LINEAGE
CELL THERAPEUTICS

The future of cell therapy.



OpRegen® - A Therapeutic Expert Discussion of the First-Reported Findings of Retinal Tissue Regeneration in Patients with Dry-AMD with Geographic Atrophy

June 10, 2021

Forward-Looking Statements

This presentation is for informational purposes only and is not an offer to sell or a solicitation of an offer to buy any securities of Lineage Cell Therapeutics, Inc. ("Lineage"). This presentation includes certain information obtained from trade and statistical services, third-party publications, and other sources. Lineage has not independently verified such information and there can be no assurance as to its accuracy.

All statements in this presentation, other than statements of historical fact, are forward-looking statements within the meaning of federal securities laws. In some cases, you can identify forward-looking statements by terms such as "may," "will," "would," "expect," "plan," "anticipate," "strategy," "designed," "could," "can," "intend," "believe," "estimate," "target," "potential," "aim," "seek," "continue," "next steps," "upcoming," or the negative of these terms and other similar expressions. Such statements include, but are not limited to, statements relating to the clinical and market potential of Lineage's investigational products, its in-house manufacturing capabilities, anticipated clinical trial advancement, timing and data, regulatory communications and approval pathway, partnership opportunities, product pipeline expansion and cash management and runway. Forward-looking statements involve risks, uncertainties and assumptions that may cause Lineage's actual results, performance, or achievements to be materially different from those expressed or implied by the forward-looking statements in this presentation, including risks and uncertainties inherent in Lineage's business and other risks described in Lineage's filings with the Securities and Exchange Commission (SEC). Lineage's forward-looking statements are based upon its current expectations and involve assumptions that may never materialize or may prove to be incorrect. All forward-looking statements are expressly qualified in their entirety by these cautionary statements. Further information regarding these and other risks is included under the heading "Risk Factors" in Lineage's periodic reports filed with the SEC, including Lineage's most recent Annual Report on Form 10-K, Quarterly Report on Form 10-Q and its other reports, which are available from the SEC's website at www.sec.gov. You are cautioned not to place undue reliance on forward-looking statements, which speak only as of the date on the cover of this presentation. Lineage undertakes no obligation to update any forward-looking statement to reflect events that occur or circumstances that exist after that date, except as required by law.

LINEAGE
CELL THERAPEUTICS

“We aim to pioneer a new branch of medicine, based on transplanting specific cell types into the body”

Brian Culley, CEO

Independent Reviewers and Contributors

Eyal Banin, MD, PhD

Christopher D. Riemann, MD

Jordi Monés, MD, PhD

Michael S. Ip, MD

Brandon Lujan, MD

Allen C. Ho, MD, FACS

LINEAGE CELL THERAPEUTICS

Agenda

Welcome & Opening Remarks	Brian Culley, CEO Lineage Cell Therapeutics
Overview of OpRegen & Dry AMD	Eyal Banin, M.D., Ph.D.
Overview of GA Assessment Tools & Update on Reported Retinal Restoration Findings	Jordi Monés, M.D., Ph.D.
Outer Retinal Analysis: Independent Review of Retinal Restoration Findings	Brandon Lujan, M.D.
OpRegen Clinical Data Update and Patient Case Study	Christopher D. Riemann, M.D.
OCT Imaging: Independent Analyses of Retinal Restoration Findings	Michael S. Ip, M.D.
Wrap Up	Brian Culley, CEO Lineage Cell Therapeutics
Analyst and Academic Q&A Session	Gary S. Hogge, SVP Clin/Med Affairs Lineage Cell Therapeutics
Conclusion	Brian Culley, CEO Lineage Cell Therapeutics

OpRegen Highlights

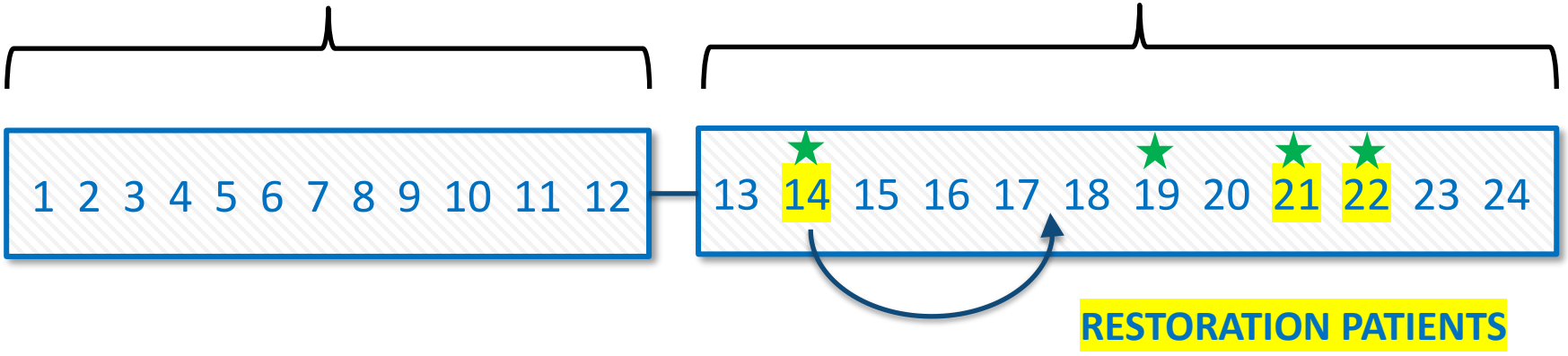
- **Product is a transplanted suspension of allogeneic RPE cells**
- **Phase 1/2a clinical trial fully enrolled in November 2020 (24 patients)**
- **In-house cGMP production**
- **>99% pure RPE cells**
  - NIH-approved cell line
  - Cell line established >20 years ago
  - Extensively characterized
  - No genetic modifications performed
- **Ready-to-use formulation**
  - No dose preparation or washing
  - From frozen cells to injection device in 5 minutes
- **Commercial production path**
  - Current production is 2,500 clinical doses/batch
  - Higher scale-up done in larger/more reactors

LINEAGE CELL THERAPEUTICS

Phase 1/2a Clinical Trial of OpRegen – Enrollment Complete

Cohorts 1-3
Safety Portion / Legally Blind

Cohort 4
Efficacy Portion / Impaired Vision



Purpose:	**To evaluate the safety and efficacy of transplanted RPE cells in patients with dry AMD with geographic atrophy**
Design:	**Open label, single arm, international, multi-center**
Dose and Administration:	**One 50-100 ul dose of cells injected into the subretinal space**

LINEAGE CELL THERAPEUTICS

★ = OpRegen placed across area of atrophy

LINEAGE
CELL THERAPEUTICS

AMD is the leading cause of irreversible vision loss in the US

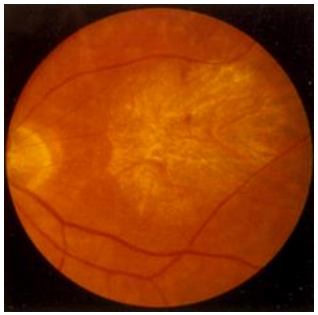
Source: aao.org

Eyal Banin, M.D., Ph.D., Professor of Ophthalmology
Director, Center for Retinal and Macular Degenerations
Department of Ophthalmology, Hadassah-Hebrew University Medical Center

Age-Related Macular Degeneration (AMD)

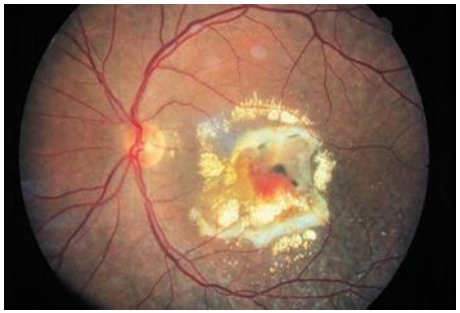
- AMD is the leading cause of blindness in people >50y in the developed world
- Dysfunction and loss of RPE cells plays an important role in the pathogenesis of AMD
- The disease often starts in its dry (non-neovascular form) and may lead to loss of central acuity by progressive atrophy or by transition to the wet (neovascular) form
- While anti-VEGF treatments have allowed better control of NVAMD, there is currently no effective treatment for the dry form except nutritional supplementation (AREDS trials)

Dry AMD

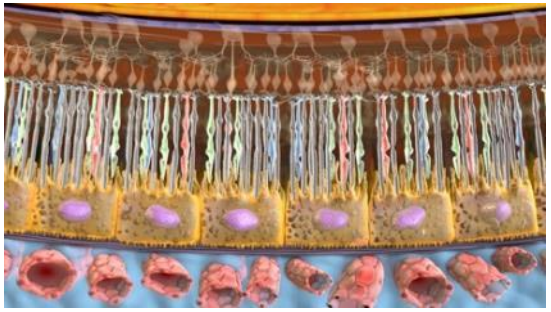


Geographic Atrophy

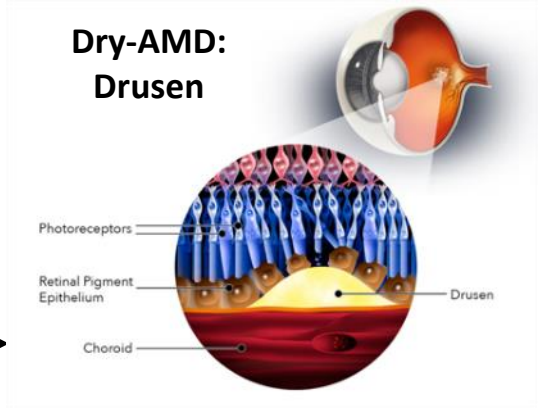
NV-AMD

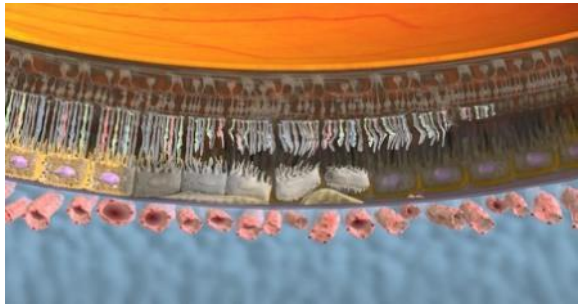


Cell-based therapy to replace/support dysfunctional and degenerated RPE in dry AMD with GA

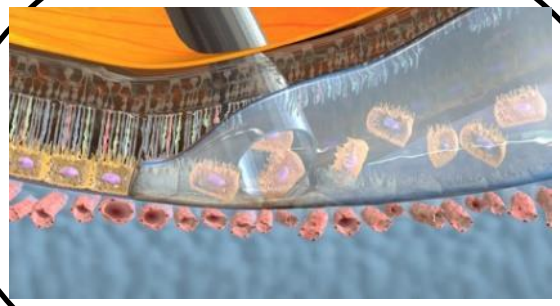


Normal Outer Retina

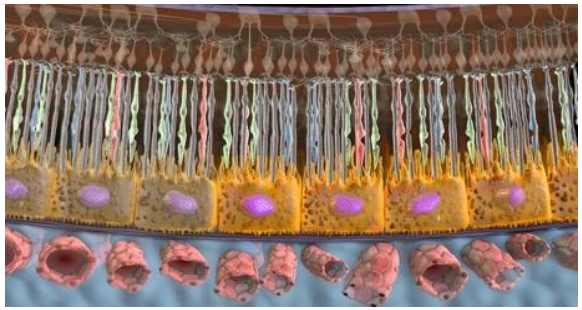




RPE dysfunction and loss, secondary photoreceptor injury

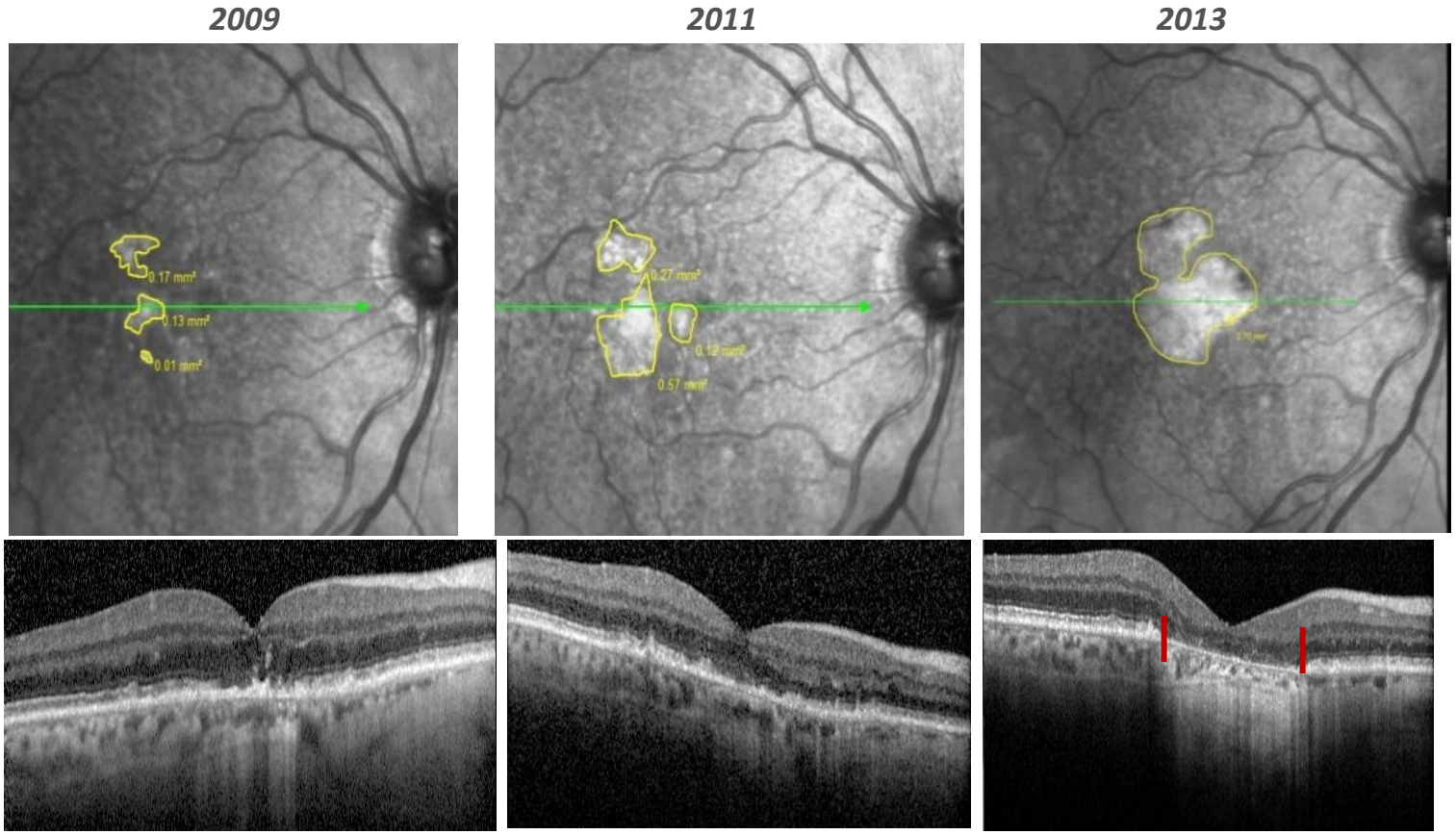


Transplantation of RPE cell suspension



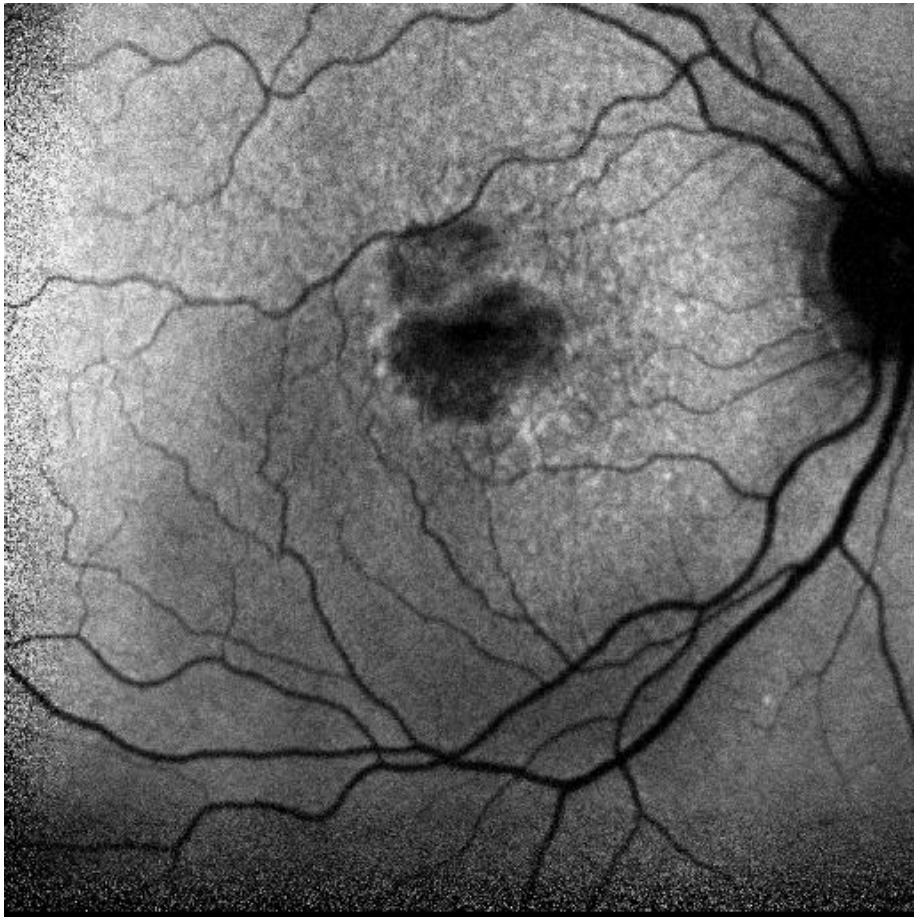
Transplanted RPE integration and function, Photoreceptor survival

Progression of Atrophy: Infrared + OCT imaging



Progression of Geographic Atrophy

Fundus Autofluorescence Imaging (FAF)



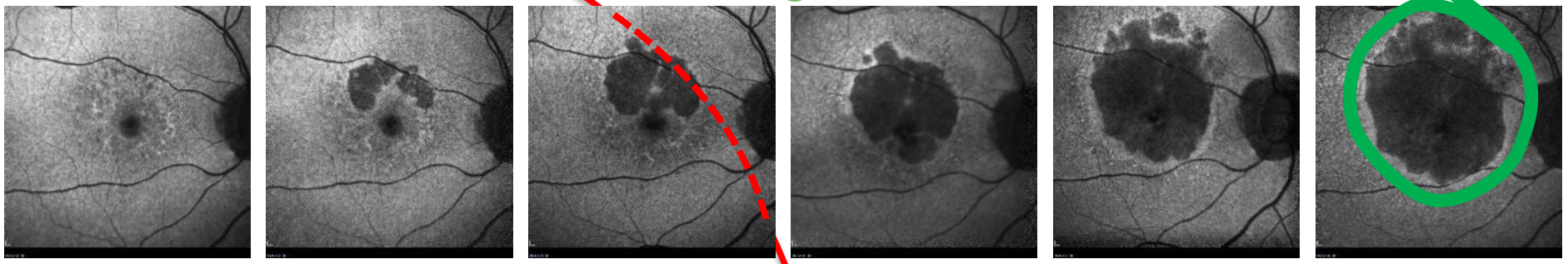
2013-2015

Dry AMD Can Lead to Loss of Central Vision and Legal Blindness

Visual acuity over time…

20/20 (normal)

The area of geographic atrophy or "GA" grows larger as retinal cells die



2012 2013 2014 2015 2017 2019

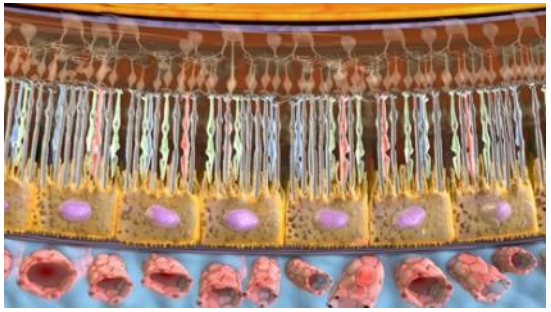
20/200 (legally blind in 3 years)

20/640

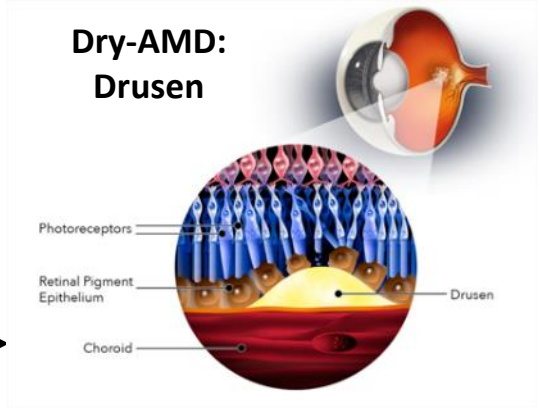
Dry AMD involves the progressive loss of retinal cells, which can lead to blindness

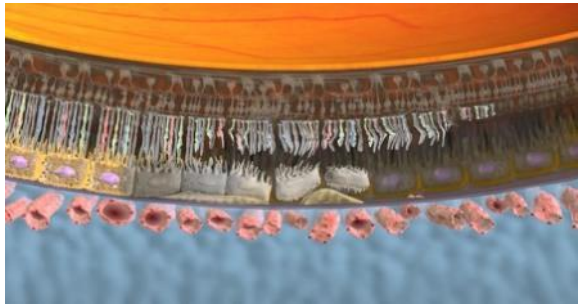
Image courtesy of Jordi Monés, MD, PhD

Cell-based therapy to replace/support dysfunctional and degenerated RPE in dry AMD with GA

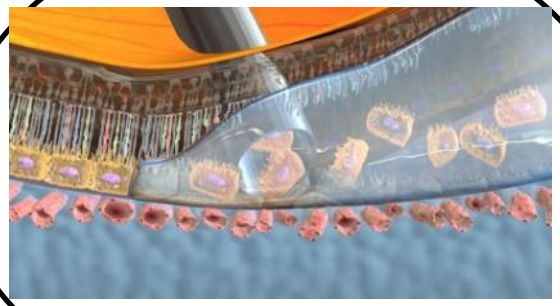


Normal Outer Retina

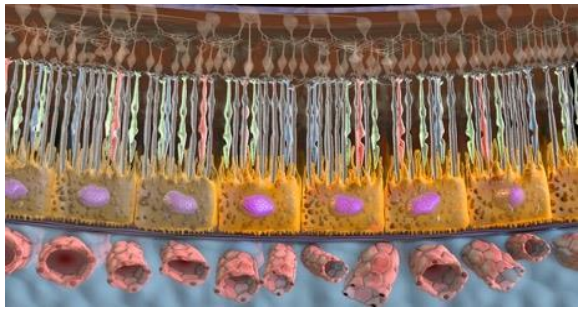




RPE dysfunction and loss, secondary photoreceptor injury

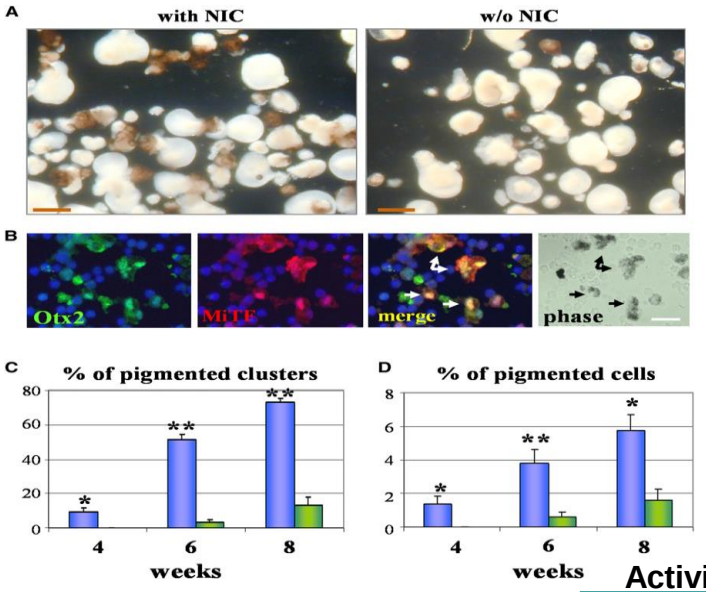


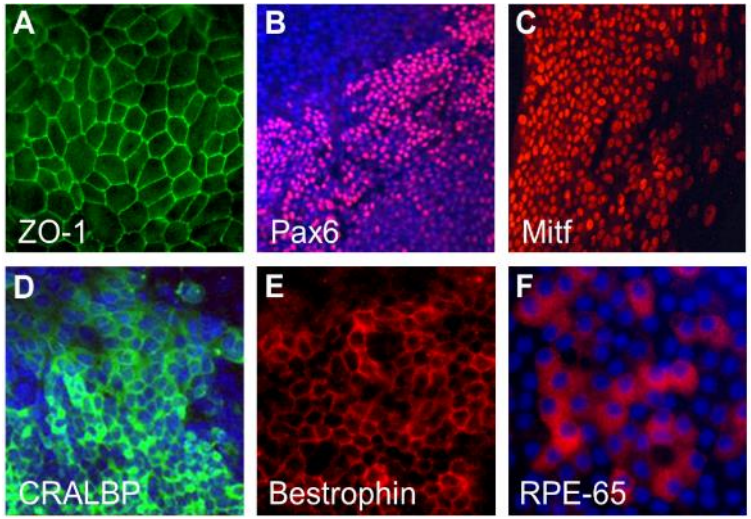
Transplantation of RPE cell suspension



Transplanted RPE integration and function, Photoreceptor survival

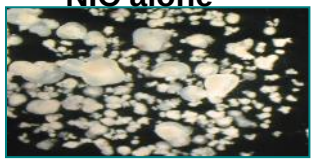
Nicotinamide (NIC;B3) and Activin A promote Differentiation of hESCs into RPE cells

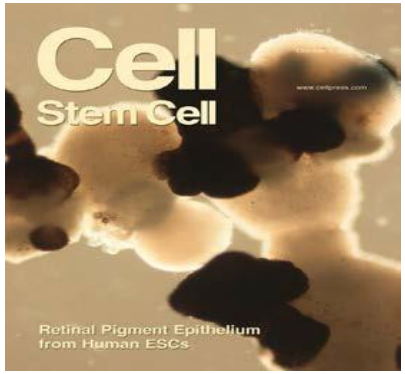




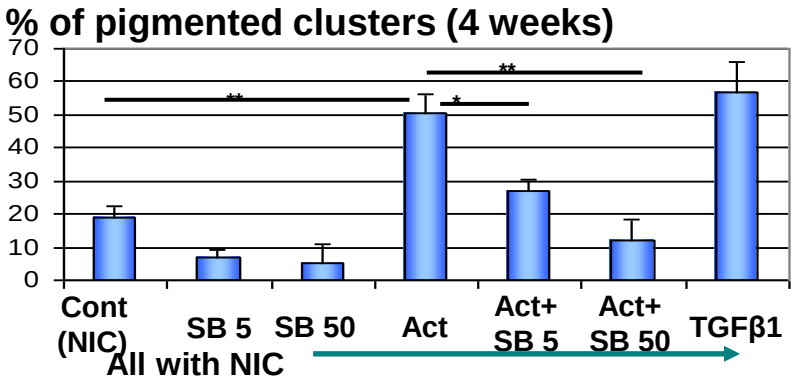
Blue - With NIC

Green - No NIC





Idelson et al, 2009



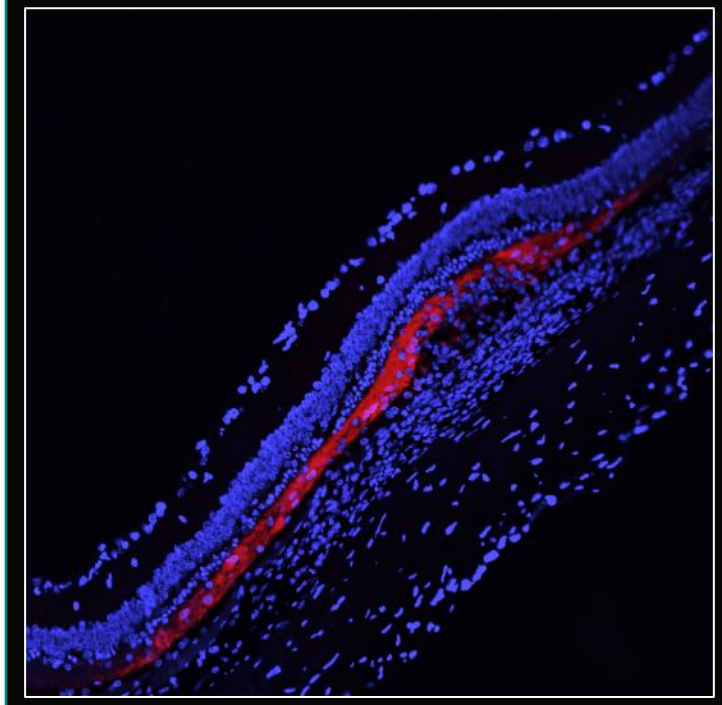
et al.,

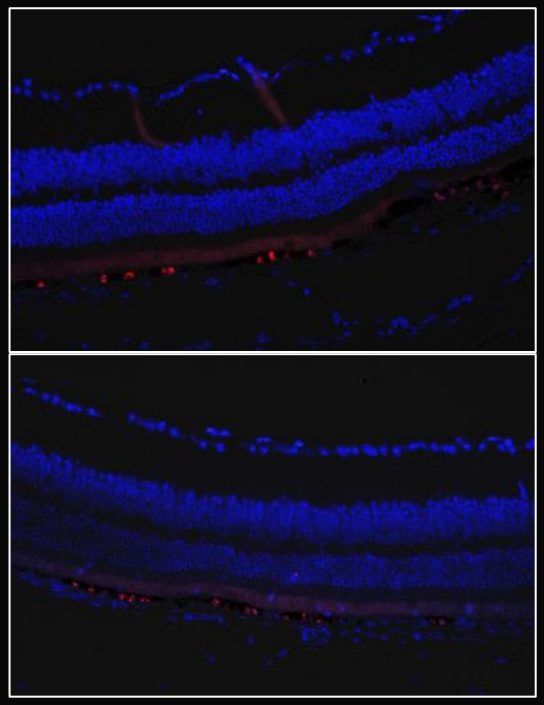
Engraftment and survival of hESC-RPE (OpRegen) in three animal species

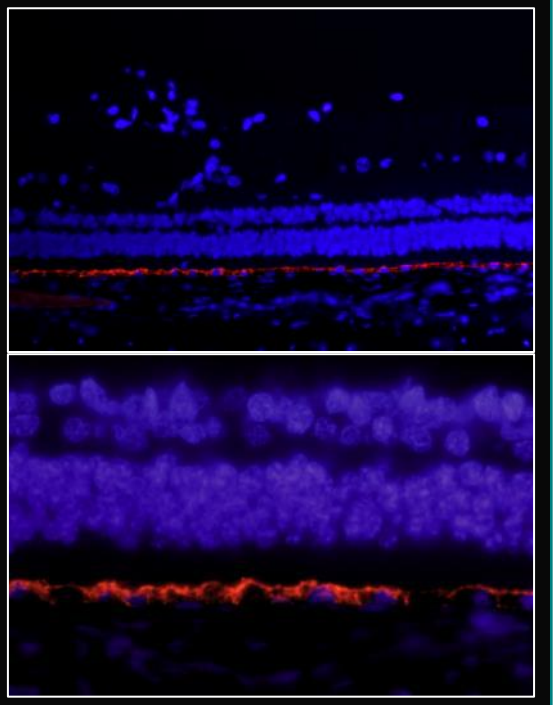
RCS rat
19 weeks post transplantation

NOD-SCID mouse

Pig retina
3 months post transplantation







anti-GFP

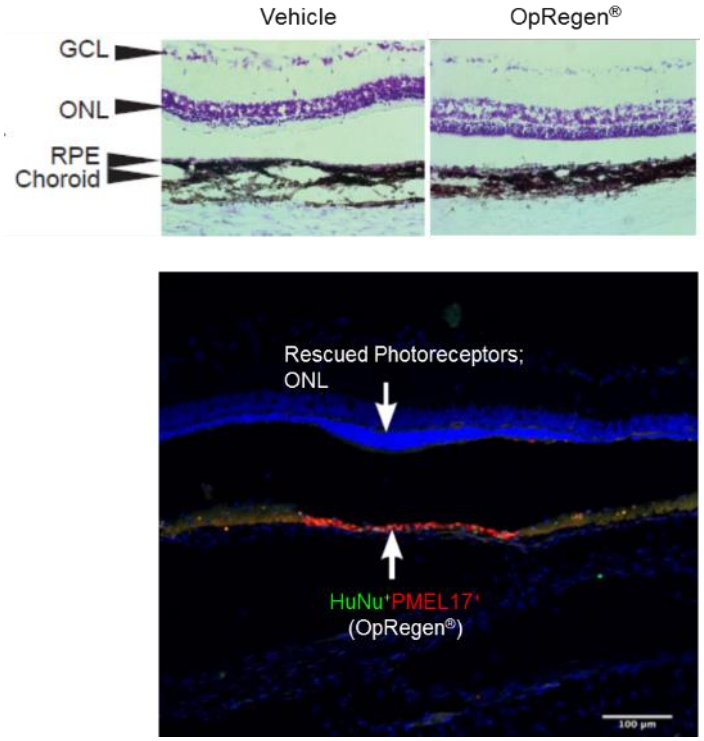
anti- human Nuclei

Human specific marker Tra-1-85

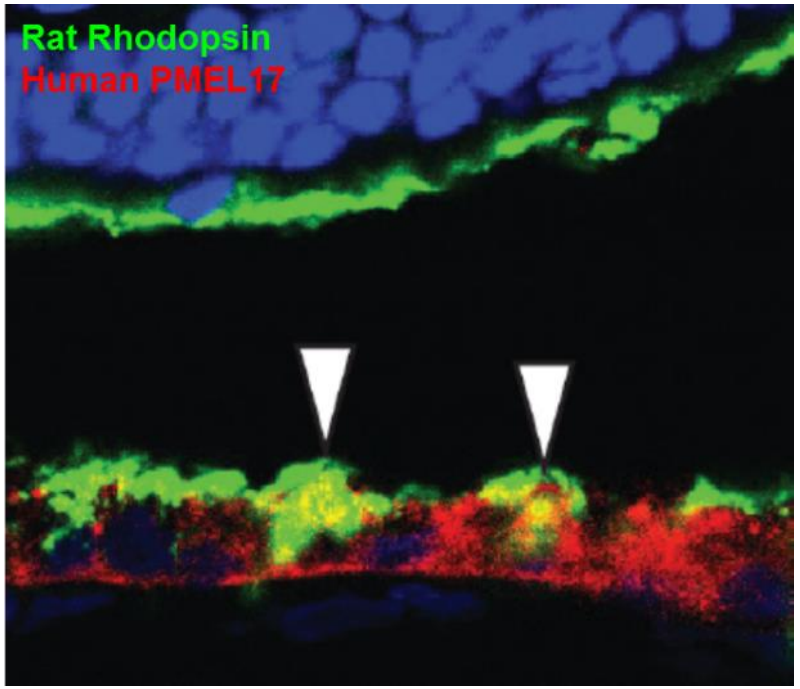
Nuclei were counter-stained with DAPI

OpRegen preclinical animal data supports function of the cells and ability to induce structural improvement in RCS rats, a model of retinal degeneration secondary to RPE dysfunction

Histological Photoreceptor Rescue in Transplanted Eyes of RCS rats



OpRegen-Mediated Phagocytosis of Rat Outer Segments (ROS) containing Rhodopsin

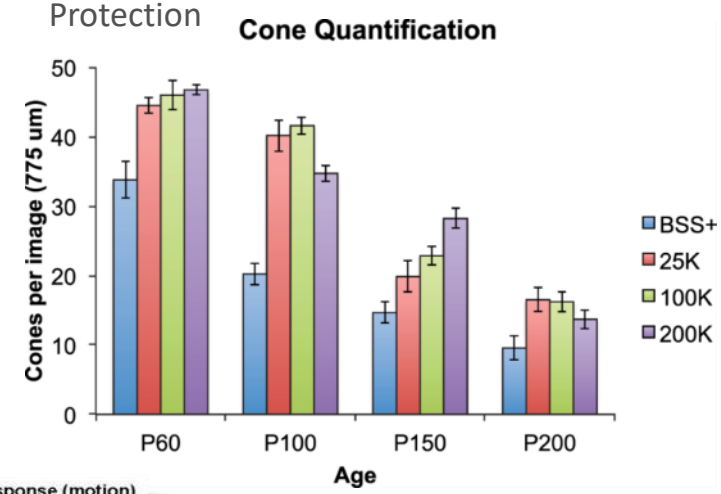


McGill TJ, et al. *Transl Vis Sci Technol*. 2017;6:17.

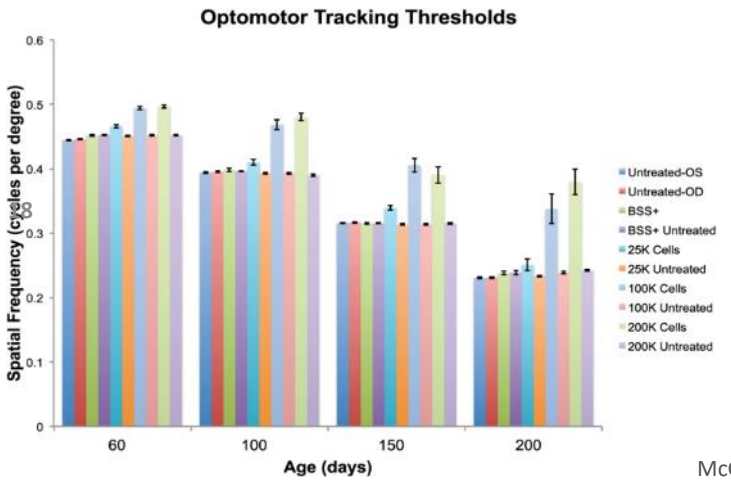
OpRegen preclinical animal data supports structural and functional improvement in the RCS rat model

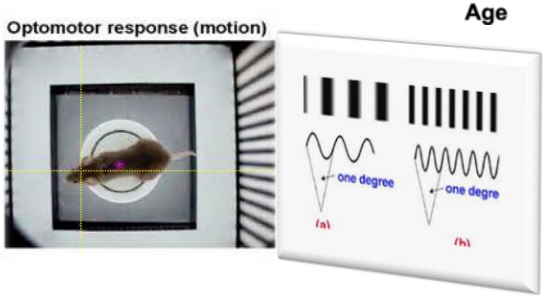
- Dose-dependent rescue of vision at all tested postnatal ages were observed based on optokinetic tracking (visual acuity test)

Enhanced Photoreceptor Sparing with OpRegen Protection



Enhanced Visual Function





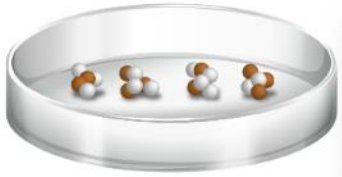
When the grading is narrower (more cycles per deg), the animal needs better vision to be able to track

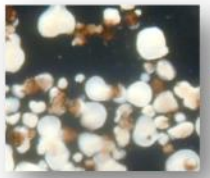
McGill TJ, et al. *Transl Vis Sci Technol*. 2017;6:17.

Large-Scale Directed *in-vitro* Differentiation of Human Embryonic Stem Cells (hESCs) into Retinal Pigmented Epithelial (RPE) Cells

Clinical-grade cell clusters from established cell line

Source of original hESC (HAD C-102) was a single supernumerary IVF blastocyst frozen >5 years. Ethically obtained, HPI maintained, informed consent granted, and without compensation. HAD-C102 is eligible for use in NIH funded research. (https://grants.nih.gov/stem_cells/registry/current.htm?id=428)



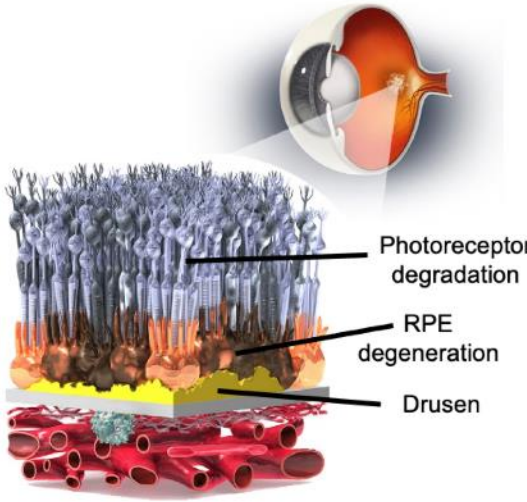


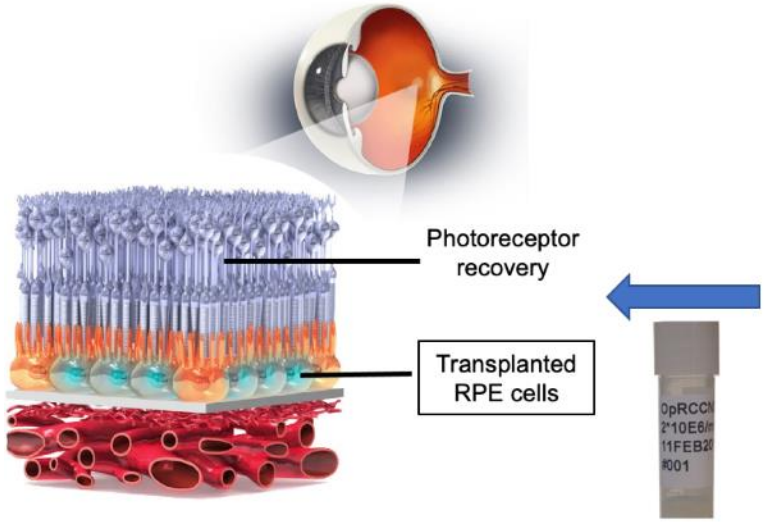
Neural Spheres with pigmented areas

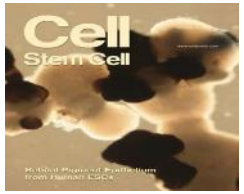
>99% pure RPE cells

Scale up to 5 billion cells per 3-liter bioreactor

M. Idelson et al., Cell Stem Cell 2009
Retinal images adapted from www.scienceofamd.org







Idelson et. al., 2009

Phase I/IIa FDA approved Clinical Study (NCT02286089): Design, Population, Management

Parameter	Cohorts 1-3 (legally blind) n = 12 of 12 planned (*complete*)	Cohort 4 (better BCVA) n = 12 of 12 planned (*complete*)
Phase / design	Phase I-IIa; staggered design; IND (NCT02286089)	
Duration	Screening up to 8 Weeks; short term F/U – 1 year; long term F/U – 4 years	
Management	Central reading/central labs/Independent DSMB/Advisory Committees	
Treated disease	Advanced Dry AMD and GA	
Subretinal Dose Delivered	Cohort 1: 50K cells Cohorts 2-3: up to 200K cells	Up to 200K cells
BCVA	≤ 20/200	≤ 20/64 and ≥ 20/250
GA size – Central Reading assessment via FAF	≥ 1.25mm^2 and ≤ 17 mm^2	≥ 4 mm^2 and ≤ 11 mm^2
Historical Growth of GA	N/A	SQRT per year of > 0.25 mm
Significant concomitant diseases exclusion (systemic / ocular)	Defined *a priori*	
Immunosuppression	PO tacrolimus from 1 week prior to Sx until 6 weeks post-op PO mycophenolate from 1 week prior to Sx to at least 3 months post-op	

OpRegen Study Status and Baseline Characteristics

	Cohorts 1-3 (legally blind) n = 12 of 12 planned (*complete*)	Cohort 4 (better BCVA) n = 12 of 12 planned (*complete*)
n (%) subjects dropout	2 (17%) (2 medical illness)	1 (12.5%) (Withdrawal of consent/COVID fears)
Age: mean (SD / min - max), yrs	78.3 (± 8.2 / 64.8 – 92.2)	75.7 (± 8.1 / 60.0 – 87.7)
ETDRS BCVA: mean (SD / min - max)	23.7 (± 11.7 / 0 – 39) letters [24 letters ≈ 20/400]	44.8 (± 7.5 / 28 – 54) letters [50 letters ≈ 20/100]
GA area: mean (SD / min - max) via central reader FAF	12.7 (± 6.7 / 6 – 30) mm^2	7.4 (± 2.9 / 1.4 – 11) mm^2
Post-op cumulative F/U period	45.0 years	18.9 years
Mean F/U (days)	1369 days (SE ± 159)	549 days (SE ± 126)

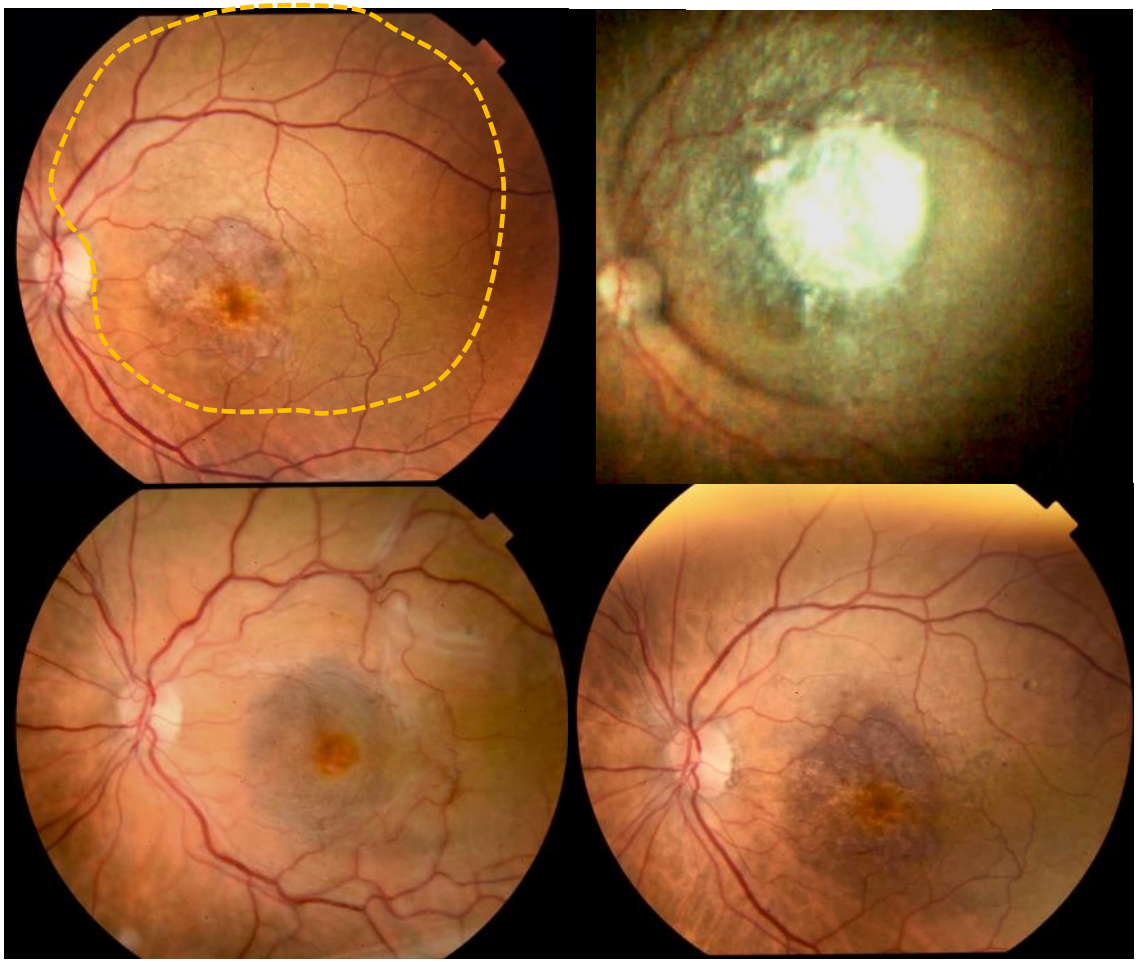
OpRegen® Transplantation

Case Report: Patient #14
1st retinal restoration

- 80-year-old female
- Ocular medical history
  - > 20-year history of AMD
  - Treated eye (OS)
    - BCVA 20/80 (54 Letters)
    - GA size 8.139 mm^2 per Central Reader
    - ~2 years prior was ~2.7 mm^2 per Central Reader
  - Fellow eye (OD)
    - BCVA 20/63 (61 Letters)
    - GA size 6.959 mm^2 per Central Reader
- Pseudophakic OU

