

# Health economic impact of a biopsy-based cell cycle gene expression assay in localized prostate cancer

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**Background:** Prior studies have established that broader incorporation of active surveillance, guided by additional prognostic tools, may mitigate the growing economic burden of localized prostate cancer in the USA. This study sought to further explore the potential of a particular gene expression-based prognostic tool to address this unmet need. **Materials & methods:** A deterministic, decision-analytic model was developed to estimate the economic impact of the Prolaris test on a US commercial health plan. **Results & conclusion:** When adopted in patients classified by the American Urological Association as low or intermediate risk, the assay was projected to reduce costs by \$1894 and 2129 per patient over 3 and 10 years, respectively, largely through the increased use of active surveillance.

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As the most common malignancy affecting American men, prostate cancer represents a substantial portion of overall cancer spending in the USA today and a significant financial burden on the healthcare system [1]. A study by researchers at the National Cancer Institute projected the costs of prostate cancer care to grow from \$11.85 billion in 2010 to \$16.34 billion by 2020 [2]. Increasing in cost more quickly than any other cancer, this ranks prostate cancer as the third most costly cancer overall, behind breast and colorectal cancer [2].

A significant driver of the treatment costs associated with localized prostate cancer is the widespread use of immediate, definitive treatment for the majority of patients upon diagnosis. Regardless of disease aggressiveness, most patients today (75–90%) receive immediate, definitive treatment for their disease, which typically includes radical prostatectomy (RP), radiation therapy (RT) androgen deprivation therapy (ADT), or some combination of these [3–7]. However, it is widely recognized that a substantial subset of patients could live with their indolent disease and ultimately die from other causes, making definitive treatment an unnecessary route for many patients [8]. In addition, all current treatment options entail side effects that affect quality of life [9]. Meanwhile, the cost of these treatments is substantial, with RT alone costing payers more than \$34,000 per patient [10,11]. Recent studies have demonstrated that active surveillance (AS) is a suitable, less aggressive treatment option for many patients with less aggressive localized prostate cancer and one that can reduce the overall cost of patient care. However, determining which patients are best suited for AS remains a challenge, especially for intermediate-risk patients [12].

Patients who have been newly diagnosed with prostate cancer may have either indolent or aggressive forms of the disease. Unfortunately, current tools such as prostate-specific antigen levels, Gleason scores and nomograms do not adequately stratify patients within American Urological Association (AUA) risk groups [13]. Today, many men receive unnecessary treatment for their disease, as evidenced by low rates of prostate cancer-specific mortality, even among untreated patients [8]. Improved stratification based on disease aggressiveness and mortality risk has the potential to spare men with indolent disease from unnecessary treatment. This enhanced triaging has the potential to improve clinical outcomes through more appropriate treatment of patients, reduce economic inefficiencies and potentially reduce costs. Several molecular assays have emerged to help physicians triage patients. However, the overall cost effectiveness of these tools remains unknown given the high costs of these tests and variability in the upfront and long-term costs associated with managing patients who receive more or less aggressive treatment.

The Prolaris<sup>®</sup> test (Myriad Genetics, UT, USA) is a gene expression-based assay that measures tumor cell growth characteristics in order to stratify patients with localized prostate cancer according to disease aggressiveness. The test combines the gene expression levels of 31 genes related to cell cycle progression and 15 housekeeping genes into a Cell Cycle Progression score that is used to predict 10-year prostate cancer-specific disease mortality and 10-year probability of progression to metastatic disease. The assay's prognostic ability at biopsy has been evaluated in 14 published clinical trial cohorts of prostate biopsy and prostatectomy samples [14–25]. These studies have validated the ability of the test to identify both lower-risk patients who would be better suited to more conservative options such as AS and higher-risk patients who would benefit from definitive treatment beyond clinicopathologic-based recommendations. A combined clinical Cell Cycle Risk (CCR) score has been developed that incorporates both prognostic molecular and clinicopathologic information. Building on these data, a threshold score has been validated [15] that optimally identifies men with low-risk disease for whom AS would be appropriate based on a 10-year risk of disease specific mortality of 3.2% [22].

Separate studies have evaluated the assay's clinical utility in terms of the ability of the test to impact clinical decision-making [26,27]. Results from prospective clinical utility registries demonstrated that the test had a significant impact on the management of patients with prostate cancer, particularly by increasing the use of AS for both low- and intermediate-risk patients. These studies evaluated 1537 total patients from geographically diverse sites. Furthermore, real-world examples have emerged supporting the utility of stratification tools such as Prolaris to increase the use of AS; when Blue Shield of California began to cover Prolaris testing, it found that AS increased by 18%, radical prostatectomies decreased by 8% and intensity-modulated radiation therapy decreased by 14% [28].

Given the recent results supporting the utility of Prolaris for guiding appropriate stratification of patients for AS, it is important to assess the downstream economic impact of this test on payers – particularly given the current economic environment and significant costs associated with prostate cancer care [29]. An increase in the use of AS in the management of low- and intermediate-risk patients associated with using the cell cycle gene expression assay could have a profound impact on the cost of prostate cancer care. The purpose of this study was to model the economic impact of the test on a hypothetical US commercial insurer using an *in silico* model.

