

EMRN GA Workshop Scientific Exchange

Session 3: Overview of structure function relationship

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EMA GA Workshop | Session 3 | Structure-Function
Relationship

Disclosures

- Consultant for AbbVie, Adverum, Alimera Sciences, Amgen, Apellis, Astellas, Bayer, Biogen, Boehringer Ingelheim, Clearside bio, Novartis, EyeBiotech, Eyepoint Pharmaceuticals, Eyexora, 4DMT, Janssen Pharmaceuticals, Kodiak Sciences, Merit, NanOptima, Nova Nordisk, Optos, Ocular Therapeutix, Kriya Therapeutics, Kodiak Sciences OcuTerra, Opharmic Technology, Roche, Sanofi, Stealth Biotherapeutics, Surrozen.
- Received honoraria/travel reimbursement from Bayer, Boehringer Ingelheim and Roche.
- Stock Options: Eyebiotech, Nanoptima, Eyexora, Opharmic Technology
- Research Grants: Boehringer Ingelheim, Roche, Bayer

The BRIDGE Study Group

- BRIDGE Study Group. BRIDGE: a multi-stakeholder workstream focused on assessing new clinical endpoints in ophthalmology clinical trials [Building Research Innovations and Developing Global Endpoints]. Eye (Lond). 2025 Aug;39(12):2337-2339.
- Aim to consolidate evidence on clinical endpoints in GA and Ischaemia to have a discussion with Regulators.

Principles for Validation of a Surrogate Structural Marker of Visual Function

Plausibility	Marker of disease pathogenesis and progression
Construct validity	Ability to distinguish disease area from normal area
Reliability	Inter-observer, test–retest, and intra-observer reproducibility
Content validity	Marker should directly represent aspects of visual function
Responsiveness/ predictability	Marker should be able to predict a future clinical outcome
Change to intervention	Marker Reduction in growth rate

Overview of structure-function relationship

- **Structural changes**

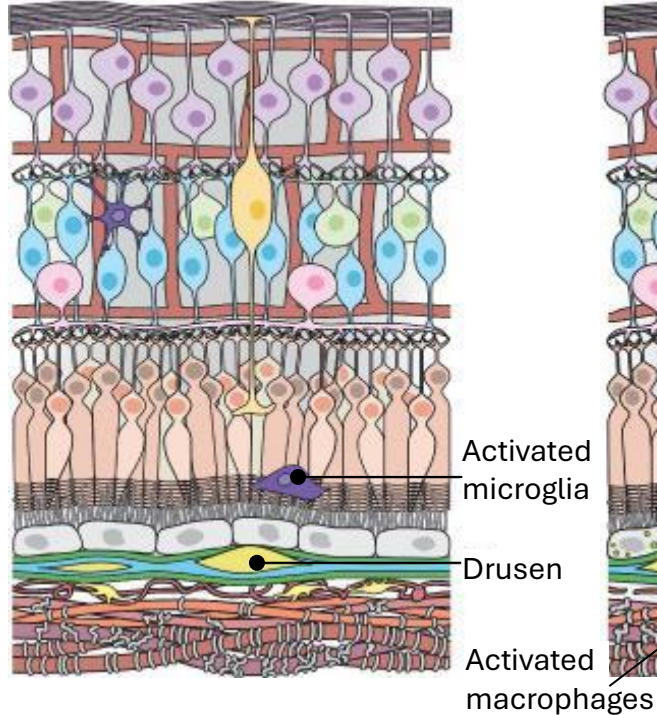
- GA Growth rate based on fundus autofluorescence (FAF)
- Outer Retinal layer changes on Optical coherence tomography (OCT)

- **Function tests**

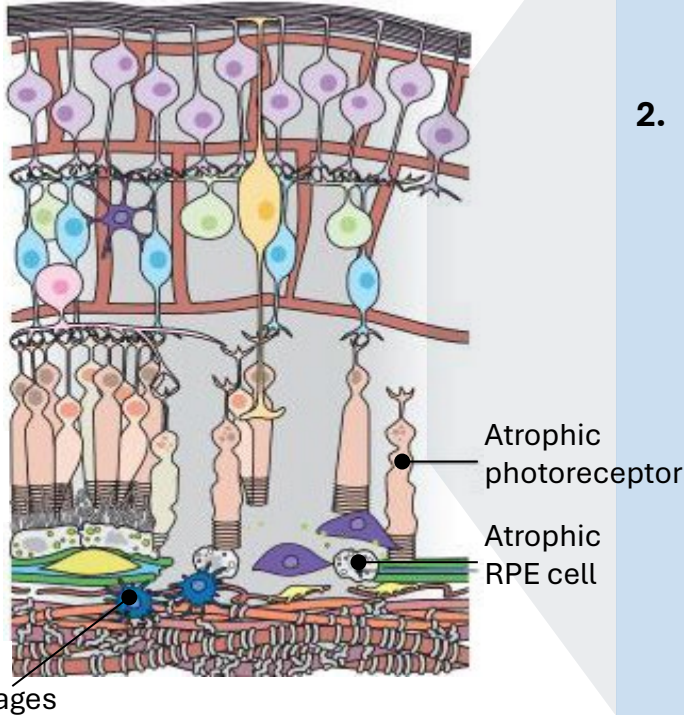
- Visual acuity
- Microperimetry
- Quantitative Contrast Sensitivity
- Low Luminance Visual Acuity
- Reading Speed
- Patient Related outcomes
- Composite endpoints

Pathology of GA

Intermediate AMD



GA



1. Intermediate stage drusen disrupt barrier function of Bruch's membrane

- Disrupts RPE ability to clear waste

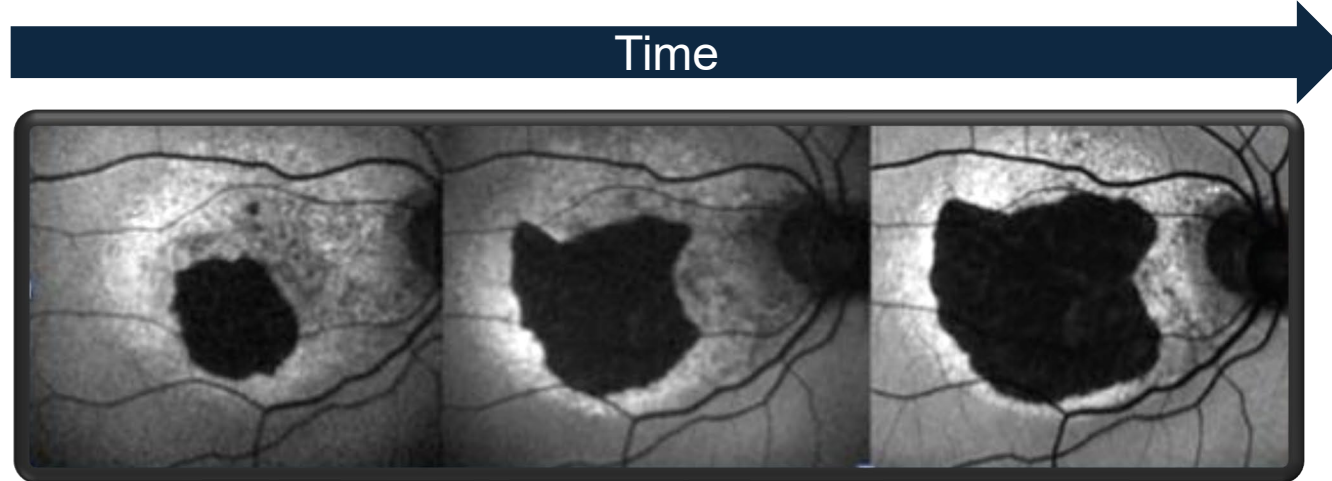
2. Advanced stage (GA)

- Bruch's membrane severely disrupted
- RPE and photoreceptors atrophy and loss are pronounced
- Loss of other retinal cell types (horizontal cells, bipolar cells, amacrine cells)
- The choriocapillaris is poorly perfused
- Inflammation is prominent (activated microglia and macrophages in the area)

Degenerative changes in the outer retina, retinal pigment epithelium (RPE) and choroid

Structure 1: GA growth rate on fundus autofluorescence (FAF): Biological plausibility

- GA is defined as a sharply demarcated round/oval area of hypopigmentation with corresponding visual field scotomas (area of depressed vision in the visual field) or reduced sensitivities¹



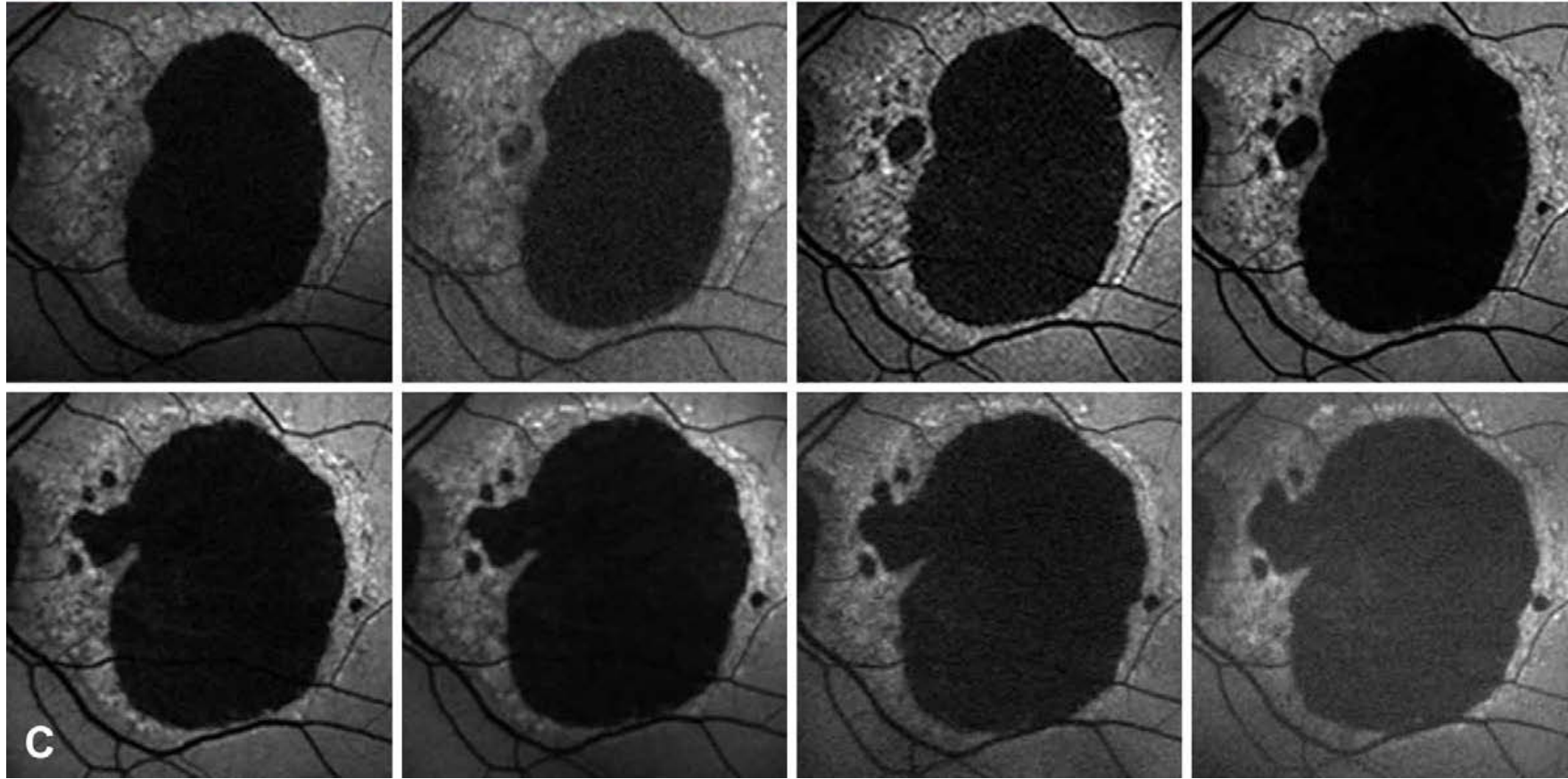
Fundus autofluorescence images courtesy of Frank Holz

- Dark patches represent RPE loss on FAF imaging
- Hyperfluorescence surrounding the atrophic lesion has been associated with more rapid progression over time²

GA is characterized by defined areas of RPE atrophy:³

1. Panorgias A, et al. Invest Ophthalmol Vis Sci 2013;26;54:4372–84; 2. Holz F, et al. Am J Ophthalmol 2007;143:463–72;
3. Biarnés M, et al. Optom Vis Sci 2011;88:881–9

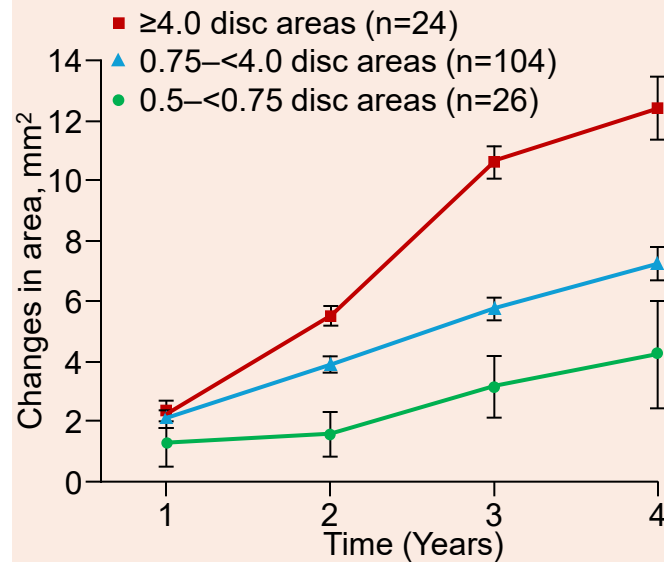
Reliability and Construct Validity: Progression of Geographic atrophy



