Published in final edited form as:

Clin Exp Optom. 2009 May ; 92(3): 246–252.

Detecting Significant Change in Wavefront Error: How long does it take?

Darren E. Koenig, OD¹, Raymond A. Applegate, OD, PhD, FAAO¹, Jason D. Marsack, PhD¹, Edwin J. Sarver, PhD², and Lan Chi Nguyen, MS¹

¹Visual Optics Institute, College of Optometry, University of Houston, Houston, TX 77204

²Sarver and Associates, Inc., Carbondale, IL 62902

Abstract

Purpose—Measurement noise in ocular wavefront sensing limits detection of statistically significant change in high-order wavefront error (HO WFE). Consequently, measurement noise is problematic when trying to detect progressive change in HO WFE. Our aim is to 1) determine the necessary amount of time to detect age-related change in HO WFE given measurement variability and HO WFE composition and magnitude and 2) minimize the length of time necessary to detect change.

Methods—Five subjects with 0.26 to 1.57 micrometers root mean square HO WFE (HO RMS) over a 6 mm pupil were measured 12 times in 10–15 minutes using a custom Shack-Hartmann wavefront sensor. Each individual's standard deviation of measures was used to calculate the 95% confidence interval around their mean HO RMS. Data previously reported on the rate of change in the HO RMS due to normal aging and pupil diameter was used to calculate time to detect change exceeding this interval given measurement variability.

Results—Single measurements limit statistical detection to a range of 8 to 30 years. Increasing the number of WFE measurements per visit decreases time to detection (e.g., 7 measurements reduce the range to 3 to 14 years). The number of years to detect a change requires consideration of the subject's measurement variability, level and distribution of aberrations and age. Uncertainty in locating pupil centre accounts for $39 \pm 8\%$ of the total variability.

Conclusions—The ability to detect change in HO WFE over a short period of time due to normal aging is difficult but possible with current WFE measurement technology. Single measurements of HO WFE become less predictive of true HO WFE with increasing measurement variability. Multiple measurements reduce the variability. Even with proper fixation and instrument alignment, pupil centre location uncertainty in HO WFE measurements is a nontrivial contributor to measurement variability.

Keywords

wavefront error; wavefront error variance; aging; longitudinal studies; pupil centre; Zernike expansion

Corresponding Author: Darren Koenig, OD, Visual Optics Institute, College of Optometry, University of Houston, 4901 Calhoun Road, Houston, TX 77204-2020, Phone: (713)-743-5221, Fax: (713)-743-2053, DKoenig@optometry.uh.edu.

Notes: Submitted for consideration as part of the call for papers for the feature on clinical applications of wavefront optics.

Conflicts of interest: None

Introduction

In cross-sectional studies, the high-order wavefront error (HO WFE)^{1, 2} has been shown to increase with age³⁻⁷ and with increasing pupil diameter.⁸⁻¹⁴ When average root mean square HO WFE (HO RMS) by decade is plotted against age and pupil size, a plane is defined which is well fit ($R^2 = 0.995$) by the formula:¹⁵

$$\log \text{HO RMS} = 0.0063 * \text{Age} + 0.2374 * \text{pupil diameter} - 2.1223 \quad \text{eq. 1}$$

This relationship can be used to estimate the average expected change in HO RMS for any given pupil size for any time period of interest in any age range of interest between the ages of 20 and 80 years. For example, this data suggests that a 60 year old with a 6mm pupil can, on average, expect to see their HO RMS increase by 0.007 micrometers between the ages of 60 and 61 and by 0.075 micrometers by age 70. For younger eyes the anticipated typical change would be less. Regardless of the age group of interest, these are small changes and are near the measurement noise limits of wavefront sensors.¹⁶ Here we use data from multiple measurements on subjects spanning a range of HO RMS to estimate how long each individual would have to be followed to detect a statistically significant difference relative to the average increase of HO RMS predicted by eq. 1. This is of particular importance when the goal of a longitudinal study is to identify individuals with a progressing optical condition (e.g., cataracts or keratoconus). In the discussion we explore ways to reduce the time to detection of statistically significant changes.

