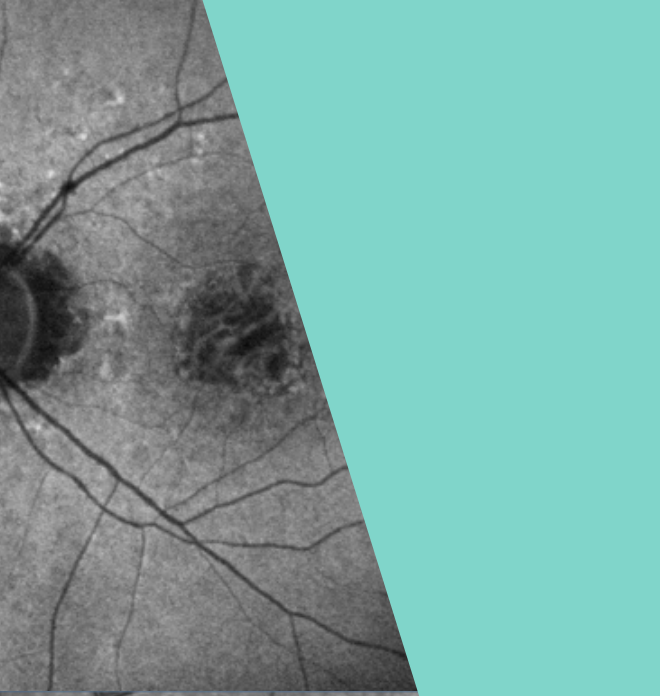
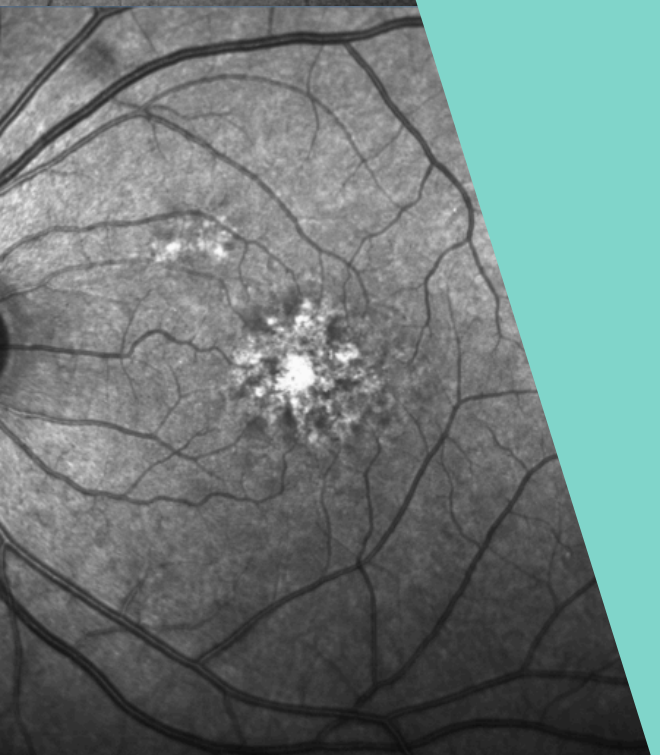
Characteristics, Risk Factors and Visual Significance of Blood-Brain Barrier Disruption Maculopathy: A Common Side-effect of a Systemic Therapy

Joseph Simonett MD, Alison Skalet MD PhD, Brandon Lujan MD, Phoebe Lin MD PhD

Retina Society 2020

OHSU
CASEY EYE Institute
MORAN EYE CENTER





I have no financial disclosures.

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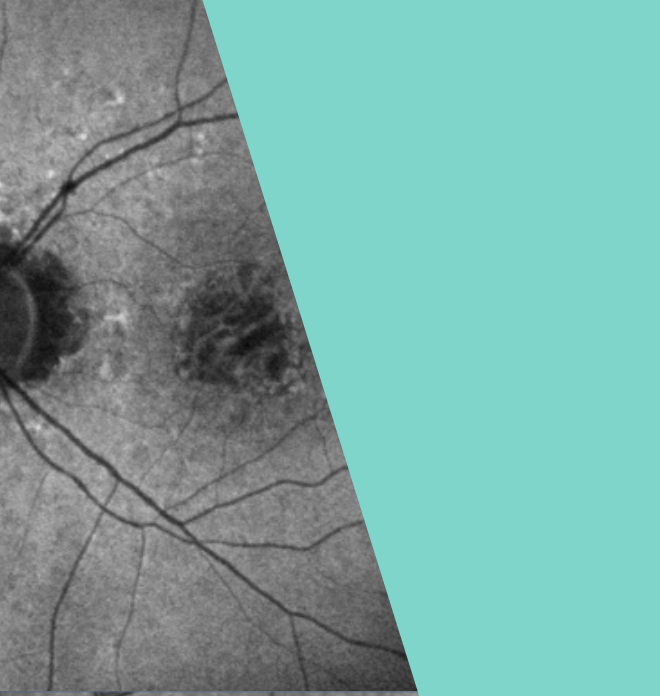
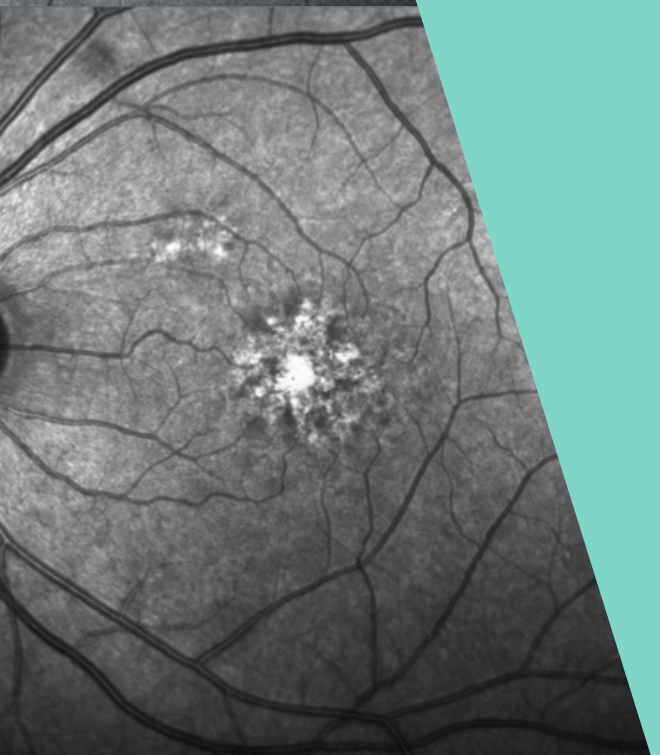




Summary:

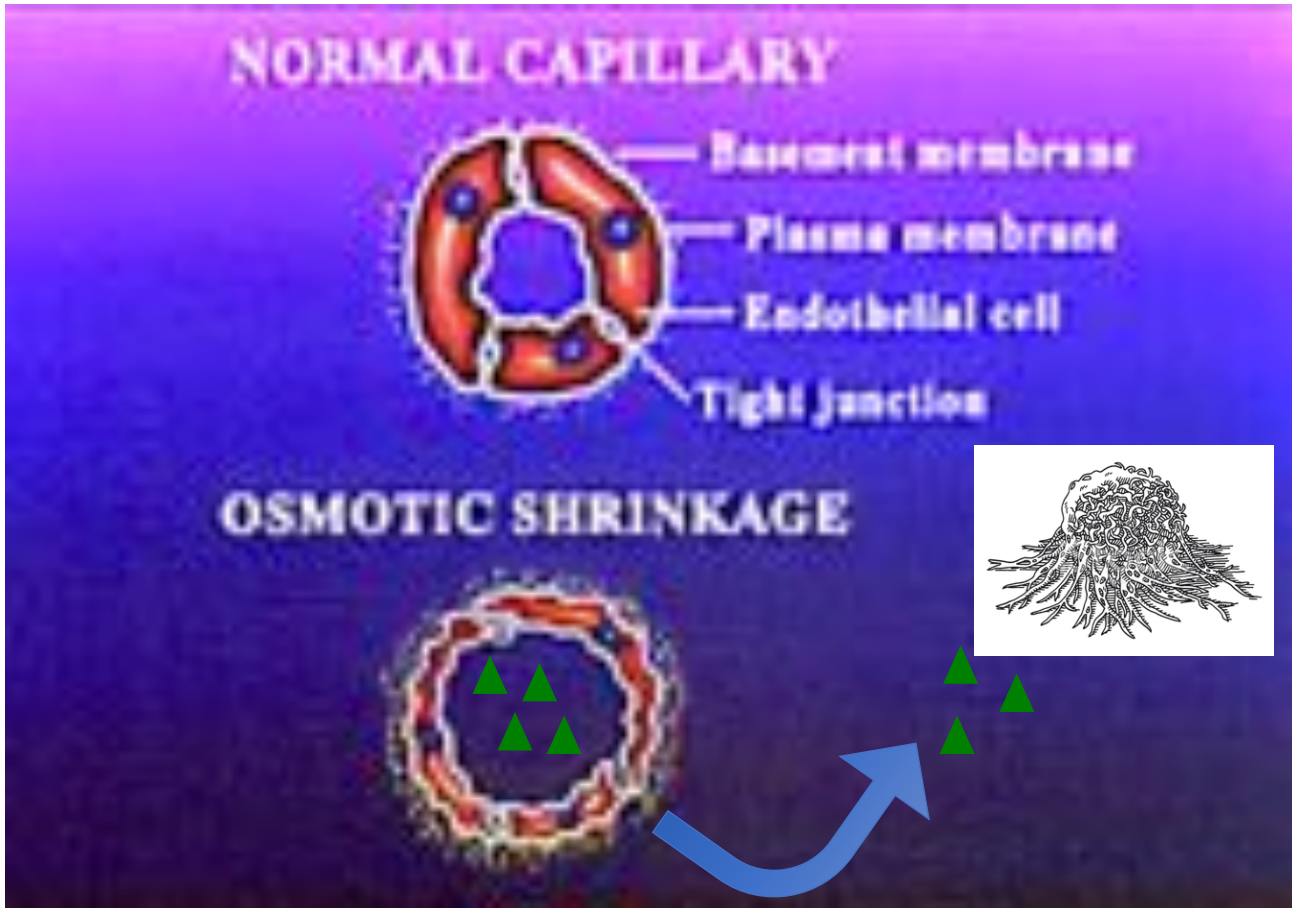
Study

- Retrospective review and post-treatment progression analysis of maculopathy in patients treated with osmotic Blood-Brain Barrier Disruption (BBBD) for CNS malignancies.

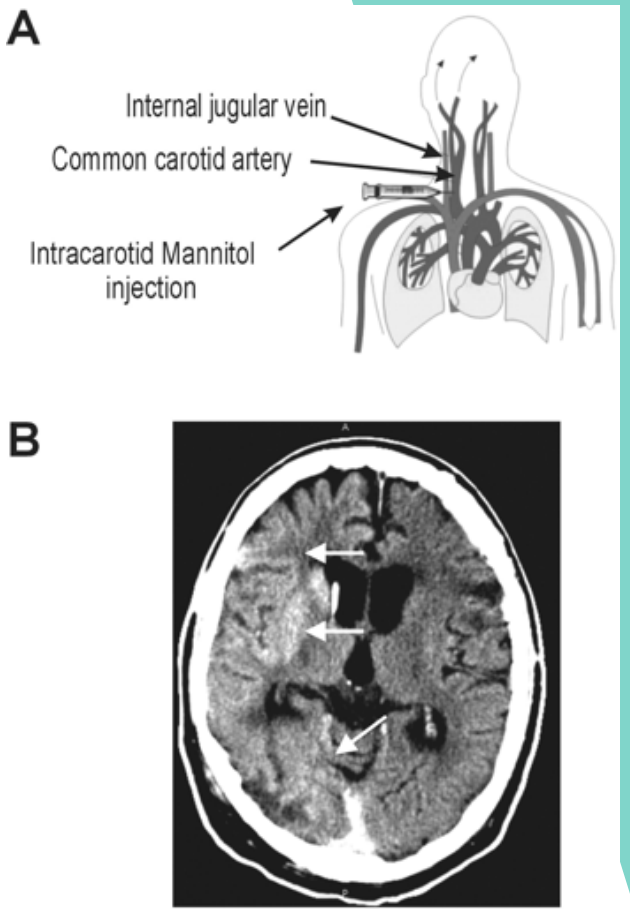
Key Findings

- BBBD associated maculopathy is common, dose dependent, and not related to underlying CNS malignancy or systemic chemotherapy agent.
- Visually significant progression (RPE and outer retinal atrophy or CNV) can occur years after completion of BBBD therapy.
- Transient, recurrent disruption of the outer blood-retinal barrier is a possible mechanism.

