

Use of the 4Kscore Test to Predict the Risk of Aggressive Prostate Cancer Prior to Prostate Biopsy: Overall Cost Savings and Improved Quality of Care to the US Healthcare System

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The 4Kscore® Test (BioReference Laboratories, Elmwood Park, NJ) is a blood test that accurately determines the risk of aggressive prostate cancer and significantly reduces prostate biopsies and associated overdiagnosis and overtreatment of indolent cancer. A budget impact model was developed to test the hypothesis that the 4Kscore Test can improve quality of care and deliver cost savings for patients who are suspected of having prostate cancer and would otherwise undergo prostate biopsy under the current standard of care (SOC) in the United States. The direct costs (diagnosis plus treatment) utilized in the model are based on Medicare payment data and were calculated over a 1-year time horizon. The model compares SOC, in which all patients have prostate biopsy, to a “4Kscore strategy,” in which the 4Kscore Test is used to guide the decision to biopsy the prostate. A set of one-way sensitivity analyses was conducted to examine the robustness of the findings. Savings of more than \$169 million (15.6% of total SOC costs) were realized in the 4Kscore strategy versus SOC (\$917 M versus \$1,086 M, respectively) in a cohort of 100,000 patients. Sensitivity analyses demonstrated that the findings are robust. Most cost savings for the 4Kscore strategy were realized in patients who, when managed by SOC, are found to have no prostate cancer or Gleason score 6 pathology. The patients with Gleason score 6 exhibited the greatest benefits from the 4Kscore strategy, avoiding both an unnecessary prostate biopsy and subsequent overtreatment. The 4Kscore Test was shown to significantly reduce costs to the healthcare system while

improving patients' quality of care. Providers and their patients suspected of having prostate cancer should consider using the 4Kscore Test prior to proceeding with prostate biopsy.

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KEY WORDS

4Kscore Test • Prostate cancer • Prostate biopsy • PSA screening • Cost savings

Prostate cancer is the most common noncutaneous cancer diagnosed in men and the second leading cause of cancer deaths in men; more than 26,000 men were estimated to die from the disease in the United States in 2016.¹ Typically, prostate cancer is suspected following routine screening with a prostate-specific antigen (PSA) blood test and/or digital rectal examination. In either case, abnormal findings typically result in referral to a urologist who will likely recommend a prostate biopsy.² It is estimated that approximately 700,000 to 1 million prostate biopsies are performed annually in the United States.³⁻⁵ Contemporary decision making with PSA testing has a low specificity and high false-positive rate for aggressive prostate cancer (defined as Gleason score ≥ 7 prostate cancer). The majority of these biopsies discover no cancer (approximately 50% of all biopsies performed) or an indolent, non-life-threatening, Gleason score 6 cancer (approximately 25% of all biopsies performed).⁶ Men who undergo an invasive prostate biopsy are subject to anxiety and associated complications that sometimes require hospitalization.⁷ Moreover, men found to have low-grade, Gleason score 6 prostate cancer are often treated aggressively with surgery or

radiation, two-thirds of whom are confirmed to have indolent, low-grade disease.⁸ Thus, many of these men were unnecessarily subjected

concluded that the harms of overdiagnosis and overtreatment from PSA screening outweigh the mortality reduction benefits.

The USPSTF concluded that the harms of overdiagnosis and overtreatment from PSA screening outweigh the mortality reduction benefits.

to complications such as incontinence and impotence. Morgan and colleagues⁹ and Wilt and colleagues¹⁰ have defined the overdiagnosis and overtreatment of nonclinically significant disease as low-value, high-cost care. Specifically, low-value care is defined as care for which the health benefits of an intervention are exceeded by its harms and costs.¹¹ Low-value care is also defined as overuse, when care is provided in the absence of a clear medical basis.¹²

Overall, the current prostate cancer diagnostic and treatment paradigms represent a significant financial burden on the US healthcare system.¹³ The United States Preventive Services Task Force (USPSTF) has recommended against all PSA-based screening for prostate cancer,¹⁴ despite the fact that a mortality reduction exceeding 50% has been observed since PSA-based screening was introduced in the 1990s.¹⁵ The USPSTF

