Cost-Effectiveness of Prostate Health Index from a Managed Care Payer Perspective

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ABSTRACT

Objective: The prostate health index (*phi*) has been shown to improve diagnostic accuracy in prostate cancer (Pca) detection compared with total and free serum prostate-specific antigen (PSA). The study assessed the cost-effectiveness of early Pca detection with *phi* plus PSA, compared with the PSA test alone, from a managed care organization perspective.

Study Design: Cost-effectiveness analysis.

Methods: A Markov model estimated expected costs and utilities of Pca detection and consequent treatment using four strategies in men aged 50-75 years. The strategies differed with the PSA test thresholds (≥2 or ≥4 ng/mL) and methods (PSA alone vs. PSA plus *phi*) to determine need for a prostate biopsy. The transition probabilities were derived from the electronic medical records of males in Kaiser Permanente Southern California during 1998-2007. Health state utilities and prostate cancer-related treatment costs were obtained from the published literature.

Results: The most cost-effective strategy used the PSA plus *phi* at PSA 2-10 ng/mL to determine need for a prostate biopsy, which had the lowest cost and highest effectiveness [cost/effectiveness (C/E)=13,650/15.491, $1,099/QALY]. Next was PSA plus *phi* at PSA 4-10 ng/mL [C/E=14,095/12.364, $1,140/QALY), followed by PSA test at threshold ≥4 ng/mL [C/E=15,256/12.304, $1,240/QALY), or PSA ≥2 ng/mL [C/E=15,789/12.287, $1,285/QALY). PSA plus *phi* at PSA 2-10 ng/mL displayed a 74% to 86% probability of being cost-effective at a willingness-to-pay range of 0 to $150,000/QALY gained.

Conclusions: Using the strategy PSA plus *phi* at PSA 2-10 ng/mL for Pca detection dominated other strategies, and was an optimal strategy under a willingness-to-pay of $150,000/QALY gained.

Keywords: prostate-specific antigen (PSA), free PSA, PSA precursor form p2PSA assay, prostate health index (*phi*), cost-effectiveness analysis.

1. INTRODUCTION

The serum prostate-specific antigen (PSA) test was recommended as screening to help for early prostate cancer detection in men by the American Urological Association (AUA)[1] and the American Cancer Society[2] in combination with counseling regarding the risks and benefits of prostate cancer screening. The United States Preventive Services Task Force (USPSTF) published the recommend-dation statement regarding against PSA-based screening for prostate cancer.[3] Although the debate is continuing,[4-7] PSA level measurement remains the preferred approach for early prostate cancer detection.[6]

Currently, several PSA derivatives or biomarkers and test methods have been suggested to improve PSA specificity in prostate cancer detection. A precursor form of PSA, measured using the Access® Hybritech® p2PSA assay, has been investigated for use with Access Hybritech PSA and free PSA (fPSA) to calculate the Prostate Health Index or *phi* (Beckman Coulter, Inc., Brea, California) to distinguish prostate cancer from benign prostatic conditions. [8-11] The *phi* result is intended for use as an aid in distinguishing prostate cancer from benign prostatic conditions in men aged 50 years and older with total PSA value between 4 and 10 ng/mL, in combination with non-suspicious digital rectal examination (DRE) findings. A U.S. multicenter study of *phi* has shown its usefulness in decreasing unnecessary biopsies with improved specificity over the PSA test alone, fPSA, and free-to-total PSA test.[8] For example, at 95% sensitivity the specificity of *phi* was 16.0%, compared to 3.5% for fPSA, 6.5% for PSA, 8.4% for free-to-total PSA in the 2 to 10 ng/mL PSA range. [8] Several studies have demonstrated that *phi* has the best overall performance characteristics for prostate cancer detection when compared with the PSA and fPSA test. [9-11]

A PSA threshold of ≥ 4 ng/mL is commonly used to recommend prostate biopsy. Lowering PSA thresholds in recommending a prostate biopsy can improve the sensitivity of prostate cancer detection, but raises concerns about overdiagnosis and overtreatment. There have been reports regarding the selection of PSA thresholds for clinical use of *phi*.[8] Our study assessed the cost-effectiveness of early prostate cancer detection with PSA plus *phi* compared to the PSA test alone at two PSA thresholds (≥ 2 and ≥ 4 ng/mL) from a managed care organization perspective.

