Pediatric Ocular Oncology

Primary Intraocular Tumors

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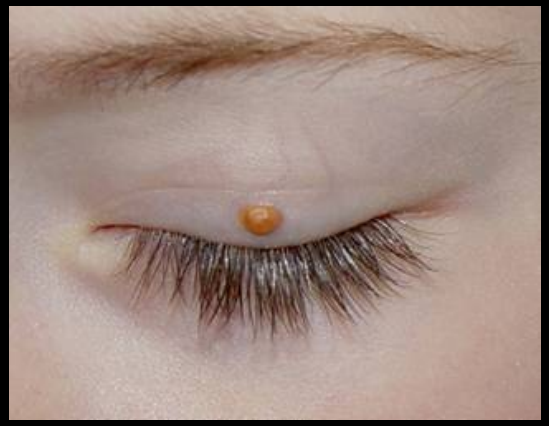
Benign neoplasms

- Xanthogranuloma
- Hamartoma
  - Astrocytic
  - Retina and RPE
- Hemangioma
  - Capillary
  - Cavernous
  - Choroidal
- Osteoma, choroidal
- Pigmented
  - Uveal Nevus
  - Melanocytoma of the optic nerve
  - Congenital Hypertrophy of the RPE

Xanthogranuloma

- Juvenile Xanthogranuloma (JXG)
  - May be a reaction to local tissue injury
    - Collection of histiocytes , lymphocytes, multinucleated giant cells
  - Usually only cutaneous (75%)
  - Rarely intraocular
    - Iris most affected (68%)
  - Usually in younger children
  - Associations
    - NF-1, Niemann-pick disease, urticaria pigmentosa
    - NF-1 + JXG = 25X higher risk of juvenile myelomonocytic leukemia (JMML)



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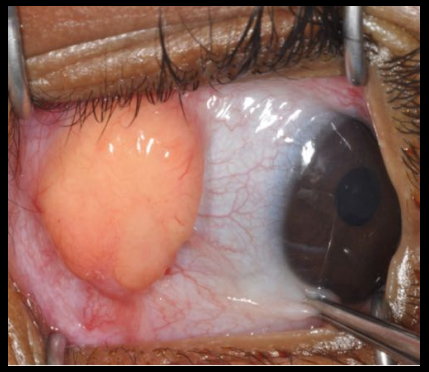
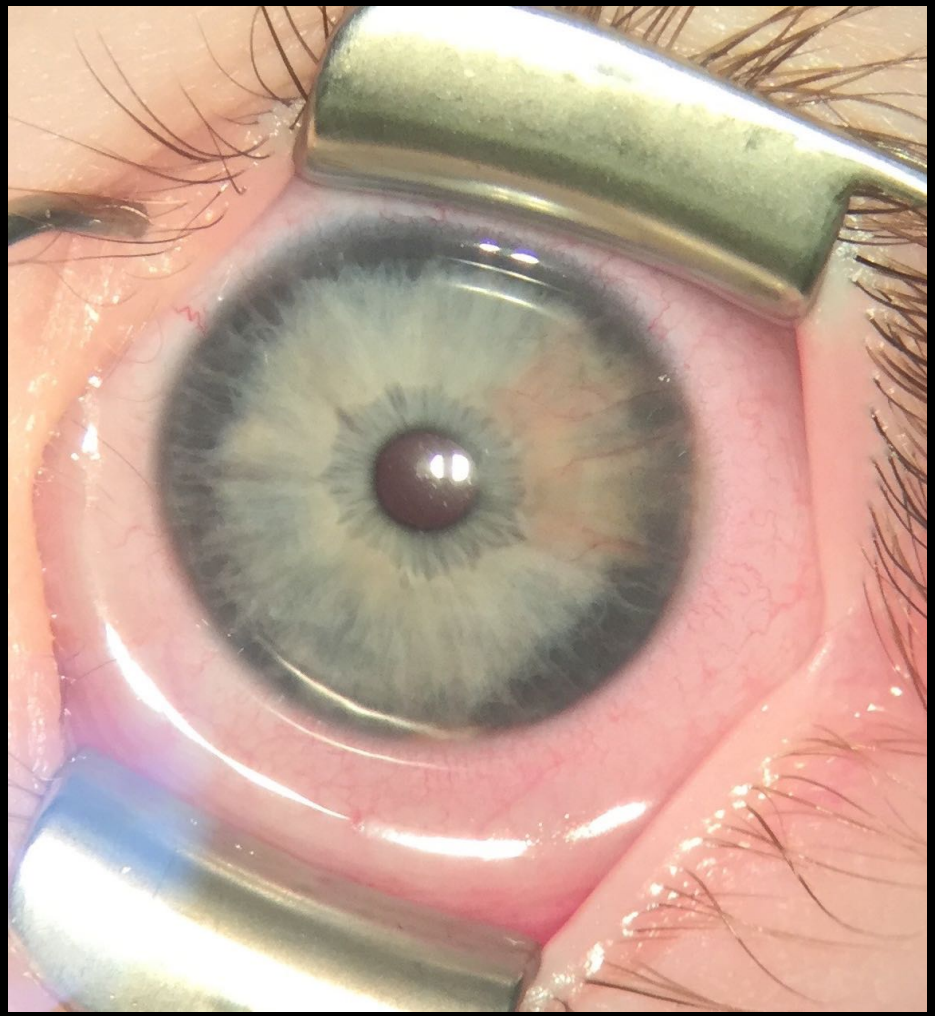
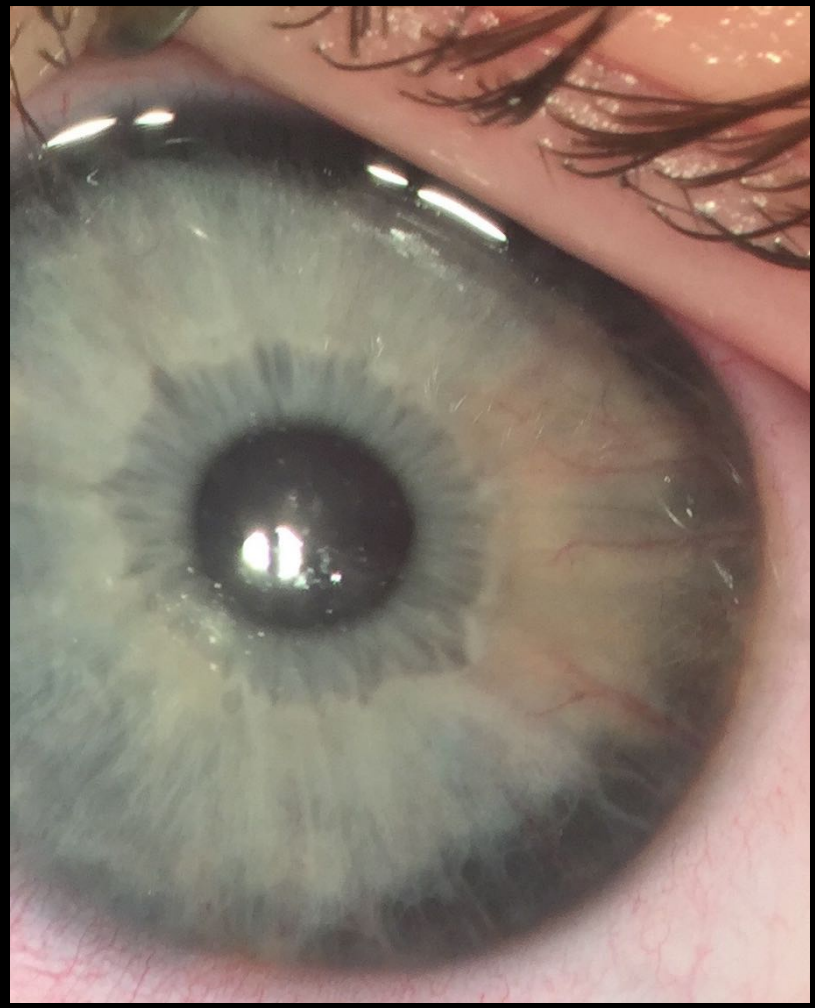
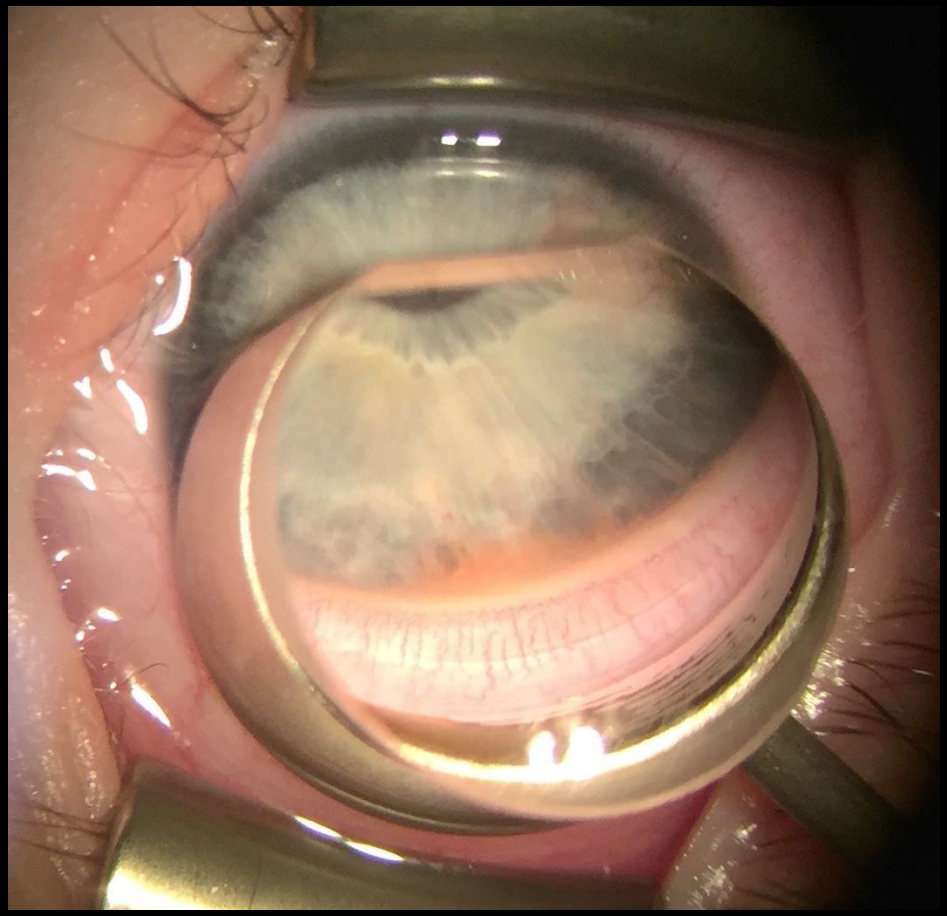
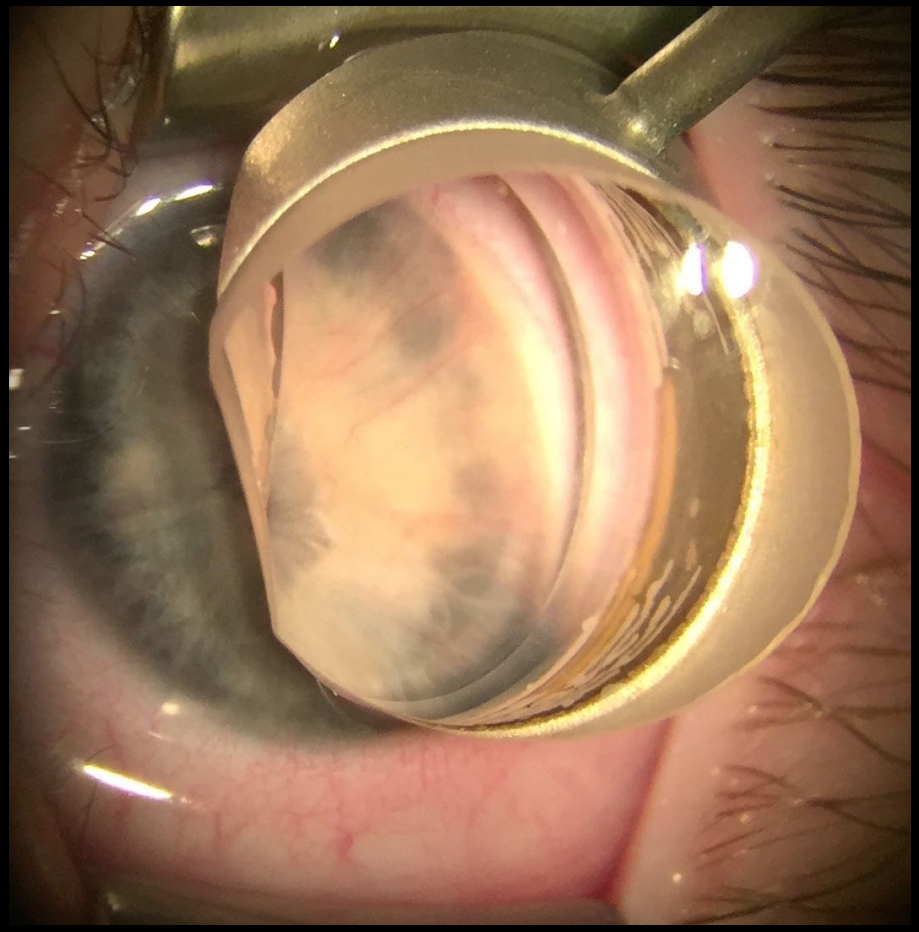


Ophthalmology 2015;122(10):2130-8.





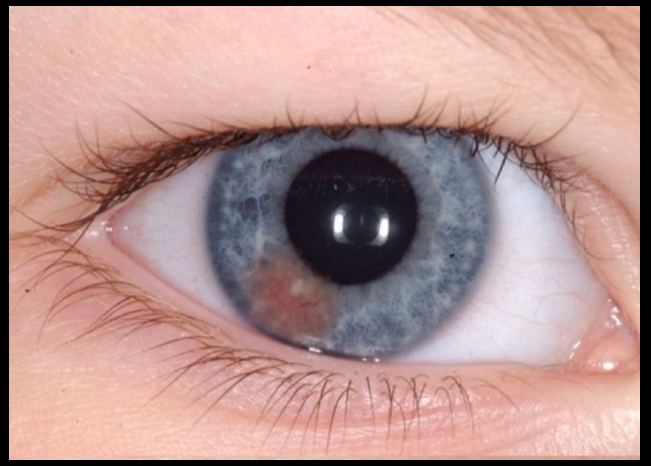




Xanthogranuloma

- Iris JXG
  - Neovascularization
    - Hyphema
  - Glaucoma

  - Corticosteroids
    - Prednisolone acetate 1% drops TID-QID
      - Taper over 3 months
    - Second line
      - Periocular steroid injection
      - Systemic corticosteroids



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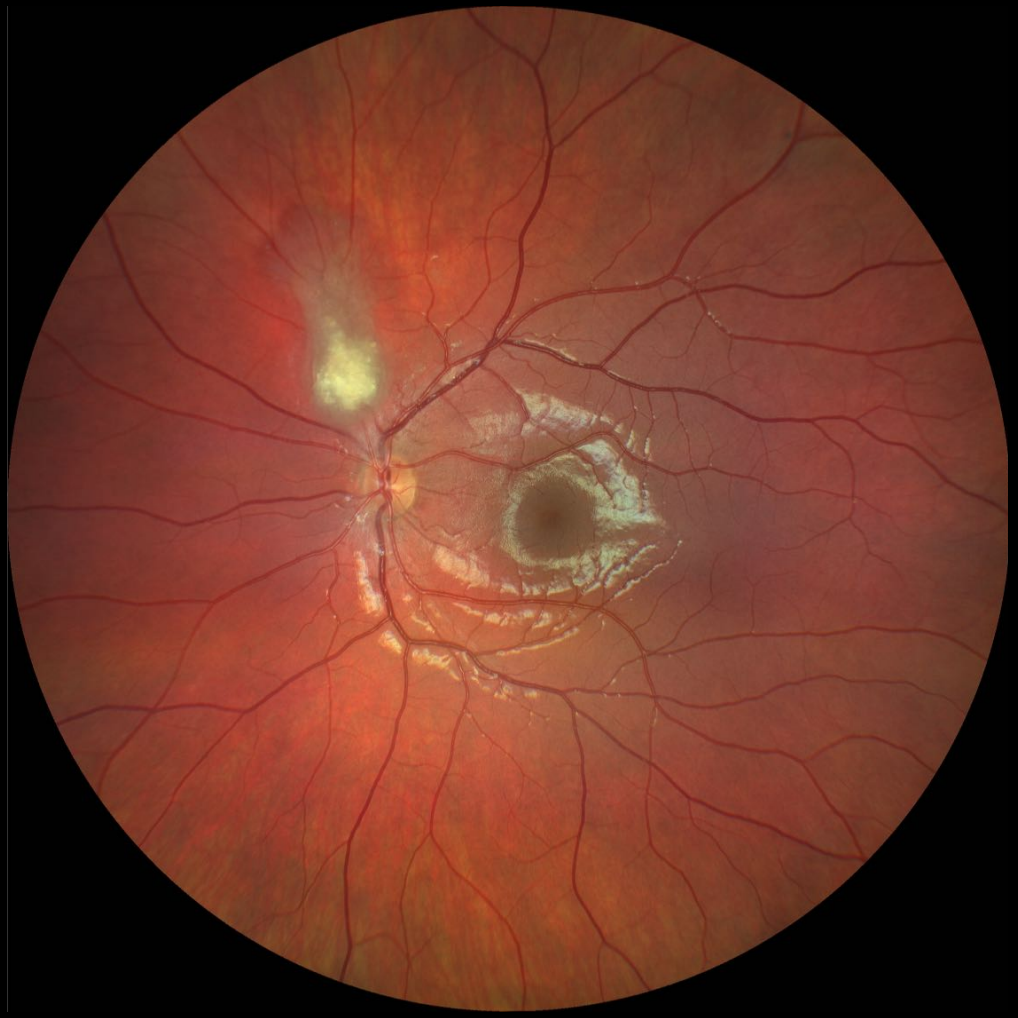
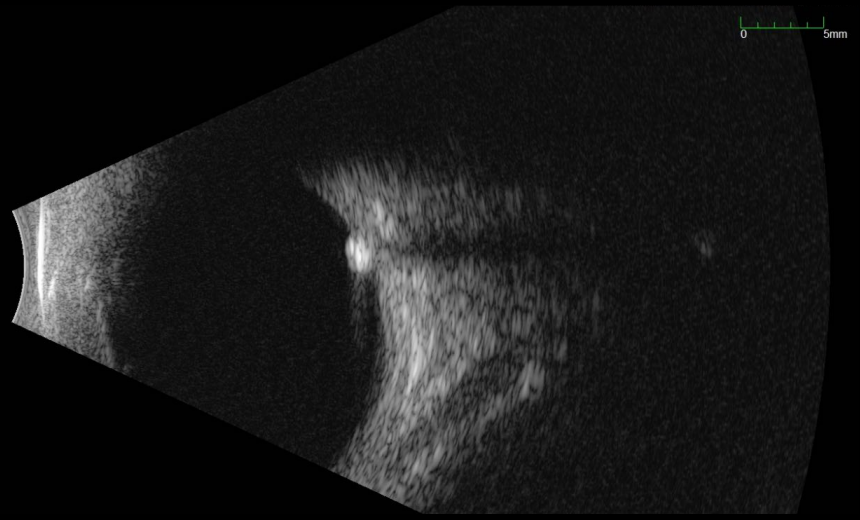
Astrocytic Hamartoma

