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Article

Impact of Pupil Diameter on Objective Refraction Determination and Predicted Visual Acuity

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Purpose: Objective refraction based on wavefront aberration measures is a potential tool for patients unable to participate in a subjective refraction, but the selection of a single pupil diameter for determination of the objective refraction may pose challenges. The purpose of this study was to investigate the impact of pupil diameter on determination of objective refractions for adults with and without Down syndrome (DS) and predicted change in acuity with increasing pupil diameter.

Methods: Wavefront error was obtained from 27 adults with DS and 24 controls, and metric-optimized refractions were identified for 4- and 6-mm pupil diameters. Total dioptric difference between refractions for the two pupil sizes was calculated, and repeated measures analysis of variance was used to evaluate differences in refractions. Next, five control observers read acuity charts produced to simulate image quality of each subject if the same refraction was applied for both a 4- and 6-mm pupil diameter. A comparison of acuity with performance on a clear chart was used to calculate letters lost for each chart. Repeated measures analysis of variance was used to test for differences in letters lost from 4- and 6-mm diameters.

Results: The dioptric difference between refractions for 4- and 6-mm pupils was significantly greater in subjects with DS (0.51 diopters vs. 0.19 diopters, $P = 0.0012$). Letters lost for predicted acuity was less for the 4-mm diameter than 6 mm for charts representing DS eyes (6.5 letters vs. 11 letters, $P < 0.0001$), as well as for typical eyes (4.5 letters vs. 8 letters, $P < 0.0001$).

Conclusions: Differences between refractions by pupil diameter were similar to the repeatability of subjective refraction. Visual acuity differences were clinically small, suggesting similar performance for objective refractions with increasing pupil diameter.

Translational Relevance: This work quantifies the potential impact of pupil diameter change on the performance of wavefront optimized refractions in clinical patients.

Introduction

Individuals with Down syndrome (DS) have been shown to have reduced visual acuity, even when wearing refractive corrections.[1] Reduced visual acuity is observed in both children with DS as well as adults.[2–6] Refractive error is commonly elevated in individuals with DS, both with high hyperopic or high myopic errors, as well as large amounts of astigmatism.[7–11] Determination of the appropriate refractive correction can pose a clinical challenge, particularly given that intellectual disability serves as a potential barrier to the requisite participation in the subjective refraction process. In addition, elevated higher order aberrations may further complicate the refraction process,[12] as it has been shown that complete correction of defocus and astigmatism exacerbate the effects of the higher order aberrations, whereas a refraction that leaves some residual defocus and astigmatic error may serve to balance out the impact of the higher order aberrations.[13]

For these reasons, objective refraction techniques

that eliminate the need for subjective feedback are desirable for this population. Metric-optimized wavefront refraction strategies are one such objective refraction technique that may show promise for individuals with DS. This technique utilizes a measurement of the wavefront error (WFE) of the eye in the presence of different sphero-cylindrical refractive corrections and then reduces the aberration data to a single value.[14–16] A variety of these single value metrics can be calculated to assess different aspects of the optical and visual image quality of the eye, some of which have been demonstrated to have strong correlations with actual acuity performance.[13,17] This methodology has been applied in typical adult populations, patients with keratoconus, and, more recently, individuals with DS.[14]

One potential source of variability in identifying a best refraction with a metric-optimized wavefront refraction is the pupil diameter at which the optimization is performed.[18] It is well known that as the pupil diameter increases, the retinal image is impacted by a greater and different pattern of higher order aberrations,[19] and thus, the refraction that performs best for a given eye could conceivably be dependent upon the pupil diameter. In a clinical setting, the pupil is typically not controlled as patients perform the subjective refraction in dim lighting with their habitual pupil diameter. Refractions are, thus, determined with a single lighting condition, but the patient is later exposed to a range of lighting conditions that may result in a large range of pupil diameters while wearing their correction.

The same would be expected with metric-optimized refraction in that the refraction is determined from a fixed pupil diameter and the patient will later experience a variety of pupil diameters while wearing the correction in daily life. However, given that the patient populations for whom metric-optimized refraction is most targeted often have elevated higher order aberrations, additional consideration regarding the impact of pupil diameter on refraction determination as well as real-life visual performance upon dispensing the correction is warranted.