2. MATERIAL AND METHODS

2.1 The Economic Model

A Markov model was constructed with three health states (no prostate cancer, detected prostate cancer, and death). The males started prostate cancer screening at 50 years of age from the no prostate cancer state, then could move to detected prostate cancer, or remain in the same health state depending on the PSA testing result. They could also transition to non-prostate cancer-related death. The individuals in the prostate cancer state could move to death, or stay in the detected prostate cancer state.

Two PSA threshold values (2 and 4 ng/mL) were used for recommending prostate biopsy or an additional reflex test in the model. Individuals have three possible test results:

1) The test is negative (PSA < threshold value). We assumed that this result indicates no cancer detection and no biopsy would be ordered if DRE is negative.
2) The test is positive (PSA > 10 ng/mL). An individual is referred to a urologist and a biopsy would be used to confirm a diagnosis of prostate cancer.
3) The test is borderline (PSA is between the threshold value and 10 ng/mL).

Four testing strategies (PSA alone vs. PSA plus *phi* under two threshold values) were compared. For the PSA strategy, an individual is referred to a urologist and has a repeated PSA test, and then receives a biopsy for prostate cancer diagnosis. Assuming a relatively short timeframe between first PSA test and urologist referral, we therefore assumed that the repeat PSA test would essentially confirm the initial result. Nonetheless, the cost of the confirmatory PSA test was added to our model as a standard of care practice. For the strategy of PSA plus *phi*, both fPSA and p2PSA would be performed as reflex tests and *phi* could be calculated. A score of *phi* greater than 30% of weighted average relative probability of prostate cancer represents a positive test that would result in a urologist referral and prostate biopsy recommendation. Conversely, a score of 30% or less prostate cancer probability is considered negative. Individuals with a positive PSA test, but without biopsy-confirmed cancers remained at the no prostate cancer state, and continued with prostate cancer screening. We assumed that missed cancers in previous screenings could be found in subsequent screenings.

Research indicates that most cancers detected at two to four years after an initial screen (1st round) will be curable.[1,12-17] Therefore, we assumed that the detected missed cancers from previous screening have similar clinical characteristics as the cancers detected in regular screening. Although individuals with biopsy-confirmed prostate cancer have different options for care (including watchful waiting, active surveillance, and treatment procedure), there are insufficient published studies on probability of selection of care, therefore our model assumed that they moved to the detected prostate cancer state, and would receive treatment.

The movement between health states over a discrete time period is defined as "Markov Cycle", and was set to 1.5 years based on the usual practices of a managed care organization for the mean length of repeated PSA test interval. The model was iterated until the individual reached age 75 years or died, whichever came first. The model used a managed care payer's perspective, with different discount rates including 0%, 3%, 5% and 7% for costs and health utilities[18].

2.2 Data Source and Inputs Data

Transition Probabilities: Probability related to the no cancer state were obtained from two sources, 1) an analysis of male members' electronic medical records in Kaiser Permanente Southern California (KPSC) for ages 45-75 years; and, 2) a study of *phi*. [8]

Data from KPSC included active male members with at least one day of membership from 1998 to 2007. They must have been at least 45 years old on January 1, 1998, or at the end of the study period. Individuals with a history of prostate cancer before their first available PSA test were excluded. The first PSA test results were analyzed to calculate the age-specific rates and 95% confidence intervals for PSA levels, subsequent prostate cancer biopsy, and prostate cancer detection (Table 1).

Since the mortality data were not available from KPSC, age-specific mortality was taken from 2006 U.S. life tables.[19] The prostate cancer-related mortalities under two common treatment options (brachytherapy and radical 1prostatectomy) were derived from a systematic literature review by Hayes et al.[20] The transition probability of cancer-related death under 1.5 years of screening interval was calculated using the "DEALE" method.[21]

