Professor H. Peter Soyer

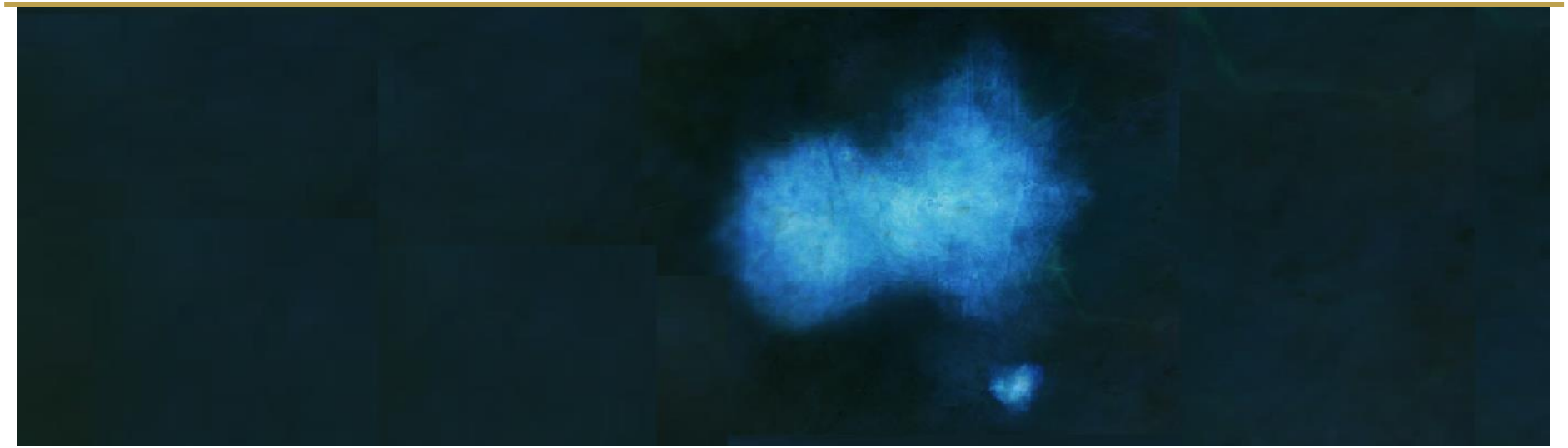
Academic Dermatologist

The University of Queensland

Brisbane

Friday, June 9, 2017

14:00 - 14:15 There are Moles and There are Moles



There are Moles and There are Moles

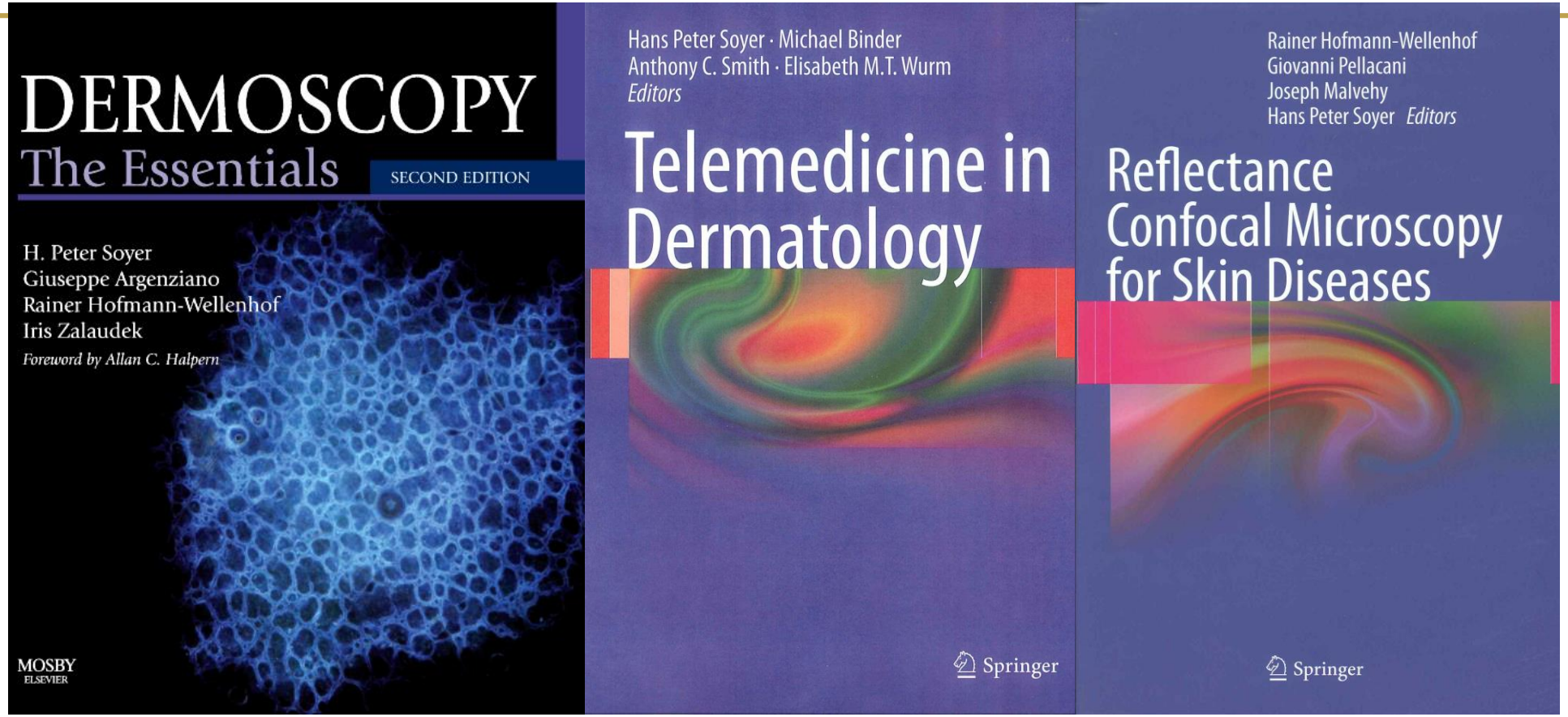
H. Peter Soyer

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

p.soyer@uq.edu.au @UQDRC @NaeviCRE

Conflicts of Interests

THE UNIVERSITY OF QUEENSLAND
AUSTRALIA



e-derm-consult

MoleMap by Dermatologists

First Derm

Morphologic Dimension

What is your diagnosis?

International Dermoscopy Diploma

Medical University Graz

- Start
- Why dermoscopy?
- Approaches
- Recognition process
- What is your diagnosis?

WHAT IS YOUR DIAGNOSIS?

Click on the correct answer?

- Melanoma
- Benign Nevus
- I don't know!

Morphologic Dimension

What is your diagnosis?

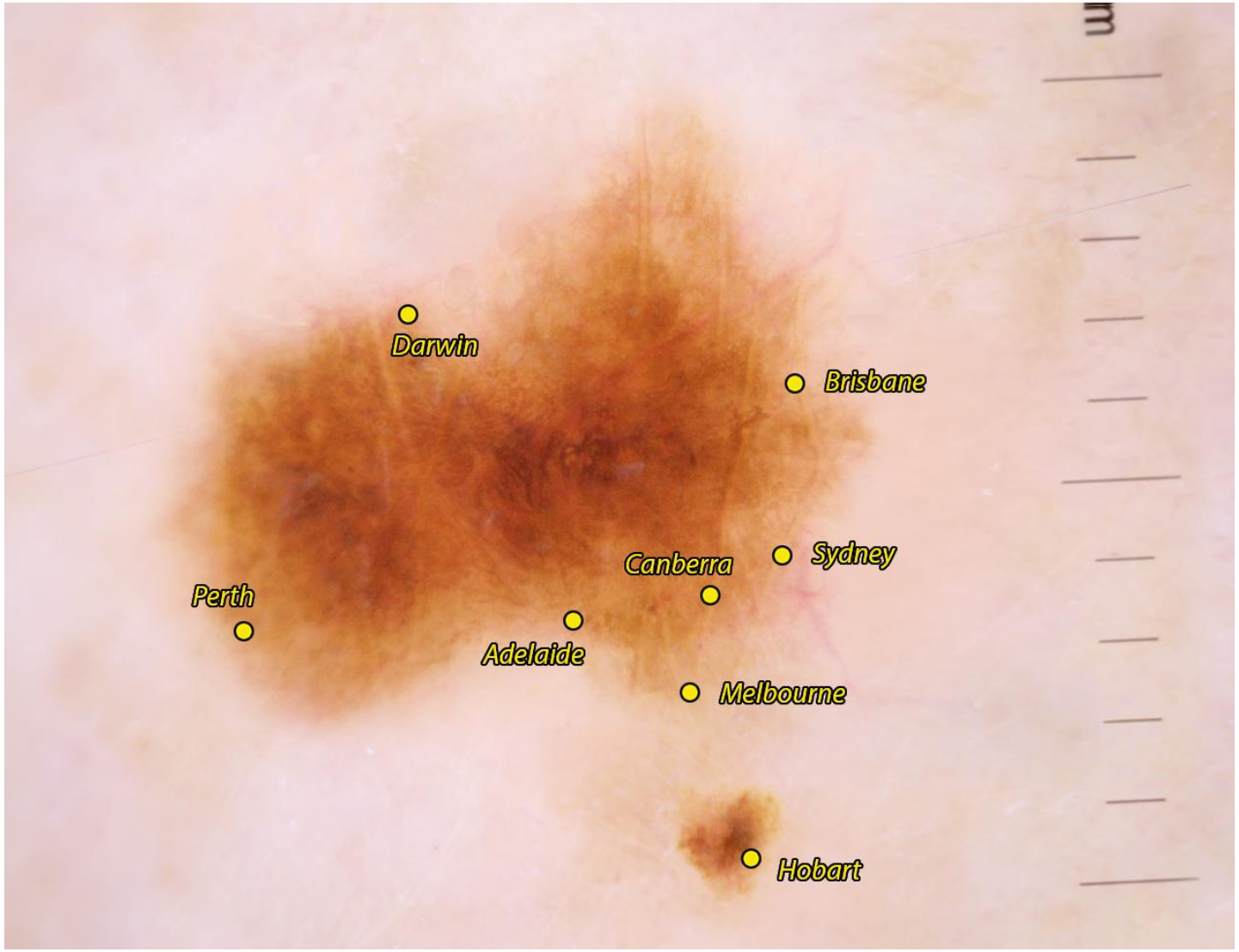
International Dermoscopy Diploma

Medical University Graz

- Start
- Why dermoscopy?
- Approaches
- Recognition process
- What is your diagnosis?

WHAT IS YOUR DIAGNOSIS?

This is the AUSTRIAN NEVUS ...


Darwin
Brisbane
Canberra
Sydney
Perth
Adelaide
Melbourne
Hobart

MELANOMA INCIDENCE IN AUSTRALIA **CONTINUES TO INCREASE**

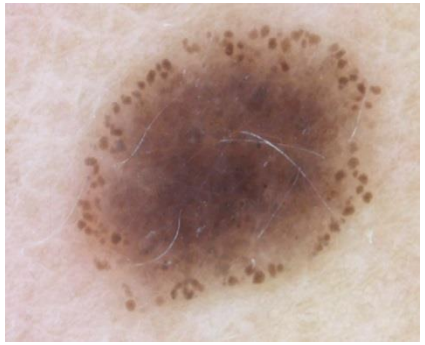
42%
increase in invasive melanoma in Queensland by 2025

Melanoma affects over
12,500
AUSTRALIANS ANNUALLY

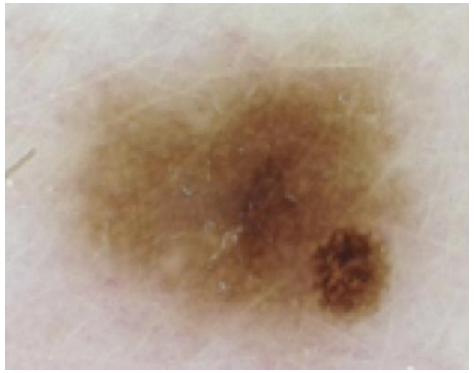
90%
OF DERMATOLOGISTS ARE PRACTISING IN MAJOR CITIES despite the highly dispersed nature of the population. It makes healthcare provision challenging

Most common cancer in Australians aged
15-39
YEARS

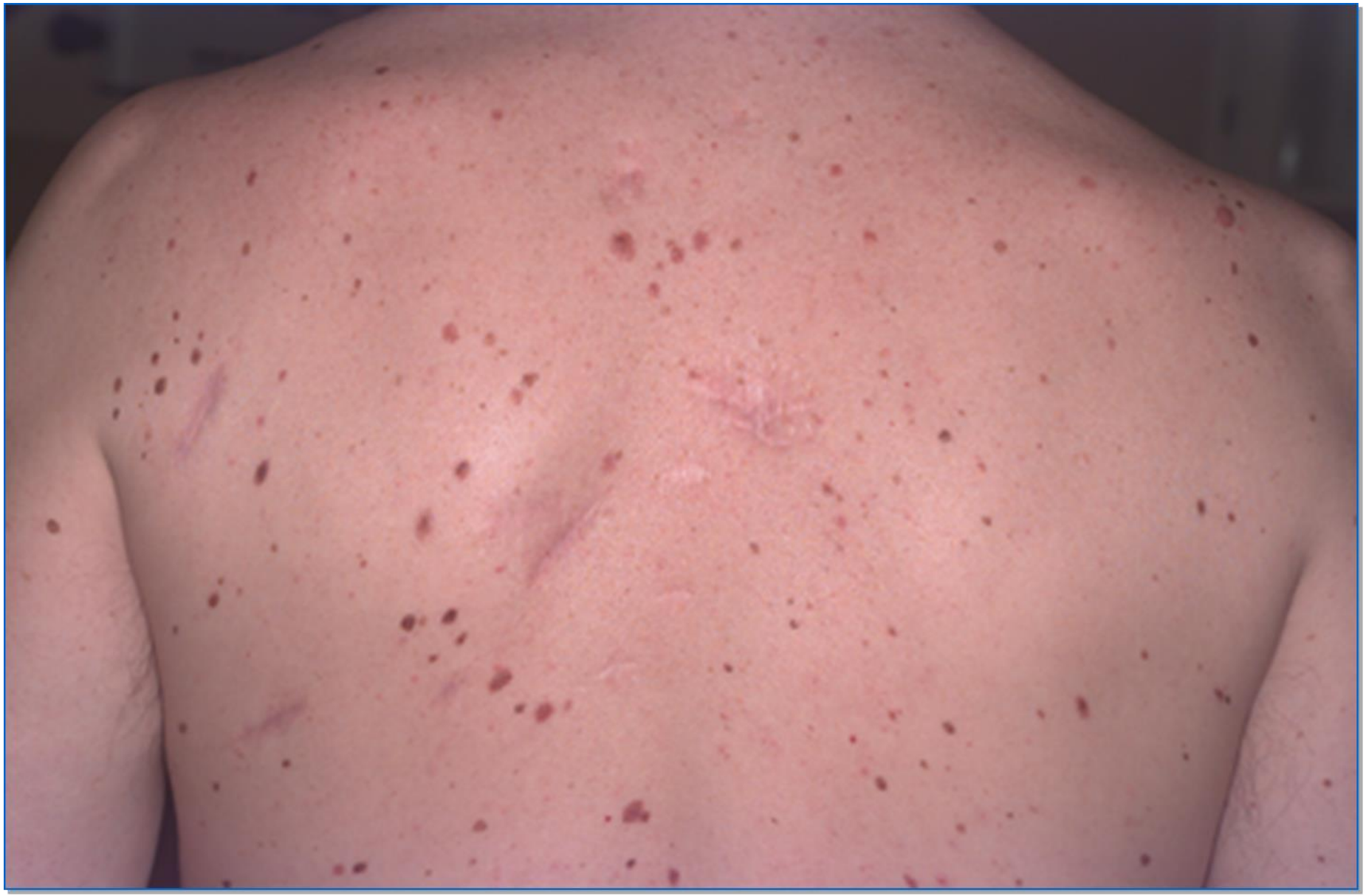
$422M
total estimated costs of advanced melanoma nationally with
LOSS OF PRODUCTIVITY
(48% ~$202M) &
HEALTH CARE COSTS
(39%, ~$164M)



Naevi and Melanoma



- Number of naevi is the strongest risk predictor for melanoma
- Many melanomas arise adjacent to or within naevi
- Naevi are the most relevant simulators of melanoma
- Naevi are dynamic structures – “life of a lesion”
- ~ 80% of naevi harbour the same BRAF V600E mutation which characterise 50% of melanomas



J Natl Cancer Inst. 2003 Jun 4;95(11):806-12.

Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma.

Whiteman DC[1], Watt P, Purdie DM, Hughes MC, Hayward NK, Green AC.

Author information

Abstract

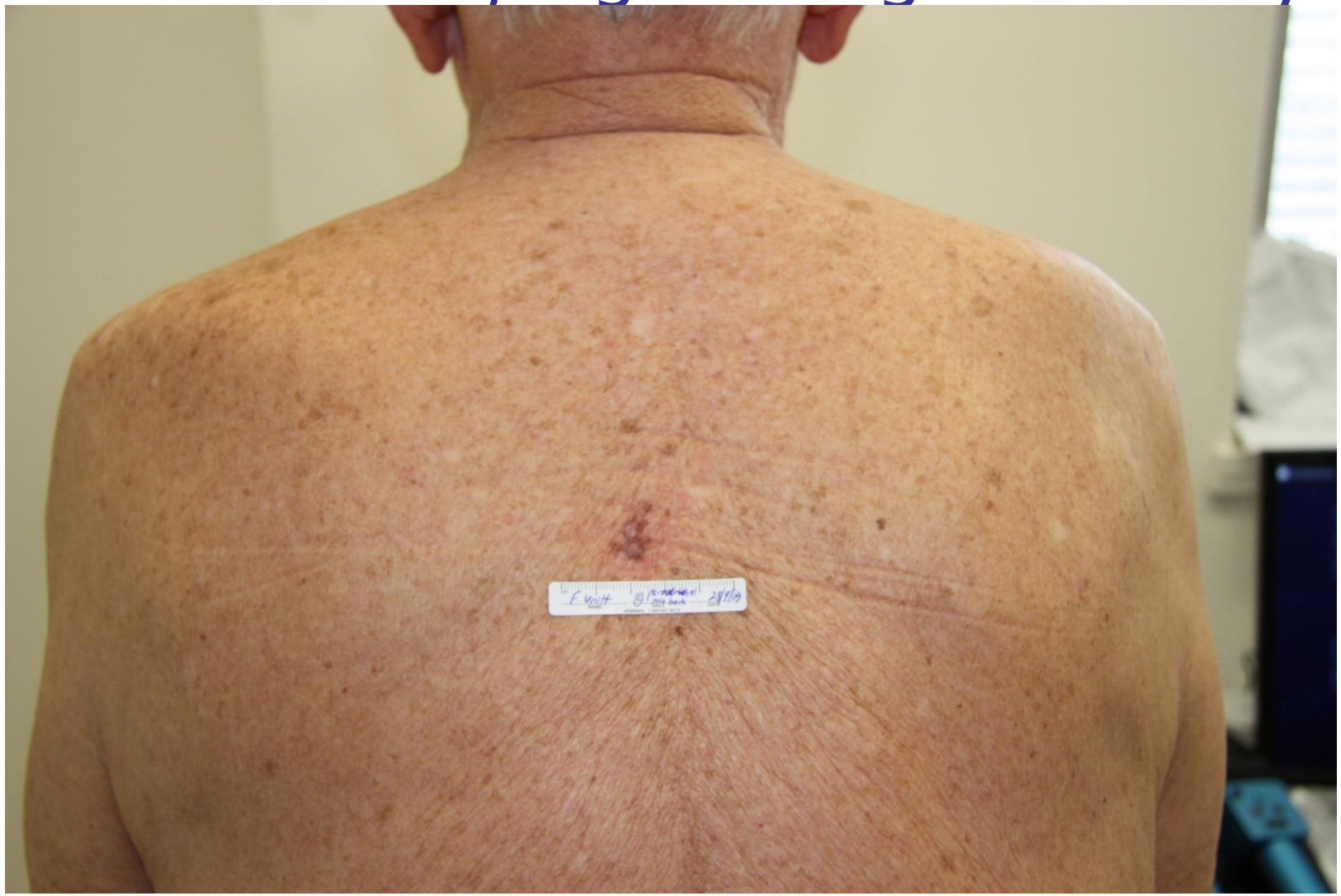
BACKGROUND: Some melanomas form on sun-exposed body sites, whereas others do not. We previously proposed that melanomas at different body sites arise through different pathways that have different associations with melanocytic nevi and solar keratoses. We tested this hypothesis in a case-case comparative study of melanoma patients in Queensland, Australia.

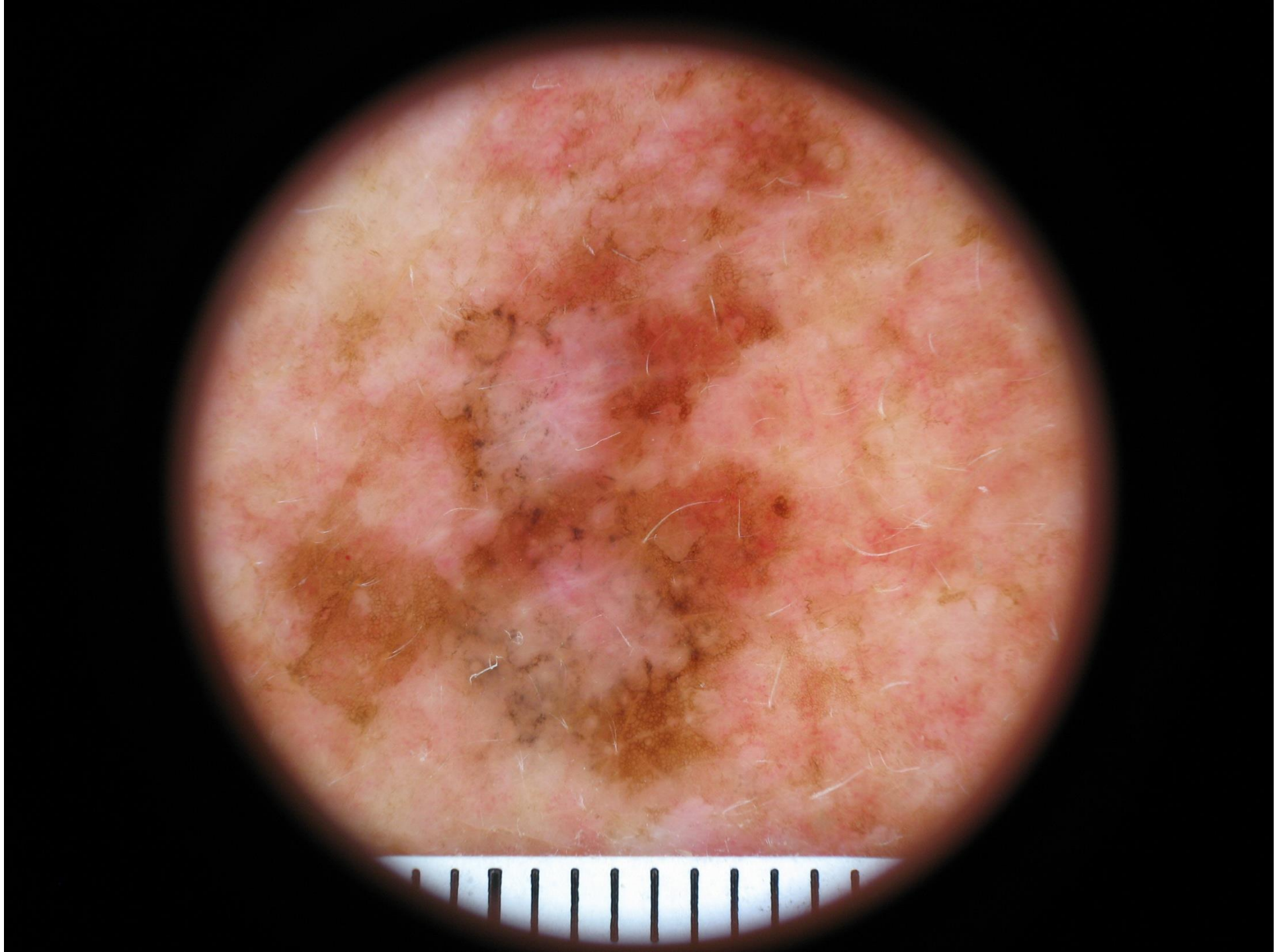
METHODS: We randomly selected patients from among three prespecified groups reported to the population-based Queensland Cancer Registry: those with superficial spreading or nodular melanomas of the trunk (n = 154, the reference group), those with such melanomas of the head and neck (n = 77, the main comparison group), and those with lentigo maligna melanoma (LMM) (n = 75, the chronic sun-exposed group). Each participant completed a questionnaire, and a research nurse counted melanocytic nevi and solar keratoses. We calculated exposure odds ratios (ORs) and 95% confidence intervals (CIs) to quantify the association between factors of interest and each melanoma group.

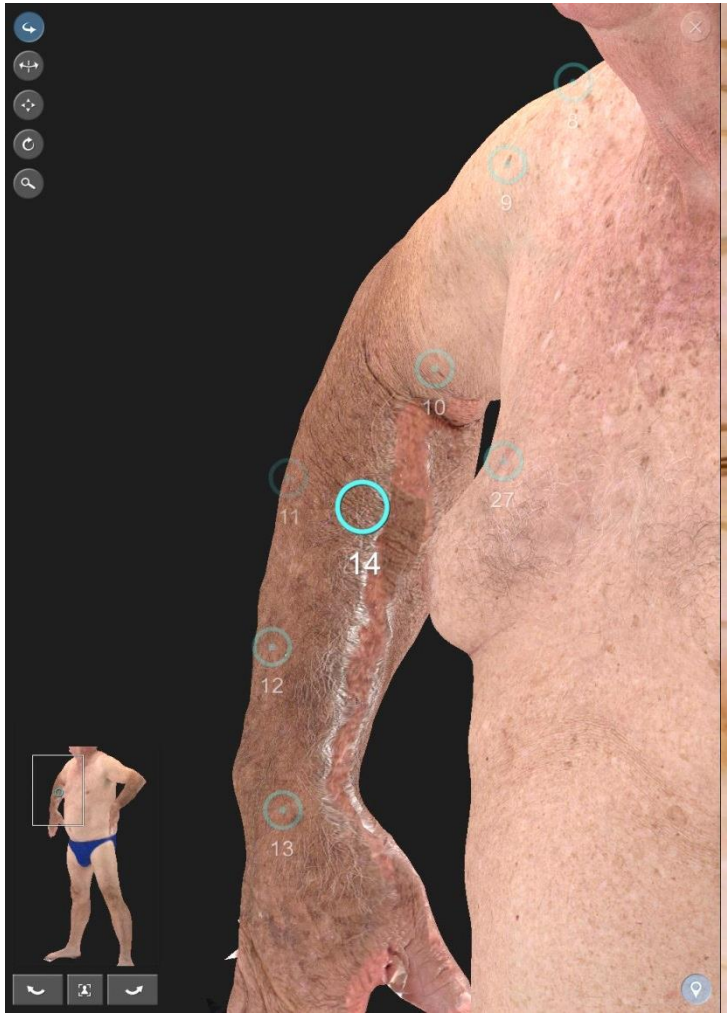
RESULTS: Patients with head and neck melanomas, compared with patients with melanomas of the trunk, were statistically significantly less likely to have more than 60 nevi (OR = 0.34, 95% CI = 0.15 to 0.79) but were statistically significantly more likely to have more than 20 solar keratoses (OR = 3.61, 95% CI = 1.42 to 9.17) and also tended to have a past history of excised solar skin lesions (OR = 1.87, 95% CI = 0.89 to 3.92). Patients with LMM were also less likely than patients with truncal melanomas to have more than 60 nevi (OR = 0.32, 95% CI = 0.14 to 0.75) and tended toward more solar keratoses (OR = 2.14, 95% CI = 0.88 to 5.16).

CONCLUSIONS: Prevalences of nevi and solar keratoses differ markedly between patients with head and neck melanomas or LMM and patients with melanomas of the trunk. Cutaneous melanomas may arise through two pathways, one associated with melanocyte proliferation and the other with chronic exposure to sunlight.

