Medical Policy

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***Current Policy Effective Date: 1/1/25**
(See policy history boxes for previous effective dates)

Title: Endothelial Keratoplasty

Description/Background

Endothelial keratoplasty also referred to as posterior lamellar keratoplasty, is a form of corneal transplantation in which the diseased inner layer of the cornea, the endothelium, is replaced with healthy donor tissue. Specific techniques include Descemet stripping endothelial keratoplasty, Descemet stripping automated endothelial keratoplasty, Descemet membrane endothelial keratoplasty, and Descemet membrane automated endothelial keratoplasty. Endothelial keratoplasty, and particularly the specific techniques mentioned, are becoming standard procedures. Femtosecond laser-assisted endothelial keratoplasty and femtosecond and excimer laser-assisted endothelial keratoplasty have also been reported as alternatives to prepare the donor endothelium.

The traditional method for cutting and shaping corneal tissue involves the use of a microkeratome, an oscillating micro-blade that thinly slices the cornea. The femtosecond clinical laser is a technology that has been developed to create corneal tissue incisions without the use of blades. This technology uses a near infrared light to create precise, three-dimensional cuts within the cornea. The computer-guided laser is focused below the surface of the cornea, and pulsating light creates thousands of microscopic bubbles within the corneal tissue. These bubbles create multiple layered patterns, thereby allowing the tissue to separate at exact predetermined sites within the donor and recipient corneal tissue.

It has been reported that the femtosecond laser is faster and more precise than traditional methods, with the ability to create smooth lamellar and side cuts. Conversely, the femtosecond laser has also introduced new complications, such as opaque bubble layering, transient light-sensitivity syndrome and rainbow glare. These potential effects must be known and understood before this technology becomes standard practice.

Corneal Disease

The cornea, a clear, dome-shaped membrane that covers the front of the eye, is a key refractive element for vision. Layers of the cornea consist of the epithelium (outermost layer); Bowman layer; the stroma, which comprises approximately 90% of the cornea; Descemet membrane; and the endothelium. The endothelium removes fluid from and limits fluid into the stroma, thereby maintaining the ordered arrangement of collagen and preserving the cornea's transparency. Diseases that affect the endothelial layer include Fuchs endothelial dystrophy, aphakic and pseudophakic bullous keratopathy (corneal edema following cataract extraction), and failure or rejection of a previous corneal transplant.

Treatment

The established surgical treatment for corneal disease is penetrating keratoplasty, which involves the creation of a large central opening through the cornea and then filling the opening with a full-thickness donor cornea that is sutured in place. Visual recovery after penetrating keratoplasty may take 1 year or more due to slow wound healing of the avascular full-thickness incision, and the procedure frequently results in irregular astigmatism due to sutures and the full-thickness vertical corneal wound. Penetrating keratoplasty is associated with an increased risk of wound dehiscence, endophthalmitis, and total visual loss after relatively minor trauma for years after the index procedure. There is also the risk of severe, sight-threatening complications such as expulsive suprachoroidal hemorrhage, in which the ocular contents are expelled during the operative procedure, as well as postoperative catastrophic wound failure.

A number of related techniques have been, or are being, developed to selectively replace the diseased endothelial layer. One of the first endothelial keratoplasty techniques was termed deep lamellar endothelial keratoplasty, which used a smaller incision than penetrating keratoplasty, allowed more rapid visual rehabilitation, and reduced postoperative irregular astigmatism and suture complications. Modified endothelial keratoplasty techniques include endothelial lamellar keratoplasty, endokeratoplasty, posterior corneal grafting, and microkeratome-assisted posterior keratoplasty. Most frequently used at this time are Descemet stripping endothelial keratoplasty, which uses hand-dissected donor tissue, and Descemet stripping automated endothelial keratoplasty, which uses an automated microkeratome to assist in donor tissue dissection. These techniques include donor stroma along with the endothelium and Descemet membrane, which results in a thickened stromal layer after transplantation. If the donor tissue comprises the Descemet membrane and endothelium alone, the technique is known as Descemet membrane endothelial keratoplasty. By eliminating the stroma on the donor tissue and possibly reducing stromal interface haze, Descemet membrane endothelial keratoplasty is considered a potential improvement over Descemet stripping endothelial keratoplasty and Descemet stripping automated endothelial keratoplasty. A variation of Descemet membrane endothelial keratoplasty is Descemet membrane automated endothelial keratoplasty. Descemet membrane automated endothelial keratoplasty contains a stromal rim of tissue at the periphery of the Descemet membrane endothelial keratoplasty graft to improve adherence and improve handling of the donor tissue. A laser may also be used for stripping in a procedure called femtosecond laser-assisted endothelial keratoplasty and femtosecond and excimer laser-assisted endothelial keratoplasty.

Endothelial keratoplasty involves removal of the diseased host endothelium and Descemet membrane with special instruments through a small peripheral incision. A donor tissue button is prepared from the corneoscleral tissue after removing the anterior donor corneal stroma by hand (e.g., Descemet stripping endothelial keratoplasty) or with the assistance of an automated microkeratome (e.g., Descemet stripping automated endothelial keratoplasty) or laser (femtosecond laser-assisted endothelial keratoplasty or femtosecond and excimer laser-assisted endothelial keratoplasty). Donor tissue preparation may be performed by the surgeon in the operating room or by the eye bank and then transported to the operating room for the final punch out of the donor tissue button. For minimal endothelial damage, the donor tissue must be carefully positioned in the anterior chamber. An air bubble is frequently used to center the donor tissue and facilitate adhesion between the stromal side of the donor lenticule and the host posterior corneal stroma. Repositioning of the donor tissue with the application of another air bubble may be required in the first week if the donor tissue dislocates. The small corneal incision is closed with 1 or more sutures, and steroids or immune-suppressants may be provided topically or orally to reduce the potential for graft rejection. Visual recovery following endothelial keratoplasty is typically 4 to 8 weeks.

Eye Bank Association of America statistics have shown the number of endothelial keratoplasty cases in the United States increased from 30710 in 2015 to 35555 in 2019.(1) The Eye Bank Association of America estimated that, as of 2016, nearly 40% of corneal transplants performed in the United States were endothelial grafts. As with any new surgical technique, questions have been posed about long-term efficacy and risk of complications. Endothelial keratoplasty-specific complications include graft dislocations, endothelial cell loss, and rate of failed grafts. Long-term complications include increased intraocular pressure, graft rejection, and late endothelial failure.

Regulatory Status

Endothelial keratoplasty is a surgical procedure and, as such, is not subject to regulation by the U.S. Food and Drug Administration (FDA). Several microkeratomes have been cleared for marketing by the FDA through the 510(k) process.

The IntraLase Fusion™ Laser was granted Section 510(k) premarket approval by the U.S. Food and Drug Administration in 2007 for use in the creation of corneal flaps in patients undergoing LASIK surgery or other treatment requiring initial lamellar resection of the cornea.

In more recent years, additional femtosecond lasers have been granted 510(k) premarket approval: FEMTO LDV devices, (formerly Femtosecond Laser), Horus Lase Keratome, iFS Laser System, IntraLase FS Laser, LenSx Laser System, Pulsion FS Laser Keratome, Technolas Fematosecond, Victus Femtosecond Laser Platform, VisuMax® Laser Keratome, VisuMax Femtosecond Laser and WaveLight® FS200.

Medical Policy Statement

Endothelial keratoplasty for the treatment of endothelial dysfunction is established. It may be considered a useful treatment option for selected indications.

The femtosecond laser, and femtosecond and excimer laser for use in endothelial disease of the cornea is experimental/investigational. Further studies are needed to evaluate the clinical utility and long-term health implications of this technology.

Inclusionary and Exclusionary Guidelines

Inclusions:
Descemet stripping endothelial keratoplasty, Descemet stripping automated endothelial keratoplasty, Descemet membrane endothelial keratoplasty, or Descemet membrane automated endothelial keratoplasty may be medically necessary for the treatment of endothelial dysfunction including:

- ruptures in Descemet membrane,
- endothelial dystrophy,
- aphakic and pseudophakic bullous keratopathy,
- iridocorneal endothelial syndrome,
- corneal edema attributed to endothelial failure,
- and failure or rejection of a previous corneal transplant
- Anterior corneal disease when endothelial disease is the primary cause of the decrease in vision

Exclusions:

- Endothelial keratoplasty when endothelial dysfunction is not the primary cause of decreased corneal clarity
- Endothelial keratoplasty used in place of penetrating keratoplasty for conditions with concurrent endothelial disease and anterior corneal disease, including any of the following:
  - Concurrent anterior corneal dystrophies
  - Anterior corneal scars from trauma or prior infection
  - Ectasia after previous laser vision correction surgery
- Femtosecond laser-assisted endothelial keratoplasty
- Femtosecond and excimer laser-assisted endothelial keratoplasty

CPT/HCPCS Level II Codes ***(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)***

Established codes:

65756 65757 V2785

Other codes (investigational, not medically necessary, etc.):

66999

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Policy Guidelines

Endothelial keratoplasty should not be used in place of penetrating keratoplasty for conditions with concurrent endothelial disease and anterior corneal disease. These situations would include concurrent anterior corneal dystrophies, anterior corneal scars from trauma or prior infection, and ectasia after previous laser vision correction surgery. Clinical input has suggested that there may be cases where anterior corneal disease should not be an exclusion, particularly if endothelial disease is the primary cause of the decrease in vision. Endothelial keratoplasty should be performed by surgeons adequately trained and experienced in the specific techniques and devices used.