Table 1. Markov Model Probabilities in Each 1.5 Year Cycle

Model parameters	PSA threshold ≥ 2 ng/mL					PSA threshold ≥ 4 ng/mL				Data source
	Base case	SD	Min	Max		Base case	SD	Min	Max	
No Cancer Health State										
Probability of PSA<threshold										
Probability of biopsy	0.0152	0.0002	0.0147	0.0156		0.0351	0.0003	0.0345	0.0357	KPSC
Probability of prostate cancer	0.2442	0.0062	0.2320	0.2564		0.3004	0.0040	0.2926	0.3081	KPSC
Probability of PSA at threshold-10 ng/mL										
Age 45-49 years	0.1280	0.0015	0.1252	0.131		0.0278	0.0005	0.0268	0.0288	KPSC
Age 50-59 years	0.2236	0.0015	0.2207	0.2264		0.0664	0.0006	0.0652	0.0675	KPSC
Age 60-64 years	0.3370	0.0030	0.331	0.3429		0.1232	0.0014	0.1205	0.1258	KPSC
Age 65-69 years	0.4005	0.0039	0.393	0.4081		0.1620	0.0018	0.1585	0.1655	KPSC
Age 70-75 year	0.4493	0.0047	0.4402	0.4585		0.2059	0.0023	0.2015	0.2104	KPSC
Probability of having a positive *phi* test	0.7510		na	na		0.7400		na	na	Catalona[8]
Probability of biopsy	0.2232	0.0013	0.2206	0.2257		0.4176	0.0027	0.4123	0.4229	KPSC
Probability of prostate cancer in PSA alone test strategy	0.3017	0.0030	0.2958	0.3077		0.2836	0.0038	0.2761	0.2911	KPSC
Probability of prostate cancer in individuals with a positive *phi* test	0.2963	0.0294	0.2387	0.3538		0.3029	0.0354	0.2341	0.3728	Catalona[8]
Probability of PSA>10 ng/mL										
Age 45-49 years	0.0060	0.0003	0.0055	0.0065		0.0060	0.0003	0.0055	0.0065	KPSC
Age 50-59 years	0.0145	0.0003	0.014	0.0151		0.0145	0.0003	0.014	0.0151	KPSC
Age 60-64 years	0.0313	0.0007	0.0299	0.0327		0.0313	0.0007	0.0299	0.0327	KPSC
Age 65-69 years	0.0485	0.0010	0.0464	0.0505		0.0485	0.0010	0.0464	0.0505	KPSC
Age 70-75 year	0.0770	0.0015	0.074	0.0799		0.0770	0.0015	0.074	0.0799	KPSC
Probability of biopsy	0.4649	0.0054	0.4544	0.4755		0.4649	0.0054	0.4544	0.4755	KPSC
Probability of prostate cancer	0.4015	0.0078	0.3863	0.4167		0.4015	0.0078	0.3863	0.4167	KPSC
Detected Prostate Cancer Health State										
Probability of prostate cancer related death*	0.0362	0.0185	0.0030	0.0754		0.0362	0.0185	0.0030	0.0754	Hayes[20]
Probability of other cause death	Center for Disease Control Life Table 2006									Arias E[19]

Abbreviations: NA, not applicable; SD, standard deviation; Min, minimum; Max, maximum; KPSC, Kaiser Permanente Southern California.

Note: We applied a beta distribution on probabilities for the second-order Monte Carlo simulation in the model. Probabilities of parameters for age 45-49 years were used for sensitivity analysis

Table 2. Cost and Health State Utility Values

Parameter	Base	Min	Max	Mode	Distribution	Data Source
Office visit costs						
Primary care visit	$37.15	$27.86	$46.44	$37.15	Not varied	MediCare fee schedule
Urologist visit	$92.33	$69.25	$115.41	$92.33	Not varied	MediCare fee schedule
PSA blood test costs						
tPSA	$26.85	$20.14	$33.56	$26.85	Not varied	MediCare fee schedule
fPSA	$26.85	$20.14	$33.56	$26.85	Not varied	MediCare fee schedule
[-2]proPSA	$71.95	$53.96	$89.94	$71.95	Not varied	MediCare fee schedule
Urinalysis costs	$11.00	$8.25	$13.75	$11.00	Not varied	MediCare fee schedule
Biopsy costs	$2,102.68	$1,577.01	$2,628.35	$2,102.68	Not varied	MediCare fee schedule
pCa related medical care costs						
First 12 months	$16,544.85	$12,408.64	$20,681.06	$16,544.85	Triangular	Stokes[22]
Continuous treatment	$3,783.80	$2,837.85	$4,729.75	$3,783.80	Triangular	Stokes[22]
Terminal phase	$0.00	$549.02	$17,583.54	$9,066.28	Triangular	Stokes[22]
Health state utility						
No pCa	1.00				Not varied	
Transition to detected pCa	-$0.13	-$0.03	-$0.22	-$0.13	Triangular	Krahn[25]
Detected pCa	$0.78	$0.63	$0.92	$0.78	Triangular	Hayes[20], Krahn[25]
Disutility due to the biopsy procedure	0.027				Not varied	Krahn[25]

Abbreviations: Min, minimum; Max, Maximum; fPSA, free PSA; pCa, prostate cancer.

