

Ridley-Tree Cancer Center

# Community Lectures



Ridley-Tree  
Cancer Center  
at Sansum Clinic



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**Ridley-Tree  
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# Community Lectures



## *Advances in Melanoma & Skin Cancer Prevention*

Ridley-Tree Cancer Center's Medical Oncologist and Hematologist Julian Davis, MD, MA and Dermatologist Mark Burnett, MD, FAAD of the

Santa Barbara Skin Institute offer a view on the latest advances in treating melanoma and what patients can do to best reduce their risk of this and other skin cancers.

Recorded May 15, 2020

Ridley-Tree Cancer Center Wolf Education & Training Center

# Community Lectures



Mark Burnett, MD, FAAD  
Dermatologist  
Santa Barbara Skin Institute



# Advances in Melanoma: Detection, Treatment and Prevention

Mark E. Burnett, MD, FAAD

I have no financial disclosures.

# Outline

What is melanoma?

Incidence of melanoma in the U.S.

What causes melanoma?

How is melanoma detected?

How is melanoma treated?

How can melanoma be prevented?

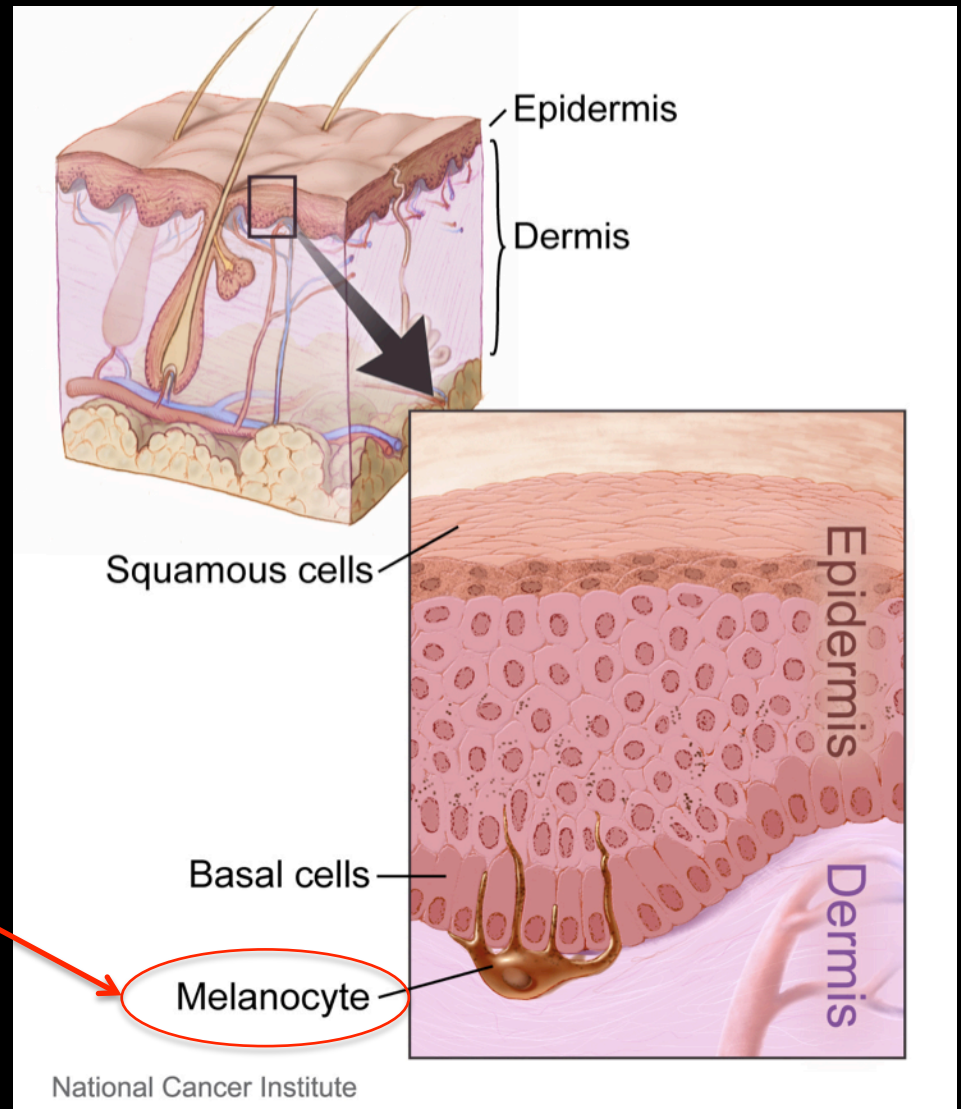


# What is melanoma?

Melanoma is a malignant tumor arising from melanocytes



Melanocytes are melanin-producing cells located in the bottom layer of the skin's epidermis.



# Types of melanoma

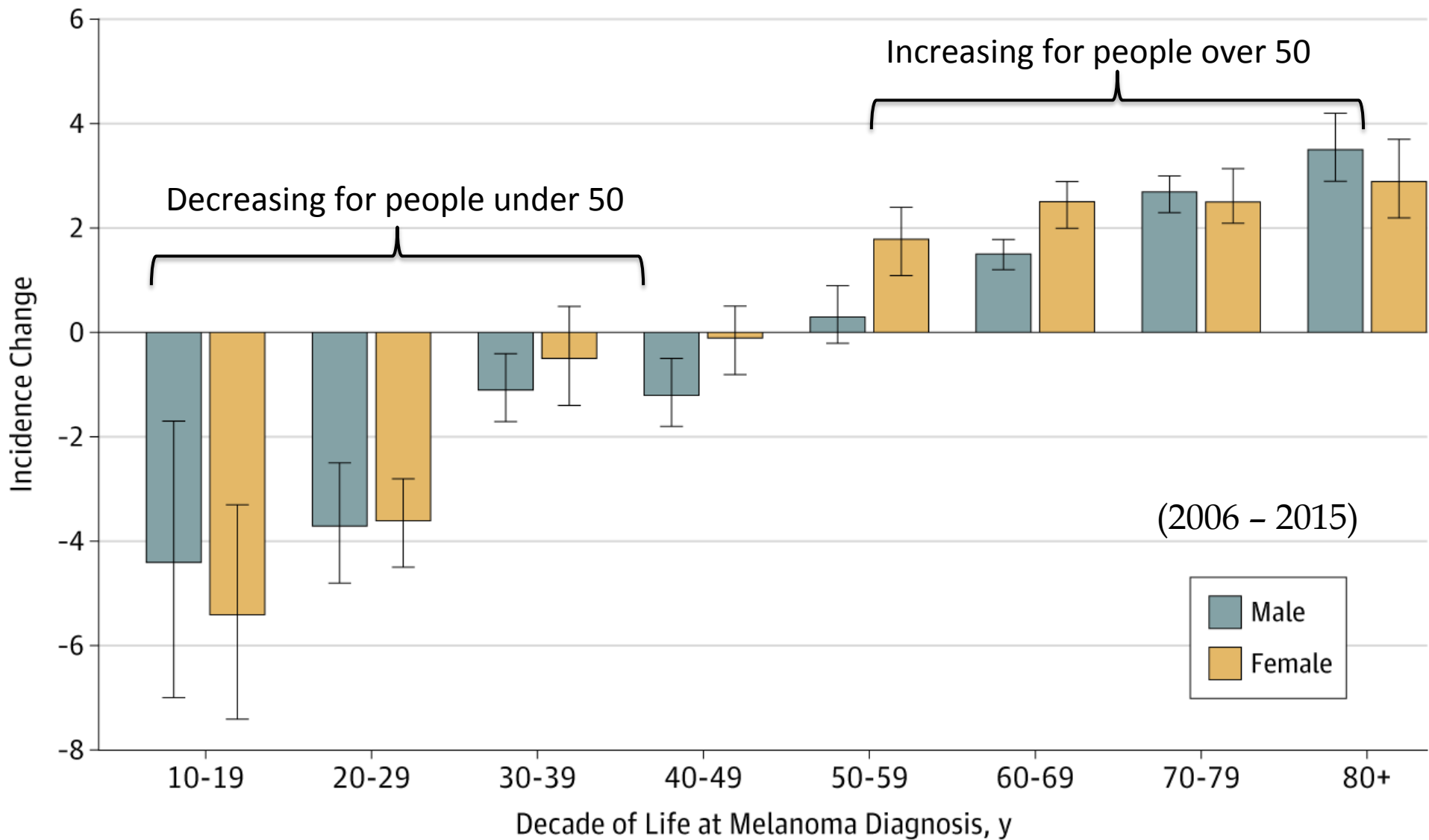
## Cutaneous (skin) melanoma

- Superficial Spreading
- Lentigo maligna
- Nodular
- Acral (palms/soles)

Some melanomas are non-cutaneous (very rare)

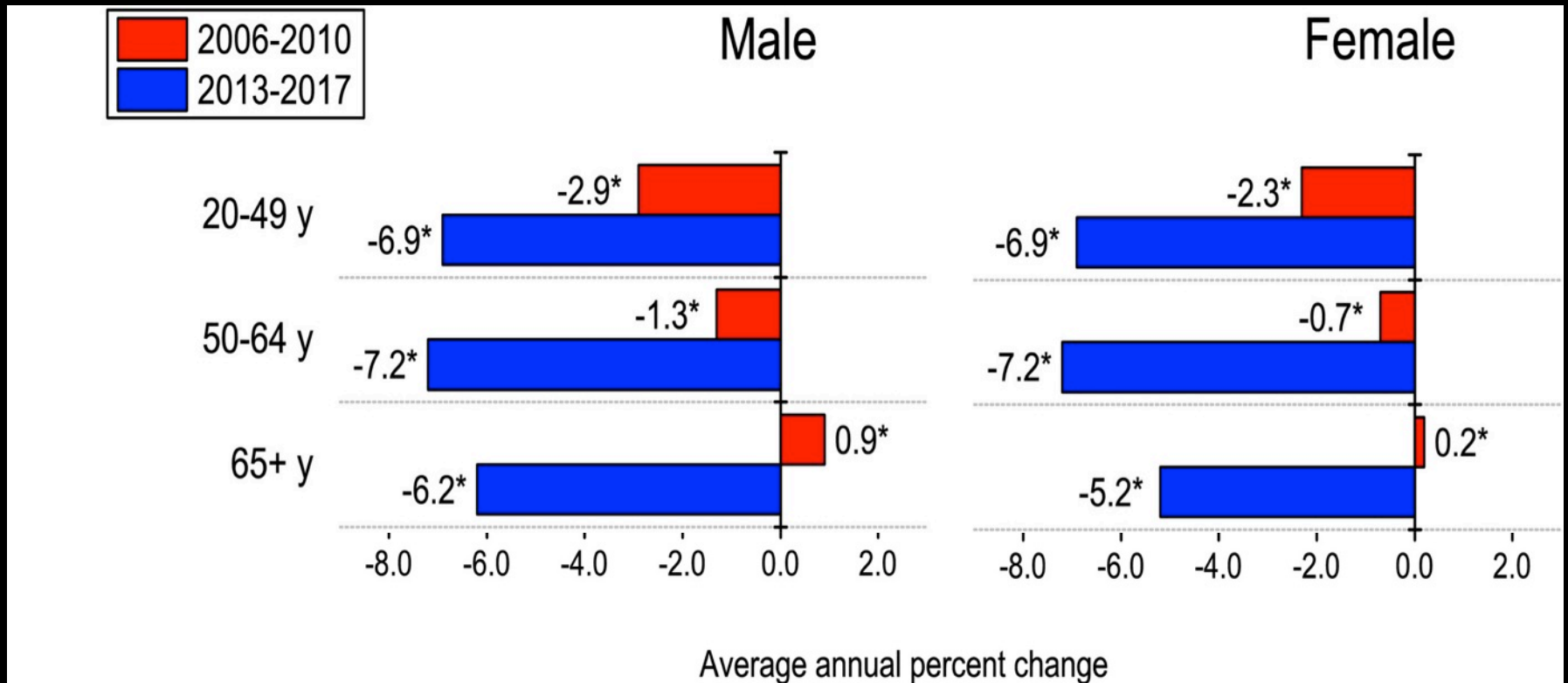
- Ocular (eyes)
- Mucous membranes (mouth, vagina, anus, and rectum)

# Incidence of Melanoma in the U.S. by Age Group





# Melanoma Mortality in the U.S.



2013 -2017: Less people are dying from melanoma (7%/year)

# What causes melanoma?

## UV Radiation

- Sun exposure, tanning beds

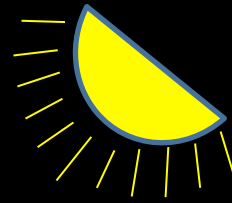
## Genetics

- Familial melanomas
- Pigmentation and nevi (mole) characteristics

## Immunosuppression

- Organ transplant patients, systemic medications

# UV Radiation



One's risk for developing melanoma doubles with a history of  $\geq 5$  sunburns



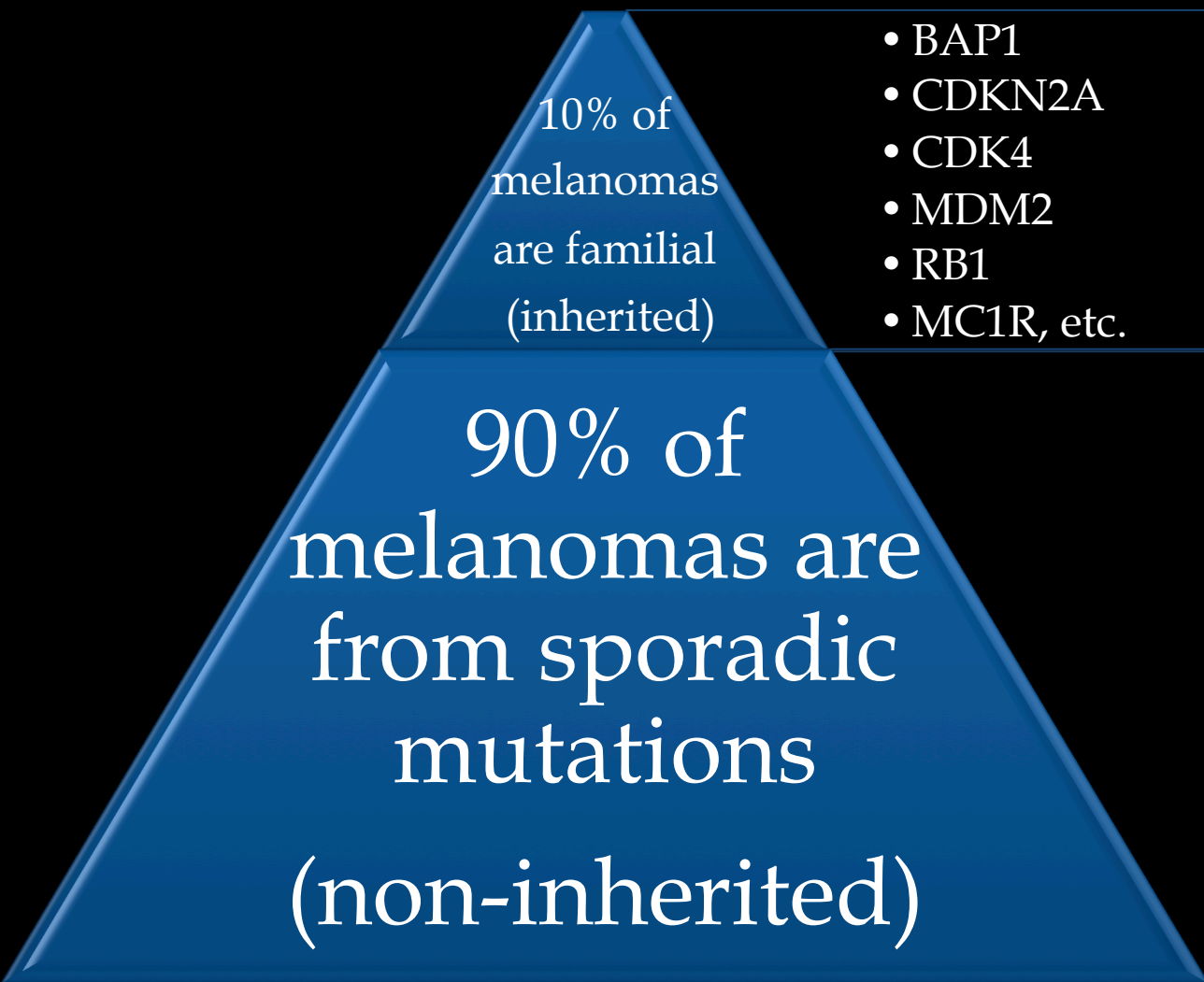
WHO classifies UV radiation and tanning beds as a "Group 1" carcinogen (other Group 1: cigarettes and plutonium)