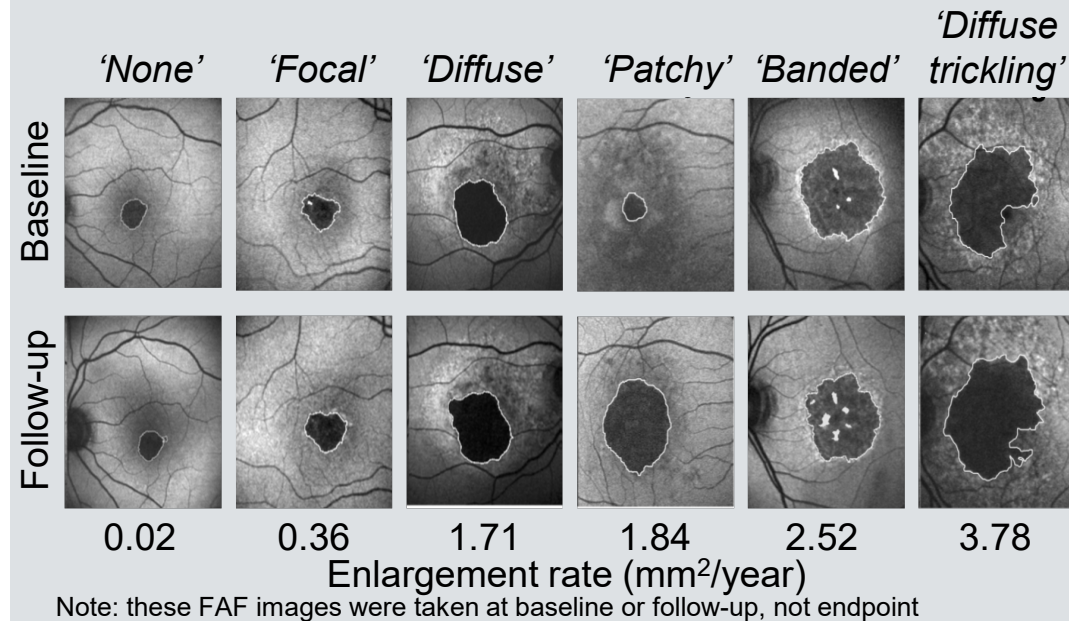
Schmitz-Valckenberg et al. - Fundus Autofluorescence and Progression of Age-related Macular Degeneration - Surv Ophthalmology 2009

GA Progression is Influenced by Lesion Size, Morphology and Atrophic Pattern: Construct Validity

Progression rate by size¹

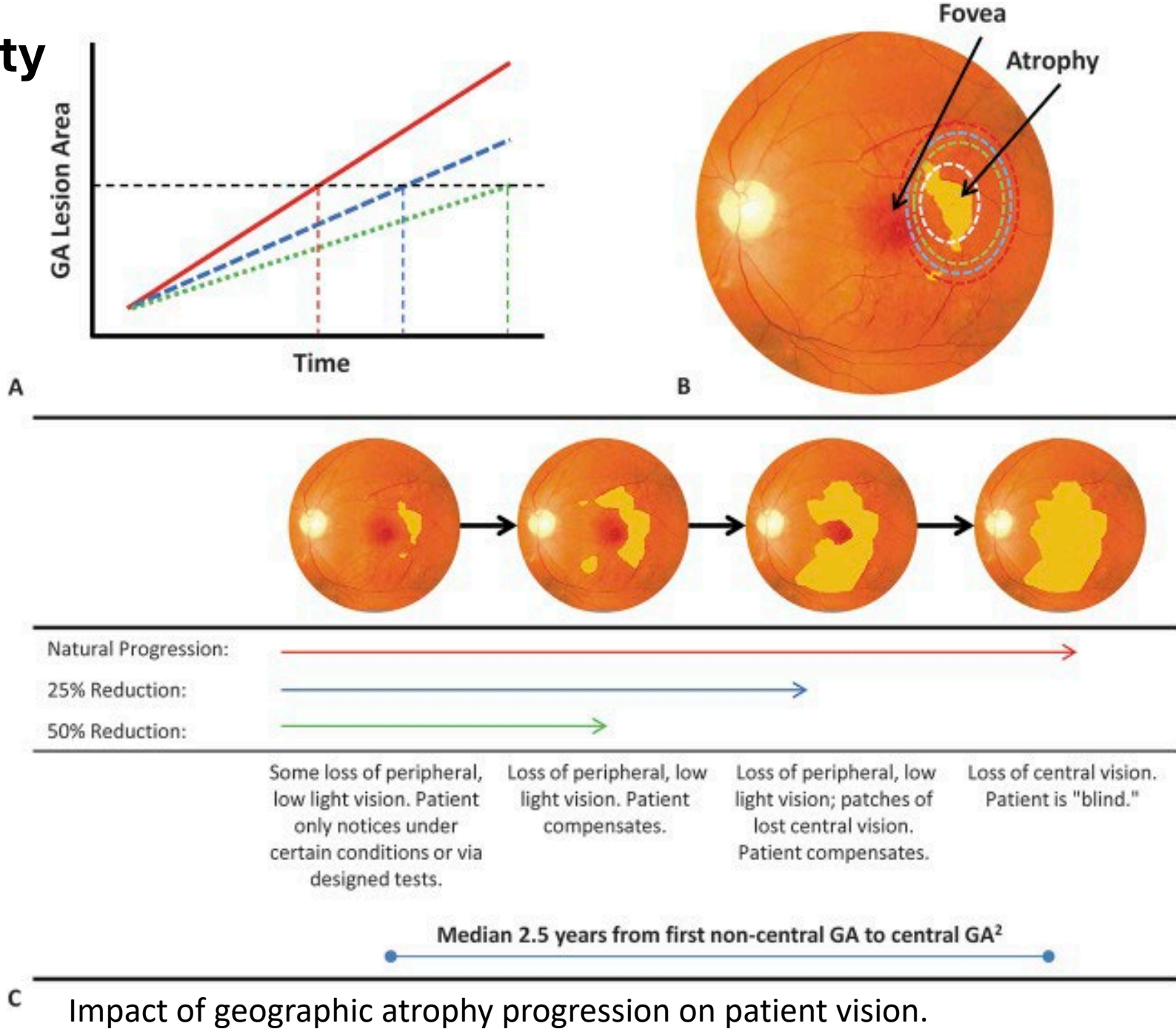


Progression rate by FAF imaging morphology²



On average, GA lesions grow by ~1.5 mm²/year

Content Validity



Impact of geographic atrophy progression on patient vision.

Classified as public by the European Medicines Agency

Pouring a Cup of Tea or Coffee

'Normal' vision



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Patient with Geographic Atrophy

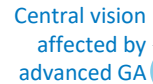


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GA lesion impact on patients despite normal visual acuity

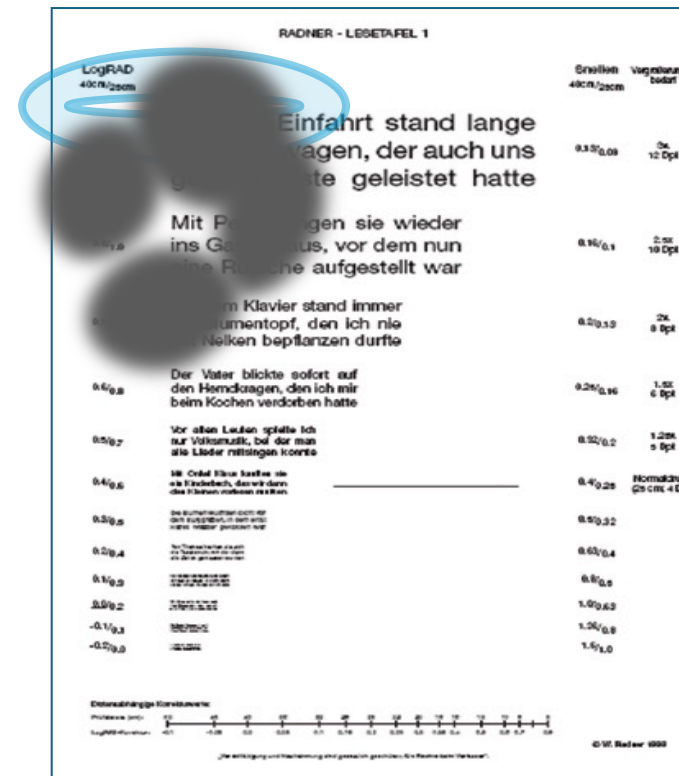
-Scotoma is a significant problem in patients with GA

GA patients may still score well on high contrast single-letter visual acuity test



Visual Acuity Test (ETDRS Eye Chart)

Visual function deficits in real-life-reading texts*



Reading Speed Test (Radner)

* EU regulators seek a link between GA area (anatomical) and functional deficits

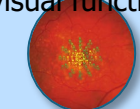
Visual function secondary endpoints in Phase 3 Studies



Reading speed



Patient-reported
visual function



Microperimetry



LLVA

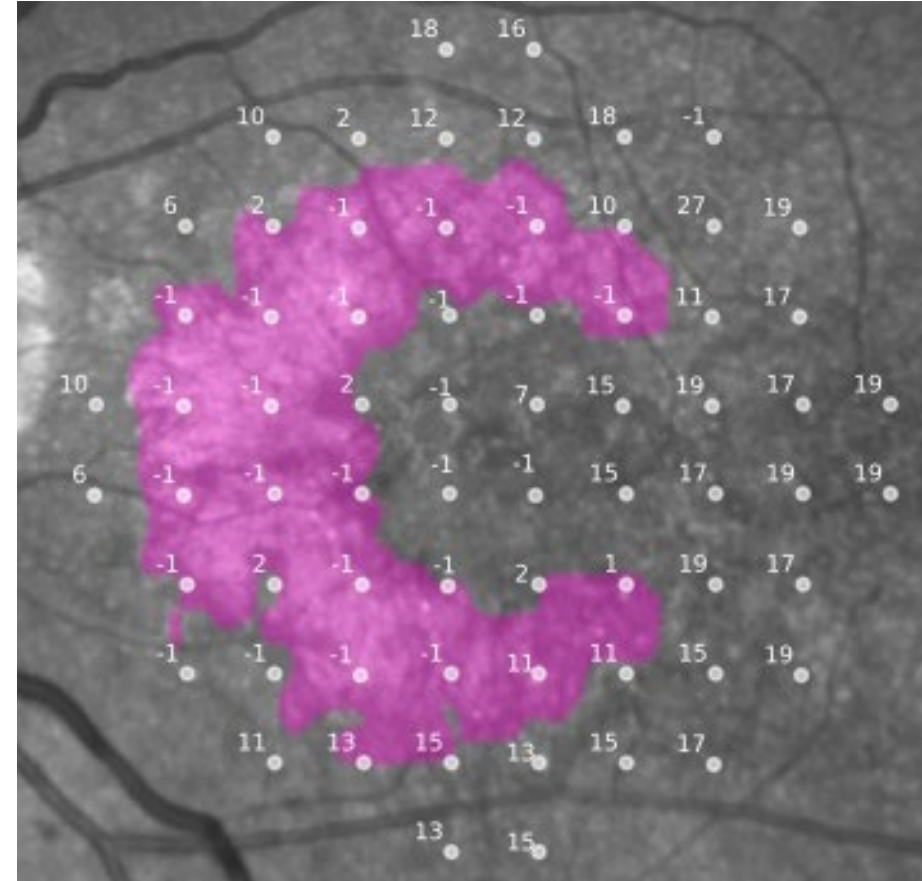
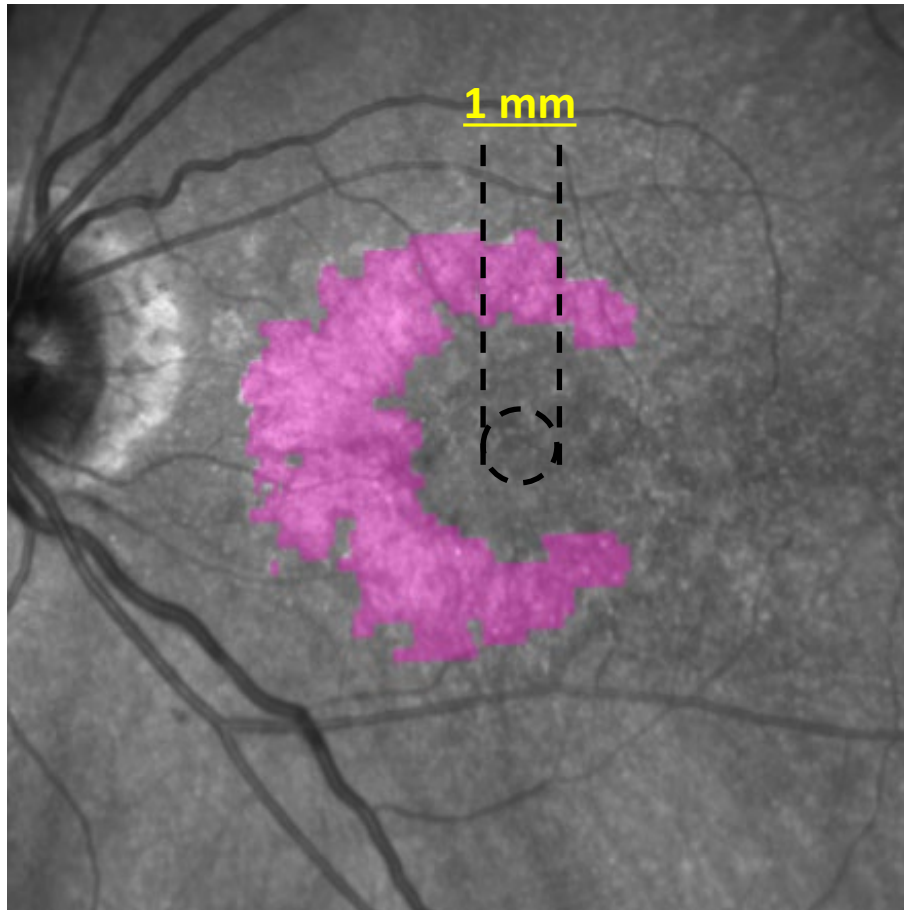


BCVA

GA lesion size correlation to retinal sensitivity on microperimetry testing

BCVA 75 ETDRS letters

~ Snellen 6/9 (20/30)



Change of FAF lesion size to Intervention

Pegcetacoplan showed clinically meaningful reductions in GA lesion growth from BL to month 24 (all nominal p-values ≤ 0.003)



GA= geographic atrophy; BL= baseline; SE= standard error. Least square (LS) means estimated from a mixed-effects model for repeated measures (MMRM). The MITT population was used for the analysis, defined as all randomized patients who received at least 1 injection of pegcetacoplan or sham and have baseline and at least one post-baseline value of GA lesion area in the study eye.

