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Validation of computerized Landolt C visual acuity measurement on ColorDx

THESIS

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for the degree of

MASTER OF SCIENCE

in Biomedical and Translational Science

by

Ang Wei

Dissertation Committee:
Professor Sheldon Greenfield, Chair
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Professor Sherrie Kaplan

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ABSTRACT OF THE THESIS

Validation of computerized Landolt C visual acuity measurement on ColorDx

by

Ang Wei

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Assistant Professor Andrew Browne, Committee Member & Mentor

Objective: Visual acuity (VA), the most common and simple measurement of visual function, is used worldwide in clinical practice and clinical research to quantify vision. However, rather than the full-letter width spacing standard on traditional visual acuity charts that might induce crowding, increased test-retest variability and bias, the visual acuity test on ColorDx is a single letter scoring, logMAR scaled and fast performed visual acuity measurement. The study aim is to study the reliability and validity of the visual acuity test on ColorDx on both healthy subjects and those with eye diseases.

Methods: This is a prospective comparative clinical study. A total of 54 participants subjects were enrolled with their right eyes. All subjects underwent test and retest visual acuity measurements at 4 meters using ColorDx and Early Treatment Diabetic Retinopathy Study (ETDRS) charts. All results were scored with logMAR units. Paired sample t-test, Pearson's correlation and independent sample t-test were performed.

Results: The mean difference between the two visits of ColorDx was 0.03 ± 0.05 and that for ETDRS chart was 0.01 ± 0.03. None of the differences between the two visits were

statistically significant (P>0.05). In Pearson correlation, r was 0.794 with a p-value less than 0.001. The mean differences between healthy and unhealthy groups were 0.23 for both tests. P-values were 0.03 and 0.01 of ETDRS chart and ColorDx, respectively.

Conclusion: The visual acuity test on ColorDx is a simple, reliable and standardized procedure for visual acuity measurement. The pilot data in our study provides preliminary evidence that it can be used as a valid alternative to ETDRS chart worldwide without the Latin alphabet barrier. The simple operation could be suitable for fast-paced clinical settings. More disease groups and larger sample size need to be evaluated in future studies.

INTRODUCTION

Visual acuity (VA), the most common and simple measurement of visual function, is used worldwide in clinical practice and clinical research to quantify vision. It reflects the angular size of the smallest recognizable detail, which determined by the health and functioning of the retina and the sensitivity of the interpretative faculty of the brain.[1]

Visual acuity is always used to screen, diagnose and monitor ocular diseases, predict the vision-related quality of life, and as the primary indicator of functional impairment due to vision loss. Visual acuity is also considered as eligibility criteria for some occupations (e.g., airline pilot) and activities (e.g., driving) by some licensing authorities and employers. [2]

Visual acuity is measured in minutes of arc to detect the minimum angle of resolution (MAR).[3] In other words, the measurement is testing the size threshold for visual recognition at a standard distance. The optotypes are usually used as the details the subjects need to identify during the visual acuity measurements. The commonly used optotypes are letters, Landolt rings, "tumbling E's, numbers and symbols. [3-6] Visual acuity is typically measured under conditions of high contrast using printed or projected charts with optotypes.[7] Snellen charts are the most widely used in clinical practice and laboratories for adults. The charts may vary in letters, and the optotypes are sometimes replaced with Landolt C, Tumbling E, or numbers, but they all considered Snellen charts. There is no standardized Snellen chart.[2] The charts using Allen optotypes, Wright figures, or the LEA symbols in the pediatric clinic are also designed and measured in similar methods. The Early Treatment Diabetic Retinopathy Study (ETDRS) chart is the "gold

standard" visual acuity test for most current clinical trials.[3] Unlike Snellen charts, using fraction or decimal to express visual acuity, ETDRS chart is scored in logMAR (logarithm of the minimal angle of resolution) units. [3, 8, 9].

However, the currently used charts have many disadvantages. First, technicians need special training.[3] Second, visual acuity results can have human error introduced by technicians while administering procedure and computing results. Third, subjects have the risk of memorizing the letters on the charts.[10] Additionally, the most commonly used letter-optotypes Snellen charts and ETDRS charts have limited international utility because letters on the charts are Latin alphabet. Furthermore, charts like Snellen can cause crowding phenomenon and diminish acuity.[3] An important, but subtle, issue with visual acuity testing is that it tests the central visual field. However, people with reduced peripheral fields may not have facility in tracking and locating letters on a line when the letters are outside of their functional visual field. This phenomenon can reduce test reliability.[6] Lastly, senior and disables with bad visions encounter more difficulties on the conventional visual acuity tests when they are asked to move forward during the measurements.

Computer-based visual acuity measurements overcome the weaknesses of human administered vision tests mentioned above. The computerized test protocols are potentially more simple, efficient, and objectively standardized.[6, 10-13] The high contrast acuity test on ColorDx (Konan Medical, Irvine, CA) is a computerized Landolt C visual acuity test, calculated with logMAR scores. This visual acuity test system uses a standardized protocol and avoids ambiguous communication by examinees. The computerized visual

acuity test presents one ring in a random direction at each time to prevent crowding phenomenon, which happens in the regular charts and decreases acuity, making the results more reliable.[3, 14] The system changes the optotype size based on the subjects' response using the Psi-marginal adaptive technique, which is a modified Bayesian statistical method for threshold determination and standard error estimation.[15] For example, a correct response will result in the optotype becoming smaller or stay in the same size, and an incorrect response may result in the optotype becoming larger. The modified algorithm improves the threshold tests more precisely. Unlike other automated tests using 8-direction Landolt C, the ColorDx only includes 4 directions and making the manipulation easier. The final logMAR threshold is computed automatically after the test is done.

In this study, we evaluated the computerized visual acuity test on ColorDx using Landolt C as optotypes and compared it with the gold standard ETDRS chart. The study aim is to study the reliability and validity of the visual acuity test on ColorDx. We hypothesize that the visual acuity test on ColorDx is reliable and valid to detect subjects' visual acuity.

CHAPTER 1. BACKGROUND

1.1 Visual acuity

The conventional visual acuity test has been widely accepted to measure and screen visual function. Changes in visual acuity often indicate the presence or changes in medical condition. Diseases like the media opacities and those affecting the central region of the retina or the optic nerve pathways are the common reasons to cause visual acuity reduction. [2]

As shown in figure 1, a subject transmits through the visual medium and posts on the retina. The details of the subject that the retina can distinguish is defined as resolution. Alpha in the figure is the angle of this resolution. In clinic or laboratories, the minimum angular size that retina can resolve is measured to express visual acuity. There are different ways of measuring MAR, such as optotypes, Teller acuity cards, and Vernier acuity cards.

