

Prostate cancer screening: a quantitative model for present and future method evaluation

James Schwoebel^{1,2}, Carolyn Carlson^{2,3}, Yazdan Raji^{2,3}, Virginia Lin^{2,3}, Angie Kamino^{2,3}, Jim Overholt^{2,3}, Pharan Evans^{2,3}, Rachel Spivey^{2,3}, and Choon Hwai Yap^{2,4}

¹First Author, ²The Wallace H. Coulter Department of Biomedical Engineering at Georgia Institute of Technology, ³Second Author, ⁴Advisor

Correspondence to: jim.schwoebel@gatech.edu

ABSTRACT

Throughout the past 20 years, a prostate cancer screening pathway has been constructed and refined to diagnose prostate cancer. Although one primary pathway for screening prostate cancer has been developed and refined within the past 20 years, there remain many problems with this pathway, including a general lack of sensitivity and specificity; an inability to diagnose the progression of the disease; a significant risk presented to screening patients resulting from confirmatory diagnostic testing; and a lack of evidence supporting the reduction in prostate cancer mortality resulting from screening. Moreover, current screening methods are becoming an increasingly significant health care cost, accounting over \$1.8 billion for the Prostate Specific Antigen (PSA) test alone in the United States each year. To address these problems, this study provides a review of both current and emerging literature regarding prostate cancer screening methods. Comparative criteria were defined and integrated into a quantitative cost effectiveness (CE) model to evaluate the effectiveness of each screening method examined in the literature search more comprehensively. Overall, the Alpha-Methylacyl Coenzyme A Racemase (AMACR) urine-based biomarker test, followed by a biopsy, was found to be the most cost-effective screening method.

INTRODUCTION

Prostate cancer is a significant health concern in the United States and other industrialized countries (ACS, 2010; BC Cancer Agency (BCCA), 2006). It is the most common type of cancer among American men, with approximately 200,000 cases diagnosed in 2009 alone (ACS 2010). Unlike other cancers, prostate cancer typically progresses slowly with few symptoms in the early stages (BCCA, 2006; De Angelis, 2007). Consequently, patients frequently remain unaware of the cancer until it has progressed to its later stages, significantly reducing their chance of survival (BCCA, 2006). Moreover, current screening methods are becoming an

increasingly significant health care cost, accounting over \$1.8 billion for the Prostate Specific Antigen (PSA) test alone in the United States each year. Hence, there is a strong diagnostic need for a screening method that includes early-stage detection, high accuracy and reliability, as well as affordability in order to increase the proportion of positive interventions among prostate cancer patients.

In this paper, data on the effectiveness of individual screening methods were obtained and scored. These results were then used in a comparison of various individual

and combined methods of prostate cancer screening and were evaluated for a more comprehensive way to measure cost effectiveness. Both current and potential future methods of screening were considered in the analysis.

Present methods in screening

The prostate-specific antigen (PSA)—a well known biomarker associated with prostate cancer (LeBeau, 2009)—test is the method of screening most commonly used in the United States, with an aggregate annual estimated cost of \$1.8 billion (De Angelis, 2007). Tumor markers such as PSA are commonly used to assess the stage of a cancer as well as to assess the severity of the disease. The expression of PSA is highly restricted to normal prostate epithelial cells in men (LeBeau, 2009). Malignant prostate tissue therefore produces more PSA than benignly enlarged tissue, and prostate cancer increases the likelihood that PSA “leaks” into the general circulatory system. When this happens, serum PSA levels appear to have some discriminating capacity to screen for prostate cancer (Sechrest, 1996).

The PSA screening method is somewhat controversial due to clinical uncertainty and a general lack of evidence supporting a reduction in prostate cancer mortality (Logan, 2004; Smith, 2009). Moreover, it is not clear that the benefits of PSA screening exceed the risks of false positives (FPs) and unnecessary cancer treatments (Logan, 2004; National Cancer Institute (NCI), 2009). For example, the PSA test may detect small cancers or other conditions, such as an enlarged prostate or bacterial infection, which are typically not life-threatening, causing unnecessary psychological harm to a patient (Logan, 2004). As well, early treatment of prostate cancer can lead to substantial physical harm to the patient in forms such as erectile dysfunction, urinary incontinence, bowel

dysfunction, and in some cases even death (Logan, 2004; U.S. Preventive Services Task Force, 2008). The fundamental problem is that the sensitivity (the proportion of people in the screened population who do not have prostate cancer and who are correctly identified as not having the disease) and specificity (the proportion of people in the screened population who have prostate cancer and who are correctly identified as having the disease) of the PSA blood test are far from ideal, leading to unnecessary prostate biopsies (Logan, 2004; Nadler, 2008).

To respond to this problem, variations in the use of PSA for screening have been proposed by the scientific community. These variations include: 1) PSA density (PSAD), a method of correcting the raw PSA value by the volume of the prostate, as measured by transrectal ultrasound (TRUS), an ultrasound-based imaging modality (De Angelis, 2007); 2) predicted PSA (pPSA), which utilizes characteristic trends in gland volume and measured PSA to aid in making decisions about proceeding to biopsy (Mikolajczyk, 1997); 3) PSA velocity, the rate of change of PSA levels over time, which is used to detect the degree to which the cancer has progressed as compared to a control (Sechrest, 1996); and 4) the free PSA test, which measures the amount of free PSA in the bloodstream (De Angelis, 2007).

PSA circulates in the blood in two forms: free or attached to a protein molecule. The free PSA test is more often used for men who have higher PSA values, and it is used to aid in biopsy decisions to help elucidate the nature of a patient’s particular prostate problem (De Angelis, 2007). With a benign prostate condition like Benign Prostatic Hyperplasia (BPH), there is more free PSA. Cancerous conditions result in the upregulation of the attached form of PSA (De Angelis 2007). If a man’s attached PSA level is high but his free PSA level is not, the presence of cancer is thus more likely (NCI, 2009).

However, evidence is lacking in supporting improved health outcomes even with these variations (Logan, 2004; U.S. Preventive Services Task Force, 2008). As a result, some governments and organizations have discouraged the use of any PSA-derived screening method (Logan, 2004).

To increase the sensitivity of the test, the PSA test is oftentimes combined with a digital rectal exam (DRE). During a DRE, the physician searches for enlargement, hardness, or abnormal growth around the prostate gland, which is located just in front of the rectum. Most tumors originate in the back end of the prostate, allowing doctors to feel any abnormalities during the exam (ACS, 2010). The DRE is almost always used in combination with the PSA test in order to confirm the presence of “lumps,” or seemingly benign cancer tumor segments, of the prostate gland (Sechrest, 1996).

The use of a DRE by itself has drawn controversy, as there exists significant subjectivity on the part of the administering clinician as to whether a lump is aberrant or normal (Vashi, 2010). Considering this variability, the efficacy of a DRE likely depends on the experience of the administering clinician. According to recent studies, the test misses 30-40% of all cases of prostate cancer when used alone, partly due to the fact that only later stages of prostate cancer, as manifested by larger tumors, can be detected (U.S. News & World Report, 2005). When used alone, the DRE has a low sensitivity of 50% and specificity of 93.6% (Hamashima, 2000). However, when it is combined with the PSA test, the method becomes the most accurate preliminary screening pathway with a high sensitivity of 92% and specificity of 86%, along with a moderate cost (Ekwueme, 2007; Hamashima, 2000).

