

OPH503294 - Ophthalmologica - ISSN 0030-3755 (for internal use only)							
Code 3	PE	CE	Copy edited	Figures	Tables	Suppl. mat.	Typesetting
OPH	Id	hw	23.10.2019	6	2		tb
Language	E	Second Language	Third Language		Template_Art		ZU

Internal info:	
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Article title	The Impact of Progressive Visual Field Constriction on Reading Ability in an Inherited Retinal Degeneration
Article title second language	
Article title third language	
Subtitle	
Short title	Near Visual Ability with Visual Field Loss
Section title	Research Article

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Citation line	Journal
	Ophthalmologica

Translation				
10.1159/000503294	Article-Nr	503294	CCCode	
ISSN	0030-3755			
ISBN				

Received	Received: February 18, 2019			
Accepted	Accepted after revision: September 9, 2019			
Revised				
Published online	Published online: ■■■			
Copyright statement	© 2019 S. Karger AG, Basel			
Copyright description				

Keywords	Keywords
	Reading Reading speed Near visual acuity Choroideremia Retina

Keywords Second Language	

Keywords Third Language	

Abbreviations	
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Abstract	Abstract
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Background: The ability to read is an important factor in the quality of life. Choroideremia is an inherited retinal degeneration presenting with gradual, progressive constriction of the central visual field, providing a useful disease model to investigate the impact of the visual field on reading ability. **Objective:** The aim of this study was to provide practical guidance on the usefulness of measuring reading ability in patients. **Method:** The Radner Reading Test was administered to 33 patients (65 eyes with choroideremia). To quantify the residual retinal area, the patients underwent microperimetry and imaging. The visual angle subtended by the largest letter read by each subject was calculated using Emsley's Model Eye. **Results:** A minimum of 1 letter must be seen to allow the eye to read, with preservation of foveal sensitivity. The relationship between reading speed and acuity varies with the visual field. The reading speed is higher in eyes with an intact fovea ($p < 0.001$ right eye, $p = 0.06$ left eye). Qualitative analysis of the direction of the intact retina did not indicate any directional impact on measurements.

Conclusions: In order to read, an eye must have enough retinal width close to the fovea to see at least 1 full letter. Direction of print does not impact the ability to read, allowing results from different languages to be combined in clinical trials.

Abstract Second Language	
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Key Messages	

Body

Introduction

Near (reading) vision has a large impact on quality of life, often being related to independence [1]. Difficulties with reading remain the most common reason for presentation to a low-vision clinic [2]. Distance visual acuity may not predict reading ability across all visual acuities, due to the variability in reading speed across different print sizes and the variability in retinal anatomy [3–5]. Reading performance should therefore be considered as a separate measure from distance vision.

Reading speed can be affected by the type of vision loss, disease state and, to a lesser degree, the presence of cataract [5, 6]. These factors can have differential impacts on reading speed versus reading acuity, making it helpful to assess these two near vision functions independently. Additionally, reading ability is thought to be affected by the area of the visual

field being used, with the central horizontal field along the reading plane (to enable tracking of the next word in a line of text) and the inferior field (to allow tracking of the next line of text) being considered the most important [6, 7]. This will impact on the area of the retina being used for reading as well as the visual span [8, 9]. Visual field loss will restrict the number of letters that are physically visible at any one time and likely reduce the reading speed due to loss of the visual span.

The Radner Reading Charts allow the measurement of both speed and acuity in a quick, systematic way. They have been validated for use in multiple languages and extensively utilised for several disease states [3, 10, 11]. The Radner charts have been shown to perform well in low-vision patients [5]. The test consists of 28 selected short sentences in Helvetica font. The sentences are of similar difficulty and syllabic content, based on logMAR size progression between paragraphs. The resulting logRAD score is comparable to logMAR and can be adjusted to the working distance used [3, 12].

Choroideremia is an X-linked inherited retinal disease characterised by peripheral visual field loss with relative preservation of central vision [13]. This provides a great model to study reading vision as the preserved central retina, including the fovea, is unlikely to change the pattern of fixation eye movements. The area of functional retina can be accurately quantified by autofluorescence (AF) imaging and microperimetry, providing information about the effective visual field to allow a real-world understanding of the impact on reading performance [13, 14]. This is becoming more important since the development of phase III gene therapy trials for choroideremia, following the successful completion of phase I/II studies [15]. This information can also be applied to other inherited retinal dystrophies, particularly rod-cone dystrophies or conditions causing variable visual field defects affecting the periphery more than the centre.

