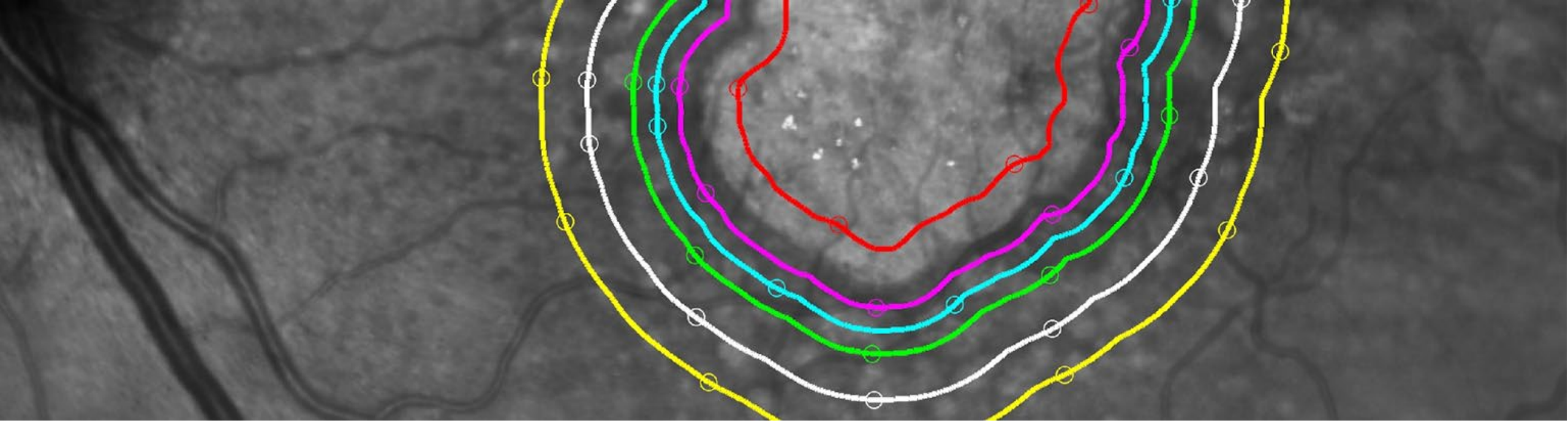


Univ.-Prof. Dr. med. Maximilian Pfau

# Microperimetry as an Outcome Assessment in Geographic Atrophy

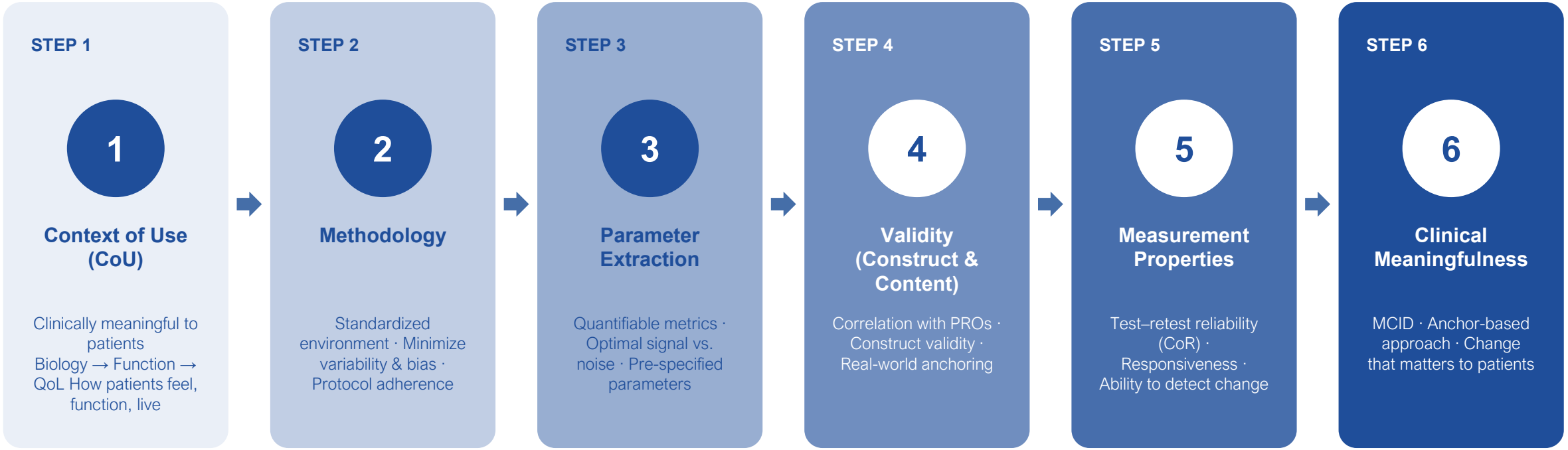
## Evidence Base, Measurement Properties and Regulatory Considerations

**European Medicines Agency**

Scientific / Regulatory Interaction
GA Endpoints Workshop

# Framework for Clinical-Outcome Assessment

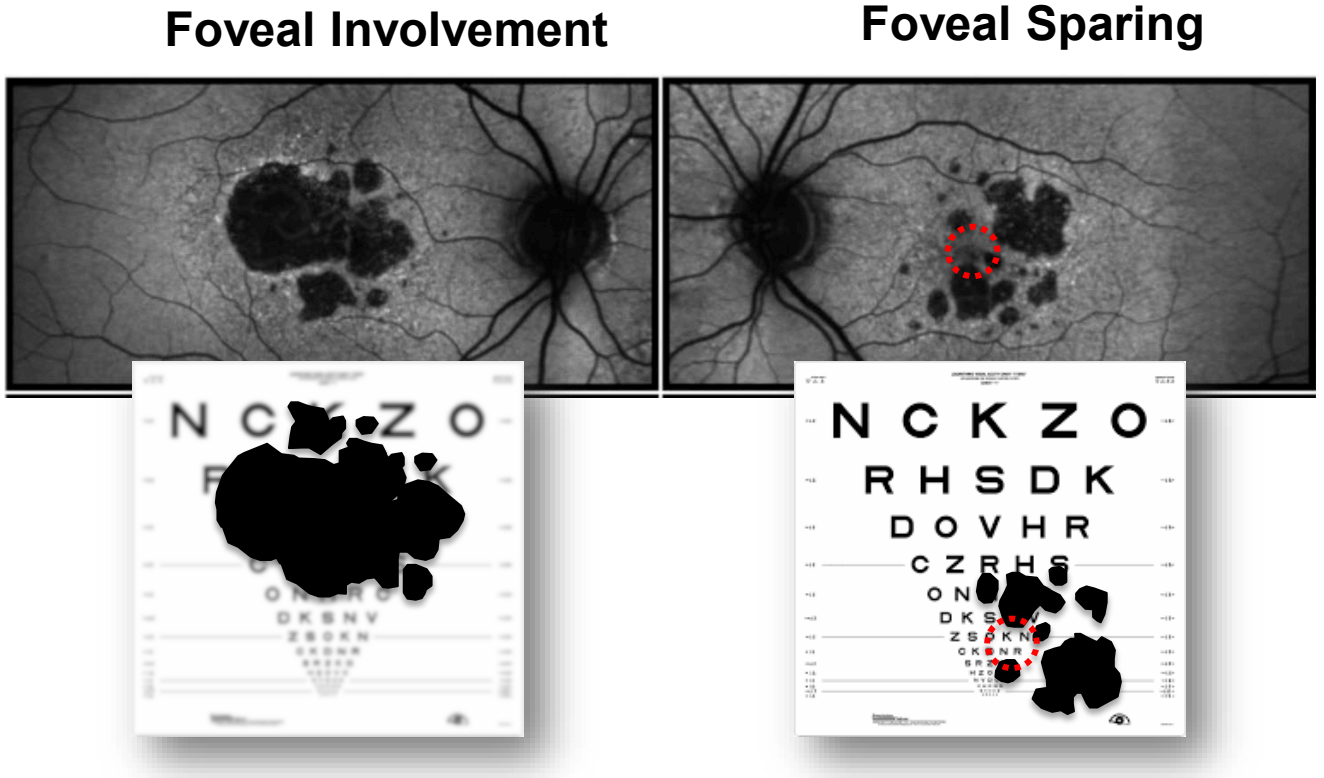
## Chain from Clinical Context to Accepted Endpoint