This study seeks to determine the magnitude to which pupil diameter impacts metric-optimized wavefront refraction determination for both patients with and without DS by quantifying the difference in refractions determined from a 4-mm pupil diameter versus a 6-mm pupil diameter. In addition, this study utilized visual acuity chart simulations and control observers reading those charts to predict the level of acuity reduction expected as the pupil dilates from 4 to 6 mm for both patients with and without DS viewing through a refraction optimized for a fixed 4-mm pupil diameter. Although this work was completed with the specific goal of developing methodology for a clinical trial to evaluate objective refraction performance in adults with DS, the findings and methodology reported here may have additional relevance for other populations who experience elevated wavefront aberrations or are unable to participate in the subjective refraction process.

Methods

This study was approved by the University of Houston Committee for the Protection of Human Subjects and adhered to the tenets of the Declaration of Helsinki. Adult participants without DS provided informed consent. Parental or guardian permission was obtained for individuals with DS, as well as participant assent.

Subjects for Wavefront Refraction Analysis

Adults with DS were recruited for study participation first, followed by recruitment of age-matched adults without DS. All subjects underwent a dilated examination with 1% tropicamide and 2.5% phenylephrine. The purpose of the examination was to quantify characteristics of each subject's visual system, particularly those that might interfere with obtaining good quality wavefront measures, as well as to assess patient safety for dilation. The examination did not include a clinical refraction, nor was a refractive correction dispensed, and thus, best-corrected acuity from the participants with DS is not available.

Thirty minutes postdilation, measures of wavefront aberrations were obtained with the wavefront sensor integrated into the Discovery System (Innovative Visual Systems, Elmhurst, IL) on each eye with a goal of obtaining five images per eye of adequate quality and pupil diameter (i.e., no missing spots, no glare, and minimum of 6-mm pupil diameter). Subjects with nystagmus or individuals unable to fixate well enough for the examiner to obtain five acceptable wavefront measurements were excluded from analysis. Subjects were also excluded if measurements with a 6-mm pupil diameter were not achieved. The Discovery System has previously been demonstrated to have excellent repeatability on dilated adults measured on two separate days (<0.25 diopters [D] for astigmatic vectors, 0.31 D

for spherical equivalent, and <0.1 μm for measures of higher order root mean square [RMS])[20]; however, the agreement of the Discovery System with other wavefront sensors has not been published.

Calculation of Metric-Optimized Wavefront Refractions

For the right eye of each subject, five images of uncorrected WFE (2nd through 10th order Zernike coefficients) were mathematically averaged and then scaled down from the dilated pupil diameter to a 6-mm diameter to provide a single representation of WFE using custom software (Spectacle Sweep, UHCO Core Programming Module, Houston, TX) written with MATLAB (MathWorks, Natick, MA). Optimized refractions were then determined by the software using the process described below after correcting for the longitudinal chromatic aberration resulting from the longer wavelength of the measurement light source.

For each eye, a minimum of 12,000 sphero-cylindrical combinations were included in the search for the optimized refraction. The search range for each subject was guided by their habitual refraction and consisted of at least ±3 D surrounding the subject's habitual sphere correction in 0.25-D steps and at least 0- to −4-D cylindrical power in 0.25-D steps (greater in cases of high habitual cylinder), and the entire range of cylindrical axes in 2 degree steps. 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 that 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.

The resultant retinal image quality for each unique refraction was determined by calculation of two separate image quality metrics: visual Strehl ratio (VSX) and pupil fraction tessellated (PFSt). The selection of these two metrics was based upon a previous study by the authors investigating predicted improvement in visual acuity for patients with DS when applying a metric-optimized wavefront refraction.[21] In the previous study, all 31 image quality metrics described by Thibos et al.[15] were initially considered but only a subset of 16 proceeded to formal testing and analysis. The overall outcome of that study included findings that many of the 16 image quality metrics identified the same refractions and that the entire subset of 16 metrics, when optimized, resulted in predicted acuity gains over habitual refractions for a greater percentage of the eyes evaluated.[21] To aid in the further development of wavefront optimized refraction techniques for adults with DS, the subset of 16 image quality metrics needed to be narrowed, as evaluating 16 different metrics in a clinical trial would not be feasible. For the present study, we have narrowed to two image quality metrics and made a selection with the specific desire that the two metrics selected would not routinely identify the same refraction for a given eye. The specific selection of VSX and PFSt for the present study from that subset of 16 metrics is further described below.

