

# Endothelial Cell Density to Predict Endothelial Graft Failure After Penetrating Keratoplasty

Jonathan H. Lass, MD; Alan Sugar, MD; Beth Ann Benetz, MA; Roy W. Beck, MD, PhD; Mariya Dontchev, MPH; Robin L. Gal, MSPH; Craig Kollman, PhD; Robert Gross, MD; Ellen Heck, MS, MA; Edward J. Holland, MD; Mark J. Mannis, MD; Irving Raber, MD; Walter Stark, MD; R. Doyle Stulting, MD, PhD;  
for the Cornea Donor Study Investigator Group

**Objective:** To determine whether preoperative and/or postoperative central endothelial cell density (ECD) and its rate of decline postoperatively are predictive of graft failure caused by endothelial decompensation following penetrating keratoplasty to treat a moderate-risk condition, principally, Fuchs dystrophy or pseudophakic corneal edema.

**Methods:** In a subset of Cornea Donor Study participants, a central reading center determined preoperative and postoperative ECD from available specular images for 17 grafts that failed because of endothelial decompensation and 483 grafts that did not fail.

**Results:** Preoperative ECD was not predictive of graft failure caused by endothelial decompensation ( $P = .91$ ). However, the 6-month ECD was predictive of subsequent failure ( $P < .001$ ). Among those that had not failed within the first 6 months, the 5-year cumulative inci-

dence ( $\pm 95\%$  confidence interval) of failure was 13% ( $\pm 12\%$ ) for the 33 participants with a 6-month ECD of less than 1700 cells/mm<sup>2</sup> vs 2% ( $\pm 3\%$ ) for the 137 participants with a 6-month ECD of 2500 cells/mm<sup>2</sup> or higher. After 5 years' follow-up, 40 of 277 participants (14%) with a clear graft had an ECD below 500 cells/mm<sup>2</sup>.

**Conclusions:** Preoperative ECD is unrelated to graft failure from endothelial decompensation, whereas there is a strong correlation of ECD at 6 months with graft failure from endothelial decompensation. A graft can remain clear after 5 years even when the ECD is below 500 cells/mm<sup>2</sup>.

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**T**HE CORNEA DONOR STUDY (CDS) was designed to determine the effect of donor age on penetrating keratoplasty outcomes. At 5 years' follow-up, no significant effect of age, up to 75 years, was found.<sup>1</sup> An ancillary study, the Specular Microscopy Ancillary Study (SMAS), detected a slight association between increasing donor age and greater postkeratoplasty corneal endothelial cell loss.<sup>2</sup> The SMAS also confirmed that there was substantial cell loss in successful grafts 5 years postoperatively for younger and older donors (69% and 75%, respectively). In the current analyses, we evaluated the effect of central donor endothelial cell density (ECD) and its rate of decline on the likelihood of corneal graft failure from endothelial decompensation during 5 years of follow-up. Specifically, we were interested in the effects on endothelial failure from decom-

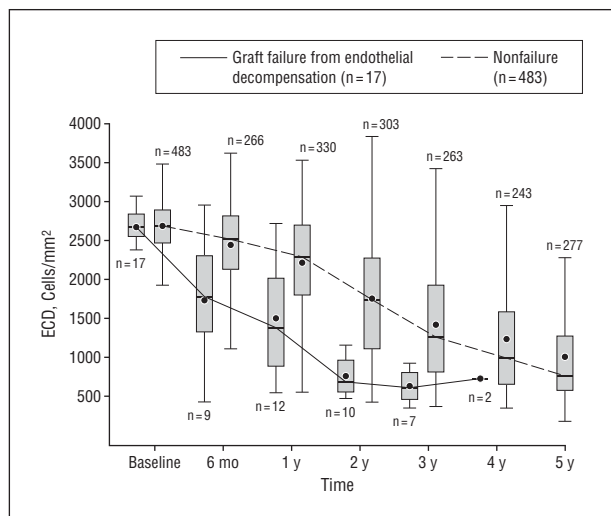
pensation occurring in the absence of acute events (eg, postoperative surgical procedure, graft rejection) that could affect ECD and endothelial function.

## METHODS

Details of the CDS, including the SMAS protocol, have been published previously,<sup>1,3-5</sup> and pertinent aspects are briefly described here. Eligible participants were aged 40 to 80 years and had corneal disease associated with endothelial decompensation and moderate risk of failure, principally, Fuchs dystrophy and pseudophakic corneal edema. Eligible corneas were from donors aged 10 to 75 years with a preoperative, baseline eye-bank-determined ECD from 2300 to 3300 cells/mm<sup>2</sup>. Participants were followed up for 5 years unless a regrant occurred before that time. In addition to a regrant, a graft was considered to have failed if there was loss of central graft clarity sufficient to compromise vision for a minimum of 3 consecutive months.

Author Affiliations are listed at the end of this article.

Group Information: The Cornea Donor Study Investigator Group is listed at the end of this article.



**Figure 1.** Endothelial cell density (ECD) over time in graft failures from endothelial decompensation (n=17) and in nonfailures (n=483). In the box plots, black dots indicate mean values; horizontal lines in the boxes, medians; and the bottom and top of the boxes, the 25th and 75th percentiles. The horizontal lines outside the boxes represent the range of ECD values.

