PREFERRED PRACTICE PATTERN®

Corneal Ectasia

AMERICAN ACADEMY OF OPHTHALMOLOGY
The Eye M.D. Association

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CORNEA/EXTERNAL DISEASE PREFERRED PRACTICE PATTERN DEVELOPMENT PROCESS AND PARTICIPANTS

The **Cornea/External Disease Preferred Practice Pattern® Panel** members wrote the Corneal Ectasia Preferred Practice Pattern® guidelines ("PPP"). The PPP Panel members discussed and reviewed successive drafts of the document, meeting in person twice and conducting other review by e-mail discussion, to develop a consensus over the final version of the document.

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The **Preferred Practice Patterns Committee** members reviewed and discussed the document during a meeting in March 2013. The document was edited in response to the discussion and comments.

Preferred Practice Patterns Committee 2013

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The Corneal Ectasia PPP was then sent for review to additional internal and external groups and individuals in June 2013. All those returning comments were required to provide disclosure of relevant relationships with industry to have their comments considered. Members of the Cornea/External Disease Preferred Practice Pattern Panel reviewed and discussed these comments and determined revisions to the document.

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FINANCIAL DISCLOSURES

In compliance with the Council of Medical Specialty Societies' Code for Interactions with Companies (available at www.cmss.org/codeforinteractions.aspx), relevant relationships with industry are listed. The Academy has Relationship with Industry Procedures to comply with the Code (available at http://one.aao.org/CE/PracticeGuidelines/PPP.aspx). A majority (70%) of the members of the Cornea/External Disease Preferred Practice Pattern Panel 2012–2013 had no related financial relationship to disclose.

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The disclosures of relevant relationships to industry of other reviewers of the document from January to August 2013 are available online at www.aao.org/ppp.

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OBJECTIVES OF PREFERRED PRACTICE PATTERN® GUIDELINES

As a service to its members and the public, the American Academy of Ophthalmology has developed a series of Preferred Practice Pattern® guidelines that **identify characteristics and components of quality eye care.** Appendix 1 describes the core criteria of quality eye care.

The Preferred Practice Pattern® guidelines are based on the best available scientific data as interpreted by panels of knowledgeable health professionals. In some instances, such as when results of carefully conducted clinical trials are available, the data are particularly persuasive and provide clear guidance. In other instances, the panels have to rely on their collective judgment and evaluation of available evidence.

These documents provide guidance for the pattern of practice, not for the care of a particular individual. While they should generally meet the needs of most patients, they cannot possibly best meet the needs of all patients. Adherence to these PPPs will not ensure a successful outcome in every situation. These practice patterns should not be deemed inclusive of all proper methods of care or exclusive of other methods of care reasonably directed at obtaining the best results. It may be necessary to approach different patients' needs in different ways. The physician must make the ultimate judgment about the propriety of the care of a particular patient in light of all of the circumstances presented by that patient. The American Academy of Ophthalmology is available to assist members in resolving ethical dilemmas that arise in the course of ophthalmic practice.

Preferred Practice Pattern® guidelines are not medical standards to be adhered to in all individual situations. The Academy specifically disclaims any and all liability for injury or other damages of any kind, from negligence or otherwise, for any and all claims that may arise out of the use of any recommendations or other information contained herein.

References to certain drugs, instruments, and other products are made for illustrative purposes only and are not intended to constitute an endorsement of such. Such material may include information on applications that are not considered community standard, that reflect indications not included in approved U.S. Food and Drug Administration (FDA) labeling, or that are approved for use only in restricted research settings. The FDA has stated that it is the responsibility of the physician to determine the FDA status of each drug or device he or she wishes to use, and to use them with appropriate patient consent in compliance with applicable law.

Innovation in medicine is essential to ensure the future health of the American public, and the Academy encourages the development of new diagnostic and therapeutic methods that will improve eye care. It is essential to recognize that true medical excellence is achieved only when the patients' needs are the foremost consideration.

All Preferred Practice Pattern® guidelines are reviewed by their parent panel annually or earlier if developments warrant and updated accordingly. To ensure that all PPPs are current, each is valid for 5 years from the "approved by" date unless superseded by a revision. Preferred Practice Pattern guidelines are funded by the Academy without commercial support. Authors and reviewers of PPPs are volunteers and do not receive any financial compensation for their contributions to the documents. The PPPs are externally reviewed by experts and stakeholders, including consumer representatives, before publication. The PPPs are developed in compliance with the Council of Medical Specialty Societies' Code for Interactions with Companies. The Academy has Relationship with Industry Procedures (available at http://one.aao.org/CE/PracticeGuidelines/PPP.aspx) to comply with the Code.

The intended users of the Corneal Ectasia PPP are ophthalmologists.

METHODS AND KEY TO RATINGS

Preferred Practice Pattern® guidelines should be clinically relevant and specific enough to provide useful information to practitioners. Where evidence exists to support a recommendation for care, the recommendation should be given an explicit rating that shows the strength of evidence. To accomplish these aims, methods from the Scottish Intercollegiate Guideline Network[1] (SIGN) and the Grading of Recommendations Assessment, Development and Evaluation[2] (GRADE) group are used. GRADE is a systematic approach to grading the strength of the total body of evidence that is available to support recommendations on a specific clinical management issue. Organizations that have adopted GRADE include SIGN, the World Health Organization, the Agency for Healthcare Research and Policy, and the American College of Physicians.[3]

- All studies used to form a recommendation for care are graded for strength of evidence individually, and that grade is listed with the study citation.
- To rate individual studies, a scale based on SIGN[1] is used. The definitions and levels of evidence to rate individual studies are as follows:

I++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
I+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
I-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
II++	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
II+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
II-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
III	Nonanalytic studies (e.g., case reports, case series)

- Recommendations for care are formed based on the body of the evidence. The body of evidence quality ratings are defined by GRADE[2] as follows:

Good quality	Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Insufficient quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate Any estimate of effect is very uncertain

- Key recommendations for care are defined by GRADE[2] as follows:

Strong recommendation	Used when the desirable effects of an intervention clearly outweigh the undesirable effects or clearly do not
Discretionary recommendation	Used when the trade-offs are less certain—either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced

- The Highlighted Findings and Recommendations for Care section lists points determined by the PPP panel to be of particular importance to vision and quality of life outcomes.
- All recommendations for care in this PPP were rated using the system described above. To locate ratings for specific recommendations, see Appendix 2 for additional information.
- Literature searches for the PPP were undertaken in May 2012 and January 2013 in PubMed and the Cochrane Library. Complete details of the literature search are available at www.aao.org/ppp.

HIGHLIGHTED FINDINGS AND RECOMMENDATIONS FOR CARE

Young patients or postkeratorefractive surgery patients who appear to have unstable refractions should be evaluated for evidence of corneal ectasia.

The ophthalmologist needs to measure and evaluate more aspects of visual function than just best-corrected visual acuity (BCVA) of patients with known or suspected ectasia, insofar as BCVA may not completely characterize visual function in these patients.

Signs of corneal ectasia can include inferior steepening, superior flattening, and/or skewing of radial axes on power maps; abnormal islands of elevation anteriorly and/or posteriorly on elevation maps; and decentered or abnormal corneal thinning or abnormal change of corneal thickening from the center to the periphery.

Prior to refractive surgery, corneal topography performed following a period of contact lens abstinence should be evaluated for evidence of irregular astigmatism or abnormalities suggestive of keratoconus or other forms of corneal ectasia.

When corneal ectasia occurs following keratorefractive surgery, it is usually determined that the residual stromal bed following surgery was thinner than expected, that the flap was thicker than expected, or that the patient had preoperative signs of a pre-existing contour abnormality.

It is impossible preoperatively to identify all patients at risk for postkeratorefractive corneal ectasia. Some patients with risk factors for ectasia do not develop the condition following LASIK surgery and some patients without obvious risk factors may develop ectasia.

Though not currently approved by the U.S. Food and Drug Administration (FDA), collagen cross-linking has the potential to reduce the risk of progressive ectasia (particularly in its early stages) and stabilize the corneal contour. This is the case particularly in mild to moderate keratoconus, and it may also hold promise in cases of corneal ectasia occurring after keratorefractive surgery.

The use of corneal mapping and the use of newer contact lens technologies may provide an alternative to surgery for treatment of corneal ectasia.

Deep anterior lamellar keratoplasty has the potential to correct the ectatic contour without the risk of corneal endothelial rejection and may slow the endothelial cell loss following keratoplasty. However, the risk for stromal rejection remains.

INTRODUCTION

DISEASE DEFINITION

Corneal ectasia (ICD-9 #371.71; ICD-10 #H18.71 [(–) = 1, right eye; 2, left eye; 3, bilateral])

Corneal ectasia is a noninflammatory condition, the hallmark of which is progressive corneal steepening and thinning. Types of corneal ectasia include keratoconus, pellucid marginal degeneration, keratoglobus, postkeratorefractive ectasia, and wound ectasia after penetrating keratoplasty (PK). Corneal ectasias are associated with decreased uncorrected visual acuity (UCVA), an increase in ocular aberrations, and often a loss of best-corrected distance visual acuity (BCVA). Corneal ectasias can result in significant ocular morbidity and may require surgical intervention.

PATIENT POPULATION

The patient population includes individuals of any age with corneal ectasia.

CLINICAL OBJECTIVES

- Identify corneal ectasia risk factors and associated conditions, and recognize signs in the clinical examination
- Establish the diagnosis of corneal ectasia, including use of appropriate diagnostic technologies
- Understand appropriate surgical and non-surgical treatment options
- Improve visual function
- Prevent loss of visual function
- Educate and involve the patient in the management of this disease

BACKGROUND

PREVALENCE AND RISK FACTORS

Corneal ectasia encompasses both naturally occurring and surgically induced thinning and protrusion. Corneal ectasia can occur shortly after LASIK and photorefractive keratectomy (PRK) in eyes that had pre-existing forme fruste keratoconus or years later in eyes that had no preoperative signs of keratoconus. Naturally occurring keratoconus typically begins in puberty and progresses until about age 40. It is typically bilateral, but it can be asymmetrical. The overall prevalence of keratoconus has been reported to be between 50 and 230 per 100,000 in the general population, with both sexes equally affected.[4-7] Keratoglobus may be seen in children and may be congenital. Pellucid marginal degeneration usually has its onset later in life.

The etiology of corneal ectasia can include genetic factors, chromosomal and enzyme abnormalities, and mechanical factors. Postrefractive ectasias can occur after LASIK and PRK.

Genetic disorders associated with keratoconus include connective-tissue diseases with abnormal collagen such as Ehlers-Danlos syndrome, osteogenesis imperfecta, congenital hip dysplasia, nail patella syndrome, Marfan syndrome and pseudoxanthoma elasticum, hyper-IgE syndrome (which is associated with eczema and atopy), oculodentodigital dysplasia, Down syndrome, and ichthyosis. Other genetic syndromes include those associated with eye rubbing and low mentation such as in Apert syndrome, Crouzon syndrome, Down syndrome, hyperornithinemia, Angelman syndrome, and Noonan syndrome. Keratoconus has been associated with disorders related to abnormal retinal function and oculodigital stimulation, including albinism, Bardet-Biedl syndrome, Leber congenital amaurosis, tapetoretinal degeneration, and Kurz syndrome.[8] See Table 1 for more information about keratoconus. Keratoconus is also associated with atopic disease, including hayfever, asthma, eczema, and vernal keratoconjunctivitis. In addition, there are well-established associations with contact lens wear, particularly hard contact lens wear, and both eye rubbing and the presence of hyperelastic joints.