Low-Nevus/High-Sunlight Pathway



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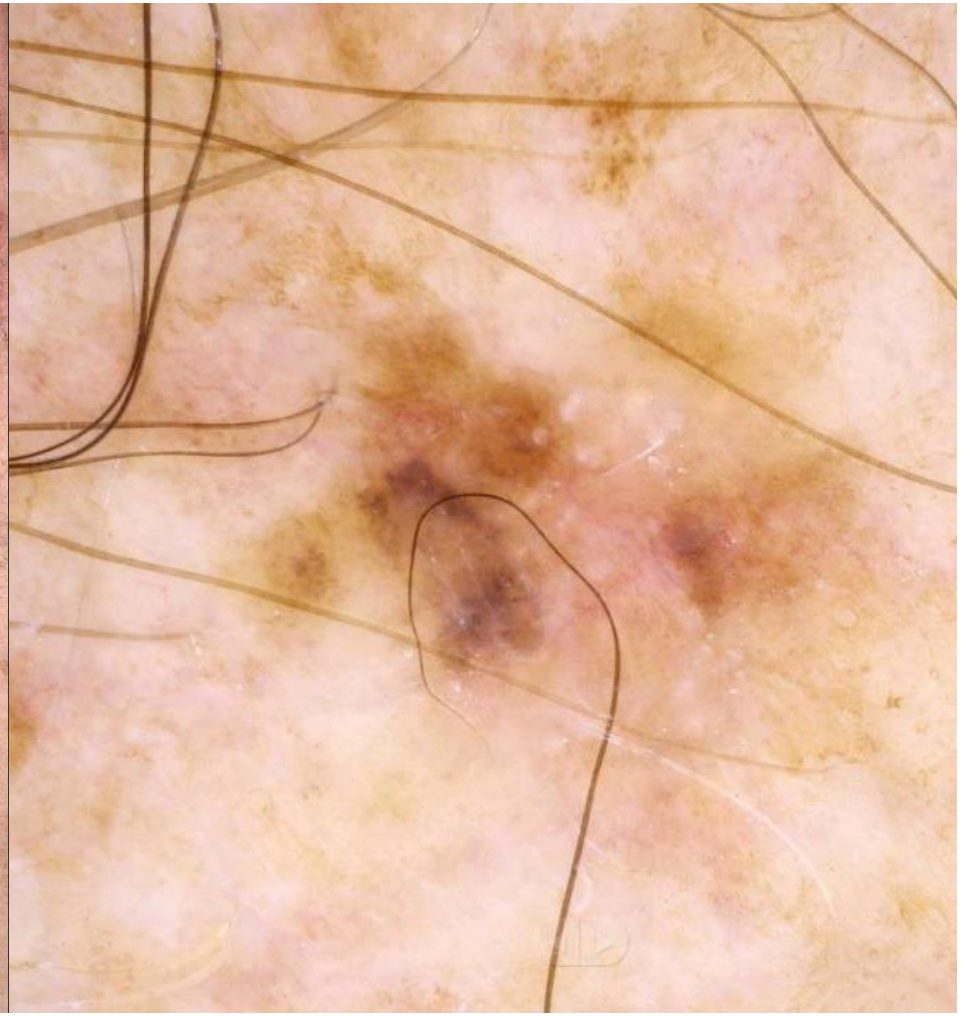

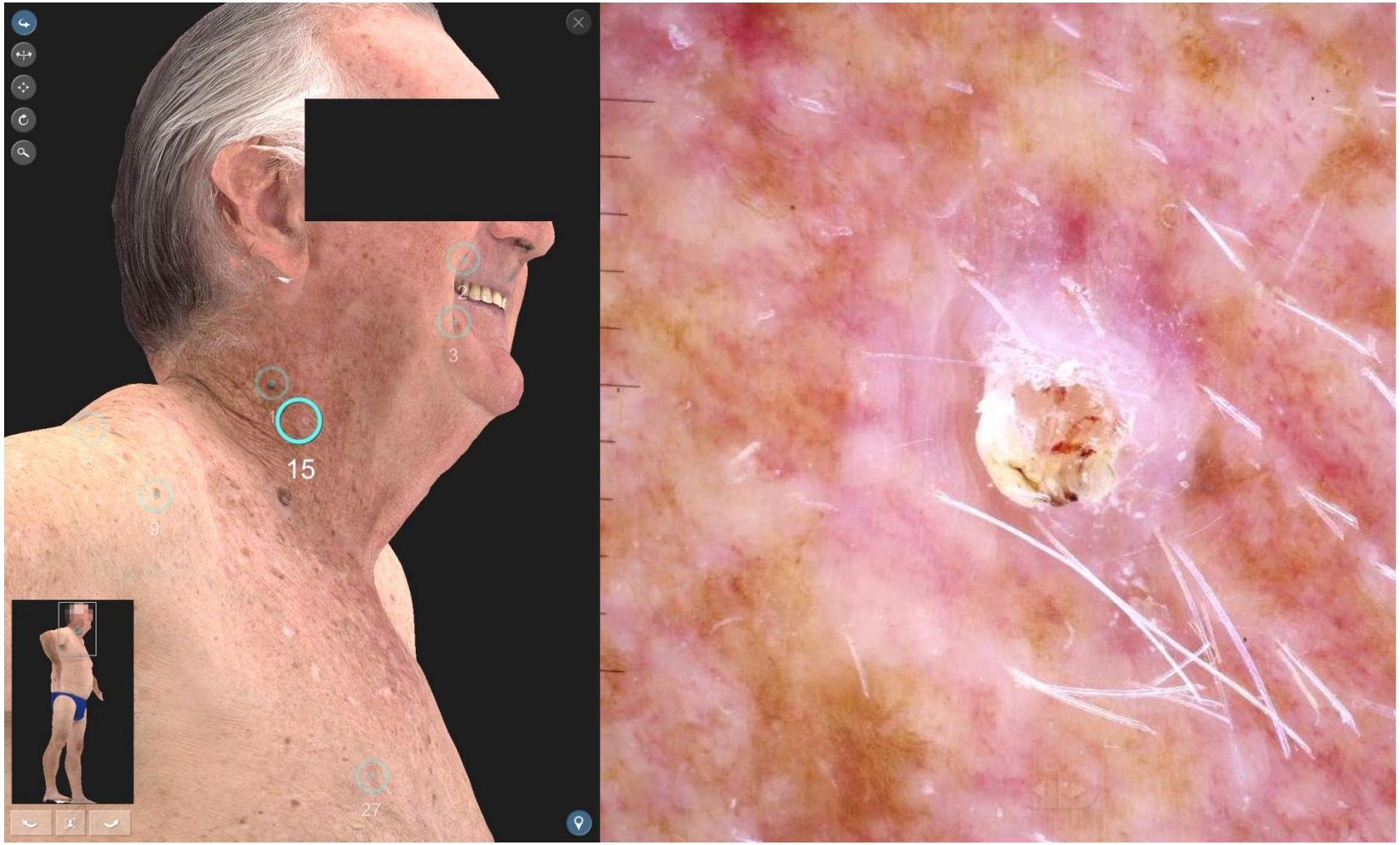
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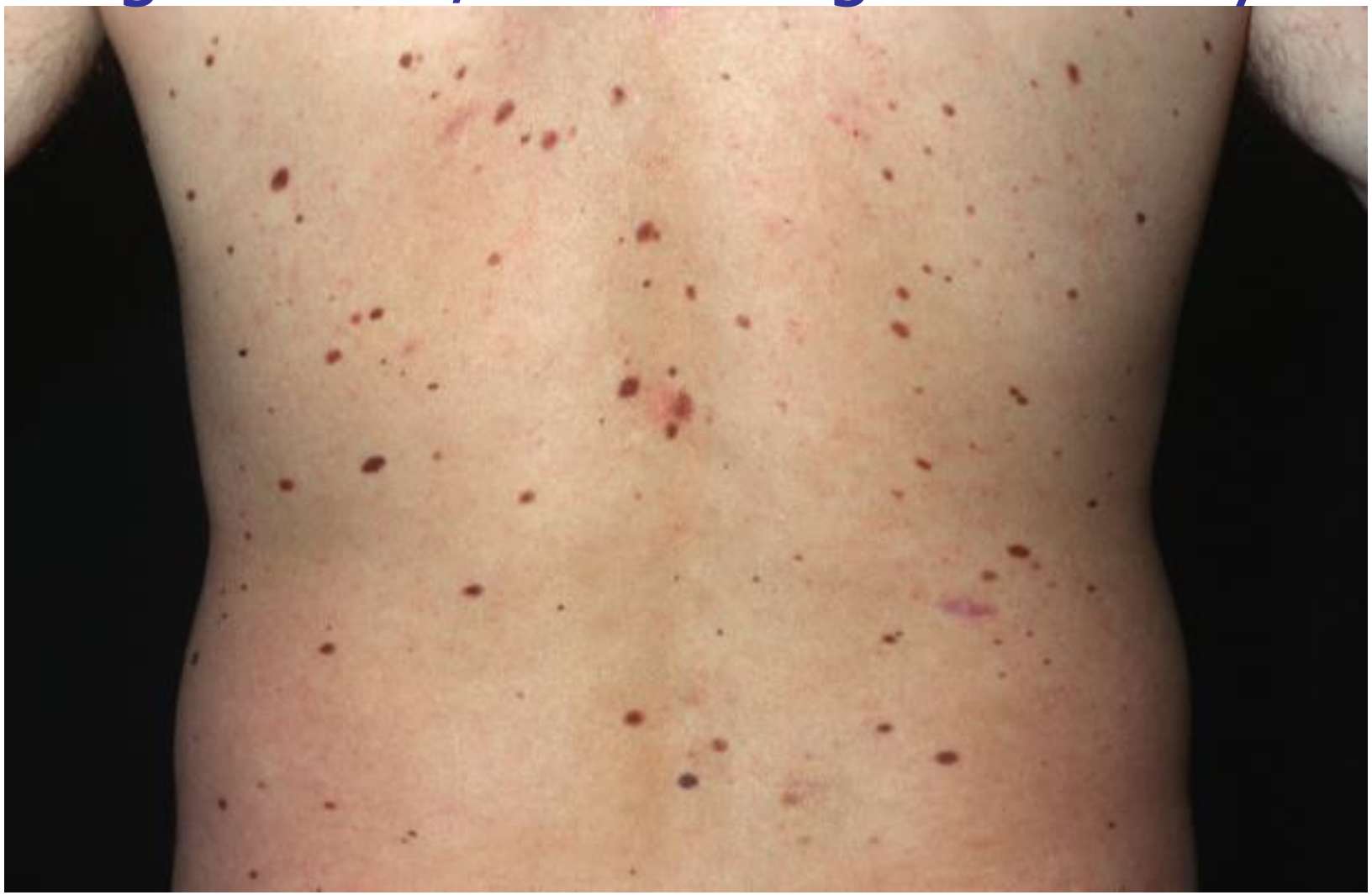
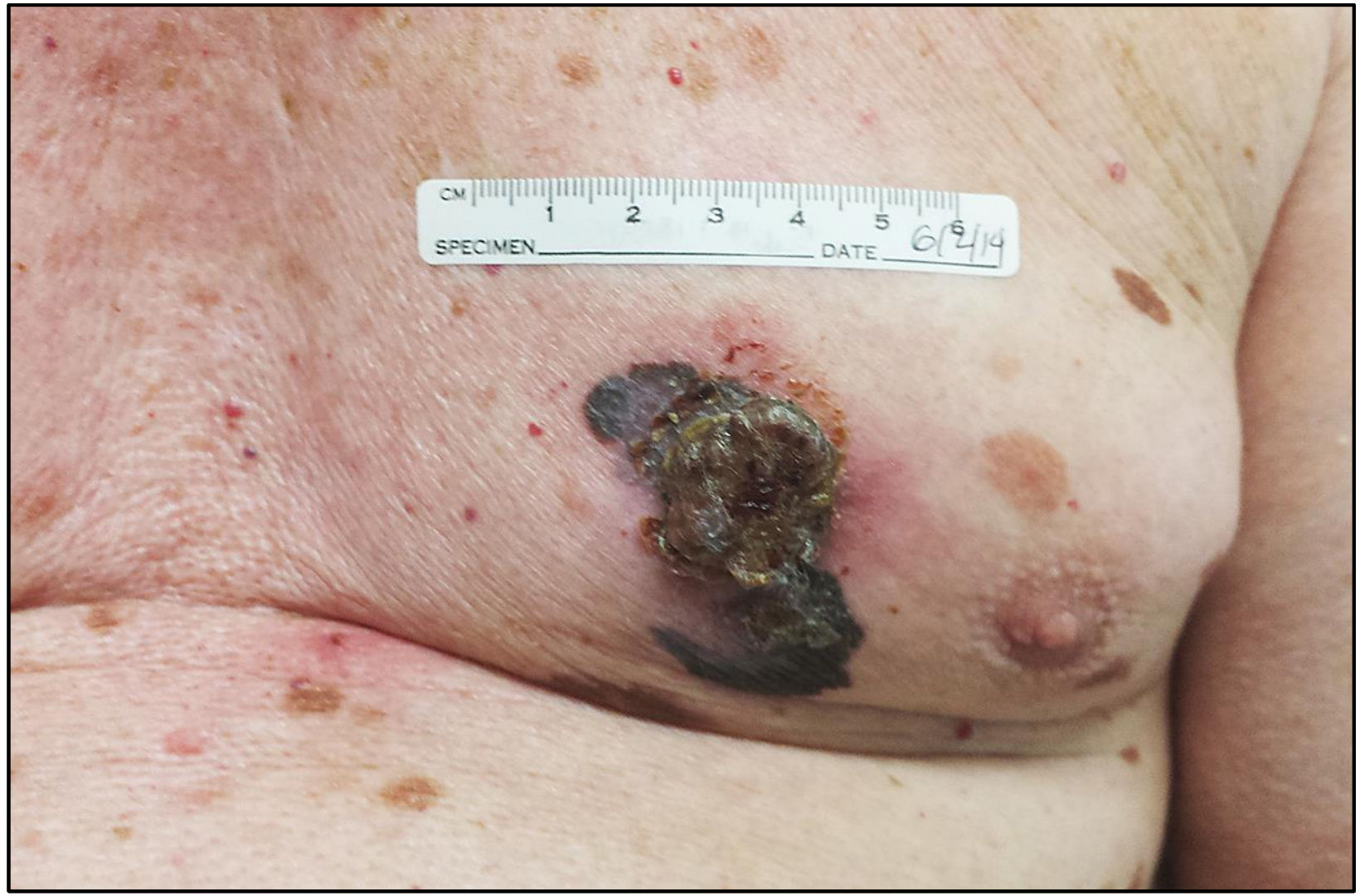
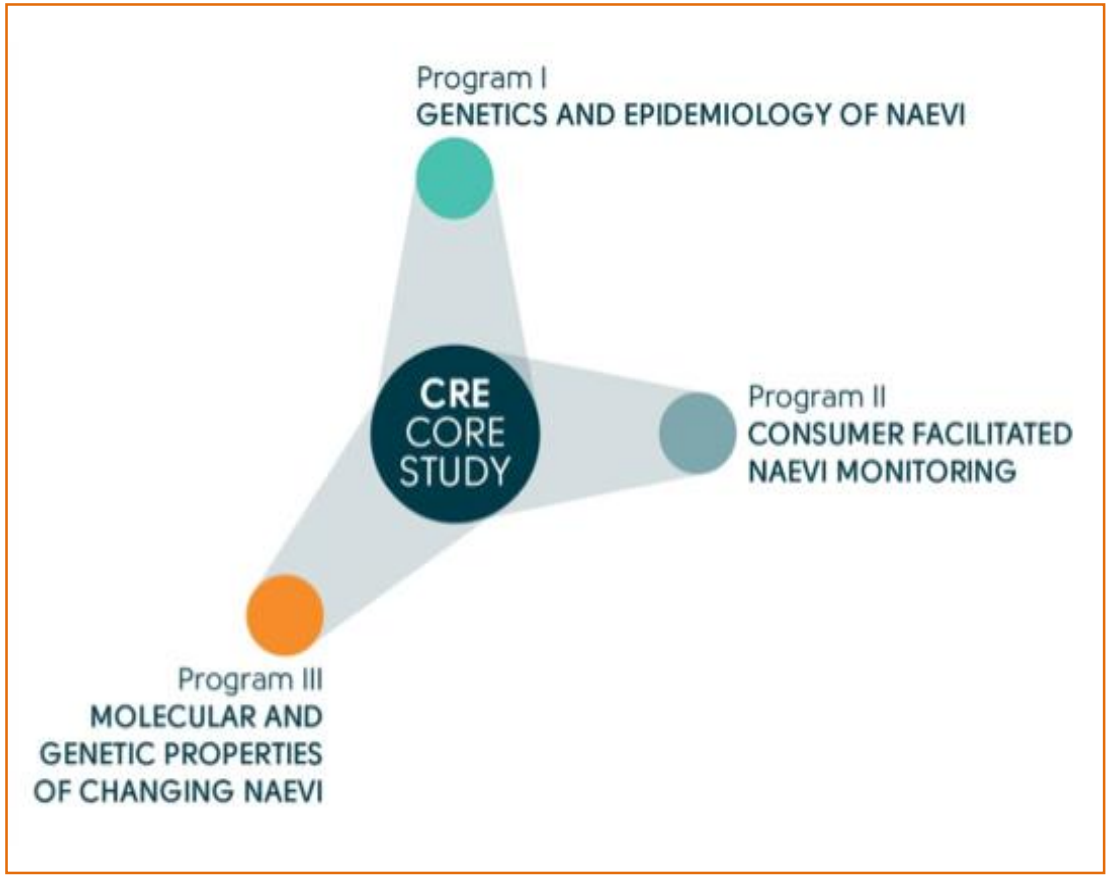
High-Nevus/Low-Sunlight Pathway




CM
1 2 3 4 5 6
SPECIMEN
DATE 6/24/14

NHMRC Centre of Research Excellence on the Study of Naevi



CRE Core Study

Study design: Prospective longitudinal population-based cohort study of the natural history of naevi in adults living in Brisbane.

