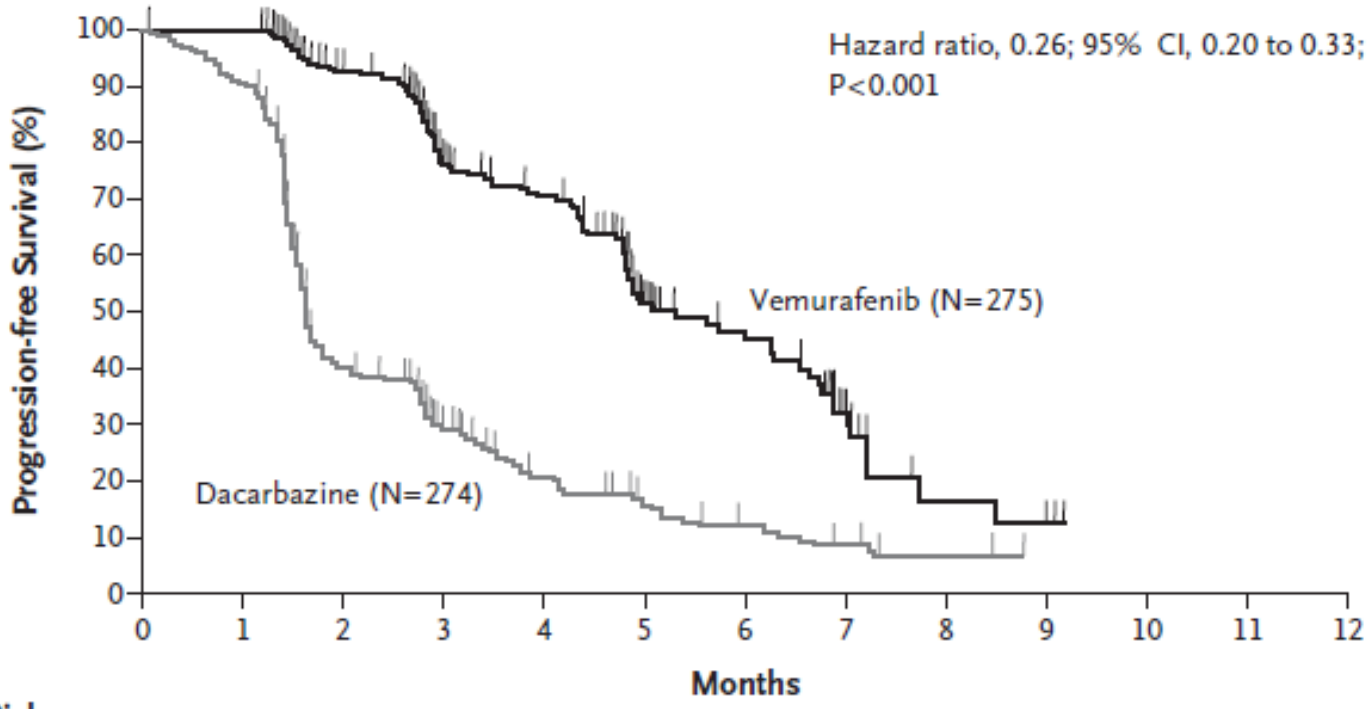
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation

Paul B. Chapman, M.D., Axel Hauschild, M.D., Caroline Robert, M.D., Ph.D., John B. Haanen, M.D., Paolo Ascierto, M.D., James Larkin, M.D., Reinhard Dummer, M.D., Claus Garbe, M.D., Alessandro Testori, M.D., Michele Maio, M.D., David Hogg, M.D., Paul Lorigan, M.D., Celeste Lebbe, M.D., Thomas Jouary, M.D., Dirk Schadendorf, M.D., Antoni Ribas, M.D., Steven J. O'Day, M.D., Jeffrey A. Sosman, M.D., John M. Kirkwood, M.D., Alexander M.M. Eggermont, M.D., Ph.D., Brigitte Dreno, M.D., Ph.D., Keith Nolop, M.D., Jiang Li, Ph.D., Betty Nelson, M.A., Jeannie Hou, M.D., Richard J. Lee, M.D., Keith T. Flaherty, M.D., and Grant A. McArthur, M.B., B.S., Ph.D., for the BRIM-3 Study Group*

A Progression-free Survival



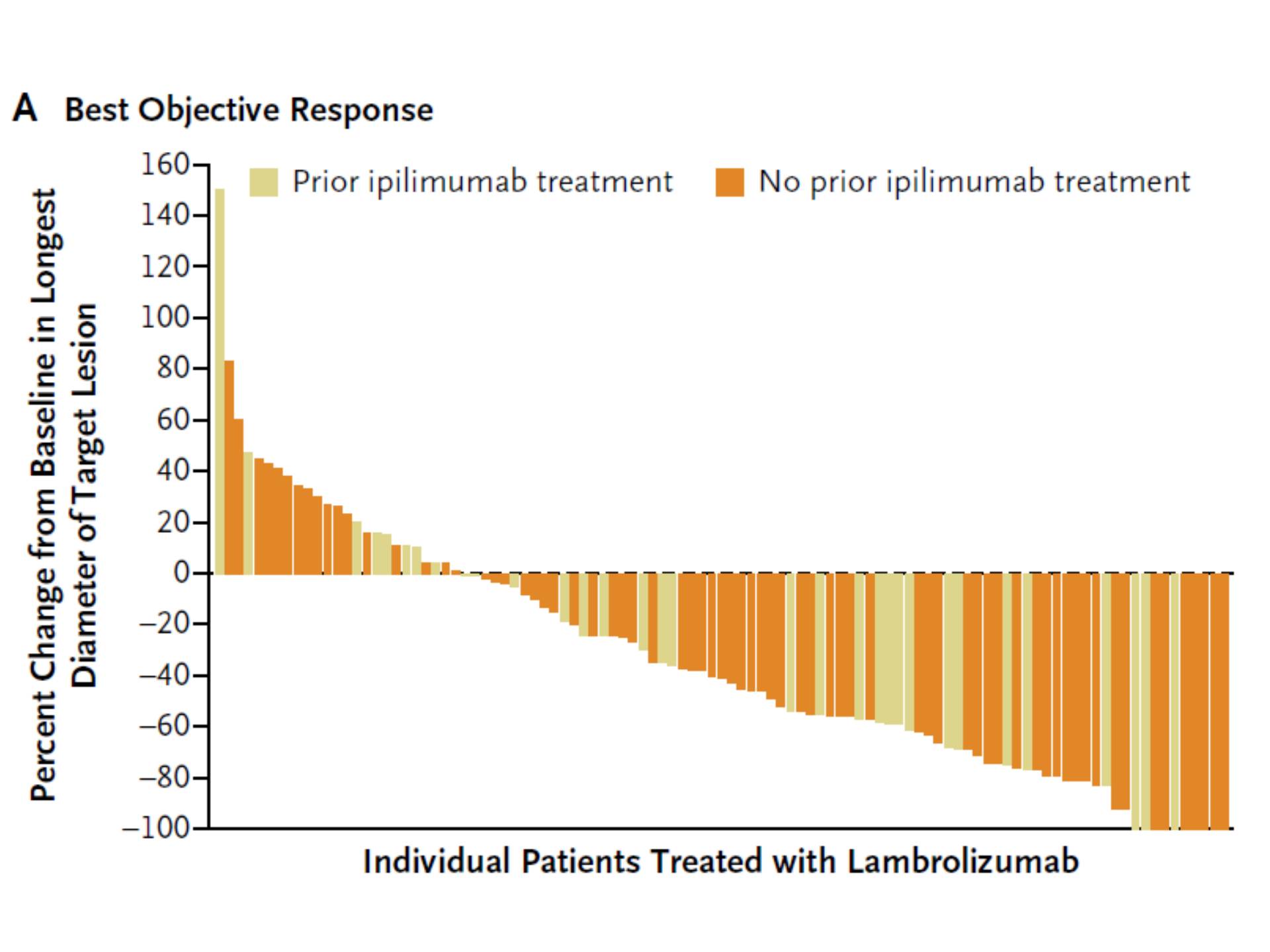
No. at Risk

Dacarbazine	274	213	85	48	28	16	10	6	3	0	0	0	0
Vemurafenib	275	268	211	122	105	50	35	16	4	3	0	0	0

ORIGINAL ARTICLE

Safety and Tumor Responses with Lambrolizumab (Anti–PD-1) in Melanoma

Omid Hamid, M.D., Caroline Robert, M.D., Ph.D., Adil Daud, M.D., F. Stephen Hodi, M.D., Wen-Jen Hwu, M.D., Ph.D., Richard Kefford, M.D., Ph.D., Jedd D. Wolchok, M.D., Ph.D., Peter Hersey, M.D., Ph.D., Richard W. Joseph, M.D., Jeffrey S. Weber, M.D., Ph.D., Roxana Dronca, M.D., Tara C. Gangadhar, M.D., Amita Patnaik, M.D., Hassane Zarour, M.D., Anthony M. Joshua, M.B., B.S., Ph.D., Kevin Gergich, M.A., Jeroen Elassaiss-Schaap, Ph.D., Alain Algazi, M.D., Christine Mateus, M.D., Peter Boasberg, M.D., Paul C. Tumeh, M.D., Bartosz Chmielowski, M.D., Ph.D., Scot W. Ebbinghaus, M.D., Xiaoyun Nicole Li, Ph.D., S. Peter Kang, M.D., and Antoni Ribas, M.D., Ph.D.


A Best Objective Response
Prior ipilimumab treatment
No prior ipilimumab treatment
Percent Change from Baseline in Longest Diameter of Target Lesion
160
140
120
100
80
60
40
20
0
−20
−40
−60
−80
−100
Individual Patients Treated with Lambrolizumab

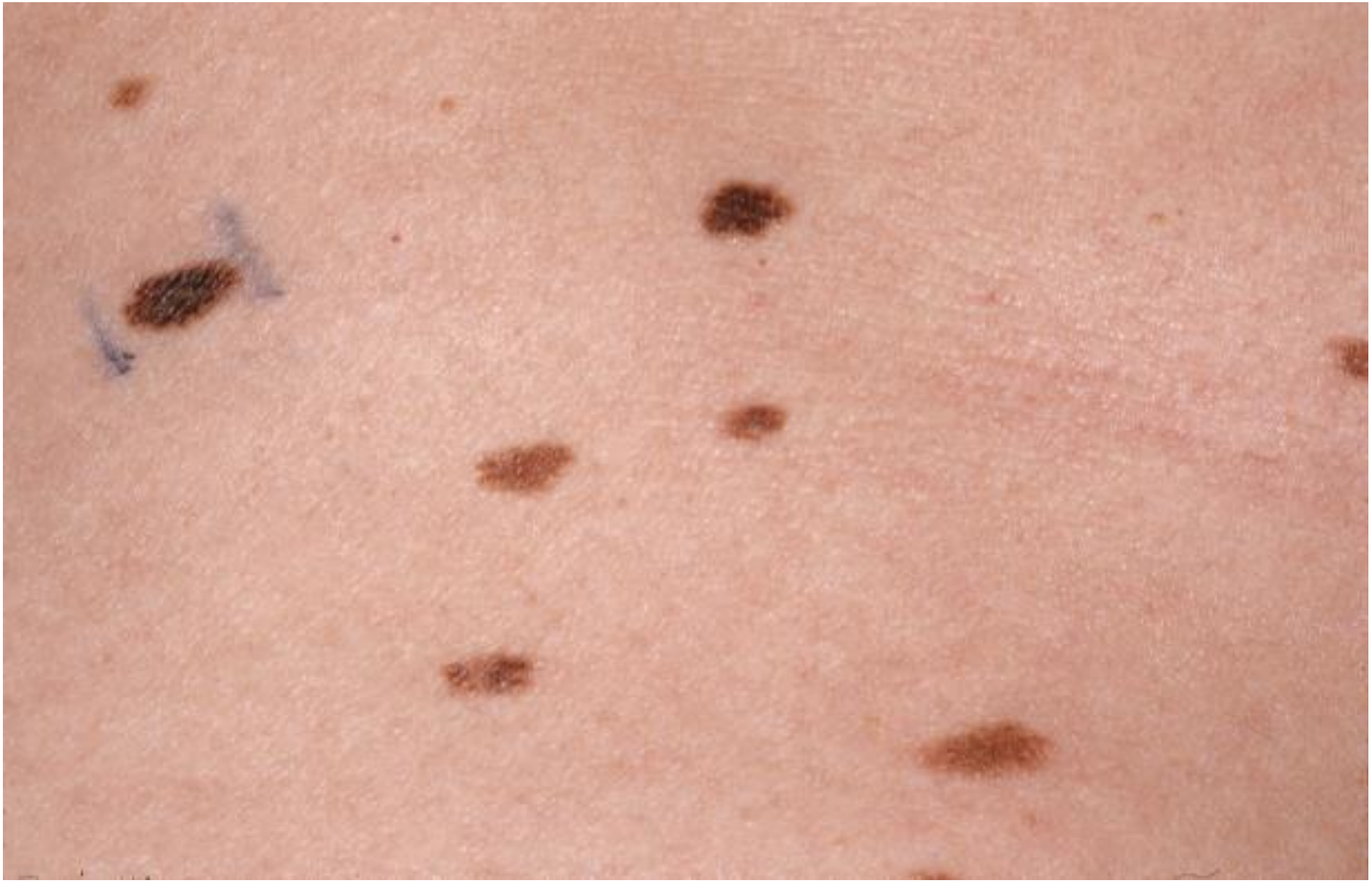
ORIGINAL ARTICLE

Clinical and Dermoscopic Stability and Volatility of Melanocytic Nevi in a Population-Based Cohort of Children in Framingham School System

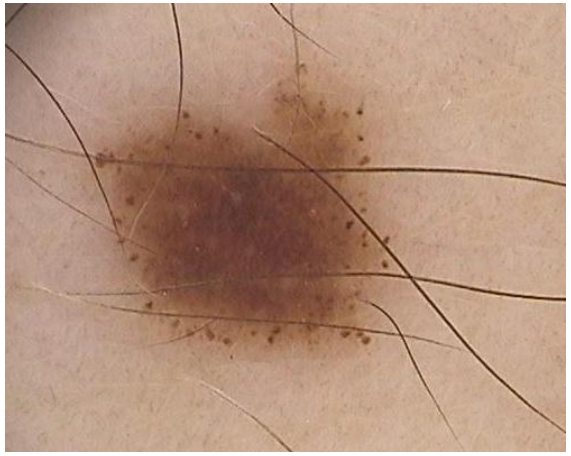
Alon Scope[1], Stephen W. Dusza[1], Ashfaq A. Marghoob[1], Jaya M. Satagopan[2], Juliana Braga Casagrande Tavoloni[1], Estee L. Psaty[1], Martin A. Weinstock[3], Susan A. Oliveria[1], Marilyn Bishop[4], Alan C. Geller[5] and Allan C. Halpern[1]

Nevi are important risk markers of melanoma. The study aim was to describe changes in nevi of children using longitudinal data from a population-based cohort. Overview back photography and dermoscopic imaging of up to 4 index back nevi was performed at age 11 years (baseline) and repeated at age 14 years (follow-up). Of 443 children (39% females) imaged at baseline, 366 children (39% females) had repeated imaging 3 years later. At age 14, median back nevus counts increased by two; 75% of students ($n=274$) had at least one new back nevus and 28% ($n=103$) had at least one nevus that disappeared. Of 936 index nevi imaged dermoscopically at baseline and follow-up, 69% (645 nevi) had retained the same dermoscopic classification from baseline evaluation. Only 4% ($n=13$) of nevi assessed as globular at baseline were classified as reticular at follow-up, and just 3% ($n=3$) of baseline reticular nevi were classified as globular at follow-up. Of 9 (1%) index nevi that disappeared at follow-up, none showed halo or regression at baseline. In conclusion, the relative stability of dermoscopic pattern of individual nevi in the face of the overall volatility of nevi during adolescence suggests that specific dermoscopic patterns may represent distinct biological nevus subsets.

