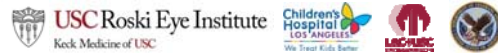


# Tall, dark and .. Uh oh

Jesse L. Berry, MD

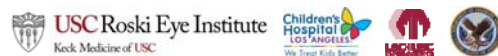
Arizona Ophthalmology Society  
2017

Ocular Oncology Service  
USC Eye Institute

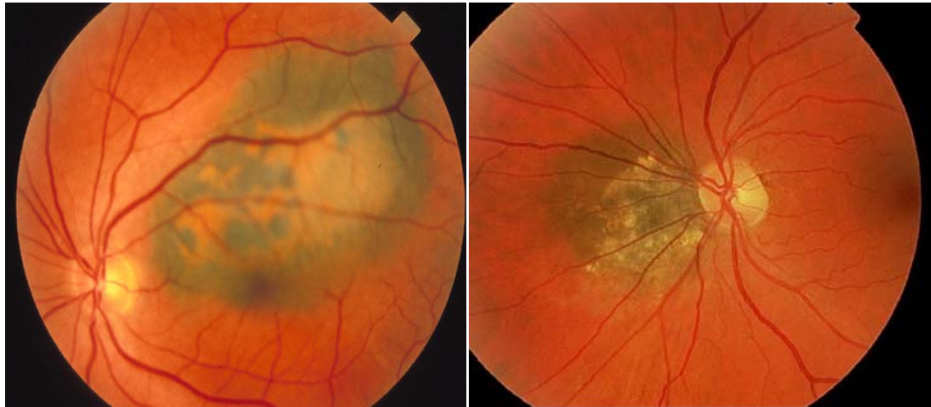


## Financial Disclosures

Research Support:  
Bright Eyes  
Nautica Foundation  
Knights Templar Foundation



## Refer or relax?



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## Choroidal Nevi

- Benign tumors
- Collection of bland spindle A melanocytes
- The edges are defined but not sharply demarcated
- Dark brown or grey pigmentation
- Amelanotic not unusual



U.S.C.

Keck



## Choroidal Nevi

Table 1. Prevalence of Choroidal Nevi (Published Studies)

First Author	Year	Country	n	Design	Study			Prevalence (%)
					Population	Race	Age (yrs)	
Albers*	1940	USA	2300	Clinic	Consecutive cases	Not stated	Not stated	1.1 <sup>†</sup>
Wilder <sup>‡</sup>	1946	USA	3882	Clinic	Surgical trauma cases	Not stated	18–38	0.2 <sup>†</sup>
Hale <sup>§</sup>	1965	USA	252	Autopsy	Consecutive cases	95% white	>18	14 <sup>  </sup>
Naumann <sup>¶</sup>	1970	Germany	187	Autopsy	Unselected cases	Not stated	All	11 <sup>†</sup>
Smith <sup>#</sup>	1972	USA	842	Population	Survey	White (64%)	>13	1.9** (3.8) <sup>††</sup>
Ganley <sup>‡‡</sup>	1973	USA	65	Population	Random sample	White	>30	3.1** (6.2) <sup>††</sup>
Gass <sup>§§</sup>	1977	USA	250	Clinic	Older	White	<90	30
Albert <sup>   </sup>	1980	USA	1126	Population	Chemical workers + controls	White	>30	7.9 <sup>¶¶</sup>
Lang <sup>##</sup>	1982	Germany	3119	Clinic	Army	Not stated	18–41	4.2
Rodriguez-Sains***	1986	USA	108	Clinic	Controls	White	11–84	4.6
Sumich <sup>†††</sup>	1998	Australia	3583	Population	Survey	White	>49	6.5 <sup>†</sup> (8.6) <sup>††</sup>
Yoshikawa <sup>†††</sup>	2004	Japan	3676	Clinic	Normal volunteers	Japanese	28–86	0.34

5%

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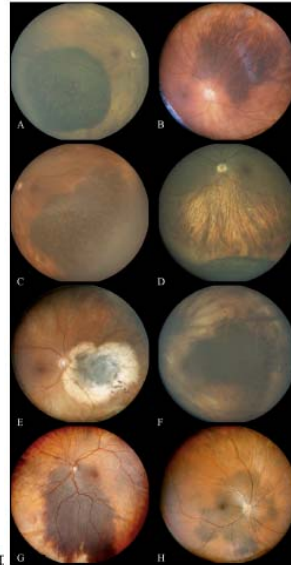
## Choroidal Nevi

- Asymptomatic
  - Metamorphopsia/photopsias/VF defect
- Induce secondary changes in overlying tissues
  - Drusen (~50%)
  - RPE changes (~80%)
  - SRF (~2%)
  - CNV (<1%)
  - Lipofuscin (~5%)
  - Halo (~1%)

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## Does size matter?

- Size, based on COMS, is  $<5 \text{ mm} \times <1 \text{ mm}$
- Small melanoma 5-16 mm x 1-2.5 (3) mm
- Controversial
- Giant nevi described: basal diameter  $>10\text{mm}$ ; height 0-4.4mm



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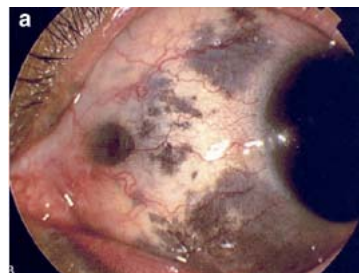
UCLA  
UCLA Medical Center  
UCLA Health System

UCLA  
UCLA Medical Center  
UCLA Health System



## Systemic Associations

- Systemic associations
  - Oculodermal melanosis
  - Dysplastic nevus syndrome
  - Neurofibromatosis