## Materials & methods

### Model structure & methodology

A deterministic, decision-analytic model was developed to estimate the direct medical costs associated with using the cell cycle gene expression assay compared with standard clinicopathologic evaluation alone to guide the management of patients with localized prostate cancer. A probabilistic-model approach with 1 year intervals was deemed optimal in this case given the level of complexity and data availability. Treatment of a single hypothetical cohort of incident-localized prostate cancer patients was simulated using a patient flow model, built in Microsoft Excel, that was structured according to prevailing management protocols, including AUA and National Comprehensive Cancer Network (NCCN) Guidelines. Two branches of the model represented patient management under different scenarios. The first branch used standard clinicopathologic diagnostic modalities alone to determine patient management (the 'Typical Practice Scenario') and the second branch incorporated the cell cycle gene expression assay (the 'Prolaris Scenario'). As is common in clinical practice, the hypothetical patient cohort was separated into cohorts based on AUA risk groups. These groups are substantially similar to the NCCN risk group classifications, which are also often used by clinicians to stratify patients. Patients assigned to low- and intermediate-risk groups were modeled to receive the test after a biopsy, in order to determine whether to pursue AS or definitive treatment. The hypothetical patient cohort focused on AUA low- and intermediate-risk patients given the demonstrated clinical impact of Prolaris to increase the use of AS in these specific cohorts. Patients in the AUA high-risk group were not modeled in this study because AS is not prevalent in the management of these patients.

Patient flow was modeled over the course of 10 years, tracking each phase of care across the cohort. Costs were assigned to each unit of care based on estimated average reimbursement rates paid by a US commercial health plan, as described below. A comparison of the overall cost of managing patients under the Typical Practice Scenario versus the Prolaris Scenario was used to determine the economic impact of the gene expression assay. A graphical schematic of the model structure is depicted in [Supplementary Figure 1](#).

**Table 1. Clinical treatment paradigm for the typical practice scenario.**

Initial treatment modality in the typical practice scenario	AUA risk group	
	Low (42% of patients with localized prostate cancer)	Intermediate (35% of patients with localized prostate cancer)
Active surveillance	24%	4%
Radical prostatectomy only	36%	40%
Radiation therapy only	25%	10%
Androgen deprivation therapy only	15%	29%
Radiation therapy and androgen deprivation therapy	0%	17%
<b>Total</b>	<b>100%</b>	<b>100%</b>

Initial treatment modality of patients with prostate cancer by AUA risk group. The Typical Practice Scenario represents the modeled average treatment paradigm using standard clinico-pathologic diagnostic modalities alone to determine patient management. The clinical practice paradigm was based on a combination of relevant sources, including published clinical guidelines, peer-reviewed articles on current treatment of patients with prostate cancer and in-depth qualitative interviews with board-certified physicians. Primarily, data from the US National Cancer Database drove the active surveillance assumptions and data from the AUA Quality Registry drove the subsequent treatment breakdown.

ADT: Androgen deprivation therapy; AS: Active surveillance; AUA: American Urological Association; RP: Radical prostatectomy; RT: Radiation therapy.

## Clinical paradigm

### *Typical practice scenario*

The Typical Practice Scenario builds upon a recently published study that utilized a decision-analytic model to estimate the medical costs associated with localized prostate cancer over 10 years for all AUA risk groups, from the perspective of a US commercial payer [30]. The key assumptions regarding the initial staging and treatment of incident-localized, AUA low- and intermediate-risk prostate cancer patients in the Typical Practice Scenario are presented in Table 1. Table 1 maps out the initial care received by each patient cohort based on AUA risk group. Additional follow-up care, as well as progression and further treatment costs, were tracked over the 10-year duration of the model to follow patients through the care continuum (see ‘Disease follow-up & progression’ section). Patients initially managed with AS were modeled to subsequently receive definitive treatment according to published rates (roughly 30% of low-risk and 60% of intermediate-risk patients over 5 years), either due to disease progression or patient choice [31–33].

The current clinical practice paradigm was based on a combination of relevant sources, including published clinical guidelines, peer-reviewed articles on current treatment for patients with prostate cancer and in-depth qualitative interviews with board-certified physicians. Data from the US National Cancer Database were used to inform baseline rates of AS, whereas data from the AUA Quality Registry served as the foundation for the treatment distribution across definitive treatment modalities [34,35]. A total of 23 board-certified urologists were interviewed about their current practice patterns and treatment paradigms to further inform the patient management paradigm. All urologists who were interviewed had been in practice for at least 5 years and were actively treating patients with prostate cancer. The urologists practiced in a mix of community and academic settings from all geographic regions in the USA. No two physicians practiced at the same institution. An in-depth review of the clinical literature, including studies on the National Cancer Database and AUA Quality Registry, was used to validate and refine physician perspectives on the management of patients with localized prostate cancer.

The options modeled for initial patient management were AS, single-modality definitive treatment (including RP, RT or primary ADT) or multimodality definitive treatment (RT plus ADT).

