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Mukherjee R, **Reese ES**, Multani MM, Yarbrough WM, Dowdy KB, Mingoia JT, Hendrick JW, Stroud RE, Hardin A, McLean JE, Leiser JS, Pilla JJ, Blom AS, Affuso J, Acker MA, Spinale FG. Passive restraint following myocardial infarction modifies left ventricular and myocyte remodeling and improves isolated myocyte contractile response. Poster presentation at the Heart Failure Society of America 7th Annual Scientific Meeting, September 2003, Las Vegas, NV.

PUBLICATIONS

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ES Reese, CD Mullins, AL Beitelshes, E Onukwugha. The cost-effectiveness of CYP 2C19 genotype screening to select clopidogrel or prasugrel for antiplatelet therapy. *Pharmacotherapy.* 2012 Apr; 32(4):323-32.

CD Mullins, D Whicher, **ES Reese**, S Tunis. Generating Evidence for CER Using More Practical Randomized Trials. *PharmacoEconomics.* 2010; 28(10). 969-76.

Mukherjee R, Yarbrough WM, **Reese ES**, Leiser JS, Sample JA, Mingoia JT, Hardin AE, Stroud RE, McLean JE, Hendrick JW, Spinale FG. Myocyte contractility with caspase inhibition and simulated hyperkalemic cardioplegic arrest. *Annals of Thorac Surg.* 2004 May; 77(5):1684-89.

Yarbrough WM, Mukherjee R, Squires CE, **Reese ES**, Leiser JS, Stroud RE, Sample JA, Mingoia JT, McLean JE, Hardin AE, Dowdy KB, Spinale FG. Caspase inhibition attenuates contractile dysfunction following cardioplegic arrest and rewarming in the setting of left ventricular failure. *J Card Pharm.* 2004 Dec; 44(6):645-50.

BOOK CHAPTERS

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Abstract

Title of Dissertation: The Need to Conduct Future Research on the Benefit of the Prostate Specific Antigen Screening Test Using Value of Information Framework

Emily S. Reese, Doctor of Philosophy, 2014

Dissertation Directed by: C. Daniel Mullins, PhD, Professor and Chair Pharmaceutical Health Services Research Department

Prostate cancer (PC) is the second most common cancer in men throughout the world and is the second leading cause of cancer deaths in men in the United States. Screening for PC is routinely conducted through the prostate specific antigen screening test (PSA); unfortunately, PSA levels change due to a variety of factors which make the threshold for a normal PSA level difficult to ascertain in all populations. Professional organizations and task forces differ with their recommendations for PSA screening. This study examined the amount of research that should be funded in order to clarify uncertainty associated with PSA screening.

The value of information (VOI) framework utilizes net monetary benefit to determine the amount of funding that should be allocated to a specific field of research in

order to reduce uncertainty. Using the VOI framework, this research examined the: 1) expected value of information (EVI); 2) population expected value of information (pEVI), a population-specific estimate by race and age group; and 3) expected value of perfect information (EVPI). Men were identified as having at least one PSA screening exam from the 2000-2007 SEER-Medicare dataset. A Cox Proportional Hazard model and phase-based costing were used to determine costs and survival increments. Bootstrapped replicates were generated and the net monetary benefit was calculated. VOI estimates were calculated from the replicates. Sensitivity analyses captured change under different willingness-to-pay (WTP) thresholds.

The matched analytic cohort contained 180,692 PC cases and controls. Among cases, 36.2% of cases had at least one PSA test and 59.1% of controls had at least one PSA test. PSA testing resulted in an additional 0.9835 life-years (359 life-days). The mean incremental cost between the two cohorts was \$1,880. Using a WTP threshold of \$50,000, the EVI was \$518,233 and the EVPI was \$616,463. The population estimate was \$8,281,979 for African Americans (AA), \$46,525,105 for Caucasians, \$22,657,186 for men aged 65 to 74, and \$24,558,627 for men aged 75+.

Estimates obtained for EVI and EVPI were lower than comparable cancer screening VOI estimates. Given results based on population estimates, future research funding for PSA screening among Medicare beneficiaries should focus on Caucasians and AA.

The Need to Conduct Future Research on the Benefit of the Prostate Specific Antigen
Screening Test Using Value of Information Framework

by
Emily S. Reese

Dissertation submitted to the Faculty of the Graduate School of the
University of Maryland, Baltimore in partial fulfillment
of the requirements for the degree of
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2014

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Dedication

To my parents, Calvin and Libby Reese, for always encouraging, supporting, and believing in me

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Chapter One

The prostate gland produces a portion of the fluid that protects and nourishes sperm in semen. The prostate is located beneath the bladder and is bisected by the urethra. As with several other components of the reproductive system, prostate growth is in part mediated by the hormone dihydrotestosterone (DHT) and ceases once a man reaches adulthood.¹ Abnormal prostate growth is common in older men. This growth can be due to either benign prostate hyperplasia (BPH) or prostate cancer (PC).² However, unlike BPH, a PC tumor can regenerate if not entirely removed, invade proximal tissue, bone and organs, and can be life-threatening.

Prostate Cancer

Epidemiology and Risk Factors

Prostate cancer is the second most common cancer in men throughout the world and the second leading cause of cancer deaths in men in the United States.³ The National Cancer Institute estimated that 233,000 new cases of PC will be diagnosed and 29,480

men will die as a result of PC in 2014.⁴ For the most recent data available, the Centers for Disease Control and Prevention reported that in 2010 196,038 new PC cases were diagnosed and there were 28,560 PC deaths.⁵ Worldwide, the burden of PC is expected to exceed nearly two million new cases and have almost 500,000 incident cases of PC by 2030 although these statistics are attributed to the natural aging of the population.⁶ However, studies have found that the actual prevalence of this disease may extend further than projected. It is estimated that approximately 40% of men aged 70 years have detectable PC at autopsy but did not die of the cancer.⁷ Figures reflect that PC is more common in African American men than in their white counterparts^{8,9} and that the mortality rate for African American is more than double that of any other racial or ethnic group (e.g. white, Asian/Pacific Islander, American Indian/Native American, and Hispanic).¹⁰

Like many other cancers, the exact cause of prostate cancer is unknown; however, many studies have identified factors associated with a man's increased risk of getting the disease. Risk factors for PC may include certain genetic mutations and certain prostatic changes, though the only established risk factors for the disease are age, race and family history.¹¹ In aging men, changes in the estrogen and testosterone ratios within the prostate are thought to provoke the development of PC.¹¹ The median age at diagnosis during 2004 to 2008 was 67 years of age and approximately one-third of men diagnosed with PC are between the ages of 65 and 74. The median age at death for those diagnosed with PC during the same period was 80 years with 39.5% of men dying from PC aged between 75 and 84 years.¹⁰ Throughout the world, PC is more common in economically developed

countries, while men of African descent have a higher risk of developing PC than their European-descended counterparts.¹² Men of African descent in the Caribbean have the highest PC mortality worldwide. Interestingly enough, the Middle East and Eastern Asian countries have the lowest age-standardized PC incidence rates in the world. These rates range between 7.5-14.0 per 100,000 men in the Middle East to less than 7.4 per 100,000 men in East Asia, compared to greater than 66.8 per 100,000 men in North America.¹³ The incidence of PC among black men in the United States is nearly double that of any other racial group (Table 1).

Table 1. Incident rates and mortality rates of PC among race/ethnic groups of US men

Population	Incident Rate (per 100,000 population men)	Mortality Rate (per 100,000 population men)
African American	233.8	54.9
Caucasian	149.5	22.4
Non-White Hispanic	107.4	18.5
Asian/Pacific Islander	88.3	10.5
American Indian/ Alaska Natives	75.3	20.7

Reprinted from Howlader N, Noone AM, Drapcho M, Neyman N, Aminou R, Waldron W, et al. (eds). SEER Cancer Statistics Review, 1975 – 2008 National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2008/, Based on November 2010 SEER Data Submission, Posted to the SEER Website, 2011. http://seer.cancer.gov/csr/1975_2008/index.html ed. Bethesda, MD; National Cancer Institute, No. 2011.

Having a first-degree relative (i.e. father, brother or son) diagnosed with PC increases a man’s risk of being diagnosed with PC.¹⁴ Studies have suggested that men with a family history undergo earlier or more intense PC screening between the ages of 30 and 50 years.¹⁵ Certain genetic factors can also put a man at greater risk for developing PC.¹⁶ Mutations that exist in the *BRCA2* gene are associated with an approximate 15% risk

increase in developing PC by the age of 65.¹⁷ Men genotyped with four of the five *LEPR*, *CRY1*, *RNASEL*, *IL4*, and *ARVCF* genes have a 50% increased risk of dying from PC.¹⁸

When in its early stages, PC rarely has symptoms; however, men with advanced PC often report urinary problems (i.e. not being able to start or stop urine flow, inability to pass urine, urine leakage), blood in the urine or semen, or in cases of metastatic PC, discomfort or pain in the pelvic area or bone pain.¹⁹

Researchers also have investigated whether elective surgery (i.e. vasectomy) or lifestyle factors like tobacco or alcohol use, BPH, sexually transmitted infections, obesity, lack of exercise or a diet high in animal fat or meat are associated with an increased risk of PC; however, studies report little to inconsistent change in risk of PC associated with lifestyle factors.^{20, 21}

Screening and Diagnosis

As with other forms of cancer, early detection through screening can increase overall survival and decrease disease-specific death. Screening for PC is often done through two different methods. The digital rectal exam (DRE) is a manual examination of the prostate gland that may allow the physician to palpate any lumps or abnormalities that may exist within the posterior lobes of the gland. The prostate specific antigen test (PSA) is a blood test that measures the level of PSA in the blood. In clinical practice, levels of PSA greater than or equal to 4ng/ml are used as a cutoff to screen men for PC, although

other permutations of PSA testing have also been evaluated in various settings, such as age-specific PSA cut-off values, PSA density, PSA velocity, free to total PSA ratios, and others.²² An elevated PSA level may potentially be indicative of a prostate gland associated problem, such as BPH or PC. Importantly, and with respect to PSA and PC, an elevated PSA result can be a false positive in some men, while in others a low PSA level is a false negative. Additionally, PSA levels can be affected by certain medical procedures (including DRE, prostate biopsy), certain medications (i.e. nonsteroidal anti-inflammatory drugs, statins, and thiazide diuretics), age, and co-morbidities (i.e. BPH, prostatitis, obesity, and obstructive uropathy).^{23, 24, 25}

Undergoing a DRE or PSA test can alert a medical provider to a problem with the prostate gland but neither test is able to ascertain whether or not cancer exists. Diagnostic procedures such as the transrectal ultrasound guided prostate biopsy may be conducted to aid in diagnosis of PC.²⁵ Once a prostatic biopsy is completed, the cells that make up the tissue undergo microscopic examination. From this examination, a Gleason score is assigned which reflects the relative architecture and ‘aggressiveness,’ or grade, of the cells within the biopsy specimen. A Gleason grade of one indicates normal cells, while a grade of five indicates mostly abnormal or malignant cells.^{26, 27} Gleason scores range from 2 to 10 by adding the primary and secondary cancer cluster classification (or grades, which range from 1 to 5) to achieve a total Gleason score. For example, while examining a biopsy, if a pathologist classifies the primary cell number as grade 4 and another secondary cancer cell number as grade 3, then the Gleason score for this biopsy would be $4 + 3 = 7$. The severity of the primary cell number signifies the severity of the cancer, so

a Gleason score of 7 with the primary cell number graded as 3 would not be as severe as if the primary cell number graded as 4.

The Gleason score categorizes the malignant cells within the prostate.^{26, 27} The American Joint Committee on Cancer (AJCC) and the International Union Against Cancer keep and update a widely accepted tumor, node and metastasis (TNM) grading system.^{28, 29} The TNM system subcategorizes the tumor stage in order to capture stage as presented in men who are diagnosed with PC through PSA screening (Table 2).^{30, 31} Overall staging for PC which incorporates PSA screen results, Gleason score and TNM progression is shown in Table 3.

Treatment

Treatment for PC is divided into six categories: active surveillance, surgery, radiation therapy, hormone therapy, chemotherapy, and experimental therapies. Active surveillance consists of regularly monitoring changes in a man's PSA levels and DRE. The decision to progress to more proactive treatment lies with the patient and healthcare provider, depending upon the changes that may develop within PSA levels, DRE, and repeated prostate biopsy results over the course of subsequent patient follow-up. Surgical treatment for PC completely removes the prostate. Radiation therapy kills cancerous cells by directing high-energy x-rays at the prostate. This treatment is broken down into external radiation therapy, where the therapy is received from a machine external to the body, or brachytherapy where radioactive seeds are surgically implanted in close

Table 2. AJCC TNM Classification for Prostate Cancer Diagnosis

<i>Tumor, Node, or Metastasis</i>	<i>Clinical Description</i>
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor neither palpable nor visible by imaging
T1a	Tumor incidental histologic finding in $\leq 5\%$ of tissue resected
T1b	Tumor incidental histologic finding in $> 5\%$ of tissue resected.
T1c	Tumor identified by needle biopsy (e.g., because of elevated PSA)
T2	Tumor confined within prostate
T2a	Tumor involves \leq one-half of one lobe
T2b	Tumor involves $>$ one-half of one lobe but not both lobes
T2c	Tumor involves both lobes
T3	Tumor extends through the prostate capsule
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall
NX	Regional lymph nodes were not assessed
N0	No regional lymph node metastasis
N1	Metastases in regional lymph node(s)
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bone(s)
M1c	Other site(s) with or without bone disease

Reprinted from AJCC: Prostate. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 457-68.

proximity to the cancer in order to kill malignant cells. Hormone therapy utilizes approved medications, as well as surgery, to remove male sex hormones, thus depriving the cancer of its growth hormone.¹⁹ Medications that are used during hormone therapy include luteinizing hormone-releasing hormone agonist/antagonists which prevent testosterone production by ultimately decreasing production of luteinizing hormone from the pituitary gland. These medications include leuprolide, goserelin and triptorelin, among others.

Table 3. Overall Staging for Prostate Cancer

Group	T	N	M	PSA	Gleason
I	T1a-c	N0	M0	PSA <10	Gleason ≤6
	T2a	N0	M0	PSA <10	Gleason ≤6
	T1-2a	N0	M0	PSA X	Gleason X
IIA	T1a-c	N0	M0	PSA <20	Gleason 7
	T1a-c	N0	M0	PSA ≥10 <20	Gleason ≤6
	T2a	N0	M0	PSA ≥10 <20	Gleason ≤6
	T2a	N0	M0	PSA <20	Gleason 7
	T2b	N0	M0	PSA <20	Gleason ≤7
IIB	T2b	N0	M0	PSA X	Gleason X
	T2c	N0	M0	Any PSA	Any Gleason
	T1-2	N0	M0	PSA ≥20	Any Gleason
III	T1-2	N0	M0	Any PSA	Gleason ≥8
	T3a-b	N0	M0	Any PSA	Any Gleason
IV	T4	N0	M0	Any PSA	Any Gleason
	Any T	N1	M0	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

Reprinted from AJCC: Prostate. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th Ed. New York, NY: Springer, 2010, pp 457-68.

Antiandrogens, flutamide bicalutamide and nilutamide, and other drugs that prevent testosterone production, ketoconazole and aminoglutethimide, are also used as hormonal therapy for PC. Recently approved hormonal therapies also include abiraterone, enzalutamide and degarelix.²⁵ Additionally, a man’s healthcare provider may suggest orchiectomy, or surgical removal of the testicles, as a form of hormonal therapy.²⁵ Chemotherapy is a type of cancer treatment that stops the growth of malignant cells by disrupting cellular DNA, protein, cytoskeletal network and/or signaling pathways, among other molecular and/or cellular targets. Chemotherapy is administered orally or through injection into a vein. Chemotherapies approved by the FDA to treat PC include docetaxel,

cabazitaxel, and mitoxantrone, although other chemotherapeutics can also be used for treating advanced disease. The landscape for treating advanced metastatic PC is changing further in that an agent that stimulates PC-specific immune system (i.e. sipuleucel-T) entered clinical practice use in 2010.²⁵ In addition to the above, other novel therapies are undergoing active investigation through clinical trials for the various stages of PC.

Due to the location of the prostate in relation to the urogenitary system, complications often arise in the diagnosis and treatment of PC. The extent of prostatic disease and treatment can affect a man's susceptibility to developing complications like urinary or fecal incontinence and erectile dysfunction. These complications may resolve on their own or can be treated with medication, external appliances or surgery.^{32, 33} More specifically, radiation therapy is associated with decline in bowel function and urinary incontinence and an increased risk of bladder and rectal cancer. Cryotherapy is associated with impotence, incontinence, urethral sloughing, urinary fistula or stricture, and bladder neck obstruction.³⁴ Hormone therapy complications depend on the specific type of hormone treatment given. Bilateral orchiectomy, estrogen therapy, luteinizing hormone-releasing hormone agonist therapy are associated with loss of libido, impotence, hot flashes, osteoporosis, and increased cardiovascular morbidity and mortality risk.^{35, 36} Antiandrogen therapy is associated with diarrhea, breast tenderness, nausea, hot flashes, decreased libido, impotence, adrenal insufficiency, osteoporosis, and increased risk of colorectal cancer.³⁷⁻⁴⁰

Prostate Specific Antigen Test

About the test

The study of PSA began in the 1960s when scientists identified a protein unique to semen; however, it wasn't until the mid-1980s that elevated PSA levels were associated with increased PC risk.⁴¹ In 1986, the PSA test was approved by the US Food and Drug Administration for monitoring disease progression in men with PC and was approved for PC screening in 1992.⁴² Because the protein is produced in the prostate, PSA is thought to have similar operating characteristics to that of a prostate biopsy; thus the test's use as a screen for prostate abnormalities and health. PSA test results of greater than or equal to 4 ng/ml represents a high risk of PC, though PSA levels are known to vary by age and race which has induced some researchers to explore age-specific and race-specific PSA thresholds.⁴³ While screening for PC via PSA has resulted in a high proportion of PC diagnoses at early stage, controversy exists regarding the clinical utility of PSA screening and its ability to accurately identify men with PC. An elevated PSA level, generally accepted as indicative of a problem in the prostate and/or the potential risk of PC, in some men is a false positive, in others a low PSA level is a false negative. Estimates from the early 1990s place the PSA test's false positive rate at approximately 70% in men older than 50 years of age.⁴⁴ In the Prostate Cancer Prevention Trial (PCPT), researchers found no simultaneous levels of sensitivity, or the probability of a test being positive given the patient had the disease in question, and specificity, the probability of a test being negative given the patient did not have the disease in question,

acceptable for healthy men in monitoring risk of PC (Table 4). The authors found that increasing sensitivity so that 83.4% of men screened were diagnosed with cancer would result in 61.1% of men without cancer undergoing biopsy.⁴⁵

Table 4. Characteristics of the PSA Test for Prostate Cancer

Test Characteristic	Description
Sensitivity	All tumors: at PSA 2.6 ng/ml = 40.5% At PSA 4.1 ng/ml = 20.5% Gleason \geq 8: at PSA 2.6 ng/ml = 78.9% At PSA 4.1 ng/ml = 50.9%
Specificity	All tumors: at PSA 2.6 ng/ml = 81.1% At PSA 4.1 ng/ml = 93.8% Gleason \geq 8: at PSA 2.6 ng/ml = 75.1% At PSA 4.1 ng/ml = 89.1%
Positive Predictive Value	29.5% for PSA and DRE, based on for-cause data 12.8% in screening study
Number Needed to Screen to detect one positive case	50-77 for men in the 50s 21-30 for men in their 60s
Cost per life-year saved	11 for men in the 70s for PSA \geq 4.0 ng/ml \$12,500-\$15,000 based on favorable screening assumptions

Reprinted from Crawford ED, Abrahamsson PA. PSA-based screening for Prostate Cancer: How does it compare with other screening tests? Eur Urol. 2008; 54: 262-73.

