

Imaging in geographic atrophy (GA)

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Disclosures

Scientific consultancy

Abbvie, Apellis Pharmaceuticals, Aviceda,
Boehringer, Complement Therapeutics,
Heidelberg Engineering, Janssen, Kodiak,
Novartis, ONL, Roche, Topcon

and research funding by institution:

Apellis, Genentech, Heidelberg Engineering,
Kodiak, Novartis, RetInSight, Roche

The Ellipsoid Zone (EZ) Has Been Suggested as a Potential Metric to Assess AMD and Connect Anatomical Structure to Functional Outcomes

Many details regarding the EZ have yet to be sufficiently established or gain consensus in the field



What is the specific anatomical location of the EZ band observed on OCT images? What does it represent?¹⁻³



What is the origin of the band's hyperreflectivity and how does it allow us to assess retinal health?³



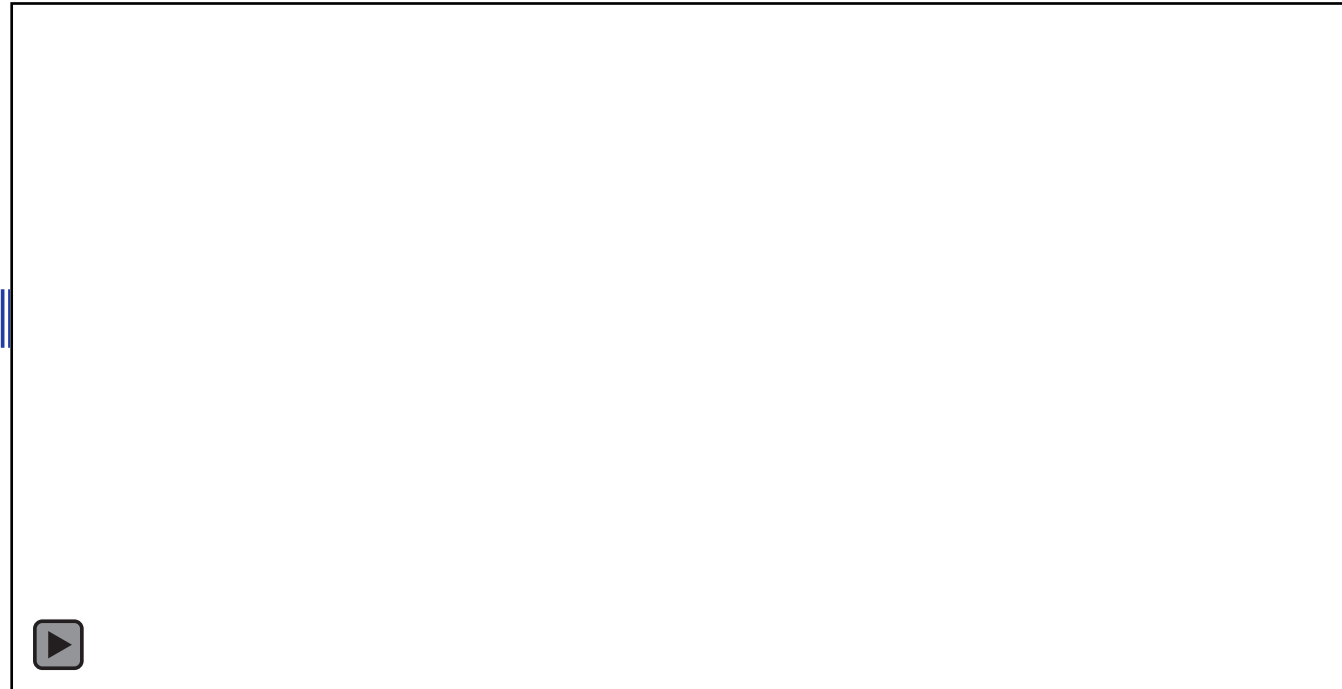
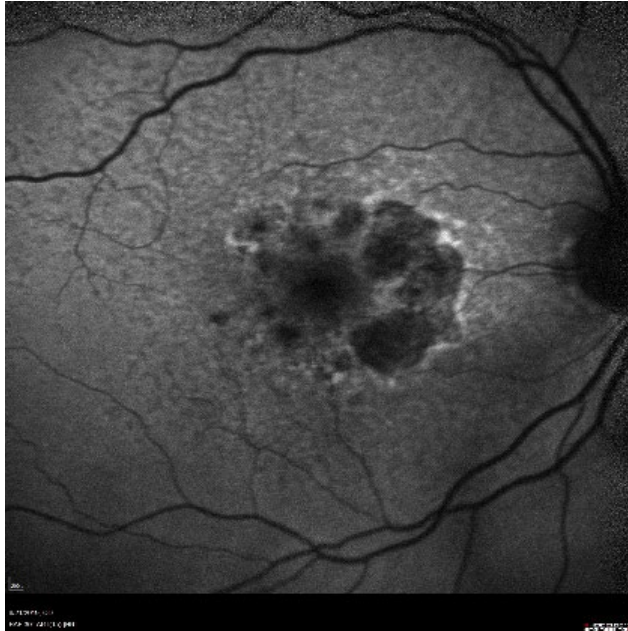
How does the EZ relate to photoreceptors? Can EZ-related metrics be used to assess photoreceptor integrity?^{1,3}



Can EZ-related metrics be used to assess all stages of AMD, including GA? Are they applicable as clinical trial endpoints?⁴

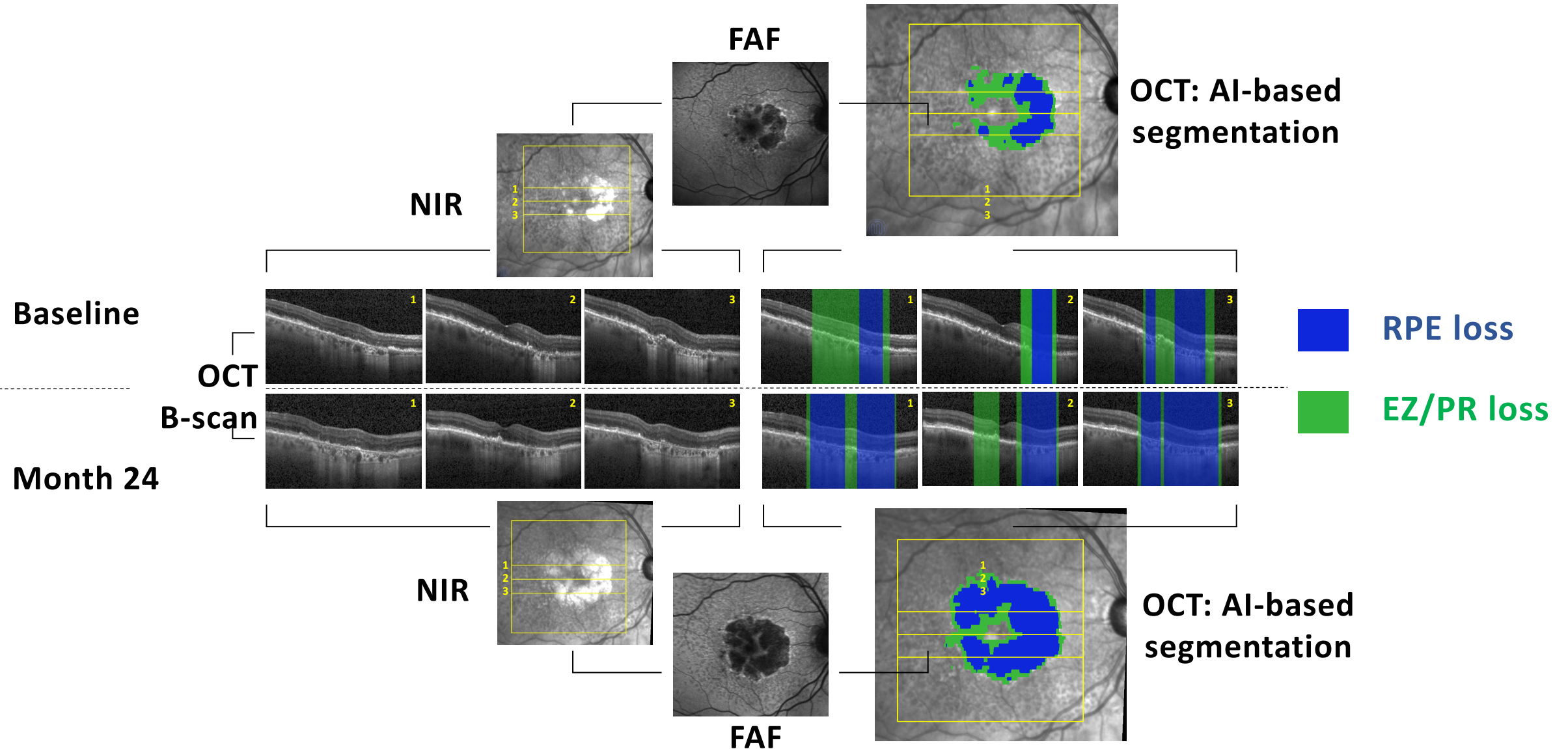
The OCT Fx Delphi Study seeks to establish a global consensus on the role of the EZ in assessing AMD and its use as a clinical trial endpoint

GA is ending with a black hole....



...only in the absence of adequate imaging!

FAF versus OCT-based AI analysis



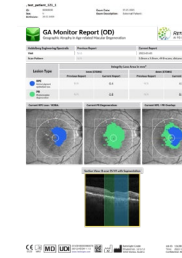
AI-POWERED OCT SEGMENTATION IN GA

EZ-Thickness EZ-layer thickness (μm) if layer is $>20\ \mu\text{m}$
measuring photoreceptors' outer segments (EZ-IB to OB-IZ)

Partial EZ-Loss Area (mm^2) if EZ-layer thickness is $<20\ \mu\text{m}$

EZ-Loss Area (m m^2) if EZ-layer is absent

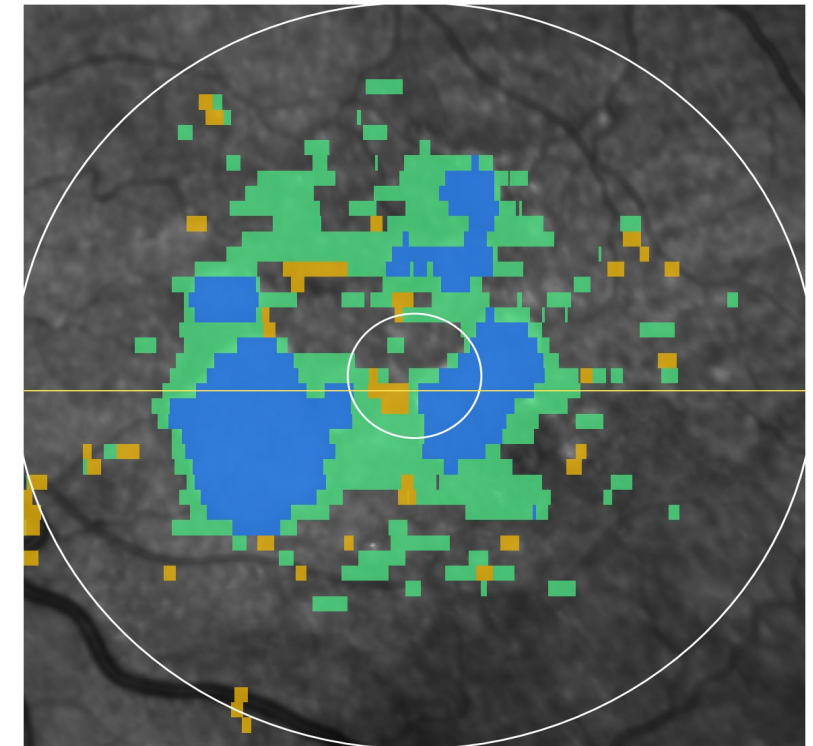
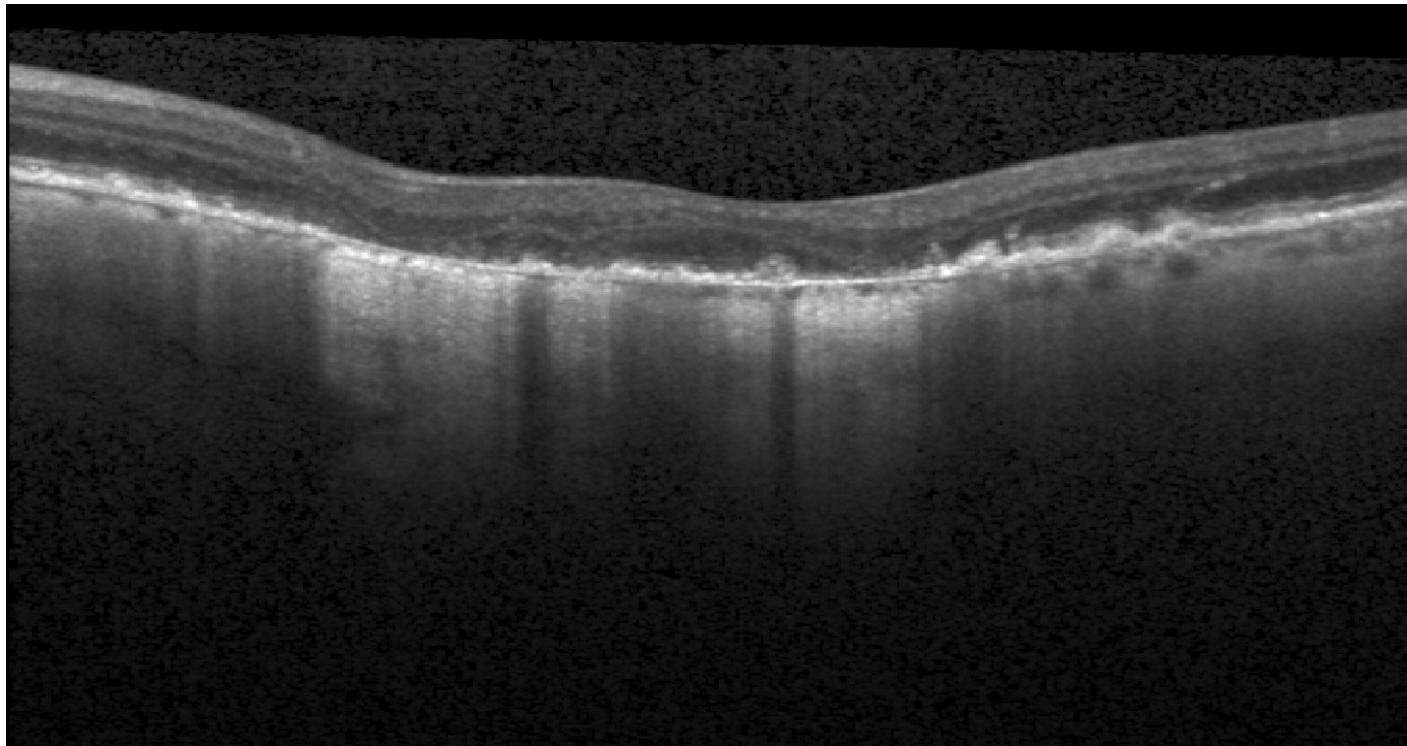
RPE-Loss Area (m m^2) if RPE loss is complete



RETINSIGHT
GA•Monitor

US: Investigational use only.

EU: MDR approval for clinical routine.