Note: All costs expressed in 2009 U.S. dollars.

Costs: PSA test-related costs were based on the national 2009 Medicare fee schedule (Table 2). Office visit costs included one primary care visit for individuals with a negative PSA test, or one primary care visit and two urologist visits for the individuals referred to the specialist. We assumed that a patient with a positive PSA test at the primary care visit obtains the biopsy from a urologist, and returns to the urologist at least one time for follow up.

Different PSA blood test cost components were applied to the PSA test strategies according to the PSA test result. If PSA was less than the threshold value or greater than 10 ng/mL, one PSA test was included. If PSA was between the threshold and 10 ng/mL, PSA test costs were calculated as the following, 1) two PSA test costs (one at the primary care visit and the other at the urologist visit) for the PSA strategy; or 2) one PSA, one fPSA, and one p2PSA for *phi* strategy. We assumed that a routine urinalysis is performed to identify possible reasons for a positive PSA or *phi*. Costs for prostate biopsies include a twelve-core prostate biopsy, echography-guided biopsy, transrectal ultrasound, tissue examination by a pathologist, and three immunohisto-chemistry stains.

Medical care costs for prostate cancer were from published data[22] and adjusted to 2009 U.S. dollars using the Consumer Price Index (CPI). The long-term prostate cancer care related costs were assumed to be the incremental differences between the prostate cancer and the non-cancer cases based on the care phase after the diagnosis of prostate cancer.[22] The costs included three prostate cancer care phases, which were six months of the initial phase, the last 12 months in the terminal phase, and continuous care between the initial and terminal phases.[22] Based on the U.S. Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial in which 95.5% of prostate cancers were classified as stage II at 10 years follow-up,[23] we assumed that screening detected prostate cancers were stage II prostate cancers. Stage II prostate cancer related costs were applied to the model.

Utilities: We incorporated value measurements from a systematic review[20] and two published studies [24,25] on health utility for prostate cancer treatment and watchful waiting. Decreased utility was used as disutility for the model transition in the cycle from no prostate cancer to the cancer state. The modal value calculated from the range of 12 months post-treatment utilities was used as the incremental utility in detected prostate cancer state. The range of utilities for the sensitivity analysis incorporated the patient utilities reported by Basu,[24] which were comparable with those summarized by Hayes *et al* [20] (less than 0.03 score differences). Prostate biopsy-related disutility was used in the model for individuals undergoing biopsies.[26]

Sensitivity Analysis: One-way sensitivity analyses were performed by investigating the effect of changes in individual base case parameters across possible value ranges. We used net monetary benefit (NMB) as the expected outcome, combining the outcomes cost and effect at a specified willingness-to-pay (WTP) threshold of $50,000 per quality adjusted life year (QALY) to construct a Tornado diagram at the decision node. [27] NMB is calculated using the formula:

NMB = E*WTP-C, where E represents effect-iveness and C represents cost. A second-order Monte Carlo simulation evaluated the joint effect of uncertainty on key estimated parameter values in the model.[28] The key parameters were simultaneously and randomly varied over the probability distributions using a Monte Carlo simulation with 10,000 iterations. The probability and cost distributions of the parameters followed the Briggs guidance (table 1-2).[29]

Based on the simulation results, we constructed a cost-benefit acceptability curve for each strategy at different WTP thresholds.[30] Each curve represents the proportion of iterations for which each comparator has the highest net benefits relative to all other strategies at different levels of the WTP. All analyses were performed using the TreeAge Pro 2009 program (TreeAge Software, Inc., Williamstown, MA), and adhered to the Panel on Cost-Effectiveness in Health and Medicine recommendations.[18]

