Wavefront-Guided LASIK with the Zyoptix 3.1 System for the Correction of Myopia and Compound Myopic Astigmatism with 1-Year Follow-up

Clinical Outcome and Change in Higher Order Aberrations

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Objective: To assess safety, efficacy, predictability, stability, and change in aberrations after wavefront-guided LASIK for myopia and myopic astigmatism.

Design: Prospective, nonrandomized, self-controlled trial.

Participants: Wavefront-guided LASIK was performed in 97 eyes in a 1-year trial. Treated eyes had a mean subjective manifest spherical equivalent (SE) of -5.22 ± 2.07 diopters (D), with a range of -0.25 to -9.00 D of myopia and 0 to -3.25 D of astigmatism.

Intervention: After a microkeratome cut, a wavefront-based excimer ablation (Zyoptix 3.1) was performed. The full treatment to achieve emmetropia of an early nomogram provided by the system manufacturer was used in all procedures.

Main Outcome Measures: Safety, efficacy, predictability, and stability were evaluated at 1, 3, and 12 months postoperatively. Wavefront changes of higher order aberrations (HOAs) at 1 year were determined for pupil sizes of 3.5 and 6 mm.

Results: At 1 year postoperatively, uncorrected visual acuity (VA) was 20/20 or better in 83% of the eyes, and 20/40 or better in 98%. The mean subjective manifest SE at 1 year was -0.25 ± 0.43 D; it was within 0.50 D in 77% and within 1.0 D in 95%. No eye lost ≥ 2 lines of best spectacle-corrected VA (BSCVA) at 1 year postoperatively; 40 eyes gained 1 line of BSCVA, and 5 eyes gained 2 lines. The total HOA root mean square (RMS) increased on average by a factor of 1.23 ± 0.57 with a 3.5-mm pupil; for the 6 mm pupil, the increase factor was 1.52 ± 0.36. No change or reduction in the total HOA RMS was observed in 45.5% of the eyes for a 3.5-mm pupil and in 20.6% for a 6-mm pupil. There was a significant increase of primary spherical aberration (*Z 4,0*) by a factor of 4.11 ± 10.17 for 3.5-mm pupils and 4.31 ± 6.76 for 6-mm pupils.

Conclusions: Wavefront-guided LASIK using Zyoptix 3.1 is an effective and safe procedure for the treatment of myopia and myopic astigmatism. Although in close to half of the eyes HOAs could be reduced, there was still undercorrection and induction of HOAs with the algorithm employed. *Ophthalmology 2004;111:2175–2185 © 2004 by the American Academy of Ophthalmology.*

LASIK has become the dominant procedure to correct refractive errors worldwide. Numerous technological developments, such as flying-spot lasers, eye trackers, and modern microkeratomes, have improved the clinical outcome.[1] The advent of wavefront measurement technology enabled the quantification of ocular aberrations.[2] Experience with adaptive optics from astronomy led to the concept of correction of ocular higher order aberrations (HOAs) by excimer laser surgery. Wavefront-guided ablation should improve the image quality of the eye and, therefore, improve visual acuity (VA), as observed with adaptive optics.[3] Reports of single cases treated with wavefront-based algorithms reaching a VA of 20/10 and better raised the hope of further improving the visual outcome of refractive corneal laser surgery.[4] Only a few studies addressing the outcome of

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Table 1. Patient Demographics

	Mean ± SD	Range	n (%)
Preoperative SE (D)	−5.22 ± 2.07	−1.0 to −9.5	
Preoperative sphere (D)	−4.76 ± 2.12	−0.25 to −9.0	
Preoperative cylinder (D)	−0.93 ± 0.69	0 to −3.25	
Age (yrs)	38 ± 8.72	22–62	
Eyes			50 (51.5%) right 47 (48.5%) left
Gender			63 (64.9%) female eyes 34 (35.1%) male eyes

D = diopters; SD = standard deviation; SE = spherical equivalent.

wavefront-guided LASIK with a reasonable follow-up and investigating the change in ocular HOAs have been published in the peer-reviewed literature.[5–7]

The purpose of this study was to assess safety, efficacy, predictability, stability, complications, and change in aberrations after wavefront-guided LASIK for myopia and astigmatism using a Hartmann–Shack wavefront-based excimer laser treatment (Zyoptix, Bausch & Lomb/Technolas, Munich, Germany).[8] Zyoptix is a system for customized ablation that incorporates the Zywave Hartmann–Shack aberrometer coupled with the Orbscan IIz multidimensional corneal topographer, which generates the individual ablation profiles to be used with the Technolas 217 Excimer Laser system.

Patients and Methods

Study Design and Participants

Ninety-seven myopic or myopic–astigmatic eyes of 51 healthy individuals with a mean age of 38±8.72 years (range, 22–62) were consecutively included in this prospective study between March and June 2001 (Table 1). Patients with a history of eye diseases, ocular surgery, morphologic eye abnormalities, and systemic affections like wound-healing disorders or autoimmune diseases were excluded. The mean sphere was −4.76±2.12 diopters (D) (range, −0.25 to −9.50), and the mean cylinder was −0.93±0.69 D (range, 0 to −3.25). All patients were informed about the surgical and study procedures and gave consent. A review by the ethics committee was not required for this study. Ninety-four eyes (96.9%) were examined after 1 month, 68 (70.1%) after 3 months, and 81 (83.6%) after 1 year. Of these 81 eyes, a subset of 68 was available for postoperative wavefront measurements in mydriasis. All preoperative and postoperative wavefront data were taken from this patient subgroup.

Preoperative Examination

Preoperative evaluation included manifest refraction, biomicroscopy of the anterior and posterior segments, applanation tonometry, partial coherence interferometry for axial length measurement (IOL Master, Zeiss, Jena, Germany), keratometry (IOL Master), slit scanning tomography (Orbscan IIz, Orbtek/Bausch & Lomb, Munich, Germany), infrared pupillometry (Colvard, Oasis Medical, Glendora, CA), and ultrasonic pachymetry (Omega, Storz/Bausch & Lomb Surgical, Heidelberg, Germany). None of these measurements revealed any finding that led to exclusion for myopic LASIK treatment. Visual acuity measurements were performed using high-contrast optotypes (Rodavist optotype projector, Rodenstock, Munich, Germany) at a test distance of 5 m.

