Published in final edited form as:

Arch Ophthalmol. 2011 September ; 129(9): 1149–1154. doi:10.1001/archophthalmol.2011.102.

Baseline Factors Related to Endothelial Cell Loss following Penetrating Keratoplasty

Jonathan H. Lass, MD¹, Roy W. Beck, MD, PhD², Beth Ann Benetz, MA¹, Mariya Dontchev, MPH², Robin L. Gal, MSPH², Edward J. Holland, MD³, Craig Kollman, PhD², Mark J. Mannis, MD⁴, Francis Price Jr., MD⁵, Irving Raber, MD⁶, Walter Stark, MD⁷, R. Doyle Stulting, MD, PhD⁸, Alan Sugar, MD⁹, and the Cornea Donor Study Investigator Group

¹ Case Western Reserve University and University Hospitals Eye Institute, Cleveland, OH

² Jaeb Center for Health Research, Tampa, FL

³ Cincinnati Eye Institute, Cincinnati, OH

⁴ University of California Davis, Sacramento, CA

⁵ Price Vision Group, Indianapolis, IN

⁶ Ophthalmic Partners of Pennsylvania, Bala Cynwyd, PA

⁷ The Johns Hopkins University School of Medicine, Baltimore, MD

⁸ Emory University (now at Woolfson Eye Institute), Atlanta, GA

⁹ W.K. Kellogg Eye Center, The University of Michigan, Ann Arbor, MI

Abstract

Objective—To identify baseline (donor, recipient, operative) factors that affect endothelial cell loss following penetrating keratoplasty for a moderate-risk condition (principally Fuchs' dystrophy or pseudophakic/aphakic corneal edema).

Methods—In a subset (n=567) of Cornea Donor Study (CDS) participants, preoperative and postoperative endothelial cell density (ECD) were determined by a central reading center. Multivariate regression analyses were performed to examine which baseline factors correlated with ECD over time.

Results—Larger grafts ($p < 0.001$), younger donor age ($p < 0.001$) and female donor gender ($p = 0.004$) were significantly associated with higher ECD during follow up. Mean endothelial cell loss at 5 years was 68% for $> 8 - 9$ mm grafts, 75% for $7 - < 8$ mm grafts and 74% for those grafts 8.0mm in diameter. Grafts from female donors experienced a 67% cell loss compared with a 72% cell loss among grafts from male donors. Method of tissue retrieval, donor cause of death, history of diabetes, and time from death to preservation or to surgery were not significantly associated with changes in ECD over time (n=567).

Corresponding Author: Jonathan H. Lass, MD, c/o Cornea Donor Study Coordinating Center, Jaeb Center for Health Research, 15310 Amberly Drive, Suite 350, Tampa, FL 33647, Phone: (813) 975-8690; Fax: (813) 975-8761; cds@jaeb.org..

Clinical Trial Registry: clinicaltrials.gov NCT00006411

Conclusions—Following penetrating keratoplasty for endothelial dysfunction conditions, larger donor graft size, younger donor age and female donor gender were associated with higher ECD over five years. This data warrants exploring the possibility that similar associations may exist following endothelial keratoplasty.

INTRODUCTION

The Cornea Donor Study (CDS) was designed to determine the effect of donor age on penetrating keratoplasty outcomes.¹ At five years, no significant effect of donor age, up to 75 years, on graft survival was found.² Other donor factors (method of retrieval, processing factors, timing of the donor cornea usage)³ and ABO incompatibility⁴ likewise had no effect on graft survival. The risk for graft failure was approximately four fold higher in eyes with pseudophakic or aphakic corneal edema than in eyes with Fuchs' dystrophy, whether pseudophakic or not.⁵ Prior glaucoma surgery and/or preoperative glaucoma medication use also substantially increased the graft failure rate.⁵

While donor age had no effect on 5-year graft survival, a slight association between increasing donor age and greater post-penetrating keratoplasty corneal endothelial cell loss was detected in an ancillary study to the CDS, the Specular Microscopy Ancillary Study (SMAS).⁶ The SMAS also confirmed that there was substantial cell loss in successful grafts at five years irrespective of donor age (mean loss preoperatively to 5 years = 69% for donors <66 years old and 75% for donors >66 years). In this study, we evaluated whether other donor,^{3, 7} recipient,⁵ and operative factors⁵ might be associated with endothelial cell loss during the first five years after penetrating keratoplasty.

