Article

Image Quality Metric Derived Refractions Predicted to Improve Visual Acuity Beyond Habitual Refraction for Patients With Down Syndrome

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Purpose: To determine which optimized image quality metric (IQM) refractions provide the best predicted visual acuity (VA).

Methods: Autorefraction (AR), habitual refraction (spectacles, $n = 23$; unaided, $n = 7$), and dilated wavefront error (WFE) were obtained from 30 subjects with Down syndrome (DS; mean age, 30 years; range, 18–50). For each eye, the resultant metric value for 16 IQMs was calculated after >25000 sphero-cylindrical combinations of refraction were added to the measured WFE to generate residual WFE. The single refraction corresponding to each of the 16 optimized IQMs per eye was selected and used to generate acuity charts. Charts also were created for AR, habitual refraction, and a theoretical zeroing of all lower-order aberrations, and grouped into 10 sets with a clear chart in each set. Dilated controls (five observers per set) read each chart until five letters were missed on a high contrast monitor through a unit magnification telescope with a 3 mm pupil aperture. Average letters lost for the five observers for each chart was used to rank the IQMs for each DS eye.

Results: Average acuity for the best performing refraction for all DS eyes was within five letters (0.11 ± 0.05 logMAR) of the clear chart acuity. Optimized IQM refractions had ~3.5 lines mean improvement from the habitual refraction (0.37 ± 0.22 logMAR, $P < 0.001$). Three metrics (Visual Strehl Ratio [VSX], VSX computed in frequency domain [VSMTF], and standard deviation of intensity values [STD]) identified refractions that were ranked first, or within 0.09 logMAR of first, in >98% of the eyes.

Conclusions: Optimized IQM refraction is predicted to improve VA in DS eyes based on control observers reading simulated charts.

Translational Relevance: Refractions identified through optimization of IQM may bypass some of the challenges of current refraction techniques for patients with DS. The optimized refractions are predicted to provide better VA compared to their habitual correction.

Introduction

Down syndrome (DS) is a genetic condition marked by the presence of a full or partial extra copy of chromosome 21. Each year, approximately 6000 babies are born with DS, or approximately 1 in every 700 babies.[1] Individuals with DS have poorer visual performance compared to age-matched controls, even when wearing refractive corrections.[2–4] In general, individuals with DS are reported to have high levels of refractive errors,[5–7] including elevated levels of higher-order ocular aberrations[8] that cannot be corrected by spectacles.

Subjective refraction is the most commonly used method to prescribe spectacle corrections in the clinic and relies on asking the patients a series of questions about their perceived visual quality that leads the clinician to the final refractive prescription. However, it is well known that the subjective refraction is variable[9–11] and, as the name suggests, it depends on subjective discriminative feedback from the patient. It has been shown that the repeatability of subjective refraction is worse in keratoconic compared to normal eyes, a finding[12] that is attributed to the blur resulting from elevated levels of optical irregularity that cannot be corrected with spectacles. In addition, studies have shown that the mean differences between subjective and aberrometry-derived objective refraction data are substantially larger in keratoconic than in normal eyes due to elevated higher order aberrations.[13] Considering that individuals with DS have elevated refractive errors, elevated levels of higher order aberrations, and intellectual disability that may increase the difficulty of the task, the subjective refraction process can be quite challenging for them.

In clinical settings, automated refractors are used frequently to determine the starting point for subjective refraction; however, there is discrepancy between autorefraction and subjective refraction endpoints.[11,14] Although autorefraction is a useful objective technique to estimate the spectacle prescription, it recently has been reported that there is greater intrasession variability in autorefraction measures for patients with DS than age-matched controls.[15] Thus, objective refraction tools that seek to provide the best possible objective refraction would benefit the population of individuals with DS.

Wavefront sensors provide a more complete description of the eye's optical imperfections than is obtained with subjective refraction, particularly when used on highly aberrated eyes. Refraction obtained from the measurement of wavefront aberrations has been more precise than subjective refraction[11] and also enables the calculation of image quality metrics (IQM) to assess the retinal image quality of the eye.[16,17] The accuracy and precision of 33 objective metrics of optical quality in determining a sphero-cylindrical refraction was previously estimated with most metrics having a spherical equivalent precision of 0.50 to 1.00 diopters (D) for predicting subjective refraction (−0.50 to −0.25 D for sphere and 1/8 D for astigmatism).[17] According to Thibos et al.,[17] optimizing a metric is a virtual "through-focus" experiment in which the computer adds or subtracts various amounts of spherical or cylindrical wavefront to the aberration map until the optical quality of the eye is maximized. A refraction process that uses image quality metrics to identify the prescription through an objective optimization of those metrics objectively considers the impact of higher order aberrations on the resultant retinal image quality for a given refraction.[18,19]

As a first step to applying a metric-derived objective refraction to eyes of individuals with DS, a simulation study using control observers was performed to compare the visual acuity (VA) obtained from metric optimized and habitual refractions. A simulation study was conducted to remove the barrier of intellectual disability on visual performance, thus isolating the impact of optical aberrations on acuity. We determined which optimized IQM-identified sphero-cylindrical refractions provide the best predicted VA for eyes from individuals with DS, as well as compared the performance of IQM refractions to subjects' habitual correction and autorefraction.