The 4Kscore® Test (BioReference Laboratories, Elmwood Park, NJ) was designed to address the dilemma presented by routine PSA screening. The 4Kscore Test is a blood-based diagnostic test that identifies a man's risk for aggressive prostate cancer. A low 4Kscore Test result ($< 7.5\%$) usually indicates that a prostate biopsy can be safely deferred. The 4Kscore Test is indicated for men who have never undergone a prostate biopsy (ie, biopsy naive) or have had a prior biopsy with no cancer detected. The 4Kscore Test is included in the National Comprehensive Cancer Network clinical practice guidelines for prostate cancer early detection.²

Voigt and associates³ conducted a meta-analysis on seven clinical studies of the 4Kscore Test conducted in Europe and suggested that, if applied to the US population, the 4Kscore Test would provide substantial cost savings based

solely on its potential to reduce unnecessary biopsies. Parekh and associates⁶ conducted a multicenter, prospective study that validated the 4Kscore Test as a precise diagnostic test for US patients. Since then, the performance of the 4Kscore Test has been further validated in another US-based prospective, multicenter clinical study in the US Department of Veterans Affairs hospital system in a predominantly African American population.¹⁶ In a retrospective clinical utility study, the 4Kscore Test reduced overall prostate biopsies by almost 65%.¹⁷

In this study, we used clinical data from the 4Kscore Test US validation study,⁶ and created a budget impact model that is inclusive of all direct costs to patients during a 1-year time frame. The objectives of this study were (1) to evaluate the cost savings of the 4Kscore Test on the 1-year total costs for the detection of prostate cancer and follow-up treatment after diagnosis; and (2) to determine if using the 4Kscore Test prior to prostate biopsy can provide cost savings to the US healthcare system through reduced biopsies, overtreatments, and cost of complications resulting from overtreatment, while ensuring appropriate treatment for men who have aggressive prostate cancer.

Methods

Study Design

A decision tree and budget impact model was developed to test the hypothesis that the 4Kscore Test provides cost savings and clinical benefits to men suspected of having prostate cancer. These patients would otherwise undergo a prostate biopsy under the current standard of care (SOC). The model was applied to a theoretic cohort of 100,000 patients suspected of having prostate cancer based on a urologist's evaluation. The patient characteristics of

this cohort were assumed to be very similar to those described in the 4Kscore US validation study.⁶ This number of patients (100,000) is of the same magnitude as the total number of Medicare patients (154,600) who underwent prostate biopsies in the 2015 fiscal year, according to the National Summary Data File of the US Centers for Medicare & Medicaid Services.¹⁸

Model metrics (including costs and probabilities) were derived from the peer-reviewed literature and from the Medicare Provider Utilization and Payment Data (Figure 1, Table 1). On the 4Kscore arm of the decision tree, patients with a 4Kscore $\geq 7.5\%$ would subsequently undergo a prostate biopsy. Those with a 4Kscore $< 7.5\%$ would be considered at low risk for aggressive prostate cancer based on the user guidelines from the 4Kscore Test developer (BioReference Laboratories, Elmwood Park, NJ), and, therefore, would not undergo a prostate biopsy. On the SOC arm, all patients would undergo a prostate biopsy. On both strategy arms, the patients' biopsy results would lead to certain treatment or active surveillance paradigms typically used by urologists in the United States (Figure 2).

Data Sources

The probabilities of biopsy outcomes for the SOC arm and the 4Kscore arm, and the probabilities of the 4Kscore groups (4Kscore $< 7.5\%$ vs 4Kscore $\geq 7.5\%$), were derived from a multicenter prospective trial of the 4Kscore Test (Figure 1A-C).⁶

We conducted a thorough review of the published clinical and health economics studies regarding the likelihood of use for various treatment options available to patients diagnosed with Gleason score ≥ 6 prostate cancer.^{19,20} The current study used the recently published probabilities from Cooperberg and

Carroll,¹⁹ which estimated a higher proportion of men who chose active surveillance versus other more invasive and more expensive treatments. Therefore, these analyses reflected the most current SOC treatment choices and probabilities (Figure 1B and C), and helped us avoid overestimation of the cost savings of the 4Kscore strategy versus SOC by accurately reflecting the growth in adoption of active surveillance for low- and intermediate-risk patients.