**Melanoma risk increases 34%  
in those who have used a  
tanning bed 10+ times**

**Melanoma risk increases by  
75% among those who have  
used tanning beds before age  
35.**



# Melanoma Genetics



10% of  
melanomas  
are familial  
(inherited)

- BAP1
- CDKN2A
- CDK4
- MDM2
- RB1
- MC1R, etc.

90% of  
melanomas are  
from sporadic  
mutations  
(non-inherited)

- Mutation is acquired as a result of exposure to environmental factors (such as UV radiation).

# Melanoma Genetics

Association studies have shown that the following features increase risk:

- Sunburn easily and tan poorly
- Have red or blonde hair
- Have fair skin that freckles.

Caveat: Melanoma can arise in patients without known risk factors.

# Melanoma Genetics

- Patients with many atypical moles ('atypical nevi') are at higher risk.
- These patients usually have over >100 moles
- Note: Having atypical moles may be familial ('genetic') or sporadic (i.e. random).





# How is melanoma detected?



# How is melanoma detected?

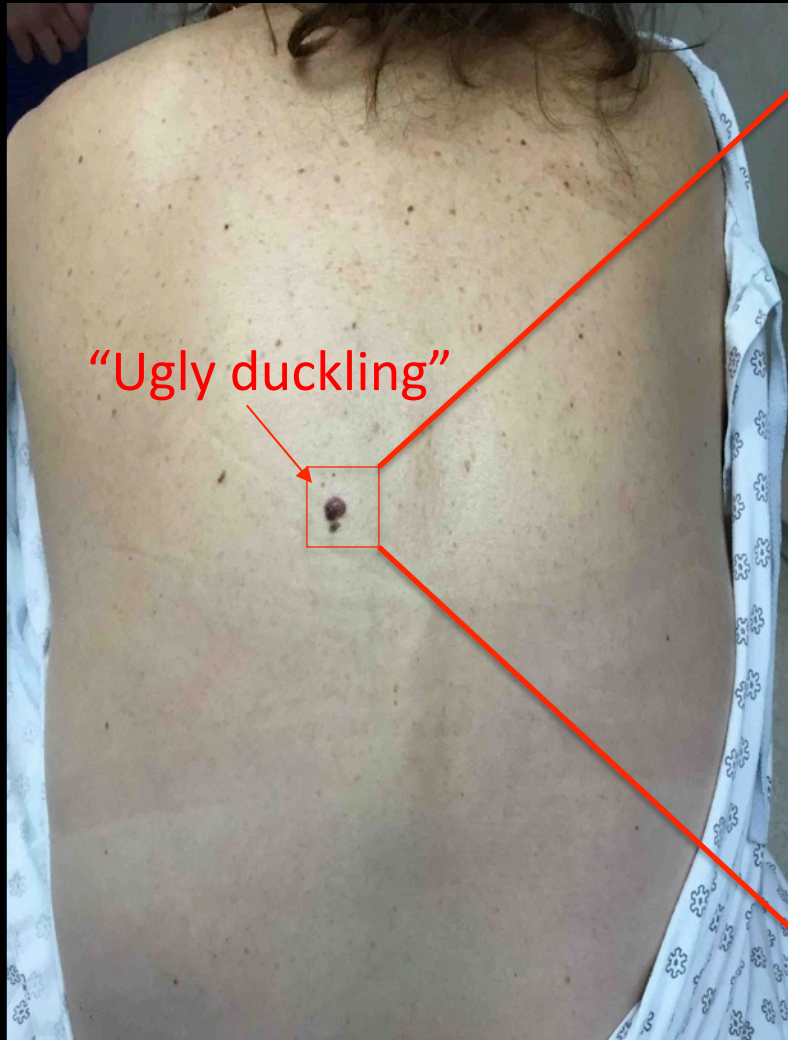
Goals of melanoma screening

```
graph LR; A[Goals of melanoma screening] --- B[Identify tumors at an early stage when surgical excision can be curative.]; A --- C[Avoid unnecessary/excessive biopsies]
```

Identify tumors at an early stage when surgical excision can be curative.

Avoid unnecessary/excessive biopsies

# How is melanoma detected?



# How is melanoma detected?

## “ABCDEs” of Melanoma detection

Asymmetry?	√
Border Irregularity?	√
Color Irregularity?	√
Diameter >6mm?	√
Evolving?	√



# Dermoscopy

- Dermatoscope: More than a magnifying lens.





# Dermoscopy

Improves diagnostic accuracy by 10 – 27%

Increases both specificity and sensitivity in the detection of melanoma.



Reduces unneeded biopsies

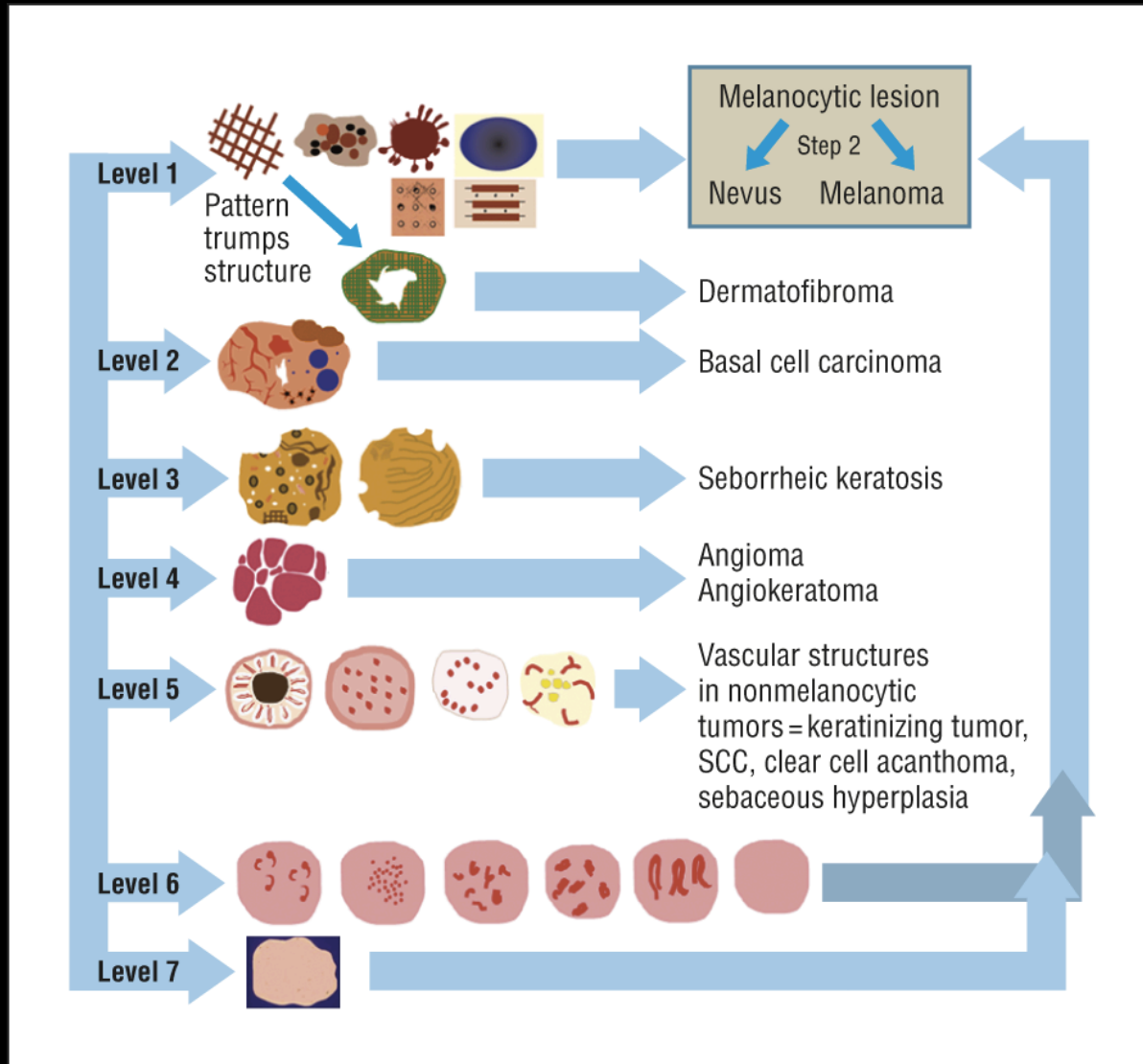
Greatest benefit for patients with many moles, and those with a personal or family history of melanoma.



Caveat: The above are true only in experienced hands.

→ Now standard part of dermatology training.

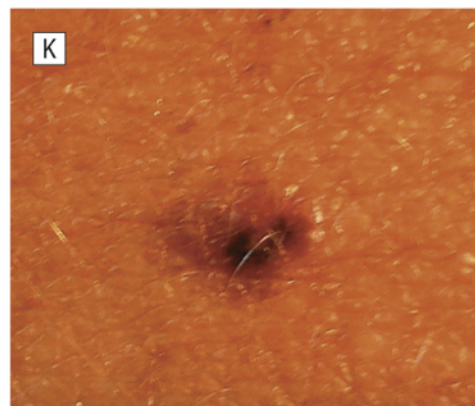
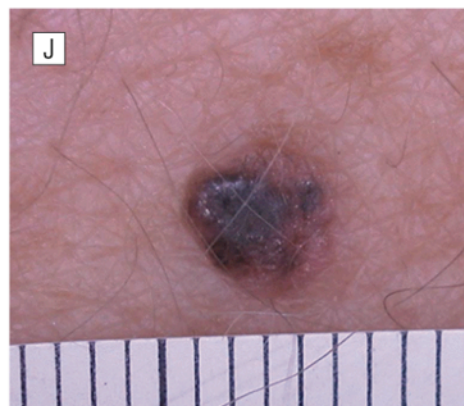
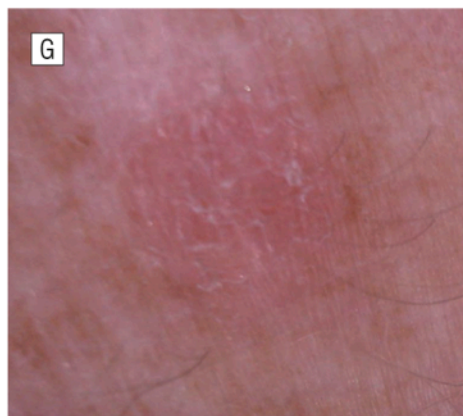
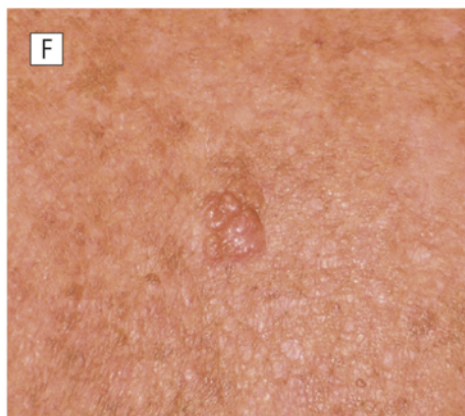
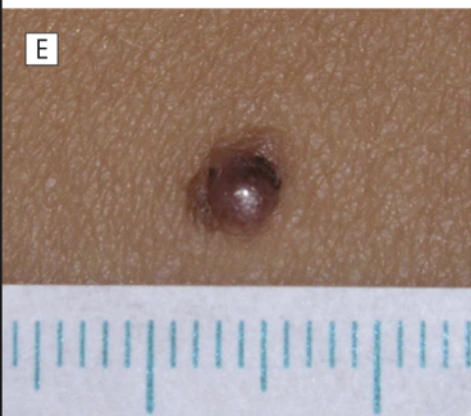
# Dermoscopy Algorithms



