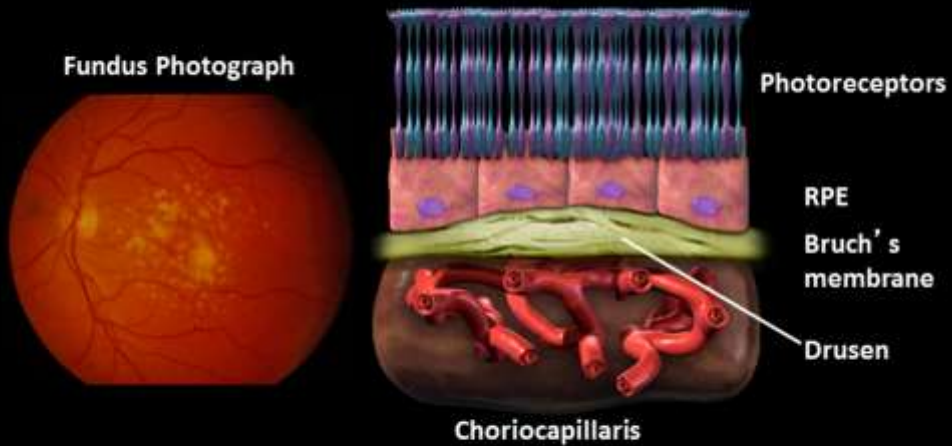


AMD is a huge problem and a major unmet need for treatment. These figures were just recently reported.



The advent of Ocular Coherence Tomography or OCT scanning has made diagnosis and monitoring of patients far more accurate, essentially we can see a cross section of the retina and resolve detail down to an accuracy of several microns. This is an example of a completely normal OCT.

Early Dry AMD: Drusen



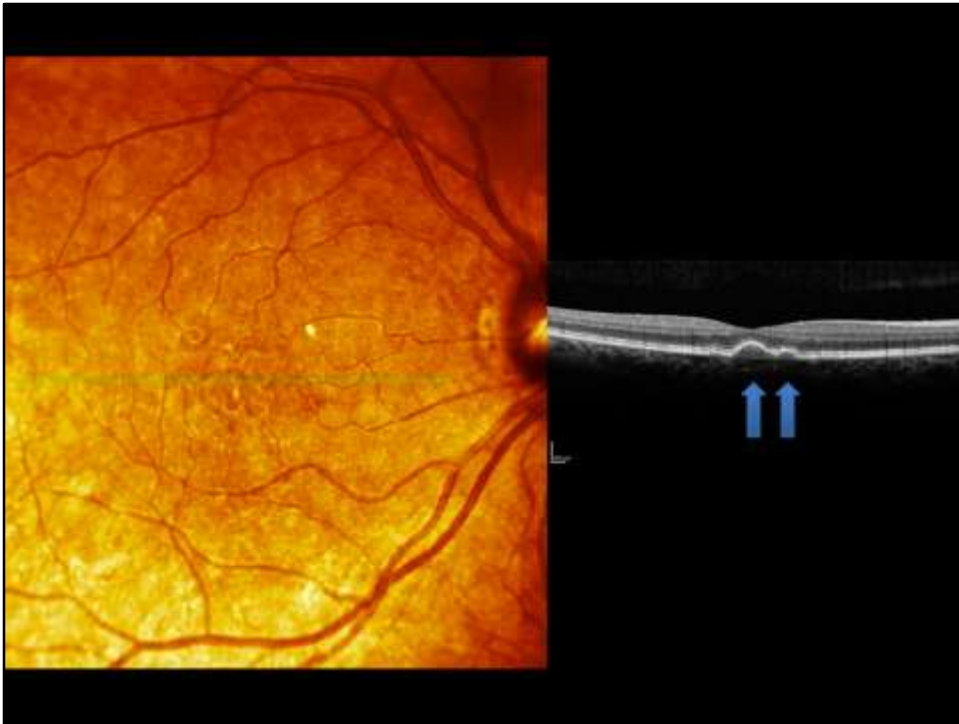
Campochiaro. *J Cell Physiol.* 2000;184:301.

Johnson et al. *Invest Ophthalmol Vis Sci.* 2003;44:4481; Reproduced with permission.

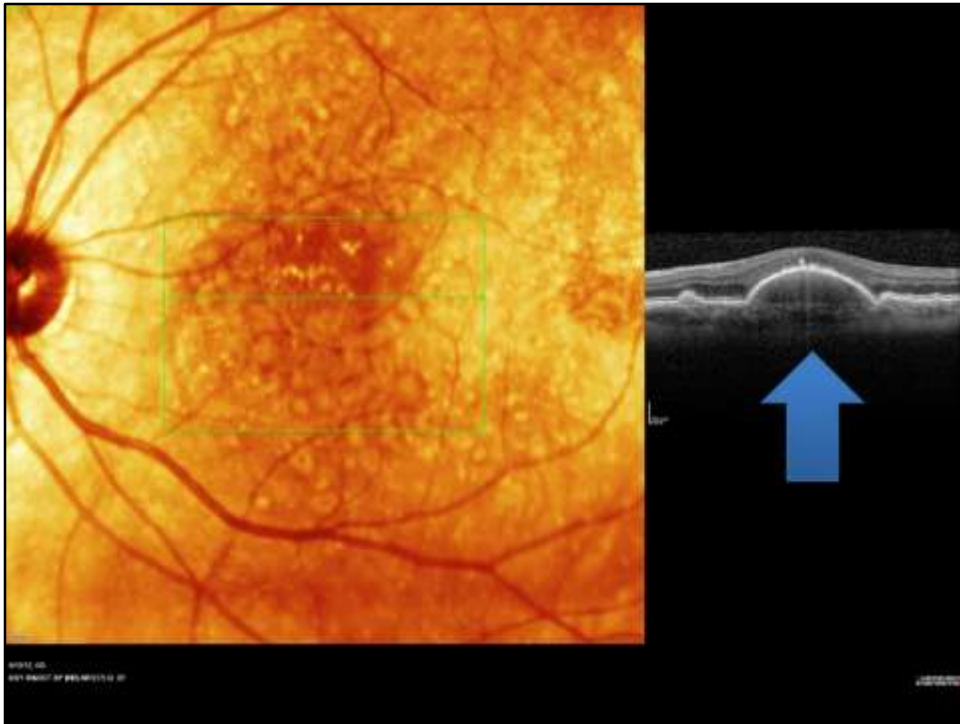
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The presence of drusen is one of the first clinical features of AMD. Drusen are made up of multiple proteinaceous and lipid components derived from the RPE, neural retina, and choriocapillaris, as well as extracellular sources.

The development of drusen leads to diffuse thickening of Bruch's membrane. This alteration in the membrane disrupts the flow of nutrients between the choroid layer and the RPE.

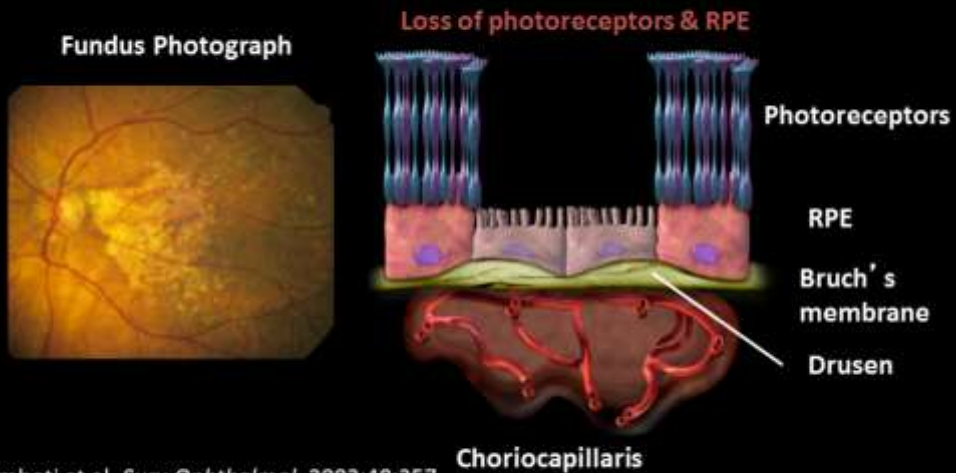


Here we see two drusen immediately under the fovea or central macular very clearly on OCT scanning



Here is another patient with a much larger confluent druse immediately under the fovea – he has noticed distortion and reduction of vision.