TABLE 1 SYSTEMIC DISEASES ASSOCIATED WITH KERATOCONUS

Syndrome	Gene	Syndrome	Gene
Alagille syndrome	*20p12*	Kurz syndrome	
Albers-Schönberg disease	*11q13.4-5*	Laurence-Moon-Bardet-Biedl	
Albinism		Marfan syndrome	*15q21.1*
Angelman syndrome	*15q11-13*	Mitral valve prolapse	
Apert syndrome	*10p26*	Mulvihill-Smith syndrome	
Autographism		Nail patella syndrome	*9q34.1*
Bardet-Biedl syndrome		Neurocutaneous angiomatosis	
Brittle cornea syndrome		Neurofibromatosis	
Congenital hip dysplasia		Noonan syndrome	*12q24.1*
Congenital rubella		Osteogenesis imperfecta	*17q21*
Crouzon syndrome		Oculodentodigital syndrome	*6q21*
Down syndrome	*trisomy 21*	Pseudoxanthoma elasticum	*16p13.1*
Ehlers-Danlos syndrome		Retinitis pigmentosa	*13q14, 4q25-26*
False chordae tendineae of left ventricle		Rieger syndrome	
Goltz-Gorlin syndrome	*9q22.3*	Rothmund syndrome	*8q24.3*
Hyper-IgE syndrome		Thalesselis syndrome	
Hyperornithinemia	*l13q14*	Tourette syndrome	
Ichthyosis		Turner syndrome	
Joint hypermobility		Xeroderma pigmentosa	

Reproduced with permission from Sugar J, Macsai MS. What causes keratoconus? Cornea 2012;31:717.

When corneal ectasia occurs following keratorefractive surgery, it is not uncommon to determine that the residual stromal bed following surgery was thinner than expected, that the flap was thicker than intended, or that the patient had preoperative signs of a pre-existing contour abnormality. However, corneal ectasia can exist in the absence of these situations.[9]

Thinning of the cornea in keratoconus occurs as a result of the degradation of corneal collagen. Altered enzyme activities and oxidative stress have been proposed as factors related to the pathogenesis of keratoconus and related corneal ectasias. In particular, matrix metalloproteinase levels have been demonstrated to be increased in keratoconic corneas compared with normal corneas, and levels of tissue inhibitor of metalloproteinases have been shown to be decreased in keratoconic corneas. These findings indicate a probable role for these enzymes in matrix degradation found in keratoconus.[8,10-15]

The tears of patients with keratoconus have been shown to contain increased levels of inflammatory mediators such as interleukin-6, TNF-alpha, and MMP-9.[16,17] These inflammatory mediators likely result in keratocyte apoptosis and the decreased keratocyte cell density associated with keratoconic corneas. It is therefore likely that this form of corneal thinning, classified as non-inflammatory, may have an inflammatory component that is either directly or indirectly related to the pathogenesis and progression of the disease.[18] Post-LASIK ectasia has been postulated to occur as a result of insufficient corneal thickness, exacerbation of pre-existing subclinical or clinical keratoconus by further weakening of the corneal structure, and/or the development of genetically predetermined ectasia occurring years after refractive surgery. A genetic predisposition to keratoconus may exist in some cases that undergo a second environmental insult, such as eye rubbing and/or the iatrogenic corneal thinning that occurs after laser vision correction.[4,8] In studies that address risk factors for post-LASIK ectasia, abnormal preoperative corneal topography has had the strongest association.[19,20]

NATURAL HISTORY

Corneal ectasia is usually bilateral, and it varies in severity and progression. Keratoconus is usually a progressive disorder resulting in corneal thinning, irregular astigmatism, and decreased vision. Eye rubbing, family history, and younger age of onset may result in greater progression of disease, resulting in more severe loss of vision due to greater irregular astigmatism, thinning, and scarring. Up to 20% of cases of keratoconus may result in progression requiring keratoplasty.[4,5,21,22]

RATIONALE FOR TREATMENT

Patients with corneal ectasia suffer from varying degrees of disability, including glare, halos, multiple images, ghosting, reduced visual acuity, and intolerance to eyeglasses and contact lenses. The loss of visual function may result in lost productivity and reduced self-esteem, and difficulties when performing high-skill visual tasks (e.g., driving). The rationale for treatment depends on the severity of disease and the amount of vision loss. When vision can no longer be corrected with eyeglasses and/or contact lenses, consideration should be given to surgical options, including intrastromal corneal ring segments (ICRS) and keratoplasty techniques. In addition, collagen cross-linking (CXL) may be considered in early stages of the disease to prevent disease progression (although this technique is not currently approved by the U.S. Food and Drug Administration [FDA]).[4,5,23]

CARE PROCESS

PATIENT OUTCOME CRITERIA

- Reduce the signs and symptoms of corneal ectasia
- Maintain, restore, or improve visual function according to the needs of the patient

DIAGNOSIS

Initial evaluation of the patient with symptoms and signs of corneal ectasia should include the relevant aspects of the comprehensive medical eye evaluation.[24] The diagnosis of corneal ectasia is usually based on a typical patient history and characteristic findings. Ancillary testing may be helpful. The diagnosis at the subclinical stage can be challenging because the findings may be subtle. It is important to properly identify the presence of corneal ectasia, particularly in patients considering keratorefractive surgery or young people who are more likely to progress to a symptomatic stage of ectasia. The terms subclinical and forme fruste are often used interchangeably to describe attenuated or subtle versions of the disease.

History

- Onset and course

  The onset of corneal ectasia varies with the type and degree of the thinning disorder. Keratoconus usually appears in the second or third decade of life. Keratoglobus can be present in early life. Pellucid marginal degeneration occurs between the third and the fifth decade of life,[25,26] and postrefractive ectasia can occur after LASIK and/or PRK. The onset of postrefractive surgery ectasia can occur months to years following the original refractive procedure.

- Vision (degree of impairment)

  The degree of impairment from corneal ectasias varies widely from minimal findings on topography with little to no visual impairment or loss of BCVA to severe corneal thinning, irregularity, and scarring that results in significant loss of visual function.

- Ocular history

  The history of the type and duration of contact lens wear is important, including the stability and comfort of the contact lens. If the contact lens corrects the patient to 20/20 but pops out frequently, it will not provide acceptable visual function. If there is a history of keratorefractive surgery, it is helpful to collect as much information about the surgery and the condition of the eyes before and after the procedure.

  Eyes with topographic abnormalities that would suggest forme fruste keratoconus can progress to clinically significant ectasia following LASIK and PRK. Preoperative risk factors potentially associated with ectasia after keratorefractive surgery may include an abnormal topographic pattern, younger age, a high manifest refraction spherical equivalent, reduced corneal thickness, and a low predicted residual stromal bed thickness.[19] Risk-scoring systems have been developed to attempt to predict the likelihood of ectasia. However, these systems have demonstrated both false positive and false negative results.[19,27]

- Medical history

  A history of atopy associated with eye rubbing, asthma, and hay fever has also been reported to be associated with keratoconus in many studies.[8,28,29] A history of systemic or topical corticosteroid use to treat atopic disease may increase the likelihood of cataract or intraocular pressure (IOP) elevation. Down syndrome and other genetic disorders can also be associated with keratoconus (see genetic disorders listed under Prevalence and Risk Factors).

- Family history

  Multiple sets of twins with keratoconus have been reported in the literature.[30] In addition, first-degree relatives of patients with keratoconus have an increased risk for the development of keratoconus as well as an increased prevalence of corneal topographic abnormalities.[30-32] The Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study showed that 14% of 1209 patients with keratoconus had a family history of the disease.[33] Genetic chromosomal abnormalities associated with keratoconus have included VSX2[34] and VSX1,[35,36] although later studies[37-41] have not been able to confirm this finding and instead suggest a minor role in pathogenesis.

Examination

- Assessment of visual function

  The inability to correct the patient to 20/20 with manifest refraction is typical of corneal ectasia, as is the scissors reflex on retinoscopy. Checking visual acuity by presenting several Snellen lines and asking the patient to read the letters as quickly as possible may reveal a level of visual acuity that is far worse than when the patient is given unlimited time to read the chart.

- External examination, which should focus on the following:

  - Corneal protrusion (Munson's sign, or protrusion of the cornea and increased angulation of the lower lid margin with the eye in downgaze)

  - Eyelids (including everting the eyelids) and surrounding periorbital skin for evidence of atopic dermatitis, thickening of skin, scaling of skin, floppy eyelid, eyelash ptosis, or papillary conjunctivitis

- Slit-lamp biomicroscopy, which should focus on the following:

  - Document the presence, extent, and location of the corneal thinning or protrusion. In pellucid marginal degeneration, there is typically a band of corneal thinning inferiorly, separated by an uninvolved area 1 to 2 mm from the inferior limbus. The area of maximal protrusion is superior to the band of thinning. This is in contrast to keratoconus, where the cornea protrudes in the area of maximal thinning.[42]

- Presence of previous ocular surgery (e.g., lamellar, PK, or LASIK flap, centered or decentered)
- Vogt striae, prominent corneal nerves, Fleischer ring, or other iron deposition
- Evidence of corneal scarring, noting location of scarring in relation to corneal thinning/protrusion; evidence of superficial scarring at Bowman's layer; mid- or deep stromal scarring and/or evidence of previous hydrops; and the presence of prominent corneal nerves.

- In addition to external examination and slit-lamp biomicroscopy of the cornea, IOP measurement and fundus assessment should be performed.
  - Intraocular pressure may be lower in patients with thinner corneas, after PRK and LASIK, and in patients with ectasia. In studies of patients following refractive surgery and patients with keratoconus, IOP measured using several devices was shown to be artifactually lower.[43-45]
  - As part of the fundus examination, the red reflex should be assessed to look for a dark area due to ectasia, and the retina should be assessed for signs of tapetoretinal degenerations, as these can be associated with keratoconus.

Diagnostic Tests

- Keratometry

  There is no keratometric value that defines ectasia. However, ectasia is usually associated with irregular astigmatism and an increase in steepening in an off-center area of the cornea. Because primary and secondary corneal ectasia can result in an inferiorly displaced area of protrusion, keratometry can differ with upgaze.

- Corneal topography

  Anterior corneal shape can be assessed by use of Placido-based devices. Alternative methods of evaluating both the anterior and posterior corneal curvatures have been developed, including slit-scanning corneal topography and rotating Scheimpflug imaging. These may have a role in expanding diagnostic criteria for keratoconus, subclinical keratoconus, pellucid marginal degeneration, and postrefractive corneal ectasias, and in screening potential refractive surgery patients.[42,46]

  Anterior segment optical coherence tomography (AS-OCT) provides high-definition, cross-sectional images of the cornea, angle, and anterior chamber. Two types of instruments are presently available: spectral domain and time domain. Spectral domain instruments have higher resolution but less depth of field. Time domain instruments, which use a longer wavelength of light (1310 nm), are capable of imaging the ciliary body as well, although not with the same clarity as ultrasound biomicroscopy (UBM). Measurement tools to document and follow changes in the corneal thickness, angle recess opening, and anterior chamber depth and size are standard with all models. Pachymetry mapping is available. Anterior segment optical coherence tomography can be used to follow changes in corneal thickness. Software is available that can use AS-OCT measurements for keratoconus detection.[47] Anterior segment optical coherence tomography also has the advantage of imaging deep and retrocorneal structures. Corneal edema or scarring may hide a detached Descemet's membrane or a retrocorneal membrane. A large Descemet's break and central stromal cleft may exist in cases of corneal edema associated with keratoconic hydrops or trauma.

- Topographic power map

  There is no keratometric power value that defines ectasia. However, ectasia is usually associated with higher/steeper corneal power measurements (i.e., greater than 46.0 diopters [D]). Inferior steepening and superior flattening are typical of keratoconus, as is skewing of the radial axes. Indices have been proposed to augment anterior corneal curvature obtained by Placido disc-based corneal topography.[48-52]

- Topographic elevation map

  Isolated islands of elevation (anteriorly, posteriorly, or both) are often seen in ectatic corneas,and can be helpful in the diagnosis of keratoconus and post-refractive ectasia. Posterior elevation mapping has been shown to have a relatively high sensitivity and specificity for the detection of keratoconus, but less so with sub-clinical keratoconus.[52,53]

- Corneal pachymetry

  Relative corneal thinning is a hallmark of corneal ectasias. Corneal thickness measurements can therefore be helpful in differentiating between normal and ectatic eyes. Pachymetry can be measured as a single point or as a tomographically derived pachymetric map. Tomographically derived pachymetry mapping provides data for characterizing corneal thickness distribution; it has been shown to differentiate between normal and keratoconic corneas, and it may also play a role in evaluating subclinical keratoconus.[42,46,49,54,55] Corneal-thickness spatial profiling and corneal-volume distribution are tomographic parameters derived by Scheimpflug imaging that can be used to differentiate keratoconic corneas from normals.