Structural slowing tracks with functional preservation

18%

↓ new scotomatous points on MP

Pegcetacoplan monthly vs sham crossover, GALE 36 months (prespecified; $P = 0.0156$)

ICC high CoR low

MP junctional-zone reliability

OAKS post-hoc within $\pm 250 \mu\text{m}$ of GA margin (Alibhai 2025)

↓ risk

Conversion to absolute scotoma, central MP loci

Pegcetacoplan in OAKS at 24 mo; also ↓ mean sensitivity loss & fewer new scotomatous points (Chakravarthy 2025)

CROSS-TRIAL COHERENCE

- FILLY & GATHER1 post-hoc: therapeutic modulation of both cRORA lesion growth and iRORA→cRORA conversion (Nittala 2022; Corradetti).
- Independent reading centres: positive FAF treatment effects replicate with OCT-based RPE atrophy measurement — evidence of endpoint validity (Mai 2023; Williamson 2024).
- LLVA / LLD correlate with MP sensitivity, GA lesion burden, and predict subsequent BCVA decline — in some cases outperforming baseline anatomy (Sunness 2008; Csaky 2019; Ansari 2023; Balaskas 2022).
- Low baseline qCSF at 1–1.5 cpd predicts progression to late AMD (GA and nAMD) at 2–3 years (Vingopoulos 2021; Romano 2024; Bennett 2025).

Predictability: Atrophy is the proximal driver of visual dysfunction

Anatomy defines function

GA = loss of RPE, photoreceptors, and choriocapillaris. Destroyed retinal tissue cannot sense light; the area and location of atrophy determine which visual tasks fail.

Location beats growth rate

Growth rate alone does not drive BCVA; where atrophy sits relative to the fovea, PRL, and reading rectangle governs functional impact.

CMV retinitis precedent

SOCA data show retinal-atrophy area and location causally precede visual-field loss, which in turn predicts VA loss (RR 1.4 per 100° lost, $p < 0.001$).

SOCA_studies of the ocular complications of AIDS

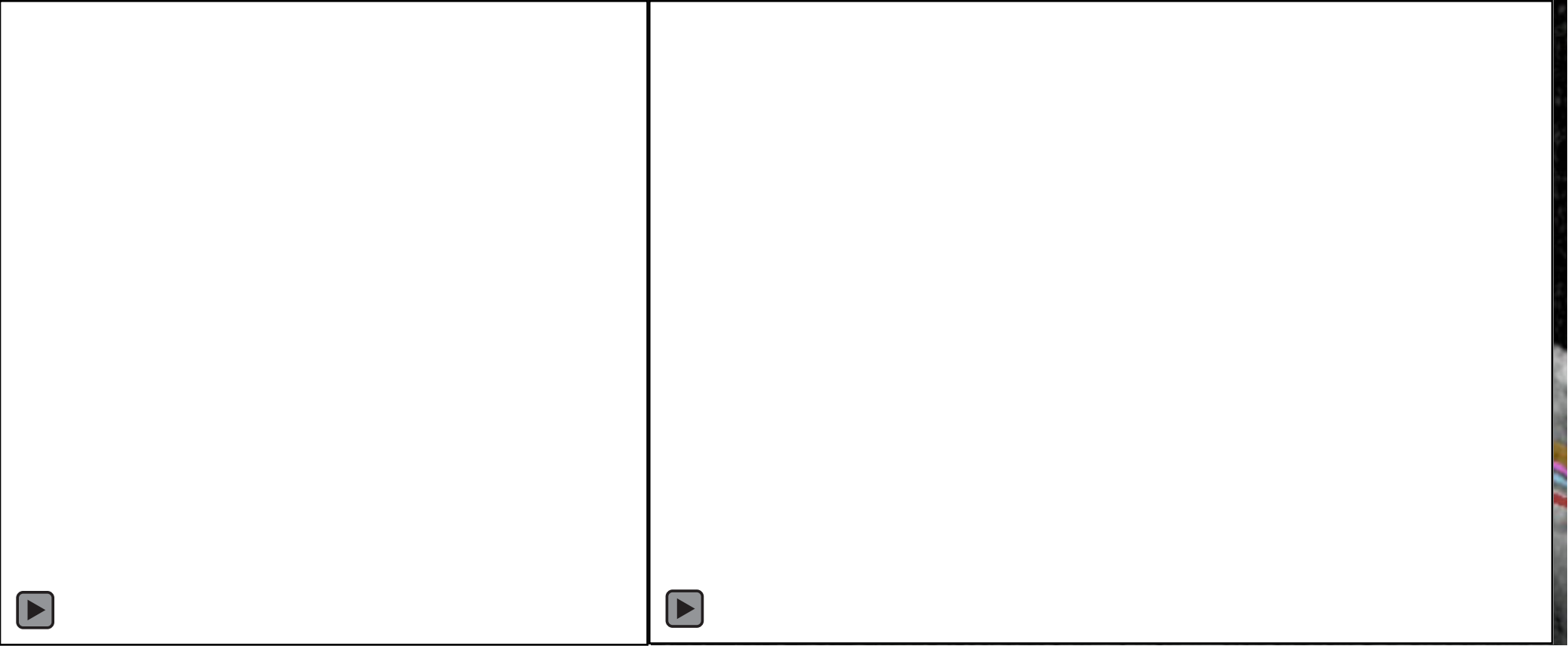
Structure leads, function follows — hard numbers

AREDS REPORT 26 — GA NATURAL HISTORY		SOCA (CMV RETINITIS) — CAUSAL PRECEDENT	
1.78 mm ² /yr	Mean GA enlargement rate (range 0.53–2.6)	Multivariate model (Holbrook 2003, Arch Ophthalmol):	
2.03 → 7.45	Mean cumulative enlargement (mm ²) at years 1 → 4	 <pre>graph LR; A[Retinal atrophy area + location] --> B[Visual field loss]; B --> C[BCVA loss]</pre>	
2.5 years	Median time from any GA to central GA (95% CI 2.0–3.0)	• Zone 1 involvement and extent of retinitis directly precede visual field loss.	
3.7 letters	Mean BCVA loss at first documentation of central GA	• Visual field loss independently predicts VA loss: RR 1.4 per 100° lost, p<0.001, even controlling for baseline VA.	
22 letters	Mean BCVA loss over 5 years AFTER central GA onset	• Confirms that retinal-tissue destruction is not merely correlated with functional loss — it causally determines it.	

GA growth rate on FAF as a primary outcome

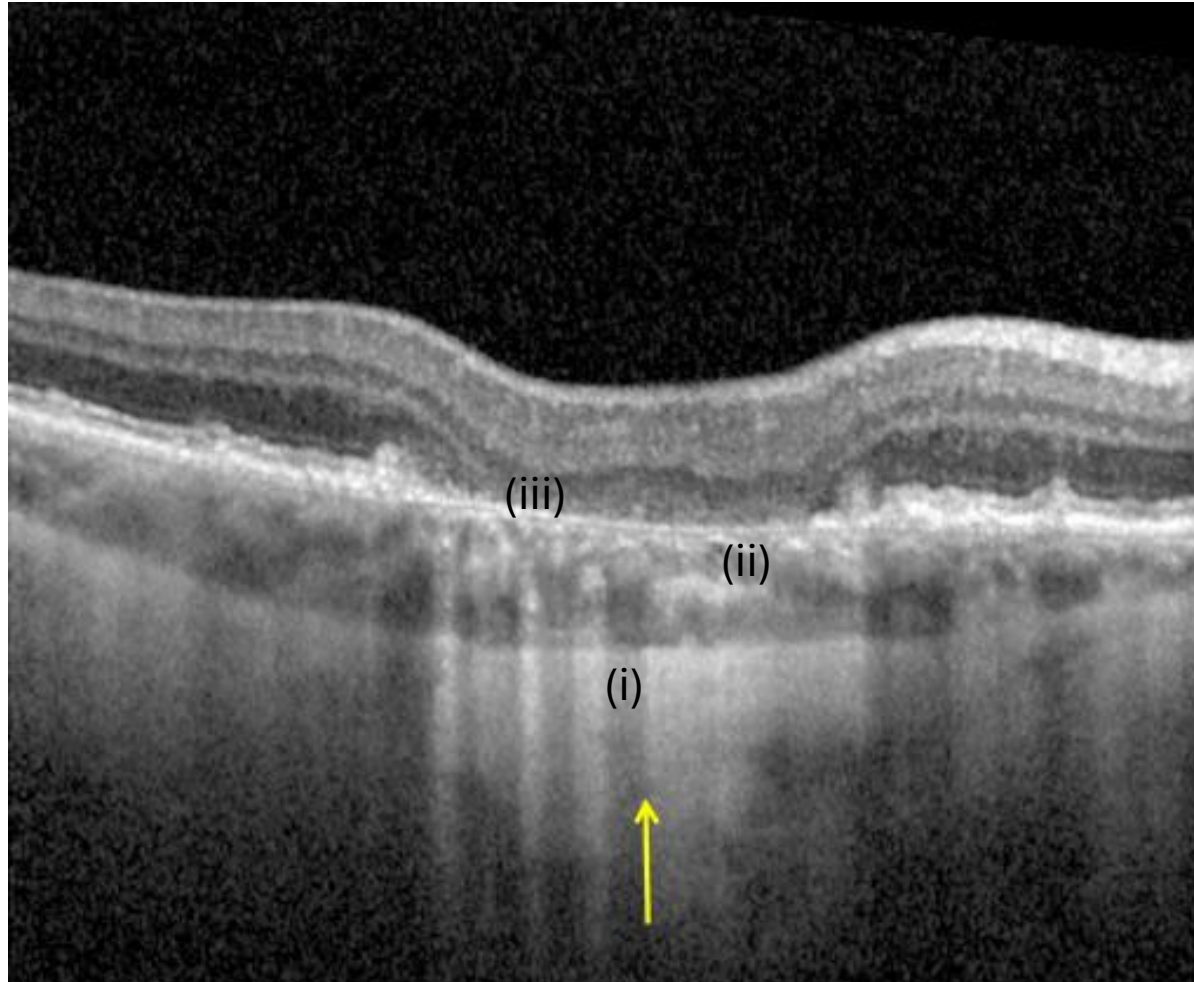
	Meet criteria of surrogate marker
Plausibility	
Construct validity	
Reliability	
Content validity	
Responsiveness/ predictability	
Change to intervention	

Structure 2: Retinal layers + Atrophy on OCT



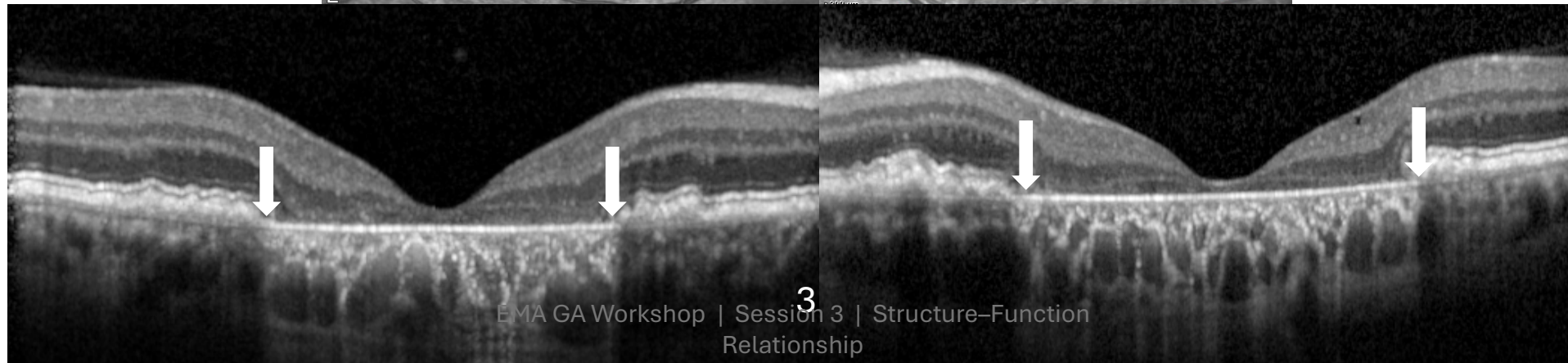
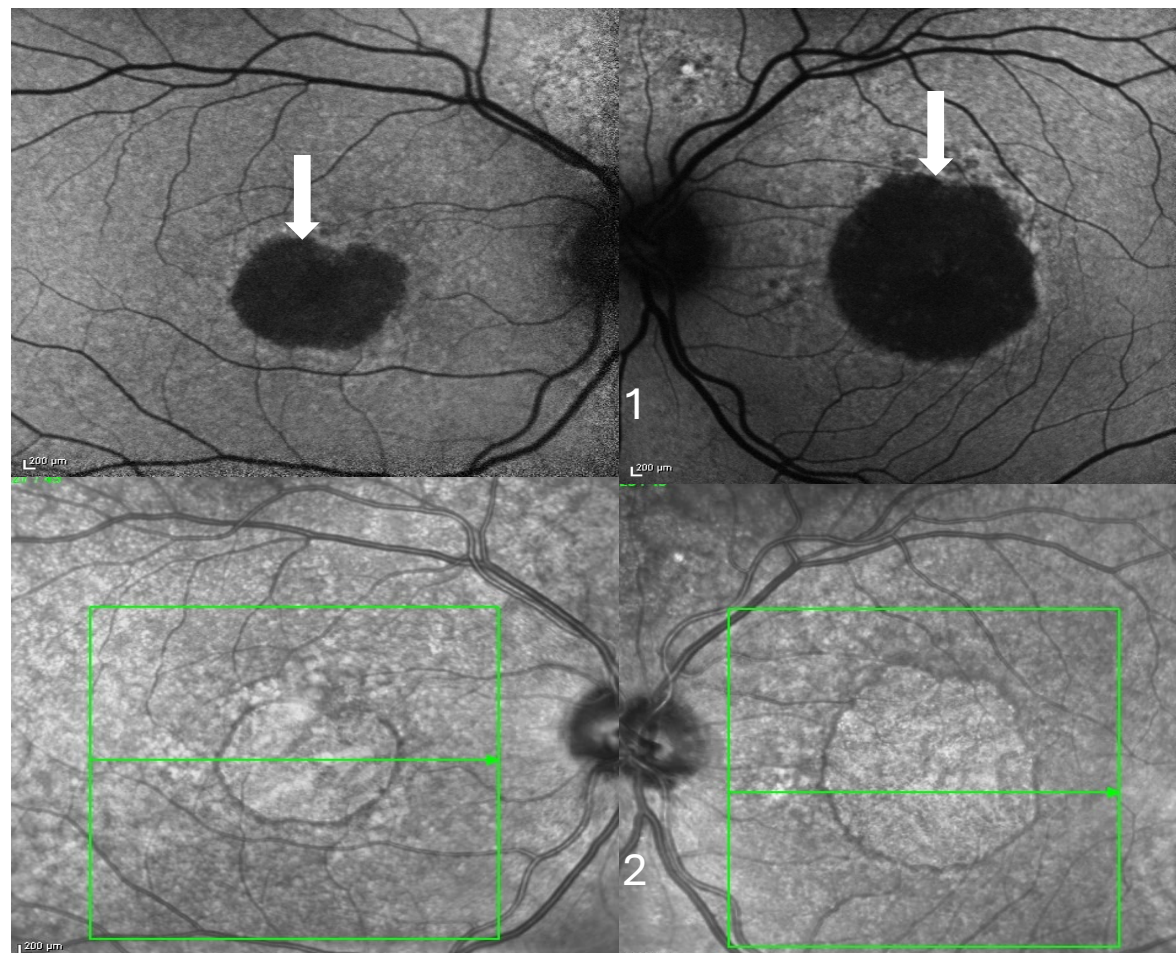
Outer Nuclear Layer
External limiting membrane
Ellipsoid Zone
Retinal Pigment Epithelium

