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# Corneal Ectasia Preferred Practice Pattern®

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Preferred Practice Pattern® guidelines are developed by the Academy's H. Dunbar Hoskins Jr., MD Center for Quality Eye Care without any external financial support. Authors and reviewers of the guidelines are volunteers and do not receive any financial compensation for their contributions to the documents. The guidelines are externally reviewed by experts and stakeholders before publication.

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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 June 2018. The document was edited in response to the discussion and comments.

## **Preferred Practice Patterns Committee 2018**

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The Corneal Ectasia PPP was then sent for review to additional internal and external groups and individuals in July 2018. 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.

# FINANCIAL DISCLOSURES

In compliance with the Council of Medical Specialty Societies' Code for Interactions with Companies (available at [www.cmss.org/codeforinteractions.aspx](http://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 [www.aao.org/about-preferred-practice-patterns](http://www.aao.org/about-preferred-practice-patterns)). A majority (100%) of the members of the Cornea/External Disease Preferred Practice Pattern Panel 2017–2018 had no financial relationships to disclose.

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The disclosures of relevant relationships to industry of other reviewers of the document from January to October 2018 are available online at [www.aao.org/ppp](http://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 US 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 [www.aao.org/about-preferred-practice-patterns](http://www.aao.org/about-preferred-practice-patterns)) 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<sup>1</sup> (SIGN) and the Grading of Recommendations Assessment, Development and Evaluation<sup>2</sup> (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 Quality, and the American College of Physicians.<sup>3</sup>

- ◆ 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<sup>1</sup> 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<sup>2</sup> 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<sup>2</sup> 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. Ratings are embedded throughout the PPP main text in italics.
- ◆ Literature searches for the PPP were undertaken in March 2017 and June 2018 in PubMed and the Cochrane Library. Complete details of the literature search are available at [www.aao.org/ppp](http://www.aao.org/ppp).

## HIGHLIGHTED FINDINGS AND RECOMMENDATIONS FOR CARE

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Patients with unstable refractions should be evaluated for evidence of corneal ectasia.

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The ophthalmologist needs to measure many aspects of visual function, since best-corrected visual acuity (BCVA) may not completely characterize visual function in these patients.

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Signs of corneal ectasia can include, but are not limited to: inferior steepening, superior flattening, skewing of radial axes on power topographic maps, abnormal islands of elevation anteriorly and/or posteriorly on tomography and decentered or abnormal corneal thinning or rate of change of corneal thickening from the center to the periphery.

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

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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 subclinical ectasia by tomography.

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

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Corneal cross-linking (CXL) reduces the risk of progressive ectasia in patients with keratoconus (particularly in its early stages) and stabilizes the corneal. It also stabilizes cases of corneal ectasia occurring after keratorefractive surgery.

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Deep anterior lamellar keratoplasty (DALK) may be used to treat ectatic disease. Its advantages include no risk for endothelial rejection and a low risk of stromal rejection. Progressive endothelial cell loss following DALK may also be less than following penetrating keratoplasty.

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# INTRODUCTION

## DISEASE DEFINITION

Corneal ectasia 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. 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 nonsurgical 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. Naturally occurring keratoconus typically was thought to begin in puberty and progresses until about age 40. Newer imaging modalities, however, have shown the ectatic disease can occur at a much earlier age (pre-puberty) and progression past the age of 40 is not that uncommon. 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.<sup>4-7</sup> Keratoglobus may be seen in children and may be congenital. Pellucid marginal degeneration usually has its onset later in

life. Corneal ectasia can occur shortly after LASIK, small incision lenticule extraction (SMILE), and photorefractive keratectomy (PRK) in eyes with a pre-existing subclinical keratoconus or years later in eyes with no preoperative signs of keratoconus.<sup>8,9</sup>

The etiology of corneal ectasia may include genetic factors, chromosomal and enzyme abnormalities, and mechanical factors (e.g., eye rubbing). Ectasias have occurred after LASIK, PRK, radial keratotomy (RK), and SMILE.

Genetic disorders associated with keratoconus include connective tissue diseases with abnormal collagen and hyperelasticity such as Ehlers-Danlos syndrome, osteogenesis imperfecta, congenital hip dysplasia, nail patella syndrome, pseudoxanthoma elasticum, hyper-immunoglobulin E syndrome associated with eczema and atopy, oculodentodigital dysplasia, Down syndrome, and ichthyosis. Other genetic syndromes associated with keratoconus include those which are associated with eye rubbing and diminished mental capacity, 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, retinitis pigmentosa, and Kurz syndrome.<sup>10</sup> Keratoconus is also associated with atopic disease, including hay fever, asthma, eczema, and vernal keratoconjunctivitis; in these patients, ocular inflammation should be controlled in order to decrease the propensity for eye rubbing. In addition, there are well-established associations with contact lens wear, particularly hard-contact lens wear.

