Optimized Clinical Decision-making: A Configurable Markov Model for Benign Prostatic Hyperplasia Treatment

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OBJECTIVE To present a configurable mathematical method to optimize long-term clinical decision-making for benign prostatic hyperplasia.

METHODS We designed a Markov chain model to simulate the different health states associated with benign prostatic hyperplasia and the transition between these states based on specific interventions: observation, pharmacotherapy, and 4 types of minimally invasive laser surgery. Transition probabilities, disutility scores, and costs for each health state were derived from the literature, expert opinion, and hospital administration data. Disutility was defined as the complement to one of the utility (1-utility), with utility representing the overall quality of life associated with a particular state. Linear programming was used to compute the Markov decision model. Primary outcomes include cost-effectiveness curves comparing the average treatment cost across permitted disutility levels while considering all modeled interventions.

RESULTS To achieve optimal patient outcomes (low International Prostate Symptoms Score), the model favored surgical interventions and increased costs of treatment. Between different desired disutility values (breakpoints), the model recommends performing 2 recommend treatments in relative proportions to achieve the lowest cost and optimal outcome. The model is limited by its theoretical basis and reliance on literature for transition probabilities and quality of life assessment.

CONCLUSION This model provides a tool for doctors, administrators, and patients to optimize cost-efficacy when considering multiple treatments and different severities of benign prostatic hyperplasia and may be configured to other disease states or clinical practices. Further studies are necessary to validate this model for real-life application. UROLOGY 132: 183−188, 2019. © 2019 Elsevier Inc.

In 2016, domestic healthcare costs in the United States reached 3.3 trillion dollars, accounting for 17.9% of gross domestic product and continuing to pressure healthcare systems and physicians to provide care more efficiently and affordably. Shifting reimbursements toward value-based payments have further emphasized quality and cost containment.[1] Cost-effectiveness analysis is an analytical tool to identify optimal management strategies that deliver more effective care. However, cost effectiveness analyses in the literature are often limited to comparisons of only 2 competing treatment modalities which do not consider varying severity of disease.

Benign prostatic hyperplasia (BPH) represents a model disease for cost-effectiveness analysis and decision optimization. BPH predominantly affects men as they age, with half of men having evidence of BPH by age 50.[2] Treatment modalities for BPH are varied and include pharmacologic and numerous surgical interventions. This study proposes a Markov model designed to optimize care efficacy and cost across numerous treatment options and patient health states, allowing physicians to tailor interventions based on the severity of patient disease, with BPH as a model system.

MATERIALS AND METHODS

A Markov chain model was developed which used computations based on linear programming to optimize treatment recommendations which minimize costs at varying disutilities or qualify of life measurements.

Markov Model for Urologic Treatments

We designed a novel Markov chain model to simulate the natural history of a patient as he experiences the different health states associated with BPH: mild to severe lower urinary tract symptoms, acute urinary retention, and resolution of symptoms (Fig. 1). Transitions between states depend on the selected

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intervention with an associated transition probability. Using estimated costs of treatment, clinical outcomes, and patient disutility in each health state, our model minimizes the average total cost of care across a range of disutility values to establish efficient and cost effective management strategy for each health state. Disutility was defined as the complement to one of the utility (1-utility), with utility representing the overall quality of life associated with a particular state. Optimal treatments were determined by a standard Linear Programming Markov Decision Model using 3-month intervals, as this is the global period designated by most insurance companies for a given treatment. Additionally, 3 months is an appropriate time period to determine if a treatment, whether it be observation, pharmacologic treatment or surgery, is effective. The model outcome was validated through a simulation with 100 patients and 10,000 cycles (Appendix).

Health States for BPH

Several health states describe the natural history of a patient with BPH in our model. Patient symptoms was classified based on International Prostate Symptoms Score (IPSS); IPSS ranges 0-7, 8-19, and 20-35 are defined as mild, moderate, and severe lower urinary tract symptoms respectively.[3]

All patients presented in an initial "healthy" state prior to transitioning immediately to one of the illness states: pretreatment mild, moderate or severe symptoms or pretreatment acute urinary retention as shown in Figure 1. Pretreatment states are patients who have either just arrived within the model without prior intervention or who were initially managed with observation. Post-treatment health states are patients who have received either surgical or pharmacologic intervention and include mild, moderate or severe symptoms or acute urinary retention. As patients may require multiple interventions, they may visit the post-treatment states multiple times within the model.