Methods

This study adhered to the tenets of the Declaration of Helsinki and was approved by the University of Houston Committee for the Protection of Human Subjects. Informed consent was obtained from all control subjects without DS. For participants with DS, written parental/legal guardian permission was obtained after explaining the nature of the study in person during the time of testing, and written or verbal assent obtained from the participants.

Study Measures for Subjects With Down Syndrome

Thirty-four individuals with DS were recruited from local DS organizations (e.g., Friends with Down syndrome, local Special Olympics chapters, and the Baylor College of Medicine Transition Medicine Clinic). Subjects wearing spectacles had their spectacle lens power measured with auto-lensometry ($n = 23$). Nondilated distance autorefraction (Grand Seiko WAM-5500; RyuSyo Industrial Co., Ltd. Hiroshima, Japan) then was used to measure the uncorrected refractive error of all subjects. No subjects with DS presented with contact lens corrections.

Aided presenting VA (or unaided if subjects did not wear correction) was measured three times in each eye (approximately 10 to 15 minutes total testing time) using a logMAR acuity method with charts presented on a gamma-corrected LCD monitor with the room lights off. The monitor had a background luminance of 415 cd/m^2 and, thus, the white background of the acuity chart provided overall dim room illumination. Each subject's pupil diameter was monitored with the PowerRef 3 (Plusoptix, Nuremberg, Germany), a dynamic, infrared photorefractor, as they performed acuity testing. To avoid false pupil size measures from spectacle lens minification/magnification, subjects' presenting spectacle powers were placed in a trial frame over the tested eye while the nontested eye was left uncorrected and visually occluded with a Wratten 89B filter (Kodak, Rochester, NY; passes infrared light, but blocks visible light). The eye with the Wratten filter was the eye monitored for pupil size during acuity testing. We tested 23 subjects with DS in this fashion with their correction in the trial frame. The other subjects with DS did not present with any correction and, thus, were tested unaided with only the Wratten filter over the fellow eye. The average pupil size during acuity testing was calculated for each subject from these data.

Subjects then were dilated with one drop of 1% tropicamide, followed by one drop of 2.5% phenylephrine. Additional drops were instilled if pupil size had not become noticeably larger after 15 minutes. At 30 minutes after dilation, wavefront aberrometry was recorded in each eye with the Discovery Wavefront Sensor (Innovative Visual Systems, Elmhurst, IL) and reported as 2nd to 10th order Zernike coefficients. Repeated measurements were taken until five good quality measurements were obtained in each eye as judged by the displayed spot pattern (large pupil, no obstruction by lashes, and minimal reflection/scatter). Two subjects were excluded due to an inability to obtain pupil size data during VA testing. One subject was excluded due to an inability to obtain wavefront measures related to poor fixation ability of the subject. One was excluded from the study due to previous cataract surgery in the left eye and visually significant cataract in the right eye.

Calculation of Image Quality Metric Optimized Refractions

Uncorrected 2nd through 10th order Zernike coefficients were generated for five good quality measurements, which then were mathematically averaged and resized to that subject's measured pupil diameter to define the wavefront error (WFE) for each eye. The WFE then was used to determine the optimized refraction for each eye (as described below) after correcting for the longitudinal chromatic aberration resulting from the longer wavelength of the measurement light source (~0.83 D when converting from 830 to 555 nm). For each eye, >25,000 sphero-cylindrical combinations were mathematically applied to the eye under study using a custom MATLAB (MathWorks, Natick, MA) algorithm. Large ranges of spherical power (at least ±3 D surrounding the habitual sphere) and cylindrical power (at least 0 to −4 D) in 0.25 D steps and the entire range of cylindrical axes in 2° steps were included in the search for the optimized refraction. The refractions were vertexed from a 12 mm spectacle plane, and also accounted for a pupil plane that is 3.05 mm behind the cornea. The sphero-cylindrical refractions in the pupil plane were mathematically converted to Zernike coefficients, which were added to each eye's uncorrected second-order Zernike terms, thereby generating the residual WFE experienced by the eye during wear of the refraction. Image quality metrics (IQMs) were calculated from each residual WFE calculation. On average, it took 8 to 10 hours to calculate 31 metrics for both eyes for one subject with DS. Once complete, the highest (best) level of each IQM and the associated refraction for each of the IQMs for each DS eye were identified. The IQMs used in this study are a subset from the 31 metrics previously published by Thibos et al.[17] These metrics are commonly referred to by abbreviated names (as used in this publication), but a complete description and definition can be found in Thibos et al.[17]

Identifying a Subset of 16 Image Quality Metrics

In selecting the subset of IQMs to be evaluated for this study, a preliminary study was conducted where simulated acuity charts representing the predicted retinal image quality for each refraction (as described below) were generated for all 31 IQM optimized refractions for both eyes of all 30 subjects with DS. Charts then were individually viewed on a high contrast monitor by the five observers in a group setting from a distance of at least 10 feet and rated by overall appearance on a scale of 1 to 100 with 100 being the best (scale step size = 1). Observers were instructed that a perfect chart that appeared to be of the highest contrast and clarity should be considered a score of 100, but no other guidance regarding the scale was provided. Given that observers set their own calibration in using the scale, observer responses then were normalized based on the range they used for each subject's set of charts. In performing this adjustment, each observer's normalized rankings ranged from 100 (best condition) to 0 (worst condition) for a given eye. For each observer, scores assigned for all charts from the same subject's eye were grouped together and the minimum and maximum scores assigned for that eye's charts determined (i.e., the worst and best ranked metric condition). Individual scores then were adjusted using the following formula:

$$Adjusted\ Score = (Actual\ Score - Minimum\ Score) / (Maximum\ Score - Minimum\ Score).$$

The adjusted scores then were averaged across all observers for each chart.

