



Kansas City

An Independent Licensee of the Blue Cross and Blue Shield Association

Endothelial Keratoplasty

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Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Endothelial Keratoplasty when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered

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

- ruptures in Descemet membrane,
- endothelial dystrophy,
- aphakic, and pseudophakic bullous keratopathy,
- iridocorneal endothelial (ICE) syndrome,
- corneal edema attributed to endothelial failure,
- and failure or rejection of a previous corneal transplant.

When Policy Topic is not covered

Femtosecond laser-assisted corneal endothelial keratoplasty (FLEK) or femtosecond and excimer lasers-assisted endothelial keratoplasty (FELEK) are considered **investigational**.

Endothelial keratoplasty is **not medically necessary** when endothelial dysfunction is not the primary cause of decreased corneal clarity.

Considerations

Endothelial keratoplasty should not be used in place 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. Clinical input 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. EK should be performed by surgeons who

are adequately trained and experienced in the specific techniques and devices used.

Description of Procedure or Service

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> With endothelial disease of the cornea 	Interventions of interest are: <ul style="list-style-type: none"> Descemet stripping endothelial keratoplasty or Descemet stripping automated endothelial keratoplasty 	Comparators of interest are: <ul style="list-style-type: none"> Penetrating keratoplasty 	Relevant outcomes include: <ul style="list-style-type: none"> Change in disease status Morbid events Functional outcomes
Individuals: <ul style="list-style-type: none"> With endothelial disease of the cornea 	Interventions of interest are: <ul style="list-style-type: none"> Descemet membrane endothelial keratoplasty or Descemet membrane automated endothelial keratoplasty 	Comparators of interest are: <ul style="list-style-type: none"> Penetrating keratoplasty 	Relevant outcomes include: <ul style="list-style-type: none"> Change in disease status Morbid events Functional outcomes
Individuals: <ul style="list-style-type: none"> With endothelial disease of the cornea 	Interventions of interest are: <ul style="list-style-type: none"> Femtosecond laser-assisted endothelial keratoplasty or femtosecond/excimer lasers-assisted endothelial keratoplasty 	Comparators of interest are: <ul style="list-style-type: none"> Penetrating keratoplasty 	Relevant outcomes include: <ul style="list-style-type: none"> Change in disease status Morbid events Functional outcomes

Summary

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

For individuals who have endothelial disease of the cornea who receive DSEK or DSAEK, the evidence 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 has indicated that these procedures improve visual outcomes and reduce serious complications associated with penetrating keratoplasty (PK). 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 evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Clinical input obtained in 2009 supported DSEK and DSAEK as the standard of care for endothelial failure, based on improved outcomes compared with PK.

For individuals who have endothelial disease of the cornea who receive DMEK or DMAEK, 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 DMEK and DMAEK procedures improve visual acuity. When compared with DSEK and DSAEK, DMEK and DMAEK 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 a meaningful improvement in the net health outcome.

Clinical input obtained in 2013 on evolving techniques for endothelial keratoplasty uniformly considered DMEK and DMAEK to be medically necessary procedures.

For individuals who have endothelial disease of the cornea who receive FLEK and femtosecond and excimer laser–assisted endothelial keratoplasty, the evidence 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 FLEK. 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, whereas complications in the PK group were related to sutures and elevated intraocular pressure. The evidence is insufficient to determine the effects of the technology on health outcomes.

Most input obtained in 2013 considered FLEK and femtosecond and excimer laser–assisted endothelial keratoplasty to be investigational.

Input obtained in 2013 was mixed on the exclusion of patients with anterior corneal disease. Additional indications suggested by the reviewers were added as medically necessary.

Background

The cornea, a clear, dome-shaped membrane that covers the front of the eye, is a key refractive element of the eye. 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 the stroma and limits entry of fluid as well, 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.

