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# Corneal Edema and Opacification 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 Edema and Opacification 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.

## **Cornea/External Disease Preferred Practice Pattern Panel 2022–2023**

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The **Preferred Practice Patterns Committee** members reviewed and discussed the document during a meeting in June 2023. The document was edited in response to the discussion and comments.

## **Preferred Practice Patterns Committee 2023**

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The Corneal Edema and Opacification PPP was sent for review in July 2023 to improve the quality of the guideline, to gather feedback on the draft recommendations, and to assess feasibility for and applicability to the target audience, including assessing the facilitators and barriers to implementing recommendations (e.g., U.S. ophthalmologists and other important groups, including patients, other physicians, international ophthalmologists, research organizations, ophthalmological organizations, and experts in the field). The PPP was sent for review to the following patient organizations to solicit the views and preferences of patients and the public: Consumers United for Evidence-Based Healthcare, American Foundation for the Blind, Foundation Fighting Blindness, Lighthouse Guild, National Federation of the Blind, and Prevent Blindness. All those who were returning comments were required to provide disclosure of relevant relationships with industry to have their comments considered (indicated with an asterisk below). Members of the Cornea/External Disease Preferred Practice Pattern Panel reviewed these comments and determined revisions to the document.

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American College of Surgeons, Advisory Council for Ophthalmic Surgery  
 American Foundation for the Blind  
 American Ophthalmological Society\*

## Corneal Edema and Opacification PPP

American Society of Cataract & Refractive Surgery  
American Uveitis Society\*  
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Association for Research in Vision and Ophthalmology  
Association of University Professors of Ophthalmology  
Canadian Ophthalmological Society  
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This guideline will be formally re-evaluated and updated on a 5-year cycle in 2028. A Summary Benchmark is a resource to facilitate application of the guideline and to provide criteria that could be used to measure the application of recommendations, which will be available to all at [www.aao.org/ppp](http://www.aao.org/ppp).

## FINANCIAL DISCLOSURES

There is no external funding, including industry/commercial support, for the development of this PPP or for the distribution of the guidelines. The Academy has fully funded the development of this PPP, and the views or interests of the Academy have not influenced the final recommendations, which are based on evidence from systematic reviews. All those individuals significantly involved in the guideline development process, including guideline panel members, PPP Committee members, Secretary for Quality of Care, and Academy Staff, have declared competing/financial interests through a financial interest disclosure process as well as an assessment of the Open Payments website (available at <https://openpaymentsdata.cms.gov/>). The interests of the guideline panel members are provided at the beginning of each meeting, and those with competing interests in a guideline topic do not participate in voting on areas of disagreement. In compliance with the Council of Medical Specialty Societies' Code for Interactions with Companies (available at <https://cmss.org/code-for-interactions-with-companies/>), relevant relationships with industry are listed. As per CMSS code, direct financial relationships with companies do not include food and beverages, research funds paid to the institution, and relationships outside of the topic of the PPP. 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 (82%) of the members of the Cornea/External Disease Preferred Practice Pattern Panel 2022–2023 had no direct 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 2023 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 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 [www.aao.org/about-preferred-practice-patterns](http://www.aao.org/about-preferred-practice-patterns)) to comply with the Code.

Appendix 2 contains the International Statistical Classification of Diseases and Related Health Problems (ICD) codes for the disease entities that this PPP covers. The intended users of the Corneal Edema and Opacification 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 (WHO), 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 on March 3, 2022 and June 7, 2023 in the PubMed database. Complete details of the literature search are available at [www.ao.org/ppp](http://www.ao.org/ppp).

- ◆ Recommendations are based on systematic reviews, as per the Institute of Medicine (Clinical Practice Guidelines We Can Trust, 2011). In formulating the recommendations, the health benefits, side effects/harms/risks, and the balance of benefits and risks are reviewed and considered. Final decisions are arrived at through informal consensus techniques. If there are areas of disagreement, a vote will be conducted among the members of the guideline panel. If there are individuals with direct financial relationships in the area of disagreement, these individuals will refrain from the vote.

## HIGHLIGHTED FINDINGS AND RECOMMENDATIONS FOR CARE

The impact of corneal edema on activities of daily living—particularly those influenced by ambient light conditions at home, work, and during leisure activities—is often under appreciated. Standard measurement of visual acuity does not give a true representation of the patient’s functional vision.

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A refraction over a rigid gas-permeable (RGP) or scleral contact lens can be very helpful in determining if visual loss is due to a corneal surface irregularity.

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Endothelial function is best evaluated by clinical history and examination with slit-lamp biomicroscopy. When diffuse endothelial guttae are present on slit-lamp biomicroscopy examination, serial pachymetric measurements and tomographic evaluation may help monitor endothelial function. Specular microscopy is not a direct measure of endothelial function or functional reserve. Corneal tomography revealing irregular isopachs, nasal displacement of the thinnest cornea, and posterior depression may help predict Fuchs dystrophy patients at greater risk of endothelial decompensation.

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If corneal decompensation is likely to occur in the near future, the surgeon should consider modifying the intraocular lens (IOL) power calculation to adjust for changes likely to be induced by future endothelial keratoplasty. This often involves a hyperopic shift after Descemet’s stripping automated endothelial keratoplasty (DSAEK) and less of a hyperopic shift with Descemet’s membrane endothelial keratoplasty (DMEK). A full discussion with the cataract and Fuchs dystrophy patient about IOL-power selection and the added risks of subsequent corneal decompensation is very important and helps to shape the patient’s expectations with respect to their condition and the surgery.

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Endothelial keratoplasty (EK) has supplanted penetrating keratoplasty (PK) as the procedure of choice in cases of endothelial failure in the absence of corneal scarring because patients achieve more rapid visual rehabilitation and reduced risk of immune-mediated rejection of the transplanted tissue and less induced astigmatism.

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Many corneal opacities start as persistent, nonhealing epithelial defects that opacify as a result of infection, inflammation, tissue breakdown, and/or scarring. Nerve growth factor has been shown to be effective in treating nonhealing epithelial defects in the setting of neurotrophic keratopathy.<sup>4-6</sup>

# INTRODUCTION

## DISEASE DEFINITION

### Corneal Edema

Corneal edema is the retention of excess fluid within one or multiple layers of the cornea. See Table 1 for a list of potential etiologies of corneal edema.

**TABLE 1 ETIOLOGIES OF CORNEAL EDEMA**

	Unilateral	Bilateral
<b>Early-Age Onset</b>		
Congenital glaucoma	•	•
Dystrophies:		
CHED		•
PPCD <sup>*</sup>		• <sup>†</sup>
Intraocular inflammation	•	•
Trauma:		
Birth/forceps delivery	•	
<b>Late-Age Onset</b>		
Acute angle-closure glaucoma	• <sup>‡</sup>	
Dystrophies:		
Fuchs dystrophy		•
PPCD		• <sup>†</sup>
Hypotony	•	
Hypoxia		• <sup>†</sup>
Intraocular inflammation/uveitis	•	•
ICE syndrome	•	
Keratitis:		
Infectious	•	
Keratoconus – hydrops	•	
Surgical trauma:		
Pseudophakic or aphakic (unilateral or bilateral)	•	•
Direct injury	•	
Toxicity:		
Amantadine		•
Cancer chemotherapy <sup>7</sup>		•
Chlorhexidine	•	•
Silicone oil	•	
Bupropion		•

AD = autosomal dominant; AR = autosomal recessive; CHED = congenital hereditary endothelial dystrophy; ICE = iridocorneal endothelial; PPCD = posterior polymorphous corneal dystrophy.

\* Includes previously classified CHED-AD

<sup>†</sup> Occasionally unilateral

<sup>‡</sup> Occasionally bilateral

## Corneal Opacification

Loss of corneal clarity, or corneal opacification, results from the presence of additional material (e.g., fluid, scar tissue, inflammatory debris, metabolic byproducts) within one or multiple layers of the cornea. In addition to the causes of corneal edema (see Table 1), corneal opacification etiologies include the following:

- ◆ Congenital
  - ◆ Axenfeld-Rieger syndrome
  - ◆ Peters anomaly
  - ◆ Sclerocornea
  - ◆ Dermoid
  - ◆ Leukoma
- ◆ Degenerations
  - ◆ Calcific band keratopathy
  - ◆ Crocodile shagreen
  - ◆ Spheroidal degeneration
  - ◆ Salzmann nodular degeneration
  - ◆ Pterygium
  - ◆ Polymorphic amyloid degeneration
- ◆ Dystrophies
  - ◆ Epithelial basement membrane dystrophy
  - ◆ Reis-Bücklers dystrophy
  - ◆ Thiel-Behnke corneal dystrophy
  - ◆ Gelatinous drop-like corneal dystrophy
  - ◆ Lattice corneal dystrophy
  - ◆ Granular corneal dystrophy
  - ◆ Macular corneal dystrophy
  - ◆ Schnyder corneal dystrophy
  - ◆ Congenital hereditary stromal dystrophy
  - ◆ Fuchs dystrophy
  - ◆ Posterior polymorphous corneal dystrophy (PPCD)
  - ◆ Congenital hereditary endothelial dystrophy (CHED)
  - ◆ Posterior amorphous corneal dystrophy
- ◆ Inflammatory and immunologic
  - ◆ Infection (bacterial, fungal, parasitic, and viral)
  - ◆ Interstitial keratitis (nonsterile and sterile)
- ◆ Metabolic
  - ◆ Mucopolysaccharidosis
  - ◆ Mucopolidoses
  - ◆ Lipidosis
  - ◆ Hypolipoproteinemias
  - ◆ Cystinosis
  - ◆ Fabry disease
- ◆ Infiltrative
  - ◆ Amyloid
  - ◆ Proteins (e.g., multiple myeloma, cryoglobulinemia, monoclonal gammopathy)
  - ◆ Drugs
  - ◆ Heavy metals
  - ◆ Lipid keratopathy
- ◆ Neoplastic
  - ◆ Conjunctival/corneal intraepithelial neoplasia
  - ◆ Melanosis/melanoma
- ◆ Postsurgical

- ◆ Corneal wound scarring
- ◆ Post-traumatic injury

## **PATIENT POPULATION**

The patient population includes individuals of any age who have corneal edema or opacification.

## **CLINICAL OBJECTIVES**

- ◆ Assess the degree of vision loss
- ◆ Evaluate the degree of functional impairment and its effect on the patient's activities of daily living
- ◆ Identify the underlying ocular condition responsible for the corneal edema or opacification
- ◆ Assess the potential for progression of the disorder, development of discomfort, and/or improvement of vision
- ◆ Determine which optical, medical, or surgical treatment alternative is most appropriate

# **BACKGROUND**

## **NATURAL HISTORY**

Corneal edema and opacification may or may not be progressive. Conditions that affect primarily the peripheral cornea may be subtle and asymptomatic (e.g., Brown-McLean syndrome, Salzmann nodular degeneration), although peripheral conditions can result in central irregularity and astigmatism that may be visually significant. The conditions that involve the central, pupillary region generally cause symptoms (e.g., Fuchs dystrophy, scarring secondary to disciform keratitis).

## **RATIONALE FOR TREATMENT**

The reduction or elimination of corneal edema or opacification is indicated when it is associated with functional visual loss or discomfort. Chronic epithelial breakdown associated with underlying stromal or endothelial dysfunction may necessitate intervention to stabilize the ocular surface and prevent further complications. Less commonly, cosmesis is an indication for treatment.

# **CARE PROCESS**

## **PATIENT OUTCOME CRITERIA**

- ◆ Reduce the signs and symptoms of corneal edema or opacification
- ◆ 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 edema or opacification should include the relevant aspects of the comprehensive medical eye evaluation.<sup>8</sup> The diagnosis of corneal edema or opacification is usually based on a typical patient history and characteristic findings. Ancillary testing may be helpful.

### **History**

- ◆ Signs and symptoms: blurred or variable vision, often with a diurnal character (worse upon waking and clearer later in the day); photophobia; redness; tearing; intermittent foreign-body sensation; intense, disabling, or task-disrupting pain; recent history of other ocular surgery/complications.
- ◆ Age of onset

- ◆ Rapidity of onset: acute symptoms versus gradual or fluctuating presentation

Most conditions associated with edema present gradually over weeks, months, or longer. At times, it may be so gradual that the patient adjusts surprisingly well and is able to function at a much higher level than the slit-lamp biomicroscopic examination might lead one to expect. Exceptions include edema that is due to the following:

- ◆ Elevated intraocular pressure (IOP), often resulting from topical corticosteroid treatment of the underlying corneal disorder but that may also result from chronic glaucoma with elevated IOP
- ◆ Moderate to severe corneal or intraocular inflammation
- ◆ Corneal hydrops associated with keratoconus, other ectatic disorders, and trauma

Noninfectious corneal opacification (e.g., depositional or scarring disorders) develops more gradually in most cases, except for acute medication-related band keratopathy.<sup>9, 10</sup>

Infectious corneal opacities frequently present acutely.

