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Glaucoma Suspects: The Impact of Risk Factor-Driven Review Periods on Clinical Load, Diagnoses, and Healthcare Costs

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Purpose: To model the healthcare impact (clinical attendance time and financial cost) and clinical outcomes (glaucoma diagnoses) of different risk factor–driven review frequencies for glaucoma suspect patients up until the point of discharge or diagnosis.

Methods: Medical records of 494 glaucoma suspects were examined to extract the clinical diagnosis. Two criteria for review periods were defined, based on contrasting stringency from established clinical guidelines: American Academy of Ophthalmology (AAO), more stringent/less frequent; and the Australian National Health and Medical Research Council (NHMRC), less stringent/more frequent. We used these data to model patient outcomes and healthcare costs using a Markov model.

Results: The less stringent/more frequent criterion resulted in more high-risk glaucoma suspects requiring more frequent review compared with the more stringent/less frequent criterion. Across the 15 Markov cycles (7.5 years), the less stringent/more frequent review criterion resulted in 6.6% more diagnoses and fewer overall clinical visits (14.7%) and reduced cost per diagnosis by 12% to 32% ($P < 0.0001$). The number of glaucoma diagnoses made using each criterion converged at 2.5 to 3 years.

Conclusions: The stringency of risk assessments for glaucoma suspects impacts review periods and therefore clinical load, healthcare costs, and diagnosis rates. Using current testing methods, more frequent review periods appear advantageous for diagnostic efficiency, with both lower clinic load and lower cost up until the point of discharge or glaucoma diagnosis.

Translational Relevance: A less stringent criterion for assessing the risk of developing glaucoma potentially offers a more cost-effective method for reviewing glaucoma suspects, especially within the first 2.5 years.

Introduction

Glaucoma is the leading cause of irreversible blindness worldwide.[1] Early diagnosis is key to optimal patient management and preservation of vision and quality of life.[2] The care of patients with glaucoma or those in whom glaucoma is suspected represents a significant burden to healthcare systems worldwide.[3] In 2005, the direct and indirect costs of glaucoma to the Australian healthcare system was estimated to be A$355 million, projected to increase to A$784 million by 2025.[4] In the United States, costs have been estimated to be greater than US$2.9 billion.[5] Therefore, the deployment of clinical tests and service providers in an efficient manner is the subject of many investigations.[6]

The assessment of glaucoma in clinical practice consists of a comprehensive range of tests, and authoritative evidence-based guidelines have been disseminated with recommendations for eye care providers.[7–9] Using the battery of possible assessment techniques

and results obtained during the examination, an expert clinician ultimately integrates and weighs each component to arrive at the final clinical disposition. In practice, the possible management outcomes for a patient undergoing glaucoma assessment can be summarized into discharge/routine review, a specific glaucoma-related review period (often 6–24 months), or treatment initiation.

A clinical conundrum related specifically to glaucoma suspect patients in the "suspect" part of their journey of care is the optimal frequency of review.[10] The decision on when to review the patient involves consideration of factors, such as the time in which clinically significant changes can be reliably identified; identification of disease at a point prior to impactful vision loss; practical financial constraints; contextual limitations, such as patient accessibility; and equality of healthcare delivery to at-need individuals. An enduring issue is the uncertainty surrounding the glaucoma diagnosis and, in borderline cases, glaucoma suspects.[11]

Guidelines on managing glaucoma suspects suggest a range of possible review periods, with general advice regarding the application of risk factors, such as family history and clinical findings (including intraocular pressure, corneal thickness, optic disc appearance and visual field integrity). The clinician's decision on review schedule can impact on the number of future attendances and ongoing healthcare costs, and this may also be affected by jurisdictional and regional differences in the healthcare system. Previous studies have modeled costs involved in the care of patients with diagnosed glaucoma,[12,13] but, despite the similar chronicity of glaucoma suspect status, its cost and impact have not been well studied.[14] Although the expected cost per patient may be lower in glaucoma suspects in comparison to established or more advanced glaucoma,[12] the overall number of patients requiring ongoing eye care to identify conversion would nonetheless present a significant burden on the healthcare system. Depending on the study population and definition, the number of suspects—or probable glaucoma—may be on par with or even exceed the number with manifest or diagnosed glaucoma.[15–20] Therefore, tackling the issue of a group of individuals at risk of developing glaucoma (i.e., suspects) is relevant and important.

In the present study, we used the medical records of open-angle glaucoma suspect patients seen within a university-based referral clinic to analyze the impact of different review periods on patient outcomes (glaucoma diagnoses) based on their potential costs (the clinician's perspective on attendance time and the healthcare system's perspective on financial costs) up until the point of discharge or diagnosis. To address this question, we modeled outcomes and costs using two criteria that are contrasted by their stringency for review. We defined a less stringent criterion that would result in more frequent reviews (the less stringent/more frequent criterion) and the converse, a more stringent criterion that would result in less frequent reviews (the more stringent/less frequent criterion). Stringency was defined by the number of risk factors required to be present (the less stringent criterion, one risk factor present; the more stringent criterion, three risk factors present). Based on primary outcome of cost per diagnosis, we aimed to provide a perspective on the cost effectiveness of these clinical paradigms.

Methods

This was a retrospective, cross-sectional modeling study. Ethics approval for the study was provided by the Human Research Ethics Committee of the University of New South Wales. The study adhered to the tenets of the Declaration of Helsinki. Participants provided written informed consent prior to inclusion in the study.

Patient Cohort and the Model of Care

A retrospective, cross-sectional review of patient records from a single center, the Centre for Eye Health, was performed. The Centre for Eye Health is a referral-only diagnostic imaging and treatment facility based at the University of New South Wales, Sydney, Australia.[21–23] The clinic receives referrals predominantly from community optometrists working in primary care; thus, the cohort of patients seen within the glaucoma service largely represents patients who are deemed at risk of glaucoma requiring further assessment and management (see below for more details regarding the model of care).[24]

The glaucoma assessment process at the Centre for Eye Health has been previously described,[21,22] but, in short, it includes history, visual acuities, anterior segment examination, applanation tonometry, pachymetry (Pachmate DGH 55; DGH Technology, Exton, PA), gonioscopy, dilated stereoscopic examination of the optic nerve head and macula, static automated perimetry (Humphrey Field Analyzer 24-2 SITA Standard; Carl Zeiss Meditec, Dublin, CA) and optical coherence tomography (OCT) imaging of the optic nerve head/retinal nerve fiber layer and macula (ganglion cell–inner plexiform layer) (Cirrus OCT; Carl Zeiss Meditec). Along with extracting the historical (medical, ocular, and family history) and

clinical (as described above) data, we also recorded the review period suggested by the attending and reviewing clinicians (see below paragraph for the clinical review process). For simplicity, we used two nominal categories for the present study: (1) review sooner than or equal to 6 months (≤6 months), or (2) review in 12 months. All examinations were performed by one of the highly trained optometrists staffing the Centre, with training provided by a glaucoma specialist ophthalmologist from the local health district.