Additional diagnostic tests, however, must be performed to allow for a

comprehensive diagnosis. If the combined PSA and DRE test returns a positive result, an individual usually undergoes a transrectal ultrasound. Transrectal ultrasound (TRUS) is the most common method of imaging the prostate gland (Ravizzini, 2009). It is a technique that uses ultrasound waves to produce an image of the prostate to further evaluate possible aberrant structures on the prostate gland found during a DRE (Ravizzini, 2009). Cancer tissue has hypoechoic foci compared to normal tissue, which are detected by the ultrasound probe (Ravizzini, 2009). In this way, TRUS enables clinicians to determine whether abnormal PSA density readings are from prostate cancer or BPH.

As with a DRE, the inherent subjectivity in evaluating a TRUS test has drawn criticism. When used individually, TRUS has a relatively high sensitivity, but a very low specificity (Tamsel, 2008; see Table 1). When used individually, it also has a Positive Prediction Value of 29% and a Negative Prediction Value of 85.2%, meaning that it is effective in confirming cancer-negative test results. However, it also does a poor job at definitively stating that an individual has cancer (Tamsel, 2008). When combined with PSA and DRE, TRUS slightly increases overall specificity and sensitivity, but this increase is not sufficient enough to completely eliminate all significant doubt in an individual’s diagnosis.

Current					
	PSA	DRE	PSA + DRE	TRUS	Tissue Biopsy
Specificity	.930	.936	.860	.284	varies
Sensitivity	.740	.500	.920	.855	varies
Estimated Cost in 2007	\$31.30	\$8.30	\$89.60	\$104.00	\$347.24

Table 1. Current screening techniques in prostate cancer screening.

If all of the preliminary screening techniques have indicated a positive reading for prostate cancer, a tissue biopsy is taken from the prostate to confirm the presence of cancer. A biopsy can also be used to diagnose the progression of the disease once cancer incidence has been confirmed (O’Dowd, 2001). The transrectal ultrasound is used to guide the biopsy, and oftentimes the needle removing the tissue sample is attached to the ultrasound probe to ensure samples are taken from the most likely regions of malignant tissue (Akduman, 2010). These tissue slide samples are analyzed under a microscope and are given a Gleason score to diagnose the severity of the malignancy (O’Dowd, 2001).

Still here, subjectivity persists in various steps in biopsy procedure. Tissue samples are selected from regions of the prostate that seem most probable for tumor invasion, but this determination is again operator-dependent, conditional upon the analysis of the evaluating clinicians. According to a newsletter published by the Brady Urological Institute at Johns Hopkins Medical School, out of one million men who receive a tissue biopsy each year, only 250,000 are diagnosed with prostate cancer (Worthington, 2007). Another study suggests that approximately 60% of men with elevated PSA levels receive unnecessary biopsies (De Angelis, 2007). Despite these statistics, many men agree to have the test performed and may suffer subsequent psychological and/or physical harm (Logan, 2004). As a result, the sheer volume of biopsies performed seems to pose significant risks to genuinely efficacious prostate cancer screening in patients.

The current prostate cancer screening pathway involves three steps, and is outlined below (Figure 1). At present, these steps represent the only pathway approved by the U.S. Food and Drug Administration (FDA) for the detection of prostate cancer in men over age 50 (Sechrest, 1996). Due to this

limitation, the public access to more accurate screening techniques is severely reduced.

All of the screening techniques described above are typically combined in the same manner to ensure as comprehensive a patient diagnosis as possible. The lack of accuracy and clinical certainty, however, as well as the relative risks and costs associated with this pathway, have cast doubt as to whether one screening method or a combined screening method pathway is the most effective way to diagnose prostate cancer patients. Many variations of PSA testing have attempted to optimize the existing prostate cancer screening pathway, but none have yet proven to be cost-effective (NCI, 2009). There is thus a pressing need to create a new, preferably single-step pathway to screen for prostate cancer (Logan, 2004).

New and alternative approaches to prostate cancer screening

To respond to the need for a more specific and sensitive prostate cancer screening pathway, alternative pathways and screening techniques are currently being investigated. The latest research paradigm has produced three broad research categories in the area of prostate cancer screening: biomarker-based approaches, nanotechnology, and imaging. Biomarker research is primarily concerned with blood-

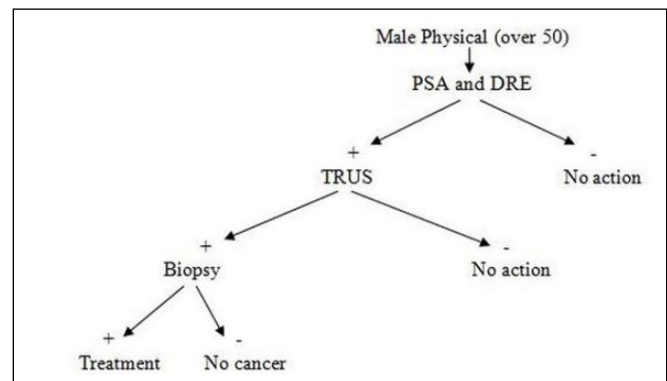


Figure 1. Typical sequence of screening tests employed in prostate cancer detection.

and urine-based detection of proteins that are over-expressed in prostate cancer cells. Nanotechnology research focuses on methods of introducing small particles or devices to target areas where prostate cancer may become manifest. Medical imaging research involves the efficient detection of prostate cancer in non- or minimally-invasive ways using various imaging modalities and fluorescent molecules.

Biomarkers as effective detection agents

Many biomarkers are being evaluated for their efficacy in the detection of prostate cancer (Table 2). This area of research is focused on identifying biomarkers that are expressed specifically in prostate cancer cells (Ploussard, 2010; Rai, 2009). Recent advances in research methods have facilitated this process, catalyzing the replacement of PSA with a more specific and sensitive biomarker test (Ploussard, 2010; Rai, 2009). However, many existing biomarkers lack confirmatory clinical data and are relatively

invasive, requiring a biopsy for analysis (Makarov, 2009).

Early Prostate Cancer Antigen (EPCA) test is a biomarker test that measures a particular antigen in the nucleus of cancer cells (Makarov, 2009). These protein antigens are unique to prostate cancer cells, and could confirm if prostate cancer incidence by immunohistochemical analysis (Makarov, 2009). According to one study, EPCA's sensitivity for detecting prostate cancer was 84% and specificity was 85%, slightly less effective than the combined PSA and DRE test (Uetsuki, 2005).

Early Prostate Cancer Antigen 2 (EPCA-2) is a blood-based biomarker (Makarov, 2009), and is a nuclear-based protein biomarker similar to EPCA, but with greater accuracy of cancer detection. This difference is mainly due to the ability of EPCA-2 to resist elevated expression in conditions like BPH and prostatitis, which prompt abnormal EPCA and PSA levels in patients (Worthington, 2007). More

	Future Biomarkers				
	Early Prostate Cancer Antigen (EPCA)	Early Prostate Cancer Antigen 2 (EPCA-2)	Glutathione S-Transferase 1 (GSPTP1)	PCA3 (urine-based biomarker)	Alpha-Methylacyl Coenzyme A Racemase (AMACR)
Specificity	.850 as blood-based	.920 as blood-based	.730 as blood-based	.790 as urine-based	1.000 as urine-based
Sensitivity	.840 as blood-based	.940 as blood-based	1.000 as blood-based	.690 as urine-based	.875 as urine-based
Estimated Cost in 2007	~\$31.30 assuming same as PSA	~\$31.30 assuming same as PSA	~\$31.30 assuming same as PSA	~\$31.30 assuming same as PSA	~\$31.30 assuming same as PSA
Clinically viable?	No, less specific than PSA	Yes, more specific and sensitive than PSA	No, less specific than PSA	No, less specific than PSA	Yes, more specific and sensitive than PSA

Table 2. Potential biomarkers in prostate cancer detection.

specifically, it has 92% specificity and 94% sensitivity (Makarov, 2009). One benefit of this biomarker is that it is able to determine the extent to which cancer has metastasized (stages 1-3 vs. stage 4) by monitoring the degree of expression of EPCA-2 (Makarov, 2009).

