Cost Effectiveness of the Oncotype DX Genomic Prostate Score for Guiding Treatment Decisions in Patients With Early Stage Prostate Cancer

Eric M. Chang, Rinaa S. Punglia, Michael L. Steinberg, and Ann C. Raldow

OBJECTIVE To determine the cost-effectiveness of using the Oncotype DX Genomic Prostate Score (GPS), a 17-gene expression assay that can be used to inform decisions regarding active surveillance (AS) vs immediate treatment.

METHODS We developed a Markov model simulating 20-year outcomes for 65-year-old men with very low-, low-, or favorable intermediate-risk prostate cancer undergoing AS vs immediate treatment using GPS vs no testing. Utilities, costs, and probabilities were extracted from the literature and National Medicare Fee Schedules to determine incremental cost-effectiveness ratios (ICER) from a payer perspective.

RESULTS In the overall cohort, the ICER of GPS-guided therapy was $31,394 per quality-adjusted life-year (QALY). When stratified by risk group, the ICER was $25,343 per QALY in very low-risk, $28,911 per QALY in low-risk, and $39,695 per QALY in favorable intermediate-risk patients. On sensitivity analysis, findings were robust against a willingness-to-pay of $100,000 per QALY to variations in key model parameters, including the cost of annual management of AS, probability of exiting AS to treatment, cost of treatment, and probability of biochemical failure post-treatment. However, the cost-effectiveness was sensitive to small differences in the utility of AS and the utility of no evidence of disease post-treatment states.

CONCLUSION The use of the GPS was cost-effective in guiding treatment decisions regarding AS vs immediate treatment. The cost-effectiveness was sensitive to small differences in the utilities of the AS and no evidence of disease post-treatment states, highlighting the importance of assessing patient preferences. UROLOGY 126: 89–95, 2019. © 2018 Elsevier Inc.

Prostate cancer is the most commonly diagnosed noncutaneous malignancy in American men with 161,360 new cases estimated in 2017.[1] National expenditure associated with prostate cancer is substantial, estimated at $14.3 billion in 2016.[2] Costs are expected to rise, due in part to earlier diagnosis and longer survival.[3] The high economic burden of prostate cancer has led to an increased focus on the relative value of various treatment approaches.

In recent years, active surveillance (AS) has become an established option for men with low- or favorable intermediate-risk prostate cancer. AS involves a protocol of regular prostate-specific antigen (PSA) measurements, office visits, and prostate biopsies in effort to defer radical treatment, thus preventing exposure to treatment-related morbidity and limiting expenditure due to overtreatment. Multiple series support the efficacy of AS, with evidence of similar prostate cancer-specific survival as compared to immediate treatment.[4] While previous studies demonstrated underutilization of AS, recent data indicate increasing use of AS.[5-6] However, challenges remain in the distinction of patients with true low risk of progression appropriate for AS from those more suitable for immediate treatment. Furthermore, studies indicate some patients may experience significant stress when deciding on AS, with evidence of dropout from AS due to anxiety as opposed to disease progression.[7]

Multiple molecular profiling tests have been developed to assist in the decision-making process. These tests aim to better characterize the aggressiveness of a patient's individual tumor and thus distinguish those more appropriate for AS vs immediate treatment.[6] The Oncotype DX (Genomic Health, Redwood City, CA) Genomic Prostate Score (GPS) is a test that measures expression of a 17-gene panel

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From the Department of Radiation Oncology, University of California Los Angeles, Los Angeles, CA; and the Department of Radiation Therapy, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

Address correspondence to: Ann C. Raldow, M.D., M.P.H., Department of Radiation Oncology, University of California Los Angeles, 200 Medical Plaza Driveway, Suite #B265, Los Angeles, CA 90095-6951. E-mail: ARaldow@mednet.ucla.edu

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utilizing biopsy tissue and assesses the probability of harboring adverse pathology at prostatectomy. Validation studies have shown the GPS to be a predictor of time to biochemical recurrence after treatment as well as development of distant metastases and prostate cancer death.[8-9] Clinical utility studies further suggest an increase in the proportion of men that chose AS when incorporating GPS in the decision-making process.[10] While AS has been demonstrated cost saving as compared to immediate treatment, the cost-effectiveness of the GPS in this setting remains unclear as genomic assays are associated with significant expense.[11] We, therefore, analyzed the cost-effectiveness of using the GPS to guide treatment among men newly diagnosed with early stage prostate cancer.

