CURRENT MEDICAL RESEARCH AND OPINION®
VOL. 24, NO. 10, 2008, 2905–2918

0300-7995
doi:10.1185/03007990802379996

ORIGINAL ARTICLE

Economic evaluation of medication, laser trabeculoplasty and filtering surgeries in treating patients with glaucoma in the US

Louis B. Cantor[a], L. Jay Katz[b], J. Wang Cheng[c], Er Chen[c], Kuo B. Tong[c] and John W. Peabody[d]

[a]*Indiana University School of Medicine, Department of Ophthalmology, Indianapolis, IN, USA*

[b]*Wills Eye Hospital, Philadelphia, PA, USA*

[c]*Quorum Consulting Inc., San Francisco, CA, USA*

[d]*Sg2 Health Care Intelligence, Skokie, IL, USA and University of California, San Francisco and Los Angeles, Departments of Epidemiology and Biostatistics, Medicine and Health Services, San Francisco and Los Angeles, CA, USA*

Address for correspondence: Er Chen, MPP, Senior Associate, Quorum Consulting, Inc., 222 Kearny Street, 10th Floor, San Francisco, CA 94108, USA. Tel.: +1 415 835 0190, Ext. 141; Fax: +1 415 835 0199; er.chen@quorumconsulting.com

Keywords: Costs – Glaucoma – Laser trabeculoplasty – Markov process – Medication – Surgery

ABSTRACT

Objective: Despite the significant clinical and economic burden associated with glaucoma, studies evaluating the long-term costs of existing treatments are limited. This study compared the 5-year costs of three treatment strategies: medication, laser trabeculoplasty, and filtering surgeries in managing patients with primary open-angle glaucoma whose intra-ocular pressures were not adequately controlled by two medications.

Research design and methods: A Markov model was developed to simulate the transition of treatment progression over a 5-year period to evaluate the total treatment costs associated with each strategy. In the medication arm, medications were the only available treatment, whereas in the laser trabeculoplasty and surgery arms, patients would receive concomitant medications both at the time of the procedure and in subsequent years. Treatment states were determined by the rate of success in controlling patients' intra-ocular pressure in each year. The distribution of treatment states and the transition probabilities between these states were derived from published literature, adjusted or supplemented by the authors' own treatment experiences. Costs assessed in the model included treatment, complications associated with each treatment, and physician office visits obtained from published literature and standardized fees and schedules.

Results: The 5-year cumulative costs were approximately $6571, $4838 and $6363 for patients in the medication, laser trabeculoplasty, and filtering surgery arms, respectively. Costs of third-line medication, first-line medication following laser trabeculoplasty, and post-surgery complications had the greatest impact on the model results in the medication, laser trabeculoplasty, and filtering surgery arms, respectively. Probabilistic sensitivity suggested the results were statistically significant ($p < 0.001$), favoring the use of laser trabeculoplasty.

Conclusions: Over 5 years laser trabeculoplasty was associated with the lowest total costs compared to treatment by medication alone or by filtering surgery for patients who were not adequately controlled by two medications. Future development of glaucoma treatment should focus on reducing the need for post-procedure medical therapy as well as lowering the rate of post-procedure complications. Limited by the availability of the transition probabilities in published literature, the model results need to be validated by prospective or retrospective observational studies.

Introduction

Glaucoma is the second leading cause of blindness worldwide[1,2]. It is projected that, by 2010, there will be 60.5 million people with glaucoma, which will increase to 79.6 million by 2020. Of these cases, 74% will be primary open-angle glaucoma (POAG)[1]. Higher intra-ocular pressure (IOP), greater cup-to-disk ratio, thinner central corneal measurement, and older age are well-documented risk factors for the disease[3]. Glaucoma disproportionately affects women and Asians worldwide. It is projected that women will comprise 59% of all glaucoma cases and Asians will comprise 47% of total cases by 2010[1]. Although their race is not an independent risk factor, African Americans tend to have a higher risk of developing glaucoma than Caucasians[3,4].

Therapeutic options to manage POAG include pharmacotherapy, laser therapy, and surgical intervention. Because IOP remains an important modifiable risk factor for delaying glaucoma progression[3,5], these interventions all attempt to lower IOP to a level that is believed to halt or inhibit disease progression. In recent years, initial medical therapy has changed with the introduction of prostaglandin analogs which have replaced β-antagonists as the therapy of first choice[6]. Other therapeutic options include the α-agonist, the carbonic anhydrase inhibitor (CAI), and the fixed-combination products containing two different medication classes, such as timolol/dorzolamide or timolol/brimonidine, which are often used to simplify the medical regimen in the hope of improving compliance. Observational studies, however, have shown that insufficient control of IOP in patients during the first 1–3 years can lead to high frequency of treatment changes and surgical interventions, and therefore, increased costs[7,8]. In addition, poor adherence to therapy has been documented to compromise effectiveness of these treatments[9]. Laser trabeculoplasty (LT) has been used to lower IOP in patients with POAG for over 25 years as an alternative for patients who cannot or will not use medications. Yet the role of LT remains controversial. Although LT may occasionally reduce the amount of medical treatment and prevent the need for more invasive intervention, 30% to more than 50% of eyes require additional filtering surgical treatment within 5 years after the first LT; repeat LTs have lower success rates, with failure occurring in nearly 90% of these eyes within 2 years[10]. Filtering surgery such as trabeculectomy or tube shunting provides a treatment alternative, and often reduces IOP and the need for subsequent medical treatment. While long-term control is often achieved, some patients will require further therapy or a second surgery, which also carries a higher failure rate[11]. For example, the 10-year treatment failure rate in the Advanced Glaucoma Intervention Study (AGIS) was 20–30%[11]. Furthermore, filtering surgery increases the likelihood of complications and the need for cataract surgery[10].

The economic implications for glaucoma management are significant. Glaucoma will cost the US health care system an estimated $2.9 billion in 2008[12]. A retrospective observational chart review showed that in 1998 the annual costs of treating a patient with newly diagnosed POAG in the US averaged $1055[13]. Medication use represented the most significant portion of costs among all glaucoma treatments, ranging from 42 to 56% for all stages[14].

Although the substantial economic burden associated with glaucoma and its related treatments has been well documented, mainly through retrospective reviews of medical charts[13–15], the step-wise approach to treatment in order to control a patient's IOP, as well as the impact of treatment change on cost, have not been well studied. Even when studies were conducted to simulate treatment changes, these studies tended to focus only on patients with new diagnoses of POAG, or evaluated the impact of one or multiple medications on the overall treatment costs[7,16]. Although medical therapy has experienced a dramatic rise with respect to the classes of medications useful for lowering IOP, adding a third or fourth medication infrequently contributes to a substantial decrease in IOP[17]. Thus there are still substantial numbers of patients who may fail medical therapy and require other interventions. For example, In the Ocular Hypertension Treatment Study, 40% of patients required more than two medications to achieve a 20% decrease in IOP[18]. In the Collaborative Initial Glaucoma Treatment Study, 75% of patients with early-to-moderate glaucoma required more than two medications to control their IOP within 5 years[19]. The long-term cost implications of different treatment strategies in patients not sufficiently controlled by two medications are unknown. The objective of this study was to compare the costs associated with treatment via medication, LT, and filtering surgeries in managing patients who were not adequately controlled by two medications.