Base-case costs of the biopsy-related procedures, blood tests, and office visits were obtained from a literature review after cross-referencing the Medicare national fee schedule. Base-case costs of the prostate cancer treatments were obtained from Optum (Eden Prairie, MN) and were based on a large-scale Medicare patient database (Table 1). The Optum database used to estimate these costs included the reimbursement information of approximately 1.5 million Medicare patients of record between July 2013 and July 2015.²¹

Analysis

We calculated the total costs for both SOC and the 4Kscore strategies, including all the direct costs of the 4Kscore Test (for the 4Kscore arm only), biopsy (where applicable), and any treatment costs attributable within 1 year of receiving the 4Kscore Test or undergoing the biopsy procedure. All costs are expressed in the 2016 value of US dollars. We then evaluated the budget impact on the US healthcare system by calculating the differences in the total costs and categorized costs between the SOC and the 4Kscore strategy. A set of one-way sensitivity analyses was performed using a tornado plot to evaluate the impacts of the key cost variables on the budget outcome, with increasing and decreasing the value of each cost variable by 25%.

Figure 1. (A) Model structure/decision scenario. The categoric costs are calculated weighted-averages for each patient in that category. SOC, standard of care. The probabilities of the test outcomes are based on data from Parekh DJ et al.⁶ (B, C) Estimation of the postbiopsy costs of patients with Gleason score 6 and patients with Gleason score ≥ 7 . The estimated risk group breakdown and probabilities of treatment options were calculated according to the method described in Cooperberg and Carroll.¹⁹ The risk group proportions were estimated based on a US patient cohort, from Halpern JA et al.⁵

