

Subject: Endothelial Keratoplasty

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Description

This document addresses a variety of endothelial keratoplasty (EK) techniques, also known as posterior lamellar keratoplasty, used to treat conditions affecting the cornea. The available EK procedures include: Descemet's membrane endothelial keratoplasty (DMEK), Descemet's stripping endothelial keratoplasty (DSEK), Descemet's stripping automated endothelial keratoplasty (DSAEK) and Descemet's membrane automated endothelial keratoplasty (DMAEK). Other similar procedures addressed in this document include Femtosecond Laser-Assisted Corneal Endothelial Keratoplasty (FLEK or FLAK) or Femtosecond and Excimer Lasers-Assisted Endothelial Keratoplasty (FELEK). These procedures differ from each other in the manner in which the recipient's endothelium is removed and the methods used to prepare the donor tissue.

Note: Please see the following related documents for additional information:

- CG-SURG-77 Refractive Surgery
- CG-SURG-94 Keratoprosthesis
- CG-SURG-105 Corneal Collagen Cross-Linking

Clinical Indications

Medically Necessary:

The use of DMEK, DSEK, DSAEK and DMAEK, is considered **medically necessary** for the treatment of disorders of the corneal endothelium, including but not limited to the following:

1. Fuchs' endothelial dystrophy;
2. Aphakic and pseudophakic bullous keratopathy (corneal edema following cataract extraction);
3. Failure or rejection of a previous corneal transplant.

Not Medically Necessary:

The use of DMEK, DSEK, DSAEK and DMAEK is considered **not medically necessary** to treat disease or injury of the corneal stroma (for example, keratoconus, corneal ulcers caused by infection and traumatic corneal injuries).

The use of FLEK or FELEK is considered **not medically necessary** for all indications.

Coding

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The following codes for treatments and procedures applicable to this guideline are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

CPT

	For the following codes when specified as endothelial keratoplasty DMEK, DMAEK, DSEK, DSAEK:
65756	Keratoplasty (corneal transplant); endothelial
65757	Backbench preparation of corneal endothelial allograft prior to transplantation

ICD-10 Procedure

	For the following codes when specified as endothelial keratoplasty DMEK, DMAEK, DSEK, DSAEK:
08R83KZ	Replacement of right cornea with nonautologous tissue substitute, percutaneous approach
08R93KZ	Replacement of left cornea with nonautologous tissue substitute, percutaneous approach

ICD-10 Diagnosis

H18.10-H18.13	Bullous keratopathy
H18.20-H18.239	Other and unspecified corneal edema
H18.331-H18.339	Rupture in Descemet's membrane
H18.501-H18.509	Unspecified hereditary corneal dystrophies
H18.511-H18.519	Endothelial corneal dystrophy (Fuchs' endothelial dystrophy)
T85.29XA-T85.29XS	Other mechanical complication of intraocular lens
T86.8401-T86.8409	Corneal transplant rejection
T86.8411-T86.8419	Corneal transplant failure
T86.8481-T86.8489	Other complications of corneal transplant

When services are Not Medically Necessary:

For the procedure and diagnosis codes listed above when criteria are not met or for all other diagnoses not listed, or when the code describes a procedure in the Clinical Indications section as not medically necessary.

When services are also Not Medically Necessary:

For the following procedure codes; or when the code describes a procedure designated in the Clinical Indications section as not medically necessary.

CPT

	For the following codes when specified as FLEK/FLAK or FELEK procedures:
65756	Keratoplasty (corneal transplant); endothelial
65757	Backbench preparation of corneal endothelial allograft prior to transplantation

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ICD-10 Procedure

08R83KZ

For the following codes when specified as FLEK/FLAK or FELEK procedures:
Replacement of right cornea with nonautologous tissue substitute, percutaneous approach

08R93KZ

Replacement of left cornea with nonautologous tissue substitute, percutaneous approach