Osmotic blood-brain barrier disruption (BBBD)



SI Rapoport, Blood-Brain Barrier in Physiology and Medicine. Raven Press, 1976



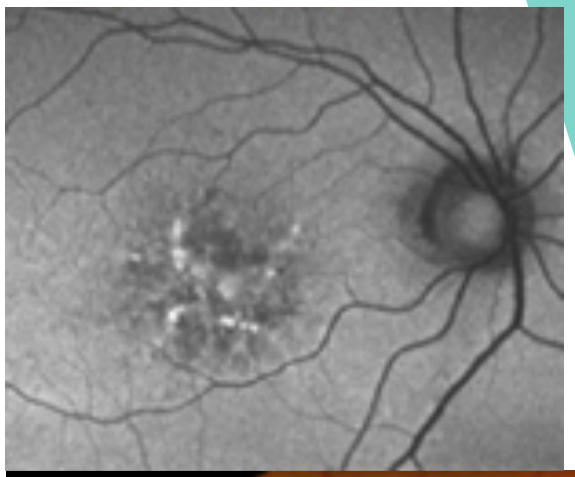
Marchi N et al. Serum transthyretin monomer as a possible marker of blood-to-CSF barrier disruption. *J Neurosci.* 2003.

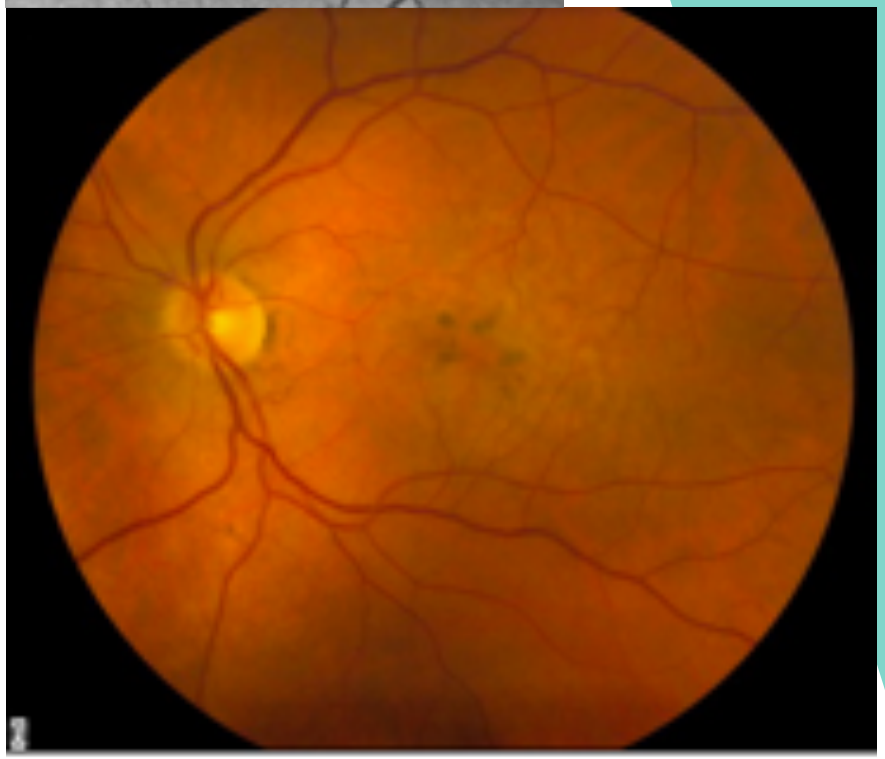
Osmotic BBBD associated Maculopathy

American Journal of Ophthalmology
Volume 102, Issue 5, November 1986, Pages 626-632

Maculopathy Associated With Combination Chemotherapy and Osmotic Opening of the Blood-Brain Barrier

Robert H. Millay M.D. [1], Michael L. Klein M.D. [1], W. Thomas Shults M.D. [1], Suellen A. Dahlborg [2], Edward A. Neuwelt M.D. [2]





Galor A, et al. Maculopathy as a Complication of Blood-Brain Barrier Disruption in Patients with Central Nervous System Lymphoma. *Am J Ophthalmol*. 2007.

Vicuna-kojchen J et al. Maculopathy in patients with primary CNS lymphoma treated with chemotherapy in conjunction with blood-brain barrier disruption. *Br J Ophthalmol.* 2008.

Pal BP et al. MULTIMODAL IMAGING DURING THE EVOLUTION OF BLOOD-BRAIN BARRIER DISRUPTION MACULOPATHY. *Retin Cases Brief Rep.* 2019.

Unanswered Questions:

- Frequency?
- Predictors?
- Visually Significant Progression?

Methods:

- Retrospective review of all patients treated with BBBD at OHSU

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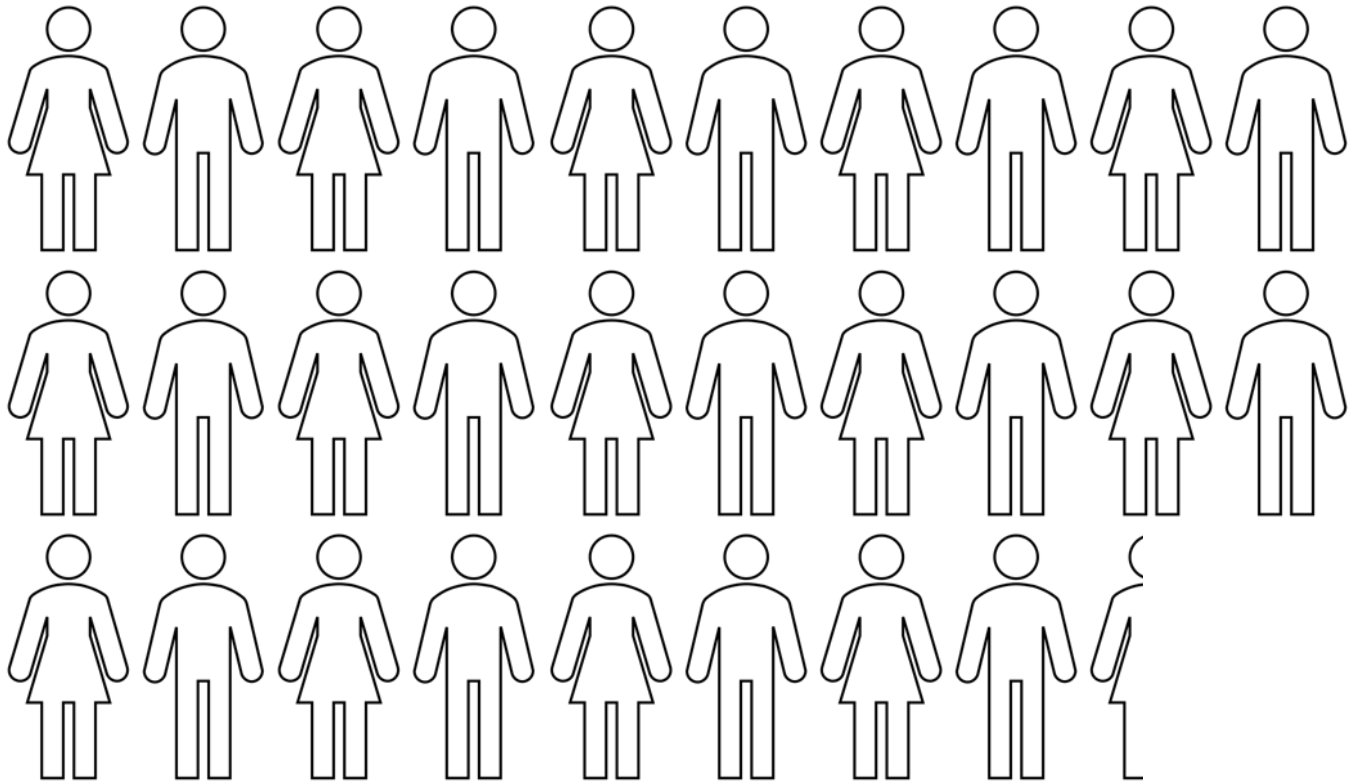
- Post-treatment progression analysis