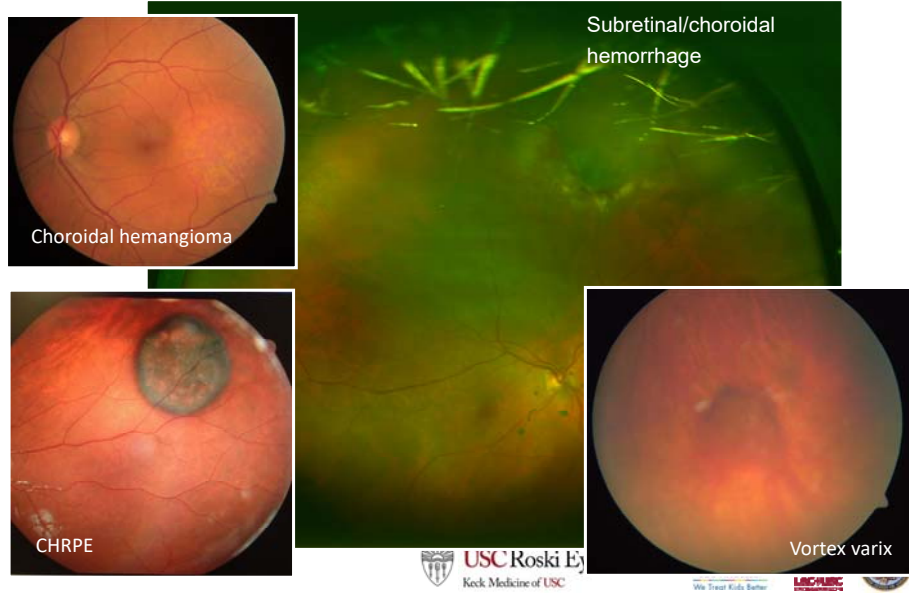
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Hospital  
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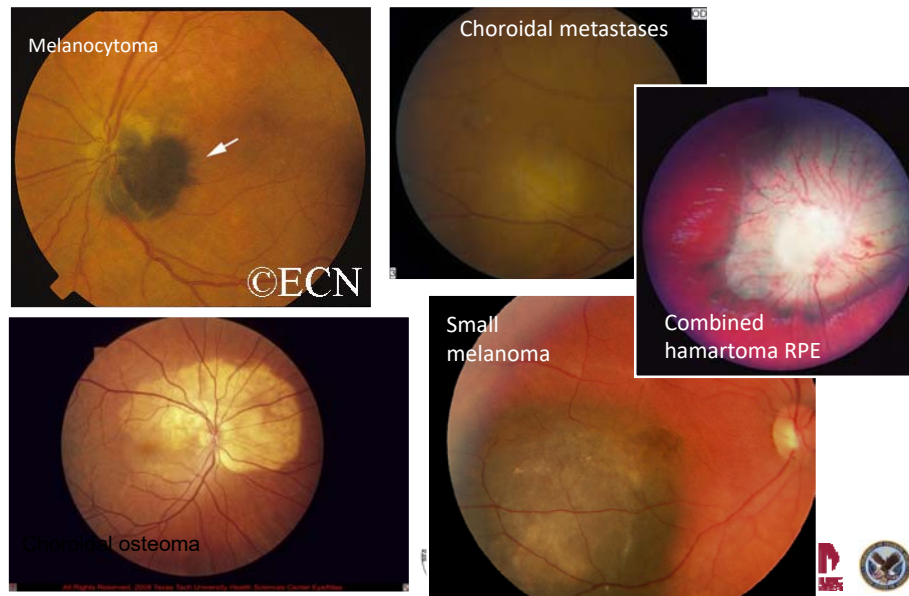
UCLA  
UCLA Medical Center  
UCLA Health System



## Differential diagnosis



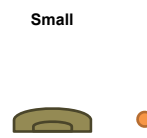
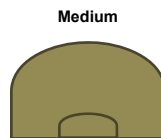
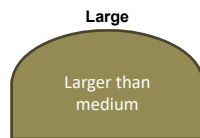
## Differential diagnosis



- Lifetime risk of malignant transformation from nevus is about 1% however increases with age

Thickness >2 mm  
Fluid  
Symptoms  
Orange pigment  
Margin  $\leq$ 3 mm to disc  
Ultrasonographic hollowness  
Halo absence  
Drusen absence

Melanoma = Nevus + growth + concerning features



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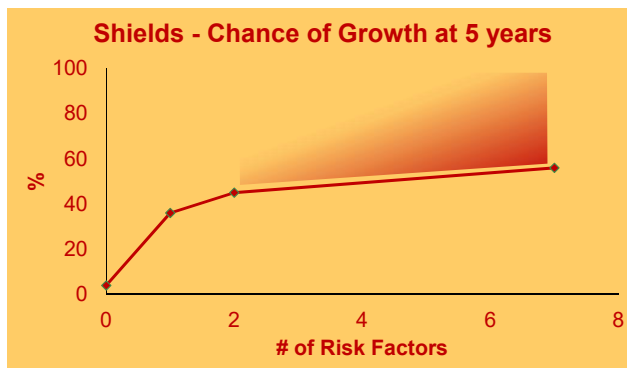
## Which nevi become melanoma?

Feature	Feature in Nevus that progress to Melanoma (%)	HR
Thickness > 2mm	19	2
Fluid	27	3
Symptoms	23	2
Orange Pigment	30	3
Margin <3mm to disc	13	2
Ultrasonographic Hollowness	25	3
Halo Absence	7	6

To	Find	Small	Ocular	Melanoma	Using Helpful	Hints
Thickness	Fluid	Symptoms	Orange	Margin to disc	Ultrasound	Halo
Thick	Orange	Fluids	Sometimes	Halo	Hollow	Melanoma
Thickness	Orange Pigment	Fluid	Symptoms	Halo	Hollowness	Disc distance

## Which nevi become melanoma?



- 27x greater risk ratio for 5 factors vs. 0 factors
- Growth not guarantee of malignancy
- Drusen are a sign of chronicity (favorable)



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## Risk Factors

- Shields Combination of clinical factors
- If zero risk factors: 4% chance of growth/5 years
- If one risk factor: 36% chance of growth/5 years
- If 2 risk factors: >45% chance of growth/5 years
- If all risk factors: >56% chance of growth/5 years
- **27x greater risk ratio for 5 factors v 0 factors**
- Growth not guarantee of malignancy
- Drusen are a sign of chronicity (favorable)



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## Even with Risk Factors can still Observe

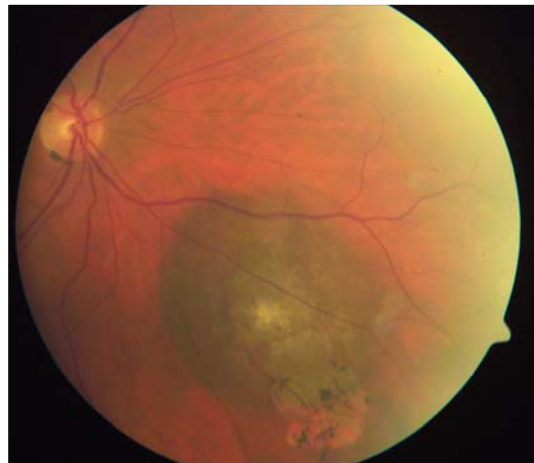
- COMS #5 observational study: 188 Small tumors
- Probability of growth over 5 years: 31%
- Risk factors:
  - Orange pigment
  - >2mm thickness
  - >12 mm basal diameter
  - Lack of drusen
- 33% of patients eventually treated
- Melanoma-related mortality 1% over 5 years (majority of patients not treated)



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## Refer or relax?