Rationale

Comparative Studies
Woo et al (2019) published the results of a retrospective comparative cohort study comparing long-term graft survival outcomes and complications of patients enrolled in the Singapore Corneal Transplant Registry.(3) Patients with Fuchs endothelial corneal dystrophy and bullous keratopathy underwent Descemet membrane endothelial keratoplasty (121 eyes), Descemet stripping automated endothelial keratoplasty (423 eyes), or penetrating keratoplasty (405 eyes). Descemet membrane endothelial keratoplasty demonstrated better graft survival compared to Descemet stripping automated endothelial keratoplasty or penetrating keratoplasty in both Fuchs endothelial corneal dystrophy and bullous keratopathy. Overall cumulative graft survival was 97.4%, 78.4%, and 54.6% ($p<.001$) in Descemet membrane endothelial keratoplasty, Descemet stripping automated endothelial keratoplasty, and penetrating keratoplasty groups, respectively. In eyes with Fuchs endothelial corneal dystrophy, the graft survival was 98.7%, 96.2%, and 73.5% ($p=.009$) in Descemet membrane endothelial keratoplasty, Descemet stripping automated endothelial keratoplasty, and penetrating keratoplasty groups, respectively. In eyes with bullous keratopathy, the graft survival was 94.7%, 65.1%, and 47.0% ($p=.001$) in Descemet membrane endothelial keratoplasty, Descemet stripping automated endothelial keratoplasty, and penetrating keratoplasty groups, respectively. Graft rejection was lowest in eyes undergoing Descemet membrane endothelial keratoplasty (1.7% vs. Descemet stripping automated endothelial keratoplasty 5.0% vs. penetrating keratoplasty 14.1%; $p=.001$).

Descemet Stripping Endothelial Keratoplasty and Descemet Stripping Automated Endothelial Keratoplasty

Clinical Context and Therapy Purpose
The purpose of Descemet stripping endothelial keratoplasty and Descemet stripping automated endothelial keratoplasty is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as penetrating keratoplasty, in individuals with endothelial disease of the cornea.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with endothelial disease of the cornea. Diseases that affect the endothelial layer include Fuchs endothelial corneal dystrophy, aphakic and pseudophakic bullous keratopathy (corneal edema following cataract extraction), and failure or rejection of a previous corneal transplant.

Interventions

The therapy being considered is Descemet stripping endothelial keratoplasty and Descemet stripping automated endothelial keratoplasty.

Comparators
Comparators of interest include penetrating keratoplasty.

Outcomes
The general outcomes of interest are change in disease status, morbid events, and functional outcomes. Relevant outcome measures include visual acuity, endothelial cell densities, patient satisfaction or quality of life, and complications including graft rejection, graft dislocation, and need for rebubble procedures. Follow-up generally occurs through 1 to 2 years post-surgery.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews
In 2009, the American Academy of Ophthalmology performed a review of the safety and efficacy of Descemet stripping automated endothelial keratoplasty, identifying a level I study (RCT of precut vs. surgeon dissected) along with 9 level II (well-designed observational studies) and 21 level III studies (mostly retrospective case series).(3) Although more than 2000 eyes treated with Descemet stripping automated endothelial keratoplasty were reported in different publications, most were reported by the same research group with some overlap in patients. The main results of this review are as follows:

- Descemet stripping automated endothelial keratoplasty-induced hyperopia ranged from 0.7 to 1.5 diopters (D), with minimal induction of astigmatism (range, -0.4 to 0.6 diopters).
- The reporting of visual acuity was not standardized in studies reviewed. The average best-corrected visual acuity (BCVA) ranged from 20/34 to 20/66, and the percentage of patients seeing 20/40 or better ranged from 38% to 100%.
- The most common complication from Descemet stripping automated endothelial keratoplasty was posterior graft dislocation (mean, 14%; range, 0%-82%), with a lack of adhesion of the donor posterior lenticule to the recipient stroma, typically occurring within the first week. It was noted that this percentage might have been skewed by multiple publications from a single research group with low complication rates. Graft dislocation required additional surgical procedures (rebubble procedures) but did not lead to sight-threatening vision loss in the articles reviewed.
- Endothelial graft rejection occurred in a mean of 10% of patients (range, 0%-45%); most were reversed with topical or oral immunosuppression, with some cases progressing to graft failure. Primary graft failure, defined as unhealthy tissue that has not cleared within 2

months, occurred in a mean of 5% of patients (range, 0%-29%). Iatrogenic glaucoma occurred in a mean of 3% of patients (range, 0%-15%) due to a pupil block induced from the air bubble in the immediate postoperative period or delayed glaucoma from topical corticosteroid adverse events.
- Mean endothelial cell loss, which provides an estimate of long-term graft survival, was 37% at 6 months and 41% at 12 months. These percentages of cell loss were reported to be similar to those observed with penetrating keratoplasty.

Reviewers concluded that Descemet stripping automated endothelial keratoplasty appeared to be at least equivalent to penetrating keratoplasty regarding safety, efficacy, surgical risks, and complication rates, although long-term results were not yet available. The evidence also indicated that endothelial keratoplasty is superior to penetrating keratoplasty regarding refractive stability, postoperative refractive outcomes, wound- and suture-related complications, and risk of intraoperative choroidal hemorrhage. The reduction in serious and occasionally catastrophic adverse events associated with penetrating keratoplasty has led to the rapid adoption of endothelial keratoplasty for treatment of corneal endothelial failure.

A Cochrane review of Descemet stripping automated endothelial keratoplasty compared to Descemet membrane endothelial keratoplasty for corneal endothelial failure was published in 2018.(4) The literature search identified 4 nonrandomized trials including 72 adult participants (144 eyes) who received Descemet stripping automated endothelial keratoplasty in the first eye followed by Descemet membrane endothelial keratoplasty in the fellow eye published between 2011 and 2015. All participants met criteria for Fuchs endothelial dystrophy and endothelial failure requiring a corneal transplant. Studies reported outcomes at various time points, including 6, 12, and 6-24 months. At 1 year post-procedure, Descemet membrane endothelial keratoplasty resulted in better best-corrected visual acuity compared to Descemet stripping automated endothelial keratoplasty (mean difference, -0.14; 95% confidence interval [CI], -0.18 to -0.10 Logarithm of the Minimum Angle of Resolution [logMar] ; low-certainty evidence). Two studies reported that Descemet membrane endothelial keratoplasty provided a higher cell density at 1 year. Graft dislocations requiring rebubbling were more common using Descemet membrane endothelial keratoplasty, although this difference could not be precisely estimated (relative risk [RR], 5.40; 95% CI, 1.51 to 19.3; very low-certainty evidence). The paired, contralateral eye studies in which Descemet stripping automated endothelial keratoplasty in 1 eye preceded Descemet membrane endothelial keratoplasty in the fellow eye for all patients was found to be at high-risk for bias due to potential unknown confounding factors.

Marques et al (2019) conducted a meta-analysis of Descemet membrane endothelial keratoplasty compared to Descemet stripping automated endothelial keratoplasty for Fuchs endothelial dystrophy.(5) A literature search through August 2017 identified 10 retrospective studies of moderate methodological quality (N=947 eyes; 646 Descemet membrane endothelial keratoplasty). The primary outcome consisted of the mean difference in best-corrected visual acuity at 3, 6, and 12 months post-procedure. Secondary outcomes included rates of graft failure, rejection, rebubbling, endothelial cell density, subjective visual outcomes, and patient satisfaction. Best-corrected visual acuity was improved with Descemet membrane endothelial keratoplasty at all time points compared to Descemet stripping automated endothelial keratoplasty (12 months: 0.16 logMAR vs. 0.30 logMAR; p<.001). Descemet membrane endothelial keratoplasty had a 60% reduced rate of rejection (RR, 0.4; 95% CI, 0.24 to 0.67; p=.0005) but required more rebubblings (RR, 2.48; 95% CI, 1.32 to 4.64; p=.005).

Descemet membrane endothelial keratoplasty had an increased number of primary graft failures and less endothelial cell density loss; however, these differences did not reach statistical significance. More patients reported being satisfied after Descemet membrane endothelial keratoplasty (odds ratio [OR], 10.29; 95% CI, 3.55 to 29.80; p<.0001).

Randomized Controlled Trials

Chamberlain et al (2018) compared clinical outcomes of ultrathin-Descemet stripping automated endothelial keratoplasty with Descemet membrane endothelial keratoplasty in patients with damaged or diseased endothelium from Fuchs endothelial dystrophy or pseudophakic bullous keratopathy in the Descemet Endothelial Thickness Comparison Trial (DETECT).(6) The primary outcome measure was best spectacle-corrected visual acuity (BSCVA) at 6 months. Secondary outcomes included 3- and 12-month best spectacle-corrected visual acuity, endothelial cell counts, and complications. The study included 50 eyes from 38 patients with 25 eyes randomized to each treatment arm. Compared to ultrathin Descemet stripping automated endothelial keratoplasty, Descemet membrane endothelial keratoplasty had superior visual acuity results. Best spectacle-corrected visual acuity was 1.5 lines better at 3 months (95% CI, 2.5 to 0.6 lines better; p=.002), 1.8 lines better at 6 months (95% CI, 2.8 to 1.0 lines better; p<.001), and 1.4 lines better at 12 months (95% CI, 2.2 to 0.7 lines better; p<.001). Average endothelial cell counts were 1855 cells/mm^2 in Descemet membrane endothelial keratoplasty and 2070 cells/mm^2 in ultrathin Descemet stripping automated endothelial keratoplasty at 12 months (p=.051). Intraoperative and postoperative complications rates were not statistically different between groups. Duggan et al (2019) reported an update on corneal higher-order aberrations after ultrathin Descemet stripping automated endothelial keratoplasty versus Descemet membrane endothelial keratoplasty in DETECT.(7) In patients receiving Descemet membrane endothelial keratoplasty, the posterior corneal surface had significantly fewer coma aberrations (p≤.003) and total higher-order aberrations (p≤.001) at 3, 6, and 12 months post-surgery compared to ultrathin Descemet stripping automated endothelial keratoplasty. Descemet membrane endothelial keratoplasty was found to decrease whereas ultrathin Descemet stripping automated endothelial keratoplasty was found to increase posterior corneal higher-order aberrations compared with presurgical values, potentially accounting for the better visual acuity observed with Descemet membrane endothelial keratoplasty. Hirabayashi et al (2020) reported on an update of corneal light scatter outcomes as measured by densitometry in DETECT.(8) Both Descemet membrane endothelial keratoplasty and ultrathin Descemet stripping automated endothelial keratoplasty were found to improve the degree of corneal light scatter after surgery, with no differences between groups observed at 12 months post-surgery.