We evaluated 49 eyes from 25 subjects with DS in this preliminary study. To determine which IQMs consistently ranked poorly, the total average across 49 eyes of the average observer adjusted scores were calculated. After all charts were viewed, seven IQMs that consistently resulted in the lowest average scores (range, 37–60) were eliminated from further consideration (RMSw, RMSs, PFWT, Bave, SM, VOTF, VNOTF). In addition, seven IQMs were eliminated due to failure to identify a single best optimized refraction for each eye (PV, PFSc, HWHH, CW, D50, SFcMTF, SFcOTF), and, thus, an inability to produce a single best acuity chart for that given metric. Failure to find a single best refraction meant that numerous refractions resulted in the same metric value for that particular IQM, thus yielding a multiway tie for optimized refraction (ties often occurred between >20 different refractions). For the seven IQM that had this result, multiway ties were observed for anywhere from 18% to 63% of eyes. Two IQMs identified the same optimized refraction for all eyes evaluated (EW, SRX), and, thus, only one of the two matching IQMs was arbitrarily retained (SRX) for further consideration. This left 16 IQMs (Appendix A) for consideration in the present simulation study (average observer quality scores range, 67–87).

Refractive Conditions Tested

In addition to the residual WFE calculations for the 16 IQM optimized refractions, residual WFE also was calculated for corrections corresponding to the measured autorefraction and the habitual spectacle corrections worn. For subjects without habitual spectacles, residual wavefront with no refraction was generated in lieu of the habitual spectacle correction condition. Lastly, a theoretical condition was generated for which lower order terms were set to zero, termed LOAZ, and the remaining higher order wavefront included in the simulation. In total, the residual WFE for 19 conditions per eye were calculated for each subject.

Generation of Acuity Charts Simulating the Refractive Conditions

VA charts were generated to simulate the retinal image quality for each DS eye for each refractive condition by convolving a clear chart of 98.9% Weber contrast (background luminance: 358.62 cd/m^2) with the point spread function determined from the residual WFE for each condition using Image Simulation software (Sarver and Associates), as described previously.[20,21] Given that some of the IQMs, when optimized, identified the same refractions for a specific eye, only one chart per unique refraction was created, and, thus, not all eyes had 19 charts created. On average, there were 15 unique charts per subject eye (range, 6–19). Acuity charts then were grouped into 10 sets which were read by control subjects without DS. Given the time demands to read large numbers of charts, these 10 sets were created to limit study visits to 1 hour to complete each set. Each set contained simulated acuity charts for both eyes of three subjects with DS, so each group had a similar number of acuity charts (range, 60–75 charts per group). Charts were shuffled within each set and an unaberrated, clear chart was inserted into each set to determine the baseline acuity for each control subject for a given session as a comparison to acuity performance for all other conditions tested during that same session.

VA Estimation

Fourteen control observers with at least 20/20 acuity were recruited to read the simulated acuity charts. A total of five of the 14 control observers viewed each set, with three of the control observers viewing all 10 sets. Subjects were first dilated with 1% tropicamide, followed with 2.5% phenylephrine. At 30 minutes after dilation, subjects viewed and read charts on a high contrast LCD monitor (1200 × 1600 pixels; Fig. 1A) through a unit magnification telescope with a 3 mm pupil aperture and their habitual correction placed with trial lenses in the spectacle plane (Fig. 1B).

Throughout testing, an examiner controlled the presentation of the charts while recording the subject's responses as correct or incorrect by looking at a clear version of the same chart on the examiner's computer. In addition, the examiner monitored the centration of the artificial pupil with the observer's pupil to ensure good alignment throughout testing. For each chart, subjects were instructed to begin with a line they could confidently see (5/5 correct). Responses then were recorded until the subject missed five letters.[20–22] In the instance of severely blurred charts, subjects began at the top line, guessing until five mistakes were made. Individual chart acuity was recorded at the time of testing. Acuity relative to the clear chart (baseline) obtained during the same session was later calculated for each refraction for each observer and expressed as the number of letters lost (most common) or gained for that refractive condition. In the instance of two or more IQMs identifying the same optimized refraction for a given