ICD-10 Diagnosis

All diagnoses

Discussion/General Information

Corneal endothelial failure may result in impairment or loss of vision. Restoration of vision with corneal transplantation, also known as penetrating keratoplasty (PK or PKP) has been the standard of care to treat diseased or damaged corneal endothelial tissue and stroma. According to the National Eye Institute (NEI), approximately 40,000 PKs, also known as corneal transplants, are performed each year in the U.S. A corneal transplant is commonly performed to replace scarred or diseased cornea. The central portion of a cloudy cornea is removed and replaced with a donor cornea. The donor cornea is sewn in place and the suture remains in place for months to allow the graft to heal properly. After the procedure, eye drops may be used for several months to assist with the healing process. PK has been associated with long healing time and significant complications such as postoperative dehiscence and astigmatism; full recovery from a PK may take up to a year or longer.

Alternatives to standard corneal transplantation (PK), known as EKs, are being used for those diagnosed with various types of endothelial failure or endothelial dysfunction such as Fuchs's endothelial dystrophy, pseudophakic/aphakic bullous keratopathy, and failed prior corneal transplant. Available EK procedures include DMEK, DSEK, DSAEK and DMAEK. DMEK, DSEK, DSAEK, and DMAEK are lamellar (non-penetrating keratoplasty) procedures in which only a portion or partial-thickness of the cornea is removed. These techniques have been developed as an alternative to PK, which involves the replacement of the full-thickness of the recipient cornea with donor cornea. A much smaller incision is needed for these procedures compared to PK, and the graft is maintained in place while healing with a gas tamponade (bubble) rather than sutures as in the full-thickness graft used in PK. PK has been associated with long healing time and significant complications such as postoperative dehiscence and astigmatism. In contrast, EK techniques replace only the diseased corneal endothelium and involve removal of Descemet's membrane (basement layer positioned between the outer corneal stroma and the inner corneal endothelial layer) and diseased endothelium from the recipient cornea. Healthy cadaveric donor corneal endothelial tissue, including Descemet's membrane and a thin layer of donor stromal tissue, are harvested and implanted into the recipient's eye. The various procedures differ in the methods used to prepare the donor cornea and the ways the recipient epithelium is removed. Endothelial keratoplasty has surpassed penetrating keratoplasty as the procedure of choice in cases of endothelial failure without corneal scarring because, most often, more rapid visual rehabilitation and reduction in rejection of the transplant is achieved (AAO, 2018).

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Two additional EK procedures, FLEK and FELEK expand on the EK procedures addressed above by using laser cutting tools for intrastromal dissection of the donor tissue prior to removal. This is proposed to provide an improved wound stability and decreased postoperative astigmatism.

As a result of a much smaller and peripheral incision, case series have demonstrated visual recovery following DSEK/DSAEK/DMEK can be achieved more quickly (less than 6 months) compared to PK (12-18 months) (Bahar, 2008; Chen, 2008a; Price, 2009). DSEK and DSAEK compare favorably with PK with respect to the proportion of individuals who achieve 20/40 vision postoperatively. In a prospective case series of 100 eyes by Chen and colleagues (2008a), DSEK and DSAEK resulted in improved vision, corneal thickness and surface regularity. Excluding 26 eyes with known retinal pathology, 97% of the 94 eyes had a vision of 20/40 or better at 6 months and 14% obtained visual acuity of 20/20 or better. The authors concluded that this newer technique of EK yields many of the benefits of its predecessor (PK) and improves visual results, while noting the importance of additional research to determine the safety of DSAEK.

In 2013, van Dijk and colleagues reported results of a case series study of 248 subjects (300 eyes) who underwent DMEK for Fuchs endothelial dystrophy, bullous keratopathy or previous corneal transplant failure. At 6 months, 98% of eyes reached a Best Spectacle Corrected Visual Acuity (BSCVA) of $\geq 20/40$, 79% reached $\geq 20/25$, 46% reached $\geq 20/20$, and 14% $\geq 20/18$. Donor endothelial cell density showed a decrease from 2561 (± 198) cells/mm² before, to 1674 (± 518) cells/mm² at 6 months after surgery (n=251; p<0.0000).