Dunker et al (2020) published the results of a prospective, multicenter RCT comparing the efficacy of ultrathin Descemet stripping automated endothelial keratoplasty (n = 25) versus Descemet membrane endothelial keratoplasty (n = 29) in patients with Fuchs endothelial corneal dystrophy.(9) Fifty-four patients were enrolled from 6 corneal centers in the Netherlands. There was no significant difference in best spectacle-corrected visual acuity at 3 (p =.15), 6 (p=.20), or 12 months post-surgery (p=.06), between study arms. However, the percentage of eyes achieving 20/25 Snellen vision was significantly higher with Descemet membrane endothelial keratoplasty at 12 months (p=.02).

Observational Studies

Fuest et al (2017) compared 5-year visual acuity outcomes in patients receiving Descemet stripping automated endothelial keratoplasty (n=423) or penetrating keratoplasty (n=405) in the

Singapore Cornea Transplant Registry.(10) Mean age of patients was 67 years. The Descemet stripping automated endothelial keratoplasty group had a higher percentage of Chinese patients, a higher percentage of patients with Fuchs endothelial dystrophy, and a lower percentage of patients with bullous keratopathy than the penetrating keratoplasty group. Controlling or preoperative best spectacle-corrected visual acuity, which differed significantly between groups, patients receiving Descemet stripping automated endothelial keratoplasty experienced significantly better vision through 3 years of follow-up than patients undergoing penetrating keratoplasty. Four- and 5-year follow-up measures showed similar best spectacle-corrected visual acuity among both treatment groups. Subgroup analyses by Fuchs endothelial dystrophy and bullous keratopathy showed similar patterns of significantly better vision through the first 3 years of follow-up in patients receiving Descemet stripping automated endothelial keratoplasty than in patients receiving penetrating keratoplasty.

Heinzelmann et al (2016) reported on 2-year outcomes in patients who underwent endothelial keratoplasty or penetrating keratoplasty for Fuchs endothelial dystrophy or bullous keratopathy.(11) The study included 89 eyes undergoing Descemet stripping automated endothelial keratoplasty and 329 eyes undergoing penetrating keratoplasty. The postoperative visual improvement was faster after endothelial keratoplasty than after penetrating keratoplasty. For example, among patients with Fuchs endothelial dystrophy, 50% of patients achieved a best-corrected visual acuity of Snellen 6/12 or more 18 months after Descemet stripping automated endothelial keratoplasty versus more than 24 months after penetrating keratoplasty. Endothelial cell loss was similar after endothelial keratoplasty and penetrating keratoplasty in the early postoperative period. However, after an early decrease, endothelial cell loss stabilized in patients who received endothelial keratoplasty whereas the decrease continued in those who had penetrating keratoplasty. Among patients with Fuchs endothelial dystrophy, there was a slightly increased risk of late endothelial failure in the first 2 years with endothelial keratoplasty than with penetrating keratoplasty. Graft failure was reported to be lower among patients with bullous keratopathy compared with patients with Fuchs endothelial dystrophy (numbers not reported).

Longer-term outcomes have been reported in several studies. Five-year outcomes from a prospective study conducted at the Mayo Clinic were published by Wacker et al (2016).(12) The study included 45 participants (52 eyes) with Fuchs endothelial dystrophy who underwent Descemet stripping endothelial keratoplasty. Five-year follow-up was available for 34 (65%) eyes. Mean high-contrast best spectacle-corrected visual acuity was 20/56 Snellen equivalent presurgery and decreased to 20/25 Snellen equivalent at 60 months. The difference in high-contrast best spectacle-corrected visual acuity at 5 years versus pre-surgery was statistically significant ($p<.001$). Similarly, the proportion of patients with best spectacle-corrected visual acuity of 20/25 Snellen equivalent or better increased from 26% at 1 year post-surgery to 56% at 5 years ($p<.001$). There were 6 graft failures during the study period (4 failed to clear after surgery, 2 failed during follow-up). All patients with graft failures were regrafted.

Previously, 3-year outcomes after Descemet stripping automated endothelial keratoplasty were reported by an eye institute.(13) This retrospective analysis (2012) included 108 patients who underwent Descemet stripping automated endothelial keratoplasty for Fuchs endothelial dystrophy or pseudophakic bullous keratopathy and had no other ocular comorbidities. Best spectacle-corrected visual acuity was measured at 6 months and 1, 2, and 3 years. Best spectacle-corrected visual acuity after Descemet stripping automated endothelial keratoplasty improved over 3 years of follow-up. The percentage of patients who reached a best spectacle-corrected visual acuity of 20/20 or greater was 0.9% at baseline, 11.1% at 6 months, 13.9% at 1 year, 34.3% at 2 years, and 47.2% at 3 years. Ninety-eight percent of patients reached a best spectacle-corrected visual acuity of 20/40 or greater by 3 years. Tables 1 and 2 describe the characteristics and results of key nonrandomized trials.

Table 1. Summary of Key Nonrandomized Trial Characteristics

Study	Study Type	Country	Dates	Participant n eyes	DSAEK, N	PK	DMEK	Follow-Up
Fuest et al (2017)[10,]	Prospective	Singapore	1991-2011	Total N=828	423	N=405	NR	5 yrs
Heinzelmann et al (2016)[11,]	Cohort	Germany	2011-2014	Total N=868	89	N=329	N=450	2 yrs
Wacker et al (2016)[12,]	Prospective	U.S.	2006-2010	Total N=52	34	NR	NR	5 yrs (n=34, 65%)
Li et al (2012)[13,]	Retrospective	U.S.	2005-2007	Total N=207	108	NR	NR	3 yrs

DMEK: Descemet membrane endothelial keratoplasty; DSAEK: Descemet stripping automated endothelial keratoplasty; NR: not reported; PK=penetrating keratoplasty.

Table 2. Summary of Key Nonrandomized Trial Results

Study	BSCVA	SE		Cylinder	
Fuest et al (2017)[10,]	at 5-yrs (n); mean(SD)	at 5-yrs (n); mean (SD)		at 5-yrs (n); mean (SD)	
Total	(n=89);0.62(0.6); p=.037	(n=62); -1.7(2.7); p=.017		(N=62); -3.1(2.1); p<.001	
DSAEK	(N=25);0.46(0.5); p=.037	(N=18); -0.8(1.7); p=.017		(N=18); -1.6(1.1); p<.001	
PK	(N=25); 0.63(0.6); p=.037	(N=44); -2.1(2.9); p=.017		(N=44); -3.75(2.1); p=.001	
Study	% of BSCVA of Snellen 6/7.5 or better at 24-months		Chronic endothelial cell loss > 500 cells/mm ^{2} at 15 mos		Chronic endothelial cell loss > 500 cells/mm ^{2} at 24 mos
Heinzelmann et al (2016)[11,]					
FED DMEK	53%		95%		NR
FED DSAEK	15%		93%		
FED PK	10%		99%		NR
BK DMEK	NR		NR		NR
BK DSAEK	NR		NR		NR
BK PK	NR		NR		90%
Study	Mean high-contrast BSCVA presurgery	Mean high-contrast BSCVA at 5-yrs			
Wacker et al (2016)[12,]					
FECD DSEK	20/56	20/25			

Study	% of eyes achieving a BSCVA of 20/40 at 3-years	% of eyes achieving a BSCVA of 20/30 at 3-yrs	% of eyes achieving a BSCVA of 20/25 at 3-years	% of eyes achieving a BSCVA of 20/20 at 3-yrs
FED+BK DSAEK	98.1% (N=106)	90.7% (N=98)	70.4% (N=76)	47.2% (N=51)

BK: bullous keratopathy; NR; not reported; PK: penetrating keratoplasty; BSCVA: best spectacle-corrected visual acuity; DMEK: Descemet membrane endothelial keratoplasty; DSAEK: Descemet stripping automated endothelial keratoplasty; DSEK: Descemet stripping endothelial keratoplasty; FED/FECDS: Fuchs' endothelial corneal dystrophy; N:eyes; NR: not reported; PK: penetrating keratoplasty; SD: standard deviation; SE: spherical equivalent.

Section Summary: Descemet Stripping Endothelial Keratoplasty and Descemet Stripping Automated Endothelial Keratoplasty

Evidence for the use of Descemet stripping endothelial keratoplasty and Descemet stripping automated endothelial keratoplasty consists of a systematic review and several large observational studies with follow-up extending from 2 to 5 years. The review and the studies showed that patients undergoing Descemet stripping endothelial keratoplasty and Descemet stripping automated endothelial keratoplasty experience greater improvements in visual acuity than patients undergoing penetrating keratoplasty. Also, patients undergoing Descemet stripping endothelial keratoplasty and Descemet stripping automated endothelial keratoplasty experienced significantly fewer serious adverse events than patients undergoing penetrating keratoplasty.

