VISUAL SYMPTOMS AFTER THE INTACS™ REFRACTIVE PROCEDURE FOR MYOPIA: RISK FACTORS AND POSTOPERATIVE RESOLUTION

by

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TABLE OF CONTENTS

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The principal goal of past efforts has been to describe corneal surface topography following the INTACS procedure and to survey potential effects of ***postoperative*** topography upon clinical visual outcomes, in an effort to establish safety and efficacy of the product. The primary aims of this project were to survey suspected ***preoperative***

topography and clinical risk factors for contribution to postoperative visual symptoms after the INTACS refractive procedure and to determine whether clinically significant postoperative visual symptoms spontaneously resolve within two years postoperatively. Stemming from work on a previous Master's degree, in Exercise Science and Health Promotion, one of my greatest interests in Public Health lies in the area of risk factor assessment and strategic health promotion policy. The concept for the current project arose from these interests and the desire to combine efforts at work with applications learned while pursuing the Master of Public Health degree. Results from this project should promote knowledge regarding potential risk factors for dissatisfaction with this refractive procedure and help define natural history of postoperative visual symptoms up to two years.

Abstract

Background: All current corneal refractive surgery techniques for myopia, including radial keratotomy (RK), photorefractive keratectomy (PRK), laser assisted in situ keratectomy (LASIK), and intrastromal corneal ring segments (KeraVision® INTACS™), have been clearly demonstrated to improve uncorrected visual acuity and effectively free most recipients from corrective eye wear. Unfortunately, these refractive procedures can also induce post-surgical visual performance disabilities, including subjective visual symptoms, loss of best-corrected visual acuity and reduced contrast sensitivity, even with greatly improved uncorrected visual acuity. **Purpose:** Potential risk factors and performance indicators were evaluated for relationship to self-report of clinical visual symptoms following the INTACS refractive procedure for myopia. **Methods:** Participants in the U.S. FDA Phase III KeraVision® INTACS™ prospective clinical trials for myopia were retrospectively classified into one of three outcome groups (n=263), based on postoperative self-reported visual symptoms and/or request for INTACS removal up to Month 24. Differences between outcome groups in visual acuity, refractive error, corneal geometry, corneal topography, type of preoperative corrective lens wear and demographic variables were evaluated using univariate statistical techniques and multivariate logistic regression. **Results:** Patients who did **not** report significant clinical visual symptoms or request INTACS removal postoperatively demonstrated specific preoperative characteristics compared to patients reporting significant visual symptoms or requesting removal. Controlling important preoperative risk factors simultaneously, patients not reporting significant clinical visual symptoms were **more** likely to have worn soft contact lenses (adjusted odds ratio=0.58, 95% CI=0.32, 1.04, p=0.07), had average keratometry readings >45 D (adjusted odds ratio=0.43, 95% CI=0.21, 0.85, p=0.02), had 0.75 or 1.0 diopter manifest refractive astigmatism (adjusted odds ratio=0.52, 95% CI=0.25, 1.08, p=0.08) and had measured uncorrected visual acuity $\geq$2 lines better than that predicted by their respective cycloplegic refractive error (adjusted OR=0.39, 95% CI=0.14, 1.12, p=0.08). Risk of clinical visual symptoms and request for INTACS removal almost doubled for each 0.50

diopter of additional postoperative defocus equivalent (crude odds ratio=1.86, 95% CI=0.53 to 3.19, p=0.00). Adjusting for postoperative defocus as well as important preoperative risk factors, patients who reported significant clinical visual symptoms and/or requested INTACS removal were more likely to have had preoperative uncorrected visual acuity that was worse than that predicted by their respective cycloplegic refractive error (adjusted odds ratio=1.84, 95% CI = 0.98, 3.42, p=0.06). Risk of reporting clinical visual symptoms was increased with mesopic pupil diameter $\geq$6.5 mm (OR=1.76, 95% CI=0.96, 3.24, p=0.07). Within the group of patients who reported significant clinical visual symptoms, 71/122 (58%) had ceased reporting them by postoperative Month 24.

Conclusion: Clinical trial INTACS participants who did not report significant postoperative clinical visual symptoms or request INTACS removal because of visual symptoms demonstrated specific preoperative characteristics. A good candidate for the INTACS refractive procedure appears to be someone who wears soft contact lenses, whose visual acuity approximates or is better than that predicted by refractive error and pupil size, and who may have a small amount of refractive astigmatism.

Chapter 1: The Research Problem and its Significance

During the last decade, elective refractive surgery for correcting myopia has become wildly popular. Active lifestyles, increased disposable income and wide availability have nudged myopic individuals to do away with the relative inconvenience of glasses or contact lenses and choose a more "permanent" refractive fix for vision correction. In the last half decade alone, the number of refractive procedures for myopia, worldwide, has jumped by 200,000 a year, going from 800,000 in 1996 to 1.4 million in 1999. For the U.S. during the same time, the annual rate has tripled, from 250,000 to 960,000 and analysts predict this figure to exceed 1.2 million by the year 2000.

Refractive surgery for myopia began in earnest during the 1940's, and has evolved through diamond knives, lasers, implants and various combinations of all of these.[1,2] The most frequently performed elective refractive interventions today, most notably photorefractive keratectomy (PRK), laser assisted in situ keratectomy (LASIK) and intrastromal corneal ring segments (INTACS™, KeraVision® Inc., Fremont, CA), are designed to correct myopia by flattening the anterior corneal surface. All of these techniques have been clearly demonstrated to improve uncorrected visual acuity and effectively free most recipients from classical corrective eye wear.[3-7] Refractive surgery is currently most commonly used as a treatment for myopia, but aggressive efforts are underway to develop surgical interventions for hyperopia and presbyopia.

Unfortunately, corneal refractive procedures can induce post-surgical visual performance disability, even with greatly improved uncorrected visual acuity.[4,8-20] In some cases, these disabilities can be described as a surgical complication.[19,20] Visual

performance disabilities manifest clinically as subjective visual symptoms, reduced contrast sensitivity and/or loss of acceptable best spectacle-corrected visual acuity. Subjective visual symptoms, specifically 'glare' and 'halos', are the most frequent postoperative visual performance complaint of refractive patients. Incidence of significant postoperative subjective visual symptoms after refractive surgery has been shown to be as high as 50%,[4] although rates are usually reported to range between 20% and 40% within study samples.[10-14, 22] Two year postoperative results from the U.S. Phase III Excimer Laser Photorefractive Keratectomy for Myopia study indicated that although 92.5% of patients achieved 20/40 or better uncorrected visual acuity, 25-50% of patients reported increased glare and halo after PRK laser surgery.[4] Similar outcomes have been demonstrated by smaller investigations.[10-14] A comparative study that explored prevalence of visual symptoms in patients who had PRK in one eye LASIK in the other, showed that rates were about the same for both laser procedures.[22] Depending on the specific visual symptom, 22% to 59% of patients reported visual symptoms postoperatively. In Britain, O'Brart and colleagues indicated that 32 of 84 (38%) patients complained of impaired night vision after laser refractive surgery[15] and in Germany, investigators from University of Tübingen demonstrated that 50% of patients following PRK refractive surgery failed the Mesoptometer (mesopic) contrast test.[20] Under German law, this suggests that they are unfit to drive at night.[20]

The goal of improving visual acuity through refractive surgery must be combined with techniques to prevent visual symptoms and other disabilities. Visual performance disabilities following corneal refractive surgery are principally caused by anterior corneal surface irregularity and astigmatism, especially with wider pupil size.[16-18,23-27] In the non-

accommodated state, the cornea contributes over eighty percent of dioptric power for vision[28] and theoretical models reveal its keen sensitivity to sources of optical aberration, including spherical aberration, astigmatism and coma.[29] Understanding the relationship between corneal surface character and visual performance has become extremely important for corneal refractive surgeons. Both physicians and industry, alike, have realized the need to maintain optical quality of the corneal surface with refractive surgery, in which visual acuity is improved by modifying corneal surface curvature in order to achieve optimal visual performance results. Collaborative efforts are underway to determine how best to tune corneal refractive procedures to prevent visual performance losses.[30, 31]

Risk of relatively poorer postoperative outcome following refractive surgery has been hypothesized to increase when refractive candidates possess specific ***preoperative*** conditions, such as corneal astigmatism, corneal irregularities and large pupil diameter.[24] No large clinical study has yet been conducted to quantify potential effects of suspected preoperative risk factors toward postoperative visual performance disability. The bulk of previous studies examining visual and optical performance with refractive surgery have been conducted postoperatively, since the principal objective of investigation has been to describe product and procedure safety and demonstrate efficacy for treating myopia. Strides in knowledge regarding measurement and relationships between clinical visual performance, corneal surface topography and ocular optics suggest we are capable of screening refractive candidates for risk factors predisposing them to postoperative visual symptoms. Armed with efficacious prognostic tools, refractive surgeons may be more

able to effectively advise patients who exhibit preoperative risk factors and customize individual procedures.

The purpose of this investigation was to examine suspected preoperative risk factors for contribution to postoperative subjective visual symptoms, after one particular corneal refractive procedure, INTACS™ micro-thin prescription inserts for myopia (KeraVision, Inc., Fremont, CA). In addition, postoperative differences in clinical visual parameters, corneal topography indices, ocular geometry and demographic characteristics were examined. Within the group of patients who reported significant postoperative clinical visual symptoms, postoperative responses were surveyed over principal postoperative time points to assess resolution of self-reported visual symptoms.

Chapter 2: Review of Previous Study

Biological Basis of Visual Symptoms with Corneal Surface Irregularity

Corneal Surface Topography and Optical Quality: Pathological Eyes

Recent advances in technology designed to measure anterior corneal surface topography have improved our ability to characterize human eye optical aberration induced by the cornea and promote understanding of its effects on visual performance. This progress has initiated improvements and new directions for refractive surgery.[2, 33, 34]

Optical performance of the eye has been most commonly described in the past by combining anterior corneal surface topography and model eye theory. The effect of corneal surface topography on optical and visual performance of the eye was classically evaluated by Camp and colleagues.[35] Corneal surface information was collected keratographically for three case study patients—one with a normal cornea, one with keratoconus, and one following epikeratophakia for aphakia. Ray trace modeling of keratographic data demonstrated that compared to a normal cornea, the pathologic corneas with irregular corneal surface topography were unable to capably direct light to promote good retinal imaging. Optical analyses of corneal integrity corresponded with visual performance difficulties reported by the two patients with compromised corneas.

Corneal Surface Topography and Optical Quality: Laser Refractive Procedures

Reduced optical performance associated with irregular corneal surface topography has been shown clinically following all laser refractive procedures (RK, PRK and LASIK).[16, 36,37] Investigators from the University of Arizona modeled the optical effects of radial keratometry by ray tracing corneal surface height variations collected from videokeratographic analysis of patient corneas.[36] Artifact induced by radial keratometry

was found to degrade modulation transfer function, an assessment of image optical quality corresponding to clinical visual performance. Corneal aberrations and visual performance in patients after radial keratometry has also been examined by Applegate and colleagues and compared to results for normal eyes.[16] Corneal surface aberrations were quantified by transforming videokeratographic data into Zernike polynomials to estimate corneal surface wavefront variance. Wavefront aberration errors in the eye are thought to manifest as reduced visual performance or visual symptoms. These investigators found that wavefront variance remained the same over postoperative time points in the normal eyes, but was significantly increased in radial keratometry eyes after surgery. Effects of increased wavefront variance after radial keratotomy corresponded clinically to losses in measured contrast sensitivity. This effect was statistically significant with relatively large pupil size (7 mm).

Using similar methodology to Applegate et al, Oshika and colleagues reported that total wavefront aberration of corneas was significantly increased in patients after both PRK and LASIK, compared to preoperative measures.[37] Wavefront variance increased substantially with pupil size, and relative contribution of specific optical aberration errors were modified from preoperative baseline following both laser refractive procedures.

Corneal Surface Topography and Optical Quality: INTACS Refractive Procedure

Qualitative analysis using corneal surface topography pattern classification has been used to relate self-reported visual symptoms with corneal topography after the INTACS procedure.[38] In a recent study, color axial topography maps representing surface topography of individual patient corneas were classified by predominant qualitative

topography pattern corresponding to the central and pericentral cornea (4 mm).[39] The pattern classification scheme was developed primarily from previously published works.[39, 40-44] Corneal topography patterns identified from color maps of pre- and postoperative patient corneas consisted of the following prolate patterns: spherical (SPH), non-toric prolate asphere (PAS), symmetrically toric (STO), asymmetrically toric (ATO), multizonal (MZA) and unclassifiable (UNC). Color topography maps were classified by two masked observers using pre-specified guidelines and topography pattern definitions. The relationship between pre- and postoperative corneal topography patterns and uncorrected and best spectacle-corrected visual acuity, manifest refractive astigmatism, achieved spherical refractive correction and self-reported frequency of visual symptoms was evaluated. The symmetrically toric (astigmatic) pattern (STO) was related to uncorrected visual acuity; patients with astigmatism tended to be under-corrected and have worse visual acuity compared to patients with other corneal topography patterns. Patients with toric (astigmatic) patterns (STO, ATO) reported higher frequency of visual symptoms compared to patients with corneas classified as one of the other topography patterns. Self-reported frequency of 'double images' was associated with the symmetrically toric, or astigmatic (STO) corneal topography pattern and 'halos' were associated with the asymmetrically toric pattern (ATO).

Findings of relationship between corneal topography and visual performance in INTACS patients contrasted with results reported by Hersh and colleagues and Kampmeier et al for patients following laser refractive surgery.[40,45] Hersh et al found no relationship between qualitative topography pattern classifications and magnitude of a subjective glare/halo index reported by their patients after photorefractive keratectomy.

The discrepancy between studies could have resulted for several reasons, including differences in topography pattern classification definitions, definition of self-reported visual symptoms, color map documentation, the surgical procedures themselves, or the prolate INTACS patient corneas versus the oblate PRK corneas. Kampmeier and colleagues suggested that visual symptoms could not be predicted from corneal topography (tangential) maps alone. However, their use of tangential slope maps, as opposed to axial curvature maps, may have hindered ability to distinguish problematic corneal topographies from normal ones. Holmes-Higgin and colleagues previously reported that axial corneal topography maps appeared to be better for differentiating patients reporting visual symptoms than tangential maps. (Holmes-Higgin DK, et al., presented at ARVO Annual Meeting, Fort Lauderdale, May, 1999)

Optical aberration with INTACS has been preliminarily examined using interferometry and wavefront sensing technology. Postoperative spherical aberration errors are within the range expected for the normal eye. (Holmes-Higgin DK, et al., presented at ARVO Annual Meeting, Fort Lauderdale, April, 2000) Specific optical aberration errors may be increased with INTACS postoperatively, although further study of optical aberration occurring with refractive surgery is necessary.

Predisposing Risk Factors for Visual Symptoms with Refractive Surgery?

INTACS patient study results indicated that self-reported visual symptoms could be a result of residual postoperative corneal astigmatism after the INTACS refractive procedure. Preliminary evidence from the INTACS clinical trial study has demonstrated that specific ***preoperative*** factors, such as corneal surface toricity or astigmatism, level of

preoperative manifest astigmatism and rigid contact lens use, may predispose some individuals for experiencing postoperative visual symptoms. (Burris TE, et al., presented at ASCRS Annual Meeting, Seattle, April 1999) Preoperative risk factors have been implicated as initiators of poor postoperative response following other corneal refractive procedures as well.[24, 31, 46-50] Findings from these previous investigations have indicated that this area merits further research for all types of refractive procedures.

Risk Factors: Personal Characteristics and Ocular Geometry

Age

Visual performance diminishes with age. This simple observation was elegantly demonstrated using the latest techniques in optical analyses for a sample of normal eyes.[51] Modulation transfer functions (MTF), a measure of average retinal image quality, were measured in sixty patients falling into one of three different age groups; 20 to 30 years, 40 to 50 years and 60 to 70 years. After controlling for pupil diameter, accommodation and ocular defocus and astigmatism, older subjects demonstrated higher magnitude of ocular aberrations, compared to younger patients. The particular source of these aberrations could not be identified by this study and it is unknown whether they manifested clinically as increased visual symptoms or relatively poorer visual performance.

The effects of age on visual performance outcome after refractive surgery has been evaluated after PRK for myopia.[52] The myopic correction achieved in the older patients (35 to 54 years) was greater than correction obtained for the same respective treatment in younger patients (18 to 26 years). As a result, a higher percentage of older eyes were overcorrected with PRK than younger ones. Findings from these studies imply

that age may be a significant factor to consider for optimum planning of refractive procedures. The relationship between hyper-correction and visual symptoms has not been examined.