Classification of Atrophy Meetings (CAM) program: Complete retinal pigment epithelium and outer retinal atrophy (cRORA)

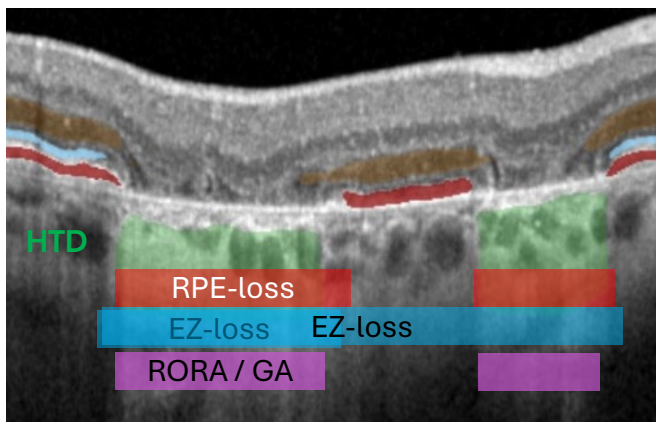


- (i) Zone of hyper transmission of $\geq 250 \mu\text{m}$
- (ii) Zone of attenuation or disruption of RPE band of $\geq 250 \mu\text{m}$
- (iii) Evidence of overlying photoreceptor degeneration characterised by features that include outer nuclear layer (ONL) thinning, external limiting membrane (ELM) loss, and ellipsoid zone (EZ) or interdigitating zone (IZ) loss.

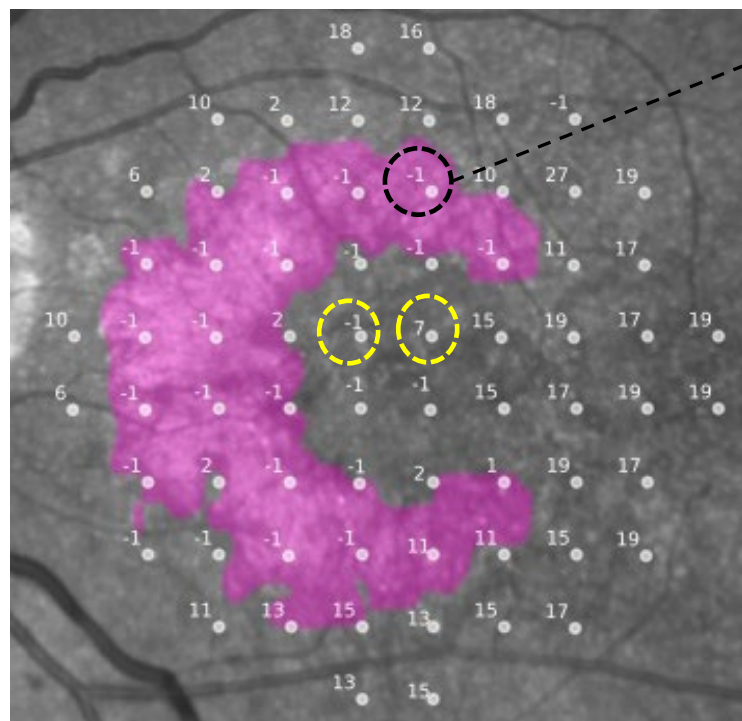
Correlation of lesion size of GA on FAF and retinal layer changes on OCT



ONL
EZ
RPE



EZ-loss in isolation
is an independent predictor of retinal sensitivity



GA + Microperimetry

Intra-GA

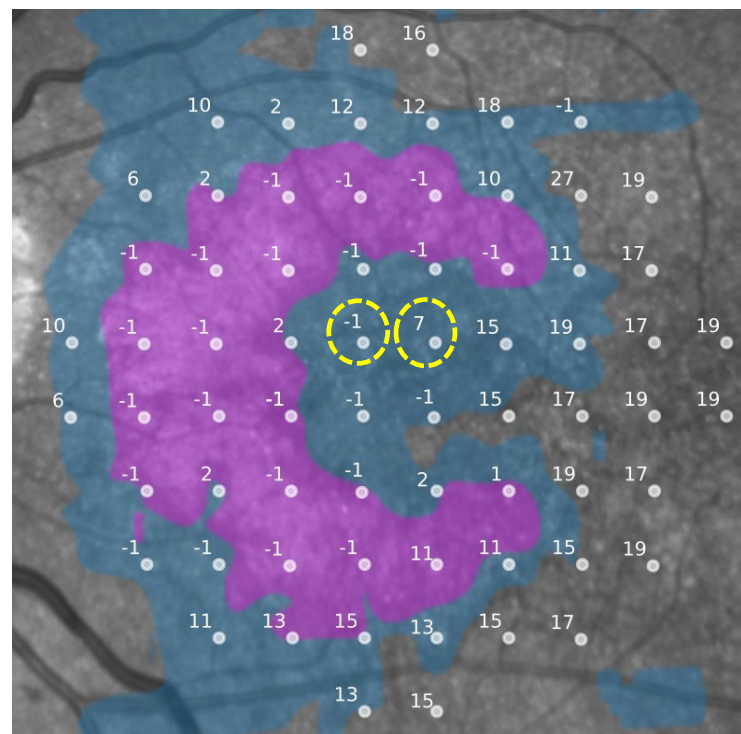


Relative Scotoma

≤ 10 dB
n=4388

Absolute Scotoma

< 0 dB
n=1476



+ EZ-loss in isolation

Relative Scotoma

84%
(3683/4388)

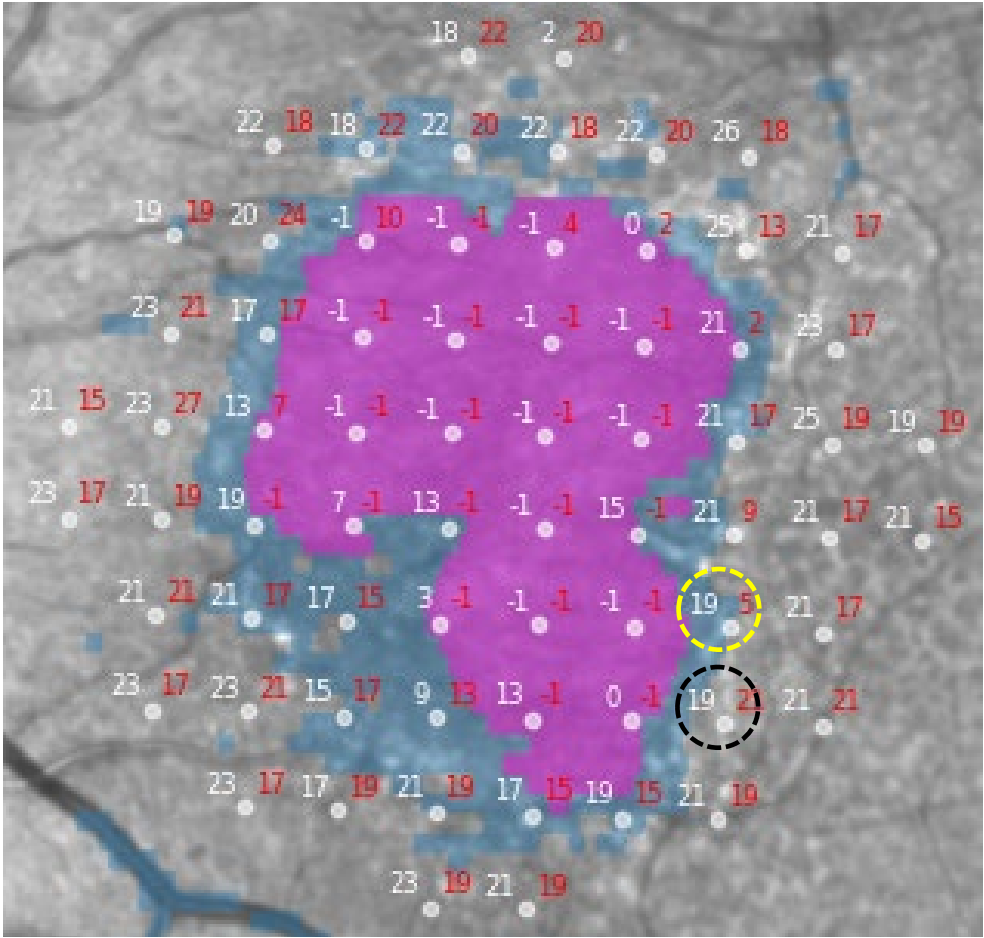
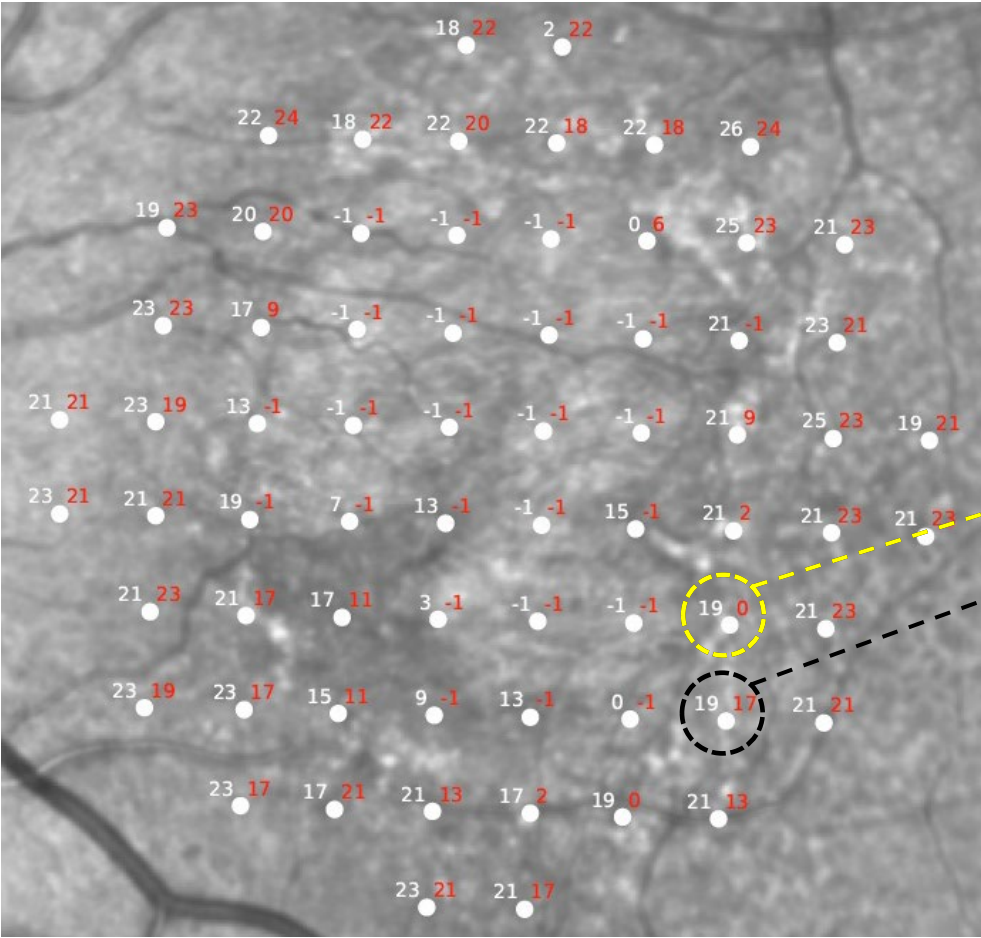
Absolute Scotoma

85%
(1245/1476)