Patients treated with BBBD at OHSU

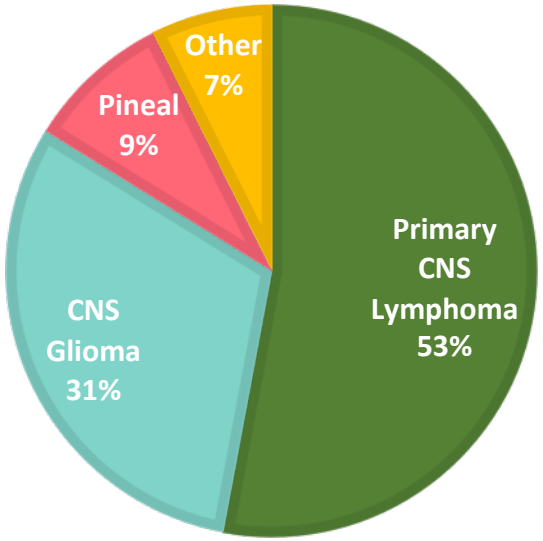
- 283 patients

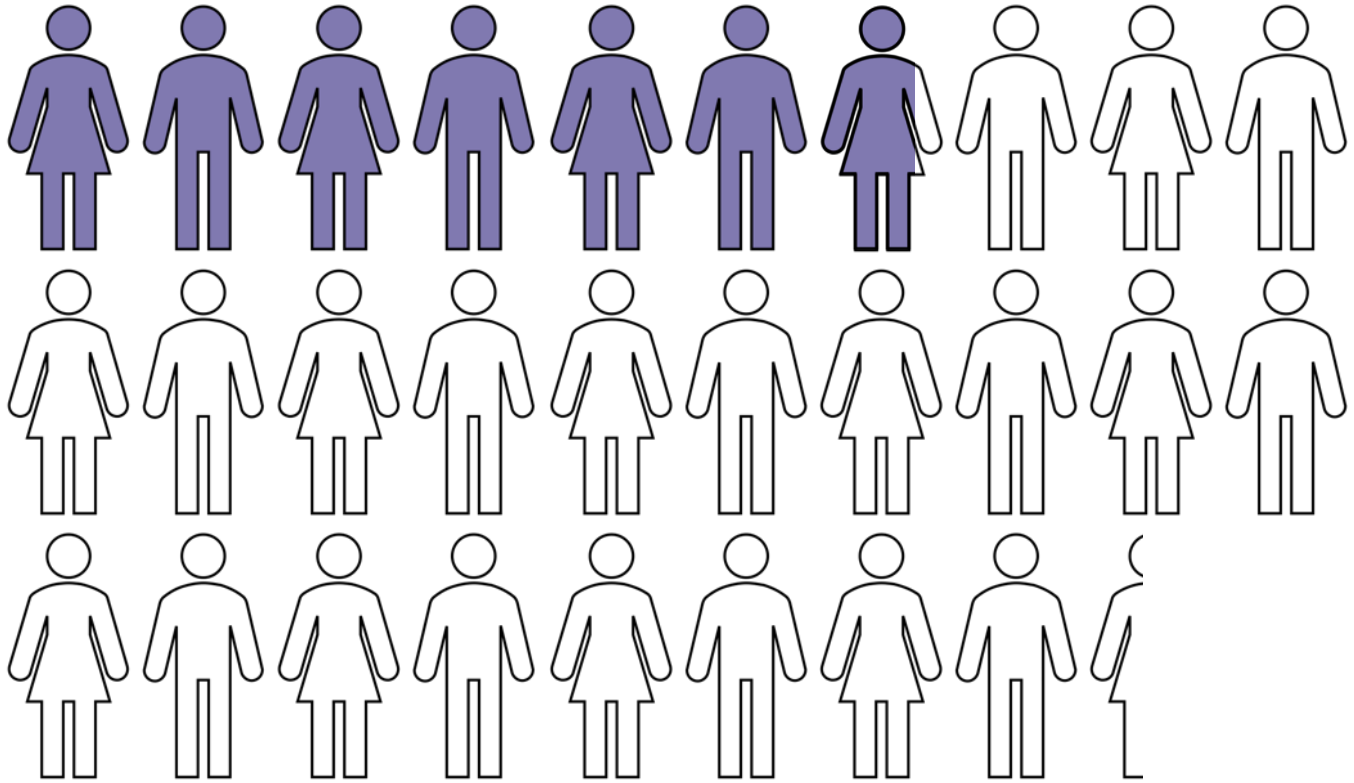


= 10 patients

Patients treated with BBBD at OHSU

- 283 patients
- 68 had ophthalmic examination after BBBD start date





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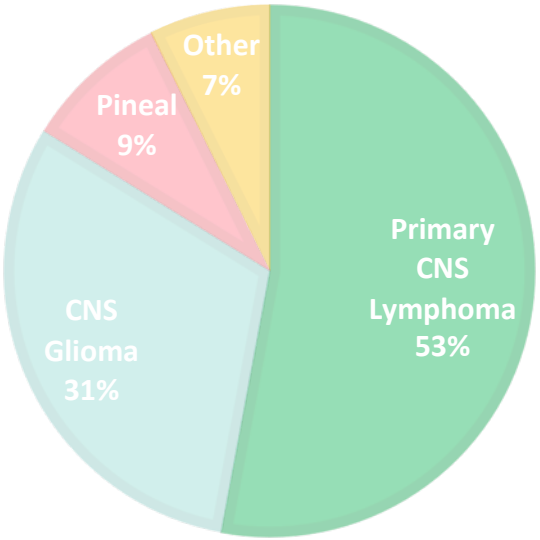
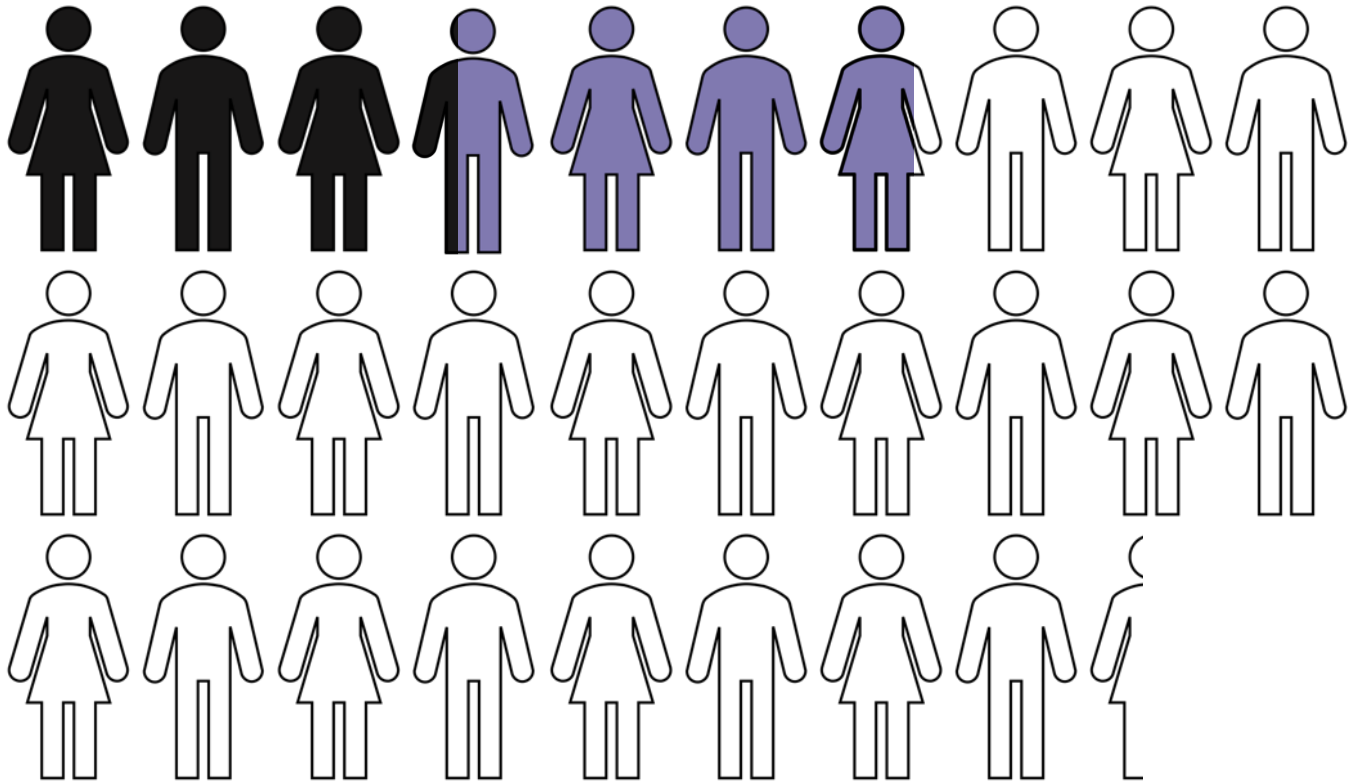
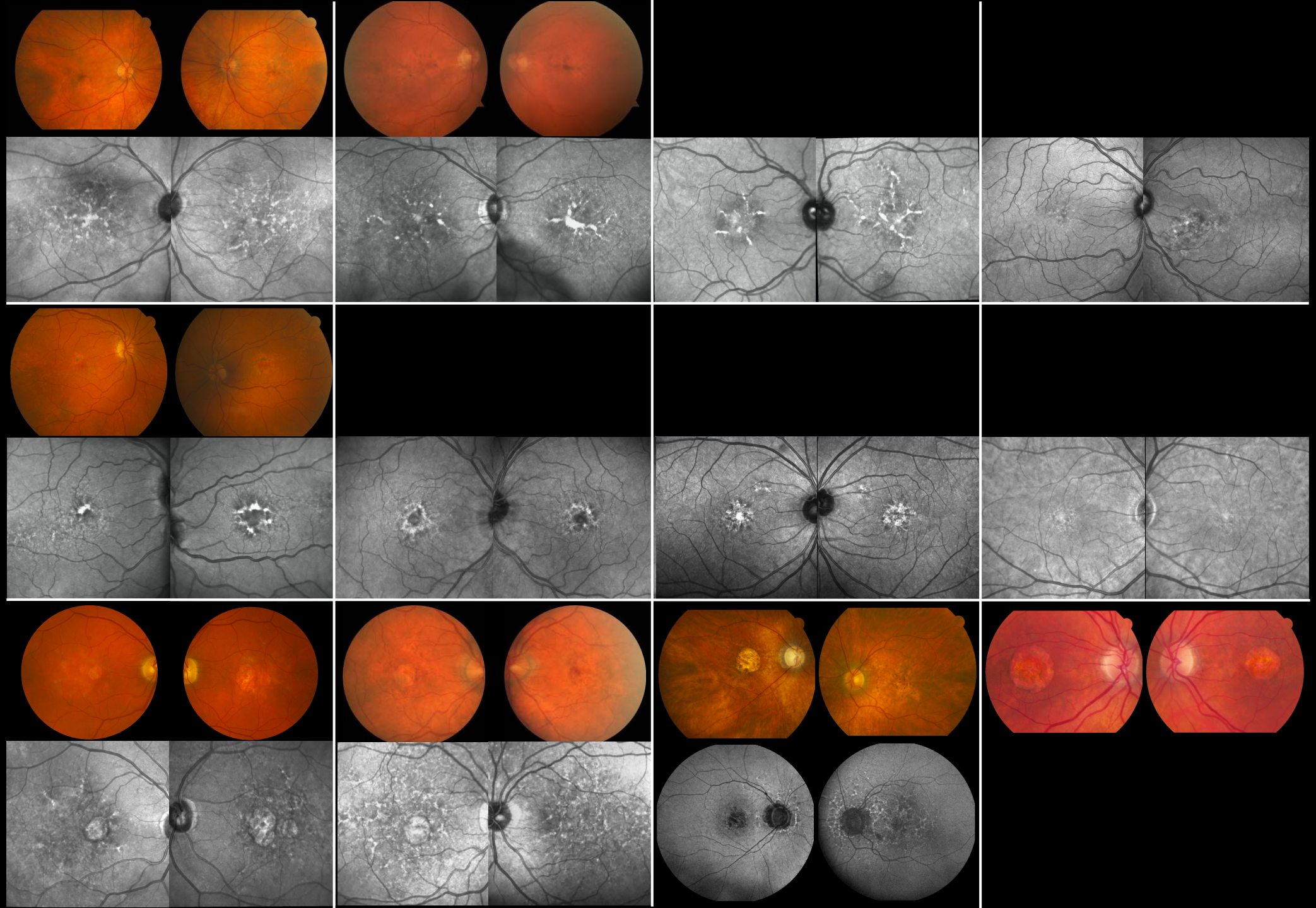




- 32 (47.1%) had evidence of a pigmentary maculopathy on imaging or examination


= 10 patients



Predictors of Maculopathy

	Maculopathy (n = 32)	No Maculopathy (n = 33)	LR Model #1		LR Model #2	
			OR (95% CI)	p	OR (95% CI)	p
Female	16 (50.0%)	9 (27.3%)	1.37 (0.30-6.31)	0.684	1.74 (0.38-8.00)	0.478
Age at first treatment	51.6	40.2	1.05 (0.99-1.11)	0.088	1.03 (0.98-1.09)	0.219
Number of BBBD treatment sessions	26.0	13.8	1.30 (1.12-1.50)	0.001*	1.27 (1.11-1.46)	0.001*
Intraocular chemotherapy	6 (18.8%)	3 (9.1%)	3.00 (0.25-36.72)	0.390	2.36 (0.21-27.10)	0.490
Systemic chemotherapy						
Methotrexate	21 (65.6%)	12 (36.4%)	1.28 (0.20-8.12)	0.792	-	
Carboplatin	17 (53.1%)	18 (54.5%)	0.21 (0.04-1.09)	0.062	-	
Tumor diagnosis						
PCNSL	21 (65.6%)	12 (36.4%)	-		Reference	
CNS Glioma	8 (25.0%)	13 (39.4%)	-		0.99 (0.15-6.53)	0.991
Pineal Tumor	1 (3.1%)	5 (15.2%)	-		0.33 (0.02-6.67)	0.471
Other	2 (6.3%)	3 (9.1%)	-		2.72 (0.12-62.87)	0.533

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Patients with Geographic Atrophy following Blood-Brain Barrier Disruption Therapy

Tumor Diagnosis	Age at first treatment	Number of BBBD sessions	Years from last treatment to last exam with no GA	Years from last treatment to diagnosis of GA	GA progression documented on imaging
PCNSL	60.2	48	2.1	3.2	yes
PCNSL	59.4	22	NA	9.9	no
PCNSL	60.0	49	2.2	2.4	yes
PCNSL	64.7	41	0.8	5.2	yes
Astrocytoma	52.4	23	2.1	2.7	yes
Mean	59.3	36.6	-	4.7	-