Subjects and Methods

Patients were assessed for inclusion in an ongoing clinical trial, an open-label phase II clinical trial of retinal gene therapy for choroideremia using an adeno-associated viral vector encoding REP1 (ClinicalTrials.gov identifier: NCT02407678; approved by the NRES Committee London – West London and GTAC, reference GTAC171 and NCT01461213), conducted in accordance with the Declaration of Helsinki at the Oxford University Hospitals NHS Foundation Trust, UK. Thirty-three male patients with a genetically confirmed diagnosis of choroideremia completed monocular Radner Reading Chart® (Precision Vision, Woodstock, IL, USA) testing with an optimised refractive error in place. Time taken to read standardised “sentence optotypes” of logarithmically reduced print size was measured and the mean reading speed calculated in words per minute across all the print sizes. Monocular best corrected distance visual acuity was measured following refraction, using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol.

The subjects also underwent microperimetry testing using the MAIA (Macular Integrity Assessment) system (CenterVue SpA, Padua, Italy) after 20 min of dark adaptation (light level <1 lux). The 10-2 grid was used using a 4-2 staircase test algorithm. The mean sensitivity around the preferred retinal locus was calculated from the average of the four points directly surrounding the preferred retinal locus. Fixation stability was analysed using the output from the bivariate contour ellipse area indices.

Anatomical methods were used to locate the precise position of the fovea in relation to the residual retina remaining. Macula enhanced-depth imaging optical coherence tomography (OCT) and BluePeak laser fundus AF images were obtained using the Spectralis HRA+OCT system (Heidelberg Engineering GmbH, Heidelberg, Germany). The images were processed using Heidelberg Eye Explorer software (Heidelberg Engineering GmbH) to first locate the foveola on the enhanced-depth imaging OCT, which was then precisely mapped onto the corresponding 30° AF image. A caliper tool was used to measure the horizontal and vertical dimensions of the AF area extending from the centre of the fovea; these dimensions were

subsequently broken down into their constituent nasal, temporal, superior and inferior parts. The horizontal and vertical dimensions of AF were used to approximate the functional visual field of each subject, the AF area being representative of the presumed surviving retina [16]. For those patients whose fovea fell outside their surviving retina, the caliper tool was used to measure the distance from the fovea to the closest edge of the surviving retina, which was assigned a negative value. For all patients, the total area of the surviving retina on the 30° AF image was also calculated using the “draw region” tool within the Heidelberg Eye Explorer software (HEYEX).

The visual angle subtended by the largest Radner letter read by each subject was calculated using the principles of Emsley’s Model Eye, which assumes an overall focal length of 22.22 mm (Fig. 1) [17]. Using HEYEX, calipers were placed on the AF image to represent the calculated theoretical retinal image size subtended by a letter on the Radner Reading Chart read at 40 cm. The resulting image was exported to Microsoft Word 2010 (Microsoft, Redmond, WA, USA) and a Radner Chart letter of matching size was overlaid onto the image. The largest letter was considered in this way in order to better understand the impact of visual field loss on reading ability. All statistical analyses were conducted in StatsDirect (StatsDirect Ltd, Cambridge, UK).

Results

A total of 65 eyes of 33 patients were examined. The patient characteristics are shown in Table 1. The eyes were classified into three groups depending on the position of the anatomical fovea relative to the remaining functional visual island based on AF imaging [14, 16]: (1) eyes whose fovea fell within the functional retinal island; (2) eyes whose fovea was at the edge of their visual island; and (3) eyes whose fovea fell outside the retinal island. This was achieved by tracing out the bright border on the AF image as per the method previously reported to delineate

the remaining retina. The foveal centre was marked on corresponding OCT images from the same appointment day and the markings were transferred to the AF image to provide accurate localisation and allow assessment of where the fovea fell in relation to the retinal island.

