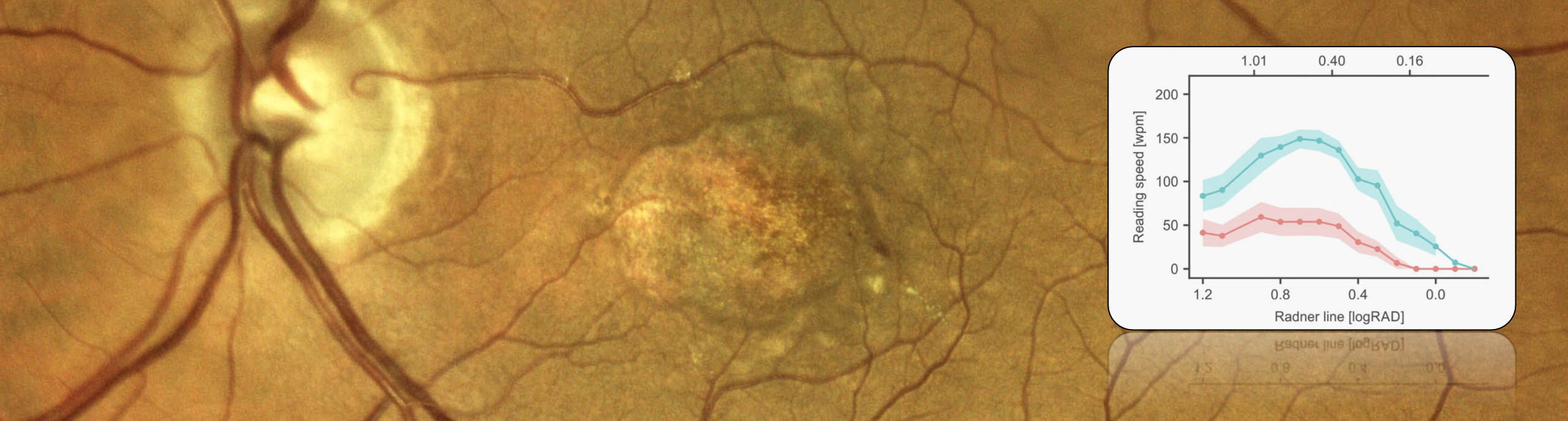




Univ.-Prof. Dr. med. Maximilian Pfau

Reading Performance as an Outcome Assessment for Geographic Atrophy

Evidence Base, Measurement Properties and Regulatory Considerations

European Medicines Agency

Scientific / Regulatory Interaction
GA Endpoints Workshop

Why Reading Performance Matters in GA

BCVA Under-Captures Patient-Relevant Dysfunction

Reading is among the dominant self-reported quality-of-life concerns

- Maps onto the near-activities domain of the NEI-VFQ-25 and the FRI Index^{1,2,3}

BCVA is necessary but insufficient

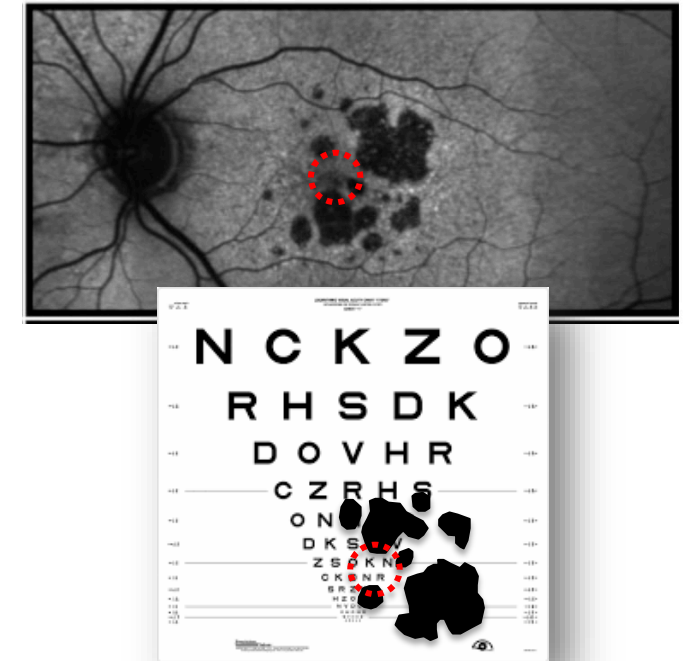
- Foveal sparing: letter acuity can stay near 20/25 while patients fail running text^{4,5}
- Chroma/Spectri: reading speed declines faster than BCVA over 24 months⁶