The model of care at the Centre for Eye Health notably differs from routine primary eye care and may also be different from other models of glaucoma service at the intermediate and tertiary level; indeed, it was the first of its kind in Australia.[24] The scope of practice within the clinic specifically focuses on the assessment of patients with borderline, suspected, or early stages of chronic eye disease such as glaucoma; thus, its patients are ideal for examining a cohort of patients at risk of developing glaucoma.[24] Specifically, the higher risk nature of the patients seen in the clinic means that the diagnosis rates of glaucoma are expectedly higher compared to rates obtained from community practice (our previous study[11] on consecutively referred patients found that approximately 14% received a diagnosis of glaucoma). Attending clinicians within the Centre for Eye Health have been shown to have higher positive predictive values and lower false-positive rates for glaucoma diagnosis compared to community optometrists,[25] have been providing effective ongoing glaucoma shared care since its inception,[26] and have shown high concordance in important metrics related to glaucoma assessment.[23]

Definition of Glaucoma Suspect and Included Patients

The cohort of patients used for the present study have been previously reported, in part, in our recent publication ($n = 862$).[11] For the purposes of this study, we focused on the review characteristics of the open-angle glaucoma suspect patients ($n = 494$; see below) seen at the Centre for Eye Health for an initial glaucoma assessment within the 2018 calendar year that have not been previously reported. The use of data from only a single, first-time visit enabled us to obtain a snapshot of characteristics that might lead a clinician to develop a specific review schedule.

Specific exclusion criteria included age < 18 years, patients not consenting to research, patients with incomplete medical records, and those with ambiguous diagnoses where the three clinicians were not in agreement. For this study, we also excluded patients for whom the review plan was referral for treatment of a disease other than glaucoma, as this did not allow us to categorize them into either the ≤6 months or 12 months cohort (see results).

A glaucoma suspect was defined as a patient with any of the following characteristics: possessing historical risk factors including but not limited to a first-degree family history of glaucoma, systemic disease (diabetes, hypertension, hypotension, migraines, or obstructive sleep apnea), or chronic corticosteroid use; elevated intraocular pressure (>21 mmHg); and/or suspicious optic nerve head appearance, including increased cup-to-disc ratio and asymmetric cup-to-disc ratio between eyes not explained by optic disc size, thin neuroretinal rim, disc hemorrhage, and/or retinal nerve fiber layer defect but without the corresponding visual field loss that is characteristic of glaucoma. Conversely, the diagnosis of glaucoma required the presence of glaucomatous optic nerve head features in conjunction with corresponding, reproducible visual field loss and/or documented evidence of glaucomatous progression over time.

The clinical diagnoses used in this study were the result of an attending clinician's assessment, reviewed virtually by another reviewing clinician at the Centre for Eye Health as per its usual protocols.[24] Patients diagnosed with glaucoma were also reviewed by a glaucoma specialist ophthalmologist for confirmation, and a subset of high-risk glaucoma suspect patients was similarly reviewed for quality control purposes as per the usual protocols of the clinic. For the purpose of the study, an additional evaluation by one of the study investigators was used to ensure robustness of the final diagnosis. Consensus on the diagnosis by all three evaluators was required as part of the inclusion criteria.

The medical records of the glaucoma suspect patients (including the data captured as part of the clinic's protocols as described above) seen within the study period were extracted for analysis and served as the baseline data. The cross-sectional baseline data were used for model development. To further develop the dataset and to better reflect the transitions between diagnostic states in the real world, we also extracted subsequent visit data from these patients. The subsequent visit outcomes are described further below and formed the basis of the transitional probabilities in the Markov models.

Risk Titration for Glaucoma Suspects

The Australian National Health and Medical Research Council[8] guidelines (in part, as subjects

from the present clinic were based on Australia) and the American Academy of Ophthalmology[9] guidelines provide assistance to clinicians in defining a high-risk glaucoma suspect patient. For the National Health and Medical Research Council, the high-risk factors were defined as the presence of one or more risk factors. For the American Academy of Ophthalmology, high-risk was defined as three or more risk factors. Although there are subtle differences between guidelines in the specifics of risk titration (in part due to the difference in age of the guidelines), we considered the commonalities between guidelines to arrive at a final list of risk factors used to identify high-risk patients in the present study (Table 1). The list of risk factors included both categorical factors and continuous variables.

Table 1. Risk Factors From the Clinical Examination Deemed Contributing to Designation of High-Risk Status for Glaucoma Suspects by the American Academy of Ophthalmology and the Australian National Health and Medical Research Council

Risk Factors Extracted and Aggregated From the American Academy of Ophthalmology Preferred Practice Patterns and Australian National Health and Medical Research Council Guidelines	Clinical Information Available From the Centre for Eye Health Glaucoma Assessment
Demographic and historical features	Comprehensive medical, ocular, and family history
Older age (>50 y)	Visual acuities
Family history of glaucoma	Anterior segment examination
African ethnic origin[a]	Applanation tonometry
Latino/Hispanic race[a]	Pachymetry
History of ocular trauma	Gonioscopy
Medical history factors	Dilated stereoscopic examination of the optic nerve head and macula
Type 2 diabetes mellitus	Static automated perimetry (24-2 test grid on a Humphrey Field Analyzer)
Low systolic and diastolic blood pressure (<90 mmHg systolic, <60 mmHg diastolic)	OCT of the optic nerve head/retinal nerve fiber layer and macula (ganglion cell–inner plexiform layer)
Hypothyroidism	
Migraine	
Peripheral vasospastic disorder	
Chronic corticosteroid usage	
Sleep apnea	
Hemodynamic crisis	
Ocular clinical features	
Elevated intraocular pressure (>21 mmHg)	
Increased cup-to-disc ratio (>0.7)	
Thinner central corneal thickness (<510 µm)	
Disc hemorrhage present	
Large-pattern SD on threshold visual field testing (>2.2 dB)	
Lower ocular perfusion pressure (<50 mmHg)	
Pigment dispersion syndrome	
Pseudoexfoliation syndrome	
Myopia	

Note that given slight differences in the manner in which some risk factors may be phrased, some of the factors are not quoted from the guidelines verbatim. For the purposes of the present study, where continuous variables are used, we have added the cut-offs used to note that a specific risk factor was present (as the presence or absence of the risk factor was binarized). The right column shows the list of clinical examination techniques used in the glaucoma assessment at the Centre for Eye Health.

[a]These risk factors were extracted from the guidelines verbatim, despite debate in the literature regarding the definition and importance of race or ethnicity with respect to their potential contributions to the manifestation of disease.

In all cases, the risk factor was binarized: either present or absent for the present model. There may also be differences in the change in risk rate or weight across the list of factors. In the present study, we did not apply weights to the list of factors nor did we adjust risk based on factors with different levels (such as myopia or age). Although titration at an individual level is essential for personalized medicine approaches in clinical practice, such adjustments would drastically increase the complexity of a simulation model at the cohort or population level (see Discussion). Furthermore, for the purposes of the model, the introduction of granular alterations in risk would still ultimately contribute to one of two designations of risk: either high-risk or non–high-risk. Accordingly, the binarized review periods (a high-risk patient was assigned a shorter review period of 6 months, and a non–high-risk patient was assigned a relatively longer review period of 12 months) meant that subtle differences in the weighting of risk factors were less likely to affect the final model.

Following the identification and definition of risk factors and review periods, we then defined two levels of stringency. The more stringent criterion required three or more risk factors present for a patient to be identified as high risk. This number of risk factors reflected the American Academy of Ophthalmology recommendation. In contrast, the less stringent criterion required only one risk factor to be present for a high-risk designation. This reflected the spirit of the National Health and Medical Research Council recommendation.

Accordingly, the contrast of stringency led to an increase or reduction in likelihood for frequent review periods. For example, a more stringent criterion is more likely to result in fewer designations of high risk and, therefore, fewer 6-month reviews. We therefore had two final assessment methods: more stringent/less frequent and less stringent/more frequent. In essence, the contrasting methods represented two philosophies for clinical management of glaucoma suspects: a more frequent review that might catch more diagnoses at the cost of greater healthcare utilization, or a less frequent review schedule that may miss more diagnoses to save on healthcare costs. Concordance between the risk assessment criteria in terms of their determination of risk (and therefore distribution of review periods) was described as a percentage and assessed using McNemar's test for discordance between high- and non–high-risk patients.