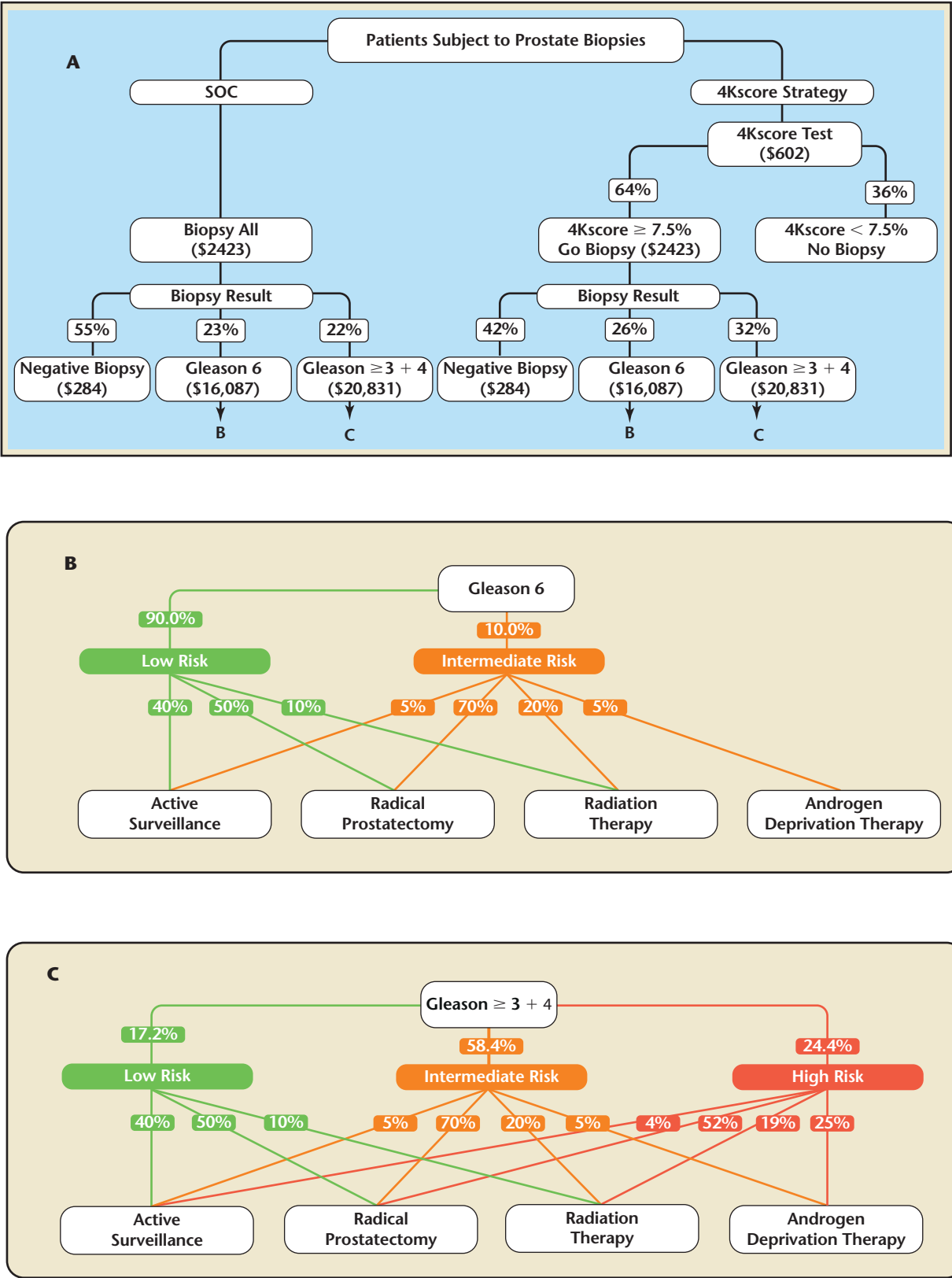


TABLE 1**Summarized Cost Components of Diagnostic and Treatment Options**

Source/Study	Cost Category	Cost (2016 \$)
	Prostate biopsy	2423
Medicare fee schedule; US Centers for Medicare & Medicaid Services ²²	Prebiopsy cost	123
Medicare fee schedule; US Centers for Medicare & Medicaid Services ²²	TRUS biopsy	1339
Optum ²¹	Pathology laboratory services within 3 mo after biopsy (weighted average cost per biopsy)	274
Medicare fee schedule; US Centers for Medicare & Medicaid Services ²² (The calculation assumes 30% of biopsy patients undergo an MRI 6 months prior to or after biopsy)	Cost of MRI before or after biopsy	604
Aubry W et al ²³	Weighted average cost of biopsy complication (per patient who undergoes biopsy)	398
Medicare fee schedule; US Centers for Medicare & Medicaid Services ²²	Postbiopsy physician evaluation	108
Medicare fee schedule; US Centers for Medicare & Medicaid Services ²²	4Kscore Test^a	602
	Negative biopsy follow-up	284
Optum ²¹	Weighted average cost of confirmation tests	234
Optum ²¹	Confirmation PSA test following the negative biopsy	50
	Gleason score 6 postbiopsy costs	16,087
Calculated based on treatment costs below, applied to Figure 1B	Gleason score 6 treatment	15,127
Calculated based on treatment complication costs below, applied to Figure 1B	Gleason score 6 treatment complication costs	605
Optum ²¹	Weighted average cost of confirming tests after biopsy	234
Medicare fee schedule; US Centers for Medicare & Medicaid Services ²²	Cost of a second opinion (urology visit and pathology reading), applied to only 40% of patients	120
	Gleason score 7 and higher postbiopsy costs	20,831
Calculated based on treatment costs below, applied to Figure 1C	Gleason score 7 and higher treatment costs	20,009
Calculated based on treatment complication costs below, applied to Figure 1C	Gleason score 7 and higher treatment complication costs	766

(Continued)