- ◆ Persistence: transient or permanent

- ◆ Inflammatory and pressure-related corneal edema often clears as the underlying problem resolves. Neonatal forceps injury, in which a break in Descemet's membrane eventually heals and the resulting stromal edema resolves, is another example. If sufficient endothelial damage occurs, corneal edema may recur years later.<sup>11</sup>
- ◆ Transient blurred vision upon waking in the morning, on humid days, or after taking a shower can occur with edema associated with endothelial dysfunction. Vision is often better later in the day due to evaporation that reduces this edema.
- ◆ Most noninflammatory corneal opacities are permanent. Inflammatory infiltrates frequently resolve when the underlying cause disappears. Metabolic deposits due to cystine crystals<sup>12</sup> and, to a lesser degree, mucopolysaccharidosis,<sup>13</sup> may resolve with treatment.<sup>14</sup>

- ◆ Unilateral or bilateral presentation (e.g., herpes simplex virus keratitis is usually unilateral, whereas corneal dystrophies are typically bilateral)

- ◆ Moderating factors or situations

- ◆ Low humidity and modest air movement may lead to visual improvement with endothelial dysfunction.
- ◆ Visual acuity and visual function may not necessarily correlate with one another. For example, a patient with mild edema associated with Fuchs dystrophy or opacification related to granular corneal dystrophy may have visual acuity of 20/40 or better but may not be able to drive because of disabling glare. Unshielded fluorescent lighting or reflections off surfaces with a high luster and computer screens may cause problems with activities of daily living.<sup>15</sup> Higher order aberrations with resulting visual distortions may also result from even mild edema associated with Fuchs dystrophy.<sup>16</sup>
- ◆ Contact lenses (particularly rigid gas-permeable [RGP] lenses) may be able to improve visual function by creating a smoother and more regular refractive surface.

- ◆ Ocular history

- ◆ Corneal edema:
  - Acute angle-closure or chronic glaucoma
  - Chemical or traumatic injury
  - Infection
  - Inflammation
  - Intraocular or keratorefractive surgery
  - Laser iridotomy
  - Keratoconus

- Ocular or periocular trauma (blunt or penetrating)
- ◆ Corneal opacification:
  - Chemical, thermal, and traumatic injury
  - Infection
  - Inflammation
  - Intraocular and keratorefractive surgery
- ◆ Medical history
  - ◆ Corneal edema:
    - Inflammatory conditions associated with uveitis (e.g., sarcoidosis, ankylosing spondylitis)
    - Systemic medications
  - ◆ Corneal opacification:
    - Developmental
    - Metabolic/hereditary (e.g., mucopolysaccharidosis, cystinosis, proteinemia)
    - Immune-mediated diseases (e.g., rheumatoid arthritis, interstitial keratitis, Stevens-Johnson syndrome, ocular mucous membrane pemphigoid [OMMP])
    - Vitamin A deficiency due to malabsorption syndromes (e.g., following colon resection, bowel surgery, hepatobiliary illness, gastric bypass surgery)
- ◆ Topical and systemic medications
  - ◆ Corneal edema:
    - Amantadine for neurologic disease may produce a reversible endothelial dysfunction if used for a short period or a permanent problem if used long term.<sup>17-19</sup>
    - When used in surgical preparation for facial trauma or reconstructive and cosmetic facial surgery, inadvertent exposure of the cornea to topical chlorhexidine preparation may cause toxicity that predisposes to endothelial failure.<sup>20</sup>
    - Topical or systemic carbonic anhydrase inhibitors
    - Bupropion
  - ◆ Corneal opacification:<sup>21</sup>
    - Amiodarone<sup>22, 23</sup>
    - Dietary calcium supplementation<sup>24</sup>
    - Periocular radiation<sup>25, 26</sup>
    - Various chemotherapeutic agents<sup>27-29</sup>
    - Rho kinase inhibitor verticillate changes<sup>21, 30</sup>
- ◆ Trauma: blunt or penetrating injury to the eye or periocular region, forceps delivery, chemical injury
- ◆ Contact lens wear: type of lens, wear time, and cleaning routine
- ◆ Family history: patients may be aware of a family history or may relate that a relative had a cloudy cornea; required corneal transplantation; or had repeat episodes of pain, tearing, and photophobia.
- ◆ Social history
  - ◆ Sun exposure at work (e.g., farming, construction) or leisure activity (e.g., boating, golfing) may be related to pterygium development.
  - ◆ Travel may increase exposure to unusual infectious agents.
  - ◆ Exposure to animals may increase exposure to unusual infectious agents (e.g., *Brucella*, *Borellia burgdorferi*/Lyme disease).



- ♦ Diet or dietary deficiencies (e.g., vitamin A deficiency from malabsorption syndromes or severely limited diets) may predispose to nutritional problems.
- ♦ Chemical exposure (longstanding and new)

### Examination

A comprehensive examination of the eye and adnexa is necessary to determine the etiology of many cases of corneal edema or opacification. Particularly relevant aspects of the examination are described below.

- ♦ Visual acuity: this should be performed under standard ophthalmic lighting conditions, with and without correction. Pinhole testing and manifest refraction should be done to assess best-corrected visual potential. Furthermore, pinhole near testing or potential acuity meter to assess visual potential is important prior to any surgical treatment decision.
- ♦ Comparison of visual acuity measurement and functional status
- ♦ Glare testing
- ♦ External examination
  - ♦ Evidence of proptosis, blepharoptosis, lagophthalmos, or floppy eyelid syndrome
  - ♦ Eyelid or facial asymmetry, scarring, and malfunction (e.g., poor blink or lid closure due to facial palsy)
  - ♦ Miscellaneous: pupil responses, corneal diameter, dry eye evaluation
- ♦ Slit-lamp biomicroscopy examination
  - ♦ Unilateral or bilateral abnormalities
  - ♦ Diffuse or localized edema
  - ♦ Primarily epithelial or stromal edema
  - ♦ Evidence of epithelial breakdown, stromal infiltration, epithelial ingrowth, striae, focal thickening, thinning, scarring, interface haze, inflammation, or stromal vascularization or deposits
  - ♦ Evidence of guttae; Descemet's membrane folds, tears, or detachment; endothelial vesicles; keratic precipitates; pigment; peripheral anterior synechiae
  - ♦ Selective involvement of host or donor tissue (if there is a corneal transplant)
  - ♦ Evidence of sectoral corneal edema and a cluster or line of keratic precipitate (as with endotheliitis), or an anterior chamber reaction. Eyes with inferior corneal edema may have a foreign body or residual lens material hidden in the inferior anterior chamber angle that may be visible on gonioscopy.
  - ♦ Use of various slit-lamp techniques such as sclerotic scatter, specular reflection, or indirect illumination to evaluate all layers of the cornea
  - ♦ Status, shape, and position of the pupil and iris
    - Sphincter rupture as evidence of past trauma
    - Iridocorneal adhesions, iris transillumination defects, peripheral anterior synechiae, or posterior synechiae as evidence of past trauma, inflammation, or surgery
    - Evidence of intraocular trauma (nonsurgical and surgical)
    - Intraocular lens (IOL) capture by iris
  - ♦ Healed or recent corneoscleral wounds, evidence of keratorefractive procedures, areas of scleral thinning associated with previous surgery, and surgical devices
  - ♦ Status and position of the crystalline lens or IOL and any other intraocular device including glaucoma tubes/shunts
- ♦ Intraocular pressure

- ◆ Goldmann applanation tonometry can be less reliable in abnormal corneas. Intraocular pressure can also be assessed using alternative methods or devices such as a pneumotonometer, handheld electronic applanation tonometer, dynamic contour tonometer, ocular response analyzer, rebound tonometer, or digital palpation.
- ◆ Fundus examination
  - ◆ Chronic serous choroidal detachment or retinal detachment may lead to hypotony and secondary corneal edema
  - ◆ B-scan ultrasonography may be useful to assess the posterior segment.
- ◆ Gonioscopy
  - ◆ Retained nuclear fragments, foreign bodies, or presence of iridocorneal adhesions as seen in iridocorneal endothelial Syndrome (ICE) syndrome or Axenfeld-Rieger syndrome

## Diagnostic Evaluation

Observations from the comprehensive eye examination are augmented by various tests.

### ◆ Genetic testing

The single nucleotide variant (rs613872) in the transcription factor 4 gene results in a CTG triplet repeat expansion that is strongly associated with Fuchs corneal dystrophy.<sup>31</sup> A small, prospective clinical study did show a significant correlation between allele repeats and achievement of corneal clearance in patients undergoing Descemet's stripping only, although it was not possible to predict time to corneal clearance.<sup>32</sup> Additional information is needed before genetic testing can be recommended for clinical management of Fuchs corneal dystrophy.

### ◆ Potential acuity testing

The potential acuity meter projects a tiny eye chart directly onto the macula in an effort to bypass anterior segment pathology (specifically, corneal opacities and cataracts). The test can be helpful when the patient can read farther down on the eye chart than he or she was able to do in a refracting lane or similar testing situation. This indicates that there is a good chance that vision may improve if the pathologic condition is corrected. A poor result, however, does not necessarily indicate poor visual potential, since the anterior segment pathology may be obstructing the optical pathway or potentially treatable conditions such as cystoid macular edema may be present. Pinhole vision using an illuminated near card in a darkened room can be used in the same way to assess potential acuity.

### ◆ Contact lens over-refraction

Disruption of the central or paracentral ocular surface due to microcystic edema or scarring can have a surprisingly large impact on vision. These changes may have a greater impact than an underlying opacity. The easiest way to differentiate between these two problems as the primary cause of visual impairment is to measure the patient's best-corrected vision with eyeglasses and then over an RGP contact lens. This can be done quickly in the office by obtaining a set of keratometry measurements, determining the average K reading, and then fitting the RGP lens slightly flatter than this measurement. Keratometry mire-pattern irregularity should be specifically noted because this correlates well with the amount of surface irregularity. Improved vision with the RGP lens but not the eyeglasses suggests that the irregular surface is a major factor in a patient's reduced vision.

### ◆ Pachymetry

The measurement of corneal thickness continues to evolve as new approaches and devices become available. Ultrasonic pachymeters (10–20 MHz), utilizing a speed of sound of 1636 to 1640 m/second, typically provide information about a single location on the cornea (i.e., the central cornea). Their range is often limited to between 200 and 1000  $\mu\text{m}$ . Most probes do not have a fixation light, so results can fluctuate from visit to visit because of positioning rather than progression of the disease. With training and careful positioning and probe angulation (kept at 90°), an interobserver standard deviation of 12  $\mu\text{m}$  and variability of less than 2% can be achieved.<sup>33</sup> When consistency, precise serial comparison, and peripheral measurements are important, optical coherence tomography (OCT) and Scheimpflug imaging

may provide greater accuracy. Both technologies, however, use light and lose accuracy and resolution as stromal edema or opacification increases. The ultrasound biomicroscope (50–70 MHz probes) provides the most accurate measurements when there is significant stromal edema.

Measurements taken with different types of devices are not directly comparable in clinical practice. Comparisons between different instruments have demonstrated varied results, though most large studies report that anterior segment optical coherence tomography (AS-OCT) measurements of central corneal thickness were systematically lower than ultrasound measurements by between 7 and 26  $\mu\text{m}$ .<sup>34–38</sup>

The greater availability of ultrasonic pachymetry has resulted in a better appreciation of the wide variability of normal corneal thickness. However, the wide variability of normal corneal thickness makes it harder to predict which corneas might decompensate after anterior segment surgery. The risk of corneal edema following cataract surgery is associated with several factors, including 1) a patient history that includes glare or blurred morning vision that improves during the day, 2) a cornea that demonstrates microcystic edema, stromal thickening, or confluent guttae by slit-lamp biomicroscopic examination, and/or 3) a cornea that demonstrates low central endothelial cell counts by specular microscopy.

Intraocular pressure and osmolarity of the tear film are factors that influence normal corneal thickness. Gradual thinning of the cornea with age (6–10  $\mu\text{m}$  per decade) has been demonstrated as well.<sup>39, 40</sup>

◆ Topography/tomography

The topographic evaluation can help assess irregular astigmatism that may be caused by the corneal edema or scar. In the setting of peripheral lesions, the degree of central irregularity seen on the topographic map may help determine management options. (See Corneal Ectasia PPP.<sup>41</sup>) These measurements are also essential when considering placement of toric, extended depth of focus and multifocal lenses.

Slit-lamp imaging systems are designed to assess the topographic characteristics of the anterior and posterior corneal surfaces and provide measurements of corneal thickness. The tomographic capability can enable assessment of the depth of corneal opacification, which can aid in surgical planning. Thickness or pachymetric mapping can also be obtained.

Scheimpflug tomography pachymetry map and posterior elevation map patterns can also help predict prognosis for Fuchs endothelial corneal dystrophy independent of pachymetry measurements. This includes loss of regular isopachs (contour lines of equal thickness over an area) and displacement of the thinnest point on the pachymetry map as well as focal posterior surface depression on the posterior elevation map.<sup>42, 43</sup>

◆ Specular microscopy

This provides information about the density of endothelial cells (cells per  $\text{mm}^2$ ), and the shape (percent hexagonality) and uniformity of the cell population. The terms polymegethism (variability in cell size) and pleomorphism (the lack of uniformity of the cell shape) are often used when describing the specular image. Although specular microscopes can image both central and peripheral areas, measurements are of the central and pupillary regions unless specifically stated. Because this is a fairly large area, from 28 to 50  $\text{mm}^2$ , some comment should be made about the number of random fields or percentage of the endothelial surface examined. A study showed that sampling greater than 20% of the surface was necessary to provide an accurate representation of the full endothelial surface.<sup>44</sup>

Specular microscopy is of greatest value when it is combined with pachymetry and slit-lamp biomicroscopy examination. Specular microscopy is not a functional test, while pachymetry over time provides an assessment of endothelial function. It can be very helpful, though, when following a patient over time; progressive loss of cells, as in a patient with vitreous touch syndrome, may be a finding that pushes the patient towards surgery, whereas stabilization of the cell count would encourage a conservative approach. When diffuse, confluent guttae are present on slit-lamp biomicroscopic examination, specular microscopy rarely provides any valuable information because it is difficult to image the endothelial cells.