Descemet Membrane Endothelial Keratoplasty and Descemet Membrane Automated Endothelial Keratoplasty

Clinical Context and Therapy Purpose

The purpose of Descemet membrane endothelial keratoplasty and Descemet membrane automated endothelial keratoplasty is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as penetrating keratoplasty, in individuals with endothelial disease of the cornea.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with endothelial disease of the cornea. Diseases that affect the endothelial layer include Fuchs endothelial dystrophy, aphakic and pseudophakic bullous keratopathy (corneal edema following cataract extraction), and failure or rejection of a previous corneal transplant.

Interventions

The therapy being considered is Descemet membrane endothelial keratoplasty and Descemet membrane automated endothelial keratoplasty. It has been suggested that by eliminating the stroma on the donor tissue, Descemet membrane endothelial keratoplasty and Descemet membrane automated endothelial keratoplasty may reduce stromal interface haze and provide better visual acuity outcomes than Descemet stripping endothelial keratoplasty or Descemet stripping automated endothelial keratoplasty.(14,15)

Comparators

Comparators of interest include penetrating keratoplasty.

Outcomes
The general outcomes of interest are change in disease status, morbid events, and functional outcomes. Relevant outcome measures include visual acuity, endothelial cell densities, patient satisfaction or quality-of-life, and complications including graft rejection, graft dislocation, and need for rebubble procedures.

Follow-up generally occurs through 1-2 years post-surgery.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews
The American Academy of Ophthalmology conducted a systematic review of the safety and outcomes of Descemet membrane endothelial keratoplasty and investigated whether Descemet membrane endothelial keratoplasty offered any advantages over Descemet stripping endothelial keratoplasty (Deng et al [2018]).(16) The literature search, conducted through May 2017, identified 47 studies for inclusion. Quality was assessed using a scale from the Oxford Centre for Evidence-Based Medicine. Two studies were rated level I evidence (well-designed and well-conducted RCTs), 15 studies were level II (well-designed case-control or cohort studies or RCTs with methodologic deficits), and 30 studies were level III (case series, case reports, or poor-quality cohort or case-control). Mean length of follow-up among the studies ranged from 5 to 68 months. A best spectacle-corrected visual acuity of 20/25 was achieved by 33% to 67% of patients (5 studies). A best spectacle-corrected visual acuity of 20/20 was achieved by 29% to 32% (3 studies) at 3 months post-surgery and by 17% to 67% at 6 months post-surgery. Seven studies, 6 of which were rated as level II evidence, directly compared Descemet membrane endothelial keratoplasty with Descemet stripping endothelial keratoplasty and all 7 showed a faster visual recovery and a better visual outcome after Descemet membrane endothelial keratoplasty compared with Descemet stripping endothelial keratoplasty. The rate of endothelial cell loss, graft failure, and intraoperative and postoperative complications was similar between Descemet membrane endothelial keratoplasty and Descemet stripping endothelial keratoplasty.
Singh et al (2017) conducted a systematic review and meta-analysis of studies comparing Descemet membrane endothelial keratoplasty with Descemet stripping endothelial keratoplasty or Descemet stripping automated endothelial keratoplasty.(17) The literature search, conducted through May 2016, identified 9 studies for inclusion in the qualitative analysis and 7 studies for inclusion in the meta-analysis. A quality assessment of studies was not presented. Meta-analyses of 343 eyes showed that the 6-month mean difference in best

spectacle-corrected visual acuity was significantly better in patients undergoing Descemet membrane endothelial keratoplasty than in patients undergoing Descemet stripping endothelial keratoplasty (-0.13; 95% CI, -0.16 to -0.09). The 6-month mean difference in endothelial cell density (n=348) did not differ significantly between groups (76.8; 95% CI, -79.8 to 233.4), though the interpretation of this result is limited due to high heterogeneity. A higher rate of air injection/rebubbling was reported among patients in the Descemet membrane endothelial keratoplasty group compared with the Descemet stripping endothelial keratoplasty group.

Pavlovic et al (2017) conducted a meta-analysis of 11 studies comparing Descemet membrane endothelial keratoplasty (n=350) with Descemet stripping automated endothelial keratoplasty (n=373).(18) The date of the literature search and quality assessment methods were not reported. The mean difference in best spectacle-corrected visual acuity did not differ significantly at the 3-month follow-up (-0.12; 95% CI, -0.28 to 0.04), but was significantly better in the Descemet membrane endothelial keratoplasty group than in the Descemet stripping automated endothelial keratoplasty group at both the 6-month (-0.12; 95% CI, -0.15 to -0.10) and at the 6-month and beyond follow-ups (-0.13; 95% CI, -0.17 to -0.09). There were no statistical differences in endothelial cell loss between the 2 procedures at 6 (mean difference, 0.2; 95% CI, -5.6 to 6.1) or 12 months (3.6; 95% CI, -3.7 to 10.9). There were more graft rejections reported among patients in the Descemet stripping automated endothelial keratoplasty group compared with those in the Descemet membrane endothelial keratoplasty group, but the difference was not significant (OR, 2.7; 95% CI, 0.6 to 11.9). There were more graft failures reported in the Descemet membrane endothelial keratoplasty group compared with the Descemet stripping automated endothelial keratoplasty group, but this difference, too, was not significant (OR, 2.8; 95% CI, 0.7 to 10.6).

Li et al (2017) conducted a systematic review and meta-analysis comparing Descemet membrane endothelial keratoplasty and Descemet stripping endothelial keratoplasty.(19) The literature search, conducted through January 2017, identified 19 studies for inclusion: 15 retrospective control studies, a prospective nonrandomized case series, and 3 for which the study designs could not be determined from the meeting abstracts. A modified version of the Newcastle-Ottawa Scale was used to assess the quality of the studies. Eight items relating to selection, comparability, and outcome were assessed, and if a study received a score greater than 6, it was considered relatively high quality. Two studies had a score of 7, 8 studies had a score of 6, 3 studies had a score of 5, and 6 studies had a score of 4. A total of 2,378 eyes were included in the studies, 1,124 receiving Descemet membrane endothelial keratoplasty and 1,254 receiving Descemet stripping endothelial keratoplasty. Meta-analyses of 13 studies showed an overall mean difference in best spectacle-corrected visual acuity that was significantly improved in the Descemet membrane endothelial keratoplasty group compared with the Descemet stripping endothelial keratoplasty group (-0.15; 95% CI, -0.19 to -0.11). This significant mean difference in best spectacle-corrected visual acuity was seen at the 3-, 6-, and 12-month follow-ups. Meta-analyses, which included 354 Descemet membrane endothelial keratoplasty and 313 Descemet stripping endothelial keratoplasty eyes (N=667), showed no significant difference in endothelial cell density between groups (mean difference, 14.9; 95% CI, -181.5 to 211.3). The most common complication in both procedures was partial or total graft detachment, with significantly more occurrences in the Descemet membrane endothelial keratoplasty group than in the Descemet stripping endothelial keratoplasty group (OR, 4.6; 95% CI, 2.4 to 8.6).

Wu et al (2021) conducted a systematic review and meta-analysis comparing Descemet membrane endothelial keratoplasty and Descemet stripping endothelial keratoplasty after failed penetrating keratoplasty.(20) A literature search was conducted through July 10, 2020 and included 25 studies (16 Descemet stripping endothelial keratoplasty; 9 Descemet membrane endothelial keratoplasty) for inclusion: 22 retrospective cohort studies and 3 prospective cohort studies. There was a total of 970 patients enrolled with 989 total eyes included in this review. The mean visual acuity of the Descemet stripping endothelial keratoplasty and Descemet membrane endothelial keratoplasty and DMEK-PK groups were 0.65 ± 0.18 and 0.43 ± 0.23 logMAR, respectively, at 6 months postoperatively. This shows a general trend for improved visual acuity following both Descemet stripping endothelial keratoplasty and Descemet membrane endothelial keratoplasty after failed penetrating keratoplasty. Graft survival and rejection rates were comparable between the 2 groups.

Maier et al (2023) conducted a systematic review and meta-analysis comparing Descemet membrane endothelial keratoplasty and ultrathin Descemet stripping automated endothelial keratoplasty.(21) A literature search was conducted through June 2022, and included 7 studies: 3 RCTs, 1 prospective case series, 1 retrospective comparative study, and 2 retrospective cohort studies. The primary outcome assessed was BSCVA and secondary outcomes included endothelial cell density and postoperative complications. Baseline BSCVA data consisted of 163 eyes treated with Descemet membrane endothelial keratoplasty and 165 eyes treated with ultrathin Descemet stripping automated endothelial keratoplasty. The BSCVA standardized mean difference (SMD) between groups after 3 months was 0.49 (95% CI, 0.22 to 0.76; p=.0004) and after 12 months was 0.50 (95% CI, 0.27 to 0.74; p=.0001); this favored Descemet membrane endothelial keratoplasty. Data at 6 months could not be evaluated due to high heterogeneity of the studies. Another significant outcome between groups was the re-bubbling rate after Descemet membrane endothelial keratoplasty compared to ultrathin Descemet stripping automated endothelial keratoplasty (RR, 0.33; 95% CI, 0.15 to 0.67; p=.0025). All other measured outcomes were not significantly different between groups. Tables 3 and 4 describe the characteristics and results of key systematic reviews and meta-analyses.