Patients and methods

General framework and model structure

A Markov model was developed in TreeAge Pro 2006 to simulate the transition of treatment progression of patients with POAG over a 5-year period. Studies have suggested that visual field loss in glaucoma patients is minimal when they are aggressively treated with either surgery or topical medications over a 3–5-year follow-up period to achieve individualized IOP levels[20,21]. Although 5 years is a limited time frame to evaluate a chronic disease, it has been widely used in other modeling studies of glaucoma treatments[21,22]. The authors believe 5 years represents an appropriate time frame to capture the majority of resource utilization and costs and it is also consistent with the time horizon recommended in the guidelines of performing cost–effectiveness analyses[23].

The American Academy of Ophthalmology (AAO) Preferred Practice Patterns for POAG was referenced to model different treatment states[10]. The Markov model was defined using treatment states determined by effectiveness of IOP control. Although the ultimate objective of managing glaucoma is to prevent vision field loss and progression to blindness, disease progression occurs over decades and is difficult to observe. Thus, these measures have rarely been used as efficacy endpoints in clinical trials. Instead, treatments have focused on controlling IOP elevation which is considered to be the primary risk factor for disease progression. Furthermore, the uncertainty surrounding quantification of glaucoma progression and the level of IOP make use of clinical states difficult and controversial.

The model included patients diagnosed with POAG who were not adequately controlled by two medications (i.e., first-line and second-line medications). These patients received one of the three treatment options: (1) *Medication Only*, (2) *LT*, or (3) *Surgery* (i.e., trabeculectomy or tube shunt). In the *Medication Only* arm, medications were the only available treatment, whereas in the *LT* and *Surgery* arms, patients would receive concomitant medications at the time of the procedure or in subsequent years. For simplicity, treatment states were considered mutually exclusive and evaluated in the 1-year intervals (i.e., a 1-year cycle length); therefore, a patient could only be in one treatment state at any given time during a year.

Assumptions

Key assumptions related to the overall modeling methodology were:

(1) The Markov model aimed to model the 5-year treatment costs associated with various treatment strategies, not outcomes. Although treatment effectiveness as measured by successful IOP control was indirectly used to determine the treatment states and the transition between them, the authors did not attempt to use treatment effectiveness or its impact on patients' quality of life as the outcome endpoints.
(2) Each treatment and treatment pathway aimed to control IOP.
(3) Patients not controlled were assumed to require additional resources (i.e., adding new medication or proceeding to an LT or surgery); however, no switching or cross-over between treatment arms was considered.
(4) Change between treatment states in the model may occur once per cycle (once a year) and cost of treatments were assumed to accrue at the beginning of the year.

In the *Medication Only* arm, after two medications (i.e., first-line and second-line) failed to control IOP, a third-line medication was added. If the three medications were insufficient to control IOP in the next cycle, patients would require a fourth-line medication. Patients who were receiving four medications were assumed to continue requiring that level of medication until the end of the 5th year. This model considered the prostaglandin class as first-line medication, the non-selective β-blockers second-line, the α-agonists third-line, and the carbonic anhydrase inhibitors (CAI) fourth-line. Detailed descriptions of medication use are provided separately in later sections. In the *LT* arm, patients underwent an LT after two medications failed to control IOP. In the *LT* arm, two medications (i.e., first-line and second-line) were still required in the year of the procedure. If patients' IOP was controlled by LT, they would continue on two medications for the subsequent year. On the other hand, if patients' IOP was not controlled, a third-line medication was added. Only those who responded to an initial LT were eligible for a repeat LT in a subsequent year. Patients with elevated IOP following the second LT would then increase their medications, adding a third-or/and fourth-line, similar to the *Medication Only* arm.

In the *Surgery* arm, the only option besides medication was filtering surgery. Patients not controlled with two medications received a trabeculectomy. In the year of the trabeculectomy, no medication was necessary. In subsequent years, patients could continue requiring no medication, or use one (i.e., first-line) or two (first-line and second-line) medications. Those not receiving medications or only first-line medication could progress to both first-and second-line medications before they received a second surgery. For the second surgery, the authors assumed 50% of the patients would receive a tube shunt, and 50% a repeat trabeculectomy. Patients then followed similar treatment pathways after the first surgery except that they were assumed not to exceed two medications after the second surgery. The structure of the Markov model is presented in Figure 1.

Data sources

The authors used published literature as the primary data source, wherever available.

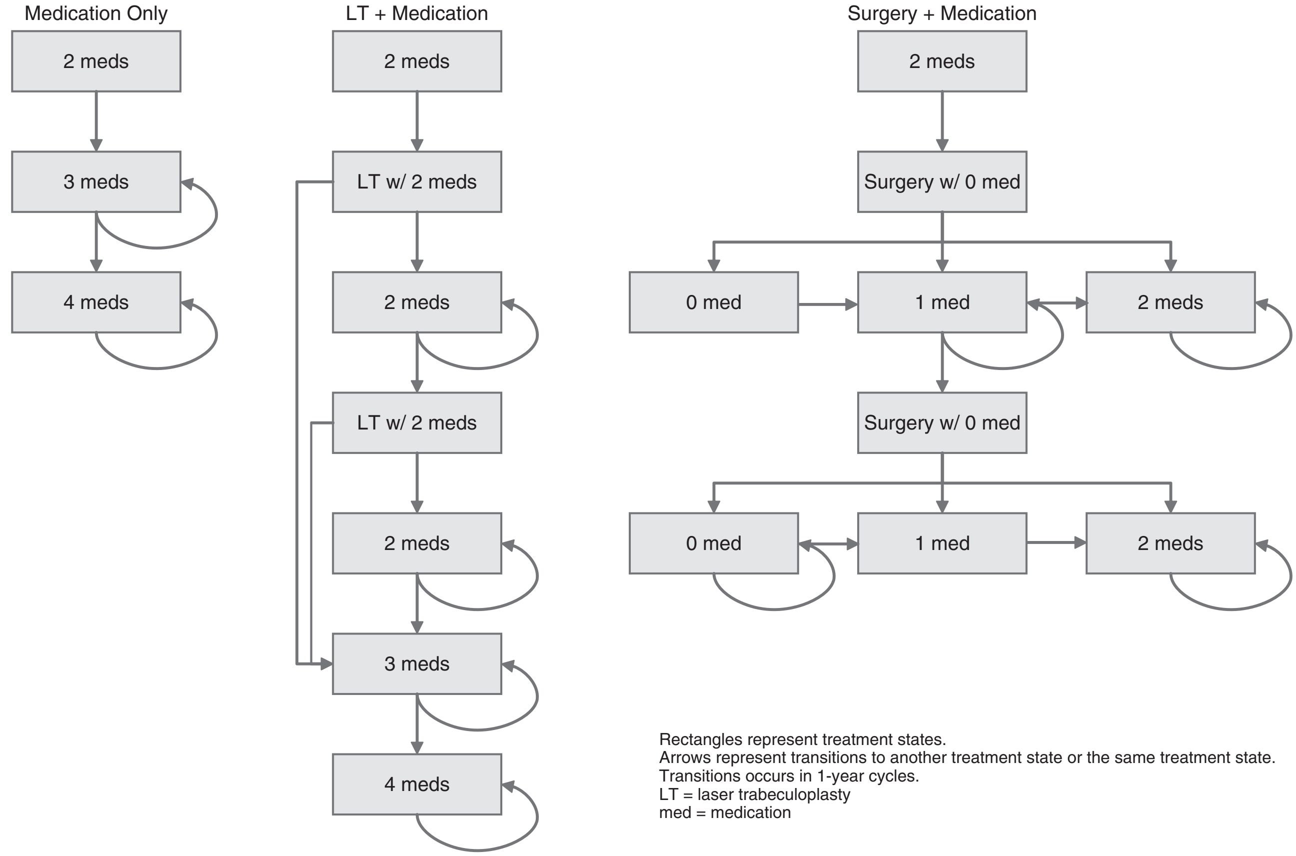


Figure 1. *Markov model structure*

PubMed (National Library of Medicine) was searched for articles and abstracts that included at least one of the following terms or medical subject headings (MeSH): 'glaucoma,' 'IOP,' 'medication,' 'laser trabeculoplasty, 'surgery (trabeculectomy or tube shunt),' 'costs,' and 'complication' from 1995 to 2008. As appropriate, distribution of treatment states and transition probabilities reported from the literature were adjusted to reflect the differences in the patient population and the study design based on experience in the authors' own institute (Dr. Louis Cantor, Eugene and Marilyn Glick Eye Institute, IN, and Dr. Jay Katz, Wills Eye Institute, PA)