EZ layer

EZ partial loss

EZ loss

RPE loss

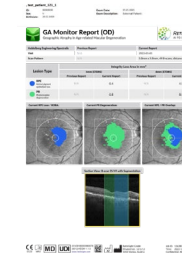
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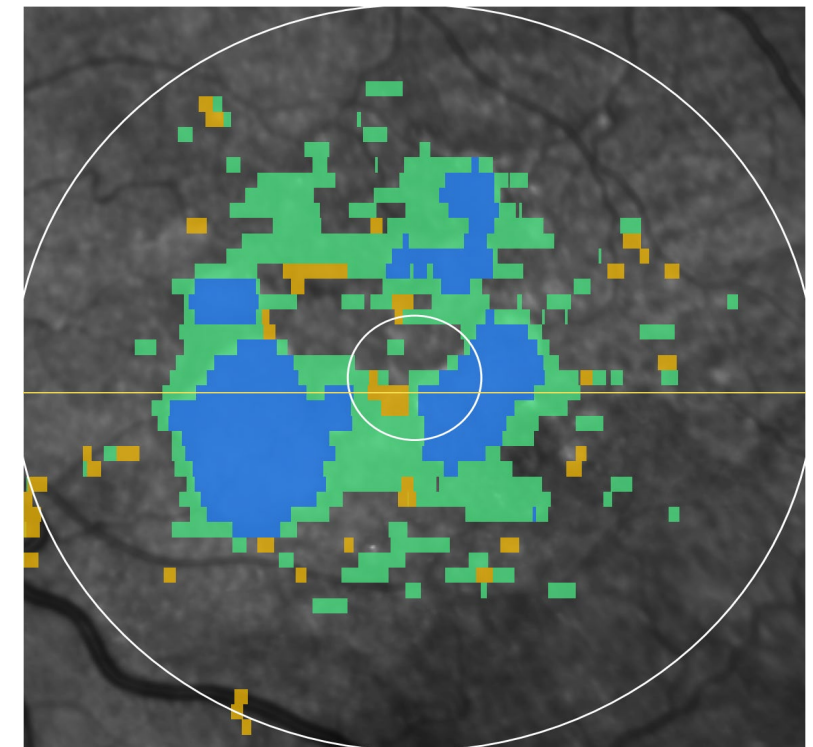
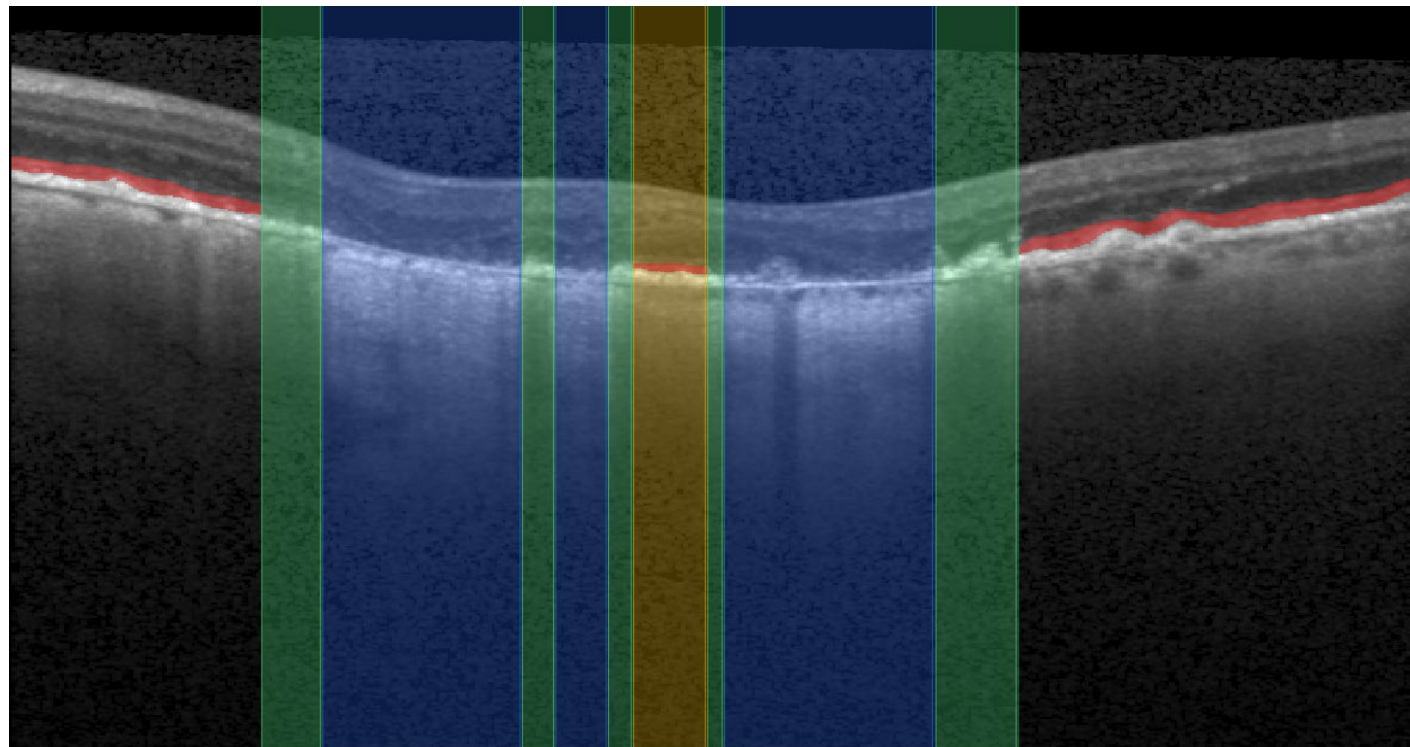
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EZ layer

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EZ loss

RPE loss

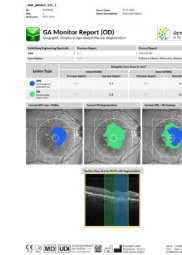
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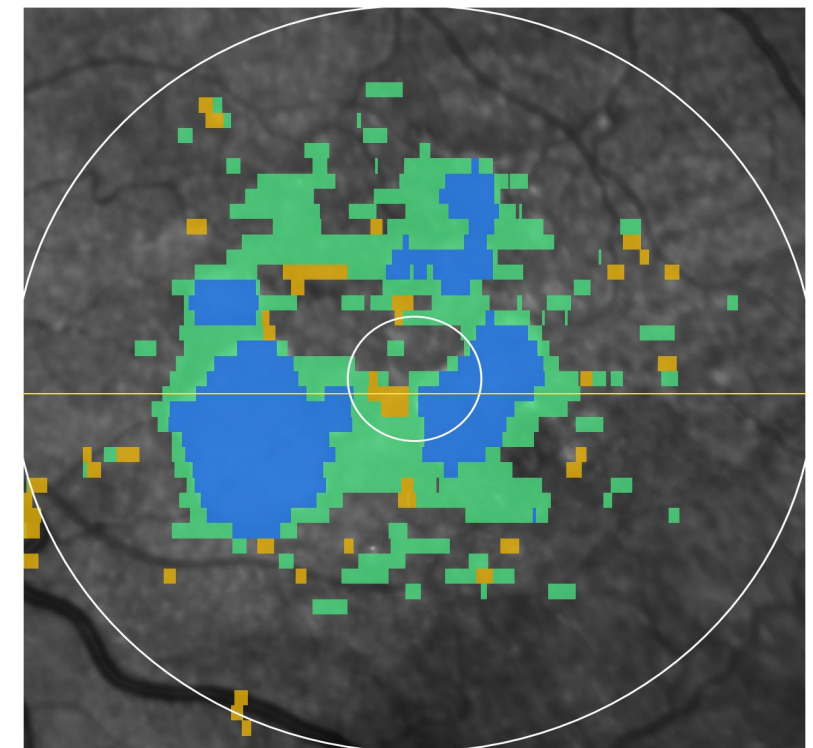
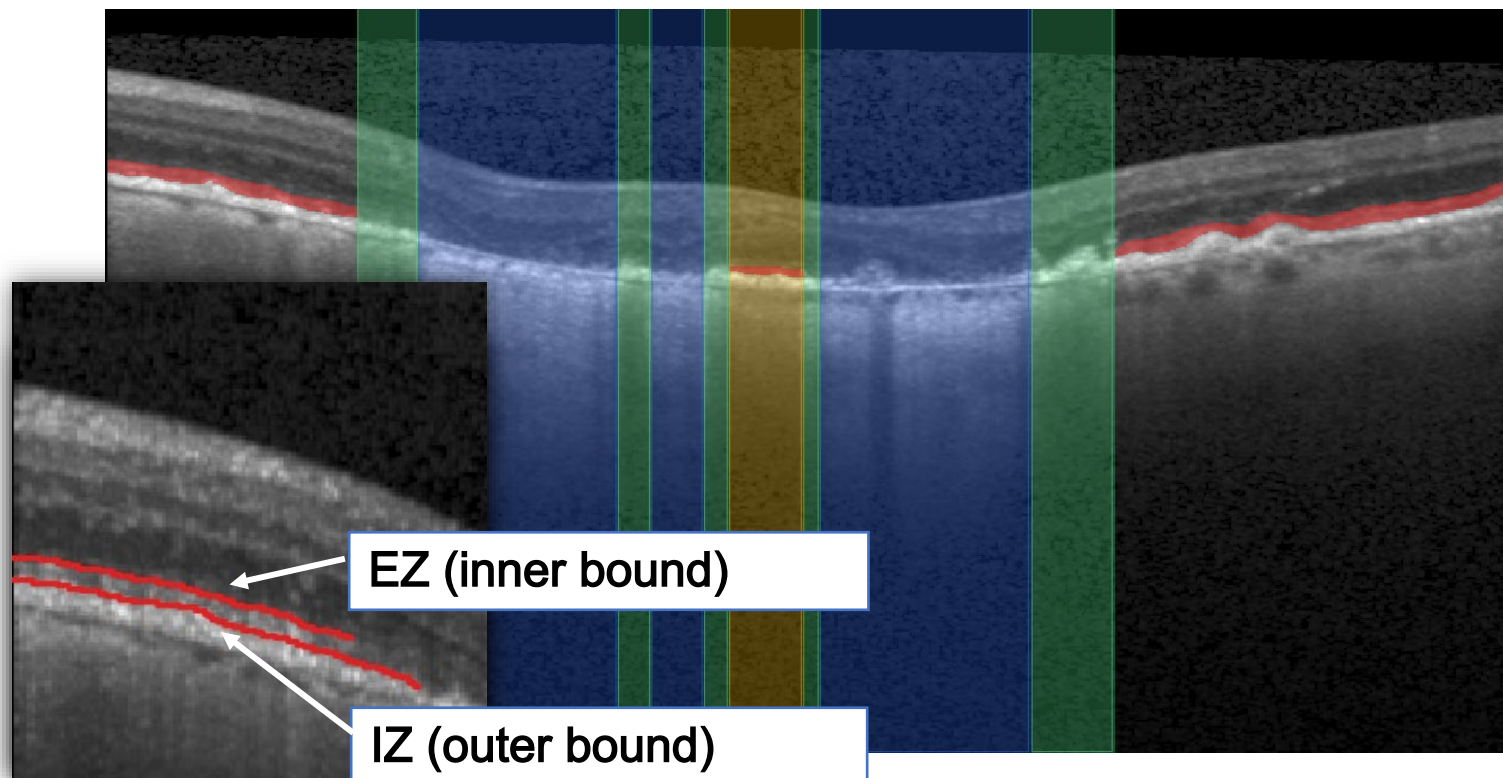
RPE-Loss Area (mm^2) if RPE loss is complete



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EZ layer

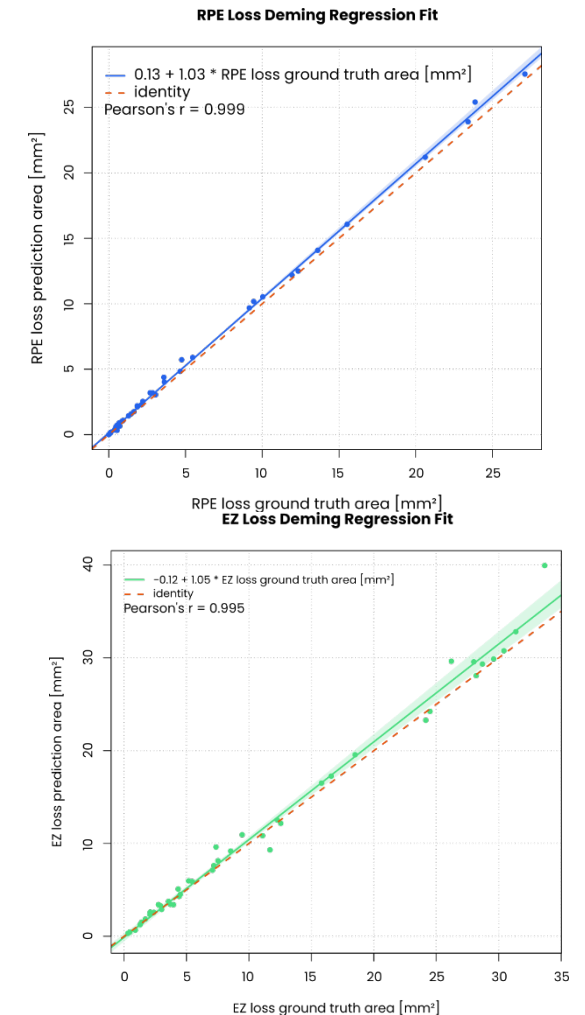
EZ partial loss

EZ loss

RPE loss

Precision level of EZ/RPE segmentation

Biomarker	Dataset	# Patients / eyes /volumes	Enface DICE $\pm$ SE	ENFACE Mean HD95 $\pm$ SE	Mean Absolute Error $\pm$ SE
RPE loss	Validation	43	0.89 $\pm$ 0.07	0.32 $\pm$ 0.31	0.30 $\pm$ 0.30 mm²
RPE loss	Pool 2.5 to 17.5 mm ²	32 / 32 / 41	0.93 $\pm$ 0.05	0.25 $\pm$ 0.18	0.12 $\pm$ 0.09 mm ²
EZ loss	Validation	43	0.86 $\pm$ 0.09	0.33 $\pm$ 0.28	0.75 $\pm$ 1.11 mm²
EZ loss	Pool 2.5 to 17.5 mm ²	32 / 32 / 41	0.93 $\pm$ 0.03	0.39 $\pm$ 0.21	0.15 $\pm$ 0.09 mm ²
EZ-Thickness	Development set test fold	26 / 27 / 36			1.57 $\pm$ 1.16 μm



High correlation between human and AI measurements ($r \geq .995$).

Absolute mean difference of RPE loss lesion size: 0.5 mm²

EZ thickness: mean absolute error 1.57 μ m, i.e. less than one pixel (~3.9 μ m):

Subpixel accuracy

Early conversion features



Prediction of early conversion

- ONL and photoreceptor thinning precede conversion
- Focal changes are identifiable > 12 months before clinical event

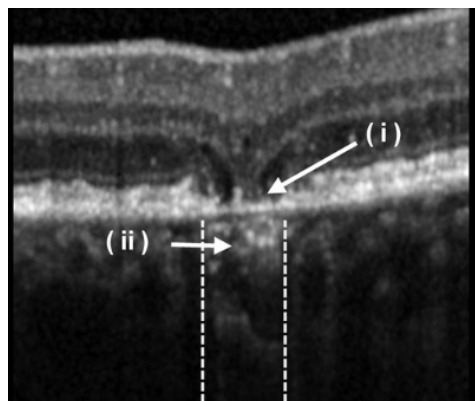


OPEN ACCESS

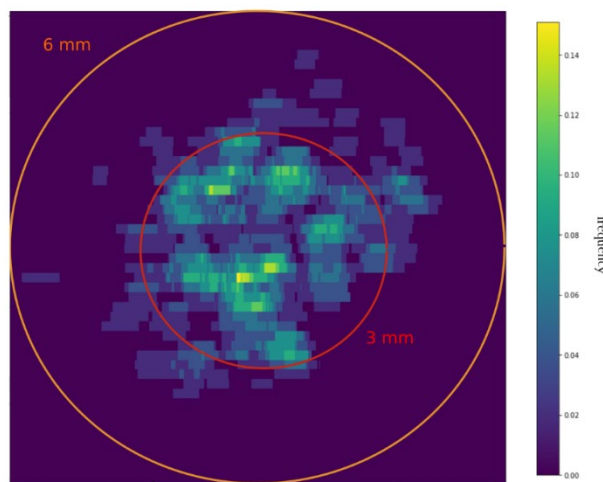
Retina | July 2018

Prediction of Individual Disease Conversion in Early AMD Using Artificial Intelligence

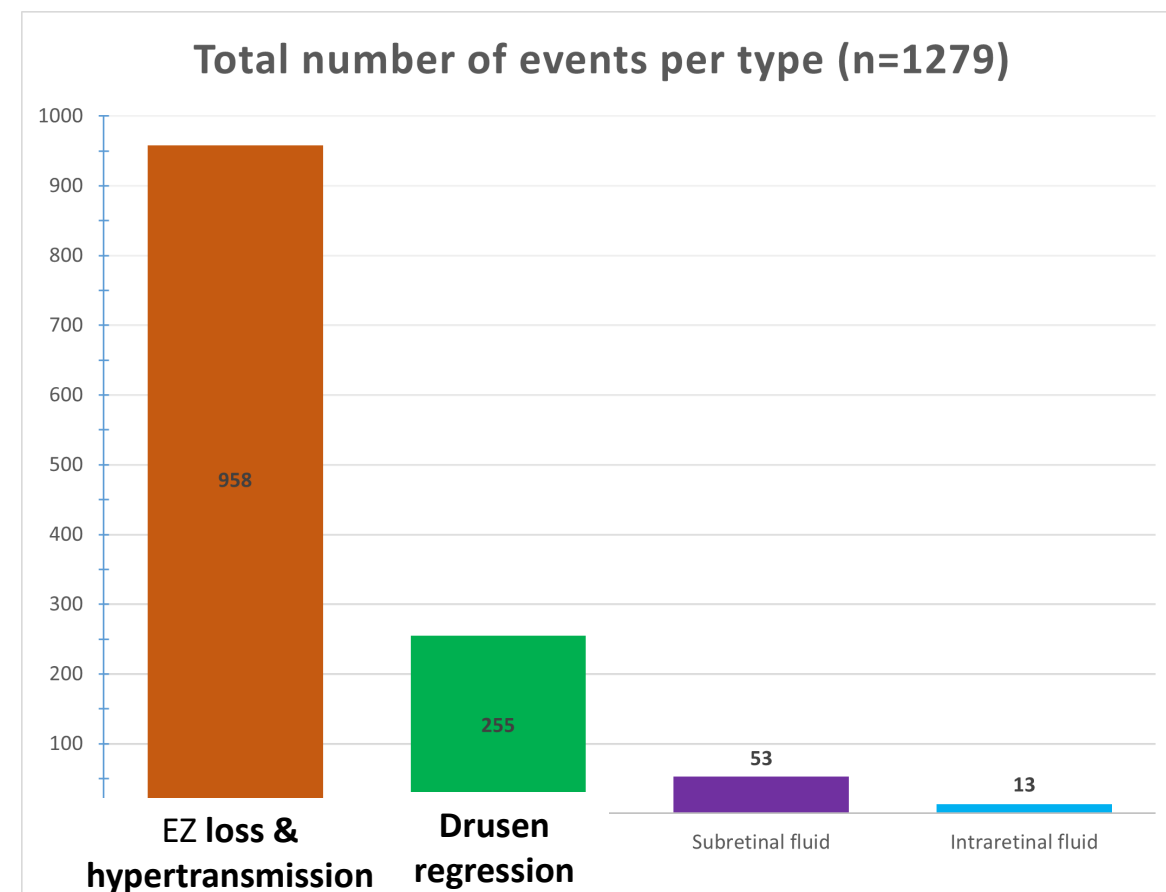
Ursula Schmidt-Erfurth; Sebastian M. Waldstein; Sophie Klimscha; Amir Sadeghipour; Xiaofeng Hu; Bianca S. Gerendas; Aaron Osborne; Hrvoje Bogunović