- Other considerations

  The dominant higher-order aberration found in keratoconus is vertical coma, which is of greater magnitude in patients with keratoconus compared with normals.[56-61]

MANAGEMENT

Prevention and Early Detection

Early detection of corneal ectasia can provide the patient with treatment options to retain and restore vision, potentially reducing loss of functional vision. In addition, newer treatment modalities such as CXL may retard progression of the disease, most importantly early in the disease process.

Ectasia should be suspected in a young patient whose refractive error keeps changing, and such patients should be screened carefully for ectasia prior to refractive surgery. Corneal topography evaluated following a period of contact lens abstinence is an essential part of this evaluation. Evidence of irregular astigmatism or abnormalities suggestive of keratoconus or other corneal ectasias may be associated with unpredictable refractive outcomes and with ectasia progression following keratorefractive surgery.[27,62-64] Corneal evaluation, including topography, is also essential if a keratorefractive surgical procedure is being considered to correct ametropia following intraocular lens implantation.

Choice of Therapy

The choice of therapy is tailored to the individual patient and depends on both the degree of visual impairment and a risk/benefit analysis for each particular treatment option.

Medical

Eyeglasses

In early keratoconus, vision can be corrected with eyeglasses, but as keratoconus and the resultant aberrations progress, contact lenses may be required to correct vision and reduce distortion. In one study, 71% of patients could be corrected to 20/40 with their eyeglasses, and 47% of patients reported wearing their eyeglasses full time or on occasion.[21] Another study reported that 58% of patients achieved 20/40 or better with best eyeglass correction.[65]

Contact Lenses

Soft Contact Lenses

In mild forms of keratoconus, spherical soft contact lenses or toric soft contact lenses may give patients acceptable vision with perhaps more comfort than a hard contact lens.

Gas-Permeable Contact Lenses

When vision can no longer be corrected to at least 20/30 in eyeglasses, long-term studies (the CLEK and the Dundee University Scottish Keratoconus Study [DUSKS]) have found that most patients are fitted with contact lenses.[21,33] Rigid corneal gas-permeable (RGP) contact lenses are hard contact lenses that have the advantage of masking corneal irregularities, thus providing a regular anterior refractive surface.[66] In DUSKS, contact lens wear was the mainstay of treatment, with 76% of patients (N = 200) being fitted with a contact lens. The majority of these patients wore their contact lenses for more than 12 hours per day, 7 days per week, and 93% achieved a BCVA of 20/30 or better.[21] In addition, 91% of these contact lens patients wore gas-permeable contact lenses, 6% wore hybrid contact lenses, and 2% wore scleral contact lenses. Only 1% wore soft contact lenses. Seventy-one percent of contact lens wearers reported some discomfort and 18% reported severe discomfort. Hyperemia was reported in 63%, and 18% described the hyperemia as severe.[21,66] In the CLEK study, 65% of patients wore rigid contact lenses on entry, and 29% had corneal scarring develop over 8 years[66] (at baseline, 53% of study patients had corneal scarring in one or both eyes[33]). In addition, flat-fitting contact lenses provided worse visual acuity than steep fitting contact lenses.[66]

Hybrid Contact Lenses

Hybrid contact lenses contain an RGP center with a soft skirt.[66,67] New-generation hybrid contact lenses provide higher oxygen permeability and greater strength of the RGP/hydrogel junction. In studies of RGP contact lens intolerance, 87% achieved success with hybrid contact lenses.[67] Unlike in RGP contact lenses, the optical center of the hybrid contact lenses remains in the center of the cornea, which may not be coincident with the center of the cone. Disadvantages of the hybrid contact lenses include late-term lens tightening, a tendency toward tight fitting, and the need for high molecular-weight fluorescein to evaluate the fit.[66,67]

Piggyback Contact Lenses

Use of piggyback contact lenses involves fitting an RGP contact lens on top of a soft contact lens to provide for greater comfort and less epithelial disruption, as in the case of corneal scarring and decentered cones. Disadvantages include the need for more than one lens care system, the increased potential for loss of the RGP contact lens, damage to the soft contact lens, and difficulty fitting the soft contact lens on the misshapen cornea.[66]

Scleral Lenses

Scleral lenses have the advantages of completely clearing the corneal surface to provide good centration, good stability, and improved central visual acuity. Scleral lenses, including custom made and mini (i.e., smaller-diameter) lenses, may be indicated in cases of failure with RGP and/or hybrid contact lenses from corneal hypoxia and neovascularization, and discomfort. A recent study found that all patients referred for scleral lens fitting due to failed RGP wear could be successfully fitted either in a conventional lens or in a custom-designed scleral lens, thus avoiding keratoplasty.[68] Custom-made lenses are fabricated in relatively few centers around the country, requiring the patient to remain on site through a lengthy process, while large-diameter intralimbal or mini scleral lenses are commercially available. These commercially available lenses are made to order similar to other specialty RGP lenses, and the patients are not required to remain on site. Disadvantages include decreased tear exchange and difficulty with insertion and removal of the lenses.[66,69] Custom-made lenses are also considerably more expensive than mini lenses and may be cost prohibitive for patients with inadequate insurance coverage.

Surgical

Many surgical options are now available, including ICRS, PK, deep anterior lamellar keratoplasty (DALK), and femtosecond laser-assisted keratoplasty (FLAK). Acronyms such as ALK, ALTK, FALK, and FLAK that describe surgical treatments abound and are often confusing due to their similarities. Table 2 lists many of the more common keratectomy and keratoplasty procedures, along with the corresponding acronyms.

TABLE 2 CONTEMPORARY KERATECTOMY AND KERATOPLASTY PROCEDURES

Acronym	Procedure
ALK (ALTK)	Anterior lamellar keratoplasty (Therapeutic)
DALK	Deep anterior lamellar keratoplasty
DLEK	Deep lamellar endothelial keratoplasty
DMEK (DMAEK)	Descemet's membrane endothelial keratoplasty (Automated)
DSEK (DSAEK)	Descemet's stripping endothelial keratoplasty (Automated)
EK	Endothelial keratoplasty
FALK	Femtosecond anterior lamellar keratoplasty
FLAK	Femtosecond laser-assisted keratoplasty
PKP/PK	Penetrating keratoplasty
PRK	Photorefractive keratectomy
PTK	Phototherapeutic keratectomy
SK	Superficial keratectomy

Intrastromal Corneal Ring Segments

Indications

Intrastromal corneal ring segment implantation is a method of improving contact lens tolerance and BCVA for patients with corneal ectasia, a clear cornea, and contact lens intolerance by improving corneal shape and reducing astigmatism.[70] There are several types of ring segments available; all are made of polymethyl methacrylate (PMMA). One type of ICRS is triangular in profile, with an inner diameter of 5.0 mm, a width of 6.0 mm, and variable thickness (0.15 to 0.30 mm in 0.05-mm steps) with arc lengths of 90, 120, 160 and 210 degrees. Other ICRS products are hexagonal in shape, measure 150 degrees in arc length, with an inner diameter of 6.8 mm and an outer diameter of 8.1 mm and are made in variable thickness from 0.25 to 0.45 mm in 0.05 mm steps. Another hexagonal design has an inner diameter of 6.0 mm, an oval cross-section, and two thicknesses, 0.40 mm and 0.45 mm.

Technique Options

Mechanical

Mechanical channel dissection for placement of an ICRS utilizes a suction ring with a specially designed stainless steel separator for creating channels at 70% to 80% depth in the cornea. Complications with mechanical channel creation include anterior corneal perforation, superficial segment implantation, and postoperative segment migration.[71]

Femtosecond Laser

Channel creation with the femtosecond laser creates channels of specifically set diameter and depth (80% of thinnest pachymetry). Care should be taken to measure pachymetry along the entire area of the corneal channel dissection to avoid intraoperative perforation.

Complications attributed to femtosecond channel creation include incomplete channel creation, postoperative segment migration,[72] and decentration due to misalignment of the cornea and pupil during applanation.[73] In a study that evaluated ICRS implantation with the femtosecond laser following CXL, the incidence of incomplete intrastromal channel creation was higher in eyes that had received CXL.[74] Higher energy settings and/or mechanical channel creation were required in these cases. It was recommended that ICRS be performed either before or concurrently with CXL. The timing of CXL relative to ICRS implantation is currently being debated without clear consensus. Wide channels will facilitate easier ring insertion but may lessen the resulting effect. One study found that using wider channel-creation settings was associated with a decrease in complications such as epithelial plugs, deposits, and segment migration.[75]

Outcomes

Intrastromal corneal ring segments have been shown to provide similar visual and refractive outcomes for keratoconus patients when either mechanical or femtosecond methods of channel creation were used.[4,76-79] Ring segment insertion can improve UCVA and BCVA as well as contact lens tolerance.[70,71,77-93] Most studies have suggested that ICRS may be most effective in patients with moderate keratoconus (<58.0 D).[70,80,90] However, the change in astigmatism can be unpredictable.[94] Loss of CDVA in both types of ICRS may be due to induced irregular astigmatism.[80] Eyes implanted with triangular ICRS segments may experience a greater decrease in scotopic contrast sensitivity with glare, which was significantly correlated with a larger pupil diameter.[87]

Contraindications

Contraindications to ICRS implantation include central corneal scarring and a corneal thickness of less than 400 microns at the incision site.

Complications

Complications with both forms of channel creation and with both types of ICRS include infection, decreased vision, intraoperative perforation, postoperative segment extrusion, epithelial defects, and corneal melting. The presence of postoperative lamellar intrastromal channel deposits has also been documented and is found in up to 74% of cases.[4,95] These deposits consist of lipids and keratocytes and are thought to arise in response to corneal injury and activation of keratocytes, but they do not appear to alter the performance of the ICRS.[4,95,96]

Collagen Cross-linking

Indications

Collagen cross-linking is a technique designed to increase the biomechanical rigidity of the cornea by increasing the biochemical bonds between collagen fibers. This is achieved by local photo-polymerization using ultraviolet-A (UV-A) light and topical riboflavin as a photosensitizing agent. Collagen cross-linking is currently not FDA approved for use in the United States, but it is currently under evaluation in clinical trials.[97]

Technique Options

The original Dresden protocol for CXL involved the removal of the corneal epithelial layer, application of topical riboflavin for 30 minutes to saturate the cornea, followed by 30 minutes of UV-A light treatment.[98] The optimal treatment parameters have yet to be determined. Current treatment protocols require either the removal of the epithelium or exposure of the intact epithelium to agents that increase the permeability of the cell layer, followed by the application of topical riboflavin and UV-A treatment. The transepithelial or “epithelium on” technique allows for passage of the riboflavin through an essentially intact epithelium and may decrease the risk of complications associated with epithelial removal, but it may also decrease its efficacy.[99,100] Both techniques continue to be studied, and the benefits of one approach over another are still in dispute.

Outcomes

Collagen cross-linking was introduced in 2003 to stabilize progressive keratoconus,[100] and it has been reported by others to arrest progression in early[101] as well as advanced cases of the disease.[100,102-105] In addition to stabilizing the cornea, CXL has been reported to induce flattening of the cornea of 1.0 to 2.5 D, thereby improving corneal optics and vision.[4,5,106,107]

Contraindications

A current contraindication to CXL is corneal stromal thickness below 400 microns to prevent endothelial damage. Also, because exposure to ultraviolet light may cause reactivation of herpes simplex virus (HSV) infection, caution should be used when performing CXL in patients with prior HSV keratitis.

Complications

Complications of CXL include infectious keratitis, sterile infiltrates, corneal haze, corneal scarring, nonhealing epithelial defects, and corneal edema. With the exception of corneal edema, which is the result of endothelial damage, it has been suggested that other complications result from the removal of or damage to the epithelial layer.[100,103] However, deep stromal haze may not be related to endothelial damage or epithelial removal.