Reading Speed across Eyes

The effective size of the print on the retina is demonstrated in [Figure 2](#) with the impact on reading described. Eyes A and B were able to read print, but eye C could not see any letters, and thus had a reading speed of 0 words/min. The full letter needs to fall within the structurally intact retina in order to allow reading, which means that smaller print is beneficial to patients with smaller visual fields. From our cohort, a minimum of 1 letter was required for the patient to be able to read. There were no instances with a minimum of 1 letter width and no ability to read. However, each eye displayed a peak sensitivity or maximum reading speed for reading as denoted by the peak of the curve, with both smaller letters and larger letters showing reduced speed ([Fig. 3](#)). The location of the peak in terms of logRAD size varied between individuals, indicating the benefit of measuring this on an individual basis ([Table 2](#)). The tests were compared for right and left eyes separately comparing group 1 eyes (24 right eyes and 23 left eyes) with group 2 and 3 eyes combined (9 right eyes and 9 left eyes) after exclusion of those eyes unable to perform the test. In the right eye, the difference in mean reading speed was significant (Mann-Whitney U test: $p < 0.001$; median difference: -76 words/min [95% CI with Hodges-Lehmann estimator: -39 to -100 words/min], $n = 24$ and 8 , respectively). The relationship was similar for left eyes, approaching statistical significance (Mann-Whitney U test: $p = 0.06$; median difference: 51 words/min [95% CI -3 to 97 words/min], $n = 23$ and 7 , respectively). The group 1 eyes were able to read faster than the group 2 and 3 eyes.

Microperimetry

The microperimetry threshold has previously been reported as a more sensitive marker of central vision than visual acuity, and we therefore felt it important to examine the relationship

to reading ability [13]. Microperimetry patterns were analysed in the fovea of group 3 individuals to assess whether the fixation pattern or the location of the seeing points was altered in those that could read versus those unable to read print. Three out of the 4 eyes that were unable to read had 3 or fewer seeing points located away from the fovea despite good fixation (Fig. 4a). One patient did have a larger seeing island, but it was very narrow at the fovea (Fig. 4b). All eyes that were able to read showed a cluster of seeing points within the central portion of the microperimetry grid (Fig. 4c). No pattern was noted between reading speed and the nearest foveal edge in group 3 (Fig. 4d).

The group 1 eyes were investigated to assess which biological and functional factors impacted on the ability to read. Mean reading speed and AF area appear to show a weak relationship to increasing speed as the AF area increases until 20 mm² (Fig. 4e), as were average reading speed and the sensitivity of the central 4 points on microperimetry (Fig. 4f).

Direction of Vision

Since reading English involves left-to-right scanning of text, we next investigated whether the meridian of the structurally preserved retina had an impact on reading characteristics. Due to the correlation between AF and microperimetry regarding the pattern of central loss [14], AF was used to approximate the functional visual field of each subject, AF being representative of the structurally surviving retina, and therefore less variable. Only eyes within group 1 were used in this analysis in order to prevent confounding from changes in fixation altering the reading ability. Patients whose fovea fell outside or was at the edge of their surviving retina were not included in this analysis. The random pattern in Figure 5 indicates that neither the horizontal nor the vertical localisation of the remaining print impacted on the reading ability.

Reading Speed versus Acuity

The relationship between mean reading speed and maximum reading acuity was investigated using Spearman's rank correlation. Data were collected on 32 right and 30 left eyes

that were able to complete the reading task. A moderate negative correlation was detected using measurements taken from the right eye ($\rho = -0.59$, $p = 0.0002$), and a weak negative correlation was detected in the left eye measurements ($\rho = -0.25$, $p = 0.09$), suggesting that the right eye might have a more critical role in reading speed (Fig. 6). Table 2 shows the minimum and maximum reading speeds measured for each eye, measured along with the print size for this measurement. The near visual acuity is also shown. In some eyes, the minimum reading speed was obtained at a print size larger than the maximum sensitivity.

Discussion and Conclusion

In order for an eye to be able to read, two conditions must be met. Firstly, the retina viewing the text must have adequate health and resolution for the size of text displayed. Secondly, the full letter must be seen within the visual field available. Our study considered both reading speed and reading acuity as important determinants of real-world visual function in retinal degenerations. Our data showed a moderate-to-weak correlation between reading speed and acuity. The shape of this relationship varies in low vision, in keeping with previous work [5], and can provide a clue as to the visual field remaining as well as the real-world function of the patient. This also shows the importance of looking at both reading speed and reading acuity as important factors. Our results also suggest that the right eye may have more influence on the reading speed, but this may be related to eye dominance, which was not measured.