3. RESULTS

3.1 Base Case

Table 3 summarizes the costs and effectiveness results from various discount rates. With 10,000 samples simulated from age 50-75 years under a 3% discount rate, PSA plus *phi* at PSA 2-10 ng/mL strategy was dominant and most effective to determine the need for a prostate biopsy. This approach had the lowest costs and highest effectiveness [cost/effectiveness (C/E)=13,650/12.416, $1,099/QALY], as compared to the strategy of PSA plus *phi* at PSA 4-10 ng/mL [C/E=14,095/12.364, $1,140/QALY], or PSA alone at PSA threshold ≥4 ng/mL [C/E=15,256/12.304, $1,240/QALY], or at PSA threshold ≥2 ng/mL [C/E=15,789/ 12.287, $1,285/QALY]. The PSA test alone at the threshold of ≥2 ng/mL was the least effective testing strategy. The differences between the most and least effective testing strategies were $2,139 in costs and 0.129 QALY in effectiveness, but ranged from $1,552 to $2,810 in costs, and 0.084 to 0.18 QALY in effectiveness, depending on discount rate (Table 3).

Table 3. Cost-effectiveness Results from Second Order Monte Carlo Simulations at Various Discount Rates

Strategy	Cost ($)	Incremental Cost ($)	Effectiveness (QALYs)	Increment Effectiveness (QALYs)	Cost/Effectiveness	ICER	NMB ($)	INMB ($)
Discount=0%								
phi strategy2	18,182		15.491		1,173.71		756,368	
phi strategy4	18,758	576	15.420	-0.071	1,216.47	(Dominated)	752,242	-4,126
PSA strategy4	20,308	2,126	15.335	-0.156	1,324.29	(Dominated)	746,442	-9,926
PSA strategy2	20,992	2,810	15.311	-0.180	1,371.04	(Dominated)	744,558	-11,810
Discount=3%								
phi strategy2	13,650		12.416		1,099.39		607,150	
phi strategy4	14,095	445	12.364	-0.052	1,140.00	(Dominated)	604,105	-3,045
PSA strategy4	15,256	1,606	12.304	-0.112	1,239.92	(Dominated)	599,944	-7,206
PSA strategy2	15,789	2,139	12.287	-0.129	1,285.02	(Dominated)	598,561	-8,589
Discount=5%								
phi strategy2	11,459		10.878		1,053.41		532,441	
phi strategy4	11,840	381	10.836	-0.042	1,092.65	(Dominated)	529,960	-2,481
PSA strategy4	12,813	1,354	10.788	-0.090	1,187.71	(Dominated)	526,587	-5,854
PSA strategy2	13,270	1,811	10.774	-0.104	1,231.67	(Dominated)	525,430	-7,011
Discount=7%								
phi strategy2	9,738		9.638		1,010.38		472,162	
phi strategy4	10,069	331	9.604	-0.034	1,048.42	(Dominated)	470,131	-2,031
PSA strateg4	10,893	1,155	9.564	-0.074	1,138.96	(Dominated)	467,307	-4,855
PSA strategy2	11,290	1,552	9.554	-0.084	1,181.70	(Dominated)	466,410	-5,752

Abbreviations: QALYs, quality adjusted life years; ICER, incremental cost-effectiveness ratio ($/QALY); NMB, net monetary benefit; INMB, incremental net monetary benefit; PSA, prostate-specific antigen; *phi* strategy2, PSA plus *phi* at PSA 2 to 10 ng/mL; *phi* strategy4, PSA plus *phi* at PSA 4 to 10 ng/mL; PSA strategy2, the PSA alone test using PSA threshold ≥ 2 ng/mL; PSA strategy4, PSA alone test using PSA threshold ≥ 4 ng/mL.

Note: all options referenced to a common baseline of *phi* strategy2. The costs were expressed in 2009 U.S. dollars. NMB was calculated given a willingness-to-pay of $50,000/QALY gained.

3.2 Sensitivity Analyses

Figure 1 shows a series of one-way sensitivity analyses at the decision node based on NMB analysis given the WTP of $50,000/QALY. The vertical line represents the base-case highest NMB estimate ($ 606,859/QALY). The expected NMB is most sensitive to the discount rate, followed by the age at initial PSA screening, age to stop screening, the utility of prostate cancer, the probability of prostate cancer related mortality, and the probability of prostate cancer when there is a positive test result of *phi* at PSA 2-10 ng/mL.