MATERIALS AND METHODS

Model Structure and Treatment Assumptions

In a Markov model, hypothetical cohorts of patients transition between various health states over fixed time increments and at defined probabilities. We constructed a Markov model with Monte Carlo microsimulations to simulate the clinical history of a cohort of 65-year-old men with newly diagnosed National Comprehensive Cancer Network (NCCN) very low-, low-, or favorable intermediate-risk prostate cancer who were eligible for immediate treatment or AS (Fig. 1). One million patients were simulated to ensure convergence in model outcomes. The cycle length was 1 year; outcomes and costs were simulated over 20-year follow-up. The model was created and analyzed using TreeAge Pro 2017 (TreeAge Software, Williamstown, MA), a software used to build decision trees to analyze on the basis of cost-effectiveness. Using probabilities, costs, and utilities inputted by the user, the software reports the outcomes (in terms of costs accrued and health outcomes achieved) of simulated cohorts of patients to allow for comparison between treatment strategies. The software includes multiple analytical features to evaluate the relative impact of each input on model outcomes. In our model, probabilities were extracted from the literature and from previously reported studies (Table 1). A utility is a weight between 0 (death) and 1 (perfect health) assigned to an individual's preference for a health state or outcome, with multiple utility valuation methodologies available.[12] In our model, utilities were extracted from previously reported cost-utility analyses, which relied on the literature and validation by expert panel (Table 1). The probability of entering the death state from any cause was based on 2014 Social Security actuarial life tables.[13] Utilities and costs were discounted at 3% annually.

In the model, men were determined to undergo AS vs immediate treatment utilizing strategies of GPS-guided therapy or no testing. The GPS reports a score scaled 0-100 that provides a biologic measure of cancer aggressiveness. A combined risk group (GPS + NCCN) including input from the GPS and NCCN risk factors is provided to assist in making treatment decisions.[14] In our model, men were assigned to undergo AS vs immediate treatment based on previously reported probabilities from a clinical utility study of the GPS.[10] In this study, a panel of urologists provided a sample of patients with early stage prostate cancer that underwent GPS testing. Relative use of AS was compared with a baseline group treated at the same practices who did not undergo GPS testing. The study reported higher use of AS in GPS-tested patients across very low-, low-, and favorable intermediate-risk groups.

Men in the AS cohort in the model at the end of each cycle had the probability of either remaining on AS vs entering the treatment cohort. Egress probabilities from AS were based on probabilities from published AS series; egress probabilities for follow-up years 1-5 and years 6+ were extracted from exit percentages at 5- and 10-year follow-up, respectively.[11,15,16] Men who elected to undergo treatment by choice were presumed to remain at their baseline risk group, while men exiting AS due to progression were treated as intermediate-risk. Upon treatment, patients were distributed among common therapies for localized prostate cancer, including radical prostatectomy, intensity modulated radiation therapy (IMRT), or brachytherapy.[11] Intermediate-risk group patients undergoing radiation therapy were presumed to be favorable intermediate-risk and were treated without androgen deprivation therapy.

Following treatment, patients cycled through 4 different health states: no evidence of disease (NED) post-treatment, biochemical failure, distant recurrence, and death. Transitioning between health states triggered 1-time work-up and treatments as determined by NCCN guidelines.[17] At first transition to biochemical failure, patients had the opportunity to undergo salvage treatment with possibility of re-entering the NED post-treatment state. Salvage treatment included IMRT with 6 months androgen deprivation therapy for patients previously treated with radical prostatectomy and