Findings in corneal ectasia that occurs following keratorefractive surgery include the following: the residual stromal bed following surgery was thinner than expected, the flap was thicker than intended, or the patient had unrecognized preoperative signs of a pre-existing subclinical keratoconus. However, corneal ectasia can develop in the absence of these situations.<sup>8</sup>

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, increased matrix metalloproteinase levels, along with decreased tissue inhibitor of metalloproteinase, have been demonstrated in keratoconic corneas when compared with normal corneas. The findings indicate a probable role for these enzymes in matrix degradation found in keratoconus.<sup>10-16</sup>

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.<sup>17,18</sup> 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 noninflammatory, may have an inflammatory component that is either directly or indirectly related to the pathogenesis and progression of the disease.<sup>19</sup> Postkeratorefractive surgical 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.<sup>9,20,21</sup> A genetic predisposition to keratoconus may exist in patients who undergo a second environmental insult, such as eye rubbing and/or the iatrogenic corneal thinning that occurs after laser vision correction.<sup>4,10</sup>

## NATURAL HISTORY

Corneal ectasia is usually bilateral, and it varies in severity from clinically undetectable, or “subclinical,” to advanced disease. Keratoconus is usually a progressive disorder that results 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. Less than 20% of keratoconus cases historically required penetrating keratoplasty. New technology that allows us to identify mild, minimally progressive, subclinical forms of keratoconus have made us realize that the true incidence of keratoconus is much higher than previous thought – making the true incidence of progression to keratoplasty much lower.<sup>4,5,22,23</sup> Corneal hydrops, caused by the acute disruption of Descemet membrane in the setting of corneal ectasia, occurs in approximately 3% of patients with keratoconus. A history of eye rubbing and seasonal allergies is associated with hydrops development.<sup>24</sup> (Management of acute corneal hydrops is addressed in the Corneal Edema and Opacification PPP.<sup>25</sup>)

## 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, a 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. As keratoconus usually presents in late childhood or adolescence, early diagnosis is very important. The greater the delay of diagnosis, the higher the risk of greater vision loss and of the patient requiring a cornea transplant.<sup>26</sup> Once progression is observed early detection and prompt

treatment with corneal cross-linking (CXL), can reduce or stop keratoconus progression and preserve good visual acuity with eyeglasses and/or contact lenses.<sup>4,5,27</sup>

## CARE PROCESS

### PATIENT OUTCOME CRITERIA

- ◆ Preventing visual loss
- ◆ Reducing the signs and symptoms of corneal ectasia
- ◆ Maintaining, restoring, or improving visual function according to the needs of the patient

### DIAGNOSIS

Initial evaluation of the patient who has symptoms and signs of corneal ectasia should include the relevant aspects of the comprehensive medical eye evaluation.<sup>28</sup> The diagnosis of corneal ectasia is usually based on a typical patient history and characteristic findings on topography and tomography. Ideally, one would like to make the diagnosis at the pre-clinical stage, before a patient becomes symptomatic, however, there currently is no simple, cost-effective, screening test available to do this. Topography alone is insufficient. It is important to properly identify the presence of potentially progressive corneal ectatic conditions, including subclinical disease, in patients considering keratorefractive surgery or young people who are more likely to progress to a symptomatic stage of ectasia.

#### 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,<sup>29,30</sup> and postkeratorefractive surgery ectasia can occur after LASIK, SMILE, and/or PRK. The onset of postkeratorefractive 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 and tomography with little to no visual impairment or loss of best-corrected visual acuity (BCVA) to severe corneal thinning, irregularity, and scarring, which results in significant loss of visual function.

- ◆ Ocular history

Obtaining a history of the type and duration of contact lens wear is important, noting the stability and comfort of the contact lens. If the contact lens corrects the vision to an acceptable level but decenters or even 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 and tomographic abnormalities that suggest pre-existing subclinical keratoconus can progress to clinically significant ectasia following LASIK, SMILE, RK, and PRK. Other preoperative risk factors potentially associated with ectasia after keratorefractive surgery may include a younger age, a high manifest refractive spherical equivalent, reduced corneal thickness, and the prediction of a thin, residual, stromal bed thickness.<sup>20</sup> Risk-scoring systems have been developed to attempt to predict the likelihood of ectasia. However, these systems have demonstrated inaccuracy in clinical use with both false positive and false negative results.<sup>20,31,32</sup>

- ◆ 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.<sup>10,33,34</sup> Down syndrome and other genetic disorders can also be associated with keratoconus (see genetic disorders referred to in the Prevalence and Risk Factors section).

- ◆ Family history

Multiple reports of twins with keratoconus have been documented in the literature.<sup>35</sup> 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.<sup>35-37</sup> The Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study showed that 14% of 1209 patients with keratoconus had a family history of the disease.<sup>38</sup> New studies using more advanced screening and diagnostic techniques developed since CLEK are likely to show an even higher incidence. Recent developments in the field of keratoconus genetics have identified polymorphism in the CXL enzyme lysyl oxidase gene and CAST gene (encoding calpastatin, inhibitor of calpains which are inhibitors of intracellular proteases), among others.<sup>39</sup>

## Examination

- ◆ Assessment of visual function

Instability of refractive error with progressive increase in astigmatism on manifest refraction, ultimately resulting in the inability to correct the patient to 20/20 is typical of corneal ectasia and is detected with 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 suggest that the visual acuity is far worse than suspected when an unlimited time to read the chart is permitted. Visual compromise is a late finding in many patients.

