The Lifetime Economic Burden of Keratoconus: Technical Appendix

The purpose of this appendix is to provide the details of the model used in our paper. With this information, a reader should be able to replicate the model when given the same data. For others, it should also provide insight into how the results were obtained. If this is deemed insufficient to a reader, questions should be directed to kymes@vrcc.wustl.edu. A copy of the decision tree (in TreeAge Pro format) is available by request to kymes@vrcc.wustl.edu.

Definition of Eye 1 and Eye 2

In order to keep track of both eyes in the model, "Eye 1" was defined as the worst eye (ie, the eye most likely to get a penetrating keratoplasty [PK]) and the first to get the PK. "Eye 1" was also always the eye with the oldest PK. Eye 2 was defined as the eye with a better visual acuity (VA), lower corneal curvature, and better contact lens comfort in year 0. It was also always the second to require a PK. When a regraft was performed in "Eye 1" and when a PK was performed in "Eye 2," "Eye 1" would become "Eye 2" since it was now the most recent PK. When an enucleation was performed in the model, the eye that was enucleated was defined as "Eye 2." All parameters and trackers in the model follow these definitions and contain either a "1" or "2" in the parameter name to represent the corresponding eye. For example, "Years_PK1" tracks the number of years since a PK has been performed in "Eye 1." However, if "Eye 1" becomes "Eye 2" after a regraft in "Eye 1," the value of "Years_PK1" is transferred to "Years_PK2."

Logic of Model

The Markov model in TreeAge Pro was created to determine the overall cost to a patient with clinically significant keratoconus over his or her lifetime. There are 13 health states in the model. Although the model is set to run for 50 years, the mean survival of a patient is approximately 37 years, which is appropriate given that the average age of the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study was 40.2 years (Kymes, unpublished CLEK data, 2008). In all but the last health state, "Death," the first decision is whether the person lives or dies. At the beginning of each cycle, the tracker variables, Age, curvature1, curvature2, comfort1, comfort2, VA1, and VA2, all progress according to preset parameters. The details of these can be seen in the section "Parameters obtained from the CLEK data." In the post-PK health states, these parameters change with each cycle, but the values become irrelevant to the costs and probabilities in the model as they are only used in predicting the first PK. Also, throughout the model branches were kept to a maximum of 2 to make it easier to create distributions around probabilities. The PK is always performed at the beginning of the cycle.

Initial States

The first 2 health states, "Contact lenses (CL)" and "Glasses," are where the cohort begins. The proportions that go into either are described in the section "Parameters obtained from the CLEK data." Subsequently, based on the parameters of age, comfort (if wearing contact lenses), curvature, high contrast, best-corrected visual acuity, and the yearly changes of these as determined by Gordon and associates,[1] the person may require a PK. Finally, if the person was in the "Contact Lenses" health state, he or she will be fitted up to 3 times, which only 10% of the CLEK participants exceeded in a given year (Kymes, unpublished CLEK data, 2008). If unable to be fitted, the person will move to the "Glasses Only" health state. If a person is in the glasses health state, the patient is assumed to be unable to be fitted with contact lenses and will go back to the "Glasses Only" health state if the person does not undergo a PK.

PK in Eye 1 States

The next 2 health states are "PK in Eye 1" and "PK in Eye 1 wearing glasses." These are 2 surgical health states and assume that the person is undergoing a PK in Eye 1 at the beginning of the year. The former health state assumes the person can currently be treated with contact lenses, and the latter assumes that the person can be treated with glasses only. The first complication encountered is enucleation, which is assumed to be a possible complication only after the first regraft. When an enucleation takes place, all values associated with Eye 1 are transferred to Eye 2 as described above in the "Definition of Eye 1 and Eye 2."