# Context of Use: Visual Field Testing in Geographic Atrophy

## Why BCVA Alone is Insufficient for Monitoring GA

- **Assessment of retinal function across the whole macula**
  - Best-corrected visual acuity (BCVA) samples only the foveal centre or - in foveal GA - the preferred retinal locus (PRL)
  - BCVA is insensitive to change in GA until the fovea is directly involved
- **Visual field deterioration is the chief complaint reported by patients with GA**
  - Loss of reading ability, difficulty navigating, scotomas in daily life

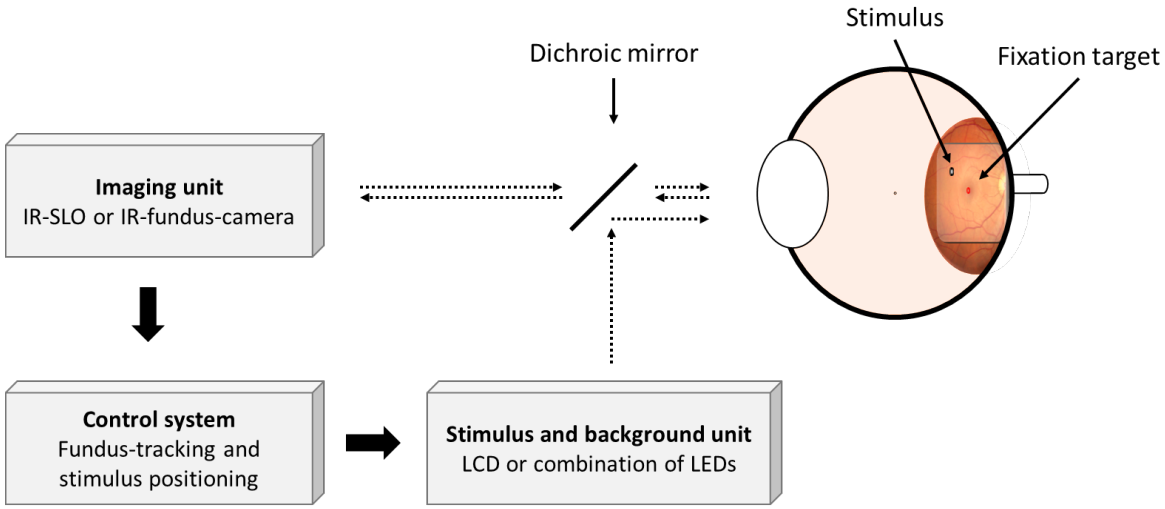



Adapted from Fleckenstein M, et al. Ophthalmology. 2018;125(3):369-390


Pfau M, et al. Prog Retin Eye Res. 2021;82:100907. PMID: 33022378
Pfau M, et al. Retina. 2020;40(1):169-180. PMID: 30300264
Fleckenstein M, et al. Ophthalmology. 2018;125(3):369-390

# Context of Use: Why Microperimetry?

## Gaze-Contingent Testing and Retinal Tracking Address GA-Specific Challenges




### Conventional perimetry

- Not gaze-contingent — stimuli projected to assumed retinal coordinates
- Prone to errors from fixation drift or extrafoveal fixation (common in GA)
- Difficult to interpret when the preferred retinal locus is eccentric
- Cannot reliably co-register sensitivity with structure (OCT / FAF)
- Limited reproducibility of point-wise loci on repeat visits

### Microperimetry (fundus-controlled)

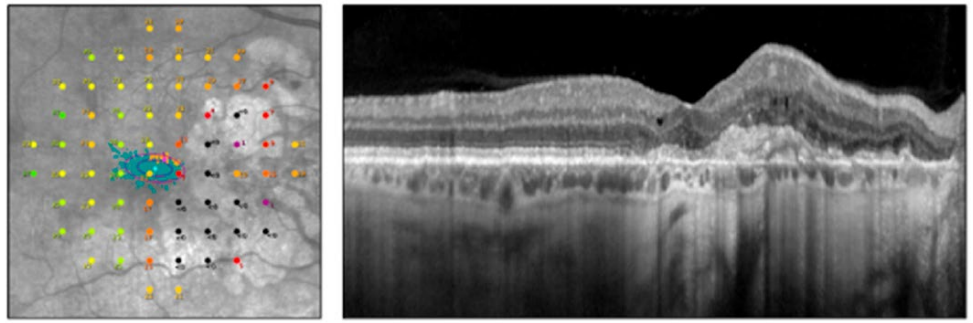
**Real-time fundus tracking → gaze-contingent stimulus placement**

1. **Improved retest reliability** (repeated presentation at the exact same retinal location)
2. **Precise point-wise structure–function correlation** with OCT / FAF
3. **Anatomically anchored visual field in GA** (applicable even in unstable or extrafoveal fixation)

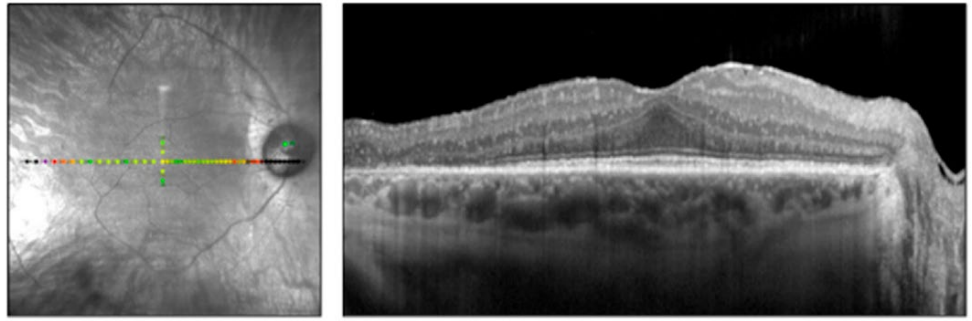

Pfau M, et al. Prog Retin Eye Res. 2021;82:100907. PMID: 33022378
Pfau M, et al. Retina. 2020;40(1):169-180. PMID: 30300264