Example of INL/OPL subsidence



En-face topographic distribution of INL/OPL subsidence



Results



OCT images from 546
eyes of 426 patients

Excluded due to nAMD: 60 eyes of 57 patients
(based on eCRF data provided)

**Converters
to cRORA**

**76 eyes of 74 patients
developed cRORA**
[Age(years): 76.2 ± 7.0 , 64% female]

Non-converters

**410 eyes of 321 patients did not
progress to late AMD**
[Age(years): 74.2 ± 8.1 , 59% female]

**Secondary analysis
iRORA**

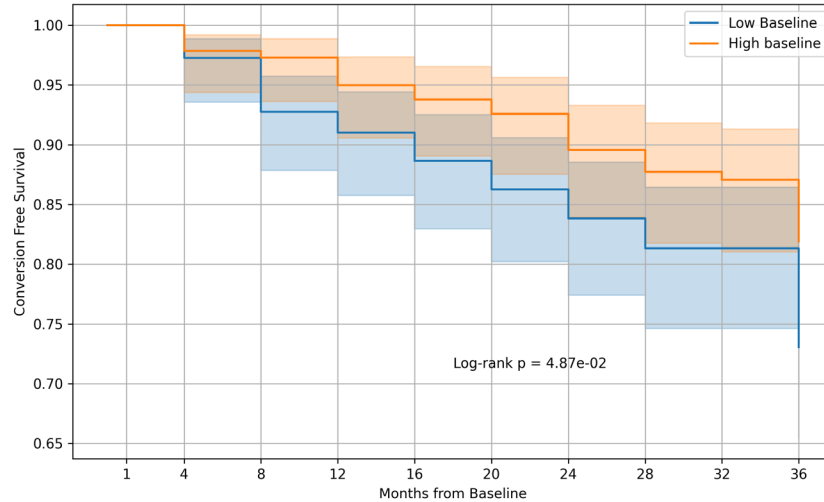
**95 eyes of 89 patients had an
EZL+HT focal event, but did
NOT develop cRORA**

Mean follow-up time: 32 months

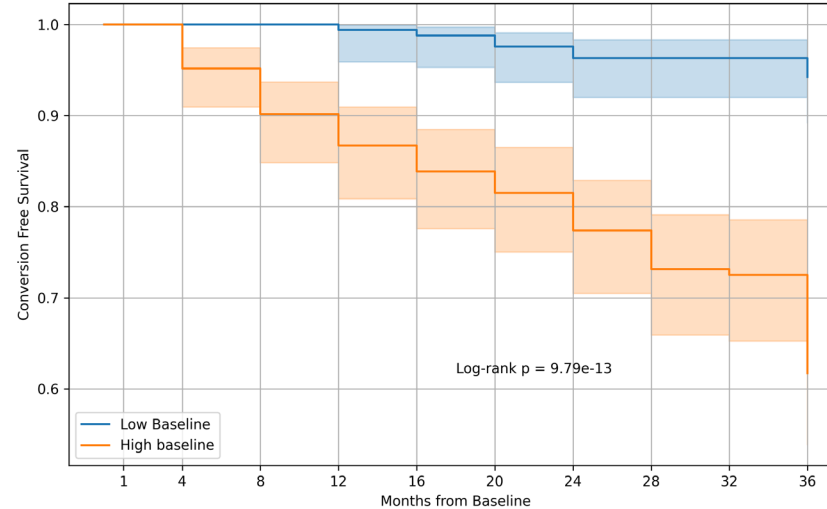
81% of eyes completed full 36 month observation period

Survival analysis based on baseline morphology/imaging

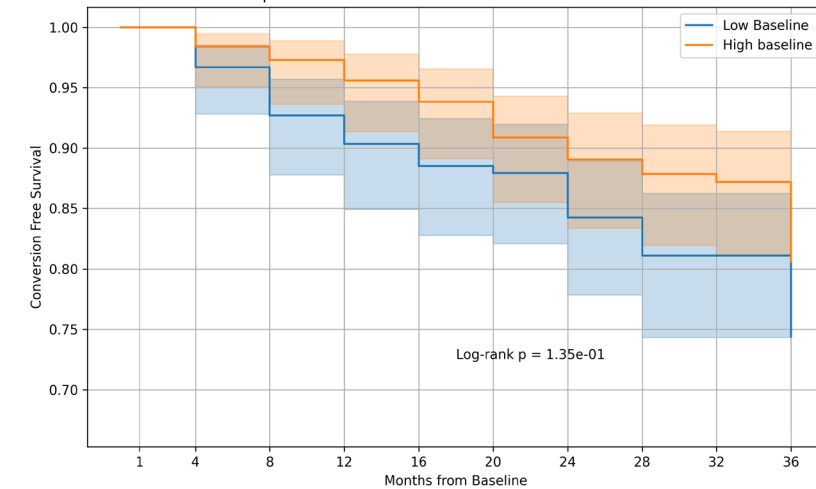
High vs Low EZ Thickness



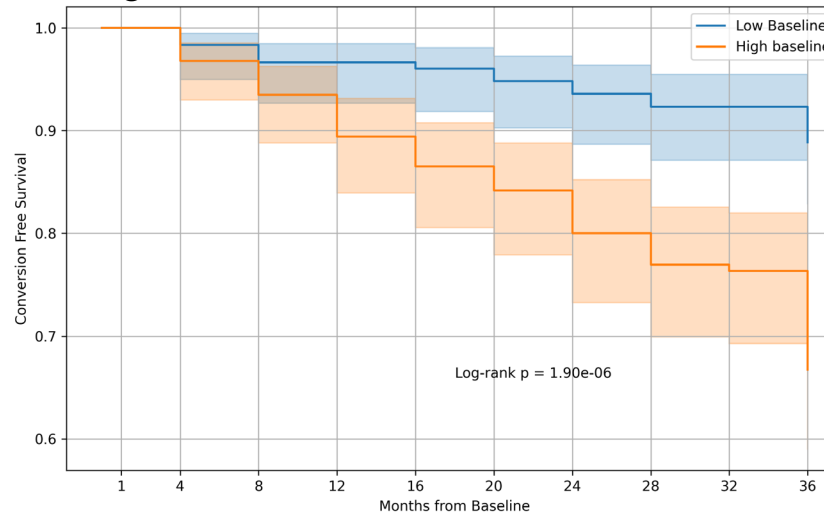
High vs Low EZ Loss Area



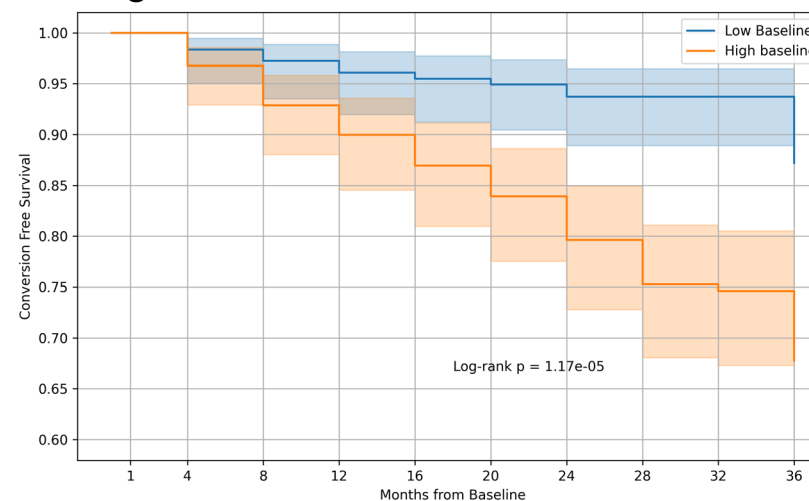
(High vs Low ONL Thickness)



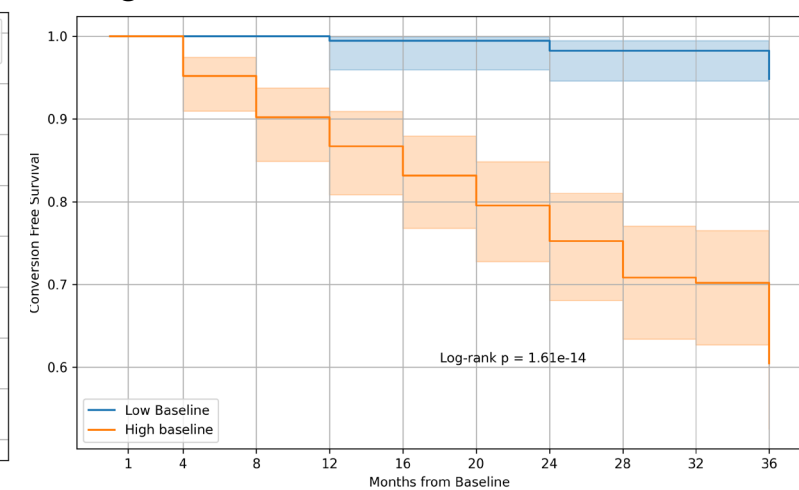
High vs Low Drusen volume



High vs Low RPD area

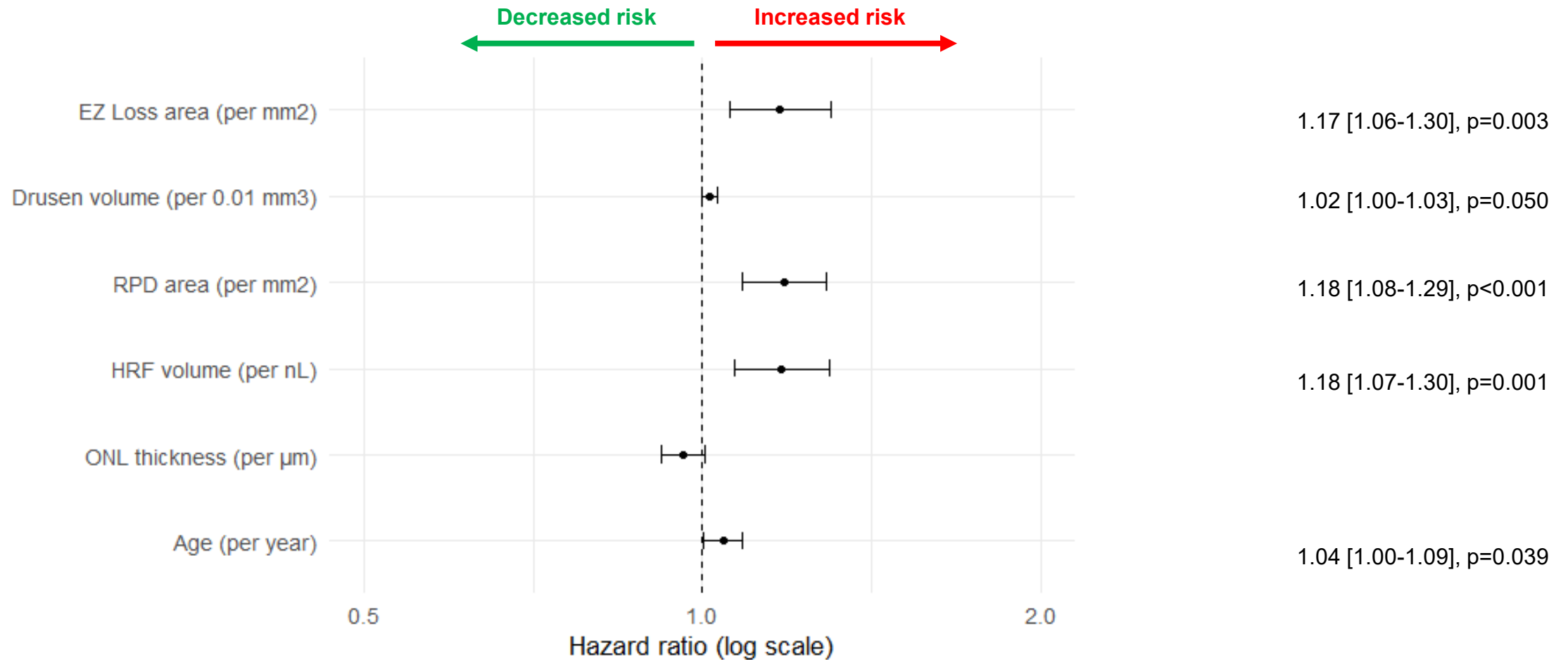


High vs Low HRF volume



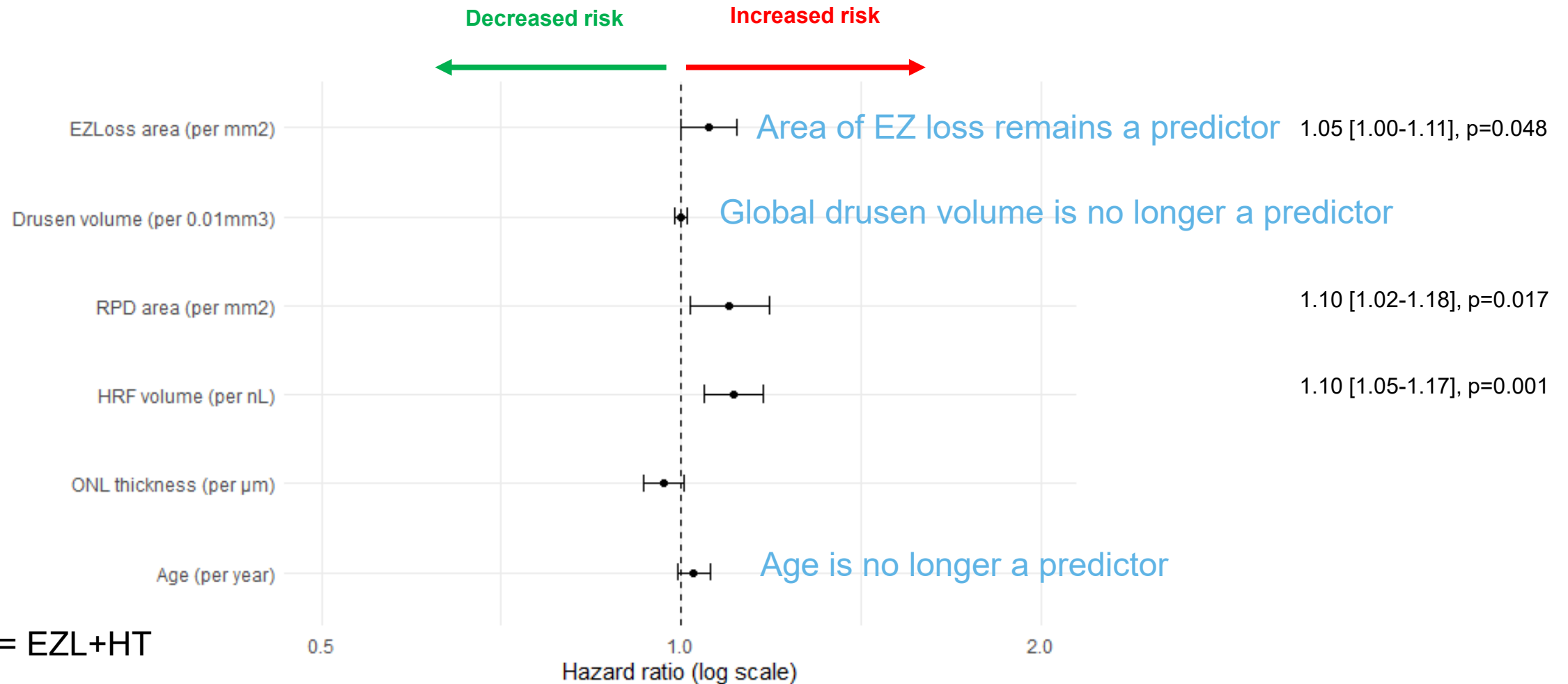
Role of baseline morphology to first event

(multivariate Cox hazard model)



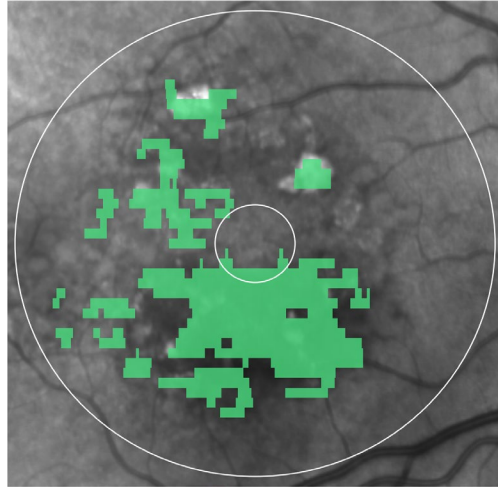
Role of morphology beyond the time of a focal event