The functional gap in numbers

- ~50 % of GA eyes with good acuity read < 100 wpm⁶
- Reading-speed correlation with NEI-VFQ-25 near-activities $r \approx 0.7$

1. Mangione CM, et al. Arch Ophthalmol. 2001;119(7):1050-1058
2. Kimel M, et al. Invest Ophthalmol Vis Sci. 2016;57(14):6298-6304
3. Künzel SH [...] Pfau M. Invest Ophthalmol Vis Sci. 2020;61(5):63
4. Sunness JS. Retin Cases Brief Rep. 2008;2(1):83-84
5. Lindner M, Pfau M, et al. Ophthalmol Retina. 2019;3(3):201-210
6. Heier JS, et al. Ophthalmol Retina. 2020;4(7):673-688
7. Sunness JS, et al. Ophthalmology. 1997;104(10):1677-1691

Foveal Sparing



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

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Other Clinically-Used Reading Tests

IReST — International Reading Speed Texts

- Booklet of 10 long paragraphs per language across 17 languages; reading-speed test, not a chart
- Normative mean $\pm$ SD from 25 normally sighted subjects (36 in Japan) given per paragraph
- No print-size progression (not an acuity chart)



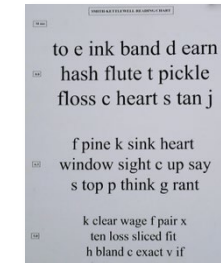
Bailey–Lovie Word Reading Charts

- Unrelated 4-, 7-, and 10-letter words in Times Roman; x-height calibration; logarithmic progression
- Simultaneous reading acuity and speed measurement; controlled word selection (alphabet distribution, frequency, no syntactic links)
- No published statistical test-item standardization; excludes sentence-level linguistic processing



Smith–Kettlewell Reading Test

- Paragraphs of 10 unrelated words + 6 single letters (60 characters); logarithmic progression 0.4 M to 4.0 M
- Designed for low vision: scotoma localization and magnification-need estimation; excludes grammar/syntax
- Only M-unit notation; significantly slower speeds and more errors than MNREAD/RADNER; repeatability reported only for maximum reading speed