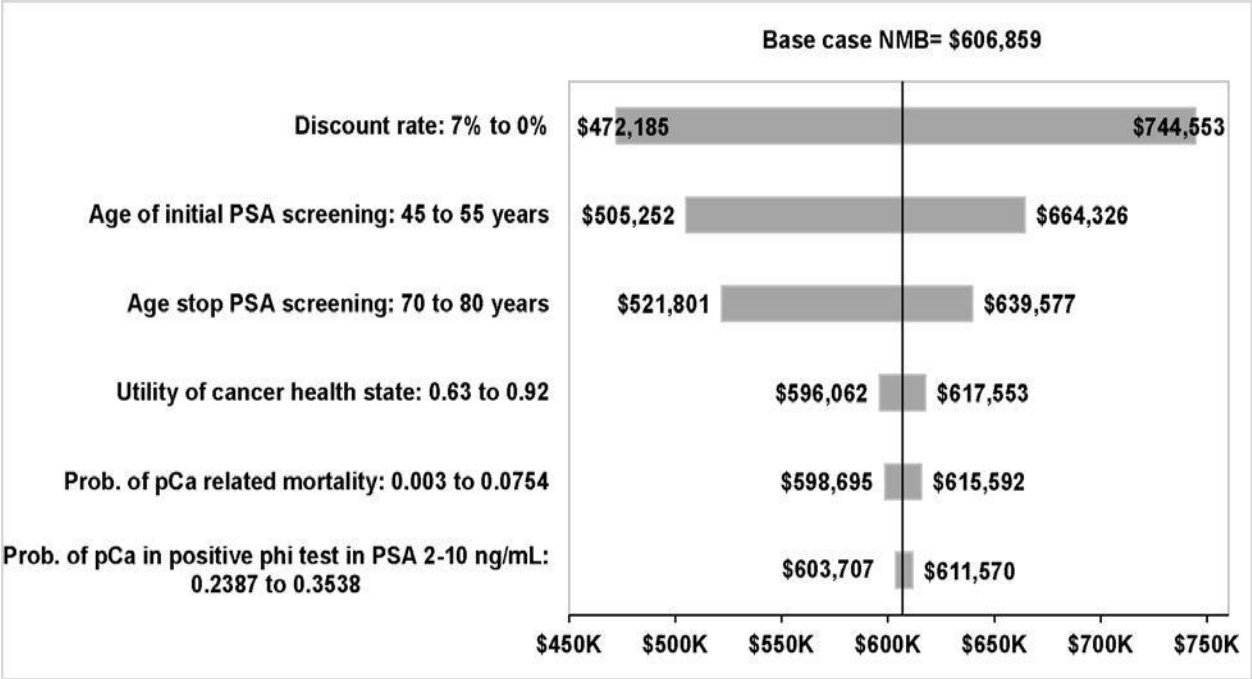

Figure 1. Tornado Diagram of One-way Sensitivity Analyses. Tornado diagram showing a series of one-way sensitivity analyses at the decision node based on net monetary benefit analysis given the willingness-to- pay $50,000/QALY.

The second-order Monte Carlo simulation analyses show that PSA plus *phi* strategies compared to the PSA test alone are dominant in 99.97%, and 98.71% of samples under the biopsy thresholds of 2 and 4 ng/mL, respectively. The net monetary benefit acceptability curves at a range of 0 to $150,000/QALY WTP indicate that 1) the strategy of PSA plus *phi* at PSA 2-10 ng/mL displays a74% to 86% probability of being cost-effective; 2) PSA plus *phi* at PSA 4-10 ng/mL shows a 26% to 14% probability of being cost-effective; 3) PSA test alone at thresholds 2 or 4 ng/mL have 0% probability of being cost-effective; 4) PSA plus *phi* at PSA 2-10 ng/mL was the optimal option relative to all other strategies under the WTP of $150,000/QALY (Figure 2).