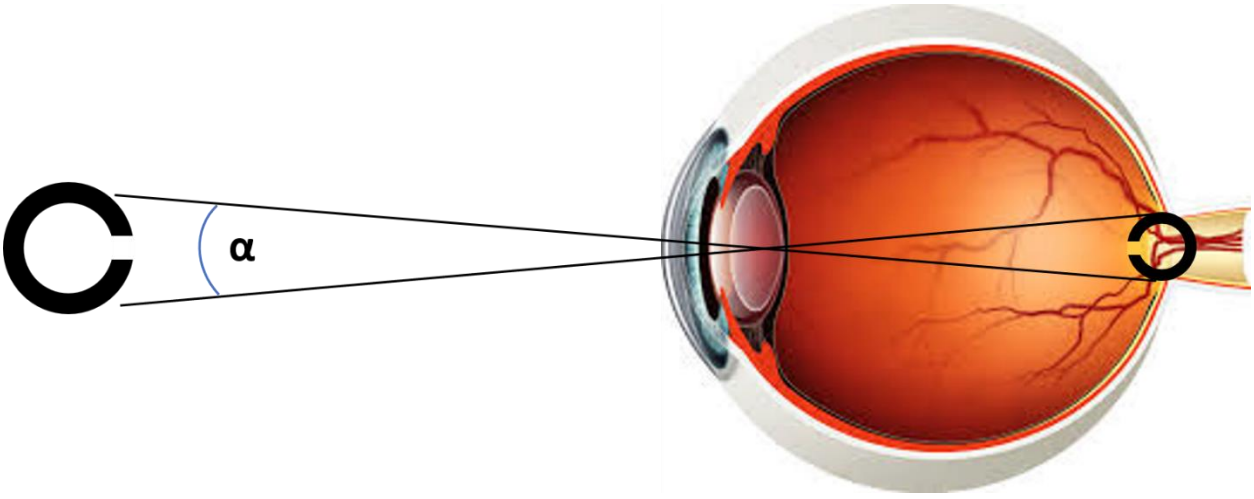


Figure 1. Angle of resolution.

1.2 Types of visual acuity tests

The optotype is one of the standardized subjects in visual acuity tests. It can be letter, number, or symbol. The smallest optotype reliably recognized at a standardized distance is recorded as visual acuity.

Letter optotype is the most commonly used, often defined as the primary outcome measures in clinical trials and well-accepted by the US Food and Drug Administration (FDA) for a registration trial.[3] Their diverse shapes make these optotypes identified quickly. One of the most widely used versions is Snellen optotypes (Fig.2), designed by Dutch ophthalmologist Herman Snellen in 1862.[16] They were designed on a 5 x 5 grid, although the letters vary by the chart versions, mostly containing nine serif Latin letters, which are C, D, E, F, L, O, P, T, and Z. The height and width of an optotype is five times the thickness of the line weight.[3, 16]

Another significant letter optotype is Sloan letter, which was developed by Louise Sloan in 1952 and now generally used in ETDRS charts (Fig. 2). This optotype includes ten uppercase sans serif Latin letters, C, D, H, K, N, O, R, S, V, and Z.[17] The letters are also formed within a square, with a stroke width equals to one-fifth of the letter height. Each visual weight is same.[3, 17] The ten Sloan Letters are considered to be the most effective letter selection for equal legibility.[3]

Developed by Edmund Landolt, the Landolt C is an optotype consisting of a ring with a gap resembling a letter “C” (Fig. 2). The optotypes are usually oriented in four or eight directions. Subjects respond to optotypes presented by indicating the orientations. The simple optotype and testing protocol make the test accessible to subjects unfamiliar with

the alphabet. However, there are discussions on the application of this optotype. The National Academy of Sciences-National Research Council Committee (NAS-NRC) accepted the Landolt rings as standards. But due to the similar optotypes, hard to track on a row and the confusion about about "left" and "right" in communicating optotype orientations with technicians, it is not recommended to use on a visual acuity chart. [10, 18] Nevertheless, according to DIN 58220, part 3, it is still more recommended by European scientists rather than other optotypes. [19, 20]

Tumbling E's is another optotype used for subjects who are unable to properly communicate or read the Latin alphabet (Fig. 2). Similar to Landolt C, the letter E is oriented in four directions, which are up, down, left, and right. It is used in Asian countries and less widely used than Landolt C in western countries.

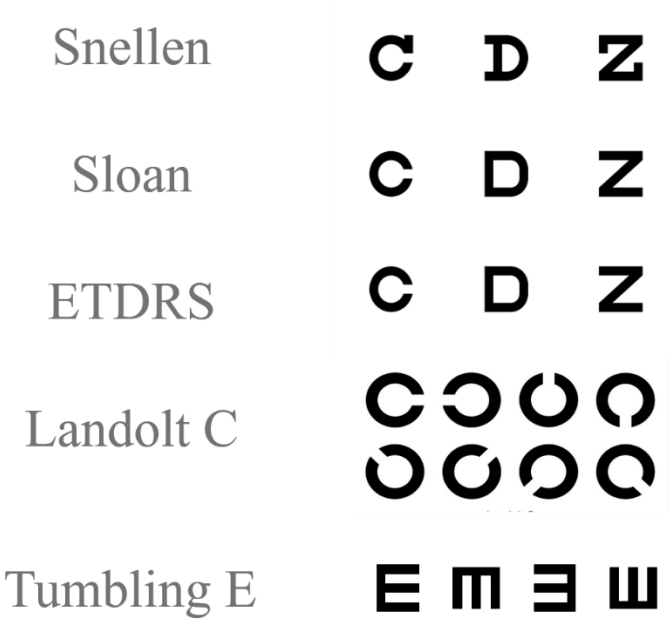


Figure 2. Letter optotypes

Symbol optotypes are often seen in the pediatric visual acuity tests. Allen optotypes, Wright figures, and the LEA symbols (Fig. 3) are the most common optotypes used in pediatric ophthalmology clinics for toddlers and preschool children. The optotypes are familiar shapes and figures that children can easily recognize.[21-24]

Figure 3. Allen optotypes (left), Wright figures (middle) and the LEA symbols (right).