- ◆ External examination:

- ◆ Look for outward bowing of the lower lid on downgaze (Munson sign), a nonspecific finding seen in severe ectasia.
- ◆ Eyelid skin is examined for evidence of thickening and scaling (atopic disease) or eyelid ptosis and a rubbery, floppy eyelid with accompanying papillary conjunctivitis on upper eyelid eversion

- ◆ Slit-lamp biomicroscopy of the cornea:

- ◆ The presence, extent, and location of corneal thinning and protrusion. In keratoconus, the cornea usually protrudes in the area of maximal thinning.<sup>42</sup> In contrast, patients with pellucid marginal degeneration typically have an area of maximal protrusion that is superior to the band of thinning. The inferior band of corneal thinning is often separated by an uninvolved area 1 to 2 mm from the inferior limbus.<sup>42</sup>
- ◆ Previous corneal surgery
- ◆ Vogt striae in the mid and deep stroma, 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.
- ◆ Intraocular pressure (IOP) measurement and fundus assessment
  - ◆ The measurement of intraocular pressure by applanation tonometry (Goldmann, Perkins, etc.) is artifactually reduced as a consequence of tissue thinning in ectatic disease and following refractive surgery (PRK, SMILE, and LASIK).<sup>40-42</sup> Therefore, use of an alternative device that is less dependent on a smooth and regular corneal surface to obtain an accurate measurement is suggested (such as

with the pneumatonometer, hand-held Mackay-Marg tonometer, ocular response analyzer, dynamic contour tonometer, or rebound tonometer<sup>43</sup>).

- ◆ The red reflex should be assessed by examining the fundus to look for a dark area caused by total internal refraction (oil droplet), 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 the paracentral or mid-peripheral area of the cornea. Because primary and secondary corneal ectasia can result in an inferiorly displaced area of protrusion, keratometry can show increased steepening in patient upgaze or downgaze.

- ◆ Corneal topography and tomography

A comprehensive evaluation of both the anterior and posterior surfaces (topographically and tomographically) as well as full pachymetric mapping of the cornea is felt to be important in establishing the diagnosis of corneal ectatic disease and following its course. Slit-scanning corneal topography and Scheimpflug imaging systems can evaluate these parameters and have expanded diagnostic criteria for keratoconus, subclinical keratoconus, pellucid marginal degeneration, and postkeratorefractive corneal ectasias. Their use are necessary to properly screen potential refractive surgery patients.<sup>44,45</sup>

- ◆ 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, superior flattening, and skewing of the radial axes are typical of keratoconus. Curvature maps, especially those from Placido-based systems, are limited to approximately 60% of the corneal surface and lack important data for peripheral or paracentral corneal pathologies, particularly pellucid marginal degeneration.<sup>42,54</sup> In eyes with positive angle kappa, Placido-based corneal topography may also result in an asymmetric bow-tie pattern that falsely suggests keratoconus.

- ◆ Topographic elevation mapping and tomography

Isolated islands of elevation (anteriorly, posteriorly, or both) are often seen in ectatic corneas and can be a helpful sign of keratoconus and postkeratorefractive ectasia when generated by slit-scanning systems or Scheimpflug imaging.

Posterior elevation mapping and tomography generated by these devices has been shown to have a relatively high sensitivity and specificity for the detection of keratoconus, but less so with subclinical keratoconus.<sup>46,47</sup>

◆ Optical coherence tomography (OCT)

Anterior segment optical coherence tomography (AS-OCT) provides high-definition, cross-sectional images of the cornea, angle, anterior chamber, and anterior lens. 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, and software is available that can use AS-OCT measurements for keratoconus detection.<sup>48-50</sup> Anterior segment optical coherence tomography also has the advantage of imaging retrocorneal structures. A large Descemet break and central stromal cleft may exist in cases of corneal edema associated with keratoconic hydrops or trauma. Anterior segment optical coherence tomography can also be used to assess LASIK flap thickness and residual bed in cases of postrefractive ectasia.

◆ Other considerations

- ◆ The ability to detect corneal ectasia at the subclinical or “biomechanical stage” prior to the development of secondary changes in thickness or curvature is being evaluated.<sup>51</sup> Parameters used to assess corneal biomechanics in clinical practice, including corneal hysteresis and corneal resistance factor, are assumed to be altered in these conditions. Commercially available devices used to characterize corneal biomechanical properties, including a dynamic bidirectional applanation device and a dynamic Scheimpflug analyzer, are being evaluated in order to develop additional parameters for early keratoconus detection.<sup>52</sup>
- ◆ Higher-order aberrations of the anterior and posterior corneal surfaces are altered in keratoconus and have been evaluated as a means of detecting both clinical and subclinical disease.<sup>65</sup> The dominant higher-order aberration found in keratoconus is vertical coma, which is of greater magnitude in patients with keratoconus compared with normal patients; however, the diagnostic value of coma alone, particularly for subclinical keratoconus, is limited.<sup>53-58</sup>