Preoperative Contact Lens Use

The effect of preoperative contact lens wear on visual performance outcome after refractive surgery has been theoretically discussed [53] and assessed in a preliminary fashion via case studies.[54-56] Preoperative rigid contact lens wear has been found to be related to corneal surface irregularities which is thought to have a deleterious effect on refractive surgery outcomes. Corneal surface irregularities associated with rigid contact lens wear has been shown to take as long as six months to resolve after ceasing lens use.[55]

Pupil Diameter

The impact of pupil diameter on visual performance, especially visual symptoms, following refractive surgery has been demonstrated by study of model eye theory,[26, 36, 57-59] as well as clinically.[12, 25, 26] A wider pupil diameter is more likely to allow aberrated light, light which has been refracted through surgically altered corneal regions, onto the retina. The aberrated light results in significantly increased visual symptoms and reduced visual performance.

Risk Factors: Preoperative Optical Quality of the Corneal Surface

Modeling and case study analyses have propelled corneal topography metrology manufacturers to develop software indices to enhance clinical evaluation of corneal topography of individual patient eyes.[60-62, 23,63-66] Indices are designed to represent optical quality of the cornea in a clinically meaningful way and motivation for development lies

in facilitating clinical diagnosis of corneal pathology. Indices describing the corneal surface are usually derived by defining the best-fit spherocylindric surface for an individual cornea and calculating the deviation of the measured corneal topographic surface from its best-fit curve, or by quantifying dioptric power variations over adjacent areas of the corneal surface. Indices signify, by way of a simple numeric index, irregular astigmatism and/or asymmetry of the anterior central corneal surface. It is unclear whether corneal topography indices are valuable as a screening tool for determining candidacy for refractive surgery.

Corneal Surface Astigmatism (Toricity)

Early studies of visual performance outcome following laser refractive surgery demonstrated the importance of assessing refractive astigmatism when planning refractive surgery. However, the ability to measure astigmatism of the entire anterior corneal surface was not possible until development of Placido disk technology (photokeratoscopy and videokeratography).[67] Planning surface incisions and laser ablations to account for preoperative corneal surface astigmatism, as well as ocular refractive astigmatism, has become standard clinical practice before performing a corneal refractive procedure. Preoperative anterior corneal surface astigmatism was not a factor for determining INTACS clinical trial candidacy. Preliminary corneal topography studies with INTACS have demonstrated that preoperative corneal surface astigmatism should potentially be considered to optimally predict refractive outcome with INTACS. (Burris TE, et al., presented at ASCRS Annual Meeting, Seattle, April 1999)

Predicted Corneal Acuity (PCA)

Predicted Corneal Acuity (PCA) is a topographic index designed to represent potential optical capability of the central anterior surface of the cornea.[64] It is derived by quantifying the difference between Placido disk ring images for a videokeratograph and their respective best-fit ellipses. Point-by-point differences in microns are summed, averaged and converted to Snellen acuity units. Large differences between captured and best-fit data points indicate anterior corneal surface micro-irregularities which theoretically reduce optical performance of the measured corneal surface.[35,65] PCA has been shown to be clinically meaningful through statistical association to irregular topography classification, spectacle-corrected visual acuity, self-reported visual performance and patient satisfaction with PRK.[23]

Weiss and Oplinger recently reported on PCA in two small cohorts—a set of patients with normal corneas and a series of patients who had corneas with different pathologic conditions, including keratoconus, corneal scarring and irregular astigmatism after corneal transplant.[68] All corneas in the normal group, with spectacle-corrected visual acuity of 20/20 or better, had correspondingly good PCA. In abnormal corneas, PCA ranged from 20/30 to 20/200. PCA was within one line of spectacle-corrected visual acuity in three-quarters of the abnormal corneas. This investigation offers support for the utility of PCA as a measure of central corneal optical quality reflecting clinical visual performance.

PCA has also been examined in a sample of eyes following laser refractive surgery.[23] Hersh and colleagues examined PCA after PRK in eyes corrected for 1.50 to 6.00 diopters of myopia. Mean PCA after PRK ranged from 20/19 in the best spectacle-corrected visual acuity group (20/10) to 20/28 in the worst spectacle-corrected visual

acuity group (20/32). These investigators found a general tendency for PCA to decrease with reduced spectacle-corrected visual acuity.

In contrast to the results from the Hersh et al. study, past study of INTACS patients have found no relationship between PCA and spectacle-corrected visual acuity.[69] In a cohort of Phase II INTACS clinical trial participants, corrected for myopia levels similar to the Hersh study, 92 of 94 corneas (98%) exhibited topographic PCA of 20/10 before and after the INTACS refractive procedure. Since that investigation was conducted, however, the topography software algorithm has been modified to more closely reflect spectacle-corrected visual acuity for patients with spectacle-corrected visual acuity of 20/20 or better. (J. Holladay, personal communication)

Topographic Corneal Asphericity

Anterior corneal surface asphericity is the primary factor to consider when assessing spherical aberration of the human cornea.[70] Modeling and optical imagery studies investigating the refractive effect of curved surfaces have demonstrated that when the surface interface of an optical system is an optimal prolate asphere, paraxial and peripheral light rays entering the system can better coincide and spherical aberration is minimized. Corneal asphericity for the normal human cornea is reported in the literature to range from 0.50 Q to -0.88 Q.[70-73] Average corneal asphericity values are suggested to under-correct spherical aberration.[70] An asphericity quotient less than zero (negative) defines a conic section curve which is a prolate ellipse, indicating that the curve is flatter in its periphery relative to its center; an asphericity quotient greater than zero (positive) represents an oblate elliptical curve which has a relatively steeper curvature at the periphery compared to its apex.[71, 74, 75] The range given in the literature for normal

corneal asphericity includes values which describe both prolate and oblate elliptical curves. The figure presented in Appendix 1 shows a graphic representation of the spherical aberration effects of 'oblate', 'prolate' and 'spherical' optical surfaces (i.e. cornea).

Maintenance of prolate asphericity with corneal refractive surgery may be optically beneficial for reducing incidence of postoperative visual performance disabilities.[35, 57, 76] Aspheric treatments with PRK have been shown to initiate fewer postoperative visual performance complaints compared to traditional, spherical laser ablations[32] and future refinements of ablative types of refractive surgery are aimed at optimizing postoperative prolate asphericity of the corneal surface.[31] Current laser refractive surgeries, RK, PRK and LASIK, [40, 74, 75, 76] usually induce oblate asphericity. In contrast, in eyes with INTACS, preoperative prolate corneal asphericity is preserved or increased (corneas made more prolately aspheric).[38, 79-81]

Potential effects of the increased prolate corneal asphericity induced by the INTACS on clinical visual performance was assessed previously in a preliminary study of twenty-five Phase II patients who had received 0.25 mm to 0.45 mm INTACS.[81] Eyes were stratified by level of corneal asphericity, and evaluated for clinical visual performance, including uncorrected visual acuity, best spectacle-corrected visual acuity and photopic contrast sensitivity. The purpose of the study was to explore whether the relatively higher prolate postoperative corneal asphericity, compared to preoperative, impacted clinical visual performance. Corneal asphericity in eyes was quantified by comparing asphericity profiles for individual eyes to profiles plotted for test objects with known surface radius of curvature and asphericity. The asphericity profile for each eye

was determined to have the same asphericity value as the test object (asphericity profile) to which it most closely corresponded.

Preoperative corneal asphericity ranged from -0.01 Q to -0.81 Q and postoperative from -0.01 Q to -1.44 Q. Postoperative asphericity was significantly more prolate in all INTACS thickness groups than preoperative. Preoperative uncorrected visual acuity was significantly related to corneal asphericity; more myopic eyes tended to have more prolate corneal asphericity. This finding supported previous study conducted in normal eyes.[82] Corneal asphericity was not found to be significantly related to postoperative uncorrected visual acuity, or to best spectacle-corrected visual acuity or photopic contrast sensitivity, pre- or postoperatively.

A later, larger study using a different derivation of videokeratographic corneal asphericity, the corneal asphericity quotient (Q), an index automatically derived by the corneal topography software to describe corneal asphericity of the central corneal surface quantitatively, was conducted in Phase III clinical trial patients.[38] This investigation also indicated that postoperative corneal asphericity with INTACS was significantly more prolate than preoperatively. The corneal asphericity quotient (Q) and clinical visual performance parameters (uncorrected visual acuity, best spectacle-corrected visual acuity and refractive correction with INTACS) were not found to be linearly related, either pre- or postoperatively.

Comparative analyses of eyes stratified by postoperative corneal asphericity quotient indicated relationships between preoperative myopia and corneal asphericity, and subsequent postoperative corneal asphericity and visual acuity. Groups of eyes with more prolate asphericity postoperatively tended to be more prolately aspheric preoperatively

and have worse preoperative uncorrected visual acuity. Preoperative results across asphericity strata reflected conclusions from previous studies of normal myopic eyes.[81, 82] These investigations reported that preoperative corneal asphericity and uncorrected visual acuity were significantly related; corneas of relatively more myopic eyes were found to be more prolately aspheric. In addition, average postoperative best spectacle-corrected visual acuity for the group of eyes with most prolate asphericity was significantly worse than average values for other groups. However, the postoperative mean value for best spectacle-corrected visual acuity for this group of patients was similar to average preoperative value. In sum, the group with the most prolate asphericity postoperatively appeared to begin with more prolate asphericity and have relatively worse uncorrected and best spectacle-corrected visual acuity preoperatively than other postoperative asphericity strata.

In addition to exhibiting differences in visual acuity, patients with the most prolate postoperative corneal asphericity may have experienced worse postoperative contrast sensitivity without glare compared to preoperative baseline, and to patients with lower levels of prolate corneal asphericity. It was not clear whether potential losses in contrast sensitivity without glare were clinically significant for individual patients. Contrast sensitivity with glare did not differ significantly between asphericity groups and all groups appeared to maintain average preoperative values. It is unknown whether reduced contrast sensitivity may be related to manifestation of visual symptoms. No study has been conducted to explore the relationship between corneal asphericity and visual symptoms with refractive surgery.

Conclusion

A number of potential risk factors exist which may predispose patients to experiencing clinical visual symptoms after refractive surgery. Examination of the relationship between corneal topography and clinical outcomes has indicated a link between astigmatic corneal topography and subjective self-reported visual symptoms. Study of corneal topography and visual performance has also tentatively demonstrated interactive relationships between preoperative corneal asphericity, postoperative corneal asphericity and clinical visual performance parameters. Continuing efforts to examine and relate clinical and visual performance, corneal topography and personal and ocular geometry to patient reported visual performance outcomes will improve future results of corneal refractive procedures.

Chapter 3: Materials and Methods

The INTACS Refractive Procedure

INTACS is a medical device designed to treat low to moderate myopia by reshaping the anterior curvature of the cornea without direct surgical intervention to the central visual axis. The device consists of two small, rigid, PMMA plastic (polymethylmethacrylate) crescent shaped segments, each having an arc length of 150° (see Appendix 2). Refractive effect is modulated by INTACS thickness; currently six different thickness products have been or are being clinically evaluated in the U.S., including 0.21, 0.25, 0.30, 0.35, 0.40 or 0.45 mm, with a predicted myopic range of correction from one to four diopters.

INTACS are surgically inserted into opposing lamellar channels at two-thirds depth in the midperipheral cornea through a radial incision less than two millimeters in length. They are designed to have an inner diameter of approximately seven millimeters and outer diameter of eight millimeters once placed in the cornea. The INTACS surgical procedure has been described previously.[6,7] The U.S. Food and Drug Administration approved INTACS to treat a specified amount of myopia (-1.0 to –3.0 diopters) in April 1999; clinical trials for FDA approval of values outside the current commercial range are underway. Clinical trials for similar devices designed for applications other than "pure" myopia, including myopia with astigmatism and hyperopia, are currently ongoing in the U.S., Europe, Mexico, Brazil and Singapore.[34, 83, 84]

Study Participants

The study cohort consisted of patients participating in the U.S. Phase III prospective clinical trials for Food and Drug Administration pre-market safety and efficacy approval of INTACS. These clinical trials have been described in detail elsewhere.[6,7] The INTACS clinical trial cohort consisted of mild myopes, who exhibited preoperative cycloplegic spherical equivalent between –1.00 and –3.00 diopters. All candidates underwent extensive preoperative examination to determine fitness for clinical trial participation. All patients had 20/20 or better preoperative best spectacle-corrected visual acuity and received INTACS of specified thickness according to cycloplegic refractive spherical equivalent. Upon enrollment and INTACS placement, patients were followed for 24 months unless the INTACS device was removed. Patients with INTACS removed were exited from the clinical trial at Month 3 after removal.

Before any patient could be enrolled in the trial, the protocol and Patient Informed Consent Form had to be approved by the Institutional Review Board (IRB) of the specific institution where the trial was being conducted. The patient was not asked to sign the informed consent documents until the trial was fully approved by the respective institution's IRB. The Sponsor required a copy of any IRB correspondence as well as the final approval letter and the final, approved Patient Informed Consent Form from each IRB. A Data and Safety Monitoring Board (DSMB) was established to serve in a medical monitoring capacity and to independently review the collective safety and efficacy data generated from the trial. The members of the DSMB were not INTACS clinical trial investigators nor were their institutions affiliated with an investigational trial for INTACS.

Research Questions

The purpose of this investigation was to explore four principal research questions. These included:

1) Do patients who request removal of INTACS ('Removals') or who experience significant postoperative visual symptoms after the INTACS refractive procedure, but keep INTACS ('Clinical Symptoms') demonstrate specific preoperative risk factors, compared to those who do NOT request removal or experience significant visual symptoms ('Infrequent Symptoms')?

2) Does the combined 'Removals' and 'Clinical Symptoms' group differ from the 'Infrequent Symptoms' group for postoperative clinical ophthalmic parameters collected at their last postoperative exam with INTACS?

3) Do patients in the 'Removal' group exhibit different risk factors compared to the 'Clinical Symptoms' group?

4) Do visual symptoms resolve between postoperative Month 3 and Month 24 for the patients in the 'Clinical Symptoms' group?

Study Design

Data was collected from eight clinical investigation sites. These included Anheuser-Busch Eye Institute, St. Louis, MO; Emory Vision Correction Center, L.P., Atlanta, GA; Hunkeler Eye Centers, P.C., Kansas City, MO; McDonald Eye Associates, Fayetteville, AR; Mount Sinai School of Medicine, New York, NY; Northwest Corneal Services, Portland, OR; University of California San Francisco, Vision Care & Research Unit, San Francisco, CA; and University of South Florida College of Medicine, Tampa,

FL. Pre- and postoperative Months 3, 6, 12 and 24 data for initial surgical eyes were analyzed for all patients except for those from one site. This site experienced computer hardware difficulties early in the trial, thus were unable to collect preoperative or postoperative Month 3 corneal topography data for initial eyes. Data collected for second surgical eyes were used from this site since, in this study, the advantage of improved statistical power with increased sample size outweighed any potential bias introduced by using contralateral eye data. All patients from that particular site underwent the INTACS procedure for both eyes. The percentage of persons reporting significant clinical visual symptoms from this site was within the range indicated for all other clinical sites (see table in Appendix 3).

Total patient (eye) sample size for this study was n=263.

Clinical trial cohort members (for initial study eye only) were retrospectively classified into one of the following three outcome groups. These were 1) 'Removals': patients who requested INTACS device removal (up to postoperative Month 24), because of dissatisfaction with visual performance outcome, 2) 'Clinical Symptoms': patients who reported significant visual symptoms at any time up to postoperative Month 24, but kept INTACS, and 3) 'Infrequent Symptoms': patients who reported no significant visual symptoms and had INTACS in place up to postoperative Month 24.

As part of the clinical trial protocol, patients were asked to orally report the frequency of four specific visual symptoms (glare, halo, double images, difficulty with night vision) to the physician at each principal postoperative visit. Responses were recorded by each clinic and sent to the Sponsor on record sheets designed for the purpose. Any patient who kept INTACS, but reported the any visual symptom as 'often' or

'always', at any principal postoperative time point (Months 3, 6, 12 or 24) was classified into the 'Clinical Symptoms' group. Patients who kept INTACS and reported frequency of visual symptoms as 'never', 'rarely' or 'sometimes' over all principal time points were classified into the 'Infrequent Symptoms' group. For the primary set of analyses, the 'Removals' group was combined with the 'Clinical Symptoms' group and compared to the 'Infrequent Symptoms' group. In secondary analyses, the 'Removals' and 'Clinical Symptoms' groups were evaluated separately and compared.