The clinical paradigm (Table 1) was intended to represent today’s prevailing practice patterns. Accordingly, initial patient management varied by AUA risk group. In the AUA low-risk group, 24% of patients were initially managed using AS, whereas 76% received single-modality therapy. In the AUA intermediate-risk group, 4% were initially managed using AS, 79% with single-modality therapy and 17% with multimodality therapy [31,32,36–40].

### *Prolaris scenario*

The impact of the Prolaris test on patient management and the use of AS was determined based on the published results of the AS Threshold Validation Study by Lin *et al.*, as well as taking into account adherence from the Outcomes of Men Who Select AS study, as shown in Table 2 [22,41]. Lin *et al.* validated the threshold for AS eligibility and determined that, on average, 92.9% of AUA low-risk patients and 43.0% of AUA intermediate-risk patients are eligible for AS based on having a CCR score and therefore a 10-year prostate cancer mortality risk, below the threshold value [22]. To account for variability in real-world practice, an adherence rate of 82.4% was

Table 2. Active surveillance rate by risk group in the polaris scenario.		
	AUA risk group	
	Low	Intermediate
% eligible for active surveillance	92.9%	43.0%
Adherence rate to a recommendation of active surveillance	82.4%	82.4%
Rate of active surveillance in the Polaris Scenario	76.5%	35.4%
Calculation for the rate of active surveillance in Polaris Scenario by risk group. The active surveillance rate in the Polaris Scenario was determined based on published results demonstrating the fraction of AUA risk groups eligible for active surveillance. Results were based on the validated CCR score and adjusted based on published rates of adherence to a recommendation of active surveillance [22,41]. AUA: American Urological Association; CCR: Cell Cycle Risk.		

Table 3. Clinical treatment paradigm in the polaris scenario.		
	AUA risk group	
	Low	Intermediate
Active surveillance	76.5% (82.4% adherence to AS recommendation rate of 92.9%)	35.4% (82.4% adherence to AS recommendation rate of 43%)
RP Only	11.1%	24.4%
RT Only	7.7%	6.0%
ADT Only	4.7%	17.7%
RT and ADT	0%	16.5%
Total	100%	100%
Initial treatment modality of patients with prostate cancer in the Polaris Scenario by AUA risk group. The Polaris Scenario represents the modeled scenario, which incorporates the cell cycle gene expression assay into the diagnostic paradigm to inform patient management. Initial treatment for men not receiving active surveillance was distributed proportionally based on the same treatment paradigm used in the Typical Practice Scenario. AUA: American Urological Association.		

applied to the threshold, based on the Outcomes of Men Who Select AS study by Kaul *et al.*, which found that 82.4% of men with prostate cancer who were determined to have a low estimated risk of disease-specific mortality based on their CCR score and NCCN guidelines initially selected AS over definitive treatment [41]. This translated to a greater than threefold increase in the use of AS in AUA low-risk patients, increasing AS from 24% in the Typical Practice Scenario to 76.5% in the Polaris Scenario. In intermediate-risk patients, using the same adherence rate translated to a greater than eightfold increase in AS use in intermediate-risk patients, from 4% in the Typical Practice Scenario to 35.4% in the Polaris Scenario (Table 2). Similar to the Typical Practice Scenario, patients initially managed with AS were modeled to subsequently receive definitive treatment according to published rates (roughly 30% of low-risk and 60% of intermediate-risk patients over 5 years), either due to disease progression or patient choice [31–33]. Initial treatment for those men not receiving AS was distributed proportionally based on the treatment paradigm used in the Typical Practice Scenario, as highlighted in Table 3.

Disease follow-up & progression

Patients were modeled to receive follow-up care and additional treatment based on standard clinical practice. Patient follow-up care and disease monitoring after initial management includes office visits, prostate-specific antigen screening and biopsies, as well as treatment for complications resulting from management, such as erectile dysfunction and incontinence. A declining annual rate of biochemical recurrence was modeled according to rates in the published literature and varied based on initial treatment type and AUA risk group [10,37]. Patients who experienced biochemical recurrence were modeled to receive additional therapy, with patients initially treated using single-modality RP going on to receive either salvage RT (50%) or ADT (50%) and patients initially treated with all other modalities going on to receive ADT [42]. For patients progressing to later stages of the disease, the rate of progression was based on published statistics. The timeline for patients experiencing progression was based on published survival statistics and estimated progression curves established during physician interviews [43].

Cost inputs

Table 4 displays the unit costs used to populate the economic model. The cost inputs and methodology used in this study build upon a prior study that utilized a decision-analytic model to estimate the medical costs associated with localized prostate cancer over 10 years for all AUA risk groups [30]. Cost inputs were established for each unit

Table 4. Cost inputs.