Trauzettel-Klosinski S, et al. Invest Ophthalmol Vis Sci. 2012;53(9):5452-5461

Bailey IL, et al. Am J Optom Physiol Opt. 1980;57(6):378-387

MacKeben M, et al. Optom Vis Sci. 2015;92(4):421-428

Eisenbarth W, et al. Ophthalmologe. 2016;113(9):754-762

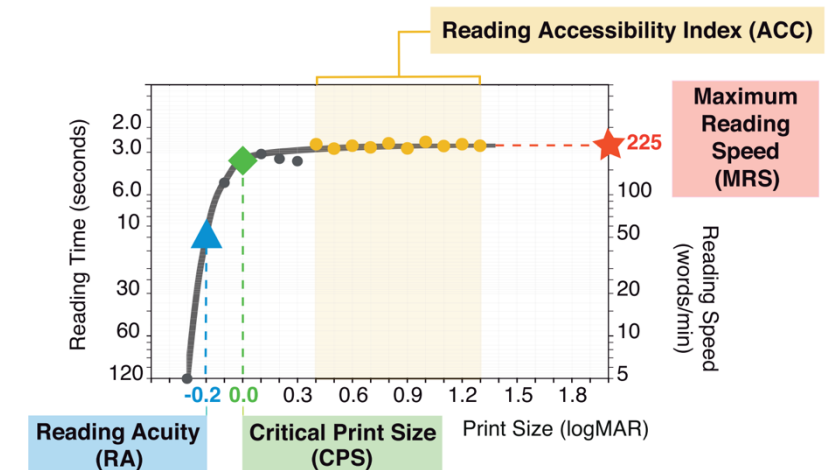
Reading Performance Parameters

From Acuity Threshold to Maximum Fluent Reading Speed

1. **Reading acuity (logRAD):** Smallest print the patient can read without major errors — analogous to BCVA at reading distance; a threshold measure.
2. **Maximum reading speed (RS_{max}):** Peak words-per-minute on the plateau above the critical print size — captures fluency and is more sensitive than acuity to retinal disease.

RS₂: mean reading speed of the 3 fastest sentences read

3. **Critical print size (CPS):** Smallest print at which RS_{max} is maintained (or smallest print size that yields 90%)
4. **Reading Accessibility Index (ACC – conceptually a ‘partial area under the curve’ metric):** Mean reading speed across the 10 largest print sizes divided by 200 wpm — single summary metric between 0 and 1



Calabrèse A et al. J Vis. 2018;18(1):8

Paradoxical Foveal-Sparing Phenomenon

„Reading Newsprint but Not Headlines“

A paradoxical near-acuity picture

- In foveal-sparing GA, atrophy encircles the fovea but a small island of functional photoreceptors persists centrally
- Letter-by-letter reading (acuity) can remain near 20/25 while natural reading collapses because neighbouring letters fall on atrophic retina.

Clinical Interpretation

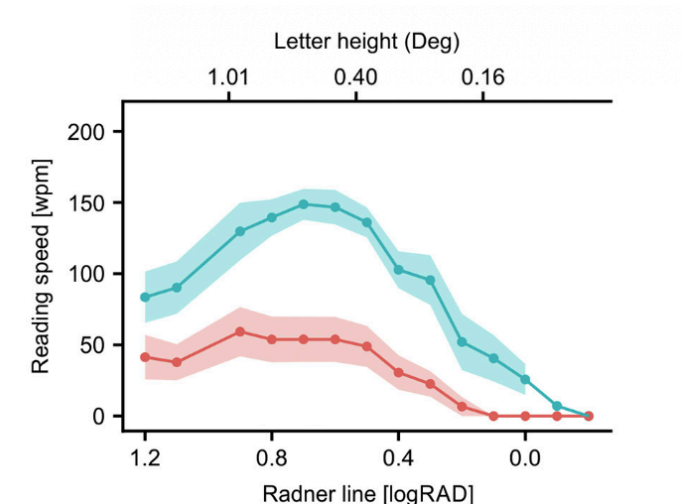
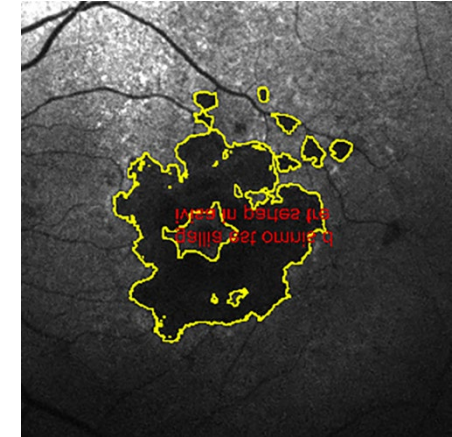
- Newsprint fits inside the spared fovea; headline-sized letters fall on atrophic retina — explaining the near-acuity paradox

The minimum required reading rectangle (M3R)

- Lindner 2019: a rectangle of ≈ 19 letters $\times$ 2.4 lines around the preferred retinal locus is needed for fluent reading.
- Atrophy encroachment on the M3R predicts reading breakdown better than BCVA.