Case Report – Patient #14
1st retinal restoration

Baseline



Intra OP

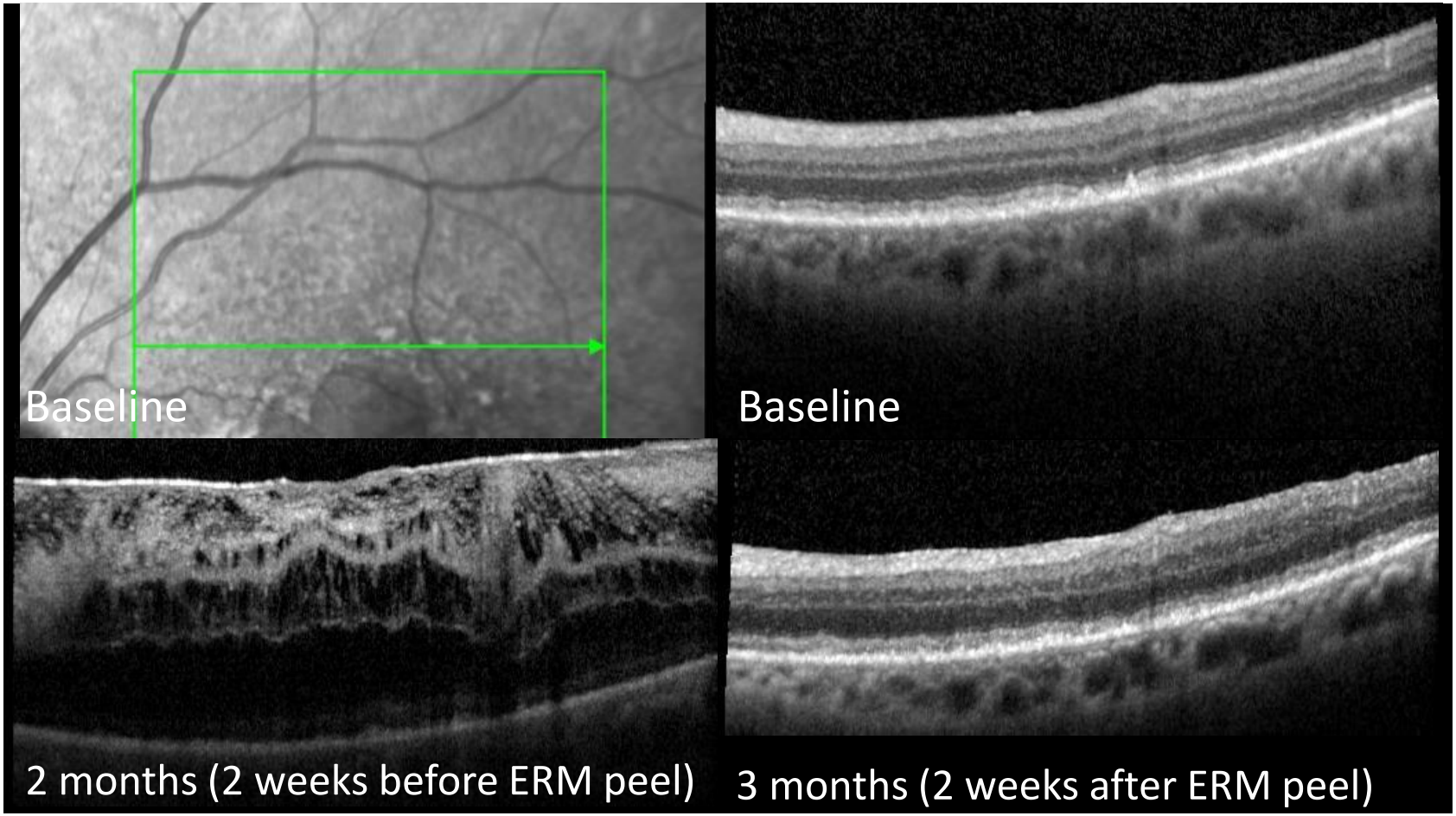
2 months

(2 weeks before peeling)

3 months

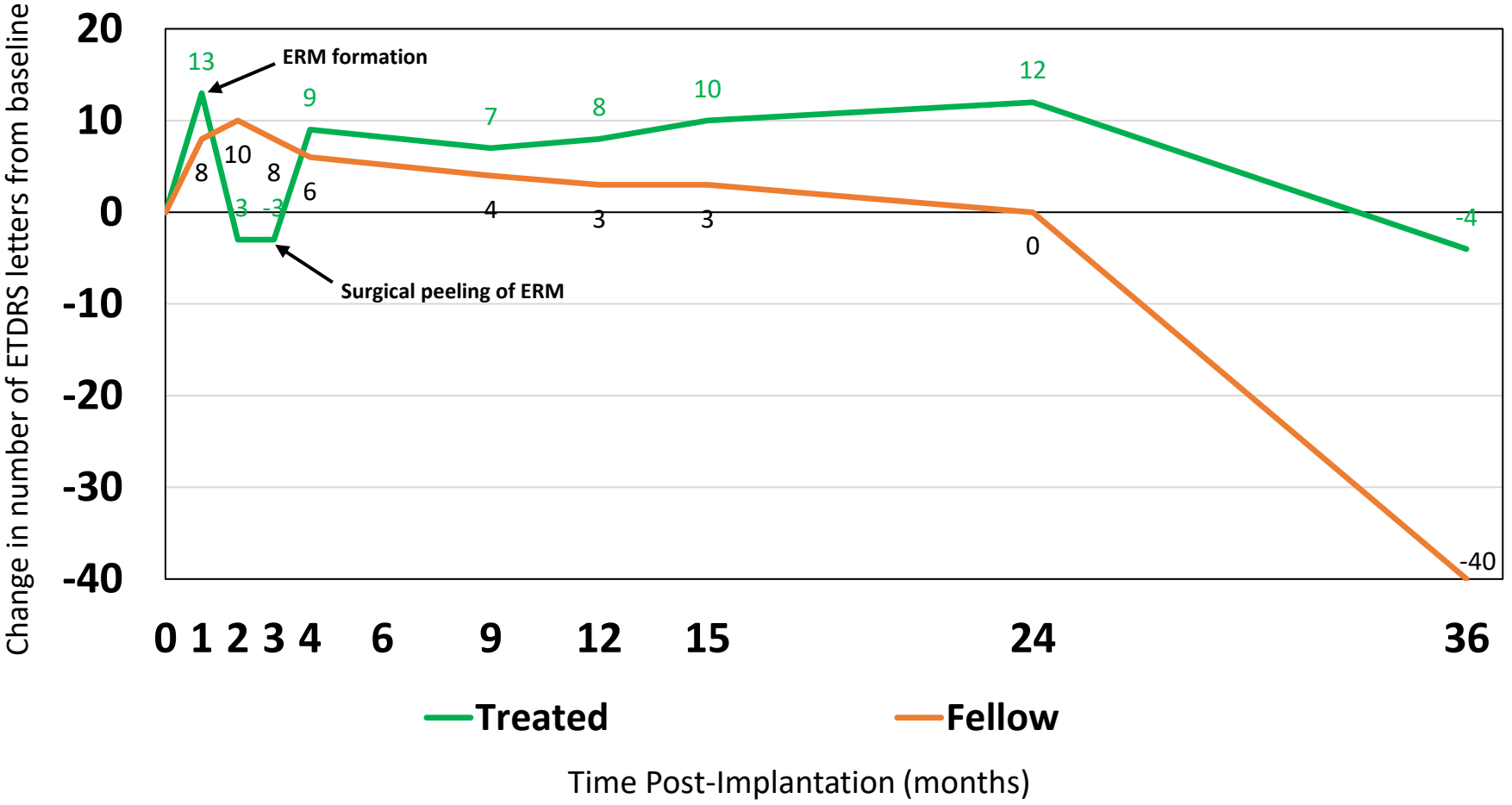
(2 weeks after peeling)

Case Report – Patient #14
1st retinal restoration

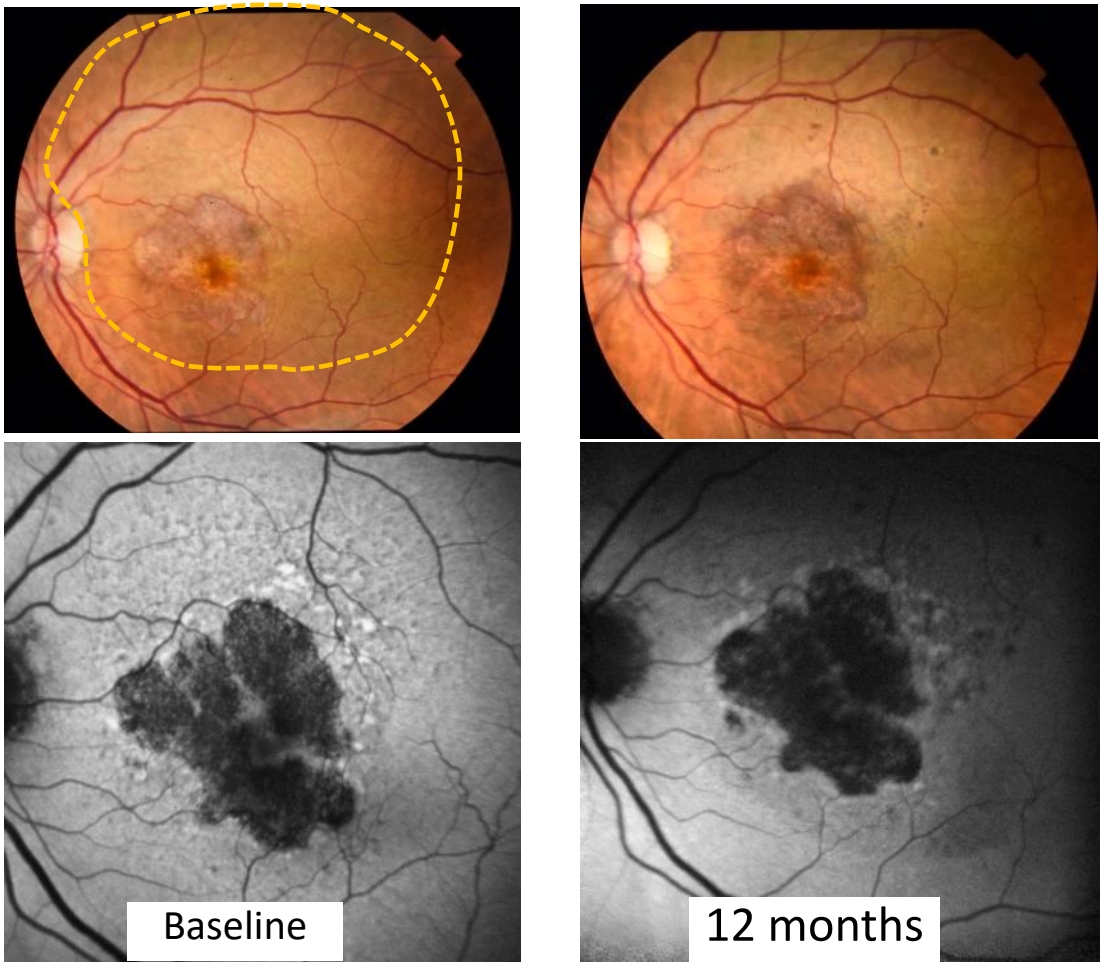


BCVA Changes for Patient #14 (1st retinal restoration)

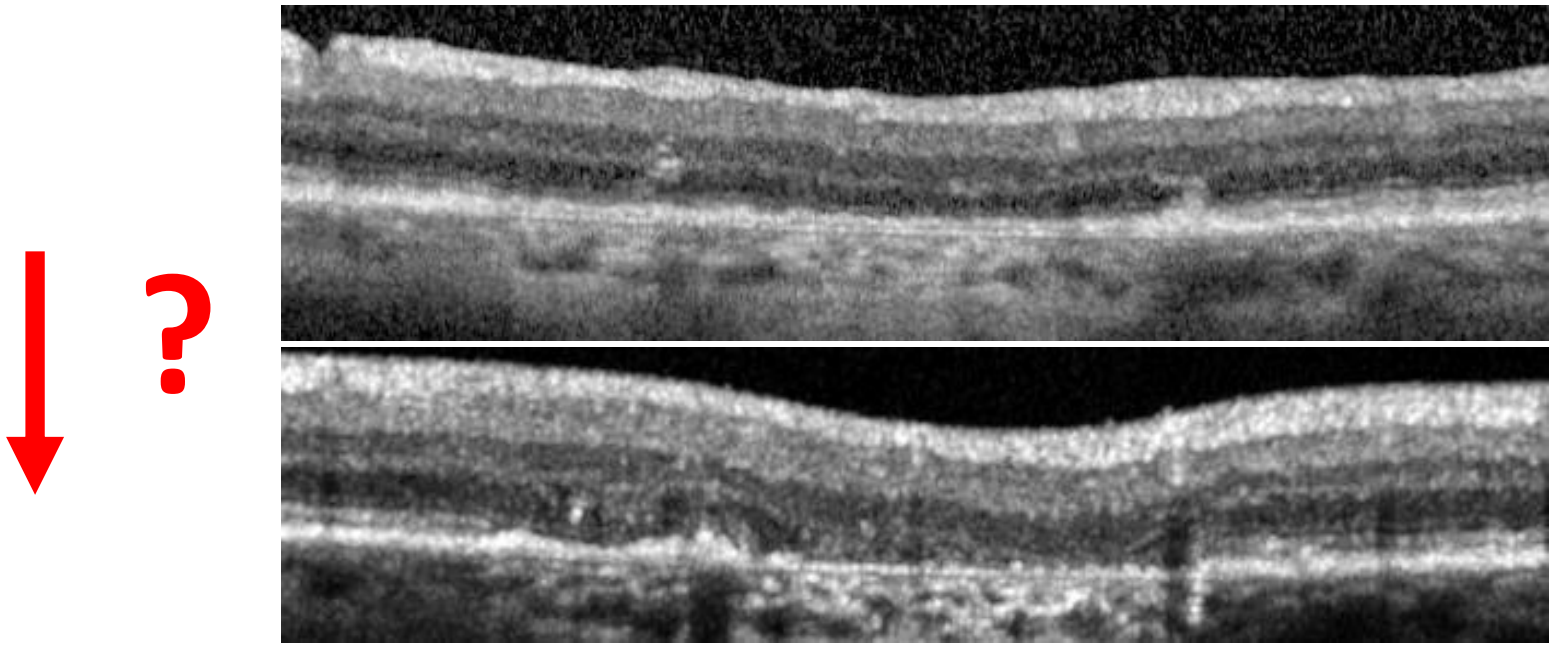
Treated vs. Fellow Eye



Case Report – Patient #14
1st retinal restoration

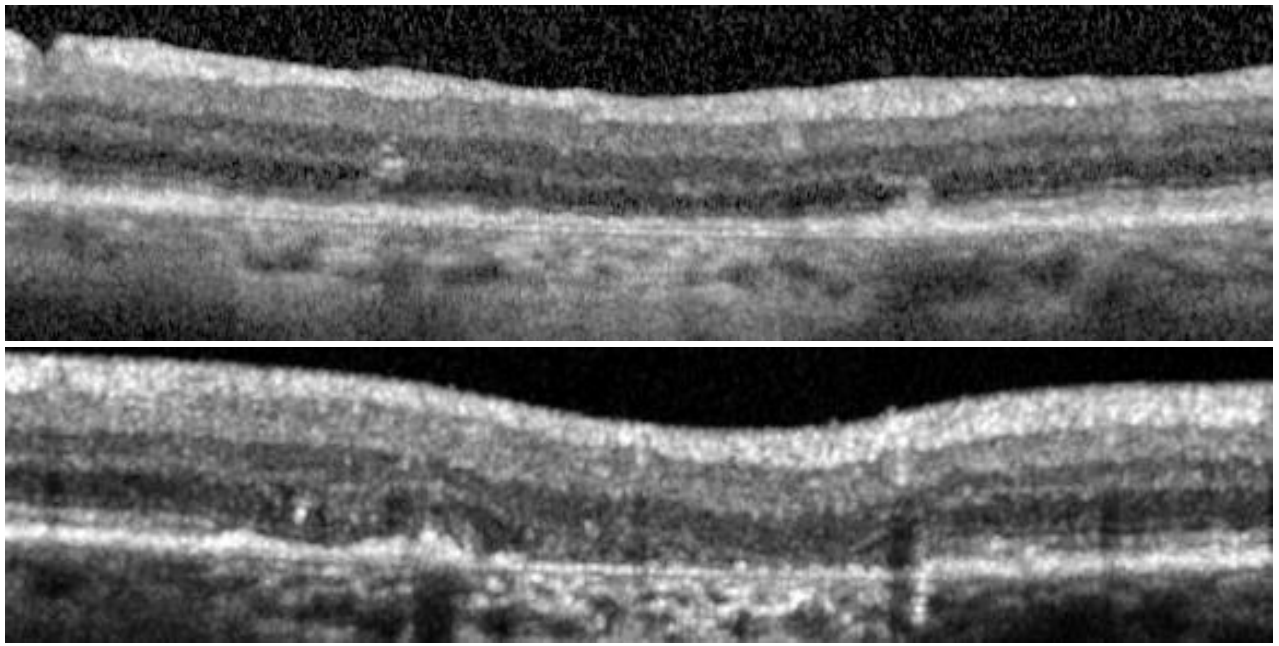


Case Report – Patient #14
1st retinal restoration



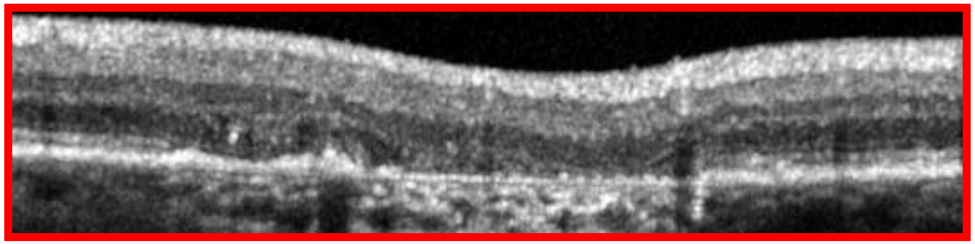
Case Report – Patient #14
1st retinal restoration

12 months

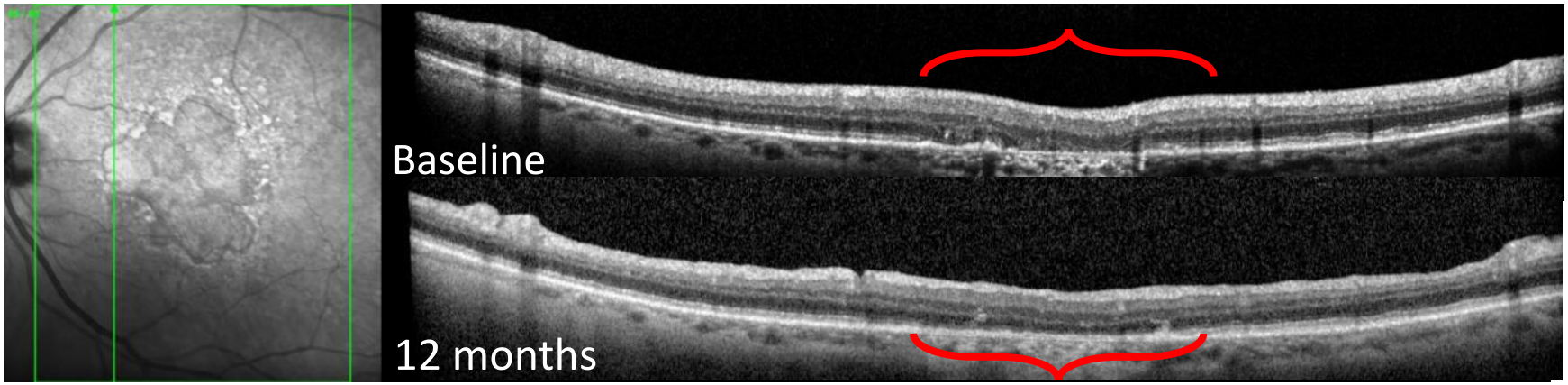


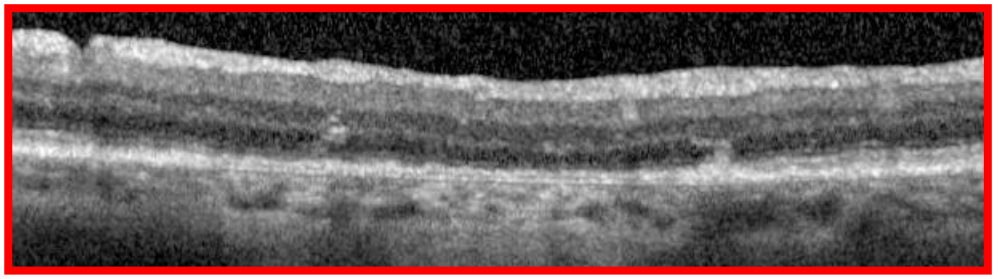
Baseline

Case Report – Patient #14



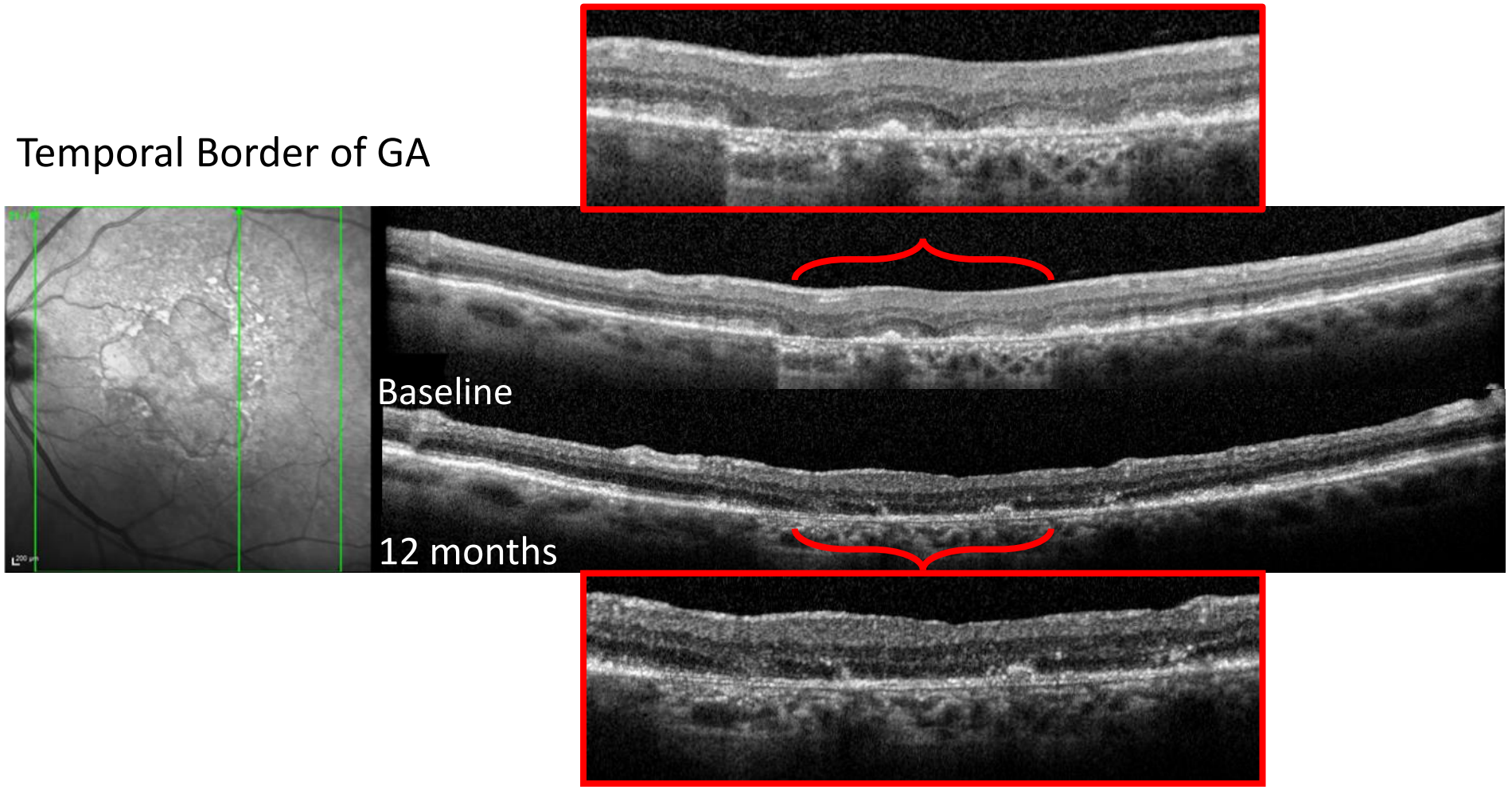
Nasal Border of GA





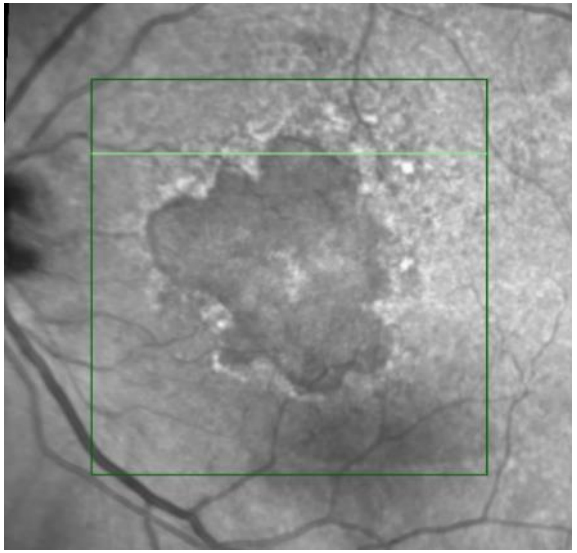
Case Report – Patient #14

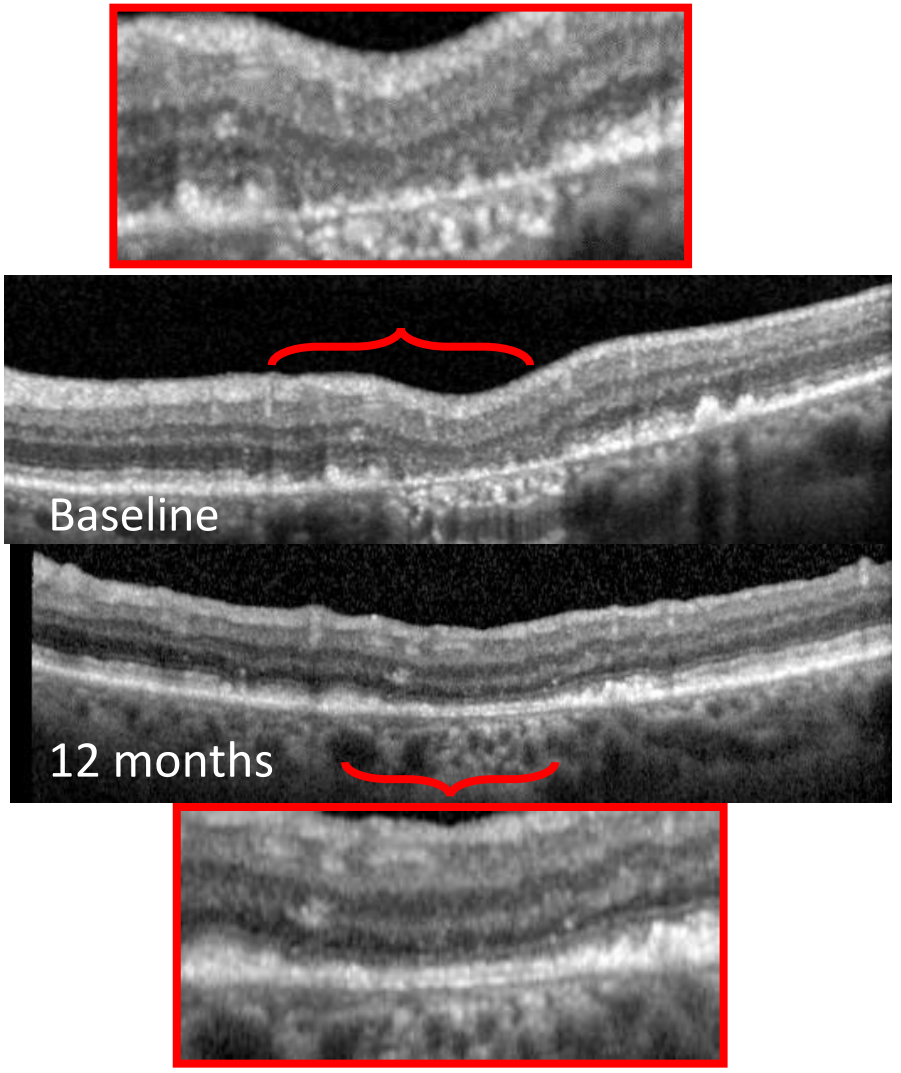
Temporal Border of GA



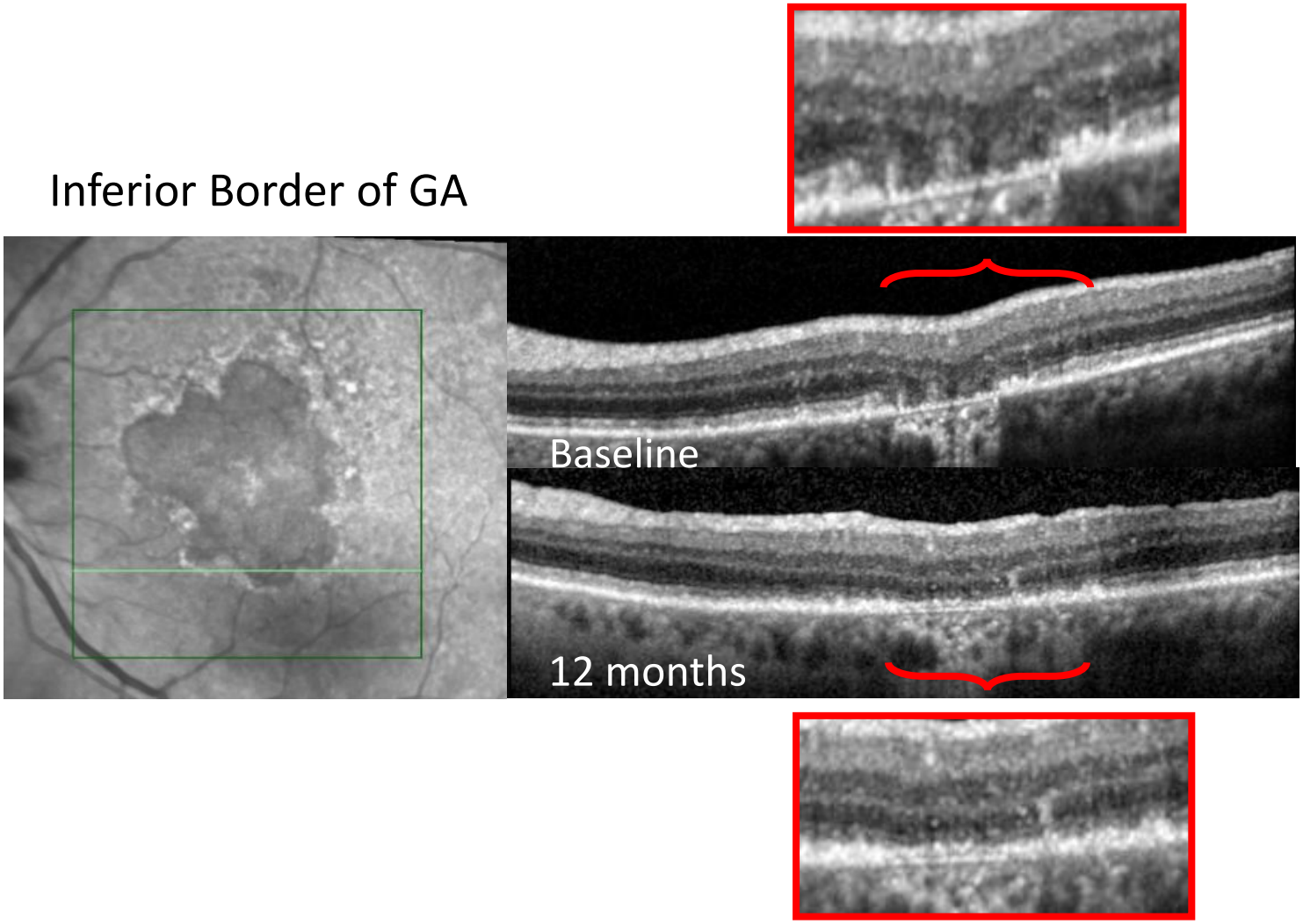
Case Report – Patient #14

Superior Border of GA





Case Report – Patient #14



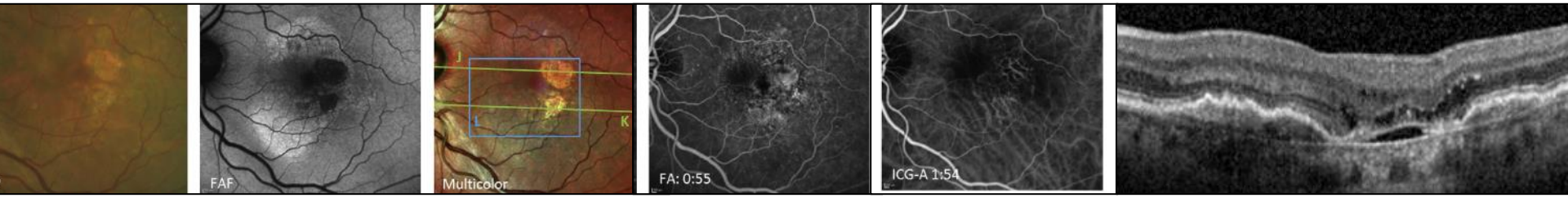
LINEAGE
CELL THERAPEUTICS

AMD is the leading cause of irreversible vision loss in the US

Source: aao.org

Jordi Monés M.D., Ph.D.
Director, Barcelona Macula Foundation: Research for Vision
Director, Institut de la Màcula

SPECIFICITIES TO ASSESS RPE-DERIVED STEM CELLS



Jordi Monés, MD, PhD

Institut de la Macula, and Barcelona Macula Foundation

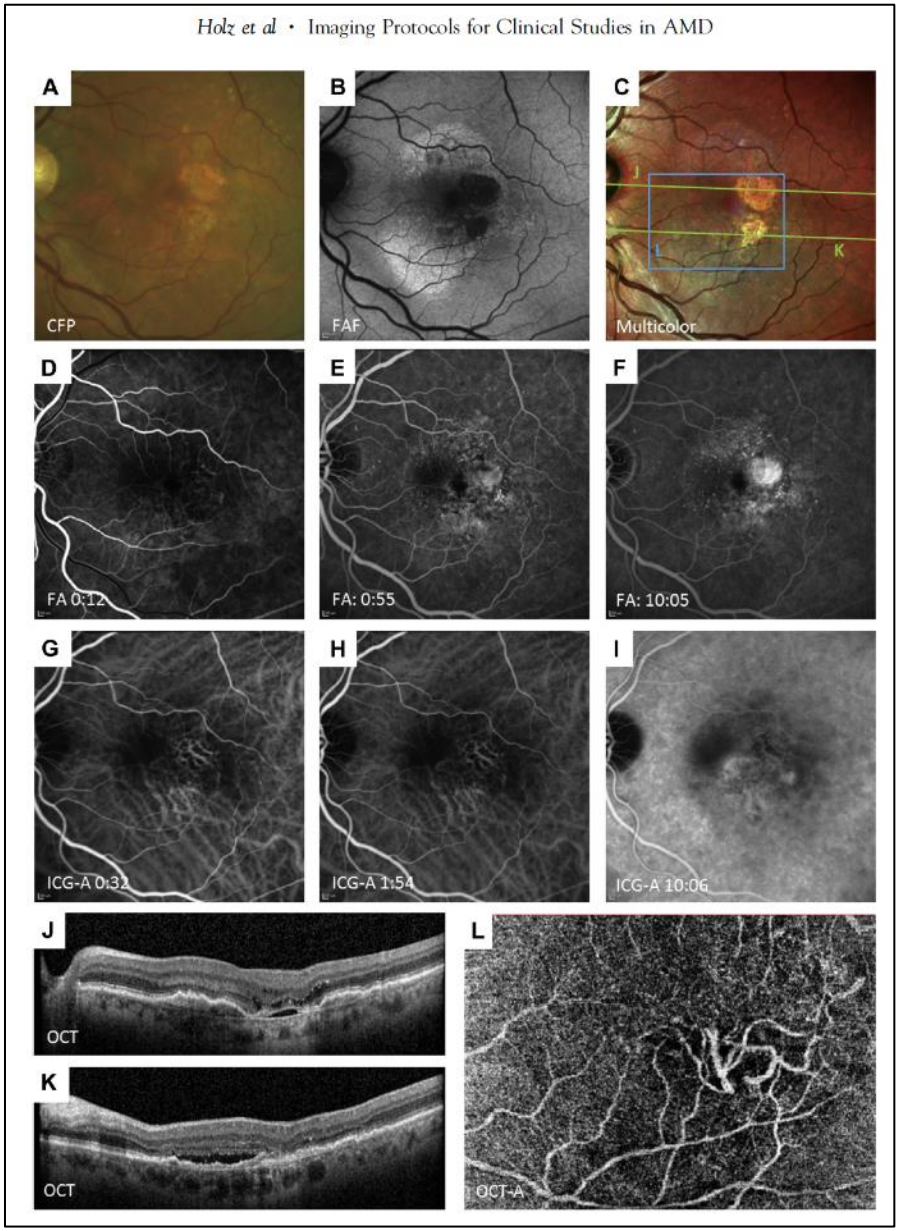
MULTIMODAL IMAGING

AMERICAN ACADEMY OF OPHTHALMOLOGY

Imaging Protocols in Clinical Studies in Advanced Age-Related Macular Degeneration

Recommendations from Classification of Atrophy Consensus Meetings

Frank G. Holz, MD, FEBO,[1] SriniVas R. Sadda, MD,[2] Giovanni Staurenghi, MD, FARVO,[3] Moritz Lindner, MD,[1] Alan C. Bird, MD, FARVO,[4] Barbara A. Blodi, MD,[5] Ferdinando Bottoni, MD, FEBO,[3] Usha Chakravarthy, MBBS, PhD,[6] Emily Y. Chew, MD, FARVO,[7] Karl Csaky, MD, PhD,[8] Christine A. Curcio, PhD, FARVO,[9] Ron Danis, MD,[5] Monika Fleckenstein, MD,[1] K. Bailey Freund, MD,[10] Juan Grunwald, MD,[11] Robyn Guymer, MBBS, PhD,[12] Carel B. Hoyng, MD, PhD,[13] Glenn J. Jaffe, MD, FARVO,[14] Sandra Liakopoulos, MD,[15] Jordi M. Monés, MD, PhD,[16] Akio Oishi, MD, PhD,[1] Daniel Pauleikhoff, MD,[17] Philip J. Rosenfeld, MD, PhD,[18] David Sarraf, MD,[19] Richard F. Spaide, MD,[13] Ramin Tadayoni, MD, PhD,[20] Adnan Tufail, MD, FRCOphth,[21] Sebastian Wolf, MD, PhD,[22] Steffen Schmitz-Valckenberg, MD, FEBO,[1] *on behalf of the CAM group**



Color fundus photography CFP

Fundus autofluorescence FAF

Infrared imaging/ Multicolor imaging IR

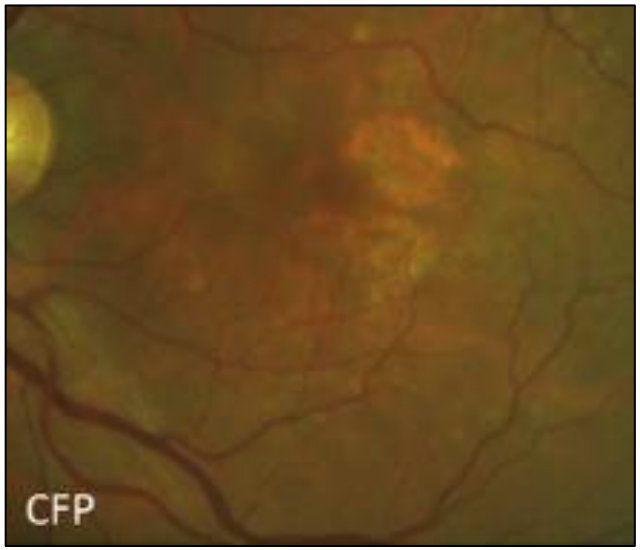
Optical Coherent Tomography OCT

Fluorescein angiography FA

Indocyanine green angiography ICG

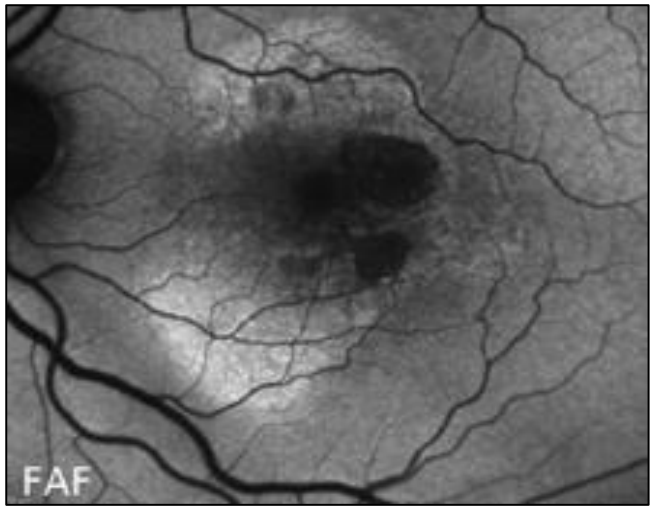
OCT angiography

COLOR FUNDUS PHOTOGRAPHY



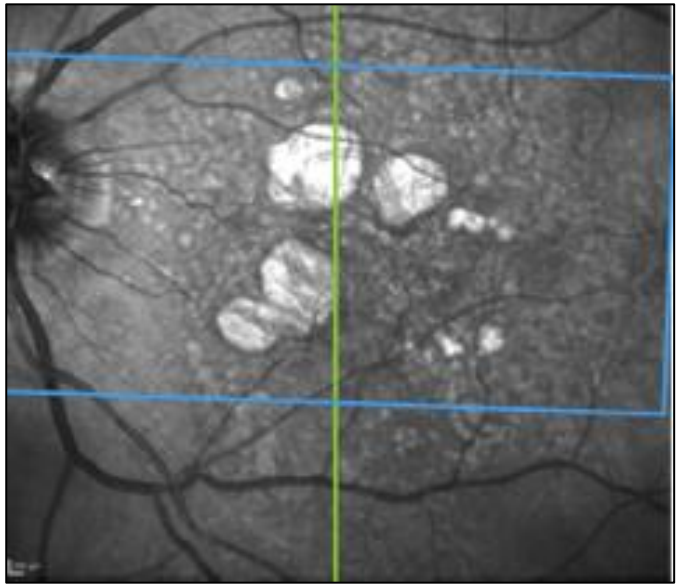
	PRO	CONS
CFP	•Historical standard •Closest correlate to biomicroscopy •Visualizes broad range of fundus abnormalities •Robust to image hemorrhages and pigmentary changes	•Reduced contrast, poor detection of GA boundaries •Limited reliability •Strongly affected by optical media •Patient discomfort •Experienced examiner required

FUNDUS AUTOFLUORESCENCE



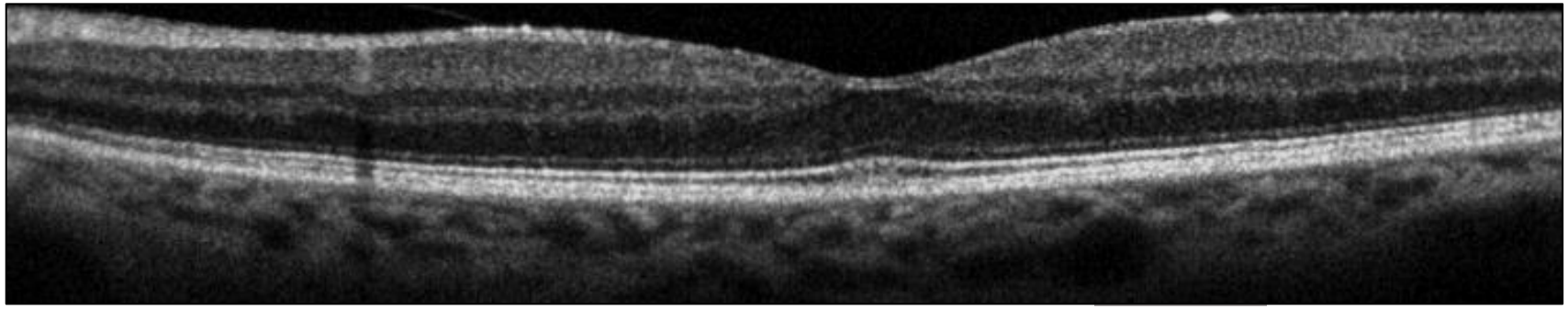
	PRO	CONS
FAF	•High contrast •Regulatory acceptance •Extensive experience •Already used for primary end point measurement •Strongly decreased signal correlates with loss of function •Allows for refined phenotyping and differential diagnosis	•Sensitive to nuclear lens opacities and vitreous floaters •Assessment of foveal region difficult •Semiautomated atrophy quantification may be hindered in certain conditions •Patient discomfort

NEAR INFRARED



	PRO	CONS
NIR	•Resistant to media opacities •Auxiliary for foveal assessment •Enables detection of reticular pseudodrusen and atrophy •Built-in in most OCT/SLO devices	•Lack of validation studies for late-stage AMD •Findings are of yet unstudied specificity •Cannot be used as stand-alone technology

OCT



	PRO	CONS
OCT	•Broadly available •Cross-sectional morphology of retina, RPE, and choroid •Correlated with histology •Validated to assess RPE atrophy progression and neovascular changes •Anatomic tracking functions for exact repositioning of follow-up scans •Identification of preatrophic features •Comfortable for patients	•Scan field limited •Interpretation strongly dependent on imaging quality •Lack of industry standards •3-dimensional datasets require sophisticated analysis software •Automated segmentation imperfect and instrument dependent

FAF used for the primary endpoint in clinical trials

FAF is the imaging modality used for the primary endpoint of rate of GA lesion change over time:

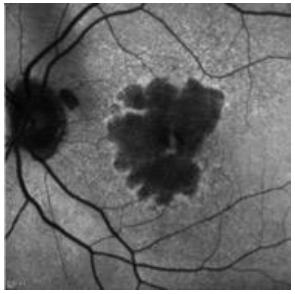
- In mm^2
- More recently as the square root transformation, in mm

Mean Change in GA Area from Baseline at 1 Year*

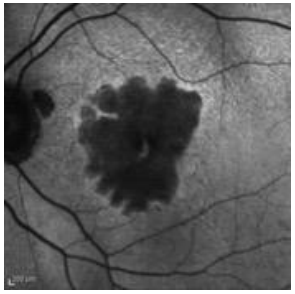
Phase III Primary Efficacy Endpoint

Chroma Spectri

MAHALO Phase II CFI+ patient treated with lampalizumab monthly



Change = 0.69 mm^2 (+7.1%)



Baseline 9.67 mm^2

Year 1 10.36 mm^2

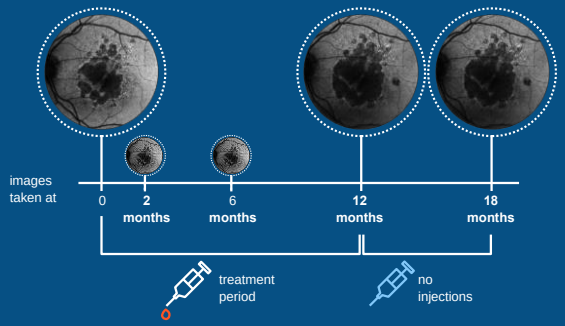
*Assessed at 48 weeks by fundus autofluorescence.

2.5 mm^2 = 1 DA

17

Endpoints

FILLY



Primary efficacy endpoint

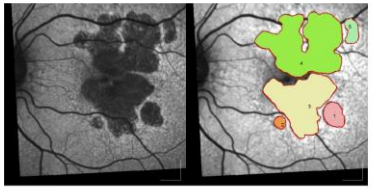
Change in square root geographic atrophy (GA) lesion size from baseline to month 12

Primary safety endpoint

Number and severity of local and systemic treatment emergent adverse events (TEAEs)

Zimura in GA: Primary Efficacy Endpoint

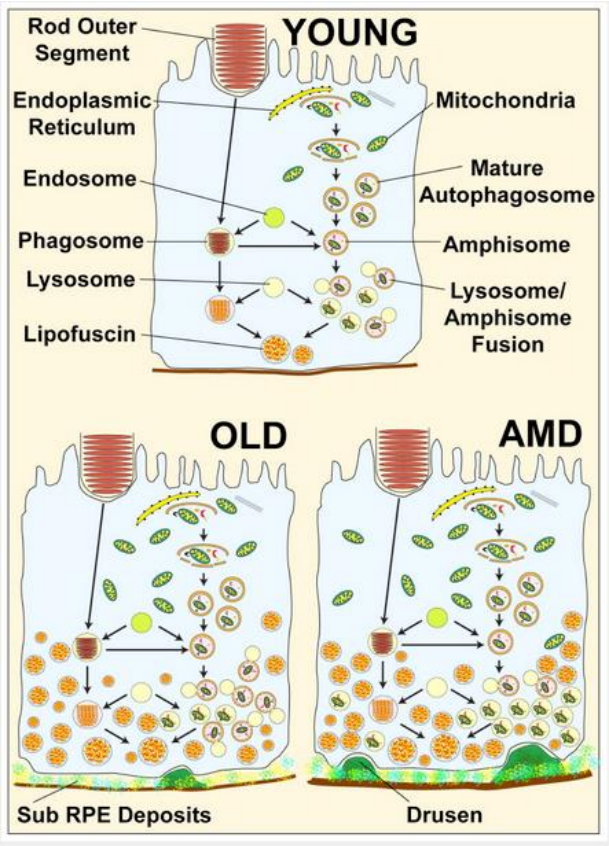
Mean rate of change in GA over 12 months measured by fundus autofluorescence (FAF) at **three time points**: Baseline, Month 6, and Month 12 (**square root** transformation of GA lesion)



11

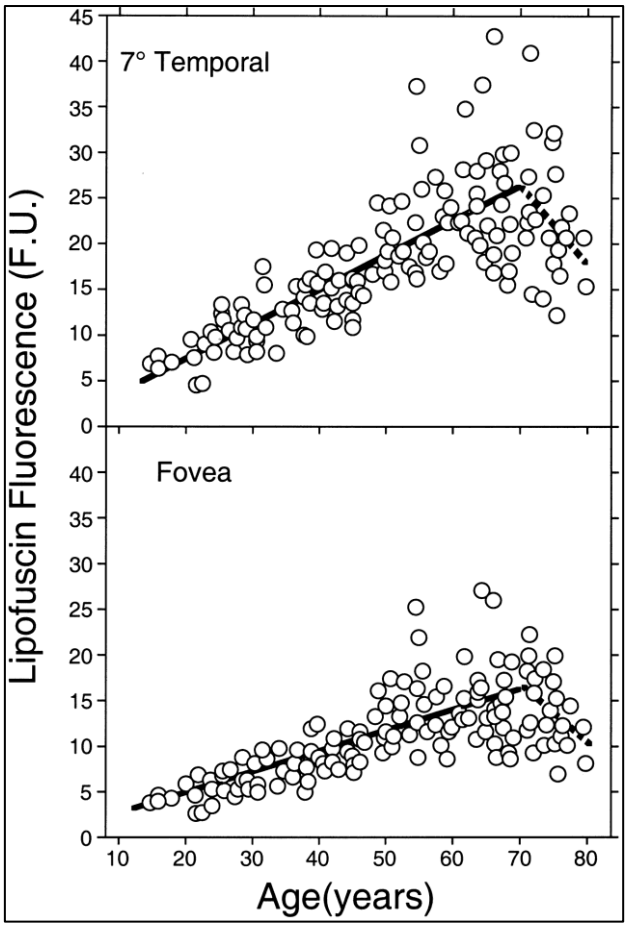
FAF depends on age-related or pathological accumulation of lipofuscin

(Delori 1995)



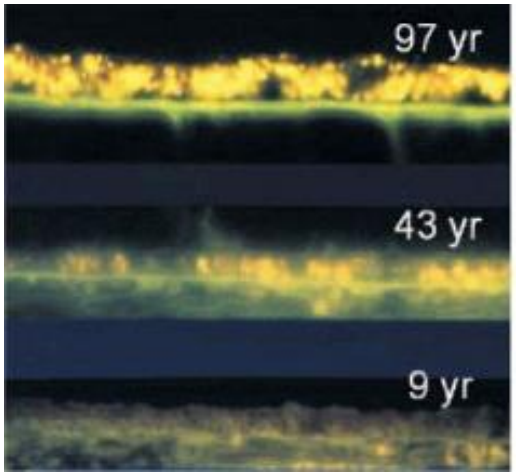
In the young lipofuscin in residual bodies is minimally present

From: Mitter SK, Rao HV, Qi X, et al. Autophagy in the retina: a potential role in age-related macular degeneration. Advances in Experimental Medicine and Biology. 2012 ;723:83-90.



