Intrastromal corneal ring segments (ICRS) for keratoconus and corneal ectasia

June 2005

MSAC application 1083

Assessment report

ISBN *<number>*

ISSN (Print) 1443-7120

ISSN (Online) 1443-7139

First printed *<add month/year>*

Paper-based publications

Internet sites

Electronic copies of the report can be obtained from the Medical Service Advisory Committee's Internet site at http://www.msac.gov.au/

Printed copies of the report can be obtained from:

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The Medical Services Advisory Committee (MSAC) is an independent committee which has been established to provide advice to the Commonwealth Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

This report was prepared by the Medical Services Advisory Committee with the assistance of Rebecca Tooher and Philippa Middleton from the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical. The report was edited by Larissa Joseph and Jenny Cook of PenUltimate. The report was endorsed by the Minister for Health and Ageing on 28 November 2005.

Publication approval number: <*number*>

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Intrastromal corneal ring segments (ICRS) are small semicircular plastic segments that are inserted, usually under topical anaesthesia, into stromal channels outside the central visual axis of the eye to reinforce the corneal stroma. The aim of ICRS implantation is to improve visual acuity without removing any corneal tissue or touching the central cornea. ICRS are manufactured by two medical device companies and marketed under the names Intacs prescription inserts (Addition Technology Inc.) and Ferrara intrastromal corneal ring segments (Mediphacos).

Medical Services Advisory Committee – role and approach

The Medical Services Advisory Committee (MSAC) was established by the Australian Government to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of the available evidence is thus the basis of decision-making when funding is sought under Medicare. A team from the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical was engaged to conduct a systematic review of literature on the use of ICRS for treating ectasia and keratoconus. An advisory panel with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of ICRS for corneal ectasia and keratoconus

Clinical need

The incidence and prevalence of keratoconus in Australia are difficult to establish. In international studies, the number of people in the general population thought to have keratoconus is usually estimated to be around 1 in 2,000 (50 in 100,000) and each year around 2 in 100,000 new cases of keratoconus are diagnosed. In Australia, this equates to around 10,000 people living with keratoconus and around 400 new cases of keratoconus per year. Of the more than 14,000 grafts registered with the Australian Corneal Graft Registry since 1987, one-third were for keratoconus.

The incidence of iatrogenic corneal ectasia after refractive surgery has not been studied extensively, but is probably less than 1 per cent. The estimate of the total number of refractive surgery patients and the proportion who develop complications such as ectasia may vary if selection criteria are refined and surgical outcomes improve. Non-iatrogenic corneal ectasias other than keratoconus are rare; the incidence is difficult to determine and likely to be underestimated as ectasia may be mistaken for keratoconus.

ICRS were originally developed for the treatment of myopia in non-diseased eyes. Their use was then extended to patients with conditions that cause thinning and steepening of

the cornea, including keratoconus; iatrogenic corneal ectasia resulting from refractive surgery for primary myopia, usually laser in situ keratomileusis or phototherapeutic keratectomy; and non-iatrogenic corneal ectasias such as pellucid marginal degeneration. ICRS may also be used in patients whose corneal contact lenses have failed or who cannot tolerate contact lenses.

Safety

ICRS implantation is associated with a range of complications, including migration or extrusion of the ICRS segments, visual symptoms such as glare or halo and infections, including keratitis. The rate of complications depends on how they are defined. The rate of explantation ranged from 4 per cent to 25 per cent (median 10%) for eyes with keratoconus. Reasons for explantation included dissatisfaction with vision, segment extrusion or decentration, chronic foreign body sensation and incorrect segment placement.

Effectiveness

ICRS implantation improved best corrected and uncorrected visual acuity for most patients with keratoconus and corneal ectasia. For keratoconus, medians of 67 per cent and 81 per cent of eyes improved for best corrected and uncorrected visual acuity respectively. The corresponding figures for iatrogenic corneal ectasia were 45 per cent and 95 per cent. However, a number of patients experienced no change in visual acuity and a small proportion experienced worsened visual acuity. ICRS implantation also resulted in flattening of the cornea and a reduction in irregular astigmatism with more normal keratometric values, spherical equivalence and refractive cylinder. Functional outcomes were only reported in two studies; patients reported reduced visual symptoms and improvements in subjective vision.

Durability of ICRS implantation, potential for ICRS to delay the need for corneal transplant and the effect of ICRS on progression of disease were not reported in any included studies.

Cost-effectiveness

Cost-effectiveness could not be assessed as there were no published comparative studies.

Recommendation

MSAC recommends that on the strength of evidence pertaining to intrastromal corneal ring segments for ectasia and keratoconus public funding should not be supported for this procedure.

The evidence pertaining to this procedure is immature and small in volume. It is not possible to be confident that the benefits demonstrated are durable, and the lack of published comparative clinical studies does not allow for any cost-effectiveness analysis.

The Minister for Health and Ageing accepted this recommendation on 28 November 2005.

Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of intrastromal corneal ring segments for treating ectasia and keratoconus. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, which are based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are at Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for the use of intrastromal corneal ring segments for treating ectasia and keratoconus.

Background

Intrastromal corneal ring segments for corneal ectasia and keratoconus

Intrastromal corneal ring segments (ICRS) are small semicircular plastic segments that are inserted, usually under topical anaesthesia, into stromal channels outside the central visual axis of the eye to reinforce the corneal stroma. The segments act as passive spacing elements that cause local separation of the corneal lamellae and shorten the arc length of the anterior corneal surface, thus flattening the central cornea (Boxer Wachler & Sharma 2004; Burris 1998; Colin et al 2001). The degree of shortening of the arc length has been found to be proportional to the thickness of the inserts and ICRS are manufactured in various sizes that are combined to suit the characteristics of each patient's corneal disease (Burris 1998; Colin & Simonpoli-Velou 2003).

The aim of ICRS implantation is to improve visual acuity without removing any corneal tissue or touching the central cornea. Advantages of ICRS over other incisional, excisional or ablative refractive surgical techniques include faster and more predictable wound healing, a simpler surgical procedure, the ability to adjust refractive outcome (by adjusting the ICRS) and reversibility (explantation) (Burris 1998; Colin & Velou 2002).

ICRS are manufactured by two medical device companies and marketed under the names Intacs prescription inserts (Addition Technology Inc.) and Ferrara intrastromal corneal ring segments (Mediphacos).

The procedure

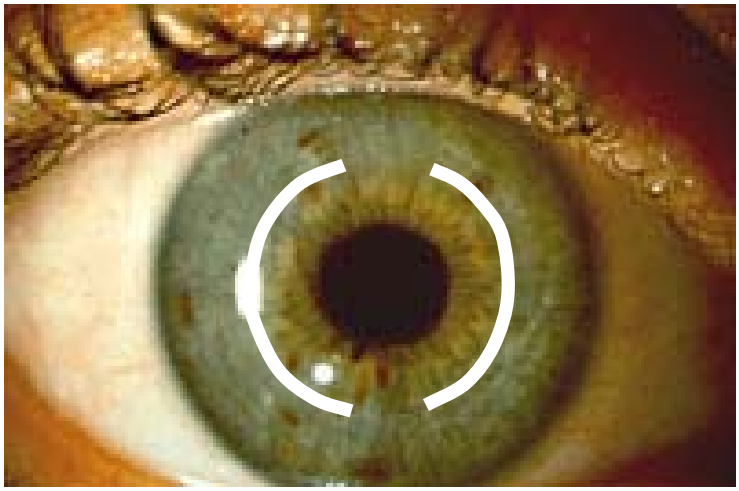
Intacs

Intacs prescription inserts are poly(methyl methacrylate) segments with thicknesses between 0.25 mm and 0.45 mm and an arc length of 150 degrees, although only 0.25 mm, 0.30 mm and 0.35 mm segments are available in the United States (Boxer Wachler & Sharma 2004) (Figure 1).

Figure 1 Intacs inserts

A diamond knife set at 66 per cent of local pachymetry (measured by ultrasound) is used to create incisions of between 1.2 mm and 1.8 mm at the edge of the 7 mm optical zone. A stromal spreader is used to create a pocket in the corneal lamellae from the floor of the incision. After it has been verified that the channels are the correct depth, a special vacuum centering device is placed on the eye to increase global rigidity. The spreader is positioned in the pocket using a guide and rotated to create two stromal channels. Particular care is taken in the creation of the inferior channel, where the cornea is usually thinner. The channels are irrigated before the Intacs segments are inserted and the incision edges are approximated or sutured. The IntraLase laser is an alternative method for channel creation (Boxer Wachler & Sharma 2004). A plastic eye shield is used for the first days after surgery and topical analgesics, antibiotics and steroids are applied for two weeks postoperatively. Any sutures are removed 10 to 15 days after surgery. Patients are asked not to rub their eyes (Boxer Wachler & Sharma 2004; Colin & Simonpoli-Velou 2003) (Figure 2).

Figure 2 Intacs inserts in situ (the inserts have been highlighted in the figure but are virtually invisible in the eye)



The Colin nomogram for keratoconus (Colin & Simonpoli-Velou 2003):

Cone type	Preop SE <3.0D	Preop SE >3.0D
Moderately asymmetrical cone	0.35 mm/0.40 mm	0.40 mm/0.45 mm
Highly asymmetrical cone	0.25 mm/0.40 mm	0.25 mm/0.45 mm
Global cone	0.40 mm/0.40 mm	0.45 mm/0.45 mm
Central cone	0.40 mm/0.40 mm	0.45 mm/0.45 mm

Abbreviations: D – dioptre; mm – millimetre; preop – preoperative; postop – postoperative; SE – spherical equivalent

Ferrara

Ferrara ring segments are made from Perspex CQ (Clinical Quality) Acrylic. They have a triangular cross-section inner radius of curvature of 2.5 mm and flat basis with fixed width of 600 µm (Miranda et al 2003; Siganos, D. et al 2002). Segments are available in thicknesses ranging from 0.15 mm to 0.35 mm with an apical diameter of 5 mm and an arc length ranging from 120 degrees to 160 degrees (Kwitko & Severo 2004). Ferrara ICRS have a prism format such that the flat posterior surface faces the corneal endothelium when implanted (Miranda et al 2003).

There are two significant differences between Ferrara ICRS and Intacs ICRS. Ferrara ring segments have a fixed radius of curvature of 2.5 mm and a triangular anterior

surface, while Intacs inserts have a variable curvature (2.5 mm to 3.5 mm) and a flat anterior surface (Colin & Simonpoli-Velou 2003; Kwitko & Severo 2004).

A diamond knife set at 80 per cent of the minimum corneal thickness is used to make two radial corneal incisions at the steep corneal meridian between the 5 mm and 7 mm optical zones (Miranda et al 2003; Siganos, D. et al 2002). A special double metallic arcuate guide (Ferrara spreader) is inserted to elevate the cornea and create two intrastromal channels around the cone with an internal radius of curvature of 2.5 mm and an extension of 170 degrees (Kwitko & Severo 2004; Miranda et al 2003). After the ICRS are implanted the wound edges are approximated and closed with hydration or 10-0 nylon sutures (Kwitko & Severo 2004; Miranda et al 2003). A therapeutic soft contact lens may be used for up to 48 hours after surgery and topical analgesics, antibiotics and steroids are applied for up to 30 days postoperatively. Any sutures are removed after 30 days.

The Miranda nomogram for ICRS (Miranda et al 2003):

Ring thickness	Cone	Predicted correction
0.20 mm	<43D	-2.00D
0.25 mm	43–45D	-4.00D
0.30 mm	45–52D	-6.00D
0.35 mm	>52D	-8.00D

Abbreviations: D – dioptre; mm – millimetre

Intended purpose

ICRS were originally developed for treating myopia in non-diseased eyes (Burris 1998; Colin & Simonpoli-Velou 2003). Their use was then extended to patients with keratoconus; iatrogenic corneal ectasia resulting from refractive surgery for primary myopia, usually laser in situ keratomileusis (LASIK) or phototherapeutic keratectomy; and non-iatrogenic corneal ectasias such as pellucid marginal degeneration (PMD) (Boxer Wachler & Sharma 2004).

Keratoconus

Keratoconus is a non-inflammatory self-limiting ectasia of the para-axial portion of the cornea. It is characterised by progressive thinning and steepening of the cornea, which causes asymmetrical irregular astigmatism and myopia (Colin & Velou 2003). Keratoconus usually affects both eyes, although in the initial phases of the condition only one eye may be affected (Krachmer et al 1984; Rabinowitz 1998). Onset of keratoconus is typically in the second or third decade of life (Rabinowitz 1998) and is more common in people who also have connective tissue disorders; Leber's congenital amaurosis; intellectual disability, in particular Down's syndrome; mitral valve prolapse; incomplete osteogenesis; keratoconjunctivitis; atopic dermatitis; and retinitis pigmentosa (Olivarez Jiminez et al 1997; Rabinowitz 1998). It has also been associated with eye rubbing (McMonnies & Boneham 2003; Owens & Gamble 2003).

Mild or moderate keratoconus can usually be treated by spectacles or contact lenses, which are the treatment of choice for around 90 per cent of patients (Rabinowitz 1998). As the disease progresses, soft contact lenses are usually replaced by rigid gas-permeable contact lenses. However, rigid lenses can be difficult to fit effectively, and in more severe

cases the cornea may become opacified and so distorted that the lenses no longer provide sufficient improvements in functional vision. Furthermore, many patients with keratoconus develop intolerance to contact lenses or corneal scarring. The usual treatment for these patients is penetrating keratoplasty (corneal transplant). Other surgical treatments include deep lamellar keratoplasty, excimer laser corneal ablation, LASIK, epikeratoplasty and phakic intraocular lenses (Colin & Velou 2003).

Iatrogenic corneal ectasia

Iatrogenic corneal ectasia is a relatively rare but serious complication after refractive surgery for myopia. It has most commonly been reported after LASIK surgery (Argento et al 2001; Faraj et al 2003; Iskander et al 2000; Twa et al 2004) and has also been reported after excimer laser photorefractive keratoplasty (Parmar & Claoué 2004), deep lamellar keratoplasty (Patel et al 2003) and repeated radial keratotomy (Wellish et al 1994). Corneal ectasia after LASIK is characterised by worsening best corrected visual acuity, increased astigmatism and myopia, corneal toricity and corneal steepening (Twa et al 2004). It is thought to occur spontaneously if the corneal bed left after LASIK is too thin (less than 250 μm) and insufficient residual stroma (less than 50%) remains (Argento et al 2001; Melki & Azar 2001; Palliarkis et al 2001; Sugar et al 2002), or if the cornea is predisposed to distortion, such as in previously undiagnosed cases of keratoconus or PMD (Chiang et al 2003; Comaish & Lawless 2002; Fogla et al 2003; Piccoli et al 2003; Seiler & Quurke 1998; Seitz et al 2003; Sugar et al 2002; Twa et al 2004).

The most common treatments for iatrogenic corneal ectasia are rigid gas-permeable contact lenses and penetrating keratoplasty (Iskander et al 2000; Melki & Azar 2001; Twa et al 2004). In general, further laser treatments are contraindicated due to the thinness of the cornea (Johnson & Azar 2001). Epikeratoplasty may also be offered (Seiler & Quurke 1998).

Non-iatrogenic corneal ectasia

Non-iatrogenic corneal ectasias include PMD, Terrien's marginal degeneration and keratoglobus (although this is sometimes considered a form of keratoconus) (Krachmer et al 1984). PMD is a bilateral progressive non-inflammatory corneal ectasia that causes a crescent-shaped thinning of the inferior cornea (Sii et al 2004; Sridhar et al 2004) with a 1 to 2 mm area of normal cornea between the limbus and the ectatic portion of the cornea (Rasheed & Rabinowitz 2000). PMD typically results in reduced visual acuity due to high irregular astigmatism, and may also be associated with an increased occurrence of hydrops and perforation (Sridhar et al 2004).

Moderate PMD may be treated with rigid gas-permeable contact lenses; however, like keratoconus, for more advanced cases penetrating keratoplasty is indicated (Sridhar et al 2004). Other surgical procedures that have been tried with varying degrees of success are crescentic wedge resection, crescentic lamellar keratoplasty, epikeratophakia, thermokeratoplasty, or combinations of these treatments (for example, peripheral lamellar keratoplasty and central penetrating keratoplasty). However, a definitive treatment has yet to emerge (Rasheed & Rabinowitz 2000; Sridhar et al 2004).

Clinical need / burden of disease

Keratoconus

Incidence and prevalence

The incidence and prevalence of keratoconus in Australia are difficult to establish. In international studies, the number of people in the general population thought to have keratoconus is usually estimated to be around 1 in 2,000 (50 in 100,000) and each year around 2 in 100,000 new cases of keratoconus are diagnosed (Kennedy et al 1986; Kymes et al 2004). In Australia, this equates to around 10,000 people living with keratoconus and around 400 new cases of keratoconus per year. As keratoconus is usually bilateral, this means around 20,000 eyes have keratoconus in Australia and around 800 eyes are diagnosed with keratoconus each year. Of the 14,000 grafts registered with the Australian Corneal Graft Registry since 1987, one-third were for keratoconus (Williams et al 2004).

Quality of life

Quality of life in patients with keratoconus has been studied by the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study group, which has collected data on over 1,200 patients with keratoconus in the United States since 1995 (Kymes et al 2004). The National Eye Institute – Visual Function Questionnaire[1] was completed by 96.4 per cent of study participants and results were compared to a reference group of rigid contact lens wearers (without keratoconus) of similar age. On all scales the keratoconus group had statistically significant lower mean scores than the reference group; however, patients wearing a contact lens in at least one eye had significantly higher scores except on the ocular pain scale. Those with a corneal graft in one eye had higher general vision scores, but were otherwise similar to patients who did not have a corneal graft. Corneal scarring was associated with lower scores for mental health, near activities, dependency and ocular pain, and higher distance activities scores. Overall the study found that keratoconus patients reported worse functional vision than would be expected from their clinically assessed loss of visual acuity. The results for patients with keratoconus were found to be similar to those for patients with advanced age-related macular degeneration. As the authors conclude, 'Keratoconus is a disease of relatively low prevalence that rarely results in blindness, but its impact on the public health is well in excess of either its prevalence or its clinical severity' (Kymes et al 2004, p533).

Iatrogenic corneal ectasia

The incidence of iatrogenic corneal ectasia after LASIK has not been studied extensively, but a review of the literature in 2003 found 83 cases in 21 separate reports (Seitz et al 2003). One retrospective study of 2,873 eyes that had LASIK surgery in Greece between 1995 and 1999 found that 19 eyes (0.7%) had developed corneal ectasia (Pallikaris et al 2001). Improvements in surgical practice over time as experience increases, and

[1] The National Eye Institute – Visual Function Questionnaire is a disease-specific quality of life instrument that measures perception of visual function in terms of general health and vision, ocular pain, near and distance activities, driving, colour vision and peripheral vision. Psychosocial wellbeing is indicated by the relationship between social function, mental health, role difficulties and dependency.

refinement of selection criteria to exclude patients with a predisposition to corneal thinning, could lead to a reduction in the incidence of iatrogenic corneal ectasia in the future.

Non-iatrogenic corneal ectasia

Non-iatrogenic corneal ectasias other than keratoconus are rare and the incidence is difficult to determine and likely to be underestimated as they may be mistaken for keratoconus (Rasheed & Rabinowitz 2000).

Existing procedures

Contact lenses and spectacles

In keratoconus and ectasia the corneal morphology is abnormal and irregular astigmatism is usually present. Spectacles may thus be of limited benefit as they cannot conform to the shape of the cornea (Rabinowitz 1998). By comparison, contact lenses provide a regular refractive surface and can reduce irregular astigmatism (Krachmer et al 1984). For mild and moderate keratoconus and ectasia soft contact lenses may be sufficient, but for severe cases rigid gas-permeable contact lenses are a more useful option. Some patients may also find hybrid or piggyback lenses (in which a soft hydrogel lens is combined with a rigid gas-permeable lens) a useful option (Rabinowitz 1998; Smiddy et al 1988; Zadnik et al 1998). In the CLEK study rigid gas-permeable contact lenses were the primary method for correcting vision in keratoconus and were used by 73 per cent of patients (Kymes et al 2004).

Penetrating keratoplasty

Penetrating keratoplasty (PKP) is a full thickness corneal graft in which the central button of the cornea is replaced by donated corneal tissue. The donor graft is punched from the endothelial surface using a hand-held trephine (Rao et al 1999) and the recipient bed trephinated either at the same size as or slightly smaller than the graft, depending on the vitreous cavity length (Brahma et al 2000). The cornea is then sutured into place with 10-0 nylon using an interrupted or running suture. Postoperative treatment with topical antibiotics and steroids is tailored to the individual patient. Sutures are generally removed from around three months postoperatively to reduce astigmatism (Brahma et al 2000), although in Australia they are typically removed at around 12 months postoperatively.

The lifetime risk of a keratoconus patient requiring PKP is between 10 per cent and 20 per cent (Cohen & Parlato 1986; Kennedy et al 1986; Smiddy et al 1988; Tuft et al 1994). Disadvantages of treating keratoconus with PKP include graft rejection, loss of endothelial cells and recurrence of keratoconus (Siganos, C.S. et al 2003). Patients may also experience residual myopia and astigmatism requiring contact lenses (Rabinowitz 1998). Recovery of visual acuity may be slow and usually each eye must be treated separately.

Deep lamellar keratoplasty

Deep lamellar keratoplasty is an alternative to PKP that preserves the endothelium and thus minimizes the loss of endothelial cells; it also avoids problems with graft rejection because the immunological integrity of the eye is retained (Colin & Velou 2003; Watson 2004). The cornea is trephinated down to two-thirds of the corneal thickness, an incision made with a diamond knife to two-thirds of the corneal depth, and a lamellar dissection performed as close as possible to Descemet's membrane (Colin & Velou 2003; Trimarchi 2001). The stroma is separated from the membrane with an injection of air and/or fluid (Amayem & Anwar 2000; Coombes et al 2001) or with a gliding rotating movement (Trimachi et al 2001). The corneal button is sutured into place with a 10-0 nylon suture that is removed after three to six months. Alternatively a corneal flap is created with a microkeratome and the donor corneal button is transplanted and covered by the corneal flap before being sutured into place (Bilgihan et al 2003; Jain & Azar 2001).

Comparators

The main comparator to ICRS implantation is PKP. Deep lamellar keratoplasty and continued treatment with contact lenses are alternative comparators. Refractive surgery such as keratotomy, LASIK and excimer laser ablation have been attempted, but none of these have been found to be acceptable treatments for keratoconus or ectasias because they weaken the already thin cornea (Colin & Velou 2002; Hladun & Harris 2004). At the present time ICRS are generally offered to patients who are contact lens intolerant and who are suitable candidates for PKP. However, there may be some patients who would not choose to have an invasive surgical procedure such as PKP, even if contact lenses were no longer effective in improving visual acuity. For these patients watchful waiting (or continued use of contact lenses) may be the appropriate comparator for ICRS implantation. It is not certain whether ICRS will halt the progression of keratoconus and ectasia, and therefore whether patients will later require a further definitive treatment (probably PKP). Consequently, ICRS may be seen as a treatment that delays the need for surgery rather than offering a true alternative.

Marketing status of the device

Ferrara ring segments do not appear to be available in Australia; they seem to be most commonly used in South America and parts of Europe.

Intacs inserts are approved by the Therapeutic Goods Administration (Australian Register of Therapeutic Goods number 94199, product number 164824) Class IIb.

Intacs inserts received a humanitarian device exemption (HDE) from the United States Food and Drug Administration. HDEs are granted to devices intended for treating conditions that affect fewer than 4,000 patients. HDE status acknowledges that the effectiveness of the device has not been shown. Addition Technology Inc. is required to state the following in marketing and promoting Intacs inserts for treating keratoconus:

> Humanitarian Device: Authorized by U.S. Federal law for use in the treatment of nearsightedness and astigmatism associated with keratoconus. The effectiveness of this device for this use has not been demonstrated.

Current reimbursement arrangement

There is currently no relevant Medicare Benefits Schedule (MBS) item for ICRS implantation. The relevant MBS item numbers for corneal transplants are shown in Table 1, including services such as running corneal sutures. The number of services for the last financial year for full thickness corneal transplants and lamellar grafts (partial thickness corneal transplants) are shown in Table 2.