Wavefront Measurements, Treatment Planning, and Excimer Device

Soft contact lenses were discontinued for at least 1 week and rigid lenses for at least 2 weeks before preoperative evaluation. Three different Orbscan IIz maps were taken, and the one featuring the least eye movements was used. The maximum movements considered acceptable were 200 μm. Preoperative and postoperative wavefront measurements were performed with a Hartmann–Shack wavefront sensor (Zywave,[9] Bausch & Lomb/Technolas, Munich, Germany). The Zywave uses a 780-nm laser beam and an array of up to 78 lenslets. Zywave examinations were done with (1) a single examination with an undilated pupil and (2) 3 examinations with a dilated pupil (noncycloplegic, using 10% phenylephrine drops [Neosynephrin-POS, Ursapharm, Saarbrücken, Germany]). Patients were asked to look at the distant fixation target. Three consecutive measurements were performed, and the measurement with best alignment and highest concordance to the subjective refraction data was chosen for treatment, as recommended by the manufacturer (Bausch & Lomb/Technolas). Treatment files were generated from wavefront data using the software[10] provided by the manufacturer. The preset optical zone (OZ) diameter equaled at least the largest scotopic pupil size, as determined by Colvard infrared pupillometry. The mean OZ diameter was 6.77±0.63 mm (range, 5.6–8.5). The mean ablation depth, as provided by the software, was 98 μm (range, 38–145).

Surgical Procedures and Postoperative Treatment

Corneas were anesthetized with oxybuprocaine eydrops (Novesine, Ciba Vision, Großostheim, Germany). A superior-hinged flap 8.5 or 9.5 mm in diameter was created using the Hansatome (Bausch & Lomb, Munich, Germany) with the conventional 160-μm head. Tissue ablation was performed with the Technolas 217z excimer laser (Technolas/Bausch & Lomb) using a wavefront-guided ablation algorithm (Zyoptix, version 3.1). Postoperative standard medication consisted of ofloxacine eyedrops (Floxal, Mann Pharma, Berlin, Germany) and fluorometholone eyedrops (Efflumidex, Pharm-Allergan, Ettlingen, Germany). Additionally, artificial tears containing hyaluronic acid (Hylo-Comod, Ursapharm) were prescribed. Patients were scheduled 1 day, 1 week, 1 month, 3 months, and 12 months after LASIK.

If there was overcorrection or undercorrection at the 3-month follow-up and patients wished an enhancement procedure, LASIK retreatment was performed by relifting the flap with a blunt spatula after topical anesthesia with oxybuprocaine eyedrops. Laser ablation was based on subjective refraction (cycloplegic refraction in case of hyperopia) and performed using a standard spherocylindrical algorithm (Planoscan V 2.9992). In case of retreatment, patients were excluded from the main patient collective.

Data Analysis and Statistics

All preoperative and postoperative VA and subjective manifest refraction data were stored in a database.[11] This program allows analysis of refractive surgery data according to the currently ac-

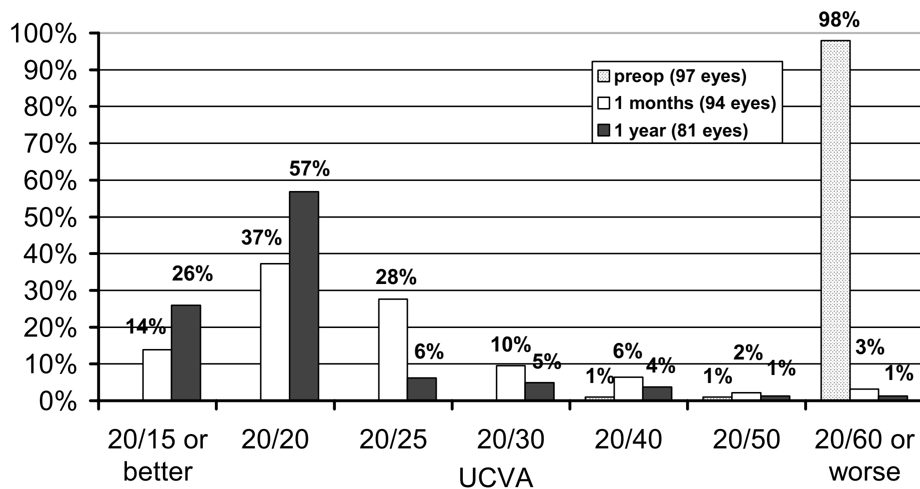

Figure 1. Distribution of uncorrected visual acuity (UCVA) preoperatively and 1 month and 1 year after wavefront-guided LASIK (efficacy).

cepted standard criteria.[8,12,13] Twelve months postoperatively, wavefront measurements were performed under maximal pupil dilation with 10% neosynephrine (Neosynephrin-POS) and 1 drop of tropicamide (Mydriaticum Stulln, Stulln Pharma, Stulln, Germany).

Wavefront errors were described using Zernike polynomials according to the VSIA (Vision Science and Its Applications) format for reporting ocular wavefront aberration data.[14] The effect of higher order wavefront aberrations on optical quality of the eye is known to depend on pupil size.[15,16] To study this effect and to assess the efficacy of the treatment for different conditions, we performed wavefront analysis for 2 virtual pupil diameters (3.5 and 6 mm) that resemble pupil size under photopic and mesopic conditions. Zywave[9] allows a Zernike approximation from second order to fourth order for 3.5-mm pupils and from second order to fifth order for 6-mm pupils. For analysis, data files were loaded into an Excel database[17] using CTView.[18]

The data were analyzed for (1) general changes of HOAs, (2) effects of pupil dilation on HOAs, and (3) predictability of the correction of HOAs. To analyze changes of wavefront data (postoperatively vs. preoperatively), a paired Wilcoxon test was applied. To describe the effects of pupil dilation on HOAs before and after wavefront-guided LASIK, we compared the preoperative and postoperative ratios of the HOA root mean square (RMS) measured over 6-mm and 3.5-mm pupils, referred to as the dilation-related increase factor ($DRIF_{HOA}$). To assess the predictability of the correction of HOAs, we performed linear regression analysis between preoperative HOA values and their change (Δ_{HOA}). The squared correlation coefficient (R^2), which reflects the scatter around the regression line, and the regression coefficient *b,* which equals the slope of the regression line, can be considered as predictability metrics for the HOA correction. The constant *a* of the regression equation is an indicator for bias (i.e., systematic overcorrection or undercorrection).

Results

Efficacy

Twelve months postoperatively, 81 eyes (83%) had an uncorrected VA (UCVA) of 20/20 or better (Fig 1). None of the examined eyes experienced supranormal VA of 20/12 or higher. The efficacy index (ratio of postoperative UCVA and preoperative best spectacle-corrected VA [BSCVA]) was 0.97.

Safety

Although at 1 month after surgery 4% still lost 2 lines of Snellen BSCVA, 1 year after surgery none of the examined eyes had lost >2 lines of BSCVA (Fig 2). Six eyes (6%) lost 1 line, 39 eyes (40%) gained 1 line, and a further 5 eyes (5%) lost 2 VA lines at 1 year. The safety index (ratio of postoperative and preoperative BSCVAs) at 1 year was 1.10.