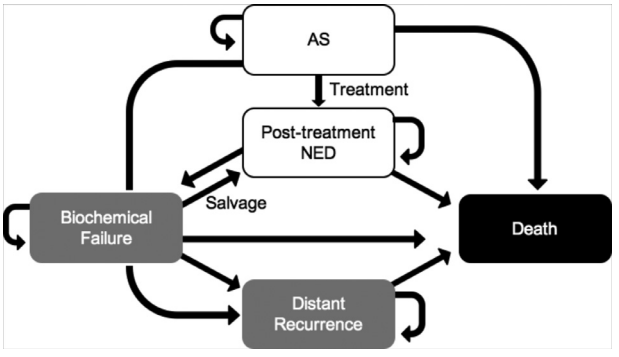

Figure 1. Markov diagram. In our Markov model, hypothetical patients began in active surveillance (AS) vs undergoing immediate treatment. Arrows in the diagram represent transitions between disease states. Patients undergoing AS then remained in AS, proceeded to treatment, or progressed to the distant recurrence state. Following treatment, patients then remained in the post-treatment no evidence of disease (NED) state or proceeded to the biochemical failure state, with chance to return to the post-treatment NED state with salvage therapy. From the biochemical failure state, patients could remain in the biochemical failure state or proceed to the distant recurrence state. Patients in the distant recurrence state then cycled in that state until death. At each cycle, patients could proceed to the death state from other causes based on Social Security actuarial life tables. Initial treatment options included radical prostatectomy, intensity modulated radiation therapy (IMRT), or brachytherapy. Salvage therapy options included prostatectomy for patients previously treated with radiation therapy and IMRT for patients previously treated with prostatectomy. (Color version available online.)

Table 1. Probabilities, utilities, and costs used in the Markov model

Probabilities	Value
Elects AS with GPS[10]	
Very low-risk	0.89
Low-risk	0.63
Favorable intermediate-risk	0.35
Elects AS without GPS[10]	
Very low-risk	0.61
Low-risk	0.37
Favorable intermediate-risk	0.20
Exits AS to treatment (years 1-5; per cycle)	
Very low-risk[11]	0.07
Low-risk[11]	0.07
Favorable intermediate-risk[15]	0.11
Exits AS to treatment (years 6+; per cycle)	
Very low-risk[11]	0.045
Low-risk[11]	0.045
Favorable intermediate-risk[15]	0.11
Exited AS to treatment, by choice vs progression	
Very low-risk[16]	0.33
Low-risk[30]	0.06
Elects prostatectomy[11]	0.44
Elects radiation[11]	0.56
Elected radiation, chooses brachytherapy vs IMRT[11]	0.30
BF following prostatectomy (per cycle)[18]	
Very low-risk	0.0106
Low-risk	0.0106
Favorable intermediate-risk	0.0374
BF following radiation (per cycle)[18]	
Very low-risk	0.0111
Low-risk	0.0111
Favorable intermediate-risk	0.0304
Undergoes salvage radiation after prostatectomy[18]	
Low-risk	0.57
Favorable intermediate-risk	0.38
Undergoes salvage prostatectomy after radiation[18]	0.0176
Salvage therapy success[18]	
Low-risk	0.70
Favorable intermediate-risk	0.60
Progression from AS to DR (per cycle)[22]	0.0023
Progression from BF to DR (per cycle)[22]	0.0127
Progression from DR to prostate cancer death (per cycle)[22]	0.022
Utilities	**Value**
AS[22]	0.99
NED post-treatment[18]	0.92
BF[18]	0.78
DR[18]	0.45
Death	0
Costs	**Value ($)**
GPS (1-time; personal communication with Medicare)	3161
AS (annual; NMFS)	2657
Observation (annual; NMFS)	312
Prostatectomy (1-time)[18]	9562
IMRT (1-time)[18]	30,299
Brachytherapy (1-time)[18]	15,781
Remission (annual)[18]	533
Work-up prior to salvage (1-time; NMFS)	
Post-prostatectomy	1033
Post-radiation	3664
BF (ADT 1-time/annual)[18]	2870/2004
DR[18]	
Annual management	2475
Work-up (one-time)	1074
Treatment (one-time)	17,646
Prostate cancer death (last year of life)[18]	45,652

ADT, androgen deprivation therapy; AS, active surveillance; BF, biochemical failure; DR, distant recurrence; GPS, Genomic Prostate Score; IMRT, intensity-modulated radiation therapy; NED, no evidence of disease; NMFS, National Medicare Fee Schedules.

salvage prostatectomy for patients previously treated with radiation therapy. Due to complexity and morbidity, salvage prostatectomy remains uncommon and thus probability was presumed to be low based on values from the literature.[18] After treatment, men were required to progress through the biochemical failure and distant recurrence states prior to exiting to the death from prostate cancer state. Biochemical failure probabilities for patients with favorable intermediate-risk prostate cancer were derived from those of patients with intermediate-risk disease. Similarly, very low-risk prostate cancer is a relatively recent risk group with limited outcomes data. Therefore, probabilities of outcomes for this subgroup were extrapolated from probabilities for low-risk patients. Following biochemical failure, patients were assumed to progress to the distant recurrence state and the death from prostate cancer state at similar probabilities regardless of initial risk group.