Traditionally, low vision rehabilitation has focused on strategies of magnification. However, when the visual field is severely restricted in retinal diseases, fewer larger letters could fit within the available functional retinal area, so that larger scanning eye movements are required, slowing down reading. Our results showed that the relationship between reading speed and letter size is variable; thus, magnification may not always represent the best strategy to aid in reading. The ability to read requires acuity reserves, explaining the drop-off in reading

speed for smaller letters [18]. Strategies for low vision rehabilitation should balance resolution and speed of the print being read.

In the English version of the Radner Reading Test, the mean reading speed achieved by a normal cohort was 201.53 ± 35.88 words/min [11]. Our choroideremia cohort rarely reached this level. When using high-contrast print, it has been reported that 160 words/min allows comfortable functional reading of print. To be able to read for a sustained period, 80 words/min is required, and 40 words/min for spot reading such as post or labels [18]. In the group of eyes with a fovea within the visibly preserved retina (group 1), the mean reading speeds were above the threshold for sustained reading and the maximum reading speed reached comfortable functional reading levels. The eyes with foveal splitting retinal degeneration (group 2) could maintain sustained reading but struggled to reach a comfortable reading speed without aids. If the fovea was outside the remaining retinal island (group 3), the eyes could only manage spot reading speed. This is indicative of the fact that while choroideremia patients may maintain high levels of distance acuity until the end stages of the disease, their quality of near vision is significantly reduced long before foveal involvement. This has important implications for optimising the reading abilities of these patients by using the an appropriate print size for maximum reading speed. Additionally, the visual span (ability to recognise multiple letters in the visual space) will be physically reduced in cases of visual field loss, explaining why the reading speed is reduced from early on [8, 9, 19]. The lack of a strong correlation between AF area and reading speed may indicate that the diameter of remaining vision at the fixation point may be the critical area rather than the full area available. In order to measure this accurately, fixation would need to be monitored and the complex shape of the remaining retinal islands taken into account.

Retinal gene therapy has been shown to help preserve or improve visual acuity in advanced choroideremia [15]. In addition, gene replacement may also improve the retinal sensitivity over the macula, thereby further benefiting reading speed. In order to preserve the

quality of life, the minimum area of functional retina to be preserved will vary depending on the tasks important to the patient [1]. If we make the assumption that spot reading is the minimum acceptable target for a therapeutic strategy, the minimum retinal island width to achieve this could be calculated. For instance, newspaper print is equivalent to around 0.4 logRAD [20]. In order for the width of a retinal island to contain a 0.4 letter, it needs to be at least 118 μm in width. In addition, maximum reading acuity can potentially be increased as the central microperimetry sensitivity increases, providing additional benefits following therapeutic intervention. In our study, the eyes unable to read had lost all sensitivity in the central fovea, showing the importance of preserving this area for therapeutic benefit. This is not the case in age-related macular degeneration and may reflect the more widespread nature of rod-cone dystrophies [21].

We also assessed whether the shape of the remaining functional retinal islands correlated with reading ability. Interestingly, the direction of the preserved retina in relation to the fovea, and therefore the direction of the adjacent letter visible, did not appear to have any impact on reading ability. Phase II and III trials for new therapies often have a multicentre design, spanning continents. The Radner Reading Test is available in a number of languages, some of which have text directions different to English. This work would suggest that the direction of the text should have no impact on the results, so measurements in different languages could be combined regardless of the direction of the text. This provides valuable information to guide near vision testing in future international multicentre clinical trials using reading ability as an outcome measure.

In conclusion, the Radner Reading Chart is a practical and useful test for the measurement of both reading speed and reading acuity in retinal disease. These factors present valuable outcome measures in therapeutic trials and should be analysed in combination rather than separately. While the relationship between text size and the functional retinal area contributes to reading speed, the centration of the retinal area in relation to the fovea does

appear to have an impact on the ability to read. Therefore, in order to be able to read, an eye must have enough retinal width close to the fovea to see at least 1 full letter of the print being read. The direction of the printed text does not impact the ability to read, allowing tests in different languages to be combined in a clinical trial setting.

Acknowledgement

The authors thank Dr Joanna Moschandreas from the Oxford Centre for Medical Statistics for statistical advice for this work.