Predictability

The mean postoperative spherical equivalent (SE) was -0.15 ± 0.46 D (range, 1.00 to -1.50) at 1 month and -0.25 ± 0.43 D (range, 0.63 to -1.63) at 1 year (Fig 3). At the final examination, 77 eyes (95%) were within 1 D of the aimed refractive change and 62 (77%) were within 0.5 D (based on SE). In this study, 58% of the eyes were $\leq$0.5 D and 93% of the eyes $\leq$1.0 D in defocus equivalent ($|sphere| + 0.5\ |cylinder|$).[19]

Stability

The change of mean SE between the 1- and 3-month examinations was -0.07 D and -0.03 D between 3-month and 1-year results (Fig 4). The overall regression from 1 month to 12 months was -0.1 D.

Retreatments

Three months after LASIK, 8 patients desired retreatment due to overcorrection or undercorrection. These patients were excluded from the main collective. Two eyes were overcorrected (SE, 1.38 and 1.13 D), 6 eyes were undercorrected (mean SE, -1.02 ± 0.31 D [range, -0.5 to -1.38]). Six months after retreatment, the overcorrected eyes had SEs of -0.88 and -0.5, respectively; the undercorrected eyes had a mean SE of -0.31 ± 0.27 D (range, 0 to -0.75). None of the eyes treated lost a line of BCVA.

Complications

No intraoperative complications occurred in the study population. In 7 eyes, peripheral epithelial defects occurred, which all healed

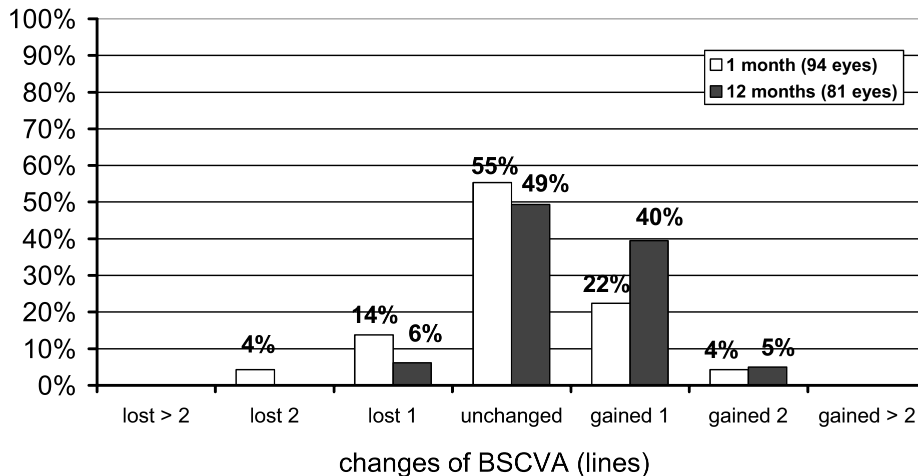

Figure 2. Changes in best spectacle-corrected VA (BSCVA) 1 month and 1 year after wavefront-guided LASIK (safety).

within 1 week. In the early postoperative period, 17 eyes showed a faint peripheral infiltrate (diffuse lamellar keratitis stage 1); in 4 eyes, stage 2 diffuse lamellar keratitis was observed. All cases of diffuse lamellar keratitis were successfully treated by topical steroids, and no surgical intervention was necessary. One week after LASIK, all infiltrates had resolved. No other complications occurred during the 12-month study period.

Higher Order Wavefront Aberrations

General Changes. The mean preoperative total HOA RMS was 0.093±0.032 μm for the 3.5-mm pupil and 0.395±0.134 μm for the 6-mm pupil (Table 2). The mean total higher order wavefront error increased by a factor of 1.23 to 0.108±0.05 μm ($P<0.05$) and by a factor of 1.52 to 0.571±0.244 μm after 12 months, respectively ($P<0.001$). For a 3.5-mm pupil we found in 45.6% of the eyes no change or reduction of the total HOA RMS; when measured with a 6-mm pupil, only 20.6% of the eyes experienced no change or reduction of the HOA RMS. Further details are shown in Figure 5 and Tables 3 and 4. The mean RMS of third order aberrations showed a slight increase, at both 3.5 and 6 mm, but these changes were not statistically significant (Table 2). Also, the rate of eyes with no change or reduction of third order RMS was similar for measurements at a virtual pupil diameter of 3.5 or 6 mm (42.6% and 39.7%, respectively). The mean fourth order RMS showed only a small increase for 3.5-mm pupils ($P>0.05$) but doubled when measured over a 6-mm pupil ($P<0.001$). Inversely, the fraction of eyes that showed reduction or at least no change in fourth order aberrations dropped from 38.2% to 17.6% when the analysis diameter was increased from 3.5 to 6 mm. Due to its dominance in post-LASIK eyes, we evaluated primary spherical aberration (*Z 4,0*) separately. This aberration almost doubled at 3.5 mm ($P<0.005$) and tripled at 6 mm, compared with baseline ($P<0.001$). The percentage of eyes with reduction or no change of

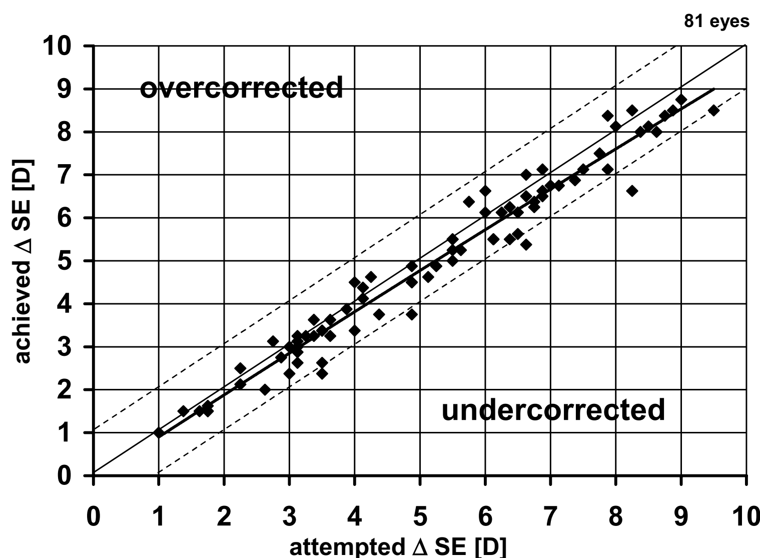

Figure 3. Attempted versus achieved change of spherical equivalent (Δ SE) 1 year after wavefront-guided LASIK (predictability). D = diopters.