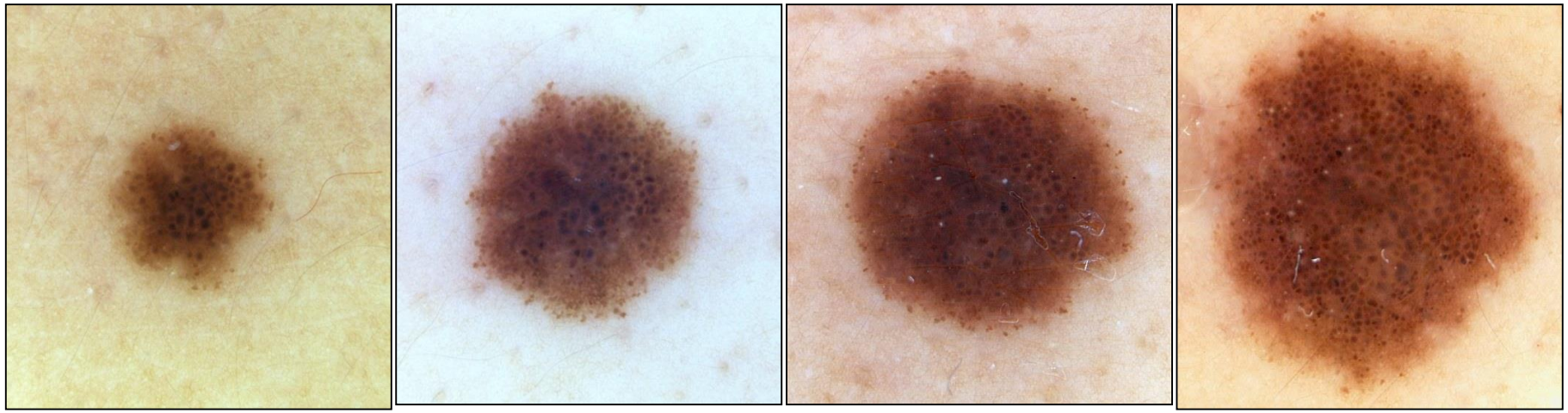
150 participants followed for 3 years with 3D total body photography and dermoscopy

Combined with germline genomic analysis from saliva.

- Average number of naevi (overall, >2mm, >5mm), average number of atypical naevi on each body site by sex and age
- Influence of phenotype and pigmentation/naevus genotype on the number and type of naevi by body site
- What changes in naevi number, size, and dermoscopic features occur over 3 years

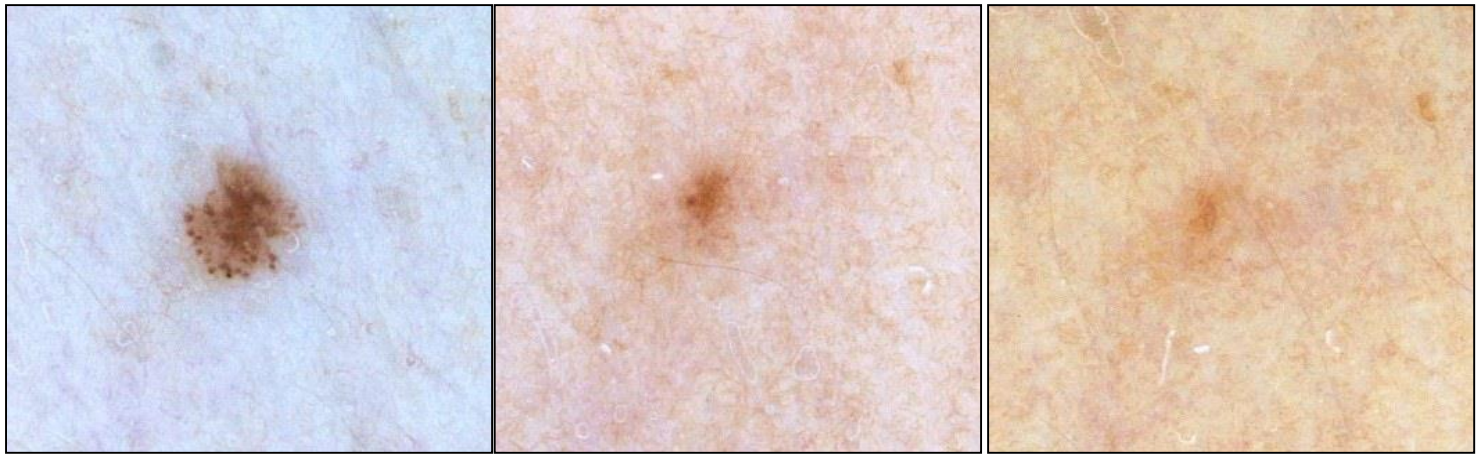
Patient: Female, 39 years old

Lesion: Central Mid Back



December 2006 August 2008 December 2009 January 2012

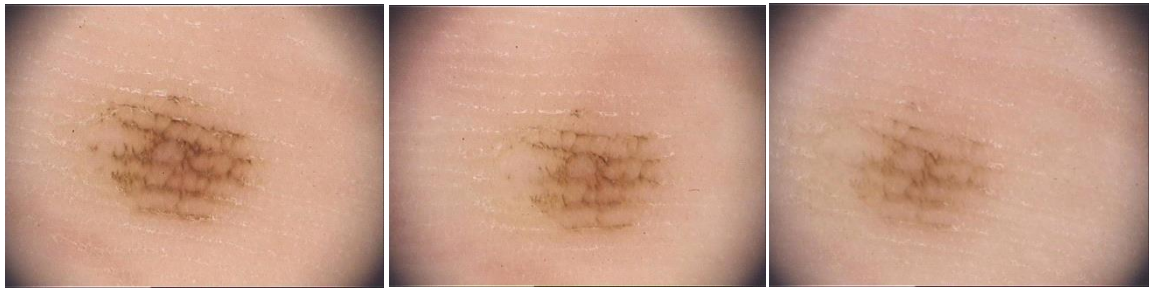
Lesion: Chest



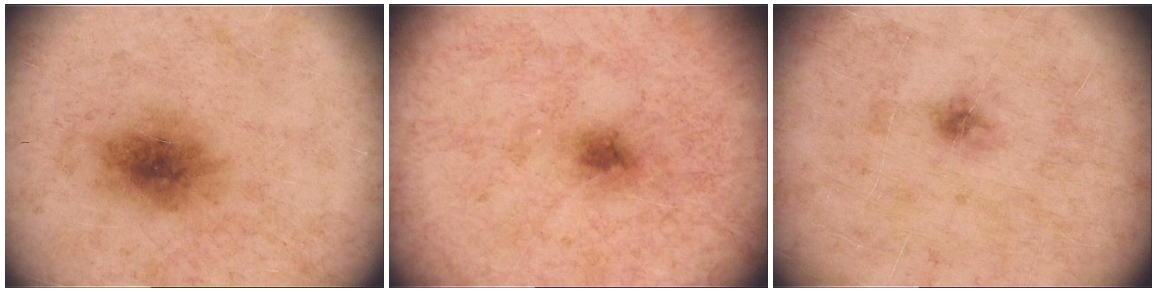
August 2008 December 2009 January 2012

28 year old male
2 melanomas to date;
2001 and 2008
Father had melanoma aged 52

INVOLUTING NAEVI

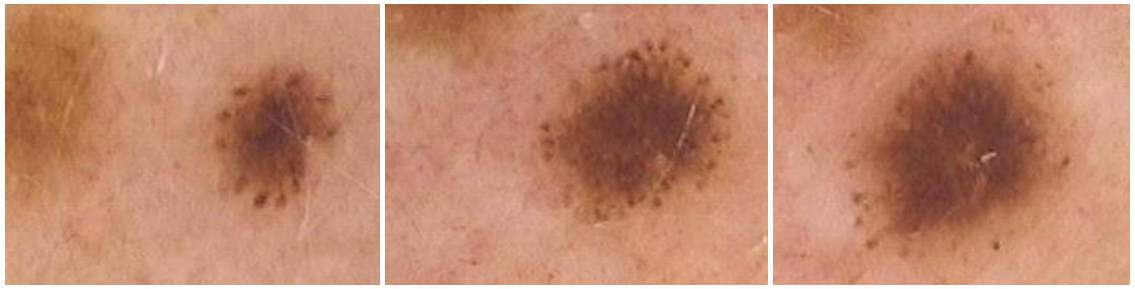


1) L palm 22/03/2010 15/11/2010 30/05/2011



2) Back 22/03/2010 15/11/2010 30/05/2011

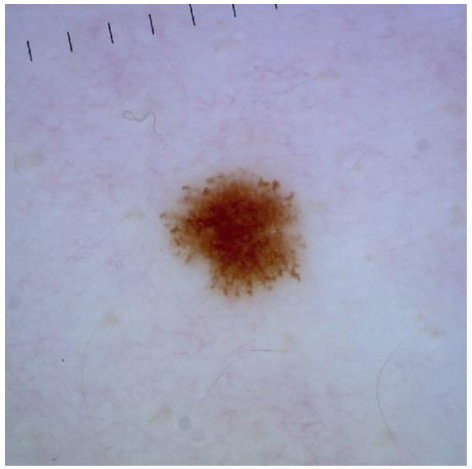
EVOLUTING NAEVUS

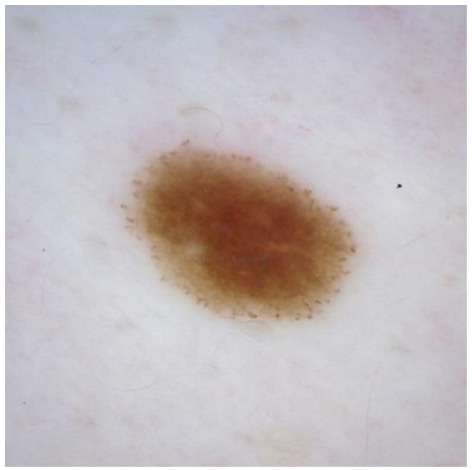


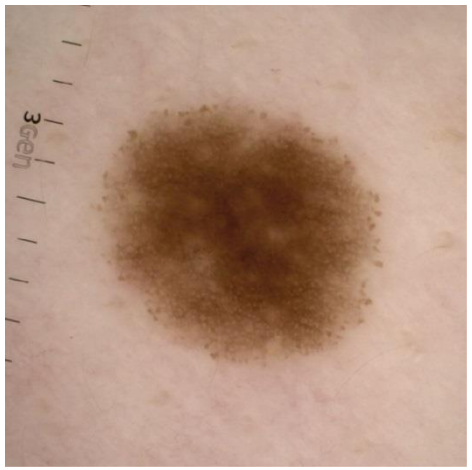
3) Back 22/03/20110 15/11/2010 30/05/2011

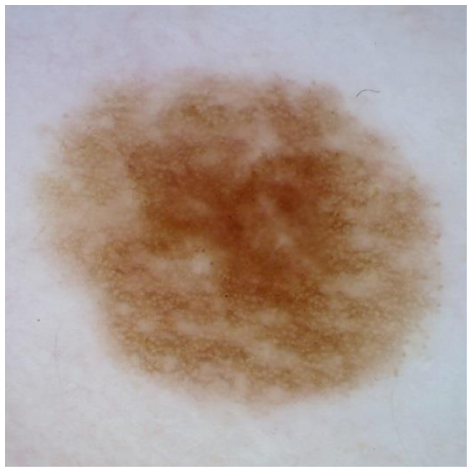
Patient: Male, 33 years old
No significant personal or family history of melanoma
Atypical Naevi: Many (> 15)
No. of Moles: Many (>50) moles > 2mm