		Cost (USD)	Source	Ref.
Initial treatment	Radical prostatectomy	\$10,604 (Year 1)	2018 Medicare fee schedules and claims databases	
	Primary radiation therapy	\$34,116 (Year 1)	Voigt 2017 <i>J. Urol.</i>	[11]
	Androgen deprivation therapy	\$2993 (Year 1)	2018 Medicare fee schedules and claims databases	
	Adjuvant/salvage radiation therapy	\$29,101 (Year 1)	Voigt 2017 <i>J. Urol.</i>	[11]
Monitoring costs	Active surveillance	\$1066 (Annual)	2018 Medicare fee schedules and claims databases	
	Post-RP/RT monitoring	\$774–845 (Annual)	2018 Medicare fee schedules and claims databases, Cooperberg 2013 <i>BJU Int.</i> , Resnick 2013 <i>NEJM</i>	[10,44]
Advanced treatment	Androgen deprivation therapy	\$2993 (Annual)	2018 Medicare fee schedules and claims databases	
	Castrate-resistant prostate cancer	\$122,323 (Annual)	2018 Medicare fee schedules and claims databases	
Medicare scale-up factor		125%	MEDPAC	[45]

Cost inputs used in the model. Costs were referenced from a variety of sources, including published, peer-reviewed clinical articles and Medicare fee schedules and claims databases. ADT: Androgen deprivation therapy; AS: Active surveillance; CRPC: Castrate-resistant prostate cancer; RP: Radical prostatectomy; RT: Radiation therapy.

of care a patient might undergo, including diagnostic procedures, surgical procedures, radiotherapy procedures and pharmacological therapy. Other costs associated with the treatment, such as office visits, anesthesiology, pathology and associated complications, were accounted for where appropriate. Cost assumptions were generated from a variety of sources given the known variability in payment rates across US commercial health plans. Sources for costs included the 2018 Medicare fee-for-service rates, peer-reviewed journal articles and other published sources. As many of these cost inputs will change over time, results of this study are most relevant from a 2018 perspective.

To estimate the pricing based on Medicare fee-for-service rates, interviews were conducted with professional coders specializing in urology coding to determine which Current Procedural Terminology (CPT), International Statistical Classification of Diseases and Health Problems (ICD-9) and Diagnosis-Related Group (DRG) codes were most commonly used in practice. The CPT, ICD-9 and DRG codes were mapped to national payment rates using 2018 Medicare fee schedules. For each code, the total Medicare reimbursement (combining both professional and facility fees, where appropriate) was calculated for four separate Place of Service settings as follows: physician's office, ambulatory surgical center, hospital outpatient and hospital inpatient. For procedures performed in a variety of settings, the payment amount(s) for each setting were then combined in a weighted average according to the frequency with which the relevant code was billed from each of the four settings. Data for the CPT codes were sourced from the 2015 Physician/Supplier Procedure Summary (PSPS) database, which contains data on fee-for-service claims billed to Medicare Part B. In cases where multiple CPT, ICD-9 or DRG codes were used to describe similar services, a single payment amount was calculated by performing a weighted average of the various codes according to their billing frequency, as recorded in the PSPS or the Nationwide Inpatient Sample, Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality. Data for the ICD-9 and DRG codes were sourced from the 2014 Nationwide Inpatient Sample. Despite the multiyear data-release lag time, this database contains the largest collection of data on procedures and diagnosis counts from publicly available payer healthcare databases, including Medicare. For the CPT codes, the same PSPS database was used. Finally, Medicare payment rates were inflated by 25% to more accurately reflect the rates paid by commercial insurers, with the exception of payment rates for pharmaceuticals [46].

Select cost inputs were determined from alternate sources. The cost inputs for certain specific therapies, including primary and adjuvant radiation therapy, were taken from the published literature [11]. The costs of oral pharmaceuticals were sourced from published wholesaler acquisition cost prices and Medicare average sales price drug pricing. The cost of the gene expression test was sourced from the manufacturer.

The cost of treating castrate-resistant prostate cancer was estimated using a hypothetical treatment regimen based on standard clinical practice (Supplementary Table 1). The analysis accounted for the percentage of patients receiving a given therapy, the duration of therapy and dosing schedule and the average cost of therapy. The cost per milligram was translated into the cost of a full course of treatment according to the dosing schedule specified by



Table 5. Total cumulative costs per patient over 10 years.				
	Cumulative cost per patient at year after diagnosis			
	Year 1	Year 3	Year 5	Year 10
Typical practice scenario	\$17,114	\$20,796	\$27,872	\$70,074
Prolaris scenario	\$13,123	\$18,902	\$26,159	\$67,945
Total cumulative cost savings per patient	\$ 3991	\$1894	\$1713	\$2129

Cumulative costs of prostate cancer management in each modeled scenario on a per patient basis in the Typical Practice Scenario and Prolaris Scenario. Prostate cancer management was modeled for all AUA low- and intermediate-risk patients within a typical payer plan. Cumulative costs were compared between scenarios to determine the overall cost savings per patient. AUA: American Urological Association.

the drug’s US FDA label, clinical guidelines, or the most relevant clinical trials. For dosing schedules dependent on body weight or surface area, an average body weight of 88.8 kg and average body surface area of 1.9 m<sup>2</sup> was used, as reported by the CDC in 2016 [45]. A final average per-patient cost of treating castrate-resistant prostate cancer was calculated and validated using various published cost analyses [42,47–52].