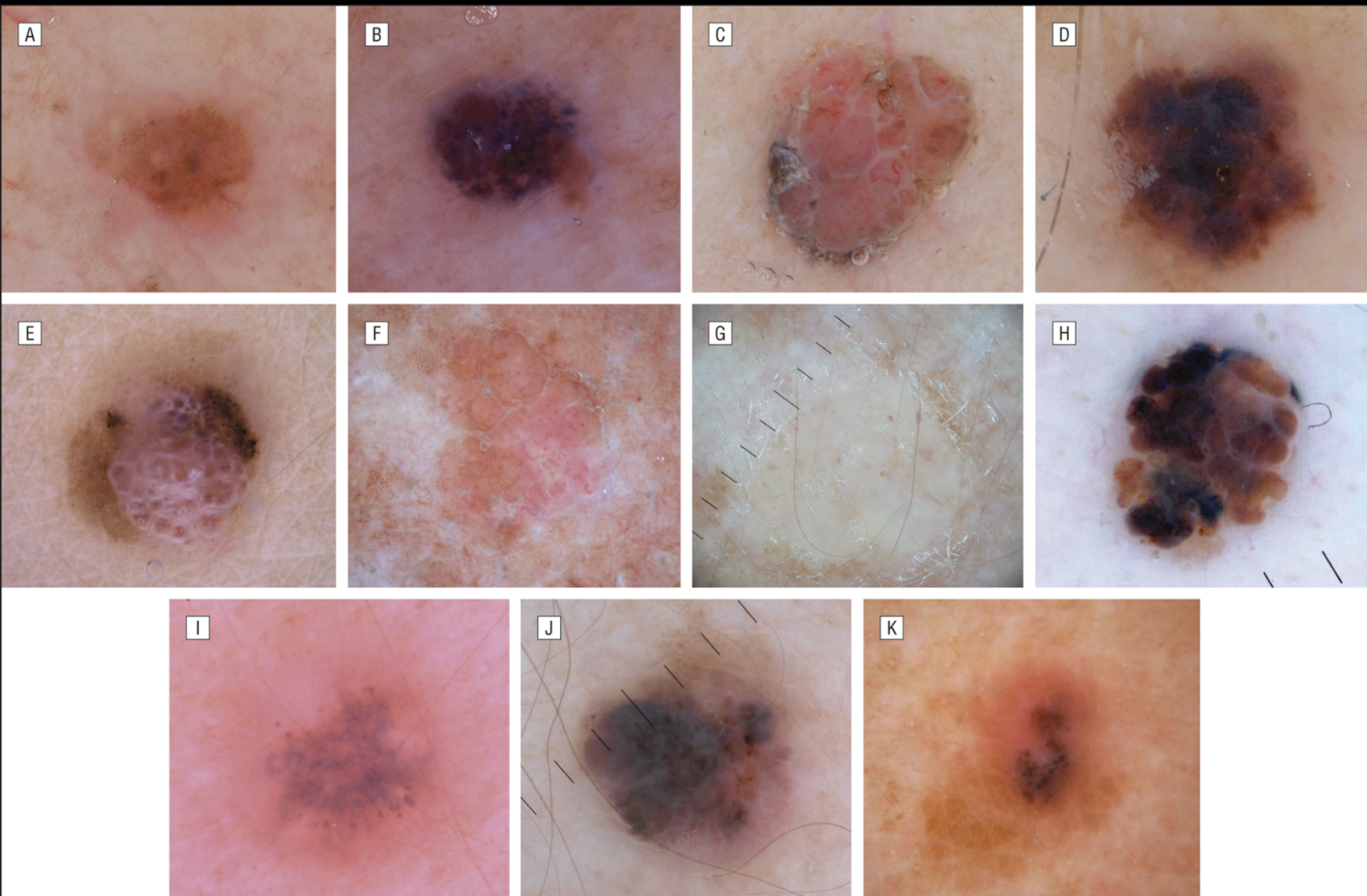
# Dermoscopy











# Total Body Photography





# Total Body Photography + Dermoscopy



# New and Emerging Technologies

- Non-invasive gene analysis (PLA)
- 3-D Whole Body Photography
- Reflectance Confocal Microscopy (RCM)
- Artificial Intelligence

# Non-invasive RNA analysis

## Pigmented Lesion Assay ("PLA")

Individual lesions  
are sampled using  
an adhesive patch

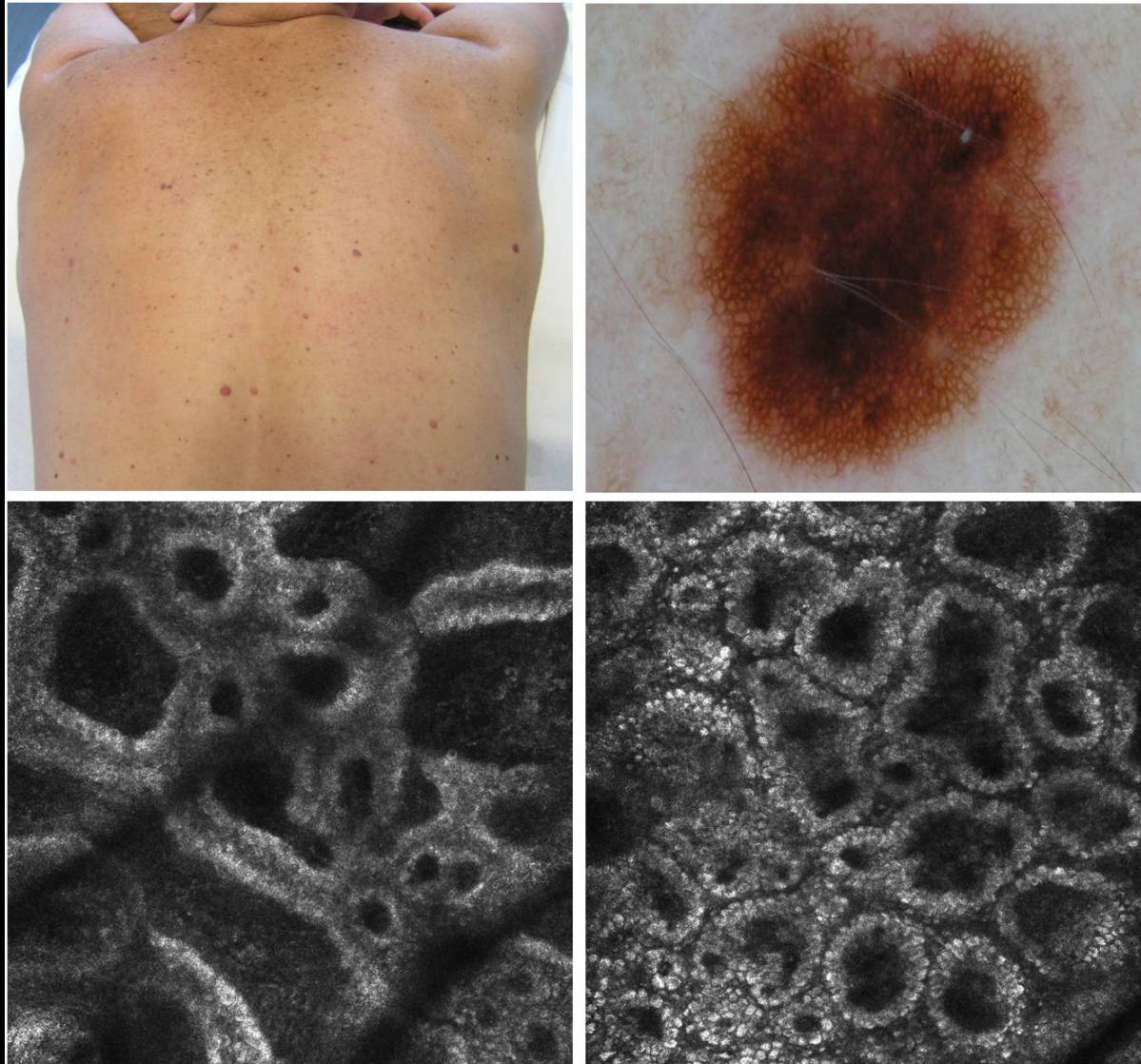
May reduce  
number of biopsies



# 3-D Total Body Photography



# Reflectance Confocal Microscopy





# Reflectance Confocal Microscopy

Noninvasive, near-histological resolution and visualization of skin

- Improved diagnostic accuracy (compared to dermoscopy)
- Prevents removal of up to 70% of benign lesions





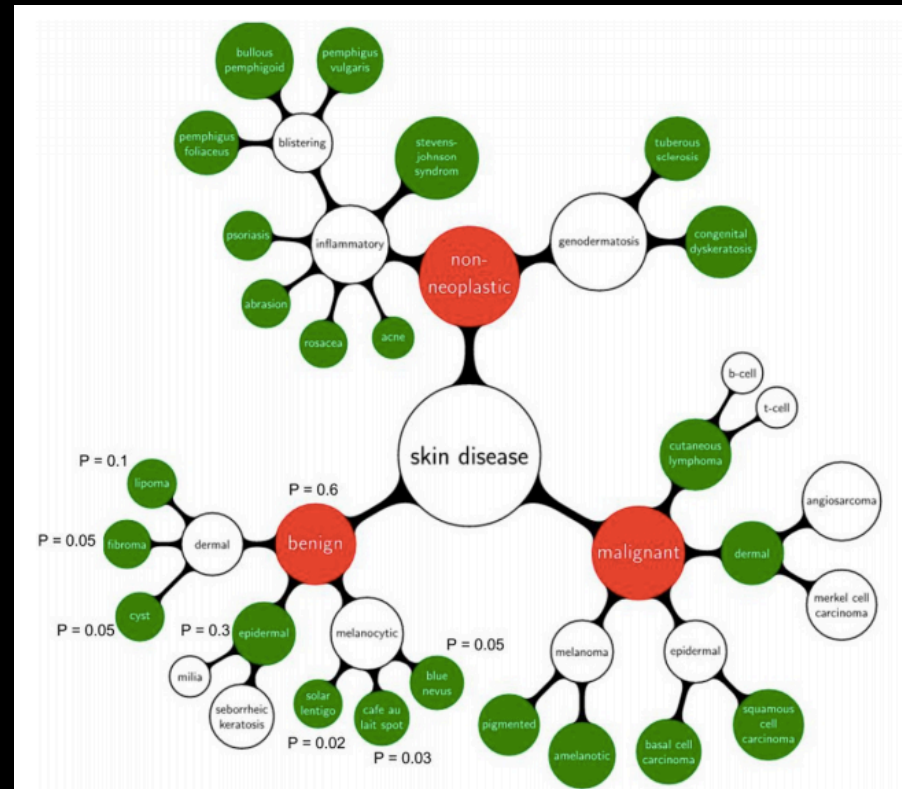
# Artificial Intelligence

## Dermatologist-level classification of skin cancer with deep neural networks

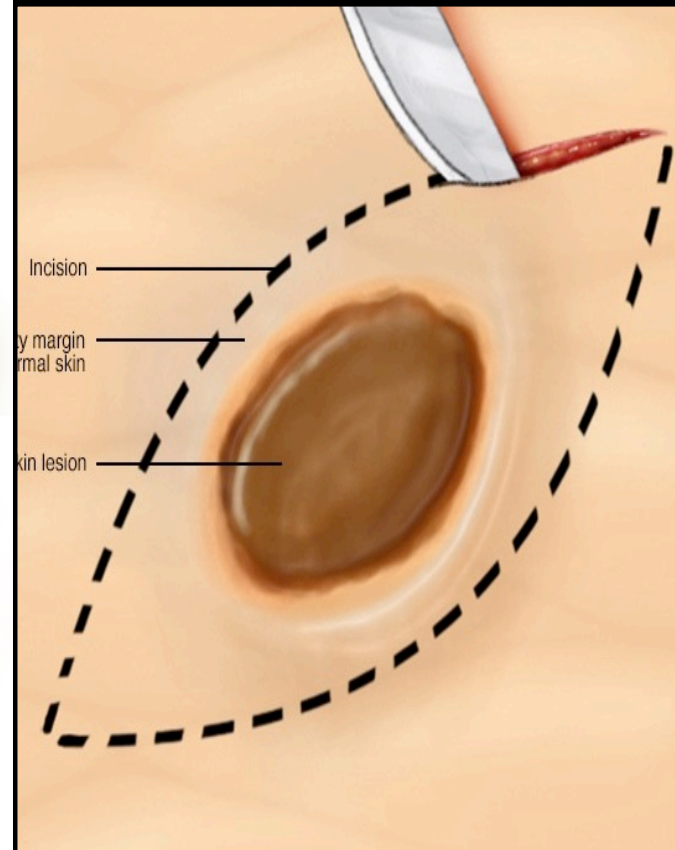
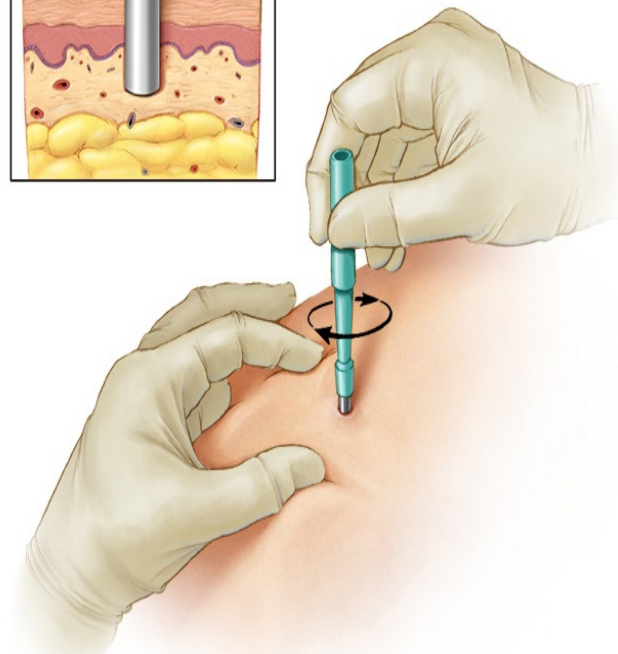
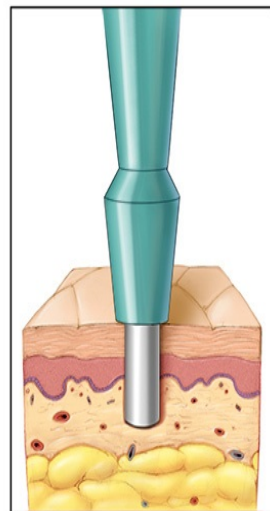
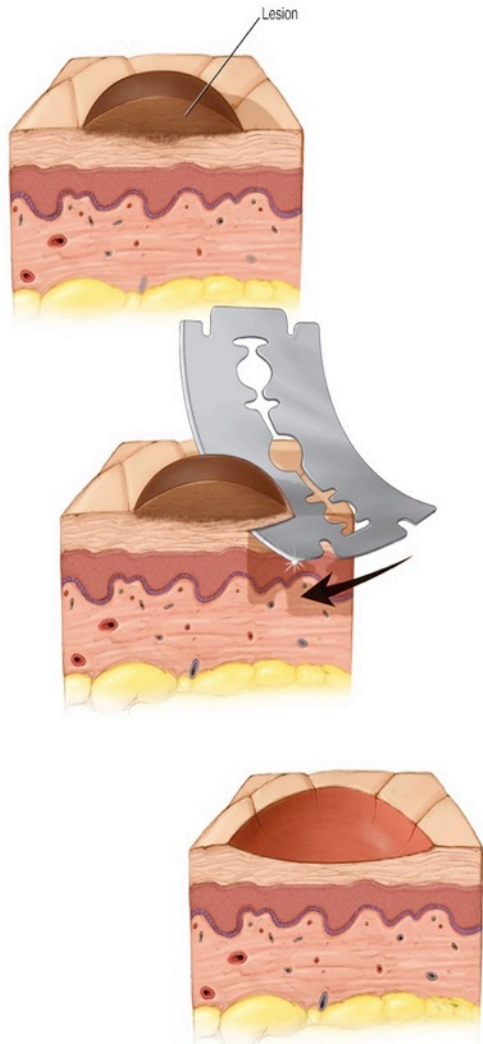
Andre Esteva<sup>1\*</sup>, Brett Kuprel<sup>1\*</sup>, Roberto A. Novoa<sup>2,3</sup>, Justin Ko<sup>2</sup>, Susan M. Swetter<sup>2,4</sup>, Helen M. Blau<sup>5</sup> & Sebastian Thrun<sup>6</sup>