Guerra and colleagues (2011) reported on the use of DMEK in 136 eyes in 112 subjects with Fuchs' endothelial dystrophy, pseudophakic bullous keratoplasty, or failed previous graft. They reported that at 1 year, 41% of subjects achieved a BSCVA of 20/20 or better; 80% could be corrected to 20/25 or better, and 98% achieved 20/30 or better vision. A slight refractive hyperopic shift was found at 1 year, but it was not statistically significant (p=0.08). Also, there was no significant change in the preoperative astigmatism (p=0.17). Endothelial cell loss at 1 year was $36 \pm 20\%$ (n=94; range, 13%-88%), with most of the loss being observed during the first 3 months after surgery. A total of 11 grafts (8%) demonstrated primary failure and 1 eye (0.7%) had secondary failure resulting from endothelial rejection. Episodes of immunologic rejection were documented in 7 eyes (5.1%) during the first year of follow-up. The authors concluded that DMEK had better visual acuity results in the first year after surgery than typically reported for other EK techniques, such as Descemet's stripping automated EK, while having less refractive changes and similar endothelial cell counts but required a higher re-bubbling rate.

A retrospective case series of DSAEK performed on 118 eyes in 99 subjects reported complications including graft detachment, graft failure, graft rejection, cystoid macular edema, and suprachoroidal hemorrhage (Suh, 2008). The most frequent complication was graft detachment. A total of 27 eyes developed graft detachment; 25 eyes underwent a second procedure with repositioning or rebubbling after surgery, or both. Of the 118 procedures, 21 failed due to ongoing edema post-DSAEK. As noted below, with experience and improvements with DSAEK there are fewer complications reported in the case series.

A published study by Bahar and colleagues (2008) provided the first prospective comparison of DSEK, DSAEK, DLEK and PK from a single center. This nonrandomized comparison reported on 177 eyes in 161 subjects with a mix of endothelial corneal diseases who underwent either PK (n=48), DLEK (n=68), DSEK (n=16) or DSAEK

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(n=45). Postoperative BSCVA outcome at 12 months for PK, DLEK, and DSEK and at 6 months for DSAEK were compared. DSAEK was measured at 6 months because of earlier stability of refraction postoperatively in this group. The BSCVA was 20/53 in the PK group, with DSAEK significantly better than PK (mean BCVA 20/44; $p=0.001$). DSAEK visual outcome was not significantly different from DSEK (20/56), but was better than DLEK (20/80; $p=0.001$). Although this study lacked randomization, the results are consistent with other case series using historic control showing DSEK/DSAEK provides earlier post-operative visual recovery, less post-surgical (sutured incision) astigmatism, and as good or better BSCVA than PK.

Although PK provides healthy donor endothelial tissue, it also replaces the overlying normal corneal stroma in individuals with disease limited to the endothelial layer. The full-thickness graft used in PK is secured with suture resulting in irregular astigmatism post operatively, often leading to the need for further corneal surgery or use of hard contact lens for visual recovery. Bahar (2008) compared postoperative astigmatism following PK, DSEK and DSAEK in a prospective, comparative nonrandomized study. Postoperative refractive astigmatism was significantly higher in the PK group (3.78 diopters) compared with DSEK (1.86 diopters) and DSAEK (1.36 diopters).

Traumatic globe rupture is a significant risk following PK and visual recovery following traumatic globe rupture is poor. In one case series by Tran and colleagues (2005), only 27% were able to recover visual acuity of 20/200 or better following attempts to repair the globe. Since both DSEK and DSAEK require a much smaller incision to introduce the endothelial graft than the sutured incision needed for a full-thickness corneal graft used in PK, the structural integrity of the globe is felt to be better maintained post operatively. Another case-control series compared the incidence of traumatic globe rupture following PK (5.8%) with traumatic rupture rates for extracapsular cataract surgery 1/221 (0.45%) and 0/6450 for phacoemulsification. Both of these rates were significantly less than after PK ($p=0.005$, $p<0.0001$). With PK, the highest risk period for traumatic globe rupture is the month following surgery, when wound strength is derived almost entirely from sutures. The month following removal of sutures is a second high-risk period. Following PK, the cornea never regains its preoperative strength and remains at risk for traumatic rupture for the remainder of the individual's life (Elder, 2004). In contrast, there have been no reports of traumatic wound failure after DSEK/DSAEK surgery.