Lipofuscin fluorescence as a function of age.

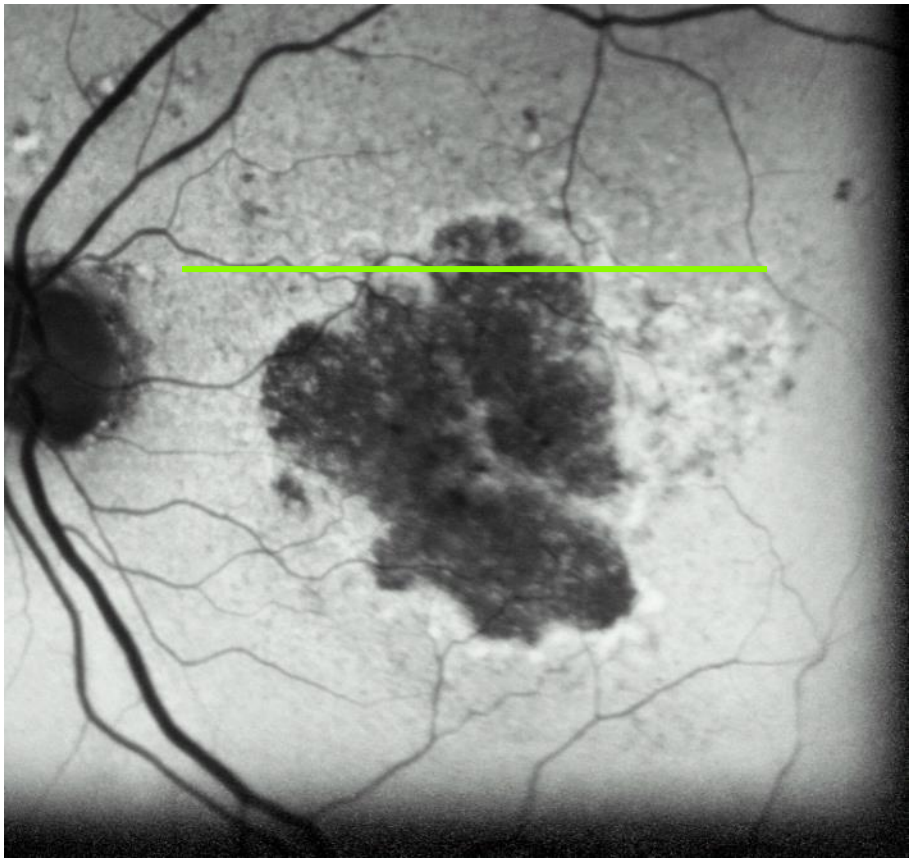
From: Age-Related Accumulation and Spatial Distribution of Lipofuscin in RPE of Normal Subjects Invest. Ophthalmol. Vis. Sci.. 2001;42(8):1855-1866.



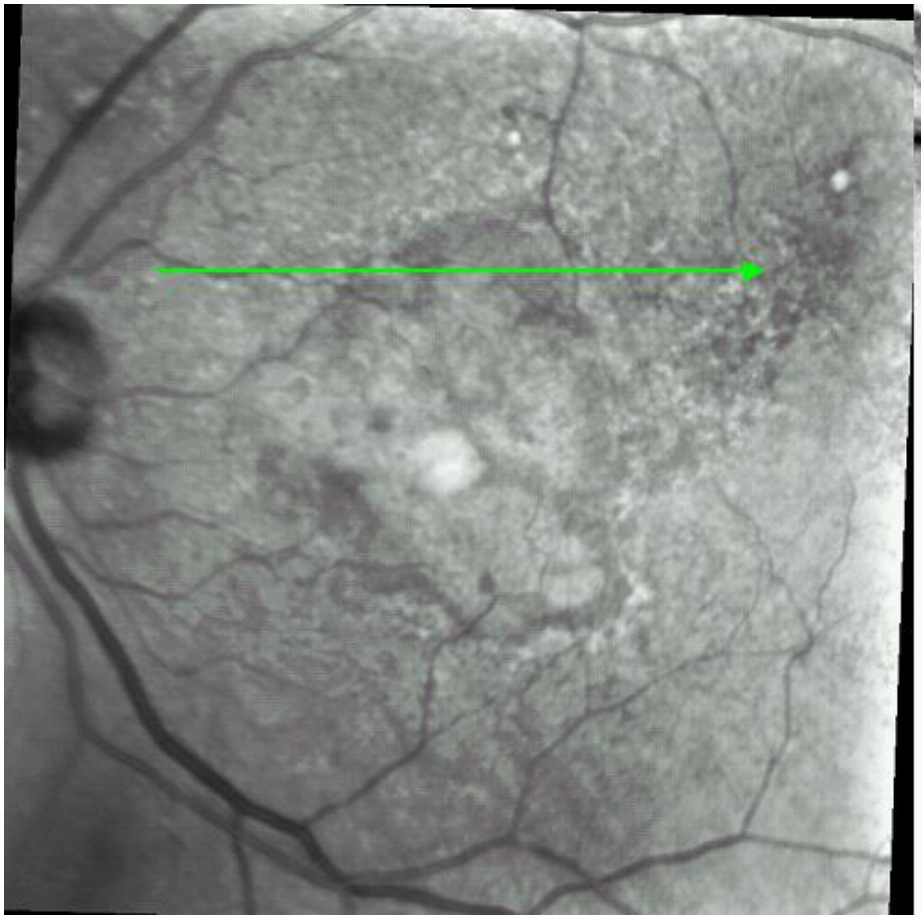
Fluorescence microscopy of tissue sections from 9-, 43-, and 97-year-old donors showing an increase in fluorescent lipofuscin granules with increasing age.

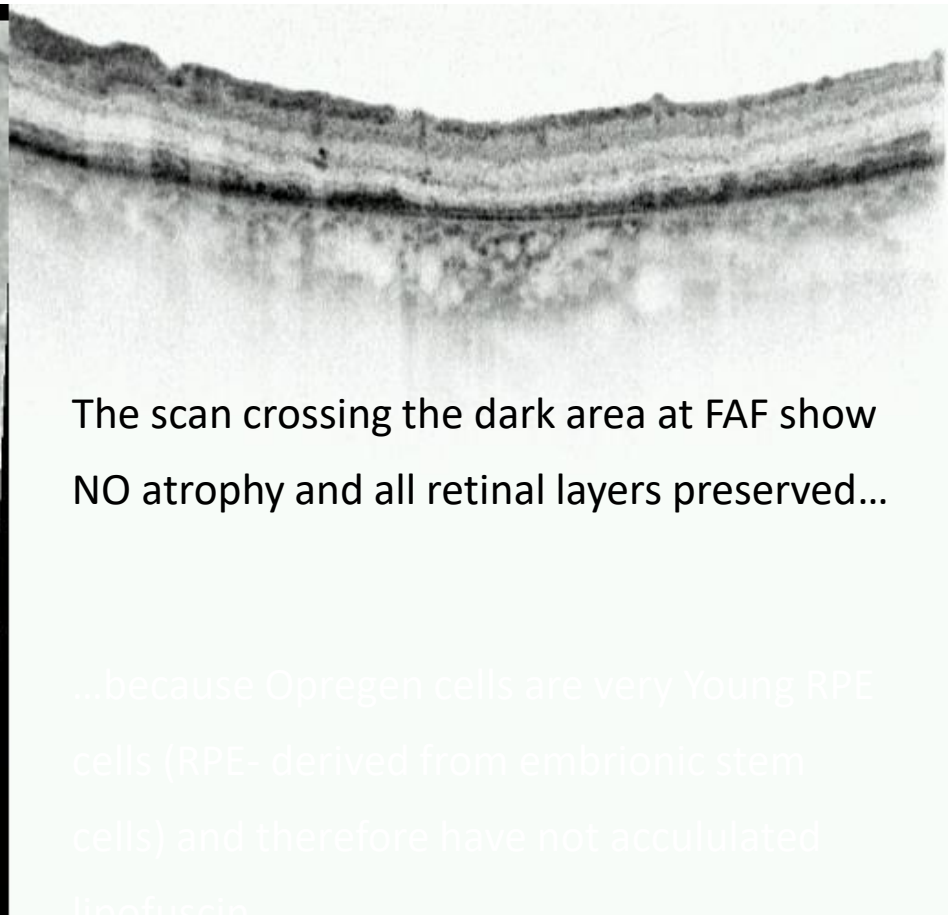
From: Boulton, ME

FAF after OpRegen cell transplantation



OCT after OpRegen cell transplantation

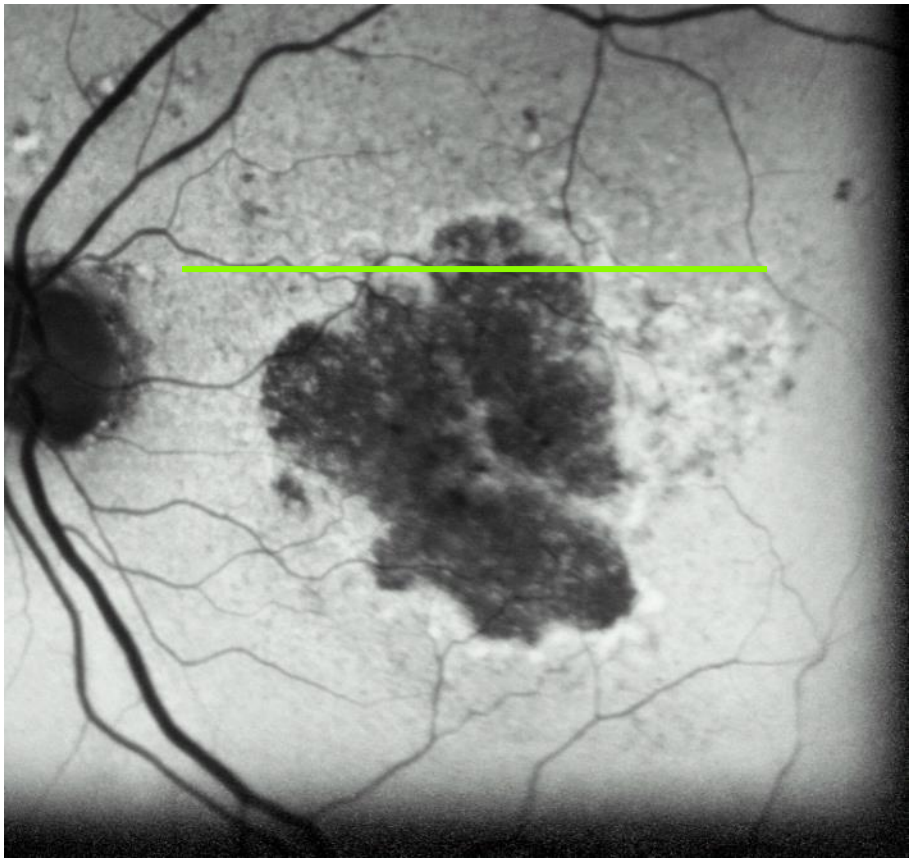




The scan crossing the dark area at FAF show NO atrophy and all retinal layers preserved…

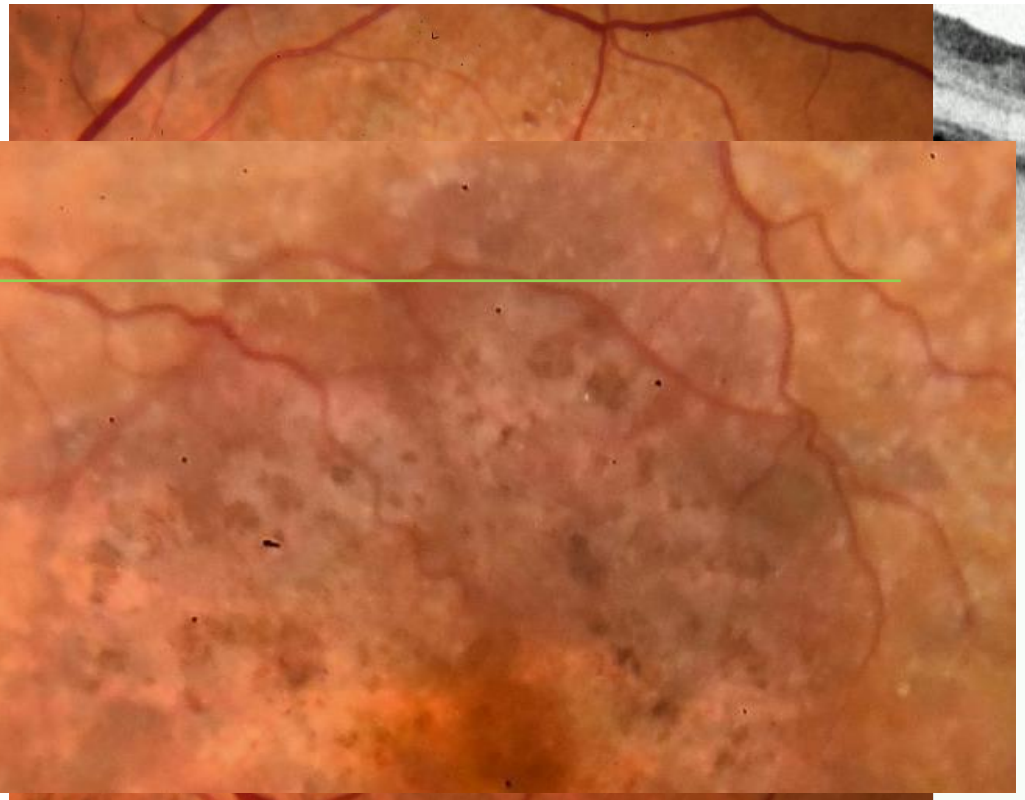
…because Opregen cells are very Young RPE cells (RPE- derived from embrionic stem cells) and therefore have not accululated lipofuccia

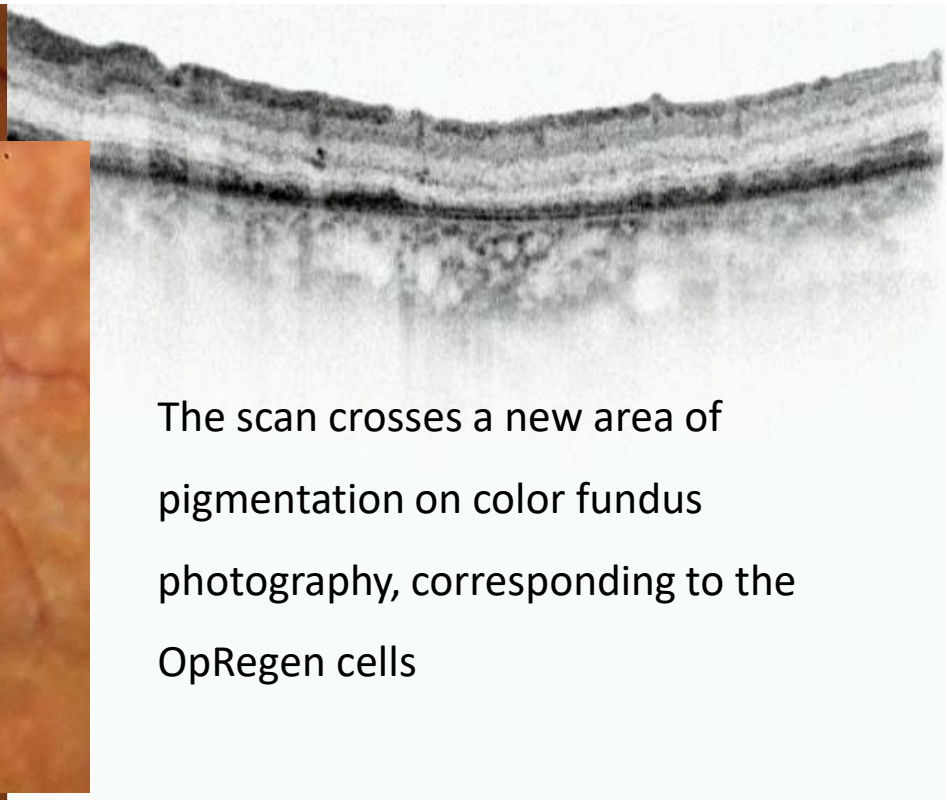
FAF after OpRegen cell transplantation



…because OpRegen cells are very young RPE cells (RPE- derived from embryonic stem cells) and therefore have not accumulated lipofuscin

OpRegen RPE cells do not show FAF





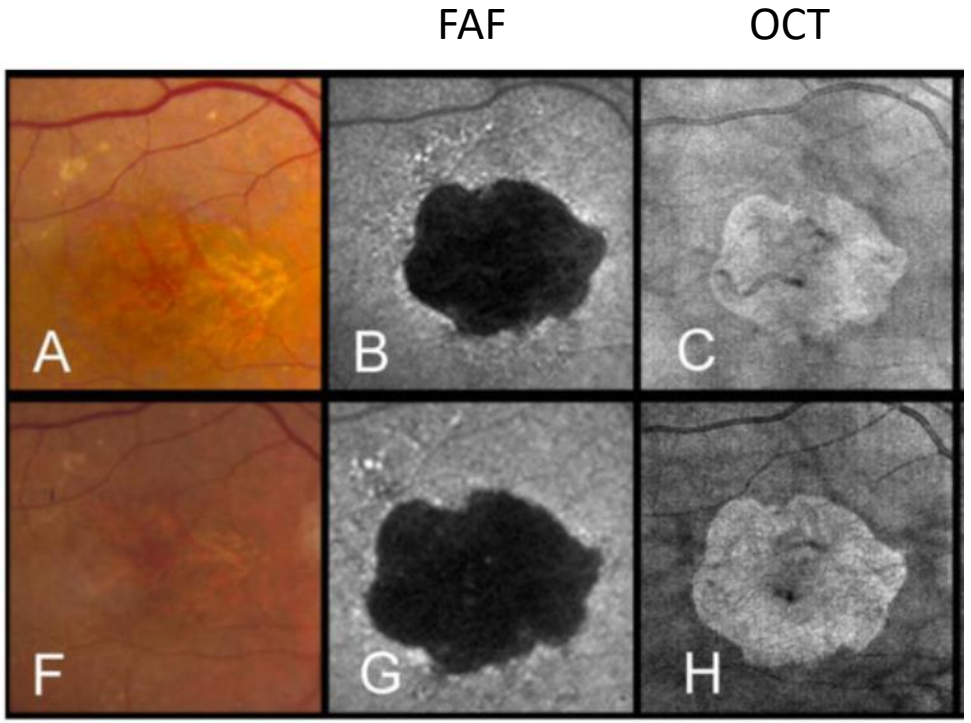
The scan crosses a new area of pigmentation on color fundus photography, corresponding to the OpRegen cells

En Face OCT as imaging to assess lesion size

Progression of Geographic Atrophy in Age-Related Macular Degeneration Imaged with Spectral Domain Optical Coherence Tomography

Zohar Yehoshua, MD, MHA, **Philip J. Rosenfeld, MD PhD**, **Giovanni Gregori, PhD**, **William J. Feuer, MS**, **Manuel Falcão, MD**, **Brandon J. Lujan, MD**, and **Carmen Puliafito, MD, MBA**
Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, FL

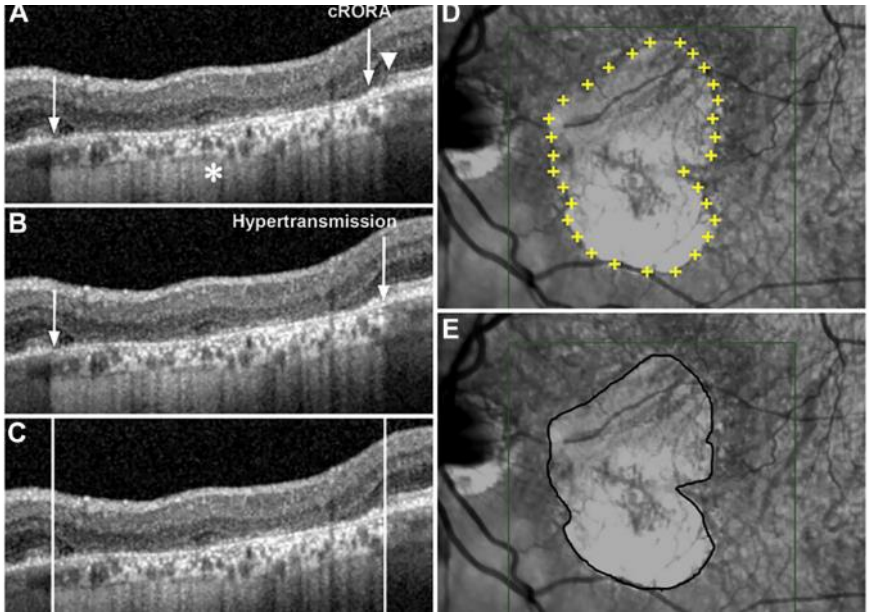
This current study showed that GA can be reproducibly identified, quantified, and followed using the en-face SDOCT fundus image.

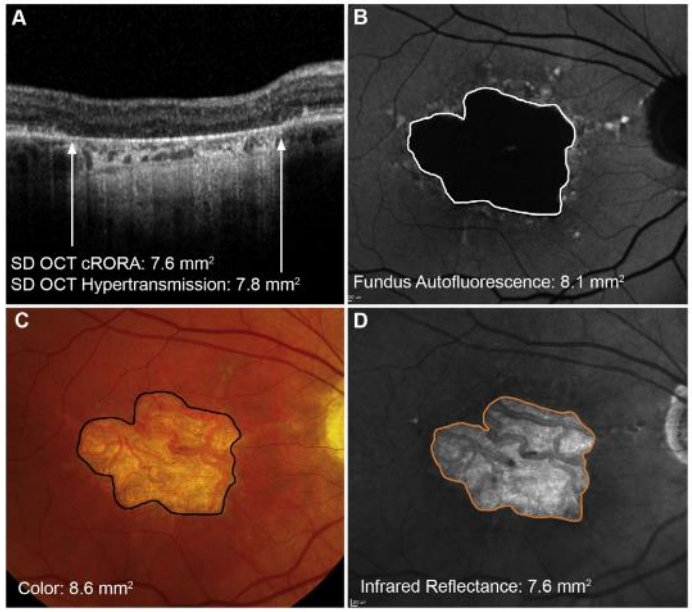


En Face OCT as imaging to assess lesion size

Quantification of Geographic Atrophy Using Spectral Domain OCT in Age-Related Macular Degeneration

Spencer C. Cleland, MD,[1] Sri Meghana Konda, MBBS,[1] Ronald P. Danis, MD,[1,2] Yijun Huang, PhD,[1,2] Dawn J. Myers, BS,[1] Barbara A. Blodi, MD,[1] Amitha Domalpally, MD, PhD[1]



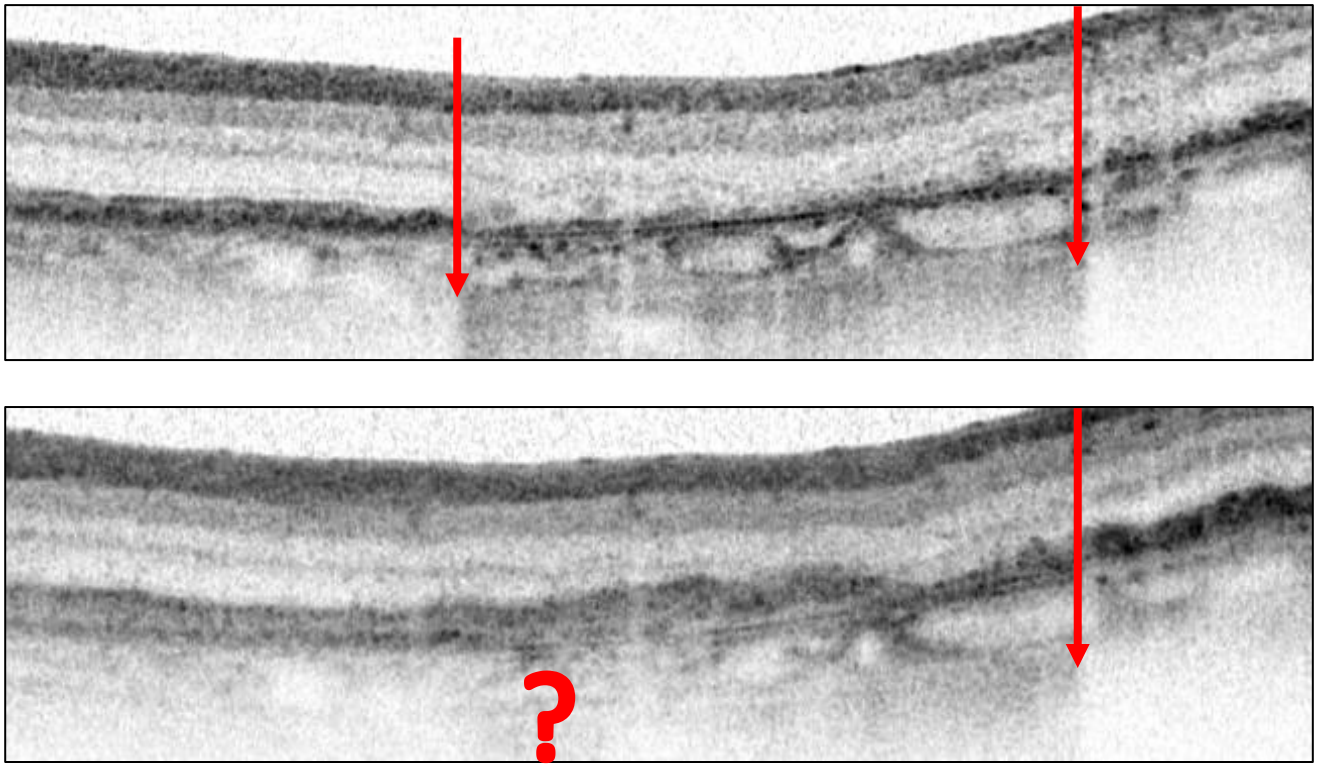


The en-face images (obtained by the choroidal hypertransmission) correlates very well with FAF

En Face OCT as imaging to assess lesion size

…However, lack of hypertransmission does not necessarily correspond to viable retina

Non-viable clumping or debris may interfere with hypertransmission



Ideal endpoint would be to assess geographic atrophy in OpRegen cell transplanted lesions

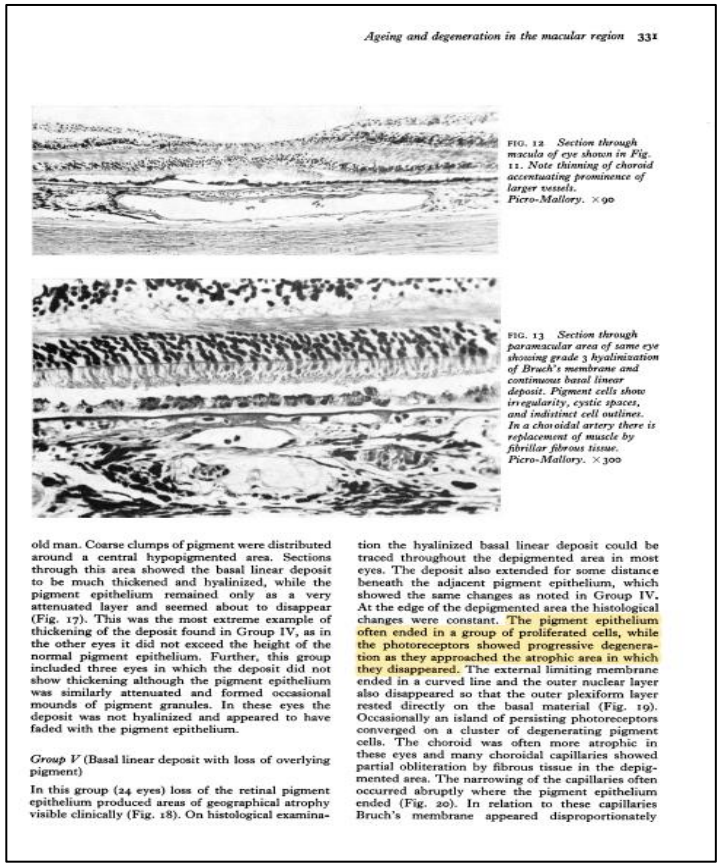
FAF does not work with very young RPE-derived stem cells because of lack of lipofuscin and therefore autofluorescence

Hypertransmission reveals atrophy. However, absence of hypertransmission do not necessarily corresponds to healthy viable retina

The ideal endpoint should reflect directly the **status of the retina** therefore the best endpoint would be and in-vivo histologic-like endpoint

Lessons from histology

1976



Ageing and degeneration in the macular region 331

FIG. 12 *Section through macula of eye shown in Fig. 11. Note thinning of choroid accentuating prominence of larger vessels. Picro-Mallory.* ×90

FIG. 13 *Section through paramacular area of same eye showing grade 3 hyalinization of Bruch's membrane and continuous basal linear deposit. Pigment cells show irregularity, cystic spaces, and indistinct cell outlines. In a choroidal artery there is replacement of muscle by fibrillar fibrous tissue. Picro-Mallory.* ×300

old man. Coarse clumps of pigment were distributed around a central hypopigmented area. Sections through this area showed the basal linear deposit to be much thickened and hyalinized, while the pigment epithelium remained only as a very attenuated layer and seemed about to disappear (Fig. 17). This was the most extreme example of thickening of the deposit found in Group IV, as in the other eyes it did not exceed the height of the normal pigment epithelium. Further, this group included three eyes in which the deposit did not show thickening although the pigment epithelium was similarly attenuated and formed occasional mounds of pigment granules. In these eyes the deposit was not hyalinized and appeared to have faded with the pigment epithelium.

Group V (Basal linear deposit with loss of overlying pigment)

In this group (24 eyes) loss of the retinal pigment epithelium produced areas of geographical atrophy visible clinically (Fig. 18). On histological examination the hyalinized basal linear deposit could be traced throughout the depigmented area in most eyes. The deposit also extended for some distance beneath the adjacent pigment epithelium, which showed the same changes as noted in Group IV. At the edge of the depigmented area the histological changes were constant. The pigment epithelium often ended in a group of proliferated cells, while the photoreceptors showed progressive degeneration as they approached the atrophic area in which they disappeared. The external limiting membrane ended in a curved line and the outer nuclear layer also disappeared so that the outer plexiform layer rested directly on the basal material (Fig. 19). Occasionally an island of persisting photoreceptors converged on a cluster of degenerating pigment cells. The choroid was often more atrophic in these eyes and many choroidal capillaries showed partial obliteration by fibrous tissue in the depigmented area. The narrowing of the capillaries often occurred abruptly where the pigment epithelium ended (Fig. 20). In relation to these capillaries Bruch's membrane appeared disproportionately

Brit. J. Ophthal. (1976) **60**, 324

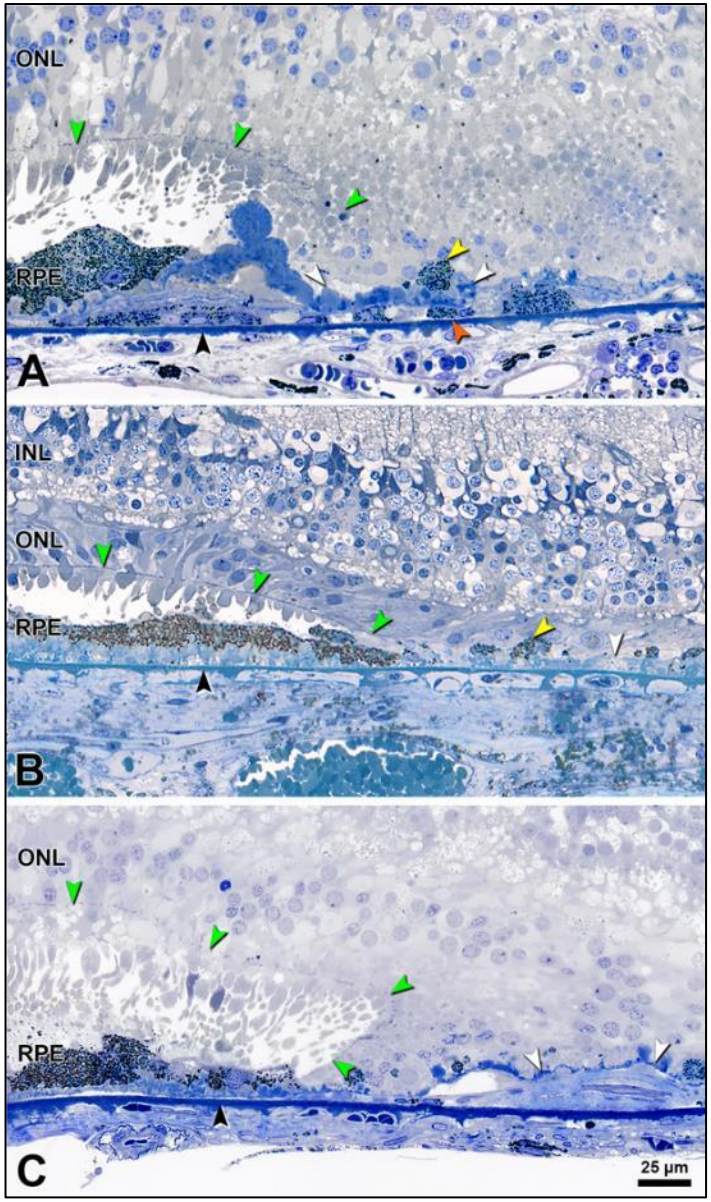
Ageing and degeneration in the macular region: a clinico-pathological study

S. H. SARKS
Lidcombe Hospital, Sydney, Australia

"The external limiting membrane ended in a curved line and the outer nuclear layer also disappeared so that the outer plexiform layer rested directly on the basal material"

Lessons from histology

2016



Published in final edited form as:
Retina. 2016 December ; 36(Suppl 1): S12–S25. doi:10.1097/IAE.0000000000001276.

Visualizing retinal pigment epithelium phenotypes in the transition to geographic atrophy in age-related macular degeneration

Emma C. Zanzottera, MD[1,2,*], Thomas Ach, MD[1,3,*], Carrie Huisingh, MPH[4], Jeffrey D. Messinger, DC[1], Richard F. Spaide, MD[5], and Christine A. Curcio, PhD[1]

"The ELM comprises junctional complexes between the Müller cells and photoreceptor inner segments [28–30] and together with junctional complexes among RPE, bounds the subretinal space". ELM presence means RPE and photorreceptor interaction

"A border of atrophy that can be precisely delimited is the ELM descent, as opposed to the termination of the RPE layer itself, because of dissociated RPE in the atrophic area"

Lessons from histology

2018

"*The ELM border descend is accepted as the delimitation of the area with near-total photoreceptor depletion*[1]*, and therefore the boundary of the atrophy in cRORA*".

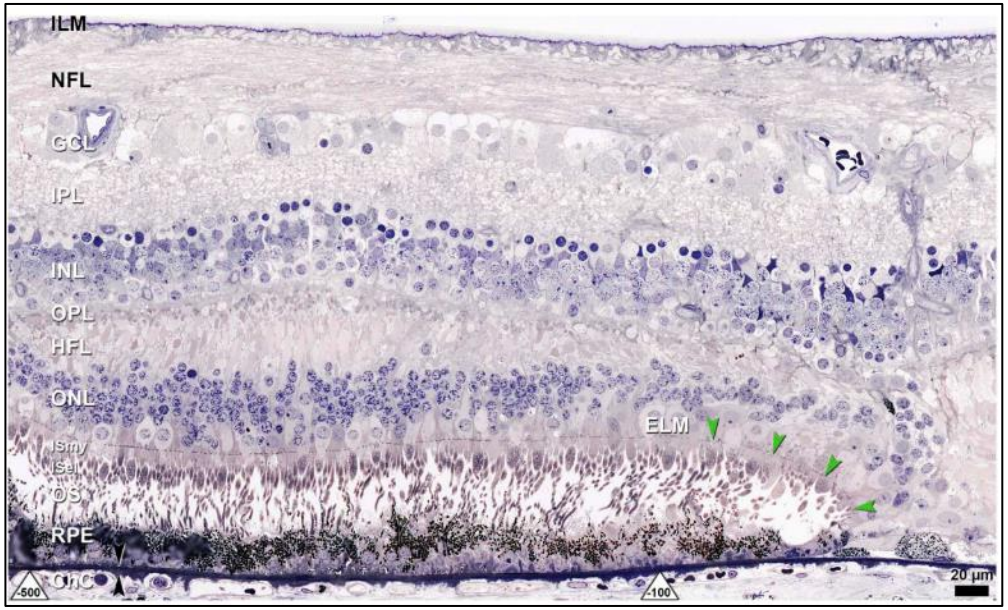
SDC

OPEN

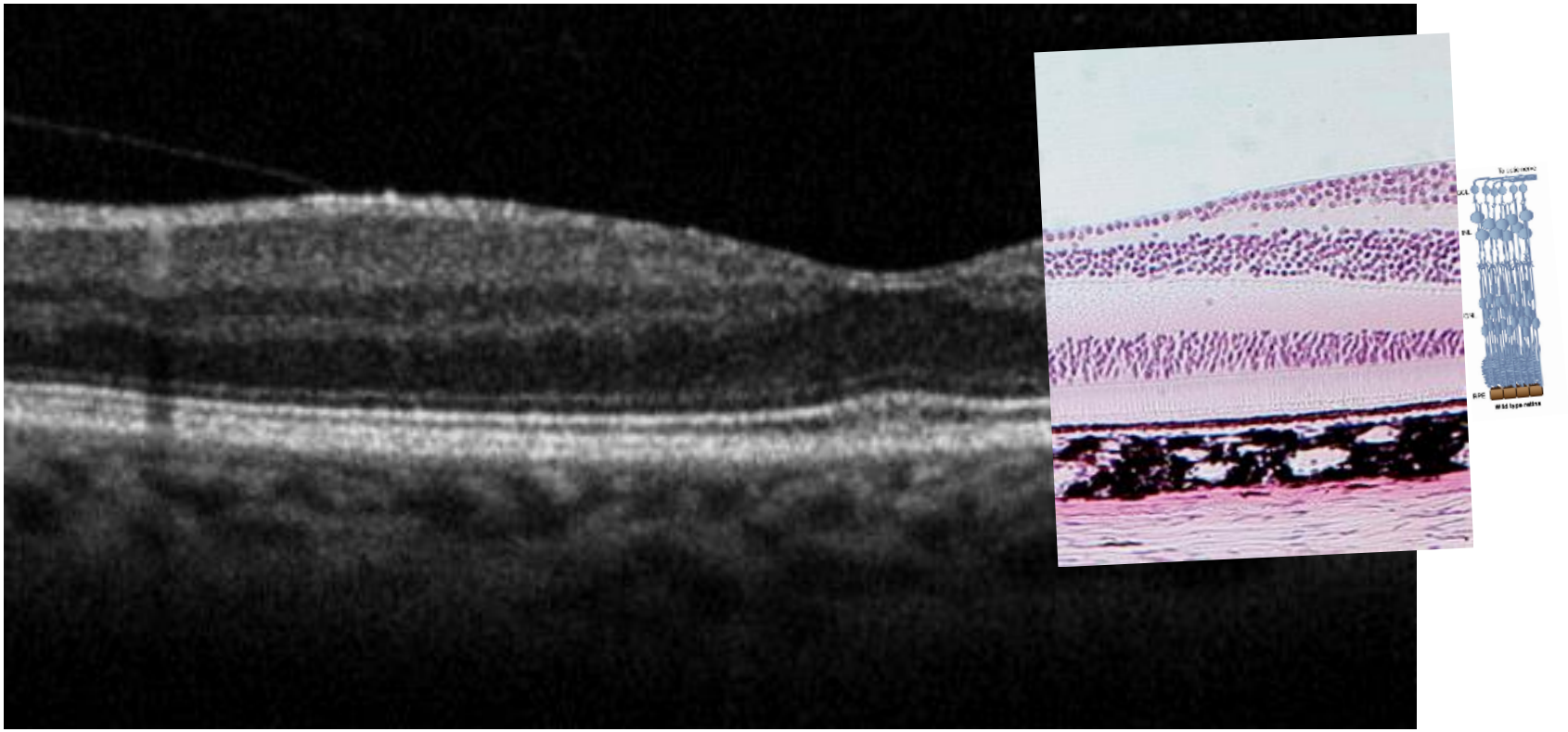
HISTOLOGY OF GEOGRAPHIC ATROPHY SECONDARY TO AGE-RELATED MACULAR DEGENERATION

A Multilayer Approach

MIAOLING LI, MD, PHD,*† CARRIE HUISINGH, MSPH,* JEFFREY MESSINGER, DC,* ROSA DOLZ-MARCO, MD, PHD,‡§¶ DANIELA FERRARA, MD, PHD,** K. BAILEY FREUND, MD,‡§†† CHRISTINE A. CURCIO, PHD*

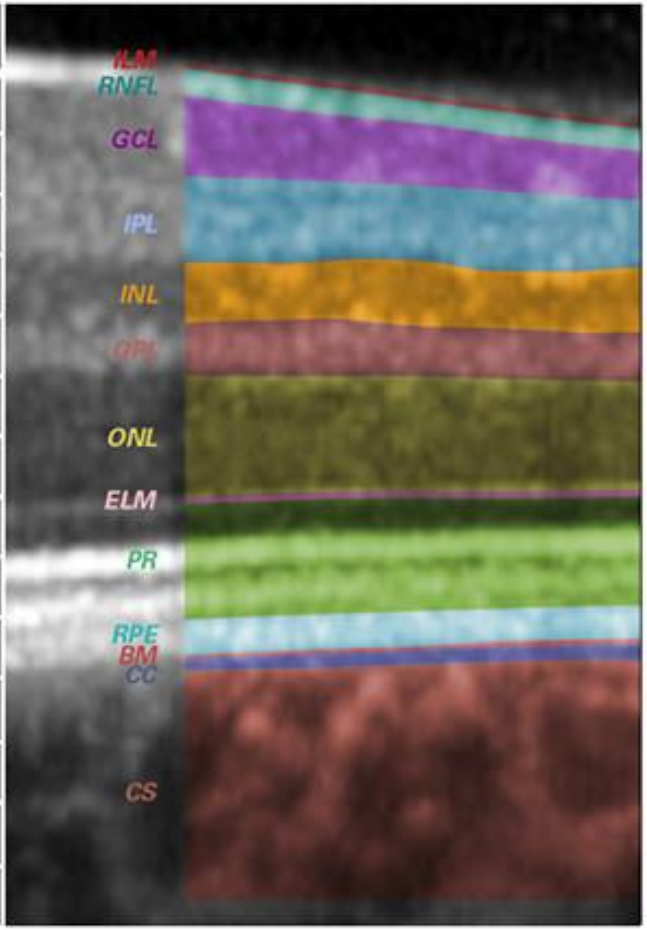


High resolution OCT provides resolution close to histology



High resolution OCT provides resolution close to histology

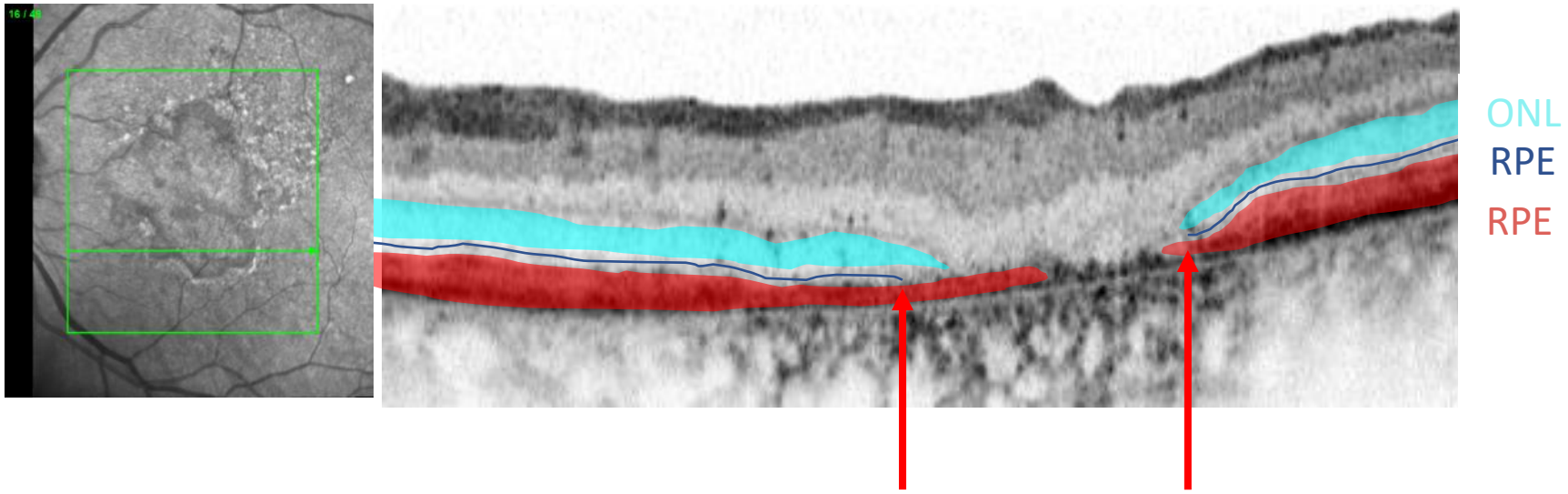
Retinal Layers	
Abbr.	Name
ILM	Internal Limiting Membrane
RNFL	Retinal Nerve Fibre Layer
GCL	Ganglion Cell Layer
IPL	Inner Plexiform Layer
INL	Inner Nuclear Layer
OPL	Outer Plexiform Layer
ONL	Outer Nuclear Layer
ELM	External Limiting Membrane
PR	Photoreceptor Layers
RPE	Retinal Pigment Epithelium
BM	Bruch's Membrane
CC	Choriocapillaris
CS	Choroidal Stroma



Source: https://www.heidelbergengineering.com/int/news/know-your-retinal-layers-33401465/

Endpoint in the OpRegen Trial to assess retinal restoration

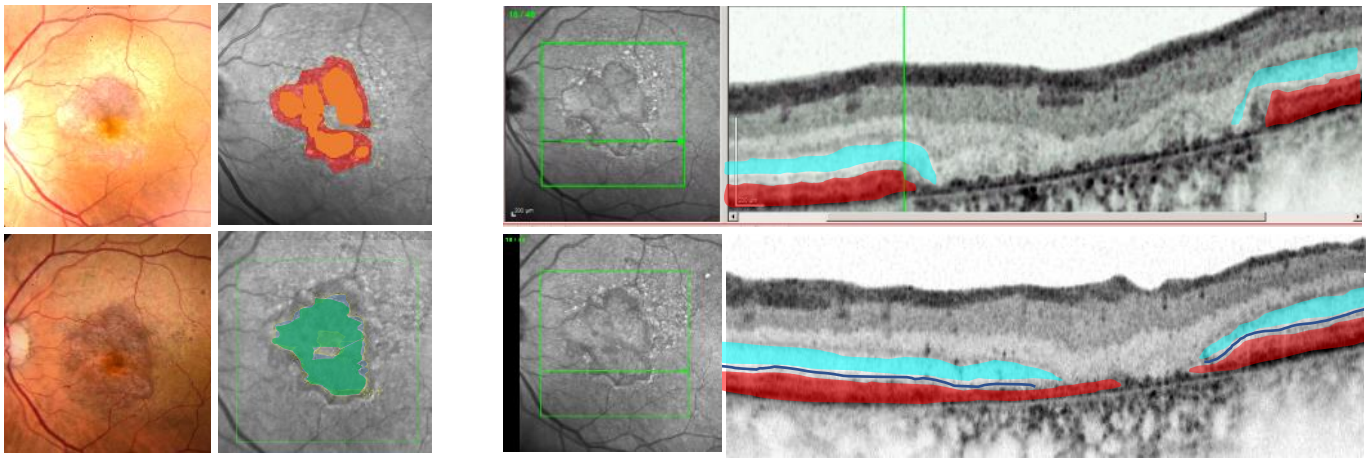
Edges of ELM, external limiting membrane



ELM-based boundaries of the atrophy

RETINAL REGENERATION IN ATROPHIC AMD

TRANSPLANTATION OF OPREGEN (ALLOGENEIC RPE CELLS)