Transition probabilities

Transition between treatment states occurred at the beginning of each year. Transitions were driven by the effectiveness of each treatment reported in the literature. As the effectiveness data were based on, or derived from, a composite of studies, treatment effectiveness was not uniformly defined. Nevertheless, IOP control was used most frequently in these studies to assess treatment effectiveness. Therefore, in this model, the authors assumed a patient would remain on the same treatment for a year if his or her IOP was adequately controlled at the beginning of that year. The following sections provide a detailed description of transition probabilities used in each treatment arm. Key transition probabilities used in the base–case and sensitivity analyses were listed in Table 1.

Medication-only arm

Patients who were refractory to two medications entered the model by adding a third-line medication. Patients were populated in a 4 : 1 ratio to approximate the distribution of patients who were prescribed four versus three medications by the end of 5 years. Based on this ratio, the annual transition probability of 33.3% was derived through back-calculation. Once a patient had been prescribed four medications, he or she was assumed to have remained on four medications until the end of 5 years.

LT arm

After the first LT, the percentage of patients using two medications in the subsequent year was referenced from a 12-month randomized clinical trial comparing selective laser trabeculoplasty (SLT) and argon laser trabeculoplasty (ALT) in 176 eyes of 153 patients[29]. In this study, 82% of eyes in the SLT group were maintained on the same number of medications (mean = 2.6) at 1 year after the treatment, and 18% had one additional medication. In the ALT group,

Table 1. *Descriptions of key clinical and economic parameters.*

Model parameter	Treatment arm			Value defined in the model			Reference
	Medication	LT	Surgery	Base-case	Deterministic sensitivity	Probabilistic sensitivity*	
Cost of medications							
First-line: prostaglandin analog	Y	Y	Y	$560	$448–672	Uniform	Thomson MICROMEDEX[24]; Rylander[25]; Lee[26]
Second-line: non-selective β-blockers	Y	Y	Y	$210	$168–252	Uniform	
Third-line: α-agonist	Y	Y		$710	$568–852	Uniform	
Fourth-line: carbonic anhydrase inhibitors	Y	Y		$580	$464–696	Uniform	
Probability of increasing to 4 meds	Y	Y		0.33	0.17–0.50	Uniform	Assumption
Cost per physician office visit (CPT 92 012)	Y	Y	Y	$62	$50–74	Uniform	CMS[27]
Cost of LT (CPT 65 855)		Y		$583	$466–700	Uniform	CMS[27], CMS[28]
Cost of LT complication†		Y		$250	$125–375	χ^2 ($n = 10$, $\sigma = 5$)	Assumption; TreeAge Pro 2006
Probability of using 2 meds after LT		Y		0.67	0.53–0.80	Uniform	Adjusted from Damji[29]
Probability of receiving 2nd LT after 2 meds		Y		0.21	0.10–0.31	Uniform	Spaeth[30]; Schwartz[31]; Krupin[32]; Shingleton[33]
Cost of trabeculectomy (CPT 66 170, 66 172)			Y	$1734	$1390–2080	Uniform	CMS[27], CMS[34]
Cost of post-surgical complications‡			Y	$1000	$500–1500	χ^2 ($n = 10$, $\sigma = 5$)	Assumption; TreeAge Pro 2006
Cost of tube shunt (CPT 66 180; HCPCS L8612)			Y	$2286	$1830–2740	Uniform	CMS[27], CMS[34]
Probability of increasing to 1 med post surgery			Y	0.24	0.12–0.36	Uniform	Assumption
Probability of increasing to 2 meds post surgery			Y	0.31	0.15–0.46	Uniform	Assumption
Probability of receiving 2nd surgery after 2 meds			Y	0.5	0.25–0.75)	Uniform	Assumption
Discount rate	Y	Y	Y	0.03	0.03 (0–0.06)	Uniform	Gold[35]

*In probabilistic sensitivity analysis, parameters in uniform distribution were defined by the same range used in the deterministic sensitivity analysis
†Costs of LT complication were based on an incidence of 25% at cost of $1000 per complication
‡Costs of surgery complication were based on an incidence of 25% at cost of $4000 per complication and were assumed to incur in subsequent years following the surgery
CMS, Centers for Medicare and Medicaid Services; CPT, Current Procedural Terminology; HCPCS, Healthcare Common Procedure Coding System; LT, laser trabeculoplasty; med, medication
Y = yes

69% of eyes remained on the same number of medications (mean = 2.4) and 29% required one additional medication. These numbers were slightly adjusted in this model as it did not differentiate the type of LT and assumed the baseline number of medications used was two, instead of 2.4 or 2.6. The authors estimated that approximately two-thirds (66.7%) of patients treated by LT would remain on two medications, while one-third (33.3%) would require three medications after 1 year. In a subsequent year, if patients were not controlled by two medications, those who responded to an initial LT were eligible for a repeat procedure. Results from four long-term outcome studies indicated that 30% to more than 50% of eyes had additional surgical treatment (i.e., second LT or filtering surgery) within 5 years after a first LT[30–33]. In the base case analysis, the authors estimated that approximately one-third (33.3%) of patients would receive a second LT in a 5-year timeframe. They then back-calculated the proportion of patients who needed a second LT on a yearly basis (20.6%). Once a patient had received two medications after the second LT, the same pathways in the *Medication Only* arm were applied.

Surgery arm

Distribution of patients to a different level of medication use post-surgery was based on a long-term outcome study of glaucoma filtering surgery published by Parc *et al.*, as well as the authors' own institutional experience. Parc *et al.* reported that the probability of using medication for IOP control postoperatively was 21% at 1 year and 42% at 5 years in patients with new diagnoses of POAG[36]. As the patients studied in this model presented more severe cases (i.e., not controlled with two medications prior to surgery), the authors' own experience indicated a slightly higher percentage of patients requiring medication. Thus, we approximated 25% of patients would use medications at 1 year. We further estimated that among the 25%, 15% of patients would require one medication and 10% would require two. Patients uncontrolled by two medications following the first trabeculectomy could receive a second surgery. For the second surgery, 50% of the patients would have received a tube shunt and 50%, a repeat trabeculectomy. The corresponding percentages of 0, 1 and 2 medication use after the second surgery were 60%, 25% and 15%, respectively. At year 5, the authors assumed one-third of patients would require 0, 1 and 2 medications. Based on this, they calculated the transition probability between 0 and 1 medication and 1 and 2 medications to be 23.7% and 30.7%, respectively, following both the first and second surgery.

