9.03.22 Endothelial Keratoplasty

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**Endothelial Keratoplasty**

**Summary**

Endothelial keratoplasty (EK), 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 (DSEK), Descemet stripping automated endothelial keratoplasty (DSAEK), Descemet membrane endothelial keratoplasty (DMEK), and Descemet membrane automated endothelial keratoplasty (DMAEK). EK, and particularly DSEK, DSAEK, DMEK, and DMAEK, are becoming standard procedures. Femtosecond laser-assisted endothelial keratoplasty (FLEK) and femtosecond and excimer lasers–assisted endothelial keratoplasty (FELEK) have also been reported as alternatives to prepare the donor endothelium.

The evidence for DSEK, DSAEK, DMEK, and DMAEK in individuals who have endothelial disease of the cornea includes a number of cohort studies and a systematic review. Relevant outcomes are change in disease status, morbidity events, and functional outcomes. The available literature indicates that these procedures improve visual outcomes and reduce serious complications associated with penetrating keratoplasty (PK). Specifically, visual recovery occurs much earlier, and because EK 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 evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for FLEK and FELEK in individuals who have endothelial disease of the cornea includes a multicenter randomized trial that compared FLEK with PK. Relevant outcomes are change in disease status, morbidity events, and functional outcomes. Mean best-corrected visual acuity was worse after FLEK than after PK, and endothelial cell loss was higher. With the exception of dislocation and need for repositioning of the FLEK, the percentage of complications was similar between groups. Complications in the FLEK group were due to pupillary block, graft failure, epithelial ingrowth, and elevated intraocular pressure (IOP), whereas complications in the PK group were related to sutures and elevated IOP. The evidence is insufficient to determine the effects of the technology on health outcomes.

**FDA REGULATORY STATUS**

There are two graft insertion devices for endothelial keratoplasty with US Food and Drug Administration (FDA) 510 (k) approval;

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The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
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1) The EndoSerter, (Ocular Systems, Inc., Winston-Salem, N.C.) 510 K(k) approval number: K090626
2) The Trimotion Injector. (Kaneka Corp, Settsu Osaka Japan) 510 k approval number: K102999

POLICY STATEMENT

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Endothelial keratoplasty (Descemet's stripping endothelial keratoplasty [DSEK], Descemet's stripping automated endothelial keratoplasty [DSAEK], Descemet's membrane endothelial keratoplasty [DMEK], or Descemet's membrane automated endothelial keratoplasty [DMAEK]) may be considered medically necessary for the treatment of endothelial dysfunction, including but not limited to:

- Ruptures in Descemet's membrane,
- Endothelial dystrophy
- Aphakic, and pseudophakic bullous keratopathy,
- Iridocorneal endothelial (ICE) syndrome,
- Corneal edema attributed to endothelial failure,
- Failure or rejection of a previous corneal transplant.

Femtosecond laser-assisted corneal endothelial keratoplasty (FLEK) or femtosecond and excimer lasers-assisted endothelial keratoplasty (FELEK) are considered not medically necessary.

BENEFIT APPLICATION

The BCBS FEP contract stipulates that FDA-approved biologics, drugs and certain devices may not be considered investigational when used for their intended purpose and thus these products may only be assessed based on medical necessity.

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. 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

Literature Review

Descemet's Stripping Endothelial Keratoplasty and Descemet's Stripping Automated Endothelial Keratoplasty (DSEK/DSAEK)
A 2009 review of the safety and efficacy of DSAEK, performed by the American Academy of Ophthalmology’s (AAO) Ophthalmic Technology Assessment Committee, identified 1 level-I study (randomized controlled trial [RCT] of precut vs. surgeon dissected) along with 9 level-II (well-designed observational studies) and 21 level-III studies (mostly retrospective case series). (1) Although more than 2,000 eyes treated with DSAEK were reported on in different publications, most were reported by one research group with some overlap in patients. The main results from this evidence review are as follows:

- **DSAEK-induced hyperopia** ranged from 0.7 to 1.5 diopters (D), with minimal induction of astigmatism (ranging from -0.4 to 0.6 D).
- The reporting of visual acuity was not standardized in the studies reviewed. The average best-corrected visual acuity (BCVA) ranged from 20/33 to 20/66, and the percentage of patients seeing 20/40 or better ranged from 38% to 100%.
- The most common complication from DSAEK in the studies reviewed was posterior graft dislocation (mean 14%; range 0–82%), with a lack of adherence of the donor posterior lenticule to the recipient stroma, typically occurring within the first week. It was noted that this figure might be skewed by multiple publications from one 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 an average 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 5% of patients (range 0–29%). Iatrogenic glaucoma occurred in an average 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 effects.
- **Endothelial cell loss**, which provides an estimate of long-term graft survival, was an average 37% at 6 months and 41% at 12 months. This percentage of cell loss was reported to be similar to that observed with penetrating keratoplasty (PK).

The technology assessment concluded that DSAEK appears at least equivalent to PK in terms of safety, efficacy, surgical risks, and complication rates, although long-term results are not yet available. The evidence also indicated that endothelial keratoplasty (EK) is superior to PK in terms of 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 PK has led to the rapid adoption of EK in place of PK for the treatment of corneal endothelial failure.

