

Supplemental Online Content

Künzel SH, Lindner M, Sassen J, et al. Association of reading performance in geographic atrophy secondary to age-related macular degeneration with visual function and structural biomarkers. *JAMA Ophthalmol*. Published online September 30, 2021. doi:10.1001/jamaophthalmol.2021.3826

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This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1. Cohort characteristics

The table lists the structural biomarkers of the cross-sectional cohort and the baseline characteristics of the longitudinal cohort with their median value [interquartile range (IQR)] or their standard deviation (\pm SD). Variables were assessed for normality using the Shapiro-Wilk test. For normally distributed variables, the mean and SD are provided. For non-normally distributed variables, the median and IQR are presented.

Characteristic		Baseline	Longitudinal
Eyes of Patients		150 eyes of 85 patients	89 eyes of 53 patients
Age [years]		77.9 [9.62]; 77.1 \pm 7.1	78.1 [13.2]; 76.5 \pm 7.4
Follow-up visits [n]		NA	1[1]; 0.9 \pm 0.9
Follow-up time[years]		NA	1.00 [0.49]; 0.5 \pm 0.49
Sqrt.-transformed GA-progression rate [mm/year]		NA	0.25 \pm 0.19
Reading acuity (monocular) [logRAD]		0.90 [0.90]; 0.82 \pm 0.47	0.80 [0.90]; 0.8 \pm 0.47
Reading speed (monocular) [wpm]		52.8[123.0]; 67.5 \pm 69.7	53.0 [123.2]; 67.38 \pm 62.06
BCVA	[logMAR]	0.49 [0.80]; 0.59 \pm 0.46	0.49 [0.80]; 0.60 \pm 0.49
	[Snellen fraction ft]	20/60 [20/125]	20/60 [20/125]
LLVA	[logMAR]	1.00 [0.60]; 0.99 \pm 0.46	1.09 [0.61.00 \pm 0.46]
	[Snellen fraction ft]	20/200 [20/80]	20/250 [20/80]
Total GA size (sqrt-transformed) [sqrt(mm ²)]		3.14 [1.98]; 3.0 \pm 1.3	3.26 [1.98]; 3.2 \pm 1.4
Foveal Sparing		57 eyes (38.0%)	36 eyes (40.4%)
Distance: GA to fovea [mm]		0.00 [0.09]; 0.1 \pm 0.2	0.00 [0.14]; 0.11 \pm 0.22
GA area right of fovea [sqrt(mm ²)]		2.14 \pm 1.01	2.25 [1.68]; 2.22 \pm 1.05
GA area left of fovea [sqrt(mm ²)]		2.13 \pm 1.00	2.24 [1.48]; 2.19 \pm 1.02
ETDRS: Central subfield [sqrt(mm ²)]		0.86 [0.35]; 0.7 \pm 0.3	0.85 [0.40]; 0.67 \pm 0.29]
ETDRS: Inner lower subfield [sqrt(mm ²)]		1.15 [0.36]; 0.96 \pm 0.37	1.15 [0.36]; 0.96 \pm 0.38
ETDRS: Inner left subfield [sqrt(mm ²)]		1.15 [0.37]; 0.95 \pm 0.38	1.13 [0.36]; 0.94 \pm 0.38
ETDRS: Inner right subfield [sqrt(mm ²)]		1.14 [0.47]; 0.93 \pm 0.38	1.14 [0.48]; 0.93 \pm 0.38
ETDRS: Inner upper subfield [sqrt(mm ²)]		1.17 [0.45]; 0.94 \pm 0.4	1.18 [0.40]; 0.96 \pm 0.39
ETDRS: Outer lower subfield [sqrt(mm ²)]		0.80 [1.13]; 0.83 \pm 0.68	0.89 [1.28]; 0.85 \pm 0.69
ETDRS: Outer left subfield [sqrt(mm ²)]		0.83 [1.35]; 0.87 \pm 0.69	0.85 [1.35]; 0.89 \pm 0.70
ETDRS: Outer right subfield [sqrt(mm ²)]		0.93 [1.33]; 0.9 \pm 0.70	0.94 [1.36]; 0.95 \pm 0.70