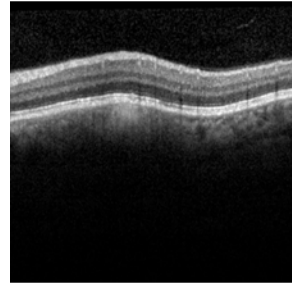
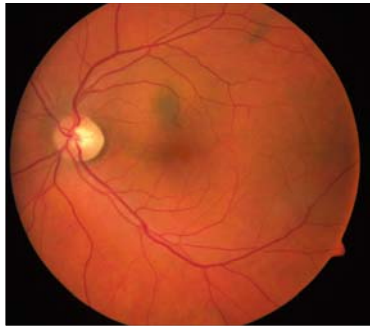


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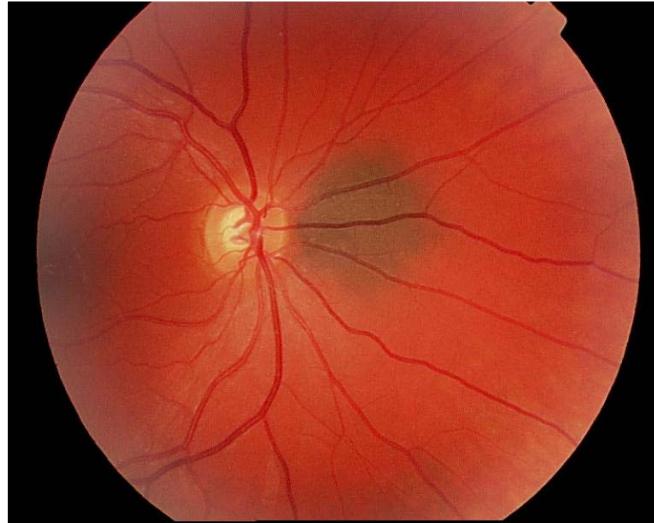
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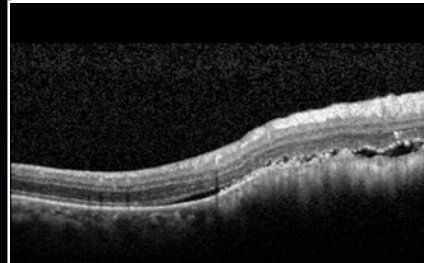
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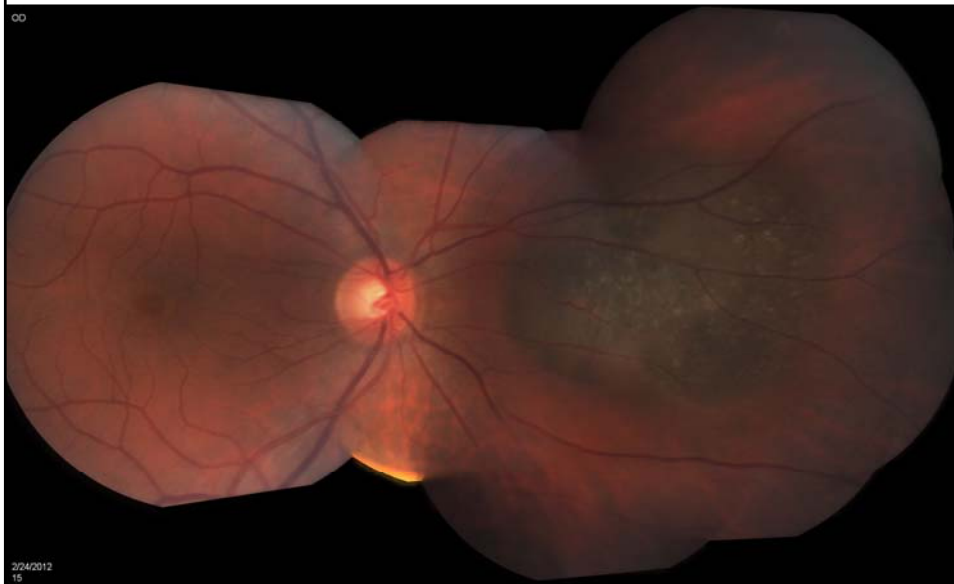
## Refer or relax?

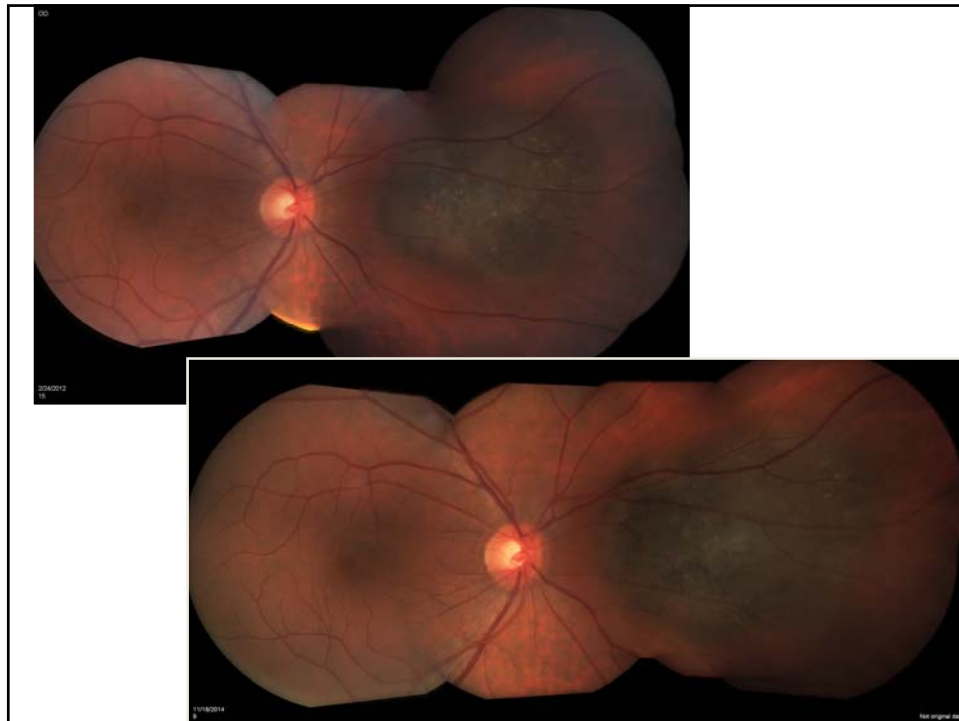


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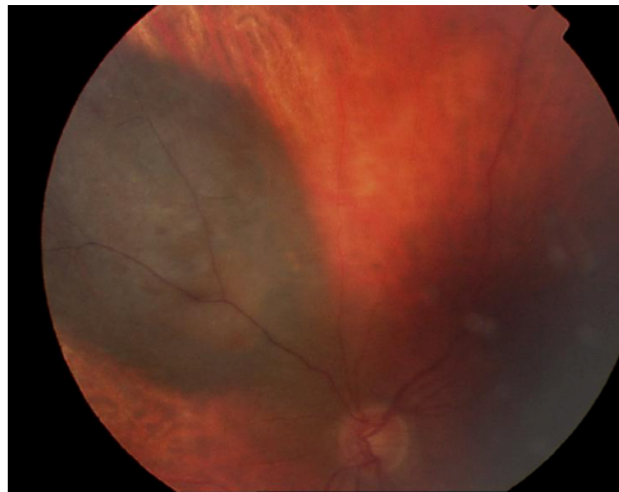