Subsequent research has determined factors including age, medications, co-morbidities, prostate massage, and recent ejaculation can influence the level of PSA in the serum.^{24, 46-}

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Controversy

Though screening for PC via PSA has resulted in a high proportion of early-stage diagnosed PC, mortality rates for PC are lower than 30 years ago even though the lifetime

risk of death from PC has remained constant.⁵⁰ Both observational studies and randomized controlled trials have examined PSA and PC mortality. A 2010 case control study that followed men for 25 years found an association between PSA levels at age 60 and lifetime risk of metastasis and death from PC. Investigators found that PSA levels at 60 years of age less than or equal to 1 ng/ml may have PC but would not be likely to die as a result of the PC by 85 years of age; however, among men with higher baseline PSA concentrations (ranging from 5-10 ng/ml) 33% died from PC by 85 years of age.⁵¹

A randomized controlled trial conducted in Sweden with 20 years of follow-up determined the rate of death from PC did not differ significantly between men who were screened and men in the control group.⁵² Some studies attribute the 45-70% decline in the US PC mortality rate over the past several years to screening, yet others cite improvements in PC treatment for the decline in mortality.⁵³ In order to have definitive evidence of its utility, some investigators have called for additional randomized controlled trials to investigate PSA testing.^{54, 55}

Efforts to Improve the PSA Test

Current efforts to improve the PSA test in order to distinguish cancer from benign conditions are underway and include investigating novel predictive biomarkers.⁵⁶ Additionally, researchers have suggested considering a PSA threshold of lower than 4ng/ml as an increased risk of PC.⁵⁷ PSA thresholds reflective of the age and ethnicity of men tested have also been proposed. Luboldt et al, conducted a literature review that

examined population-based age-specific reference PSA thresholds for men (Table 4).⁴³ Age-specific PSA thresholds have increased the detection of PC by 18% in men less than 60 years of age and decreased detection of PC by 22% in men older than 60 years of age. Controversially, when the age-specific PSA reference ranges are used in older men, fewer tumors were detected. The tumors detected with age-specific PSA reference ranges tended to be nonpalpable, pathologically favorable tumors, thus increasing the utilization for healthcare resources which may not be needed.⁵⁸ Luboldt et al. concluded that the use of age-specific ranges are controversial and not recommended or approved by the manufacturers of commercially-available PSA assays, but physicians should be aware that PSA test characteristics are different among men with and without PC of varying age and ethnicity.⁴³ Proposed upper limits for PSA testing in PC-free men of various age and race are reflected in Table 5.

While not highly sensitive in its current form, the PSA test is considered acceptable and on the same level with other cancer screening modalities for colon, cervical, and breast cancers. The test's sensitivity could be improved by using a threshold lower than the accepted 4.0 ng/ml but specificity and positive predictive value would be negatively impacted. These changes would create an increase in false positive PC diagnosis.⁵⁹

Table 5. Mean age-specific upper reference limits for PSA (ng/ml) in cancer-free men

Race/Nationality	Age (years by decade)						
	21-30	31-40	40-49	50-59	60-69	70-79	80-89
Caucasian*	1.05	1.41	1.93	3.09	4.89	6.77	
African-American			2.5	5.45	9.00	10.1	
Japanese			2.03	3.46	4.63	5.66	5.90
Chinese	1.20	1.21	1.23	2.35	3.20	3.39	
Hispanic			2.1	4.3	6.0	6.6	

* Caucasian population was virtually cancer free

Reprinted from Lubold HJ, Schindler JF, Rubben J. Age-specific reference ranges for prostate-specific antigen as a marker for prostate cancer. *EAU-EBU Update Series*. 2007; 5: 38-48.

Varying Results in Randomized Controlled Trials

The two best known randomized controlled trials on how PSA impacts survival are the Prostate, Lung, Colorectal and Ovarian Cancer Screening trial (PLCO) and the European Randomised Study of Screening in Prostate Cancer (ERSPC). The PLCO was a US-based multicenter study with 76,000 men, aged 55 to 75, randomized into screening and control arms. After a median follow-up of 11.5 years from the time of randomization, 9% of the men in the screening arm and 7.8% of the men in the control arm were diagnosed with PC. No difference in PC mortality was reported between the study's two arms. PLCO investigators cited wide-spread PSA testing and DRE in the control arm, resulting in significant 'contamination' of this arm. Of note is that approximately 44% of men in each arm underwent PSA testing at least once prior to enrollment in the study. Consistent with clinical practice and practicing restraint with respect to over-detection, the PLCO study used a PSA cutoff of 4ng/ml, but other investigators pose that aggressive

PC can exist below the 4ng/ml threshold.⁵⁵ Furthermore, PLCO investigators were criticized that the 11.5 years of follow up was insufficient because it began at study participants' randomization, not from time of PC diagnosis. In the study, 15% of tumors in the screening arm were found at initial screening, 43% were found in the first 5 years of the trial, and 25% were found after the 6th year of the trial. The remaining tumors were found outside the study protocol and in the 'never screened' group. Studies using the Surveillance, Epidemiology, and End Results (SEER) database classified the types of tumors seen in the PLCO trial as moderately differentiated. These types of tumors are known to not show significant rates of cancer-specific mortality until 10-years after diagnosis.⁶⁰

The European Randomized Study of Screening in Prostate Cancer (ERSPC) was a multi-center European trial with each center having differing characteristics. Men in the ERSPC had variable PSA screening examinations; depending on study center, PSA screens were administered between one to four years, and PSA cut off used was 3ng/ml, with some centers using higher thresholds. After a median of 9 years of follow-up, 8.2% of men in the screened arm and 4.8% of men in the control arm were diagnosed with PC. The risk ratio of mortality from PC in the screened arm was 0.80. After adjusting for screening protocol adherence, the risk ratio dropped to 0.70.⁶¹ Critics of ERSPC claim this trial was a more valid comparison of the screened and unscreened populations than the PLCO due to a greater difference in cancer detection rates between study arms, but cite study flaws such as varying indications for biopsies and screening interviews for study sites, and a screening schedule atypical of the United States.⁶²

In 2010, The Cochrane Library updated their 2006 review of PC screening.⁶³ This review included the PLCO and ERSPC, in addition to three other trials (Table 6), Norrkoping, Quebec, and Stockholm. All five examined studies were randomized controlled trials that examined screening (the PSA test, DRE, and the transrectal ultrasound (TRUS)) interventions for PC. All studies assessed PC-specific and all-cause mortality and secondary outcomes (i.e. incident PC by stage, grade, metastatic disease status, health-related quality of life, etc.). Studies were evaluated on the basis of sequence generation, allocation concealment, ‘blinding’ of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias which is defined as inappropriate data analysis in accordance with the Cochrane Handbook for Systematic Reviews of Intervention.⁶⁴ Of the five studies, two were graded with a low risk of bias, the ERSPC and the PLCO trials.⁶³ The Cochrane report stated that the allocation concealment was unclear in the ERSPC trial but that early pilots of the trial demonstrated adequate allocation concealment. Additionally, the PLCO was graded as ‘low risk bias’ due to a high (98%) follow-up over 7 years but was mitigated by a modest (67%) participant follow up over 10-years. Three trials, the Norrkoping, Quebec, and Stockholm trials were all graded as ‘high risk of bias.’ The Quebec and Stockholm trials were graded as high risk due to lack of allocation concealment, not using the intent-to-treat principle (Quebec) and uncertainty associated with sequence generation (Stockholm). The Norrkoping trial was graded ‘high risk of bias’ because of poor allocation sequence generation and lack of allocation concealment. Ultimately, the Cochrane review stated PC screening did not significantly decrease primary outcomes

(all-cause or PC-specific mortality) and may take greater than 10 years for screening to have an effect.⁶³ One other randomized trial (the Comparison Arm for ProtecT (CAP)) is an ongoing subtrial of the Prostate testing for cancer and Treatment (ProtecT) trial. The CAP trial evaluates clusters of primary screening centers who offer PSA screening test or standard of care for PC screening. Preliminary results revealed that risk of PC with raised PSA was lower in men with urinary symptoms (OR: 0.44, 0.35-0.52). Preliminary results also concluded that risk of PC with raised PSA values was lower if a repeat PSA decreased by $\geq 20\%$ before biopsy (OR: 0.43, 0.35-0.52). Men between the ages of 45-49 years were less likely to attend the clinical randomized for PSA screening as compared to those conducting standard of care.⁵⁵ Table 6 reflects a brief summary of RCTs that examined screening for PC using PSA.

Recommendations on PSA Screening

Although both the PLCO and ERSPC trials were considered discouraging by the clinical community because neither determined conclusively the clinical utility of PSA testing, these RCTs spurred action by professional organizations.^{62, 65, 66} The American Urological Association (AUA) recommends routine PSA screening with baseline PSA test when men reach 40 years of age, followed by tailored surveillance. However, the AUA did not specify a PSA threshold for any men undergoing PSA screening.⁶⁷ The Japanese Urological Association changed its position of ‘no recommendation for routine PSA testing’ to ‘recommended’ for all men.^{68, 69}

Table 6. Summary of RCTs that examined screening for PSA.

Publication	Trial Name	Comparators	Setting	Follow-up Time (years)	Screening Properties	Participants	Statistical Analysis	Study Endpoints	Results	Conclusions
Labrie F, Candas B; Cusan L; Gomez JL; Belanger A; et al. Screening decreases prostate cancer mortality: 11-year follow-up of the 1988 Quebec prospective randomized controlled trial. <i>Prostate</i> . 2004; 59: 311-8.	Quebec	Screening (PSA and DRE at 1st visit) to no screening	Single-center (university), Canada	11	PSA: 3.0 ng/ml as cut off with DRE at 1st visit	registered male voters aged 45-80 years in Quebec City, Canada	Cox proportional hazard model	Cause-specific mortality	67% reduction of cause-specific mortality in screened group vs not screened	results are consistent with other North American studies that examined the decrease of PC mortality in a screened population
Kjellman A; Akre O; Norring U; Tomblom M; Gustafsson O. 15-year follow up of a population based prostate cancer screening study. <i>J Urol</i> . 2009; 181: 1614-21.	Stockholm South Hospital	1-time screening (PSA, DRE, TRUS) vs no screening	Stockholm, Sweden	15 years	Initial examination with DRE, TRUS and PSA. • If abnormal findings on DRE and/or TRUS, underwent guided biopsies • If PSA > 7ng/ml, TRUS repeat • If PSA > 10 ng/ml, randomized quadrant biopsy taken	Males aged between 55 and 70 years, in the catchment area of Stockholm South Hospital	Poisson regression	1: PC death mortality 2: overall survival	No effect of screening on risk of death from PC or overall survival (IRR: 1.10; 95% CI: 0.83-1.46 and 0.98; 95% CI: 0.92-1.05, respectively) as compared to entire population	No evidence of screening benefit but screening had a benefit on overall survival
Andriole GL; Crawford ED; Grubb RL 3rd; Buys SS; Chia D; et al. Mortality results from a prostate-cancer screening trial. <i>N Engl J Med</i> . 2009; 360: 1310-9.	PLCO	Screening via PSA test and DRE	Multicenter, US	PSA: 6 DRE: 4	PSA serum: > 4.0 ng/ml = + for PC DRE: conducted by physicians, 'qualified' nurses or physician assistants	Men aged 55-59 years	event rates: ratio of number of events in a given time period to person-years at risk for the event (cancer diagnosis or death)	Men aged 55-59 years	At 7-10 years of follow up, the rate of death from PC was very low and didn't differ significantly between study groups	At 7-10 years of follow up, the rate of death from PC was very low and didn't differ significantly between study groups

Table 6. Summary of RCTs that examined screening for PSA (cont'd).

Publication	Trial Name	Comparators	Setting	Time (years)	Screening Properties	Participants	Statistical Analysis	Study Endpoints	Results	Conclusions
Schroder FH; Hugosson J; Roobol MJ; Tammela TL; Ciatto S; et al. Screening and prostate-cancer mortality in a randomized European study. <i>N Engl J Med.</i> 2009; 360:1320-8.	ERSPC	screening (PSA, DRE, transrectal ultrasound) vs no screening	Multicenter, Europe	9	PSA cut off: 3.0 ng/ml (most centers) Belgium, Finland, Italy, Netherlands; PSA cut off: 4.0 ng/ml Spain: 5.5-7.4 years Belgium: 5.5-6.9 years Finland: 5.5-6.7 years were included in final data set with PSA cut off of 10.0 ng/ml	Men aged 55-69 years at study entry Sweden: 50-54 years Belgium, Italy, Netherlands, Spain: 5.5-7.4 years Switzerland: 5.5-6.9 years Finland: 5.5-6.7 years	Poisson regression stratified by site, age group at randomization	1. overall mortality needed to screen (NNS): number of men needed to screen to prevent one PC death	rate ratio of death in screening group vs control group: 0.80 absolute risk difference: 0.71 death per 1,000 men NNS: 1,410	PSA reduced death rate from PC by 20% but was associated with over diagnosis
Sandblom G; Varenhorst E; Rosell J; Lofman O; Carlsson P. Randomised prostate cancer screening trial: 20 year follow-up. <i>BMJ.</i> 2011; 342: d1539.	Nonkoping	PC screening every 3 years w/ DRE and addition of PSA in 1993 and 1996	Multicenter, Sweden	14	PSA cut off: > 4ug/L	Men aged 50-69 in the city of Nonkoping, Sweden	PC- specific survival	tumor stage, grade and treatment prostate-specific mortality	Hazard comparing control group to screened group (death from PC) 1.23 adjusting for age at start of study: 1.58	Rates of death from PC did not differ significantly between screening group and controls
Hugosson J; Carlsson S; Aus G; Bergdahl S; Khatami A; et al. Mortality results from the Goteborg randomized population-based prostate-cancer screening trial. <i>Lancet Oncol.</i> 2010; 11:725-32.	Goteborg Center of ERSPC	screening (PSA, DRE, transrectal ultrasound) vs no screening	Single-center, Sweden	20	PSA cut off: 3.4 ng/ml (WHO correct value of 3.0 ng/ml between 1995 and 1998 threshold was 2.9 ng/ml (nominal 2.5 ng/ml) consistent with other ERSPC sites 2005 cut off: 2.5 ng/ml (assay calibration)	Men aged 50-64 years, residents of Goteborg, Sweden	Cox regression for survival, Poisson regression for mortality rate ratio	1. absolute and relative risk reduction in cumulative PC mortality 2. cumulative PC incidence, proportion of screenings attended	Cumulative PC incidence: 12.7% (screening group), 8.2% (control group) absolute cumulative risk reduction of death from PC at 14 years was 0.40% rate ratio of death from PC was 0.56 compared to control and screening	PC screening was reduced by ~1/2 but over-diagnosis was high Screening for PC is comparable to other cancer screening programs

DRE: digital rectal exam; PSA: prostate specific antigen screening test; PC: prostate cancer; TRUS: transrectal ultrasound; IRR: incidence rate ratio

The European Urology Association, American College of Preventative Medicine, and the US Preventative Services Task Force (USPSTF) endorse ‘No recommendation for [PSA] testing’ for men.^{70, 71} The American Cancer Society recommends that asymptomatic men who are at least 50 years old with at least a 10-year life expectancy should make an informed decision with their physician if PSA screening is appropriate for them. Men who are at high risk (i.e. African Americans, men with a first-degree relative who had a PC diagnosis before 65 years of age) should begin this conversation prior to age 50.^{72, 73} The Cochrane Library’s 2006 systematic review determined the evidence was insufficient to support or refute the routine use of mass, selective, or opportunistic screening for PC compared to no screening for PC.⁷⁴ Cochrane updated these recommendations in 2011 and 2013 with data for five RCTs to reflect that men with a life expectancy of less than 10 to 15 years should not be screened for PC and could potentially experience harm as a result of the screening.^{63, 75} Furthermore, the USPSTF states that screening for PC via PSA testing is associated with psychological harms due to false positive rates and further downgraded their evidence in May 2012 for PSA screening to ‘not recommended for asymptomatic men, regardless of age, race or family history’^{76, 77} The evidence for USPSTF PSA screening recommendations was supplied by two of the trials discussed in Cochrane’s 2011 review of screening for PC – the PLCO and ERSPC trials.⁷⁶

Though guidelines, like randomized controlled trials and observational studies, provide mixed recommendations on the appropriateness of PSA screening for PC, studies

demonstrate approximately half of the men deemed age-appropriate by guidelines undergo prostate screening regularly in the United States.⁵¹ Among men who undergo PSA screening, those who are falsely identified as having PC often begin treatment much to their peril and, ultimately experience urinary, bowel, and/or sexual dysfunction, and potentially death.^{78,78, 65} Additionally, unnecessary PC treatment often carries a psychological and financial toll for patients.^{79,80}

Though unnecessary PC treatment carries a toll for patients, it carries a larger toll on those who pay for medical services because payment is multiplied by the number of beneficiaries eligible for certain procedures. It is estimated that the US spends \$91 billion annually on unnecessary medical treatment.⁸¹ A portion of this spending can be attributed to false positive PSA tests and the subsequent diagnostic testing like biopsies. However, payers cannot reject coverage for these tests because many states mandate PSA testing coverage. Twenty-nine states have PC screening coverage laws.⁸² Medicare mandates complete coverage for one screening PSA test (a screening PSA and a diagnostic PSA, which occurs around the time of a PC diagnosis, have different billing code) annually for men over the age of 50.⁸³ Payers, among other stakeholders, could benefit from knowing what populations and under what parameters a PSA test could produce a useful result to the provider and patient. The USPSTF identified this as one gap of knowledge for PSA testing and added new screening modalities and knowledge of benefits and harms of immediate treatment and observational waiting in men with screen-positive PC as research needs in its 2012 recommendation for PSA screening. In their recommendations,

the USPSTF ultimately gave PSA screening a grade of D, or recommended against PSA-based screening for PC for any man in the US population, regardless of age.⁷⁶

Chapter Two

Uncertainty in Decision Making

Uncertainty inherently exists in decision making. While some decisions are made with more certainty (i.e. whether or not to go to work), others contain significantly more uncertainty (i.e. Do I have enough money to retire?). Results from clinical trials and observational studies serve as an evidence base to lower the uncertainty threshold that surrounds decision making. Often, evidence from these types of studies is assembled into guidances and clinical recommendations that are sponsored by professional organizations and federal agencies intended to set the ‘standard of care’ for a condition. The evidence surrounding the utility of PSA tests for screening of PC is varied. The USPSTF has identified different types of research that is needed to identify ways to reduce over-diagnosis and over-treatment of PC. These recommendations focus on altering PSA thresholds, identifying indolent disease, developing more sensitive screening modalities, and researching topics that allow for comparison of the long-term benefits and harms of immediate treatment versus active surveillance or delayed intervention in screened-positive men PC cases.⁷⁶ While these recommendations vary in terms of field of research (i.e. basic science to health outcomes research), decision analysis methods can help

determine and identify where resources for research efforts would be best placed. The value of information (VOI) framework can help to determine where resource allocation and research efforts should be concentrated in order to increase certainty around a decision. Many men and their physicians would like greater certainty to help decide whether PSA screening is useless or of decreased clinical value to some patient populations. The incomplete information surrounding PSA screening test makes a decision of whether or not to use the test challenging for society; thus the need exists for more information about the test and the subgroups it affects.