Graft dislocation is the most common significant risk of DSEK/DSAEK and may increase the risk of graft failure. However, most cases of dislocation can be corrected with repositioning of the graft and gas tamponade (bubble) in an office-based procedure. Several case series report graft dislocation rates of 1-15%. In a comparative trial (Bahar, 2008), graft dislocation rates were 12.5% for DSEK and 15.6% for DSAEK. In this series, acute rejection rates were 4.2%, 0% and 2.2% for PK, DSEK and DSAEK, respectively and primary graft failure rates were 2.1%, 0%, and 2.2% for PK, DSEK, and DSAEK, respectively. These rates of acute rejection and primary graft failure were not significantly different between PK and DSEK/DSAEK.

The occurrence and extent of initial endothelial cell loss after DSEK/DSAEK is uncertain. In some, but not all case series it has been found to be higher with DSEK/DSAEK than PK. However, in the Bahar 2008 comparative series, endothelial cell loss 1 year after surgery was similar in the DSEK/DSAEK and PK groups (40%). In subsequent trials, larger incision sizes (5 mm rather than 3 mm) and improved insertion techniques have resulted in lower initial endothelial cell loss than reported in early studies (Chen, 2008b). In addition, the DSEK/DSAEK graft is larger (7.5-8.0 mm vs. 8.5-9.0 mm) than the PK graft which does compensate for early cell loss. A prospective case

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series by Price and colleagues (2010) evaluated outcomes in DSAEK (n=173) in comparison to PK (n=410) from the Cornea Donor Study. The surgeons used donor tissue between 8.25 mm and 9.0 mm with incision size of 3.2 mm or 5 mm. The author concluded, Descemet's stripping automated endothelial keratoplasty performed by experienced surgeons resulted in a higher 6-month and 12-month percent cell loss than PKP with comparable graft survival and comparable donor and recipient characteristics.

The 3-year results of this trial were published in 2013 (Price, 2013). The 3-year survival rate of the grafts did not differ significantly between DSAEK and PK procedures performed for either Fuchs' dystrophy (96% for both; $p=0.81$) or non-Fuchs' cases (86% vs. 84%; $p=0.41$). The 3-year predicted probability of a rejection episode was 9% with DSAEK versus 20% with PK ($p=0.0005$). The median 3-year cell loss in Fuchs' dystrophy cases for DSAEK and PK were 46% and 51%, respectively ($p=0.33$), and in the non-Fuchs' cases 59% and 61% ($p=0.70$). The authors concluded that graft success rate and endothelial cell loss were comparable at 3 years for DSAEK and PK procedures and that a 5-mm DSAEK incision width was associated with significantly less cell loss than a 3.2-mm incision.

The advantages of DSEK/DSAEK cited above (little if any globe rupture, earlier post-operative visual recovery, and less post-surgical astigmatism), have led to their rapid adoption over PK for the treatment of corneal endothelial failure. According to the Eye Bank Association of America (EBAA) Statistical Report (2014), more than half (54.6%) of corneal transplants performed in 2014 in the United States (U.S.) were endothelial grafts; exceeding the number of PK procedures for the third consecutive year. EK is currently the most commonly performed keratoplasty in the U.S. Although the advantages of EK procedures over PK have yet to be demonstrated in large, randomized controlled trials (RCTs), evidence from a growing body of case series studies is compelling and has resulted in the rapid adoption of these newer techniques for treating corneal endothelial disease.

The American Academy of Ophthalmology (AAO) released a report in 2009 entitled "Descemet's Stripping Endothelial Keratoplasty: Safety and Outcome". The conclusions of the report include:

The evidence reviewed is supportive of DSEK being a safe and effective treatment for endothelial diseases of the cornea. In terms of surgical risks, complication rates, graft survival (clarity), visual acuity, and endothelial cell loss, DSEK appears similar to penetrating keratoplasty (PK). It seems to be superior to PK in terms of earlier visual recovery, refractive stability, postoperative refractive outcomes, wound and suture-related complications, and intraoperative and late suprachoroidal hemorrhage risk. The most common complications of DSEK do not appear to be detrimental to the ultimate vision recovery in most cases. Long-term endothelial cell survival and the risk of late endothelial rejection are beyond the scope of this assessment.