*Cost-savings analysis*

The cumulative costs of the Typical Practice Scenario and the Prolaris Scenario were compared in order to determine the economic impact of the assay on a hypothetical commercial payer. Cost impact was calculated on a ‘per patient tested’ and a ‘per member per month’ basis and as the ‘total health plan savings’, for commercial health plans ranging in size from one to five million members. It is important to note that cost savings results in the model are directly comparable year to year as no discount rate was used in this model.

*Sensitivity analyses*

To assess the model’s sensitivity to changes in specific inputs, Individual model assumptions on the clinical treatment paradigm and cost inputs were varied across a range of plausible values and the overall cost savings per patient over 3 years was recalculated. For this univariate analysis, each model input was changed in a way that lowered the cost savings (‘financially conservative’) and in a way that increased cost savings (‘financially aggressive’). The assay’s cost impact per patient over the first 3 years was reassessed using the minimum and maximum plausible value of each major assumption.

**Results**

**Overall savings**

The average cumulative cost of treating a patient with localized prostate cancer at Year 10 in the Typical Practice Scenario was approximately \$70,074 per patient. In the Prolaris Scenario, the average cumulative cost was approximately \$67,945 – a savings of \$2129 per patient tested after accounting for the cost of the test (Table 5). Throughout the duration of the model, there was no year in which the Prolaris Scenario resulted in increased cumulative costs compared with the Typical Practice Scenario, meaning that using the test results in savings to the payer regardless of the payer’s economic time horizon (Table 5).

The economic impact varied across each AUA risk group. The AUA low-risk group generated the greatest cost savings due to a significant reclassification of patients into management with AS. Although the AUA intermediate-risk group also generated significant cost savings because many patients initially switched to AS, these savings were eroded over time as the majority of those patients ultimately chose definitive treatment. Table 6 illustrates this cost-savings dynamic over time for each risk group, as well as the overall cost savings per patient after taking into account the relative distribution of AUA risk groups in the general population.

Based on cited epidemiological rates, a typical commercial health plan of five million members can expect to insure approximately 3078 patients who receive new prostate cancer diagnoses per year [53]. Use of the test in all AUA low- and intermediate-risk patients would result in approximately 2370 patients tested. Commercial insurers are most focused on the impact of an intervention over the first 3 years, given the frequency with which patients change insurance plans. On average, after 3 years >50% of members will have changed or left a typical plan [54,55]. Thus, the first 3 years was selected for assessing the economic impact on a typical commercial insurer. The model demonstrated that testing these patients would result in approximately \$4.5 million in savings over 3 years. This equates to approximately \$0.11 in savings per member, per month for the health plan. Table 7 summarizes the

**Table 6. Cumulative cost savings per patient by risk group.**

	Cumulative cost per patient at year after diagnosis			
	Year 1	Year 3	Year 5	Year 10
AUA low risk	\$6986	\$4376	\$4270	\$5039
AUA intermediate risk	\$396	-\$1084	-\$1354	-\$1363
<b>Overall</b>	<b>\$3991</b>	<b>\$1894</b>	<b>\$1713</b>	<b>\$2129</b>

Cost savings by AUA risk group. The cumulative cost savings per patient was modeled for AUA low- and intermediate-risk groups. Positive numbers represent cost savings whereas negative numbers represent cost increases. Although the AUA intermediate-risk group costs increase in year 3 and onward, it is possible that results would differ if the intermediate-risk group was broken out into 'favorable' and 'unfavorable' risk groups, as is commonly done in clinical practice. This distinction was not modeled in the current study because extensive data on the treatment mix for these subgroups are not yet available to support robust model inputs.

AUA: American Urological Association.

**Table 7. Economic impact of the polaris test on costs to a commercial health plan.**

	(A) Number of localized aua low- and intermediate-risk prostate cancer patients	(B) Cumulative cost at year 3 in the typical practice scenario	(C) Cumulative cost at year 3 in the polaris scenario	(D) Cumulative savings with polaris at year 3
Per tested patient	1	\$20,797	\$18,903	\$1894
1-million member commercial health plan	474	\$9,857,686	\$8,959,825	\$897,861
5-million member commercial health plan	2370	\$49,288,431	\$44,799,127	\$4,489,303

Economic impact of the test. (A) Total number of patients with localized prostate cancer and AUA low- or intermediate-risk disease in the plan. The number of patients with AUA low- and intermediate-risk disease per health plan is based on published rates of the incidence of prostate cancer in the general population and published stage distribution rates. The Prolaris Scenario assumes 100% of low- and intermediate-risk health plan members receive the Prolaris test. (B) Total cost of managing all of the patients in the plan with localized prostate cancer in the Typical Practice Scenario at year 3. (C) Total cost of managing all of the patients in the plan with localized prostate in the Prolaris Scenario at year 3. (D) Cumulative savings per patient tested at year 3.

AUA: American Urological Association.

cost savings that plans would achieve after using the test in a single-incident patient cohort based on a commercial health plan size of one million or five million members.