# Variety of Test-Patterns

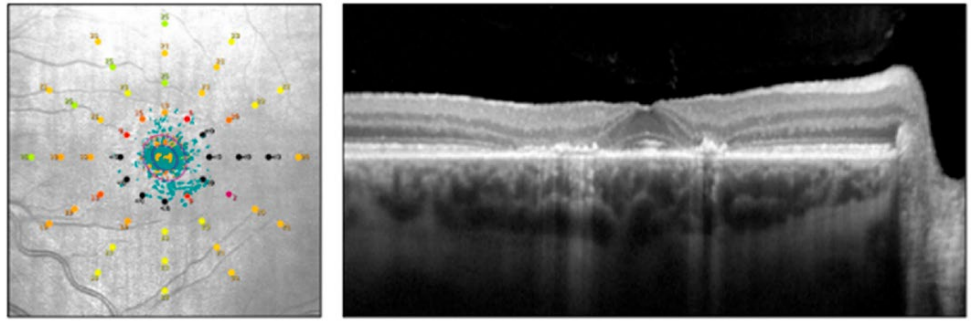
Rectilinear pattern



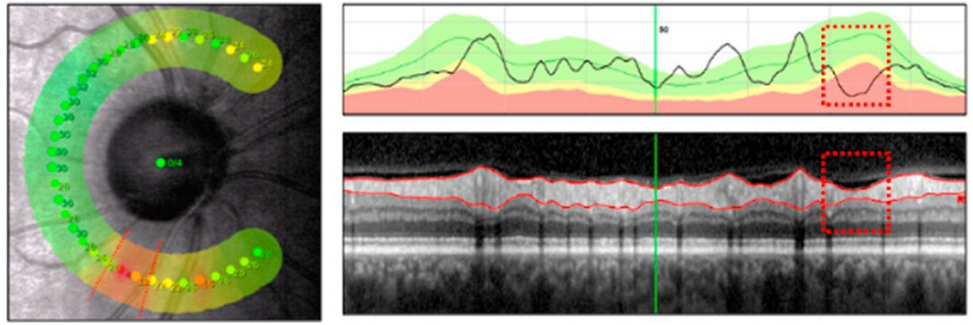
Profile (horizontal or vertical meredian)



Radial pattern



Circular peripapillary pattern

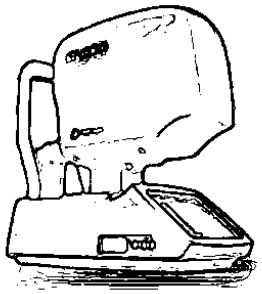


Pfau M, et al. Prog Retin Eye Res. 2021;82:100907. PMID: 33022378

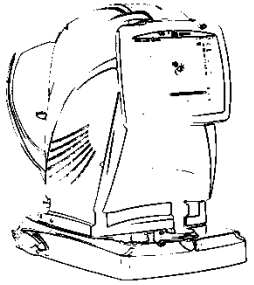
# Methodology: Established Technology Landscape

## Commercial Retina-Tracked Microperimeters and Emerging VR Approaches

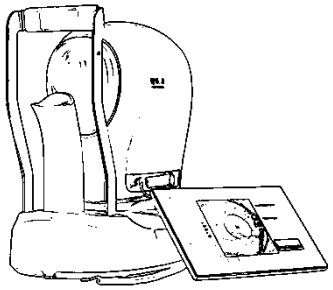
### Retina-Tracked Microperimetry



iCare
MAIA2 and
S-MAIA



Nidek
MP3 and
MP3 type-S



iCare
MAIA3

### Eye-Tracked Gaze-Contingent Perimetry


VIVID
Vision

**Standardized Output Framework**

**Device vs. Device Comparison Studies**

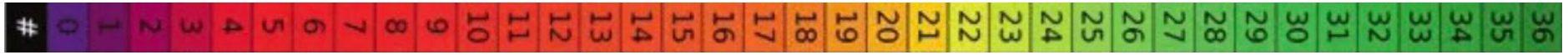
- MAIA2 vs. MAIA3 - *Ansari G et al. Ophthalmol Sci. 2025;5(6):100886. PMID: 40980023*
- MAIA2 vs. VIVID - *Csaky KG et al. ARVO Annual Meeting; May 4-8, 2025; Salt Lake City, UT*
- MAIA2 vs. MP3 - Schrittwieser J et al. Ophthalmol Sci. 2025 Jun 10;5(6):100850. PMID: 40689254

# Validity: Decibel Scale Across the AMD Spectrum

## Interpreting Microperimetric Sensitivity in GA

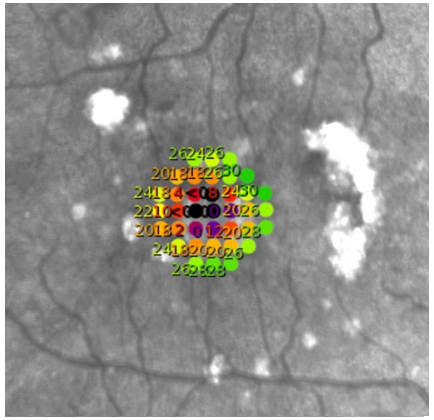
dB-scale expressed in MAIA2 units
(i.e., background luminance: 4 asb and maximum luminance: 1000 asb)

**Non-Seeing Retina**



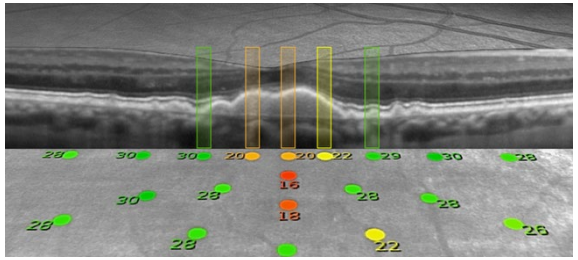

**Seeing Retina**

**Atrophy**
**~ Deep-Defects**
(<10 dB mostly non-seeing upon retesting)



*Wu Z, et al. Invest Ophthalmol Vis Sci. 2024;65(8):44. PMID: 39078733*

**Intermediate AMD ~ Mild and Moderate Defects**
(~11 to 24 dB)

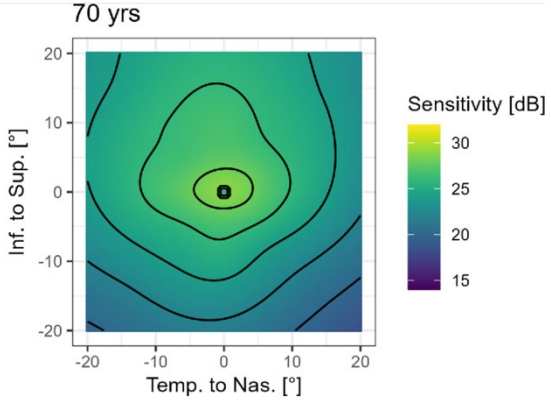


*Lad EM et al. Ophthalmol Sci. 2022;2(3):100173*

*Welker SG, et al. Invest Ophthalmol Vis Sci. 2018;59(4):AMD152-159. PMID: 30372731*

*Pfau M et al. Eye (Lond). 2018;32(12):1819-1830*

**Normal Range and Aging**
(>24 dB)




*Pfau M et al. Invest Ophthalmol Vis Sci. 2024 Oct 1;65(12):27. PMID: 39422918*

# Validity: Local Sensitivity

## Construct Validity Against Structure

**Local metrics (point-wise and topographic)**

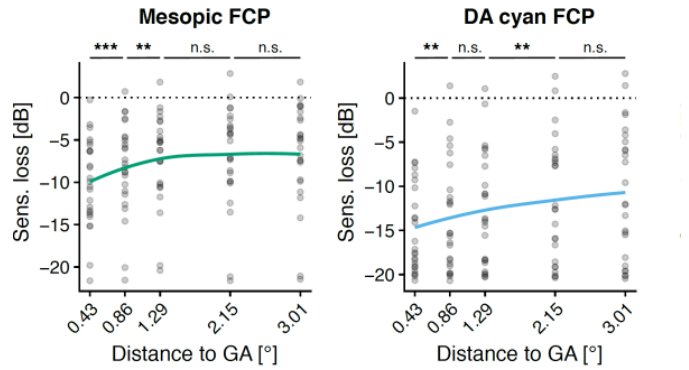
- Spatially map junctional-zone dysfunction and perilesional loss
- Sensitivity declines gradually within ~2° (~580 µm) of the GA border