### Convolutional neural networks (CNNs)

- Software algorithms trained to distinguish benign vs. malignant lesions from images.
- Comparable performance with dermatologists in melanoma diagnosis

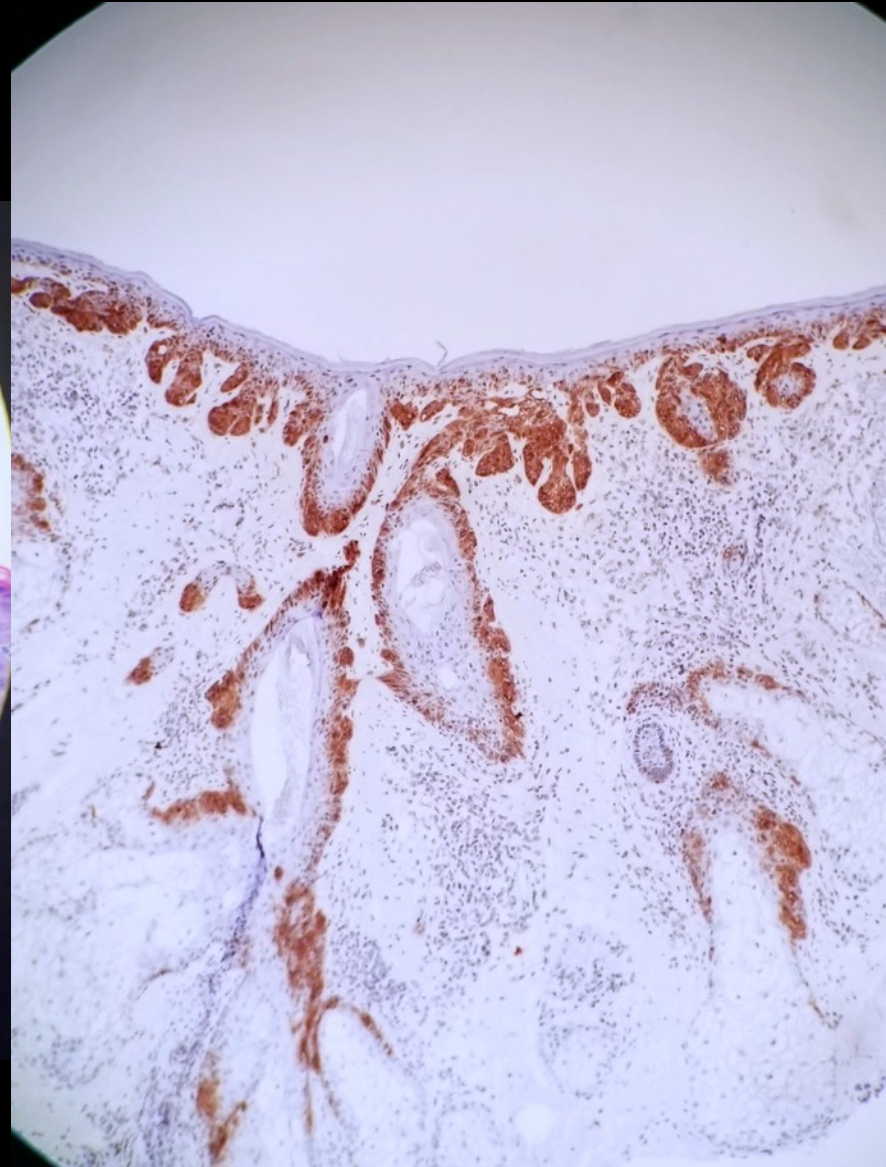
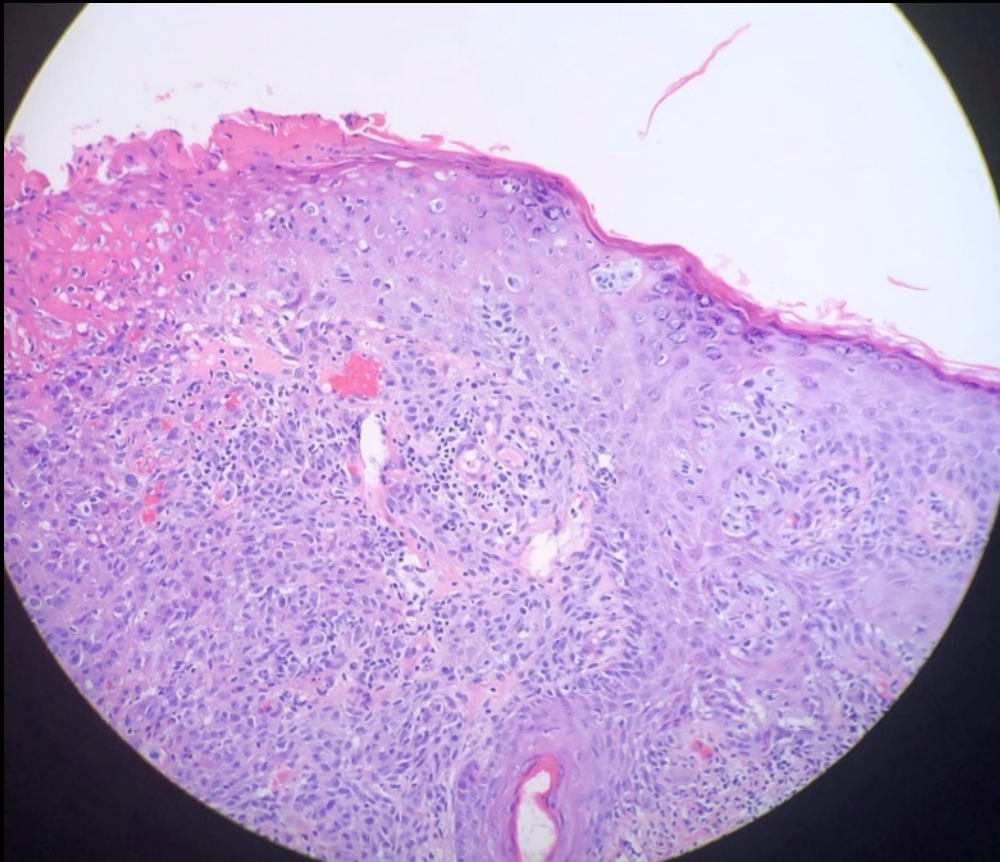


# Diagnosis of melanoma: Biopsy

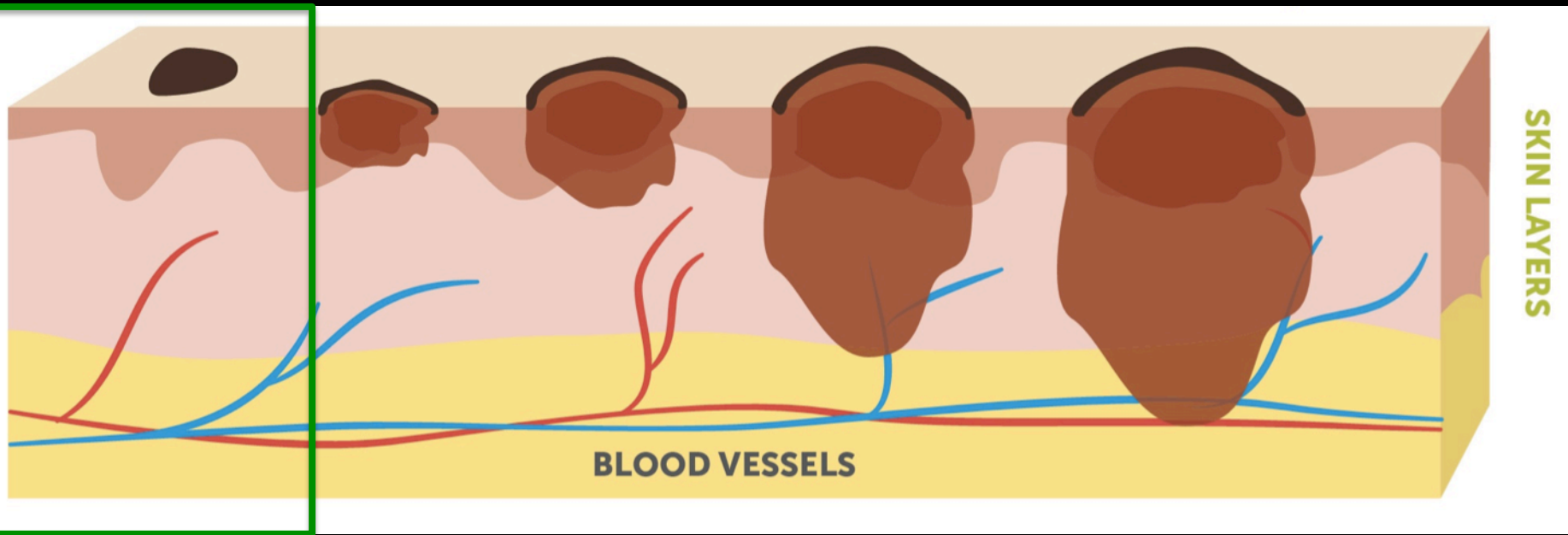




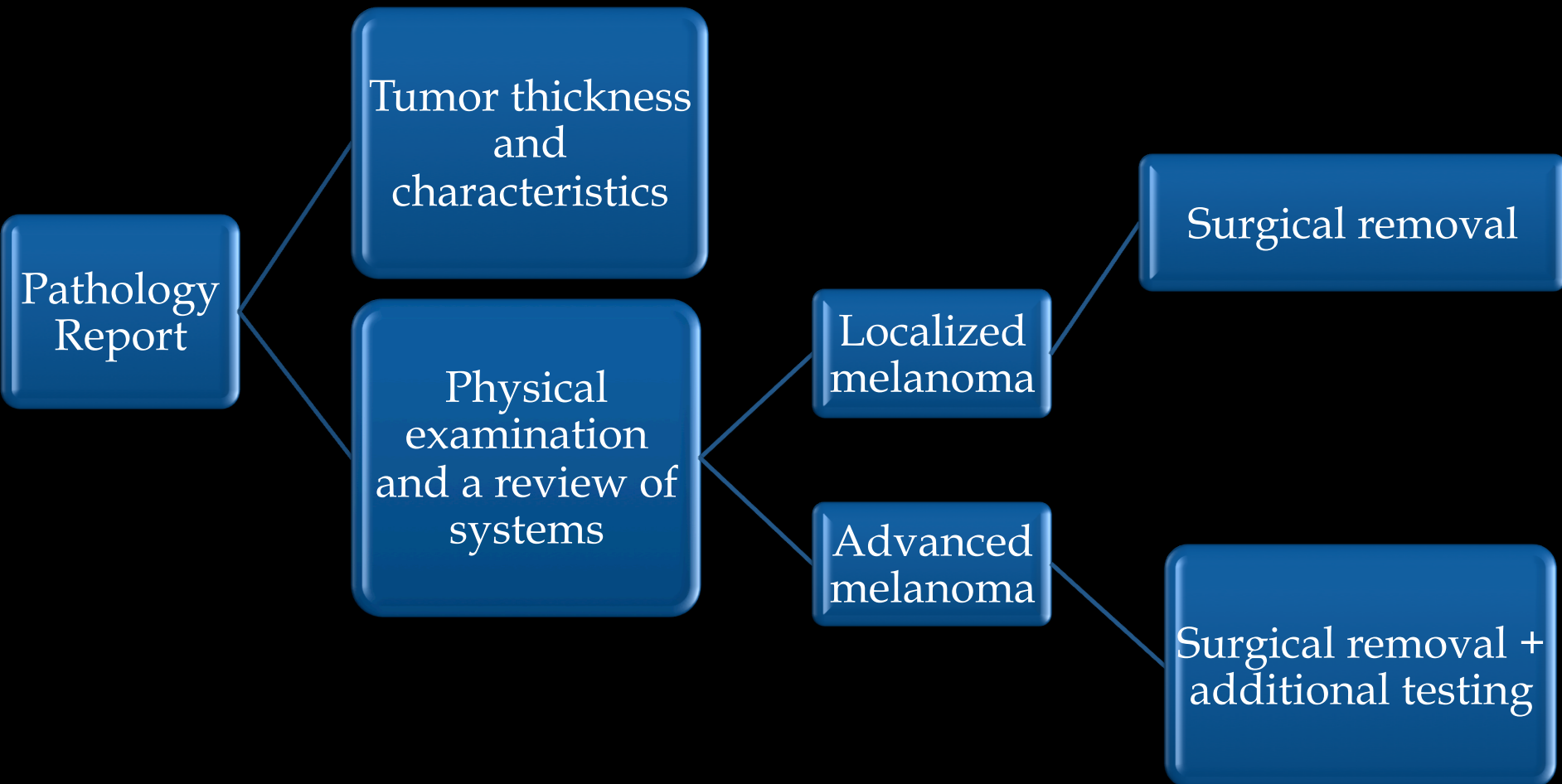
# Diagnosing Melanoma: Pathology



# “In Situ” vs. Invasive Melanoma



# How is melanoma treated?



# Gene Expression Profile (GEP) testing for melanoma

Genes from the original biopsy specimen are analyzed



Goal is to provide an estimation of metastatic risk and likelihood of a positive sentinel lymph node biopsy.



# Gene Expression Profile (GEP) testing is standard of care for:

Breast cancer (MammaPrint, Oncotype Dx)

- Used to predicting recurrence and response to chemotherapy or radiation (post-surgery).