Risk Factor Variables

Personal Characteristics

Age, sex, ethnicity and contact lens use history was collected as part of the patient history questionnaire during the preoperative exam. Patients were asked to indicate type of corrective lens wear they historically used (soft, rigid or no contact lenses) and how long each type was worn. Contact lens use was polytomously stratified during analyses to assess effects for each of the three precursors. Patients received 0.25, 0.30 or 0.35 mm thick INTACS, depending on preoperative cycloplegic refraction spherical equivalent and individual needs. Clinical trial results have indicated that INTACS thickness may be related to achieved visual performance outcome.

Ocular Geometry

Pupil diameter was measured during both cycloplegic and manifest refraction under standardized lighting conditions of 25 foot-candles (+/- 3 foot-candles). Pupil diameter was measured with an ocular ruler to the nearest 0.5 mm while the patient fixated on the distance visual acuity chart.

Corneal thickness and limbal diameter were examined because of their potential impact upon INTACS device mechanical performance. Limbal diameter measurements were performed as part of the preoperative screening for the clinical trial. Measurements were taken superior to inferior and nasal to temporal using standard clinical calipers. Only the nasal to temporal (horizontal) measure was assessed since it is more reliably obtained than the vertical value. Corneal thickness was measured centrally and over the mid-peripheral incision site for the INTACS procedure. Central corneal thickness was assessed during the preoperative exam. Corneal thickness over the incision site was measured during the INTACS surgical procedure in order for the surgeon to determine diamond knife depth setting. The same ultrasonic pachymeter was used for both corneal thickness measurements.

The average keratometry value for the central 3-mm diameter zone of the cornea was examined to assess potential effects of relative corneal curvature (relatively steep central curvature versus flat central curvature). The same keratometer at each clinical site was used on individual patients for the duration of the trial.

Clinical Visual and Refractive Performance

Uncorrected and best spectacle-corrected visual acuity were measured in the clinical trial using the ETDRS (Early Treatment Diabetic Retinopathy Study) visual acuity charts and light box. The level of illumination in the testing room was standardized to less than 15 foot-candles between centers participating in the trial.

Refractive error was assessed using a measure proposed by Holladay and colleagues.[26] Similar to spherical equivalent, defocus equivalent is a measure of refractive error but is weighted to account for the effects of refractive astigmatism upon

visual performance. It is equal to the sum of the absolute value of the spherical equivalent plus half the absolute value of the cylinder. These investigators assembled twelve previously published studies, between 1928 and 1990, in order to demonstrate methods of predicting uncorrected visual acuity from refractive error (or vice versa) in normal eyes, when pupil size was known. The "reference grid" provided by their study demonstrated that if uncorrected visual acuity was assessed and compared in two eyes with similar refractive spherical equivalent error but different levels of astigmatism, the eye with the greater refractive astigmatism would have worse visual acuity. Defocus equivalent was calculated using cycloplegic refractive data.

Refractive astigmatism was assessed using the absolute cylinder value measured by manifest refraction. Orientation of refractive astigmatism was also evaluated, due to its potential relationship to mechanical performance of INTACS. Values given for the principal axis of orientation were categorized as with-the-rule (WTR), against-the-rule (ATR) or spherical (SPH). Eyes were classified as WTR axis values fell between 45° and 135°, ATR if axis values fell between 0° and 44° or 136° and 180°, and SPH if the cylinder value (amount of astigmatism) was zero.

Corneal Topography Parameters

All clinical sites included in this study acquired corneal topography data using the EyeSys Corneal Analysis System (EyeSys Technologies, Houston, TX). Corneal topography data from clinical sites was electronically imported into a central topography reading computer system (Northwest Corneal Services Topography Reading Center) and read using the EyeSys System 2000 software (version 4.0). Corneal topography

measurements representing corneal astigmatism (toricity), irregular corneal surface topography and corneal asphericity were assessed.

Topographic Corneal Astigmatism (Toricity)

Topographic toricity for this study was evaluated using the total topographic astigmatism value (dioptric power) given by EyeSys System 2000 software. This is a measure of total topographic toricity within the three-millimeter diameter optical zone of the cornea.[64]

Irregular Corneal Surface Topography

Two corneal surface indices automatically calculated by the topography software were used to quantify irregular corneal surface topography—the Predicted Corneal Acuity (PCA) Index and Corneal Uniformity Index (CUI). The PCA Index is designed to represent the potential best-corrected visual acuity capability of the central anterior surface of the cornea.[64] It is a measure of detected corneal surface micro-irregularities which potentially reduce optical performance of the cornea. In normal eyes with best spectacle-corrected visual acuity of 20/20 or better, PCA is expected to be 20/20 or better. PCA has been shown to be statistically associated best spectacle-corrected visual acuity, self-reported visual symptoms and patient satisfaction with PRK.[23,64]

The PCA index has been suggested to be most useful when assessed in combination with the Corneal Uniformity Index (CUI).[64] The CUI represents fluidity of the central anterior corneal surface. Normal corneas are indicated to have a CUI of 80% or better. In corneas following laser-assisted in situ keratomileusis (LASIK refractive surgery), CUI was reported to range between 50% and 90% (Holladay, JT, presented at the pre-AAO ISRS Meeting, Chicago, 1996).

Anterior Corneal Surface Asphericity

Modeling studies of the cornea have indicated that the ideal anterior corneal shape is aspheric, with relatively steeper curvature centrally than peripherally.[70, 71, 76, 85, 86] In one of the simpler mathematical corneal modeling methods, conic section analyses (e.g. flattening ellipse, steepening ellipse, parabola, hyperbola), are most commonly used to describe and represent aspheric surfaces.[87] The asphericity of a conic section is determined by quantifying how the curvature changes between the apex and periphery. If the surface of the curve flattens as it moves away from the apex, the curve is considered to be prolate and has a positive shape factor; if the curve steepens toward the periphery away from the apex, it is oblate and has a negative shape factor.[71, 74, 75] Clinical corneal topography studies have confirmed corneal shape modeling investigations and enabled us to describe the normal anterior corneal surface as a prolate or flattening ellipse.[70-75, 77, 88] Theoretically, this shape reduces anterior corneal spherical aberration [70, 86, 89] and is believed to promote optimal visual performance.[35, 57, 76, 90]

Corneal asphericity was assessed for this study using the Asphericity Quotient (Q) calculated by the topography software.[64] The EyeSys index of corneal asphericity is derived from axial radius of curvature data collected within the central 4.5 mm diameter region for a given cornea. It is based on assumptions developed by the literature reporting derivation of asphericity through conic section analyses.[64]

Risk Factor Variable Transformations

Visual Acuity "Disconnect"

For any given pupil diameter, visual acuity can be predicted using refractive data.[26] We were interested in determining whether patients in the 'Clinical Symptoms/Removal' group exhibited a larger discrepancy between preoperative measured refractive data and measured visual acuity, compared to the 'Infrequent Symptoms' group.[26, 90] The purpose of this analyses was to evaluate, how *well* patients reported that they could see preoperatively (uncorrected visual acuity), compared to how well they could be expected to see with their given refractive error. "Visual acuity disconnect" can be described as a phenomenon in which measured visual acuity does not predictably correspond to visual acuity predicted by measured refractive data.

The first step in creating the visual acuity disconnect parameter was to determine "predicted" preoperative visual acuity using methods proposed by Holladay and colleagues.[26] Visual acuity can be predicted by resolving the relationship between defocus equivalent (derived using cycloplegic refractive data) and a given pupil diameter under lighting conditions simulating where a given visual acuity is taking place.[26] During the INTACS clinical trial, non-dilated pupil diameter and uncorrected visual acuity were measured in the same room and under the same lighting conditions. Non-dilated pupil diameter was used in the calculation to estimate predicted preoperative uncorrected visual acuity for individual patients.

The second step was to transform both measured visual acuity and predicted visual acuity into logarithm of the minimum angle of resolution (logMAR) notation in which each tenth unit represents a Snellen visual acuity line value.[92] The difference in

Snellen line values for measured visual acuity and predicted visual acuity was calculated for each patient. A 'zero' sum indicated no difference between measured and predicted visual acuity. A positive integer indicated how many lines better measured visual acuity was compared to predicted; a negative integer showed how many lines worse measured visual acuity was compared to predicted. For example, if a patient was calculated to have visual acuity disconnect of –2, this means that his/her measured visual acuity was two Snellen lines worse than that expected for their given refractive error and pupil diameter under conditions in which uncorrected visual acuity was measured.

Statistical Analyses

All patient data except for corneal topography data were acquired from the clinical trial sponsor as an Excel (Microsoft Office, Bellevue, WA) spreadsheet and imported into the Systat (version 8.0) for Windows (SPSS, Chicago, IL) statistical package. Corneal topography data was entered in an Excel spreadsheet, imported to Systat and merged with the sponsor data file.

The principal postoperative data examined consisted of postoperative Month 24 for all patients but 'Removals'. For these patients, the principal postoperative exam data was acquired from the last exam with INTACS in place. Stability of outcome for patients was assessed by examining results for postoperative Months 3, 6, 12 and the final exam time.

Univariate analyses of outcome groups were conducted by reviewing descriptive statistics (mean, standard deviation, confidence intervals, median and range) for

continuous variables and by surveying percentage counts, odds ratios and confidence intervals for dichotomous or polytomous variables.

Two multivariate logistic regression models were developed; one for the 'Clinical Symptoms/Removals' versus 'Infrequent Symptoms' outcome group analysis, and one for the 'Removals' versus 'Clinical Symptoms' outcome group analysis. Risk factor variables were entered into the multivariate model based on findings of univariate analyses and clinical interest as suggested by past investigation.

Resolution of self-reported visual symptoms over time was determined for patients in the 'Clinical Symptoms' group. 'Clinical Symptoms' patient data for frequency of self-reported visual symptoms was reviewed and the last postoperative time point at which individual patients reported significant clinical visual symptoms ('often' or 'always') was tabulated.

Determination of Study Power

Because the study drew its sample from a clinical study currently underway (with delimited sample size), the *power* of the proposed study to nullify the hypothesis derived from Research Question One was calculated using approximately estimated sample sizes. The hypothesis given for the preoperative analysis was chosen as the basis for power determination for two reasons: (1) it was the primary research question, and (2) detection of differences between groups was expected to be more difficult preoperatively than postoperatively.

1. Sample size.

Predicted population size was n=**263,** the number of patients participating in the KeraVision Phase IIIA clinical trials at the eight clinical sites which collected corneal topography data with the EyeSys corneal topography unit.

The estimated number of patients classified as 'Removals' were approximated from the FDA pre-market approval application reporting results for Month 12 (April 1999). INTACS removal rate for this patient cohort, which included patients with 0.25, 0.30 and 0.35 mm INTACS thickness, at postoperative Month 12 was approximately 7% (18/263). At postoperative Month 24, six additional eyes (24/263) from this patient group had INTACS removed. Of these removals, 22 were related to dissatisfaction with vision, 1 was safety related and 1 was for other reasons. This study followed patients up to postoperative Month 24. It was reasonable to assume that additional patients would opt for INTACS removal during the second twelve month. We projected that number to be an additional three percent after examining patient status at postoperative Month 18. The 'Removals' group was predicted to include **26/263** or 10% of the proposed project cohort.

Incidence of self-reported visual symptoms was also reported for postoperative Month 12 in the FDA pre-market approval application. Month 24 data had not yet been audited and was unavailable for review. For PMA cohort patients at Month 12, 7-17% of individuals reported frequency of postoperative visual symptoms (glare, halos, double images and difficulty with night vision, respectively) as 'often' or 'always', depending on specific visual symptom. All of these patients kept INTACS until at least postoperative Month 12. I estimated that **12%** (17% total reporting visual symptoms - 5% of subsequent INTACS removals through Month 24) of patients (**28/263**) would report

visual symptoms as 'often' or 'always' at some time up to postoperative Month 24 but keep their INTACS.

The remainder of the study cohort was projected to make up the 'Infrequent Symptoms' group, patients who keep INTACS and report no significant visual symptoms. This group was estimated to be **205/263 (78%)** of all patients.

2. Alpha level.

The cutoff for type I (alpha) error, or the probability of rejecting a true hypothesis, was set at **5%**.

3. Effect size (magnitude of differences between groups)

Effect size estimations for individual preoperative risk factors are shown in Appendix 4.

4. Power Calculation

Power of the study is equivalent to the probability that rejection is the correct decision if the test hypothesis is false. The means (bolded numbers in appendix tables) given for the 'Infrequent Symptoms' group were calculated from data previously collected from 165 eyes for the corneal topography report of the KeraVision, Inc. pre-market approval application cohort. Predicted mean data given for the 'Clinical Symptoms/Removals' group was determined by calculating a new mean based on the indicated effect size difference between the 'Clinical Symptoms/Removal' group and the 'Infrequent Symptoms' group.

Power for each continuous variable was calculated using the normal two sample, with equal variances option on the statistics web page designed by the University of California at Los Angeles (http://www.stat.ucla.edu/calculators).[93] Power for

dichotomous variables was estimated using the binomial two sample arcsine method provided by the same UCLA web page. The power of the proposed study to detect differences between 'Clinical Symptoms/Removals' and 'Infrequent Symptoms' groups for specific preoperative risk factors is presented in Appendix 4. All power calculations were conducted using one-sided hypothesis testing. One-sided hypothesis testing was used since we felt we were able to hypothesize the direction of potential relationships between each dependent variable and outcome. Adequate power was demonstrated by these analyses to conduct this study.

Power was also calculated to determine the feasibility of conducting comparative analyses between 'Removals' and 'Clinical Symptoms' groups in order to address Research Question 3. Proposed risk factor variable means for 'Removals' and 'Clinical Symptoms' (shown in Appendix 3) were determined by adding or subtracting half the effect size value of the 'Clinical Symptoms/Removals' means, depending on predicted direction for separated 'Removals' and 'Clinical Symptoms' groups. Estimated power for this analysis appeared to be reasonable for all variables of interest.

Chapter 4: Results

'Clinical Symptoms/Removals' Compared to 'Infrequent Symptoms':

Risk Factors for Reporting Clinical Visual Symptoms

The 'Clinical Symptoms/Removals' group consisted of 152/263 or 58% of the total cohort. The 'Infrequent Symptoms' group was comprised of 111/263 patients (42%). Postoperative event sequence and reasons for INTACS removal or exchanges are listed for affected patients in Appendix 5.

Analysis of demographic variables indicated that most study participants were Caucasian (89%) and ranged in age from 23 to 66 years old (mean=40.5, SD=9.2, median=40.0). Participants were approximately evenly distributed by sex (males = ~46%; females = ~54%). Outcome groups did not differ significantly by sex, ethnicity or age (Table 1). Patients reporting clinical visual symptoms or requesting INTACS removal were more likely to have worn rigid contact lenses preoperatively, and less likely to have worn soft lenses, although univariate odds ratios were not significant. Self-reported visual symptoms and/or request for INTACS removals occurred almost twice as often with 0.30 mm and 0.35 mm INTACS (crude odds ratio=1.72, 95% CI=0.95, 3.11; 1.80, 95% CI=0.99, 3.28, respectively) compared to 0.25 mm INTACS.

Range values for all ocular geometry variables were tight for both outcome groups due to the limitations of available metrology for measuring the eye. Ocular geometry variables were stratified in a way to determine whether patients with relatively more outlying values, compared to the norm, had higher risk for visual symptoms. Stratification borders for ocular geometry variables were equal to approximately one

standard deviation difference from the mean value for the entire cohort. Odds ratios indicated that risk of clinical visual symptoms and/or INTACS removal was increased, although not significantly, for patients who had relatively larger horizontal limbal (corneal) diameter (crude odds ratio=1.91, 95% CI=0.65, 5.62; Table 2). Small cell sample sizes on each end of the distribution for corneal diameter reduced statistical power for conducting these analyses. Risk for reporting clinical visual symptoms and/or requesting INTACS removal was increased, though not significantly, for patients with relatively thinner corneas (crude odds ratio central cornea=2.18, 95% CI=0.43, 11.00; crude odds ratio incision site=2.09, 95% CI=0.54, 8.11). Occurrence of significant clinical visual symptoms and/or removals were significantly less frequent among those with corneas steeper than 45 diopters preoperatively than for patients with relatively flatter corneas (crude odds ratio=0.45, 95% CI=0.23, 0.86).