Materials and Methods

Study Protocol

The CDS and the SMAS protocols are described in detail in earlier publications.^{2, 3, 5-11} Briefly summarized, subjects eligible for the study were between 40 and 80 years old with corneal disease associated with endothelial decompensation and moderate risk of failure (principally Fuchs' dystrophy and pseudophakic corneal edema). Eligible corneas were from donors 10 to 75 years old meeting Eye Bank Association of America standards.^{3, 7, 12} Eligibility criteria also included a preoperative baseline eye bank determined endothelial cell density (ECD) of the central corneal endothelium from 2300 to 3300 cells/mm². Clinical investigators and subjects were masked to donor age and ECD of the donor cornea. Subject characteristics, including age, were not taken into account when the cornea assignment was made. Study protocols were approved by institutional review boards at each participating site and written consent was obtained from each subject.

Preoperative care, surgical technique, and postoperative care (including prescription of medications), were provided according to each clinical investigator's customary routine.^{2, 5, 11} Study follow-up visits were required at 6 months, 12 months and thereafter annually for 5 years. Annual follow up continued unless a regrant was performed.

The eye bank obtained preoperative specular microscopic images of the central donor corneal endothelium. Each clinical site obtained postoperative specular microscopic images of the central corneal endothelium of the graft at the 6 month and annual follow-up visits. The preoperative donor images and postoperative subject images were evaluated for quality and ECD by a central reading center, the Cornea Image Analysis Reading Center or CIARC (formerly the Specular Microscopy Reading Center or SMRC) at Case Western Reserve University and University Hospitals Eye Institute, using a previously described variable frame analysis method.^{6, 8-10} If the independent ECD determinations of two readers differed by > 5.0%, a third determination of ECD was made by an independent adjudicator.⁸

Statistical Methods

Analysis was restricted to 567 subjects with at least one gradable postoperative image before either the date of graft failure or the end of 5-year follow up. Subjects with graft failures due to trauma or infection were excluded from the analysis. Images obtained after graft failure were not included in the analysis and no attempt was made to impute missing image data after graft failure. The analysis, therefore, was conditional on graft survival.

Baseline donor ECD was determined by the reading center for 376 (66%) cases and by the eye bank for the remaining 191 (34%). The relationships between baseline (donor, recipient, and operative) factors and ECD were explored in multivariate analyses. Cross-sectional regression models were used to evaluate change in ECD from baseline to 5 years and longitudinal repeated measures models were used to evaluate ECD change throughout follow up. All models were fit with the rank-normalized transformation (van der Waerden scores). Final multivariate models were generated through stepwise selection of covariates at a significance level of 0.01 after adjusting for baseline ECD. The large number of statistical comparisons increases the likelihood of a false positive and no attempt was made to control the overall type I error probability in these exploratory analyses. A threshold of $p < 0.01$ was used to define statistical significance as a compromise to balance the risks of type I vs. type II errors.

All reported p-values are two-sided. Statistical analyses were conducted using SAS version 9.1 software (SAS Institute Inc., Cary, NC).

Results

The mean age ($\pm$ SD) of the 567 transplant recipients at the time of penetrating keratoplasty was 70 ± 8 years; 357 (63%) were women and 536 (95%) were white, non-Hispanic. Endothelial failure indications included Fuchs' dystrophy in 382 (67%), pseudophakic or aphakic corneal edema in 165 (29%), and a variety of other diagnoses in 20 (4%) participants. The mean donor age at time of death was 58 ± 15 years; 191 (34%) donors were women and 539 (95%) were white, non-Hispanic. The primary cause of donor death was cardiovascular disease or stroke (61%), followed by cancer (19%), trauma (9%), respiratory (7%) and other causes (4%). Other baseline donor, recipient, and operative characteristics were comparable to previous CDS results.^{3, 5, 7, 11}

The changes in ECD over time are illustrated for the entire 567 recipients with at least one postoperative image (Figure 1A) and for the 345 recipients with a 5-year image (Figure 1B). The baseline median (25th, 75th percentiles) ECD was 2698 (2481, 2892) cells/mm², which dropped to 778 (576, 1267) cells/mm² at 5 years, representing a 70% (55%, 77%) loss of cells during the course of the study (Figure 1B).

