

Diabetic Macular Oedema

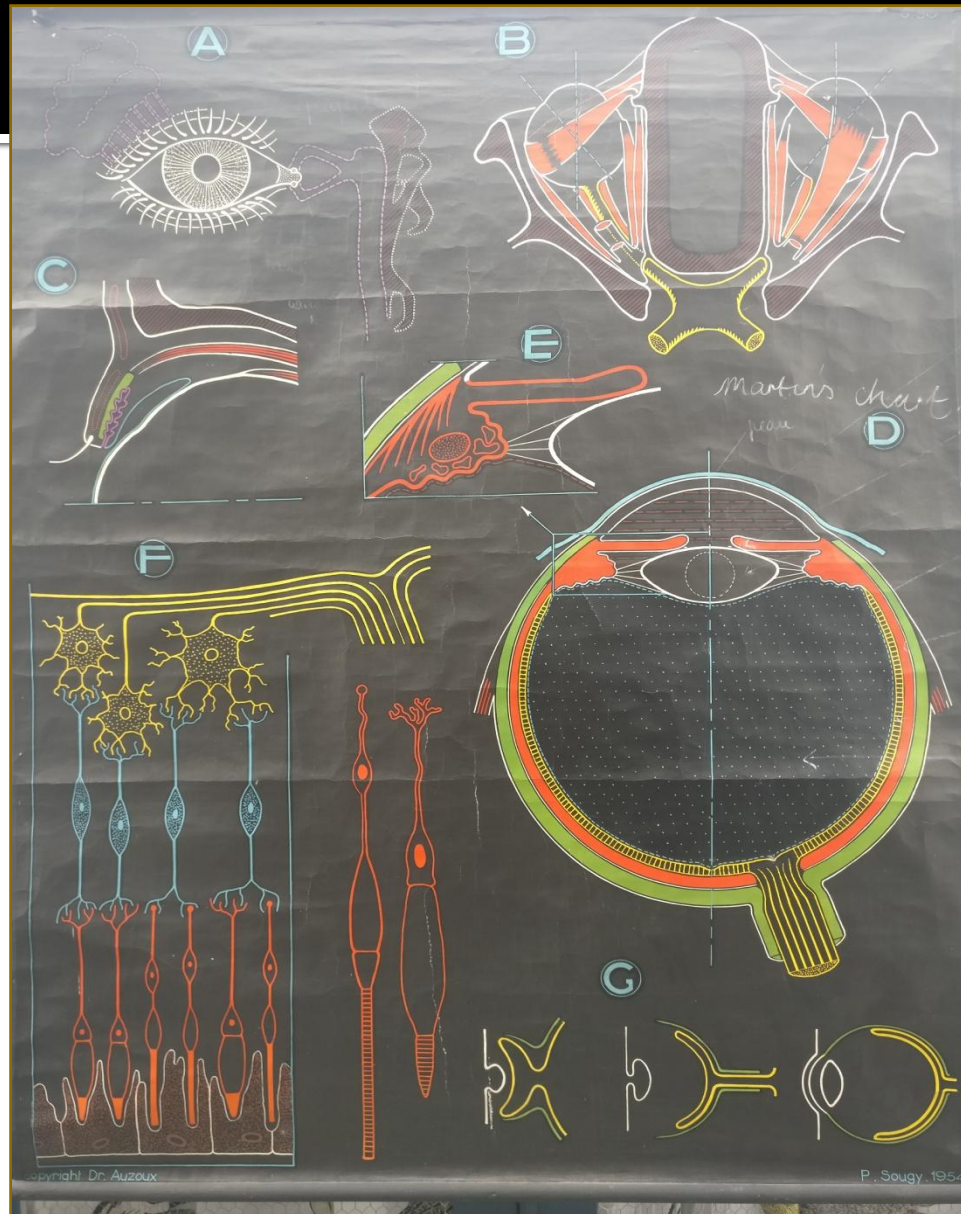
BARS 2017

Martin Harris

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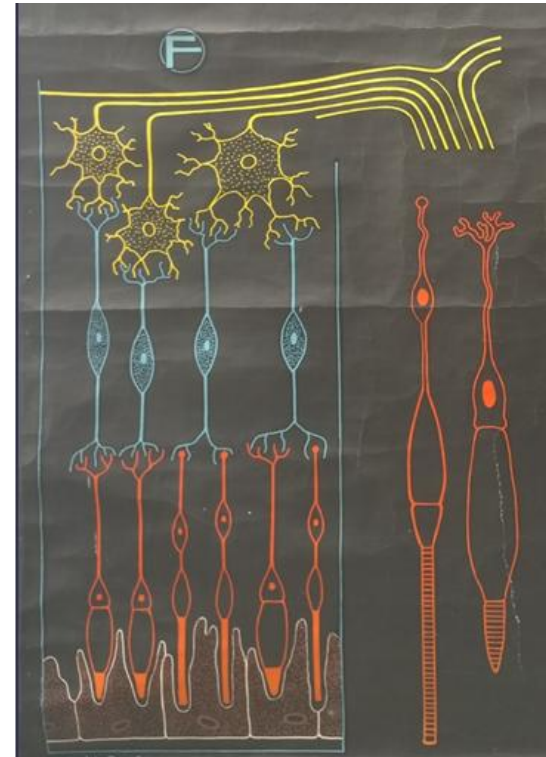
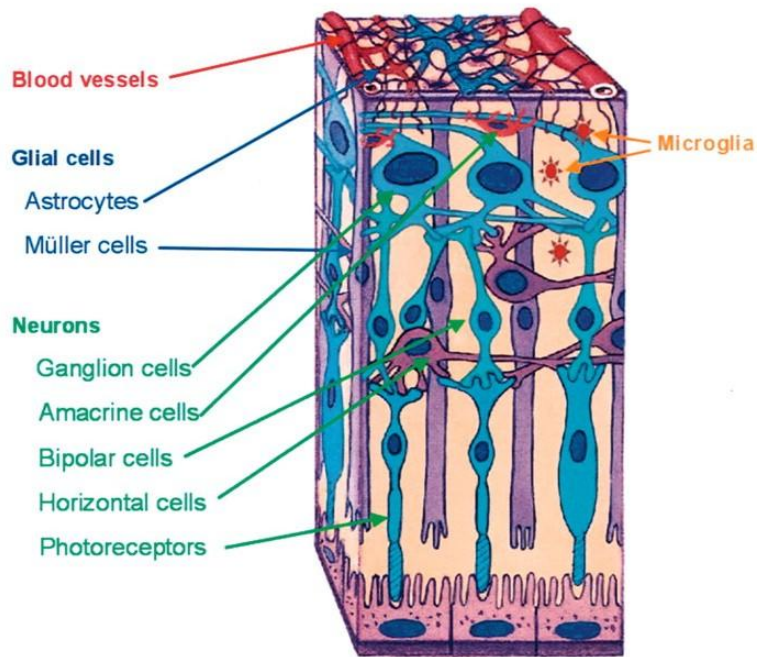
Diabetic Macular Oedema

- Diagnosis
- Pathology
- Alphabet soup- Current treatment
- Horizon gazing



B

light



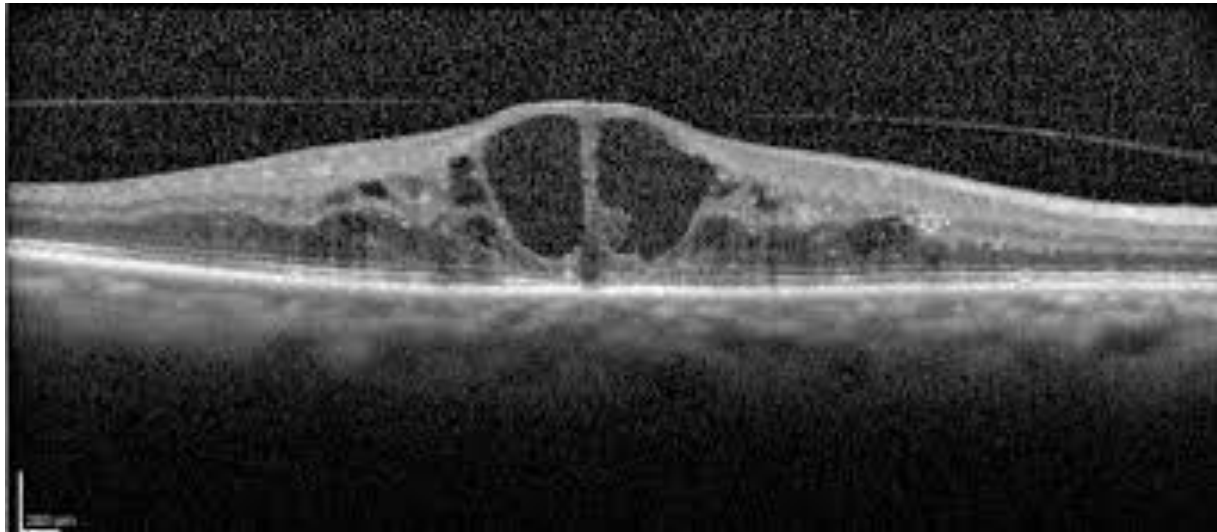
ETDRS completed 1985 n=3711

- *Focal Macular Laser*
- The ETDRS demonstrated that focal macular laser reduced the risk of moderate vision loss (defined as a doubling of the visual angle) by up to 50% in eyes with "clinically significant macular oedema." Clinically significant macular oedema was defined as:
 - Retinal thickening at or within 500 microns or 1/3 disc diameter of center of macula
 - Hard exudates at or within 500 microns of the center of the macula with adjacent retinal thickening.
 - Retinal thickening GREATER than 1 disc diameter in size which is within 1 disc diameter from the center of the macula
- There was also an increase of moderate visual gain in eyes receiving focal treatment as well as a decrease in the amount of retinal thickening. The recommendation was that eyes with clinically significant macular oedema should be considered for focal photocoagulation.

Diabetic Macular Oedema- Diagnosis

- SD-OCT
 - Central retinal thickness
 - Intraretinal cystoid fluid
 - Disorganisation of the retinal inner layers (DRIL)
 - Hyperreflective dots
 - VMT
 - Subretinal fluid

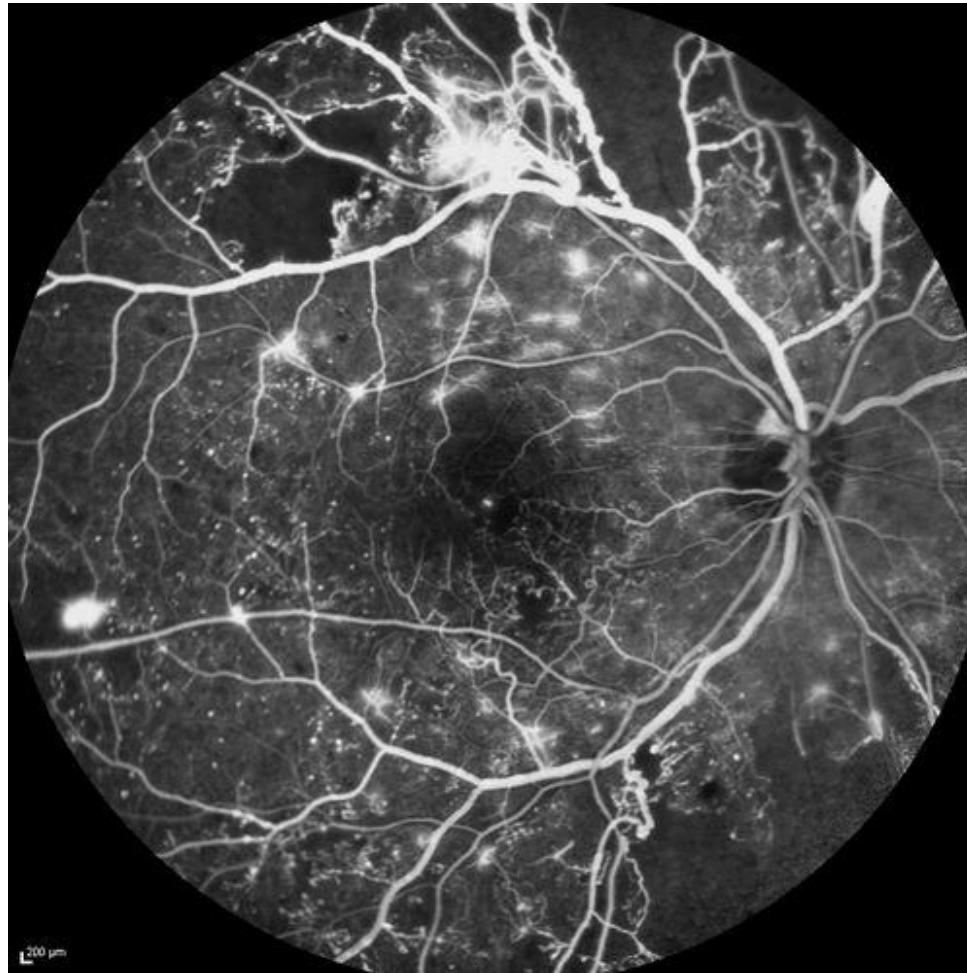
DMO-OCT example



Diabetic Macular Oedema- Diagnosis

- Fundus fluorescein angiography
 - Dynamic picture
 - Leakage
 - Foveal avascular zone
 - Areas of non-perfusion

