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Value of Serial PSA Measurements for Prostate Cancer Prediction on Screening Using a Maximum Likelihood Estimation − Prostate Specific Antigen (MLE-PSA) Model

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Abstract:

PSA measurements are used to assess the risk for prostate cancer. PSA range and PSA kinetics such as PSA velocity have been correlated with increased cancer detection and assist the clinician in deciding when prostate biopsy should be performed. Our aim is to evaluate the use of a novel, maximum likelihood estimation - prostate specific antigen (MLE-PSA) model for predicting the probability of prostate cancer using serial PSA measurements combined with PSA velocity in order to assess whether this reduces the need for prostate biopsy.

A total of 1976 Caucasian patients were included. All these patients had at least 6 PSA serial measurements; all underwent trans-rectal biopsy with minimum 12 cores within the past 10 years. A multivariate logistic regression model was developed using maximum likelihood estimation (MLE) based on the following parameters (age, at least 6 PSA serial measurements, baseline median natural logarithm of the PSA (ln(PSA)) and PSA velocity (ln(PSAV)), baseline process capability standard deviation of ln(PSA) and ln(PSAV), significant special causes of variation in ln(PSA) and ln(PSAV) detected using control chart logic, and the volatility of the ln(PSAV). We then compared prostate cancer probability using MLE-PSA to the results of prostate needle biopsy. The MLE-PSA model with a 50% cut-off probability has a sensitivity of 87%, specificity of 85%, positive predictive value (PPV) of 89%, and negative predictive value (NPV) of 82%. By contrast, a single PSA value with a 4ng/ml threshold has a sensitivity of 59%, specificity of 33%, PPV of 56%, and NPV of 36% using the same population of patients used to generate the MLE-PSA model. Based on serial PSA measurements, the use of the MLE-PSA model significantly (p-value < 0.0001) improves prostate cancer detection and reduces the need for prostate biopsy.

Key words: Logistic regression, prostate cancer, PSA, PSAV, quality control.

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1. Introduction

According to the American Cancer Society [1] prostate cancer is the second leading cause of death in men after lung cancer and the most diagnosed cancer in men after skin cancer. The use of prostate-specific antigen (PSA) measurements to assess the potential for prostate cancer has been reported since 1979 [2, 3, 4, 5, 6, 7, 8] and according to an article dated June 16, 2009 in the Wall Street Journal, Peter Carroll, M.D., chair of the department of urology at the University of California, San Francisco was reported to say that the PSA test at age 40 can be used to predict the future risk of prostate cancer. Most doctors recommend using a PSA threshold to indicate the presence of cancerous lesions in the prostate and to guide the clinician in deciding if and when a biopsy should be performed on the patient [5, 9]. The upper limit recommended to define "abnormal" varies from 2.5 ng/ml to as high as 10 ng/ml, but 4 ng/ml is the most commonly applied threshold. Glass and Kaplan [10] noted that living organisms are characterized by time ordered sub-cellular, cellular, and super-cellular processes that can have specific, recognizable patterns. In particular, the dynamics of changes in the PSA level and its relationship to the presence of cancerous tumors in the prostate has been studied in the past [11, 12]. For instance, the PSA velocity (PSAV) has been proposed [12]. PSA kinetics which includes PSAV and PSA doubling time has been proposed for the early diagnosis of prostate cancer. However, Schroder *et al.* [13] noted that PSAV may not be useful in detecting prostate cancer, disclosing that 985 needle biopsies for men who had a PSA value 4.0 to 9.0 ng/ml resulted in a positive predictive value of only 24.5%. Similarly, Ross *et al.* [14] concluded that PSA kinetics fail to predict detectable prostate tumors consistently and should not replace annual surveillance biopsies for men being checked for tumor growth. Use of the "Individualized Risk Assessment of Prostate Cancer" software (see www.uroweb.org) [15] for a 62 year man with a PSA of 4.0 ng/ml, abnormal Digital Rectal Exam (DRE), and no prior prostate biopsy resulted in only a 17.4% risk of biopsy-detectable high grade prostate cancer with a 95% confidence interval from 12.1% to 22.8%. Vickers *et al.* [16] noted that calculating PSAV and doubling time proffer inadequate information concerning prostate cancer in untreated patients than PSA values and hence is of minimal help to the clinician for decision making before treating men with early stage prostate cancer. But there are conflicting arguments. For example in a study of 12,090 men, Lilja *et al.* [17] concluded that PSA is highly predictive of long-term risk of prostate cancer and that almost 50% of all deaths could be prevented by monitoring the PSA levels of those with the highest PSA levels at age 44-50.