EPCA-2 is a protein within cells that causes the DNA within cells to become deformed, increasing the tendency for cells to aggregate into tumors and reproduce rapidly (Worthington, 2007). Therefore, the greater the protein is expression, the greater the capacity for a cell to rapidly reproduce and become cancer-like, correlating well with the various stages of prostate cancer (Worthington, 2007). Because this biomarker is more specific and more sensitive than PSA, it could eventually act as an effective replacement for PSA-based tests (Worthington, 2007).

Glutathione S-Transferase 1 (GSTP1) is a biomarker and detoxification enzyme that determines the extent of methylation of cancerous nuclei (Makarov, 2009). PCR assays are used to multiply DNA and examine the amount of this particular biomarker present in potentially affected tissue (Makarov, 2009). If GSTP1 levels are above a certain threshold methylation, prostate cancer can be detected with 100% sensitivity and 73% sensitivity (Makarov, 2009).

PCA3 is a new urine-based biomarker. It has 69% sensitivity and 79% specificity (Makarov, 2009). Although this biomarker is relatively noninvasive, its accuracy is relatively low (less than PSA). However, when it is combined with another biomarker, the prostate-specific G-protein coupled receptor (PSGR), the sensitivity of the test increases to 95%, but the specificity decreases to 34% (Rigau, 2010). The PCA3-PSGR test is not specific enough to be used alone, but could possibly be combined with PSA to allow for a more sensitive screening (Rigau, 2010).

Alpha-Methylacyl Coenzyme A Racemase (AMACR) is the most accurate new biomarker that has yet been discovered. The AMACR test is a tissue-based biomarker test that screens for an over-expressed protein of the prostate, and is carried out in a similar fashion as the EPCA-2 test. Like EPCA-2, AMACR is different from PSA in that the biomarker is only expressed in men who have prostate cancer, whereas PSA tests can be elevated even for men who do not have cancer (Makarov, 2009). According to one research study, the AMACR test has 97% sensitivity and 100% specificity, indicating a very efficient means of diagnosing prostate cancer (Makarov, 2009). It is of note, however, that the study was conducted on human cadavers and had a relatively low sample size. This data seem to be consistent with two concurrent studies, where AMACR was determined to be an excellent potential biomarker for prostate cancer. Not only was it consistently over-expressed by a factor of 9 in 88% of cancer tissue relative to benign tissue, AMACR was also over-expressed at a higher rate in localized cancer, meaning that the use of AMACR as a biomarker rather than PSA could allow for stronger mean cancer detection at stages 1 or 2, thus making the cancer easier to treat (Luo, 2002; Rubin, 2005).

The AMACR test can also be used as a urine biomarker, providing a noninvasive method for detecting prostate cancer. However, these tests have a lower overall sensitivity and specificity (Rogers, 2004; Zielie, 2004). Though AMACR alone is not indicative of prostate cancer, normalized AMACR to PSA levels, the ratio is conspicuously higher (Zielie, 2004). This test provides 100% specificity and 70% sensitivity; however, 20% of the false negatives were proven to be “clinically insignificant disease,” resulting in a final sensitivity of 87.5% (Zielie, 2004).

Nanotechnology-based screening methods

Nanotechnology has emerged as a relatively new field in prostate cancer detection. Various forms of nanotechnology are oftentimes combined with other methods, such as biomarkers and imaging modalities, in order to detect prostate cancer with greater accuracy. However, many of these biomarker-nanotechnology and imaging-nanotechnology hybrid screening techniques lack clinically significant data (Table 3). Four principal nanotechnology-based areas of interest have been identified: gold-based nanoparticle cancer detection, Quartz Nanotube High Sensitive PSA testing, Magnetic Nanoparticles (for imaging, MRI, cancer-targeted regions), and Quantum Dots.

Gold-based nanoparticles have been found to bind specifically to many different types of cancer cells, both in vivo and in vitro (Ireland, 2010). Gold nanoshells can thus be designed to bind only to prostate cancer cells (Ireland, 2010). These nanoshells can also absorb or scatter certain wavelengths of light (Ireland, 2010; Loo, 2005), which determine

whether the gold particles will absorb or scatter light, and upon binding to the prostate cancer shells, offer a noninvasive way to detect prostate cancer with very high accuracy (estimated to be around 90% specificity and 90% sensitivity) (Ireland, 2010). However, current imaging methods are expensive and are thus economically unappealing.

Quartz nanotubes can be used as biosensors to detect certain biomarkers in the body (Palaniappan, 2010). Recently, scientists have optimized this approach and have developed nanotubes capable of binding very specifically and sensitively to PSA biomarkers (Palaniappan, 2010). However, due to the controversy of the PSA test, these studies would have to calibrate to other protein biomarkers to allow for a more specific and accurate biomarker test.

Magnetic nanoparticles have been utilized with a gold-packed nanoparticle platform to make an ultrasensitive biosensor for biomarkers, such as PSA, in blood serum (Mani, 2009). By using magnetic beads with gold nanoparticles, sensitivity and specificity

Future Nanotechnology				
	Gold-based Nanoparticles + Imaging	Quartz Nanotubes	Magnetic Nanoparticles	Semiconductor Quantum Dots (QDs)
Specificity	.900	>.930	>.930	No data
Sensitivity	.900	>.240	>.240	No data
Estimated Cost in 2007	~\$3,500 assuming combined with MRI	Variable	~\$3,500 from American Hospital Directory	Variable
Clinically viable?	Yes, more specific and sensitive than PSA	Yes, more specific and sensitive than PSA	Yes, more specific and sensitive than PSA	No, not enough data

Table 3. Methods in nanotechnology for prostate cancer detection.

Future Imaging				
	MRI and MRSI Imaging	PET 18-Fluorodeoxyglucose Imaging	PET 11C-choline and 18F-fluorocholine (18F-FCH) Imaging	PET Anti-18F-FACBC scanning
Specificity	.926	>.900	.81	n/a
Sensitivity	.723	>.240	.66	n/a
Estimated Cost in 2007	~\$3,500 from American Hospital Directory	~\$5,000 from American Hospital Directory	~\$5,000 from American Hospital Directory	~5,000 from American Hospital Directory
Clinically viable?	Yes	No, detects cancer at later stage	No, less specific than PSA	No, not enough data

Table 4. Imaging technology in prostate cancer detection.

were greatly increased when compared with the PSA test, and show much promise for future research (Mani, 2009).

Semiconductor Quantum Dots have emerged as a nanoscale technique used for image-based cancer screening (Li, 2010). These quantum dots (QDs), although potentially very efficacious, are only in the preliminary stage of research (Li, 2010).

While there exists significant promise in nanotechnology-based prostate cancer screening techniques, the most promising future nanotechnology technique, according to available specificity and sensitivity data, seems to be the combination of gold nanoparticles with imaging (Ireland, 2010).