Uveal melanoma (DecisionDx-UM)

- Significantly ( $P < 0.0001$ ) more accurate at predicting metastatic risk than any other prognostic factor

Thyroid cancer (Afirma, ThyraMIR, Thyroseq)

Lung Cancer, NSCLC

# How is melanoma treated?

FROM THE ACADEMY

January 2019

## Guidelines of care for the management of primary cutaneous melanoma



NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# Cutaneous Melanoma

Version 2.2019 — March 12, 2019

Surgery should be the primary treatment modality for cutaneous melanoma.

# Surgery for Melanoma

Goal of surgery is to completely remove tumor



Highest clearance rates are when 100% of surgical margin is evaluated

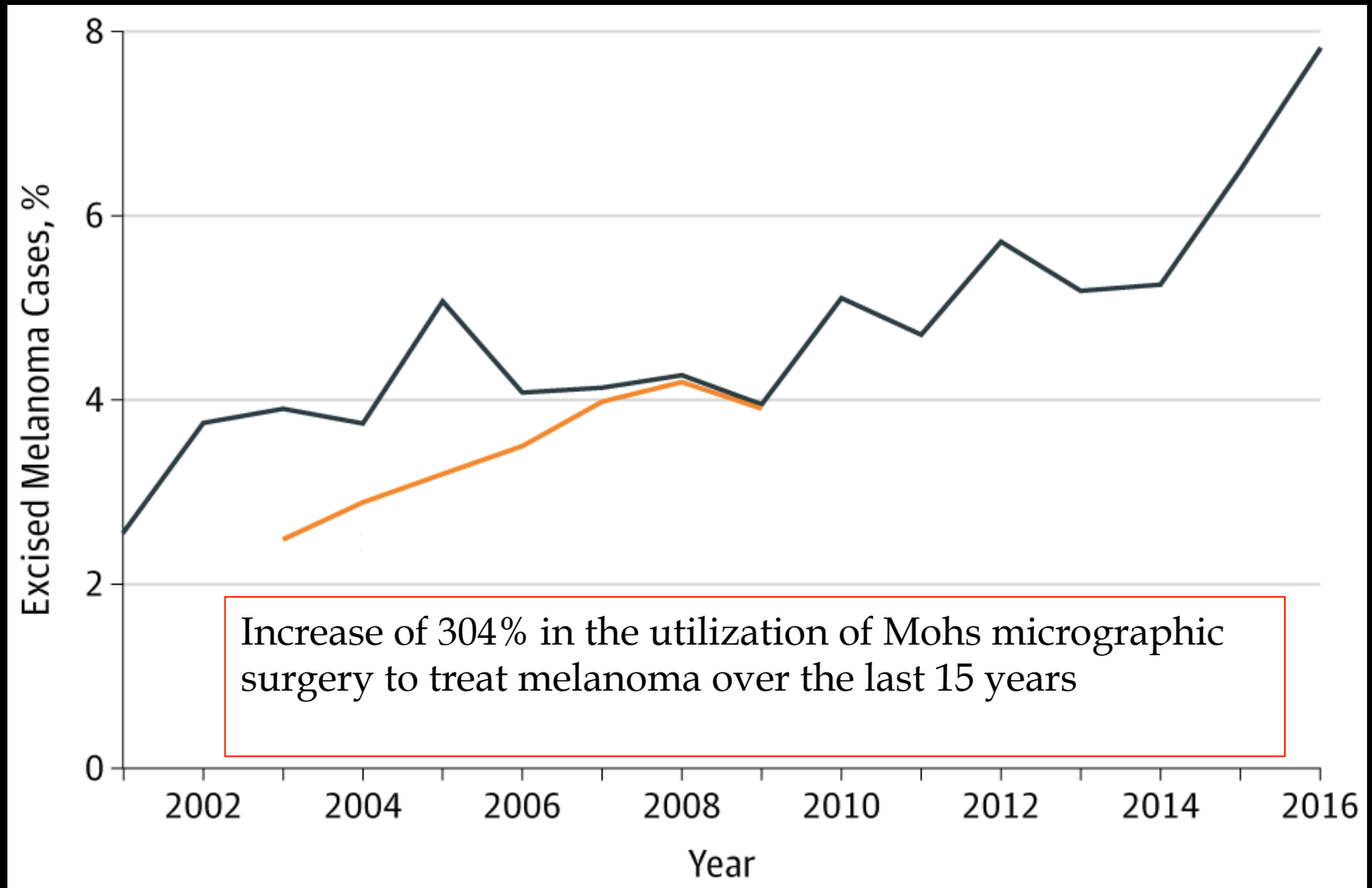


Two ways to achieve goal:

Mohs micrographic surgery (same-day)

“Slow Mohs” technique (several days)

# Trends in Mohs Surgery for Melanoma



## Low recurrence rates for in situ and invasive melanomas using Mohs micrographic surgery with melanoma antigen recognized by T cells 1 (MART-1) immunostaining: Tissue processing methodology to optimize pathologic staging and margin assessment

Jeremy Robert Etzkorn, MD,<sup>a</sup> Joseph F Sobanko, MD,<sup>a</sup> Rosalie Elenitsas, MD,<sup>a</sup> Jason G. Newman, MD,<sup>a</sup> Hayley Goldbach, BS,<sup>b</sup> Thuzar M. Shin, MD,<sup>a</sup> and Christopher J. Miller, MD<sup>a</sup>  
*Philadelphia, Pennsylvania*

## Digit-Sparing Mohs Surgery for Melanoma

VITALY TERUSHKIN, MD,\* DAVID G. BRODLAND, MD,\* DANNY J. SHARON, MS,†  
AND JOHN A. ZITELLI, MD\*

## Cutaneous head and neck melanoma treated with Mohs micrographic surgery

Gregory M. Bricca, MD,<sup>a</sup> David G. Brodland, MD,<sup>b</sup> Dianxu Ren, MS,<sup>c</sup> and John A. Zitelli, MD<sup>c</sup>  
*Sacramento, California, and Pittsburgh, Pennsylvania*

## Mohs Micrographic Surgery Using MART-1 Immunostain in the Treatment of Invasive Melanoma and Melanoma In Situ

SHEILA M. VALENTÍN-NOGUERAS, MD, FAAD,\* DAVID G. BRODLAND, MD, FAAD, FACMS,††  
JOHN A. ZITELLI, MD, FAAD, FACMS,†† LORENA GONZÁLEZ-SEPÚLVEDA, MS,<sup>§</sup>  
AND CRUZ M. NAZARIO, PhD<sup>||</sup>

JAMA Dermatology | Original Investigation

## Outcomes of Melanoma In Situ Treated With Mohs Micrographic Surgery Compared With Wide Local Excision

Adi Nosrati, MD; Jacqueline G. Berliner, MD; Shilpa Goel, MD; Joseph McGuire, MD; Vera Morhann, MD; Juliana R. de Souza, BSc; Widyay Yanjay, MD; Rasnik Singh, BS; Kristina Lee, MS; Mio Nakamura, MD; Rachel R. Wu; Ann Griffin, PhD, CTR; Barbara Grimes, PhD; Eleni Linos, MD, DrPH; Mary Margaret Chron, MD; Roy Gorkin, MD; Maria L. Wei, MD, PhD

## Improved overall survival of melanoma of the head and neck treated with Mohs micrographic surgery versus wide local excision

Jamie Hanson, MD,<sup>a,b</sup> Addison Demer, MD,<sup>a,b</sup> Walter Liszewski, MD,<sup>a,b</sup>  
Neal Foman, MD, MS,<sup>b</sup> and Ian Maher, MD<sup>b</sup>  
*Minneapolis, Minnesota*

## Mohs micrographic surgery for melanoma: A prospective multicenter study

Patrick M. Ellison, MD,<sup>a</sup> John A. Zitelli, MD,<sup>b</sup> and David G. Brodland, MD<sup>b</sup>  
*Honolulu, Hawaii, and Pittsburgh, Pennsylvania*

## Local recurrence rates of melanoma in the setting of Mohs micrographic surgery versus wide local excision: A systematic review and metaanalysis

## Mohs micrographic surgery for the treatment of primary cutaneous melanoma

John A. Zitelli, MD,<sup>a</sup> Christine Brown, MD,<sup>c</sup> and Barbara H. Hanusa, PhD<sup>b</sup>  
*Pittsburgh, Pennsylvania, and Dallas, Texas*

## The use of Mohs micrographic surgery (MMS) for melanoma in situ (MIS) of the trunk and proximal extremities

Landon E. Stigall, MD, David G. Brodland, MD, and John A. Zitelli, MD  
*Pittsburgh, Pennsylvania*



# Melanoma Prevention

Avoidance of excessive UV radiation

Most UV damage is accumulated during teenage years and early 20s



Use of sun protective clothing, seeking shade and sunscreens

Sunscreen technology has made great strides in recent years, but has also become highly controversial

# Sunscreen is highly controversial

REVIEW

## Current sunscreen controversies: a critical review

Mark E. Burnett & Steven Q. Wang

Dermatology Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

**Safety of Oxybenzone: Putting Numbers Into Perspective**

## Photoprotection

### Part I. Photoprotection by naturally occurring, physical, and systemic agents

Rebecca Jansen, MD,<sup>a</sup> Steven Q. Wang, MD,<sup>b</sup> Mark Burnett, MD,<sup>b</sup> Uli Osterwalder, MS,<sup>c</sup> and Henry W. Lim, MD<sup>a</sup>  
*Detroit, Michigan; New York, New York; and Monheim, Germany*

## Sunscreens: Obtaining adequate photoprotection

MARK E. BURNETT,\* JUDY Y. HU† & STEVEN Q. WANG\*

*\*Department of Dermatology, Memorial Sloan-Kettering Cancer Center, New York, New York and †Department of Dermatology, Laser & Skin Institute, Chatham, New Jersey*

## Reduced Melanoma After Regular Sunscreen Use: Randomized Trial Follow-Up

Adèle C. Green, Gail M. Williams, Valerie Logan, and Geoffrey M. Strutton

**Table 2.** First Primary Melanomas During 1993-2006 According to Randomized Sunscreen Intervention During 1992-1996 and Risk of Melanoma

Melanoma by Level	No. of Participants Affected		Analysis		
	Sunscreen (n = 812)	No Sunscreen (n = 809)	Hazard Ratio	95% CI	P*
All	11	22	0.50	0.24 to 1.02	.051
I: In situ	8	11	0.73	0.29 to 1.81	.493
Invasive	3	11	0.27	0.08 to 0.97	.045
II: In papillary dermis	3	4			
III: filling papillary dermis	0	1			
IV: reticular dermis	0	5			

\*P values were calculated from Cox regression that used sunscreen and beta carotene as main effects.

### Analysis of melanoma incidence:

50% reduction in primary melanomas.

Substantial reduction in invasive melanomas, when compared to preinvasive melanomas.

# Preventative recommendations

## Sunscreen

- SPF >30
- “Thick and often”
- U.S. sunscreens are (mostly) created equal
  - The “best” is whichever one you will use

## Self-examinations

- Two mirrors
- “Selfies” with phone
- One minute
- Monthly

# Summary

- Detection:
  - New and emerging technologies are enhancing our ability to detect melanomas earlier
- Treatment:
  - Most melanomas require only surgical treatment
  - Mohs micrographic surgery is increasingly utilized to treat melanoma
- Prevention:
  - UV radiation exposure is the only modifiable factor
  - Sunscreens are effective in reducing melanoma risk



# Community Lectures

## Q&A

# Are sunscreens safe?



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# Community Lectures

## Q&A

Do I need to wear sunscreen  
if I have dark skin?



# Community Lectures

## Q&A

# Are skin cancers hereditary?



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Julian Davis, MD, MA  
Medical Oncologist  
Ridley-Tree Cancer Center



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# **ADVANCES IN MELANOMA**

## **Globally and Locally**

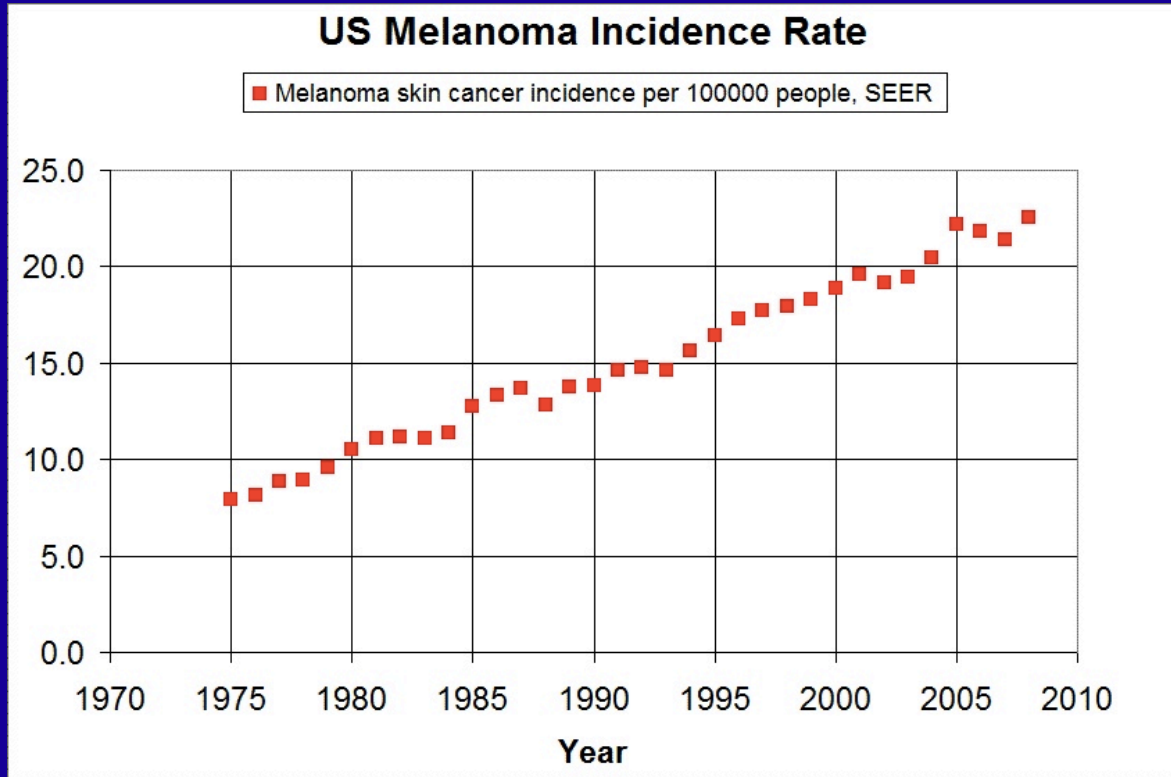
**Julian R. Davis, MD, MA**  
Oncology and Hematology  
Ridley-Tree Cancer Center