Imaging biomarkers are phase-sensitive

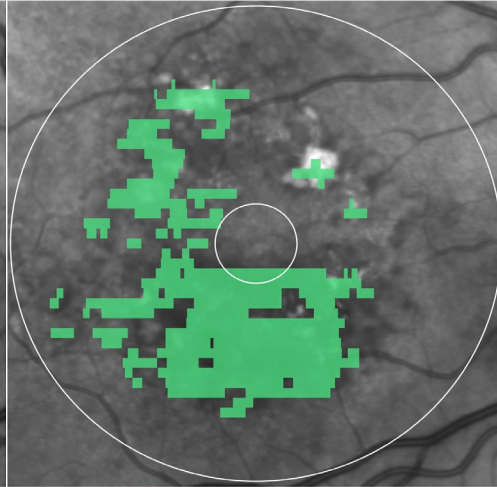


EZ loss consistently precedes RPE loss

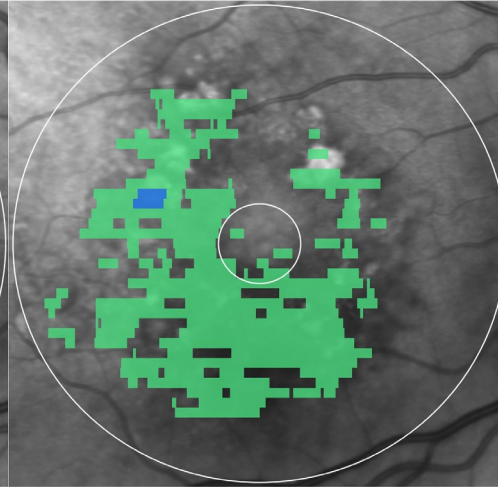
0 Month



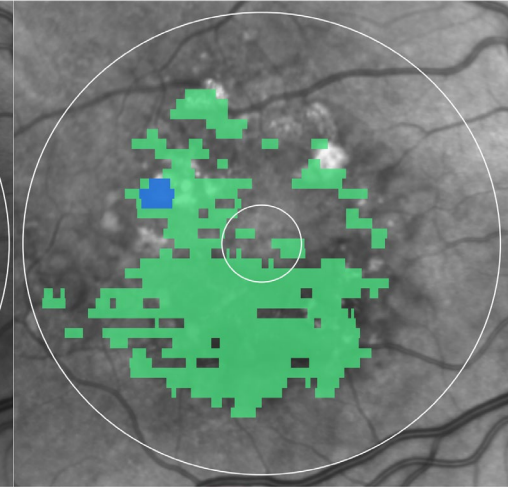
6 Month



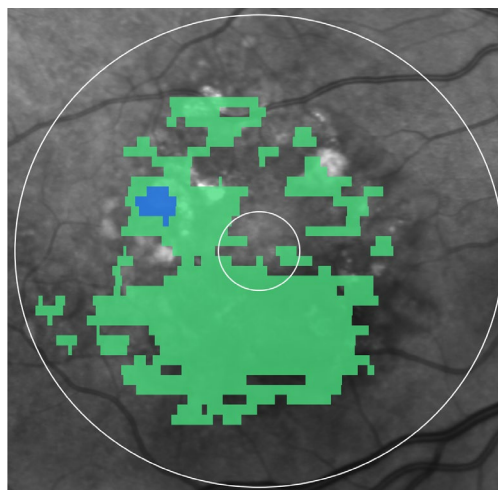
12 Month



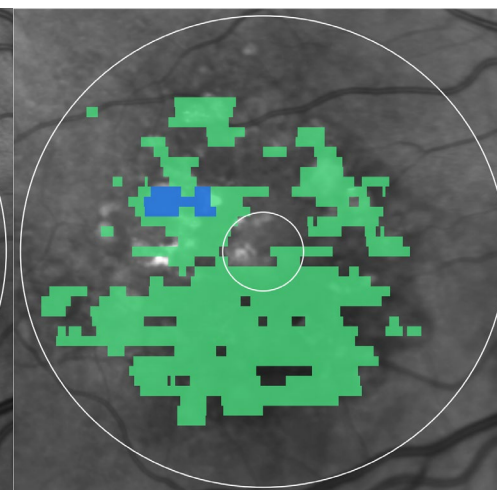
18 Month



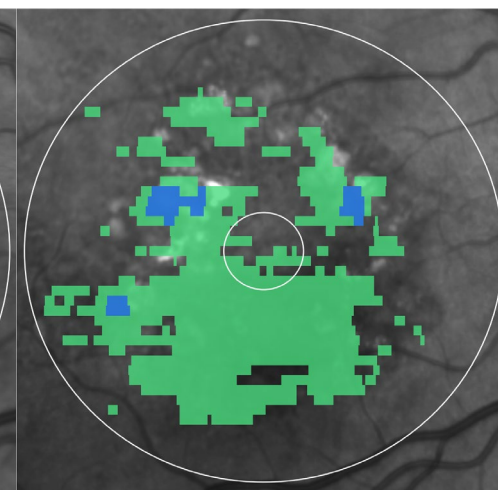
24 Month



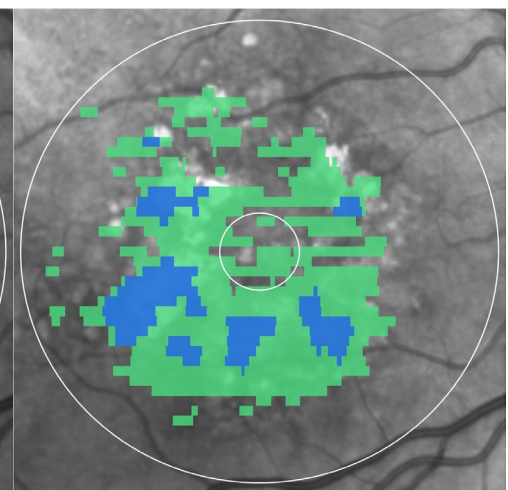
30 Month



36 Month



42 Month



Monitoring structural progression

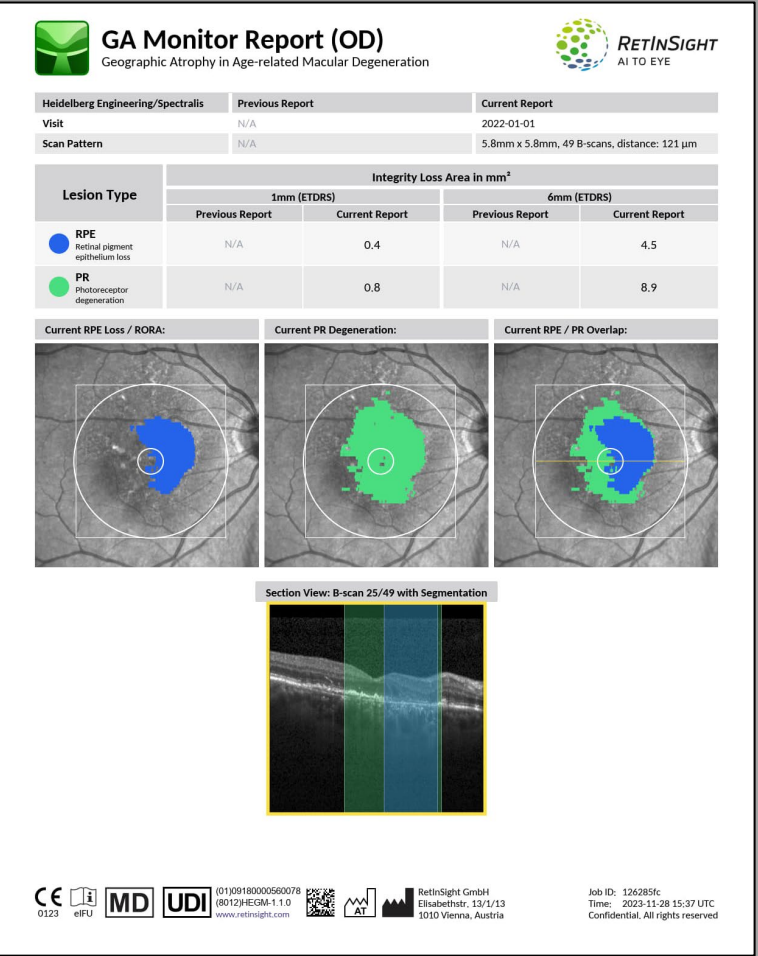


RPE and EZ loss quantification by a mouse click

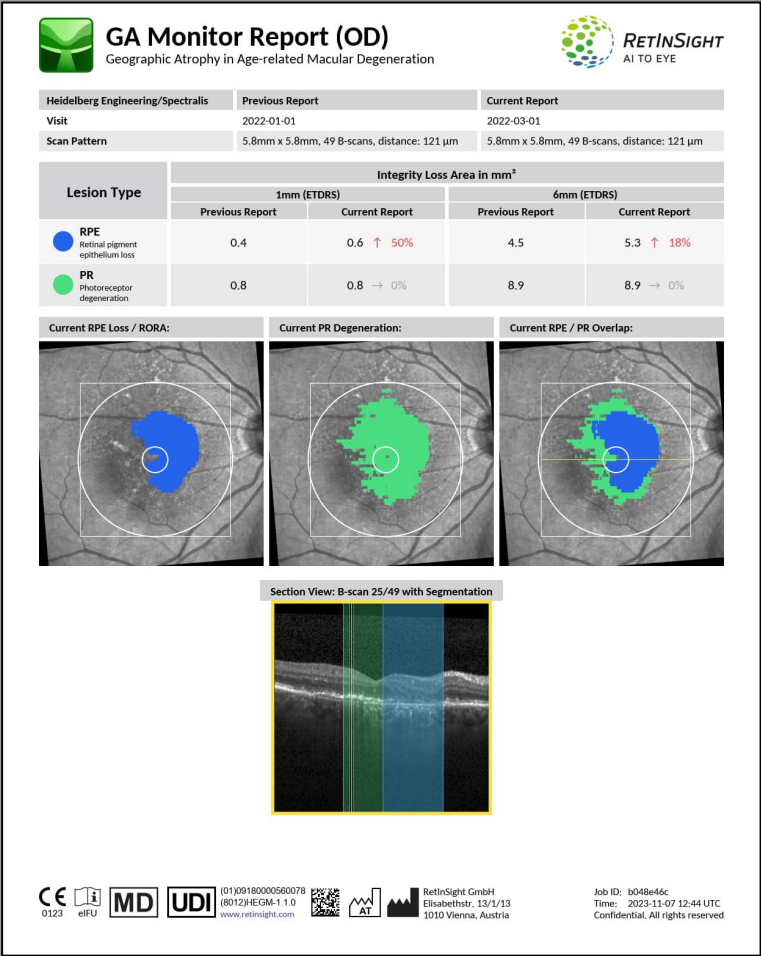


GA monitoring: Visualization and quantification

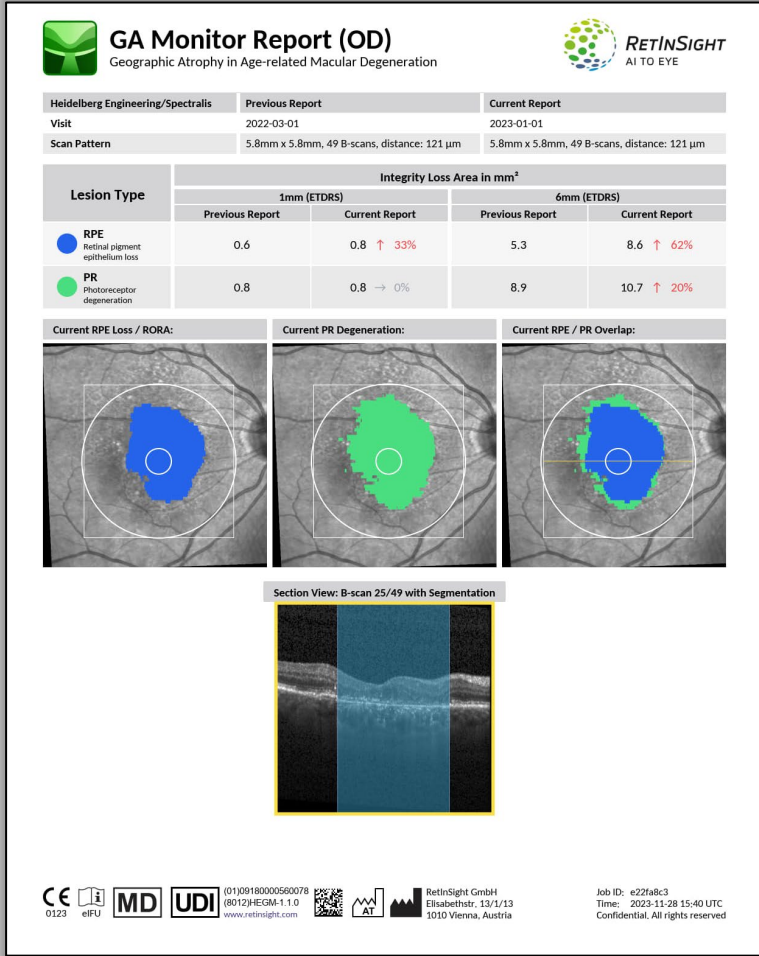
Baseline



Month 2

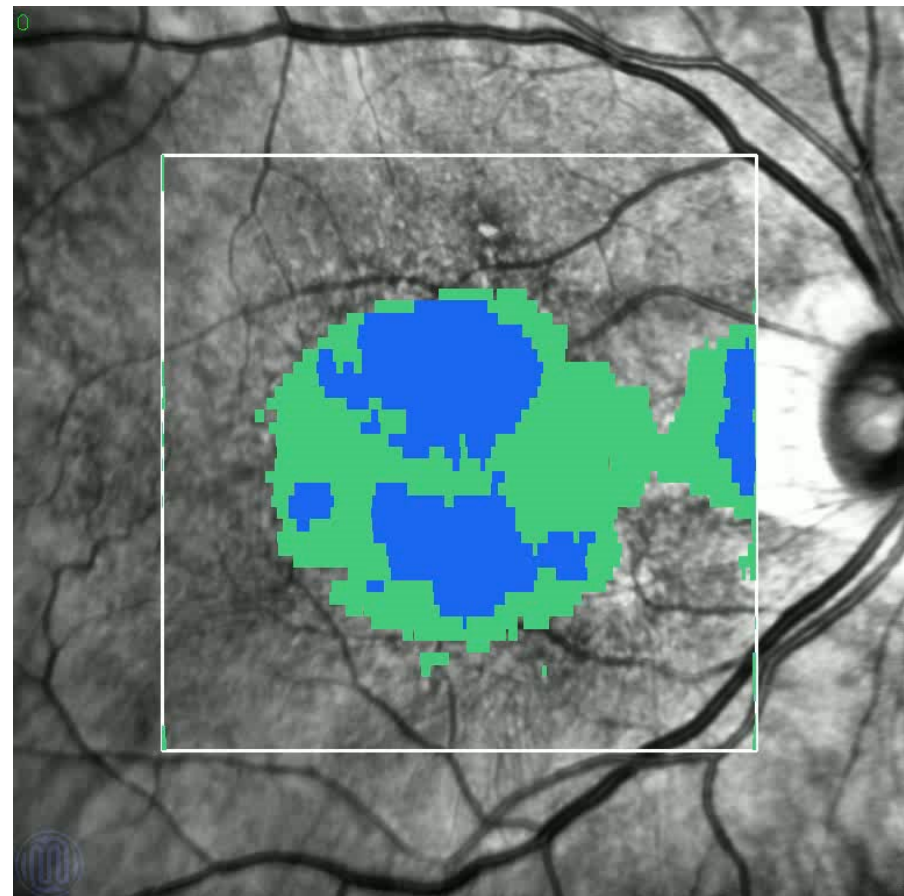
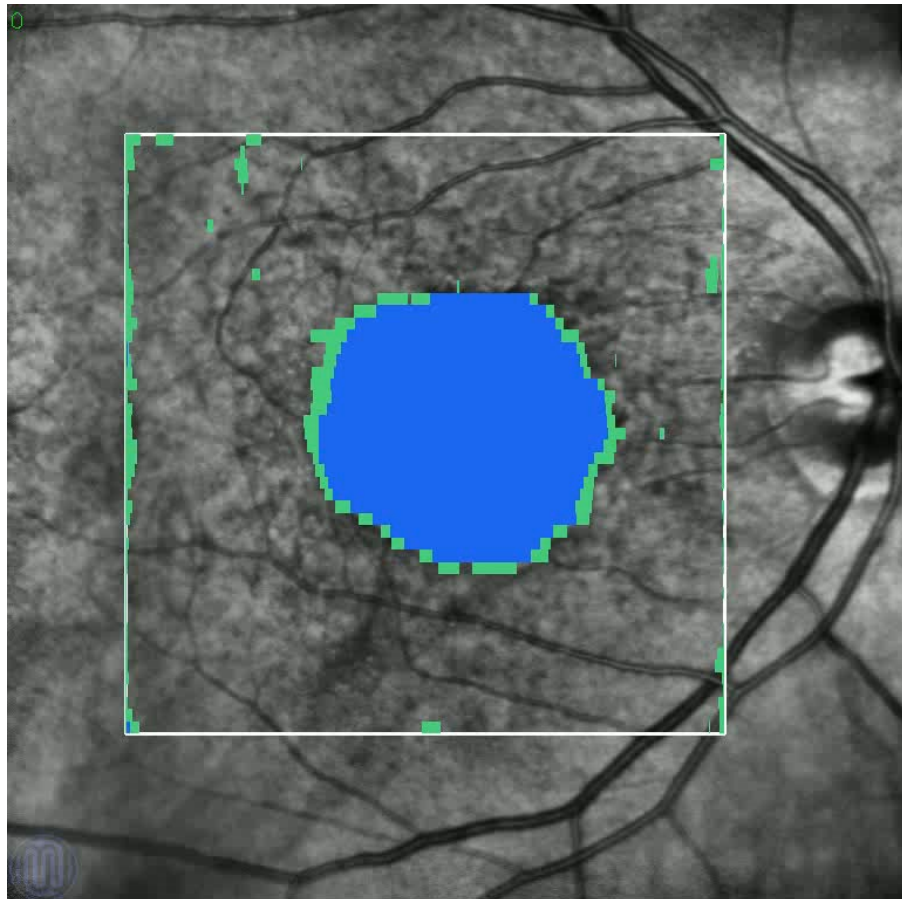


