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Intrastromal Corneal Ring Implants for Corneal Thinning Disorders

An Evidence-Based Analysis

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About the Medical Advisory Secretariat

The Medical Advisory Secretariat (MAS) is part of the Ontario Ministry of Health and Long-Term Care (MOHLTC). The mandate of MAS is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the MOHLTC and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies to improve patient outcomes.

The Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC). It conducts systematic reviews of scientific evidence and consultations with experts in the health care services community to produce the *Ontario Health Technology Assessment Series*.

About the Ontario Health Technology Assessment Series

To conduct its comprehensive analyses, MAS systematically reviews available scientific literature, collaborates with partners across relevant government branches, and consults with clinical and other external experts and manufacturers, and solicits any necessary advice to gather information. The MAS makes every effort to ensure that all relevant research, nationally and internationally, is included in the systematic literature reviews conducted.

The information gathered is the foundation of the evidence to determine if a technology is effective and safe for use in a particular clinical population or setting. Information is collected to understand how a new technology fits within current practice and treatment alternatives. Details of the technology's diffusion into current practice and input from practising medical experts and industry add important information to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist policy makers to make timely and relevant decisions to optimize patient outcomes.

If you are aware of any current additional evidence to inform an existing evidence-based analysis, please contact the Medical Advisory Secretariat: MASinfo.moh@ontario.ca. The public consultation process is also available to individuals wishing to comment on an analysis prior to publication. For more information, please visit http://www.health.gov.on.ca/english/providers/program/ohtac/public_engage_overview.html.

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Abbreviations

BCVA	Best corrected visual acuity
BSCVA	Best spectacle-corrected visual acuity
CLEK	Collaborative Longitudinal Evaluation of Keratoconus
HDE	Humanitarian device exemption
ICRS	Intrastromal corneal ring segment
IOL	Intraocular lens
KC	Keratoconus
LASIK	Laser in situ keratomileusis
LogMAR	Logarithm of the minimum angle of resolution
NR	Not reported
PKP	Penetrating keratoplasty
PMCD	Pellucid marginal corneal degeneration
RCT	Randomized controlled trial
SE	Spherical equivalent
UCVA	Uncorrected visual acuity
VA	Visual acuity

Executive Summary

Objective

The purpose of this project was to determine the role of corneal implants in the management of corneal thinning disease conditions. An evidence-based review was conducted to determine the safety, effectiveness and durability of corneal implants for the management of corneal thinning disorders. The evolving directions of research in this area were also reviewed.

Subject of the Evidence-Based Analysis

The primary treatment objectives for corneal implants are to normalize corneal surface topography, improve contact lens tolerability, and restore visual acuity in order to delay or defer the need for corneal transplant. Implant placement is a minimally invasive procedure that is purported to be safe and effective. The procedure is also claimed to be adjustable, reversible, and both eyes can be treated at the same time. Further, implants do not limit the performance of subsequent surgical approaches or interfere with corneal transplant. The evidence for these claims is the focus of this review.

The specific research questions for the evidence review were as follows:

1. Safety
2. Corneal Surface Topographic Effects:
    a. Effects on corneal surface remodelling
    b. Impact of these changes on subsequent interventions, particularly corneal transplantation (penetrating keratoplasty [PKP])
3. Visual Acuity
4. Refractive Outcomes
5. Visual Quality (Symptoms): such as contrast vision or decreased visual symptoms (halos, fluctuating vision)
6. Contact lens tolerance
7. Functional visual rehabilitation and quality of life
8. Patient satisfaction:
9. Disease Process:
    a. Impact on corneal thinning process
    b. Effect on delaying or deferring the need for corneal transplantation

Clinical Need: Target Population and Condition

Corneal ectasia (thinning) comprises a range of disorders involving either primary disease conditions such as keratoconus and pellucid marginal corneal degeneration or secondary iatrogenic conditions such as corneal thinning occurring after LASIK refractive surgery. The condition occurs when the normally round dome-shaped cornea progressively thins causing a cone-like bulge or forward protrusion in response to the normal pressure of the eye. Thinning occurs primarily in the stoma layers and is believed to be a breakdown in the collagen network. This bulging can lead to an irregular shape or astigmatism of the cornea and, because the anterior part of the cornea is largely responsible for the focusing of light on the retina, results in loss of visual acuity. This can make even simple daily tasks, such as driving, watching television or reading, difficult to perform.

Keratoconus (KC) is the most common form of corneal thinning disorder and is a noninflammatory chronic disease process. Although the specific causes of the biomechanical alterations that occur in KC are unknown, there is a growing body of evidence to suggest that genetic factors may play an important role. KC is a rare condition (<0.05% of the population) and is unique among chronic eye diseases as it has an early age of onset (median age of 25 years). Disease management for this condition follows a step-wise approach depending on disease severity. Contact lenses are the primary treatment of choice when there is irregular astigmatism associated with the disease. When patients can no longer tolerate contact lenses or when lenses no longer provide adequate vision, patients are referred for corneal transplant.

Keratoconus is one of the leading indications for corneal transplants and has been so for the last three decades. Yet, despite high graft survival rates of up to 20 years, there are reasons to defer receiving transplants for as long as possible. Patients with keratoconus are generally young and life-long term graft survival would be an important consideration. The surgery itself involves lengthy time off work and there are potential complications from long term steroid use following surgery, as well as the risk of developing secondary cataracts, glaucoma etc. After transplant, recurrent KC is possible with need for subsequent intervention. Residual refractive errors and astigmatism can remain challenging after transplantation and high refractive surgery rates and re-graft rates in KC patients have been reported. Visual rehabilitation or recovery of visual acuity after transplant may be slow and/or unsatisfactory to patients.

Description of Technology/Therapy

INTACS® (Addition Technology Inc. Sunnyvale, CA, formerly KeraVision, Inc.) are the only currently licensed corneal implants in Canada. The implants are micro-thin poly methyl methacrylate crescent shaped ring segments with a circumference arc length of 150 degrees, an external diameter of 8.10 mm, an inner diameter of 6.77 mm, and a range of different thicknesses. Implants act as passive spacers and, when placed in the cornea, cause local separation of the corneal lamellae resulting in a shortening of the arc length of the anterior corneal curvature and flattening the central cornea. Increasing segment thickness results in greater lamellar separation with increased flattening of the cornea correcting for myopia by decreasing the optical power of the eye. Corneal implants also improve corneal astigmatism but the mechanism of action for this is less well understood.

Treatment with corneal implants is considered for patients who are contact lens intolerant, having adequate corneal thickness particularly around the area of the implant incision site and without central corneal scarring. Those with central corneal scarring would not benefit from implants and those without an adequate corneal thickness, particularly in the region that the implants are being inserted, would be at increased risk for corneal perforation. Patients desiring to have visual rehabilitation that does not include glasses or contact lenses would not be candidates for corneal ring implants.

Placement of the implants is an outpatient procedure with topical anesthesia generally performed by either corneal specialists or refractive surgeons. It involves creating tunnels in the corneal stroma to secure the implants either by a diamond knife or laser calibrated to an approximate depth of 70% of the cornea. Variable approaches have been employed by surgeons in selecting ring segment size, number and position. Generally, two segments of equal thickness are placed superiorly and inferiorly to manage symmetrical patterns of corneal thinning whereas one segment may be placed to manage asymmetric thinning patterns.

Following implantation, the major safety concerns are for potential adverse events including corneal perforation, infection, corneal infiltrates, corneal neovascularization, ring migration and extrusion and corneal thinning. Technical results can be unsatisfactory for several reasons. Treatment may result in an over or under-correction of refraction and may induce astigmatism or asymmetry of the cornea.

Progression of the corneal cone with corneal opacities is also invariably an indication for progression to corneal transplant. Other reasons for treatment failure or patient dissatisfaction include foreign body sensation, unsatisfactory visual quality with symptoms such as double vision, fluctuating vision, poor night vision or visual side effects related to ring edge or induced or unresolved astigmatism.

Evidence-Based Analysis Methods

The literature search strategy employed keywords and subject headings to capture the concepts of 1) intrastromal corneal rings and 2) corneal diseases, with a focus on keratoconus, astigmatism, and corneal ectasia. The initial search was run on April 17, 2008, and a final search was run on March 6, 2009 in the following databases: Ovid MEDLINE (1996 to February Week 4 2009), OVID MEDLINE In-Process and Other Non-Indexed Citations, EMBASE (1980 to 2009 Week 10), OVID Cochrane Library, and the Centre for Reviews and Dissemination/International Agency for Health Technology Assessment. Parallel search strategies were developed for the remaining databases. Search results were limited to human and English-language published between January 2000 and April 17, 2008. The resulting citations were downloaded into Reference Manager, v.11 (ISI Researchsoft, Thomson Scientific, U.S.A), and duplicates were removed. The Web sites of several other health technology agencies were also reviewed including the Canadian Agency for Drugs and Technologies in Health (CADTH), ECRI, and the United Kingdom National Institute for Clinical Excellence (NICE). The bibliographies of relevant articles were scanned.

Inclusion Criteria

- English language reports and human studies
- Any corneal thinning disorder
- Reports with corneal implants used alone or in conjunction with other interventions
- Original reports with defined study methodology
- Reports including standardized measurements on outcome events such as technical success, safety, effectiveness, durability, vision quality of life or patient satisfaction
- Case reports or case series for complications and adverse events

Exclusion Criteria

- Non-systematic reviews, letters, comments and editorials
- Reports not involving outcome events such as safety, effectiveness, durability, vision quality or patient satisfaction following an intervention with corneal implants
- Reports not involving corneal thinning disorders and an intervention with corneal implants

Summary of Findings

In the MAS evidence review on intrastromal corneal ring implants, 66 reports were identified on the use of implants for management of corneal thinning disorders. Reports varied according to their primary clinical indication, type of corneal implant, and whether or not secondary procedures were used in conjunction with the implants. Implants were reported to manage post LASIK thinning and/or uncorrected refractive error and were also reported as an adjunctive intervention both during and after corneal transplant to manage recurrent thinning and/or uncorrected refractive error.

Ten pre-post cohort longitudinal follow-up studies were identified examining the safety and effectiveness of INTAC corneal implants in patients with keratoconus. Five additional cohort studies were identified using the Ferrara implant for keratoconus management but because this corneal implant is not licensed in Canada these studies were not reviewed.

The cohorts implanted with INTACS involved 608 keratoconus patients (754 eyes) followed for 1, 2 or 3 years. Three of the reports involved ≥ 2 years of follow-up with the longest having 5-year follow-up data for a small number of patients. Four of the INTAC cohort studies involved 50 or more patients; the largest involved 255 patients. Inclusion criteria for the studies were consistent and included patients who were contact lens intolerant, had adequate corneal thickness, particularly around the area of the implant incision site, and without central corneal scarring. Disease severity, thinning pattern, and corneal cone protrusions all varied and generally required different treatment approaches involving defined segment sizes and locations.

A wide range of outcome measures were reported in the cohort studies. High levels of technical success or ability to place INTAC segments were reported. Technically related complications were often delayed and generally reported as segment migration attributable to early experience. Overall, complications were infrequently reported and largely involved minor reversible events without clinical sequelae.

The outcomes reported across studies involved statistically significant and clinically relevant improvements in corneal topography, refraction and visual acuity, for both uncorrected and best-corrected visual acuity. Patients' vision was usually restored to within normal functioning levels and for those not achieving satisfactory correction, insertion of intraocular lenses was reported in case studies to result in additional gains in visual acuity. Vision loss (infrequently reported) was usually reversed by implant exchange or removal. The primary effects of INTACS on corneal surface remodelling were consistent with secondary improvements in refractive error and visual acuity. The improvements in visual acuity and refractive error noted at 6 months were maintained at 1 and 2-year follow-up

Improvements in visual acuity and refractive error following insertion of INTACS, however, were not noted for all patients. Although improvements were not found to vary across age groups there were differences across stages of disease. Several reports suggested that improvements in visual acuity and refractive outcomes may not be as large or predictable in more advanced stages of KC. Some studies have suggested that the effects of INTACs were much greater in flattening the corneal surface than in correcting astigmatism. However, these studies involved small numbers of high risk patients in advanced stages of KC and conclusions made from this group are limited.

INTACS were used for other indications other than primary KC. The results of implant insertion on corneal topography, refraction, and visual acuity in post-LASIK thinning cases were similar to those reported for KC. The evidence for this indication, however, only involved case reports and small case series. INTACS were also successfully used to treat recurrent KC after corneal transplant but this was based on only a single case report. Corneal implants were compared to corneal transplantation but these studies were not randomized and based on small numbers of selected patients.

The foremost limitation of the evidence base is the basic study design in the reports that involved longitudinal follow-up only for the treated group; there were no randomized trials. Follow-up in the trials (although at prescribed intervals) often had incomplete accounts of losses at follow-up and estimates of change were often not reported or based on group differences. Second, although standardized outcome measures were reported, contact lens tolerance (a key treatment objective) was infrequently specified. A third general limitation was the lack of reporting of patients' satisfaction with their vision quality or functional vision. Outcome measures for vision quality and impact on patient quality of life were available but rarely reported and have been noted to be a limitation in ophthalmological literature in

general. Fourth, the longitudinal cohort studies have not followed patients long enough to evaluate the impact of implants on the underlying disease process (follow-up beyond 3 years is limited). Additionally, only a few of these studies directly examined corneal thinning in follow-up. The overall quality of evidence determined using the GRADE hierarchy of evidence was moderate.

There is some evidence in these studies to support the claim that corneal implants do not interfere with, or increase the difficultly of, subsequent corneal transplant, at least for those performed shortly after INTAC placement. Although it's uncertain for how long implants can delay the need for a corneal transplant, given that patients with KC are often young (in their twenties and thirties), delaying transplant for any number of years may still be a valuable consideration.

Conclusion

The clinical indications for corneal implants have evolved from management of myopia in normal eyes to the management of corneal thinning disorders such as KC and thinning occurring after refractive surgery. Despite the limited evidence base for corneal implants, which consists solely of longitudinal follow-up studies, they appear to be a valuable clinical tool for improving vision in patients with corneal thinning. For patients unable to achieve functional vision, corneal implants achieved statistically significant and clinically relevant improvements in corneal topography, refraction, and visual acuity, providing a useful alternative to corneal transplant. Implants may also have a rescue function, treating corneal thinning occurring after refractive surgery in normal eyes, or managing refractive errors following corneal transplant. The treatment offers several advantages in that it's an outpatient based procedure, is associated with minimal risk, and has high technical success rates. Both eyes can be treated at once and the treatment is adjustable and reversible. The implants can be removed or exchanged to improve vision without limiting subsequent interventions, particularly corneal transplant.

Better reporting on vision quality, functional vision and patient satisfaction, however, would improve evaluation of the impact of these devices. Information on the durability of the implants' treatment effects and their affects on underlying disease processes is limited. This information is becoming more important as alternative treatment strategies, such as collagen cross-linking aimed at strengthening the underlying corneal tissue, are emerging and which might prove to be more effective or increase the effectiveness of the implants, particularly in advances stages of corneal thinning.

Ontario Health System Considerations

At present there are approximately 70 ophthalmologists in Canada who've had training with corneal implants; 30 of these practice in Ontario. Industry currently sponsors the training, proctoring and support for the procedure. The cost of the implant device ranges from $950 to $1200 (CAD) and costs for instrumentation range from $20,000 to $30,000 (CAD) (a one time capital expenditure). There is no physician services fee code for corneal implants in Ontario but assuming that they are no higher than those for a corneal transplant, the estimated surgical costs would be $914.32(CAD) An estimated average cost per patient, based on device costs and surgical fees, for treatment is $1,964 (CAD) (range $1,814 to $2,114) per eye. There have also been no out of province treatment requests. In Ontario the treatment is currently being offered in private clinics and an increasing number of ophthalmologists are being certified in the technique by the manufacturer.

KC is a rare disease and not all of these patients would be eligible candidates for treatment with corneal implants. Based on published population rates of KC occurrence, it can be expected that there is a prevalent population of approximately 6,545 patients and an incident population of 240 newly diagnosed cases per year. Given this small number of potential cases, the use of corneal implants would not be expected to have much impact on the Ontario healthcare system. The potential impact on the provincial budget for managing the incident population, assuming the most conservative scenario (i.e., all are eligible and all receive bilateral implants) ranges from $923 thousand to $1.1 million (CAD). This estimate would vary based on a variety of criteria including eligibility, unilateral or bilateral interventions, re-interventions, capacity and uptake

Keywords

Keratoconus, corneal implants, corneal topography, corneal transplant, visual acuity, refractive error

Subject of the Evidence-Based Analysis

The purpose of this evidence based analysis was to examine the safety and effectiveness of intrastromal corneal ring implants for corneal thinning disorders.

Clinical Need: Target Population and Condition

Corneal ectasia (thinning) comprises a range of disorders involving either primary disease conditions such as keratoconus (KC) and pellucid marginal corneal degeneration (PMCD), or secondary iatrogenic conditions such as corneal ectasia occurring after laser in-situ keratomileusis (LASIK) refractive surgery. It occurs when the normally round dome-shaped cornea (the clear outer area of the eye) progressively thins causing a cone-like bulge or forward protrusion in response to the normal pressure of the eye pushing out on the thinned areas of the cornea. (1) The thinning occurs primarily in the stoma layers and is believed to be a breakdown in the collagen network.

This bulging can lead to irregular astigmatism or shape of the cornea and because the anterior part of the cornea is responsible for most of the focusing of the light on the retina, results in loss of visual acuity, both uncorrected visual acuity (UCVA) and best-spectacle corrected visual acuity (BSCVA). The visual acuity loss is secondary to high irregular astigmatism that can occur with and without myopia. (2) The reduced visual acuity can make even simple daily tasks, such as driving, watching television or reading, difficult to perform. The subsequent corneal protrusion or distortions can also result in corneal scarring and treatment related sequelae such as abrasions from contact lenses.

There are a variety of corneal thinning disorders but it is unknown if these represent distinct forms of the disease or variants of the same disease process. KC is the most common forms of thinning disorders and involves a noninflammatory chronic disease process of progressive corneal thinning. (3) Although the condition may initially present in one eye it is a progressive disorder and eventually affects both eyes. (4) In KC, localized thinning can occur in a variety of patterns but when it occurs in the inferior cornea in a crescent type pattern it is referred to as pellucid marginal corneal degeneration (PMCD). (5)

Aetiology

KC leads to biomechanical alterations of the cornea involving the collagen scaffold and collagen compound and their bonding with the collagen fibrils. (6;7) The biochemical resistance of the cornea in KC patients is half that of normal values. (8) The specific cause for these biochemical alterations, however, is unknown but there is a growing body of evidence to suggest that genetic factors may play an important role. (9) Reported positive family history of KC in affected individuals ranges from 6% to 24%. In a multicenter longitudinal follow-up cohort study known as the 'Collaborative Longitudinal Evaluation of Keratoconus' (CLEK), sponsored by the National Eye Institute (NEI), 13.5% of 1,209 KC patients recruited over a one year period (May 1995 to June 1996) reported a family history of KC. (2) Occurrence of the disease in second- and third-generation studies and a high concordance between monozygotic twins has also been reported. (10;11) A study evaluating corneal topography in first degree-relatives of patients with KC found an 11% (8/72) incidence of KC compared to 0.05% in general population. (12)

Additional information on KC patients is available from the CLEK study, which remains the largest cohort study of KC patients to date. (2) A reported high percentage (53%) of atopia (allergies) has unknown clinical significance in these patients. Unlike findings in smaller clinical series, no patients reported systemic diseases such as Down's syndrome, Marfan syndrome, focal dermal hypoplasia, Ehlers-Danlos syndrome, oculodentodigital syndrome, osteogenesis imperfecta, or Reigers anomaly.

Diagnosis

The diagnosis of KC depends on the methods used and can be difficult for several reasons. The onset of the disease process is gradual and, in some patients, it may never progress beyond subtle irregular astigmatism. Such patients may never seek or require medical or optometric care. Subclinical forms (forme fruste) of KC are particularly difficult to diagnose. Representative diagnostic patterns of subclinical forms have been described as having a corneal topographic pattern with at least one of the following: Inferior-Superior (I-S) asymmetry index >1.4 diopters (D), central corneal power >47.2 D, or a fellow eye diagnosed with KC. (13)

Computer-assisted videophotokeratoscopes provide a means to detect subtle changes and provide quantitative measures of corneal surface topographic changes. (14) The most commonly employed grading or classification system for KC is that developed by Amsler-Krumeich et al. (3;15) The classification system consists of four stages of disease based on the degree of corneal topography, myopia or induced astigmatism, clinical signs (Vogl's striae, etc), central corneal scarring, and corneal thickness.

The disease stages are as follows:

Stage 1 - Eccentric corneal steepening, induced myopia and/or astigmatism <5 D, corneal radii ≤ 48 D, slit lamp findings (Vogl's striae), no scars;

Stage 2 - induced myopia and/or astigmatism >5 D to <8 D, corneal radii ≤ 53 D, no central scars, corneal thickness ~400 μm;

Stage 3 - induced myopia and/or astigmatism >8 D to <10 D, corneal radii >53 D, no central scars, corneal thickness 200 to 400 μm;

Stage 4 - refraction not measurable, corneal radii >55 D, central scars, perforation, corneal thickness 200 μm.

Disease prevalence and natural history

KC is a rare (<0.05% of the population) disorder (http://rarediseases.info.nih.gov) with estimates of prevalence ranging from a rate of approximately 50 to 230 per 100,000 population. (16) An American population based 48-year survey estimated an overall prevalence of 54.5 per 100,000 with an overall annual incidence rate of 2.0 per 100,000. (17) The age-adjusted prevalence rate was significantly higher (P <.05) in males than in females (69.5 vs. 39.2 per 100,000).

KC is unique among major chronic eye diseases as it has an early onset. (18) In the Kennedy et al. study of 64 cases, the median age of disease onset was reported to be 25 years (ranging from 12 to 77 years) and the condition was unilateral in 41% of patients at diagnosis. In the CLEK study, the median age at study entry was 39.3 years and the impact of KC on vision was already detectable. (2) The variable visual acuity of KC patients in this study (outlined in Table 1) shows that 22% already had fair or worse (≥ 20/40) BSCVA in their worst eye. A Snellen visual acuity range of up to 20/40 is interpreted as a range in which many individuals can function without optical correction. (19) A visual acuity above 20/40 is the most common cut off level for unrestricted drivers' license and 20/200 or worse is part of the legal definition of blindness.

Table 1. Baseline Visual Acuity of Keratoconus Patients in the CLEK Cohort Study*

Vision Quality	Best Corrected † Visual Acuity Range	Snellen Visual Acuity Better Eye, No. (%)	Snellen Visual Acuity Worse Eye, No. (%)
Normal range	20/20 or better	538 (44.7)	169 (14.0)
Normal (without optical correction)	20/21 to 20/40	612 (50.8)	769 (63.9)
Fair	20/40 to 20/69	43 (3.6)	183 (15.2)
Poor	20/70 to 20/199	10 (0.8)	71 (5.9)
Poor (legal definition blindness)	20/200 or worse	1 (0.08)	12 (0.9)

*CLEK = Collaborative Longitudinal Evaluation of Keratoconus. † Best corrected high-contrast monocular visual acuity

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Disease Management

Disease management for corneal thinning disorders such as KC generally follows a basic treatment algorithm in a step-wise approach that depends on disease severity. (20) In the early stages of the disease, initial visual disturbances may be managed with spectacles, while rigid, gas-permeable contact lenses are the primary treatment of choice when there is irregular astigmatism associated with the disease. Occasionally, hydrogel lenses are used in later stages with rigid lenses in a piggyback fashion (hard lens placed on top of soft lens) to correct vision. Management with contact lenses may later fail in patients as they become intolerant or unable to wear their contacts, or when lenses can no longer provide sufficient visual improvement. The baseline visual correction reported for the KC patients in the CLEK cohort demonstrates variability and custom fitting in refractive correction for these patients (Table 2). (2) Only 3.6% of patients were unaided in both eyes. The type of contact lenses used ranged from rigid gas-permeable (790; 65%) to soft lenses, piggyback contact lens, and hybrid (soft and hard) lenses.

Table 2. Baseline Visual Correction in Patients in CLEK Cohort Study*

Type of Correction	Number of Patients, (%)
Same in Both Eyes	
Unaided	43 (3.6)
Glasses	194 (16.1)
Contact lenses	321 (26.6)
Glasses and contacts	571 (47.2)
Different in Each Eye	
One eye unaided and fellow eye contact lenses	37 (3.1)
One eye glasses and contacts with fellow eye unaided	2 (0.2)
One eye glasses and contacts with fellow eye contact lenses	1 (0.1)
One eye glasses and contacts with fellow eye glasses	40 (3. 3)
Total	1209

*CLEK = Collaborative Longitudinal Evaluation of Keratoconus.

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Vision Quality of Life

The impact of declining visual acuity and uncertain variable disease progression affects KC patients who are often diagnosed in adolescence or early adulthood. The National Eye Institute-Visual Function Questionnaire (NEI-VFQ) is a vision related quality of life instrument designed to measure patients' perception of visual function and quality of life. (18) The reported VFQ scores for each of the 12 subscales were significantly (P <.05) poorer for patients with KC than for non-KC patients of similar age wearing rigid gas permeable contact lenses. The reported VFQ sub-scores for KC patients, except for color vision and general health, were rated at levels similar to those reported by patients with macular degeneration. The ocular pain score for KC patients, however, was significantly worse than even that of patients with advanced macular degeneration.