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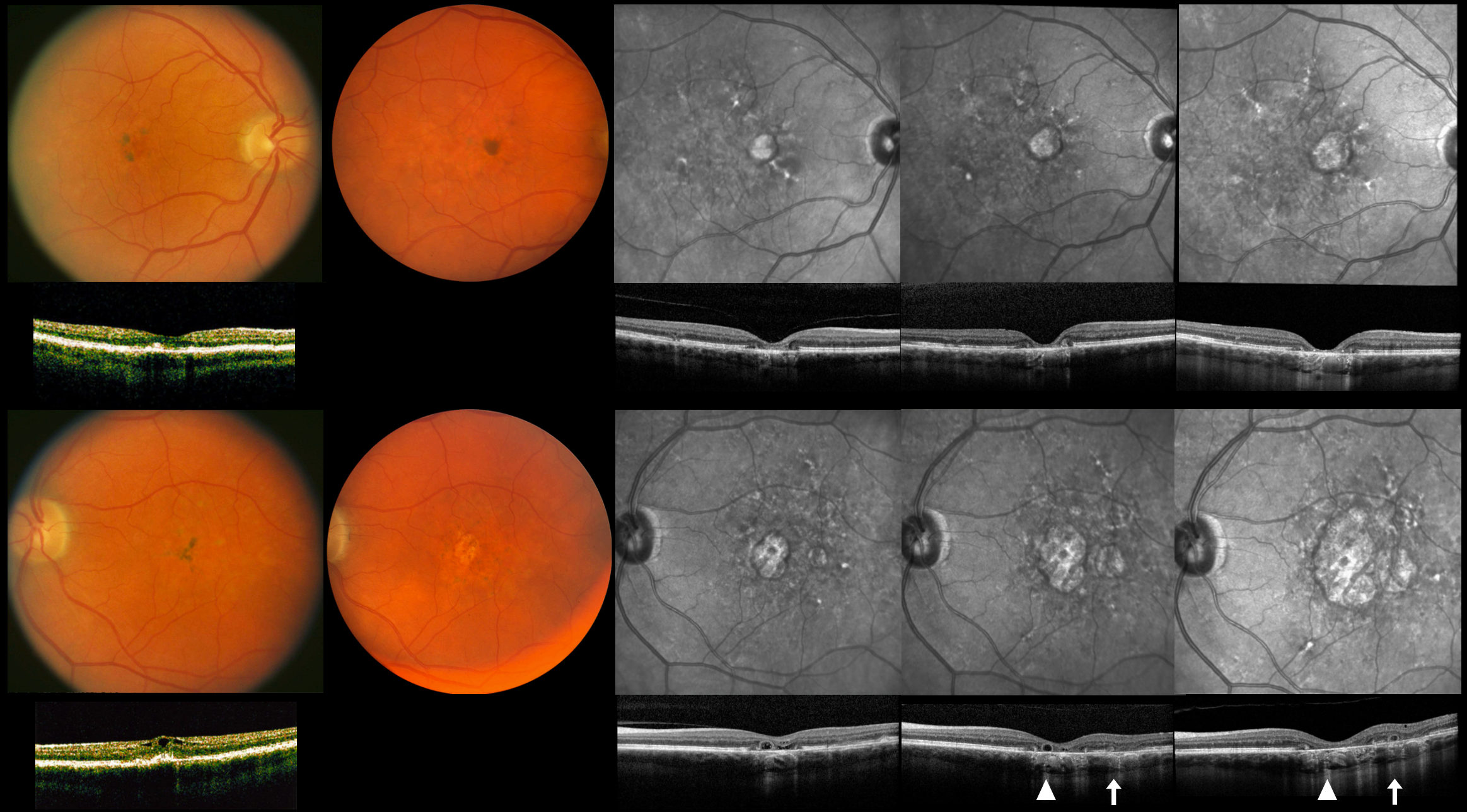
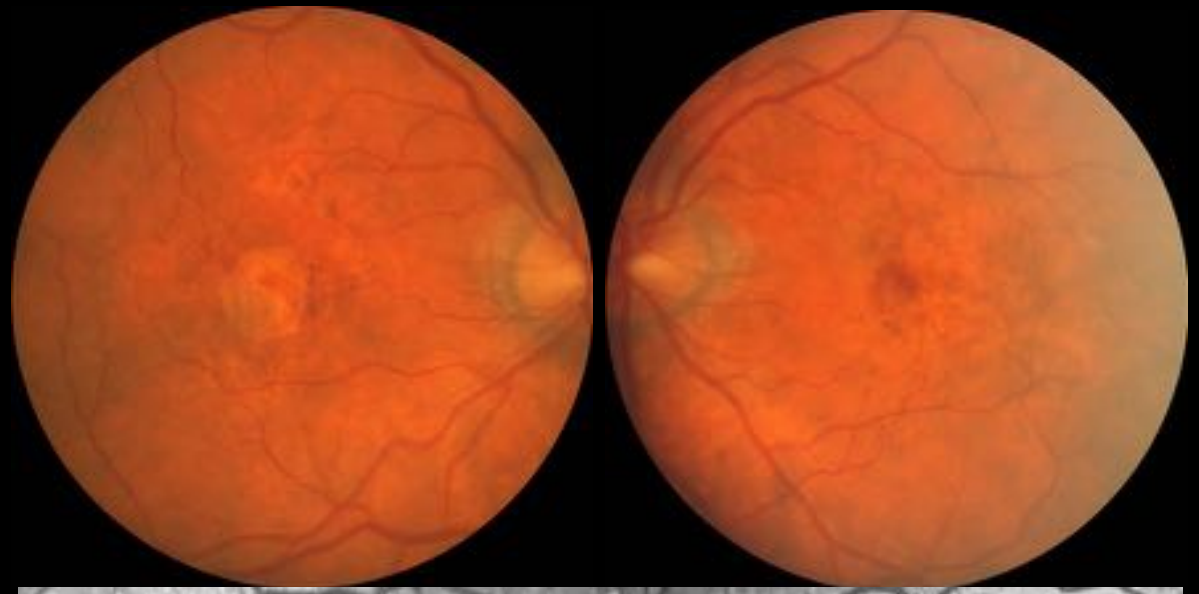
Disease progression after completion of BBBD therapy

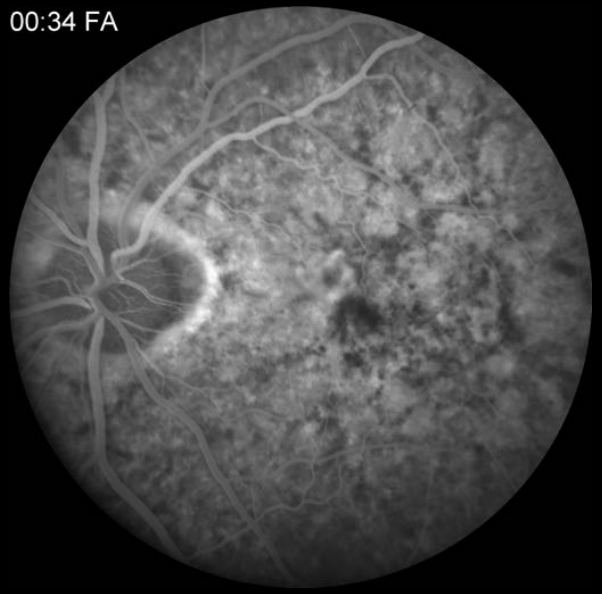
Time from end of BBBD therapy for Astrocytoma

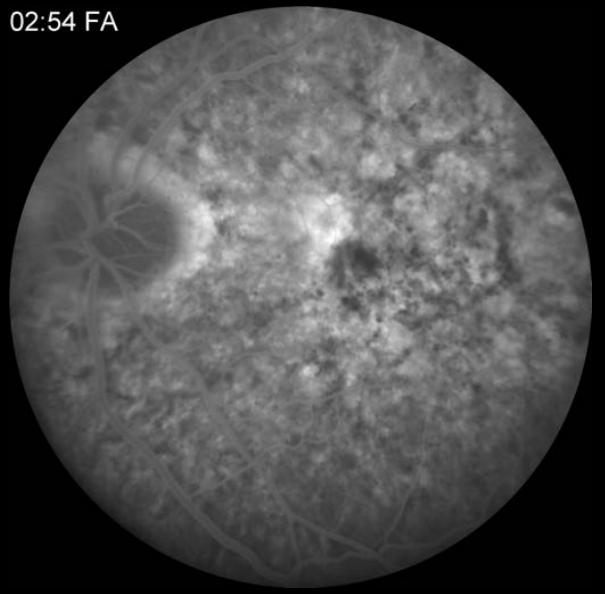
10 months | 4 years | 8 years | 12 years | 14 years

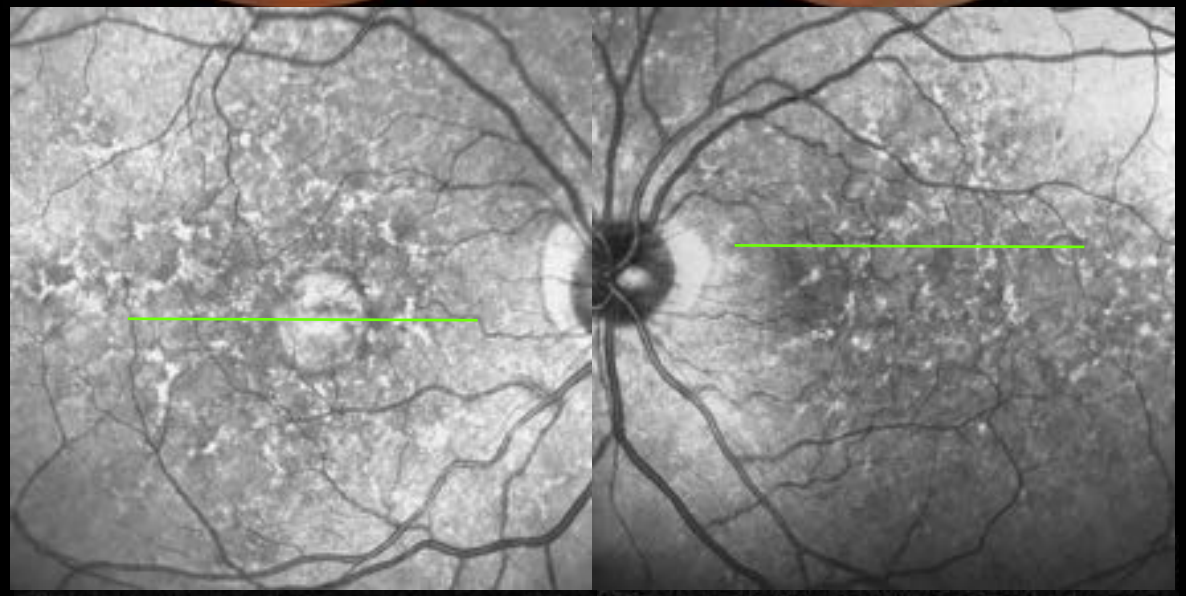


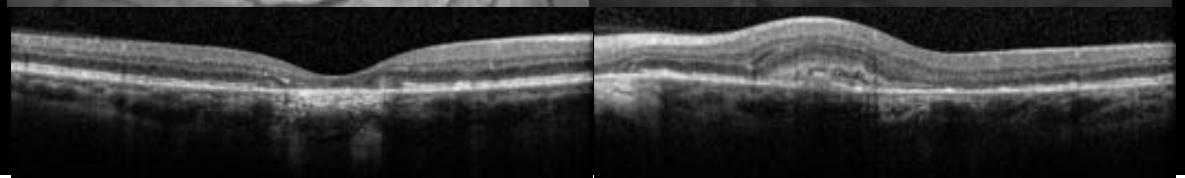
Time from end of BBBD therapy for CNS lymphoma 5 years