Use of medical imaging modalities for prostate cancer screening

Medical imaging is also another category that is being investigated as a possible way to screen for prostate cancer (Table 4 above). As of now, MRI and MRSI (Magnetic Resonance Imaging and Magnetic Resonance Spectroscopy) are two imaging techniques that can scan and

diagnose the stage of the prostate cancer within the patient, both of which use induced magnetic fields to produce an image (Kurhanewicz, 2006). MRI images can provide a clear-cut view of tissue structure. Normal tissues are depicted with a higher signal intensity and potentially cancer-infected tissues are depicted with a lower signal intensity, as cancerous cells lose their ability to differentiate (Kurhanewicz, 2006). In contrast, the MRSI can determine the relative concentrations at specific frequencies of cellular metabolites, such as choline and citrate (a higher choline-citrate ratio usually means cancer is present) (Villeirs, 2010). When combined, these two imaging techniques can compare any structural abnormalities with any biochemical abnormality, giving this method a moderate sensitivity of 72.3% and a high specificity of 92.6% (Villeirs, 2010).

Due to the moderate sensitivity of this screening technique, there still is a small margin of error in ruling out people who may not have prostate cancer. Various conditions such as prostatitis, hemorrhage, atrophy, and

benign hyperplasia, can give FP results (Ravizzini, 2009). Also, a preliminary PSA test must be combined with this imaging modality for optimum accuracy. Hence, it lacks the standalone feature that would be present in an ideal screening test. Imaging is also very expensive, with costs usually ranging from \$3000 to \$4000, making this method less accessible to the general public (American Hospital Directory, 2010).

The main alternative to MRI and MRSI is PET scanning. One PET alternative is 18F-fluorodeoxyglucose imaging. This imaging technique uses a fluorescent glucose (FDG) molecule to tag cells that are rapidly consuming ATP (Ravizzini, 2009). This method is useful for detecting cancer that has progressed into its later stages, but is generally ineffective at tracing prostate cancer in the earlier stages (Ravizzini, 2009). As a result, this method tends to cause false negative results in patients that are in the earlier stages of prostate cancer (Ravizzini, 2009). This method is also fairly expensive and can range from \$4000 to \$6000 (American Hospital Directory, 2010).

Another imaging technique that uses a PET-based platform is PET 11C-acetate scanning. Acetate tends to accumulate in cancer tumors, and can be used as a marker for cancerous cells (Ravizzini, 2009). This PET-based imaging technique seems to be more promising, as it is much more accurate than PET-FDG imaging, but the data is still inconclusive as to whether it is accurate enough to implement in a hospital setting due to the cost of the test.

11C-choline and 18F-fluorocholine (18F-FCH) imaging has also been found to give significant results in prostate cancer detection. Like acetate, choline is a compound that is overproduced in cancer tumors (Ravizzini, 2009). According to one study, the sensitivity and specificity of this technique are 66% and 81%, respectively (Ravizzini, 2009). This technique seems to still have high

rates of false positive and false negative values, so it seems like an ineffective method to screen for prostate cancer (Ravizzini, 2009). Improvements must be made in the technique to improve the accuracy before it would be worthwhile to implement in clinical practice.

Another imaging technique that utilizes PET scanning is Anti-18F-FACBC. This technique utilizes a chemical analog for an amino acid, and can be used to determine whether or not a tumor has progressed to malignancy (Ravizzini, 2009). However, this technique has just emerged and not enough data has been made available in this area to fully support claims of significant efficacy.

In conclusion, MRI and MRSI remain the main imaging techniques, other than TRUS, to screen for prostate cancer. The primary emerging screening technique is PET scanning, combined with a variety of radiotracers and fluorescent molecules. The best technique seems to involve optimizing MRI and MRS (combined with radiotracers and new compounds) to produce a more accurate reading (higher sensitivity and specificity). However, imaging is very expensive and seems to be the least cost-effective out of all the alternative future methods.

Comparing present and future screening modalities

The current screening method pathway encompasses four steps: PSA, then DRE, then TRUS, then biopsy (Table 5); however, not enough data were collected from the literature search used in this paper to define the comprehensive sensitivity and specificity for the entire pathway. Instead, each test has specificity and sensitivity data as a standalone test that can allow for comparison between all the current screening methods. Of all current screening methods, the DRE is the most specific standalone test and the combined

	Current					Future		
	PSA	DRE	PSA + DRE	TRUS	Tissue Biopsy	AMACR Biomarker	Gold Nanoparticles and Imaging	MRI and MRSI
Specificity	.930	.936	.86	.284	varies	1.000	.900	.926
Sensitivity	.740	.500	.920	.855	Varies	.875	.900	.723
Estimated Cost in 2007	\$31.30	\$8.30	\$89.60	\$104.00	\$347.24	~\$31.30	~\$3,500	~\$3,500

Table 5. Current and future methods in screening. Future methods are all assumed to be clinically viable.

PSA and DRE is the most sensitive standalone test.

Out of all the different categories of future screening methods (biomarker, nanotechnology, and imaging), biomarkers seem to show the most promise as cost-effective alternatives to the PSA test. Specifically, the AMACR urine-based biomarker test has 100% specificity and 87.5% sensitivity, surpassing the PSA and DRE test in both sensitivity and specificity data with a relatively low-cost similar to that of a PSA test. In addition, the AMACR urine-based test is notably less invasive than the PSA test, requiring only a sample of urine from a patient. The other two future methods examined in this paper, gold nanoparticles and MRI and MRSI, are very expensive and only slightly improve upon the PSA-based biomarker tests (Tables 5, 6).

To allow for further comparison of future screening methods with current

screening methods, a model is needed that encompasses appropriate, definable criteria to evaluate the overall effectiveness of a screening method. This study proposes such a screening model constructed through the use of specific objective criteria to describe overall cost effectiveness.

THE COST EFFECTIVENESS MODEL

To individually compare the optimal screening methods (both current and future), a cost effectiveness (CE) model is proposed to correlate the accuracy, risk, stage of detection, and monetary cost of each screening method (Equation 1). The ratings of each category range from 0 to 4 when calculating the CE score. These categories are then divided by a normalized cost (on a scale from 1-4, 1 being the most affordable), to give an overall cost effectiveness (Table 7). These categories will be justified and defined more explicitly throughout the rest of this section.

Defining accuracy in the CE Model

Accuracy is here defined as the ability for a particular test to give a correct screen for prostate cancer (subdivided into specificity and sensitivity). This area is the most important area with regard to prostate cancer screening, and is thus weighted as 50% of the CE model. Because accuracy is subdivided into both sensitivity (Equation 2), defined as the proportion of people in the screened population who do not have prostate cancer and who are correctly identified as not having

	Best Future Combined		
	AMACR Biomarker	Gold Nanoparticles and Imaging	MRI and MRSI
Specificity	1.000	.900	.926
Sensitivity	.875	.900	.723
Estimated Cost in 2007	~\$31.30 assuming same as PSA	~\$3,500 assuming combined with MRI	~\$3,500 from American Hospital Directory

Table 6. Comparison of best future methods. Evaluated using the cost effectiveness model.

$$CE = \frac{.50(\textit{accuracy rating}) + .25(\textit{stage of detection rating}) + .25(\textit{risk rating})}{\textit{normalized cost rating}}$$

where accuracy rating = .25(specificity rating) + .25(sensitivity rating)

Equation 1. Cost effectiveness (CE) model, used to calculate overall effectiveness of any given screening method.

$$\textit{Sensitivity Rating} = \frac{TP}{TP + FN} \times 4$$

Equation 2. Sensitivity rating, defined to be the number of true positives (TP)—those who actually have prostate cancer—divided by the number of TP added to the false negatives (FN)—those who have prostate cancer but were not correctly diagnosed by the screening method. In this way, sensitivity can be defined as the ability of a screening test to correctly diagnose an individual as having prostate cancer. The fraction is multiplied by four to maintain the four-point rating system. It is of note that most of the sensitivity data were obtained from research papers.

$$\textit{Specificity Rating} = \frac{FN}{TN + FP} \times 4$$

Equation 3. Specificity rating, defined to be the number of false negatives (FN)—those who have cancer but are diagnosed as not having cancer—divided by the FN added to the false positives—individuals who do not have the disease and are incorrectly diagnosed as having the disease. In this way, specificity can be defined as the ability of a screening test to correctly diagnose a person as not having prostate cancer. The fraction is multiplied by four to maintain the four-point rating system. It should be noted that most of the specificity data were obtained from research papers.

the disease, and specificity (Equation 3), defined as the proportion of people in the screened population who have prostate cancer and who are correctly identified as having the disease, 25% of the overall CE accounts for specificity and 25% of the overall CE would account for sensitivity (Logan, 2004). After the specificity and sensitivity data are obtained, it is expressed as a percent of 4 to allow for consistent weighting with the other rating categories.