Specular microscopic images of the central endothelium were obtained for the donor cornea preoperatively by the eye bank and postoperatively by the clinical site 6 and 12 months after transplantation and then annually for 5 years, provided that a regraft had not been performed. The ECD determinations for the available preoperative donor images and all postoperative participant images were made by the Specular Microscopy Reading Center (SMRC) at Case Western Reserve University and University Hospitals Eye Institute using standardized procedures. Details of the SMRC procedures used to evaluate preoperative donor images have been previously described.<sup>3</sup> Similar procedures were used for assessment of postoperative images. The ECD of all analyzable images was independently determined by 2 readers using the variable frame analysis method. If the ECDs differed by 5.0% or more, a third independent determination of ECD was made by an adjudicator (B.A.B.). The final ECD was the mean of all ECDs that were within 5.0% of each other. Low-ECD images create a challenge for readers, where inclusion or exclusion of 1 cell in the analyzed area can make an ECD difference of more than 100 cells/mm<sup>2</sup>. Although the corneal area measured is comparable to images with higher ECD, fewer cells are analyzed. As a result, there is a slightly greater rate of adjudication; through the adjudication process, however, the disparity between 2 readers' scores is resolved.

For this analysis, graft failures were limited to the 17 cases classified by the investigators as failures from endothelial decompensation in which no acute events had occurred that might have adversely affected the ECD. Acute events were defined as postoperative intraocular surgical procedures, including cataract extraction, and graft rejection. Therefore, graft failures were excluded if an acute event had been diagnosed on the date of the last image or between the last image date and the date of graft failure. In order to have a suitable comparison group, for all other participants included in the analysis, ECD data were excluded after the first occurrence of an acute event. The comparison group included 483 cases without graft failure that had at least 1 postoperative ECD measurement meeting criteria for inclusion in the analysis. Seventy-three participants in the SMAS who had no specular images that met inclusion criteria and 26 who had graft failure not meeting the previously defined criteria were not included in the analysis. The preoperative baseline ECD used in analyses was determined by the eye bank for

4 of the graft failure cases (24%) and 165 of the comparison group cases (34%) because the corneas were from eye banks that did not participate in the SMAS. The remainder of the baseline ECD measurements were determined by the SMRC from the preoperative baseline specular images captured by the eye bank. Thus, the eye-bank-determined ECD was not used in analyses when an SMRC-determined ECD was available. Although the protocol required a minimum eye-bank-determined ECD of 2300 cells/mm<sup>2</sup> or greater, the comparable baseline ECD determined by the SMRC was below 2300 cells/mm<sup>2</sup> for 41 corneas (ECD,  $\geq 2000$  to  $< 2300$  cells/mm<sup>2</sup> for 32 corneas and  $< 2000$  cells/mm<sup>2</sup> for 9 corneas).

Five-year rates of graft failure from endothelial decompensation were calculated using cumulative incidence. Data for a participant were censored at the first occurrence of either an acute event, a graft failure from another cause, or the last visit date. The proportional hazards model was used to assess the association of graft failure and ECD preoperatively at baseline and at 6 months postoperatively. Models also were fit with the most recent ECD value as a time-dependent variable. The rate of change as a time-dependent variable was calculated as the least-squares slope over all previous ECD measurements (eg, the rate of change at 1 year would be the slope fit to the baseline, 6-month, and 1-year ECD values). For the models with ECD as a time-dependent covariate, missing values were imputed by the Rubin method.<sup>6</sup> No significant deviation from the proportional hazards assumption was detected for these models.

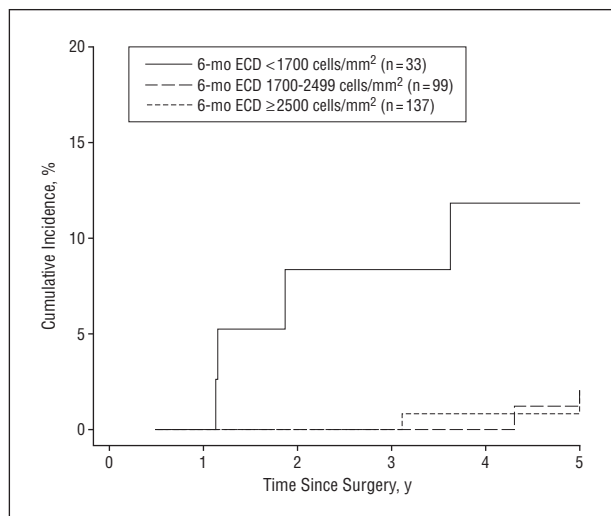
All reported *P* values are 2-sided. Statistical analyses were conducted using SAS statistical software, version 9.1 (SAS Institute Inc, Cary, North Carolina).

## RESULTS

Mean age (SD) at time of penetrating keratoplasty for the 500 participants with ECD data included in the analysis was 70 (8) years; 315 participants (63%) were women, and 475 (95%) were white, non-Hispanic. Moderate risk indications for penetrating keratoplasty included Fuchs dystrophy in 339 (68%), pseudophakic or aphakic corneal edema in 144 (29%), and a variety of other diagnoses in 17 participants (3%). Postoperatively, 74 eyes (15%) were phakic, 415 (83%) pseudophakic, and 11 (2%) aphakic.

Preoperative ECD was not predictive of graft failure from endothelial decompensation (*P* = .91). Median ECD was 2670 cells/mm<sup>2</sup> (interquartile range, 2556-2840 cells/mm<sup>2</sup>) in the 17 graft failure cases and 2687 cells/mm<sup>2</sup> (2468-2892 cells/mm<sup>2</sup>) in the 483 nonfailure cases. The 5-year cumulative incidence ( $\pm 95\%$  confidence interval [CI]) of failure from endothelial decompensation was 3% ( $\pm 3\%$ ) in the 141 participants with baseline ECDs of 2500 cells/mm<sup>2</sup> or less, 5% ( $\pm 3\%$ ) in the 280 participants with baseline ECDs between 2501 and 2999 cells/mm<sup>2</sup>, and 3% ( $\pm 4\%$ ) in the 79 participants with baseline ECDs of 3000 cells/mm<sup>2</sup> or higher. The results did not differ when the analysis was limited to participants with baseline ECDs determined by the SMRC (data not shown) or to participants with baseline ECDs of 2300 cells/mm<sup>2</sup> or higher (data not shown).