Methods

Subjects

Testing was performed on one eye of five different subjects. Subjects were selected to span a large range of HO WFE over a 6mm pupil. Subject ages are 38, 59, 59, 55 and 33 years with corresponding HO RMS of 0.26 ± 0.03 , 0.35 ± 0.06 , 0.50 ± 0.03 , 0.63 ± 0.06 , and 1.57 ± 0.09 micrometers respectively (averages and standard deviations based on 12 measurements). Subjects 2, 3 and 4 were chosen from the Longitudinal Cataract Study to represent the lower 25th percentile, the 50th percentile and the upper 25th percentile among the population of 50 to 80 year old subjects currently enrolled in that study. Subjects 1 and 5 were chosen to extend the range of HO RMS. Subject 5 has keratoconus and the highest HO WFE. The study followed the tenets of the Declaration of Helsinki, was approved by the Institutional Review Board of the University of Houston and each subject signed an informed consent.

Wavefront sensing

WFE was measured 12 times over a 10 to 15 minute interval on one eye of each subject using a custom Shack-Hartmann wavefront sensor. The design of the Shack-Hartmann wavefront sensor has been described in detail in prior literature.¹⁷ Briefly, the wavefront sensor consists of a micro lenslet array with 400 μm spacing between square lenslet centres and a focal length of 24 mm. A superluminescent diode with a wavelength of 835 nm forms a point source on the retina which is then diffusely reflected back through the pupil of the eye as a wavefront bearing the aberrations of the eye. The lenslets, which are conjugate with the entrance pupil of the eye, sample the wavefront discretely and form a Shack-Hartmann spot image on a CCD camera (Figure 1). The slope of the wavefront (in x and y) over each lenslet is extracted from the Shack-Hartmann image and used to calculate the wavefront error which is fit with a normalized Zernike expansion through the 10th radial order according to the ANSI Z80.28 standard.¹

The uncorrected eye fixated the SLD probe beam focused at optical infinity. Measurements were taken in the dark and the non-test eye was unoccluded. Tropicamide 1% and phenylephrine hydrochloride 2.5% ophthalmic solutions were used for dilation and to minimize accommodation. Subjects were uncorrected during WFE measurements and a standard chin and forehead rest was used for stabilization. Measurement variability was further reduced by using the same operator and the same instrument for the repeated WFE measurements. This is not always practical in a longitudinal study, wherein the measurement variability will be higher and the probability of detecting subtle changes in HO WFE will be lower.

Data analysis

The mean, variance and standard deviations of the HO RMS over a 6mm pupil were calculated for each subject. To determine how long it would take to detect a change, the standard deviation of the repeat measures for each subject was used to determine the conservative two-tailed 95% confidence limits to their individual mean total HO RMS (confidence interval = HO RMS mean $\pm$ 1.96 SD). The upper half of the confidence interval (1.96*SD) and the expected incremental change in HO RMS at a given pupil diameter (here 6mm) derived from equation 1 were used to calculate the number of years to detect change as expressed in eq. 2 below.

To determine the number of years (here x) to detect a change in aberration for a given subject at a given pupil diameter (PD) and with SD as an estimate of the standard deviation of repeat measures (SD is assumed to remain stable over time):

$$x = \frac{\log(1.96 * SD * 10^{(-0.0063 * Age - 0.2374 * PD + 2.1223)} + 1)}{0.0063} \quad \text{eq. 2}$$

The rate of change in HO RMS is most likely greater for an individual with keratoconus than a normal and the rate of change for subject 5 is not expected to be predicted from eq. 1. We use this eye (subject 5) as an example of a highly aberrated eye for illustration purposes only to demonstrate that as between measurement variability increases so does the time to detect a change.