Teller acuity cards were developed to assess the grating acuity of infants and toddlers. The rectangular grating cards consist of one or two 12 x 12 cm in size, square blocks of black-and-white stripes pattern on a gray background (Fig. 4). The widths of the strings on the patterns are different.[25] During the test, a trained tester pays attention to the patient's eye and head movement towards the gratings on each card, and decide the acuity based on the smallest grating the patient can correctly respond.[26] The narrower stripes optotypes indicate better vision. This procedure was studied to be reliable. [25-31]

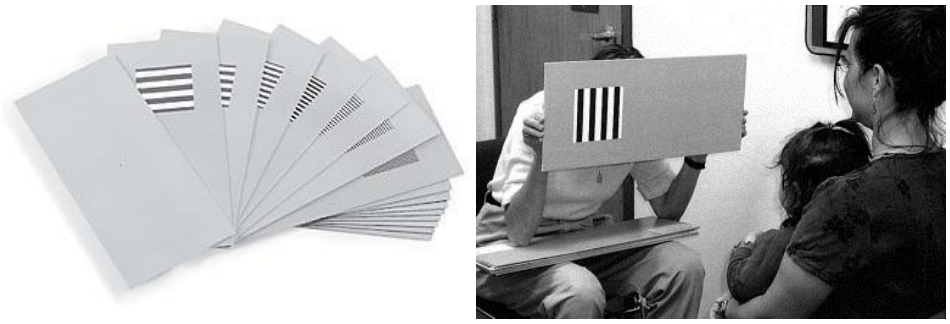


Figure 4. Teller acuity cards. [32]

Vernier acuity cards are to assess Vernier acuity, as known as hyperacuity. The limit of Vernier acuity is about 8 arc seconds or 0.13 arc minutes.[33] Vernier acuity is considered as a process of the visual cortex rather than the retina.[34] It's also suggested to be more sensitive to detect amblyopia of infants and toddlers, especially to the cases of amblyopia with small tropias or no misalignment and large-angle strabismus.[33, 34] The subjects are asked to determine the offset between two parallel line segments binocularly or monocularly.[35]

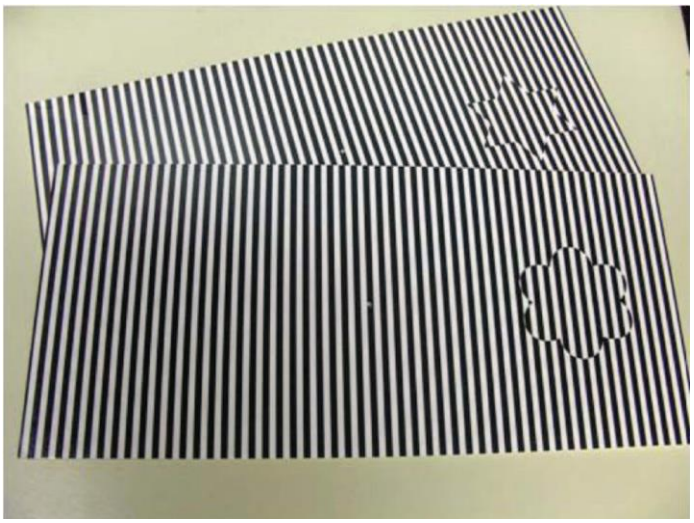


Figure 5. Vernier acuity cards from "Vernier Acuity Cards: Examination of Development and Screening Validity."[34]

1.3 Methods of testing

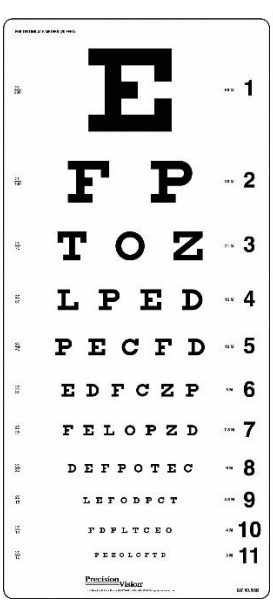
The visual acuity tests are primarily performed using hard-copy or projected charts. These charts consist of a few lines of optotypes which typically start with large size in the top row and progressively become smaller to the bottom row. The number and arrangement of optotypes in each row vary by the type of charts. In the visual acuity test, the examinee will be asked to stay at a standard distance away from the chart and identify the optotypes from the largest in size to the smallest reliably recognized with one eye covered at each time.

Designed by Herman Snellen, Snellen chart (Fig. 6), the first letter optotype chart, is the current standard visual acuity measurement for adults in US clinical practice.[16] The present Snellen charts mostly include eleven lines of Snellen letters. The number of letters progressively increases from top to the bottom. The examinee stays 20 feet (or 6 meters) away from the charts and gets fraction scores for lowest recognized lines. The fraction

consists of a numerator equals to the distance between the chart and the examinee (e.g., 20 in the United States and 6 in the United Kingdom) and a denominator stands for the identified smallest letter size line. The reciprocal of the fraction equal to the minimum angle of resolution (MAR). In some Asian and European counties, visual acuity is expressed as decimal, which is equivalent to the fraction value or the reciprocal of the visual angle in minutes.[2, 3, 7] For instance, the normal vision for 20/20 in the United States, 6/6 in the United Kingdom or 1.0 in some Asian and European counties indicates 5 minutes of arc vertically and horizontally, and 1 minute between each stroke. However, there are limitations to this method. Kaiser et al.[3] have mentioned a few disadvantages. For example, as each line becomes smaller and the number of letters becomes greater, the difference of scores between each line is different, which means the visual angle or even the level of dysfunction is not comparable. What is more, since the letter size progresses irregularly, it could overestimate the visual acuity at the lower end when the subject changes the distance to the chart. Furthermore, some Snellen letters are easier to read than others, such as C, D, and G compared to A, J, and L.