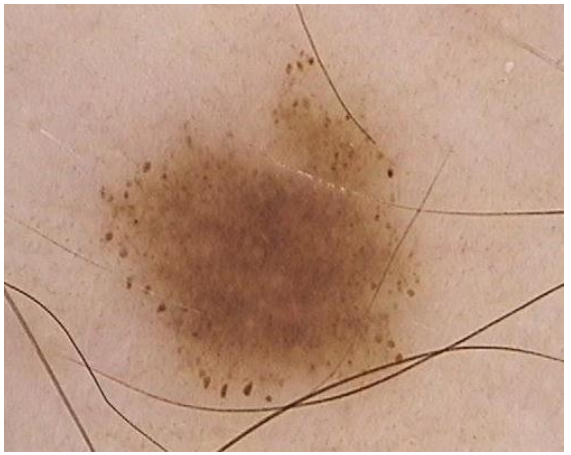
Journal of Investigative Dermatology advance online publication, 12 May 2011; doi:10.1038/jid.2011.107



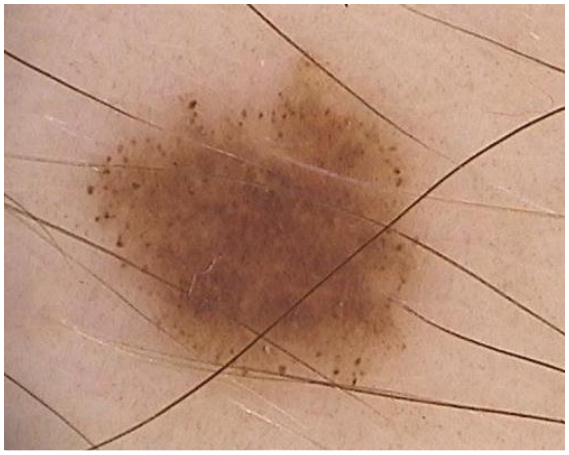
Male
Age: 26 years old
Lesion on Abdomen



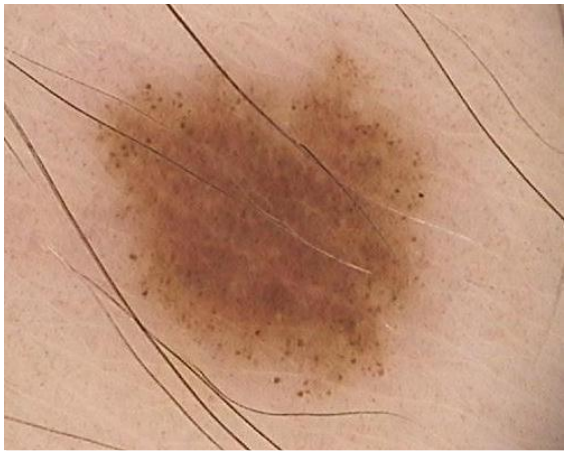
August 2010



April 2011

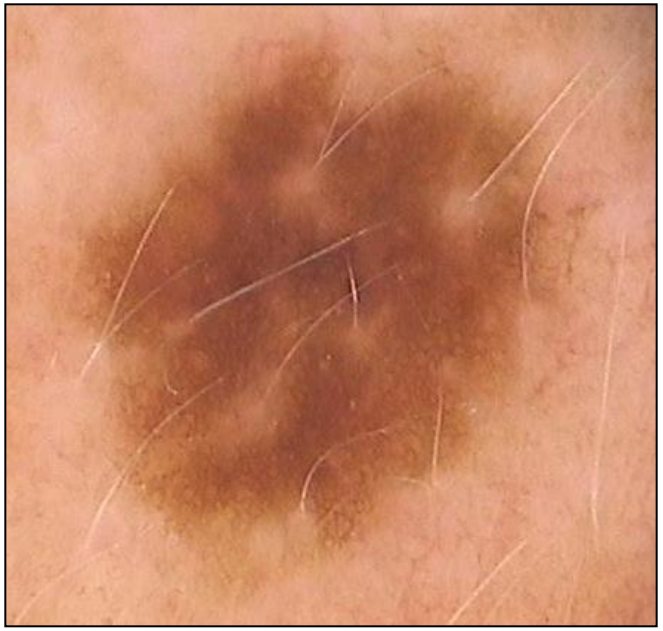


February 2012

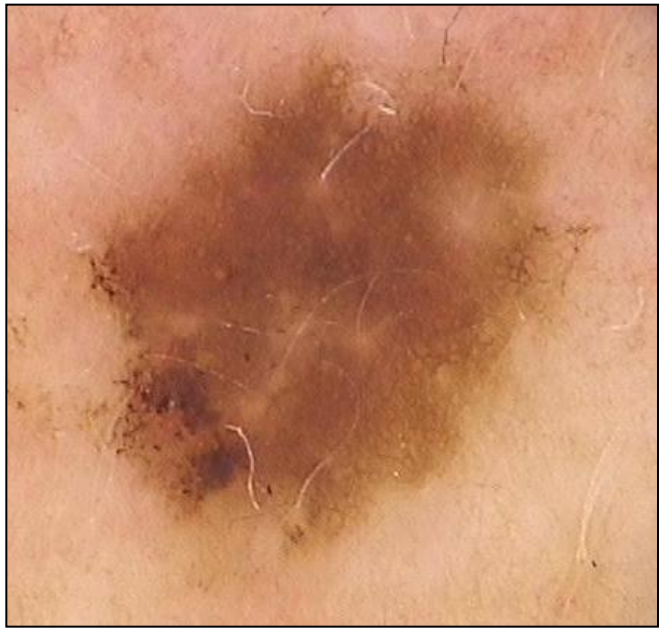


October 2012

Patient: Male, 55 years old
Lesion: Central upper back



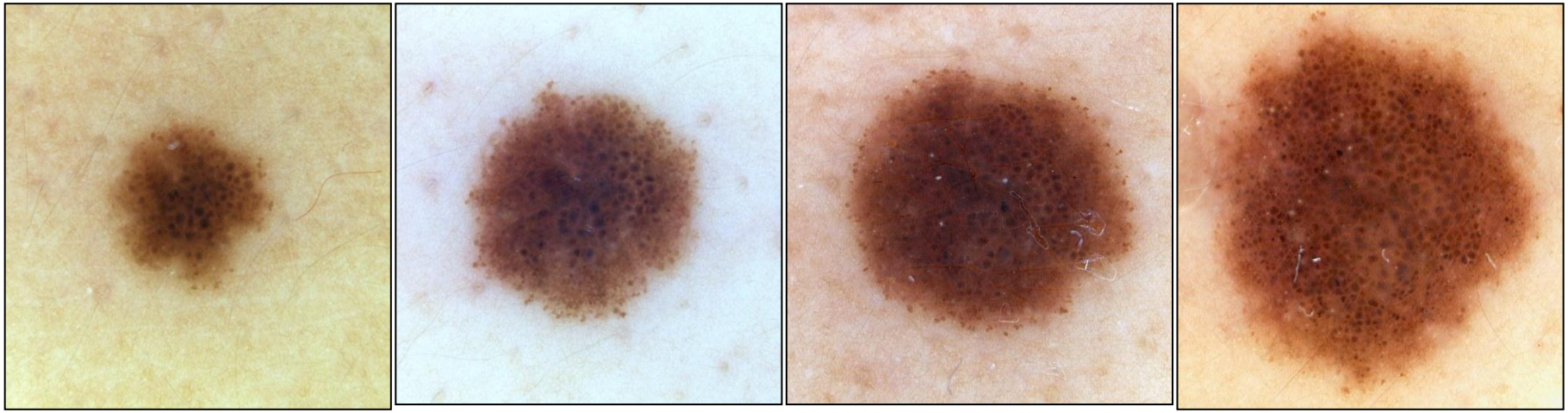
June 2011



November 2011

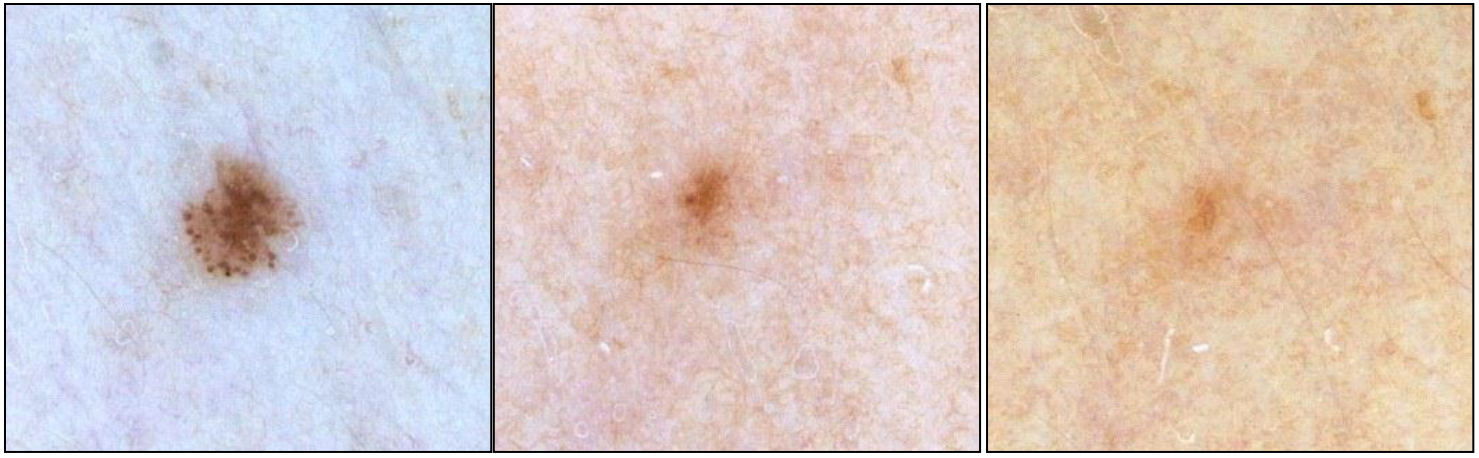
Patient: Female, 39 years old

Lesion: Central Mid Back



December 2006 August 2008 December 2009 January 2012

Lesion: Chest



August 2008 December 2009 January 2012

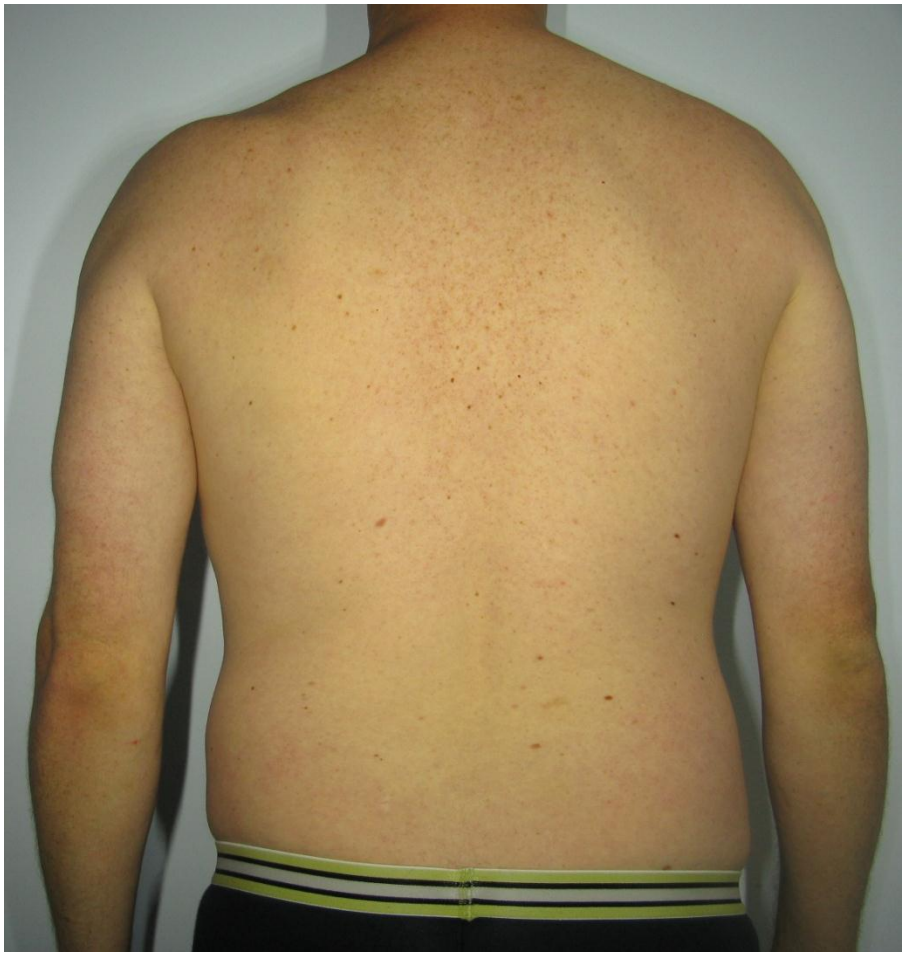
BRAFi Naevus Surveillance Case

39 year old male

History:
•April 2007, primary melanoma anterior left shoulder, Level 3 superficial spreading melanoma, 0.64mm thick.
•May 2007, Sentinel node biopsy, left subclavicular node, benign with no evidence of metastases.