Source/Study	Cost Category	Cost (2016 \$)
Medicare fee schedule; US Centers for Medicare & Medicaid Services ²²	Gleason score 7 and higher cost of a second pathology opinion (applied to 40% of the Gleason score 3 + 4 patients only)	56
First-year treatment costs		
Optum ²¹	Active surveillance	2380
Optum ²¹	RP	20,086
Optum ²¹	RT	34,116
Optum ²¹	ADT	12,338
Cooperberg MR et al ²⁴	RP complication cost (weighted average per patient who undergoes RP)	980
Cooperberg MR et al ²⁴	RT complication cost (weighted average per patient who undergoes RT)	870

The items in **bold** are those used in Figure 1A.

*The 4Kscore Test is available from BioReferences Laboratories (Elmwood Park, NJ).

ADT, androgen deprivation therapy; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiation therapy; TRUS, transrectal ultrasound.

All analyses were conducted with TreeAge Pro 2016 (Williamstown, MA) and Microsoft® Office Excel 2013 (Redmond, WA). We followed the International Society for Pharmacoeconomics and Outcomes Research (Lawrenceville, NJ) principles of good practice for budget impact analysis in designing the study and analyzing the study data.

Results

Base Case

The line items associated with the cost savings of the 4Kscore strategy versus SOC over a 1-year time horizon are shown in Table 2. In the base-case analysis, the 1-year time horizon costs associated with a theoretic cohort of 100,000 patients receiving a prostate biopsy according to SOC was \$1.086 billion. On the 4Kscore Test arm, only patients with a 4Kscore $\geq 7.5\%$ would undergo a biopsy procedure and follow-up treatment, leading to a cost reduction of more than \$169 million (–15.6%) compared with the SOC arm. The savings stem from the fact that the 4Kscore Test would prevent 36% of the biopsy procedures; this category alone accounted for saving \$87.2

million (38% of the total savings). Using the 4Kscore strategy, the number of negative biopsy results would be reduced by 51% from 55,000 to 26,880. The number of Gleason score 6 biopsy outcomes would be reduced by 27%—or 6360—from 23,000 to 16,640. The postbiopsy cost savings for patients who would otherwise be diagnosed with Gleason score 6 disease contributed \$102 million in savings (45% of the total savings). The average cost to detect and treat each high-grade cancer case was reduced by \$4587 in the 4Kscore strategy arm compared with the SOC arm (\$49,373 for SOC vs \$44,786 for the 4Kscore strategy).

and the cost of radical prostatectomy. For instance, if the biopsy cost is increased by 25%, the maximum expected cost saving of the 4Kscore strategy versus SOC would reach \$1912 per patient.

Discussion

The predictive performance of the 4Kscore Test and its proprietary combination of kallikrein biomarkers has been extensively studied in 12 clinical studies of more than 20,000 patients and reported in several peer-reviewed publications.^{6,25-27} These previous studies have consistently demonstrated

... based on a cohort of 100,000 men suspected of having clinically significant prostate cancer requiring a prostate biopsy, the 4Kscore Test has resulted in an average net savings of \$169 million (\$1694 per patient) during the 1-year period after the first urologist visit.

Sensitivity Analysis

The one-way sensitivity analyses using a tornado plot (Figure 2) demonstrated that the cost savings of the 4Kscore strategy are robust when the cost variables fluctuate by $\pm 25\%$. The model results were most sensitive to the biopsy cost

that the 4Kscore Test, if performed prior to proceeding with a prostate biopsy, can significantly reduce the number of unnecessary biopsies and overtreatment of indolent disease. In this study, based on a cohort of 100,000 men suspected of having clinically significant prostate

TABLE 2

Base Case Budget Impact Over a 1-year Time Horizon: SOC vs 4Kscore Strategy for a 100,000-patient Targeted Population (Patients Recommended to Undergo Biopsy by the Current SOC)