Statement of Ethics

The subjects gave their written informed consent. The study protocol was approved by the NHS Research Ethics Committee (NCT02407678 and NCT01461213).

Disclosure Statement

R.E.M. is the scientific founder of Nightstar Therapeutics, receives grant funding from Nightstar Therapeutics and is a consultant to Nightstar Therapeutics and Spark Therapeutics. These companies did not have any input into the work presented. There are no other conflicts of interest.

Funding Sources

The research was supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC) and funded by the NIHR (Clinical Doctoral Research Fellowship CA-CDRF-2016-02-002 for J.K.J.). The views expressed are those of the authors

and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

The sponsor and funding organisation had no role in the design or conduct of this research.

Author Contributions

J.K.J. was involved in the design of the work, collecting data and analysis and wrote the paper; C.E.C.-S. was involved in data collection, data analysis and reviewing the manuscript; K.X. reviewed the manuscript; R.E.M. was involved in the design of the work, data analysis and reviewing the manuscript.

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Appendix after References (Editorial Comments)

Legend(s)

Fig. 1. Emsley's Model Eye used to calculate the projected retinal image size. $L' = D' \times (L/D)$. L' , retinal image size; L , maximum letter height; D , distance from the principle point to the nodal point = 5.55 mm + working distance of the test; D' , distance between the nodal point and the retina = 16.67 mm.

Fig. 2. Demonstration of the predicted reading image size projected onto the retina as calculated by the Emsley model. **a** Patient A was able to comfortably read logRAD print 1.0 as shown. **b, c** Patient B (**b**) was able to slowly read the logRAD 1.1 letters shown, whereas patient C (**c**) was unable to read the same size, as the full letter did not fit within the island.

Fig. 3. Alteration in reading speed with letter size in a representative patient with good central vision (**a**) and one with poor central vision (**b**). The reading speed appears to decrease at acuities smaller and larger than the optimal point, but the shape of the curve changes across the cohort.

Fig. 4. **a** Example of an eye unable to read from group 3, showing microperimetry seeing points far from the fovea. **b** Example of an eye unable to read from group 3, showing large preserved microperimetry islands but an insufficient width at the fovea. **c** Example of an eye able to read from group 3, showing a cluster of seeing points enclosing the central visual field. **d** Reading speed of all group 3 eyes. **e** Relationship between mean reading speed and autofluorescence (AF) area in group 1 eyes. **f** Relationship between maximum reading speed and mean central microperimetry sensitivity in group 1 eyes.

Fig. 5. Person plots demonstrating the relationship between reading speed and nasal-temporal (upper panel) and superior-inferior (bottom panel) location of the surviving retina in relation to the fovea. AF, autofluorescence.

Fig. 6. Correlation between reading speed and reading acuity for right (OD) and left (OS) eyes. NVA, near visual acuity.

Table(s)

Footnote(s)

Table 1. Patient characteristics for the full cohort as well as each fovea-defined group

	Full cohort	Fovea within visual island (fovea group 1)	Fovea at the edge of the visual island (fovea group 2)	Fovea outside the visual area (fovea group 3)
Eyes, <i>n</i>	65	47	5	13
Patient age, years	40 (19–68)	36 (19–55)	47 (42–53)	48 (31–68)
Mean reading speed, words/min	114.9±43.2	129.0±30.2	87.0±41.6	62.6±52.0
Maximum reading speed, words/min	153.2±57.8	169.4±42.4	130.7±50.1	88.1±77.1
Total AF foveal width, µm		3,113.9±1,559.2	NA	NA
Total AF foveal height, µm		3,417.2±1,907.4	NA	NA
Total AF area, mm ²	11.2±11.0	14.0±11.6	4.2±1.4	3.6±5.0
Reading area under the curve, words per minute/logRAD		107.0±55.1	NA	NA
Average microperimetry threshold, dB	7.2±6.8	9.2±6.6	0.8±1.1	1.8±3.0
Mean central microperimetry sensitivity, dB	17.2±9.8	21.3±7.12	2.2±3.8	6.4±6.0
Distance VA, logMAR	0.2 (1.0 to –0.1)	0.1 (0.9 to –0.1)	0.3 (0.8–0.1)	0.5 (1.0–0.1)
Near VA, logRAD	0.16 (1.1 to –0.11)	0.10 (1.1 to –0.11)	0.18 (0.4–0.01)	0.42 (1.1–0.1)

Unless specified otherwise, the data are presented as the mean ± SD, as all reading and imaging parameters followed a normal distribution. VA and age data are presented as the median and interquartile range. AF, fundus autofluorescence; NA, not applicable; VA, visual acuity.