◆ Confocal microscopy

◆ Confocal microscopy

This noninvasive diagnostic technique allows in vivo, microscopic imaging of all the layers of the cornea. Endothelial cells are characterized by a relatively regular hexagonal hyper-reflective shape surrounded by hyporeflective borders. Endothelial cell counts with confocal and specular microscopy are comparable.<sup>45</sup> Whereas specular microscopy is often ineffective at visualizing the endothelium in cases of corneal edema, confocal microscopy is capable of imaging the endothelium in cases of moderate corneal edema. This is particularly helpful when assessing unilateral cases of corneal edema. Iridocorneal endothelial syndrome, epithelial and fibrous ingrowth, and PPCD have distinctive confocal appearances (of the posterior surface) that may be very helpful in identifying an underlying cause for the decompensation preoperatively. Additionally, stromal opacities and certain infectious organisms, such as fungal hyphae and *Acanthamoeba* cysts, have a distinct appearance on confocal microscopy that can help guide diagnosis and treatment. Challenges associated with confocal microscopy include dependence on technical expertise in obtaining and interpreting the images as well as access to the technology because it is primarily available in academic centers.

◆ Anterior segment optical coherence tomography

Anterior segment optical coherence tomography provides high-definition, cross-sectional images of the cornea, angle, and anterior chamber. Measurement tools to document and follow changes in the corneal thickness, anterior chamber angle configuration, and anterior chamber depth are standard with all models. Pachymetry mapping is available. Anterior segment optical coherence tomography can be used to follow changes in corneal thickness; however, its greatest value lies in its ability to image deep and retrocorneal structures. The depth of a corneal scar or deposits in the cornea can be analyzed on the images. Corneal edema or scarring may be masking a detached Descemet's membrane or a retrocorneal membrane, which can be visualized using AS-OCT. A large Descemet's 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 guide endothelial keratoplasty management in the immediate postoperative period. Images can help determine areas of poor donor tissue adherence. Early DMEK graft detachments more than 30% of total graft area are predictive of persistent or complete detachment compared with detachments less than 30% that tend to completely reattach.<sup>46</sup>

◆ Ultrasound biomicroscopy

Ultrasound can provide real-time cross-sectional images of the anterior and posterior segment. Its advantage over light-emitting imaging devices is that it is not impeded by opacities of the cornea, anterior segment, or vitreous. Conventional ultrasound uses a frequency of 10 MHz. Ultrasound biomicroscopy (UBM) uses much higher frequencies (35 to 80 MHz) that results in a significant improvement in resolution. Ultrasound biomicroscopy systems are suitable for imaging virtually all anterior segment anatomy and pathology, including the cornea, iridocorneal angle, anterior chamber, iris, ciliary body, and lens. The imaging of a ruptured or dislocated Descemet's membrane, retrocorneal membranes, and iridocorneal and lenticulocorneal adhesions help to determine the root causes of an edematous or opaque cornea and aid in surgical planning. Ultrasound biomicroscopy is particularly helpful in congenital and traumatic cases. Additionally, it can locate small anterior segment foreign bodies that are difficult to detect by slit-lamp biomicroscopy examination or AS-OCT.

## MANAGEMENT

### General Treatment Goals

The primary therapeutic goal is to control the underlying cause of the corneal edema or opacity (when active or progressive) and enhance the patient's quality of life by improving visual acuity and maximizing comfort. The ophthalmologist should provide the patient with an understanding of available treatment alternatives, balanced expectations of the amount of visual function that can realistically be preserved or recovered, and the risks of potential complications. The requirements for visual function will vary from individual to individual, and these needs must be

considered when discussing treatment alternatives. Treatment may be optical, medical, surgical, or a combination, depending on the etiology, nature, and severity of the opacity as well as the needs, desires, and health status of the patient.

In most cases, treatment starts with medical management. When these measures are insufficient, surgery may be considered. Although improving visual acuity and maximizing comfort are the most frequent reasons to recommend surgery, improving visualization of the posterior segment, reducing the risk of infection, and improving a disfiguring condition may also be reasons to consider surgery.

## Medical Management of Corneal Edema

Chronic corneal edema is most commonly related to endothelial dysfunction, elevated IOP, and/or intraocular inflammation.<sup>47</sup> A careful ophthalmologic examination will often assist in determining the most likely cause. The hyperosmotic effect of topical sodium chloride 5% drops or ointment or the use of a hairdryer (for either primary or secondary edema) are commonly suggested temporizing routines. Their ability to improve vision or reduce symptoms, however, is often limited.<sup>48</sup> They should be discontinued after a number of weeks if no benefit is noted. A dry eye patient with corneal edema may benefit from less aggressive dry eye treatment, since increased tear osmolarity may reduce corneal edema. Topical antibiotics may reduce the risk of secondary infection when bullae rupture. Rho kinase inhibitors may play a role in reducing corneal edema in Fuchs corneal dystrophy, but randomized controlled trials are needed to establish efficacy and safety.<sup>49</sup> However, Rho kinase inhibitors may also result in adverse events, including a honey-comb patterned edema, pain, conjunctival hyperemia, and cornea verticillate, which are often reversible.<sup>50</sup>

Lowering the IOP may be helpful when it is elevated or at the upper end of the normal range. Although any hypotensive agent may be beneficial in theory, prostaglandin analogues have a potentially inflammatory character and should be avoided in patients for whom inflammation is a possible contributing factor.<sup>51, 52</sup> When endothelial dysfunction is a possible contributing factor, topical carbonic anhydrase inhibitors should not be first-line therapy because of their potential to interfere with the endothelial pump.<sup>53, 54</sup> When inflammation is present, it should be controlled by adding a topical corticosteroid once possible infection has been ruled out or controlled, and follow-up is needed to rule out steroid responsiveness and elevated IOP from steroid use.

Microcystic or bullous epithelial disease may produce discomfort or pain, necessitating the placement of a bandage contact lens (BCL) to alleviate these symptoms. Although many different lenses may be used, thin lenses with high water content and high oxygen diffusion coefficients (i.e., Dk levels) are thought to be safest.<sup>55</sup> Generally, a flat lens with some movement on blinking is desirable. If there is concomitant dry eye disease, preservative-free artificial tears may be necessary to facilitate sufficient movement of the lens. When a BCL is used, a topical prophylactic broad-spectrum antibiotic should be considered to decrease the risk of secondary infection.

Patients should be informed of the risk of infectious keratitis when wearing a BCL and the need to contact their treating ophthalmologist if redness, pain, or increased photophobia develops. One study suggested an increased risk of infectious keratitis associated with use of BCLs, and antibiotics may not prevent the risk of infection.<sup>56</sup> Ideally, BCLs should be used for a limited treatment period; however, in many cases, longer-term use may be required. In this situation, periodic exchange of the lens is advised. In most cases the same lens should not remain on the eye for longer than one month. Regular follow-up is necessary under these circumstances to reassess the lens, look for evidence of a change in the patient's ocular status, and re-emphasize the need for vigilance on the part of the patient.<sup>56</sup> In general, a therapeutic bandage soft contact lens should not be considered a long-term solution for the treatment of corneal edema. In severe cases with advanced edema or scarring, soft contact lens or RGPs may be difficult to fit due to trauma to the edematous epithelial layer and irregular corneal surface. In these cases, scleral lenses may be useful to provide improved visual outcomes and symptom improvement. Visual potential may also be better assessed in severe cases with scleral lens over-refraction.

For cases of acute hydrops, supportive management should be initiated to reduce inflammation and/or pain. Patients can be started on topical corticosteroids, cycloplegic agents, hyperosmotic drops and ointments, and/or topical antibiotics while monitoring for improvement and resolution

of edema. With hydrops, resolution may be more rapid with the use of intraocular gas to reduce corneal edema and closure of endothelial break. In the case of an acute perforation, surgical intervention may be necessary.

### Surgical Management of Corneal Edema

To treat pain associated with bulbous keratopathy, when visual rehabilitation is not being considered, several approaches can be used. Patients with longstanding bullous keratopathy often develop a layer of subepithelial scar tissue that is associated with reduced bullae production and reduced pain. Intentional scarification of the corneal surface to recreate this effect has been a longstanding surgical approach when improved vision was not the principal concern. Anterior stromal puncture with electrocautery<sup>57</sup> or a needle<sup>58</sup> has been found to be effective. Intentional scarification requires caution, because overtreatment can lead to necrosis and corneal melt.<sup>59</sup>

Numerous keratectomy and keratoplasty procedures can be considered for treating persistent corneal edema. Acronyms abound and are often confusing because of their similarities. Good examples are anterior lamellar keratectomy (ALK), automated lamellar therapeutic keratoplasty (ALTK), femtosecond laser-assisted anterior lamellar keratoplasty (FALK), and femtosecond laser astigmatic keratotomy (FLAK). Table 2 lists many of the more common keratectomy and keratoplasty procedures.

**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	Descemet's membrane endothelial keratoplasty
DSEK (DSAEK)	Descemet's stripping (automated) endothelial keratoplasty
DSO/DWEK	Descemet's stripping only/Descemet's stripping without endothelial keratoplasty
EK	Endothelial keratoplasty
FALK	Femtosecond anterior lamellar keratoplasty
FLAK/FLEK	Femtosecond laser assisted (enabled) keratoplasty
PD-DALK	Predescemet deep anterior lamellar keratoplasty
PDEK	Predescemet's endothelial keratoplasty
PKP/PK	Penetrating keratoplasty
PRK	Photorefractive keratectomy
PTK	Phototherapeutic keratectomy
SK	Superficial keratectomy

### Phototherapeutic Keratectomy

Excimer laser phototherapeutic keratectomy (PTK) with ablations to a depth of 100  $\mu\text{m}$  or greater has been used alone<sup>60-62</sup> or in combination with self-retaining amniotic membrane grafts<sup>63, 64</sup> to reduce pain and promote surface stability. Pain relief is purportedly achieved by ablation of the sub-basal nerve plexis.<sup>65</sup> A less involved technique for achieving the same result is an annular keratotomy created by corneal trephination to a mid-stromal depth.<sup>66</sup> Phototherapeutic keratectomy for corneal edema will not produce long-term visual rehabilitation.

## Conjunctival Flap

Rapid corneal healing, ocular comfort, and reduction in ocular inflammation can be achieved with a conjunctival flap.<sup>67, 68</sup> Full conjunctival flaps (Gundersen) are often used as definitive surgery when additional reconstructive surgery is not anticipated.<sup>67</sup> Conversely, conjunctival flaps can be used to allow an eye to quiet before more definitive therapy is performed.

## Amniotic Membrane Tissue Transplantation

An improved understanding of the importance of preserving stem cells has led to the use of amniotic membrane.<sup>69-71</sup> Placement of an amniotic membrane can be performed using an “inlay”<sup>72</sup> or “overlay”<sup>73</sup> technique. In the inlay method, the amniotic membrane acts as a scaffold for epithelial cells that migrate onto the membrane from the surrounding region. It is hoped that some of the membrane will persist after healing to create a barrier effect and prevent new bullae from forming. In the overlay method, the amniotic membrane is applied as a patch and sutured to the conjunctival surface.<sup>73</sup> Here, it functions as a biologic contact lens, and epithelial healing takes place underneath the layer of amniotic membrane, which then resorbs. Self-retaining amniotic membranes are available for use under a therapeutic lens or fixated to a scleral ring. These are “onlay” in nature and require no suturing, making them convenient for use in the office setting.

Patients with corneal edema and persistent discomfort but who have limited or no visual potential are generally better candidates for a conjunctival flap, amniotic membrane transplant, or one of a number of scarification procedures. Occasionally, patients with good vision will opt for one of these treatments when extenuating circumstances affecting general health or follow-up care/transportation are an issue.

## Corneal Transplantation

Corneal transplantation, either full-thickness penetrating keratoplasty (PK) or as a lamellar procedure (Descemet’s stripping automated endothelial keratoplasty [DSAEK] or Descemet’s membrane endothelial keratoplasty [DMEK]), is the most common therapeutic option chosen by patients who have corneal edema and reduced vision or significant pain due to bullous keratopathy. Factors that impact success after keratoplasty as determined by patient reported outcomes include lower preoperative visual acuity and visual functioning, younger age, and male gender.<sup>74</sup> (*II++*, *Moderate*, *Strong*) Factors that determine whether full-thickness or lamellar surgery are to be recommended include the presence and extent of subepithelial or stromal scarring, concerns about the impact of ocular surface disease on epithelial healing and stability, anterior segment anatomy, and the extent of any reconstructive intraocular surgery that might be necessary at the time of surgery. Prior posterior vitrectomy, aphakia, filtering or shunt surgery for glaucoma, iris/pupil irregularity, extensive anterior or posterior synechiae, and a shallow anterior chamber are findings that impact the success of endothelial keratoplasty (EK) and should be taken into consideration.

## Penetrating Keratoplasty

Graft failures in PK generally occur as a consequence of graft rejection within the first few years and, because of endothelial failure, during the later years. Although primary donor failure in endothelial keratoplasty (EK) is greater than in PK due to increased donor manipulation, data suggest that overall endothelial loss after the initial learning curve is comparable between DSAEK and DMEK.<sup>75, 76</sup> The problem of graft dislocation is a unique complication of EK surgery and is frequently associated with added tissue trauma owing to the efforts of the surgeon to reposition or reattach the tissue.