Table 1 2004 Medicare Benefits Schedule of fees for corneal transplant, sutures and incisions

Category	Item number	Fee
Cornea, transplantation of, full thickness (Anaes.) (Assist.)	42653	$1,135.70
Cornea, transplantation of, second and subsequent procedures (Anaes.) (Assist.)	42656	$1,416.50
Cornea, transplantation of, superficial or lamellar (Anaes.) (Assist.)	42659	$765.65
Corneal sutures, removal of, not earlier than 6 weeks after operation requiring use of slit lamp or operating microscope (Anaes.)	42668	$63.60
Running corneal sutures, manipulation of, performed within 4 months of corneal grafting, to reduce astigmatism where a reduction of 2 dioptres of astigmatism is obtained, including any associated consultation	42667	$120.45

Source: MBS Book 1 November 2004 and 1 May 2005 Supplement

Table 2 Number of services in Australia by states and territories, July 2003 to June 2004 (MBS)

Item	NSW	Vic	Qld	SA	WA	Tas	NT	ACT	Total
42653	257	145	179	34	40	21	4	11	691
42659	29	1	7	8	1	0	0	1	47
Total	286	146	186	42	41	21	4	12	738

Source: http://www.hic.gov.au/statistics/dyn_mbs/forms/mbs_tab4.shtml

Approach to assessment

Review of literature

The medical literature was searched to identify relevant studies for the period between 1996 and March 2005. Searches were conducted via Medline, EMBASE, Current Contents, PubMed and the Cochrane Library. Also searched were the York (UK) Centre for Reviews and Dissemination databases, Clinicaltrials.gov, National Research Register, relevant online journals and the Internet. Searches were conducted without language restriction.

The search terms used were Intacs OR Ferrara OR (intrastromal corneal ring* or intrastromal corneal ring segment*) AND keratoconus/ OR (corneal ectasia or keratoectasia or keratectasia).

Articles were retrieved if they were judged to possibly meet the inclusion criteria. Two reviewers independently applied the inclusion criteria and any differences were resolved by discussion. Excluded studies are listed in Appendix C with reasons for exclusion. The bibliographies of all retrieved publications were hand searched for any relevant references missed in the database search (pearling).

As it was anticipated that the database searches would yield very little evidence, hand searching of the following online conference proceedings was also undertaken:

- Annual Symposium on Cataract, IOL and Refractive Surgery (2002, 2003, 2004)
- Joint Meeting of the American Academy of Ophthalmology and European Society of Ophthalmology (2004, 2003, 2002, 2001)
- Association for Research in Vision and Ophthalmology Annual Meeting (2002, 2003, 2004)
- International Congress of Eye Research (2003, 2004).

Inclusion criteria

Participants

Human studies of patients with myopia and astigmatism secondary to keratoconus (ie a non-inflammatory self-limiting ectasia of the axial portion of the cornea), iatrogenic corneal ectasia secondary to refractive surgery, or non-iatrogenic corneal ectasia (PMD, keratoglobus or Terrien's marginal degeneration) were included. Patients with primary myopia and astigmatism (ie not secondary to keratoconus) or corneal conditions that were not ectasias but rather corneal opacification (such as Fuch's dystrophy, keratitis,

pseudo-phakic bullous keratopathy, aphakic bullous keratopathy, corneal dystrophy and oedema)[2] were excluded.

New intervention

Included studies related to the use of intrastromal corneal ring segments (Intacs prescription inserts or Ferrara ring segments). Studies relating to ICRS implantation performed at the same time as other surgery (eg lamellar keratoplasty or LASIK) were excluded.

Comparative intervention

There are three potential comparators for ICRS surgery. The primary comparator is PKP (ie full thickness corneal transplant). Other possible comparators are deep lamellar transplant (ie partial, half or three-quarter corneal transplant) and continued use of contact lenses.

Outcomes

Studies were included if they contained information on at least one of the following outcomes:

- peri- and postoperative morbidity
- uncorrected and best corrected visual acuity, refractive outcome or keratometric outcome
- explantation of implants (after complication or dissatisfaction)
- delay of corneal transplant surgery
- successful use of contact lenses following ICRS implantation
- patient satisfaction
- costs and resource use.

Types of studies

Randomised controlled trials, other controlled or comparative studies and case series were included. Conference abstracts and manufacturer's information were included if they contained relevant safety and effectiveness data. The English abstracts from foreign language articles were included if they met the study inclusion criteria and contained safety and effectiveness data. In the case of duplicate publications, the latest and most complete study was included.

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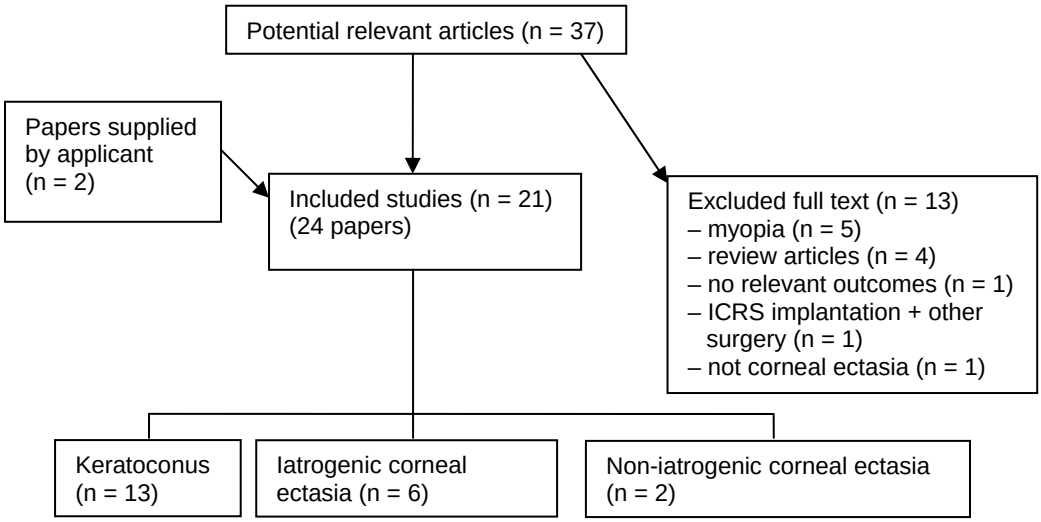
[2] These lists of conditions are based on the American Academy of Ophthalmology 2000 report *Preferred practice pattern for corneal opacification and ectasia*, American Academy of Ophthalmology, San Francisco.

Results of search

The database searches located 37 potentially relevant articles, of which 22, representing 19 unique studies, were included and 13 were excluded (see Appendix C). The applicant supplied two manuscripts regarding keratoconus patients; one of these is in press (Colin in press) and the other is currently unpublished but has been submitted (Colin et al unpub.). These were included with the keratoconus studies located from the database searches, making a total of 21 included studies. The results of the searches are shown in Figure 3.

Figure 3 Flowchart of search results



Conference proceedings

Hand searching of conference proceedings identified a further 19 studies that met the inclusion criteria (two separate presentations reporting the same study were identified, and four abstracts that have since been published in full are included in this review as full publications). Outcomes from these studies are reported separately at the end of the results section and tabulated in Appendix F (13 excluded abstracts are also listed in Appendix F).

Data extraction and synthesis

The evidence presented in the selected studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC 2000).

These dimensions (Table 3) consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of the determination.

Table 3 Evidence dimensions

Type of evidence	Definition
Strength of evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design[a]
Quality	The methods used by investigators to minimise bias within a study design
Statistical precision	The p-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used

[a] See Table 4

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in Table 4.

Table 4 Designations of levels of evidence[a]

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials
II	Evidence obtained from at least one properly designed randomised controlled trial
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method)
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies or interrupted time series with a control group
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies or interrupted time series without a parallel control group
IV	Evidence obtained from case series, either post-test or pre-test/post-test

[a] Modified from NHMRC (1999)

Data were extracted by one researcher and checked by a second using standardised data extraction tables developed a priori. Included studies were critically appraised for study quality according to the guidelines in *Cochrane reviewers' handbook* (Alderson et al 2004, ch. 6). Included randomised controlled trials were to be examined for adequacy of allocation concealment and blinding (if possible), handling of losses to follow-up and any other aspect of the study design or execution that may have introduced bias. Non-randomised comparative studies were to be evaluated for the method of patient selection, comparability of the patient groups, completeness of follow-up and any other feature of the study design or execution that may have introduced bias. Case series were examined with respect to the use of consecutive patient selection, losses to follow-up and reporting of outcomes. Two reviewers critically appraised each of the included studies, and any differences in interpretation were resolved through discussion. A quality score was not assigned; instead the quality of the included studies was described in a narrative fashion, and any important quality issues were highlighted in the discussion of outcomes. Meta-analyses of main outcomes were not undertaken as it was judged there were no data suitable for statistical pooling.

Expert advice

An advisory panel with expertise in ophthalmology, refractive surgery and visual problems caused by corneal conditions was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for advisory panels, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the advisory panel is provided at Appendix B.

Results of assessment

Studies included in the review

No randomised controlled trials or other comparative studies were identified. For keratoconus, the main search identified 10 case series studies and one case report; two additional manuscripts (Colin in press; Colin unpub.) were supplied by the applicant. For iatrogenic corneal ectasia, five case series studies and one case report were identified, and for non-iatrogenic corneal ectasia two case reports were located, both for patients with PMD. The included studies are summarised in Table 5 and Appendix E. Where more than one report for a single study exists, all relevant references are shown in the table but the underlined reference was used as the main resource.

Table 5 Studies included in the review

Study	Device	Design	Dates	Number of eyes/patients	Follow-up (months)
Keratoconus					
Alio et al 2004 *SPAIN*	Intacs	Case series	Feb 00 – Dec 03	5 eyes/4 patients	15.5
Boxer Wachler et al 2003[a], Chou & Boxer Wachler 2000 *USA*	Intacs	Case series	Dec 99 – May 01	74 eyes/50 patients	9
Colin et al 2001[b], Colin et al 2000 *FRANCE*	Intacs	Case series	Not stated	10 eyes/10 patients	10.6
Colin in press[b] *FRANCE*	Intacs	Case series	Not stated	100 eyes/82 patients	24
Colin et al unpub.[b] *EUROPE* (multicentre study)	Intacs	Case series	Not stated	57 eyes	6
Hofling-Lima et al 2004[c] *BRAZIL*	Ferrara	Case series	Dec 00 – Jan 02	7 eyes/7 patients	Up to 24
Kwitko & Severo 2004 *BRAZIL*	Ferrara	Case series	Not stated	51 eyes/47 patients	13
Miranda et al 2003[c] *BRAZIL*	Ferrara	Case series	Not stated	36 eyes/35 patients	12
Nepomuceno et al 2003[a] *USA*	Intacs	Case series	Apr 00 – Apr 02	3 eyes/3 patients	0.5–6.6
Siganos, C.S. et al 2003 *GREECE*	Intacs	Case series	Not stated	33 eyes/26 patients	11.3
Siganos, D. et al 2002 *GREECE*	Ferrara	Case series	Not stated	26 eyes/26 patients	6
Tunc et al 2003 (French language) *TURKEY*	Intacs	Case series	Dec 98 – Jun 00	9 eyes/7 patients	36.6
Hladun & Harris 2004 *USA*	Intacs	Case report	Not stated	1 eye/1 patient	3

[a] There may be patient overlap between these two studies
[b] There may be patient overlap among these three studies
[c] There may be patient overlap between these two studies

Table 5 continued

Study	Device	Level	Dates	Number of eyes/patients	Follow-up (months)
Iatrogenic corneal ectasia					
Alio et al 2002 *SPAIN*	Intacs	Case series	Not stated	3 eyes/2 patients	8.3
Guell et al 2004 *SPAIN*	Intacs	Case series	Not stated	5 eyes	6
Kymionis et al 2003, Siganos, D et al 2002 *GREECE*	Intacs	Case series	Not stated	10 eyes/7 patients	15
Lovisolo & Fleming 2002 *ITALY*	Intacs & Ferrara	Case series	Jan 00 – Jan 02	4 eyes/4 patients	0.5–17
Pokroy et al 2004 *ISRAEL*	Intacs	Case series	During 2002	5 eyes/5 patients	At least 9
Shehadeh-Masha'our et al 2004 *ISRAEL*	Intacs	Case report	Sep 02	1 eye/1 patient	Immediate postoperative
Non-iatrogenic corneal ectasia					
Kymionis et al 2004 *GREECE*	Intacs	Case report	Not stated	1 eye/1 patient	3
Rodriguez-Prats et al 2003 *SPAIN*	Intacs	Case report	Not stated	1 eye/1 patient	3

Critical appraisal

This body of evidence is both relatively sparse and poor. For keratoconus there are 412 eyes, for iatrogenic corneal ectasia there are 36 eyes and for non-iatrogenic corneal ectasia there are two eyes. There may be a significant amount of patient overlap between studies; however, as dates for the studies were rarely reported and authors did not comprehensively reference previous reports of the same patients it is not possible to determine the extent of double reporting. In most studies it is not clear whether all patients presenting for treatment were given ICRS rather than PKP or whether some patients were considered suitable for ICRS and others (not reported in the studies) were considered better candidates for PKP or another treatment. In general, outcomes were relatively well reported, although it is not always clear whether all eyes in a series contributed data to all outcomes. Patient-relevant outcomes (such as functional vision or quality of life) were rarely reported, with most studies concentrating on improvements in visual acuity, astigmatism and keratometry. No data were identified regarding durability of ICRS, delay in need for PKP, impact on disease progression or costs and resource use. Length of follow-up was relatively short (no more than three years).

Several included papers reported subgroups of patients with specific outcomes such as explantation or a particular complication. Although all studies are shown in Table 5, the results from these studies are reported separately as the patients were specifically selected from a sample of patients receiving ICRS. Alio et al (2004) reported five eyes in four keratoconus patients who were explanted and the subsequent outcomes for two of the five who were reimplanted with Intacs implants. Hofling-Lima et al (2004) reported seven eyes in seven keratoconus patients with culture-proven infectious keratitis after Ferrara implantation. Nepomuceno et al (2003) reported three eyes in three keratoconus patients who were referred for contact lens fitting after Intacs implantation. Hladun & Harris (2004) also reported a patient who received contact lens fitting after Intacs implantation.

Is it safe?

Complications

No intraoperative complications were reported in seven studies of keratoconus patients (Boxer Wachler et al 2003; Colin 2001 et al; Colin in press; Colin et al unpub.; Siganos, C.S. et al 2003; Siganos, D. et al 2002; Tunc et al 2003), four studies of iatrogenic corneal ectasia (Guell et al 2004; Kymionis et al 2003; Lovisolo & Fleming 2002; Shehadeh-Masha'our et al 2004) and two studies of non-iatrogenic corneal ectasia (Kymionis et al 2004; Rodriquez-Prats et al 2003).

The studies do not report postoperative complications consistently (Table 6). For keratoconus patients, rates of complications ranged from 3 per cent to 39 per cent in six studies (Boxer Wachler et al 2003; Colin et al 2001; Colin et al unpub.; Kwitko & Severo 2004; Miranda et al 2003; Siganos, C.S. et al 2003), but varied depending on how complications were defined (if visual problems were considered complications, the rate tended to be higher). In general, lamellar channel deposits at the edge of the ICRS were not considered to be complications. For non-keratoconus indications there were fewer complications but also far fewer patients reported.

Hofling-Lima et al (2004) (not shown in Table 6) reported culture-proven infectious keratitis in seven eyes in seven keratoconus patients who received Ferrara ICRS. It is not clear what proportion of the total ICRS patient sample these seven patients represent; however, it is possible they are part of the series of 36 eyes reported by Miranda et al (2003). Hofling-Lima et al (2004) noted that three of the patients had identifiable risk factors for infection, including contact lens use, trauma and diabetes, but that the other four patients had no identifiable risk factors. Infection developed after less than one week postoperatively in two eyes, between two and four weeks postoperatively in two eyes and after more than eight weeks postoperatively in three eyes. Four of the seven eyes required exploration of the Ferrara segments to control infection, and two of those eyes went on to have PKP. Hofling-Lima et al (2004) suggest that the triangular shape and depth of the Ferrara implant may lead to superficialisation of the ICRS segments, particularly in thin keratoconic corneas. They also propose that the multiple incisions required to insert Ferrara segments may increase the risk of wound infection.

Shehadeh-Masha'our et al (2004) (included in Table 6) reported a case of a patient with post-LASIK corneal ectasia who received Intacs implants in one eye. The patient experienced a complicated postoperative infection that was not controlled until the patient had been twice hospitalised. The final outcome was a neovascularised opacity in the nasal part of the lower channel and best corrected visual acuity of 0.3 logMAR (logarithm of the minimum angle of resolution).

Table 6 Postoperative complications in included studies (where complications reported)

Study	n/N eyes	%	Complications
Keratoconus			
Boxer Wachler et al 2003	4/74	5.4	Superficial channel dissection and anterior Bowman's layer perforation (1 eye), transient inflammatory reaction (2 eyes), segment migration and externalisation (1 eye), night halos (2 patients) There were no cases of keratolysis infection or anterior chamber perforation
Colin et al 2001	10 eyes	NA	Most eyes had mild to moderate intralamellar channel deposits at superior edge of inferior segment (there were no cases of neovascularisation)
Colin et al unpub.	10/34	29.4	Severe conjunctival infection (1 eye), discomfort (1 eye), itching (1 eye), burning (1 eye), photophobia (1 eye), difficulty with night vision (1 eye), glare (3 eyes), fluctuating vision (1 eye) There were no cases of ocular infection, extrusion or stromal thinning
Kwitko & Severo 2004	14/51	27.4	Ring decentration due to blunt trauma (2), ring extrusion (10), disciform keratitis (1), presumed bacterial keratitis after ring extrusion (1)
Miranda et al 2003	14/36	38.9	Segment decentration (1), segment asymmetry (2), segment migration (2), segment extrusion (5), conjunctivitis (1), hydrops (1), infection (1), inadequate depth of placement (2)
Siganos, C.S. et al 2003	1/33	3.0	Superficial mild wound site neovascularisation (1 eye) Most eyes had channel deposits at inner edge of segments by 6 months
Iatrogenic corneal ectasia			
Guell et al 2004	1/5	–	Progressive stromal lysis Dry eye symptoms in some patients for 3–6 weeks
Kymionis et al 2003	2/10	–	Superficial mild wound site neovascularisation Most eyes had mild channel deposits at inner edge of segments after 9 months
Lovisolo & Fleming 2002	0/4	0.0	No intraoperative or postoperative complications
Pokroy et al 2004	–	–	No flap disruption, no corneal buttonholing, no segment extrusion
Shehadeh-Masha'our et al 2004	Case report	NA	Complicated diffuse keratitis requiring hospitalisation
Non-iatrogenic corneal ectasia			
Rodriguez-Prats et al 2003	Case report	NA	No refractive or surgical complications; at 3 months inferior segment migration and minute crystalline deposits, halos and epithelial cysts within incision

Abbreviations: NA – not applicable; n/N – number affected over total number

Explantations

Explantation (the removal of ICRS) occurs if the outcome is not considered successful, either by the patient or the treating physician. Explantations and reasons (when given) are shown in Table 7. Rates of explantation for keratoconus patients ranged from 4 per cent to 25 per cent (median 10%) in nine studies (Boxer Wachler et al 2003; Colin et al 2001; Colin in press; Colin et al unpub.; Kwitko & Severo 2004; Miranda et al 2003; Siganos, C.S. et al 2003; Siganos, D. et al 2002; Tunc et al 2003). Reasons for explantation included dissatisfaction with vision in 18 eyes, segment extrusion or decentration in eight eyes, chronic foreign body sensation in four eyes, superficial or incorrect placement in four eyes and hyperopia in two eyes (in one patient). There were two cases of explantation after ICRS implantation for iatrogenic corneal ectasia (Guell et al 2004; Shehadeh-Masha'our et al 2004).

Table 7 Explantations in included studies

Study	n/N eyes	%	Reasons
Keratoconus			
Boxer Wachler et al 2003	6/74	8.1	Hyperopia (2 eyes/1 patient), chronic foreign body sensation (4 eyes/2 patients)
Colin et al 2001	1/10	–	Superficial placement; explantation at 2 months
Colin in press	4/100	4.0	Extrusion of one segment (2), poor visual outcome (2) → both patients had PKP after explantation
Colin et al unpub.	7/57	12.3	Dissatisfaction with vision
Kwitko & Severo 2004	13/51	25.5	No improvement in best corrected visual acuity (3), segment extrusion (5), dissatisfaction with visual acuity (4), segment decentration (1) → all patients had PKP after explantation
Miranda et al 2003	3/36	8.3	No reasons given → 2 eyes had PKP after explantation
Siganos, C.S. et al 2003	2/33	6.1	Patient dissatisfaction (2 eyes both segments); in 1 eye 1 segment removed and the other adjusted
Siganos, D. et al 2002	2/26	7.6	Superficial placement (1), incorrect placement (1)
Tunc et al 2003	1/9	–	Superficial placement
Iatrogenic corneal ectasia			
Guell et al 2004	1/5	–	Progressive stromal lysis
Shehadeh-Masha'our et al 2004	Case report	–	To control infection; both segments explanted

Abbreviations: n/N – number affected over total number; PKP – penetrating keratoplasty

Alio et al (2004) reported five eyes in four patients who required explantation of Intacs implants identified from a retrospective chart review. The size of the patient sample from which these four patients were drawn was not reported. All five eyes were successfully explanted. Reasons for explantation were segment migration and partial extrusion with moderate corneal melting in four eyes, and segment migration with significant corneal thinning and melting in one eye. In three eyes there was no improvement in visual acuity after Intacs implantation, and visual acuity remained at the post-implant level after explanation. Two eyes were reimplanted with Intacs six months after explantation. In both eyes visual acuity worsened after the initial implantation but returned to preimplant levels after explantation. In both eyes there was an improvement in uncorrected visual acuity after reimplantation, but only one eye experienced an improvement in best corrected visual acuity after reimplantation.

Is it effective?

Visual acuity

Visual acuity was reported as the postoperative mean or number of lines of change in visual acuity. The measure was either the mean change or the proportion of eyes/patients with a particular gain or loss of lines. Mean visual acuity is reported in this review in logMAR units (logarithm of the minimum angle of resolution) and all original data have been converted to logMAR units using the visual acuity conversion chart of Holladay (2004) (see Appendix D). Normal visual acuity is 0.00 logMAR (equivalent to 20/20 vision).

Best corrected visual acuity

The mean best corrected visual acuity (BCVA) in logMAR improved in all studies. Mean postoperative BCVA ranged from 0.20 logMAR to 0.42 logMAR (median of means 0.22 logMAR) in five studies of keratoconus (Boxer Wachler et al 2003; Colin et al 2001; Kwitko & Severo 2004; Siganos, C.S. et al 2003; Siganos, D. et al 2002) and from 0.10 logMAR to 0.35 logMAR (median of means 0.23 logMAR) in four studies of iatrogenic corneal ectasia (Alio et al 2002; Guell et al 2004; Lovisolo & Fleming 2002; Pokroy et al 2004). For keratoconus patients, mean preoperative to postoperative change ranged from 1 line to 5.5 lines of improvement (median of means 1.9 lines) in four studies (Boxer Wachler et al 2003; Colin et al 2001; Kwitko & Severo 2004; Siganos, C.S. et al 2003), and for iatrogenic corneal ectasia from no lines to 4.5 lines of improvement (median of means 1.0 line) in five studies (Alio et al 2002; Guell et al 2004; Kymionis et al 2003; Lovisolo & Fleming 2002; Pokroy et al 2004) (see Table 8).