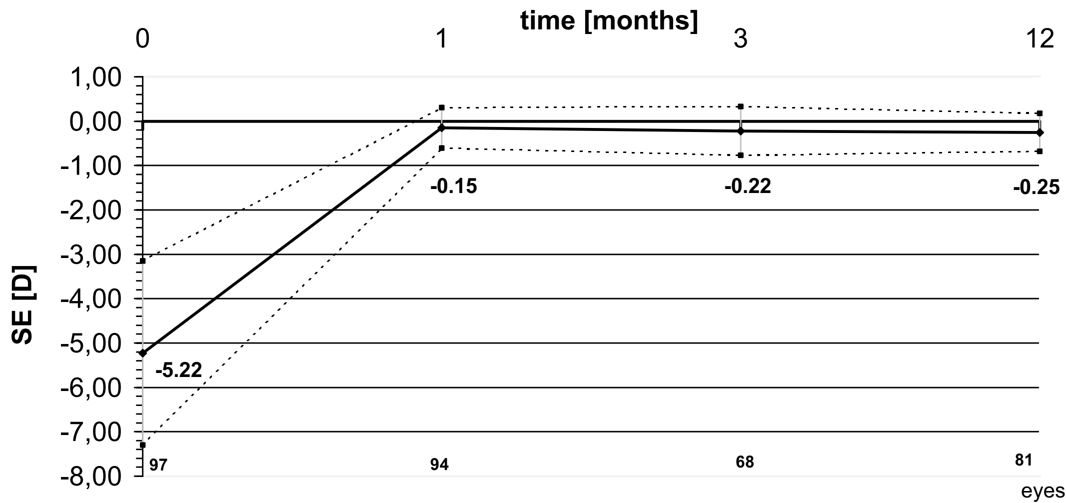

Figure 4. Time course of the manifest subjective refraction (spherical equivalent [SE]) after wavefront-guided LASIK (stability). D = diopters.

Z 4,0 was 33.8% in the 3.5-mm pupil group. Moreover, only 10.3% of the eyes experienced no change or reduction for a 6-mm pupil. Fifth order aberrations, as measured for a 6-mm pupil diameter, showed a small mean increase after LASIK; in nearly one third (32.4%) of the eyes, the fifth order RMS was reduced or showed no change.

Effects of Pupil Dilation on Higher Order Aberrations. The mean preoperative total HOA RMS, measured at a 6-mm analysis diameter, was 4.52-fold higher than the total HOA RMS measured at 3.5 mm. Twelve months after LASIK, we found a ratio of 5.93. Thus, $DRIF_{HOA}$ increased by a factor of 1.4 after LASIK ($P<0.001$). For third order aberrations, we found only a small mean increase of $DRIF_{HOA3}$ by a factor of 1.18, which did not reach statistical significance ($P = 0.806$; Table 5). Compared with $DRIF_{HOA}$ and $DRIF_{HOA3}$, $DRIF_{HOA4}$ was slightly higher preoperatively ($P>0.05$) but more than doubled after LASIK ($P<0.001$). The amount of primary spherical aberration (|*Z 4,0*|) showed the highest dependence on pupil diameter. Preoperative $DRIF_{|Z\ 4,0|}$ reached 14.51. Because of several outliers, the range of values was high (0.39–115), and this difference did not reach statistical significance compared with other preoperative DRIF values ($P>0.05$). Twelve months after LASIK, $DRIF_{|Z\ 4,0|}$ had increased on average by a factor of 4.65. Like preoperatively, an extreme range of values (0.36–488) could be noted. However, the increase of $DRIF_{|Z\ 4,0|}$ was statistically significant ($P<0.01$).

Predictability of Higher Order Aberration Changes. All postoperative changes of RMS wavefront error and primary spherical aberration (*Z 4,0*) were correlated negatively with the preop-

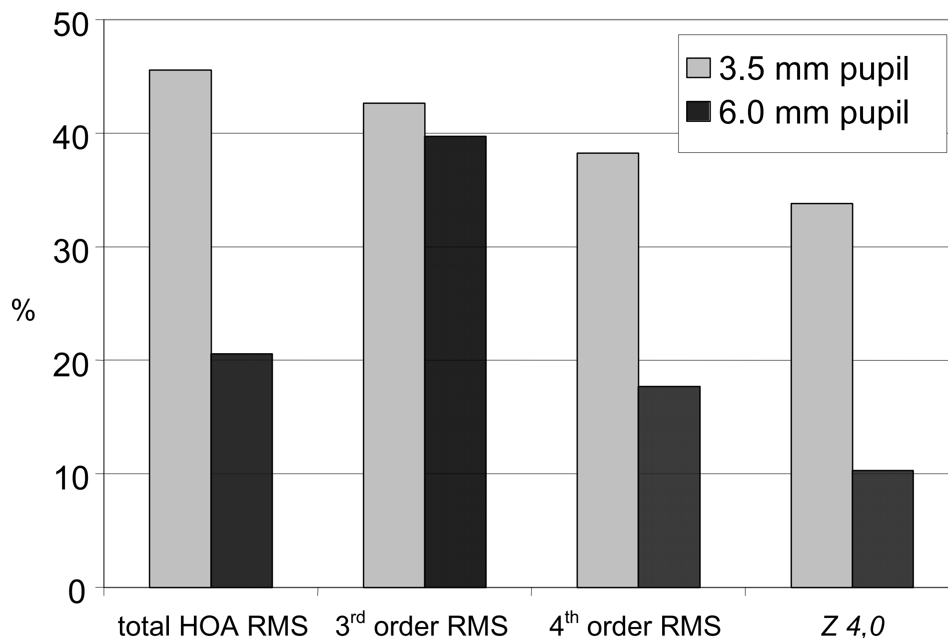

Figure 5. Percentage of eyes with reduction or no change in higher order aberrations (HOAs) for 3.5- and 6-mm pupil diameters. RMS = root mean square.

Table 2. Mean Changes of Higher Order

	Total HOA RMS		Third Order RMS	
	3.5 mm	6 mm	3.5 mm	6 mm
Preoperatively	0.093 ± 0.032	0.395 ± 0.134	0.078 ± 0.033	0.308 ± 0.141
12 mos postoperatively	0.108 ± 0.05	0.571 ± 0.244	0.092 ± 0.051	0.365 ± 0.197
Increase factor	1.23 ± 0.57	1.52 ± 0.63	1.34 ± 0.81	1.36 ± 0.83
P value	0.035	<0.001	0.058	0.244

RMS = root mean square.
All wavefront error values are in microns.
*Increase factors for primary spherical aberration (Z 4,0) reflect the mean increase of |Z 4,0|.

erative value. For a 3.5-mm pupil, the total HOA RMS and third order RMS showed only low correlation (total HOA: $R^2 = 0.05$, $b = -0.32$; third order: $R^2 = 0.09$, $b = -0.44$). The fourth order RMS and *Z 4,0* were slightly higher correlated (fourth order: $R^2 = 0.31$, $b = -0.70$; *Z 4,0*: $R^2 = 0.28$, $b = -0.55$) with preoperative values. All R^2 and b values, except for the third order RMS, were lower for 6-mm pupils (total HOA: $R^2 = 0.03$, $b = -0.31$; third order: $R^2 = 0.14$, $b = -0.53$; fourth order: $R^2 = 0.02$, $b = -0.3$; *Z 4,0*: $R^2 = 0.05$, $b = -0.31$). The fifth order RMS, which was only determined for 6-mm pupils, showed better correlation ($R^2 = 0.26$, $b = -0.63$) than all other HOAs. For all HOAs, the constant a was positive (data not shown). For 6-mm pupils it increased markedly compared with the 3.5-mm ones and was well correlated with the mean increase (Δ_{HOA}) of each order ($r = 0.86$).