Phenotype:
•Dark brown hair
•Green eyes
•10 naevi larger than 5mm
•25 naevi on back larger than 2mm
•9 naevi have significantly changed

Imaged: May 2011, December 2011, July 2012, February 2013



BRAF-i Naevus Surveillance Case

Hx continued:

•February 2010, supraclavicular lump identified

•March 2010, left neck lymph node dissection, 1 node positive for metastases.

•April 2010 begin MAGE trial participation

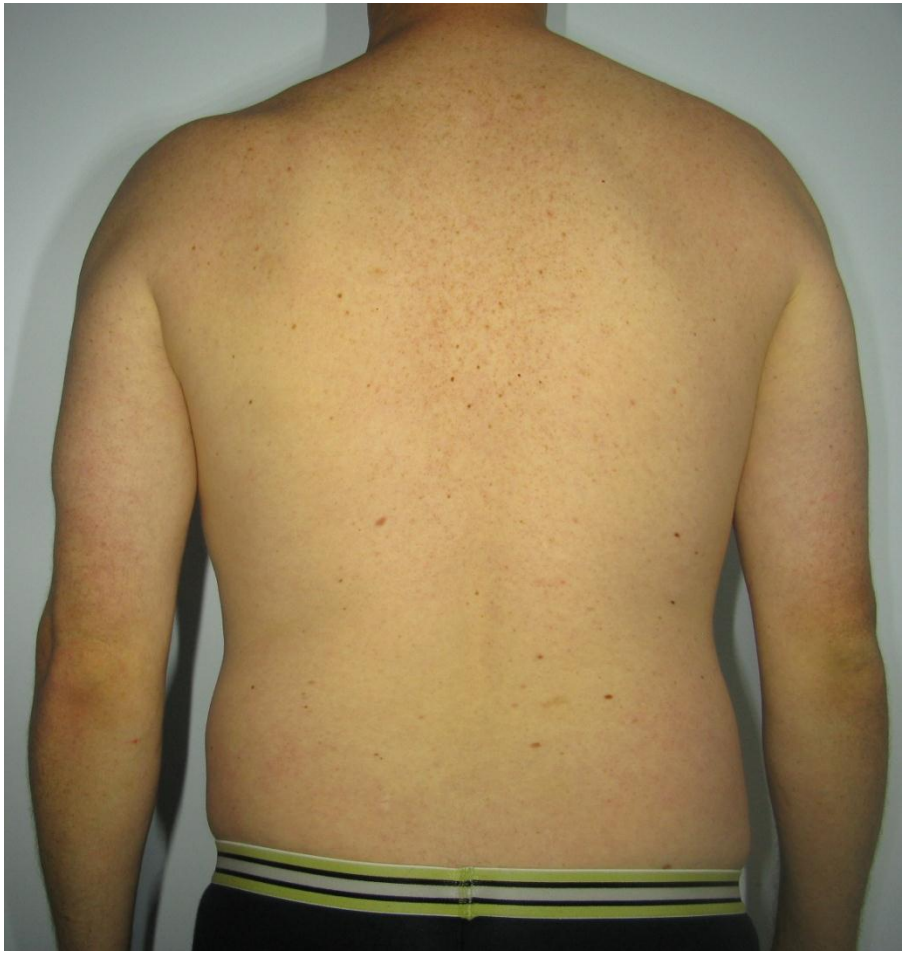
•October 2010, 5mm deposit of metastatic melanoma in left neck node resection.

•May 2011, begin naevus surveillance imaging.

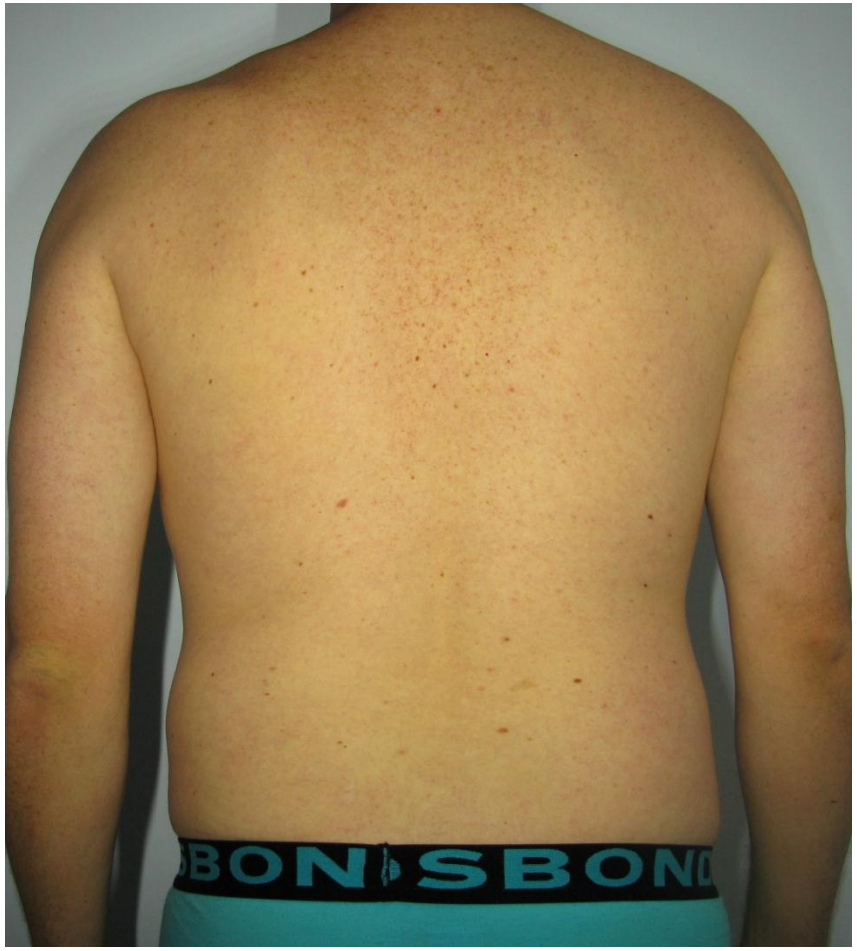
•July 2012, metastases found on pancreas, liver and mesenteric lymph nodes. BRAF positive.

•August 2012, Start Combi-D Trial with BRAFi Debrafenib +/- Trametinib

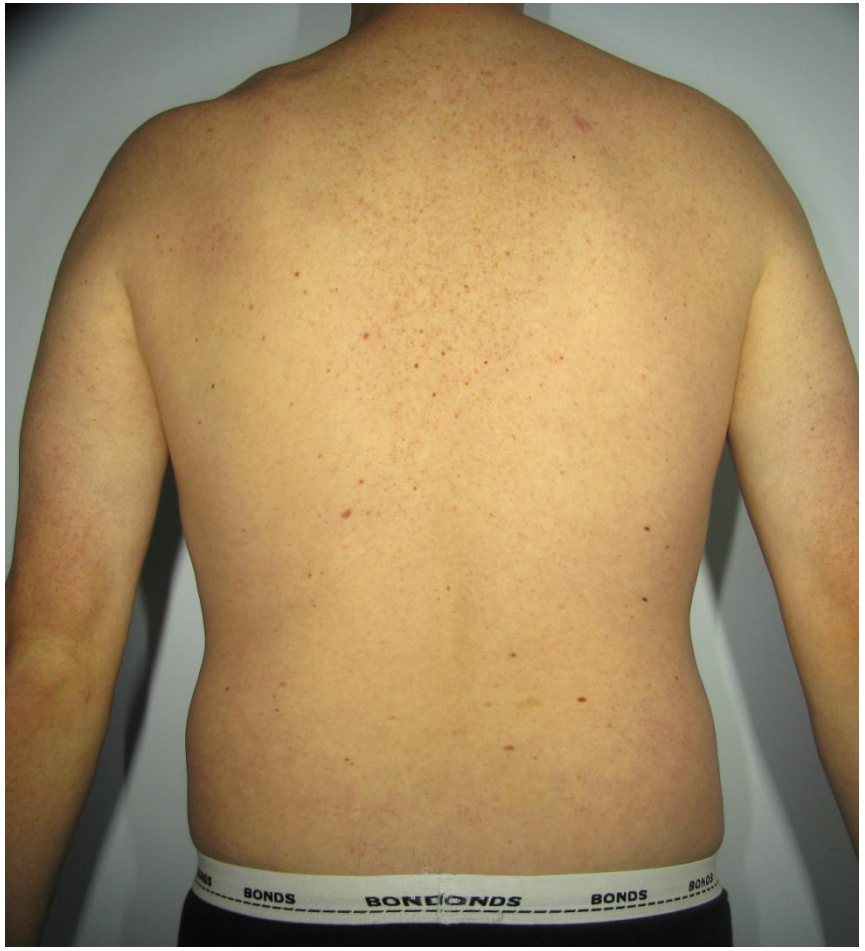
•February 2013, imaged naevi faded.