# Financial disclosures

- None

# Epidemiology/Risk



Incidence is rising both in US & worldwide

?partially due to more screening/Bx  
- Some data

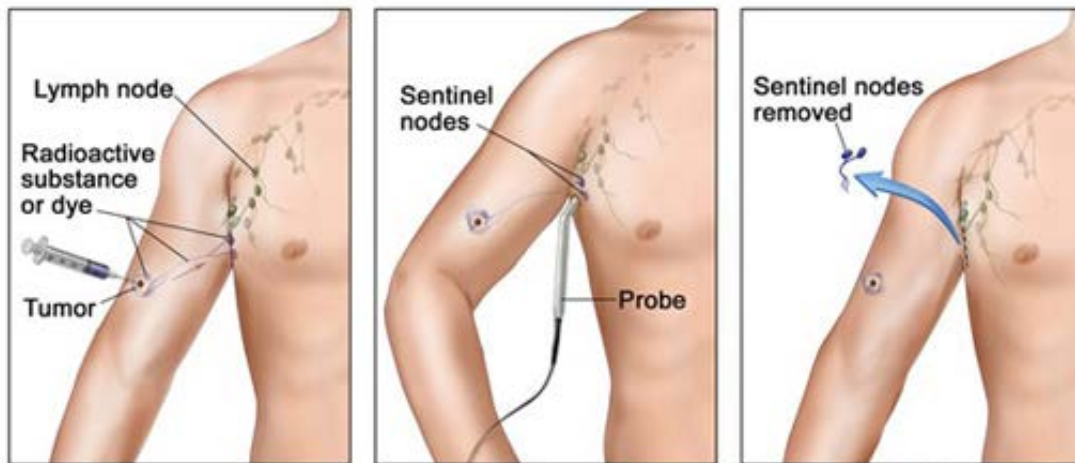
>9000 die of melanoma in US/year, mortality  $\uparrow\downarrow$  in different age groups

- Risk factors:

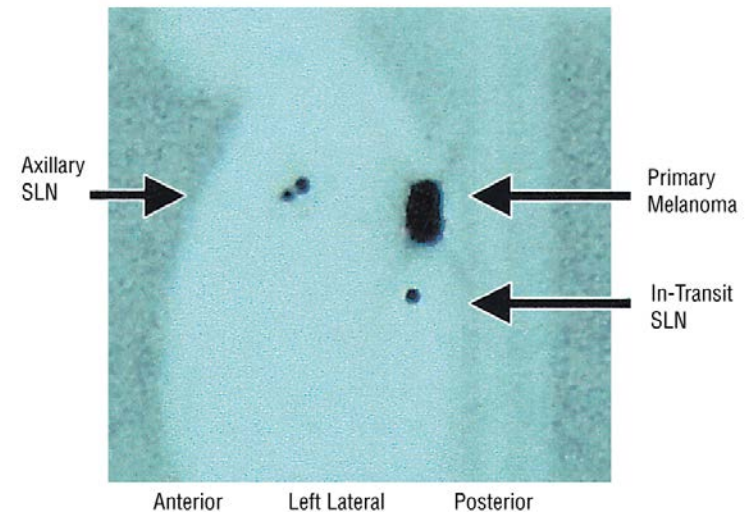
- UV radiation causes DNA damage (sunburns/tanning beds)
- Personal Hx of melanoma or other nonmelanoma skin cancer
- Immunosuppression (transplant, lymphoma, HIV)
- Rare: familial atypical multiple mole & melanoma syndrome (FAMMM) or with inherited cancer syndromes like BAP1

# Staging

- Dermatology punch/shave/local excision
- Wide local excision w adequate margins & sentinel LN Bx recommended for T2+ (>1mm deep)
- Sentinel lymph node biopsy usually uses both blue dye and lymphoscintigraphy ( $^{99m}\text{Tc}$ )



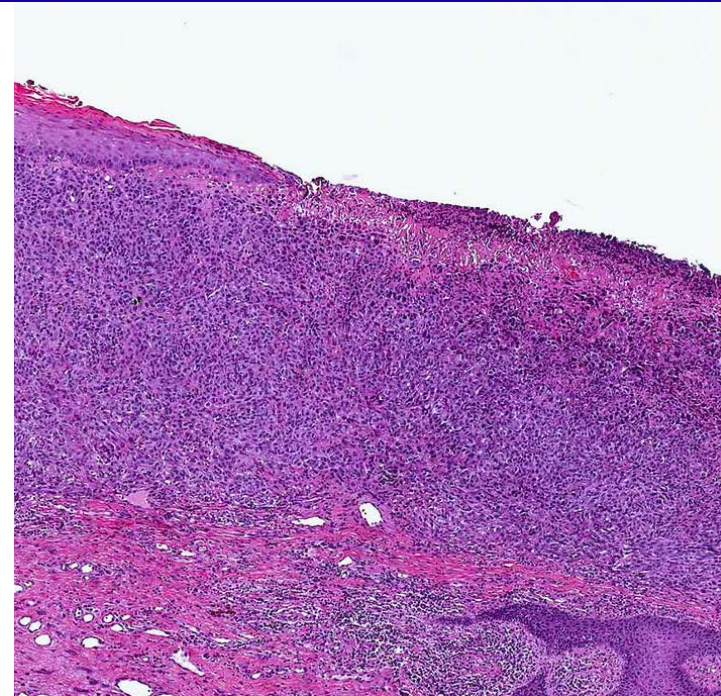
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# Staging cont'd

- 2010 AJCC 7<sup>th</sup> Ed staging updated to 8<sup>th</sup> Ed on Jan 1<sup>st</sup>, 2018
- T: primary melanoma thickness

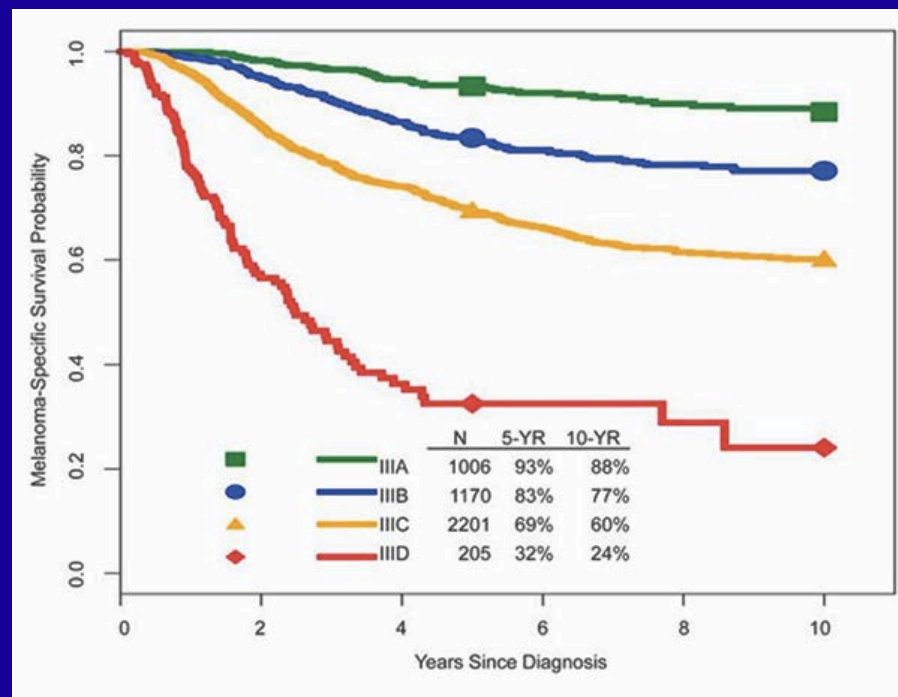
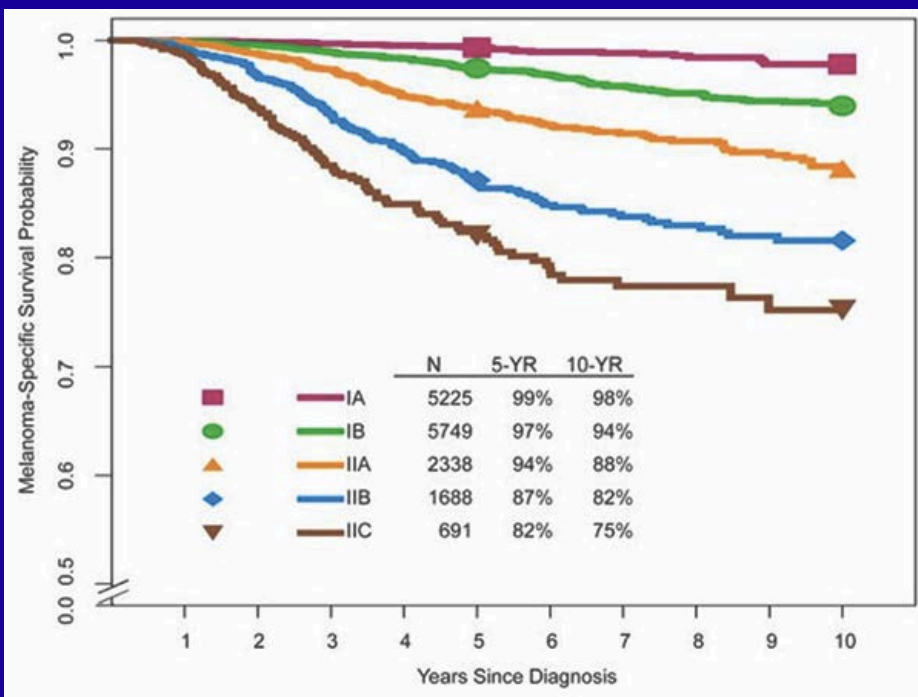
T CLASSIFICATION	THICKNESS (mm)	ULCERATION STATUS
<b>T1</b>	≤1.0	a: Breslow < 0.8 mm w/o ulceration b: Breslow 0.8-1.0 mm w/o ulceration or ≤ 1.0 mm w/ ulceration.
<b>T2</b>	1.1-2.0	a: w/o ulceration b: w/ ulceration
<b>T3</b>	2.1-4.0	a: w/o ulceration b: w/ ulceration
<b>T4</b>	>4.0	a: w/o ulceration b: w/ ulceration





# Prognosis

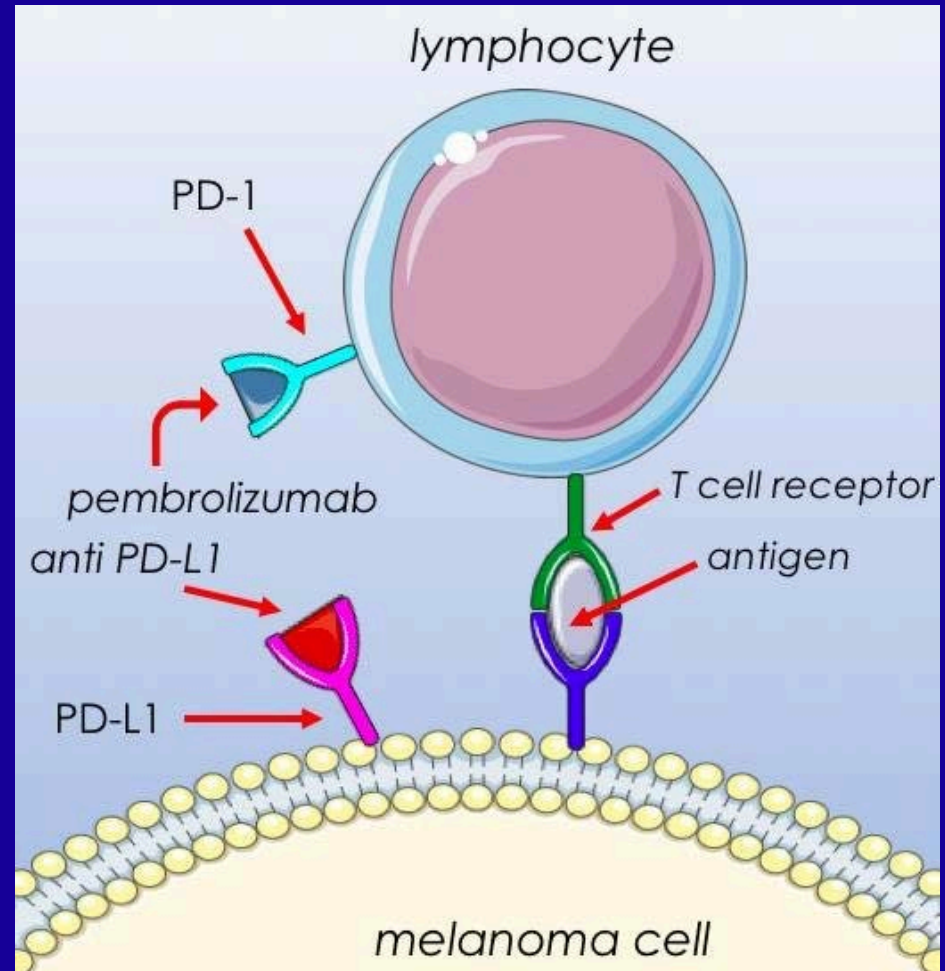
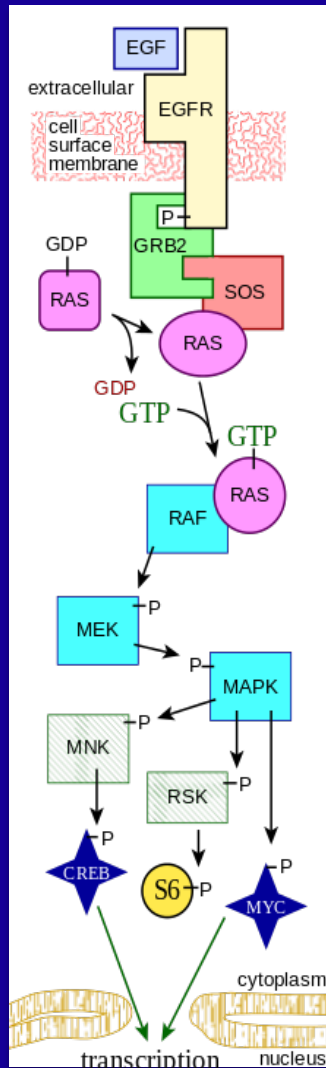
- High rates of distant recurrence/mets even in node negative disease
  - Stage IIB 5-yr RFS = 23-56%
- Stage III outcomes are very heterogeneous
  - Some node negative melanomas worse than node positive



