Contrast Sensitivity

Karl Csaky, MD, PhD – Professor – Retina
Foundation of the Southwest

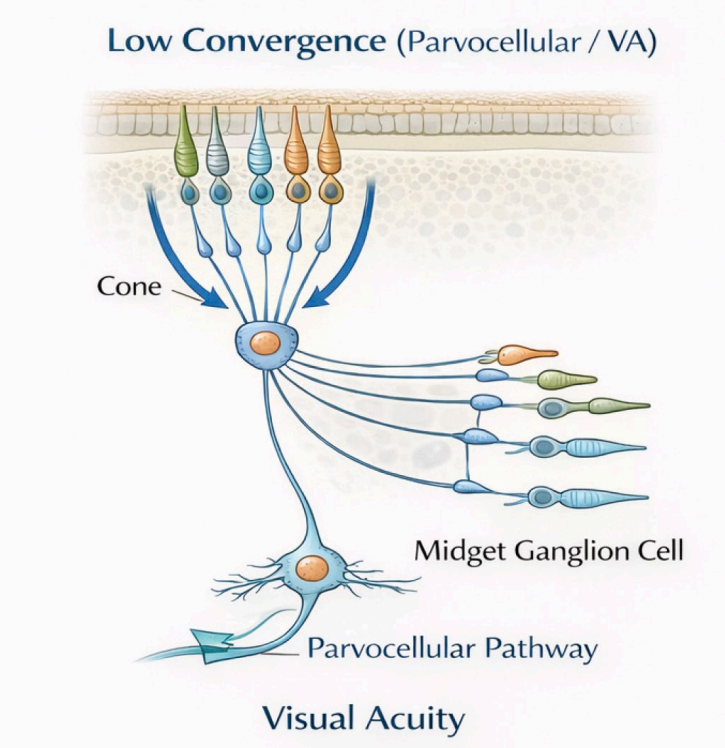
EMRN workshop on Geographic Atrophy endpoints – 29 April 2026

Disclosure statement

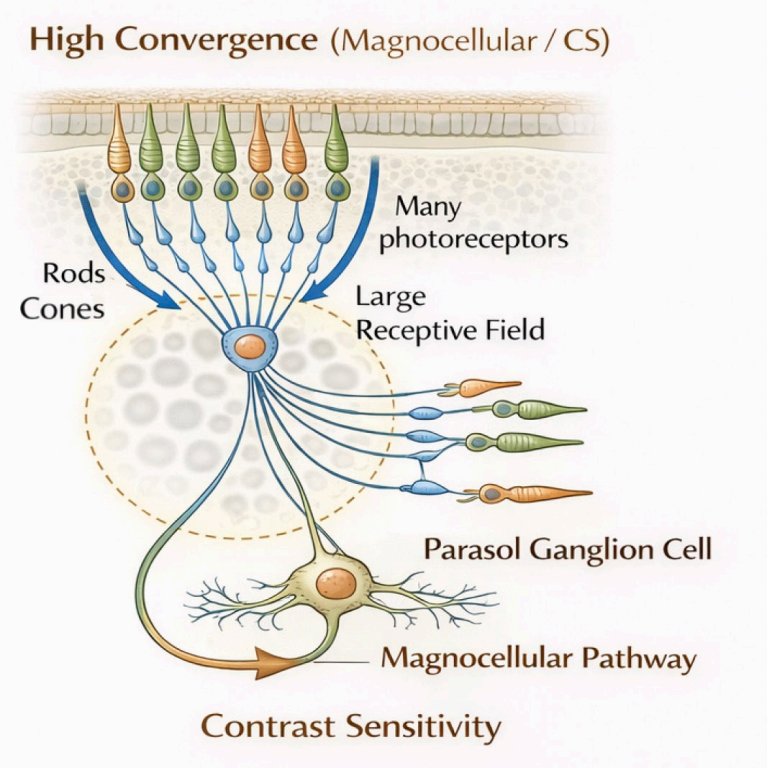
The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to any organization with which the presenter is employed or affiliated.

- Abbvie (Consultant)
- Adverum Biotechnologies (Data and Safety Monitoring)
- Annexon Biosciences (Consultant, Grant Support)
- Boehringer Ingelheim (Consultant, Grant Support)
- EyeBio (Consultant)
- F. Hoffman-La Roche AG (Consultant, Grant Support)
- Genentech, Inc. (Consultant, Grant Support)
- Heidelberg Engineering, Inc. (Consultant)
- Johnson & Johnson Health Care Systems Inc. (Consultant, Grant Support)
- Life Sciences (Consultant)
- Merck (Consultant)
- Novartis (Consultant, Grant Support)
- PYC Biotherapeutics (Consultant)
- Ray Therapeutics (Consultant)
- Regeneron Pharmaceuticals, Inc. (Consultant, Grant Support)
- Vinci Pharmaceuticals (Consultant, Stock Options)

Visual Acuity vs Contrast Sensitivity: Retina and Brain Circuitry



- High spatial resolution
- Low sensitivity



- High sensitivity to contrast & motion
- Low spatial resolution

Kuffler 1953; Kaplan & Shapley 1986; Owsley 2003; Pelli & Bex 2013; Sunness et al. 2008; Sunness et al. 2008

Visual Acuity vs Contrast Sensitivity:

Visual acuity measures resolution at high contrast; Contrast sensitivity determines real-world visual function

What the Patient Experiences / Activities of Daily Living (ADLs)

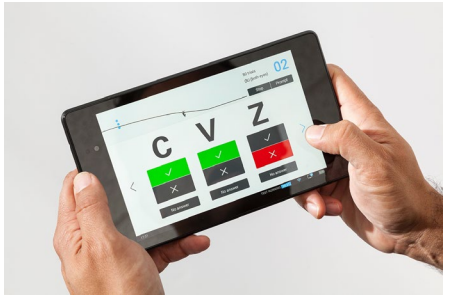
Visual Acuity Loss

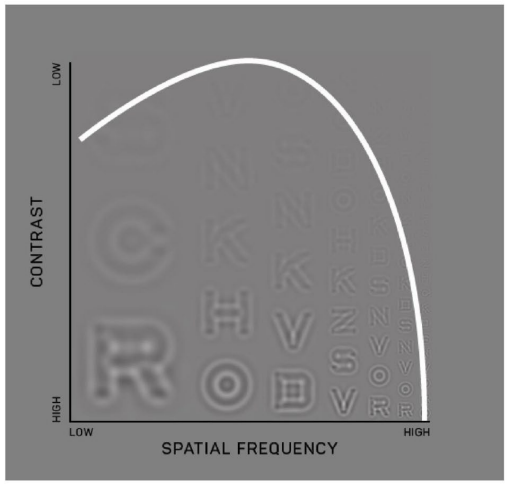
- *"I can't read small print"*
- Blurred central detail
- Difficulty with high-resolution tasks

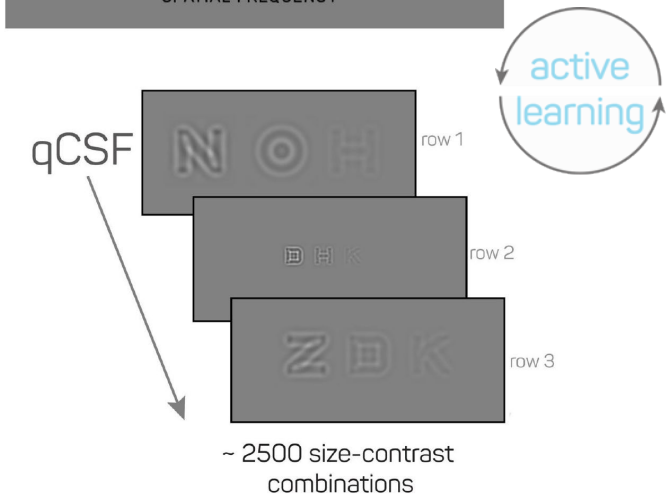
Contrast Sensitivity Loss

- *"I can see it-but I can't make it out"*
- Washed-out vision, poor edge detection
- Difficulty in low contrast or low light environments – mobility and fall risk