Rejection can occur with full and partial keratoplasties. The differences in the rejection rates between all keratoplasty procedures may be due to the introduction of less antigenic tissue (specifically, dendritic cells, which are generally found in the superficial stroma, and donor epithelium),<sup>77</sup> and because loose sutures, a recognized risk factor for rejections, are not an issue with EK.<sup>78</sup> Data from the Swedish Corneal Transplant Registry disclosed a rejection rate of 13% over 1 year for PKs in patients with Fuchs dystrophy and pseudophakic bullous keratopathy (PBK).<sup>79, 80</sup> This is similar to a study<sup>81</sup> that reported on a

group of DSAEK patients who had rejection rates of 6.0%, 14.0%, and 22.0% at 1, 2, and 3 years, respectively. Similar values of 7.6% at 1 year and 12.0% at 2 years were reported in a different study.<sup>82</sup> Two studies that specifically compared the results of PK and DSAEK in Fuchs and PBK showed no statistically significant difference between the two groups with regard to rejection rates.<sup>83, 84</sup> However, reports in large cohorts show a significantly decreased risk of rejection in DMEK compared with both PK and DSAEK.<sup>85</sup>

Graft survival for both PK and DSAEK at 5 years for Fuchs dystrophy and PBK is 95% and 73%, respectively.<sup>86, 87</sup> Endothelial decompensation, with or without a prior rejection episode, is the leading cause of graft failure for both. Other causes of PK graft failure such as traumatic wound rupture and ocular surface complications are rarely seen with EK.<sup>88, 89</sup> One often underappreciated advantage of EK is the decreased incidence of delayed surface healing and postoperative surface irregularity in patients with ocular surface disease, specifically dry eye and blepharitis. These factors significantly influence the speed of visual recovery and visual quality of many patients. Regrafting a PK that has developed endothelial decompensation using a DSAEK or DMEK is being considered with greater frequency. Interface opacities (e.g., epithelial ingrowth) and wrinkling of the donor button, with resulting reduction in correctable distance visual acuity, are causes of graft failure that are unique to EK and may be an indication for regrafting.

The most common problems following PK are ametropia and irregular astigmatism. The average postoperative astigmatism following PK was 4 to 6 diopters (D) up to 1 year.<sup>90-93</sup> The problem is similar in both phakic and pseudophakic cases. This compares with 1.50 D of total cylinder for DSAEK, where the surgically induced portion ranges from 0.40 to 0.60 D.<sup>94</sup> Induced hyperopia following DSAEK, resulting from the donor lenticule being thicker in the periphery, averages 1.10 D with a range of 0.70 to 1.50 D.<sup>95, 96</sup> The more predictable optical result in DSAEK (e.g., postoperative spherical equivalent, astigmatism) is helpful for obtaining accurate IOL calculations for combined transplant/cataract procedures and for individual adjustments in IOL power when combining DMEK with cataract surgery. The overall hyperopic refractive shift with DMEK is minimal, and individual adjustments in IOL power create less variance and decrease range of error.

The preoperative indications for surgery may vary, but short-term results for different surgical techniques for corneal edema are included in Table 3.

**TABLE 3** COMPARISON OF RESULTS FOR DIFFERENT SURGICAL TECHNIQUES FOR CORNEAL EDEMA (FUCHS AND PSEUDOPHAKIC BULLOUS KERATOPATHY)

	PK	DSAEK	DMEK
Dislocation rate	0.0%	14.5% <sup>94</sup> –15% <sup>97</sup>	5.9%–27.4% <sup>98, 99</sup>
Wound dehiscence	1.3%–5.8% <sup>89, 100, 101</sup>		
Donor failure within 60 days	0.3% <sup>102</sup>	0%–29.0%; mean 5.0% <sup>94, 103</sup>	2.2%–8.0%, <sup>103-105</sup>
Rejection rate at:			
1 yr	17.0% <sup>106</sup>	2.0%–9.0% <sup>75, 106</sup>	0%–6.0% <sup>104, 106</sup>
2 yrs	9.7%–13.0% <sup>79, 80</sup>	12.0%–14.0% <sup>81, 84</sup>	5.6%–6.4% <sup>76, 85</sup>
5 yrs	22.2% <sup>102</sup>	22.0%	2.8% <sup>107</sup>
Graft failure rate at 5 yrs	5.0% for Fuchs/ 27.0% for PBK <sup>87</sup>	5.0% for Fuchs/ 24.0% for PBK <sup>87</sup>	0%–12.5% <sup>76, 108</sup>
BSCVA:			
% 20/40 or better at 1 yr	65.0%–84.0% with selective suture removal <sup>109</sup>	38.0%–90.0% <sup>94</sup>	94.0% at 6 mos <sup>110</sup> 97.0% 20/30 or better at 1 yr <sup>111</sup>
% 20/20 or better			37.6%–85% 20/25 or better <sup>76</sup> 17%–67% <sup>76</sup>



**TABLE 3** COMPARISON OF RESULTS FOR DIFFERENT SURGICAL TECHNIQUES FOR CORNEAL EDEMA (FUCHS AND PSEUDOPHAKIC BULLOUS KERATOPATHY)

	PK	DSAEK	DMEK
Time to BCVA	6–12 mos with selective suture removal <sup>112</sup>	NA	2/3 stable by 3 mos <sup>110</sup>
Mean keratometric cylinder:			
sutures out	4.40±2.80 D		
at 2 yrs	3.70±3.20 D <sup>113</sup>	0.40–0.60 D induced; mean 0.10 D <sup>113</sup>	+0.40 D hyperopic shift, <sup>113</sup> no change <sup>104</sup>
with sutures in at 1 yr	2.50 D <sup>109</sup>		
Mean spherical equivalent change	2.80±2.10 D <sup>114</sup>	+1.10 D induced hyperopia <sup>94, 106</sup>	+0.24 to +0.32 D <sup>111, 115</sup>
Endothelial cell loss:			
1 yr	9.0%–19.0% Fuchs <sup>†</sup> 34.0% Fuchs/PBK <sup>102, 116</sup>	37.0%, <sup>87</sup> 40% <sup>97</sup>	32.0±20.0%, 34.0% <sup>104, 110</sup> 36.0%, <sup>111, 117</sup> 25%–57% <sup>76</sup>
2 yrs	27.0%–42.0% Fuchs, 54.0% Fuchs/PBK <sup>102, 116</sup>	44.0% <sup>87</sup>	
5 yrs	69.0%–75.0% Fuchs, 61.0% Fuchs/PBK <sup>102, 116</sup>	53.0% <sup>87</sup>	42%–48% <sup>108</sup>

BCVA = best-corrected visual acuity; BSCVA = best spectacle-corrected visual acuity; D = diopter; DLEK = deep lamellar endothelial keratoplasty; DMEK = Descemet's membrane endothelial keratoplasty; DSAEK = Descemet's stripping automated endothelial keratoplasty; NA = data not available; PBK = pseudophakic bullous keratopathy; PK = penetrating keratoplasty.

\* Only includes dislocations that influenced the result; edge dislocation or tag not counted. If all dislocations are counted = 8.0%–24.0%.

† Range – two donor age groups.

### ***Endothelial Keratoplasty***

The development of EK has profoundly influenced the surgical management of corneal edema.<sup>118</sup> Prior to 2000, virtually all corneal transplant candidates with decompensated corneas underwent PK. That is in contrast to the 2022 Eye Bank Association of America's (EBAA) Statistical Report, which indicates that approximately 62% of keratoplasties done in the United States were EK versus 32% PK (see Figure 1).

### Domestic Surgery Use of U.S. Supplied Intermediate-Term Preserved Tissue

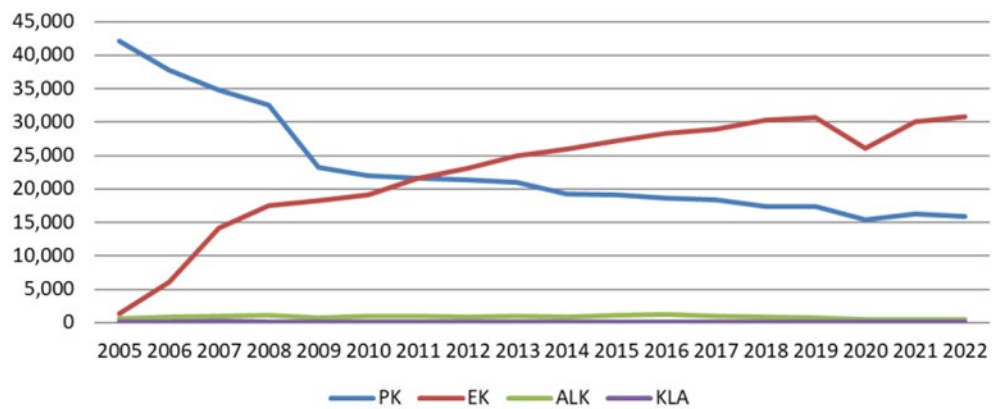


Figure 1 Number of Keratoplasties Performed in the United States Annually. Eye Bank Association of America 2021 Statistical Report.

ALK = anterior lamellar keratoplasty; EK = endothelial keratoplasty; KLA = keratolimbal allograft; PK = penetrating keratoplasty.

Furthermore, the report indicates that 95% of patients with Fuchs dystrophy were treated with EK.<sup>119</sup> This is a technique that is still improving as surgical techniques and graft handling evolve. It began as deep (posterior) lamellar endothelial keratoplasty (DLEK), which required the removal and replacement of a posterior stromal/Descemet's membrane lenticule. The optical imperfections from the stroma-to-stroma interface and dissection difficulties limited implementation of the DLEK technique, but EK surgery quickly evolved into DSEK or DSAEK. Both DSEK and DSAEK involve the removal of the recipient Descemet's membrane and its replacement with a thin donor lenticule that includes posterior stroma and Descemet's membrane. The DSEK donor tissue is usually manually prepared by the surgeon, whereas DSAEK donor tissue is pre-cut by a microkeratome. In effect, the DSAEK technique adds a posterior donor lenticule that acts as a net negative lens, causing a hyperopic shift to the optics of the eye. This shift should be taken into consideration at the time of cataract surgery when DSEK surgery is likely to follow. Finally, the recent addition of DMEK for cases of mild to moderate corneal edema enables a direct exchange of the diseased Descemet's membrane/endothelium with a healthy donor Descemet's membrane/endothelium. Unlike DSAEK, the inserted DMEK tissue will form a scroll or other folded configuration upon insertion with endothelium on the outside. The skilled DMEK surgeon can successfully and safely unfurl the tissue, center it, and place a bubble under it to attach it to the host cornea. Despite the challenges of learning a new surgical technique, it is now well accepted that EK procedures decrease long-term rejection risk,<sup>85</sup> provide more rapid visual recovery, and improved optical outcomes.<sup>120, 121</sup> (*II-, Insufficient, Discretionary*) Descemet's membrane endothelial keratoplasty accounted for 47% of all endothelial keratoplasties performed in the United States in 2021.<sup>122</sup> Cataract extraction is often performed prior to or at the same time as EK. Less IOL-power adjustment is required in DMEK compared with DSAEK; however, the accuracy of IOL power calculations is still limited with evidence of induction of corneal astigmatism.<sup>123</sup>

The broad acceptance of EK is due to the rapid visual recovery, significantly greater optical predictability (both astigmatic and refractive), smaller and more stable wounds, and decreased risk of graft rejection compared with PK.<sup>81, 82, 94</sup>

The intraoperative and postoperative surgical complications of EK are quite different from those seen with PK. Suture and wound-related complications such as suture erosion and infection, vascularization, and spontaneous or traumatic wound dehiscence encountered in PK patients are rare with EK procedures.<sup>94</sup> On the other hand, graft decentration or dislocation with the need to recenter or rebubble in the office or operating room, acute angle-closure glaucoma, and lamellar interface problems may occur with EK.

For DMEK surgery, the addition of an “S” stamp or other orientation marking to help with graft orientation and the use of SF<sub>6</sub> gas has significantly reduced the rate of iatrogenic primary graft failures and rebubbling rates.<sup>124, 125</sup> Preloaded DMEK tissue prepared by the eye bank is another innovation making insertion into the anterior chamber easier. These advances have made DMEK a leading surgical choice for standard endothelial failure with good anterior chamber visibility.

Descemet’s stripping automated endothelial keratoplasty surgery continues to be a leading surgical choice for eyes with decreased anterior chamber visibility or complex situations such as previous glaucoma surgery or iris defects. Ultrathin DSAEK tissue (defined as <100 µm thick) has shown some benefit in terms of visual recovery compared with standard DSAEK, although complication rates and refractive outcomes are similar.<sup>97</sup> Nanothin DSAEK tissue (defined as <50 µm thick) may provide similar results to DMEK though nanothin DSAEK is still an additive and not a true replacement surgery.<sup>126</sup> Descemet’s membrane endothelial keratoplasty may also be considered in eyes with similar preoperative findings.

Preparation of donor tissue for EK surgery is performed mostly by eye banks. Precutting DSAEK tissue to the surgeon’s specified thickness is routinely done. It can be more difficult to prepare DMEK tissue and the result is slightly more tissue wastage. However, in the hands of a skilled eye bank technician this is negligible.

### ***Descemet’s Stripping Only/Descemet’s Stripping without Endothelial Keratoplasty***

Primary descemetorhexis procedure with or without the use of a topical Rho kinase inhibitor to facilitate endothelial health has been successfully performed in patients with Fuchs but not PBK.<sup>127, 128</sup> This procedure involves the removal of a 4 to 5 mm central portion of Descemet’s membrane and diseased endothelium without transplantation of donor tissue. Candidates must have focal central pathology and a peripheral endothelial cell count of at least 1,000 cells/sq mm. Visual rehabilitation takes up to 6 weeks. A unique honeycomb appearing edema may occur as the cornea heals. The potential for future ex vivo expansion of injectable endothelial cells is also under investigation.<sup>129</sup>

## **Medical Management of Corneal Opacification**

Treatment of a corneal opacity can be divided into two phases: the management of the principal, initiating process (i.e., infection, trauma)<sup>14</sup> (*I-, Moderate, Strong*) and the management of the resulting problems (i.e., surface erosions and irregularity, scarring, thinning, and vascularization). This PPP is focused on the second phase.