The next branch is refractive surgery, which has been shown to be protective of grafts in the first year.[2] A tracker, "refraction," is set to 1, and an associated modifier is applied to subsequent survival rates through the year. Subsequently, a person can have a complication. The order of complications is "rejection," "rise in intraocular pressure (IOP)," and "Other complication." Tracker values are applied if the complications took place. The person then had the option of undergoing a regraft of the same eye. The survival of the graft was based upon which complication, if any, had occurred as defined by the tracker variable. If there was a rise in IOP, glaucoma surgery was another branch, assuming there was no regraft performed on the eye. As in the previous 2 health states, a patient was fitted up to 3 times with contact lenses in the contralateral eye unless the patient was wearing glasses only. If there had been a regraft performed, the person would go back to the "PK in Eye 1" health states. If not, the person would continue on to the "Post-PK in Eye 1" states.

Post-PK in Eye 1 States

These 2 states are identical in logic to the initial health states except that after the "No death" branch, there is a branch for "Regraft of Eye 1." The regraft proportion is based upon which, if any, complications had been present and how many prior grafts had been performed.[2] If there is no regraft in Eye 1, there is a branch for a PK in Eye 2 that is based on the same parameters as for Eye 1 but with values unique to this eye. We assumed that there would not be 2 PKs performed in a given year, and that a surgery would be performed in Eye 1 first. If there is no PK, contact lenses could again be fitted up to 3 times in Eye 2 if in the "Post-PK in Eye 1" state and not the "Post-PK in Eye 2 Wearing Glasses" state.

Enucleation Post-PK in Eye 2 States

These 2 states represent a person who has had an enucleation in Eye 2 but no surgery in Eye 1. The health states are identical to the initial health state except that the terminal nodes return to these 2 health states if a PK is not performed that year. If a PK is to be performed, the person goes to the health state of "Enucleation in Eye 2 and With New PK/Regraft in Eye 1," which is where a person has had an enucleation in Eye 2 but is now having a PK in the other eye, Eye 1.

PK in Eye 2 State

This health state represents a year in which a person has had a PK in Eye 1 and is now getting a PK or regraft in Eye 2. It should be noted that Eye 2 could have been Eye 1 at one point, but since it is now the eye with the most recent PK, it is defined as Eye 2. This health state is identical to the "PK in Eye 1 Wearing Glasses" state, with a few notable differences. After the branches describing the complications after a PK in Eye 2, the person has the option to have a regraft first in Eye 2 and then Eye 1. Again, only 1 surgery is assumed to be performed per year. When a regraft is performed in Eye 1, it becomes Eye 2, and all values associated with Eye 2 become associated with Eye 1. A regraft will send the person back to the health state "PK in Eye 2." An enucleation will send the person to the health state "Enucleation in Eye 2 and Post-PK in Eye 1." If there is no regraft, no contact lens fitting will be required as it is assumed that a contact lens will be used to treat the patient instead of glasses. The patient would then go to the health state "Post-PK in 2 Eyes."

Post-PK in 2 Eyes

This health state represents a year in which a patient has had a PK in both eyes. It is assumed that a regraft would happen in Eye 1 first and if not in Eye 1, then in Eye 2. If there is a regraft in Eye 1, then all values associated with Eye 2 would then be associated with Eye 1. Persons requiring a regraft will go to the "PK in 2 Eyes" health state, and those not requiring a regraft will remain in the "Post-PK in 2 Eyes" health state.

Enucleation in Eye 2 and With New PK/Regraft in Eye 1

This health state represents a year in which a person has had an enucleation in Eye 2 and is having a PK performed in Eye 1. A second enucleation is not an option in this health state. Complications of rejection, a rise in IOP, subsequent glaucoma surgery, and "other complication" are represented. It is also possible to require a regraft in Eye 1. The person remains in this state if he or she requires another regraft or, if not, goes to the state "Enucleation in Eye 2 and Post-PK in Eye 1."

Enucleation in Eye 2 and Post-PK in Eye 1

This health state represents a person who has had an enucleation in Eye 2 and has had a PK in Eye 1. Regraft of Eye 1, no regraft of Eye 1, and death are the only options here. The person can remain in this health state if not requiring a regraft or return to the state "Enucleation in Eye 2 with New PK/Regraft in Eye 1."