Characteristic (cont.)	Baseline	Longitudinal
ETDRS: Outer upper subfield [sqrt(mm ²)]	0.97 [1.67]; 1.04 ±0.79	1.14 [1.68]; 0.96±0.39
Distance: GA to PRL-initial [mm]	0.11 [0.35]; 0.28±0.48	0.08 [0.35]; 0.29±0.54
Distance: fovea to PRL-initial [mm]	0.00 [0.00]; 1.11±1.02	0.00 [0.001]; 0.29±0.54
GA right of PRL-initial [sqrt(mm ²)]	2.38 ± 1.33	2.41 ±1.37
GA left of PRL-initial [sqrt(mm ²)]	1.55 [1.90]; 1.56±1.16	1.54 [1.79]; 1.64±1.21
Distance: GA to PRL-final [mm]	0.01 [0.03]; 0.25±0.47	0.00 [0.35]; 0.27±0.54
Distance: fovea to PRL-final [mm]	0.00 [0.001]; 1.28±0.8	0.00 [0.002]; 1.27±0.99
GA right of PRL-final [sqrt(mm ²)]	2.47 [1.77]; 2.45 ±1.36	2.49[1.87]; 2.46±1.42
GA left of PRL-final [sqrt(mm ²)]	1.39 [1.67]; 1.45±1.11	1.53 [1.83]; 1.56±1.17
Distance: PRL-initial to PRL-final [mm]	0.00 [0.001]; 0.6±0.47	0.00 [0.001]; 0.55±0.36
PRL-final nasal?	89 eyes (59.3%)	54 eyes (60.7%)

eTable 2. Determinants reading performance (univariable cross-sectional analysis)

The table shows the association of the different structural and functional biomarkers with reading acuity and speed. The first and fourth column denote the effect estimate with regard to change in reading acuity (logRAD) or speed (wpm) per unit change of the feature. The *t*-statistic (effect estimate divided by its standard error) can be compared across features as measure of variable importance. P-values were calculated using likelihood-ratio tests.