Month 12



Disease activity in GA depends on EZ/RPE ratio

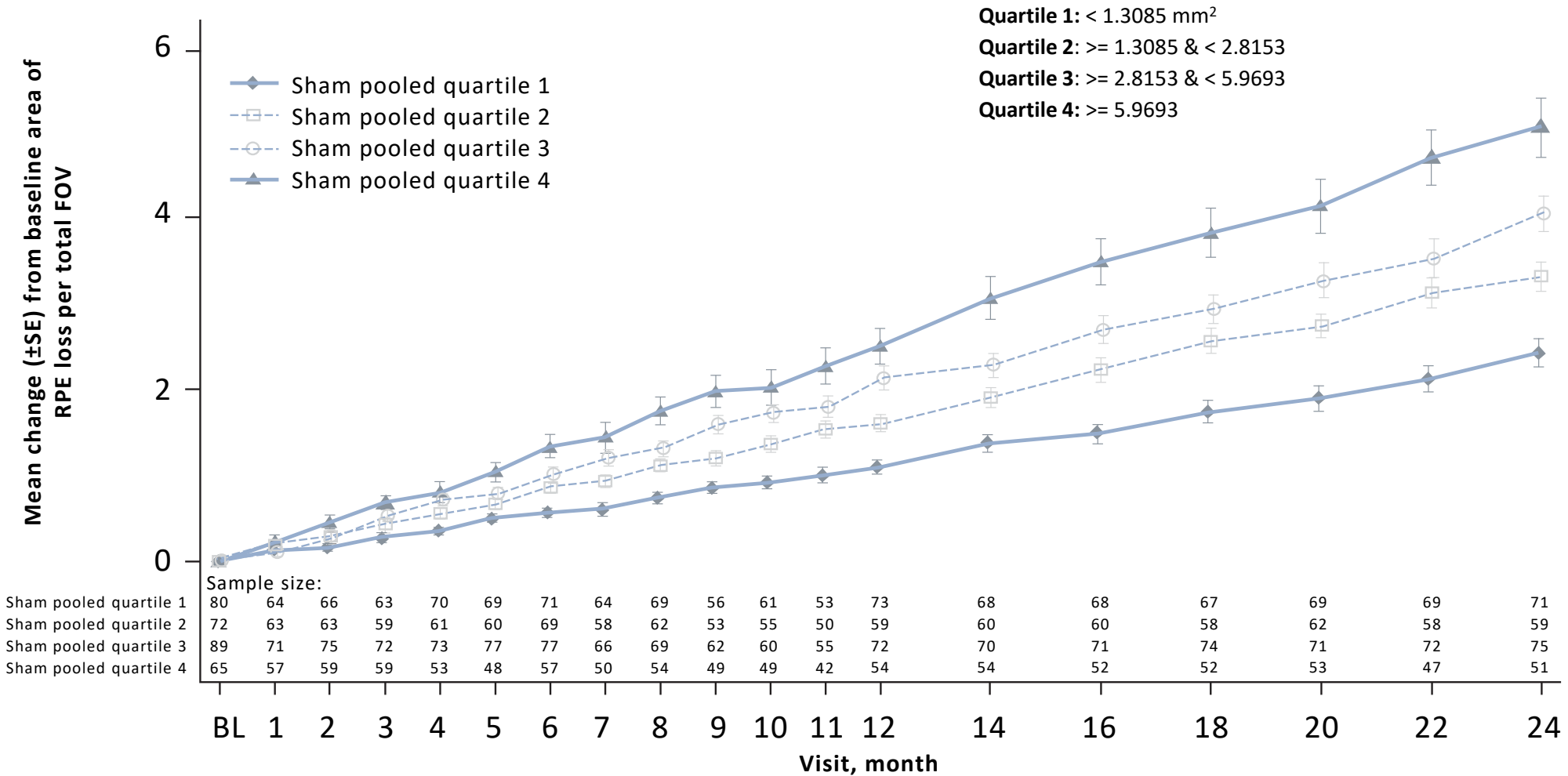
Ratio allows to differentiate fast vs slow progressors



 RPE loss  EZ loss

Disease activity is predicted by EZ/RPE ratio

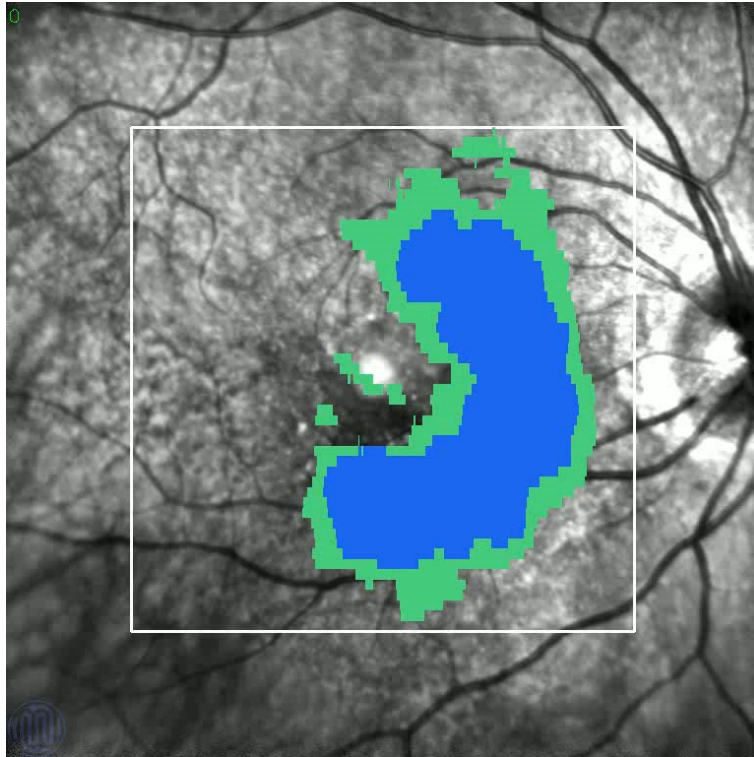
GA lesion progression by quartiles in sham arms



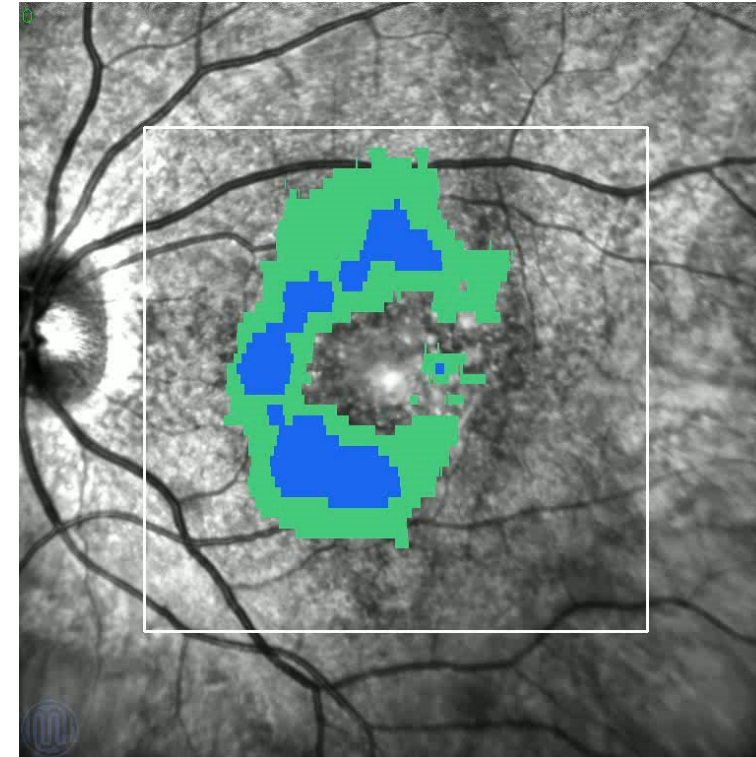
FOV, field of vision; PR, photoreceptor; RPE, retinal pigmented epithelium; SE, standard error.

Complement-inhibition reduces the speed of progression

Fellow eye



Study eye



Follow-up over 2 years in the same patient



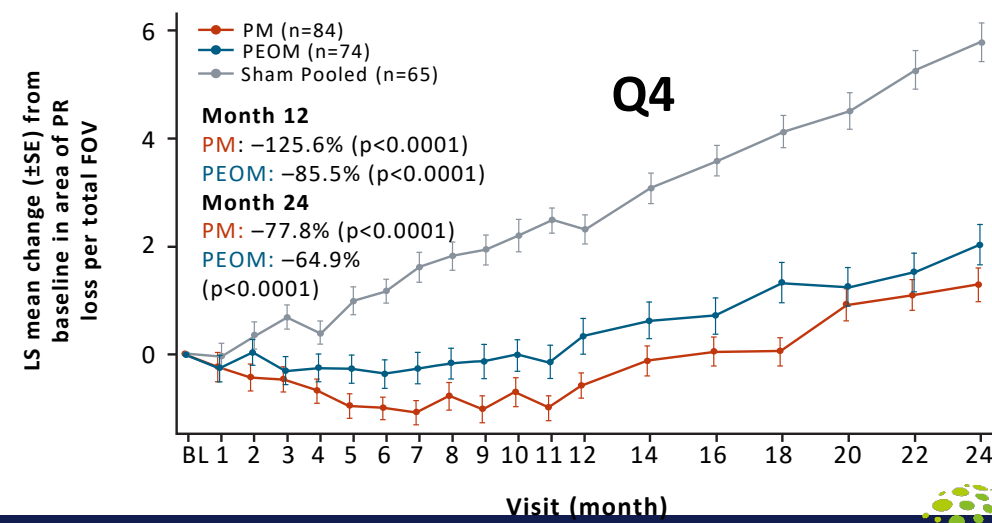
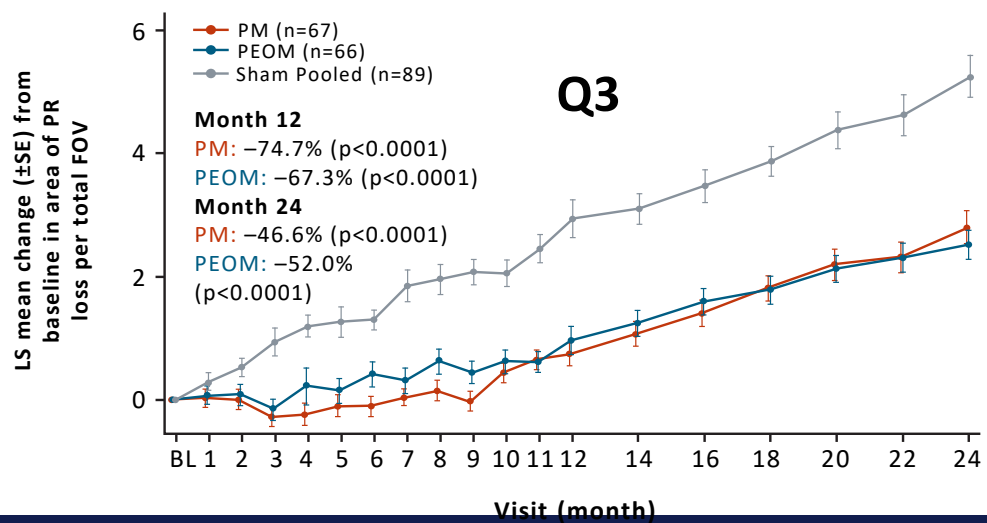
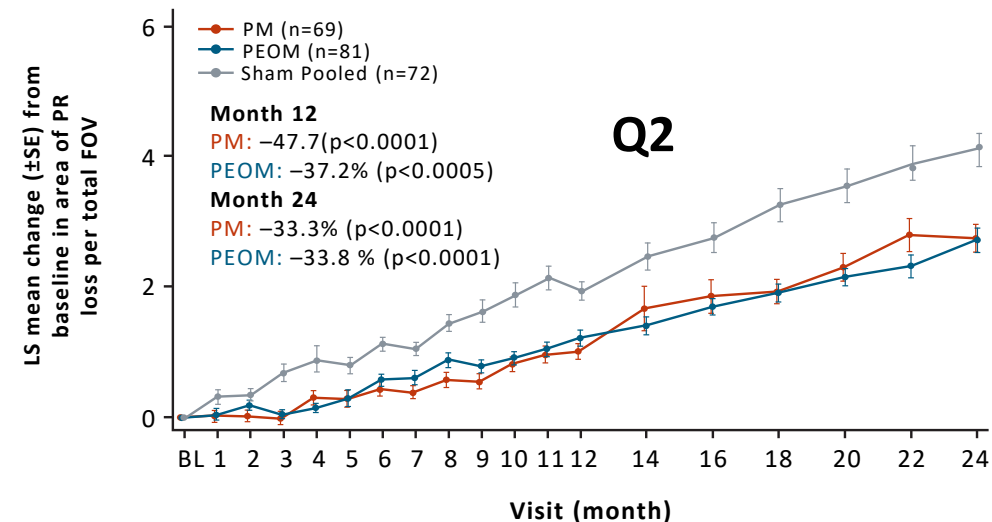
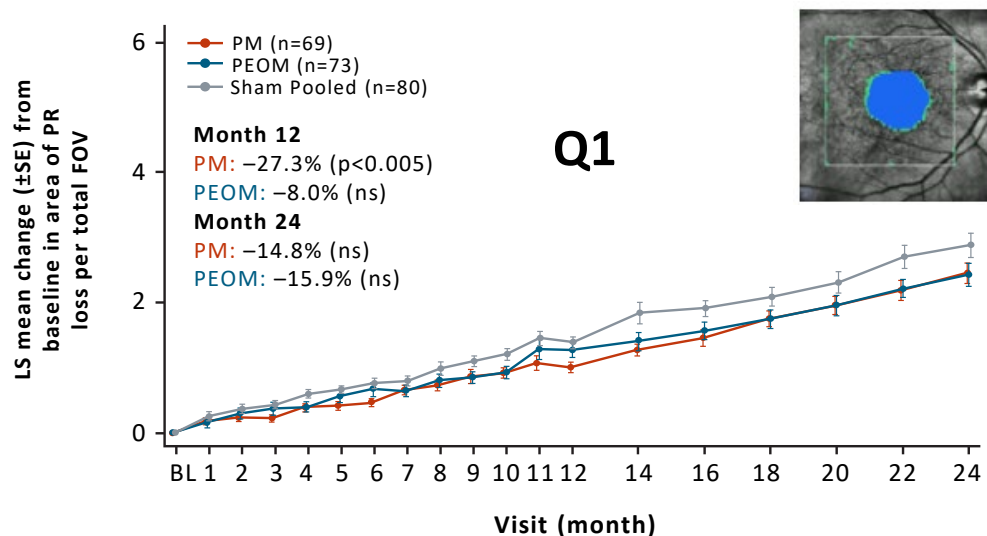
RPE loss



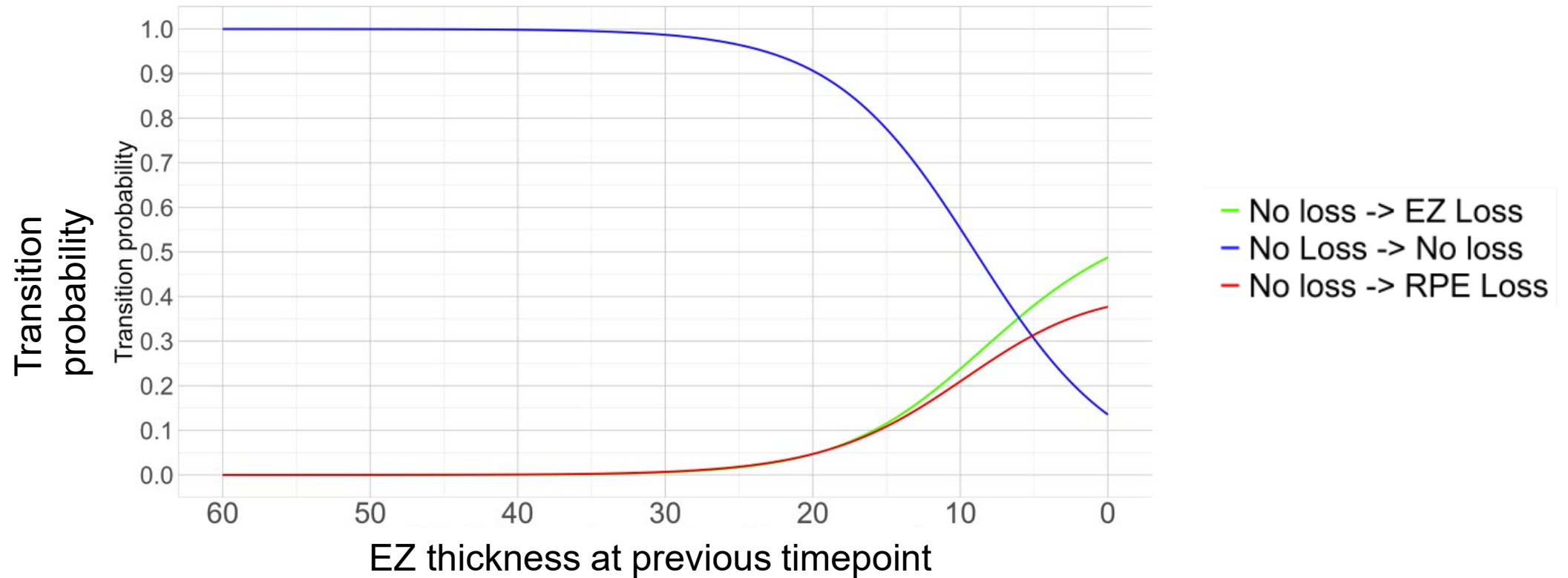
EZ loss

Therapeutic efficacy is predicted by EZ/RPE ratio

PR response by EZ-RPE quartile



Transition probability based on EZ thinning



Decreased EZ thickness leads to higher transition probability to EZ loss and RPE loss