Cost Category	SOC Strategy: All Patients Receive a Biopsy		The 4Kscore Strategy: (Biopsy-only Patients With 4Kscore \geq 7.5%)		Cost Savings of 4Kscore Strategy vs SOC \$ (%)	Additional Costs of 4Kscore Strategy vs SOC (\$)
	Patients Involved (N)	Cost (\$)	Patients Involved (N)	Cost (\$)		
4Kscore ^a Test	0	0	100,000	60.2 M		60.2 M
Biopsy-related	100,000	242.3 M	64,000	155.1 M	87.2 M (38)	
Follow-up on negative biopsy result	55,000	15.6 M	26,880	7.6 M	8 M (3)	
Follow-up on Gleason score 6 patients	23,000	370 M	16,640	268 M	102 M (45)	
Follow-up on Gleason score \geq 7 patients	22,000	458.3 M	20,480	426.6 M	31.7 M (14)	
Total annual cost (\$)		1086.4 M	917.0 M		Net savings: 169.4 M	
Annual cost per patient (\$)		10,864	9170		Net savings: 1694 per patient	

^aThe 4Kscore Test is available from BioReference Laboratories (Elmwood Park, NJ).
SOC, standard of care.

cancer requiring a prostate biopsy, the 4Kscore Test has resulted in an average net savings of \$169 million (\$1694 per patient) during the 1-year period after the first urologist visit. All of these men would have undergone a prostate biopsy under SOC. Thus, the savings associated with reducing unnecessary biopsies and treatments will recover nearly three times the upfront cost of the 4Kscore Test. The data also demonstrated that 86% of the cost

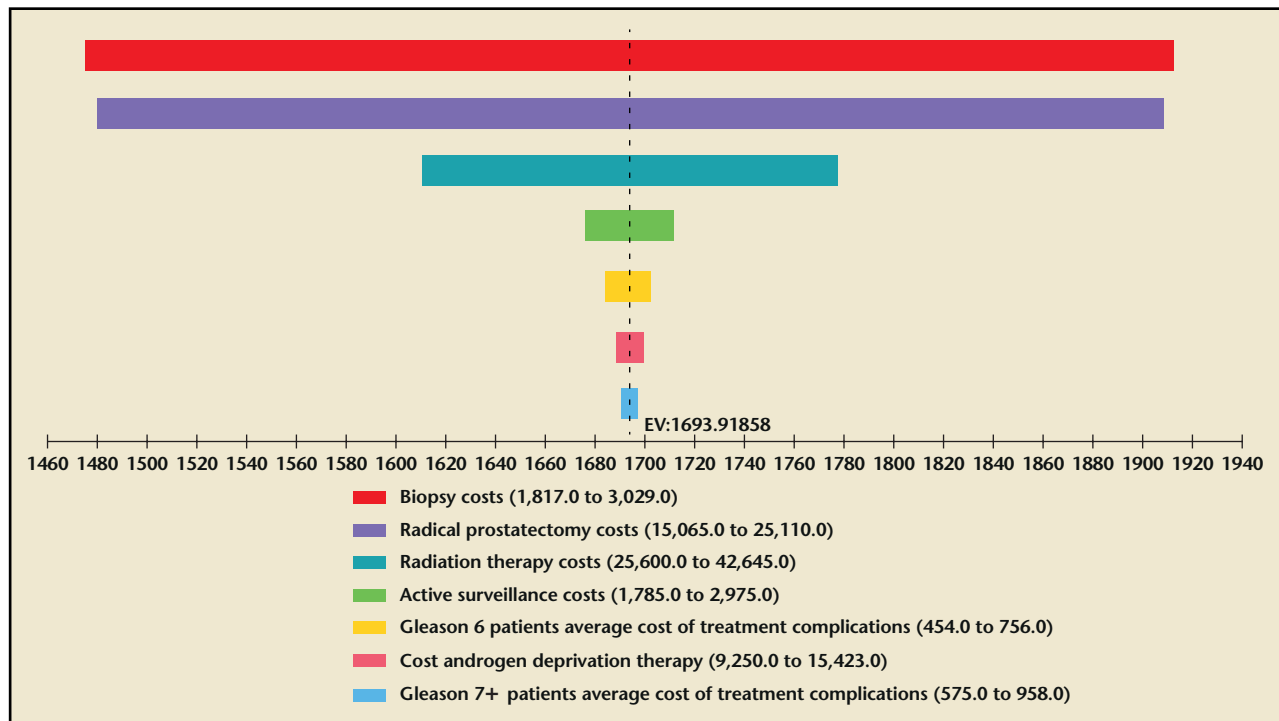
savings resulted from men who, if biopsied, would either be cancer free or diagnosed with indolent Gleason score 6 disease, and could have avoided the biopsy altogether.