Means and confidence intervals (95%) for clinical visual performance (visual acuity, defocus equivalent and manifest refractive astigmatism) in outcome groups are presented in Figures 1 to 4 (actual values are presented in Appendix 6). Preoperative Differences in uncorrected visual acuity and defocus equivalent between outcome groups indicated potential disparity between outcome groups for preoperative level of myopia. The 'Clinical Symptoms/Removals' group exhibited worse average preoperative uncorrected visual acuity (logMAR mean=0.71, 95% CI=0.67, 0.75) than the 'Infrequent Symptoms' group (logMAR mean=0.64, 95% CI=0.59, 0.68). Mean difference corresponded to approximately one Snellen line of visual acuity. The trend for preoperative defocus equivalent was similar (respectively for outcome groups, mean=2.29, 95% CI=2.19, 2.39; mean=2.16, 95% CI=2.05, 2.28)

Postoperative final exam uncorrected visual acuity, defocus equivalent and manifest refractive astigmatism differed significantly between outcome groups. Average uncorrected visual acuity in the 'Clinical Symptoms/Removals' group was approximately 20/25 (logMAR 0.08, SD=0.24), with a lower bound confidence value which was equivalent to worse than 20/20 visual acuity (logMAR=0). The 'Infrequent Symptoms' patients had mean uncorrected visual acuity of approximately 20/16 (logMAR –0.06 (SD=0.15), with upper bound confidence value equivalent to better than 20/20 (logMAR=0). Results for defocus equivalent in outcome groups mirrored findings for uncorrected visual acuity. Postoperative manifest refractive astigmatism was significantly greater in the 'Clinical Symptoms/Removals' group (mean=0.55, SD=0.46 diopters) than in the 'Infrequent Symptoms' group (mean=0.36, SD=0.41 diopters). Outcome groups did not differ significantly (one or more lines of Snellen visual acuity) for best spectacle-corrected visual acuity.

Univariate odds ratios for the preoperative visual acuity disconnect parameter are presented in Table 3. Clinical visual symptoms and/or INTACS removal occurred more often in patients with worse than predicted visual acuity and less often in patients with better than predicted visual acuity, although univariate odds ratios were not significant. Preoperative manifest refractive astigmatism was dichotomized to facilitate its interpretation (Table 3). Occurrence of self-reported significant clinical visual symptoms and/or request for INTACS removal was half as frequent among people with preoperative manifest refractive astigmatism greater than 0.50 diopter (crude odds ratio=0.51, 95% CI=0.26, 1.01). Neither against-the-rule (ATR) or with-the-rule (WTR) orientation of preoperative manifest refractive astigmatism were associated with increased risk for self-

reported clinical visual symptoms and/or INTACS removal compared to spherical (SPH) orientation (crude odds ratio ATR=0.68, 95% CI=0.38, 1.23; crude odds ratio WTR=1.10, 95% CI=0.60, 2.02).

Univariate odds ratios for pre- and postoperative corneal topography parameters are presented in Tables 4 and 5. Four of five preoperative corneal topography parameters were not associated with increased risk of reporting clinical visual symptoms or removal of INTACS. The Effective Refractive Power index, developed as a surrogate measure to keratometry, mirrored findings for risk associated with mean keratometry. Self-reported clinical visual symptoms and/or removal of INTACS occurred almost nine times more often in patients whose postoperative corneal surface topography was measured as 'oblate' (Q>0.00) compared to the referent, normal 'prolate' corneal asphericity (crude odds ratio=8.95, 95% CI=1.94, 41.36).

Postoperative values for visual and refractive variables and corneal topography parameters were stable throughout the follow-up period (Months 3, 6, 12 and final exam) for both outcome groups. Mean values with 95% confidence intervals were calculated and plotted for individual variables across time. These figures are presented in Appendix 7.

A multivariate logistic regression model was developed to assess effects of suspected preoperative risk factors simultaneously. Dependent variables included in the multivariate model were selected based on clinical interest, biologic plausibility and statistical significance indicated by univariate analyses. Adjusted odds ratios and confidence intervals for preoperative risk factors included in the multivariate model are presented in Table 6, in order of statistical significance. With all included preoperative

risk factors controlled for, patients who were less likely to report significant clinical visual symptoms or request INTACS removal postoperatively were **more** likely to have worn soft contact lenses preoperatively (adjusted odds ratio=0.58, 95% CI=0.32, 1.04). Controlling for all other potential preoperative risk factors, patients who had average keratometry readings >45 D (adjusted odds ratio=0.43, 95% CI=0.21, 0.85), three-quarters to one diopter of manifest refractive astigmatism (adjusted odds ratio=0.52, 95% CI=0.25, 1.08) and measured uncorrected visual acuity ≥2 Snellen lines better than that predicted by their respective cycloplegic refractive error (adjusted odds ratio=0.39, 95% CI=0.14, 1.12) were less likely to report postoperative clinical visual symptoms or request INTACS removal than respective reference stratum (strata in which odds ratio=1.00). Adjusting for important preoperative risk factors, patients who required relatively more correction (0.30 mm or 0.35 mm INTACS) were twice as likely to report clinical visual symptoms or request INTACS removal postoperatively than patients who received the 0.25 mm INTACS (adjusted odds ratio=2.12, 95% CI=1.12, 4.00; adjusted odds ratio=2.05, 95% CI=1.06, 3.97 for 0.30 mm and 0.35 mm INTACS, respectively).

Preliminary exploratory modeling study demonstrated that postoperative clinical visual performance (defocus equivalent or uncorrected visual acuity and manifest refractive astigmatism) was clearly the most significant indicator suggesting which patients were most likely to report clinical visual symptoms or request INTACS removal. Risk of clinical visual symptoms and request for INTACS removal almost doubled for each 0.50 diopter of additional postoperative defocus equivalent (crude odds ratio=1.86, 95% CI=0.53 to 3.19, p=0.00). A multivariate model was created to control for effects of postoperative defocus, potentially introduced by any number of procedure, product and/or

healing-related phenomena, in order to survey preoperative risk factors while adjusting for this significant postoperative factor. Multivariate adjusted odds ratios and confidence intervals for variables included in this model are presented in Table 7. Controlling for postoperative defocus and important preoperative risk factors, soft contact lens wear (adjusted odds ratio=0.46, 95% CI=0.24, 0.89) and keratometry values >45 diopters (adjusted odds ratio=0.49, 95% CI=0.23, 1.03) were protective factors against reporting clinical visual symptoms, similar to results indicated by the initial multivariate model. When postoperative defocus was adjusted for, patients who reported clinical visual symptoms or requested INTACS removal were almost twice as likely to have had measured preoperative visual acuity two Snellen lines or worse than that predicted by their respective cycloplegic refraction and pupil size (adjusted odds ratio=1.84, 95% CI=0.98, 3.42). Patients with mesopic pupil size ≥6.5 mm were twice as likely (adjusted odds ratio=1.76, 95% CI=0.96, 3.24) to report clinical visual symptoms and/or request INTACS removal.

'Removals' Compared to 'Clinical Symptoms' Group:

Risk Factors for Requesting INTACS Removal

The intention of this analysis was to determine whether patients who ultimately requested INTACS removal could be differentiated from those who reported clinical visual symptoms but chose to keep INTACS in place. Patients within the 'Clinical Symptoms/Removals' outcome group were specifically stratified as 'Removals' or 'Clinical Symptoms' and compared using similar methods for evaluating results from the complete patient sample.

Means and confidence intervals for visual acuity, defocus equivalent and manifest refractive astigmatism were plotted for all outcome groups (Figures 5-8). The 'Infrequent Symptoms' group has been included for reference. Pre- and postoperative uncorrected visual acuity was worse in the 'Removals' group (~20/125, ~20/40, respectively) than either the 'Clinical Symptoms' (~20/100, ~20/20) or 'Infrequent Symptoms' (~20/80, ~20/16) groups. Defocus equivalent results corresponded to the trend demonstrated by visual acuity. Manifest refractive astigmatism was similar for groups preoperatively, but significantly worse in the 'Removals' group postoperatively.

Multivariate odds ratios for preoperative risk factors are presented in Table 8. Adjusting for other potential preoperative risk factors, within the group of patients reporting significant clinical visual symptoms postoperatively, those who requested INTACS removal were significantly more likely to have received 0.35 mm INTACS compared to 0.25 mm INTACS (adjusted odds ratio=5.14, 95% CI=1.58, 16.77). Patients requesting INTACS removal were more likely to have had preoperative manifest refractive astigmatism greater than 0.50 diopter (adjusted odds ratio=2.72, 95% CI=0.73, 10.00).

Multivariate odds ratios adjusted for postoperative defocus are presented in Table 9. Adjusting for postoperative defocus and important preoperative risk factors, patients who ultimately requested removal of INTACS were three times more likely to have had measured preoperative visual acuity two or more Snellen lines worse than predicted (adjusted odds ratio=3.33, 95% CI=1.03, 10.73). Patients who requested INTACS removal were four and a half times more likely to have had greater than 0.50 diopter of preoperative manifest refractive astigmatism, compared to patients who kept INTACS

even though they reported significant visual symptoms (adjusted odds ratio=4.68, 95% CI=0.91, 24.00). Taking postoperative defocus equivalent and all other preoperative risk factors into consideration, patients who had 0.35 mm INTACS were over 4 times more likely to request removal than patients with 0.25 mm INTACS (adjusted odds ratio=4.48, 95% CI= 1.00, 20.13). Compared to the 'Clinical Symptoms' group, 'Removals' patients were three and a half times more likely to have mesopic pupil size ≥6.5 mm (adjusted odds ratio=3.42, 95% CI=1.00, 11.75) and three and a half times more likely to have worn rigid contact lenses preoperatively (adjusted odds ratio=3.74, 95% CI=0.66, 21.36).

Resolution of Clinical Visual Symptoms up to Postoperative Month 24

Clinical visual symptoms resolved progressively over time within the patient group reporting them (Table 10). Fifty-eight percent (71/122) of patients in the 'Clinical Symptoms' group stopped reporting clinical visual symptoms by postoperative Month 24.

Chapter 5: Discussion

Preoperative profiling of refractive surgery candidates is valuable for the refractive surgeon for ensuring postoperative patient satisfaction. This study had indicated that controlling for important potential ***preoperative*** risk factors simultaneously, INTACS clinical trial candidates who reported significant postoperative clinical visual symptoms or requested INTACS removal were less likely to have worn soft contact lenses preoperatively or to have had preoperative refractive astigmatism. These patients were also less likely more likely to have had measured preoperative visual acuity that was approximate to or better than that predicted by refractive error and pupil size. Patients who had corneas larger than 12.0 mm or relatively thinner corneas demonstrated increased risk for reporting clinical visual symptoms, although risk was not statistically significant. Risk of significant clinical visual symptoms with INTACS appeared to be reduced with full postoperative myopic correction.

Postoperative visual and refractive results validated the classification scheme used to define outcome groups. Postoperative defocus equivalent and manifest refractive astigmatism were worst in the 'Removals' group, next highest in the 'Clinical Symptoms' group and lowest in the 'Infrequent Symptoms' group. A corresponding trend was noted in values for uncorrected visual acuity. The 'Removal' group had the worst mean postoperative uncorrected visual acuity (~20/40), compared to the 'Clinical Symptoms' group with average visual acuity equivalent to 20/20, and the 'Infrequent Symptoms' group with average visual acuity better than 20/20.

Postoperative defocus equivalent for the 'Clinical Symptoms' group (mean=0.69, SD=0.53) was significantly higher than in the 'Infrequent Symptoms' group (mean=0.49, SD=0.42). Defocus equivalent was calculated using cycloplegic refractive data, measured with mesopic pupil. Patients who report symptoms after a refractive procedure are most likely to experience them with a nighttime (relatively more dilated) pupil.[12,25,26] The 'Clinical Symptoms' group appeared to have had, on average, values for uncorrected visual acuity and manifest refractive astigmatism which correspond to good daytime vision (uncorrected visual acuity of ~20/20 and acceptable manifest refractive astigmatism of 0.50 diopter). Neither of these measures was significantly different from measures collected for the 'Infrequent Symptoms' group. The refractive error (defocus equivalent) threshold for experiencing significant visual symptoms at night, with wider pupil, may have been exceeded by the 'Clinical Symptoms' group. According to the Holladay et al. model,[26] a pupil size of 6 mm and defocus equivalent of 0.50 diopter would result in approximately 20/28 predicted visual acuity. Predicted visual acuity for the same pupil diameter and 1.0 diopter of defocus equivalent be approximately 20/52. With 0.50 diopter additional defocus equivalent, these investigators suggested that visual acuity is decreased by three lines. Our study demonstrated that risk of visual symptoms approximately doubled with every 0.50 diopter of increased defocus equivalent. The 'under-correction' or 'night myopia' experienced by patients who have exceeded some theoretical limit for defocus equivalent with a given pupil diameter may result in more severe or frequent clinical visual symptoms following INTACS refractive surgery. Patients in the 'Removals' group appeared to have had less than optimal visual performance during both day and night.

Multivariate analysis techniques allowed us to determine significance of individual risk factors while controlling for effects of other important dependent variables. Preoperative use of soft contact lenses was indicated to be a 'protective' factor against reporting clinical visual symptoms with INTACS. Soft contact lens wear has been previously shown to be associated with increased optical light scatter, compared to spectacle or hard contact lens wear or PRK laser refractive surgery.[94] Visual performance for these patients, described using low-contrast visual acuity results, corresponded to the optical analyses. Patients who wore soft contact lenses had significantly worse low-contrast visual acuity than patients in other corrective wear groups. Findings of a protective effect with preoperative soft contact lens wear against reporting visual symptoms, compared to not wearing contacts, imply that our patients had experienced less than optimal visual performance ***before*** their refractive procedure and, thus, they may have been less inclined to report clinical visual symptoms afterward. Hersh and colleagues recently described incidence of visual symptoms in a group of patients who underwent PRK in one eye and LASIK in the other eye.[22] Their results showed that many patients reported no change in or less severe visual symptoms postoperatively compared to preoperatively, regardless of procedure. It would have been interesting for these investigators to evaluate whether patients reporting less severe postoperative visual symptoms after PRK or LASIK were most likely to have worn soft contact lenses preoperatively (compared to rigid or no contacts).

This investigation indicated that 'visual acuity disconnect' may be associated with self-reported clinical visual symptoms after the INTACS refractive procedure. Adjusting for all other preoperative risk factors, patients who had preoperative measured

uncorrected visual acuity that was two or more Snellen lines ***better*** than that expected for their refractive error and pupil size were ***less*** likely to report postoperative clinical visual symptoms. In addition, patients who had preoperative visual acuity two Snellen lines or ***worse*** than that predicted by their refractive error were ***more*** than likely to report clinical visual symptoms with INTACS and/or request its removal, after controlling for other preoperative risk factors and postoperative defocus equivalent. Historical study has demonstrated the relationship between refractive error and uncorrected visual acuity for defining myopia.[26,90,95,96] The relationship between the two is approximately linear for low levels of myopia, although, it can be highly variable in normal eyes.[26,90,95,96] The inherent variability between visual and refractive performance suggests that other factors, besides refractive error, play a significant role in our ability to finely resolve letters or shapes. The importance of personal and ocular characteristics for predicting postoperative visual acuity has been shown in patients prior to cataract surgery.[97] Kora and colleagues were able to improve prediction of postoperative visual acuity before cataract surgery (to aid in IOL calculation) when they accounted for ocular axial length, age, corneal opacity, corneal refractive power and history of retinal detachment surgery. Our study indicated that significantly better or worse than predicted disparity between preoperative measured visual acuity and the visual acuity predicted by refractive error, or visual acuity disconnect, was shown to significantly impact reporting of postoperative clinical visual symptoms with INTACS. Visual acuity disconnect may be a surrogate measure for important predictive factors that are currently impossible to measure clinically or were not measured for this study.

Disparity between measured and predicted visual acuity with refractive surgery was first noted during the Prospective Evaluation of Radial Keratotomy (PERK) clinical trial.[95] Visual acuity was evaluated in postoperative patients following radial keratotomy and compared to normal myopic controls matched by refractive error. Postoperative radial keratotomy patients exhibited significantly better uncorrected visual acuity for a given refractive error than control patients. The authors speculated that visual acuity differences could have occurred because of pupil size differences between groups or changes in corneal multifocal optical quality with radial keratotomy.