## Refer or relax?





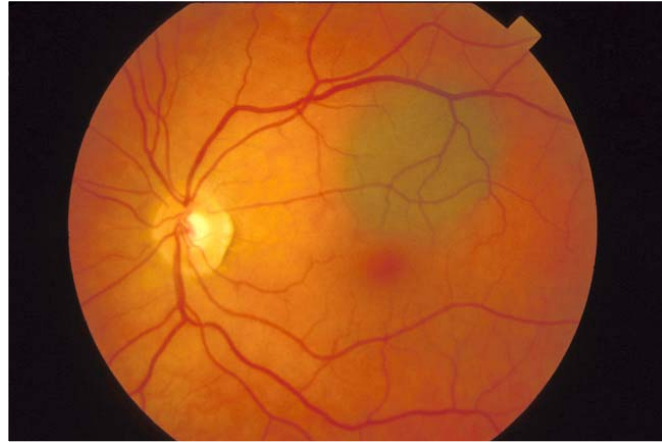
Refer or relax?



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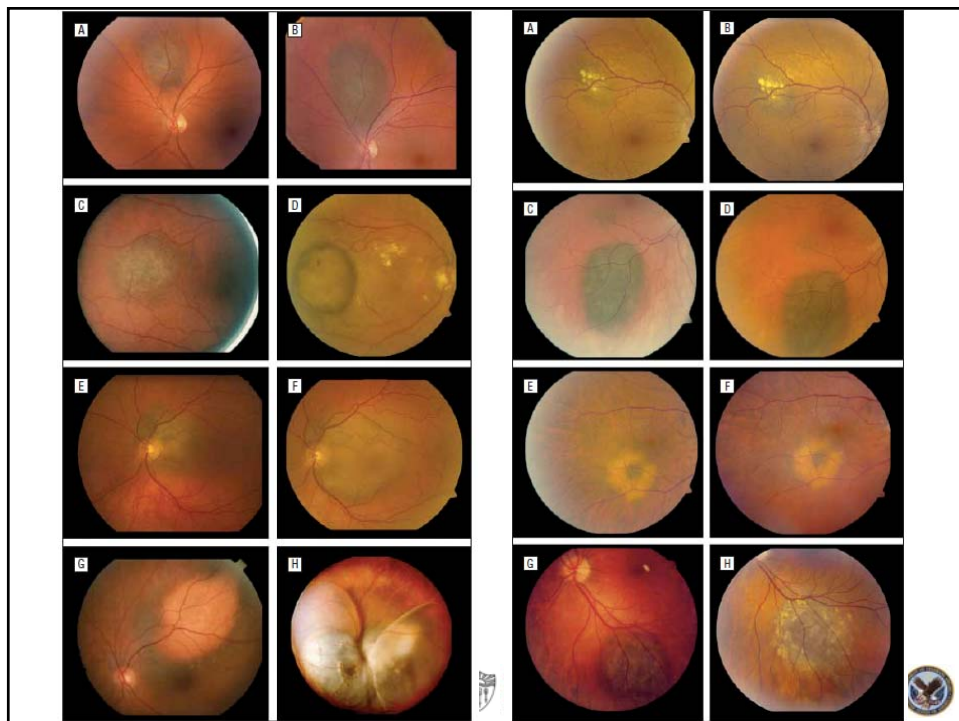
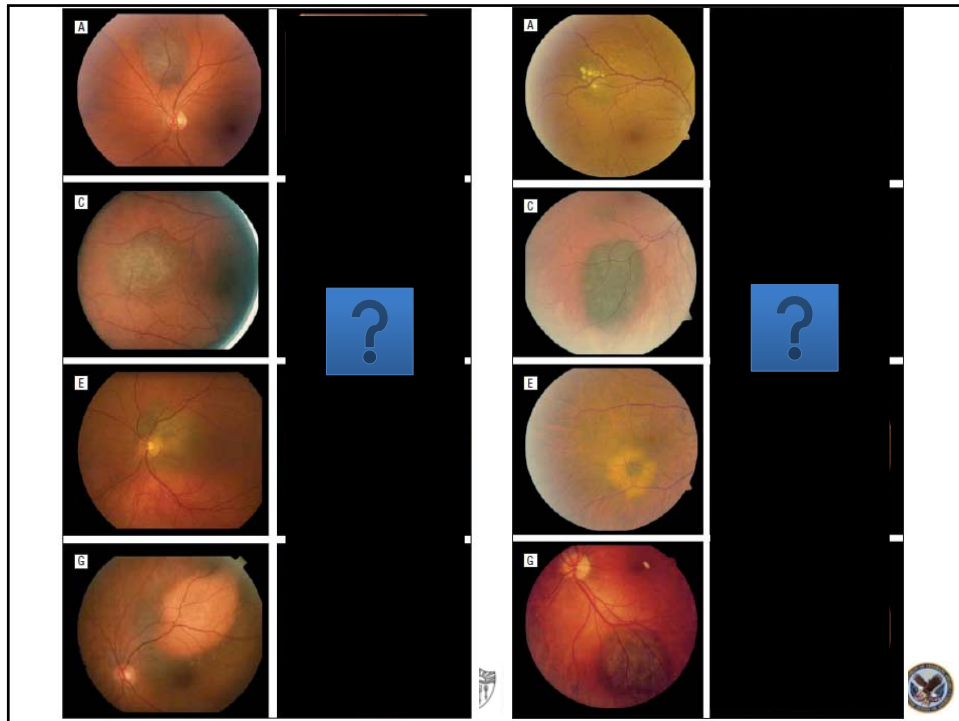


Refer or relax?