Lesion: Right lower back

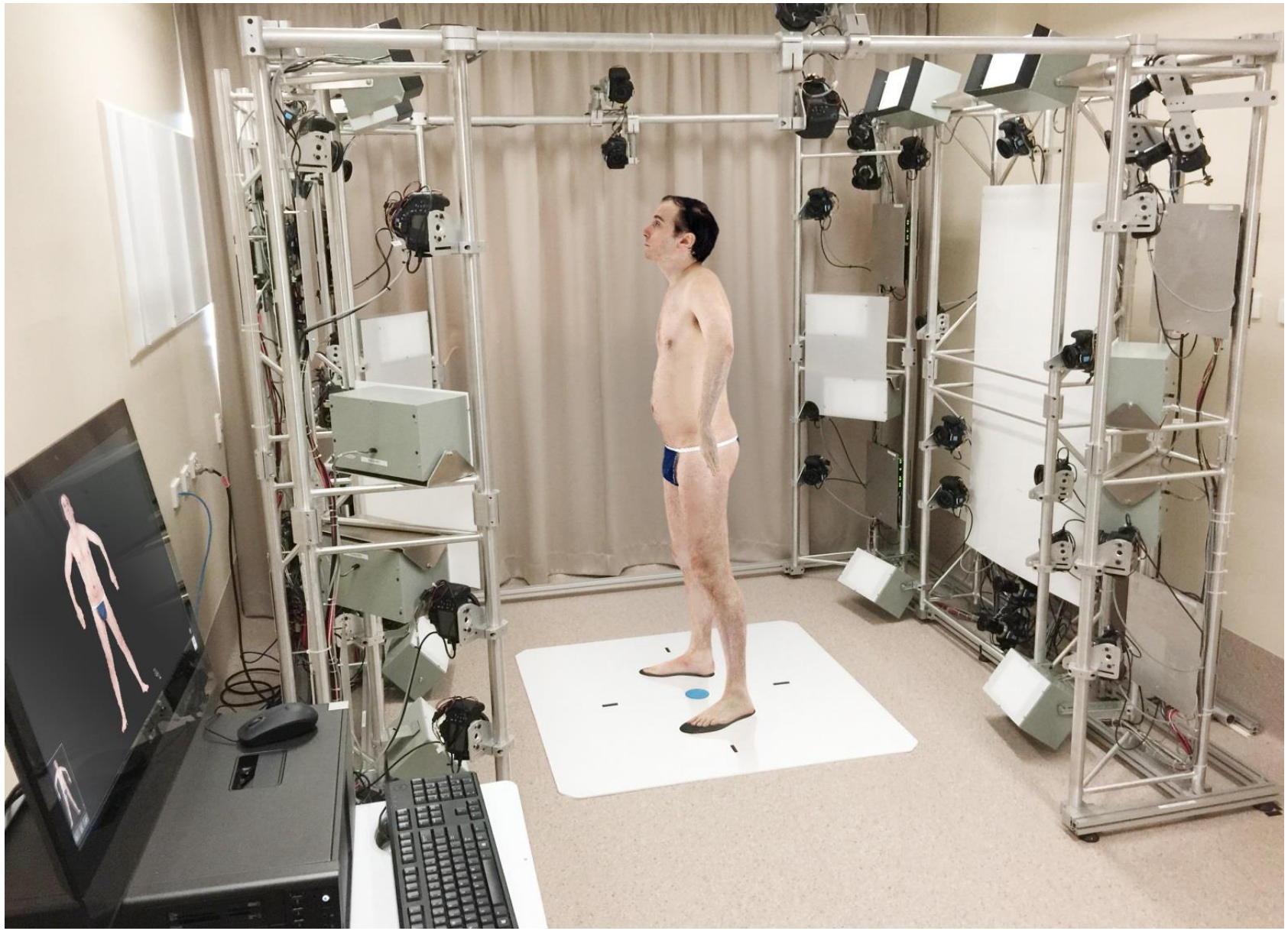

Oct 2012

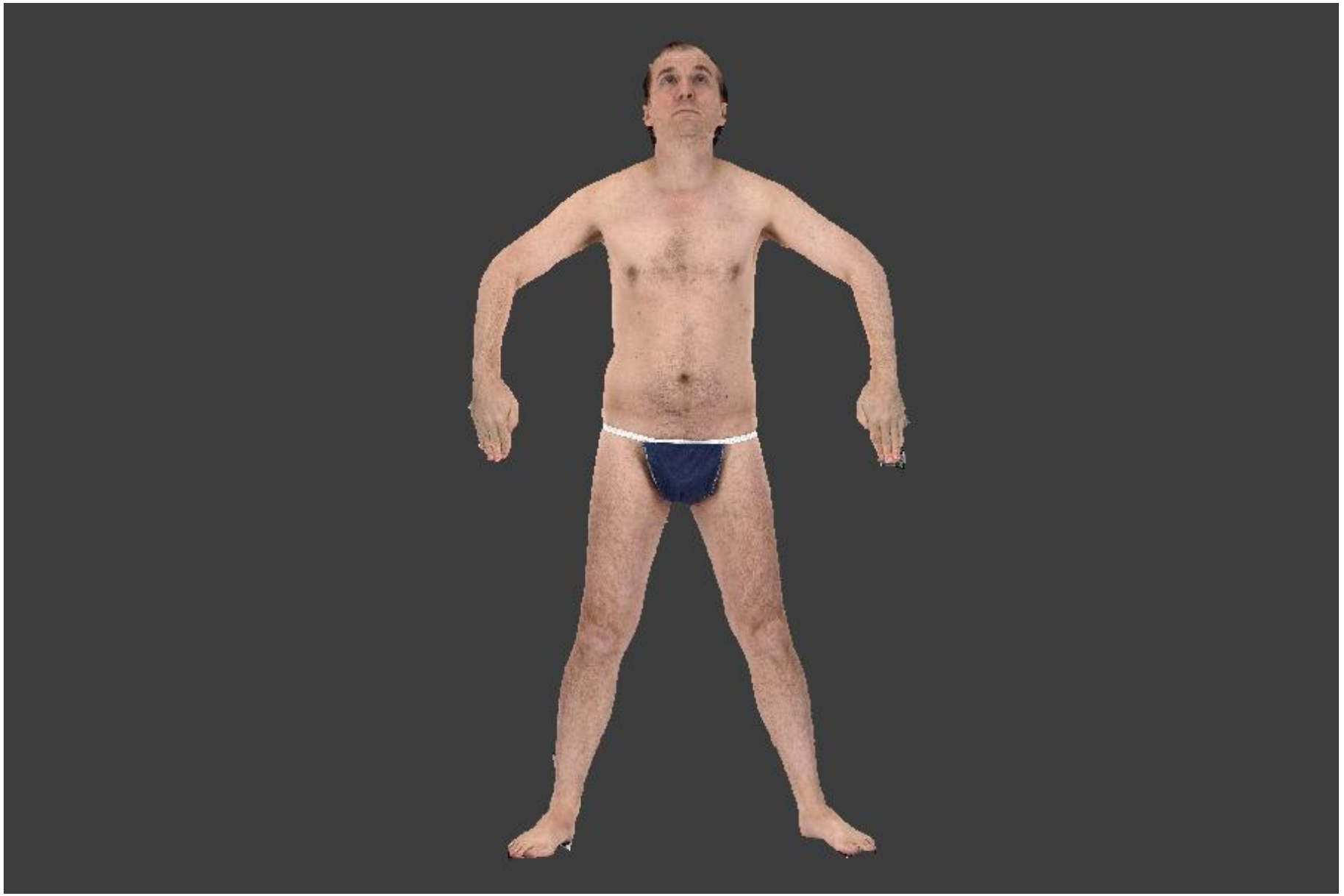

Jan 2014


Feb 2015

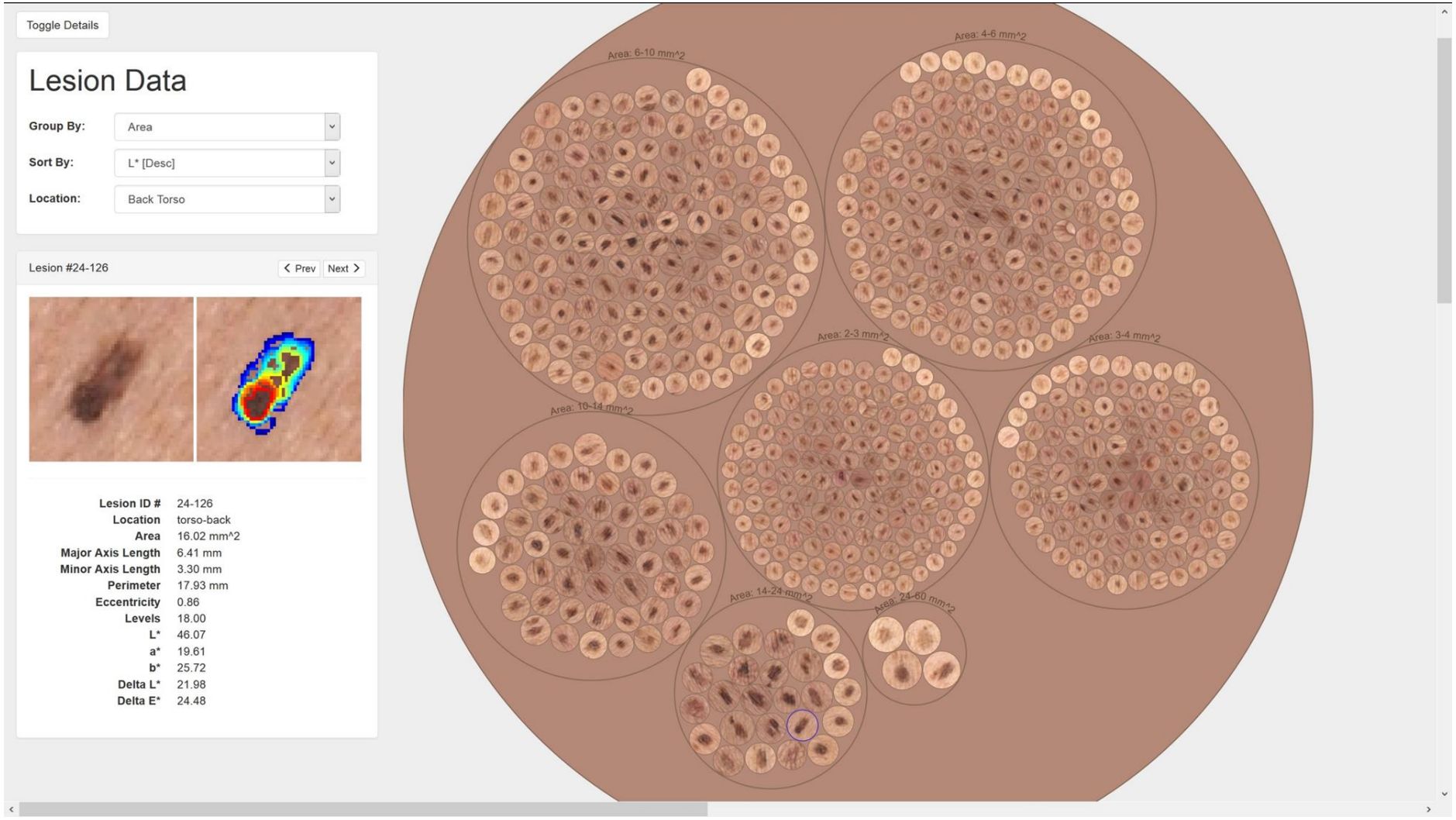

Mar 2017

Snapshot “all in one” approach: The Vectra





Automated Image Analysis by Naevus Size



Program I

Genetics and Epidemiology of Naevi

Study Design: A case-control study, including participants who have been diagnosed with melanoma in the past and non-melanoma controls.

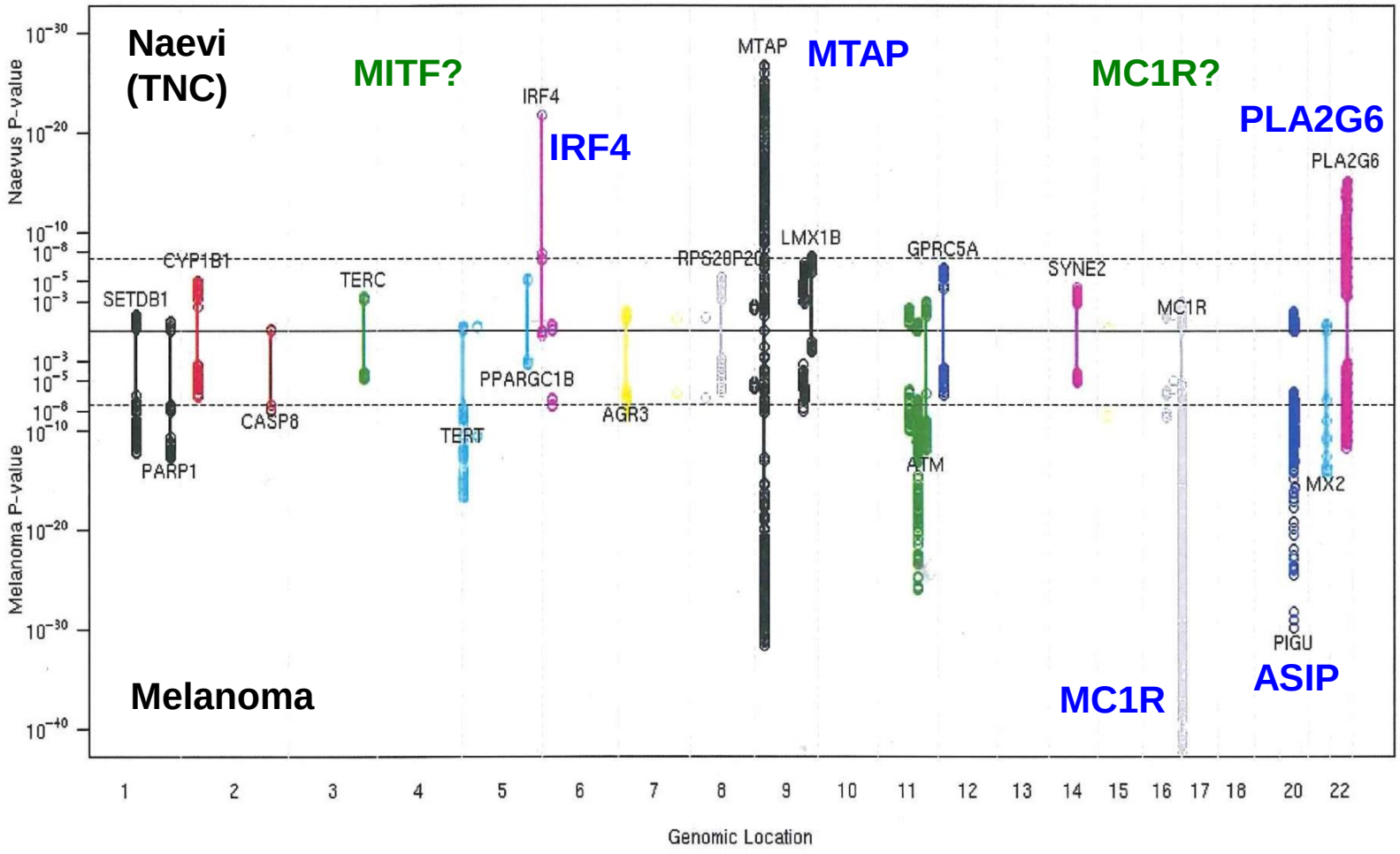
Aims:

- Study associations between clinical and dermoscopic phenotype (globular & reticular pattern) and genotype
- Determine the contribution of novel candidate pigmentation and naevogenic genes to naevus count, morphology and dermoscopic patterns
- Provide information to allow the development of risk prediction models for melanoma based on pigmentation and naevogenic phenotype
- Perform whole exome sequencing of up to 30 melanoma patients and 30 controls to search for genetic polymorphisms associated with contrasting naevus phenotype traits.