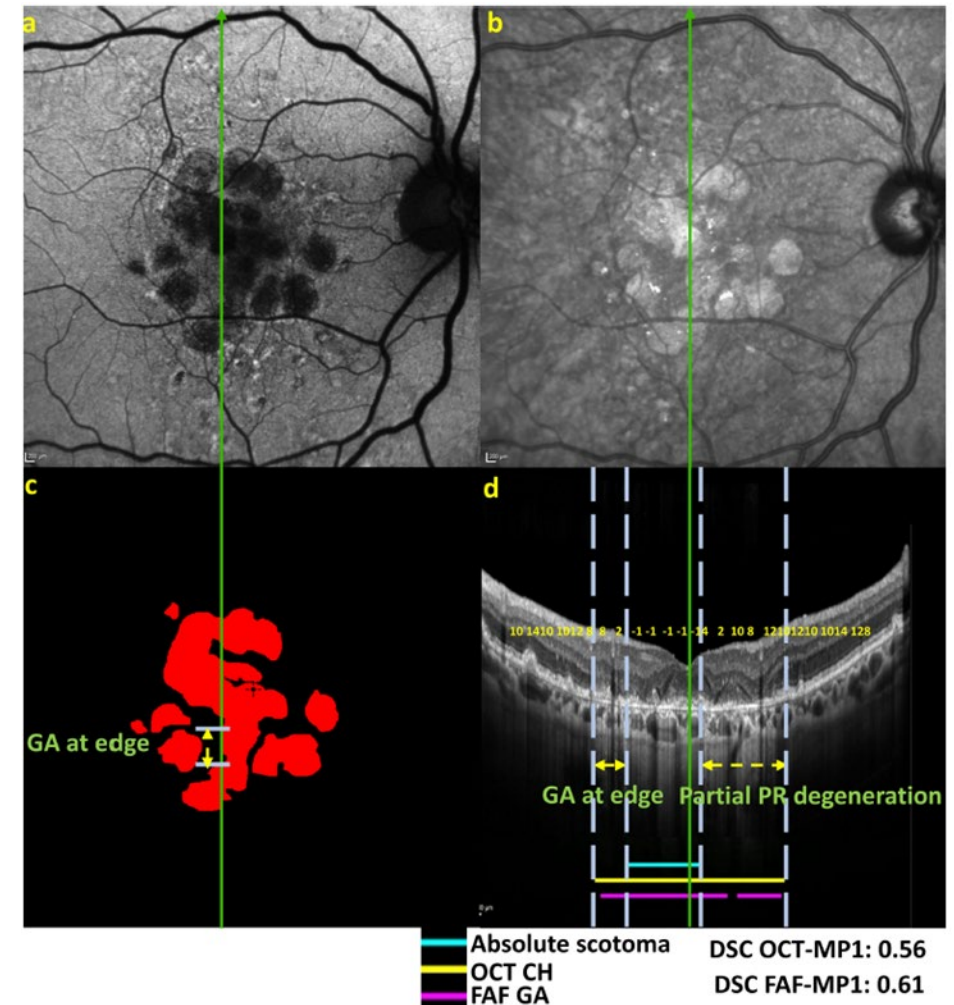
SDOCT biomarkers of photoreceptor integrity can predict future loss

GA EZ-loss in isolation



Spatial concordance between absolute scotomas on mesopic microperimetry and atrophy

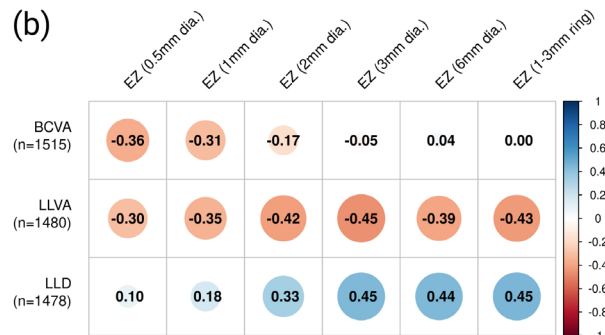
- Choroidal hypertransmission on OCT and/or geographic atrophy on fundus autofluorescence without absolute scotomas.



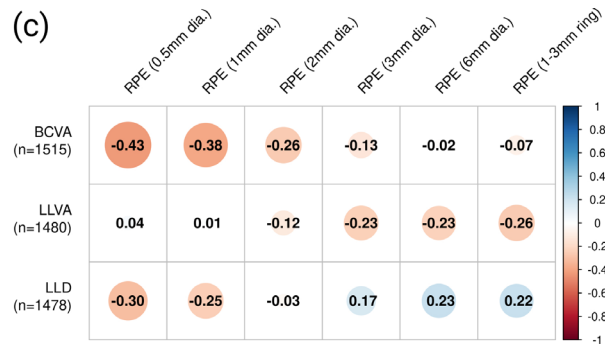
Recent studies demonstrated stronger correlation between EZ and BCVA/LLVA/LLD – supporting relevance of structural endpoints to photoreceptor loss

Structural GA presence in the macula correlates with visual acuity

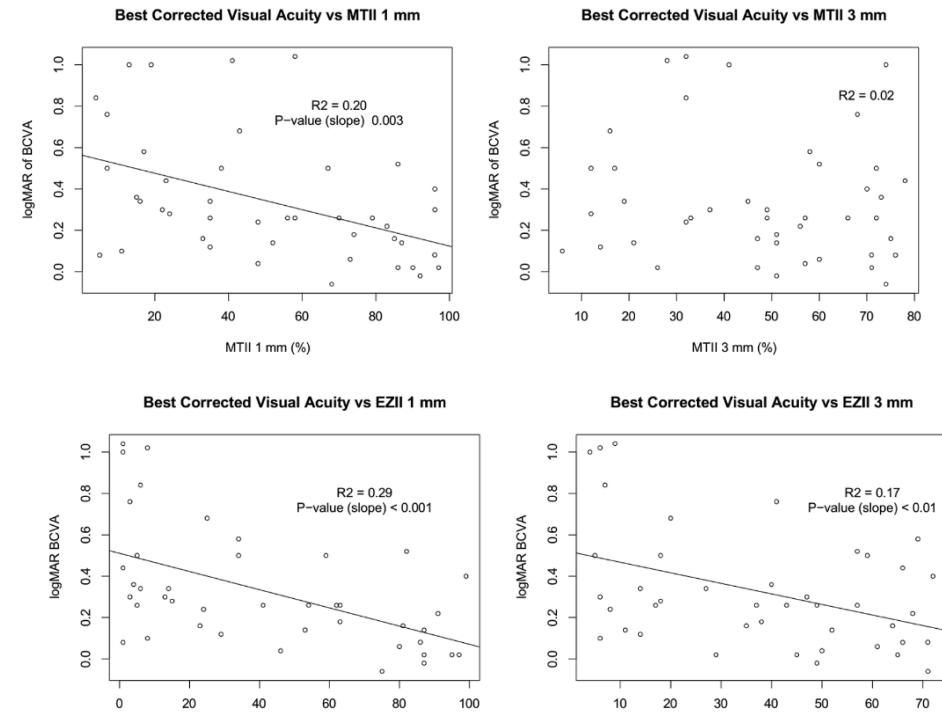
- Post-hoc analyses from Lampalizumab trials revealed central RPE and photoreceptor loss correlate with BCVA while paracentral photoreceptor loss and RPE loss correlate strongly with LLVA. Lending additional support for the functional significance of such structural endpoints



Pearson's correlation coefficient between baseline BCVA, LLVA, or low luminance deficit (LLD), and the OCT-based layer loss areas in the center region of the OCT scan.



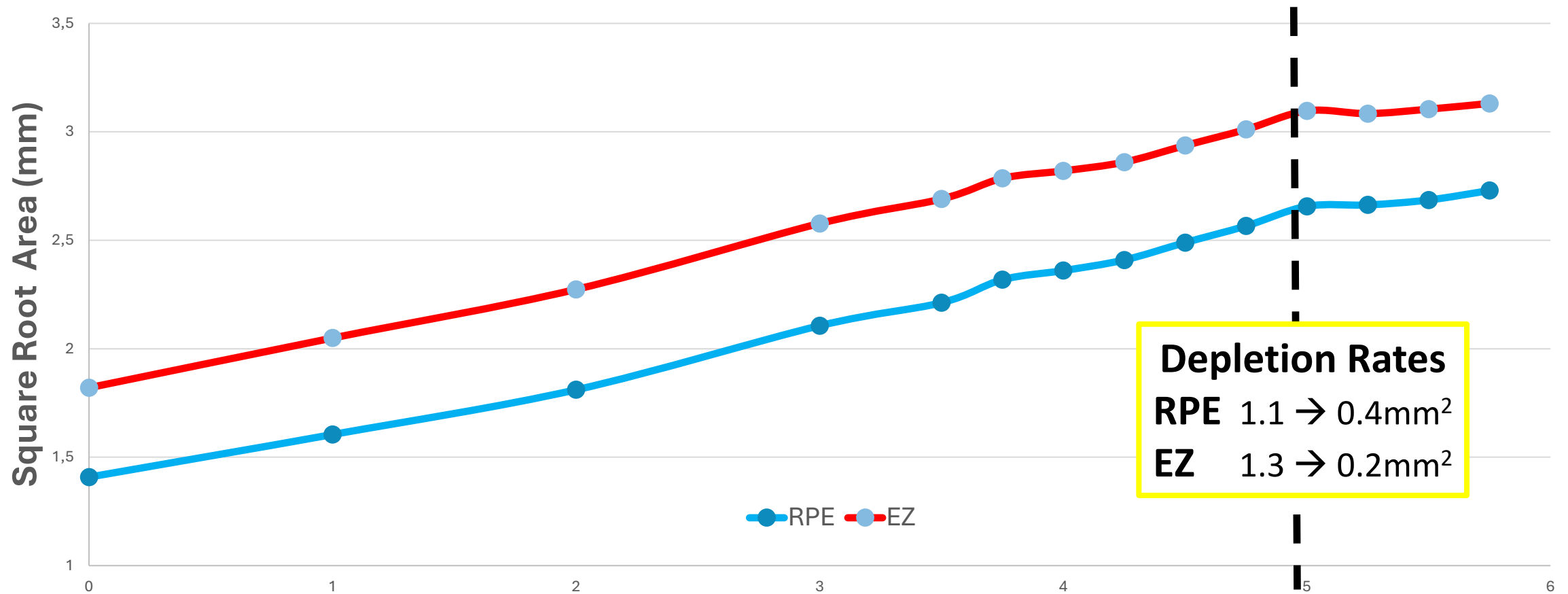
- Post-hoc analyses from GSK933776 phase 1 trial also reported similar correlations: GA presence and photoreceptor loss in the central 1 mm fovea is significantly correlated with BCVA while photoreceptor loss in the central 3 mm macula is significantly correlated with LLVA



1. Catherine A Cukras, Kenta Yoshida, Miao Zhang, Adam Pely, Verena Steffen, Simon S. Gao, Usha Chakravarthy, Christina Rabe, Sascha Fauser, Daniela Ferrara; Structure-function correlations in GA using AI-based retinal layers loss measurements on OCT. Invest. Ophthalmol. Vis. Sci. 2025;66(8):4588.
 2. Erb BM, Botros E, Saunders TF, Haas AM, Voland R, Linderman R, Domalpally A, Csaky KG. Investigating Macular Tissue Integrity Index as a Novel Biomarker in Geographic Atrophy. Ophthalmol Sci. 2025 Jun 30;5(6):100871. doi: 10.1016/j.xops.2025.100871. PMID: 40893624; PMCID: PMC12396552.

RPE & EZ Depletion

OCT-based Longitudinal Assessment: >50% slowing following Pegcetacoplan Initiation



Depletion Rates

RPE 1.1 → 0.4mm²

EZ 1.3 → 0.2mm²

N=168 eyes; 110 patients

Routine Clinical Practice

Years from Baseline

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Relationship

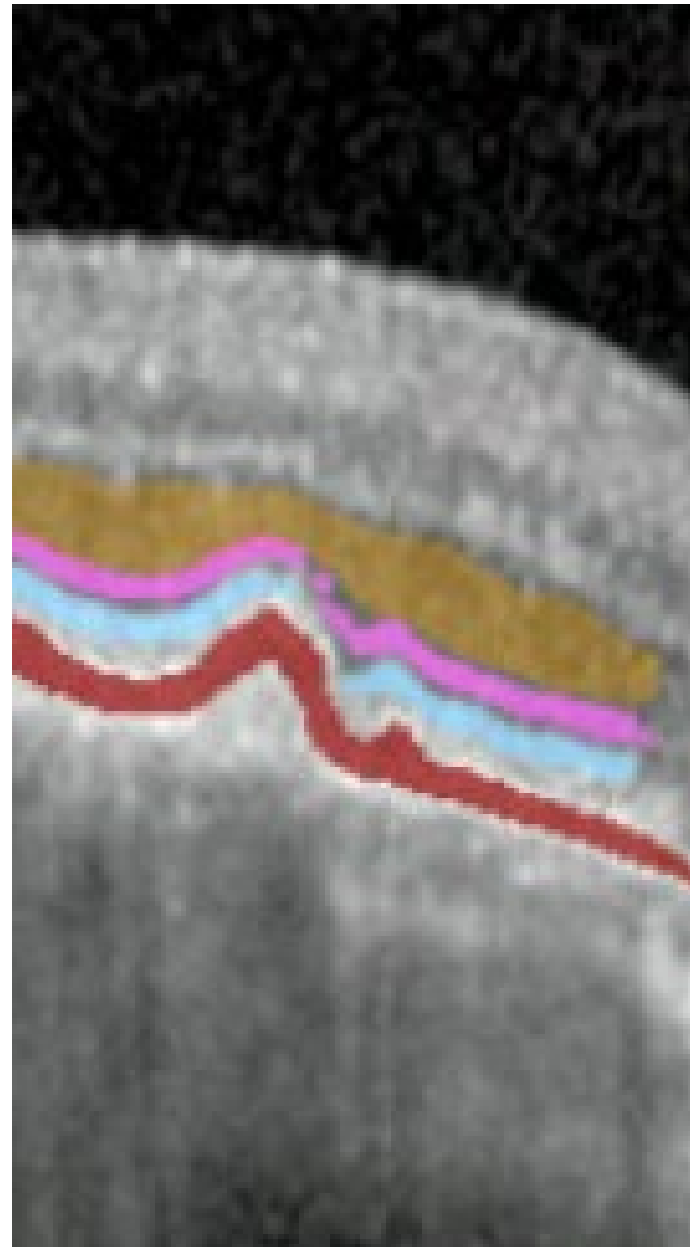
Geographic Atrophy Progression in Clinical Practice Before and After Pegcetacoplan Treatment. Cao JA *et al. Vision*. 2025; 9:95.