VSX is a metric that assesses how a point of light is imaged by the eye (point spread function) compared to a diffraction-limited case, while weighting each PSF by a measure of neural contrast sensitivity.[15] VSX has been reported to have a strong correlation with visual performance as measured by visual acuity.[13] VSX was also one of the top metrics predicted to identify refractions resulting in improved visual acuity over habitual refractions in individuals with DS.[21]

PFSt is a metric that assesses how much of the optical quality within the pupil area can be considered "good" by analyzing the wavefront slope of numerous tiny subapertures tessellated over the pupil.[15] PFSt has been reported to have a strong correlation with visual performance, as measured by visual acuity.[13] It was also one of the metrics least likely to identify the same refraction as VSX with the metric-optimized refraction process but still providing predicted improvement in visual acuity over habitual refractions in individuals with DS.[21] After calculation of VSX and PFSt for each of the refractions applied to the eye, the resultant metric values were ranked (range 0 to 1, with 1 being the best for both VSX and PFSt) to determine the single refraction providing the best predicted retinal image quality for each of the two metrics. This procedure was repeated in its entirety for analysis at a 4-mm pupil diameter.

Comparison of Refractions

In order to compare refractions identified by analysis for a 4-mm versus 6-mm pupil diameter, refractions were converted to vector notation (M, J0, and J45) where M represents the spherical equivalent, J0 represents the astigmatic component in the 180/090 orientation, and J45 represents the astigmatic component in the 045/135 orientation.[22] The differences in

each vector component ($\triangle$M, $\triangle J_0$, and $\triangle J_{45}$) were then calculated between the 4- and 6-mm refractions within each metric and eye and the total dioptric difference between refractions calculated as the square root of the sum of the square of $\triangle$M, $\triangle J_0$, and $\triangle J_{45}$.[23]

Generation of Acuity Charts

To investigate the impact of pupil diameter on visual acuity for a given refraction, a chart simulation study was carried out utilizing previously developed methodology[1,17] in which Bailey Lovie-style visual acuity charts simulating the retinal image quality for both 4-mm and 6-mm pupil diameters for the same refraction were generated. First, the residual WFE for refractions identified to optimize both VSX and PFSt at a 4-mm pupil diameter were calculated. Next, the residual WFE over a 6-mm pupil diameter was determined in the presence of the 4-mm refractions. Each chart was then generated by convolving a clear chart of 98.9% contrast (weber contrast, background luminance is 358.62 cd/m^2) with the point spread function determined from the residual WFE for each condition by using Image Simulation software (Sarver and Associates, Cookeville, TN). A set of charts depicting 4-mm and 6-mm pupil diameter retinal image quality for each VSX- and PFSt-optimized refractions at 4 mm was generated for subjects with and without DS. Acuity charts were then shuffled and grouped into 4 sets of $\sim$70 charts with a clear unaberrated chart randomly inserted within each set to obtain baseline acuity.

Measurement of Predicted Acuity

Five control subjects without DS and with at least 20/20 corrected distance acuity were recruited to read each set of charts in four separate 1-hour sessions. At each session, subjects were dilated with 1% tropicamide and 2.5% phenylephrine. Thirty minutes postdilation, subjects monocularly viewed each chart through a unit magnification telescope with a 3-mm pupil aperture and their habitual refractive correction placed with trial lenses in the spectacle plane. Charts were displayed on a high-contrast LCD monitor (1200 $\times$ 1600 pixels). For each chart, subjects were instructed to begin with a line they could confidently see (5/5 correct), and then read subsequently smaller lines. Responses were recorded until the subject missed five total letters. Throughout testing, an examiner entered subject responses and monitored the centration of the artificial pupil with the observer's pupil by using a unit magnification telescope with an infrared camera to ensure good alignment throughout testing. Acuity relative to the clear chart (baseline) was calculated for each chart for each observer, resulting in a value for the number of letters lost for that simulated refraction. The number of letters lost was averaged across the five observers for each condition.