Developing utility values is one method to evaluate the value of vision or the impact of declining vision to individuals. A time trade-off technique provides a measure of how valuable a level of visual acuity is and is theoretically measured by the number of years remaining to the patient that he or she is willing to trade or give up to have that level of vision. A significant relationship between decreasing visual acuity in the better seeing eye and ocular utility values was seen in a large group of patients with ocular disorders (Table 3). (21) The utility values for vision are even more striking when comparing utility values across disease states (Table 4). (21) The utility at the first level of vision loss (around 20/40) is rated as being similar to having a myocardial infarct, while visual acuity of 20/200 (around the definition of legal blindness) is rated as being similar to having a moderate stroke requiring some help but still ambulatory.

Table 3. Patient-based Time Trade-off Utility Values Associated with Visual Acuity Levels in the Better Seeing Eye

Patients With Ocular Disorders, N	Vision Range In Better Seeing Eye	Mean Utility Value	Standard Deviation	95% Confidence Interval
127	20/20 to 20/25	0.88	0.15	0.85–0.91
218	20/30 to 20/50	0.81	0.21	0.78–0.84
83	20/60 to 20/100	0.72	0.21	0.67–0.77
72	20/200 to no light perception	0.61	0.19	0.57–0.65

This article was published in Opthalmology, Volume 110; Brown MM, Brown GC, Sharma S, Busbee B. Quality of life associated with visual loss, a time tradeoff utility analysis comparison with medical health states, p. 1076-1081. Copyright Elsevier (2003).

Table 4. Patient-based Time Trade-off Utility Values Across Disease States

Disease State/Event	Time Trade Off Utility Value
Diabetes	0.88
Visual acuity 20/40 (most common cut off for driver's licence)	0.80
Myocardial infarction, moderate	0.80
Stroke, moderate (requiring some help but able to walk)	0.69
Visual acuity 20/200 (definition of legal blindness)	0.66
Osteoarthritis hip, mild	0.69
Ulcerative colitis, pre-operative	0.58
Renal disease, end-stage, home dialysis	0.49
Total blindness (no light perception)	0.26
Stroke, severe (total paralysis)	0.30

From: Brown MM, Brown GC, Sharma S, Busbee B. Quality of life associated with visual loss, a time trade-off utility analysis comparison with medical health states. Ophthalmology 2003; 110:1076-81.

Surgical Interventions

Prior to penetrating keratoplasty (corneal transplantation) a range of surgical options have been considered to delay or avoid transplantation. (1;3) These options are generally classified as either subtractive or additive procedures. Subtractive procedures are those that remove corneal tissue to alter the corneal surface and are not reversible. These approaches include various techniques such as radical keratotomy, asymmetric kerotomy, photorefractive keratectomy (PRK), photo astigmatic refractive keratectomy, phototherapeutic keratotomy, and LASIK. Intuitively, procedures that involve further tissue loss would not be an optimal approach for a disease condition that already involves progressive tissue loss. There are fewer additive approaches that involve reinforcing corneal tissue. Intrastromal corneal rings (ICRS) (22) and, more recently, collagen cross-linking (6;7) are two such techniques.

Corneal Transplant

Patients are referred for corneal transplant as a last option when they can no longer tolerate contact lenses or when lenses no longer provide adequate vision. Corneal transplant becomes necessary when severe irregular corneal astigmatism or stromal opacities develop. Decreasing visual function in almost 20 years of follow-up in a longitudinal cohort study of KC patients led to corneal transplant in 18.8% of patients (12 of 64). (17) The interval from diagnosis to corneal transplant ranged from less than 2 years to 46 years. The rate of progression to transplant in the fellow eye of KC patients, however, was much shorter and accelerated in patients with high measures of corneal surface abnormalities (5.48 vs. 22.11 years $P = .018$). (4)

KC is one of the leading indications for corneal transplants (11% to 16%) (23;24) The overall corneal graft survival rate reported for 3,992 cases referred to a tertiary care center was 82% at 10-year follow-up; re-graft survival rate, however, was 41%. (25) Grafts for KC had higher survival rates with 92% at 10-year follow-up. A follow-up study (mean 13.8 years, range 0.5 to 30.4 years) of 112 KC eyes in 84 patients treated by 18 surgeons between 1970 and 1983 resulted in graft failure in 7 of 112 transplanted eyes. (26) Graft survival estimates at 20 and 25 years were 93.7 % (95% CI; 88.1–99.3) and 85.4% (95% CI; 72.8–98).

Despite the success of corneal transplants there are reasons to defer it as long as possible. First, KC patients are generally young and long term graft survival of at least 30 or 40 years may be necessary. The surgery itself involves lengthy time off work as post-operative recovery ranges from 4 to 12 weeks (mean 6.7 ± 3.1 wks). Following surgery there are also potential complications from long term steroid use, as well as secondary cataracts, glaucoma etc. After transplant, recurrent KC is possible with the possible need for subsequent interventions. The refractive surgery rates for high astigmatism and re-graft rate in KC patients have been reported to be 26.8% and 9% respectively. (23;27) In another report, recurrent KC was diagnosed by breaks in the Bowman's layer in 6 eyes of 5 (6.%) patients and high irregular astigmatism was suggestive of KC in an additional 8 eyes (7.1%). (26)

Residual regular and irregular astigmatism, myopia and hyperopia can remain challenging after transplantation. Visual rehabilitation or recovery of visual acuity may be slow and or unsatisfactory to patients. Limitations in satisfaction with vision and contact lens tolerance following transplant have been also reported. (28) Only 62% of patients felt that the post-transplantation result was as expected or better post-operatively; however, 9.5% of subjects wore no vision correction of any type after surgery. Tolerance for contact lenses was improved in many patients (67% easier to wear), although 25% reported no difference and 8% that they were more difficult to wear.

Description of Technology/Therapy

Intrastromal Corneal Ring Implants

Regulatory Status

Although several models of corneal implant are available, the most commonly used are INTACS® (Addition Technology Inc. Sunnyvale, CA). ICRS devices under the brand name KeraVision® (AdditionTechnology, Fremont, CA) were first introduced in Europe in 1996 for the treatment of myopia. (29) In April 1999, the FDA approved INTACS for the treatment of myopia (−1.00 to −3.00 D) based on several FDA Phase 1 – 3 clinical trials. (30-32)

INTACS® were first approved by the FDA in 2004 for treatment of KC in the United States under a Humanitarian Device Exemption for treatment of rare medical conditions. (29) On December 19, 2007 Health Canada approved a license (license number 75922) for INTACS as a class 3 device and, as of December 2008, INTACS are the only licensed ICRS implant in Canada.

INTACS are micro-thin poly methyl methacrylate crescent shaped ring segments. (22) The ring segments have a circumference arc length of 150 degrees, a hexagonal transverse shape and a conical longitudinal section. Ring segments have an external diameter of 8.10 mm, an inner diameter of 6.77 mm, and are available in different thicknesses. In Canada, segments are available in three thicknesses (0.25-mm, 0.30-mm and 0.35-mm), while in Europe a broader range of thicknesses from 0.25-mm to 0.45-mm are available.

Treatment Procedures

The treatment is an outpatient based procedure performed either by corneal specialists or refractive surgeons. (33) Patients are pre-medicated with sublingual lorazepam and topical anaesthesia. (Personal Communication). A lid speculum is inserted. An 11 mm corneal marker, with a cross hair wire, is used to determine the geometric center of the cornea. Corneal thickness measurements are made to make sure there are no "thin" zones that would prevent surgery.

There are two ways to create the channels in the cornea to secure the implants, either manually using a calibrated knife or a laser. The manual procedure involves the use of a diamond knife calibrated to an approximate depth of 70% of the cornea to create the incision. A stromal spreader is used to create a pocket in the cornea from the floor of the incision. A vacuum centering guide is then placed on the eye to increase rigidity. A blunt lamellar spreader blade is then placed in the suction ring to create two stromal tunnels or channels.

When a femtosecond laser (FS) is used, a laser docking ring is placed on the center of the cornea and the patient is positioned under the laser. The laser software is then used to ensure a 360 degree channel in the cornea at 70% depth of the thinnest area of the cornea with specifications for width and channel size. An INTACS channel guide is used to spread and open the incisions, made either by the knife or the laser, to develop a channel whereby the INTACS segments can be inserted into the cornea. The INTAC segment is then bathed in antibiotic drops, grabbed with specially designed forceps and manoeuvred into the

channels. Typically two INTACS are inserted and the second INTACS segment is implanted in the same manner. Stitches are typically used to close the wound (one or two 10-0 nylon sutures are recommended) but are at the discretion of the surgeon. Topical antibiotic and steroid eye drops are instilled, analgesics are infrequently required. Post-operative follow-up varies as it can take up to a year in some cases for the effects of implants to stabilize.

Mechanism of Action

Implants act as passive spacers and when placed in the cornea cause local separation of the corneal lamellae resulting in a shortening of the arc length of the anterior corneal curvature and flattening the central cornea. (29) When a single segment is used two actions occur, a flattening in the area of the segment and a steepening in the opposite direction from the segment. An increasing segment thickness results in greater separation with increased flattening. A nearly linear relationship exists between device thickness and increases in corneal surface flattening. (22) The flattening of the cornea corrects for myopia by decreasing the optical power of the eye. ICRS also improve corneal astigmatism but the mechanism for this action is less well understood.

A number of approaches have been employed by surgeons for the selection of ring segment size, number and position. Some surgeons have a blanket approach, while others have a custom approach that depends on the topography of the cornea, the degree of myopia, and/or the degree of astigmatism.

There are a variety of published nomograms (graphical or tabular calculation device) used to guide selection of ICRS segments based on corneal topography, and refractive error. An example of a nomogram commonly used appears in (Table 5). (33) Cases where the same segment thickness are used are referred to as symmetric placement (0.40/0.40 mm), as opposed to asymmetric placement (0.25/0.35 mm) in which different thickness segments are used to balance patterns of asymmetrical thinning.

Table 5. Nomogram for Recommended Segment Thickness for Keratoconus

Type of Cone	Recommended Segment Thickness (mm)			
	Pre-Operative Spherical Equivalent < 3.00 Diopters		Pre-operative Spherical Equivalent >3.00 Diopters	
Asymmetrical	0.25	0.35	0.25	0.35
Moderately asymmetric	0.35	0.40	0.40	0.45
Highly asymmetric	0.25	0.40	0.25	0.45
Global	0.40	0.40	0.45	0.45
Central	0.40	0.40	0.45	0.45

Reprinted from the Journal of Cataract & Refractive Surgery, Vol. 32(5), Colin J. European clinical evaluation: use of Intacs for the treatment of keratoconus, p. 747-755, Copyright 2006, with permission from the American Society of Cataract and Refractive Surgery and the European Society of Cataract and Refractive Surgeons.

Potential Advantages, Risks and Limitations

Corneal ring implants involve adding material to reinforce the cornea. The treatment is reversible, adjustable, and does not limit the possibility of other surgical interventions. The technique also provides predictable and durable improvements in visual acuity and refractive error, secondary to improvements in corneal surface topography. The enhanced visual acuity achieved by the corneal remodelling process may also avoid or defer the later need for corneal transplantation. However, because the rings act as passive mechanical stabilizers of the stromal layer, the impact that this treatment might have on the underlying stromal thinning disease process is uncertain.

Following implantation, the major safety concerns are for potential adverse events including: corneal perforation, infection, corneal infiltrates, corneal neovascularization, ring migration and extrusion and corneal thinning. Technical results can also be unsatisfactory for several reasons. An under correction resulting in residual myopia (nearsightedness), is potentially correctable by adding thicker ring segments or with refractive phakic intraocular lens if anterior chamber depth is sufficient. Similarly, potential over correction resulting in hyperopia (farsightedness) can be corrected by adding thinner ring segments. The ring may also induce astigmatism or asymmetry of the cornea (a superior cornea that has become too flat) and with increasing astigmatism the superior ring can be removed. Development of corneal opacities would be an indication for corneal transplant.

There are other reasons for patient dissatisfaction with results including foreign body sensation, unsatisfactory visual quality with symptoms such as double vision, fluctuating vision, poor night vision, or visual side effects related to ring edge or astigmatism.

Treatment with ICRS is not always an option for KC patients. Those with central corneal scarring would not benefit from ICRS. Those without an adequate corneal thickness, particularly in the region that the implants are being inserted, would be at increased risk for corneal perforation and would not be candidates. Lastly, patients desiring to have visual rehabilitation that does not include glasses or contact lenses would not be candidates for corneal ring implants.

Clinical Indications

ICRS were first evaluated and approved for the treatment of myopia in normal eyes. Evidence for this indication consisted of eight follow-up studies evaluating safety and effectiveness, generally for 2 years (Table 6). These studies all reported improved corneal topography, visual acuity and refractive error. Two studies (34;35) reported 5 and 10 year follow-up results but these reports involved a circle type of corneal ring implant that was an earlier prototype to the newer forms, which consist of two semicircular segments. In those longer term studies, the effects of improved visual acuity and refractive errors were maintained.

Table 6. Clinical Trial Follow-Up of Intrastromal Corneal Ring Management of Myopia

Author, Year	Trials, sites	Population*	Follow-up
Schwartz A, 2006 (34;35)	FDA Phase 11 & 111– multicenter	(113 e)	5 and 10-yr
Asbell P, 2001 (30)	FDA Phase 11 & 111 – 1 site	73 p (114 e)	17.5 yr (mean)
Holmes-Higgins D, 2000 (31)	FDA Phase 111 – 8 sites	(165 e)	6-mo
Ruckhofer J, 2000 (36)	FDA Phase 111 – 10 sites	359 p (359 e)	24-mo
Ruckhofer J, 2001 (37;38)	European Collaborative(Austria, Germany & France) – 12 sites	110 p (163 e)	12-mo
Schanzlin D, 2001 (32)	FDA Phase 11 & 111 – 11 sites	452 p (454 e)	2-yr
Twa M, 1999 (39)	FDA Phase 111 – 2 sites	110 p (95 e)	1-yr
Wijdh R, 2000 (40)	Netherlands – 1 site	15 p (21 e)	3- and 6-mo

*e refers to eyes; mo, month; p, patients; yr, year.

Although there have been a number of studies reporting on the safety and effectiveness of ICRS for myopia in normal eyes, the devices have not emerged as a treatment option for myopia. LASIK has instead become the preferred approach, both by patients and physicians. [Personal communication, expert

advisor, November 2, 2008) Preference for LASIK has been credited to rapid visual rehabilitation and improved corrective refractive effects. LASIK does, however, have a risk of causing corneal thinning in normal eyes or inadvertently being performed in patients undiagnosed with a corneal thinning disease (41) and is, therefore, not an option for individuals who have diseased corneas. This evidence review therefore focus on the clinical utility of ICRS for corneal thinning disease conditions of the cornea.

Evidence-Based Analysis of Safety and Effectiveness

Objective(s) of Evidence Based Analysis

The purpose of this evidence review was to determine the role of ICRS implants in the management of corneal thinning disease conditions. The main objectives for the evidence review were to determine the safety, effectiveness and durability of ICRS management of corneal thinning disorders.

The primary treatment objectives for ICRS implants are to normalize corneal topography, restore contact lens tolerability, and rehabilitate vision in order to delay or defer the need for corneal transplant. Implant placement is a minimally invasive procedure that is purported to be safe and effective. The procedure is also claimed to be adjustable, reversible, and both eyes can be treated at the same time. Moreover, ICRS is also reported not to limit the performance of subsequent surgical approaches or interfere with corneal transplant. The evidence for these claims will be the focus of this review.

The specific research questions for the evidence review were as follows:

1. Technical: How technically demanding is ICRS placement and what are the operative risks?
2. Safety: What is known about the broader safety profile of ICRS?
3. Corneal Surface Topographic Affects;
    a. What, if any, corneal surface remodelling affects do ICRS have?
    b. Do these changes interfere with subsequent interventions, particularly corneal transplant, also known as penetrating keratoplasty (PKP)?
4. Visual Acuity:
    a. What impact does the remodelling have on visual acuity?
    b. Are these impacts predictable, stable, adjustable and durable?
5. Refractive Outcomes: What impact does remodelling have on refractive outcomes?
6. Visual Quality (Symptoms):
    a. What impacts do ICRS have on vision quality aspects such as contrast vision?
    b. To what extent do ICRS create visual symptoms (halos, fluctuating vision)?
7. Contact lens tolerance: To what extent was contact lens intolerance improved after corneal remodelling?
8. Vision Related QOL: What is the impact of ICRS on functional visual rehabilitation and quality of life?
9. Patient satisfaction: Are patients satisfied with their vision?
10. Disease Process:
    a. What impact do ICRS have on the underling corneal thinning disease process?
    b. Do ICRS delay or defer the need for corneal transplant?

Methods

Search Strategy

The literature search strategy employed keywords and subject headings to capture the concepts of 1) intrastromal corneal rings and 2) corneal diseases, with a focus on keratoconus, astigmatism, and corneal ectasia. The initial search was run on April 17, 2008, and a final search was run on March 6, 2009 in the following databases: Ovid MEDLINE (1996 to February Week 4 2009), OVID MEDLINE In-Process and Other Non-Indexed Citations, EMBASE (1980 to 2009 Week 10), OVID Cochrane Library, and the Centre for Reviews and Dissemination/International Agency for Health Technology Assessment. The literature search strategies for MEDLINE and EMBASE are reproduced in Appendix 1. Parallel search strategies were developed for the remaining databases. Search results were limited to human and English-language published between January 2000 and April 17, 2008. The resulting citations were downloaded into Reference Manager, v.11 ((ISI Researchsoft, Thomson Scientific, U.S.A)), and duplicates were removed. The Web sites of several other health technology agencies were also reviewed including the Canadian Agency for Drugs and Technologies in Health (CADTH), ECRI, and the United Kingdom National Institute for Clinical Excellence (NICE). The bibliographies of relevant articles were scanned.

Inclusion Criteria

- English language reports and human studies
- Reports with corneal implants used alone or in conjunction with other interventions
- Reports involving ICRS for any corneal thinning disorder
- Original reports with defined study methodology
- Reports including standardized measurements on outcome events such as technical success, safety, effectiveness, durability, vision quality of life or patient satisfaction
- Case reports or case series for complications and adverse events

Exclusion Criteria

- Non-systematic reviews, letters, comments and editorials
- Reports not involving outcome events such as safety, effectiveness, durability, vision quality or patient satisfaction following an intervention with ICRS
- Reports not involving corneal thinning disorders

The citations from different databases were merged into one database using Reference Manager software and duplicates were subsequently removed. In total**,** 402 citations were identified. The citation lists were reviewed, and articles were excluded based on title and abstract. Excluded articles included those discovered to be review articles or commentaries or not involving an outcome related to an intervention with intrastromal corneal rings. Copies of original articles of eligible articles were obtained and reference lists were further hand searched.

Additional Information Sources

Consultations held with clinical experts and industry representatives.

Assessment of Quality of Evidence

An evaluation of the quality of evidence was based on the grading of recommendations assessment, development, and evaluation (GRADE) system. (42) The recommendations of the GRADE working group can be viewed at http://www.gradeworkinggroup.org. Accordingly, the quality of the evidence was assessed as either high, moderate, low, or very low according to the GRADE method. The potential level of impact of further evidence on decision making was also rated according to the following GRADE definitions:

High: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low: Any estimate of effect is very uncertain.

Results of Evidence-Based Analysis

Other Systematic Reviews

The Medical Advisory Secretariat evidence-based review identified two previous health technology assessment reports on ICRS, each involving management of KC. The first assessment was performed by the Medical Services Advisory Committee (MSAC) in Australia in 2005 (43) and the second was performed by the National Institute for Health and Clinical Excellence (NICE) in Great Britain in 2007. (44)

The MSAC report reviewed evidence between 1996 and March 2005 for ICRS management of KC. Thirteen studies involving clinical follow-up after two different implant devices for KC were identified – 9 studies (235 patients, 287 eyes) involving the use of the INTAC ICRS and 4 studies (115 patients, 120 eyes) involving the Ferrara ICRS. Studies on the management of pellucid marginal corneal degeneration (n = 2) and iatrogenic corneal thinning (n= 6) were also identified. No intra-operative complications were identified and post-operative complications, although inconsistently reported, were uncommon. Visual acuity and refractive errors were significantly improved in all studies in which they were reported. The authors concluded that the evidence pertaining to ICRS was immature and small in volume and that it was not possible to be confident of their benefits.

The NICE report, a rapid review, evaluated evidence up until September 2006 on ICRS. In that review, 10 reports also involving two different implants were identified: eight studies examined the INTAC ICRS (283 patients, 344 eyes) and two studies examined the Ferrara ICRS (82 patients, 87 eyes). In all of the reports cited, the implants were placed for treatment of KC, except one where they were used to treat PMCD (8 patients, 8 eyes). Visual acuity and astigmatism was reported to be significantly improved in the studies. The review concluded that the evidence and safety of ICRS for KC appeared to be adequate to support the use of the procedure. Emphasis was also placed on the requirements for arrangements concerning consent, audit ,and clinical governance of ICRS use..

Medical Advisory Secretariat Systematic Evidence Review

In the MAS review, 66 reports (23 case reports) were identified involving the use of ICRS for management of corneal thinning disorders. The reports are summarized in Table 7 and are grouped according to their primary clinical indication, the type of implant, and whether or not secondary procedures were used in conjunction with implants. The clinical indications for ICRS were for the management of KC (41 reports), pellucid marginal corneal degeneration (7 reports), post-LASIK ectasia, and/or uncorrected refractive error (14 reports). Corneal implants were also reported as an adjunctive intervention both during and after corneal transplant to manage recurrent thinning and/or uncorrected refractive error (4 reports).

The majority of the reports involved corneal implant management of KC. None of the reports, however, involved randomized clinical trials. Case reports and case series, particularly for complication events were included in this review because of the rarity of corneal thinning disorders such as keratoconus and particularly pellucid corneal marginal degeneration, an unusual form of KC. The reports involving longitudinal follow-up evaluating treatment effectiveness for KC are summarized by study design in Table 8.

Table 7. Summary of Reports on Intrastromal Corneal Ring Implants for Corneal Thinning Disorders*

	Number of Reports (Number of Case Reports)				
	ICRS for Post LASIK Ectasia and/or Residual Refractive Error	**ICRS for Keratoconus**	**ICRS for Pellucid Corneal Marginal Degeneration**	**ICRS Pre- and Post-Penetrating Keratoplasty for Recurrent Keratoconus**	**Total**
ICRS INTACS	14 (5)	28 (5)	6 (4)	4 (I)	52 (15)
ICRS Ferrara		8 (3)	1 (1)		9 (4)
ICRS INTACS + Intraocular Lens		3 (3)			3 (3)
ICRS INTACS + Collagen Cross-Linking		2 (1)			2 (1)
Total	14 (5)	41 (12)	7 (5)	4 (1)	66 (23)

* LASIK refers to laser in situ keratomileusis; ICRS, intrastromal corneal ring segment.

Table 8. Level of Evidence Summary for INTAC Management of Keratoconus*

Study Design	Level of Evidence†	Number of Eligible Studies
Large RCT, systematic review of RCTs	1	0
Large RCT unpublished but reported to an international scientific meeting	1(g)	0
Small RCT	2	0
Small RCT unpublished but reported to an international scientific meeting	2(g)	0
Non-RCT with contemporaneous controls	3a	0
Non-RCT with historical controls	3b	10
Non-RCT presented at international conference	3(g)	0
Surveillance (database or register)	4a	0
Case series (multisite)	4b	0
Case series (single site)	4c	0
Retrospective review, modelling	4d	0
Case series presented at international conference	4(g)	0

RCT refers to randomized controlled trial; g, grey literature designation given to preliminary reports presented at international scientific meetings.
†For each included study, levels of evidence were assigned according to a ranking system based on a hierarchy proposed by Goodman. (45)

INTAC Corneal Implant Management of Keratoconus

A. Longitudinal Follow-Up Pre-Post Cohort Studies

Ten pre-post cohort longitudinal follow-up studies examining safety and effectiveness of ICRS in patients with KC were identified in the review and detailed below in Table 9. Five additional cohort studies (46-50) were identified using the Ferrara ICRS, but because this corneal implant is not licensed in Canada these studies were not reviewed.

The cohorts involved 608 KC patients (754 eyes) implanted with INTACS and followed for 1, 2 or 3 years. Three of the reports (51-53) involved ≥ 2 years of follow-up, with the longest being 5-year follow-up. Four of the INTAC cohort studies (33;52;54;55) involved 50 or more patients, the largest involved 255 patients. The inclusion criteria for the studies were consistent and included KC patients who were contact lens intolerant, had adequate corneal thickness particularly around the area of the implant incision site, and without central corneal scarring. The severity of KC, however, varied in the studies with most including a range from mild to advanced stages of disease. Patterns of thinning and corneal cone protrusions also varied and generally required different treatment approaches involving segment sizes and locations.