**Figure 1** illustrates the changes in ECD over time in the 17 graft failure cases and 483 nonfailure cases. Six months after penetrating keratoplasty, the median ECD fell to 1774 cells/mm<sup>2</sup> (interquartile range, 1331-2305



**Figure 2.** Cumulative incidence of graft failure from endothelial decompensation by endothelial cell density (ECD) at 6 months (n=269); 231 participants were excluded, 1 for graft failure before 6 months' follow-up, 5 were censored before or at 6 months' follow-up, and 225 for missing 6-month ECD values. See the penultimate paragraph in the "Methods" section.

cells/mm<sup>2</sup>) in the graft failure group and to 2514 cells/mm<sup>2</sup> (2130-2815 cells/mm<sup>2</sup>) in the nonfailure group, which represented a 27% and 7% relative cell loss, respectively. In univariate analyses, the 6-month ECD and the change in ECD from baseline to 6 months were predictive of subsequent graft failure ( $P < .001$  and  $P = .001$ , respectively). The 6-month ECD and the change in ECD from baseline to 6 months were highly correlated (Spearman correlation coefficient, 0.83;  $P < .001$ ). Among those whose grafts had not failed within the first 6 months, the 5-year cumulative incidence ( $\pm 95\%$  CI) of failure from endothelial decompensation was 13% ( $\pm 12\%$ ) in the 33 participants with a 6-month ECD of less than 1700 cells/mm<sup>2</sup>, 3% ( $\pm 4\%$ ) in the 99 participants with a 6-month ECD between 1700 and 2499 cells/mm<sup>2</sup>, and 2% ( $\pm 3\%$ ) in the 137 participants with a 6-month ECD of 2500 cells/mm<sup>2</sup> or higher (**Figure 2**). Change from baseline to 6 months was not predictive of graft failure ( $P = .76$ ) when added to the model with 6-month ECD (**Table**; Model No. 4).

Results were similar when ECD was analyzed as a time-dependent variable in a proportional hazards regression model. The hazard ratio for graft failure for the most recent ECD value was 1.29 per 100 cells/mm<sup>2</sup> lower (95% CI, 1.15-1.45;  $P < .001$ ; **Table**). The rate of ECD change as a time-dependent covariate was not predictive of graft failure when added to the model ( $P = .74$ ).

There were 62 participants who had a surviving graft with an ECD value of less than 500 cells/mm<sup>2</sup> at some point during the 5 years of follow-up (range, 178-497 cells/mm<sup>2</sup>). The graft was still clear at last follow-up for 58 of these participants, 30 of whom were followed up for at least 1 year and 13 of whom were followed up for at least 2 years beyond the initial drop below 500 cells/mm<sup>2</sup>. At the 5-year follow-up visit, the ECD was below 500 cells/mm<sup>2</sup> for 40 of the 277 participants (14%) with a clear graft and an ECD measurement (range, 178-3341 cells/mm<sup>2</sup>).

**Table. Proportional Hazards Regression Analyses for ECD and Graft Failure Resulting From Endothelial Decompensation**

Covariate	No. of Participants	Hazard Ratio (95% Confidence Interval) <sup>a</sup>	P Value
Model 1 (univariate): preoperative (baseline) ECD	500	1.01 (0.86-1.18)	.91
Model 2 <sup>b</sup> (univariate): ECD change from baseline to 6 mo	269	1.18 (1.07-1.31)	.001
Model 3 <sup>b</sup> (univariate): ECD at 6 mo	269	1.24 (1.10-1.39)	<.001
Model 4 <sup>b</sup> (multivariate) ECD at 6 mo	269	1.28 (1.00-1.64)	.05
ECD change from baseline to 6 mo		0.96 (0.76-1.22)	.76
Models with time-dependent variables			
Model 5 <sup>c</sup> (univariate): most recent ECD	500	1.29 (1.15-1.45)	<.001
Model 6 <sup>c</sup> (multivariate) Most recent ECD	500	1.27 (1.10-1.48)	.002
Rate of change		1.03 (0.88-1.20)	.74

Abbreviation: ECD, endothelial cell density.

<sup>a</sup>Hazard ratio is per 100 cells/mm<sup>2</sup> lower. A value greater than 1.0 denotes increased graft failure with lower ECD values, and ECD is treated as a continuous variable in all models.

<sup>b</sup>The Cox model is conditional on graft survival at 6 months. Exclusion criteria include graft failure before 6 months (n = 1), participants censored before or at 6 months (n = 5), or missing a 6-month ECD value (n = 225). Results were similar using the Rubin method of multiple imputation for the 225 missing 6-month ECD values (data not shown).

<sup>c</sup>The Cox model was fitted with ECD and rate of change as time-dependent covariates. Missing ECD values were handled by the Rubin method of multiple imputation.