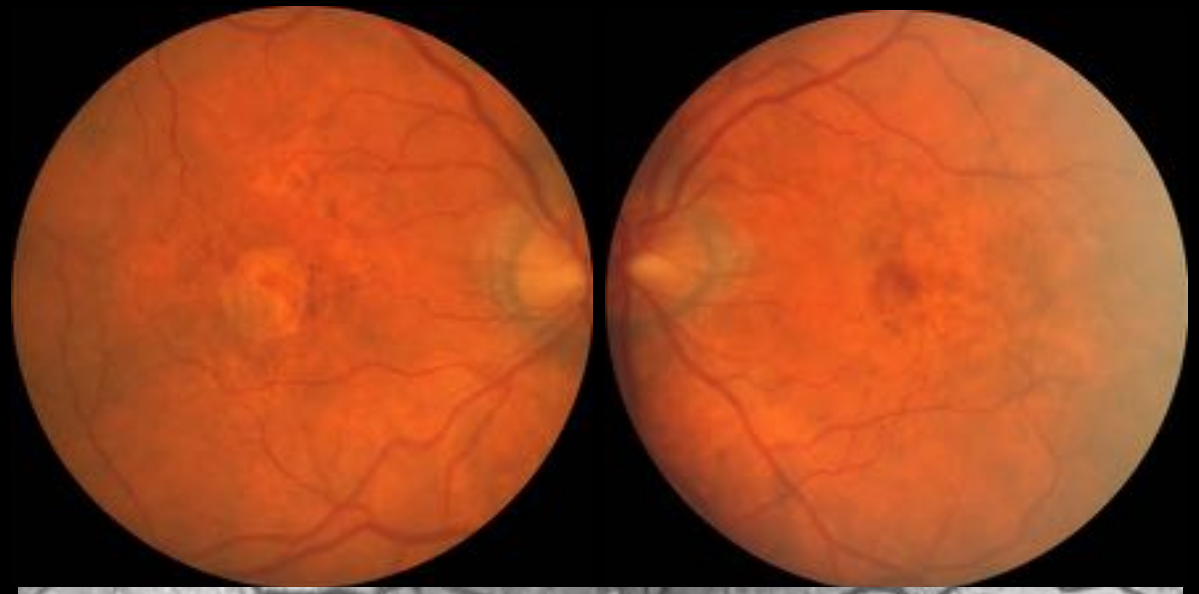


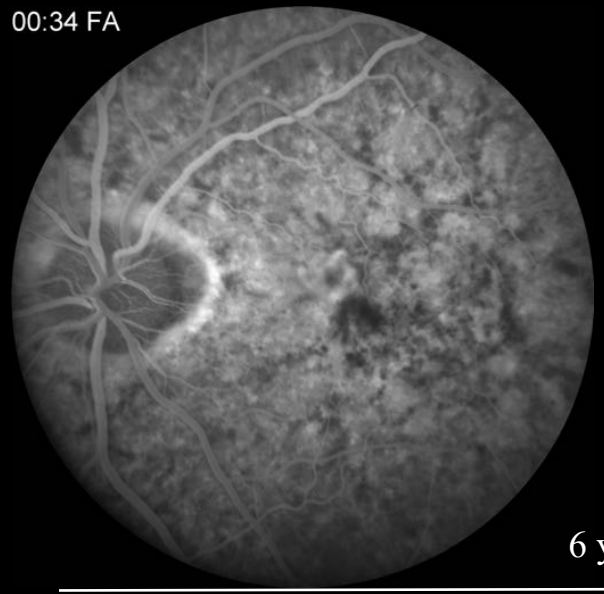


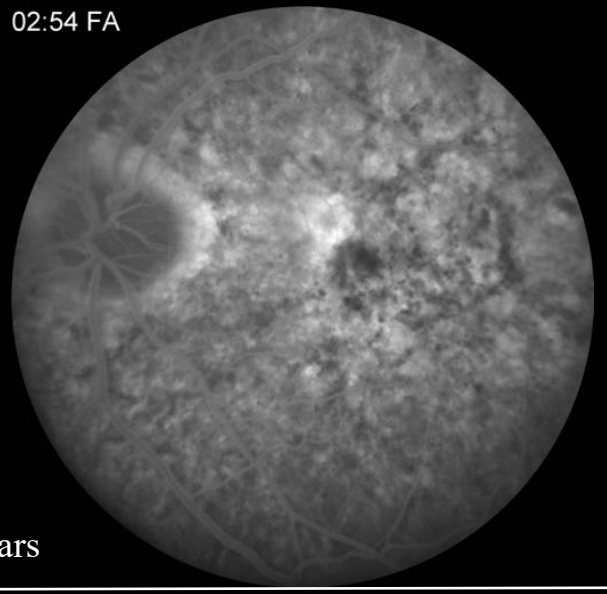


Time from end of BBBD therapy for CNS lymphoma

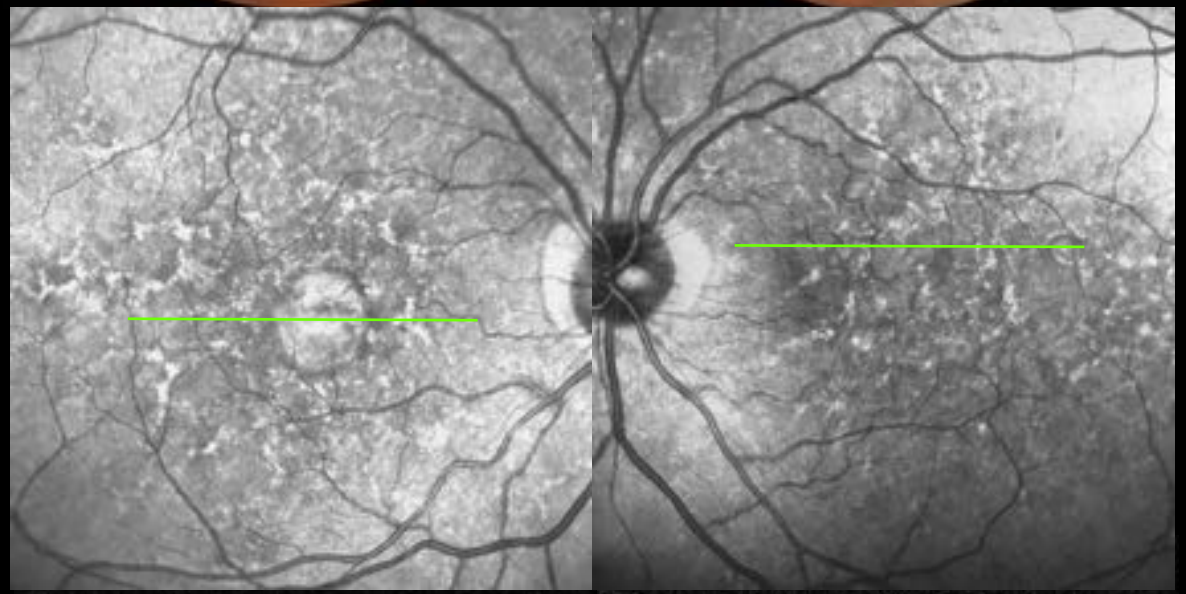
5 years

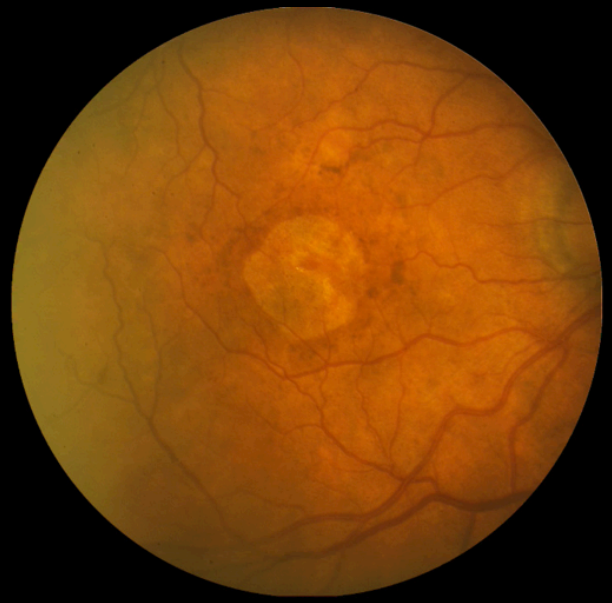


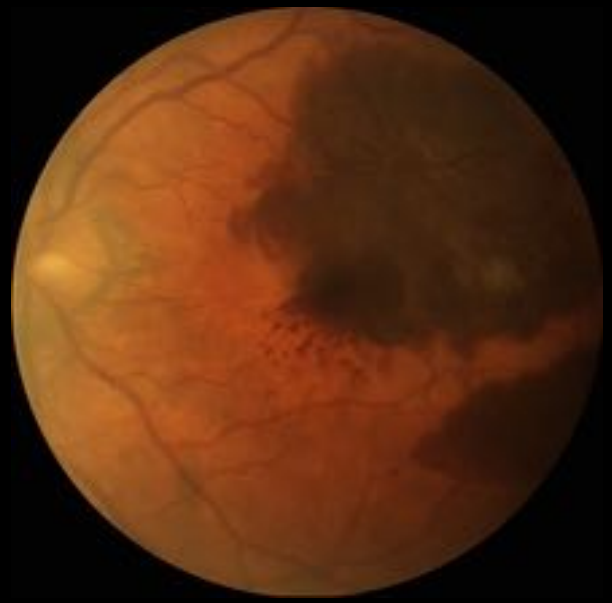




6 years







Time from end of BBBD therapy for CNS lymphoma

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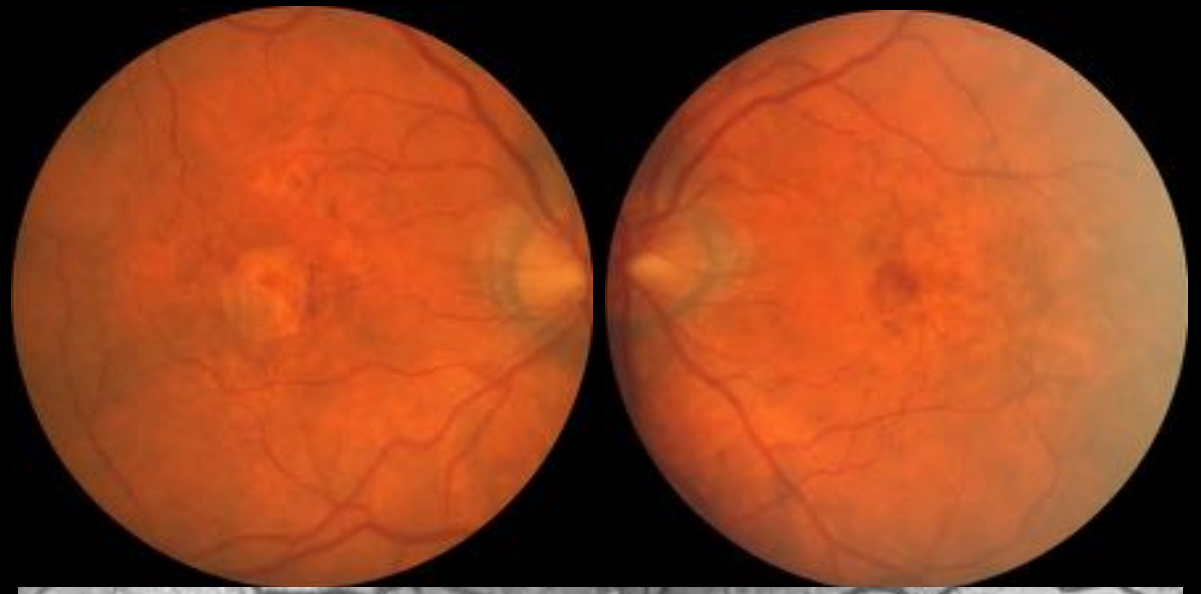
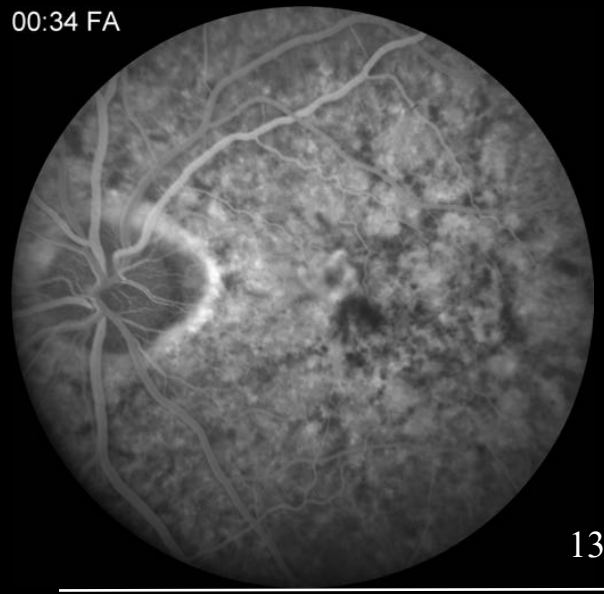
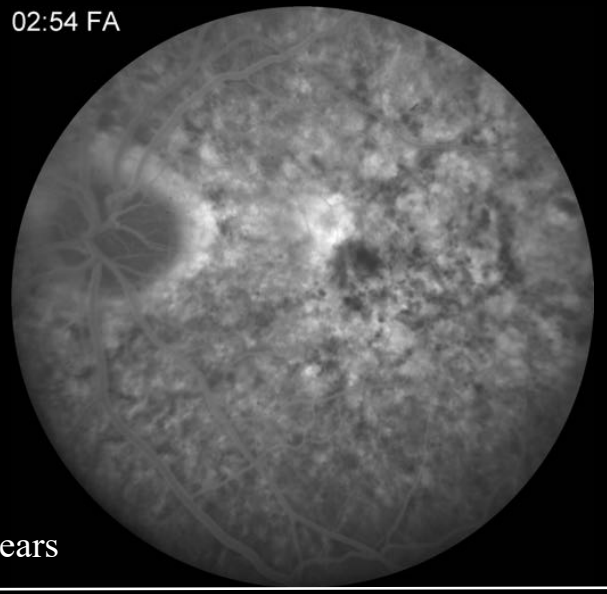
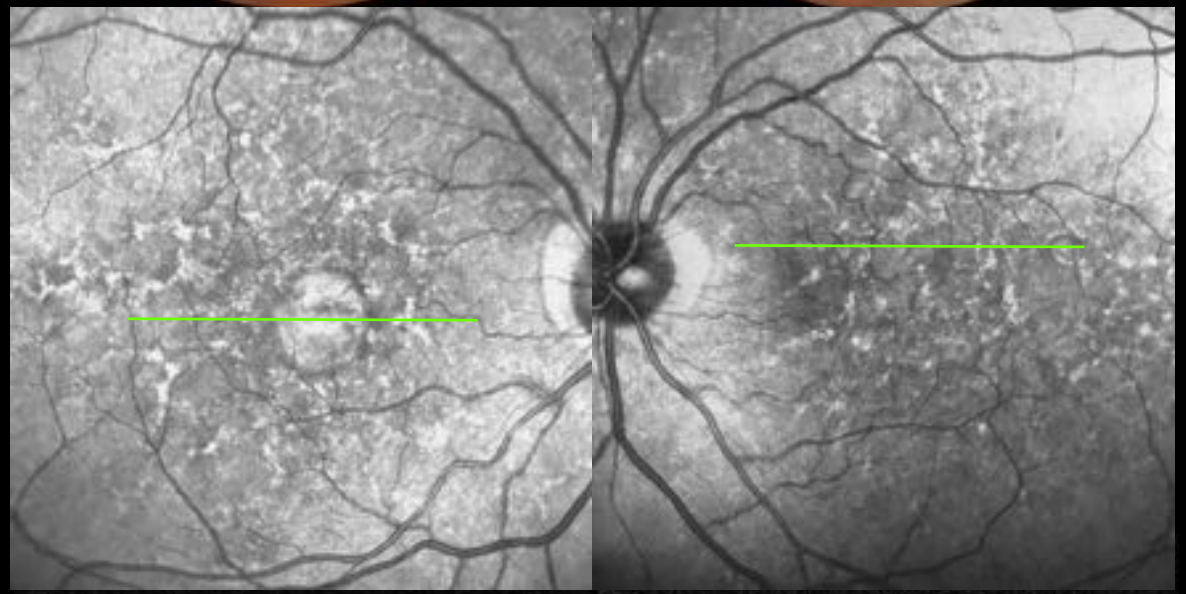
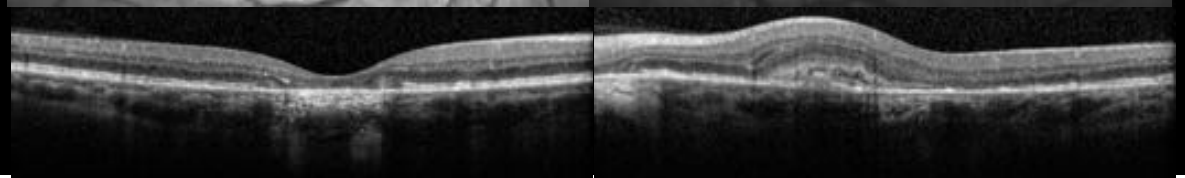