Table 9. Management of Keratoconus with Intrastromal Corneal Ring Corneal Remodelling – Clinical Follow-Up Trials

Author, Year	Country, Sites	Population*	Follow-Up Duration
Alio J, 2006 (51)	Spain, 1 site	11 p (13 e)	48 mo
Wachler B, 2003 (54)	United States, 1 site	50 p (74 e)	9-mo (mean)
Colin J, 2000,2001,2007 (52;56;57)	France, 1 site	10 p (10 e)	10-mo (mean)
			12-mo
		82 p (100 e)	24-mo
Colin J, 2006 (33)	European Collaborative France, Germany, United Kingdom, 4 sites	57 p (57 e)	12-mo
Ertan A, 2006, 2008, 2008 (55;58;59)	Turkey, 1 site	69 p (118 e)	12-mo
		255 p (306 e)	10.4 mo (mean)
		62 p (109 e)	12-mo
Hellstedt T, 2005 (60)	Finland, 1 site	37 p (50 e)	6.3-mo (mean)
Kanellopoulos A, 2006 (61)	United States, 1 site	15 p (20 e)	6-mo
Kymionis G, 2007 (53)	Greece, 1 site	26 p (36 e)	5- yr
Levinger S, 2005 (13)	Israel, 1 site	43 p (58 e)	12-mo
Zare M, 2007 (62)	Iran, 1 site	22 p (30 e)	6-mo
ICRS Ferrara			
Coskunseven E, 2008 (46)	Greece, 1 site	32 p (50 e)	1-yr
Kwitko S, 2004 (47)	Brazil, 1 site	43 p (58 e)	13-mo (mean)
Miranda D, 2003 (48)	Brazil, 1 site	35 p (36 e)	12-mo
Shabayek M, 2007 (49)	Spain, 1 site	16 p (21 e)	6-mo
Siganos D, 2002 (50)	Greece, 1 site	26 p (30 e)	6-mo

*e refers to eyes; mo, month; p, patients; y, year.

A broad range of outcome measures were reviewed to evaluate the clinical utility of INTAC management of corneal thinning disorders (Appendix 2**)**. Among the outcome measures reported were: technical success, safety profile, corneal topographic effects, visual acuity, vision quality, refractive outcomes, contact lens tolerance, vision quality of life, and patient vision satisfaction. Evidence on the impact of INTACS on the underlying corneal thinning disease process was also evaluated by direct measurement of central corneal thinning and by indirect measures of altered corneal topography and loss of visual acuity. The results of the outcome measures are reported in the following sections.

Technical Success of INTAC Placement

High levels (>98%) of technical success or ability to place INTAC segments were reported. (33;50;60) Technical difficulties, however, were delayed and generally reported as segment migration, usually within the first few months. Migration usually occurred due to inadequately created tunnels for the segments that were usually not made deep enough into the stromal bed. This was generally attributed to early surgeon experience and mainly occurring in early cases. The explantation rate or segment removal rate was 6.2% (41/659) and ranged from 0.98% to 19.4%. The most common indication for explantation was segment migration **(**Table 10). In those studies indicating when explantation was followed by corneal transplant, the transplant surgeries were reported to be uneventful. A summary of the overall technical success, re-interventions, and complications reported in the follow-up cohort studies for INTAC management of KC is outlined in Appendix 3.

Table 10. Explantation Rate Following ICRS Management of KC*

Author, Yr	Explant Rate, Eyes (%)	Indications	Corneal Transplant Performed for Explants
Wachler B, 2003 (54)	3/74 (4.1)	Migration (n=2), foreign body sensation (n=1)	NR
Colin J, 2000 (56)	1/10 (10)	Superficial implantation	NR
Colin J, 2007 (52)	4/100 (4)	Extrusion (n=2), poor visual outcome (n=2)	All eyes
Ertan A, 2008 (55)	3/306 (0.98)	Migration and extrusion (n=3)	NR
Hellstedt T, 2005 (60)	9/50 (18)	Migration and extrusion (n=1), high myopia (n=1), high astigmatism (n=6), low BSCVA (n=1)	NR
Kanellopoulos A, 2006 (61)	7/20 (35)	Migration (n=6), corneal infiltrate (n=1)	NR
Kymionis G, 2007 (53)	7/36 (19.4)	Vision unsatisfactory (n=7)	All eyes
Siganos D, 2003 (63)	2/33 (6.1)	Migration (n=1), superficial placement (n=1)	Both eyes
Zare M, 2007 (62)	5/30 (16.7)	Foreign body reaction (n=1), corneal infiltrate (n=1), migration (n=4)	NR
Total	41/ 659 (6.2)		

*BSCVA refers to best spectacle-corrected visual acuity; ICRS, intrastromal corneal ring segment; NR, not reported.

Complications and Safety

The complication events reported in the follow-up outcome studies for INTAC management of KC are detailed in Appendix 3 and summarized below in Table 11. Based on the longitudinal follow-up studies, the overall complication rate was 4.6% (29/636) and mainly involved reversible minor complications such as segment migration. Major complications such as infection and vascularisation were uncommonly reported. Vascularization, when reported, was self limiting and without clinical sequelae.

Table 11. Complication Rates Following ICRS Placement for Keratoconus*

Author, Year	Complication Rate (%)	Events
Alio J, 2005 (64)	3/26 (11.5)	Mild neovascularization and self-limiting (3 eyes)
Alio J, 2006 (51)	1/13 (7.7)	Superficial vascularization at incision site regressing at 2-yr follow-up (1 eye)
Wachler B, 2003 (54)	6/74 (8.1)	Superficial channel dissection (1 eye), transient inflammatory reaction at incision site (2 eyes), segment migration and extrusion day 1 post-op (1 eye), foreign body reaction and explanted (2 eyes same patient)
Colin J, 2007 (52)	1/10 (10)	Segment migration (1 eye)
Ertan A, 2008 (55)	3/306 (1.0)	Segment migration within 6 mos (3 eyes)
Hellstedt T, 2005 (60)	3/50 (6)	Migration and extrusion (2 eyes), infection with loosening incision (1 eye)
Kanellopoulos A, 2006 (61)	7/20 (35)	Segment migration (6 eyes), corneal infiltrates (1 eye)
Kymionis G, 2007 (53)	0/20 (0-)	No complications
Levinger S, 2005 (13)	0/58 (-0)	No segment migration, no infection
Siganos D, 2003 (63)	1/33 (3)	Superficial mild wound neovascularization after 2 mos and stable at 11 mo follow-up (1 eye)
Zare M, 2007 (62)	4/26 (15.4)	Segment migration (3 eyes), extreme foreign body reaction (1 eye)
Overall	29/636 (4.6)	

*ICRS refers to intrastromal corneal ring segment; mo(s), month(s); yr, year.

Of the 13 case reports or small case series involving complications following the use of INTACS, five reports involved management of KC (65-69) , seven reports were for ectasia following LASIK (70-76) and one report (77) described ectasia following LASIK as a secondary procedure after unsuccessful implant management of myopia. Neovascularization and bacterial infections were both reported as a complication that occurred after managing KC and ectasia following LASIK treatment. In one series, (67) following the timing of infection following INTACS, although most occurred within the first week, infections did occur after two months and close follow-up of these patients was recommended. In another report, (75) infection following INTAC management of post LASIK ectasia required hospitalization and aggressive antibiotic therapy. In most cases the complication event was managed by removing the INTACS. Individual case reports involving INTAC related complications are detailed in Table 12.

Table 12. Complication Events Reported for INTACS in Case Reports

Author, Yr	Indication	Complication Event	Outcome
Al-Torbak, 2005 (70)	ICRS for post–LASIK ectasia	Corneal neovascularization	Segment removed
Bourcier T, 2002 (71)	ICRS post–laser assisted subepithelial keratectomy	Bacterial keratitis 3 months post-op	Resolved
Bourges J, 2003 (77)	Post-myopia	Corneal anterior stroma necrosis	Segment removed
Deobhakta A, 2008 (65)	Post-keratoconus	Focal edema	Segment removed
Galvis V, 2007 (66)	Post-keratoconus	Bacterial keratitis 4 months post-op	Segment removed
Hofling-Lima A, 2004 (67) (series)	Post-keratoconus	Infectious keratitis (n=8); within first week (n=3), between 2nd and 8th week (n=2), and >2 months (n=3)	Segment removed in 5 cases, corneal transplant in 2 cases, 1 case resolved
Katsoulis K, 2006 (72)	ICRS for post-LASIK ectasia	Central opacification of anterior stroma	Not resolving
Liu M, 2008 (73)	ICRS for post-LASIK ectasia	Extruded segment with corneal neovascularization	Segment removed
McAlister J, 2006 (78)	Post-keratoconus	Keratitis 3 days post-op	Segment removed
Randelman J, 2006 (74)	ICRS for post-LASIK ectasia	Aberrant corneal nerve regeneration	Segment removed
Samimi S, 2007 (69) (Series)	Post-keratoconus	Explants for poor vision (n=6), segment extrusion (n=2)	Segment removed and corneal transplant performed
Shehadeh-Masha'our, 2004 (75)	ICRS for post-LASIK ectasia	Infiltrate at gap at corneal incision, diffuse infective keratitis	Hospitalized for aggressive antibiotic treatment
Spirn M, 2005 (76)	ICRS for post- LASIK enhancement ectasia	Progressively worsening vision to high irregular astigmatism	Corneal transplant

ICRS; Refers to intrastromal corneal ring segment; LASIK, laser in-situ keratomileusis

Adjustability and Reversibility of INTAC Intervention

One report (79) examined the adjustment surgery rate in a cohort of 58 consecutive KC patients with clear corneas and contact lens intolerant eyes managed with INTACS. Selection of implant segment thickness was dependent on the spherical equivalent, patient age, and site of the corneal cone. Additional surgery was performed in seven eyes (12.1%) involving explanting segments in 6 cases and implanting an additional segment in one case. The segments were removed because visual acuity (both UCVA and BSCVA) improved only minimally, or not at all, and in one case deteriorated (UCVA 20/400 to 20/800 and BSCVA 20/160 to 20/400). The indications for adjustment surgery were: surgically induced astigmatism in 4 cases, induced hyperopia (defined as spherical equivalent becoming positive) in 2 cases, and residual myopic astigmatism in 1 case. All adjustments were performed without difficulty and no operative complications were reported. Visual acuity improved following the adjustment surgery in most

cases. The BSCVA was within 20/40 for all patients except one and UCVA was improved in most cases: three were ≥ 20/40, two were ≥ 20/70 and two had no improvement i.e., <20/200. Those without improvement had advanced KC in one case with manifest astigmatism ≥10 D and in the other case astigmatism ≥10 D with little spherical myopia. After the failed adjustment surgery, one of these cases underwent successful corneal transplant.

Alio et al. (80) reported on re-interventions in four patients (5 eyes) in whom segment extraction became necessary in follow-up; all interventions occurred between the third and sixth month of follow-up. INTAC placement initially involved two segments (0.25-mm superiorly and 0.45 inferiorly) in three eyes and one segment (0.45-mm inferiorly) in two eyes. All extractions were easily performed and in 4 of the 5 eyes, extraction was performed for migration, partial extrusion and moderate melting. In the fifth case, migration, corneal thinning, and melting occurred over the segment. In two cases, a single segment resulting in decreasing visual acuity and pain and discomfort was removed and another implantation restored both UCVA and BSCVA to within 20/40.

Two other reports supported the reversibility of INTAC segments. Both demonstrated an improvement in visual acuity following explantation and reversal of INTAC segments that were initially unsuccessful. (81;82)

In one report involving asymmetric placement of segments that had not provided improvement in visual acuity (0.25 UCVA and 0.4 BSCVA), a significant improvement was achieved in both UCVA and BSCVA by explanting and reversing the segments. The second report demonstrated the successful reversal of INTAC segments, followed by improvements in visual acuity in a KC patient. Originally two segments, one (0.25-mm) placed superiorly and one (0.35-mm) placed inferiorly to the cone, resulted in decreased BSCVA two months post-operatively.

Corneal Topographic Affects

The affects of INTACS on corneal topography were reported as keratometry measures (K-values) in diopters which represent the radius of corneal curvature and provides a measure of cone protrusion. K-values are also reported as mean, minimum (K_1), or maximum (K_2) values. In a comparative study evaluating keratometry values in KC compared to normal eyes, mean k-values for normal subjects (n= 40 eyes) was 43.28 ± 1.17 D (range 41.53 to 45.40 D) and the mean k-values for KC subjects (n=40 eyes) was 49.29 ± 4.37 D (range 42.97 to 60.33 D). (14) Other authors have indicated a range of increasing K-values reflecting the progressive severity of KC corneas: mild ≤ 48 D, moderate 48–53, and advanced D >53 D. (62)

The remodelling affects of INTAC on corneal surface topography represented by k-values are summarized below for short term follow-up outcomes at 6 months (Table 13) and for longer term outcomes at 1, 2 and 5-yr follow–up (Table 14). All studies reported significantly improved (P <.05) corneal surface topography as measured by keratometry at 6-month and at 1-year follow-up. Two studies reported significantly (P <.05) improved keratometry at 2- and 5-year follow-up.

Table 13. Impact of INTACS on Corneal Curvature in Keratoconus – Short Term Topographic Findings at 6 Months

Author, Yr	Eyes	Follow-up Interval	Corneal Curvature Keratometry, (K- value in Diopters			P Value
			K-Value	Baseline	6-Month Follow-up	
Colin J, 2000 (57)	10	Pre-op to 6 mo	Mean	51.73 ± 4.46	46.88 ± 5.11	< .05
Colin J, 2006 (33)	59	Pre-op to 6 mo	Mean	49.7 ± 4.9	46.0 ± 3.5	≤ .002
Ertan A, 2008 (55)	306	Pre-op to 4 mo	Mean	50.70 ± 5.45	47.91 ± 5.28	< .05
Hellstedt T, 2005 (60)	50	Pre-op to 6 mo	Maximum	52.8 ± 6.3	48.6 ± 5.7	<.05
			Minimum	47.7 ± 5.7	44.4 ± 4.1	< .05
Kanellopoulos A, 2006 (61)	20	Pre-op to 6 mo	Mean	49.45 ± 1.64	46.35 ± 1.50	.00
Zare M, 2007 (62)	30	Pre-op to 6 mo	Maximum	52.19 ± 4.03	50.22 ± 4.20	<.001
			Minimum	47.46 ± 3.33	45.58 ± 3.19	<.001
			Mean	49.84 ± 3.58	47.90 ± 3.58	<.001

mo; refers to month; pre-op, pre -operative

Table 14. Impact OF INTACS on Corneal Curvature in Keratoconus – Longer Term Topographic Findings

Author, Yr	Eyes	Follow-up Interval	Corneal Curvature Keratometry, (K- value in Diopters			P - Value
			K Value	Baseline	12-Month F-Up	
Colin J, 2007 (52)	100	Pre-op to 1 yr	Mean	50.1 ± 5.6	46.4 ± 5.3	< .001
		Pre-op to 2 yr		50.1 ± 5.6	46.8 ± 4.9	< .001
Ertan A, 2006 (58)	118	Pre-op to 1-yr	Mean	51.56 ± 5.22	47.66 ± 4.3	< .05
Kanellopoulos A, 2006 (61)	20	Pre-op to 1 yr	Mean	49.45 ± 1.64	46.50 ± 1.22	.00
Kymionis G, 2007 (53)	17	Pre-op to 5 yr	Mean	49.59 ± 5.10	48.02 ± 4.99	.009
Levinger S, 2005 (13)	58	Pre-op to 1 yr	Maximum	48.06 ± 3.87	44.62 ± 3.18	< .001
			Minimum	44.73 ± 2.29	41.99 ± 2.59	< .001

Pre-op refers to pre-operative; yr, year

Visual Acuity

Visual acuity, both UCVA and BCVA, were reported in all studies, but in different formats. Snellen VA was reported in several studies and is the most commonly known measure (Appendix 2). Visual acuity has also been summarized by the impact of visual loss on an individuals' level of functioning. Many individuals function in the range of up to 20/40 without optical correction; 20/40 is the most common cut-off for an unrestricted drivers' license; 20/200 or worse is the legal definition of blindness. (19) VA was also measured using the Snellen rating and transformed into the logarithm of the minimum angle of resolution (LogMAR) and expressed as LogMAR ± SD (Standard Deviation). Change in visual acuity was also represented as a gain or loss of lines of vision. Generally, a gain or loss of 1 line was considered to be within normal variability and represented no change. (19) LogMAR values within 0.1 are considered within 1 line and values within 0.2 are within 2 lines. The relationship between Snellen VA, LogMAR values, and suggested levels of vision quality are outlined in Table 15. (13) Gains or loss of ≥ 2 lines were considered to be clinically significant losses or gains of visual acuity. A loss of ≥ 2 lines of BCVA was also considered to be a vision safety concern.

Table 15. Relationship Of Refractive Parameters and Suggested Vision Quality*

Vision Quality	Range LogMAR Value	Snellen Visual Acuity
Poor	<0.50	<20/63
Fair	0.50–0.31	≥20/63<20/40
Good	>0.30	≥20/40

*LogMAR refers to logarithm of the minimum angle of resolution.

Significant improvements in both UCVA and BSCVA after INTAC placement, were reported in all studies at 6-month (Table 16) and 1-year (Table 17) follow-up. Colin et al. (33) demonstrated the degree to which INTACS restored visual acuity in KC patients to within functional levels (i.e., 20/32 or better). After INTAC placement, those in the study group having UCVA 20/32 or better, increased from only 2% at baseline to 21%, while those with BCVA 20/32 or better increased from 26% at baseline to 62%.

An important adverse visual acuity outcome was also the degree to which patients lost acuity following implant placement. Loss in visual acuity, either for UCVA or BCVA was variably defined in the studies as thresholds involving more than 1 Snellen line of loss or more than 2 Snellen lines. (Table 18) A loss of more than 1 Snellen line, particularly for BSCVA, is considered clinically significant. The rate of loss of UCVA, for those reporting 2 or more lines ranged from 0 to 9%, with the largest study reporting 2.9%. The rate of loss for BSCVA, for those reporting 2 or more lines ranged from 4% to 12%.

Table 16. Visual Acuity in Keratoconus Following INTACS at 6-Month Follow-up*

Author, Year	Eyes	Uncorrected Visual Acuity, Mean ± SD			Best Spectacle-Corrected Visual Acuity, Mean ± SD		
		Pre-op	6-Month	*P Value*	Pre-op	6-Month	*P Value*
Wachler B, 2003 (54)	74	20/200 (Snellen IVA)	20/80	NR	20/50	20/32	NR
Colin J, 2000 (56)	10	0.12 ± 0.08 (decimal scale)	0.30 ± 0.19	NR	0.38 ± 0.11	0.63 ± 0.29	NR
Colin J, 2006 (33)	34	NR	80% (27/34) gained ≥2 Snellen lines	<.0001		62% (21/340) gained 2–8 Snellen lines	< .033
Ertan A, 2008 (55)	306	1.10 ± 0.54 (LogMAR)	0.64 ± 0.41	<.05	0.48 ± 0.34	0.28 ± 0.23	< .05
Hellstedt T, 2005 (60)	30	NR	Mean change =2.2 ± 2.3 Snellen lines Improved (23, 77%) No change (4, 13%) Worse (3, 12%)	NR		Mean change =1.0 ± 2.0 Snellen lines Improved (22, 73%) No change (6, 20%) Worse (2, 7%)	NR
Zare M, 2007 (62)	30	0.60 ± 0.31 (LogMAR)	0.29 ± 0.20	<.001	0.25 ± 0.17	0.13 ± 0.14	< .001

***Note:** The studies represented in Table 16 reported visual acuity in different measurement scales. The original scales used by the authors are reported.

LogMAR refers to logarithm of the minimum angle of resolution; NR, not reported; Pre-op, pre-operative; SD, standard deviation.

Table 17. Visual Acuity in Keratoconus Following INTACS at 1-Year and Longer Follow-up*

Author, Year	Eyes	Uncorrected Visual Acuity, Mean ± SD			Best Spectacle Corrected Visual Acuity, Mean ± SD		
		Pre-op	1-year	*P*	Pre-op	1-year	*P- Value*
Colin J, 2007 (52)	100	11% ≥ 20/100 (Snellen VA)	35% ≥ 20/100 [61% (50/82) gained 1–5 lines] 32%>20/100 (2-yr)	< .001	22% ≥ 20/40	50% ≥ 20/40 at 1- and 2-yr	< .001
Ertan A, 2006 (58)	118	1.32 ± 1.53 (Snellen lines)	3.29 ± 2.64	< .05	4.20 ± 2.43	6.02 ± 2.70	< .05
Kanellopoulos A, 2006 (61)	20	20/154 ± 0.11 (Snellen VA)	20/29 ± 0.13	NR	20/37 ± 0.21	20/23 ± 0.11	NR
Kymionis G, 2007 5-YR (53)	17	100%>20/50 (Snellen VA)	59% > 20/50 (at 5-yr) Mean gain was 2.8 Snellen lines	NR		94% (16/17) gained 1–8 lines	NR
Levinger S, 2005 (13)	58	20/200 ± 0.1 [All ≥20/200] (Snellen VA)	20/50 ± 3.1 Poor (<20/63) n=21, Fair ≥(20/63) n=12, Good (≥20/40) n=25	< .001	20/32 ± 3.1	20/32 ± 0.18	.75

*NR refers to not reported; Pre-op, pre-operative; SD, standard deviation.

Table 18. Loss in Visual Acuity Following ICRS for Keratoconus*

Author, Year	Follow-Up	Eyes	Eyes With Loss of VA, %		
			Threshold VA Loss, Snellen Lines	UCVA	BSCVA
Wachler, 2003 (54)	6-month	74	≥ 2 lines	9%,	4%
Colin, 2007 (52)	1-year	100	1–4 lines	12%	12%
Colin, 2006 (33)	6-month	34	2 lines	0%	6%
Ertan, 2008 (55)	6-month	306	>2 lines	2.9%	3.7%
Hellstedt T, 2005 (60)	6-month	50	≥ 2 lines	7%	12%
Siganos D, 2003 (63)	1-year	33	1 line	6%	12%
Zare M, 2007 (62)	6-month	30	2 lines	3%	12%

*BCVA refers to best corrected visual acuity; UCVA; uncorrected visual acuity.

Refractive Outcomes

Refractive outcome measures include the refractive sphere (S) and the refractive cylinder (C); spherical equivalent (SE) is a summary measure of the sphere and the cylinder [SE = S + 0.5 C]. The spherical correction is the amount of power [(in diopters (D)] required in a lens to correct visual acuity to an acceptable level, usually 20/20. The refractive cylinder, also measured in diopters is a measure of astigmatism. High degrees of astigmatism are normally considered to be ≥ 3 diopters (Personal Communication, November 25, 2008). Refractive changes of 1 diopter or more are considered clinically significant as they usually require an optical correction. (19)

The changes in refractive outcome measures for spherical equivalent and cylinder in KC after placement of INTACS are outlined in Tables 19 – 22. Refractive outcome measures were reduced in all studies reporting them at 6-month and 1-year follow-up. The reductions in spherical equivalent ranged from 1.50 to 3.70 diopters at 6-month follow- up (Table 19) and from 0.94 to 2.97 diopters at 1-year follow-up (Table 20). Reductions in refractive cylinder ranged from 0.75 to 2.54 at 6-month follow-up (Table 21) and from 0.75 to 2.50 diopters at 1-year follow-up (Table 22)**.** The significant reductions in spherical equivalent and refractive cylinder were maintained at two (51;52) and three (51) year follow-up.

Table 19. Change in Spherical Equivalent Following INTACS for Keratoconus at 6-Month Follow-up*

Author, Year	Eyes	Mean Spherical Equivalent (Diopters)			*P Value*
		Pre-op	Post-op	Change	
Colin J, 2000 (56)	10	−5.13 ± 4.77	−3.01 ± 4.32	2.12	NR
Colin J, 2006 (33)	34	−4.6 ± 3.5	−3.1 ± 2.5	1.50	<.001
Kanellopoulos A, 2006 (61)	20	−5.33 ± 3.40	−1.64 ± 1.84	3.69	NR
Kymionis G, 2007 (53)	36	−5.54 ± 5.02	−2.68 ± 2.83	2.86	NR
Zare M, 2007 (62)	30	−6.93 ± 3.52	−3.23 ± 2.81	3.70	.001

*NR refers to not reported; Pre-op, pre-operative; Post-op, post-operative.

Table 20. Change in Spherical Equivalent Following INTACS for Keratoconus at 1-Year or Longer Follow-up*

Study	Eyes	Follow-up	Mean Spherical Equivalent (Diopters)			*P* - Value
			Pre-op	Post-op	Change	
Alio J, 2006 (51)	13	1-year	−5.40 ± 4.11	−4.46 ± 5.10	0.94	NR
		2-year		−4.69 ± 5.32	0.71	
		3-year		−4.86 ±5.09	0.54	
Colin J, 2007 (52)	74	1-year	−6.93 ± 3.01	−4.01 ± 3.16	2.92	< .002
		2-year		−3.80 ± 2.73	3.13	
Ertan A, 2006 (58)	118	1-year	−5.70 ± 4.32	−2.73 ± 2.91	2.97	< .05
Kanellopoulos A, 2006 (61)	20	1-year	−3.38 ± 3.12	−1.46 ± 2.19	1.92	NR
Kymionis G, 2007 (53)	17	5-year	−5.54 ± 5.02	−3.02 ± 2.65	2.52	.01
Levinger S, 2005 (13)	58	1-year	−3.88 ± 1.64	−1.04 ± 1.51	2.84	< .001

*NR refers to not reported; Pre-op, pre-operative; Post-op, post-operative.