Advanced Dry AMD: Geographic Atrophy (GA)

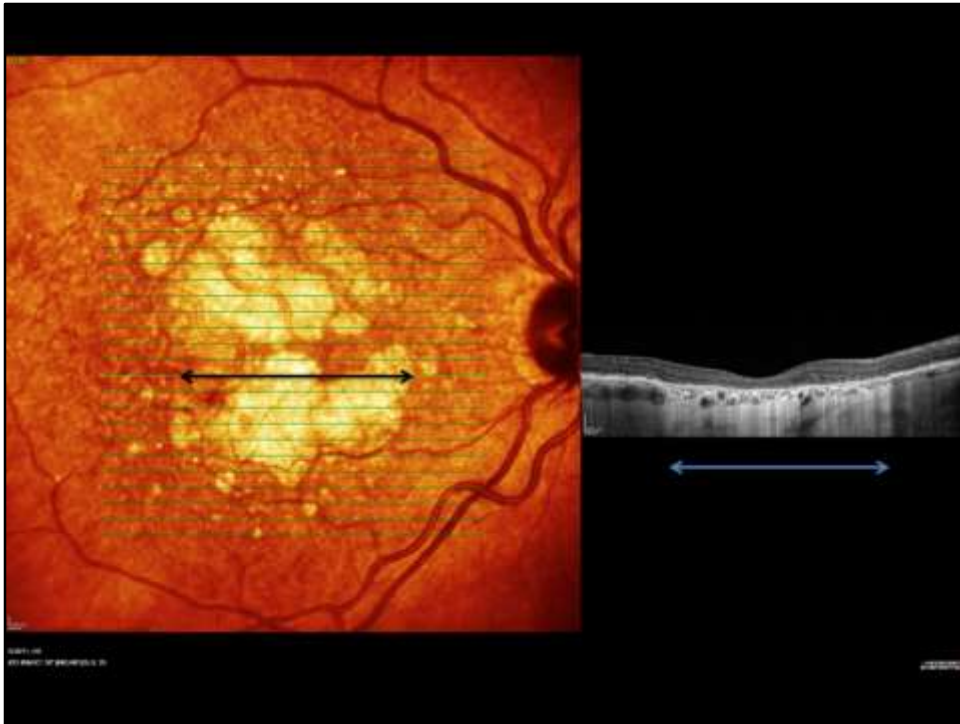


Ambati et al. *Surv Ophthalmol.* 2003;48:257.

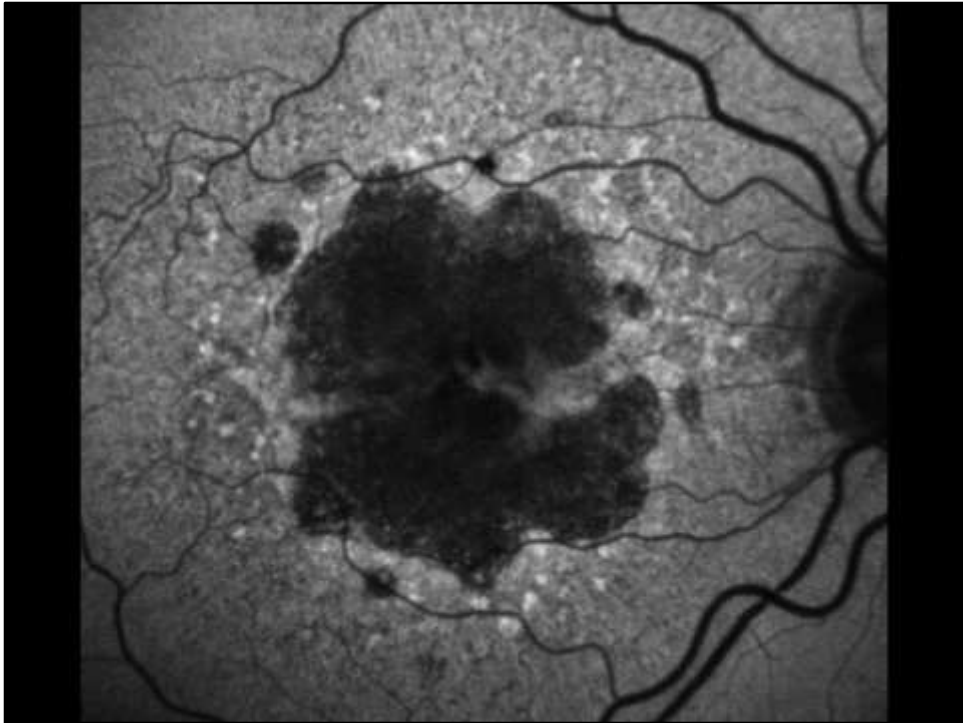
Hahn et al. *Arch Ophthalmol.* 2003;121:1099; Image reproduced with permission. Copyright © 2003 AMA.

Zarbin. *Arch Ophthalmol.* 2004;122:598.

In advanced dry AMD the RPE cells succumb to oxidative stress, chronic inflammation and injury and cannot support the overlying photoreceptors. They die leaving an atrophic area of non functioning retina. Note here the loss of photoreceptors overlying the dead RPE cells.



Here is the OCT taken through an area of geographic atrophy – note here the loss of retinal thickness and the complete loss of the RPE layer corresponding to the marked line



This is the fundus autofluorescence scan of the same patient. The dark area in the centre is atrophic and non functioning, the glowing white areas shows areas of lipofuscin accumulation under the RPE cells which will atrophy and turn black with the progression of disease. Lipofuscin autofluoresces when excited by a blue wavelength light. Lipofuscin is a lipid protein aggregate derived from vitamin A metabolism and is a generator of Reactive Oxygen Species. This progression can occur quite rapidly causing blindness within several years.

Vitamins

Current recommendation is Vitalux S or Preservision

However:

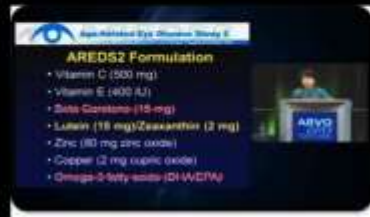
Recent analysis of genotypes (AREDS):

High CFH/Low ARMS2 - risk of progression to advanced was 135% higher within 7 years.

Low CFH/High ARMS2 - 37% lower

High CRF/High ARMS2 and Low CRF/Low ARMS2 – no significant benefit or harm

Dr Carl Awh, Tennessee Retina, presented ASRS Aug 10 2014



The only treatment apart from lifestyle changes is vitamins, the current recommendations are for vitalux s and preservision. Dr. Emily Chew from the National Eye Institute is seen here presenting the AREDS 2 results at ARVO in 2013. However there has been some very recent controversial analysis that shows that certain genotypes may have greater risk of progression by using vitamins, this could indicate a greater need to evaluating patients with genetic testing.

Wet AMD – all cases were dry initially
Vascular Endothelial Growth Factor – VEGF
15-20% conversion rate
Rx Intra ocular injections of ant VEGF drugs



15 to 20% of dry AMD patients will convert to the wet form, largely driven by VEGF which causes new blood vessels to grow into the retina.

Toronto and Oak Ridge
Photobiomodulation study in dry AMD
(TORPA)

Presented at ARVO 2012

Photobiomodulation:

Modify cellular behaviour

LEDs and other light sources can be used

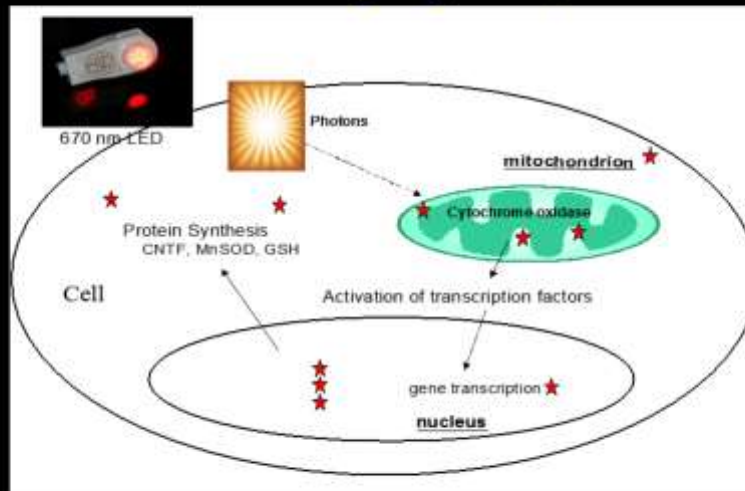
Avoid thermal damage

Rejuvenate and Revitalise target cells

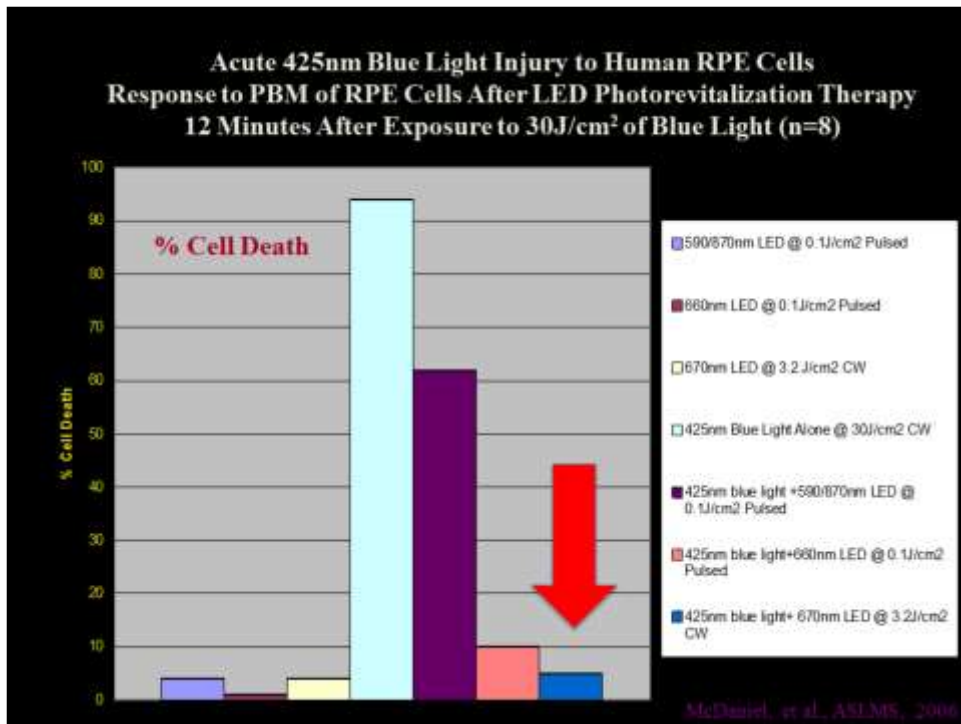
Photobiomodulation, also known as low level light therapy can modify cellular behaviour. Non coherent or non laser light sources used at low powers avoid thermal damage to the target cells. PBM can improve the functioning of compromised cells moving them to a survival pathway.

LLPT - Photon Therapy

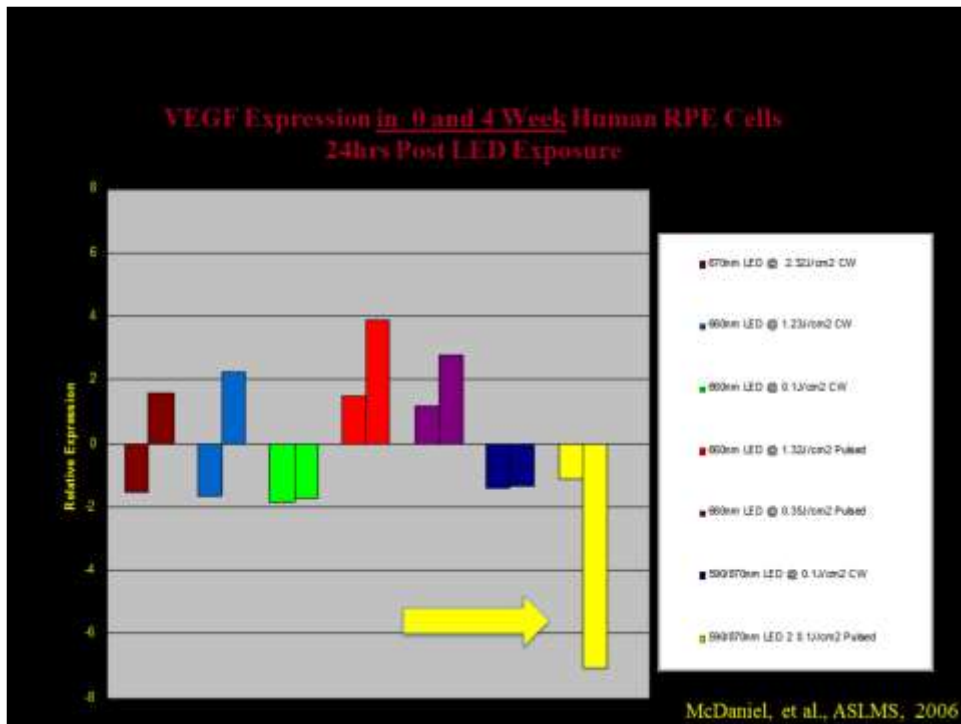
Postulated Signaling Pathway



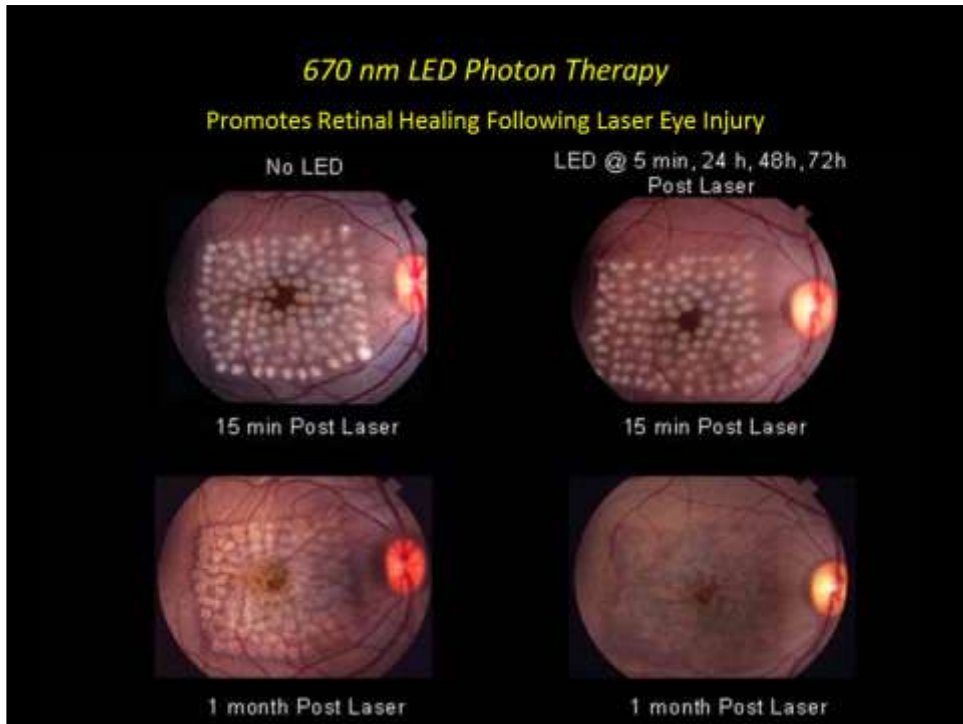
Not only do photons have a direct ATP producing role but more importantly there are downstream effects with activation of transcription factors and promotion of cellular anti inflammatory and anti oxidant properties.



Some work by Dr. McDaniel with human cultured RPE cells shows the photorevitalization effect of 670 nm red light after exposure to a high powered 425nm blue light. This column in the middle shows over 90% RPE cell death after exposure to blue light but less than 5% cell death after blue light insult and red light treatment.



This shows the relative expression of VEGF 24 hrs after exposure to different light codes in human rpe cells. Note here that VEGF expression is markedly reduced by low powered PULSED YELLOW light. VEGF is implicated in conversion from dry to wet AMD and we have utilised this property of pulsed yellow light to reduce VEGF expression and hopefully reduce the conversion to wet AMD.



This is dramatic photographic evidence from Professors Eels and Whelan (University of Wisconsin) of the healing effect of PBM on deliberate monkey retina laser burn. The retina on the right screen was treated after the laser burn with 670 nm light just four times over 3 days. The retinal healing is apparent at one month.



**Yellow 590nm LED device.
35 sec. treatment time.**

590nm +/- 8nm at 4mW, 790nm +/- 60nm at 0.6mW, for 35 seconds, pulsed at 2.5 Hz (250 milliseconds on, 150 milliseconds off) while delivering 0.1J/cm²/treatment.

**Red and near-infrared
670nm device.
80 sec. treatment time.**

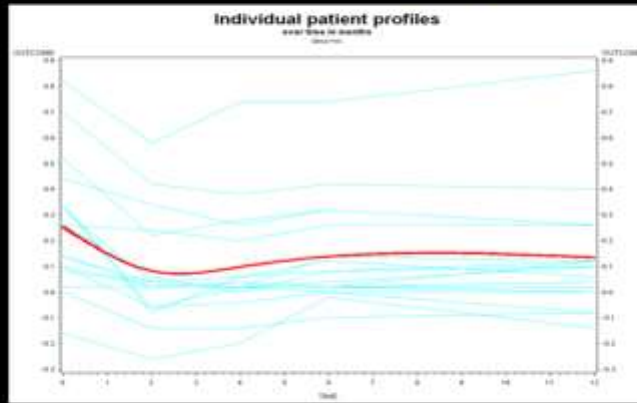
670nm +/- 15nm at 50-80 mW/cm², 4-7.68 J/cm², for 88 +/- 8 seconds.