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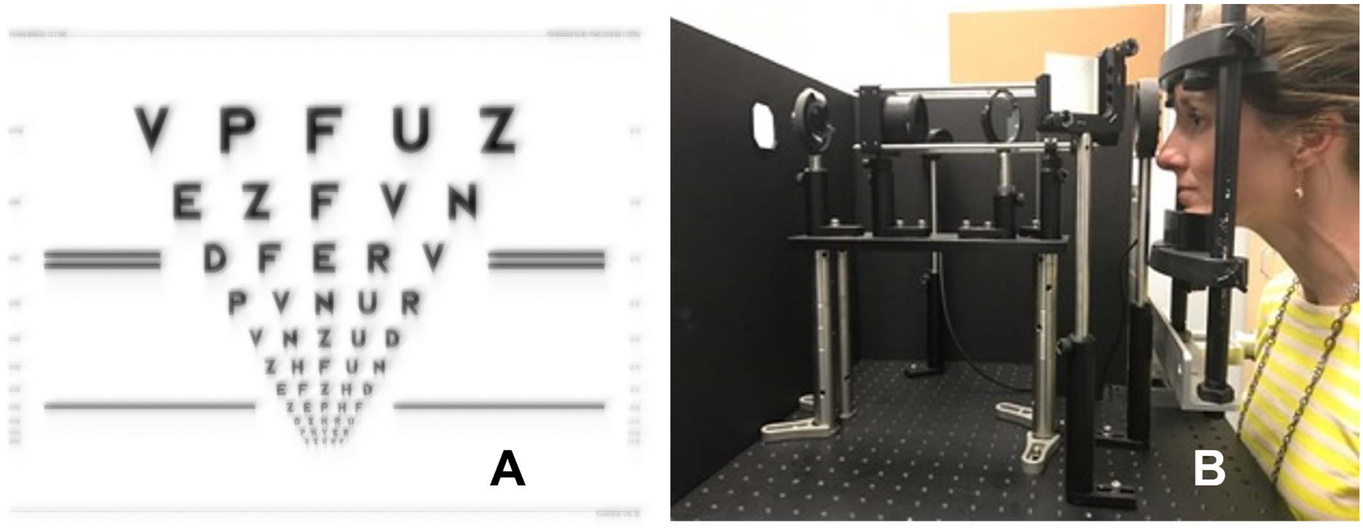

Figure 1. (A) A simulated chart. (B) Observer on a headrest with additional temple guides to help the subject maintain alignment while viewing the simulated chart for each refraction through a unit magnification (×1) telescope with a 3 mm artificial pupil and habitual refraction in place.

eye, acuity for that condition was measured only once per observer and the resultant relative acuity was assumed to be same for all IQM conditions identifying that refraction. Figure 2 diagrammatically summarizes the experimental procedure and logMAR acuity calculation.

Data Analysis

The overall goal was to identify the top performing conditions. First, for each DS eye, the relative acuity across five observers was averaged and the refractions were ranked based on their relative acuity (least to most letters lost compared to baseline). Second, the condition with the best relative acuity was identified. Third, any additional refraction(s) with a relative acuity within 0.09 logMAR of the best condition were identified as top performing refractions for that individual eye. The criterion of 0.09 logMAR was chosen based on previously published values of repeatability of VA for control subjects performing the same VA task used in this study.[23]

Speaking to how frequently metrics identified the same refractions, we computed the percentage of eyes (out of 60) for which pairs of the metrics identified the same refraction. This tally was performed with a strict exact match criterion and then repeated with a less strict criterion that counted two refractions as the same if they differed by no more than the ANSI standard tolerances for manufacturing spectacles (listed in Table 1).[24]

For example, the following three refractions would not be counted as the same for the exact match criterion, but would all be counted as the same per the ANSI standard criterion:

$$\text{Optimized Metric SRX:}\ +2.50 - 3.00 \times 150$$

$$\text{Optimized Metric VSMTF:}\ +2.50 - 3.00 \times 152$$

$$\text{Optimized Metric VSX:}\ +2.50 - 3.00 \times 154$$

Results

Habitual Pupil Diameter of Subjects With Down Syndrome

The individual natural pupil size of each eye from the subjects with DS was used to calculate the

Table 1. ANSI Standards[24] Used to Compare Refractions

Measurement	Power Range, D	Tolerance
Sphere power	0.00 to ≤ ±6.50	±0.13 D
	≥ ±6.50	±2%
Cylinder power	0.00 to ≤ 2.00	±0.13 D
	>2.00 to ≤ 4.50	±0.15 D
	>4.50	±4%
Cylinder axis	0.00 to ≤ 0.25	±14°
	>0.25 to ≤ 0.50	±7°
	>0.50 to ≤ 0.75	±5°
	>0.75 to ≤ 1.50	±3°
	>1.50	±2°