According to the National Summary Data File of the US Centers for Medicare & Medicaid Services, 154,600 Medicare patients in the 2015 fiscal year underwent prostate biopsies.¹⁸ At the cost savings of \$1694 per patient, adoption of the 4Kscore strategy could

potentially save the Medicare system \$262 million annually.

The cost of some medical procedures, such as a prostate biopsy, has decreased in recent years, whereas other costs, such as those of radical prostatectomy and radiotherapy, have remained stable or increased due to regional differences in reimbursement. The utilization of magnetic resonance imaging (MRI) and active surveillance has also increased in recent

Figure 2. Tornado plot of sensitivity analysis. Horizontal axis is cost savings in US dollars (\$).



years. In the base-case analysis, the model reflects 2016 Medicare reimbursement rates for prostate biopsy and the recent trends in prostate cancer treatment selection. These considerations ensured that cost savings were not overestimated. In addition, to account for the uncertainty and changing trends in treatments and costs, a series of one-way sensitivity analyses across a broad range ($\pm 25\%$) of costs was also used. The results of the sensitivity analyses support the robustness of the estimated savings in these analyses.

In a blinded, prospective clinical trial of the 4Kscore in a US population of 1012 men suspected of having clinically significant prostate cancer, the 4Kscore Test had 30% to 58% biopsy reduction potential, with very few aggressive prostate cancer diagnoses delayed ($< 2\%$ of all patients when utilizing a 4Kscore cutpoint of 7.5%).⁶ In particular, no biopsies of patients with Gleason

score 8-10 cancers were delayed, and the delayed diagnoses of men with Gleason score 7 cancer were not clinically significant in most cases; the majority were likely to be managed by active surveillance rather than aggressive treatment. Furthermore, men with a 4Kscore $< 7.5\%$ are at very low risk for developing adverse long-term outcomes. In a large-scale case-control study, Stattin and colleagues²⁷ showed that men with an elevated PSA level, but without a diagnosis of prostate cancer and a 4Kscore $< 7.5\%$, are unlikely to develop distant prostate cancer metastases

their risk of distant prostate cancer metastases 20 years later is $< 2\%$.

Since the USPSTF 2012 recommendation against routine prostate cancer screening based on PSA testing, there has been no medical consensus as to how to screen and identify men with aggressive prostate cancer. However, since the USPSTF recommendations were released, several diagnostic tests have been introduced to stratify men by prostate cancer risk. The 4Kscore Test has been extensively studied, with clinical research spanning over a decade in more than 20,000

Performing the 4Kscore Test prior to a prostate biopsy provides a noninvasive alternative method for accurate prediction of risk for aggressive prostate cancer and can significantly reduce unnecessary prostate biopsies.

up to 20 years later. Thus, men suspected of having prostate cancer but who have a 4Kscore $< 7.5\%$ can be monitored, knowing that

men,^{6,25-27} and has been included in urologists' guidelines both in the United States² and Europe.²⁸ Performing the 4Kscore Test prior

to a prostate biopsy provides a noninvasive alternative method for accurate prediction of risk for aggressive prostate cancer and can significantly reduce unnecessary prostate biopsies. Use of the 4Kscore risk stratification helps to address the concerns of overdiagnoses and overtreatment of indolent prostate cancer associated with contemporary PSA-based prostate cancer screening. These benefits will accrue not only in terms of the improved quality of care (ie, high-value care) for patients, but also as significant cost savings for prostate cancer early detection programs.