Value of Information

In decision making the word 'value' has different connotations to different stakeholders. The value of the PSA screening test depends not only on the clinical specifications of the test but also on the downstream clinical sequelae that can be attributed to the screening test. Additionally, researchers argue that clinical impact alone is insufficient to measure value for diagnostics because a patient's value of the test's result can affect whether or not they participate in and adhere to treatment.^{84, 85}

Diagnostic tests have three dimensions of value: medical value, planning value, and psychic value; medical value is a diagnostic test's ability to inform clinical treatment, planning value is a diagnostic test's ability to inform patients' choices (i.e. long term health, financial, reproduction), and psychic value is how a diagnostic test can affect a patient's sense of 'knowing.'⁸⁶ Patients rely greatly on psychic value and planning value

while providers and payers place more value on medical value.⁸⁶ VOI focuses on the medical value of a technology, intervention, or treatment.

In order to adopt a technology the only dimension that should be examined is medical value. One of two questions must be answered when deciding to adopt a technology. These questions are 1) whether or not to adopt or reimburse for a technology given the existing information and level of uncertainty and 2) whether or not to acquire additional information for adoption or reimbursement decisions. In deciding to adopt or reimburse given existing information, an investigator must question whether or not the existing information for all patient groups is the same for both the cost of the technology and the outcomes associated with the technology. In acquiring additional information, an investigator must decide what type of evidence (i.e. study design, outcomes of interest) is needed and how much evidence is ‘enough.’ Within these two questions, uncertainty is prevalent.⁹ VOI provides an analytic framework with which researchers can establish the value of additional information to inform a decision process and inform the value of future research. This framework allows for the comparison of potential benefits of additional research and the cost of further investigation, a comparison and prioritization of alternative research recommendations, in addition to assessing the value of investing in research or investing in other health services.⁸⁷ A VOI analysis seeks to monetarily quantify uncertainty in decision making. The result of such analysis is an estimation to help decision makers allow for greater or less resource allocation in a specific therapy area or in specific populations. The smaller the VOI estimate, the less, if any, resources should be committed to a therapy area; the larger the VOI estimate, the more resources

should be committee to a therapy area in order to eliminate uncertainty from its use. It is, however, inherent in decision making that uncertainty will exist. If a wrong decision is made, uncertainty can manifest into loss of health benefit, resources and money. Through VOI, the anticipated cost of uncertainty is determined by both the probability of a decision made on existing information will be wrong and the consequences of the wrong decision.⁸⁸ With VOI, the PSA screening test can be examined within a framework that utilizes evidence from a range of sources and allow for the extrapolation of costs and effects over time between clinical and lay stakeholders.⁸⁹

The Role of Inference

VOI requires three generic items to be accomplished in order to determine the amount of uncertainty in a decision. The first and most straight forward step is to construct a decision analytic model. The second step is to conduct probabilistic analysis of the decision model in order to characterize uncertainty. The third step is to establish the VOI. The second and third steps are not as straight forward as the first. For the second step, uncertainty is propagated throughout a decision model via Monte Carlo simulation. The output of which is the joint distribution and range of the costs and outcomes for each technology compared. From the joint distribution output, one could assemble the incremental cost-effectiveness ratio (ICER) of each therapy but a problem arises when trying to interpret the output with traditional tools of inference.⁹

Traditionally, rules of statistical inference work to reject a pre-defined hypothesis. VOI is designed not to reject a hypothesis but to determine whether additional information is

needed about a specific technology. One researcher has concluded that the traditional tools of inference are not necessary when conducting VOI because these tools restrict patient choice and impose inherent costs on a patient. These inherent costs are not necessarily monetary costs but also the costs associated with a patient foregoing the benefit of a treatment.⁹ Claxton argues that once a choice is given, [it] sets current practice. No one would suggest adopting a new treatment whose net benefit is less than current practice but this implied with traditional rules of inference.⁹⁰

Expected Value of Information

Perfect information eliminates the eventual costs attributed to uncertainty. The expected value of information (EVI) grows from a probabilistic decision model and is interpreted as the expected costs of uncertainty on a per person basis.⁹¹ A payer could be presented with a variety of therapies from which to choose that will positively impact the health of its beneficiaries. The payer should choose the therapy with the greatest net benefit (NB) in order to maximize the health outcomes of beneficiaries but will be subject to a constraint (i.e. technology constraint, budget constraint). The expected net benefit ($E_{\theta}NB$) of a therapy (tx) with uncertain parameters, Θ , is the expected health outcomes multiplied by the willingness-to-pay threshold, λ , minus the costs associated with the therapy.⁹²

Equation 1. $E_{\theta}NB(tx, \theta) = \lambda * E_{\theta}O(tx, \theta) - C_{\theta}(tx, \theta)$

If the payer was all-knowing and no uncertainty surrounded the decision of which therapy to choose, it would be guaranteed that the therapy with the greatest NB would be best for beneficiaries. However, uncertainty is prevalent in choosing which therapy to cover, and the therapy with the greatest NB potentially, could not be the best choice for beneficiaries. The EVI begins from a probabilistic model that defines NB. Net benefit is extracted from two treatments (treatments (tx) =1, 2) with Θ . When provided existing information, the best decision is the therapy that results in the maximum amount of expected NB. Once a decision maker knows how uncertainty propagates a model, the treatment could be selected that maximizes NB. It is expected that the real values of uncertainty are unknown over a range of information and values (I); as such, the expected value of information (EVI) from research on a per person basis can be described by the generalized equation below.⁹¹

Equation 2. $EVI = E_I \max_{tx} E_{\theta|I} NB[\theta, tx] - \max_{tx} E_{\theta} NB[\theta, tx]$

Population Expected Value of Information

The EVI for a *population* requires additional information that allows for the translation of the value of research to a population-level statistic. The *incidence* of a condition must be incorporated into a population model because the examined research can impact the *population* affected and the population at risk for the condition can change over time (t). Additionally, the likelihood that relevant information may not be implemented perfectly for a portion of the affected population must also be considered in

a population model (*implementation*). The depreciation in today's benefit of the technology or treatment must also be considered in a population model. This depreciation could account for improved or newly implemented treatments or clinical evidence that may alter the expected clinical benefit of the technology studied. In VOI, this concept of depreciation is referred to as *durability*. The final additional piece of information that must be included in forming a population EVI is the discount rate to future populations of current technology.⁸⁸ Discounting is vital because future cohorts may value today's technology less than those currently benefiting from the technology. This discount rate, β_t , will be categorized as $0 < \beta_t < 1$. The population EVI (pEVI) can be characterized by including the durability, implementation, incidence, population, EVI, and the discount rate.⁸⁸

Equation3.

$$pEVI = \beta_t \times durability_t \times implementation_t \times incidence_t \times population_t \times EVI$$

Population EVI provides a structure for determining whether or not to acquire more information about a treatment or intervention. One would select an intervention if its pEVI exceeded the cost of further investigation. If the pEVI for a specific intervention were high, research for this intervention may have as great returns than if the pEVI were low.⁸⁷ It is important to note that pEVI will vary based on the indications and outcomes of the specific treatment examined, patient populations, and cost-effectiveness threshold chosen.

Expected Value of Perfect Information

Uncertainty exists in any decision making. The ‘wrong’ decision could result in increased costs and decreased health benefits. Given the objective of a stakeholder making a medical decision (for a single patient or a population of beneficiaries) is to maximize health benefits given a budget constraint, a further extension of EVI is to establish the maximum amount that should be willing to pay to reduce uncertainty – a theoretical upper bound on research.⁸⁹ The expected value of perfect information (EVPI) is the difference of the maximum expected net benefit from a decision among various mutually exclusive treatment options with perfect information and the expected value with current information.⁹¹

$$\text{Equation 4. } EVPI = (E_{\theta} \max_{tx} NB [tx, \theta]) - (\max_{tx} E_{\theta} NB[\theta, tx]).$$

In applications, EVPI could point to specific endpoints that need further examination or EVPI could point to the need for more precise estimates of parameters. The latter could help triage what type of research is needed to refine existing research priorities.⁸⁷ More research should to reduce decision uncertainty and thereby reduce the probability of delaying the adoption of a beneficial technology or making a wrong decision about that technology. However, given economic constraints, more research for a technology is only justified if EVI is positive.^{93, 94} VOI methods can address important questions related to research funding. These questions are: 1) is further research for a technology potentially worthwhile, 2) is the cost of a given research design less than its expected value, 3) what

is the optimal research design for investigating a technology, and 4) how can research funding be best prioritized across alternative technologies?⁹⁵ Given the current environment that draws into question the clinical utility of PSA screening, determining the value of additional information of PSA screening to the clinical and lay community could provide a great deal of value.

The Minimal Modeling Approach for VOI

Value of information is recognized for providing a framework for estimating the expected benefits of clinical research.^{87, 88, 94-96} However, researchers conducting this type of research are confronted with many challenges. In fact, most VOI estimates lack sufficient data to fully characterize the uncertainty surrounding a decision process around a technology. In this case, decision analytic models are used to estimate VOI. These models, known as full models, characterize the technology by incorporating a decision model (i.e. decision tree, Markov model, or discrete event simulation) or other simulation methods to model the health state and decisions associated with the technology.⁸⁸ The full modeling approach to VOI is time-consuming, complex, and often too burdensome for practical applications.⁸⁸ The alternatives to full modeling are to use the ‘no modeling’ approach, in which the direct replication or calculation of effects on comprehensive health outcomes and the ‘minimal or limited modeling’ approach (**Table 7**). The minimal or limited modeling approach (MMA) models any clinical or cost characteristic (i.e. patient survival, mapping of treatment effect to utilities, aggregation of costs) without the aid of decision models or other forms of simulation of health states.⁸⁸ The MMA is

ideally suited when a body of existing clinical trials provides data on comprehensive measures of net benefit of the technology examined. Comprehensive measures used in MMA are generally quality-adjusted life-year (QALY) and costs. Valid representation of net benefit of the technology examined without the use of modeling would necessitate that the outcomes collected from trials be measured comprehensively, to the point where all study participants were followed until recovery or death. No modeling is conducted at the individual-level in the MMA. Bootstrapped replicates, simulations, replication or resampling decision values on raw patient-level data on relevant parameters can aid determining using MMA to VOI estimates.⁸⁸ Additionally the MMA method can be used when a technology affects one outcome but not another (i.e. quality-of-life but not survival while quality-of-life is directly measured by a clinical trial). Some modeling is needed to build a survival model of the technology but a full decision analysis is not necessary.⁸⁸

Though a relatively new method, previous MMA studies focus on clinical interventions like emerging medications, surgical procedures, and medical devices. The MMA method most often used to obtain VOI estimates is one in which modeling approximates patient survival or life expectancy, often using exponential distributions. Some researchers have used the MMA method to obtain the incremental cost-effectiveness ratio (ICER) for future trials or evidence based on prior information collected on costs and effects of the technology and research. Furthermore, other researchers used a parametric simulation technique that incorporated bootstrapped estimates of patient-level data on cost and effect, typically a ‘comprehensive’ effect like

QALY.⁸⁸ The most often reported outcome in applied VOI analyses is the person-level estimate of VOI, the EVI. The population-level estimate of VOI (pEVI) is reported less often, but the combination of the EVI and pEVI provide conditions which are necessary and sufficient for establishing the value of research and its funding.⁸⁸

The method of MMA has several limitations. The largest of which is the application of MMA to VOI framework. The MMA requires the use of comprehensive outcomes derived from an RCT in order to circumvent full modeling and is most appropriate when either expertise or data for full modeling are not available. MMA results are not as time consuming as full modeling and can quickly supply information to investigators deciding to fund or to continue an RCT. In the case of adaptive trials, MMA results can help to inform subsequent arms of the trial. Additionally, MMA can help to inform investigators about the promise held by new and emerging technologies by providing information about the need for larger, more strongly powered studies or trials. If a technology is new or impacts a disease which is chronic in nature, there may not be enough data to conduct MMA.⁸⁸ Furthermore, since MMA incorporates existing data, it may be difficult to completely estimate the expected value of partial information for specific parameters, unless these parameters are included in existing data, but investment in MMA findings can help identify parameters and other areas in which a greater return on research investment will be achieved.⁸⁸

Table 7. Modeling Approaches to Value of Information Calculations

Approaches	Definitions ^a	VOI Calculations	Data Requirements	Clinical Applications	Advantages (+) and Disadvantages (-)
Full Modeling	Full characterization of the disease/treatment using a decision model or other simulation model of relevant health state	Simulation/bootstrapping, parametric and/or nonparametric equation-based computation, parametric	Data on all model parameters	<ul style="list-style-type: none"> • Chronic conditions • Complex conditions 	+ Detailed uncertainty analysis and VOI estimates, including calculation of EVPPI - Complex and time-consuming modeling exercises
No modeling	Direct replication or direct calculation of (incremental) effects on comprehensive health outcomes (i.e. QALYs and/or net benefits)	Simulation/bootstrapping, parametric and/or nonparametric equation-based computation, parametric	Distribution of comprehensive health outcomes or QALYs and/or net benefits	<ul style="list-style-type: none"> • Acute conditions • End-of-life treatments • Direct measurement of final health outcomes 	+ No need for complex and time consuming modeling + Complementary to adaptive clinical trial design - Requires clinical trial that can provide comprehensive measure of net benefit - No comprehensive uncertainty analysis and VOI estimates (EVPPI)
Limited/ Minimal Modeling	Any modeling necessary (i.e. modeling of patient survival, mapping of treatment effect to utilities or aggregate approximation of costs) without using a decision model or other simulation methods of relevant health states	Simulation/bootstrapping, parametric and/or nonparametric equation-based computation, parametric	Intermediate measures for health outcomes or QALYs, costs, and/or NB, survival data	<ul style="list-style-type: none"> • Acute conditions • End-of-life treatments 	+ Reduced need for complex and time-consuming modeling + Complementary to adaptive clinical trial design - Requires clinical trial that can require only modeling of survival or other limited modeling to generate comprehensive measure of net benefit - No comprehensive uncertainty analysis and VOI estimates (EVPPI)

VOI: Value of Information; EVPPI: Expected Value of Partial Perfect Information; NB: Net Benefit; ^a: All approaches seek to address specific treatment or coverage decisions, characterize decision uncertainty, and establish VOI estimates
 Reprinted from: Meltzer DO, et al. Minimal modeling approaches to value of information analysis for health research. *Med Decis Making*. 2011; 31: E1-E2.

The MMA is well suited for the estimation of VOI of PSA screening. Several different RCTs exist whose primary outcomes examine comprehensive outcomes, PC-specific survival and overall mortality;⁹⁷⁻⁹⁹ however, these analyses utilized estimates from the SEER-Medicare dataset in order to estimate a realistic picture of uncertainty surrounding the use of and the research needed for the PSA screening test. Other randomized trials reviewed in Cochrane and discussed in the 2011 Cochrane review and

2010 metaanalysis on PC screening will not be used due to high risk of bias.^{76, 100} This dissertation research conducted VOI analysis from the perspective of a public or private health plan. This perspective includes direct medical costs accrued by a patient unlike a societal perspective, which may include indirect costs associated with care taking or loss of productivity.

Chapter Three

Methodology

This chapter describes the study population, data sources, and data analysis methods. The goal of these methods is to achieve the following aims:

- 1) Estimate the expected value of information (EVI) from research on a per-person basis for PSA screening based on the 2000-2007 SEER-Medicare
- 2) Estimate the population-level expected value of information (pEVI) on PSA screening in the US Medicare population
- 3) Estimate the expected value of perfect information (EVPI) of PSA screening in the US Medicare population

Study Population

The population used in this study is from the 2000-2007 Surveillance, Epidemiology, and End-Result (SEER)-Medicare Dataset. This dataset includes

information from two data sources, the SEER registry and the Medicare administrative fee-for-service claims. Male Medicare beneficiaries are included in this study.