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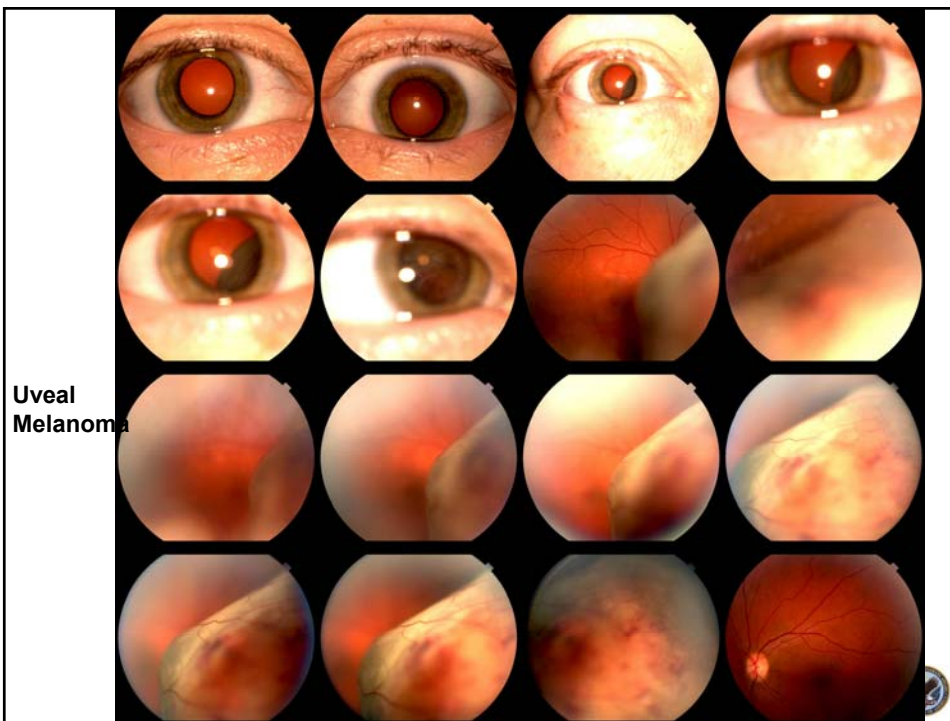
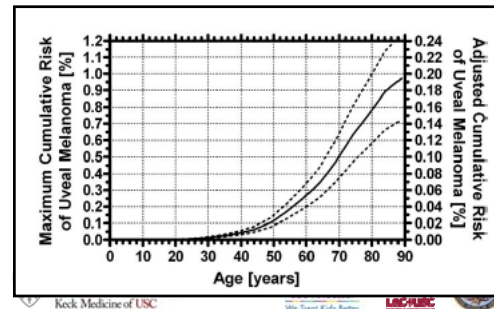






## When to refer

- Patients with associated systemic disorders
- Patients with high risk features – thickness, fluid, symptoms, orange pigment, margin
- Lack of good features: drusen, halo
- Atypical pigmentation
- Overall risk is low





## Spectrum of Uveal Melanoma

iris melanoma



CB melanoma



Uveal  
melanoma

choroidal  
melanoma

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## Epidemiology

- 5% of all melanomas in the US
- most common primary IO tumor in adults
- 6 cases/million

↓  
1500 cases  
per year in US

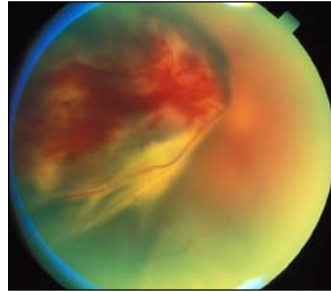


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## Risk Factors

- 50-70 years
- women=men
- Caucasian
- light hair and eyes
- sun exposure

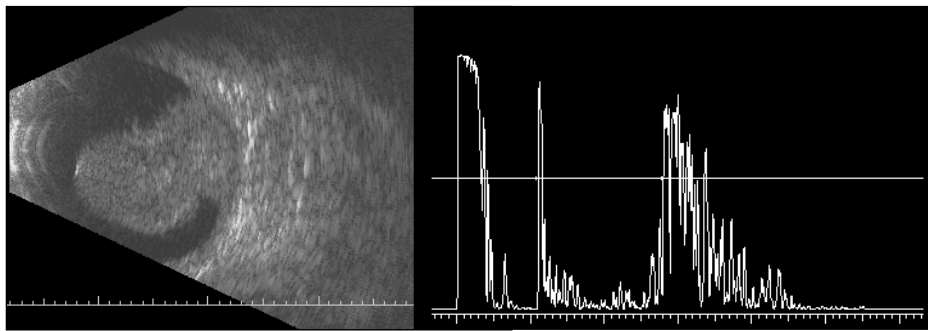


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## Clinical Diagnosis

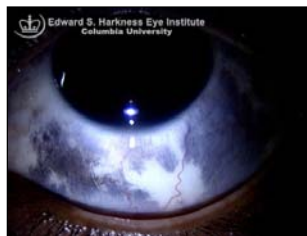
>99% accuracy

Fundoscopy  
+  
ultrasound



## Predisposing conditions

Choroidal nevi



Ocular Melanocytosis  
AKA nevus of ota

Melanocytoma



Dysplastic Nevus  
Syndrome

NF1



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## Timeline

Pre-1960s:  
Enucleation as  
primary therapy

20%  
misdiagnosis  
rate



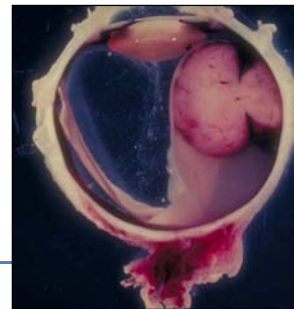
1985-86:  
prospective  
COMS trials  
designed