Results

The mean, variance and standard deviation for the HO RMS for each subject is presented in Table 1. To explore the source of the measurement to measurement variation in the HO RMS, a similar analysis was performed on each type of aberration in the 3rd and 4th radial orders. In Table 2 the mean, variance and standard deviation is reported for each aberration type in the 3rd radial order. Table 3 reports similar data for the 4th radial order. For comparison of variability across multiple measurements the low or 2nd radial order WFE is presented in Table 4. The effect of measurement variability in higher order aberrations on lower order aberrations is described in the discussion.

Using these data along with the expected rate of change in HO RMS calculated from eq. 1 appropriate for each subject's age, the length of time necessary to detect a change in HO RMS relative to normal aging with 95% confidence is presented in Table 5.

Single measurements of wavefront error may not accurately reflect the true wavefront error at any one point in time. The uncertainty that any one measurement accurately reflects the WFE at any moment in time increases with measurement variability. Therefore, change in HO RMS in normal aging cannot be detected in a reasonable amount of time (say 3 to 5 years) using this custom built wavefront sensor from a single measurement. In the discussion we present strategies to shorten the amount of time necessary to detect change.

Discussion

The ability to detect change over time is negatively affected by measurement noise. The inability to detect change in a short amount of time, as described above, is based on the assumption that only one WFE measurement is taken at any point in time. The accuracy with which an individual's HO RMS is estimated in any one session can be improved by using an average of several measurements as the best estimate of the HO RMS. This assumes that the individual sources of measurement noise provide only random fluctuations around the true value of the parameter being measured (here HO RMS and/or individual components of the higher order aberrations). This is a reasonable assumption for instrument-generated noise such as uncertainty in the location of the pupil center. It is not as reasonable for measurements taken at different time intervals after a blink.^{18, 19} Factors such as tear film deterioration increasing with time after a blink should be controlled for in order to improve the quality of measurements. Assuming confounding factors such as this are controlled for, another benefit of averaging multiple measurements is that multiple measurements reduce the time to detect a change by decreasing the 95% confidence interval depending on the number of samples (n). For averaging n HO RMS measurements the two-tailed 95% confidence interval = HO RMS mean $\pm$ 1.96 SD / $\sqrt{n}$, where n equals the number of averaged WFE measurements necessary to reduce both the confidence interval and the time to detect a significant change in HO RMS WFE. Table 6 displays the number of measurements that would be necessary to detect in 3 years the change predicted by aging for each of these 5 subjects.

To determine the number of WFE measurements (here n) to average to detect a change in x number of years for a given subject at a given pupil diameter (PD) and with SD being an estimate of the standard deviation of repeat measures (SD is assumed to remain stable over time):

$$n = \left(\frac{1.96 * SD * 10^{(-0.0063 * Age - 0.2374 * PD + 2.1223)}}{10^{(0.0063 * x)} - 1} \right)^2 \quad \text{eq. 3}$$

Variations in how well the S/H spot image defines the true pupil centre from measurement to measurement add variance to any given WFE measurement. This variance in the estimation of the true pupil centre has predictable consequences. For example, assume an eye has positive spherical aberration (as typical normal eyes do).^{20, 21, 22} If the S/H spot image identifies the pupil as being slightly displaced from the true pupil centre, then all Zernike modes in lower orders will be altered depending on the amount of spherical aberration (C_4^0) as well as on the direction and magnitude of the pupil centre displacement. In general, WFE in each radial order will load into lower radial orders. Given that the majority of the HO RMS resides in the 3rd and 4th radial orders,^{20, 21, 22} it is most important to consider the magnitude of the 4th radial order WFE that is being displaced into the 3rd radial order. Therefore, in the normal eye one expects that uncertainty in the pupil centre location will create variability principally in trefoil and coma. To explore whether the largest source of variation in repeat measures of HO RMS is due to variation in trefoil and coma, we regressed HO RMS for the 12 measurements for each subject against the HO RMS due to each radial order of aberration (3rd through 10th). It is expected that the 3rd radial order will account for the largest amount of variation in the total HO RMS.