Based on Bailey and Lovie's chart [36], the ETDRS chart was developed by Ferris et al.[8] which is the "gold standard" for most current clinical trials (Fig. 6). Without the shortcomings of Snellen charts as mentioned above, all letters have almost equal legibility. The most commonly used optotype is Sloan letter. Other optotypes can be numbers and Landolt C. In the ETDRS charts, there are 14 rows and 5 letters in each row. Between each letter, the space is consistent and proportional to the size of letters. ETDRS chart is scored in logMAR units. In logMAR notation, 0 logMAR indicates standard vision, which is 20/20 (6/6 or 1.0) in Snellen charts. Positive logMAR values indicate reduced vision and negative

values indicate vision better than 20/20. Unlike Snellen charts using line assignment method, the score in ETDRS chart is calculated by the number of letters that the subject can read. Each letter has a score value of 0.02. Therefore, the total score for a line represents 0.1 log units. According to the criteria suggested by the World Health Organization (WHO), low vision is defined as a best-corrected visual acuity worse than 0.5 logMAR (20/63 in Snellen charts) but equal or better than 1.3 logMAR (20/400 in Snellen charts).[37] Blindness is defined as a best-corrected visual acuity worse than 1.3 logMAR. The ETDRS chart has better reliability and test-retest variability than Snellen charts, especially in low vision. [3, 8, 9] In addition, the logMAR scoring system can be used internationally.



Snellen Fraction	ETDRS Equivalent Snellen Fraction	logMAR*	ETDRS Letter Score	Approximate ETDRS Letter Score†
1/200 (CF)		2.30		0
2/200		2.00		2
	20/800	1.60	5	5
6/200		1.52		9
	20/640	1.51	10	10
	20/500	1.40	15	15
20/400	20/400	1.30	20	20
	20/320	1.20	25	25
20/300		1.18		26
	20/252	1.10	30	30
20/250		1.10		30
20/200	20/200	1.00	35	35
	20/160	0.90	40	40
	20/125	0.80	45	45
20/100	20/100	0.70	50	50
20/80	20/80	0.60	55	55
20/70		0.54		58
	20/63	0.50	60	60
20/60		0.48		61
20/50	20/50	0.40	65	65
20/40	20/40	0.30	70	70
	20/32	0.20	75	75
20/30		0.18		76
	20/25	0.10	80	80
20/20	20/20	0.00	85	85
	20/16	−0.10	90	90
20/15		−0.12		91
	20/13	−0.19	95	95
	20/10	−0.30	100	100

*Snellen converted to logMAR = −1 × log(Snellen fraction).
†Snellen converted to approximate ETDRS letters = 85 + 50 × log(Snellen fraction), which may be rounded to the nearest letter.
CF, counting fingers.

Figure 6. Snellen chart(left), Early Treatment Diabetic Retinopathy Study (ETDRS) chart from Precision Vision (middle) and Conversion of Visual Acuity Measurements Between Snellen Fraction, logMAR, and ETDRS chart Letter score (right,[38]).

The pediatric charts are designed and measured similar to Snellen chart.

An ideal visual acuity test should present accurate and reliable results in order to identify the changes only caused by disease. However, as mentioned in the introduction section, there are many weaknesses for the printed or projected charts. For instance, technicians require specialised training. The test protocols are usually complex. This is especially true for the ETDRS charts, which requires not only test performance, but also the calculation of visual acuity scores by the subjects' responses. What is more, all these processes can cause human error introduced by technicians administering and recording results.[3] Second, subjects have the chance of memorizing the letters on the charts.[10] Since the charts are widely used in clinic settings, they are commonly seen and easily remembered. Even though the ETDRS chart sets have one chart for refraction and two charts for the visual acuity test, subjects are still able to memorize due to the standardized letter arrangements and the small number of optotypes on the charts. Further, the Latin alphabet optotypes on the commonly used Snellen charts and ETDRS charts have limited the international application. This characteristic also reduces its utility among illiterate subjects period. What is more, different test charts and protocols can result in measurement error and make the test values less comparable.[3] For instance, even if there is a conversion table available for Snellen fraction and logMAR units, the line assignment protocol is less accurate than the letter assignment protocol. Besides, as Kaiser et al. [3] mentioned, charts like Snellen were designed with an unstandardized distance between letters and rows. This can lead to crowding phenomenon and result in inaccurate visual

acuity. The interactions vary by lines that good acuity lines have worse crowding and poor vision lines have less crowding. In addition, visual acuity testing is focusing on the central visual field. Whereas, people with reduced peripheral fields may not have facility in tracking and locating letters on a line of the printed charts when they are outside of their functional visual field. This phenomenon can reduce test reliability.[6] Lastly, the charts are not friendly to bad vision subjects. The FDA requires that the Snellen charts visual acuity tests should start at 6 meters (20 feet) while ETDRS charts start at 4 meters (13 feet).[3] The subjects will need to move forward if insufficient letters are perceived. Walking in the low illuminance environment is hard for bad vision subjects. This is even difficult for the seniors and disables.

As technology develops, more and more automated charts became available based on the existing printed or projected charts and installed in computers or smart devices. They make the tests easier, faster, and more accurate by reducing biases, fitting better to the rapid clinical practice. (Table. 1)

Table 1. Automated visual acuity tests have been studied

Articles	Year	Author	Optotype strategy	Comparison/Control
An automated visual acuity testing computer program using the Apple II system	1995	Friendly DS, Weiss IP.	Tumbling E	Ferris-type letter chart

Visual acuity measured via the Freiburg visual acuity test (FVT), Bailey Lovie chart and Landolt Ring chart	2002	Wesemann W	Landolt C (Freiburg visual acuity test)	Bailey-Lovie chart Landolt C chart
A Computerized method of visual acuity testing: Adaptation of the Early Treatment of Diabetic Retinopathy Study Testing Protocol	2002	Roy W. Beck, Pamela S. Moke, Andrew H. Turpin, Frederick L. Ferris Iii, John Paul Sangiovanni, Chris A. Johnson, Eileen E. Birch, Danielle L. Chandler, Terry A. Cox, R. Clifford Blair, And Raymond T. Kraker	Sloan letter	ETDRS chart
Visual acuity testing in diabetic subjects: the decimal progression chart versus the Freiburg visual acuity test	2003	Lars Loumann Knudsen	Landolt C (Freiburg visual acuity test)	Decimal progression chart
Repeatability of an automated Landolt C test, compared with the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart testing	2003	Paisan Ruamviboonsuk, Montip Tiensuwan, Catleya Kunawut, Patcharapim Masayaanon	Landolt C	ETDRS chart