BRAF-i Naevus Surveillance Case



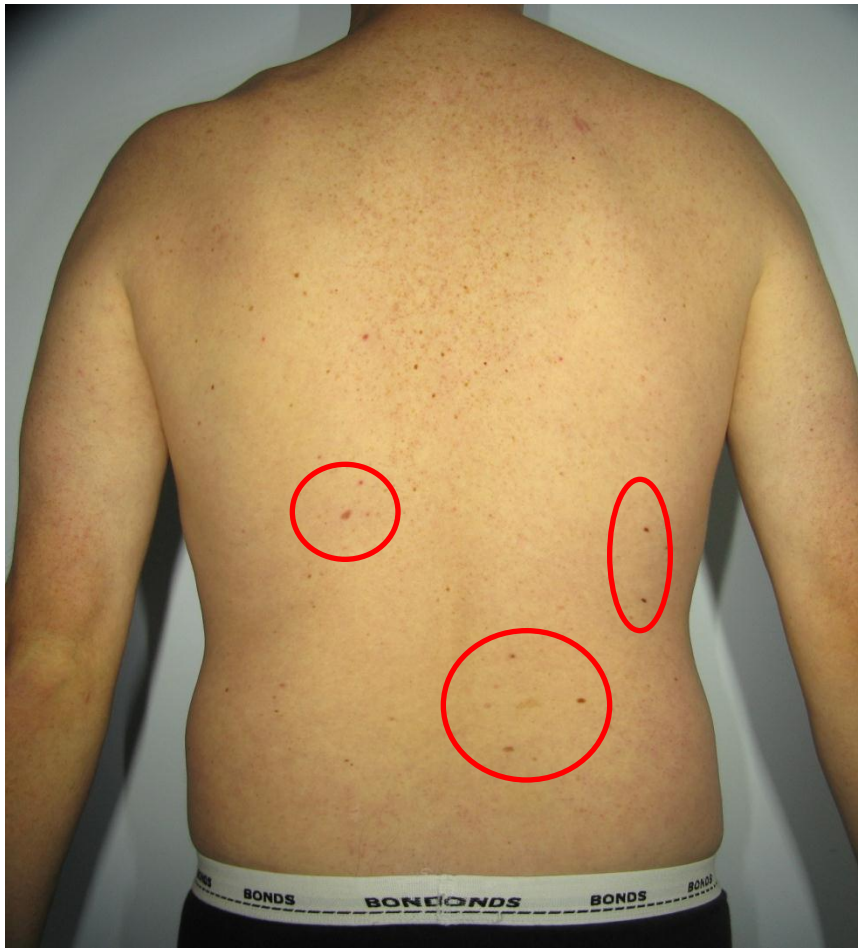
May 2011



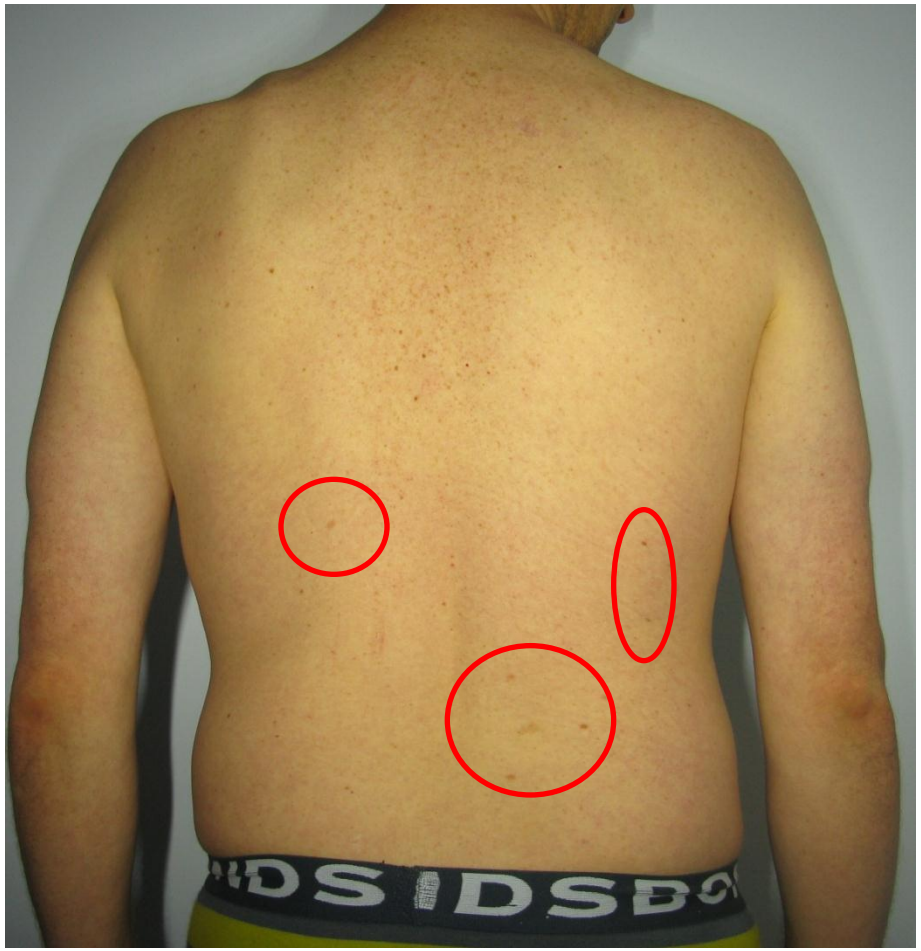
July 2012

BRAF-i Naevus Surveillance Case

August 2012, Start Combi-D Trial with BRAFi Debrafenib +/- Trametinib

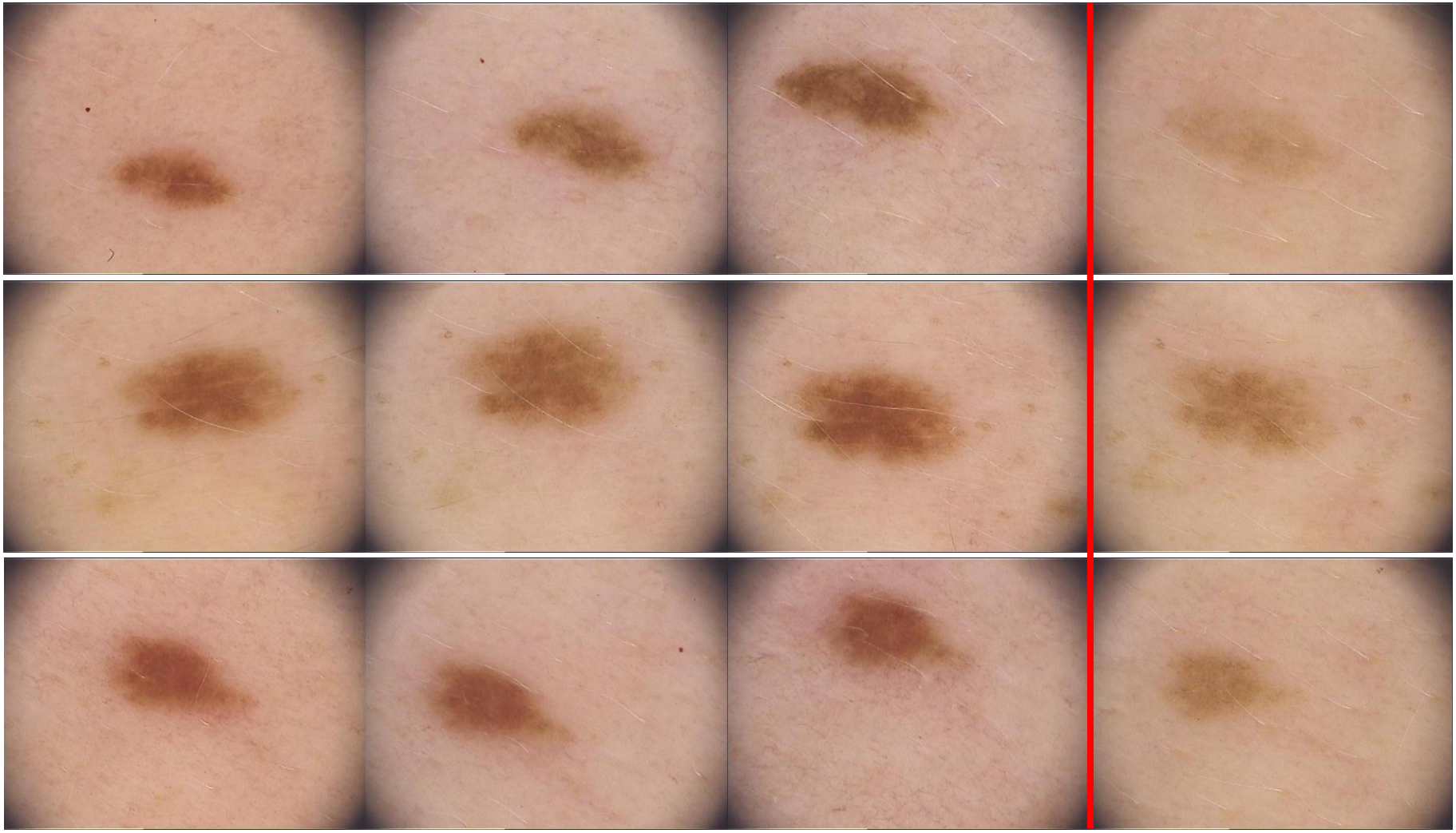


July 2012



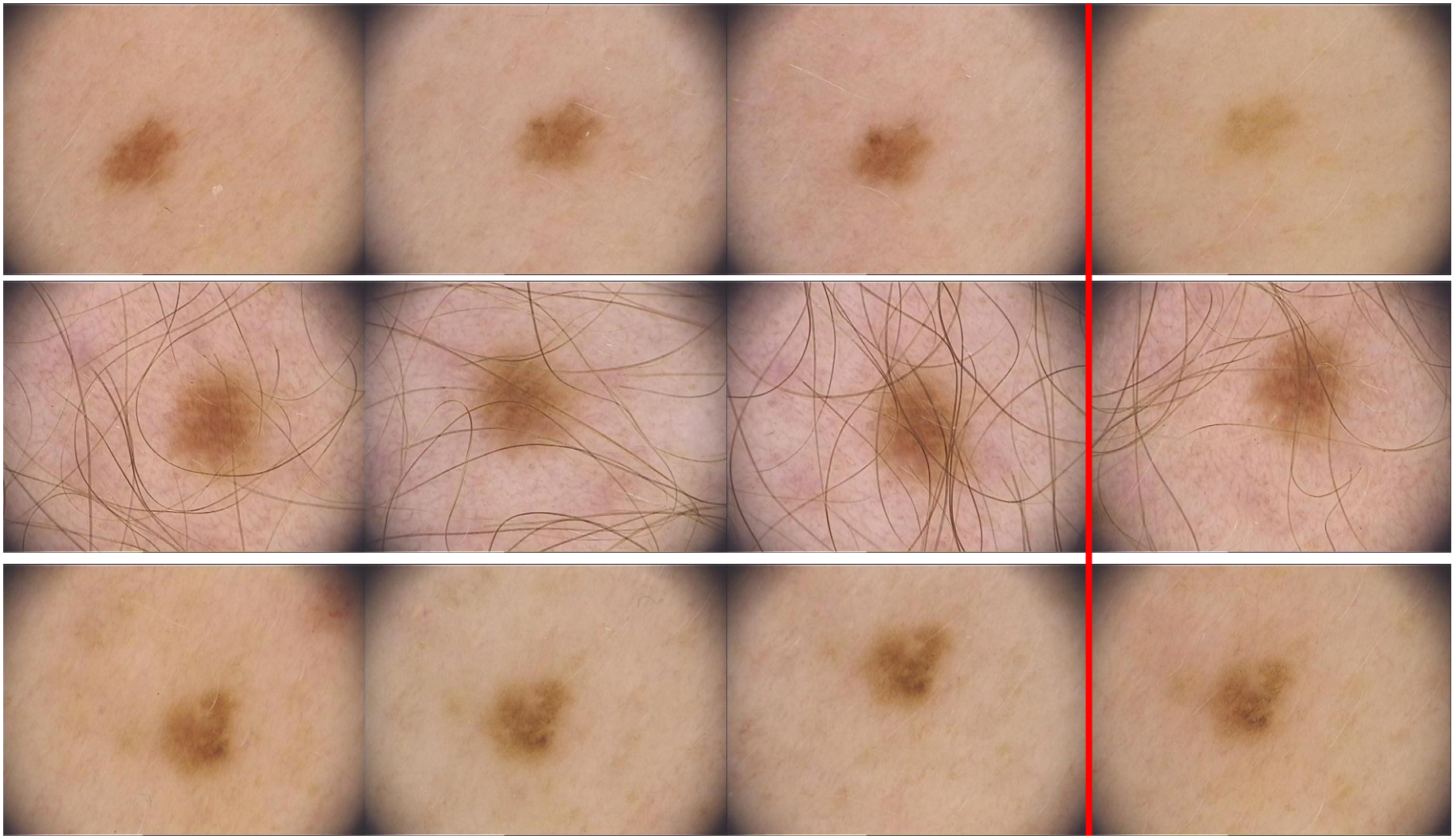
February 2013

BRAFi Changing Naevi



May 2011 December 2011 July 2012 February 2013

BRAFi Changing Naevi



May 2011 December 2011 July 2012 February 2013

ONLINE FIRST

Dynamic Changes in Nevi of a Patient With Melanoma Treated With Vemurafenib

Importance of Sequential Dermoscopy

Holger A. Haenssle, MD; Sophie L. Kraus, MD; Franziska Brehmer, MD; Lutz Kretschmer, MD; Bernward Völker, MD; Hiba Asper, MD; Alexander Kapp, MD; Ralf Gutzmer, MD

Background: Therapy with vemurafenib, an inhibitor of mutated BRAF, yields a response rate of approximately 50% in patients with metastatic melanoma harboring a *BRAF* V600E mutation. As an adverse effect of vemurafenib, proliferative disorders of keratinocytes, including squamous cell carcinoma, have been described. Low concentration of vemurafenib as present in the epidermis were found to activate wild-type RAF, which, in combination with a preexisting *RAS* mutation, can promote keratinocyte proliferation. While activating *BRAF* mutations occur in approximately 50% of melanomas, they are even more frequently observed in melanocytic nevi.

Observation: We present the case of a patient with dynamic changes of melanocytic nevi well documented by sequential digital dermoscopy during vemurafenib therapy. A variety of dermoscopic changes were observed. First, nevi involuted, and all of these originally showed a centrally elevated papillomatous and predominant globular pattern. Second, preexisting nevi increased in size, and pigmentation that rendered them atypical. Such lesions were flat and showed a predominant reticular pattern at baseline. Third, multiple new nevi occurred. One example of each of the latter 2 categories was excised and showed wild-type *BRAF*.

Conclusion: Our findings of changing nevi in a patient treated with vemurafenib highlight the need for sequential skin examinations, including dermoscopy.

Arch Dermatol.
Published online August 20, 2012.
doi:10.1001/archdermatol.2012.2649

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Atypical Melanocytic Proliferations and New Primary Melanomas in Patients With Advanced Melanoma Undergoing Selective *BRAF* Inhibition

Lisa Zimmer, Uwe Hillen, Elisabeth Livingstone, Mario E. Lacouture, Klaus Busam, Richard D. Carvajal, Friederike Egberts, Axel Hauschild, Mohammed Kashani-Sabet, Simone M. Goldinger, Reinhard Dummer, Georgina V. Long, Grant McArthur, André Scherag, Antje Sucker, and Dirk Schadendorf

mmer, Uwe Hillen, Elisabeth
stone, Antje Sucker, and Dirk
andorf, University Hospital Essen;

ABSTRACT

Table. Patient and Melanoma Characteristics in Study Cases

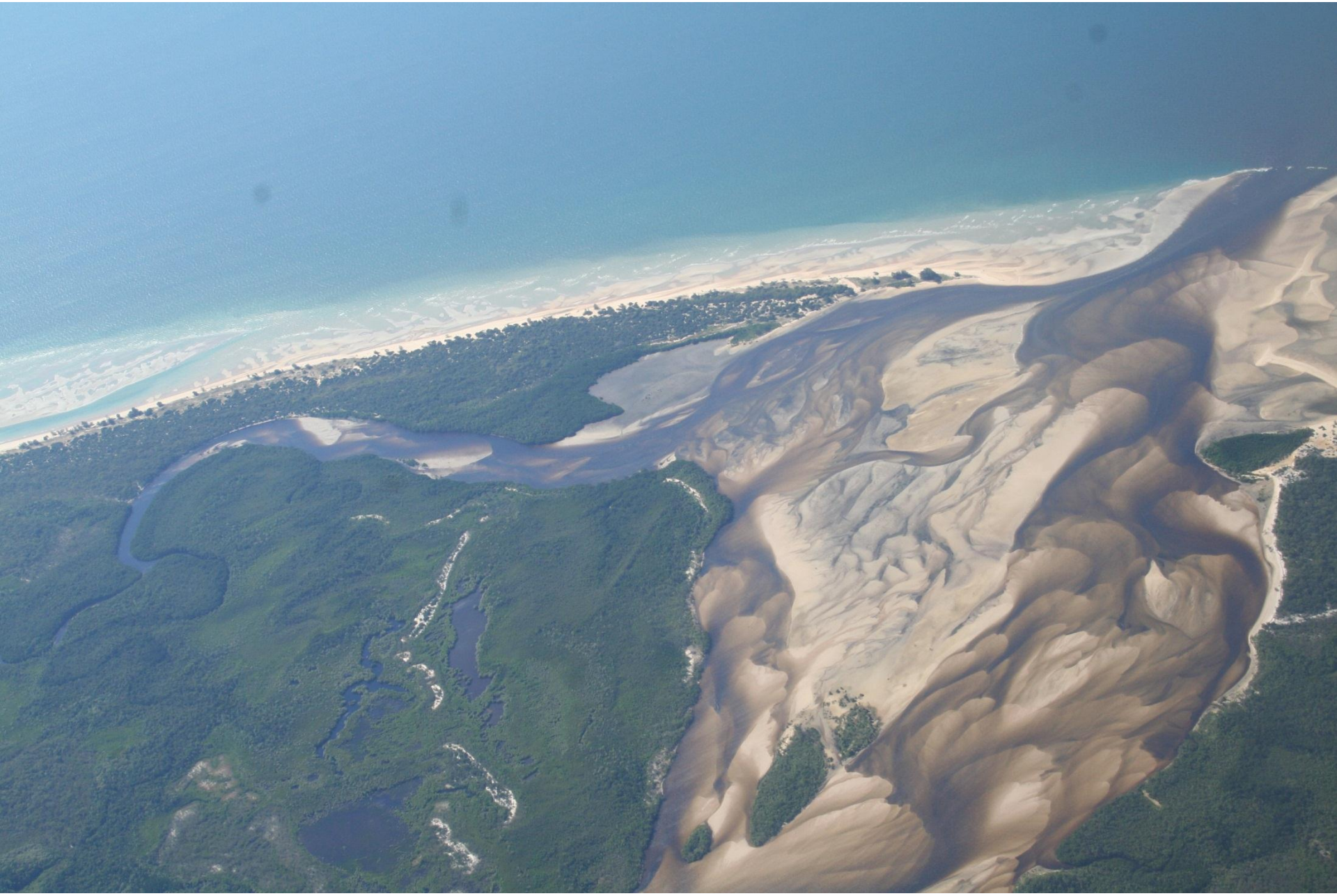
Patient No./ Sex/Age, y (n = 16)	Melanomas, No. (n = 25)	Lesion Location	Interval from Treatment Start to Lesion Excision, wk	Detection Method	Melanoma Breslow Thickness, mm	Mutation Status	Phospho-ERK Immunostaining
1/F/55	1	Right forearm	11	Patient reported	0.7	Wild type	NA
2/F/58	2	Left forearm	12	Patient reported	0.65	Wild type	NA
		Right Cheek	20	Dermoscopy	0.3	Wild type	NA
3/M/67	1	Right breast	10	Dermoscopy	0.45	NRAS Q61R mutated	NA
4/M/75	2	Right shoulder	6	Dermoscopy	0.4	NA	Positive focal
		Right flank	6	Dermoscopy	0.4	NA	Positive focal
5/F/38	1	Upper back	12	Dermoscopy	0.35	Wild type	Positive diffuse
6/M/63	2	Right leg	8	Dermoscopy	In situ	Wild type	NA
		Left cheek	12	Dermoscopy	0.3	Wild type	NA
7/M/57	2	Left back	12	Dermoscopy	In situ	Wild type	NA
		Right lower back	22	Dermoscopy	In situ	Wild type	NA
8/M/47	1	Right abdomen	16	Dermoscopy	0.45	Wild type	Positive focal
9/F/81	2	Right calf	14	Digital dermoscopy	In situ	NA	Positive focal
		Right calf	14	Digital dermoscopy	0.35	NA	Positive focal
10/F/53	1	Back	42	Digital dermoscopy	0.3	Wild type	NA
11/M	2	Back	15	Digital dermoscopy	0.3	Wild type	Positive focal
		Back	15	Digital dermoscopy	0.35	Wild type	Positive focal
12/F/37	2	Left thigh	11	Dermoscopy	In situ	NA	NA
		Right shoulder	26	Digital dermoscopy	In situ	NA	NA
13/M/45	1	Back	28	Digital dermoscopy	In situ	NA	NA
14//F/38	1	Back	4	Digital dermoscopy	In situ	NA	NA
15/M/47	3	Back	14	Digital dermoscopy	0.15	Wild type	NA
		Left flank	14	Digital dermoscopy	0.3	Wild type	Positive focal
		Chest	14	Digital dermoscopy	0.2	Wild type	Positive focal
16/M/46	1	Back	11	Digital dermoscopy	0.3	Wild type	Positive diffuse

Abbreviations: ERK, extracellular signal-related kinase; NA, not applicable.