Figure 2 displays the regression of total HO RMS against HO RMS due to the 3rd radial order WFE of subject 3. The coefficient of determination (R^2) for the regression is 0.93 revealing that 93% of the variance in total HO RMS is due to variance in the 3rd radial order. It is important to note here that the high coefficient of determination is not due to the magnitude of the 3rd radial order WFE relative to the other radial orders. It is due to the direction of change of the

3rd radial order WFE relative to the direction of change of HO RMS from measurement to measurement.

Figure 3 displays a bar graph of the coefficients of determination obtained by regressing total HO RMS against the HO RMS from each radial order (3rd through 10th) for the 12 measurements of each of these five individuals. As can be seen in Figure 3, the 3rd radial order aberrations of trefoil and coma account for a majority of the variance in total HO RMS during repeated measures suggesting that uncertainty in the pupil centre is adding significant variance to measurements.

To further evaluate how much of the variation in the 12 measurements can be attributed to the uncertainty with which the S/H image locates the pupil centre from measurement to measurement, we conducted a simulation experiment using the average measured HO RMS for each of the 5 subjects to explore variability of repeated measures due solely to variation in the determination of the pupil centre.

To understand pupil centre location uncertainty in S/H wavefront sensing, it is useful to understand that the spots in an S/H image (Figure 1) are typically used to define the pupil centre in lenslet space (the square grid of lenslets described in methods). The sampling of the pupil by individual lenslets is discrete (here sampling defined by the 400 micrometer separation of lenslet centres in lenslet space). Consequently, the uncertainty with which the pupil centre is located in the instrument is principally due to the lenslet spacing, which in our system allows the pupil centre to be mislocated up to ~ 200 micrometers.

The uncertainty in pupil centre location is modeled on the assumptions that the pupil centre between any two measurements can vary randomly by up to 200 μm in any direction and that the inherent underlying wavefront error at the true pupil centre remains stable. With these assumptions a custom program was developed that takes a Zernike expansion (here the average of 12 measurements) with a pupil diameter larger (here 7mm) than the pupil size of interest (here 6mm) with the wavefront error specified to the Nth radial order (here “N” is the 10th radial order) and computes a series of Zernike expansions whose origins are randomly shifted by a distance r (here between 0 and 200 micrometers), and an angle θ (here between 0 and 2π). The output Zernike expansions have the same number of radial orders, N , as the input Zernike expansion, but the new pupil diameter is reduced (here to 6mm) so that the extent of the shifted Zernike fit remains within the valid data region of the original Zernike defined over RMax. To calculate each output Zernike, a uniform grid of 1200 samples is taken over the input Zernike for each pupil centre shift and a least squares fit is performed to calculate the new coefficients. Here we sample 1000 new pupil origins for each subject.

As above, we regress total HO RMS as determined for each of the 1000 simulations against the HO RMS WFE present in each of the 1000 simulations due to the individual 3rd through 10th radial orders for each of the five subjects. Figure 4, like Figure 3, displays the coefficients of determination (R^2) derived from regressing total HO RMS against the WFE in each radial order.

As can be seen by comparing the coefficients of determination displayed in Figure 3 for real subject data to Figure 4, where the variation in WFE is due only to uncertainty in pupil centre location, the 3rd radial order is again the most highly correlated to total HO RMS for the five subjects.

Finally, using these data it is worth noting that we can estimate the amount of measurement variability due to the combined effects of alignment errors and actual changes in WFE due to short term variation in the optical properties of the eye (e.g., tear film instability). Because variances add, and assuming the factors contributing to variance are independent, the total