None of the corneal topography performance parameters, except the preoperative Effective Refractive Power index and postoperative asphericity quotient, were associated with risk of reporting clinical visual symptoms, even though corneal topography measures are designed to be indicators of corneal optical quality and subsequent visual performance. Patients with postoperative corneas measured as oblate ($Q > 0.00$) were almost nine times more likely to report clinical visual symptoms or request INTACS removal than patients with normal, prolate corneas ($Q = 0.00$ to -0.50). It has been well established using different techniques and methods, including Placido-disk topography and optical interferometry, that anterior corneal surface asphericity remains prolate following the INTACS refractive procedure.[38,79-81] The finding of postoperative oblate asphericity with INTACS was most likely an artifact of Placido-disk based corneal topography. In these patient cases, the corneal topography unit probably detected some corneal surface anomaly, which corresponded to increased risk for reporting clinical visual symptoms.

The corneal topography indices analyzed in this study were derived by the manufacturer and are based on values or assumptions provided by the literature for normal (preoperative) eyes.[64] The indices did not appear to be useful for differentiating either pre- or postoperative refractive patients for risk of subjective self-reported clinical visual symptoms. Placido-disk based corneal topography has been revealed to have application limitations, including excessive smoothing of collected raw data and inherent weaknesses in assumptions when developing software algorithms.[98,99]

Placido-disk based corneal topography analyses has been shown to be useful for predicting visual performance by examining raw radius of curvature or elevation slope maps.[16,35,36,37] It has been previously found that distinct ***qualitative*** postoperative corneal topography color map patterns, based on radius of curvature data, were associated with type of self-reported clinical visual symptom.[38] In this study, color axial curvature topography maps for individual patients were assessed by classifying qualitative anterior corneal surface topography patterns. Corneal topography patterns were categorized as one of the following prolate patterns: spherical (SPH), non-toric prolate asphere (PAS), symmetrically toric (STO), asymmetrically toric (ATO), multizonal (MZA) and unclassifiable (UNC), corresponding to previously published works.[39, 40-44] The postoperative symmetric toricity or astigmatic (STO) pattern was found to be associated with self-reported frequency of 'double images' and the asymmetric toricity (ATO) pattern was related to frequency of self-reported 'halos'. Preoperative color map classifications however were not associated with risk for reporting visual symptoms postoperatively. It may be more useful in future study to use *qualitative* measures of corneal topography, rather than quantitative indices automatically provided by topography

software for examining relationships between visual symptoms and associated risk factors.

Power of our study may have been limited by sample size, even though calculations conducted antecedent to the study indicated adequate power for detecting clinical differences between groups at $p \leq 0.05$ with our fixed sample size. Future study of this nature might be improved by with increased sample size.

Small sample size precludes any definitive conclusions about differences between the 'Removals' and 'Clinical Symptoms' patients. However, it is interesting to note the trend differences between this multivariate model and the model in which outcome groups were combined. Risk associated with preoperative manifest refractive astigmatism was essentially reversed after stratifying the 'Clinical Symptoms/Removals' group into 'Clinical Symptoms' and 'Removals'. Preoperative manifest refractive astigmatism provided a protective effect against self-report of significant postoperative clinical visual symptoms when the outcome groups were combined; however, relatively higher levels of refractive astigmatism were associated with increased risk for INTACS removal when the groups were compared against each other.

Additionally, comparison of the 'Removal' and 'Clinical Symptoms' patients indicated that preoperative **rigid** contact lens wear might increase risk for requesting INTACS removal within patients reporting clinical visual symptoms postoperatively. After adjusting for postoperative defocus and other important potential preoperative risk factors, patients who wore rigid contact lenses had three to four times increased risk for requesting INTACS removal compared to other patients reporting clinical visual symptoms who had not worn contacts before this refractive procedure. Previous

investigation has demonstrated corneal pathophysiology following long-term rigid contact lens wear[54-56,100] and corneal surface irregularity associated with rigid contact lens wear has been shown to take up to six months to resolve.[55] It is also possible that expectations of acceptable postoperative visual performance may differ between people who choose to wear rigid contact lenses compared to those who choose not to wear them. When expectations were not met following INTACS placement, rigid contact lens wearers may have been more likely to request INTACS removal than those with "lower expectations". Refractive astigmatism and contact lens wear trend differences suggest that the 'INTACS Removal' and 'Clinical Symptoms' patient outcome groups may have differed fundamentally and should not have been combined for our primary analysis.

Because we wished to preserve power of our study for detecting differences between outcome groups, the decision was made to include data for the second surgical eye for one clinical site which failed to collect corneal topography data for initial eyes preoperatively and at postoperative Month 3. Retrospective data analyses were run excluding information collected from this site to explore whether results would be modified by any selection bias that might have occurred because we used second eye data. Noted trends for risk factors were similar between the original and revised models, although power for detecting statistical differences was diminished when sample size was reduced, as would be expected.

Conclusions drawn from this study stem from a clinical trial cohort. Preoperative characteristics of a clinical trial population may differ from a sample of patients who are willing to pay for refractive procedure on their own, therefore applying findings from this study to 'commercial' patients must be undertaken with care. Future study of

preoperative risk factors with refractive surgery should be conducted within patient groups seeking other types of refractive procedures, besides INTACS, and within patient subsets not participating in a clinical trial. Other improvements to this type of investigation would include using more precise metrology to assess ocular geometry and survey of different types of corneal topography information.

The current study indicated that preoperative as well as postoperative factors may predispose patients for reporting clinical visual symptoms following the INTACS refractive procedure. By postoperative Month 24, 58% of patients who had reported significant clinical visual symptoms at some time point over the clinical trial had stopped reporting them. A good candidate for the INTACS refractive procedure appears to be someone who wore soft contact lenses preoperatively, whose uncorrected visual acuity approximates or is better than that predicted by refractive error and pupil size, and who may have a small amount of astigmatism preoperatively. Preoperative screening of INTACS refractive surgery candidates for risk factors associated with postoperative visual performance is important. Advising potential candidates openly and knowledgeably about potential optical side effects and their personal risk for experiencing them, before they undergo refractive surgery, will improve overall patient satisfaction and will likely optimize preoperative procedure planning by the physician.

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Table 1. Risk factors for postoperative clinical visual symptoms and Intacs removal associated with demographic variables, preoperative contact lens use and Intacs thickness in outcome groups.

Independent Variable	All Patients (n=263)	'Infrequent Symptoms' (n=111)	'Clinical Symptoms / Removals' (n=152)	Univariate Odds Ratio	95% CI# (p-value)
Gender					
Male	122 (46%)	49 (44%)	73 (48%)	1.00	
Female	141 (54%)	62 (56%)	79 (52%)	0.86	0.52, 1.40 (p=0.53)
Ethnicity					
Caucasian	234 (89%)	99 (89%)	135 (89%)	1.00	
All Others	29 (11%)	12 (11%)	17 (11%)	1.04	0.48, 2.27 (p=0.92)
Age					
≤ 39 years	127 (48%)	53 (48%)	74 (49%)	1.00	
≥ 40 years	136 (52%)	58 (52%)	78 (51%)	0.96	0.59, 1.57 (p=0.88)
Preop Contact Lens Use					
No contacts	94 (36%)	36 (32%)	58 (38%)	1.00	
Rigid	18 (7%)	4 (4%)	14 (9%)	2.17	0.66, 7.12 (p=0.20)
Soft	150 (57%)	71 (64%)	80 (53%)	0.70	0.41, 1.18 (p=0.18)
Intacs Distribution					
0.25 mm	88 (33%)	46 (37%)	42 (28%)	1.00	
0.30 mm	90 (34%)	34 (31%)	56 (37%)	1.80*	0.99, 3.28 (p=0.05)
0.35 mm	85 (32%)	31 (28%)	54 (36%)	1.91*	1.04, 3.51 (p=0.04)

* $p \leq 0.05$, # CI = confidence interval

Table 2. Risk factors for postoperative clinical visual symptoms and Intacs removal associated with ocular geometry variables in outcome groups.

Independent Variable	All Patients (n=263)	'Infrequent Symptoms' (n=111)	'Clinical Symptoms / Removals' (n=152)	Univariate Odds Ratio	95% CI (p-value)
Mesopic Pupil Size					
<6.5 mm	147 (56%)	65 (59%)	82 (54%)	1.00	
≥6.5 mm	116 (44%)	46 (41%)	70 (46%)	1.21	0.74, 1.98 (p=0.46)
Limbal diameter (horizontal)					
11.00 to 12.00 mm	192 (73%)	85 (77%)	107 (70%)	1.00	
<11.00 mm	54 (21%)	21 (19%)	33 (22%)	1.24	0.67, 2.31 (p=0.48)
>12.00 mm	17 (6%)	5 (5%)	12 (8%)	1.91	0.65, 5.62 (p=0.24)
Central pachymetry					
0.5 to 0.6 mm	233 (89%)	98 (88%)	135 (89%)	1.00	
<0.5 mm	8 (3%)	2 (2%)	6 (4%)	2.18	0.43, 11.0 (p=0.35)
>0.6 mm	22 (8%)	11 (10%)	11 (7%)	0.73	0.30, 1.74 (p=0.47)
Incision site pachymetry					
0.6 to 0.7 mm	198 (75%)	87 (78%)	111 (73%)	1.00	
<0.6 mm	11 (4%)	3 (3%)	8 (5%)	2.09	0.54, 8.11 (p=0.29)
>0.7 mm	54 (21%)	21 (19%)	33 (22%)	1.23	0.67, 2.28 (p=0.51)
Keratometry					
42 to 45 D	191 (73%)	74 (67%)	117 (77%)	1.00	
<42 D	25 (10%)	10 (9%)	15 (10%)	0.95	0.41, 2.00 (p=0.90)
>45 D	46 (17%)	27 (24%)	19 (13%)	0.45*	0.23, 0.86 (p=0.02)

* $p \leq 0.05$, # CI = confidence interval

Table 3. Risk factors for postoperative clinical visual symptoms and Intacs removal associated with visual performance variables in outcome groups.

Independent Variable	All Patients (n=263)	'Infrequent Symptoms' (n=111)	'Clinical Symptoms/ Removals' (n=152)	Univariate Odds Ratio	95% CI[#] (p-value)
Measured visual acuity compared to predicted					
Approximate (0-1 line)	124 (47%)	53 (48%)	71 (46%)	1.00	
Worse ($\geq$ 2 lines)	120 (46%)	46 (41%)	74 (49%)	1.20	0.72, 2.00 (p=0.48)
Better ($\geq$ 2 lines)	19 (7%)	12 (10%)	7 (5%)	0.44[‡]	0.16, 1.18 (p=0.10)
Preop Manifest Refractive Astigmatism Magnitude					
$\leq$0.50 D	222 (84%)	88 (79%)	134 (88%)	1.00	
>0.50 D	41 (16%)	23 (21%)	18 (12%)	0.51*	0.26, 1.01 (p=0.05)
Preop Manifest Refractive Astigmatism Orientation					
SPH	105 (40%)	42 (38%)	63 (41%)	1.00	
ATR	81 (31%)	40 (36%)	41 (27%)	0.68	0.38, 1.23 (p=0.20)
WTR	77 (29%)	29 (26%)	48 (32%)	1.10	0.60, 2.02 (p=0.75)

[‡] $p \leq 0.10$, * $p \leq 0.05$, [#] CI = confidence interval

Table 4. Risk factors for postoperative clinical visual symptoms and Intacs removal associated with **preoperative** corneal topography variables in outcome groups.

Independent Variable	All Patients (n=263)	'Infrequent Symptoms' (n=104)	'Clinical Symptoms/ Removals' (n=138)	Univariate Odds Ratio	95% CI[#] (p-value)
Topographic Astigmatism					
≤0.75 D	162 (67%)	73 (70%)	89 (65%)	1.00	
>0.75 D	80 (33%)	31 (30%)	49 (35%)	1.30	0.75, 2.24 (p=0.35)
Effective Refractive Power					
42 to 45 D	169 (70%)	65 (63%)	104 (75%)	1.00	
<42 D	47 (19%)	24 (23%)	23 (17%)	0.60	0.31, 1.15 (p=0.12)
>45 D	26 (11%)	15 (14%)	11 (8%)	0.46[‡]	0.20, 1.06 (p=0.07)
Asphericity Quotient (Q)					
0.00 to –0.50	153 (63%)	67 (65%)	86 (62%)	1.00	
All others	89 (37%)	37 (36%)	52 (38%)	1.10	0.65, 1.86 (p=0.74)
Corneal Uniformity Index (CUI)					
100%	219 (90%)	92 (88%)	127 (92%)	1.00	
<100%	23 (10%)	12 (12%)	11 (8%)	0.66	0.28, 1.57 (p=0.35)
Predicted Corneal Acuity (PCA)					
20/20 or better	234 (97%)	99 (95%)	135 (98%)	1.00	
25/25 or worse	7 (3%)	4 (4%)	3 (2%)	0.55	0.12, 2.51 (p=0.44)

[‡] $p \leq 0.10$, [#] CI = confidence interval

Table 5. Risk factors for postoperative clinical visual symptoms and Intacs removal associated with **postoperative** corneal topography variables in outcome groups.

Independent Variable	All Patients (n=147)	'Infrequent Symptoms' (n=63)	'Clinical Symptoms/ Removals' (n=84)	Univariate Odds Ratio	95% CI # (p-value)
Topographic Astigmatism					
≤0.75 D	74 (50%)	34 (53%)	40 (48%)	1.00	
>0.75 D	73 (50%)	29 (47%)	44 (52%)	1.29	0.67, 2.48, p=0.45
Effective Refractive Power					
42 to 45 D	69 (47%)	30 (48%)	39 (46%)	1.00	
<42 D	75 (51%)	32 (51%)	43 (51%)	1.03	0.53, 2.00, p=0.92
>45 D	3 (2%)	1 (2%)	2 (2%)	1.54	0.13, 17.78, p=0.73
Asphericity Quotient (Q)					
0.00 to –0.50	78 (53%)	40 (64%)	38 (45%)	1.00	
>0.00 (oblate)	19 (13%)	2 (3%)	17 (20%)	8.95*	1.94, 41.36, p=0.01*
<-0.50 (more prolate)	50 (34%)	21 (33%)	29 (35%)	1.45	0.71, 2.97, p=0.31
Corneal Uniformity Index (CUI)					
100%	88 (60%)	39 (62%)	49 (58%)	1.00	
<100%	59 (40%)	24 (38%)	35 (42%)	1.16	0.60, 2.27, p=0.62
Predicted Corneal Acuity (PCA)					
20/20 or better	118 (80%)	52 (83%)	66 (79%)	1.00	
25/25 or worse	29 (18%)	11 (17%)	18 (21%)	1.29	0.56, 2.97, p=0.55

* $p \leq 0.05$, # CI = confidence interval

Table 6. Multivariate odds ratios for preoperative risk factors predicting postoperative visual symptoms and/or removals with Intacs.

Independent Variable	Multivariate Odds Ratio	95% CI [#] (p-value)
Keratometry		
42 to 45 D	1.00	
<42 D	1.00	0.41, 2.41 (p=0.99)
>45 D	0.43*	0.21, 0.85 (p=0.02)
Intacs		
0.25 mm	1.00	
0.30 mm	2.12*	1.12, 4.00 (p=0.02)
0.35 mm	2.05*	1.06, 3.97 (p=0.03)
Preop Contact Lens Use		
No contacts	1.00	
Rigid	2.07	0.58, 7.43 (p=0.26)
Soft	0.58[‡]	0.32, 1.04 (p=0.07)
Measured visual acuity compared to predicted		
Approximate (0-1 line)	1.00	
Worse ($\geq$ 2 lines)	1.21	0.70, 2.10 (p=0.50)
Better ($\geq$ 2 lines)	0.39[‡]	0.14, 1.12 (p=0.08)
Preop Manifest Refractive Astigmatism		
$\leq$0.50 D	1.00	
>0.50 D	0.52[‡]	0.25, 1.08 (p=0.08)
Mesopic Pupil Size		
<6.5 mm	1.00	
$\geq$6.5 mm	1.25	0.73, 2.15 (p=0.42)

[‡] $p \leq 0.10$, * $p \leq 0.05$, [#] CI = confidence interval

Table 7. Multivariate odds ratios for preoperative risk factors predicting postoperative visual symptoms and/or removals with Intacs, adjusting for postoperative defocus.