Table 21. Change in Refractive Cylinder Following INTACS for Keratoconus at 6-Month Follow-up*

Study	Eyes	Mean Refractive Cylinder (Diopters)			
		Pre-op	Post-op	Change	*P* - Value
Colin J, 2000 (56)	10	−3.31 ± 1.59	−1.81 ± 3.34	1.50	NR
Colin J, 2006 (33)	34	NR	NR	1.52	< .001
Kanellopoulos A, 2006 (61)	20	−3.75 ± 2.04	−1.21 ± 0.84	2.54	NR
Zare M, 2007 (62)	30	−4.65 ± 1.85	−3.90 ± 1.70	0.75	.054

*NR refers to not reported; Pre-op, pre-operative; Post-op, post operative.

Table 22. Change in Refractive Cylinder Following ICRS for Keratoconus at 1-Year or Longer Follow-up*

Study	Eyes	Follow-up	Mean Refractive Cylinder (Diopters)			
			Pre-op	Post-op	Change	*P* - Value
Alio J, 2006 (51)	13	1-year	−5.15 ± 3.19	−3.48 ± 3.19	1.67	NR
		2-year		−3.13 ± 1.01	2.02	
		3-year		−3.36 ± 1.26	1.79	
Colin J, 2007 (52)	74	1-year	−4.62 ± 2.80	−3.87 ± 2.50	0.75	.002
		2-year		−3.31 ± 1.83	1.31	
Ertan A, 2006 (58)	118	1-year	−3.90 ± 2.11	−2.20 ± 1.50	1.70	<.05
Kanellopoulos A, 2006 (61)	20	1-year	−3.75 ± 2.04	−1.25 ± 0.89	2.50	NR

ICRS refers to intrastromal corneal ring segment; NR, not reported; Pre-op, pre-operative; Post-op, post-operative.

Variability in Response to INTACS

Improvements in visual acuity and refractive errors after INTAC placement were not noted in all study participants. Four studies evaluated treatment response to INTACS across various patient subpopulations. (55;59;62;83)

A report by Ertan et al. (59) examined differences in visual acuity and corneal topography across three age groups: young (13 to 19 years); middle (20 to 34 years) and older (35 to 56 years). The impact of age on the change in corneal topography as measured by keratometry was not found to differ across age groups (Table 23). Visual acuity, both in terms of UCVA and BSCVA, was also not found to vary significantly ($P > .05$) across age groups (Table 24).

Table 23. Impact of INTACS on Keratoconus Corneal Topography Across Age Groups*

	Mean K-Value ± SD (Diopters)		
	Younger (n = 20) 13–19 Years	Middle (n = 75) 20–34 Years	Older (n = 14) 35–56 Years
Pre-op	50.24 ± 4.44	51.77 ± 5.39	50.48 ± 5.27
Post-op	46.96 ± 3.29	47.96 ± 4.63	47.44 ± 4.32
Change	3.75 ± 2.15	3.72 ± 1.92	3.12 ± 1.67

*Post-op refers to post-operative; Pre-op, pre-operative; SD, standard deviation.

Table 24. Mean Change in Visual Acuity Across Age Groups After INTACS for Keratoconus*

	Visual Acuity (LogMAR ± SD)		
	Younger (n = 20) 13–19 Years	Middle (n = 75) 20–34 Years	Older (n = 14) 35-56 Years
Mean Change UCVA	−0.63 ± 0.84	−0.85 ± 0.71	−0.74 ± 0.72
Mean Change BSCVA	−0.21 ± 0.33	−0.20 ± 0.24	−0.12 ± 0.30

*BSCVA refers to best spectacle-corrected visual acuity; LogMAR, logarithm of the minimum angle of resolution; SD, standard deviation; UCVA; uncorrected visual acuity.

In a report by Ertan et al., (55) outcomes after INTACS were compared across various stages of KC (as classified by the Amsler-Krumeich system) according to mean keratometry values for corneal curvature. Their patient group was divided as follows:

- 155 eyes in stage 11 (mean K-value 48.00 D to 53.00D);
- 83 eyes in stage 111 (mean K-value 53.00 to 55.00 D); and
- 68 eyes in stage 1V (mean K-value >55.00 D).

The overall response was a significant ($P < .05$) increase in BCVA and UCVA of 71.6% and 75.7%, respectively, and a significant ($P < .05$) decrease in mean K-value from 50.7D to 47.0 D. Only 2.9% of patients lost 2 Snellen lines or more of UCVA and only 3.7% lost 2 or more lines of BCVA. Overall, UCVA, BCVA, sphere and mean K-values were significantly improved from baseline in every stage of KC.

However, the refractive cylinder (a measure of astigmatism) was significantly improved from baseline only in the stage 11 disease category. The amount of improvement from baseline for BCVA, refractive sphere and cylinder were not significantly different across disease stages. There was however, less change in UCVA in stage 1V disease and a greater increase in mean K-values in the stage 1V disease than the other stages. That the refractive cylinder was not improved in stage 11 and 111 disease was attributed to the higher degree of astigmatism in these patients.

In a smaller study by Zare et al. (62) a range of patients with various grades of KC (6 eyes in Grade 1, 16 eyes in Grade 11, 4 eyes in Grade 111 and 4 eyes in Grade 1V) was examined. Overall, both UCVA and BCVA significantly improved at 6–month follow-up from baseline and 3.3% (1/30) lost 2 Snellen lines of UCVA and BCVA. The mean spherical equivalent ($P = .001$) and the mean keratometry ($P < .001$) were significantly improved over baseline. The change in mean refractive cylinder over baseline, however, was not significant ($P = .054$) and was not significantly improved for any stage of KC. Increasing pre-operative keratometry values (≤48 D, 48 – 53 D, >53 D) were found to influence the significance of improvements in BCVA and mean cylinder, but not the UCVA and spherical equivalent. Mean BCVA was not significantly improved over baseline ($P = .256$) for preoperative keratometry values >53 D i.e., greater than stage 111 of disease. The authors conclude that in this group, INTACS had a greater effect on flattening of the cornea (decrease spherical equivalent and keratometry measures) than on the asymmetry of corneal shape or astigmatism (refractive cylinder).

Alio et al. (83) compared the predictive factors in two groups of KC patients based on visual outcome. Group A, which consisted of 17 patients (20 eyes) with a good treatment response (gained more than 3 Snellen lines BCVA) ,was compared to Group B, which consisted of four patients (5 eyes) who did not have a good treatment response (lost 1 Snellen line BCVA). Patients who exhibited poor treatment response had higher preoperative measures than those with good treatment response for mean keratometry (6.91 D, $P \leq .001$), refractive sphere (3.90 D, $P \leq .007$), and sphere equivalent (4.36 D, $P \leq .007$), but not for refractive cylinder 1.46 D ($P \leq .38$). Significant improvements at 6-month follow-up occurred

in Group A for mean K-value (4.30, $P \leq .0001$), BSCVA (0.38, $P = .0001$), sphere (2.11 D, $P \leq .027$), and spherical equivalent (2.81 D, $P \leq .003$), but not for cylinder (1.50 D, $P \leq .10$). In Group B, significant improvements were only noted for mean keratometry (6.19 D, $P = .014$). In this study the effect of INTACS, even in Group A, was much greater for refractive sphere or flattening the cornea surface than it was for refractive cylinder or forming a more regular corneal surface or decreasing the astigmatism. In general, patients with mild or moderate stages of KC (mean K-value ≤ 53 D) were more likely than those with more advanced stages (mean K-value ≥53 D) to have good outcomes.

Contact Lens Tolerance Following INTAC Placement

One of the main treatment objectives with INTACS for KC patients was to restore tolerability to contact lenses. Only 3 cohort follow-up studies (51;52;84) reported on contact lens tolerability following implant placement for KC and tolerability in these studies was variably reported. In the report by Alio et al., (51) all 13 patients reported contact lens tolerance following implant surgery. In a study by Kymionis et al., (84) however, only 35% (6/17) of patients tolerated rigid-gas-permeable contact lenses without replacement. Greater detail on contact tolerance was reported by Colin et al., (52) in a study involving 82 patients (100 eyes). Forty four eyes required contact lenses following implant surgery, 47 needed correction with spectacles, and 9 required no correction. Of the 44 fitted with contact lenses, 89% (39/44) were contact tolerable at 1-year follow-up and 84% at 2-year follow-up.

The use of custom fitting of contact lenses following INTACS placement was also reported in four case reports. (85-88) Two of these reports involved a piggyback system where rigid gas-permeable hard contact lenses are fitted on top of soft contacts to improve tolerability. (85;86) A report by Nepomuceno et al. (88) indicated that contact lens fitting following INTAC placement in patients previously intolerant to contact lenses was challenging and required ongoing diagnostics and lens adjustments. In three of their patients, all of whom had an UCVA of 2.0 LogMAR or counting fingers prior to INTACS, UCVA improved to 0.81± 0.25 LogMAR (20/125-1). The number of diagnostic lenses used in a 4-month follow-up period ranged from 1 to 3 and the mean final wearing time ranged from 2.5 to 12 hours daily.

Vision Related Quality of Life and Patient Satisfaction

Four studies reported different measures of KC patient's vision satisfaction and quality of life after INTAC placement. (13;33;53;60) Only one of these studies (60) reported on the impact of INTACS on vision functional impairment.

Hellstedt et al. reported patient vision satisfaction according to a basic 4-point scale (very unsatisfied, unsatisfied, satisfied, very satisfied) along with an index of vision functional impairment (VF-7), which scores vision from 0 (unable to perform any activity) to 100 (able to perform all activities without impairment). (60) Vision satisfaction was reported to increase gradually after the procedure at the 6-month and 1-year follow-up. At six-month follow-up with 26 of the recruited 37 patients, 89% (23/26) reported their satisfaction improved by at least one category, none were unchanged, and 12% (3/26) were worse. The VF-7 improved from 61.6 ± 21.1 for 37 patients at baseline to 80.8 ± 22.5 at 6-month follow-up for 26 patients. Patient's change in satisfaction at 6 months was significantly correlated with change in BSCVA ($r = 0.453$; $P = .039$) and visual function ($r = 0.568$; $P = .002$).

In the report by Kymionis et al. (53), patient satisfaction with visual outcome was rated from 1 (very unsatisfied) to 5 (very satisfied). Patients completed a questionnaire on visual outcomes that included details on UCVA, BSCVA, night vision, and day and night driving. Sixteen of the original 26 patients treated completed 5-year follow-up and 82% (14/16) of these considered themselves to be satisfied (scores = 5). Two patients, both having an advanced stage of KC, were considered unhappy (scores = 2–3).

In the Colin et al. report (33), visual symptoms such as photophobia, fluctuating vision, halos etc. were reported pre-operatively and for those followed up at 6 months, fewer events were reported. The authors did note that patient dissatisfaction with visual symptoms resulted in 12.3% (7/57) of them requesting that their implants be removed. Patients also rated their satisfaction with their vision quality. At baseline, only 10% (4/39) rated their vision satisfaction as good, while none reported their satisfaction as excellent. At 6-month follow-up, 38% (8/21) reported their vision as good and 10% (2/21) as excellent.

Levinger et al. (13) reported measures of patient satisfaction in the largest group of patients. The study initially recruited 43 patients who were given questionnaires on vision improvement and visual symptoms such as visual distortion, night vision, blurring, glare, halos, and photophobia. At follow-up between 9 and 12 months, 54 questionnaires were completed. Of these, significant improvement was reported in 72% (39/54), while 28%% (15/54) reported no improvement. Five patients reporting satisfaction with UCVA also reported a loss of BSCVA. Many patients complained of near vision and intermittently "seeing the ring". The author commented that there was an impression that "patients with high myopia may be more satisfied with the implants than patients with high astigmatism and little spherical myopia".

INTAC Impact on Corneal Thinning Disease Process

The impact of INTACS on the underlying disease process was examined in several ways. Measurement of corneal thinning by ultrasound pachymetry in longitudinal follow-up provides a direct measure of the impact of INTACS on the corneal thinning disease process. Only a few authors , however, reported longitudinal measures of central corneal thinning and the longest follow-up period was two years (Table 25). (33;52;55;62)Two of these studies reported that corneal thinning had not changed from baseline at 4-month (P >.05) and at 6-month (P = .054) follow-up. Colin et al. (33) reported that corneal thinning at one-year follow-up was not significantly (P = .085) changed from baseline but no pachymetry values were reported. However the Colin et al.(52) report in 2007 with a larger study group also showed that corneal thinning was not significantly different from baseline at one-year (P = .002) and two-year (P = .0008) follow-up but there was a trend of steadily decreasing pachymetry values.

Examining the long term maintenance or stability of the induced corneal changes and the subsequent improvements in visual acuity provides an indirect measure of the underlying thinning process. Although visual acuity and refractive effects were generally stable at follow-up in the clinical trials, the follow-up was limited generally only for 2 years. Although the visual acuity and refractive effects of keratoconus patients were stable in the one trial (53) with a longer follow-up term of 5 years, only a small group of patients from the original cohort remained at follow-up (17 of 26).

Table 25. Pachymetry Measures of Central Corneal Thinning in Keratoconus Following INTAC Placement

Author, Yr	Eyes	Follow-up Interval	Central Corneal Thinning Mean Pachymetry, µm at Thinnest Point ± SD		
			Baseline	Follow-up	*P*-Value
Colin J, 2006 (33)	57	Pre-op to 1-year	NR	NR	.085
Ertan J, 2008 (55)	306	Pre-op to 4-month	450.05 ± 54.59	454.06 ± 54.46	>.05
Zare M, 2007 (62)	30	Pre-op to 6-month	428.33 ± 44.69	405.05 ± 50.34	.054
Colin J, 2007 (52)	100	Pre-op to 1-year	478 ± 55	434 ± 56	.002
		Pre-op to 2-year	478 ± 55	421 ± 54	.0008

NR refers to not reported; Pre-op, pre-operative

B. Technical and Comparative Investigations for INTACS in Keratoconus

INTAC Segment Selection

Selection of the number of INTAC segments, their thickness (equal or unequal), and the location of their placement was variable in the reports and depended on the degree and location of the corneal thinning and subsequent corneal cones. Two studies (64;89) evaluated the effects of placing one or two INTAC segments, one for correction of KC in a prospective study (64) and one (89) for correction in a mixed patient population of KC and post-LASIK ectasia.

The Alio et al. study (64) divided consecutive series of KC patients into two groups based on their preoperative corneal topography. The objectives were not to compare one versus two ICRS segments but to show that in some cases one segment was better and in others two segments were needed. In Group 1 (8 patients, 11 eyes), those with topographic findings with corneal surface steepening not involving the 180 degree meridian of the cornea (inferior cone), only one ICRS segment was placed inferiorly. In Group 2 (11 patients, 15 eyes), those patients whose corneal topography revealed steepening of at least 1 mm above and beyond the 180 degree meridian, two segments were implanted in an asymmetric fashion (0.45 mm segment inferiorly and 0.25 mm segment superiorly). All patients were followed for one year.

In both groups, visual acuity (both UCVA and BSCVA) and keratometry significantly improved at one-year follow-up (Table 26). Efficiency values (mean post-operative UCVA / mean pre-operative BCVA) were approximately the same in both groups (0.92 in group 1 and 0.90 in group 2). The number of eyes with improved UCVA to $\geq$ 0.50 (20/40) was 4/11 in Group 1 and 5/15 in Group 2. The safety index (mean post-operative BCVA/ pre-operative BCVA) was similar in both groups (1.53 in Group 1 and 1.63 in Group 2). Maximum K-values were significantly decreased in both groups – by 4.3 diopters in Group 1 and by 4.0 diopters in Group 2. Refractive cylinder was also significantly decreased in both groups – by 2.46 D (P = .002) in Group 1 and by 2.39 D (P <.001) in Group 2. Spherical equivalent was reduced more in Group 1 (3.27 D, P = .002) than in Group 2 (1.24 D, P = .047).

Other advantages of placing one or two segments were noted. In the one-segment group, no eyes needed reinforcement with another segment, confirming that under-correction had not occurred. In the two-segment group, no segments needed to removal, suggesting that over-correction had not occurred. A low rate of complications was reported. Although neovascularisation was reported in three cases, it occurred before suture removal at the suture site and the condition was self-limiting. As in other reports, white lamellar deposits not extending beyond the channel were seen at follow-up (no affect on visual outcome).

Table 26. One Year Follow-up After Placement of One or Two INTAC Segments*

	One Segment			Two Segments		
	Baseline	**1-Year**	***P*- Value**	**Baseline**	**1-Year**	***P* - Value**
UCVA (decimal)	0.2 ± 0.13 (20/100)	0.38 ± 0.22 (20/50)	.001	0.06 ± 0.02 (20/400)	0.34 ± 0.17 (20/63)	<.001
BSCVA (decimal)	0.4 ± 0.21 (20/63)	0.62 ± 0.24 (20/32)	<.001	0.38 ± 0.22 (20/63)	0.62 ± 0.27 (20/32)	<.001
Cylinder (D)	−5.36 ± 2.77	−2.89 ± 1.39	.002	−4.65 ± 2.29	−2.26 ± 1.33	<.001
Spherical (D) equivalent	−5.00 ± 3.76	−1.73 ± 1.51	.002	−5.50 ± 4.26	−3.25 ± 2.55	.047
K-minimum (D)	43.12 ± 3.36	40.44 ± 2.99	.002	48.35 ± 3.77	45.41 ± 3.77	.011
K-maximum (D)	49.51 ± 4.81	44.82 ± 2.74	<.001	53.30 ± 5.23	48.03 ± 5.41	<.011

*BSCVA refers to best spectacle-corrected visual acuity; D, diopters;
K, keratometry; UCVA, uncorrected visual acuity.

The Sharma et al. study (89) also evaluated the effect of one versus two ICRS segments for ectasia with a non central or peripheral corneal cone. The study group consisted of a consecutive series of 28 patients and 37 eyes, 32 eyes with KC and 5 eyes with post-LASIK ectasia with follow-up to 3 months. In Group 1, two segments were placed in 17 patients (20 eyes) and, at a later time, a second group (11 patients and 17 eyes) matched to the first were implanted with one ICRS segment. At follow-up, improvements in UCVA and BSCVA were greater (P <.01) in the single-segment group than double-segment group. The decrease in mean cylinder was also greater in the single-segment group (1.62 D vs. 1.15 D; P = .02).

Segment Channel Creation by Femtosecond Laser or Blade Manual Technique

A second technical issue was the method of channel creation in the corneal stroma for the INTAC segments. In the longitudinal follow-up cohort studies of KC patients treated by INTACS, only one study (58) involved laser creation of the corneal tunnels for the INTAC segments. Two additional studies, (90;91) compared the results of creating tunnels for the segments by two techniques, using a manual technique with a knife or using the femtosecond laser to create the channels (neither of the studies was randomized). The study by Carrasquillo et al. (90) involved 33 eyes (25 KC and 8 post-LASIK)) from 29 patients in which the segment channel was manually created in one group in the first phase of the study and in a second group by the femtosecond laser in the second phase of the study. In both groups, consistent with other studies, improvements were reported for visual acuity, refractive error and contact lens tolerance. Differences between the study groups for these outcomes were not significant.

Intraoperative complications did not occur but major post operative complications occurred in two patients in the laser created tunnel group. A fungal infection occurred 7 months post-operatively and a bilateral corneal neovascularisation occurred at 12 months. The deep stromal neovascularisation necessitated segment removal and treatment with high dose systemic and topic corticosteroids. The fungal infection initially presented as a superficial central corneal ulcer unrelated to the segments or the incision and progressed to deeper stromal involvement during treatment for presumed herpes simplex keratitis. Subsequently, the ring segments were removed, aggressive antifungal therapy undertaken and a corneal transplant was performed. A major limitation expressed in the study was the limitation of the early laser prototype that did not allow for an adequate depth of stromal penetration for optimal placement. Despite this limitation, no cases of segment migration were reported. Laser software upgrades later became available that increased the laser depth from 400 μm to 500 μm – a better approximation of the 60% to 70% corneal stromal penetration required for optimal placement.

A study by Rabinovitz et al. included 24 consecutive KC patient (30 eyes), the first 8 of which (10 eyes) were assigned to have manually created channels and the next 16 patients (20 eyes) were assigned to have femtosecond laser created channels. (91) The channel depth setting for the laser was 400 μm as in the Carrisquilo et al. (90) study. This group was among the first to use the femtosecond laser for this indication and a nomogram of channel size had not been developed. The company had initially recommended a channel with an inner diameter of 6.6 mm and an outer diameter of 8.0 mm. The authors noted that wider channels were easier to create but had minimal clinical effect. They subsequently changed their protocol to narrower channels with an inner diameter of 6.6 mm and an outermost channel of 7.4 mm for the majority of patients.

Following implant placement, contact lens tolerability was improved in both the manual (70%; 7/10) and laser (85%; 17/20) tunnel created groups (all patients were lens intolerant prior to receiving the implants). Few complications were reported for either group. In the mechanically created channel group, one patient, despite good results in both eyes, complained of continuous fluctuations persisting up to one year of follow-up and elected to undergo a corneal transplant. In the femtosecond laser created channel group, one patient developed a gram-positive infection at the site of entry. The segments were removed and infection controlled with intensive fortified antibiotics. In two other patients, the corneal cone was too

advanced and the patients remained intolerant to rigid or soft toric contact lenses; both later underwent a successful corneal transplant procedure.

There were no significant differences (P >.05) at 6-month follow-up between the two methods of channel creation for visual acuity, refractive outcomes, or corneal topography. Other comparisons, however, were made between the methods of channel creation for the INTACS. The time to create channels with the laser was about 10 to 15 minutes (only 12 seconds to create both channels once the laser was applied), whereas the manual procedure took 25 to 30 minutes to perform. There were also significant epithelial defects noted in half of the patients on the first post-operative day, along with moderate to severe patient discomfort in the manually created tunnel group.

The effects of creating a narrow versus a wider segment channel with a femtosecond laser were compared in a retrospective review of 103 consecutive KC patients (159 eyes). (92) Patients received the same size INTAC segments bilaterally for central cones and different size segments for asymmetric cones ranging from 0.25-mm to 0.45-mm, based on preoperative spherical equivalent. The femtosecond laser channels were dissected either as wide (6.7 mm x 8.2 mm) or narrow (6.6 mm x 7.6 mm); wide channels were used in 65 patients (97 eyes) and narrow channels in 38 patients (62 eyes). Preoperatively the groups differed only by mean K-value (51.57 vs. 49.16; P < .05).

At six-month follow-up, both groups had significantly increased mean gains in UCVA of 1.92 ± 1.94 and 1.76 ± 1.90 Snellen lines in the wide and narrow channel group respectively. Differences between the groups were not significant. Refractive errors also improved in both groups and were not significantly different between groups. Mean refractive cylinder improved by more than 1diopter in the wide-channel group in 59.8% of patients and in the narrow channel group in 54.8% of patients. Mean spherical equivalent improved by more than 1 diopter in 89.6% of the wide channel group and in 95.1% of the narrow-channel group. Corneal topography by mean K-values were significantly improved in both groups [51.6 ± 5.39 D to 47.85 ± 4.50 D in the wide and 49.16 ± 4.11 D to 46.14 ± 3.19 D in the narrow group] and between-group differences (3.75 vs. 3.02 diopters) were not significant.

Complications occurred more frequently in the narrow-channel group with 68 events occurring among these patients versus 25 events in the wide channel cohort. The majority of the events were minor complications: epithelial plugs (26 eyes in narrow vs. 12 eyes in wide), yellow deposits (29 eyes in narrow vs. 10 eyes in wide), tunnel haze (4 eyes in narrow vs. 2 eyes in wide). Segment migration managed with repositioning occurred only in the narrow channels (4 eyes). The only major complication, corneal melting, occurred in one eye in the wide channel group and was treated with segment removal and antibiotic treatment.

C. Adjunct Interventions with INTACS

Intraocular Lenses

Intraocular lenses (IOL) have been reported to correct high astigmatism and myopia present in KC patients. One of these lenses, the Artisan IOL is available with a wide range of cylindrical powers up to 7.0 diopters and spherical powers between −3.0 and −23.5 diopters for myopia, and +1` and +12 for hyperopia. (92). Four case reports detailed the use of phakic intraocular lens (IOL) to correct for residual extreme myopia and irregular astigmatism (Table 27). (93-96) Three of these reports (94-96) involved IOL implantation in KC patients following INTAC placement. Patients in these reports ranged in age from 24 to 44 years. Additional improvements in refractive error, visual acuity with IOLs following INTACS were reported in all cases. In one report, residual myopia following INTAC placement was corrected from −9.00 diopters to −2.00 diopters. (94)

A separate report involved implantation of phakic intraocular lenses, without INTAC implantation, to correct astigmatism and spherical error in three patients (6 eyes) with KC. (93) Follow-up ranged from 6-months to a year and improvements in BSCVA were noted in five eyes and remained unchanged in one eye. All patients tolerated spectacle correction for the remaining refractive error. The mean preoperative spherical equivalent refraction was −13.88 D (range: −4.00 to −29.00D) and post-operatively it was −0.29 D (range +1.00 to −2.00).