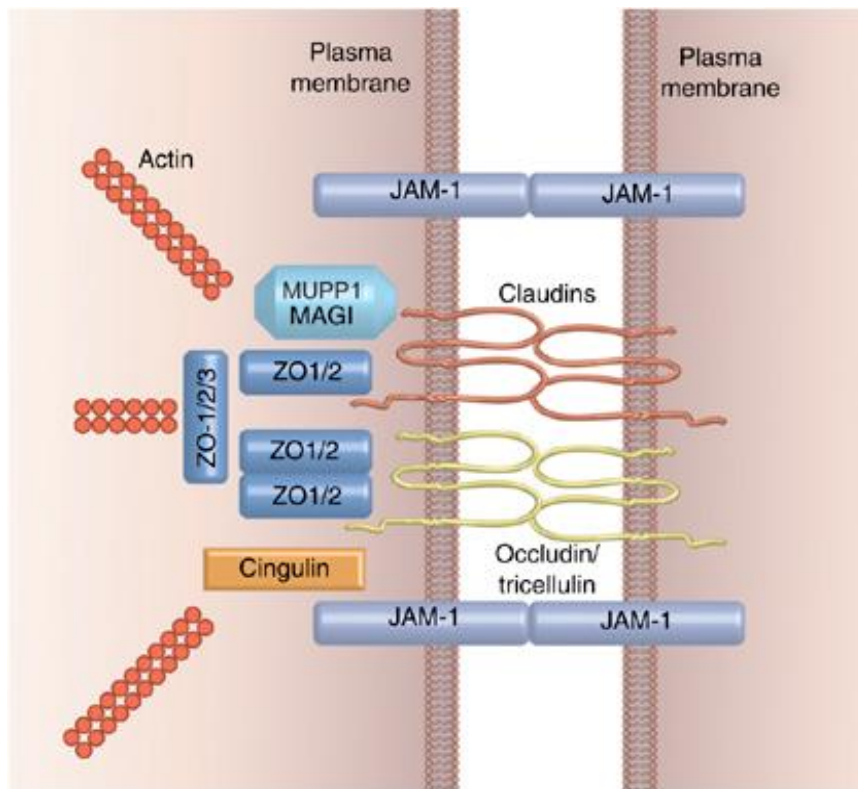
Fundus fluorescein angiogram



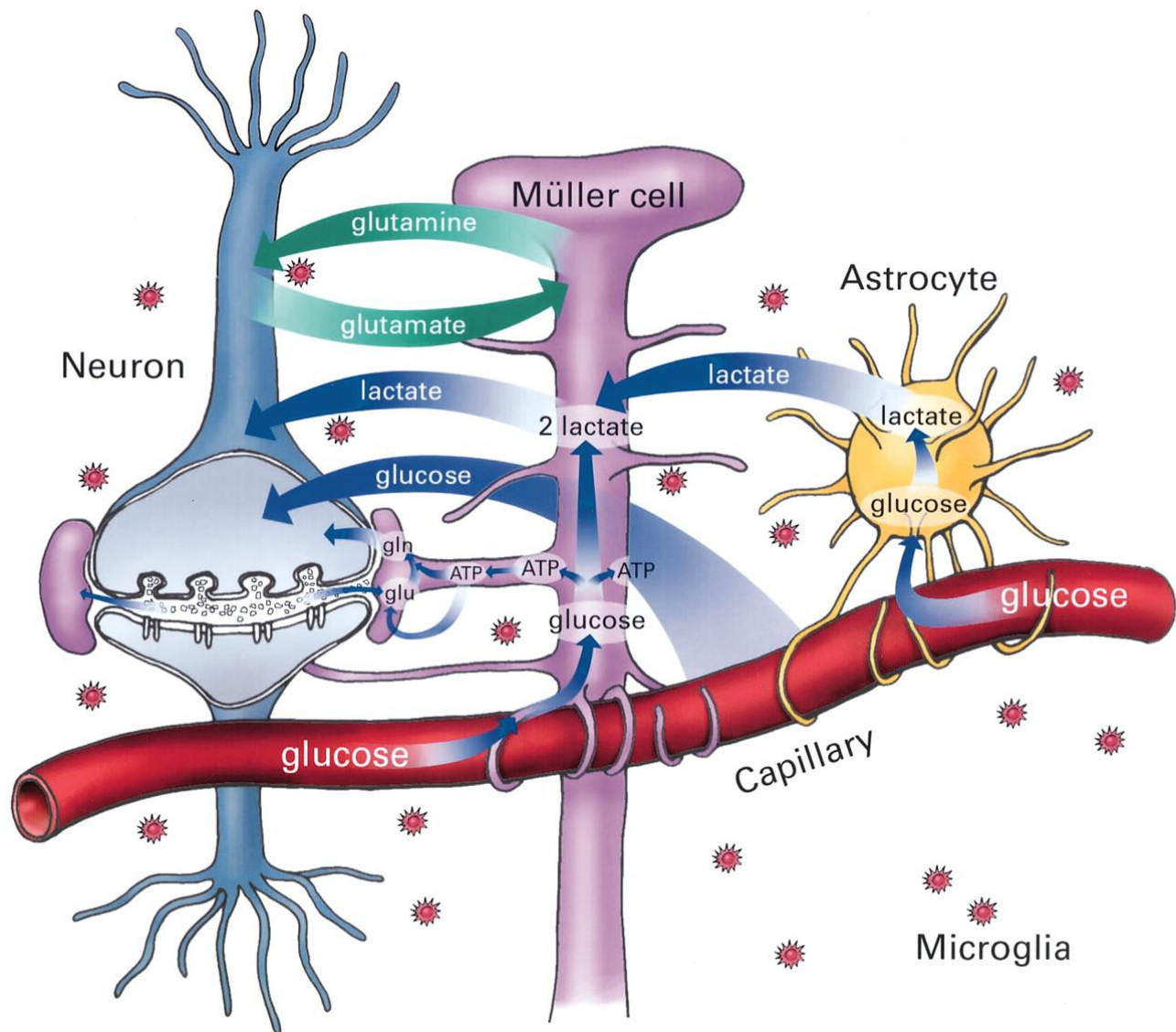
BLOOD RETINAL BARRIERS

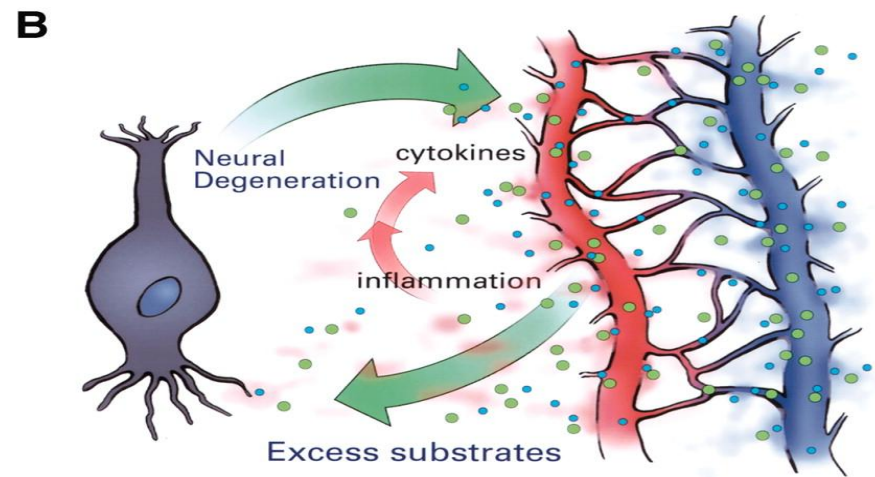
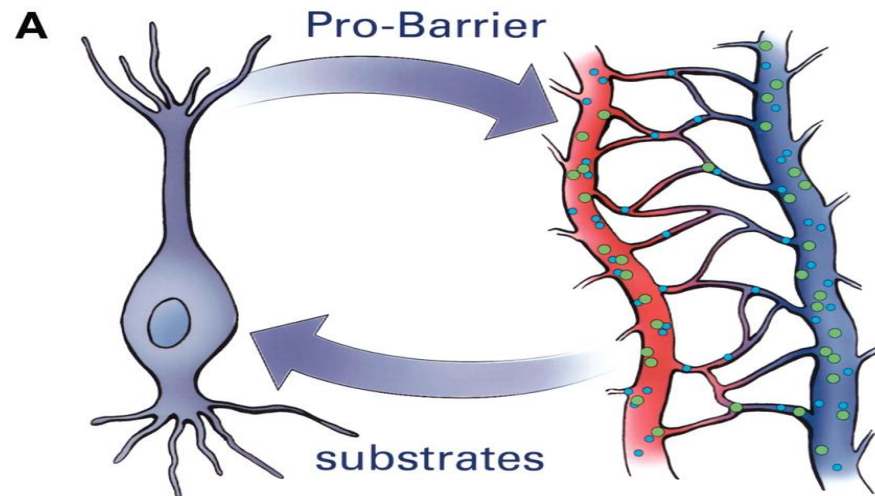
- OUTER BLOOD RETINAL BARRIER
 - Tight junctions RPE cells
- INNER BLOOD RETINAL BARRIER
 - Tight junctions RVE cells
 - Pericytes
 - Mueller cells

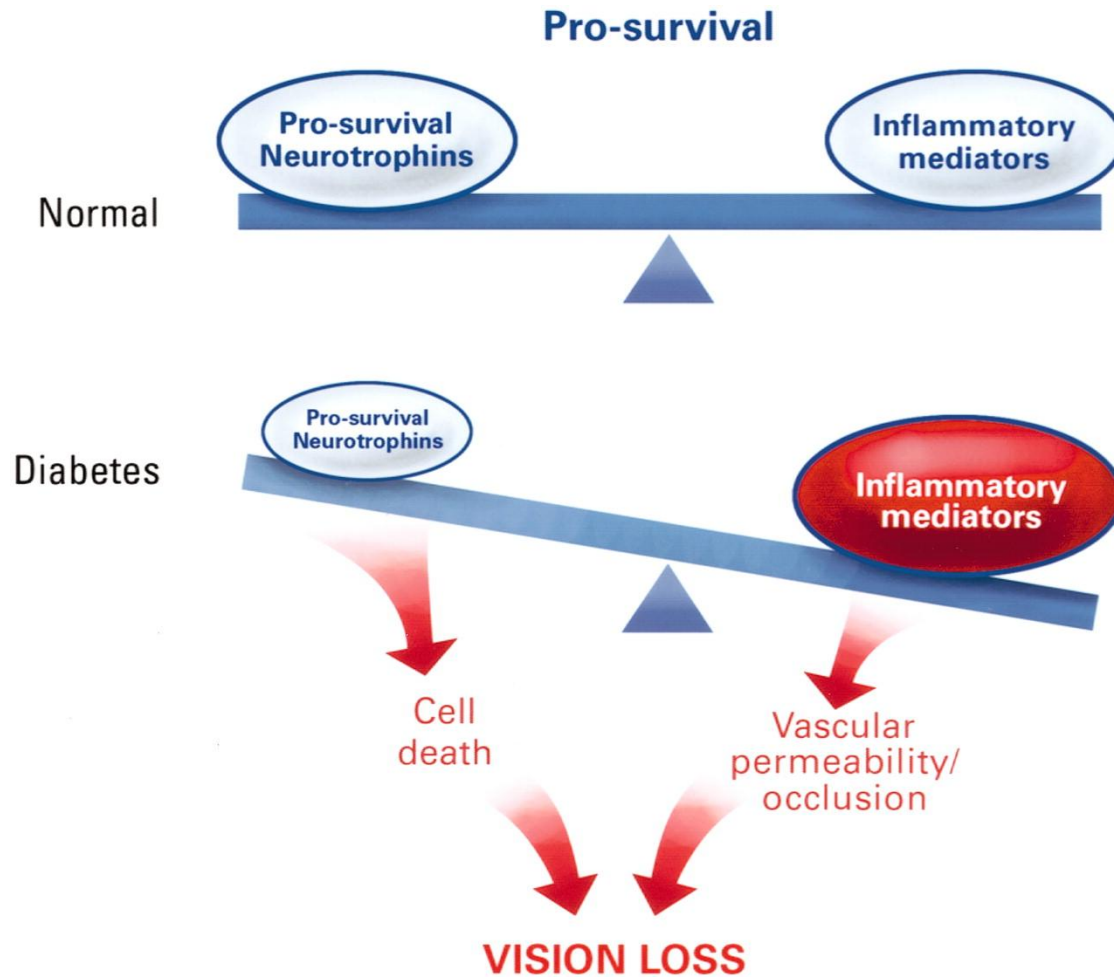
TIGHT JUNCTIONS



- VEGF and HGF
 - Decrease occludin content
 - Increase tight junction internalisation
- Glucocorticoids
 - Increases occludin gene expression
 - But, ZO-1 also needed