Table 3. SR & M-A Characteristics

Study	Dates	Trials	N (Eyes)	Intervention	N (Range)	Design	Duration
Deng et al (2018)[16,]	NR-05/2017	47	9046; patients with corneal endothelial dysfunction	DMEK	9046 (25-905)	RCT; case-control and cohort; case series, case reports	5.3-68 mos
Singh et al (2017)[17,]	NR-05/2016	9	586	DMEK, DSAEK	586 (20-155)	NR	NR
Pavlovic et al (2017)[18,]	NR	11	723	DMEK (n=350); DSAEK (n=373)	NR	NR	NR
Li et al (2017)[19,]	NR-01/2017	19	2378	DMEK; DSEK	2378 (20-739)	NR	3.1-22.55 mos
Wu et al (2021) [20,]	NR-07/2020	25	989	DMEK, DSAEK	989 (7-246)	prospective and retrospective cohorts	6-36.1 mos
Maier et al (2023)[21,]	NR-06/2022	7	328	DMEK; UT-DSAEK	NR	RCT; case series; retrospective cohorts	NR

DMEK: Descemet membrane endothelial keratoplasty; DSAEK: Descemet stripping automated endothelial keratoplasty; DSEK: Descemet stripping endothelial keratoplasty; M-A: meta-analysis; NR: not reported; RCT: randomized controlled trial; SR: systematic review; UT-DSAEK: ultrathin Descemet stripping automated endothelial keratoplasty.

Table 4. SR & M-A Results

Study	Mean BCVA at 6 mos	Mean endothelial cell loss at time	Change in SE	Minimal induced astigmatism
Deng et al (2018)[16,]				
Total N*=9046	Range: 20/21 to 20/31	33% (range, 25%-47%) [6-mos]	+0.43 D (range, -1.17 to +1.2 D)	+0.03 D (range, -0.03 to +1.11 D)
	BCVA at 6-mos	ECD at 6-mos	Graft detachment overall	Graft rejection
Singh et al (2017)[17,]				
After DMEK, mean; SD, p-value	0.161; 0.129; p<.0001; N=184	1855; 442; p=.708	NR	NR
After DSAEK, mean; SD, p-value	0.293; 0.153; p<.0001; N=159	1872; 429; p=.708	NR	NR
Pooled mean difference (CI, SD)	-0.13 (95% CI, 0.16 to 0.09); N=343	Could not be interpreted due to high statistical heterogeneity	NR	NR
Pavlovic et al (2017)[18,]	Not available	ECL* at 6-mos	Not available	Not available
Mean difference between DSAEK and DMEK group	-0.12; 95% CI, -0.15 to -0.10	0.2; 95% CI, -5.6 to 6.1	Not available	Not available
Li et al (2017)[19,]	N=108	N=108	N=108	N=108
Comparison between DMEK and DSEK (MD[95%CI] % weight)	-0.13 (-0.17, -0.08) 51.29	25.59 (-183.15, 234.32) p=.810	4.56 (2.43, 8.58)	-0.04 (-0.08, -0.002)
Pooled mean difference (CI, SD)	-0.15 (-0.19 to -0.11) p<.001)	14.88 (-181.5 to 211.27) p=.882	NR	NR
Wu et al (2021) [20,]				
After DMEK, mean; SD	0.43; 0.23; N=243	47.6% (range 37.1%-61.4%) [12-mos]	NR	NR
After DSAEK, mean; SD	0.65; 0.18; N=746	NR	NR	NR
	BCVA at 12 mos	**ECD at 6 mos**	**Graft detachment overall**	**Graft rejection**
Maier et al (2023)21,				
Comparison between DMEK and UT-DSAEK groups	MD, 0.50; (95% CI, 0.27 to 0.74); p<.0001	Could not be interpreted due to high statistical heterogeneity	RR, 0.33 (95% CI, 0.16 to 0.67); p=.0025	RR, 1.4 (95% CI, 0.27 to 7.30); p=.69

*N=eyes
BCVA: best-corrected visual acuity; CI: confidence interval; D: diopters; DMEK: Descemet membrane endothelial keratoplasty; DSAEK: Descemet stripping automated endothelial keratoplasty; DSEK: Descemet stripping endothelial keratoplasty; ECD: endothelial corneal dystrophy; ECL: endothelial cell loss; M-A: meta-analysis; MD: mean difference; NR: not reported; RR: risk ratio; SD: standard deviation; SE: spherical equivalent; SR: systematic review; UT-DSAEK: ultrathin Descemet stripping automated endothelial keratoplasty.

Observational Studies

Oellerich et al (2017) reported on 6-month outcomes of a large cohort of patients undergoing Descemet membrane endothelial keratoplasty by 55 surgeons from 23 countries.(22) Outcomes of interest were best spectacle-corrected visual acuity, a decrease in endothelial cell density, and complications. Subgroup analyses were conducted by a number of procedures performed by the surgeon (1 to 24 [39%], 25 to 99 [38%], and ≥100 [23%]). In the total population, 91% of patients achieved best spectacle-corrected visual acuity improvement, with 5% experiencing no change and 5% experiencing deterioration in visual acuity. Subgroup analyses showed that the proportion of patients achieving best spectacle-corrected visual acuity improvement did not differ significantly between patients whose surgeons had performed 100 or more procedures and those whose surgeons had performed fewer than 25 procedures. Nine percent of patients experienced intraoperative complications, with the rate decreasing significantly as the surgeon performed more procedures. The most frequent postoperative complication was partial graft detachment (27%), which also decreased significantly with surgeon experience. Rates of other postoperative complications such as graft failure, cataract, and glaucoma did not differ based on surgeon experience.

Tourtas et al (2012) conducted a retrospective comparison of 38 consecutive patients/eyes that underwent Descemet membrane endothelial keratoplasty and 35 consecutive patients/eyes who had undergone Descemet stripping automated endothelial keratoplasty.(23) Only patients with Fuchs endothelial dystrophy or pseudophakic bullous keratopathy were included. After Descemet membrane endothelial keratoplasty, 82% of eyes required rebubbling. After Descemet stripping automated endothelial keratoplasty, 20% of eyes required rebubbling. Best spectacle-corrected visual acuity in both groups was comparable at baseline (Descemet membrane endothelial keratoplasty=0.70 logMAR; Descemet stripping automated endothelial keratoplasty=0.75 logMAR). At 6-month follow-up, mean visual acuity improved to 0.17 logMAR after Descemet membrane endothelial keratoplasty and 0.36 logMAR after Descemet stripping automated endothelial keratoplasty. This difference was statistically significant. At 6 months following surgery, 95% of Descemet membrane endothelial keratoplasty treated eyes reached a visual acuity of 20/40 or better, and 43% of Descemet stripping automated endothelial keratoplasty treated eyes reached a visual acuity of 20/40 or better. Endothelial cell density decreased by a similar amount after both procedures (41% after Descemet membrane endothelial keratoplasty, 39% after Descemet stripping automated endothelial keratoplasty).

Van Dijk et al (2013) reported on outcomes of their first 300 consecutive eyes treated with Descemet membrane endothelial keratoplasty.(24) Indications for Descemet membrane endothelial keratoplasty were Fuchs endothelial dystrophy, pseudophakic bullous keratopathy, failed penetrating keratoplasty, or failed endothelial keratoplasty. Of the 142 eyes evaluated for visual outcomes at 6 months, 79% reached a best spectacle-corrected visual acuity of 20/25 or more, and 46% reached a best spectacle-corrected visual acuity of 20/20 or more. Endothelial cell density measurements at 6 months were available in 251 eyes. Average cell density was 1674 cells/mm^2, representing a decrease of 34.6% from preoperative donor cell density. The major postoperative complication in this series was graft detachment requiring rebubbling or regraft, which occurred in 10.3% of eyes. Allograft rejection occurred in 3 eyes (1%), and intraocular pressure was increased in 20 (6.7%) eyes. Except for 3 early cases that may have been prematurely regrafted, all but 1 eye with an attached graft cleared in 1 to 12 weeks.

A 2009 review of cases from another group in Europe suggested that a greater number of patients achieve 20/25 vision or better with Descemet membrane endothelial keratoplasty.(25) Of the first 50 consecutive eyes, 10 (20%) required a secondary Descemet stripping endothelial keratoplasty for failed Descemet membrane endothelial keratoplasty. For the remaining 40 eyes, 95% had a best spectacle-corrected visual acuity of 20/40 or better, and 75% had a best spectacle-corrected visual acuity of 20/25 or better. Donor detachments and primary graft failure with Descemet membrane endothelial keratoplasty were problematic. In 2011, this group reported on the surgical learning curve for Descemet membrane endothelial keratoplasty, with their first 135 consecutive cases retrospectively divided into 3 subgroups of 45 eyes each.(25) Graft detachment was the most common complication, which decreased with surgeon experience. In their first 45 cases, a complete or partial graft detachment occurred in 20% of cases, compared with 13.3% in the second group and 4.4% in the third group. Clinical outcomes in eyes with normal visual potential and a functional graft (n=110) were similar across the 3 groups, with an average endothelial cell density of 1747 cells/mm^2 and 73% of cases achieving a best spectacle-corrected visual acuity of 20/25 or better at 6 months.

A North American group reported on 3-month outcomes from a prospective consecutive series of 60 cases of Descemet membrane endothelial keratoplasty in 2009, and in 2011, they reported on 1-year outcomes from these 60 cases plus an additional 76 cases of Descemet membrane endothelial keratoplasty.(27,28) Preoperative best spectacle-corrected visual acuity averaged 20/65 (range of 20/20 to counting fingers). Sixteen eyes were lost to follow-up, and 12 (8.8%) grafts had failed. For the 108 grafts examined and found to be clear at 1 year, 98% achieved a best spectacle-corrected visual acuity of 20/30 or better. Endothelial cell loss was 31% at 3 months and 36% at 1 year. Although visual acuity outcomes appeared to be improved over a Descemet stripping automated endothelial keratoplasty series from the same investigators, preparation of the donor tissue and attachment of the endothelial graft were more challenging. A 2012 cohort study by this group found reduced transplant rejection with Descemet membrane endothelial keratoplasty.(29) One (0.7%) of 141 patients in the Descemet membrane endothelial keratoplasty group had a documented episode of rejection compared with 54 (9%) of 598 in the Descemet stripping endothelial keratoplasty group and 5 (17%) of 30 in the penetrating keratoplasty group.