In the TORPA study patients were treated with these two devices 18 times over 6 weeks. I have seen equivalent results of vision and contrast sensitivity with a condensed treatment regime of 18 treatments in 9 sessions over 3 weeks which is far easier for patients to manage

Repeated Measures ANOVA

ETDRS Visual Acuity logMAR

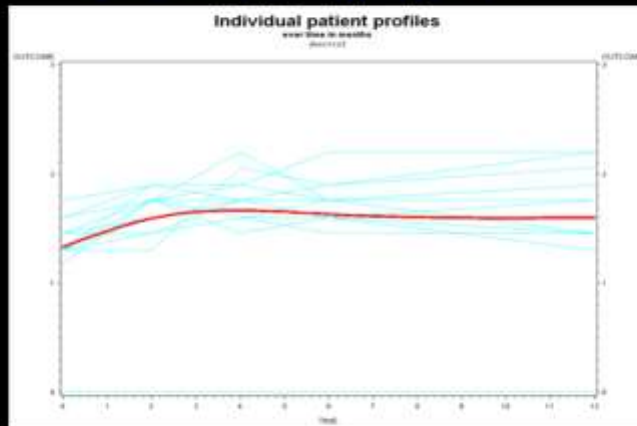


$$F(4,68) = 18.86, p < 0.0001$$

This is the repeated measures anova for ETDRS logmar visual acuity showing statistically significant vision improvement with a notable p value.

Repeated Measures ANOVA

Contrast Sensitivity 3cpd



$$F(4,68) = 11.44, p < 0.0001$$

This is the repeated measures anova for contrast sensitivity at 3 cpd over the study course of one year. Note the very significant p value.

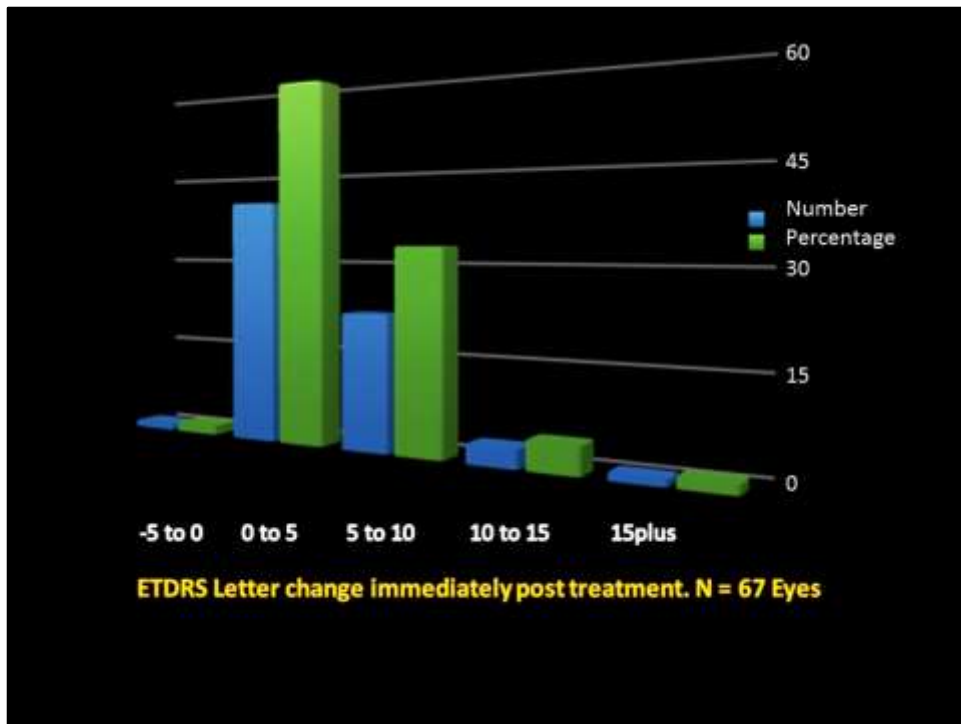
Off Label patients

Condensed treatment time

No IRB

OCT every visit

Close to an additional 90 eyes have been treated to date outside the original study.



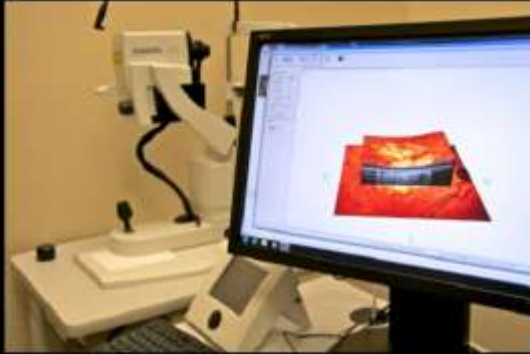
This shows the number and percentage of eyes achieving a letter score change. 5 letters is the equivalent of one line on the chart. 60% improve up to one line, 30% improved better than one line up to 2 lines and a small percentage did better than 2 lines. One patient got worse by one letter – he has severe dry eyes that may account for his result.

Case studies of central retinal thickness reduction following Photobiomodulation (PBM)

Updated 2nd October 2014

Confidential – not for distribution without consent of LumiThera Inc.

I have now seen drusen reduction in dry AMD patients following PBM treatment, a small case study was presented at NAALT-WALT 2014.