Jordi Monés, MD, PhD

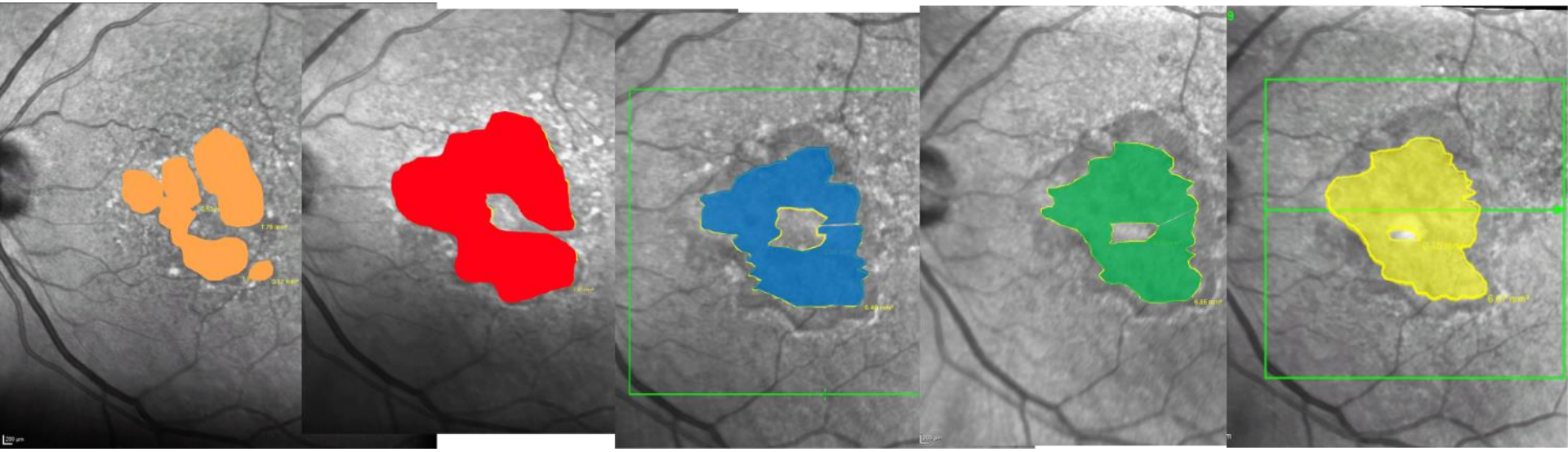
Institut de la Macula and Barcelona Macula Foundation

LINEAGE
CELL THERAPEUTICS

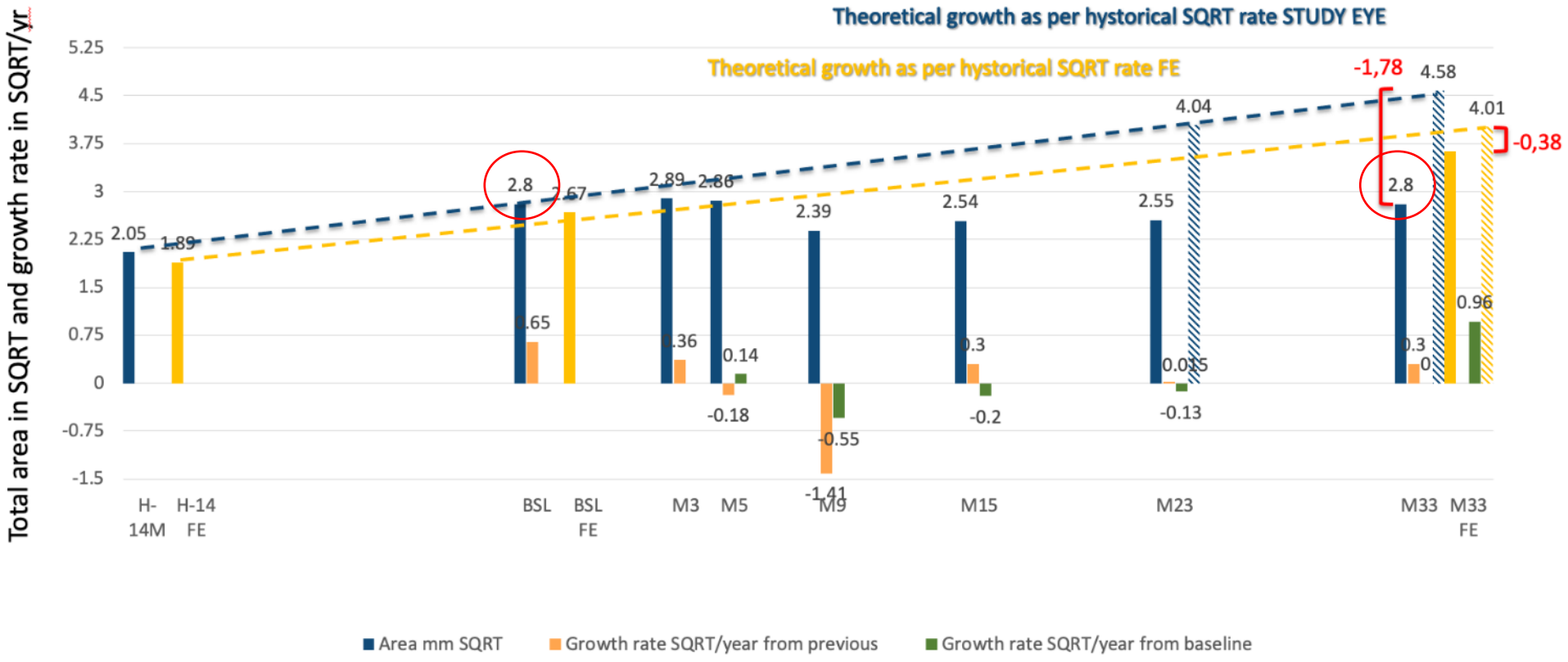
OpRegen Patient #14
1st Retinal Restoration

Rate of Atrophic Progression Over Time in Patient #14 (1st Retinal Restoration)

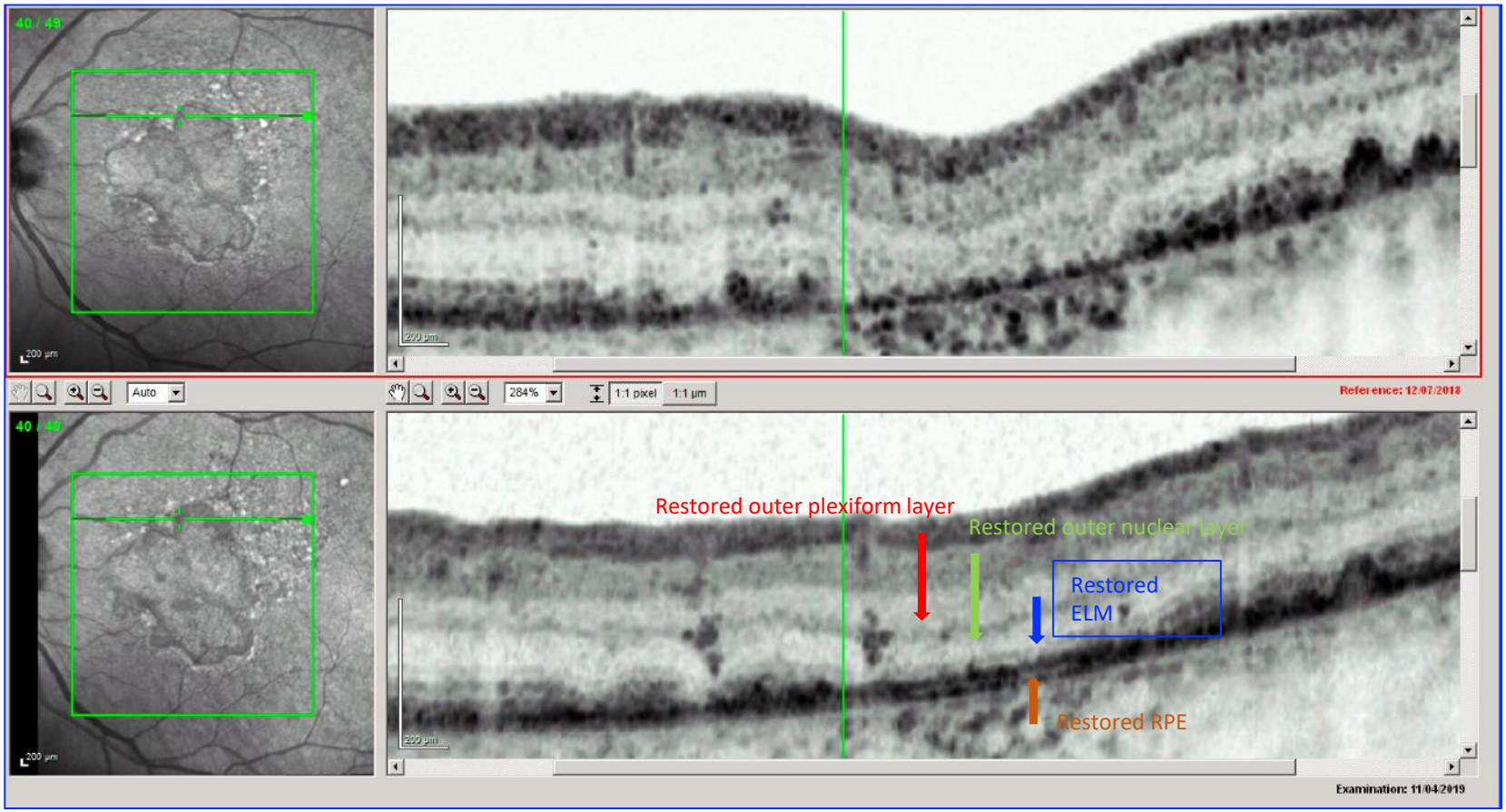
Date	Time in Study	Colored area on Figure below	Area mm^2 (SQRT)	Changes in rate of progression from previous	Changes in rate of progression from baseline
May 2017	Historical image	Orange	4.21 mm^2 (2.05)	N/A	N/A
July 2018	Baseline	Red	7.90 mm^2 (2.8)	+ 0.64 mm sqrt/yr	N/A
April 2019	Month 9	Blue	5.74 mm^2 (2.39)	- 0.61 mm sqrt/yr	- 0.61 mm sqrt/yr
October 2019	Month 15	Green	6.48 mm^2 (2.54)	+ 0.3 mm sqrt/yr	- 0.2 mm sqrt/yr
June 2020	Month 23	Yellow	6.52 mm^2 (2.55)	+ 0.015 mm sqrt/yr	- 0.13 mm sqrt/yr



Change of total size of atrophic lesion in SQRT both eyes and rate of change in mm SQRT/yr from previous and from baseline (expected growth from historical plotted)

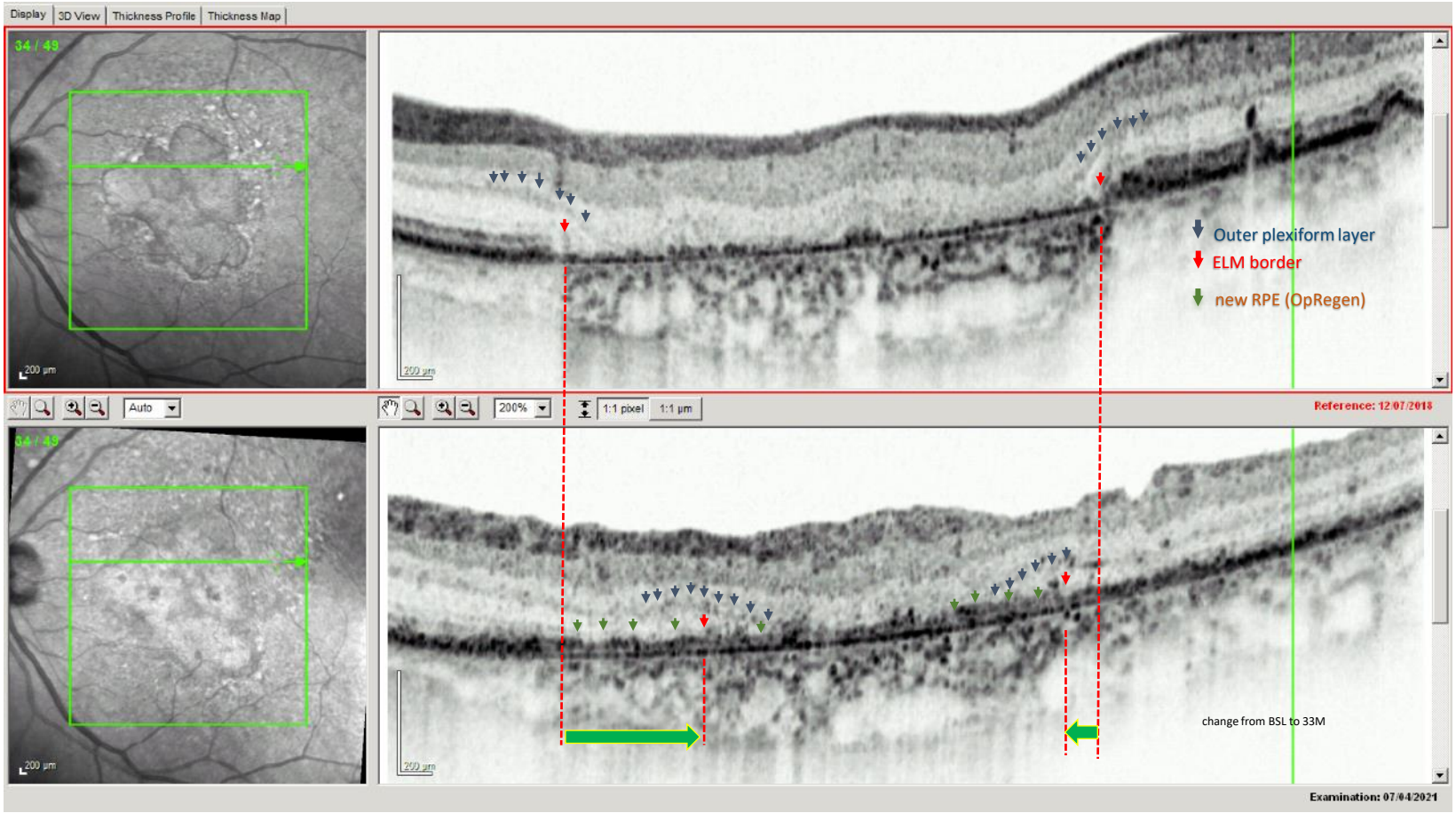


First images of patient #14 with clear signs of outer retinal layer restoration/regeneration at 9M



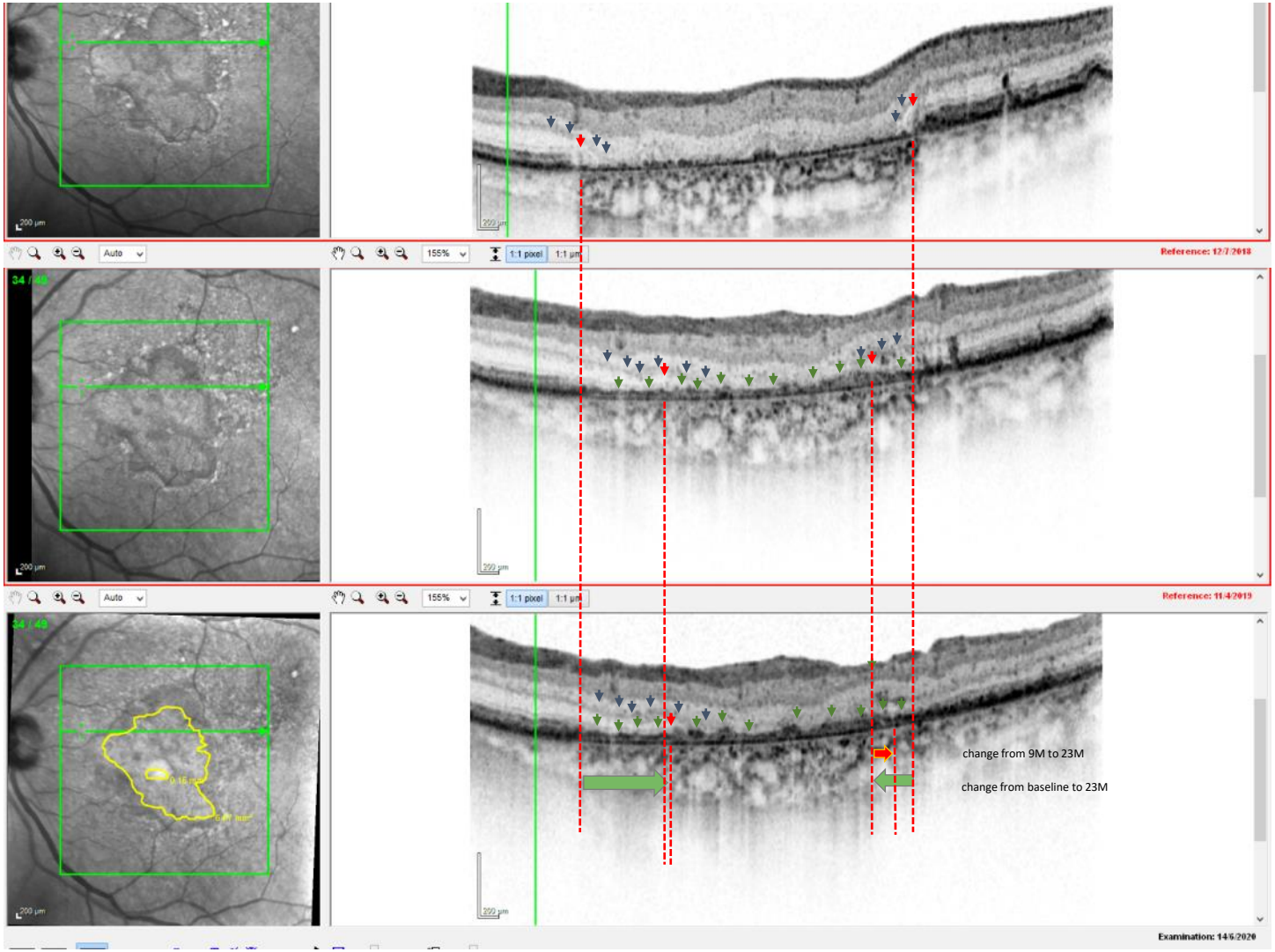
Boundaries of the atrophy based on the ELM border (scan 34/49) BSL to 35M

Central growth of ELM border and/or ONL/OPL and new presumable RPE at 35M comparing to BSL



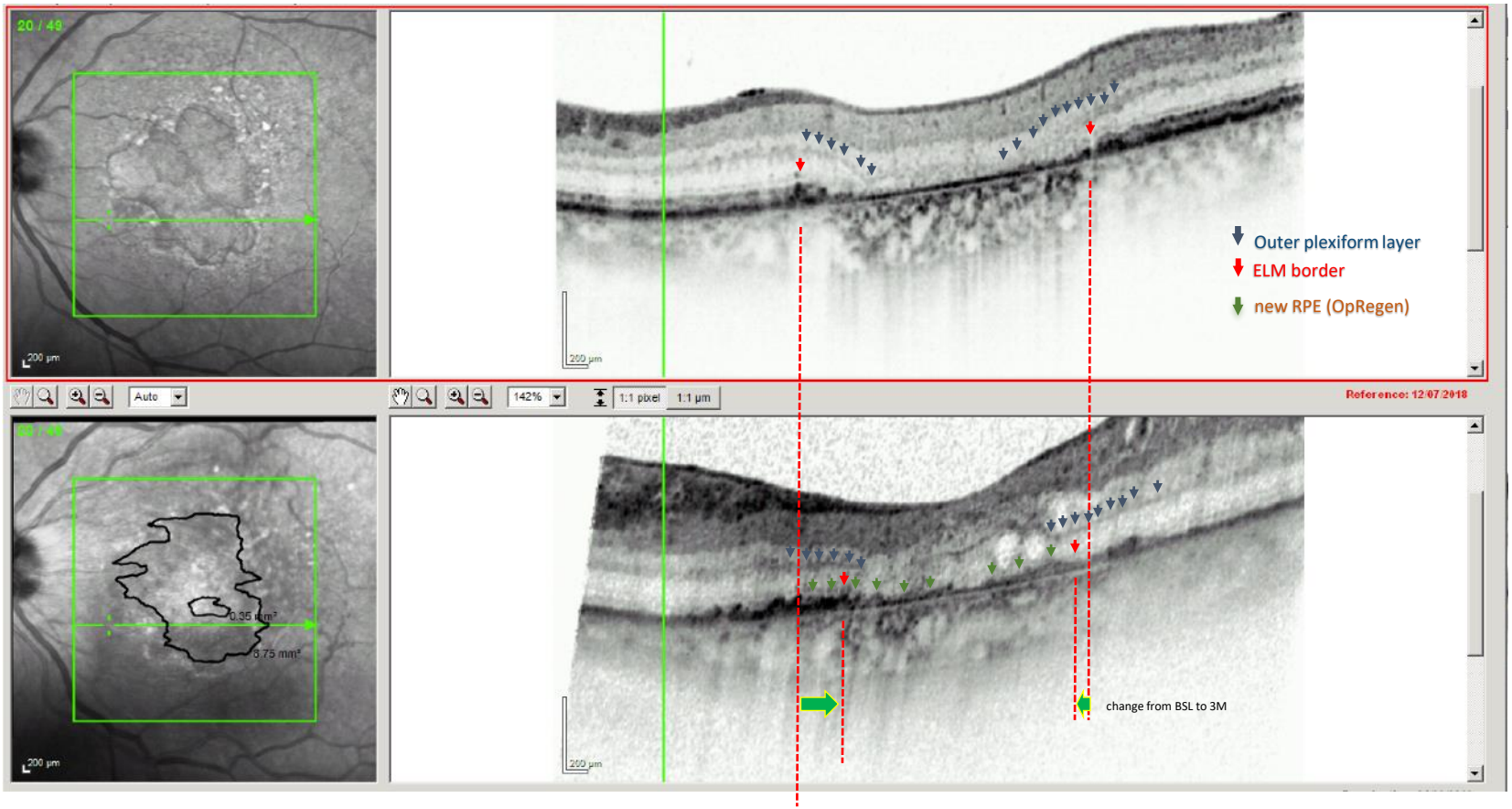
Boundaries of the atrophy based on the ELM border (scan 34/49) BSL to 9M and 23M

Central growth of ELM border and/or ONL/OPL and new presumable RPE at M9 with small regression at M23



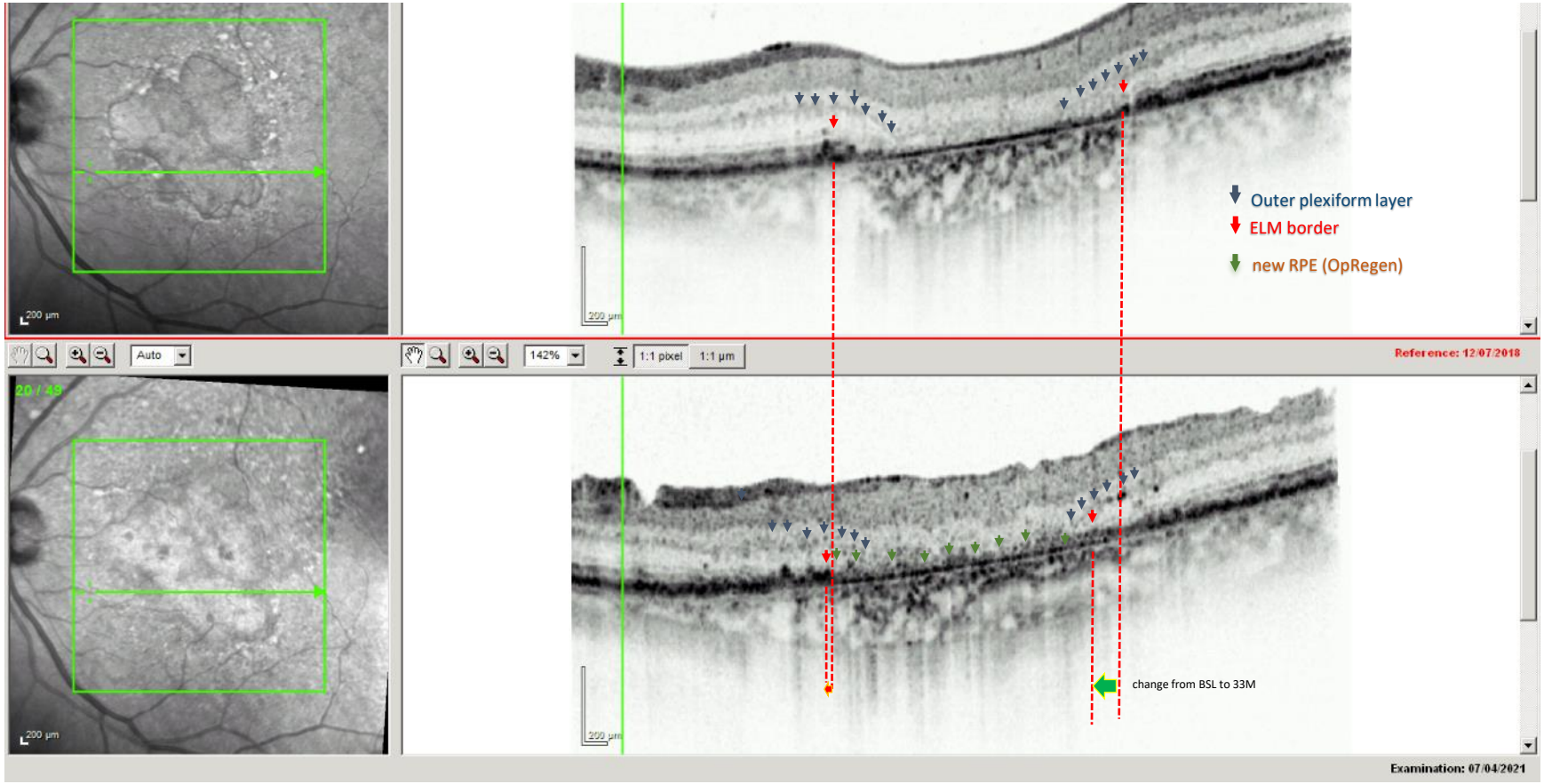
Boundaries of the atrophy based on the ELM border (scan 20/49) BSL to 3M

Central growth of ELM border and/or ONL/OPL and new presumable RPE already at M3 despite the ERM



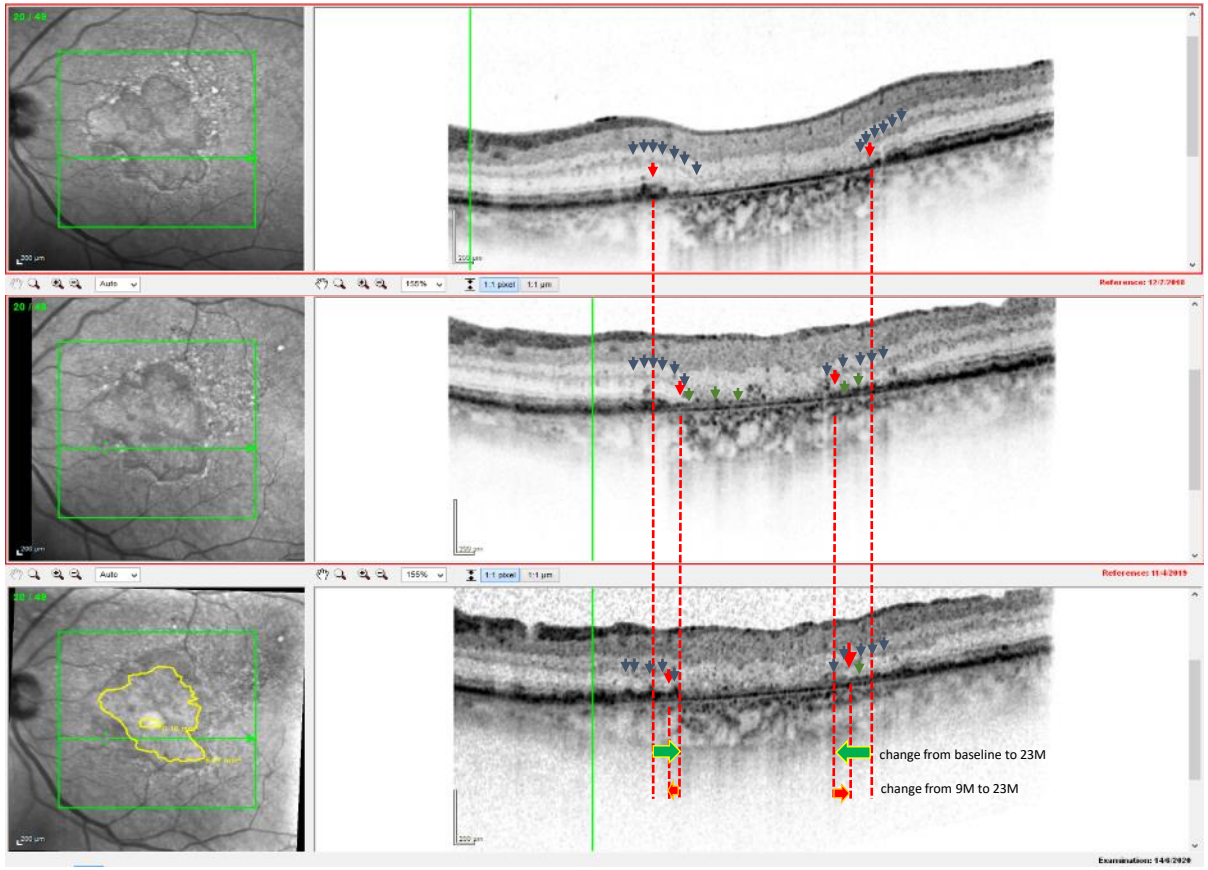
Boundaries of the atrophy based on the ELM border (scan 20/49) BSL to 33M

Signs of outer retinal layer restoration still present at M33 at the temporal border



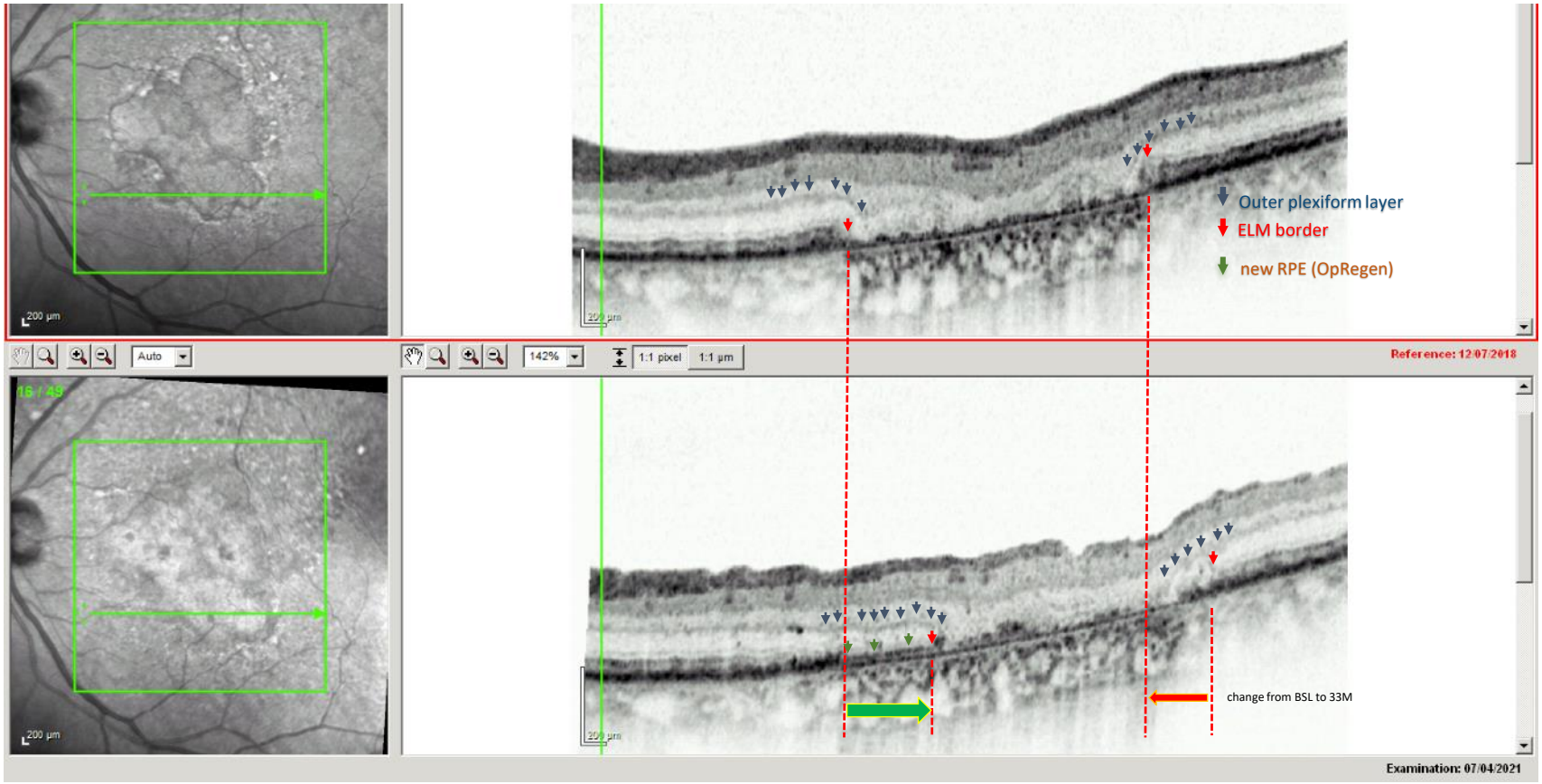
Boundaries of the atrophy based on the ELM border (scan 20/49) BSL to 9 and 23M

Central growth of ELM border and/or ONL/OPL and new presumable RPE at M9 with small regression at M23

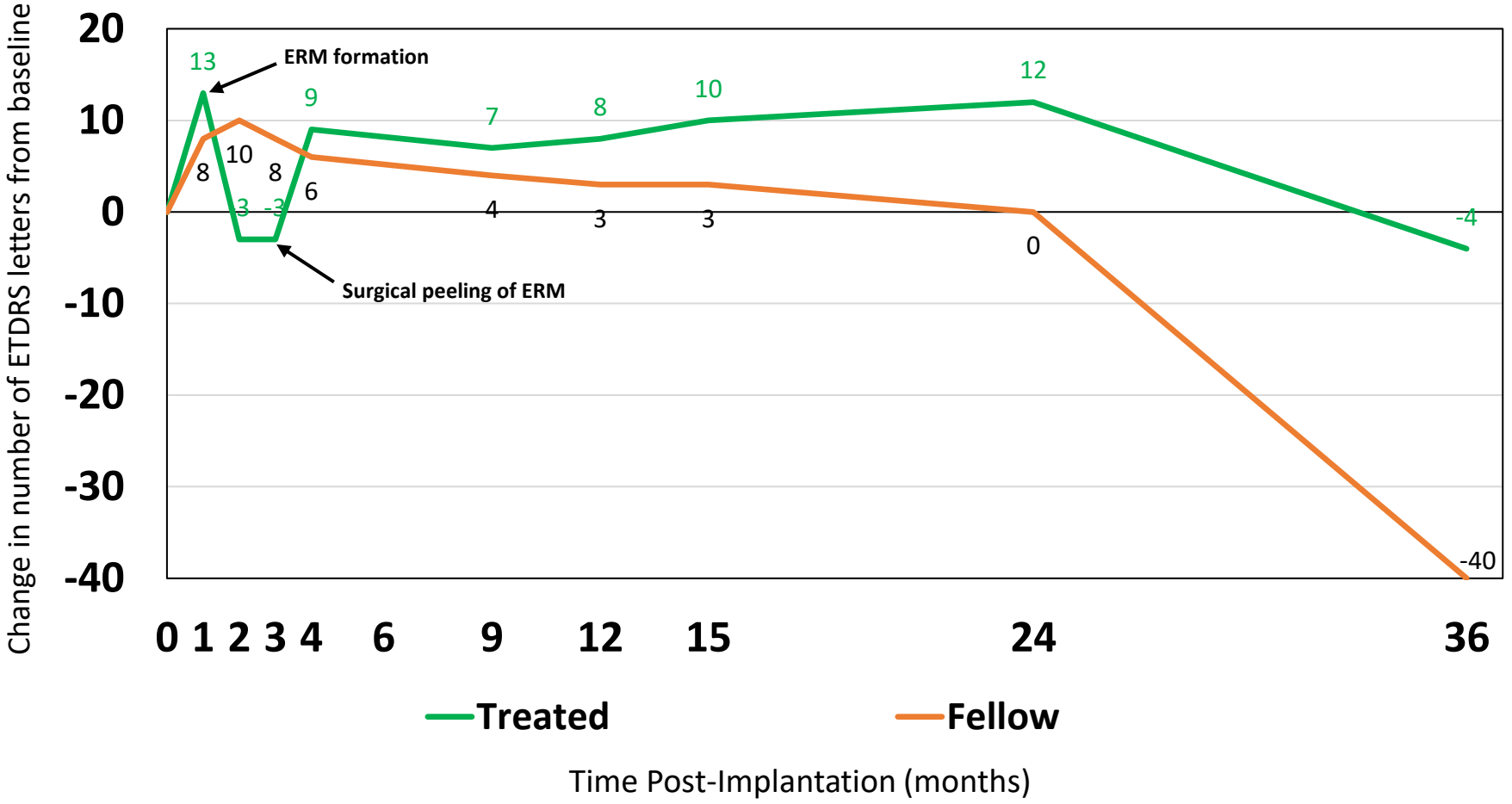


Boundaries of the atrophy based on the ELM border (scan 16/49) BSL to 33M

Central growth of ELM border and/or ONL/OPL and new presumable RPE at the nasal side, with regression at the temporal border, at 33M comparing to BSL

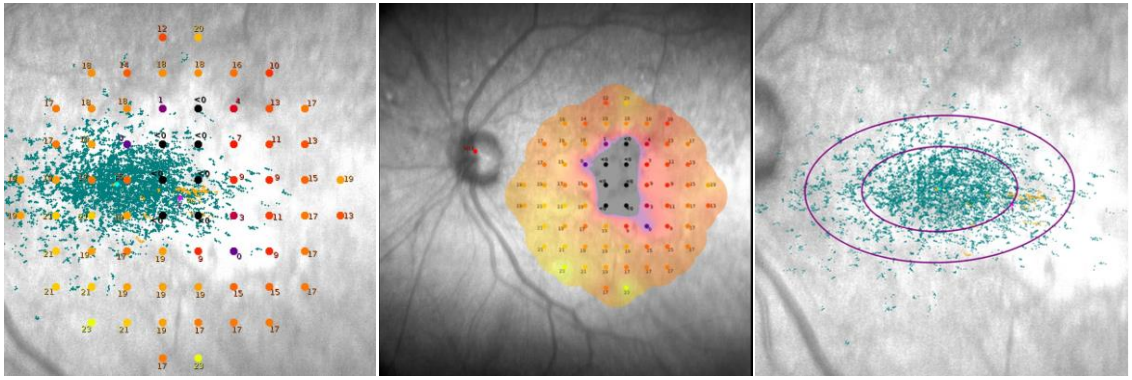


BCVA Changes for Patient #14
1st retinal restoration
Treated vs. Fellow Eye

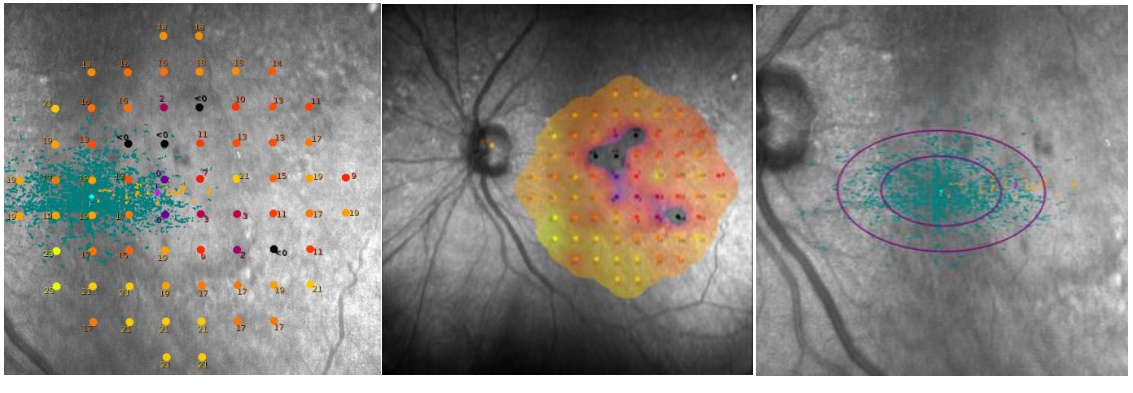


Microperimetry for Patient #14
1st retinal restoration
M23 to M35 changes

2Y post-op



3Y post-op

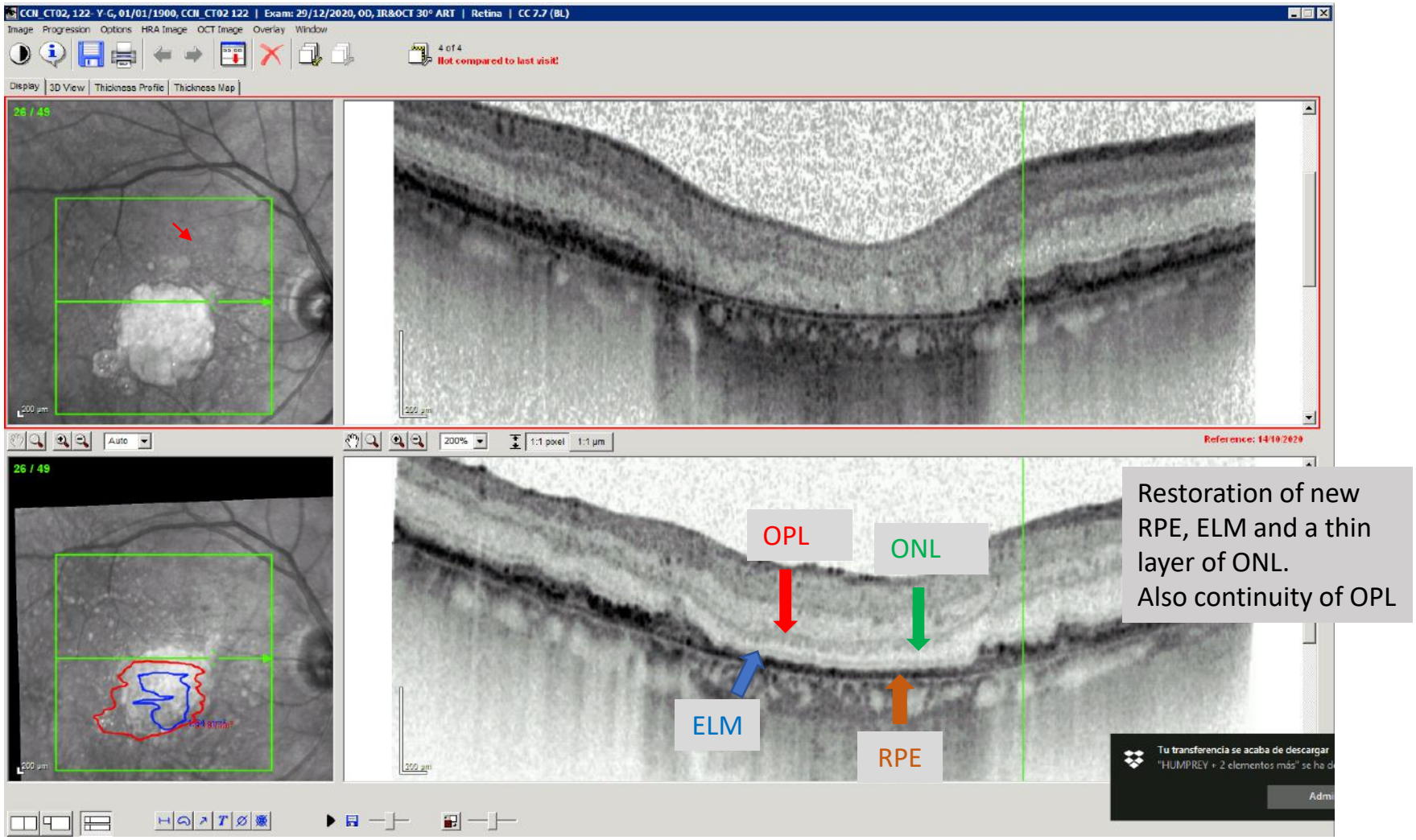


LINEAGE
CELL THERAPEUTICS

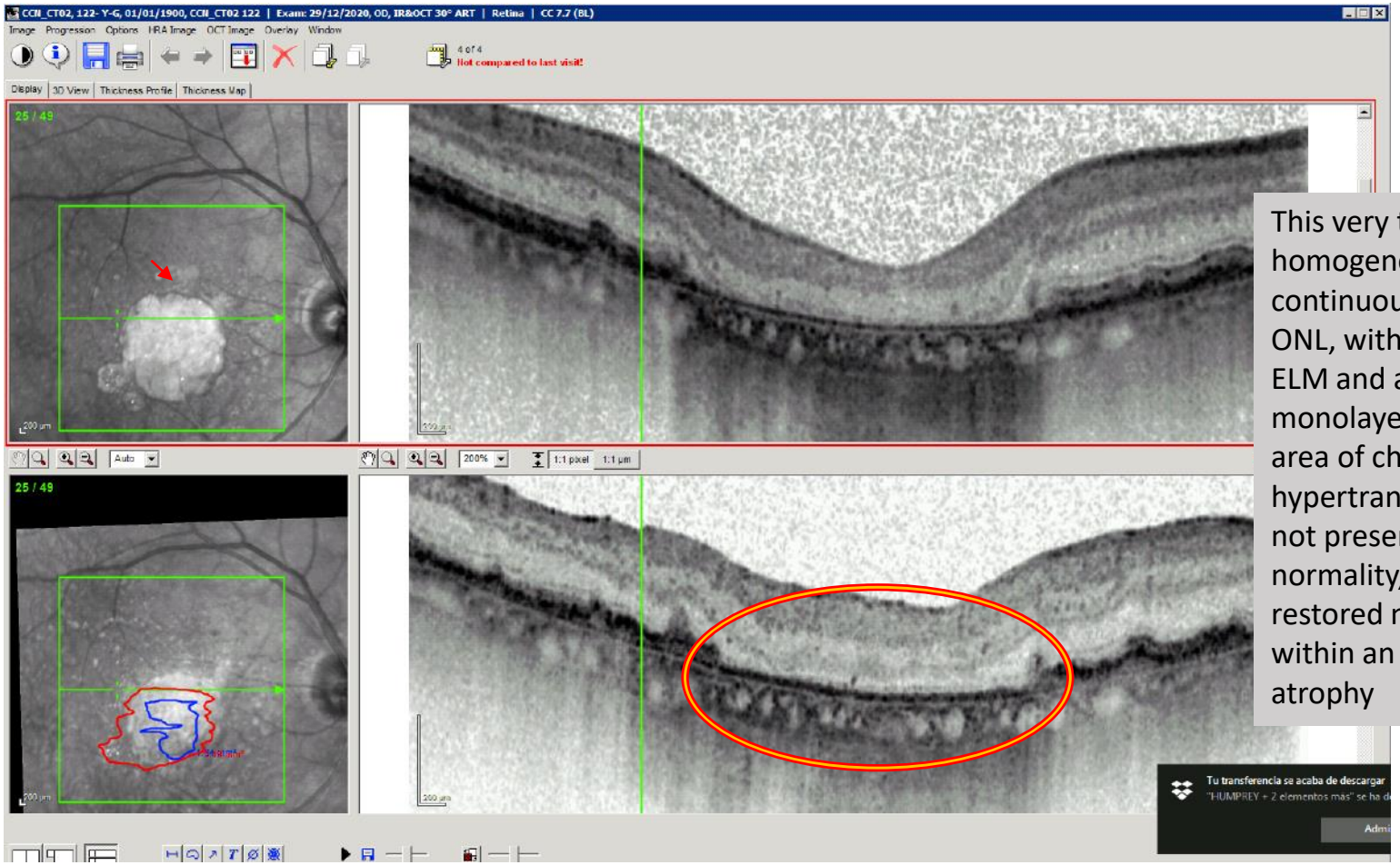
OpRegen Patient #21
2nd Retinal Restoration