GWAS for Naevi and CMM

Numerous GWAS have identified associations between non-coding SNPs at IRF4, MTAP and PLA2G6 loci and naevus count and melanoma susceptibility

David Duffy, "A meta-analysis of GWAS scans for naevus counts"



Law et al., Nature Genetics 2015

Brisbane Naevus Morphology Study (BNMS)
2011 to 2016

AIM

600 CMM cases or Family History
vs
600 control subjects

Actual Total N = 1255

Final analysis of survey at 6 years

594 CMM cases + 160 Family History

501 control subjects (no melanoma history)

Australian Government
National Health and Medical Research Council
N H M R C

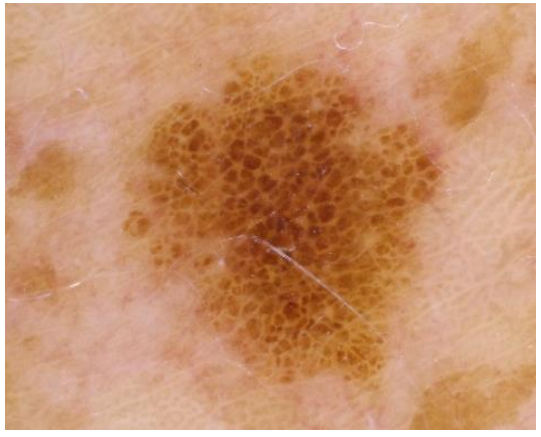
All have been submitted for Illumina HumanCoreExome genotyping = 500,000 SNPs

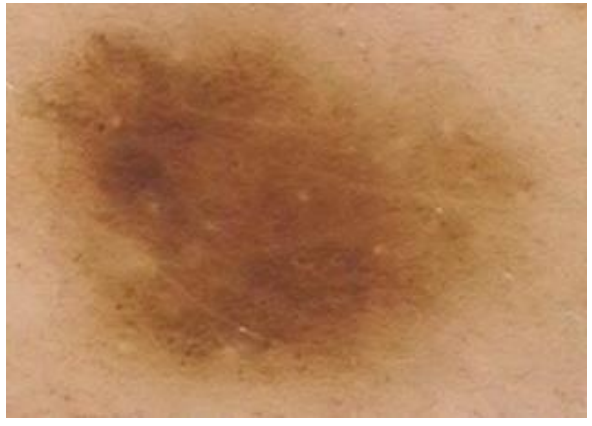
62 analysed by Whole Exome Sequencing (100x depth)

BNMS: Naevi classified by size, profile, colour and dermoscopic naevus pattern

37,205 melanocytic naevi >5mm

Globular
3378
(9.1%)

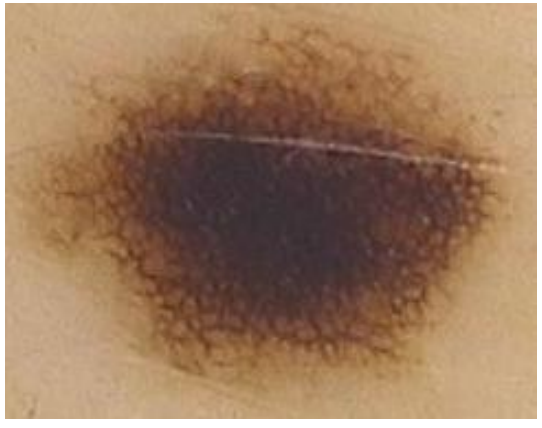


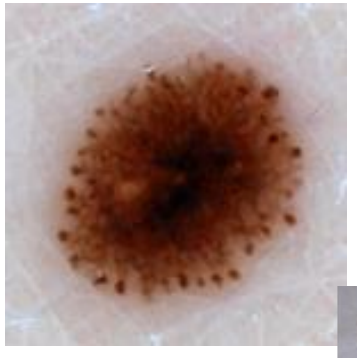


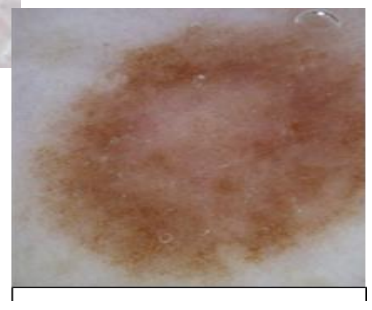
Homogeneous

25,456
(68.4%)

Reticular
8371
(22.5%)



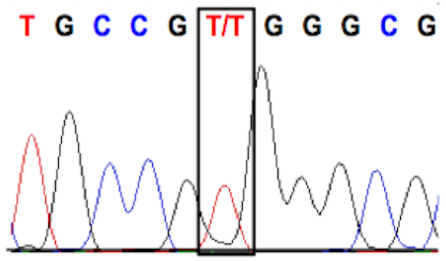




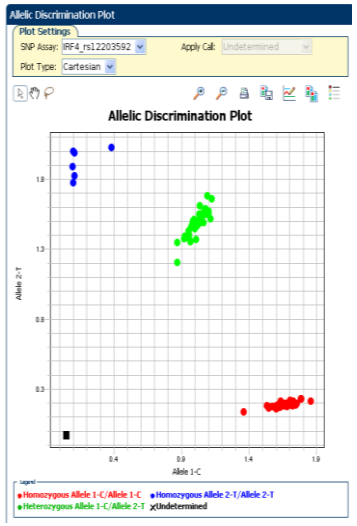
Genotyping platforms

Sanger Sequencing

MC1R Genotyping



Sequenom and Taqman based SNP Genotyping



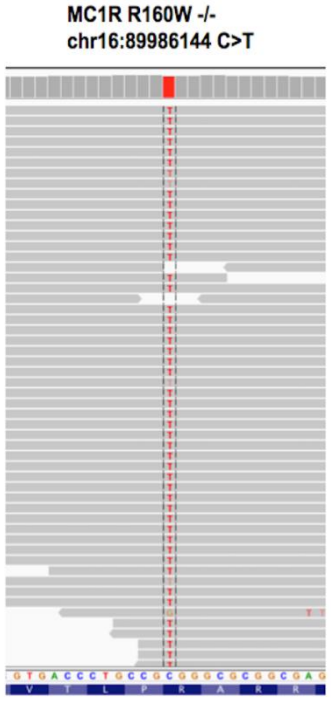
Illumina CoreExome

500,000 SNPs

Figure 1: HumanCoreExome-24 BeadChip

The HumanCoreExome-24 BeadChip enables informative genotyping of tag SNP and exome-focused markers across diverse world populations, delivering high-quality data that can be used in various downstream applications.

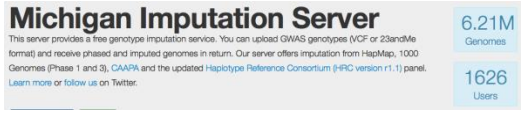
Whole Exome Sequencing (WES)



Gen	rs	Chr	Nucleotide Change		Protein Change
SLC45A2	rs16891982	5	c.1122 G>C	TTC>TTG	p.Phe374Leu
HERC2	rs12913832	15	c.13272+874T>C	-	-
SLC24A5	rs1426654	15	c.331A>G	ACA>GAC	p.Thr111Ala
IRF4	rs12203592	6	c.492+386 C>T	-	-
OPN/SPP1	rs11730582	4	g.88896421T>C	-	-
OGG1	rs1052133	3	c.977C>G	TCC>TGC	p.Ser326Cys
GSTP1	rs1695	11	c.313A>G	ATC>GTC	p.Ile105Val
MITF	rs149617956	3	c.952G>A	GAA>AAA	p.Glu318Lys
TYR	rs1042602	11	c.575C>A	TCT>TAT	p.Ser192Tyr
TYR	rs1126809	11	c.1205G>A	CGA>CAA	p.Arg402Gln

Imputed using HRC reference population

8,000,000 SNPs



MITF E318K is a medium penetrance melanoma risk gene

LETTER

Bertolotto et al., Nature 480: 94-98, 2011

doi:10.1038/nature10539

A SUMOylation-defective MITF germline mutation predisposes to melanoma and renal carcinoma

Corine Bertolotto[1,2,3]*, Fabienne Lesueur[4]†*, Sandy Giuliano[1,2]*, Thomas Strub[5], Mahaut de Lichy[4], Karine Bille[1], Philippe Dessen[6],

LETTER

Yokoyama et al., Nature 480: 99-103, 2011

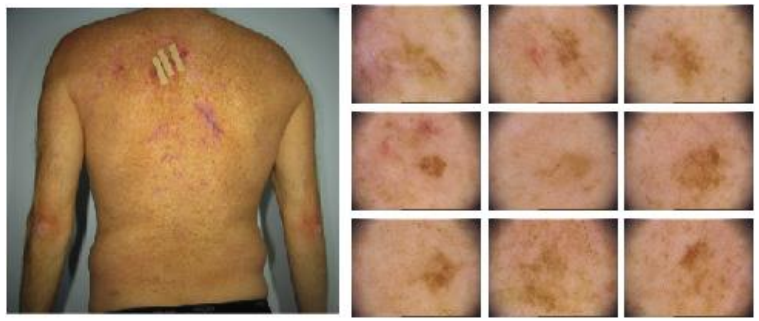
doi:10.1038/nature10630

A novel recurrent mutation in *MITF* predisposes to familial and sporadic melanoma

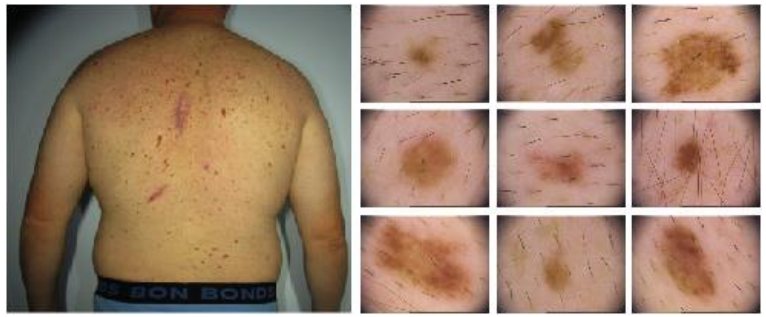
Satoru Yokoyama[1]*, Susan L. Woods[2]*, Glen M. Boyle[2]*, Lauren G. Aoude[2]*, Stuart MacGregor[2]*, Victoria Zismann[3]*,

Naevus and tumour patterns in MITF E318K carriers

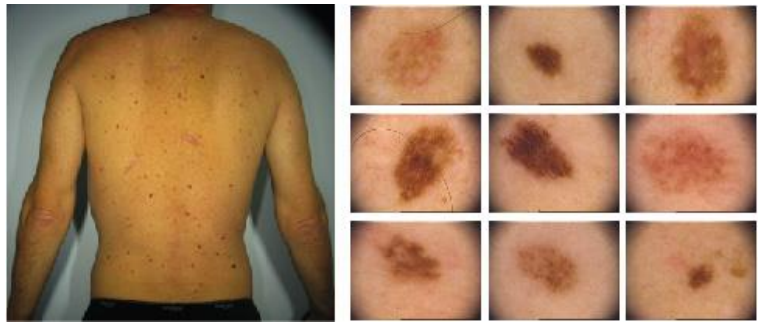
149DC



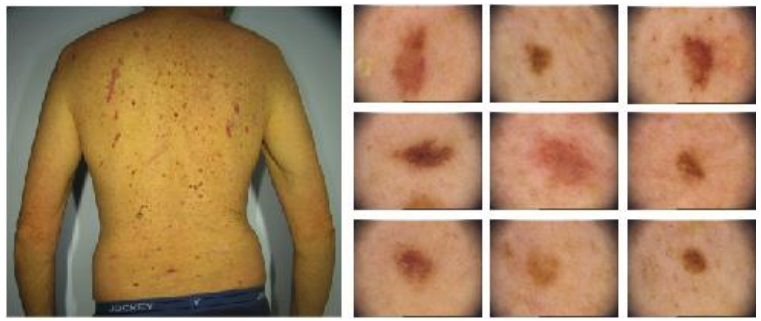
130MV



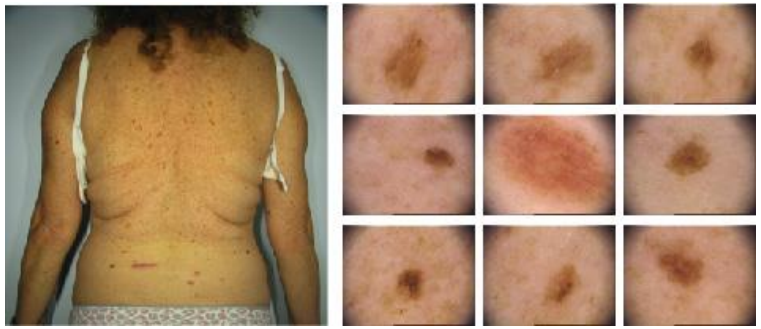
155IN



158RP



176SP



Sturm et al., JID 2014
6 CMM (f= 0.018)

BNMS as of 2016
18 Heterozygote carriers
12 CMM, 3 FH, 2 control, 1 unknown

MITF E318K mutation carrier melanoma patients

- Multiple primary melanomas (metachronous; developing at intervals)
- Some melanomas amelanotic
- High naevus count
- Association with renal cell carcinoma?

Extreme Naevi Substudy: WES gene discovery

1	2	3	4	5	6
401CM	07LW	230NM	347LM	690KB	197CN
608GN	136SP	341CE	61JB	669GB	186DH
623JG	525HW	531DF	587MJ	140JB	943DS
668LW	657LP	475PM	941MC	211KH	015KJ
323WP	510AN	198GV	940NB	188DW	130MV
334SW	373BD	01AR	703PG	229CH	716GB
357SN	108LT	588AS	809CK	376TH	918DW
360SJ	670RE	743HH	930HM	509VS	176SP
371MR	714EP	210GB	242PM	889GS	443EF
387JL	02DB	564JA	228CM	215EA	777JB
					28RH
					155IN
Low Naevus count with NO melanoma	**High Naevus count with NO melanoma**	**Low Naevus count with ONE melanoma**	**High Naevus count with ONE melanoma**	**Low Naevus count with MULTIPLE CMM**	**High Naevus count with MULTIPLE CMM**
N=10	**N=10**	**N=10**	**N=10**	**N=10**	**N=12**

Extremes of Naevus and Melanoma Count

1. Low Naevus count with No CMM

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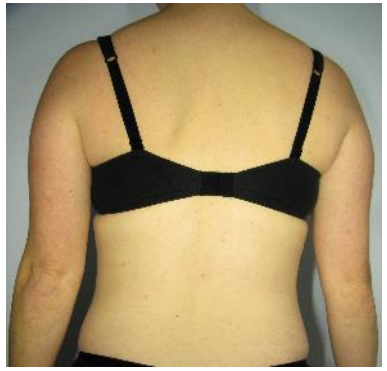
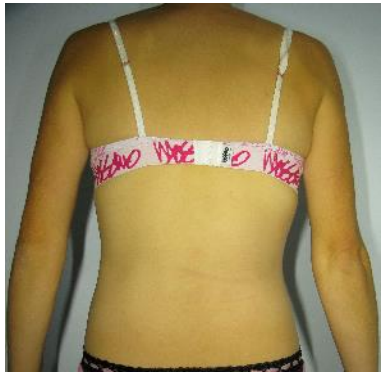
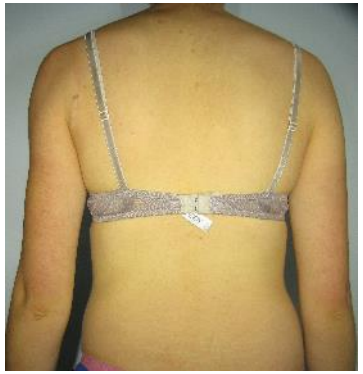
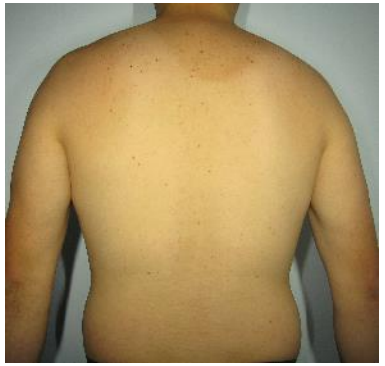
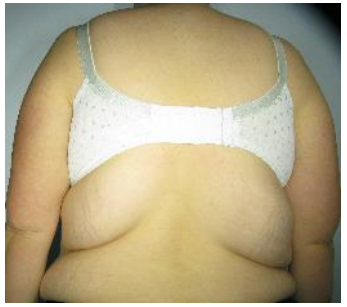
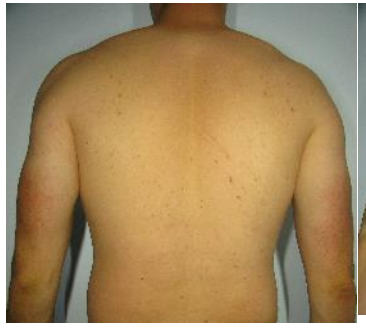
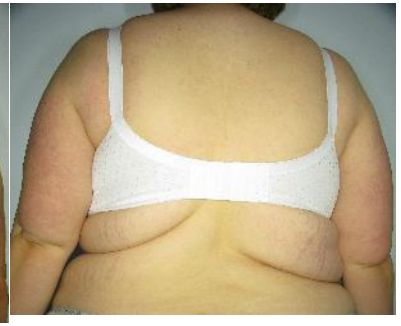
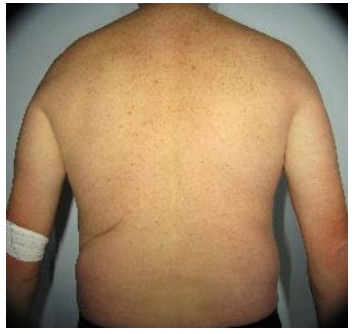
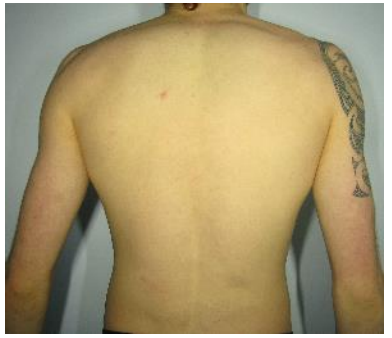
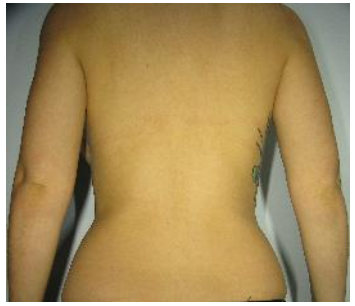
323WP	334SW	357SN	360SJ	371MR
				