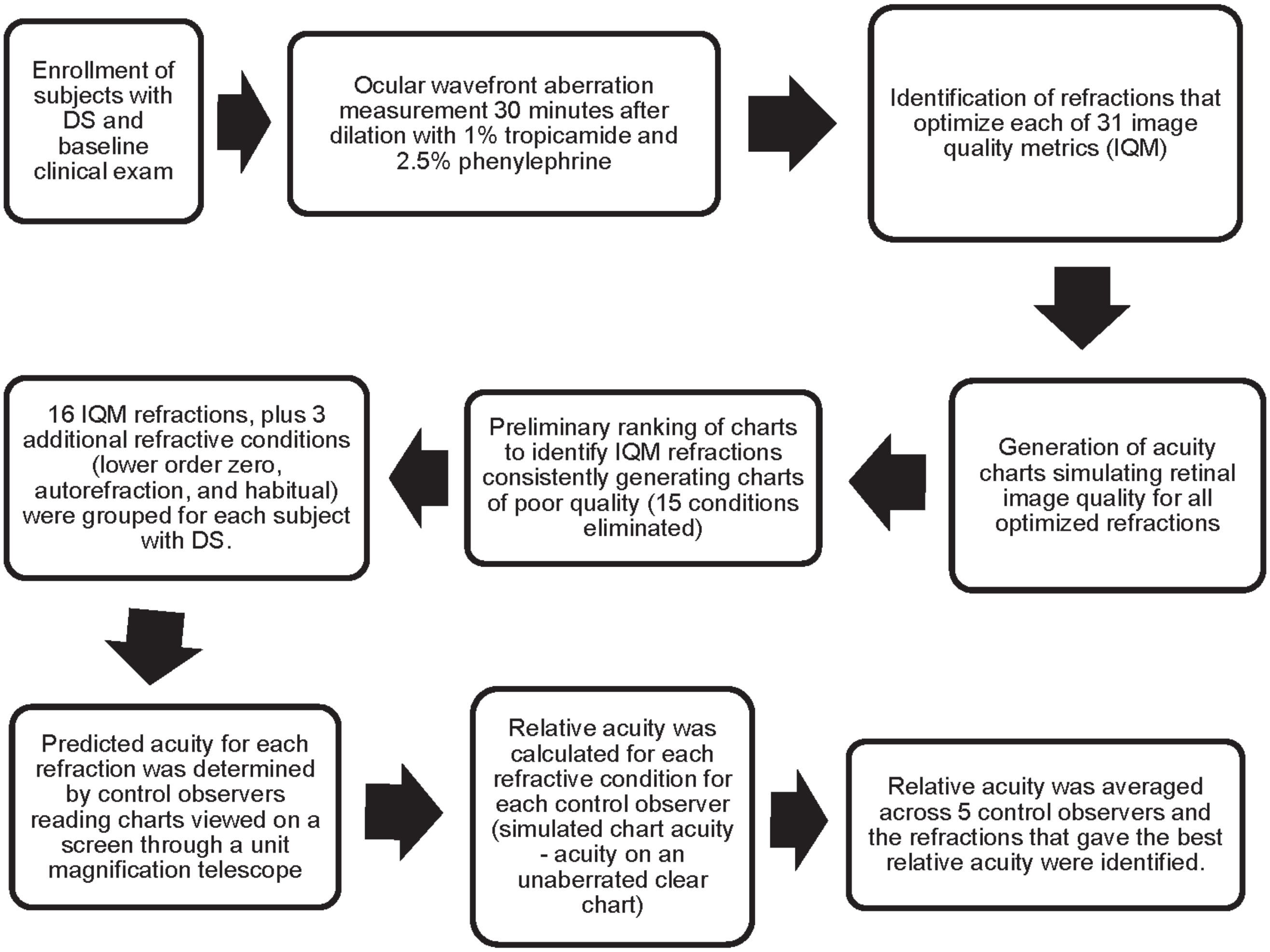

Figure 2. A diagrammatic summary of the experimental procedure.

wavefront refraction for each eye and ranged from 2.79 to 6.94 mm (average, 4.38 ± 0.97 mm).

Identification of Top Performing Conditions

The top performing conditions were identified for each DS eye. Table 2 shows an example of the ranked refractive conditions ordered from poorest average relative acuity to best average relative acuity for the left eye of one subject with DS. For this subject's eye, AreaMTF was the metric that identified the refraction providing the best average relative acuity. Thirteen additional refractions had relative acuity within 0.09 logMAR of AreaMTF, and, thus, all were classified as top performing refractions for this eye (shown in bold). It should be noted that many of these refractions were identical, indicating that multiple metrics identified the same refraction, when optimized. Additionally, there is no refraction listed for the LOAZ condition, given that we simulated this condition by setting all lower order terms to zero.

The ranking of each metric and identification of top performing conditions was performed for each individual eye. The percentage of time each metric was identified as a top performing refraction among the 60 eyes was computed. Seven metrics (VSX, VSMTF, STD, SRX, NS, LIB, and AreaMTF) were identified as overall top performing metrics in >95% of eyes (58 of 60 eyes). Figure 3 shows the percentage of eyes in which the refractions identified by each metric were ranked as the overall best, or within 0.09 logMAR of the best relative acuity (i.e., top performing).