Resource use and costs

Primary data for resource utilizations and costs were obtained from published literature and standardized fees and schedules. When published data were not available, the authors' own institutional experience was used. Costs captured in the model included medication use, physician office visits, LT and filtering surgery procedures, and complications associated with these procedures. The cost per bottle of each representative selection of common glaucoma medications in both brand and generic formulations was obtained based on the 2007 Average Wholesale Price (AWP)[24]. Number of drops and actual volume for each bottle of medication were referenced from Rylander *et al.*[25]. Medications were grouped into four categories: first-line, second-line, third-line, and fourth-line based on the most common sequential use as described by Lee *et al.*[26]. The costs associated with these medical therapies were added to the treatment regimens where appropriate. Because the authors did not specify with which formulation patients would be treated, an average price of all formulations was calculated for each class of medication. These costs varied by 20% in the sensitivity analyses.

First-line is the prostaglandin class consisting of bimatoprost, travoprost, and latanoprost. The second-line non-selective β-blockers are comprised of timolol, carteolol, levobunolol, and metipranolol. The α-agonist class is considered third-line and includes both 0.15% and 0.2% brimonidine. Carbonic anhydrase inhibitors (CAI), consisting of brinzolamide and dorzolamide, are used as fourth-line (Table 2). Although fixed-combination products, such as timolol/dorzolamide or timolol/brimonidine, have been frequently used as second- or third-line therapy to simplify the medication regimen, they do not change the treatment paradigm; therefore, these products were not considered in this model. Medication class added to the *LT* and *Surgery* arm followed the same order as added in the *Medication Only* arm. Patients were assumed to adhere fully to medication across all arms. The authors included the cost of a physician office visit whenever a change in treatment states occurred, such as when a new medication was added to the overall treatment regimen or a procedure was performed. They used the national Medicare physician fee schedule facility payment for LT procedures performed in the hospital outpatient setting. The costs of trabeculectomy and tube shunt were based on procedures performed at ambulatory surgical centers. Costs of adverse reactions and complications post-LT and post-surgery were included in the model based on the authors' institutional experiences. These costs of complications following surgery were

Table 2. *Costs of glaucoma medications by class.*

Drug class	Name	Size (ml)	Volume (ml)	No. drops/ml	No. drops/bottle	No. drops daily	No. days/bottle	2007 AWP ($)	2007 cost/year ($)
First-line: prostaglandin analog	Bimatoprost (Lumigan)	2.5	3.24	32	105	2	52.2	71.68	500
		5	5.29	32	170	2	85.25	143.32	614
		7.5	7.76	33	254	2	127	214.98	618
	Travoprost (Travatan)	2.5	2.61	39	102	2	51.2	71.28	508
		5	5	41	204	2	102.15	142.56	509
	Travoprost (Travatan Z)	2.5	2.76	34	94	2	47.05	71.28	553
		5	5.03	34	169	2	84.45	142.56	616
	Latanoprost (Xalatan)	2.5	3.13	30	93	2	46.4	68.11	536
AVERAGE									560
Second-line: non-selective β-blockers	Timolol maleate (Istalol 0.5%)	5	5.21	32	168	2	84.25	79.06	343
	Timolol maleate (Timoptic 0.5%)	5	5.61	28	157	4	39.4	24.74	230
		10	10.35	30	309	4	77.15	50.19	238
	Timolol maleate (Timoptic 0.5% XE)	5	5.21	22	113	2	56.25	40.3	261
	Carteolol 1.0%	5	4.92	28	137	4	34.3	21.28	226
		10	10.03	28	278	4	69.55	40.1	210
		15	15.16	28	421	4	105.35	57.25	198
	Levobunolol 0.5%	5	5.03	27	136	4	34.03	16.6	178
		10	10.01	26	257	4	64.35	32.25	183
		15	15.06	25	371	4	92.8	48.25	190
	Metipranolol 0.3%	5	5.05	26	132	4	33.08	16.61	183
		10	10.18	25	258	4	64.5	26.85	152
	Timolol 0.5% gel	5	5	27	136	4	67.85	21.84	235
	Timolol maleate 0.5%	5	5.03	32	160	4	39.88	17	156
		10	10.03	30	297	4	74.2	32.35	159
		15	15.34	31	473	4	118.2	48.75	151
AVERAGE									210
Third-line: α-agonist	Brimonidine (Alphagan P 0.15%)	5	5.17	23	121	6	20.12	50.32	838

(*continued*)

Table 2. Continued.

Drug class	Name	Size (ml)	Volume (ml)	No. drops/ml	No. drops/bottle	No. drops daily	No. days/bottle	2007 AWP ($)	2007 cost/year ($)
		10	10.37	23	234	6	38.92	100.61	874
		15	15.48	23	357	6	59.58	150.92	856
	Brimonidine 0.2%	5	5.15	25	128	6	21.32	32.65	559
		10	10.28	26	270	6	45.03	65.24	529
		15	15.51	24	373	6	62.25	97.92	574
AVERAGE									710
Fourth-line: carbonic anhydrase inhibitors	Brinzolamide (Azopt)	5	4.99	30	148	6	24.65	38.24	566
		10	10.04	29	296	6	49.35	80.52	596
		15	15.21	32	484	6	80.77	120.78	546
	Dorzolamide (Trusopt)	10	9.98	24	235	6	39.15	65.96	615
AVERAGE									580

included in subsequent years. Table 1 summarizes the medication and non-medication resource use and costs in the model.

All costs incurred beyond the first year were discounted, reflecting time preference for money. According to the recommendation from the Panel on Cost Effectiveness Analysis of the US Public Health Service, annual costs were discounted at 3% in the base–case analysis and varied from 0 to 6% in the sensitivity analyses; costs were assumed to occur at the beginning of the year[35].

Sensitivity analysis

Both deterministic and probabilistic sensitivity analyses were conducted. One-way sensitivity analyses were conducted on all variables, such that the impact for the total treatment costs was examined by altering one variable at a time within a pre-specified range to determine which variable affected the cost the most. The effects of uncertainties in each input variable on the total treatment costs were determined for the three treatment arms, and presented using tornado diagrams, in which a horizontal bar was generated for each input variable examined over a continuous range of values. The bars in the tornado diagrams were stacked in order of the potential impact of the variable on the model results. As rule of thumb, input data derived from the authors' own experience (e.g., costs of complications related to LT or surgery) and those adjusted from published literature (e.g., transition probabilities from treatment states) were varied by 50% to reflect the uncertainties associated with these variables, unless specified otherwise. All the cost data obtained from published sources were varied by 20%. Variables that had the greatest impact on the total treatment costs were identified for each treatment arm.

Probabilistic sensitivity analyses were performed via Monte Carlo simulation. One advantage of probabilistic sensitivity analysis is that all parameter uncertainties can be simultaneously incorporated into an analysis. In other words, sampling parameters are randomly assigned from probability distributions, rather than simply using the minimum and maximum values as performed in deterministic sensitivity analyses. As such, the simulation results quantified the total impact of uncertainty on the model, in terms of the confidence that can be placed in the results[37] based on 1000 iterations generated for each treatment arm. Based on the mean cost and standard deviation produced from these iterations, a statistical test was carried out via ANOVA to determine the statistical significance in the differences observed for the 5-year treatment costs among the three treatment arms.

Because the exact distribution of the value taken by the parameter was unavailable, the authors assumed a uniform distribution for all transition probabilities, cost of medications and cost of procedures (e.g., physician office visit, LT, surgery), in which all intervals within the minimum and maximum values were equally probable. The minimum and maximum values were consistent with those used in the one-way sensitivity analysis. The uniform distribution was chosen over other forms of distributions because it allows more variability in parameters examined than does a unimodal distribution, hence accounting for a greater degree of uncertainties. Costs of complications, both for LT and surgery, were based on the chi-square distribution because these values were likely to be positively skewed with minimum of zero. Range for each of the parameters and their probability distribution used in deterministic and probabilistic sensitivity analyses are presented in Table 1.