### Sources of savings

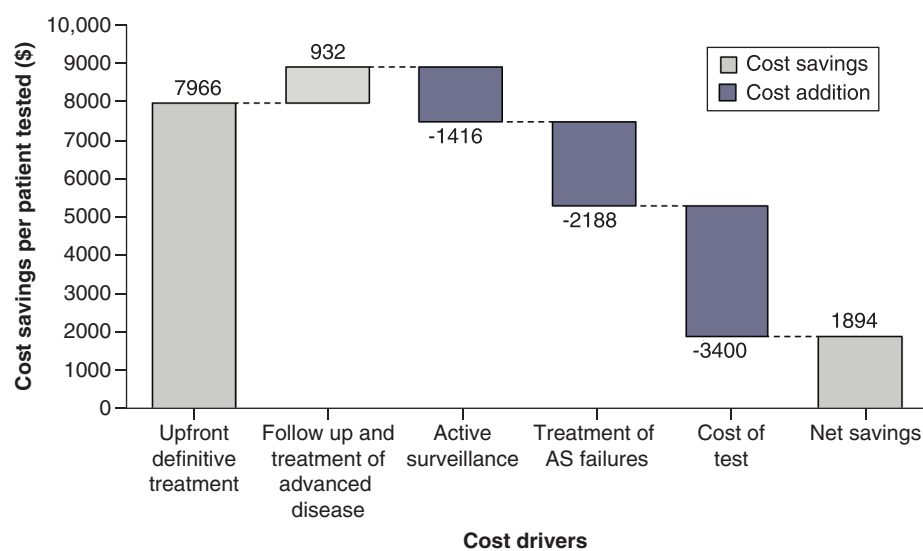
Figure 1 demonstrates the cumulative cost savings by source, modeled over 3 years. With the significant increase in the utilization of AS in the modeled cohort, there was an average reduction of \$7966 in upfront treatment costs per patient. In addition, there was an average cost savings of \$932 from definitive treatment follow-up and downstream treatment of advanced disease over the 3-year period. These cost savings were offset by the addition of AS costs, which averaged \$1416 per patient, as well as costs associated with the definitive treatment of patients that fail AS, which averaged \$2188 per patient. Finally, after accounting for the cost of the test (\$3400), the resultant cost savings was approximately \$1894 per patient tested.

### Sensitivity analysis

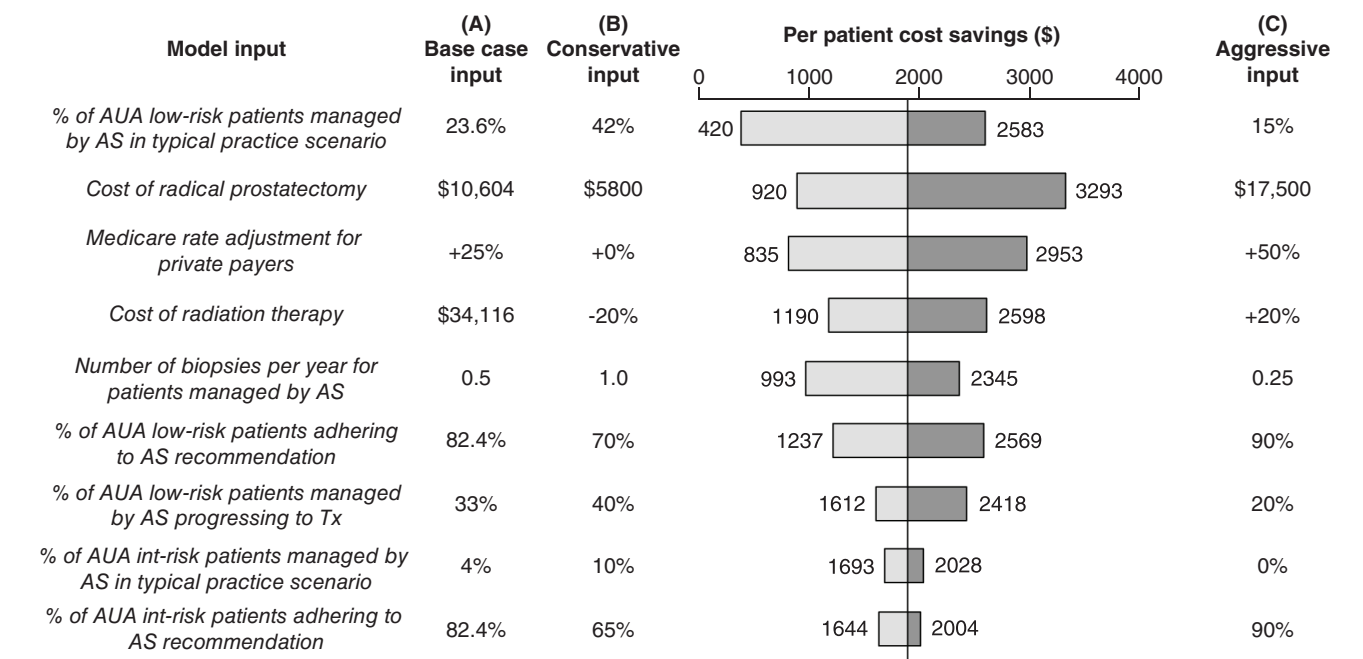
No single input, when changed within a reasonable range of values, caused the model to project that the test was no longer cost-saving (Figure 2). The results of the sensitivity analysis are shown in Figure 2. Several key assumptions drove the model, including, the percentage of AUA low-risk patients managed by AS in the Typical Practice Scenario, the cost of RP, the percentage markup that private payers pay relative to Medicare for certain procedures and the cost of RT. The model was also driven by the number of biopsies performed per year for patients managed by AS and the percentage of AUA low-risk patients that adhere to the recommendation for AS after receiving the test.