Combined Cross-linking and Intrastromal Corneal Ring Segments

Implantation of ICRS combined with CXL has been shown to be effective in stopping progression of and improving visual function in patients with keratoconus. The combination of these treatments may result in a greater improvement than when these individual treatment modalities are used alone.[78] There is a lack of consensus as to whether CXL should be performed before or after ICRS. Some studies have suggested that the greatest improvement in keratoconus occurs when ICRS and CXL are performed in the same session.[81] Other studies have demonstrated the greatest improvements when implantation of ICRS was followed by CXL treatment.[78,108] Additional studies described the need for modification of laser power settings with femtosecond channel creation when attempting ICRS following CXL because it is difficult to create channels for ICRS using the laser in corneas that have undergone CXL.[74]

Combined Cross-linking and Photorefractive Keratectomy

Combining CXL and PRK has been proposed to stabilize the cornea while providing greater improvement in visual function. A study of sequential CXL versus same-day CXL and topography-guided PRK found that the same-day treatment protocol yielded better results in UCVA, best spectacle-corrected visual acuity (BSCVA), and greater reduction in keratometric power.[109] Other studies also concluded that simultaneous CXL and topography-guided PRK are effective in improving functional vision in keratoconic patients, on average.[110-112]

Keratoplasty

Corneal transplantation has been the mainstay of treatment for keratoconus and other corneal ectasias in patients in whom the disease has progressed to a point that it cannot be corrected by optical devices (i.e., eyeglasses and contact lenses). While penetrating keratoplasty has traditionally been the corneal transplant, there has recently been increasing interest in lamellar keratoplasty. The CLEK study found that risk factors for patients requiring PK included younger age, corneal scarring, steeper keratometry values, poorer visual acuity, and poorer contact lens comfort.[113] The vast majority of patients in these studies had keratoconus.

Partial-Thickness/Lamellar Keratoplasty

Indications

Lamellar keratoplasty using DALK techniques can be considered for cases of progressive keratoconus that do not have significant scarring or hydrops. The DALK technique removes all or nearly all of the corneal stroma down to Descemet's membrane. The benefits of DALK are that it preserves the host endothelial layer, thereby eliminating the risk of endothelial rejection and avoiding the higher chronic endothelial cell loss associated with PK.[5,114,115]

Crescentic lamellar keratoplasty is a less commonly used option when the area of maximal thinning is in the periphery, such as in cases of pellucid marginal degeneration. The crescentic recipient bed is achieved by using a smaller trephine on the central edge. Peripheral thinning and ectasia can also be managed in two stages by performing a standard decentered lamellar procedure for tectonic support, followed 4 to 6 months later by a central PK. In cases of keratoglobus in which thinning is diffuse, particularly in the periphery, lamellar keratoplasty may lend tectonic support and flatten the cornea. However, prominent folds may result.

DALK Technique Options

Technique options include the Melles technique, the big-bubble technique, and variations on the big-bubble technique.[5,116] The Melles technique involves injecting air into the anterior chamber to better assess the depth of the lamellar resection.[5,114,117] The big-bubble technique involves trephining the cornea, followed by injecting air to achieve baring of Descemet's membrane.[5,114] The large-bubble modification of the big-bubble technique utilizes a shallower trephination with a larger expansion of the bubble to the periphery.[118,119] The femtosecond-assisted big-bubble technique utilizes a femtosecond laser program to trephine the cornea, followed by creating a big bubble to separate Descemet's membrane, remove residual stroma, and place a femtosecond-laser trephined cornea.[120]

Outcomes

There are conflicting reports on the data comparing DALK and PK. Poorer visual outcomes with DALK have been ascribed to the thickness of the host residual stromal bed after dissection,[121] which has been correlated with variation in postoperative visual acuity and contrast sensitivity following DALK. When baring of Descemet's membrane was achieved, visual results are reported to be comparable with PK.[114,122-128] The best visual acuity is achieved in DALK cases that have a residual bed of less than 20 microns, which is ideal for achieving similar visual results when compared with PK.[122] Similar BCVA outcomes have been achieved with the two procedures, but more studies have found a higher percentage of patients achieving 20/20 visual acuity with PK when compared with DALK,[5,114,129] although this difference was not always statistically significant.[130] This may be associated with the surgeon's learning curve and may decrease with increased surgeon experience with the technique.[114,131] One study found that DALK resulted in significantly higher myopia when compared with PK.[132] Endothelial cell loss was significantly lower with DALK that was performed without Descemet's membrane perforation when compared with full-thickness keratoplasty.[133-137]

Risk Factors and Complications

Relative contraindications to DALK include severe corneal scarring associated with hydrops, in which corneal perforation is more likely. Other challenges include deep stromal vascularization and severe thinning. Complications include infection, suture-related complications, stromal graft rejection, and graft failure due to interface opacity. Complications unique to DALK include perforation of the cornea during surgery, leading to conversion to PK, a higher overall failure rate than PK, and greater variation in visual acuity, since DALK patients are less likely to achieve 20/20 vision compared with PK recipients.[114] The incidence of stromal rejection is reported to be between 2% and 12%,

suggesting that corticosteroid treatment regimens play an important role in the postoperative management of DALK.[138] Deep anterior lamellar keratoplasty carries no risk of endothelial rejection; thus the overall rejection rate is lower when compared with PK.

Full-Thickness/Penetrating Keratoplasty

Penetrating keratoplasty has been the mainstay of treatment for keratoconus, and long-term graft survival has been reported at 95% at 5 years and 89% at 10 years according to the Australian Corneal Graft registry.[5]

Indications

Penetrating keratoplasty is indicated when the patient can no longer achieve functional vision with eyeglasses or contact lenses. Persistent corneal edema following hydrops is another indication for PK. Descemet's stripping endothelial keratoplasty is not a suitable option in this setting, as it cannot correct the ectatic disorder. Penetrating keratoplasty is preferred over DALK in cases of deep stromal scarring, in which perforation is more likely to occur during deep lamellar resection. When ectasia occurs in the far periphery of the cornea, a lamellar graft can be performed for tectonic support as a primary procedure, and additional PK can be performed later for visual rehabilitation.

Technique Options

- Mechanical: Trephination for PK includes the use of oversize and same-size trephines for donors and recipients. Axial length and graft-host disparity may have an impact on postoperative refractive error. Same-size grafts for PK in short eyes can result in postoperative hyperopia, whereas myopia will likely result when an oversized graft is used in eyes with long axial lengths.
- Femtosecond laser: Femtosecond laser-assisted keratoplasty (FLAK) is a relatively new technique that utilizes the femtosecond laser for trephining both the donor and recipient corneas. With this technique, both donor and recipient are trephined using the same pattern of laser trephination, designated as top-hat, mushroom, or zigzag patterns. Theoretical advantages of FLAK over standard PK are stronger wound healing, earlier removal of sutures, earlier visual rehabilitation,[139-142] and potentially decreased astigmatism.[140-144]

Outcomes

- Mechanical: Penetrating keratoplasty has been shown to be a safe and effective procedure with good visual acuity outcomes for all levels of severity in keratoconus.[145-147] Suturing techniques have not been demonstrated to affect outcomes. Less graft/host-size disparity seems to induce less myopic shift.[146,147] Repeat PK has also been performed with success for cases of recurrent ectasia after corneal grafts and is related either to incomplete excision of the cone or to progression of the disease. These cases occurred, on average, two decades following the original PK and were often bilateral, suggesting that the etiology of recurrence may relate to host cellular and/or biochemical factors.[145,148] There have also been case reports of keratoconus following PK in patients with no pre-existing keratoconus, suggesting that donor tissue may have had undiagnosed corneal pathology.[149]
- Femtosecond laser: Studies have shown that the FLAK procedure resulted in significant improvement in astigmatism up to 6 months following the procedure; this improvement did not persist beyond 6 months following surgery.[140] In addition, earlier suture removal is possible with FLAK due to greater mechanical stability and wound-healing advantages.[141]

Contraindications and Complications

- Penetrating keratoplasty may be contraindicated if many prior full-thickness corneal transplants have failed or if extensive anterior segment scarring is present. When corneal thinning extends near the limbus, PK is more challenging and carries a greater risk of failure. The complications of PK in ectasia include infection, rejection, failure, glaucoma, cataract, and poor refractive outcome (including anisometropia or high corneal astigmatism).

FOLLOW-UP EVALUATION

Follow-up evaluation and visit intervals for patients are dictated by the choice of treatment and the severity and/or progression of the disease. Medical follow-up visits should include measurement of visual acuity, external examination, slit-lamp biomicroscopy, and assessment of corneal contour. Surgical follow-up visits should include the above as well as additional measurements specific to the type of surgical follow-up care indicated.

Annual follow-up is recommended for cases of ectasia unless the patient has significant changes in visual function. In these cases, the examination should include assessment of corneal contour according to the clinician's judgment. Patients who see well with contact lenses but experience an unstable fit should be examined to assess contact lens stability. After refractive surgery, a refractive and diagnostic evaluation should be performed to look for signs of ectasia. After keratoplasty, a slit-lamp biomicroscopic examination should be performed to assess the clarity and health of the cornea and to check for suture erosion. Selective suture removal can be initiated in accordance with topographic findings to control and decrease astigmatism, which improves visual function. Suture removal typically begins after 3 months to ensure corneal wound stability and to minimize wound dehiscence. In the case of loose sutures and/or suture erosion, sutures may be removed earlier to prevent infection.

Patients should be made aware of the warning signs of rejection, including redness, sensitivity to light, vision change, and/or pain, and they should be advised to seek medical attention promptly if these signs or symptoms occur. The practitioner should be aware of the slit-lamp biomicroscopic findings of epithelial, stromal, and endothelial rejection. Epithelial rejection may appear as sub-epithelial infiltrates. Stromal and endothelial rejection may include stromal edema, and endothelial rejection may include pigmented keratic precipitates on the endothelium as well as an endothelial rejection line and possible anterior chamber reaction. Therapeutic modalities for treating graft rejection include topical and oral corticosteroids as well as subconjunctival or sub-Tenon's corticosteroid injections.

Corneal pachymetry may be useful in evaluating endothelial function, particularly if baseline thickness data is available. Serial corneal topography with enhanced capability may be used to manage postoperative astigmatism as well as track corneal thickness over time. The potential diurnal variation in corneal thickness should always be considered when comparing measurements. Patients using long-term topical corticosteroids should also have their IOP checked at regular intervals to rule out corticosteroid-induced IOP elevation.[150] Other assessments that should be considered include pupil dilation to estimate the cup-to-disc ratio, visual field testing, and stereo disc photography or OCT imaging of the retinal nerve fiber layer, to look for early signs of optic nerve damage associated with elevated IOP. (See Appendix 3 for additional information on how IOP is determined in diseased or postsurgical corneas.)

PROVIDER AND SETTING

The diagnosis and management of corneal ectasia requires broad medical skills. Patients with corneal ectasia who are evaluated by non-ophthalmologist health care providers should be promptly referred to an ophthalmologist with expertise in the management of corneal disorders if any of the following occurs:

- Visual loss
- Loss of functional vision
- Acute hydrops
- Progression of the disease
- Onset at a young age

COUNSELING AND REFERRAL

Patients with corneal ectasia have many treatment options, including medical and surgical approaches. When medical therapy with eyeglasses and/or contact lenses cannot improve visual function, or when there is loss of visual function using these methods of vision correction, referral to an ophthalmologist trained in surgical treatments for corneal ectasia is indicated. In addition, patients with a history of allergy and atopy may also need referral to a dermatologist and/or allergist. Patients with floppy eyelid disease may be best managed by an oculoplastics specialist. If there is evidence of newly diagnosed asthma, or in the case of obstructive sleep apnea or heart valve disease associated with floppy eyelid syndrome, referral to primary care and/or other medical specialists may also be indicated.

SOCIOECONOMIC CONSIDERATIONS

Keratoconus is relatively rare, with a prevalence between 50 and 230 per 100,000 in the general population.[7] In contrast to other chronic eye diseases, such as glaucoma and age-related macular degeneration, corneal ectasia, particularly keratoconus and post-refractive ectasias, are commonly seen in younger people. The average patient-reported age of onset of keratoconus ranges from 9 to 28 years.[7,33,151]

Corneal ectasias rarely lead to blindness, so these conditions are thought by some to have limited socioeconomic and public health significance. However, because ectasias such as keratoconus occur in younger individuals who are considerably more active and in their prime earning and child-rearing years, modest deficits in visual function can result in a disproportionate impact on quality of life and social burden.