Table 8 Mean BCVA after ICRS implantation

Study	Number of eyes	Follow-up (months)	BCVA preop (logMAR)	BCVA postop (logMAR)	Mean change in lines	p-value
Keratoconus						
Boxer Wachler et al 2003	74	9	0.41 [0.48]	0.24 [0.31]	+2 (-5 to +10)	0.0004
Colin et al 2001	10	12	0.38 [0.13]	0.22 [0.12]	+1	NR
Kwitko & Severo 2004	51	13	0.95 [0.47]	0.42 [0.25]	+5.5 (-3 to +16)	NR
Siganos, C.S. et al 2003	33	11	0.35 [0.50]	0.20 [0.60]	+1.7 (-2 to +6)	<0.01
Siganos, D. et al 2002	26	6	0.40 [0.54]	0.20 [0.70]	NR	NR
Tunc et al 2003	9	24	2.45 lines/10 [2.15]	5.66 lines/10 [2.18]	NR	NR
Iatrogenic corneal ectasia						
Alio et al 2002	3	6	0.25 (0.2 to 0.3)	0.25 (0.2 to 0.3)	0	NR
Guell et al 2004	5	6	0.32 [0.10]	0.22 [0.04]	+1.0 (0 to +2)	NR
Kymionis et al 2003	10	15	NR	NR	+1.0 (0 to +2)	NR
Lovisolo & Fleming 2002	4	0.5–17	0.80 [0.40]	0.35 [0.26]	+4.5 (+1.8 to +7)	NR
Pokroy et al 2004	5	9	0.28 (0.1 to 0.4)	0.10 (0.0 to 0.2)	+1.8 (+1 to +3)	NR
Non-iatrogenic corneal ectasia						
Kymionis et al 2004	Case report	11	0.40	0.10	–	–
Rodriguez-Prats et al 2003	Case report	3	1.00	0.50	–	–

Abbreviations: BCVA – best corrected visual acuity; logMAR – logarithm of the minimum angle of resolution; NR – not reported; ( ) – range; [ ] – standard deviation

For keratoconus patients, a gain of between 1 and 8 lines was reported for between 45 per cent and 88 per cent of eyes (median 67%), no change was reported for between 2 per cent and 51 per cent of eyes (median 20%), and a loss of at least 1 line was reported for between 0 per cent and 15 per cent of eyes (median 8%) in six studies (Boxer Wachler et al 2003; Colin in press; Colin et al unpub.; Kwitko & Severo 2004; Miranda et al 2003; Siganos, C.S. et al 2003). In two studies of iatrogenic corneal ectasia including a total of 15 eyes, six eyes experienced a gain of at least 1 line, five eyes experienced no change, and four eyes experienced a loss of 2 lines (Guell et al 2004; Kymionis et al 2003) (see Table 9).

Table 9 Proportion of eyes with a gain or loss of BCVA after ICRS implantation

Study	Number of eyes	Follow-up (months)	Change in BCVA from preoperative		
			Change in lines	n/N	%
Keratoconus					
Boxer Wachler et al 2003	74	9	≥+2 none ≥-2	33/74 38/74 3/74	45 51 4
Colin in press	82 patients	24	+1 to 5 none -1 to 4	56/82 21/82 12/82	68 26 15
Colin et al unpub.[a]	34	6	+2 to 8 none ≥-2	21/34 11/34 2/34	62 32 6
Kwitko & Severo 2004	51	13	improvement no change deterioration	45/51 1/51 5/51	88 2 10
Miranda et al 2003	31	12	≥+2 none ≥-2	27/31 4/31 0/31	87 13 0
Siganos, C.S et al 2003	33	13	+1 to 6 none -1 to 2	25/33 4/33 4/33	66 12 12
Iatrogenic corneal ectasia					
Guell et al 2004	5	6	+2 +1 none	2/5 1/5 2/5	– – –
Kymionis et al 2003	10	15	+1 none -2	3/10 3/10 4/10	– – –

Abbreviations: BCVA – best corrected visual acuity; n/N – number affected over total number

[a] 23 eyes lost to follow-up

Uncorrected visual acuity

The mean uncorrected visual acuity (UCVA) in logMAR improved in all studies. Mean postoperative UCVA ranged from 0.35 logMAR to 0.74 logMAR (median of means 0.40 logMAR) in five studies of keratoconus (Boxer Wachler et al 2003; Colin et al 2001; Kwitko & Severo 2004; Siganos, C.S. et al 2003; Siganos, D. et al 2002), and from 0.32 logMAR to 0.53 logMAR (median of means 0.33 logMAR) in four studies of iatrogenic corneal ectasia (Alio et al 2002; Guell et al 2004; Lovisolo & Fleming 2002; Pokroy et al 2004). Mean change for keratoconus patients ranged from 2 lines to 6.5 lines of improvement (median of means 2.7 lines) in four studies (Boxer Wachler et al 2003; Colin et al 2001; Kwitko & Severo 2004; Siganos, C.S. et al 2003), and for iatrogenic corneal ectasia from 4 lines to 10.2 lines of improvement (median of means 7.4 lines) in five studies (Alio et al 2002; Guell et al 2004; Kymionis et al 2003; Lovisolo & Fleming 2002; Pokroy et al 2004) (see Table 10).

For keratoconus patients a gain of between 1 and 10 lines was reported for between 72 per cent and 85 per cent of eyes (median 81%), no change was reported for between 8 per cent and 21 per cent of eyes (median 9%), and a loss of at least 1 line was reported for between 0 per cent and 9 per cent of eyes (median 6%) in six studies (Boxer Wachler et al 2003; Colin in press; Colin et al unpub.; Kwitko & Severo 2004; Miranda et al 2003; Siganos, C.S. et al 2003). In two studies of iatrogenic corneal ectasia including a total of 15 eyes, 14 eyes experienced a gain of at least 5 lines, and one eye experienced no change (Guell et al 2004; Kymionis et al 2003) (see Table 11).

Table 10 Mean UCVA after ICRS implantation

Study	N of eyes	Follow-up (months)	UCVA preop (logMAR)	UCVA postop (logMAR)	Mean change in lines	p-value
Keratoconus						
Boxer Wachler et al 2003	74	9	1.05 [0.48]	0.61 [0.52]	+3 (-7 to +18)	0.0001
Colin et al 2001	10	12	1.05 [0.33]	0.35 [0.16]	+2	<0.05
Kwitko & Severo 2004	51	13	1.37 [0.36]	0.74 [0.40]	+6.5 (-4 to +15)	NR
Siganos, C.S. et al 2003	33	11	0.90 [0.90]	0.40 [0.56]	+2.5 (-1 to +10)	<0.01
Siganos, D. et al 2002	26	6	1.18 [1.00]	0.40 [0.70]	NR	NR
Tunc et al 2003	9	24	0.41 lines/10 [0.28]	3.73 lines/10 [2.70]	NR	NR
Iatrogenic corneal ectasia						
Alio et al 2002	3	6	0.76 (0.6 to 1.0)	0.35 (0.3 to 0.4)	+4 (+4 to +6)	NR
Guell et al 2004	5	6	1.34 [0.61]	0.32 [0.20]	+10.2 (+5 to +18)	NR
Kymionis et al 2003	10	15	NR	NR	+7.4 (0 to +9)	NR
Lovisolo & Fleming 2002	4	0.5 to 17	1.33 [0.53]	0.53 [0.29]	+8.1 (+6 to +13)	NR
Pokroy et al 2004	5	9	0.80 (0.3 to 1.3)	0.32 (0.2 to 0.6)	+4.8 (0 to +10)	NR
Non-iatrogenic corneal ectasia						
Kymionis et al 2004	Case report	11	1.3	1.0	–	–
Rodriguez-Prats et al 2003	Case report	3	1.3	0.7	–	–

Abbreviations: logMAR – logarithm of the minimum angle of resolution; NR – not reported; preop – preoperative; postop – postoperative; UCVA – uncorrected visual acuity; ( ) – range; [ ] – standard deviation

Table 11 Proportion of eyes with a gain or loss of UCVA after ICRS implantation

Study	Number of eyes	Follow-up (months)	Change in UCVA from preoperative		
			Change in lines	n/N	%
Keratoconus					
Boxer Wachler et al 2003	74	9	≥+2 none ≥-2	53/74 14/74 7/74	72 19 9
Colin in press	82 px	24	+1 to 5 none -1 to 5	66/82 11/82 5/82	81 13 6
Colin et al unpub.[a]	34	6	≥+2 none ≥-2	27/34 7/34 0/34	79 21 0
Kwitko & Severo 2004	51	13	improvement no change deterioration	43/51 4/51 4/51	84 8 8
Miranda et al 2003	31	12	≥+2 none ≥-2	25/31 6/31 0/31	81 19 0
Siganos, C.S. et al 2003	33	13	+1 to 10 none -1	28/33 3/33 2/33	85 9 6
Iatrogenic corneal ectasia					
Guell et al 2004	5	6	+9 +5 to 8 none	2/5 3/5 0/5	– – –
Kymionis et al 2003	10	15	+9 +6 to 8 none	5/10 4/10 1/10	– – –

Abbreviations: n/N – number affected over total number; UCVA – uncorrected visual acuity

[a] 23 eyes lost to follow-up

Fitting contact lenses after ICRS implantation

Three studies reported fitting of contact lenses after ICRS implantation, two for patients with keratoconus and one for a patient with PMD. Nepomuceno et al (2003) reported three eyes in three keratoconus patients identified from retrospective chart review. The size of the patient sample from which these three patients were drawn was not reported; however, it is possible they are part of the series of 74 eyes reported by Boxer Wachler et al (2003). After Intacs implantation, the mean change in BCVA was an improvement of 2 (1 to 3.5) lines and the mean change in UCVA an improvement of 12 (10 to 15) lines. After contact lens fitting, the mean change in BCVA was 2.7 (2 to 3) lines. The three patients wore the contact lenses for between 2.5 and 12 hours per day. One patient experienced a contact lens–related complication on the day of the fitting (a trace papillary reaction under the upper eyelid), and during the four-month follow-up period another patient developed 3-9 staining and a dellen, which was treated and resolved.

Hladun & Harris (2004) reported a single case of a patient with keratoconus who received Intacs implants in one eye and experienced a loss of 4 lines of BCVA compared to preoperatively. He was fitted with a rigid gas-permeable contact lens and his BCVA improved to 0.10 logMAR, a gain of 5 lines over his post-Intacs visual acuity and an improvement of between 2 and 4 lines compared to preoperatively. However, the effect of the ICRS implant on the corneal topography resulted in formation of bubbles and epithelial erosion around the inferior segment. This was resolved by fitting the patient with a piggyback soft-rigid contact lens system.

Rodriguez-Prats et al (2003) reported a single case of a patient with PMD who received Intacs implants in one eye but received insufficient benefit and decided to try a hybrid rigid-soft contact lens as well. BCVA improved from 1.00 logMAR prior to Intacs implantation to 0.50 after implantation and to 0.10 after contact lens fitting. Three months postoperatively the inferior segment migrated, but this did not affect visual acuity or contact lens use. Minute crystalline deposits around the segments, halos and epithelial cysts within the incision were also reported, but these did not cause problems for the patient.

Topographic findings

Measures of corneal curvature include keratometry, spherical equivalent and refractive cylinder. For each of these measures the change from preoperative to postoperative values was calculated by deducting the postoperative mean from the preoperative mean. This method of calculation may produce an overestimate of the mean change as it cannot account for variability between patients. In some studies the mean change was reported separately and calculated from the raw patient data. These studies are clearly identified.

Refractive cylinder

Refractive cylinder was reduced postoperatively in all the studies in which it was reported (Table 12). In seven studies of keratoconus, postoperative mean refractive cylinder ranged from -1.3 to -4.3 dioptres (median of means -2.4 dioptres) and reduction in mean refractive cylinder ranged from 1.3 to 2.7 dioptres (median of means 1.5 dioptres) at between six and 24 months postoperatively (Colin et al 2001; Colin in press; Colin et al unpub.; Kwitko & Severo 2004; Siganos, C.S. et al 2003; Siganos, D. et al 2002; Tunc et al 2003). One study reported the mean reduction in refractive cylinder from

preoperatively to the last follow-up point as 1.8 [3.3] dioptres (Siganos, C.S. et al 2003). This figure differs from the change figure calculated and shown in Table 12 because it is the mean of each individual patient's change in refractive cylinder calculated from the raw data.

Table 12 Refractive cylinder for keratoconus patients only

Study	Number of eyes	Mean refractive cylinder (D)			p-value	Follow-up (months)
		Preop	Postop	Reduction		
Colin et al 2001	10	-4.0 [1.9]	-1.3 [1.4]	2.7	<0.05	12
Colin in press	77	-4.6 [2.8]	-3.3 [1.8]	1.3	<0.001	24
Colin unpub.[a]	30	-4.4 [2.4]	NR	1.5 [1.6]	<0.001	6
Kwitko & Severo 2004	31	3.7 [2.2]	-2.2 [2.1]	1.5	<0.01	13
Siganos, C.S. et al 2003	33	-5.7 [4.9]	-4.3 [3.9[	1.4	0.05	11
Siganos, D. et al 2002	26	-4.4 [2.2]	-2.2 [1.0]	2.2	NR	6
Tunc et al 2003	9	-5.1 [2.3]	-2.6 [1.9]	2.5	NR	24

Abbreviations: D – dioptre; NR – not reported; preop – preoperative; postop – postoperative; [ ] – standard deviation

[a] Reports mean reduction in refractive cylinder from preop to last follow-up (calculated from raw data)

Spherical equivalent

Spherical equivalent was reduced postoperatively in all studies in which it was reported (Table 13). In seven studies of keratoconus, postoperative mean spherical equivalent ranged from -1.1 to -3.8 dioptres (median of means -3.4 dioptres) and reduction in mean spherical equivalent ranged from 1.4 to 5.7 dioptres (median of means 3.1 dioptres) at between six and 24 months postoperatively (Boxer Wachler et al 2003; Colin in press; Colin et al unpub.; Kwitko & Severo 2004; Miranda et al 2003; Siganos, D. et al 2002; Tunc et al 2003). In two studies of iatrogenic corneal ectasia, postoperative mean spherical equivalent was -1.0 dioptre and the mean reduction in spherical equivalent (calculated from raw patient data) was 3.1 [0.3] dioptres (Guell et al 2004) and 3.9 [1.3] dioptres (Kymionis et al 2003).

Table 13 Spherical equivalent

Study	Number of eyes	Mean spherical equivalent (D)			p-value	Follow-up (months)
		Preop	Postop	Reduction		
Keratoconus						
Boxer Wachler et al 2003	74	-3.9 [5.2]	-1.5 [4.1]	1.4	NR	9
Colin in press	77	-6.9 [3.9]	-3.8 [2.7]	3.1	<0.001	24
Colin et al unpub.[a]	30	-4.6 [3.5]	NR	3.1 [2.5]	<0.001	6
Kwitko & Severo 2004	31	-6.1 [5.0]	-3.8 [4.0]	2.3	<0.01	13
Miranda et al 2003	36	-7.3 [3.1]	-4.8 [3.0]	2.5	NR	12
Siganos, D. et al 2002	26	-6.9 [5.0]	-1.1 [2.6]	5.5	NR	6
Tunc et al 2003	9	-8.7 [6.4]	-3.0 [2.2]	5.7	NR	24
Iatrogenic corneal ectasia						
Guell et al 2004[a]	5	-4.0 [0.3]	-1.0 [0.5]	3.1 [0.3]	NR	6
Kymionis et al 2003[a]	10	-4.8 [3.2]	-1.0 [1.9]	3.9 [1.3]	0.001	15

Abbreviations: D – dioptre; NR – not reported; preop – preoperative; postop – postoperative; [ ] – standard deviation

[a] Mean reduction in spherical equivalent calculated from raw data

Keratometry

Keratometry was reduced postoperatively in all the studies in which it was reported (Table 14). Mean postoperative keratometry ranged from 43.2 to 51.7 dioptres (median of means 48.6 dioptres), and reduction in keratometry ranged from 3.3 to 8.5 dioptres (median of means 4.7 dioptres) at between six and 24 months postoperatively in seven

studies (Colin et al 2001; Colin in press; Colin et al unpub.; Kwitko & Severo 2004; Miranda et al 2003; Siganos, C.S. et al 2003; Tunc et al 2003). One study reported the mean reduction in keratometry from preoperatively to the last follow-up point as 1.9 [3.5] dioptres (Siganos, C.S. et al 2003). This figure differs from the change figure calculated and shown in Table 14 because it is the mean change for each individual eye calculated from the raw data. Mean keratometry was also reduced for iatrogenic corneal ectasia patients in three studies (Alio et al 2002; Guell et al 2004; Kymionis et al 2003). Postoperative mean keratometry ranged from 34.2 to 53.8 dioptres (median of means 37.1 dioptres). In all three studies the mean reduction was calculated from raw patient data. Alio et al (2002) reported mean reduction of 2.1 dioptres (1.3 to 2.8 dioptres) in three eyes, Guell et al (2004) reported mean reduction of 3.6 [0.6] dioptres in five eyes, and Kymionis et al (2003) reported mean reduction of 3.1 [0.8] dioptres in 10 eyes.

Table 14 Keratometry

Study	N of eyes	Mean keratometry (D)			p-value	Follow-up (months)
		Preop	Postop	Reduction		
Keratoconus						
Colin et al 2001	10	53.2 [3.0]	48.6 [2.8]	4.6	sig.	12
Colin in press	77	50.1 [5.6]	46.8 [4.9]	4.9	<0.001	24
Colin et al unpub.	56	49.7 [4.9]	46.0 [3.5]	3.7	<0.002	6
Kwitko & Severo 2004	51	48.8 [4.0]	43.2 [4.8]	5.6	<0.001	13
Miranda 2003	21	60.2	51.7	8.5	sig.	12
Siganos, C.S. et al 2003[a]	33	50.9 [6.6]	47.6 [5.4]	3.3	<0.01	11
Tunc 2003	9	55.3 [8.1]	50.9 [7.4]	4.4	NR	24
Iatrogenic corneal ectasia						
Alio et al 2002	3	53.8	51.8	2.1	NR	6
Guell et al 2004[a]	5	37.8 [1.2]	34.2 [1.1]	3.6	NR	6
Kymionis et al 2003[a]	10	40.2 [3.5]	37.1 [3.9]	3.1	<0.01	15

Abbreviations: D – dioptre; NR – not reported; preop – preoperative; postop – postoperative; [ ] – standard deviation

[a] Mean reduction in keratometry calculated from raw data. Siganos, C.S. et al (2003): 1.9 [3.5] (4.6 to -13.8) D; Guell (2004): 3.6 [0.6] (3.0 to 4.4) D; Kymionis et al (2003): 3.1 [0.8] (-4.4 to -1.9) D

Patient-reported outcomes

Patient-reported outcomes were included in one study of patients with keratoconus (Colin et al unpub.), and one study of patients with iatrogenic corneal ectasia (Pokroy et al 2004).

In Colin et al (unpub.), visual symptoms including discomfort, foreign body sensation, photophobia, fluctuations, night vision, double vision, glare and halos were reported by 31 out of 39 (80%) patients preoperatively. Three months after Intacs implantation, 21 out of 28 patients (75%) reported visual symptoms and after six months, nine out of 23 patients (39%) reported visual symptoms. Patients were also asked to rate the quality of their vision as either poor, fair, good or excellent. The number of patients rating their vision as poor decreased from 69 per cent preoperatively to 24 per cent six months postoperatively, whereas the number of patients rating their vision as good or excellent increased from 10 per cent preoperatively (with no patients giving an excellent rating) to 48 per cent postoperatively. A similar number of patients reported that their vision was fair preoperatively (29%) and postoperatively (21%).

Pokroy et al (2004) reported five eyes in five patients with corneal ectasia after LASIK surgery. Two of the five reported subjective improvements in vision after Intacs were

implanted. Two reported improvements in distance vision and one reported little change in vision.

Conference presentations (see Appendix F)

Conference abstracts identified from hand searching conference proceedings are shown in Table 15. Fourteen of the conference abstracts reported outcomes of ICRS implantation for keratoconus patients, including one comparative study using concurrent controls; four reported outcomes for iatrogenic corneal ectasia, including one (Swanson 2004) that combined results for keratoconus and ectasia patients; and one reported outcomes for non-iatrogenic corneal ectasia (PMD). Much of the data reported in these abstracts, particularly for keratoconus, may also be reported in full publications or in more than one abstract; however, insufficient detail was provided to determine exactly where this might have occurred. It is very likely that Fouraker (2004), which combines the results of three separate studies of Intacs for keratoconus, reports data that have been reported elsewhere.

Table 15 Conference abstracts identified from conference proceedings[a]

Study	Level	Device	Eyes/patients	Follow-up
Keratoconus				
Costa et al 2001	IV	Not reported	18 patients	3 months
De Lange 2003	IV	Intacs	11 eyes	7–13 months
Dvali et al 2004	IV	Ferrara	14 eyes	6–12 months
Forseto 2003	IV	Intacs	10 eyes	14 months
Fouraker 2004, Lemp 2004	IV	Intacs	164 eyes (from 3 studies)	12–24 months
Fuhrman et al 2002	IV	Intacs	8 eyes	3 months
Hirsh et al 2004	IV	Intacs	10 eyes	Not reported
Jackson 2004	IV	Intacs	30 eyes	Minimum 3 months
Murta & Quadrado 2001	IV	Not reported	12 eyes	Immediate postoperative
Oliveira et al 2001	IV	Ferrara	10 eyes	3 months
Rabinowitz 2004	IV	Intacs	20 eyes	12 months
Swanson 2004	IV	Intacs	348 eyes with keratoconus or ectasia	1–11 months
Tran 2002	IV	Intacs	3 eyes	3 months
Yilmaz 2004	III-2	Ferrara	ICRS: 10 eyes Keratotomy: 8 eyes	4–6 months
Iatrogenic corneal ectasia				
Hashemi et al 2002	IV	Intacs	3 eyes	3 months
Lovisolo 2001	IV	Intacs	3 eyes	Not reported
Pallikaris et al 2001	IV	Intacs	6 patients	12 months
Non-iatrogenic corneal ectasia				
Lopez-Canedo & Swanson 2004	IV	Intacs	38 eyes with pellucid marginal degeneration	1–11 months

[a] Full details of the presentation title and conference are given in Appendix F; they are not listed in the references

Keratoconus

Complications

No intraoperative complications were reported in four conference abstracts (Furhman et al 2002; Hirsh et al 2004; Jackson 2004; Tran 2002) and complications (other than explantation) were not reported in six abstracts (Costa et al 2001; De Lange 2003; Dvali et al 2004; Forseto 2003; Rabinowitz 2004; Swanson 2004). Yilmaz (2004), a Level III-2 study, reported complications only for the ICRS group. Three out of 10 eyes had

complications including corneal abscess requiring PKP and dislocation of ring segments. Fouraker (2004) reported eight out of 164 eyes (4.9%) with complications, including non-infection keratitis, superficial tunnel dissection, transient inflammatory reaction, visual symptoms and neovascularisation. It is likely that some of the patients in the study are also reported in other published or unpublished studies included in this review. Murta & Quadrado (2001) reported that foreign body sensation was the major complication in 12 eyes in the early postoperative period. Oliveira et al (2001) reported two eyes out of 10 with microperforations intraoperatively, one eye out of 10 with a segment extrusion and four eyes out of 10 with segment displacement during the three-month follow-up.

Explantations

Explantations were reported in three of the 14 conference abstracts. Yilmaz (2004) reported that one out of 10 eyes was explanted due to superficial placement of the segment. Rabinowitz 2004 reported that three out of 20 eyes (15%) were explanted due to erosion of the segment in one eye, and persistent visual fluctuation in two eyes. Fouraker 2004 reported that 14 out of 164 eyes (8.5%) were explanted because of visual symptoms, segment migration, superficial placement, astigmatism and topographic irregularity. However, it is likely that the patients in that report overlap with patients in other published and/or unpublished studies included in this review.

Visual acuity

BCVA was reported in all but one (Dvali et al 2004) of the conference abstracts. Yilmaz (2004) compared eight eyes receiving radial keratotomy with 10 eyes receiving Ferrara implants. There was no difference seen in mean BCVA between the keratotomy group (0.20 [0.50] logMAR) and the ICRS group (0.19 [0.60] logMAR). All the other abstracts reported a gain of between 0 and 8 lines for between 48 per cent and 100 per cent of eyes (Costa et al 2001; Forseto 2003; Fouraker 2004; Furhman et al 2002; Hirsh et al 2004; Jackson 2004; Murta & Quadrado 2001; Oliveira et al 2001; Rabinowitz 2004; Swanson 2004; Tran 2002). Swanson (2004) noted that improvements were greatest for patients with severe keratoconus.