New features suggesting outer retinal regeneration

New features suggesting outer retinal regeneration

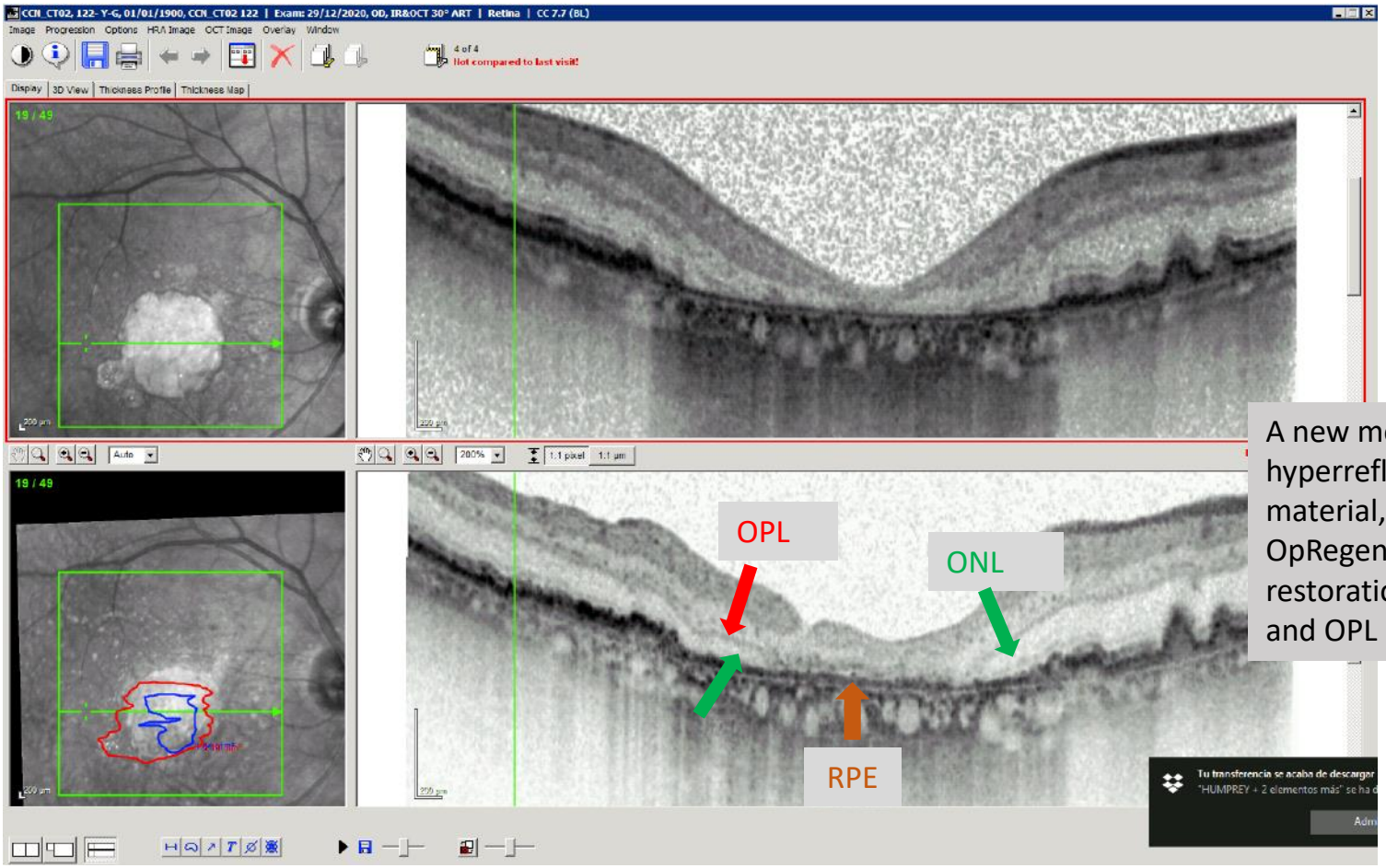


New features suggesting outer retinal regeneration



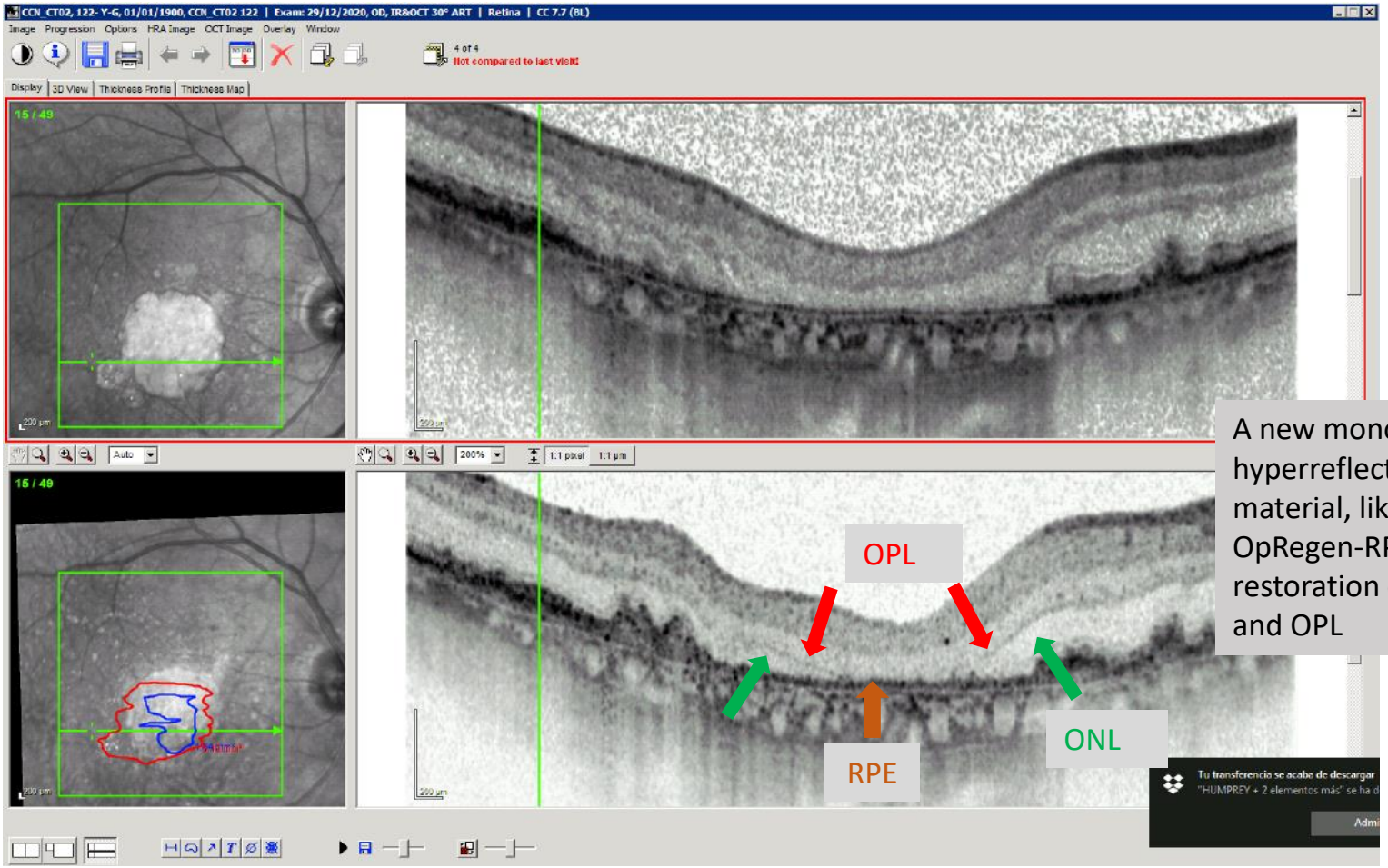
This very thin but homogeneous and continuous layer of ONL, with preserved ELM and a RPE monolayer over an area of choroidal hypertransmission is not present in normality, supporting restored new layers within an area of atrophy

New features suggesting outer retinal regeneration



A new monolayer of hyperreflective material, likely OpRegen-RPE with restoration of ONL and OPL

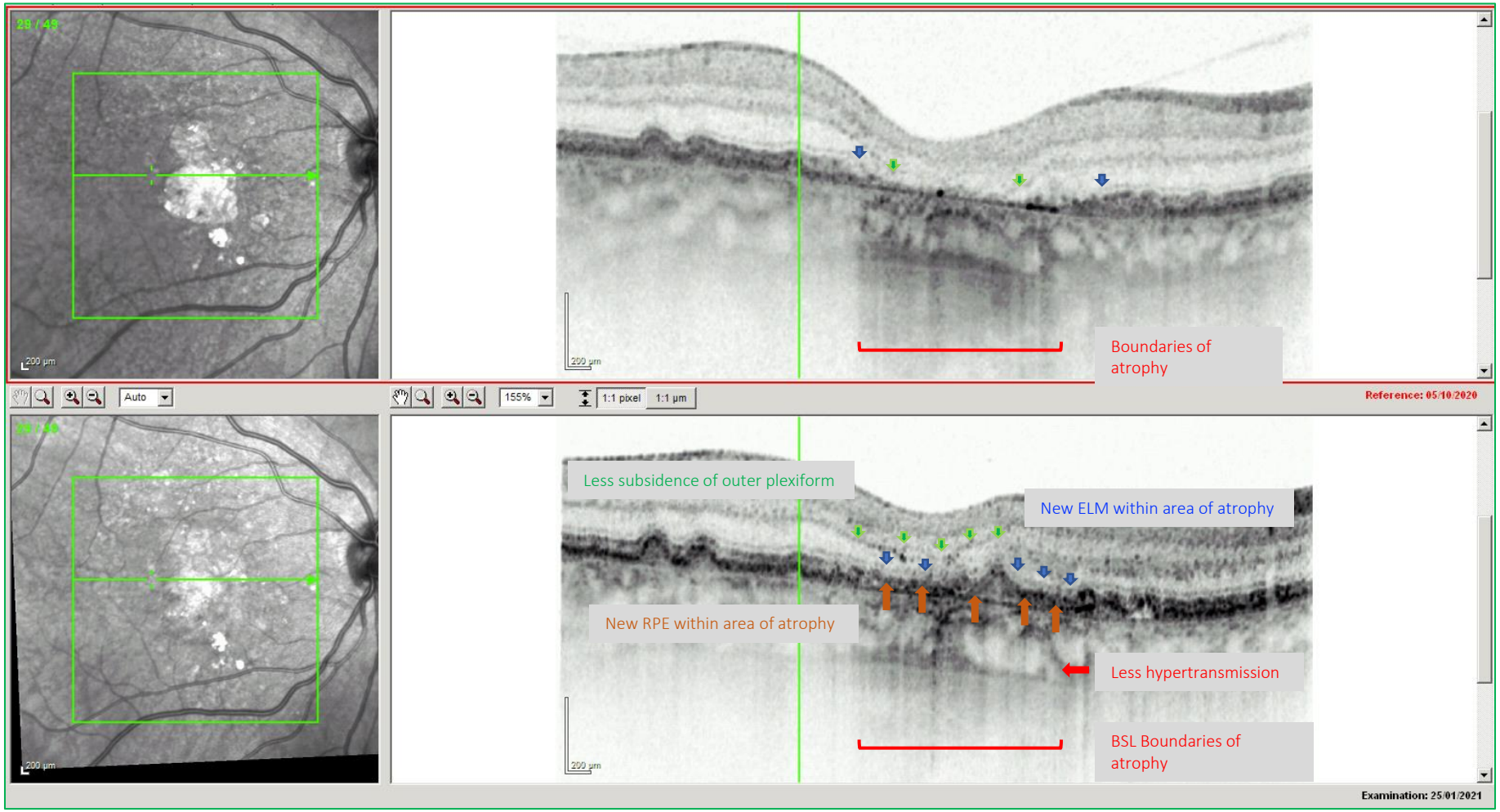
New features suggesting outer retinal regeneration



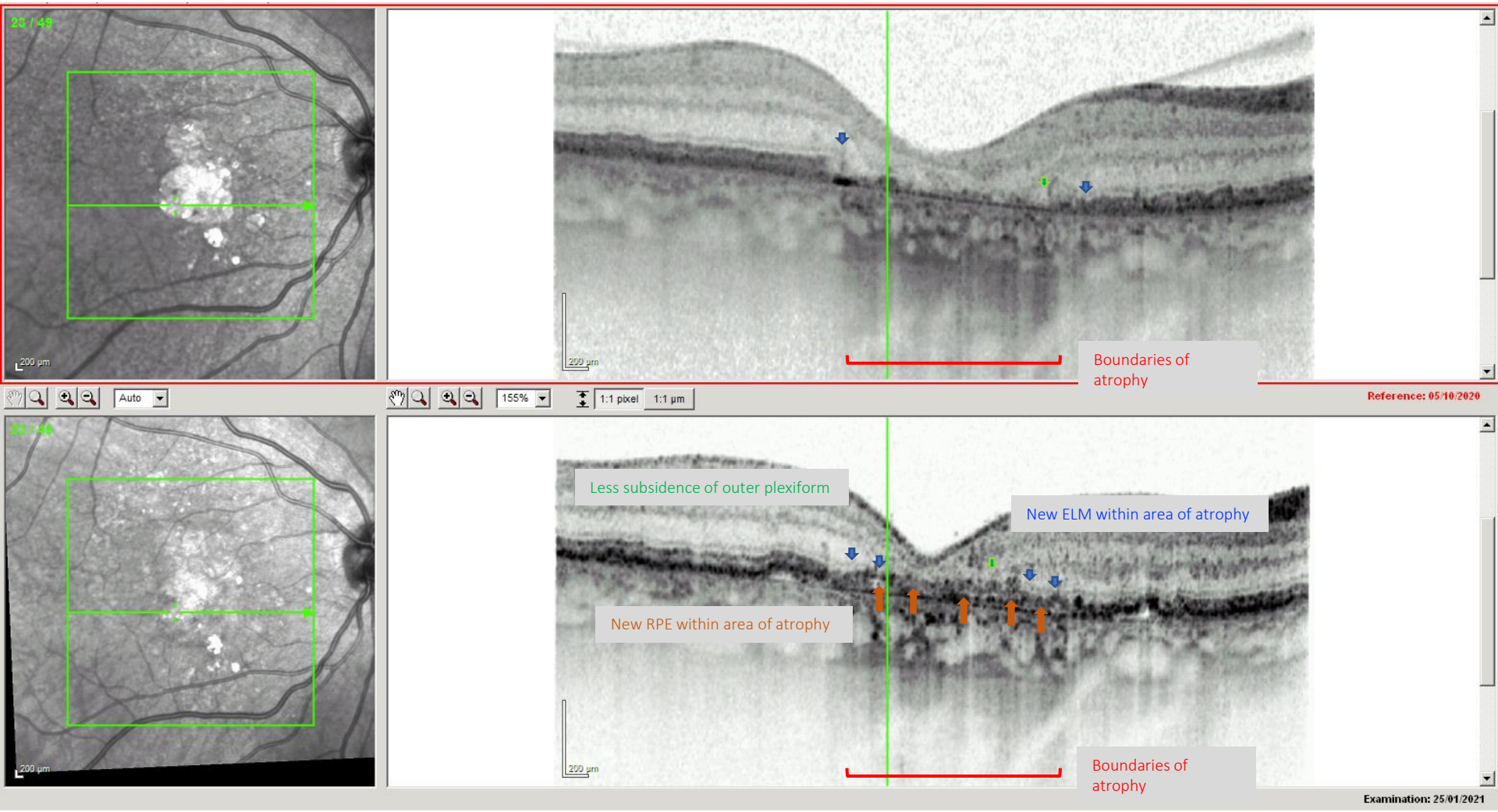
LINEAGE
CELL THERAPEUTICS

OpRegen Patient #22
3rd Retinal Restoration

Patient #22 (BSL to 3M)
3rd Retinal Restoration



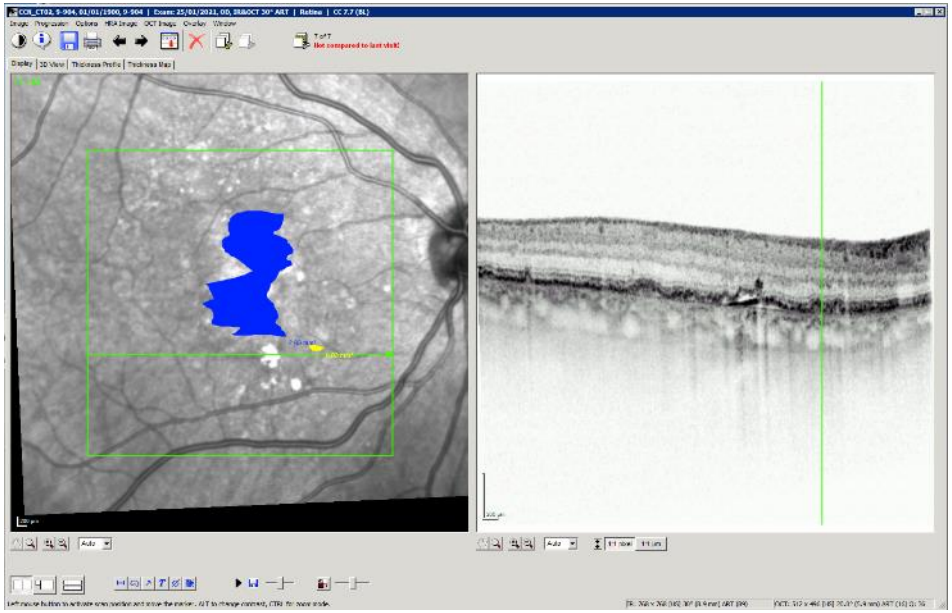
Patient #22 (BSL to 3M)
3rd Retinal Restoration



Follow-up ELM-based GA area #22 (BSL to 3M)
3rd Retinal Restoration

OCT 5, 2020

JAN 21, 2021



TOTAL AREA: 3.56 mm^2

TOTAL AREA: 2.69 mm^2

Total area	3M GROWTH RATE: – 0.87 mm^2	(ANNUAL RATE – 3.48 mm^2)
SQRT transformation	3M GROWTH RATE: – 0.23 mm	(ANNUAL RATE – 0.92 mm)

LINEAGE
CELL THERAPEUTICS

AMD is the leading cause of irreversible vision loss in the US

Source: aao.org

Brandon Lujan, M.D.
Assistant Professor, Casey Eye Institute of OHSU
Medical Director, Casey Reading Center

OpRegen Patient #21 (OD)

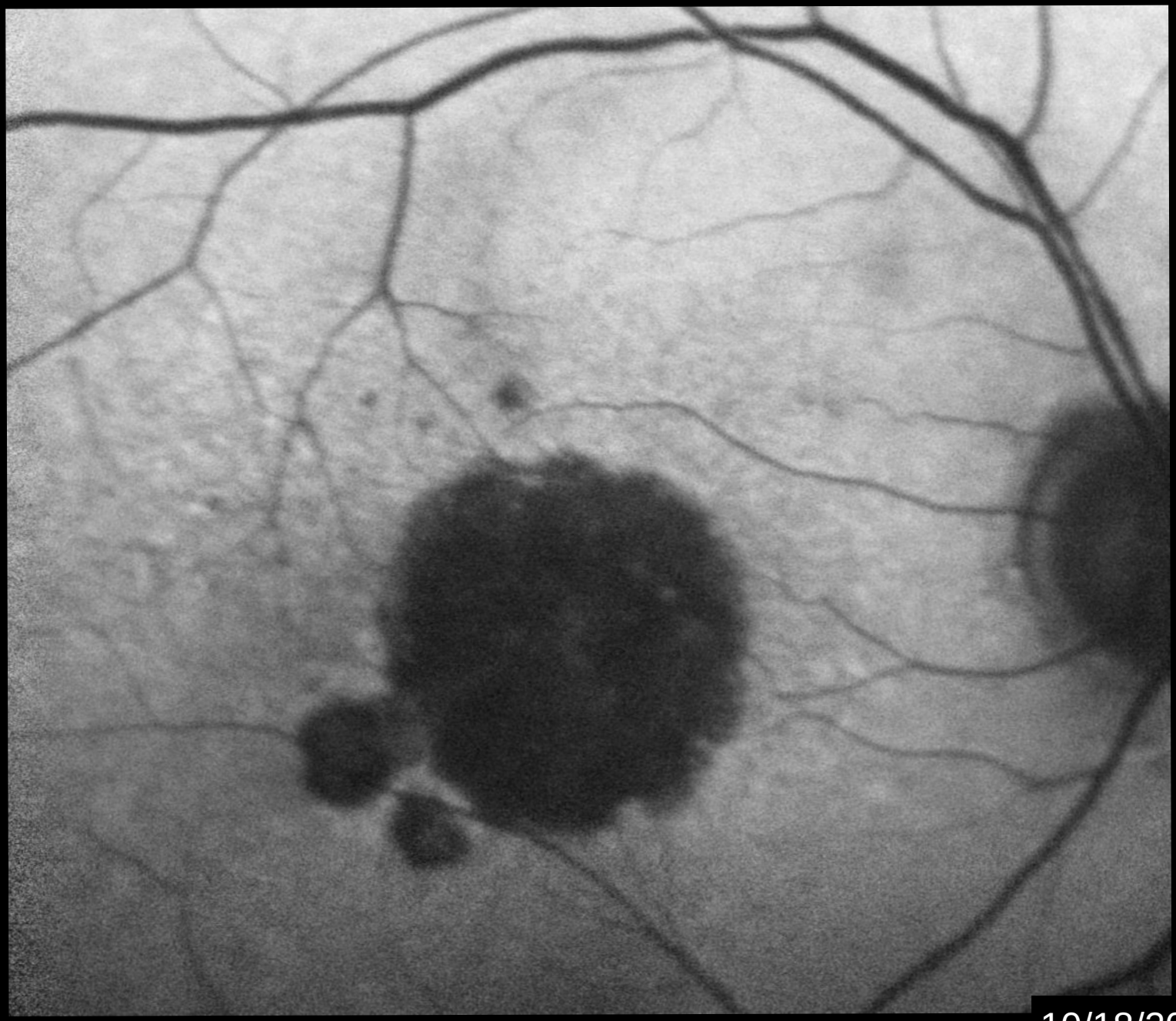
Through 01/25/2021

Lujan Imaging LLC


Lujan Imaging LLC
10/14/2020


Lujan Imaging LLC
11/08/2020

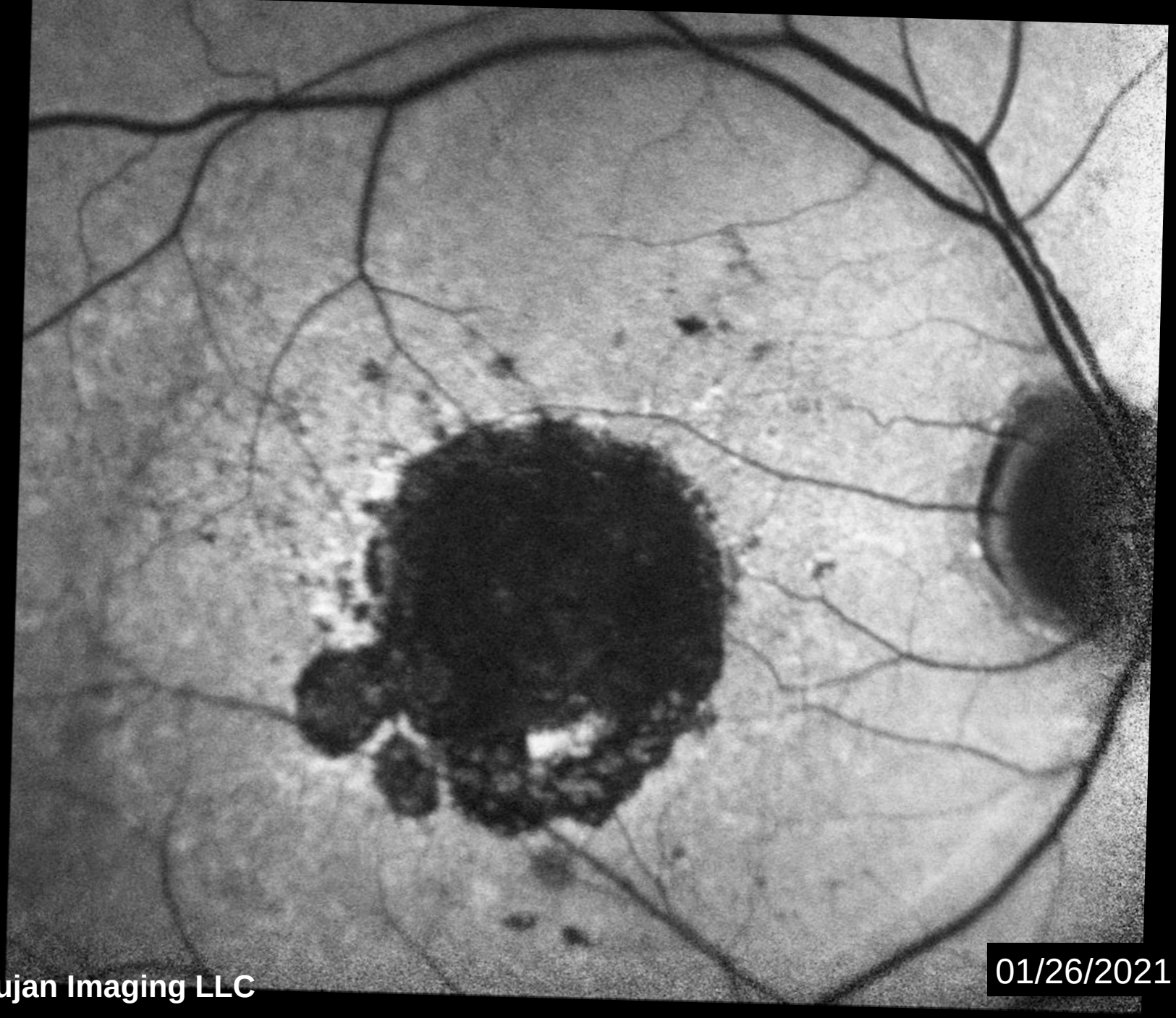

Vessel Distortion compared to baseline/prior timepoints
Lujan Imaging LLC
01/26/2021