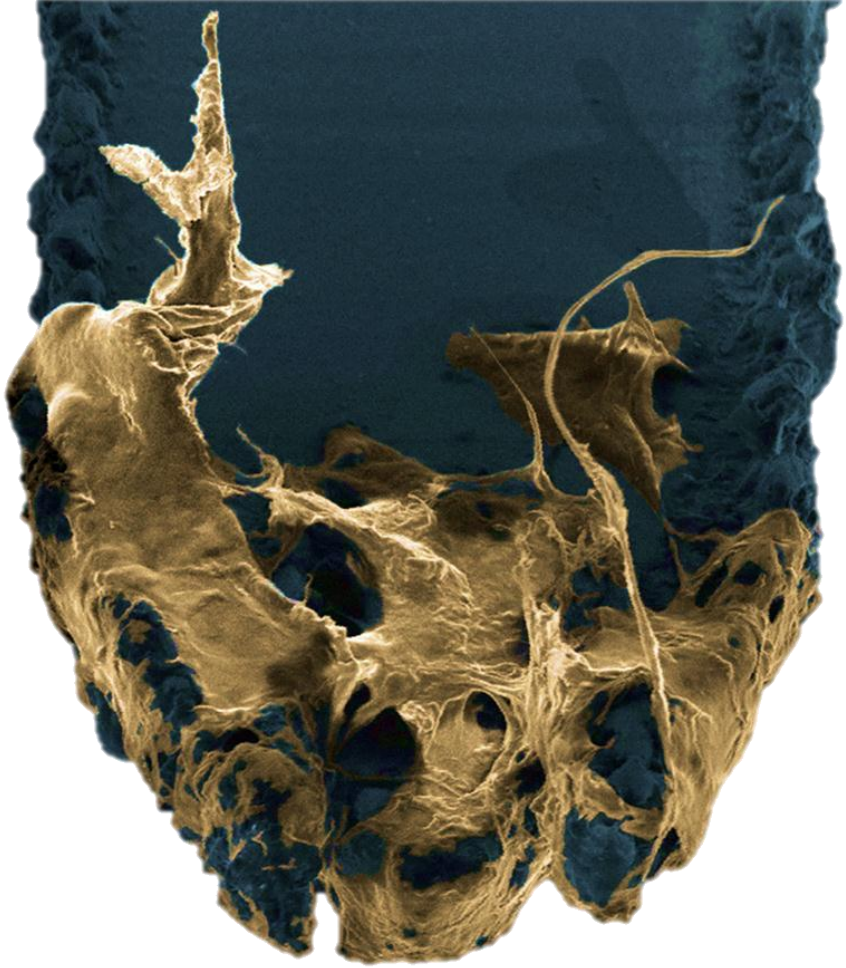
JAMA Dermatol. 2013 Apr 1;149:488-90

Tracking of second primary melanomas in vemurafenib-treated patients.

Dalle S et al.



The University Of Queensland
AUSTRALIA

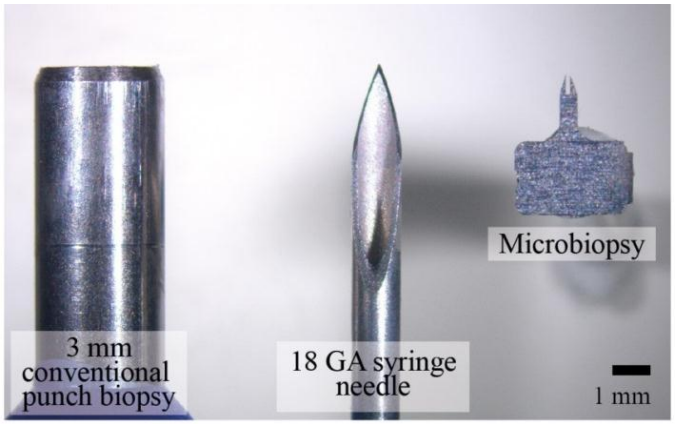


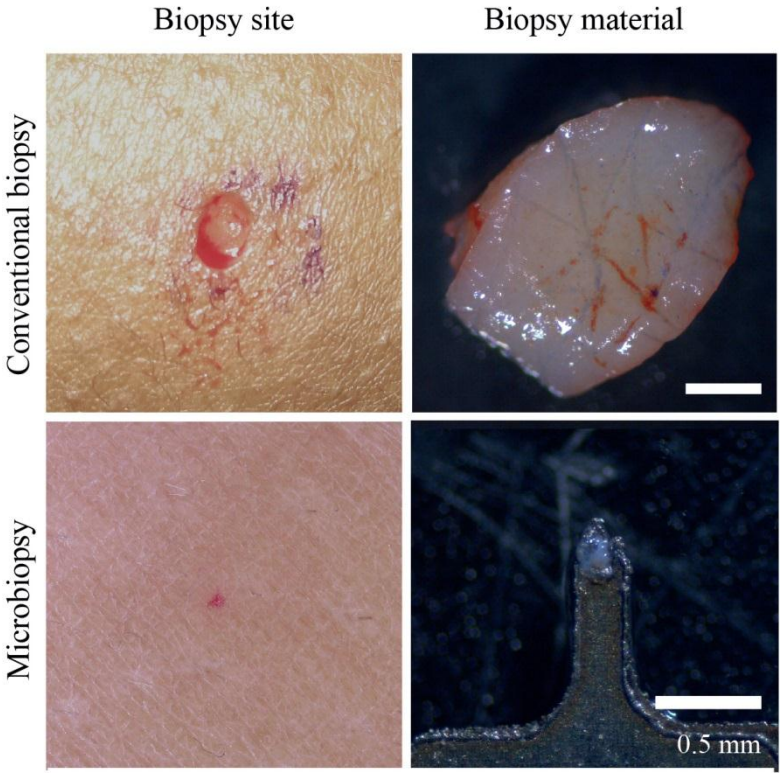
Microbiopsy

Lynlee L. Lin,
(PhD Student)

There is a need for minimally invasive biopsy for molecular analysis

Conventional punch biopsy and Microbiopsy™



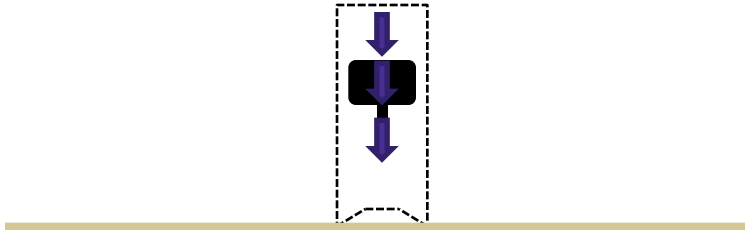


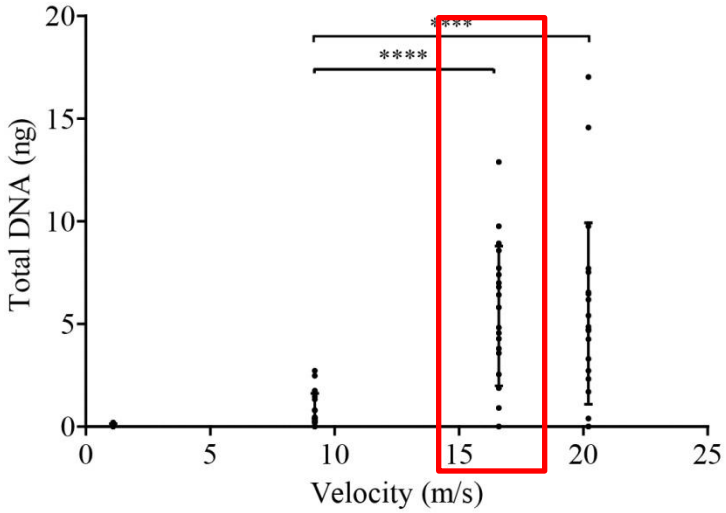
Conventional punch biopsy and Microbiopsy™

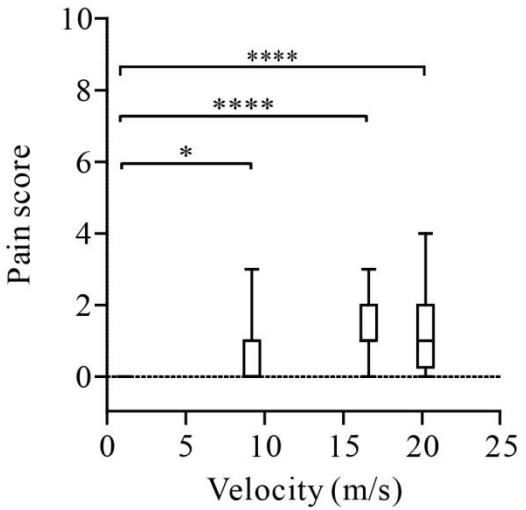
	Microbiopsy	Conventional Biopsy
Histopathological data	X	√
RNA analysis	√	√
DNA analysis	√	√
Live tissue analysis	√	√
No Local anaesthetic	√	X
No Suture	√	X
No Pain	√	X
No Scar	√	X

Effects of application velocity on Microbiopsy™

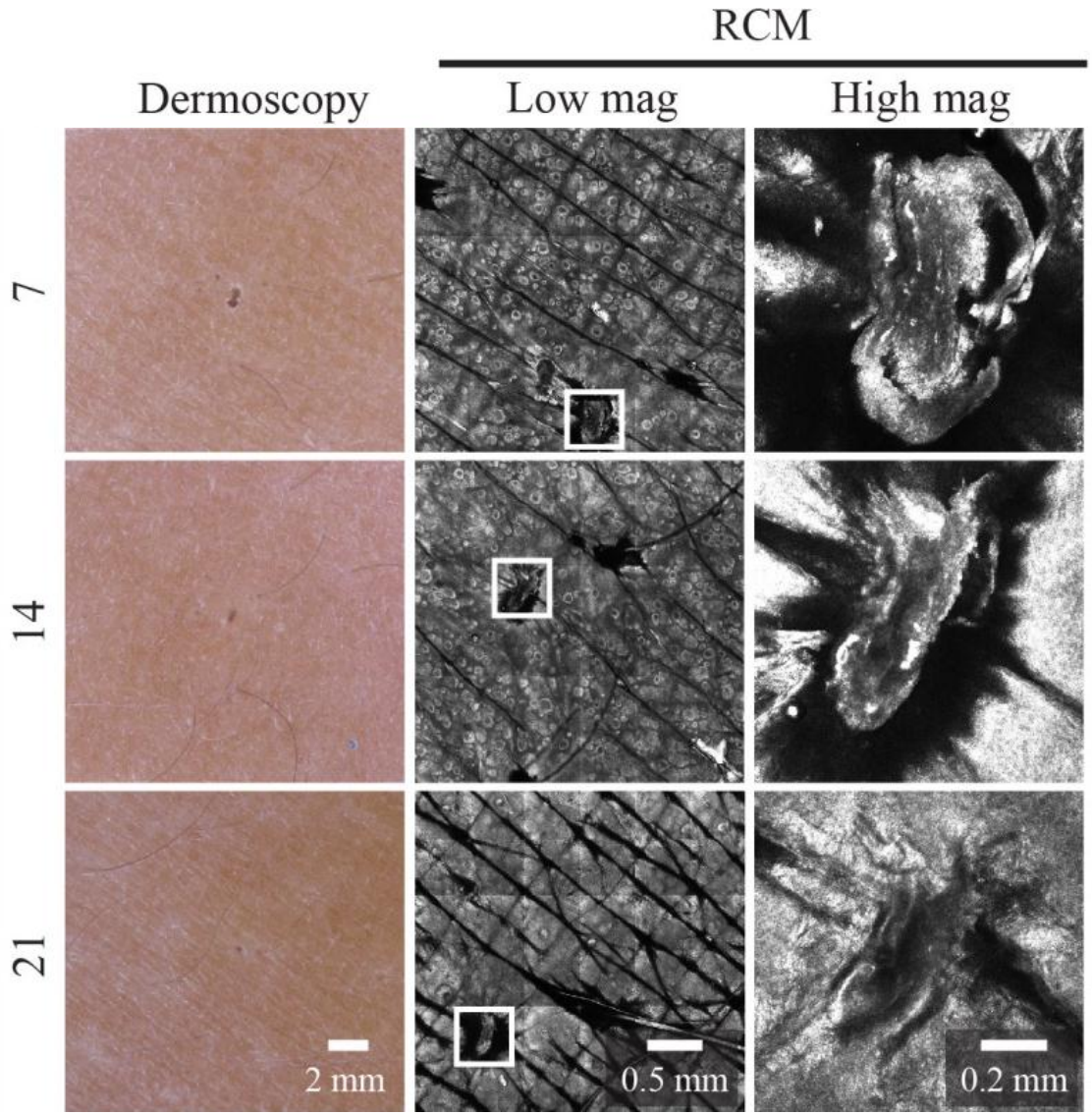
Current administration
High impact velocity
Modified lancet device