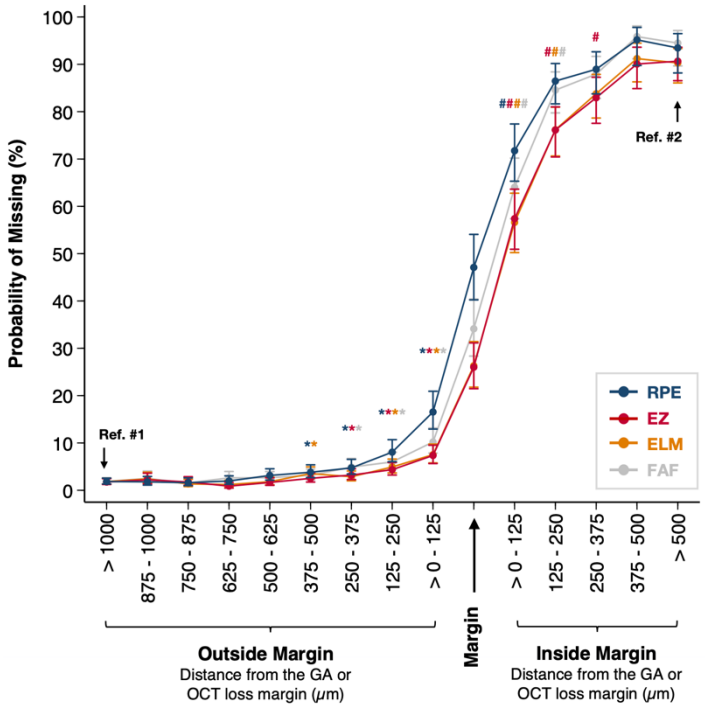
**Structure–function concordance**

- Global: ρ 0.85–0.89 with OCT RPE/EZ/ELM loss and FAF-defined GA
- Spatial: Dice 0.60–0.64 between structural loss and deep functional defects

**Disease-stage correlation — reflects various lesion severities within each eye with GA**

- Local OCT phenotypes (SDD, HRF, nascent GA) show locally differential microperimetric deficits





*Pfau M et al. Am J Ophthalmol. 2020;217:162-173. PMID: 32289293*
*Ansari G, et al. Invest Ophthalmol Vis Sci. 2025;66(11):34 PMID: 40801672*
*Blair JPM, et al. Ophthalmol Sci. 2026;6(3):101035. PMID: 41660488*
*Birner K et al. Invest Ophthalmol Vis Sci. 2025 Mar 3;66(3):26. PMID: 40067294*

# Measurement Properties: Repeatability

## Test-Retest Benchmarks and Effective Dynamic Range

**Point-wise coefficient of repeatability (PWS CoR) — AMD cohorts**

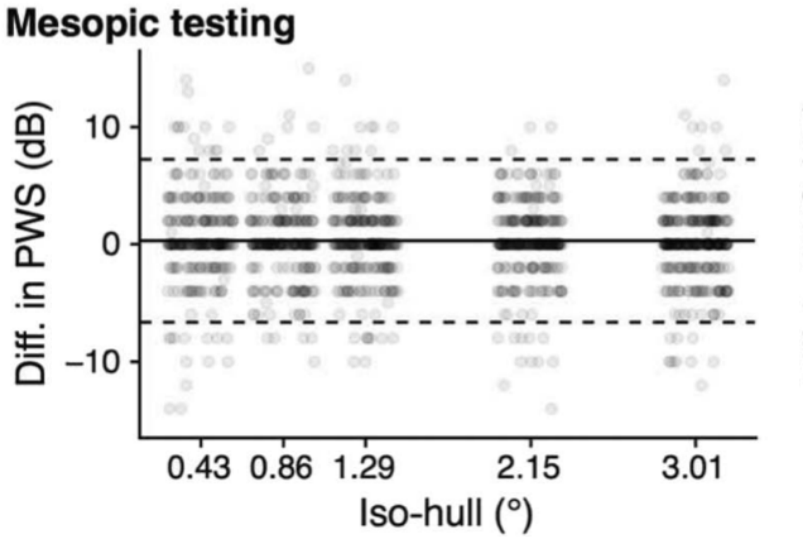
- iAMD, standard MAIA: ±4.12–4.37 dB (Wu 2013)
- GA AMD, S-MAIA: ±6.64 dB for mesopic testing, ±5.78 dB for DA cyan testing, and 7.24 dB for dark-adapted red

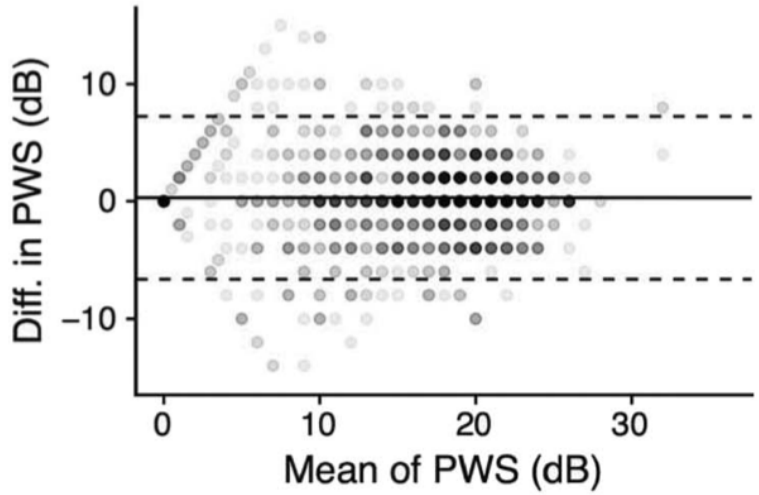
**GA-specific evidence**

- Effective dynamic range concept: usable range depends on disease stage and floor effects
- Mesopic microperimetry in GA: junctional-zone loss is reliably detectable on patient-tailored grids

**Learning effect and staircase bias**

- 4-2 staircase underestimates loss on the first test — CoR can fall between 1st and 2nd, 2nd and 3rd test.
- First test used as seed and excluded from analysis; patient reliability indices as trial eligibility criteria





***References:***

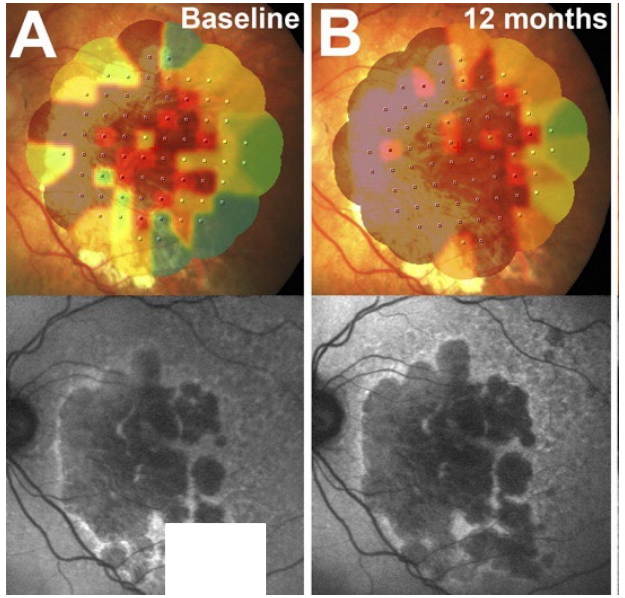
*Wu Z, et al. Invest Ophthalmol Vis Sci. 2013;54(12):7378-7385. PMID: 24135753*