Quality of Life

The CLEK Study Group utilized the National Eye Institute Visual Function Questionnaire (NEI-VFQ) to assess vision-related quality of life (V-QoL) in their cohort. The NEI-VFQ is a vision-related quality of life instrument designed to assess a patient's perception of visual function and quality of life in 12 different domains (general health, general vision, ocular pain, near and distance activities, driving, color vision, peripheral vision, social function, mental health, role difficulties, and dependency). In one report, the NEI-VFQ was administered to 1166 CLEK Study patients at their first annual follow-up evaluation.[152] This study revealed that binocular entrance visual acuity worse than 20/40 was associated with lower quality of life scores on each of the 12 scales except General Health and Ocular Pain. A keratometric reading averaging over 52.0 D (average of both eyes) was associated with lower scores on the Mental Health, Role Difficulty, Driving, Dependency and Ocular Pain scales.

A follow-up study demonstrated that keratoconus is associated with a significantly impaired visual quality of life that continues to decline over time.[153]

Economics

Because of the significantly reduced vision-related quality of life and the relatively young onset of this disease, the economic burden of caring for keratoconus patients is a significant public health problem. One recent study estimated the incremental lifetime cost of treatment of keratoconus compared with the lifetime expected cost of treating myopia using a Markov decision model. This study looked at costs for clinic visits, contact lenses, fitting fees, surgical procedures, and complications. This expected value of the lifetime cost of treating keratoconus compared with treating myopia was determined to be $25,168, with a standard deviation of $16,247 and a median of $17,596.[154] The factors that most influenced the lifetime cost were the probability of corneal transplantation and subsequent regraft. This study found that the cost of routine care likely has relatively little influence on the lifetime cost of care, although for keratoconus the cost of routine care is not trivial. This study concluded that the expected lifetime cost for treatment of keratoconus presents a significant cost to both patient and payers.

Another study attempted to quantify the conferred patient value (improvement in quality of life and/or length of life), comparative effectiveness, and cost-effectiveness of PK for keratoconus compared with other interventions across different medical specialties.[155] These parameters were assessed using cost-utility analysis with value-based medicine criteria. This study concluded that PK for patients with severe keratoconus seems to be very cost-effective compared with other health care interventions.

APPENDIX 1. QUALITY OF OPHTHALMIC CARE CORE CRITERIA

Providing quality care
is the physician's foremost ethical obligation, and is
the basis of public trust in physicians.
AMA Board of Trustees, 1986

Quality ophthalmic care is provided in a manner and with the skill that is consistent with the best interests of the patient. The discussion that follows characterizes the core elements of such care.

The ophthalmologist is first and foremost a physician. As such, the ophthalmologist demonstrates compassion and concern for the individual, and utilizes the science and art of medicine to help alleviate patient fear and suffering. The ophthalmologist strives to develop and maintain clinical skills at the highest feasible level, consistent with the needs of patients, through training and continuing education. The ophthalmologist evaluates those skills and medical knowledge in relation to the needs of the patient and responds accordingly. The ophthalmologist also ensures that needy patients receive necessary care directly or through referral to appropriate persons and facilities that will provide such care, and he or she supports activities that promote health and prevent disease and disability.

The ophthalmologist recognizes that disease places patients in a disadvantaged, dependent state. The ophthalmologist respects the dignity and integrity of his or her patients, and does not exploit their vulnerability.

Quality ophthalmic care has the following optimal attributes, among others.

- The essence of quality care is a meaningful partnership relationship between patient and physician. The ophthalmologist strives to communicate effectively with his or her patients, listening carefully to their needs and concerns. In turn, the ophthalmologist educates his or her patients about the nature and prognosis of their condition and about proper and appropriate therapeutic modalities. This is to ensure their meaningful participation (appropriate to their unique physical, intellectual and emotional state) in decisions affecting their management and care, to improve their motivation and compliance with the agreed plan of treatment, and to help alleviate their fears and concerns.
- The ophthalmologist uses his or her best judgment in choosing and timing appropriate diagnostic and therapeutic modalities as well as the frequency of evaluation and follow-up, with due regard to the urgency and nature of the patient's condition and unique needs and desires.
- The ophthalmologist carries out only those procedures for which he or she is adequately trained, experienced and competent, or, when necessary, is assisted by someone who is, depending on the urgency of the problem and availability and accessibility of alternative providers.
- Patients are assured access to, and continuity of, needed and appropriate ophthalmic care, which can be described as follows.
  - The ophthalmologist treats patients with due regard to timeliness, appropriateness, and his or her own ability to provide such care.
  - The operating ophthalmologist makes adequate provision for appropriate pre- and postoperative patient care.
  - When the ophthalmologist is unavailable for his or her patient, he or she provides appropriate alternate ophthalmic care, with adequate mechanisms for informing patients of the existence of such care and procedures for obtaining it.
  - The ophthalmologist refers patients to other ophthalmologists and eye care providers based on the timeliness and appropriateness of such referral, the patient's needs, the competence and qualifications of the person to whom the referral is made, and access and availability.
  - The ophthalmologist seeks appropriate consultation with due regard to the nature of the ocular or other medical or surgical problem. Consultants are suggested for their skill, competence, and accessibility. They receive as complete and accurate an accounting of the problem as necessary to provide efficient and effective advice or intervention, and in turn respond in an adequate and timely manner.

- The ophthalmologist maintains complete and accurate medical records.
- On appropriate request, the ophthalmologist provides a full and accurate rendering of the patient's records in his or her possession.
- The ophthalmologist reviews the results of consultations and laboratory tests in a timely and effective manner and takes appropriate actions.
- The ophthalmologist and those who assist in providing care identify themselves and their profession.
- For patients whose conditions fail to respond to treatment and for whom further treatment is unavailable, the ophthalmologist provides proper professional support, counseling, rehabilitative and social services, and referral as appropriate and accessible.

- Prior to therapeutic or invasive diagnostic procedures, the ophthalmologist becomes appropriately conversant with the patient's condition by collecting pertinent historical information and performing relevant preoperative examinations. Additionally, he or she enables the patient to reach a fully informed decision by providing an accurate and truthful explanation of the diagnosis; the nature, purpose, risks, benefits, and probability of success of the proposed treatment and of alternative treatment; and the risks and benefits of no treatment.
- The ophthalmologist adopts new technology (e.g., drugs, devices, surgical techniques) in judicious fashion, appropriate to the cost and potential benefit relative to existing alternatives and to its demonstrated safety and efficacy.
- The ophthalmologist enhances the quality of care he or she provides by periodically reviewing and assessing his or her personal performance in relation to established standards, and by revising or altering his or her practices and techniques appropriately.
- The ophthalmologist improves ophthalmic care by communicating to colleagues, through appropriate professional channels, knowledge gained through clinical research and practice. This includes alerting colleagues of instances of unusual or unexpected rates of complications and problems related to new drugs, devices or procedures.
- The ophthalmologist provides care in suitably staffed and equipped facilities adequate to deal with potential ocular and systemic complications requiring immediate attention.
- The ophthalmologist also provides ophthalmic care in a manner that is cost effective without unacceptably compromising accepted standards of quality.

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APPENDIX 2. PREFERRED PRACTICE PATTERN RECOMMENDATION GRADING

The grades herein report the SIGN grade associated with the included studies supporting each recommendation (I++; I+; I-; II++; II+; II-; III), the GRADE evaluation of the body of evidence (Good, Moderate, Insufficient), and the GRADE assessment of the strength of the recommendation (Strong, Discretionary). Details of these grading systems are reported in the Methods and Key to Ratings section at the beginning of this document.

Highlighted Findings and Recommendations for Care

Page 4: Young patients or postkeratorefractive surgery patients who appear to have unstable refractions should be evaluated for evidence of corneal ectasia: III; Insufficient; Discretionary

Page 4: The ophthalmologist needs to measure and evaluate more aspects of visual function than just BCVA in patients with known or suspected ectasia, insofar as BCVA may not completely characterize visual function in these patients: III; Insufficient; Discretionary

Page 4: Prior to refractive surgery, corneal topography should be performed and evaluated for evidence of irregular astigmatism, corneal warpage, or abnormalities suggestive of keratoconus or other forms of corneal ectasia: III; Insufficient; Discretionary

Care Process – Diagnosis

Page 9: In addition to external examination and slit-lamp biomicroscopy of the cornea, IOP measurement and fundus assessment should be performed: III; Insufficient; Discretionary

Page 9: Slit-scanning corneal topography and rotating Scheimpflug imaging play an increasing role in establishing diagnostic criteria for keratoconus, subclinical keratoconus, pellucid marginal degeneration, post-refractive corneal ectasias, and screening potential refractive surgery patients: II-; Moderate; Strong

Page 10: Posterior elevation mapping has been shown to have a relatively high sensitivity and specificity for the detection of keratoconus, but less so with sub-clinical keratoconus: II+; Moderate; Discretionary

Page 10: Tomographically derived pachymetry mapping provides data for characterizing corneal thickness distribution; it has been shown to differentiate between normal and keratoconic corneas, and it may also play a role in evaluating subclinical keratoconus: II++; Good; Strong

Care Process – Management

Page 10: Ectasia should be suspected in a young patient whose refractive error keeps changing, and such patients should be screened carefully for ectasia prior to refractive surgery: III; Insufficient; Discretionary

Page 10: Topography is also essential if a keratorefractive surgical procedure is necessary to optimize the refractive result after intraocular lens implantation: III; Good; Strong

Page 10: As keratoconus and the resultant aberrations progress, contact lenses may be required to correct vision and reduce distortion: II+; Good; Strong

Page 12: Intrastromal corneal ring segment implantation is a method of improving contact lens tolerance and BCVA for patients with corneal ectasia, a clear cornea, and contact lens intolerance by improving corneal shape and reducing astigmatism: II-; Moderate; Discretionary

Page 12: Care should be taken to measure pachymetry along the entire area of the corneal channel dissection to avoid intraoperative perforation: III; Insufficient; Discretionary

Page 13: Contraindications to ICRS implantation include central corneal scarring and a corneal thickness of less than 400 microns at the incision site for implantation of the ring segments: III; Insufficient; Discretionary

Page 13: Current CXL protocols require either the removal of the epithelium or exposure of the intact epithelium to agents that increase the permeability of the cell layer, followed by the application of topical riboflavin and UV-A treatment: II-; Insufficient; Discretionary

Page 14: A current contraindication to CXL is corneal stromal thickness below 400 microns to prevent endothelial damage: III; Insufficient; Discretionary

Page 14: Because exposure to ultraviolet light may cause reactivation of herpes simplex virus (HSV) infection, caution should be used when performing CXL in patients with prior HSV keratitis: III; Insufficient; Discretionary

Page 14: There is a lack of consensus as to whether CXL should be performed before or after ICRS: I-; Insufficient; Discretionary

Page 15: Lamellar keratoplasty using DALK techniques can be considered for cases of progressive keratoconus without significant scarring or hydrops: II++; Moderate; Discretionary

Page 15: Crescentic lamellar keratoplasty is a less commonly used option when the area of maximal thinning is in the periphery, such as in cases of pellucid marginal degeneration: III; Insufficient; Discretionary

Page 15: Peripheral thinning and ectasia can also be managed in two stages, by performing a standard decentered lamellar procedure for tectonic support followed 4 to 6 months later by a central PK: III; Insufficient; Discretionary

Page 16: Penetrating keratoplasty is indicated when the patient can no longer achieve functional vision with eyeglasses or contact lenses: III; Insufficient; Discretionary

Page 16: Persistent corneal edema following hydrops is another indication for PK: III; Insufficient; Discretionary: III; Insufficient; Discretionary

Page 16: Descemet's stripping endothelial keratoplasty is not a suitable option in this setting, as it cannot correct the ectatic disorder: III; Insufficient; Discretionary

Page 16: Penetrating keratoplasty is preferred over DALK in cases of deep stromal scarring, in which perforation is more likely to occur during deep lamellar resection: III; Insufficient; Discretionary

Page 16: When ectasia occurs in the far periphery of the cornea, a lamellar graft can be performed for tectonic support as a primary procedure, with additional PK performed later for visual rehabilitation: III; Insufficient; Discretionary

Page 16: Penetrating keratoplasty may be contraindicated if many prior full-thickness corneal transplants have failed or if extensive anterior segment scarring is present: III; Insufficient; Discretionary

Care Process – Follow-Up

Page 17: Medical follow-up visits should include measurement of visual acuity, external examination, slit-lamp biomicroscopy, and assessment of corneal contour: III; Insufficient; Discretionary