The same group also reported on a prospective consecutive series (2011) of their initial 40 cases (36 patients) of Descemet membrane automated endothelial keratoplasty (microkeratome dissection and a stromal ring).(30) Indications for endothelial keratoplasty were Fuchs endothelial dystrophy (87.5%), pseudophakic bullous keratopathy (7.5%), and failed endothelial keratoplasty (5%). Air was reinjected in 10 (25%) eyes to promote graft attachment; 2 (5%) grafts failed to clear and were successfully regrafted. Compared with a median best spectacle-corrected visual acuity of 20/40 at baseline (range, 20/25 to 20/400), median best spectacle-corrected visual acuity at 1 month was 20/30 (range, 20/15 to 20/50). At 6 months, 48% of eyes had 20/20 vision or better, and 100% had 20/40 or better. Mean endothelial cell loss at 6 months relative to baseline donor cell density was 31%.

Tables 5 and 6 describe key characteristics and results of these observational studies.

Table 5. Summary of Key Observational Study Characteristics

Study	Study Design	Country	Dates	Participants	Treatment 1	Treatment 2	Follow-Up
Oellerich et al (2017)	Retrospective cohort	Europe, Asia, Africa, North America, South America, Australia	Aug 2008-July 2015	Mean age, 69.8 +/- 11.0 (range, 16-99 yrs); 37% male, 57.9% female, 5.2% not specified; 74.4% FED, 16.8% BK; 7.6% failed transplant, 0.9% other; 0.3% not specified	DMEK (n=2448)	NR	6-mos
Van Dijk et al (2013)	Prospective	Netherlands	NR	Mean age, 67 +/- 13 (range, 30-93 yrs), 166 female/134	DMEK (N=300)	NR	6-mos

				male; FED=272 patients; BK=17 patients; Failed DSEK/PK=9/1 patients			
Tourtas et al (2012)	Retrospective cohort	Germany	Aug 2009-Dec 2009; DSAEK: Aug 2008-Mar 2009	DMEK: mean age, 68.3 +/- 9 (range, 42-85 yrs), 16 female/22 male; DSAEK: mean age, 68.1 +/- 11 (range, 48-87 yrs), 20 female/15 male	DMEK (N=38)	DSAEK (N=35)	6-mos
Ham et al (2009)	Prospective case	Netherlands	NR	Patients with FED; 23 men, 27 women; age range 41-88 yrs	DMEK (N=40)	DMEK followed by DSEK as a back-up procedure in the event of DMEK graft failure (N=10)	6-mos
Dapena et al (2011)	Retrospective	Netherlands	Feb 2005-Dec 2010	118 patients with FED, 49 male, 69 female; age range, 33-93 yrs	DMEK (N=135)	NA	6-mos
Price et al (2009)	Prospective	U.S.	Feb 2009-Oct 2009	58 patients with FED, PK, or failed previous graft; mean age 68 +/- 9.9 (48-85 yrs); 34 female/26 male	DMEK (N=60)	NA	3-mos
Guerra et al (2011)	Prospective	U.S.	Feb 2009-Oct 2009	112 patients with FED, PK, or failed previous graft; +/- 78 +/- 10.36 72 female/40 male	DMEK (N=136)	NA	1-y
McCauley et al (2011)	Prospective	U.S.	NR	36 patients treated with DMAEK. Mean age 69 yrs (range: 48-88 yrs); 53% female	DMAEK (N=40)	NA	6-mos
Anshu (2012)	Comparative	U.S.	Feb 2009-Oct 2009	Patients undergoing DMEK compared retrospectively with matched cohort undergoing DSEK (598) and PK (n=30), treated at same center, with similar demographics, follow-up, duration, indications for surgery	DMEK/DSEK (N=598)	PK (n=30)	2-yrs

BK: bullous keratopathy; DMAEK: Descemet membrane automated endothelial keratoplasty; DMEK: Descemet membrane endothelial keratoplasty; DSAEK: Descemet stripping automated endothelial keratoplasty; DSEK: Descemet stripping endothelial keratoplasty; FED/FECD: Fuchs endothelial corneal dystrophy; N=eyes except where indicated otherwise. NA: not applicable; PK: penetrating keratoplasty.

Table 6. Summary of Key Observational Study Results

Study	BCVA preoperative	BCVA 6 mos FU	ECD preoperative mean +/- SD (cells/mm ^{2})	ECD 6 mos FU mean +/-SD (cells/mm ^{2})	Postoperative complications
Oellerich et al (2017)	N=2430	N=1959	N=1956	N=1405	N=2363
DMEK	N (%) ≥ 20/25 Snellen = 46.17 (1.9%)	N (%) ≥ 20/25 Snellen = 889 (45.4%)	2635 +/- 294	1575+/- 489	647 (27.4%) [for all types of post-operative complications]
Van Dijk et al (2013)	N=221	N=221	N=251	N=251	N=300
DMEK	N (%) ≥ 20/25 Snellen = 16 (7%)	N (%) ≥ 20/25 Snellen = 175 (79%)	NR	1674 +/- 518	31 (10%) for most frequent complication, (partial) graft detachment
Tourtas et al (2012)	N=73	N=73	N=73 total	N=73	N=73
DMEK (n=38)	Mean +/- SD; 0.70 +/- 0.48 logMAR	Mean +/- SD; 0.17 +/- 0.12 logMAR (n=38)	2575 +/- 260	1520 +/- 299	31 (82%) required air injections for partial dehiscence of the EDM
DSAEK (n=35)	N +/- SD; 0.75 +/- 0.32 logMAR	N +/- SD; 0.36 +/- 0.15 logMAR (n=35)	2502 +/- 220	1532 +/- 495	7 (20%) required air injections for partial dehiscence of the EDM
Ham et al (2009)					
Pooled (N=50)	NR	N (%) ≥ 20/25 Snellen = 47 (66%)	2623	2623	All complications, N=14 (28%)
			+/-193 (n=47)	+/- 193 (n=43)	
DMEK only (N=40)	NR	N (%) ≥ 20/25 Snellen = 30 (75%)	2618	1876 +/- 522 (n=35)	NR
			+/-201 (n=40)		
Dapena et al (2011)	N=135	N=110	N=135	174 +/- 527 (n=106)	Primary graft failure (2.2%, 3/135)
DMEK N=135	NR	N (%) ≥ 20/25 Snellen = 80 (73%)	NR		
Price et al (2009)	N=60	N=57 at 3-mos	N=60	N=57 at 3-mos	NR
DMEK	Median preoperative BSCVA =20/50	N (%) ≥ 20/25 Snellen=36 (63%),	3010 +/- 200 (range, 2520-3430)	30% +/- 20% (range, 2.7%-78%)	NR

	BSCVA	BSCVA FU [time]	ECD pre-operative (mean +/- SD, cells/mm ^{2})	ECD 6m FU (mean +/- SD, cells/mm ^{2})	Donor Tissue Loss (N=corneas)
Guerra et al (2011)	N=108				
DMEK	0.51+/- 0.44 logMar of the minimum angle of resolution units (20/65; range, 20/20 - 20/2000)	1-year: 0.07 1 +/- 0.09 logMar of the minimum angle of resolution units (20/24; range, 20/15 - 20/40); p<.001	2980+/-252 (2514-3706) *at 1-year	1911+/-593 (range, 347-2976) at 1-year	N=6 (4.2%)
McCauley et al (2011)					
DMAEK (N=40)	Median pre-op BSCVA was 20/40 (range: 20/25-20/400)	6-mo: median BSCVA was 20/25 (range: 20/15-20/40); 48%? 20/20; 74%? 20/25; 93%? 20/30; all ≥ 20/40	The median donor ECD=3140 cells/mm 2 (range: 2695-4630 cells/mm^2)	6m FU, median ECD was 2121 cells/mm2 (range: 1204-4268 cells/mm 2 centimeter, n=30)	Not statistically significant
	Probability of Rejection % at 1-y	**Probability of Rejection % at 2-yrs**	**Eyes still followed without rejection (n) at 1-y**	**Eyes still followed without rejection (n) at 2-yrs**	
Anshu (2012)					
DMEK (n=141)	N=769	N=769	N=349	N=125	-
DSEK (N=598)	1	1	80	35	
PK (N=30)	8	12	246	79	

BCVA: best-corrected visual acuity; BSCVA: best spectacle-corrected visual acuity; CI: confidence interval; DMAEK: Descemet membrane automated endothelial keratoplasty; DMEK: Descemet membrane endothelial keratoplasty; DSAEK: Descemet stripping automated endothelial keratoplasty; DSEK: Descemet stripping endothelial keratoplasty; EDM: endothelium-Descemet's membrane; ECD: endothelial corneal dystrophy; FU: follow-up; logMar: Logarithm of the Minimum Angle of Resolution; NR: not reported; OS: overall survival; PK: penetrating keratoplasty; SD: standard deviation.