Clinical follow-up of microbiopsy site



Downstream molecular analysis

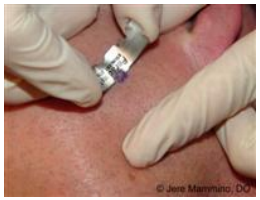
Microbiopsy

RNA isolation

14 ng RNA

Whole transciptome amplification

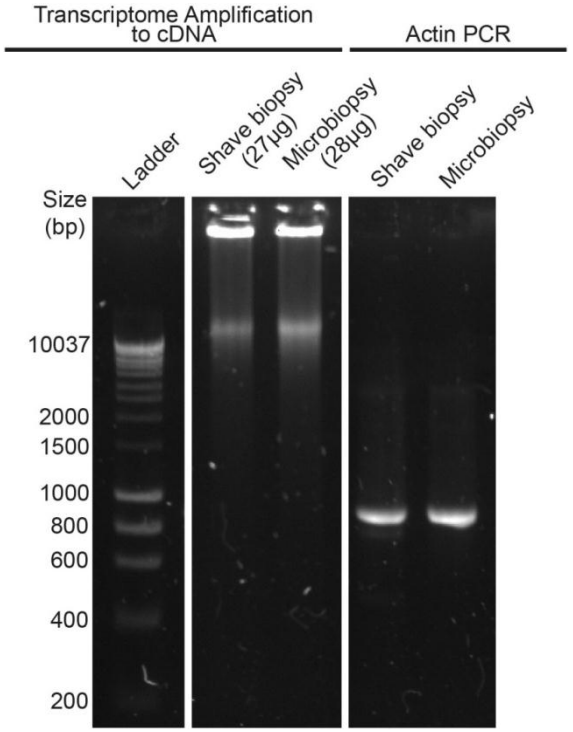
28 µg cDNA



Shave Biopsy from patient

14 ng RNA

26 µg cDNA

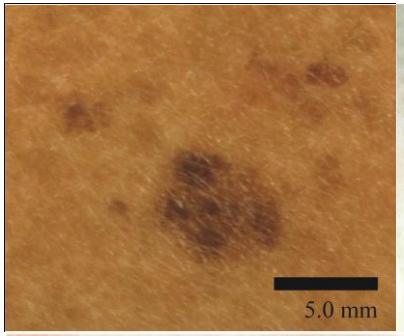


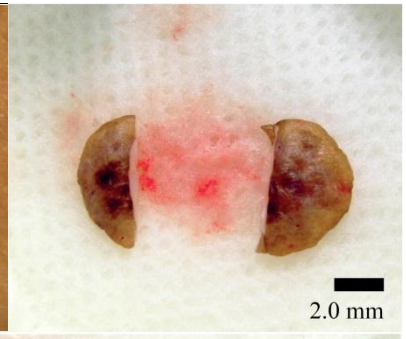
The microbiopsy extracts a nanogram sized sample

Molecular amplification increase the sample size by 3 orders of magnitude

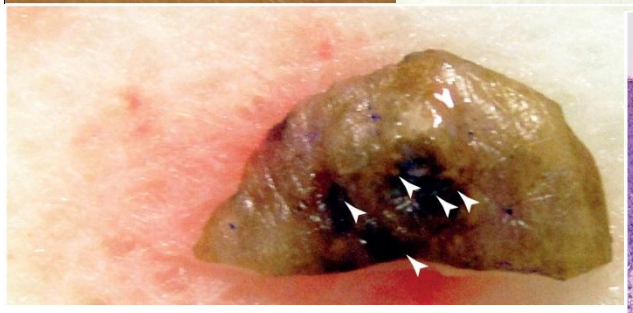
This amount of cDNA can be used for virtually any relevant assay

Poster#90: Skin microbiopsy effects on histopathological diagnosis of pigmented lesions

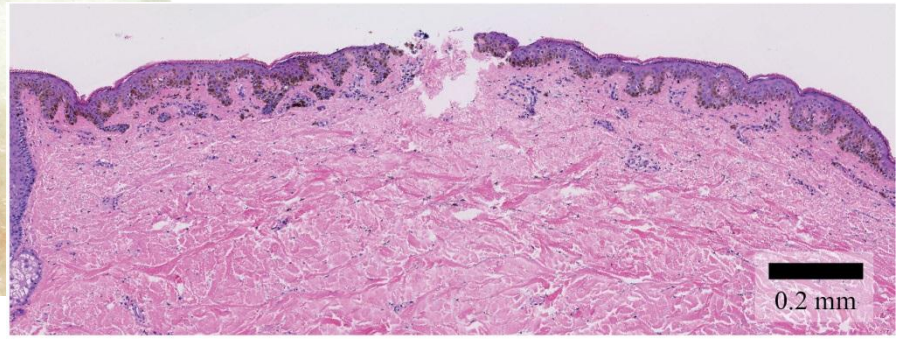


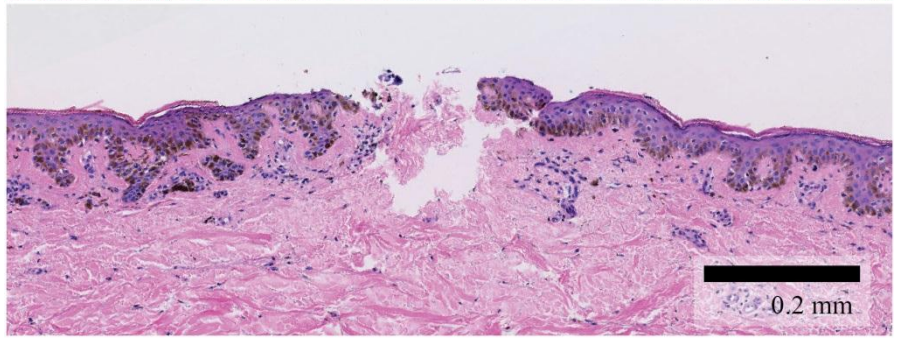


Diagnosis: Junctional lentiginous nevus



Deep shave biopsy of suspicious nevus

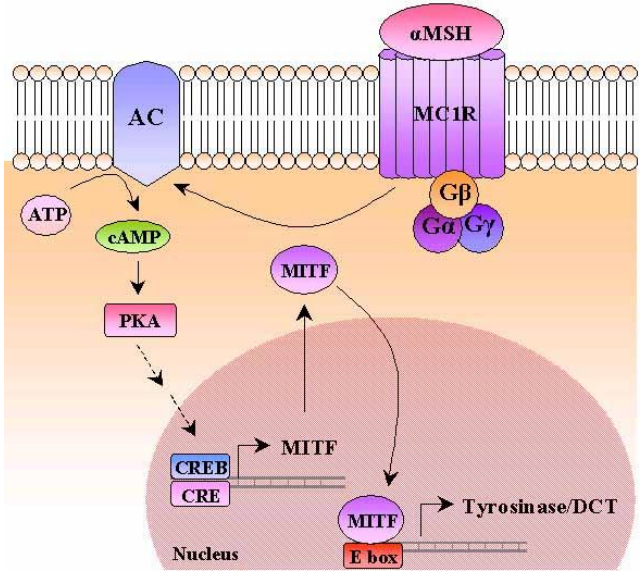




In Press: Banan P, Lin LL, Lambie D, Prow TW, Soyer HP. Ex-vivo skin microbiopsy effects on histopathological diagnosis in melanocytic skin lesions. JAMA Dermatology.

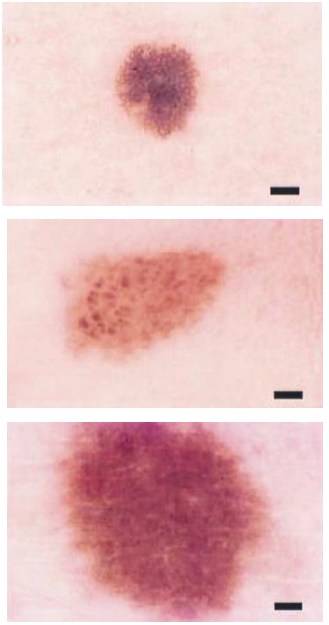

STURM
frischer
STURM
Murauer
Glühwein
Jagertee
Punsch
Kakao mit
Rum
Rein das Beste

MC1R Study: pigmentation genotype and naevus phenotype



Kabbarah and Chin, 2006

?



Hofmann-Wellenhof, 2001

Do pigmentation genes such as MC1R dictate the dermoscopic characteristics of naevi?

Are there gene Variants that control mole morphology?

MC1R and dermoscopic features of melanoma
Cuellar et al. BJD 160: 48-53 (2009)

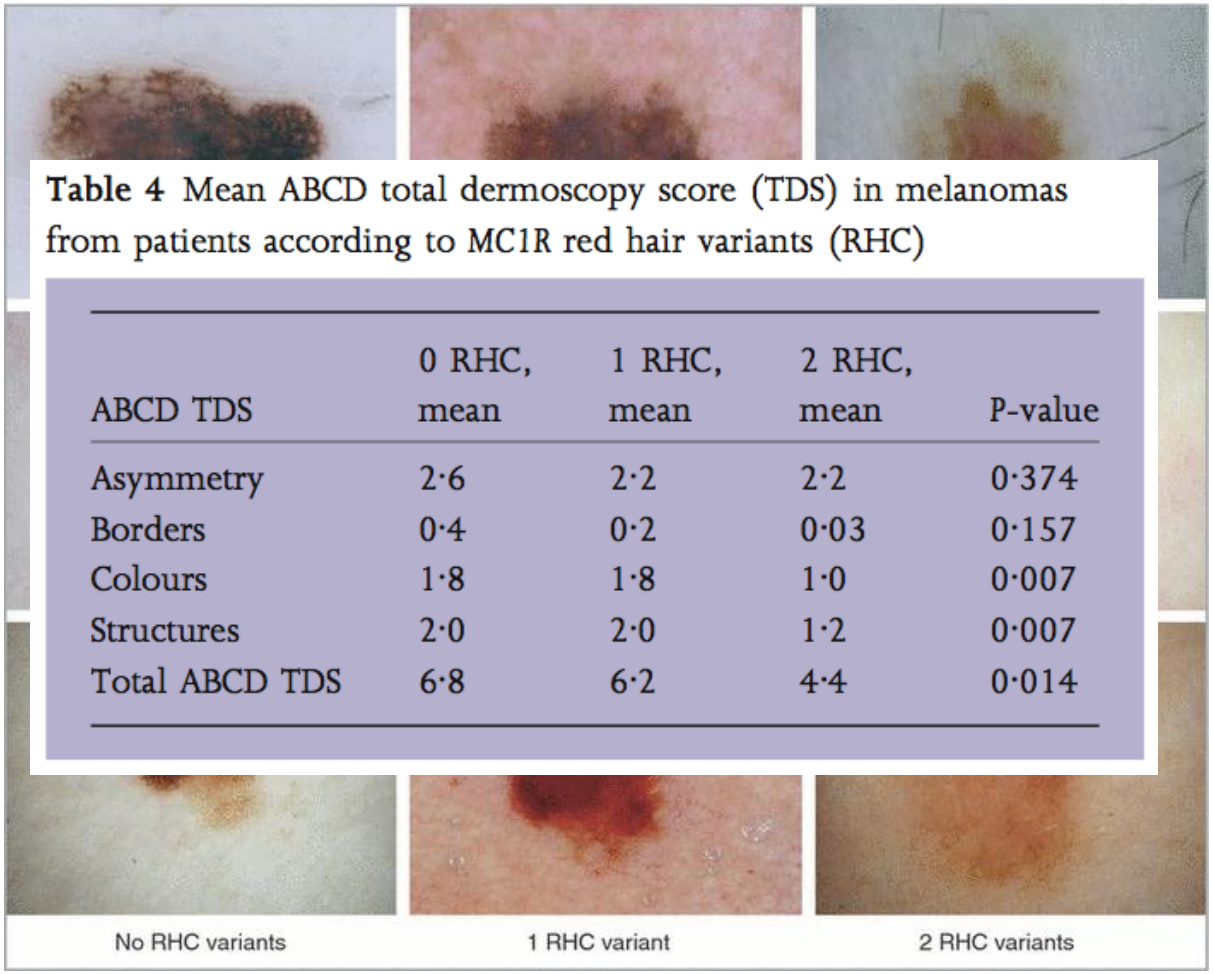


Table 4 Mean ABCD total dermoscopy score (TDS) in melanomas from patients according to MC1R red hair variants (RHC)

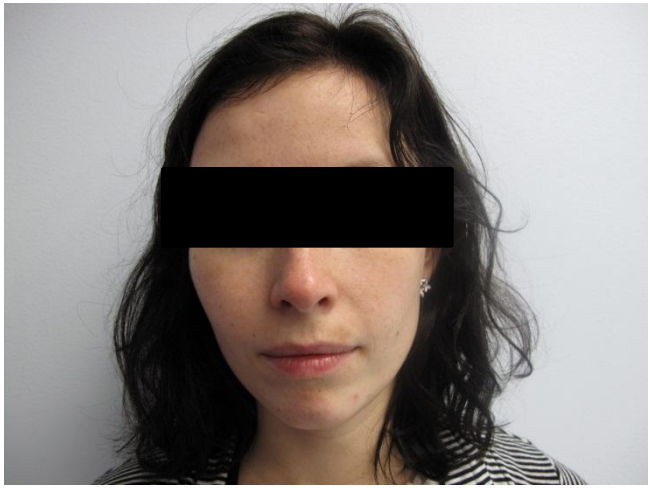
ABCD TDS	0 RHC, mean	1 RHC, mean	2 RHC, mean	P-value
Asymmetry	2·6	2·2	2·2	0·374
Borders	0·4	0·2	0·03	0·157
Colours	1·8	1·8	1·0	0·007
Structures	2·0	2·0	1·2	0·007
Total ABCD TDS	6·8	6·2	4·4	0·014