As previously noted in Table 2, it was not uncommon for multiple conditions to identify the same refraction, when optimized. In Table 3, the similarity of refractions between paired metrics is shown with the top half showing the percentage of

Table 2. Refractions Identified for the 19 Conditions for One Eye of One Subject

Condition	Average Relative Acuity, logMAR	Sphere, D	Cylinder, D	Axis, Degrees
HABITUAL	−0.54	+0.50	−1.75	020
AUTOREF	−0.37	−2.25	−1.50	030
NS	−0.24	−1.75	−1.25	040
SROTF	−0.20	−1.00	−2.25	042
PFCT	−0.19	−1.50	−1.25	042
LIB	***−0.14***	***−1.75***	***−1.00***	***048***
SRMTF	***−0.14***	***−1.75***	***−1.00***	***048***
SRX	***−0.14***	***−1.75***	***−1.00***	***048***
STD	***−0.14***	***−1.75***	***−1.00***	***048***
VSOTF	***−0.14***	***−1.75***	***−1.00***	***048***
PFST	***−0.12***	***−1.50***	***−1.25***	***038***
VSX	***−0.12***	***−1.75***	***−1.25***	***044***
AREAOTF	***−0.11***	***−1.75***	***−1.00***	***050***
LOAZ	***−0.11***			
ENT	***−0.11***	***−1.75***	***−1.25***	***036***
PFCTC	***−0.10***	***−1.50***	***−1.50***	***044***
PFWC	***−0.10***	***−1.50***	***−1.50***	***044***
VSMTF	***−0.10***	***−1.75***	***−1.25***	***042***
AREAMTF	***−0.08***	***−1.75***	***−1.00***	***046***

Top performing conditions (defined as 0.09 logMAR within the best relative acuity) are bold and italic.

matched refractions for the 60 eyes based on the ANSI standard criterion and the bottom part showing the percentage of matched refractions for the 60 eyes based on the exact match criterion. The six most common top performing conditions (STD, VSMTF, VSX, NS, SRX, and LIB) identified matched refractions to each other >33% of the time by the exact match criterion and >43% of the time by the ANSI standard criterion.

Acuity of Best-Performing Refractive Condition Versus Habitual Refraction Condition

Average relative acuity for the single best performing conditions for all DS eyes was within 5.5 letters (–0.11 ± 0.05 logMAR) of the average acuity obtained with the unaberrated, clear chart, indicating good performance of the best performing conditions. The average numbers of letters lost was significantly lower for the combined single best metric conditions for right (RE) and left (LE) eyes than the number of letters lost for the condition simulating habitual refraction for

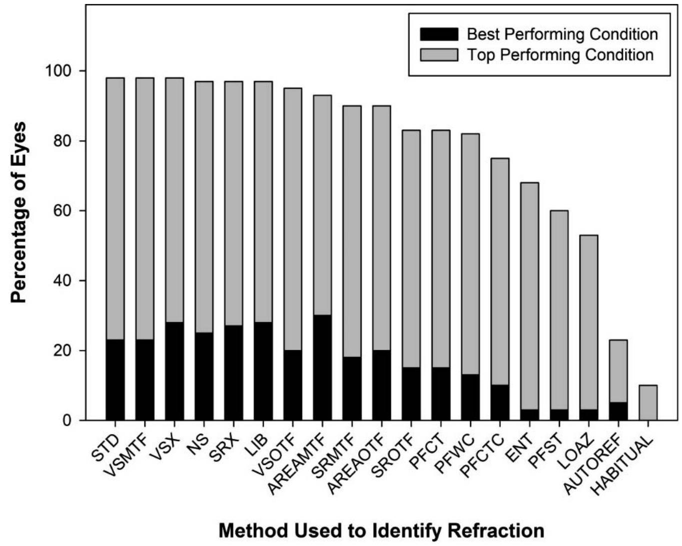

Figure 3. Distribution of best and top performing (best + acuity within 0.09 logMAR of best) metrics for all 60 eyes.

REs and LEs: Habitual (RE, –0.47 ± 0.25 logMAR; LE, –0.50 ± 0.21 logMAR) versus Best (RE, –0.11 ± 0.06; LE, –0.11 ± 0.05 logMAR; paired *t*-test; $P < 0.001$), with an average improvement of 3.8 lines over the habitual in the REs and 3.5 lines in the LEs. Figure 4 shows the average acuity relative to the clear chart of the simulated habitual versus best metric refractions for REs and LEs combined.

Our previously published data on the VA of adults with DS that included the same subjects from this study found an average logMAR VA of 0.51 ± 0.16 for REs and 0.53 ± 0.18 logMAR for the LEs.[23] In the present study, we showed that the VA obtained by simulating the habitual refractions of the subjects with DS resulted in a loss of five lines in both eyes from the clear chart acuity. This comparison of acuity

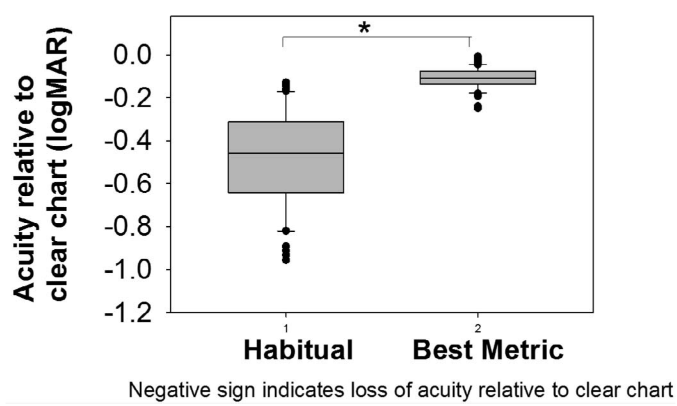

Figure 4. The relative acuity measured from control observers with charts simulating habitual and best metric refractions.