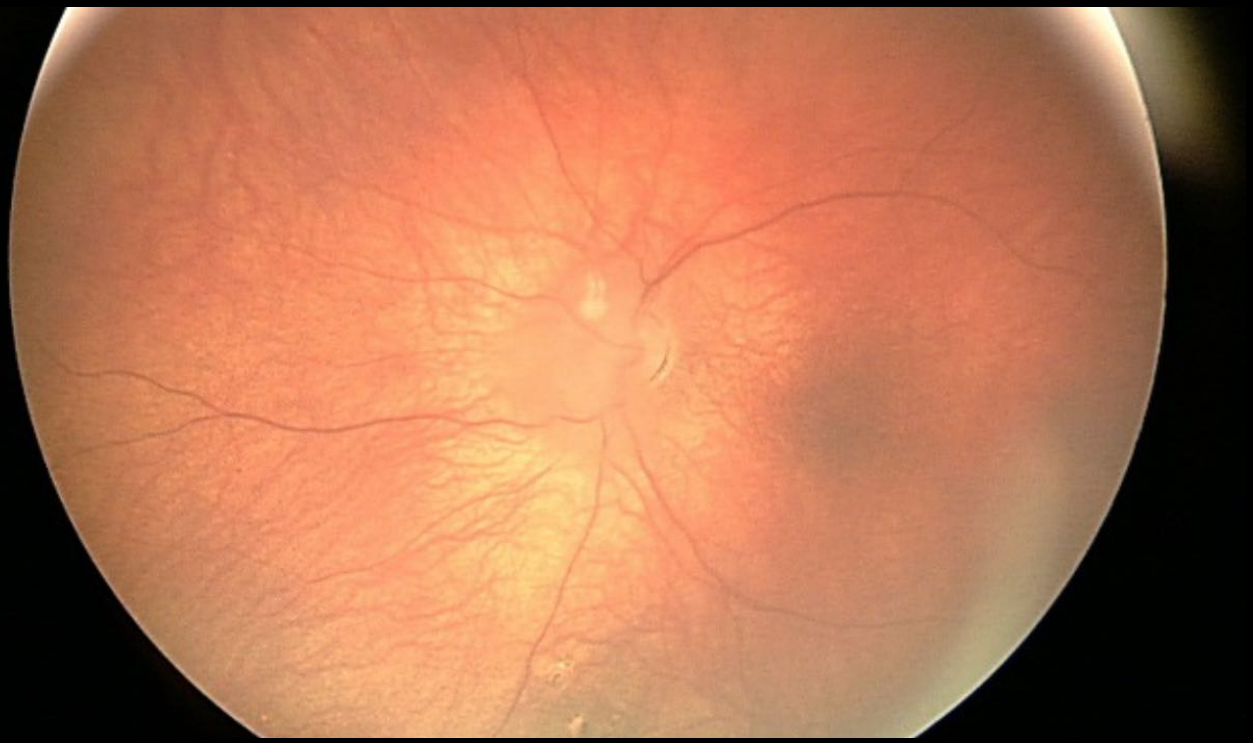
- Retinal tumors in Tuberous Sclerosis
  - Also in neurofibromatosis
  - Non-calcified- may resemble retinoblastoma
  - Calcified - “Mulberry lesions”

  - Typically don’t affect vision significantly
    - May consider laser if associated sub-retinal fluid





Courtesy Alina Dumitrescu, MD



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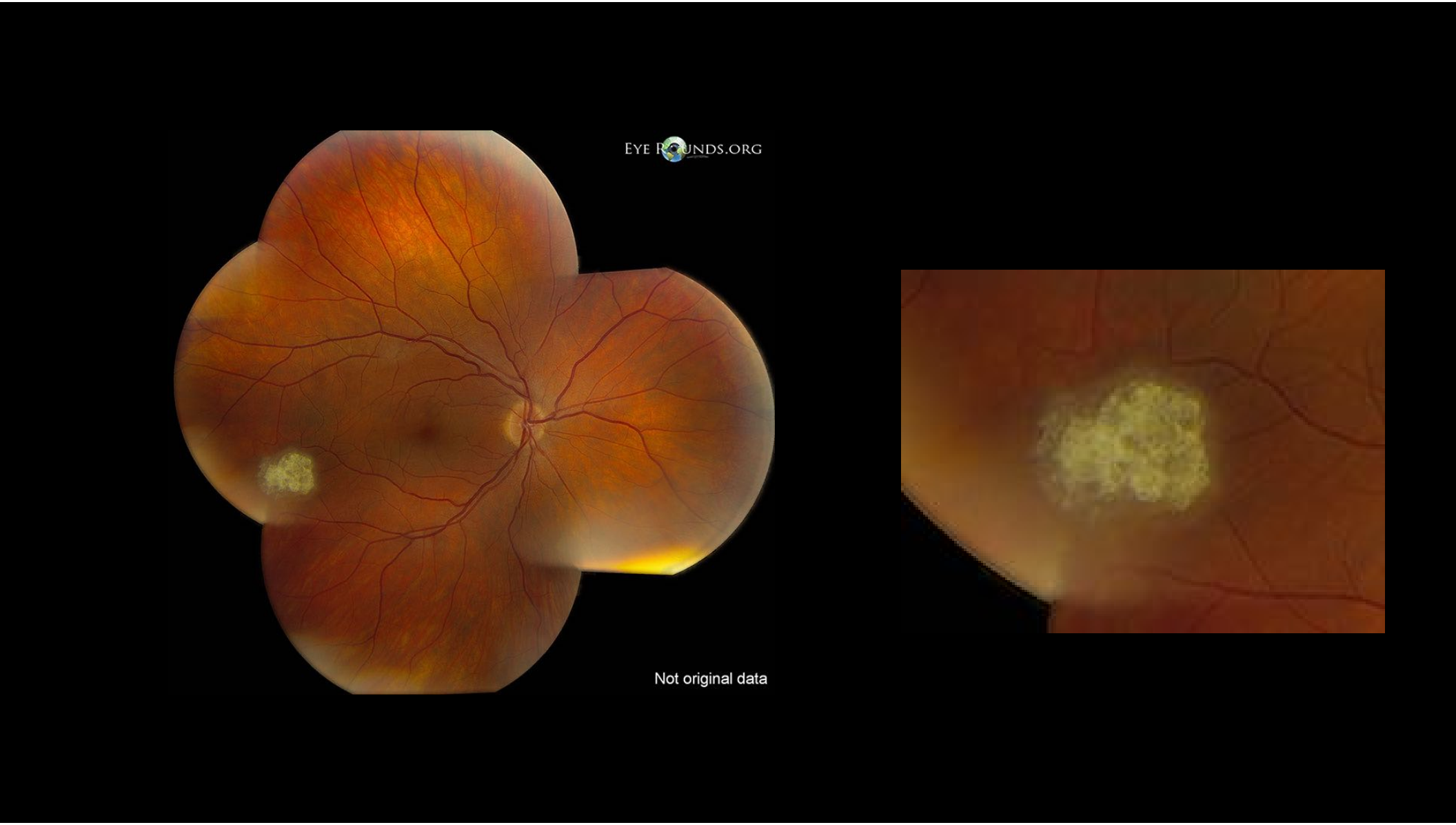
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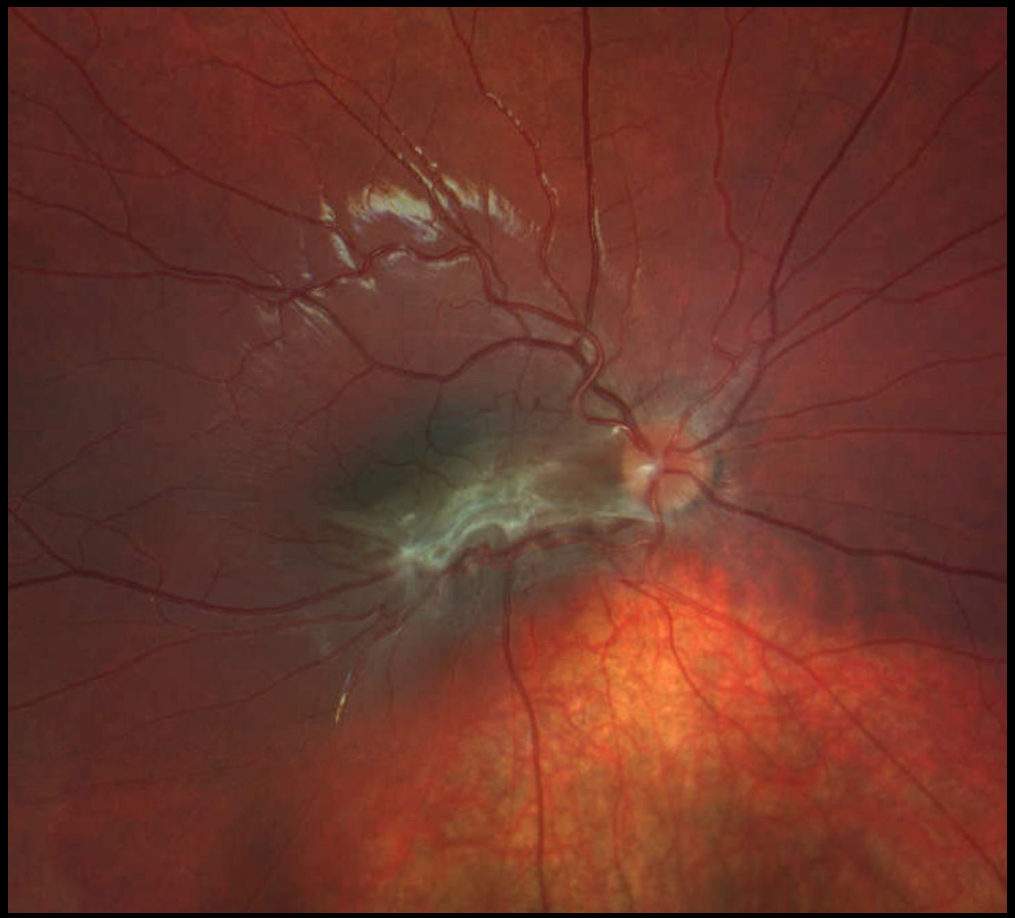
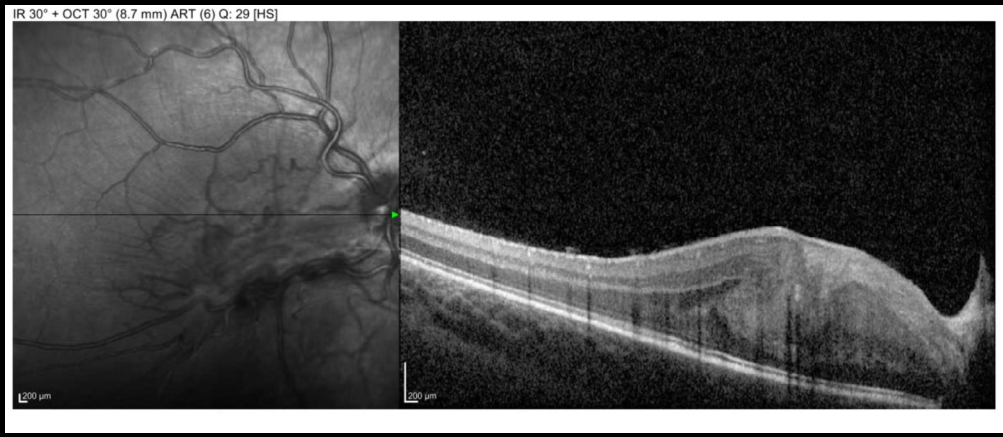
Combined Hamartoma of Retina and RPE

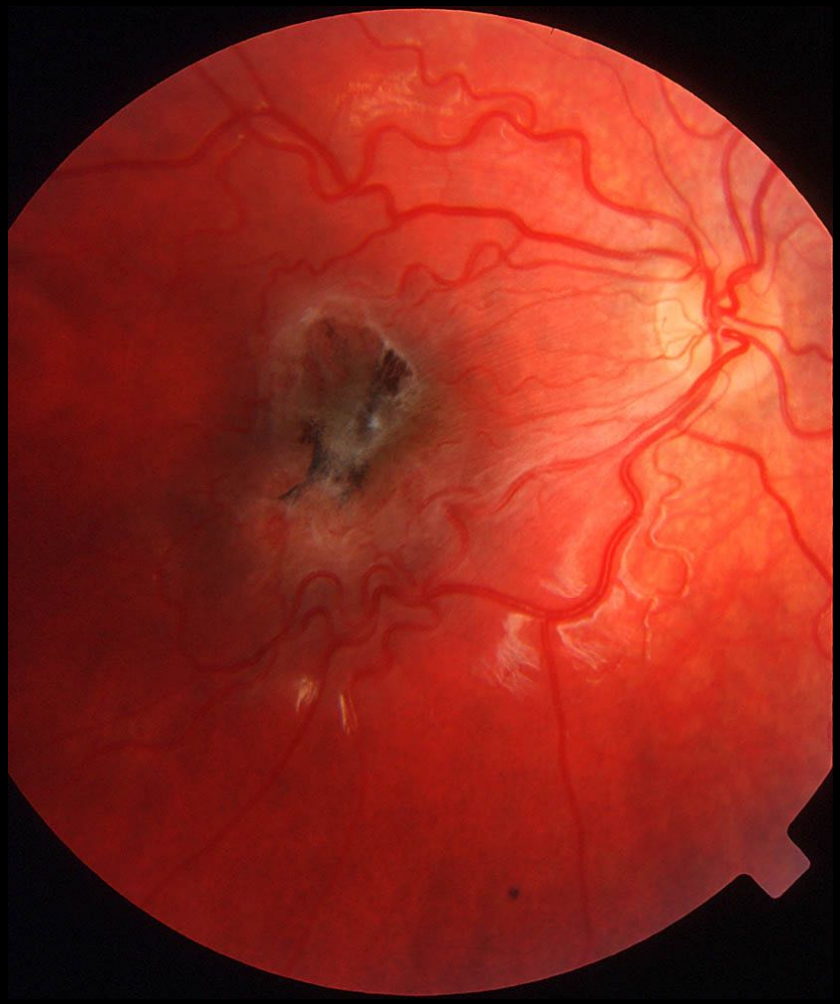
- Mildly elevated mass involving the RPE, retina and overlying vitreous
- Probably congenital
- May be undifferentiated ectopic RPE progenitor cells

- Association: NF2 (especially if bilateral)
- Treatment: pealing epiretinal membranes usually doesn't improve vision





Courtesy Lindsay De Andrade, MD



Courtesy of David Dries, MD

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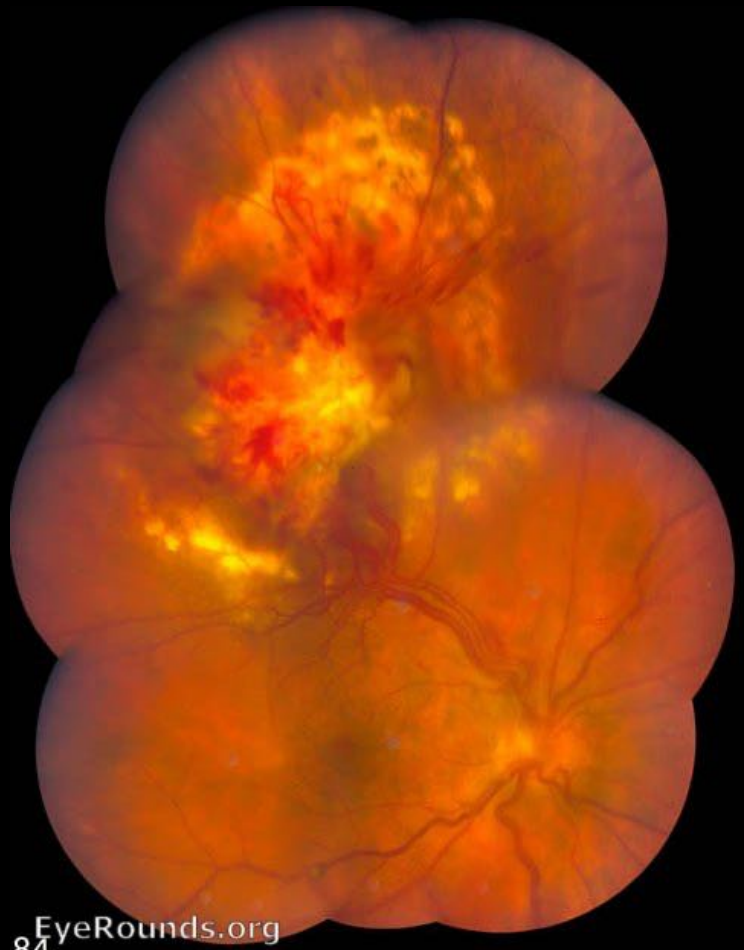
Retinal Capillary Hemangioma

- Also Known As: hemangioblastoma, retinal angioma

- Usually earliest manifestation of von Hippel-Lindau disease
  - Results from a germline mutation in the VHL gene (tumor suppressor)
- Rarely occurs without systemic disease

- Usually appears in young adulthood rarely in children
- Larger lesions associated with elevation and exudation
- Treatments:
  - Laser/ Cryo / Anti-VEGF / vitrectomy for retinal detachment