In the multivariate analysis, younger donor age ($p<0.001$), female donor gender ($p=0.004$) and larger graft size ($p<0.001$) were significantly associated with higher ECD over the course of follow up, after adjusting for baseline ECD and diagnosis/lens status (Table 1). The association between graft size and ECD loss over time remained significant after adjusting the model for potential effect by site in order to control for any influence of the individual surgeon's technique on the size of the graft. At 5 years, among 345 eyes that had not experienced graft failure, a smaller drop in ECD from baseline was associated with larger graft size ($p<0.001$) and younger donor age ($p=0.009$), after adjusting for baseline ECD (Table 1). When female donor gender was added to the above multivariate model, it demonstrated a weaker association with the 5-year change in ECD ($p=0.09$) than it did in the longitudinal analysis. No other donor, recipient, and operative factors, notably method of tissue retrieval, cause of death, diabetes history, time from death to preservation or to surgery, baseline recipient diagnosis and lens status, prior use of glaucoma medications and/or surgery, and postoperative intraocular pressure demonstrated significant association with changes in ECD over time (Table 1).

Discussion

As we previously reported⁶, subjects who received a cornea from a younger donor experienced slightly less long term endothelial cell loss. This association was most evident with corneas from <40 years old donors. Among grafts that survived for 5 years postoperatively, the 44 donors <40 years of age experienced 62% cell loss compared with a 75% loss among the 62 grafts from donors between 70 and 76 years of age (Table 1). In addition to the reported association with age, the current analyses also identified associations between endothelial cell loss and donor graft size and donor gender.

Graft size was associated with endothelial cell loss after adjusting for baseline ECD and diagnosis/lens status. At 5 years, those grafts > 8.0 – 9.0 mm in diameter experienced a median 68% cell loss compared to a 75% loss for those grafts 7.0 to < 8.0 mm in diameter and a 74% loss for those grafts 8.0mm in diameter. This effect did not appear to be related to the disparity between the graft and recipient bed diameters. Previous authors have found a similar correlation with larger graft diameters following penetrating keratoplasty and less endothelial cell loss.^{13, 14} However, the advantage of less postoperative cell loss after penetrating keratoplasty with larger donor diameter may be offset by a higher risk for graft rejection.^{15, 16}

The observed effect of less postoperative cell loss after penetrating keratoplasty with larger donor diameter may also be applicable in endothelial keratoplasty, as grafts >8.0 mm in diameter are commonly used and the observed rate of cell loss after six months postoperatively is slower when compared to penetrating keratoplasty.^{17, 18} With endothelial

keratoplasty 26% more cells are transplanted with a 9 mm donor than an 8 mm donor and the peripheral cornea may have a higher density of cells than the central cornea, further adding to this benefit.^{19, 20} The postulated beneficial effect of larger endothelial keratoplasty grafts may be greater for those with pseudophakic corneal edema compared to those with Fuchs' dystrophy, since the peripheral endothelium is more compromised in the former condition.

In the longitudinal multivariate analysis, female donor gender was significantly associated with higher ECD during the course of follow up ($p=0.004$) (Table 1), but this association was not statistically significant at 5 years in those grafts that had not failed (5-year cell loss of 72% vs. 67% in grafts from male and female donors respectively). Kinoshita made a similar observation in a cohort of 340 penetrating keratoplasties (225 male and 125 female donors) followed over a 7 year period (personal communication), while another study reported that normal females had a 2.9% greater cell density than males²¹. Receptors for both male and female hormones have been shown to be present in the epithelium, keratocytes, and most relevantly, the endothelium of the human cornea²², which raises the possibility that these hormones may play a biologic role in corneal function. While some studies have reported an effect of these hormones on lacrimal²³ and meibomian gland function and corneal thickness²⁴ none have reported effects on corneal endothelial viability. One study has suggested a differential effect of the sex hormones on cellular apoptosis.²⁵ Further *in vitro*, *ex vivo*, and clinical studies are warranted to determine if hormones, particularly estrogens, play a role in endothelial survival following keratoplasty.