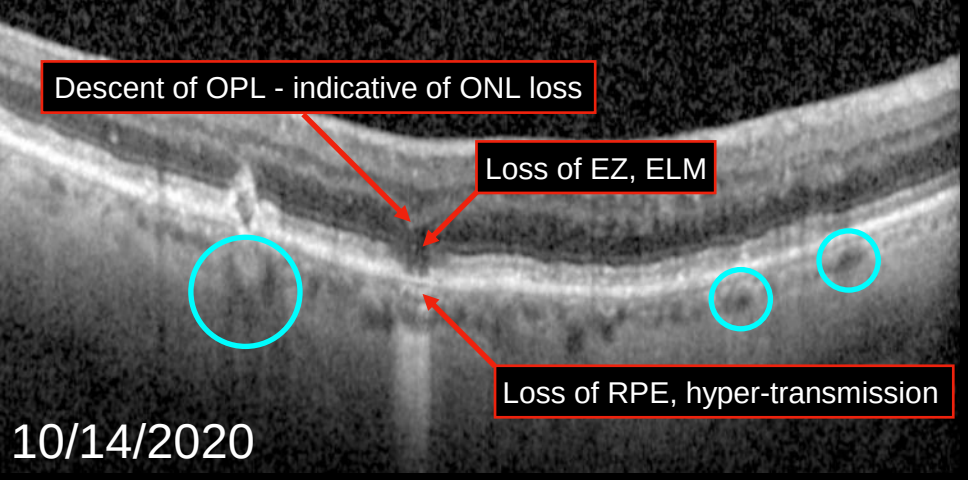


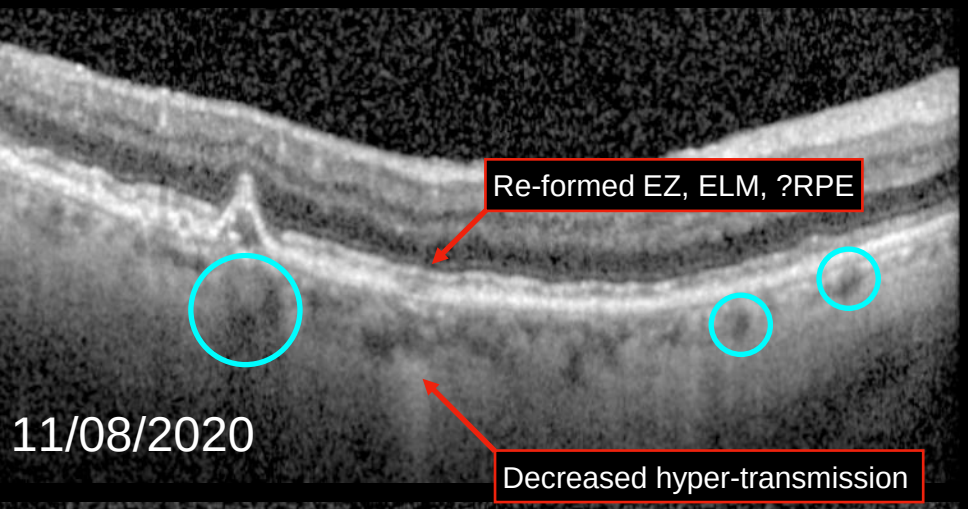
Lujan Imaging LLC

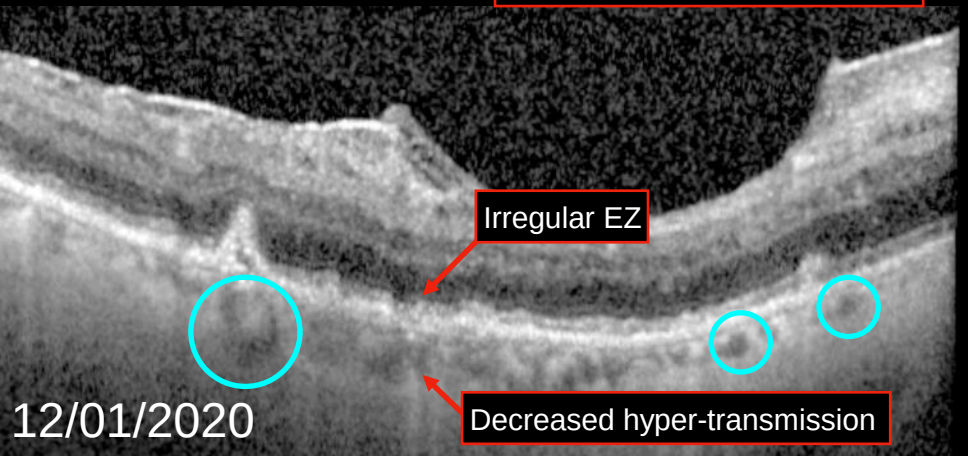
10/18/2020

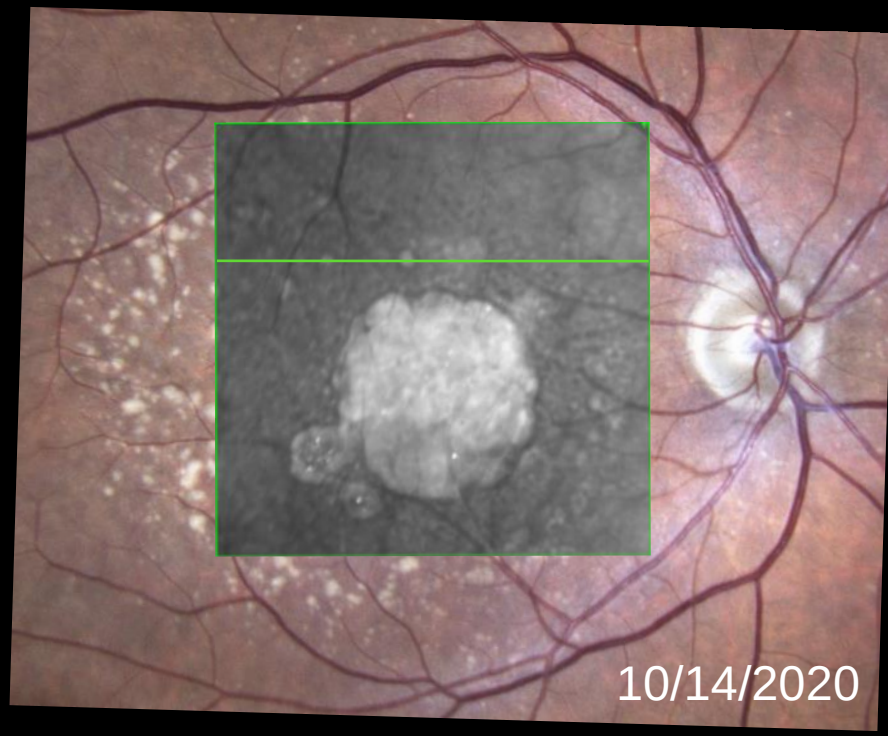

Lujan Imaging LLC
11/17/2020


Lujan Imaging LLC
01/26/2021

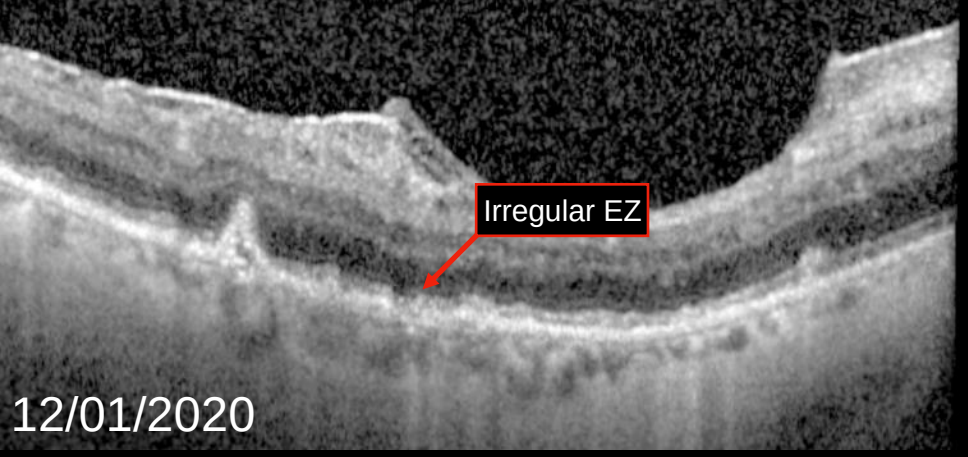


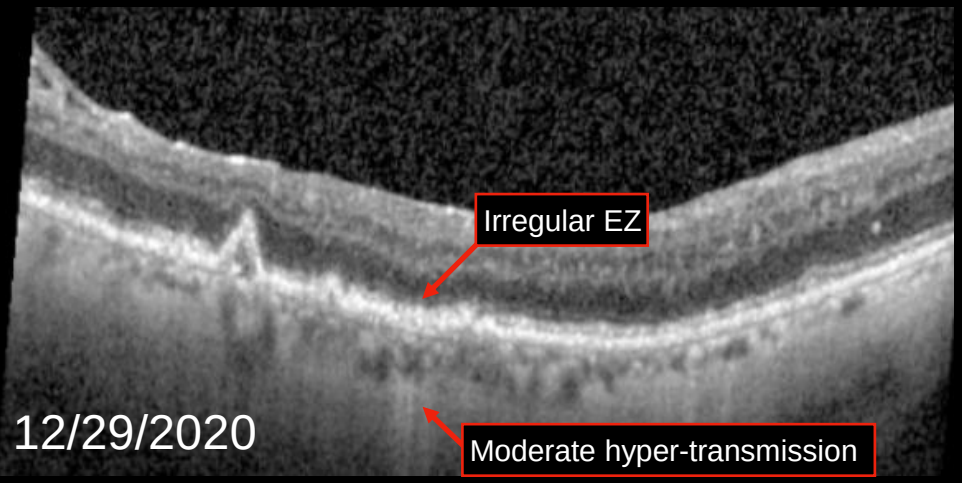


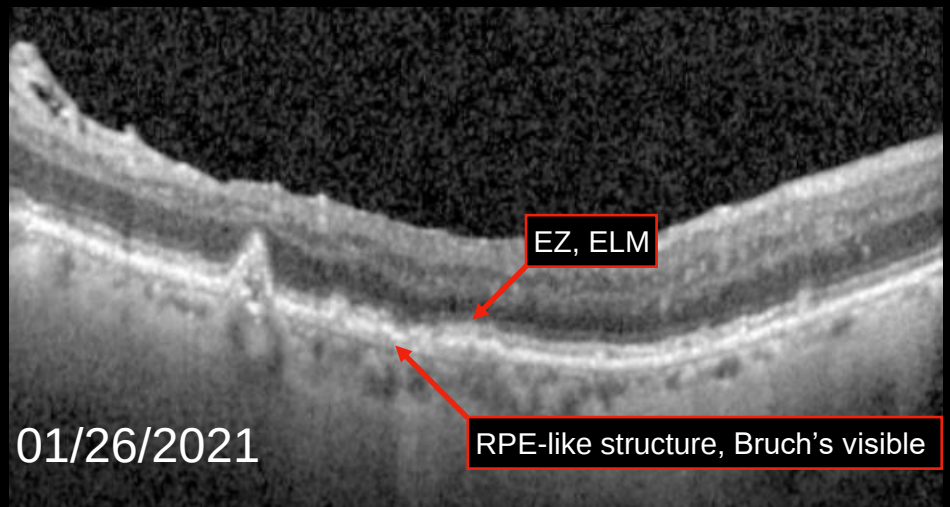




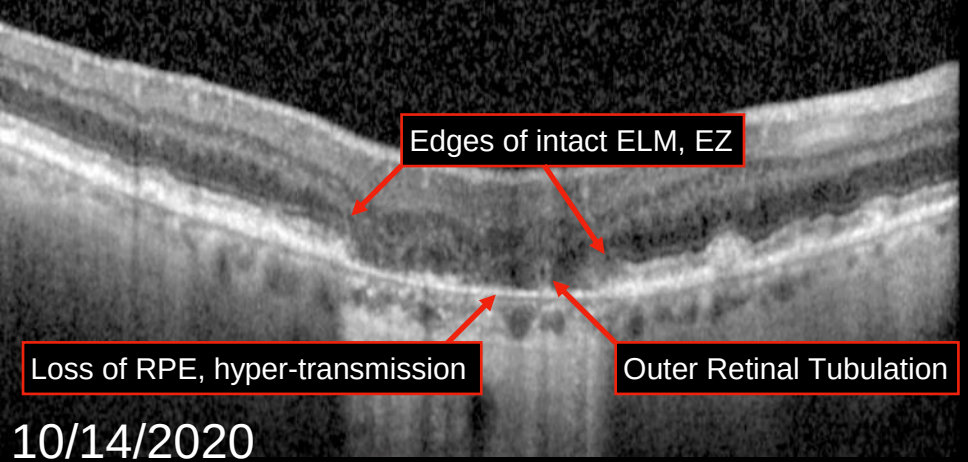
Lujan Imaging LLC

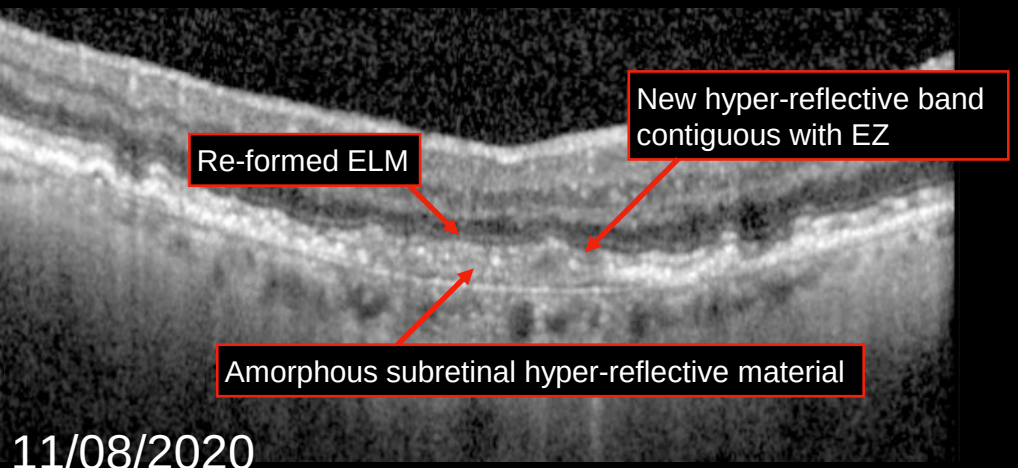


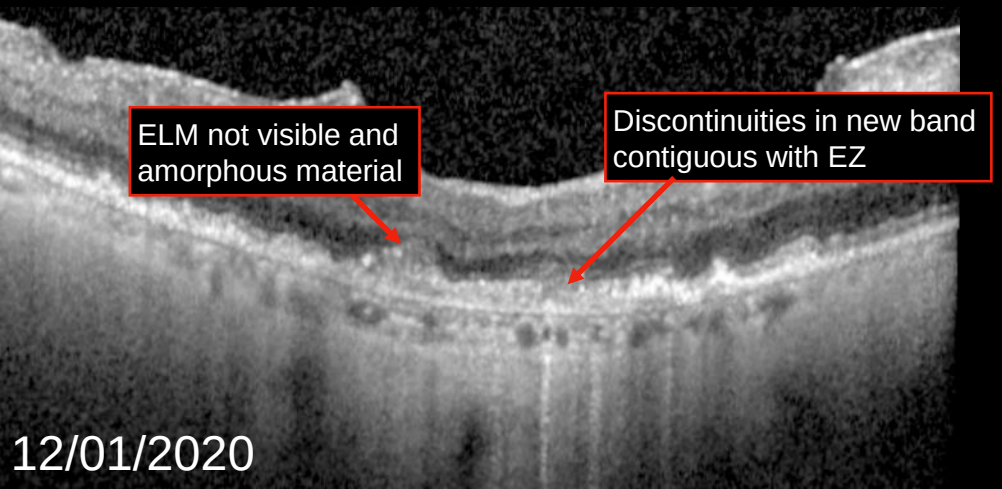


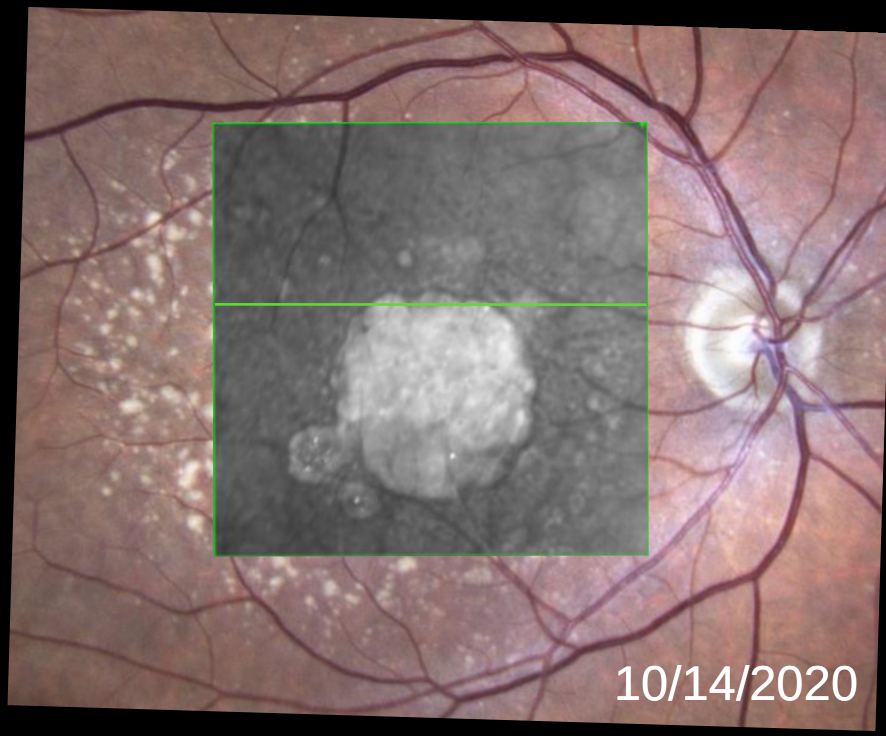


Lujan Imaging LLC

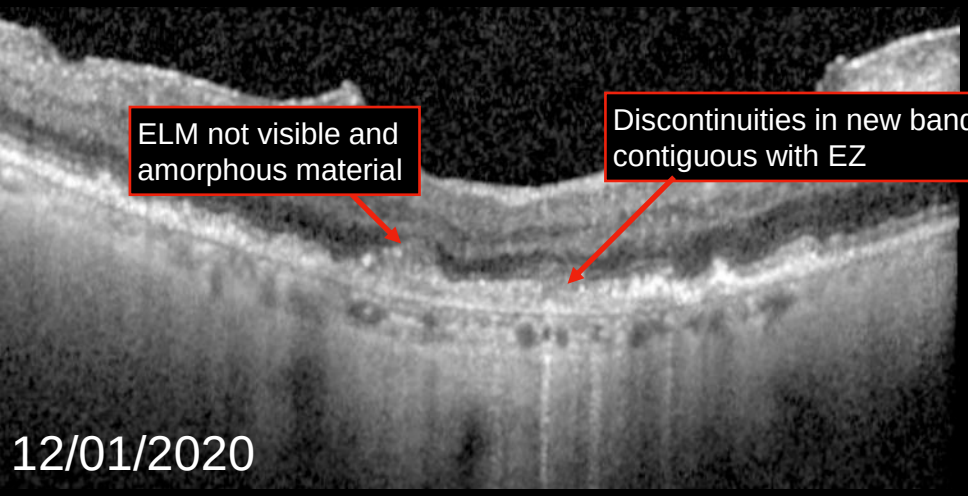


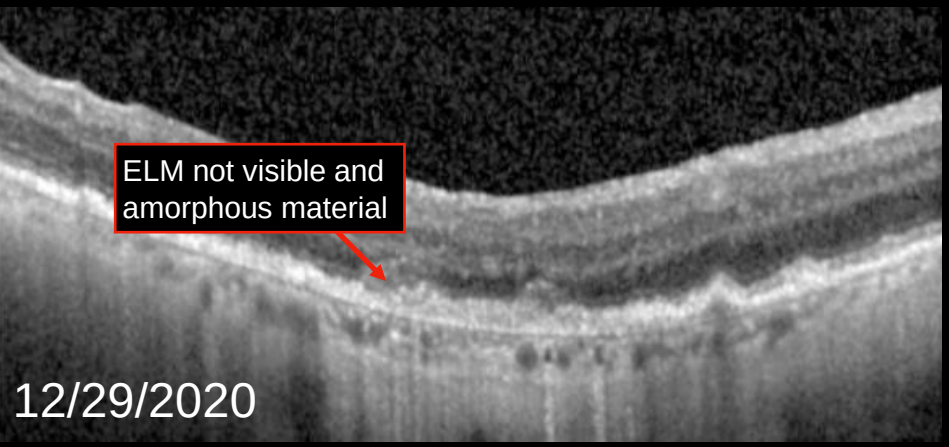


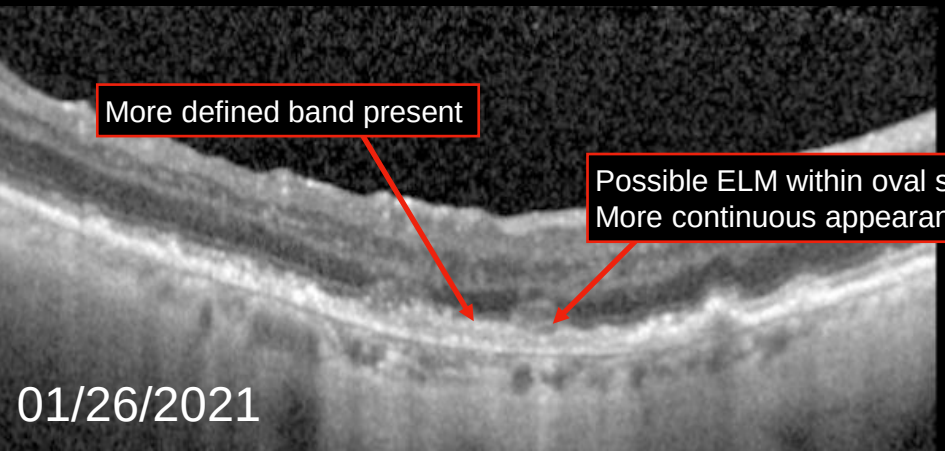




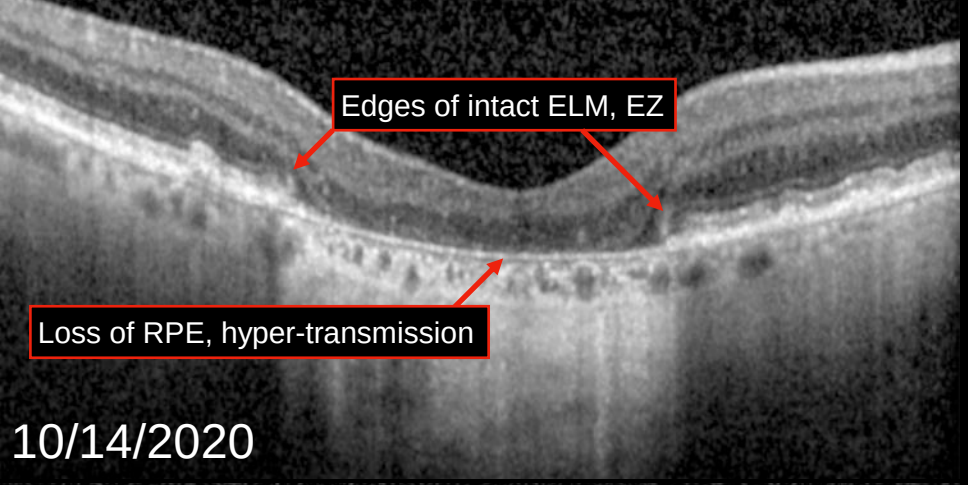
Lujan Imaging LLC

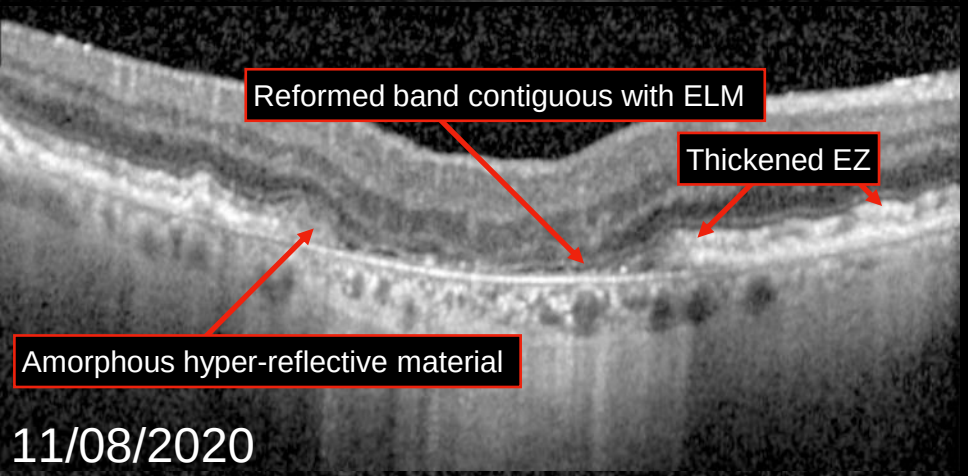


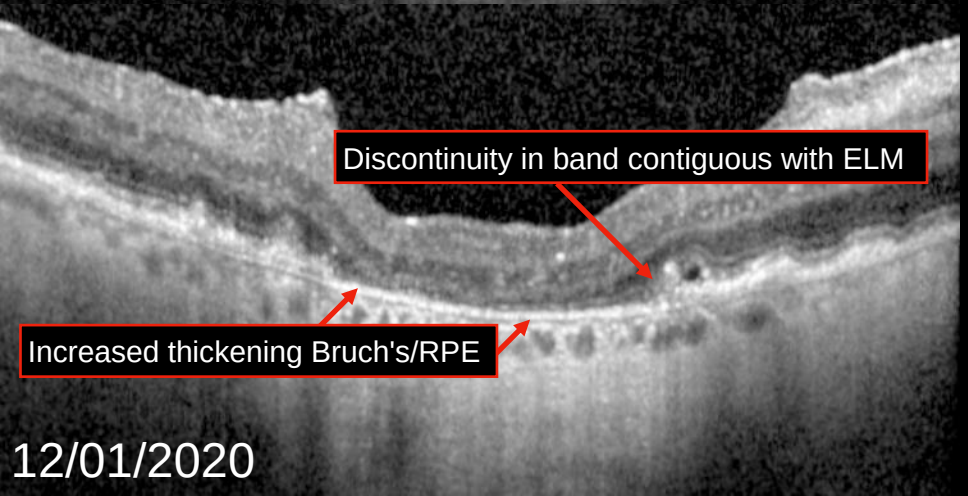


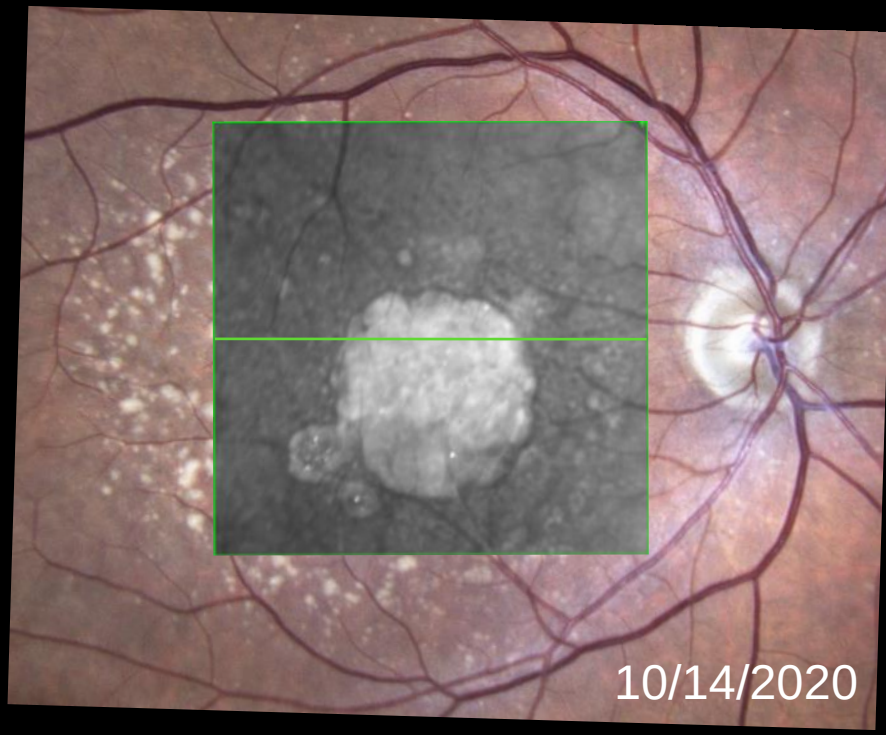


Lujan Imaging LLC

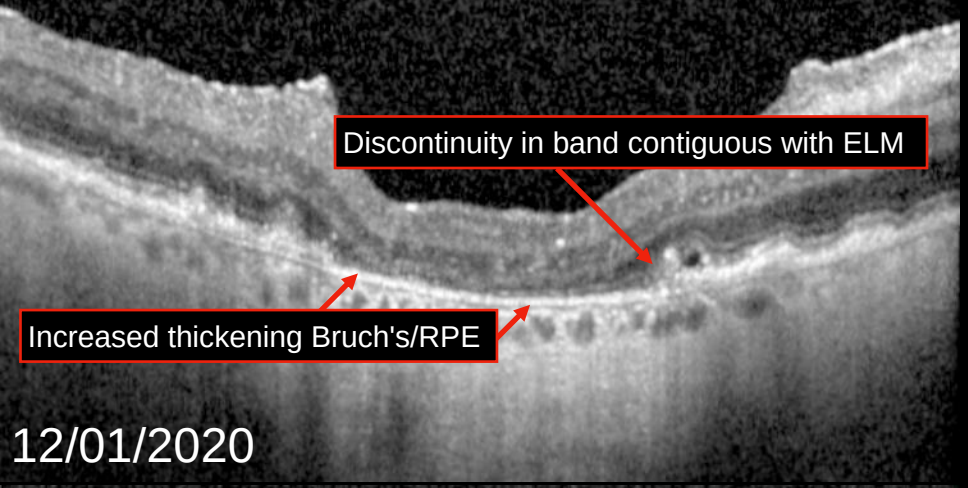


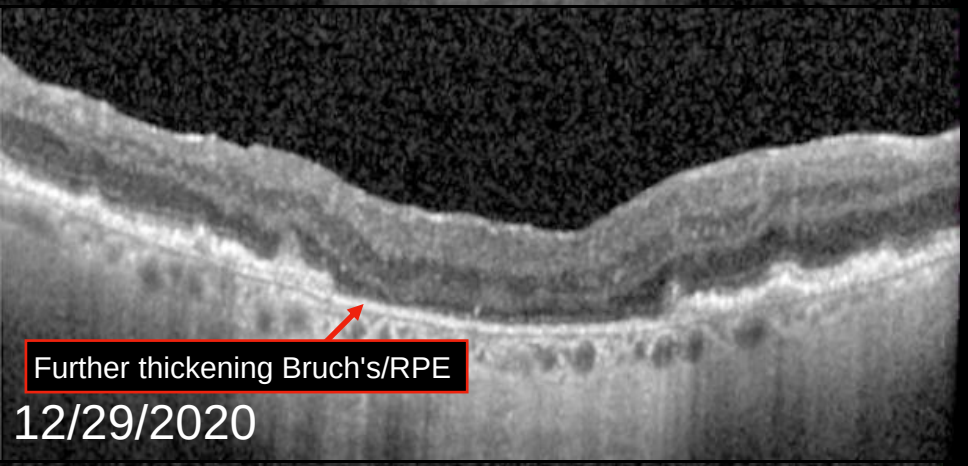


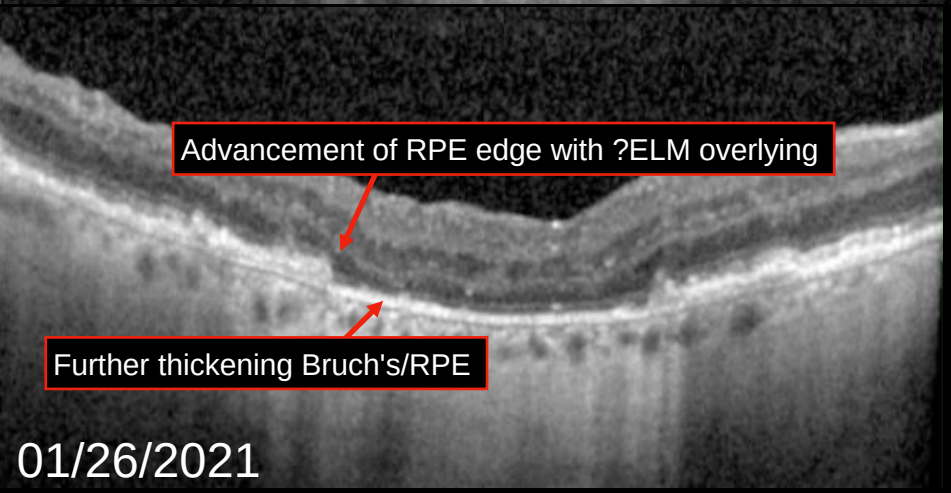


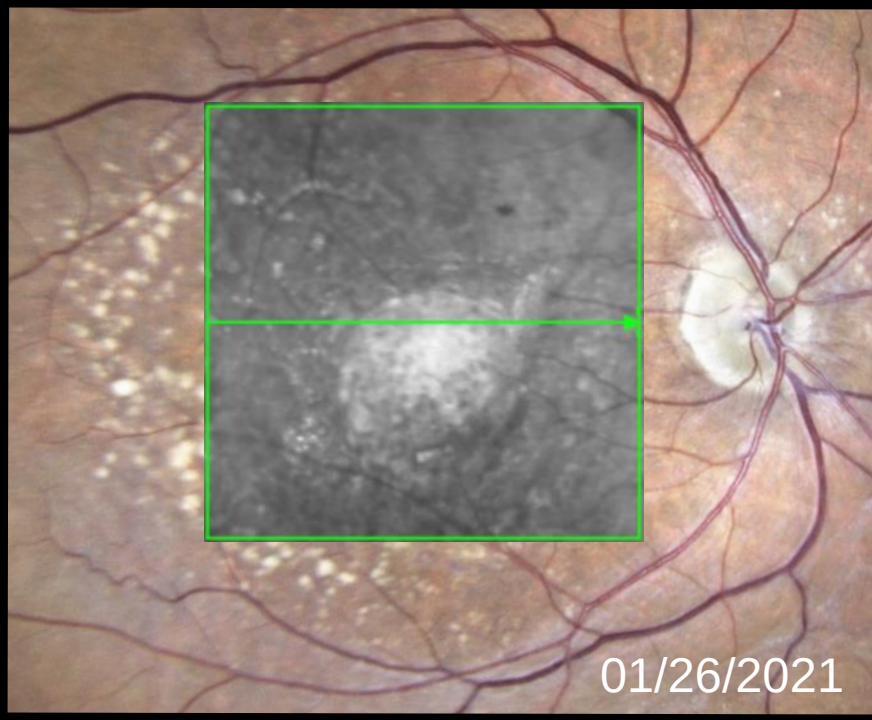


Lujan Imaging LLC

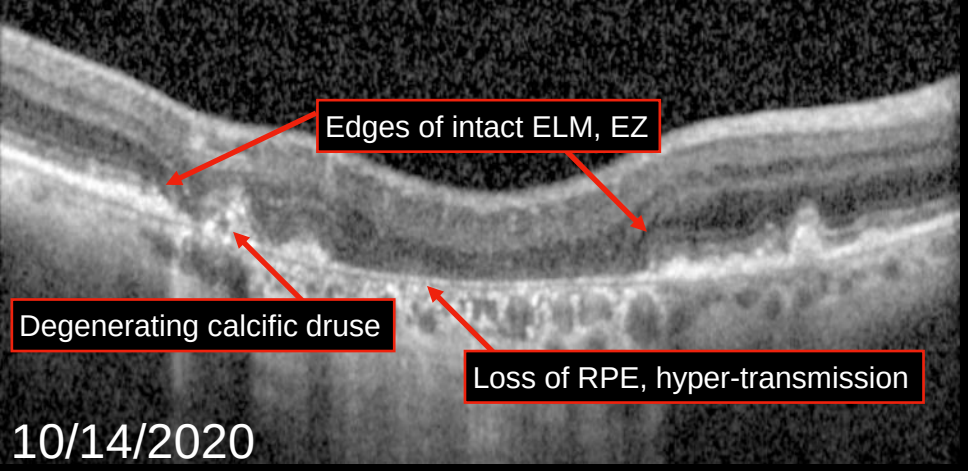


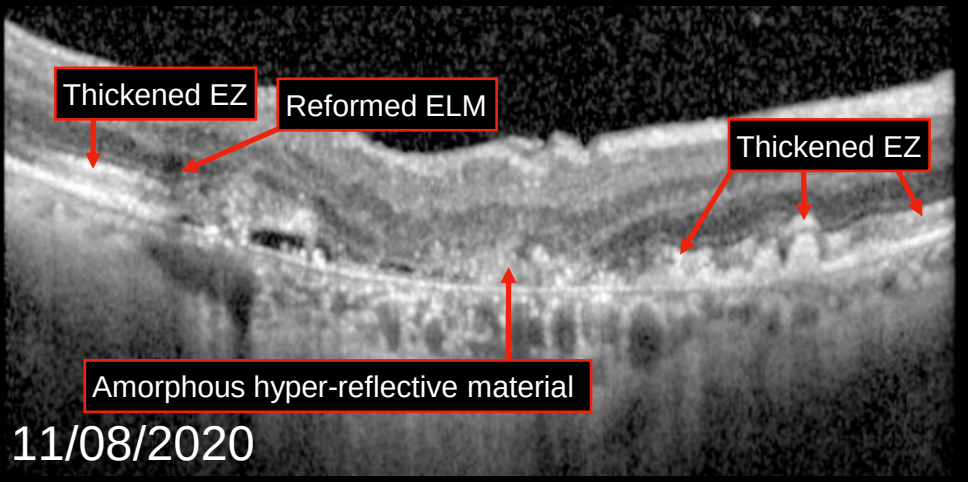


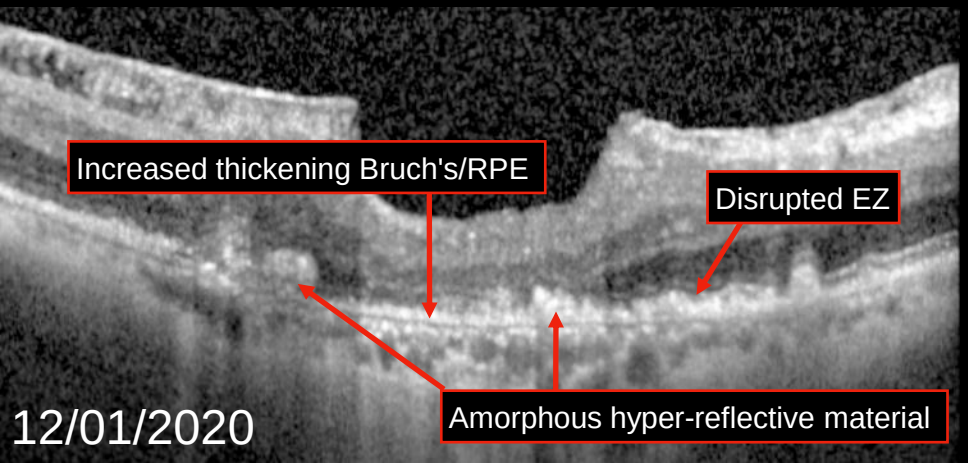


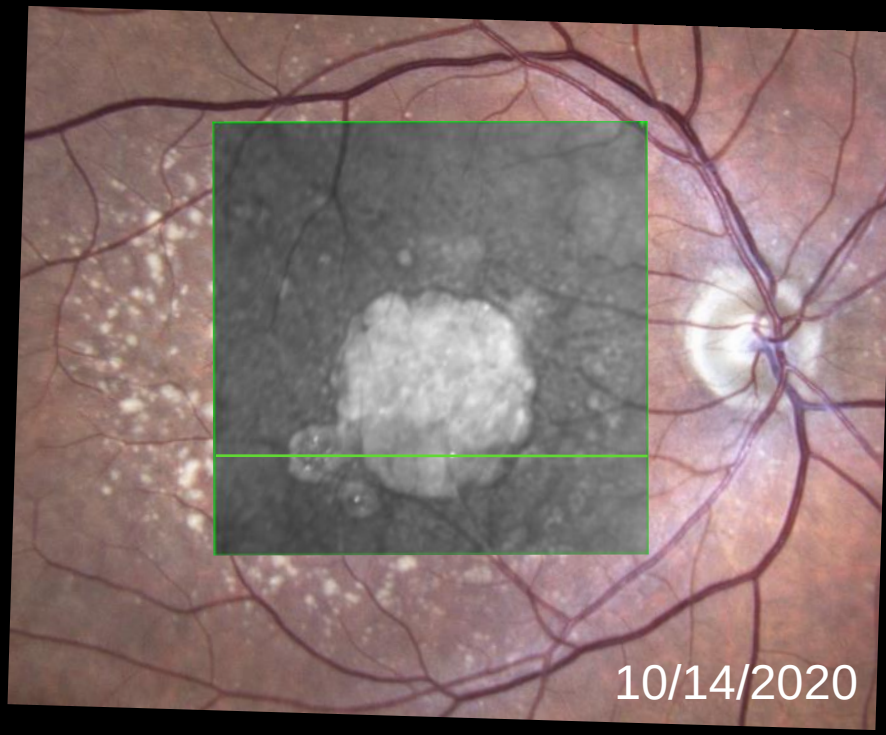


Lujan Imaging LLC

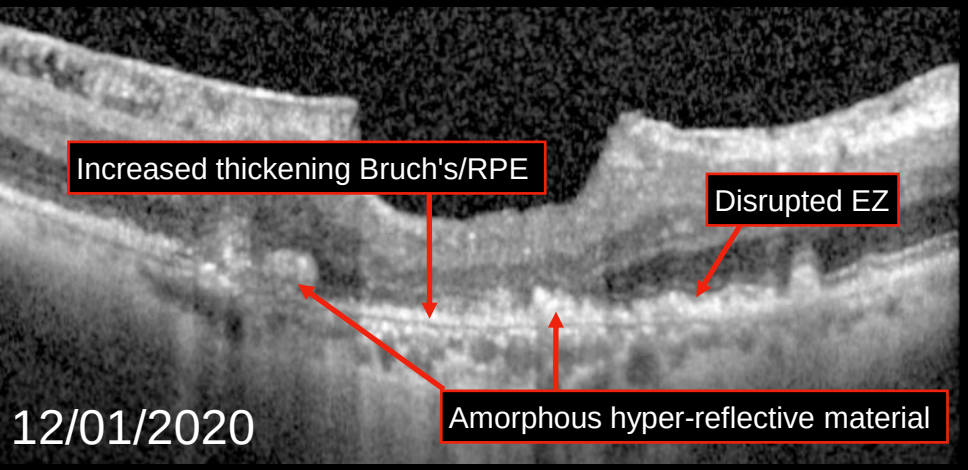


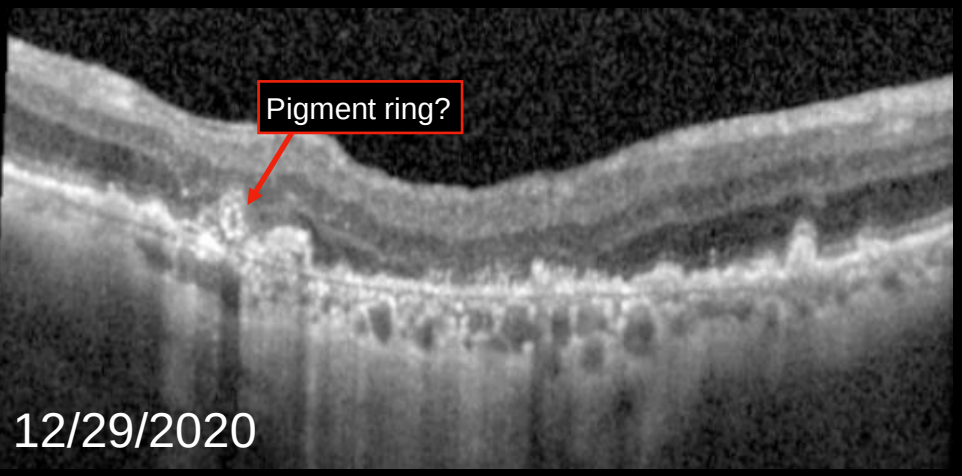


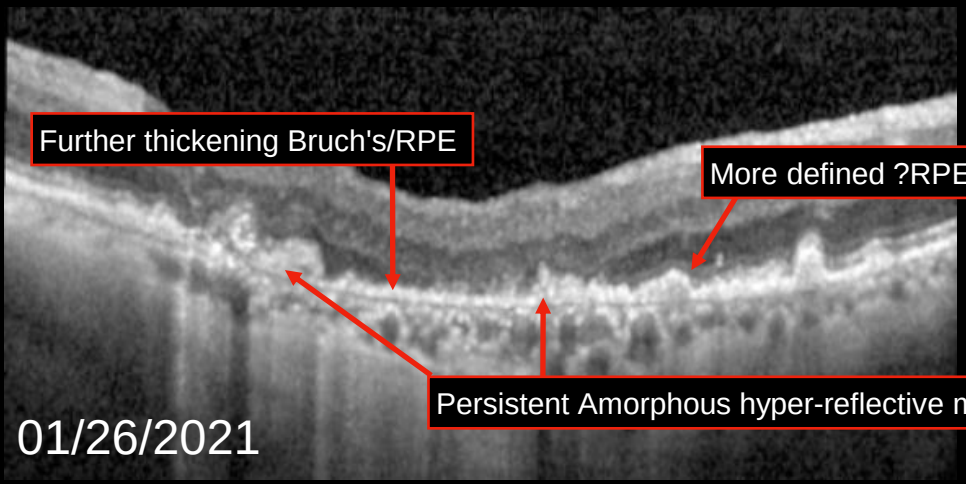




Lujan Imaging LLC

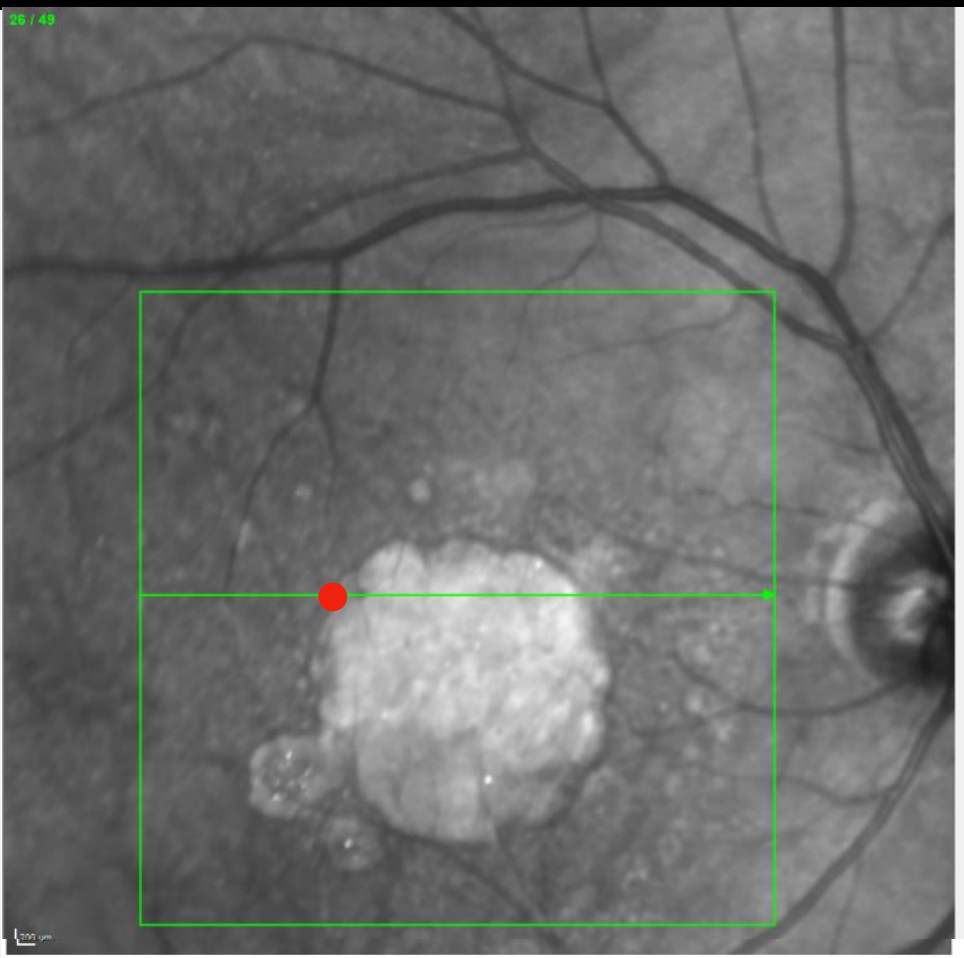


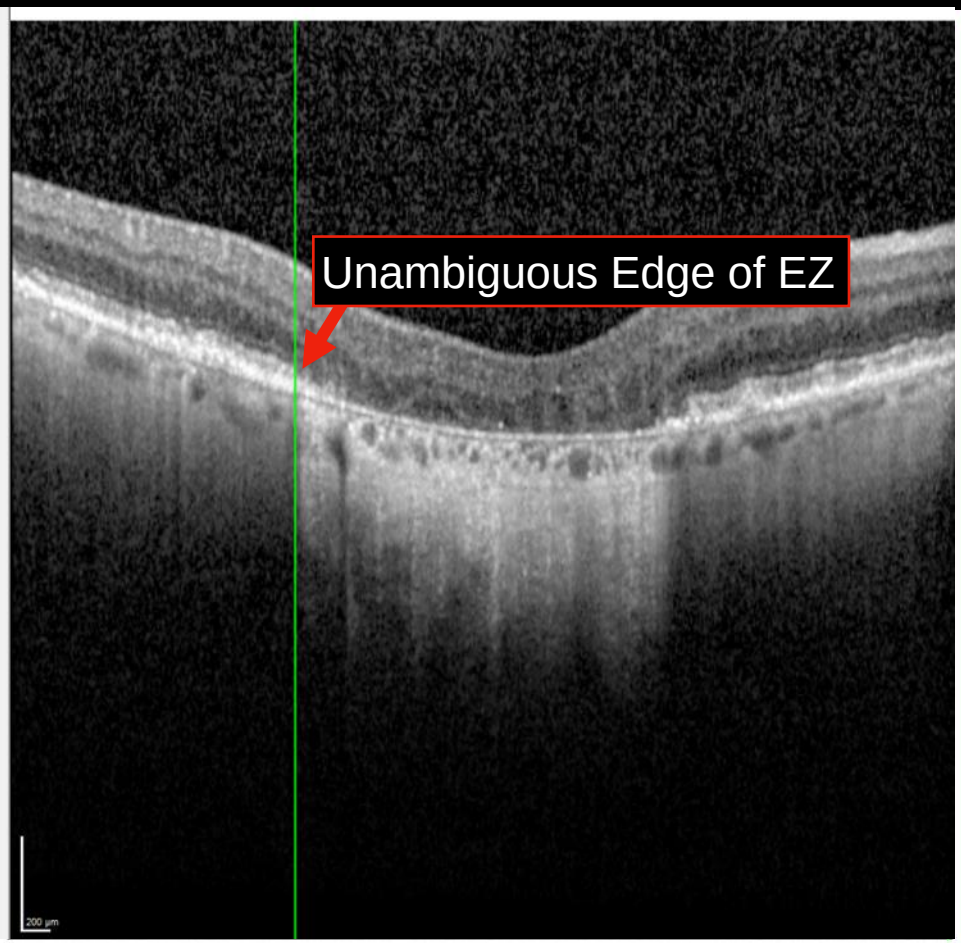




Lujan Imaging LLC

EZ Area Analysis

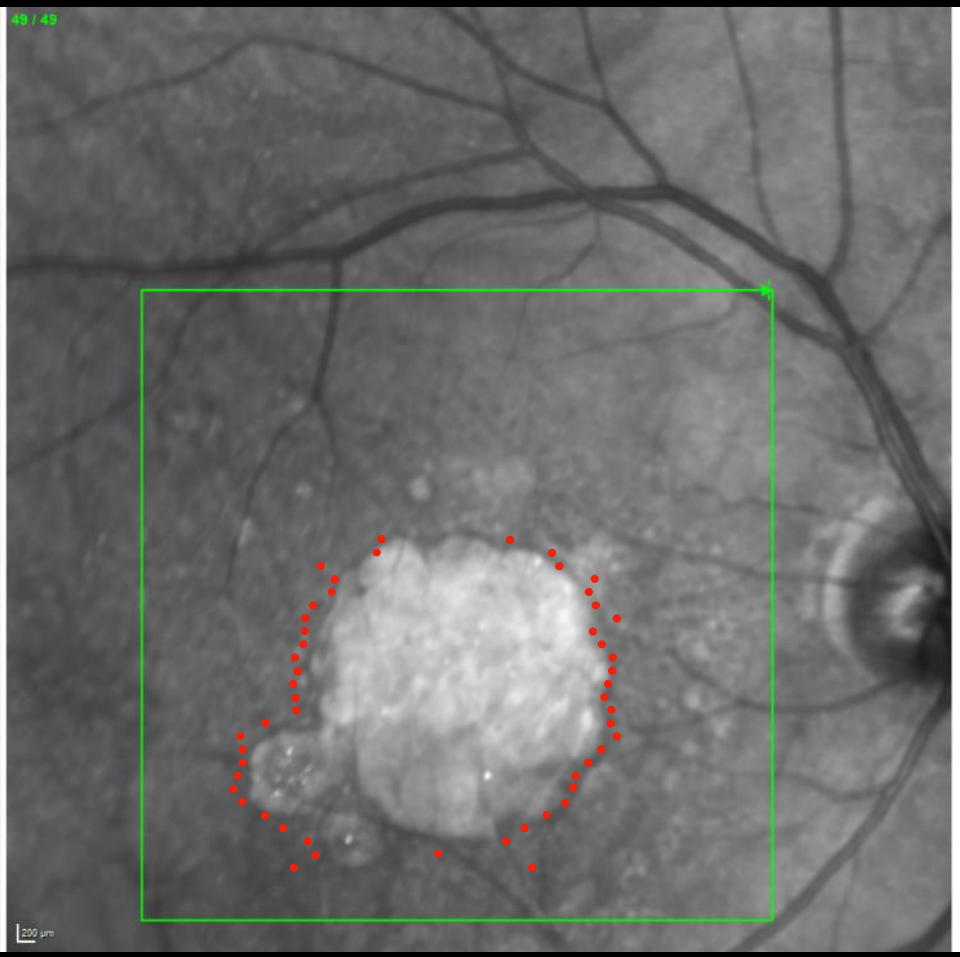


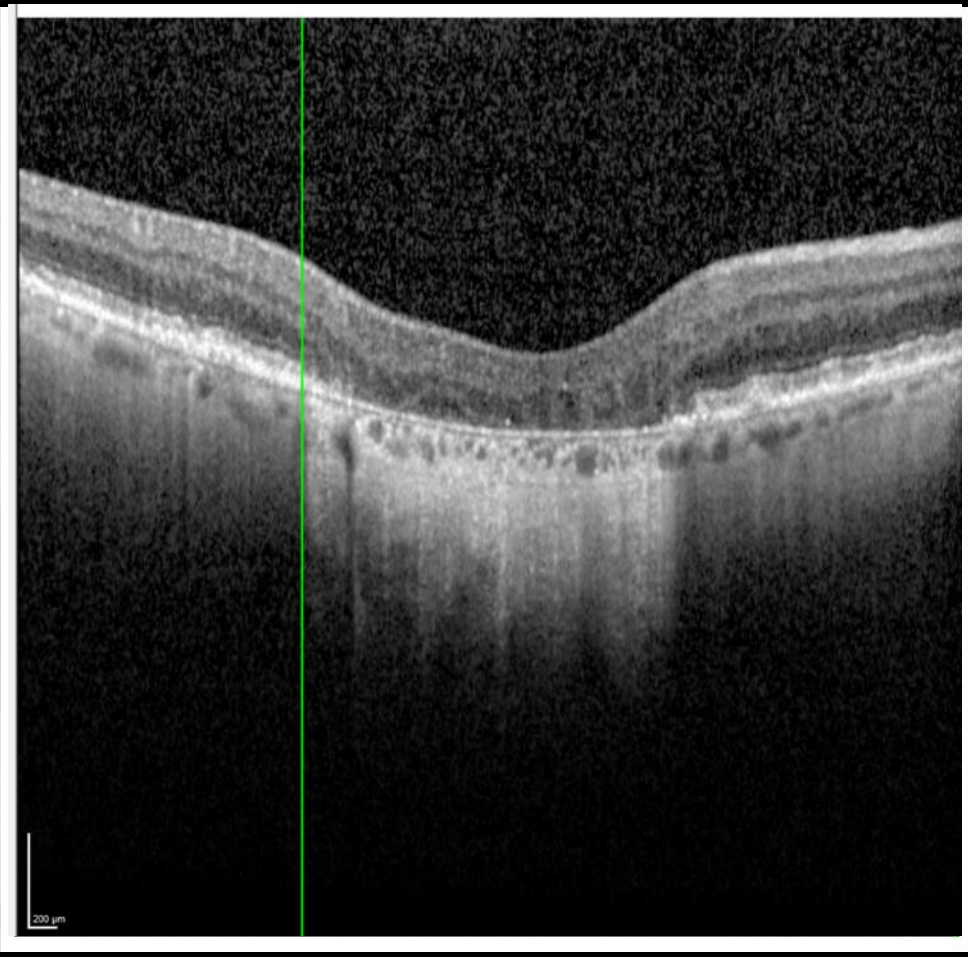


10/14/2020

Lujan Imaging LLC

EZ Area Analysis

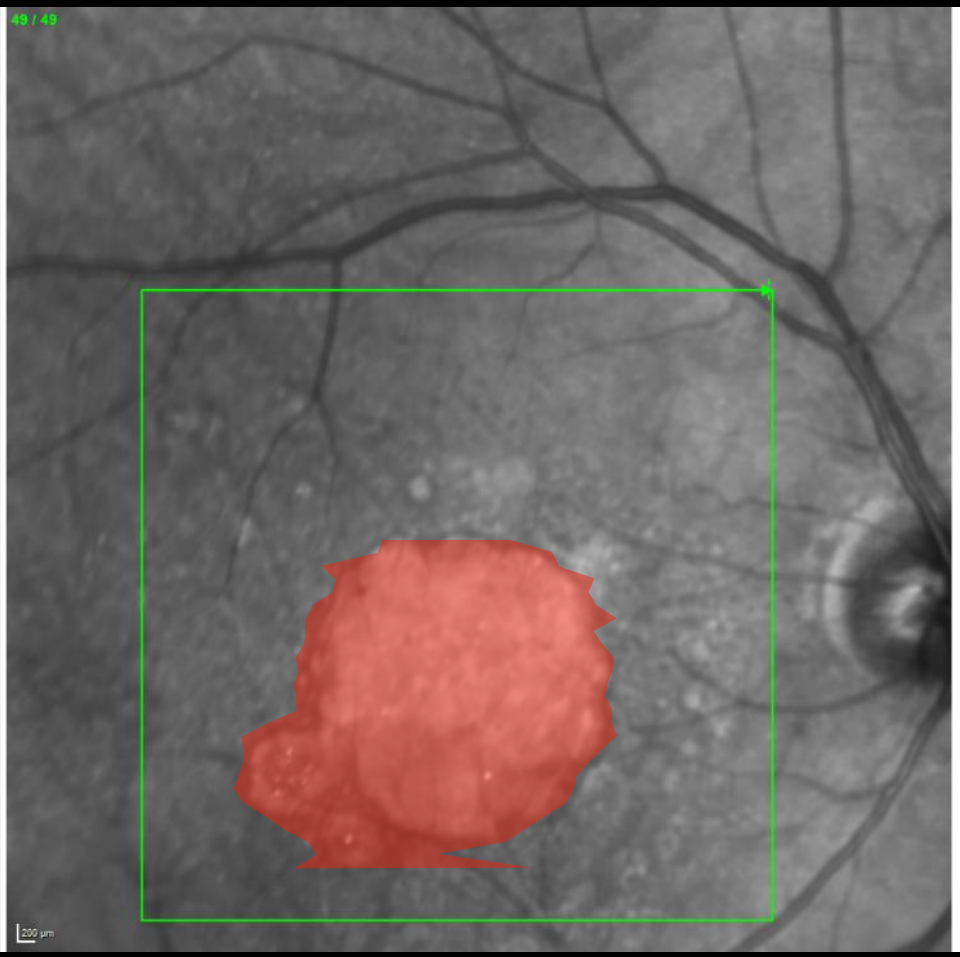


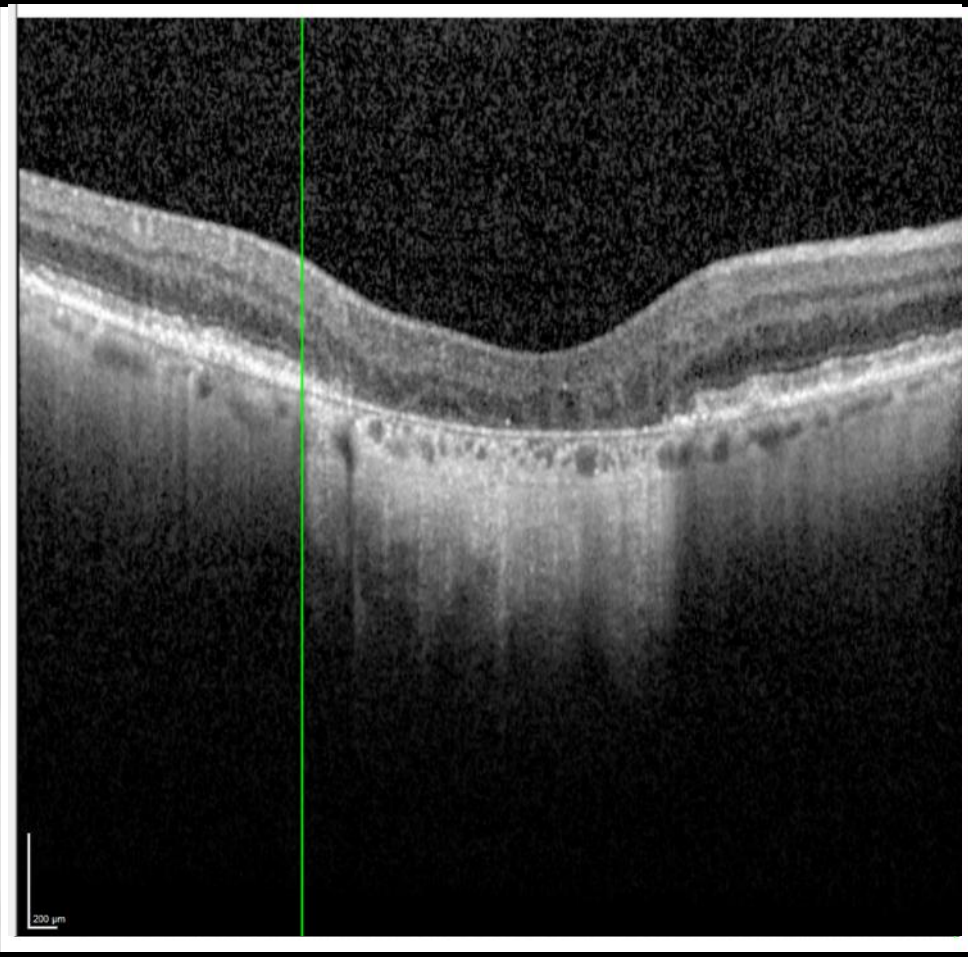


10/14/2020

Lujan Imaging LLC

EZ Area Analysis





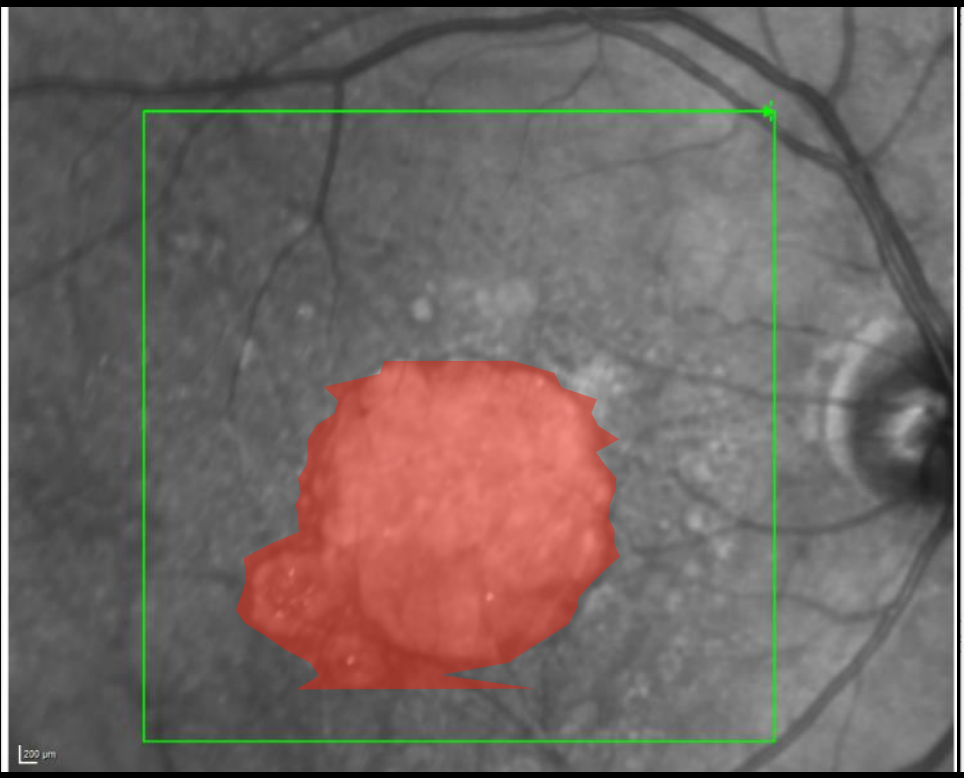
10/14/2020

Lujan Imaging LLC

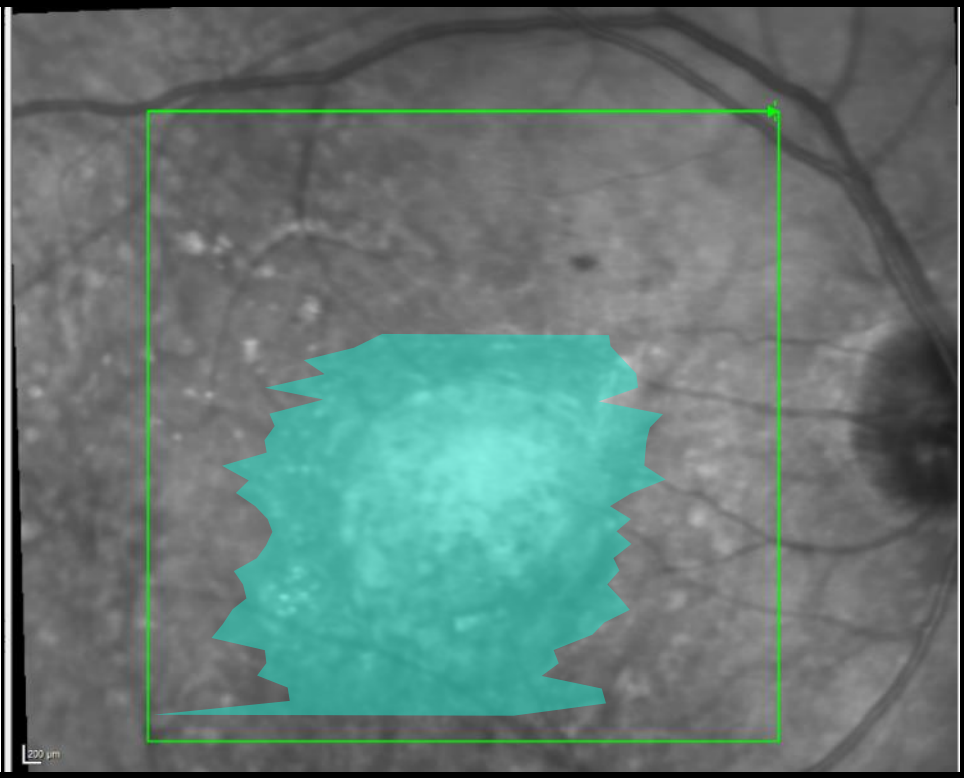
EZ Area Analysis

- Edges of *unambiguous* EZ were identified

10/14/2020



01/26/2021

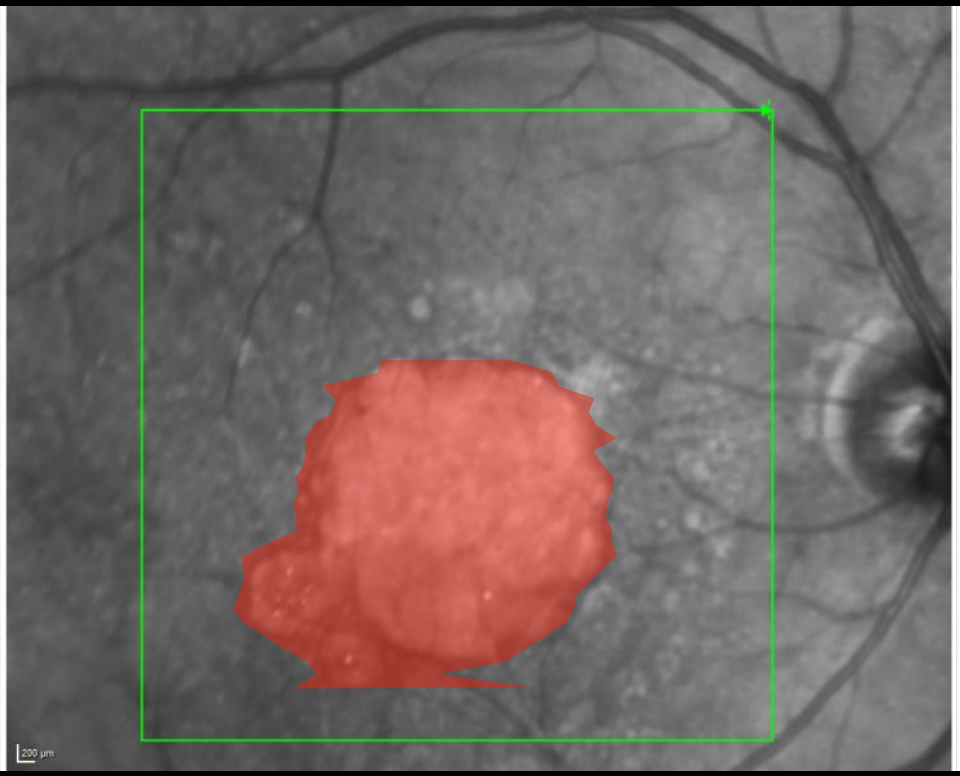


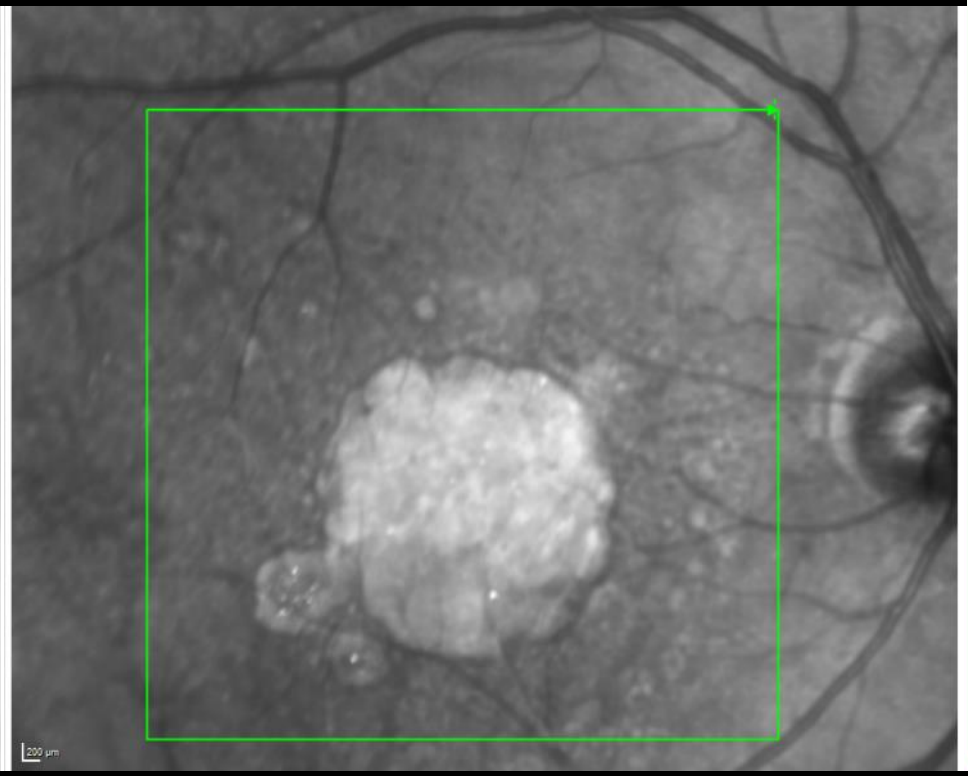
Lujan Imaging LLC

EZ Area Analysis

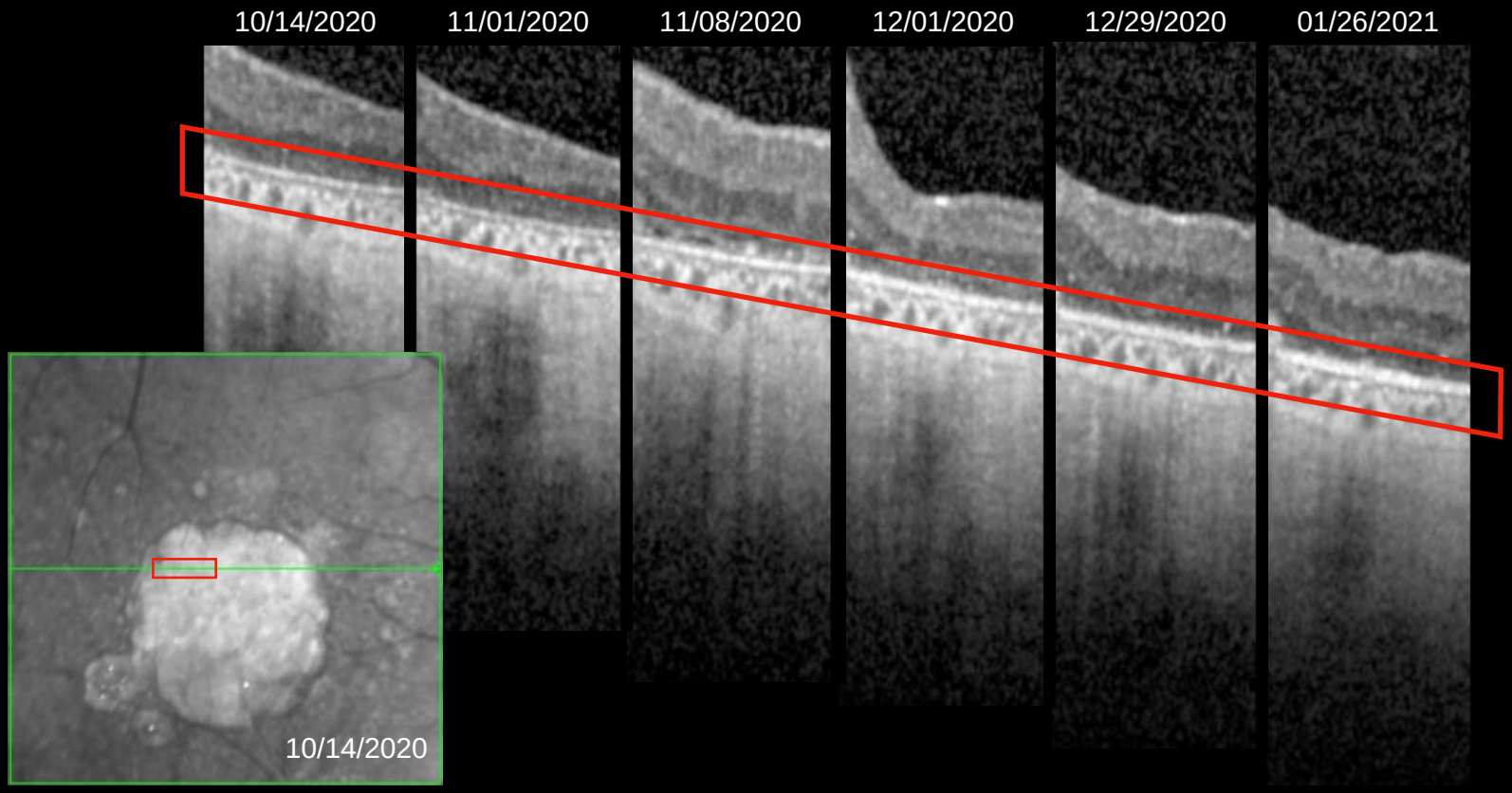
- Edges of *unambiguous* EZ were identified

10/14/2020





RPE / Bruch's Thickening



Definite progressive thickening at the level of RPE / Bruch's membrane complex observed at a single and representative retinal location

Lujan Imaging LLC

OpRegen #21 Findings to Date

Baseline showed expected GA/cRORA with loss of ELM, EZ in appropriate retinal locations.