This category is weighted more than the others because clinical certainty is critical in diagnostic medicine, particularly in prostate cancer screening. The main reason why certain methods of prostate cancer screening are considered controversial is because of the lack of specificity and sensitivity up to the third step in the current prostate screening pathway (TRUS imaging).

Lack of sensitivity and specificity cause unnecessary psychological and physical harm to screening patients, as noted before, and greater accuracy is needed for the benefits of prostate cancer screening to clearly outweigh the risks (Logan, 2004; U.S. Preventive Services Task Force, 2008). More specifically, an FP given to a patient contributes to unnecessary cost, as well as unnecessary treatment, most notably an invasive biopsy. Therefore, this category should carry the greatest weight because it has the potential to save the most number of lives through a high specificity, and to avoid additional patient risk associated with false positives through a high sensitivity.

Defining risk in the CE Model

Risk is the overall physical harm the test can do to a patient. Risk is ranked according to various levels of invasiveness of

each screening technique, along with patient comfort level in the procedure (Table 7).

Risk is an important concept in the screening process because the greater the risk involved in a procedure, the more difficult it will be to obtain FDA approval and to persuade patients to agree to have the screening technique performed. In other words, the more risk embedded within a screening technique, the less lives it is likely to save because of the above two hindering factors. Because of its importance to prostate cancer screening, risk is weighted 25% in our model. A risk rating of 4 indicates the least amount of risk, whereas a risk rating of 1 indicates the most amount of risk involved in a screening procedure. The risk rating is then plugged back into the numerator of the CE equation as 25% of the risk rating.

Defining stage of detection in the CE Model

The CE equation also integrates the stage at which a screening method could detect prostate cancer. This category is based on a study that recorded the 5-year survival rates of people in stages 1-4 of prostate cancer (Table 7). A nonlinear survival rate was found with regard to the various stages of prostate cancer. If cancer is detected in stages 1-3, there is a 100% survival rate, and that would be ranked 4 on the stage of detection scale, which is indicative of the highest effectiveness (ACS, 2010). If cancer is detected in stage 4 (meaning cancer has metastasized), cancer survival rates dropped down to 31%, ranking 1.24 on the stage of detection scale (least effective) (ACS, 2010). Therefore, the stage of detection rating must be one of these two values, as there are only 4 stages of prostate cancer. After the stage of detection rating is defined, it is plugged back into the numerator of the CE equation as 25% of the stage of detection rating.

The stage of detection is another very important factor when considering the efficacy of a prostate cancer screen. If a

clinician catches cancer in a very late metastatic phase of prostate cancer, the rate of survival declines significantly and a patient is less likely to survive (ACS, 2010). It has a weight of 25% because it is important to recognize such a nonlinear pattern and progressive nature of the disease in order to categorize the overall cost effectiveness of the available screening methods. By increasing the ability to detect cancer during the phases that allow for prevention or treatment, more lives are saved in the process.

Defining monetary cost in the CE Model

Monetary cost is the total cost per dollar of the test, and is in the denominator of the cost effectiveness (CE) equation. The costs are normalized to a certain set of values (Table 7), and the cost assumes that the screening test is more specific and sensitive than the PSA and DRE test to allow for an accurate diagnostic screen. This assumption was made because if a test is not accurate, such as the PSA test, it leads to wasted money circulating through the hospital system as well as skepticism as to the validity of the test (Logan, 2004). One source was used for the costs for each of the current screening methods, which are expressed in terms of 2003 US dollars. Although these are not the exact costs that are currently being charged, they provide a consistent basis for comparison (Ekwueme, 2007).

It is very important to integrate health care cost into the equation because it is a key factor as to whether any given prostate cancer screening test is accessible to the targeted population. According to the National Health Committee of New Zealand, “one of the criteria for accessing prostate cancer screening programs is that there must be an effective and accessible treatment or intervention for the condition identified through early detection” (Logan, 2004).

Increased health care costs disadvantage poorer populations. Assuming

		CE Rating Scale		Accuracy	Accuracy	
	Risk Rating (.25)	Stage of Detection Rating (.25)	Specificity Rating (.25)	Sensitivity Rating (.25)	Normalized Scale of Cost	
Meaning of a Value of 4	Noninvasive Procedure	Prostate Cancer is in Stages 1-3	Specificity value of 1	Sensitivity value of 1	Expensive	
Definition	Example: Urine Test	A 100% 5 year survival rate if prostate cancer is correctly diagnosed	A perfectly specific test	A perfectly sensitive test	A cost >\$1000	
Meaning of a Value of 3	Minimally-Invasive Procedure	Prostate Cancer is in Stage 4	Specificity value of .75	Sensitivity value of .75	Somewhat Affordable	
Definition	Example: Drawing Blood	75% 5 year survival rate	A moderately specific test	A moderately sensitive test	A cost in the range of \$200-1000	
Meaning of a Value of 2	Moderately Invasive Procedure	Prostate Cancer is in Stage 4	Specificity value of .75	Sensitivity value of .75	Moderately Affordable	
Definition	Example: Endoscopy	50% 5 year survival rate	A somewhat specific test	A somewhat sensitive test	A cost in the range of \$50-200	
Meaning of a Value of 1	Open Surgery	Prostate Cancer is in Stage 4	Specificity value of .25	Sensitivity value of .25	Affordable	
Definition	Example: surgical procedure	25 % 5 year survival rate	A poorly specific test	A poorly sensitive test	A cost in the range of \$0-50	
Meaning of Value of 0	n/a	Prostate Cancer is in Stage 4	Specificity value of 0	Sensitivity value of 0	A screening test is free	
Definition	n/a	0% 5 year survival rate	Test exhibits no specificity	Test exhibits no sensitivity	\$0	

Table 7. Ratings used in the CE model (Equation 1). Risk is weighted as 25% and is categorized from 1-4, with 4 being the rating of least risk. Stage of detection is weighted as 25% and is categorized from 1-4, but only inputs values of 1.24 (stage 4) and 4 (stages 1-3) due to the nonlinear nature of the variable. The accuracy is weighted as 50% and encompasses the specificity and sensitivity of a screening test. Costs are normalized to a set of values based upon relative affordability.

an accurate diagnostic screen, the majority of the screening techniques should be targeted to a lower to middle class population. As costs rise above a certain threshold value, fewer and fewer people would get screened, and increasingly more people would die from prostate cancer. The normalized costs correspond to the hierarchical structure of income, from the poorest class (most affordability) to the richest class (least

affordability). Therefore, an ideal screening test should have the most affordability and target a poorer population stratum to allow for all members of society (or as many as possible) to have access to the test and to save the most number of lives.