Death

This health state represents a person who has died. The person remains in this health state for the rest of the model, accruing no additional costs.

Parameters Obtained From the CLEK Data[1]

We looked at patients with a curvature of less than 48.5 diopters (D), 3 data points, and contacts in each eye. Expected values are shown below, but a triangular distribution (for probabilities) or normal distribution (for the rest of the parameters) was used in the model.

Age

The age of the patients was found to be 40.2 years, with a standard deviation of 9.7.

pGlasses_at_start

This is the probability that a patient is unable to be treated with contact lenses from the beginning of the model. In the first year, approximately 6 out of 170 were unable to be treated with contact lenses.

pContact1, pContact2, pContact3

These parameters are the probability that a patient could be treated with contact lenses throughout the year. Since 89.86% of patients visited a provider 3 or fewer times, 3 is the maximum number of visits per year we assumed in the model. The values of the pContacts were once assumed to be different when creating the model, but for simplicity the average value (99.5%) of the change in number of patients only wearing glasses was used for each value.

Comfort1, Comfort 2

In the CLEK Study, patients rated the comfort of their contact lenses on a 5 point scale: “1 = very comfortable,” “2 = quite comfortable,” “3 = comfortable,” “4 = somewhat irritating,” and “5 = very irritating.” The value of the comfort was assumed to be the same in both eyes. The expected value was found to be 2.4, and the standard deviation was 1.2.

Curvature1, Curvature2

The values of “Curvature1” and “Curvature2” were the worst and best curvatures, respectively. The means were 46.6 D and 44.8 D, respectively.

VA1, VA2

The values of “VA1” and “VA2” were the worst and best high-contrast best-corrected visual acuities, respectively. The Bailey-Lovie charts were used. The means were 50.6 and 52.9, respectively.

Change_curv1, Change_curv2, Change_VA1, Change_VA2, Change_comfort1, Change_comfort2

These parameters represented the change in curvature, best-corrected visual acuity, and comfort yearly. The “1” represented the worst eye and the “2” represented the best eye. The means were 0.207, .0148, -0.119, -0.117, -0.023, -0.035, respectively.

pPK, pPK_glasses

These were the probabilities of a PK in any given year. The work previously done by Gordon and associates[1] provided the parameters predictive of PK. The values for this model were obtained by logistic regression analysis. pPK used the parameters comfort, curvature, age, visual acuity, change in comfort, change in curvature, and change in visual acuity. pPK_glasses predicted PK for a person only wearing glasses and used the parameters curvature, age, visual acuity, change in curvature, and change in visual acuity. The formula used was:

$$P(X) = \frac{1}{1+e^{-(\alpha+\Sigma\beta_i X_i)}}$$ P(X)=11+e−(α+ΣβiXi)

Turn MathJax on

where P(X) is the probability, α is the intercept, and β is the coefficient of the parameter X.

The values of the parameters can be seen in TABLE S1 and TABLE S2.

TABLE S1.

Parameters for pPK

Parameter	Estimate	Standard Error
Intercept	-13.3161	2.3632
Best-corrected visual acuity	-0.0376	0.0147
bcah_worst	-0.00009	0.0181
Curvature	0.2103	0.0306
Change in curvature	0.6771	0.1309
Change in visual acuity	0.0281	0.0443
Comfort	0.1333	0.1348

Table options

TABLE S2.

Parameters for pPK_Glasses

Parameter	Estimate	Standard Error
Intercept	-9.8341	6.7986
Age	-0.0456	0.0559
Best-corrected visual acuity	-0.0366	0.0391
Curvature	0.1734	0.0840
Change in curvature	1.6610	0.5680
Change in visual acuity	0.0164	0.1725
Comfort	0.1333	0.1348

Table options

Distributions

Distributions were sampled once per trial if they represented a parameter that was tracked throughout the model. These included the age, lens comfort, visual acuity, and corneal curvature. All other distributions were sampled once per set of trials in order to represent parameter uncertainty.