Cost and Outcomes of Reviewing Patients in a Clinical Practice: Core Data

For the core data used to build the models, we counted and modeled the number of appointments that would arise from patients meeting or not meeting specific high-risk criteria, depending on the stringency of the risk assessment (more stringent/less frequent or less stringent/more frequent). Then, using this data, we modeled the total cost (appointments and monetary) for the patients reviewed under the different criteria and the outcomes. For simplicity, high-risk patients (as defined above) were assigned a review period of 6 months (more frequent), and non–high-risk patients were assigned a review period of 12 months (less frequent). After obtaining the distribution of dispositions at the first baseline visit, we then documented the diagnoses and dispositions at the subsequent visit. As our clinic had a primarily referral-only model during the 2018–2019 period, there was a high attrition rate that would reduce the overall number of returning patients. Therefore, we captured data only at the patient's next visit and not beyond that. The subsequent visits formed the outcomes of the initial disposition, informing the transitional states that were then used to build the Markov models. The flow of patients and the determination of their distributions (the number of patients in each outcome group; see further details below) are shown in Figure 1A.

Cost and Outcomes of Reviewing Patients in a Clinical Practice: Markov Models

We used a dynamic, decision-analytic Markov model to determine costs and outcomes using each review schedule. This model incorporated the transitions between clinical outcomes in glaucoma suspect patients which have been previously applied to glaucoma diagnosis and treatment outcomes.[27,28] In the present work, the model allowed us to follow step-by-step the costs and review outcomes for a predetermined cohort of glaucoma suspect patients. This approach would also allow back and forth transitions between states, which could realistically occur in clinical practice due to the uncertainty surrounding glaucoma diagnosis.

The Markov models were built using a custom-written program (MATLAB R2019b; MathWorks, Natick, MA). The outputs of the Markov models included distribution of subjects within each state, the number of final manifest glaucoma patients, the number of clinical appointments, and the cost of the

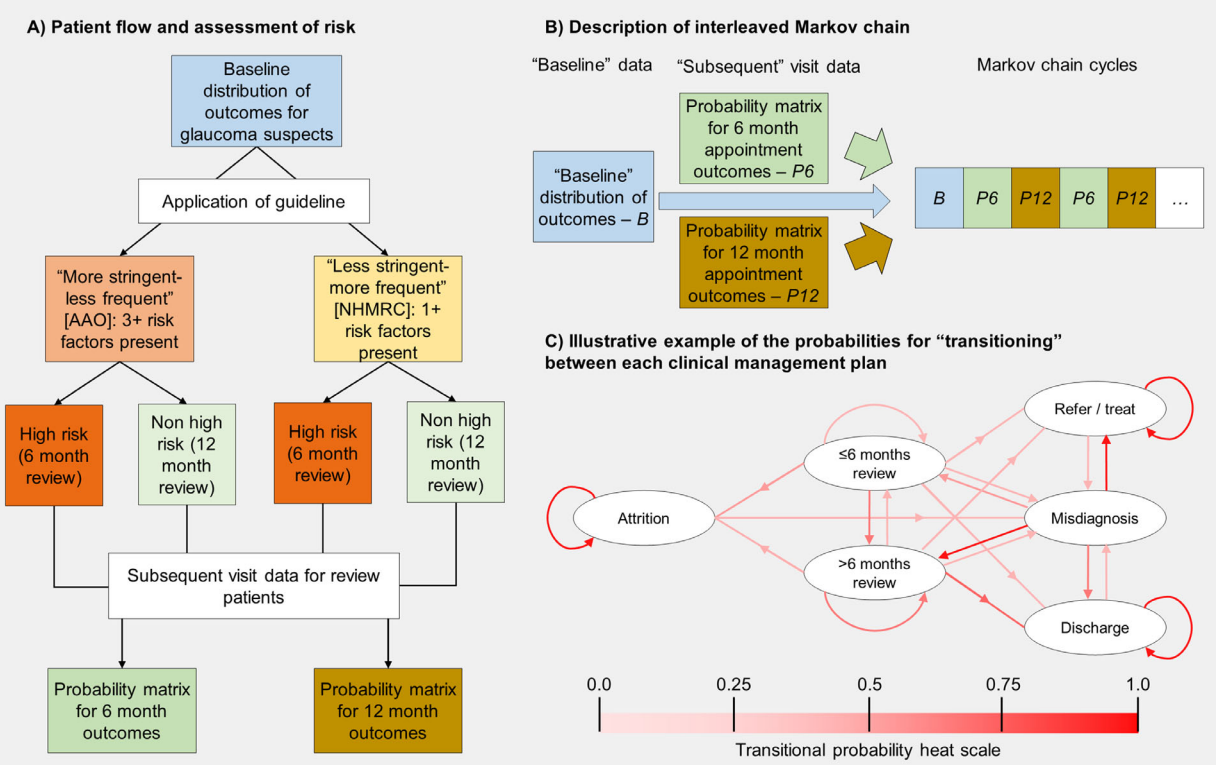

Figure 1. Description of the patient flow and modeling methods. (**A**) We began with a baseline distribution of outcomes (e.g., review, refer/treat, discharge) for a cross-sectional cohort of glaucoma suspects. We applied two different criteria (a more stringent criterion requiring three or more risk factors present to deem high-risk status, and a less stringent criterion requiring only one or more risk factors present) to ascertain the risk category for each patient. For their subsequent visits, we identified the distribution of outcome states to form the probability matrices used for each Markov model. (**B**) Description of the interleaved Markov chain. Baseline distribution of patients ("B") and the subsequent visit data (used to create the probabilities of transitioning from one state to another, P6 and P12 for the 6-month and 12-month reviews, respectively) were combined to create the Markov chain. Beginning with an initial distribution ("B"), the Markov model sequentially modulates the distribution of patients based on their transitions between one of six states (attrition, discharge, review in 6 months, review in 12 months, treat/refer, or misdiagnosis). (**C**) An illustration of the transition pathways among the six states. Each directional arrow has been color-coded by the probability level at which the transition occurs; a *lighter red* indicates a lower probability of moving between states, and a *darker red* indicates a higher probability.

appointments during the totality of cycles. Because the work focused on the review of glaucoma suspect patients and not on the treatment of patients with manifest glaucoma, we did not examine quality of life nor measure quality-affected life years against cost.

We built two Markov models based on the distributions of high-risk or non–high-risk individuals as determined by the stringency of the risk assessment (more stringent/less frequent, requiring three or more risk factors; less stringent/more frequent, requiring one or more risk factors). Figure 1 shows the basic framework of the model. First, baseline data were used to describe the distribution of patients who had specific levels of risk (i.e., their designated review periods). The baseline data also incorporated a fixed attrition, discharge, and treatment/referral (glaucoma diagnosis) rate (Fig. 1B, "B"). Then, the subsequent visit data were analyzed for the distribution of outcomes depending on the initial impression of risk; therefore, we obtained two different probability distributions: one for the 6-month appointment outcomes (P6) and one for the 12-month appointment outcomes (P12). These distributions formed the basis of the interleaved Markov chain. An interleaved Markov chain was used to cycle through the probability transitions, as in the 6-month review there would be no 12-month appointment outcome, as it would not have happened yet.

In addition to the initial five baseline states, we added a sixth state to the subsequent visit data: misdiagnosis. Misdiagnosis was added as a sixth state to account for uncertainty surrounding the management of the glaucoma suspect. Typically, attrition, discharge, and disease may represent terminal states where a patient exits the model; however, with a rate of misdiagnosis added, it was possible that patients may re-enter the model. Misdiagnosis was added to all

transitions except for manifest glaucoma. We considered this to be a terminal state, as it has its own subsequent monitoring and management plan involving specific review periods and treatment costs that were not part of the primary outcome of the present study.