Page 17: Surgical follow-up visits should include the above as well as additional measurements specific to the type of surgical follow-up care indicated: III; Insufficient; Discretionary

Page 17: Annual follow-up is recommended for cases of ectasia unless the patient has significant changes in visual function: III; Insufficient; Discretionary

Page 17: In these cases, the examination should include assessment of corneal contour, according to the clinician's judgment: III; Insufficient; Discretionary

Page 17: Patients who see well with contact lenses but experience an unstable fit should be examined to assess contact lens stability: III; Insufficient; Discretionary

Page 17: After refractive surgery, a refractive and diagnostic evaluation should be performed to look for signs of ectasia: III; Good; Strong

Page 17: After keratoplasty, a slit-lamp biomicroscopic examination should be performed to assess the clarity and health of the cornea and to check for suture erosion: III; Good; Strong

Page 17: Selective suture removal can be initiated in accordance with topographic findings to control and decrease astigmatism and to improve visual function: III; Insufficient; Discretionary

Page 17: Patients should be made aware of the warning signs of rejection, including redness, sensitivity to light, vision change, and/or pain, and should be advised to seek medical attention promptly if these signs or symptoms occur: III; Good; Strong

Page 17: The practitioner should be aware of the slit-lamp findings of epithelial, stromal, and endothelial rejection: III; Good; Strong

Page 17: Therapeutic modalities for treating graft rejection include topical and oral steroids as well as subconjunctival or sub-Tenon's steroid injections: III; Good; Strong

Page 17: Corneal pachymetry may be useful in evaluating endothelial function: III; Insufficient; Discretionary

Page 17: Patients using long-term topical corticosteroids should also have their IOP checked at regular intervals to rule out corticosteroid-induced IOP elevation: II++; Good; Strong

Page 17: Other assessments that should be considered include optic nerve dilation to estimate the cup-to-disc ratio, visual field testing, and stereo disc photography or OCT imaging of the retinal nerve fiber layer to look for early signs of optic nerve damage associated with elevated IOP: III; Insufficient; Discretionary

Provider and Setting

Page 17: Patients with corneal ectasia who are evaluated by non-ophthalmologist health care providers should be promptly referred to an ophthalmologist with expertise in the management of corneal disorders if visual loss, loss of visual function, acute hydrops, progression of disease, or onset at a young age occurs: III; Insufficient; Discretionary

Counseling and Referral

Page 18: When medical therapy with eyeglasses and/or contact lenses cannot improve visual function, or when there is loss of visual function with these methods of vision correction, referral to an ophthalmologist trained in surgical treatments for corneal ectasia is indicated: III; Good; Strong

Page 18: In addition, patients with a history of allergy and atopy may also need referral to a dermatologist and/or allergist: III; Good; Strong

Page 18: Patients with floppy eyelid disease may be best managed by an oculoplastics specialist: III; Good; Strong

Page 18: If there is evidence of newly diagnosed asthma, or in the case of obstructive sleep apnea or heart valve disease associated with floppy eyelid syndrome, referral to primary care and/or other medical specialists may also be indicated: III; Good; Strong

APPENDIX 3: Determination of Intraocular Pressure in Diseased or Postsurgical Corneas

Page 25: Use of alternative and less subjective techniques for IOP determination in these diseased, abnormal, or surgically altered corneas is strongly advised: III; Good; Strong

Page 25: It is very important to use the same technique consistently, from visit to visit, to detect clinically significant and meaningful IOP elevations: III; Good; Strong

APPENDIX 3. DETERMINATION OF INTRAOCULAR PRESSURE IN DISEASED OR POSTSURGICAL CORNEAS

Intraocular pressure (IOP) assessment in diseased corneas may be very inaccurate when measured only by Goldmann applanation tonometry (GAT). This is due to a host of reasons, such as disease-induced and treatment-induced alterations in corneal thickness, hydration, corneal curvature/astigmatism, an irregular corneal epithelial surface, or corneal stromal scarring. All of these factors can affect the estimation of the inherently subjective endpoint of GAT (i.e., the "just touching" inside edges of the semicircular mires viewed through the Goldmann applanation prism tip). Therefore, use of alternative and less subjective techniques to determine IOP in these diseased, abnormal, or surgically altered corneas is strongly advised. Such techniques are described below.

- Applanation techniques use various devices to measure IOP:
  - Pneumatonometer. This technology uses a pneumatic sensor (consisting of a piston floating on an air bearing) with a 5 mm fenestrated silicone tip that conforms to the cornea. The balance between the flow of air from the machine and the resistance to flow from the cornea affects the movement of the piston, and this movement is used to calculate the IOP. This device generates 40 readings per second and also measures ocular pulse amplitude. Topical anesthesia is required.
  - Non-Goldmann applanation tonometer. This technology utilizes a free-floating 1 mm microstrain gauge transducer to detect transmitted IOP. The transducer is surrounded by an outer ring that flattens the adjacent cornea, reducing its influence on measurement. These devices measure 500 samples per second and average 8 or 10 readings for each IOP determination within confidence limits. Topical anesthesia is required.
  - Ocular response analyzer. This technology uses a collimated air pulse to cause the cornea to move inward and then outward in a bidirectional applanation process to measure the biomechanical properties of the cornea (i.e., hysteresis) and calculate a "corneal compensated" and GAT-equivalent IOP. This technology also measures ocular pulse amplitude and does not require topical anesthesia.
- The contour-matching Pascal technique utilizes a piezoresistive sensor embedded into the tonometer tip to digitally sample IOP 100 times per second. The concave tip shape causes a relaxation of the cornea to conform to the dynamic contour tonometer tip and minimizes any influence of corneal properties on IOP measurements. An internal microprocessor then analyzes this direct proportional signal and extracts IOP and ocular pulse amplitude. The device calculates an IOP independent of corneal properties. It requires 6 seconds or 6 ocular pulse cycles to determine the IOP and requires topical anesthesia.
- The rebound tonometry deceleration technique utilizes an induction coil to magnetize a small plastic-tipped metal probe that is rapidly fired against the cornea (0.25 m/sec). Software analyzes the rate of deceleration and the contact time of the probe against the cornea (approximately 0.05 sec), the relative magnitude of which is proportional to IOP and from which the IOP is calculated. Six measurements are required for accuracy. This technology does not require topical anesthesia.

Although applanation and rebound tonometers are more influenced by corneal properties compared with other devices, they are more objective than GAT. Therefore, they may more accurately and reproducibly estimate "true IOP" (relative to GAT) over the course of a patient's corneal disease state. Nevertheless, it is very important to use the same technique consistently, from visit to visit, to detect clinically significant and meaningful IOP elevations. Early detection of elevated IOP will allow timely initiation of IOP-lowering therapy before irreversible optic nerve damage occurs. These eyes are frequently subject to either disease-induced or treatment-induced secondary IOP elevation, which often goes undetected when relying on GAT alone to determine IOP.

RELATED ACADEMY MATERIALS

Basic and Clinical Science Course
External Disease and Cornea (Section 8, 2013–2014)

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Innovations in Advanced Surface Laser Refractive Surgery (2010)

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Comprehensive Adult Medical Eye Evaluation (2010)

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REFERENCES

1. Scottish Intercollegiate Guidelines Network. Annex B: key to evidence statements and grades of recommendations. In: SIGN 50: A Guideline Developer's Handbook. Available at: www.sign.ac.uk/guidelines/fulltext/50/annexb.html. Accessed October 2, 2012
2. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.
3. GRADE Working Group. Organizations that have endorsed or that are using GRADE. Available at: www.gradeworkinggroup.org/society/index.htm. Accessed October 2, 2012.
4. Espandar L, Meyer J. Keratoconus: overview and update on treatment. Middle East Afr J Ophthalmol 2010;17:15-20.
5. Jhanji V, Sharma N, Vajpayee RB. Management of keratoconus: current scenario. Br J Ophthalmol 2011;95:1044-50.
6. Pinero DP, Nieto JC, Lopez-Miguel A. Characterization of corneal structure in keratoconus. J Cataract Refract Surg 2012;38:2167-83.
7. Krachmer JH, Feder RS, Belin MW. Keratoconus and related noninflammatory corneal thinning disorders. Surv Ophthalmol 1984;28:293-322.
8. Sugar J, Macsai MS. What causes keratoconus? Cornea 2012;31:716-9.
9. Binder PS. Analysis of ectasia after laser in situ keratomileusis: risk factors. J Cataract Refract Surg 2007;33:1530-8.
10. Atilano SR, Coskun P, Chwa M, et al. Accumulation of mitochondrial DNA damage in keratoconus corneas. Invest Ophthalmol Vis Sci 2005;46:1256-63.
11. Arnal E, Peris-Martinez C, Menezo JL, et al. Oxidative stress in keratoconus? Invest Ophthalmol Vis Sci 2011;52:8592-7.
12. Balasubramanian SA, Pye DC, Willcox MD. Are proteinases the reason for keratoconus? Curr Eye Res 2010;35:185-91.
13. Chwa M, Atilano SR, Hertzog D, et al. Hypersensitive response to oxidative stress in keratoconus corneal fibroblasts. Invest Ophthalmol Vis Sci 2008;49:4361-9.
14. Kenney MC, Chwa M, Atilano SR, et al. Increased levels of catalase and cathepsin V/L2 but decreased TIMP-1 in keratoconus corneas: evidence that oxidative stress plays a role in this disorder. Invest Ophthalmol Vis Sci 2005;46:823-32.
15. Smith VA, Matthews FJ, Majid MA, Cook SD. Keratoconus: matrix metalloproteinase-2 activation and TIMP modulation. Biochim Biophys Acta 2006;1762:431-9.

16. Lema I, Duran JA. Inflammatory molecules in the tears of patients with keratoconus. Ophthalmology 2005;112:654-9.
17. Lema I, Sobrino T, Duran JA, et al. Subclinical keratoconus and inflammatory molecules from tears. Br J Ophthalmol 2009;93:820-4.
18. Matthews FJ, Cook SD, Majid MA, et al. Changes in the balance of the tissue inhibitor of matrix metalloproteinases (TIMPs)-1 and -3 may promote keratocyte apoptosis in keratoconus. Exp Eye Res 2007;84:1125-34.
19. Randleman JB, Trattler WB, Stulting RD. Validation of the Ectasia Risk Score System for preoperative laser in situ keratomileusis screening. Am J Ophthalmol 2008;145:813-8.
20. Binder PS, Trattler WB. Evaluation of a risk factor scoring system for corneal ectasia after LASIK in eyes with normal topography. J Refract Surg 2010;26:241-50.
21. Weed KH, MacEwen CJ, McGhee CN. The Dundee University Scottish Keratoconus Study II: a prospective study of optical and surgical correction. Ophthalmic Physiol Opt 2007;27:561-7.
22. Gordon MO, Steger-May K, Szczotka-Flynn L, et al. Baseline factors predictive of incident penetrating keratoplasty in keratoconus. Am J Ophthalmol 2006;142:923-30.
23. Mannis MJ. Keratoconus: why and when do we turn to surgical therapy? Am J Ophthalmol 2006;142:1044-5.
24. American Academy of Ophthalmology Preferred Practice Patterns Committee. Preferred Practice Pattern® Guidelines. Comprehensive Adult Medical Eye Evaluation. San Francisco, CA: American Academy of Ophthalmology; 2010. Available at: www.aao.org/ppp.
25. Jinabhai A, Radhakrishnan H, O'Donnell C. Pellucid corneal marginal degeneration: a review. Cont Lens Anterior Eye 2011;34:56-63.
26. Feder RS, Gan TG. Non-inflammatory ectatic disorders. In: Krachmer JH, Mannis MJ, eds. Cornea: Fundamentals, Diagnosis, and Management. Vol. 1. 3rd ed. London: Elsevier, Inc.; 2011:879.
27. Randleman JB, Woodward M, Lynn MJ, Stulting RD. Risk assessment for ectasia after corneal refractive surgery. Ophthalmology 2008;115:37-50.
28. Weed KH, MacEwen CJ, Giles T, et al. The Dundee University Scottish Keratoconus study: demographics, corneal signs, associated diseases, and eye rubbing. Eye (Lond) 2008;22:534-41.
29. Bawazeer AM, Hodge WG, Lorimer B. Atopy and keratoconus: a multivariate analysis. Br J Ophthalmol 2000;84:834-6.
30. McMahon TT, Shin JA, Newlin A, et al. Discordance for keratoconus in two pairs of monozygotic twins. Cornea 1999;18:444-51.
31. Steele TM, Fabinyi DC, Couper TA, Loughnan MS. Prevalence of Orbscan II corneal abnormalities in relatives of patients with keratoconus. Clin Experiment Ophthalmol 2008;36:824-30.
32. Kaya V, Utine CA, Altunsoy M, et al. Evaluation of corneal topography with Orbscan II in first-degree relatives of patients with keratoconus. Cornea 2008;27:531-4.
33. Zadnik K, Barr JT, Edrington TB, et al. Baseline findings in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study. Invest Ophthalmol Vis Sci 1998;39:2537-46.
34. Liskova P, Hysi PG, Waseem N, et al. Evidence for keratoconus susceptibility locus on chromosome 14: a genome-wide linkage screen using single-nucleotide polymorphism markers. Arch Ophthalmol 2010;128:1191-5.
35. Bisceglia L, Ciaschetti M, De Bonis P, et al. VSX1 mutational analysis in a series of Italian patients affected by keratoconus: detection of a novel mutation. Invest Ophthalmol Vis Sci 2005;46:39-45.
36. De Bonis P, Laborante A, Pizzicoli C, et al. Mutational screening of VSX1, SPARC, SOD1, LOX, and TIMP3 in keratoconus. Mol Vis 2011;17:2482-94.
37. Aldave AJ, Bourla N, Yellore VS, et al. Keratoconus is not associated with mutations in COL8A1 and COL8A2. Cornea 2007;26:963-5.
38. Aldave AJ, Yellore VS, Salem AK, et al. No VSX1 gene mutations associated with keratoconus. Invest Ophthalmol Vis Sci 2006;47:2820-2.
39. Gajecka M, Radhakrishna U, Winters D, et al. Localization of a gene for keratoconus to a 5.6-Mb interval on 13q32. Invest Ophthalmol Vis Sci 2009;50:1531-9.
40. Dash DP, George S, O'Prey D, et al. Mutational screening of VSX1 in keratoconus patients from the European population. Eye (Lond) 2010;24:1085-92.