Applicability of the CE Model

Overall, this model allows for the comprehensive comparison of cost

effectiveness between two different screening methods. By plugging in the values into the CE equation and outputting a number, a graph can be used to evaluate the efficacy of two different screening methods relative to each other. The CE equation can also guide research into the direction that will allow for a more optimized and tailored screening method for prostate cancer. This solution can be accomplished by creating a screening technique according to the design parameters proposed in the equation.

RESULTS

Evaluation of current screening techniques

First, the CE model was used to compute values and compare the individual screening methods in the current prostate cancer screening pathway (Table 8). Figure 2 is a graphical representation of the results. As shown in the graph, the PSA test alone provided the highest amount of cost effectiveness (CE) with an overall score of 3.42 out of 4, making this method the best

current screening pathway, whereas the other methods are subpar in comparison.

Evaluation of future screening methods

For future screening methods, three of the most promising methods were compared: the AMACR biomarker, gold nanoparticles, and the MRI and MRSI imaging test. To compare the three remaining methods, numbers from research were plugged into the equation discussed earlier (Table 9), providing cost effectiveness outputs. Using the equation, the most cost-effective method was determined to be the AMACR biomarker, with a cost effectiveness number of 3.875, compared to nanotechnology's 0.825 and imaging's cost effectiveness number of 0.850 (Figure 3). This clearly makes the AMACR biomarker the most cost-effective future method of screening, with the highest sensitivity, a high specificity, low risk and low cost.

Comparison of current and future screening techniques

Current Method Comparison				
	PSA	DRE	PSA + DRE	TRUS
Overall Cost Effectiveness Rating	3.42/4.000	2.940/4.000	1.640/4.000	1.320/4.000
Specificity	.930	.936	.860	.284
Specificity Rating (.25)	3.720	3.744	3.440	1.136
Sensitivity	.740	.500	.920	.855
Sensitivity Rating (.25)	2.960	2.000	3.680	3.420
Stage of Detection	1 st Stage	2 nd Stage	2 nd Stage	2 nd Stage
Stage of Detection Rating (.25)	4.000/4.000	4.000/4.000	4.000/4.000	4.000/4.000
Risk Classification	Minimally Invasive	Moderately Invasive	Moderately Invasive	Moderately Invasive
Risk Rating (.25)	3.000/4.000	2.000/4.000	2.000/4.000	2.000/4.000
Estimated Cost in 2007	\$31.30	\$8.30	\$89.60	\$104.00
Normalized Cost Rating	1.000/4.000	1.000/4.000	2.000/4.000	2.000/4.000

Table 8. Ratings by category for the CE model as well as the overall CE rating for each current method of screening.

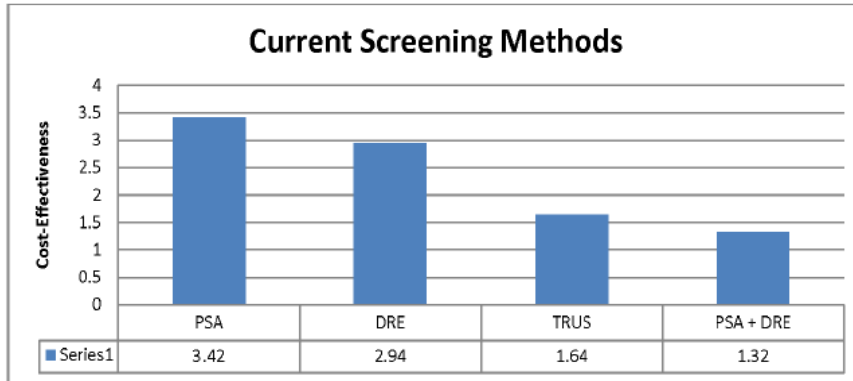


Figure 2. Cost effectiveness for each screening test currently available to health providers for prostate cancer screening.

After scoring all the current and future screening methods using the cost effectiveness model, the scores were then collectively depicted in the following bar graph (Figure 4). From this bar graph, it can be observed that the use of biomarkers, specifically the AMACR urine-based test, is not only more cost-effective than the other future screening techniques under development, but also is more cost-effective than the other current screening methods. This method is currently undergoing the FDA approval process, and will most likely become a more popular screening test than the PSA and DRE test in the near future.

Final screening pathway recommendation

The screening pathway that this paper recommends is the AMACR urine test combined with a biopsy for confirmation. This pathway assumes that the AMACR urine test has 100% specificity and 87.5% sensitivity, which may need to be more thoroughly validated through clinical testing. Along with the test's high sensitivity and specificity, it has a low risk

and cost, with the highest cost effectiveness of all the screening techniques considered in the analysis. The procedural change from PSA-based screening to AMACR-based preliminary screening alone would save \$1.2 billion as calculated using cost data (De Angelis, 2007; see Table 10). However, to further decrease cost and to save lives, it is also recommended that all men over the age of 50 be screened, as long as the individual is expected to live at least five more years (that is, as long as the individual does not have any other disease or extenuating circumstance that will kill them before slow-acting prostate cancer) (American College of Physicians, 1991; Lim, 2008; Smith, 2006; American Urological Association, 2006). Men with a genetic predisposition towards prostate

Future Method Comparison			
	AMACR Urine Biomarker	Gold Nanoparticles and Imaging	MRI and MRSI
Overall Cost Effectiveness Rating	3.875/4.000	.825/4.000	.850/4.000
Specificity	1.000	.900	.926
Specificity Rating (.25)	4.000/4.000	3.600/4.000	3.704/4.000
Sensitivity	.875	.900	.723
Sensitivity Rating (.25)	3.500/4.000	3.600/4.000	2.892/4.000
Stage of Detection	1 st Stage	2 nd stage	2 nd stage
Stage of Detection Rating (.25)	4.000/4.000	4.000/4.000	4.000/4.000
Risk Classification	Noninvasive	Moderate Risk	Minimal Risk
Risk Rating (.25)	4.000/4.000	2.000/4.000	3.000/4.000
Estimated Cost in 2007	~\$31.30 assuming same as PSA	~\$3,500 assuming combined with MRI	~\$3,500 from American Hospital Directory
Normalized Cost Rating	1.000 (least expensive)	4.000 (most expensive)	4.000 (most expensive)

Table 9. Ratings by category for the CE model as well as the overall CE rating for each future method of screening.

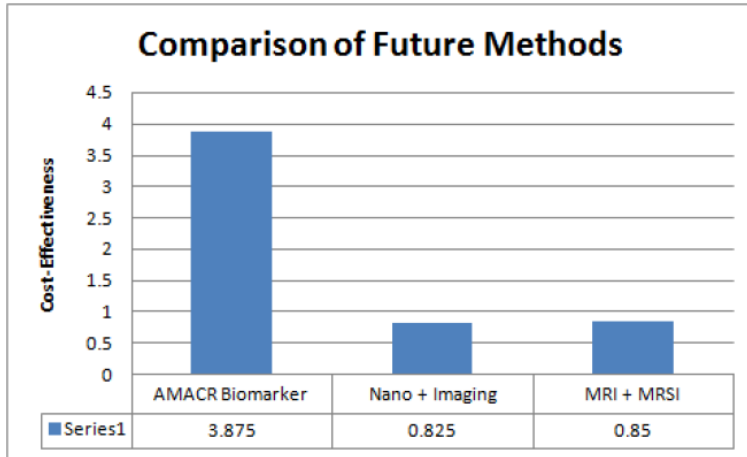


Figure 3. CE model as applied to selected screening methods currently in development for future use. The scores given are graphed above for comparison.

cancer, such as those with a familial history of prostate cancer, and men with an ethnic disposition should also be screened earlier to provide an early baseline as to make the cancer easier to detect (BCCA, 2006).