Sunness JS. Retin Cases Brief Rep. 2008;2(1):83-84
Lindner M, Pfau M, et al. Ophthalmol Retina. 2019;3(3):201-210

Lindner M, et al. Ophthalmol Retina. 2019;3(3):201-210



Test-Retest Reliability

Repeatability Coefficients Across Parameters

- Reading acuity (MNREAD/Radner):
CoR $\approx$ 0.1 to 0.3 logMAR
- Maximum reading speed for
 $\text{Log}(\text{RS}_{\text{max}}) \approx 0.1$ to $0.2 \text{ Log}(\text{wpm})$
- Reading Accessibility Index (ACC)
and RS2 parameters: Best
coefficient of variation (CV) at W48
based on change from baseline

	CV (%)	P-Value vs.		
		RS ₂	RS ₃	ACC
Reading speed measures				
Definition 1 (RS ₁): Reading speed of the fastest sentence read	255	<0.001	0.061	0.002
Definition 2 (RS ₂): Mean reading speed of the fastest 3 sentences read	208	-	0.068	0.362
Definition 3 (RS ₃): Mean reading speed of the sentences larger than the CPS	224	-	-	0.095
Definition 4 (ACC): Mean reading speed across the 10 largest print sizes	204	-	-	-
Visual acuity measures				
Reading acuity (RA)	272	0.004	0.049	0.001
Best-corrected visual acuity (BCVA)	243	0.076	0.234	0.043
Low luminance visual acuity (LLVA)	374	<0.001	<0.001	<0.001
GA area				
Square root transformed	48	<0.001	<0.001	<0.001
Untransformed	52	<0.001	<0.001	<0.001

ACC = Reading Accessibility Index; CPS = critical print size; CV = coefficient of variation; GA = geographic atrophy; RS = reading speed.
Note that the analyses were performed using a mixed model for repeated measures adjusting for the baseline value of each parameter, and all reading speed measures were not corrected for errors made.

Wu Z, et al. Ophthalmol Sci. 2025;5(3):100700

Validity of Reading Performance in GA

Patient-reported (convergent validity)

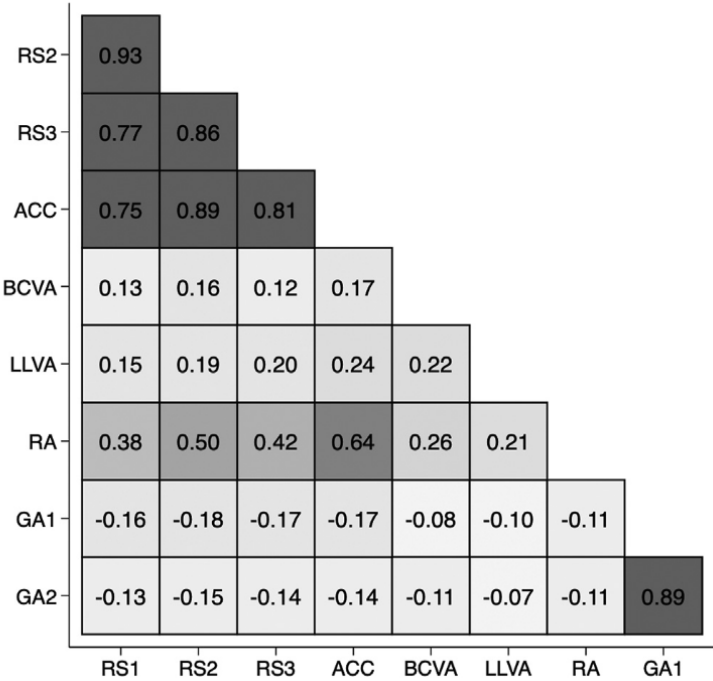
- MNREAD reading speed correlates with NEI-VFQ-25 near-activities ($r \approx 0.5\text{-}0.7$)
- Reading speed correlates with GA-specific FRI Index (Kimel et al., 2016)
- Thresholds have been proposed: 40 wpm required for “spot reading” and 80 wpm for fluent reading (Whittaker et al., 1993)

Structural: Reading acuity tracks BCVA and the central / inner-right ETDRS subfields; reading speed also reflects LLVA and the inner-upper subfield. Foveal-sparing studies localise the M3R anatomically.

Functional: In the largest GA cohort (Chroma/Spectri), reading speed captured disease severity beyond BCVA alone; baseline reading rate predicts future BCVA loss.