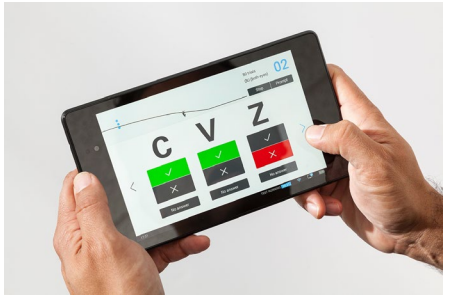
Logistics of Quantitative CSF (qCSF): Active Learning for Contrast Sensitivity

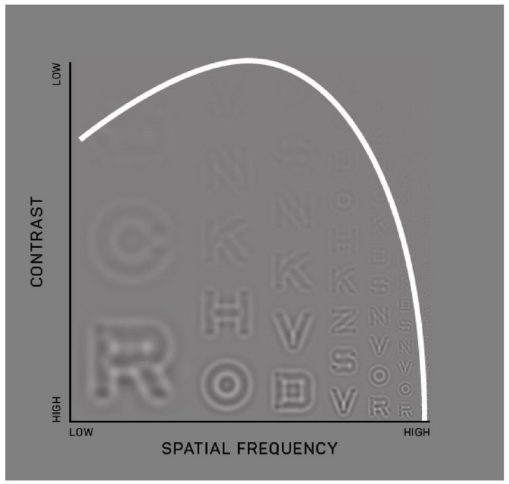


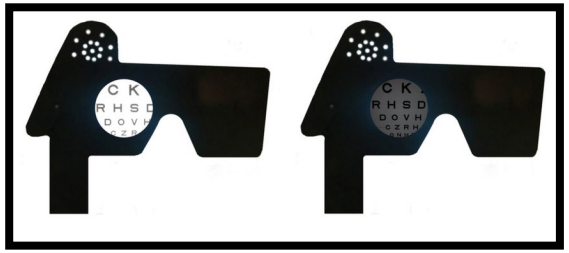




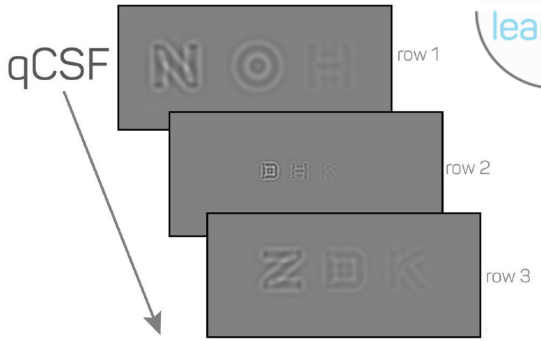
Logistics of Quantitative CSF (qCSF): Active Learning for Contrast Sensitivity





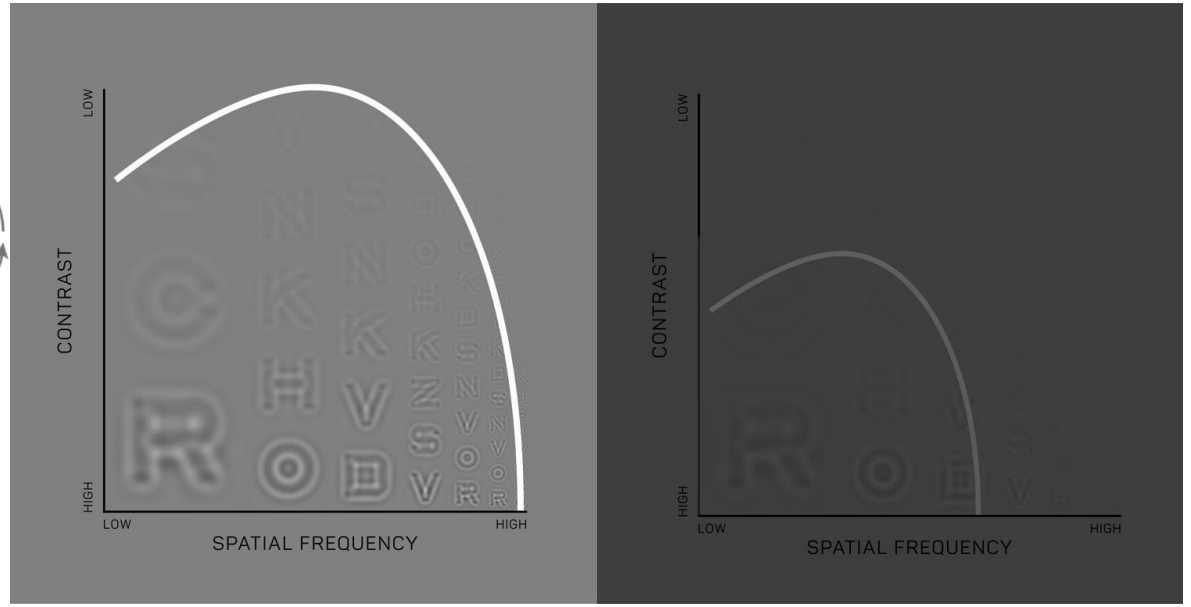


+ 2 N.D. Filter



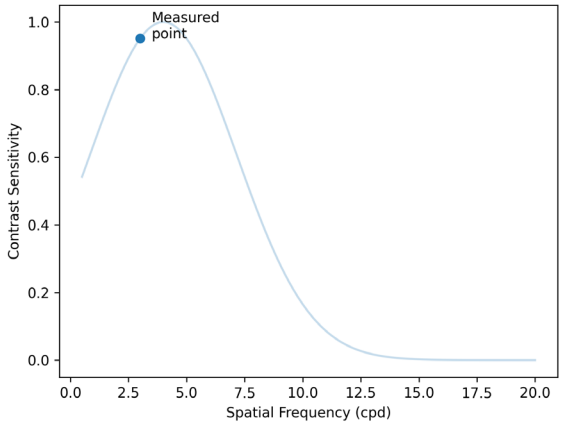
active learning

~ 2500 size-contrast combinations



Pelli-Robson vs qCSF in AMD

Pelli-Robson
- Single spatial frequency
- Coarse resolution
- No low-luminance

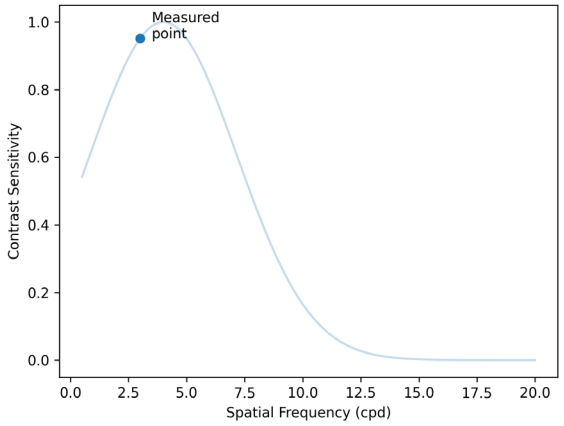


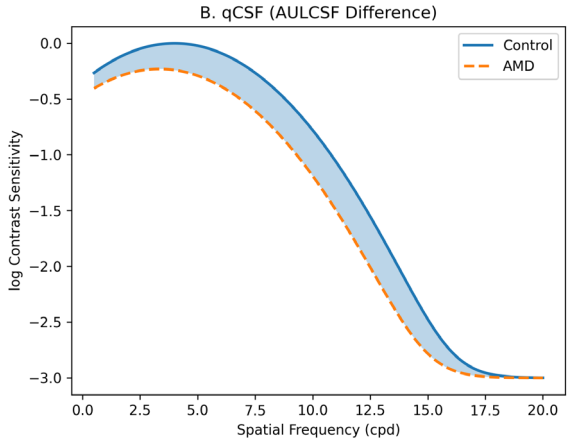
Pelli-Robson samples one point of the CSF; qCSF reconstructs the full function.