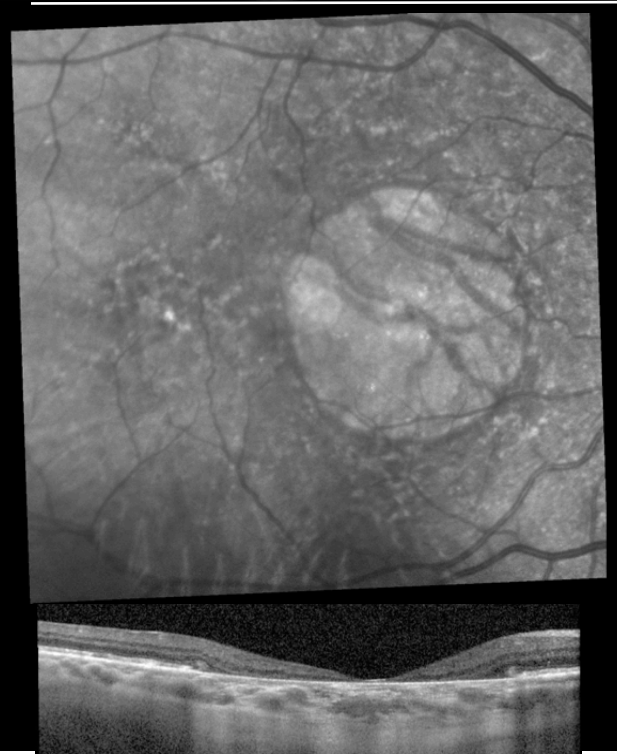


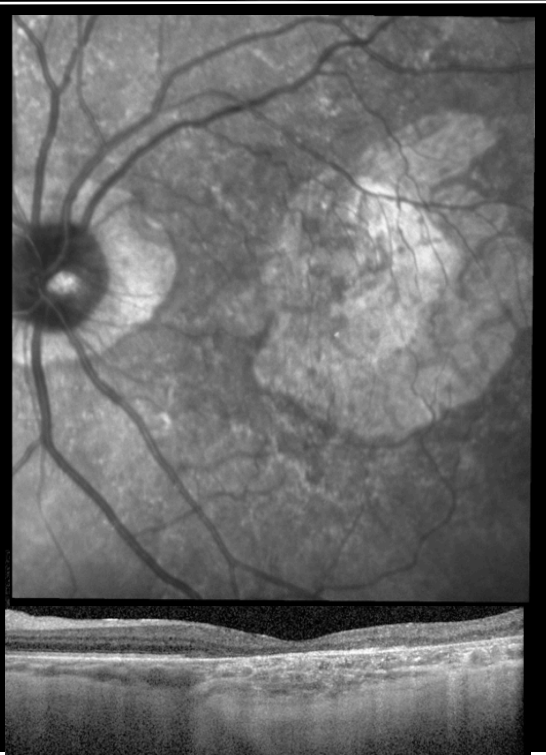


13 years









Mechanism?

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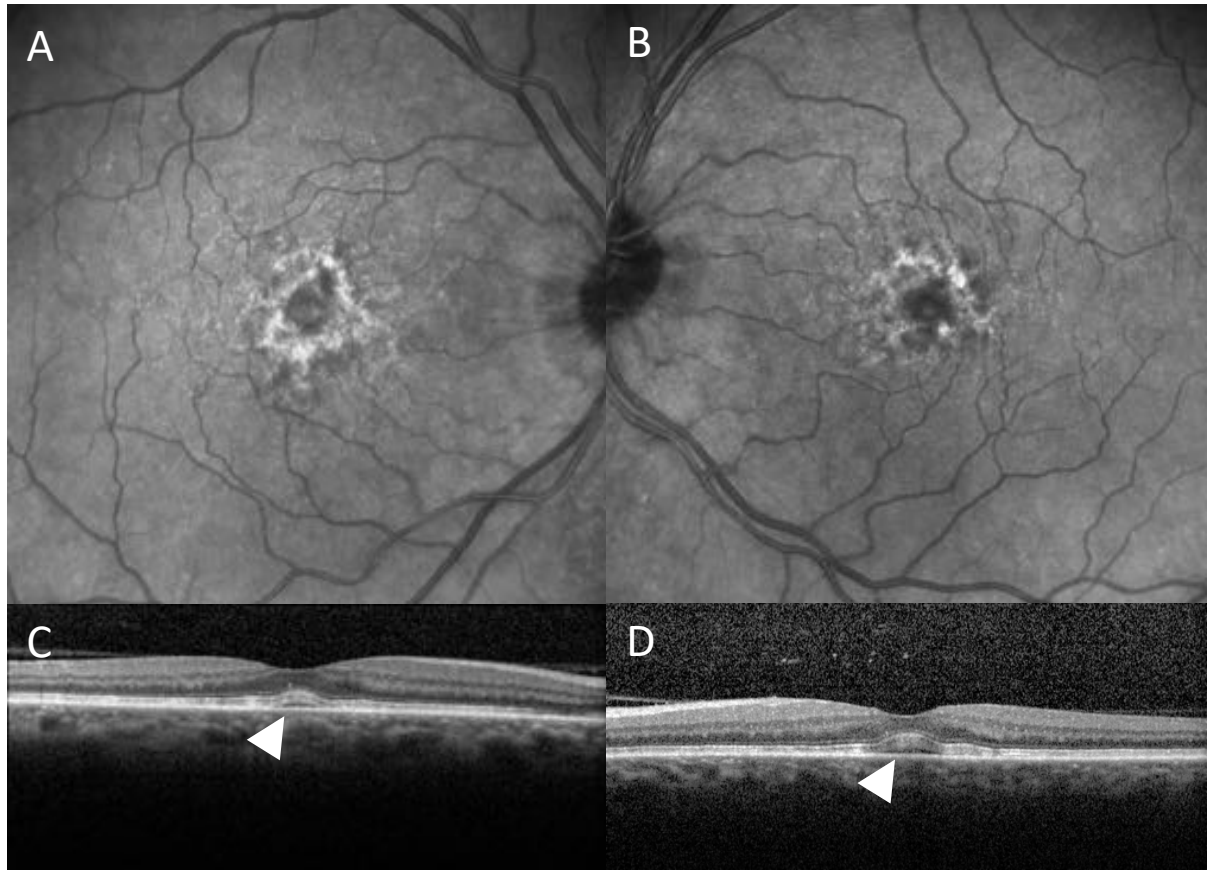
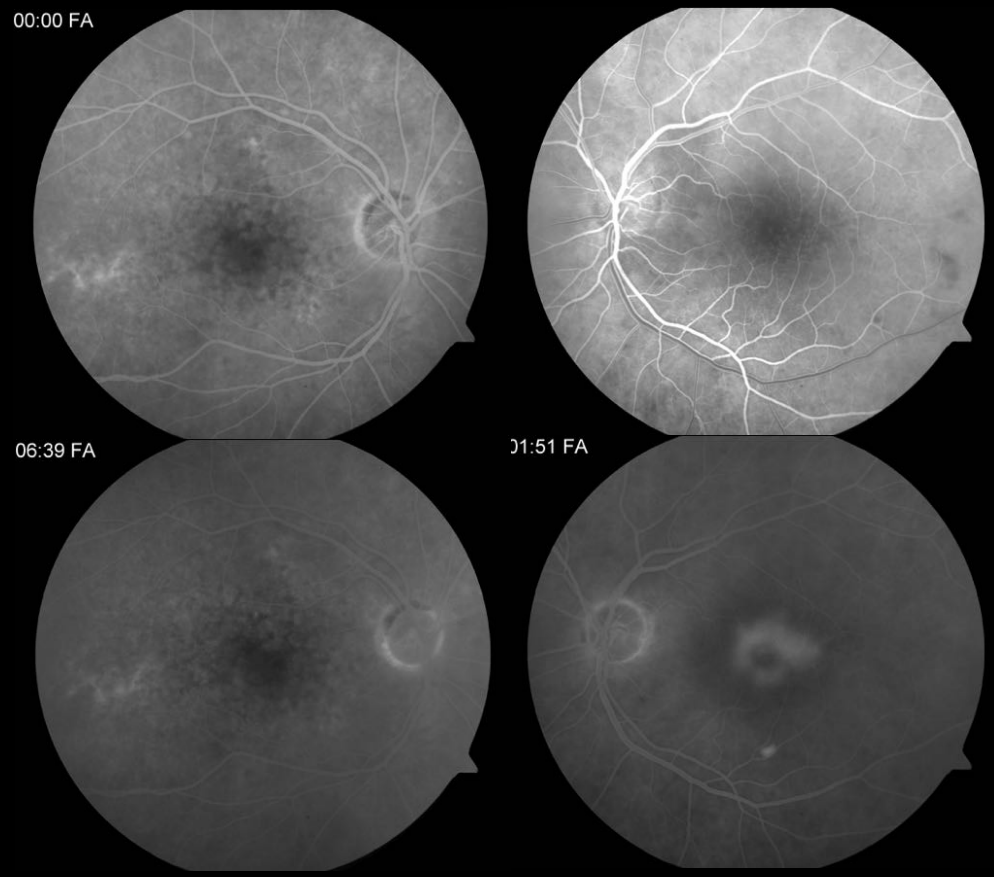


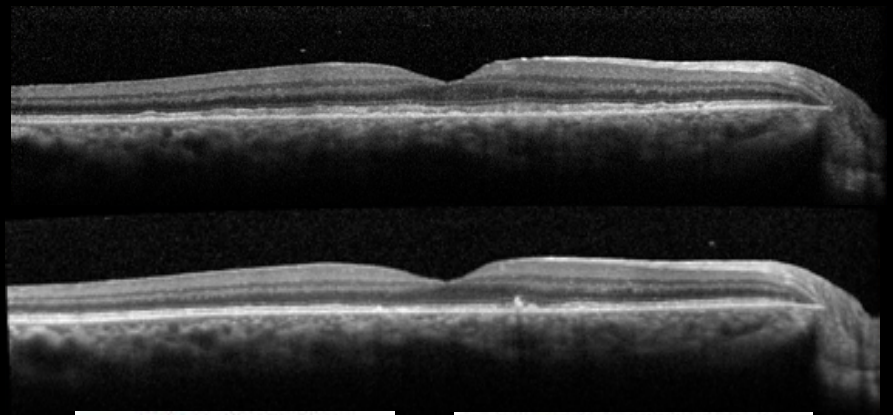
Transient, recurrent disruption of the outer blood-retinal barrier?