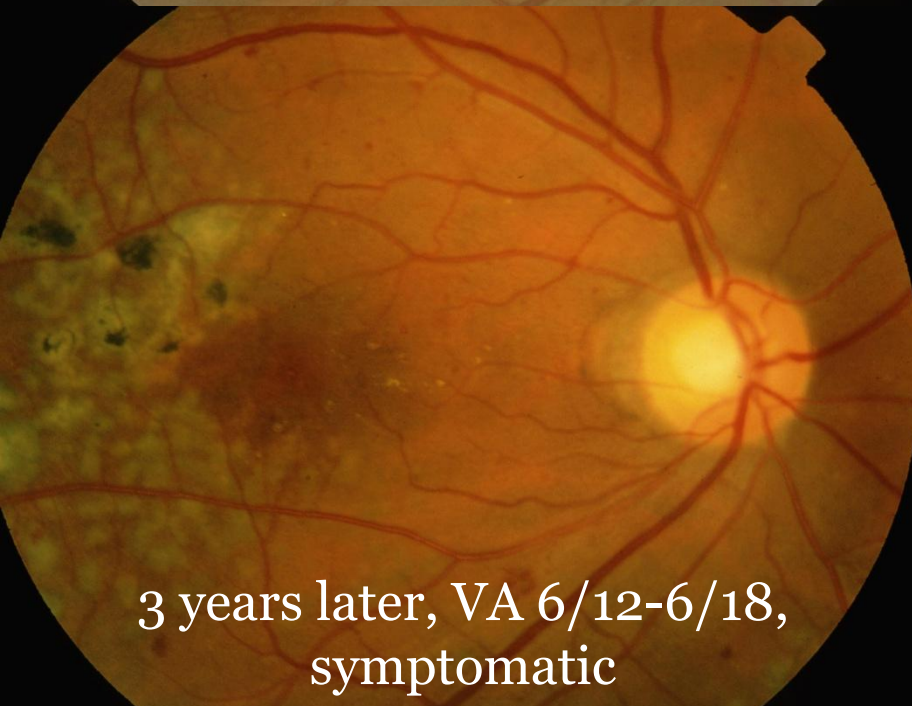
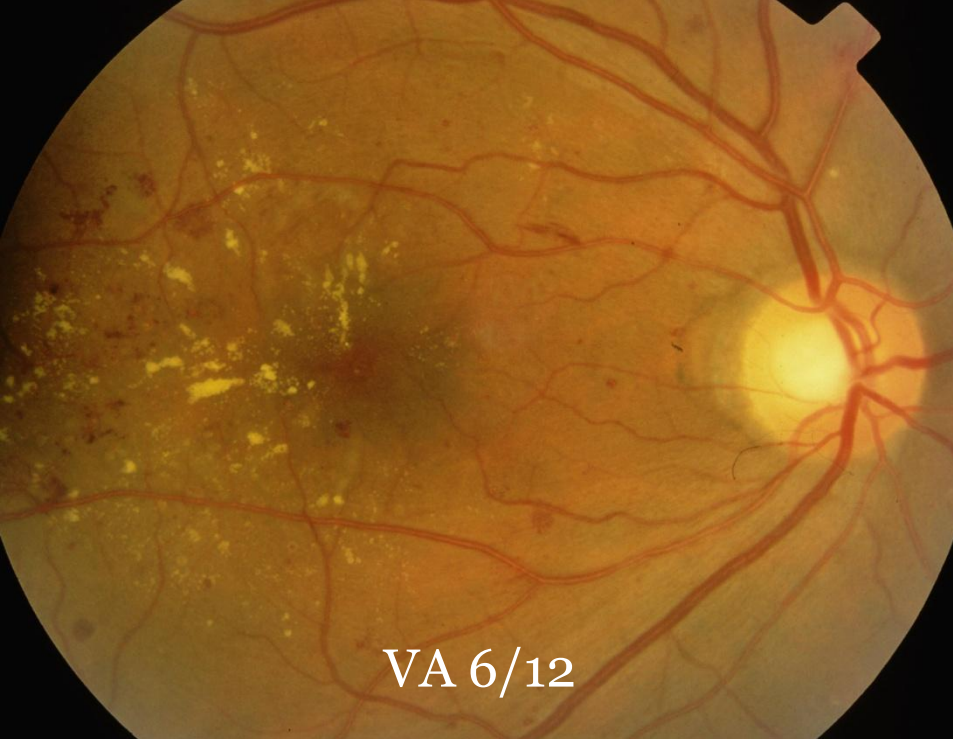






Unmet Medical Need in DME Treatment

- Better preventive ('upstream') medical therapies
- A substantial proportion of T2DM patients continue to lose vision and do not achieve a satisfactory visual outcomes
- ...Not just patients with chronic 'diffuse' DME
- Failure to prevent DR progression & other complics
- Many cases with laser side effects from chronic Rx

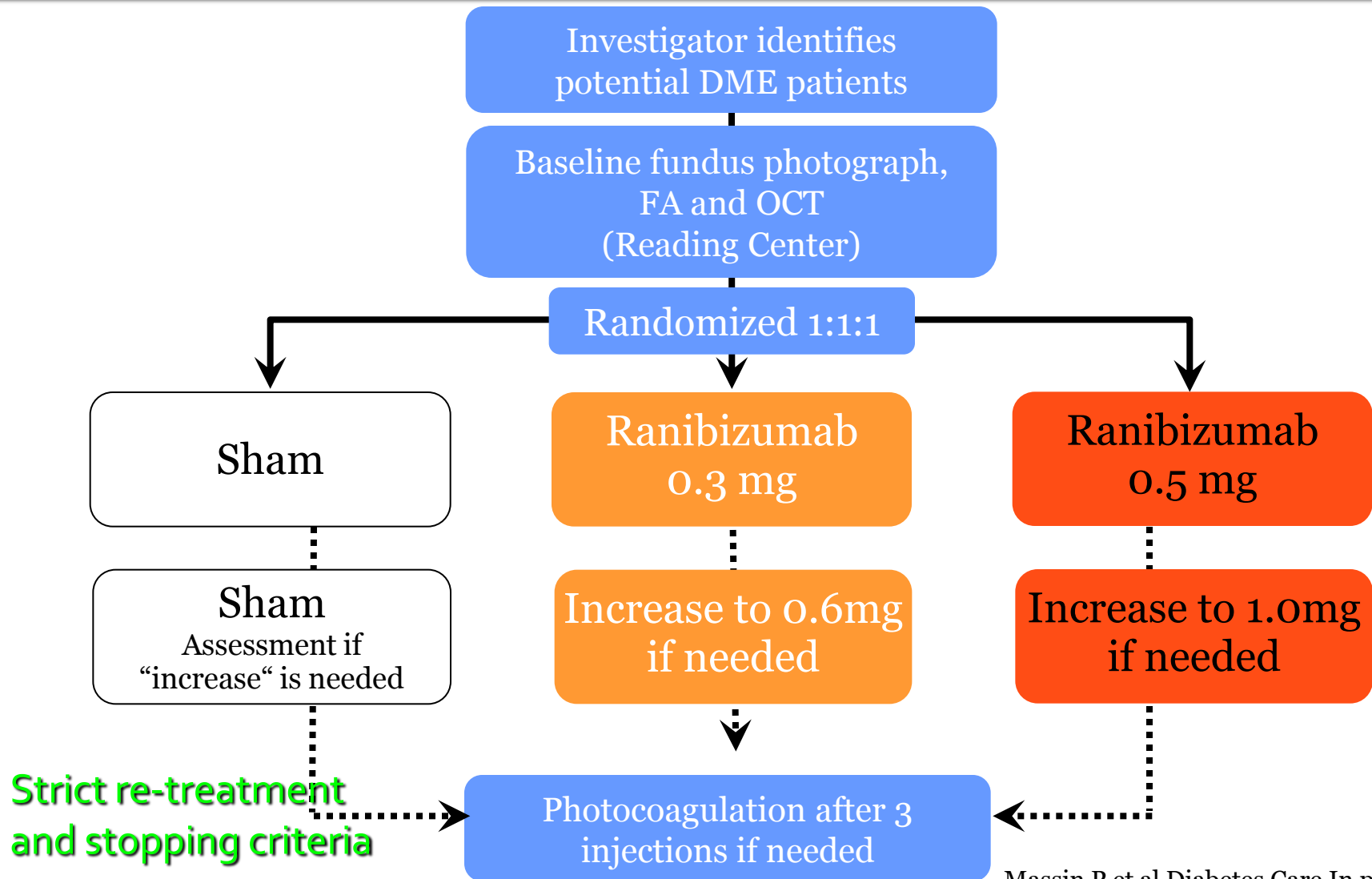


Focal / Grid laser treatment is often effective in treating DME, but multiple treatments may be needed, leading to later risk of 'laser creep', and rarely, secondary CNV

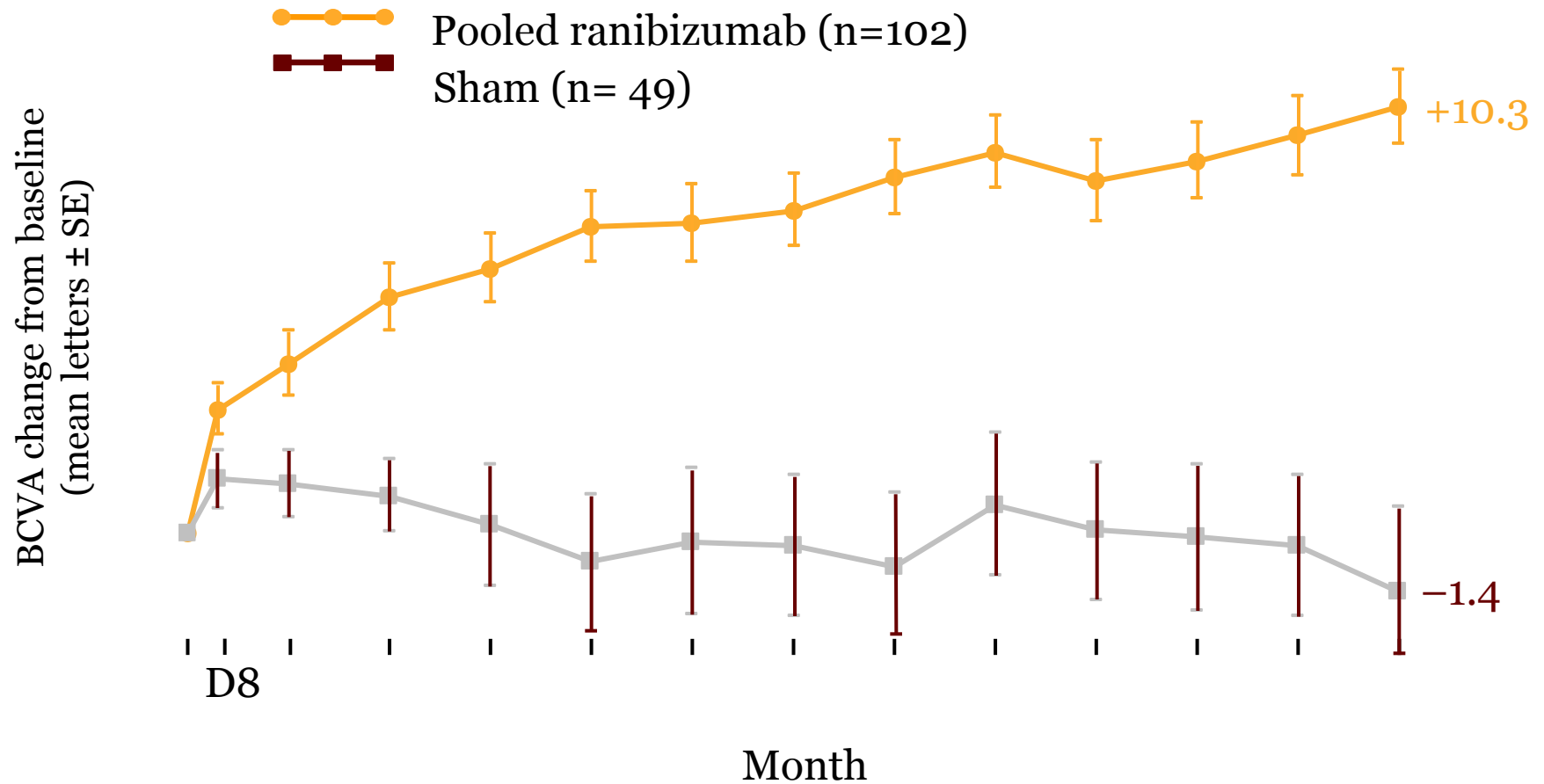
Alphabet soup

RESOLVE Trial Design (Phase II)