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

Longer term outcomes were reported in several studies. Five-year outcomes from a prospective study conducted at the Mayo Clinic were published in 2016 by Wacker et al. (3) The study included 45 participants (52 eyes) with Fuchs endothelial corneal dystrophy who underwent Descemet stripping endothelial keratoplasty (DSEK). Five-year follow-up was available for 34 (65%) eyes. Mean high-contrast BCVA was 20/56 Snellen equivalent presurgery, and decreased to 20/25 Snellen equivalent at 60 months. The difference in high-contrast BCVA at 5 years versus presurgery was statistically significant (p<0.001). Similarly, the proportion of those with BCVA of 20/25 Snellen equivalent or better increased
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from 26% at 1 year postsurgery to 56% at 5 years (p<0.001). 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, in 2012, 3-year outcomes after DSAEK were reported by the Devers Eye Institute.4 This retrospective analysis included 108 patients who underwent DSAEK for Fuchs endothelial dystrophy or pseudophakic bullous keratopathy and had no other ocular comorbidities. BCVA was measured at 6 months and 1, 2, and 3 years. BCVA after DSAEK improved over the 3 years of the study. For example, the percentage of patients who reached a BCVA 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 BCVA of 20/40 or greater by 3 years.

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 (DMEK) and Descemet membrane automated endothelial keratoplasty (DMAEK) may reduce stromal interface haze and provide better visual acuity outcomes than DSEK or DSAEK. (5,6) Tourtas et al reported a retrospective comparison of 38 consecutive patients/eyes that underwent DMEK versus 35 consecutive patients (35 eyes) who had undergone DSAEK. (7) Only patients with Fuchs endothelial dystrophy or pseudophakic bullous keratopathy were included. After DMEK, 82% of eyes required rebubbling. After DSAEK, 20% of eyes required rebubbling. BCVA in the 2 groups was comparable at baseline (DMEK=0.70 logMAR; DSAEK=0.75 logMAR). At 6-month follow-up, mean visual acuity improved to 0.17 logMAR after DMEK and 0.36 logMAR after DSAEK. This difference was statistically significant. At 6 months following surgery, 95% of DMEK-treated eyes reached a visual acuity of 20/40 or better and 43% of DSAEK-treated eyes reached a visual acuity of 20/40 or better. Endothelial cell density decreased by a similar amount after the 2 procedures (41% after DMEK, 39% after DSAEK).

In 2013, van Dijk et al reported outcomes of their first 300 consecutive eyes treated with DMEK. (8) Indications for DMEK were Fuchs dystrophy, pseudophakic bullous keratopathy, failed PK, or failed EK. Of the 142 eyes evaluated for visual outcome at 6 months, 79% reached a BCVA of 20/25 or more and 46% reached a BCVA of 20/20 or more. Endothelial cell density measurements at 6 months were available in 251 eyes. An average cell density was 1674 cells/mm², 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 (IOP) 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 review of cases from another group in Europe suggested that a greater number of patients achieve 20/25 vision or better with DMEK. (9) Of the first 50 consecutive eyes, 10 (20%) required a secondary DSEK for failed DMEK. For the remaining 40 eyes, 95% had a BCVA of 20/40 or better, and 75% had a BCVA of 20/25 or better. Donor detachments and primary graft failure with DMEK were problematic. In 2011, this group reported on the surgical learning curve for DMEK, with their first 135 consecutive cases retrospectively divided into 3 subgroups of 45 eyes. (10) Graft detachment was the most common complication, and decreased with 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 and 73% of cases achieving a BCVA of 20/25 or better at 6 months.

A North American group reported 3-month outcomes from a prospective consecutive series of 60 cases of DMEK in 2009, and in 2011, they reported 1-year outcomes from these 60 cases plus an additional 76 cases of DMEK. (11, 12) Preoperative BCVA 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 BCVA 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 DSAEK series from the same investigators, preparation of the donor tissue and attachment of the endothelial graft
Endothelial Keratoplasty were more challenging. A 2012 cohort study by this group found reduced transplant rejection with DMEK. (13) One (0.7%) of 141 patients in the DMEK group had a documented episode of rejection compared with 54 (9%) of 598 in the DSEK group and 5 (17%) of 30 in the PK group.

The same group also reported a prospective consecutive series of their initial 40 cases (36 patients) of DMAEK (microkeratome dissection and a stromal ring) in 2011. (14) Indications for EK were Fuchs endothelial dystrophy (87.5%), pseudophakic bullous keratopathy (7.5%), and failed EK (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 BCVA of 20/40 at baseline (range, 20/25 to 20/400), median BCVA 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% were 20/40 or better. Mean endothelial cell loss at 6 months relative to baseline donor cell density was 31%.