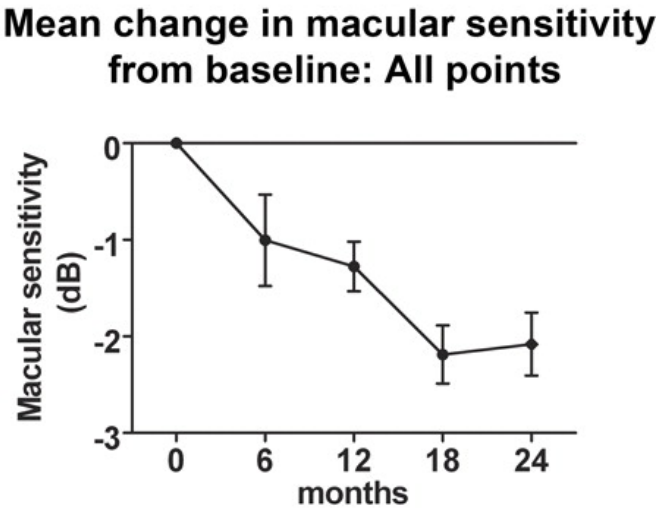
*von der Emde L, et al. Transl Vis Sci Technol. 2019;8(1):7. PMID: 30637177*

*Wu Z, et al. Transl Vis Sci Technol. 2023;12(7):11. PMID: 37428130*

# Measurement Properties: Change Over Time

- Testing with a standard 10-2 grid
- Mean Sensitivity declines significantly over time (approx. -1 to -1.5 dB/yr in a 10-2 grid)
- Number of scotomatous points (<0 dB) increases over time (approx. +4 to +5 points/yr in a 10-2 grid)

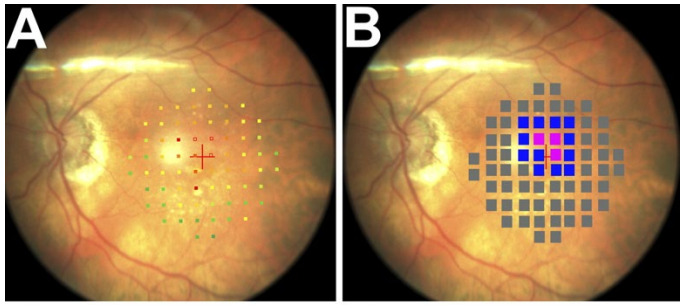


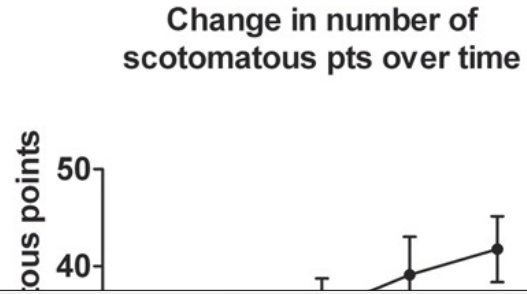



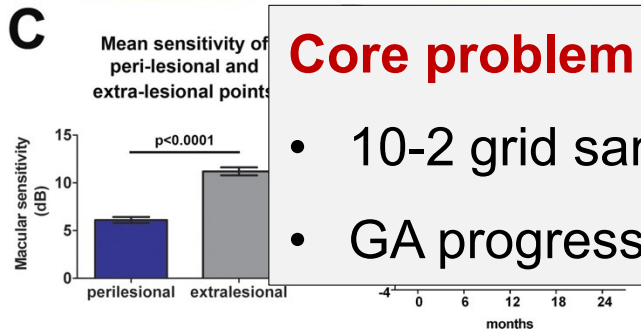

*Meleth AD et al. Invest Ophthalmol Vis Sci. 2011;52(2):1119-1126*
*Chen FK et al. Retina. 2011;31(2):371-379*

# Post-Hoc Analyses to Improve Ability to Detect Changes

Optimized Parameter Extraction / Post-Acquisition Workarounds







**Core problem persists: Spatially Sparse Sampling**

- 10-2 grid samples with 600 µm spacing
- GA progresses only by 100 to 200 µm per year

- Peri-lesion analysis to only monitor test-locations at risk

- Binarization of sensitivity data to <0 dB (non-seeing) and seeing locations
- Minimizes noise from fluctuation (measurement variability) within the seeing retina


Meleth AD et al. Invest Ophthalmol Vis Sci. 2011;52(2):1119-1126
Chen FK et al. Retina. 2011;31(2):371-379
Schönbach EM [...] Scholl HPN. Am J Ophthalmol. 2020 Aug;216:219-225

# Innovation 1: Patient-tailored perimetry

## OCT- and FAF-guided grids targeting the junctional zone

**Concept — place stimuli where biology predicts change**

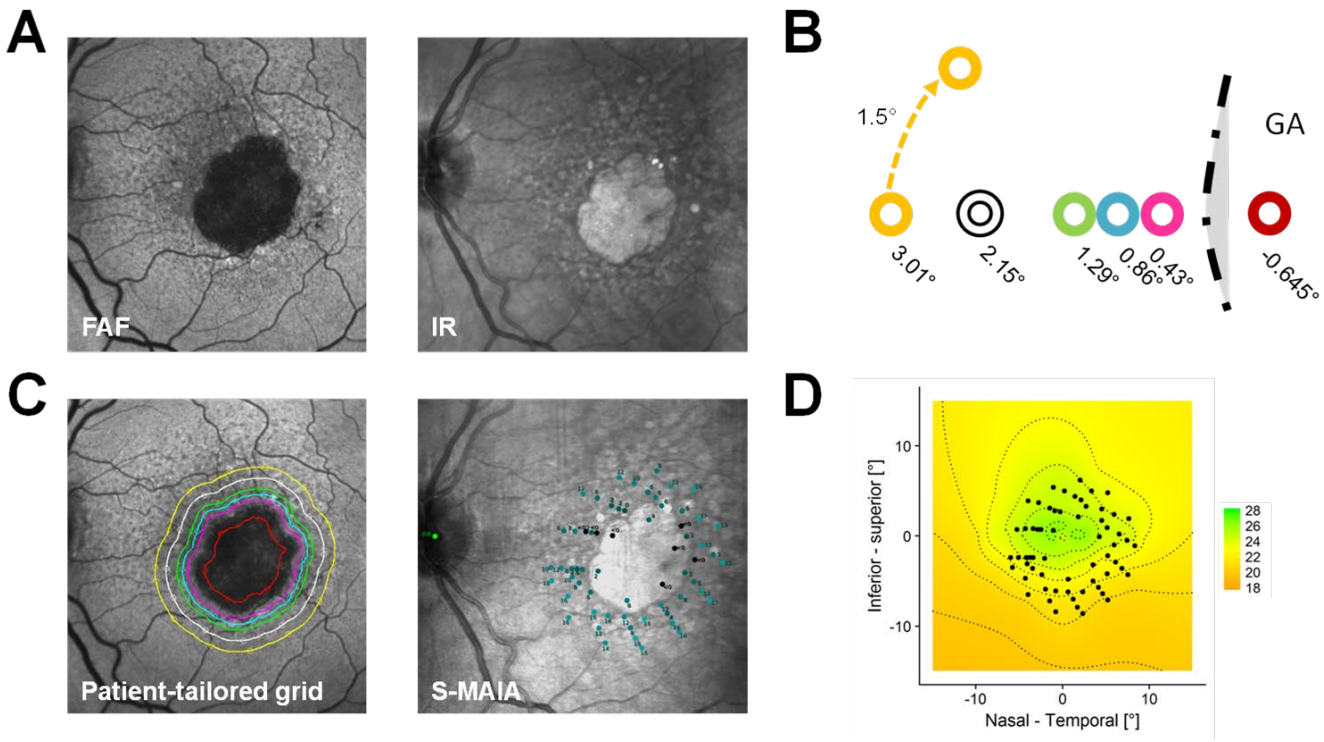
- Iso-hull grids around the GA border (0.43°, 1.03°, 1.65°, 2.31°, 3.01°)