## COMMENT

In this analysis of SMAS data, preoperative ECD did not influence the likelihood of graft failure from endothelial decompensation. The hazard ratio for preoperative (baseline) ECD was 1.01 per 100 cells/mm<sup>2</sup> (95% CI, 0.86-1.18;  $P = .91$ ) (**Table**). In contrast to our results, Nishimura et al<sup>7</sup> reported that 21 graft failures caused by endothelial decompensation had a lower preoperative donor ECD compared with 367 cases that did not fail (mean, 2710 vs 2991 cells/mm<sup>2</sup>). The explanation for the difference in findings could be the variation in corneal disorders represented in the 2 cohorts. The cohort in the study by Nishimura et al included cases with preoperative conditions at low risk of failure, such as keratoconus, whereas the CDS cohort included only cases of corneal disease associated with endothelial decompensation and moderate risk of failure.

The most important finding from our analysis was that the ECD at 6 months predicted failure from endothelial decompensation. Change in ECD from baseline to 6 months was also predictive of failure but was highly correlated with the 6-month ECD and thus was not associated with subsequent failure after controlling for the 6-month ECD. The 5-year endothelial failure rate of grafts with fewer than 1700 cells/mm<sup>2</sup> at 6 months was 6 times

(13%) that of those with 2500 cells/mm<sup>2</sup> or more (2%). Nishimura et al<sup>7</sup> noted a similar relationship between cell loss at 2 months and endothelial failure. The studies by Nishimura et al,<sup>7</sup> Bourne et al,<sup>8</sup> and Patel et al<sup>9</sup> have shown that the greatest cell loss after penetrating keratoplasty occurs initially, with 30% to 50% loss in the first year, and then declines gradually as the endothelium stabilizes. They found an annual ECD decline of 7.8% from 3 to 5 years,<sup>8</sup> 4.2% from 5 to 10 years,<sup>10</sup> and no change between 10 and 15 years postkeratoplasty,<sup>9</sup> compared with an annual rate of cell loss in normal corneas of 0.6%.<sup>11</sup> However, this observed decrease in the decline in annual cell loss most likely is artifactual, resulting from continued graft failure and subsequent loss to follow-up over time as ECD drops below a certain level and the graft fails.

The ECD at 6 months was more predictive of failure from endothelial decompensation than was the change from baseline to 6 months. Armitage et al<sup>12</sup> have proposed a model of postkeratoplasty cell loss with 2 exponential components, 1 rapid and 1 slow. Further analysis of the SMAS data with longer-term follow-up through 10 years, now under way, may allow testing of the hypothesis by Armitage et al. A graphic view of ECD over time (Figure 1) appears to show a linear decline for those not failing and possibly an accelerated initial exponential decline for failing grafts. Both plots appear roughly asymptotic to a line at about 500 to 800 cells/mm<sup>2</sup>, consistent with the fact that some grafts fail and endothelial cell images become difficult to obtain below this ECD because of corneal thickening.

We attempted to separate the role of immunological endothelial rejection from endothelial failure alone, recognizing the possibility that clinically undetectable immunologic rejection may occur. The effect of rejection on ECD is variable and dependent on the promptness and success of treatment.<sup>13,14</sup> Factors affecting rejection and the effects of rejection on ECD will be further analyzed in a separate analysis.

Another important and remarkable finding was graft survival in many eyes with an ECD below 500 cells/mm<sup>2</sup>. At 5 years, there were 40 such grafts, with ECDs as low as 178 cells/mm<sup>2</sup>. This phenomenon was first noted by Abbott et al,<sup>15</sup> who reported a mean ECD of 684 cells/mm<sup>2</sup> among grafts that were followed up for a mean of 17.4 years after penetrating keratoplasty, with ECDs as low as 320 cells/mm<sup>2</sup>. When a subset of the same cohort was examined 4 to 6 years later, 80% of the grafts remained clear.<sup>16</sup> Other series have noted mean ECDs of 852 cells/mm<sup>2</sup> at 20 years<sup>17</sup> and 808 cells/mm<sup>2</sup> at 22 years.<sup>18</sup> Chronic endothelial decompensation has been shown to occur when the central ECD declines to 400 to 700 cells/mm<sup>2</sup>.<sup>19,20</sup> Although corneas with an ECD below 1000 cells/mm<sup>2</sup> are considered at risk for swelling and decompensation,<sup>21</sup> our findings suggest that corneas with an ECD even below 500 cells/mm<sup>2</sup>, and in one case at 178 cells/mm<sup>2</sup>, can continue to function well and remain clear, as long as no further intraocular procedures are performed, which may affect endothelial function and ECD.

When endothelial cells are enlarged, the area of intercellular spaces available for pump sites decreases, while the barrier to flow into the cornea increases.<sup>19,22</sup> This balance does not depend on ECD alone, likely making the

minimum ECD for maintaining corneal thickness and graft clarity variable. The histopathologic findings in grafts with endothelial failure and low ECD suggest that the remaining endothelial cells are unstable, stressed, and vulnerable.<sup>23</sup> It will be interesting to assess the grafts with low ECD during the next 5 years of follow-up in the SMAS.

The finding that early cell loss is predictive of failure suggests that further investigations look for the causes of that early cell loss. If those causes are preventable, then this information has likely significance for improving surgical and postoperative care. It is not yet clear, however, how cell densities lower than 1700 cells/mm<sup>2</sup> at 6 months can be used to alter the subsequent course in a given patient. Therefore, we cannot recommend that periodic postoperative specular microscopy be done on all corneal transplants merely to improve prognostication.