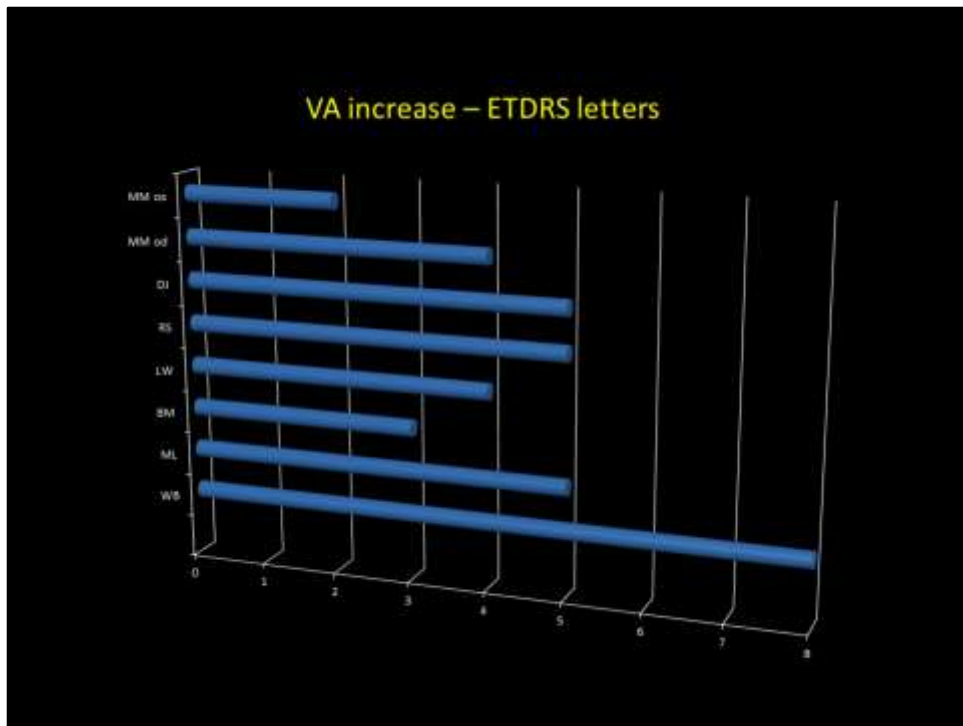


The SPECTRALIS SD-OCT

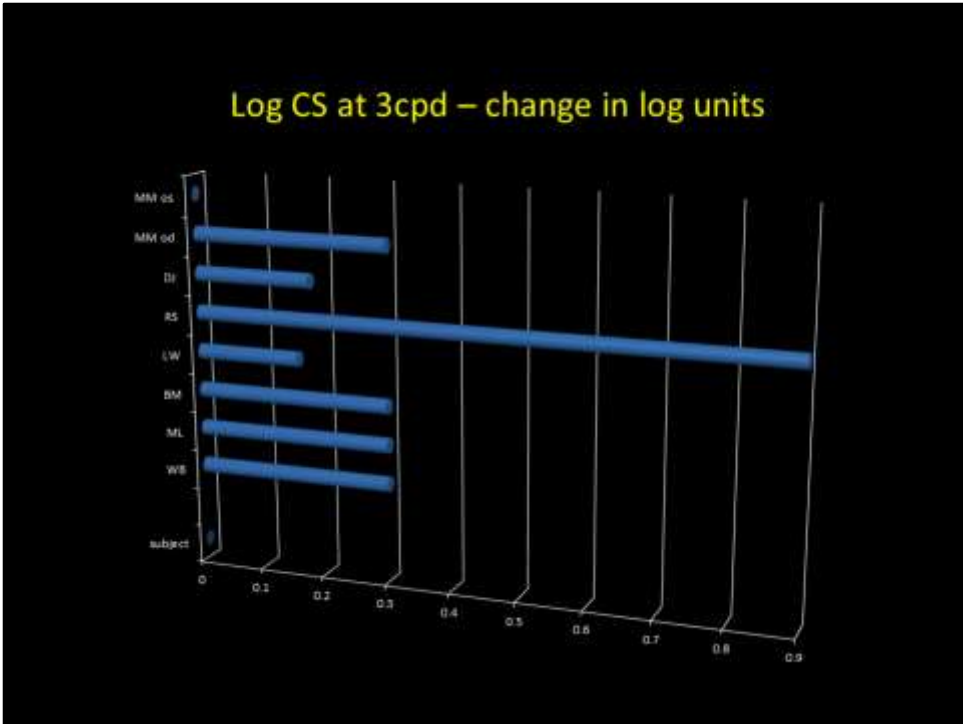
The SPECTRALIS SD-OCT system combines high-speed image acquisition with custom **TruTrack technology** to actively track the eye during imaging. Tracking eye movement with simultaneous dual-beam imaging minimizes motion artifact, enables noise reduction and allows the instrument to **precisely track change over time**. The result is point-to-point correlation between fundus and OCT scans which **enables accurate and repeatable alignment of OCT and fundus images**, greater image detail and clarity, and more confident assessment of small changes.

By integrating SD-OCT with confocal laser scanning ophthalmoscopy (cSLO), the Heidelberg SPECTRALIS platform allows for precise follow-up scan placement.

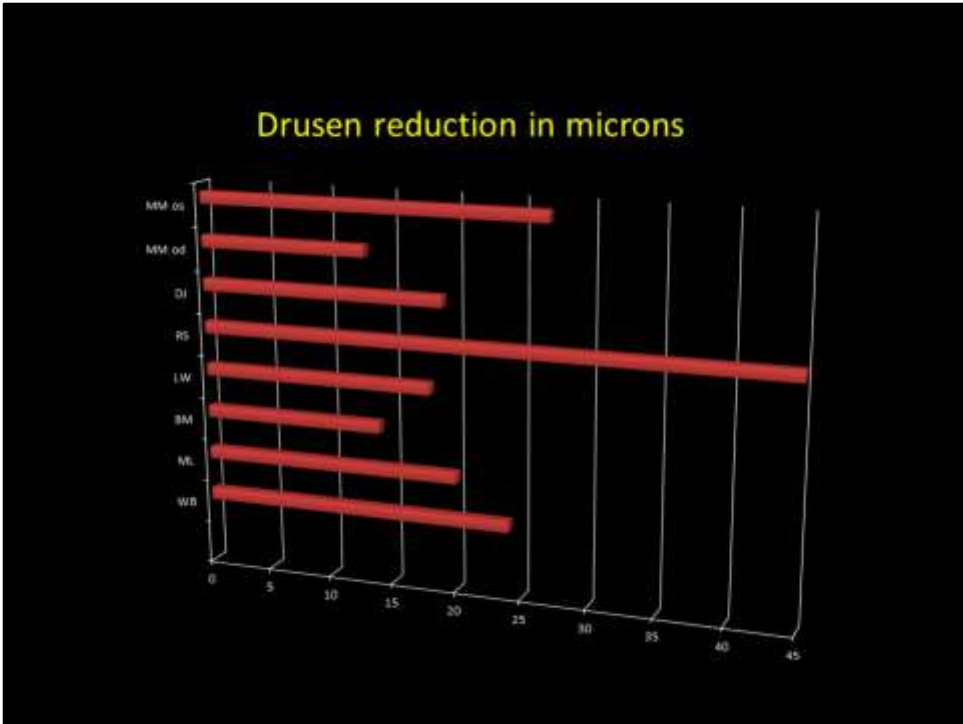
The spectralis OCT from Heidelberg Engineering has a number of technical features that allows for precisely tracking changes over time and enables accurate and repeatable alignment of OCT and fundus images. I have reported and presented changes in drusen size along with vision improvement in several cases.



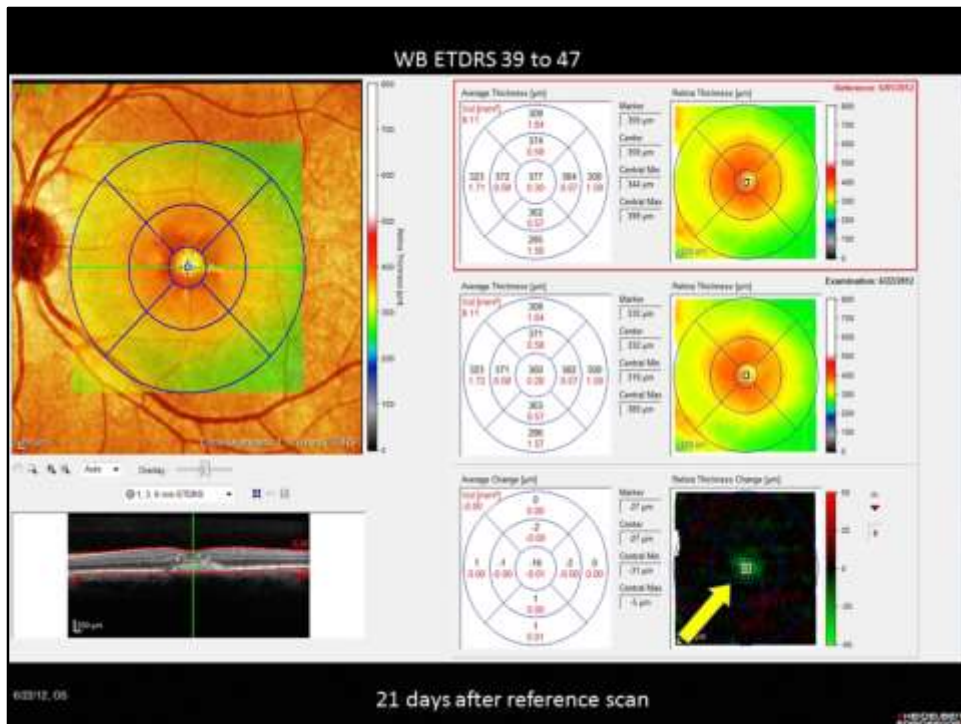
In this assesment of eight eyes we can see that visual acuity improved in all eyes following the treatment.



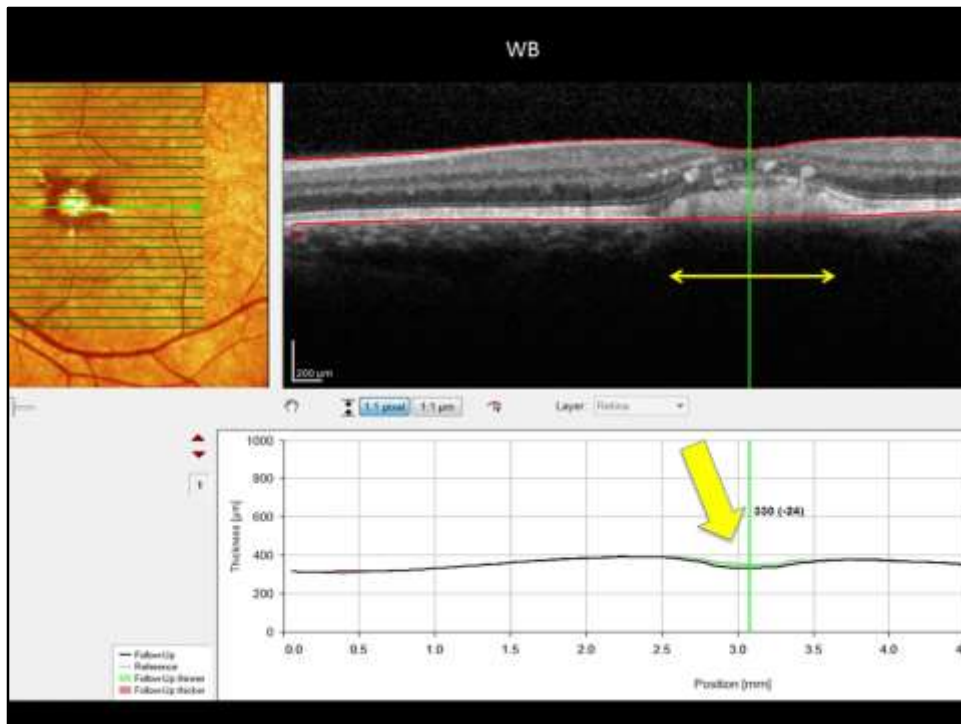
Contrast sensitivity also improved in all eyes except one that remained stable.