Discussion

Clinical Outcome

In our institution, wavefront-guided LASIK using the Zyoptix system was introduced in January 2001. After an initial learning phase, the present study was initiated. Taking into account that a new laser algorithm may be less predictable, the outcome of the present data is encouraging. With our standard LASIK treatment using the same laser system, 51% reached a UCVA of ≥20/20; however, 83% after wavefront-guided ablation could achieve this visual outcome after 1 year.[1] This points out that the efficacy with an index of 0.97 was good, although none of the eyes reached a supranormal VA of 20/12 or higher. It should also be pointed out that VA values are highly dependent on the method of testing. When the threshold is defined as the steepest point of the psychometric function and rigorous forced-choice is applied, acuity values can be around 20/10, even in normal, physiologically aberrated eyes.[20] Compared with our results, other studies on conventional LASIK[21,22] or wavefront-guided LASIK[6,7] had similar outcomes. Interestingly, we observed a major gain of BCVA between 1 month and 1 year. This might be due to wound healing still unfinished at 1 month postoperatively or adaptation of the visual system (neuronal plasticity) to the new aberration pattern.[23,24] Also, predictability was good, as more than three quarters of the eyes (77%) were within the 0.5-D range in SE. However, there was still undercorrection in the case of myopia beyond −6.5 D (Fig 3). Compared with the standard LASIK treatments,[1,21,22] more patients were within 0.5 D or 1.0 D of emmetropia. Stability with a mean regression of −0.1 over 11 months was excellent for myopic corneal refractive surgery and was very much comparable to that of the standard LASIK procedure. No algorithm-specific complications (e.g., decentered ablation zones) could be observed. We have gained long-term experience with the standard LASIK procedure (Planoscan, Bausch & Lomb/Technolas) performed with the same laser (Keracor 217, Bausch & Lomb/Technolas).[1] Efficacy, predictability, and stability after 1 year were comparable to the present data; however, in the Planoscan group only 29% of the eyes experienced a gain in BCVA over 1 year, compared with 45% in the present study. This could be an effect of the wavefront-guided excimer ablation, but could also be an overall improvement of laser surgery over the last 3 years (e.g., increased surgical experience and quality or, in general, improved laser, algorithms, or eye trackers). Only a randomized prospective study comparing intraindividually standard and wavefront-guided ablation will provide a final answer.

Table 3. Distribution (Percentage) of Changes of Higher Order Aberrations (HOAs) for a 3.5-mm Pupil (Subgroup of 68 Eyes)

Δ_{HOA} (μm)	Total HOA RMS	Third Order RMS	Fourth Order RMS	Z 4,0
<−0.05	5.9	7.4	1.5	1.5
−0.05–0	39.7	35.3	36.8	32.4
0–0.05	32.4	35.3	60.3	61.8
0.05–0.1	16.2	16.2	1.5	4.4
0.1–0.15	4.4	4.4	0.0	0.0
>0.15	1.5	1.5	0.0	0.0

RMS = root mean square.

Table 4. Distribution (Percentage) of Changes of Higher Order Aberrations (HOAs) for a 6-mm Pupil (Subgroup of 68 Eyes)

Δ_{HOA} (μm)	Total HOA RMS	Third Order RMS	Fourth Order RMS	Z 4,0	Fifth Order RMS
<−0.2	4.4	7.4	0.0	2.9	2.9
−0.2–0	16.2	32.4	17.6	7.4	29.4
0–0.2	41.2	38.2	32.4	33.8	54.4
0.2–0.4	22.1	16.2	35.3	33.8	11.8
0.4–0.6	10.3	4.4	14.7	22.1	1.5
>0.6	5.9	1.5	0.0	0.0	0.0

RMS = root mean square.

Aberrations (HOAs, Subgroup of 68 Eyes)

Fourth Order RMS		Z 4,0*		Fifth Order RMS
3.5 mm	*6 mm*	*3.5 mm*	*6 mm*	*6 mm*
0.046 ± 0.019	0.216 ± 0.094	0.022 ± 0.024	0.158 ± 0.135	0.061 ± 0.028
0.052 ± 0.020	0.414 ± 0.189	0.032 ± 0.024	0.387 ± 0.203	0.073 ± 0.031
1.27 ± 0.66	2.26 ± 1.53	4.11 ± 10.17	4.31 ± 6.76	1.45 ± 1.17
0.060	<0.001	0.002	<0.001	0.002

Higher Order Wavefront Aberrations

General Changes. In 45.6% of the eyes treated, the HOA RMS could be reduced or remained unchanged when measured with a 3.5-mm pupil. For a 6-mm pupil, only 20.6% of the eyes experienced no change in or reduction of the HOA RMS. In the majority of eyes in this study, HOAs were induced, with a 3.5-mm pupil less than 0.05 μm (Table 3) and with a 6-mm pupil less than 0.2 μm (Table 4). Although for postoperative measurements an additional drop of tropicamide was used to accelerate mydriasis, we do not suspect any systematic errors affecting the results, as wavefront error changes due to accommodative microfluctuations seem to be negligible compared with the changes induced by LASIK.[25] Although third and fifth order (comalike) aberrations increased only moderately or could be reduced in one third of the eyes, a significant increase of fourth order (spherical-like) aberrations could be observed. The increase factor (ratio between postoperative and preoperative RMS values) reflects the change of a HOA with respect to its amount in the eye preoperatively. For the total HOA RMS and for comalike aberrations, mean increase factors ranged from 1.23 to 1.52, whereas spherical-like aberrations—namely, primary spherical aberration (*Z 4,0*)—increased more pronouncedly (Table 2). Spherical-like aberrations have been reported to be dominant in eyes after corneal refractive surgery for myopia.[16,26–29] The high standard deviations of the |*Z 4,0*| increase factors reflect that, in some eyes, preoperative *Z 4,0* was very low, sometimes near zero. Increase factors of the optical aberrations measured in the present study were similar to those reported by Mrochen et al 3 months after wavefront-guided LASIK with a different laser system[5] but were markedly lower compared with conventional LASIK.[28,29]