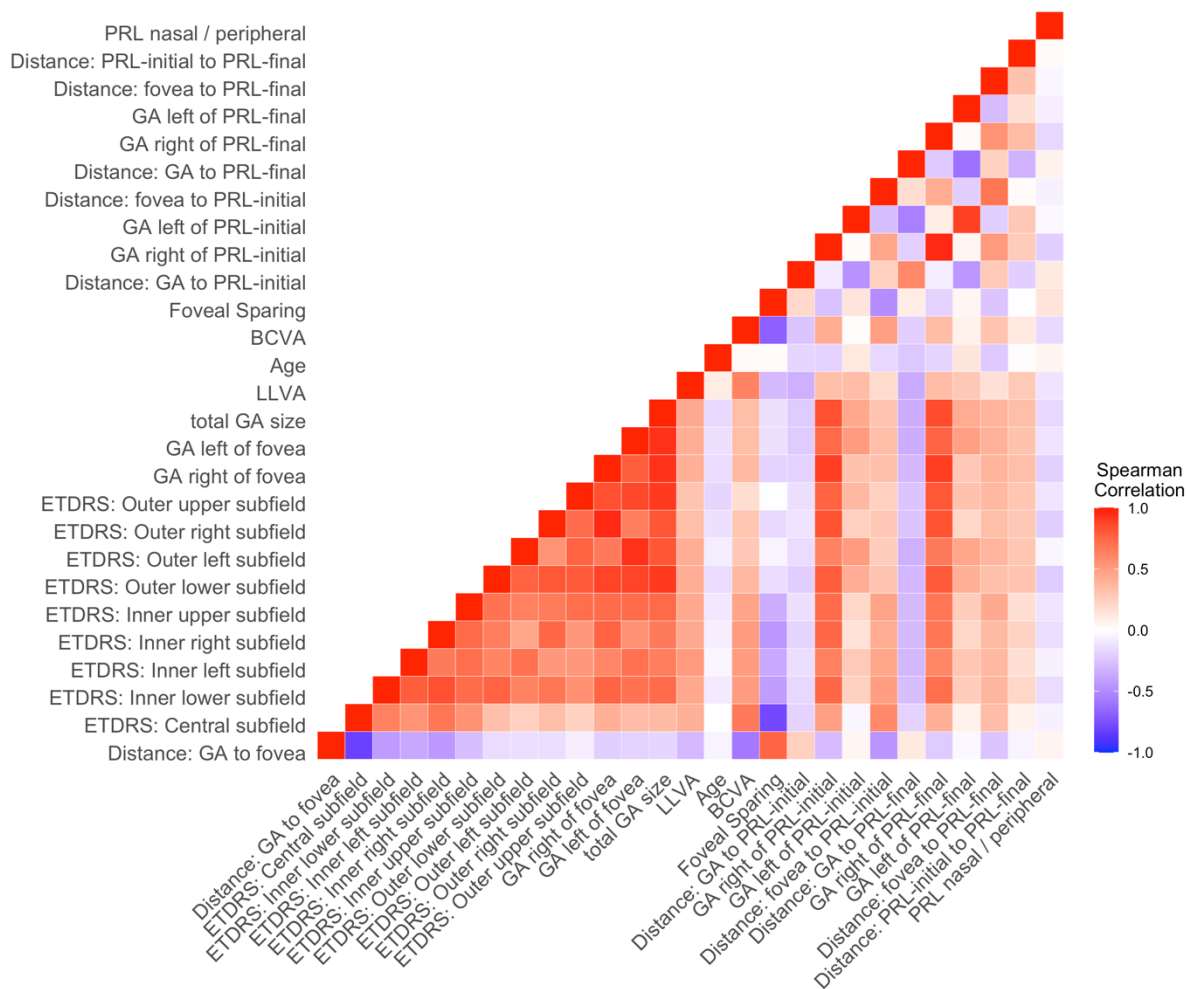
Determinant	Reading Acuity:			Reading Speed:		
	Effect Estimate [95% CI]	<i>t</i> - statistic	P- Value	Effect Estimate [95% CI]	<i>t</i> - statistic	P-Value
Distance: GA to fovea [mm]	-1.22 [-1.56; - 0.88]	-7.1	<0.001	188.48 [137.91; 239.06]	7.45	<0.001
ETDRS: Central subfield [sqrt(mm ²)]	1.2 [0.98; 1.42]	10.87	<0.001	-176.99 [-210.50; -143.49]	-10.56	<0.001
ETDRS: Inner lower subfield [sqrt(mm ²)]	0.64 [0.46; 0.82]	7.11	<0.001	-107.07 [-132.90; -81.25]	-8.29	<0.001
ETDRS: Inner left subfield [sqrt(mm ²)]	0.59 [0.42; 0.76]	6.64	<0.001	-93.05 [-118.92; -67.18]	-7.19	<0.001
ETDRS: Inner right subfield [sqrt(mm ²)]	0.68 [0.51; 0.84]	8.11	<0.001	-112.73 [-136.27; -89.20]	-9.58	<0.001
ETDRS: Inner upper subfield [sqrt(mm ²)]	0.58 [0.40; 0.75]	6.62	<0.001	-97.77 [-122.22; -73.32]	-8	<0.001
ETDRS: Outer lower subfield [sqrt(mm ²)]	0.26 [0.15; 0.38]	4.61	<0.001	-43.31 [-59.92; -26.69]	-5.21	<0.001
ETDRS: Outer left subfield [sqrt(mm ²)]	0.16 [0.05; 0.27]	2.96	<0.05	-27.42 [-43.53; -11.31]	-3.4	<0.001
ETDRS: Outer right subfield [sqrt(mm ²)]	0.23 [0.13; 0.34]	4.48	<0.001	-43.23 [-58.29; -28.17]	-5.74	<0.001
ETDRS: Outer upper subfield [sqrt(mm ²)]	0.14 [0.04; 0.25]	2.82	<0.05	-23.87 [-38.65; -9.09]	-3.23	<0.05
GA right of fovea [sqrt(mm ²)]	0.21 [0.14; 0.29]	5.94	<0.001	-37.51 [-47.68; -27.35]	-7.38	<0.001
GA left of fovea [sqrt(mm ²)]	0.18 [0.11; 0.25]	4.91	<0.001	-28.78 [-39.43; -18.14]	-5.41	<0.001