Costs

We adopted a payer perspective to derive costs. To determine costs, we assigned medical resource utilization (including office visits, procedures, imaging, and laboratory tests) to each health state and 1-time treatments and/or work-ups. Costs were derived from the Fiscal Year 2016 National Medicare Fee Schedules, with certain costs extracted from previously published decision models when available (Table 1). Extracted costs were updated using the consumer price index for 2016. Cost for the GPS was based on Medicare reimbursement. Patients undergoing AS were presumed to undergo follow-up per NCCN guidelines (PSA no more than every 6 months, exam no more than every 12 months, prostate biopsy as often as every 12 months).[17] Patients undergoing AS transitioned to observation (PSA and exam every 6 months) when life expectancy was less than 10 years per 2014 Social Security actuarial life tables. Patients undergoing radiation therapy were presumed to undergo IMRT or brachytherapy based on previously published probabilities with the cost calculated as a weighted average of the treatment modalities. Probability of biochemical failure following radiation therapy was presumed to be the same regardless of modality. Costs of complications from treatment were not included as they were assumed to bias the model toward GPS-guided therapy due to increased uptake of AS, with results to be taken as robust if the GPS was found to be cost-effective under this assumption.

Analysis

The incremental cost-effectiveness ratio (ICER) assesses the relative economic value of an intervention, calculated by dividing the difference in total costs for 2 strategies by the difference in

health outcomes achieved. For this calculation, health outcomes are commonly measured in quality-adjusted life-years (QALYs), defined as the duration of time a subject spends in a certain health state multiplied by the utility of that health state. Thus, use of QALYs incorporates the subject's gains in both quantity and quality of life over the follow-up period. ICERs are then compared against a predefined threshold, termed the willingness-to-pay (WTP), to determine if an intervention represents an efficient use of resources. In our analysis, we report the ICER when a therapeutic approach is deemed both more effective and more costly (Table 2). A strategy was deemed cost-effective when the ICER was less than the societal WTP of $100,000 per QALY. In our base case analysis, the cohort was initially stratified by risk group based on published incidences from 2004 to 2005 Medicare Surveillance, Epidemiology, and End Results Program (low- and intermediate-risk, assuming 50% of low-risk patients qualified as very low-risk).[19] We repeated the analysis with all patients assigned to a single risk group to assess the cost-effectiveness of the GPS per risk group. Analysis was additionally repeated using 10- and 30-year follow-up to assess the impact of the duration of follow-up on the outcomes of the model. To assess the impact of age at diagnosis, analysis was repeated using patients age 55 and 75. Sensitivity analyses evaluate the effect of altering the assumptions of the model. We performed a wide range of 1-way sensitivity analyses (Table 3).

RESULTS

To validate our model, we compared outcomes for patients who underwent immediate treatment to patients from ProtecT, a trial evaluating prostate-cancer mortality in men randomized to active monitoring, prostatectomy, or radiation therapy.[20] Ten-year cancer-specific survival for men undergoing immediate treatment in this trial was 99.0%-99.6% compared to 100% in our model. For patients undergoing AS, a systematic review of 10 published AS series indicated 10-year cancer-specific survival between 96% and 100% for both low- and intermediate-risk patients compared to 99.9% in our model.[21]

In the overall cohort, the ICER of GPS-guided therapy was $31,394 per QALY, below the predefined societal WTP of $100,000 per QALY as well as WTP of $50,000 per QALY. When stratified by risk group, the ICER was $25,343 per QALY in patients with very low-risk, $28,911 per QALY in patients with low-risk, and $39,695 per QALY in patients with favorable intermediate-risk prostate cancer (Table 2).

As shown in Table 3, the ICER of GPS-guided therapy over non-GPS-guided therapy in 1-way sensitivity analyses was below $100,000 per QALY for the vast majority of parameters. Notable exceptions included lower utility of the AS state and higher utility of the NED post-treatment state. In our base case analysis, utility of the AS state was 0.99 and utility of the NED post-treatment state was 0.92.[18,22] In 1-way sensitivity analysis varying the utility of AS, GPS testing was favored at utilities above 0.938. In 1-way sensitivity analysis varying the utility of the NED post-treatment state, GPS testing was favored at utilities below 0.976 (Supplementary Figure 1). An additional exception was choice of AS with GPS testing in patients with favorable intermediate-risk disease, in which GPS-guided therapy became dominated at the lower bound. Due to potential for wide variation in the cost of annual monitoring on AS, we conducted a separate threshold analysis varying this cost, in which GPS-guided therapy only became not cost-effective against a WTP of $100,000 per QALY at the extreme cost of $8822.