41. Tan DT, Por YM. Current treatment options for corneal ectasia. Curr Opin Ophthalmol 2007;18:284-9.
42. Belin MW, Asota IM, Ambrosio R Jr, Khachikian SS. What's in a name: keratoconus, pellucid marginal degeneration, and related thinning disorders. Am J Ophthalmol 2011;152:157-62.
43. Montes-Mico R, Charman WN. Intraocular pressure after excimer laser myopic refractive surgery. Ophthalmic Physiol Opt 2001;21:228-35.
44. Rashad KM, Bahnassy AA. Changes in intraocular pressure after laser in situ keratomileusis. J Refract Surg 2001;17:420-7.
45. Kirwan C, O'Keefe M. Measurement of intraocular pressure in LASIK and LASEK patients using the Reichert Ocular Response Analyzer and Goldmann applanation tonometry. J Refract Surg 2008;24:366-70.
46. Ucakhan OO, Cetinkor V, Ozkan M, Kanpolat A. Evaluation of Scheimpflug imaging parameters in subclinical keratoconus, keratoconus, and normal eyes. J Cataract Refract Surg 2011;37:1116-24.
47. Li Y, Meisler DM, Tang M, et al. Keratoconus diagnosis with optical coherence tomography pachymetry mapping. Ophthalmology 2008;115:2159-66.
48. Ambrosio R Jr. Percentage thickness increase and absolute difference from thinnest to describe thickness profile. J Refract Surg 2010;26:84-6; author reply 86-7.
49. Ambrosio R Jr, Caiado AL, Guerra FP, et al. Novel pachymetric parameters based on corneal tomography for diagnosing keratoconus. J Refract Surg 2011;27:753-8.
50. Dumitrica DM, Colin J. Indices for the detection of keratoconus. Oftalmologia 2010;54:19-29.
51. Buhren J, Kook D, Yoon G, Kohnen T. Detection of subclinical keratoconus by using corneal anterior and posterior surface aberrations and thickness spatial profiles. Invest Ophthalmol Vis Sci 2010;51:3424-32.
52. Schlegel Z, Hoang-Xuan T, Gatinel D. Comparison of and correlation between anterior and posterior corneal elevation maps in normal eyes and keratoconus-suspect eyes. J Cataract Refract Surg 2008;34:789-95.
53. de Sanctis U, Loiacono C, Richiardi L, et al. Sensitivity and specificity of posterior corneal elevation measured by Pentacam in discriminating keratoconus/subclinical keratoconus. Ophthalmology 2008;115:1534-9.
54. Ambrosio R Jr, Alonso RS, Luz A, Coca Velarde LG. Corneal-thickness spatial profile and corneal-volume distribution: tomographic indices to detect keratoconus. J Cataract Refract Surg 2006;32:1851-9.
55. Bessho K, Maeda N, Kuroda T, et al. Automated keratoconus detection using height data of anterior and posterior corneal surfaces. Jpn J Ophthalmol 2006;50:409-16.
56. Atchison DA, Mathur A, Read SA, et al. Peripheral ocular aberrations in mild and moderate keratoconus. Invest Ophthalmol Vis Sci 2010;51:6850-7.
57. Alio JL, Shabayek MH. Corneal higher order aberrations: a method to grade keratoconus. J Refract Surg 2006;22:539-45.
58. Buhren J, Kuhne C, Kohnen T. Defining subclinical keratoconus using corneal first-surface higher-order aberrations. Am J Ophthalmol 2007;143:381-9.
59. Kosaki R, Maeda N, Bessho K, et al. Magnitude and orientation of Zernike terms in patients with keratoconus. Invest Ophthalmol Vis Sci 2007;48:3062-8.
60. Mihaltz K, Kranitz K, Kovacs I, et al. Shifting of the line of sight in keratoconus measured by a hartmann-shack sensor. Ophthalmology 2010;117:41-8.
61. Pantanelli S, MacRae S, Jeong TM, Yoon G. Characterizing the wave aberration in eyes with keratoconus or penetrating keratoplasty using a high-dynamic range wavefront sensor. Ophthalmology 2007;114:2013-21.
62. Pallikaris IG, Kymionis GD, Astyrakakis NI. Corneal ectasia induced by laser in situ keratomileusis. J Cataract Refract Surg 2001;27:1796-802.
63. Argento C, Cosentino MJ, Tytiun A, et al. Corneal ectasia after laser in situ keratomileusis. J Cataract Refract Surg 2001;27:1440-8.
64. Binder PS, Lindstrom RL, Stulting RD, et al. Keratoconus and corneal ectasia after LASIK. J Cataract Refract Surg 2005;31:2035-8.
65. Zadnik K, Barr JT, Steger-May K, et al. Comparison of flat and steep rigid contact lens fitting methods in keratoconus. Optom Vis Sci 2005;82:1014-21.

66. Barnett M, Mannis MJ. Contact lenses in the management of keratoconus. Cornea 2011;30:1510-6.
67. Abdalla YF, Elsahn AF, Hammersmith KM, Cohen EJ. SynergEyes lenses for keratoconus. Cornea 2010;29:5-8.
68. Baran I, Bradley JA, Alipour F, et al. PROSE treatment of corneal ectasia. Cont Lens Anterior Eye 2012;35:222-7.
69. Schornack MM, Patel SV. Scleral lenses in the management of keratoconus. Eye Contact Lens 2010;36:39-44.
70. Alfonso JF, Lisa C, Fernandez-Vega L, et al. Intrastromal corneal ring segment implantation in 219 keratoconic eyes at different stages. Graefes Arch Clin Exp Ophthalmol 2011;249:1705-12.
71. Kubaloglu A, Sari ES, Cinar Y, et al. Comparison of mechanical and femtosecond laser tunnel creation for intrastromal corneal ring segment implantation in keratoconus: prospective randomized clinical trial. J Cataract Refract Surg 2010;36:1556-61.
72. Coskunseven E, Kymionis GD, Tsiklis NS, et al. Complications of intrastromal corneal ring segment implantation using a femtosecond laser for channel creation: a survey of 850 eyes with keratoconus. Acta Ophthalmol 2011;89:54-7.
73. Ertan A, Kamburoglu G. Analysis of centration of Intacs segments implanted with a femtosecond laser. J Cataract Refract Surg 2007;33:484-7.
74. El-Raggal TM. Effect of corneal collagen crosslinking on femtosecond laser channel creation for intrastromal corneal ring segment implantation in keratoconus. J Cataract Refract Surg 2011;37:701-5.
75. Ertan A, Kamburoglu G, Akgun U. Comparison of outcomes of 2 channel sizes for intrastromal ring segment implantation with a femtosecond laser in eyes with keratoconus. J Cataract Refract Surg 2007;33:648-53.
76. Pinero DP, Alio JL, El Kady B, et al. Refractive and aberrometric outcomes of intracorneal ring segments for keratoconus: mechanical versus femtosecond-assisted procedures. Ophthalmology 2009;116:1675-87.
77. Colin J, Malet FJ. Intacs for the correction of keratoconus: two-year follow-up. J Cataract Refract Surg 2007;33:69-74.
78. Coskunseven E, Jankov MR 2nd, Hafezi F, et al. Effect of treatment sequence in combined intrastromal corneal rings and corneal collagen crosslinking for keratoconus. J Cataract Refract Surg 2009;35:2084-91.
79. Coskunseven E, Kymionis GD, Tsiklis NS, et al. One-year results of intrastromal corneal ring segment implantation (KeraRing) using femtosecond laser in patients with keratoconus. Am J Ophthalmol 2008;145:775-9.
80. Ertan A, Kamburoglu G. Intacs implantation using a femtosecond laser for management of keratoconus: Comparison of 306 cases in different stages. J Cataract Refract Surg 2008;34:1521-6.
81. El-Raggal TM. Sequential versus concurrent KERARINGS insertion and corneal collagen cross-linking for keratoconus. Br J Ophthalmol 2011;95:37-41.
82. Ferrara G, Torquetti L, Ferrara P, Merayo-Lloves J. Intrastromal corneal ring segments: visual outcomes from a large case series. Clin Experiment Ophthalmol 2012;40:433-9.
83. Ferrara P, Torquetti L. Clinical outcomes after implantation of a new intrastromal corneal ring with a 210-degree arc length. J Cataract Refract Surg 2009;35:1604-8.
84. Gharaibeh AM, Muhsen SM, AbuKhader IB, et al. KeraRing intrastromal corneal ring segments for correction of keratoconus. Cornea 2012;31:115-20.
85. Hamdi IM. Optical and topographic changes in keratoconus after implantation of Ferrara intracorneal ring segments. J Refract Surg 2010;26:871-80.
86. Khan MI, Injarie A, Muhtaseb M. Intrastromal corneal ring segments for advanced keratoconus and cases with high keratometric asymmetry. J Cataract Refract Surg 2012;38:129-36.
87. Kaya V, Utine CA, Karakus SH, et al. Refractive and visual outcomes after Intacs vs ferrara intrastromal corneal ring segment implantation for keratoconus: a comparative study. J Refract Surg 2011;27:907-12.
88. Kubaloglu A, Sari ES, Cinar Y, et al. Intrastromal corneal ring segment implantation for the treatment of keratoconus. Cornea 2011;30:11-7.