Classified as public by the European Medicines Agency

How to quantify
photoreceptor
thickness?

More validation
required

Anterior EZ
Posterior EZ



Outer Nuclear Layer
External limiting membrane
Ellipsoid Zone
Retinal Pigment Epithelium

EMA GA Workshop | Session 3 | Structure-Function
Relationship

Retinal layer change on OCT as a primary outcome

	Meet criteria of surrogate marker
Plausibility	
Construct validity	
Reliability	
Content validity	
Responsiveness/ predictability	
Change to intervention	

The problem with visual acuity as an endpoint

- Visual Acuity **CANNOT** be Estimated from Multimodal Imaging of Geographic Atrophy in Age-related Macular Degeneration.
- **Reasons:**
 - No Correlation Between GA Growth and BCVA
 - Fast vs Slow GA Growth Shows No BCVA Difference
 - Visual Acuity Cannot Be Reliably Estimated From Imaging
 - Slowing GA growth $\neq$ BCVA preservation (relationship too weak)
 - 15-letter loss is **borrowed from anti-VEGF** — it does not apply to GA

No Correlation Between GA Growth and BCVA

Data from CHROMA, SPECTRI, and PROXIMA A trials

BASELINE GA AREA VS BCVA CHANGE (24-96 WEEKS)

$r = -0.04$ to -0.07

Essentially no correlation

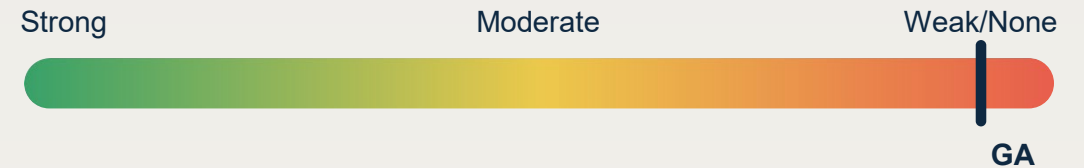
GA GROWTH RATE VS BCVA CHANGE (24-96 weeks)

$r = -0.05$ to -0.17

Weak, even at 96 weeks

GA lesion area and growth are **not** correlated with visual acuity changes

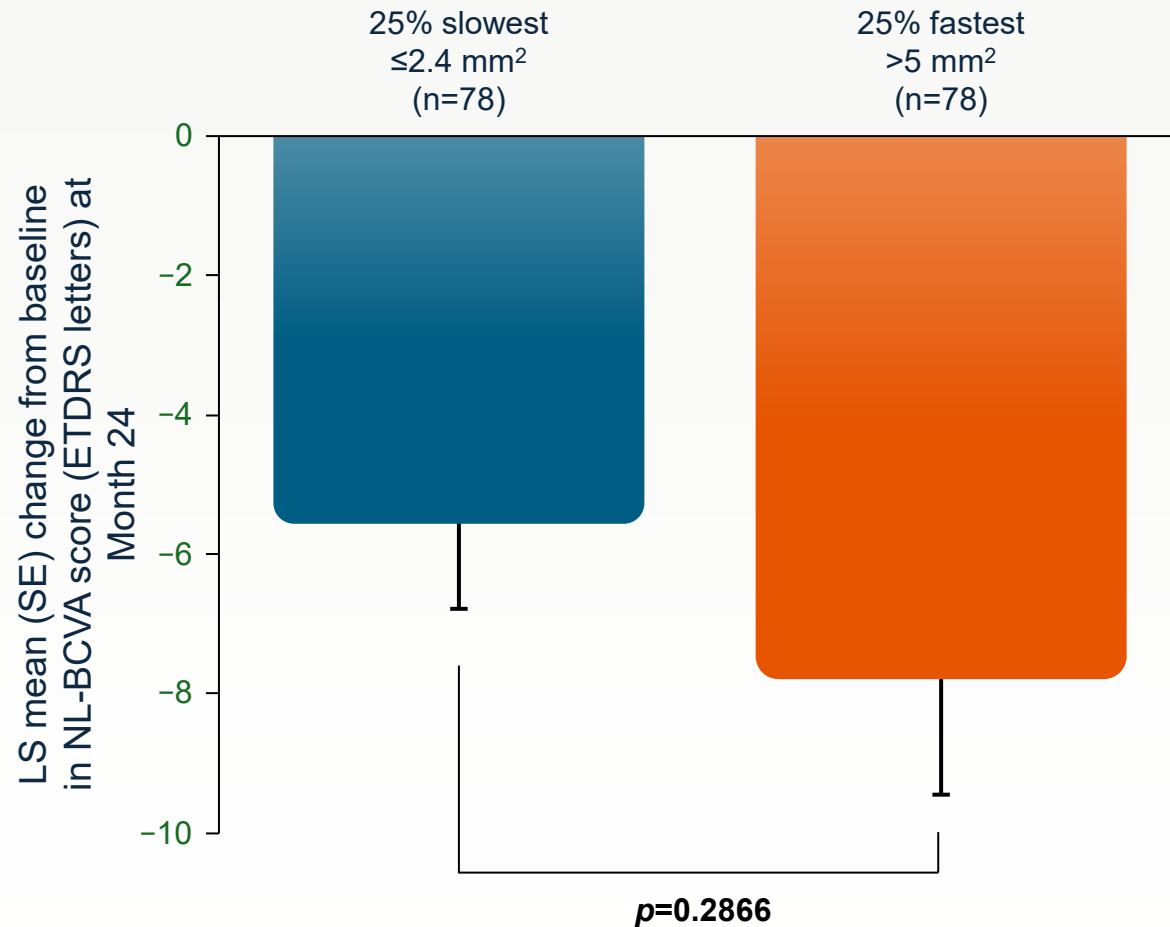
Correlation Strength Scale



Compare to nAMD/DME/RVO: Strong correlation between treatment effect and visual outcome

Fast vs Slow GA Growth Shows No BCVA Difference

OAKS/DERBY sham observed arm analysis at Month 24



STATISTICAL RESULT

$p=0.2866$

No significant difference

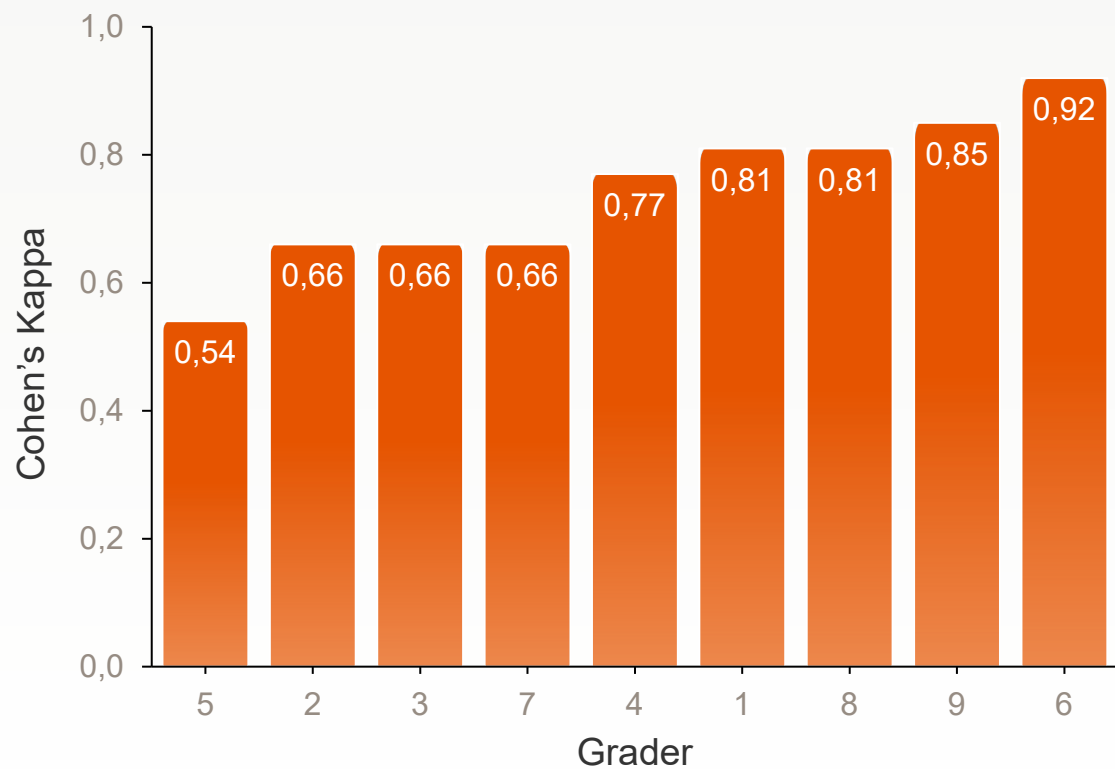
Patients with **fastest** and **slowest** GA progression experienced **similar BCVA loss**

If growth doesn't correlate BCVA loss, why use BCVA as an endpoint?

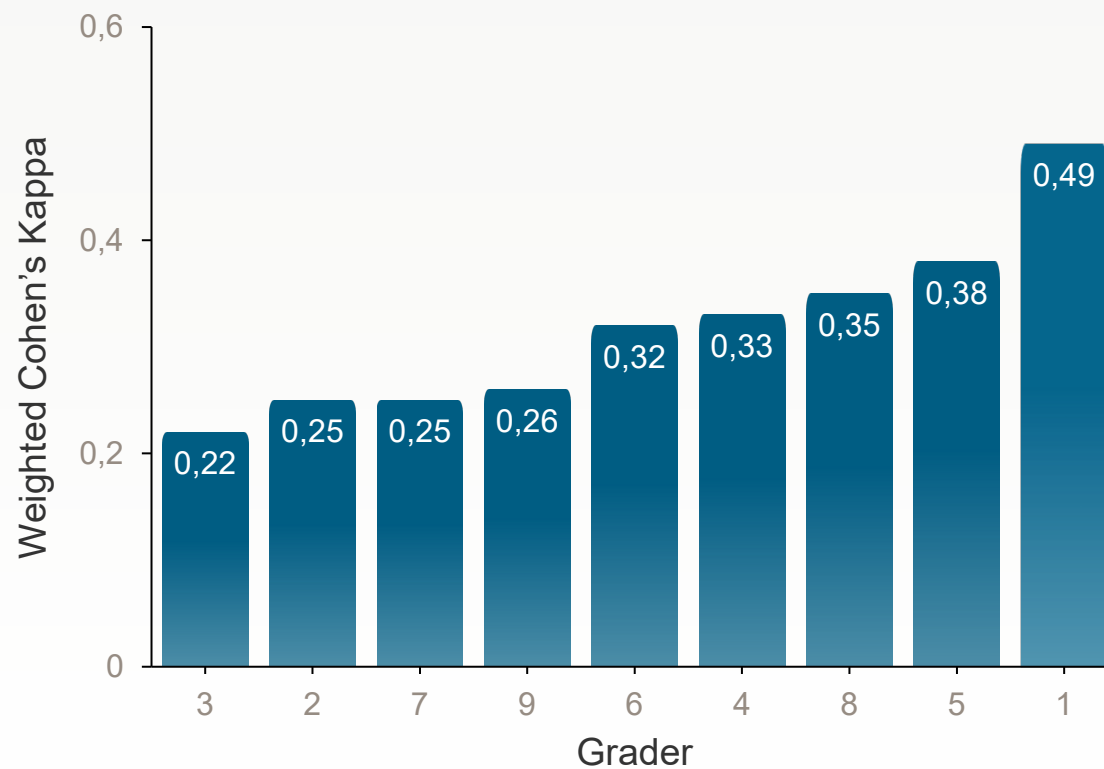
Visual Acuity Cannot Be Reliably Estimated From Imaging

9 senior retina specialists (>25 years experience) | 49 multimodal images from OAKS/DERBY baseline

Grader vs Ground Truth Agreement for GA Location



Grader vs Ground Truth Agreement for Visual Acuity



Visual Acuity Cannot Be Reliably Estimated From Imaging

9 senior retina specialists (>25 years experience) | 49 multimodal images from OAKS/DERBY baseline

GA LOCATION AGREEMENT

Experts can identify subfoveal vs nonsubfoveal

$\kappa = 0.74$

Substantial

Neither human expertise nor AI can reliably estimate visual acuity from GA imaging

VISUAL ACUITY AGREEMENT

Experts cannot predict VA from imaging

$\kappa = 0.31$

Fair only

THE IMPLICATION

Even **experts cannot estimate VA** from structure, further indicating a lack of correlation

36%

Human Accuracy

0.38

AI Kappa (also fair)

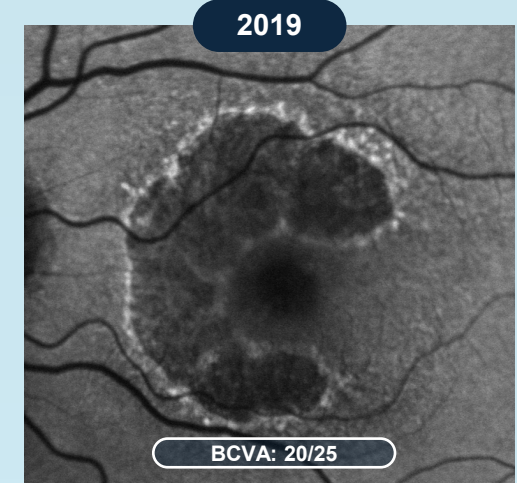
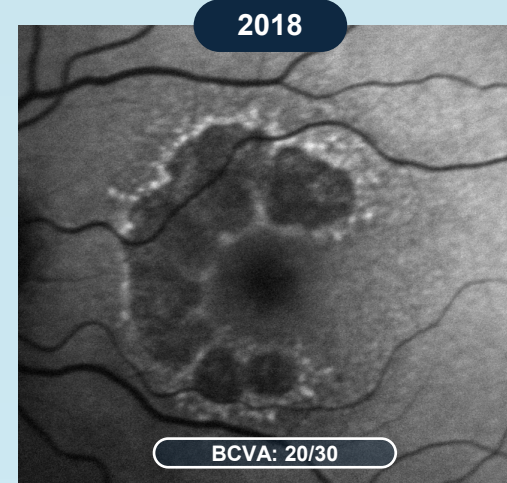
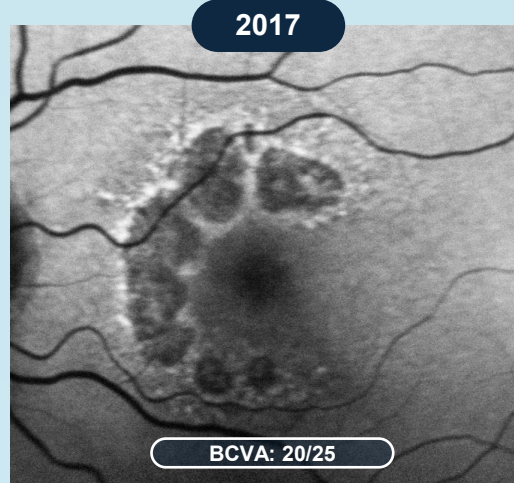
Why BCVA Fails in GA

BCVA is preserved even as other measures of function decline

1. FOVEAL SPARING

GA often starts **parafoveally** - the fovea is initially preserved

BCVA remains normal early despite disease progression



Why BCVA Fails

SHAM observed eyes from DERBY

2. LOCATION MATTERS

Visual acuity is **fovea driven**.