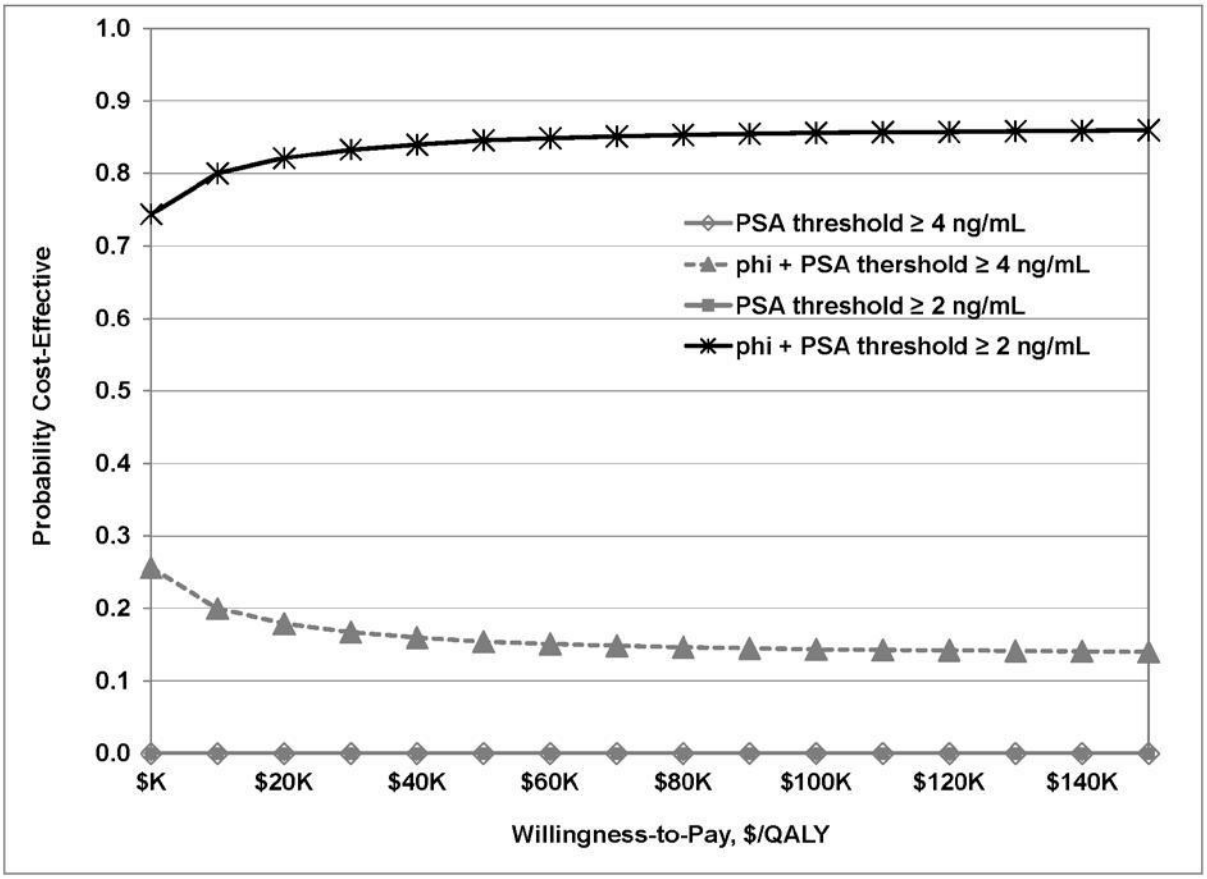

Figure 2. The cost-effectiveness acceptability curves

4. DISCUSSION

Our cost-effectiveness analysis based on a managed care payer's perspective on PSA test for prostate cancer detection produced three major findings, 1) using *phi* at PSA 2-10 ng/mL or 4-10 ng/mL are the dominant strategies compared to using the PSA test alone; 2) using *phi* at PSA 2-10 ng/mL is the optimal strategy among all four PSA testing strategies across a range of WTP from $0 to $150,000/QALY gained; 3) without adding *phi*, the PSA test alone using PSA threshold ≥2 ng/mL to recommend a prostate biopsy was the most costly and least effective strategy in prostate cancer detection and consequent treatment.

Our model included all levels of PSA test results. In each screening cycle, PSA plus *phi* reduced 1.6% and 1.1% biopsies compared to the PSA test alone at PSA 2-10 ng/mL and 4-10 ng/mL, respectively. The reduction of unnecessary biopsies through increased *phi* specificity produced the cost savings. Therefore, the strategies with *phi* generated greater cost savings than the strategies using PSA only, regardless PSA thresholds. These findings are consistent with our previously published budget impact analysis of *phi*[31] and cost-effectiveness analysis from the U.S. societal perspective.[32]