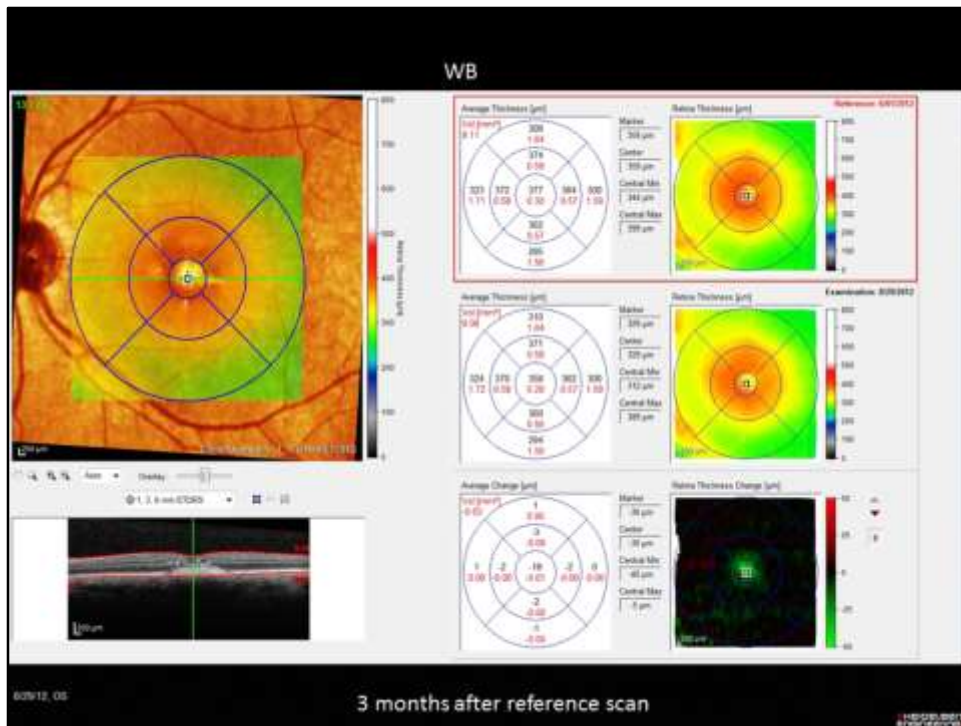
All eyes had central retinal thickness decrease of varying degrees following the treatment seen on OCT scanning.



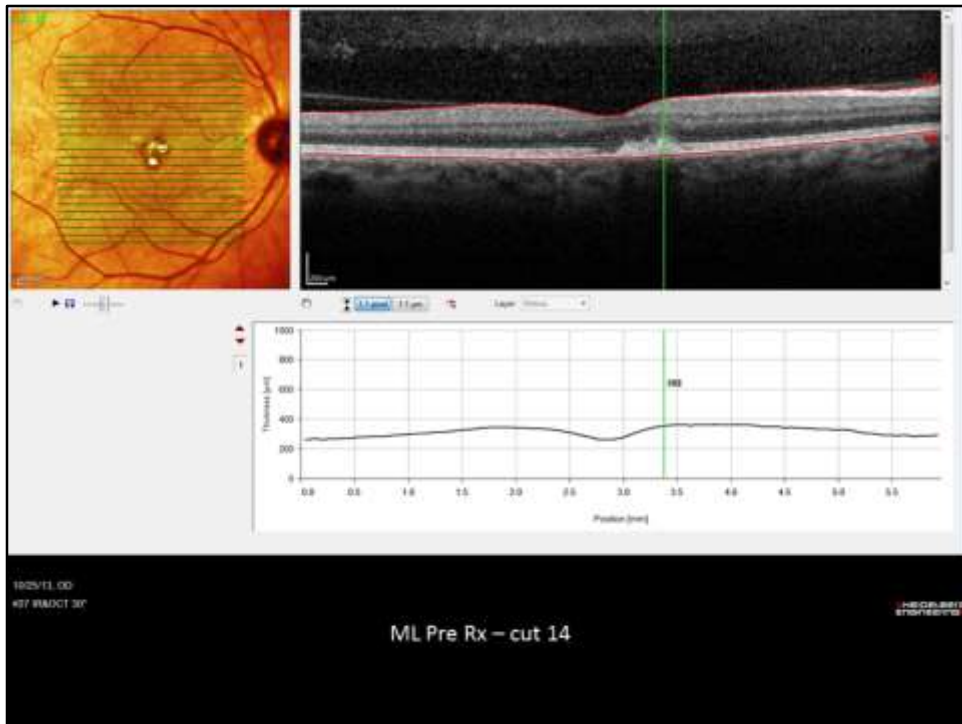
This is subject WB, a 55 yr old caucasian female who had an increase of 8 letters immediately following the treatment and quite marked drusen height reduction as evidenced by the colour scale in the subtraction map. The yellow arrow indicates the area of drusen reduction.



In the detailed cross section cut the green area shows the reduction in height profile note that the decrease in retinal thickness is only over the drusen or diseased retina – there is no reduction in thickness over the normal areas of retina- this indicates to me that we are only seeing a treatment effect that is beneficial over diseased areas and not affecting normal retina as far as we can tell from OCT scanning.



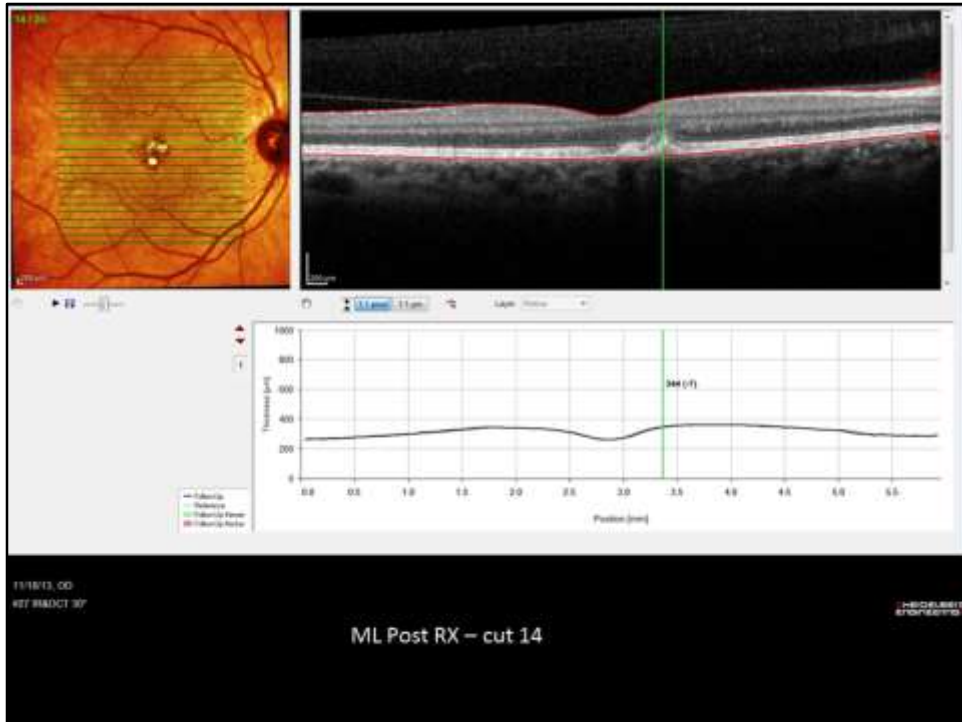
3 months after the initial treatment there has been some further reduction in central druse.