The established surgical treatment for corneal disease is penetrating keratoplasty (PK), which involves the creation of a large central opening through the cornea and then filling the opening with full-thickness donor cornea that is sutured in place. Visual recovery after PK 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. PK 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 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 (EK) techniques was termed *deep lamellar endothelial keratoplasty*, which used a smaller incision than PK, allowed more rapid visual rehabilitation, and reduced postoperative irregular astigmatism and suture complications. Modified EK 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 Descemet membrane and endothelium alone, the technique is known as Descemet membrane endothelial keratoplasty (DMEK). By eliminating the stroma on the donor tissue and possibly reducing stromal interface haze, DMEK is considered a potential improvement over Descemet stripping endothelial keratoplasty and Descemet stripping automated endothelial keratoplasty. A variation of DMEK is Descemet membrane automated endothelial keratoplasty. Descemet membrane automated endothelial keratoplasty contains a stromal rim of tissue at the periphery of the DMEK 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.

EK 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 (eg, DSEK) or with the assistance of an automated microkeratome (eg, 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 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 one or more sutures, and steroids or immune-suppressants may be provided topically or orally to reduce the potential for graft rejection. Visual recovery following EK is typically 4 to 8 weeks.

Eye Bank Association of America statistics have shown the number of EK cases in the United States increased from 30,710 in 2015 to 32,221 in 2016.¹ 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. EK-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.

Rationale

This evidence review was created in August 2009 and has been updated regularly using the MEDLINE database. The most recent literature update was performed through January 8, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long

enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Descemet Stripping Endothelial Keratoplasty and Descemet Stripping Automated Endothelial Keratoplasty

Systematic Review

In 2009, the American Academy of Ophthalmology performed a review of the safety and efficacy of Descemet stripping automated endothelial keratoplasty (DSAEK), 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).² Although more than 2000 eyes treated with DSAEK 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:

- DSAEK-induced hyperopia ranged from 0.7 to 1.5 diopters (D), with minimal induction of astigmatism (range, -0.4 to 0.6 D).
- The reporting of visual acuity was not standardized in studies reviewed. The average best-corrected visual acuity 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 DSAEK 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 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 (PK).

Reviewers concluded that DSAEK appeared to be at least equivalent to PK regarding safety, efficacy, surgical risks, and complication rates, although long-term results were not yet available. The evidence also indicated that endothelial keratoplasty (EK) is superior to PK 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 PK has led to the rapid adoption of EK for treatment of corneal endothelial failure.

Observational Studies

Fuest et al (2017) compared 5-year visual acuity outcomes in patients receiving DSAEK (n=423) or PK (n=405) in the Singapore Cornea Transplant Registry.³ Mean age of patients was 67 years. The DSAEK group had a higher percentage of Chinese patients, a higher percentage of patients with Fuchs endothelial dystrophy (FED), and a lower percentage of patients with bullous keratopathy (BK) than the PK group. Controlling for preoperative best spectacle-corrected visual acuity (BSCVA), which differed significantly between groups, patients receiving DSAEK experienced significantly better vision through 3 years of follow-up than patients undergoing PK. Four- and 5-year follow-up measures showed similar BSCVA among both treatment groups. Subgroup analyses by FED and BK showed similar patterns of significantly better vision through the first 3 years of follow-up in patients receiving DSAEK than in patients receiving PK.