GPS-guided therapy remained cost-effective against WTP of $100,000 per QALY when simulation was repeated with patients ages 55 and 75 years at diagnosis, with ICERs of $35,404 per QALY and $14,508 per QALY, respectively. GPS-guided therapy additionally remained cost-effective against WTP of $100,000 per QALY when simulation was run with 10- and 30-year follow-up, with ICERs of $34,966 per QALY and $30,125 per QALY, respectively.

COMMENT

Our model found use of the GPS to guide treatment decisions regarding AS vs immediate treatment cost-effective among men newly diagnosed with very low-risk, low-risk, and favorable intermediate-risk prostate cancer. The GPS was further cost-effective at the more favorable WTP of $50,000 per QALY, potentially suggestive of higher value interventions.[23] As might be expected, greatest incremental effectiveness was found for men with very low-risk disease, who potentially stand at the highest risk of

Table 2. Incremental cost-effectiveness ratios (ICER) for strategies of non-GPS-guided vs GPS-guided therapy

	Cost ($)		Effectiveness (QALY)		
	Mean (10%-90%)	Incremental	Mean (10%-90%)	Incremental	ICER ($/QALY)
Overall cohort					
Non-GPS	29,964 (14,104-47,369)		10.48 (4.21-13.75)		
GPS	33,486 (17,553-50,682)	3522	10.59 (4.28-14.18)	0.11	31,394
Very low-risk					
Non-GPS	28,488 (14,104-44,051)		10.72 (4.35-14.35)		
GPS	32,227 (17,391-47,806)	3739	10.87 (4.53-14.45)	0.15	25,343
Low-risk					
Non-GPS	28,116 (14,104-43,447)		10.59 (4.35-14.40)		
GPS	31,896 (17,265-47,806)	3781	10.73 (4.21-13.92)	0.13	28,911
Favorable intermediate-risk					
Non-GPS	31,738 (14,489-51,003)		10.29 (4.21-13.43)		
GPS	35,008 (17,553-53,951)	3270	10.37 (4.21-13.62)	0.08	39,695

GPS, Genomic Prostate Score; QALY, quality-adjusted life-year.
Data presented as mean of total (10th percentile-90th percentile range). Costs and QALYs presented as rounded values with incremental values/ICERs calculated prior to rounding.

Table 3. One-way sensitivity analyses comparing the incremental cost-effectiveness ratios of GPS-guided therapy vs non-GPS-guided therapy