### Discussion

Previous economic analyses have demonstrated that increasing the use of AS can result in savings compared with single-modality therapy, but this option has not been universally embraced and fully implemented in clinical practice due in part to the difficulty of properly selecting patients with less aggressive disease. In addition, AS is not the optimal approach for all patients or even all low-risk patients. In a subset of patients, prostate cancer can progress quickly if left untreated. Unfortunately, the tools historically used to risk-stratify patients are insufficient



**Figure 1. Source of model savings.** Source of model savings. Analysis of the factors in the management of AUA low- and intermediate-risk prostate cancer patients that resulted in cost increases or cost savings within the model. Positive numbers represent cost reductions whereas negative numbers represent cost increases. AS: Active surveillance; AUA: American Urological Association.



**Figure 2. Sensitivity analysis of model inputs.** Sensitivity analysis. The economic impact of the test over the first 3 years was reassessed using (B) more conservative inputs and (C) more aggressive inputs and compared with (A) the base case input over the 3-year period. The center axis of the graph represents the base case cost savings per patient over 3 years (\$1894 per patient). Light grey bars represent the change in cost savings with more conservative inputs and dark grey bars represent the cost savings with more aggressive inputs. AS: Active surveillance; Int: Intermediate; Tx: Therapy.



in their ability to identify patients likely to experience disease progression. Therefore, physicians are still in need of additional information when determining which treatment path to recommend to their patients.

Prolaris is a gene expression assay designed to provide additional information on the aggressiveness of a patient's prostate cancer in order to help physicians and patients determine the best treatment option. Previous studies have shown that utilizing this cell cycle gene expression assay to triage prostate cancer patients often results in a change in clinical treatment decisions and increase in the use of AS [14,15,28,56]. The economic analysis presented here demonstrates that these changes in treatment patterns would also result in significant short- and long-term cost savings compared with use of standard clinicopathologic tools.

Much of the reduction in cost to payers is derived from the increased use of AS in the subset of AUA low-risk patients who have less aggressive disease. Given that AUA low-risk patients account for nearly half of patients with incident-localized prostate cancer, this represents a significant opportunity for savings. Additional savings are also accrued through the increased use of AS in intermediate-risk patients. These savings are realized in the first year and reverse over time, due to the higher rate of AS failure in AUA intermediate-risk patients. Despite this, there is still an overall cost savings per patient when the distribution rate of AUA risk groups in the general population is accounted for.

Incorporation of the cell cycle progression gene expression assay is projected to result in a reduction in the overall cost to payers of treating a cohort of patients with prostate cancer, even after accounting for added costs, including the cost of the test and the cost of biopsies and office visits associated with AS. Per-patient cost savings are greatest to payers within the first year after patients are tested and placed on AS because the bulk of the cost savings is derived from the reduction in the upfront costs of definitive treatment. The cumulative cost savings decline after the first year due to the interplay between cost savings associated with follow-up for definitive treatment and treatment of advanced disease and the cost additions associated with patients that ultimately fail AS and are placed on definitive treatment.

## Limitations

Although several limitations exist when modeling real-world costs associated with clinical care using an *in silico* model, this model benefited from the availability of real-world clinical utility data demonstrating how clinicians use the results of the test to guide treatment. Many *in silico* models have been built based on the assumption that physicians will adhere perfectly to the results of the test when treating patients. However, it is well recognized that compliance in real-world practice is not always the case due to a multitude of other clinical factors at play. For this analysis, populating the model with real-world data on adherence to the test recommendations for AS enhanced the robustness of the output and further supports validates the likelihood that the savings are transferable to a real-world setting. Furthermore, the AS adherence and failure rates used in this model were conservative, as it is reasonable to hypothesize that these rates would further improve in a real-world setting with increased confidence in the cell cycle risk score's stratification and predictive capabilities. For example, this model does not take into account that fewer patients may progress from AS to definitive treatment in the Prolaris Scenario due to patient choice and because they would have lower average predicted risks.