As **EZ thickness decreases**, the likelihood of disease progression increases, and an **MP point** is **more likely to transition to EZ loss or RPE loss** rather than remaining in intact retina

Morphological transition probabilities for each individual MP point (Markov model)

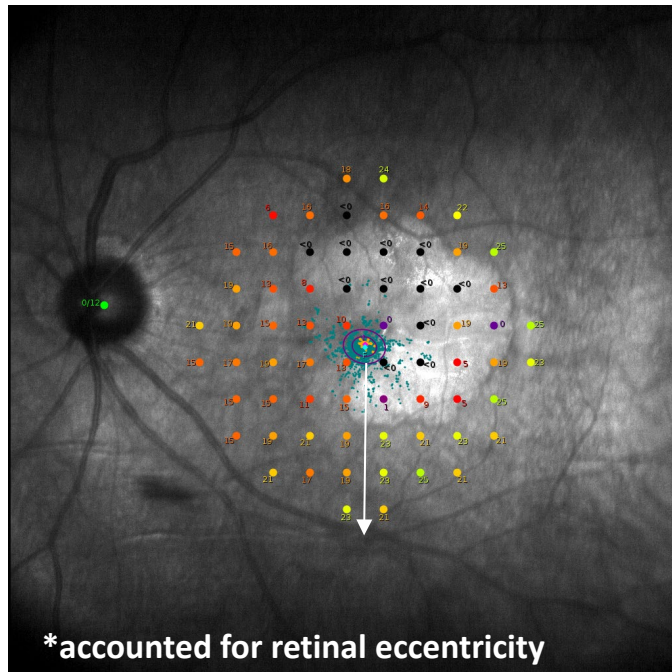
Month 6			
From	To Intact retina	To EZ loss	To RPE loss
Intact retina	0.975 (97.5%)	0.014 (1.4%)	0.011 (1.1%)
EZ loss	0	0.772 (77.2%)	0.228 (22.8%)
RPE loss	0	0	1
Month 12			
Intact retina	0.947 (94.7%)	0.026 (2.6%)	0.027 (2.7%)
EZ loss	0	0.596 (59.6%)	0.404 (40.4%)
RPE loss	0	0	1

For MP points starting from intact retina the probability is as low as 1.1%.
From EZ loss, the probability of transition to RPE loss within the next 6 months is 23%.

Progressive functional loss

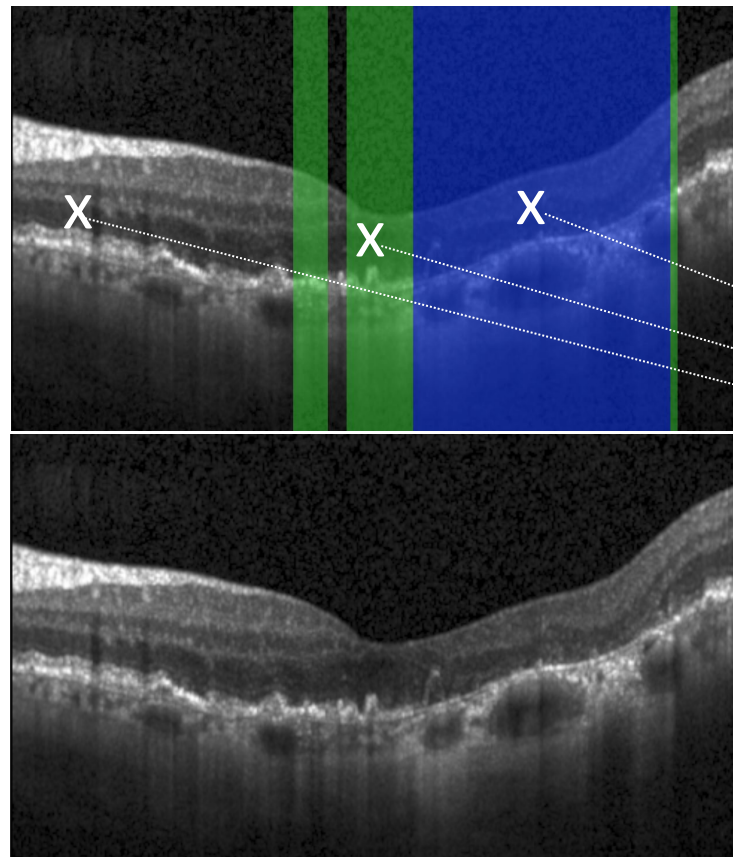
Pointwise co-registration between MP and OCT

Retinal sensitivity (RS)
on MP grid MAIA

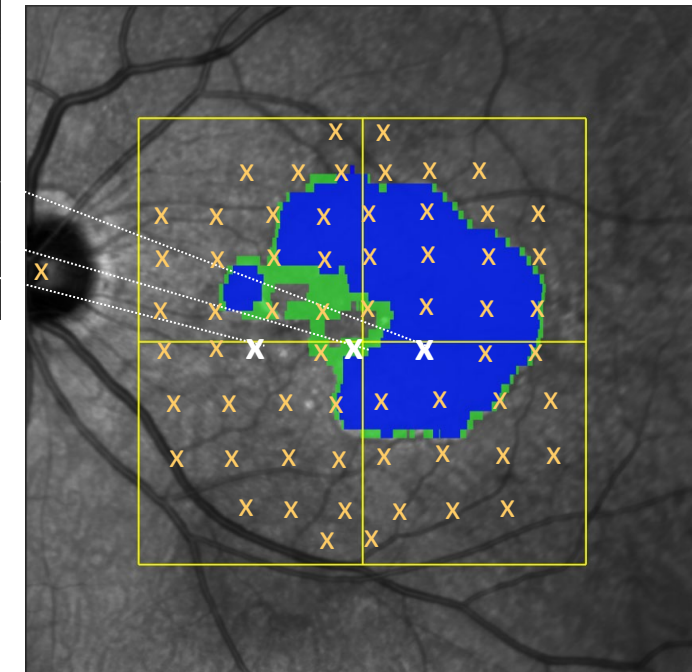


68 MP points grid

Quantification of EZ
thickness, EZ, RPE loss



Co-registration between
OCT and MP grid



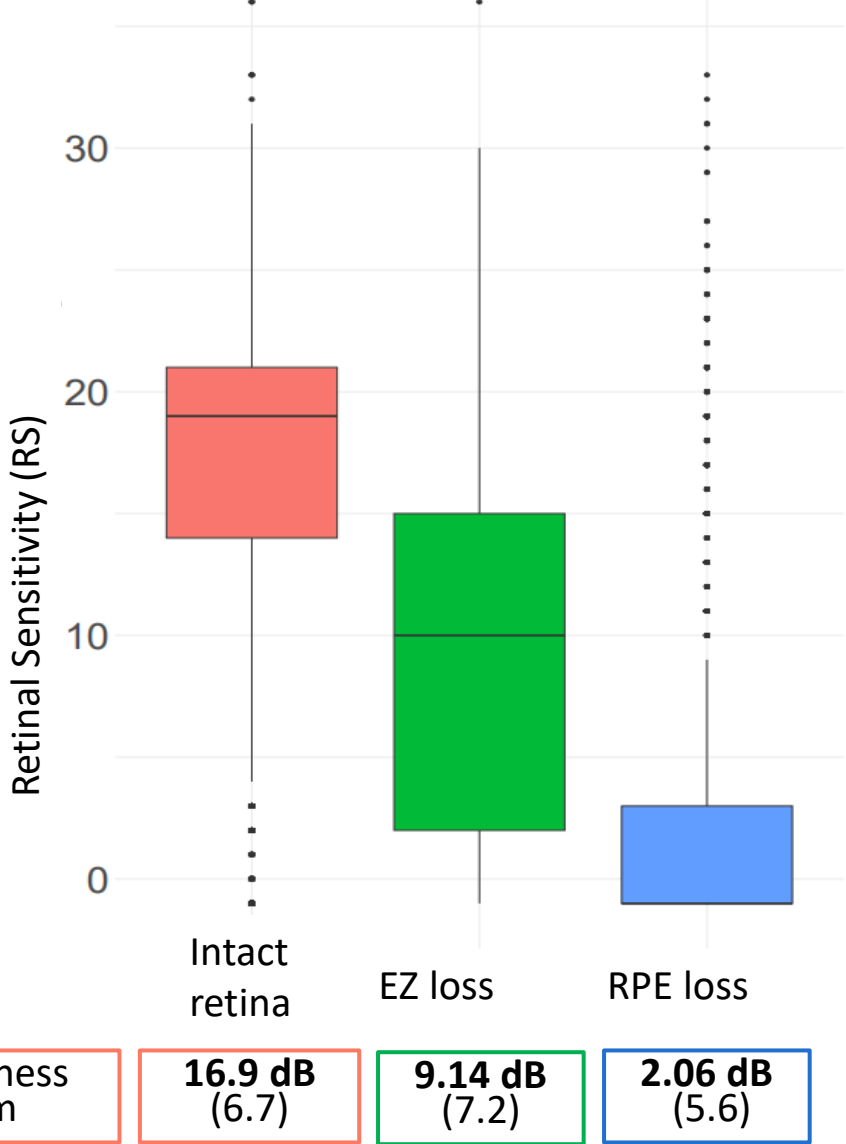
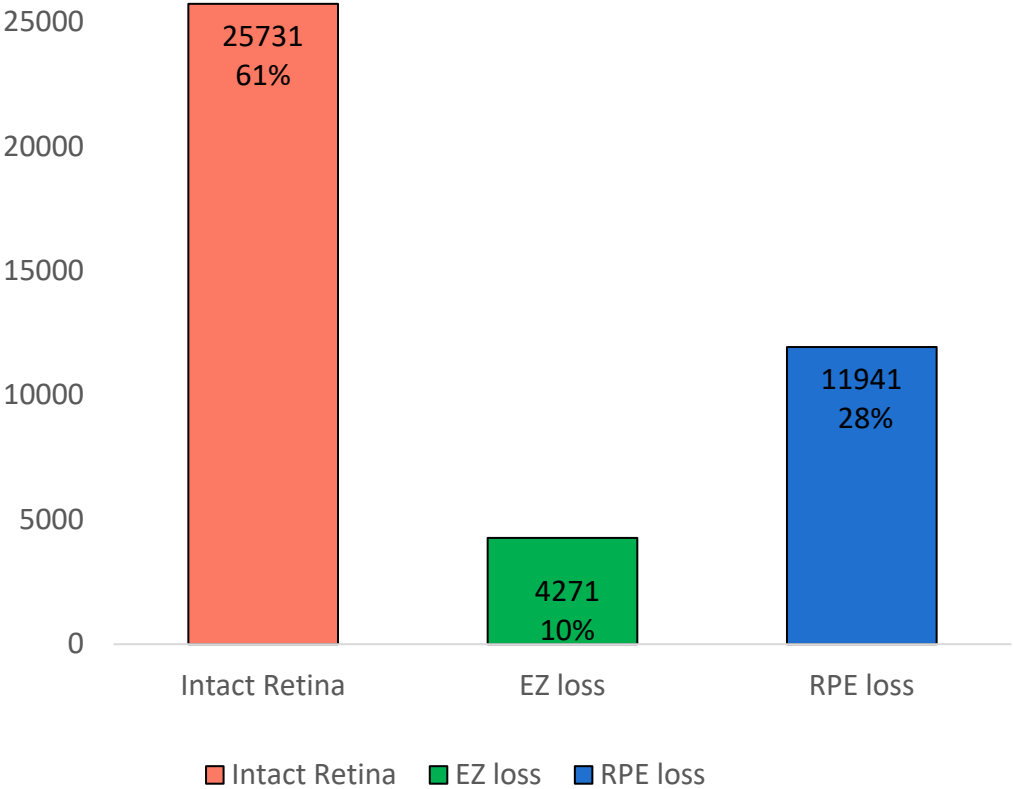
Intact retina
EZ thickness

EZ loss

RPE loss

Baseline structure/function correlation (678 eyes)

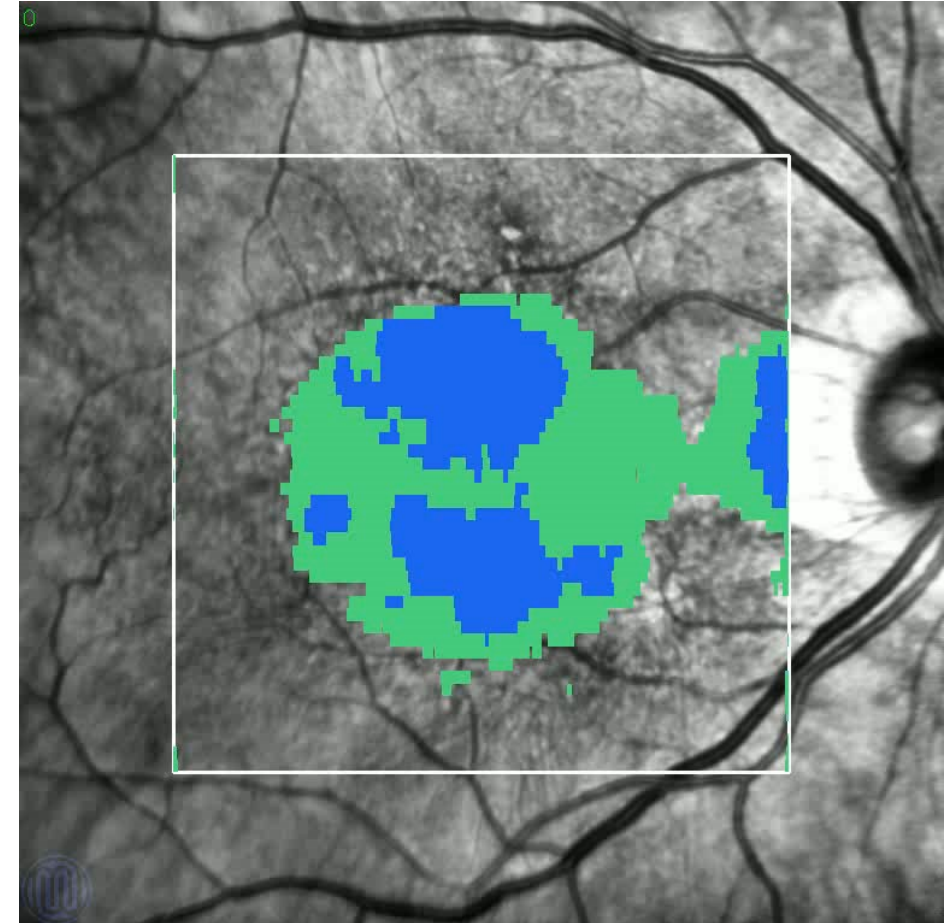
Number of MP stimuli n = 41925



Monitoring retinal function based on EZ morphology



Progressive loss of retinal sensitivity in EZloss areas over 24 months (point - to - point correlation in OAKS with 39861 MP points from 406 patients)



Speed of progression varies according to EZ/RPEloss ratio with (blue) RPEloss wiping out (green) EZ loss converting relative scotoma into absolute scotoma

Thickness/loss in μm vs. RS in dB

(678 eyes 41925 MP points)

Category	Estimate	Upper limit	Lower limit	p value
Intercept* for intact retina	15.0 dB	15.6 dB	14.5 dB	<0.0001
EZ thickness	0.2 dB/ μm	0.2 dB	0.2 dB	<0.0001
EZ loss presence Reference: no loss	- 8.2 dB	-7.7 dB	-8.7 dB	<0.0001
RPE loss presence Reference: no loss	- 14.4 dB	-14.9 dB	-14.9 dB	<0.0001
Eccentricity	0.3 dB/mm	0.2 dB	0.4 dB	<0.0001
EZ loss*Eccentricity	1.7 dB	1.4 dB	1.9 dB	<0.0001
RPE loss*Eccentricity	1.5 dB	1.3 dB	1.7 dB	<0.0001

¹ Pseudo R-squared (marginal) = 0.44

² Pseudo R-squared (conditional) = 0.74

³ Correlation between predicted and observed retinal sensitivity = 0.88

⁴ ICC = 23.03

*The intercept, estimated at 15 dB signifies the models prediction of retinal sensitivity (RS) in areas with no loss and mean **EZ-thickness 23 μm**