Conclusions from this initial 5-year observation period of the SMAS must be considered cautiously because there were only 17 cases of graft failure from endothelial decompensation. With longer-term follow-up, the number of failures from endothelial decompensation will increase, expanding the power and detail of this analysis. Missing ECD data points decreased the statistical power of this study as well. The strengths of this analysis include its prospective nature and large population for future comparisons. Detailed preoperative donor, operative, and postoperative data will be separately analyzed in relation to ECD changes and clinical outcomes during a longer follow-up period to assist in validation of eye banking and keratoplasty procedures over an extended period.

A possible criticism of the CDS and the SMAS is that the relevance of penetrating keratoplasty in the management of Fuchs dystrophy and pseudophakic corneal edema is declining since this procedure is increasingly supplanted by endothelial keratoplasty procedures for these indications. Graft survival and endothelial cell loss data after endothelial keratoplasty are limited.<sup>24-26</sup> The influences on endothelial survival are not yet fully understood with this new procedure, but the principles emerging from the careful long-term analyses in the CDS and the SMAS may apply to endothelial keratoplasty. At the same time, penetrating keratoplasty remains a common method for the surgical treatment of these conditions. In light of our findings, continued efforts to improve upon donor, operative, and postoperative factors influencing endothelial survival apparent at the 6-month ECD determination should continue to be pursued.

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**Author Affiliations:** Department of Ophthalmology and Visual Sciences, Case Western Reserve University and University Hospitals Eye Institute, Cleveland, Ohio (Dr Lass and Ms Benetz); W. K. Kellogg Eye Center, University of Michigan, Ann Arbor (Dr Sugar); Jaeb Center for Health Research, Tampa, Florida (Drs Beck and Kollman and Mss Dontchev and Gal); Cornea Consultants of Arizona, Phoenix (Dr Gross); Transplant Services Center, The University of Texas Southwestern Medical Center at Dallas (Ms Heck); Cincinnati Eye Institute, Cincinnati, Ohio (Dr Holland); Department of Ophthalmology and Vision Sci-

ence, University of California–Davis, Sacramento (Dr Mannis); Ophthalmic Partners of Pennsylvania, Bala Cynwyd (Dr Raber); The Johns Hopkins University School of Medicine, The Wilmer Ophthalmological Institute, Baltimore, Maryland (Dr Stark); and Department of Ophthalmology, Emory University, Atlanta, Georgia (Dr Stulting).

**Correspondence:** Jonathan H. Lass, MD, Cornea Donor Study Coordinating Center, Jaeb Center for Health Research, 15310 Amberly Dr, Ste 350, Tampa, FL 33647 (cds@jaeb.org).

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**Corneal Donor Study Investigator Group Clinical Sites:**

Listed in order of number of patients enrolled (in parentheses); names of CDS Investigator Group members are ordered alphabetically. *Michigan Cornea Consultants, PC, Southfield* (n=77): Christopher Y. Chow, MD; Steven P. Dunn, MD; David G. Heidemann, MD. *Cornea Consultants of Albany, Albany, New York* (n=58): Michael W. Belin, MD; Robert L. Schultze, MD. *Ophthalmic Consultants Northwest, PS, Seattle, Washington* (n=47): Matthew S. Oliva, MD; Walter M. Rotkis, MD. *Verdier Eye Center, PC, Grand Rapids, Michigan* (n=41): David D. Verdier, MD. *Case Western Reserve University and University Hospitals Case Medical Center, Cleveland, Ohio* (n=33): Jonathan H. Lass, MD; William J. Reinhart, MD; Joseph M. Thomas, MD. *Eye Consultants of Atlanta, PC, Atlanta, Georgia* (n=30): Stephen M. Hamilton, MD; Gina C. Jayawant, MD; W. Barry Lee, MD. *Cornea Consultants of Arizona, Phoenix* (n=28): Robert H. Gross, MD; Edward L. Shaw, MD. *Cornea and Eye Surface Center, Tampa, Florida* (n=28): Steven L. Maskin, MD. *Ophthalmic Partners of Pennsylvania, Bala Cynwyd* (n=26): Parveen K. Nagra, MD; Irving Raber, MD. *University of Illinois at Chicago* (n=25): Joel Sugar, MD; Elmer Tu, MD. *Eye Associates of Fort Myers, Fort Myers, Florida* (n=24): Mark S. Gorovoy, MD. *Eye Physicians of Lancaster, Lancaster, Pennsylvania* (n=24): Francis J. Manning, MD. *Northeastern Eye Institute, Scranton, Pennsylvania* (n=23): Thomas S. Boland, MD; Stephen E. Pascucci, MD. *W. K. Kellogg Eye Center, University of Michigan, Ann Arbor* (n=21): Qais A. Farjo, MD; Roger F. Meyer, MD; H. Kaz Soong, MD; Alan Sugar, MD. *Horizon Eye Care, Charlotte, North Carolina* (n=21): Paul G. Galentine, MD; David N. Ugland, MD. *Oxford Valley Laser Vision Center, Langhorne, Pennsylvania* (n=21): Sadeer B. Hannush, MD. *Eye Care of San Diego, San Diego, California* (n=21): John E. Bokosky, MD. *Charleston Eye Care, PLLC, Charleston, West Virginia* (n=20): James W. Caudill, MD. *Northwestern University, Chicago, Illinois* (n=20): Robert S. Feder, MD. *In-*