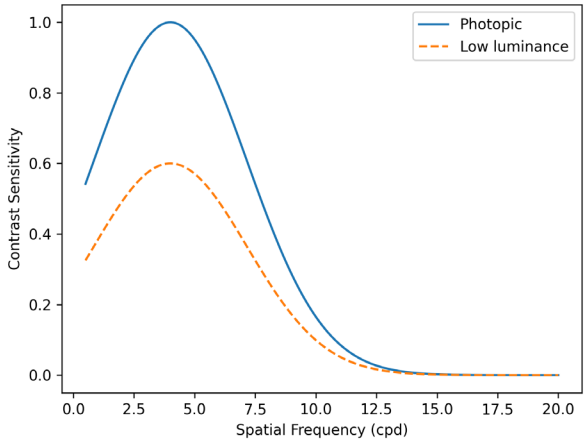
Pelli-Robson vs qCSF in AMD

Pelli-Robson
- Single spatial frequency
- Coarse resolution
- No low-luminance

qCSF
- Full CSF
- High precision
- AULCSF difference (AMD vs control)
- Low-luminance capable
- Captures functional loss







Pelli-Robson samples one point of the CSF; qCSF reconstructs the full function.

Contrast sensitivity repeatability in AMD: Pelli-Robson vs qCSF

Chart-based Pelli-Robson has the most direct AMD repeatability data. **Quantitative CSF shows stronger precision and richer phenotype capture.**

Study-level evidence

Within-patient repeatability findings most relevant to AMD trials and longitudinal monitoring

Method	Study / cohort	Repeatability result	Interpretation
Pelli-Robson	Patel 2009 AMD	High intersession variability	Early signal that repeat-test noise can materially affect AMD trial design.
Pelli-Robson	Aslam 2014 AMD	CoR 3.6 dB ICC 0.93	Good rank-order reliability, but a clinically real change should exceed ~7 letters.
Pelli-Robson	MACUSTAR 2022 iAMD	ICC 0.73 LoA −02.7 to 02.4 dB	Feasible in multicenter studies, but repeatability is only moderate.
qCSF	Finn 2024 retina clinic	**CoR 1.6–2.7 dB** **AULCSF ICC 0.971**	Very strong precision, but the best repeatability paper is not AMD-only.
qCSF	Ou 2021 / Anders 2023 / Bennett 2025 AMD	Separates severity; detects subtle deficits; relates to OCT/progression	Supports qCSF as a richer endpoint if AMD-specific repeatability is confirmed.

Synthesis for trial design

Pelli-Robson

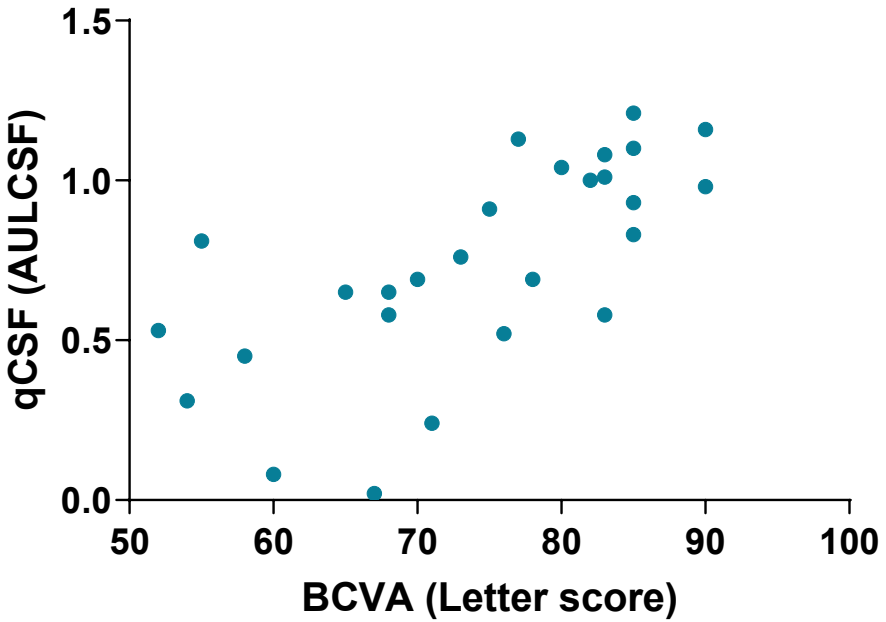
Most pragmatic and most directly validated in AMD, but within-patient noise is substantial and the measurement samples only a single coarse spatial-frequency region.

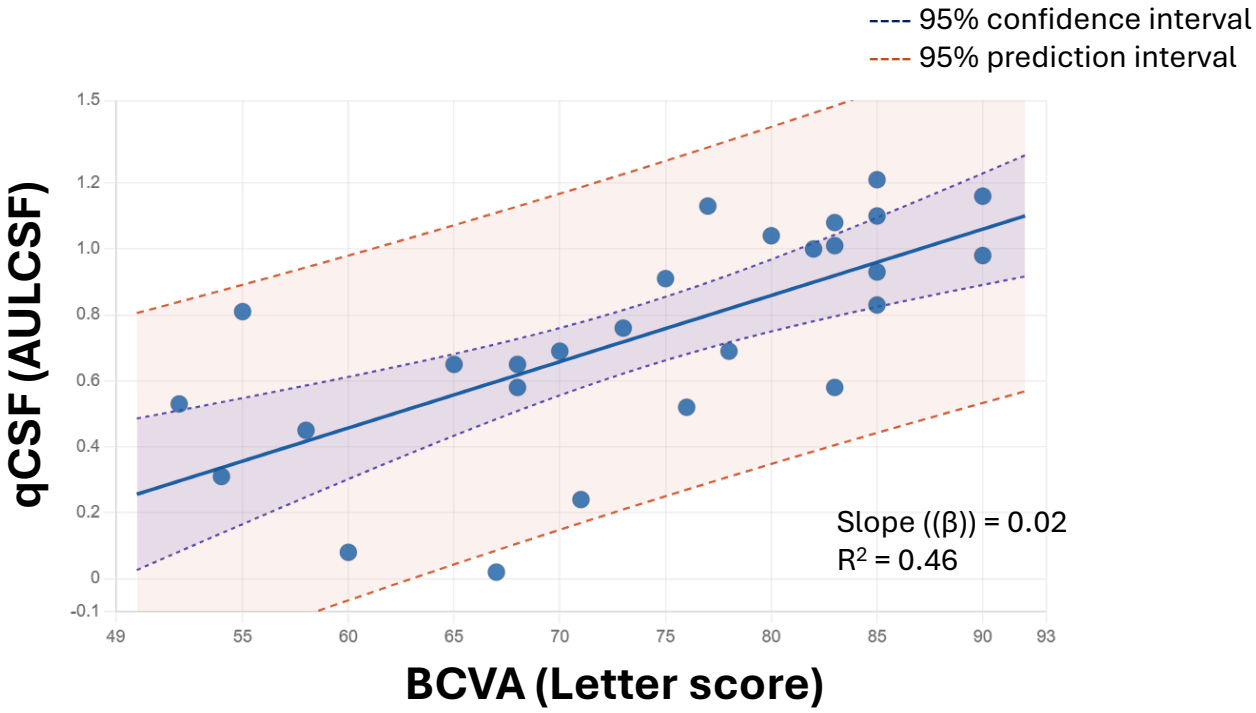
Quantitative CSF

More physiologically rich. The full CSF can reveal subtle AMD dysfunction that Pelli-Robson or visual acuity may miss, and published precision signals are stronger.