The six transitional states that we used for the model were (1) attrition (including death, loss to follow up/loss of contact, no show, and cancellation); (2) discharge (routine review by the primary carer); (3) review in 6 months (high-risk; for simplicity, we condensed all <6 month reviews into this group); (4) review in 12 months (non–high-risk; for simplicity, this was considered a 12-month review cycle); (5) treatable/referable manifest disease (i.e., glaucoma); and (6) misdiagnosis. An example of the transitions between each of the six states is shown in Figure 1C. The heat scale shows the transitional probability (i.e., the probability of moving from one state to another or remaining within the same state) across each cycle.

Although rates of transitioning between states may evolve over the natural course of a patient's clinical history, we did not incorporate dynamic transitions across the six states for several reasons. First, given attrition, discharge, and referral rates, the expected number of patients with real data monitored over time would diminish exponentially, limiting the value of estimates of transitional probability as it evolves. Second, our specific model was simplified into the probability of reaching a particular management plan or outcome: one of three possible exit points from the cycle of glaucoma suspect care. These do not necessarily represent a specific health state. For example, the inference is that a patient that reaches the referred/treated state has some level of risk that becomes significant but may not indicate a true diagnosis of glaucoma. Similarly, a discharge in the present cohort means that the patient may be at low immediate risk of glaucoma, but that patient would still receive continuing care with their primary care provider. Third, an approach to adjusting transitional probabilities is also reliant on a wealth of individual-level data, which was beyond the scope of the study. Such factors could either elevate or reduce probability values, and their potentially interactive effects would dramatically increase the complexity of the model. It also requires an understanding of the individual's trajectory, which was also not captured in the present dataset. Thus, for our simulation purposes, we used static transitional probabilities within the Markov chain (see Dudel and Myrskyla[29] for further discussion).

A cohort of 5000 patients was followed through a total of 15 6-month-spaced Markov cycles (7.5 years). This was to ensure that an asymptote was reached in terms of the final states for the patients. For simplicity, we followed the sample of 5000 patients throughout the cycles without adding further patients into the model.

The final modification to the dataset was a non-parametric bootstrap of the probabilities. This was because the dataset that we used had fixed transition states; for example, there were fixed numbers of patients transitioning from 6-month review to 12-month review or from 6-month review to glaucoma. Thus, the pathway to the final outcomes and costs would be deterministic, and we would be unable to obtain distributions of the resultant model using these data. To overcome this, we applied non-parametric bootstrapping (with replacement) of the baseline and subsequent data (1000 repetitions) to obtain a mean and standard deviation of each transitional state. With a bootstrapping distribution of transitional probabilities, we inserted this into the Markov model. We performed Monte Carlo simulation ($n = 10{,}000$ repetitions) of the Markov model to obtain the final estimations of cost and outcomes and the standard deviation (SD); 95% confidence intervals of these means were not reported in the subsequent figures as they would be, in general, too small to visualize.

As described above, we chose two review time frames (6 months and yearly) to reduce the amount of complexity in the model, and this was especially for the purposes of describing the financial outputs. Three cost models were used: Australian Medicare Benefits Scheme for optometry and for ophthalmology (from mbsonline.gov.au, utilizing the November 2019 schedule, correct as of May 20, 2020),[30] and U.S. Medicare items (cms.gov, for all eye care providers; non-facility costs for an examination by an eye care practitioner, correct as of May 20, 2020) (Table 2). Costs are reported in the local currency of the healthcare system to ensure relevance. We elaborate on details pertaining to the assumptions of the model in the Discussion.

Primary Outcome

Our primary outcome was cost per glaucoma diagnosis during the simulated period. The cost incorporates the Medicare rebates per visit (and effectively represents an amalgamation of the number of review visits and their costs) until the point when a simulated patient exits the model (diagnosis, discharge, or attrition). This primary outcome therefore represented a form of cost-effectiveness comparison between the two review paradigms.

Statistical Analyses

Aside from the models described above, we used conventional statistics to briefly analyze the

Table 2. Consultation Item Description, Item Number, and Cost Assignment for Each Review Interval for Each Healthcare System Model

	Australian Medicare Benefits Scheme								
	Optometry Provider			Ophthalmology Provider			U.S. Medicare (Eye Care Provider)		
	Short Description	Item	Cost (AUD)	Short Description	Item	Cost (AUD)	Short Description	Item	Cost (USD)
Baseline	Initial comprehensive	10910 or equivalent	$57.70	Initial comprehensive	104	$76.15	Initial comprehensive (new patient)	92004	$152.66
	Bilateral perimetry	10940	$55.05	Bilateral perimetry	11221	$59.45	Gonioscopy	92020	$28.15
							Pachymetry	76514	$12.27
							Ocular imaging for glaucoma	92133	$37.89
							Bilateral perimetry	92083	$64.24
3 mo	Short subsequent examination	10918	$28.90	Short subsequent	105	$38.25	Subsequent examination (short)	92012	$89.86
6 mo	Bilateral perimetry	10940	$55.05	Short subsequent	105	$38.25	Subsequent examination (short)	92012	$89.86
				Bilateral perimetry	11221	$59.45	Ocular imaging for glaucoma	92133	$37.89
							Bilateral perimetry	92083	$64.24
12 mo	Initial comprehensive	10910 or equivalent	$57.70	Short subsequent	105	$38.25	Initial comprehensive (established patient)	92014	$128.12
	Bilateral perimetry	10940	$55.05	Bilateral perimetry	11221	$59.45	Ocular imaging for glaucoma	92133	$37.89
							Bilateral perimetry	92083	$64.24

For Australian Medicare Benefits Schedule items, the 85% fee is reported as per a bulk-billing arrangement by the eye care provider.

characteristics of the patient cohort reported in the present study. Demographic and basic clinical information was first assessed using a D'Agostino Pearson test to determine whether the continuous data were normally distributed. Pairwise comparisons for continuous data were assessed using unpaired *t*-tests or the Mann–Whitney *U* test; $P < 0.05$ was considered to be significant.

Results

Out of the 862 patients seen for an initial glaucoma assessment in 2018, a total of 494 patients (57.3%) received a diagnosis of glaucoma suspect (126 had manifest glaucoma and 242 were ophthalmically normal). After excluding all patients not meeting the criteria for the present study (54 discharged/referred for reasons other than primary open-angle glaucoma, and 21 excluded for not meeting the study criteria), we used the medical records of 419 patients, divided into 243 patients in the ≤6 months group and 176 patients in the 12 months group according to their clinical dispositions. The basic clinical and demographic data are shown in Table 3. Most notably, the ≤6 months group was on average older than the 12 months group ($P = 0.0001$). The overall demographic characteristics were otherwise similar between the two groups. The only significant differences between groups in terms of risk factors were found for positive first-degree family history. Several risk factors were found to have a low occurrence and thus were underpowered for finding a statistically significant effect; thus, statistical analyses were not performed for these variables.