A 2014 Cochrane review of PK versus EK as treatment for Fuchs endothelial dystrophy analyzed three RCTs representing a total 123 eyes and did not find evidence of improved visual recover after EK procedures and although higher order aberrations were lower in EK recipients, endothelial cell loss was greater. Authors acknowledge that the overall quality of the trials chosen for inclusion were not satisfactory given their small sample size and unmasked design. The review concluded that:

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More RCTs are needed to compare PKP with commonly performed EK procedures such as DSEK, DSAEK and DMEK in order to determine the answers to two key questions, whether there is any difference in the final visual outcome between these techniques and whether there are differences in the rates of graft survival in the long term?

A long-standing corneal transplant registry in Australia has provided long-term prospective data for a large cohort of 13,920 PKs, 88 DLEKs, and 2287 EKs performed between 1996 and 2013 (Coster, 2014). The primary outcome of interest in this cohort study was graft survival. Using Kaplan-Meier functions, investigators found that survival of EKs performed for Fuchs' dystrophy or pseudophakic bullous keratopathy were poorer than survival of PKs for the same indications over the same time-frame ($p < 0.001$). Visual outcomes were significantly better for PKs than for EK performed for Fuchs' dystrophy ($p < 0.001$), but EKs achieved better visual outcomes than PKs for pseudophakic bullous keratopathy ($p < 0.001$). Authors conclude that the primary outcome, graft failure, favored PK for longevity. Given the poor outcomes seen following graft failure, including increased risk for subsequent graft failure (Mitry, 2014) more long-term data from randomized, controlled-trials are needed to further define the long-term efficacy of EK compared to the more traditional PK approach. A major-shortcoming of this study design that warrants caution when interpreting results, is its failure to differentiate results by the type of EK technique performed (i.e., DSEK, DSAEK, DMEK, or DMAEK).

A meta-analysis by Yang and colleagues (2020) sought to compare the outcomes of graft survival, endothelial cell loss and vision improvement between PK and DSAEK for treating corneal endothelium diseases. A total of 10 2-arm prospective and retrospective studies ($n = 2634$ subjects; 910 eyes treated with DSAEK and 1804 eyes treated with PK) were chosen for inclusion. DSAEK was associated with a greater improvement from baseline in BSCVA, (change from baseline $= -0.225$, 95% Confidence Interval [CI] $= -0.341$ to -0.109 , $p < 0.001$) and a reduced loss of endothelial cell density, (diff. in means $= -292.05$ cells/mm², 95% CI $= -419.53$ to -146.57 cells/mm², $p < 0.001$); graft survival rates were similar (odds ratio $= 1.005$, 95% CI $= 0.329$ -3.071, $p = 0.993$). The overall results suggested that DSAEK may have an advantage over PK for corneal endothelial dysfunction in terms of the BSCVA, however the lack of definitive time frames limits conclusions with respect to endothelial cell loss and graft survival.

Two more EK techniques to be developed, called FLEK or FLAK and FELEK, utilize laser techniques to prepare the donor tissue for transplantation as opposed to manual methods used for other EK procedures. The literature addressing this procedure is limited. Cheng (2009) reported the results of a randomized trial comparing FLEK with PK for 80 subjects (80 eyes) with Fuchs' endothelial dystrophy, pseudophakic bullous keratopathy, or posterior polymorphous dystrophy, and best spectacle-corrected visual acuity less than 20/50. Subjects were randomly assigned in a 1:1 manner. In the FLEK group, 4 of the 40 eyes which did not receive the procedure were excluded from the analysis. A total of 8 eyes failed (22% of 36), and 2 participants were lost to follow-up due to death. In the PK group, only 1 participant was lost to follow-up. At 12 months postoperatively, refractive astigmatism was lower in the FLEK group than the PK group (86% vs. 51%), but there was greater hyperopic shift. Mean BSCVA was better following PK than FLEK at 3-, 6-, and 12-month follow-up. Endothelial cell loss was reported as greater in the FLEK group (65%) versus 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. The authors

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concluded that FLEK effectively reduced postoperative astigmatism and eliminated wound healing related problems compared to PK. However, they note that visual acuity is lower compared with conventional PK, and the rate of endothelial cell loss is concerning.