Table 2. Results for each participant

Eye Nr.	Near visual acuity, logRAD	Maximum reading speed, words/min	Print size for this measurement	Minimum reading speed, words/min	Print size for this measurement
1	0.200	148.673	0.900	60.650	0.200
2	0.100	182.609	0.500	69.421	0.100
3	0.020	145.581	0.200	26.038	0.000
4	-0.030	140.234	0.800	32.420	0.100
5	0.115	220.472	0.600	31.461	-0.100
6	-0.075	180.645	0.800	31.461	-0.100
7	0.100	177.590	0.400	85.977	0.100
8	0.000	169.697	0.700	64.073	0.000
9	-0.085	152.450	0.600	9.251	0.000
10	0.110	209.476	0.900	62.454	0.100
11	0.100	180.258	0.200	57.338	0.100
12	0.100	169.697	1.100	23.204	0.100
13	0.210	166.667	0.800	80.614	0.300
14	0.060	177.966	0.400	33.967	0.100
15	0.100	181.818	0.900	91.304	0.200
16	0.000	205.379	0.800	28.103	0.000
17	0.110	145.833	0.800	31.111	0.100
18	0.130	166.667	0.800	38.621	0.100
19	0.110	251.497	0.500	27.741	0.000
20	-0.110	192.220	1.100	43.344	-0.200
21	0.100	129.231	0.700	54.545	0.100
22	0.315	168.675	0.900	91.803	0.400
23	0.200	150.000	0.900	47.673	0.200
24	0.215	135.484	0.700	22.642	0.200
25	0.000	170.040	0.400	103.576	0.900
26	0.400	67.851	0.700	22.783	1.100
27	0.205	145.329	0.800	37.053	0.200
28	0.305	57.931	0.800	6.925	0.300
29	0.600	54.194	0.600	40.191	1.100
30	unable to read				
31	0.300	40.580	1.000	13.440	0.400
32	0.410	33.202	0.600	9.459	0.400
33	1.100	11.748	1.200	5.512	1.100
34	0.000	176.842	0.900	48.138	0.000
35	0.100	172.840	0.600	70.529	0.100
36	0.140	98.824	0.500	40.462	0.100
37	-0.090	132.911	0.400	35.578	-0.100
38	0.010	187.500	0.500	61.584	0.000
39	-0.095	200.477	0.200	73.814	-0.100
40	0.050	190.909	0.500	36.522	0.000
41	-0.080	138.386	0.400	64.615	-0.100
42	0.015	150.268	0.200	72.351	0.000
43	0.100	213.198	0.200	123.348	0.100
44	0.035	138.614	1.000	19.503	0.000
45	0.280	121.916	0.900	29.546	0.200
46	0.100	152.450	1.000	89.172	0.100
47	0.080	174.274	0.900	35.413	0.000
48	0.105	160.305	0.800	47.511	0.100
49	0.030	163.107	0.900	22.234	0.000
50	0.080	138.614	1.100	14.508	0.000
51	0.170	181.818	1.100	28.966	0.100
52	0.210	216.495	0.600	34.105	0.100
53	-0.095	197.183	0.500	45.405	-0.200
54	0.225	133.333	0.700	39.810	0.200
55	0.200	138.614	0.400	94.595	0.200
56	0.010	94.382	1.000	21.429	0.000
57	0.000	218.750	0.400	128.440	0.100
58	0.200	150.538	1.000	33.667	0.300
59	unable to read				
60	0.300	262.500	0.600	97.674	0.300

61	unable to read				
62	0.405	280.000	1.000	103.704	0.600
63	0.100	178.723	0.400	100.000	0.100
64	0.620	51.852	0.800	12.000	0.600
65	1.100	16.406	1.300	7.113	1.100

The near visual acuity, the maximum reading speed and the print size this was achieved at, as well as the minimum reading speed at the corresponding print size are shown to demonstrate the variability in results.

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