Costs

Discount

All costs were discounted at a yearly rate of 3%.

Regimens

All regimens were obtained from the literature and confirmed by clinical ophthalmologists at Washington University (Michael Kass, Edward Barnett, Andrew Huang, and Anthony Lubniewski, in personal e-mail communications, September 2008).

Medicare Costs

These CPT and HPCPS codes were based on the 2008 Medicare allowable.[3]

Glasses

Glasses were assumed to be a component of the treatment of a typical myopic patient and therefore were not considered in this incremental cost of keratoconus model.

Contact Lenses, Annual Visit and New Patient Visit, Fitting, First Fitting, and Follow-up

We sent a survey to the CLEK (co-) principal investigators asking them what they charged for their services. Six out of 21 responded. There were 6 types of contact lenses (CLs) (Hard, RGP, Soft Sphere, Soft Toric, Piggyback, and Softperm) that were included in the original CLEK data set. We calculated a weighted average of the costs of the contact lenses using the relative proportions from CLEK data and the average of the charges obtained from the survey. We used an average of the survey responses to determine the costs of an annual visit, new patient visit, fitting, first fitting, and follow-up. The cost of the contact lenses was applied at the beginning of each year and whenever a refit was required. The cost of an annual visit was applied at the beginning of every health state except "Death." The cost of the new patient visit and first fitting was applied in the first year of the model. The fitting cost was applied at the beginning of every health state except when wearing glasses and whenever there was another visit. The follow-up cost was applied whenever there was a subsequent visit in a given year. This cost included the visit and the fitting.

Number of Bottles of Medication

The paper by Fiscella and associates[4] was used to determine the number of bottles required for treatment of glaucoma related problems. Timoptic (0.50%, 10 mL) was assumed to have 74.2 days/bottle and Xalatan had 46.4 days/bottle at the estimated treatment regimen. When the specific medication was not represented in the paper, the range of 20 to 35 drops/mL was used. This was the range seen in the paper by Fiscella and was assumed to be representative of other ophthalmic drops.

Rise in Intraocular Pressure

The rise in IOP after a PK was assumed to be treated with a beta blocker for 6 months and Xalatan for the following 6 months (information supplied by Michael Kass in a personal conversation on September 16, 2008). Following the first year of treatment, we assumed that treatment would continue and that Xalatan would be used. Prices were based on the average wholesale prices (AWP) in the 2007 Red Book.[5] The costs came to $443 for the first year and $577.60 for the second year.

Penetrating Keratoplasty

The costs of the PK included the CPT code for a PK, anesthesia, ambulatory surgery center (ASC), corneal graft, Tobradex for the first month, and Vigamox and Lotemax for the rest of the year. The values can be seen in Table S3. It was assumed that Vigamox and Lotemax would be continued for the rest of the patient's life at a cost of $674.56 to $2246.60 per year. The cost of the corneal graft was based on the cost of a shipped cornea to Washington University from the Heartland Lions Eye Bank in St. Louis, Missouri (information provided by Melissa Williams at the Eye Bank on October 6, 2008).

TABLE S3.

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cPK	Low	High
CPT 65730	$975.63	$975.64
Anesthesia (CPT 00144) 90-120 min	$900.00	$1050.00
ASC (65710)	$1552.11	$1552.11
Corneal graft	$2600.00	$2600.00
Tobradex for 1 month (10 mL)	$157.44	$157.44
11 bottles Lotemax (10 mL)	$405.94	$1420.77
Vigamox (11 months) (3 mL)	$212.41	$638.61
Total	$6803.53	$8394.57

Table options

Rejection

Rejection was assumed to occur only during the first year. The regimen was assumed to be hourly Kenalog for 3 to 5 days and slowly tapered. An incremental 3 bottles of Lotemax was assumed over the following year. The total cost was $190.07 to 559.