Table 27. Intraocular Lens Management of Visual Defects Following INTAC Placement for Keratoconus

Author, Year Location	Lens	Report	Objectives	Outcomes
Budo C, 2005,Rotterdam, Netherlands (93)	Artisian toric phakic intraocular lens	Case series 3 p (6 eyes) 27- yr-old male 26- yr-old male 44 yr-old female	Correct astigmatism and spherical errors	Follow-up 6 month to 1 year
Colin J, 2003, Bordeaux, France (94)	Anterior chamber phakic IOL (Nuvita, Bausch & Lomb) after INTACS	Case report 42-yr-old female	Right eye mild and left eye advanced KC To correct residual myopia −8.25 D residual error	Residual myopia of −9.00 D corrected to −2.00 D
Coskunseven E, 2007,Istanbul, Turkey (95)	Posterior chamber toric implantable Collamer lens (Vision ICL; Starr Surgical) after INTACS	Case reports 32-yr-old female 36-yr-old female	For extreme myopia and irregular astigmatism; 3 eyes in 2 patients	32 year old: significant improvements in refraction. After INTAC BSCVA from 20/200 to 20/50 and after IOL from 20/50 to 20/40. 36 year-old: significant improvements in refraction. After INTACS BSCVA in right eye from 20/63 to 20/50, in left eye from 20/80 to 20/40; after IOL in right eye from 20/50 to 20/40; in left eye from 20/40 to 20/32. Results stable 8 months post IOL implant.
Kamburoglu G 2007, Ankara, Turkey (96)	Artisian toric phakic intraocular lens following INTACS	Case report 24-yr-old male	To correct residual myopic and astigmatic refractive error	Significant improvements in refraction. After INTAC, BSCVA in right eye from 0.4 to 0.6 and in the left eye from 0.2 to 0.3 and after IOL BSCVA in right eye from 0.6 to 0.7 and in the left eye from 0.3 to 0.7 (decimal)

*BSCVA refers to best spectacle-corrected visual acuity; D, diopters; IOL, intraocular lens;

Collagen Cross-Linking

Another emerging intervention for corneal thinning disorders is a technique called corneal collagen cross-linking (C3-R) which involves using photosensitive riboflavin and ultraviolet-A (UVA) light to increase the stiffness of the corneal stroma. (6) Three clinical studies have reported on the outcomes of this treatment as the primary intervention with patients having moderate to advanced KC. (6-8) So far, the studies have been preliminary reports with short term follow-up: 130 patients (241 eyes) for a minimum of 6 months follow-up (6), 22 patients (23 eyes) for 3 months follow-up, (7) and 10 patients (10 eyes) for 6 months follow-up (8).

Corneal implants used as a joint intervention with collagen cross-linking for KC was evaluated in a small clinical series. (97) An initial group of KC patients (12 patients, 13 eyes) treated with INTACS and collagen cross-linking was compared to a subsequent consecutive group of patients (9 patients, 12 eyes) receiving only INTACS. In the combined treatment group, collagen cross-linking was performed immediately after INTAC placement. In both groups a single inferior INTAC segment was placed. The collagen cross-linking procedure consisted of a 30 minute application of ultraviolet-A (UVA) light to the central cornea combined with topical application of riboflavin solution every 3 minutes. In this study, prior stripping of the endothelium was not performed. Mean follow-up was 102 days for the INTAC only group and 97 days for the jointly treated group.

No complications were reported for either group postoperatively. Significant improvements in UCVA were reported for both groups: 6.5 Snellen lines in the combined treatment group and 9.5 Snellen lines in the INTAC only group. An improvement in BSCVA of 1 Snellen line was reported for each group. Mean change was not significant between groups ($P > .05$). The impact on the corneal topography, however, was greater in the collagen cross-linking group. Keratometry flattening in the k-steep (1.94 ± 1.32 vs. 0.89 ± 2.07; $P = .03$) and K-mean (1.34 ± 1.27 vs. 0.21 ± 2.70; $P = .04$) was significantly greater in the collagen cross-linking group. The mean change in refractive cylinder (2.73 ± 1.87 D vs. 1.48 ± 1.17 D; $P = .04$) but not the refractive sphere (0.12 ± 1.72 D vs. 0.25 ± 2.12 D; $P = .66$) was also significantly greater in the collagen cross-linking group.

Collagen cross-linking was also used as an adjunct therapy in a case report involving a 33 year-old woman with keratoconic paracentral corneal cones. (82) The patient was initially treated with asymmetric placement of INTAC segments 0.35-mm superiorly and 0.25-mm inferiorly, resulting in a loss of 2 lines BSCVA. The loss of BSCVA was thought to be attributable to excessive flattening above the cone. The superior segment was explanted, the inferior segment was replaced with a heavier segment (0.35-mm), and corneal cross linking with riboflavin was performed. There were marked topographic and refractive improvements 3 months post-operatively and BSCVA returned to 20/20.

D. INTAC Comparison with Corneal Transplant Approaches

Four studies compared the effectiveness of INTACS to surgical transplantation treatments for KC. (20;98-100) One study (98) involved comparisons to lamellar keratoplasty, where only the lamellar lenticule is transplanted, and three studies (20;99;100) involved comparisons to full thickness keratoplasty. None of the reports were randomized studies and all involved small series of selected patients.

Lameller Corneal Transplantation

The lamellar transplantation study involved a mixed patient population, KC and post LASIK ectasia. (98) Same thickness INTAC segments were implanted using the femtosecond laser in 11 KC patients (5 eyes) and seven patients (8 eyes) with post LASIK ectasia. Lamellar keratoplasty was performed on 4 patients (4 eyes), all with severe central ectatic cones. In the INTAC group, visual acuity (both UCVA and

BSCVA increased) by 1 Snellen line at 6-month follow-up, but these increases were not significant (*P* >.05). The mean topographic astigmatism (5.48 D to 3.19 D; *P* = .01) and the refractive cylinder (4.67 D to 1.90 D; *P* = .003) significantly improved at 6-month follow-up but the refractive spherical equivalent (*P* = .58) remained unchanged at 6 month follow-up. In the lamellar keratoplasty group mean UCVA also increased by 1 Snellen line and the mean BSCVA increased 4 Snellen lines at 6-month follow-up. The mean topographic astigmatism (6.35 D to 5.21 D) and mean refractive cylinder (3.5 D to 1.68 D) were improved at follow-up. No complications were reported in either study group. Contact lens tolerability was improved in both groups, but more so in the INTAC group. In the INTAC group at 6 months follow-up, 12 of 13 eyes were successfully fitted with contact lens [soft toric (n=7), rigid gas permeable (n=2) and hybrid contact lenses (n=3)] whereas 2 out 4 eyes were able to wear contact lenses after transplant surgery.

Full Thickness Corneal Graft

INTACS have been employed at different stages with corneal transplant for KC - as an alternative to corneal transplant (20), as an adjunct intervention (99), and following transplant for management of recurrent KC. (100)

In the study examining INTACS as an alternative to corneal transplant (20), patients acted as their own controls. Those receiving corneal transplant for corneal ectatic disorders performed 2 to 10 years prior were offered INTAC placement for the fellow eye. Patients were divided into 2 groups, a symmetric group involving 9 patients with the same grade of KC (grade 11) and an asymmetric group of 4 patients with different grades of KC in each eye. In the asymmetric group, transplant was performed in the worse eye. Follow-up was 2 or more years in the transplant group and 10 or more months in the implant group.

In the asymmetric group, significant improvements after INTAC placement were noted in UCVA (*P* = .0088) and corneal topography (K2- value; steep meridian; *P* = .0002) whereas after transplant, UCVA (*P* <.0001), BCVA (*P* <.0001) as well as K2-value (*P* <.0001) were significantly improved. In the symmetric group, UCVA was significantly improved in both groups (*P* = .0046). Astigmatism was significantly better in the INTAC eyes than the transplant eyes (*P* = .0059).

The major difference between the two procedures was that visual acuity recovered more quickly patients in the INTAC cohort than those who had received a transplant. Complications were also higher following transplant. Three transplant patients had graft rejections, vascularisation, a significant decrease in endothelial count, and required long-term steroid therapy. One had an elevation in intraocular pressure necessitating glaucoma treatment and two others required cataract surgery.

Comparisons between the techniques were also noted for adolescent patients. A 14-year old patient in the study had two episodes of graft rejection after transplant, both of which were successfully managed. The fellow KC eye with INTAC implantation had no complications as of the 10 month follow-up. Experience with another adolescent patient was reported to be successful with INTAC versus a lamellar keratoplasty.

A second study evaluated whether or not INTAC ring placement during corneal transplant could reduce the amount of residual astigmatism remaining or created following transplant. (99) The study was a prospective clinical trial comparing visual acuity and refractive cylinder between a consecutive series of patients (Group 1, 179 eyes) undergoing corneal transplant followed by INTAC ring placement and another consecutive series (Group 2, 101 eyes) receiving transplant without INTACS. The main indications for transplant included keratoconus (18%), corneal dystrophy (29%) and scarification (12%). The INTACS device used in this study was a titanium-cobalt-chrome-molybdenum alloy with a 7.95 mm inner diameter and a 8.10 outer diameter, and a 0.15-mm thickness.

The changes (1.47 D vs. 0.93 D) in refractive cylinder (a measure of astigmatism) at one year follow-up were similar between the two groups. The pattern of improvement of BCVA was also similar over a two year observation period with the mean BCVA at 2 years being 20/33 in both groups. Immune reactions, however, were higher in the 'no ring' versus the 'ring' group. At 4 year follow-up there were two immune reactions (1.1%) in Group 1, while in Group 2 there were 6 immune reactions that were unresponsive to treatment (7%). There were a further three endothelial immune reactions medically managed in Group 1 and in Group 2 there were 7 immune reactions. In the ring group, superficial vascularisation was noted to stop growing at the ring and not continue into the transplant. Evaluation of vascularisation, however, was not the intent of the study and patients at high risk of deep vascularisation had not been enrolled in the study.

A case study by Coskunseven et al. reported on the use of INTACS to correct recurrent KC after corneal transplant performed fifteen years prior. (100) Tunnels were carefully created by femtosecond laser to take into account the graft decentration and to avoid graft-host intersection. At 10 months post-operation, BSCVA improved from 20/63 to 20/32 and a clinically significant 2.0 diopter reduction in refractive cylinder was achieved.

E. Other INTAC Applications

INTAC Management of Pellucid Marginal Corneal Degeneration

Pellucid marginal corneal degeneration (PMCD) presents with a pattern of corneal thinning in the inferior area above which the cornea protrudes, often creating a highly irregular astigmatism that cannot be corrected with glasses and rarely with contact lenses. Due to the rarity of this particular subset of corneal thinning disorders, outcomes on interventions with INTACS for PMCD were only reported in case reports (101-105) and small case series. (5;106) A summary of these reports involving 19 patients (24 eyes) is detailed in Appendix 4.

All reports involved INTAC implants, except for one in which a Ferrara ICRS implant was used. (102) The reports dealt mainly with the treatment of inferiorly located PMCD, while one case report (103) involved superior thinning. INTAC placement involved channel creation with femtosecond laser in two of the reports (5;103) and by manual technique involving a blade in the others. ICRS segments were bilaterally placed inferiorly and superiorly in all cases except for two (101) (R – R), one in which inferior corneal thinning prevented placement (101;103) and the other involving superior PMCD. (103)

Follow-up was variable among the studies, ranging from 3 months to more than 12 months. Placement was reported to be uncomplicated in all cases and no major complications were reported. Improvements in visual acuity were reported in all studies. One case report noted additional refractive correction after ICRS placement with a hybrid lens (central permeable soft and rigid hydrophilic peripheral zone). (105)

Two small case series reported more detail on outcomes following ICRS placement in PMCD patients. (5;106) In the Ertan et al. report (5) of 6 consecutive cases (9 eyes), UCVA (P = .008), BSCVA (P = .011) and keratometry (P = .008) were significantly improved over baseline at 6-month follow-up. Effects on refractive errors were greater for refractive cylinder (-2.41 ± 2.27 to -0.94 ± 1.07; P = .046) than for refractive sphere (-3.86 ± 2.91 to -2.27 ± 1.43; P = .091).

The second series involved a small group of patients (8 patients, 16 eyes) with mean age of 54.5 years with PMCD treated by INTACS. (106) Patients were followed prospectively at 3, 6 and 12 months with a mean follow-up of 2 years. The only complication reported was the development of white deposits seen

around the edges of the intrastromal channel in about half the eyes, appearing at around 3 months and remaining unchanged at last follow-up at 12 months and beyond. Both UCVA and BSCVA improved in all patients. The mean UCVA of 20/325 (range 20/1000 – 20/200) at baseline improved at 12-month follow-up to 20/50 (range 20/200 – 20/32). The mean BSCVA at baseline of 20/45 (range 20/63 – 20/25) improved to 20/30 (range 20/63 – 20/25). Refractive errors, both sphere and cylinder, also significantly improved at follow-up. Mean spherical equivalent improved from -4.75 D (range – 12.25 to -1 D) at baseline to -1.36 D (range -7.50 to +2.50 D) at 12-month follow-up.

INTAC Management of Residual Refractive Error and/or Ectasia Post LASIK

After LASIK, the cornea is structurally weakened by the laser central stromal ablation and flap creation, which in some cases can lead to corneal thinning – a major potential complication following refractive surgery. (107) The incidence of this complication is largely unknown but has been estimated to occur in between 0.04% and 0.6% of cases. (74) In a 2003 review by Binder et al., 85 published cases of post LASIK ectasia were reviewed for predictive factors for this complication. (41) Corneal thinning was reported to occur post-LASIK in eyes with less than 470 μm pre-operative central corneal thickness and in those with more than 591 μm. Enhancement or secondary corrective LASIK procedures remove even more tissue and residual stroma thicknesses reported for enhancement cases developing ectasia ranged from 200 μm to 318 μm. The authors also noted that a lack of reporting of post-operative corneal thickness limited interpretation of adequate corneal thickness. There is also no consensus on what the ideal stromal depth should be to preserve corneal mechanical stability (Chuck 2008). Corneal thinning after LASIK follows a similar deteriorating visual pattern as with keratoconus: increasing myopia and astigmatism, loss of UCVA and BSCVA, and, in some cases, corneal transplantation. Prior to INTACS, there were no treatment alternatives to corneal transplant for this condition.

Eight studies (76;84;108-113) involving 33 patients (45 eyes) reported on the use of INTACS following LASIK to manage post–LASIK corneal thinning and/or refractive errors. One of these reports involved a pathological examination of the cornea following an unsuccessful outcome after ICRS placement to manage myopic regression and central corneal ectasia after LASIK. (76) An additional report (114) compared the use of INTACS before and after performing LASIK to treat moderately high myopia.

The studies managing post-LASIK ectasia each involved less than 10 patients and follow-up was generally within one year. A study by Kymionins et al. involved two reports on a small group of patients at 1 year (110) and 5-year (84) follow-up. The 1-year follow-up study involved 7 patients (10 eyes) and the 5-year study followed 5 patients (8 eyes) from an original group of 14 patients. INTACS were generally placed 12 months or longer following LASIK and were often placed after a second or enhancement LASIK procedure. All of the studies reported improvements in visual acuity and refractive error in the short term

Quality of the Evidence

Tables 28 summarizes the quality of evidence for INTAC management of corneal thinning disorders according to the GRADE quality of evidence criteria. Evidence for the impact of the implants on corneal thinning following LASIK refractive surgery was based solely on selected case reports and was therefore inadequate to evaluate along these criteria. Evidence for the impact of INTACS on corneal topography, refractive effects, and visual acuity in keratoconus were rated at a moderate level based on several considerations. The studies were prospectively designed pre-post change studies involving similar patient selection criteria. Outcomes were evaluated by standardized outcome measurements compared to clinically and functionally defined normal ranges. The natural history of keratoconus is that of a

progressive chronic condition and as such, outcomes such as visual acuity would at best remain the same or progressively worsen without intervention. The results in corneal remodelling, refraction, and visual acuity were consistent across clinical studies and involved statistically significant and clinically relevant improvements. Results for refraction and visual acuity were also shown to be improved by removing or exchanging implants in patients where improvements were inadequate or not acceptable. The evidence for durability, vision quality of life, and patient satisfaction was infrequently reported or not yet evaluated. The follow-up in the longitudinal studies was 2 or 3 years at most and was inadequate to determine the durability of the treatment or the impact of the implants on the underlying disease. Evidence on vision quality of life and patient satisfaction was limited in the studies and therefore rated as low.

Table 28. GRADE Quality of Evidence for INTAC Management of Keratoconus

Outcome	Design	Quality	Consistency	Directness Appropriate Range of Patients	Other* Modifying Factors	Overall Quality
Visual Acuity (Critical outcome)	10 Observational pre-post longitudinal follow-up studies	Small study sizes, defined standardized measurements No serious limitations	Results were consistent across studies	No limitations Inception cohorts specified with appropriate range of patients	* Visual acuity changes were large, statistically significant and clinically relevant **+ 1**	
	Low →			Low	Moderate	Moderate
Durability (Beyond 2 years)	2 Observational pre-post longitudinal follow-up studies	Not yet evaluated past two years	Not evaluated past two years	Not evaluated past two years	-	
	Low →			Low		Low
Vision QOL, patient satisfaction	4 Observational pre-post longitudinal follow-up studies	Small study sizes, limited evaluation	Limited assessment but consistently high across studies	Inception cohorts specified with appropriate range of patients		
	Low →			Low		Low

*Ten clinical longitudinal cohort studies (608 patients, 754 eyes), *large for a rare condition*;
No control group but given disease natural history, visual acuity at best would remain the same; Outcomes were based on standardized validated measurements; Estimates of natural variability or normal ranges exist; Improvements in corneal surfacing were consistent with subsequent improvements in visual acuity and refraction; Improvements in visual acuity were large, clinically relevant and statistically significant; Estimates of improvements to functional vision were consistent across studies – average visual acuity scores were improved to within functional range, proportion that were legally blind (20/200) improving to functional range (better than 20/40) was 43% (25/58). (13)

Discussion

Intrastromal corneal ring implants have evolved through several design stages and indications for clinical use. The current model involves the use of two semicircular segments of varying sizes and has been used to treat various clinical conditions. Initially implants were introduced and evaluated for the management of myopia in normal eyes and, more recently, for corneal thinning disorders such as KC and PMCD. Corneal implants have also been increasingly reported as a rescue option for the management of corneal thinning following LASIK, an increasingly common type of refractive surgery.

The main focus of this review was to evaluate the safety, effectiveness and proposed treatment advantages of corneal implants for corneal thinning diseases such as KC. Overall, ten longitudinal studies on INTAC treatment of KC were found meeting the study criteria, involving 609 patients (744 eyes). Three studies involved more than 50 patients and one involved 255 patients. Inception cohorts were assembled in these studies and the inclusion criteria were well defined, targeting patients unable to be corrected to functional levels of visual acuity, being contact lens intolerant, having no central corneal scarring, and having adequate corneal stromal depth (particularly in the region of the implant).

Several issues related to implantation of the ring segments were addressed in various technical reports. The issues of ring segment selection, their thickness, and placement have evolved over time to fit the unique patterns of an individual's corneal thinning. Technical reports have demonstrated that optimal results could be achieved by matching implant selection to corneal topography. In cases of asymmetric thinning, a single implant could effectively restore corneal surface topography and effect improvements in refractive error and visual acuity. Reporting on the effectiveness of INTACS for PMCD, a rare subset of corneal thinning diseases with an asymmetric thinning pattern, is another example of the adaptation of placement of one rather than two segments. Because of the rarity of this condition, however, only case reports or small series were available to detail the outcomes of INTACS. However the refraction and visual acuity outcomes in these small studies paralleled the results in larger KC cohort studies.

The primary treatment objective of corneal implants is to restore corneal surface topography and increase tolerability to contact lenses thereby reducing refractive error and improving visual acuity. Improving patients' quality and functional vision is the ultimate measure of the implants utility. The effectiveness of implants for visual rehabilitation in KC patients therefore, depends on a series of outcomes. In the longitudinal follow-up studies a diverse range of outcomes were evaluated at baseline and at follow–up following placement of INTACS. The safety profile of the implant is an initial concern. High levels of technical success for implant placement were reported and complications, intra operatively or peri-operatively, were infrequently reported. Those complications that were reported were generally minor, reversible, and attributable to early surgeon experience. \

A broad range of outcome measures including corneal topography, refractive error, and visual acuity were routinely evaluated using standardized measurements at baseline and at follow-up. None of the studies, however, were randomized clinical trials. The nature of KC is that it is a chronic progressive disease (rather than a relapsing disease process) and baseline values are unlikely to improve or have sustained improvement over 1 and 2 year follow-up without intervention. With INTACS it is also not possible to have masking or blinding in studies as the devices are clearly distinguishable from other modes of treatment. The cohort studies, however, could have been strengthened by using independent observers of the outcome events.

The outcomes reported across trials were consistent and involved statistically and clinical significant improvements in corneal topography, refraction and visual acuity. The primary effects of INTACS on corneal surface remodelling were consistent with secondary improvements in improved refractive error

and visual acuity. Improvements noted at 6 months for visual acuity for UCVA, BSCVA, and refractive error were maintained at 1 and 2 year follow-up. Although one study reported follow-up information at 5 years, the results were only for a small number of patients

Improvements in visual acuity and refractive error following INTACS, however, were not noted for everyone. Although improvements were not found to vary across age groups, there were differences across disease stage. Several reports suggested that improvements in visual acuity and refractive outcomes may not be as good or predictable in more advanced stages of KC. Some studies have suggested that INTAC effects were much greater in flattening the corneal surface than in correcting astigmatism. However, these studies involved small numbers of high risk patients with advanced stages of disease and conclusions should be taken in context.

There are several limitations of the evidence base for INTACS. Foremost among these is the basic study design in all the reports involving longitudinal follow-up only in the treated group in that there were no randomized trials. The follow-up in the trials, although at prescribed intervals, often involved incomplete accounting of losses at follow-up and estimates of change were often not reported or based on group differences.

Second, although standardized outcome measures were provided, contact lens tolerance following INTAC placement (a key treatment objective) was infrequently reported. In those studies that did report it, contact lens tolerance was variably defined. For example, contact lens tolerance lasting for as long as patients' daily work requirement was a minimum requirement in some cases. The largest study reporting on this stated that the majority (89%) of patients needing contact lenses continued to be tolerant at one and two year follow-up. Contact lens fitting, however, was described in several case reports as being challenging and requiring multiple test lenses in these patients. In more recent studies, innovation in lens technology assisted these patients through unusual methods such as the piggyback system where hard lenses are placed on top of soft lenses, or novel lens designs such as hybrid lenses, which incorporate hard and soft regions.

A third general limitation was the lack of reporting of patients' satisfaction with their vision quality or their functional vision. Key outcome measures such as vision quality and the impact on patient quality life as measured by vision related QOL measures are available but were rarely used. The lack of focus on this type of information has been noted to be a limitation in ophthalmological literature in general. (115) Although the four studies reporting vision satisfaction after INTAC placement stated that the majority of patients were satisfied with their vision, some requested removal of their implants because of dissatisfaction with vision. In one study, dissatisfaction with visual symptoms, whether because of unresolved symptoms prior to INTAC or induced symptoms following INTAC, was a reason for implant removal.

Only one study reported on the impact of INTAC placement on functional vision as measured by VF-7. In that study, a gain of almost 20 points (61.6 to 80.8) in functional vision was reported at 6-month follow-up. Of interest was the high correlation of patient satisfaction at 6 months with gains in BSCVA and with gains in functional vision. Comparable results were seen in a follow-up study of 18 KC patients undergoing corneal transplant. (116) Median gains over baseline in vision health status with the VF-14 in these patients were 15 (72.9 to 87.9) at 3 months and 18 (72.9 to 90.9) at 9 months. In order to more fully evaluate the impact of INTACS, however, follow-up in studies should routinely include more detailed assessments on vision quality, functional vision and patients' vision satisfaction.

Fourth, the longitudinal cohort studies have not followed patients long enough to evaluate the impact of INTACS on the underlying disease process. Although the studies have reported improvement in vision for up to 3 years follow-up, beyond that information is limited. Additionally, only a few of these studies

examined corneal thickness in longitudinal follow-up and in one study a trend of significantly declining central corneal thickness 1 and 2-years postoperatively was reported. There is some evidence in these studies to support the claim that corneal implants do not interfere with or increase the difficultly of a subsequent corneal transplant (at least those performed in the short term after INTAC placement), but, it is uncertain for how long INTACS can delay or defer the need for such a transplant. Given that patients with KC are often young, however, delaying transplant for any number of years may still be a valuable option.

Issues and Research Directions

Laser Channel Creation

Other advances and innovations have accompanied the introduction of corneal implants. A major one has been the development of ultrafast femtosecond lasers and their increasing application in cutting procedures involved in corneal interventions such as implants, refractive surgery and transplantation. For corneal implants, the technique for channel creation in the corneal stroma for the insertion of the implant segments has been evolving. Although the majority of the longitudinal trials for implants with KC patients have involved manual corneal cutting techniques using a blade, more recent reports have involved the use of femtosecond lasers. Differences in these techniques have not yet been evaluated in randomization trials and a prospective comparative study evaluating these differences was too small to detect differences in main outcomes such as corneal topography and visual acuity, or to evaluate the risks. Nevertheless, the perceived advantages that lasers can provide, such as increased precision, shorter procedure times, and increased patient comfort and recovery, will likely support greater use of the technology in the future.

Use of Adjunct therapies With INTACS

In some KC cases, particularly those with high degrees of astigmatism, uncorrected or residual refractive errors may have limited improvement in visual acuity to below functional levels or levels that were unsatisfactory to patients. In these cases, insertion of an intraocular lens (IOLS) with adequate anterior chamber depth contributed additional improvements in refraction and visual acuity. So far, evidence for the effectiveness of IOLS has been documented only in case reports. Determining which patients might benefit from IOLS, and from which type of IOL they may benefit from, is less well defined and decided on a case by case basis.