Total GA size [sqrt(mm ²)]	0.15 [0.09; 0.21]	5.39	<0.001	-25.7 [-17.58; -33.83]	-6.33	<0.001
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Determinant (cont.)	Reading Acuity:			Reading Speed:		
	Effect Estimate	t-statistic	P-Value	Effect Estimate	t-statistic	P-Value
Distance: GA to PRL-initial [mm]	-0.04 [-0.19; 0.12]	-0.46	0.65	7.67 [-15.65; 31.00]	0.66	0.51
GA right of PRL-initial [sqrt(mm ²)]	0.17 [0.12; 0.23]	6.6	<0.001	-26.83 [-34.57; -19.09]	-6.94	<0.001
GA left of PRL-initial [sqrt(mm ²)]	0.006 [-0.06; 0.07]	0.17	0.86	-4.49 [-14.57; 5.57]	-0.89	0.37
Distance: fovea to PRL-initial [mm]	0.19 [0.12; 0.26]	5.67	<0.001	-26.34 [-36.76; -15.91]	-5.05	<0.001
Distance: GA to PRL-final [mm]	-0.07 [-0.23; 0.10]	-0.83	0.41	13.59 [-10.91; 38.10]	1.11	0.27
GA right of PRL-final [sqrt(mm ²)]	0.16 [0.11; 0.21]	5.96	<0.001	-25.03 [-32.77; -17.29]	-6.47	<0.001
GA left of PRL-final [sqrt(mm ²)]	0.03 [0.004; 0.1]	0.73	0.47	-7 [-17.48; 3.47]	-1.34	0.18
Distance: fovea to PRL-final	0.18 [0.1; 0.26]	4.44	<0.001	-24.61 [-36.88; -12.34]	-4.01	<0.001
Distance: PRL-initial to PRL-final [mm]	0.12 [-0.3; 0.29]	1.61	0.11	-30.61 [53.60; -7.61]	-2.66	<0.05
PRL position [nasal / peripheral]	-0.22 [-0.35; -0.08]	-3.13	<0.05	30.28 [9.34; 51.23]	2.89	<0.05
LLVA [logMAR]	0.62 [0.76; 0.47]	8.29	<0.001	-105.49 [-125.73; -85.25]	-10.42	<0.001
Age [years]	0.004 [-0.008; 0.02]	0.64	0.53	-1.1 [-2.90; 0.70]	-1.23	0.24
BCVA [logMAR]	0.82 [0.73; 0.92]	17.24	<0.001	-110.37 [-127.15; -93.58]	-13.15	<0.001
Foveal Sparing	-0.67 [-0.78; -0.55]	-11.18	<0.001	87.74 [67.83; 107.65]	8.81	<0.001