Software

TreeAge Pro 2006 was used to construct the model and conduct the analysis.

Results

Baseline results

The Markov model simulated the transitions of a hypothetical POAG patient cohort through various treatment states using 1-year cycles over 5 years. The results of the base–case cumulative costs of treatment of *Medication Only*, *LT*, and *Surgery* are presented in Table 3. At the end of the 5th year, patients treated by *LT* incurred the lowest costs among the three treatment options. The 5-year total costs were approximately \$6571, \$4838 and \$6363 for patients treated by *Medication Only*, *LT*, and *Surgery*, respectively (Table 3).

Sensitivity analyses

The results of deterministic (i.e., one-way) sensitivity analyses were presented in Figures 2–4. Medication was the only treatment option available in the *Medication Only* arm. Not surprisingly, cost of medication had the greatest impact on this arm. As all patients in this arm received a third-line medication, choice of the third-line therapy was the most important cost driver. In the *LT* arm, cost of first-line therapy, as well as the need for two medications post-LT, bore a greater impact on the total treatment costs than other parameters. Total treatment costs for the *Surgery* arm were primarily driven by the costs of managing complications following the trabeculectomy or tube shunt procedures. Reduction in surgical complications would offer great opportunity for cost savings in the *Surgery* arm compared to the *Medication Only* and *LT* arms. As the model simulated the costs over 5 years, the discount rate had a significant impact on results obtained from all arms.

Results from the probabilistic sensitivity analysis of 1000 simulations for each treatment strategy were presented in Table 3. The mean 5-year treatment costs were \$6553 (SD = \$531), \$4849 (SD = \$409), and \$6386 (SD = \$1651) for the *Medication Only*, *LT* and *Surgery* arms ($p < 0.001$). Data obtained from these simulations suggested that *LT* resulted in statistically lower 5-year costs than *Medication Only* and *Surgery* after accounting for the uncertainties surrounding the key model parameters.

Discussion

As a chronic disease, long-term outcomes and economic data of POAG are not usually obtainable from clinical trials. Moreover, trials usually only compare one intervention to another, but in actual practice, many therapeutic and surgical interventions may be used in conjunction with one another. As such, this study relies on modeling techniques and represents a conceptual framework to evaluate treatment strategies commonly used in managing POAG patients who are not adequately controlled by two medications. It explores the influences of these strategies in IOP control, direct medical costs, and glaucoma-related health care resource use, and ranks the treatment strategies with respect to overall treatment costs.

Table 3. *Five-year treatment costs: base–case analysis and probabilistic sensitivity analysis*

	Baseline	Probabilistic sensitivity analysis		
		Mean (SD)	Range	*p*-value*
Medication only	\$6571	\$6553 (531)	\$4956–8006	< 0.001
Laser trabeculoplasty	\$4838	\$4849 (409)	\$3653–6088	
Surgery	\$6363	\$6386 (1651)	\$2996–13 475	

*ANOVA test

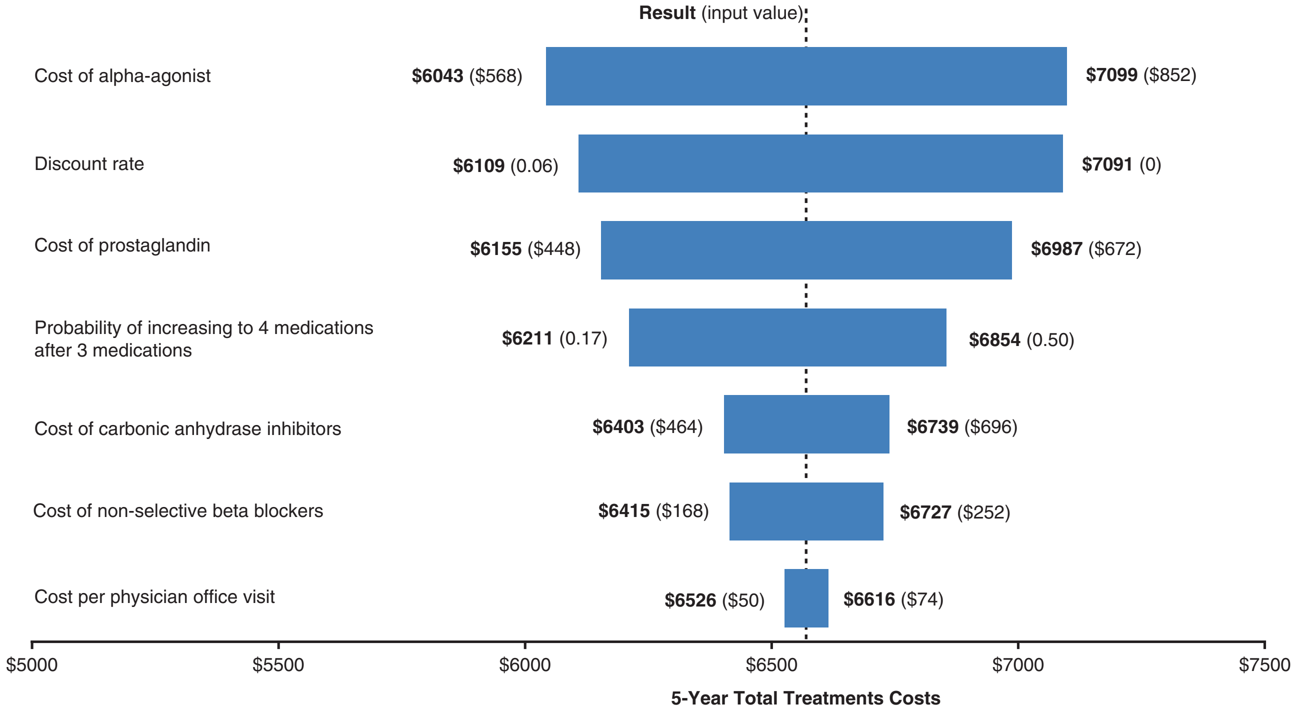
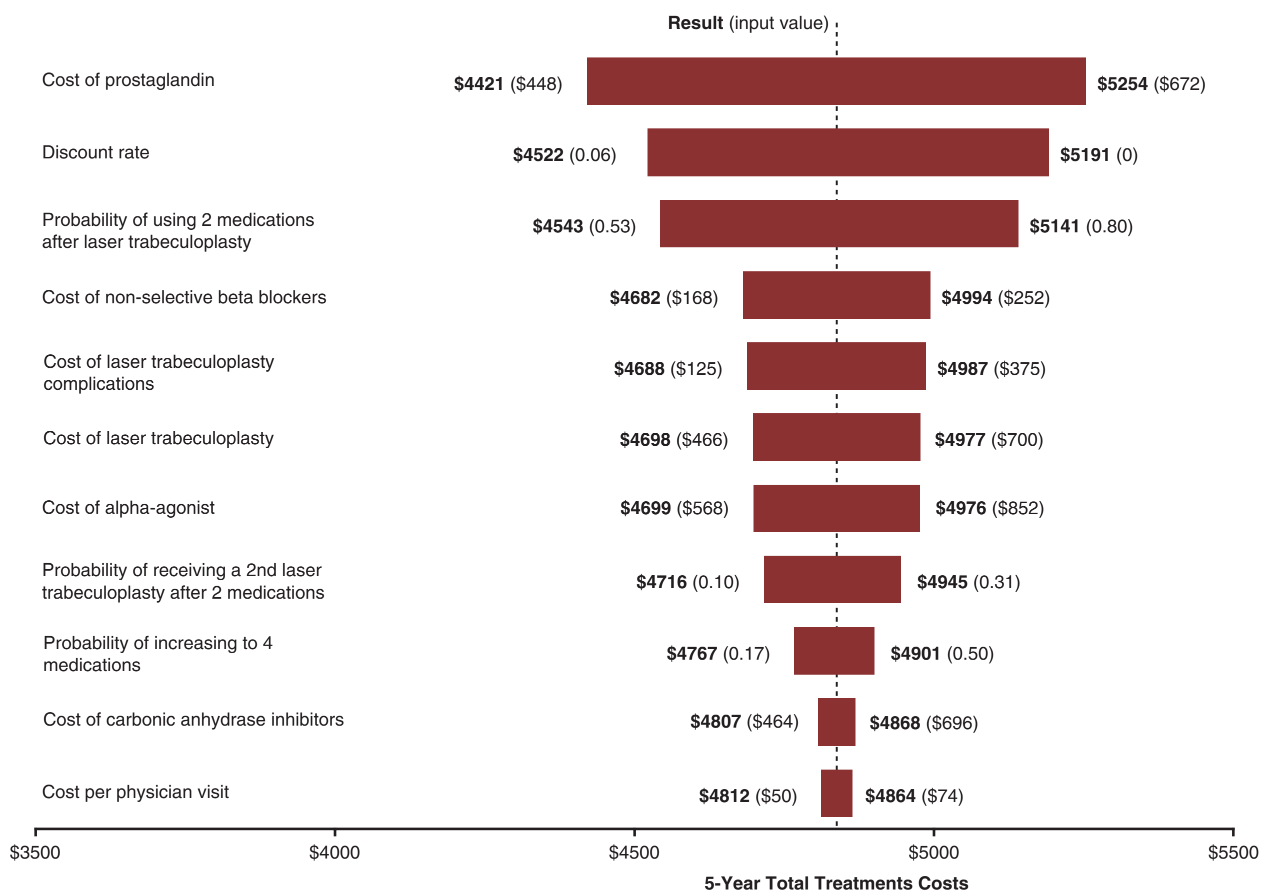