(n=151)

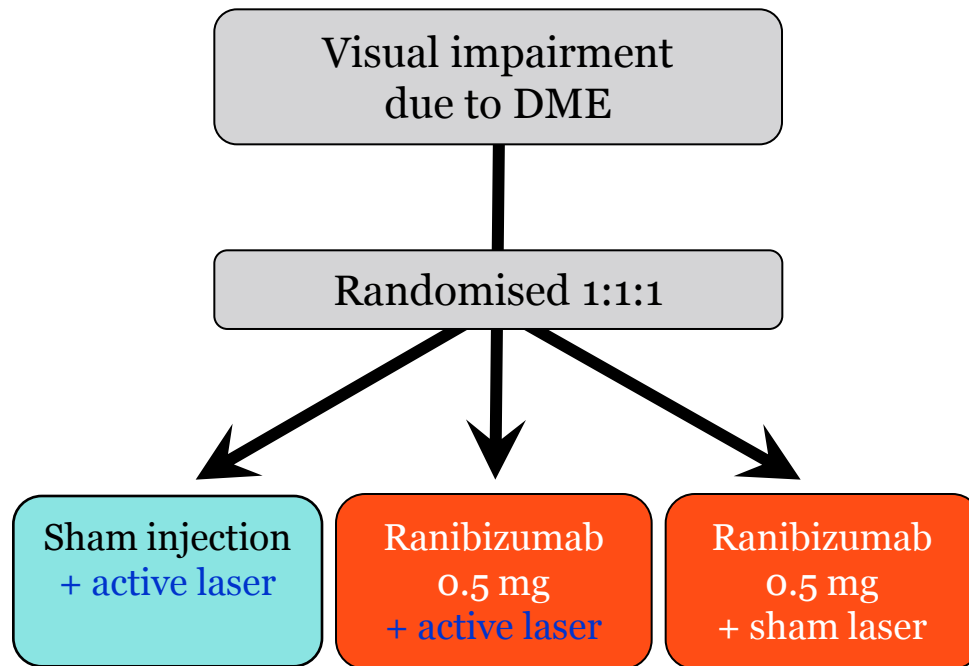


RESOLVE Mean BCVA change* from baseline



Mean injections Y1 = 10

RESTORE Trial Design (Phase III)



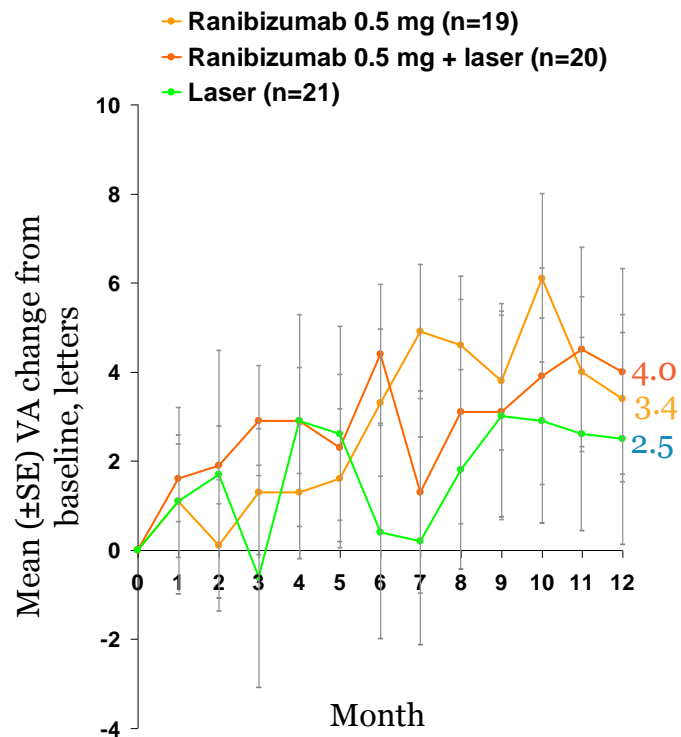
- Phase III, double-masked
- N=345
- evaluate the efficacy and safety of monthly ranibizumab (0.5 mg) as adjunctive therapy with laser photocoagulation and/or monotherapy in patients with visual impairment due to DME
- 12 months
- Primary endpoint: mean change from baseline in BCVA over 12 months

3 injections, then 'prn' injections according to well defined re-treatment and stopping criteria

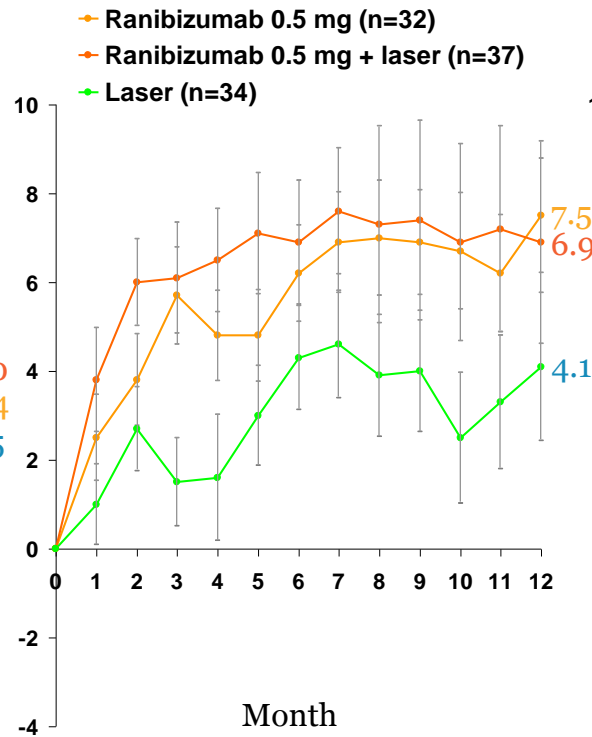
RESTORE

Mean VA change from baseline by baseline CRT

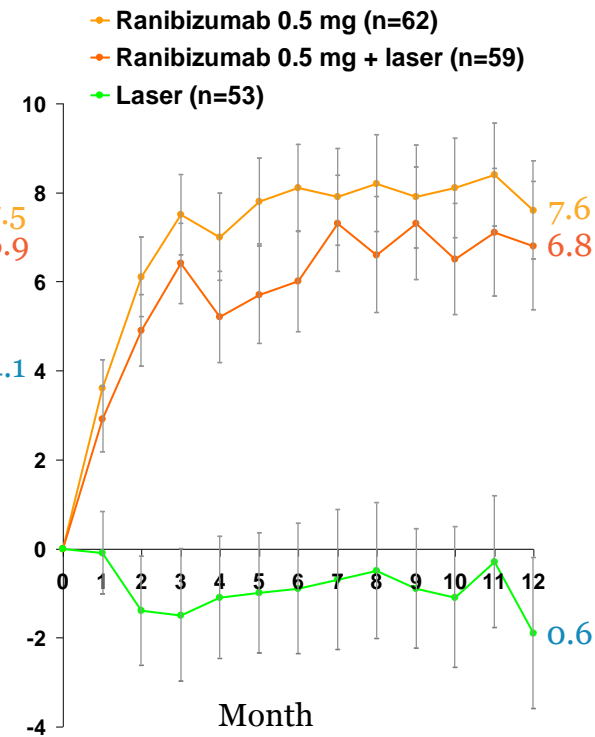
<300 μm



300–400 μm

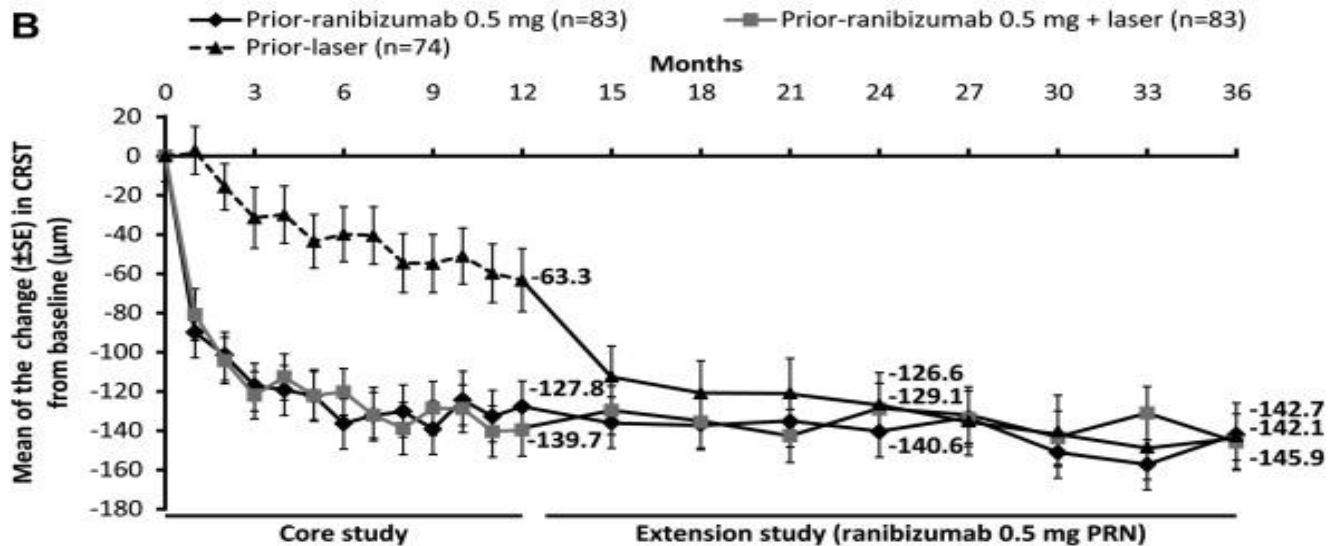
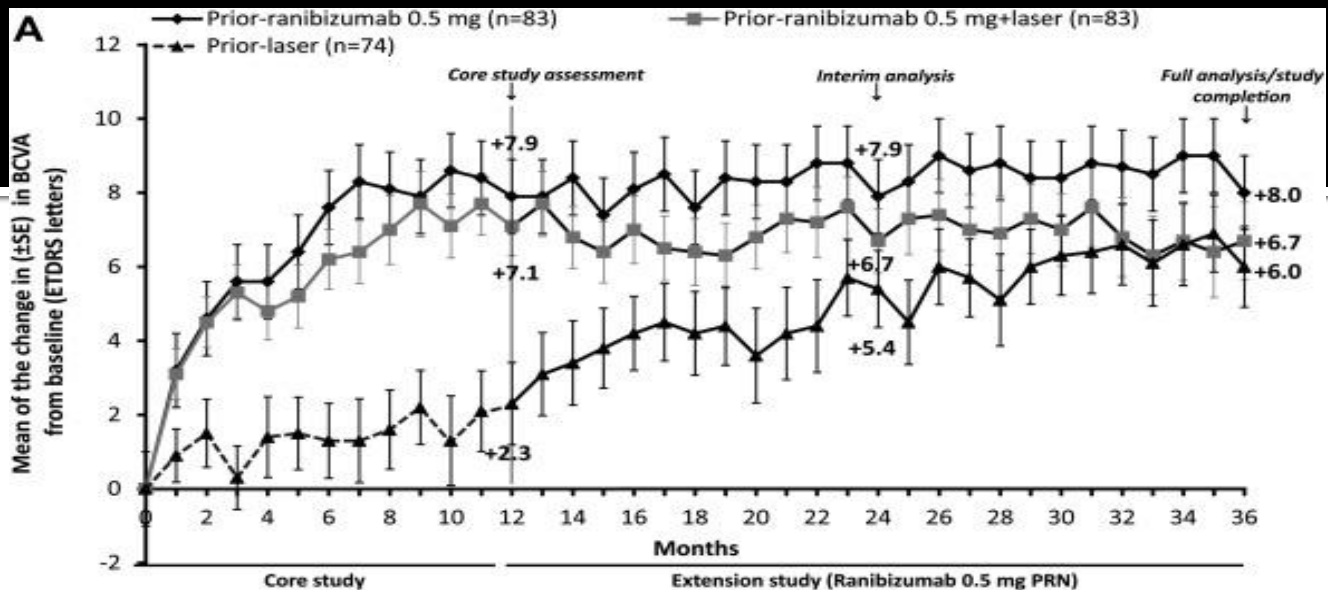