Similar to our finding of no relationship with any donor factors and graft failure,³ the condition of the donor, cause of death, history of diabetes, death to preservation time, death to surgery time, and method of retrieval were unrelated to the degree of endothelial cell loss. In the CDS, although those with a diagnosis of pseudophakic/aphakic corneal edema were found to have a 4 times higher graft failure rate than the Fuchs' dystrophy group, independent of lens status⁵, recipient diagnosis was not found to be related to cell loss over time. There was also no observed relationship between prior treatment for glaucoma and endothelial cell loss, although these factors also had a highly significant impact on graft failure in the CDS.⁵ Although this may be related to the small number in the preoperative glaucoma/surgery group ($n=69$) compared with the group with no medication/surgery ($n=498$), Lee and Kim reported results for a similarly sized study where those without preoperative glaucoma ($n=53$) had substantially less cell loss ($38 \pm 19\%$) at two years than those with preoperative glaucoma ($n=30$, $57 \pm 21\%$)²⁶. The deleterious effect of elevated intraocular pressure remains ill-defined, while tube shunts continue to be a major risk for progressive loss of endothelial function with both penetrating^{27, 28} and endothelial keratoplasty¹⁸. This is not surprising considering the marked endothelial cell loss associated with a commonly used shunt, the Ahmed glaucoma valve, without keratoplasty.²⁹

Our findings are strengthened by the prospective study design, large sample size, and the determination of the ECD by a central reading center. However, as with all studies of changes of ECD over time following keratoplasty, there are problems inherent in these analyses that cannot be overcome by statistical methods. Outcome data are conditional on surviving grafts; thus, there is the potential for bias due to dropout of eyes from the analysis

dataset when grafts fail. However, none of these factors reported to be related to endothelial cell loss over time are associated with graft failure over five years in the CDS.

In addition to the baseline factors examined in this study, there may be post-operative factors that impacted the endothelial cell loss we observed in this cohort. In this analysis, post-operative factors were not examined either because data was not collected (e.g. duration of topical corticosteroid usage), or because impact was difficult to determine due to visit frequency and timing of specular microscopic examination (e.g. graft rejection).

The SMAS has expanded our understanding of the various baseline factors that influence (donor age, graft size, and surprisingly, female gender) and appear to have no influence (notably death to surgery, cause of death, diabetes, method of retrieval) on endothelial survival following penetrating keratoplasty for conditions with endothelial dysfunction. However, while endothelial cell loss may be a proxy measure for later graft failure, this relationship is not straightforward. The CDS data showed that an ECD < 1700 cells/mm² at 6 months was associated with a graft failure rate of 13% at 5 years, while an ECD of > 2500 cells/mm² at 6 months was associated with a 2% failure rate at 5 years⁹. On the other hand, 14% of clear grafts had an ECD of < 500 cells/mm² at 5 years. Thus, further observation is warranted to determine how the observed decrease in ECD at 5 years impacts the graft success rate over a longer time period.

Acknowledgments

A list of the members of the Cornea Donor Study Investigator Group is available at <http://archophth.amaassn.org/> (Archives of Ophthalmology 2010; 128: 63-69.)

Roy Beck, M.D., Ph.D., the Principal Investigator for the Cornea Donor Study, had full access to all the study data and take responsibility for the integrity of the data and the accuracy of the data analysis.

The following CDS Publications Committee members independently reviewed and approved this manuscript for submission: Christopher R. Croasdale, M.D., Mark D. Mifflin, MD, Joel Sugar, MD.

We would like to acknowledge M. Edward Medof, M.D., Ph.D. for his consultation on the relationship of gender and endothelial cell loss.

Funding/Support: Supported by cooperative agreements with the National Eye Institute, National Institutes of Health, Department of Health and Human Services EY12728 and EY12358. Additional support provided by: Eye Bank Association of America, Bausch & Lomb, Inc., Tissue Banks International, Vision Share, Inc., San Diego Eye Bank, The Cornea Society, Katena Products, Inc., ViroMed Laboratories, Inc., Midwest Eye-Banks (Michigan Eye-Bank, Illinois Eye-Bank), Konan Medical Corp., Eye Bank for Sight Restoration, SightLife, Sight Society of Northeastern New York (Lions Eye Bank of Albany), Lions Eye Bank of Oregon.