Many corneal opacities start as persistent, nonhealing epithelial defects that opacify as a result of infection, inflammation, tissue breakdown, and/or scarring. Conventional treatment of an epithelial defect involves the use of an antibiotic drop or ointment to protect against secondary bacterial infection. The choice of antibiotic should take into account the normal flora of the skin, eyelid margin, and conjunctiva; history of contact lens wear; the patient’s immune status; and any underlying medical problems (i.e., diabetes, Parkinsonism).

Adequate blinking during waking hours and complete eyelid closure when sleeping are very important for ocular surface healing and need to be assessed in any situation where a defect persists. A temporary tarsorrhaphy with botulinum toxin or suture can be helpful when blinking or eyelid closure is inadequate. Pressure patching used to be standard treatment for abrasions and erosions; however, a study found that this does not positively impact comfort or the speed of healing.<sup>130</sup> A BCL or amniotic membrane may be helpful in cases of delayed healing.

The fact that many ocular surface defects are unresponsive to the above measures has spawned a search for alternative agents to promote ocular surface healing. Oral doxycycline,<sup>131</sup> topical N-acetylcysteine, and medroxyprogesterone have been shown to inhibit matrix metalloproteinases and have been investigated, with varying results, as ways to manage persistent epithelial and stromal defects. In vivo benefits are hard to assess, particularly in a structured, double-masked setting. Autologous serum,<sup>132</sup> cord blood tears,<sup>133</sup> and platelet-rich plasma<sup>134</sup> have demonstrated beneficial effects for persistent epithelial defects. The need to have these products prepared by a blood and eye bank and/or compounding pharmacy limits their availability. Nerve growth factor has been shown to be effective in treating nonhealing epithelial defects in the setting of

neurotrophic keratopathy.<sup>4,6</sup> Cenegermin 20 µg/ml 6 drops daily for 8 weeks with follow-up to 24 to 48 weeks showed higher rates of corneal healing than vehicle. In addition, other agents including substance P and insulin-like growth factor-1,<sup>135</sup> fibronectin,<sup>136</sup> and thymosin beta 4<sup>137</sup> have all shown some benefit in selected cases but remain investigational.

Amniotic membranes, either as an onlay<sup>73</sup> protective flap or as an inlay<sup>72</sup> tissue substitute, are thought to promote healing by their release of various anti-inflammatory, anti-angiogenic, and prohealing mediators.<sup>138-140</sup> The introduction of these membranes, attached to scleral rings<sup>141</sup> and as wafers that can be placed under a BCL, has expanded their flexibility and allows for in-office utilization.

Progressive thinning of the cornea or a small perforation usually requires structural support with the application of a tissue adhesive. A small area of marked thinning or an early descemetocoele may be coated with a thin layer of adhesive (e.g., cyanoacrylate), which may remain in place for 6 weeks or longer if applied to a clean and compact base. If located peripherally, this may be definitive treatment; if located centrally or paracentrally, the adhesive will facilitate the nonemergent repair of the defect. Leaking descemetocoeles may sometimes require the injection of an air bubble into the anterior chamber to halt the leakage temporarily while glue is applied. The area to be glued needs to be dry and de-epithelialized for the adhesive to adhere properly. Tissue adhesive will work best when the area of impending perforation is small and at the bottom of a crater and not with a ballooning descemetocoele. Various techniques have been advocated for the application of tissue glue, including the use of a 30-gauge needle, the wooden end of a cotton applicator, or a micropipette.<sup>142</sup> The least amount of glue that will seal or support the defect should be applied. While tissue adhesive has not been approved by the U.S. Food and Drug Administration (FDA) for use on the eye, it has been widely used for many years. It is advisable to use a sterile product to reduce the risk of a secondary infection. Fibrin glue should not be used with corneal perforations or descemetocoeles because it biodegrades rapidly before healing can occur. Bandage contact lenses are applied to prevent dislocation of the glue and provide comfort.

Topical corticosteroids are often used to reduce intraocular as well as corneal inflammation. Intraocular pressure and cataract formation should be monitored with long-term topical corticosteroid use. Their role in limiting corneal scar tissue development after an acute or subacute process has resolved has not been well established.<sup>143, 144</sup> Additionally, a number of studies have looked at their effect on healing and visual acuity when used in the treatment of acute corneal ulcers and overall found limited benefit to their use.<sup>145, 146</sup> The Steroids for Corneal Ulcers Trial did show some benefit in patients with central bacterial ulcers with worse initial visual acuity except those where the causative agent was *Nocardia*.<sup>146</sup> Agents that have been used to reduce the development of scar tissue following glaucoma and refractive surgery (mitomycin-C [MMC],<sup>147</sup> 5-fluorouracil,<sup>145</sup> tacrolimus,<sup>143</sup> octreotide,<sup>146</sup> and pirfenidone<sup>148</sup>) have been associated with epithelial surface toxicity at the commonly used doses<sup>149</sup> or have not been evaluated as to their anti-scarring effect in corneal disease.

Reduced vision in cases of corneal opacification is often related to surface irregularity (easily demonstrated with a keratometer or topographer) in addition to the opacity itself. An RGP lens (hybrid or scleral lens when greater stability is needed) will often improve the vision when surface irregularity is a major factor and may obviate the need for more invasive procedures. A trial fitting with spectacle overcorrection (to demonstrate potential improvement) can be performed easily in the office with a small set of RGP lenses.

Painted contact lenses and scleral shells are also available to hide an opacity when the visual potential is poor. The greater thickness of the scleral shell makes it an ideal choice when there is reduced orbital volume or phthisis bulbi. Painted contact lenses are available with a clear pupillary zone and opaque periphery for patients with peripheral opacities.

## Surgical Management of Corneal Opacification

The surgical strategy for managing corneal opacities depends on which tissue layer(s) is involved. Table 4 highlights the relationship between depth of disease and surgical alternatives.

**TABLE 4 LAYER-BASED APPROACH TO THE SURGICAL MANAGEMENT OF CORNEAL OPACITIES**

Layer of Pathology	Representative Disease	ED	SK	PTK	ALK	DALK	PK
Epithelium	Redundant, irregular epithelium	•					
Subepithelial	Salzmann nodular degeneration	•	•	•			
Bowman	Band keratopathy	•	•	•			
Bowman	Reis-Bücklers dystrophy		•	•	•		
Anterior – mid-stroma	Granular dystrophy		•	•	•	•	•
Mid-posterior stroma	Scarring				•	•	•

ALK = anterior lamellar keratectomy; DALK = deep anterior lamellar keratoplasty; ED = epithelial debridement; EK = endothelial keratoplasty; PK = penetrating keratoplasty; PTK = phototherapeutic keratectomy; SK = superficial keratectomy.

### Epithelial Debridement

Lesions anterior to Bowman's layer can be managed with epithelial debridement. Epithelial basement membrane dystrophy and recurrent erosions are examples. Complete epithelial removal is performed until the smooth, shiny Bowman's layer is exposed. Following epithelial debridement, a therapeutic BCL and prophylactic topical antibiotics are often applied. A short course of topical nonsteroidal anti-inflammatory (NSAID) drops can help control discomfort with close follow-up due to a concern for corneal melting or perforation associated with topical NSAIDs. For certain lesions, adjunctive techniques are described below.

### Management of Subepithelial Fibrosis

Subepithelial fibrosis is present in lesions such as Salzmann nodular degeneration or apical nodules that develop in keratoconic eyes. When epithelial debridement results in an irregular stromal surface, or if the subepithelial lesion is highly adherent, surgical techniques can be used to smooth the surface and reduce optical aberrations. These include use of the corneal burr and PTK, which are discussed below. For cases in which the risk of recurrent fibrosis or haze is high, adjunctive MMC can be used as a preventative and therapeutic measure.<sup>150, 151</sup>

### Management of Band Keratopathy

Band keratopathy is deposition of hydroxyapatite in the anterior surface of Bowman's layer and epithelial basement membrane from inflammation, local injury, and/or systemic hypercalcemia. It is generally asymptomatic; therefore, debridement is reserved for cases with glare, visual disability, or pain from epithelial disruption.

Surgery to remove deposits can be mechanical and/or chemical via chelation. Thick plaques can be readily extracted with forceps. Finer deposits may require epithelial debridement followed by chelation using ethylene-diamine-tetra-acetic acid (EDTA). Challenges obtaining EDTA have resulted in the use of alternative compounded sources, for which there are studies demonstrating safety and efficacy.<sup>152</sup> Treatment time and concentration of EDTA varies depending on the density of the calcium and the approach used.<sup>152</sup>

The mean time to healing may be delayed after EDTA chelation when compared with normal eyes that have a similar-sized corneal abrasion (5–7 days vs. 2–3 days). Faster re-epithelialization might be achieved by avoiding limbal exposure to EDTA and minimizing exposure.

Slower healing risks formation of stromal scarring and infection. Cases with concomitant comorbidities such as limbal stem cell deficiency, neurotrophic keratopathy, and severe dry eye, may benefit from adjunctive techniques to facilitate re-epithelialization such as amniotic membrane grafting and/or temporary tarsorrhaphy. If the ocular surface disease is severe, the risks of a keratectomy may not outweigh the benefits.

Another method to alleviate band keratopathy is PTK. Phototherapeutic keratectomy is unique in this case because calcific deposits will ablate more quickly compared with the

surrounding tissue and can result in crevices and irregularities.<sup>153</sup> Avoiding this outcome is detailed in the following section.

## Management of Anterior Stromal Opacities

Anterior corneal lesions that extend beyond Bowman layer into the anterior and mid stroma require more extensive excision than described above. The depth, diameter, and technique of stromal dissection can be guided by anterior segment OCT, UBM, or confocal microscope.

## Anterior Lamellar Keratectomy

Visually significant anterior stromal opacities can be removed by a variety of surgical techniques. “Freehand” lamellar keratectomies require minimal equipment (a microblade, lamellar dissector, or spatula), but visual outcomes may be limited by an irregular surface.<sup>154</sup> Use of excimer or femtosecond lasers, or a microkeratome, can result in a better refractive surface and improved visual acuity.

Excimer laser PTK ablates a preprogrammed depth of superficial and anterior stromal lesions within the treatment zone.<sup>155-160</sup> To avoid replicating a highly irregular surface, masking agents such as methylcellulose or sodium hyaluronate are applied to fill depressions within topographic irregularities or adjacent to deposits such as calcium.<sup>161</sup> The result is a smoother post-ablation refractive surface to improve vision.<sup>161</sup> The drawback of tissue removal is the flattening of the corneal curvature, creating a hyperopic shift. This refractive change can be mitigated by treating along the outer edge of the ablation zone with small spot ablations<sup>162</sup> or by using a refractive setting.<sup>155, 163, 164</sup>

Improvement in visual acuity is correlated with corneal transparency, corneal regularity, and optical quality.<sup>153, 165, 166</sup> In cases of simple microkeratome/femtosecond laser keratectomy or combined procedures (with PTK), the visual results (i.e., final best-corrected visual acuity [BCVA] and contrast sensitivity) show significant improvement.<sup>163</sup> In most cases, uncorrected visual acuity (UCVA) is not significantly improved at 6 months.<sup>166, 167</sup> Best-corrected visual acuity, however, is significantly improved at 2-, 6-, and 12-month time points in cases of mechanical/femtosecond flaps combined with PTK.<sup>166, 167</sup>

There are some limitations of all lamellar keratectomies including recurrence of the underlying disease process, and post-treatment surface irregularity and haze.<sup>168</sup> Application of MMC at the time of the initial or follow-up treatment has been investigated as a means of diminishing recurrent scar tissue or stromal deposits.<sup>169, 170</sup> Phototherapeutic keratectomy may also be repeated.<sup>164</sup> In some cases, such as with granular and lattice corneal dystrophies, PTK is a reasonable means to defer an eventual DALK or PK but may result in postoperative haze. Another risk is the development of corneal ectasia, particularly if ablation exceeds the anterior third of corneal stroma or if the residual stromal bed is less than 250  $\mu\text{m}$ .

As with any procedure that disrupts the protective epithelial layer, infectious keratitis can occur. The differential diagnosis should include herpes virus, which can reactivate from excimer laser exposure, corticosteroid use, and corneal trauma. Any history of herpetic eye disease warrants strong consideration for perioperative antiviral prophylaxis.<sup>171</sup>

Delayed epithelial healing tends to happen with some of the underlying conditions for which keratectomy was indicated. Autologous serum and/or amniotic membrane (self-retained, glued, or sutured) may be used to facilitate healing.

Another technique for treatment of deeper opacification is the construction of superficial corneal flaps combined with excimer laser ablation to the stromal bed.<sup>172-174</sup>

## Use of Mitomycin-C

Following superficial or anterior lamellar keratectomy, both haze and/or scarring can occur. Haze tends to be transient, but scarring is permanent with visual sequelae. Risk factors include the underlying etiology such as dystrophies, delayed re-epithelialization, and ablation depth beyond 50 to 75  $\mu\text{m}$ . Postoperative anti-inflammatory use may be

inadequate for prophylaxis against corneal scarring, and in such cases, adjunctive intraoperative MMC can be helpful.<sup>166, 167</sup>

Mitomycin-C is an alkylating agent that inhibits activation and proliferation of any cellular tissues involved in wound healing at the surgical site.<sup>175, 176</sup> The utility of this cytotoxic effect is used off-label for the prevention or treatment of corneal scars. However, there are risks, including depletion of keratocytes,<sup>177</sup> endothelial failure, and limbal stem cell deficiency. Care must be taken to ensure that the proper dose of MMC is formulated by the pharmacy and that close attention is paid to the exposure time. Definitive criteria for use of MMC, as well as the most effective method, dose, and period of application, have yet to be established for corneal disorders.