There are 3 absorbing health states within the model that represent endpoints in the conventional treatment for BPH and thus terminate the simulation: a diagnosis of cancer following surgical intervention; intractable severe disease that is refractory to intervention; and resolution of symptoms requiring no further treatment.

Actions and Transitions

Within the model simulation patient movement between health states depended on the given intervention and the corresponding transition probability to each subsequent state. The possible BPH interventions included observation, pharmacologic treatment with combined alpha blocker (Tamsulosin) and Type II 5α-reductase inhibitor (Finasteride), and 4 types of minimally-invasive laser surgeries: GreenLight (Boston Scientific Corporation, Marlborough, MA) laser photovaporization (GL), bipolar transurethral resection of the prostate (TURP), holmium laser (HL) enucleation, and thulium laser (TL) enucleation. Estimate transition probabilities were based on expert opinion and the available literature using a mathematical approach (Appendix).[4] Transition probabilities are displayed in Appendix Table S2. Open and robotic simple prostatectomies, aquablation technologies and prostatic artery embolization procedures were excluded as options for surgical intervention as there is limited data in the literature on their efficacy, and in order to simplify the model. In our clinical experience, open prostatectomy is rarely indicated as enucleation procedures are significantly less invasive and equally effective.

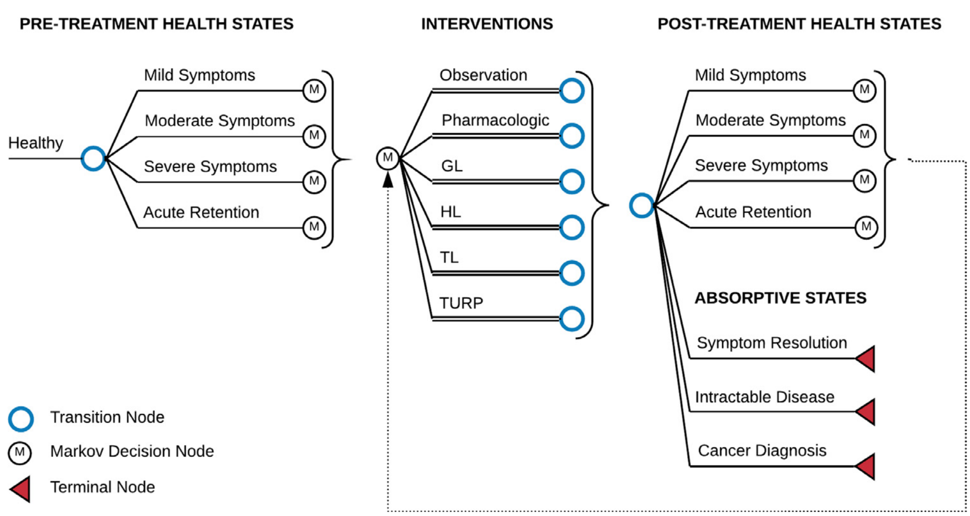

Figure 1. Benign prostatic hyperplasia Markov model structure. This figure demonstrates the Markov model used to optimize care efficacy and cost across BPH treatment options and patient health states. Simulated patients enter the model as "Healthy" and immediately transition to a pretreatment health state. The Markov model then identifies a specific intervention with an associated transition probability to each of the post-treatment health states or absorptive states. As BPH patients may require multiple interventions, simulated patients may cycle through the model multiple times from nonabsorptive health states. The encircled "M" indicates a Markov decision node, where interventions are selected by the model; blue circles indicate transition nodes with entry into the resultant health states based on the selected intervention and associated transition probabilities; red triangles indicate terminal nodes within the model, as patients in these health states fall out of the model. Post-treatment health states are considered as 3-month intervals. GL, Greenlight laser photovaporization; HL, holmium laser enucleation; TL, Thulium laser enucleation; TURP, bipolar transurethral resection of prostate. (Color version available online.)