Validation of a computerized logMAR visual acuity measurement system (COMPlog): comparison with ETDRS and the electronic ETDRS testing algorithm in adults and amblyopic children	2007	D A H Laidlaw, V Tailor, N Shah, S Atamian, C Harcourt	Sloan letter (COMPlog)	ETDRS chart
Computer-based test to measure optimal visual acuity in age-related macular degeneration	2007	Esther G. Gonza´lez, Luminita Tarita-Nistor, Samuel N. Markowitz, Martin J. Steinbach	Tumbling E	ETDRS chart
Automated determination of distance visual acuity: towards teleophthalmology services	2008	Sajeesh Kumar Max Bulsara Kanagasingam Yogesan	Tumbling E (computer based visual function testing)	ETDRS chart
An assessment of the iPad as a testing platform for distance visual acuity in adults	2013	J M Black, R J Jacobs, G Phillips, L Chen, E Tan, A Tran, B Thompson	Sloan letter	ETDRS chart Externally illuminated Bailey Lovie Letter Chart Externally illuminated HOTV letter chart
Visual acuity measured with a smartphone app is more accurate than Snellen testing by emergency department providers	2016	Akhilesh S. Pathipati, Edward H. Wood, Carson K. Lam, Christopher S. Sáles, Darius M. Moshfeghi	Snellen letters	Rosenbaum near chart (near vision) Snellen chart

Development and testing of an automated computer tablet-based method for self-testing of high and low contrast near visual acuity in ophthalmic patients	2016	Tariq M. Aslam, Neil R. A. Parry, Ian J. Murray, Mahani Salleh, Caterina Dal Col, Naznin Mirza, Gabriela Czanner, Humza J. Tahir	5 × 5 open square (Restructured Landolt C)	Near Landolt C chart 25 % contrast near EDTRS chart
Comparison of two visual acuity tests in school enrolment examinations: Tumbling E test versus Freiburg visual acuity test	2016	Bach M, Reuter M, Lagrèze WA.	Landolt C (Freiburg visual acuity test)	Tumbling E chart
Validation of an automated-ETDRS near and intermediate visual acuity measurement	2019	Yi Pang Lauren Sparschu Elyse Nylin	Sloan letter	ETDRS chart
Validation of electronic visual acuity (EVA) measurement against standardized ETDRS charts in patients with visual field loss from inherited retinal degenerations	2019	Jasleen K Jolly , Kristin Juenemann, Heather Boagey, Marie Nadsady, Holly Bridge, Robert E Maclaren	Sloan letter (single letter, single line)	ETDRS chart

The majority of automated visual acuity measurements include Sloan letter, Snellen letter, Tumbling E, and Landolt C as optotypes. The most commonly used optotypes are Sloan letters and Landolt C. ETDRS chart was transferred into a few electronic versions and tested to be reliable and valid.[6, 12, 13, 39-41] However, the limitations of Sloan letter optotypes still exists. The Freiburg Visual Acuity test is one of the automatic Landolt C vision measurements developed by Michael Bach.[42, 43] Subjects stay 5 meters away from

the monitor and take the test by selecting the gap direction of Landolt C. Lancolt C is oriented in eight directions. This measurement used best Parameter Estimation by Sequential Testing (best PEST) to estimate the acuity threshold. It is more widely applied in European countries. The reliability and validity among different groups of people were studied during the past decades.[44-47]

The automated tests are useful in situations where accuracy is critical or similar issues need to be addressed regularly.[11] The psychometric algorithms applied in the automated visual acuity test programs improve the visual acuity threshold precisely. The psychological function used in the algorithm has four parameters, which are threshold, slope, lapse rate, and guessing rate.[15] In the psi-method, which is also known as Bayesian adaptive method, the nuisance parameters such as the lapse rate and guessing rate are fixed. Therefore, this method only targets the threshold or/and slope, and this could generate bias in parameter estimates. [48] Psi-marginal adaptive psychological method is an optimized algorithm based on psi-method.[15] This modified psi-method adaptively targets nuisance parameters and maximizes the expected information from interested parameters to gain a smaller bias and a more precise threshold. Even though the value of slope chosen has little influence on the acuity outcome, which supporting the constant slope used in the best-PEST algorithm[44], this new method allows specifying the four parameters of the psychometric function alone making the measurement much more flexible.[15]

Therefore, the ColorDx (Konan Medical, Irvine, CA, Fig. 7) using psi-marginal takes the nuisance parameters into measurement so that the threshold of the user's visual acuity

could be estimated more precisely with smaller bias than the hard version charts and even other algorithms used in the automated charts. The high contrast acuity test on ColorDX is a computerized Landolt C visual acuity test, scoring in logMAR. These characteristics contribute to its full application. Subjects are tested 4 meters away from the monitor and presented Landolt C in different sizes and one of four orientations based on the psi-marginal threshold estimation.

Figure 7. ColorDx from Konan Medical

Our study will evaluate the reliability and validity of the computerized visual acuity test on ColorDx using Landolt C as optotypes by comparing them with the ETDRS chart.

CHAPTER 2. METHODS

Ethical approval for this study was Institutional Review Board approval from the University of California Irvine and it was conducted in accordance with the Declaration of Helsinki. All participants were required to give informed consent. This was a prospective study. Fifty-four volunteers were recruited from UC Irvine's Gavin Herbert Eye Institute (GHEI), Long Beach V.A. medical center, and students and faculties of UCI.

Our inclusion criteria were: 1) Age between 18-85 years old; 2) Be able to understand English instructions and know alphabet;3) Visual acuity better than counting fingers on the right eye; 4) Without central visual field loss on the right eye.

Each subject underwent the following tests: ETDRS chart, visual acuity test on ColorDx, Optical Coherence Tomography Angiography (OCTA), and fundus imaging. There was two minutes break between each test to control fatigue. Only the right eyes were recruited in this study. OCTA and fundus images were read by two trained fellow ophthalmologists to evaluate comorbidities. When disagreement happened, a third senior ophthalmologist from GHEI helped adjudicate. Demographic data, including the presence of systemic disease, smoking status, age, gender, race, family history of eye diseases and medical histories were collected before the tests. No dilation was performed during the tests. All measurements were conducted by the two trained researchers.