SEER

The SEER registry was established in 1973 and collects information from cancer registries from 17 geographical areas (Atlanta, GA; Connecticut; Detroit, MI; Hawaii; Iowa; New Mexico; San Francisco-Oakland, CA; Seattle-Puget Sound, WA; Utah; Los Angeles, CA; San Jose-Monterey, CA; Rural Georgia, the Alaska Native Tumor Registry; Greater California; Kentucky; Louisiana; and New Jersey) in the United States. The SEER geographical areas are population-based and generalizable to the US Medicare population. This program collected information on demographic and clinical variables associated with incident cancer cases in each coverage area. Clinical information from each participant included date of diagnosis, cancer histology, stage and grade of tumor, cancer treatment recommendations (i.e. for prostate cancer watchful waiting, radiation, and chemotherapy), vital status, and cause of death.^{101, 102}

Medicare

Medicare is the government-supported health insurance entitlement for US citizens aged 65 years and older and for those with specific health-related disabilities. The Medicare program consists of four parts that cover different aspects of health care. Part A provides inpatient benefits for Medicare beneficiaries. Part B covers physician services, outpatient clinic care, durable medical equipment, and medications that are administered in an inpatient visit (i.e. certain chemotherapies). A majority of

beneficiaries (96%) who have Part A also enroll in Part B.¹⁰³ Part C consists of managed care plans into which beneficiaries must enroll. Medicare maintains a database of de-identified claims and fee-for-service transactions for all services covered under its respective plans for beneficiaries. Medicare Part D provides prescription drug coverage for beneficiaries who enroll into the plan. The Centers for Medicare and Medicaid Services estimates approximately 60% of its beneficiaries have enrolled into Part D.¹⁰⁴

SEER-Medicare

Linked, the SEER registry and Medicare administrative claims data includes all Medicare beneficiaries who also appear in the SEER registry from 1991 to 2009. The dataset provides the clinical measures as recorded in the SEER registry with healthcare utilization which is reflected in Medicare claims. Unique SEER identifiers (i.e. 8-digit SEER case ID number and a 2-digit registry ID) are used to link individuals with incident-case cancer who overlap each population; the linkage has been established to be accurate in 93% of SEER cases.¹⁰² Though the data are established to be accurate, there is a lag in data availability due to processed Medicare claims. The SEER-Medicare data set also includes a random 5% sample of Medicare beneficiaries who reside in SEER geographical areas who do not have cancer. Information available for the 5% non-cancer sample only includes that which is in the fee-for-service administrative claims and limited demographic characteristics (see SUMDENOM).

Patient Entitlement and Diagnosis Summary File (PEDSF)

The PEDSF was used to obtain basic demographic information (i.e. birth date; date of death; sex; race; state of residence; Medicare eligibility; reason for Medicare entitlement; HMO enrollment; and socioeconomic information from the 1990 and 2000 Census on each cancer case, etc.). The PEDSF also contained information regarding a beneficiary's Part D enrollment status from 2006 forward.

Summarized Denominator File (SUMDENOM)

The SUMDENOM file was used for obtaining basic information (birth date, sex, race, state of residence, enrollment in Part A and/or Part B, enrollment in an HMO, etc.) for the 5% non-cancer cases.

Medicare Provider Analysis and Review (MEDPAR)

MEDPAR files included information about Medicare Part A claims for short stay, long stay, and skilled nursing facility stays by beneficiaries. This file contained hospitalization information, including up to 10 International Classification of Disease 9th edition (ICD-9) codes for diagnoses and up to 10 procedure codes per hospitalization.

Carrier Claims (NCH)

Information obtained from the NCH files include all Medicare Part B claims resulting from physician services in clinics, hospitals or other provider sites.

Outpatient Claims (OUTPT)

The OUTPT files included information from all Medicare Part B claims from institutional outpatient providers for each calendar year. Together, the NCH and OUTPT files were used to obtain procedural Health Care Procedure Classification Codes (HCPCS) diagnoses, dates of claims, chemotherapy administration, and/or chemotherapy agents used during treatment and reimbursement amounts.

Home Health Agency (HHA)

The HHA files provided information from home health on number and type of visits and diagnosis.

Hospice

Hospice files were used to obtain information on claims submitted by hospice providers regarding type of care during inpatient care or home case care and the terminal diagnosis associated with that care.

Durable Medical Equipment (DME)

The DME files were used to collect information on use of oral and intravenous chemotherapeutic agents and infusion pumps used during cancer treatment by regional carriers.

Part D Events (PDE)

The PDE files contained information about a beneficiary's drug utilization, including date of prescription fill, drug dispensed (identified by National Drug Code), quantity dispensed, days supplied, total cost and out-of-pocket cost. Enacted in 2006, the Medicare Part D policy only available from 2007 for these analyses.

Identification of Key Covariates

The primary outcome of interest in this study was net monetary benefit (NMB); however, several steps were required in order to obtain this estimate. As previously

discussed, NMB is comprised of a survival effect and costs. In order to obtain these estimates, the analytic cohort was established by defining key demographic and clinical covariates.

Demographic variables included in the dataset, age, race, reason for censoring, SEER-registry area, state buy-in, urban location, and observation date were obtained from the SEER-Medicare datasets reflected in Table 8.

Table 8. SEER-Medicare datasets from which variables were collected for cases and controls.

Variable	Data Set Source from SEER-Medicare	
	Cases	Controls
<i>Demographic Variables</i>		
Age	PEDSF	SUMDENOM
Race	PEDSF	SUMDENOM
Urban Location	PEDSF	SUMDENOM
SEER-Registry Area	PEDSF	SUMDENOM
State Buy-in	PEDSF	SUMDENOM
<i>Analysis Variables</i>		
Last Observation Date	DME, HHA, HOSPICE, MEDPAR, NCH, OUTPT, PDE	DME, HHA, HOSPICE, MEDPAR, NCH, OUTPT, PDE
Reason for Censoring	PEDSF	SUMDENOM
<i>Clinical Variables</i>		
Charlson Comorbidity Index	DME, HHA, HOSPICE, MEDPAR, NCH, OUTPT, PDE	DME, HHA, HOSPICE, MEDPAR, NCH, OUTPT, PDE
PSA Screening Definition	DME, HHA, HOSPICE, MEDPAR, NCH, OUTPT, PDE	DME, HHA, HOSPICE, MEDPAR, NCH, OUTPT, PDE
Preventive Services	DME, HHA, HOSPICE, MEDPAR, NCH, OUTPT, PDE	DME, HHA, HOSPICE, MEDPAR, NCH, OUTPT, PDE
Prior Primary Care Provider Relationship	DME, NCH	DME, NCH

DME: Durable Medical Equipment, HHA: Home Health Agency, HOSPICE: Hospice Provider, MEDPAR: Medicare Provider Analysis and Review, NCH: National Carrier Claims, OUTPT: Outpatient Claims, PDE: Part D Events

Key demographic variables of interest in the analyses were age, race, urban location, SEER registry area, and state buy-in. Age was an important covariate because reviews of the published literature demonstrate that age is associated with an increase in PC diagnosis.¹⁰⁵ Literature reviews also include race as an important variable associated with diagnosis of PC.¹⁰⁵ African-Americans tend not to seek preventive care (i.e. PSA screening for PC), tend to be diagnosed disproportionately with PC compared to their non-African-American counterparts,¹⁰⁶ and have different test characteristics that may affect appropriate treatment of suspected PC.^{106, 107} Urban location was included as a covariate in the analysis because it helped to identify individuals who live in more densely populated areas. One could conclude more densely populated areas have an increased availability of healthcare providers which would make it easier to seek care. SEER registry area was included as a covariate because SEER regions are population-based and generalizable to the US Medicare population¹⁰² State buy-in was used as a proxy for socioeconomic status since it indicates whether an individual's Part A and/or Part B premiums are paid by the state. When this occurs, Medicare bills the state instead of the individual for premiums. These individuals have resources less than two times the SSI threshold. In SEER-Medicare, this variable is a count of the number of months of state buy in a year.¹⁰⁸

Key demographic variables are defined by case and control status in Table 9. In this study, two key analysis variables were date of last observation and reason for censoring. As reflected in Table 8, date of last observation was collected from claims

files. This date indicated the day, month, and year of last observation for each case and control. This variable was crucial in matching for index date and in estimating costs.

Table 9. Description of key demographic variables for cases and controls

Covariate	Operationalization of Covariates		Reference Category
	Cases	Controls	
Age	Age in 5 year increments at cancer diagnosis (i.e. 65-69 = 2, 70-74 = 3, 75-79 = 4, 80-84 = 5, 85-89 = 6, 90-94 = 7, 95+ = 8)	Age was calculated by subtracting days of age from date of Medicare birth from last month of observation of the study and dividing by 12 (converting days of age into years of age) Age in 5 year increments at cancer diagnosis (i.e. 65-69 = 2, 70-74 = 3, 75-79 = 4, 80-84 = 5, 85-89 = 6, 90-94 = 7, 95+ = 8)	65-69
Race	Defined as white = 1, black = 2, other = 0	Defined as white = 1, black = 2, other = 0	White
Reason for Censoring	Defined as Censored/End of Study: 0, Loss of Medicare Part A and B or gained Medicare Part C: 1,2, Death from any cause: 4 This variable also made up survival censoring variable where death = 1 and censoring = 0	Censoring variable corresponded with episode of eligibility Defined as Censored/End of Study: 0, Loss of Medicare Part A and B or gained Medicare Part C: 1,2, Death from any cause: 4 This variable also made up survival censoring variable where death = 1 and censoring = 0	N/A
SEER-Registry Area	Made into a dichotomous for each SEER region: San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose, Los Angeles, rural Georgia, greater California, Kentucky, Louisiana, New Jersey	Made into a dichotomous for each SEER region: San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose, Los Angeles, rural Georgia, greater California, Kentucky, Louisiana, New Jersey	Connecticut
State Buy-in	0-12, defined as 1 if any state buy-in; otherwise 0	0-12, defined as 1 if any state buy-in; otherwise 0	0
Urban Location	Recoded into dichotomous variable:	Recoded into dichotomous variable:	1

With the date of last observation, men were classified into one of the following categories: end of study (i.e. 31 December 2009), HMO enrollment, loss of Medicare Parts A and B, loss of Medicare Parts A and B, enrolled in an HMO, or died. Men who died were considered to contribute complete costs and thus contribute all of their observed costs to the study. Men who did not die were considered censored and contributed a portion of their costs to the study.

Clinical covariates used in these analyses were critical to its outcome. Charlson comorbidity index (CCI) was used to classify the wellness of individuals. CCI is useful in that it classifies comorbidities based on their risk of mortality.¹⁰⁹ This variable was defined by using the macro texts available on NCI’s website.¹¹⁰ In this study, CCI was classified as ‘0’ for having no comorbidities, ‘1’ for having at least one comorbidities, and ‘2+’ for having greater than two comorbidities.

PSA screening exam was the primary independent covariate in these analyses. PSA screening was identified by capturing the codes shown in Table 10 in any position on the administrative claim. For these analyses, it was important to distinguish the difference between a PSA screening exam and a PSA diagnostic exam. For these analyses, PSA screen was defined as not having a PC diagnosis code (ICD-9 code: 185) on the claim, the date on the claim is less than or equal to the cancer diagnosis data for cases, and having either HCPCS code G0103 or ICD-9 code V7644.

Table 10. Codes Used to Identify PSA Screening Tests

	HCPCS	Definition	ICD-9*,+	Definition
PSA screening exam	G0103	Prostate Cancer Screening – Prostate Specific Antigen Test	V7644	Screening for malignant neoplasms of prostate

*: codes included were captured if in any position on the claim

+: for PSA screening tests, ICD-9 V-code is required as an ordering diagnosis code

Use of preventive services was another key covariate in these analyses. Medicare identifies which preventive services for which it provides coverage.¹¹¹ From this list of services covered, only those for which men are eligible and those that would require a

pre-planned visit, similar to planning for a PSA test (i.e. cholesterol and diabetes screenings were not selected because it was seen as a service that a man could easily request his physician to perform at a routine visit or check-up). Using Medicare's 'Quick Reference Information: Preventive Services,'¹¹² to help identify billing codes, the following preventive services were selected: Medicare wellness exam, colorectal cancer screening, influenza vaccination, and pneumococcal vaccination. Administrative claim codes used in these analyses to identify each preventive service are shown in Table 11. For these analyses, an index date was used in order to distinguish the temporal relationship between a PSA screen and PC diagnosis. The matching algorithm of cases and controls for index date is described later in the chapter. Once matched, a control assumed the index date of his PC counterpart.

Having a prior primary care provider relationship is another covariate that was identified in the claims as shown in Table 12. Thinking this variable would be valuable in these analyses in that if a man has an existing relationship with a health care provider, he would be more likely to seek other healthy behaviors (i.e. seek preventive screening services). For these analyses, any man in the dataset who had at least one claim (i.e. at least one visit) for seeing a primary care provider was determined as having a relationship with a health care provider.

Since these analyses use both cases and controls, an index date needed to be established in order to distinguish the temporal relationship between a PSA screen and PC diagnosis. In this case, the index date was determined to be the date of cancer

diagnosis for cases. The index date for controls was determined from a modified one-to-one match on cases based on the same last observation date, last observation year, quarter, and/or month, and reason for censoring. This approach was modified in that

Table 11. Codes Used to Identify Preventive Services

Preventive Service	HCPCS	Definition	BETOS	ICD-9*	
Medicare	1. G0402	1. 'Welcome to Medicare Preventive Visit'		V700	
Wellness Exam	2. G0403	2. 'Welcome to Medicare Preventive Visit'			
	3. G0404	3. 'Welcome to Medicare Preventive Visit'			
	4. G0405	4. 'Welcome to Medicare Preventive Visit'			
	5. G0438	5. Codes used primarily after ACA (c. 2011)			
	6. G0439	6. Codes used primarily after ACA (c. 2011)			
	7. 99387	7. Preventive visit, age 65 and older			
	8. 99397	8. Preventive visit, age 65 and older			
	9. 99429	9. 'Unlisted Preventive Medicine Service'			
	Colorectal Cancer Screening	1. G0328, 82270, G0107	1. 'Fecal Occult Blood Test'		V7651
2. G0104, G0106		2. Flexible sigmoidoscopy			
3. G0105, G0121, 0066T		3. Colonoscopy			
4. G0120, G0122		4. Ba enema			
Flu Shot	4037F, 4274F, 90470, 90653, 90654, 90655, 90656, 90657, 90658, 90659, 90660, 90661, 90662, 90663, 90664, 90666, 90667, 90668, 90672, 90685, 90686, 90687, 90688, G8482, G8636, G8639, G9141, G9142, Q0034, Q2034, Q2035, Q2036, Q2037, Q2038, Q2039	Influenza Virus Vaccine Administration	O1G	V0481 C066	
	Pneumonia Shot	1. 90670	1. 'Pneumonoccal Conjugate Virus'		V0382
		2. 90732	2. 'Pneumonoccal Polysaccharide Vaccine'		C066
		3. G0009	3. Administration		

* codes included were captured if in any position on the claim

matches were sorted and chosen randomly for cases and controls that fit the desired criteria. A randomly matched pair was created; however, once a match was created, other

controls who qualified for the match on the same criteria were matched to the same case. For example, all cases with a last observation year of 2002, last observation month of July, and reason for censoring was due to death were matched to a single control of who met the same criteria. Among all cases who matched to the control, one was randomly chosen as the case match. All other controls who met the match criteria were assigned an index date of the randomly chosen case. These variables were chosen to help anchor the index date from the case to that of a control with the same reasons for leaving the study (i.e. people who left the study due to change in insurance coverage status are much different and do not provide complete information for costs), quarter and month were chosen to help control for any impacts seasonality may contribute to the cohort, and, finally, matching on year of last observation helped ensure members of the cohort had similar exposures to technology or treatment practice.

Table 12. Codes Used to Identify Relationship with Primary Care Provider

	<u>Claim file variable</u>			<u>Definition</u>
		<u>HCFASPEC</u>		
Primary Care Provider	1.	01	1.	General Practice
	2.	08	2.	Family Practice
	3.	11	3.	Internal Medicine
	4.	38	4.	Geriatric Medicine
	5.	84	5.	Preventive Medicine

This study also used matching to identify similar cases and controls. The final analytical cohort was matched in a one-to-one fashion base on 5-year age group, race, having had preventive services in the year prior to the index date, SEER registry area of index year, and state buy-in status during index year. As previously stated, race was

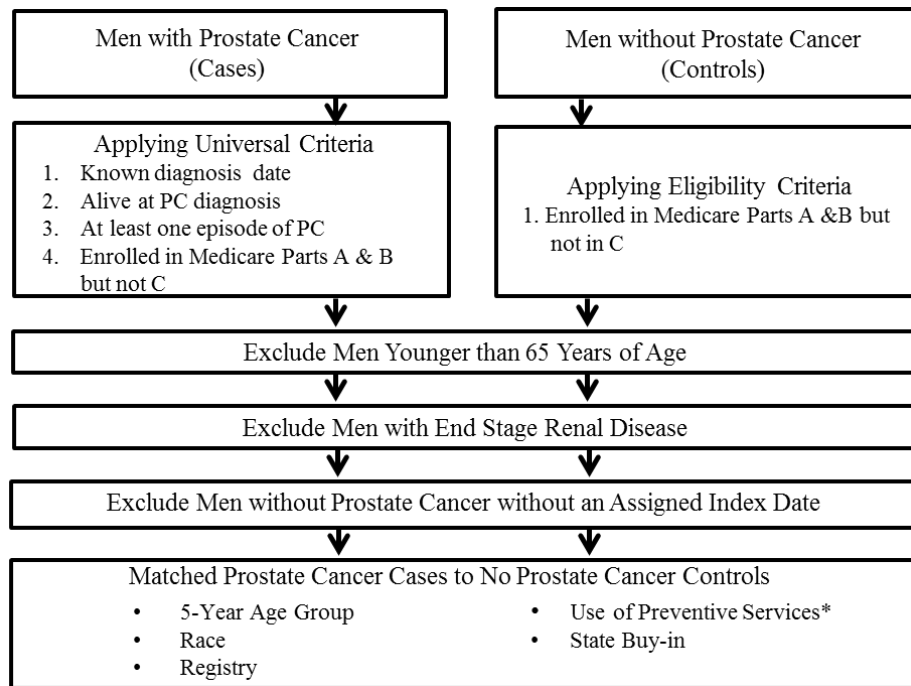
defined as African American, Caucasian, or other. For matching purposes, state buy-in was defined as a dichotomous variable (i.e. having state buy-in during index year, yes or no). For these analyses, the group of identified preventive services that made up the dichotomous 'preventive services' variable contained a variety of services of varying degree on invasiveness (i.e. influenza vaccine versus colonoscopy). The rationale for including a wide variety of services is that if a person was going to get a more invasive service, then he would be likely to get a less invasive service (i.e. wellness exam or PSA exam). Preventive services were defined as having at least one claim for the preventive health services described in Table 11.

Demographic characteristics of cases and controls were categorized by use of the chi-square (X^2) test to compare the distribution of frequencies within the entire cohort.