>400 μm

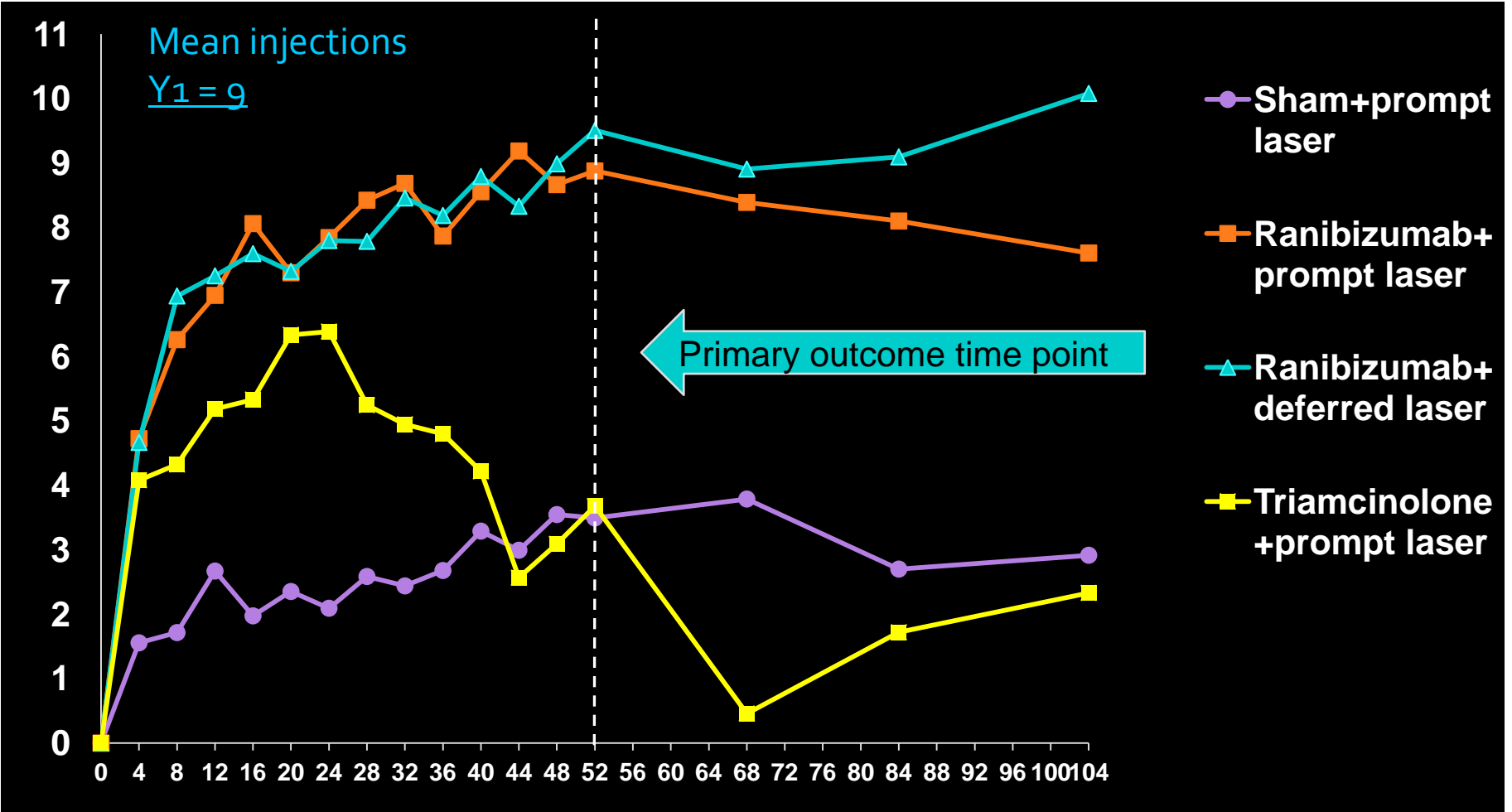


Efficacy numbers represent mean BCVA over time from Month 1 to Month 12 according to baseline characteristics

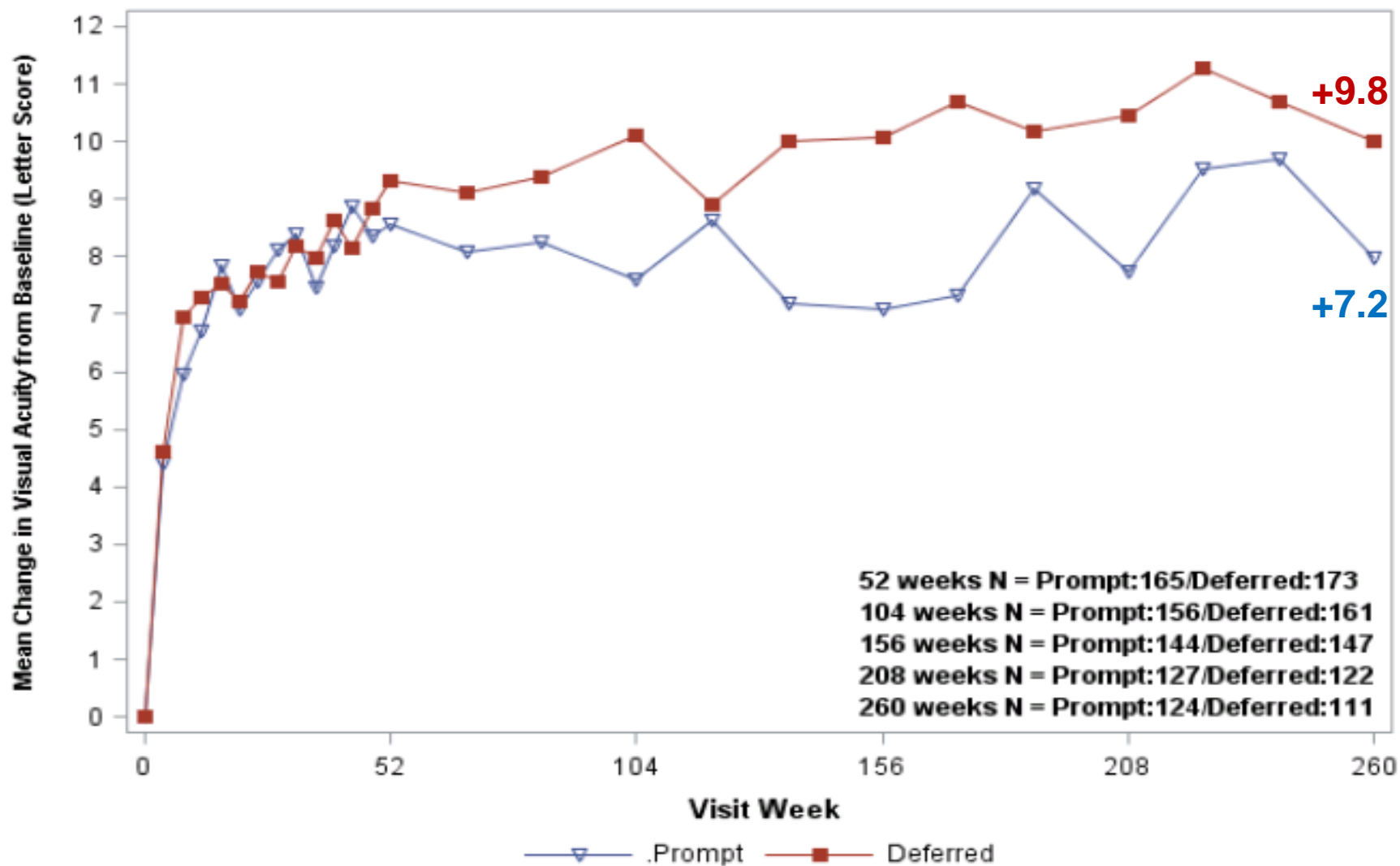
Data on file, Novartis



DRCR.net-Protocol Mean VA Change* from baseline



Mean Change in Visual Acuity* at Follow-up Visits



Focal/Grid Laser Prior to 5 Years*

	Ranibizumab + Prompt Laser N = 124	Ranibizumab + Deferred Laser N = 111
% of eyes that did NOT receive laser treatments prior to the 5 year visit	0	56%
Median # laser treatments prior to the 5 year visit	3	0

Protocol T

**Randomly Assigned Eyes
(one per participant):
N = 660**

Baseline

**Aflibercept
(2.0 mg)
N = 224**

**Bevacizumab
(1.25 mg)
N = 218**

**Ranibizumab
(0.3 mg)
N = 218**

One Year

N = 208 (93%)

N = 206 (94%)

N = 206 (94%)