No RHC variants | 1 RHC variant | 2 RHC variants

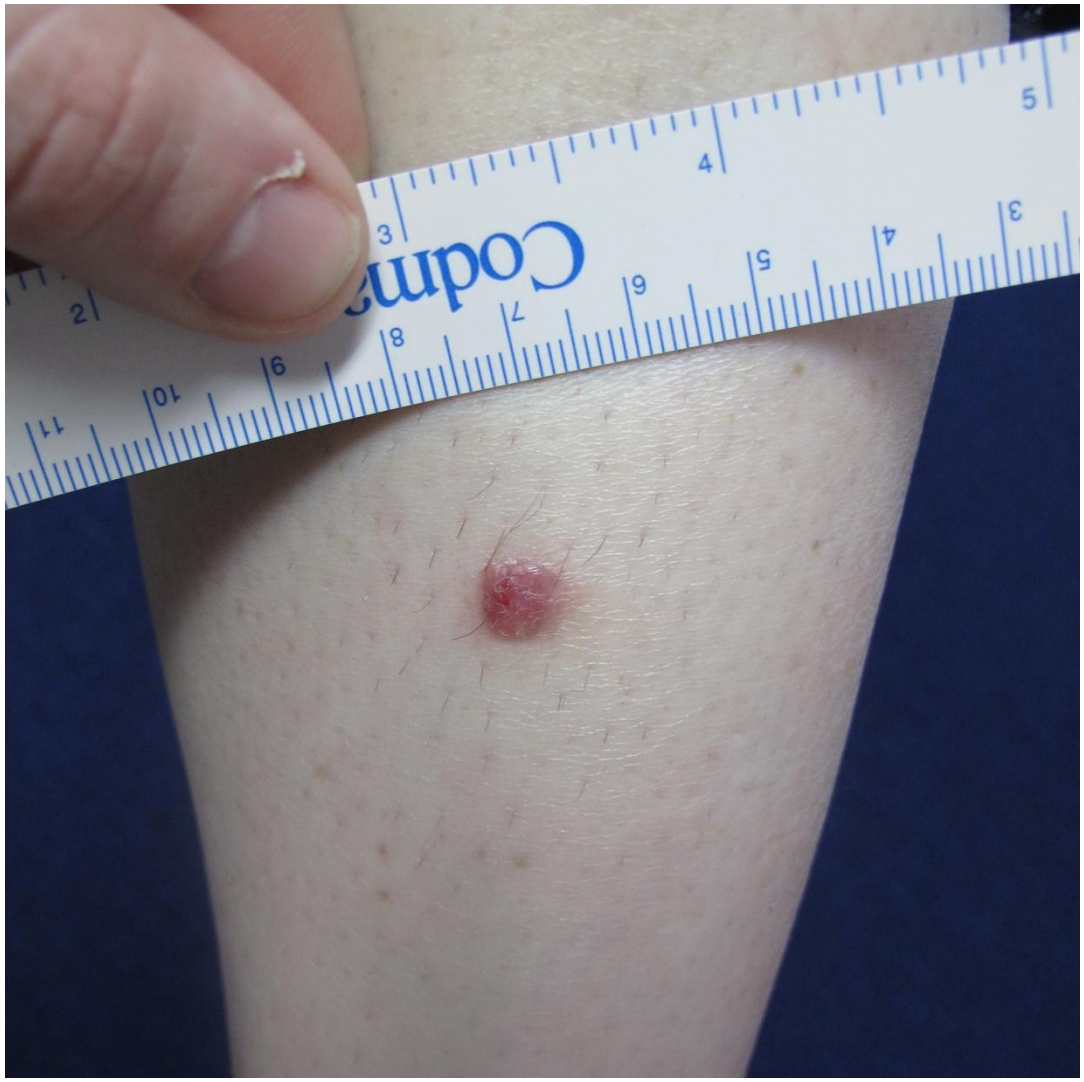
WT/WT **WT/R** **R/R**

Case Study

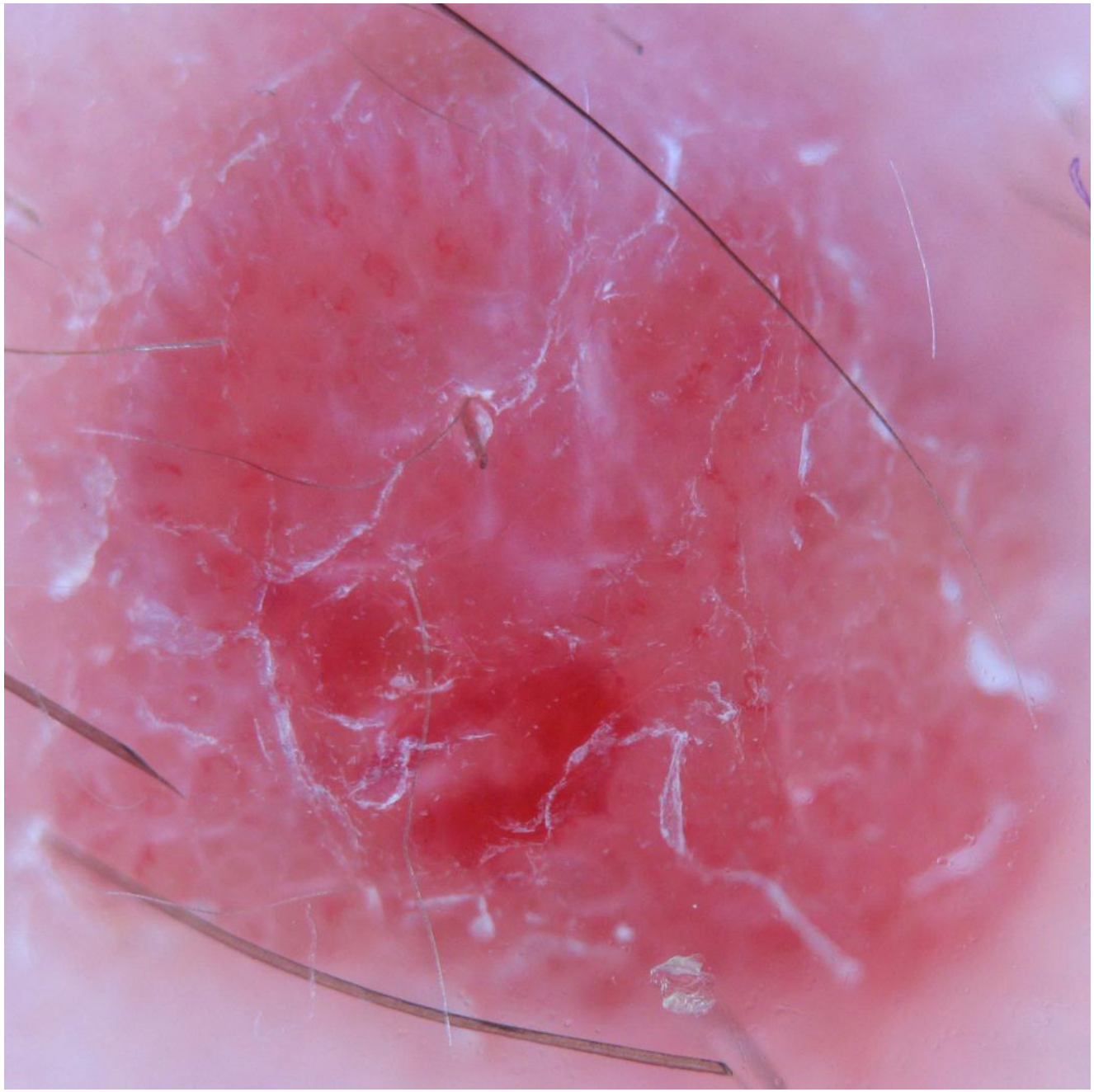
- 26 year old female
- Fitzpatrick's skin type II?
- Fair skin
- Brunette; hazel eyes



- Lived entire life in Queensland
- Had always been vigilant with sun protection
- No significant medical history
- No family history of melanoma
- Basically no moles



- 10 x 7mm pink nodule her left lower leg
- Present for 2 years; growing for 6 months
- Frequently bled when shaved legs



Polymorphous blood vessels on a pink background

Australasian Journal of Dermatology

Australasian Journal of Dermatology (2012) 53, 291–294 doi: 10.1111/j.1440-0960.2012.00882.x

BRIEF REPORT

Dermoscopy, reflectance confocal microscopy and histopathology of an amelanotic melanoma from an individual heterozygous for MC1R and tyrosinase variant alleles

Claudia Curchin,[1,3] Elisabeth Wurm,[1] Kasturee Jagirdar,[2] Richard Sturm[2] and Peter Soyer[1,3]

[1]School of Medicine Dermatology Research Centre, University of Queensland, [2]Institute for Molecular Bioscience, University of Queensland, and [3]Department of Dermatology, Princess Alexandra Hospital, Brisbane, Queensland, Australia

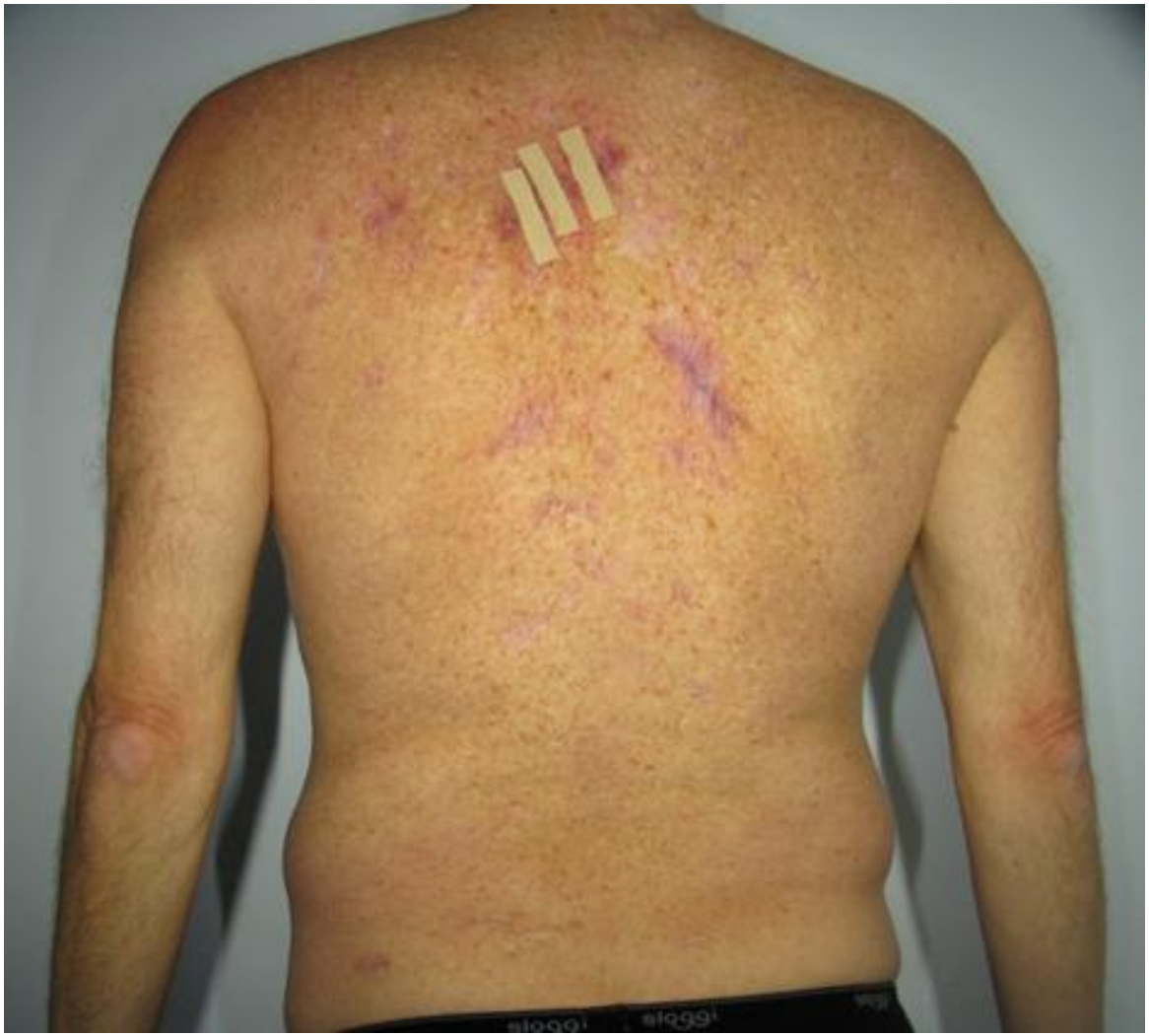
Patient Subset with MC1R R/R

Began February 2011, interim analysis performed February 2013.

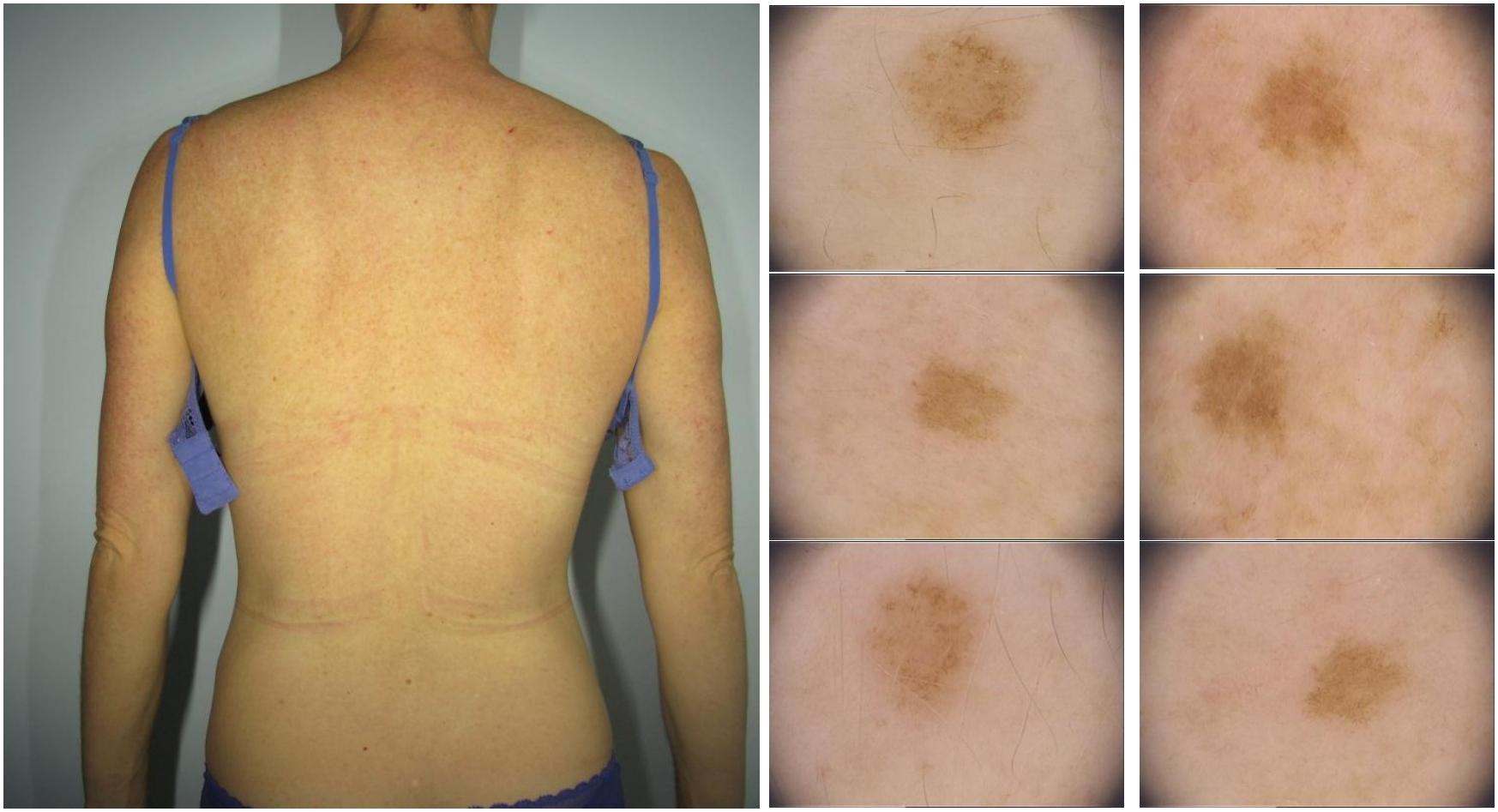
Total 301 participants in analysis

22 are MC1R R/R (7.3%)

Any naevi larger than 5mm were included in analysis.