UCVA was reported in 11 abstracts. An improvement compared to preoperative status of between 2 and 8 lines was reported for between 5 per cent and 100 per cent of eyes in four abstracts (Fouraker 2004; Furhman et al 2002; Rabinowitz 2004; Swanson 2004). The other abstracts reported improvements but did not quantify them (Dvali et al 2004; Forseto 2003; Hirsh et al 2004; Jackson 2004; Murta & Quadrado 2001; Oliveira et al 2001).

Topographic findings

Topographic findings were not well reported in any of the conference abstracts. Yilmaz (2004) found no difference in mean postoperative keratometry between the keratotomy group (0.23 [0.54] dioptres) and the ICRS group (0.21 [0.60] dioptres). Nine other abstracts reported that corneal flattening and reduction in astigmatism occurred postoperatively (Costa et al 2001; Dvali et al 2004; Forseto 2003; Furhman et al 2002; Hirsh et al 2004; Jackson 2004; Murta & Quadrado 2001; Rabinowitz 2004; Tran 2002).

Iatrogenic corneal ectasia

Four of the conference abstracts reported outcomes for patients with iatrogenic corneal ectasia. In Hashemi et al (2002), none of three eyes lost any lines of BCVA immediately after surgery, but after three months two eyes experienced no improvement in BCVA or UCVA and one eye experienced a dramatic increase in UCVA and an improvement in BCVA (the size of the effect is not stated). There were no intraoperative complications in these three eyes. Lovisolo (2001) studied three eyes with post-LASIK corneal ectasia and concluded that asymmetrical ICRS implantation appeared to be a promising alternative to PKP, but the abstract did not include any specific results. Pallikaris et al (2001) found increased topographical regularity and visual acuity in six eyes with post-LASIK corneal ectasia and stability in refraction and visual acuity three months postoperatively. Swanson (2004) reported that 100 per cent of cases experienced corneal stabilisation, but the degree of stabilisation was dependent on the ectasia. Iatrogenic corneal ectasia resulted in the most normalising effect from Intacs implantation. Postoperatively 60 per cent of cases required soft contact lenses to improve visual acuity.

Non-iatrogenic corneal ectasia

Only one conference abstract for non-iatrogenic corneal ectasia was identified. Lopez-Canedo & Swanson (2004) reported results from 38 eyes with PMD who received Intacs implants. Visual acuity improved for all patients postoperatively, with 30 eyes (80%) having postoperative UCVA of 0.30 logMAR or better and 15 eyes (40%) having UCVA of 0.00 logMAR. BCVA improved to 0.18 logMAR or better in 34 eyes (90%), 38 eyes (100%) gained at least 1 line of visual acuity and 27 eyes (70%) gained 3 or more lines. All patients reported improved visual function. Thirty-four eyes (90%) showed improved corneal surface and all showed flattening of the curvature and central cone displacement.

Results from corneal transplant registries

No published studies comparing ICRS implants to other treatments for ectasia and keratoconus were identified. In order to provide a point of comparison, results from the Australian Corneal Graft Registry and other large registries and studies of corneal transplant for keratoconus have been summarised in Appendix G and are discussed below. It should be kept in mind that these data are not directly comparable with the data from individual studies of ICRS implantation. Case series studies typically represent the best possible outcomes for an individual surgeon or surgical team and may be influenced by more restrictive selection criteria than a registry study. Ideally, registry studies will include all surgeons performing corneal grafts and include patients with relatively poor preoperative visual acuity, and thus reflect a wider variety of postoperative outcomes than are found in single-centre or single-surgeon case series.

Graft registries and databases

The Australian Corneal Graft Registry (Williams et al 2004) has been collecting data on Australian corneal grafts since 1985. At July 2003 more than 14,000 grafts were registered, 4,309 (31%) of which were for keratoconus. The Cornea and External Disease Service of the University Health Network at Toronto Western Hospital in Canada reported results for 468 corneal grafts from 1986 to 1993, 50 (11%) of which were for keratoconus (Sit et al 2002). Corneal Consultants of Indiana in the United States

collected data on 3,992 corneal grafts between 1982 and 1996, 449 (11%) of which were for keratoconus (Thompson et al 2003). The Swedish Corneal Transplant Registry (Claesson et al 2002) collected data on 1,957 corneal transplants between 1997 and 1999, 566 (29%) of which were for keratoconus. Other studies reported single-centre experience from corneal transplant databases. Buzard & Fundingsland (1997) reported results from the Buzard Eye Institute in Las Vegas for 104 corneal grafts for keratoconus. Hargrave et al (2003) reported 84 corneal grafts for keratoconus at the University of Texas Southwestern Medical Center. Koralewska-Makar et al (1996) reported resulted from 212 corneal transplants between 1989 and 1991, 77 of which were for keratoconus. Olson et al (2000) reported 93 grafts for keratoconus at the John Moran Eye Center at the University of Utah in Salt Lake City and Lim et al (2000) reported the results of one surgeon contributing data to the Australian Corneal Graft Registry (93 grafts).

Graft survival

Three graft registries or databases reported Kaplan-Meier survival analyses (Table 16). In all three registries graft survival up to 10 years was 90 per cent or more. The Australian Corneal Graft Registry followed some grafts for up to 20 years and found survival of over 80 per cent at 15 and 20 years.

Table 16 Graft survival after PKP for keratoconus

Study	Location	Total grafts	Keratoconus grafts	Kaplan-Meier survival (%)					
				1 yr	2 yrs	5 yrs	10 yrs	15 yrs	20 yrs
Sit et al 2002	Canada	468	50	96	96	–	–	–	–
Thompson et al 2003	USA	3,992	449	–	–	–	92	–	–
Williams et al 2004	Australia	14,649	4,309	97	–	95	90	82	82

Abbreviation: PKP – penetrating keratoplasty

Visual acuity

Best corrected visual acuity was reported in six studies (Table 17). Between 71 per cent and 87 per cent of eyes had a BCVA of 0.30 logMAR or better in the follow-up period. Claesson 2002 reported that 8/105 (8%) eyes had BCVA of 0.70 logMAR or worse and Lim 2000 reported 5/93 (5%) eyes with BCVA of 0.80 logMAR or worse. Koralewska-Makar 1996 reported 30/75 (39%) eyes with BCVA of 0.00 logMAR. The Australian Corneal Graft Registry (Williams et al 2004) reported that 1,613 out of 2,068 eyes (78%) had a BCVA of 0.48 logMAR or better, and 1,841 (84%) gained at least 1 line of visual acuity, with 901 (44%) gaining 1 to 5 lines, 833 (40%) gaining 7 or more lines, 108 (5%) achieving no change and 226 (11%) losing 1 to 8 lines.

Table 17 BCVA after PKP for keratoconus

Study	Location	Total grafts	Keratoconus grafts	BCVA at follow-up
Buzard & Fundingsland 1997	USA	–	104	60/104 (58%) 0.30 logMAR at 1 month 92/104 (88%) 0.30 logMAR at 3 months 89/104 (86%) gained lines of visual acuity
Claesson et al 2002	Sweden	1,957	526	90/105 (86%) 0.30 logMAR or better 8/105 (8%) 0.70 logMAR or worse
Koralewska-Makar et al 1996	Sweden	212	77	65/75 (84%) 0.30 logMAR or better 30/75 (39%) 0.00 logMAR
Lim et al 2000	Australia	–	93	Mean 0.24 (0.1 to 1.3) 81/93 (87%) 0.30 logMAR or better 5/93 (5%) 0.80 logMAR or worse
Olson et al 2000	USA	–	93	72/93 (77%) 0.10 logMAR or better
Williams et al 2004	Australia	14,649	4,309	1,468/2,068 (71%) 0.30 logMAR or better 1,613/2,068 (78%) 0.48 logMAR or better 1,841/2,068 (84%) gained at least 1 line of visual acuity 901/2,068 (44%) gained 1 to 5 lines 833/2,068 (40%) gained 7 or more lines 108/2,068 (5%) no change 226/2,068 (11%) lost 1 to 8 lines

Abbreviations: BCVA – best corrected visual acuity; logMAR – logarithm of the minimum angle of resolution; PKP – penetrating keratoplasty

Reoperations

The rate of reoperations varies depending on whether only regrafts are reported or whether all types of additional corneal surgery are reported (Table 18). Regraft was reported for between 1 per cent and 6 per cent of grafts for keratoconus. The most common reoperative procedure was refractive surgery (relaxing incisions) for astigmatism, which was reported for 23 per cent of eyes in Lim et al (2000) and 32 per cent of eyes in Buzard & Fundingsland (1997).

Table 18 Reoperations after PKP for keratoconus

Study	Location	Total grafts	Keratoconus grafts	Reoperation rate
Buzard & Fundingsland 1997	USA	–	104	9/104 (9%) (lamellar keratoplasty (4), corneal wedge resection (5)) 33/104 (32%) relaxing incisions for astigmatism 2/104 (2%) regraft
Claesson et al 2002	Sweden	1,957	526	7/105 (6%) regraft
Hargrave et al 2003	USA	–	84	5/84 (6%) regraft
Koralewska-Makar et al 1996	Sweden	212	77	15/77 (19%)
Lim et al 2000	Australia	–	93	1/93 (1%) regraft 21/93 (23%) refractive surgery for astigmatism

Abbreviation: PKP – penetrating keratoplasty

Complications

Like for reoperations, the rate of complications varies depending on how complications are defined and reported (Table 19). Complication rates ranged from 13 per cent to 62 per cent. Complications reported included retrocorneal fibrous membrane, keratitis, postoperative leakage, cataract, secondary glaucoma, corneal vascularization, loose suture, resuturing, raised intraocular pressure, severe astigmatism, corneal ulceration and scarring, stromal outgrowth, late epithelial defect, allograft reaction, filaments, suture infiltrate and anisometropia.

Secondary graft rejection was reported in 21 out of 104 eyes (20%) (Buzard & Fundingsland 1997); 22 out of 449 eyes (5%) (Thompson et al 2003); 4 out of 93 eyes (4%) (Lim et al 2000); and 1 out of 93 eyes (1%) (Olson et al 2000).

Table 19 Complications after PKP for keratoconus

Study	Location	Total grafts	Keratoconus grafts	Complications
Buzard & Fundingsland 1997	USA	–	104	21/104 (20%) secondary graft failure (19/21 successfully treated) No endophthalmitis, primary graft failure or expulsive haemorrhage
Claesson et al 2002	Sweden	1,957	526	14/105 (13.4%)
Hargrave et al 2003	USA	–	84	No primary graft failure
Koralewska-Makar et al 1996	Sweden	212	77	15/77 (19%) Retrocorneal fibrous membrane (1), keratitis (2), postoperative leakage (3), cataract (7), secondary glaucoma (1)
Lim et al 2000	Australia	–	93	12/93 (26%) Corneal vascularisation (8), rejection (4), loose suture (3), resuturing (3), cataract (3), raised intraocular pressure (3)
Olson et al 2000	USA	–	93	58/93 (62%) Cataract (5), keratitis (7), severe astigmatism (3), vascularisation (1), corneal ulceration and scarring (1), stromal outgrowth (1), late epithelial defect (1), allograft reaction (7), secondary graft failure (1), elevated intraocular pressure (16), filaments (5), suture infiltrate (2), wound leak (3), anisometropia (2), mechanical abrasion or loose suture (3)
Thompson et al 2003	USA	3,992	449	22/449 (5%) graft failure Endothelial failure (11), endothelial rejection (3), surface complications (1), glaucoma (0), astigmatism (0), other (15)

Abbreviation: PKP – penetrating keratoplasty

What are the economic considerations?

Cost-effectiveness could not be assessed as there were no published comparative studies.

Estimation of the potential patient pool for ICRS

Three sources of data suggest that around 100 to 200 patients (or around 200 to 400 eyes assuming almost all have bilateral keratoconus) may receive corneal transplants for keratoconus each year in Australia.[3] It is possible that at least as many patients may be

[3] **Australian Corneal Graft Registry**: of the 14,000 grafts registered, around 30 per cent were for keratoconus, amounting to 4,000 grafts over the past 18 years or around 200 grafts per year (Williams et al 2004); **Australian Institute of Health and Welfare**: each year at least 600 PKP procedures are performed that are eligible for Medicare rebate (based on MBS data for item number 42653, corneal transplant) (AIHW 2004). Doubling this figure to account for public hospital patients, perhaps 1,200 PKP procedures are carried out in Australia each year, and thus around one-third (200 to 400) of these would be for keratoconus; **this report**: incidence of 1 in 2,000 for keratoconus, and a prevalence of 50 in 100,000 (Kennedy et al 1986; Kymes et al 2004), and around 10 per cent to 20 per cent of keratoconus patients may eventually need a corneal transplant in their lifetime (Cohen & Parlato 1986; Kennedy et al 1986; Smiddy et al 1988; Tuft et al 1994).

eligible for ICRS, including patients who do not wish to have invasive surgery and others who are still able to use contact lenses but may prefer another option. Assuming that all current PKP recipients instead received ICRS, the potential patient pool may be as large as 200 to 400 patients (400 to 800 eyes). However, a number of patients might not be suitable for ICRS because of corneal scarring, which would reduce the potential patient pool to perhaps 150 to 300 patients (300 to 600 eyes) per year.

Cost of ICRS implantation

Notional costs of ICRS implantation compared with PKP are shown in Table 20. Ranges have been used for the notional MBS fee for ICRS, costs of anaesthesia for both procedures and hospital stay cost for PKP.

The total cost of ICRS implantation is estimated to be between $2,439.60 and $3,449.60 per eye compared with a total cost for PKP of between $3,889.30 and $5,089.30 per eye.

Based on these estimates, per year the total cost of ICRS for between 300 and 600 eyes would be between $731,880 and $2,069,760.

Assuming that around 200 to 400 eyes receive PKP each year in the Australia for keratoconus, the current cost is probably around $777,860 to $2,035,720.

However, it must be borne in mind that these costs are not directly comparable as ICRS implantation may replace or delay the need for some corneal transplants for ectasia and keratoconus. At this time, however, there is insufficient evidence to determine the extent to which this may occur.

Table 20 Costs for ICRS implantation compared to PKP per eye

Intacs			PKP	
Notional MBS fee for ICRS MBS item 42668	$500–$1,000 $63.60		MBS item 42653 MBS item 42668	$1,135.70 $63.60
Subtotal	$563.60–$1,063.60		Subtotal	$1,199.30
Implants	$1,080		Tissue	$1000
Hospital or clinic stay	$60		Hospital or clinic stay	$60–$320
Anaesthesia	$0–$510		Anaesthesia	$0–$510
Medications	$36		Medications	$240
Postoperative care	$150		Postoperative care	$720
Theatre band 3	$550		Theatre band 4 or 5	$670–$1,100
Total	$2,439.60–$3,449.60		Total	$3,889.30–$5,089.30

Abbreviations: MBS – Medicare Benefits Schedule; PKP – penetrating keratoplasty

Summary

The unit cost of ICRS implantation is estimated to be between $2,440 and $3,450 per eye. However, the number of eligible patients is small (around 300 to 600 eyes per year) and therefore the economic impact on the Australian healthcare system is likely to be low (in the order of $731,880 to $2,069,760 per year). There is currently insufficient evidence to determine the extent to which ICRS may replace or delay the need for corneal transplant, and hence it is not possible to assess the overall economic impact of ICRS.

Discussion

Limitations of the evidence

Intrastromal corneal ring segments are a new technology for treating corneal ectasias and keratoconus and the evidence base supporting their use is immature. Consequently, it is difficult to draw firm conclusions about their safety and effectiveness and impossible to determine cost-effectiveness. No comparative studies were identified in full publications, although one small comparative study was identified from hand searching recent conference proceedings. The studies that have been published report on a reasonable number of eyes for keratoconus, but a very small number for corneal ectasia (particularly non-iatrogenic corneal ectasia). Follow-up was short (no more than three years) and certainly not long enough to determine whether ICRS will provide a long-term alternative to PKP or other invasive surgery. Functional outcomes were rarely reported and there appeared to be a relatively high level of patient overlap between studies with the same authors, although insufficient detail was provided to establish the extent of this.

Safety

Complication rates for ICRS implantation varied widely depending on how complications were defined. The major complications reported were segment migration and extrusion, visual symptoms such as halos and glare, and infections including keratitis. Although intralamellar channel deposits were noted in many eyes, they were not considered to be a complication and did not change the clinical pathway postoperatively. In two studies using Ferrara ICRS the rates of complications appeared to be higher than the rates typically reported in studies of Intacs ICRS. The additional incisions required for Intacs insertion and difficulties with appropriate placement may explain this result (Hofling-Lima et al 2004). Additional data are needed to clarify this issue. Rates of complications after PKP for keratoconus (derived from transplant registries and databases) also varied widely, making it difficult to draw any sensible comparisons with ICRS. Complications after PKP included retrocorneal fibrous membrane, keratitis, postoperative leakage, cataract, secondary glaucoma, corneal vascularisation, loose sutures, raised intraocular pressure, severe astigmatism, corneal ulceration and scarring, stromal outgrowth, late epithelial defect and allograft reaction. Secondary graft rejection also occurred in up to one-fifth of grafts.

Explantations of ICRS ranged from 4 per cent to 25 per cent (median 10%) of eyes with keratoconus. The procedure was typically performed because of dissatisfaction with vision, segment extrusion or decentration, chronic foreign body sensation and incorrect segment placement.

Effectiveness

The effectiveness of ICRS implantation is difficult to judge in the absence of comparative studies. Data from corneal graft registries were provided in this review as a point of comparison. However, these data are not directly comparable with the data from the included ICRS studies because the registry data provide a broader picture of corneal

graft outcomes than that typically obtained from small case series from single surgeons or surgical teams testing a new intervention such as ICRS. Furthermore, the included studies did not make clear whether patients' best corrected visual acuity was with spectacles or contact lenses. As wearing contact lenses may be problematic for patients with keratoconus and ectasia, this may be an important point of difference with the outcomes of PKP. The data also did not provide any indication of the number of ICRS patients who may still require PKP in the future, thus making assessment of cost-effectiveness impossible.

Visual acuity

ICRS implantation improved best corrected and uncorrected visual acuity for most patients with keratoconus and corneal ectasia (range 45% to 88%, median 67% in six studies). The degree of improvement was greater for uncorrected than corrected visual acuity and was fairly similar for keratoconus and iatrogenic corneal ectasia patients. However, a number of patients experienced no change in visual acuity (range 2% to 51%, median 20% in six studies) and a small number of eyes experienced a deterioration (range 0% to 15%, median 8%). The outcomes for patients with iatrogenic corneal ectasia also followed this pattern.

Although there appeared to be little difference between the typical mean best corrected visual acuity for patients with ICRS (around 0.20 logMAR) and that reported in corneal graft registries (around 0.30 logMAR), the results may not be genuinely similar. The improvement in visual acuity after PKP is typically much higher than that reported after ICRS implantation. For example, in the Australian Corneal Graft Registry, more than 80 per cent of patients experienced between 1 and 8 lines of improvement in BCVA (Williams et al 2004) compared with a median of 67 per cent of keratoconus patients. The mean improvement in BVCA for keratoconus patients was around 2 lines.

Topographic findings

ICRS implantation did result in flattening of the cornea and reduction in irregular astigmatism for keratoconus patients, with more normal keratometric values, spherical equivalence and refractive cylinder. A similar pattern was observed for iatrogenic corneal ectasia, although mean postoperative keratometry was substantially lower than for keratoconus. This may be a result of the initial LASIK treatment causing significant thinning of the cornea from which ectasia then subsequently developed. There were no comparative topographic findings from corneal transplant registries. Several studies demonstrated the feasibility of fitting contact lenses after ICRS, and one study indicated the possibility of ICRS explantation in keratoconus patients and subsequent reimplantation.

Patient-relevant outcomes

Functional or subjective outcomes were only reported in two studies, one of which showed a reduction in patient-reported symptoms and an increased proportion of patients reporting subjectively good vision after ICRS implantation for keratoconus. The other small study of iatrogenic corneal ectasia was less clear, although the majority of patients reported an improvement in subjective visual acuity. Other outcomes of

importance to patients, such as the durability of ICRS implantation, the length of time it may delay the need for PKP, and whether it arrests the progression of keratoconus and ectasia have not been reported to date. By comparison, graft survival after PKP for keratoconus is reported to be 90 per cent or more up to 10 years post transplant, and the Australian Corneal Graft Registry has reported survival of over 80 per cent with 15 and 20 years' follow-up (Williams et al 2004). The regraft rate after PKP is low; however, perhaps around one-third of all grafts may require relaxing incisions for astigmatism.

Conference proceedings

The results from the conference proceedings generally mirrored the results from the published and unpublished case series. Results from new studies are likely to be presented at future conferences, but the evidence base is not growing rapidly. Comparative data identified to date exist in the form of one abstract of a small historical comparison; this situation is also unlikely to change rapidly.

Cost-effectiveness

The almost complete lack of comparative data does not permit a valid cost-effectiveness analysis to be done. However, the small number of ICRS procedures likely to be performed in Australia does not represent a large economic impact on the Australian healthcare system.

Conclusions

ICRS are a new minimally invasive intervention for the treatment of ectasia and keratoconus. Implantation of ICRS offers a potential alternative to corneal transplant or may delay the need for corneal transplant. Compared to corneal transplant, the potential benefits of ICRS include reduced recovery time, ability to treat both eyes at the same time, and possibility of explantation if necessary. However, at the present time the evidence base supporting their use in patients with ectasia and keratoconus is immature and no comparative evidence has been published to date. ICRS implantation is a relatively safe procedure, but there is the potential for a variety of complications including migration or extrusion of the implants, visual symptoms and infections. ICRS have been shown to improve visual acuity (corrected and uncorrected) and corneal curvature and astigmatism. No long-term follow-up data for ICRS implantation are available, and it is not clear how durable the treatment will be or whether it will obviate the need for corneal transplant in the future. Without comparative studies it is not possible to make any assessment of the relative effectiveness of ICRS compared to corneal transplant, and therefore no assessment of cost-effectiveness can be made. However, as keratoconus and ectasia are rare conditions (affecting in the order of around 10,000 Australians), the economic impact of ICRS implantation on the Australian healthcare system would be minimal.

Recommendation

MSAC recommends that on the strength of evidence pertaining to intrastromal corneal ring segments for ectasia and keratoconus public funding should not be supported for this procedure.

The evidence pertaining to this procedure is immature and small in volume. It is not possible to be confident that the benefits demonstrated are durable, and the lack of published comparative clinical studies does not allow for any cost-effectiveness analysis.

The Minister for Health and Ageing accepted this recommendation on 28 November 2005.

Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported;
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness;
- advise the Minister for Health and Ageing on references related to new and/or existing medical technologies and procedures; and
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

The membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	**Expertise or affiliation**
Dr Stephen Blamey (Chair)	General surgery
Associate Professor John Atherton	Cardiology
Professor Syd Bell	Pathology
Dr Michael Cleary	Emergency medicine
Dr Paul Craft	Clinical epidemiology and oncology
Dr Gerry FitzGerald	AHMAC representative
Dr Kwun Fong	Thoracic medicine
Dr Debra Graves	Medical administrator
Professor Jane Hall	Health economics
Professor John Horvath	Chief Medical Officer, Department of Health and Ageing
Ms Samantha Robertson	Department representative
Dr Terri Jackson	Health economics
Professor Brendon Kearney	Health administration and planning
Associate Professor Donald Perry-Keene	Endocrinology
Dr Ray Kirk	Health research
Dr Michael Kitchener	Nuclear medicine
Professor Alan Lopez	Medical statistics and population health
Dr Ewa Piejko	General practice
Ms Sheila Rimmer	Consumer health issues
Professor Jeffrey Robinson	Obstetrics and gynaecology
Professor Michael Solomon	Colorectal surgery, clinical epidemiology
Professor Ken Thomson	Radiology
Dr Douglas Travis	Urology

Appendix B Advisory panel

Advisory panel for MSAC application 1083 Intrastromal corneal ring segments for ectasia and kerotoconus

Dr Douglas Travis, MBBS, FRACS (Urol) Head of Urology Western Health Melbourne Vic	Chair of Advisory Panel MSAC Member
Dr Debra Graves, MBBS, MHA, FRACMA CEO Royal College of Pathologists of Australasia Surry Hills NSW	MSAC Member
Dr Iain Dunlop, MBBS (Hons), FRANZCO, FRACS VMO Ophthalmologist Sydney Eye Hospital Sydney NSW	Royal Australian and New Zealand College of Ophthalmologists nominee
Mr Craig Ellis, BA, BSW (Hons), Adv Cert Eng Health Services Consumer Representative Consumers' Health Forum of Australia Evandale Tas	Consumers' Health Forum of Australia nominee
Dr Gerard Sutton, MBBS, FRANZCO, FRACS Senior Staff Specialist in Laser Refractive and Corneal Surgery Sydney Eye Hospital Sydney NSW	Royal Australian and New Zealand College of Ophthalmologists nominee
Ms Philippa Middleton, MPH Research Manager Australian Safety and Efficacy Register of New Interventional Procedures – Surgical Adelaide SA	Evaluator
Dr Rebecca Tooher, PhD Senior Researcher Australian Safety and Efficacy Register of New Interventional Procedures – Surgical Adelaide SA	Evaluator
Ms Bianca Ledbrook MSAC Department of Health and Ageing Canberra ACT	Project manager

Appendix C Excluded studies

Barbara, A., Shehadeh-Masha'our, R. & Garzozi H. 2004, 'Intacs after laser in situ keratomileusis and photorefractive keratectomy', *Journal of Cataract & Refractive Surgery*, 30 (9), 1892–5.

reason: myopic regression, not ectasia, after keratoconus

Boxer Wachler, B. & Sharma, M. 2004, 'Intacs for keratoconus and LASIK-induced ectasia', *Techniques in Ophthalmology*, 2 (4), 137–41.

reason: review article

Chalita, M. & Krueger, R. 2004, 'Wavefront aberrations associated with the Ferrara intrastromal corneal ring in a keratoconic eye', *Journal of Refractive Surgery*, 20 (6), 823–30.

reason: no relevant outcomes (focus of article is not clinical outcomes)

Colin, J. & Velou, S. 2002, 'Utilization of refractive surgery technology in keratoconus and corneal transplants', *Current Opinion in Ophthalmology*, 13 (4), 230–4.

reason: review article

Colin, J. & Velou, S. 2003, 'Implantation of Intacs and a refractive intraocular lens to correct keratoconus', *Journal of Cataract & Refractive Surgery*, 29 (4), 832–4.

reason: ICRS implantation concurrent with other surgery

Colin, J. & Velou, S. 2003, 'Current surgical options for keratoconus', *Journal of Cataract & Refractive Surgery*, 29 (2), 379–86.

reason: review article

Ehrich, D. & Duncker, G. 2004, 'The use of intracorneal rings in penetrating keratoplasty', *Klinische Monatsblatter fur Augenheilkunde*, 221 (2), 92–95.

reason: not all patients had corneal ectasia

Ito, M., Arai, H., Fukumoto, T., Toda, I. & Tsubota K. 2004, 'Intacs before or after laser in situ keratomileusis: correction of thin corneas with moderately high myopia', *Journal of Refractive Surgery*, 20 (6), 818–22.

reason: myopia

McDonald, J. & Deitz, D. 2004, 'Removal of Intacs with a fractured positioning hole', *Journal of Refractive Surgery*, 20 (2), 182–3.

reason: myopia

Mian, S.I., Jarade, E.F., Scally, A. & Azar, D.T. 2004, 'Combined ICRS insertion and LASIK to maximize postoperative residual bed thickness in high myopia', *Journal of Cataract & Refractive Surgery*, 30 (11), 2383–90.

reason: myopia

Primack, J. & Azar, D. 2003, 'Laser in situ keratomileusis and intrastromal corneal ring segments for high myopia – three-step procedure', *Journal of Cataract & Refractive Surgery*, 29 (5), 869–874.

reason: myopia

Ruckhofer, J. 2002, 'Clinical and histological studies on the intrastromal corneal ring segments (ICRS, Intac)', *Klinische Monatsblatter fur Augenheilkunde*, 219 (8), 557–74.

reason: review article

Twa, M.D., Kash, R.L., Costello, M. & Schanzlin, D.J. 2004, 'Morphologic characteristics of lamellar channel deposits in the human eye: a case report', *Cornea*, 23 (4), 412–20.

reason: no relevant outcomes (focus of article is not clinical outcomes)

Appendix D Visual acuity conversion chart

The following table is adapted from Holladay (2004). Counting fingers has been assumed to be at 20/2000 (2.0 logMAR) unless otherwise stated, as per Boxer Wachler et al (2003).

Line number	logMAR	Snellen (feet 20/)	Decimal
-3	-0.30	10	2.00
-2	-0.20	12.5	1.60
-1	-0.10	16	1.25
0	0.00	20	1.00
1	0.10	25	0.80
–	0.18	30	0.67
2	0.20	32	0.63
3	0.30	40	0.50
4	0.40	50	0.40
–	0.48	60	0.33
5	0.50	63	0.32
–	0.54	70	0.29
6	0.60	80	0.25
7	0.70	100	0.20
–	0.76	114	0.18
8	0.80	125	0.16
–	0.88	150	0.13
9	0.90	160	0.13
10	1.00	200	0.10
11	1.10	250	0.08
–	1.18	300	0.07
12	1.20	320	0.06
13	1.30	400	0.05
16	1.60	800	0.03
20	2.00	2000[a]	0.01
30	3.00	20000[b]	0.001

[a] 20/2000 is equivalent to counting fingers at 2 feet
[b] 20/20000 is equivalent to hand motion at 2 feet

Appendix E Included studies

Keratoconus

Study	Patients	Visual acuity postoperatively	Topographic findings
Alio et al 2004 (IV) Dates: Feb 00 – Dec 03 Location: Refractive Surgery and Cornea Department, Instituto Oftalmológico de Alicante, Medical School, Miguel Hernández University, Alicante, SPAIN Patient selection: Patients who required explantation of ICRS were selected through retrospective chart review Mean follow-up: 15.5 months (12–22) Losses to follow-up: Not reported Exclusions: Not reported Device: Intacs	Keratoconus patients with clear corneas n=4 patients/5 eyes Mean age: Not reported M/F: Not reported Preop mean UCVA: (logMAR) 1.42 [0.16] (1.30–1.60) Preop mean BCVA: (logMAR) 0.64 [0.30] (0.20–1.00) Preop mean keratometry: (D) 52.2 [5.1] (46.5–58.4) Preop mean refractive cylinder: (D) Px 1: 0, -4 x 50 Px 2: -4, -5 x 170 Px 3: -4, -7 x 25 Px 4: 2.5, -6 x 30 Px 5: -2, -6 x 70 **Details of surgery** Anaesthesia: Not reported Intacs segments: 0.25 mm, 0.45 mm Segment placement: (superior/inferior) 0.25 mm/0.45 mm – 3 eyes no superior implant/0.45 mm – 2 eyes Depth of placement: Not reported Sutures: Not reported Postoperative eye treatment: Antibiotic and steroid eye drops for 5 days, artificial tears for 1–3 months, instructed not to rub eyes. Surgeon details: All explantation procedures done by one surgeon (JLA)	Postop mean BCVA: (logMAR) 0.78 [0.13] (0.7–1.0) Change in BCVA preop to postop: (lines) -1 to 5 – 2/5 eyes no change – 3/5 eyes Mean change in BCVA preop to postop: (lines) -1.4 (0 to -5) Postop mean UCVA: (logMAR) 1.48 [0.16] (1.3–1.6) Change in UCVA preop to postop: (lines) +3 – 1/5 eyes -3 – 2/5 eyes no change – 2/5 eyes Mean change in UCVA preop to postop: (lines) -0.6 [2.5] (-3 to +3) For two patients who were reimplanted BCVA 12 months after reimplant: (logMAR) Px 1: 0.3, Px 2: 0.2 Change in BCVA from preimplant/initial postimplant: (lines) Px 1: +2/+4, Px 2: 0/+5 UCVA 12 months after reimplant: (logMAR) Px 1: 0.3, Px 2: 0.3 Change in UCVA from preimplant/initial postimplant: (lines) Px 1: +10/+13, Px 2: +10/+13	Mean keratometry: (D) 51.8 [5.1] (46.0–59.1) Mean change in keratometry preop to postop: (D) 0.4 [2.8] (-3.1 to 4.8) Preop mean refractive cylinder: (D) Px 1: -2, -5 x 80 Px 2: -5, -7 x 160 Px 3: -9, -7 x 165 Px 4: 2, -6 x 50 Px 5: -4, -4.5 x 70 **Complications and adverse events** Successful explantation: (n of eyes) 5/5 Reasons for explantation: (n of eyes) Segment migration, partial extrusion, moderate corneal melting – 4/5 Segment migration, significant corneal thinning and melting – 1/5

Study	Patients	Visual acuity postoperatively	Topographic findings
Boxer Wachler et al 2003, Chou & Boxer Wachler 2000 (IV) Dates: Dec 99 – May 01 Location: Jules Stein Eye Institute, University of California, Los Angeles, California, USA Patient selection: Not reported Mean follow-up: 9 months (1–20) Losses to follow-up: Not reported Exclusions: Patients with ectasia after surgical procedures who received Intacs Device: Intacs	Keratoconus patients intolerant to rigid gas-permeable contact lenses n=50 patients/74 eyes Mean age: 35 (20–73) years M/F: 41/9 Corneal clarity: (n of eyes) clear 57/74 (77%) scarred 17/74 (23%) Preop mean UCVA: (logMAR) 1.05 [0.48] (1.30–2.00) Preop mean BCVA: (logMAR) 0.41 [0.48] (0.40–0.00) Preop mean spherical equivalent: (D) -3.89 [5.16] (-18.38–3.38) Preop mean I-S value: 25.62 [25.1] (1.18–101.9) (n=65) **Details of surgery** Anaesthesia: Not reported Intacs segments: 0.25 mm, 0.3 mm, 0.35 mm bilateral – 24/50 unilateral – 26/50 Segment placement: (superior/inferior) – for spherical equivalent <-3.0D – 0.25/0.30 mm – for spherical equivalent >-3.0D – 0.25/0.35 mm Depth of placement: 66% of peripheral corneal depth Sutures: Not sutured Postoperative eye treatment: Ciprofloxacin ophthalmic solution 4 times daily for 3 days, fluorometholone 4 times daily for 7 days, ketorolac 4 times daily for 2 days Surgeon details: All procedures done by one surgeon (BSBW)	Mean: (logMAR) UCVA BCVA All eyes 0.61 [0.52] (2.0–0.24) 0.24 [0.31] (0.8–0.34) 0.25 mm/0.30 mm 0.36 [0.21] (0.4–0.22) 0.04 [0.14] (0.04–0.16) 0.25 mm/0.35 mm 0.69 [0.58] (2–0.24) 0.32 [0.34] (0.8–0.5) Mean difference all eyes preop to postop: (lines) UCVA: +3 (-7 to +18) p=0.0001 BSCVA: +2 (-5 to +10) p=0.0004 Mean difference 0.25/0.30 mm preop to postop: (lines) UCVA: +0.45 (-2 to +18) p<0.0001 BSCVA +0.17 (-2 to +6) p=0.003 Mean difference 0.25/0.35 mm preop to postop: UCVA: +0.41 (-7 to +18) p<0.001 BSCVA: +0.18 (-5 to +15) p=0.003 Gain or loss in lines preop to last postop: Lines UCVA (n of eyes) BCVA (n of eyes) ≥-2 7/74 (9%) 3/74 (4%) 0 14/74 (19%) 38/74 (51%) ≥+2 53/74 (72%) 33/74 (45%) Eyes that gained postoperative BCVA had worse preoperative BSCVA than eyes with no change in BSCVA (p<0.0001) Eyes that gained postoperative BCVA had higher preoperative I-S values compared to group that showed no change (p=0.036) Statistically significant relationship between postoperative change in BCVA and preoperative spherical equivalent refraction (p<0.001) and preoperative I-S value (p=0.002)	Spherical equivalent: (D) All eyes 0.25/0.30 0.25/0.35 preop -3.89 [5.16] -0.24 [2.01] -5.12 [5.55] postop -1.46 [4.11] 0.56 [1.44] -2.28 [4.65] p-value NR 0.05 <0.0001 I-S values: All eyes (n=65) 6.6 [3.55] (1.3 – 26.46) Difference preop to postop I-S value: 19.02 p=0.01 **Complications and adverse events** Successful implantation: (n of eyes) Not reported Explantation: (n of eyes) 6/74 (8.1%) – for hyperopia – 2 eyes/1 patient – for chronic foreign body sensation – 4 eyes/2 patients Complications (n of eyes) 4/74 (5.4%) Superficial channel dissection and anterior Bowman's layer perforation – 1 Transient inflammatory reaction – 2 Segment migration and externalisation – 1 Halos at night – 2 patients (? eyes) Keratolysis infection – 0 Anterior chamber perforation – 0

		No significant difference in change in BCVA and preoperative cylinder (p=0.43) In eyes with no change in postop BCVA, 24/40 (60%) gained ≥2 lines in UCVA, 11/40 (28%) had no change in UCVA and 5/40 (13%) lost ≥2 lines in UCVA Statistically significant relationship between postop change in UCVA and preop UCVA (p<0.001), preop spherical equivalent refraction (p<0.001) and preop I-S ratio (p=0.004). No significant difference in change in UCVA and preop cylinder (p=0.42)	

Study	Patients	Visual acuity postoperatively	Topographic findings
Colin et al 2001,[a] Colin et al 2000 (IV) Dates: Not stated Location: Bordeaux University Hospital, Pellegrin, Bordeaux; Brest University Hospital, Brest, FRANCE; and KeraVision Inc., Fremont, California, USA Patient selection: Consecutive Mean follow-up: 10.6 months Losses to follow-up: All 10 patients followed for 12 months but at 6 months UCVA n=8 and BSCVA and refraction n=9, and for keratometry at 1 month n=7, at 6 months n=5 and at 12 months n=7 Exclusions: BCVA <20/100 in treatment eye, corneal thickness <400 µm at location of implant insertion, corneal scarring When both eyes eligible for inclusion, eye with worse visual acuity included in analysis Device: Intacs	Keratoconus patients referred for penetrating keratoplasty with contact lens intolerance and clear corneas n=10 patients/10 eyes Mean age: 30.9 [6.1] years M/F: Not reported Central corneal thickness: 479 [32] µm Preop mean UCVA: (logMAR) 1.05 [0.33] Preop mean BCVA: (logMAR) 0.38 [0.13] Preop mean keratometry: (D) 53.2 [3.0] (50.2–58.2) Preop mean refractive cylinder: (D) -4.0 [1.9] **Details of surgery** Anaesthesia: Topical Intacs segments: 0.45 mm, 0.25 mm Segment placement: 0.45 mm inferiorly to lift conus, 0.25 mm superiorly to flatten cornea Depth of placement: Not reported Sutures: Single 10-0 nylon removed 1–4 weeks postop Postoperative eye treatment: Topical antibiotic/steroid combination and clear shield Surgeon details: One surgeon (JC)	Mean: (logMAR) 1 month 0.54 [0.22] 0.35 [0.19] 3 months 0.54 [0.31] 0.30 [0.31] 6 months 0.64 [0.37] 0.30 [0.21] 12 months 0.35 [0.16] 0.22 [0.12] Improvement in visual acuity over baseline: (Lines) UCVA p BCVA p 1 month 2 ≤0.05 2 NR 3 months 2 ≤0.05 3 NR 6 months 4 pns 2 NR 12 months 2 ≤0.05 1 NR	(Dioptres) Keratometry Refractive cylinder 1 month NR -1.9 [1.5] 3 months NR -2.1 [1.9] 6 months 48 [4.2] -2.8 [2.0] 12 months 48.6 [2.8] -1.3 [1.4] Preop to last follow-up: Keratometry p significant (?), but value not reported Refractive cylinder p<0.05 **Complications and adverse events** Successful implantation: (n of eyes) 10/10 (100%) – no intraoperative complications Explantation: (n of eyes) 1/10 at 2 months for superficial placement Complications (n of eyes): Mild to moderate intralamellar channel deposits at superior edge of inferior segment – 8 (?) to 10 (most eyes) Neovascularisation – 0

[a] It is likely there is patient crossover between this study and Colin (in press) and Colin et al (unpub.)

Study	Patients	Visual acuity postoperatively	Topographic findings
Colin in press [b] (IV) Dates: Not stated Location: Bordeaux University Hospital, Pellegrin, Bordeaux, FRANCE Patient selection: Consecutive Follow-up: 24 months Losses to follow-up: 14/100 eyes Exclusions: Not reported 4/100 explanted eyes excluded from analysis Total eyes in analysis: 82 Device: Intacs	Keratoconus patients referred for penetrating keratoplasty with contact lens intolerance and clear corneas and no corneal scarring n=82 patients/100 eyes Mean age: Not reported M/F: 53/29 Central corneal thickness: 478 [55] µm Proportion of patients with UCVA: (logMAR) <0.10 – 36/82 (43.9%) 0.10 to 0.20 – 37/82 (45.1%) 0.30 to 0.40 – 7/82 (8.5%) ≥0.50 – 2/82 (2.4%) Proportion of patients with BCVA: (logMAR) <0.10 – 3/82 (3.7%) 0.10 to 0.20 – 25/82 (30.5%) 0.30 to 0.40 – 36/82 (43.9%) ≥0.50 – 18/32 (22%) Preop mean keratometry: (D) 50.1 [5.6] Preop mean refractive cylinder: (D) -4.62 [2.8] Preop mean spherical equivalent: (D) -6.93 [3.91]	BCVA: (n of px) (logMAR) 12 months 24 months <0.10 0/82 (0%) 0/82 (0%) 0.10 to 0.20 15/82 (18.3%) 11/82 (13.4%) 0.30 to 0.40 25/82 (30.5%) 27/82 (32.9%) ≥0.50 42/82 (51.2%) 44/82 (53.7%) preop to last follow-up: p<0.001 Change in BCVA from preop: (n of px) 12 months 24 months +1 to +5 lines 50/82 (60.9%) 56/82 (68.3%) no change 28/82 (26.8%) 21/82 (25.6%) -1 to -4 lines 10/82 (12.2%) 12/82 (14.6%) p <0.001 for distribution of values for 12 and 24 months UCVA: (n of px) (logMAR) 12 months 24 months <0.10 4/81 (4.9%) 0/82 (0%) 0.10 to 0.20 49/81 (60.5%) 56/82 (68.3%) 0.30 to 0.40 18/81 (22.2%) 18/82 (22%) ≥0.50 10/81 (12.4%) 8/82 (9.8%) Preop to last follow-up: p<0.001 Change in UCVA from preop: (n of px) 12 months 24 months gain of 1 to 5 lines 56/81 (69.1%) 66/82 (80.5%) no change 18/81 (22.2%) 11/82 (13.4%) loss of 1 to 4 lines 7/81 (8.6%) 4/82 (4.9%) loss of ≥5 lines 0/81 (0%) 1/82 (1.2%) p <0.001 for distribution of values for 12 and 24 months	Keratometry: (D) 12 months 46.4 [5.3] p<0.001 compared to preop (n=81) 24 months 46.8 [4.9] p<0.001 compared to preop (n=77) Refractive cylinder: (D) 12 months -3.87 [2.5] p=0.002 compared to preop (n=81) 24 months -3.31 [1.83] p<0.001 compared to preop (n=77) Spherical equivalent: (D) 12 months -4.01 [3.16] p<0.001 compared to preop (n=81) 24 months -3.8 [2.73] p<0.001 compared to preop (n=77) Central corneal thickness: (µm) 12 months 434 [56] (n=81) 24 months 421 [54] (n=77)
	Details of surgery Anaesthesia: Topical Intacs segments: 0.45 mm, 0.40 mm Segment placement: Preop SE ≤3.0D – 0.40/0.40 mm Preop SE >3.0D – 0.45/0.45 mm Depth of placement: 70% of corneal thickness Sutures: None Postoperative eye treatment: Not reported Surgeon details: Not reported		Complications and adverse events 100/100 (100%) – no intraoperative complications Explantation: (n of eyes) 4/100 (4%) – one at 5 months, one at 8 months due to extrusion of one segment – two between 12 and 24 months due to poor visual outcome (→ penetrating keratoplasty) Complications: (n of eyes) Not reported

[b] It is likely there is patient crossover between this study and Colin (in press) and Colin et al (unpublished manuscript)

Study	Patients	Visual acuity postoperatively	Topographic findings
Colin et al unpub.[c] (IV) Dates: Sep 99 – Mar 02 Location: Bordeaux University Hospital, Pellegrin, Bordeaux, and Centre Hospitalier Regional et Universitaire de Brest, Brest, FRANCE The Rosen Eye Surgery Centre, The Alexandra Hospital Victoria Park, Manchester, UK ALZ Augenklinik, Munich, GERMANY Patient selection: Consecutive Follow-up: 6 months (some patients 12 months) Losses to follow-up: At 6 months 23/57 (40.3%) Exclusions: Not reported 1/58 eyes lost to follow-up before 1 month; not included in analysis Total eyes in analysis: 57 Device: Intacs	Patients with moderate to severe keratoconus and clear corneas n=57 eyes Mean age: Not reported M/F: Not reported Central corneal thickness: 487 [79.1] µm (n=56) Preop mean UCVA: (logMAR) 1.06 [0.33] (n=53) Preop mean BCVA: (logMAR) 0.40 [0.24] (n=57) Preop mean keratometry: (D) 49.7 [4.9] (n=56) Preop mean refractive cylinder: (D) -4.4 [2.4] (n=57) Preop mean spherical equivalent: (D) -4.6 [3.5] (n=57) **Details of surgery** Anaesthesia: Topical, oral, intravenous, general Intacs segments: 0.25 mm, 0.30 mm, 0.35 mm, 0.40 mm, 0.45 mm Segment placement: Asymmetrical cone – thicker segment inferiorly, thinner segment superiorly Global or central cone – same thickness superiorly and inferiorly Sutures: 10-0 or 11-0 nylon Postoperative eye treatment: Antibiotic/corticosteroid, plastic shield Surgeon details: Not reported Mean operative time: 20 [7] minutes	BCVA: (n of eyes) (logMAR) 3 months 6 months ≤0.10 6/31 (19.3%) 14/34 (41.2%) 0.10 to 0.20 11/31 (35.5%) 7/34 (20.6%) 0.20 to 0.30 5/31 (16.1%) 4/34 (11.8%) 0.30 to 0.40 3/31 (9.7%) 3/34 (8.8%) ≥0.50 6/31 (19.4%) 6/34 (17.6%) Significant improvement from 1 month to 6 month follow-up (p<0.033) Change in BCVA from preop to 6 months: (n of eyes) gain of 6–8 lines – 1/34 (3%) gain of 2–5 lines – 20/34 (59%) no change – 11/34 (32%) loss of ≥2 lines – 2/34 (6%) UCVA: (n of eyes) (logMAR) 3 months 6 months ≤0.10 0/29 (0%) 1/34 (2.9%) 0.10 to 0.20 1/29 (3.4%) 6/34 (17.6%) 0.20 to 0.30 4/29 (18.8%) 2/34 (5.6%) 0.30 to 0.40 4/29 (18.8%) 3/34 (8.8%) 0.50 to 0.70 8/29 (27.6%) 9/34 (26.5%) ≥0.80 12/29 (41.4%) 14/34 (41.2%) Change in UCVA from preop to 6 months: (n of eyes) gain of 2 or more lines – 27/34 (79%) no change or +/-1 line – 7/34 (21%) loss of ≥2 lines – 0/34 (0%)	Keratometry: (D) 3 months 46.5 [4.3] p<0.002 vs preop 6 months 46.0 [3.5] p<0.002 vs preop Change in refractive cylinder from preop: (D) 3 months -2.0 [1.6] (-5.0 – 1.0) (n=28) P<0.001 vs preop 6 months -1.5 [1.6] (-4.2 – 2.5) (n=30) p<0.001 vs preop Change in spherical equivalent from preop: (D) 3 months -2.8 [3.0] (-6.0 – 10.0) (n=28) 6 months -3.1 [2.5] (-1.6 – 8.7) (n=30) p<0.001 vs preop Central corneal thickness: (µm) No statistically significant changes over 12 months (p>0.085) **Complications and adverse events** Successful implantation: (n of eyes) 58/59 (98.3%) – no intraoperative complications Explantation: (n of eyes) 7/57 (12.3%) dissatisfaction with vision Complications (n of eyes) 10/34 (29.4%) Ocular infection – 0 Extrusion of implant – 0 Stromal thinning – 0 Severe conjunctival infection – 1 (at 7 months) Visual symptoms – 9/34 (26.4%): discomfort (1), itching (1), burning (1), photophobia (1), difficulty with night vision (1), glare (3), fluctuating vision (1)