## MANAGEMENT

### Prevention and Early Detection

Early detection and treatment of corneal ectasia attempts to preserve or improve vision and prevent loss of functional vision. Preventing disease progression has been an elusive goal. Patients should be advised to halt eye rubbing which has been associated with progression. Newer treatment modalities such as corneal cross-linking (CXL) have been demonstrated to retard or arrest 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 these patients should be carefully evaluated and followed. Additionally, all patients seeking refractive surgery must be carefully screened for ectasia. Corneal topography and tomography following a period of contact lens abstinence is an essential part of this evaluation. Evidence of irregular astigmatism or abnormalities of the posterior cornea suggestive of keratoconus or other corneal ectasias may be associated with unpredictable refractive outcomes and with ectasia progression following keratorefractive surgery.<sup>31,59-61</sup>

### Choice of Therapy

The choice of therapy, medical or surgical, 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.<sup>22</sup> Another study reported that 58% of patients achieved 20/40 or better with best eyeglass correction.<sup>62</sup>

##### *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*

Long-term studies (the CLEK and the Dundee University Scottish Keratoconus Study [DUSKS]) have found that most patients are fitted with contact lenses when vision can no longer be corrected to at least 20/30 in eyeglasses.<sup>22,38</sup> Rigid corneal gas-permeable contact lenses have the advantage of masking corneal irregularities, thus providing a regular anterior refractive surface.<sup>63</sup> In DUSKS, contact lens wear was the mainstay of treatment; 76% of the 200 patients were 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.<sup>22</sup> 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. With advances in contact lens design and an increasing number of hybrid and scleral lenses now available, it is likely that updated studies would show similar even better results. Hyperemia was reported in 63%, and 18% described the hyperemia as severe.<sup>22,63</sup> In the CLEK study, 65% of the 1209 patients wore rigid contact lenses on entry,<sup>64</sup> and 29% had corneal scarring develop over 8 years.<sup>63</sup> (At baseline, 53% of study patients had corneal scarring in one or both eyes.<sup>38</sup>) In addition, flat-fitting contact lenses provided worse visual acuity than steep-fitting contact lenses.<sup>63</sup>

#### *Hybrid Contact Lenses*

Hybrid contact lenses contain a rigid gas-permeable (RGP) center with a soft skirt.<sup>63,65</sup> 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.<sup>65</sup> Unlike 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 lens tightening, a tendency toward tight fitting, and the need for high molecular-weight fluorescein to evaluate the fit.<sup>63,65</sup>

#### *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. 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.<sup>63</sup>

#### *Scleral Lenses*

Scleral lenses have the advantages of completely vaulting the corneal surface to provide centration, stability, and improved central visual acuity. A recent study found that all patients referred for scleral lens fitting owing to failed RGP wear could be successfully fitted either with a conventional lens or a custom-designed scleral lens, thus avoiding keratoplasty.<sup>66</sup> Custom-made lenses, are now widely available, and allow for scleral lenses to be custom designed for patients with scleral irregularities, such as patients with pterygia, glaucoma blebs, etc. These commercially available lenses are made to order similar to other specialty RGP lenses. Disadvantages include decreased tear exchange and difficulty with insertion and removal of the lenses.<sup>63,67</sup> Custom-made lenses are considerably more expensive than larger-diameter or mini lenses and may be cost prohibitive for patients with inadequate insurance coverage.

None of the above treatments arrest the disease process, and the ectasia can progress in spite of good visual acuity. It is not uncommon today for keratoconus patients to be maintained in some type of contact lens and then to be referred for cross-linking at a very late stage when the benefits are more limited or when they have progressed (thinned) to the point where they may no longer be a CXL candidate.

### Surgical

#### *Intrastromal Corneal Ring Segments*

##### *Indications*

Intrastromal corneal ring segments (ICRS) help to create a more uniform corneal surface in ectatic corneas that are clear centrally and have a corneal thickness of 400 µm or greater. They are not indicated in subclinical disease and do not alter the progression of the disease process. Visual acuity improvements are usually the result of less astigmatism, central flattening, and greater contact lens tolerance.<sup>68</sup> One type of ICRS is triangular in profile and has an inner radius of 4.4 mm, outer radius of 5.6 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, have an inner radius of 6.8 mm and an outer radius 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). Only one type of ICRS is currently available in the U.S.

### *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.

Femtosecond Laser Surgery: The femtosecond laser creates channels of a specifically set diameter and depth (80% of thinnest pachymetry).

Either Scheimpflug or OCT generated pachymetry maps are required to measure thickness along the entire course of the corneal channel dissection to avoid intraoperative perforation.

#### *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.<sup>4,69-72</sup> Ring segment insertion can improve UCVA and BCVA as well as contact lens tolerance.<sup>68,70-87</sup> Most studies have suggested that ICRS may be most effective in patients with moderate keratoconus (<58.0 D).<sup>68,73,84</sup> However, the change in astigmatism can be unpredictable.<sup>88</sup> Loss of corrected distance visual acuity (CDVA) in both types of ICRS may be due to induced irregular astigmatism.<sup>73</sup> 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 but the evidence is low to very low quality, and controlled studies are needed.<sup>80,89</sup>

#### *Contraindications*

Contraindications to ICRS implantation include central corneal scarring and a corneal thickness of less than 400  $\mu\text{m}$  at the incision site. Additionally, ICRS implantation is contraindicated in true pellucid marginal degeneration.<sup>44,90</sup>

#### *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.<sup>4,91</sup> 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 functional outcomes of the ICRS.<sup>4,91,92</sup> In some cases, the ring segments may need to be removed owing to complications.