Data Analysis

A primary aim of this work was to quantify differences in refractions with increasing pupil diameter. In addition, we sought to answer whether the magnitude of the change in refraction with increasing pupil diameter differs by the metric used or the population studied. To address these questions, dioptric differences between refractions were calculated and repeated measures analysis of variance were used to test for mean differences across the dioptric differences between groups (subjects with and without DS) and across metrics (VSX and PFSt) within subjects. A second aim of this work was to quantify predicted change in acuity with increasing pupil diameter for a given refraction. To address this question, repeated measures analysis of variance was used to test for differences in letters lost between groups and within subjects for two factors (pupil size and metric) as well as two-way interactions involving pupil size and metric.

Results

Thirty-four subjects with DS and 30 controls were recruited for wavefront measurements. Four subjects with DS were excluded from participation due to an inability to fixate for pupil diameter measures or wavefront measures, as well as one subject with a history of cataract extraction. Of the remaining subjects who all attempted wavefront measurements, 27 adults with DS (mean age, 29 $\pm$ 10 years; range, 18–50) and 24 controls (mean age, 34 $\pm$ 12 years; range, 19–58) had good quality wavefront measurements with a minimum of 6-mm pupil diameter for inclusion in this study. The range of spherical equivalent refractive errors and cylindrical power, as determined by optimization of VSX for a 4-mm pupil diameter are shown in Figure 1. Consistent with previous reports, subjects with DS had a larger range of refractive errors and higher amounts of astigmatism. Higher order ocular aberrations (3rd through 10th order) were also elevated in the group of subjects

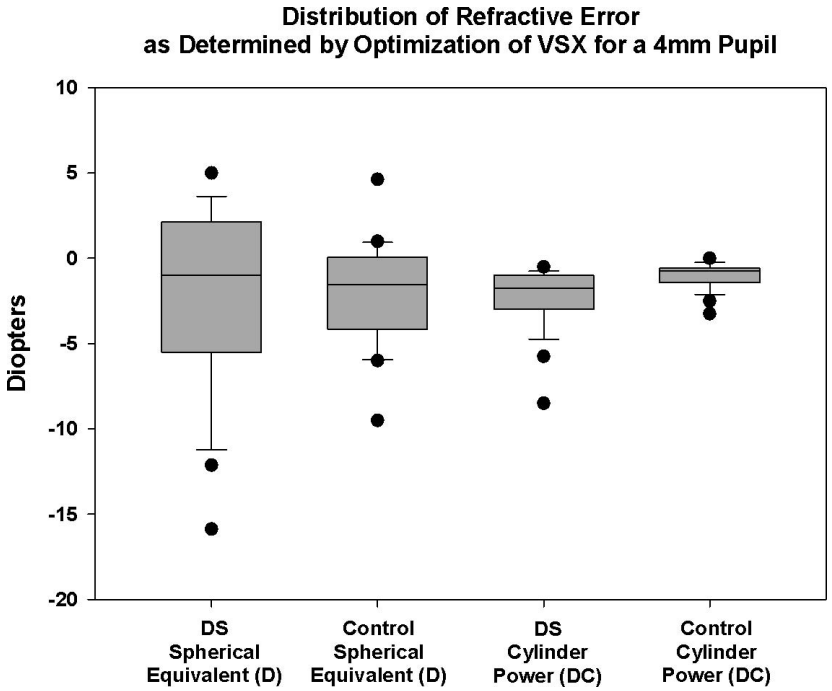

Figure 1. Refractive error distribution in diopters (D) and diopters cylinder (DC) for subjects with and without Down syndrome (DS), as determined by optimization of VSX for a 4-mm pupil diameter.

with DS (Table 1), although not to the levels previously reported for individuals with keratoconus.[24,25]

The dioptric differences for refractions determined for a 4-mm pupil diameter versus a 6-mm pupil diameter are shown in Figure 2. Dioptric difference was significantly greater for subjects with DS versus controls (DS: 0.50 ± 0.63 D, controls: 0.19 ± 0.16 D; f = 11.92, $P = 0.0012$; diff = −0.32 D; 95% confidence interval [CI], −0.51 to −0.13) and significantly greater for PFSt refractions versus VSX refractions (PFSt: 0.45 ± 0.47 D, VSX: 0.26 ± 0.50 D; f = 4.24, $P = 0.0447$; diff = 0.188 D; 95% CI, 0.005–0.371). In controls, 92% had dioptric differences less than 0.50 D for PFSt versus 100% for VSX, whereas 56% of individuals with DS had dioptric differences less than 0.50 D when optimizing PFSt versus 85% when optimizing VSX. There was no significant interaction