Patel et al., 2009; Aslam et al., 2014; MACUSTAR, 2022; Finn et al., 2024; Ou et al., 2021; Anders et al., 2023; Bennett et al., 2025

Relationship between Baseline BCVA and qCSF in 27 Subjects with Non-Foveal GA

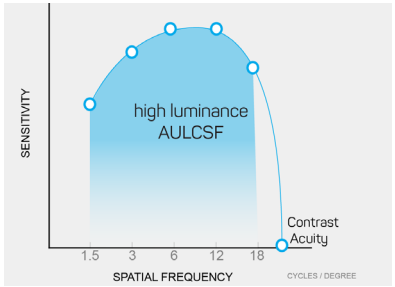


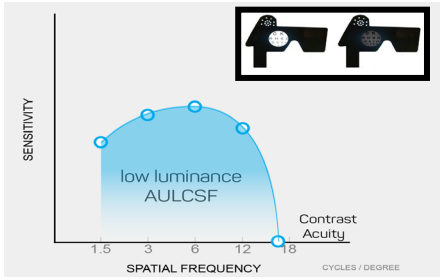


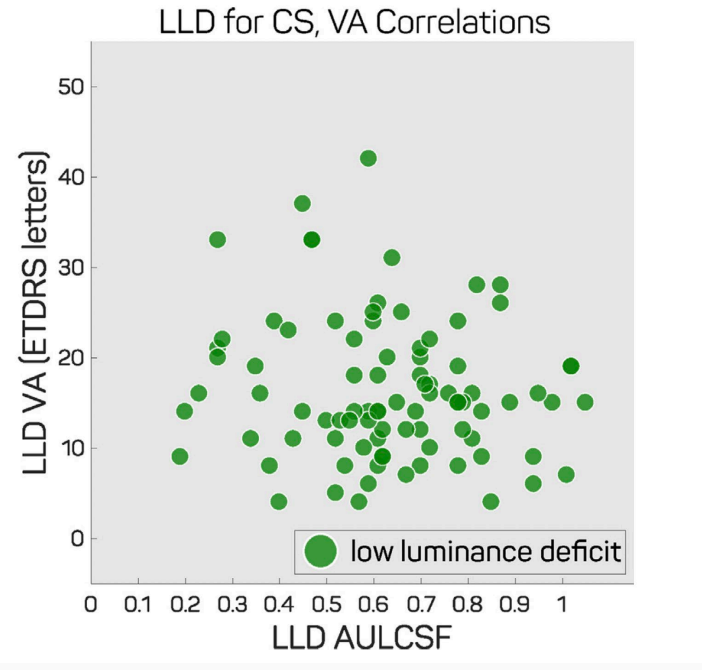
46% of the variability in qCSF is explained by BCVA

Tandon and Csaky: Personal Communication

Visual Acuity Testing Alone Misses Vision Loss in Intermediate AMD and Geographic Atrophy Subjects





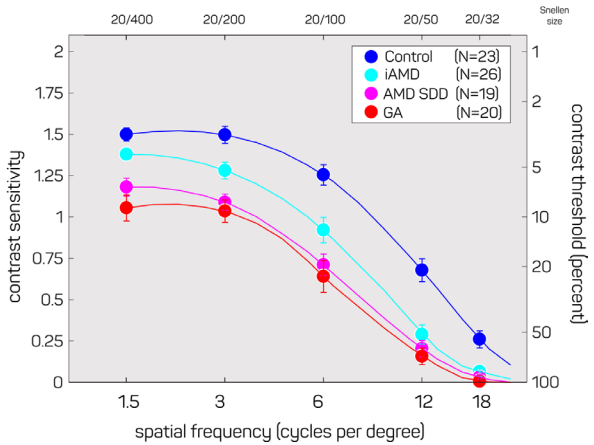


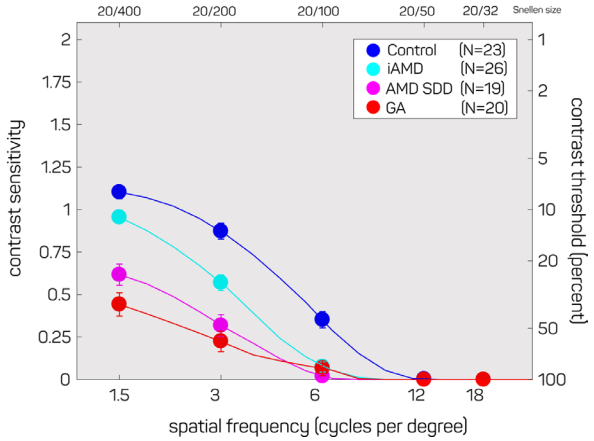
No correlation between low luminance deficits as detected by low luminance visual acuity and low luminance qCSF from subjects with varying stages of dry AMD

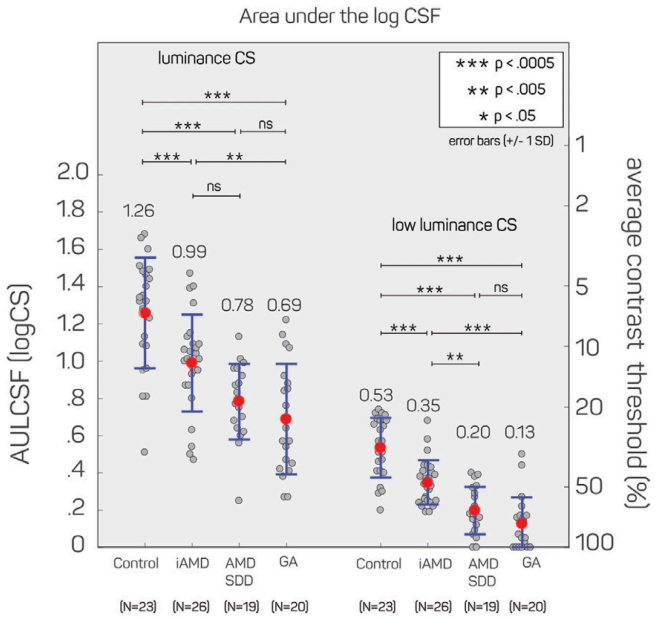
Data from Ou, Lesmes, Christie, Denlar, & Csaky (2021) American Journal of Ophthalmology

Retina Foundation of the Southwest
Leading Research .... Saving Sight

Statistical Differences in both Normal and Low Luminance qCSF between Groups of Dry AMD Subjects – Area under the Log