References

1. Beck RW, Gal RL, Mannis MJ, et al. Is donor age an important determinant of graft survival? Cornea. 1999; 18:503–510. [PubMed: 10487423]
2. Cornea Donor Study Investigator Group. The effect of donor age on corneal transplantation outcome: results of the cornea donor study. Ophthalmology. 2008; 115:620–626. [PubMed: 18387407]
3. Cornea Donor Study Investigator Group. Donor risk factors for graft failure in the cornea donor study. Cornea. 2009; 28:981–985. [PubMed: 19724216]
4. Cornea Donor Study Investigator Group. The effect of ABO blood incompatibility on corneal transplant failure in conditions with low-risk of graft rejection. Am J Ophthalmol. 2009; 147(3): 432–438. [PubMed: 19056078]

5. Cornea Donor Study Investigator Group. Recipient risk factors for graft failure in the cornea donor study. *Ophthalmology*. 2009; 116(6):1023–1028. [PubMed: 19395036]
6. Cornea Donor Study Investigator Group. Donor age and corneal endothelial cell loss five years after successful cornea transplantation: specular microscopy ancillary study results. *Ophthalmology*. 2008; 115:627–632. [PubMed: 18387408]
7. Cornea Donor Study Group. Baseline donor characteristics in the Cornea Donor Study. *Cornea*. 2005; 24:389–396. [PubMed: 15829793]
8. Benetz BA, Gal RL, Ruedy KJ, et al. Specular Microscopy Ancillary Study methods for donor endothelial cell density determination of Cornea Donor Study images. *Curr Eye Res*. 2006; 31:319–327. [PubMed: 16603465]
9. Cornea Donor Study Investigator Group. Endothelial cell density to predict endothelial graft failure after penetrating keratoplasty. *Arch Ophthalmol*. 2010; 128:63–69. [PubMed: 20065219]
10. Cornea Donor Study Group. An evaluation of image quality and accuracy of eye bank measurement of donor cornea endothelial cell density in the Specular Microscopy Ancillary Study. *Ophthalmology*. 2005; 112:431–440. [PubMed: 15745770]
11. Cornea Donor Study Group. Clinical profile and early surgical complications in the Cornea Donor Study. *Cornea*. 2006; 25:164–170. [PubMed: 16371775]
12. Eye Bank Association of America. EBAA. Washington, DC: 2000. Medical Standards..
13. Langenbucher A, Nguyen NX, Seitz B. Predictive donor factors for chronic endothelial cell loss after nonmechanical penetrating keratoplasty in a regression model. *Graefes Arch Clin Exp Ophthalmol*. 2003; 241:975–981. [PubMed: 14618338]
14. Chung SH, Kim HK, Kim MS. Corneal endothelial cell loss after penetrating keratoplasty in relation to preoperative recipient endothelial cell density. *Ophthalmologica*. 2009; 224:194–198. [PubMed: 19864930]
15. Boisjoly HM, Tourigny R, Bazin R, et al. Risk factors of corneal graft failure. *Ophthalmology*. 1993; 100(11):1728–1735. [PubMed: 8233403]
16. Epstein AJ, de Castro TN, Laibson PR, Cohen EJ, Rapuano CJ. Risk factors for the first episode of corneal graft rejection in keratoconus. *Cornea*. 2006; 25(9):1005–1011. [PubMed: 17133044]
17. Price MO, Gorovoy M, Benetz BA, et al. Descemet's stripping automated endothelial keratoplasty outcomes compared with penetrating keratoplasty from the Cornea Donor Study. *Ophthalmology*. 2010; 117:438–444. [PubMed: 20031230]
18. Price MO, Fairchild KM, Price DA, Price FWJ. Descemet stripping endothelial keratoplasty: 5-year graft survival and endothelial cell loss. *Ophthalmology*. In press.
19. Price MO, Price FWJ. Endothelial cell loss after descemet stripping with endothelial keratoplasty. *Ophthalmology*. 2008; 115:857–865. [PubMed: 17868873]
20. Amann J, Holley GP, Lee SB, Edelhauser HF. Increased endothelial cell density in the paracentral and peripheral regions of the human cornea. *Am J Ophthalmol*. 2003; 135:584–590. [PubMed: 12719063]
21. Snellingen T, Rao GN, Shrestha JK, Huq F, Cheng H. Quantitative and morphological characteristics of the human corneal endothelium in relation to age, gender, and ethnicity in cataract populations of South Asia. *Cornea*. 2001; 20:55–58. [PubMed: 11189005]
22. Suzuki T, Kinoshita Y, Tachibana M, Matsushima Y, Kobayashi Y, et al. Expression of sex steroid hormone receptors in human cornea. *Cur Eye Research*. 2001; 22(1):28–33.
23. Sullivan DA, Jensen RV, Suzuki T, Richards SM. Do sex steroids exert sex-specific and/or opposite effects on gene expression in lacrimal and meibomian glands. *Mol Vis*. 2009; 15:1553–1572. [PubMed: 19693291]
24. Keskin N, Canturk S, Aydin S, Saygili H, Ozgun C. An objective method to determine corneal changes during menopause. *Clin Exp Obstet Gynecol*. 2009; 36(3):176–178. [PubMed: 19860363]
25. Cutolo M, Capellino S, Montagna P, Ghiorzo P, Sulli A, Villaggio B. Sex hormone modulation of cell growth and apoptosis of the human monocytic/macrophage cell line. *Arthritis Res Ther*. 2005; 7(5):R1124–1132. [PubMed: 16207329]
26. Lee HS, Kim MS. Influential factors on the survival of endothelial cells after penetrating keratoplasty. *Eur J Ophthalmol*. 2009; 19(6):930–935. [PubMed: 19882586]