variance in repeated measures (total measurement variability) can be thought of as the sum of the variances of all factors contributing to measurement variability, known and unknown. We have described our measurement variability as consisting of at least 1) the variability in calculating pupil centres from the centres of the lenslets active in the determination of the wavefront error, 2) the variability due to alignment errors and 3) actual variation in the optical properties (e.g., variations in tear film). Assuming that the latter two factors are reasonably independent of the uncertainty in locating the pupil centre provides an upper bound to the estimate of the amount of variability contributed by alignment and actual optical factors combined. The percentage of measurement variability in the total HO RMS accounted for by simulated jitter is calculated by dividing the variance determined with the jitter program by the variance for the 12 measurements. This resulted in simulated jitter accounting for 31, 15, 37, 53 and 61% for each of the five subjects, respectively. Consequently, on average approximately $39 \pm 8\%$ of the HO RMS measurement variance is accounted for by jitter in the calculation of the pupil centre. The average total HO RMS measurement variance in our repeat measures study was $0.0032 \pm 0.001 \mu\text{m}^2$ and the amount accounted for by jitter was $0.0012 \mu\text{m}^2$. Utilizing the additive property of variance, the average amount of measurement variability attributable to the combined effects of subject alignment, physiological instabilities and any unknown sources of variance is $0.002 \mu\text{m}^2$ or about 61%.

The amount of measurement variance for total HO RMS for these five individuals is 0.0009, 0.0038, 0.0007, 0.0031 and $0.0075 \mu\text{m}^2$. The mean amount of HO RMS measurement variability is $0.0032 \pm 0.001 \mu\text{m}^2$. These amounts are greater than reported by Cheng et al. for similar experiments using the COAS wavefront sensor from Wavefront Sciences with a lenslet spacing of $144 \mu\text{m}$ and a magnification factor of 0.5 (effective sampling of the wavefront every $288 \mu\text{m}$ in the pupil plane).¹⁶ In this experiment, they report the variance at a similar time scale to be $0.0003 \mu\text{m}^2$ (~ 10-fold difference in the variance or 3-fold difference in the standard deviation of repeat measures).¹⁶ We attribute the majority of this difference to two factors. First we used eyes with considerably higher amounts of aberration and second, the sampling density of the lenslet array in the COAS system is higher and provides a better estimate of the pupil centre location.

Conclusions

Detecting changes in total HO RMS such as those due to the normal aging process over a short period of time (e.g., 3 years) is difficult but possible given current WFE measurement technology. However, single measurements in any one session are unlikely to provide useful data for monitoring change in the normal aging eye.

Averaging several measurements increases the ability to detect change over time. The number of measurements needed can be estimated by knowing the magnitude of change one wishes to detect and the variance in WFE for the population of interest. Reducing pupil centre uncertainty will reduce instrument measurement variance, thereby reducing the total variance. Pupil centre uncertainty can be reduced by improving the algorithms used to estimate the true pupil centre and increasing the sampling density of the pupil by employing high density lenslet arrays or a separate pupil monitoring camera.

Acknowledgments

Support: NIH/NEI R01 EY08520 (RAA); NIH/NEI P30 EY 07551 (Core Grant to the College of Optometry); Borish Endowment funding for the Chair of Optometry to (RAA)