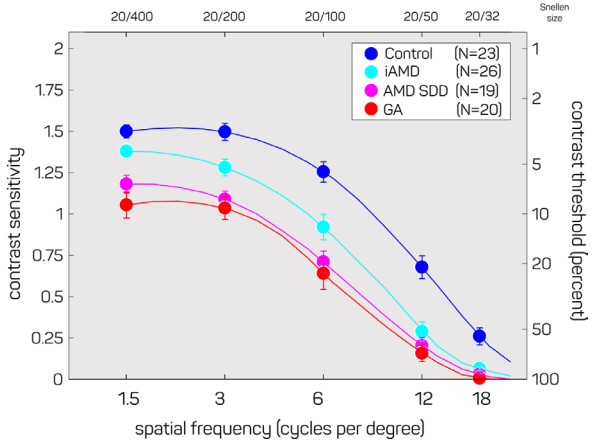


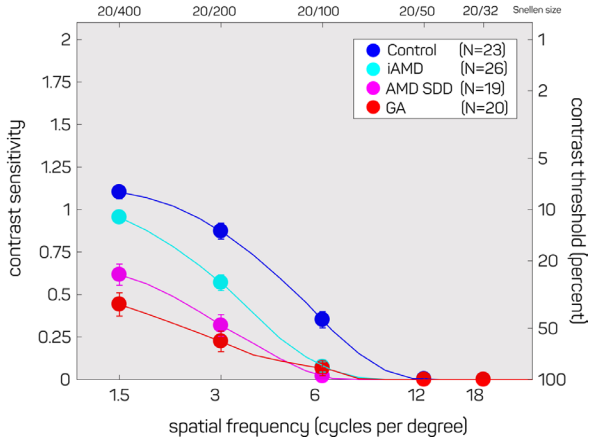


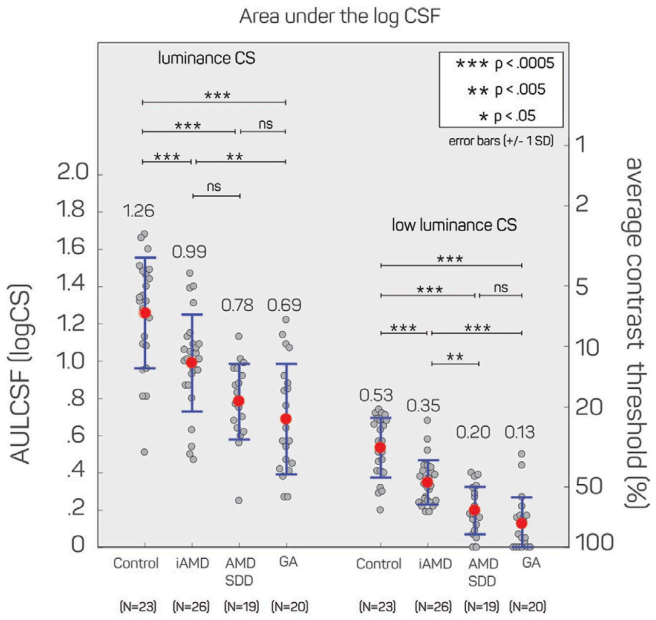
Ou et al 2021

Owsley et al 2026

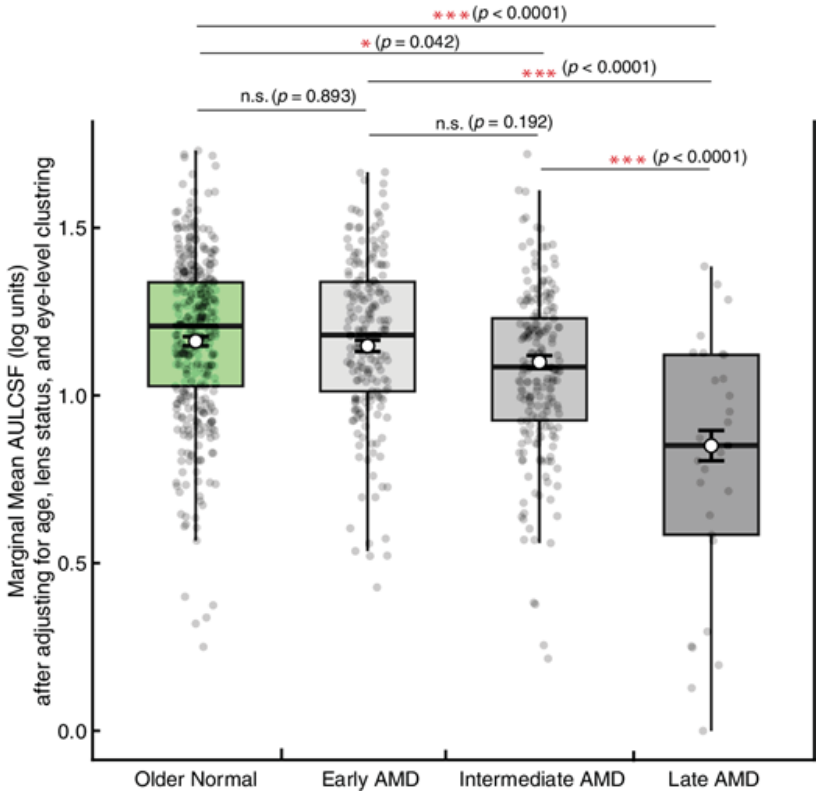
Statistical Differences in both Normal and Low Luminance qCSF between Groups of Dry AMD Subjects – Area under the Log