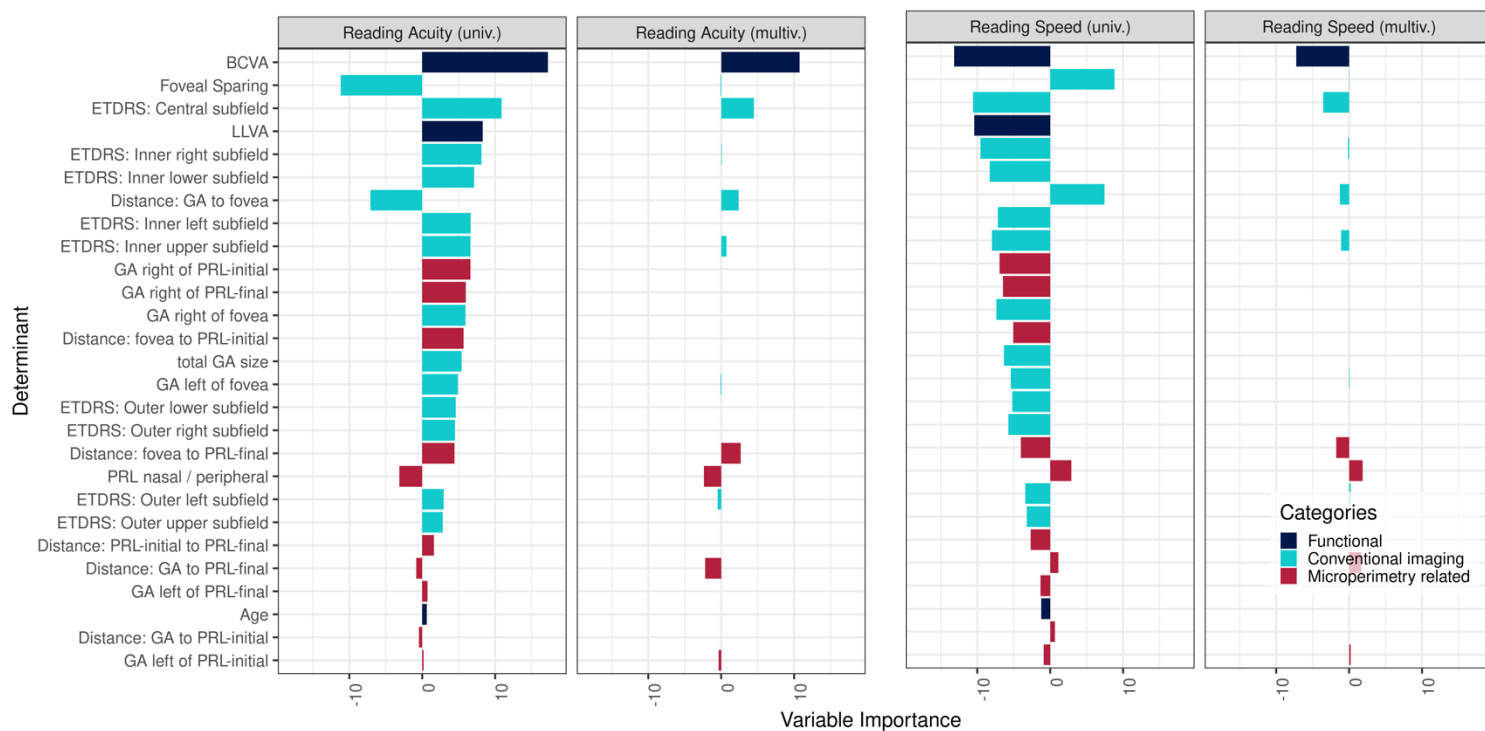
eFigure 1. Correlation among candidate features

The heatmap shows the Spearman correlation among all of the candidate features. The correlation is color-labelled (red – positive correlation; no color – no correlation; blue – negative correlation). Note that strong correlations in value indicate multicollinearity.