Group	1	3	5	1, 3, 5
Av Age	31yr	40.7yr	42.1yr	35.9yr
Av TNC >5mm	0	0.8	1.7	0.4

387JL	401CM	608GN	623JG	668LW
				

Extremes of Naevus and Melanoma Count

2. High Naevus count with No CMM

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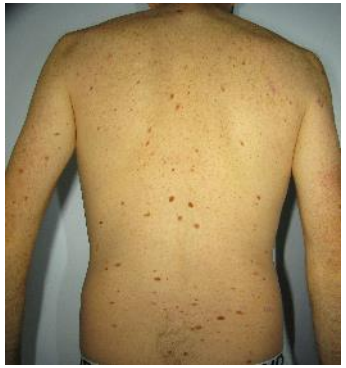
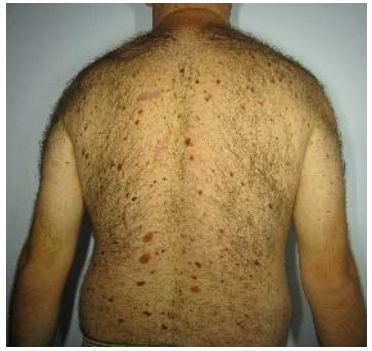
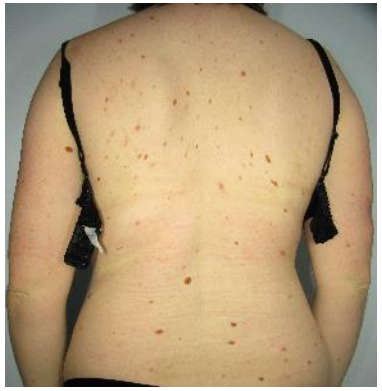
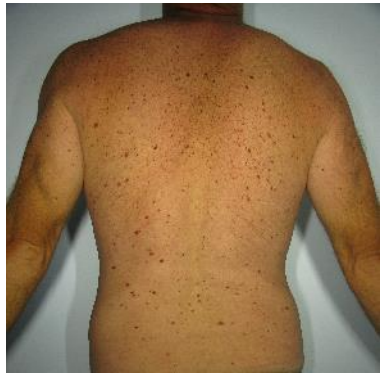
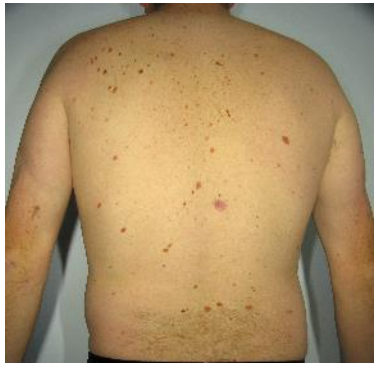
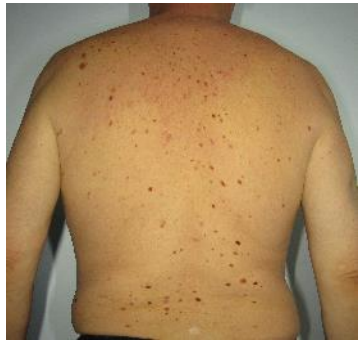
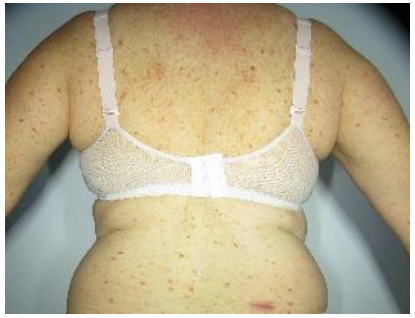
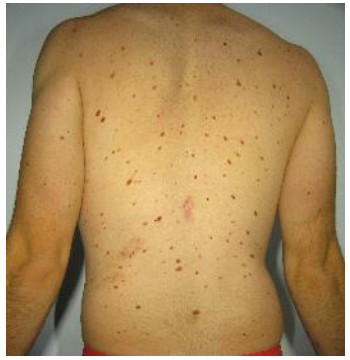
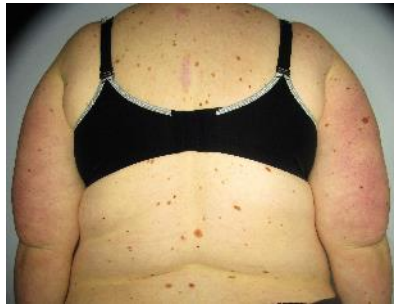
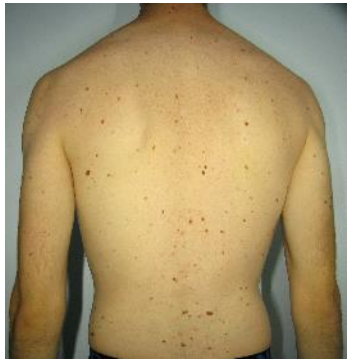
02DB	07LW	108LT	136SP	373BD
				
Group	2	4	6	2, 4, 6
Av Age	37.8yr	48.8yr	55.1yr	47.7yr
Av TNC >5mm	98.3	127.7	133.7	120.8

510AN	525HW	657LP	670RE	714E
				

Extreme Naevi Substudy: Candidate Gene Analysis of WES

401CM
608GN
623JG
668LW
323WP
334SW
357SN
360SJ
371MR
387JL

1

Low Naevus count

MITF E318K	0.0%
MC1R V60L	6.7%
NF1 intronic rs141114572	1.7%
TERT intronic rs7734992	3.3%
CDKN2A A148T	0.0%
CDKN2B-as rs974336	1.7%
ATM P1054R	3.7%

07LW
136SP
525HW
657LP
510AN
373BD
108LT
670RE
714EP
02DB

2

High Naevus count

MITF E318K	8.0%
MC1R V60L	23.4%
NF1 intronic rs141114572	10.9%
TERT intronic rs7734992	20.3%
CDKN2A A148T	4.7%
CDKN2B-as rs974336	14.1%
ATM P1054R	7.9%

230NM
341CE
531DF
475PM
198GV
01AR
588AS
743HH
210GB
564JA

3

347LM
61JB
587MJ
941MC
940NB
703PG
809CK
930HM
242PM
228CM

4

690KB
669GB
140JB
211KH
188DW
229CH
376TH
509VS
889GS
215EA

5

197CN
186DH
943DS
015KJ
130MV
716GB
918DW
176SP
443EF
777JB
28RH
155IN

6

Program II

Consumer facilitated naevi monitoring

Study Design: Provide participants with instructions and dermatoscope iPhone attachments to conduct skin self-examinations every 3 months for a period of 3 years (part of Core Study).

Aims:

- Create evidence for how we can best support consumers in the detection of transforming naevi, using the latest technological developments.
- Evaluate if mobile teledermoscopy used in skin self-examinations improve participants' sensitivity and specificity for identifying naevi requiring clinical management
- Decipher if repeated mobile teledermoscopy improves sensitivity further
- Measure consistency between dermatologists' tele-diagnoses and whether concordance is dependent on years of practice

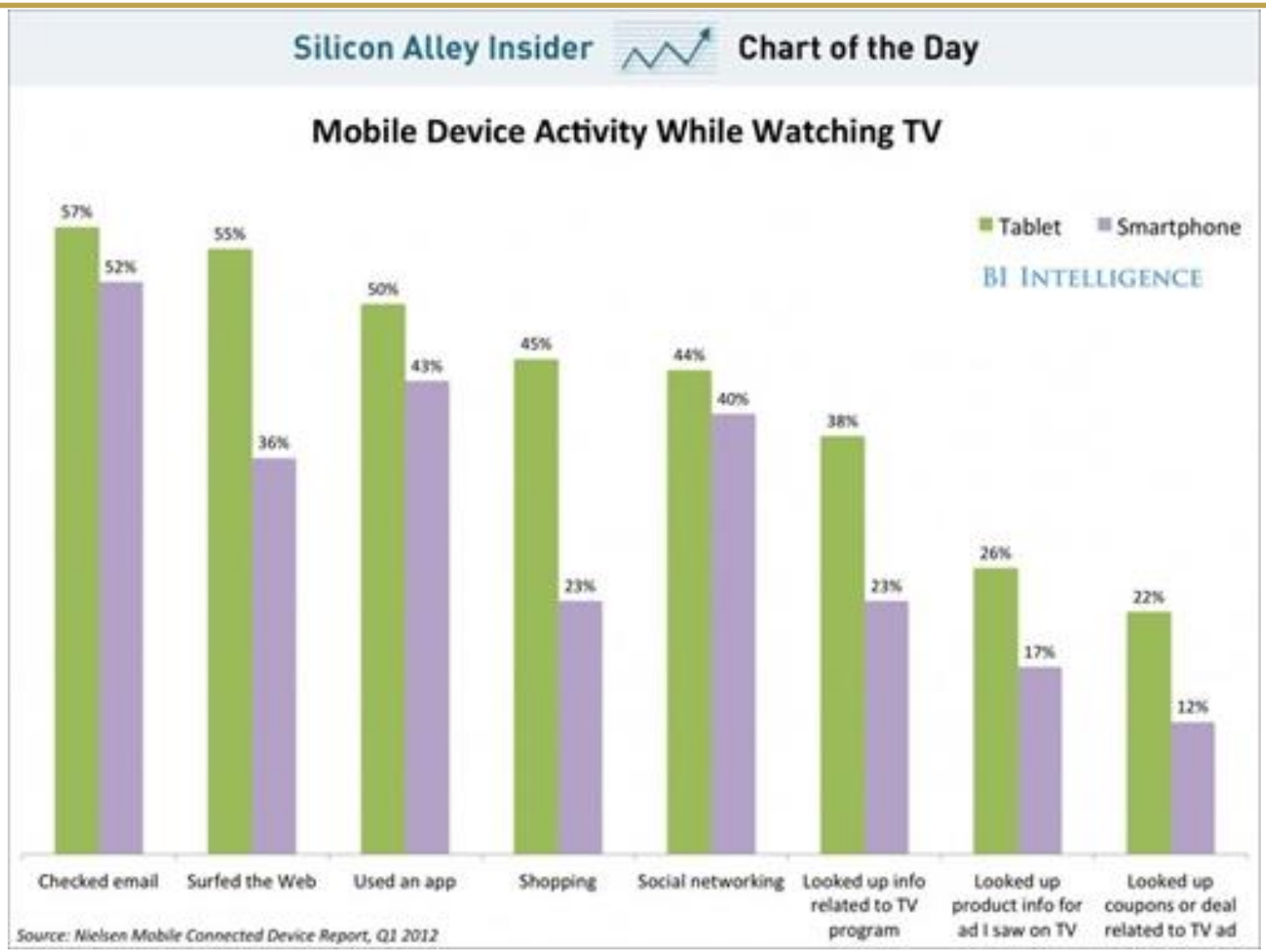
Cell Phone Addiction

We check these devices up to 150 times per day.

How we use our smartphones

ACTIVITY BY AVERAGE TIME PER DAY

www.telegraph.com.uk


Silicon Alley Insider
Chart of the Day
Mobile Device Activity While Watching TV
Tablet
Smartphone
BI INTELLIGENCE
57%
52%
55%
36%
50%
43%
45%
23%
44%
40%
38%
23%
26%
17%
22%
12%
Checked email
Surfed the Web
Used an app
Shopping
Social networking
Looked up info related to TV program
Looked up product info for ad I saw on TV
Looked up coupons or deal related to TV ad
Source: Nielsen Mobile Connected Device Report, Q1 2012