An emerging issue is the comparability of INTACS with other additive technologies such as collagen cross-linking and their joint ability to improve outcomes and stabilize the underlying disease process. Collagen cross-linking is a new technique that uses photopolymerization, a combined action of photosensitizing substance (riboflavin) and ultraviolet type A rays (UVA), to increase the rigidity of the underlying corneal stroma. Unlike implants, cross-linking is not a reversible procedure. It has been evaluated as a first line treatment for KC and as an adjunct therapy in combination with corneal implants. Studies on these approaches are currently in the preliminary or investigational phase. Whether these techniques have an additive effect or whether they should be employed in different conditions, such as low versus high grade KC disease, is unknown. There are currently a number of clinical trials underway (http://clinicaltrials.gov) evaluating the effectiveness of collagen cross-linking compared to sham treatment for both for KC and ectasia (thinning) following refractive surgery. The effectiveness of this new technology and its relative role with corneal implants has yet to be determined.

Other Indications for INTACS

Although corneal implants were initially developed for myopia in normal eyes, the treatment of this condition has largely been overtaken by LASIK surgery. An emerging use of corneal implants has been the treatment of corneal ectasia following LASIK as they are the only treatment alternative prior to transplantation in the event of this complication. The effectiveness of INTACS for this indication has only been reported in small case studies and series. These did, however, report outcomes of improved visual acuity and refractive errors at levels comparable to those patients who've received INTACS for KC.

Ectasia following LASIK is a potentially major complication of refractive surgery and can occur in several ways. The removal of corneal tissue in the LASIK procedure may have a destabilizing effect on the corneal stroma or the surgery may have been performed in patients with undetected or subclinical forms of KC. The prevalence of this potentially serious complication is largely unknown and there have been recent efforts in the ophthalmological community to evaluate these adverse events. Ectasia risk factor scores are being developed and an on line registry (www.ectasiaregistry.com) for reporting ectasia cases following LASIK has been established to support future clinical research in this area. (107)

INTAC Management of Recurrent Keratoconus Post Corneal Transplant

Visual rehabilitation following corneal transplant in KC patients can be a slow process and residual or recurrent myopia and astigmatism can be difficult to treat. The ability of corneal implants to correct these errors would be a valuable alternative particularly to re-graft procedures, which have lower success rates and might involve similar ongoing recurrent astigmatism and refractive errors. The effectiveness of INTACS following corneal transplant was only reported in one case report involving a 15 year prior corneal transplant.

Corneal implants have not been evaluated as alternative to corneal transplant in any direct comparisons. One study indirectly compared outcomes in the same patient who was first treated with a corneal transplant in one eye and later with INTACS in the fellow eye. It was interesting that outcomes after INTAC placement were as least as good as those of transplant and, while complications were fewer and visual recovery better with INTACS. Advantages for INTACS were also found for younger adolescent patients in that graft rejections could be avoided with the devices. Comparisons in these small studies limited, however, because they were not randomized and treatment assignment was biased with the worse eye generally being treated first with corneal transplant and the second eye with INTACS and often many years later.

Conclusion

Despite the limited evidence base for INTAC treatment consisting solely of uncontrolled longitudinal follow-up studies, INTACS appear to be a valuable technology to improve vision in patients with corneal thinning diseases such as KC (Table 29). For patients unable to achieve functional vision, INTACS provides a useful alternative to corneal transplant. The treatment is an outpatient based procedure, is associated with high technical success rates, and minimal risk. Both eyes can be treated at once and the treatment is adjustable and reversible. In the event that the implants require removal or exchange, they can be they can be removed without limiting subsequent interventions such as corneal transplant. In short term follow-up, statistically significant and clinically relevant improvements in corneal topography, refraction and visual acuity were consistently reported across studies.

Although the main indication for corneal implants is an alternative to corneal transplant for patients with corneal disease, the treatment can also be used for patients who acquire corneal thinning after undergoing refractive surgery such as LASIK for myopia correction. Implants have also been used to correct residual refraction and astigmatism re-occurring after corneal transplant. Similar improvements were reported for acquired corneal thinning occurring in patients after having LASIK refractive surgery, although the information on effectiveness for these indications was limited to case reports.

Better reporting on vision quality, functional vision and patients' vision satisfaction, however, would improve evaluation of the value or impact of these devices on patients. Information on the durability of the implants' treatment effects and their affects on the underlying chronic disease process are limited. This information is becoming more important as alternative treatment strategies such as collagen cross-linking aimed at strengthening the underlying corneal tissue are emerging, which might be more effective or may increase the effectiveness of the implants, either in the early or the advanced stages of the disease.

Table 29. Summary of Clinical Utility of Intrastromal Corneal Ring Implants for Keratoconus

Attribute	Summary
Patient acceptability	Limited information on patient acceptability, reactivity or preferences
Technical difficulty	Performed in outpatient setting with high technical placement rates, well within ability of corneal surgeons (refractive)
Safety	Low risk, minor complications often attributable to early experience
Corneal topography, refraction and visual acuity	Statistically significant and clinically relevant improvements in corneal topography, visual acuity, both UCVA and BSCVA, and refractive errors - few patients lost BSCVA
Reversibility, adjustability and stability	Initial results were adjustable, reversible and stable within 2 year follow-up period – did not limit or increase difficulty of subsequent corneal transplants
Durability	Significant improvements maintained up to 2 or 3 years, limited information beyond that follow-up
Patient satisfaction, vision quality of life	Vision quality, vision-related quality of life measures and patient satisfaction are rarely measured, consistent with ophthalmological and general medical literature reporting practices
Competitive performance with other technologies	Limited information on comparative effectiveness of INTAC with other treatments - collagen cross-linking, corneal transplants
Impact on underlying corneal thinning disease process	No evidence supporting effects on underlying disease process, evidence to suggest that corneal thinning continues

BSCVA refers to best spectacle-corrected visual acuity; UCVA, uncorrected visual acuity.

Existing Guidelines

There are no professional guidelines on the use of ICRS implant devices.

Ontario Health System Impact Analysis

Considerations and/or Implications

At present there are approximately 70 ophthalmologists in Canada who've received training with corneal implants; 30 of these practice in Ontario. Industry currently sponsors the training, proctoring and support for the procedure. The cost of the implants ranges from $950 to $1200 (CAD) and costs for instrumentation range from $20,000 to $30,000 (CAD) (a one time capital expenditure) (Personal Communication). There is no physician services fee code for corneal implants in Ontario but assuming that they are no higher than those for a corneal transplant, the estimated surgical costs would be $914.32 (CAD) [(surgeon fee ($740.00), assistant fee ($68.40), anesthesia ($105.92)] (Ontario Schedule of Benefits). An estimated average cost per patient for treatment is $1,964 (CAD) (range $1,814 to $ 2,114) per eye. Pre- and post-operative costs involving consults and medications (antibiotics and steroids) have not been included in the average costing. There have also been no out of province treatment requests. In Ontario the treatment is currently being offered in private clinics and increasing numbers of ophthalmologists are being certified in the technique by the manufacturer. Ultrafast lasers like the femtosecond laser, which improve corneal cutting procedures, are also mainly available in private eye clinics.

KC is a rare disease and not all of these patients would be eligible candidates for treatment with corneal implants. Based on published population rates of KC occurrence (17), there is an estimated prevalent population of approximately 6,540 patients and an incident population of 240 newly diagnosed patients per year in Ontario. Given the small numbers of potential cases, the treatment would not be expected to have much impact on the province's health care system. Assuming the most conservative scenario (i.e., all are patients are eligible and all receive bilateral implants), the cost of managing the incident population could range from $923 thousand to $1.1 million (CAD). This estimate would vary based on a variety of criteria including eligibility, unilateral or bilateral interventions, re-interventions, capacity, and uptake. At start up, clinical prioritization of the treatment may be needed to manage the existing prevalent population.

For patients with corneal thinning disorders and eligible for corneal transplants, access to corneal transplants is an issue. KC is one of the leading indications for corneal transplantation and represents 12% of corneal transplants performed annually in Ontario. The average wait time from diagnosis to transplantation is 44 weeks. The 28 corneal transplant surgeons in Ontario currently have average waiting lists of approximately 50 patients. Unlike the other provinces where long wait lists are being caused by a lack of donor tissue, in Ontario the most common reason for extended wait lists is limited operating room time.

Offering corneal implants in Ontario would provide patients, particularly those affected by KC in early adulthood, with a treatment alternative that could potentially defer or delay the need for a corneal transplant. The procedure is a minimally invasive technique and can be performed in outpatient clinics. There are few risks with the treatment and the procedure rarely has a negative impact on vision. Even in such cases where it arises, it can be reversed by removing and/or exchanging the implants. Further, when implant placement improves vision to a less than functional level, additional gains can be achieved by supplementing treatment with intraocular lenses.

Glossary

Astigmatism: Optical defect in which the refractive power of the eye is not uniform in all directions (meridians). Light rays entering the eye are bent unequally by the different meridians, which prevents the formation of a sharp image focus on the retina. This results in imprecise near and far vision and an inability to see contrasts between oblique, vertical, and horizontal lines

Corneal transplantation: also known as corneal grafting or penetrating keratoplasty, corneal transplantation is a surgical procedure in which a diseased or damaged cornea is replaced by donor corneal tissue that has been removed from a recently deceased individual having no known ocular diseases.

Diopter: a unit of measure of the refractive power of a lens or an eye. The dioptic power is the inverse of the focal length of the lens or of the eyes optical system in meters

Hyperopia: also known as farsightedness, it is a focusing defect in which the eye is underpowered. Light rays coming from a distant object strike the retina before coming into sharp focus, blurring vision.

Intrastromal corneal ring segments: are two clear curved plastic pieces that are surgically inserted into the perimeter of the cornea to alter its shape and correct certain types of nearsightedness caused by keratoconus.

Intraocular lens: an implanted lens used to change the optical power of the eye, Usually used as a replacement for an existing crystalline lens because it has clouded over by a cataract or following refractive surgery.

Keratoconus: a progressive thinning of the cornea resulting in a outward bulging of the eye and the formation of a rounded cone; produces moderate to severe corneal distortion and an increase in myopia; can cause corneal scarring, requiring corneal transplantation to restore vision.

LASIK: a surgical procedure where the cornea is opened to form a type of “cap” using an automated instrument (automatic keratome). The corneal tissue is exposed to an excimer laser altering the shape of the cornea to correct the refractive error. When the cap is positioned back onto its original location on top of the eye, the cornea and the cap adhere to each other eliminating the need for sutures.

Legal blindness: best-corrected visual acuity of 20/200 or less, or that the visual field is restricted to 20 degrees or less.

Myopia: also known as nearsightedness, it is a focusing defect in which the eye is overpowered. Light rays coming from a distant object are brought into focus in front of the retina.

Ontario

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Photorefractive keratectomy: a surgical procedure in which an excimer laser is used to remove corneal tissue to correct myopia, hyperopia or astigmatism.

Radical keratectomy: a surgical procedure to correct myopia by flattening the curvature of the cornea using a series of 4 to 16 equally spaced radial cuts in the peripheral cornea.

Refractive error: optical defect in an accommodating eye; parallel light rays are not brought to a sharp focus precisely on the retina, producing a blurred retinal image.

Refraction: Test to determine an eye's refractive error and the best corrective lenses to be prescribed. Series of lenses in graded powers are presented to determine which provides the sharpest, clearest vision.

Visual acuity: assessment of the eye's ability to distinguish object details and shape, using the smallest identifiable object that can be seen at a specified distance (usually 20 feet or 16 inches).

Appendices

Appendix 1: Search Strategy

INTACS – Final Search Strategy

Search date: March 6, 2009
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, OVID Cochrane Library, Centre for Reviews and Dissemination/International Agency for Health Technology Assessment

Database: Ovid MEDLINE(R) <1996 to February Week 4 2009>
Search Strategy:
---
1 exp Corneal Diseases/ (11803)
2 keratoconus.mp. or exp Keratoconus/ (1386)
3 (cornea$ adj3 ectasia$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (167)
4 astigmatism.mp. or exp Astigmatism/ (3490)
5 ((cone or conical) adj3 (ectasia or cornea)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (7)
6 keratoectasia.mp. (2)
7 keratectasia.mp. (111)
8 or/1-7 (14803)
9 intacs.mp. (115)
10 Ferrara.mp. (154)
11 keravision.mp. (22)
12 ((intra?cornea$ or intra?stromal or cornea$) adj3 (implant$ or insert$ or ring$ or disc$ or disk$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (750)
13 or/9-12 (939)
14 8 and 13 (384)
15 exp Cornea/ or exp Corneal Diseases/ (23638)
16 "Prostheses & Implants".mp. [mp=title, original title, abstract, name of substance word, subject heading word] (7)
17 15 and 16 (0)
18 14 or 17 (384)
19 limit 18 to (english language and humans and yr="2000 - 2009") (261)

Database: EMBASE <1980 to 2009 Week 10>
Search Strategy:
---
1 exp Cornea Disease/ (28673)
2 keratoconus.mp. or exp KERATOCONUS/ (2349)
3 (cornea$ adj3 ectasia$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (218)
4 astigmatism.mp. or exp Astigmatism/ (5570)

5 ((cone or conical) adj3 (ectasia or cornea)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (12)
6 keratoectasia.mp. (4)
7 keratectasia.mp. (124)
8 or/1-7 (33189)
9 (Ferrara or intacs or keravision).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (435)
10 ((intra?cornea$ or intra?stromal or cornea$) adj3 (implant$ or insert$ or ring$ or disc$ or disk$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (1450)
11 9 or 10 (1777)
12 8 and 11 (731)
13 limit 12 to (human and english language and yr="2000 - 2009") (352)

Appendix 2: Outcome Reporting for INTAC Management of Keratoconus

Author Year, Country	Outcome Measures	Study Details		
Alio J, 2006 Spain (51)	Evaluate long term results and stability of INTACS	F-Up at 6, 12, 24, 36 (all eyes) and 48 months (6 e)	Study loss: Incomplete follow-up (n = 6 eyes), Extrusion in first year (n = 7 eyes) Report on 11 patients and 13 eyes	Krumeich system keratoconus ; Grade 1 n= 4 eyes, Grade 11 n = 6 eyes, Grade 111 n = 3 eyes Advanced keratoconus K ≥ 55 D
	BSCVA	Mean BSCVA increased significantly (P ≤ .001) from pre-op 0.46 (20/50) to the 6 month period 0.66 (20/30). No significant difference between BSCVA from pre-op to 3-yr F-Up (0.62 ± 0.18)		
	Inferior-superior (I-S) asymmetry	Mean I-S asymmetry significantly (P ≤ .02) decreased from -7.09 D pre-op to -4.27 D at 6 months post.		
	Keratometric values (K-V)	Mean average K-value significantly (P ≤ .001) decreased by 3.13 D at 6 months F-UP. After the 1-yr F-Up the mean-K decrease was 2.16 D at 2-yr F-Up and 1.46 at 3-yr F-Up.		
	Refractive sphere (D)	Stable refraction – Sphere (D) at pre-op (-2.84 ± 3.78), 1-yr (-3.03 ± 4.60) 2-yr (-2.94 ± 4.71) and 3- yr -3.19 ± 4.96)		
	Refractive cylinder (D)	Stable refraction – Cylinder (D) at pre-op (-5.15 ± 3.19), 1-yr (-3.48 ± 1.02) 2-yr (-3.13 ± 1.01) and 3- yr (-3.36 ± 1.26)		
	Spherical equivalent (D)	Stable refraction – spherical equivalent (D) at pre-op (-5.40 ± 4.11), 1-yr (-4.46± 5.10) 2-yr (-4.69 ± 5.32) and 3-yr (-4.86 ± 5.09)		
	Extrusions	Extrusion occurred in 7 eyes, 3 of them with advanced keratoconus, in the first year F-Up, believed to be due to surgical learning curve.		
	Clinical complications	Channel deposits were seen in 4 eyes (3 eyes with 2 segments and 1 eye with 1 segment). They did not regress over the F-Up period but did not interfere with visual axis or visual outcome. Superficial vascularisation in at incision site and peripheral part of tunnel in 2 eyes, regressed in year 2 F-Up		
	Contact lens tolerance	All patients were contact lens tolerant post surgery		

Boxer Wachler B 2003, United States (54)	Evaluate safety and efficacy of INTAC placement	Mean F-Up = 9 months range 1 mo to 20 months.	50 patients (41 M, 9 F) and 74 eyes 26 patients had single eye treatment, 24 subjects had both eyes treated	Severity of keratoconus based on inferior-superior (I-S) value 23% (17/74) had anterior central or paracentral corneal scarring ranging in location, size and elevation – all received 25/35-mm segment combination. Non standard myopic technique – thicker ring was placed inferior and thinner segment placed superiorally to preferentially flatten the inferior cornea. Ring segment thickness based on spherical equivalent (SE) – SE <-3.00 D had a 0.25-mm superior segment and a 0.30-mm inferior and for SE > -3.00 D had a 0.25-mm superior segment and a 0.35-mm inferior.
	UCVA	Mean uncorrected LogMAR visual acuity increased preop from 1.05 (20/200 - 2) SD ± 0.48 at F-Up to 0.61 (20/80 -) (SD ±0.52) corresponds to 4 lines of improvement. Gain in UCVA: 72% (53/74) ≥ 2 lines; 19% (14/74) no change (± 1 line), 9% (7/74) lost ≥ 2 lines.		
	BSCVA	Mean best-corrected LogMAR visual acuity increased preop from 0.41 (20/50 - 1) SD ± 0.48 to 0.24 (20/32 – 2) SD ± 0.31 corresponds to 2 lines of improvement Gain in BSCVA: 45% (33/74) ≥ 2 lines; 51% (38/74) no change (± 1 line), 4% (3/74) lost ≥ 2 lines. Many eyes that had no gain in BSCVA (n = 40) did gain lines of UCVA – 60% (24/40) ≥ 2 lines; 28% (11/40) no change (± 1 line), 13% (5/40) lost ≥ 2 lines. Changes in UCVA and BSCVA was compared across 3 groups of refractive cylinder 0 – 3 D, 3 – 6 D and >6 D. Increases in both BSCVA and UCVA occurred in all 3 refractive cylinder groups at F-Up but were only significantly increased for the 0-3 and 3-6 D refractive cylinder groups but not for the >6 D.		
	Spherical Equivalent	Mean spherical equivalent before surgery was reduced from -3.89 D (SD ± 5.16) to mean -1.46 D (± 4.11)		
	Inferior-superior (I-S) asymmetry	For 65 eyes, mean I-S value significantly decreased (P = .01) from 25.62 (SD ± 25.10) pre-op to 6.60 (SD ± 3.55) at F-Up.		
	Refractive adjustments	Additional refraction adjustment performed on 2 eyes of 1 patient. Patient had become hyperopic as a result of INTAC placement (0.25/0.30), treated by explanting the superior segments bilaterally.		
	Complications	During surgery, one eye had a superficial channel dissection with anterior Bowman's layer perforation. Treated by re-deepening the entry incision and successfully rechannelling followed by segment insertion. Two eyes had transient inflammatory reaction to epithelium incision resolving in first week. One eye, with an I-S value of 100 suggestive of advanced keratoconus, had segment migration and externalization in one eye on first post-op day. The segment could not be stabilized and was explanted, subsequently the other segment and segments in fellow eye were explanted because of chronic foreign body sensation. Segments were removed from one other patient because of foreign body sensation. Two patients complained of halos around lights at nights, both had pupils larger than 7.5 mm. Neither requested explantation and 1 patient was using brimonidine for night vision.		

Colin J, 2000 Brest, France (56)	Evaluate ability INTACS to correct keratoconus	Mean F-Up = 10.6 mos (2 yrs,1 eye; 1 year, 5 eyes; 3	10 p (10 e)	3 and 6-mo F-Up 10 eyes
	Manifest refraction	SE, sphere and cylinder all increased at 1 month and continued to decrease at 3 and 6 mo follow-up. SE; pre-op = -5.13 ± 4.77 6 mo = -3.01 ± 4.32 Sphere; pre-op = -3.50 ± 4.54 6 mo = -1.75 ± 4.41 Cylinder; pre-op = -3.31 ± 1.59 6 mo = -1.81 ± 3.34		
	UCVA *decimal scale*	UCVA improved at 1 month and progressively increased at 3 and 6 months: pre-op = 0.12 ± 0.08, 1 mo = 0.28 ± 0.10, 3 mo = 0.28 ± 0.10, 6 mo = 0.30 ± 0.19		
	BSCVA *decimal scale*	BSCVA also improved at 1 month and increased at 3 and 6 months: pre-op = 0.38 ± 0.11, 1 mo = 0.42 ± 0.25, 3 mo = 0.58 ± 0.23, 6 mo = 0.63 ± 0.29		
	Keratometry (D)	Mean k decreased over 1 to 6 month F-Up : pre-op = 51.73 ± 4.46, I mo = 46.64 ± 3.46, 3 mo = 46.94 ± 3.81, 6 mo = 46.88 ± 5.11		
	Complication	No intraoperative complications occurred. At 3 months all eyes experienced mild to moderated intralamellar channel deposits at superior edges of inferior segments		
	Explant	In 1 eye segments explanted after 2 mos because of superficial implantation. Segments were easily removed and refraction, visual acuity and corneal typography returned to pre-op status.		
Colin J, 2007 Brest, France (52)	Evaluate long term safety and efficacy of INTACS correction or myopia and irregular astigmatism	1-yr and 2-yr F-Up Safety, VA, efficacy in treating ectasia, restore contact lens tolerance	Single site, single surgeon 82 p (100 e) (53 M, 29 F) 68 patients and 82 eyes (54 unilateral and 14 bilateral) evaluated at all time points. 14 eyes lost to F-Up, 5 at 1-yr and 9 at the 2-yr F-Up.	Conscious sedation (45 eyes) or general anesthesia (55 eyes) was performed. Contact lens intolerance defined as comfortable working time less than required for working purposes (usually <8 hours). Keratoconus defined by Amsler-Krumeich grades and most were moderate or severe: Grade 1 (n=16), Grade 11 (n = 26) and Grade 111 (n = 40). Majority of the cone type was asymmetrical (n = 66) versus global (n= 7) or central (n = 9). No central opacity or scarring on slit lamp exam Nomogram segment selection based on pre-op spherical equivalent (SE); SE <3.00 D segments of 0.40-mm thickness and SE >3.00 D segments 0.45-mm thickness
	Technical success	Implantations were uneventful in all 100 eyes.		

	BSCVA	Proportion eyes with a BSCVA of ≥ 0.5(20/40) increased from 22% pre-op to 50% at the 1 and 2 yr-Fup (P <.001) At 1-yr F-Up: gain of 1 to ≥ 5 lines (61%, 50/82), no change (27%, 22/82), loss of 1-4 lines (12%; 10/82)
	UCVA	Proportion eyes with a UCVA of ≥ 0.2(20/100) increased from 11% pre-op to 35% and 32% at 1-yr and 2-yr F-Up At 1-yr F-Up: gain of 1 to ≥ 5 lines (61%, 50/82), no change (27%, 22/82), loss of 1 - 4 lines (12%; 10/82)
	Stability	BSCVA remained stable (within 2 lines) between 1 and 2-yr follow-up in 90% of eyes. Patients with low BSCVA had sufficient overall visual acuity for daily activities due to better visual acuity in the fellow eye. At 2-yr F-Up 89% of the eyes were within 2 lines of UCVA at 1-yr
	Corneal thickness (μm)	Pachymetry showed an increasing central corneal thinning over baseline (478 ± 55) at the 1-yr (434 ± 56) P = .002and 2-yr (421 ± 54) F-Up P = .0008 . Unsure if related to stretching by the segments of the disease process.
	Corneal curvature Keratometry (D)	Mean keratometry (K) values were significantly lower at 1-yr (45.4 5.3) and 2-yr (46.8 ± 4.9) F-Up than at baseline (50.1 ± 5.6) (P <.001) The decrease in K1 (at the steepest meridian) was greater than at K2 (5.1 D vs. 2.4D) and was associated with a significant improvement in refractive astigmatism.
	Refractive cylinder (D)	Refractive cylinder significantly decreased from -4.62 ± 2.80 at baseline to -3.87 ± 2.50 D at 1-yr F-Up (P = .002) and -3.31± 1.83 at 2- yr F-Up (P <.001)
	Refractive sphere (D)	Refractive sphere also significantly decreased from baseline to the 1-yr and 2-yr F-Up points.
	Spherical equivalent (D)	SE significantly (P <.002) decreased from baseline (-6.93 ± 3.91) at the 1-yr (-4.01 ± 3.16) F-Up and 2-yr (-3.80 ± 2.73) F-Up
	Contact lens tolerance	44 eyes required a contact lens following implants: 21 eyes for SE worse than -5.0 D 23 eyes for SE better than -5.0 D due to residual myopia and astigmatism or astigmatism. 9 eyes did not require a correction Remaining eyes needed correction with spectacles. Of the contact fitted cases, 89% (39/44) at the 1-yr and 84% (37/44) at the 2-yr F-Up were contact tolerant. All intolerant had required lenses for SE better than -5.0 D and were prescribed spectacles.
	Complications / Observations Slit-lamp exams	All eyes had well centered INTACs with no migration or displacement. No evidence of vascularisation at the incision site; No cases of early or late post-op infection. Non-progressive epithelial cysts were present in 21 eyes at both F-Up exams. White yellow deposits were in the segment tunnels in 17 eyes at 1- yr and 22 eyes at 2-yr F-Up. The lamellar channel deposits had no effect on visual level or quality.
	Explants	Segments were removed from 4 eyes for: extrusion at incision site (n=2 eyes, at 5 mos and >8 mos) and poor visual outcome (n=2 eyes, between 1-yr and 2-yr). In all eyes segments were easily removed without post op sequelae and a penetrating keratoplasty was subsequently performed.