**One Year
Excluding
Deaths**

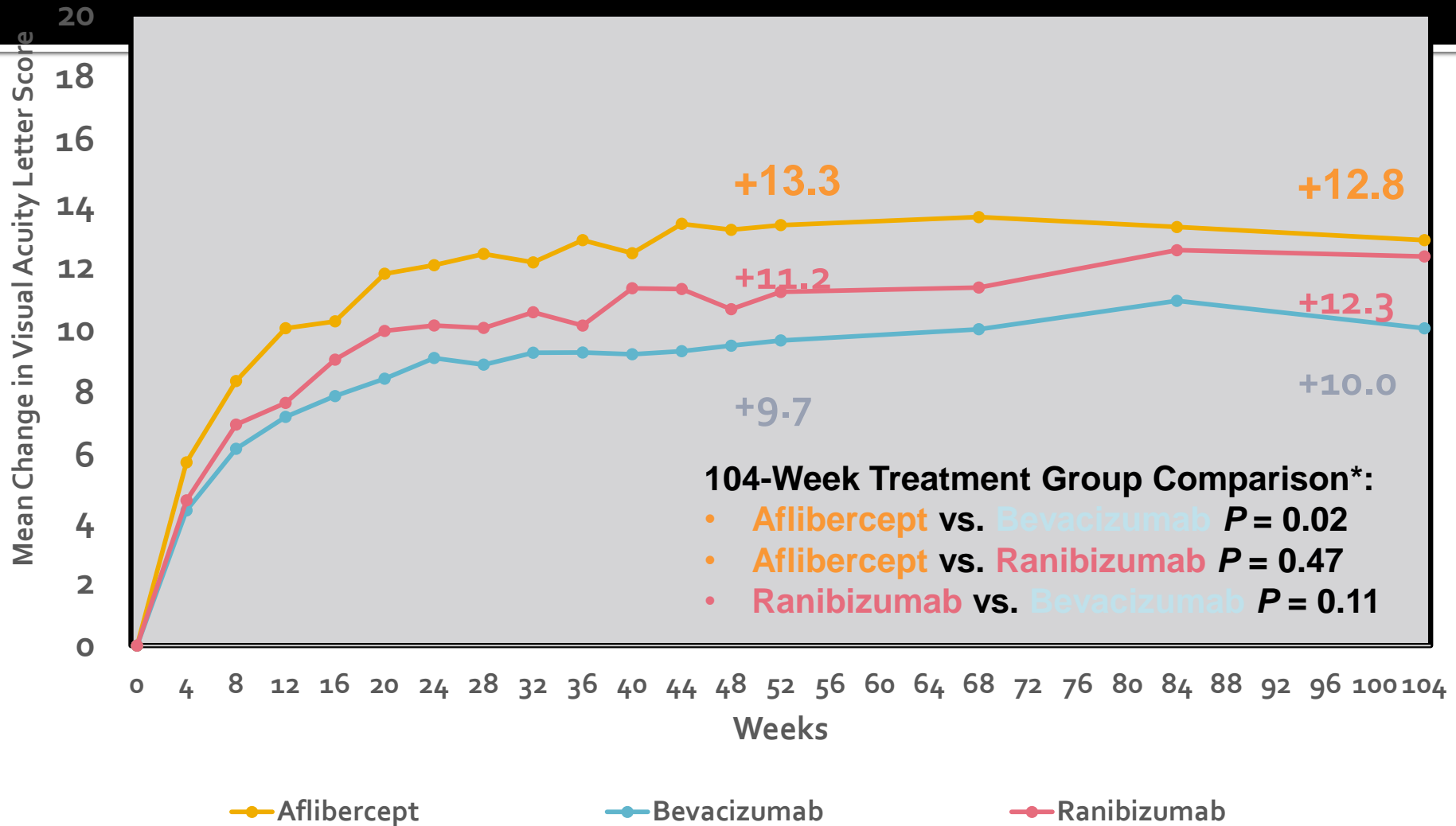
94%

97%

96%

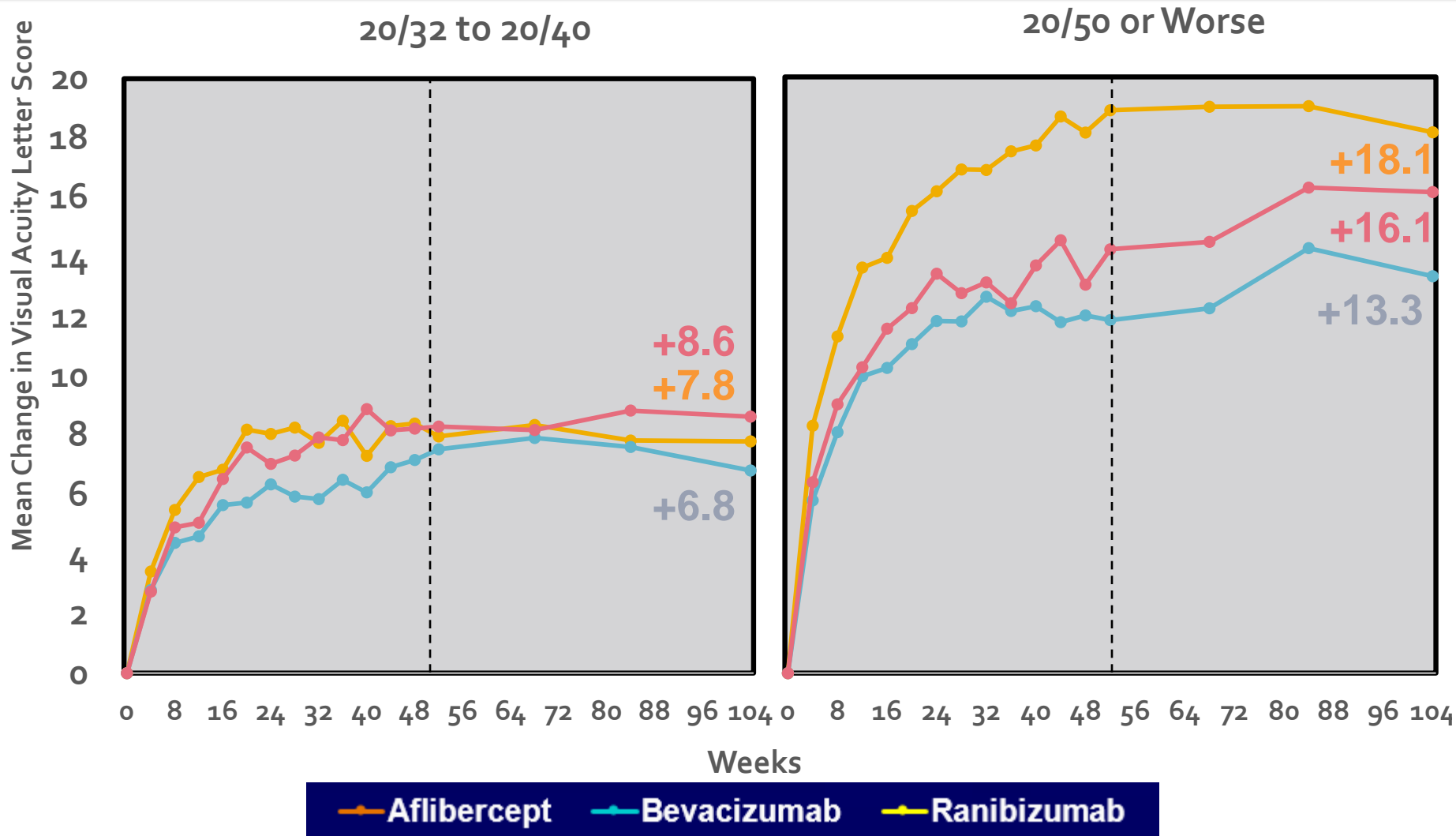
Protocol T-Mean Change in Visual Acuity Over 2 Years

Full Cohort

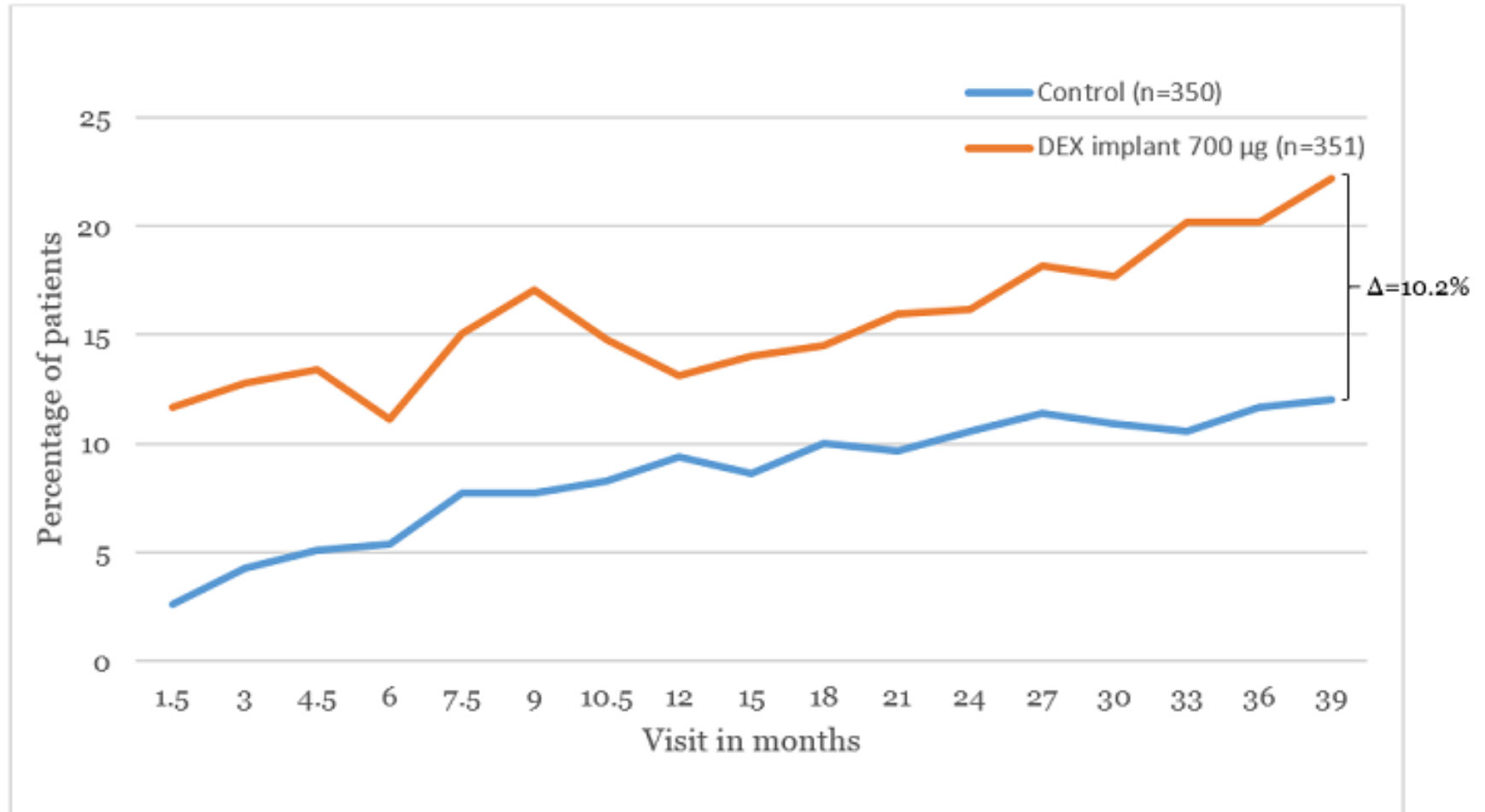


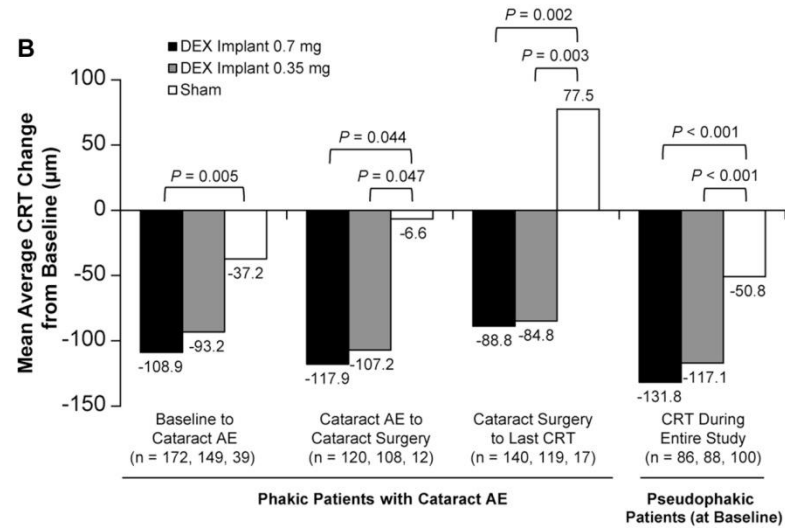
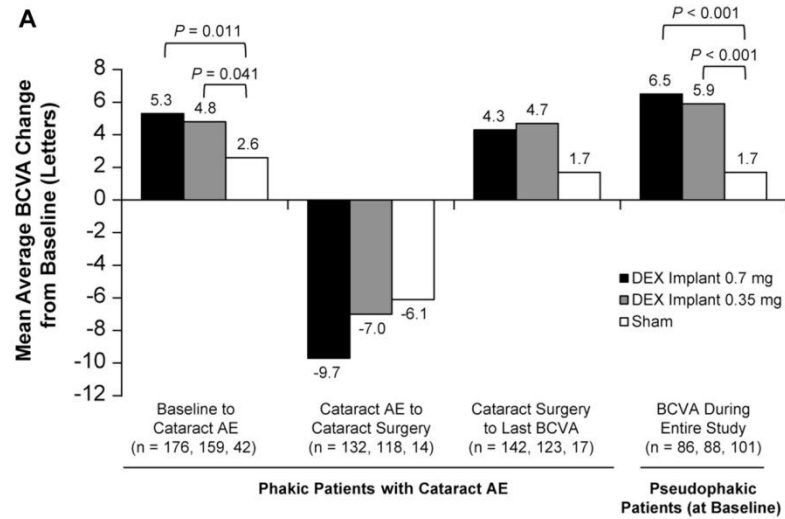
* P -values adjusted for baseline visual acuity and multiple comparisons

Protocol T-Mean Change in Visual Acuity Over 2 Years By Baseline Visual Acuity Subgroup



MEAD study Ozurdex





Horizon gazing

- Imaging swept source OCT-A
- Subliminal/micropulse laser
- Photobionics- CLEOPATRA, NIRD
- Topical VEGF inhibitors