27. Rapuano CJ, Schmidt CM, Cohen EJ, et al. Results of alloplastic tube shunt procedures before, during, or after penetrating keratoplasty. *Cornea*. 1995; 14(1):26–32. [PubMed: 7712732]
28. Hollander DA, Giacony JA, Holland GN, et al. Graft failure after penetrating keratoplasty in eyes with Ahmed valves. *Am J Ophthalmol*. 2010; 150(2):169–178. [PubMed: 20537311]
29. Lee EK, Yun YJ, Lee JE, Yim JH, Kim CS. Changes in corneal endothelial cells after Ahmed glaucoma valve implantation: 2-year follow up. *Am J Ophthalmol*. 2009; 148(3):361–367. [PubMed: 19505676]

Endothelial Cell Density Change over Time

Figure 1. Endothelial cell density change over time. **A:** Includes all subjects that have at least one gradable postoperative image before either the date of graft failure or the end of 5-year follow up available (n=567), **B:** Restricted to subjects without graft failure at 5 years (n=345). Black dots indicate mean values; horizontal lines in the boxes, medians; and the bottom and top of the boxes, the 25th and 75th percentiles, respectively.

Endothelial Cell Density Over Time According to Donor Gender

Figure 2.

Endothelial cell density over time according to donor gender. Black dots indicate mean values; horizontal lines in the boxes, medians; and the bottom and top of the boxes, the 25th and 75th percentiles, respectively.

Table 1

Endothelial Cell Density (ECD) over Time by Baseline Recipient/Donor Factors

Baseline Factors		ECD at:												5 Year ECD			
		Baseline		6 Months		1 Year		2 Years		3 Years		4 Years		5 Years		Change [*]	% Loss ^{**}
	N	Median	N	Median	N	Median	N	Median	N	Median	N	Median	N	Median	N	Median	Median
Overall	567	2687	296	2479	373	2244	353	1626	311	1212	290	996	345	778	345	-1818	-70%
RECIPIENT FACTORS																	
Age (years)																	
40 – <50	19	2866	7	N/A	10	2212	12	1924	11	1272	7	N/A	12	1206	12	-1683	-58%
50 – <60	64	2692	34	2622	38	2349	35	1822	31	1328	41	1028	50	878	50	-1699	-65%
60 – <70	152	2672	71	2300	99	2156	89	1597	85	1287	87	1132	97	721	97	-1854	-74%
70 – <80	310	2687	171	2515	211	2259	203	1493	170	1084	147	929	175	778	175	-1804	-71%
80 – 86	22	2726	13	2517	15	2287	14	1967	14	1480	8	N/A	11	670	11	-2009	-75%
Race																	
White (non-Hispanic)	536	2687	280	2499	357	2259	341	1637	297	1236	279	1028	331	779	331	-1810	-70%
Nonwhite (or Hispanic)	31	2752	16	2125	16	1859	12	1249	14	1104	11	879	14	648	14	-1924	-74%
Gender																	
Male	210	2691	115	2477	147	2156	136	1574	121	1165	107	952	122	779	122	-1850	-71%
Female	357	2686	181	2480	226	2274	217	1676	190	1236	183	1099	223	778	223	-1783	-70%
Baseline Diagnosis and Lens Status																	
Fuchs; pre/post phakic	86	2696	45	2466	53	2302	48	1891	46	1635	53	1174	65	939	65	-1704	-65%
Fuchs; pre phakic/post PA	177	2686	89	2513	121	2352	116	1881	105	1272	103	978	128	750	128	-1880	-70%
Fuchs; pre/post PA	119	2668	58	2381	74	2189	74	1481	71	1118	62	914	69	683	69	-1809	-74%
PACE; post PA	165	2655	91	2368	114	1985	103	1338	78	1041	61	972	72	786	72	-1786	-71%
Other diagnoses ¹	20	2907	13	2809	11	2635	12	1933	11	1250	11	834	11	578	11	-2386	-81%
History of diabetes ²																	
No	480	2690	246	2466	323	2244	306	1625	276	1197	246	1029	298	778	298	-1818	-70%