Concordance With Assessment of High-Risk Glaucoma Suspect Status

We used the features listed in Table 3 to determine high-risk status in accordance with the two defined criteria that we utilized in the present study (Table 4). Note that, as per the methods, the clinical disposition represented the management plan instituted at the clinical appointment, which may differ from the application of the criterion-driven risk status for the purposes of the present study. As expected, the less stringent/more frequent (requiring only at minimum one risk factor present) criterion characterized more patients as high-risk (94.5%) compared to the more stringent/less frequent (requiring three or more risk factors) criterion (47.7%; $P < 0.0001$). Correspondingly, the discordances with the original clinical disposition were most evident where the less stringent/more frequent criterion assessed a patient as high-risk (38.7%; $P < 0.0001$) and where the more stringent/less frequent criterion assessed a patient as non–high-risk (31.0%; $P < 0.0001$). Accordingly, these results suggest that a less stringent/more frequent criterion may lead to excessive healthcare utilization, whereas a more stringent/less frequent criterion may identify fewer patients as high-risk, at the risk of potentially underservicing the cohort. The characterization of concordance effectively served as sensitivity (true positive) and specificity (true negative) comparisons against the reference standard using the original clinical disposition. The clinical disposition was the reference standard for comparative purposes only, as it was inferred from the patient's review schedule (i.e., a surrogate indicator for likelihood of glaucomatous change and therefore risk). We also note that this was not

Table 3. Demographic and Clinical Characteristics of the Cohort of Glaucoma Suspect Patients in the Present Study, Divided Into Review Periods of ≤6 Months and 12 Months

	Reviewed at ≤6 Months ($n = 243$)	Reviewed at 12 Months ($n = 176$)	*P*
Age (y), median (IQR)	59.1 (50.7–67.2)	53.5 (46.5–61.1)	0.0001
Self-reported gender, *n* (%)			
Male	127 (52.3)	79 (44.9)	0.1392
Female	116 (47.7)	97 (55.1)	
Self-reported ethnicity, *n* (%)			
Caucasian	132 (55.9)	93 (53.4)	0.0867
East Asian	79 (33.5)	56 (32.2)	
Indian	18 (7.6)	14 (8.0)	
Aboriginal/Pacific Islander	3 (1.3)	1 (0.6)	
African	1 (0.4)	3 (1.7)	
Hispanic	3 (1.3)	1 (0.5)	
Mixed	0 (0)	6 (3.4)	
Family history (1st degree)	43 (17.7)	60 (34.1)	0.0001
Family history (2nd degree or more distant)	23 (9.5)	12 (6.8)	0.3750
History of ocular trauma	9 (3.7)	8 (4.5)	0.8029
Diabetes	24 (9.9)	9 (5.1)	0.0973
Hypertension	69 (28.4)	37 (21.0)	0.0893
Hypotension	1 (0.4)	0 (0)	>0.9999
Previous hemodynamic crisis	1 (0.4)	2 (11.4)	0.5749
Migraine and/or vasospastic disorder	34 (14.0)	20 (11.4)	0.4630
Thyroid disease	1 (0.4)	5 (2.8)	0.0868
Chronic corticosteroid use	19 (7.8)	12 (6.8)	0.8504
Sleep apnea	14 (5.8)	6 (3.4)	0.3545
Pigment dispersion syndrome	9 (3.7)	1 (0.6)—[a]	—[a]
Pseudoexfoliation syndrome	3 (1.2)	1 (0.6)	—[a]
Disc hemorrhage	3 (1.2)	0 (0)	—[a]

[a] *P* value cannot be calculated due to small sample sizes.

an indicator of a final diagnosis of glaucoma. Based on these proportions, we obtained the final distributions of high-risk and non–high-risk individuals for the Markov models when performed using the two criteria.

Subsequent Visit Data

Patients had their subsequent visit data recorded and placed into one of five states based on the Markov model states. The proportions of patients fitting into each of these five states based on their original risk delineation according to the clinical disposition and two criteria are shown in Table 5. As expected, the non–high-risk group of patients tended to have higher discharge rates, longer subsequent reviews, and lower referral/treatment rates compared to the high-risk group. These data were then used to build the Markov models. Note that, because the review periods were nearly all limited to reviews of 12 months or sooner (approximately 80%), we did not have the sample size to assess the effect of 12-month versus 24-month review periods, and we proceeded with 6-month and 12-month frequencies only.

Modeling Clinical Visits and Outcomes in a Cohort of Glaucoma Suspect Patients

In addition to the baseline distributions of outcomes for the frequency of review suggested by each criterion (described in Table 4), we also added a baseline attrition rate of 0%, discharge rate of 1.3%, referral/treatment rate of 7.5%, and nominal misdiagnosis rate of 5.0%. The transitional probabilities were based on the subsequent visit dataset as described in Table 5, and we further modulated these probabilities by including a false-positive and

Table 4. Comparison of High-Risk and Non–High-Risk Groups Between Clinical Disposition and the Less Stringent/More Frequent Criterion (1+ Risk Factors) and More Stringent/Less Frequent Criterion (3+ Risk Factors)

	Less Stringent/More Frequent Criterion (1+ Risk Factors), *n* (%)			More Stringent/Less Frequent Criterion (3+ Risk Factors), *n* (%)		
	High-Risk	Non–High-Risk	*P*[a]	High-Risk	Non–High-Risk	*P*[a]
Original clinical disposition						
High-risk	234 (55.8)	9 (2.1)	<0.0001	113 (27.0)	130 (31.0)	<0.0001
Non–high-risk	162 (38.7)	14 (3.3)		87 (20.8)	89 (21.2)	
More stringent/less frequent criterion (3+ risk factors)						
High-risk	200 (47.7)	0 (0)	<0.0001			
Non–high-risk	196 (46.8)	23 (5.5)				

[a]The *P* value was the result of McNemar's test highlighting the discordance between the recommendation and the clinical disposition.

Table 5. Bootstrapped Proportion of Patients Who Had Subsequent Clinical States of Attrition, Discharge, ≤6-Month Review, >6-Month Review, or Referral/Treatment

	Original Risk Designation	Attrition (%)	Discharge (%)	≤6-Month Review (%)	>6-Month Review (%)	Referral/ Treatment (%)
3+ risk factors (more stringent/less frequent)	≤6-mo review, high-risk	18.4	13.4	19.1	36.9	6.0
	>6-mo review, non–high-risk	16.1	20.6	12.9	40.6	4.2
1+ risk factors (less stringent/more frequent)	≤6-mo review, high-risk	16.8	14.5	16.4	37.8	7.6
	>6-mo review, non–high-risk	17.3	52.0	0.0[a]	23.1	2.6

The sum of the rows is approximately 95%, as 5% were considered misdiagnosis for the model.

[a]Note that the proportion of ≤6-month review plans was 0% due to the very small group of subjects that were deemed non–high-risk by the less stringent/more frequent criterion.

false-negative rate (i.e., misdiagnosis rate) of 5%, based on the rate of changed diagnoses (i.e., diagnostic instability) in our present cohort.

The results of the 15 6-month cycle Markov models are shown in Figure 2. At the end of these cycles, interestingly, there were 14.7% more clinical visits arising due to the more stringent/less frequent criterion (more stringent mean = 11,588, SD = 196; less stringent/more frequent mean = 10,101, SD = 178; $P < 0.0001$) (Fig. 2A). Although seemingly counterintuitive, this likely represented the greater number of exit points for patients seen in the less stringent/more frequent criterion that resulted in a greater diminishing rate of clinical visits. Over time, both models demonstrated asymptotic distributions of glaucoma diagnoses, with the less stringent/more frequent criterion resulting in 6.6% more glaucoma diagnoses (mean = 1572; SD = 89) compared to the more stringent/less frequent criterion (mean = 1469; SD = 85; $P < 0.0001$) (Fig. 2B).