Inclusion/Exclusion Criteria

For inclusion in this study, men identified as cancer cases were obtained from the 2000-2007 SEER-Medicare dataset. Men must have a known PC diagnosis date, one or more episode of PC with at least 12 months prior to diagnosis date, be enrolled in Medicare Parts A and B and not be enrolled in a Medicare HMO or managed care plan (Medicare Part C), and be 66 years of age or greater. Men identified as non-cancer controls were identified in the 5% Medicare sample who met the following criteria: 1) enrolled in Medicare Parts A and B and not enrolled in Medicare Part C, and 2) have at least 12 months prior observation. Men identified as cases and controls who met the

inclusion criteria were excluded if they had end-stage renal disease. Furthermore, controls were matched to a case for an index date. Controls who did not match for an index date were excluded. For the final analysis dataset, cases and controls were matched on five covariates as previously described. Figure 1 demonstrates the flow of patients identified from the SEER-Medicare dataset through inclusion and exclusion criteria.



* The preventive services variable is defined as having at least one of the following procedures in the year prior to cancer diagnosis for cases and index date for controls, vaccination for influenza, vaccination for pneumonia, colorectal cancer screening (at least one of fecal occult blood test, flexible sigmoidoscopy, barium enema, or colonoscopy, or a billing code for colorectal cancer screening), or a Medicare wellness exam.

Figure 1. Flowchart of study inclusion/exclusion criteria.

Analytic Approaches

Survival

The survival portion of NMB was investigated via Cox Proportional Hazard Model. The Cox model is a semi-parametric model and does not require the modeler to make assumptions on the probability distribution to represent survival times, thus making the model more robust. Additionally the Cox model allows the user to control for covariates.¹¹³ The generic equation that encompasses the Cox assumptions is written as the following equation:

$$\text{Equation 5. } h_i(t) = \lambda_0 t * \exp(\beta_1 x_{i1} + \dots + \beta_k x_{ik})$$

Equation 5 generally defines the hazard for the i th individual at time t as the product of an unspecified, non-negative function, $\lambda_0 t$, and an exponentiated linear function that is a set of fixed variables (i.e. k). The unspecified, non-negative function, $\lambda_0 t$, can be consider the baseline hazard function for an individual whose covariate values all equal zero. The proportionality of the Cox Proportional Hazard model comes into play because the hazard for an individual, i , is a fixed value proportional to another individual, j .

$$\text{Equation 6. } \frac{h_i(t)}{h_j(t)} = \exp\{\beta_1(x_{i1} - x_{j1}) + \dots + \beta_k(x_{ik} - x_{jk})\}$$

In Equation 6, the term $\lambda_0 t$ cancels out in the numerator and denominator, leaving the constant ratio of the hazards.¹¹³ Survival regressions were conducted using SAS version 9.2 (Cary, NC), more specifically, the PROC PHREG command was used to estimate

Cox Proportional Hazards. Tests for proportionality will be conducted to ensure the model complies with the tenants of a Cox Proportional Hazard Model.

The primary independent variable in these analyses was a binary variable for having a PSA screen. Additional explanatory variables used in the regression included a binary indicator for urban location, preventive service use, having any state buy-in, African American race, other race, San Francisco registry area, Detroit registry area, Hawaii registry area, Iowa registry area, New Mexico registry area, Seattle registry area, Utah registry area, Atlanta registry area, San Jose registry area, Los Angeles registry area, rural Georgia registry area, greater California registry area, Kentucky registry area, Louisiana registry area, and New Jersey registry area. Clinical covariates included in the regression include binary variables for case status, having Charlson comorbidity index of one, having Charlson comorbidity index of two or greater, having a prior preventive service, and having a previous relationship with a primary care provider.

Costs

Costs, for these analyses, were divided into phase of care (i.e. initial, continuing, and terminal) for all men in the cohort. Assessing costs in this manner required several assumptions on part of the investigator. Primarily, one assumption was that no other regression-based method was better suited for estimating costs. Considering this cohort included men aged 66 and greater and, for cases, all stages of PC, a cancer whose patients tend to be diagnosed early and live with the disease for a number of years,¹⁰⁵ the

possibility existed for a high amount of administrative censoring due to the nature of PC. An additional contributor to potentially not capturing all deaths of the cohort is that this analysis captured a maximum of eight years of administrative claims. Some evidence suggests that studies examining the survival benefits of PSA needed at least 10 to 15 years of follow up data in order to detect any impact of PSA screening.¹¹⁴ Phases of care for PC typically reflect three phases: initial, continuing, and terminal. The initial and terminal phases typically consist of 12-months post diagnosis and 12-months pre-death, respectively.^{42, 115-117} Some researchers define the initial and terminal phase as a six month period as opposed to a 12 month period.¹¹⁸ The time in between the initial and terminal phases is considered the continuing phase of care. In keeping with the definitions and hierarchy of phases of care defined by the National Cancer Institute (NCI),¹¹⁶ these analyses defined the terminal phase as the first 12 months post diagnosis or index date for controls, the last 12 months before death as the terminal phase, and the time in between was considered the continuing phase. In terms of hierarchy of contributing to each phase, the terminal phase and the initial phase were the highest, respectively. This is the case because in the months following diagnosis and those preceding death are when costs accumulate the greatest amount. The continuing phase is considered a period of homeostasis until the treatment fails or disease progresses. Holding to these attributes, a plot of phases of care should result in a u-shaped curve, with costs increasing in the 12 months post diagnosis and 12 months prior to death.^{116, 118} In assigning phase of care, individuals' costs were allocated first to the terminal phase, for men who contributed complete costs. Costs were accrued for a man's contribution to each phase. Prioritization of costs to each phase of care was first to the terminal phase,

then to the initial phase, and lastly to the continuing phase for men who contributed complete costs. For men who were censored, priority of costs was to the initial phase and then to the continuing phase. For example, if a man contributed nine months of observation to the study and died, all nine months' worth of costs would be allocated to the terminal phase. If another man who was censored contributed 13 months of observation to the study, the first 12 months from diagnosis or index date would be allocated to the initial phase and the last month would be allocated to the continuing phase. If a man contributed 36 months of observation and died at the end of the follow up, the last 12 months from death would be allocated to the terminal phase, the first 12 months post-diagnosis would be allocated to the initial phase and months 13 to 24 would be allocated to the continuing phase.

Monthly allocation of costs was determined by first rolling the cost file up to a person-level file for the last month of observation. This person-level file also contained information that distinguished each individual as one who was censored or one who contributed complete costs. Using the last month of observation as the total months of observation and censoring status, individuals were divided up by the number of months contributed to the analytic file. For example, if an individual had complete costs and contributed 14 months of observation, he would go into the 'terminal phase' bucket, if an individual was censored and had 36 months of observation, he would go into the 'continuing phase' bucket. Once the cohort was divided into their respective phase of care by censoring status, each phase of care group was merged back into the monthly file to assign costs to phases by months from diagnosis or months from last observation. For example, a man who contributed 13 months of observation and was censored would

contribute his first 12 months of observation from diagnosis or index date to the initial phase and his 13th month would contribute to costs in the continuing phase bucket. Another man who died and contributed 36 months of observation to the cohort would contribute observed costs to each respective phase of cost. His last 12 months before death were contributed to the terminal phase. His first 12 months of observation after diagnosis or index date were contributed to the initial phase and his months 13 through 24 were contribute costs into the continuing phase bucket. Any man in the cohort who was censored did not contribute to the terminal phase, even if they were censored prior to the end of the study. The reason for not allowing censored men to contribute to the terminal phase is because of his censoring, investigators do not know anything about his costs or life after the censoring date. Thus men who were censored were only allowed to contribute to the initial and continuing phases of care.

Value of Information Analyses

The PROC PHREG command outputs a hazard ratio. These analyses incorporated the ‘baseline’ statement in order to output a data set that incorporated length of observation and an estimated survival for each length of observation. The mean estimated survival was determined for two groups: men with a PSA screening test and men without a PSA screening test. Using the Trapezoidal Rule, for the range of observations, each estimated survival was multiplied by the number of observations observing the survival. This product was summed for the range of observations to get a mean estimated survival PSA and for no PSA. This method is an algebraic formula of taking the area under the

survival curve. Once a mean estimated survival was obtained for each PSA cohort, the mean estimated survival of no PSA was subtracted from the mean estimated survival of PSA to obtain the incremental mean estimated survival for the study.

Descriptive analyses were conducted on each phase of care costs. These analyses included obtaining the mean, median, standard deviation, and number of months contributed to the phase in order to characterize each phase of costs. With each phase characterized, a distribution was chosen to use for NMB simulations. While some analyses assume that costs are normally distributed^{119,120} due to a large enough sample size where data could approach the normal distribution these analyses assumed a lower bound of zero and have no upper bound. Given these assumptions, the distribution used for NMB simulations was a gamma distribution. Using the mean and standard deviation, the alpha and beta parameters were calculated to designate skewness and shape for the distribution in preparation for bootstrapped simulation. Equations used for the alpha and beta parameters for a gamma distribution are shown in Equation 7 and Equation 8:

$$\text{Equation 7. } \alpha = \frac{\textit{mean}^2}{\textit{standard deviation}^2}$$

$$\text{Equation 8. } \beta = \frac{\textit{standard deviation}^2}{\textit{mean}}$$

The program used to calculate costs for the NMB estimates randomly took one cost from each phase of care for the PSA cohort and no PSA cohort. To get the distribution of costs, one cost from each phase of care was randomly drawn from the

distribution. The randomly selected costs were summed to obtain an estimate for the No PSA and PSA cohorts. To get the incremental cost, the difference was taken between the two cohorts over for the entire distribution. The difference of the sum of the three phases for each PSA cohort resulted in the incremental costs used in NMB calculations.

Willingness to pay (WTP) is an important threshold used in economic evaluation. This threshold (denoted as λ) helps to define what an entity (i.e. government, insurance company, etc.) is willing to give up in order to gain one unit of ‘something,’ where ‘something’ could equal a hospitalization, adverse event, or life-year. In these analyses the unit of ‘something’ is life year, as defined in incremental survival methodology above. The amount an entity is willing to give up, or pay, is traditionally accepted to be between \$20,000 and \$100,000, depending on the therapy examined.¹²¹ The WTP for cancer screening modalities is typically \$50,000. The types of cancer screening using this WTP includes cervical cancer screening,¹²² human papillomavirus screening,¹²³ breast cancer,¹²⁴ skin cancer,¹²⁵ colorectal cancer,¹²⁶ and prostate cancer via the PSA screening test.¹²⁷ Among these, two studies used a \$50,000 to \$100,000 WTP threshold as a form of sensitivity analysis.^{122, 123} Considering this evidence, these analyses used a base case WTP threshold of \$50,000 and included sensitivity analyses of a lower WTP threshold of \$20,000 and an upper WTP threshold of \$100,000.

In order to obtain NMB, a gamma distribution of incremental costs from phase of care from each cohort and incremental mean life years was created in Microsoft Excel (Excel). In Excel, 10,000 random replicates were drawn from each phase of care and

incremental mean life year distribution. A program run via excel randomly choose one cost from each phase of cost and one incremental mean life year and used these estimates to get NMB by applying them in the manner shown in Equation 1. NMB replicates were generated and the mean, max of NMB, and max of average NBM across all replicates were selected and applied to EVI equations. Figure 2 visually describes this process.

The incremental cost from each of the 10,000 simulations was taken. The maximum and mean values obtained from subtracting the summed phase of care of the no PSA cohort from that of the PSA cohort. The NMB for the sample population was calculated using Equation 1. The EVI was calculated by subtracting the mean NMB from the max NMB.

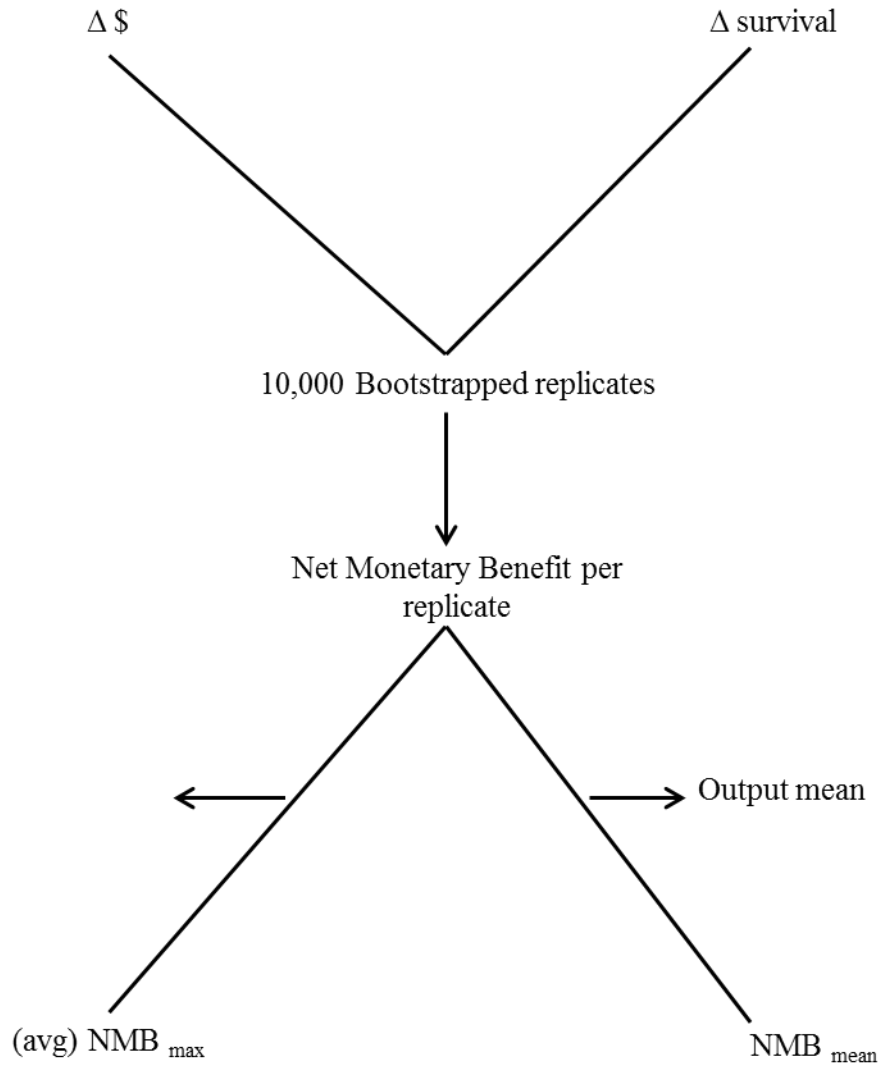


Figure 2. Pictorial Representation of Microsoft Excel Code Used to Generate VOI Estimates

Estimates for population expected value of information (pEVI) were calculated for race/ethnic subgroups (i.e. African Americans and Caucasians) and for age subgroups (i.e. men aged 65-74 and men aged 75+). The race subgroups were chosen because literature reflects that African Americans are more likely to have PC and more likely to die from PC than their white counterparts.^{8, 10} The age subgroup was selected because it is known that PSA levels change as a man ages and studies have suggested age-specific

PSA thresholds.⁴³ Estimates provided through these analyses could help guide whether or not additional research funding should further explore the use of age-specific thresholds for PSA. Equation 3 reflects the parameters necessary to determine pEVI. Other multipliers included in the pEVI calculations include the incidence for each subgroup which was obtained from SEER-Medicare estimates,¹²⁸ population Medicare which was obtained from the 2012 Medicare report of the board of trustees and the percentage of each subgroup's makeup from Medicare was obtained from the Chronic Condition Warehouse, a research database that contains administrative claims for Medicare and Medicaid beneficiaries,^{129, 130} durability and implementation. Values for durability and implementation remained at 1.0 for base case analyses.

To calculate the EVPI, 1,000 bootstrapped replicates were generated from the EVI simulations. The mean of the means and mean of the maxes was calculated from the 1,000 replicates. EVPI was estimated by subtracting the mean of the means from the mean of the maxes. As with estimating the EVI, various λ thresholds were used as sensitivity analyses from the base case.

Chapter Four

This chapter presents the results from the data analyses previously described. The purpose of these analyses was to achieve the study's aims which are as follows:

- 1) Estimate the expected value of information (EVI) from research on a per-person basis for PSA screening based on the 2000-2007 SEER-Medicare
- 2) Estimate the population-level expected value of information (pEVI) on PSA screening in the US Medicare population
- 3) Estimate the expected value of perfect information (EVPI) of PSA screening in the US Medicare population

The results of the descriptive analyses are reported first and are followed by the results of the analytical analyses.

Descriptive Analyses

From the 2000-2007 SEER-Medicare Dataset, 335,242 men with PC and 274,133 men without PC were identified as potentially being eligible for the study. As described in Figure 3, the following numbers of men were excluded from the study due to not

meeting the ‘universal’ criteria for being considered for the case cohort: 1) known diagnosis date: 2,674; 2) alive at PC diagnosis: 3,013; 3) at least one episode of PC: 9; 4) enrolled in Medicare Parts A and B but not C: 166,038; thus a total of 163,204 men with PC met the ‘universal’ criteria. Furthermore, 7,754 men were excluded for being younger than 65 years of age and 571 men with PC were excluded for having end-stage renal disease. The total number of men with PC who meet all eligibility criteria was 154,879. For men without PC, the following numbers were excluded due to not meeting the ‘universal’ criteria for controls, enrolled in Medicare Parts A and B but not C: 88,022 which left 186,111 non-PC controls who met the ‘universal’ criteria. Among these men, 37,259 were excluded for being less than 65 years of age, and 779 were excluded for having end-stage renal disease. A total of 148,073 men without PC, or controls, met all eligibility criteria. Figure 3 provides a visual reference of how men were excluded from the study.

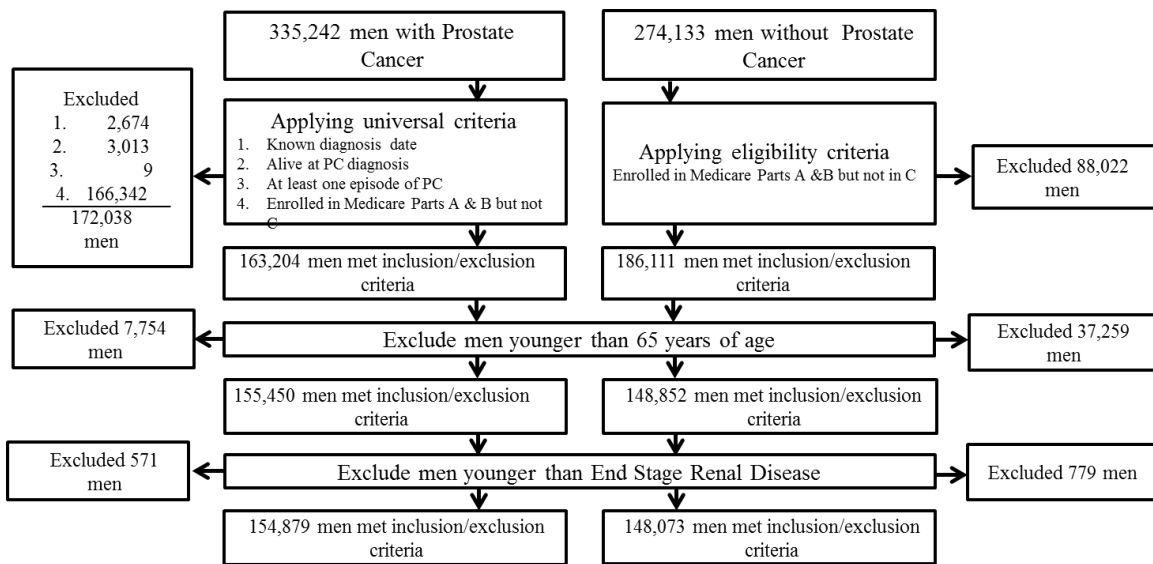


Figure 3. Flowchart for eligibility into study cohort.