		Patient-reported outcomes Visual symptoms: (n of reports) Preop 31/39 (79.5%): discomfort (4), foreign body sensation (1), photophobia (7), fluctuations (7), night vision (2), double vision (2), glare (1), halos (3), other (4) 3 months 21/28 (75%): foreign body sensation (1), photophobia (6), night vision (3), double vision (3), glare (5), halos (3) 6 months 9/23 (39%): discomfort (1), itching (1), burning (1), fluctuation (1), night vision (1), double vision (1), halos (3) Subjective quality of vision rating: (n of patients) Preop: poor 27/39 (69.2%) fair 8/39 (20.5%) good 4/39 (10.2%) excellent 0/39 (0%) 6 months: poor 5/21 (23.8%) fair 6/21 (28.6%) good 8/21 (38.1%) excellent 2/21 (9.5%) p<0.001 vs preop	

[c] It is likely there is patient crossover between this study and Colin (in press) and Colin et al (unpub.); these data were also presented to the 2004 Annual Symposium on Cataract, IOL and Refractive Surgery, San Diego, May 1–5, 2004 by J Colin

Study	Patients	Visual acuity postoperatively	Topographic findings
Hofling-Lima et al 2004 (IV) Dates: Dec 00 – Jan 02 Location: Department of Ophthalmology, Federal University of São Paulo/Paulista School of Medicine, São Paulo; Department of Ophthalmology, Federal University of Paraná, Paraná; and Department of Ophthalmology, Federal University of Rio Grande do Sul, Rio Grande do Sul, BRAZIL Patient selection: All patients with culture-proven infectious keratitis after ICRS Mean follow-up: 13.0 [7.7] (3 to 39) months Losses to follow-up: Not reported Exclusions: Stage I or IV keratoconus Only patients with 3 months of follow-up included in analysis Device: Ferrara	Keratoconus patients n=7 patients/7 eyes Mean age: 35 (28–47) years M/F: 2/5 Preop mean UCVA: Not reported Preop mean BCVA: Not reported Preop mean keratometry: Not reported Preop mean refractive cylinder: Not reported Preop mean astigmatism: Not reported Preop mean spherical equivalent: Not reported Risk factors for infection: Diabetes – 1 Contact lens use – 1 Trauma – 1 No identifiable risk factor – 4 Details of surgery Anaesthesia: Not reported Ferrara segments: Not reported Segment placement: Not reported Incision depth: Not reported Sutures: Not reported Postoperative eye treatment: Prophylactic antibiotics for 1 week after surgery Surgeon details: Not reported	Not reported	Not reported Complications and adverse events No intraoperative complications Time elapsed between surgery and infection: Less than 1 week – 2/7 eyes 2 to 4 weeks – 2/7 eyes More than 2 months – 3/7 Explantation as a result of infection: 4/7 eyes (2 eyes required PKP to control infection) Authors note that the triangular shape and depth of the Ferrara implant may lead to superficialisation of the ring particularly in thin keratonic corneas; Ferrara segments require multiple incisions possibly increasing the risk of wound infection (p548)

Study	Patients	Visual acuity postoperatively	Topographic findings
Kwitko & Severo 2004 (IV)[d] Dates: Not stated Location: Department of Ophthalmology, Hospital de Clinicas de Porto Alegre, Porto Alegre, BRAZIL Patient selection: All patients on waiting list for PKP Mean follow-up: 13.0 [7.7] (3 to 39) months Losses to follow-up: Not reported Exclusions: Stage I or IV keratoconus Only patients with 3 months of follow-up included in analysis Device: Ferrara	Keratoconus patients with clear central corneas and contact lens intolerance n=47 patients/51 eyes Mean age: Not reported M/F: Not reported Corneal ectasia: (central/inferior) 24/27 Preop mean UCVA: (logMAR) 1.37 [0.36] (0.60–2.00) Preop mean BCVA: (logMAR) 0.95 [0.47] (0.18–2.00) Preop mean keratometry: (D) 48.8 [4.0] Preop mean refractive cylinder: (D) -3.7 [2.2] (n=31) Preop mean astigmatism: (D) 6.4 [3.0] (n=31) Preop mean spherical equivalent: (D) -6.1 [5.0] (n=31) **Details of surgery** Anaesthesia: topical proximetacaine 0.5%) Ferrara segments: 0.20 mm, 0.25 mm, 0.30 mm, 0.35 mm Segment placement: – 0.20 mm for stage I keratoconus – 0.25 mm for stage II keratoconus (5 eyes) – 0.30 mm for stage III keratoconus (43 eyes) – 0.35 mm for stage IV keratoconus (3 eyes) Incision depth: 70% (14 eyes) or 80% (37 eyes) of local pachymetry Sutures: 10-0 nylon radial if implant in inferior corneal quadrant Postoperative eye treatment: Ketorolac every 15 minutes for 3 hours postop, 0.1% dexamethasone/0.3% tobramycin every 4 hours for 7 days, methylcellulose 0.5% every 6 hours for 30 days Surgeon details: All procedures done by same surgeon (SK)	Postop mean BCVA: (logMAR) 0.42 [0.25] (0.00 – 1.30) Change in BCVA preop to postop: (n of eyes) improvement – 45/51 (88.2%) no change – 1/51 (1.9%) deterioration – 5/51 (9.8%) Mean difference preop to last postop BCVA: (lines) +5.5 (-3 to +16) Postop mean UCVA: (logMAR) 0.74 [0.40] (0.00–2.00) Change in UCVA preop to postop: (n of eyes) improvement – 43/51 (84.3%) no change – 4/51 (7.8%) deterioration – 4/51 (7.8%) Mean difference preop to last postop UCVA: (lines) +6.5 (-4 to +15)	Postop mean keratometry: (D) 43.2 [4.8] p<0.001 compared to preop Postop mean refractive cylinder: (D) -2.2 [2.1] p<0.01 compared to preop Postop mean spherical equivalent: (D) -3.8 [4.0] p<0.01 compared to preop Postop mean astigmatism: (D) 4.8 [2.9] p<0.01 compared to preop **Complications and adverse events** Explantation: (n of eyes) 13/51 (25.5%) → all 13 had PKP – 3/51 (5.9%) no improvement in BCVA – 5/51 (9.8%) segment extrusion – 4/51 (7.8%) dissatisfied with visual acuity –1/51 (1.9%) segment decentration Complications: (n of eyes) 14/51 (27.4%) Ring decentration due to blunt trauma – 2/51 (3.9%) Ring extrusion – 10/51 (19.6%) (5 due to blunt trauma, 5 spontaneously) Disciform keratitis adjacent to segment – 1/51 (1.9%) (→ PKP) Presumed bacterial keratitis after ring extrusion – 1/51 (1.9%)

[d] VA in logMAR calculated from Snellen; VA for each individual eye from conversion chart in Holladay (2004); means and standard deviations calculated from individual patient data

Study	Patients	Visual acuity postoperatively	Topographic findings
Miranda et al 2003 (IV) Dates: Not stated Location: Department of Ophthalmology, Federal University of São Paulo/Paulista School of Medicine, São Paulo, and Department of Ophthalmology, São General Hospital, Belo Horizonte, BRAZIL Patient selection: Not stated Follow-up: 12 months Losses to follow-up: 5/36 (13.9%) – explantation (1) – unavailable for follow-up (2) – PKP (2) Exclusions: Corneal thickness <400 µm, previous corneal or ocular surgery, mean corneal curvature >80D, previous hydrops, PMD, monocular vision or other ocular disease that contraindicated for surgery, Down's syndrome, pregnancy, diabetes, collagen vascular disease, inherited metabolic disease, inability to attend follow-up Device: Ferrara	Keratoconus patients with clear central corneas and contact lens intolerance and suitable for PKP n=35 patients/36 eyes Mean age: 25.7 [7.8] (17–52) years M/F: 18/17 Central corneal thickness: 372 [55.5] µm Preop mean UCVA: Not reported Preop mean BCVA: Not reported Preop mean keratometry[e]: (D) 60.2 (n=21) Preop mean refractive cylinder: Not reported Preop mean astigmatism: Not reported Preop mean spherical equivalent: (D) -7.29 [3.12] **Details of surgery** Anaesthesia: Topical Ferrara segments: 0.25 mm, 0.30 mm, 0.35 mm Segment placement: – 0.20 mm for stage I keratoconus – 0.25 mm for stage II keratoconus (3 eyes) – 0.30 mm for stage III keratoconus (19 eyes) – 0.35 mm for stage IV keratoconus (14 eyes) Incision depth: 80% (37 eyes) of local pachymetry Sutures: None Postoperative eye treatment: Bandage contact lens, topical antibiotics, corticosteroids, nonsteroidal drops immediately postop; topical corticosteroid for 1 month postop Surgeon details: Not reported	Change in BCVA preop to 1 month postop: (n of eyes) gained ≥2 lines – 20/36 (55.6%) lost ≥2 lines – 1/36 (2.8%) gained or lost 1 line – 15/36 (41.6%) Change in BCVA preop to 3 months postop: (n of eyes) gained ≥2 lines – 26/36 (72.2%) lost ≥2 lines – 0/36 (0%) gained or lost 1 line – 10/36 (27.8%) Change in BCVA preop to 6 months postop: (n of eyes) gained ≥2 lines – 29/36 (80.6%) lost ≥2 lines – 0/36 (0%) gained or lost 1 line – 7/36 (19.4%) Change in BCVA preop to 12 months postop: (n of eyes) gained ≥2 lines – 27/31 (87.1%) lost ≥2 lines – 0/31 (0%) gained or lost 1 line – 4/31 (12.9%) Change in UCVA preop to 1 month postop: (n of eyes) gained ≥2 lines – 22/36 (61.2%) lost ≥2 lines – 1/36 (2.8%) gained or lost 1 line – 13/36 (36.1%) Change in UCVA preop to 3 months postop: (n of eyes) gained ≥2 lines – 28/36 (77.8%) lost ≥2 lines – 0/36 (0%) gained or lost 1 line – 8/36 (22.2%) Change in UCVA preop to 6 months postop: (n of eyes) gained ≥2 lines – 27/35 (77.1%) lost ≥2 lines – 0/35 (0%) gained or lost 1 line – 8/35 (22.9%) Change in UCVA preop to 12 months postop: (n of eyes) gained ≥2 lines – 25/31 (80.6%) lost ≥2 lines – 0/31 (0%) gained or lost 1 line – 6/31 (19.4%)	Postop mean keratometry at 1 month: (D) 53.7 sig compared to preop (p not reported) Postop mean keratometry at 3 months: (D) 52.9 sig compared to preop (p not reported) Postop mean keratometry at 6 months: (D) 52.1 sig compared to preop (p not reported) Postop mean keratometry at 12 months: (D) 51.7 sig compared to preop (p not reported) Postop mean spherical equivalent at 12 months: (D) -4.8 [3.0] **Complications and adverse events** Explantation: (n of eyes) 3/36 (8.3%) → 2 eyes PKP Complications: (n of eyes) 14/36 (38.9%) segment decentration – 1/36 segment asymmetry – 2/36 segment migration – 2/36 segment extrusion – 5/36 conjunctivitis – 1/36 hydrops – 1/36 infection (*Nocardia sp*) – 1/36 (eye had segment extrusion) inadequate depth – 2/36

[e] Keratometry measured using EyeSys Technologies 2000 System; flat and steep keratometry averaged

Study	Patients	Visual acuity postoperatively	Topographic findings
Nepomuceno et al 2003 (IV) Dates: Apr 00 – Apr 02 Location: Jules Stein Eye Institute, University of California, Los Angeles, California, and Boxer Wachler Vision Institute, Beverly Hills, California, USA Patient selection: Patients who received Intacs in one eye and were referred for contact lens fitting were identified from retrospective chart review Follow-up: 0.5 to 6.6 months Losses to follow-up: Not reported Exclusions: Patients with ectasia after surgical procedures who received Intacs Device: Intacs	Keratoconus patients n=3 patients/3 eyes Mean age: 36 (31–44) years M/F: 2/1 Preop mean UCVA: (logMAR) 2.00 (all 3 patients) Preop mean BCVA: (logMAR) 0.51 [0.30] (0.22–0.82) Preop manifest refraction: Px 1: -4.25, +3.0 x 154 Px 2:-10.25, +2.0 x 159 Px 3: -10.0, +5.75 x 043 **Details of surgery** Anaesthesia: Not reported Intacs segments: 0.25 mm, 0.30 mm, 0.35 mm Segment placement: Px 1: 0.30/0.35 Px 2: 0.25/0.35 Px 3: 0.30/0.35 Incision depth: Not reported Sutures: Not reported Postoperative eye treatment: Not reported Surgeon details: All procedures done by one surgeon (BBW)	Mean postop BSCVA: (logMAR) 0.30 [0.16] (0.12–0.44) Mean postop UCVA: (logMAR) 0.81 [0.25] (0.52–1.00) After contact lens fitting Mean BCLVA: (logMAR) 0.02 [0.10] Number of contact lenses ordered during 4-month follow-up ranged from 1 to 3 Mean final wearing time: 2.5–12 hours One patient had contact lens–related complications on the day of fitting (trace papillary reaction under upper eyelid) Over 4-month follow-up, 1 patient developed 3-9 staining and a dellen – addressed and resolved	Postop manifest refraction: Px 1: -6.25, +5 x 031 Px 2: -3.0, +4.0 x 151 Px 3: -6.75, +1.5 x 60 **Complications and adverse events** Not reported

Study	Patients	Visual acuity postoperatively			Topographic findings		
Siganos, C.S. et al 2003 (IV) Dates: Not stated Location: Department of Ophthalmology and the Vardinoyannion Eye Institute of Crete, University of Crete, Heraklion, Crete, GREECE Patient selection: Not reported Mean follow-up: 11.3 [6.5] (1–24) months Losses to follow-up: Not reported Exclusions: Previous intraocular or corneal surgery, history of herpes keratitis, diagnosed autoimmune disease, systemic connective tissue Device: Intacs	Keratoconus patients with clear central corneas and contact lens intolerance n=26 patients/33 eyes Mean age: 32.0 [9.7] years M/F: 17/9 Corneal ectasia: (central/interior) 14/19 Preop mean UCVA: (logMAR) 0.90 [0.90] Preop mean BCVA: (logMAR) 0.35 [0.50] Preop mean keratometry: (D) 50.86 [6.62] (41.67–71.0) Preop mean refractive cylinder: (D) -5.67 [4.81] Preop mean astigmatism: 3.33 [2.1] **Details of surgery** Anaesthesia: Topical Intacs segments: 2 x 0.45 mm Segment placement: – in eyes with inferior corneal ectasia Intacs segments inserted superiorly-inferiorly (embracing steep axis) – in eyes with central corneal ectasia Intacs segments inserted nasally-temporally Depth of placement: 70% of corneal thickness Sutures: Single 10-0 nylon removed 2 weeks postop Postoperative eye treatment: Antibiotic/corticosteroid combination eye drops 4 times daily for 2 weeks Surgeon details: All procedures done by 2 surgeons (CSS, IGP)	Mean: (logMAR)	UCVA	BCVA		Keratometry (D)	Refractive cylinder (D)
		1 month	0.44	0.25	1 month	47.56	-4.2
		3 months	0.40	0.19	3 months	46.5	-2.5
		6 months	0.32	0.15	6 months	46.2	-2.2
		9 months	0.30	0.14	9 months	46.1	-2.2
		12 months	0.30	0.13	12 months	47.1	-3.3
		18 months	0.30	0.11	18 months	46.2	-2.5
		24 months	0.29	0.10	24 months	45.0	-1.9
		Last follow-up	0.40 [0.56]	0.20 [0.60]	Last follow-up	47.63 [5.41] (37.54–57.56]	-4.28 [3.86] (0 to -16.5)
		Preop to last follow-up: UCVA p<0.01 BCVA p<0.01			Preop to last follow-up: keratometry p<0.01 refractive cylinder p=0.05		
		Correlation between preop and last follow-up: UCVA r^2 = 0.13 BCVA r^2 = 0.62			Mean reduction in keratometry preop to last follow-up: (D) 1.94 [3.51] (4.56 to -13.75) Mean reduction in refractive cylinder preop to last follow-up: (D) 1.82 [3.3]		
		Change in BCVA preop to postop: (n of eyes) gain of 1 to 6 lines – 25/33 (66%) no change – 4/33 (12%) loss of 1 to 2 lines – 4/33 (12%)			Astigmatism at last follow-up: (D) 3.06 [2.14] (preop to last follow-up: p=0.44)		
		Change in UCVA preop to 6 months: (n of eyes) gain of 1 to 6 lines – 28/33 (85%) no change – 3/33 (9%) loss of 1 to 2 lines – 2/33 (6%)			**Complications and adverse events** All procedures uneventful Successful implantation: (n of eyes) 33/33 (100%) Explantation: (n of eyes) 2/33 (6%) – one due to patient dissatisfaction, one due to superficial placement 1/33 (3%) – one segment removed and the other adjusted at 6 months Channel deposits at inner edge of segments: most eyes (6 months) Superficial mild wound site neovascularisation – 1 eye (2 months)		
		Mean difference preop to last postop UCVA: (lines) +2.5 (-1 to +10) Mean difference preop to last postop BCVA: (lines) +1.7 (-2 to +6)					

Study	Patients	Visual acuity postoperatively	Topographic findings
Siganos, D. et al 2002 (IV) Dates: Not stated Location: Vlemma Eye Institute, Athens, GREECE Patient selection: Not reported Follow-up: At least 6 months Losses to follow-up: Not reported Exclusions: Corneal thickness <400 µm 2 patients explanted and excluded from postop analysis Device: Ferrara	Keratoconus patients with clear central corneas and contact lens intolerance and eligible for PKP n=26 patients/26 eyes Mean age: 29.6 [9.6] years M/F: 18/8 Corneal ectasia: (central/interior) 14/19 Preop mean UCVA: (logMAR) 1.18 [1.00] Preop mean BCVA: (logMAR) 0.40 [0.54] Preop mean keratometry: Not reported. Preop mean refractive cylinder: (D) -4.4 [2.2] Preop mean spherical equivalent: (D) -6.9 [5.0] **Details of surgery** Anaesthesia: Topical Ferrara segments: 2 x 160° segments, 0.15 mm, 0.20 mm, 0.25 mm, 0.30 mm, 0.35 mm Segment placement: <-4.0D myopia – 0.15 mm -4.25D to -6.0D myopia – 0.20 mm -8.25D to -10.0D myopia – 0.30 mm >-10.0D myopia – 0.35 mm Incision depth: 80% of minimum corneal thickness Sutures: None – wound closed by hydration Postoperative eye treatment: Therapeutic soft contact lens for 48 hours; topical antibiotic/steroid (tobramycin 0.3% dexamethasone 0.1%) 4 times a day for 2 weeks, artificial tears 4 times a day for 2 weeks Surgeon details: Not stated	Postop mean BCVA: (logMAR) 1 month – 0.30 [0.40] 6 months – 0.20 [0.70] Postop mean UCVA: (logMAR) 1 month – 0.54 [1.00] 6 months – 0.40 [0.70]	Postop mean refractive cylinder: (D) 1 month -3.2 [1.5] 6 months -2.2 [1.0] Postop mean spherical equivalent: (D) 1 month -2.8 [2.6] 6 months -1.1 [2.6] **Complications and adverse events** All procedures uneventful Successful implantation: (n of eyes) 24/26 (92.3%) Explantation: (n of eyes) 2/26 (7.6%) – one due to superficial placement, other due to incorrect placement No patient complained of nighttime glare or halos after first month

Study	Patients	Visual acuity postoperatively			Topographic findings
Tunc et al 2003 (IV) (French language) Dates: Dec 98 – Jun 00 Location: Service D'Ophthalmologie, Kadir Has University, Istanbul, TURKEY Patient selection: Could not determine Mean follow-up: 36.6 months Losses to follow-up: None Exclusions: Opacified cornea (1) Device: Intacs	Keratoconus patients with asymmetrical astigmatism, clear corneas and contact lens intolerance n=7 patients/9 eyes Mean age: 27.7 [11.2] years M/F: Not reported Central corneal thickness: Not reported Preop mean UCVA[f]: (logMAR) 0.41 [0.28] Preop mean BCVA[f]: (logMAR) 2.45 [2.15] Preop mean keratometry: (D) 55.28 [8.08] Preop mean refractive cylinder: (D) -5.08 [2.27] Preop mean SE: (D) -8.65 [6.43]	Mean visual acuity[f]	UCVA	BCVA	Keratometry: (D) 1 month 50.64 [6.74] 3 months 50.26 [7.68] 12 months 50.77 [7.89] 24 months 50.86 [7.35] Refractive cylinder: (D) 1 month -2.11 [0.98] 3 months -2.88 [1.93] 12 months -2.72 [1.91] 24 months -2.61 [1.87] Spherical equivalent: (D) 1 month -3.56 [1.93] 3 months -3.01 [2.16] 12 months -2.97 [2.31] 24 months -3.04 [2.23]
		1 month	3.55 [2.70]	4.51 [2.66]	
		3 months	4.33 [3.32]	5.11 [2.93]	
		12 months	4.62 [3.17]	5.55 [2.88]	
		24 months	3.73 [2.37]	5.66 [2.18]	
		2 eyes: UCVA 10/10 (=20/20?) after 2 months 7 eyes: UCVA 2/10 to 7/10 Results stable up to 24 months			
	Details of surgery				Complications and adverse events
	Anaesthesia: Topical Intacs segments: Not reported Segment placement: Centred to the cone of the cornea Depth of placement: 68% of peripheral corneal depth Sutures: 10-0 nylon removed 1 to 4 weeks postop Postoperative eye treatment: Steroids, antibiotics and eye drops Surgeon details: One surgeon (ZT)				No intraoperative complications Explantation: (n of eyes) 1/9 due to superficial placement

[f] Visual acuity in mean lines/10

Study	Patient	Visual acuity postoperatively	Topographic findings
Hladun & Harris 2004 (IV) Case report Dates: Not stated Location: University of California at Berkeley, College of Optometry, Berkeley, California Patient selection: Not applicable Follow-up: 3 months Losses to follow-up: Not applicable Exclusions: Not applicable Device: Intacs	Keratoconus patient with contact lens intolerance n=1 patient/1 eye Age: 51 years M/F: Male Preop UCVA: Not reported Preop BCVA: (logMAR) Right: 0.50, left: 0.30 Preop keratometry: Not reported Preop refractive cylinder: Not reported Preop astigmatism: Not reported Preop SE: Not reported Corneal thickness: 520 µm **Details of surgery** Anaesthesia: Not reported Intacs segments: 0.25 mm, 0.35 mm Segment placement: 0.25 mm superior nasal to cone centre, 0.35 mm inferior temporal to cone centre Incision depth: 66% of peripheral depth (390 µm) Sutures: Not reported Postoperative eye treatment: Not reported Surgeon details: Not reported	Postop BCVA: (logMAR) 0.60 Change in BCVA preop to postop: (logMAR) -0.20 Difference preop to last postop BCVA: (lines) Loss of 4 Postop UCVA: (logMAR) 1.00 Change in UCVA preop to postop: Not reported Difference preop to last postop UCVA: Not reported **Contact lens fitting** Post contact lens BCVA: 0.10 logMAR Improvement over Intacs alone: 5 lines Improvement over pre-Intacs: 2–4 lines	Postop keratometry: (D) Approximately 60.0 Postop refractive cylinder: Not reported Postop spherical equivalent: Not reported Postop astigmatism: Not reported **Complications and adverse events** Due to topography of cornea with Intacs present, eye had bubbles of varying size constantly just above corneal ridge created by lower segment (did not interfere with vision) and area of bearing on epithelial surface overlying inferior segment – led to irritation and light sensitivity caused by corneal edema overlying inferior segment – patient given a piggyback soft-rigid contact lens system to use – over 3-month follow-up no problems with irritation or corneal staining