Table 1. Higher Order RMS

Group	4-mm Pupil	6-mm Pupil
DS, μm (n = 27)	0.21 (0.09)	0.63 (0.34)
Controls, μm (n = 24)	0.13 (0.04)	0.43 (0.17)
Keratoconus,[24,25] μm	0.72 (0.35)	2.24 (1.22)

Mean (standard deviation) higher order RMS for subjects with Down syndrome (DS) and controls compared to previously published values for individuals with keratoconus. Note that the values reported from the present study represent 3rd- through 10th-order measures, whereas the 4-mm pupil values for keratoconus represent 3rd- and 4th-order measures[25] and the 6-mm pupil values represent 3rd-, 4th-, and 5th-order measures.[24]

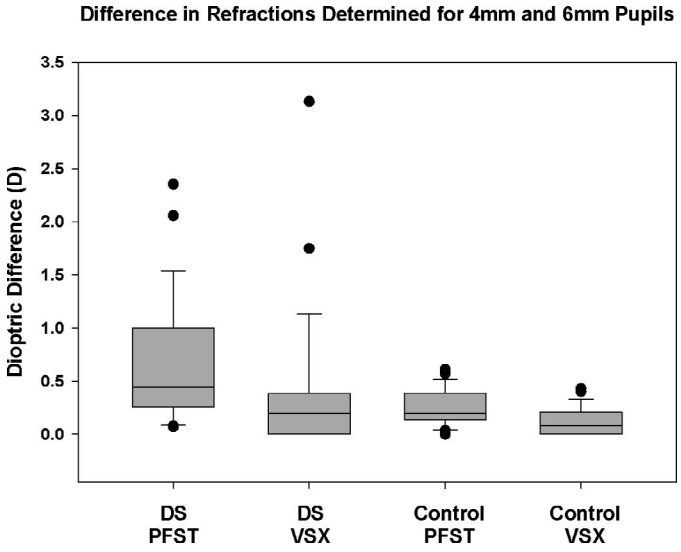

Figure 2. Dioptric difference in refractions determined with a 4-mm pupil diameter versus a 6-mm pupil diameter by group (Down syndrome [DS] versus control) and metric optimized (PFSt versus VSX).

Table 2. Reduction in Acuity from Baseline

	PFSt (Letters Lost)		VSX (Letters Lost)	
Group	4 mm	6 mm	4 mm	6 mm
Subjects with DS	7.7 ± 4.2	12.5 ± 6.1	5.5 ± 2.0	10.2 ± 3.4
Controls	4.3 ± 1.9	7.6 ± 2.8	3.8 ± 1.7	6.8 ± 2.3

Average and standard deviation of letters lost for PFSt and VSX for 4-mm and 6-mm pupil diameter in both controls and subjects with Down syndrome (DS).

between subject group and the metric used ($f = 0.48$, $P = 0.47$).

Predicted Acuity Performance

Acuity data for this analysis were obtained from controls without DS reading charts produced to represent the retinal image quality from measured eyes of individuals with DS. Each chart was read by five control observers, and the resultant performance was averaged across observers for each chart. Analyses incorporating main effects interacting with observer did not suggest any inconsistencies across observers. Observer reliability in assessing acuity of aberrated charts was found to be high (above 90%). Specifically, we found that variability explained by observer was 2.9% in an unconditional variance component multilevel model after accounting for subject level, pupil size, and metric.