Once men were identified as being included in the study, there were then prepared to be matched for their index date. In order to match the men, the cases and controls were identified as having a PSA screening exam or not and divided into four groups: Group 1: men with a PSA screening exam and diagnosed with PC; Group 2: men with a PSA screening exam and not diagnosed with PC; Group 3: men without a PSA screening exam and diagnosed with PC; and Group 4: men without a PSA screening exam and not diagnosed with PC. Figure 4 shows a breakdown of the numbers of men in each of the four groups.

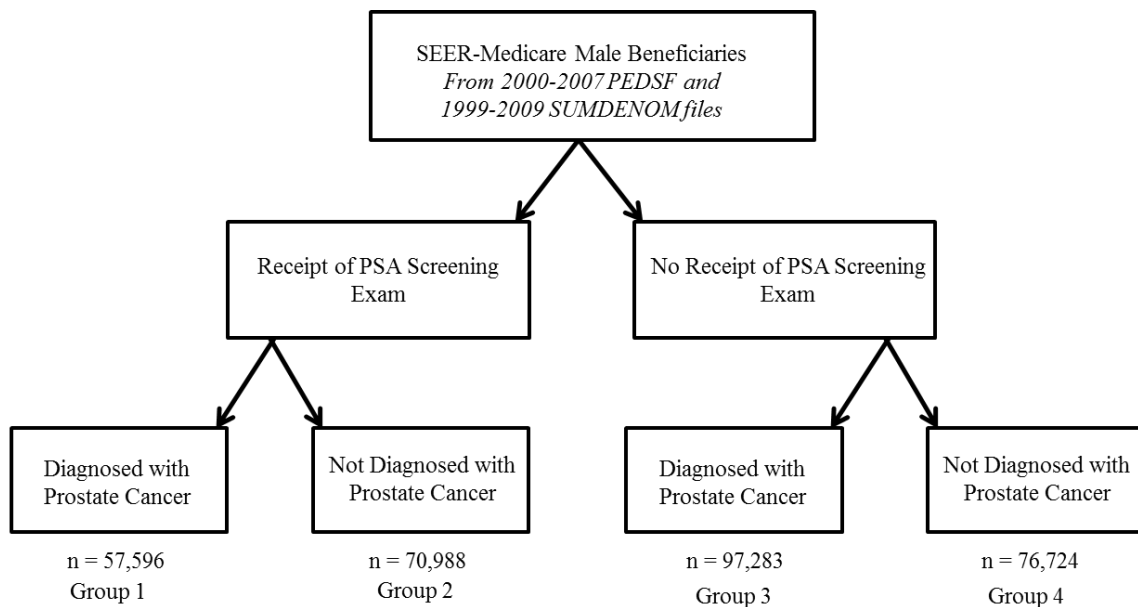


Figure 4. Four Groups of Men by PSA Screening Status and PC Status.

The men in Group 2 and Group 4 were matched to their counterparts in Group 1 and Group 3 in order to obtain an index date, or a proxy diagnosis date, for further study analyses. The match for index date was described in detail in Chapter 3. Two approaches were taken to determine the best way to achieve the match for index case, the case and

control having the same: 1) last observation year; 2) last observation month or quarter; and 3) reason for censoring. Table 13 shows the results of these two methods for identifying a match cohort. Matching cases and controls on last observation year, month, and reason for censoring resulted in a loss of 361 men from Group 2 and none in Group 4 since there were more cases than controls. In other words, all men in Group 1 and Group 2 had a corresponding study participant with the same last observation year, last month of observation and reason for censoring. As such, the men in Group 2 (the controls) were assigned the diagnosis date/index date of their matched counterpart from Group 1. Matching the four groups on last year of observation, last quarter of observation, and reason for censoring resulted in dropping 164 men from Group 2 and none from Group 4.

Table 13. Matching Controls to Cases to Identify an Index Date.

Method	Group 1 (n = 57,596)	Group2 (n = 71,349)	Group 3 (n = 97,283)	Group 4 (n = 76,724)
Match on:				
1) Year of Last Observation				
2) Month of Last Observation		n = 70,988		n = 76,724
3) Reason				
Dropped from cohort due to lack of matching index date:	-	361	-	-
Match on:				
1) Year of Last Observation				
2) Quarter of Last Observation		n = 71,185		n = 76,724
3) Reason				
Dropped from cohort due to lack of matching index date:	-	164	-	-

Even though the method resulted in more men disqualified for the study, analyses proceeded with the four groups matched on year of last observation, month of last observation, and reason for censoring in order to allow for a more diverse group of men

in terms of index date included in the analyses. With men excluded from each control group, Group 2 consisted of 70,988 men and Group 4 consisted of 76,724 men. With 154,879 cases and 147,712 controls identified, the analysis proceeded with matching cases and controls to ensure cohort similarities. After matching on 5-year age group, race, registry, use of preventive services (i.e. at least one of the following in the year prior to diagnosis date/index date: vaccination for influenza or pneumonia, colorectal cancer screening (at least one of fecal occult blood test, flexible sigmoidoscopy, barium enema, or colonoscopy), or a Medicare wellness exam)), the final analytical cohort resulted in 64,533 cases and 57,366 controls being excluded from the study. All-in-all, study attrition resulted in a loss of 73% of the cases and 67% of the controls. Figure 5 demonstrates the reduction of the entire cohort to the final analytical cohort.

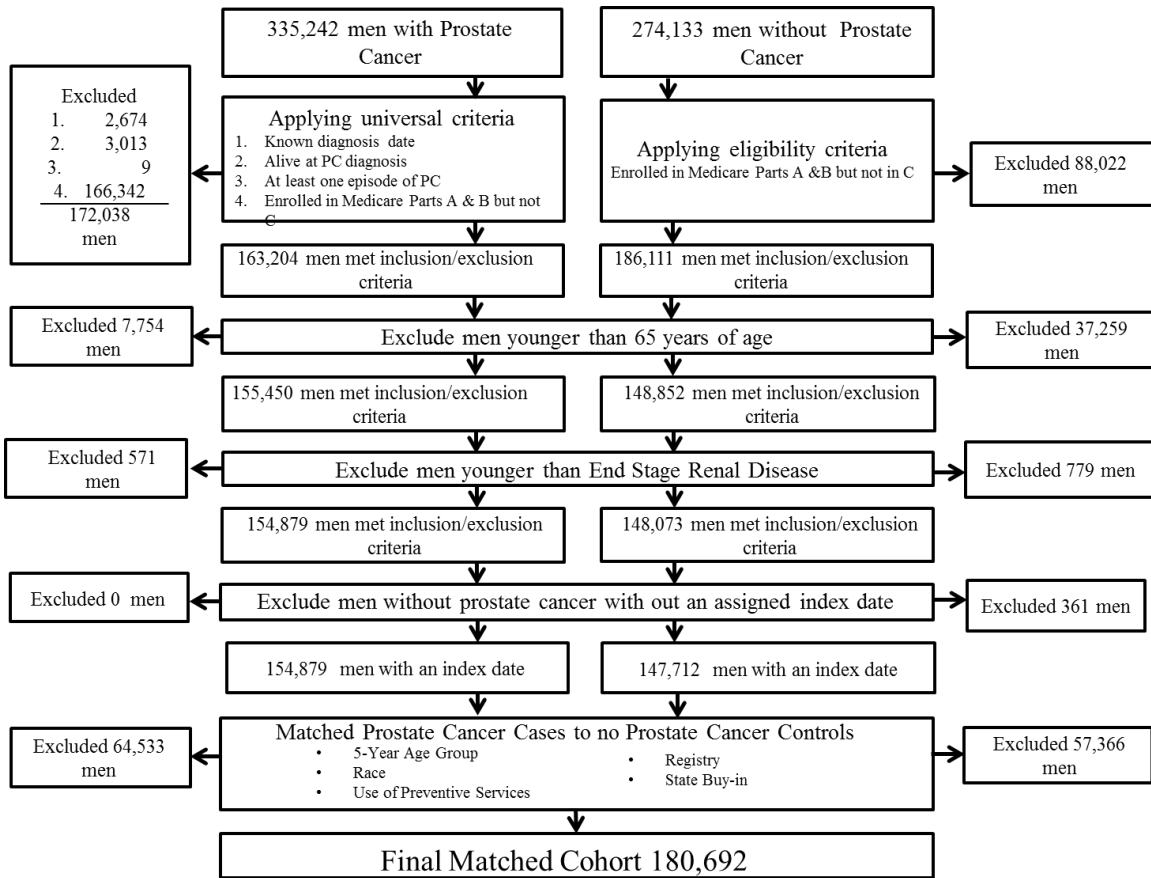


Figure 5. Flow Chart of the Final Analytical Cohort

Accurately identifying a true PSA screening test versus a PSA test that was considered part of a PC diagnosis was very important to the outcomes of this study. In order to accurately categorize the timing between PSA screen and PC diagnosis, a simple frequency of time from PSA screen (as identified by the PSA screening algorithm described in Chapter Three) to PC diagnosis, in days was conducted. As reflected in Table 14, most PSA screens (69.75%) occurred more than 180 days prior to PC diagnosis; however, one could determine around 15 days prior to PC diagnosis, a drop in screening occurred.

Table 14. Days from PSA Screening Test to PC Diagnosis.

Days from prostate cancer diagnosis	Frequency	Percent	Cumulative Frequency	Cumulative Percent
PSA screen is greater than 180 days from prostate cancer diagnosis	82,905	69.75	118,861	100.00
PSA screen is 91 to 180 days from prostate cancer diagnosis	8,139	6.85	35,956	30.25
PSA screen is 61 to 90 days from prostate cancer diagnosis	4,888	4.11	27,817	23.40
PSA screen is 31 to 60 days from prostate cancer diagnosis	9,109	7.66	22,929	19.29
PSA screen is 15 to 30 from prostate cancer diagnosis	7,624	6.41	13,820	11.63
PSA screen is 8 to 14 from prostate cancer diagnosis	3264	2.75	6,196	5.21
PSA screen is 1 to 7 days from prostate cancer diagnosis	2,594	2.18	2,932	2.47
PSA screen is 0 days from prostate cancer diagnosis	338	0.28	338	0.28

Data in table contain multiple PSA screens per person from the inclusion cohort.

Estimating that this timing (approximately 2 weeks) coincided with an approximate timeline of getting a PSA screening test completed, having lab work conducted on the collected blood specimen, results confirmed, and laboratory results returned to the physician, we determined a true PSA screening exam was indicated rather than one used to aid in PC diagnosis. This decision was confirmed by a clinician (Dr. Arif Hussain). Taking this decision into consideration, and refining the definition of a true PSA screening exam to be as follows: 1) having HCPCS or ICD-9 code^a in any position on an administrative claim; 2) not having a PC diagnosis^b code; 3) the date of the testing claim is 15 days or greater from the PC diagnosis date.

Table 15 reflects the distribution in the final analytical cohort using the refined definition of PSA screening test in days until PC diagnosis.

^a HCPCS code G0103 (Prostate cancer screening; prostate specific antigen test, total) and ICD-9 code V7644 (Screening malignant neoplasm of the prostate)

^b ICD-9 code 185 (malignant neoplasm of the prostate)

Table 15. Frequency of PSA Screens in the Final Analytical Cohort.

Days from prostate cancer diagnosis	Frequency	Percent	Cumulative Frequency	Cumulative Percent
PSA screen is 15 to 30 from prostate cancer diagnosis	7,624	6.77	7,624	6.77
PSA screen is 31 to 60 days from prostate cancer diagnosis	9,109	8.09	16,733	14.85
PSA screen is 61 to 90 days from prostate cancer diagnosis	4,888	4.34	21,621	19.19
PSA screen is 91 to 180 days from prostate cancer diagnosis	8,139	7.22	29,760	26.41
PSA screen is greater than 180 days from prostate cancer diagnosis	82,905	73.59	112,665	100.00

Data in table contain multiple PSA screens per person from the inclusion cohort and exclude screens that occur within 14 days or less of PC diagnosis

Dividing the cohort by PSA-status, Table 16 reflects demographic characteristics of the analytical cohort. Among men who were cases, 63.81% were screened while 59.1% of controls did not obtain a PSA screen. Age was fairly evenly distributed among 5-year age groups and by PSA screening status; however older people (i.e. those older than 80 years of age) did not obtain screening (no screening vs screening, 80-84: 55.07%, 40.26%; 85-89: 59.74%, 40.26%; 90-94: 68.41%, 31.69%; 95+: 78.46%, 21.54%). SEER Registry area was fairly evenly split among PSA screening status; although several regions reflected either a high proportion of individuals being screened (i.e. Connecticut, 63.49%; Iowa, 62.87%) or a high proportion of individuals not being screened (i.e. Los Angeles, 68.79%, San Francisco, 72.55%; and San Jose, 63.07%). Men who had a relationship with a primary care provider were fairly evenly split among those who did and did not obtain PSA screens and the proportion of men who did not have a primary care provider relationship and obtained a PSA screen was lower than those who did not obtain a screening exam (31.49% vs 68.51%). More men who obtained a PSA screening test also obtained preventive services (57.46% vs. 42.54%). Men who did not obtain PSA screening were less likely to seek preventive services (61.04% vs. 38.96%).

Table 16. Descriptive Characteristics of the Analytical Cohort

	<u>No PSA Screening</u>		<u>PSA Screening Exam</u>			
	N	%	N	%		
Prostate Cancer Diagnosis						
	No	36,954	40.9	53,392	59.1	< 0.01
	Yes	57,652	63.81	32,694	36.19	
Age Group						
	65-69	8,782	46.67	10,034	53.33	< 0.01
	70-74	22,281	46.1	26,053	53.9	
	75-79	27,381	53.73	23,577	46.27	
	80-84	20,992	55.07	17,126	44.93	
	85-89	11,312	59.74	7,622	40.26	
	90-94	3,246	68.31	1,506	31.69	
	95+	612	78.46	168	21.54	
Race/Ethnic Group						
	African American	8,791	62.39	5,299	37.61	< 0.01
	Caucasian	76,546	50.6	74,738	49.4	
	Other	9,269	60.51	6,049	39.49	
Urban Living Area						
	No	8,975	45.04	10,950	54.96	< 0.01
	Yes	85,631	53.26	75,136	46.74	
SEER Registry Area						
	Atlanta	2,382	45.7	2,830	54.3	< 0.01
	Connecticut	4,136	36.51	7,192	63.49	
	Detroit	6,377	50.8	6,177	49.2	
	Greater California	19,676	56.34	15,246	43.66	
	Hawaii	1,560	49.43	1,596	50.57	
	Iowa	4,767	37.13	8,071	62.87	
	Kentucky	7,526	48	8,152	52	
	Los Angeles	9,299	68.79	4,219	31.21	
	Louisiana	5,893	42.41	8,001	57.59	
	New Jersey	14,622	58.57	10,342	41.43	
	New Mexico	3,046	58.53	2,158	41.47	
	Rural Georgia	208	43.7	268	56.3	
	San Francisco	4,511	72.55	1,707	27.45	
	San Jose	2,538	63.07	1,486	36.93	
	Seattle	4,976	46.6	5,702	53.4	
	Utah	3,089	51.24	2,939	48.76	
Primary Care Provider						
	No Prior Relationship with a Primary Care Physician	34,306	68.51	15,772	31.49	< 0.01
	Prior Relationship with a Primary Care Physician	60,300	46.17	70,314	53.83	
Use of Preventive Services						
	No	58,534	61.04	37,368	38.96	< 0.01
	Yes	36,072	42.54	48,718	57.46	

The use of preventive services was fairly evenly distributed among men in the no PSA screen and PSA screen group (Table 17) The most commonly obtained preventive

service was an influenza vaccine (72.5% of all preventive services) and the least commonly obtained service was the pneumonia vaccine (6.37% of all preventive services obtained).

Table 17. Frequency of Preventive Services by PSA Screening Status

	No PSA Screening		PSA Screening		
	N	%	N	%	
Wellness Screen					< 0.01
	No	92,438	53.02	81,918	46.98
	Yes	2,168	34.22	4,168	65.78
Colorectal Cancer Screen					< 0.01
	No	88,772	52.72	79,608	47.28
	Yes	5,834	47.38	6,478	52.62
Influenza Vaccine					< 0.01
	No	67,859	58.17	48,790	41.83
	Yes	26,747	41.76	37,296	58.24
Pneumonia Vaccine					< 0.01
	No	92,011	52.56	83,046	47.44
	Yes	2595	46.05	3040	53.95

Individuals could have any preventive service

Fifty percent of the final analytic cohort was comprised of PC cases. Most tumors were well or moderately differentiated (Table 18). Among all men, those who did not obtain PSA screening had more advanced extent of disease (Distant: 77.27%; Local or Regional: 62.26%). Also among men who did not obtain PSA screening, a greater proportion had a higher staged disease (i.e. stage 3: 65.80%; stage 4: 75.06%; stage 5: 71.59%). Overall, men who received PSA screening were diagnosed with lower stage of disease than their study counterparts who did not obtain PSA screening.

Table 18. Tumor/Disease Characteristics Among Cases in the Final Analytical Cohort.