## **Corneal Tattooing**

Corneal tattooing has been used to treat corneal leukomas cosmetically and to occlude visually significant iridotomies and other iris defects. The technique involves imbedding commercially available sterile India ink or carbon particles in the anterior and mid stroma using a process similar to corneal stromal puncture or the creation of a lamellar pocket or flap (by hand or femtosecond laser) into/under which pigment is instilled.<sup>178</sup> The density and color distribution of the pigment varies from case to case.

## **Keratoplasty**

Corneal transplantation (keratoplasty) has been the mainstay of treatment for corneal opacities involving the mid and deep stroma. The dramatically reduced risk of graft rejection and traumatic wound rupture are advantages of partial thickness transplants compared with PK.

### ***Lamellar***

#### ***Anterior Lamellar Keratoplasty***

Anterior lamellar keratoplasty is a partial-thickness corneal transplant. Techniques have evolved to construct clearer stromal interfaces and improve visual outcomes.<sup>179, 180</sup>

#### ***Therapeutic Anterior Lamellar Keratoplasty***

Automated lamellar therapeutic keratoplasty is a procedure to provide tectonic support after melting disorders (e.g., central corneal ulcers, peripheral ulcerative keratitis, Terrien marginal degeneration) or peripheral ectasia (e.g., pellucid marginal degeneration, post-PK wound thinning) particularly if excessive thinning or a descemetocele develops. Central grafts are usually circular in shape, and the size is determined by the size of the defect and whether the graft's edge will impinge on the pupil. In the periphery, the pathology may be annular in nature and require a concentric donut or partial crescentic graft. In some cases, a full-thickness patch or crescentic graft is needed. Donor tissue for ALTK procedures may be partial-thickness irradiated tissue, glycerin preserved tissue, or preserved tissue provided by an eye bank.<sup>181-183</sup>

#### ***Deep Anterior Lamellar Keratoplasty***

Deep anterior lamellar keratoplasty is a surgical procedure in which all or nearly all of the corneal stroma is removed for visual rehabilitation for deep stromal opacities or scarring, corneal ectasia, and keratolysis from ocular surface disease or infectious keratitis. This technique can also be used after prior ocular procedures.

There are several benefits of DALK that preserve the patient Descemet's membrane and endothelium. An intact globe reduces the risk of intraoperative expulsive hemorrhage, globe rupture from traumatic wound dehiscence, and hastens postoperative recovery time. The second advantage is absence of endothelial rejection.<sup>184-186</sup> A lower topical steroid burden reduces steroid-induced complications. Stromal rejection is still possible, however. Most importantly, graft survival is prolonged in DALK compared with PK, which is a significant consideration, especially for young transplant recipients.

The surgical technique in DALK is more difficult than PK. The host cornea is trephined using a hand-held trephine or a femtosecond laser. Laser-assisted DALK can be used to

create various side-cut patterns that allow interlocking at the graft-host interface to facilitate wound healing and guide dissection to enable efficient stromal extraction.<sup>187, 188</sup>

A variety of surgical techniques exist to separate the posterior stroma, namely, the Melles stromal pocket, Anwar's big-bubble technique, and manual dissection techniques.<sup>24, 189-192</sup> The donor is fixated in place using suture techniques similar to PK.

### Outcomes

Most of the studies comparing DALK and PK relate to keratoconus; however, similar results and issues would be expected to apply to noninflammatory, nonvascularized and nonprogressive central corneal opacities as well. The studies comparing visual results of these procedures in keratoconus patients appear conflicting until they are viewed according to residual posterior stroma. Greater variation in the postoperative visual acuity and contrast sensitivity following DALK has been correlated to increased thickness of the residual recipient posterior stromal bed and donor-host interface reaction. When baring of Descemet's membrane is achieved, visual results are reported to be comparable with those of PK.<sup>185, 193-199</sup> Unfortunately, baring of Descemet's membrane is not consistently achieved; successful baring has been reported in 47% to 82% of eyes, even in experienced hands.<sup>189, 196, 200, 201</sup> Conversion to a full-thickness PK may be required if there is perforation of the Descemet's membrane. The need for conversion may be associated with the surgeon's learning curve and may decrease with increased surgeon experience with DALK surgery.<sup>185, 200</sup> Endothelial cell loss was significantly lower with DALK performed without Descemet's membrane perforation when compared with full-thickness keratoplasty.<sup>201-205</sup> Corneas with high-risk features such as more than 1 quadrant of deep vascularization, ocular surface disease, concomitant glaucoma, and/or peripheral anterior synechiae have significantly longer graft survival with DALK than PK. See Table 5.

**TABLE 5 Survival Rates for DALK and PK**

	Overall		High Risk		Low Risk	
	DALK	PK	DALK	PK	DALK	PK
Year 1	95.8%	94.4%	84.6%	90.3%	97.6%	96%
Year 5	93.9%	80.4%	82.1%	59%	95.8%	88.9%
Year 10	93.9%	72.1%	82.1%	48.7%	95.8%	81.1%

DALK = deep anterior lamellar keratoplasty; PK = penetrating keratoplasty; PTK = phototherapeutic keratectomy.

Note: The table is based on the 2021 article by Arundhati.<sup>206</sup>

The indication for keratoplasty also played a role in long-term outcomes. Survival at 10 years was highest for keratoconus followed by post-infectious scars, and worst for inflammatory disorders such as Stevens-Johnson syndrome or ocular cicatricial pemphigoid.

A small study compared visual functions between DALK and PK. There was no statistical significance between the two keratoplasty techniques for higher order aberrations, objective/ocular scatter index, measures of optical quality (e.g. modular transfer function, Strehl ratio), or corneal cylinder.<sup>207</sup>

Patient quality of life a year or more following corneal transplantation with either DALK or PK was not significantly different.<sup>208</sup>

### Complications

Complications related to DALK include suture-abscess formation, surface erosions, interface scarring/opacities, infectious keratitis, neovascularization, and stromal graft rejection and failure. Endothelial rejection, however, is not seen.

Complications that are unique to DALK include rupture of Descemet's membrane while attempting to separate it from the overlying stroma (more likely with scarring that involves Descemet's membrane or a history of a Descemet's membrane rupture



[spontaneous, as with hydrops, or surgical])). The risk of Descemet's membrane perforation is higher with a deeper stromal scar.<sup>209</sup>

When the rupture is small, the procedure may be completed or, if large, conversion to PK may be needed. If lamellar keratoplasty is attempted in the presence of a larger perforation, fluid may accumulate in the space between Descemet's membrane and the graft, resulting in a double anterior chamber.<sup>210</sup> Delayed Descemet's membrane detachment can also occur later when the endothelium repopulates the posterior cornea or if there is traction with progressive fibrosis.

Studies on visual outcomes after DALK demonstrate a benefit of thinner residual stroma defined as less than 80  $\mu\text{m}$ .<sup>211</sup> Furthermore, baring of Descemet's membrane in DALK results in acuity equivalent to PK.<sup>212</sup>

Overall, allograft rejection occurs at a much lower rate in DALK compared with PK (1.9% vs. 7.8%, respectively).<sup>206</sup> In DALK, the incidence of stromal rejection was reported between 2% and 12%, and reversal can usually be achieved with topical corticosteroids.<sup>213</sup>

Endothelial cell loss after DALK is biphasic. There is loss from intraoperative manipulation particularly if Descemet's membrane is perforated. Then there is a slow, chronic decline of about 3.9% annually, which is higher than physiologic endothelial loss.<sup>202</sup>

Post-DALK infections can be related to the suture, nonhealing epithelium, pathogens sequestered at the interface, or postsurgical endophthalmitis. Bacterial, atypical bacteria, and fungi are generally the causative pathogens. In the case of interface infection, surgical treatment is generally needed to resolve the multiple infiltrates at the donor-host interface. The donor button can be exchanged or a PK can be performed.<sup>214, 215</sup>

When used as a therapeutic measure in Acanthamoeba keratitis, obtaining a big bubble was more difficult. Recurrent infection was noted in 20% of cases, and therefore measures to avoid these outcomes should be undertaken such as confocal microscopy or creating a large margin around the involved cornea. Another issue is the high graft failure rate, which was reported up to about 60%, mostly from poor endothelial function.<sup>216</sup>

## ***Penetrating Keratoplasty***

### *Indications*

The objectives of PK depend on the corneal pathology and related problems. Visual improvement is the most common reason for a full-thickness cornea transplant. Another important indication is to restore structural support when a cornea is thin or perforated.

### *Pediatric keratoplasty*

According to data from the EBAA, the majority of pediatric corneal transplants are performed for ectasias and thinning followed by congenital opacities.<sup>217</sup> In contrast, global indications include infectious keratitis and chemical or mechanical trauma.<sup>218</sup>

Assessment of the patient's overall health, support system, and laterality of the corneal opacification all play a role in the timing of surgical intervention to gain the optimal outcome. The critical period of visual development ranges from 2 to 6 months after birth, and it's shorter for unilateral versus bilateral media opacities. Among pediatric corneal ophthalmologists, surgical intervention is preferred between 1 to 3 months of age.<sup>219</sup> However, one study that included both unilateral and bilateral cases observed no difference in visual acuity and graft survival when keratoplasty was performed from age 0 to 90 days compared with age 3 to 12 months.<sup>220</sup> Amblyopia management is important to achieve an optimal outcome, so co-management with a pediatric optometrist or ophthalmologist is recommended.

### *Alternative Types of Keratoplasty*

Crescentic patch grafts and rotational autografts are special forms of PK. Peripheral opacities that are associated with significant tissue loss and increased astigmatism (e.g., Terrien marginal degeneration, postinfectious keratitis) but with a clear central cornea

may require either partial or full-thickness grafting. These may take the form of oval or crescentic grafts.<sup>221, 222</sup>

In some situations, a central corneal scar may be managed by an ipsilateral rotational full-thickness autograft. The graft position is offset (rather than in the more typical central position) so that, on rotation, the scar is shifted into the far periphery.<sup>223</sup> Care should be taken to avoid having the graft-host junction too close to the pupil, causing postoperative distortion. Because of the eccentricity of the graft, irregular astigmatism is a common postoperative problem that has limited the use of this approach.<sup>224</sup>

Oversized or tectonic grafts are typically used in conditions of significant peripheral thinning (e.g., decentered keratoconus, pellucid marginal degeneration, or keratoglobus) or infection (e.g., sclerokeratitis) when the peripheral edge of the pathologic process extends beyond the central 7.5 to 9.0 mm. In some cases, the treatment should be staged. The first stage is an eccentric corneal patch that thickens the stromal bed. Months later, the second stage is a conventional PK through the thickened bed. Many of these cases are accompanied by other anterior segment reconstructive procedures (e.g., angle reconstruction, pupilloplasty, lensectomy, or IOL repositioning).

Opacified corneas may at times be associated with serious vitreoretinal pathology (e.g., following accidental or surgical trauma). The opacified cornea will preclude the safe repair of the retina. A temporary plastic or silicone corneal insert—typically referred to as a temporary keratoprosthesis—may be placed at the time of the retinal surgery, left in place for the duration of the vitreoretinal procedure, and then removed and replaced with a full-thickness penetrating graft. The view through the temporary keratoprosthesis is excellent and, in most cases, is superior to the view through the alternative, a recently performed corneal transplant.

Autokeratoplasty is another option reserved for functionally monocular patients. In this technique, the clear cornea from the blind eye is transplanted to replace the opacified cornea of the eye with visual potential.<sup>225</sup>

Femtosecond laser-assisted keratoplasty utilizes the femtosecond laser for trephining both the donor and recipient corneas. Trephination with top-hat, mushroom, or zigzag patterns have greater wound surface area that might result in faster wound healing and a stronger interface. As a result, sutures can be removed earlier with overall quicker visual rehabilitation.<sup>187, 226-229</sup> Another advantage specifically of the top-hat pattern is preserving more host endothelium.<sup>230</sup>

Studies have shown that FLAK results in less astigmatism in the early postoperative period compared with conventional PK techniques, but by 6 months there is no significant difference.<sup>227</sup> On the contrary, the quality of vision demonstrates the advantage of FLAK based on higher order aberrations compared with conventional PK.<sup>231</sup>

Access, logistics, cost, and lack of insurance reimbursement for a femtosecond laser limits its use.

### *Outcomes*

Outcomes, defined as graft clarity and visual improvement, can be quite varied in this diverse group of conditions. In the case of a nonvascularized central scar with no other related ocular damage, the percent achieving graft clarity is well over 90%.<sup>232</sup> This is in contrast to scarring related to a chemical injury where there is also extensive corneal vascularization and limbal stem cell damage, in which the success rate is quite poor. Therefore, the limbal stem cell deficiency must be addressed before keratoplasty. Visual acuity will often depend on whether other factors such as a cataract, glaucomatous damage, or retinal pathology are present. Variable and unpredictable postkeratoplasty astigmatism remains an issue. It is common practice for surgeons to leave sutures in place long term when selective suture removal has achieved a low level of astigmatism and good vision. The disadvantage of this practice is the risk of late suture breakage, irritation, and infection or rejection.<sup>233, 234</sup>

### *Contraindications*

Corneal transplant success is improved by addressing as many active or concomitant problems as possible in advance of the surgery. Good control of IOP, resolution of adnexal and intraocular inflammation and infection (e.g., chronic dacryocystitis, blepharitis, conjunctivitis, keratitis), and repair of any eyelid abnormality (e.g., trichiasis, entropion, ectropion, lagophthalmos, and exposure) are crucial. The presence of thinned areas in which a graft-host thickness mismatch may occur, deep stromal vascularization that may increase the risk of rejection, and ocular surface disease (e.g., dry eye, past chemical or radiation injury, OMMP, or Stevens-Johnson syndrome) are important factors contributive to reduced graft survival.