At 3W significant outer retinal changes including apparent partial reformation of ELM/EZ. Diffuse thickening of EZ and amorphous hyper-reflective sub-retinal material present.

At 6W some EZ changes persist, but EZ loss also occurs. Thickening of RPE/Bruch's.

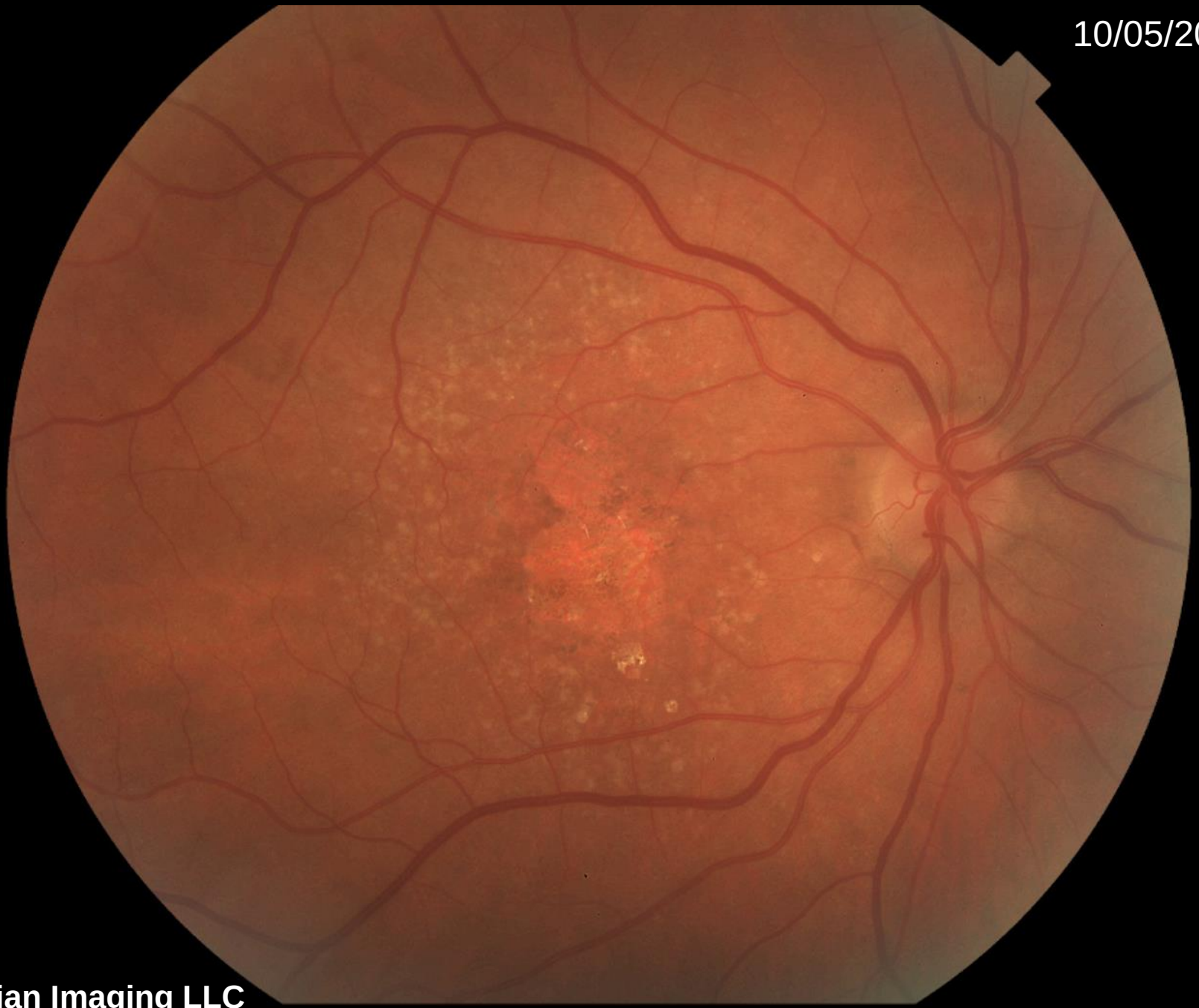
By 3M thickening of RPE/Bruch's continued, ELM more visible and continuous over multiple locations in study eye.

EZ Area showed progression of loss of *unambiguous* EZ from baseline to 3M visit. This is a conservative estimate based on grading the edge of EZ only when most characteristic anatomical findings were no longer present.

OpRegen Patient #22 (OD)

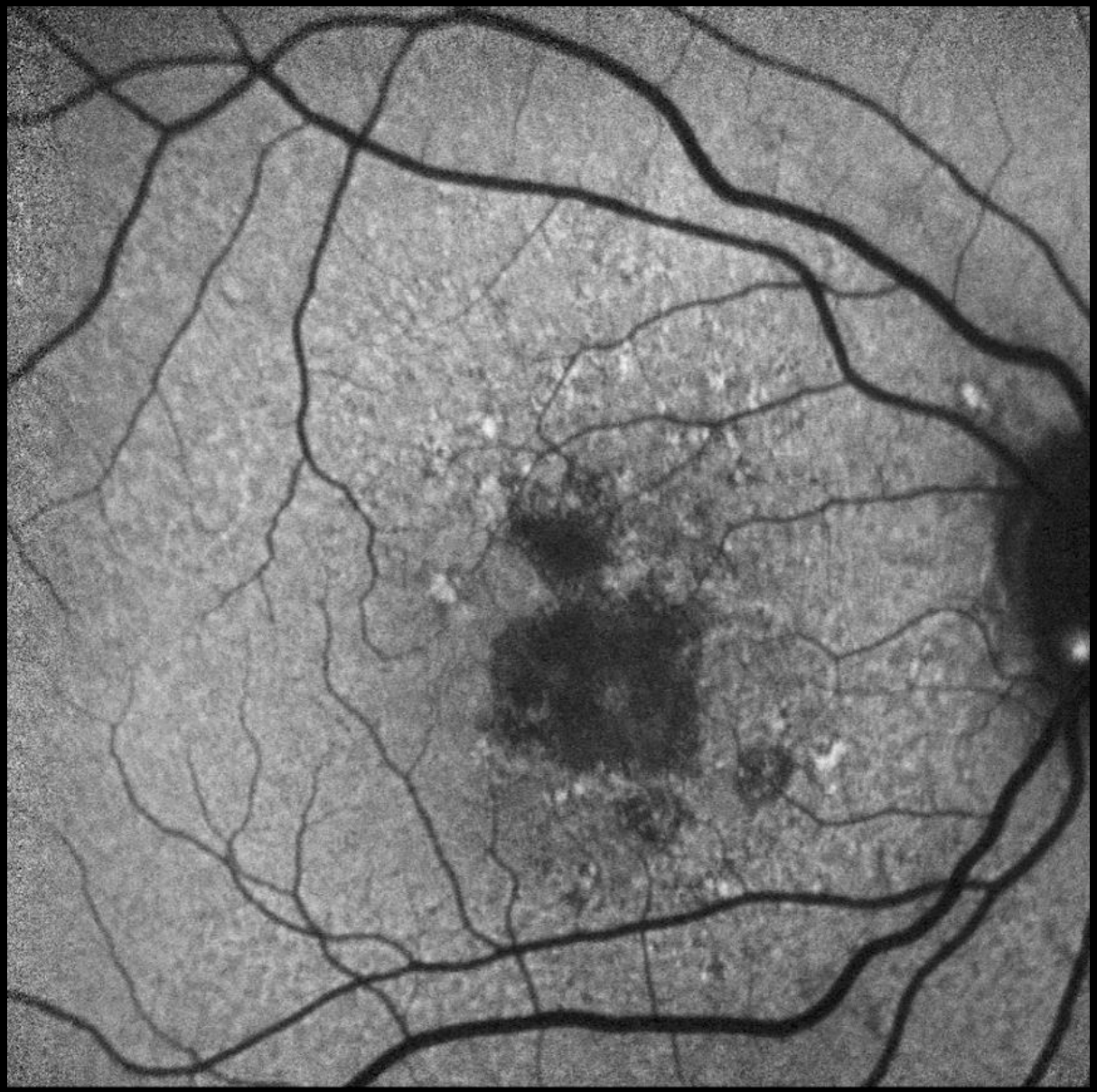
Through 01/25/2021

Lujan Imaging LLC


10/05/2020
Lujan Imaging LLC

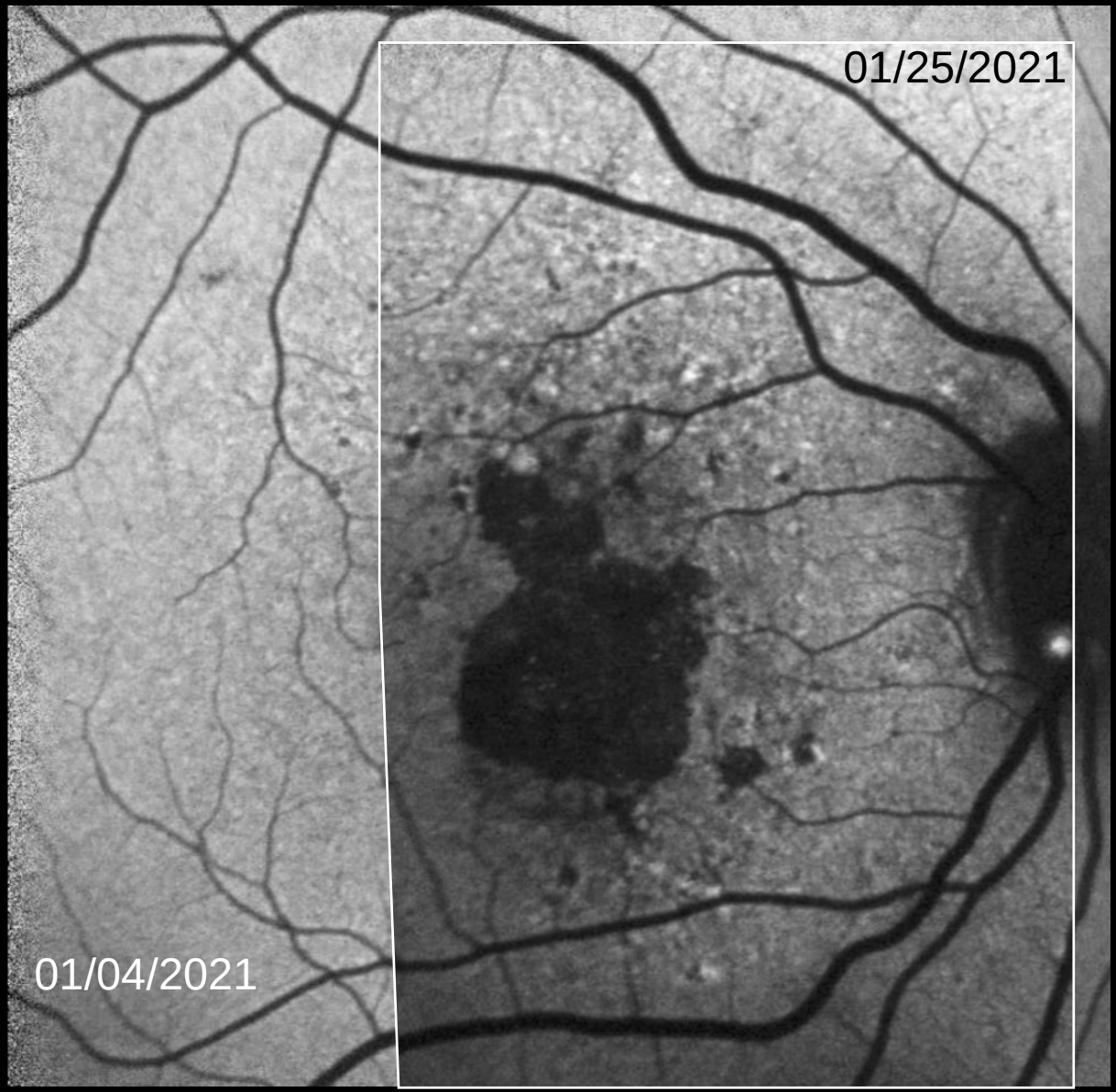

01/25/2021
Lujan Imaging LLC

10/05/2020

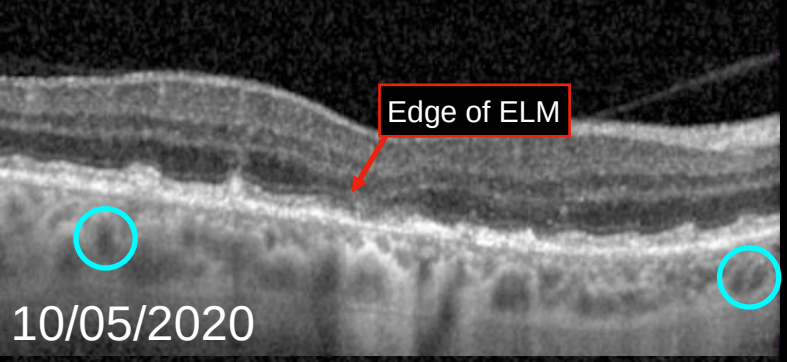


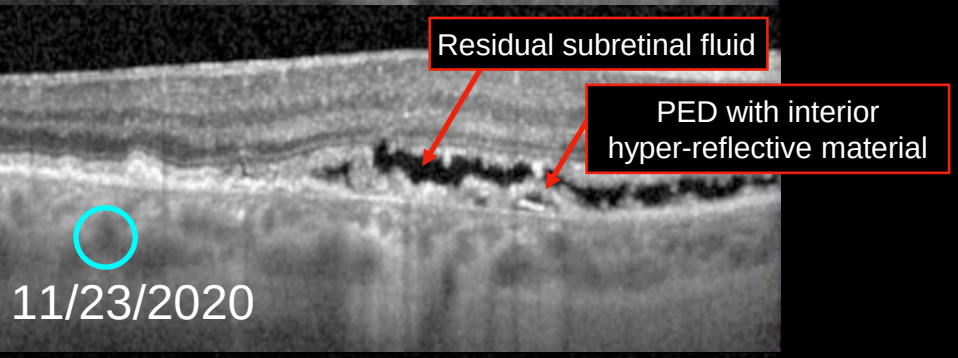
Lujan Imaging LLC

01/2021

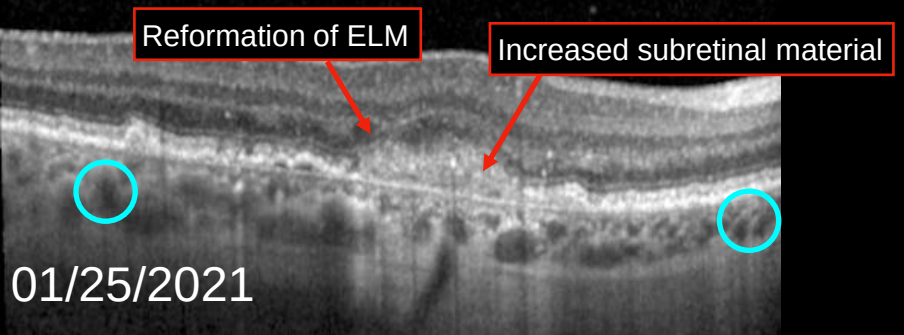


Lujan Imaging LLC

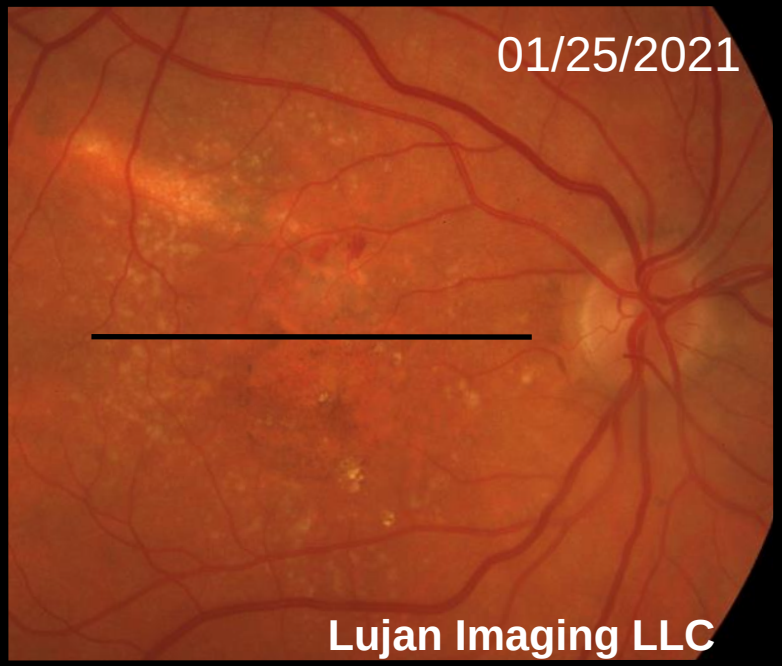

Edge of ELM
10/05/2020

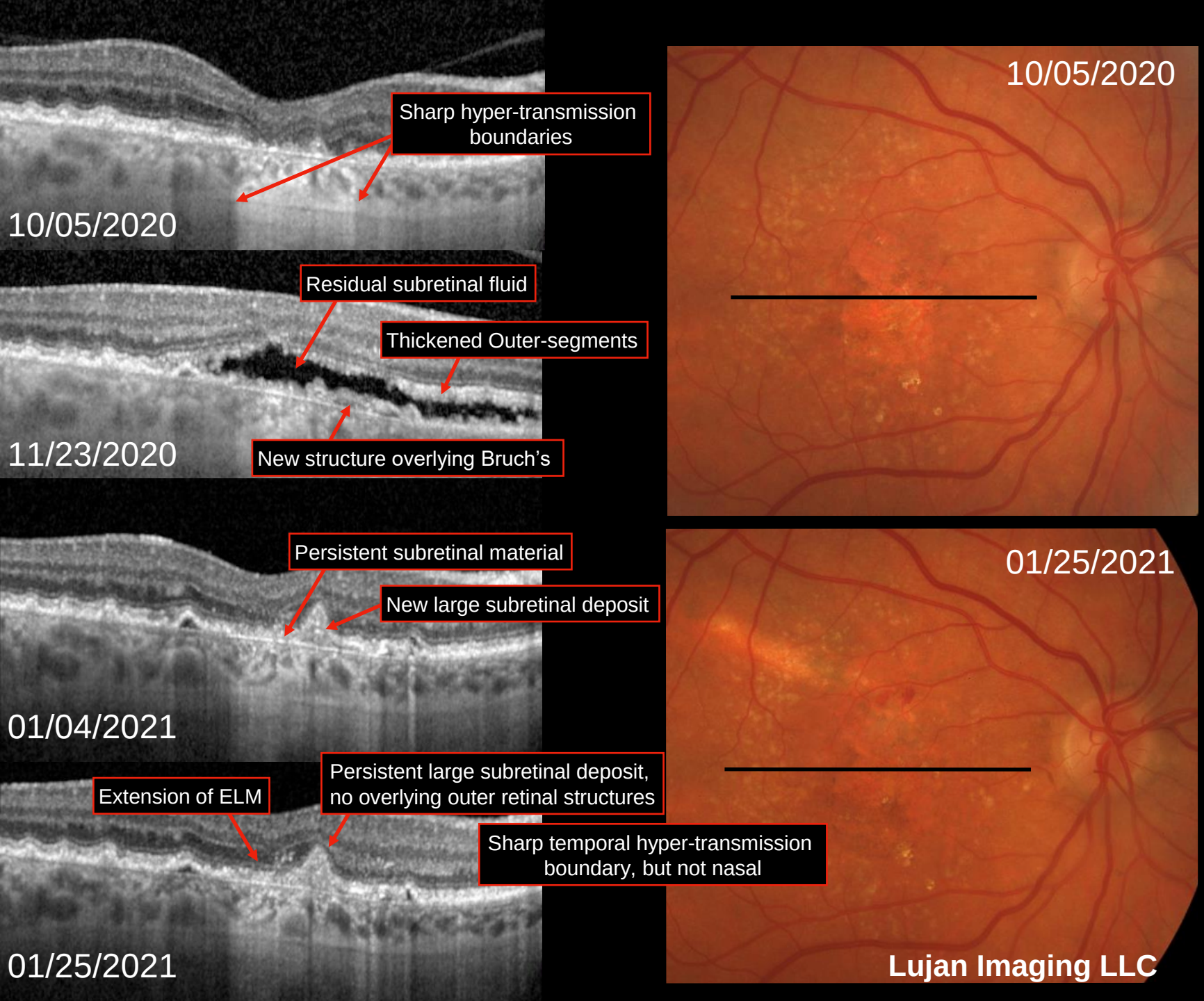

Residual subretinal fluid
PED with interior hyper-reflective material
11/23/2020

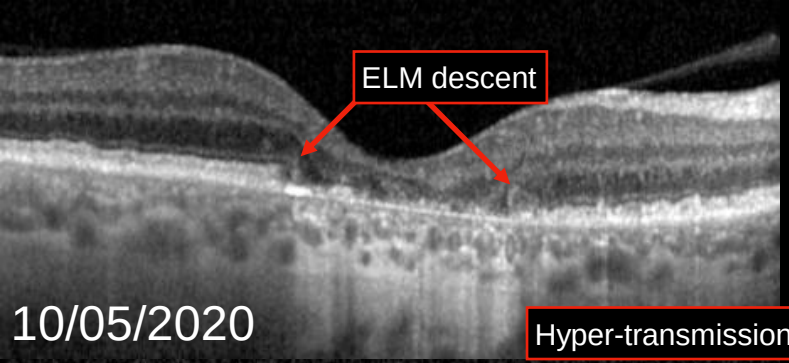

New subretinal material, Resolution of PED
01/04/2021

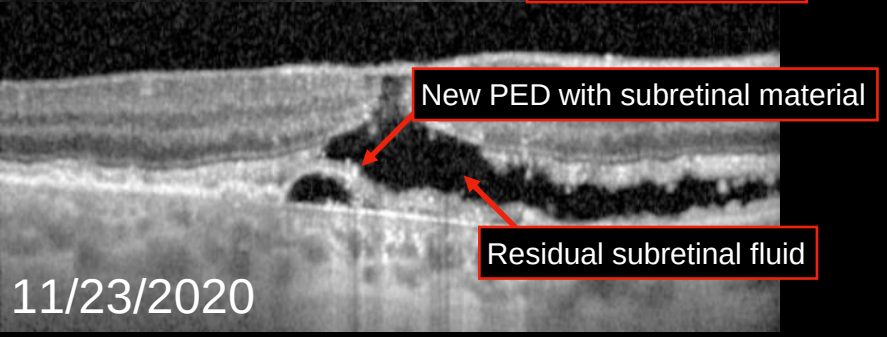

Reformation of ELM
Increased subretinal material
01/25/2021

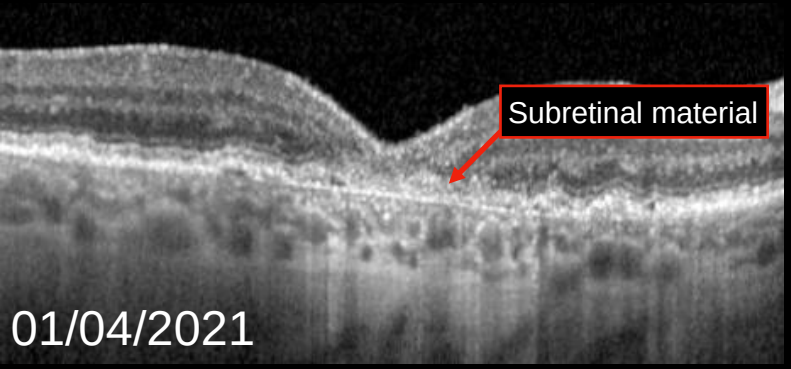

10/05/2020

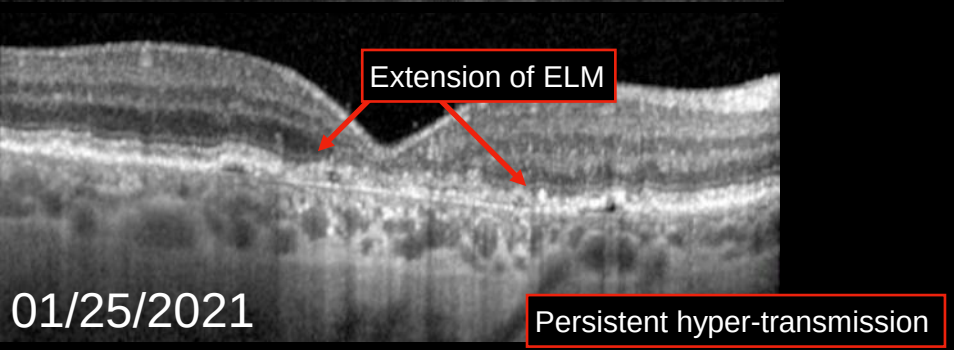

01/25/2021
Lujan Imaging LLC


Sharp hyper-transmission boundaries
10/05/2020
Residual subretinal fluid
Thickened Outer-segments
New structure overlying Bruch's
11/23/2020
Persistent subretinal material
New large subretinal deposit
01/04/2021
Extension of ELM
Persistent large subretinal deposit, no overlying outer retinal structures
Sharp temporal hyper-transmission boundary, but not nasal
01/25/2021
10/05/2020
01/25/2021
Lujan Imaging LLC

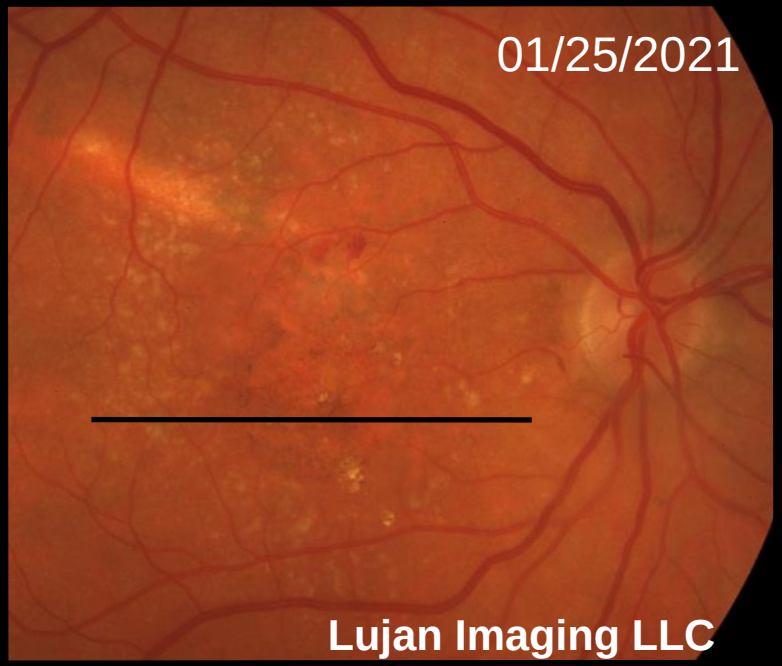

ELM descent
10/05/2020
Hyper-transmission


New PED with subretinal material
Residual subretinal fluid
11/23/2020


Subretinal material
01/04/2021


Extension of ELM
01/25/2021
Persistent hyper-transmission


10/05/2020


01/25/2021
Lujan Imaging LLC

OpRegen #22 Findings to Date

Baseline with central GA/cRORA with multifocal satellites. Expected loss of EZ/ELM/hyper-transmission through RPE.

At 4W macular hole formation with large sub-retinal fluid collection.

At 6W residual subretinal fluid, new material apparent on surface of RPE.

By 3M all subretinal fluid resolved, subretinal material persists, and large central subretinal deposit appears.

By 4M extension of ELM noted at many locations. Increased subretinal material.

Overall expansion of RPE loss on FAF, but increased pigmentation and extension of ELM into boundaries of defined atrophy.

LINEAGE
CELL THERAPEUTICS

AMD is the leading cause of irreversible vision loss in the US

Source: aao.org

Christopher D. Riemann, M.D.
Cincinnati Eye Institute & University of Cincinnati

Overview of Clinical Safety Observed to Date and Review of Patient #22 - 3rd Retinal Restoration

Christopher D. Riemann, MD

Cincinnati Eye Institute &
University of Cincinnati

Study Status and Baseline Characteristics

	Cohorts 1 - 3 (legally blind) Recruitment complete (n = 12)	**Cohort 4 (better VA)** Recruitment complete (n = 12)
n (%) subjects dropout	2 (17%) (2 medical illness)	1 (12.5%) (Withdrawal of consent/COVID fears)
Age: mean (SD / min - max), yrs	78.3 (± 8.2 / 64.8 - 92.2)	75.7 (± 8.1 / 60.0 - 87.7)
ETDRS BCVA: mean (SD / min - max)	23.7 (± 11.7 / 0 - 39) letters [24 letters ≈ 20/400]	44.8 (± 7.5 / 28 - 54) letters [45 letters ≈ 20/125]
GA area: mean (SD / min - max)	12.7 (± 6.7 / 6 - 30) mm^2	7.4 (± 2.9 / 1.4 - 11) mm^2
Post-op cumulative F/U period	45.0 years	18.9 years
Mean F/U (days)	1369 days (SE ± 159)	549 days (SE ± 126)

Note: Summary of data presented at 2021 ARVO

Study Status and Baseline Characteristics

	Cohorts 1 - 3 (legally blind) Recruitment complete (n = 12)	**Cohort 4 (better VA)** Recruitment complete (n = 12)
n (%) subjects dropout	2 (17%) (2 medical illness)	1 (12.5%) (Withdrawal of consent/COVID fears)
Age: mean (SD / min - max), yrs	78.3 (± 8.2 / 64.8 - 92.2)	75.7 (± 8.1 / 60.0 - 87.7)
ETDRS BCVA: mean (SD / min - max)	23.7 (± 11.7 / 0 - 39) letters [24 letters ≈ 20/400]	44.8 (± 7.5 / 28 - 54) letters [45 letters ≈ 20/125]
GA area: mean (SD / min - max)	12.7 (± 6.7 / 6 - 30) mm^2	7.4 (± 2.9 / 1.4 - 11) mm^2
Post-op cumulative F/U period	45.0 years	18.9 years
Mean F/U (days)	1369 days (SE ± 159)	549 days (SE ± 126)

Note: Summary of data presented at 2021 ARVO

Primary Endpoint (N = 24):
Systemic and ocular safety and tolerability (*continued*)

AE Term	Numbers of Patients Reporting (n / 24; %) and Relevant Details
Limited Subretinal Hemorrhage	5 / 24; 20.8% (asymptomatic & auto resolved)
Any form of Macular Fibrosis (ERM)	16 / 24; 66.7% (majority were mild to moderate in severity)
Subretinal Pigmentation	12 / 24; 50.0% (potentially a positive finding)
Subretinal Fluid, persisting >24h	8 / 24; 33.3% (majority resolved <72 hrs, none required treatment)
CNV	4 / 24; 16.7% • One (1) began >2 yrs post-op, responsive to regular anti-VEGF treatment • One (1) Type 2 CNV – 6M post-op at choroidal puncture site, successfully treated with single administration of an anti-VEGF • Two others at area of GA occurred <6M post-op and have received at least one anti-VEGF, appear responsive
Lamellar or macular hole	3 / 24; 12.5% (Two were associated with ERM, one other resolved without treatment or sequelae)
Retinoschisis	3 / 24; 12.5%
Retinal tear	2 / 24; 8.3%

Note: Summary of data presented at 2021 ARVO

Primary Endpoint (N = 24):
Systemic and ocular safety and tolerability (*continued*)

AE Term	Numbers of Patients Reporting (n / 24; %) and Relevant Details
Limited Subretinal Hemorrhage	5 / 24; 20.8% (asymptomatic & auto resolved)
Any form of Macular Fibrosis (ERM)	16 / 24; 66.7% (majority were mild to moderate in severity)
Subretinal Pigmentation	12 / 24; 50.0% (potentially a positive finding)
Subretinal Fluid, persisting >24h	8 / 24; 33.3% (majority resolved <72 hrs, none required treatment)
CNV	4 / 24; 16.7% • One (1) began >2 yrs post-op, responsive to regular anti-VEGF treatment • One (1) Type 2 CNV – 6M post-op at choroidal puncture site, successfully treated with single administration of an anti-VEGF • Two others at area of GA occurred <6M post-op and have received at least one anti-VEGF, appear responsive
Lamellar or macular hole	3 / 24; 12.5% (Two were associated with ERM, one other resolved without treatment or sequelae)
Retinoschisis	3 / 24; 12.5%
Retinal tear	2 / 24; 8.3%

Note: Summary of data presented at 2021 ARVO

Primary Endpoint (N = 24):
Systemic and ocular safety and tolerability (*continued*)

AE Term	Numbers of Patients Reporting (n / 24; %) and Relevant Details
Limited Subretinal Hemorrhage	5 / 24; 20.8% (asymptomatic & auto resolved)
Any form of Macular Fibrosis (ERM)	16 / 24; 66.7% (majority were mild to moderate in severity)
Subretinal Pigmentation	12 / 24; 50.0% (potentially a positive finding)
Subretinal Fluid, persisting >24h	8 / 24; 33.3% (majority resolved <72 hrs, none required treatment)
CNV	4 / 24; 16.7% • One (1) began >2 yrs post-op, responsive to regular anti-VEGF treatment • One (1) Type 2 CNV – 6M post-op at choroidal puncture site, successfully treated with single administration of an anti-VEGF • Two others at area of GA occurred <6M post-op and have received at least one anti-VEGF, appear responsive
Lamellar or macular hole	3 / 24; 12.5% (Two were associated with ERM, one other resolved without treatment or sequelae)
Retinoschisis	3 / 24; 12.5%
Retinal tear	2 / 24; 8.3%

Note: Summary of data presented at 2021 ARVO

Primary Endpoint (N = 24):
Systemic and ocular safety and tolerability (*continued*)

AE Term	Numbers of Patients Reporting (n / 24; %) and Relevant Details
Limited Subretinal Hemorrhage	5 / 24; 20.8% (asymptomatic & auto resolved)
Any form of Macular Fibrosis (ERM)	16 / 24; 66.7% (majority were mild to moderate in severity)
Subretinal Pigmentation	12 / 24; 50.0% (potentially a positive finding)
Subretinal Fluid, persisting >24h	8 / 24; 33.3% (majority resolved <72 hrs, none required treatment)
CNV	4 / 24; 16.7% • One (1) began >2 yrs post-op, responsive to regular anti-VEGF treatment • One (1) Type 2 CNV – 6M post-op at choroidal puncture site, successfully treated with single administration of an anti-VEGF • Two others at area of GA occurred <6M post-op and have received at least one anti-VEGF, appear responsive
Lamellar or macular hole	3 / 24; 12.5% (Two were associated with ERM, one other resolved without treatment or sequelae)
Retinoschisis	3 / 24; 12.5%
Retinal tear	2 / 24; 8.3%

Note: Summary of data presented at 2021 ARVO

Primary Endpoint (N = 24):
Systemic and ocular safety and tolerability (*continued*)

Ocular SAEs	5 Events (reported in 4 patients) and Relevant Details
ERM	In three (3) patients (all PPV/retinotomy), clinically significant, severe ERM requiring surgical peel, were all treated successfully
Retinal Detachment	In two (2) patients (all PPV/retinotomy) • Occurred approximately 2 weeks post-procedure • Events appear unrelated to study medication/RPE cells • Considered to be potentially related to surgical procedure/PPV and/or due to existing peripheral retinal tear/hole • One RD was successfully repaired, and visual acuity exceeds baseline values, one legally blind, early Cohort patient was repaired but failed to recover complete visual acuity, though follow-up was brief due to diagnosis of Stage 4 lung cancer and early withdrawal from the trial

Note: Summary of data presented at 2021 ARVO

Case Review of Patient #22

3rd Case of Retinal Restoration

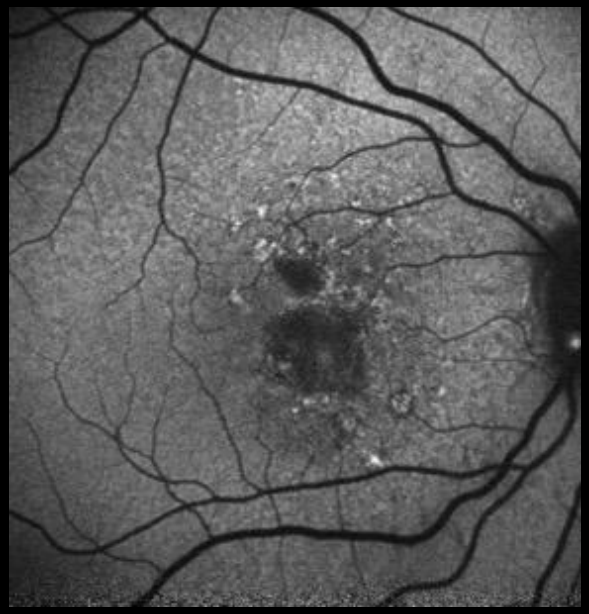
Ocular Medical History

Patient #22 - 3rd case of retinal restoration

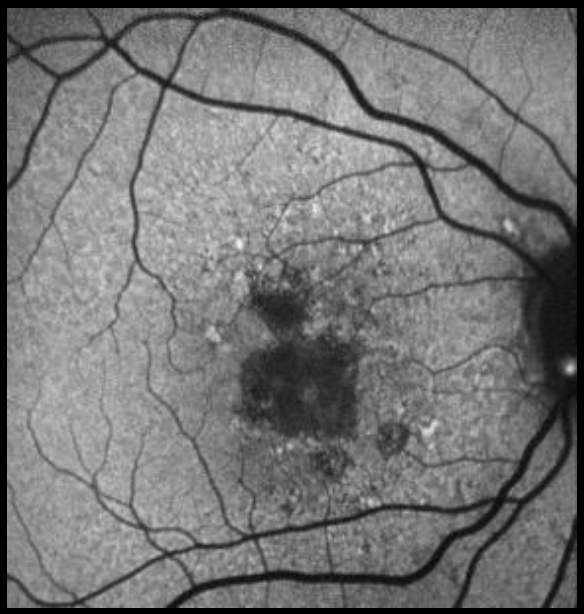
- 65 year old female
- Study Eye OD
  - 20/100 (53 letters read), GA - 4.133 mm2 per Central Reader FAF
  - Phakic, mild ERM present at baseline
- Fellow Eye OS
  - 20/32 (75 letters read), GA - 2.493 mm2 per Central Reader FAF
  - Phakic
- Diagnosed with COVID, mildly symptomatic, immunosuppression modified, recovered without sequelae

History of GA Progression

Patient #22 - 3rd case of retinal restoration



12 Months Pre-op

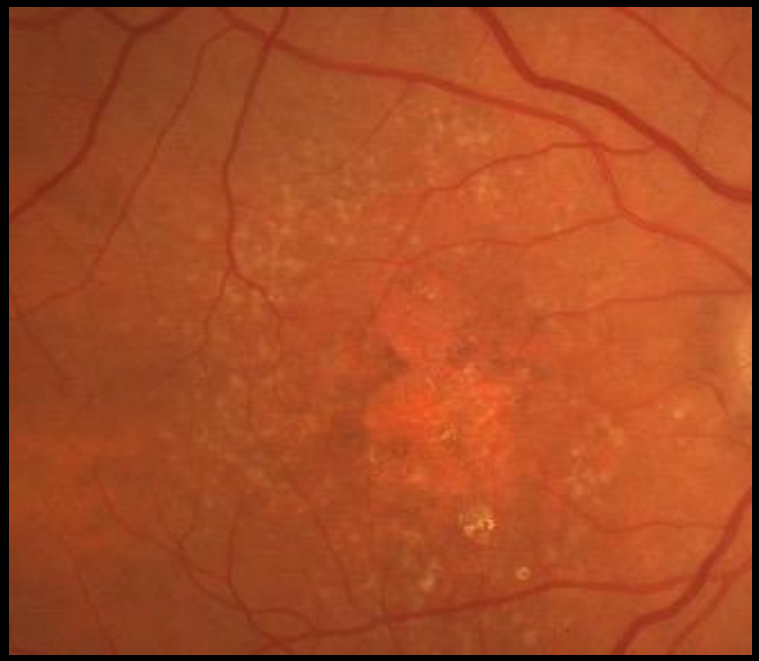


Baseline

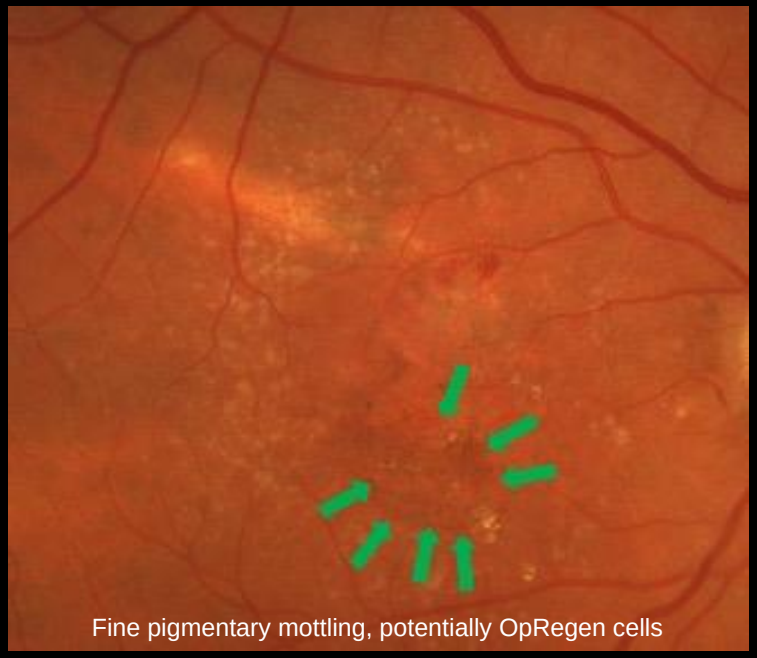
Historical Growth: 0.3-0.35 SQRT/Year

Potential Presence of OpRegen Cells (M3)

Patient #22 - 3rd case of retinal restoration



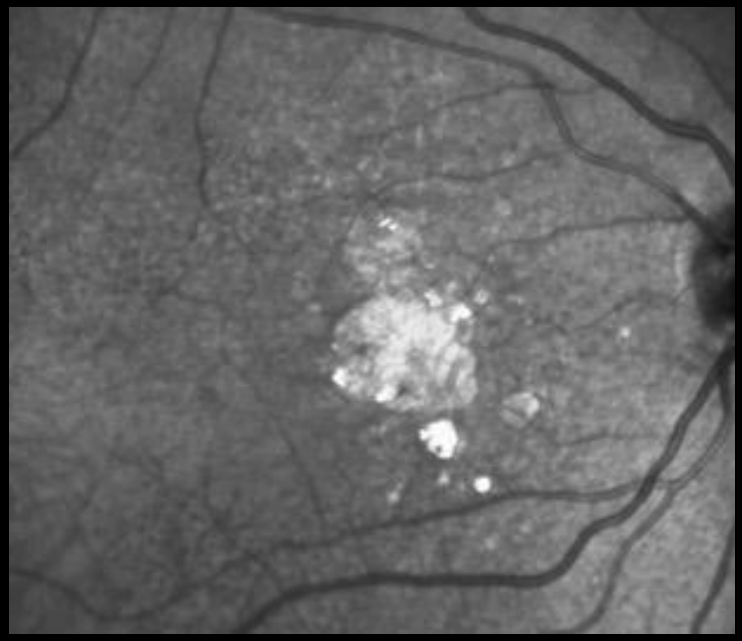
Baseline



Month 3 post-op

Lesion appearance by IR (M3)

Patient #22 - 3rd case of retinal restoration

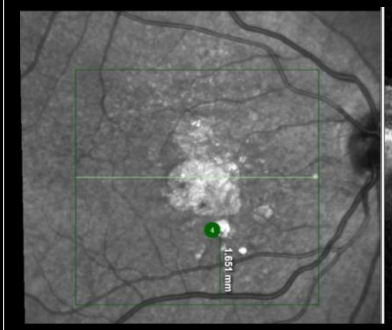


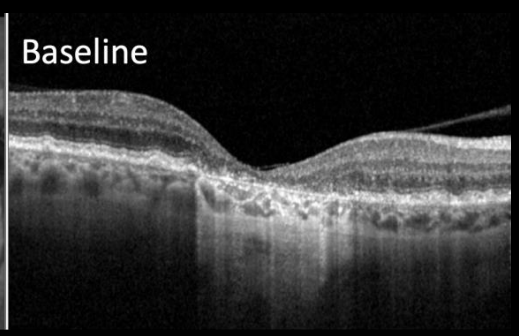
Baseline

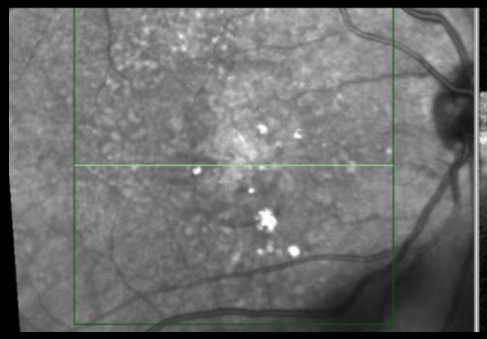
Month 3 post-op

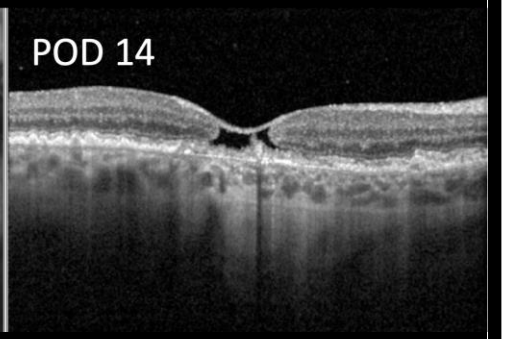
Autoresolving Incomplete Macular Hole

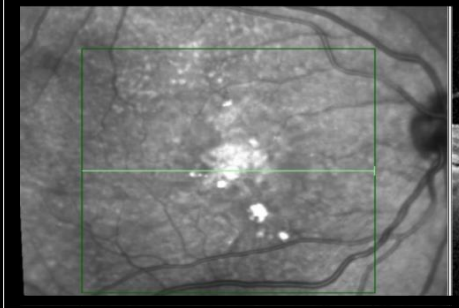
Patient #22 - 3rd case of retinal restoration