Acuity data were analyzed as letters lost compared to acuity on a clear, unaberrated chart (termed baseline acuity), with greater letters lost representing worse acuity (Fig. 3; Table 2). The acuity drop from baseline was greater when comparing performance for a 4-mm pupil versus a 6-mm pupil for charts representing DS eyes (6.5 letters vs. 11 letters [0.09 logMAR difference; 95% CI, 0.07–0.11], $P < 0.0001$), as well as for charts depicting control eyes (4.5 letters vs. 8 letters [0.066 logMAR difference; 95% CI, 0.049–0.083], $P < 0.0001$). There was a significant interaction between group (DS versus control) and pupil size ($P = 0.03$) with charts representing DS eyes having more letters lost with increasing pupil diameter (4.5 letters) than the additional letters lost with increasing pupil diameter for charts representing control eyes (3.5 letters). In assessing the main effect of group, the acuity for charts representing eyes with DS had a significantly greater loss of letters (2.5 more letters lost [0.05 logMAR difference; 95% CI, 0.02–0.07]) than charts for control eyes ($P = 0.0002$). There was no statistically significant interaction between pupil diameter and metric ($P = 0.66$).

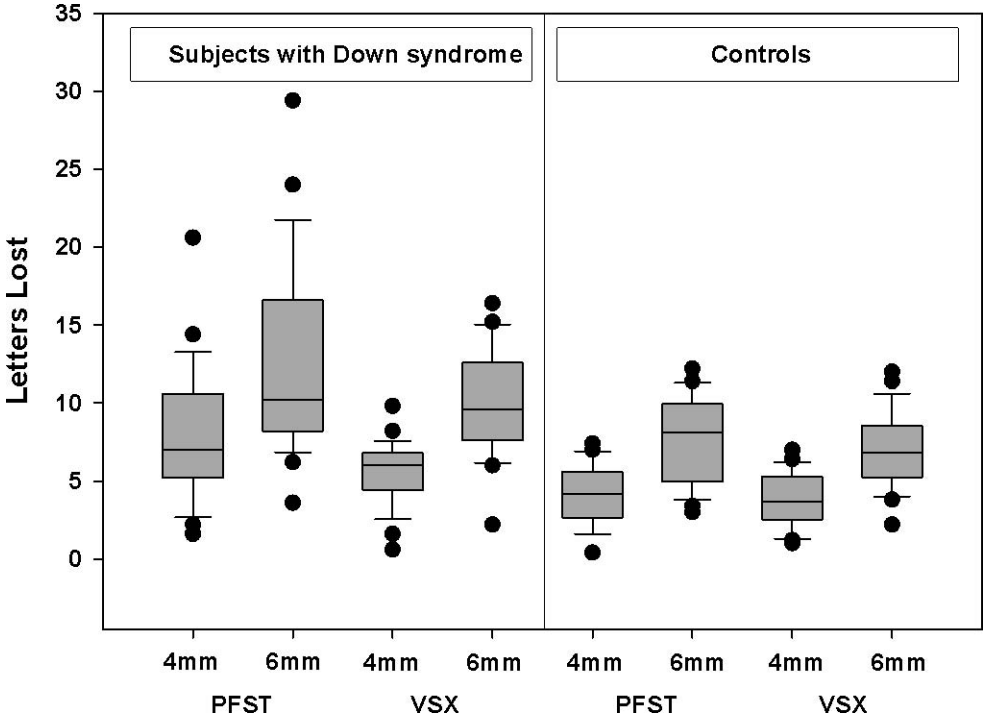

Figure 3. Relative acuity (letters lost compared to a baseline clear chart) for 4-mm and 6-mm pupil diameters for refractions determined with optimization of PFSt or VSX for controls and subjects with Down syndrome (DS).