Cost Analysis

Treatment costs depended on the selected intervention and each transition between health states prior to reaching an absorbing state. Treatment outcomes and adverse event rates were extracted from meta-analyses, randomized clinical trials and large retrospective studies.[5-18] Costs were based on the average cost incurred by a hospital during a 3-month period as determined from healthcare administration software and the literature, considering all variable costs and adverse event rates.[19-24] The only included fixed cost for surgical procedures was laser rental. Prescription cost was based on the average out-of-pocket price for 90 days of Tamsulosin and Finasteride as determined from the literature. The cost computed by the model reflected the average total cost incurred by the hospital per patient during the 3-month period (a patient-cycle). Refer to Appendix Table S1 for specific cost values.

Quality of Life Assessment

Quality of life was calculated by summing the disutility experienced by a patient in each transient health state of a given simulation. In our example of BPH, the utility value is the quality of life associated with the patient's IPSS score. While utility values are often used in cost effectiveness analyses, they had an inherent disadvantage in our model: usually the longer a patient is within the system, the higher the utility, and hence the better the calculated quality of life. Within our model, the longer a patient is in the system, the longer they have unresolved lower urinary tract symptoms. To avoid this paradoxical outcome our model considered quality of life using disutility. Utility values were derived from the literature using the least square fit solved via a mathematical method (Appendix).[25-27] Disutility was then defined as the complement to one of the utility as previously explained (Appendix Tables S1 and S3).

RESULTS

The Trade-off Curve

Calculated trade-off curves between disutility thresholds and the average total cost of treatment per patient-cycle are shown in Figure 2. The cumulative trade-off curve (Fig. 2A) demonstrates an inflection near a disutility value of 0.21, corresponding to a quality of life value of severe LUTS and a cost of $1460 (See Appendix Table S3 for explanation of disutility values). At this point on the curve, a further cost reduction can only be performed at the expense of a large disutility increase, or worsening quality of life. Treatment strategies at disutility values greater than 0.21 did not achieve sufficient cost savings to be attractive alternatives. The critical decision-making range is the subset of simulation outcomes for disutility values 0.1626-0.21 (between moderate to severe LUTS) and minimum average costs of treatment $10,587-$1136 per patient.

The trade-off curve is piece-wise linear and defined by points of slope variation named breakpoints. Table 1 reports the optimal treatments at the breakpoints in the trade-off curve for the critical area. Surgical interventions are favored at lower disutility thresholds, or improved quality of life values, leading to increased average costs of treatment. In other words, considering this in clinical practice, the model recommends performing surgery if you desire the patient to achieve the lowest IPSS score, which would lead to higher costs due to the higher cost of surgery over pharmacologic treatment. For disutility values between breakpoints with different treatment recommendations, the optimal policy is a combination of the 2 recommended treatments in relative proportion. For example, choosing a disutility value at 0.17 is between breakpoints 0.1666 and 0.1794; the recommended intervention for the Pretreatment mild symptoms health state is a combination of HL enucleation and pharmacologic therapy, where one should choose pharmacologic therapy with probability (0.17-0.1666)/(0.1794-0.1666) = 0.266.