**Advantages for GA trials**

- Maximizes local spatial resolution
- Keeps number of test-points reasonable (reduced test burden)

**Risks:**

- May miss in the long-term new satellite lesions (mostly relevant in the context of trials >18 months)




*Pfau M, et al. Retina. 2020;40(1):169-180. PMID: 30300264*

# Innovation 2: Defect-Mapping Microperimetry (DMP)

## Single-Presentation of 10 dB Stimulus to Quantify Deep Defects

**Protocol**

- 208 locations within the central 8° radius; 10 dB stimulus presented once per point; seen/missed response

**Criterion for truly non-responding locations (Wu 2024 IOVS 65:44)**

- ≤10 dB on both tests + <0 dB on one: 87% sensitivity, 0.4% false-positive rate

**Measurement properties in GA (Wu 2024, Saeed 2025)**

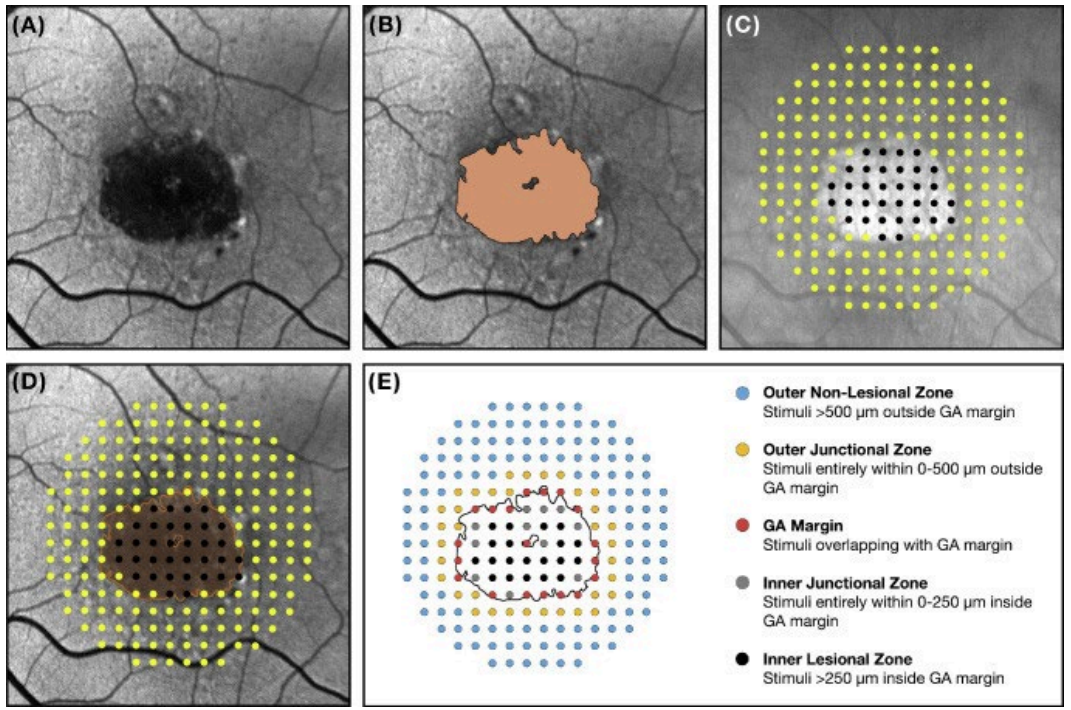
- GA extent explains ~90% of cross-sectional PLM variance

**Advantages for GA trials**

- Straightforward to implement and interpret
- Well-characterized (regarding longitudinal performance in natural history study)

**Risks:**

- Could theoretically miss minor sensitivity changes within the seeing retina (i.e., subtle adverse effect on visual function)




*Saeed A, et al. Ophthalmol Sci. 2025;5(4):100763. PMID: 40276124*
*Saeed A, et al. Ophthalmol Sci. 2025;5(6):100856. PMID: 40778363*
*Wu Z, et al. Invest Ophthalmol Vis Sci. 2024;65(8):44. PMID: 39078733*

# Innovation 1+2: Patient-Tailored DMP

## OCT- and FAF-guided grids + Single-Presentation of 10 dB Stimulus

**“Best of Both Worlds”**

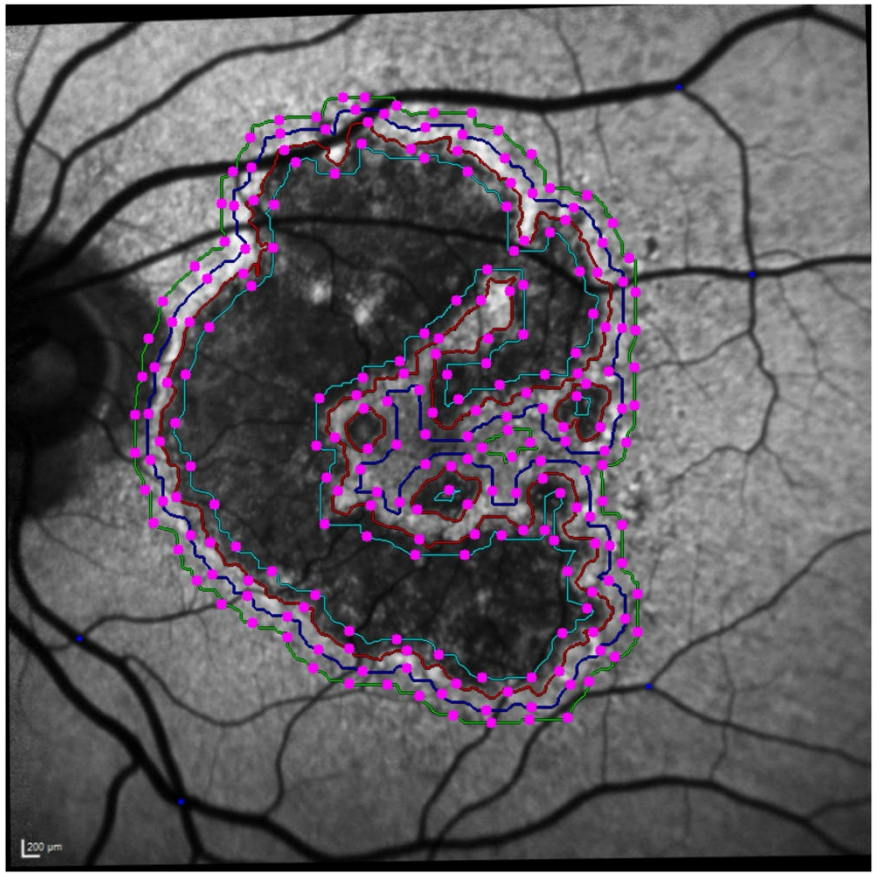
- 208 locations placed at four iso-hulls relative to GA border (-0.215°, 0.215°, 0.645°, 1.08°; sampling a -125 to 375 µm region)