Independent Variable	Multivariate Odds Ratio	95% CI [#] (p-value)
Postoperative Defocus Equivalent (Crude OR=risk for every 0.50 D increase)	1.86*	0.53, 3.19 (p=0.00)
Preop Contact Lens Use		
No contacts	1.00	
Rigid	1.13	0.30, 4.30 (p=0.86)
Soft	0.46*	0.24, 0.89 (p=0.02)
Intacs		
0.25 mm	1.00	
0.30 mm	2.20*	1.09, 4.41 (p=0.03)
0.35 mm	1.65	0.78, 3.50 (p=0.19)
Measured visual acuity compared to predicted		
Approximate (0-1 line)	1.00	
Worse ($\geq$ 2 lines)	1.84[‡]	0.98, 3.42 (p=0.06)
Better ($\geq$ 2 lines)	0.39	0.12, 1.28 (p=0.12)
Keratometry		
42 to 45 D	1.00	
<42 D	0.95	0.37, 2.46 (p=0.91)
>45 D	0.49[‡]	0.23, 1.03 (p=0.06)
Mesopic Pupil Size		
<6.5 mm	1.00	
$\geq$6.5 mm	1.76[‡]	0.96, 3.24 (p=0.07)
Preop Manifest Refractive Astigmatism		
$\leq$0.50 D	1.00	
>0.50 D	0.57	0.25, 1.31 (p=0.21)

[‡] $p \leq 0.10$, * $p \leq 0.05$, [#] CI = confidence interval

Table 8. Multivariate odds ratios for preoperative risk factors predicting request for Intacs removal within a patient sub-group reporting significant clinical visual symptoms postoperatively.

Independent Variable	'Clinical Symptoms' (n=122)	'Removals' (n=30)	Multivariate Odds Ratio	95% CI [#]
Intacs				
0.25 mm	37/122 (30%)	5/30 (16%)	1.00	
0.30 mm	50/122 (40%)	6/30 (23%)	1.09	0.30, 3.98, p=0.90
0.35 mm	35/122 (30%)	19/30 (61%)	5.14*	1.58, 16.77, p=0.01
Preop Manifest Refractive Astigmatism				
≤0.50 D	109/122 (91%)	25/30 (81%)	1.00	
>0.50 D	13/122 (9%)	5/30 (19%)	2.72	0.73, 10.00, p=0.14
Preop Contact Lens Use				
No contacts	46/122 (40%)	10/30 (32%)	1.00	
Rigid	8/122 (7%)	5/30 (16%)	2.20	0.52, 9.27, p=0.29
Soft	62/122 (53%)	16/30 (52%)	0.92	0.34, 2.47, p=0.87
Measured visual acuity compared to predicted				
Approximate (0-1 line)	56/122 (47%)	12/30 (42%)	1.00	
Worse (≥ 2 lines)	59/122 (47%)	18/30 (58%)	1.58	0.64, 3.86, p=0.32
Better (≥ 2 lines)	7/122 (6%)	0/30 (0%)	0.00	
Mesopic Pupil Size				
<6.5 mm	65/122 (53%)	17/30 (58%)	1.00	
≥6.5 mm	57/122 (47%)	13/30 (42%)	1.16	0.47, 2.86, p=0.75

[‡] $p \leq 0.10$, * $p \leq 0.05$, [#] CI = confidence interval

Table 9. Multivariate odds ratios for preoperative risk factors predicting request for Intacs removal within a patient sub-group reporting significant clinical visual symptoms postoperatively, adjusting for postoperative defocus equivalent.

Independent Variable	Multivariate Odds Ratio	95% CI [#]
Postoperative Defocus Equivalent (Crude OR=risk for every 0.50 D increase)	2.38*	0.91, 3.85, p=0.00
Measured visual acuity compared to predicted		
Approximate (0-1 line)	1.00	
Worse ($\geq$ 2 lines)	3.33*	1.03, 10.73, p=0.04
Better ($\geq$ 2 lines)	0.00	
Mesopic Pupil Size		
<6.5 mm	1.00	
$\geq$6.5 mm	3.42*	1.00, 11.75, p=0.05
Intacs		
0.25 mm	1.00	
0.30 mm	1.06	0.21, 5.37, p=0.94
0.35 mm	4.48*	1.00, 20.13, p=0.05
Preop Manifest Refractive Astigmatism		
$\leq$0.50 D	1.00	
>0.50 D	4.68[‡]	0.91, 24.00, p=0.06
Preop Contact Lens Use		
No contacts	1.00	
Rigid	3.74	0.66, 21.36, p=0.14
Soft	1.68	0.48, 5.89, p=0.42

[‡] $p \leq 0.10$, * $p \leq 0.05$, [#] CI = confidence interval

Table 10. Postoperative exam at which significant clinical visual symptoms were last reported for individual patients.

	Clinical Visual Symptoms Last Reported	Cumulative
Month 3	9 / 122 (7%)	9 / 122 (7%)
Month 6	32 / 122 (26%)	41 / 122 (34%)
Month 12	30 / 122 (25%)	71 / 122 (58%)

*51/122 reported significant clinical visual symptoms at postoperative month 24

Figure Legends

Figure 1. Average pre- and postoperative uncorrected visual acuity for 'clinical symptoms/removals' and 'infrequent symptoms' outcome groups. Vertical bars through the mean are 95% confidence intervals.

Figure 2. Average pre- and postoperative best spectacle-corrected visual acuity for 'clinical symptoms/removals' and 'infrequent symptoms' outcome groups. Vertical bars through the mean are 95% confidence intervals.

Figure 3. Average pre- and postoperative defocus equivalent for 'clinical symptoms/removals' and 'infrequent symptoms' outcome groups. Vertical bars through the mean are 95% confidence intervals.

Figure 4. Average pre- and postoperative manifest refractive astigmatism for 'clinical symptoms/removals' and 'infrequent symptoms' outcome groups. Vertical bars through the mean are 95% confidence intervals.

Figure 5. Average pre- and postoperative uncorrected visual acuity for 'clinical symptoms' and 'removals' outcome groups. Vertical bars through the mean are 95% confidence intervals.

Figure 6. Average pre- and postoperative best spectacle-corrected visual acuity for 'clinical symptoms' and 'removals' outcome groups. Vertical bars through the mean are 95% confidence intervals.

Figure 7. Average pre- and postoperative defocus equivalent for 'clinical symptoms' and 'removals' outcome groups. Vertical bars through the mean are 95% confidence intervals.

Figure 8. Average pre- and postoperative manifest refractive astigmatism for 'clinical symptoms' and 'removals' outcome groups. Vertical bars through the mean are 95% confidence intervals.

Figure 1

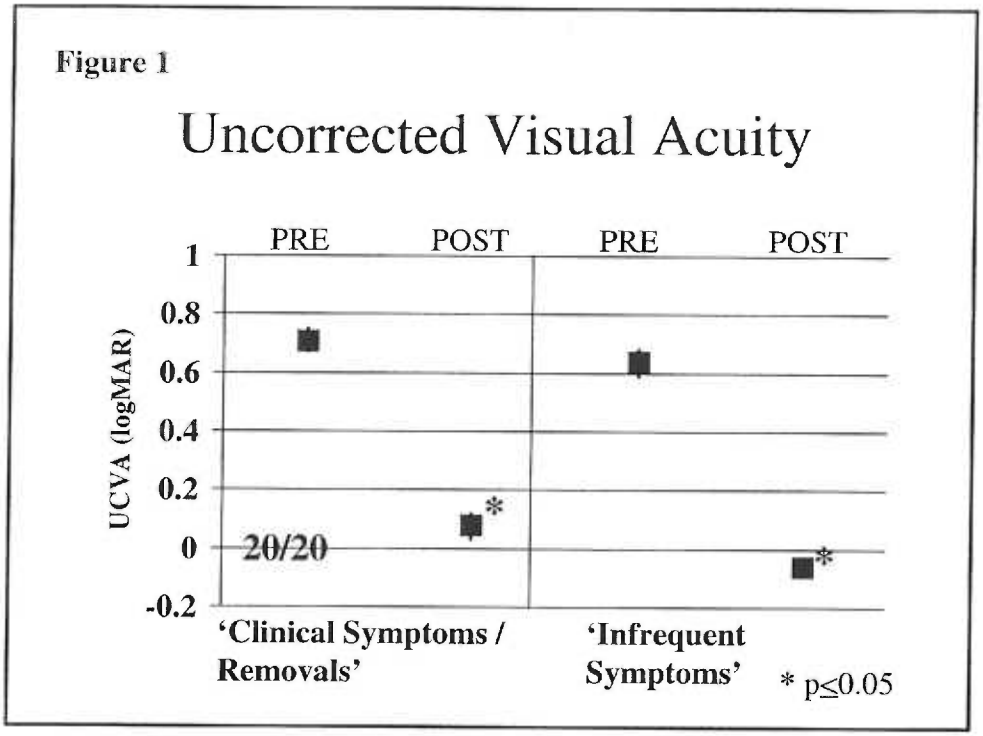


Figure 2

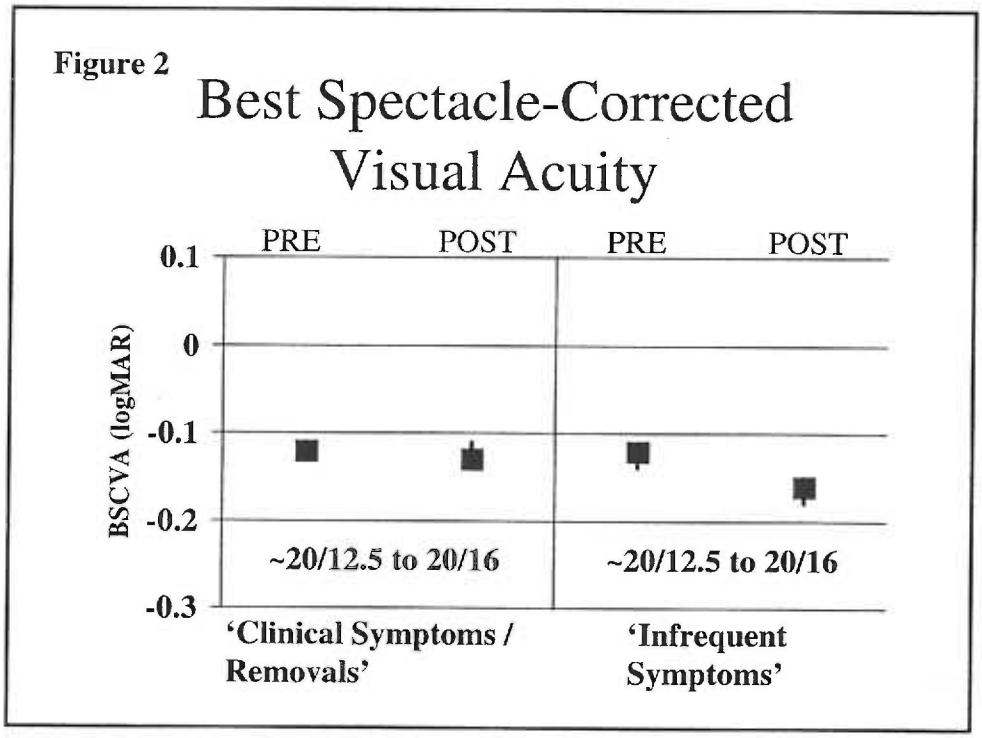


Figure 3

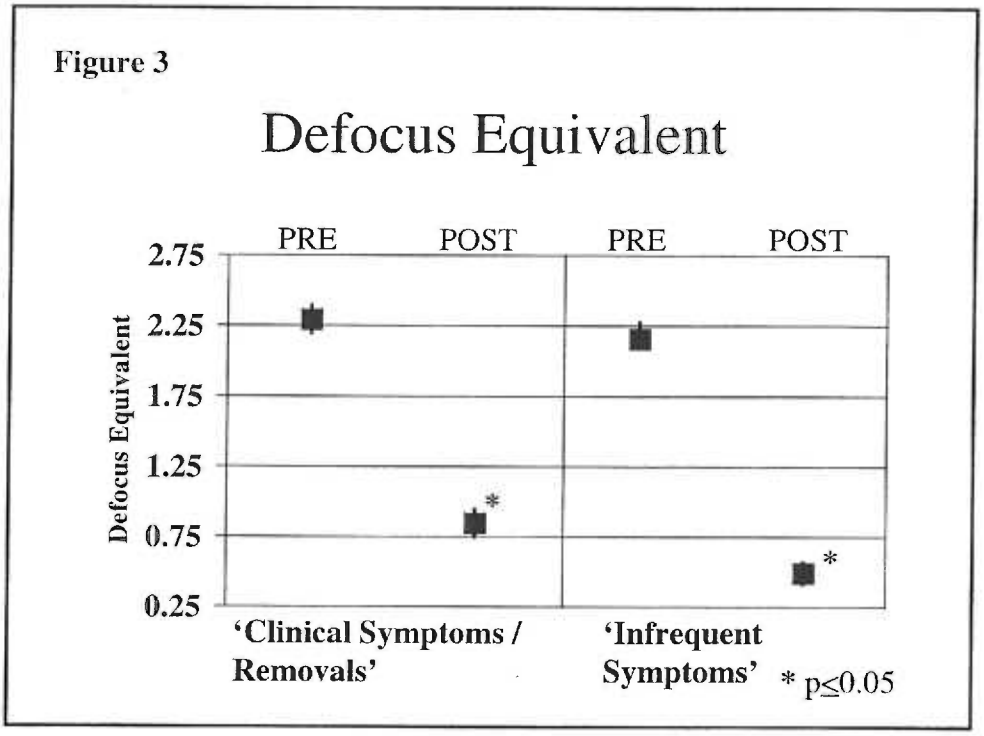


Figure 4

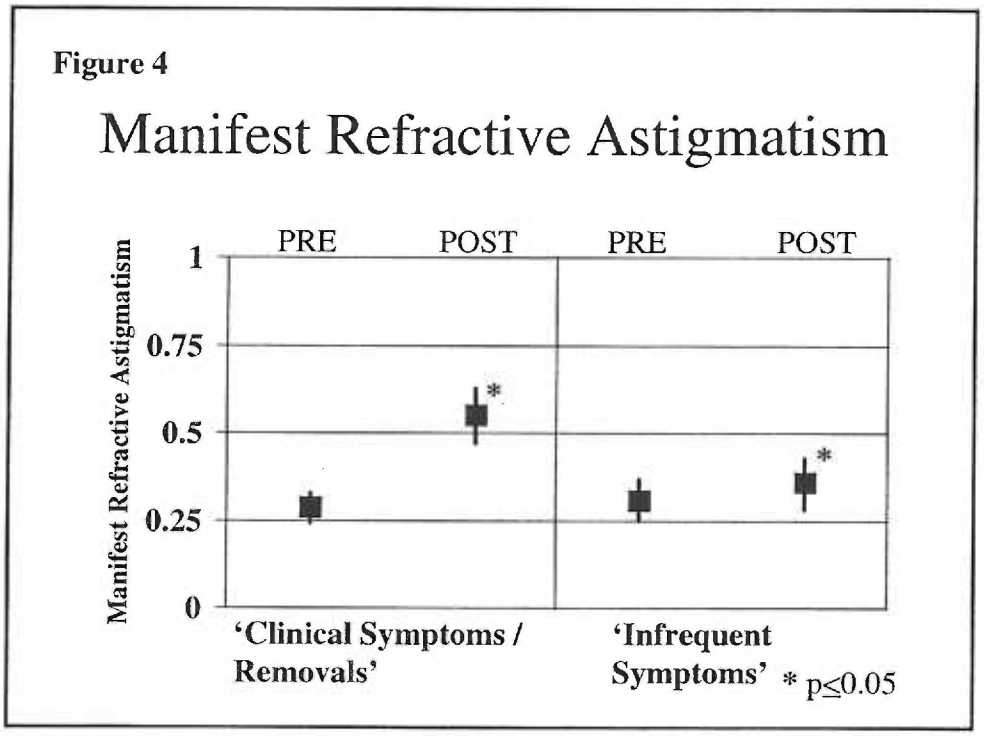
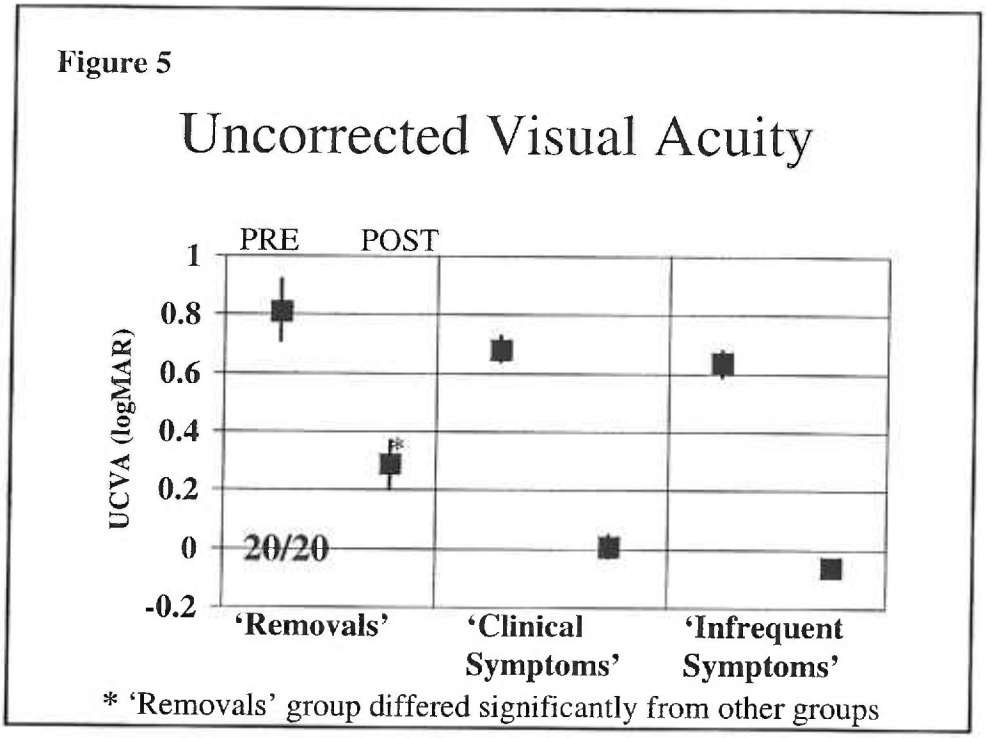