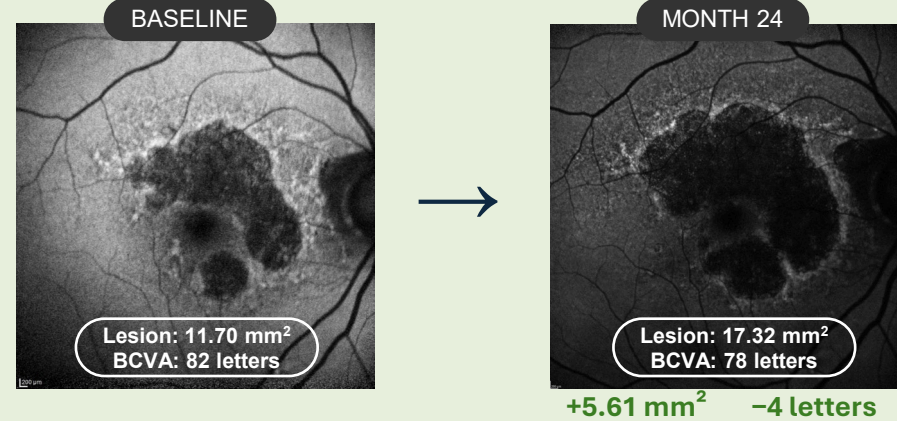
~5.6 mm² growth in both cases

But VA loss: **-4** vs **-16** letters

Identical growth →
4× difference in VA loss —
location determines functional impact

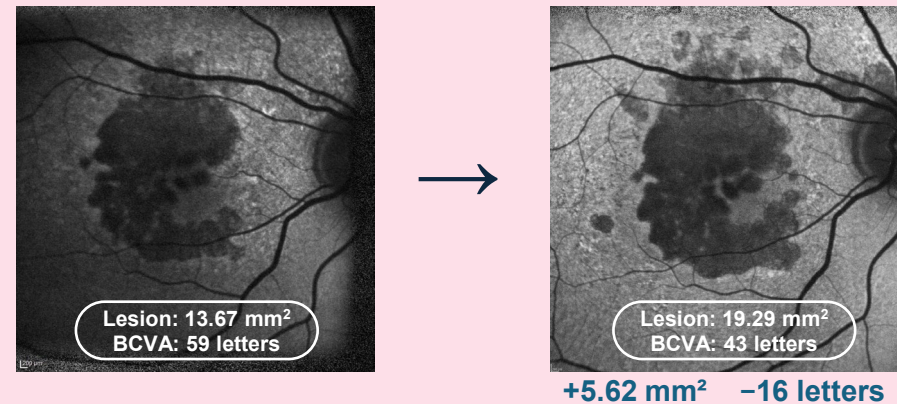
CASE 1

Nonsubfoveal →
Nonsubfoveal



CASE 2

Nonsubfoveal →
Subfoveal



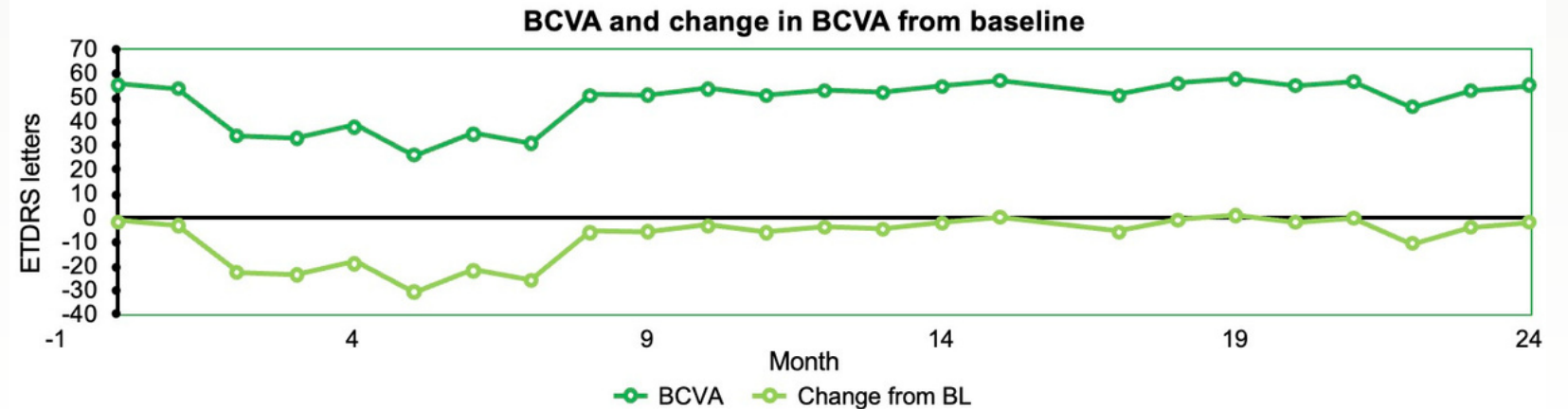
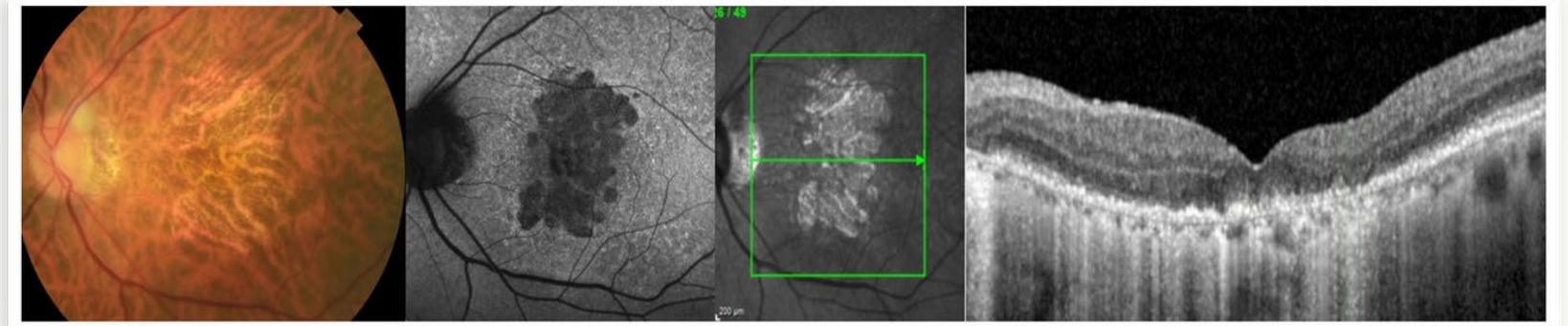
Why BCVA Fails (Sham Observed Patient, OAKS)

PRL shifts preserve BCVA while underlying GA advances

3. PRL ADAPTATION

Patients develop **eccentric fixation** to compensate

Temporary measure until complete central vision loss.



Why BCVA Fails

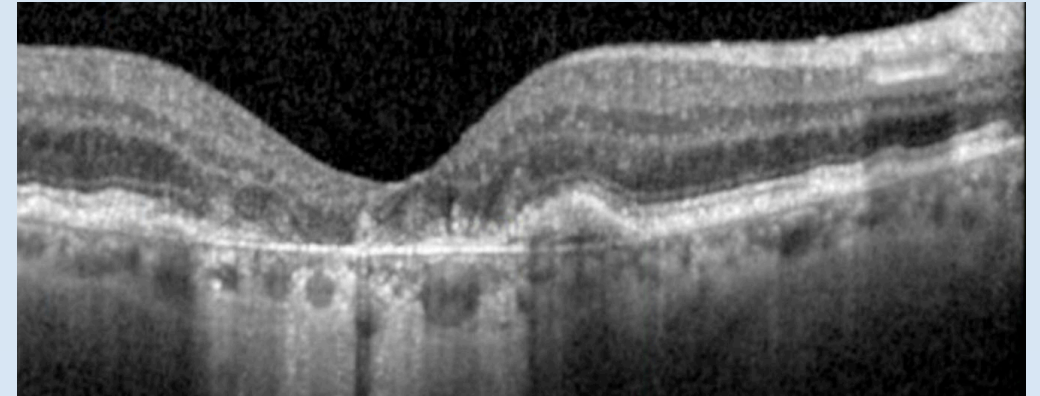
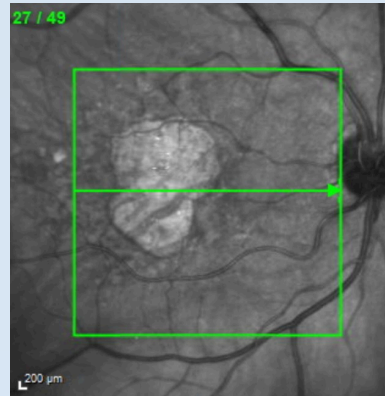
PRL shifts preserve BCVA while underlying GA advances

3. PRL ADAPTATION

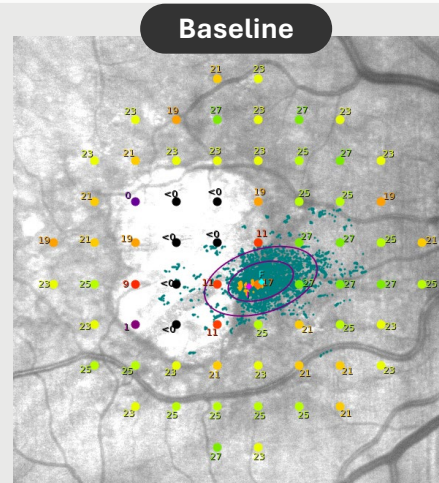
Patients develop **eccentric fixation** to compensate

Temporary measure until complete central vision loss.

OCT

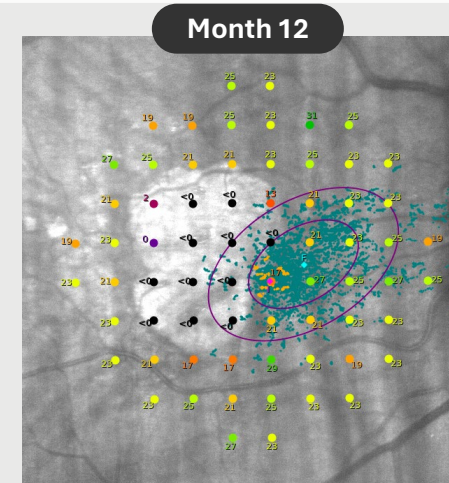


Microperimetry

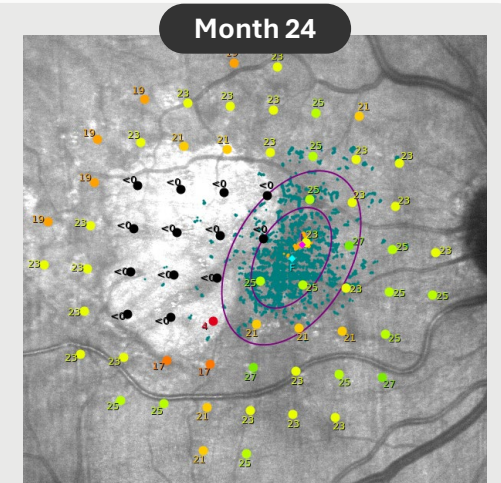


Area
BCVA

5.1 mm²
77 letters



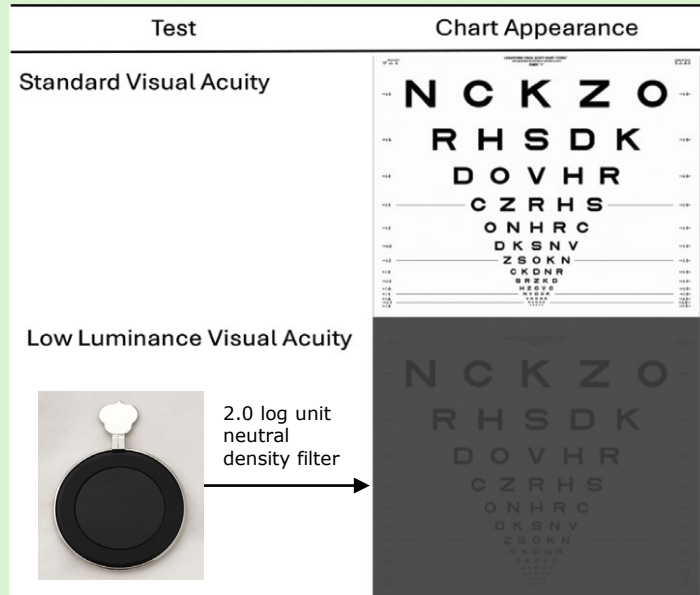
5.7 mm² +0.6
67 letters -10



5.9 mm² +0.2
70 letters +3

High contrast vision – BCVA, LLVA, LLD in GA

Strengths, limitations and what they mean for GA



- **BCVA** tests for photopic cone function, reflects vision function at its **peak efficiency**, different from day-to-day life experiences
- **LLVA** tests for mesopic cone function, reflects vision function **under stress**
- **LLD**, the difference between BCVA and LLVA, reveals **early dysfunction**

BCVA & LLVA are highly depended on PRL, which is known to change for GA patients

BCVA & LLVA: effort-based test with high test-rest variability

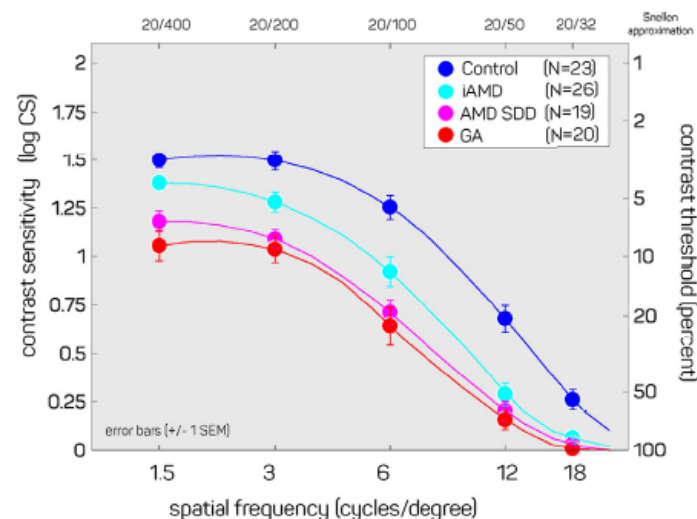
- Past studies such as Arditi and Cagenell (1993), Rosser et al (2003) and Lim et al (2010) all reported high variability in BCVA testing, test-retest variability (TRV) ranged from ± 0.09 to ± 0.14 logMAR (4.5-7 ETDRS letters)
- LLVA test results could vary with different dark adaptation duration
- LLD compounds the measurement error of both BCVA and LLVA

BCVA is a **lagging** indicator of vision function with many factors that affect its measurement accuracy

Quantitative contrast sensitivity function as AULCSF shows significant differences between groups under standard and low luminance.