Section Summary: Descemet Membrane Endothelial Keratoplasty and Descemet Membrane Automated Endothelial Keratoplasty

Evidence for the use of Descemet membrane endothelial keratoplasty or Descemet membrane automated endothelial keratoplasty consists of several systematic reviews with overlapping studies, and several observational studies, some of which had no comparators and some of which compared Descemet membrane endothelial keratoplasty or Descemet membrane automated endothelial keratoplasty with Descemet stripping endothelial keratoplasty or Descemet stripping automated endothelial keratoplasty. Analyses in the individual studies and the meta-analyses consistently showed that patients receiving Descemet membrane endothelial keratoplasty or Descemet membrane automated endothelial keratoplasty experienced significantly better visual acuity outcomes post procedure than patients receiving Descemet stripping endothelial keratoplasty or Descemet stripping automated endothelial keratoplasty, both short-term and through 1 year of follow-up. A large cohort study showed that intraoperative complications decreased as surgeon experience increased. Some studies reported similar complication rates between the procedures, some reported more complications with Descemet membrane endothelial keratoplasty than Descemet stripping endothelial keratoplasty, though the complications were not considered severe.

Femtosecond Laser-Assisted Endothelial Keratoplasty and Femtosecond and Excimer Laser-Assisted Endothelial Keratoplasty

Clinical Context and Therapy Purpose

The purpose of femtosecond laser-assisted endothelial keratoplasty and femtosecond and excimer laser-assisted endothelial keratoplasty is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as penetrating keratoplasty, in individuals with endothelial disease of the cornea.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with endothelial disease of the cornea. Diseases that affect the endothelial layer include Fuchs endothelial dystrophy, aphakic and pseudophakic bullous keratopathy (corneal edema following cataract extraction), and failure or rejection of a previous corneal transplant.

Interventions

The therapy being considered is femtosecond laser-assisted endothelial keratoplasty and femtosecond and excimer laser-assisted endothelial keratoplasty. Variations of femtosecond laser-assisted endothelial keratoplasty include femtosecond laser-assisted Descemet stripping automated endothelial keratoplasty.

Comparators

Comparators of interest include penetrating keratoplasty.

Outcomes

The general outcomes of interest are change in disease status, morbid events, and functional outcomes. Relevant outcome measures include visual acuity, endothelial cell densities, patient satisfaction or quality-of-life, and complications including graft rejection, graft dislocation, and need for rebubble procedures. Follow-up generally occurs through 1-2 years post-surgery.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

Liu et al (2021) conducted a systematic review and meta-analysis of studies comparing femtosecond laser-enabled keratoplasty with conventional penetrating keratoplasty.(31)The literature search was conducted through April 2018 and identified 7 comparative studies for inclusion. Follow-up periods of the included studies spanned from 6 months to 3.5 years, with the majority of patients having up to 1 year of follow-up. The meta-analyses of 1855 eyes illustrated that mean best-corrected visual acuity after femtosecond laser-enabled keratoplasty was significantly better than after penetrating keratoplasty (p=.00, standardized mean difference [SMD]: −0.23; 95% CI: −0.37 to −0.10). Endothelial cell density was also significantly better preserved in the femtosecond laser-enabled keratoplasty group (p=.03, SMD: 0.63; 95% CI: 0.07-1.20). Results were comparable amongst both groups in spherical equivalent, graft rejection, graft failure, and complication.

Randomized Controlled Trials

Ivarsen et al (2018) conducted an RCT of ultrathin Descemet stripping automated endothelial keratoplasty or femtosecond-prepared Descemet stripping automated endothelial keratoplasty using the Ziemer LDV Z8 femtosecond laser.(32) Outcome measures were planned after 1, 3, 6, 12 and 24 months with visual acuity, refraction, Scheimpflug tomography, whole eye scatter measurement, and anterior optical coherence tomography. However, graft dislocation occurred in all patients randomized to femtosecond-prepared Descemet stripping automated endothelial keratoplasty which was managed with rebubbling. No patients with ultrathin Descemet stripping automated endothelial keratoplasty experienced graft dislocation. Additionally, all patients treated with femtosecond-prepared Descemet stripping automated endothelial keratoplasty had significantly poorer clinical outcomes compared with ultrathin Descemet stripping automated endothelial keratoplasty patients. After 3 months, visual acuity was scored as approximately 2.5 times worse. The optical scatter index was also significantly greater in patients receiving femtosecond-prepared Descemet stripping automated endothelial keratoplasty compared to ultrathin Descemet stripping automated endothelial keratoplasty at 3 months (12 standard deviation [SD], 3; range, 8 to 16] vs. 5 [SD], 3; range, 2 to 9]). While the planned enrollment was set at 80, after 1 month only 6 patients were treated with femtosecond-prepared Descemet stripping automated endothelial keratoplasty and 5 patients received ultrathin Descemet stripping automated endothelial keratoplasty. Due to the large differences in observed clinical outcomes, no further patients were recruited and the study was suspended.

Cheng et al (2009) conducted a multicenter randomized trial in Europe that compared femtosecond laser-assisted endothelial keratoplasty with penetrating keratoplasty.(33) Eighty patients with Fuchs endothelial dystrophy, bullous keratopathy, or posterior polymorphous dystrophy, and a best spectacle-corrected visual acuity less than 20/50 were included in the trial. In the femtosecond laser-assisted endothelial keratoplasty group, 4 of the 40 eyes did not receive treatment due to significant preoperative events and were excluded from the analysis. Eight (22%) of 36 eyes failed, and 2 patients were lost to follow-up due to death in the femtosecond laser-assisted endothelial keratoplasty group. One patient was lost to follow-up in the penetrating keratoplasty group due to health issues. At 12 months postoperatively, refractive astigmatism was lower in the femtosecond laser-assisted endothelial keratoplasty group (86%) than in the penetrating keratoplasty group (51%, with astigmatism of ≥3 D)); however, there was a greater hyperopic shift in the femtosecond laser-assisted endothelial keratoplasty group than in the penetrating keratoplasty group. Mean best spectacle-corrected visual acuity was better following penetrating keratoplasty than femtosecond laser-assisted endothelial keratoplasty at the 3-, 6-, and 12-month follow-ups. There was greater endothelial cell loss in the femtosecond laser-assisted endothelial keratoplasty group (65%) than in the penetrating keratoplasty group (23%). With the exception of dislocation and need to reposition the femtosecond laser-assisted endothelial keratoplasty grafts in 28% of eyes, the percentage of complications was similar between groups. Complications in the femtosecond laser-assisted endothelial keratoplasty group were due to pupillary block, graft failure, epithelial ingrowth, and elevated intraocular pressure, whereas complications in the penetrating keratoplasty group were related to the sutures and elevated intraocular pressure.

Nonrandomized Studies
Sorkin et al (2019) reported 3-year outcomes of a retrospective, interventional study comparing femtosecond laser-assisted Descemet membrane endothelial keratoplasty with manual Descemet membrane endothelial keratoplasty in patients with Fuchs endothelial corneal dystrophy.(34) Sixteen eyes of 15 patients were evaluated in the femtosecond-prepared Descemet membrane endothelial keratoplasty group for an average follow-up up 33.0 ± 9.0 months and 45 eyes of 40 patients were evaluated in the manual Descemet membrane endothelial keratoplasty group for an average follow-up of 32.0 ± 7.0 months. Best spectacle-corrected visual acuity was not statistically different at 1, 2, and 3 years post-surgery (p=.849, p=.465, and p=.936, respectively). Rates of significant graft detachment were significantly higher in the manual Descemet membrane endothelial keratoplasty group than in the femtosecond prepared Descemet membrane endothelial keratoplasty group (35.6% vs. 6.25%; p=.027). Rebubbling rates were also significantly higher in the manual Descemet membrane endothelial keratoplasty group (33.3% vs. 6.25%; p=.047). Endothelial cell loss rates were significantly lower in the femtosecond prepared Descemet membrane endothelial keratoplasty group at 1 year (26.8% vs. 36.5%; p=.042) and 2 years (30.5% vs. 42.3%; p=.008), however, this trend was lost at 3 years (37% vs. 47.5%; p=.057).(35) The primary graft failure rate was 0% in femtosecond prepared Descemet membrane endothelial keratoplasty compared to 8.9% in manual Descemet membrane endothelial keratoplasty (p=.565). While study authors speculate that the higher detachment and rebubbling rate in manual Descemet membrane endothelial keratoplasty may be related to retained Descemet tags and islands, this study is limited by its retrospective nature and nonrandomized design and cannot account for potential baseline differences in patient anatomy. Hosny et al (2017) reported on results from a case series on 20 eyes (19 patients) that underwent a femtosecond prepared Descemet stripping automated endothelial keratoplasty.(36) After 3 months of follow-up, patients experienced significant improvements in corneal thickness, measured by anterior segment optical coherence tomography. Visual acuity significantly improved each month of the 3-month follow-up, with the largest improvement seen in the first month post-procedure. Complications specific to the femtosecond laser-assisted procedure were thickness disparities causing protrusion of the posterior disc (n=6) and air trapping in the interface (n=2). The former complication was corrected by modifying procedure parameters, and the latter was corrected by venting of the air bubble.

In a small retrospective cohort study, Vetter et al (2013) found a reduction in visual acuity when the endothelial transplant was prepared with a laser (femtosecond laser-assisted endothelial keratoplasty=0.48 logMAR; n=8) compared with a microtome (Descemet stripping automated endothelial keratoplasty=0.33 logMAR; n=14).(37) There was also greater surface irregularity with femtosecond laser-assisted endothelial keratoplasty.

Section Summary: Femtosecond Laser-Assisted Endothelial Keratoplasty and Femtosecond and Excimer Laser-Assisted Endothelial Keratoplasty
Evidence for femtosecond laser-assisted endothelial keratoplasty consists of 3 small observational studies, 2 RCTs, and 1 systematic review. The systematic review reported that femtosecond laser-assisted endothelial keratoplasty may have advantages to achieving better outcomes in best-corrected visual acuity and endothelial cell density preservation. One observational study showed improvements following the procedure, though there was no comparison group and the other showed worse outcomes with the laser compared with Descemet stripping automated endothelial keratoplasty. One RCT indicated that patients undergoing penetrating keratoplasty experienced better outcomes than patients in the femtosecond laser-assisted endothelial keratoplasty group after 1 year of follow-up. Complication rates were similar between groups. Another RCT reported better clinical outcomes and no instances of graft dislocation with microkeratome-prepared Descemet stripping automated endothelial keratoplasty compared to femtosecond prepared Descemet stripping automated endothelial keratoplasty.