Complications of mechanical channel creation include anterior corneal perforation, superficial segment implantation, and postoperative segment migration.<sup>81</sup>

Complications attributed to femtosecond channel creation include incomplete channel creation, intraoperative perforation, postoperative segment migration,<sup>93</sup> and decentration due to misalignment of the cornea and pupil during ablation.<sup>94</sup>

In a study that evaluated ICRS implantation with the femtosecond laser surgery following CXL, the incidence of incomplete intrastromal channel creation was higher in eyes that had received CXL than in eyes that had not received CXL.<sup>95</sup> Higher energy settings and/or mechanical channel creation were required in these cases. It was recommended that ICRS be performed either prior to or concurrently with CXL rather than at some point after CXL. The timing of CXL relative to ICRS implantation remains unclear due to the lack of well controlled studies. Wide channels facilitate easier ring insertion but may lessen the treatment 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.<sup>96</sup>

### *Corneal Cross-Linking*

#### *Indications*

Corneal cross-linking is a procedure designed to increase the biomechanical rigidity of the cornea and is thought to achieve this 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.<sup>97</sup> The aim of CXL is to arrest or slow the progression of corneal ectasia in its earliest stage. The US Food and Drug Administration (FDA) approved the procedure for patients between the ages of 14 and 65 years with progressive keratoconus or corneal ectasia following keratorefractive surgery. No consistent or clear definition of ectasia progression has been identified,<sup>98</sup> yet several tomography-derived values (alone or in combination) have been evaluated as

progression determinants.<sup>99,100</sup> These include maximum keratometry, steepening of the anterior or posterior corneal surface and thinning and/or an increase in the rate of corneal thickness change from the periphery to the thinnest point are some of these determinants as well refractive changes such as increasing myopia and astigmatism.

#### *Technique Options*

The original Dresden protocol for CXL (“conventional” CXL) involved removal of the corneal epithelial layer, application of topical riboflavin every 2 minutes for 30 minutes to saturate the cornea, followed by 30 minutes of UV-A light treatment with continued instillation of riboflavin (again, every 2 minutes) until UV-A treatment is completed.<sup>102</sup> Although this is the FDA-approved protocol, the optimal treatment parameters have yet to be determined. Because the Dresden protocol requires a long treatment time of 60 minutes, accelerated protocols have been proposed to shorten the treatment time.<sup>103-106</sup> Recent studies include evaluations of pulsed or fractionated UV-A protocols in order to improve the effectiveness of accelerated protocols.<sup>107</sup> 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; it may decrease the risk of complications associated with epithelial removal, but it may also decrease its efficacy.<sup>108,109</sup> Both techniques continue to be studied, and the benefits of one approach over another are still in dispute.

#### *Outcomes*

Corneal cross-linking was introduced in 2003 to stabilize progressive keratoconus,<sup>109</sup> and it has been reported by others to arrest progression in early<sup>110</sup> as well as advanced cases of the disease.<sup>109,111-114</sup> 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. In addition to a plethora of international clinical data supporting the use of corneal crosslinking,<sup>115</sup> other recent studies have contributed additional direct<sup>116,117</sup> and indirect evidence to support the efficacy of it.<sup>118 119</sup> Two European studies have reported significant reductions in the number of penetrating keratoplasties performed for keratoconus since the introduction of CXL; however, these findings were concurrent with advances in contact lens technology, which has also decreased keratoplasty rates.<sup>120,121</sup>

The phase III study data that supported the FDA approval of CXL for progressive keratoconus included 205 patients at multiple US centers who had documented progressive keratoconus and who were randomized into treatment (using the Dresden protocol) and a sham control group. In the treatment group, the topography-derived maximum keratometry value decreased by 1.6 +/- 4.2 D from baseline to 1 year, whereas keratoconus continued to progress in the control group. The cross-linked eyes also showed improved corrected distance visual acuity compared with the sham-control eyes.<sup>122</sup>

The phase III study that evaluated CXL for corneal ectasia after refractive surgery randomized 179 patients with postkeratorefractive surgery ectasia into treatment and sham groups. The treatment group received CXL per the Dresden protocol. In the treatment group, the mean maximum keratometry value decreased by 0.7 +/- 2.1 D compared with to an increase in the mean maximum keratometry value in the control group of 0.6 +/- 2.1 D.<sup>123</sup>

Long-term studies confirm that standard, Dresden CXL stops the deterioration and progression of keratoconus (the principal goal of treatment). Meta-analysis of 75 publications with greater than 36 months follow-up also showed improvement in uncorrected vision more so than corrected distance vision and that there is a late reduction in keratometry (corneal topography) values. Some reduction in astigmatism was seen, however, spherical equivalent did not materially change. A transient reduction in the endothelial cell count has been noted, but this typically returns to normal by 6 months. Biomechanical parameters (CRF and CH) did not appear to change with treatment.<sup>123</sup>