Effects of Pupil Dilation on Higher Order Aberrations. Optical performance was significantly better for 3.5-mm pupils than for 6-mm ones. The ratio of the HOA RMS measured over 6-mm and 3.5-mm pupils ($DRIF_{HOA}$) increased significantly after LASIK. Whereas the DRIF for third order aberrations ($DRIF_{HOA3}$) did not change significantly, $DRIF_{HOA4}$ and $DRIF_{Z\ 4,0}$ increased markedly after treatment. The amount of primary spherical aberration is known to be highly dependent on pupil size.[30] At smaller pupil sizes, corneal prolateness will not be recognized as spherical aberration but will be interpreted as defocus (Invest Ophthalmol Vis Sci ARVO E-abstract 2043, 2002; Invest Ophthalmol Vis Sci ARVO E-abstract 966, 2003). Our data show that the significant induction of spherical-like aberrations is more prevalent for larger pupil diameters. We could not find a similar effect for third order aberrations, which may be a result of either reduction or less induction. The mean preset OZ size of our cohort was 6.71±0.66 mm. In relation to the 6-mm analysis diameter, the mean (analysis) pupil/OZ ratio (pupil excess [Invest Ophthalmol Vis Sci ARVO E-abstract 2592, 2003]) was 0.90±0.09. In 92.8% of the eyes, the OZ diameter was at least as wide as the virtual pupil (6 mm). However, in only 20.6% of the eyes, HOAs were reduced when analyzed at 6 mm. These results and recent work on this subject (Invest Ophthalmol Vis Sci ARVO E-abstract 2592, 2003)[31,32] suggest that the effective OZ is smaller than the nominal value.

Predictability of Higher Order Aberration Changes. Linear regression analysis was performed to assess the predictability of the HOA reduction algorithm. For an ideal predictability, the regression coefficient *b* should be −1,

Table 5. Pupil Dilation-Related Increase Factors ($DRIF_{HOA}$s, Subgroup of 68 Eyes)

	Total HOA RMS	Third Order RMS	Fourth Order RMS	Z 4,0
Mean DRIF preoperatively	4.52 ± 1.57	4.46 ± 2.47	5.18 ± 2.50	14.51 ± 22.80
Mean DRIF 12 mos postoperatively	5.93 ± 3.10	4.51 ± 2.48	8.98 ± 5.12	27.17 ± 65.39
Mean increase of DRIF	1.40 ± 0.63	1.18 ± 0.72	2.22 ± 1.93	4.65 ± 8.04
P value	<0.001	0.806	<0.001	0.006

HOA = higher order aberration; RMS = root mean square.

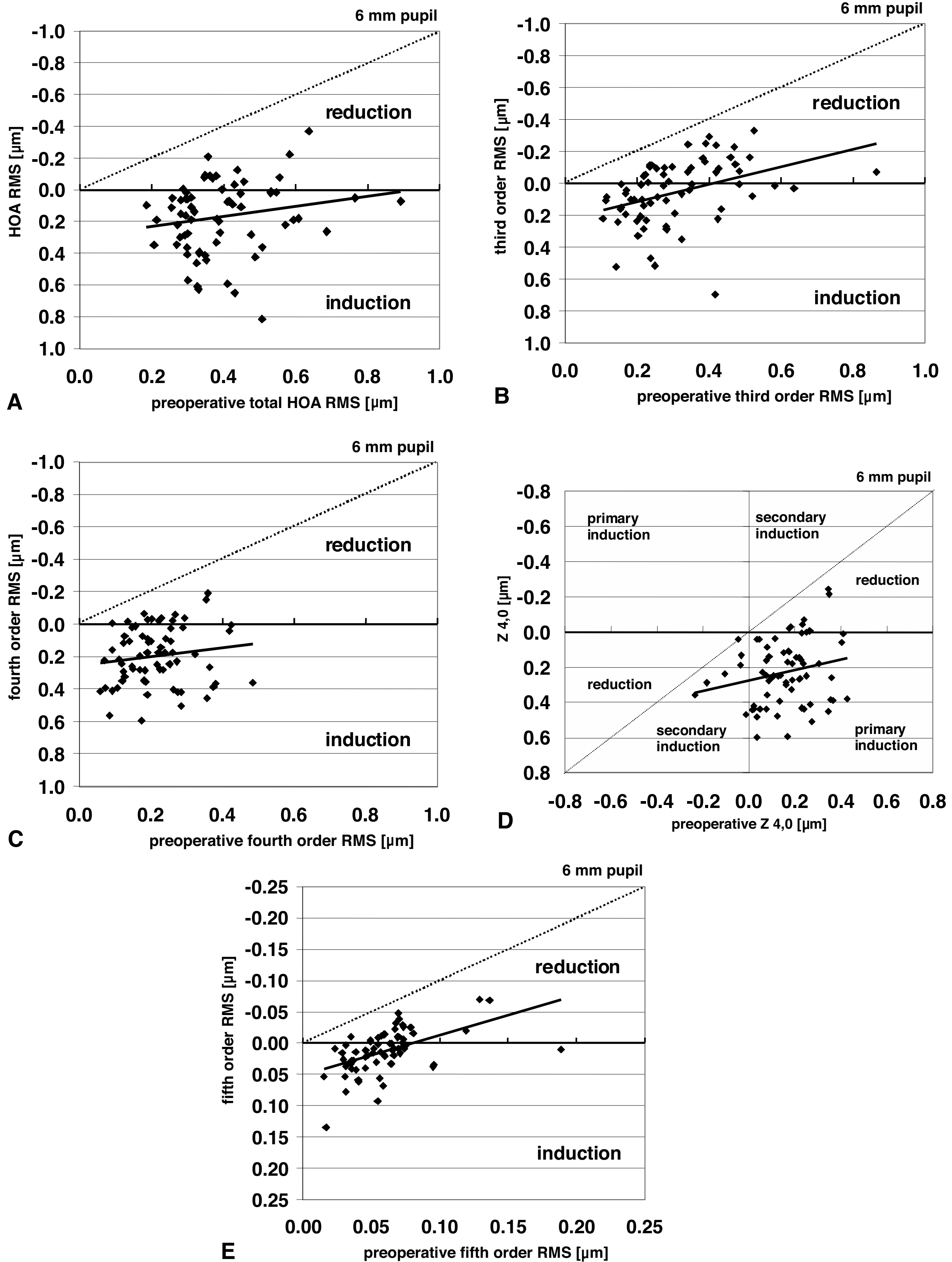

Figure 6. Change (Δ) in higher order aberrations (HOAs) as a function of preoperative HOA values (predictability of HOA correction) for the 6-mm pupil. The dotted line indicates the ideal total HOA reduction. Note that Δ root mean square (RMS) cannot be larger than the preoperative value, as RMS values cannot become negative. **A**, The total HOA RMS. **B**, Third order RMS. **C**, Fourth order RMS. **D**, Primary spherical aberration (*Z 4,0*). **E**, Fifth order RMS. All data are taken from a subgroup of 68 eyes.