This study provides the analyses on the 1-year saving of the SOC versus 4Kscore strategy and lays the groundwork for future studies that investigate the long-term cost-effectiveness impact of the 4Kscore, with consideration of patients' costs and health-based quality of life over many years.

Strengths of the Analyses

Actual data collected from a large-scale, multicenter clinical study in the United States were used to precisely estimate the probability input variables for the budget analysis model. The data from large databases of actual Medicare patients were also used to estimate many of the cost input variables for the model, and these data were obtained through one of the largest healthcare service organizations in the United States.

The most recent literature and data evidence was referenced to account for recent cost and treatment trends, such as changing treatment options (ie, active surveillance) and decreasing costs of prostate biopsy. Therefore,

overestimation of biopsy costs and treatment costs was avoided, resulting in a robust, up-to-date cost savings estimation.

Limitations of the Analyses

The reference used in calculating the treatment costs¹⁶ did not include probabilities of combined treatments (such as radiotherapy following radical prostatectomy). However, because the probabilities of treatment options estimated in the referred article were obtained from an actual payer database and reflect the most current trends in prostate cancer treatment, these data remain the most valid and up-to-date among all sources. In addition, the combined treatments are mostly applied to very aggressive cancers, which is a category of patients associated with very similar costs in both arms of the model. Therefore, the omission of combined treatments in the model did not significantly bias the cost savings estimation.

The analysis did not include patients who would typically have undergone prostate biopsies under the SOC, but instead were treated with procedures of uncon-

would further increase the savings in the 4Kscore arm.

The budget impact model did not include indirect costs, such as patients' time cost due to medical procedures and complications resulting from these procedures. Again, this would further increase the savings in the 4Kscore arm.

Conclusions

Early detection of prostate cancer results in curative treatment for the majority of men. This is a direct result of the effectiveness of PSA screening programs and the development of effective treatment modalities. The downside of these mortality reductions that stem from PSA testing is the number of men who undergo unnecessary biopsy procedures and overtreatment of indolent prostate cancer. The 4Kscore Test was designed and validated to significantly improve the specificity of detecting aggressive prostate cancer in men in whom a suspicion for clinically significant prostate cancer exists. Furthermore, the use of the 4Kscore Test to guide prostate biopsy decisions significantly reduces costs to the healthcare system compared with the SOC,

... the use of the 4Kscore Test to guide prostate biopsy decisions significantly reduces costs to the healthcare system compared with the SOC, while improving the quality of patient care.

firmed diagnostic sensitivity (ie, MRI) performed by the urologist to avoid biopsy. Although MRI costs were included if performed in conjunction with a prostate biopsy, they could not be captured if the MRI results precluded a prostate biopsy. Inclusion of the costs of these MRI procedures

while improving the quality of patient care. This study has demonstrated the 4Kscore Test provides improved quality of care by avoiding unnecessary prostate biopsies and consequent downstream treatments, complications and costs. ■

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MAIN POINTS

- The 4Kscore Test is a blood test that accurately determines the risk of aggressive prostate cancer and significantly reduces prostate biopsies and associated overdiagnosis and overtreatment of indolent cancer. A budget impact model was developed to test the hypothesis that the 4Kscore Test can improve quality of care and deliver cost savings for patients who are suspected of having prostate cancer and would otherwise undergo prostate biopsy under the current standard of care (SOC) in the United States
- Most cost savings for the 4Kscore strategy were realized in patients who, when managed by SOC, are found to have no prostate cancer or Gleason score 6 pathology. The patients with Gleason score 6 exhibited the greatest benefits from the 4Kscore strategy, avoiding both an unnecessary prostate biopsy and subsequent overtreatment.
- At a cost savings of \$1694 per patient, adoption of the 4Kscore strategy could potentially save the Medicare system \$262 million annually.
- The use of the 4Kscore Test to guide prostate biopsy decisions significantly reduces costs to the healthcare system compared with the SOC, while improving the quality of patient care.