In pediatric patients, where keratoconus can present at an advanced stage and progress more aggressively than in adult counterparts, standard CXL is effective in halting progression (one year and three year data). Longer-term studies are needed to evaluate its ultimate effectiveness.<sup>101</sup>

The plethora of international clinical data supports the use of CXL in the early management of keratoconus. It's long term safety and stability, combined with the recent data indicating a reduction in the need for corneal transplantation are significant benefits in a population who all too often see their vision and overall functionality decrease after the diagnosis is made. CXL helps to prevent vision loss that impacts an individual's personal and professional life due to the increasing difficulty getting contact lenses to fit properly (despite newer developments in this area) and necessitates others to undergo corneal

transplantation with its lifelong risks of rejection and rupture. The progressive nature of early keratoconus makes this a particularly important group to consider for treatment, though any patient with progression should be considered.

#### *Contraindications*

A contraindication to CXL is corneal stromal thickness below 400  $\mu\text{m}$  at the time of UV light exposure to prevent endothelial damage. Hypotonic riboflavin can be used to transiently thicken a cornea to the 400  $\mu\text{m}$  threshold in some cases that fall below this value. Also, because exposure to UV light may cause reactivation of herpes simplex virus infection, caution should be used when performing CXL in patients with prior herpes simplex virus keratitis.

#### *Complications*

Complications of CXL include punctate keratitis, corneal striae, photophobia, dry eye, eye pain, infectious keratitis, sterile infiltrates, corneal haze, corneal scarring, nonhealing epithelial defects, and corneal edema. With the exception of corneal edema, which is the likely result of endothelial damage, it has been suggested that other complications result from the removal of or damage to the epithelial layer.<sup>109,112</sup> However, deep stromal haze may not be related to endothelial damage or epithelial removal. Complications seem to occur more frequently in patients older than 35 years, pre-op CDVA better than 20/25 and pre-op maximum steepening greater than 58D.

#### *Combined Cross-Linking and Intrastromal Corneal Ring Segments*

Implantation of ICRS combined with CXL has been shown to be effective in stopping progression of keratoconus and improving visual function. The combination of these treatments may result in a greater improvement than when these individual treatment modalities are used alone.<sup>71</sup> 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.<sup>74</sup> Other studies have demonstrated the greatest improvements when implantation of ICRS was followed by CXL treatment.<sup>71,124</sup> 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.<sup>95</sup> Many of these studies were performed with ICRS products not available in the United States.

#### *Combined Cross-Linking and Photorefractive Keratectomy*



Combining CXL and PRK has been proposed to stabilize the cornea while providing greater improvement in visual function. The exact sequence of these procedures, whether simultaneous or sequential, has yet to be determined.<sup>125-127</sup>

### *Partial-Thickness/Lamellar Keratoplasty*

#### *Indications*

Lamellar keratoplasty using deep anterior lamellar keratoplasty (DALK) techniques can be considered for contact-lens-intolerant patients who do not have significant scarring at Descemet's membrane or persistent hydrops. The DALK technique removes all or nearly all of the corneal stroma down to Descemet membrane. The benefit of DALK is 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.<sup>5,128,129</sup>

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*

Procedure options for DALK include the Melles technique, the big-bubble technique, and variations on the big-bubble technique.<sup>5,130</sup> The Melles technique involves injecting air into the anterior chamber to better assess the depth of the lamellar resection.<sup>5,128,131</sup> The big-bubble technique involves trephining the cornea, followed by injecting air to achieve baring of Descemet membrane.<sup>5,128</sup> The large-bubble modification of the big-bubble technique utilizes a shallower trephination with a larger expansion of the bubble to the periphery.<sup>132,133</sup> The femtosecond-assisted big-bubble technique utilizes a femtosecond laser program to trephine the cornea and then to create a big bubble to separate Descemet membrane, remove residual stroma, and place a femtosecond-laser trephined cornea.<sup>134-136</sup>

#### *Outcomes*

There are conflicting reports on the data comparing DALK and PK. The thickness of the host residual stromal bed after dissection<sup>25</sup> has been correlated with variation in postoperative visual acuity and contrast sensitivity following DALK. When

baring of Descemet membrane was achieved, visual results were reported to be comparable to PK.<sup>128,137-143</sup> The best visual acuity is achieved in DALK cases that have a residual bed of less than 20  $\mu\text{m}$ , which is ideal for obtaining visual results when similar to PK.<sup>137</sup> Similar BCVA outcomes have been reached with the two procedures, but more studies have found a higher percentage of patients achieving 20/20 visual acuity with PK compared with DALK,<sup>5,128,144,145</sup> although this difference was not always statistically significant.<sup>146</sup> The difference be associated with the surgeon's learning curve and may decrease with increased surgeon experience with the technique.<sup>128,147</sup> One study found that DALK resulted in significantly higher myopia compared with PK.<sup>148</sup> Endothelial cell loss was significantly lower with DALK that was performed without Descemet membrane perforation compared with full-thickness keratoplasty.<sup>149-153</sup> A 2014 Cochrane review reported no difference in BCVA, graft survival, or keratometric outcomes between patients undergoing DALK or PK.<sup>154</sup> They did report some evidence that rejection is more likely in the PK group compared with the DALK group. The review authors concluded that there was insufficient evidence to determine which technique may offer better overall outcomes. [I+, Good, Discretionary]