In addition to the number of diagnoses made that resulted in one avenue of model exit, we also examined the number of patients that exited due to attrition and who were discharged (effectively low risk of glaucoma). The more stringent/less frequent criterion resulted in a slightly higher attrition rate in the same time period (mean number of patients = 1721; SD = 67) compared to the less stringent/more frequent criterion (mean = 1521; SD = 73; $P < 0.0001$) (Fig. 2C). The more stringent/less frequent criterion also resulted in a lower discharge rate (mean = 1810; SD = 69) compared to the less stringent/more frequent criterion (mean = 1907; SD = 78; $P < 0.0001$) (Fig. 2D). This demonstrated an opposite tendency for patient exit compared to glaucoma diagnosis (Fig. 2B), which may represent factors including lower patient follow-up compliance or forgetfulness with longer reviews, lower perceived glaucoma risk over time, and the reassurance of long-term stability. In combination, Figure 2 shows fewer clinical visits for more or similar exit points when using the less stringent/more frequent criterion.

Case Detection Per Time Point

The number of glaucoma diagnoses made at each cycle was also plotted as a function of time and as a normalized (to the maximum number of cases

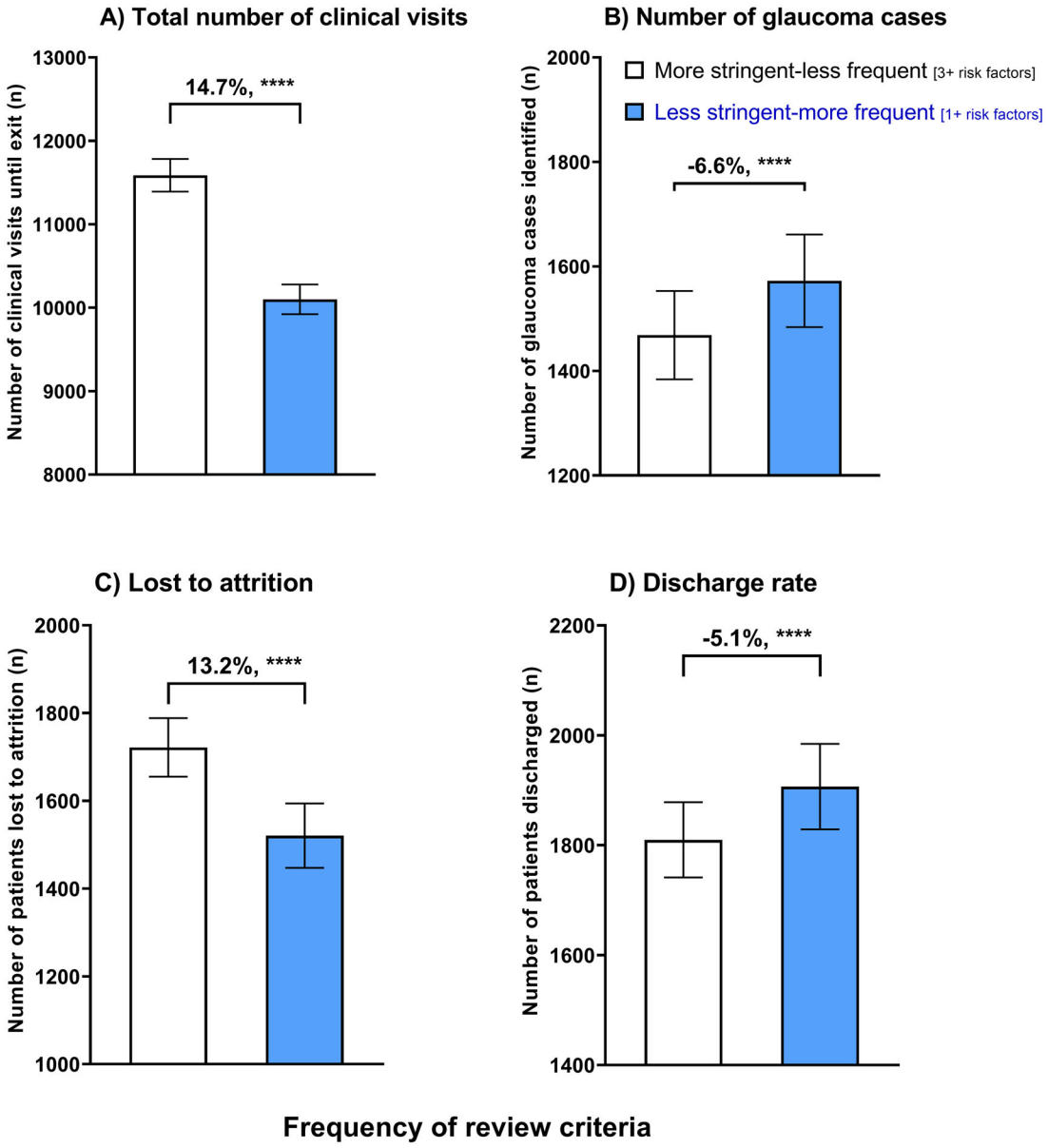

Figure 2. (**A**) Total number of clinical visits occurring for 5000 simulated patients across 15 6-month Markov cycles. (**B**) Number of glaucoma cases identified during the time period. (**C**) The number of patients lost to attrition. (**D**) The number of patients discharged out of the glaucoma suspect review cycle. In all panels, each *bar* represents one of the two criteria used to delineate glaucoma risk and therefore the frequency of review: *white*, more stringent/less frequent criterion (3+ risk factors); *blue*, less stringent/more frequent criterion (1+ risk factors). The *bar* indicates the mean of 10,000 simulated runs of the model, and the *error bars* indicate the standard deviation.

identified by each criterion at its asymptotic point) cumulative distribution (Fig. 3). There was a slightly higher proportion of total glaucoma diagnoses with the less stringent/more frequent criterion until approximately 3 years, after which the overall proportion of diagnosed patients converged. The point at which half of the cohort of glaucoma cases (at 0.6, between the minimum of 0.2 and 1.0) was at year 1.0 for the less stringent/more frequent criterion and was at year 1.2 for the more stringent/less frequent criterion (difference of approximately 2–3 months). The critical point of benefit in early diagnosis appears to be within the first 2.5 to 3 years.

Primary Outcome: Cost Per Glaucoma Diagnosis for Each Criterion

The above results were coalesced into the calculation of our primary outcome, which was cost per diagnosis. With more clinical visits, the more stringent/less frequent criterion expectedly had a higher total cost