A nonrandomized retrospective comparative study by Chamberlain (2013) involving 100 subjects compared FLEK (n=50) to PK (n=50). Significantly lower topographic astigmatism was achieved in the FLEK group over the PK group in the 4- to 6-month follow-up period (p=0.0324). However, this difference was not present in any other follow-up period up to 24 months postoperatively. A subset analysis of subjects with keratoconus or post-LASIK ectasia did not show any difference in either astigmatism or visual acuity at any time. No significant improvement in BSCVA was noted at any time point.

Cheng (2011) reported a prospective, randomized clinical trial involving 80 subjects (80 eyes) with corneal endothelial dysfunction randomized to undergo FLEK or PK. At the end of 12 months, only 29 (72.5%) FLEK subjects were available for analysis versus 39 (97.5%) in the PK group. In the FLEK group, postoperative refractive and topographic astigmatism values were not significantly different from preoperative values. In the PK group, all postoperative refractive and topographic astigmatism values were significantly higher compared with those before surgery. At 12 months after surgery, the percentage of subjects with a refractive astigmatism of ≤ 3.0 diopters was significantly higher in the FLEK group compared with the PK group (86.2% vs. 51.3%; p=0.004). Post-operatively, the mean BSCVA in the PK group was significantly better when compared with the FLEK group at all follow-up visits. The mean gain in BSCVA at 12 months was not significantly different between the FLEK and PK groups (p=0.103).

A small (n=22) retrospective cohort study from 2013 reported a reduction in visual acuity when the endothelial transplant was prepared with FLEK versus DSAEK (Vetter, 2013). There was also greater surface irregularity with the laser-assisted EK. Given this data, it is unclear that there is any benefit to FLEK, and it may be deduced by the available evidence that PK may be superior to FLEK with regard to postoperative visual acuity.

Currently, FELEK is not in accordance with generally accepted standards of medical practice and is not considered clinically appropriate.

Definitions

Aphakia: The absence of the natural crystalline lens.

Cornea: The outermost layer of the eye; dome shaped and covers the front of the eye.

Epithelium: The outermost layer of tissue.

Phakia: The presence of the natural crystalline lens.

Pseudophakia: The substitution of the natural crystalline lens with a synthetic lens.

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Websites for Additional Information

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Descemet's membrane automated endothelial keratoplasty (DMAEK)
 Descemet's membrane endothelial keratoplasty (DMEK)
 Descemet's stripping automated endothelial keratoplasty (DSAEK)
 Descemet's stripping endothelial keratoplasty (DSEK)
 Endothelial keratoplasty (EK)
 Femtosecond and Excimer Lasers-Assisted Endothelial Keratoplasty (FELEK)
 Femtosecond Laser-Assisted Corneal Endothelial Keratoplasty (FLEK or FLAK)
 Partial-thickness, corneal transplant

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
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Reviewed	11/05/2020	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Discussion/General Information, References and Websites sections. Reformatted Coding section.
	10/01/2020	Updated Coding section with 10/01/2020 ICD-10-CM changes; added H18.501-H18.509, H18.511-H18.519 replacing H18.51, H18.59 and T86.8401-T86.8409, T86.8411-T86.8419, T86.8481-T86.8489 replacing T86.840, T86.841, T86.848.
Reviewed	11/07/2019	MPTAC review. Updated References and Websites sections.
Reviewed	01/24/2019	MPTAC review. Updated Discussion/General Information and References sections.
New	01/25/2018	MPTAC review. Initial document development. Moved content of SURG.00108 Endothelial Keratoplasty to new clinical utilization management guideline document with the same title.

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