#### *Risk Factors and Complications*

Relative contraindications to DALK include severe corneal scarring associated with hydrops, in which corneal perforation is more likely. Other potential contraindications 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 than PK recipients.<sup>128</sup> The incidence of stromal rejection is reported to be between 2% and 12%. This variation prompted the authors to suggest that postoperative corticosteroid treatment regimens may play an important role in the postoperative management of DALK.<sup>155</sup> Deep anterior lamellar keratoplasty carries no risk of endothelial rejection; thus the overall rejection rate is lower when compared with PK.

#### *Full-Thickness Keratoplasty/Penetrating Keratoplasty*

Penetrating keratoplasty was the mainstay of incisional surgical treatment for keratoconus prior to the introduction of DALK, 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.<sup>5</sup>

### *Indications*

Keratoplasty is indicated when the patient can no longer achieve functional vision with eyeglasses and contact lenses and CXL is contraindicated. Persistent corneal edema following hydrops is an indication for full-thickness keratoplasty.

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 surgery: Femtosecond laser-assisted keratoplasty (FLAK) is a technique that utilizes the femtosecond laser for trephining both the donor and recipient corneas. With this technique, the same pattern of laser trephination is used for both donor and recipient, designated as top-hat, mushroom, or zigzag. Theoretical advantages of FLAK over standard PK are stronger wound healing, earlier removal of sutures, earlier visual rehabilitation,<sup>156-159</sup> and potentially decreased astigmatism.<sup>157-161</sup> However, studies have shown no long-term benefit when compared with mechanical trephination.

### *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.<sup>162-164</sup> Suturing techniques have not been demonstrated to affect outcomes. Less graft/host-size disparity seems to induce less myopic shift.<sup>163,164</sup> Repeat PK has also been performed with success for cases of recurrent ectasia following 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.<sup>162,165</sup> 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.<sup>166</sup>

- ◆ Femtosecond laser surgery: 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.<sup>157</sup> In addition, earlier suture removal is possible with FLAK owing to greater mechanical stability and wound-healing advantages.<sup>158</sup>

#### *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 and thickness by both topography and tomography. Typically, annual follow-up was recommended for cases of ectasia; however, with the advent of CXL, more frequent follow-up (i.e., every 3–6 months) to look for progression is now warranted. Younger patients may need to be followed even more frequently. One would like to identify progression before it starts to affect vision. Patients who see well with contact lenses yet experience an unstable fit should be examined to assess contact lens stability. Surgical follow-up visits should include the above as well as additional measurements specific to the type of surgical follow-up care indicated. After keratoplasty, slit-lamp biomicroscopic examinations should be performed to assess the clarity and health of the cornea and to check for suture erosion and rejection. Corneal thickness should be measured at every exam. Selective suture removal can be initiated in accordance with topographic findings to manage astigmatism that then improves visual function. Depending on the method of closure, suture removal typically begins after 3 to 6 months to ensure corneal wound stability and to minimize the risk of wound dehiscence. In the case of loose sutures, suture erosion, or vascularization, sutures may be removed earlier to prevent infection or rejection.

Post-PK 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. An epithelial rejection line/ridge may appear alone or with subepithelial 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 corticosteroid injections, and occasionally intravenous corticosteroids.

Corneal pachymetry may be useful in evaluating endothelial function, particularly if baseline thickness data are available. Serial corneal tomography 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.<sup>167</sup> 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 2 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 ophthalmic medical and surgical skills. Patients with corneal ectasia who are evaluated by nonophthalmology vision 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 medical and surgical treatment options. When ectasia is diagnosed early tomographic evaluation to determine the extent of the disease and

to establish a baseline to determine when and if progression occurs is crucial. A discussion of the benefits and potential risks of early crosslinking in patients at high risk for progression (e.g., pre-puberty) or who historically have noted progressive loss of vision should be undertaken. Waiting for additional loss of best corrected vision or progression in patients with ectasia should be avoided whenever possible. Referral is appropriate in this situation. Eyeglasses and contact lens are the mainstay of treatment for the majority of patients with ectasia. When these approaches cannot improve vision, or when there is loss of visual function, referral to an ophthalmologist trained in surgical treatments for corneal ectasia is indicated. As well, patients with a history of allergy and atopy may also need referral to a dermatologist and/or allergist. All patients should be counseled to avoid eye rubbing whether they have a history of allergies or not. 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. Many patients ask if life-style change can alter the course of the disease. To date, only eye rubbing has been linked to progression. This should be discussed with all patients, since many may not be fully aware to what extent they do rub their eyes and inadvertently worsen their disease.