*land Eye Institute, Colton, California* (n=20): John C. Affeldt, MD; Christopher L. Blanton, MD. *University of Minnesota, Minneapolis* (n=20): Edward J. Holland, MD (now at Cincinnati Eye Institute, Cincinnati, Ohio); *The University of Texas Southwestern Medical Center at Dallas* (n=20): R. Wayne Bowman, MD; H. Dwight Cavanagh, MD, PhD; Mohamed-Sameh H. El-Agha, MD; James P. McCulley, MD. *Eye Associates NW Inc, PS, Seattle, Washington* (n=20): Thomas E. Gillette, MD. *Lehigh Valley Eye Center, PC, Allentown, Pennsylvania* (n=19): Alan B. Leahey, MD. *Davis Duehr Dean Clinic, Madison, Wisconsin* (n=19): Christopher R. Croasdale, MD. *Suburban Excimer Laser Center, Louisville, Kentucky* (n=16): Richard A. Eiferman, MD. *Lahey Clinic, Burlington, Massachusetts* (n=15): Sarkis H. Soukiasian, MD. *Emory University, Atlanta, Georgia* (n=14): R. Doyle Stulting, MD, PhD. *The Johns Hopkins University School of Medicine, Baltimore, Maryland* (n=14): Walter Stark, MD. *Eye Health Vision Center, North Dartmouth, Massachusetts* (n=14): Kenneth R. Kenyon, MD; Richard C. Rodman, MD. *Cornea Associates of Texas, Dallas* (n=13): Walter E. Beebe, MD; Henry Gelender, MD. *University of Rochester, Rochester, New York* (n=13): Steven S. Ching, MD; Ronald D. Plotnik, MD. *The Eye Institute, Tulsa, Oklahoma* (n=13): Marc A. Goldberg, MD. *Karen D. Summers, MD, PC, Atlanta, Georgia* (n=12): Karen D. Summers, MD. *Center for Eye Research and Education, Boston, Massachusetts* (n=12): Nicoletta A. Fynn-Thompson, MD; Ann Z. McColgin, MD; Michael B. Raizman, MD. *Delray Eye Associates, PA, Delray Beach, Florida* (n=12): Steven I. Rosenfeld, MD. *Minnesota Eye Consultants, PA, Minneapolis* (n=12): Elizabeth A. Davis, MD; David R. Hardten, MD; Richard L. Lindstrom, MD. *University of California–Davis* (n=12): Mark J. Mannis, MD. *Eye Associates of Tallahassee, Tallahassee, Florida* (n=12): Jerry G. Ford, MD. *The Cleveland Clinic Foundation, Cleveland, Ohio* (n=11): David M. Meisler, MD. *Price Vision Group, Indianapolis, Indiana* (n=11): Kendall Dobbins, MD; Francis W. Price, Jr, MD; William G. Zeh, MD. *Novak Berkowitz and Rosenberg, PC, Pittsburgh, Pennsylvania* (n=11): Peter J. Berkowitz, MD. *Virginia Mason Medical Center, Seattle, Washington* (n=11): Thomas D. Lindquist, MD, PhD. *Daniel F. Goodman, MD, San Francisco, California* (n=10): Daniel F. Goodman, MD; Niraj P. Patel, MD. *Colorado Eye Physicians and Surgeons, Denver* (n=9): Abdulfatah M. Ali, MD; Richard F. Beatty, MD. *University of Iowa, Iowa City* (n=9): John E. Sutphin, MD; Ayad A. Farjo, MD; Kenneth M. Goins, MD. *Northwest Corneal Services, Portland, Oregon* (n=9): Terry E. Burris, MD. *Southeast Eye Institute, PA, Pinellas Park, Florida* (n=9): Peter A. Shriver, DO. *Eastern Maine Eye Associates, PA, Bangor* (n=8): Cynthia A. Self, MD; Garth A. Wilbanks, MD. *University of California–Irvine* (n=8): Roy S. Chuck, MD, PhD; Ronald N. Gaster, MD. *Southcoast Eye Care, Inc, North Dartmouth, Massachusetts* (n=7): David W. Kielty, MD. *University of Texas Medical Branch at Galveston, Galveston* (n=6): Garvin H. Davis, MD; Stefan D. Trocme, MD (now at Case Western Reserve University and University Hospitals of Cleveland). *Woodford S. Van Meter, MD, Lexington, Kentucky* (n=6): Woodford S. Van Meter, MD. *Raleigh Ophthalmology and Surgical Eye Assoc., Raleigh, North Carolina* (n=6): Patricia W. Smith, MD (now at Tri-