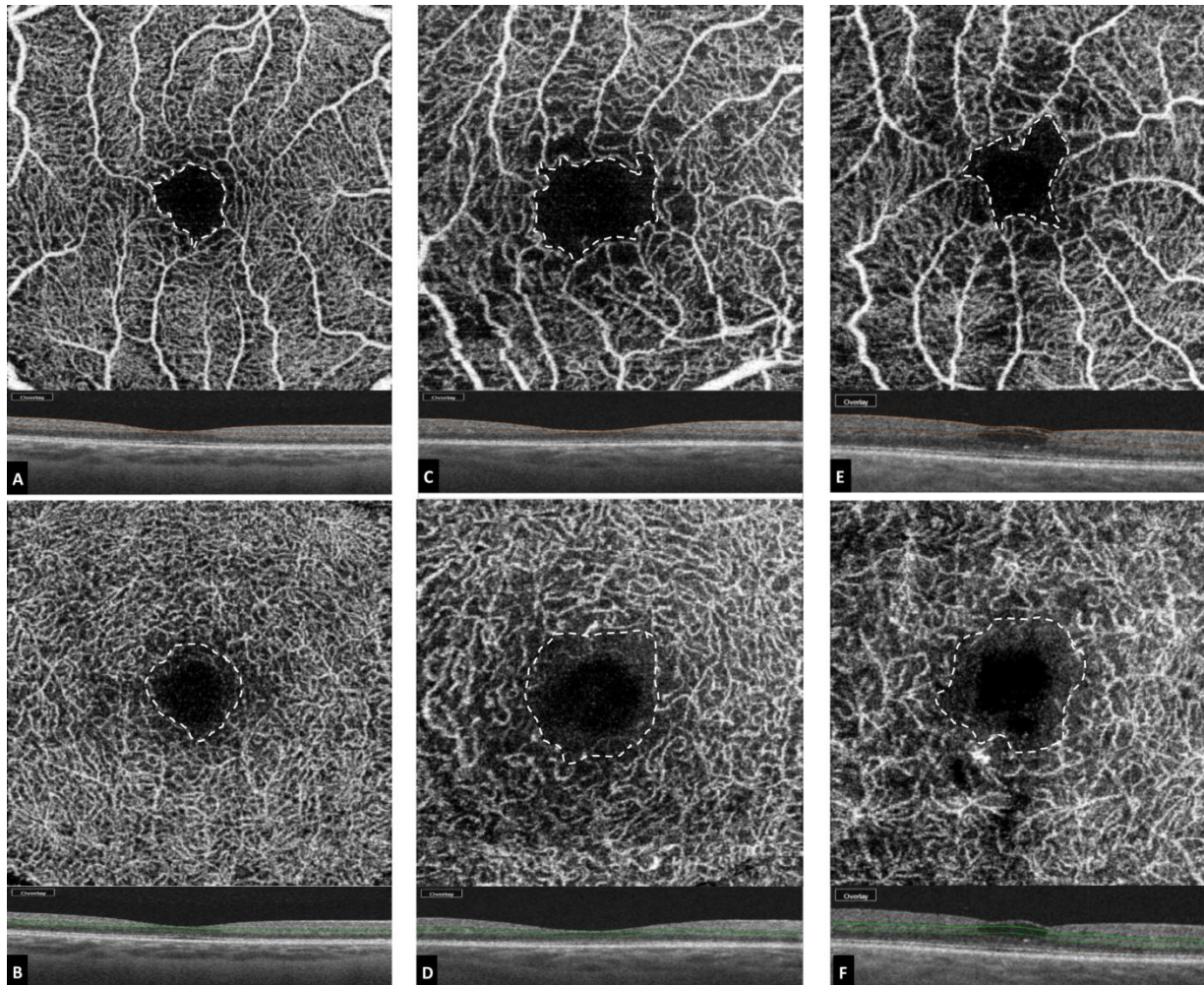


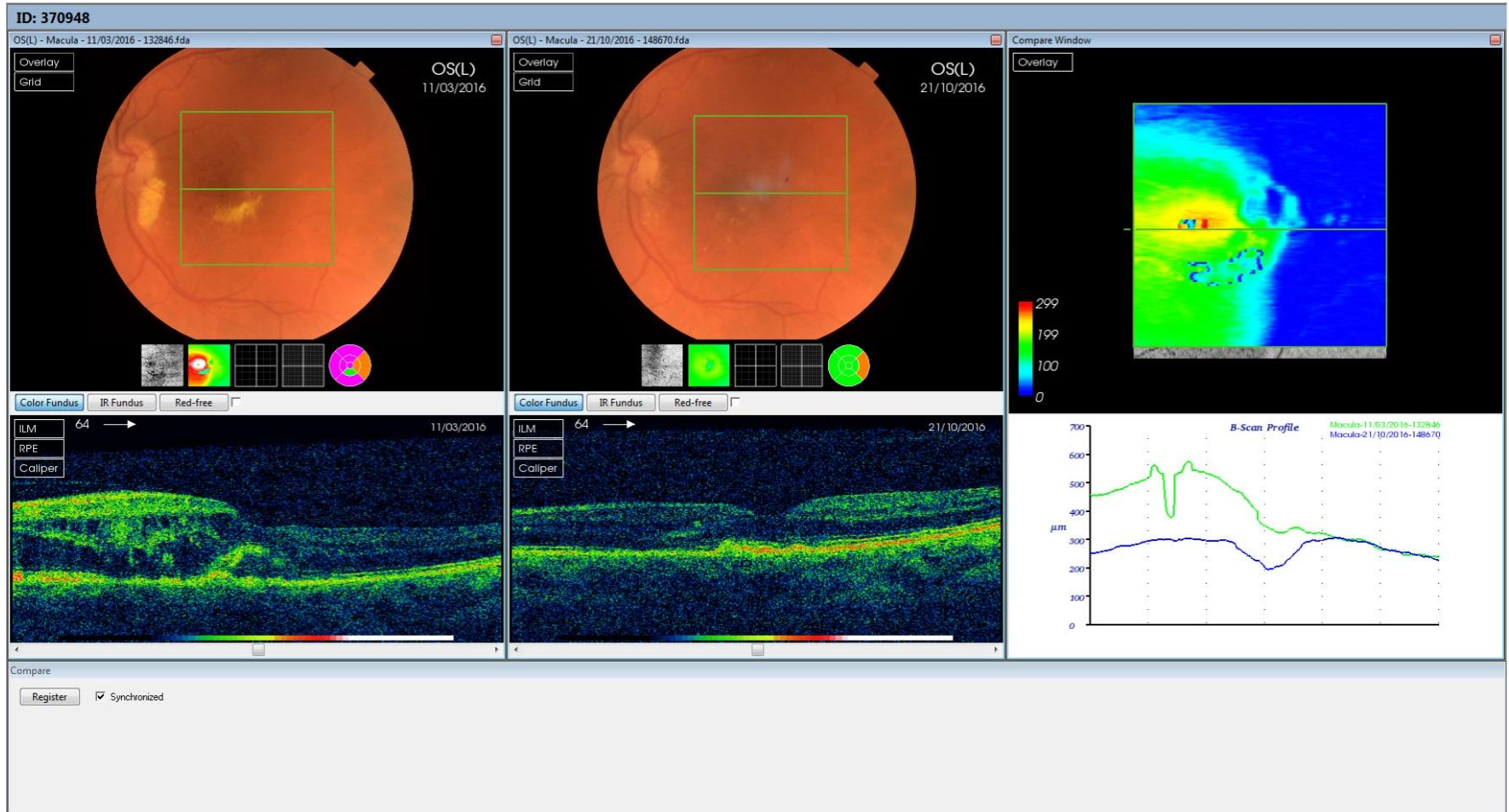
Figure Legend:

Swept-source OCT-A images of three subjects centered on the fovea. (A, B) En face projection image of the foveal avascular zone (outlined) of the superficial and DRLs in a healthy individual with segmentation. (C, D) Corresponding en face projection images of a patient with DR without DME. (E, F) En face OCT-A images of a patient with DR with DME.

Subthreshold/Micropulse laser

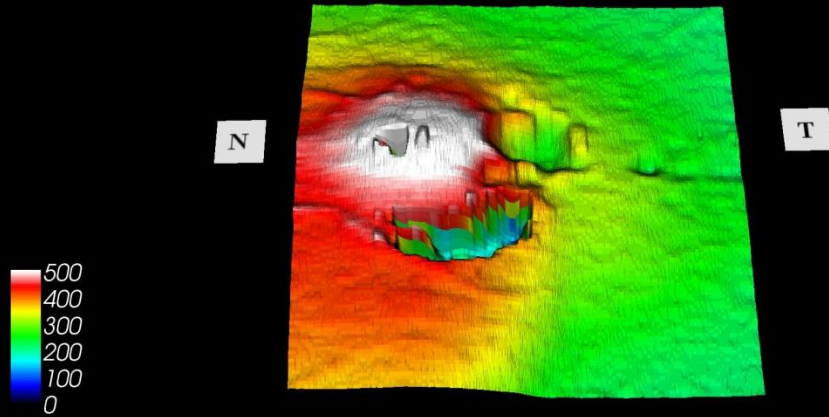
- Described 1990s
- Multiple pulses of laser delivered in a burst / envelope
- No visible change at time of laser application
- No changes on OCT
- Effects limited to the RPE

Micropulse laser

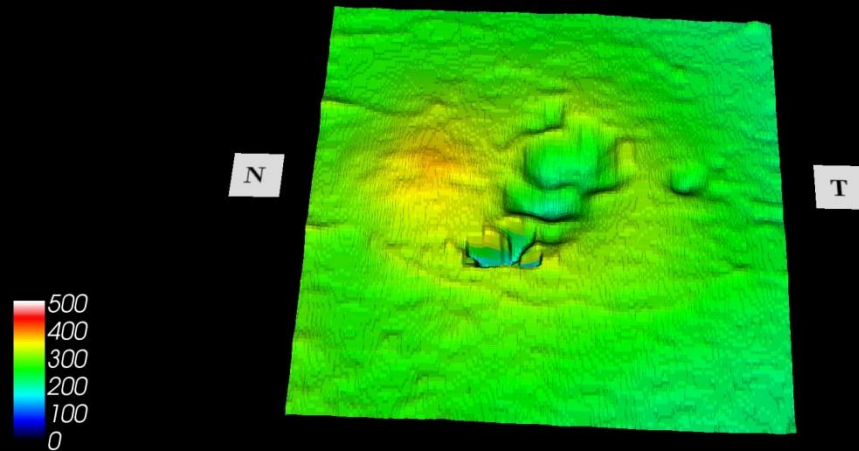


Micropulse laser

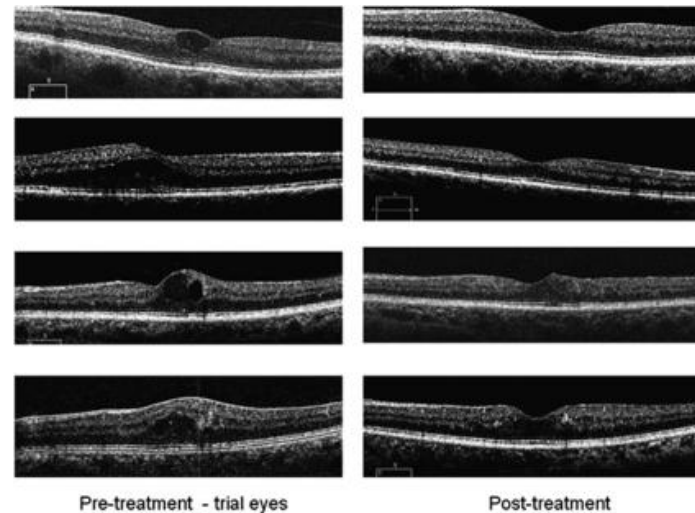
Surface



Surface

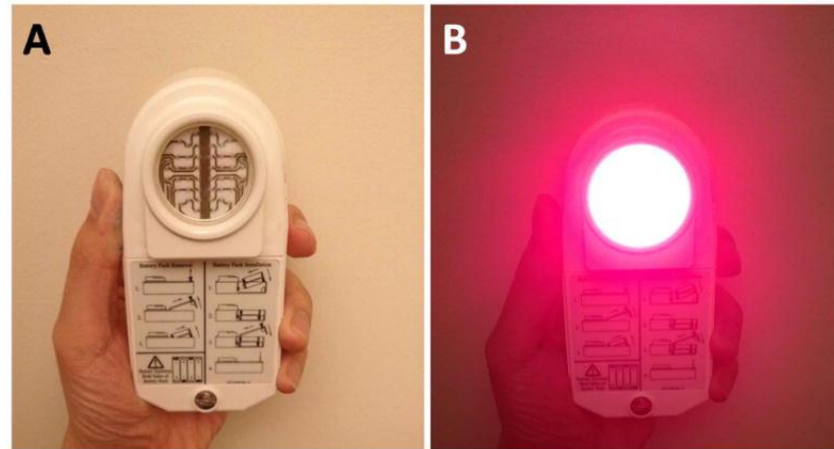


Photobionics-Keeping the lights on



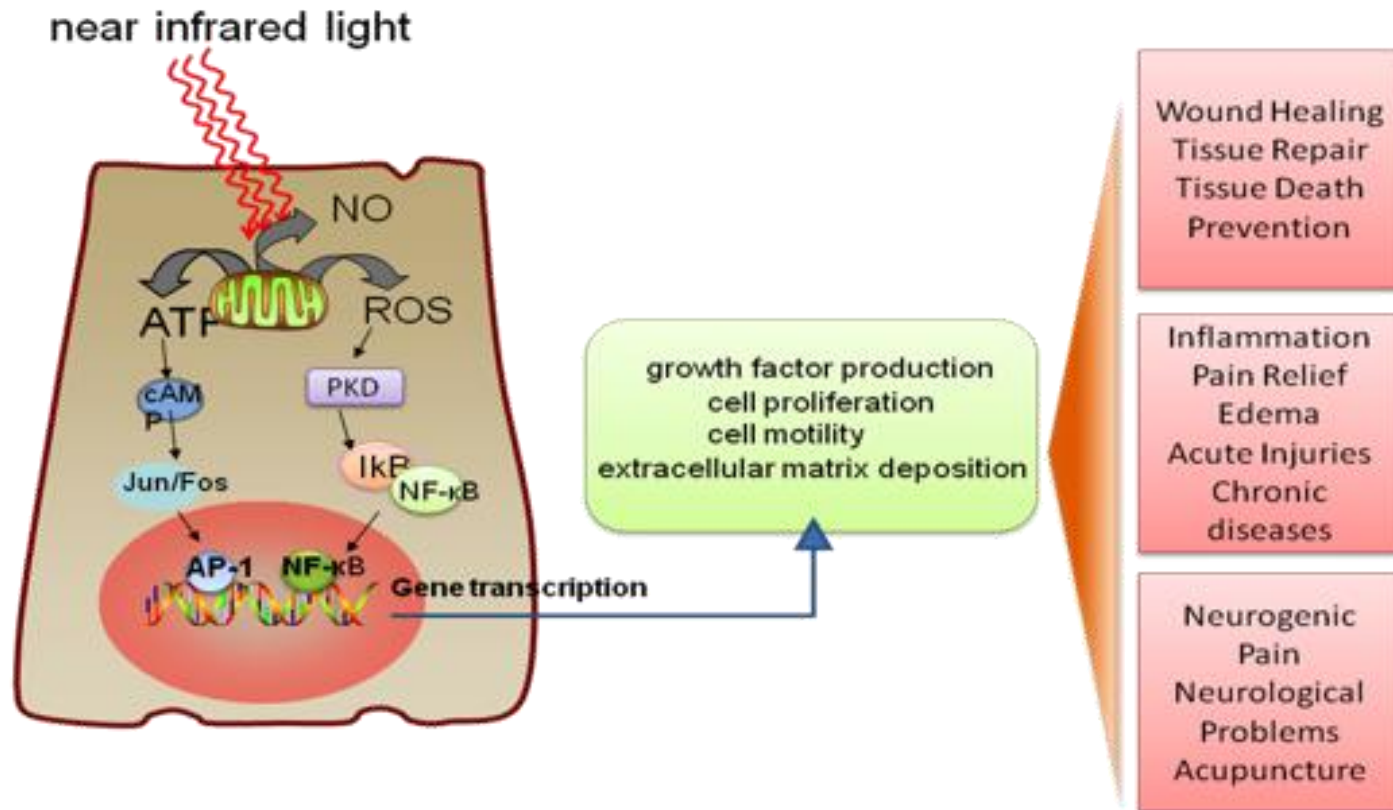
- [Eye \(Lond\)](#). 2011 Dec; 25(12): 1546–1554.
- Published online 2011 Oct 21. doi: [10.1038/eye.2011.264](https://doi.org/10.1038/eye.2011.264)
- PMCID: PMC3234487
- Regression of early diabetic macular oedema is associated with prevention of dark adaptation
- [G B Arden](#),^{1,*} [S Jyothi](#),² [C H Hogg](#),³ [Y F Lee](#),² and [S Sivaprasad](#)²