Iatrogenic corneal ectasia

Study	Patients	Visual acuity postoperatively	Topographic findings
Alio et al 2002 (IV) Dates: Not reported Location: Department of Corneal and Refractive Surgery, Instituto Oftalmológico de Alicante, and Miguel Hernández University School of Medicine, Alicante, SPAIN Patient selection: Not reported Mean follow-up: 8.3 (7–11) months Losses to follow-up: Not reported Exclusions: Not reported Device: Intacs	Post-LASIK corneal ectasia n=2 patients/3 eyes Age: (years) Px 1: 28, Px 2: 29 M/F: Px 1: male, Px 2: female Eyes implanted: Px 1: right, Px 2: right and left Preop UCVA: (logMAR) Px 1: 0.60 Px 2: right: 0.70, left: 1.00 Mean: 0.77 Preop BCVA: (logMAR) Px 1: 0.20 Px 2: right: 0.30, left: 0.30 Mean: 0.27 Preop keratometry: (D)[g] Px 1: 53.0 Px 2: right: 53.3, left: 55.2 Mean: 53.8 Preop manifest refraction: (D) Px 1: -3.25 sphere Px 2: right: -2.00 -1.00 x 30, left: -5.00 -0.50 x 90 Time since LASIK: (months) Px 1: 37, Px 2: 36 **Details of surgery** Anaesthesia: Not reported Intacs segments: Px 1: 2 x 0.35 mm Px 2: 2 x 0.45 mm in each eye Segment placement: Not reported Depth of placement: 70% of corneal thickness Sutures: 1–2 imbedded 10-0 nylon Postoperative eye treatment: Topical antibiotic and fluorometholone eye drops, topical diclofenac sodium 1% Surgeon details: Not reported	BCVA at 6 months postop: (logMAR) Px 1: 0.20 (no change) Px 2: right: 0.30, left: 0.30 (no change either eye) Mean: 0.27 (0 lines) UCVA at 6 months postop: (logMAR) Px 1: 0.30 (gain of 3 lines) Px 2: right: 0.30 (gain of 3 lines), left: 0.40 (gain of 6 lines) Mean: 0.33 (gain of 4 lines)	Keratometry at 6 months postop: (D) Px 1: 50.9; Px 2: right: 52.0, left: 52.4 Mean: 51.8 Change in keratometry preop to 6 months postop: (D) Px 1: 2.1; Px 2: right: 1.3, left: 2.8 Mean: 2.1 Manifest refraction at 6 months postop: (D) Px 1: +0.50 -0.50 x 60 Px 2: right: -1.00 cylinder x 70, left: -1.50 -1.00 x 70 **Complications and adverse events (n of eyes)** All procedures uneventful No complications reported

[g] Posterior surface elevation

Study	Patients	Visual acuity postoperatively	Topographic findings
Guell et al 2004 (IV) Dates: Not reported Location: Cornea and Refractive Surgery Unit, Instituto de Microcirugia Ocular, Barcelona, SPAIN Patient selection: Not reported Mean follow-up: 6.0 (3–10) months Losses to follow-up: Not reported Exclusions: Not reported Device: Intacs	Post-LASIK corneal ectasia or decentration n=5 eyes Mean age: Not reported M/F: Not reported Residual corneal stromal thickness: Not reported Preop mean UCVA: (logMAR) 1.34 [0.61] (0.70–2.00) Preop mean BCVA: (logMAR) 0.32 [0.10] (0.20–0.40) Preop mean keratometry: (D) 37.8 [1.2] (36.2–39.3) Preop mean spherical equivalent: (D) -4.00 [0.31] (-3.75 to -4.50) Time since LASIK: (months) 14 to 72 **Details of surgery** Anaesthesia: Topical Intacs segments: 0.25 mm, 0.30 mm, 0.35 mm, 0.40 mm, 0.45 mm Segment placement: Centred on steepest meridian Depth of placement: 66% of corneal thickness Sutures: Single 10-0 nylon Postoperative eye treatment: Dexamethasone and tobramycin eye drops every 6 hours for 2 weeks Surgeon details: Not reported	BCVA at last follow-up: (logMAR) 0.22 [0.04] (0.20–0.30) Change in BCVA preop to last follow-up: +2 lines – 2/5 +1 line – 1/5 no change – 2/5 Mean change in BCVA preop to last follow-up: (lines) +1.0 [1.0] (0 to +2) UCVA at last follow-up: (logMAR) 0.32 [0.20] (0.20–0.70) Change in UCVA preop to last follow-up: +5 to +8 lines – 3/5 +9 or more lines – 2/5 no change – 0/5 Mean change in UCVA preop to last follow-up: (lines) +10.2 [5.3] (+5 to +18)	Postop mean keratometry: (D) 34.2 [1.1] (33.2–36.1) Mean reduction in keratometry: (D) 3.6 [0.6] (3.0–4.4) Postop mean spherical equivalent: (D) -0.95 [0.48] (-0.25 to -1.25) Mean reduction in spherical equivalent: (D) -3.1 [0.33] (-2.75 to -3.5) **Complications and adverse events** All procedures uneventful except for some epithelial damage at incision site (n of eyes not reported) No disruption to LASIK flap Successful implantation: (n of eyes) Not reported Explantation: (n of eyes) 1/5 due to progressive stromal lysis Complications: (n of eyes) 1/5 progressive stromal lysis – after explantation no sign of ulceration or epithelial growth and VA stable Dry eye symptoms in some patients for 3 to 6 weeks after surgery

Study	Patients	Visual acuity postoperatively	Topographic findings
Kymionis et al 2003, Siganos, D. et al (IV) Dates: Not reported Location: Department of Ophthalmology and the Vardinoyannion Eye Institute of Crete, University of Crete, Heraklion, Crete, GREECE Patient selection: Not reported Mean follow-up: 15.0 [6.5] (6–24) months Losses to follow-up: 1/10 at 12 months, 7/10 at 24 months, but 'last follow-up' 0/10[g]. Exclusions: Other ocular diseases Device: Intacs	Post-LASIK corneal ectasia n=7 patients/10 eyes Mean age: 40.7 [6.0] (33–46) years M/F: 2/5 Ectasia: (unilateral/bilateral) 3/4 Residual corneal stromal thickness: 240 [49.2] µm (175–325) Preop mean UCVA: (logMAR) 2.00 to 0.70 Preop mean BCVA: (logMAR) 0.30 to 0.00 Preop mean keratometry: (D) 40.2 [3.5] (37.4–48.3) Preop mean spherical equivalent: (D) -4.8 [3.2] (-13.8 to -2.5) Mean time since LASIK: (months) 47.1 [36.9] (12–108) Details of surgery Anaesthesia: Topical Intacs segments: 2 x 0.30 mm (2 eyes), 0.35 mm (3 eyes), 0.40 mm (4 eyes), 0.45 mm (1 eye) Segment placement: Nasotemporal Depth of placement: 70% of corneal thickness Sutures: Single interrupted 10-0 nylon; removed 2 weeks postop Postoperative eye treatment: Antibiotic/steroid eye drops 4 times daily for 1 week, artificial tears frequently Surgeon details: All procedures done by 2 surgeons (IGP, CSS)	BCVA at last follow-up: (logMAR) 6/10 eyes ≤0.10 (0.40 to 0.00) Change in BCVA preop to last follow-up: +2 lines – 3/10 +1 line – 4/10 no change – 3/10 Mean change in BCVA preop to last follow-up: (lines) +1.0 [0.8] (0 to +2) Postop BCVA compared with pre-LASIK BCVA: same – 8/10 (ie restored pre-LASIK BCVA) +1 line – 1/10 -2 lines – 1/10 UCVA at last follow-up: (logMAR) 9/10 eyes ≥0.3 (1.3 to 0.0) Change in UCVA preop to last follow-up: +6 to +8 lines – 4/10 +9 lines – 5/10 no change – 1/10 Mean change in UCVA preop to last follow-up: (lines) +7.4 (0 to +9)	Postop mean keratometry: (D) 37.1 [3.9] (33.0–45.5) (p<0.01 compared to preop) Mean reduction in keratometry: (D) 3.1 [0.8] (-4.4 to -1.9) Postop mean spherical equivalent: (D) -1.0 [2.9] (-8.8 to 2.5) (p=0.001 compared to preop) Mean reduction in spherical equivalent: (D) 3.9 [1.3] (-6.8 to -2.5) Complications and adverse events (n of eyes) All procedures uneventful No disruption to LASIK flap Successful implantation: (n of eyes) 10/10 Explantation: (n of eyes) Not reported Complications (n of eyes) 2/10 – superficial mild wound site neovascularisation At 9 months most eyes showed mild channel deposits at the inner edge of the segments In one eye (with advanced ectasia) 3 to 6 months postop BSCVA decreased and topographic irregularity increased → repeat LASIK, adjustment of Intacs segments – BSCVA improved and remained stable up to 10 months later

[g] This probably indicates variable follow-up for all 10 eyes when results reported as 'at last follow-up'

Study	Patients	Visual acuity postoperatively	Topographic findings
Lovisolo & Fleming 2002 (IV) Dates: Jan 00 – Jan 02 Location: Vista Vision Laser Center, Milan, ITALY Patient selection: Not reported. Follow-up: (months) Px 1 – 17 Px 2 – 5 Px 3 – 0.5 Px 4 – 10 Losses to follow-up: None Exclusions: Not reported Device: Intacs and Ferrara	Patients with post-LASIK or post-PRK corneal ectasia after treatment for myopia or keratoconus n=4 patients/4 eyes Mean age: 36.0 [5.0] (30–41) years M/F: 3/1 Residual corneal stromal thickness: Not reported Preop mean UCVA: (logMAR) All patients: 1.33 [0.53] (0.70–2.00) Px 1 to 3: 1.10 [0.35] (0.70–1.30) Px 4: 2.00 Preop mean BCVA: (logMAR) All patients: 0.80 [0.40] (0.18–1.00) Px 1 to 3: 0.70 [0.50] (0.18–1.00) Px 4:1.00 Preop keratometry: (D) Px 2: 44.8, Px 4: 66.0 Previous refractive surgery: Px 1, 4: PRK (for myopia px 1, for keratoconus px 4) Px 2, 3: LASIK (for myopia) Mean time since surgery: (months) 45.8 (33–60) **Details of surgery** Anaesthesia: Topical Intacs segments: Intacs: 0.25 mm, 0.30 mm, 0.35 mm, 0.45 mm; Ferrara: 0.30 mm Segment placement: (inferior/superior) Px 1: 0.45 mm/0.30 mm Intacs Px 2: 0.45 mm/0.25 mm Intacs Px 3: 0.35 mm/0.25 mm Intacs Px 4: 0.30 mm x 2 Ferrara Depth of placement: Px 2: inferior segment at 80%, superior segment at 60% Sutures: None Postoperative eye treatment: Antibiotic/steroid eye drops 4 times daily for 1 week, artificial tears frequently Surgeon details: All procedures done by 2 surgeons (IGP, CSS)	BCVA at last follow-up: (logMAR) All patients: 0.35 [0.26] (0.00–0.54) Px 1 to 3: 0.38 [0.27] (0.00–0.54) Px 4: 0.54 Mean change in BCVA preop to last follow-up: (lines) All patients: +4.5 [2.1] (+1.8 to +7) Px 1 to 3: +4.5 [2.6] (+1.8 to +7) Px 4: +4.6 Postop BCVA compared with pre-surgery BCVA: Px 1: return to pre-surgery BCVA Px 2: deterioration of 5.4 lines Px 3: return to pre-surgery BCVA Px 4: return to pre-surgery BCVA UCVA at last follow-up: (logMAR) All patients: 0.53 [0.29] (0.10–0.70) Px 1 to 3: 0.48 [0.33] (0.10–0.70) Px 4: 0.70 Mean change in UCVA preop to last follow-up: (lines) All patients: +8.1 [3.3] (+6 to +13) Px 1 to 3: +6.5 [0.5] (+6 to +7) Px 4: +13	Postop keratometry: (D) Px 2: 44 Px 4: 66 Change in keratometry from preop: (D) Px 2: 0.79 Px 4: 21.2 **Complications and adverse events** No intraoperative or postoperative complications and short-term results stable

Study	Patients	Visual acuity postoperatively	Topographic findings
Pokroy et al 2004 (IV)[h] Dates: 2002 Location: Enamin Refractive Surgery Center, Jerusalem, ISRAEL Patient selection: Consecutive Follow-up: At least 9 months Losses to follow-up: Not reported Exclusions: LASIK flap or interface pathology, central corneal scarring, ocular surface or intraocular pathology, follow-up less than 9 months, spherical equivalent greater than -4.5D (received 2 Intacs segments not 1) Device: Intacs	Patients with keratectasia after LASIK n=5 patients/5 eyes Mean age: 35.6 (24–44) years M/F: Not reported. Central corneal thickness: Not reported Preop mean UCVA: (logMAR) 0.80 (0.30–1.30) Preop mean BCVA: (logMAR) 0.28 (0.10–0.40) Preop mean keratometry: Not reported Preop mean refractive cylinder: Not reported Preop mean I-S: (D) 7.9 Preop manifest refraction: Px 1: -2.25 -4.00 x 60 Px 2: -0.50 -2.25 x 130 Px 3: +0.75 -2.25 x 120 Px 4: +1.00 -2.00 x 110 Px 5: +2.75 -9.00 x 125 Mean time since LASIK surgery: (months) 27.2 (17–32) **Details of surgery** Anaesthesia: Not reported Intacs segments: 1 x 0.25 mm, 0.30 mm, 0.35 mm, 0.40 mm, 0.45 mm Segment placement: Inferior only SE >-0.5D – 0.25 mm or 0.30 mm SE -0.75 to -2.25D – 0.35 mm or 0.40 mm SE -2.5 to -4.5D – 0.45 mm Depth of placement: 66% of corneal thickness Sutures: 10-0 nylon removed 1 to 4 weeks postop Postoperative eye treatment: Steroids, antibiotics and eye drops for 3 weeks Surgeon details: Not reported	Postop mean BCVA: (logMAR) 0.10 (0.00–0.20) Postop mean UCVA: (logMAR) 0.32 (0.60–0.20) Mean change in visual acuity preop to postop: (lines) BSCVA: +1.8 (+1 to +3) UCVA: +4.8 (0 to +10) All eyes had improved visual acuity postoperatively **Patient-reported visual function** Px 1: blurred to improved Px 2: blurred to distance vision improved Px 3: blurred to distance vision improved Px 4: blurred and distorted to little change Px 5: blurred and distorted to improved 2/5: vision improved 2/5: distance vision improved 1/5: little change	Keratometry: Not reported Refractive cylinder: Not reported Spherical equivalent: Not reported Postop mean I-S asymmetry value: (D) 2.5 Manifest refraction: Px 1: -1.00 -2.25 x 70 Px 2: +0.50 -1.25 x 130 Px 3: +1.00 -1.00 x 110 Px 4: +1.00 -1.00 x 110 Px 5: -0.75 -2.00 x 130 **Complications and adverse events** No flap disruption No corneal buttonholing No segment extrusion

[h] Means were calculated from individual data for all five patients

Study	Patient	Visual acuity postoperatively	Topographic findings
Shehadeh-Masha'our et al 2004 (IV) Case report. Dates: September 2002. Location: Bnai Zion Medical Center – Rappaport Faculty of Medicine Technion and Vision Without Glasses Medical Centre, Haifa, and Porriah Governmental Hospital, Porriah, ISRAEL Patient selection: NA Follow-up: Immediately postoperative Losses to follow-up: NA Exclusions: NA Device: Intacs	53-year-old man with post-LASIK corneal ectasia in the left eye UCVA: (logMAR) 1.00 Manifest refraction: -4.25 -5.00 x 116 Details of surgery Anaesthesia: Not reported Intacs segments: 1 x 0.25 mm, 1 x 0.35 mm Segment placement: Corneal midperiphery Depth of placement: Not reported Sutures: Suture removed 2 days after implantation to improve visual acuity Postoperative eye treatment: Topical antibiotics and steroids Surgeon details: Not reported	No improvement in visual acuity immediately postop After resolution of infection, BCVA 0.30 logMAR at last follow-up	Not reported Complications and adverse events Procedure uneventful No disruption to LASIK flap Explantation: Lower 0.25 mm segment replaced with 0.45 mm segment after no improvement in VA After infection developed both segments explanted Complications: 3 days after sutures removed a gap in corneal incision developed and there was infiltrate at the incision site. Patient treated with topical tobramycin, lomefloxacin and dexamethasone hourly. Infection progressed to lower channel infection; after removal of Intacs infection progressed to diffuse keratitis with infiltrates in upper channel and VA deteriorated to count fingers at 1 metre. Cultures returned positive for *Staphylococcus* and patient was hospitalised and treated with topical fortified cefamezin, gentamicin, vancomycin and ciprofloxacin hourly and with subconjunctival injections of gentamicin and vancomycin. No improvement so channel irrigation with vancomycin; next 3 weeks some resolution but gas bubbles developed at corneal interface. Transferred to second hospital and amikacin treatment. Over 2 months anterior chamber reaction resolved completely and corneal infiltrate regressed. Patient left with neovascularised opacity in nasal part of lower channel.

Non-iatrogenic corneal ectasia

Study	Patient	Visual acuity postoperatively	Topographic findings
Kymionis et al 2004 (IV) Case report Dates: Not stated Location: Department of Ophthalmology and Vardinoyannion Eye Institute of Crete, University of Crete, Heraklion, GREECE Patient selection: NA Follow-up: 11 months Losses to follow-up: NA Exclusions: NA Device: Intacs	42-year-old man with pellucid marginal degeneration and contact lens intolerance Eye implanted: right UCVA: (logMAR)1.30 BCVA: (logMAR) 0.40 Manifest refraction: +3.75 -8.50 x 85 Central corneal thickness: 550 µm **Details of surgery** Anaesthesia: Topical Intacs segments: 2 x 0.45 mm Segment placement: Nasal-temporal Depth of placement: 70% of thinnest corneal measurement Sutures: Single 10-0 nylon removed after 2 weeks Postoperative eye treatment: Antibiotic-steroid eye drops 4 times a day for 2 weeks Surgeon details: Not reported	BCVA at 11 months postop: (logMAR) 0.10 UCVA at 11 months postop: (logMAR) 1.00	Manifest refraction 11 months postop: +4.50 -5.50 x 85 **Complications and adverse events** Procedure was uneventful No complications reported

Study	Patient	Visual acuity postoperatively	Topographic findings
Rodriguez-Prats et al 2003 (IV) Case report Dates: Not stated Location: Department of Corneal and Refractive Surgery and Department of Contact Lenses, Instituto Oftalmológico de Alicante and Miguel Hernández University School of Medicine, Alicante, SPAIN Research Institute of Ophthalmology, Cairo, EGYPT Patient selection: NA Follow-up: 3 months Losses to follow-up: NA Exclusions: NA Device: Intacs	36-year-old man with pellucid marginal degeneration UCVA: (logMAR) 1.30 BCVA: (logMAR) 1.00 Manifest refraction: -2.0 -7.0 x 90 Corneal thickness: 420 µm at periphery Details of surgery Not reported.	No improvement in visual acuity immediately postop so contact lens fitting trialled Visual acuity without contact lens at 1month postop: (logMAR) BCVA: 0.50 UCVA: 0.70 BCVA with hybrid rigid-soft contact lens: (logMAR) 1 month: 0.10 6 months: 0.00	Manifest refraction 1 month postop: -8.0 -7.0 x 50 Complications and adverse events No refractive or surgical complications No decreased corneal sensation or iron line inside ring At 3 months inferior segment migrated but this did not affect VA or contact lens use Minute crystalline deposits surrounding the ring, grade I halos and epithelial cysts within the incision were reported

Appendix F Abstracts from conference presentations

Keratoconus

Study	Level	Conference	Patient group	Effectiveness	Safety
Costa et al 2001 Costa, P., Marinho, A., Pinto, C., Vaz, F., Pinto, R. & Torres, P. 'ICR in keratoconus' Device: Not reported	IV	2001 Annual Symposium on Cataract, IOL and Refractive Surgery, Fort Lauderdale, Florida, USA, 29 April – 1 May 2001	18 patients with keratoconus Follow-up: 3 months	Gains in lines of BCVA in all patients and changes in refraction and keratometry Size of change was not predictable and poor correlation between topographic change and number of lines of VA gained	Not reported
De Lange 2003 De Lange, J. 'Intacs for keratoconus' Device: Intacs	IV	2003 Annual Symposium on Cataract, IOL and Refractive Surgery, San Francisco, California, USA, 12–16 April 2003	11 eyes with keratoconus or forme fruste keratoconus and no benefit from glasses or contact lenses Follow-up: 7–13 months 2 groups: Group 1: patients with keratoconus Group 2: patients with forme fruste keratoconus	Group 1: patients with keratoconus BCVA: 0.3–0.7 UCVA: 0.2–0.6 Results not as satisfactory as for Group 2 Group 2: patients with forme fruste keratoconus BCVA: 0.8–1.2 UCVA: 0.6–0.8 High patient satisfaction	Not reported
Dvali et al 2004 Dvali, M., Tsintasadze, N., Sirbiladze, B. & Gilbradze, K. 'New approach to the treatment of keratoconus' Device: Ferrara	IV	2004 Joint Meeting of the American Academy of Ophthalmology and European Society of Ophthalmology, New Orleans, Louisiana, USA, 23–26 October 2004	14 cases of keratoconus Follow-up: 6–12 months	UCVA and keratometry data for anterior and posterior surface (minimum by 3.0D) were improved in 14/14 (100%) p<0.001 Topographical irregularity stable over follow-up	Not reported

Study	Level	Conference	Patient group	Effectiveness	Safety
Forseto 2003 Forseto, A. 'Keratoconus evaluation after Intacs insertion: one-year follow-up' Device: Intacs	IV	2003 Annual Symposium on Cataract, IOL and Refractive Surgery, San Francisco, California, USA, 12–16 April 2003	10 eyes (10 patients) with keratoconus and contact lens intolerance 2 vertical segments inserted through a stromal radial incision Segments used: 0.25 mm – 1 0.35 mm – 1 0.40 mm – 3 0.45 mm – 5 Mean follow-up: 13.6 [2.1] months	BCVA: (n of eyes) gain of 3 or more lines – 4/10 gain or loss of less than 3 lines – 4/10 no change – 2/10 Mean UCVA improved significantly and remained stable throughout follow-up Mean central corneal flattening: 4.13 [1.82] D Anterior corneal surface height: 26.7 µm Posterior corneal surface height: 1.1 µm	Not reported
Fouraker 2004, Lemp 2004 Fouraker, B. 'Comparison of safety for Intacs for keratoconus vs for myopia' Lemp, M. 'Intrastromal corneal segments (Intacs) safety in keratoconic eyes' Device: Intacs	IV III-3? IV	2004 Joint Meeting of the American Academy of Ophthalmology and European Society of Ophthalmology, New Orleans, Louisiana, USA, 23–26 October 2004 2004 Association for Research in Vision and Ophthalmology Annual Meeting, Florida, USA, 25–29 April 2004	164 keratoconic eyes (from three studies) and 188 myopic eyes Follow-up: 12–24 months for keratoconus and 36 months for myopia	BCVA: gain of ≥2 lines 79/164 (48%) UCVA: gain of ≥2 lines 119/164 (72%)	8/164 (4.9%) keratoconic eyes with postoperative complications: non-infectious keratitis, superficial tunnel dissection, transient inflammatory reaction, visual symptoms, neovascularisation Intacs explanted in 14/164 (8.5%) for visual symptoms, segment migration, superficial placement, astigmatism, topographic irregularity (some had corneal transplant) 5/188 (2.7%) myopic eyes with postoperative complications.