Heinzelmann et al (2016) reported on 2-year outcomes in patients who underwent EK or PK for FED or BK.⁴ The study included 89 eyes undergoing DSAEK and 329 eyes undergoing PK. The postoperative visual improvement was faster after EK than after PK. For example, among patients with FED, 50% of patients achieved a best-corrected visual acuity of Snellen 6/12 or more 18 months after DSAEK vs more than 24 months after PK. Endothelial cell loss was similar after EK and 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 FED, there was a slightly increased risk of late endothelial failure in the first 2 years with EK than with PK. Graft failure was reported to be lower among patients with BK compared with patients with FED (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).⁵ The study included 45 participants (52 eyes) with FED who underwent DSEK. Five-year follow-up was available for 34 (65%) eyes. Mean high-contrast BSCVA was 20/56 Snellen equivalent presurgery and decreased to 20/25 Snellen equivalent at 60 months. The difference in high-contrast BSCVA at 5 years vs presurgery was statistically significant ($p < 0.001$). Similarly, the proportion of patients with BSCVA of 20/25 Snellen equivalent or better increased 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, 3-year outcomes after DSAEK were reported by an eye institute.⁶ This retrospective analysis (2012) included 108 patients who underwent DSAEK for FED or pseudophakic BK and had no other ocular comorbidities. BSCVA was measured at 6 months and 1, 2, and 3 years. BSCVA after DSAEK improved over 3 years of follow-up. The percentage of patients who reached a BSCVA 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 BSCVA of 20/40 or greater by 3 years.

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

Evidence for the use of DSEK and DSAEK 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 DSEK and DSAEK experience greater improvements in visual acuity than patients undergoing PK. Also, patients undergoing DSEK and DSAEK experienced significantly fewer serious adverse events than patients undergoing PK.

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.^{7,8}

Systematic Reviews

The American Academy of Ophthalmology conducted a systematic review of the safety and outcomes of DMEK and investigated whether DMEK offered any advantages over DSEK (Deng et al [2018]).⁹ 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-controls). Mean length of follow-up among the studies ranged from 5 to 68 months. A BSCVA of 20/25 was achieved by 33% to 67% of patients (5 studies). A BSCVA of 20/20 was achieved by 29% to 32% (3 studies) at 3 months postsurgery and by 17% to 67% at 6 months postsurgery. Seven studies, six of which were rated as level II evidence, directly compared DMEK with DSEK and all seven showed a faster visual recovery and a better visual outcome after DMEK compared with DSEK. The rate of endothelial cell loss, graft failure, and intraoperative and postoperative complications was similar between DMEK and DSEK.

Singh et al (2017) conducted a systematic review and meta-analysis of studies comparing DMEK with DSEK or DSAEK.¹⁰ 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 patients showed that the 6-month mean difference in BSCVA was significantly better in patients undergoing DMEK than in patients undergoing DSEK (-0.13; 95% confidence interval [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 DMEK group compared with the DSEK group.

Pavlovic et al (2017) conducted a meta-analysis of 11 studies comparing DMEK (n=350) with DSAEK (n=373).¹¹ The date of the literature search and quality assessment methods were not reported. The mean difference in BSCVA 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 DMEK group than in the DSAEK 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 DSAEK group compared with those in the DMEK group, but the difference was not significant (odds ratio, 2.7; 95% CI, 0.6 to 11.9). There were more graft failures reported in the DMEK group compared with the DSAEK group, but this difference, too, was not significant (odds ratio, 2.8; 95% CI, 0.7 to 10.6).

Li et al (2017) conducted a systematic review and meta-analysis comparing DMEK and DSEK.¹² 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 2378 eyes were included in the studies, 1124 receiving DMEK and 1254 receiving DSEK. Meta-analyses of 13 studies showed an overall mean difference in BSCVA that was significantly improved in the DMEK group compared with the DSEK group (-0.15; 95% CI, -0.19 to -0.11). This significant mean difference in BSCVA was seen at the 3-, 6-, and 12-month follow-ups. Meta-analyses 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 DMEK group than in the DSEK group (odds ratio, 4.6; 95% CI, 2.4 to 8.6).

Observational Studies

Oellerich et al (2017) reported on 6-month outcomes of a large cohort of patients undergoing DMEK by 55 surgeons from 23 countries.¹³ Outcomes of interest were BSCVA, a decrease in endothelial cell density, and complications. Subgroup analyses were conducted by 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 BSCVA improvement, with 5% experiencing no change and 5% experiencing deterioration in visual acuity. Subgroup analyses showed that the proportion of patients achieving BSCVA 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 DMEK and 35 consecutive patients/eyes who had undergone DSAEK.¹⁴ Only patients with FED or pseudophakic BK were included. After DMEK, 82% of eyes required rebubbling. After DSAEK, 20% of eyes required rebubbling. BSCVA in both 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 both procedures (41% after DMEK, 39% after DSAEK).