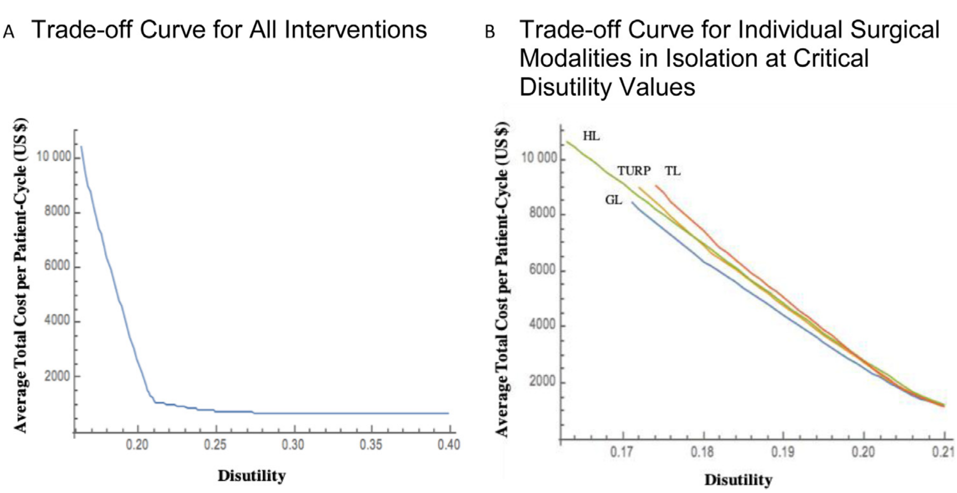

Figure 2. Trade-off curves of disutility vs the average total cost of treatment per patientcycle. Panel A shows the average total cost of treatment per patient cycle determined by our Markov decision model when optimizing all treatment recommendations to minimize costs at a determined disutility threshold. An inflection point near disutility 0.21 and cost $1460 represents the critical point, beyond which alternative treatments are no longer cost-effective. Panel B considers each surgical modality in isolation across the critical area of disutility values. Greenlight laser photovaporization produces equivalent outcomes at lower cost but is only effective to disutility level of 0.1794. At low disutility values Holmium enucleation is effective. Thulium and bipolar resection are not cost-effective at any disutility. GL, Greenlight laser photovaporization; HL, holmium laser enucleation; TL, thulium laser enucleation; TURP, bipolar transurethral resection of prostate. (Color version available online.)

Table 1. Total disutility, cost, patient outcomes, and optimized BPH treatment recommendations by Markov decision model

Calculated cost at varying levels of disutility								
Total disutility	0.1626	0.1656	0.1666	0.1794	0.1973	0.2026	0.2063	0.2100
Average total cost per patient-cycle (USD $)	10,587	9582	9290	6455	2984	2059	1499	1136
Simulation patient outcomes								
Total utility	1.493	1.523	1.529	1.579	1.645	1.651	1.649	2.642
Average utility	0.902	0.902	0.902	0.898	0.893	0.891	0.889	0.926
Average time in model (no. of cycles)	1.655	1.689	1.695	1.759	1.842	1.854	1.855	2.852
Average time in model (months)	4.965	5.067	5.085	5.277	5.526	5.562	5.565	8.556
Distribution of patients in terminating patient health states								
% Resolution of symptoms	92.1	91.8	91.7	91.0	90.0	89.9	90.1	90.8
% Intractable disease	6.6	6.9	6.9	7.6	8.4	8.5	8.6	6.8
% Cancer	1.3	1.3	1.4	1.4	1.6	1.6	1.3	2.4
Treatment recommendations for specific patient health states								
Pretreatment								
Mild symptoms	HL	HL	HL	Ph	Ph	Ph	Ph	Obs
Moderate symptoms	HL	GL	GL	GL	Ph	Ph	Ph	Ph
Severe symptoms	HL	HL	GL	GL	GL	Ph	Ph	Ph
Acute urinary retention	Ph	Ph	Ph	Ph	Ph	Ph	Ph	Ph
Post-treatment								
Mild symptoms	Obs	Obs	Obs	Obs	Obs	Obs	Obs	Obs
Moderate symptoms	Obs	Obs	Obs	Obs	Obs	Obs	Obs	Obs
Severe symptoms	GL	GL	GL	GL	GL	GL	Obs	Obs
Acute urinary retention	GL	GL	GL	GL	GL	GL	GL	GL

GL, Greenlight laser photovaporization; HL, holmium laser enucleation; Obs, observation; Ph, pharmacologic treatment; TL, thulium laser enucleation; TURP, bipolar transurethral resection of prostate.

Trade-off curves were also calculated for each surgical intervention in isolation (Fig. 2B). GL is more cost effective at all disutility values over 0.170. HL is the only treatment modality that attains the absolute minimum disutility at 0.1626. Table 1 demonstrates that to achieve the best disutility value, HL is recommended for surgery naïve patients. However, for patients who have already undergone intervention the same disutility can be reached by using GL, a less expensive procedure. As we consider cost optimization, HL is superior to GL below the 0.1794 disutility breakpoint while at higher disutility thresholds GL achieves the same quality of life but at lesser cost.