Figure 5



* 'Removals' group differed significantly from other groups

Figure 6

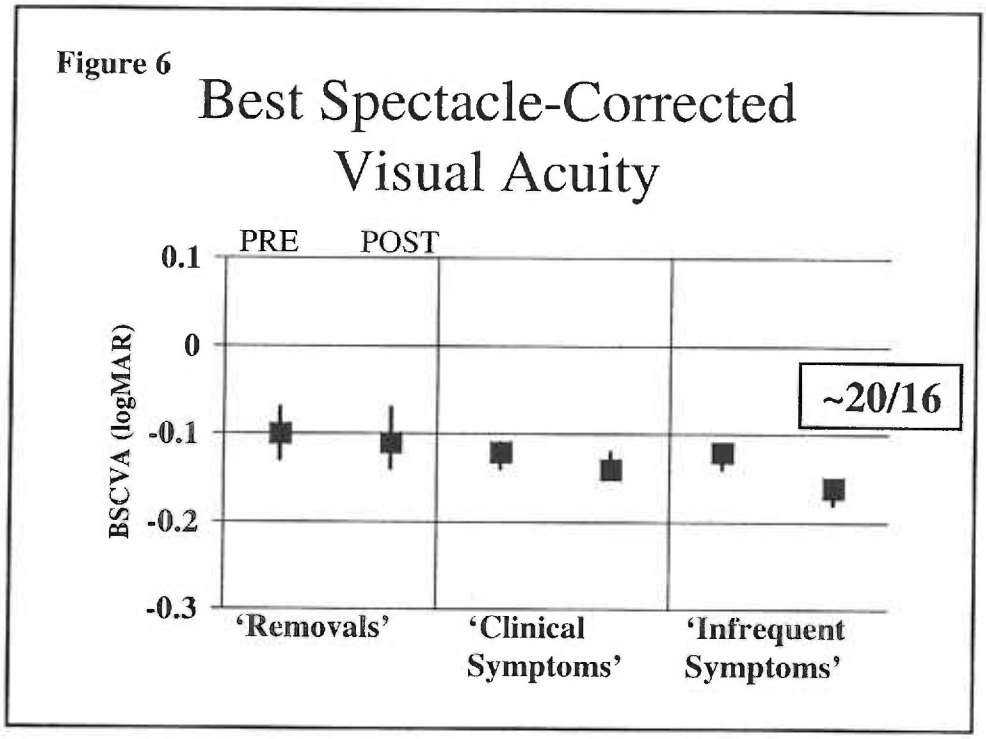
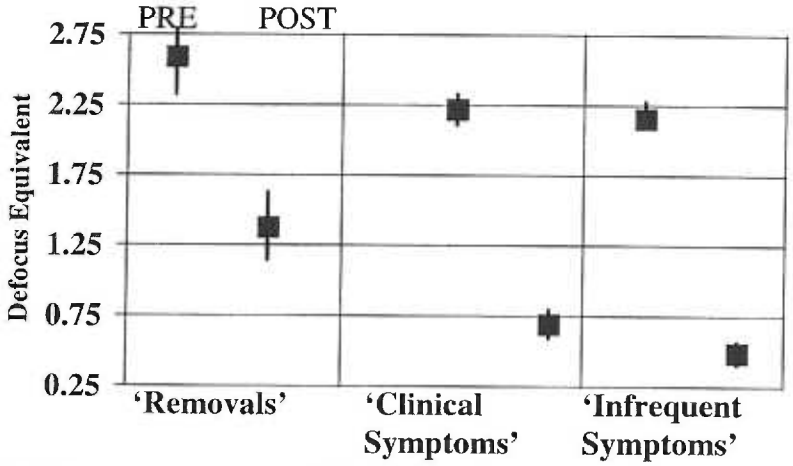


Figure 7

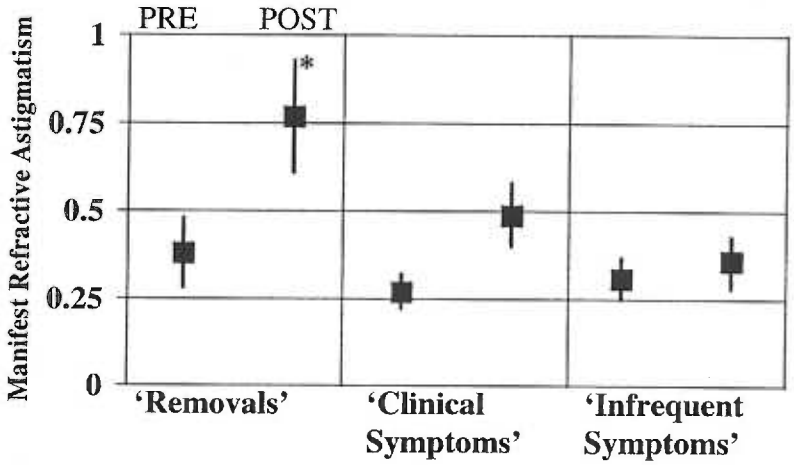
Defocus Equivalent



* All outcome groups differed significantly from each other

Figure 8

Manifest Refractive Astigmatism



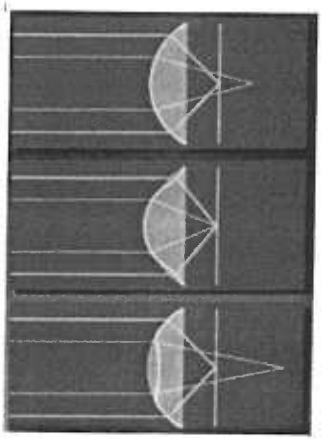
* 'Removals' group differed significantly from other groups

Appendices

Appendix 1.

Graphical representation of spherical aberration produced by spherical, prolate and oblate elliptical surfaces. The red lines represent rays of light refracted by the central region of the optical surface (cornea); yellow lines represent rays of light refracted by peripheral regions of the optical surface. The blue line on the right represents the imaging plane (retina). Note that the prolately-shaped optical surface refracts light rays from both areas directly onto the imaging plane.

Asphericity



Spherical Ellipse,
$Q = 0$

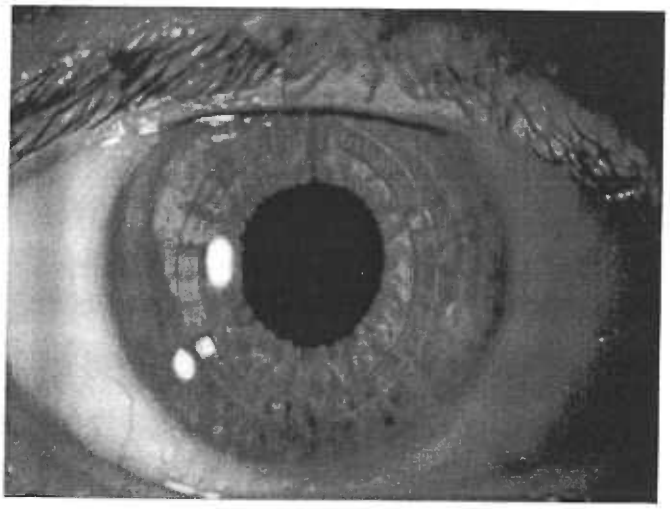
Prolate Ellipse,
$-1.0 < Q < 0$

Oblate Ellipse,
$Q > 0$

Appendix 2.

KeraVision® Intacs™ in place

Correction of Myopia
--KeraVision® INTACS™--



Appendix 3.

Outcome Group Distribution by Clinical Site

	Infrequent Symptoms	Removals / Clinical Symptoms	Total
ABEI	8 (57%)	6 (43%)	14 (100)
EVCC	15 (31%)	34 (69%)	49 (100%)
USF	17 (46%)	20 (54%)	37 (100%)
MEA*‡ *(2nd eye)	13 (68%)	6 (32%)	19 (100%)
NWCS	17 (47%)	19 (53%)	36 (100%)
HEC	23 (46%)	27 (54%)	50 (100%)
MSH	13 (41%)	19 (59%)	32 (100%)
UCSF	5 (19%)	21 (81%)	26 (100%)
Total	111 (42%)	152 (58%)	263 (100%)
MEA (1st eye)	10 (53%)	9 (47%)	19 (100%)

‡ First eye data used for all clinical sites except for MEA

Appendix 4.

Study Power Estimates
Group A = 'Removals'
Group B = 'Clinical Symptoms'
Group C = 'Infrequent Symptoms'

Table A. Estimation of effect size differences between outcomes groups for preoperative risk factors.

Corneal Topography	Effect Size	Group C (n=205) Mean (SD)	Group A/B (n=54) Mean (SD)	Power
Total Astigmatism (D)	0.75	**0.60 (0.5)**	1.35 (0.5)	~1.0000
CUI Index (%)	10%	**100 (10)**	90 (10)	~1.0000
PCA Index (logMAR)	2 lines	**-0.3 (0.1)**	-0.1 (0.1)	~1.0000
Asphericity (Q)	0.25	**0.00 (0.2)**	0.25 (0.2)	~1.0000
Keratometry (D)	1.5	**42.5 (1.25)**	44.0 (1.25)	~1.0000
Visual and Refractive Performance				
Manifest Cylinder (D)	0.25	**0.27 (0.25)**	0.45 (0.25)	0.9999
Ocular and Personal Characteristics				
Pupil Diameter (mm)	0.75	**6.2 (0.8)**	7.0 (0.8)	~1.0000
Limbal Diameter (mm) Nasal to temporal	1.0	**11.5 (1.0)**	12.5 (1.0)	~1.0000
Corneal Thickness (microns)				
Central	25	**530 (50)**	555 (50)	0.9804
Incision Site	50	**640 (50)**	690 (50)	~1.0000
Patient Age (years)	5	**41 (9.0)**	36 (9.0)	0.9932

Table B. Power for detecting differences between outcomes groups stratified by specified preoperative corrective lens wear.

Corrective Lens Wear	Effect Size	Group C (n=205)	Group A/B (n=54)	Power
Glasses	.2	**0.40**	0.20	0.9500
Contacts	.2	**0.60**	0.80	

Table C. Power for detecting differences between outcomes groups stratified by specified preoperative corrective lens wear.

Corrective Lens Wear	Effect Size	Group C (n=205)	Group A/B (n=54)	Power
Glasses or Soft Contacts	.2	**0.80**	0.60	0.9500
Rigid Contacts	.2	**0.20**	0.40	

Table D. Power for detecting differences between outcomes groups stratified by orientation of topographic toricity.

Orientation of Toricity	Effect Size	Group C (n=205)	Group A/B (n=54)	Power
With-the-rule	.15	**0.80**	0.95	0.9712
Against-the-rule	.15	**0.20**	0.05	

Table E. Estimation of effect size differences between Group A and Group B for preoperative risk factors.

Predictor Variable	**Group A (n=26) versus Group B (n=28)**			
Corneal Topography	Effect Size	Case Group 1 Mean (Std)	Case Group 2 Mean (Std)	Power
Total Astigmatism (D)	0.75	1.73 (0.5)	0.98 (0.5)	~1.0000
CUI Index (%)	10%	85 (10)	95 (10)	0.9931
PCA Index (logMAR)	1 line	-0.05 (0.1)	-0.15 (0.1)	0.9931
Asphericity (Q)	0.125	0.375 (0.2)	0.125 (0.2)	0.9997
Keratometry (D)	0.75	44.4 (1.25)	43.6 (1.25)	0.8434
Visual and Refractive Performance				
Manifest Cylinder (D)	0.25	0.58 (0.25)	0.33 (0.25)	0.9931
Ocular and Personal Characteristics				
Pupil Diameter (mm)	0.75	7.38 (0.8)	6.63 (0.8)	0.9866
Limbal Diameter (mm)				
Nasal to temporal	1.0	13.0 (1.0)	12.0 (1.0)	0.9931
Corneal Thickness (microns)				
Central	25	568 (50)	543 (50)	0.6654
Incision Site	50	715 (50)	665 (50)	0.9931
Patient Age (years)	2.5	30.5 (9.0)	35.5 (9.0)	0.7449

Table F1. Power for detecting differences between Groups A and B stratified by specified preoperative corrective lens wear.

Corrective Lens Wear	Effect Size	Group A (n=26)	Group B (n=28)	Power
Glasses	.2	0.1	0.3	0.6976
Contacts	.2	0.9	0.7	

Table F2. Power for detecting differences between Groups A and B stratified by specified preoperative corrective lens wear.

Corrective Lens Wear	Effect Size	Group A (n=26)	Group B (n=28)	Power
Glasses	.3	0.15	0.35	0.9618
Contacts	.3	0.95	0.65	

Table G1. Power for detecting differences between Groups A and B stratified by specified preoperative corrective lens wear.

Corrective Lens Wear	Effect Size	Group A (n=26)	Group B (n=28)	Power
Glasses or Soft Contacts	.2	0.30	0.50	0.5321
Rigid Contacts	.2	0.70	0.50	

Table G2. Power for detecting differences between Groups A and B stratified by specified preoperative corrective lens wear.

Corrective Lens Wear	Effect Size	Group A (n=26)	Group B (n=28)	Power
Glasses or Soft Contacts	.3	0.25	0.55	0.8341
Rigid Contacts	.3	0.75	0.45	

Table H. Power for detecting differences between Groups A and B stratified by orientation of topographic toricity.

Orientation of Toricity	Effect Size	Group A (n=26)	Group B (n=28)	Power
With-the-rule	.1	1.00	0.90	0.8538
Against-the-rule	.1	0	0.10	

Appendix 5.

Table A. Patients with Intacs removed within postoperative Month 24 ('Removals' Group)

ID	Intacs	
14308-1	0.30	Month 6; visual symptoms
14312-1	0.35	Month 3; astigmatism
14325-1	0.35	Month 9; visual symptoms
14327-1	0.30	Exchanged to 0.40 @ Month 9; Removed Month 1PE; REASON?
14329-1	0.25	Month 12; over-corrected
14335-1	0.35	Month 12; over-corrected; Exchanged to 0.21 @ Month 9PR
14340-2	0.30	Month 6; visual symptoms
14346-1	0.25	Month 1; over-corrected
15317-1	0.35	Month 12; astigmatism
15323-1	0.35	Month 18; over-correction
15329-1	0.25	Month 18; under-correction
16306-2	0.30	Month 18; dryness, can't see near
20308-1	0.35	Month 9; under-correction
20321-1	0.35	Month 9; visual symptoms
20327-1	0.30	Month 2; visual symptoms
20334-1	0.35	Month 9; visual symptoms
30311-1	0.35	Month 6; under-correction
30320-1	0.25	Month 12; visual symptoms
30327-1	0.35	Month 3; over-correction
30345-1	0.30	Month 9; under-correction
40304-1	0.35	Month 6; visual symptoms
50305-1	0.35	Month 18; visual symptoms
50311-1	0.35	Exchanged to 0.45 @ Month 12; Removed Month 3PE; REASON?
50312-1	0.35	Exchanged to 0.45 @ Month 9; Removed Month 6PE; REASON?
50316-1	0.35	Month 18; visual symptoms

Table B. Patients with Intacs exchanged within postoperative Month 24 ('Removal' Group)

ID	Intacs	
14310-1	0.35	Exchanged @ Month 12 to 0.40
14318-1	0.35	Exchanged @ Month 12 to 0.40
20309-1	0.30	Exchanged @ Month 9 to 0.40
30312-1	0.35	Exchanged @ Month 12 to 0.45
40308-1	0.25	Exchanged @ Month 9 to 0.35
50313-1	0.35	Exchanged @ Month 12 to 0.45

Appendix 6.