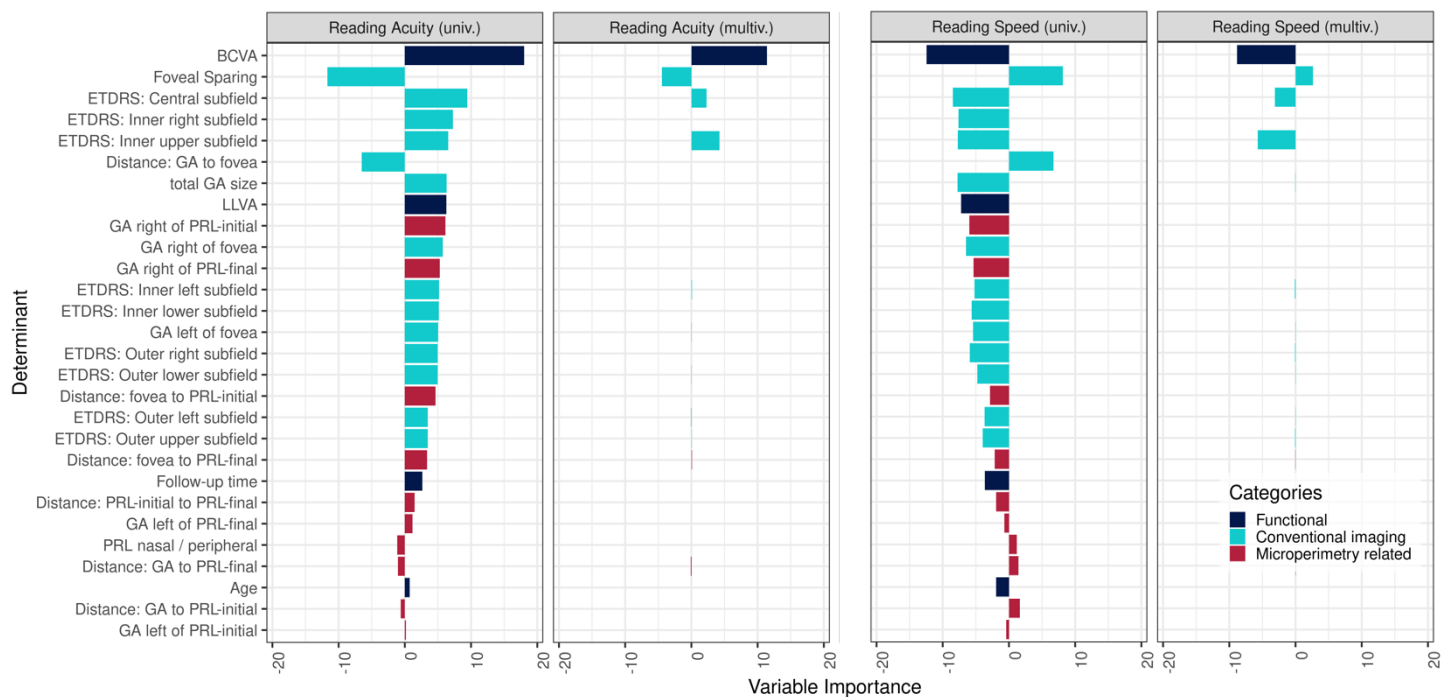
eFigure 2. Backward-selected Linear Model: Feature Importance at Baseline

The variable importance was measured by the t-statistic for the univariable and multivariable analysis each for the reading speed and reading acuity. (red: microperimetry related; light blue: conventional imaging; dark blue: functional).



eFigure 3. Backward-selected LM: Longitudinal Feature Importance

The variable importance was measured by the cross-validated t-statistics each for the reading speed and reading acuity (red: microperimetry related; light blue: conventional imaging; dark blue: functional). Note the drastically difference of selected variables compared to the cross-sectional model, which points to the instability of backward-selection due the presence of strong multicollinearities between our variables.



eFigure 4. Model accuracy

The plot shows the mean absolute error (MAE) of the cross-validated multivariable *LASSO* regression model compared to a random forest (RF) model, that was trained on the same dataset for (A) reading acuity and (B) reading speed. Since the MAE is comparable in both models, preference was given to *LASSO* regression in consideration of interpretability.