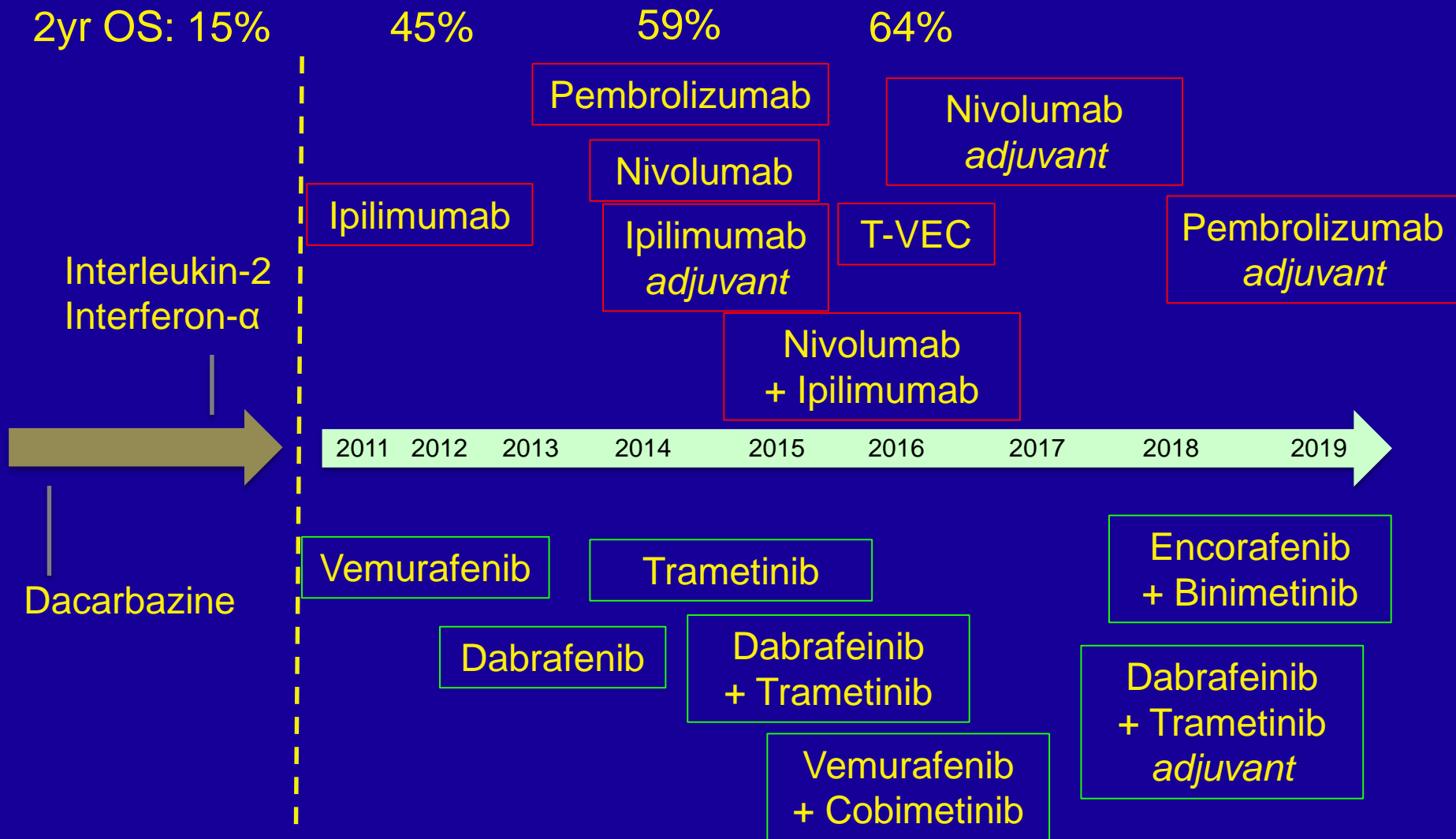
# Mechanisms of Action of Melanoma Therapy

Targeted Molecular Therapy  
If BRAF-mutated (~50%)

Immunotherapy  
for any BRAF status

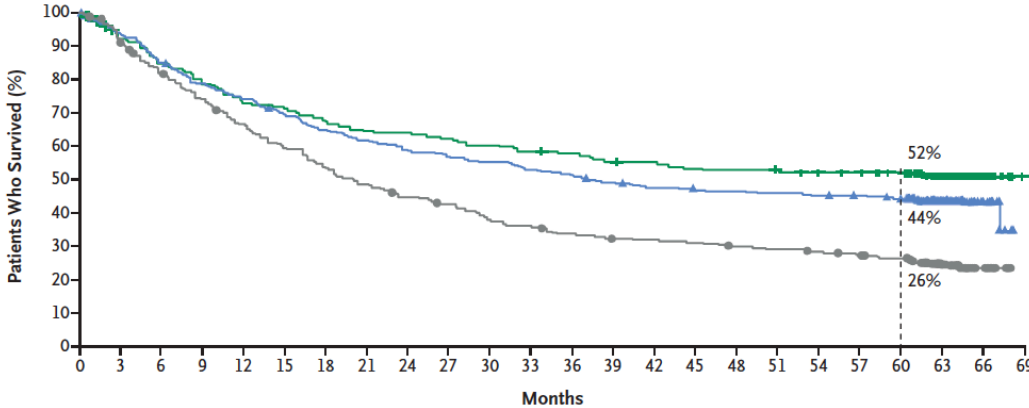


# Dramatic Progress



# CheckMate-067: 4-year followup

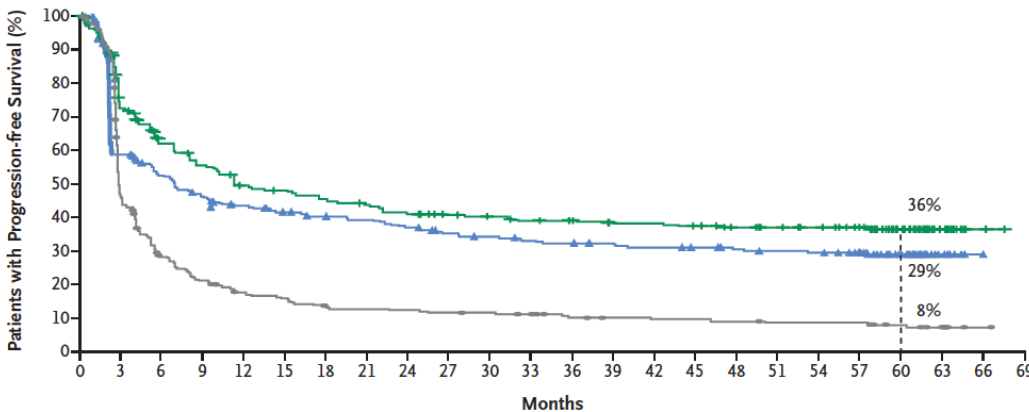
**A Overall Survival**



**No. at Risk**

Nivolumab plus ipilimumab	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	157	155	150	92	14	0
Nivolumab	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	135	130	78	14	0
ipilimumab	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	73	36	12	0

**B Progression-free Survival**



**No. at Risk**

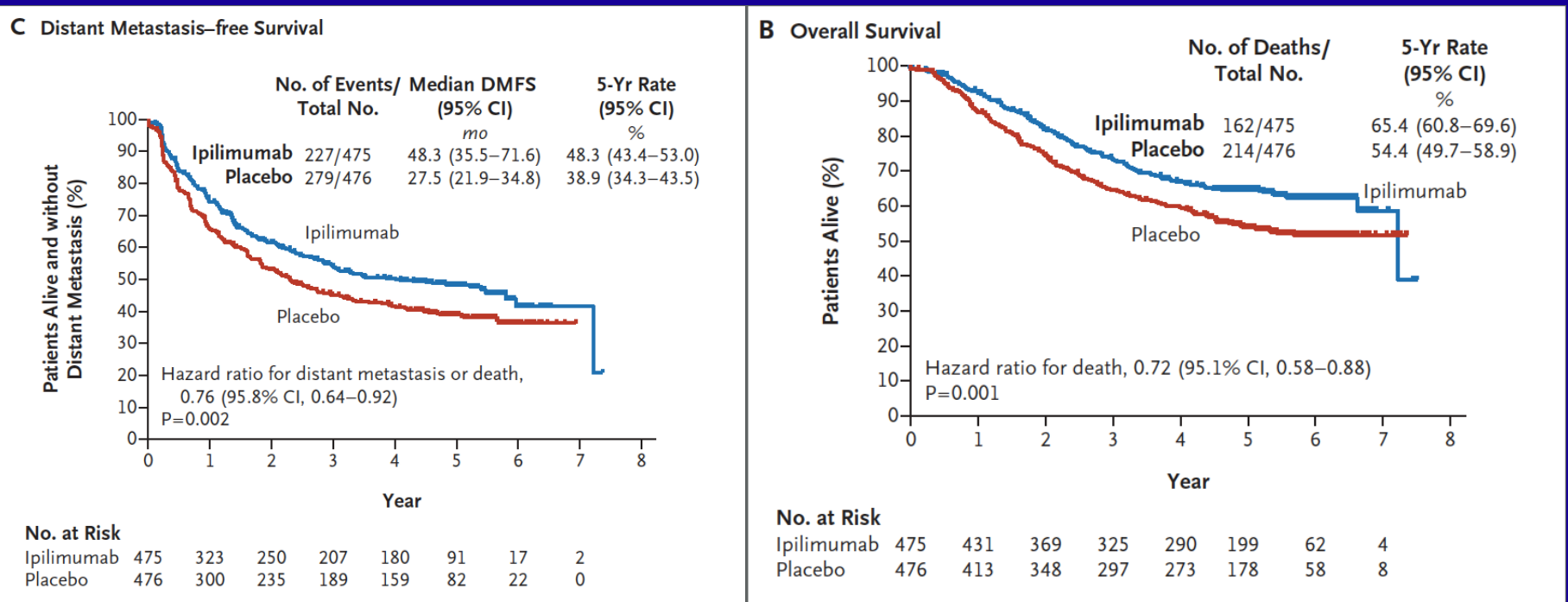
Nivolumab plus ipilimumab	314	218	174	155	136	131	124	117	110	104	101	97	95	91	90	88	82	79	76	69	45	19	2	0
Nivolumab	316	177	151	132	120	112	106	103	97	88	84	80	78	76	73	71	68	66	65	60	40	13	1	0
ipilimumab	315	136	78	58	46	42	34	32	31	29	28	26	21	19	18	18	17	15	15	15	11	8	1	0

Combination  
Nivolumab and  
ipilimumab  
immunotherapy for  
Metastatic melanoma  
- Included BRAF WT  
and mutated

Combo Nivo/Ipi  
5-year OS: 52%

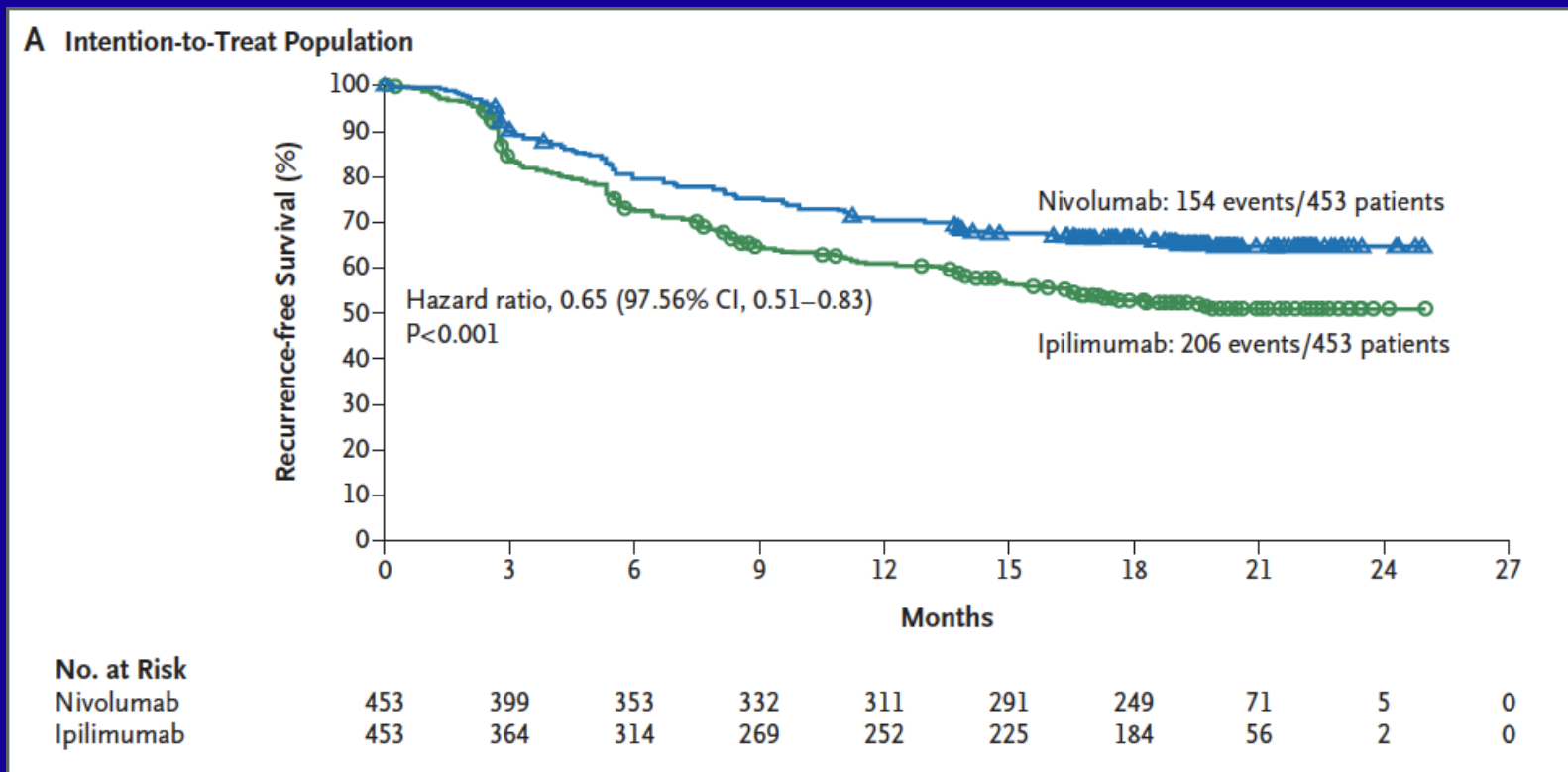
# Adjuvant Therapy in Node-Positive Disease

- EORTC 18071 trial (pub 2015, 2016)
  - Ipilimumab (anti-CTLA-4 antibody) vs placebo
  - 5-yr Recurrence-free survival 40% vs 30%
  - 5-yr Overall survival 65% vs 55%
  - 54% in treatment arm had bad side effects, rare deaths