Due to these conflicting reports on the predictive power of PSA measurements, the U.S. Preventative Services Task Force on October 7, 2011 recommended do-not-screen advice to healthy men of all ages using the PSA blood test because

biopsies given to patients with positive PSA tests can cause infection and other adverse effects [18, 19]. Though the literature is inconclusive regarding how best to use the PSA test to improve the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the test, our research reinforces the strong evidence as regards the benefits of using the PSA test for detection of localized prostate cancer. The present study is based on the hypothesis that each patient is a system and, as such, this system has its unique or age-related profiles: heart rate, metabolic rate, PSA profile, to name a few. Age-related profiles can be parameterized by sufficient statistics, some based on quality control methods that summarize the central tendency, variation, and skewness of the time ordered characteristics of the system. In particular, a patient's PSA signature can be characterized as follows: a baseline (consisting of six historical PSA tests at approximately one to two year intervals); median natural logarithm of the PSA (ln(PSA)); baseline, median moving range process capability standard deviation of the ln(PSA); baseline, median natural logarithm of the PSA velocity (ln(PSAV)); baseline, median moving range process capability standard deviation of ln(PSAV); and significant special causes of variation in ln(PSA) and ln(PSAV) detected using control chart logic. These quality control metrics are discussed in detail in the next section along with their use in predicting prostate cancer.

The paper is organized as follows. Section 2 includes the study data and an explanation of the potential predictors for the risk of prostate cancer, along with the development of the MLE model for the probability of prostate cancer. In Section 3 the predictability of the MLE model probability of prostate cancer and the conditional probability of cancer on needle biopsy are presented. Sections 4 and 5 consist of a discussion of the results, in addition to the strengths and limitations of this retrospective study, respectively.

2. Data and Methods

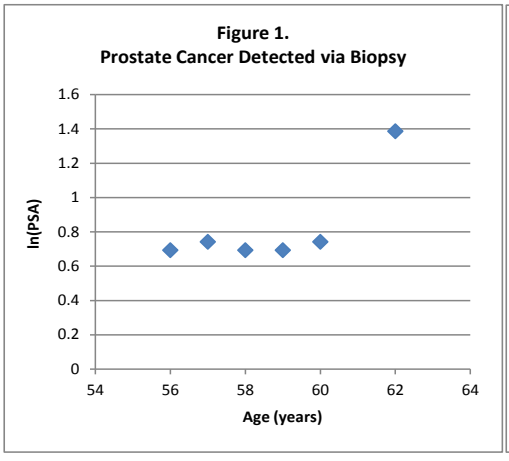
2.1 Study Design

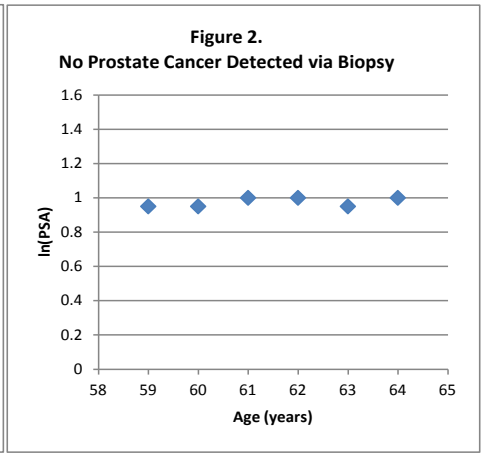
This is a retrospective study. Current and historical PSA data were obtained from the medical records of de-identified male patients of a Midwestern hospital's urology department for patients who were found to have cancer and were not found to have cancer based on needle biopsies. The inclusion criterion admitted only those patients for whom at least six historical PSA tests were available (approximately every year or every other year) as well as needle biopsy results. The six historical PSA tests were used to characterize a patient's PSA signature. A total of 2,344 patients were available for study. This is not a random sample but rather a sample of all male patients from the hospital whose PSA records

met the above inclusion criterion. Of this total, there were 1167 Caucasian and 277 African Americans found to have prostate cancer and 809 Caucasian and 91 African Americans found not to have prostate cancer following needle biopsies. Since the historical PSA data from the 368 African Americans did not cover a time frame suitable for quantifying the baseline median and process capability standard deviation for ln(PSA), the current analysis is based only on the data from the 1,976 Caucasians. The needle-biopsy protocol since 2005 is to use a non-random sample of 12 cores from the prostate focusing on areas of the gland most likely to contain tumors in order to increase the odds of detecting cancerous cells in the prostate if present. Of the sample material obtained in the biopsy, 100% is inspected by a pathologist for non-normal cells. If less than 1% of the cell material is found to be abnormal in every sample, then the decision is that the biopsy did not detect cancer. If any sample has more than 1% of abnormal cells, then the decision is that the patient has prostate cancer. With this protocol, it is well recognized that biopsy will fail to detect many small prostate cancers, so approximately 1/3 of men that had a negative biopsy might have clinically undetected cancer, a point to which we will return in Section 3.