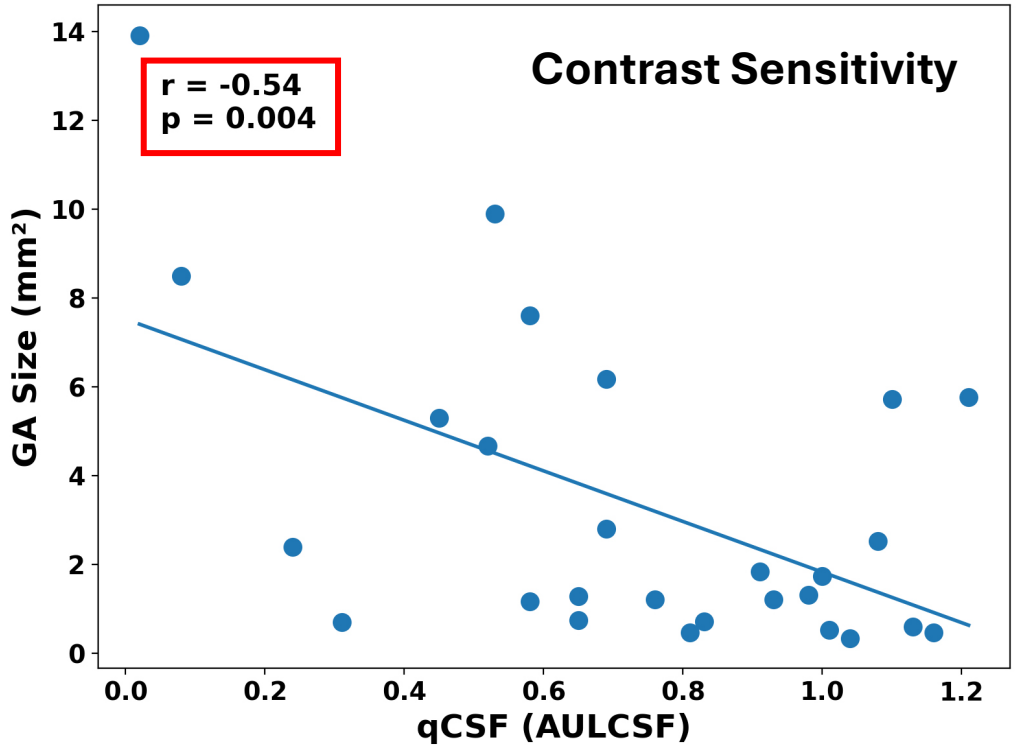
Ou et al 2021



Owsley et al 2026

Relationship between GA Size and qCSF and Visual Acuity

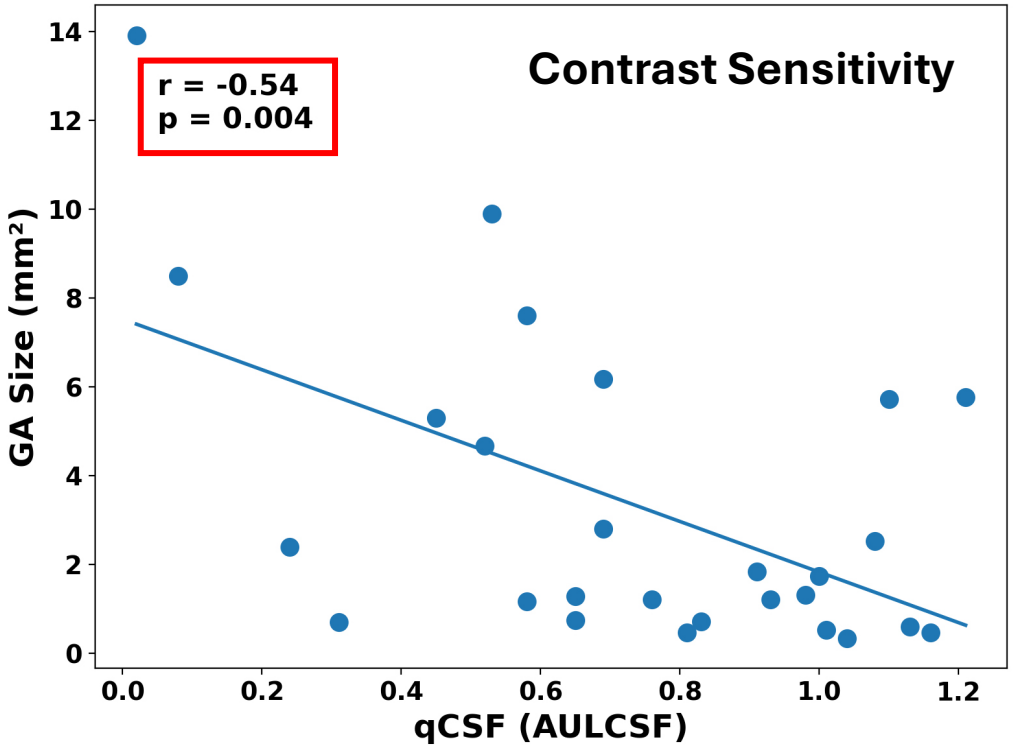
27 Subjects with Non-Foveal GA

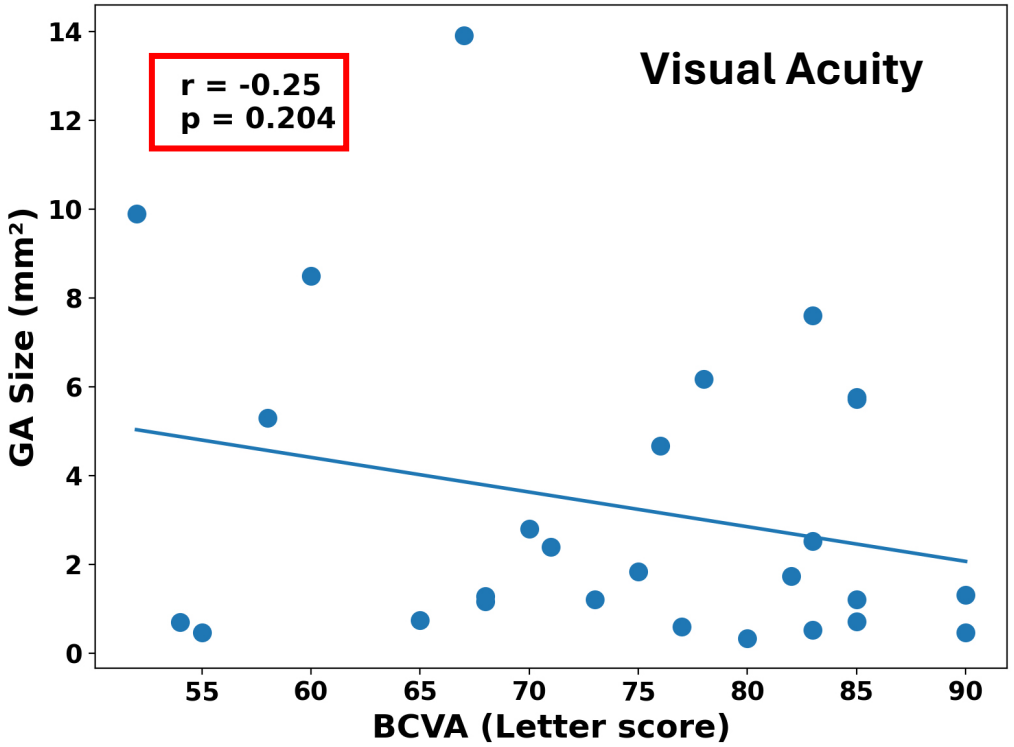


Tandon and Csaky: Personal Communication

Relationship between GA Size and qCSF and Visual Acuity

27 Subjects with Non-Foveal GA

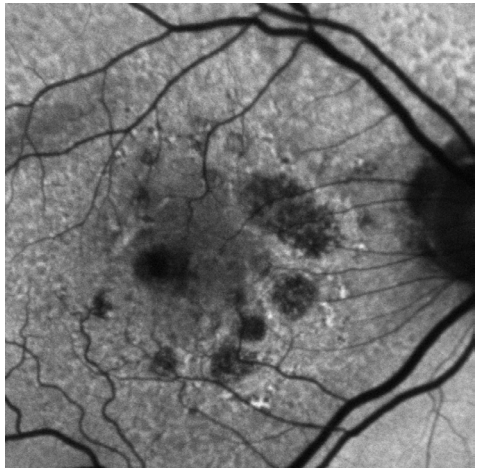




Tandon and Csaky: Personal Communication

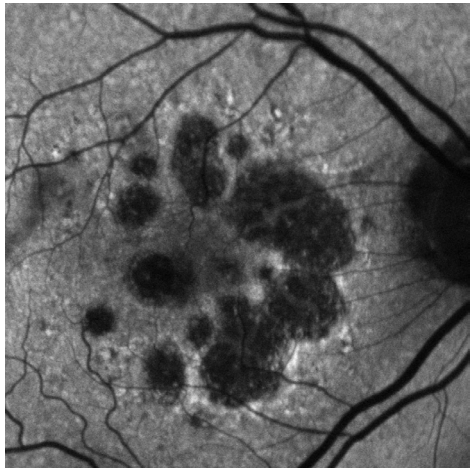
GA Progression: Contrast Sensitivity vs Visual Acuity

Baseline FAF
(Smaller GA lesion)



2 years

Follow-up FAF
(Enlarged GA lesion)

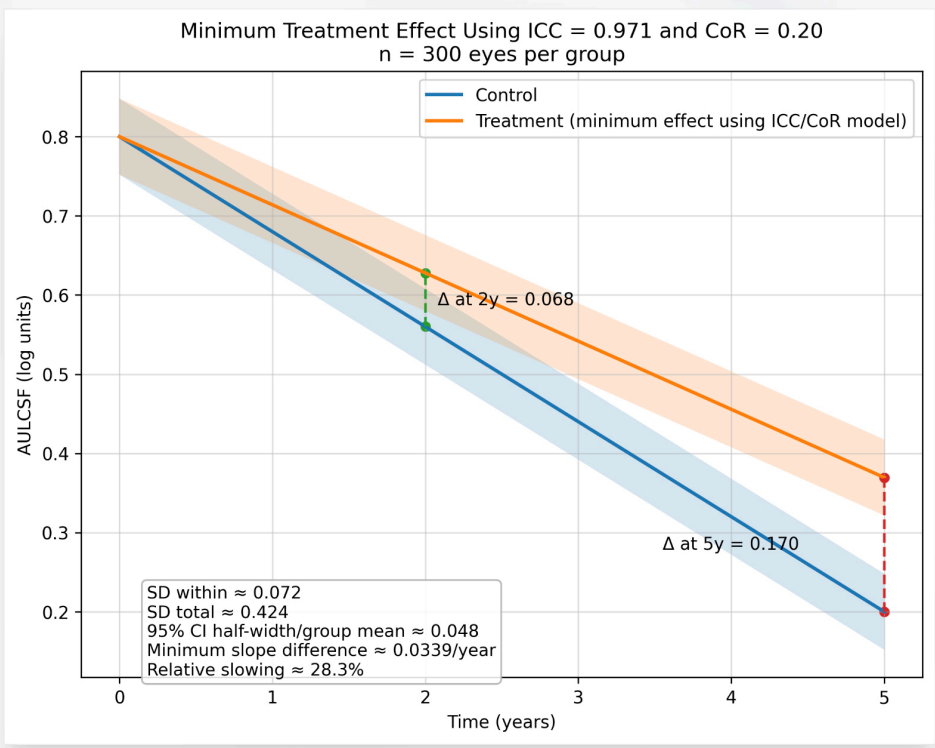


GA enlargement → support to suggest that the decline in contrast-related function is greater than the loss of visual acuity

Contrast function declines before visual acuity in GA – *CENTRAL HYPOTHESIS*

Holz FG et al.; Fleckenstein M et al.; Pelli & Bex 2013; Owsley 2003; Sunness JS et al. 2008

Potential Effect of Intra-patient Repeatability on Detectable Rate of qCSF Contrast Loss



One Approach to Reach Minimally Clinically Important Difference

Hypothetical Outcomes:

A minimum difference of **0.68 dB at 2 years** is required for statistical significance (n = 300/group, ***ICC = 0.971, CoR = 2.0 dB***)

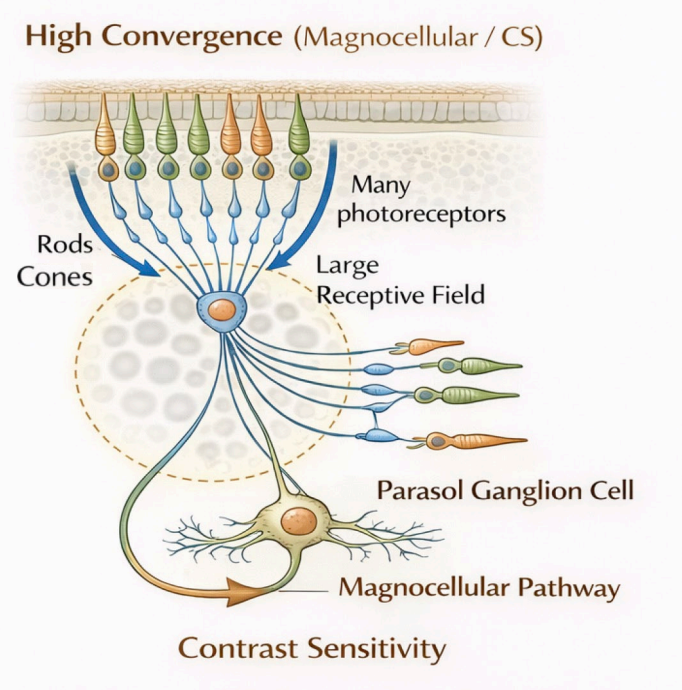
This corresponds to a treatment slope of **−0.086/year vs −0.12/year → <u>~28% slowing of decline</u>**

Resulting difference at 5 years ≈ 1.70 dB

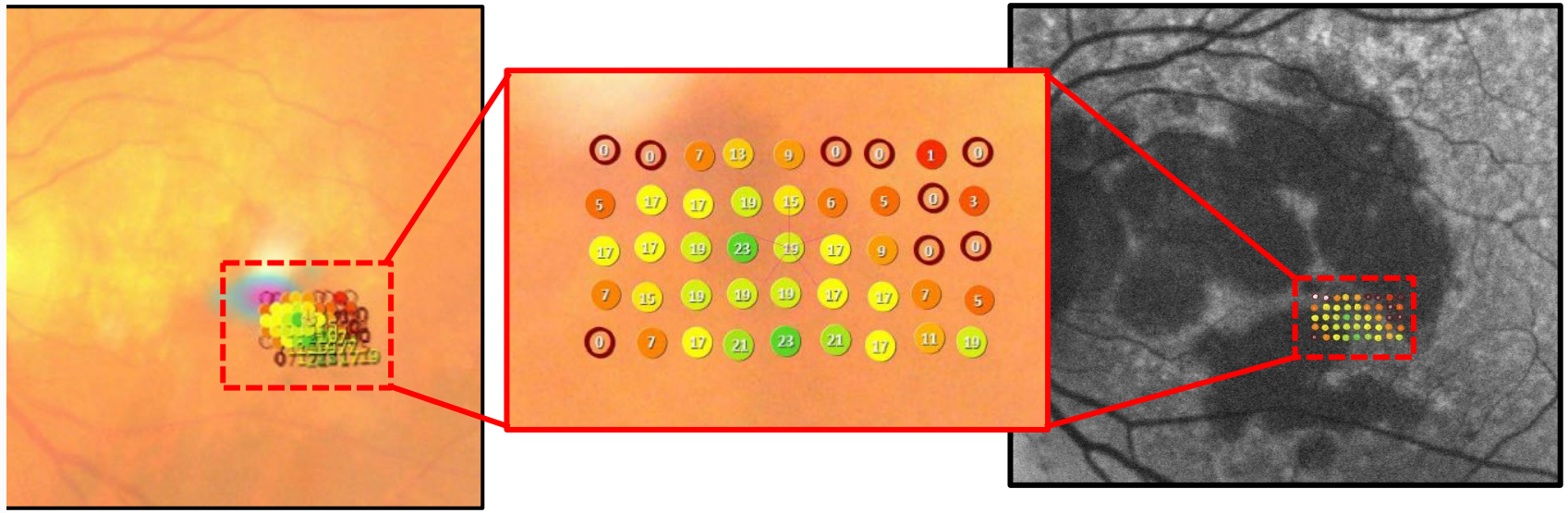
On-Going Longitudinal Clinical Studies with qCSF in AMD

STUDY NAME	Title	Sponsor	Disease / Indication	NCT
MACUSTAR (extension)	Development of Novel Clinical Endpoints in Intermediate AMD	Univ. H. Bonn/IMI	**Intermediate AMD**	*NCT03349801*
HONU	An Observational Study of the Progression of Intermediate Age-Related Macular Degeneration	Genentech	**Intermediate AMD**	*NCT05300724*
CLNP023	A Masked, Placebo-controlled Study to Assess Iptacopan in Age-related Macular Degeneration	Novartis	**Intermediate AMD**	*NCT05230537*
OMEGA	Optical Coherence Tomography and Microperimetry Biomarker Evaluation in Patients With Geographic Atrophy Study (OMEGA)	Univ. H. Basel/ Boehringer	**Geographic Atrophy**	*NCT05963646*
SIENNA	A Study Investigating Subcutaneously Administered Pozelimab in Combination With Cemdisiran or Cemdisiran Alone in Adult Participants With Geographic Atrophy	Regeneron	**Geographic Atrophy**	*NCT06541704*
SIGLEC	A Multiple Dose Study of AVD-104 for Geographic Atrophy (GA) Secondary to Age-Related Macular Degeneration (AMD)	Aviceda	**Geographic Atrophy**	*NCT05839041*
STELLAR	Study to Evaluate ACDN-01 in ABCA4-related Stargardt Retinopathy	Ascidian	**Stargardt's**	*NCT06467344*
GALLOP	A Phase 2, Randomized, Placebo Controlled, Multicenter, Masked Study to Evaluate …Multidose APL 3007 … Geographic Atrophy Secondary to Age Related Macular Degeneration	Apellis	**Geographic Atrophy**	*NCT07215390*
CIRCLE	A Study to Investigate Efficacy and Safety of FWY003 Compared With Placebo in Participants With Geographic Atrophy Secondary to Age-related Macular Degeneration	Novartis	**Geographic Atrophy**	*NCT07441642*

On-Going Clinical Studies to Fully Understand qCSF in Dry AMD



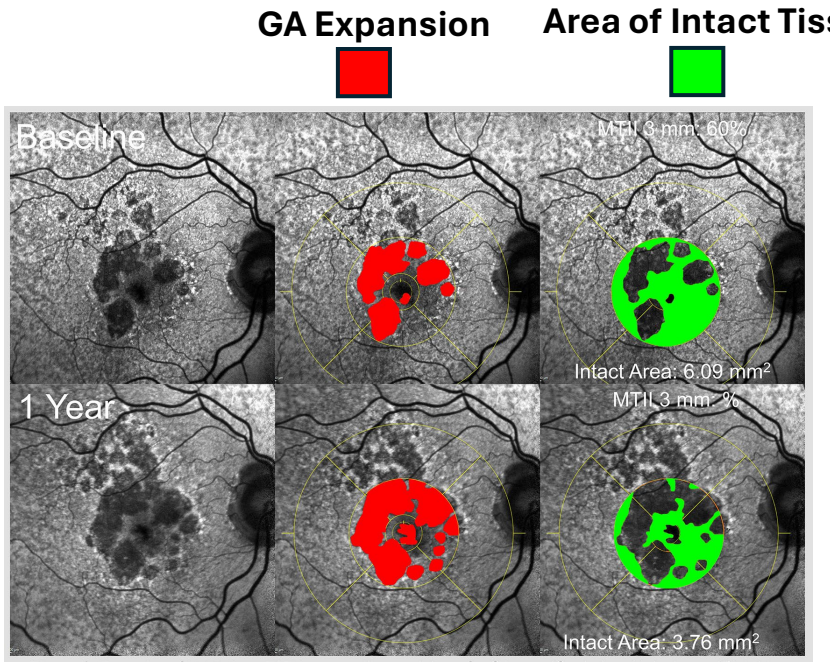
Central Macular Cone Sensitivity



NIDEK Photopic (Illuminated Background) - Central 1.0 mm – Goldmann II

Tandon and Csaky: *Test-retest Repeatability of a Novel Photopic Microperimetry Approach in Patients with Geographic Atrophy*: Under Review