Table A. **Preoperative** visual and refractive performance for 'Clinical Symptoms/Removals' and 'Infrequent Symptoms' outcome groups.

Visual and Refractive Performance	'Clinical Symptoms / Removals' (152/263, 56%)	'Infrequent Symptoms' (111/263, 44%)
UCVA (logMAR)		
Mean (SD)	0.71 (0.25)	0.64 (0.23)
Snellen VA	~20/100	~20/80
Range	0.00 to 1.30	0.00 to 1.10
CI (95%)	0.67 to 0.75	0.59 to 0.68
BSCVA (logMAR)		
Mean (SD)	-0.12 (0.08)	-0.12 (0.08)
Snellen VA	~20/16	~20/16
Range	-0.30 to 0.00	-0.30 to 0.00
CI (95%)	-0.13 to –0.11	-0.14 to –0.11
Defocus Equivalent (D)		
Mean (SD)	2.29 (0.61)	2.16 (0.63)
Range	1.00 to 3.51	1.00 to 3.76
CI (95%)	2.19 to 2.39	2.05 to 2.28
Manifest Astigmatism (D)		
Mean (SD)	0.29 (0.28)	0.31 (0.31)
Range	0.00 to 1.00	0.00 to 1.00
CI (95%)	0.24 to 0.33	0.25 to 0.37

Table B. **Postoperative final exam** visual and refractive performance for 'Clinical Symptoms/Removals' and 'Infrequent Symptoms' outcome groups.

Visual and Refractive Performance	'Clinical Symptoms / Removals' (129/236, 55%)	'Infrequent Symptoms' (107/236, 45%)
UCVA (logMAR)*		
Mean (SD)	0.08 (0.24)	-0.06 (0.15)
Snellen VA	~20/25	~20/16
Range	-0.30 to 0.90	-0.30 to 0.40
CI (95%)	0.03 to 0.12	-0.09 to –0.03
BSCVA (logMAR)		
Mean (SD)	-0.13 (0.09)	-0.16 (0.07)
Snellen VA	~20/16	~20/12.5
Range	-0.30 to 0.20	-0.30 to 0.00
CI (95%)	-0.14 to –0.11	-0.18 to –0.15
Defocus Equivalent (D)*		
Mean (SD)	0.85 (0.63)	0.49 (0.42)
Range	0.00 to 3.00	0.00 to 2.00
CI (95%)	0.74 to 0.95	0.41 to 0.57
Manifest Astigmatism (D)*		
Mean (SD)	0.55 (0.46)	0.36 (0.41)
Range	0.00 to 2.50	0.00 to 2.25
CI (95%)	0.47 to 0.63	0.28 to 0.43

* $p \leq 0.05$

Appendix 7.

Table A. **Postoperative Month 3** visual and refractive performance for 'Clinical Symptoms / Removals' and 'Infrequent Symptoms' outcome groups.

Visual an Refractive Performance	'Clinical Symptoms / Removals' (143/257, 56%)	'Infrequent Symptoms' (114/257, 44%)
UCVA (logMAR)		
Mean SD)	0.04 (0.22)	-0.08 (0.12)
Range	-0.30 to 0.80	-0.30 to 0.40
CI (95%)	0.01 to 0.08	-0.10 to –0.06
BSCVA (logMAR)		
Mean (SD)	-0.14 (0.09)	-0.16 (0.08)
Range	-0.30 to 0.10	-0.30 to 0.00
CI (95%)	-0.15 to –0.12	-0.17 to –0.14
Defocus Eq. (D)		
Mean (SD)	0.80 (0.57)	0.61 (0.44)
Range	0.00 to 3.00	0.00 to 1.75
CI (95%)	0.70 to 0.90	0.52 to 0.69
Manifest Astigmatism (D)		
Mean (SD)	0.45 (0.43)	0.36 (0.43)
Range	0.00 to 2.00	0.00 to 2.00
CI (95%)	0.38 to 0.53	0.28 to 0.44
Keratometric Astigmatism (D)		
Mean (SD)	1.05 (0.80)	0.90 (0.72)
Range	0.00 to 6.75	0.00 to 5.50
CI (95%)	0.92 to 1.18	0.77 to 1.04
Average Keratometry (D)		
Mean (SD)	41.9 (1.9)	41.8 (1.7)
Range	38.4 to 45.1	36.8 to 44.9
CI (95%)	41.6 to 42.1	41.5 to 42.1
Keratometry		
With-the-rule	118/146 (81%)	97/111 (87%)
Against-the-rule	28/146 (19%)	14/111 (13%)

Table B. **Postoperative Month 3** corneal topography for 'Clinical Symptoms/Removals' and 'Infrequent Symptoms' outcome groups.

Corneal Topography	'Clinical Symptoms / Removals' (128/232, 55%)	'Infrequent Symptoms' (104/232, 45%)
Total Astigmatism (D)		
Mean (SD)	0.82 (0.50)	0.79 (0.48)
Range	0.08 to 2.53	0.15 to 3.50
CI (95%)	0.73 to 0.91	0.70 to 0.89
Effective Refractive Power		
Mean (SD)	41.8 (1.5)	42.0 (1.9)
Range	38.3 to 46.1	38.2 to 50.4
CI (95%)	41.6 to 42.1	41.6 to 42.4
CUI Index (%)		
Mean (SD)	90.1 (15.0)	87.0 (15.8)
Range	0 to 100	40 to 100
CI (95%)	87.5 to 92.7	83.9 to 90.2
PCA Index (logMAR)		
Mean (SD)	-0.04 (0.19)	-0.01 (0.190)
Range	-0.3 to 0.9	-0.3 to 0.5
CI (95%)	-0.08 to -0.01	-0.04 to 0.03
Asphericity (Q)		
Mean (SD)	-0.59 (0.50)	-0.50 (0.42)
Range	-2.00 to 1.99	-2.00 to 0.72
CI (95%)	-0.69 to –0.51	-0.58 to –0.41

Table C. **Postoperative Month 6** visual and refractive performance for 'Clinical Symptoms / Removals' and 'Infrequent Symptoms' outcome groups.

Visual and Refractive Performance	'Clinical Symptoms / Removals' (142/257, 55%)	'Infrequent Symptoms' (115/257, 45%)
UCVA (logMAR)		
Mean SD)	0.04 (0.20)	-0.06 (0.12)
Range	-0.30 to 0.70	-0.30 to 0.30
CI (95%)	0.01 to 0.08	-0.08 to –0.04
BSCVA (logMAR)		
Mean (SD)	-0.14 (0.08)	-0.15 (0.08)
Range	-0.30 to 0.10	-0.30 to 0.00
CI (95%)	-0.15 to –0.12	-0.16 to –0.13
Defocus Eq. (D)		
Mean (SD)	0.86 (0.61)	0.57 (0.42)
Range	0.00 to 3.00	0.00 to 2.00
CI (95%)	0.76 to 0.96	0.49 to 0.65
Manifest Astigmatism (D)		
Mean (SD)	0.52 (0.47)	0.35 (0.40)
Range	0.00 to 2.00	0.00 to 2.25
CI (95%)	0.45 to 0.60	0.27 to 0.42
Keratometric Astigmatism (D)		
Mean (SD)	1.01 (0.68)	0.92 (0.60)
Range	0.00 to 3.75	0.00 to 2.75
CI (95%)	0.90 to 1.13	0.81 to 1.03
Average Keratometry (D)		
Mean (SD)	41.8 (1.6)	41.8 (1.6)
Range	38.1 to 43.4	37.8 to 44.8
CI (95%)	41.5 to 42.1	41.5 to 42.1

Table D. **Postoperative Month 6** corneal topography for 'Clinical Symptoms / Removals' and 'Infrequent Symptoms' outcome groups.

Corneal Topography	'Clinical Symptoms / Removals' (125/230, 54%)	'Infrequent Symptoms' (105/230, 46%)
Total Astigmatism (D)		
Mean (SD)	0.94 (0.57)	0.82 (0.40)
Range	0.11 to 2.83	0.08 to 1.79
CI (95%)	0.84 to 1.04	0.74 to 0.90
Effective Refractive Power		
Mean (SD)	41.7 (1.5)	41.8 (1.6)
Range	38.2 to 45.3	38.6 to 44.7
CI (95%)	41.4 to 41.9	41.5 to 42.1
CUI Index (%)		
Mean (SD)	90.4 (13.5)	91.5 (12.6)
Range	20 to 100	40 to 100
CI (95%)	88.0 to 92.8	89.0 to 94.0
PCA Index (logMAR)		
Mean (SD)	-0.04 (0.17)	-0.06 (0.16)
Range	-0.3 to 0.7	-0.3 to 0.5
CI (95%)	-0.07 to -0.01	-0.09 to -0.02
Asphericity (Q)		
Mean (SD)	-0.55 (0.45)	-0.43 (0.36)
Range	-1.65 to 1.53	-1.67 to 0.74
CI (95%)	-0.62 to –0.47	-0.50 to –0.36

Table E. **Postoperative Month 12** visual and refractive performance for 'Clinical Symptoms / Removals' and 'Infrequent Symptoms' outcome groups.

Visual and Refractive Performance	'Clinical Symptoms / Removals' (129/244, 53%)	'Infrequent Symptoms' (115/244, 47%)
UCVA (logMAR)		
Mean SD)	0.02 (0.21)	-0.09 (0.12)
Range	-0.30 to 0.80	-0.30 to 0.20
CI (95%)	-0.02 to 0.05	-0.10 to –0.06
BSCVA (logMAR)		
Mean (SD)	-0.14 (0.09)	-0.16 (0.08)
Range	-0.30 to 0.20	-0.30 to 0.00
CI (95%)	-0.16 to –0.13	-0.17 to –0.14
Defocus Eq. (D)		
Mean (SD)	0.72 (0.58)	0.52 (0.41)
Range	0.00 to 3.00	0.00 to 2.25
CI (95%)	0.62 to 0.82	0.45 to 0.60
Manifest Astigmatism (D)		
Mean (SD)	0.46 (0.47)	0.37 (0.40)
Range	0.00 to 1.75	0.00 to 2.00
CI (95%)	0.38 to 0.54	0.29 to 0.44
Keratometric Astigmatism (D)		
Mean (SD)	0.98 (0.64)	0.94 (0.70)
Range	0.00 to 3.00	0.00 to 5.25
CI (95%)	0.87 to 1.09	0.81 to 1.07
Average Keratometry (D)		
Mean (SD)	41.8 (1.5)	41.9 (1.6)
Range	38.2 to 45.0	37.4 to 45.6
CI (95%)	41.5 to 42.5	41.6 to 42.2
Keratometry		
With-the-rule	101/131 (77%)	103/112 (92%)
Against-the-rule	30/131 (23%)	9/112 (8%)

Table F. **Postoperative Month 12** corneal topography for 'Clinical Symptoms / Removals' and 'Infrequent Symptoms' outcome groups.

Corneal Topography	'Clinical Symptoms / Removals' (79/151, 52%)	'Infrequent Symptoms' (72/151, 48%)
Total Astigmatism (D)		
Mean (SD)	0.85 (0.52)	0.76 (0.40)
Range	0.12 to 2.73	0.07 to 1.73
CI (95%)	0.74 to 0.97	0.67 to 0.86
Effective Refractive Power		
Mean (SD)	41.5 (1.5)	41.6 (1.6)
Range	38.3 to 45.1	37.4 to 44.4
CI (95%)	41.2 to 41.9	41.2 to 41.9
CUI Index (%)		
Mean (SD)	91.4 (15.0)	91.1 (14.9)
Range	20 to 100	10 to 100
CI (95%)	88.0 to 94.8	87.6 to 94.6
PCA Index (logMAR)		
Mean (SD)	-0.07 (0.19)	-0.06 (0.19)
Range	-0.3 to 0.7	-0.3 to 0.8
CI (95%)	-0.11 to -0.03	-0.09 to -0.01
Asphericity (Q)		
Mean (SD)	-0.45 (0.43)	-0.40 (0.35)
Range	-1.59 to 1.20	-1.19 to 0.30
CI (95%)	-0.56 to –0.37	-0.48 to –0.31

Table G. Visual and refractive performance for 'Clinical Symptoms / Removals' and 'Infrequent Symptoms' outcome groups at **final postoperative exam**.

Visual and Refractive Performance	'Clinical Symptoms / Removals' (129/236, 55%)	'Infrequent Symptoms' (107/236, 45%)
UCVA (logMAR)		
Mean (SD)	0.08 (0.24)	-0.06 (0.15)
Snellen VA	~20/25	~20/16
Range	-0.30 to 0.90	-0.30 to 0.40
CI (95%)	0.03 to 0.12	-0.09 to –0.03
BSCVA (logMAR)		
Mean (SD)	-0.13 (0.09)	-0.16 (0.07)
Snellen VA	~20/16	~20/12.5
Range	-0.30 to 0.20	-0.30 to 0.00
CI (95%)	-0.14 to –0.11	-0.18 to –0.15
Defocus Equivalent (D)		
Mean (SD)	0.85 (0.63)	0.49 (0.42)
Range	0.00 to 3.00	0.00 to 2.00
CI (95%)	0.74 to 0.95	0.41 to 0.57
Manifest Astigmatism (D)		
Mean (SD)	0.55 (0.46)	0.36 (0.41)
Range	0.00 to 2.50	0.00 to 2.25
CI (95%)	0.47 to 0.63	0.28 to 0.43
Keratometric Astigmatism (D)		
Mean (SD)	1.03 (0.82)	0.98 (0.70)
Range	0.00 to 6.75	0.00 to 4.50
CI (95%)	0.89 to 1.17	0.84 to 1.12
Average Keratometry (D)		
Mean (SD)	41.9 (1.6)	41.9 (1.6)
Range	38.4 to 45.4	37.8 to 45.0
CI (95%)	41.6 to 42.1	41.6 to 42.2
Orientation of Cycloplegic Astigmatism[§]		
WTR	70/130 (54%)	47/107 (44%)
ATR	25/130 (19%)	20/107 (17%)
SPHERE	35/130 (27%)	40/107 (37%)

Table H. Corneal topography for 'Clinical Symptoms / Removals' and 'Infrequent Symptoms' outcome groups at **final postoperative exam**.

Corneal Topography	'Clinical Symptoms / Removals' (82/147, 56%)	'Infrequent Symptoms' (65/147, 44%)
Total Astigmatism (D)		
Mean (SD)	0.91 (0.56)	0.80 (0.42)
Range	0.20 to 2.83	0.17 to 1.73
CI (95%)	0.79 to 1.03	0.70 to 0.90
Effective Refractive Power (D)		
Mean (SD)	41.7 (1.8)	41.9 (1.6)
Range	36.4 to 45.3	37.5 to 45.3
CI (95%)	41.3 to 42.1	41.5 to 42.3
CUI Index (%)		
Mean (SD)	91.5 (12.6)	92.6 (14.0)
Range	40 to 100	30 to 100
CI (95%)[§]	85 to 98	86 to 99
PCA Index (logMAR)		
Mean (SD)	-0.06 (0.17)	-0.06 (0.18)
Snellen VA	~20/16	~20/16
Range	-0.3 to 0.5	-0.3 to 0.6
CI (95%)	-0.10 to -0.02	-0.12 to -0.03
Asphericity (Q)		
Mean (SD)	-0.42 (0.54)	-0.40 (0.33)
Range	-2.00 to 1.53	-1.41 to 0.23
CI (95%)	-0.54 to –0.30	-0.48 to –0.31

[§] based on estimated proportion