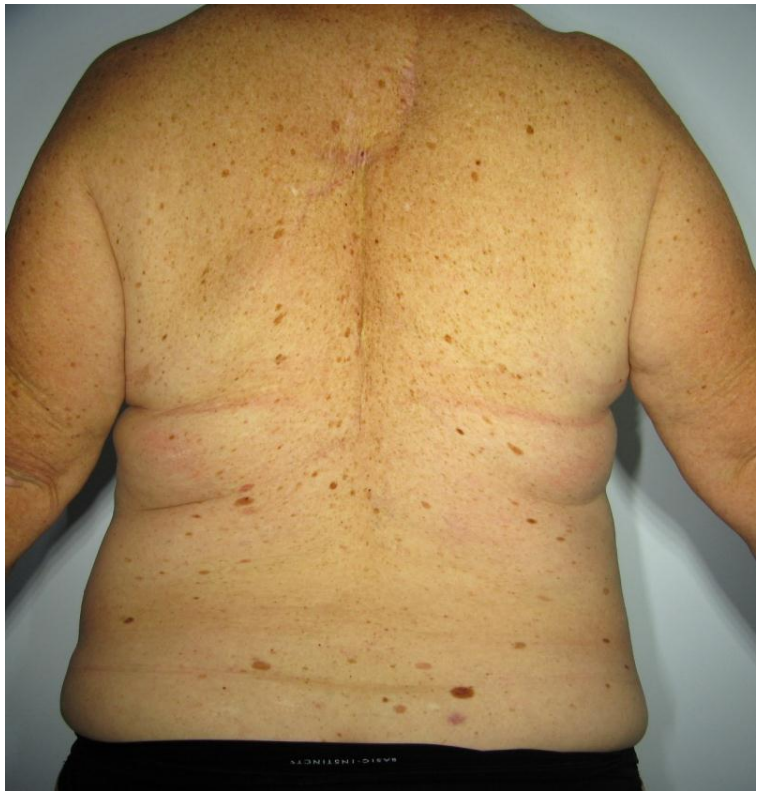


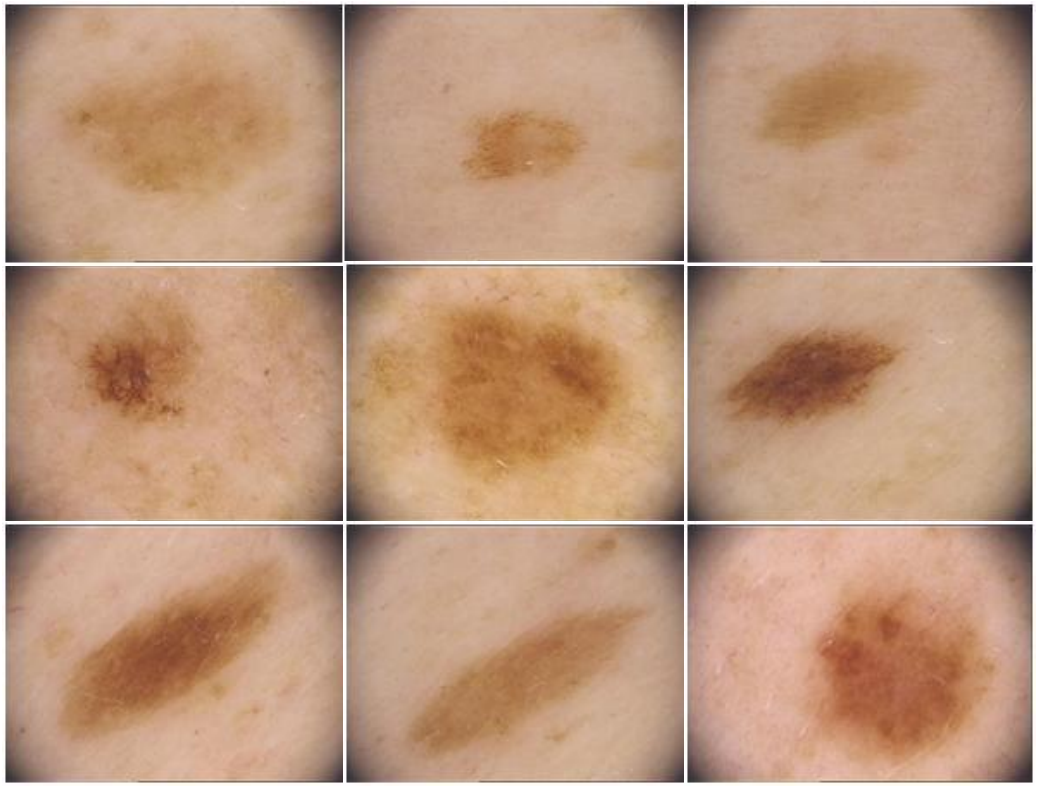
Patient ID	MC1R Genotype		Sex	Age at Baseline	Hair Colour	Freckling	Naevi >5mm	# Melanomas
004PF	R151C +/-; R160W +/-	R/R	M	52	Light Brown	Mild	35	1
014JM	R151C +/-; R160W +/-	R/R	M	34	Red	Severe	35	13
015KJ	R160W +/-; D294H +/-	R/R	F	48	Red	Moderate	173	5
019MC	R151C +/-; R160W +/-	R/R	F	60	Red	Severe	130	5
031KR	D84E +/-; R160W +/-	R/R	F	38	Dark Brown	Severe	16	0
044CI	R160W -/-	R/R	F	28	Red	Moderate	7	0
149DC	D84E+/-; R160W+/-	R/R	M	61	Red	Severe	28	4
168CF	R151C -/-	R/R	F	58	Red	Moderate	17	2
176SP	R151C -/-	R/R	F	57	Red	Moderate	111	4
203DM	R151C -/-	R/R	F	46	Red	Moderate	6	1
206NK	R160W +/-; D294H+/-	R/R	M	49	Red	Severe	27	2
215EA	R151C -/-	R/R	F	37	Red	Moderate	3	2



Patient 1, Female, 37 years old. History of 2 melanomas.

Total of 9 naevi > 5mm on the whole body. Only 6 identified on the back.





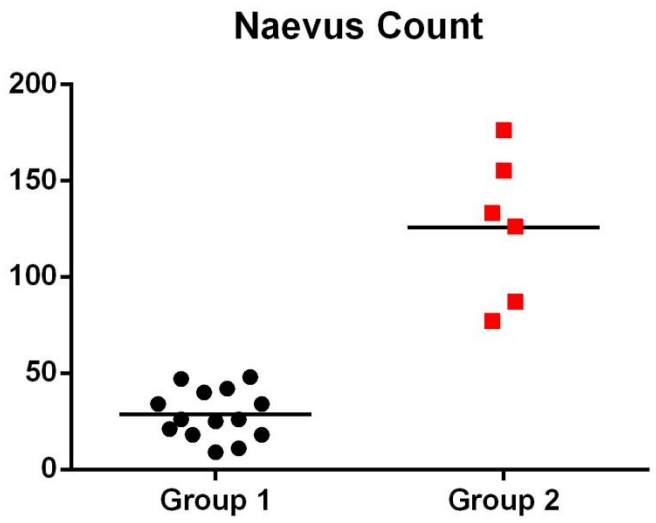
Patient 2. Female, 60 years old. History of five melanomas.

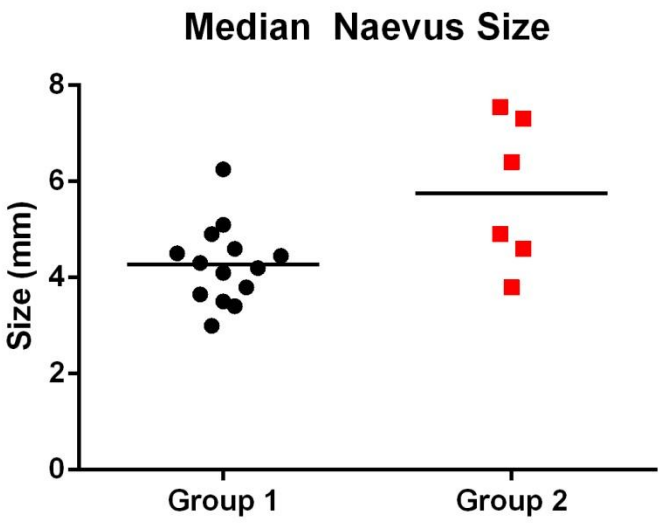
Total of 155 naevi > 5mm on the whole body. 50 of these naevi are on the back.

Analysis of Phenotypes

Groups were determined based on these two clinical phenotypes then assessed for statistical differences.

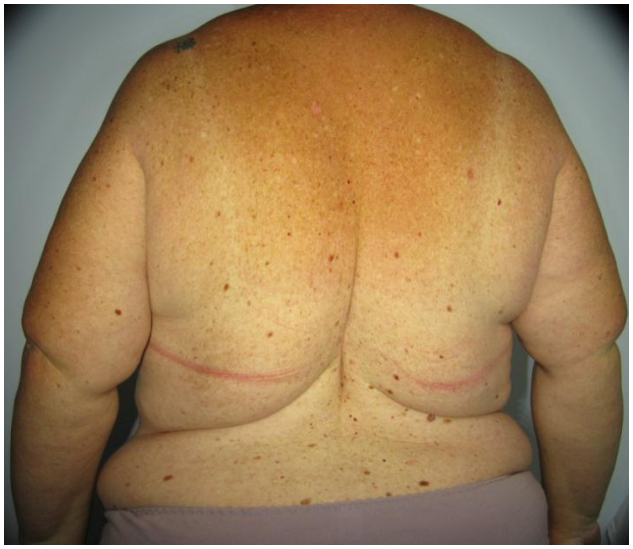
Of the MC1R R/R group we found 16 low naevus count subjects and 6 high naevus count subjects.

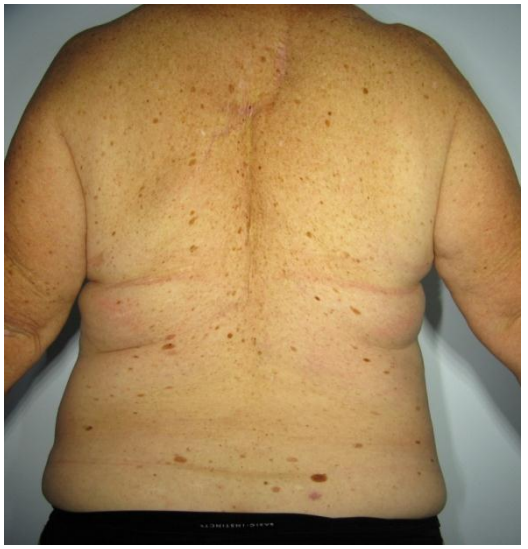




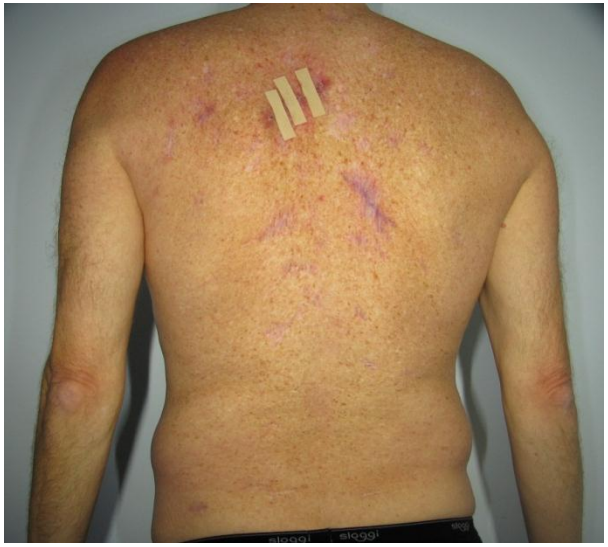
Two MC1R R/R Phenotypes

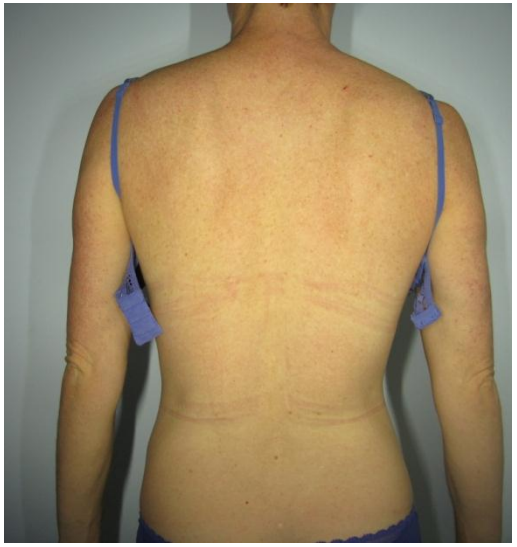
Numerous Naevi (n= 6)





Relatively Few Naevi (n=14)





Research Collaborations in Naevus Research

The University of Queensland, School of Medicine, Dermatology Research Centre

H. Peter Soyer
Phil McClenahan
Elizabeth McEniery
Sam Beh
Tristan Blake
Natalie Ong
Sandy Lee
Tarl Prow
Li Lin
Sam Hames

The University of Queensland, Institute for Molecular Bioscience

Rick Sturm
Kasturee Jagirdar

Queensland Institute of Medical Research

David Duffy
Graeme Walker
Adele Green
David Whiteman

Queensland University of Technology

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Queensland Health, Princess Alexandra Hospital, Melanoma Unit

Mark Smithers

The University of Queensland, Diamantina Institute

Brian Gabrielli

Queensland Health, Princess Alexandra Hospital, Dermatology

Victoria Atkinson
Euan Walpole

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