Figure 2. *One-way sensitivity analyses of the 5-year costs – medication only*



This model represents a novel approach in a number of ways. One of the key features differentiating this model from previous models is the use of treatment state transition as a proxy for treatment effectiveness (e.g., IOP control). The model considers the diversity in treatment strategies and captures the sequential use of single and combination therapies following LT and surgery. Thus, it overcomes some of the limitations in

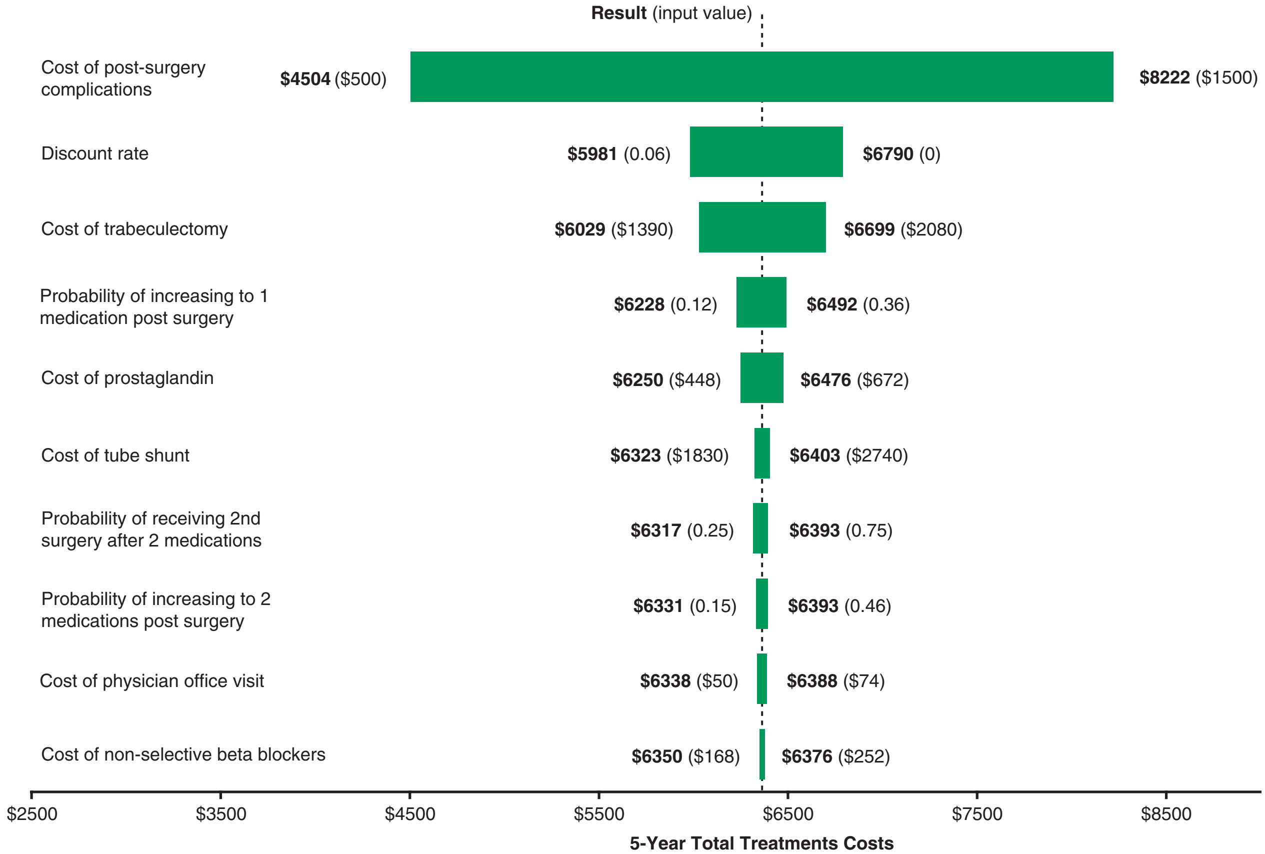


Figure 4. *One-way sensitivity analyses of the 5-year costs – filtering surgery*

the previous studies which only evaluated treatment strategies specified in clinical protocols during limited time frames. It incorporates the treatment outcomes (e.g., IOP control) into the transition between treatment states, which are commonly observed in the current clinical practice. By doing so, it enables readers to translate the impact of treatment outcomes into economic consequences. The model structure is transparent, easy to understand, and simple to customize. It accommodates the variability in medication utilization; users of the model could define the individual medications to be considered by assigning treatment success rate and costs associated with those medications.

For many years, the primary goal of glaucoma treatment has been to control IOP, which can be achieved through medical therapy, laser treatment, and surgery[8,38].With the advancement of new medication development in the past two decades, medical management offers a wider range of choices than ever before with improved availability and efficacy in lowering IOP. As a result, a decrease in glaucoma surgical procedures has been observed since the 1990s in many countries[39,40]. For example, in the current management of POAG, most clinicians begin treating a patient with prostaglandin classes. If only minimal IOP decrement is seen, or the IOP does not reach target level, the patient is switched to β-blockers. If these maneuvers are unsuccessful, clinicians will add a CAI, usually in the form of the fixed combination of timolol 0.5% and dorzolamide. If still unsuccessful, the dorzolamide is stopped and substituted with brimonidine[6]. Usually only after three or four medicines have been tried and the IOP remains refractory, is LT or surgery considered, despite continued advances in laser and filtering surgery. This study, on the other hand, underscores the economic implications of exclusive medical management in medication-refractory patients. The study results indicate that *LT* may offer a potential for cost savings compared to the *Medication Only* approach. This is not to say that the decision of treatment should be based upon economic reasons. Factors such as age, disease stage, and rate of progression, among others, shall still be the primary decision drivers; however, cost shall be one of the many considerations in the environment of rising health-care costs and constraining health-care budgets that most countries and regions are facing today.