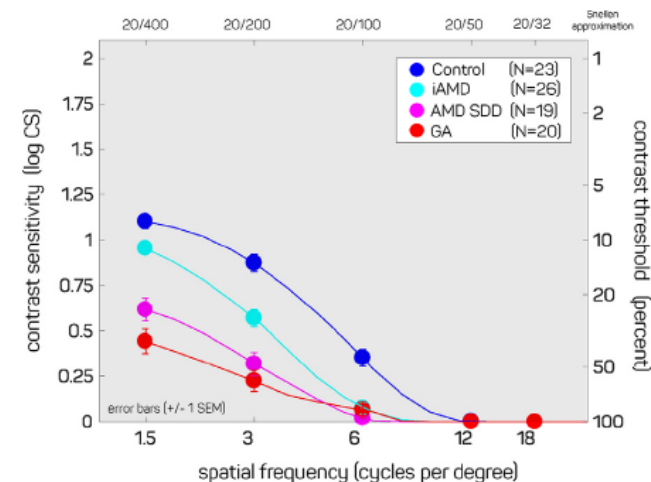
Patients with various stages of AMD and age-matched controls were tested using the Manifold Contrast Vision Meter and qCSF

AULCSF decreased progressively with disease severity.



**Standard-luminance
contrast sensitivity functions.**

**Low-luminance
contrast sensitivity functions.**



[Ou et al. 2021]

Visual Acuity

	Meet criteria
Plausibility	Too late
Construct validity	
Reliability	
Content validity	
Responsiveness/ predictability	
Change to intervention	

Other Visual Function Endpoints That Reflect True Visual Disability

Functional endpoints that better capture GA progression

Microperimetry

Enhanced-sampling microperimetry maps retinal sensitivity in the transitional zone where GA progresses

Quantitative Contrast Sensitivity (qCSF)

qCSF detects contrast loss that correlates with GA size and PROs

Low-Luminance Functional Vision

Low-luminance tests (LL-BCVA, LL-qVA, LL-qCSF) may better detect visual dysfunction

OCT-F

High-definition sensitivity maps allowing for granular detection of sensitivity loss

Patient-Reported Outcomes

PROs reflect daily visual difficulties, though signals can be noisy in GA

Composite Endpoints

Combine **structure + function** for comprehensive assessment

These alternatives measure what matters: **vision across the entire affected area** and **functional impact on daily life**

Denser, anatomy-anchored structure–function mapping

Inferred microperimetry (OCT-F)

MAE $\approx$ 4–5 dB

AI predicts point-wise MP thresholds from OCT (IS thickness, ONL integrity, EZ reflectivity). Error is on par with the test–retest variability of mesopic MP itself — no psychophysical testing required.

von der Emde 2019; Pfau 2020; Müller 2021

Patient-tailored MP

Anchored to lesion edge

Loci placed in concentric rings at predefined distances from the GA margin on FAF; or perilesional masks targeting responding loci. Stronger correlations with GA lesion growth than mean macular sensitivity.

Pfau 2020; Chang 2025

Defect-mapping MP (DMP)

1° spacing | ~6 min

Suprathreshold 10 dB, single presentation per locus → denser grid in central 8°. Test–retest 1.8% vs 3.3% for threshold MP ($P < 0.001$). Modelling suggests substantially smaller required sample sizes in GA trials.

Wu 2019; Wu 2024; Saeed 2025

qCSF on Manifold platform

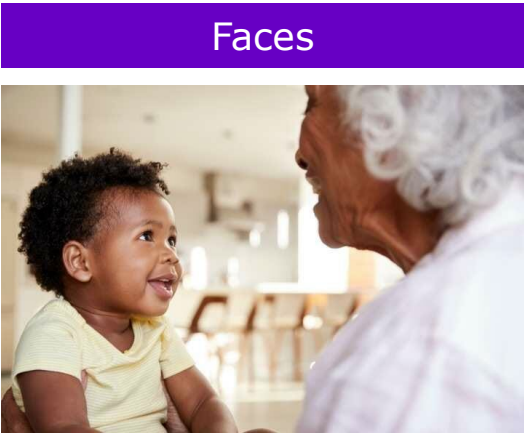
ICC > 0.90 | <5 min/eye

Bayesian adaptive estimate of full CSF; AULCSF detects deficits in AMD with BCVA > 20/25; correlates with photoreceptor integrity, ONL thickness, and choriocapillaris perfusion.

Vingopoulos 2021; Ou 2021; Anders 2023; Finn 2024

Contrast is more relevant for day-to-day vision function than BCVA

Contrast sensitivity is a better predictor of day-to-day vision function than BCVA



Owsley and Sloane (1987) demonstrated the following in 93 patients from a primary care clinic:

- Visual acuity was correlated with age
- Visual acuity was correlated with patients' ability to detect and identify signs, faces and daily objects
- When including multiple variables, **contrast sensitivity at medium frequency** – instead of visual acuity - was identified as a **key predictor for subjects' ability to detect and identify signs, faces and objects**

Independent variables evaluated

Contrast threshold at:
0.5 c/deg
1.0 c/deg
3.0 c/deg
6.0 c/deg
11.4 c/deg
22.8 c/deg
Letter acuity
Age

3 cpd: ~ 20/200
6 cpd: ~ 20/100
30 cpd: ~20/20

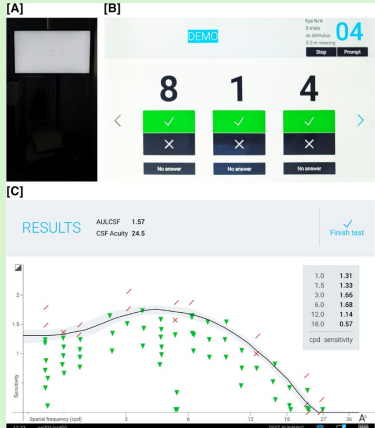
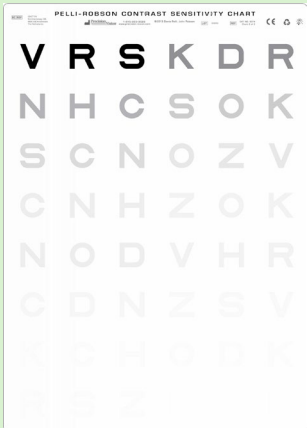
Table 3 Best-fitting model for each dependent variable

Dependent variable	Independent variable	R ² for model
Face detection	Age	0.29
	3 c/deg	
	0.5 c/deg	
Face identification	6 c/deg	0.25
	Age	
Sign detection	6 c/deg	0.40
	Age	
Sign identification	6 c/deg	0.30
	Age	
Object detection	Age	0.28
	6 c/deg	
Object identification	Age	0.40
	6 c/deg	

Owsley C, Sloane ME. Contrast sensitivity, acuity, and the perception of 'real-world' targets. Br J Ophthalmol. 1987 Oct;71(10):791-6. doi: 10.1136/bjo.71.10.791. PMID: 3676151; PMCID: PMC1041308.

Contrast sensitivity in GA – promising endpoints with limited data

A more comprehensive test of functional vision



Test	Pelli-Robson	MARS	qCSF
Type	Wall mounted chart	Handheld booklet	Computer/ tablet based
Distance	Typically 1 m	40—50cm	3 m ()
Letter Size	One spatial frequency	One spatial frequency	Multiple spatial frequencies
Step Size	0.15 log-unit steps	0.04 log-unit steps	0.02 log-unit steps, digitally implemented
Output	Peak contrast sensitivity (CS) at one spatial frequency	Peak CS at one spatial frequency	CS function curve (Peak CS at various spatial frequencies, low contrast visual acuity)

qCSF: multiple outputs to choose from

- Area Under the Log CSF (AULCSF)
- Peak CS at 1, 1.5, 3, 6, 12, 18 cycles per degree (log unit - dB)
- Low contrast visual acuity (LCqVA)
- Low luminance area Under the Log CSF (AULCSF)
- Low luminance peak CS at 1, 1.5, 3, 6, 12, 18 cycles per degree (log unit -dB)
- Low luminance low contrast visual acuity (logMAR, equivalent ETDRS)

Multiple outcomes possible: AULCSF is most comprehensive, peak CS at medium frequencies most relevant for day-to-day vision, LC-qVA easier to comprehend

Promising early evidence in AMD

- The MUMОВI study demonstrated statistically different CS between eAMD, iAMD and control patients while no differences in visual acuity was observed, highlighting its sensitivity.
- Revealed larger changes in CS (0.55 log unit step) comparing to VA (0.1 logMAR) for nAMD – single example
- Structure - function correlation with CC flow deficits, photoreceptors, RPE, HRF etc

Contrast sensitivity is an emerging promising measurement, data not mature enough to support a specific primary endpoint

*AMD: age-related macular degeneration; eAMD: early AMD; iAMD: intermediate AMD; CS: contrast sensitivity

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2. Csaky KG. Cross-Sectional Study of Cone Function in Age-Related Macular Degeneration Subjects With Non-foveal Nascent Geographic Atrophy. Am J Ophthalmol. 2023 Mar;247:25-34.

3. Romano F, Vingopoulos F, Yuan M, Ding X, Garcia M, Ploumi I, Rodriguez J, Garg I, Tracy JH, Bannerman A, Choi H, Stettler I, Bennett C, Overbey KM, Lains I, Kim LA, Vavvas DG, Husain D, Miller JW, Miller JB. Decreased Macular Choriocapillaris Perfusion Correlates with Contrast Sensitivity Function in Dry Age-Related Macular Degeneration. Ophthalmol Retina. 2024 Dec;8(12):1140-1150.

4. Bennett C, Romano F, Vingopoulos F, Garcia M, Ding X, Bannerman A, Ploumi I, Ntentakis D, Stettler I, Overbey K, Baldwin G, Bejjani R, Garg I, Rodriguez J, Lains I, Kim LA, Vavvas D, Husain D, Miller JW, Miller JB. Associations Between Contrast Sensitivity, Optical Coherence Tomography Features and Progression From Intermediate to Late Age-related Macular Degeneration. Am J Ophthalmol. 2025 Mar;271:175-187.

5. Owsley C, Gao L, Gooden L, Thomas TN, Pu J, Crosson JN, Curcio CA, McGwin G Jr, Kwon M. Preserved Contrast Sensitivity in Early and Intermediate Age-Related Macular Degeneration and Marked Loss in Late Stage: ALSTAR2. Invest Ophthalmol Vis Sci. 2026 Jan 5;67(1):58.

Imaging endpoints map point-for-point to function

STRUCTURE (IMAGING)	FUNCTIONAL CORRELATE	EVIDENCE
FAF-defined atrophy	Absolute scotomas; perilesional MP sensitivity loss	<i>Spatial correspondence on fundus-tracked MP; Pfau 2020</i>
EZ loss / attenuation (OCT)	Reduced mesopic sensitivity on microperimetry	<i>MACUSTAR (2025); Yordi 2024 — co-localization at the loss rim</i>
cRORA (OCT)	Absolute scotomas, ↓ retinal sensitivity, ↓ contrast sensitivity, even with preserved BCVA	<i>MACUSTAR; post-hoc FILLY & GATHER1 (Liao 2020; Jaffe 2021; Wu 2023, 2024)</i>
ONL thickness (OCT)	MP sensitivity; in SDD phenotypes precedes EZ disruption	<i>Birner 2024; Jaffe 2021</i>
OAKS junctional-zone grid	MP mean sensitivity & scotomatous points within ±250 µm of GA margin	<i>Alibhai 2025 — high ICC, low CoR</i>
Central 4 / 16 MP loci lost	Greater BCVA decline	<i>Chakravarthy 2025 (OAKS post-hoc)</i>
Choriocapillaris perfusion ↓	qCSF contrast sensitivity ↓, even without VA loss	<i>Romano 2024</i>
ONL thinning, ↑ RPE volume, hyperreflective foci	qCSF AULCSF ↓	<i>Chan 2024; Bennett 2025</i>

Thank you

Discussion welcome — on behalf of the BRIDGE Study Group.

References: BRIDGE anatomical endpoints manuscript (Sanofi draft, 16 Feb 2026) and cited primary literature therein.