Table 3. The Top (Unshaded) Section Shows the Percentage of Eyes for Which Paired Metrics Identified Matched Refractions Based on the ANSI Standard Criterion and the Bottom (Gray Shaded) Part Shows the Percentage of Eyes for Which Pairs of Metrics Identified the Same Refraction Based on the Exact Match Criterion

	AREAMTF	AREAOTF	AUTOREF	ENT	HABITUAL	LIB	NS	PFCT	PFCTC	PFST	PFWC	SRMTF	SROTF	SRX	STD	VSMTF	VSOTF	VSX
AREAMTF		42%	0%	27%	0%	60%	58%	10%	15%	13%	18%	48%	23%	62%	68%	67%	37%	67%
AREAOTF	23%		0%	12%	0%	37%	28%	7%	7%	5%	8%	22%	58%	40%	37%	42%	67%	42%
AUTOREF	0%	0%		2%	0%	0%	0%	2%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
ENT	15%	3%	0%		2%	17%	25%	7%	18%	25%	27%	43%	5%	20%	27%	22%	13%	18%
HABITUAL	0%	0%	0%	0%		0%	0%	0%	0%	2%	2%	0%	0%	0%	0%	0%	0%	0%
LIB	32%	22%	0%	13%	0%		**52%**	15%	15%	8%	17%	42%	28%	**62%**	**60%**	**72%**	37%	**73%**
NS	40%	13%	0%	17%	0%	**33%**		15%	17%	15%	23%	63%	23%	**63%**	**78%**	**78%**	32%	**72%**
PFCT	3%	7%	0%	2%	0%	7%	3%		15%	7%	8%	17%	7%	17%	15%	15%	10%	13%
PFCTC	12%	5%	0%	10%	0%	8%	12%	5%		13%	35%	15%	3%	10%	17%	17%	7%	17%
PFST	3%	3%	0%	10%	0%	2%	7%	3%	0%		17%	17%	2%	10%	13%	13%	7%	12%
PFWC	12%	2%	0%	15%	0%	8%	17%	2%	22%	5%		20%	5%	18%	22%	22%	8%	22%
SRMTF	38%	10%	0%	37%	0%	33%	45%	7%	8%	7%	10%		17%	55%	68%	60%	30%	55%
SROTF	15%	45%	0%	2%	0%	15%	10%	3%	0%	2%	0%	10%		33%	25%	28%	63%	30%
SRX	43%	23%	0%	15%	0%	**47%**	**53%**	5%	7%	5%	12%	47%	18%		**72%**	**75%**	45%	**73%**
STD	50%	13%	0%	20%	0%	**43%**	**53%**	7%	10%	5%	10%	60%	12%	**60%**		**85%**	43%	**80%**
VSMTF	47%	20%	0%	15%	0%	**48%**	**55%**	7%	10%	7%	7%	47%	15%	**57%**	**72%**		47%	**95%**
VSOTF	20%	47%	0%	7%	0%	30%	20%	8%	7%	2%	3%	20%	42%	28%	25%	28%		45%
VSX	42%	22%	0%	15%	0%	**57%**	**62%**	3%	12%	3%	10%	42%	13%	**63%**	**63%**	**77%**	30%	

Percentages are bolded for the six most common top performing metrics to illustrate the large degree to which these metrics identified matched refractions.

with the actual acuity obtained from DS eyes suggests that the simulations were robust.

Although PFST was the least frequent top performing IQM for this optimized refraction simulation, a significant improvement in acuity (RE, 0.27 logMAR and LE, 0.30 logMAR) still was observed over that of the habitual refraction condition: Habitual (RE, –0.47 ± 0.25 logMAR; LE, –0.50 ± 0.21 logMAR) versus PFSt (RE, –0.19 ± 0.11; LE, –0.20 ± 0.10 logMAR; *t*-test, $P < 0.001$). Autorefraction was the second worst performing condition next to the habitual refraction based on ranking of relative acuity for top performing conditions (Fig. 3).

Discussion

This study sought to determine which metrics identified refractions that were predicted to be top performing with respect to relative VA. As seen in Figure 3, VSX, VSMTF, and STD were included as top performing in 98.3% of the eyes, although frequently identifying the same refraction, and, thus, not uniquely different from each other. In addition, many of the other metrics performed similarly well (Fig. 3). Even the metric that was least likely ranked as top performing (PFST) was predicted to improve acuity significantly over the habitual refraction, and, thus, many of the metrics may be worth considering in the evaluation of metric optimized refraction techniques for individuals with DS.

In designing the study, we considered LOAZ as a theoretical condition to provide a reasonable simulation of a refractive condition whereby the clinician attempts to correct all spherical and cylindrical refractive errors. The results of this study showed that the LOAZ condition was not included as a top performing metric for >45% of the eyes. It is well known that the presence of lower order aberrations interact with higher order aberrations in ways that can improve or decrease the image quality,[20] and, thus, eliminating all lower order aberrations can exacerbate the effects of the higher order aberrations. Our observation that the LOAZ condition performed more poorly than the metric optimized refractions supports this past observation that some level of lower order aberrations may be beneficial.