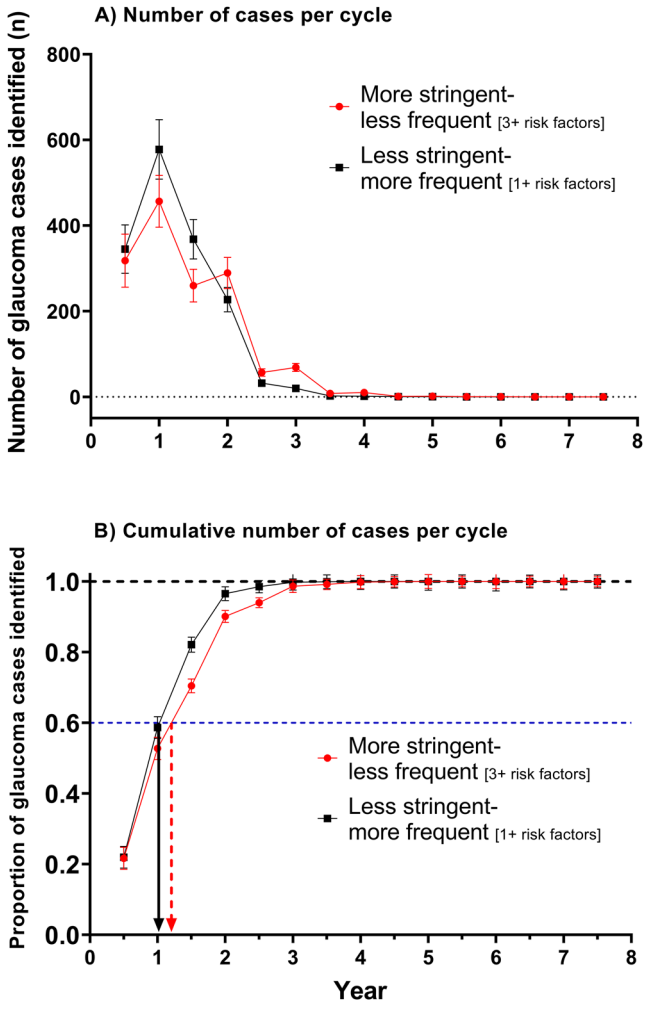

Figure 3. (**A**) Number of glaucoma cases identified at each 6-month period. (**B**) The normalized (to the maximum number of cases detected by each criterion: 1468 by the more stringent/less frequent criterion and 1572 by the less stringent/more frequent criterion, signified by the *black horizontal dashed line*) cumulative number of glaucoma cases over the simulated time period. The *red circles* indicate the results for the more stringent/less frequent criterion, and the *black squares* indicate the results for the less stringent/more frequent criterion. *Error bars* indicate the standard deviation; 95% confidence intervals are too small to be shown. Note that the *y*-axis extends slightly higher than a proportion of 1.0 to include the upper error bar for some data points. In (B), the *blue dashed horizontal line* indicates $y = 0.6$, the point at which approximately half of the total cohort given a minimum of 0.2 and maximum of 1.0 was reached. The *vertical arrows* indicate the corresponding time points at the *x*-axis for each group.

over this simulated period (11.8%–27.5%, depending on provider) (Fig. 4A). The cost per glaucoma diagnosis was also higher with the more stringent/less frequent criterion (17.8%–32.4%, depending on provider), due to the fewer number of cases and the greater number of clinical visits (Fig. 4B). All pairwise differences according to the main independent variable (stringency of the review criterion) were significant at the $P < 0.0001$ level. Thus, for the purposes of the endpoint of discharge or diagnosis, there was a significant cost reduction and better cost-effectiveness when using less stringent/more frequent reviews, due to the sooner exit of patients from the simulated period.

Discussion

Glaucoma suspects represent an important transitional, uncertain stage preceding manifest glaucoma seen in clinical practice. In the present study, we described and modeled the impact on clinician attendance time and healthcare costs associated with different frequencies of review appointments for glaucoma suspects based on two levels of stringency of risk assessment, as well as the patient outcomes in terms of glaucoma diagnoses.

Despite both criteria eventually reaching an asymptote at 3 years in terms of their diagnosis rates, the less stringent/more frequent criterion appeared to be relatively more cost-effective according to our primary outcome, providing a reduction in cost (magnified across the entire cohort) up until the point of diagnosis. The benefit of cost-effectiveness, based on this model, was due to the sooner exit of patients from the glaucoma suspect pathway, thus shifting the cost away from this specific pathway. Thus, although seemingly counterintuitive, the less stringent/more frequent criterion resulted in fewer overall clinical visits, as patient reviews quickly diminished over time due to the patients reaching the exit points sooner. In essence, more frequent reviews (and therefore testing) may potentially improve the initial clinical confidence of stability or provide means for a more conclusive diagnosis (which may also be potentially earlier, as we have recently illustrated[31]). In contrast, less frequent reviews may introduce more uncertainty, requiring more reviews later in the clinical course before a more conclusive diagnosis can be made.

Factors Affecting Real-World Practice Patterns of Reviewing Glaucoma Suspects

A benefit of using strict study protocols and employing strategies such as reading centers or endpoint committees in large-scale clinical trials[32,33] is enhancing the consistency of change detection,[34,35] but this may not necessarily reflect real-world clinical practices titrating risk at an individual level. A major contributing factor that has been recognized by clinical trial protocols is the potential variability in clinical test results or judgments.[36,37] Making

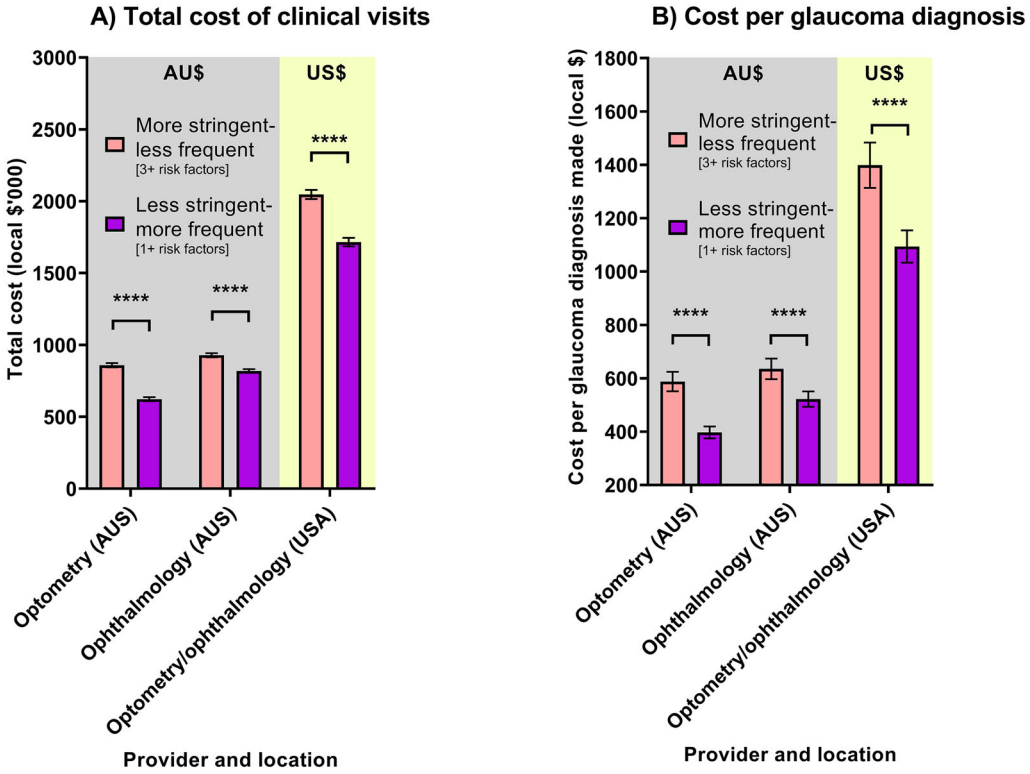

Figure 4. Markov model outcomes of (**A**) total cost of clinical visits and (**B**) cost per glaucoma diagnosis in local currency as denoted by the lower right key (AU$ for an Australian cohort, *gray shaded area*; and US$ for a United States cohort, *yellow shaded area*). Each *bar* represents one of the two criteria used to delineate glaucoma risk and therefore the frequency of review: *orange*, more stringent/less frequent criterion (3+ risk factors); *purple*, less stringent/more frequent criterion (1+ risk factors). The *bar* indicates the mean of 10,000 simulated runs of the model, and the *error bars* indicate the standard deviation. *Bars* are grouped by the provider type and country. All differences were significant at the $P < 0.0001$ level (indicated by *asterisks*).

consistent judgments of risk titration in the real world, although desirable for optimizing the management plan, remains a challenge. This in part reflects the diverse permutations of patient presentations that are impossible for general and discretely categorical clinical criteria to adequately individualize patient risk, especially with a wide spectrum of possible definitions of glaucoma suspect status. Delineations of risk are further complicated by the interactions between risk factors. Discordance between guidelines in risk titration in the present study could have represented situations in which patient-level parameters were used, such as the clinically projected likelihood of lifetime blindness in older individuals.[38] Additionally, socioeconomic or educational factors also influence follow-up adherence in glaucoma services and could create situations where patients may be reviewed sooner or later.[10,39–41] Accordingly, clinicians are mandated to utilize a broad and integrated spectrum of patient-level information, especially within the context of costs, to ascribe glaucoma risk and review benefits, which cannot be distilled into abnormal discrete binary clinical variables. Thus, the inefficiencies within the glaucoma suspect review journey, in part, represent inherent limitations of methods for assigning risk that do not necessarily capture the breadth and diversity of an individual's circumstance.