Automated targeted Microperimetry

Standardized

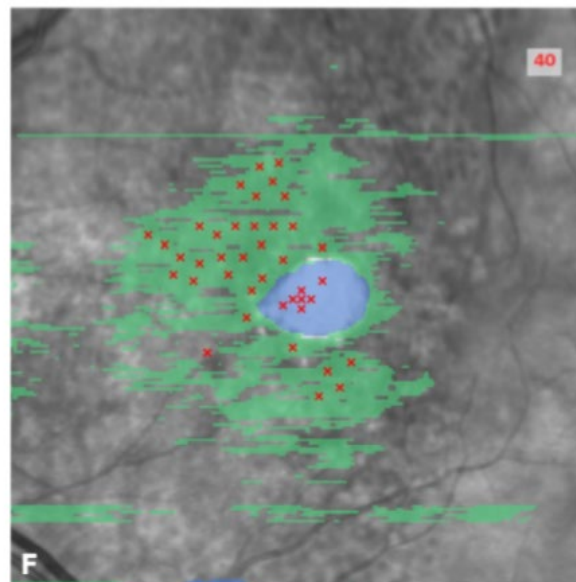
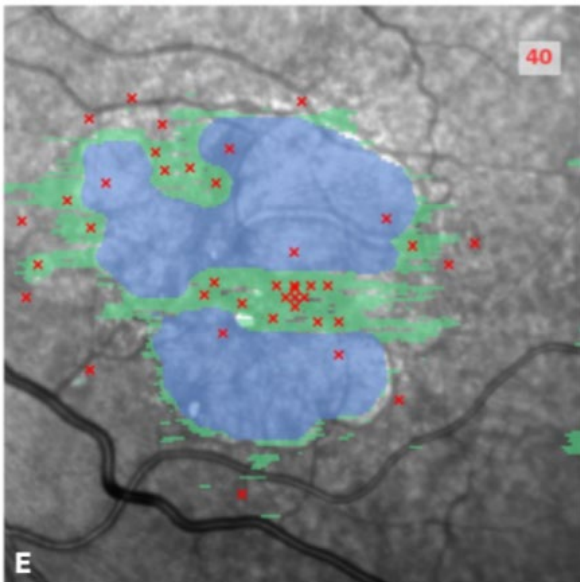
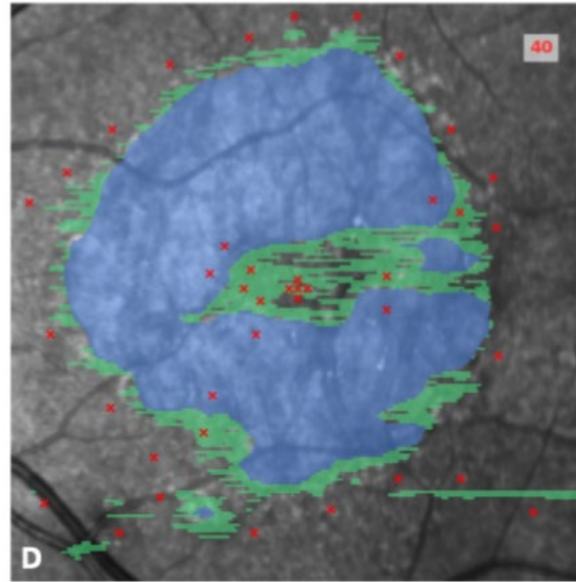
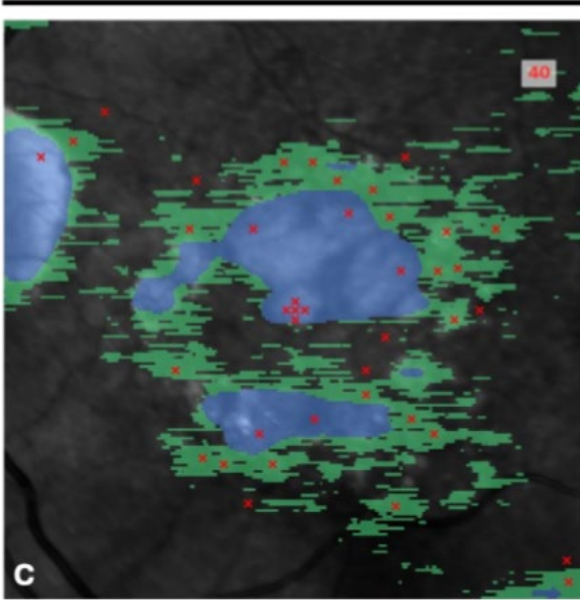
Fast

**User-
independent**

Reproducible

Prospective Study in GA (RW)

in 64 eyes from 44 RW GA patients



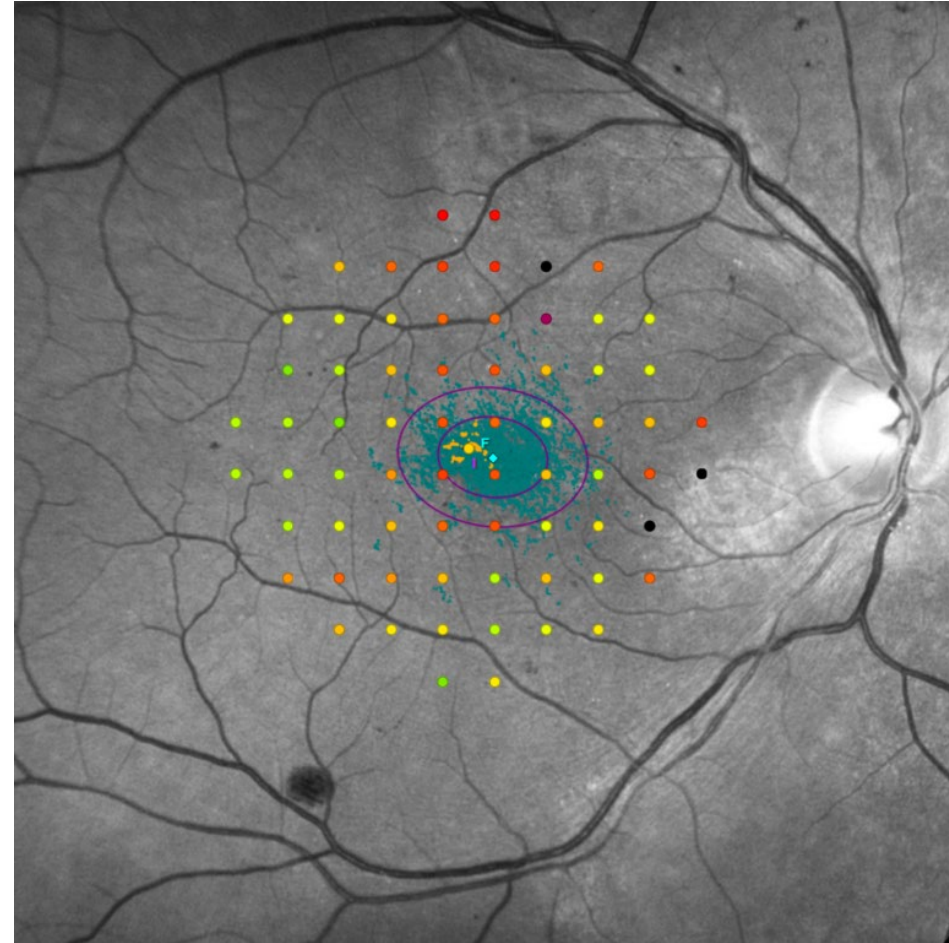
- Across **all locations**, mean RS declined from 14.6 at baseline to 12.6 dB at month 6
- At 3m, **junctional RPEL** showed a fast decline (-3.6 dB), consistent with residual sensitivity (ONL)
- **Foveal points** showed a rapid decline (-2.2 dB), reflecting encroaching parafoveal atrophy
- In contrast, **EZL** (-1.2 dB) exhibited a **continuous gradual loss** to 6m and further on (all $p < 0.0001$)

Optimizing functional assessment based on imaging

Microperimetry Patterns

Standard (sG) Grid

- 68 equidistant points
- Assesses overall macular function
- Problems:
 - Misses **lesion - specific areas**
 - Many points already within **absolute scotoma** at baseline
 - Long testing time
 - High variability

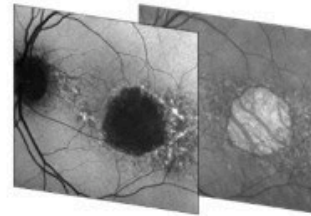


Microperimetry Patterns

Circumferential Grid

- Circumferential perimetry (onion ring)
- 60 points around the entire GA lesion
- More disease - relevant and lesion - specific
- Problems:
 - No distinction between level of disease activity
 - More lower - yield points and more patient burden

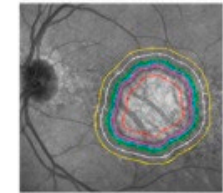
1. Multimodal imaging data



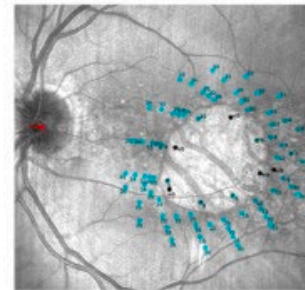
2. Pattern defining rules



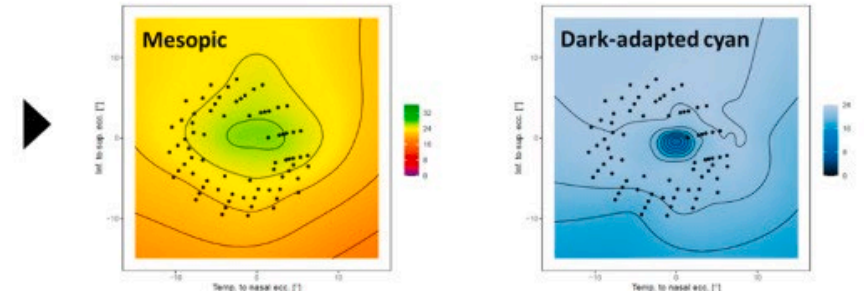
3. Patient-tailored pattern



4. Perimetry test



5. Analysis with consideration of age-matched, spatially-corresponding normal data (flipped to right eye coordinate system)

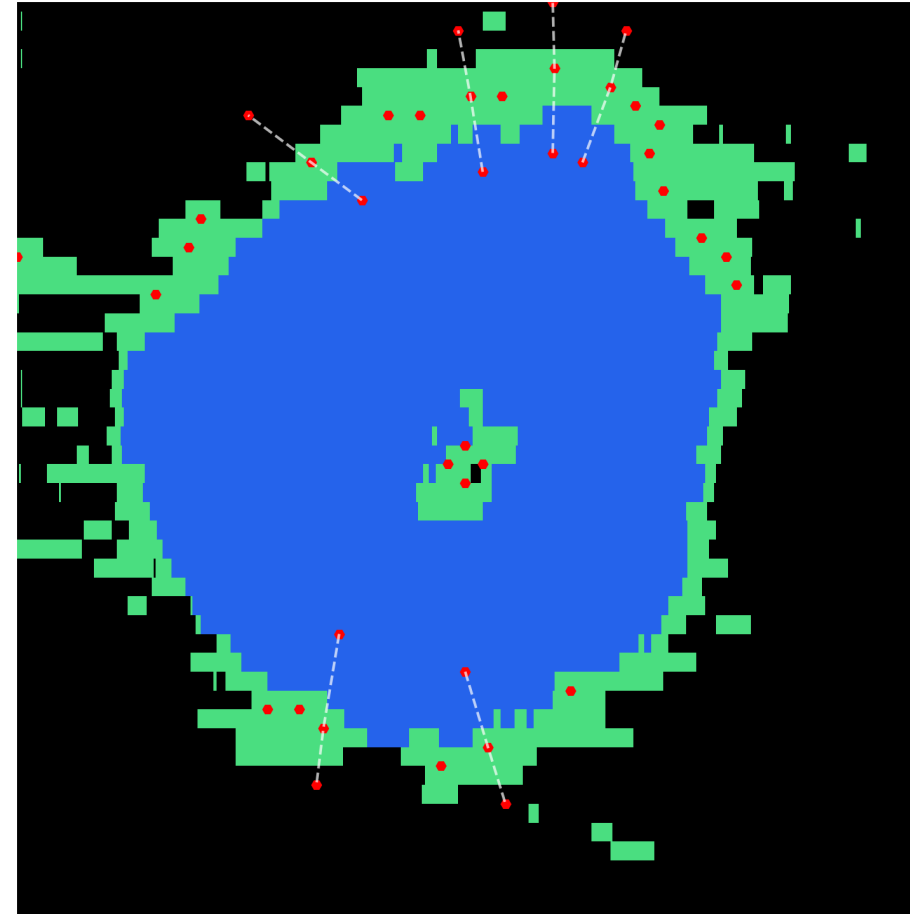




EZ-targeted (tG) Grid

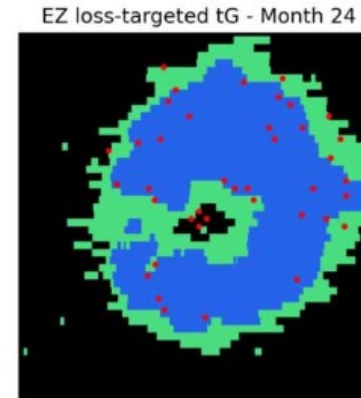
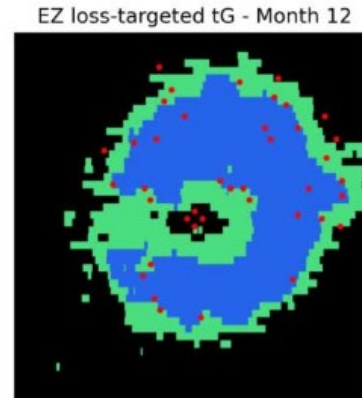
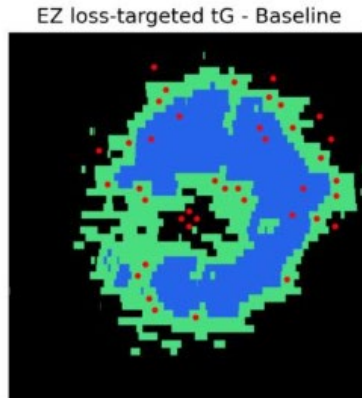
- Fully automated and standardized
- By AI- based segmentation of loss and EZ loss
- 40 test points per eye
- Most points in areas of EZ loss/disease activity
- Optimized for morphological conversion from EZ to RPE loss
- Reduced patient burden

RPE



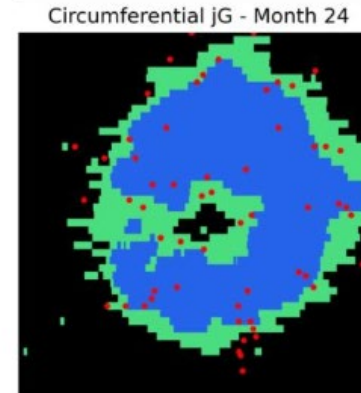
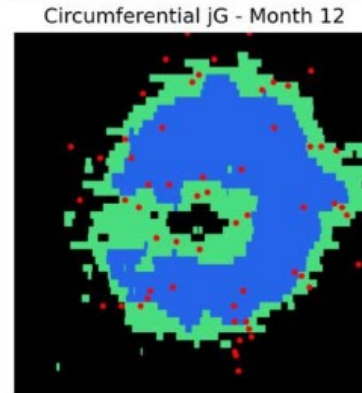
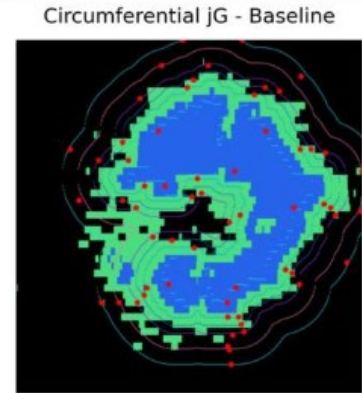
Point distributions per pattern over time (BL - 12m- 24m)

Targeted grid
40 points



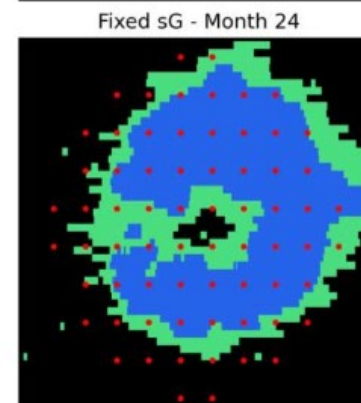
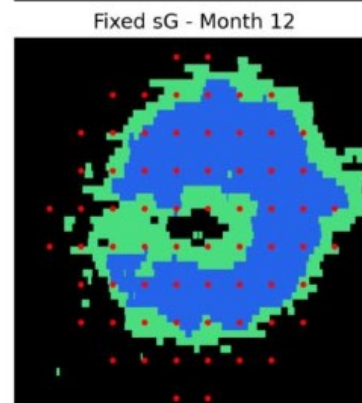
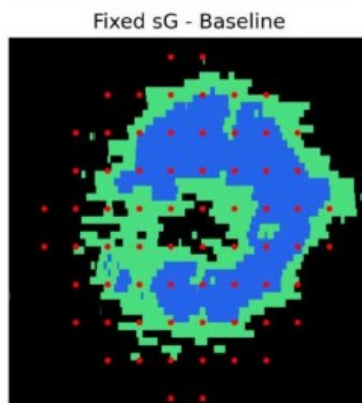
**Targeting
morphological
conversion**