89. Pesando PM, Ghiringhello MP, Di Meglio G, Romeo S. Treatment of keratoconus with Ferrara ICRS and consideration of the efficacy of the Ferrara nomogram in a 5-year follow-up. Eur J Ophthalmol 2010;20:865-73.
90. Pinero DP, Alio JL, Teus MA, et al. Modification and refinement of astigmatism in keratoconic eyes with intrastromal corneal ring segments. J Cataract Refract Surg 2010;36:1562-72.
91. Renesto Ada C, Melo LA Jr, Sartori Mde F, Campos M. Sequential topical riboflavin with or without ultraviolet a radiation with delayed intracorneal ring segment insertion for keratoconus. Am J Ophthalmol 2012;153:982-93.
92. Shabayek MH, Alio JL. Intrastromal corneal ring segment implantation by femtosecond laser for keratoconus correction. Ophthalmology 2007;114:1643-52.
93. Torquetti L, Berbel RF, Ferrara P. Long-term follow-up of intrastromal corneal ring segments in keratoconus. J Cataract Refract Surg 2009;35:1768-73.
94. Hellstedt T, Mäkelä J, Uusitalo R, Emre S. Treating keratoconus with intacs corneal ring segments. J Refract Surg 2005;21:236-46.
95. Ruckhofer J, Twa MD, Schanzlin DJ. Clinical characteristics of lamellar channel deposits after implantation of intacs. J Cataract Refract Surg 2000;26:1473-9.
96. Twa MD, Kash RL, Costello M, Schanzlin DJ. Morphologic characteristics of lamellar channel deposits in the human eye: a case report. Cornea 2004;23:412-20.
97. Klyce SD. UVA-riboflavin collagen cross-linking: a misnomer perhaps, but it works! Invest Ophthalmol Vis Sci 2013;54:1635.
98. Raiskup-Wolf F, Hoyer A, Spoerl E, Pillunat LE. Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: long-term results. J Cataract Refract Surg 2008;34:796-801.
99. Filippello M, Stagni E, O'Brart D. Transepithelial corneal collagen crosslinking: bilateral study. J Cataract Refract Surg 2012;38:283-91.
100. Stulting RD. Corneal collagen cross-linking. Am J Ophthalmol 2012;154:423-4.
101. Derakhshan A, Shandiz JH, Ahadi M, et al. Short-term outcomes of collagen crosslinking for early keratoconus. J Ophthalmic Vis Res 2011;6:155-9.
102. Vinciguerra P, Albe E, Frueh BE, et al. Two-year corneal cross-linking results in patients younger than 18 years with documented progressive keratoconus. Am J Ophthalmol 2012;154:520-6.
103. Hovakimyan M, Guthoff RF, Stachs O. Collagen cross-linking: current status and future directions. J Ophthalmol 2012;2012:Article ID 406850.
104. Arbelaez MC, Sekito MB, Vidal C, Choudhury SR. Collagen cross-linking with riboflavin and ultraviolet-A light in keratoconus: One-year results. Oman J Ophthalmol 2009;2:33-8.
105. Asri D, Touboul D, Fournie P, et al. Corneal collagen crosslinking in progressive keratoconus: multicenter results from the French National Reference Center for Keratoconus. J Cataract Refract Surg 2011;37:2137-43.
106. Brooks NO, Greenstein S, Fry K, Hersh PS. Patient subjective visual function after corneal collagen crosslinking for keratoconus and corneal ectasia. J Cataract Refract Surg 2012;38:615-9.
107. Wittig Silva C, Whiting M, Lamoureux E, et al. A randomized controlled trial of corneal collagen cross-linking in progressive keratoconus: preliminary results. J Refract Surg 2008;24:S720-5.
108. Ertan A, Karacal H, Kamburoglu G. Refractive and topographic results of transepithelial cross-linking treatment in eyes with intacs. Cornea 2009;28:719-23.
109. Kanellopoulos AJ. Comparison of sequential vs same-day simultaneous collagen cross-linking and topography-guided PRK for treatment of keratoconus. J Refract Surg 2009;25:S812-8.
110. Kymionis GD, Kontadakis GA, Kounis GA, et al. Simultaneous topography-guided PRK followed by corneal collagen cross-linking for keratoconus. J Refract Surg 2009;25:S807-11.
111. Kymionis GD, Portaliou DM, Kounis GA, et al. Simultaneous topography-guided photorefractive keratectomy followed by corneal collagen cross-linking for keratoconus. Am J Ophthalmol 2011;152:748-55.
112. Stojanovic A, Zhang J, Chen X, et al. Topography-guided transepithelial surface ablation followed by corneal collagen cross-linking performed in a single combined procedure for the treatment of keratoconus and pellucid marginal degeneration. J Refract Surg 2010;26:145-52.

113. Gordon MO, Steger-May K, Szczotka-Flynn L, et al, CLEK Study Group. Baseline factors predictive of incident penetrating keratoplasty in keratoconus. Am J Ophthalmol 2006;142:923-30.
114. Jones MN, Armitage WJ, Ayliffe W, et al. Penetrating and deep anterior lamellar keratoplasty for keratoconus: a comparison of graft outcomes in the United Kingdom. Invest Ophthalmol Vis Sci 2009;50:5625-9.
115. Reinhart WJ, Musch DC, Jacobs DS, et al. Deep anterior lamellar keratoplasty as an alternative to penetrating keratoplasty a report by the american academy of ophthalmology. Ophthalmology 2011;118:209-18.
116. Feizi S, Javadi MA, Jamali H, Mirbabaee F. Deep anterior lamellar keratoplasty in patients with keratoconus: big-bubble technique. Cornea 2010;29:177-82.
117. Caporossi A, Balestrazzi A, Simi C, et al. Manual deep lamellar keratoplasty: alternative methods and air-guided technique. Transplant Proc 2005;37:2697-701.
118. Behrooz MJ, Daneshgar F. "Large-bubble" modification of the "big-bubble" technique for performing maximum-depth anterior lamellar keratoplasty. Cornea 2010;29:820-4.
119. Daneshgar F, Fallahtafti M. 'Expanding bubble' modification of 'big-bubble' technique for performing maximum-depth anterior lamellar keratoplasty. Eye (Lond) 2011;25:803-8.
120. Buzzonetti L, Laborante A, Petrocelli G. Refractive outcome of keratoconus treated by combined femtosecond laser and big-bubble deep anterior lamellar keratoplasty. J Refract Surg 2011;27:189-94.
121. American Academy of Ophthalmology Cornea/External Disease Panel. Preferred Practice Pattern® Guidelines. Corneal Edema and Opacification. San Francisco, CA: American Academy of Ophthalmology; 2013. Available at: www.aao.org/ppp.
122. Ardjomand N, Hau S, McAlister JC, et al. Quality of vision and graft thickness in deep anterior lamellar and penetrating corneal allografts. Am J Ophthalmol 2007;143:228-35.
123. Al-Torbak AA, Al-Motowa S, Al-Assiri A, et al. Deep anterior lamellar keratoplasty for keratoconus. Cornea 2006;25:408-12.
124. Feizi S, Javadi MA, Rastegarpour A. Visual acuity and refraction after deep anterior lamellar keratoplasty with and without successful big-bubble formation. Cornea 2010;29:1252-5.
125. Fontana L, Parente G, Sincich A, Tassinari G. Influence of graft-host interface on the quality of vision after deep anterior lamellar keratoplasty in patients with keratoconus. Cornea 2011;30:497-502.
126. Fontana L, Parente G, Tassinari G. Clinical outcomes after deep anterior lamellar keratoplasty using the big-bubble technique in patients with keratoconus. Am J Ophthalmol 2007;143:117-24.
127. Han DC, Mehta JS, Por YM, et al. Comparison of outcomes of lamellar keratoplasty and penetrating keratoplasty in keratoconus. Am J Ophthalmol 2009;148:744-51.
128. Javadi MA, Feizi S, Yazdani S, Mirbabaee F. Deep anterior lamellar keratoplasty versus penetrating keratoplasty for keratoconus: a clinical trial. Cornea 2010;29:365-71.
129. Bahar I, Kaiserman I, Srinivasan S, et al. Comparison of three different techniques of corneal transplantation for keratoconus. Am J Ophthalmol 2008;146:905-12.
130. Cohen AW, Goins KM, Sutphin JE, et al. Penetrating keratoplasty versus deep anterior lamellar keratoplasty for the treatment of keratoconus. Int Ophthalmol 2010;30:675-81.
131. Smadja D, Colin J, Krueger RR, et al. Outcomes of deep anterior lamellar keratoplasty for keratoconus: learning curve and advantages of the big bubble technique. Cornea 2012;31:859-63.
132. Kim KH, Choi SH, Ahn K, et al. Comparison of refractive changes after deep anterior lamellar keratoplasty and penetrating keratoplasty for keratoconus. Jpn J Ophthalmol 2011;55:93-7.
133. Cheng YY, Visser N, Schouten JS, et al. Endothelial cell loss and visual outcome of deep anterior lamellar keratoplasty versus penetrating keratoplasty: a randomized multicenter clinical trial. Ophthalmology 2011;118:302-9.
134. Fogla R, Padmanabhan P. Results of deep lamellar keratoplasty using the big-bubble technique in patients with keratoconus. Am J Ophthalmol 2006;141:254-9.
135. Kubaloglu A, Koytak A, Sari ES, et al. Corneal endothelium after deep anterior lamellar keratoplasty and penetrating keratoplasty for keratoconus: a four-year comparative study. Indian J Ophthalmol 2012;60:35-40.
136. Kubaloglu A, Sari ES, Unal M, et al. Long-term results of deep anterior lamellar keratoplasty for the treatment of keratoconus. Am J Ophthalmol 2011;151:760-7.

137. Sarnicola V, Toro P, Sarnicola C, et al. Long-term graft survival in deep anterior lamellar keratoplasty. Cornea 2012;31:621-6.
138. Olson EA, Tu EY, Basti S. Stromal rejection following deep anterior lamellar keratoplasty: implications for postoperative care. Cornea 2012;31:969-73.
139. Mashor RS, Rootman DB, Bahar I, et al. Outcomes of deep anterior lamellar keratoplasty versus intralase enabled penetrating keratoplasty in keratoconus. Can J Ophthalmol 2011;46:403-7.
140. Chamberlain WD, Rush SW, Mathers WD, et al. Comparison of femtosecond laser-assisted keratoplasty versus conventional penetrating keratoplasty. Ophthalmology 2011;118:486-91.
141. Chan CC, Ritenour RJ, Kumar NL, et al. Femtosecond laser-assisted mushroom configuration deep anterior lamellar keratoplasty. Cornea 2010;29:290-5.
142. Farid M, Kim M, Steinert RF. Results of penetrating keratoplasty performed with a femtosecond laser zigzag incision initial report. Ophthalmology 2007;114:2208-12.
143. Farid M, Steinert RF. Femtosecond laser-assisted corneal surgery. Curr Opin Ophthalmol 2010;21:288-92.
144. Cheng YY, Tahzib NG, van Rij G, et al. Femtosecond laser-assisted inverted mushroom keratoplasty. Cornea 2008;27:679-85.
145. Pramanik S, Musch DC, Sutphin JE, Farjo AA. Extended long-term outcomes of penetrating keratoplasty for keratoconus. Ophthalmology 2006;113:1633-8.
146. Javadi MA, Motlagh BF, Jafarinasab MR, et al. Outcomes of penetrating keratoplasty in keratoconus. Cornea 2005;24:941-6.
147. Javadi MA, Naderi M, Zare M, et al. Comparison of the effect of three suturing techniques on postkeratoplasty astigmatism in keratoconus. Cornea 2006;25:1029-33.
148. Patel SV, Malta JB, Banitt MR, et al. Recurrent ectasia in corneal grafts and outcomes of repeat keratoplasty for keratoconus. Br J Ophthalmol 2009;93:191-7.
149. Unal M, Yucel I, Akar Y, et al. Recurrence of keratoconus in two corneal grafts after penetrating keratoplasty. Cornea 2007;26:362-4.
150. American Academy of Ophthalmology Glaucoma Panel. Preferred Practice Pattern® Guidelines. Primary Open-Angle Glaucoma. San Francisco, CA: American Academy of Ophthalmology; 2010. Available at: www.aao.org/ppp.
151. Gordon MO, Schechtman KB, Davis LJ, et al. Visual acuity repeatability in keratoconus: impact on sample size. Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study Group. Optom Vis Sci 1998;75:249-57.
152. Kymes SM, Walline JJ, Zadnik K, Gordon MO. Quality of life in keratoconus. Am J Ophthalmol 2004;138:527-35.
153. Kymes SM, Walline JJ, Zadnik K, et al. Changes in the quality-of-life of people with keratoconus. Am J Ophthalmol 2008;145:611-7.
154. Rebenitsch RL, Kymes SM, Walline JJ, Gordon MO. The lifetime economic burden of keratoconus: a decision analysis using a markov model. Am J Ophthalmol 2011;151:768-73.
155. Roe RH, Lass JH, Brown GC, Brown MM. The value-based medicine comparative effectiveness and cost-effectiveness of penetrating keratoplasty for keratoconus. Cornea 2008;27:1001-7.

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