2.1 Visual acuity testing

The visual acuity tests were performed in the dimly lit room. Each visual acuity test was performed twice with one hour to seven days interval by the same examiner in the same room conditions. Since visual acuity is not affected by gender or corrected refractive error in a clinically significant way according to previous studies, all subjects came with their habitual refractive correction and used the same correction for the two visits.[49, 50] They were seated at 4 meters (13 feet) from the charts placed at eye level with left eye patched. Subjects were tested at their own pace and required to guess the answer when they were unsure of the identity until they met the termination criteria for each test (forced-choice).[51] The ETDRS chart test was performed first and followed by the visual acuity test in ColorDx with a 2 minutes break in between. The results were documented in logMAR.

2.1.1 ETDRS charts

The charts were displayed in the standard light box with a luminance of 85 cd/m^2, which is in compliance with recommendations for the standardization of visual acuity measurement.[36] Charts 1 and 2 were placed without a sequence in the two administration (Fig. 8). Subjects started to read the letter from the top row of the charts until they read three letters or less correctly at 4 meters. If the subjects were only able to read less than 20 letters at 4 meters, they were asked to moved to 1 meter away from the chart (the chart is not mobile). The examiner identified the responded letters on a scoring sheet. Patients had to identify each letter and couldn't correct previous letters. They were encouraged to guess if they were not sure which optotypes were seen. The final scores

were calculated using the formula: logMAR acuity = x + 0.02y, where x is the logMAR value of the last line that the subject meets the terminal criteria ringing from -0.3 on the bottom to 1.0 on the top, and y is the number of letters read incorrectly during the test. Each letter was scored 0.02 logMAR units at 4 meters or 0.08 logMAR units at 1 meter, while the full line was scored 0.1 logMAR at 4 meters or 0.4 logMAR at 1meter.

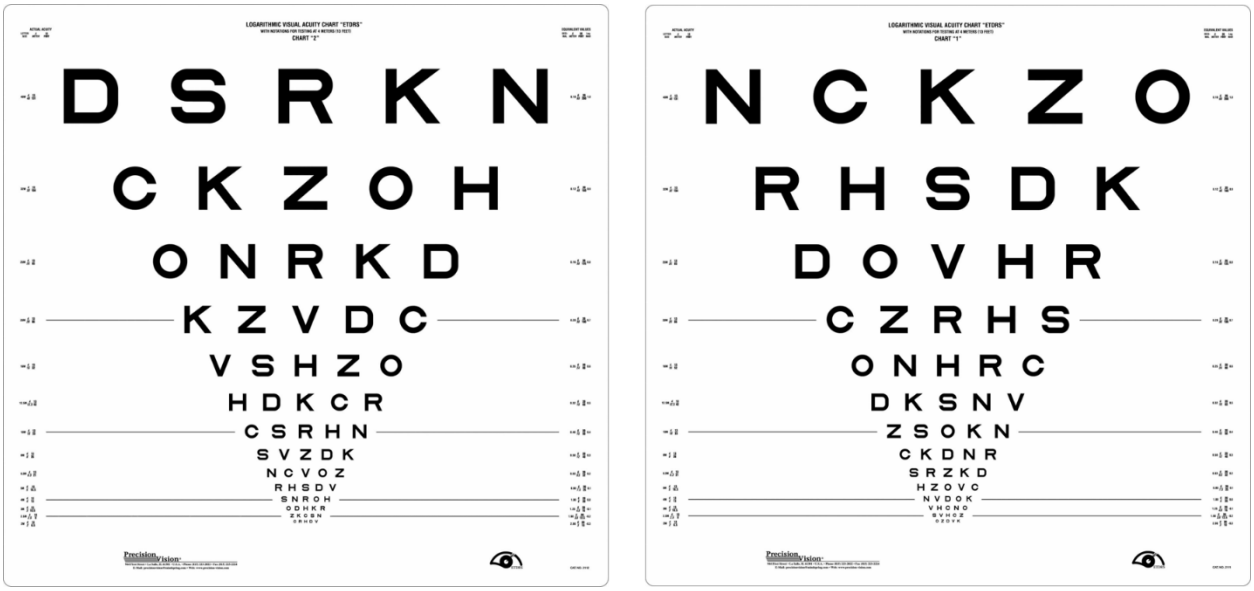


Figure 8. ETDRS chart 1 (left) and chart 2 (right) from Precision Vision.

2.1.2. ColorDx

The visual acuity tests were performed using ColorDx, which was daily calibrated. The software was set in the "4 meters" mode. The Landolt C was displayed in the center of the monitor with an 85cd/m^2 luminance background. The subjects were asked to indicate which direction the opening of the "C" was. Because the keyboard has a wire shorter than 4 meters, the examiner pressed the corresponding direction button on the keyboard for the subjects. The subjects could choose to either orally answer or point the direction by hand if they were not confident enough to speak the answers orally. This is to prevent the error

when subjects mixed “left” and “right”. The test began with a specific size of “C”. The C disappeared after 5 seconds, and since the test was “forced choice”, the next Landolt C didn’t display until a selection was made, the subjects were encouraged to make their best guess. A high tone indicates “correct” and a low tone indicates “wrong”. As the subjects answered correctly or wrong, the next optotype size decreased, increased, or stayed the same respectively. The test calculated the limit of what they perceived. The test ended after several wrong answers and the results displayed.

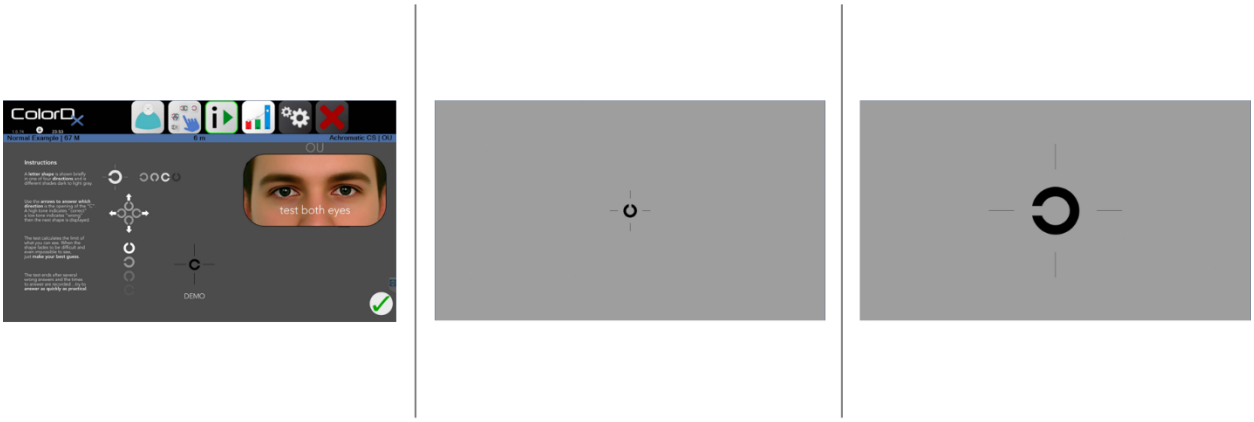


Figure 9. Visual acuity test on ColorDx (High-contrast acuity test). Test instructions and demo (left), and test screens (middle and right).