Comparison With Companion Studies

Since this is the first study evaluating the use of IQM optimization as a means to determine refractions for DS eyes, there are little data with which to compare our results. However, comparing our results with studies performed in other populations, top performing metrics in this study also were top performing in other studies estimating wavefront refractions in normal eyes,[19,25] or estimating subjective judgment of best focus,[16,17] as well as those

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metrics highly correlated with VA measures.[16,21,26] Hastings et al.[19] studied the optimized refraction identified by VSX and found that it provided equivalent visual performance to a subjective refraction in normal eyes. Based on the simulations in this study, there is a three-line predicted improvement in VA with an optimized refraction, and, therefore, metric optimized refraction may be a useful tool for prescribing spectacle corrections for patients with DS, particularly in instances where elevated aberration exists or cooperation is not sufficient to perform a reliable subjective refraction. This methodology also may be useful for other populations with intellectual disability, or reduced ability to perform subjective refractions.

Limitations in the Study

In identifying metric optimized refractions, we considered the chromatic correction between the wavefront aberration measured in infrared to the visible light,[27] but we did not consider the Stiles-Crawford effect (SCE) or appropriate weighting of the pupil function when computing image quality for pupil size differences between aberrometry data and autorefraction. However, Kilintaris et al.[28] investigated the objective refraction with and without the SCE and did not find a significant difference between them. We also did not consider the error associated with the axial length difference between the photoreceptor layer and the RPE layer (light used in wavefront sensors may reflect from deeper structures other than photoreceptors).[29]

The visual image quality metrics incorporate neural factors into their calculation (examples are NS, VSX, SFcMTF, AreaMTF, SFcOTF, AreaOTF, VSOTF, VNOTF, VSMTF) whereas the retinal image quality metrics do not have a neural component in their calculation. Although the visual quality metric VSX has been found to correlate with VA[26] and, thus, is a likely choice for IQM optimized refraction, the image quality metrics also have been shown to provide accurate objective refraction (comparable to subjective).[17] In our study (Table 2) there is a large overlap between metrics identifying similar refractions, a finding that previously has been reported by Thibos et al.[17] However, we do not know whether the neurally-weighted metrics will perform as well when they are applied to actual patients with DS who may have a different underlying neural component than the one used for the calculation of the neurally-weighted metrics.

The wavefront measurements in this study were obtained using the Discovery System wavefront sensor. A recent study has shown that the Discovery system is repeatable with no bias between visits and can be used to track changes in higher order aberration.[30] However, the study has also implied that the Discovery System cannot be used interchangeably with the COAS wavefront sensor, which is considered the gold standard in the field of wavefront measurement.[30] While comparisons between optimized metrics in this study are robust in that all refractions were based upon measurements obtained with the Discovery, comparisons among metric refractions, habitual refraction, and autorefraction may be in question if the Discovery is not in agreement with other instrumentation. Thus, the comparative performance of these refraction methods is reported with caution.

An additional limitation in this study is that the higher order aberrations of the control observers were not corrected, which could potentially influence the simulated chart reading activity. To mitigate this issue, a 3 mm pupil was chosen for the unit magnification telescope, as it is known to be the optimal pupil diameter to balance between diffraction and aberration effects.[31] The 3 mm pupil also allows all visually relevant spatial frequencies of interest in the simulated aberrated charts to pass to the observer's eye. This approach is a common methodology previously used in the literature.[20,26,32]

Conclusions

Optimized IQM refractions obtained from dilated wavefront measurement are predicted to improve VA in DS eyes based on control observers reading simulated charts; however, further study in which refractions are tested directly on individuals with DS is ongoing.

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Appendix

PFWc: Pupil fraction when critical pupil is defined as the concentric area for which RMSw < criterion (e.g., wavelength/4)
PFSt: Pupil fraction when a "good" subaperture satisfies the criterion horizontal slope and vertical slope are both < criterion (e.g., 1 arcmin)
PFCt: Pupil fraction when a "good" subaperture satisfies the criterion Bave < criterion (e.g., 0.25 D)
PFCc: Pupil fraction when critical pupil is defined as the concentric area for which Bave < criterion (e.g., 0.25 D)
EW: Equivalent width of centered PSF (arcmin)
SRX: Strehl ratio computed in spatial domain
LIB: Light in the bucket: the percentage of total energy falling in an area defined by the core of a diffraction-limited PSF
STD: Standard deviation of intensity values in the PSF, normalized to diffraction-limited value
ENT: Entropy of the PSF
NS: Neural sharpness: weighting the PSF with a bivariate Gaussian weighting function normalized to the diffraction-limited case
VSX: Visual Strehl ratio computed in the spatial domain is an inner product of the PSF with a neural weighting function normalized to the diffraction-limited case
AreaMTF: Area of visibility for rMTF (normalized to diffraction-limited case)
AreaOTF: Area of visibility for rOTF (normalized to diffraction-limited case)
SROTF: Strehl ratio computed in frequency domain (OTF method)
VSOTF: Visual Strehl ratio computed in frequency domain (OTF method)
SRMTF: Strehl ratio computed in frequency domain (MTF method)
VSMTF: Visual Strehl ratio computed in frequency domain (MTF method)