First Check Mini Dermatoscope

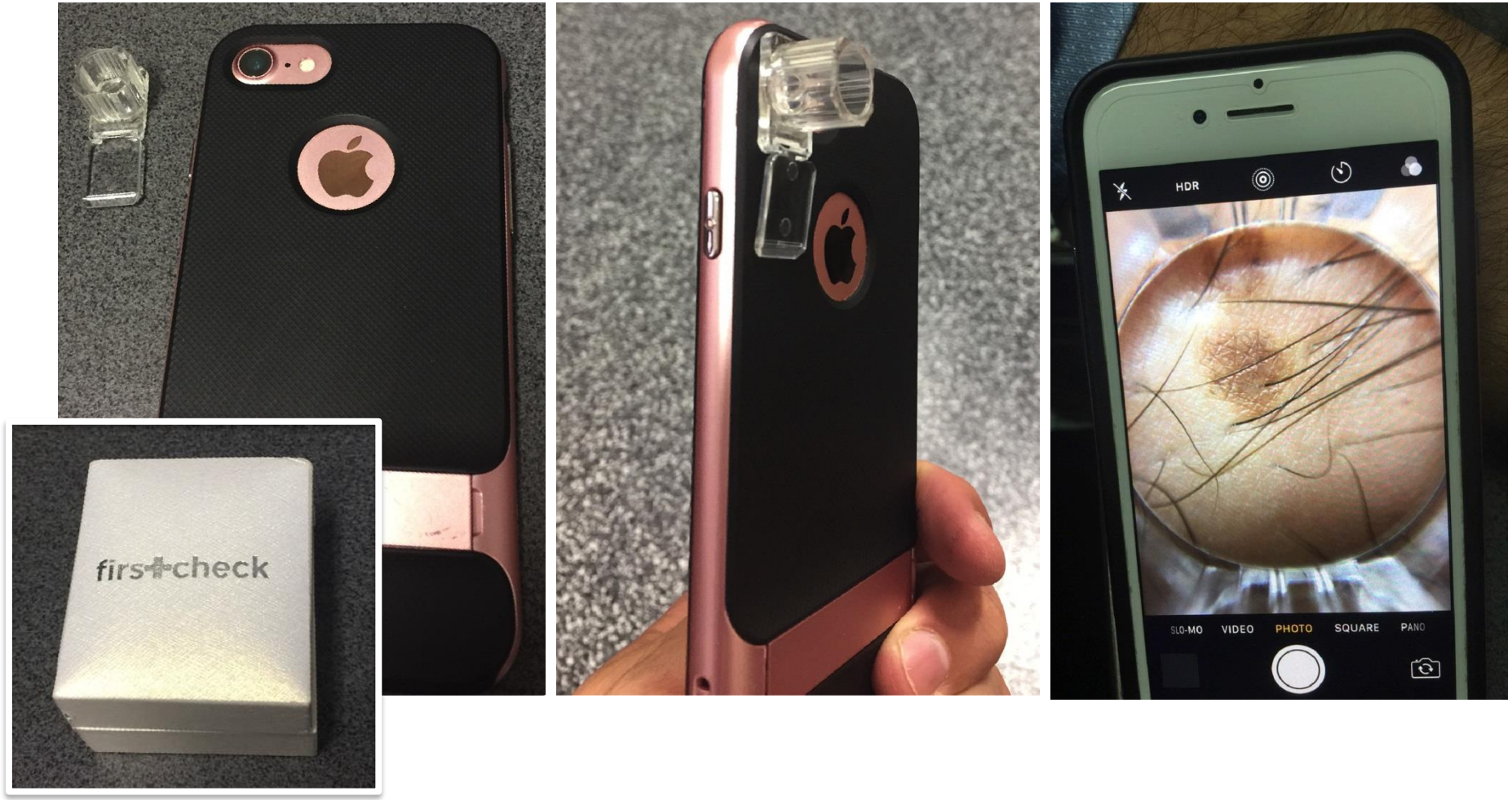
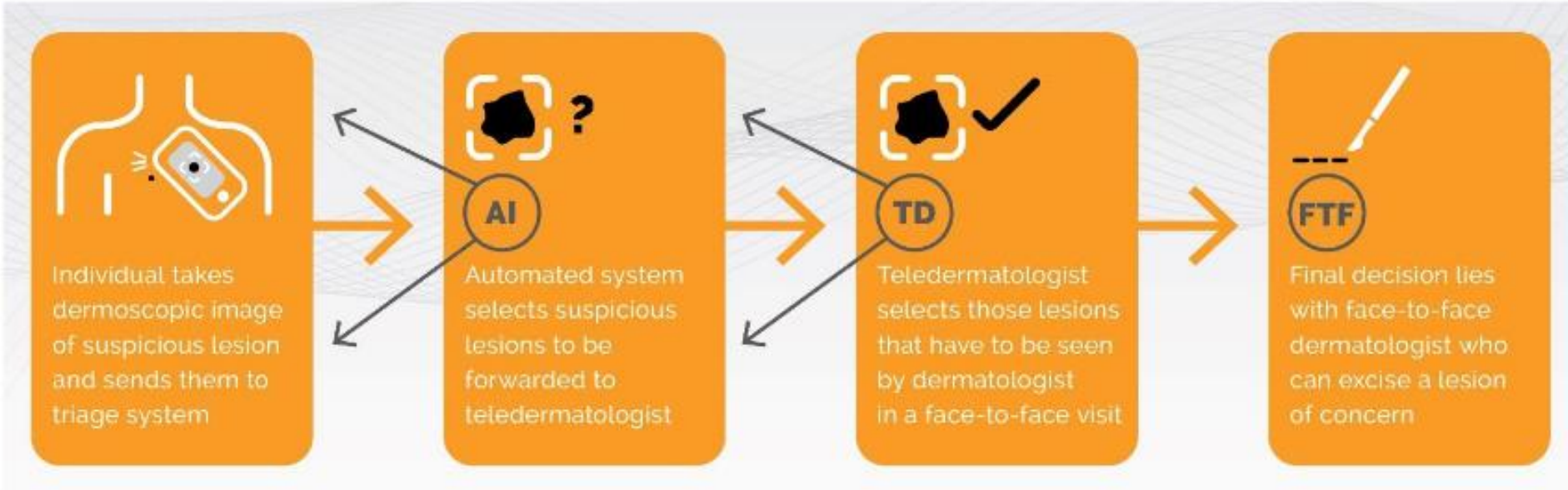


Figure 2: Consumer-driven mobile teledermoscopy with artificial intelligence (AI)



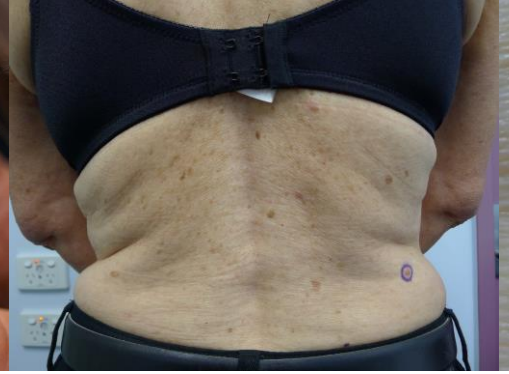
Program III

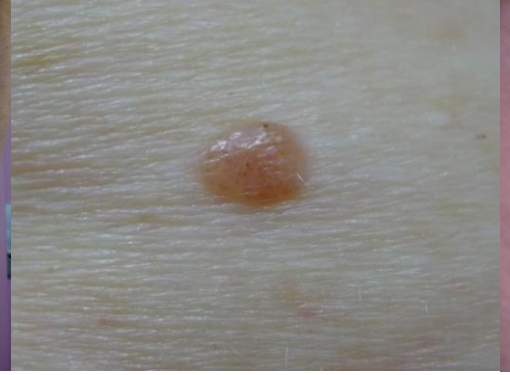
Molecular and Genetic Properties of Changing Naevi

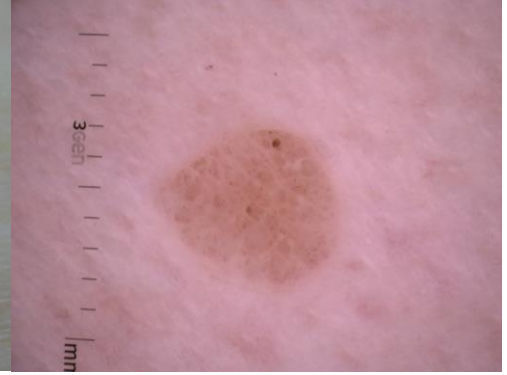
Study design: An observational study to examine the natural history and molecular properties of naevi in advanced melanoma patients undergoing treatment over a one year period using dermoscopy, 3D full body photography and molecular analysis of excised naevi.

Aims:

- Ascertain how rapidly naevi are changing in Stage III and IV melanoma patients undergoing treatment, and which germline/somatic genotypes predict these changes?
- Determine if involuting and/or growing naevi are clinical markers of response to treatment.
- Define distinct epigenetic profiles attributable to changeable naevi and how this relates to dermoscopic and histopathologic naevus types







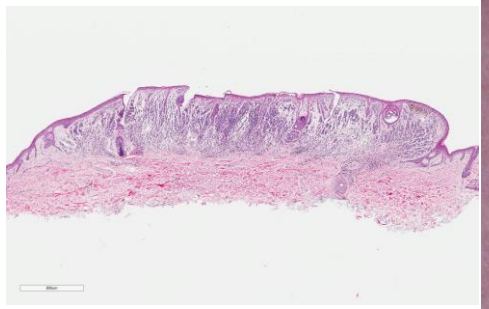
Clinical Assessment → **Clinical Photos** → **Dermoscopic Photo**

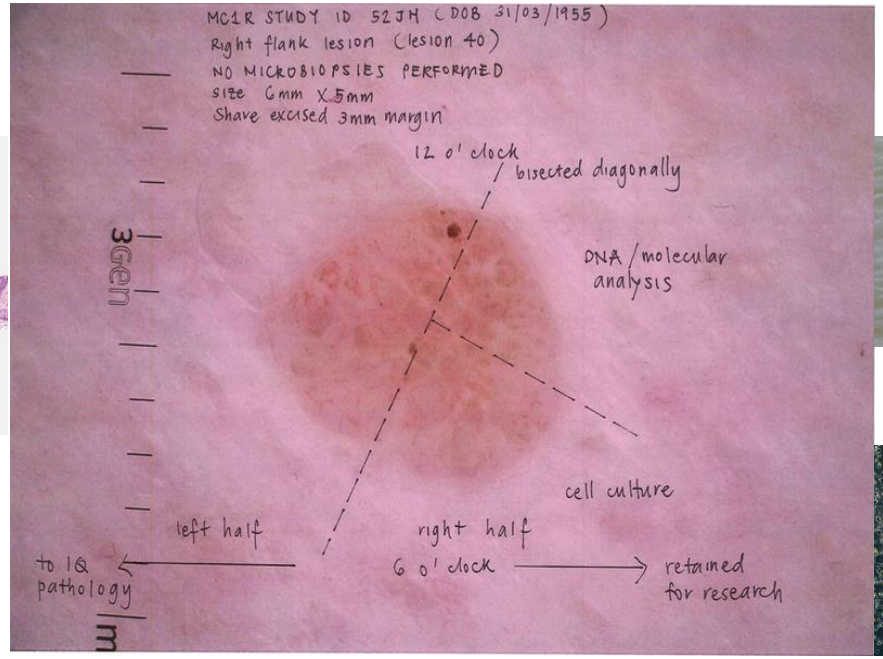
Age, gender, melanoma history, anatomical location, size

Shave excision 2-3mm margin

Routine Histopathology

Molecular Work-Up





SALIVA

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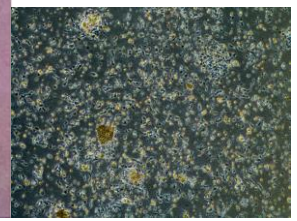


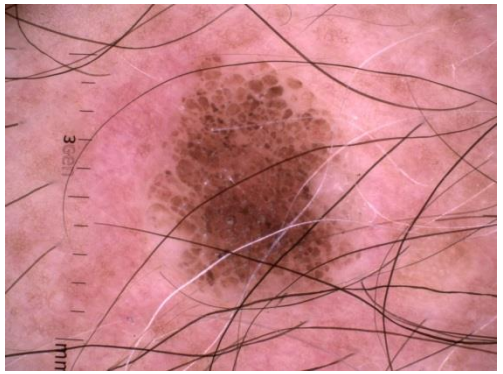
DNA Isolation

WES ± Targeted Resequencing

Naevus excision study of somatic mutation spectrum

100% MAPK pathway activation (Tan et al. in submission)

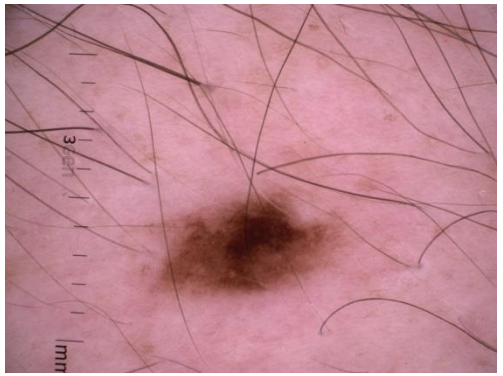
No.	Patient ID	Sampling Date	Lesion Number	DERMOSCOPIC PATTERN/HISTOPATHOLOGY
1	155IN	2/05/14	30	Reticular
2	130MV	9/05/14	160	Reticular
3	733EF	30/05/14	35	pigmented SCC in situ arising in background of AK merging with seb K and solar lentigo
4	736TP	13/06/14	3	Globular
5	736TP	13/06/14	13	Reticular
6	125RP	25/07/14	4	pigmented large cell acanthoma
7	759BS	8/08/14	49	solar lentigo, large cell acanthoma and seb K
8	739DC	15/08/14	67	solar lentigo
9	747LH	5/09/14	133	Reticular
10	772DW	26/09/14	75	Reticular
11	18MT	3/10/14	35	Globular
12	18MT	3/10/14	65	Reticular
13	007LW	10/10/14	152	Globular
14	007LW	10/10/14	155	Reticular
15	763RM	17/10/14	63	junctional lentiginous naevus with seb K
16	774AS	24/10/14	17	Reticular
17	28RH	31/10/14	110	Reticular
18	28RH	31/10/14	134	reticulated pattern seb K
19	28RH	31/10/14	135	Globular
20	769RR	7/11/14	38	large cell acanthoma
21	673PS	21/11/14	2	Reticular
22	764SA	5/12/14	1	AK arising in background of solar lentigo
23	764SA	5/12/14	42	large cell acanthoma transitioning to reticulated pattern seb K with background changes of solar lentigo
24	806SG	19/12/14	11	large cell acanthoma and solar lentigo
25	903JA	8/05/15	33	Reticular
26	695MB	5/06/15	59	Reticular
27	52JH	24/07/15	40	Globular
28	39RB	31/07/15	6	Globular
29	1030NW	18/08/15	28	Non-Specific (Peripheral Rim Globules)
30	1030NW	18/08/15	54	Non-Specific (Peripheral Rim Globules)
31	61JB	11/09/15	115	Globular
32	61JB	11/09/15	133	Globular
33	1062DM	18/09/15	76	Non-Specific (Peripheral Rim Globules)



Globular

BRAF= 92%

NRAS= 8%



Reticular

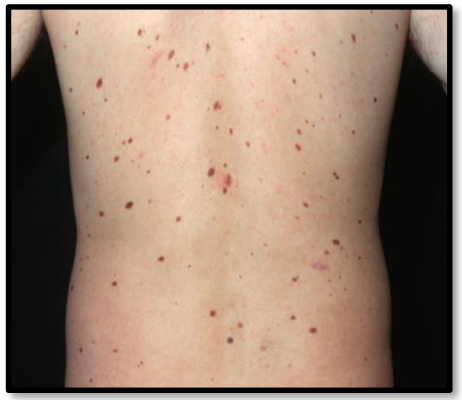
BRAF= 67%

NRAS= 33%

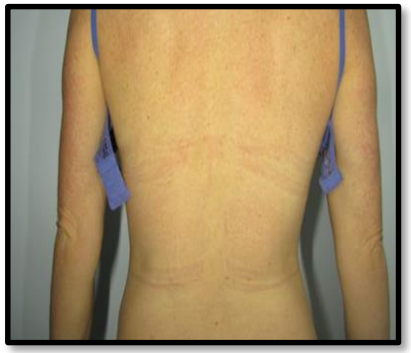
Nonspecific (Peripheral Rim Globules)

BRAF= 100%

The Vision



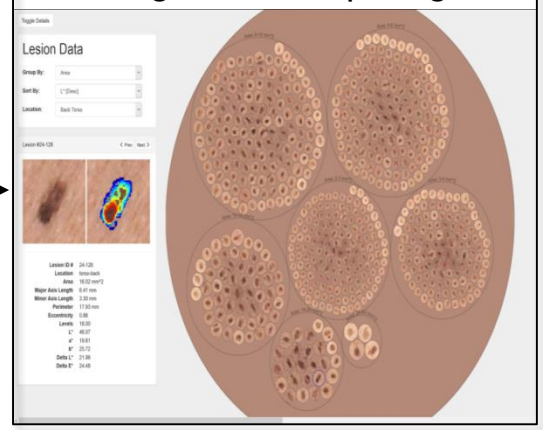
Germline genomics will complement phenotypic risk assessment



3D Telederm Network via PACS

Partner assisted skin self-examination

Cognitive Computing



Protocol-driven Decision Support Systems (AI) will lead to early intervention

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SAVE THE DATE!

MELANOMA 2017

A joint meeting of the 9th World Congress of Melanoma &
14th International Congress of the Society for Melanoma Research

18–21 October 2017, Brisbane Australia

SMR Society for Melanoma Research

Cancer Council Queensland

brisbane
australia's new world city