Photobiomodulation

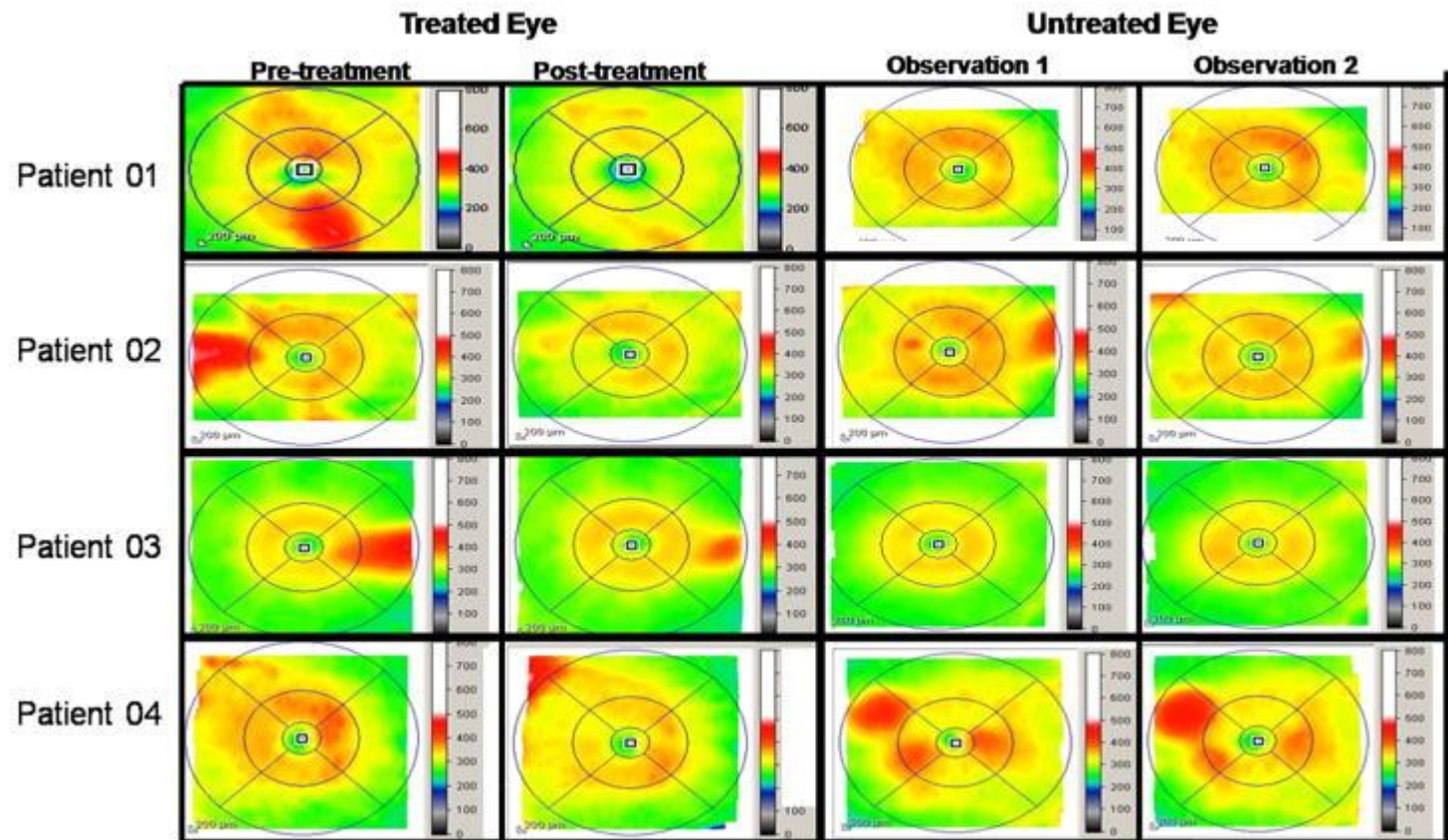


- [Br J Ophthalmol. 2014 Aug; 98\(8\): 1013–1015.](#)
- Photobiomodulation in the treatment of patients with non-center-involving diabetic macular oedema
- [Johnny Tang](#),^{1,2} [Ashley A Herda](#),¹ and [Timothy S Kern](#)^{2,3}

Photobiomodulation



Photobiomodulation

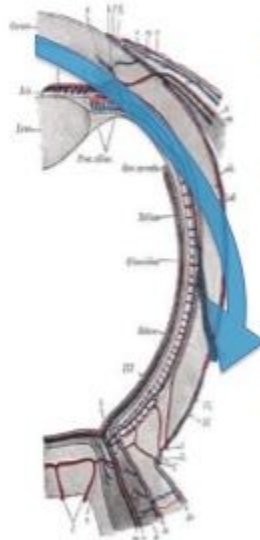


Topical anti VEGF agents

PAN-90806:

Potent, Selective, Small-Molecule VEGFR Antagonist

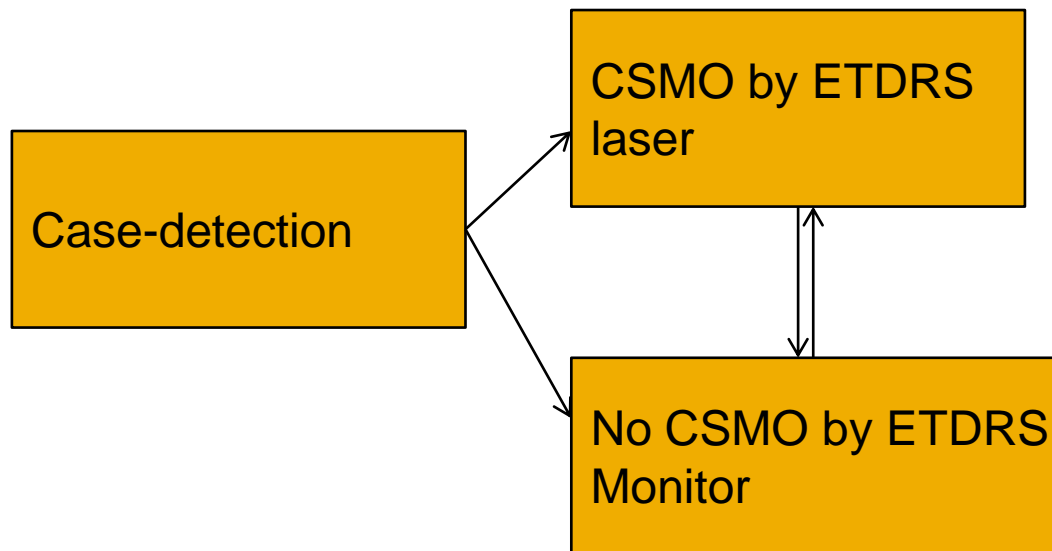
Unusually Favorable Characteristics for Topical Delivery to Back of Eye



- pK supports circumferential distribution route
 - Cornea > choroid > retina > aqueous > vitreous
 - Reproducible findings in rabbit, dog, primate
- Excellent target tissue distribution
 - Central choroid \approx 400-2,500 fold over kD at VEGFR2
 - Central retina \approx 200-1,000 fold over kD at VEGFR2
- Concentrations sustained at 17 hours post-dose
- Extremely low systemic exposure on topical dosing
- Performs as well as IVT anti-VEGF AB in animal models
 - P. Campochiaro, Johns Hopkins Univ.; J. Penn, Vanderbilt Univ.

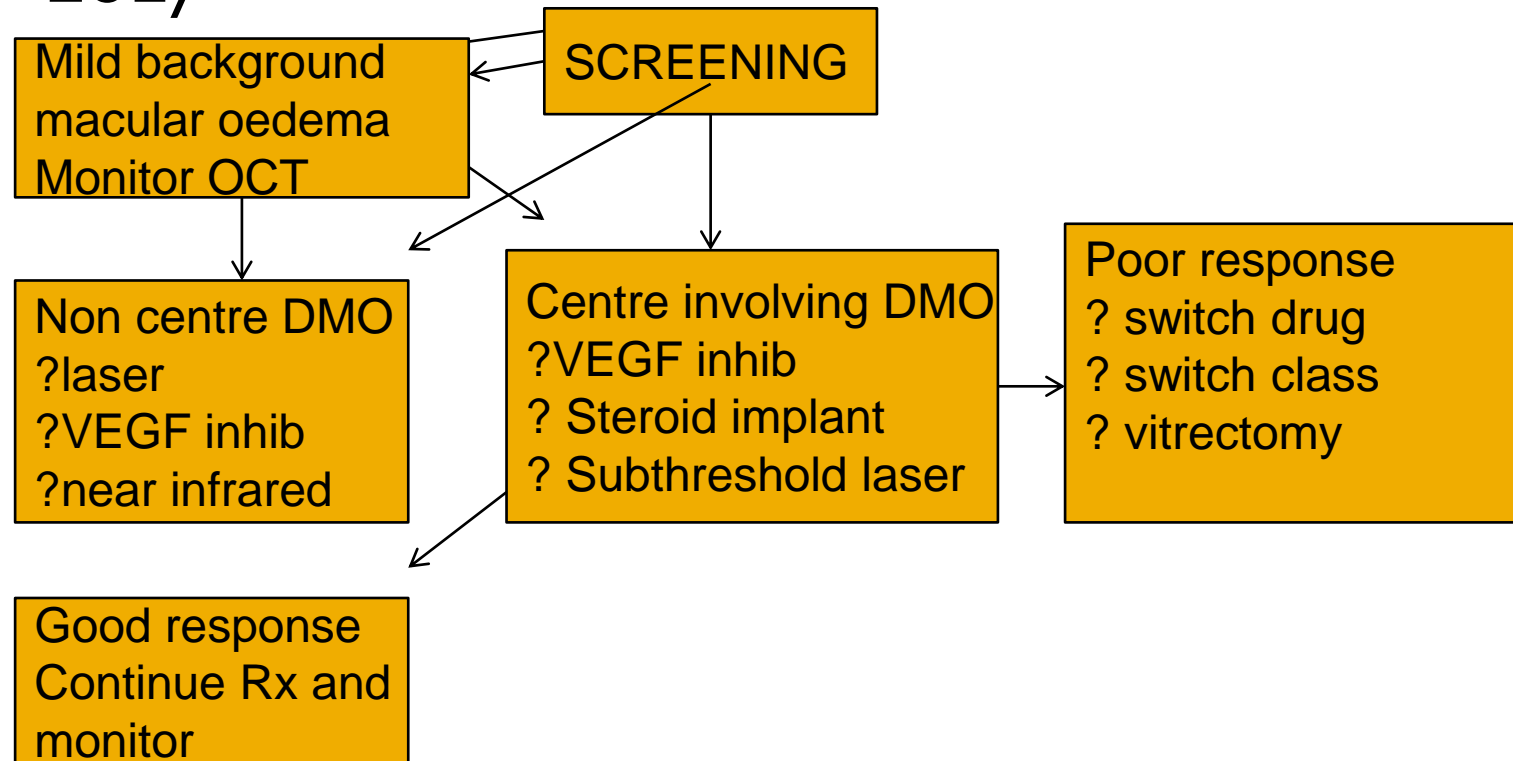
Diabetic Macular Oedema

■ 1986



Diabetic Macular Oedema

■ 2017



DIABETIC MACULAR OEDEMA- CONCLUSIONS

- Prevention is better than cure
- Knowledge of the pathological mechanisms incomplete
- VEGF inhibition results in better visual outcomes than photocoagulative laser
- Steroid implants can improve vision particularly in the pseudophakic