with R^2 values up to 1. In fact, predictability of HOA changes in terms of correlation between the preoperative amount and its change (attempted vs. achieved HOA correction) was poor for the HOA RMS of all orders examined. Flat slopes of the regression line (b) and low R^2 values suggest influence of other factors. Except for the third order RMS, predictability was worse for a virtual pupil diameter of 6 mm. Interestingly, for the 3.5-mm pupil, correlation with preoperative values was highest for the fourth order RMS and *Z 4,0,* whereas for the 6-mm pupil, correlation coefficients for the fourth order RMS and *Z 4,0* were the lowest compared with third and fifth order RMSs. This is likely to be a result of primary induction of spherical aberrations by the treatment. Obviously, the algorithm includes preoperative *Z 4,0,* but the effect is overridden by the inherent induction of spherical aberrations, particularly at larger pupil diameters: at 3.5-mm pupil diameters, 33.9% of the eyes experienced reduction or no change of *Z 4,0*. At 6 mm, the fraction of eyes with no change or reduction dropped to 10.3%. The different predictability of different orders is also reflected by the number of eyes with a reduced or stable HOA RMS compared with baseline (Fig 5). The constant a of the regression equation was positive for RMS values of all orders examined and was well correlated with the mean change of each order ($r = 0.86$ for 6-mm pupils). This constant reflects the systematic inadvertent induction of HOAs by the procedure (Fig 6). Therefore, the probability of reduction of HOAs increased with growing preoperative HOAs, whereas eyes with low preoperative HOAs nearly always experienced an increase of HOAs. A reduction to level zero could be achieved in none of the eyes. It has to be stated that correlation of preoperative and postoperative RMS values is a rather rough method of analysis, as it neither discriminates between overcorrection and undercorrection nor respects individual changes of particular Zernike coefficients. However, analysis of changes of the individual Zernike coefficients of the corneal wavefront and total wavefront will be the subject of future work.

Why Is the Correction of Higher Order Wavefront Aberrations Still Incomplete? The present study showed better performance of the wavefront-guided treatment algorithm for the 3.5-mm pupil. However, absolute changes observed for 3.5-mm pupil diameters are rather small and might not be relevant for quality of vision, although statistically significant. Ocular wavefront aberrations become clinically relevant at larger pupil diameters. Results from the present study show that, particularly for larger pupil diameters (here, 6 mm), predictability of HOA correction is insufficient. In general, 2 reasons for insufficient correction of HOAs could be found analyzing the present data: inadvertent induction of HOAs (primary induction) or overcorrection or undercorrection of preexisting HOAs (secondary induction).

The precision of HOA correction and, therefore, overcorrection and undercorrection might be influenced by several factors:

1. *Variations in measurement of HOAs.* Wavefront sensors provide a single snapshot of ocular aberrations. Fluctuation due to accommodation and tear film changes[25,33] and potential misalignment of the measurement system might lead to high intraindividual variations, as shown for the Zywave sensor in a recent study: Mirshahi et al[34] found coefficients of variation of 18.4% for the third order RMS and 15.8% for the fourth order RMS when comparing 6 consecutive measurements of the same eye. The setup used for treatment did not allow checking RMS errors or individual Zernike terms.
2. *Registration of the HOA ablation pattern to the cornea.* Discrepancy of measurement and treatment position of the eye due to laser misalignment or cyclotorsion[35] can lead to overcorrection or undercorrection of HOAs. A higher degree of misalignment will induce HOAs.[36] The 217z excimer laser is equipped with a video-based eye tracker that recognizes the pupil but does not compensate for cyclotorsion. As we did not mark the limbus before treatment, the effect of cyclotorsion in the supine position was not controlled in the present study. Measurement and treatment were aligned with the center of the pupil. For treatment, pupils were not dilated. As it is known that the pupil center varies for miotic and mydriatic pupils,[37] this shift might be another source of misalignment.
3. *Ablation rate per excimer pulse.* The single excimer laser pulse delivered to the cornea might have different effects at different corneal areas. Differences in corneal hydration and a potentially lower fluence per pulse at the corneal periphery[38] could be responsible for insufficient correction of HOAs. A spot diameter of 1 mm might still not be fine enough to model a specific ablation pattern, especially if the fluence per pulse is inconstant. Apart from only partial correction, inadvertent (primary) induction of HOAs could be found in the majority of the eyes (Tables 2–4, Fig 6).
4. *Prolateness of the cornea.* Induction of spherical aberration is a typical side effect in the correction of myopia.[26–29,39,40] The more the corneal shape is prolate, the more spherical aberration prevails in the eye, given an identical lens, axial length, and posterior segment.
5. *Biomechanical effects.* A biomechanical response and a lower fluence at the corneal periphery increase prolateness of the cornea and, therefore, spherical aberration, whereas the effective OZ diameter minimizes.[31,32,38,41,42] Besides excimer ablation, cutting of a LASIK flap itself induces biomechanical effects and HOAs.[43,44]
6. *Decentration of ablation.* Apart from misalignment of the ablation pattern, subclinical and gross decentration are likely to induce comalike aberrations.[27,29]

In summary, although reduction of HOAs was possible in a certain amount of the eyes treated, the predictability of the algorithm has to be improved. Conversely, primary induction of HOAs, particularly the dominance of spherical aberrations, should be minimized or accounted for (e.g., by

compensation for biomechanical effects or aspherical ablation patterns).[45,46]