Funded by NEI



1970s:  
Zimmerman  
hypothesis:  
enucleation  
caused tumor  
spread

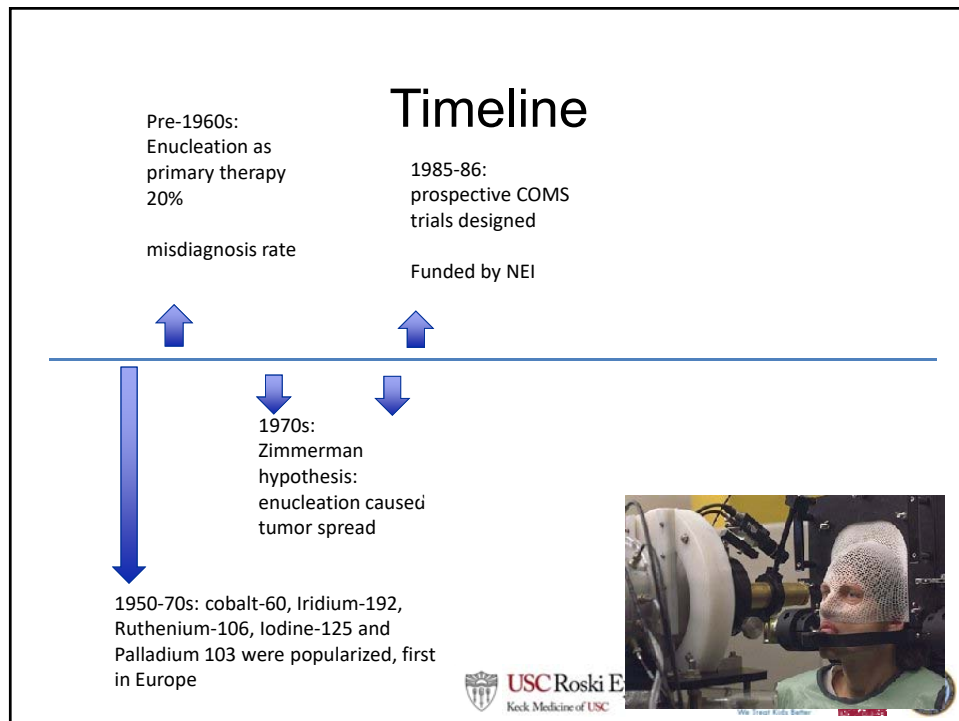
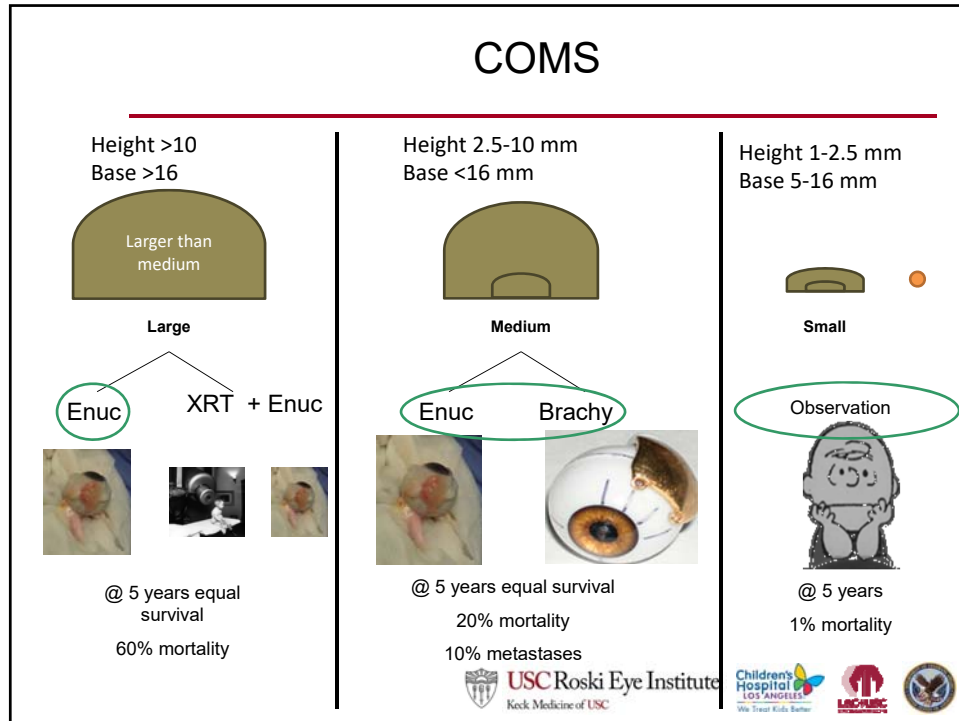
1950-70s: cobalt-60, Iridium-192,  
Ruthenium-106, Iodine-125 and  
Palladium-103 were popularized,  
first in Europe



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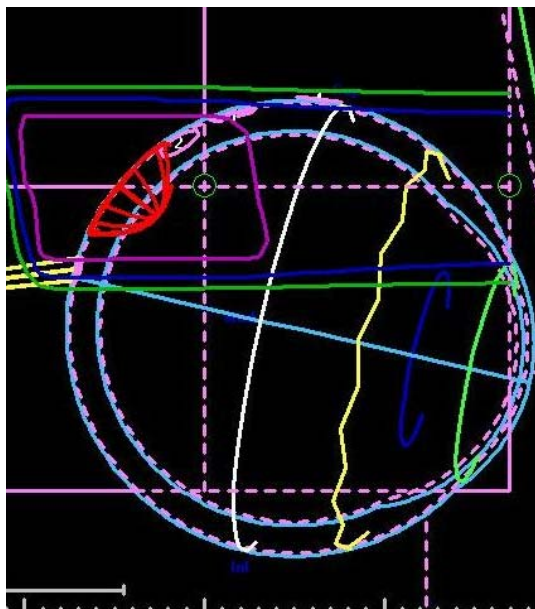
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## Proton Beam

- charged particle irradiation
- Advantages:
  - cover tumor with minimal scatter
  - Uniform dose of irradiation
  - Sharp treatment margins
  - May minimize toxicity to other structures
- tantalum markers as reference
- 70 CGy in 5 treatments over 7-10 days (1-4 min)



## Brachytherapy vs Proton Beam Irradiation: fairly equivalent modalities

### Brachytherapy

- Slightly higher recurrence rate (2-10%)
- Best for anterior/peripheral tumors
- 10 mm is maximum thickness (debatable)
- Two procedures (insertion/removal)

### Proton Beam Irradiation

- Slightly lower recurrence rate (2-5%)
- Advantage for posterior tumors (peripapillary tumors)
- Can treat slightly larger tumors
- Higher risk of neovascular glaucoma (15-30%)
- External side effects
- More subretinal fluid
- ? Better visual outcomes



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## Brachytherapy vs Proton Beam Irradiation: fairly equivalent modalities

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## Timeline

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20%  
misdiagnosis rate

1985-86:  
prospective COMS  
trials designed  
Funded by NEI

1989-  
present:  
USC Eye  
Physics  
Plaque

1970s:  
Zimmerman  
hypothesis:  
enucleation caused  
tumor spread

1975: Proton Beam  
irradiation at the  
Harvard Cyclotron –  
by mid 2000s 20  
centers worldwide

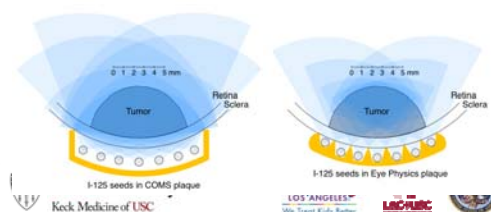
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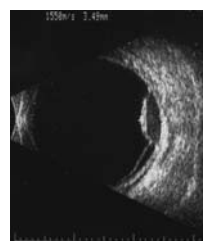
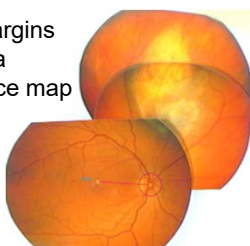
## Eye Physics plaques:

- Custom designed plaques
  - Thinner profile ( $<2$  mm), curved to fit the globe
  - Variable shapes
  - Slotted design
  - Collimation prevents scatter



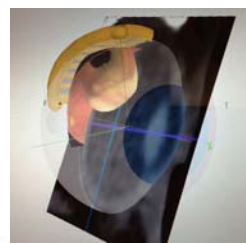
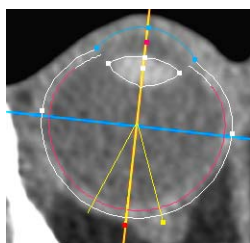
## Eye Physics® plaques: 3-D computer modeling process

Tumor margins outlined on a retinal surface map



Ultrasound for tumor dimensions

CT/MRI localizes landmarks

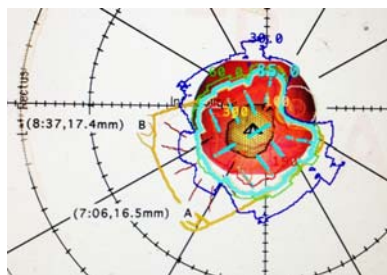


3-D overlay for plaque dosimetry



## Eye Physics® plaques:

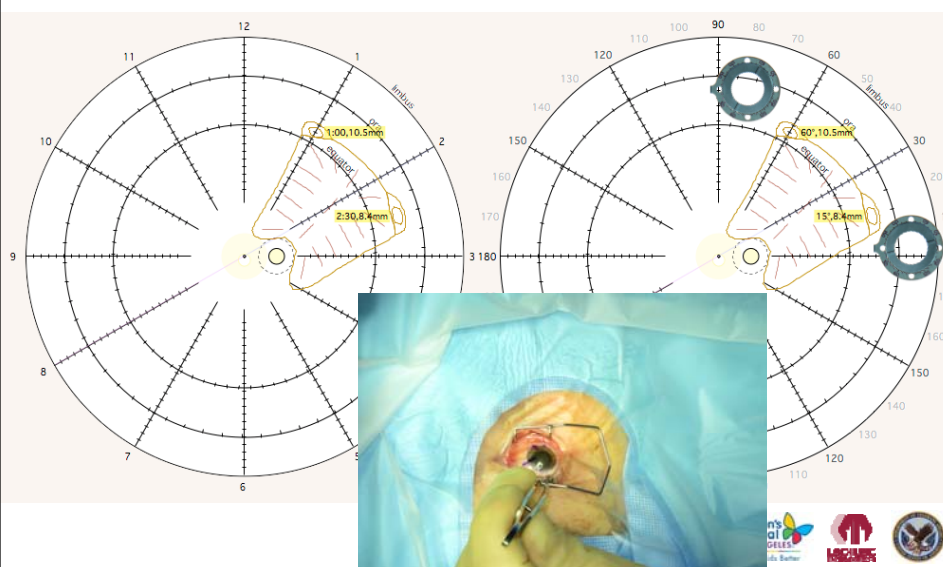
- Dosimetry:
  - optimize tumor coverage
  - minimizing exposure to critical ocular structures
    - Size and shape of plaque
    - Location and number of seeds
- Suture coordinate system
  - Location of plaque eyelets:
  - Meridian clock hours
  - Chord distance from limbus



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## Toric Marker



Original Investigation | CLINICAL SCIENCES

## Outcomes of Choroidal Melanomas Treated With Eye Physics A 20-Year Review

Jesse L. Berry, MD; Savita V. Dandapani, MD, PhD; Marta Stevanovic; Thomas C. Lee, MD; Melvin Astrahan, PhD;  
A. Linn Murphree, MD; Jonathan W. Kim, MD



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## Baseline Characteristics: COMS vs. USC

Table 2. Collaborative Ocular Melanoma Study vs University of Southern California Eye Physics Plaques

	Collaborative Ocular Melanoma Study	University of Southern California
Baseline Clinical Characteristics		
Patients, No.	638	82
Median follow up, mo	67	47
Patients, %		
White	98	94
Male	50	60
Mean tumor height, mm	4.2	4.6
Mean basal diameter, mm	11.5	10.7
Anterior border posterior to equator, %	55	57

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Children's Hospital Los Angeles

LAC+USC



## Tumor Control: COMS vs. USC

Tumor Control		
Dose to tumor apex, Gy	85	85
Dose to optic nerve, Gy	52.1	46.6
Dose to macula/fovea, Gy	79	66.6
Dose to lens, Gy	15.6	15.2
Kaplan-Meier-estimated tumor recurrence at 5 y, %	10	3.0
Enucleation at 5 y, %	13	3.0
Metastatic disease at 5 y, %	10	11



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## Ocular Outcomes: COMS vs. USC

Visual and Ocular Outcomes, %		
Preoperative visual acuity		
20/40 or better	70	63
20/200 or worse	10	18
Postoperative visual acuity		
20/40 or better	34	35
20/200 or worse	43	43
Optic neuropathy	27	15
Radiation retinopathy	49	38
Cataracts	83	32



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Outcomes of Medium sized choroidal melanomas treated with USC Eye Physics plaques: a 20 year Review.

- USC outcomes comparable to COMS data:
  - Tumor recurrence
  - Enucleation
  - Survival
  - Visual status
- Eye Physics technique for ocular brachytherapy:
  - simplifies the process of plaque placement
  - Is a valid and accurate method for treating medium-sized choroidal melanomas