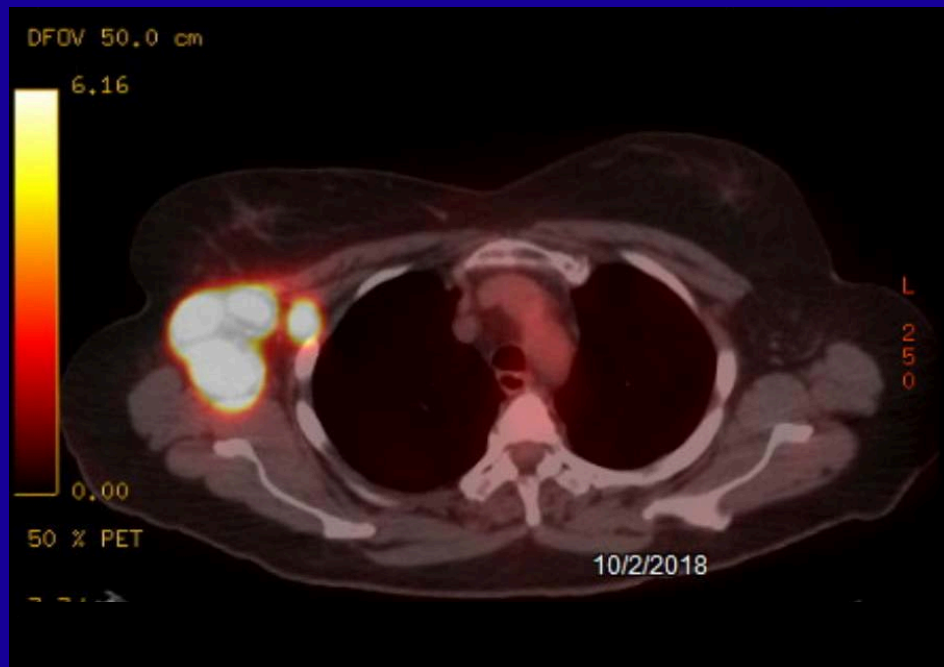
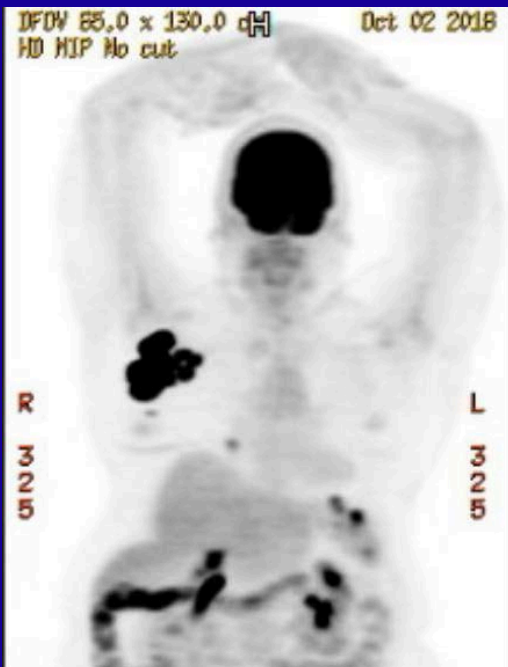


- **Checkmate-238:** International, phase III randomized, double-blind
  - Resected stage III (node positive) or stage IV (distant metastases)
  - Nivolumab vs ipilimumab (1yr of Therapy)
  - ~1:1 BRAF mutated & unmutated
  - 1-yr RFS: Nivo 70% vs Ipi 60%, OS not mature
  - Significant side effects: Nivolumab 14% vs Ipilimumab 46%

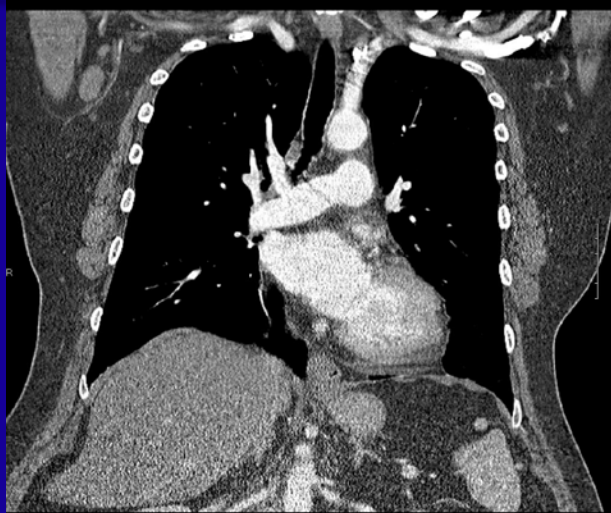


# Immunotherapy Clinical Trial at RTCC

At  
diagnosis



6 mos  
later

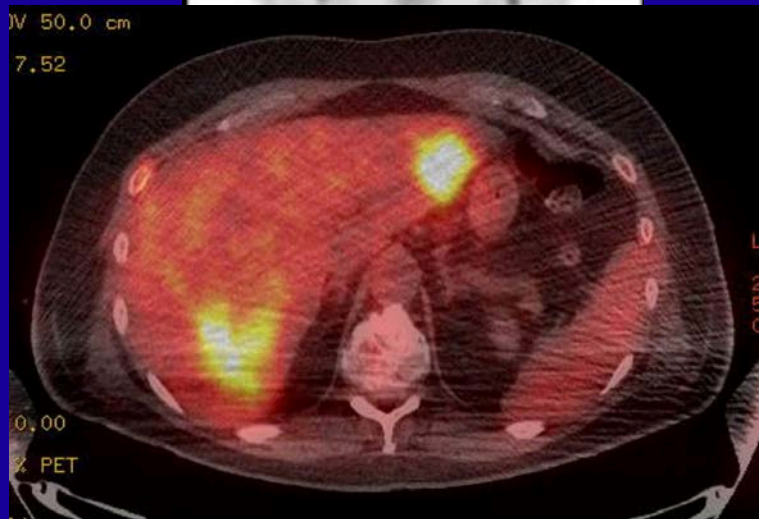
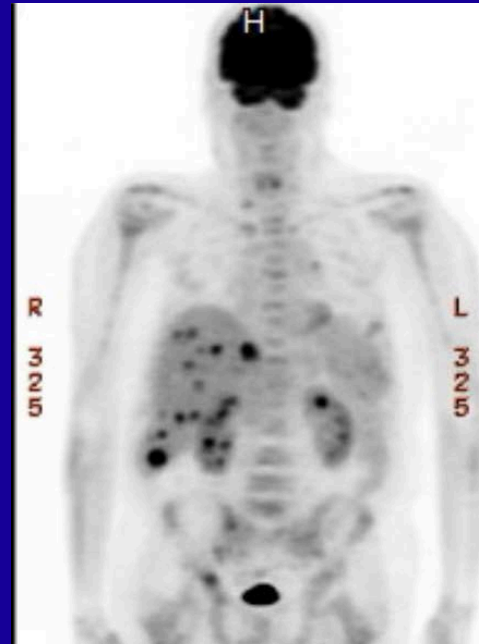


# BRAF/MEK Molecular Therapy

At  
diagnosis



2 mos  
later

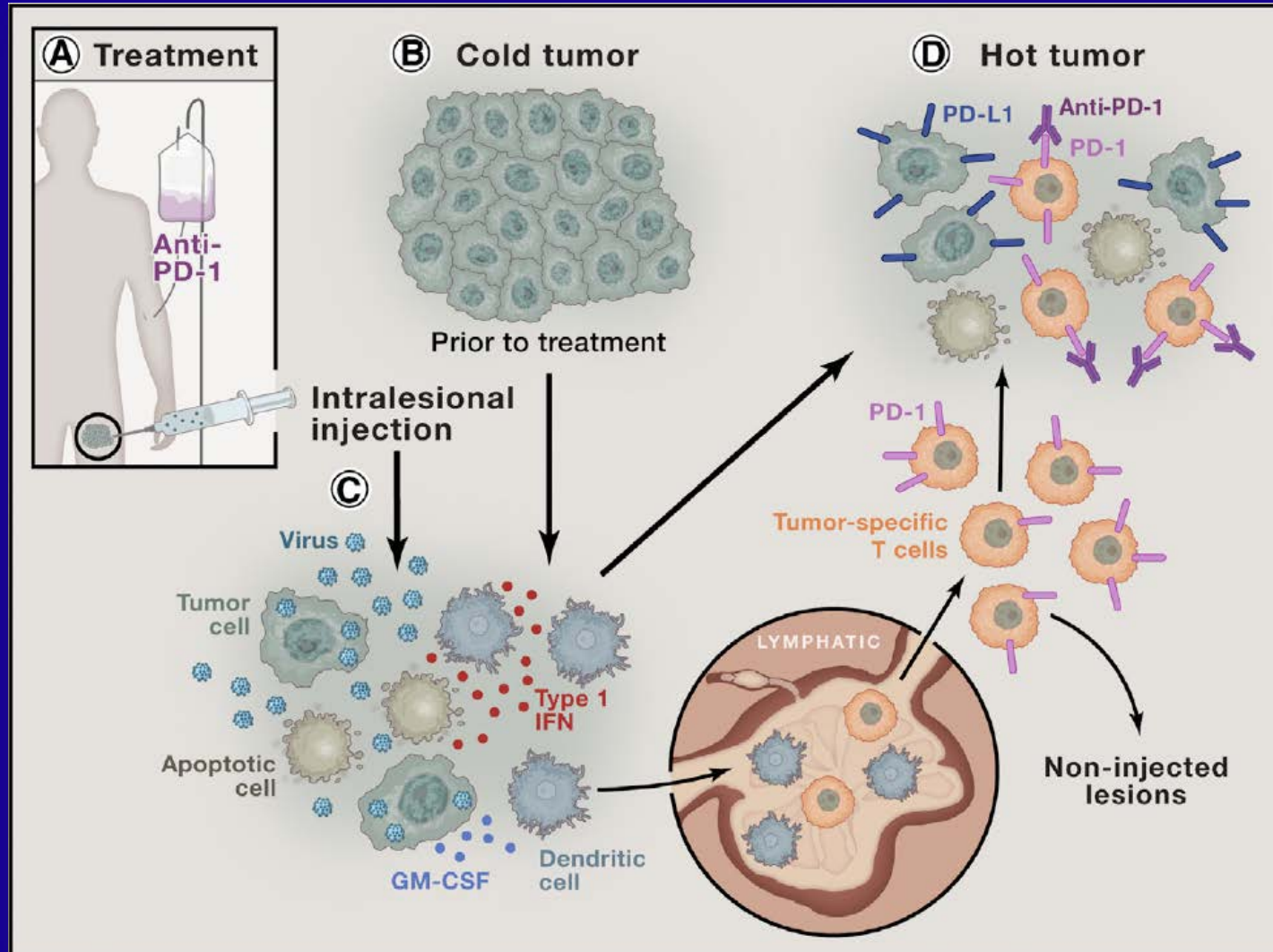


# New Directions: 2020 and beyond

- Neoadjuvant therapy
  - Early studies using BRAF/MEK, Nivo/Ipi, and T-VEC
- More patients eligible for adjuvant therapy?
  - Ongoing studies in high-risk node-negative with immunotherapy vs placebo
- Better combinations and targets for advanced disease
  - “boosting” immunotherapy with less side effects
  - Targeted therapy + immunotherapy?
  - Biomarkers for patient selection

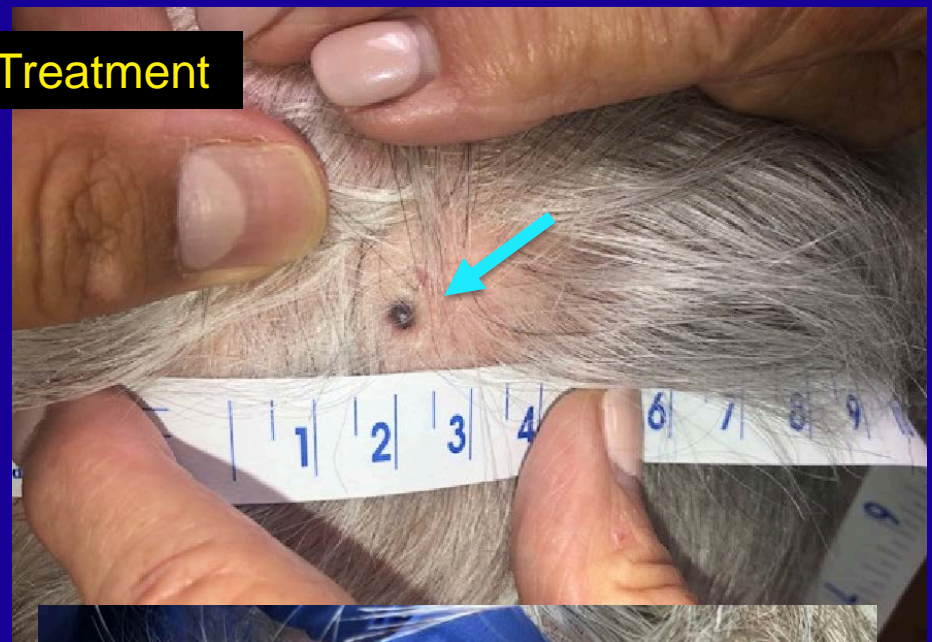


# Making a “cold” tumor “Hot” with an engineered herpes virus (“TVEC”)





# TVEC + Pembro at work



# Santa Barbara Multidisciplinary Cutaneous Oncology Program

- Besides Melanoma, includes:
  - Advanced Squamous cell carcinoma
  - Merkel cell carcinoma
  - Other advanced skin cancers
- Local dermatology, pathology, surgical oncology, radiology, medical oncology and radiation oncology
- A growing robust clinical trial portfolio at RTCC

# Melanoma Clinical Trials at Ridley-Tree Cancer Center

- BMS CA224-047: A Randomized, Double-blind Phase 3 Study of Relatlimab Combined with Nivolumab versus Nivolumab in Participants with Previously Untreated Metastatic or Unresectable Melanoma
  - Reopening after COVID hold
- Amgen 20180115: Phase 2 Study Of Talimogene Laherparepvec (TVEC) In Combination With Pembrolizumab In Subjects With Unresectable/Metastatic Stage IIIb-IVM1c Melanoma Who Have Progressed On Prior Anti PD-1 Based Therapy
  - OPEN
- Ultimovacs UV1-2020: A Randomized Phase II, Open-label, Active-controlled, Multicenter Study Investigating the Efficacy and Safety of UV1 Vaccination in Combination with Nivolumab and Ipilimumab as First-line Treatment of Patients with Unresectable or Metastatic Melanoma (UV1-202)
  - In approval process