The one-way sensitivity analyses identified the cost drivers by analyzing the impact of a change of key clinical and economic parameters on the model results and the probabilistic sensitivity analyses illustrated the confidence with which the results were obtained from the model. The authors realized that many of these parameters were adapted from the literature or based on the authors' treatment experience; hence, they tested the robustness of the model results by applying a wide range of values to these parameters. The sensitivity analyses suggest that medication costs are a primary cost driver of overall costs, particularly in the *Medication Only* arm. As concomitant medications are often required post-LT or post-surgery, medication costs also have a significant impact in the *LT* and *Surgery* arms. This finding is consistent with many previous publications[41,42]. A retrospective medical record review study concluded that medication costs comprised the largest proportion of total direct cost for all stages of the disease ranging from 24–61%, depending on level of medication compliance[15]. In addition, post-surgery complications are also shown to be a significant cost driver for the *Surgery* arm. These results combined highlight the need to reduce post-procedure medication use and complications in new therapeutic interventions. The finding of the probabilistic sensitivity analyses showed that despite the wide variation for the input parameters, three sets of 1000 simulations generated statistically significant results, attesting the robustness of the model.

Although the overall results from this modeling exercise appear to align well with similar glaucoma economic studies, due to differences in the methodological approaches and study population, direct comparisons of study results are not recommended. For example, a Canadian study modeled the 6-year costs of primary SLT versus primary medication therapy for Ontario patients with POAG aged 65 years and above[26]. The study suggested that SLT as primary therapy, at a per-patient level, offered a modest cost savings over primary medical therapy. Specifically, SLT repeated every 2 years produced cost savings of $206, $1669 and $2993 over mono-, bi- and tri-medication therapy over 6 years. This study showed that LT offered a cost savings of approximately $1700 per patient treated by titration of medication from two to four over 5 years, which compares well with the Canadian study. In a recent published analysis based on a review of 151 patients' medical charts in the US by the Costs of Glaucoma Study Group, the projected total cost of surgery (including both LT and filtering surgeries), with or without medication use, was $9631 and the total cost for medication use, with or without surgery, was $11 284 within 5 years of continuous follow-up, after adjusting for covariate of interest[42]. When compared to unadjusted costs from the US, a previous study by the same study group estimated cost per person-year ranged from $623 per patient with early-stage disease, to $2511 for patients with end-stage disease[15]. As the patients included in this study may be comparable to those with moderate disease according to the classification system set forth in the Cost of Glaucoma Study group, the projected annual costs align well with these numbers. Despite the fundamentally different methodologies adopted in these studies, these data provided an external validation to the model structure and assumptions.

Limitations

The study presented here focused on costs rather than clinical outcomes. The authors did not model clinical states such as visual field loss or blindness. Instead, the treatment states, to which the costs were assigned, were determined based on the effectiveness of IOP control as assessed in most clinical trials and current clinical practice. It might be possible to incorporate the clinical states into the model in the future when more epidemiological and clinical trial data on those outcomes become available.

When modeling the changes between treatment states, the authors did not allow cross-over between treatment arms in order to isolate the effects of different treatment strategies on costs. In a real-world practice, patients may switch therapy at any time. In this model, surgery and LT were assumed to be a third-line therapy (after patients had failed two medications). Although patients may receive these interventions at an earlier stage of their disease, studies had generally shown that as more effective medications are introduced, surgical intervention may be delayed to third-line or fourth-line treatment[16,17].

Due to limited data availability in the published studies, certain transition probabilities used in this model were derived or obtained directly from the authors' own treatment experience. Although these opinions reflect, in some respect, the current practices and outcomes associated with various glaucoma treatments, these data need to be validated either by clinical trials or retrospective observational studies.

Adequate medical treatment of glaucoma requires a high level of adherence to therapy. Frequently, this is not achieved; studies indicated relatively poor adherence to therapy in one-third or more of patients, depending on the medications used[9,10]. In a retrospective population-based study analyzing pharmacy claims, the persistence rate for the 12-month period was shown to be 69.4, 70.6, and 68.1% for latanoprost, travoprost, and bimatoprost, respectively, and the mean adherence for these medications were 75.4, 77.1, and 78.2%, respectively, indicating great room for improvement in medication compliance[43]. Poor medication compliance would compromise treatment effectiveness without necessarily reducing payment from the payer. In this model, the authors used the annual cost per class of medication calculated in theory, not an empirical account of the number of bottles actually used by patients. On the contrary, a retrospective claims study on the prescription refills of 27 000 patients revealed that on average the observed pharmacy refill rate increased the theoretical annual medication cost by 21%[26]. If the authors include these factors in this model, the cost saving in the *LT* and *Surgery* arm compared to the *Medication Only* arm would have been greater.

In the current exercise, the authors did not model patients' quality of life associated with treatment failure, therapy modification, adverse events, and disease progression, and how they affect patients' activities of daily living and productivity. However, the authors believe the construct of this model enables the user to assign utility values to each treatment state, and then characterize the benefit of different treatment strategies in terms of quality adjusted life years (QALYs), which are commonly used in economic evaluations of therapeutic interventions[44].

The authors estimated direct costs from the perspective of third-party payers. Although they could include costs related to patient or caregiver time for office visits and procedures performed in a facility or non-facility setting, previous studies have shown that the direct costs represented about 75% of the total costs, with indirect costs accounting for the remaining costs[13].

Conclusion

This model shows laser trabeculoplasty is associated with the lowest costs of treatment over 5 years compared to medication alone and filtering surgery. Medication costs, post-procedure medication use, post-surgical complications have a significant impact on overall treatment costs. This model provides a framework for future glaucoma model development and offers a foundation for decision-makers to evaluate the economic value of new glaucoma interventions. Future development of glaucoma treatment should focus on reducing the need for post-procedure medication as well as lowering the rate of post-procedure complications.

Acknowledgements

Declaration of interest: Financial support for this study was provided by Glaukos Corporation. Glaukos Corporation had no involvement in the design and conduct of the study, collection, management, analysis and interpretation of the data, or preparation of the manuscript, except for providing editorial review and approval of the manuscript. LBC has consulted for Allergan, received research support from Allergan and Pfizer, and received speaker honoraria from Merck. LJK has received honoraria and research grants from Allergan, Alcon, Merck, Pfizer and Lumenis. The other authors have no conflict of interests that are directly relevant to the content of this study. The authors thank Stephanie Ching and George M. Gee, Quorum Consulting, Inc., for their assistance in editing the manuscript, and Warren Schonfeld, Quorum Consulting, Inc, for his statistical advice.