EyeRounds.org
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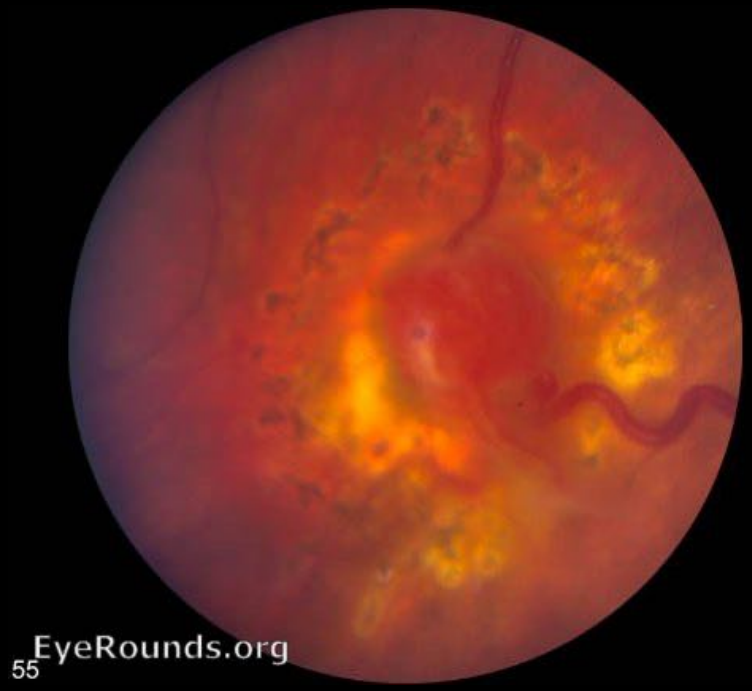
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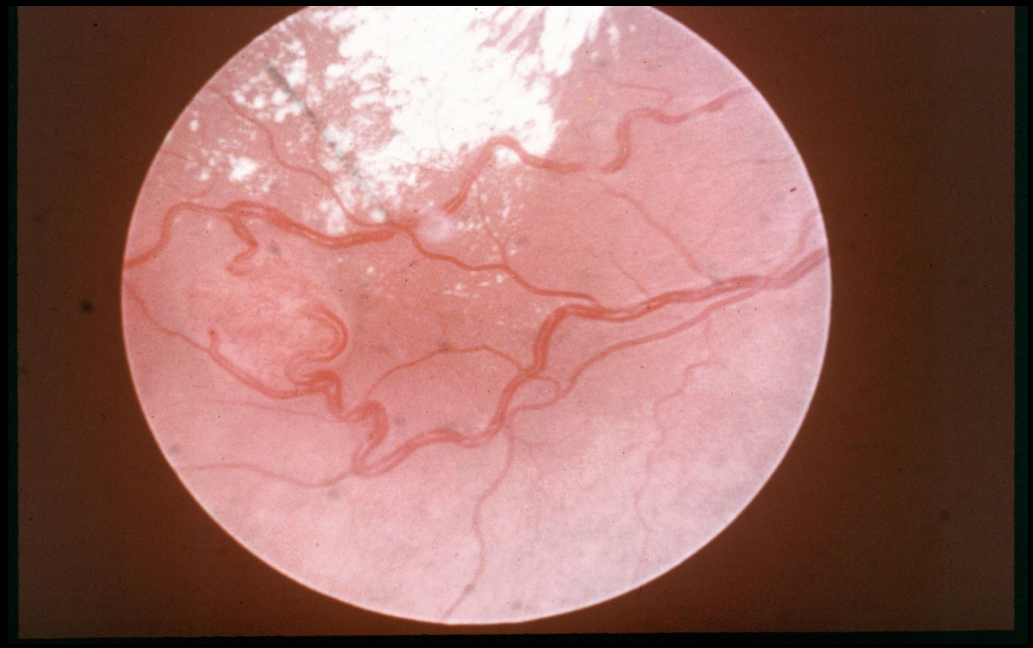
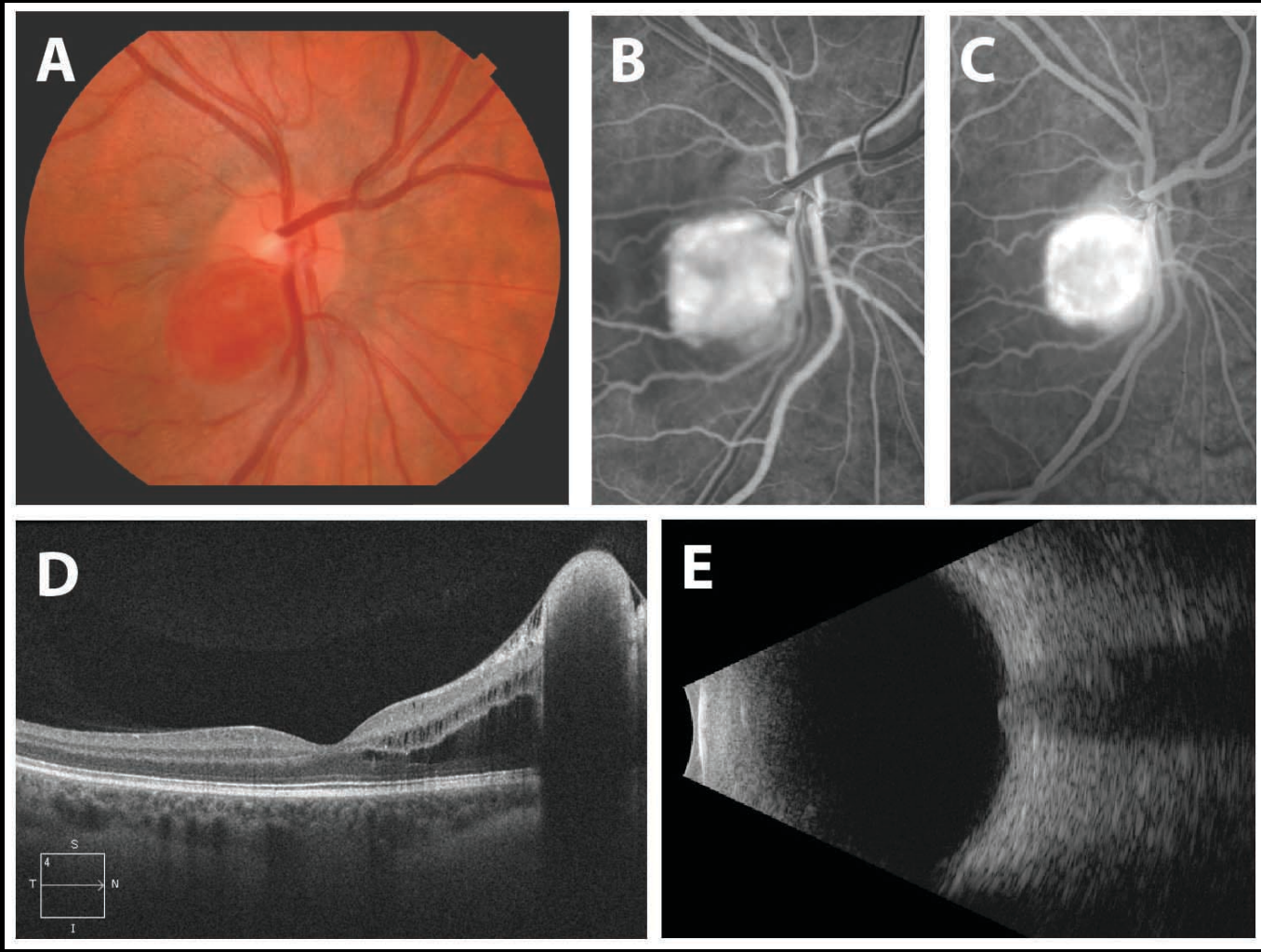


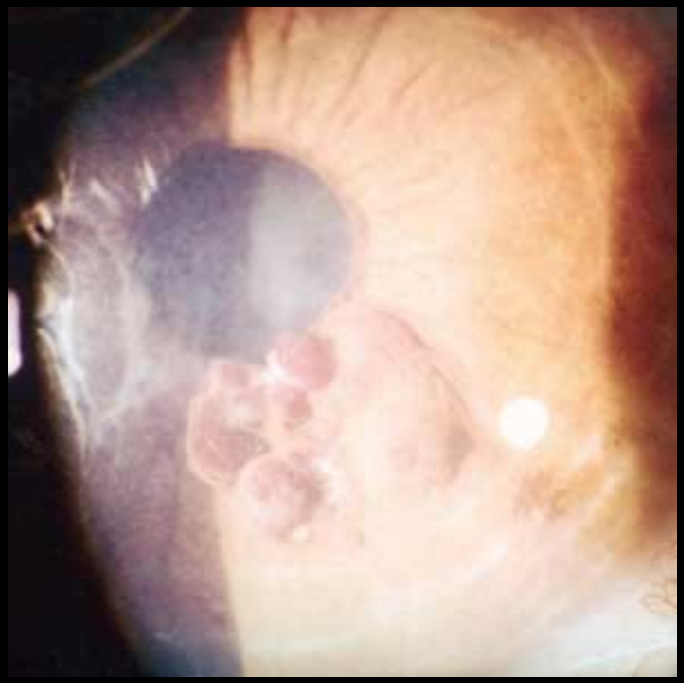
Courtesy Alan Richards, MD

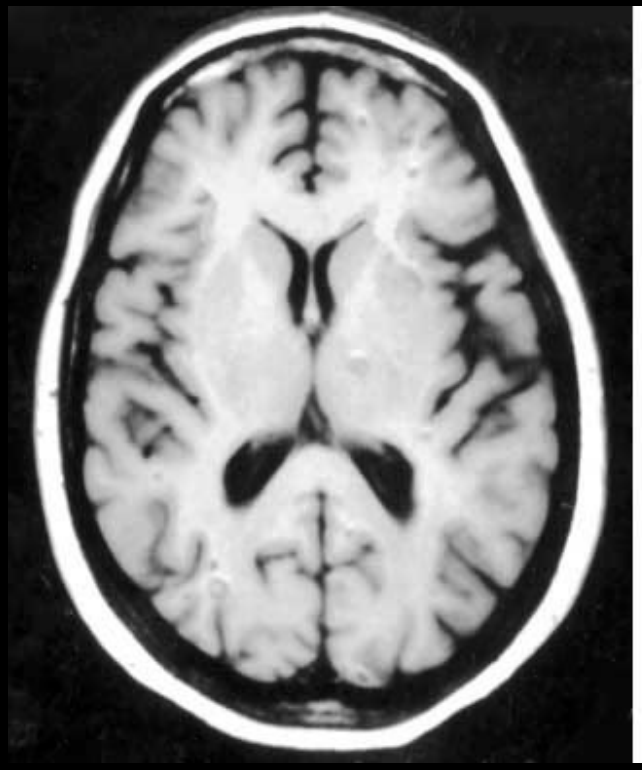


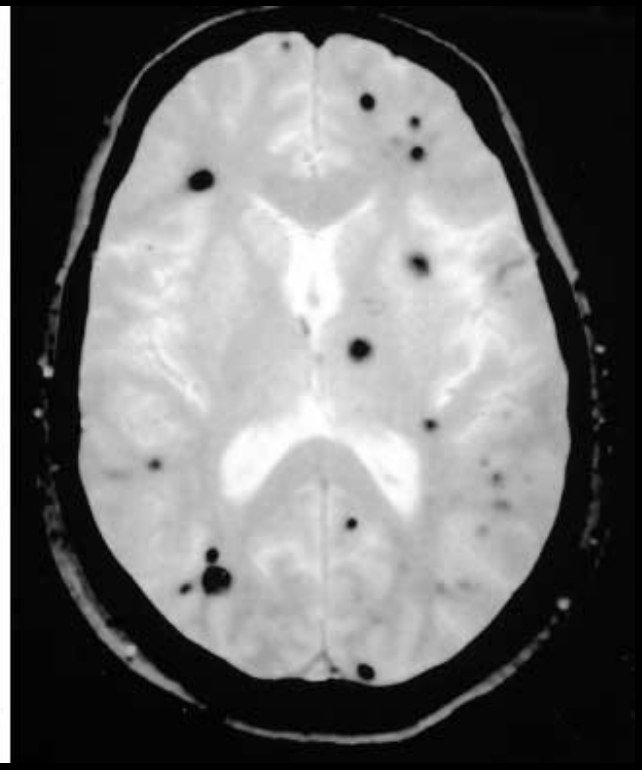
https://eyewiki.aao.org/w/images/1/e/e1/VHL_Fig3.jpg

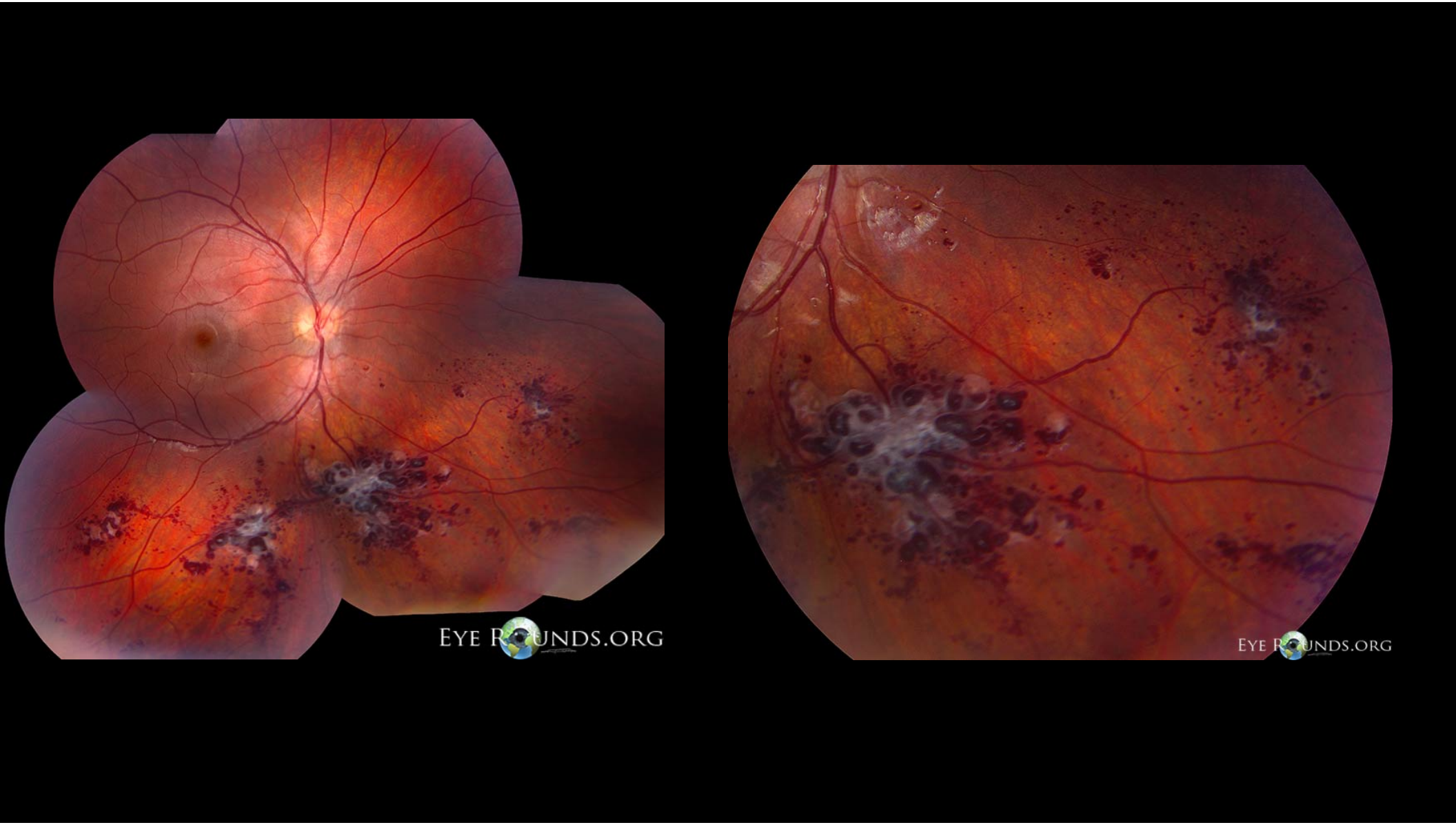
Cavernous Hemangioma

- Globular lesion with multiple vascular channels
- May be associated with CNS, liver and cutaneous vascular lesions
- Hyphema/ vitreous hemorrhage possible
- Plaque radiotherapy to induce sclerosis





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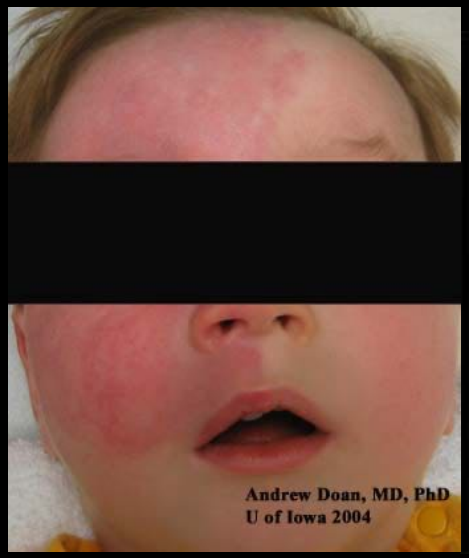
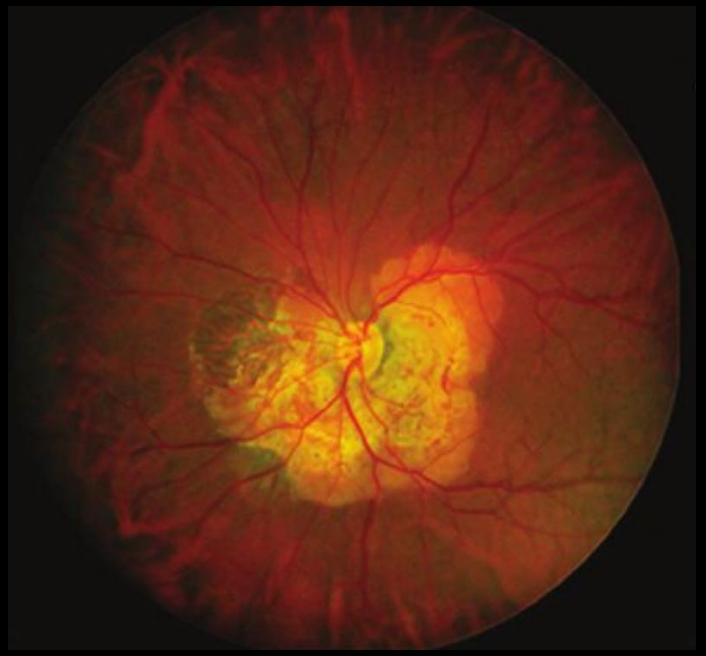
Choroidal Hemangioma

- Diffuse Choroidal Hemangioma in children
  - Sturge Weber Syndrome- encephalo-facial hemangiomatosis

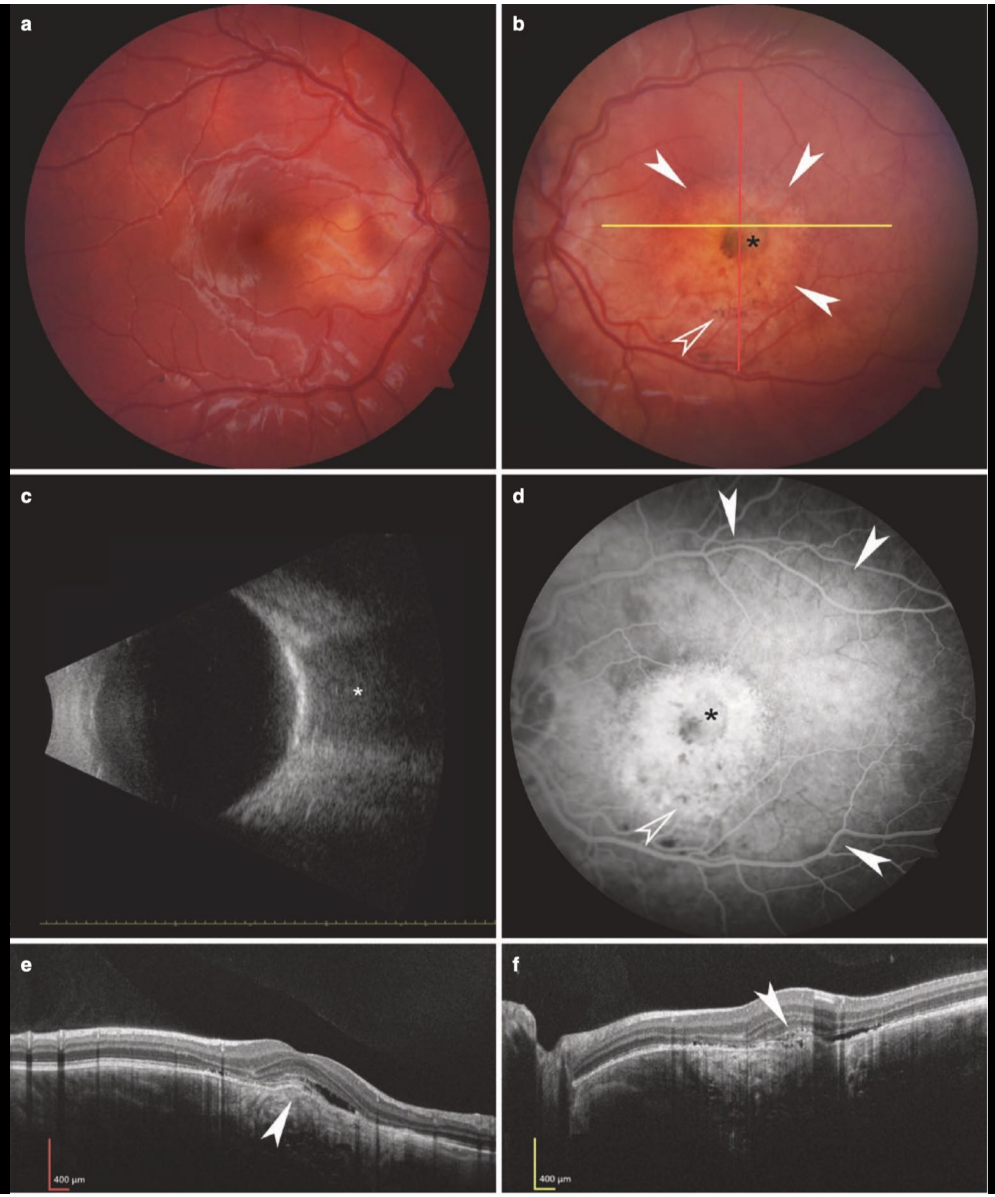


Choroidal Osteoma

- Likely congenital, more common in females
- Plaque of mature bone
- Often adjacent to the optic disc
- Slow enlargement
- Choroidal neovascularization
  - Subretinal hemorrhage
- Intravitreal Anti-VEGF
  - 1.25 mg bevacizumab
  - 0.5 mg ranibiumab



Harley's Pediatric Ophthalmology, 2013.