Within the critical disutility range 0.1626-0.2100, the proportion of patients with complete symptom resolution (ie, become asymptomatic and exit the simulation) varied between 89.9% and 92.1%. However, while the proportion decreased as expected with higher disutility thresholds, there is a large inflection near disutility 0.21 (Fig. 3A). The total disutility incurred by a patient depended on the total time in the system, as

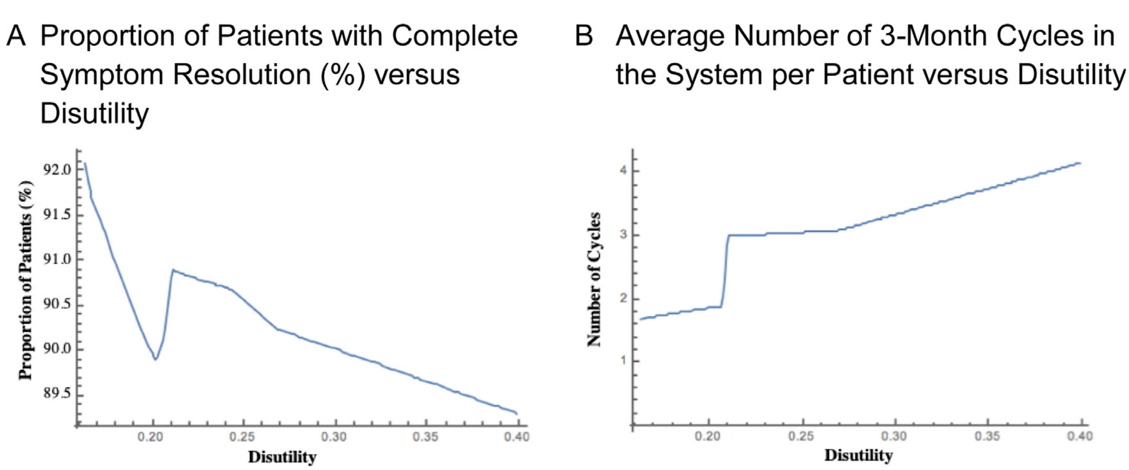

Figure 3. Distribution of patients with complete symptom resolution and the average number of 3-month cycles in the system vs disutility, according to optimized BPH treatment recommendations by Markov decision model. Panel A shows the proportion of patients within the Markov model who experience complete symptom resolution, and thus exit the simulation, for each disutility level. We observe fewer patients with resolution at higher disutility limits, although there is a local peak near disutility of 0.21. Panel B shows the average number of cycles spent within the system for a patient at each disutility level. As expected, patients accrue greater disutility with more time spent within the system; this increases dramatically near the inflection point at disutility of 0.21. (Color version available online.)

disutility is cumulative. Fig. 3B demonstrates a sharp increase in the amount of time spent near disutility 0.21.

Model Reliability

All disutility values and costs in our model calculations are averages. Simulating 100 sample patients and 10,000 cycles, the actual global cost, disutility, and time in the system histograms reflect a normal distribution (See Supplementary Fig. 1). Almost all cost values of the simulation fall in the interval \$8000-\$9000 with an average of \$8532, consistent with the theoretical value \$8537.

DISCUSSION

Given rapidly rising healthcare costs, there is a significant need for comprehensive models for cost-effective clinical decision-making that can be used by any one of the major stakeholders: patient, provider, or payer. Classic cost-effectiveness studies are limited to comparing 2 treatment modalities and do not consider the severity of disease. Our model is unique within the medical literature in its ability to predict the average cost necessary to obtain a given effectiveness (eg, disutility threshold) while considering all available clinical options, including observation, in the decision-making process. As such, this model may provide significant value to all stakeholders in making clinical and policy decisions. For example, hospitals or providers using bundled payments may estimate an average cost to provide care per patient for an acceptable level of clinical effectiveness. Conversely, a payer in a fee-for-value environment may predict clinical outcomes at a certain spending level. Patients may also use the model to negotiate a fair price to attain a certain clinical outcome.