Citations

1. American National Standards Institute. "Ophthalmics – Methods for reporting optical aberrations of the eye," ANSI Z80, 28-2004 (ANSI, 2004).
2. Thibos LN, Applegate RA, Schwiegerling JT, Webb R. Standards for reporting the optical aberrations of eyes. *J Refract Surg* 2002;18(5):S652–S660. [PubMed: 12361175]
3. Artal P, Berrio E, Guirao A, Piers P. Contribution of the cornea and internal surfaces to the change of ocular aberrations with age. *J Opt Soc Am A Opt Image Sci Vis* 2002;19(1):137–143. [PubMed: 11778716]
4. Calver RI, Cox MJ, Elliott DB. Effect of aging on the monochromatic aberrations of the human eye. *J Opt Soc Am A Opt Image Sci Vis* 1999;16(9):2069–2078. [PubMed: 10474888]
5. Guirao A, Gonzalez C, Redondo M, Geraghty E, Norrby S, Artal P. Average optical performance of the human eye as a function of age in a normal population. *Invest Ophthalmol Vis Sci* 1999;40(1):203–213. [PubMed: 9888445]
6. Guirao A, Redondo M, Artal P. Optical aberrations of the human cornea as a function of age. *J Opt Soc Am A Opt Image Sci Vis* 2000;17(10):1697–1702. [PubMed: 11028517]
7. McLellan JS, Marcos S, Burns SA. Age-related changes in monochromatic wave aberrations of the human eye. *Invest Ophthalmol Vis Sci* 2001;42(6):1390–1395. [PubMed: 11328756]
8. Artal P, Navarro R. Monochromatic modulation transfer function of the human eye for different pupil diameters: an analytical expression. *J Opt Soc Am A Opt Image Sci Vis* 1994;11(1):246–249. [PubMed: 8106911]
9. Campbell FW, Green DG. Optical and retinal factors affecting visual resolution. *J Physiol* 1965;181(3):576–593. [PubMed: 5880378]
10. Charman WN. Wavefront aberration of the eye: a review. *Optom Vis Sci* 1991;68(8):574–583. [PubMed: 1923333]
11. Charman WN, Jennings JA, Whitefoot H. The refraction of the eye in the relation to spherical aberration and pupil size. *Br J Physiol Opt* 1978;32:78–93. [PubMed: 737383]
12. Martinez CE, Applegate RA, Klyce SD, McDonald MB, Medina JP, Howland HC. Effect of pupillary dilation on corneal optical aberrations after photorefractive keratectomy. *Arch Ophthalmol* 1998;116(8):1053–1062. [PubMed: 9715686]
13. Venkateswaran K, Roorda A, Romero-Borja F. Theoretical modeling and evaluation of the axial resolution of the adaptive optics scanning laser ophthalmoscope. *J Biomed Opt* 2004;9(1):132–138. [PubMed: 14715065]
14. Wang Y, Zhao K, Jin Y, Niu Y, Zuo T. Changes of higher order aberration with various pupil sizes in the myopic eye. *J Refract Surg* 2003;19(2 Suppl):S270–S274. [PubMed: 12699188]
15. Applegate RA, Donnelly WJ 3rd, Marsack JD, Koenig DE, Pesudovs K. Three-dimensional relationship between high-order root-mean-square wavefront error, pupil diameter, and aging. *J Opt Soc Am A Opt Image Sci Vis* 2007;24(3):578–587. [PubMed: 17301847]
16. Cheng X, Himebaugh NL, Kollbaum PS, Thibos LN, Bradley A. Test-retest reliability of clinical Shack-Hartmann measurements. *Invest Ophthalmol Vis Sci* 2004;45(1):351–360. [PubMed: 14691194]
17. Liang J, Grimm B, Goelz S, Bille JF. Objective measurement of wave aberrations of the human eye with the use of a Hartmann-Shack wave-front sensor. *J Opt Soc Am A Opt Image Sci Vis* 1994;11(7):1949–1957. [PubMed: 8071736]
18. Himebaugh NL, Wright AR, Bradley A, Begley CG, Thibos LN. Use of retroillumination to visualize optical aberrations caused by tear film break-up. *Optom Vis Sci* 2003;80(1):69–78. [PubMed: 12553546]
19. Li XY, Yoon G. Changes in aberrations and retinal image quality due to tear film dynamics. *Optics Express* 2006;25:12552–12559. [PubMed: 19529690]
20. Porter J, Guirao A, Cox IG, Williams DR. Monochromatic aberrations of the human eye in a large population. *J Opt Soc Am A Opt Image Sci Vis* 2001;18(8):1793–1803. [PubMed: 11488483]
21. Thibos LN, Hong X, Bradley A, Cheng X. Statistical variation of aberration structure and image quality in a normal population of healthy eyes. *J Opt Soc Am A Opt Image Sci Vis* 2002;19(12):2329–2348. [PubMed: 12469728]

22. Wang L, Koch DD. Ocular higher-order aberrations in individuals screened for refractive surgery. J Cataract Refract Surg 2003;29:1896–1903. [PubMed: 14604708]

Figure 1.
A Shack/Hartmann (S/H) spot image for subject 1.

Figure 2.
Total HO RMS is regressed against 3rd radial order WFE for subject 3.