The current analysis indicated that applying *phi* at PSA 2-10 ng/mL produced greater savings through reductions in the number of biopsies, than applying *phi* at PSA 4-10 ng/mL. Higher PSA levels are associated with increased probability of prostate cancer.[33,34] However, a widely used cutoff value PSA ≥4 ng/mL was unable to detect all prostate cancers.[34] Some clinicians use a 2 ng/mL cutoff to recommend a prostate biopsy, which may increase detection of clinically insignificant cancers, and may lead to overtreatment.[35] Recent research shows that applying *phi* in conjunction with PSA range 2-10 ng/mL significantly improves specificity in discriminating prostate cancer from benign disease while avoiding unnecessary prostate biopsy. [8,9,10] Our study provides evidence of the cost-effectiveness of prostate cancer detection using *phi* as compared with PSA test alone. These results further validate our previous findings[31,32] of the benefits of *phi* as an aid to detect prostate cancer. Our model shows the long-term costs and health state utility benefits of using *phi* for a 25-year time horizon, especially using *phi* at PSA 2-10 ng/mL.

Our model shows that using a lower PSA threshold, (*e.g*. 2 ng/mL) without adding *phi*, would increase costs and decrease QALYs gained as compared to using a higher PSA threshold alone, (*e.g*. 4 ng/mL) or PSA plus *phi*. Using the PSA test alone to detect prostate cancer resulted in more prostate biopsies, and may detect more cancers than using PSA plus *phi*. These additional biopsies and prostate cancer treatment following cancer detection were associated with higher costs and lower health utility or lower QALYs. Using PSA test alone at a PSA threshold ≥2 ng/mL should be used with caution, and using PSA plus *phi* at PSA 2-10 ng/mL could generate the highest net monetary benefit as compared to other PSA test strategies.

Applying *phi* when the initial PSA test produces borderline test results generated higher health utilities than using PSA test alone. Interestingly, the health utilities differences between PSA plus *phi* and PSA test alone were greater in PSA threshold ≥2 ng/mL (0.129) than ≥4 ng/mL (0.060). These results imply that men from aged 50-75 years through a 25-year life span may have higher QALYs if *phi* was used as an aid in distinguishing prostate cancer from benign prostatic conditions than using PSA test alone to detect prostate cancer, especially when *phi* was used at a PSA threshold ≥2 ng/mL.

One of the strengths of this study is the use of electronic medical record data from a managed care organization to obtain health state transition probabilities. These results may approximate real world managed care practices, especially the results for PSA test alone. However, since p2PSA was not available in the U.S. when we performed this analysis, we assumed that the performance of *phi* in a managed care environment would be the same as that in the multicenter clinical trial.[8] Future studies should be considered to evaluate the clinical use of *phi* along with costs and quality of life outcomes.

We had to make some assumptions in our model due insufficient data on practice patterns. Therefore, our model may lack precision on some of the point estimates. For example, for the individuals with a borderline PSA test result, we assumed that repeated test would essentially provide the same result as that in the first test. This could potentially overestimate prostate cancer rates, for example considering the possibly of a negative repeat PSA test result (i.e. below the decision cutoff). We assumed that men with biopsy confirmed prostate cancer received definitive treatment because lack of published data for active surveillance. This

could also have resulted in an over-estimation treatment according to our model. Because mortality data were not available from the KPSC, we used published mortality data in our model. In addition, our model did not incorporate cancer stage or identification of non-clinical relevant prostate cancer. Another potential limitation of the current study was that the decision to order a prostate biopsy was made within PSA threshold values instead of a continuous probability of comprehensive prostate cancer risk, which is recommended in the 2009 AUA PSA Best practice Policy.[1] Nevertheless, the current analysis provides an appropriate comparison of cost-effectiveness between the strategies of PSA test alone and PSA plus *phi*, and the sensitivity analyses reinforced the robustness of the conclusions. Although a higher *phi* score has been shown to be predict increased risk of Gleason score greater than or equal to 4+3=7 pathology,[8,9] these studies are preliminary and therefore were not included in the current model. Future research should consider incorporating Gleason grade pathologies in the model as a method of stratifying clinically insignificant prostate cancers from more aggressive disease.

5. CONCLUSIONS

From a managed care payer perspective, *phi* as an aid to distinguish prostate cancer from benign prostatic conditions in the PSA range of 2-10 ng/mL dominated other strategies, and was optimal in all strategies under the WTP of $150,000/QALY gained for prostate cancer detection. This strategy could be an important method of prostate cancer detection in improving men's health outcomes.

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