	No PSA Screening		PSA Screening		
	N	%	N	%	
Tumor Grade					< 0.01
Poorly or Undifferentiated	21,706	60.00	14,473	40.00	
Well or Moderately Differentiated	35,946	66.36	18,221	33.64	
Extent of Disease					< 0.01
Distant	4,460	77.27	1,312	22.73	
Local or Regional	49,390	62.26	29,938	37.74	
In situ		NR		NR	
Unstaged	3,772	72.43	1,436	27.57	
Stage					< 0.01
0		NR		NR	
1	13,070	75.33	4,281	24.67	
2	19,723	51.28	18,741	48.72	
3	2,184	65.80	1,135	34.20	
4	5,516	76.06	1,736	23.94	
5	17,109	71.59	6,788	28.41	

NR:Due to data requirements from SEER-Medicare, numbers not shown due to low N

Survival

After matching cases and controls, tests for proportionality were conducted to ensure the proportional hazard assumption of the Cox model was completed. No variables violated the proportional hazard assumption. Results from the Cox model are shown in Table 19. The primary independent variable, PSA screen, was impactful in reducing the risk of death (HR: 0.608; 95% CI: 0.596-0.620). Two clinical variables included in the model had a different survival impact than anticipated. Having a preventive service reduced the risk of death by 8% (HR: 0.925; 95% CI: 0.887-0.965) but

having a primary care provider relationship increased the hazard of death in the model (HR: 1.192; 95% CI: 1.148-1.238). Not surprisingly, as CCI increased, the hazard increased compared to having a CCI of 0. Demographic variables behaved as one would anticipate. Men who lived in an urban location had a lower hazard as compared to those who did not (HR: 0.959; 95% CI: 0.930-0.989). As age increased in the cohort, the hazard of death significantly increased for all age groups at the $p < 0.001$ level (HR 70-74: 1.286; HR 75-79: 1.769; HR 80-84 2.894; HR 85-90: 4.691; HR 90-94: 7.548; HR 95+: 12.080). African American men had a 15% increase in hazard (HR: 1.157 95% CI: 1.122-1.103) compared to their Caucasian counterparts and men of 'other' race had a decreased hazard compared to their Caucasian counterparts (HR: 0.68 95% CI: 0.655-0.707). Men with any state buy-in had an increased risk of death (HR: 1.587 95% CI: 1.547-1.628) compared to men who did not have any state buy-in. For SEER registry area, as compared to Connecticut, San Francisco (HR: 0.739 95% CI: 0.697-0.783), Detroit (HR: 0.941 95% CI: 0.899-0.986), New Mexico (HR: 0.941 95% CI: 0.856-0.970), Seattle (HR: 0.936 95%CI: 0.891-0.984), San Jose (HR: 0.721 95%CI: 0.672-0.772), Los Angeles (HR: 0.671 95%CI: 0.640-0.704), Greater California (HR: 0.860 95%CI: 0.826-0.895), and New Jersey (HR: 0.845 95%CI: 0.811-0.880) had a statistically significant reduced risk in dying as compared to men in the Connecticut SEER-area; however, men in Louisiana had a slight increase in the risk of death (HR: 1.063 95%CI: 1.015-1.113)

Bivariate analyses revealed one critical characteristic of the cohort – a very high amount of censoring. Approximately 70% of the sample is censored in these analyses, thus survival estimates were based off of 30% of the entire population.

Costs

Analyses of costs were completed by using the ‘phase of care’ approach due to the high amount of censoring in the cohort. Though several methods for controlling for censored costs existed in the literature, no review exists to compare these methods.¹³¹ Two common methods that weight costs to address censoring include Bang and Tsiatis’¹³² and Lin’s¹³³ approach for dealing with censored costs; however, researchers have found that using a phase-based cost approach for censored data provided costs estimates that are similar to the re-weighted methods. With heavy censoring, phase-based cost estimates was determined as a feasible alternative to re-weighting methods.¹³⁴ This approach is commonly described by researchers at NCI in estimating their cost projections for various cancers.¹¹⁶ Indicative of the phase-based costing approach, is a ‘u-shaped’ curve that demonstrates the phases of care (e.g. initial phase – 12 months directly after diagnosis, terminal phase – 12 months prior to death, and the continuing phase which describes the months in between the initial and terminal phase) among study participants who contribute complete costs, or die during the course of the study period. The u-shaped curve for these analyses plotted the estimated mean monthly costs for each phase of care where any costs were contributed for months in the phase. In other words, the mean cost

Table 19. Results from Cox Proportional Hazard Model

Parameter		Hazard Ratio	95% Hazard Ratio Confidence Interval
PSA Screen	No	<i>Reference</i>	
	Yes	0.608*	0.596 - 0.620
Preventive Service	No	<i>Reference</i>	
	Yes	0.925 ⁺	0.887 - 0.965
Prior Relationship with Primary Care Provider	No	<i>Reference</i>	
	Yes	1.192*	1.148 - 1.238
Urban Location	No	<i>Reference</i>	
	Yes	0.959 ⁺	0.930 - 0.989
5-Year Age Group	65-69	<i>Reference</i>	
	70-74	1.286*	1.230 - 1.344
	75-79	1.769*	1.695 - 1.845
	80-85	2.894*	2.775 - 3.018
	85-90	4.691*	4.492 - 4.898
	90-94	7.548*	7.174 - 7.942
Charlson Comorbidity Index	95+	12.080*	11.113 - 3.132
	0	<i>Reference</i>	
	1	1.631*	1.596 - 1.667
	2+	2.775*	2.714 - 2.836
	Race	White	<i>Reference</i>
Black		1.157*	1.122 - 1.193
Other		0.680*	0.655 - 0.707
State Buy In	No	<i>Reference</i>	
	Yes	1.587*	1.547 - 1.628
SEER-Registry Area	Connecticut	<i>Reference</i>	
	San Francisco	0.739*	0.697 - 0.783
	Detroit	0.941 [§]	0.899 - 0.986
	Hawaii	1.026	0.947 - 1.112
	Iowa	1.048	0.999 - 1.099
	New Mexico	0.911 ⁺	0.856 - 0.970
	Seattle	0.936 ⁺	0.891 - 0.984
	Utah	0.975	0.919 - 1.033
	Atlanta	1.009	0.948 - 1.075
	San Jose	0.721*	0.672 - 0.772
	Los Angeles	0.671*	0.640 - 0.704
	Rural Georgia	0.996	0.845 - 1.174
	Greater California	0.860*	0.826 - 0.895
	Kentucky	1.044	0.997 - 1.093
	Louisiana	1.063 ⁺	1.015 - 1.113
New Jersey	0.845*	0.811 - 0.880	

*: p-value < 0.001; +: p-value < 0.01; §: p-value < 0.05

for each month contributed to each phase was plotted for the entire sample. The initial and terminal phase definitions only allow for 12 months in each phase; however the continuing phase could vary depending on the observation time and type for the men in that phase. The phase of care plot (Figure 6) reveals the entire cohort contributed 96 months to the continuing phase of care. The costs for the initial phase increase slightly and decrease around 13 months after diagnosis or index date. As expected, costs remained constant through the entire continuing phase and begin to increase in the last 12 months of observation.

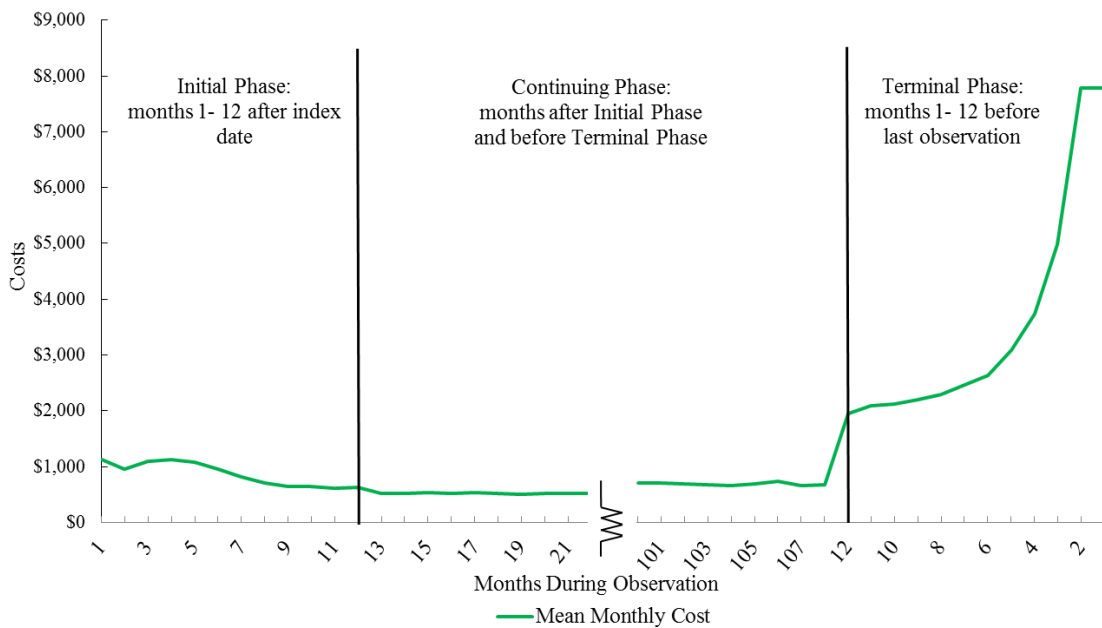


Figure 6. Plot of Phase-based Costs for All Study Participants over Months of Observation.

The mean number of months contributed to each phase by the entire cohort and PSA or No PSA cohort are reported in Table 20. Consistently among the three cohorts, the number of months contributed to the initial phase was approximately the same (i.e. entire

cohort: 11.45 months; no PSA cohort: 11.26 months; PSA cohort: 11.66 months). This trend continued in the terminal phase (i.e. entire cohort: 10.49 months; no PSA cohort: 10.36 months; PSA cohort: 10.81 months). The mean monthly contributions were consistent among the continuing phase, too (i.e. entire cohort: 59.50 months; no PSA cohort: 56.61 months; PSA cohort: 62.27 months). The mean and median number

Table 20. Months Contributed to the Entire Cohort, No PSA Cohort, and PSA Cohort.

Phase of Care	Mean	Median	Minimum	Maximum
Entire Cohort				
Initial	11.45	12.00	1.00	12.00
Continuing	59.50	58.00	1.00	108.00
Terminal	10.49	12.00	1.00	12.00
No PSA Cohort				
Initial	11.26	12.00	1.00	12.00
Continuing	56.61	54.00	1.00	108.00
Terminal	10.36	12.00	1.00	12.00
PSA Cohort				
Initial	11.66	12.00	1.00	12.00
Continuing	62.27	60.00	1.00	108.00
Terminal	10.81	12.00	1.00	12.00

Note: Phases of care are not mutually exclusive.

of months contributed to each phase in each cohort was similar and, though the maximum amount contributed to the initial and terminal phase was set at 12, the maximum months contributed to the continuing phase was consistent for all cohorts at 108 months. The costs contributed to each cohort and phase of care was consistent across mean, median, and maximum values. This is demonstrated in Table 21. The mean values for the initial phase of care for the entire cohort, PSA Cohort and No PSA Cohort are \$9,603, \$8,443; and \$10,732; and their maximum values range from \$426,214 for the No PSA Cohort to \$312,773 for the PSA Cohort. Not surprisingly, the continuing phase was the phase with

the highest costs across all three cohorts. Mean values for the continuing phase were approximately \$34,000 for all three cohorts and their maximum values were \$2,342,667 for the entire cohort, \$1,570,933 for the PSA cohort, and \$2,342,667 for the no PSA Cohort. We anticipated a u-shaped curve from these costs, meaning the most costs would be reflected in the initial and terminal phases. Terminal phase costs were much greater than those of the initial phase across all cohorts but not more than those of the continuing phase. This is because the continuing phases have approximately 60 months of costs in them while the terminal phase, only has a maximum of 12 months (shown in Table 20).

Table 21. Descriptive Costs for the Entire Cohort, PSA Cohort, and No PSA Cohort.

Phase of Care	Mean	Median	Minimum	Maximum	Standard Deviation
Entire Cohort					
Initial	\$9,604	\$3,271	\$0	\$426,214	\$14,874
Continuing	\$34,587	\$16,690	\$0	\$2,342,667	\$50,639
Terminal	\$28,384	\$18,066	\$0	\$464,903	\$35,754
PSA Cohort					
Initial	\$8,445	\$2,261	\$0	\$312,773	\$13,748
Continuing	\$34,612	\$17,329	\$0	\$1,570,933	\$49,163
Terminal	\$31,030	\$21,594	\$0	\$377,888	\$35,747
No PSA Cohort					
Initial	\$10,733	\$5,113	\$0	\$426,214	\$15,813
Continuing	\$34,560	\$15,937	\$0	\$2,342,667	\$52,136
Terminal	\$27,483	\$16,912	\$0	\$464,903	\$35,713

Each cohort was broken down into its composition of cases and controls. Table 22 presents the number of men in each phase of care by case status. The initial and continuing phases were split fairly evenly among the cases and controls (i.e. 48.05% and 51.95% for cases and controls, respectively in the initial cohort; 46.27% and 53.73% for cases and controls, respectively in the continuing cohort). Not surprisingly, however, was

that a greater proportion of cases contributed to the terminal phase (i.e. 85.54% and 14.46% for cases and controls, respectively). Because the PSA and no PSA cohorts are mutually exclusive groups and the phases of care for the entire cohort are not, the

Table 22. Case and Control Makeup of the Entire Cohort by Phase of Care

Phase of Care	Case		Control	
	N	(%)	N	(%)
Entire Cohort				
Initial	81,286	(48.05)	87,901	(51.95)
Continuing	71,864	(46.27)	83,449	(53.73)
Terminal	14,465	(85.54)	2,445	(14.46)

Note: Phases of care are not mutually exclusive.

numbers of cases and controls are equal by PSA cohort status (Table 23). The three cohorts (i.e. the entire cohort, the PSA cohort, and the no PSA cohort) were examined regarding proportion of individuals in each who were censored. Results are shown in Table 24. Men who were censored did not contribute complete costs. Men who were

Table 23. Case and Control Makeup of the PSA and No PSA Cohorts

Phase of Care	Case		Control	
	N	(%)	N	(%)
PSA Cohort	32,694	(37.98)	53,392	(62.02)
No PSA Cohort	57,652	(60.94)	36,954	(39.04)

censored did not contribute costs to the terminal phase. More men who were censored men contributed costs to the initial and continuing phases (i.e. 74.57% and 77.35%, respectively). Since men who were censored did not contribute complete costs, no men

who were censored contributed costs to the terminal phase. Table 25 captures mutually exclusive groups of men who died and censored by PSA cohort status.

Table 24. Censoring Status Among the Entire Cohort

Entire Cohort	Died		Censored	
	N	(%)	N	(%)
Phase of Care				
Initial	43,019	25.43	126,168	74.57
Continuing	35,183	22.65	120,130	77.35
Terminal	16,910	100.00	–	–

Note: Phases of care are not mutually exclusive.

Interestingly, more men who contributed to the no PSA cohort died during the study than those in the PSA cohort (40.56% and 18.76%, respectively).

Table 25. Censoring Status Among the PSA and No PSA Cohorts

Phase of Care	Died		Censored	
	N	(%)	N	(%)
PSA Cohort	16,151	(18.76)	69,935	(81.24)
No PSA Cohort	38,373	(40.56)	56,233	(59.44)

Analytical Analyses

Survival

From the Cox model, estimated mean survival was predicted for each PSA screening group. A plot of the probability of survival over the course of the observation period is shown in Figure 7. The ‘No PSA’ screening group is shown by the solid line

and the 'PSA' screening group is shown by the dotted line. Each line reflects the probability of survival throughout the study observation period, in days. Both groups start out with nearly 100% survival but the probability of survival begins to fall over the course of the study. The 'No PSA' group appears to have a steeper decline in survival than that of the 'PSA' group.

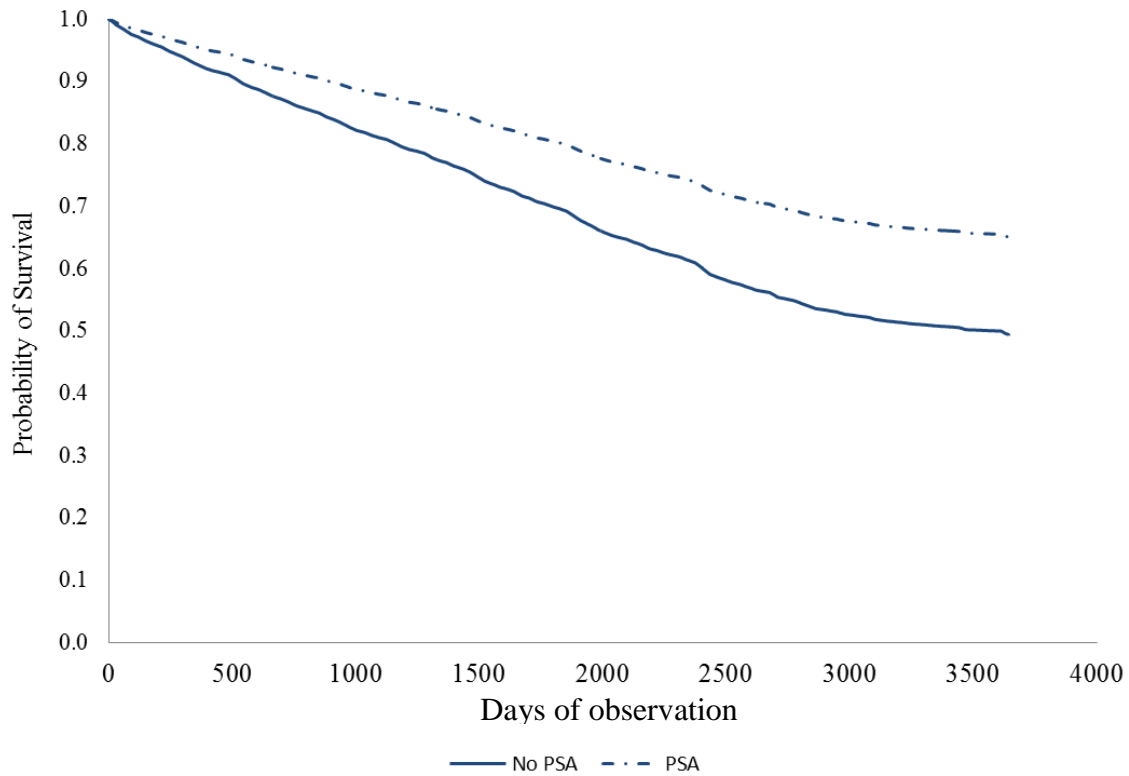


Figure 7. Estimated Probability of Survival throughout the Study Period.