**Advantages for GA trials**

- Maximizes local spatial resolution
- Takes advantage of well-established measurement properties in GA (strong structure-function correlation)

**Risks:**

- May miss in the long-term new satellite lesions
- Could theoretically miss minor sensitivity changes within the seeing retina



# Innovation 3: Inferred Sensitivity Mapping (OCT-F)

## Machine-Learning Surrogate for Psychophysical Testing

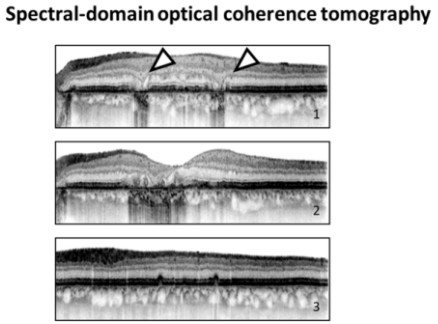
**Concept — predict microperimetric sensitivity point-wise from multimodal imaging**

- Inputs: SD-OCT layer thicknesses and reflectivity, FAF, retinal location
- Models: random forests, gradient boosting, deep learning

**Advantages**

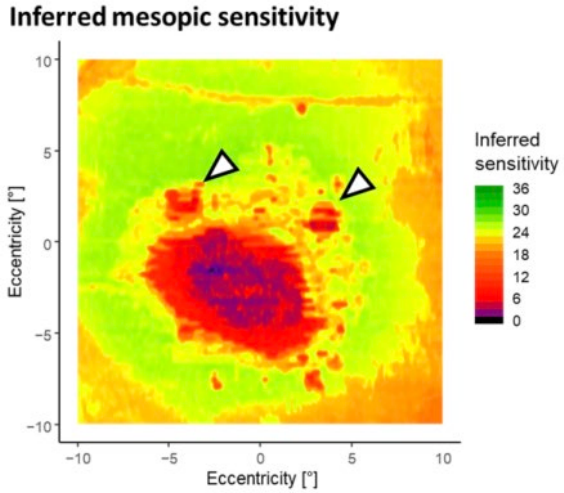
- Dense, high-resolution (supra-resolution) functional maps without extensive psychophysics
- Quasi-functional surrogate endpoint concept
- Free from psychophysical noise

### 1. Input:

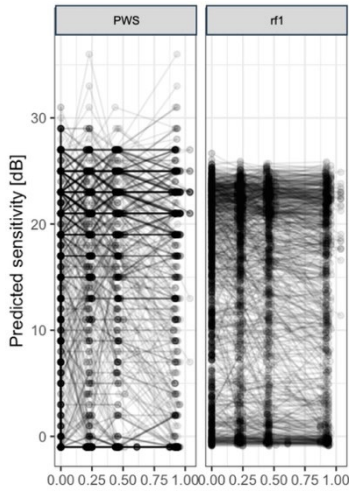



### 2. Pretrained AI Model


### 3. Output:




"Noise-free change-over time"




*Pfau M, et al. Am J Ophthalmol. 2020;217:162-173. PMID: 32289293*
*Ansari G, et al. Invest Ophthalmol Vis Sci. 2025;66(11):34 (OMEGA 2). PMID: 40801672*
*von der Emde L, et al. Eye (Lond). 2021;35(8):2110-2118. PMID: 33767409*

# Inferred Sensitivity Mapping (OCT-based)

## Machine-Learning Surrogate for Psychophysical Testing

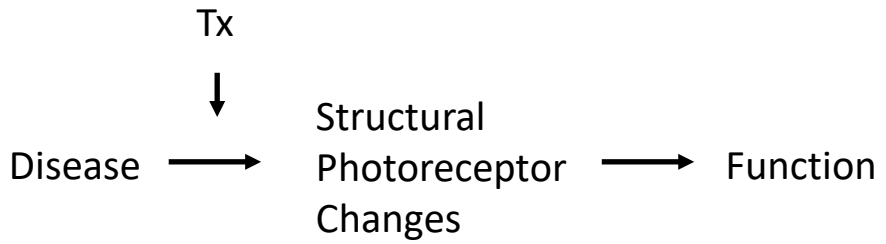
**Performance in GA (Pfau 2020, Ansari 2025 OMEGA 2)**

- Mean absolute error 3.67 dB (unknown patient) and 2.96 dB (patient-seeded)
- **Residual variance (progression-over-time models) reduced ~3-fold**

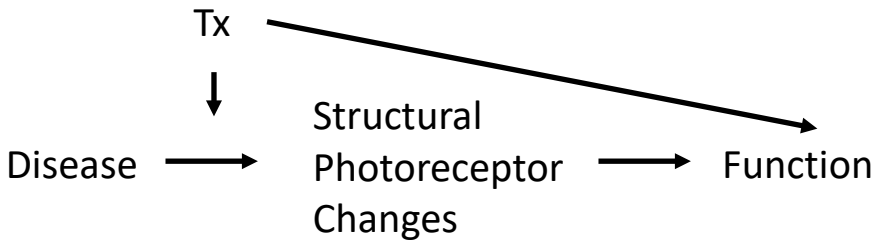
**Caveats**

- **Requires for each investigational product a "validation cohort"** to ensure that model predictions are still valid/calibrated with treatment

**Scenario 1:** Inferred Sensitivity Mapping Valid




**Scenario 2:** Problematic Scenario

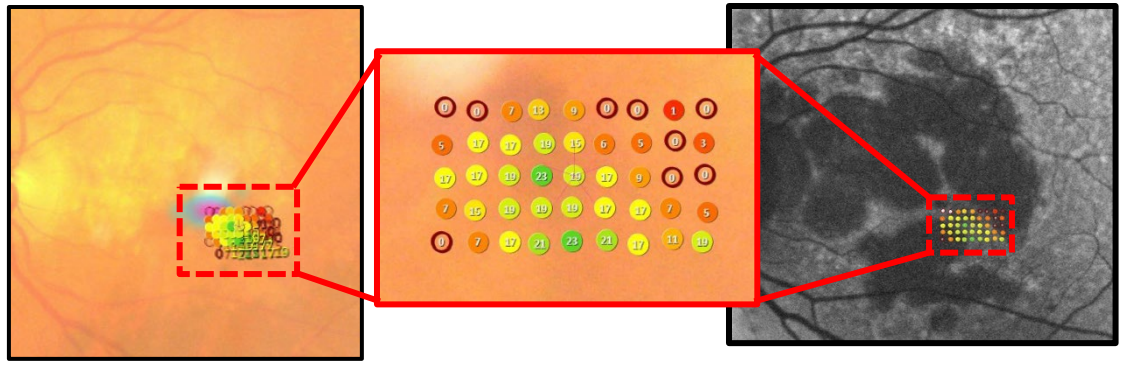



*Pfau M, et al. Am J Ophthalmol. 2020;217:162-173. PMID: 32289293*
*Ansari G, et al. Invest Ophthalmol Vis Sci. 2025;66(11):34 (OMEGA 2). PMID: 40801672*
*von der Emde L, et al. Eye (Lond). 2021;35(8):2110-2118. PMID: 33767409*

# Innovation 4: Fovea/Cone-Focused Testing

**Concept — Measuring QoL-Relevant**

- Using the combination of (i) densely–spaced grid centered on the fovea, (ii) cone-isolating photopic testing and small (iii) Goldmann III stimuli to characterize foveal cone vision
- Focused ‘functional vision’ instead of more general ‘visual function assessment’