Totality of evidence

- Content validity — reading is the near-task patients name as most disabling.
- Construct validity — reading metrics correlate with BCVA, LLVA, GA area and PRO scores.
- Criterion validity — reading change tracks PRO change and predicts BCVA loss.



Wu Z, et al. Ophthalmol Sci. 2025;5(3):100700

- RA_i: speed of the fastest sentence read
- RS₂: mean reading speed of the fastest 3 sentences read
- RS₃: mean reading speed above the critical print size
- Reading Accessibility Index (ACC)
- RA: Reading acuity
- GA1: GA area - square root-transformed
- GA2: GA area - untransformed GA area

Sivaprasad S, et al. Am J Ophthalmol. 2018;190:1-8.
Kimel M, et al. Invest Ophthalmol Vis Sci. 2016;57(14):6298-6304
Whittaker SG, et al. Optom Vis Sci. 1993;70(1):54-65.
Lindner M, et al. Ophthalmol Retina. 2019;3(3):201-210

Künzel SH [...] Pfau M. JAMA Ophthalmol. 2021;139(11):1191-1199
Ricardi F, et al. Invest Ophthalmol Vis Sci. 2024;65(1):41.
Wu Z, et al. Ophthalmol Sci. 2025;5(3):100700

Decline of Reading Performance Over Time

Annual decline in untreated GA

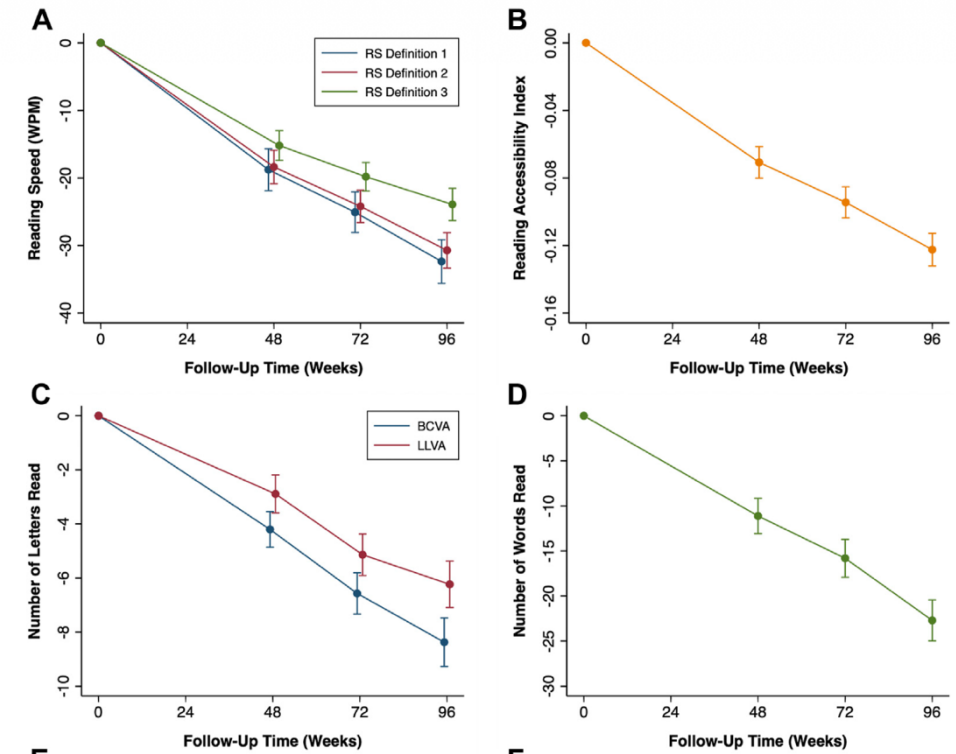
- BCVA ≈ -5 letters / year
- LLVA ≈ -5 letters / year
- Reading speed ≈ -10 wpm / year
- ACC ≈ -0.05 / year