References

1. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol 2006;90:262-7
2. Resnikoff S, Pascolini D, Etya'ale D, et al. Global data on visual impairment in the year 2002. Bull World Health Organ 2004; 82:844-51
3. Friedman DS, Wilson MR, Liebmann JM, et al. An evidence-based assessment of risk factors for the progression of ocular hypertension and glaucoma. Am J Ophthalmol 2004; 138:S19-S31
4. Congdon N, O'Colmain B, Klaver CC, et al. Causes and prevalence of visual impairment among adults in the United States. Arch Ophthalmol 2004;122:477-85
5. Le A, Mukesh BN, McCarty CA, et al. Risk factors associated with the incidence of open-angle glaucoma: the visual impairment project. Invest Ophthalmol Vis Sci 2003;44:3783-9
6. Schwartz K, Budenz D., Current management of glaucoma. Curr Opin Ophthalmol 2004;15:119-26
7. Kobelt G, Jonsson L, Gerdtham U, et al. Direct costs of glaucoma management following initiation of medical therapy. A simulation model based on an observational study of glaucoma treatment in Germany. Graefes Arch Clin Exp Ophthalmol 1998;236:811-21
8. Jonsson B, Krieglsten G. Primary open-angle glaucoma: differences in international treatment patterns and costs. Oxford: Isis Medical Media Ltd. 1998
9. Kass MA, Gordon M, Morley RE, Jr., et al. Compliance with topical timolol treatment. Am J Ophthalmol 1987;103:188-93
10. Primary Open-Angle Glaucoma. Preferred Practice Pattern. Online. American Academy of Ophthalmology. San Francisco: American Academy of Ophthalmology, 2005. Available at: http://www.aao.org/education/guidelines/ppp/poag_new.cfm [last accessed 29 January 2008]
11. Ederer F, Gaasterland DA, Dally LG, et al. The Advanced Glaucoma Intervention Study (AGIS): 13. Comparison of treatment outcomes within race: 10-year results. Ophthalmology 2004;111:651-64
12. Reeder CE, Franklin M, Bramley TJ. Managed care and the impact of glaucoma. Am J Manag Care 2008;14:S5-S10
13. Kobelt-Nguyen G, Gerdtham UG, Alm A. Costs of treating primary open-angle glaucoma and ocular hypertension: a retrospective, observational 2-year chart review of newly diagnosed patients in Sweden and the United States. J Glaucoma 1998;7:95-104
14. Traverso CE, Walt JG, Kelly SP, et al. Direct costs of glaucoma and severity of the disease: a multinational long term study of resource utilisation in Europe. Br J Ophthalmol 2005; 89:1245-9
15. Lee PP, Walt JG, Doyle JJ, et al. A multicenter, retrospective pilot study of resource use and costs associated

with severity of disease in glaucoma. Arch Ophthalmol 2006;124:12-19
16. Kobelt G, Jonsson L. Modeling cost of treatment with new topical treatments for glaucoma. Results from France and the United Kingdom. Int J Technol Assess Health Care 1999;15:207-19
17. Neelakantan A, Vaishnav HD, Iyer SA, et al. Is addition of a third or fourth antiglaucoma medication effective?. J Glaucoma 2004;13:130-6
18. Kass MA, Heuer DK, Higginbotham EJ, et al. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol 2002;120:701-13
19. Lichter PR, Musch DC, Gillespie BW, et al. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery. Ophthalmology 2001;108:1943-53
20. Althin R, Grima DT, Dhawan R, et al. Considerations in developing model-based economic evaluations of glaucoma treatment. J Glaucoma 2006;15:541-7
21. Stewart WC, Stewart JA, Mychaskiw MA. Cost-effectiveness of latanoprost and timolol maleate for the treatment of glaucoma in Scandinavia and the United Kingdom, using a decision-analytic health economic model. Eye 2007;Aug 24. [Epub ahead of print]
22. Stewart WC, Stewart JA, Nassar QJ, et al. Cost-effectiveness of treating ocular hypertension. Ophthalmology 2008;115:94-8
23. Petitti DB. Advanced cost-effectiveness analysis. Meta-Analysis, Decision Analysis, and Cost-Effectiveness Analysis Methods for Quantitative Synthesis in Medicine, 2nd edn. New York: Oxford University Press, 2000
24. ReadyPrice® System. Thomson MICROMEDEX, 2007
25. Rylander NR, Vold SD. Cost analysis of glaucoma medications. Am J Ophthalmol 2008;145:106-13
26. Lee R, Hutnik CM. Projected cost comparison of selective laser trabeculoplasty versus glaucoma medication in the Ontario Health Insurance Plan. Can J Ophthalmol 2006; 41:449-56
27. Medicare Physician Fee Schedule 2007. Centers for Medicare and Medicaid Services. Baltimore: Centers for Medicare and Medicaid Services, 2006. Available at: http://www.cms.hhs.gov/PhysicianFeeSched/[Last accessed 29 January 2008]
28. Final Changes to the Hospital Outpatient Prospective Payment System and CY 2007 Payment Rates. Centers for Medicare and Medicaid Services. Baltimore: Centers for Medicare and Medicaid Services, 2006. Available at: http://www.cms.hhs.gov/HospitalOutpatientPPS/HORD/itemdetail.asp?itemID=CMS1204971 [Last accessed 29 January 2008]
29. Damji KF, Bovell AM, Hodge WG, et al. Selective laser trabeculoplasty versus argon laser trabeculoplasty: results from a 1-year randomised clinical trial. Br J Ophthalmol 2006;90:1490-4
30. Spaeth GL, Baez KA. Argon laser trabeculoplasty controls one third of cases of progressive, uncontrolled, open angle glaucoma for 5 years. Arch Ophthalmol 1992;110:491-4
31. Schwartz AL, Love DC, Schwartz MA. Long-term follow-up of argon laser trabeculoplasty for uncontrolled open-angle glaucoma. Arch Ophthalmol 1985;103:1482-4
32. Krupin T, Patkin R, Kurata FK, et al. Argon laser trabeculoplasty in black and white patients with primary open-angle glaucoma. Ophthalmology 1986;93:811-16
33. Shingleton BJ, Richter CU, Dharma SK, et al. Long-term efficacy of argon laser trabeculoplasty. A 10-year follow-up study. Ophthalmology 1993;100:1324-9
34. Proposed Changes to the ASC Payment System and CY 2007 Payment Rate. Centers for Medicare and Medicaid Services. Baltimore: Centers for Medicare and Medicaid Services, 2006. Available at: http://www.cms.hhs.gov/ASCPayment/05_CMS-1932-P(ASC).asp [Last accessed 29 January 2008]
35. Gold MR, Siegel JE, Russell LB, et al. Cost-effectiveness in Health and Medicine. New York: Oxford University Press, 1996
36. Parc CE, Johnson DH, Oliver JE, et al. The long-term outcome of glaucoma filtration surgery. Am J Ophthalmol 2001;132:27-35
37. TreeAge Software Inc. TreeAge Pro 2006 User's Manual. Online. 2006
38. Alward WL., Medical management of glaucoma. N Engl J Med 1998;339:1298-307
39. Baudouin C, Rouland JF, Le Pen C. Changes in medical and surgical treatments of glaucoma between 1997 and 2000 in France. Eur J Ophthalmol 2003;13 Suppl 4:S53-60
40. Paikal D, Yu F, Coleman AL. Trends in glaucoma surgery incidence and reimbursement for physician services in the Medicare population from 1995 to 1998. Ophthalmology 2002;109:1372-6
41. Gricar JA, Wilson PR, Cave DG. Glaucoma. Manag Care Interface 1998;11:42-4
42. Lee PP, Kelly SP, Mills RP, et al. Glaucoma in the United States and Europe: predicting costs and surgical rates based upon stage of disease. J Glaucoma 2007; 16:471-8
43. Wilensky J, Fiscella RG, Carlson AM, et al. Measurement of persistence and adherence to regimens of IOP-lowering glaucoma medications using pharmacy claims data. Am J Ophthalmol 2006;141:S28-S33
44. Weinstein MC, Siegel JE, Gold MR, et al. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. JAMA 1996;276:1253-8

CrossRef links are available in the online published version of this paper:
http://www.cmrojournal.com
Paper CMRO-4611_4, *Accepted for publication:* 31 July 2008
Published Online: 2 September 2008
doi:10.1185/03007990802379996