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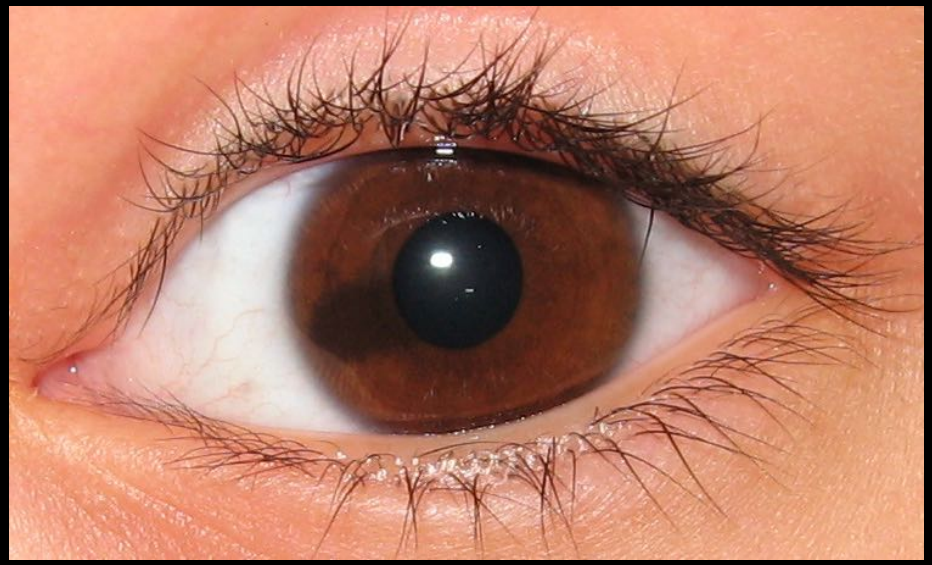
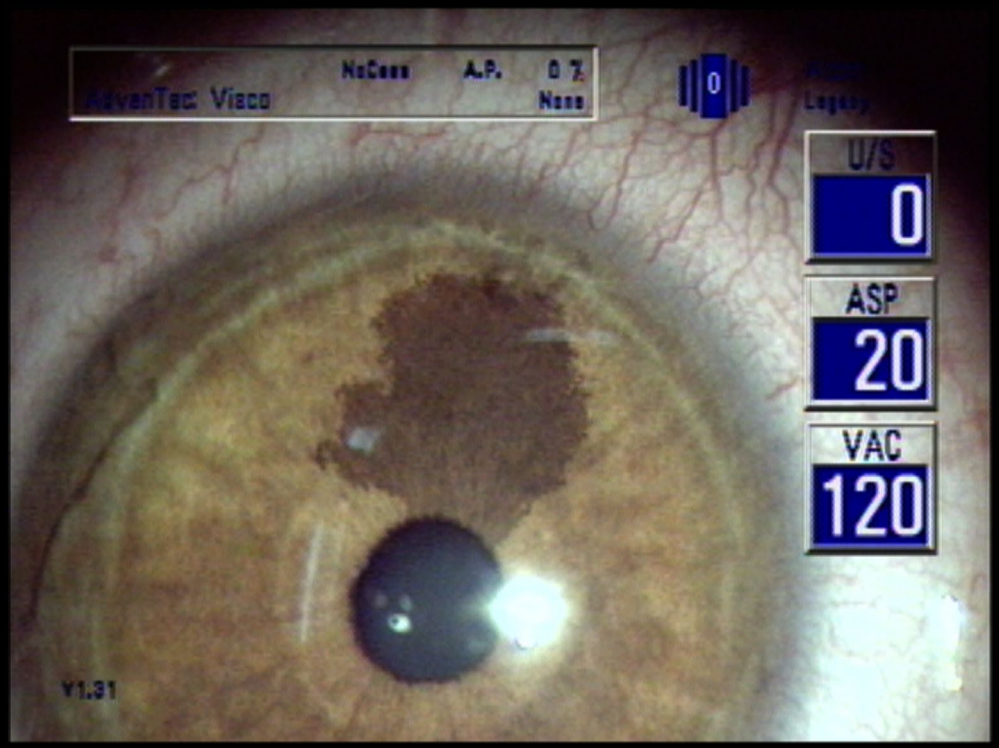
Uveal nevus

- Flat or minimally elevated variably pigmented tumor of the iris or choroid
- Malignant transformation 1 in 8000

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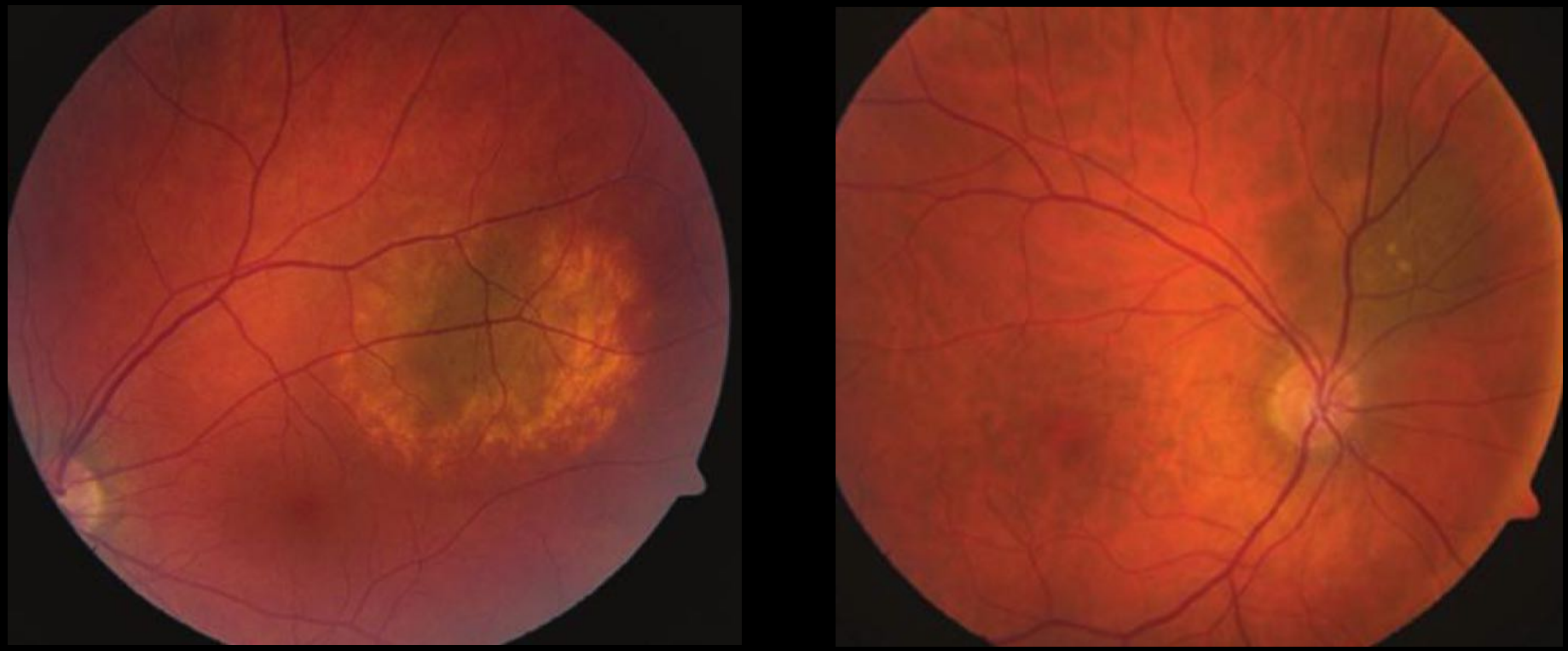

Harley's Pediatric Ophthalmology, 2013.

Features predictive of transformation from nevus to melanoma (Carol Shields)

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Iris Lesion "ABCDEF"	
A	Age < 40 years
B	Blood (hyphema)
C	Clock hours inferiorly
D	Diffuse configuration
E	Ectropion
F	Feathery margins

Choroidal lesion "To Find Symptoms of Ocular Melanoma- Use Helpful Hints Daily"	
To	Thickness > 2 mm
Find	Fluid, subretinal
Symptoms	Symptoms, visual
Ocular	Orange pigment
Melanoma	Margin within 3 mm of optic disc
Use Helpful	Ultrasound Hollow (low internal reflectivity)
Hints	Halo absent
Daily	Drusen absent

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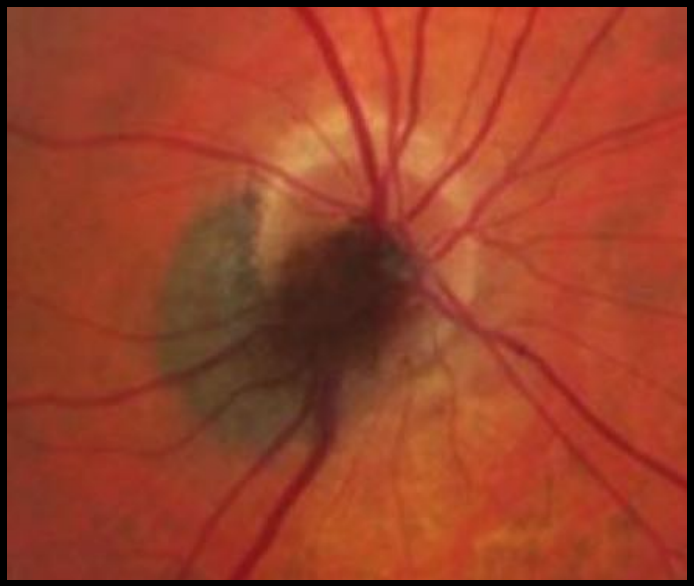
Melanocytoma of the optic nerve

- Deeply pigmented lesion, likely congenital tumor
- Histologically like nevus
  - Hyperpigmented magnocellular nevus of the optic disc
- May start amelanotic
- Occurs in equal frequency in all races
- Watch for progression
  - 1-2% change of progression to melanoma



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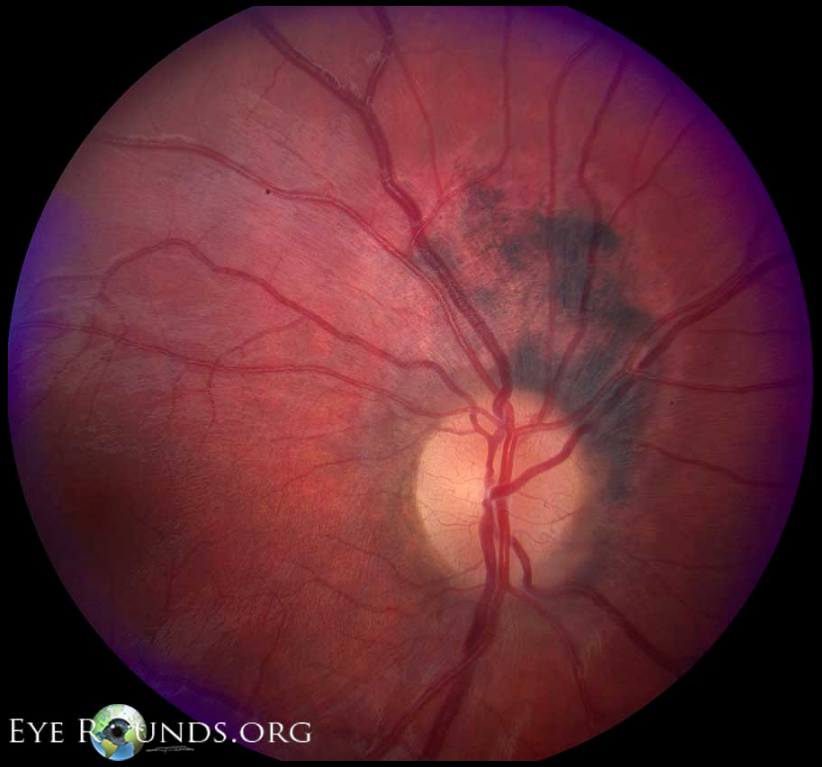
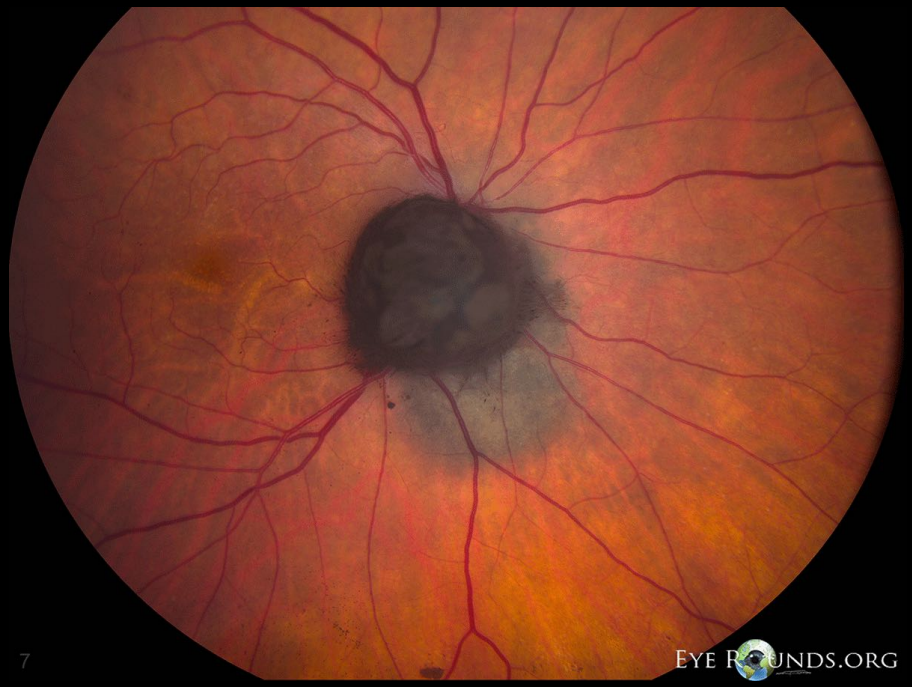
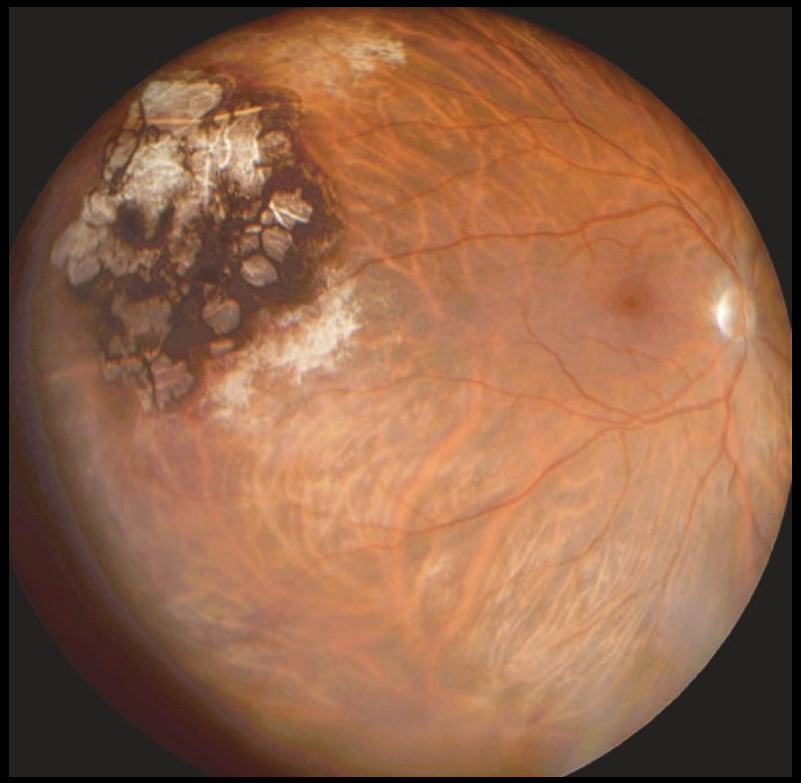
Melanocytoma of the optic nerve

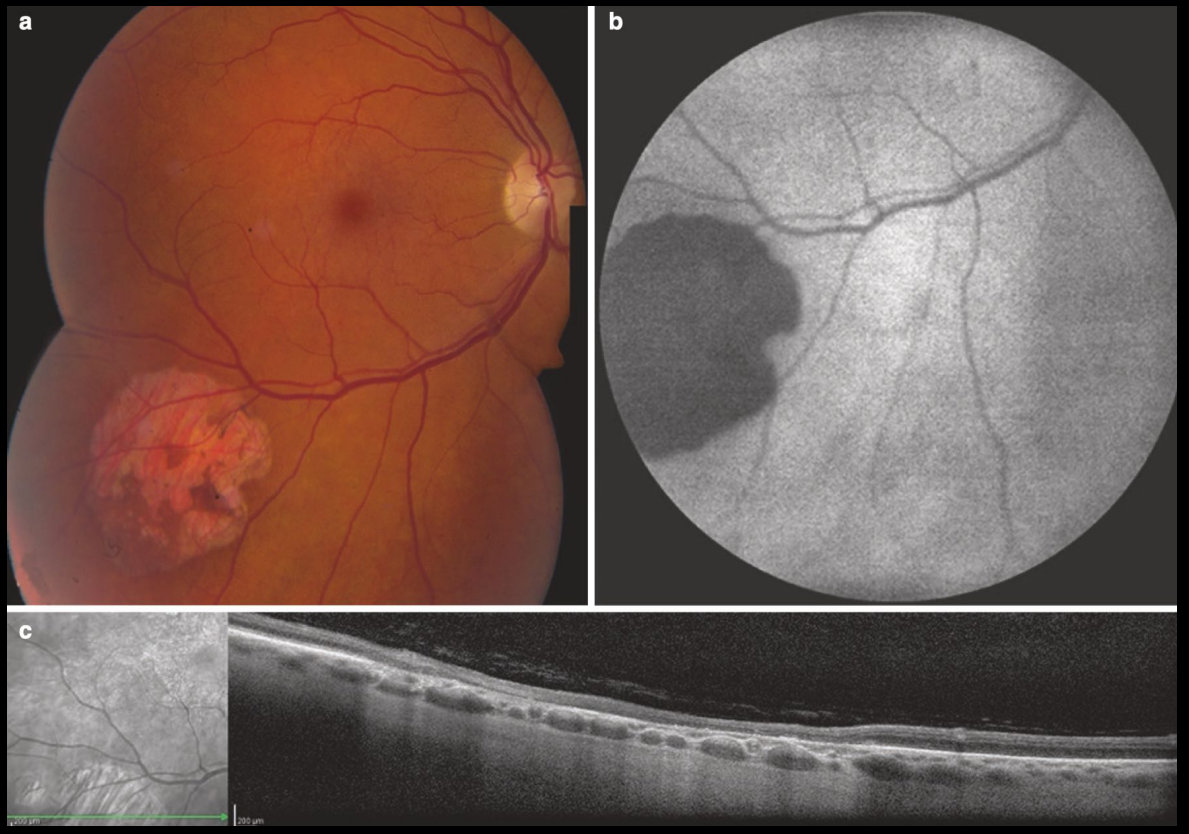




Congenital Hypertrophy of the RPE

- Solitary
  - Round, flat pigmented lesion, usually midperiphery or far periphery
  - Frequent depigmented lacunae
  - Very gradual increase in size
  - Rare transformation into RPE adenoma or adenocarcinoma (aka. Malignant epithelioma)
  - Not associated with familial adenomatous polyposis (Gardner Syndrome)
- Multifocal (“Bear Tracks”)
  - Numerous well delineated, flat, grouped lesions, often sectoral
  - No related ocular or systemic abnormalities