Study	Level	Conference	Patient group	Effectiveness	Safety
Furhman et al 2002 Fuhrman, M., Haji, S., Dualan, I. & Asbell, P. 'Intacs for keratoconus' Device: Intacs	IV	2002 Association for Research in Vision and Ophthalmology Annual Meeting, Fort Lauderdale, Florida, USA, 6–10 May 2002	8 eyes with keratoconus and contact lens intolerance Follow-up: At least 3 months Segments used: 0.25 mm, 0.30 mm, 0.35 mm	BCVA: All patients gained 0 to 8 lines, no patients lost lines UCVA: All patients gained 2 to 8 lines Mean keratometry flattening: 0 to 6 D Mean asphericity (Q value) change: -1.50 (increased prolate) Mean predicted corneal acuity: 20/40 All patients reported improved visual function	No intraoperative complications
Hirsh et al 2004 Hirsh, A., Barequet, I. & Levinger, S. 'IntraLase-assisted Intacs insertion for treatment of keratoconus: a new alternative approach' Device: Intacs	IV	2004 Joint Meeting of the American Academy of Ophthalmology and European Society of Ophthalmology, New Orleans, Louisiana, USA, 23–26 October 2004	10 eyes with keratoconus Tunnels for insertion of Intacs formed using IntraLase femtosecond laser Follow-up: Not reported	Significant reduction in astigmatism and improved BCVA and UCVA	No complications occurred
Jackson 2004 Jackson, M. 'Clinical management of keratoconus: Intacs or not?' Device: Intacs	IV	2004 Annual Symposium on Cataract, IOL and Refractive Surgery, San Diego, California, USA, 1–5 May 2004	30 eyes with Krumeich stage I or II keratonconus, no corneal scarring and contact lens intolerance Segments ranged from 0.25 mm to 0.45 mm, segment placement thinner superior segment and thicker inferior segment Follow-up: Minimum 3 months	BCVA: (n of eyes) 30/30 (100%) gained 1 line 0/30 (0%) lost 1 line UCVA: All eyes gained, though not all to functional levels Topographic measurement: all eyes had flattening in keratometry compared to baseline	No intraoperative complications

Study	Level	Conference	Patient group	Effectiveness	Safety
Murta & Quadrado 2001 Murta, J. & Quadrado, M. 'Intracorneal rings (Intacs) for the correction of keratoconus' Device: Intacs	IV	2001 Annual Symposium on Cataract, IOL and Refractive Surgery, Fort Lauderdale, Florida, USA, 29 April – 1 May 2001	12 eyes with keratoconus and contact lens intolerance and clear central corneas Temporal corneal incision for asymmetrical implant of thicker segment inferiorly and thinner segment superiorly Follow-up: Immediate postoperative	Significant reduction in astigmatism and increased topographic regularity, UCVA and BCVA in all eyes	Foreign body sensation was the major complication in early postoperative period
Oliveira et al 2001 Oliveira, C., Moreira H., de Godoy G. & Wahab S. 'Ferrara intracorneal ring for keratoconus' Device: Ferrara	IV	2001 Annual Symposium on Cataract, IOL and Refractive Surgery, Fort Lauderdale, Florida, USA, 29 April – 1 May 2001	10 patients with keratoconus, clear corneas, contact lens intolerance and BCVA ≥0.70 logMAR BCVA preop: 0.75 [0.37] Follow-up: 3 months	Postoperative BCVA: 0.44 [0.34] p=0.026 compared to preop Postoperative UCVA immediately after surgery: 0.67 [0.45] (n=9) Postoperative UCVA at end of follow-up: 0.56 [0.27] 5/10 patients BCVA ≤0.50 logMAR One patient had no significant flattening of cornea	Microperforations during incision for the interior tunnel – 2 Segment extrusion – 1 Segment displacement of one or both segments – 4
Rabinowitz 2004 Rabinowitz, Y. 'Intacs for keratoconus: one-year follow-up of 20 eyes' Device: Intacs	IV	2004 Annual Symposium on Cataract, IOL and Refractive Surgery, San Diego, California, USA, 1–5 May 2004	20 eyes with keratoconus, clear corneas and contact lens intolerance and eligible for penetrating keratoplasty 2 symmetrical 0.35 mm segments placed at 70% depth through a temporal incision Follow-up: 12 months	17/20 (85%) improved vision and now contact lens tolerant Mean improvement BCVA: 2.4 lines (-2 to 6) Mean improvement UCVA: 3 lines (0 to 7) Mean reduction sphere: 3D (0.5 to 5.75) Mean reduction astigmatism: 1.43D (2.25 to 5.75) Mean reduction in SRI surface irregularity index: 0.68 (2.0 to 0.6)	1/20 explanted due to erosion of segment 2/20 explanted due to persistent visual fluctuation at 12 months postop (1 patient)

Study	Level	Conference	Patient group	Effectiveness	Safety
Swanson 2004 1) Swanson, M. 'Modified implantation of Intacs for keratoconus and iatrogenic keratectasia' 2) Swanson, M. 'New techniques for Intacs inserts implantation for the treatment of keratoconus and iatrogenic keratectasia' 3) Swanson, M. 'Intacs on keratoconus using the steepest axis incision technique: two-year results' NOTE: 1) and 2) are identical abstracts, 3) includes additional patients. Results data appear to be the same in all three abstracts. Device: Intacs	IV	2004 Annual Symposium on Cataract, IOL and Refractive Surgery, San Diego, California, USA, 1–5 May 2004 2004 Association for Research in Vision and Ophthalmology Annual Meeting, Florida, USA, 25–29 April 2004 2004 Joint Meeting of the American Academy of Ophthalmology and European Society of Ophthalmology, New Orleans, Louisiana, USA, 23–26 October 2004	348 eyes with keratoconus or corneal ectasia (iatrogenic and non-iatrogenic) Exclusions: corneal scarring, hydrops or severe thinning of cornea (≤300 µm) Modified technique places inserts on opposite sides of the conus, displacing the thinnest area toward the centre into a steepest refractive axis incision Follow-up: 1–11 months	Keratoconus BCVA: improved to 0.18 logMAR or better in 100% of mild cases, 90% of moderate cases and 62% of severe cases UCVA: improved to 0.30 logMAR or better in 100% of mild cases and 55% of moderate to severe cases, and to 0.00 logMAR in 62% of mild and 20% of moderate to severe cases All cases gained at least one line of vision 100% of patients improved visual function and quality of life Stage III (severe) keratoconic patients benefited most from the procedure	Not reported
Tran 2002 Tran, B. 'Single-segments Intacs inserts for keratoconus' Device: Intacs	IV	2002 Annual Symposium on Cataract, IOL and Refractive Surgery, Philadelphia, Pennsylvania, USA, 1–5 June 2002	3 eyes with highly asymmetric keratoconus cones, clear central corneas and contact lens intolerance 0.35 mm segment inferiorly and 0.25 mm segment superiorly in 2 eyes using IntraLase femtosecond laser (the superior segments were removed after 3 months) Single segment placed in one eye with standard Intacs technique Follow-up: 3 months	BCVA: All patients had at least 2 lines improvement with decreased symptoms of polyopia SE and astigmatism reduced in all eyes with only a single insert Size and height of corneal cones contracted in all eyes	No intraoperative complications

Study	Level	Conference	Patient group	Effectiveness	Safety
Yilmaz 2004 Yilmaz, O. 'Results of radial keratotomy and intrastromal ring implantation in keratoconus patients' Device: Ferrara	III-2	2004 Annual Symposium on Cataract, IOL and Refractive Surgery, San Diego, California, USA, 1–5 May 2004.	18 eyes/10 patients with keratoconus with corneal thickness of 400 µm or more Group 1: 8 eyes/8 patients Radial keratotomy Mean UCVA: 1.00 [0.80] Mean BCVA: 0.50 [0.70] Group 2: 10 eyes/10 patients Ferrara ICRS Mean UCVA: 0.50 [0.0.65] Mean BCVA: 0.40 [0.76] Follow-up: 4–6 months	BCVA at 6 months postoperatively: Keratotomy – 0.20 [0.50]; Ferrara – 0.19 [0.60] UCVA at 6 months postoperatively: Keratotomy – 0.23 [0.54]; Ferrara – 0.21 [0.60]	Group 2 (Ferrra ICRS): 3/10 Complications: corneal abscess – 1 → PKP dislocation of ring segments – 1 dislocation of one ring segment into anterior segment due to trauma – 1 Explantations: 1/10 due to superficial placement Complications not reported for keratotomy patients

Iatrogenic corneal ectasia

Study	Level	Conference	Patient group	Effectiveness	Safety
Hashemi et al 2002 Hashemi, H., Sadeghi, N. & Gholaminejad, A. 'Implantation of Intacs in post-LASIK keratectasia' Device: Intacs	IV	2002 Annual Symposium on Cataract, IOL and Refractive Surgery, Philadelphia, Pennsylvania, USA, 1–5 June 2002	3 eyes with post-myopic LASIK keratectasia and clear central corneas Preop BCVA at least 0.7 logMAR and UCVA 1.3–0.7 0.45 mm segment inferiorly and 0.35 mm segment superiorly inserted to embrace the cone determined according to topographic analysis Follow-up: 3 months	No patient lost any lines of BCVA immediately postimplant At 3 months: – 2/3 eyes with preoperative BCVA of 0.3 logMAR or worse did not benefit from Intacs implantation either for UCVA or BCVA – 1/3 eye dramatic increase in UCVA and considerable improvement in BCVA	No intraoperative complications
Lovisolo 2001 Lovisolo, C. 'Intacs after post-LASIK keratectasia' Device: Intacs	IV	2001 Annual Symposium on Cataract, IOL and Refractive Surgery, Fort Lauderdale, Florida, USA, 29 April – 1 May 2001	3 eyes with post-myopic LASIK keratectasia and clear central corneas Asymmetrical temporal-oblique incision of different thickness segments Follow-up: Not reported	Not reported Abstract concludes that asymmetrical ICRS implantation appears to be a promising technique to avoid penetrating keratoplasty after LASIK-induced iatrogenic corneal ectasia	Not reported
Pallikaris et al 2001 Pallikaris, I., Kymionis, G. & Siganos, C. 'Stability of post-LASIK corneal ectasia after Intacs implantation' Device: Intacs	IV	2001 Annual Meeting of the American Academy of Ophthalmology, New Orleans, Louisiana, USA, 11–14 November 2001	6 eyes with post-LASIK iatrogenic corneal ectasia Follow-up: 12 months	Increase in topographical regularity and visual acuity and after 3 months stability in refraction and visual acuity	Not reported

Study	Level	Conference	Patient group	Effectiveness	Safety
Swanson 2004 1) Swanson, M. 'Modified implantation of Intacs for keratoconus and iatrogenic keratectasia' 2) Swanson, M. 'New techniques for Intacs inserts implantation for the treatment of keratoconus and iatrogenic keratectasia' 3) Swanson, M. 'Intacs on keratoconus using the steepest axis incision technique: two-year results' NOTE: 1) and 2) are identical abstracts, 3) includes additional patients. Results data appear to be the same in all three abstracts. Device: Intacs	IV	2004 Annual Symposium on Cataract, IOL and Refractive Surgery, San Diego, California, USA, 1–5 May 2004 2004 Association for Research in Vision and Ophthalmology Annual Meeting, Florida, USA, 25–29 April 2004 2004 Joint Meeting of the American Academy of Ophthalmology and European Society of Ophthalmology, New Orleans, Louisiana, USA, 23–26 October 2004	348 eyes with keratoconus or corneal ectasia (iatrogenic and non-iatrogenic) Exclusions: Corneal scarring, hydrops or severe thinning of cornea (≤300 µm) Modified technique places inserts on opposite sides of the conus, displacing the thinnest area toward the centre into a steepest refractive axis incision Follow-up: 1–11 months	Ectasia In 100% of cases the cornea stabilised but results were variable depending on ectasia Most normalising effect seen on patients with iatrogenic corneal ectasia 60% of cases required soft contact lenses or glasses	Not reported

Non-iatrogenic corneal ectasia

Study	Level	Conference	Patient group	Effectiveness	Safety
Lopez-Canedo & Swanson 2004 Lopez-Canedo, J. & Swanson, M. 'Corneal architecture remodeling with Intacs for pellucid marginal degeneration' Device: Intacs	IV	2004 Joint Meeting of the American Academy of Ophthalmology and European Society of Ophthalmology, New Orleans, Louisiana, USA, 23–26 October 2004	38 eyes with pellucid marginal degeneration Asymmetrical placement of Intacs with a thinner one in the bottom or under the cone and a thicker one opposite using new nomogram based on steepest axis incision technique Follow-up: 1–11 months	UCVA: Improved to 0.30 logMAR or better in 80% Improved to 0.00 logMAR or better in 40% BCVA: Improved to 0.18 logMAR or better in 90% 100% of patients gained at least 1 line of visual acuity and 70% gained 3 or more lines 100% of patients experienced improved visual function Topographic maps improved corneal surface in 90% and flattening of curvature and central cone displacement in 100%	Not reported

Conference abstracts excluded from Appendix F

Batra, N. & Schwaderer, K. 'Intacs following PRK in keratoconus', 2003 Annual Symposium on Cataract, IOL and Refractive Surgery, San Francisco, California, USA, 12–16 April 2003.

reason: ICRS after previous PRK in a patient with keratoconus

Colin, J. & Malet, F. 'Intacs for the correction of keratoconus: two-year follow-up', 2004 Joint Meeting of the American Academy of Ophthalmology and European Society of Ophthalmology, New Orleans, Louisiana, USA, 23–26 October 2004.

reason: duplicates Colin in press (included study)

Colin, J. 'Intacs prescription inserts to treat keratoconus: European data', 2004 Joint Meeting of the American Academy of Ophthalmology and European Society of Ophthalmology, New Orleans, Louisiana, USA, 23–26 October 2004.

reason: duplicates Colin et al unpub. (included study)

Cunha, P., Castro, R., Bicalho, F. & Alves E. 'Ferrara intrastromal ring segments to correct contact lens intolerant keratoconus patients', 2001 Annual Symposium on Cataract, IOL and Refractive Surgery, Fort Lauderdale, Florida, USA, 29 April – 1 May 2001.

reason: no results reported in abstract

Hardten, D. 'Treatment of keratoconus using intracorneal ring segments and conductive keratoplasty', 2003 Annual Symposium on Cataract, IOL and Refractive Surgery, San Francisco, California, USA, 12–16 April 2003.

reason: ICRS implantation combined with other surgical procedure

Macedo, M., Ferreira, N., Coelho, P., Vas, F., Ceu, A. & Marinho, A. 'Intracorneal rings as a secondary procedure', 2002 Annual Symposium on Cataract, IOL and Refractive Surgery, Philadelphia, Pennsylvania, USA, 1–5 June 2002.

reason: cannot separate patients with iatrogenic corneal ectasia from those with residual myopia or myopic regression

Malet, F. & Colin, J. 'Intacs for keratoconus: review of six-month European outcomes for several different nomograms', 2004 Joint Meeting of the American Academy of Ophthalmology and European Society of Ophthalmology, New Orleans, Louisiana, USA, 23–26 October 2004.

reason: duplicates Colin et al unpub. (included study)

Miranda, D., Sartori, M., Francesconi, C., Allemann, N., Ferrara, P. & Campos, M. 'Management of severe keratoconus with intrastromal Ferrara ring segments: a two-year follow-up', 2003 Annual Meeting of the American Academy of Ophthalmology, Anaheim, California, USA, 15–18 November 2003.

reason: duplicates Miranda et al 2003 (included study)

Miranda, D., Sartori, M., Francesconi, C., Allemann, N., Ferrara, P. & Campos, M. 'Intrastromal Ferrara ring segments in patients with keratoconus', 2001 Annual Symposium on Cataract, IOL and Refractive Surgery, Fort Lauderdale, Florida, USA, 29 April – 1 May 2001.

reason: duplicates Miranda 2003 (included study)

Moreira, H., Oliveira, C., Godoy, G. & Wahab, S. 'Technique for Ferrara ring implantation for keratoconus', 2002 Annual Symposium on Cataract, IOL and Refractive Surgery, Philadelphia, USA, 1–5 June 2002.

reason: only addresses implantation technique

Salgado, R., Vaz, F., Pinto, C., Vieira, F., Costa, J. & Marinho, A. 'Intracorneal rings as a secondary procedure', 2001 Annual Symposium on Cataract, IOL and Refractive Surgery, Fort Lauderdale, Florida, USA, 29 April – 1 May 2001.

reason: cannot separate patients with iatrogenic corneal ectasia from those with residual myopia or myopic regression (and duplicates Macedo et al 2002 abstract)

Swanson, M. 'Lamellar keratoplasty using the Moria Microkeratome with Intacs placement for severe keratoconus', 2004 Annual Symposium on Cataract, IOL and Refractive Surgery, San Diego, California, USA, 1–5 May 2004.

reason: ICRS implantation combined with other surgical procedure

Appendix G Results from corneal transplant registries or studies

Study	Location	Patients	Outcomes
Lim et al 2000 Jan 1988 – May 1995	Australian Corneal Graft Registry (results for just one surgeon)	Keratoconus: n=93 grafts	Graft failure: 1/93 (at 46.5 months) due to traumatic wound dehiscence Reoperations: 1/93 regraft (1.1%) 21/93 (22.6%) refractive surgery for astigmatism at 26 months postop Complications: 12/93 (25.8%) corneal vascularization – 8 rejection – 4 loose suture – 3 resuturing – 3 cataract – 3 raised intraocular pressure – 3 Mean BCVA: 0.24 (0.1–1.3) logMAR 5/93 (5%) BCVA >0.8 logMAR 81/93 (87%) BCVA <0.3 logMAR Postoperative correction: glasses 67%, unaided 7%, contact lenses 28% Mean keratometry: 45 [2] D Mean astigmatism: 5 [3] D Spherical equivalent: -0.33 [3.87] D (n=33)

Study	Location	Patients	Outcomes
Buzard & Fundingsland 1997 Dates not stated	Buzard Eye Institute, Las Vegas, Nevada, USA	Keratoconus: n=104 grafts	Astigmatism: 4.07 [2.5]D at 1 year and 3.1 [1.8] at last follow-up Spherical equivalent: -1.85 [2.8] D at 3 months and -1.75 [3.1] D at 1 year Refractive cylinder: 2.73 [1.7] D at 3 months and 2.61 [1.5] D at 1 year Keratometry: 43.3 [2.6] D at 3 months UCVA: 0.36 [0.3] D at 3 months and 1 year, and 0.43 [0.3] D at last follow-up 46/104 (44%) 20/40 or better BCVA at last follow-up: 89/104 (86%) gained lines 2/104 (2%) lost 2 lines no eye lost more than 2 lines 60/104 (58%) 0.30 logMAR or better at 1 month 92/104 (88%) 0.30 logMAR or better at 3 months Reoperations: 44/104 (42.3%) automated lamellar keratoplasty 4/104 (3.8%) relaxing incisions for astigmatism 33/104 (31.7%) corneal wedge resection 5/104 (4.8%) regraft 2/104 (1.9%) Complications: endophthalmitis – 0 expulsive haemorrhage – 0 primary graft failure – 0 secondary graft failure – 21/104 (20.2%) 19/21 successfully treated
Claesson et al 2002 2 years from 1997	Swedish Corneal Transplant Registry	Total n=1,957 Keratoconus: n=566 (29%) 526 grafts 105 available for 2-year follow-up	BCVA at 2 years: (logMAR) 0.30 or better – 90/105 (86%) 0.70 or worse – 8/105 (8%) Astigmatism at 2 years: 4.0 (3.5–4.5) (n=105) Rejection at 2 years: 12/105 (11.7%) Regraft at 2 years: 7/105 (6.3%) Other complications: 14/105 (13.4%) Other pathology: 10/105 (9.7%)
Hargrave et al 2003 1994–99	University of Texas Southwestern Medical Center, Dallas, Texas, USA	Keratoconus: n=84 grafts	Graft rejection: 7/84 (8.3%) no primary graft failure (all immunological graft rejection) 5/7 repeat PKP

Study	Location	Patients	Outcomes
Koralewska-Makar et al 1996 Jan 89 – Dec 91	Department of Ophthalmology, University Hospital of Lund, Lund, SWEDEN	Total n=212 full thickness PKP Keratoconus n=77 grafts	BCVA: (logMAR) 0.30 or better – 65/75 (84.4%) 0.00 – 30/75 (39%) Mean spherical equivalent: -3.4 (-15 to +4.75) D Astigmatism: 3.75 (0 – 12.5) D Reoperations: 15/77 (19.4%) Complications: 15/77 (19.4%) retrocorneal fibrous membrane – 1 keratitis – 2 postop leakage – 3 cataract – 7 secondary glaucoma – 1 Graft rejection: 6/77 (7.8%) (5/6 within 1 year)
Olson et al 2000 Mar 92 – Oct 95	John Moran Eye Center, University of Utah, Salt Lake City, Utah, USA	Keratoconus: n=93 grafts	BCVA: 0.10 or better – 72/93 (77%) Astigmatism: 2.76 [1.99] D at 24 months Complications: 58/93 (62.3%) cataract – 5 keratitis – 7 severe astigmatism – 3 vascularisation – 1 corneal ulceration and scarring – 1 stromal outgrowth – 1 late epithelial defect – 1 allograft reaction – 7 graft failure secondary to infection, corneal scarring – 1 elevated intraocular pressure – 16 filaments – 5 suture infiltrate – 2 wound leak – 3 anisometropia – 2 mechanical abrasion or loose suture – 3
Sit et al 2002 Jan 86 – Jun 93	Cornea and External Disease Service, University Health Network, Toronto Western Hospital, Toronto, CANADA	Total n=468 grafts Keratoconus: n=50 (10.7%)	2-yr graft survival: 95.9% 5-yr graft survival: 95.9%

Study	Location	Patients	Outcomes
Thompson et al 2003 1982–96	Corneal Consultants of Indiana, Indianapolis, Indiana, USA	Total n=3,992 grafts Keratoconus: n=449 (11.2%)	Graft failure: 22/449 (4.9%) no obvious cause 11/449 (2.5%) endothelial failure 3/449 (0.7%) endothelial rejection 3/449 (0.7%) surface complications 1/449 (0.2%) glaucoma 0/449 astigmatism 0/449 other 4/449 (0.9%) 10-year graft survival (Kaplan-Meier): 92%
Williams et al 2004 May 1985 – July 2003	Australian Corneal Graft Registry	Total n=14,649 Keratoconus: 4,309 grafts (31%) 94% PKP 5% diffuse lamellar keratitis <1% limbal Corneal degenerations including ectasia: 68 grafts (<1%)	Keratoconus (for PKP) Graft survival: mean 17.9 SE 0.23; 95% CI 17.44 – 18.36; median ~ 20 years Kaplan-Meier graft survival rate: 1 yr: 97% 5 yrs: 95% 10 yrs: 90% 15 yrs: 82% 20 yrs: 82% BCVA: (logMAR) 1468/2068 (71%) ≤0.30 1613/2068 (78%) ≤0.48 1841/2068 (89%) at least one line of gain Change from preop: Loss of 1 to 8 lines: 226/2068 (10.9%) No change: 108/2068 (5.2%) Gain of 1 to 5 lines: 901/2068 (43.6%) Gain of 7+ lines: 833/2068 (40.3%)

Abbreviations

AHMAC	Australian Health Ministers' Advisory Council
AIWH	Australian Institute of Health and Welfare
BCLVA	best corrected lens visual acuity
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 segments
IOL	intraocular lens
I-S	inferior-superior
LASIK	laser in situ keratomileusis
MBS	Medicare Benefits Schedule
M/F	male/female
NA	not applicable
NHMRC	National Health and Medical Research Council
NR	not reported
PMD	pellucid marginal degeneration
PKP	penetrating keratoplasty
pns	p-value not significant (ie > 0.05)
postop	postoperative
preop	preoperative
PRK	photorefractive keratectomy
SE	spherical equivalent
VA	visual acuity

Units of measurement

[ ]	standard deviation
( )	range
D	dioptre
logMAR	logarithm of the minimum angle of resolution
µm	micrometre
mm	millimetre
r^2	a measure of correlation

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