### *Complications*

Complications can be divided into those that occur during surgery and those that occur afterward.

#### **Intraoperative**

- ◆ Scleral perforation with fixation suture
- ◆ Improper trephination
- ◆ Damaged or lost donor button
- ◆ Retained Descemet's membrane
- ◆ Iris damage
- ◆ Lens loss
- ◆ Torn posterior lens capsule with or without vitreous loss
- ◆ Lens damage or dislocation
- ◆ Anterior chamber or vitreous hemorrhage
- ◆ Vitreous posterior pressure
- ◆ Suprachoroidal hemorrhage

#### **Postoperative**

- ◆ Rejection
- ◆ Graft interface dehiscence
- ◆ Irregular astigmatism
- ◆ Primary or late graft failure
- ◆ Wound leak or misalignment
- ◆ Persistent epithelial defect
- ◆ Filamentary keratitis
- ◆ Suture-related immune infiltrate
- ◆ Suture infection/abscess
- ◆ Cataract
- ◆ Endophthalmitis
- ◆ Elevated IOP
- ◆ Blepharoptosis
- ◆ Anterior synechia formation
- ◆ Hyphema
- ◆ Choroidal detachment
- ◆ Retinal detachment
- ◆ IOL dislocation

- ◆ Graft dislocation
- ◆ Lamellar interface infection

Primary graft failure occurs when the donor tissue fails to clear during the first 8 weeks postoperatively in the absence of other problems that may be causing stromal edema (e.g., a persistent epithelial defect, elevated IOP, rejection, or inflammation). It is thought to be due to inadequate endothelial cell function because of a damaged endothelium or an inadequate number of cells. It is generally viewed as a problem related to corneal selection, processing, or storage. Excess trauma or manipulation of the donor tissue at the time of surgery can also lead to primary graft failure. Management generally requires regrafting.

Endophthalmitis following PK is a rare but disastrous complication of corneal transplantation. In addition to traditional periocular sources that inoculate the eye intraoperatively or postoperative defects in the ocular surface or interface, pathogens may also originate from the donor tissue and/or storage media. Routine cultures of the donor rim correlate poorly with bacterial endophthalmitis and fungal cultures have a low positive predictive value for the development of infection.<sup>235</sup> Therefore, fungal cultures may be considered, but management still depends on the clinical signs of endophthalmitis.

Late graft failure refers to failure of the donor tissue when it occurs years after the transplant. This is thought to be related to progressive endothelial cell loss,<sup>102, 116, 236</sup> but it may be accelerated by prior rejection reactions, infections, traumatic iritis, or elevated IOPs. Excess manipulation of the donor tissue at the time of surgery, shallowing of the anterior chamber due to wound dehiscence, or repositioning or rubbing of the donor tissue following EK may also contribute to premature graft failure.

Corneal transplant rejection reactions are the most frequent cause of corneal graft failure. Early aggressive treatment with topical, periocular, and systemic corticosteroids may be able to reverse an endothelial rejection reaction. Identification of high-risk cases or those with a history of recurrent inflammation (e.g., herpes simplex virus keratitis, herpes zoster ophthalmicus, uveitis) is important because standard treatment protocols following PK may need to be augmented with higher daily doses of corticosteroid or oral antiviral agents. Two studies that specifically compared the results of PK and DSAEK in Fuchs dystrophy and PBK showed no statistically significant difference between the two groups with regard to rejection rates.<sup>83, 84</sup> However, more recent studies suggest that the less allogenic tissue that is implanted into the eye (as in EK tissue), the lower the long-term risk of rejection.<sup>106</sup> Maintaining the patient on long-term topical steroid may reduce the risk of rejection, but the patient should be monitored for steroid-related pressure increase and infectious keratitis (e.g., infection crystalline keratitis).

In 2012, EK surpassed PK as the most commonly performed type of keratoplasty in the United States.<sup>237</sup> Along with the popularity of EK came an increase in fungal infections, from 0.014% in a 2013 report to 0.023% in a 2016 report.<sup>238-240</sup> Multiple studies show positive fungal culture donor rims to have predictive value with three quarters of the mate tissues also having a positive rim culture, and two thirds of those with a culture-positive mate resulted in an infection.<sup>235, 239-242</sup> This highlights the importance of fungal cultures and sharing results with the source eye bank so that the mate tissue recipient may be more closely monitored. Currently, there is no consensus as to prophylactic antifungal treatment when a positive fungal culture is discovered. Research on antifungal supplementation of cold corneal-storage media is ongoing.

## Keratoprosthesis

Ophthalmologists have pursued the ideal artificial cornea for well over 100 years, with glass as the first material.<sup>243</sup> Innovative designs, materials, and surgical procedures have characterized this endeavor. Cardona,<sup>244</sup> osteo-odonto-keratoprosthesis,<sup>245</sup> AlphaCor,<sup>246</sup> and the Boston keratoprosthesis<sup>247, 248</sup> are designs that have attracted the most interest over the past decades.

The Boston type 1 keratoprosthesis (BKPro) is the most commonly used artificial cornea. When it was FDA approved in 1992, it was initially for cases that would be poor

candidates for other forms of corneal transplantation such as severe bilateral corneal blindness due to multiple corneal transplant failures.<sup>249-252</sup> Since then, the BKPro has been used in the management of ocular trauma,<sup>253, 254</sup> herpetic keratitis,<sup>255, 256</sup> aniridia,<sup>257</sup> Stevens-Johnson syndrome,<sup>258</sup> limbal stem cell deficiency, silicone oil filled eyes, neurotrophic keratopathy, and extensive corneal neovascularization.

The BKPro consists of a full-thickness corneal graft carrying a central polymethylmethacrylate (PMMA) optic with a power in 1 diopter increments corresponding to the axial length of the recipient. The main advantage is that this is an option for vision in patients who are not candidates for other forms of corneal transplantation. Visual acuity improved to 20/200 or better in 50% to 65% of patients at 3 years of follow-up, with a device retention rate of 80% to 87.8% at last follow-up.<sup>259</sup> Quality of life measures also demonstrated significant gains.<sup>260</sup>

The retention rate of the Boston type 1 keratoprosthesis at 1 year, 2 years, and 5 years is 90% to 92%,<sup>261, 262</sup> 80% to 88%,<sup>251, 261, 263</sup> and 74%, respectively.<sup>264</sup> Retention also depends on ocular comorbidities, which can reduce the retention rate to 37.5% to 55% in patients with autoimmune conditions such as Stevens-Johnson syndrome and mucous membrane pemphigoid.

The design's limitation is its nonbiointegrated optic. The permanent interface between biologic tissue and the prosthetic material can lead to persistent nonhealing epithelial defects, sterile necrosis, and perforation. Risks to the structural integrity of the eye predisposes to vision-threatening endophthalmitis, so lifelong antimicrobial prophylaxis is recommended. The prophylaxis for a typical BKPro is either a daily instillation of polymyxin B combined with trimethoprim or a fourth-generation fluoroquinolone with or without vancomycin. High-risk patients with an autoimmune condition and/or monocular patients require dual coverage with vancomycin combined with polymyxin B/trimethoprim or a fourth-generation fluoroquinolone daily, or a fluoroquinolone with chloramphenicol daily.<sup>265</sup> Any suspicion of fungal infiltrates on the therapeutic contact lens or along the stem of the prosthetic warrant immediate discontinuation of topical corticosteroids and use of natamycin 5%, amphotericin B, or voriconazole 1%. Soft therapeutic BCLs are also routinely used to improve retention of the BKPro device by preventing microtrauma and desiccation of the ocular surface.

Adjunctive therapies are particularly effective in maintaining excellent outcomes for corneas affected by limbal stem cell deficiency, and they deserve extra attention in cases such as chemical injury, autoimmune cicatricial conjunctivitis, and herpes zoster, which tend towards worse anatomic and functional success.<sup>259</sup> Optimizing the ocular surface with limbal stem cell transplantation, mucous membrane grafting, or amniotic membranes prior to BKPro may be beneficial.<sup>249-251, 261, 266-269</sup> (*II++*, *Moderate*, *Discretionary*) Success with concomitant conjunctival flaps have also been reported.<sup>268</sup>

Glaucoma is the leading cause of permanent vision loss with BKPro use. As much as 72% to 89% of patients undergoing keratoprosthesis placement already have glaucoma; 14% to 36% develop glaucoma; and 13% to 33% suffer progression of glaucoma. The cause and progression of glaucoma is multifactorial, with progressive angle closure and chronic intraocular inflammation as important contributing causes.<sup>270</sup> Since management of glaucoma is complicated by the inability to reliably measure IOP after implantation, a low target pressure by finger palpation is advised. When tube-shunt surgery is performed prior to or concomitant with keratoprosthesis implantation, the rate of glaucoma progression in eyes with poorly controlled IOP was as low as 2% with 17 months of follow-up. Others, however, report rates as high as 38%, particularly when patients with other co-morbidities such as autoimmune ocular surface diseases were included. Reassessment of the optic nerve and visual field studies are necessary to monitor these patients optimally and preserve their vision.<sup>271-273</sup>

Other complications include hypotony, inflammation, and retroprosthetic membranes. (See Table 6 for the incidence of each complication.) The incidence of postoperative complications tended to decrease significantly over the first 10 years in patients who had BKPro for previous graft failure.<sup>274</sup> Management of BKPro may require a multispecialty approach with glaucoma and retina specialists.

There are no long-term comparisons of keratoprosthesis to PK.<sup>275</sup> Pediatric cases are also not ideal for BKPro implantation, particularly as primary treatment.<sup>276</sup>

For cases that are not ideal for the BKPro type 1 because of advanced ocular surface compromise, the Boston type 2 keratoprosthesis<sup>247</sup> may be an alternative. A complete tarsorrhaphy is performed with the PMMA optic projecting through the eyelid. Also, the osteo-odonto-keratoprosthesis has been implanted with some success in cases such as Stevens-Johnson syndrome and OMMP.<sup>245</sup>

**TABLE 6** COMPLICATIONS OF BOSTON KERATOPROSTHESIS<sup>259, 264, 277, 278</sup>

Complication	Incidence
Glaucoma <sup>251, 278</sup>	Pre-existing in 72.0%–86.0%; 14%–39.3% new/progressive
Retroprosthetic membrane formation <sup>102, 250, 261, 274, 278, 279</sup>	25.0%–55.0%
Vitreoretinal complications: detachments, hemorrhage, cystoid macular edema, choroidal effusion, epiretinal membrane, vitreous hemorrhage, vitritis, choroidal detachment <sup>278</sup>	14%–29.5%
Persistent epithelial defects <sup>261</sup>	38.0%
Stromal necrosis <sup>261, 278</sup>	11%–16.0%
Endophthalmitis <sup>251, 278</sup>	6.1%–12.5%
Uveitis/sterile vitritis	8.9%
Infectious keratitis <sup>261, 280</sup>	8.0%

NOTE: Changes in prosthetic design, the use of therapeutic hydrophilic contact lenses, and the chronic use of topical antibiotics have reduced the frequency of many of these complications. Complication rates will also vary based on preoperative etiology.

## Follow-up Evaluation

The urgency in cases involving corneal edema and scarring is highly variable. Emphasis on the patient's vigilance deserves mention. New or worse pain, redness, photophobia, and/or vision can herald disruption of the ocular surface, infection, inflammation, recurrence, or worsening that prompts immediate medical attention. Timely diagnosis and intervention is paramount to limit ocular complications and improve outcomes.

Follow-up intervals to ensure clinical improvement or stability in the diagnostic phase is based on clinical judgment. Likewise, monitoring after intervention, whether it is conservative medical measures or postoperative care, requires acumen to dictate intervals of clinical visits.

For the management of corneal opacification, follow-up is required to monitor corneal clarity and the degree of surface irregularity. Coexisting problems, particularly intraocular inflammation and IOP (which may be caused by underlying problems or by treatment), need to be reassessed regularly (See Appendix 3 for additional information on determining of IOP in diseased or postsurgical corneas.)

## PROVIDER AND SETTING

The ophthalmologist in the outpatient setting is best equipped to diagnose many of the conditions that result in corneal opacification and corneal edema. The medical management may also be within the experience and expertise of a comprehensive ophthalmologist. It should be noted that infants and young children may require evaluations under anesthesia to obtain all the information necessary to determine a course of treatment. Superficial keratectomies and excimer laser PTKs can often be performed in the office setting or in minor-procedure suites. However, most other procedures require the facilities and sterile conditions found in an operating room.

## COUNSELING AND REFERRAL

Once a definitive diagnosis is made and the related work-up has been completed, a detailed discussion of the causes of the edema or opacity, and of various treatment options, becomes important. When more sophisticated diagnostic or medical management approaches (i.e., those exceeding the training or the level of comfort of the treating physician) are required, or if complex surgical treatments may be needed, the corneal subspecialist may be more equipped to handle the situation. At this point, referral for consultation to a corneal specialist is recommended. Referrals to retina, glaucoma, or pediatric ophthalmic subspecialists may be needed in some situations. Once the condition has been resolved or has stabilized, referral back to the comprehensive ophthalmologist is appropriate. A team approach is often of great advantage, particularly when geography makes subspecialist visits challenging. The primary care physician should be included in the discussion, especially when surgery is being considered.

When the disease process or its management is complex, every effort should be made to counsel the patient appropriately. This will enable the patient to understand the challenges involved in care more clearly, to have appropriate expectations, and to make informed decisions.