Discussion

This study sought to quantify the impact of pupil diameter on the determination of refractions by using two different metric-optimized techniques. Refractions at 4-mm and 6-mm pupil diameters differed more for eyes of subjects with DS than controls; however, the differences in refractions were still relatively small, with 85% of refractions for DS eyes having differences less than 0.50 D when utilizing VSX. These findings are in line with reports of test-retest for subjective refraction of typical subjects with myopia reported by Raasch et al.[23] That study reported median test-retest of 0.20 D with 95% limits of agreement of 0.62 D for myopic adults.[23] The median and 95% limits of agreement for the present study was 0.28 D (1.23) for subjects with DS and 0.16 (0.31) for controls when combining both metric techniques. Although the 95% limits of agreement are larger for the DS eyes, the difference in refractions is more comparable to controls from both the present study and the Raasch study than the individuals with keratoconus reported in the Raasch et al.[23] study (0.75 D [6.01]). These findings are also consistent with the hypothesis that elevated higher order aberrations may negatively impact repeatability of refraction determination either through the subjective process or when pupil diameter is altered in an objective method. As shown in Table 1, the aberrations of the subjects with DS were slightly elevated compared to the controls but not approaching the levels previously reported for individuals with keratoconus. The pattern observed in the differences between refractions is of a similar magnitude as the pattern for differences in the magnitude of higher order aberrations for controls, patients with DS, and patients with keratoconus. An individual analysis of the two metric techniques found that the refractions differed more between pupil diameters for PFSt-optimized refractions than VSX-optimized refractions for both subjects with and without DS. Given that PFSt is a metric that specifically analyzes the WFE over the entire pupil diameter, giving equal weight to each tessellation analyzed, this outcome is not unexpected. VSX, by contrast, represents a more vision-related analysis of the wavefront without consideration of individual tessellations. Further inspection of the data also revealed that of the five individuals with DS having dioptric differences greater than 1 D between 4- and 6-mm derived refractions with PFSt, four of the individuals had spherical equivalent refractive error of −10.00 D or greater. In the control sample, there were no individuals with dioptric differences greater than 1 D, but also only one subject had a spherical equivalent refractive error of −10 D. The relationship between high myopia and the impact of pupil diameter on objective refractions optimizing PFSt may warrant further investigation. Despite these differences in identifying best refractions, metric was not a factor in the loss of acuity with increasing pupil diameter for a fixed refraction.

This study also sought to determine the acuity loss predicted to occur when a patient's natural pupil dilates from 4 mm to 6 mm while wearing a refraction determined from analysis of a 4-mm pupil diameter. Although the acuity change was statistically significantly greater for the eyes with DS, the overall decrease in acuity was only 4.5 letters (compared to a decrease of 3.5 letters for control eyes), and thus, the difference between groups is not clinically meaningful. The acuity drop predicted from the DS eyes was also the same as the test-retest of the Bailey Lovie-style acuity testing on control observers (4.5 letters) by using the same acuity system as in the present study and, thus, is not likely to be clinically meaningful even in isolation.[1]

Although pupil diameter may impact the resultant refraction identified from an objective metric optimization process, the differences occurring for 4-mm versus 6-mm diameters were within the test-retest variability of standard clinical refraction and thus do not create any less certainty in the endpoint in its utilization. We chose to evaluate the impact of increasing pupil diameter on visual acuity by applying the refraction determined at 4 mm, as we felt this moderate pupil diameter would most likely represent the pupil diameter experienced in typical room illumination. In using a 4-mm pupil diameter for refraction determination, acuity was not predicted to decrease beyond the repeatability of visual acuity testing, as individuals experience pupil dilation up to 6-mm diameter in their daily activities. As is typical with all refractive corrections, patients are predicted to perform worse in dim illumination whereupon the pupil dilates to a large diameter, but the detrimental effects for eyes of patients with DS is not predicted to be clinically worse than those without DS.

One limitation of this study is that only 4-mm and 6-mm pupil diameters were considered, and thus, the findings are not indicative of the impact of pupil diameters outside this range. However, the range of pupil diameters tested in this study is a reasonable estimation of the dynamic pupil range experienced by

nonpresbyopic adults in photopic conditions.[26] Smaller pupils of a 3-mm diameter could reasonably be expected but are likely to provide improvements in visual acuity[27,28] due to limiting the exposure to higher order aberrations, and pupil diameters greater than 6 mm are less likely to occur unless under dark viewing conditions for which the limited luminance would likely reduce acuity more substantially than any impact from exposure to higher order aberrations.[28] In moving forward with objective prescribing techniques, however, it may be best to customize the refraction determination to the individual subject's habitual pupil diameter in the examination room rather than applying a single common pupil diameter to all.

Conclusions

This study found that metric-optimized objective refraction techniques are robust in the identification of refractions for typical adults and adults with Down syndrome in that pupil diameter does not impact the refraction identified beyond the repeatability of clinically utilized subjective refraction techniques. In addition, for a given refraction, the acuity loss with increasing pupil diameter did not exceed that of the repeatability of acuity for administration of the acuity test over time.

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