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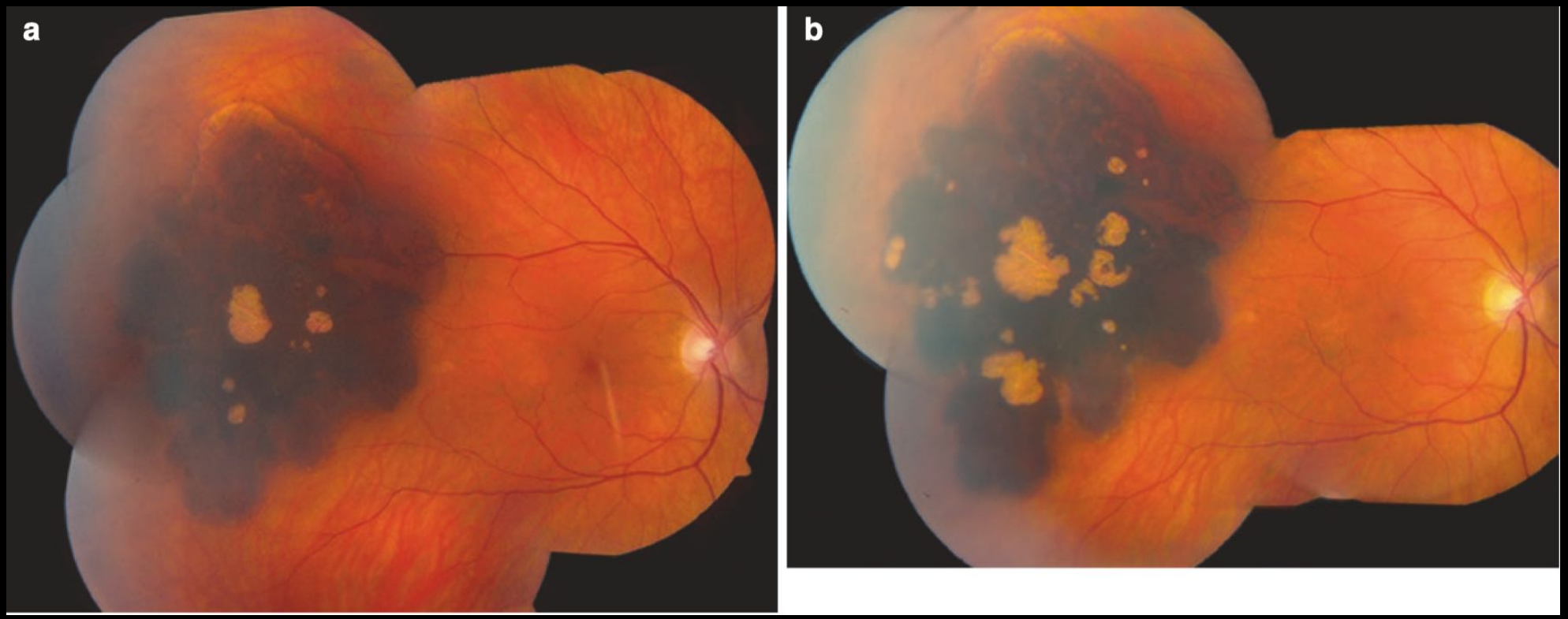

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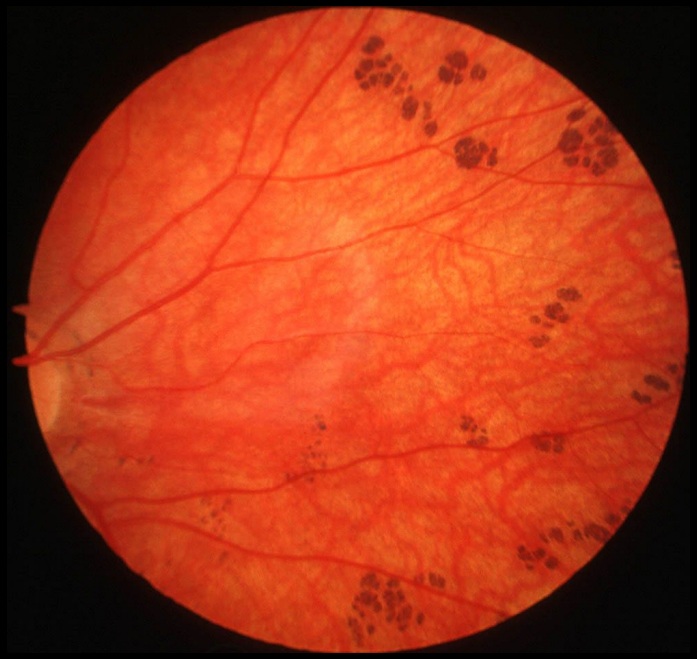

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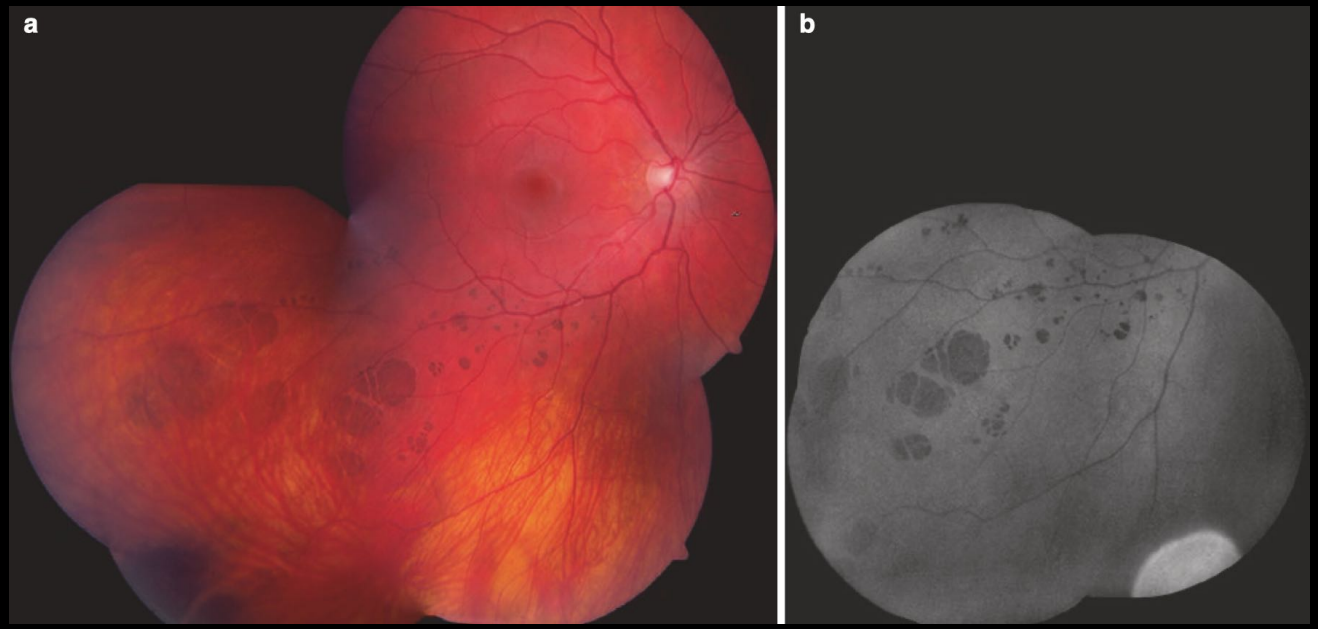

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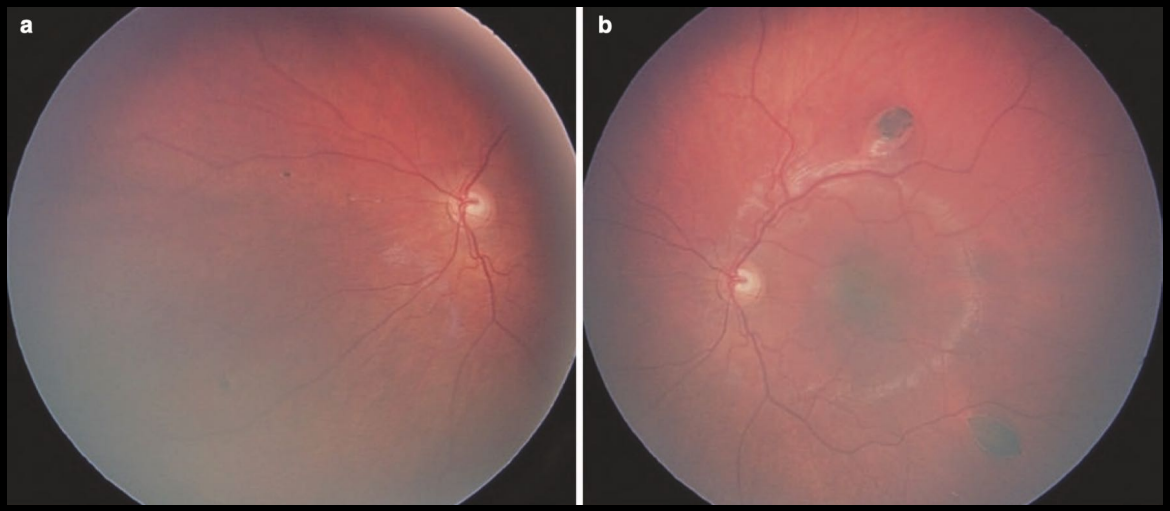
Pigmented Lesions associated with Familial Adenomatosis Polyposis

- Variable, random distribution with irregular margins
- Pisiform shape with irregular depigmented tail
- 4 or more lesions typically present (may be hundreds)



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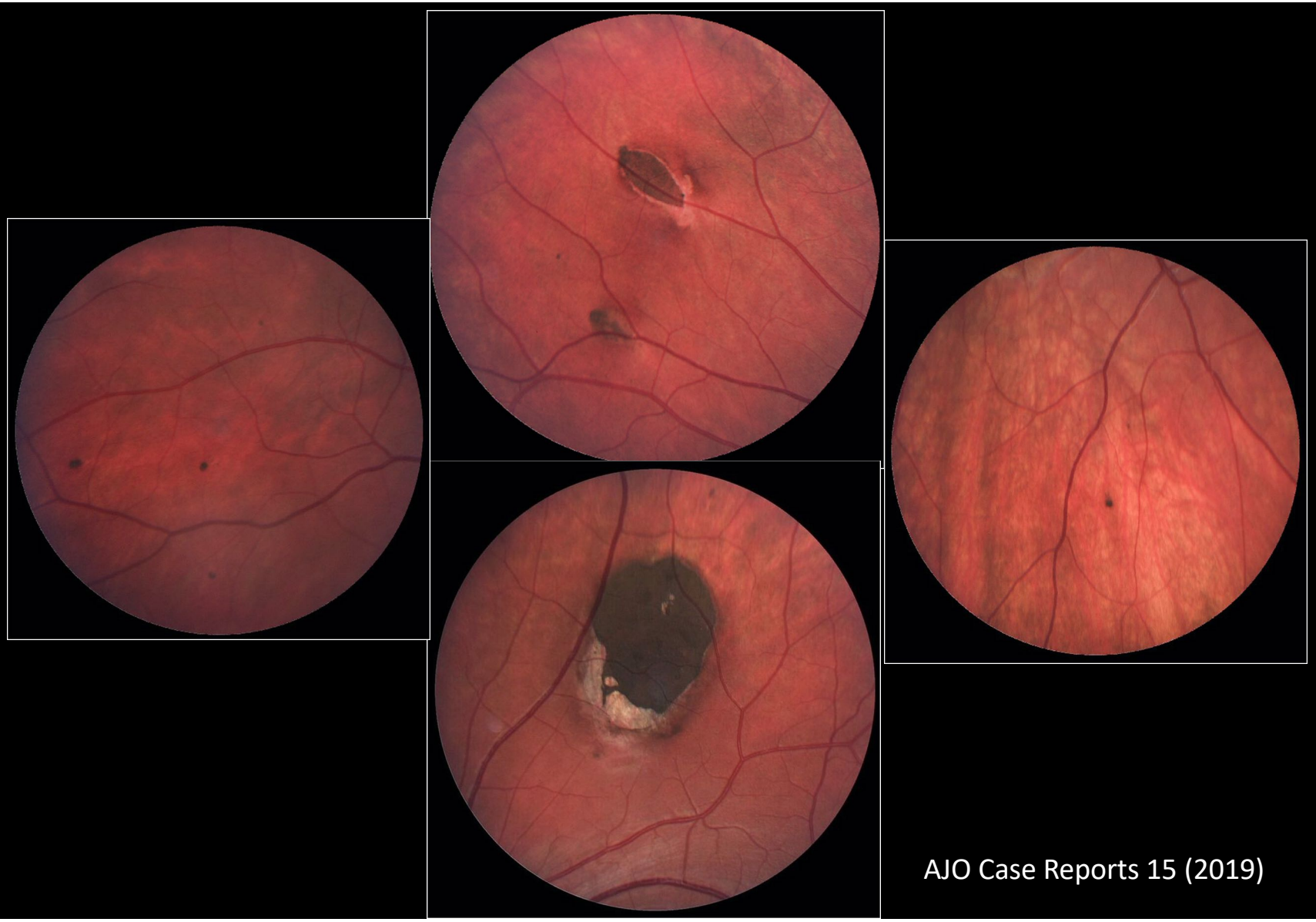

AJO Case Reports 15 (2019)

Malignant Neoplasms

- Uveal Melanoma
- Medulloepithelioma
- Retinoblastoma

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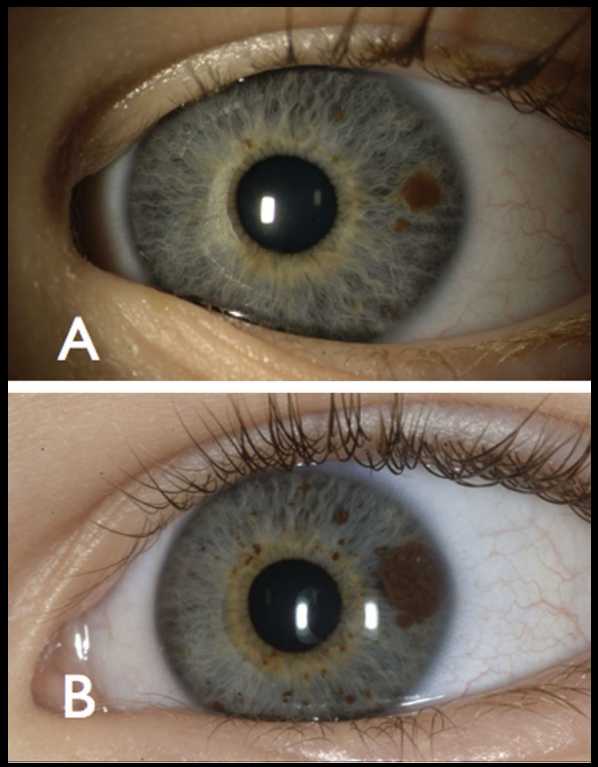
Uveal Melanoma

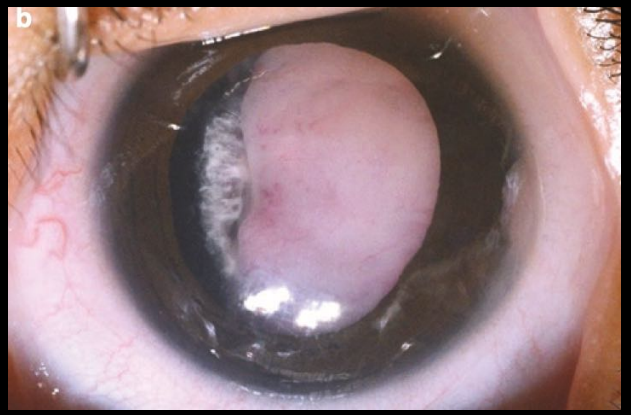
- 1% of cases occur < 20 year old
- Shields Data (2013)
  - No Cases before age 3
  - Location
    - Choroid 67%
    - Iris 25%
    - Ciliary Body 8%
  - Metastasis
    - 10 years: 8.8% (vs 25% for all ages)
    - 20 years: 20% (vs 36% for all ages)



Saudi Journal of Ophthalmology (2013) 27, 197–201

Medulloepithelioma

- Second most common primary intraocular neoplasm in children
  - Median age 2-5 years
  - 90% present in the first decade of life
  - Bilateral rare
- Embryonal neuroepithelial tumor
  - Undifferentiated nonpigmented ciliary epithelium in children
  - Hyperplastic ciliary epithelium in adults (inflamed or traumatized eyes)
- May be benign or malignant
- Discovered in:
  - Ciliary body
  - Iris
  - Retina
  - Optic nerve
  - CNS



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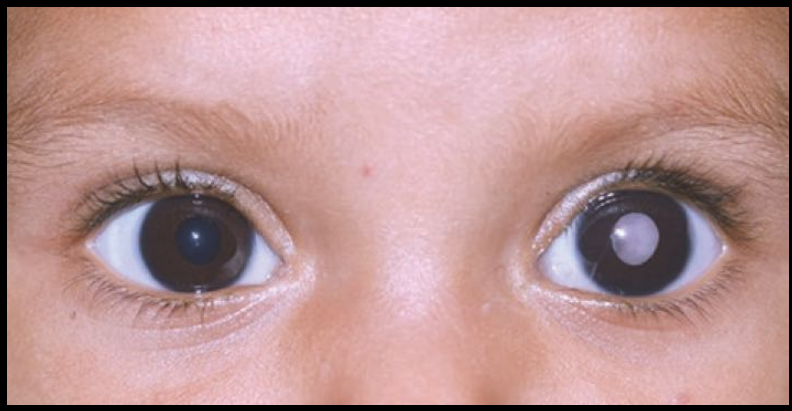
Medulloepithelioma