			Results at Lower Bound of Range		Results at Upper Bound of Range	
Parameters	Baseline Value	Range in 1-Way Analysis	Efficacy	ICER	Efficacy	ICER
Probabilities						
Overall cohort						
Elects RT	0.56	0.28-0.84	GPS	<$50k	GPS	<$50k
Elects brachytherapy	0.30	0.15-0.45	GPS	<$50k	GPS	<$50k
Salvage RT, low-risk	0.57	0.38-0.75	GPS	<$50k	GPS	<$50k
Salvage RT, int-risk	0.38	0.25-0.50	GPS	<$50k	GPS	<$50k
Salvage RP	0.0176	0.0100-0.0250	GPS	<$50k	GPS	<$50k
Salvage success, low	0.70	0.50-0.90	GPS	<$50k	GPS	<$50k
Salvage success, int	0.60	0.40-0.80	GPS	<$50k	GPS	<$50k
DR from AS	0.0023	0.0015-0.0032	GPS	<$50k	GPS	<$50k
DR from BF	0.0127	0.0033-0.0221	GPS	<$50k	GPS	<$50k
PC death from DR	0.022	0.010-0.067	GPS	<$50k	GPS	<$50k
Very low-risk group						
Elects AS with GPS	0.89	0.74-0.99	GPS	$50-100k	GPS	<$50k
Exits AS, years 1-5	0.07	0.03-0.12	GPS	<$50k	GPS	<$50k
Exits AS, years 6+	0.045	0.02-0.08	GPS	<$50k	GPS	<$50k
Exits AS by choice	0.33	0-0.50	GPS	<$50k	GPS	<$50k
BF after RP	0.0106	0.0050-0.0500	GPS	<$50k	GPS	<$50k
BF after RT	0.0111	0.0050-0.0500	GPS	<$50k	GPS	<$50k
Low-Risk Group						
Elects AS with GPS	0.63	0.48-0.78	GPS	$50-100k	GPS	<$50k
Exits AS, years 1-5	0.07	0.03-0.12	GPS	<$50k	GPS	<$50k
Exits AS, years 6+	0.045	0.02-0.08	GPS	<$50k	GPS	<$50k
Exits AS by choice	0.06	0-0.50	GPS	<$50k	GPS	<$50k
BF after RP	0.0106	0.0050-0.0500	GPS	<$50k	GPS	<$50k
BF after RT	0.0111	0.0050-0.0500	GPS	<$50k	GPS	<$50k
Favorable Intermediate-Risk Group						
Elects AS with GPS	0.35	0.20-0.50	Non-GPS	DOM	GPS	<$50k
Exits AS, years 1-5	0.11	0.05-0.17	GPS	<$50k	GPS	<$50k
Exits AS, years 6+	0.11	0.05-0.17	GPS	<$50k	GPS	<$50k
BF after RP	0.0374	0.0100-0.0700	GPS	<$50k	GPS	<$50k
BF after RT	0.0304	0.0100-0.0700	GPS	<$50k	GPS	<$50k
Utilities						
AS	0.99	0.90-1.00	Non-GPS	DOM	GPS	<$50k
NED post-treatment	0.92	0.82-1.00	GPS	<$50k	GPS	>$100k
BF	0.78	0.68-0.88	GPS	<$50k	GPS	<$50k
DR	0.45	0.35-0.55	GPS	<$50k	GPS	<$50k
Costs ($)						
Oncotype GPS	3161	1581-4742	GPS	<$50k	GPS	<$50k
AS, annual	2657	1328-3985	GPS	<$50k	GPS	<$50k
Observation, annual	312	156-468	GPS	<$50k	GPS	<$50k
RP	9562	7192-11,988	GPS	<$50k	GPS	<$50k
IMRT	30,299	22,792-37,987	GPS	<$50k	GPS	<$50k
Brachytherapy	15,781	11,871-19,785	GPS	<$50k	GPS	<$50k
Remission, annual	533	267-1068	GPS	<$50k	GPS	<$50k
Post-RP, work-up	1033	516-1549	GPS	<$50k	GPS	<$50k
Post-RT, work-up	3664	1832-5495	GPS	<$50k	GPS	<$50k
BF, one-time	2870	0-5,756	GPS	<$50k	GPS	<$50k
BF, annual	2004	1005-4019	GPS	<$50k	GPS	<$50k
DR, annual	2475	1241-4964	GPS	<$50k	GPS	<$50k
DR, work-up	1074	539-2154	GPS	<$50k	GPS	<$50k
DR, treatment costs	17,646	8850-35,397	GPS	<$50k	GPS	<$50k
PC death	45,652	22,895-91,576	GPS	<$50k	GPS	<$50k

AS, active surveillance; BF, biochemical failure; C, prostate cancer; DR, distant recurrence; GPS, Genomic Prostate Score; IMRT, intensity modulated radiation therapy; NED, no evidence of disease; PRT, radiation therapy; RP, radical prostatectomy.
One-way sensitivity analyses examine the effect of altering one value in the model on the model's results. The name under Efficacy (GPS vs non-GPS) denotes the strategy that was more efficacious when the parameter was varied across the specified range. The range under ICER indicates the incremental cost-effectiveness ratio: <$50k = <$50,000 per QALY; $50-100k = between $50,000 and $100,000 per QALY; >$100k = ICER >$100,000 per QALY; DOM = dominated. Results are reported by risk group when variation was presumed to have greater impact on the model than in the overall cohort. As men exiting AS by choice were presumed to remain at their baseline risk group and men exiting AS due to progression were treated as intermediate-risk, varying the probabilities of salvage RT/salvage success isolated by risk group had less impact on the model and thus analyses in these instances are presented for the overall cohort.