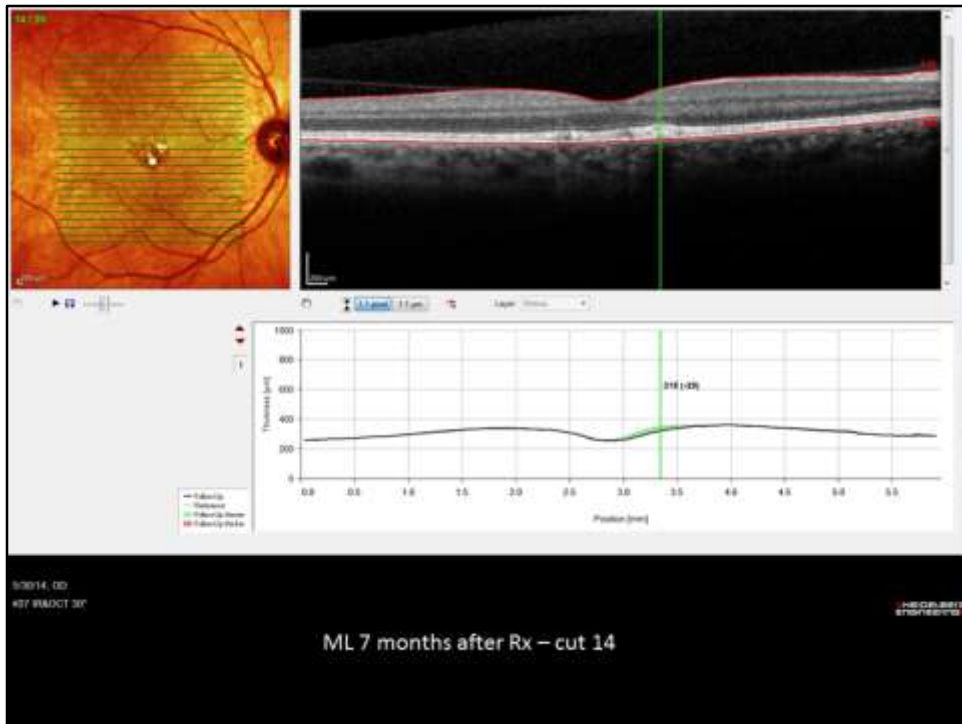
ML, Caucasian male aged 52.

ML increased his letter score from 52 to 57 immediately post treatment and there was also a contrast sensitivity increase from log 1.76 to log 2.06.

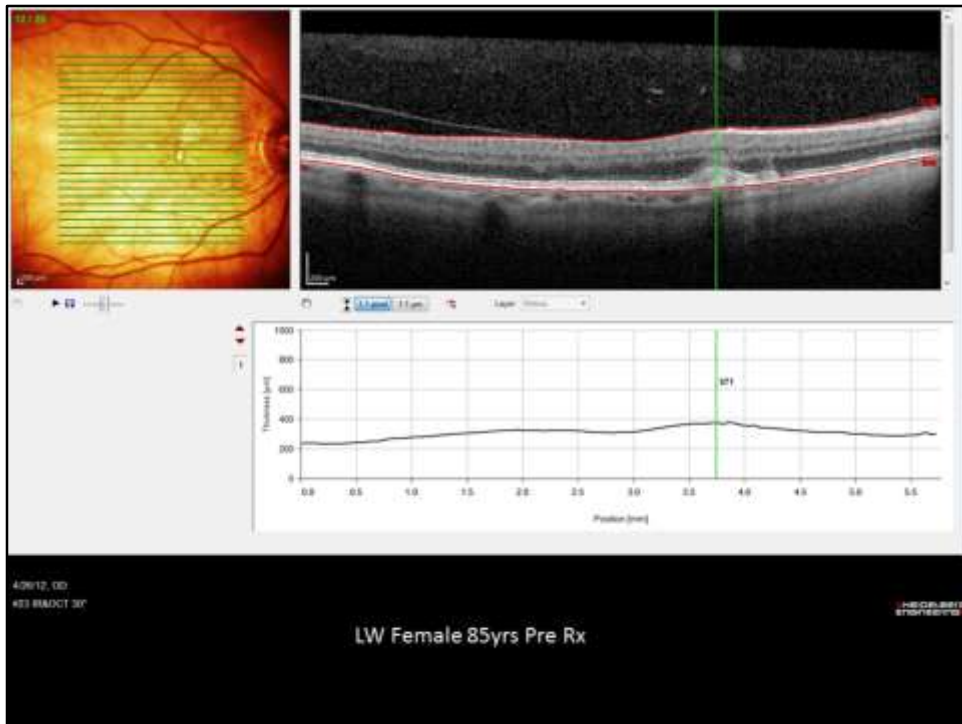
This is his pre treatment OCT scan on cut 14 through multiple central drusen.



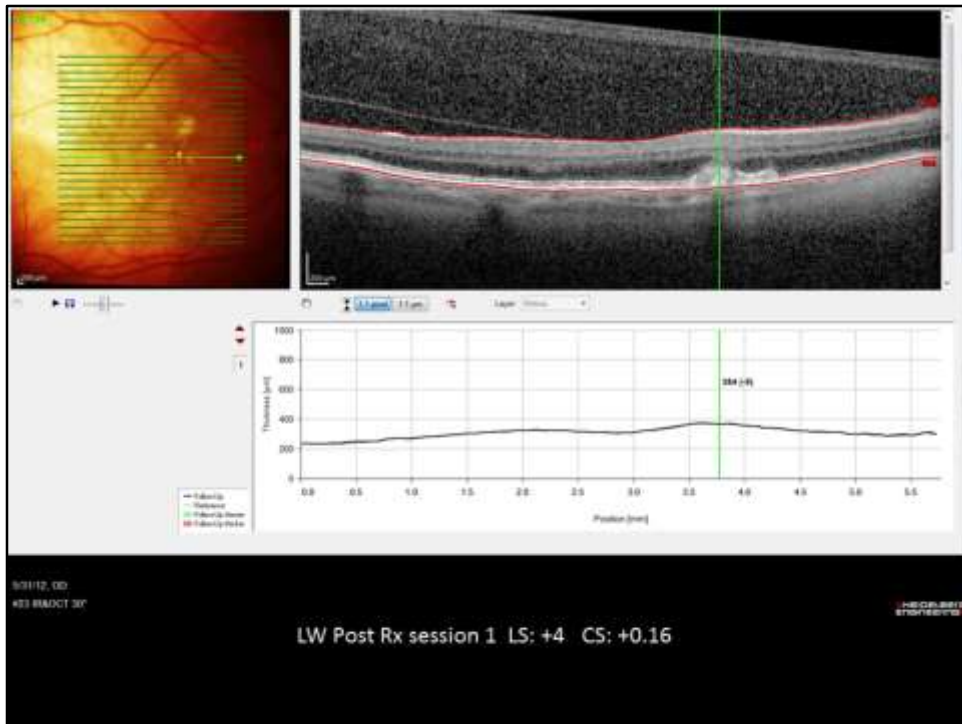
There is a very slight reduction noted on the immediate post treatment scan of his central drusen.



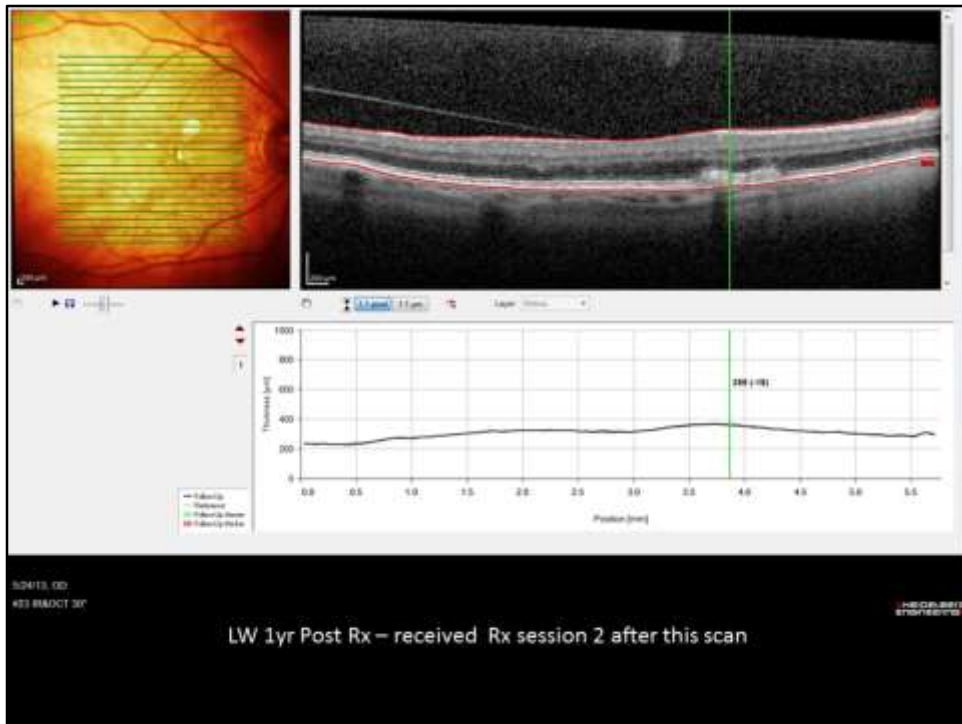
At 7 months follow up with no additional treatments there has been a very significant change in his central drusen – they have essentially disappeared!