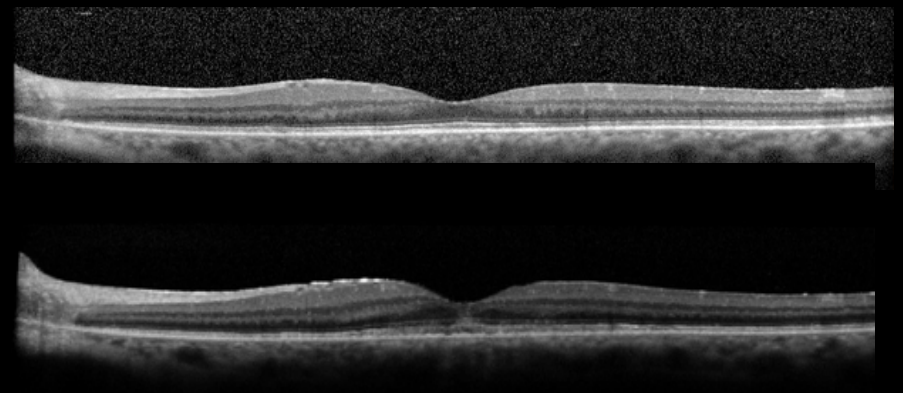
Blurry vision in the left eye following BBBD via the left internal carotid artery

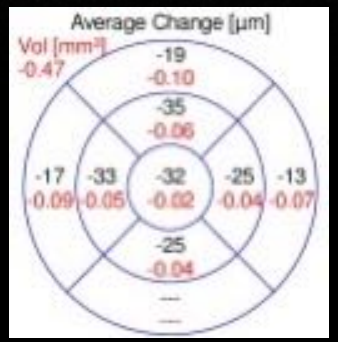


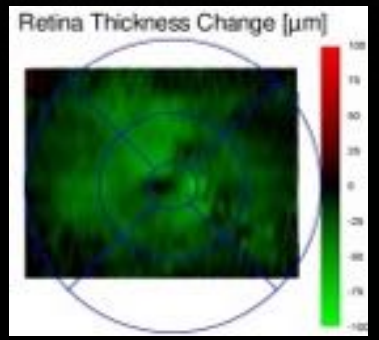
4 days prior to therapy via the left internal carotid artery

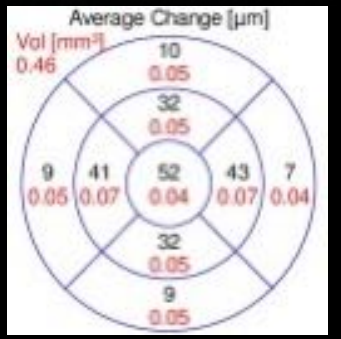
7 days after therapy

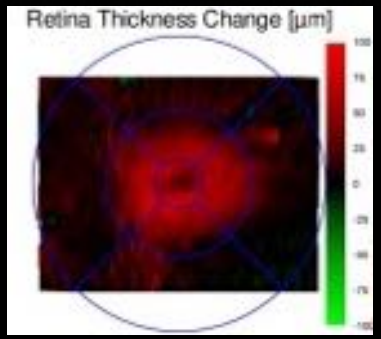












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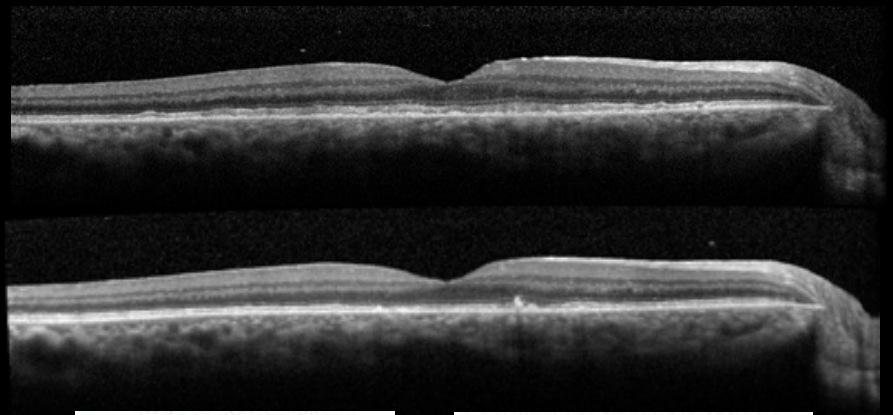
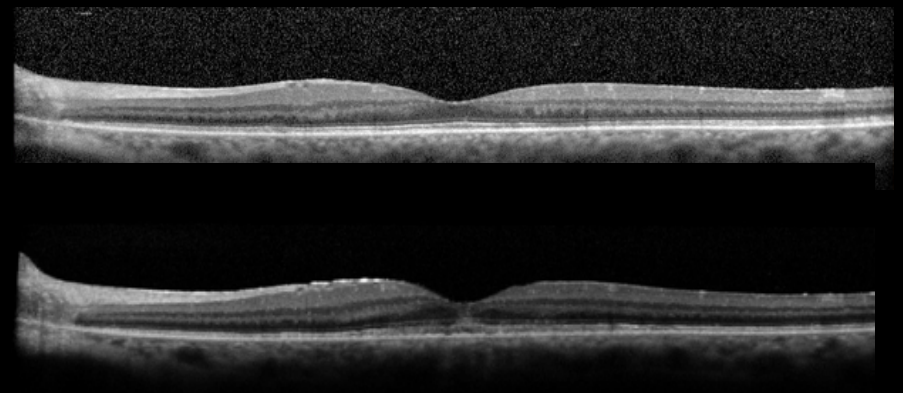
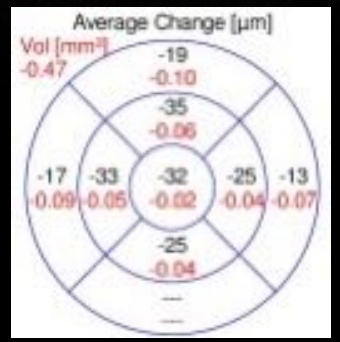
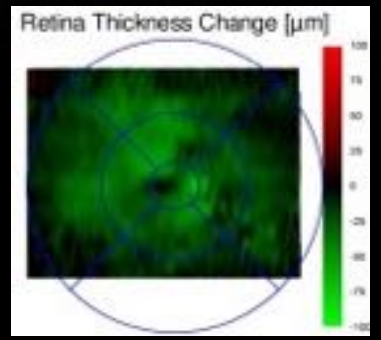
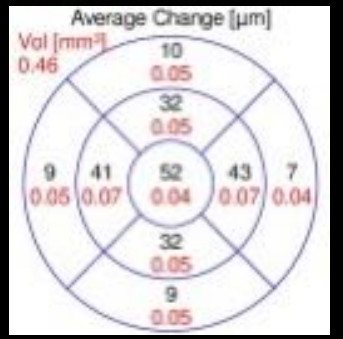
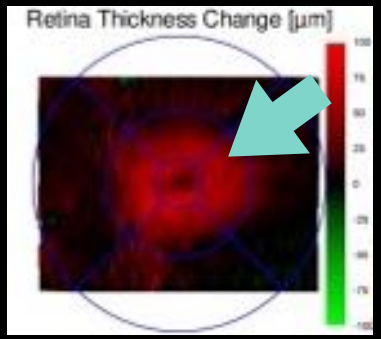