CONCLUSION AND DISCUSSION

The current prostate screening pathway lacks sufficient sensitivity and specificity, encompasses substantial risk, and is a significant health care cost. Considering these issues, this paper proposes a model that evaluated the relative cost effectiveness of each current and future screening method found during an extensive literature search. The model took into account screening accuracy (specificity and sensitivity), risk (in terms of invasiveness), stage of detection, and monetary cost. After inputting values into the model, comparative analysis of current and future methods could be made to offer a final recommendation as to the best possible screening method.

The CE equation is a powerful tool for evaluating the overall effectiveness of a prostate cancer screening method. One of the most important conclusions embedded in the equation is that accuracy is the most important facet of prostate cancer screening. A combination of a high sensitivity method and a high specificity method is advantageous because it eliminates unnecessary psychological and physical harms to screening patient resulting from false positive and false negative (FN) screens. A more accurate test will yield a greater validity and overall acceptance, provided that enough clinical and scientific evidence verifies the correlation (Logan, 2004).

Assuming all the data to be correct, the most effective pathway determined here was the AMACR urine-based test, as an initial screening technique followed by a biopsy. According to our model, this model is notably more cost-effective than the current pathway for prostate cancer screening. Altogether, it would dramatically lower the health care cost, require fewer number of steps in a screening

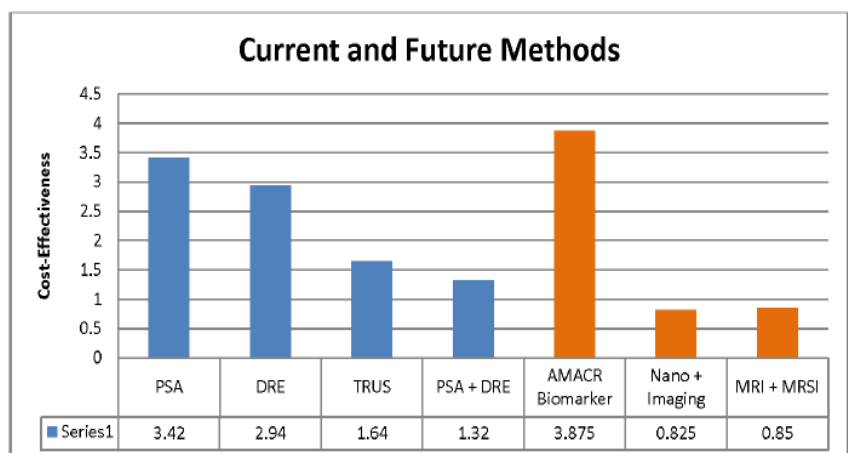


Figure 4. Collective graph of current and future screening methods. As shown, the AMACR urine-based screen outscores all other tests and thus has the greatest potential as a cost-effective screening method when released for clinical use.

Current vs. Future CE		
	PSA + DRE	AMACR
Specificity	0.86	1.00
Sensitivity	0.92	0.875
Risk	Moderately Invasive	Non-Invasive
Detection	Stage II	Stage I
Cost	\$89.60	\$30
Total CE	3.00	3.70
Estimated Cost	\$1.8 billion	\$0.60 billion

Note: ~\$1.2 billion estimated savings

Table 10. Comparison of best current and future screening methods. Estimated savings is the amount that can be saved by healthcare providers, based on the number of patients screened per year in the United States.

pathway, and be markedly more accurate than the current prostate screening pathway.

However, additional clinical testing and scientific verification would need to be conducted to allow for this technique to replace the PSA test. A more efficient strategy may be to combine the AMACR test with various other techniques, such as PSA and DRE, to increase specificity within the current pathway (Rogers, 2004). However, more data would have to be available to allow for consistent comparison of new pathways with the current screening pathway.

Though this proposed pathway seems much more efficient than the current pathway in terms of monetary cost, accuracy, and risk, the proposed pathway still requires two steps along with a relatively invasive biopsy. An optimized pathway, as indicated from our model, would require only one step, would have a perfect accuracy (100% sensitivity and 100% specificity), would be non-invasive, could detect cancer at stage I, and would be as affordable as possible. There is still much work needed in order to make such a standalone and "ideal" screening test, but this model lays the framework for screening test evaluation. As a result, it can be adopted for

evaluating screening techniques which may be discovered in the near future.

ACKNOWLEDGEMENTS

This project was completed as part of BME 1300, the introductory biomedical engineering problems-based learning (PBL) class at Georgia Tech. The class was created by Dr. Wendy Newstetter and Dr. Paul Benkeser to focus on developing foundational skills in research inquiry in a group-oriented environment (Newstetter, 2006).

We would like to thank Mr. Choon Hwai Yap for being our mentor and facilitator for this particular research project.

REFERENCES

1. American Cancer Society (2009) Can Prostate Cancer Be Found Early? Retrieved 5/18/2010, from http://www.acevents.org/docroot/cr/content/cr_2_4_3x_can_prostate_cancer_be_found_early_36.asp
2. American Cancer Society (2010) How Is Prostate Cancer Staged? Retrieved 6/1/2010, from http://www.cancer.org/docroot/cr/content/cr_2_4_3x_how_is_prostate_cancer_staged_36.asp
3. American Cancer Society (2010). "What Are the Key Statistics About Prostate Cancer?" Retrieved May, 2010, from http://www.cancer.org/docroot/CRI/content/CRI_2_4_1X_What_are_the_key_statistics_for_prostate_cancer_36.asp?sitearea.
4. American College of Physicians. Screening for prostate cancer. *Ann Intern Med* 1997; 126:480-4.
5. "American Hospital Directory - Medical Diagnosis Costs." (2010),

- from http://www.ahd.com/sample_oupatient.html.
6. American Urological Association. Prostate-specific antigen (PSA) best practice policy. *Oncology (Williston Park)* 2000;14:267-72, 277-8, 280 passim.
 7. Akduman Bülent (2010). "Transrectal ultrasound-guided prostate biopsy: current approach." *Türk Üroloji Dergisi - Turkish Journal of Urology* 36(1): 25-32.
 8. Association, A. U. (2009). "Prostate-Specific Antigen Best Practice Statement: 2009 Update." from <http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/psa09.pdf>.
 9. BC Cancer Agency (2006) Retrieved 6/10/10, 2010, from <http://www.bccancer.bc.ca/PPI/TypesofCancer/Prostate/default.htm>.
 10. Becker, A. L. (2010). "Debate Continues Over Best Way to Screen for Prostate Cancer." *The Hartford Courant*.
 11. De Angelis G, Rittenhouse HG, Mikolajczyk SD, Blair Shamel L, Semjonow A (2007). "Twenty years of PSA: from prostate antigen to tumor marker". *Rev Urol* 9 (3): 113–23. PMID 17934568. PMC 2002501. <http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=2002501&blobtype=pdf>.
 12. Ekwueme, D. U., Stroud, L. A., & Chen, Y. (2007). Cost analysis of screening for, diagnosing, and staging prostate cancer based on a systematic review of published studies. *Prev Chronic Dis*, 4(4), A100.
 13. Hamashima, C., & Yoshida, K. (2000). Cost-effectiveness Analysis of Prostate Cancer Screening. *Environ Health Prev Med*, 5, 111-117.
 14. Ireland, J. R., J. McMath, et al. (2010). "Insights in Nanomedicine: Fighting Cancer with Gold Nanoshells." Retrieved 2010, from http://www.nanoed.org/concept_s_apps/AuNanoShells/indepth.
 15. Jiang, S., M. K. Gnanasammandhan, et al. (2010). "Optical imaging-guided cancer therapy with fluorescent nanoparticles." *Journal of the Royal Society Interface* 7(42): 3-18.
 16. Kurhanewicz, John C. K. S., Fergus Coakley (2006) *Magnetic Resonance Anatomic and Spectroscopic Imaging of Prostate Cancer - Current Status*. PCRI Insights 9,
 17. LeBeau, Aaron P. S., John T. Isaacs, Samuel R. Denmeade (2009). "Prostate-Specific Antigen Is a "Chymotrypsin-like" Serine Protease with Unique P1 Substrate Specificity." *Biochemistry* 48(15): 3490-3496.
 18. Li, Y. and C.-W. Peng (2010). "Application of quantum dots-based biotechnology in cancer diagnosis: Current status and future perspectives." *Journal of Nanomaterials* 2010(Compendex).
 19. Lim LS, Sherin K. ACPM Prevention Practice Committee. Screening for prostate cancer in U.S. men ACPM position statement on preventive practice. *Am J Prev Med* 2008; 34:164-70.
 20. Logan, R. (April 2004). "Prostate Cancer Screening in New Zealand ". from [http://www.nhc.health.govt.nz/moh.nsf/pagescm/709/\\$File/nhcprostadocument.pdf](http://www.nhc.health.govt.nz/moh.nsf/pagescm/709/$File/nhcprostadocument.pdf)
 21. Loo, L. Hirsch, M. -H. Lee, E. Chang, J. West, N. Halas, and R. Drezek (2005) "Gold nanoshell bioconjugates for molecular imaging in living cells," *Optics Letters* 30, 1012-1014 (2005).