Baseline Factors			ECD at:												5 Year ECD		
Baseline			6 Months		1 Year		2 Years		3 Years		4 Years		5 Years		Change * % Loss **		
N	Median	N	Median	N	Median	N	Median	N	Median	N	Median	N	Median	N	Median	Median	
Yes	77	2709	45	2552	44	2299	42	1703	35	1360	42	900	46	784	46	-1802 -71%	
Smoking status at time of surgery																	
No	529	2682	273	2473	346	2238	328	1625	291	1188	272	996	325	779	325	-1809 -70%	
Yes	38	2806	23	2613	27	2283	25	1708	20	1369	18	1034	20	733	20	-2042 -74%	
Prior use of glaucoma medications/ surgery																	
No meds and no surgery	498	2681	254	2499	328	2223	313	1656	277	1250	263	1002	315	778	315	-1821 -70%	
Meds and/or surgery	69	2736	42	2432	45	2250	40	1129	34	972	27	914	30	819	30	-1754 -68%	
OPERATIVE FACTORS																	
Donor tissue size																	
7.00 - <8.0	119	2722	60	2362	80	2113	77	1298	57	976	60	910	62	719	62	-1974 -75%	
8.0	104	2729	53	2412	66	2289	56	1752	52	1086	50	783	64	678	64	-1879 -74%	
>8.0 - 9.0	344	2666	183	2516	227	2251	220	1692	202	1362	180	1123	219	866	219	-1749 -68%	
Donor tissue-recipient bed size disparity ³																	
Graft (0.25-0.50mm) smaller	62	2614	24	2189	39	1944	38	1128	26	656	29	778	38	615	38	-1790 -76%	
Same size	39	2722	14	2221	19	2174	21	1310	16	1141	22	1331	26	728	26	-1854 -73%	
Graft 0.25 mm larger	343	2700	205	2524	246	2274	228	1662	198	1263	182	1016	210	789	210	-1821 -70%	
Graft 0.50mm larger	122	2695	52	2466	68	2289	66	1770	71	1340	56	1009	70	817	70	-1793 -70%	
Vitrectomy																	
No	492	2700	247	2519	318	2294	307	1656	272	1224	263	983	309	758	309	-1820 -70%	
Yes	75	2611	49	2166	55	1932	46	1397	39	1177	27	1099	36	807	36	-1769 -71%	
Post-operative Intraocular Pressure ⁴ (mmHg)																	
≤25	498	2699	260	2484	329	2259	313	1643	273	1238	256	1029	305	778	305	-1820 -70%	
>25	68	2580	36	2473	44	1993	40	1308	38	1013	34	905	39	782	39	-1758 -71%	