## SOCIOECONOMIC CONSIDERATIONS

Keratoconus is uncommon and has a prevalence of between 50 and 230 per 100,000 in the general population.<sup>7</sup> These figures, which date back to the pretomography era, likely underreport the prevalence. In contrast to other chronic eye diseases such as glaucoma and age-related macular degeneration, ectasia, particularly keratoconus and postrefractive ectasias, is more commonly seen in younger people. The average estimated age of onset of keratoconus ranges from 9 to 28 years.<sup>7,38,168</sup>

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 V-QoL instrument designed to assess a patient's perception

of visual function and quality of life in 12 different domains. It was administered to 1166 CLEK study patients at their first annual follow-up evaluation.<sup>169</sup> The questionnaire 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 V-QoL that continues to decline over time.<sup>170</sup>

## 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 study used a Markov decision model to estimate the incremental lifetime cost for treatment of keratoconus compared with the lifetime expected cost of treating myopia. This study looked at costs for clinic visits, contact lenses, fitting fees, surgical procedures, and complications. The expected increment in the lifetime cost of treating keratoconus compared with treating myopia was determined to be \$25,168.<sup>171</sup> The factors that most influenced the lifetime cost were the probability of corneal transplantation and subsequent regrant. 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.<sup>172</sup> These parameters were assessed using cost-utility analysis with value-based medicine criteria. This study concluded that PK for patients with severe keratoconus was very cost-effective compared with other health care interventions.

A recently published study evaluated the cost-effectiveness of corneal collagen cross-linking for progressive keratoconus using a Markov-type model.<sup>173</sup> The authors compared two cohorts, one receiving CXL treatment and the other no treatment, and followed both groups over a lifetime, taking into account the probability of need for corneal transplantation and associated complications and costs. Assuming a 10-year

stabilizing effect of CXL, this treatment would be cost-effective relative to what treatments and associated costs were predicted to occur over 10 years within the no-treatment cohort. A longer stabilizing effect of CXL further increases its cost-effectiveness.



# 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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4<sup>th</sup> Printing: July 2005

## APPENDIX 2. 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, including disease-induced and treatment-induced alterations in corneal thickness, hydration, corneal curvature/astigmatism, an irregular corneal epithelial surface, and 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.
  - ◆ Pneumatometer: 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 eight or ten 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 (dynamic contour tonometer) 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 six ocular pulse cycles to determine the IOP, and it requires topical anesthesia. This is mounted to the slip lamp.

- ◆ 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.
- ◆ The Mackay-Marg tonometer combines mechanisms of both applanation and indentation. It is available as a small, handheld, battery-powered device that requires topical anesthesia. The tonometer has a small applanating plunger from which the IOP is read electronically. Multiple readings are averaged.

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 valid 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- or treatment-induced secondary IOP elevation, which often goes undetected when relying on GAT alone to determine IOP

## LITERATURE SEARCHES FOR THIS PPP

Literature searches of the PubMed and Cochrane databases were conducted in March 2017; the search strategies were as follows. Specific limited update searches were conducted after June 2018.

### **Treatment:**

(cornea\*[tiab] AND ectasia[tiab]) OR (keratectasia[tiab] OR "corneal ectasia"[tiab] OR keratoectasia[tiab]) OR (dilatation, pathologic[mh]) OR (cornea[tiab] AND (Corneal Diseases/surgery[mh] OR Corneal Diseases/therapy[mh] OR "Keratoconus/surgery"[Mesh] OR Keratoconus/therapy[mh] OR intrastromal[tiab] OR ring\*[tiab] OR collagen cross\*[tiab] OR keratectomy[tw] OR lamellar keratoplasty[tiab] OR Keratoplasty, Penetrating[mh] OR Contact Lenses[mh] OR Eyeglasses[mh] OR manage[tiab] OR management[tiab] OR treat[tiab] OR treatment\*[tiab]))

### **Diagnostic:**

((cornea\*[tiab] AND ectasia[tiab]) OR keratectasia[tiab] OR "corneal ectasia"[tiab] OR keratoectasia[tiab] OR (dilatation, pathologic[mh] AND cornea[tiab])) AND ((Corneal Diseases/diagnosis[mh]) AND (Corneal Topography[mh] OR keratometry[tiab] OR pachometr\*[tiab] OR ultra-structur\*[tiab] OR ultrastructure\*[tiab] OR pachymetr\*[tiab] Diagnostic Techniques, Ophthalmological[mh]))

### **Physiopathology:**

((cornea\*[tiab] AND ectasia[tiab]) OR keratectasia[tiab] OR "corneal ectasia"[tiab] OR keratoectasia[tiab] OR (dilatation, pathologic[mh] AND cornea[tiab])) AND (Corneal Diseases/pathology[MAJR] OR Corneal Diseases/physiology[MAJR] OR Corneal Diseases/physiopathology[MAJR])

# RELATED ACADEMY MATERIALS

## **Basic and Clinical Science Course**

External Disease and Cornea (Section 8, 2018–2019)

## **Focal Points**

Diagnosis and Management of Noninfectious Corneal Ulceration and Melting (2015)

Risk Factors for Post-LASIK Ectasia (2015)

**Preferred Practice Pattern® Guidelines – Free download available at [www.aao.org/ppp](http://www.aao.org/ppp).**

Comprehensive Adult Medical Eye Evaluation (2015)

Pediatric Eye Evaluations (2017)

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