References

1. Kohnen T, Steinkamp GW, Schnitzler EM, et al. LASIK mit superiorem Hinge und Scanning Spot-Excimerlaserablation zur Korrektur von Myopie und myopem Astigmatismus. Einjahresergebnisse einer prospekturen klinischen Studie an 100 Augen. Ophthalmologe 2001;98:1044–54.
2. 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 1994; 11:1949–57.
3. Liang J, Williams DR, Miller DT. Supernormal vision and high-resolution retinal imaging through adaptive optics. J Opt Soc Am A 1997;14:2884–92.
4. Mrochen M, Kaemmerer M, Seiler T. Wavefront-guided laser in situ keratomileusis: early results in three eyes. J Refract Surg 2000;16:116–21.
5. Mrochen M, Kaemmerer M, Seiler T. Clinical results of wavefront-guided laser in situ keratomileusis 3 months after surgery. J Cataract Refract Surg 2001;27:201–7.
6. Nuijts RM, Nabar VA, Hament WJ, Eggink FA. Wavefront-guided versus standard laser in situ keratomileusis to correct low to moderate myopia. J Cataract Refract Surg 2002;28: 1907–13.
7. Aizawa D, Shimizu K, Komatsu M, et al. Clinical outcomes of wavefront-guided laser in situ keratomileusis: 6-month follow-up. J Cataract Refract Surg 2003;29:1507–13.
8. Koch DD, Kohnen T, Obstbaum SA, Rosen ES. Format for reporting refractive surgical data. J Cataract Refract Surg 1998;24:285–7.
9. Zywave [computer program]. Version 3.21. Munich: Bausch & Lomb/Technolas; 2000.
10. Zylink [computer program]. Version 2.3. Munich: Bausch & Lomb/Technolas; 2000.
11. Datagraph [computer program]. Version 2.70. Wendelstein, Germany: Ingenieurbüro Pieger; 2000.
12. Kohnen T. Criteria for evaluating and publishing refractive surgery interventions [in German]. Klin Monatsbl Augenheilkd 1999;215:326–8.
13. Mirshahi A, Kohnen T. Scientific evaluation and quality assurance in refractive surgical interventions. Evaluation of the Datagraph med computer program [in German]. Ophthalmologe 2002;99:629–35.
14. Thibos LN, Applegate RA, Schwiegerling JT, Webb R, VSIA Taskforce Members. Standards for reporting the optical aberrations of eyes. J Refract Surg 2002;18:S652–60.
15. Applegate RA, Gansel KA. The importance of pupil size in optical quality measurements following radial keratotomy. Refract Corneal Surg 1990;6:47–54.
16. Martinez CE, Applegate RA, Klyce SD, et al. Effect of pupillary dilation on corneal optical aberrations after photorefractive keratectomy. Arch Ophthalmol 1998;116:1053–62.
17. Excel 97 [computer program]. Redmond, WA: Microsoft; 1996.
18. CTView [computer program]. Version 4.0. Celibration, FL: Sarver and Associates; 2001.
19. Waring GO 3rd. Standard graphs for reporting refractive surgery. J Refract Surg 2000;16:459–66.
20. Wesemann W. Visual acuity measured via the Freiburg visual acuity test (FVT), Bailey Lovie chart and Landolt Ring chart. Klin Monatsbl Augenheilkd 2002;219:660–7.
21. McDonald MB, Carr JD, Frantz JM, et al. Laser in situ keratomileusis for myopia up to -11 diopters with up to -5 diopters of astigmatism with the summit autonomous LADARVision excimer laser system. Ophthalmology 2001;108:309–16.
22. Chitkara DK, Rosen E, Gore C, et al. Tracker-assisted laser in situ keratomileusis for myopia using the autonomous scanning and tracking laser: 12-month results. Ophthalmology 2002; 109:965–72.
23. Artal P, Chen L, Fernandez EJ, et al. Adaptive optics for vision: the eye's adaptation to point spread function. J Refract Surg 2003;19:S585–7.
24. Wilson SE. Wave-front analysis: are we missing something? Am J Ophthalmol 2003;136:340–2.
25. Ninomiya S, Fujikado T, Kuroda T, et al. Changes of ocular aberration with accommodation. Am J Ophthalmol 2002;134: 924–6.
26. Applegate RA, Howland HC, Sharp RP, et al. Corneal aberrations and visual performance after radial keratotomy. J Refract Surg 1998;14:397–407.
27. Seiler T, Kaemmerer M, Mierdel P, Krinke HE. Ocular optical aberrations after photorefractive keratectomy for myopia and myopic astigmatism. Arch Ophthalmol 2000;118:17–21.
28. Moreno-Barriuso E, Lloves JM, Marcos S, et al. Ocular aberrations before and after myopic corneal refractive surgery: LASIK-induced changes measured with laser ray tracing. Invest Ophthalmol Vis Sci 2001;42:1396–403.
29. Oshika T, Miyata K, Tokunaga T, et al. Higher order wavefront aberrations of cornea and magnitude of refractive correction in laser in situ keratomileusis. Ophthalmology 2002; 109:1154–8.
30. 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.
31. Holladay JT, Janes JA. Topographic changes in corneal asphericity and effective optical zone after laser in situ keratomileusis. J Cataract Refract Surg 2002;28:942–7.
32. Boxer Wachler BS, Huynh VN, El-Shiaty AF, Goldberg D. Evaluation of corneal functional optical zone after laser in situ keratomileusis. J Cataract Refract Surg 2002;28:948–53.
33. Koh S, Maeda N, Kuroda T, et al. Effect of tear film break-up on higher-order aberrations measured with wavefront sensor. Am J Ophthalmol 2002;134:115–7.
34. Mirshahi A, Bühren J, Gerhardt D, Kohnen T. In vivo and in vitro repeatability of Hartmann-Shack aberrometry. J Cataract Refract Surg 2003;29:2295–301.
35. Pansell T, Schworm H, Ygge J. Torsional and vertical eye movements during head tilt dynamic characteristics. Invest Ophthalmol Vis Sci 2003;44:2986–90.
36. Bueeler M, Mrochen M, Seiler T. Maximum permissible lateral decentration in aberration-sensing and wavefront-guided corneal ablation. J Cataract Refract Surg 2003;29:257–63.
37. Yang Y, Thompson K, Burns SA. Pupil location under mesopic, photopic, and pharmacologically dilated conditions. Invest Ophthalmol Vis Sci 2002;43:2508–12.
38. Hersh PS, Fry K, Blaker JW. Spherical aberration after laser in situ keratomileusis and photorefractive keratectomy. Clinical results and theoretical models of etiology. J Cataract Refract Surg 2003;29:2096–104.
39. Hammer RM, Holden BA. Spherical aberration of aspheric contact lenses on eye. Optom Vis Sci 1994;71:522–8.
40. Nio YK, Jansonius NM, Wijdh RH, et al. Effect of methods of myopia correction on visual acuity, contrast sensitivity, and depth of focus. J Cataract Refract Surg 2003;29:2082–95.
41. Roberts C. The cornea is not a piece of plastic. J Refract Surg 2000;16:407–13.
42. Roberts C. Biomechanics of the cornea and wavefront-guided laser refractive surgery. J Refract Surg 2002;18:S589–92.

43. Pallikaris I, Kymionis G, Panagopoulou S, et al. Induced optical aberrations following formation of a laser in situ keratomileusis flap. J Cataract Refract Surg 2002;28:1737–41.
44. Porter J, MacRae S, Yoon G, et al. Separate effects of the microkeratome incision and laser ablation on the eye's wave aberration. Am J Ophthalmol 2003;136:327–37.
45. Manns F, Ho A, Parel JM, Culbertson W. Ablation profiles for wavefront-guided correction of myopia and primary spherical aberration. J Cataract Refract Surg 2002;28:766–74.
46. Mrochen M, Donitzky C, Wüllner C, Löffler J. Wavefront-optimized ablation profiles: theoretical background. J Cataract Refract Surg 2004;30:775–85.