## SOCIOECONOMIC CONSIDERATIONS

Globally, corneal opacity is the fifth leading cause of bilateral blindness.<sup>281</sup> Of the 7 to 9 million people with bilateral corneal blindness, 90% live in the low- to middle-income countries.<sup>282</sup> Major causes of global corneal blindness include infectious keratitis from bacteria, fungi, viruses, or parasites. Another major cause is ocular trauma, which has visual impact by itself, but in areas with limited medical care, this condition is further complicated by the inability to prevent and/or manage post-traumatic infections. Major investments in public health infrastructure and primary eye care services have built a strong foundation for preventing future corneal blindness, as nearly 80% of all corneal blindness is avoidable.<sup>283</sup>

Corneal diseases are associated with poverty and lead to a marked reduction in life expectancy, especially among children with corneal blindness. Efforts aimed at reducing corneal blindness in low- to middle-income countries are being managed through primary health interventions to combat trachoma, onchocerciasis, vitamin A deficiency, and ophthalmia neonatorum.<sup>284</sup>

The cost of harvesting and preparing donor corneal tissue, the infrastructure setup of eye banks in low- to middle-income countries, as well as the additional cost of specialized donor preparations such as precutting of tissue with microkeratome or femtosecond lasers add a financial burden to corneal transplantation. This is weighed against the financial burden of correctable causes of blindness to society.

The socioeconomic impact of corneal blindness relative to cataract blindness is not reflected just by its prevalence but is also magnified by the younger age of those with corneal blindness who have a very high number of disability-adjusted life years. Corneal blindness impacts many in their most productive and child-rearing years compared with the more geriatric population blinded by cataracts.<sup>284</sup>

## 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 they 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. INTERNATIONAL STATISTICAL CLASSIFICATION OF DISEASES AND RELATED HEALTH PROBLEMS (ICD) CODES

Corneal edema, which includes entities with the following ICD-10 classifications:

ICD-10 CM	
Idiopathic corneal edema	H18.22-
Secondary corneal edema	H18.23-
Bullous keratopathy	H18.11-
Corneal edema due to wearing contact lenses	H18.21- (corneal edema secondary to contact lenses)
Congenital glaucoma	Q15.0
Congenital hereditary endothelial dystrophy – autosomal dominant (CHED – AD)	H18.51
Congenital hereditary endothelial dystrophy – autosomal recessive (CHED – AR)	H18.51
Posterior polymorphous corneal dystrophy (PPCD)	H18.59
Intraocular inflammation	H57.8
Birth/forceps delivery trauma	P15.3
Acute angle-closure glaucoma	H40.21-
Fuchs dystrophy	H18.51
Primary hypotony	H44.44-
Hypoxia	R09.02
Iridocorneal endothelial (ICE) syndrome	H18.89-
Infectious keratitis	H16.8
Keratoconus – hydrops	H18.62-
Pseudophakic or aphakic bullous keratopathy (unilateral or bilateral)	H18.1-
Direct injury (surgical trauma)	T81.31XA

CM = Clinical Modification used in the United States; ICD = International Classification of Diseases.

Corneal opacification, which includes entities with the following ICD-10 classifications:

ICD-10 CM	
Minor corneal opacity	H17.81-
Peripheral corneal opacity	H17.82-
Central corneal opacity	H17.1-
Phthisical cornea	A18.59, H44.52-

CM = Clinical Modification used in the United States; ICD = International Classification of Diseases

Additional Information for ICD-10 Codes:

- Certain ICD-10 CM categories have applicable 7<sup>th</sup> characters. The applicable 7<sup>th</sup> character is required for all codes within the category, or as the notes in the Tabular List instruct. The 7<sup>th</sup> character must always be the 7<sup>th</sup> character in the data field. If a code that requires a 7<sup>th</sup> character is not 6 characters, a placeholder X must be used to fill in the empty characters.
- For bilateral sites, the final character of the codes in the ICD-10 CM indicates laterality. If no bilateral code is provided and the condition is bilateral, assign separate codes for both the left and right side. Unspecified codes should only be used when there is no other code option available.
- When the diagnosis code specifies laterality, regardless of which digit it is found in (i.e., 4<sup>th</sup> digit, 5<sup>th</sup> digit, or 6<sup>th</sup> digit):
  - Right is always 1
  - Left is always 2
  - Bilateral is always 3

## 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 state, 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 techniques for IOP determination in these diseased, abnormal, or surgically altered corneas is strongly advised. Such techniques are described below.

- ◆ Applanation techniques, which are measured using the following technology:
  - ◆ Pneumotonometer. 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 micro-strain 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 bi-directional 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. In this way, the device calculates an IOP independent of corneal properties. It requires 6 seconds or 6 ocular pulse cycles to determine the IOP, and it requires topical anesthesia. This is mounted to the slit lamp.
- ◆ The rebound tonometry deceleration technique utilizes an induction coil to magnetize a small plastic-tipped metal probe, which is rapidly fired against the cornea (0.25 m/sec). Software analyzes the rate of deceleration, the contact time of the probe against the cornea (approximately 0.05 sec), and the relative magnitude of which is proportional to IOP, 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. This 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 than other devices, 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 database were conducted on March 3, 2022; the search strategies are listed below. Specific limited update searches were conducted on June 7, 2023. The searches had added filters for human, English-language randomized controlled trials and systematic reviews and date limiters to capture literature published since June 27, 2018. The panel analyzed 973 studies of which 42 were included in the PPP. The literature searches with the disease condition and the search term patient values and patient preferences didn't yield results. The literature search for economic evaluation and treatment cost yielded 33 studies, 33 of which were provided to the panel, none of which merited inclusion.

**Edema/Surgery/Keratoplasty/DSEK/EK/PTK:** (corneal edema/surgery[mh]) AND (Keratoplasty, Penetrating[mh] OR Descemet Stripping Endothelial Keratoplasty[mh] OR endothelial keratoplasty[tiab] OR phototherapeutic keratectomy[tiab] OR Gunderson[tiab] OR (amniotic[tiab] AND graft\*[tiab]) OR anterior stromal punct\*[tiab])

**Edema/Surgery/Transplantation:** (corneal edema/surgery[mh]) AND (Corneal Transplantation/methods[mh])

**Edema/Therapy:** (corneal edema/drug therapy[mh] OR corneal edema/therapy[mh]) AND (sodium chloride[tiab] OR Saline Solution, Hypertonic[mh] OR hair dryer[tiab] OR bandage soft contact lens\*[tiab] OR Contact Lenses[mh] OR Intraocular Pressure[mh] OR Steroids[mh] OR Antiviral Agents[mh] OR Anti-Bacterial Agents[mh])

**Opacity/Surgery/Keratoplasty:** (corneal opacity/surgery[mh]) AND (lamellar keratoplasty[tiab] OR superficial keratectomy[tiab] OR phototherapeutic keratectomy[tiab] OR microkeratome\*[tiab] OR femtosecond[tiab] OR free-hand[tiab] OR Keratoplasty, Penetrating[mh] OR keratoprosthesis\*[tiab] OR EDTA[tiab] OR Ethylenediaminetetraacetic acid[tiab])

**Opacity/Surgery/Transplantation:** (corneal opacity/surgery[mh]) AND (Corneal Transplantation/methods[mh])

**Opacity/Therapy:** (corneal opacity/drug therapy[mh] OR corneal opacity/therapy[mh]) AND (Contact Lenses[mh] OR bandage soft contact lens\*[tiab] OR Anti-Inflammatory Agents[mh] OR Anti-Infective Agents[mh])

**Corneal Diseases/Surgery/Transplantation:** Corneal Diseases/surgery[MAJR] AND Corneal Transplantation[MAJR]

**Edema/Keratoplasty/DSEK/DLEK/PTK:** (corneal edema\*[tiab] OR corneal oedema\*[tiab]) AND (keratoplasty[tiab] OR DSEK[tiab] OR DMEK[tiab] OR DLEK [tiab] OR PK[tiab] OR PTK[tiab] OR phototherapeutic keratectomy[tiab] OR anterior stromal[tiab] OR Gunderson[tiab] OR amniotic[tiab])

**Opacity/Keratoplasty/ALTK/HALK/DALK:** (cornea\*[tiab] AND opaci\*[tiab]) AND (keratectom\*[tiab] OR keratoplast\*[tiab] OR ALTK[tiab] OR HALK[tiab] OR DALK[tiab] OR keratoplasty[tiab] OR PK[tiab] OR keratoprosthesis\*[tiab] OR EDTA[tiab] OR Ethylenediaminetetraacetic acid[tiab])

**Edema/Diagnosis:** (corneal edema/diagnosis[MAJR]) AND (pachymetry\*[tiab] OR corneal

edema/ultrasonography[mh] OR ultrasound[tiab] OR ultrasonograph\*[tiab] OR specular[tiab] OR (corneal edema/diagnosis[MAJR]) AND (Diagnostic Techniques, Ophthalmological[mh])

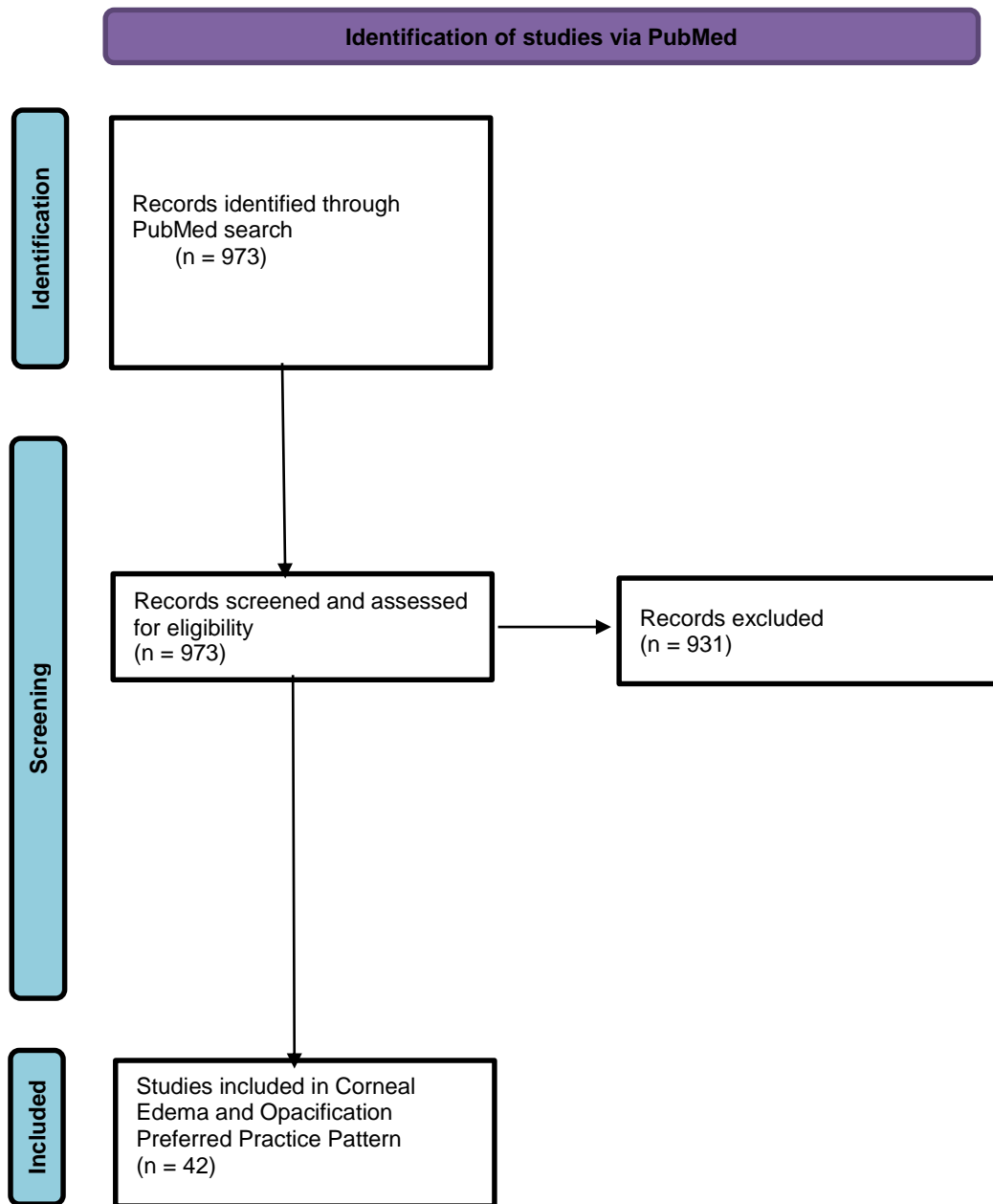
**Opacity/Diagnosis:** (corneal opacity/diagnosis[MAJR]) AND (Tomography, Optical Coherence[mh] OR Microscopy, Confocal[mh] OR potential acuity[tiab] OR overrefract\*[tiab] OR corneal opacity/ultrasonography[mh] OR ultrasound[tiab] OR ultrasonograph\*[tiab]) OR (corneal opacity/diagnosis[MAJR]) AND (Diagnostic Techniques, Ophthalmological[mh])

**Edema/Pathology/Physiology/Physiopathology:** ("corneal edema/pathology"[MAJR] OR "corneal edema/physiology"[MAJR] OR "corneal edema/physiopathology"[MAJR])

**Opacity/Pathology/Physiology/Physiopathology:** ("corneal opacity/pathology"[MAJR] OR "corneal opacity/physiology"[MAJR] OR "corneal opacity/physiopathology"[MAJR])

**Socioeconomic:** ("corneal edema"[All Fields] OR "corneal opacity"[All Fields]) AND (economics[All Fields] OR economics[MeSH Terms] OR cost[All Fields] OR cost[MeSH Terms] OR "quality of life"[All Fields] OR QoL[All Fields] OR quality of life[MeSH Terms] OR burden[All Fields] OR burden of illness[MESH Terms])

**Patient Values:** corneal edema[tiab] AND (patient values[tiab] OR patient preferences[tiab])



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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