Figure 3.

Coefficients of determination (R^2) derived from regressing total HO RMS against the WFE in each radial order (3rd through 10th) for 5 subjects.

Figure 4.

Coefficients of determination (R^2) derived from regressing total HO RMS against the WFE in each radial order (3rd through 10th) resulting from randomly varying the location of the pupil centre using the average WFE for each of the 5 subjects presented above as the best estimate of the true wavefront error.

Table 1

Mean, variance and standard deviation of the HO RMS for each subject from one session of 12 measurements taken within 15 minutes.

Subject	HO RMS WFE		
	Mean	Variance	SD
1	0.2607	0.0009	0.0305
2	0.3482	0.0035	0.0589
3	0.5021	0.0007	0.0269
4	0.6313	0.0031	0.0556
5	1.5706	0.0075	0.0866

Mean, variance and standard deviation of the root mean square error in micrometers for components of the third radial order, coma (C_3^{-1} and C_3^1) and trefoil (C_3^{-3} and C_3^3), for each subject from one session of 12 measurements taken within 15 minutes.

Table 2

Subject	Coma			Trefoil		
	Mean	Variance	SD	Mean	Variance	SD
1	0.1158	0.0016	0.0395	0.1172	0.0005	0.0219
2	0.1644	0.0062	0.0788	0.1321	0.0019	0.0432
3	0.2178	0.0011	0.0327	0.3926	0.0005	0.0224
4	0.4519	0.0075	0.0866	0.1995	0.0010	0.0320
5	1.3489	0.0110	0.1049	0.5412	0.0030	0.0548

Mean, variance and standard deviation of the root mean square error in micrometers for components of the fourth radial order, tetrafoil (C_4^{-4} and C_4^4) and secondary astigmatism (C_4^{-2} and C_4^2) and spherical aberration (C_4^0), for each subject from one session of 12 measurements taken within 15 minutes.

Table 3

Subject	Tetrafoil			Secondary Astigmatism			Spherical Aberration		
	Mean	Variance	SD	Mean	Variance	SD	Mean	Variance	SD
1	0.0259	0.0001	0.0094	0.0782	0.0002	0.0138	0.1573	0.0003	0.0168
2	0.0470	0.0007	0.0258	0.0825	0.0006	0.0237	0.2099	0.0011	0.0325
3	0.1403	0.0004	0.0208	0.0547	0.0003	0.0181	0.0958	0.0003	0.0180
4	0.0933	0.0010	0.0321	0.0286	0.0003	0.0175	0.3562	0.0007	0.0257
5	0.1858	0.0008	0.0275	0.5078	0.0003	0.0177	0.1826	0.0007	0.0260

Mean, variance and standard deviation of the root mean square error in micrometers for components of the second radial order, defocus (C_2^0) and astigmatism (C_2^{-2} and C_2^2), for each subject from one session of 12 measurements taken within 15 minutes.

Table 4

Subject	Defocus			Astigmatism		
	Mean	Variance	SD	Mean	Variance	SD
1	0.2365	0.0010	0.0320	0.2166	0.0008	0.0288
2	4.9054	0.0053	0.0729	1.9447	0.0157	0.1252
3	0.9814	0.0008	0.0276	0.4138	0.0017	0.0417
4	0.3801	0.0071	0.0845	0.2008	0.0034	0.0580
5	2.4108	0.0482	0.2195	1.7699	0.0243	0.1558

Table 5

Time, in years, to detect a statistically significant change in HO RMS with 95% confidence for each subject, as determined from eq. 2 and rounded up to the next whole number of years.

Subject	Time to Detect a Significant Change Due to Normal Aging (Years)
1	11
2	16
3	8
4	16
5	30

Table 6

Number of WFE measurements necessary to reduce to 3 years the time to detect a statistically significant change in HO RMS relative to normal aging, as determined from eq. 3 and rounded up to the next whole number of measurements.

Subject	Number of WFE Measurements to Detect a Change in 3 years
1	15
2	31
3	7
4	31
5	140