2.2 Statistical analysis

Data summaries were based on the mean and standard deviation (SD) for continuous variables, and frequency and percent for categorical variables. The paired sample t-test was performed to assess the test-retest reliability of the visual acuity test on ColorDx. Pearson’s correlation was used to test the criterion validity of ColorDx. Independent sample t-test was run to test the discriminant validity of both tests.

A total of 54 patients (31 minimum) was estimated to be statistically significant to detect a 0.13 difference by logMAR in the visual acuity test on ColorDx results and ETDRS chart results with 80% power (α=0.05) and a standard deviation of 0.18. An effect size of 0.13 was chosen because the previous study suggests that there was a difference between the two types of visual acuity charts.[3] However, in order to make the comparation between the new measurement and gold standard measurement meaningful, a 1/3 SD was used intead of SD in the power analysis, and the sample size came out with 145.

All statistical analyses were performed using IBM SPSS Statistics 25. A P-value of less than 0.05 was considered statistically significant.

CHAPTER 3. RESULTS

In this study, we recruited 54 subjects (27 males and 27 females; 54 eyes; 56.2 years old on average with a standard deviation of 21.2) who met the inclusion criteria. (Table 2) Eye conditions include age-related macular degeneration (13 eyes [24.1%]), age-related cataract (2 eyes [3.7%]), non-proliferative diabetic retinopathy (1 eye [1.9%]), and retinitis pigmentosa (1 eye [1.8%]), as well as 37 healthy eyes (68.5%).

Table 2. Demographic Characteristics of Participants

	All subjects (n=54)	**Healthy Subjects (n=37)**	**Unhealthy Subjects (n=17)**
Age	56.2 (21.2)	48.6 (21.2)	72.6 (7.4)
Gender			
Male	27 [50.0%]	17 [45.9%]	10 [58.8%]
Female	27 [50.0%]	20 [54.1%]	7 [41.2%]
Race			
Asian	18 [33.3%]	16 [43.2%]	2 [11.8%]
White	33 [61.1%]	18 [48.6%]	15 [88.2%]
Hispanic or Latino	3 [5.6%]	3 [8.2%]	0 [0%]

* Mean (SD) or Frequency [percentage]

The visual acuity scores for all participants are listed in Table 3. The average scores and SD of ColorDx were higher than ETDRS chart in all tests. The mean difference for the two visits of ColorDx was 0.03 ranging from -0.02 to 0.08, while that for ETDRS chart was 0.01 ranging from -0.02 to 0.04. None of the differences between the two visits were statistically significant ($P>0.05$). In the healthy group and unhealthy group, except for the results of the healthy group tested by ETDRS chart slightly increased, the average scores

decreased in the second visit. The mean difference of healthy group testing by ColorDx was higher than that of the unhealthy group, while the ETDRS chart showed the opposite trend.

Table 3. Comparison of logMAR visual acuity scores for ETDRS charts and ColorDx in two visits

Groups	Visual acuity tests	1st visit*	2nd visit*	Mean Difference** (95% Confidence Interval)	P Value
All eyes (n=54)	ETDRS	0.16±0.22	0.15±0.21	0.01 (-0.02, 0.04)	0.46
	Color Dx	0.217±0.250	0.19±0.26	0.03 (-0.02, 0.08)	0.25
Healthy eyes (n=37)	ETDRS	0.09±0.14	0.09±0.15	-0.003 (-0.04, 0.03)	0.86
	Color Dx	0.15±0.21	0.10±0.22	0.04 (-0.02, 0.11)	0.19
Unhealthy eyes (n=17)	ETDRS	0.32±0.27	0.28±0.27	0.04 (-0.006, 0.08)	0.089
	Color Dx	0.37±0.27	0.37±0.26	<0.001 (-0.08, 0.08)	1

The two groups were divided by clinical diagnosis.
*Mean±SD
**Differece = 1st visit – 2nd visit in logMAR
Paried sample t-test was performed to test the mean difference.

A Pearson correlation was run using the first visit values. The r was 0.794, with a p-value less than 0.001.

Table 4 shows the results of discriminant validity. The mean differences between healthy and unhealthy groups were both 0.23 for the two measurements, and that of ColorDx was slightly higher in the fourth place after the decimal point than ETDRS chart.

Both tests were statistically significant to differentiate the two groups, with p-values 0.03 and 0.01 of ETDRS chart and ColorDx, respectively.

Table 4. Mean differences between healthy and unhealthy subjects on ETDRS chart and Color Dx

Groups	**Mean difference (95% Confidence Interval)***	**P Value**
ETDRS	0.23 (0.09, 0.37)	0.03
ColorDx	0.23 (0.10, 0.36)	0.01

The two groups were divided by clinical diagnosis.
*Differece = Unhealthy - Healthy in logMAR
Independent sample t-test was performed to test the mean difference.

CHAPTER 4. DISCUSSION

As outlined in the introduction, vision is one of the most significant senses for humans. Clinical practice and trials use visual acuity to screen disease, estimate severity, and measure treatment response. The measurement of visual acuity is influenced by several factors, including light intensity; number, size, contrast, and shape of the optotypes; and the chart design. [3, 52] The readability varies between chart letters could be caused by different chart construction, examination protocols, or subject selection. [3, 52-54]

This prospective study is the first to test the reliability and validity of the visual acuity test on ColorDx, which used the psi-marginal adaptive psychological method to estimate the threshold. In this study, we found that the visual acuity on ColorDx and ETDRS had reproducible results. In table 3, even though the average scores of ColorDx were slightly higher than those of ETDRS chart (worse visual acuity), they were very close to each other. Although ETDRS chart is the gold standard, it still has biases. We don't know which measurement is more acurate and its result is closer to the acuity threshold. The reason why the scores improved (number decreased) in the second visit could because the subjects were more familiar with the tests and environment in the second visit. The minimal changes of ColorDx in unhealthy group between two visit, especially when compared with the changes of both tests performed in the healthy group and ETDRS chart performed in the unhealthy group, suggests this measurement may be more reliable to unhealthy patients. Despite the fact that the extremely large p-value in this condition is due

to the insufficient sample size, the large number could, to some extent, explain the slight variation in the two visits.