Baseline Factors			ECD at:												5 Year ECD			
Baseline			6 Months		1 Year		2 Years		3 Years		4 Years		5 Years		Change *		% Loss **	
N	Median		N	Median	N	Median	N	Median	N	Median	N	Median	N	Median	N	Median	N	Median
DONOR FACTORS																		
Age (years)																		
12 – <40	68	2891	33	2726	44	2600	39	2264	43	1827	41	1313	44	1102	44	–1759		–62%
40 – <50	59	2673	33	2359	41	2124	31	1313	31	1247	28	806	33	785	33	–1854		–73%
50 – <60	136	2644	75	2334	97	2307	96	1823	80	1334	67	1276	85	802	85	–1699		–69%
60 – <70	186	2677	86	2516	114	2258	114	1477	100	1031	95	837	121	706	121	–1879		–73%
70 – 76	118	2635	69	2409	77	2038	73	1427	57	941	59	896	62	661	62	–1884		–75%
Race																		
White (non-Hispanic)	539	2680	284	2466	359	2214	339	1626	294	1209	273	990	325	751	325	–1820		–71%
Non-white (or Hispanic)	28	2845	12	2774	14	2424	14	1797	17	1218	17	1002	20	1038	20	–1763		–63%
Gender																		
Male	376	2664	192	2420	252	2151	236	1522	200	1120	189	934	240	737	240	–1843		–72%
Female	191	2749	104	2591	121	2452	117	1891	111	1504	101	1218	105	853	105	–1775		–67%
Cause of death																		
Cardio/Stroke	346	2669	181	2428	233	2170	225	1508	193	1182	178	944	216	732	216	–1842		–72%
Cancer	105	2700	49	2513	61	2244	60	1535	54	1151	57	972	58	863	58	–1763		–68%
Trauma	49	2803	28	2599	37	2444	25	2026	28	1459	23	1144	28	1089	28	–1794		–63%
Respiratory	42	2693	22	2503	28	2329	26	2033	24	1431	19	1319	27	758	27	–1898		–73%
Other	25	2611	16	2493	14	2095	17	1474	12	1063	13	983	16	839	16	–1740		–68%
History of diabetes																		
No	453	2696	239	2508	301	2259	287	1676	252	1256	237	1028	278	786	278	–1810		–70%
Yes	114	2658	57	2365	72	2067	66	1421	59	897	53	912	67	726	67	–1894		–74%
Tissue retrieval																		
Enucleation	129	2670	64	2445	84	2225	86	1753	76	1466	69	1118	83	786	83	–1810		–69%
In situ	438	2695	232	2485	289	2244	267	1584	235	1165	221	980	262	766	262	–1819		–71%

Baseline Factors	ECD at:												5 Year ECD				
	Baseline		6 Months		1 Year		2 Years		3 Years		4 Years		5 Years		Change [*]	% Loss ^{**}	
	N	Median	N	Median	N	Median	N	Median	N	Median	N	Median	N	Median	Median	Median	
Tissue refrigerated																	
No	113	2702	50	2329	55	2152	59	1498	50	1076	55	929	64	791	64	-1775	-70%
Yes	454	2687	246	2514	318	2257	294	1650	261	1218	235	1054	281	767	281	-1823	-70%
Time from death to preservation																	
0-<5 hrs	92	2713	49	2528	53	2286	51	1593	43	1188	46	1003	56	796	56	-1787	-70%
5-<9 hrs	309	2686	159	2513	199	2265	200	1718	174	1268	160	1099	193	786	193	-1842	-70%
9-<11 hrs	94	2688	49	2359	69	2182	56	1346	57	1046	46	916	54	762	54	-1819	-72%
11- 12 hrs	58	2650	32	2294	41	2048	38	1444	28	939	31	846	38	690	38	-1819	-73%
>12 hrs	14	2795	7	N/A	11	2253	8	N/A	9	N/A	7	N/A	4	N/A	4	N/A	N/A
Time from death to surgery																	
0-2 days	76	2700	37	2480	45	2107	45	1584	41	1082	43	1228	49	853	49	-1783	-67%
3-4 days	315	2664	168	2515	207	2251	199	1637	172	1209	154	987	188	739	188	-1876	-72%
5-8 days	176	2725	91	2365	121	2253	109	1623	98	1227	93	973	108	850	108	-1802	-68%

N/A = analysis not done for subgroups with N < 10

PACE = Pseudophakic/Aphakic Corneal Edema

PA = Pseudophakic or Aphakic

* 5-Year ECD Change is calculated as the difference between the ECD values at 5 years and baseline (5-Year ECD – Baseline ECD)

** 5-Year ECD Loss is calculated as (5-Year ECD – Baseline ECD)/Baseline ECD and expressed as percent

¹ Includes 20 subjects with variety of diagnoses; 5 with Interstitial Keratitis, 4 with Posterior Polymorphous Dystrophy, 2 with Perforating Corneal Injury and 9 with other causes of endothelial failure

² Unknown for 10 subjects

³ 1 subject with missing value for bed size

⁴ 1 subject with missing value for post-operative intraocular pressure