Other Complications

We took into account the post-PK complications of synechiae, abscesses, uveitis, and vascularization. From the data in the Australian Graft Registry, we were able to calculate a pooled estimate of the costs using the probability of each complication.[2] It should be noted that although approximately 17% of postsurgical complications were synechiae, only 1.5% of them were lysed according to the registry. We assumed a CPT code of 65865 ($385.68) for lysis. We assumed that an abscess would be treated with 1 bottle of Vigamox and uveitis would be treated with 1 bottle of Lotemax. The total expected cost came to $27.11 to $36.45. The relative weights can be seen in Table S4.

TABLE S4.

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Post-PK Complication	Relative Weight
Synechiae	0.36
Abscess	0.28
Uveitis	0.30
Vascularization	0.94

Table options

Refraction

Refractive surgery was performed after approximately 12% of PKs according to the Australian data.[2] As in the calculation of the costs of other complications, we were able to calculate a pooled estimate of the refractive surgeries using the data from the Australian Graft Registry.[2] All of the surgeries were assumed to be performed in the office. The cost of laser in situ keratomileusis (LASIK) was the cost to an uncomplicated patient at Washington University, based on a conversation with Washington University clinical ophthalmologist Anthony Lubniewski on September 9, 2008. The weighted total was $250.54. The ranges were taken into account in the sensitivity analysis. This is illustrated in Table S5.

TABLE S5.

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cRefraction	Relative Weight	Cost	Expected Cost
Suture adjustment	0.34	$0.00	$0.00
Relaxing incision (CPT 65772)	0.31	$360.85	$111.86
Compression sutures (CPT 65772)	0.14	$360.85	$50.52
LASIK	0.05	$1500.00	$75.00
Laser/excimer/PARK	0.04	$0.00	$0.00
Wedge resection (CPT 65775)	0.03	$438.74	$13.16
Weighted total			$250.54

Table options

Enucleation

In estimating the cost of an enucleation, we assumed that prosthesis would be inserted with a 4-muscle attachment. The cost of the prosthesis was estimated using the posted cost on the Wills Eye website.[6] The anesthesia time was based on a 1.25-hour procedure. The total was $3136.79. This is illustrated in Table S6.

TABLE S6.

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cEnucleation	Cost
Physician (CPT 65105)	$686.79
Anesthesia 85 min (CPT 00140)	$950.00
Prosthesis	$1500.00
Total	$3136.79

Table options

Glaucoma Surgery

The cost of a glaucoma surgery was assumed to be the average of a shunt procedure and a trabeculectomy. The shunt procedures were more common in the Australian data, but since trabeculectomies are more common in the United States, we assumed them to be equally likely. The procedures were also assumed to be performed in an ambulatory surgery center. The cost of the valve is the 2008 Medicare allowable HCPCS Code.[3] The average was $3360.65. This is illustrated in Table S7.

TABLE S7.

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cGlaucoma Surgery	Physician CPT	Anesthesia (CPT 00140)	Ambulatory Surgery Center	Valve (L8612)	Total
Shunt at 75 min (CPT 66180)	$931.90	$900.00	$1644.00	$522.33	$3998.23
Trabeculectomy at 60 min (CPT 66170)	$938.57	$825.00	$959.50	$0.00	$2723.07
				Average	$3360.65

Table options

Probabilities

The majority of the probabilities in the model were obtained from the 2007 Australian Graft Registry, which included data from 13 350 grafts over approximately 20 years.[2]

Graft Survival Curves

Since the overall graft survival is greater for an indication of keratoconus, we used the survival curve of keratoconus as our basis. However, the survival curves with complications and refractive surgeries were based upon a pool of all grafts. Therefore, we calculated a modifier to be the ratio of survival in a given year of a PK for indication of keratoconus to the pooled total. This was then applied to the survival curves. After factoring out the complications, the survival for the first year without complications approached 1 and was assumed to such. Table S8 shows the survival curves given complications after PK. Table S9 shows the survival curves after each successive graft. When the model continued beyond the years shown in the tables, the values were extrapolated by TreeAge Pro.

TABLE S8.