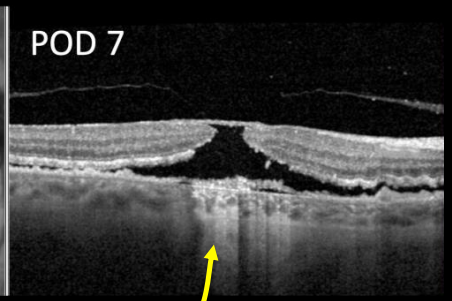


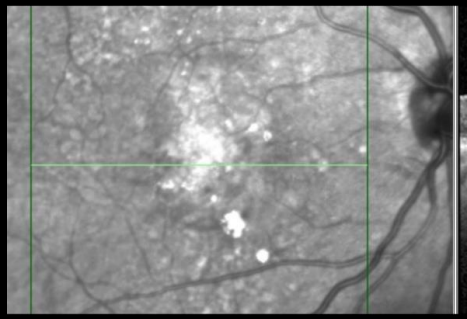


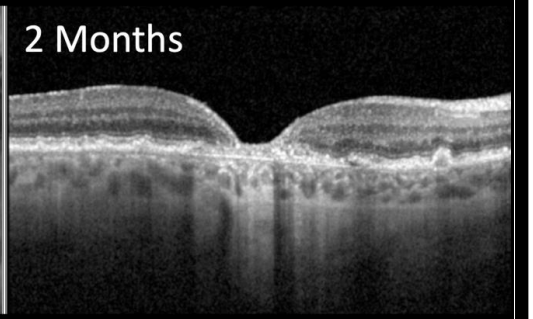










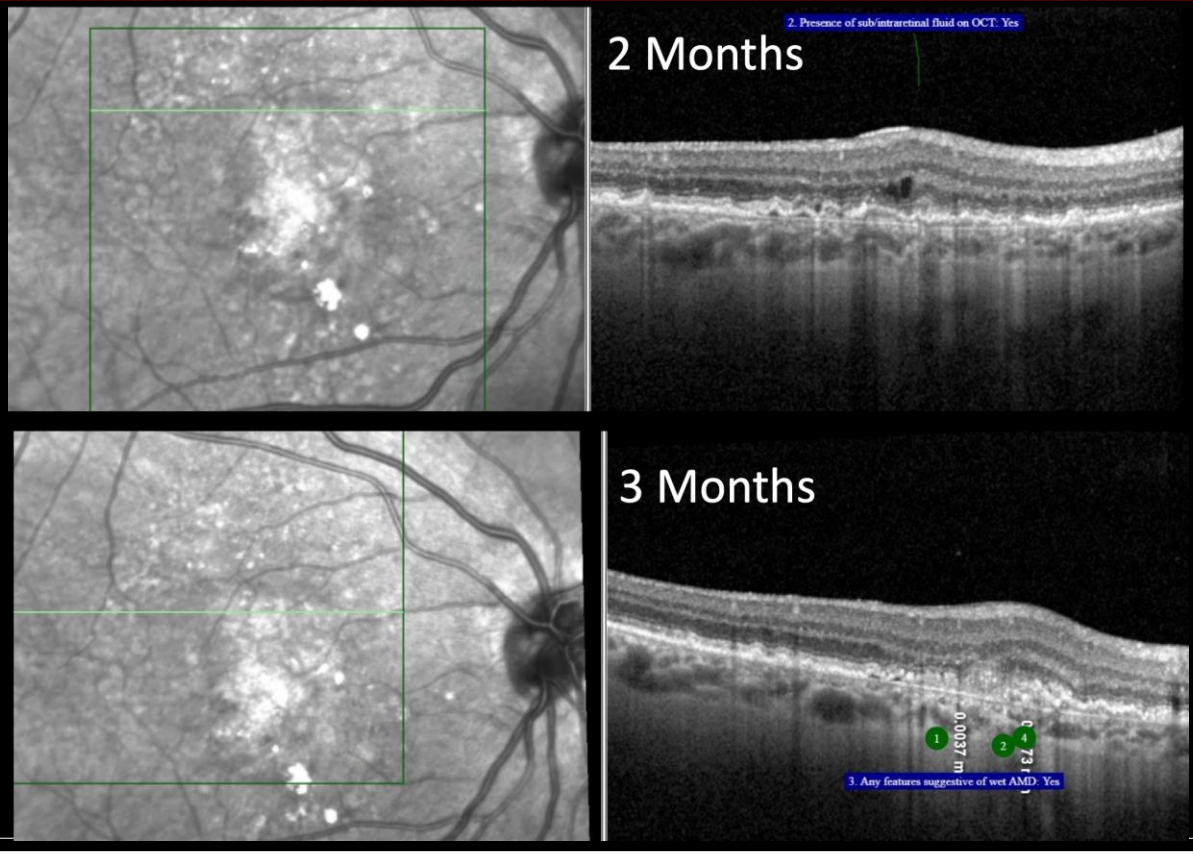


Incomplete macular hole with hyaloid & ILM bridge

Note: Summary of data presented at 2021 ARVO

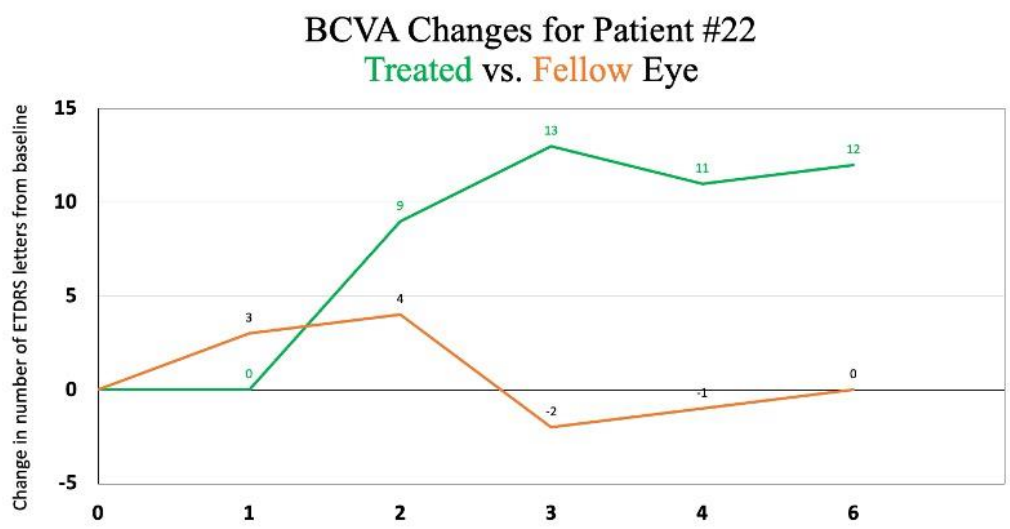
New CNV, Successfully treated with αVEGF

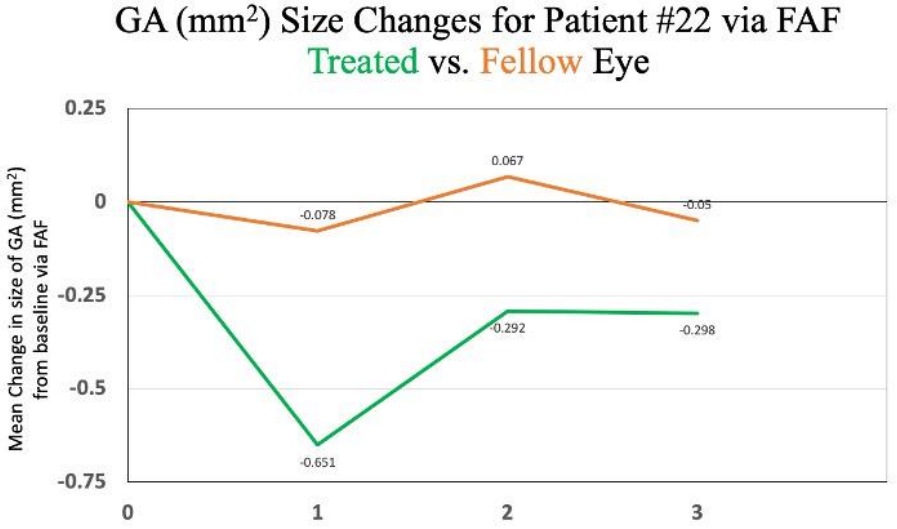
Patient #22 - 3rd case of retinal restoration



Note: Summary of data presented at 2021 ARVO

BCVA and GA (mm^2) Changes for Patient #22
Treated vs. Fellow Eye





Treated Fellow

Time Post-Implantation (months)

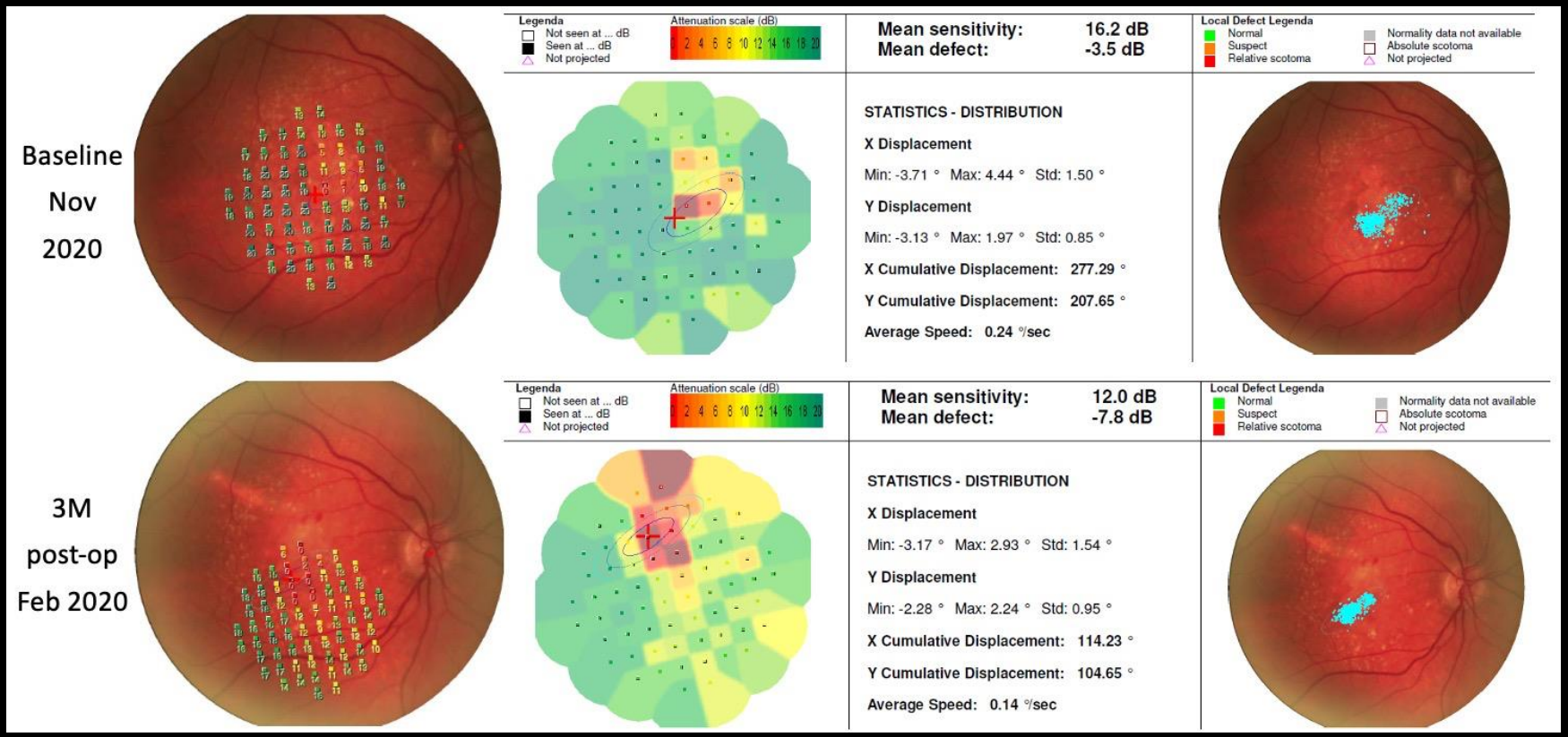
BCVA and Low Luminance Vision

Patient #22 - 3rd case of retinal restoration

Patient #22: Treated Eye - OD	OD		OS		Low Lum. OD		Low Lum. OS	
	VA	LR	LR	VA	VA	LR	LR	VA
			75	20/32	20/125	46	56	20/80
Screening	20/100	53	74	20/32	20/125	46	57	20/80
Baseline	20/125	47	75	20/32	20/200	34	59	20/63
Visit 7 - **7 days**	20/100	50	74	20/40	20/200	36	57	20/80
Visit 8 - **14 Days**	20/100	49	77	20/32	20/160	41	59	20/63
Visit 9 - **1 Month**	20/125	47	78	20/32	20/125	45	59	20/63
Visit 10 - **2 Months**	20/80	56	78	20/32	20/125	45	59	20/63
Visit 11 - **3 Months**	20/63	60	73	20/32	20/100	49	60	20/63
Visit 12 - **4.5 Months**	20/63	58	74	20/32	20/125	47	61	20/63
Visit 13 - **6 Months**	20/63	59	74	20/32	20/100	52	58	20/80

Microperimetry Changes Observed at M3

Patient #22 - 3rd case of retinal restoration

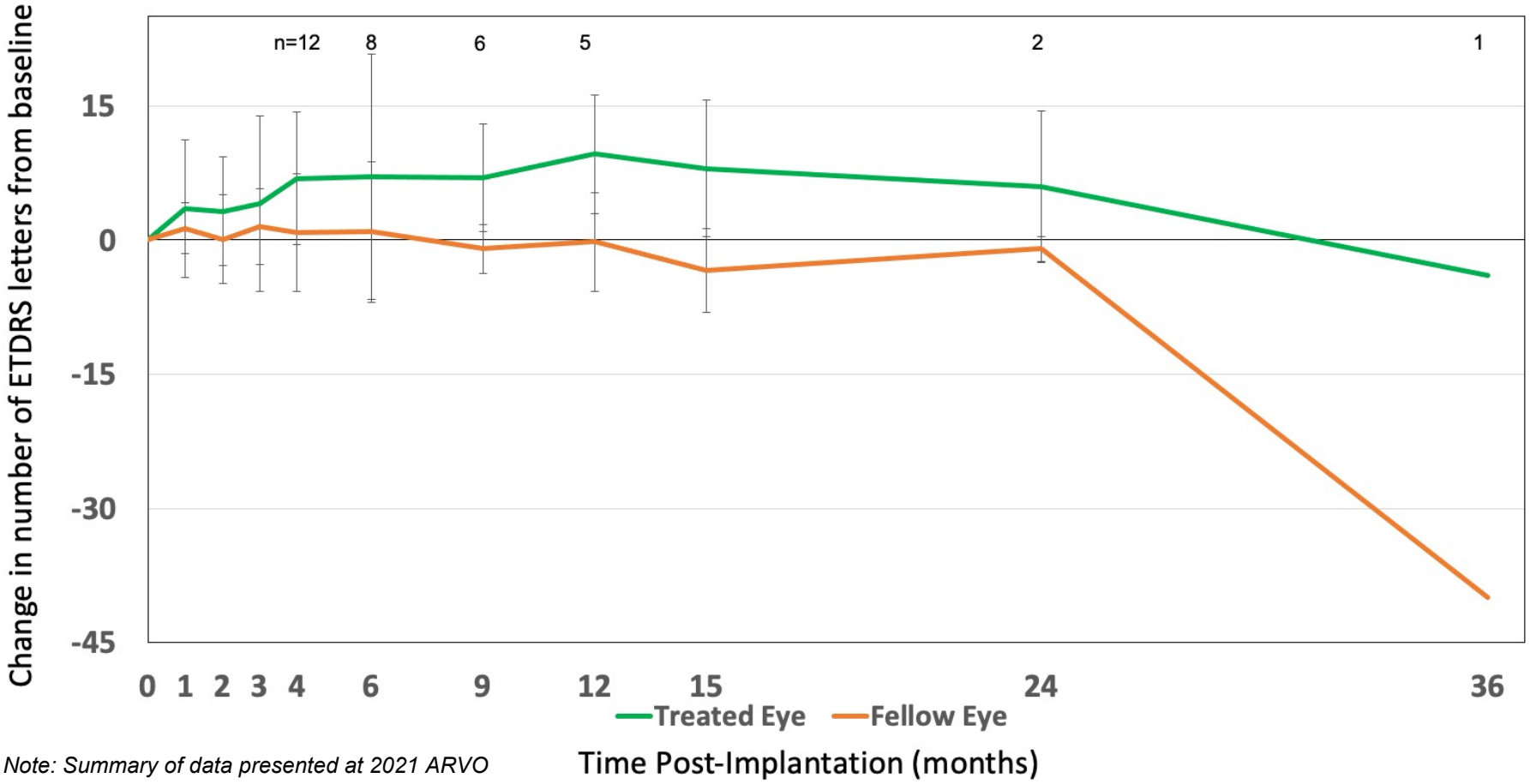


Cohort 4

Clinical Efficacy Assessments
BCVA, MNRead, NEI-VFQ-25

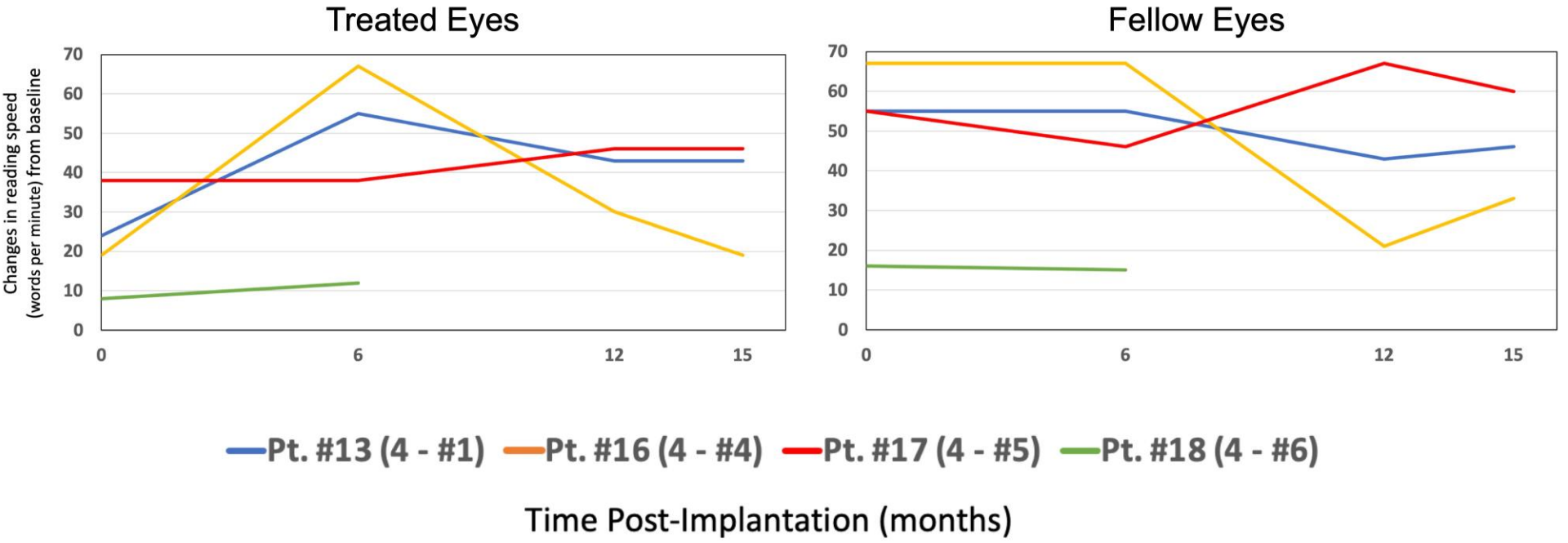
N = 12 Better VA (≤ 20/64 and ≥ 20/250)

Mean Change in Cohort 4 BCVA – Treated and Fellow Eye



Note: Summary of data presented at 2021 ARVO

Cohort 4 Reading Speed (MNRead) – Individual Changes in All Eyes with Post-Baseline Assessment



Note: Summary of data presented at 2021 ARVO

Cohort 4 Patient-Reported Outcomes (Preliminary Results)

- National Eye Institute (NEI) Visual Function Questionnaire (VFQ-25)
- 25 vision-related questions reported across 11 constructs
- Improvement occurred in 9 of 11 categories and remained unchanged in one category

	Category	N (%) Change from Screening to Year 1 (n=5 available to date)
1.	General Vision	4/5 (80%) patients reported improvement
2.	Ocular Pain	2/5 (40%) patients reported improvement
3.	Near Activities	5/5 (100%) patients reported improvement
4.	Distance Activities	3/5 (60%) patients reported improvement
5.	Vision Specific: Social Functioning	3/5 (60%) patients reported improvement
6.	Vision Specific: Mental Health	5/5 (100%) patients reported improvement
7.	Vision Specific: Role Difficulties	4/5 (80%) patients reported improvement
8.	Vision Specific: Dependency	3/5 (60%) patients reported improvement
9.	Driving	0/5 (0%) patients reported improvement (only 2 subjects were driving at screening)
10.	Color Vision	0/5 (0%) no change from screening (all patients previously reported highest possible score, no improvement possible)
11.	Peripheral Vision	2/5 (40%) patients reported improvement

Note: Summary of data presented at 2021 ARVO

Discussion and Conclusions

Previously Reported Observations Continue To Hold True

- OpRegen continues to be well-tolerated in all treated patients (N = 24)
  - Even in 2 patients with less immunosuppression (COVID or other health conditions)
- Sustained subretinal pigmentation continues to suggest OpRegen durability.
- Improved anatomy and function continue to be observed.
  - Reduction in drusen
  - Restoration of photoreceptor and RPE layers in some patients.
  - Localized slowing of GA progression in treated areas and a trend towards slower GA growth in treated versus fellow eyes continue to be observed.
  - Better visual acuity, VFQ-25 scores, and reading speed have been observed in some early Cohort patients and most Cohort 4 patients.

Earlier intervention in less severely affected patients and more central placement of the transplanted OpRegen cells may increase likelihood of a clinically beneficial effect.

Note: Summary of data presented at 2021 ARVO

Discussion and Conclusions (*continued*)

Cohort 4 enrollment is complete and long-term follow-up is ongoing.

Ongoing assessments of clinical benefit are utilizing detailed OCT analyses in addition to standard FAF measurements over time.

Due to the slow progressive nature of dry AMD with GA, patients will be followed for further evaluation of reductions in growth rate of GA.

Note: Summary of data presented at 2021 ARVO

LINEAGE
CELL THERAPEUTICS

AMD is the leading cause of irreversible vision loss in the US

Source: aao.org

Michael S. Ip, M.D., Chief of the Vitreoretinal Surgery Service at the Doheny Eye Centers, UCLA and Doheny Image Reading and Research Lab (DIRRL)

Phase I/IIa Clinical Trial of Transplanted Allogeneic Retinal Pigmented Epithelium Cells in Advanced Dry Age- Related Macular Degeneration: Further Insights from an Imaging Analyses at Doheny Eye Institute

Michael S. Ip, MD
Gavin S. Herbert Endowed Chair
Professor of Ophthalmology
David Geffen School of Medicine
University of California - Los Angeles
Medical Director, Doheny Image Reading Center

DOHENY EYE INSTITUTE | UCLA Stein Eye Institute

Analyses of Images by Doheny Image Reading and Research Lab (DIRRL)

- SD-OCT images were captured using
  - Spectralis (Spectralis; Heidelberg Engineering, Inc., Heidelberg, Germany)
  - Macular volume consisting of 512x49 equally spaced B-scans within a 20x20 degree field centered on the fovea
- Retinal layers in all B-scans were manually segmented for thickness and area measurements using 3D-OCTOR (developed at Doheny Eye Institute)
  - Validated, part 11-compliant, image-grading software tool
  - Graders use a computer mouse to draw the boundaries of all structures of interest to gather quantitative information in eyes with complex disease

Grading of Various Retinal Layers (3D-OCTOR)

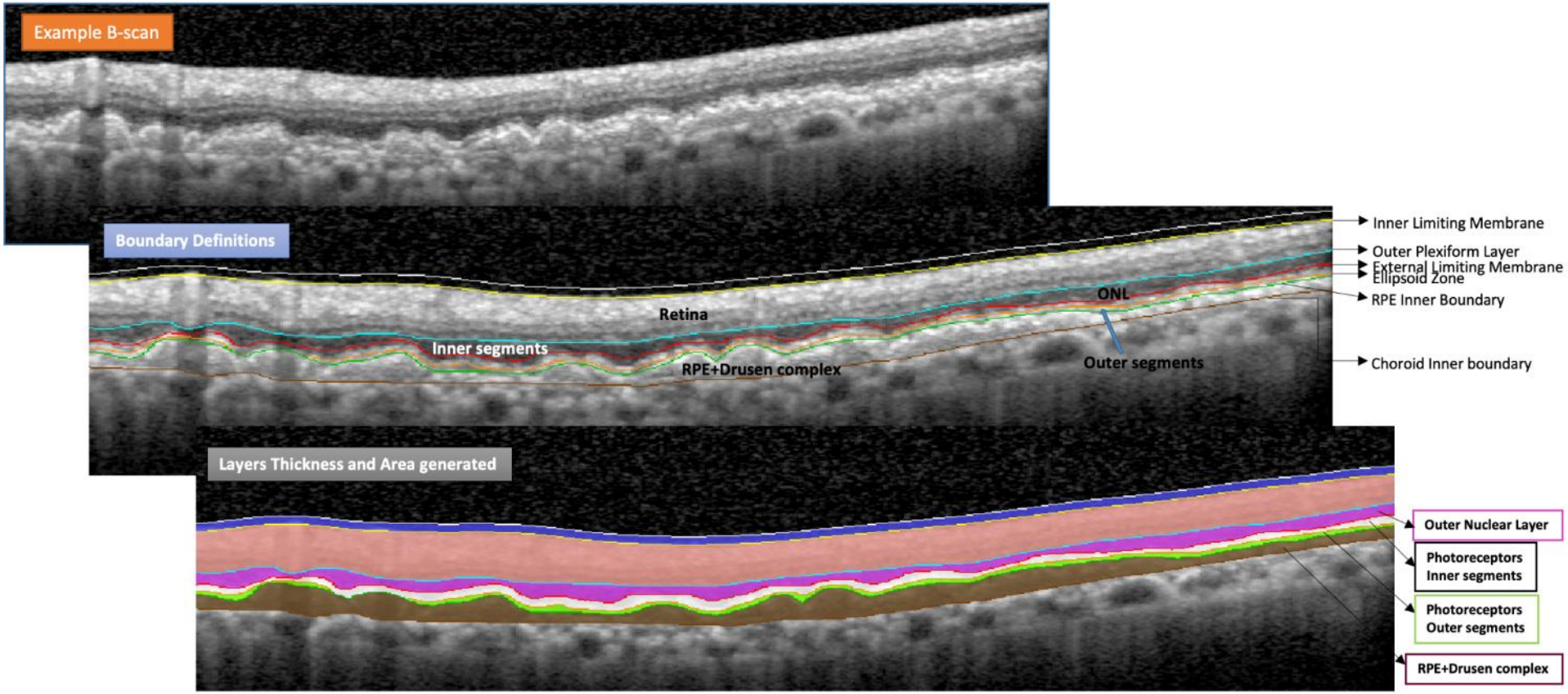


Illustration of Thickness and Area Maps Generated from 3D-OCTOR Grading

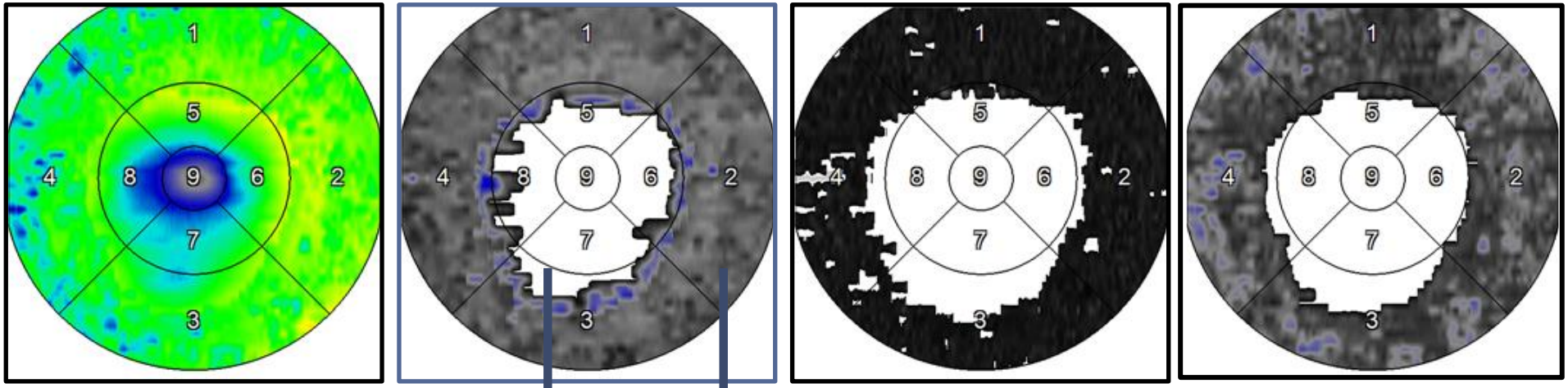
Areas in white or (dark blue/gray for total retina) represent absence or loss of various retinal tissues of interest, while areas in gray or black (green for total retina) show areas of preserved retinal tissue

Total Retina

Outer Nuclear Layer

Photoreceptors Outer Segments

RPE + Drusen Complex



Areas of tissue loss

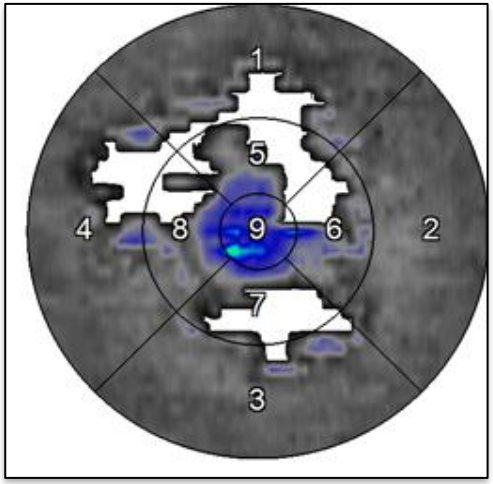
Areas of tissue preservation

Outer Nuclear Layer (ONL) – Area (mm^2) (preserved area)

Patient #14, First case of potential restoration

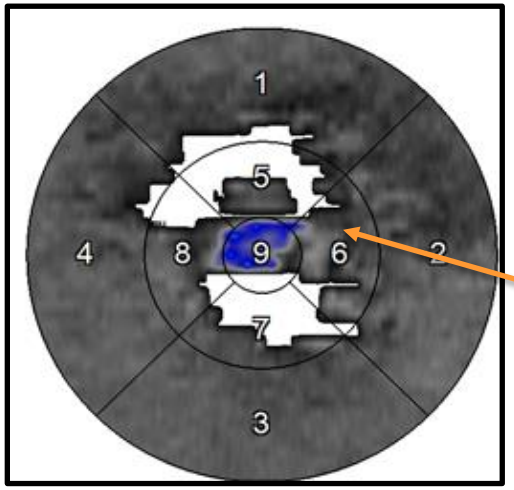
Baseline – 36.14 mm^2

Study Eye



Month 12 – 36.59 mm^2

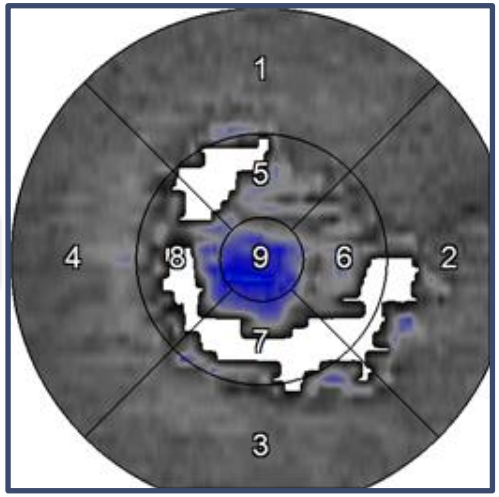
➡



Example of an improved region of ONL area

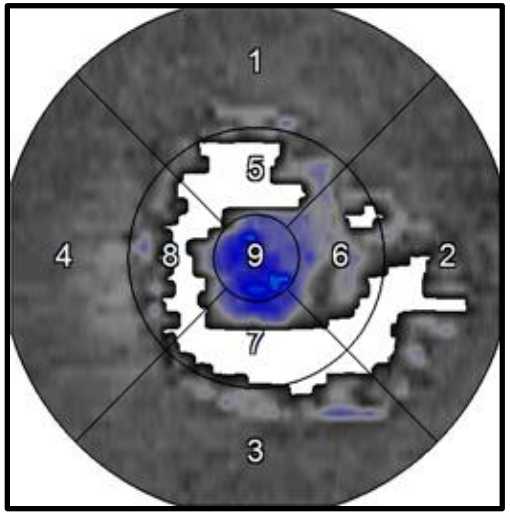
Baseline – 31.11 mm^2

Fellow Eye



Month 12 – 30.09 mm^2

➡



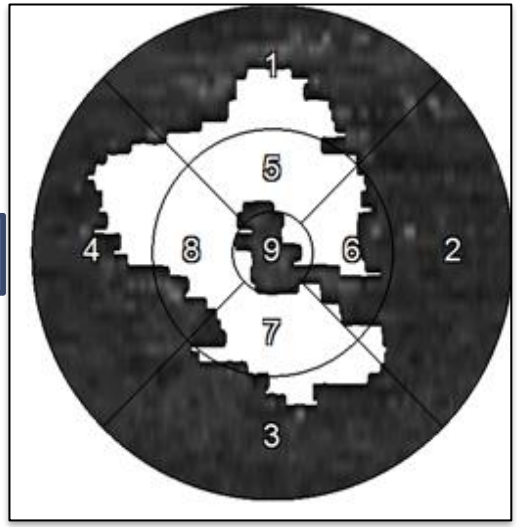
Increased RPE + Drusen Complex – Area (mm^2) (preserved area)

Patient #14, First case of potential restoration

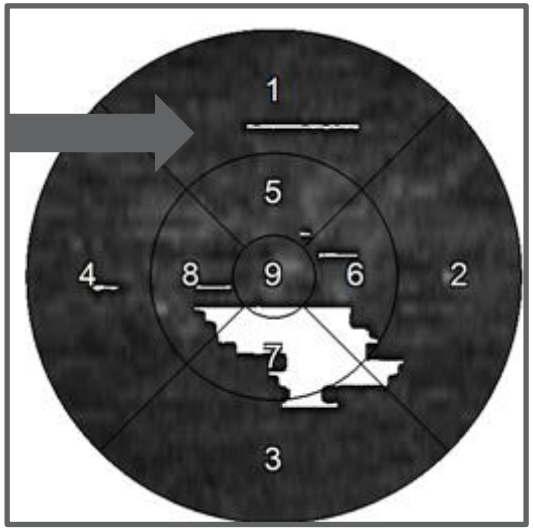
Increased RPE + drusen complex area in study eye at Month 12

Study Eye

Baseline – 31.85 mm^2

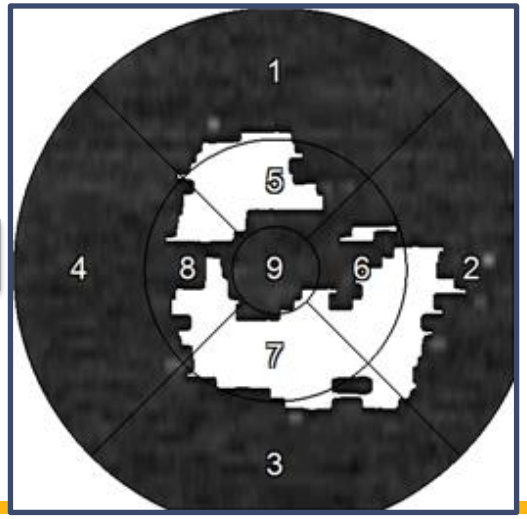


Month 12 – 37.59 mm^2

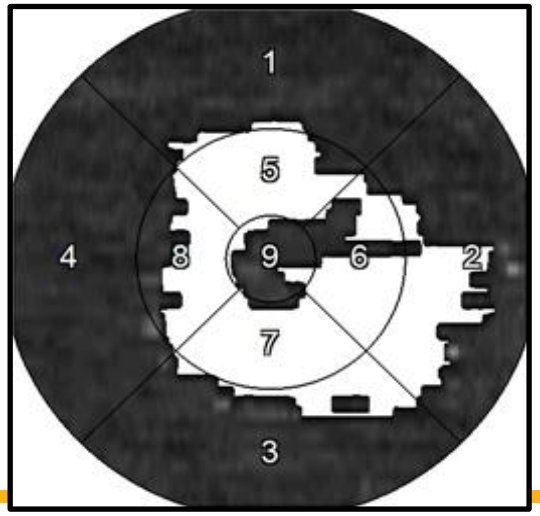


Baseline – 28.66 mm^2

Fellow Eye



Month 12 – 26.26 mm^2



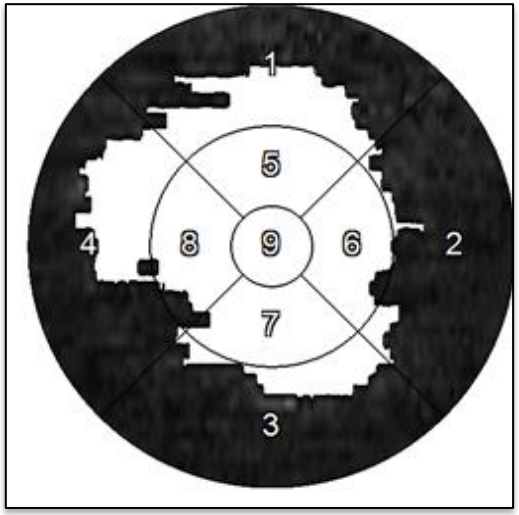
DOHENY EYE INSTITUTE | UCLA Stein Eye Institute

Photoreceptor Outer Segments – Area (mm^2) (preserved area)

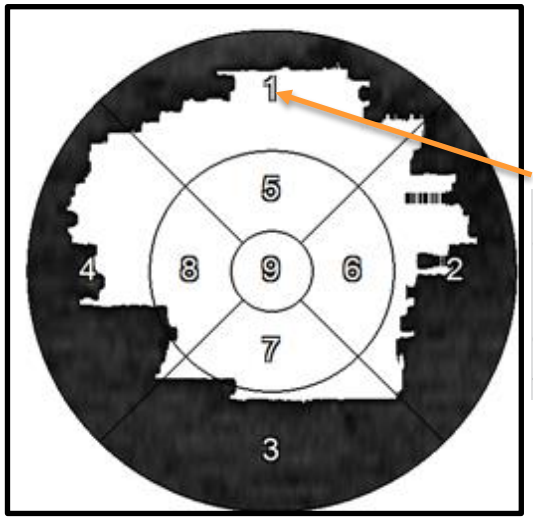
Patient #14, First case of potential restoration

Baseline – 28.47mm^2

Study Eye



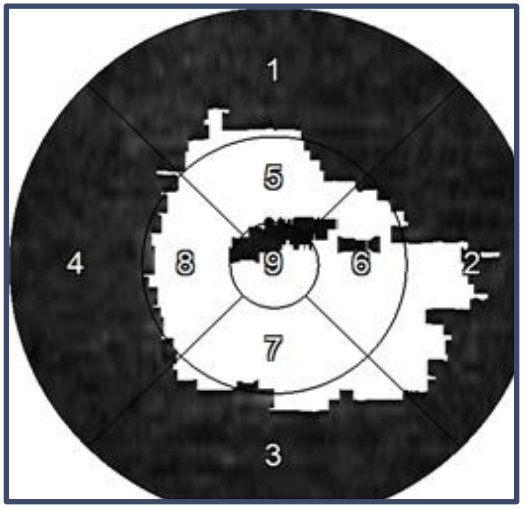
Month 12 – 25.79 mm^2



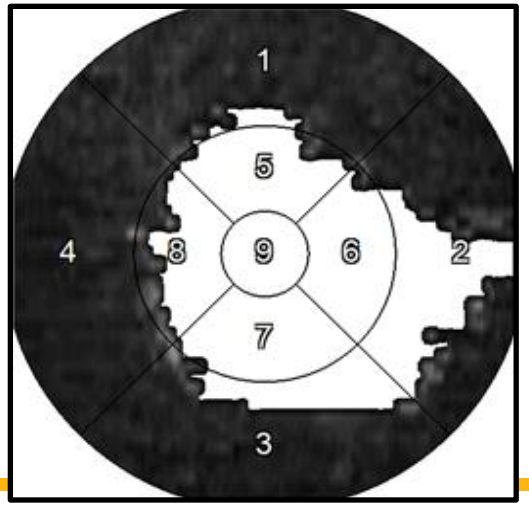
Example of areas with a loss of photoreceptor outer segments

Baseline – 25.39 mm^2

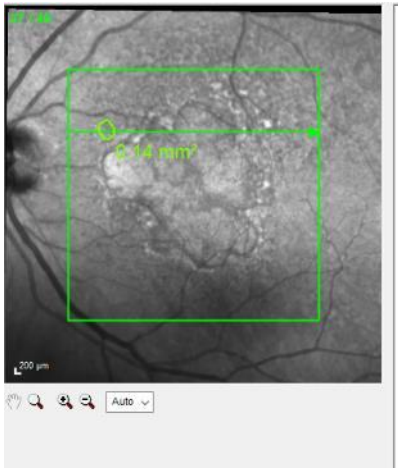
Fellow Eye

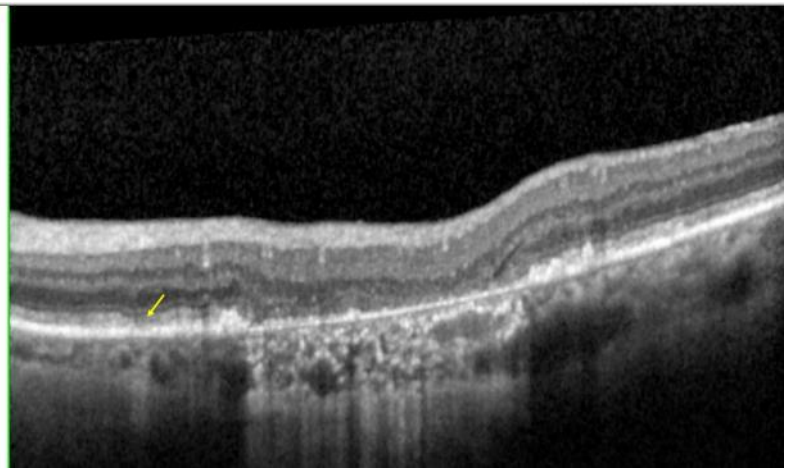


Month 12 – 24.20 mm^2

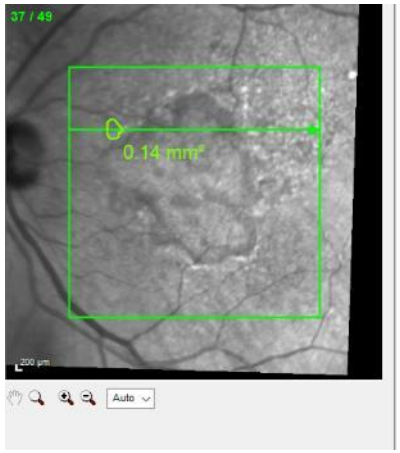


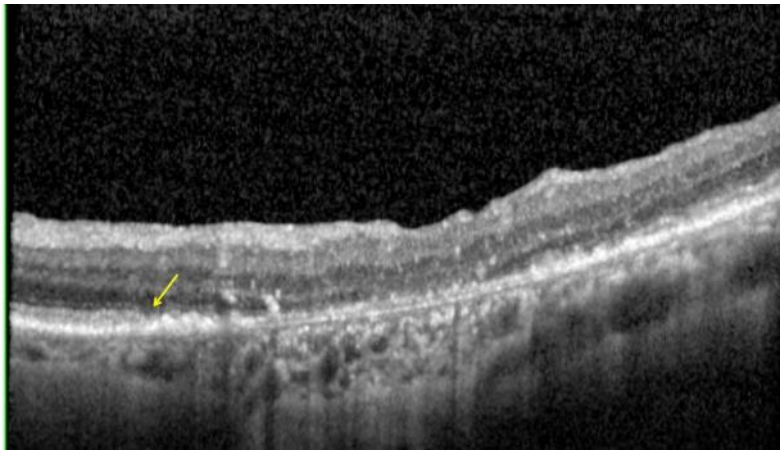
Incomplete RPE and outer retinal atrophy (iRORA)
Study eye (OS) – Patient #14, First case of restoration





Baseline





Month 12

Baseline to M12 results for Cohort 4

SD-OCT parameters in total macular volume in Fellow eye

Fellow eye at Month 12	Baseline (n = 4 eyes)	Month 12 (n = 4 eyes)	*p*
Foveal_center_retinal_thickness_Fellow_Eye	197.5 ± 83.87	146.5 ± 28.24	0.5
Sub_foveal_choroidal_thickness_Fellow_Eye	123.67 ± 44.53	112.34 ± 48.51	0.28
ONL_Area_Fellow_Eye	30.77 ± 1.8	30.5 ± 1.29	0.63
ONL_Volume_Fellow_Eye	1.77 ± 0.12	1.81 ± 0.25	0.69
ONL_Thickness_Fellow_Eye	52.97 ± 2.46	54.3 ± 7.16	0.69
IS_Area_Fellow_Eye	26.6 ± 3.98	25.16 ± 3.29	0.22
IS_Thickness_Fellow_Eye	22.94 ± 2.41	18.24 ± 2.98	0.11
IS_Volume_Fellow_Eye	0.77 ± 0.1	0.61 ± 0.1	0.11
EZ_Area_Fellow_Eye	26.13 ± 3.3	24.85 ± 3.26	**0.01**
EZ_Thickness_Fellow_Eye	13.3 ± 3.35	17.47 ± 3.99	0.15
EZ_Volume_Fellow_Eye	0.45 ± 0.13	0.58 ± 0.14	0.15
RPE+Drusen_Complex_Area_Fellow_Eye	28.33 ± 2.73	26.35 ± 2.43	**0.02**
RPE+Drusen_Complex_Thickness_Fellow_Eye	23.77 ± 3.43	22.84 ± 5.35	0.55
RPE+Drusen_Complex_Volume_Fellow_Eye	0.8 ± 0.14	0.76 ± 0.18	0.3

Note: Statistical analyses showed significant worsening when comparing values at Baseline to Month 12 in the fellow eye

Baseline to M12 results for Cohort 4

SD-OCT parameters in total macular volume in **Study eye**

Study eye at Month 12	Baseline (n = 4 eyes)	Month 12 (n = 4 eyes)	*p*
Foveal_center_retinal_thickness_Study_Eye	188.15 ± 49.14	224.73 ± 107.71	0.47
Sub_foveal_choroidal_thickness_Study_Eye	134.5 ± 22.52	142 ± 41.28	0.72
ONL_Area_Study_Eye	33.25 ± 2.17	34.44 ± 1.39	0.15
ONL_Volume_Study_Eye	2 ± 0.11	2.08 ± 0.3	1
ONL_Thickness_Study_Eye	56.4 ± 5.04	56.13 ± 10.57	0.72
IS_Area_Study_Eye	27.75 ± 0.78	27.78 ± 1.98	0.72
IS_Thickness_Study_Eye	19.25 ± 3.77	17.6 ± 2.42	0.47
IS_Volume_Study_Eye	0.69 ± 0.13	0.66 ± 0.1	0.47
EZ_Area_Study_Eye	26.88 ± 1.84	26.33 ± 2.36	0.47
EZ_Thickness_Study_Eye	12.45 ± 2.12	14.88 ± 2.83	0.07
EZ_Volume_Study_Eye	0.44 ± 0.08	0.55 ± 0.1	0.07
RPE+Drusen_Complex_Area_Study_Eye	29.19 ± 2.15	29.45 ± 1.8	0.47
RPE+Drusen_Complex_Thickness_Study_Eye	26.45 ± 5.48	24.15 ± 2.97	0.28
RPE+Drusen_Complex_Volume_Study_Eye	0.94 ± 0.19	0.9 ± 0.09	0.47

Analyses comparing values at baseline to Month 12 in the treated eye showed stability or trends towards improvement

Conclusions

- ONL preserved area increased in the study eye at Month 12 compared to baseline and fellow eye showed a decrease (patient #14)
- RPE + Drusen complex area increased in area at Month 12 when compared to baseline and fellow eye showed a decrease (patient #14)
- PRL outer segments loss is persistent at Month 12 (patient #14)
- iRORA lesion resolution in some images
- Summary findings from initial imaging analysis of Cohort 4 (better vision) showed that
  - Fellow eyes had a statistically significant reduction in EZ and RPE/drusen area (M12)
  - Study eyes had a stabilization of EZ and RPE/drusen area (M12)
- We will await
  - Longer term data and complete follow up from Cohort 4
  - Additional analyses such as iRORA lesion assessment and count

Acknowledgments

- Muneeswar Gupta Nitala
- Swetha Velaga
- Ken Marion
- Kirstie Baker
- Sowmya Srinivas
- Ayesha Karamat
- Christopher Okonkwo
- Vas Sadda, MD

LINEAGE
CELL THERAPEUTICS

AMD is the leading cause of irreversible vision loss in the US

Source: aao.org

Brian Culley, CEO

OpRegen Phase 1/2a Trial – Promising Interim Results Continue

STRUCTURE (ANATOMICAL CHANGES):

- **3 OpRegen treated patients have shown evidence of retinal tissue restoration**
  - First case restoration has been maintained for nearly 3 years
  - Reductions in drusen also occurred in some patients

FUNCTION:

- **83% of all Cohort 4 patients experienced *increased* BCVA (min 4.5mo to ~3y post-treatment)**
- **Visual acuity *declined* in 83% of untreated (contralateral) eyes**
- **Directionally-positive data collected on a) patient-reported visual function, b) reading speed, and c) microperimetry**

SAFETY and TOLERABILITY:

- **OpRegen transplants have been well tolerated with no unexpected AEs or SAEs**

DURABILITY:

- **Earliest grafts have persisted for more than 5 years with no cases of rejection (N=24)**
- **Immunosuppression has been reduced to ~90 days (less in some instances)**

LINEAGE
CELL THERAPEUTICS

AMD is the leading cause of irreversible vision loss in the US

Source: aao.org

Gary S. Hogge, SVP, Clinical and Medical Affairs
Q & A

Final Thoughts

- **OpRegen RPE is being positioned to address a multi-billion commercial opportunity in atrophic dry AMD:**
  - **Transplanting RPE cells may provide benefits unreachable by other approaches**
  - **The desired patient population is not limited to certain dysfunctional pathways; the entire cell is replaced**
  - **Treatment has been well-tolerated with some patients exhibiting positive changes consistent with the desired treatment effect**
  - **Strong commercial protections via intellectual property, cell therapy know-how, and regulatory designations**
  - **New technologies often hold opportunities for improvement, including further scale up, improved PPV delivery, safety, and/or efficacy**

OpRegen: Delivering the best cells, the best way, for the best outcomes.

LINEAGE CELL THERAPEUTICS

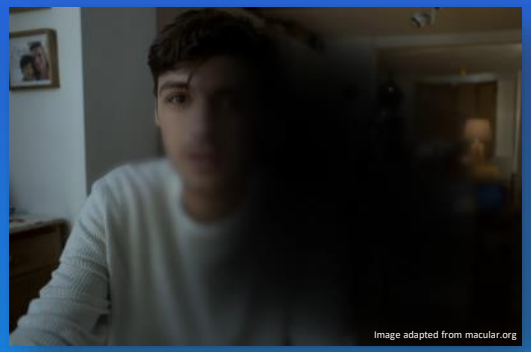
The Patients Are Our Inspiration.

View their stories at **lineagecell.com/media/#patients**

The Millions Worldwide Suffering from Dry AMD Vision Loss

"Macular degeneration is a very frustrating condition which can greatly affect your day-to-day life."

- Macular Society



Lineage would like to thank all patients and clinical personnel involved in this study.

Courtesy American Macular Degeneration Foundation, and Macular Society