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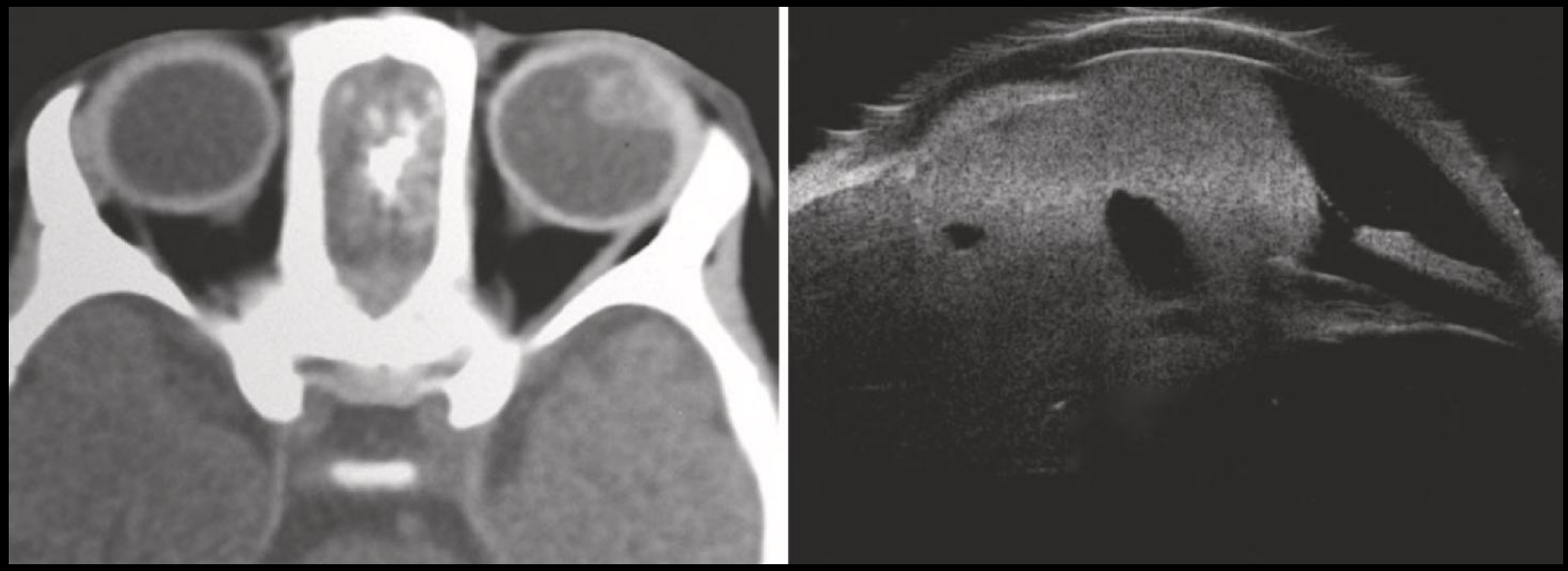
- Initial presentation
  - Poor vision (40%)
  - Pain (30%)
  - Leukocoria (18%)
- Clinical Signs
  - White/grey/yellow or fleshy pink non-pigmented mass in the ciliary body, iris or anterior chamber (50%)
  - Iris neovascularization (80%)
    - Secondary Glaucoma (50-60%)
  - Lens
    - Cataract with or without subluxation (25-50%)
    - lens ”coloboma”
    - Retrolental membrane (tumor growing along hyaloid face)
  - Cystic spaces within the tumor



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Medulloepithelioma

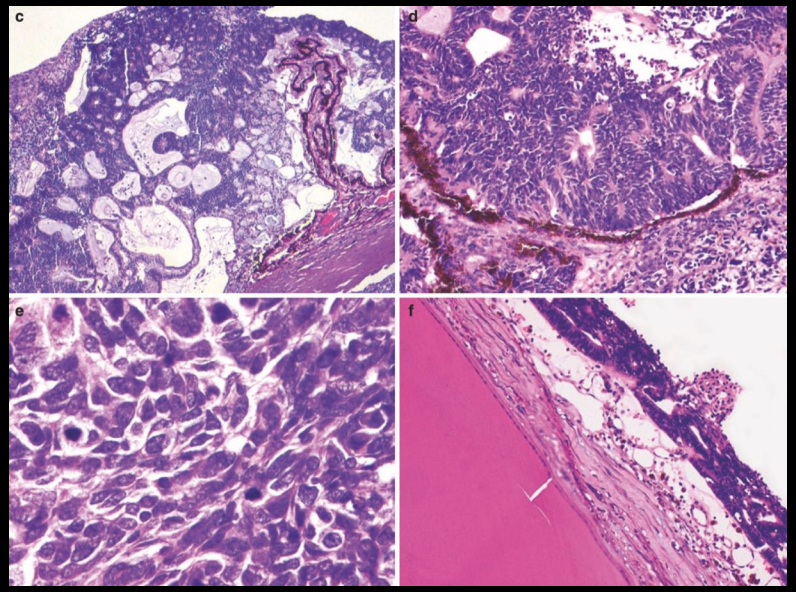
- Most are sporadic
- Associations
  - CNS malformations
    - Schizencephaly
    - Agenesis of the corpus callosum
    - Promient quadrigeminal plate
  - DICER 1-related pleuopulmonary blastoma (5%)
  - Retinoblastoma and pineoblastoma have occurred concurrently (single cases)

Medulloepithelioma- diagnosis

- Ultrasonography
  - Ciliary body origin
  - Heterogenous- irregular internal reflectivity
  - Intratumoral cystic spaces
  - Diffuse thickening of ciliary body
  - Teratoid type can have calcification
- CT
  - Used less commonly now
- MRI
  - Supportive and help confirm extraocular extension
  - Hyperintense in T1, hypointense in T2
  - Moderate intense contrast enhancement
- Fluorescein Angiography
  - Retrolental cyclitic membrane- rapid filling with large haphazard vessels from the ciliary body

Medulloepithelioma- histopathology

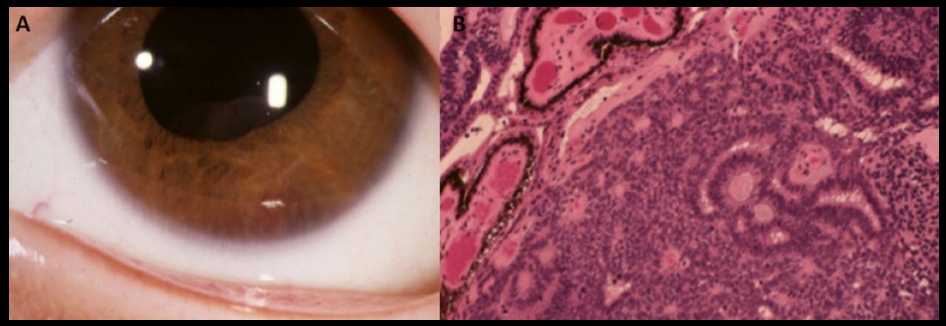
- Required for definitive diagnosis in most cases
  - Nests, sheets, cords and tubules of small round blue cells
  - Loose hyaluronic acid-rich mesenchymal tissue
  - Can contain rosettes
- Classification
  - Nonteratoid
    - Benign
    - Malignant
  - Teratoid
    - Benign
    - Malignant



Ocular Oncology in Retina Atlas Series, Springer 2019

Medulloepithelioma- prognosis

- Slow growing and locally invasive
- Many eyes go to enucleation
- Low risk of metastatic disease
  - Extraocular tumor extension
    - Optic nerve
    - Emissary veins
    - Inadvertent spread from intraocular surgery



Ophthalmology 2012;119:2507–2513

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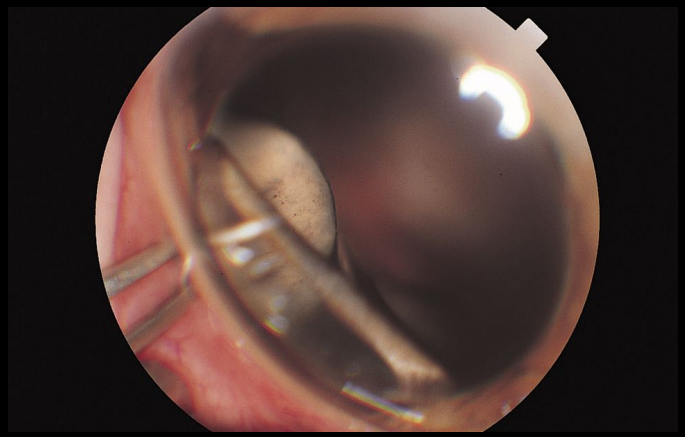
Medulloepithelioma- management

- Cryotherapy
  - Small or locally recurrent tumors
- Local resection?
  - Small tumors
  - High recurrence rates
    - Most end with enucleation
- Plaque Radiotherapy
  - Primary or adjuvant therapy after resection
- Enucleation
  - Large tumors or unresponsive smaller tumors
- External Beam Radiotherapy
  - Used as an adjuvant in extrascleral or orbital extension
- Chemotherapy
  - Not used for primary tumors
  - Adjuvant in in extrascleral or orbital extension or distant metastasis



Arch Ophthalmol. 2002;120(2):207-210

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Retinoblastoma

- Most common intraocular cancer in children
  - 1/15,000 – 20,000 (0.007% - 0.005%) live births
  - 300 new cases per year in USA
- 4% of all pediatric malignancies
- 97% survival with modern screening and treatment
  - Survival parallels economic development
    - Africa 30%
    - Asia 60%
    - Latin America 80%

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Retinoblastoma- clinical features

- Presentation
  - Leukocoria 56%
  - Strabismus 24%
  - Poor vision 8%
- Median age 15 months
- 51% male
- 53% unilateral
- Variable presentation
  - Small nearly translucent tumors
  - Large tumors with dilated vessels, vitreous seeding and retinal detachment

- Growth Patterns
  - Intraretinal
  - Endophytic (growth into the vitreous)
  - Exophytic (growth under the retina)
  - Diffuse infiltrating (simulating uveitis or endophthalmitis)

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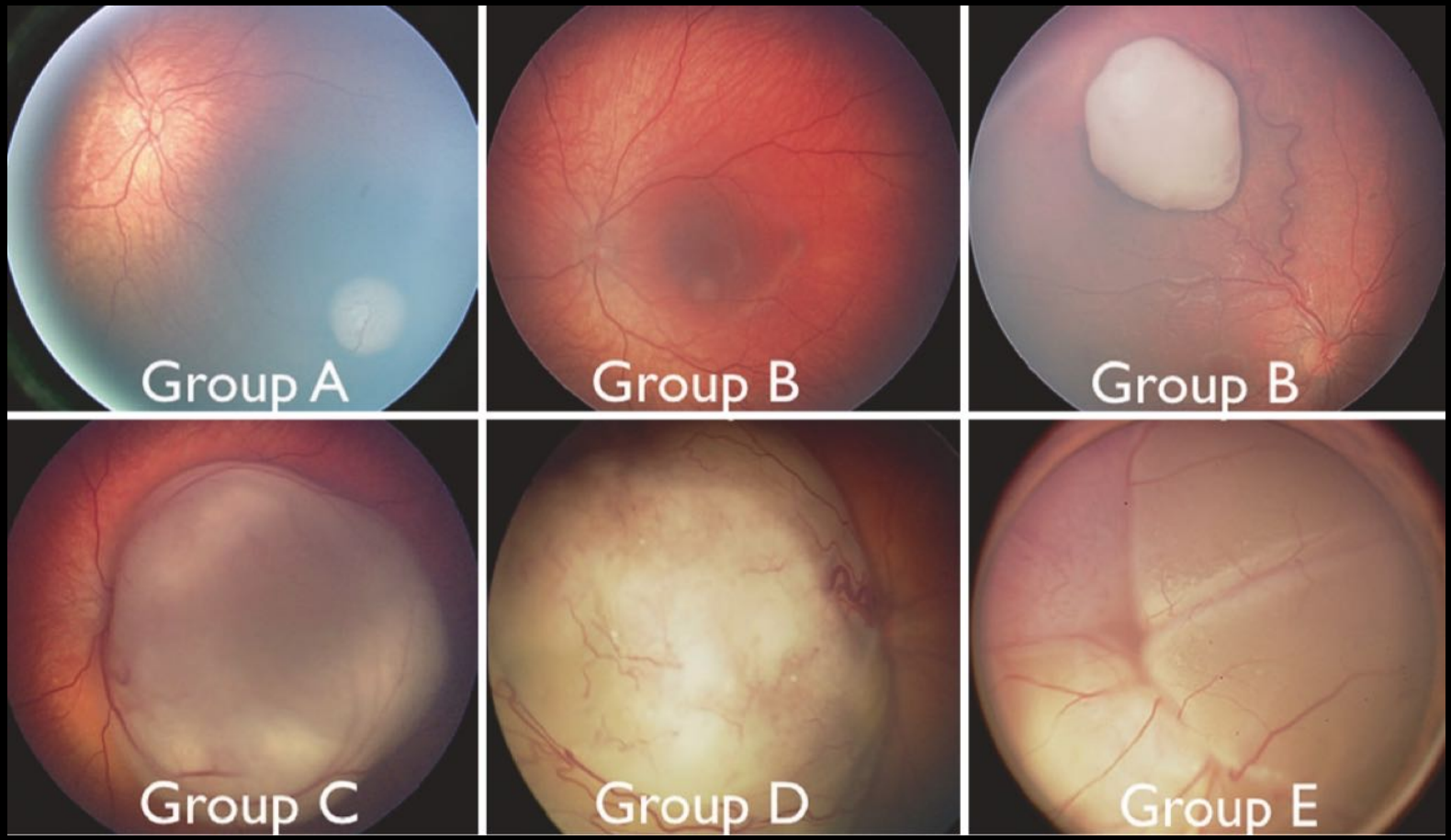
Retinoblastoma- Classification

- International classification

Group	Summary	Sub-Group	Specific Features
A	Small Tumor		Tumor ≤ 3mm (in greatest dimensions)
B	Large Tumor		Tumor >3mm or macular retinoblastoma location (≤3 mm to foveola) juxtapupillary retinoblastoma location (≤1.5 mm to disc) additional subretinal fluid (≤3 mm from margin)
C	Focal seeds	C1	Subretinal Seeds ≤ 3 mm from tumor
		C2	Vitreous Seeds ≤ 3 mm from tumor
		C3	Both Subretinal and vitreous seeds ≤ 3mm from tumor
D	Diffuse Seeds	D1	Subretinal seeds >3 mm from tumor
		D2	Vitreous seeds >3 mm from tumor
		D3	Both subretinal and vitreous seeds > 3 mm from tumor
E	Extensive retinoblastoma		Extensive tumor occupying >50% globe or neovascular glaucoma, opaque media from hemorrhage in anterior chamber, vitreous or subretinal space invasion of postlaminar optic nerve, choroid (>2 mm), sclera, orbit, anterior chamber



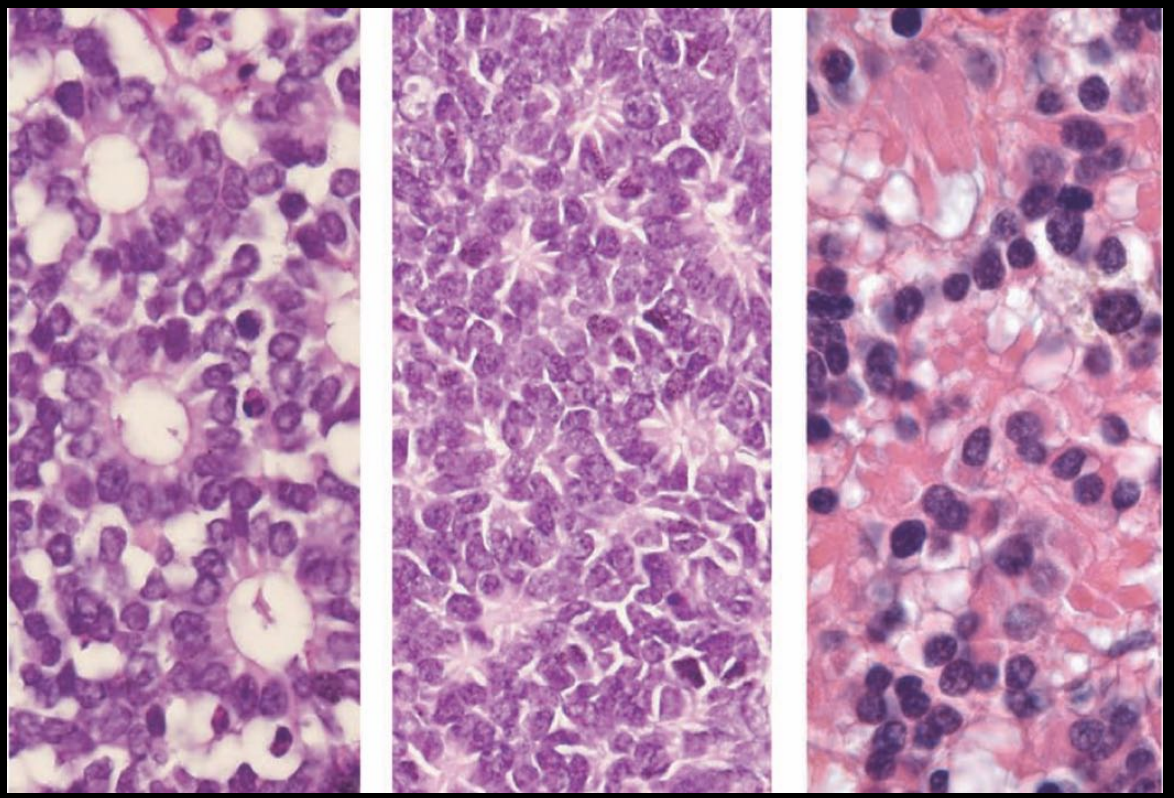
Ocular Oncology in Retina Atlas Series, Springer 2019

Retinoblastoma- diagnostic testing

- Eye exam
  - Retinal tumor with calcification
- Ultrasound
  - Solid tumor with calcification and orbital shadowing
  - 5% have no calcification
- MRI orbits and Brain
  - Assess optic nerve, orbit and Brain (especially parasellar & pineal area)
- Needle Biopsy contraindicated due to tumor seeding

Retinoblastoma- histology

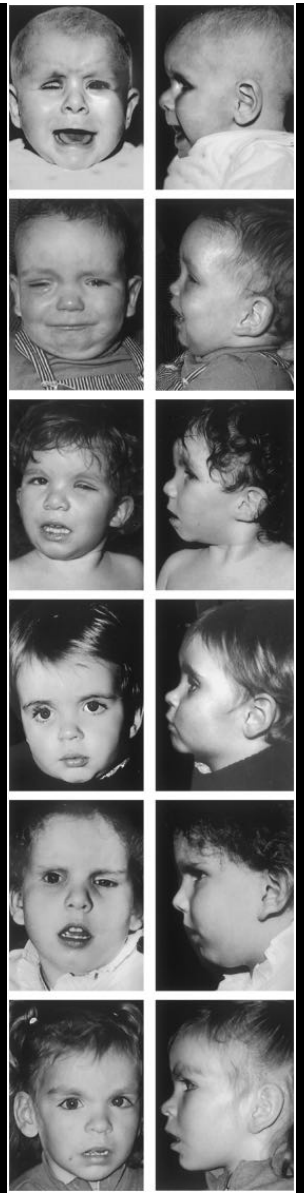
- Small hyperchomatic cells with large nuclei
- Large areas of necrosis
- Multifocal calcifications
- Rosettes
  - Flexner-Wintersteiner
  - Homer Wright
- Fleurettes



Retinoblastoma. Springer 2010

Retinoblastoma- genetics

- RB1 mutation
  - Tumor suppressor gene (13q14)
  - Germline
    - Usually bilateral
      - Unilateral germline tumors in 10-15%
    - Often familial
    - Heritable
  - Somatic
    - Unilateral
    - Not heritable
  - 13q deletion syndrome
    - Dysmorphic features,
    - Mental and motor delays
    - Genital malformation, perineal fistula
    - Digit abnormalities



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Baud et. al. Clin. Genet 1999:55-478-82

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Retinoblastoma- Treatment

- Small tumors (<3 mm) without seeding can be treated with local therapy
  - Photocoagulation (532 or 810 nm laser)
  - Transpupillary Thermotherapy (810 nm laser with large spot size)
  - Cryotherapy
- Larger tumors require chemo reduction
  - Systemic (vincristine, carboplatin, etoposide) 6 cycles 1 month apart
  - Intra-arterial (melphalan, carboplatin, topotecan) 2-6 cycles 1 month apart
- Vitreous seeding
  - Intravitreal melphalan (+/-topotecan)