**Femtosecond Laser-Assisted Corneal Endothelial Keratoplasty (FLEK)**

In 2009, Cheng et al. reported a multicenter randomized trial from Europe that compared FLEK with PK. (15) Eighty patients with Fuchs’ endothelial dystrophy, pseudophakic bullous keratopathy, or posterior polymorphous dystrophy, and best spectacle-corrected visual acuity lower than 20/50, were included in the study. In the FLEK group, 4 of the 40 eyes did not receive the treatment due to significant preoperative events and were excluded from the analysis. Eight eyes failed (22% of 36), and 2 patients were lost to follow-up due to death in the FLEK group. Only 1 patient was lost to follow-up in the PK group due to health issues. At 12 months postoperatively, refractive astigmatism was lower in the FLEK group than the PK group (86% vs. 51%, respectively, with astigmatism < 3.0 D), but there was greater hyperopic shift. Mean best corrected visual acuity was better following PK than FLEK at 3-, 6-, and 12-month follow-up. There was greater endothelial cell loss in the FLEK group (65%) than the PK group (23%). With the exception of dislocation and need for repositioning of the FLEK grafts in 28% of eyes, the percentage of complications were similar in the 2 groups. Complications in the FLEK group were due to pupillary block, graft failure, epithelial ingrowth, and elevated intraocular pressure, whereas complications in the PK group were related to the sutures and elevated intraocular pressure.

A small retrospective cohort study from 2013 found a reduction in visual acuity when the endothelial transplant was prepared with laser (FLEK: 0.48 logMAR, n=8) compared with microtome (DSAEK: 0.33 logMAR, n=14). (16) There was also greater surface irregularity with the laser-assisted EK.

**SUPPLEMENTAL INFORMATION**

**Ongoing and Unpublished Trials**

Currently unpublished trials that might influence this review are listed in Table 1.

**Table 1. Summary of Key Trials**

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NCT: national clinical trial.

**Practice Guidelines and Position Statements**

In 2009, the Health Policy Committee of the American Academy of Ophthalmology (AAO) published a position paper on EK, stating that the optical advantages, speed of visual rehabilitation, and lower risk of catastrophic wound failure have driven the adoption of EK as the standard of care for patients with endothelial failure and otherwise healthy corneas. The AAO position paper was based in large part on a
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comprehensive review of the literature on DSAEK by AAO’s Ophthalmic Technology Assessment Committee. (1) This committee concluded that “the evidence reviewed suggests DSAEK appears safe and efficacious for the treatment of endothelial diseases of the cornea. Evidence from retrospective and prospective DSAEK 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." "DSAEK should not be used in lieu of PK 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."

The United Kingdom’s National Institute for Health and Clinical Excellence released guidance on corneal endothelial transplantation in 2009. (17) The studies reviewed used DLEK, DSEK, and DSAEK. Additional data reviewed from the UK Transplant Register showed lower graft survival rates after EK than after PK; however, the difference in graft survival between the two procedures was noted to be narrowing with increased experience in EK use. The guidance concluded that “current evidence on the safety and efficacy of corneal endothelial transplantation (also known as endothelial keratoplasty [EK]) is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance and consent.” The Committee noted that techniques for this procedure continue to evolve, and thorough data collection should continue to allow future review of outcomes.

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Medicare National Coverage**

There is no national coverage determination.

**Summary of Evidence**

Endothelial keratoplasty (EK), 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 (DSEK), Descemet stripping automated endothelial keratoplasty (DSAEK), Descemet membrane endothelial keratoplasty (DMEK), and Descemet membrane automated endothelial keratoplasty (DMAEK). EK, and particularly DSEK, DSAEK, DMEK, and DMAEK, are becoming standard procedures. Femtosecond laser-assisted corneal endothelial keratoplasty (FLEK) and femtosecond and excimer lasers—assisted endothelial keratoplasty (FELEK) have also been reported as alternatives to prepare the donor endothelium.

The evidence for Descemet stripping endothelial keratoplasty, Descemet stripping automated endothelial keratoplasty, Descemet membrane endothelial keratoplasty, and Descemet membrane automated endothelial keratoplasty in individuals who have endothelial disease of the cornea includes a number of cohort studies and a systematic review. Relevant outcomes are change in disease status, morbid events, and functional outcomes. The available literature indicates that these procedures improve visual outcomes and reduce serious complications associated with penetrating keratoplasty (PK). Specifically, visual recovery occurs much earlier, and because endothelial keratoplasty maintains an intact globe without a sutured donor cornea, astigmatism, or the risk of severe, sight-threatening complications such as exulsive suprachoroidal hemorrhage and postoperative catastrophic wound failure are eliminated. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for femtosecond laser-assisted corneal endothelial keratoplasty (FLEK) and femtosecond and excimer lasers—assisted endothelial keratoplasty (FELEK) in individuals who have endothelial
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disease of the cornea includes a multicenter randomized trial that compared FLEK with PK. Relevant outcomes are change in disease status, morbid events, and functional outcomes. Mean best-corrected visual acuity was worse after FLEK than after PK, and endothelial cell loss was higher. With the exception of dislocation and need for repositioning of the FLEK, the percentage of complications was similar between groups. Complications in the FLEK group were due to pupillary block, graft failure, epithelial ingrowth, and elevated intraocular pressure (IOP), whereas complications in the PK group were related to sutures and elevated IOP. The evidence is insufficient to determine the effects of the technology on health outcomes.

REFERENCES

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POLICY HISTORY

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