The optimal management strategy for each patient health state (Table 3) guides clinical decision-making toward a guaranteed average outcome for an average cost. It is noteworthy that the model never chooses 2 of the 4 available surgical treatments. Looking at the single treatment trade-off curves (Fig. 2B), some surgical treatments (ie, HL) have a very effective but more expensive trade-off while others (ie, GL) have a good cost-effectiveness trade-off but do not guarantee the minimal possible disutility. The other 2 surgical treatments (TURP and TL) are less effective and thus are not sensibly less costly than the others. The pharmacologic treatment (PH) is least expensive option but is also least effective. The model, therefore, recommends HL, GL, and, PH to achieve the best, moderate, and lowest respective outcomes. Despite the literature showing little association between overall spending and improved outcomes, our model projects that better outcomes imply increasing expenditure due to more frequent surgical intervention.[28-30]

The percentage of symptom-free patients, those with complete resolution of obstructive symptoms, provides another metric to evaluate treatment efficacy within the model. Clinically, this information allows a provider and patient to have an informed discussion of the patients' health state, the possible interventions, and the associated cost to achieve a targeted symptom-free rate. This calculus also applies to hospitals and providers, who may evaluate the efficiency of an intervention by considering the average cost of treatment with the likelihood of a symptom-free outcome. For example, at a disutility of 0.1794, the percentage of symptom-free patients is 91.0% at an average cost \$6455 per patient treated, or \$7093 per symptom-free outcome. One surprising result of the model is the nonmonotonic behavior of the percentage of symptom-free patients (Fig. 3B). We expect fewer symptom-free patients as we relax the disutility constraint and invite less-effective therapies; however, the symptom-free rate demonstrates a local nadir within the critical area of 89.9% at disutility 0.2026 before increasing to 90.8% at disutility 0.2100.

The time spent in the system for any given disutility (Fig. 3A) is a unique feature of this model. Figure 3B demonstrates that a lower efficacy threshold implies more time may be spent receiving treatment in the system. The ideal treatment needs to have a good cost effectiveness trade-off in a reasonable time. Our model enables patients to evaluate a given cost-effective treatment against the projected treatment duration.

The primary limitation of any mathematical model relates to the reliance on estimations to establish model parameters. Transition probabilities are inferred from expert opinion and published data and are thus inherently limited in their ability to reflect the true local transition probabilities of the population under study. Model accuracy would be improved with transition probabilities, cost analysis, and complications rates for the specific provider(s) and patients whose performance we want to project given potential geographic variations in costs. Individual providers may have differences in training and experience with specific surgical operations which are not incorporated in this model and could influence clinical outcomes. Similarly, patient utility, and therefore disutility, values are inferred from IPSS data in the literature that may not reflect the local population. IPSS also does not capture all related factors of quality of life, such as stress or urge incontinence which may result from different therapeutic interventions. Additionally, the model does not consider differences in prostate size, anticoagulation status, other comorbidities, life expectancy, age, or prior urologic surgeries. Such limitations may be overcome by adding more health states to the model, although there is a trade-off in the ability to accurately estimate the relevant transition probabilities of more granular health states. The model utilizes averages for data input and output, but individual differences in patient factors must be considered when applying the model in clinical practice and specifically when applying different surgical treatments. Finally, validation and applicability of the Markov model depend on the total compliance by the clinical provider in using the model as an algorithm for decision-making. As discussed above, the model is designed to give an overall guideline for management, but ultimately the user must input their own outcomes and costs, and consider each patient individually, prior to making a decision.

CONCLUSION

Markov models offer a unique tool for medical decision-making. Our model uses a generalizable approach to optimize medical decision-making for men with BPH that can inform treatment selection for patients with varying severity of lower urinary tract symptoms. Additionally, the model can be customized to specific providers or local provider networks using local outcomes and costs. This model needs further validation with actual patient populations but represents an innovative and practical approach to apply cost-effectiveness analysis in day-to-day clinical urological practice.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2019.06.022.

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