Summary of Evidence
For individuals who have endothelial disease of the cornea who receive Descemet stripping endothelial keratoplasty or Descemet stripping automated endothelial keratoplasty, the evidence includes a number of cohort studies, RCTs, and systematic reviews. Relevant outcomes are change in disease status, morbid events, and functional outcomes. The available literature has indicated that these procedures improve visual outcomes and reduce serious complications associated with penetrating keratoplasty. Specifically, visual recovery occurs much earlier. Because endothelial keratoplasty maintains an intact globe without a sutured donor cornea, astigmatism or the risk of severe, sight-threatening complications such as expulsive suprachoroidal hemorrhage and postoperative catastrophic wound failure are eliminated. The Descemet Endothelial Thickness Comparison Trial (DETECT) RCT reported improved visual acuity outcomes with Descemet membrane endothelial keratoplasty compared to ultra-thin Descemet stripping automated endothelial keratoplasty. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have endothelial disease of the cornea who receive Descemet membrane endothelial keratoplasty or Descemet membrane automated endothelial keratoplasty, the evidence includes a number of cohort studies and systematic reviews. Relevant outcomes are change in disease status, morbid events, and functional outcomes. Evidence from the cohort studies and meta-analyses has consistently shown that the use of Descemet membrane endothelial keratoplasty and Descemet membrane automated endothelial keratoplasty procedures improve visual acuity. When compared with Descemet stripping endothelial keratoplasty and Descemet stripping automated endothelial keratoplasty, Descemet membrane endothelial keratoplasty and Descemet membrane automated endothelial keratoplasty showed significantly greater improvements in visual acuity, both in the short term and through 1 year of follow-up. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have endothelial disease of the cornea who receive femtosecond laser-assisted endothelial keratoplasty and femtosecond and excimer laser-assisted endothelial keratoplasty, the evidence includes a multicenter RCT and a systematic review comparing femtosecond laser-assisted endothelial keratoplasty with penetrating keratoplasty, and an RCT comparing femtosecond-prepared Descemet stripping automated endothelial keratoplasty to microkeratome-prepared Descemet membrane automated endothelial keratoplasty. Relevant outcomes are change in disease status, morbid events, and functional outcomes. There were conflicting results in the evidence regarding mean best-corrected visual acuity and endothelial cell loss after femtosecond laser-assisted endothelial keratoplasty versus penetrating keratoplasty. Mean best-corrected visual acuity was worse after femtosecond laser-assisted endothelial keratoplasty than after penetrating keratoplasty, and endothelial cell loss was higher with femtosecond laser-assisted endothelial keratoplasty. With the exception of dislocation and need for repositioning of the femtosecond laser-assisted endothelial keratoplasty, the percentage of complications was similar between groups. Complications in the femtosecond laser-assisted endothelial keratoplasty group were due to pupillary block, graft failure, epithelial ingrowth, and elevated intraocular pressure, whereas complications in the penetrating keratoplasty group were related to sutures and elevated intraocular pressure. Worsened visual acuity and a 100% graft dislocation rate were reported for femtosecond-prepared Descemet stripping automated endothelial keratoplasty compared to 0% in manually-prepared Descemet stripping automated endothelial keratoplasty. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 7.

Table 7. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03619434	Pilot Study of Femtolaser Assisted Keratoplasty Versus Conventional Keratoplasty	30	Dec 2021 (unknown)
Unpublished			
NCT00543660	Descemet Stripping (Automated) Endothelial Keratoplasty (DSEK or DSAEK) (DSAEK)	20	Mar 2018 (unknown)
NCT00521898	Prospective Clinical Study on Descemet Membrane Endothelial Keratoplasty	1000	Feb 2020 (unknown)
NCT00800111	Open-enrollment, Prospective Study of Endothelial Keratoplasty Outcomes	2593	Feb 2018 (completed)
NCT02793310	Corneal Transplantation by DMEK - is it Really Better Than DSAEK?	54	Feb 2019 (completed)
NCT02470793	Technique and Results In Endothelial Keratoplasty (TREK)	62	Jan 2021 (completed)

NCT: national clinical trial; DMEK: Descemet membrane endothelial keratoplasty; DSAEK: Descemet stripping automated endothelial keratoplasty.

Supplemental Information

2013 Input

In 2013, BCBSA sought clinical input to help determine whether the use of endothelial keratoplasty for individuals with endothelial disease of the cornea would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, BCBSA received clinical input from 3 specialty society-level response(s) and 3 academic medical centers.

For individuals who have endothelial disease of the cornea who receive Descemet membrane endothelial keratoplasty and Descemet membrane automated endothelial keratoplasty, clinical input supported a clinically meaningful improvement in net health outcome and the use is consistent with generally accepted medical practice.

For individuals who have endothelial disease of the cornea who receive femtosecond laser-assisted endothelial keratoplasty and femtosecond and excimer laser-assisted endothelial keratoplasty, clinical input does not support a clinically meaningful improvement in net health outcome and does not indicate this use is consistent with generally accepted medical practice.

2009 Input

In 2009, BCBSA sought clinical input to help determine whether the use of endothelial keratoplasty for individuals with endothelial disease of the cornea would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, BCBSA received clinical input from 3 specialty society-level response(s) and 2 academic medical centers.

For individuals who have endothelial disease of the cornea who receive Descemet stripping endothelial keratoplasty and Descemet stripping automated endothelial keratoplasty, clinical input supported a clinically meaningful improvement in net health outcome and the use is consistent with generally accepted medical practice.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Academy of Ophthalmology

In 2009, the American Academy of Ophthalmology (AAO) published a position paper on endothelial keratoplasty, stating that the optical advantages, speed of visual rehabilitation, and lower risk of catastrophic wound failure have driven the adoption of endothelial keratoplasty as the standard of care for patients with endothelial failure and otherwise healthy corneas. The 2009 AAO position paper was based in large part on an AAO comprehensive review of the literature on Descemet stripping automated endothelial keratoplasty.(3) AAO concluded that "the evidence reviewed suggests Descemet stripping automated endothelial keratoplasty appears safe and efficacious for the treatment of endothelial diseases of the cornea. Evidence from retrospective and prospective Descemet stripping automated endothelial keratoplasty reports described a variety of complications from the procedure, but these complications do not appear to be permanently sight-threatening or detrimental to the ultimate vision recovery in the majority of cases. Long-term data on endothelial cell survival and the risk of late endothelial rejection cannot be determined with this review." "Descemet stripping automated endothelial keratoplasty should not be used in lieu of penetrating keratoplasty for conditions with concurrent endothelial disease and anterior corneal disease. These situations would include concurrent anterior corneal dystrophies, anterior corneal scars from trauma or prior infection, and ectasia after previous laser vision correction surgery."

In 2018, AAO published a Preferred Practice Pattern on corneal edema and opacification.38, Based on their findings, the following statement and recommendation was made by AAO: "Endothelial keratoplasty has supplanted penetrating keratoplasty as the procedure of choice in cases of endothelial failure in the absence of corneal scarring because patients achieve more rapid visual rehabilitation and reduction in rejection of the transplanted tissue."

National Institute for Health and Care Excellence
In 2009, NICE released guidance on corneal endothelial transplantation.(39) Additional data reviewed from the United Kingdom Transplant Register showed lower graft survival rates after endothelial keratoplasty than after penetrating keratoplasty; however, the difference in graft survival between the 2 procedures was noted to be narrowing with increased experience in endothelial keratoplasty use. The guidance concluded that “current evidence on the safety and efficacy of corneal endothelial transplantation (also known as endothelial keratoplasty is adequate to support the use of this procedure.” The guidance noted that techniques for this procedure continue to evolve, and thorough data collection should continue to allow future review of outcomes.

Government Regulations

National:

Medicare does not have an NCD addressing femtosecond clinical laser technology; however, there is an NCD that addresses laser procedures in general titled “National Coverage Determination (NCD) for “Laser Procedures” (140.5)”. Effective date: 5/1/97

Indications and Limitations of Coverage
“Medicare recognizes the use of lasers for many medical indications. Procedures performed with lasers are sometimes used in place of more conventional techniques. In the absence of a specific noncoverage instruction, and where a laser has been approved for marketing by the Food and Drug Administration, contractor discretion may be used to determine whether a procedure performed with a laser is reasonable and necessary and, therefore, covered.”

“The determination of coverage for a procedure performed using a laser is made on the basis that the use of lasers to alter, revise, or destroy tissue is a surgical procedure. Therefore, coverage of laser procedures is restricted to practitioners with training in the surgical management of the disease or condition being treated.”

Local:

No local determination was found.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Refractive Keratoplasties and Implantation of Intrastromal Corneal Ring Segments

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 7/18/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/23	12/2/22		• Joint policy established (slp) • Replaced Femtosecond Laser in Keratoplasty
1/1/24	10/17/23		• Routine maintenance (slp) • Vendor managed: N/A • V2785 added as EST
1/1/25	10/15/24		• Routine maintenance (slp) • Vendor managed: N/A

Next Review Date: 4th Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: ENDOTHELIAL KERATOPLASTY

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member’s certificate and is not guaranteed. Please consult the individual member’s certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.
- Duplicate (back-up) equipment is not a covered benefit.