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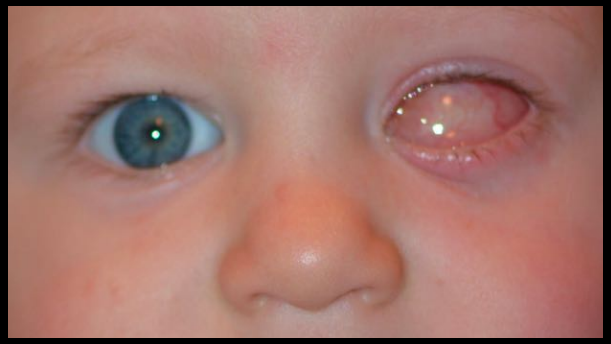
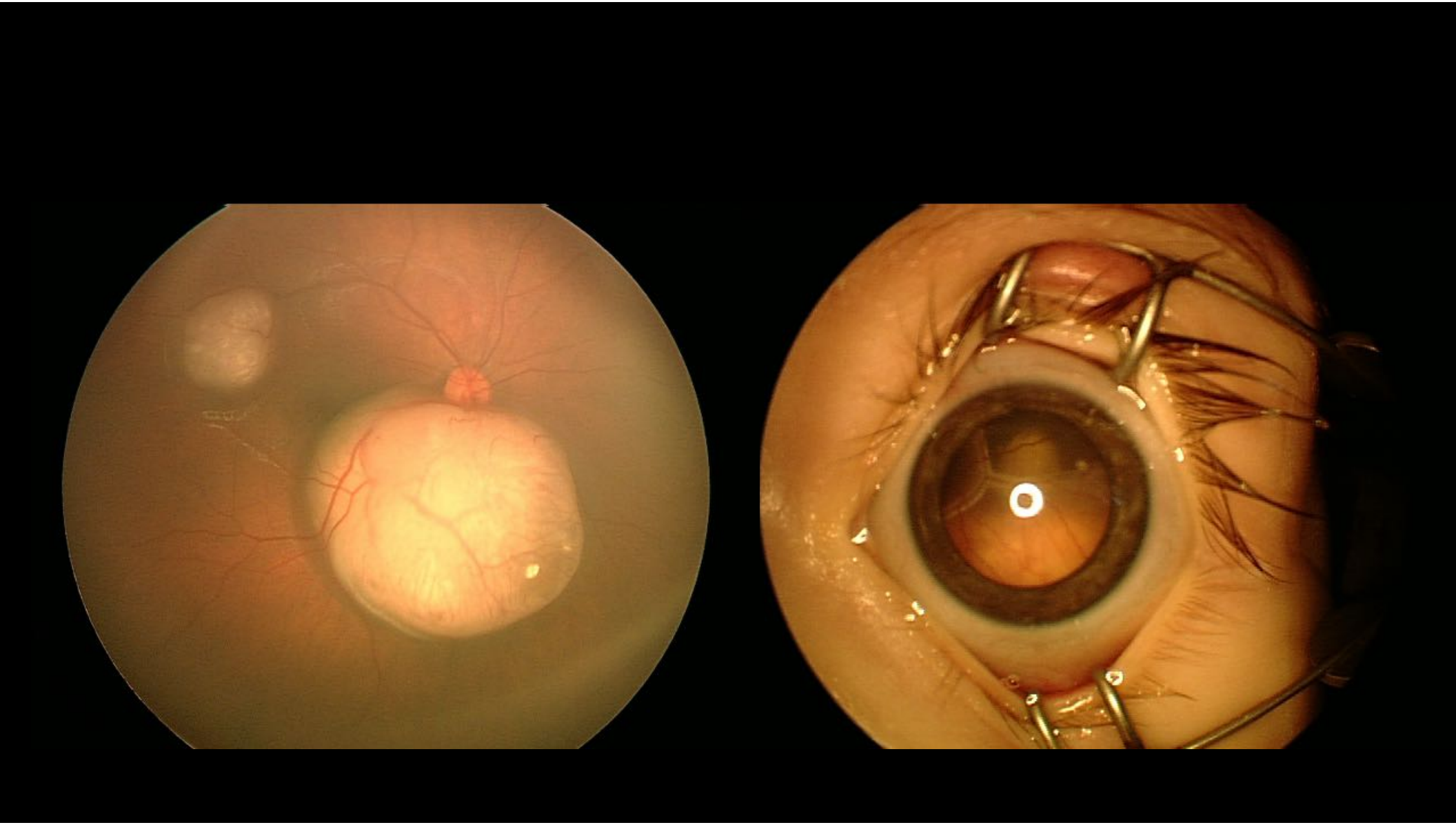
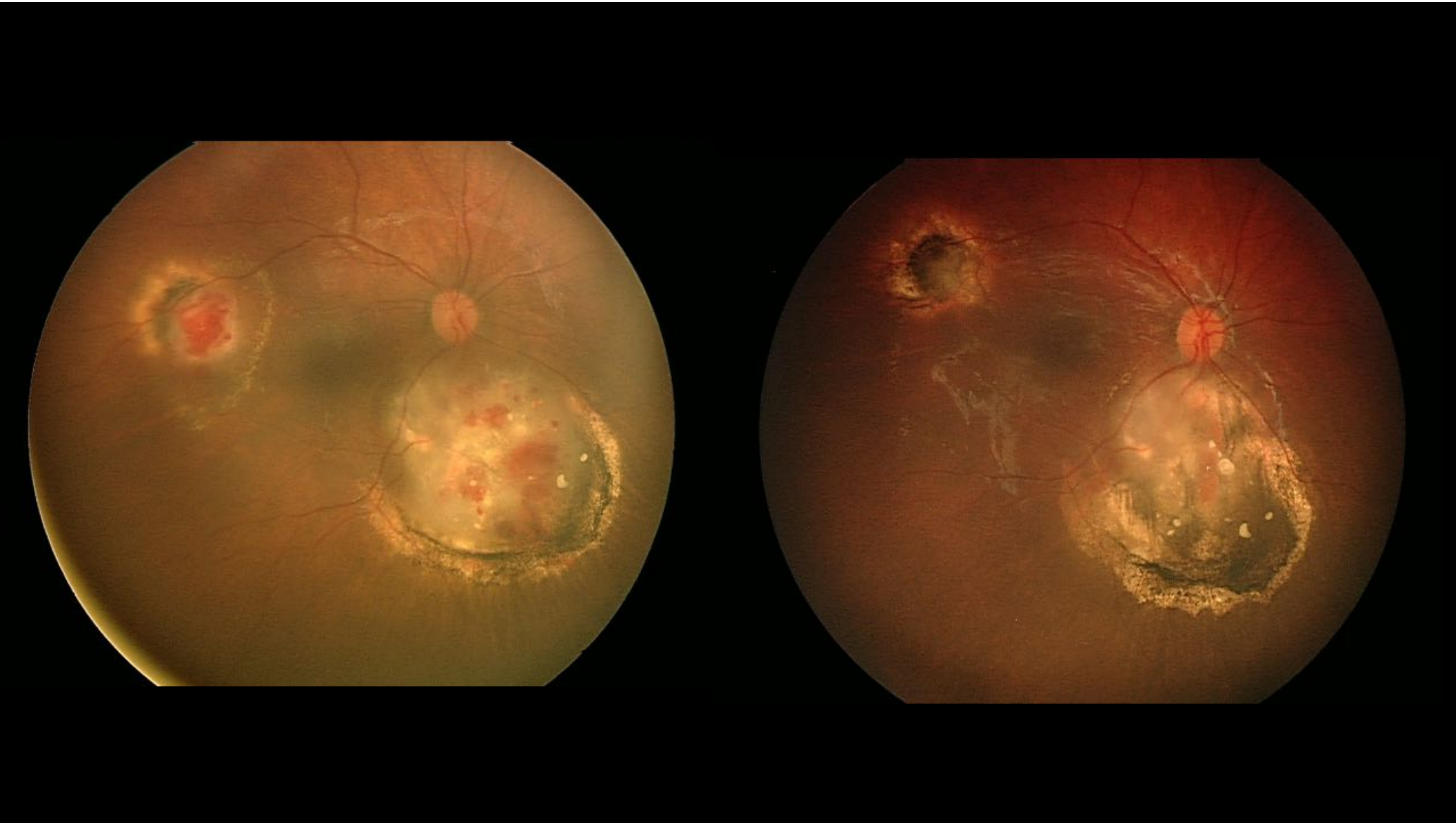
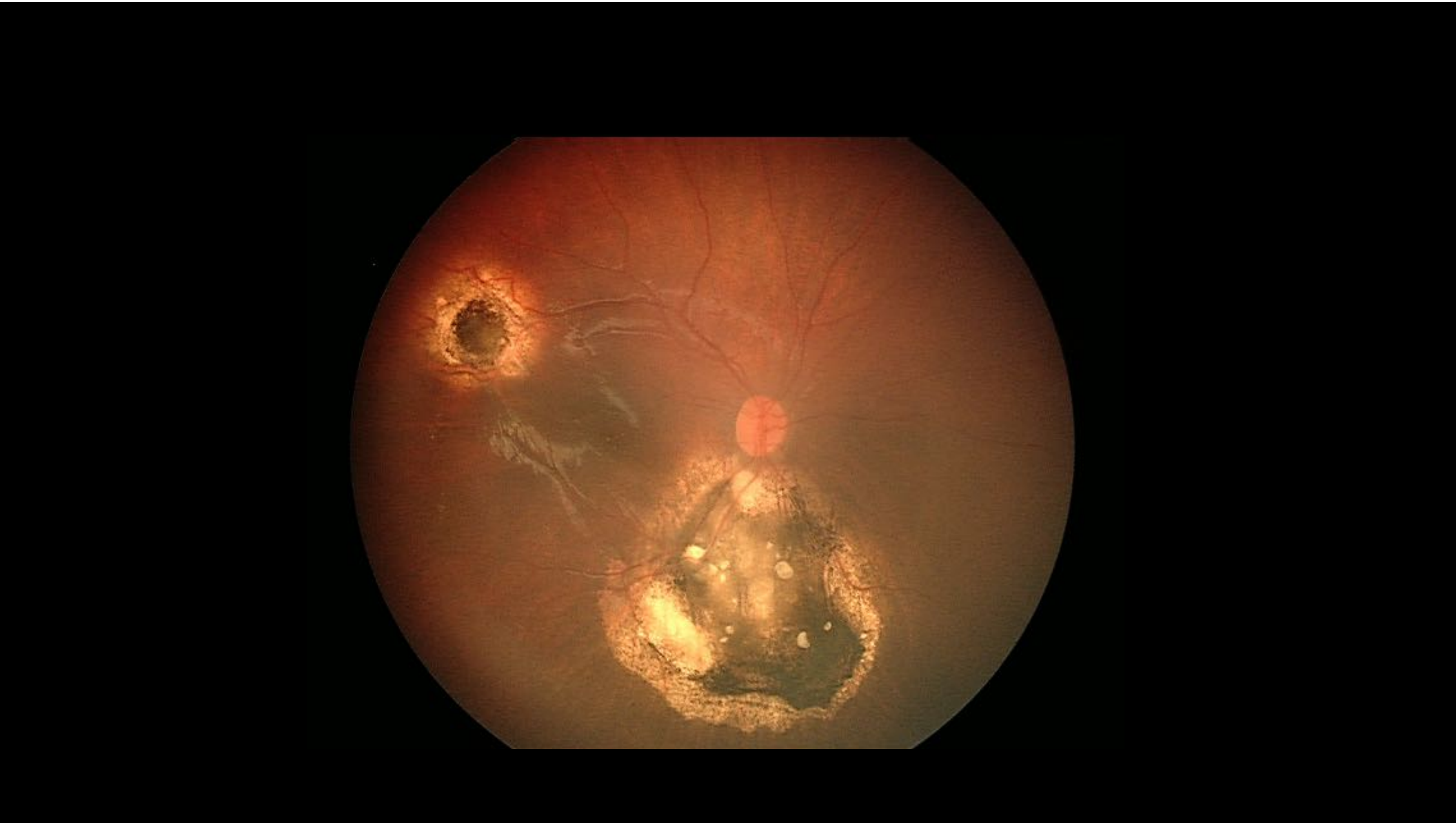
Retinoblastoma- Treatment

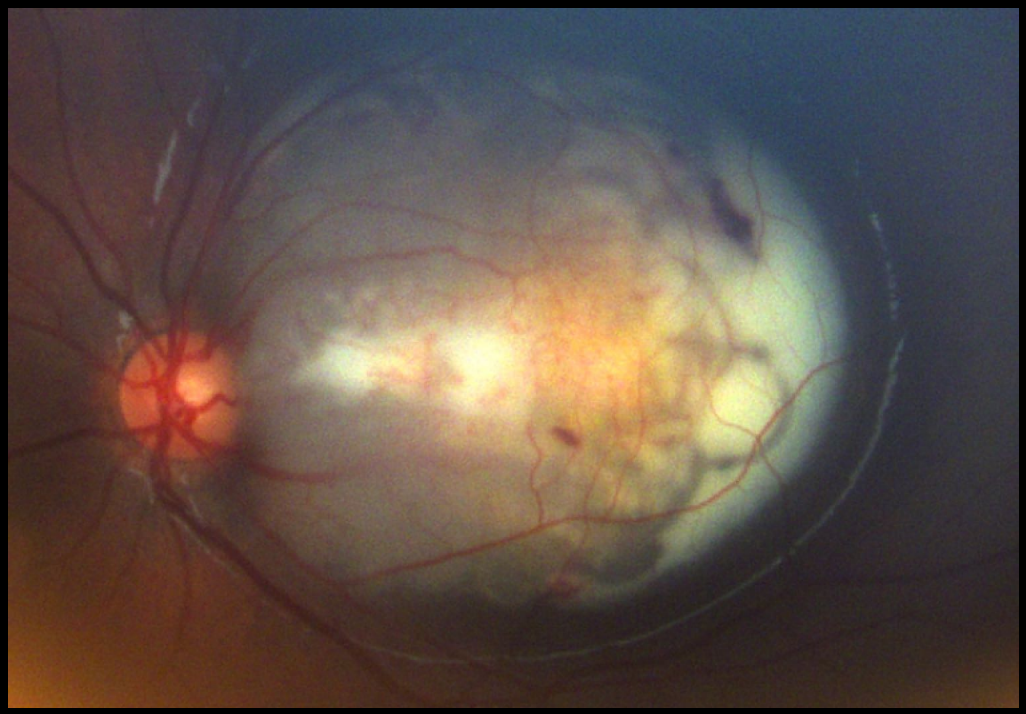
- Resistant Tumors
  - Intravitreal melphalan (+/-topotecan)
  - Brachytherapy
  - External Beam radiotherapy
- Enucleation
  - Instantly reduces tumor burden
  - Histologic diagnosis of high-risk features
  - Genetic testing is amplified with tumor tissue