Colin J, 2006 Brest, France (33)	Safety and efficacy of INTACs in keratoconic eyes to alter corneal shape, refractive power and stabilize progression of corneal ectasia	F-UP 1 day, 7 day and 1, 3, 6 and 12 months 12-mo F-Up	European study group – 5 surgeons 59 e enrolled – report on 34 eyes at 6 mo F-Up	Patients had moderate to severe keratoconus and had clear corneas and contact lens intolerant Nomogram: 5 INTAC segment thicknesses available (0.25,0.30, 0.35, 0.40, 0.45 and selected based on both type of keratoconus cone (asymmetric, global, central) and pre-op SE <3.00 D or >3.00 D.
	Technical success	Successfully implanted into 58 / 59 eyes (1 inadequate documentation) and 1 case lost to follow-up after 1 month exam		
	Safety – (maintenance BCVA)	No cases of ocular infection, segment migration or extrusion, stromal thinning over the insert at any post op period were observed. Intrastromal deposits on or near inserts and haze in the incision area were commonly observed		
	BCVA Safety – (maintenance BCVA)	Pre operatively, 53% (30/57) eyes had BCVA of 20/40 or better increasing to 71% and 74% at 3 and 6 mo-Fup. The increase in BCVA between 1 and 6 mo F-Up was statistically significant (P ≤ .033) Of the 34 eyes at 6 mo - 62% (21/34) had a gain 2 to 8 lines, 32% (11/34) had no change (gains ± 1 line of acuity), 6% (2 eyes) had a loss of 2 lines.		
	UCVA	Pre operatively, 4% (2/53) eyes had UCVA of 20/40 or better increasing to 17% (5/29) and 24% (8/34) at 3 and 6 mo-Fup; the increase in UCVA between 1 and 6 mo F-Up was statistically significant (P <.0001). Of the 34 eyes at 6 mo: 80% had a gain ≥ 2 lines, 20% had no change, none had a loss of 2 lines.		
	Stability VA	Stability defined as the number of eyes within a BCVA within 2 lines (0.2 logMAR) of the previous exam. Percentage of eyes with a stable BCVA exceeded 84% for all intervals after 1 month. - 1 month to 3 month (89%; 24/27) 3 month to 6 month (84%; 16/19), 6 month to 12 month (89%; 8/9) Stability also defined as the number of eyes within a UCVA within 2 lines (0.2 logMAR) of the previous exam. Percentage of eyes with a stable UCVA exceeded 78% for all intervals from 1 month to 6 months. 1 mo to 3 mo 78%; 21/27), 3 mo to 6 mo (78%; 14/18), 6 mo to 12 mo (33%; 3/9)		
	Spherical equivalent (D)	Mean refraction spherical equivalent change from baseline at 1, 3 and 6 month follow-up was significantly (P <.001) improved at 6 month (3.1 ± 2.5 D) from preoperative (-4.6 ± 3.5 D)		
	Refractive cylinder (D)	Absolute value of cylinder was measure of the change of astigmatism. Mean refractive cylinder change was improved at each follow-up and change at 3 (-2.00 D) and 6 (-1.52 D) months were statistically significant (P <.001)		
	Corneal thickness	Central pachymetry measurements showed no statistically significant (P >.085) changes occurring over the 1-yr follow-up.		
	Keratometry (D)	Keratometry readings showed the corneal curvature was significantly (P ≤ .002) reduced from baseline (49.7 ± 4.9) at the 3 (46.5 ± 4.3) and 6 (46.0 ± 3.5) month F-Up. Remodelling of corneal curvature continued with changes up till 1 year.		

	Observations and Complications	No intraoperative complications were noted			
	Visual symptoms	Preoperatively patients reported visual symptoms – main symptoms photophobia (n = 7), fluctuating vision (n = 7), discomfort (n = 4), halos (n = 3). At 3 months main visual symptoms were photophobia (n = 6) and glare (n = 5). Visual symptoms decreased from 3 to 6 month F-Up. At 6-mo F-Up 9 patients reported moderate to severe visual symptoms: discomfort (n = 1), itching (n = 1), burning (n = 1), photophobia (n = 1), difficulty with night vision (n = 1), glare (n = 3) and fluctuating vision (n = 1)			
	Patient satisfaction	Dissatisfaction with visual symptoms was the main reason for insert removal from 7 eyes (12%). Patient satisfaction with vision quality significantly improved from baseline at 6 month F-Up. Pre-Op: poor(69%, 27/39), fair (21%, 8/39), good (10%, 4/39) excellent (0/39) At 6 month F-Up: poor (24%, 5/21), fair (29%, 6/21), good (38%, 8/21) excellent (10%, 2/21)			
Ertan A, 2006 Turkey (58)	Femtolaser created channels for INTACS	1-yr F- Up	69 p (118 e) 39 M, 30 F	Consecutive cases Single site	Moderate to severe keratoconus with clear corneas. Two segment thicknesses were used, 0.25-mm placed superiorly to flatten cornea and decrease baseline asymmetric astigmatism and a 0.45-mm placed inferiorly to lift the conus.
	UCVA (Snellen line)	Mean UCVA significantly improved from baseline (1.32 ± 1.53) to the 1-yr (3.29 ± 2.64) F-Up (P <.05)			
	BSCVA (Snellen line)	Mean BCVA significantly improved from baseline (4.20 ± 2.43) to the 1-yr (6.02 ± 2.70) F-Up (P <.05)			
	Sphere (D)	Mean sphere significantly improved from baseline (-5.70 ± 4.32) to the 1-yr (-2.73 ± 2.91) F-Up (P <.05)			
	Cylinder (D)	Mean cylinder significantly improved from baseline (-3.90 ± 2.11) to the 1-yr (-2.20 ± 1.50) F-Up (P <.05)			
	Spherical equivalent (D)	Mean UCVA significantly improved from baseline (-7.57 ± 4.51) to the 1-yr -3.72 ± 2.78 F-Up (P <.05) Improvements of 2.00 diopters or more were noted in manifest cylinder and spherical correction in 42 eyes (36%) and 72 eyes (61%).			
	Corneal curvature Keratometry (D)	Mean keratometry significantly decreased from baseline (51.56 ± 5.22) to the 1-yr (47.66 ± 4.3) Up P <.05)			
	Complications	Epithelial plugs occurred at the incision site in 15% eyes. Granulomatosis particles were observed around segments in 8.5% eyes during the first 6 months post-op resolving with steroid drops.			

Ertan A, 2008 Turkey (55)	INTAC implanted using femtosecond laser for management of various stages keratoconus	Mean F-Up 10.30 mos Minimum 4 mo F-Up with range 4 to 30 mos. Post op follow-up not uniformly specified.	255 p (306 e) 145 M, 110 F Mean age = 27.03 (SD 8.10 yrs) (range 11 to 56 years)	Consecutive cases Single site	Amsler-Krumeich classification: stage 11 having mean K value 48.00 D - 53.00 D (n= 155 e); stage 111 with mean K value from 53.00 D to 55.00 D (n = 83 eyes); Stage 1V with mean K values >55.00 D (n = 68 eyes). No patient had a central cornea scar. Two segment thicknesses were used, 0.25-mm placed superiorly to flatten cornea and decrease baseline asymmetric astigmatism and a 0.45-mm placed inferiorly to lift the conus
	UCVA (logMAR)	Significantly (P <.05) improved overall (1.10 ±0.54 pre-op to 0.64 ± 0.41 post-op) and significantly in each group in each group Loss of >2 Snellen lines (2.9%) Gain >4 lines Snellen lines (15.0%)			
	BCVA (logMAR)	Significantly (P <.05) improved overall (0.48 ±0.34 pre-op to 0.28 ± 0.23 post-op) and there was no significant difference between the 3 groups Loss of >2 Snellen lines (3.7%) Gain >4 lines Snellen lines (10.70%). Loss of visual acuity thought to be attributable to the induced irregular astigmatism			
	Refractive sphere (D)	Significantly (P <.05) improved overall (-6.04 ± 4.76 pre-op to -3.09 ± 4.03 post-op) and there was no significant difference between the 3 groups. Improved >2D (57.1%), Gain 2D (28.7%), no change (3.4%), loss of 2D (6.9%), worse >2D (3.9%)			
	Refractive cylinder (D)	Did not significantly improve overall (-4.11 ± 2.47 pre-op to -3.82 ± 2.50) post-op and only significantly improved in the stage 11 group (-4.70 ± 1.90 pre-op to -3.10 ± 1.89 post-op). Lack of response in higher degree keratoconus presumed attributable to higher astigmatism. Improved >2D (33.1%), Gain 2D (37.7%), no change (7.8%), loss of 2D (15.7%), worse >2D (5.7%)			
	Spherical equivalent (D)	Significantly (P <.05) improved overall (-7.81 ± 4.85 pre-op to -4.72 ± 11.96 post-op) and there was no significant difference between the 3 groups.			
	Keratometry	Mean K values did not significantly (P >0.5) change from preoperative (50.70 ± 5.45) to post-op (47.91 ± 5.28)			
	Corneal thickness (µm)	Mean pachymetry values for central corneal thickness did not change from baseline (450.05 ± 54.59) to post operative minimum 4 mo F-Up (454.06 ± 54.46).			
	Complications	No surgical complications were noted. INTAC segment extrusion occurred in 3/306 eyes within 6 months of implantation (all in the stage IV ages 18 yrs, 20 yrs and 23 yrs)			

Ertan A 2008 Turkey (59)	Effect of age on INTAC implanted using femtosecond laser for management of keratoconus	1-yr F-Up.	62 p (109 e) 33 M, 29 F	Consecutive cases Single site	All had clear corneas and were contact lens intolerant 3 patient age groups: : younger (13-19 y) n = 20 middle (20-34 y) n = 75 older (35-56 y) n = 14 Two segment thicknesses were used, 0.25-mm placed superiorly to flatten cornea and decrease baseline asymmetric astigmatism and a 0.45-mm placed inferiorly to lift the conus
	UCVA (logMAR)	There were no differences in mean BCVA change between the 3 age groups younger middle older pre op 1.30 ± 0.96 1.66 ± 0.91 1.37 ± 0.81 post-op 0.66 ± 0.63 0.80 ± 0.65 0.65 ± 0.65 Change -0.63 ± 0.84 -0.85 ± 0.71 -0.74 ± 0.72 younger middle older pre-operative 20/40 or worse 20 (100%) 75 (100%) 14 (93%) 20/40 or better 7 (35%) 21 (28%) 1 (7%) 20/20 or better 0 0 0 Post-operative 20/40 or worse 14 (70 %) 61 (81%) 12 (86 %) 20/40 or better 6 (30 %) 10 (13 %) 1 (7 %) 20/20 or better 0 4 (5 %) 1(7 %)				
	BCVA (logMAR)	Differences in mean BCVA change between the 3 age groups were not statistically significant. younger middle older pre op 0.54 ± 0.58 0.48 ± 0.30 0.34 ± 0.28 post-op 0.33 ± 0.45 0.27 ± 0.24 0.22 ± 0.31 Change -0.21 ± 0.33 -0.20 ± 0.24 -0.12 ± 0.30 younger middle older pre-operative 20/40 or worse 12 (60 %) 54 (72 %) 9 (60 %) 20/40 or better 7 (35 %) 21 (28 %) 5 (30 %) 20/20 or better 1 (5 %) 0 1 (7 %) Post-operative 20/40 or worse 10 (50 %) 37 (49 %) 4 (29 %) 20/40 or better 8 (40 %) 25 (33 %) 6 (43 %) 20/20 or better 2 (10 %) 13 (17 %) 4 (29 %)				

	Refractive sphere (D)	Differences in mean manifest sphere change between the 3 age groups were not statistically significant younger middle older pre op -5.37 ± 4.35 -6.08 ± 4.43 -4.13 ± 3.61 post-op -2.25 ± 2.74 -2.98 ± 3.09 -1.98 ± 2.25 Change 3.15 ± 2.45 3.14 ± 1.90 2.32 ± 2.09 younger middle older Improved by >1.00 D 17 (85 %) 66 (88 %) 9 (64 %) Within 1.00 D of pre-op 3 (15 %) 8 (11 %) 4 (29 %) Worse by >1.00 D 0 1 (1%) 1 (7 %)
	Refractive cylinder (D)	Differences in mean manifest cylinder change between the 3 age groups were not statistically significant younger middle older pre op -3.33 ± 2.37 -4.01 ± 2.11 -3.71 ± 1.53 post-op -1.72 ± 1.44 -1.93 ± 1.36 -2.41 ± 1.10 Change 1.20 ± 2.16 2.09 ± 2.02 1.28 ± 1.15 younger middle older Improved by >1.00 D 12 (60 %) 46 (61 %) 7 (50 %) Within 1.00 D of pre-op 6 (30 %) 26 (35 %) 7 (50%) Worse by >1.00 D 2 (10 %) 3 (4 %) 0
	Spherical equivalent	Differences in mean spherical equivalent change between the 3 age groups were not statistically significant younger middle older pre op -3.33 ± 2.37 -4.01 ± 2.11 -3.71 ± 1.53 post-op -1.72 ± 1.44 -1.93 ± 1.36 -2.41 ± 1.10 Change 1.20 ± 2.16 2.09 ± 2.02 1.28 ± 1.15 younger middle older Improved by >1.00 D 9 (95 %) 68 (91 %) 9 (64 %) Within 1.00 D of pre-op 1 (5 %) 6 (8 %) 4 (29 %) Worse by >1.00 D 0 1 (1%) 1 (7 %)
	Keratometry (D)	Differences in mean Keratometry change between the 3 age groups were not statistically significant younger middle older pre op 50.24 ± 4.44 51.77 ± 5.39 50.48 ± 5.27 post-op 46.96 ± 3.29 47.96 ± 4.63 47.44 ± 4.32 Change 3.75 ± 2.15 3.72 ± 1.92 3.12 ± 1.67

Hellstedt T, 2005 Finland (60)	Safety and efficacy of INTACS for mild/moderate Goal to achieve zero astigmatism at the corneal and spectacle plane	3 and 6 mo F-Up Mean F-Up = 6.3 mo ± 3.2 mo. Outcomes mainly to 6 months F-Up >12 mos in first consecutive cases 8 p (10 e)	2 surgeons 37 p (50 e) 26 M, 11 F Age range 20 to 69 yrs	Keratoconus with clear cornea, contact lens intolerant, BSCVA ≥20/100, best contact lens-corrected visual acuity ≥ 20/40, corneal thickness ≥ 400 µm at INTAC placement Two segment thicknesses were used, 0.25-mm placed superiorly to flatten cornea on the basis of spherical equivalent refraction and a 0.45-mm placed inferiorly to lift the conus
	Technical success	Asymmetric implants successfully inserted in 49/50 eyes. One intraoperative complication difficulty in forming superior intrastromal tunnel and was unable to implant.		
	Adjustments and removal	7 re-operations (7 eyes in 7 patients) in which superior segment was removed to improve visual results and were successful. In 4 of 7 eyes BSCVA improved ≥ 2 lines and Visual Function score improved from 65.8 to 74.5 at 3 month post-op 2 patients had inferior segment migration and externalization. Both underwent re-operation, in 1 patient the segment was successfully re-implanted and in the other the segment again migrated and both segments were removed. 1 patient (25-yr old M) had both segments removed 3 mos post-op due to high myopia (-9.0 D). Myopia was corrected with an intraocular lens. 6 Patients had both segments removed at 6 mos because surgical goal was not achieved (astigmatism >than at baseline. 1 patient (45-yr old M) has segments removes at 1 yr for low BSCVA (20/400) with irregular cornea		
	Complications	1 patient had an external infection caused by loosening sutures 10 days post-op and were treated with topical antibiotics and sutures were successfully removed.		
	BSCVA (Snellen lines)	At 6-mo F-Up mean change in BSCVA 2.2 ± 2.3 improved (23, 77%), no change (4 (13%), worse 3 12%)		
	UCVA	At 6-mo F-Up mean change in UCVA 1.0 ± 2.0 improved (22, 73%), no change (6, 20%), worse 2 (7%)		
	Keratometry (D)	Change in Corneal shape from Pre-op to 6-mo F-Up K_1 (mean steep axis) 52.8 ± 6.3 48.6 ± 5.7 K_2 (mean on flat axia) 47.7 ± 5.7 44.4 ± 4.1 $K_1 - K_2$ (mean keratometric cylinder) 5.0 ± 4.1 4.2 ± 3.4 K average 52.76 40.92		
	Visual Funct.-7 Score	VF-7 score improved from 61.6 ± 21.1 to 80.0 at 6 mo (n= 26) and 80.8 ± 22.5 (12 mo N= 8)		
	Patient vision satisfaction	4-point satisfaction with vision level (very unsatisfied, unsatisfied, satisfied, very satisfied). At 6-mo F-Up satisfaction was improved (at least 1 category) in 89% (23), none unchanged, worse in 12% (3). Satisfaction with vision gradually improved over time from 24.3% at baseline to 87.5% at 12 mos (n = 8)		

Kanellopoulos A, 2006 United States (61)	Evaluate the safety and efficacy of modified INTAC implantation	Prospective case series Single site / one surgeon 1-yr F-Up	15 p (20 e) 6 M, 9 F Mean age = 30.2 yrs (SD = 5.44; range = 23 - 40	Patients referred for possible penetrating keratoplasty , Mild and moderate keratoconus as defined by Krumeich stages 2 and 3, intolerant to contact lens and spectacle correction, clear central cornea, BCVA ≥20/200, central corneal pachymetry at least 300 µm Segment selection nomogram based on spherical equivalent (SE) from lowest level (0 to -2.00) to highest level (> -6.00 D) increasing segment thickness from 0.25-mm to 0.45-mm in asymmetric fashion – 0.25-mm upper segment with 0.35-mm lower segment in lowest SE group to 0.40 upper segment with a 0.45 lower segment in highest SE group.
	UCVA	Mean Pre-Op N = 20 20/154 (SD ± 0.11)	Mean 6-mo F-Up N = 20 20/28 (SD ± 0.21)	Mean 12-mo F-Up N= 13 20/29 (SD ± 0.13)
	BSCVA	Mean Pre-Op 20/37 (SD ± 0.21)	Mean 6-mo F-Up 20/22 (SD ± 0.13)	Mean 12-mo F-Up 20/23 (SD ± 0.11)
	Refraction (D)	Mean Pre-Op Sphere -3.38 ± 3.12 Cylinder -3.75 ± 2.04 SE -5.33 ± 3.40	Mean 6-mo F-Up -1.15 ± 1.84 -1.21 ± 0.84 -1.64 ± 1.84	Mean 12-mo F-Up -1.46 ± 2.19 -1.25 ± 0.89 -1.87 ± 1.75
	Keratometry	Mean Pre-Op 49.45 ± 1.64	Mean 6-mo F-Up 46.35 ± 1.50	Mean 12-mo F-Up 46.50 ± 1.22
	Explant	By 1-yr, 7 eyes were excluded because implants had to be removed: 6 eyes for ring movement, 4 of them through the incision, exposure and subsequent corneal thinning over implants 3-6 mos post-op and were unsuccessfully treated by repositioning and incision closure. 1 eye for corneal melt and significant corneal infiltrate over 1 ring at 7 mos post-op)		
	Complications	1 operative complication of anterior chamber perforation; 1 patient had dense corneal infiltrate at 7 mos post op		
Kymionis G, 2007, Greece (53)	To evaluate the long term F-Up of INTAC management of keratoconus	5-yr F-UP Mean F-Up = 67.2 mos SD = 7.5 mos (range 58 to 78 mos) Of the 28 patients (36 eyes), 15 completed 5-yr F-Up. Losses: 5 patients had segments removed within a year and 8 patients were unable to keep up 5 yr follow-ups due to work commitments.	28 p (36 e) At 5-yr F-UP; 15 p (17 e) 8M, 7F, mean age = 34.0 yrs SD = 10.5 yrs)	Clear central corneas, rigid gas-permeable contact lens intolerance, frequent contact lens displacement, unsatisfactory VA with contact lens. Symmetric placement of 0.45-mm segments – Eyes with central ectasia (n = 6 eyes and in those with inferior ectasia (n = 11)

	UCVA (Snellen charts)	UCVA improved in 13 eyes (77%). Pre-op UCVA in all eyes ≤ 20.50 (range counting fingers to 20/50 and at 5-yr F-Up 10 (59%) of 17 eyes had UCVA ≥ 20/50 (range counting fingers to 20/32). Mean difference (pre-op to 5-yr F-Up) was a gain of 2.8 lines (range, unchanged to gain of 9 lines)
	BSCVA	In all eyes except one, BSCVA experienced a gain of one up to 8 lines. One eye with advanced KC (Mean keratometric astigmatism 8.14 D) a decrease of 3 lines was found. The patient still not want INTACS removed.
	Spherical equivalent (D)	Pre-op 6-mo 5-yr Mean ±SD -5.54 ± 5.02 -2.68 ± 2.83 -3.02 ± 2.65 Range -12.50 to 3.63 -8.25 to 1.88 Spherical equivalent was reduced from pre-op to 5 yrs (P = .01) and was stable from 6 mo to 5 yrs (P = .52)
	Keratometry (D)	Significant reduction in mean keratometric reading (P = .009) Pre-Op 5-yr F-Up Mean ±SD 49.59 ± 5.10 48.02 ± 4.99 (P = .009) Range 41.66 to 57.77 39.04 to 56.93 Keratometric astigmatism Pre-Op 5-yr F-Up Mean ±SD 4.46 ± 2.74 3.48 ± 2.23 (P = .03) Range 0.20 to 8.14 1.13 to 8.72
	Stability keratometry	Between the 6=mo F-Up and 5-yr follow-up the topographic findings remained stable 6-mo F-Up 5-yr F-Up Mean ±SD 45.20 ± 4.62 48.02 ± 4.99 (P = .28) Keratomic value Pre-Op 5-yr F-Up Mean ±SD 3.77 ± 2.74 3.48 ± 2.23 (P = .55) Keratometric astigmatism
	Confocal microscopy	Most exhibited normal central corneal images in all layers with normal epithelial cells, subepithelial nerve plexus, keratocyte scattering and endothelial morphology. In one patient needle shaped keratocytes suggestive of collagen disruption or fibrosis. No evidence of corneal ectasia
	Complications	No intra-operative or late post operative serious complications occurred.
	Explants	Segments were removed in 5 patients (7 eyes) 3 to 7 mos post-op because patient dissatisfaction with vision, all underwent uneventful penetrating keratoplasty
	Patient satisfaction	Overall satisfaction of visual outcome using an analog scale (1 to 5) 5 being very satisfied to1 being extremely dissatisfied. Satisfaction with night vision, daytime and night driving specifically evaluated. 82% (14 patients) were considered to be happy (score 5) with the overall results. The rest of the patients (3 eyes), all having an advanced stage of keratoconus, were considered unhappy (score 2-3).
	Contact lens tolerance	In 6 (35%) of the 17 eyes, rigid gas-permeable contact lens were tolerated without replacement

Levinger S, 2005 Israel (13)	To describe visual outcome of INTAC managed keratoconus	Single site F-Up at 1 day, 1 week, 1, 3 6 and 12 months post-INTACS	43 p (58 e) 25 M, 18F Mean age = 35.9 yrs SD = 10 yrs (range 21-55 yrs)	Keratoconus (51e) defined by clinical slitlamp signs (localized corneal thinning, Vogt striae, Fleisher ring) or videokeratography using Rabinowitz indices (a keratopographic topographic pattern of inferior steepening or skewed bow-tie axis, with inferior-superior (I-S) asymmetry >1.9 diopters, central cornea power >48.7 D, or a central corneal power difference >0.92 D between the 2 eyes. Segment selection (0.35-mm, 0.45-mm and nomogram, involved symmetric and asymmetric approach depending on manifest refraction SE >, <-3.00 D, patients age (amount presbyopia) and site of the cone. For SE <-3.00 D used asymmetric technique usually a single 45-mm thick segment Forme fruste (sub clinical) keratoconus (7 e**)** diagnosed as having a topographic pattern of at least 1 of the following: I-S asymmetry >1.4 D, central corneal power >47.2 D or fellow eye with keratoconus as defined. Patients were contact lens intolerant
	Additional surgery	Six eyes underwent additional surgery: In 4 of these visual function worsened due to surgically induced astigmatism managed by removing superior segment. Two of these eyes attained UCVA of 20/40 and 2 remained close to 20/160. In one patient induced hyperopia managed by removing superior segment yielding UCVA of $20/50^{-2}$ In one patient received a single inferior segment and remained myopic, treated by implanting a 25-mm superior segment with subsequent UCVA >20/40.		
	Complications	No segment extrusions occurred. Eight eyes had post-op loss of 2 or more lines BSCVA		
	UCVA	Pre-op UCVA was ≥ 20/200 in almost all 58 eyes Post-op UCVA outcomes: poor (<20/63) n = 21 eyes……. mean UCVA = $20/125^{-1}$ ± 1.7 lines fair (20/63 to 20/40) n = 12 eyes …mean UCVA = 20/50 ± 0.6 line good (>20/40) n = 25 eyes……mean UCVA = 2032 ± 0.9 line 60% (34 / 58 eyes) improved UCVA ≥ 6 lines UCVA significantly improved from pre-op to 1-yr F-Up Pre-Op 1-yr F-Up Mean ± SD 20/200 ± 0.1 line $20/50^{-3}$ ± 3.1 lines (P <.001) Median (logMAR) ±SD 20/200 ± 1.00 line $20/50^{+1}$ ± (0.38)		
	BSCVA	BSCVA did not improve at F-Up Pre-Op 1-yr F-Up Mean ± SD 20/32-1 ± 0.23 line 20/32 ± 0.18 lines (P = .75) Median (logMAR) ±SD $20/32^{12}$ (0.15) $20/32^{12}$ ± (0.38)		