Circumferential
grid : 60 points



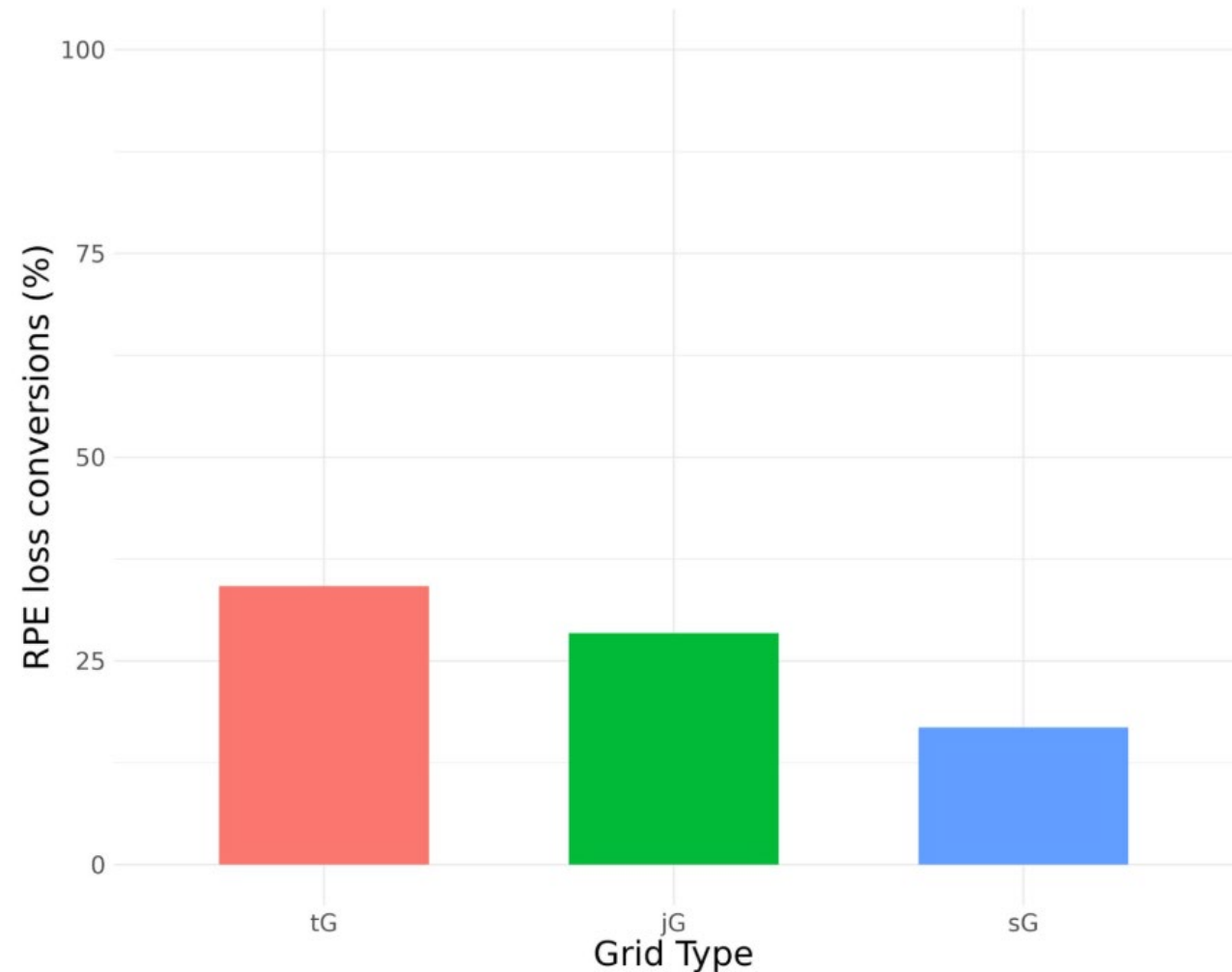
Development: 130 eyes
Test: 110 eyes
Endpoint: Conversion by month 24
Statistics: GLMM, ORs, Holm-adjusted p-values

Standard grid
68 points



Results: Predicting morphological conversion

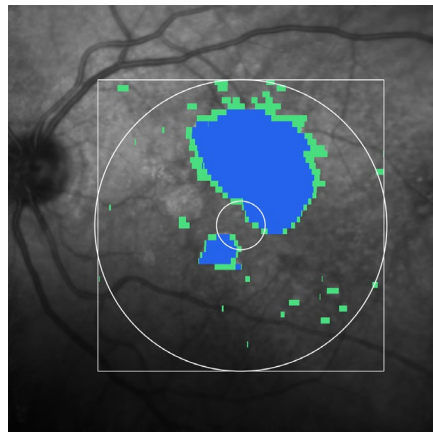
- **Morphological conversion rates** differed across grids at 24 months ($p < 0.0001$)
- Highest detection reached with **tG > cG > sG**
- **EZ/Outside Loss towards RPE conversion:** 34.2% tG, 27.5% jG, 16.8% sG
- **General conversion** (any transition from intact retina towards EZ or RPE loss): 48.0% tG, 44.2% cG, 27.3% sG



EZ- guided targeted testing showed the strongest signal

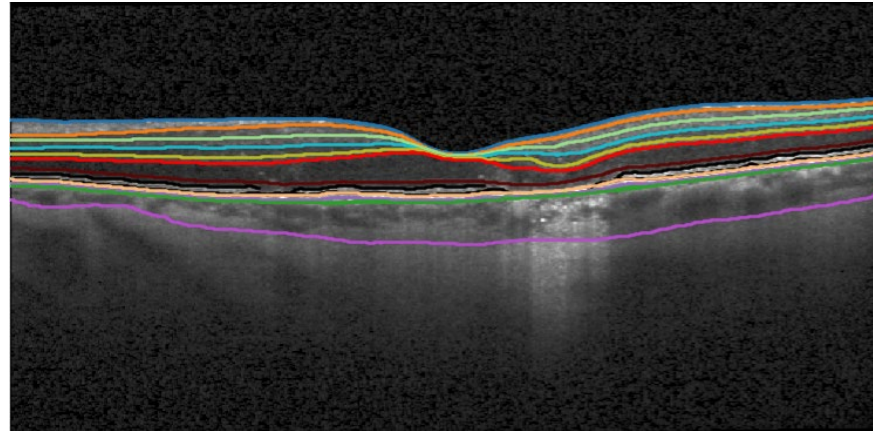
Methods: Prediction of Retinal Sensitivity

- Using a machine learning **model** trained on **paired OCT cans** and **(MP) retinal sensitivity (RS)** data (from DERBY and OAKS trials)
- Model predicts **dense RS maps** from **structural OCT imaging**: “functional OCT”
- Calculated mean predicted **RS** at **sG**, **cG**, and **tG** locations
- and **efficiency per test point**



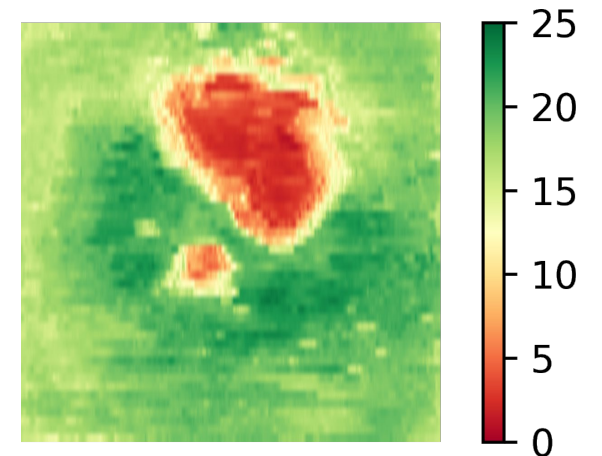
RPEloss / EZ loss

+



Morphology

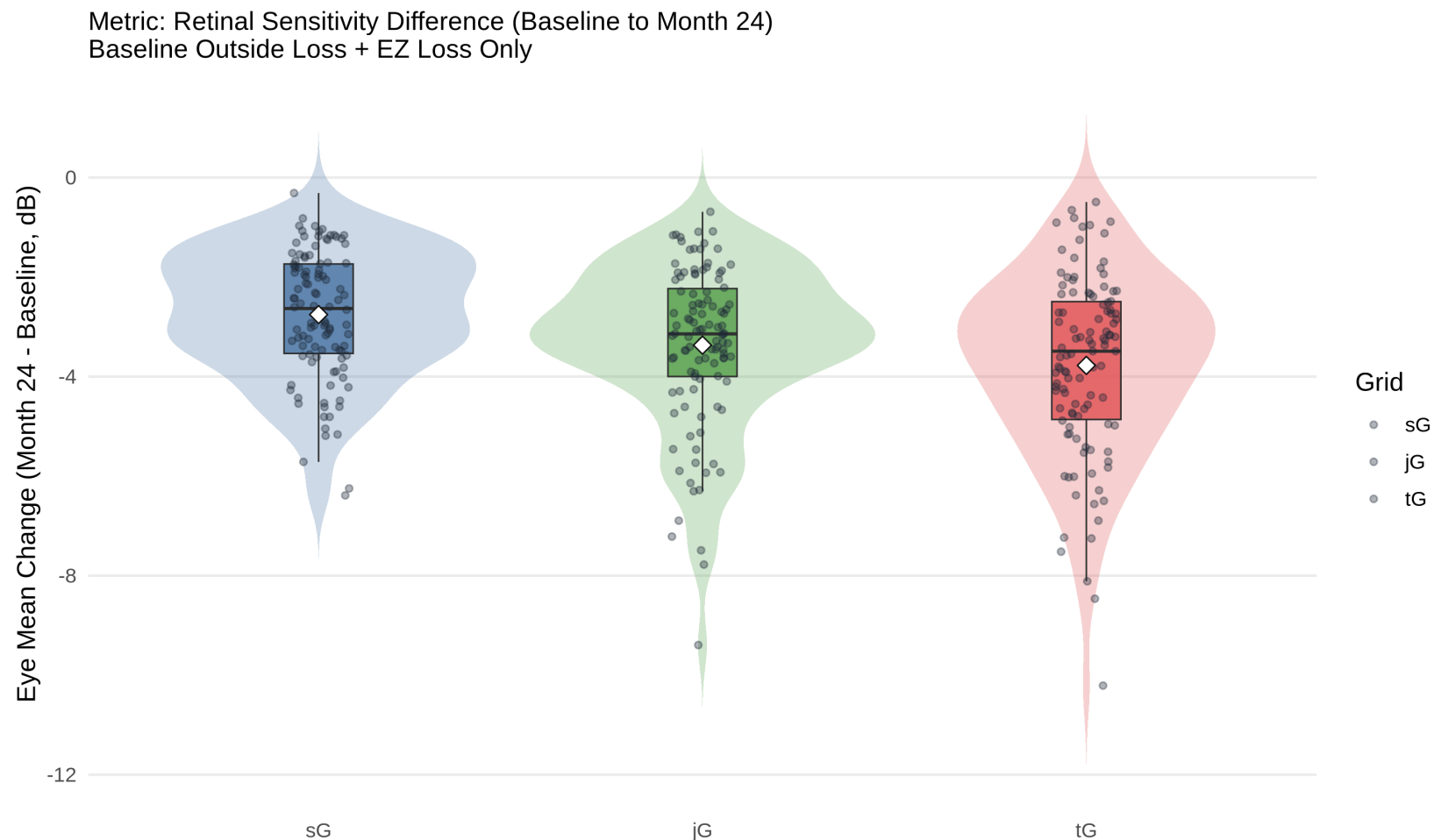
⇒



Retinal Sensitivity

Results: Grid Comparison using the Predicted RS Values

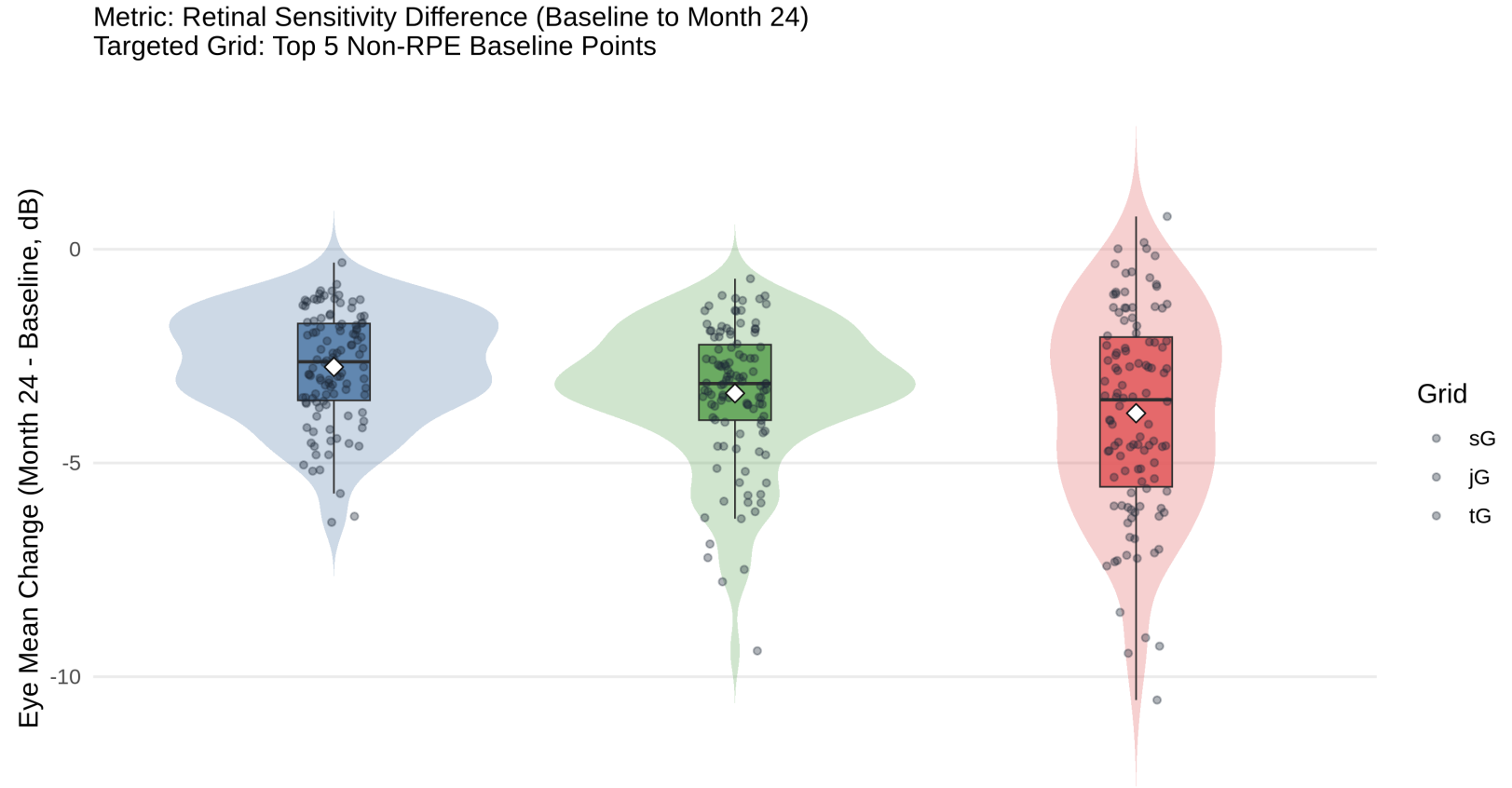
- **Raw change** (all points): **sG - 2.49** , **cG - 3.24** , **tG - 3.41**
- **Raw change** (outside loss + EZ loss): **sG - 2.75** , **jG - 3.37** , **tG - 3.78**
- **Efficiency** favored **tG**



tG detects more loss in RS with less test points

Results: Top 5 Scoring tG Points vs sG and cG

- Compared top 5 tG points vs all sG and all cG points
- Raw change: sG - 2.49 , cG - 3.24 , tG - 3.84 dB
- tG vs cG: - 0.598 dB
- tG vs sG: - 1.341 dB
- Efficiency: sG - 0.0367 , cG - 0.0540 , tG - 0.767 dB/point



Efficiency favored tG (in ideally only 5 points selected from a full baseline MP assessment or from a „functional OCT“)

Conclusions

- **OCT is superior to FAF imaging** due to EZ segmentation
- **Precision tools for AI-based segmentation** are available
- **EZ thinning/loss, (RPD) and HRF** volumes are predictive
- **EZ loss preceeds and predicts** lesion progression
- **EZ/RPE loss ratio indicates activity** in GA lesions
- We designed a **framework to simulate different MP grids** on large data sets
- **Targeted grid (tG)** is superior in respect to morphological conversion
- The framework also identifies the **most valuable subset of points**
- Promising for **regulatory approval**



Seeing Outcomes



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FWF

Der Wissenschaftsfonds.



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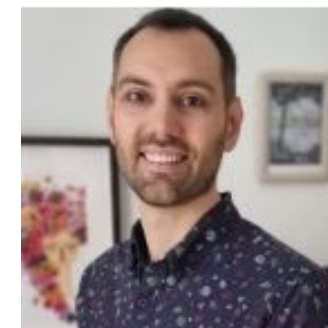
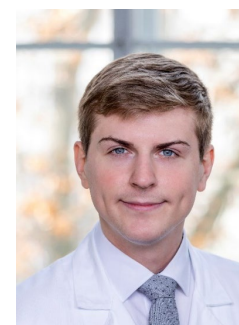
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OPTIMA
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DEPARTMENT OF OPHTHALMOLOGY
AND OPTOMETRY
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Science from humans for humans