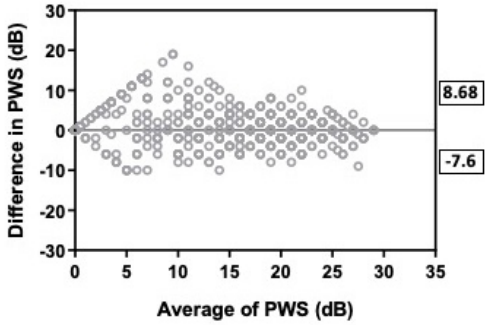


**Advantages**

- Most likely closer correlation to vision-related quality-of-life and BCVA as an established endpoint

**Disadvantages**

- Necessitates – like trials focusing on LLVA or qCSF – enrichment (in/exclusion criteria) relating to extra-foveal GA/foveal sparing GA (difficult to enroll)




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

# Innovation 5: VR-Based Testing

Idea: Repeated Testing (High-Temporal Resolution) to Improve the Ability to Detect a Change

**Concept — Frequent Testing**

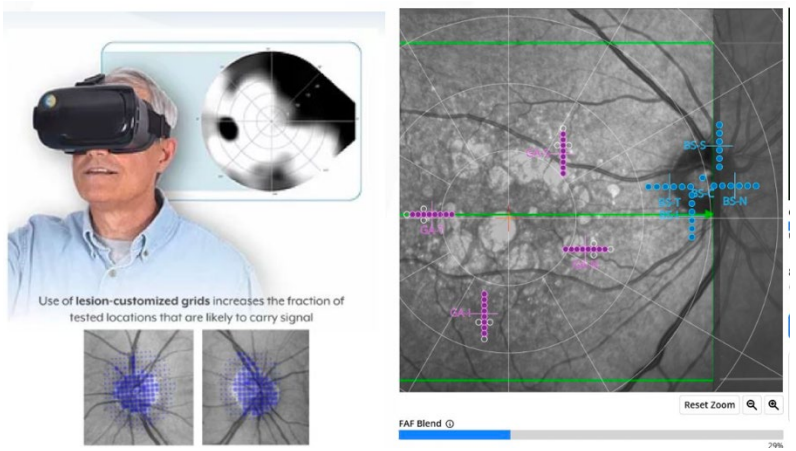
- Tracking based on **gaze-** instead of **retinal-tracking**
- Testing at home possible

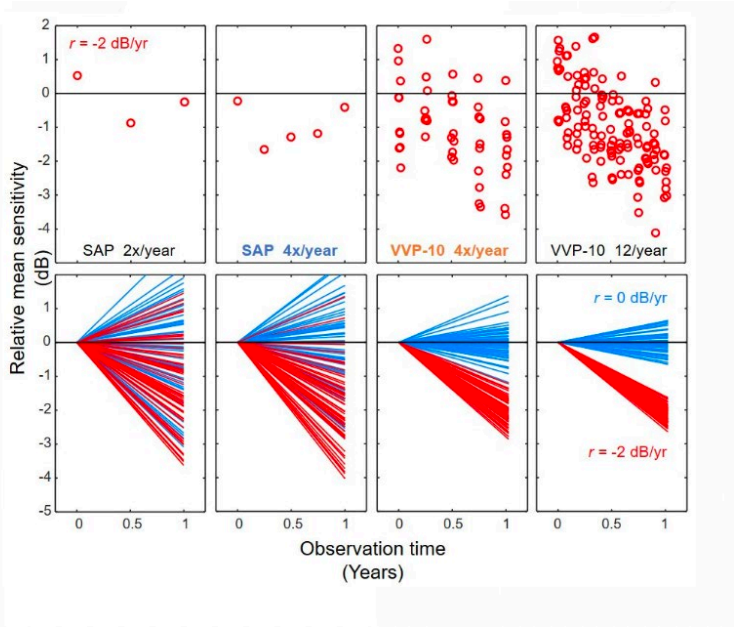
**Advantages**

- Repeated testing can markedly reduce psychophysical noise in threshold estimation.

**Disadvantage / Knowledge Gaps**

- Unknown (to date) how well gaze-tracked (instead of fundus-tracked) perimetry works with central scotomata/severe fixation instability
- Approach to blind-spot monitoring may be problematic in cases with continuity between peripapillary atrophy
- Some atrophy shapes might be challenging to monitor with the proposed spindle grid




*By courtesy of Karl Csaky, MD/PhD, James Blaha, Vivid Vision*
*Csaky KG et al. ARVO Annual Meeting; May 4-8, 2025; Salt Lake City, UT*

# Clinical Meaningfulness and MCID

## Clinical Consensus on What Change Matters to Patients

***1. Benchmark from Standard Automated Perimetry in glaucoma (Csaky 2008)***

- MCID commonly anchored to ≥5 test locations showing ≥7 dB change (pointwise progression criterion)
- ≥2 dB change in Mean Deviation (MD) also used as a clinically meaningful global index shift

***2. CAM 7 Modified Delphi (Wu 2025)***

- 91% consensus: depth of functional loss representing the onset of end-stage atrophic AMD should be ≤10 dB on two microperimetry tests

***3. Quality-of-Life-Based Argument (Künzel 2020)***

- **Anchoring to QoL data is infeasible due to the shortcomings of the NEI-VFQ-25**
- MCID of NEI-VFQ-25 ~ ***4 points*** (SST Report Number 19)
- Association of NEI VFQ25 and Sqrt. Atrophy

  ***= -6.87 points per mm*** (better eye association)

  Or 0.58 mm (sqrt. atrophy) preservation by Tx
- Unattainable in a disease progressing at 0.3-0.4 mm/year

***References:***
*Csaky KG et al. Invest Ophthalmol Vis Sci. 2008; 49(2): 479–48*
*Wu Z, et al. Ophthalmol Sci. 2025;5(5):100777 (CAM 7). PMID: 40469898*
*Künzel SH […] Pfau M. Invest Ophthalmol Vis Sci. 2020 May 11;61(5):63. PMID: 32462198*

# Conclusions and Future Directions

## Toward a regulator-ready functional endpoint in GA

- Microperimetry (overall) meets all endpoint framework pillars
- Leading endpoint candidates
  - Patient-tailored (micro)perimetry (PTP)
  - Defect-mapping microperimetry (DMP)
  - OCT-inferred sensitivity mapping (OCT-F)
  - Fovea-focused dense grid testing

  Optimized for ability to detect change → Candidates as key secondary endpoints (or even primary endpoint)

  Optimized for association with QoL → Well-positioned as a supportive endpoint (but necessitates challenging in/exclusion criteria)
- Consensus anchors
  - Single locus: ≤10 dB repeatable on two tests — working criterion for truly non-responding retina
  - Or point-wise changes ≥ 7 dB at multiple locations (well defensible based on CoR)
  - Uncertainty, across what retinal area such change should be observed (FDA specified 5-point criterion without specifying density )

*Pfau M, et al. Prog Retin Eye Res. 2021;82:100907. PMID: 33022378*
*Wu Z, et al. Ophthalmol Sci. 2025;5(5):100777 (CAM 7). PMID: 40469898*
*Huang A, et al. Asia Pac J Ophthalmol. 2025;14(3):100207. PMID: 40398512*


Univ.-Prof. Dr. Maximilian Pfau

Maximilian.Pfau@ukbonn.de

Department of Ophthalmology
University of Bonn

Venusberg-Campus 1
53127 Bonn,
Germany