This study is subject to a number of limitations. Recognizing that the quality and reliability of any budget-impact model is directly related to the data used to generate it, this analysis used both an extensively sourced clinical paradigm and associated cost inputs based on validated reimbursement practices. However, the data are based on a hypothetical cohort of patients and the inputs may therefore not be perfectly representative of a given payer's management of prostate cancer patients. If the clinical paradigm is not reflective of clinical practice within a payer's physician network, the actual cost savings may differ from the model outputs. Populating the model with data specific to a given patient or provider mix might provide a more accurate representation of the impact of the test for a given payer. For example, RP costs for payers may differ from the conservative inputs used in this study. Indeed, other studies estimating prostatectomy costs based on Medicare reimbursement rates have suggested a range of \$5900–17,500 and these inputs have a significant effect on the cost savings of the Prolaris Test Scenario, as seen in the sensitivity analysis [57]. Further evaluation of the test using real-world data would provide a more robust understanding of the cost savings generated in the Prolaris Scenario. Last, clinical data inputs are based on averages and it is therefore difficult to statistically analyze the results of the study.

Another limitation of the model is the decision to exclude nonpayer-related expenses related to prostate cancer. Incorporating these costs into the model would likely serve to increase the cost savings of the Prolaris Scenario, because a significant increase in AS would result in less of a decrease in productivity in the workplace [58]. In

addition, this model does not incorporate the treatment of all potential side effects associated with the treatment of prostate cancer, such as the costs associated with the treatment of depression after treatment due to urinary and sexual side effects. If included, these factors would also increase the cost savings of the Prolaris Scenario.

Other limitations to the model exist. The model assumes utilization of the test in all AUA low- and intermediate-risk patients; use of the test in a different set of patients with prostate cancer could positively or negatively alter the economic impact of the test. Furthermore, clinicians frequently sub-classify intermediate-risk prostate cancer into 'favorable' or 'unfavorable' risk subgroups. This distinction was not modeled in the current study because extensive data on the treatment mix for these subgroups is not yet available to support robust model inputs. As data become available, future studies could build upon the model to assess how the test's clinical utility and associated cost savings differ between these groups.

Despite these limitations, robust sensitivity analyses around various parameters demonstrated that the model was not driven by a single input or assumption, indicating that even moderate discrepancies between the inputs used to populate the model and those associated with a given payer would still result in substantial cost savings. This was true even when more conservative inputs were modeled for key parameters. For example, even when higher baseline AS rates were used in the Typical Practice Scenario, the Prolaris Scenario still resulted in cost savings. One study that analyzed data from The Surveillance, Epidemiology and End Results Program has suggested that AS use is higher than the inputs used in the current model, with approximately 42% of AUA low- and 10% of AUA intermediate-risk patients utilizing AS in 2015 [7]. While modeling these conservative inputs for the Typical Practice Scenario did have a significant impact on the cost savings, neither individually resulted in the Prolaris scenario no longer being cost saving. This finding was also true when both values (for AUA low- and intermediate-risk rates) were input to the model. Furthermore, it is plausible that adherence to a recommendation of AS in the AUA intermediate-risk group should be lower than adherence in the low-risk group, given the increased clinical risk and patient anxiety of the group. Regardless, the sensitivity analyses demonstrated that the cost savings were not substantially affected by a more conservative input of 65% adherence that some reports have suggested for the intermediate-risk group [59].

## Conclusion

The health economic evaluation of the impact of the cell cycle gene expression assay demonstrates that use of the test within a US commercial health plan has the potential to result in cost savings to payers. These savings are primarily the result of increased use of AS in low- and intermediate-risk patients with less aggressive disease. Further studies that assess the impact of the assay in collaboration with third-party payers could be performed to validate these findings and refine the economic impact for a given health plan in a real-world setting.

### Summary points

- Prostate cancer represents a significant portion of cancer spending in the USA today.
- A key driver of these costs is the widespread use of immediate surgical and radiation treatment for the majority of patients upon diagnosis.
- Prior studies have established that broader incorporation of active surveillance, guided by additional prognostic tools, may mitigate the growing economic burden of localized prostate cancer in the USA.
- This study sought to further explore the potential of a particular gene expression-based prognostic tool to address this unmet need.
- A deterministic, decision-analytic model was developed to estimate the economic impact of the Prolaris test on a US commercial health plan.
- When adopted in American Urological Association low- and intermediate-risk patients, the cell cycle gene expression assay was projected to reduce costs by \$1894 per patient tested over 3 years, growing to \$2129 per patient over 10 years, after accounting for the cost of the test itself.
- For a large health plan with five million members, this would translate to approximately \$4.5 million in savings over 3 years, which is the average time period commercial insurers are most focused on an intervention's impact given frequency of member churn.
- The majority of savings was derived from reduced use of initial definitive treatment as a result of increased use of active surveillance.
- When employed in clinical practice under the assumptions used in this study, the cell cycle gene expression assay reduces the overall cost of managing prostate cancer patients by better tailoring patient management to disease aggressiveness.

### Author contributions

G Gustavsen performed conceptualization of study, project administration, supervision, methodology, writing – original draft preparation, writing – review and editing. K Taylor performed data curation, formal analysis, investigation and methodology, writing – review and editing. D Cole performed data curation, formal analysis, investigation, methodology and writing – review and editing. L Gullet performed data curation, formal analysis, investigation, methodology and writing – review and editing. N Lewine performed data curation, formal analysis, investigation, methodology and writing – review and editing.

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