	Refractive Outcomes (D)	Mean manifest spherical equivalent, spherical correction and astigmatic correction all improved significantly (P <.001) Pre-op 1-yr F-Up P-Value Mean manifest spherical equivalent -3.88 ± 1.64 -1.04 ± 1.51 <.001 Mean spherical correction -2.21 ± 1.96 -0.05 ± 1.27 <.001 Mean manifest astigmatic -334 ± 2.23 -1.97 ± 1.51 <.001		
	Keratometry (D)	All keratometry values significantly improved at F-Up Mean ± SD Pre-Op 1-yr F-Up P Value Maximum Keratometry 48.06 ± 3.87 44.62 ± 3.18 <.001 Minimum Keratometry 44.73 ± 2.29 41.99 ± 2.59 <.001 Central corneal power 47.04 ± 3.90 44.95 ± 4.01 .006 Effective Refractive power 47.01 ± 3.74 44.72 ± 3.90 .002		
	Visual symptoms	54/58 completed questionnaires – 39 reported significant improvement and 15 reported no improvement. 5 patients reported satisfied with improved UVCA but reported a loss of BSCVA. Many patients mildly complained of decreased near vision and intermittently “seeing the ring”.		
		Conclude that patient with high myopia may be more satisfied than patient with high astigmatism and little spherical myopia.		
Siganos D, 2003 Greece (63)	Evaluate INTAC ICR management of keratoconus	Prospective case series Two surgeons 2-yr F-Up F-Up days 1,3,15, 30 and every 3 mos to 24 mos. Mean F-Up =11.3 mos SD = 6.5 mos (range 1 – 24 mos USED Last F-Up Point	26 p (33 e) 17 M, 9 F Mean age = 32 (SD = 9.7 yrs, range 21 to 51 yrs)	Clear central corneas and contact lens intolerance. 19 eyes had inferior corneal ectasia and 14 eyes had central corneal ectasia. Symmetric placement – 2 segments 0.45-mm thickness inserted to embrace the steepest keratoconus meridian.
	Technical success	All surgical procedures were uneventful		
	UCVA (logMAR)	UCVA significantly improved at F-Up Pre-op Post-Op P value Mean UCVA ± SD 0.13 ± 0.14 0.39 ± 0.27 <.01 Range CF – 0.50 Of 33 eyes – 2 eyes lost 1 line UCVA, 3 eyes no change, 28 eyes gained 1 to 10 lines. Mean difference pre-op to post-op was a gain of 2.5 lines (range 1 line to 10 lines)		

	BCVA (logMAR)	BCVA significantly improved at F-Up Pre-op Post-Op P value Mean BCVA ± SD 0.47 ± 0.31 0.64 ± 0.26 <.01 Range (CF – 1.00) Of 33 eyes – 4 eyes lost 1 to 2 lines BSCVA, 4 eyes no change, 25 eyes gained 1 to 6 lines. Mean difference pre-op to post-op was a gain of 1.7 ± 1.9 lines (range loss 2 lines to gain 6 lines)		
	Spherical equivalent (D)	Mean spherical equivalent refraction significantly decreased Pre-op Post-Op P value Mean spherical equivalent ± SD -5.67 ± 4.87 -4.28 ± -3.86 .05 Range (0 - -22.25) (0 - -16.50)		
	Keratometry (D)	Pre-op Post-Op P value Mean keratometry ± SD 50.86 ± 6.62 47.63 ± 5.41 <.01 Range (41.67 – 71.00) (37.54 – 57.56) Mean keratometric astigmatism 3.33 ± 2.10 3.06 ± 2.14 .44		
	Complication	In one eye 6 mos post-op significant decrease in UCVA (0.4 to CF) and BCVA (0.8 with contact lens to 0.2) and increases in topographic irregularity were observed. Treated by removing the superior segment and advancing the inferior segment resulting in an increase UCVA (0.8) and BSCVA (0.9) and in topographic findings remaining stable for the next 10 months F-Up . In another eye with a central cone, due to superficial placement and lack of improvement removed segments at 3 mo F-Up. In one eye, segments removed due to patients dissatisfaction and PKP performed 3 months following without complication. At 6 months the majority of eyes demonstrated mild channel deposits at the inner edge of the segments. In one eye, superficial mild wound neovascularisation after 2 months remaining stable up to 11 months without impact on visual acuity or topographic findings.		
Zare M, 2007 Iran (62)	Evaluate safety, efficacy and optical effects of INTAC management keratoconus	Prospective case series 1 site, 2 surgeons F-Up at 1 wk and 1, 3 and 6 months (all patients).	22 p (30 e) 17 M, 5 F Mean age = 25.9 yrs SD = 5.3 yrs	Inclusion criteria keratoconic eyes with clear central cornea, contact lens intolerance, a BSCVA ≥ 20/100 (0.2 decimal) and a minimum corneal thickness of 450 µm at site of incision and 350 µm at central cornea. Keratoconus staging was based on the Krumeich classification. (Stage 1 (n = 6), Stage 11 (n = 16 eyes), Stage 111 (n = 4 eyes), Stage IV (n = 4 eyes). Nomogram for segment selection based on spherical equivalent ranging from lowest SE group (0 to -2.00 D) with 0.25-mm upper segment and 0.35-mm lower segment to highest SE range (> -8.00 D) with a 0.40-mm upper segment and 0.45-mm segment.

	UCVA (logMar)	Mean UCVA steadily improved from baseline at each follow-up point and was significantly improved over baseline at each comparison (P <.001). Of the 30 eyes, 1 lost 2 lines UCVA, 7 remained unchanged (within 1 line), 22 gained ≥ 2 lines at last F-Up. Pre-op 6-mo F-Up P value Mean UCVA ± SD 0.60 ± 0.311 0.29 ± 0.20 <.001
	BSCVA (logMAR)	Mean BCVA also steadily improved from baseline at each follow-up point and was significantly improved at the 3 and 6 month F-Up comparison (P <.001). Of the 30 eyes, 1 lost 2 lines BSCVA, 13 remained unchanged (within 1 line, 16 gained ≥ 2 lines at last F-Up. Pre-op 6-mo F-Up P value Mean BCVA ± SD 0.25 ± 0.166 0.13 ± 0.14 <.001
	Spherical equivalent (D)	Mean spherical equivalent steadily improved from baseline at each follow-up point and was significantly improved over baseline at each comparison (P <.001). Pre-op 6-mo F-Up P value Mean SE ± SD -6.93 ± 3.52 -3.23 ± 2.81 = .001
	Refractive cylinder (D)	Mean manifest refraction cylinder improved from baseline but the changes were not statistically significant. Pre-op 6-mo F-Up P value Mean Cylinder ± SD -4.65 ± 1.85 - 3.90 ± 1.70 = .054
	Keratometry (D)	Mean decrease in keratometry was significant at all F-Up points (P <.001) Pre-op 6-mo F-Up P value Mean K1 (minimum) ± SD 47.46 ± 3.33 45.73 ± 2.91 Mean K2 (maximum) ± SD 52.19 ± 4.03 50.22 ± 4.20 Mean K (average) ± SD 49.84 ± 3.58 47.90 ± 3.58 <.001
	Corneal thinning (µm)	Pre-op 6-mo F-Up P value Mean Pachymetry ± SD 428.33 ± 44.69 405.05 ± 50.34 = .054 (µm at thinnest point)
	Keratometry, Visual Acuity and Refractive outcomes	Change from Pre-op to 6-mo F-Up UCVA BSCVA SE Cylinder Pre-Op keratometry ≤ 48.0 D ↓ p=.002 ↓ p=.047 ↓ p=.007 ↓ p=.599 Pre-Op keratometry 48.0 – 53.0 D ↓ p=.002 ↓ p<.001 ↓ p<.001 ↓ p=.140 Pre-Op keratometry ≥ 53.0 D ↓ p=.027 ↓ p=.256 ↓ p=.005 ↓ p=.323
	Complications	In 3 cases segment (all inferior) movement and exposure through the wound occurred 3 to 5 months post implant. In 1 of these cases the inferior ring had moved to corneal tissue overlying the upper ring segment and the corneal tissue melted. In the 2 other cases segments were repositioned subsequent movement and exposure necessitated removal of rings. In one case, a superior ring caused a severe foreign body sensation and discomfort necessitating the removal of the ring 4 months post-op. In one case significant corneal melting and severe corneal infiltration necessitated segment and treatment with topical antibiotics 25 months post-op. The complications were noted to occur in initial cases and were attributed to surgeon learning curve.
	Explant	In total, segments were removed from 5 cases (see complication)

Appendix 3: Technical Success, Re-Interventions and Complications Following INTAC Placement

Author, Year Study Details	Events	Event Details
Alio J, 2006 (51) F-Up at 6, 12, 24, 36 (all eyes) and 48 mos (6 e) Study loss: Incomplete follow-up (n = 6 eyes), Extrusion in first year (n = 7 eyes) Report on 11 patients and 13 eyes	Extrusions	Extrusion occurred in 7 eyes, 3 of them with advanced keratoconus, in the first year F-Up, believed to be due to surgical learning curve.
	Complications	Channel deposits were seen in 4 eyes (3 eyes with 2 segments and 1 eye with 1 segment). They did not regress over the F-Up period but did not interfere with visual axis or visual outcome. Superficial vascularisation occurred at the incision site and peripheral part of segment tunnel in 2 eyes, regressed in year 2 F-Up
Wachler B 2003 (54) Mean F-Up = 9 mos range 1 mo (2 e) to 20 months. 50 patients (41 M, 9 F) and 74 eyes 26 patients had single eye treatment, 24 subjects had both eyes treated	Complications	During surgery, one eye had a superficial channel dissection with anterior Bowman's layer perforation. Treated by re-deepening the entry incision and successfully rechannelling followed by segment insertion. Two eyes had transient inflammatory reaction to epithelium incision resolving in first week. One eye, with an I-S value of 100 suggestive of advanced keratoconus, had segment migration and externalization in one eye on first post-op day. The segment could not be stabilized and was explanted, subsequently the other segment and segments in fellow eye were explanted because of chronic foreign body sensation. Segments were removed from one other patient because of foreign body sensation. Two patients complained of halos around lights at nights, both had pupils larger than 7.5 mm. Neither requested explantation and 1 patient was using brimonidine for night vision.
Colin J, 2000 (56) 10 p (10 e) Mean F-Up = 10.6 mos (2 yrs,1 eye; 1 year, 5 eyes; 3 3 and 6-mo F-Up 10eyes	Complication	No intra-operative complications occurred. At 3 months all eyes experienced mild to moderated intralamellar channel deposits at superior edges of inferior segments
	Explant	In 1 eye segments explanted after 2 mos because of superficial implantation. Segments were easily removed and refraction, visual acuity and corneal topography returned to pre-op status.

Colin J, 2007 Brest, France (52) 1-yr and 2-yr F-Up	Technical success	Implantations were uneventful in all 100 eyes.
68 patients and 82 eyes (54 unilateral and 14 bilateral) evaluated at all time points. 14 eyes lost to F-Up, 5 at 1-yr and 9 at the 2-yr F-Up	Complications / Observations Slit-lamp exams	All eyes had well centered INTACS with no migration or displacement. No evidence of vascularisation at the incision site. No cases of early or late post-op infection. Non-progressive epithelial cysts were present in 21 eyes at both F-Up exams. White yellow deposits were in the segment tunnels in 17 eyes at 1- yr and 22 eyes at 2-yr F-Up. The lamellar channel deposits had no effect on visual level or quality.
	Explants	Segments were removed from 4 eyes for: extrusion at incision site (n=2 eyes, at 5 mos and >8 mos) and poor visual outcome (n=2 eyes, between 1-yr and 2-yr). In all eyes segments were easily removed without post op sequelae and a penetrating keratoplasty was subsequently performed.
Colin J, 2006 (33) 59 e enrolled –report on 34 eyes at 6 mo F-Up F-UP 1 day, 7 day and 1, 3, 6 and 12 months 12-mo F-Up	Technical success	Successfully implanted into 58 / 59 eyes (1 inadequate documentation) and 1 case lost to follow-up after 1 month exam
	Safety – (maintenance BCVA)	No cases of ocular infection, segment migration or extrusion, stromal thinning over the insert at any post op period were observed. Intrastromal deposits on or near inserts and haze in the incision area were commonly observed
	BCVA Safety – (maintenance BCVA)	Pre operatively, 53% (30/57) eyes had BCVA of 20/40 or better increasing to 71% and 74% at 3 and 6 mo-F-up. The increase in BCVA between 1 and 6 mo F-Up was statistically significant (P ≤ .033) Of the 34 eyes at 6 mo - 62% (21/34) had a gain 2 to 8 lines, 32% (11/34) had no change (gains ± 1 line of acuity), 6% (2 eyes) had a loss of 2 lines.
	Observations and Complications	No intraoperative complications were noted
Ertan A, 2006 (58) 1-yr F-Up 69 p (118 e)	Complications	Epithelial plugs occurred at the incision site in 15% eyes. Granulomatosis particles were observed around segment sin 8.5% eyes during the first 6 months post op resolving with steroid drops.

Ertan A, 2008 (55) Mean F-Up 10.30 mos Minimum 4 mo F-Up with range 4 to 30 mos. Post op follow-up not uniformly specified	Complications	No surgical complications were noted. INTAC segment extrusion occurred in 3/306 eyes within 6 months of implantation (all in the stage IV ages 18 yrs, 20 yrs and 23 yrs)
Hellstedt T, 2005 (60) 37 p (50 e) 3 and 6 mo F-Up Mean F-Up = 6.3 mo ± 3.2 mo. *Outcomes mainly to 6 months* F-Up >12 mos in first consecutive cases 8 p (10 e)	Technical success	Asymmetric implants successfully inserted in 49/50 eyes. One intraoperative complication difficulty in forming superior intrastromal tunnel and was unable to implant.
	Adjustments and removal	7 re-operations (7 eyes in 7 patients) in which superior segment was removed to improve visual results and were successful. In 4 of 7 eyes BSCVA improved ≥ 2 lines and Visual Function score improved from 65.8 to 74.5 at 3 month post-op 2 patients had inferior segment migration and externalization. Both underwent re-operation, in 1 patient the segment was successfully re-implanted and in the other the segment again migrated and both segments were removed. 1 patient (25-yr old M) had both segments removed 3 mos post-op due to high myopia (-9.0 D). Myopia was corrected with an intraocular lens. 6 Patients had both segments removed at 6 mos because surgical goal was not achieved (astigmatism >than at baseline. 1 patient (45-yr old M) has segments removes at 1 yr for low BSCVA (20/400) with irregular cornea
Kanellopoulos A, 2006 (61) 15 p (20 e) 1-yr F-Up	Explant	By 1-yr, 7 eyes were excluded because implants had to be removed - 6 eyes for ring movement, 4 of them through the incision, exposure and subsequent corneal thinning over implants 3-6 mos post-op and were unsuccessfully treated by repositioning and incision closure. 1 eye for corneal melt and significant corneal infiltrate over 1 ring at 7 mos post-op)
	Complications	1 operative complication of anterior chamber perforation 1 patient had dense corneal infiltrate at 7 mos post op
Kymionis G, 2007 (53) 28 p (36 e) 5-yr F-UP Mean F-Up = 67.2 mos SD = 7.5 mos (range 58 to 78 mos)	Complications	No intraoperative or late post operative serious complications occurred.
	Explants	Of the 28 patients (36 eyes), 15 completed 5-yr F-Up. Losses - 5 patients (7 eyes) had segments removed within first year and 8 patients (12 eyes) were unable to keep up 5 yr follow-ups due work and family commitments Segments were removed in 5 patients (7 eyes) 3 to 7 mos post-op because patient dissatisfaction with vision, all underwent uneventful penetrating keratoplasty

Levinger S, 2005 (13) 43 p (58 e) F-Up at 1 day, 1 week, 1, 3 6 and 12 months	Additional surgery	Six eyes underwent additional surgery – In 4 of these visual function worsened due to surgically induced astigmatism managed by removing superior segment. Two of these eyes attained UCVA of 20/40 and 2 remained close to 20/160. In one patient induced hyperopia managed by removing superior segment yielding UCVA of $20/50^{-2}$ In one patient received a single inferior segment and remained myopic, treated by implanting a 25-mm superior segment with subsequent UCVA >20/40.
	Complications	No segment extrusions occurred. Eight eyes had post-op loss of 2 or more lines BSCVA
Siganos D, 2003 (63) 26 p (33 e) F-Up days 1,3,15, 30 and every 3 mos to 24 mos. Mean F-Up =11.3 mos SD = 6.5 mos (range 1 – 24 mos USED Last F-Up Point	Technical success	All surgical procedures were uneventful
	Complication	In one eye 6 mos post-op significant decrease in UCVA (0.4 to CF) and BCVA (0.8 with contact lens to 0.2) and increases in topographic irregularity were observed. Treated by removing the superior segment and advancing the inferior segment resulting in an increase UCVA (0.8) and BSCVA (0.9) and in topographic findings remaining stable for the next 10 months F-Up . In another eye with a central cone, due to superficial placement and lack of improvement removed segments at 3 mo F-Up. In one eye , segments removed due to patient dissatisfaction and PKP performed 3 mos following without complication. At 6 mos the majority of eyes demonstrated mild channel deposits at the inner edge of the segments. In one eye, superficial mild wound neovascularisation after 2 mos remaining stable up to 11 months without impact on visual acuity or topographic findings.
Zare M, 2007 (62) 22 p (30 e) F-Up at 1 wk and 1, 3 and 6 mos (all patients).	Complications	In 3 cases segment (all inferior) movement and exposure through the wound occurred 3 to 5 months post implant. In 1 of these cases the inferior ring had moved to corneal tissue overlying the upper ring segment and the corneal tissue melted. In the 2 other cases segments were repositioned subsequent movement and exposure necessitated removal of rings. In one case, a superior ring caused a severe foreign body sensation and discomfort necessitating the removal of the ring 4 months post-op. In one case significant corneal melting and severe corneal infiltration necessitated segment and treatment with topical antibiotics 25 months post-op. The complications were noted to occur in initial cases and were attributed to surgeons learning curve.
	Explant	In total segments were removed from 5 cases (see complication)

Appendix 4: Outcome Reporting for Intrastromal Corneal Ring Management of Pellucid Marginal Corneal Degeneration

Author Year, Country	Study Design and Objective	Case History and Interventions	Outcome
Akaishi L, 2004 Brasilia, Brazil (102)	Case report Ferrara ICRS and cataract surgery for correction of PMCD	70-yr-old man with pellucid marginal corneal degeneration (PMCD) experienced decreased visual function in both eyes due to cataract formation. ICR segments were inserted superiorly (0.2 mm) and inferiorly (0.250 mm). Uneventful bilateral cataract surgery was performed one month after Ferrara ICRS placement.	Pre –operatively, BSCVA was 0.50 with -2.00 -11.25 x 80 in the right eye and 0.60 with -2.00 – 5.50 X 95 in the left eye. At I month post ICR, BSCVA was 0.50 with -2.50 -1.75 X 90 in the right eye and 0.40 with -0.75 – 2.25 X 170 in the left eye. At I month post cataract surgery, best corrected distance acuity was 0.80 with -1.00 in the right eye and 0.60 with -0.75 – 2.25 X 160 in the left eye.
Barbara A, 2005 Haifa, Israel (101)	Case report INTAC management of inferior PMCD	41-yr-old man with congenital nystagamus and contact lens intolerance. BSCVA was 6/60 in both eyes. PMCD was diagnosed based on corneal topography and pachymetry. A single INTAC (0.45-mm thickness) was inserted in the left eye upper periphery but not at the inferior cornea due to corneal thinning	Thirty minutes postoperatively, UCVA improved from 2/60 to 6/60 remaining stable till 1-year follow-up. At 1-year follow-up eliminated -5.00 diopters cylinder and improved irregularity of the astigmatism.

Ertan A, 2006 Ankara, Turkey (5)	Case series INTAC with femtosecond laser created channels for management PMCD	6 p (9 e) 4 M, 2 F mean age = 32 yrs SD 9.4 yrs (range 17 to 46 yrs) Diagnosis made on basis of slit-lamp findings of inferior corneal thinning above the area of maximum thinning. Corneal topography showing a very steep contour in the extreme peripheral inferior cornea with high keratometric powers radiating toward the center from the inferior oblique meridians. In all cases 0.25 mm and 0.45 mm INTAC segments were inserted superiorly and inferiorly	6 mo F-Up UCVA was significantly improved in all eyes. Mean UCVA Pre-op 0.18 ± 0.24 to 0.53 ± 0.23 (*P* = 0.008) BCVA was unchanged in 1 eye and significantly improved in 8 eyes Mean BCVA pre-op 0.63± 0.26 to 0.85± 0.18 *P* = 0.011 Mean astigmatism - cylinder Pre-op -2.41 D ± 2.27 to -0.94 D ± 1.07 (*P* = 0.046) Mean Sphere Pre-op -3.86 D ± 2.91 to -2.27 D ± 1.43 (*P* = 0.091) Mean K-Value Pre-op 48.17 ± 4.19 to 46.9 ± 5.00 (*P* = 0.008) Four eyes received glasses prescription and 3 patients were satisfied without correction
Ertan A, 2007 Ankara, Turkey (103)	Case report Management of superior PMCD with single INTAC segment using femtosecond laser	26-yr-old man progressive visual loss in the left eye. An INTAC of 45-mm thickness was inserted into the superior steep area. Channel created by femtosecond laser	At presentation BSCVA was 0.15 and manifest refraction was -4.50 x 85. At 3 months post-operatively topography showed decrease in corneal astigmatism and BCVA was 0.4 and manifest refraction was -2.50 x 90.
Kymionis G, 2004 Crete, Greece (104)	Case report INTAC management of early PMCD	42-yr-old man for correction of ametropia. UCVA was counting fingers in both eyes and BSCVA was 20/50 in right eye and 20/32 in left eye and the patient was contact-lens intolerant. Corneal topography revealed inferior perilimbal steepening in both eyes, more advanced in the right eye. Two INTACS (0.45 mm thickness) were inserted in the right eye	11-mo F-Up Improvements in UCVA, BSCVA and topographic findings were noted. Right eye UCVA was 20/200 and BSCVA was 20/25

Mularoni A, 2004 Bologna, Italy (106)	Case series INTAC management of early and moderate PMCD	8p (4 M , 4 F) bilateral PMCD Mean age = 54.5 yrs (range 44 to 78 yrs), all were unsatisfied with spectacle or contact lens correction. Diagnosis of PMCD was made with Orbscan tomography. In all cases a 0.45 mm INTAC was inserted inferiorly and a 0.25-mm insert was placed superiorly. Surgical procedures were performed in the eye with the higher astigmatism by the same surgeon.	Mean F-Up = 24.8 mos (range 12 – 42 mos) At 12 months all patients had improved UCVA and BCVA. Mean pre-op UCVA increased from 20/325 (range, 20/100 to 20/200) to 20/63 (range, 20/200 to 20/32) at last exam. Mean BCVA increased from 20/45 (range 20/63 to 20/25) to 20/25 (range, 20/32 to 20/20). All patients had BCVA ≥20/63. All patients gained Snellen lines of BCVA: 5 lines (n = 1), 4 lines (n = 3), 3 lines (n = 1), 2 lines (n = 2) and 1 line (n=1) Four patients received prescription for glasses, 1 patient could wear contact lens again and 3 patients were satisfied without any correction. Keratometry improved from 43.95 (SD 2.08) to 42.46 (SD 1.86) Refractive errors improved from baseline at 12-month F-Up: Sphere: -4.74 (SD 3.56) to -1.36 (SD 3.24) Cylinder -6.31 (SD 1.81) to -1.72 (SD 2.60) Mean astigmatism changed from -6.31 preop to -1.72 and in only one case did cylinder exceed 3 diopters
Rodriguez-Prats J, 2003 Alicante, Spain (105)	Case report INTAC management of inferior PMCD	36-yr-old man evaluated for manifest and cycloplegic refraction. Pre-operative UCVA in right eye was 0.05 and BSCVA was 0.1 with a refraction of -2.0 -7.0 x 90.	1 Month F-Up UCVA was 0.2 the BSCVA 0.3 and the refraction was -8.0 -7.0 X 50. Visual acuity was still not acceptable so a hybrid contact lens (SoftPerm®, Ciba Vision) with a central permeable soft zone, a rigid hydrophilic peripheral zone with a base curve of 8.00 mm, a diameter of 14.3 mm and a power of -9.00 diopters was inserted and VA improved to 0.9. The patient was able to wear the lens for 8 to 10 hours a day and at 6-month F-up VA improved to 1.0 (20/20).

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