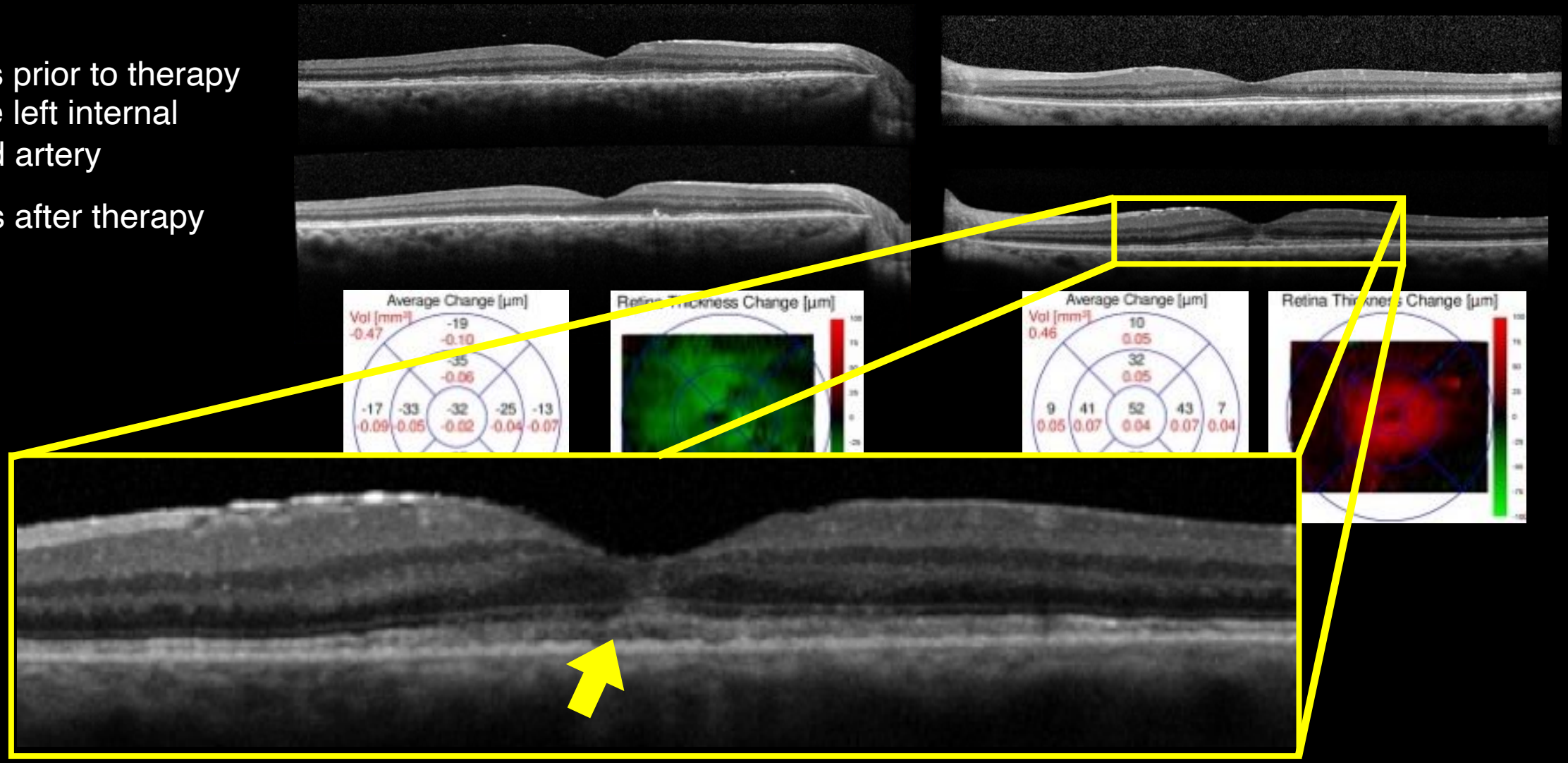






4 days prior to therapy via the left internal carotid artery

7 days after therapy



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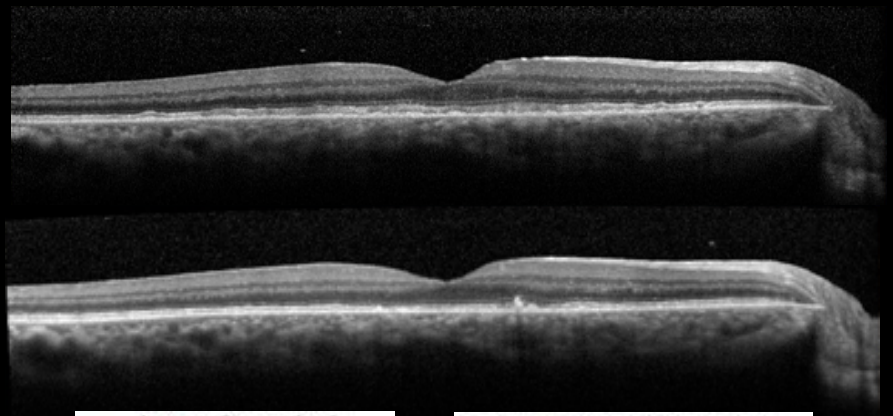
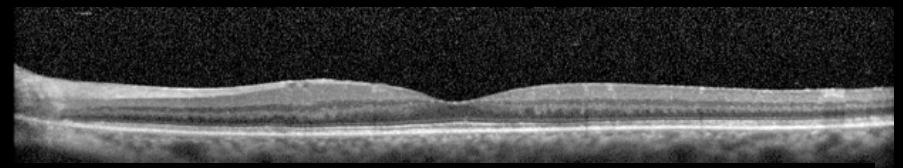
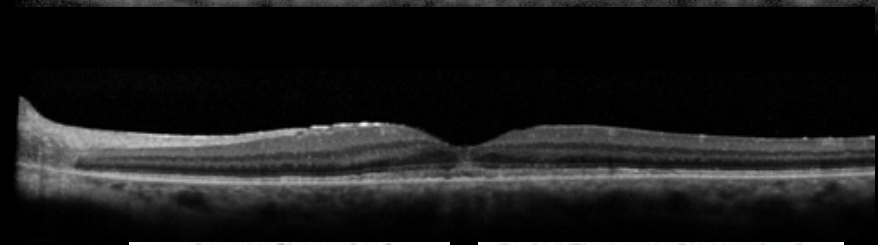
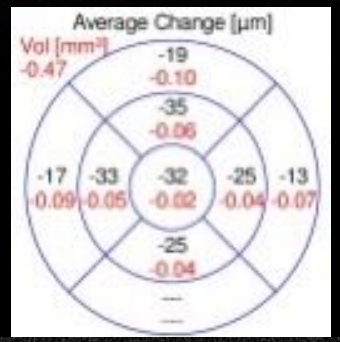
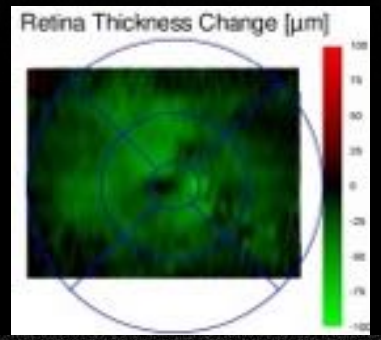
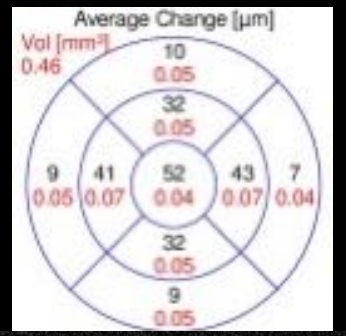


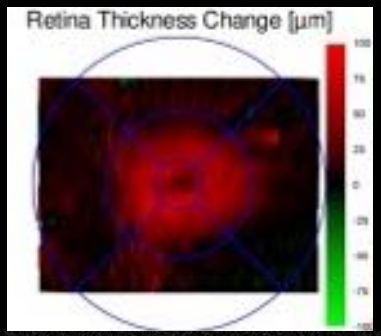




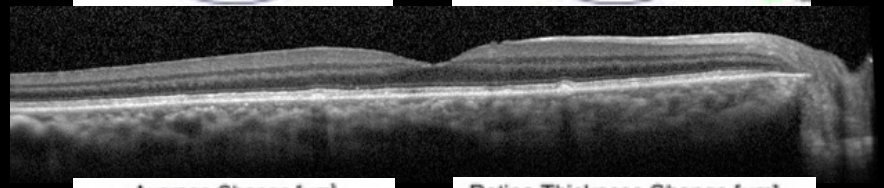


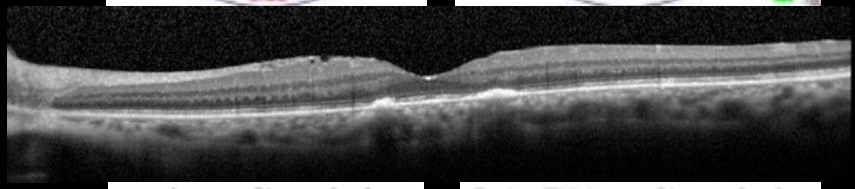


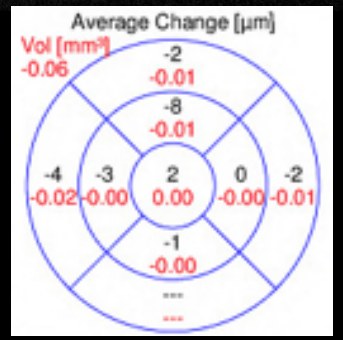


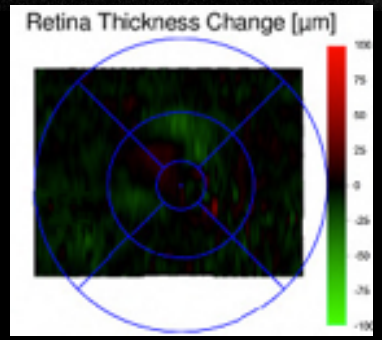


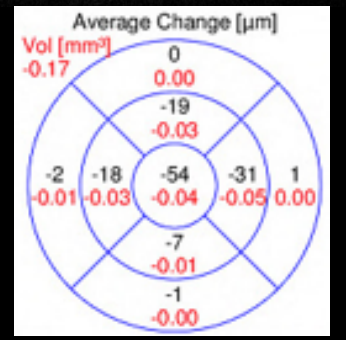
1 month after therapy

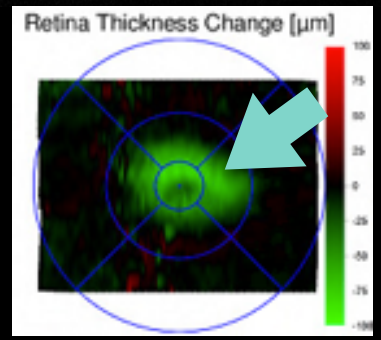












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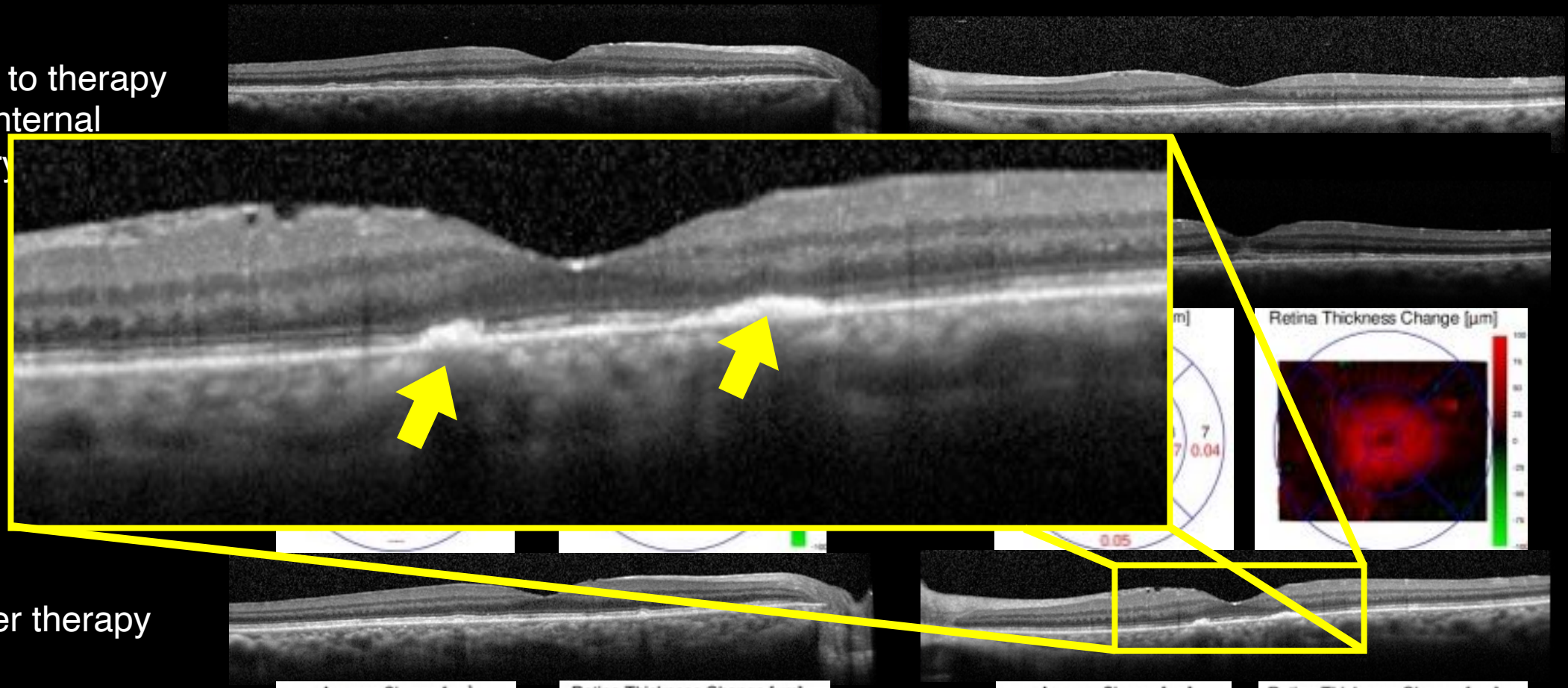

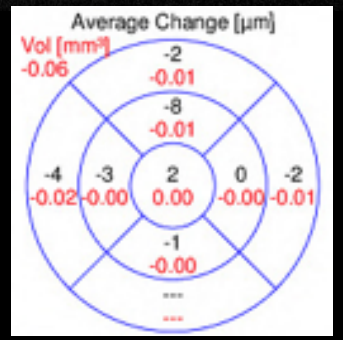

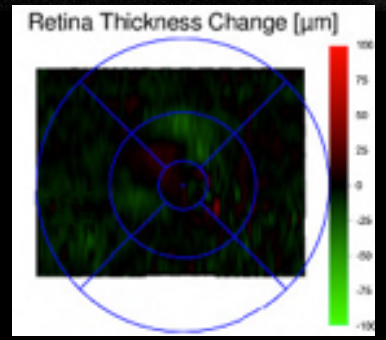

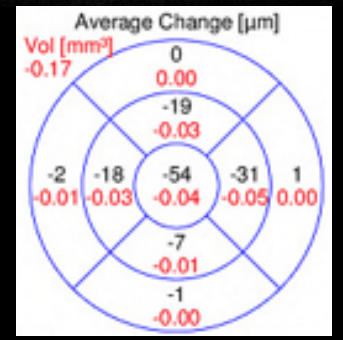

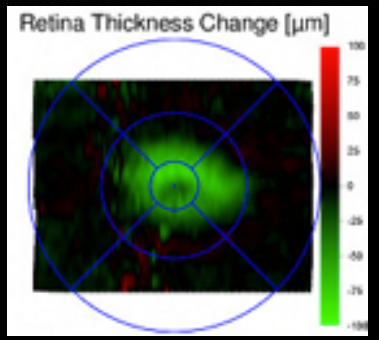

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- Need for Education and Screening

Thank you!