angle Eye Physicians, Raleigh). *Associated Ophthalmic Specialists, Memphis, Tennessee* (n=6): Alan R. Schaeffer, MD. *Corneal Associates, PC, Philadelphia, Pennsylvania* (n=6): Elisabeth J. Cohen, MD; Peter R. Laibson, MD; Christopher J. Rapuano, MD. *Mayo Clinic College of Medicine, Rochester, Minnesota* (n=6): Keith H. Baratz, MD. *Eye Doctors of Lancaster, Lancaster, Pennsylvania* (n=5): Barton L. Halpern, MD; Mark A. Pavilack, MD (now at Tidewater Eye Centers, Virginia Beach, Virginia). *Rosen Eye Center, Lansdale, Pennsylvania* (n=5): Gerald B. Rosen, MD (now at Horizon Eye Care, Charlotte, North Carolina). *University of Minnesota, Minneapolis* (n=5): Donald J. Doughman, MD. *Corneal Associates of New Jersey, West Orange* (n=5): Soo Mee Pak, MD; Theodore Perl, MD. *University of Missouri, Columbia* (n=4): John W. Cowden, MD. *Rhode Island Eye Institute, Providence* (n=4): Elliot M. Perlman, MD. *Spokane Eye Clinic, Spokane, Washington* (n=4): Lance E. Olson, MD; Erik D. Skoog, MD. *Pacific Cataract and Laser Institute, Tacoma, Washington* (n=4): William D. Gruzensky, MD. *Cornea Consultants of Nashville, PLLC, Nashville, Tennessee* (n=3): Erich B. Groos, Jr, MD. *University of Utah, Salt Lake City* (n=3): Mark D. Mifflin, MD; Maureen K. Lundergan, MD. *Springfield, Massachusetts* (n=3): Steven T. Berger, MD. *Boston University School of Medicine, Boston, Massachusetts* (n=2): Kenneth C. Chern, MD. *Medical University of South Carolina, Charleston* (n=2): Kerry D. Solomon, MD. *Rush University Medical Center, Chicago, Illinois* (n=2): Richard F. Dennis, MD; Jonathan B. Rubenstein, MD. *Atlantic Eye Center, Palm Coast, Florida* (n=2): Alexandra M. P. Kostick, MD. *Christenbury Eye Center, PA, Raleigh, North Carolina* (n=2): Samuel H. Santander, MD, MPH. *The Cleveland Clinic Foundation, Cleveland, Ohio* (n=1): Allen S. Roth, MD. *Eye Physicians and Surgeons, PC, Decatur, Georgia* (n=1): Laura A. Bealer, MD. *Macy Eye Center, Los Angeles, California* (n=1): Jonathan I. Macy, MD. *Charleston Cornea & Refractive Surgery, PA, Mount Pleasant, South Carolina* (n=1): David G. O'Day, MD. *Devers Eye Institute, Portland, Oregon* (n=1): Mark A. Terry, MD. *Palm Beach Eye Clinic, West Palm Beach, Florida* (n=1): Nunzio P. Sossi, MD, PhD. *Wake Forest University School of Medicine, Winston-Salem, North Carolina* (n=1): Keith A. Walter, MD.

**Eye Banks:** Listed in order of number of patients enrolled in the CDS (in parentheses); C indicates eye bank coordinator and D, director. *Midwest Eye-Banks* (n=192) (*Michigan Eye-Bank, Ann Arbor* [n=145] and *Illinois Eye-Bank, Chicago* [n=47]): Florence M. Johnston (D); Kyle L. Mavin (C); Kristen E. McCoy (C); Michael B. O'Keefe (C). *Tissue Banks International* (n=119) (*New England Eye & Tissue Transplant Bank, Boston, Massachusetts* [n=47]; *Indiana Lions Eye & Tissue Transplant Bank, Indianapolis* [n=22]; *Lions Eye Bank of North Dakota, Inc, Bismarck* [n=19]; *Lions Eye Bank of West Central Ohio, Dayton* [n=11]; *Medical Eye Bank of Maryland, Baltimore, and Washington Eye Bank, Washington, DC* [n=4]; *Orange County Eye & Tissue Bank, Santa Ana, California* [n=4]; *New Mexico Lions Eye Bank, Albuquerque* [n=3]; *Doheny Eye and Tissue Transplant Bank, Los Angeles, California* [n=3]; *Medical Eye Bank of Florida, Orlando* [n=2]; *Northern California Transplant Bank, Oakland* [n=2]; *Lions Eye Bank of New Jersey, Springfield* [n=2]): Gerald J.