Van Dijk et al (2013) reported on outcomes of their first 300 consecutive eyes treated with DMEK.¹⁵ Indications for DMEK were FED, pseudophakic BK, failed PK, or failed EK. Of the 142 eyes evaluated for visual outcomes at 6 months, 79% reached a BSCVA of 20/25 or more, and 46% reached a BSCVA of 20/20 or more. Endothelial cell density measurements at 6 months were available in 251 eyes. 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 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 DMEK.¹⁶ Of the first 50 consecutive eyes, 10 (20%) required a secondary DSEK for failed DMEK. For the remaining 40 eyes, 95% had a BSCVA of 20/40 or better, and 75% had a BSCVA 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 each.¹⁷ 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/mm² and 73% of cases achieving a BSCVA 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 DMEK in 2009, and in 2011, they reported on 1-year outcomes from these 60 cases plus an additional 76 cases of DMEK.^{18,19} Preoperative BSCVA 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 BSCVA 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 were more challenging. A 2012 cohort study by this group found reduced transplant rejection with DMEK.²⁰ 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 on a prospective consecutive series (2011) of their initial 40 cases (36 patients) of DMAEK (microkeratome dissection and a stromal ring).²¹ Indications for EK were FED (87.5%), pseudophakic BK (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 BSCVA of 20/40 at baseline (range, 20/25 to 20/400), median BSCVA 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%.

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

Evidence for the use of DMEK or DMAEK consists of several systematic reviews with overlapping studies, and several observational studies, some which had no comparators and some which compared DMEK or DMAEK with DSEK or DSAEK. Analyses in the individual studies and the meta-analyses consistently showed that patients receiving DMEK or DMAEK experienced significantly better visual acuity outcomes postprocedure than patients receiving DSEK or DSAEK, 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 DMEK than DSEK, though the complications were not considered severe.

Femtosecond Laser–Assisted Endothelial Keratoplasty and femtosecond and excimer laser–assisted endothelial keratoplasty

Hosny et al (2017) reported on results from a case series on 20 eyes (19 patients) that underwent a femtosecond laser–assisted DSAEK.²² 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 postprocedure. 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.

Cheng et al (2009) conducted a multicenter randomized trial in Europe that compared femtosecond laser–assisted endothelial keratoplasty (FLEK) with PK.²³ Eighty patients with FED, BK, or posterior polymorphous dystrophy, and a BSCVA less than 20/50 were included in the trial. In the FLEK 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 FLEK group. One 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 (86% with astigmatism of ≤ 3 D); however, there was a greater hyperopic shift in the FLEK group than in the PK group. Mean BSCVA was better following PK than FLEK at the 3-, 6-, and 12-month follow-ups. There was greater endothelial cell loss in the FLEK group (65%) than in the PK group (23%). With the exception of dislocation and need to reposition the FLEK grafts in 28% of eyes, 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, whereas complications in the PK group were related to the sutures and elevated intraocular pressure.

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 (FLEK=0.48 logMAR; n=8) compared with a microtome (DSAEK=0.33 logMAR; n=14).²⁴ There was also greater surface irregularity with FLEK.

Femtosecond and excimer laser–assisted endothelial keratoplasty was reported in a small case series (N=3) by Trinh et al (2013)²⁵; no further studies of this technology have been noted.

Section Summary: Femtosecond Laser–Assisted Endothelial Keratoplasty and Femtosecond and Excimer Laser–Assisted Endothelial Keratoplasty

Evidence for FLEK consists of 2 small observational studies and an RCT. 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 DSAEK. The RCT showed that patients undergoing PK experienced better outcomes than patients in the FLEK group after 1 year of follow-up. Complication rates were similar between groups.