Survival Curves After Penetrating Keratoplasty

Year	Rejection	Other Complication	Rise in IOP
1	0.772	0.769	0.887
5	0.579	0.626	0.731
10	0.439	0.493	0.586
15	0.305	N/A	0.380

IOP = intraocular pressure.

Table options

TABLE S9.

Survival Curves After Each Successive Graft

Years	Number of Grafts				
	≥5	4	3	2	1
1	0.517	0.649	0.683	0.846334	0.964
5	0.181	0.358	0.475	0.686908	0.933
10	N/A	0.111	0.238	0.543648	0.866
15	N/A	N/A	N/A	0.328696	0.75
19	N/A	N/A	N/A	N/A	0.4

Table options

Probabilities of Complications

The probabilities of a complication were based on data from the 2007 Australian Graft Registry.[2]

The first complication in the tree was enucleation. We assumed that there would be no enucleation after the first PK, but in regrafts we assumed a probability of 1%. However, enucleation was only performed on 1 eye, regardless of the complications in the second eye.

The probabilities of the complications of abscess, uveitis, and synechiae neovascularization were pooled into an “other complications” probability at approximately 14.6%. A rise in IOP and rejection were more common, at a probability of 18.1% and 22.9%, respectively, and were not pooled with other complications. In addition, the survival of the grafts after these complications was shown to be different.

The Australian Graft Registry showed that refractive surgeries were performed on 12% of all corneal grafts and that the survival would increase with doing so. Therefore, a modifier was applied during the first year when a refractive surgery took place. This modifier was calculated as the ratio of survival after refractive surgery to the survival of a PK with indication of keratoconus. This modifier was not applied in subsequent years as there was not shown to be a survival benefit after the first year.

Probability of Death

The probability of death in each year was estimated using the CDC website for health statistics.[7]

Tracker Variables

We tracked the curvature, visual acuity, and comfort of each eye as they changed throughout the person's lifetime. Age was tracked and used to determine the probability of death. Lifespan was tracked and used to determine the length of time spent alive in the model. The years a person has had a complication of IOP, rejection, and "other" was also tracked. It was assumed that the complications would affect graft survival and costs of the current graft but not of subsequent grafts. In a given cycle, having had a refractive surgery was tracked and used to apply the appropriate modifier to graft survival. The total number of regrafts, years of all complications, and years after each PK were tracked and used in the determination of graft survival. We also included a tracker variable for all costs that were not associated with surgery or medication to determine the best-case scenario for a patient with keratoconus.

Conducting Probabilistic Sensitivity Analyses

We estimated that the following parameters were the most likely to vary when looking at the total cost of keratoconus to a patient: age of diagnosis, the costs of 1 contact lens, the cost of a PK, the discount rate, the probability of being able to be fitted with a contact lens, the probability of a complication after PK, the probability of regraft, and the probability of requiring a PK. The range of age at diagnosis was 18 to 65 years. The age of 18 was used because keratoconus can manifest as early as puberty but the impact will be more significant when an adult.[8] The retirement age of 65 was used for comparison. The costs of 1 contact lens determined by the CLEK survey ranged from $18.00 to $300.00, which are the 2 endpoints we used. The limits of the cost of PK were the lowest value determined, $6800, and a round number slightly above the upper limit, $10 000. The discount rate was estimated to range from 1% to 5%. The limits of the probability of being fitted were determined to be the round numbers of 98% and 100%, which were near the upper and lower limits as determined by unpublished CLEK data.[1] The probability of complication after a PK was arbitrarily chosen to be approximately ±50% of the usual complication rate at 25% and 75%. The probability of regraft limits was 0% and 20%, which represented a perfect survival and a survival arbitrarily chosen to be approximately 5 times worse than the typical first-year survival. Finally, the probability of requiring a PK had limits of 1% and 10%, which represented a lower limit slightly lower than the average yearly rate of 1.25% and an upper limit equal to the average rate of PK over the 8-year period of the CLEK Study.[1]