Cole, MBA (D); Diane F. Johnston (C); Mark A. Jones (C); Sameera M. Farazdaghi, MPH (C); Elizabeth N. Walunas (C). *SightLife, Seattle, Washington* (n=86): Monty M. Montoya, MBA (D); Bernie Iliakis (C); Rick D. McDonald (C); Misty L. Ostermiller (C); Cathy E. Saltwick (C). *Central Florida Lions Eye & Tissue Bank, Inc, Tampa* (n=73): Jason K. Woody (D, C). *Northeast Pennsylvania Lions Eye Bank, Inc, Allentown* (n=70): Mark H. Weaver (D); Michael J. Christ (C); Mark B. Gross (C). *Minnesota Lions Eye Bank, Minneapolis* (n=61): Carol R. Engel (D); Raylene A. Dale (C); Stephanie K. Hackl (C); Elena J. Henriksen (C); Kathryn J. Kalmoe (C); Jennifer M. Larson (C); Jackie V. Malling (C); Brian J. Philipp (C). *Sight Society of Northeastern New York, Albany* (n=58): Maryann Sharpe-Cassese, RN, MSN (D); Sue M. Hayes (C). *Lions Eye Bank of Delaware Valley, Philadelphia, Pennsylvania* (n=58): Robert E. Lytle (D); David A. Rechtshaffen (C). *Georgia Eye Bank, Inc, Atlanta* (n=57): Bruce Varnum (D); Erin B. Angel (C); Matt D. Durell (C); Teresa R. Williams (C). *Cleveland Eye Bank, Cleveland, Ohio* (n=45): Susan V. Janssen (D); Brian E. Kraus (C); Marcy B. McLain (C); Jackie A. Rossi (C). *Transplant Services Center, The University of Texas Southwestern Medical Center at Dallas* (n=33): Ellen L. Heck, MS, MA (D); Marilyn S. Hayes (C). *Donor Network of Arizona, Phoenix* (n=28): Gregory C. Davis (D); Tara L. Chavez (C); Lori D. Oswald (C); Noreen B. Ruiz (C). *San Diego Eye Bank, San Diego, California* (n=26): Jeffrey G. Penta, MBA (D); Wayne E. Dietz (C); Jennifer L. Nary (C). *Medical Eye Bank of West Virginia, Charleston* (n=21): Kenneth R. Sheriff (D); Nancy C. Driver (C). *Lifeshare of the Carolinas, Charlotte, North Carolina* (n=21): William J. Faircloth (D); Paul E. Williams (C). *The North Carolina Eye Bank, Inc, Winston-Salem* (n=21): Kurt Weber, MA, MBA (D); Jerry W. Barker (C); Donna M. Bridges (C); Lee Chenier (C); Mark Soper (C). *Inland Eye & Tissue Bank, Redlands, California* (n=20): Betsy Allen (D); Samantha J. Wright (C). *University of Louisville Lions Eye Bank, Louisville, Kentucky* (n=16): James R. Martin (D); Anne J. Watson (C). *Sierra Eye & Tissue Donor Services, DCI, Sacramento, California* (n=15): Greg McDonough, MS (D); Kristel D. Beilby (C). *Rochester Eye & Human Parts Bank, Inc, Rochester, New York* (n=13): Linda K. Fraser (D); Tammi S. Sharpe (C). *Center for Organ Recovery and Education, Pittsburgh, Pennsylvania* (n=11): Robert C. Arffa, MD (D); Michael A. Tramber (C). *Lions Eye Bank of Oregon, Portland* (n=10): Barbara L. Crow (D); Matthew M. Fisher (C); Chris G. Stoeger (C). *Rocky Mountain Lions Eye Bank, Aurora, Colorado* (n=9): Edmund Jacobs (D); Michael P. Filbin (C); James I. Mather (C); Christopher M. McGriff (C); Eric E. Meinecke (C). *Iowa Lions Eye Bank, Iowa City* (n=9): Patricia J. Mason (D); Garret D. Locke (C); Janice F. Reiter (C). *Lions Medical Eye Bank of Eastern Virginia, Inc, Norfolk* (n=7): David E. Korroch (D); Penelope M. Thomas (C). *Southeast Texas Lions Eye Bank, Inc, Galveston* (n=6): Wayne A. Lange (D, C); Rosemary F. Moore (C). *Mid-South Eye Bank for Sight Restoration, Memphis, Tennessee* (n=6): Lee J. Williams (D); Yvette D. Friedhoff (C). *Heartland Lions Eye Bank, Columbia, Missouri* (n=4): Ronald J. Walkenbach, PhD (D); Jennifer E. Glover (C); Brenda A. Kafton (C); Kraig J. Lage (C). *South Carolina Lions Eye Bank, Inc, Charles-*

ton (n=3): Brenda S. Horn (D); H. Tommy Bottoms (C); Ellen R. Kerns (C). *Utah Lions Eye Bank, Salt Lake City* (n=3): Raymond Jessen, MPH (D, C); William H. Dennis (C).

**Coordinating Center:** *Jaeb Center for Health Research, Tampa, Florida:* Roy W. Beck, MD, PhD (Director); Mariya Dontchev, MPH; Robin L. Gal, MSPH; Craig Kollman, PhD; Lee Anne Lester; Shelly T. Mares; Yazandra A. Parrimon; Alandra S. Powe; Katrina J. Ruedy, MSPH; Heidi J. Strayer, PhD; Jean Paul Tanner, MPH.

**Specular Microscopy Reading Center:** *Case Western Reserve University and University Hospitals Case Medical Center:* Jonathan H. Lass, MD (Medical Director); Beth Ann Benetz, MA (Technical Director); Carmella Gentile (Head Technician); Stephanie Burke; Shannon Edwards; Lori Karpinecz.

**National Institutes of Health:** *National Eye Institute, Bethesda, Maryland:* Maryann Redford, DDS, MPH; Mary Frances Cotch, PhD.

**Data and Safety Monitoring Committee:** Marian Fisher, PhD (Chair); William Bourne, MD; Maryann Redford, DDS, MPH; Rabbi Samuel Fishman; Gary Foulks, MD; David C. Musch, PhD, MPH.

**Steering Committee:** Edward J. Holland, MD (Study Co-chair, 1999-present); Mark J. Mannis, MD (Study Co-chair, 1999-present); Mary Frances Cotch, PhD (1999-2001); Steven Dunn, MD (2001-2002); Ellen Heck, MS, MA (1999-2000); Florence Johnston (2000-2001, 2002-2004); Jonathan H. Lass, MD (1999-present); Thomas Lindquist, MD, PhD (2000-2001); Monty M. Montoya, MBA (2004-present); Maryann Redford, DDS, MPH (2001-present); Alan Sugar, MD (2004-present); Joel Sugar, MD (1999-2000); Jason Woody (2001-2002).

**Data Analyses Advisory Committee:** Mark J. Mannis, MD; Edward J. Holland, MD; Michael W. Belin, MD; Steven Dunn, MD; Robert H. Gross, MD; Mark S. Gorovoy, MD; Stephen M. Hamilton, MD; Ellen Heck, MS, MA; Jonathan H. Lass, MD; Thomas Lindquist, MD, PhD; Francis J. Manning, MD; Steven L. Maskin, MD; Monty M. Montoya, MBA; Irving M. Raber, MD; Maryann Redford, DDS, MPH; Walter M. Rotkis, MD; Robert L. Schultze, MD; Walter J. Stark, MD; Robert Doyle Stulting, MD, PhD; Alan Sugar, MD; Joel Sugar, MD; Bradley Tennant; David D. Verdier, MD; Jason Woody.

**The following CDS Publications Committee members independently reviewed and approved the manuscript for submission:** Christopher R. Croasdale, MD; Mark D. Mifflin, MD; Patricia W. Smith, MD; Joel Sugar, MD.

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