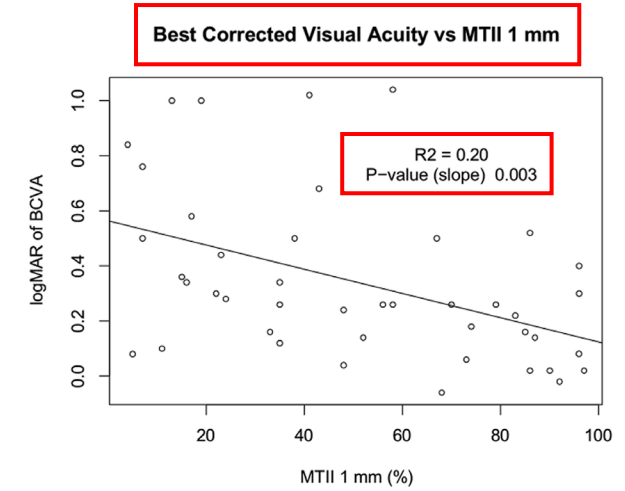
Understanding the Role of the Center 1 mm Involvement on Visual Function in Subjects with Geographic Atrophy

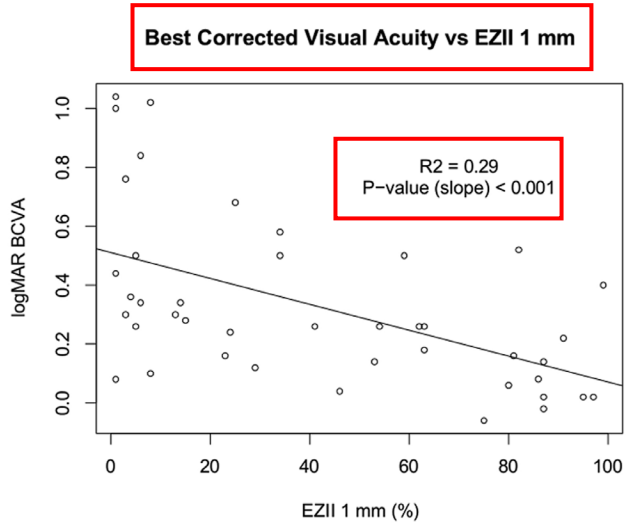


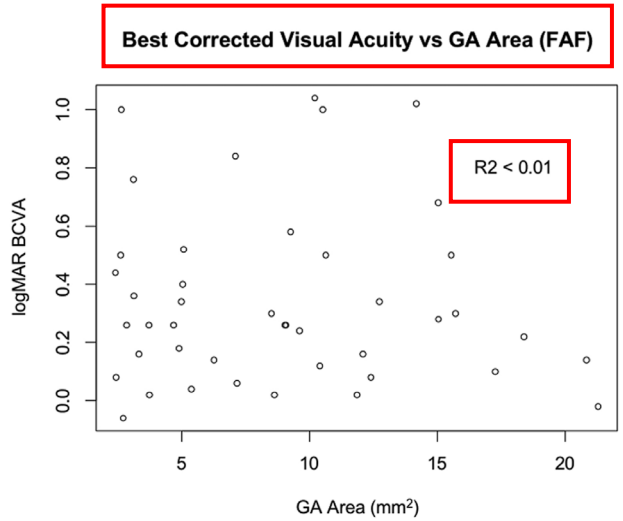
Baseline

1 Year Follow-Up

The Importance of the Center 1 mm







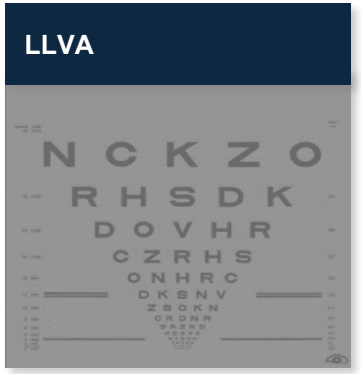
Erb et al: 2025

Understanding the Totality of Visual Function in Subjects with Geographic Atrophy

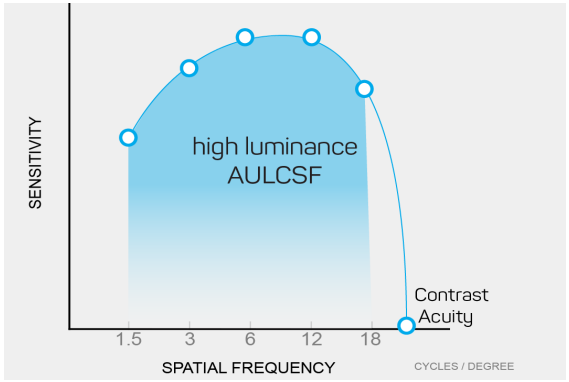
Composite Endpoint?

– Statistical Approach to Understanding Multiple Visual Function Assessments Easily Assessed in a Phase 3 Trial in Patients with Dry AMD

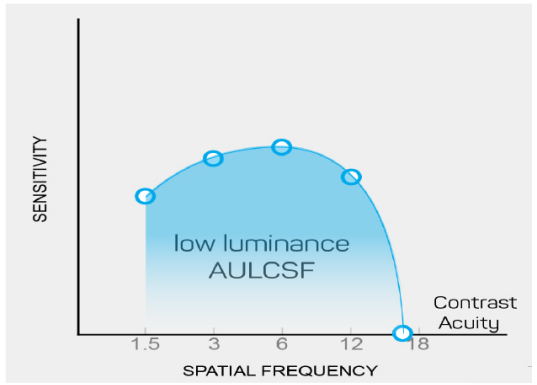
Visual Acuity



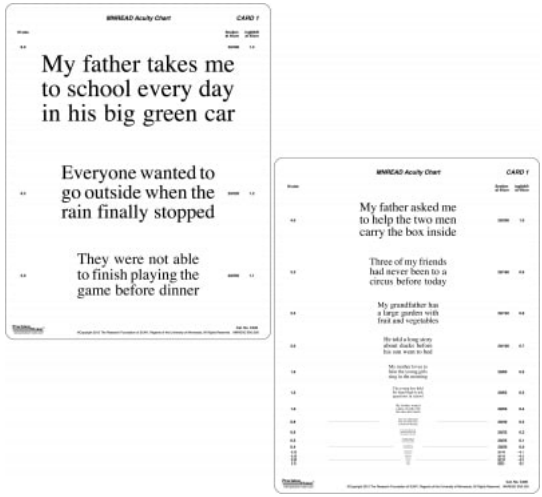
Low Luminance Visual Acuity



qCSF



Low Luminance qCSF



Reading Speed

Do all of these important visual function assessments “move” in the same direction?

Take Home Messages

- Novel contrast sensitivity endpoints especially those that measure the full functional contrast sensitivity range (qCSF) under normal and low luminance can be easily obtained in clinical trials
- qCSF measures an additional aspect of visual function that is not captured by visual acuity and may be more relevant to activities of daily living
- qCSF in demonstrating high repeatability has the potential to demonstrate statistical significant differences in a short time frame that can predict continued MCID for patients
- Understanding the role of the center 1 mm involvement in regards to anatomic (including EZ) and focal photopic microperimetry in qCSF is under investigation
- qCSF Could be part of examining the totality of central visual functions using a composite endpoint

Thank you