Signal vs. noise

- 95% CoR exceeds two to three years of average decline
- BCVA: ~ 12 to 15 letters needed to exceed noise (~ 3 yrs)
- Reading speed: ~ 30 – 45 wpm needed (~ 3 – 4 yrs)
- ACC: ~ 0.15 – 0.20 needed (~ 3 – 4 yrs)

Implication

- 3–5 years of follow-up to clear retest limits
- Too few events accrue in 1–2-year trials
- Time-to-event designs infeasible
- **Continuous endpoints (MMRM) preferred**



Challenges

Patient Selection, Language and Practice

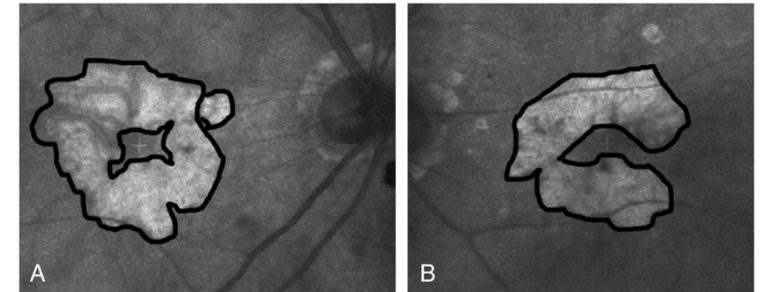
Patient Selection

- Current trial designs (enrichment strategies) focus on progression rates
- Reading performance trials would require vastly different inclusion criteria (i.e., patients with foveal-sparing, horseshoe-shaped atrophy)
 - Challenging/potentially **unfeasible to recruit**

Language, literacy and familiarity

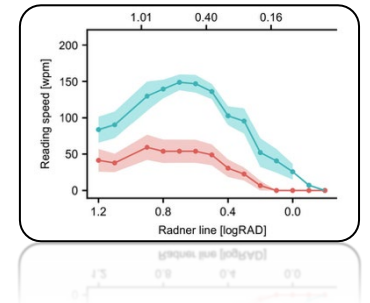
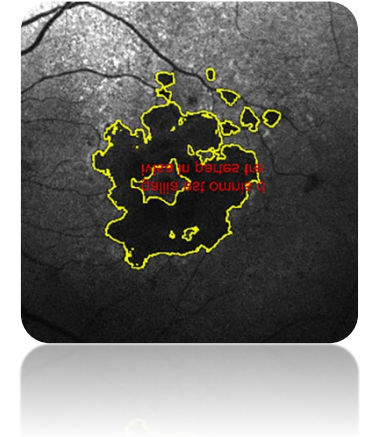
- IReST and Radner provide texts across 15-17 languages
 - However, not all languages may be available in the context of large phase 3 trials
- Literacy, dyslexia and cognitive load must be screened at baseline

Sunness JS. Retin Cases Brief Rep. 2008;2(1):83-84



Summary

1. **Reading is clinically meaningful:** BCVA alone misses disability in patients with foveal sparing GA
 2. **Measurement is mature:** MNREAD, Radner are well-established
 3. **Validity is well supported:** Convergent evidence with BCVA, LLVA, topography of atrophy (FAF), NEI-VFQ-25 and FRI Index
 4. **Retest properties are known:** CoR $\approx 0.2\log\text{RAD}$ and ≈ 40 wpm; ACC and RS2 yield the strongest longitudinal signal
 5. **Major Challenges:**
 - **Patient-selection:** Exact enrichment criteria for patients at risk of loss in reading performance not well-defined (**knowledge gap**) and recruitment of these patients – foveal-sparing with close boundaries – **infeasible at scale**
 - **High variability:** Reading performance measures show comparable variability to chart-based vision tests
 - **MCID:** Current thresholds — 40 wpm for spot reading and 80 wpm for fluent reading, together with 95% test–retest CoR estimates — render **time-to-event designs infeasible**, and thus evaluation of their **cohort-level rate of change is preferred**
- **Well-positioned as a supportive (or supplementary) endpoint:** May complement anatomic primary endpoints and anchor clinical-meaningfulness of lesion-size changes, but **currently unsuitable as a primary or key secondary outcome**





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