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## FNAB

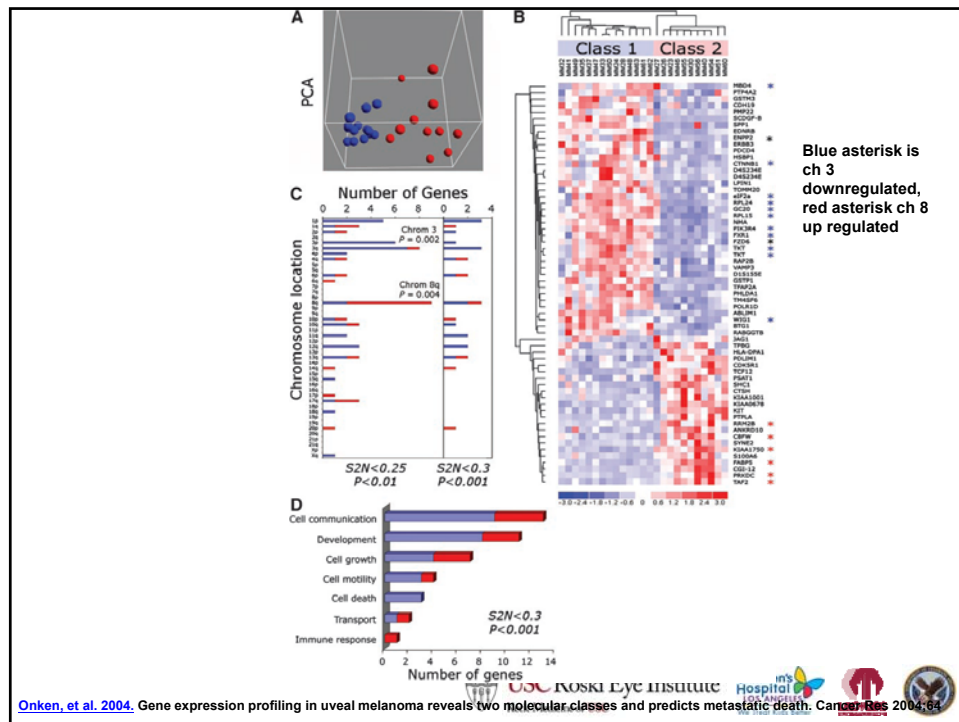


- 26 gene assay for uveal melanoma (Harbour's lab at Wash University)
- FNAB taken prior to plaque or enucleation
- Classifies UM metastatic risk
  - Low (Class 1a)
  - Intermediate (Class 1b)
  - High (Class 2)
- BAP1 correlates better than GNAQ

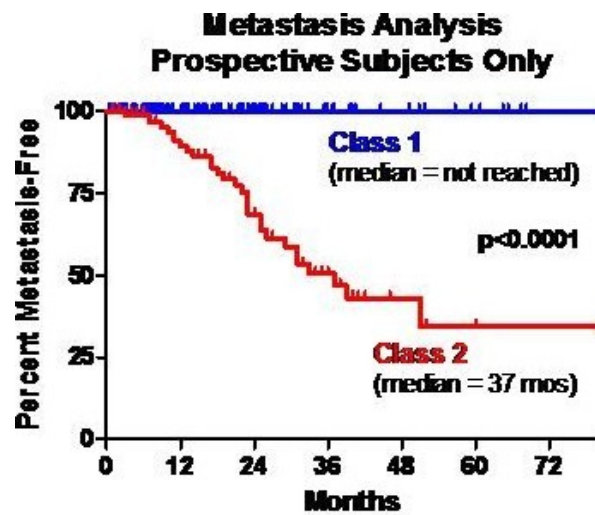


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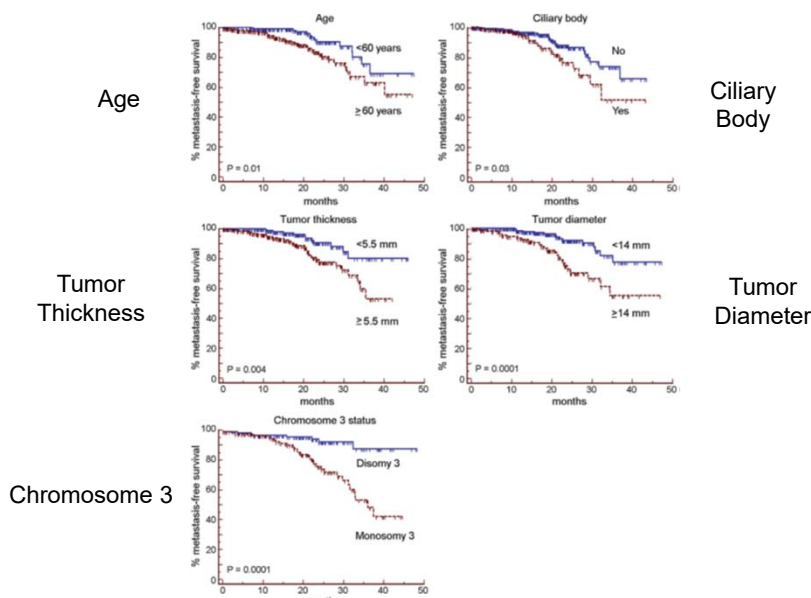
## Decision Dx UM



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## Metastasis-free Survival



## PRAME

Clin Cancer Res. 2016 Mar 1;22(5):1234-42. doi: 10.1158/1078-0432.CCR-15-2071.

### PRAME as an Independent Biomarker for Metastasis in Uveal Melanoma.

Field MG<sup>1</sup>, Decatur CL<sup>1</sup>, Kurtenbach S<sup>1</sup>, Gezgün G<sup>2</sup>, van der Velden PA<sup>2</sup>, Jager MJ<sup>2</sup>, Kozak KN<sup>1</sup>, Harbour JW<sup>3</sup>.

Author information

#### Abstract

**PURPOSE:** Uveal melanoma (UM) can be classified by gene expression profiling (GEP) into Class 1 (low metastatic risk) and Class 2 (high metastatic risk), the latter being strongly associated with mutational inactivation of the tumor suppressor BAP1. Nevertheless, a small percentage of Class 1 tumors give rise to metastatic disease. The purpose of this study was to identify biomarkers of metastasis in Class 1 tumors.

**EXPERIMENTAL DESIGN:** A total of 389 consecutive patients with UM were assigned to Class 1 or Class 2 using a prospectively validated 12-gene prognostic classifier. Selected tumors were further analyzed using global GEP and single nucleotide polymorphism microarrays. PRAME (preferentially expressed antigen in melanoma) mRNA expression was analyzed in 64 Class 1 tumors by qPCR.

**RESULTS:** Among Class 1 UMs, the most significant predictor of metastasis was PRAME mRNA expression ( $P = 0.0006$ ). The 5-year actuarial rate of metastasis was 0% for Class1(PRAME-), 38% for Class1(PRAME+), and 71% for Class 2 tumors. Median metastasis-free survival for Class1(PRAME+) patients was 88 months, compared to 32 months for Class 2 patients. Findings were validated using three independent datasets, including one using disomy 3 to identify low-risk UM. Chromosome copy number changes associated with Class1(PRAME+) tumors included gain of 1q, 6p, 8q, and 9q and loss of 6q and 11q. PRAME expression was associated with larger tumor diameter ( $P = 0.05$ ) and SF3B1 mutations ( $P = 0.003$ ).

**CONCLUSIONS:** PRAME is an independent prognostic biomarker in UM, which identifies increased metastatic risk in patients with Class 1 or disomy 3 tumors. This finding may further enhance the accuracy of prognostic testing and precision medicine for UM.

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PMID: 26933176 PMCID: PMC4780366 [Available on 2017-03-01] DOI: 10.1158/1078-0432.CCR-15-2071



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## Melanoma Summary

- **Choroidal melanoma rare**
- **Treatment depends on size, location and visual potential**
- **Metastatic work up at diagnosis focusing on the liver**
- **USC Eye Physics plaques allow for pre-operative plaque localization**
- **gene expression profiling classifies risk**



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