22. Luo, Jun, et al (2002) "Alpha-Methylacyl-Coa Racemase: A New Molecular Marker for Prostate Cancer." *Cancer Research* 62 8 (2002): 2220-26.
23. Makarov, D. V., S. Loeb, et al. (2009). "Biomarkers for Prostate Cancer." *Annual Review of Medicine* 60: 139-151.
24. Mani, V., B. V. Chikkaveeraiah, et al. (2009). "Ultrasensitive immunosensor for cancer biomarker proteins using gold nanoparticle film electrodes and multienzyme-particle amplification." *ACS Nano* 3(Compendex): 585-594.
25. Mikolajczyk SD, Grauer LS, Millar LS, et al. A precursor form of PSA (pPSA) is a component of the free PSA in prostate cancer serum. *Urology*. 1997;50:710-714
26. Nadler, R. B. (2008). "The case for prostate-specific antigen screening starting at age 40." *Cancer* 113(6): 1278-1281.
27. "National Cancer Institute: Early Prostate Cancer". 2009. (03/18/2009). <<http://www.cancer.gov/cancertopics/factsheet/Detection/early-prostate>>.
28. National Cancer Institute (2009) "Prostate Cancer Treatment." Retrieved 5/18/2010, 2009 from <http://www.cancer.gov/cancertopics/pdq/treatment/prostate/Patient/page1>.
29. Newstetter WC. Fostering integrative problem solving in biomedical engineering: the PBL approach. *Ann Biomed Eng*. 2006 Feb; 34(2):217-25.
30. O'Dowd, Gerry R. W. V., M. Craig Miller, Stephen B. Strum (2001). "The Gleason Score: A Significant Biologic Manifestation of Prostate Cancer Aggressiveness on Biopsy." Retrieved 5/27/10, 2010, from http://www.prostate-cancer.org/education/staging/Dowd_GleasonScore.html.
31. Palaniappan, A., W. H. Goh, et al. (2010). "Aligned carbon nanotubes on quartz substrate for liquid gated biosensing." *Biosensors and Bioelectronics* 25(Compendex): 1989-1993.
32. Ploussard, G. and A. de la Taille (2010). "Urine biomarkers in prostate cancer." *Nature Reviews Urology* 7(2): 101-109.
33. Rai, A. J., R. M. Kamath, et al. (2009). "Analytical validation of the GeXP analyzer and design of a workflow for cancer-biomarker discovery using multiplexed gene-expression profiling." *Analytical and Bioanalytical Chemistry* 393(Compendex): 1505-1511.
34. Ravizzini, G., B. Turkbey, et al. (2009). "New horizons in prostate cancer imaging." *European Journal of Radiology* 70(2): 212-226.
35. Rhodes, M. (2008). Digital Rectal Examination (DRE). from <http://www.webmd.com/colorectal-cancer/digital-rectal-examination-dre>
36. Rigau, M., J. Morote, et al. (2010). "PSGR and PCA3 as Biomarkers for the Detection of Prostate Cancer in Urine." *Prostate* 70(16): 1760-1767.
37. Rogers, Craig G., et al. "Prostate Cancer Detection on Urinalysis for Alpha Methylacyl Coenzyme a Racemase Protein." *The Journal Of Urology* 172 4 Pt 1 (2004): 1501-03.
38. Rubin, Mark A., et al. (2005) "Decreased Alpha-Methylacyl Coa Racemase Expression in Localized Prostate Cancer Is Associated with an Increased Rate of Biochemical Recurrence and Cancer-Specific Death." *Cancer Epidemiology, Biomarkers & Prevention: A*

- Publication Of The American Association For Cancer Research, Cosponsored By The American Society Of Preventive Oncology 14 6 (2005): 1424-32.
39. Sechrest, S. (1996). "Federal documents -- Costs and Effectiveness of Prostate Cancer Screening in Elderly Men." *Library Journal* 121(9): 34.
 40. Smith RA, Cokkinides V, Eyre HJ. American Cancer Society guidelines for the early detection of cancer, 2006. *CA Cancer J Clin* 2006;56:11-25; quiz 49-50.
 41. Smith, Stephanie L McFall ; David W. (2009) "Lack of Follow-up of Prostate-Specific Antigen Test Results." *Public Health Reports* 124 5: 718-25.
 42. Tamsel, R. K. (2008). "Transrectal Ultrasound in Detecting Prostate Cancer Compared With Total Prostate Specific Antigen Levels." *Journal of Medical Imaging and Radiology* 52(1): 24-28.
 43. U.S. News and World Report (2005) Prostate Cancer Tests.
 44. U.S. Preventive Services Task Force. *Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement*. August 2008.
<http://www.uspreventiveservicestaskforce.org/uspstf08/prostate/prostaters.htm>
 45. Uetsuki H, Tsunemori H, Taoka R (2005) Expression of a novel biomarker, EPCA, in adenocarcinomas and precancerous lesions in the prostate. *J. Urol.* 174:514-18
 46. Vashi, D. (2010). Phone Interview with Dr. Vashi from Emory Clinic. Atlanta.
 47. Villeirs, G. M., W. Oosterlinck, et al. (2010). "A qualitative approach to combined magnetic resonance imaging and spectroscopy in the diagnosis of prostate cancer." *European Journal of Radiology* 73(2): 352-356.
 48. Worthington, J. F. (2007). Breakthrough: New Prostate Cancer Test is More Specific than PSA. Prostate Cancer Discovery, The Brady Urological Institute - Johns Hopkins Medicine. **3:** 1-2.
http://urology.jhu.edu/newsletter/discovery_III_07.pdf
 49. Zielie, P. J., et al. (2004) "A Novel Diagnostic Test for Prostate Cancer Emerges from the Determination of Alpha-Methylacyl-Coenzyme a Racemase in Prostatic Secretions." *The Journal of Urology* 172 3 (2004): 1130-33.