In table 3, all p values were over 0.05. This indicates that there is no statistical significance between the two visits, and the repeatability of the result is comparable to the ETDRS chart.

Pearson's correlation was run to test the criterion validity. The positive correlation and statistically significant p-value suggest that there is a strong association between ColorDx and the gold standard. A comparison of the mean difference between healthy and unhealthy subjects on ETDRS chart and ColorDx was performed. We chose the results from the first visit to analyze was because it was considered closer to the real conditions in clinical practice. Both tests have adequate discriminant validity, detecting the difference of the visual acuity between healthy and unhealthy subjects sensitively. Therefore, the visual acuity test on ColorDx has adequate validity. (Table 4)

Various automated visual acuity tests have been developed since the 1980s, and a few studies compared those tests with contemporary widely performed visual acuity tests. Those automated tests mostly chose Sloan letter and Landolt C as optotypes since they are most commonly used in the clinic. Given that our study is aiming at the broader application, this section will only discuss the Landolt C tests.

Ruamviboonsk et al. studied a computerized acuity test system using the 4-direction Landolt rings as optotypes.[11] This study divided healthy participants into an automated test group and an ETDRS chart group and compared the values. It came up with no statistical difference between these two charts in those with normal vision. Although our

study had a smaller sample size, we included unhealthy subjects and found ColorDx is comparable to ETDRS chart in both healthy and unhealthy groups. In addition, it is more reliable to perform the same tests on every participant to diminish the bias from sampling.

Freiburg visual acuity test (FVT) is another automated vision test developed in Europe in 1995.[43] This program used eight directions Landolt C as optotypes. A few studies have compared this test with different hard-copy charts targeting different populations. Wesemann W performed Bailey Lovie chart and Landolt Ring chart as comparisons to this automated measurement.[47] Both eyes from 130 healthy students were recruited in this study. The FVT was proved to have good reproducibility. It also demonstrated one of the advantages for automated tests that they measure visual acuity on a continuous scale, unlike the traditional visual acuity tests. However, the sample in this study could not represent the whole population, including people in different age stages and health conditions. Lars Loumann Knudsen studied FVT and the decimal progression chart, which was the most commonly used chart in Denmark.[13] This study was aimed at the diabetic population. 22 eyes from 11 diabetic patients were included. It came to the conclusion that FVT was comparable with decimal progression chart in diabetic subjects. Even though the sample size was small, the study offers a good reference of the validation of automated vision chart study in diabetic group patients. Bach M et al. used FVT and Tumbling E chart in school enrolment examinations.[45] The enrolled children were aged 3.8-6.9 years and the results suggested a good agreement between the two tests. This provides an excellent support for the feasiblity of Landolt C automated vision tests among preschool children. In addition, the examiners in this study unanimously preferred FVT, suggesting the automated tests are more welcomed and userfriendly.

Nevertheless, the FVT used the PEST as the algorithm on estimating threshold, which is less advanced and flexible than psi-marginal. What is more, this measurement is testing with eight-direction Landolt C. Too many directions could increase the difficulty of the test, and the examinees become fatigued easily and confused about the buttons on the keyboard. This potentially develops measurement errors. It is more practical for subjects to choose from four options rather than eight options on FVT, nine options on Snellen letters and ten options on Sloan letters.[11] Surely, fewer options could result in a higher chance to guess the right answer. However, the test program fills this gap with algorithm and achieves closer to the real threshold. In addition, the adaptive psychophysical procedure improves the efficiency of the tests by determining the threshold with the fewest number of measurement so that the effort during the measurement is minimized. [55, 56] This characteristic especially fits the fast-paced clinical practice.

Monica Camparini et al. suggested that the incorrectly read letters above the acuity threshold region might be considerer as false-negative responses.[55] This may more frequently happen in specific diseases. In our unhealthy group, the ColorDx with smaller test-retest variability compared with ETDRS chart tends to support this point. Whereas the small sample size in the unhealthy group is not sufficient to draw the conclusion, this needs to be further studied.

Advantages of this measurement include avoiding memorizing optotypes and crowding phenomenon, international recognition without a Latin alphabet barrier, the same legibility of each optotype, and being friendly to people with bad vision or visual field loss and seniors.[6, 11] Apart from the application in pediatric and adult clinical settings

and researches, the logMAR score system also contribute to the international application. Further, the simply operated procedure diminishes the intraexaminee and interexaminer variations.[57] In addition, other visual acuity measurement programs run by computer or smart devices are less applicable than a medical device with installed measurement software. When applying those independent programs on different devices, the diverse screen resolution, brightness, material and size can give rise to measurement errors. The visual acuity test on ColorDx has the same background illuminance with ETDRS chart box, making these two measurements more comparable.

The disadvantages of the ColorDx include machine dependency and cost.[58] However, as computers renew fast, the expense could decrease correspondingly. Our limitation includes sample size and the number of disease groups and low vision subjects. Due to COVID-19, we had to stop recruiting subjects and collecting data. This drives our future study directions to larger sample size, diverse disease groups and broader vision range. Disease-specific researches can also be developed to study if this measurement is more sensitive to those diseases or even their specific stages. Besides, we also lost track of a few subjects who were not able to come for the second visit. In the analysis of this thesis, we excluded the data of these subjects. Due to the short wire of the keyboard of ColorDx, examiners get the responses from examinees and pressed the buttons for them. This could generate errors between examiner and examinee. But we were trying to diminish this bias by double-checking the answers. Hopefully, a wireless keyboard could be developed by the company. In this study, we were not able to record the test time, which could be a potential advantage for ColorDx. In future studies, the preference of the measurements can also be investigated from the subjects.

In conclusion, the visual acuity test on ColorDx is a simple, reliable and standardized procedure for visual acuity measurement. The pilot data in our study provides preliminary evidence that it can be used as a valid alternative to ETDRS chart worldwide without the Latin alphabet barrier. The simple operation could be suitable for fast-paced clinical settings. More disease groups and larger sample size need to be evaluated in future studies.

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