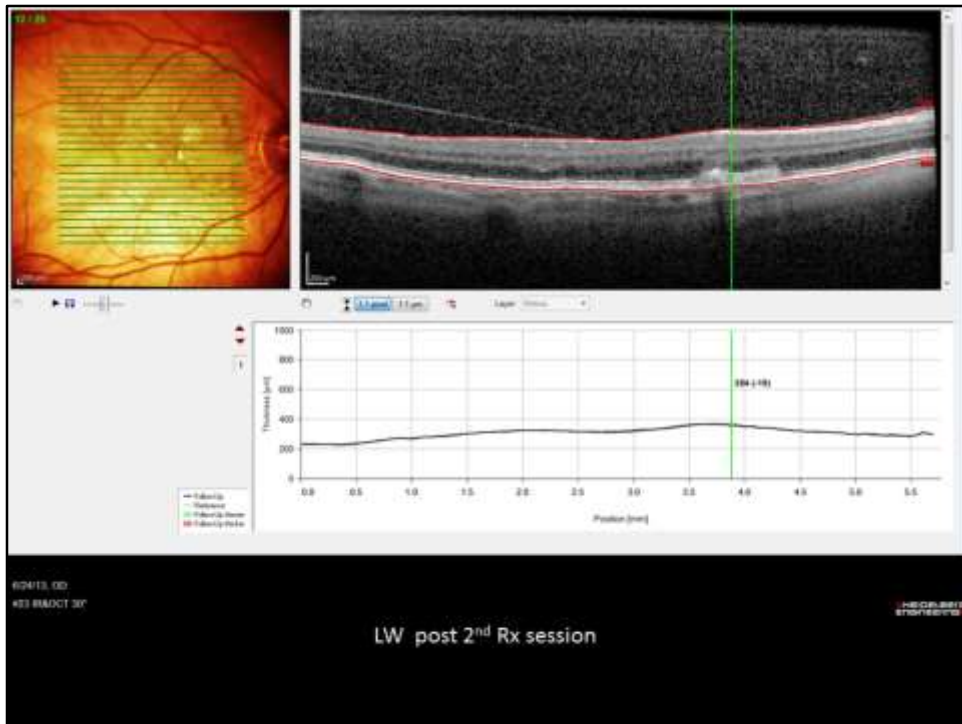
LW is one of my first patients to undergo off label PBM treatment and has had 3 treatment sessions over two and a half years to maintain her visual acuity gain and further reduce her drusen load. This is her pre treatment OCT.



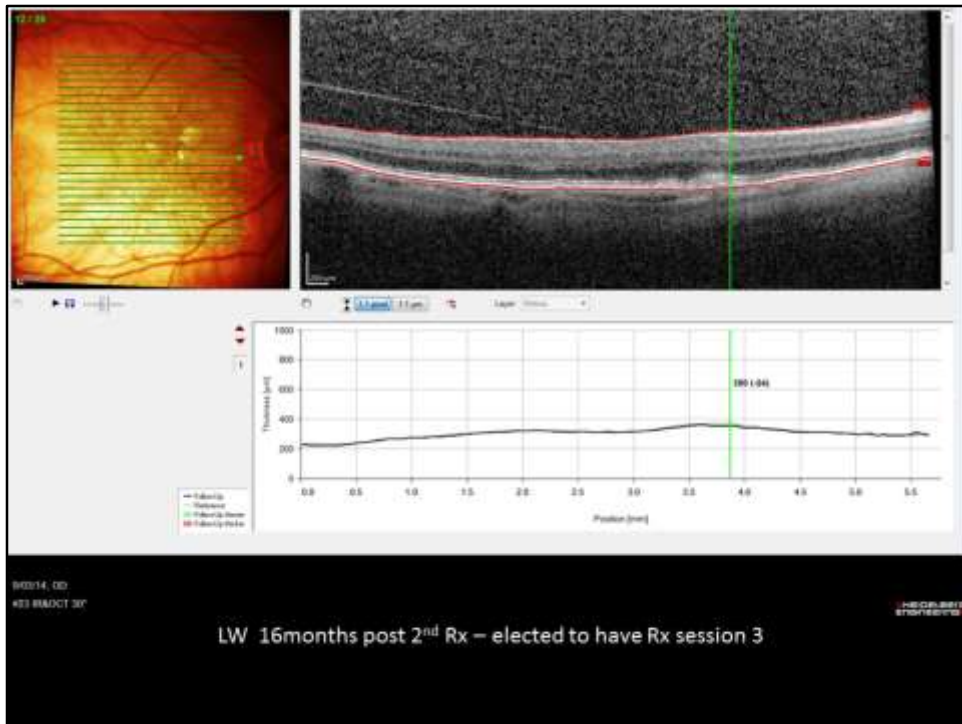
Post treatment scan showing some reduction in drusen associated with an increase in vision and contrast sensitivity.



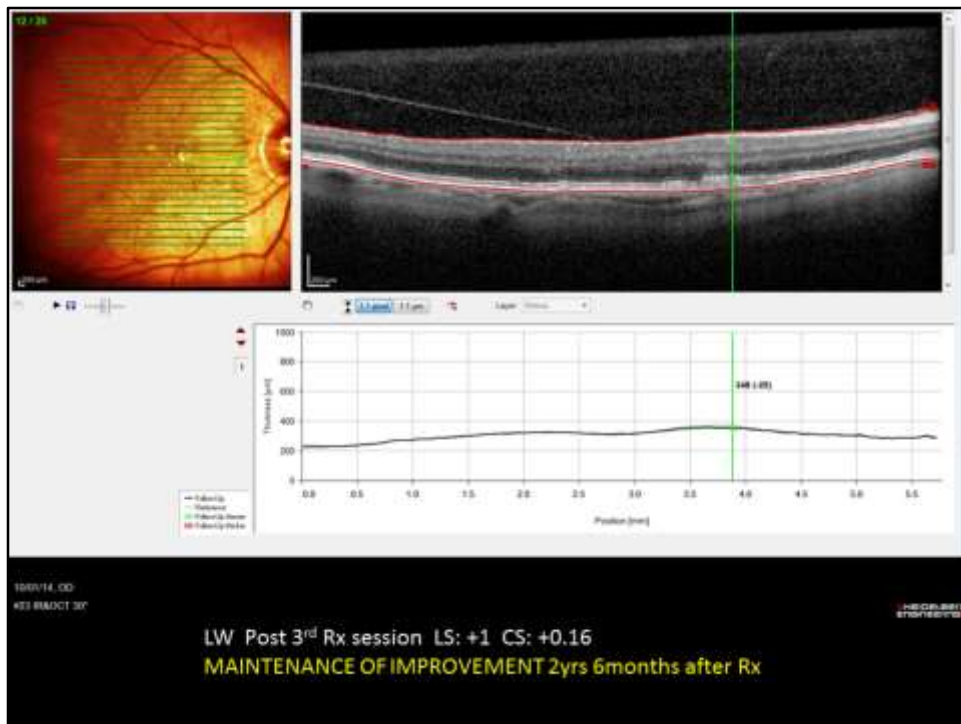
At the one year follow up she elected to have another treatment session to maintain her condition.



There has been further reduction of the drusen.



16 months after the second treatment her vision has been maintained. There is further reduction of her drusen and she elected to have a further treatment session.



Immediately after the third treatment session she has maintained her vision and contrast sensitivity and there has been further quite significant reduction in her drusen. On OCT it appears we have REVERSED the natural progression of AMD where drusen load increases and vision decreases.

This evidence of objective change in retinal anatomy following PBM therapy and correlating with improved subjective parameters (ETDRS VA and CS), albeit with small numbers and a non-randomized case series, deserves consideration for evaluation of PBM as a useful, non-invasive treatment for dry AMD.

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I am very confident that we are on our way to seeing the benefit of PBM in what can be a devastating disease currently with no proven active treatment options. My aim along with my colleagues and co founders of Lumithera Inc. is to prove our patented multi wavelength device as a new approved treatment for AMD by undertaking the necessary clinical trials in Europe and North America. We are all completely committed to this aim and are convinced that within the next few years we will be able to provide a simple, effective and safe treatment to millions of patients.