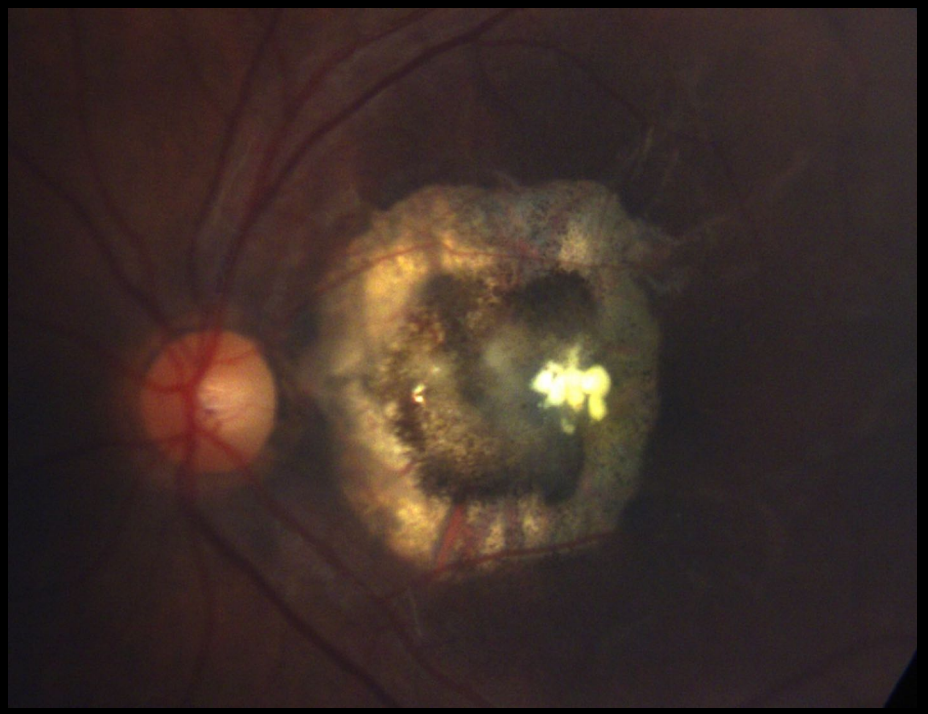


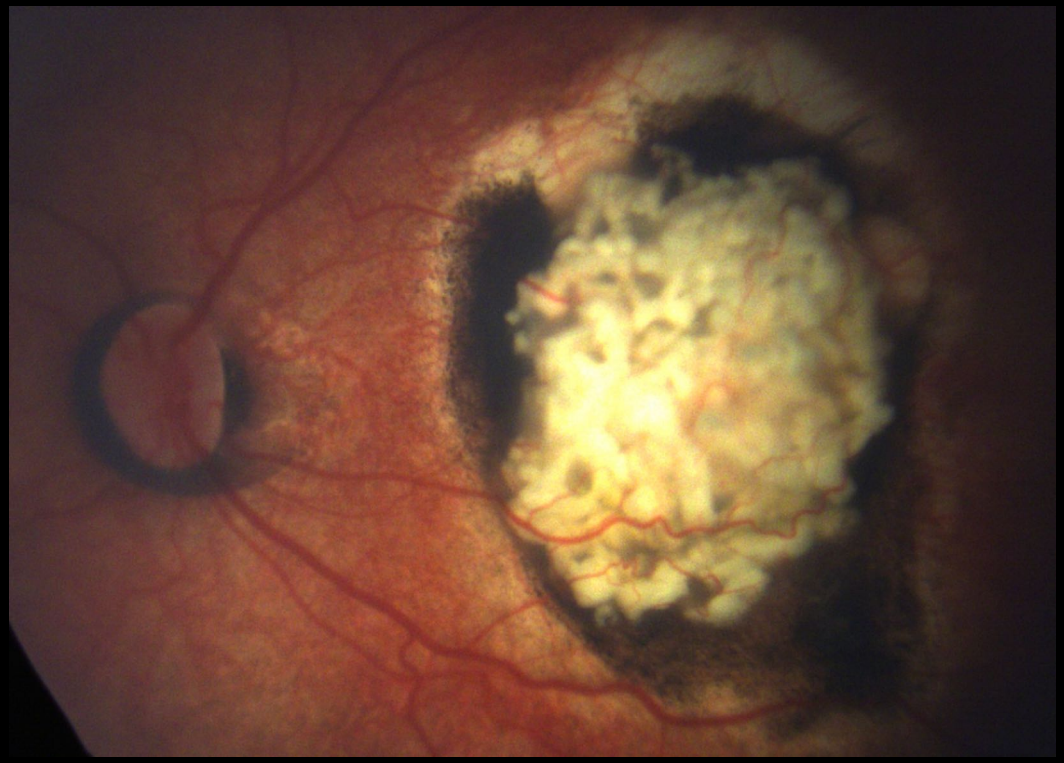


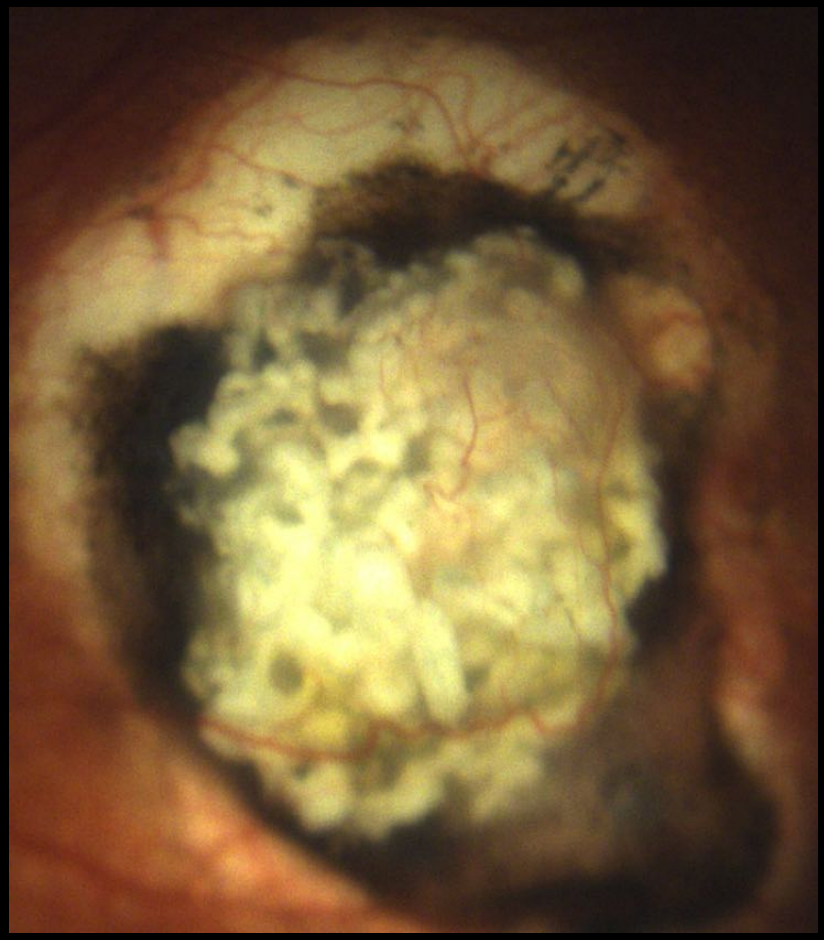


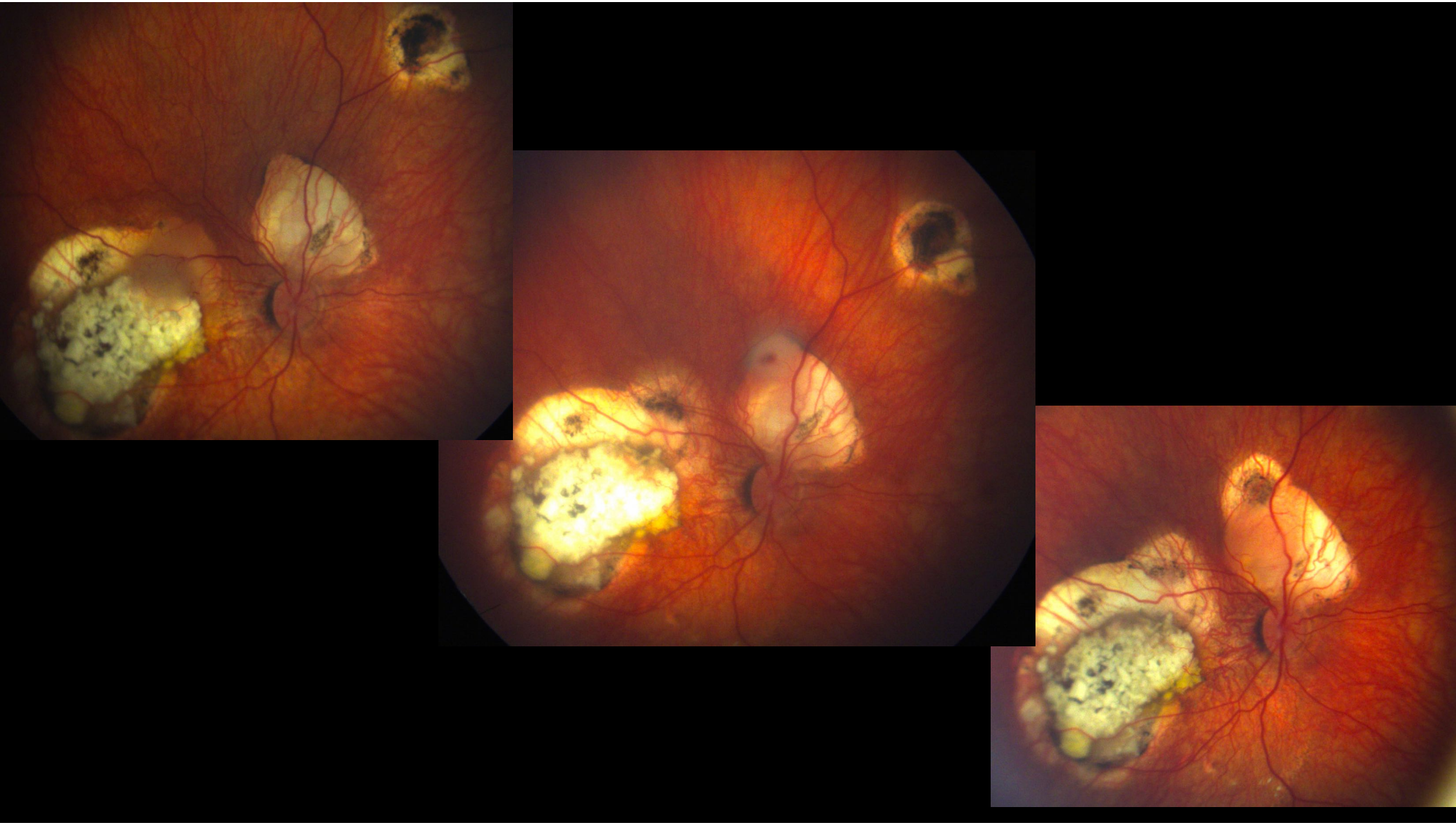


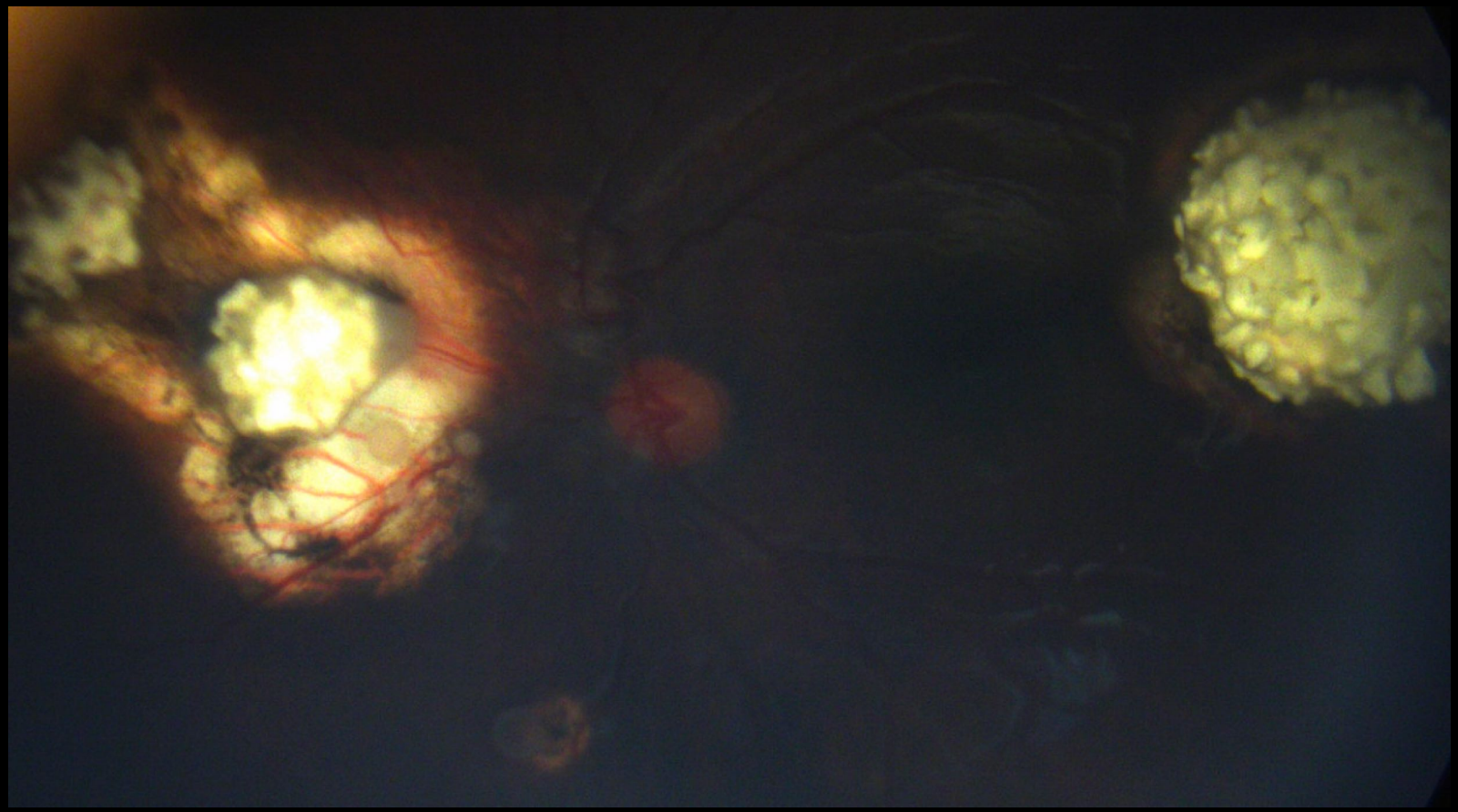












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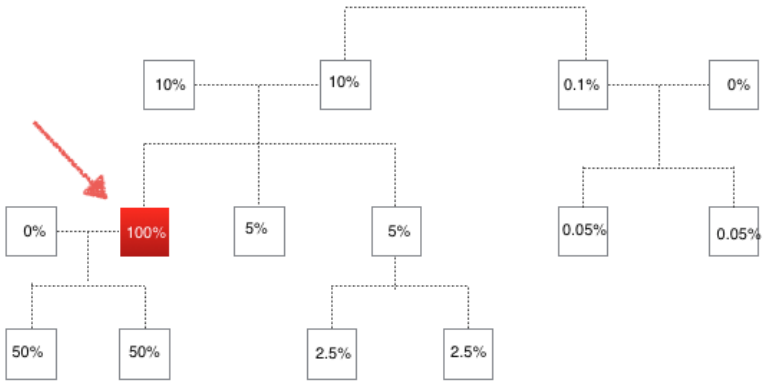
Retinoblastoma Monitoring

- Life threatening risks
  - Metastasis
    - Higher risk with invasion beyond lamina cribrosa, anterior chamber, choroid, sclera and orbit
    - Systemic chemotherapy reduces risk
  - Intracranial neuroblastic malignancy (trilateral disease)
    - Pineoblastoma or parasellar tumors
  - Other primary cancers (30% cumulative incidence after 30 years)
    - Higher risk with external beam radiotherapy
    - #1 Osteogenic sarcoma of the femur
    - Others: soft tissue, nasal, melanoma, brain
    - Any type of neoplasm possible

Bilateral & Familial RB Screening

Name: _____

Relation to Proband: _____



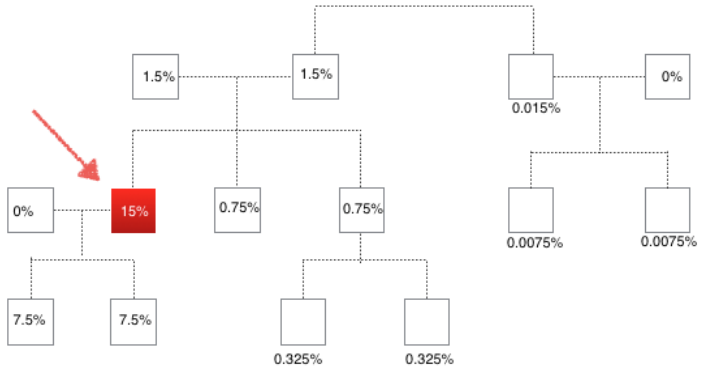
Age / Risk	1wk	6wk	3m	6m	9m	12m	16m	20m	24m	30m	3y	3.5y	4y	4.5y	5y	5.5y	6y	6.5y	7y	Yearly
100 50 5 2.5	Clinic	Clinic	Clinc	EUA	EUA	EUA	EUA	EUA	EUA	EUA	EUA	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic
	1wk		3m	6m	9m	12m	18m		24m	30m	3y	3.5y	4y	4.5y	5y	5.5y	6y	6.5y	7y	Yearly
0.1 0.05	Clinic	none	Clinic	EUA	EUA	EUA	EUA	none	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	none	Clinic	Clinic

https://childrenseye.org/wiki/doku.php?id=retinoblastoma_screening_schedules

Unilateral RB Screening

Name: _____

Relation to Proband: _____



Age / Risk	1wk	6wk	3m	6m	9m	12m	16m	20m	24m	30m	3y	3.5y	4y	4.5y	5y	5.5y	6y	6.5y	7y	Yearly
15 7.5 0.75 0.32	Clinic	Clinic	Clinc	EUA	EUA	EUA	EUA	EUA	EUA	EUA	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic
	1wk		3m	6m	9m	12m	18m		24m	30m	3y	3.5y	4y	4.5y	5y		6y		7y	yearly
0.015 0.007	Clinic	none	Clinic	Clinic	Clinic	Clinic	Clinic	none	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	Clinic	none	Clinic	none	Clinic	Clinic

impact genetics

	proband	relative	NO molecular testing: risk for *RB1* mutation	NO molecular testing: Surveillance plan	Proband *RB1* mutation found (96%) (15% for unilateral): positive blood test: risk for *RB1* mutation	positive blood test: Surveillance plan	negative blood test: risk for RB1 mutation	negative blood test: Surveillance plan	Proband *RB1* mutation NOT found (4%*) (nothing to test for relative): risk for *RB1* mutation	Surveillance plan
Conventional clinical care		proband	100%	**EUAs**	100%	**EUAs**	na	na	100%	**EUAs**
		offspring	50% (0.5 x 1)	**EUAs**	100%	**early delivery cancer surveillance**	0.007%	clinic	50% (0.5 x 1)	**EUAs**
Personalized clinical care based on genetics	bilateral	unaffected parent	4% (0.04* x 1)	retinal exam for retinoma	100%	retinal exam for retinoma **cancer surveillance**	4% (0.04* x 1)	retinal exam for retinoma	4% (0.04* x 1)	retinal exam for retinoma
		sibs	2% (0.04* x 1 x 0.5)	**EUAs**	100%	**early delivery clinic visits EUAs cancer surveillance**	0.007%	clinic	2% (0.04* x 1 x 0.5)	**EUAs**
	unilateral NO tumor available	proband	15%	**EUAs**	100%	**EUAs**	0.6% (0.04 x 0.15)	clinic exams	15%	**EUAs**
		offspring	7.5% (0.5 x 0.5)	**EUAs**	100%	**early delivery clinic visits EUAs cancer surveillance**	0.3% (0.04 x 0.15 x 0.5)	clinic exams	7.5% (0.5 x 0.5)	**EUAs**
		unaffected parent	0.6% (0.04* x 0.15)	retinal exam for retinoma	100%	retinal exam for retinoma **cancer surveillance**	0.24% (0.04* x 0.04* x 0.15)	retinal exam for retinoma	0.6% (0.04* x 0.15)	retinal exam for retinoma
		sibs	0.3% (0.04* x 0.15 x 0.5)	**EUAs**	100%	**early delivery clinic visits EUAs cancer surveillance**	0.012% (0.04* x 0.15 x 0.04* x 0.5)	clinic exams	0.3% (0.04* x 0.15 x 0.5)	**EUAs**
	unilateral **tumor** *RB1* mutations found (96%)	proband	15%	**EUAs**	100%	**EUAs cancer surveillance**	0.024% (0.04* x 0.15 x 0.04*)	clinic exams	*2 tumor mutations not detected in blood*	
		offspring	7.5% (0.15 x 0.5)	clinic exams	100%	**early delivery clinic visits EUAs cancer surveillance**	0.012% (0.04* x 0.15 x 0.04* x 0.5)	clinic exams		
		unaffected parent	0.6% (0.04 x 0.15)	retinal exam for retinoma	100%	retinal exam for retinoma cancer surveillance	0.001% (0.04* x 0.15 x 0.04* x 0.04*)	**population risk**		
		sibs	0.3% (0.04 x 0.15 x 0.5)	**EUAs**	100%	**early delivery clinic visits EUAs cancer surveillance**	0.0005% (0.04* x 0.15 x 0.04* x 0.04* x 0.5)	**population risk**		
	unilateral tumor *RB1* normal, *MYCN* amplified (2%)**	proband	15%	**EUAs**	na	na	0.007%	**population risk****		
		offspring	7.5% (0.15 x 0.5)	clinic exams	na	na	0.007%	**population risk****		
		unaffected parent	0.6% (0.04 x 0.15)	retinal exam for retinoma	na	na	0.007%	**population risk****		
		sibs	0.3% (0.04 x 0.15 x 0.5)	**EUAs**	na	na	0.007%	**population risk****	***Rushlow et al. The lancet oncology. 2013 Apr;14:327-34.*	

Population risk 1:15000 per live birth 0.007%

Risk for offspring of RB1 mutant parent 50%

**Risk to miss RB1 mutant allele or that parent is unaffected carrier (most undetectable mosaic)* 4%

*** Based on Rushlow et al 2013, unconfirmed*

na; not applicable

impactgenetics.com

https://childrenseye.org/wiki/doku.php?id=retinoblastoma_screening_schedules

Retinoblastoma- mimickers

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Table 10.2 Pseudoretinoblastoma in 604 children

Pseudoretinoblastoma diagnosis	All ages $n = 604$ (%)
Coats disease	244 (40)
Persistent fetal vasculature PFV	158 (26)
Vitreous hemorrhage	27 (5)
Toxocariasis	22 (4)
Familial exudative vitreoretinopathy FEVR	18 (3)
Rhegmatogenous retinal detachment	18 (3)
Coloboma	17 (3)
Astrocytic hamartoma	15 (2)
Combined hamartoma	15 (2)
Endogenous endophthalmitis	10 (2)
Myelinated nerve fibers	9 (1)
Congenital cataract	8 (1)
Peripheral uveoretinitis	7 (1)
Retinopathy of prematurity	7 (1)
Non-rhegmatogenous retinal detachment	5 (<1)
Medulloepithelioma	4 (<1)
X-linked retinoschisis	4 (<1)
Vitreoretinal tuft	3 (<1)
Incontinentia pigmenti	2 (<1)
Juvenile xanthogranuloma	2 (<1)
Norrie's disease	2 (<1)
Vasoproliferative tumor	2 (<1)
Choroidal osteoma	1 (<1)
Morning glory disc anomaly	1 (<1)
Retinal capillary hemangioma	1 (<1)
Retrolental fibrosis	1 (<1)
Toxoplasmosis	1 (<1)

Adapted from Shields CL, Schoenfeld E, Kocher K, et al. Lesions simulating retinoblastoma (pseudoretinoblastoma) in 604 cases. Ophthalmology 2013;120:311-6