Evidence for the use of femtosecond and excimer laser-assisted endothelial keratoplasty consists of a single small case series described in a letter publication.

Summary of Evidence

For individuals who have endothelial disease of the cornea who receive DSEK or DSAEK, the evidence 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 has indicated that these procedures improve visual outcomes and reduce serious complications associated with PK. 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 evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have endothelial disease of the cornea who receive DMEK or DMAEK, 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 DMEK and DMAEK procedures improve visual acuity. When compared with DSEK and DSAEK, DMEK and DMAEK 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 a meaningful improvement in the net health outcome.

For individuals who have endothelial disease of the cornea who receive FLEK and femtosecond and excimer laser–assisted endothelial keratoplasty, the evidence 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 FLEK. 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, whereas complications in the PK group were related to sutures and elevated intraocular pressure. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2013 Input

In response to requests, input was received from 3 physician specialty societies (2 reviewers) and 3 academic medical centers while this policy was under review in 2013. Input uniformly considered Descemet membrane endothelial keratoplasty and Descemet membrane automated endothelial keratoplasty to be medically necessary procedures, while most input considered femtosecond laser-assisted

endothelial keratoplasty and femtosecond and excimer laser–assisted endothelial keratoplasty to be investigational. Input was mixed on the exclusion of patients with anterior corneal disease. Additional indications suggested by the reviewers were added as medically necessary.

2009 Input

In response to requests, input was received from physician specialty societies (3 reviewers representing 3 associated organizations) and 2 academic medical centers while this policy was under review in 2009. Input supported Descemet stripping endothelial keratoplasty and Descemet stripping automated endothelial keratoplasty as the standard of care for endothelial failure, due to improved outcomes compared with penetrating keratoplasty.

Practice Guidelines and Position Statements

American Academy of Ophthalmology

The American Academy of Ophthalmology (AAO) published a position paper (2009) on endothelial keratoplasty (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 an AAO comprehensive review of the literature (2009) on Descemet stripping automated endothelial keratoplasty (DSAEK).² AAO 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 [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.”

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence released guidance on corneal endothelial transplantation in 2009.²⁶ Additional data reviewed from the U.K. Transplant Register showed lower graft survival rates after EK than after penetrating keratoplasty; however, the difference in graft survival between the 2 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.” The guidance 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. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

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

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT00543660	Descemet Stripping (Automated) Endothelial Keratoplasty (DSEK or DSAEK)	1000	Mar 2018
NCT02793310	DMEK Versus DSAEK Study	56	Apr 2019
NCT00521898	Descemet Membrane Endothelial Keratoplasty (DMEK)	100	Feb 2020
NCT00800111	Study of Endothelial Keratoplasty Outcomes	5000	Feb 2025
NCT02470793	Technique and Results In Endothelial Keratoplasty (TREK)	100	Dec 2025

NCT: national clinical trial.

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Billing Coding/Physician Documentation Information

- | | |
|--------------|--|
| 65756 | Keratoplasty (corneal transplant); endothelial |
| 65757 | Backbench preparation of corneal endothelial allograft prior to transplantation (List separately in addition to code for primary |

procedure)

ICD-10 Codes

- H18.10-** Bullous keratopathy, code range
- H18.13**
- H18.50-** Hereditary corneal dystrophies, code range
- H18.59**
- T85.390A-** Other mechanical complication of other ocular prosthetic devices,
- T85.398S** implants and grafts, code range
- T86.840-** Complications of corneal transplant, code range
- T86849**

Additional Policy Key Words

N/A

Policy Implementation/Update Information

- 11/1/15 New Policy. Considered medically necessary.
- 11/1/16 No policy statement changes.
- 11/1/17 No policy statement changes.
- 11/1/18 No policy statement changes.

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