The estimated sample mean life days for the no PSA screening group was 2,568 days. This estimate divided by 365 resulted in approximately 7 life-years (standard deviation: 0.154) for the no PSA screening group. The estimated sample mean for the PSA screening group was 2,927 days. This estimated translated into approximately 8 life-years (standard deviation: 0.113). To obtain the estimated incremental mean life-years,

the mean estimated life-years of the no PSA screening group was subtracted from the PSA screening group. The mean estimated incremental life days were 359. This translated into just under one life-year gained (mean estimated incremental life-years: 0.9835; standard deviation: 0.041). Each calculated survival estimate represents the area under the survival curve. The incremental survival would be the area under the ‘PSA’ screening group curve minus the area under the ‘No PSA’ screening group curve. The incremental survival estimates were used to obtain the NMB to use in VOI calculations.

Costs

Costs for the analytical portion of these analyses used the mean and median and standard deviation of the costs for each phase of care, for the PSA cohort and the no PSA cohort. Using the mean and standard deviation for each phase of care, the alpha and beta parameters were determined for the PSA cohort and the No PSA cohort (Table 26).

Table 26. Cost Parameters Used to Simulate a Cost Distribution

	Mean	Median	Standard Deviation	α	β
PSA Cohort					
Initial Phase	\$8,445	\$2,261	\$13,748	\$0.38	\$22,382
Continuing Phase	\$34,612	\$17,329	\$49,163	\$0.50	\$69,832
Terminal Phase	\$31,030	\$21,595	\$35,747	\$0.75	\$41,182
No PSA Cohort					
Initial Phase	\$10,733	\$5,114	\$15,813	\$0.46	\$23,298
Continuing Phase	\$34,561	\$15,937	\$52,136	\$0.44	\$78,649
Terminal Phase	\$27,483	\$16,912	\$35,713	\$0.59	\$46,407

Table 27 shows the maximum and mean values obtained from the gamma distributions for each cohort and phase of costs.

Table 27. Simulated Cost Characteristics for each Phase of Care Using the Gamma Distribution

	Initial phase	Continuing phase	Terminal phase
PSA Cohort			
Maximum Value	\$131,634	\$493,833	\$322,033
Mean Value	\$8,297	\$35,565	\$31,268
No PSA Cohort			
Maximum Value	\$172,175	\$530,530	\$382,219
Mean Value	\$11,103	\$34,630	\$27,517

Value of Information

The incremental cost from each of the 10,000 simulations was taken and the maximum and mean values incremental costs and incremental life-years gained are reflected in Table 28. The NMB for the population was calculated using equation (Equation 1). The EVI was calculated by subtracting the mean NMB from the max NMB. Values for these calculations are shown in Table 29. The base case willingness-to-pay threshold, or λ , and sensitivity analyses λ thresholds are reported for each aim.

Table 28. Incremental Costs and Survival Simulations Used in VOI Calculations

	Incremental Costs from Gamma	Incremental Life-years from Gamma
Maximum Value	\$543,859	1.138
Mean Value	\$1,880	0.983

*: estimates obtained from incremental calculations of the 10,000 simulated replicates

The EVI at the base case λ threshold was \$518,233 (Table 29) and \$515,842 and \$522,216 for λ thresholds of \$20,000 and \$100,000, respectively.

Table 29. Expected Value of Information at Various Lambda Thresholds

NMB	λ		
	\$20,000	\$50,000	\$100,000
Maximum Value	\$533,630	\$565,522	\$618,674
Mean Value	\$17,788	\$47,289	\$96,458
Expected Value of Information	\$515,842	\$518,233	\$522,216

λ : Willingness-to-Pay Threshold

As previously discussed, the calculation of pEVI incorporates parameters specific to the populations of interest. These analyses examined pEVI for two racial subgroups, African Americans and Caucasians. Parameters used for the base cases analyses are shown in Table 30.

Table 30. Base Case Parameter Values for pEVI Calculations

	Incidence of PC per 100,000	Medicare Population	Discount Rate	Durability	Implementation
Race					
African American	1,319	4,040,000	3%	1.0	1.0
Caucasian	892	33,532,000	3%	1.0	1.0
Age					
65-74	839	17,372,000	3%	1.0	1.0
75+	978	16,160,000	3%	1.0	1.0

Table 31 shows pEVI results for base case and sensitivity analyses which also included variation for the parameters of durability and implementation. For the base case in the race subgroups, African American pEVI was lower than that of Caucasians (i.e. \$828,197,915 and \$4,652,510,471, respectively). The pEVI for the younger group and the older group were very similar (i.e. \$2,265,718,598 and \$2,455,862,665, respectively). When exploring sensitivity analyses by changing λ thresholds, pEVI stayed relatively stable throughout all population subgroups. Exploring the effect of durability and implementation, results changed proportionately to the values input for the parameters since the two parameters are multipliers (data not shown). For example, pEVI for African Americans at a λ threshold of \$50,000 was \$8,281,979 when durability and implementation were assumed to be 0.1.

Table 31. Population Expected Value of Information Across Various Lambda Thresholds

Population	λ		
	\$20,000	\$50,000	\$100,000
<i>Race</i>			
African American	\$824M	\$828M	\$834M
Caucasian	\$4,631M	\$4,652M	\$4,688M
<i>Age</i>			
65-74 years of age	\$2,255M	\$2,265M	\$2,283M
75+ years of age	\$2,444M	\$2,455M	\$2,474M

Results shown above reflect Durability and Implementation values of 1.0

λ : Willingness-to-Pay Threshold

M: Millions

Table 32 shows the EVPI for the base cases analysis, a λ threshold of \$50,000, was \$616,463. The EVPI for sensitivity analyses calculations was \$616,421 and \$616,592 for the \$20,000 and \$100,000 thresholds, respectively.

Table 32. Expected Value of Perfect Information Across Various Lambda Thresholds

NMB	λ		
	\$20,000	\$50,000	\$100,000
Maximum Value	\$634,775	\$664,324	\$713,631
Mean Value	\$18,354	\$47,861	\$97,039
Expected Value of Perfect Information	\$616,421	\$616,463	\$616,592

λ : Willingness-to-Pay Threshold

Chapter Five

Discussion

The final cohort used in these analyses contained 180,692 cases and controls. Among cases, 36.19% of cases had at least one PSA test and 59.10% of controls had at least one PSA test. The cohort had a very high amount of censoring which could be attributed to not limiting study participants to a specific stage of PC and/or to the fact that men typically live a long time once diagnosed with PC as reflected in studies with very long follow up (i.e. greater than 10 years) that reveal no real survival benefit to PSA screening.^{52, 114, 135, 136} This research found that PSA screening lead to an approximate one life-year gain compared to men who did not get PSA screening. While the calculated life year estimate did not compare the two groups for significance, the results from the Cox Proportional Hazard model suggested that there was a significant difference between the two (HR: 0.608; p-value < 0.001). The results from the Cox model was similar to evidence seen in the clinical literature for PC screening;¹³⁵ however, comparison across all trials are not fair comparisons because most trials randomized men to PC screening via a digital rectal exam or a PSA protocol and most often capture incident cases of PC among the two group and present relative differences among the groups. Furthermore,

these analyses incorporated overall survival while trials tend to present PC-specific survival. For exploration and comparison of results, future research could include PC-specific survival. Observational studies that examine PSA typically explore diagnostic use or therapeutic use of PSA in determining effect of specific treatment.

The cost results from this study follow the u-shaped curve presented by Mariotto et al.,¹¹⁶ but based on the u-shaped curve, costs for the initial phase were lower than anticipated. This could be because a treatment strategy for PC is active surveillance²⁵ or because approximately 62% of cases have a lower stage cancer (i.e. stage 2, 1, or 0) and potentially choose not to seek active treatment. Of course, multiple factors influence treatment patterns (i.e. patient and physician preference, patient medical and family history, etc.) and this study was not designed to examine those factors.

The EVPI estimate from this study was low (\$616,463 for the base case) when compared to other VOI studies that examined similar cancer screening modalities. Rojnik et al. (2008) used Gaussian process metamodeling to examine mammography in Europe. Their 2008 estimates for EVPI was €580 million, which translates to approximately \$800,000,000.¹³⁷ Payne et al. (2000) conducted a comparison of liquid-based cytology for cervical cancer screening and PAP screening for the National Institute for Clinical Excellence. Their 2000 estimates for EVPI was £1,500,000 which translates to approximately \$2,400,000.¹³⁸ The results from this study estimate the EVPI of PSA screening as \$616,463. In comparison, one may begin to think that additional funding for PSA screening research isn't necessarily 'worth it;' however, the population estimates

reveal racial groups and age groups may be where research investment should take place. Base case estimates for African Americans was approximately \$828,000,000 and Caucasians was approximately \$4,652,000,000. At first glance, one may suggest research funding should focus support on Caucasian men because of the difference in population estimates between the two racial subgroups; however, after further inspection of the parameters that influence pEVI one would see why this difference existed. Equation 3, listed the other variables included in the pEVI calculation as EVI, incidence of PC, population of interest, discount rate, durability, and implementation. In these analyses, discount rate was held at a constant rate of 3% and for the base case analyses, durability and implementation were held at a value of 1.0. The factors that impact the calculation of pEVI were the variables of incidence of PC and size of the population of interest. As shown in Table 30, the Medicare population of Caucasians (33,532,000) is nearly nine times that of African Americans (4,040,000). Furthermore, the incidence of PC for African Americans (1,319 new cases per 100,000 men) is nearly double that of Caucasian men (892 new cases per 100,000 men). The higher incidence of PC in African Americans is not enough to compensate for the lower proportion of African Americans in the Medicare population and as a result, their pEVI estimates were lower than the Caucasian subgroup. However, if the population were the same for the two subgroups and incidence rates remained the same, the pEVI for Caucasians would be nearly 50% of that of the pEVI for African Americans. Hence the population of interest and the incidence of the disease of interest are important drivers behind the pEVI estimate. These estimates should be carefully considered in the full context of the calculation. The two other factors that influence pEVI, durability and implementation, remained at 1.0 for the base cases

analyses. After careful review of the literature, little evidence existed that included estimates of these parameters. How a technology is used in clinical practice and that technology's lifespan in clinical practice are also important factors that should be considered in pEVI calculations; however, there is little guidance on how a researcher could adequately build these estimates for inclusion into VOI calculations. One could consider the PSA test's positive predictive value, negative predictive value, sensitivity, and specificity could contribute to its implementation but also how healthcare workers handle and perform the test could also affect its implementation. Conceptually, the value of durability could be ascertained through study of the patent life cycle and consideration of the pipeline of products that could be considered substitutes to the PSA test. Complementary technology (i.e. genetic tests that accompany the PSA test) could also affect the PSA test's durability and implementation.

With the evidence that demonstrates no real benefit for PSA screening, one must ask whether or not previous investigators not been focusing on the 'right' question. Perhaps the 'right' question isn't 'does PSA screening extends survival in all comers?' but, rather, 'does certain populations benefit more, with respect to disease-specific or overall survival, than an all comers populations?'

Study Strengths and Limitations

This study has many strengths. The first strength is that the study sample is from a SEER-Medicare, a dataset that merges two data sources to create a unique perspective

to examine clinical factors and resource utilization. The link between these two data sets is verified to be accurate and data can be considered to be generalizable to the Medicare population of the US.¹⁰² This study builds upon the base of traditional cost-effectiveness framework and extends incremental findings of cost and effect into tools that decision makers could use to help determine resource allocation. A unique strength of this work is that this study is one of the first to examine VOI in context of an administrative claims data set. Traditionally, VOI models are constructed from full decision models which are costly and time consuming. Data for these models often comes from randomized clinical trials with some data supplemented by literature. Since the true purpose of VOI is to help guide resource allocation and observational studies are less costly than randomized trials, conducting the methods with observational data makes sense if a decision maker were trying to first explore what needs to be researched and then fund the appropriate research.

Despite the novel nature of this research, limitations exist in the form of dataset construction and population. While the SEER-Medicare data set provided information that would not exist in other data sets, its construction of the controls file was not optimal for a true comparison to the case file. For example, the control file did not have marital status as a variable; therefore, this variable was not included in any analyses and was unable to be incorporated into cohort matching. Marital status has been shown to have a significant impact on being diagnosed at an earlier stage, seeking more aggressive treatment, and longer survival.¹³⁹⁻¹⁴¹ One could postulate having a close social support (i.e. a spouse) could make either partner want to take better care of themselves, thus seek preventive services and more aggressive treatment, if needed. Furthermore, variables

exist for receiving PSA (i.e. tumor2 and cs2cs variables), but these variables are collected through the SEER-side of the dataset so controls do not have these variables. These variables, however, do not distinguish a screening PSA and a PSA used in a PC diagnosis as such, investigators would still need to rely upon an administrative claim algorithm to distinguish between the two types of PSA. The SEER-Medicare does not capture non-Medicare reimbursed medical treatment (i.e. enrollment in RCTs), so costs captured are potentially reflecting a more conservative picture of costs associated with medical care. Despite these few shortcomings, the SEER-Medicare dataset is one of the few datasets that links clinical information to information available in the administrative claims.

While the data content had few limitations for this research, after applying study inclusion/exclusion criteria the study population was restricted to a level where certain methods were not feasible. Due to the low numbers in the four cancer and PSA groups (i.e. Group 1: men with a PSA test and PC diagnosis; Group 2: men with a PSA test and a no PC diagnosis; Group 3: men without a PSA test and with a PC diagnosis; and Group 4: men without a PSA test and without a PC diagnosis) and the overall cohort, controls were matched in a 1:1-style match and not a 1:many match in order to preserve sample size. For the index match, there were fewer men in Group 1 compared to Group 2 and more men in Group 3 than in Group 4. Furthermore, then match for index date had to be conducted with a modified 1:1 match, with all controls getting the index date for one randomly drawn case that fit their matching criteria. Ideally, the cohort match among all cases and controls could be obtained with a 1:many match but overall there were more cases than controls.

After the analysis cohort was created, several issues became apparent after descriptive analyses were completed. One of the major limitations of this study is the fact that approximately 70% of the cohort was censored. Considering the study did not limit men to stage of PC, this was not surprising especially considering the 5-year relative survival for men exceeds 90%.³ Original plans for these analyses was for costs to be analyzed via the Bang and Tsatis method for dealing with censored cost data or via inverse probability weighting. Some literature cites that these methods are robust when dealing with a population that is heavily censored;^{132, 142} however, the method used to analyze costs, the phase of care costing approach, was cited to be robust despite censoring and was generally accepted as an alternative costing method.¹³⁴ Since completing these analyses, other methods to deal with large amounts of censoring have come to the author's attention. A possible future direct of research would be to re-analyze costs with the new methods to determine if cost outcomes are similar between the two methods.

Though the phase of care method is accepted for dealing with cohorts with heavy censoring, the results from these analyses reveal that the costs associated with the initial phase of care were not as pronounced as with the estimated annualized net costs for PC obtained by the National Cancer Institute.¹¹⁶ Transforming costs obtained by phase of care estimates of the PSA and No PSA cohort into annualized costs, results were more similar to the NCI estimates. Figure 6 shows a plot of mean monthly costs for each phase of care. The plot for the initial phase of care was not as pronounced as one would expect

when considering in the initial phase men would be consuming resources after a cancer diagnosis; however, considering that active surveillance is an accepted form of treatment for PC,²⁵ the mean monthly costs during the initial phase was put into context.

Unfortunately, these analyses were designed to examine total medical costs not resource-specific costs, so examining the reason for the lower mean monthly costs could be an area of future research.

The VOI analyses used in this research focuses on overall survival (or morbidity); however, most studies that examine the effect of PSA on survival utilize PC-specific survival and not overall survival.^{52, 99} The minimal model approach and no modeling approach of VOI used in these analyses, require comprehensive endpoints (for the no modeling approach) and intermediate endpoints (i.e. QALYs, survival) of costs and effect for the minimal modeling approach in order to accurately estimate how research should be invested. Using disease-specific survival could return conservative VOI estimates and thus underestimate the true needs of research funding for a specific disease state. Another nuanced aspect of VOI for these analyses is the large estimate of pEVI. A comparison of VOI equations included in the literature and in this research revealed the EVI estimate shown in Equation 2 used as a multiplier for the population estimate (Equation3). To get a more fine-tuned estimate, future research could examine the EVI in specific populations and then apply that measure to the population-specific estimates. By using the general EVI it is possible the pEVI estimates are over estimated even though individualizing research has shown to have a greater value that for the population as a whole.¹⁴³ Though VOI seems to be a natural fit in screening modalities because it helps to

identify research gaps and where funds should be invested within a given therapy area, VOI estimates in oncology literature are more often used as an aid in decision making for a treatment pathway once a population already has cancer.¹⁴⁴ One drawback with VOI methods was that despite its theory based in economic optimization, in healthcare, there is no set threshold for what constitutes a 'high' or 'low' value as such, the researcher must use his or her discretion for recommendations of what VOI estimates mean. VOI is a tool that could help determine resource allocation but, so far, it has been used predominately as a form of sensitivity analyses to estimates from cost-effectiveness research. Once the methods are more widely accepted, it they could be used to help determine resource allocation for private industry or government payers.

Chapter Six

Conclusions

This dissertation was built off of three cumulative aims: 1) Estimate the expected value of information (EVI) from research on a per-person basis for PSA screening based on the 2000-2007 SEER-Medicare; 2) Estimate the population-level expected value of information (pEVI) on PSA screening in the US Medicare population; 3) Estimate the expected value of perfect information (EVPI) of PSA screening in the US Medicare population. Aim two examined pEVI between two race/ethnicity subgroups, African Americans and Caucasians, and two age groups, men aged 65-74 and men aged 75+.

The initial focus of this work was to estimate the EVPI of PSA screening in Medicare. This result could be translated into the most a funding body should spend in order to resolve uncertainty surrounding PSA screening. Results from these studies suggest that PSA screening for all comers may not be the most beneficial area in which funding bodies could get the greatest return on their research investment. These analyses suggest additional research that could fine tune the PSA screening strategy for specific

racial and age groups could help to reduce uncertainty regarding PSA screening for these populations.

Future research is necessary to confirm findings and to explore nuances of these analyses. Beside further investigation into methods that aid in evaluating a heavily censored population or, ideally, having other variables that could further explain results, research on the VOI methods used in these analyses could be beneficial to researchers and policy makers in the long run. Of particular interest would be to re-create these analyses using the no modeling or limited/minimal modeling approach with data obtained from published literature instead of a database. Additionally, further subgroup analyses could be conducted in Medicare aged men in a different dataset (i.e. men with Medicare Part C) to determine differences in the groups of men and whether or not these differences influence VOI estimates. An extension of this could be to ascertain if additional PSA research should be focused on men younger than 65. Of particular interest would be to build a full decision model with complete data on all participants to determine how estimates would differ. Using a full modeling approach would enable investigators to examine the value of additional parameter information, or determining if specific aspects of the screening could benefit from additional research.

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