Cost-Effectiveness of More Frequent Reviews: A Product of Current Testing and Management Paradigms?

The uncertainty surrounding glaucoma diagnosis and the transition between glaucoma suspect and manifest glaucoma suggests that a more frequent review schedule would enable the clinician to be more confident in the clinical disposition. However, broadly, the present results may reflect issues with current testing and management paradigms in the volume of visits required for confident and greater number of diagnoses.

The difference in case detection was accounted for by the difference in attrition and discharge rates, which

were found to be slightly higher with the more stringent/less frequent criterion. In particular, the higher attrition rate might reflect patient drop-out due to extended review periods, with reasons such as forgetfulness or nonadherence due to the perceived low seriousness of the glaucoma suspect status.[10] A danger of high attrition rates potentially relates to missed and therefore late diagnoses, as glaucoma patients non-adherent to follow-up have been shown to exhibit more instances of disease progression.[42] In some cases, a longer interval may confirm patients as having long-term stability, accounting for the higher discharge rate with the more stringent/less frequent criterion.

That not all cases of glaucoma may result in actual impactful disease manifestations has been widely recognized and acknowledged in patient-centric care.[38] Thus, the question that follows probes the significance of the missed cases, with a time differential of approximately 6 to 12 months, according to the cumulative distribution. The less frequent review strategy may be supported by the relatively low conversion rate and generally slow natural history for most cases of primary open-angle glaucoma.[17,43] Therefore, although a patient may have exited from the review cycle as a glaucoma suspect, their burden of disease continues as a manifest glaucoma patient and thus still presents an ongoing cost to the healthcare system.

The proliferation of proposed more sensitive testing strategies[31,44] and fast data acquisition,[45–47] lower cost testing strategies,[48] and telehealth platforms[49] may further assist in reducing the impact of both clinical attendance and cost to the healthcare system while maintaining similar diagnostic sensitivity. Further assistance—and potentially reduction in human user input—can be garnered from supplementary artificial intelligence systems.[50,51] Aside from the robustness of the algorithms, there also remain ethical issues regarding screening processes and patient-facing technologies.[52] The integration of these systems in glaucoma suspect management remains a subject of worthwhile investigation, given the costliness of this transitional phase.

Costs in the Care of Glaucoma Suspect Patients Up Until the Point of Glaucoma Diagnosis

Given the differences in the timing of diagnoses between the criteria, it was not surprising to find lower cost per diagnosis for the more frequent review cycle, especially within the first 2.5 to 3 years. However, this cost difference reflects only the patient's journey as a glaucoma suspect: when that patient requires ongoing care for manifest glaucoma, additional costs will be required, but the patient has effectively been reallocated to a different stage of the disease journey.[53] Although this may represent eventual convergence of the costs associated with the glaucoma family of diseases, another potential advantage of more frequent reviews is that early disease detection lessens the impact on overall health costs and individual quality of life. Nonetheless, the pathways for glaucoma care themselves result in more branches and complexities, including the evolution of costs of comparative treatments.[54]

Our analyses focused largely on the Medicare rebate costs and number of appointments (public health and practitioner levels), but there may also be costs at the patient level associated with glaucoma suspect monitoring, which is also a potential deterrent for compliance at the detection[55] and follow-up[41] levels. Such personal costs may result in a divergence of costs among eye care providers. Finally, excessive points of contact with particularly older or systemically vulnerable patients pose a problem beyond vision due to the recent emergence and continued proliferation of COVID-19.[56] The impact of review schedules and costs at the provider and patient levels presents an opportunity for lower cost providers, methods for promoting health literacy, and new, suitable models of collaborative and telemedicine care to reduce the financial burden of glaucoma, while preserving the same diagnostic acumen for long-term sustainability.[24,57]

Limitations

Our study was limited to a cohort of subjects examined within a referral-only clinical practice. The model that we described was applicable to a cohort of patients presenting to such a clinic for suspected glaucoma and thus specifically had proportionally small numbers of patients with pseudoexfoliation, pigment dispersion syndrome, and disc hemorrhage at presentation. As reflected in our previous study,[11] this clinic had an overall proportion of glaucoma diagnoses that was higher than that expected in the general population. Our suggested model can be tailored to other clinics by modifying factors such as exit rates and review periods, as well as different distributions of patient characteristics.

Our primary outcomes were related to the costs associated with the review of patients at risk of glaucoma, highlighting issues pertaining to this transitional stage toward glaucoma. This was a statistical model, and the purpose of the exercise was not to substitute judicious and personalized medicine approaches for individual patients,[38] including

understanding their individual disease trajectory on structural and functional measurements.[58] This is especially due to the nature of some risk factors remaining relatively static over time, whereas clinical parameters demonstrating worsening or fluctuations are more likely to impact clinical decision making at subsequent visits. Similarly, more diverse review periods, such as sooner (3 months) or later (24 months), can be activated in practice.

Finally, the model was not equipped to determine an output number of false positives (the nominal misdiagnosis rate was applied). False-positive diagnoses of glaucoma have important practical implications, due to a potentially long course of medical or surgical therapy before the patient is re-characterized as stable or identified as a misdiagnosis. For example, a recent study suggested that potentially over half of cases of glaucoma have been incorrectly diagnosed.[59] Although overdiagnosis may occur with more frequent reviews, such a paradigm may be equally useful in providing more conclusive evidence of stability or opportunities to catch misdiagnoses. Again, clinicians need to understand the risk of not only cases of missed glaucoma but also misdiagnosis of glaucoma.

Like any other theoretical model, the present work makes several assumptions that need to be contemporaneously addressed over time, such as incorporating new, potentially more cost-effective and sensitive technologies or techniques; altering healthcare rebates; adding out-of-pocket expenses at the individual level; and paradigm shifts in review criteria, all of which affect the outcomes of the model. We described a cohort of glaucoma suspects followed over time, rather than a screening process by which glaucoma case identification is performed, and we did not incorporate different stages of glaucoma severity, which could also impact costs and patient quality of life.[53,60] Our goal was to describe a model that could serve to highlight issues pertaining to the clinical burden of glaucoma suspect patients, and future models could adjust the parameters of the model according to idiosyncratic clinical features or paradigms. A list of assumptions made for the models and some of their proposed effects in the present study are shown in Supplementary Table S1.

Conclusions

Frequency of review of glaucoma suspects is an important consideration for clinicians, as, based on current testing and diagnostic strategies, a less stringent/more frequent assessment of glaucoma risk, especially within the first 2.5 years, provides a greater diagnostic yield at lower cost per diagnosis made over time up until the point of glaucoma diagnosis, in comparison to less frequent reviews. The implication of stringency of risk assessment—irrespective of the parameters used for assessing the risk—indicates that more frequent reviews in the initial follow-up period potentially increase confidence in the clinical results and thus provide advantages in cost-effectiveness for the assessment of glaucoma suspects until diagnosis or discharge out of this cycle of care.

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