overtreatment. Our findings were consistent across a wide range of deterministic sensitivity analyses, suggestive of the robustness of these results to variations in the majority of costs and probabilities used. The GPS remained cost-effective with wide variation in the cost of annual monitoring while on AS, of importance given current uncertainty in the ideal combination and frequency of tests for men on AS, including incorporation of potentially expensive ancillary radiographic studies. A prior cohort study compared payer costs in the first 180 days post-biopsy in GPS-tested and untested patients and found cost savings of on average $2286 per patient in men incorporating the GPS.[24] Our study further suggests the GPS to be cost-effective, modeled over longer duration of follow-up. The Prolaris (Myriad Genetics, Salt Lake City, UT) genomic test can be used similarly to the GPS in assisting patients in the decision between AS and immediate treatment. A prior economic model indicated potential cost savings with use of the Prolaris in a hypothetical cohort of prostate cancer patients over 10-year follow-up.[25] Of note, a budget impact analysis from the Ontario Ministry of Health and Long-Term Care did not find the cost savings to offset the cost of the test in the Ontario setting, potentially reflective of differences in reimbursement and where practices may be more conservative than in the United States.[26]

A key finding of our study was the influence of utility on the cost-effectiveness of the GPS. In our study, we relied on previously published utilities to inform our model, which were best available though not extensively validated with notable variation across multiple studies.[18,27,28] The utility of AS in particular is not well-studied, with potential for disutility of anxiety secondary to untreated disease.[28] Similar to Hayes et al, we presumed the AS state to be associated with a higher utility than the NED post-treatment state in our base case analysis. However, in sensitivity analyses, GPS-guided therapy became not cost-effective at the upper bound of the utility of the NED post-treatment state and dominated at the lower bound of the utility of the AS state. This dependence occurred over a narrow range, with threshold of 0.938 when varying the utility of AS from baseline of 0.99 and threshold of 0.976 when varying the utility of NED post-treatment from baseline of 0.92, suggesting high sensitivity to these utilities. Furthermore, the extremes of these parameters used in the 1-way sensitivity analyses included plausible values previously used in the literature. Dependence on small variations in utility is notable given utilities may vary among individual patients, based on personal perceptions regarding the anxiety of going untreated while on AS and the fear, adverse effects, and inconvenience of treatment. This has been documented in the literature, with varying levels of anxiety and quality of life scores seen in men on AS and men undergoing treatment.[29] Prior decision analyses comparing AS vs prostatectomy have indicated a similar sensitivity of outcomes to variations in utilities.[22,28] Together with our findings, these results overall reinforce the importance of eliciting patient preference and shared decision-making in the determination of the most cost-effective strategy for men with early stage prostate cancer, including incorporation of the GPS.

We note several limitations of our study. Given limited randomized controlled evidence regarding disease-specific outcomes with AS, our assumptions were based primarily on a variety of prospective cohort studies, which utilized different AS protocols and included patients of varying baseline risk. Furthermore, we made multiple simplifying assumptions regarding the natural history and treatment of disease. For instance, we did not account for the costs of specific treatment-related adverse effects (eg, impotence). Importantly, preferential selection of AS in GPS-tested patients vs untested patients was based on a relatively small clinical utility study of the GPS.[10] Due to this study's significance in our model, extensive sensitivity analyses were performed. Given the robustness of our findings to variations in a broad range of parameters, we are confident in the outcomes of our model. We note that as use of AS has increased in recent years, the relative increase in use of AS with GPS testing may be smaller than assumed and continue to decline with increasing acceptance of AS.[6] Our findings may be improved with further understanding of a patient's relative use of AS based on his individual GPS score and baseline risk factors. Lastly, as long-term clinical studies of disease-specific outcomes for patients undergoing GPS-guided therapy are not yet available, we assumed similar risks of progression between GPS-guided and untested patients. The previously described clinical utility study of the GPS did not confirm that patients motivated to choose AS based on GPS results demonstrated improvement in outcomes. However, presuming the GPS provides an accurate measure of a patient's cancer aggressiveness, our assumption of similar risk of progression between GPS-tested and untested patients would likely be conservative. Given the proliferation of genomic testing, standardization of how to best incorporate risk information from genomic tests into cost-effectiveness analyses may be beneficial.

CONCLUSION

In conclusion, we found use of the GPS to guide treatment decisions regarding AS vs immediate treatment in men newly diagnosed with early stage prostate cancer to be cost-effective. This finding was robust in multiple sensitivity analyses, indicating minimal dependence on choice and/or cost of treatment modality or AS protocol used. However, our model did demonstrate the cost-effectiveness of the GPS to be sensitive to narrow variations in the utilities of the AS and NED post-treatment states, reinforcing the importance of assessing patient preferences in the decision-making process.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.urology.2018.12.016.

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