2.2 Potential Predictors for the Risk of Prostate Cancer

The raw data plots shown in Figures 1 and 2 illustrate baseline PSA records for two patients, one eventually diagnosed with cancer and the other without cancer, based on biopsies of eight to 12 needle biopsies when the PSA was measured on the last sample. These two plots (Figures 1 and 2) illustrate ln(PSA) profiles from two patients from which potential predictors can be estimated.





Six sufficient statistics were considered as potential predictors for characterizing a patient's PSA signature, as described below. The medians and moving

range standard deviations for samples of size six are as efficient as the mean and root-mean-square standard deviation of symmetric distributions, which are sufficient statistics [20, pp. 352-360], [21].

1. Median, baseline ln(PSA) based on the first six ln(PSA) values for a patient, which are obtained approximately yearly or every two years.

2. Baseline process capability standard deviation for ln(PSA) using the data from item (1):

$$S_{\text{pcl-ln(PSA)}} = \text{median}\{|\ln[\text{PSA}(t)] - \ln[\text{PSA}(t-1)]|/0.954\}, \text{ for } t = 2, \cdots, 6.$$

   The numerator is referred to as the moving range of the first six time ordered ln(PSA) values, and measures the inherent variation in the patient's ln(PSA). The divisor, 0.954, which converts the moving range (MR) into an estimate of the standard deviation, is used in quality control to estimate the process capability standard deviation.

3. Incidence of a special cause of variation in the ln(PSA) from the baseline median ln(PSA). A special cause variation occurs if at least; one ln(PSA) value is measured following the determination of the baseline parameters that exceed the following upper control limit.

$$\ln(\text{PSA}) > \text{median}\ln(\text{PSA}) + 3S_{\text{pcl-ln(PSA)}}.$$

4. Median, baseline ln(PSAV) based on the first five ln(PSAV) values for a patient using data described in item (1):

$$\ln[\text{PSAV}(t)] = \{\ln[\text{PSA}(t)] - \ln[\text{PSA}(t-1)]\}/\{\text{age}(t) - \text{age}(t-1)\}, \quad \text{for } t = 2, \cdots, 6.$$

   The ages are computed from the date of the PSA test and the date of birth. If for some reason the patient's records indicate that the PSA sample was drawn on the same day, then the age difference is assumed to be 0.003 days, which corresponds to a difference of about 45 minutes in clock time.

5. Baseline process capability standard deviation for ln(PSAV) using data described in item (1):

$$S_{\text{pcl}-\ln(\text{PSAV})} = \text{median}\{|\ln[\text{PSAV}(t)] - \ln[\text{PSAV}(t-1)]|/0.954\}, \quad \text{for } t = 2, \cdots, 6.$$

   This measures the inherent variation in the ln(PSAV).

6. Incidence of a special cause of variation in the ln(PSAV), which is an indicator variable. A special cause of variation occurs if at least one ln(PSAV) value, measured following the determination of the baseline parameters, exceeds the following upper control limit

$$\ln(\text{PSAV}) > 3\text{S}_{\text{pcl-ln(PSAV)}}.$$

Parameters 1, 2, and 3 refer to the ln(PSA) and the last three, 4, 5, and 6 refer to the ln(PSAV) signatures. In both cases the median and median MR are used to estimate the central tendency and dispersion and are sufficient statistics to characterize the patient specific ln(PSA) distributions, which are approximately normal. The third parameter, which is an indicator variable in the analysis, identifies the presence of special causes of variation relative to these distributions with the following convention: 1 signals a special cause occurred and zero signals no special cause occurred. In order to characterize the patient-specific ln(PSA) baseline distribution, a minimum of six PSA values, approximately one per year or one every other year, though not optimal based on process control experience, provides unbiased and statistically efficient estimates of the central tendency and dispersion of the baseline PSA profile [20, pp. 352-360], [21], [22, pp. 199-200].

2.3 Maximum Likelihood Estimation of Probability of Prostate Cancer

Once the above six metrics were computed for the 1,976 Caucasian males for whom de-identified data was available, these metrics were combined into the final data file with the patient's age when the last PSA was measured, and whether the patient was known to have or not have cancer based on needle biopsies from a sample of eight to 12 prostate cores. Logistic regression analysis was used to develop a model based on the PSA, patient-specific, signature parameters for the probability that a patient has prostate cancer. It should be noted that these cores used to detect the cancer are not a random sample, but are systematically extracted based on the urologist's awareness of sites where cancerous cells are more likely to exist in the prostate gland. The clinical criterion as to whether the patient does or does not have prostate cancer depends upon the nature of the cells in each core sample. If each of the samples contains no malignant cells, the patient is deemed to have no prostate cancer, recognizing the potential for false negative readings that have been reported to be as high as 38%. However; if at least one of the core samples contain enough cells to confirm malignancy (typically more than 1% of the biopsy core), the pathologist concludes that the patient has prostate cancer.

Let the random variable Y be defined as $Y = 1$, and $Y = 0$ if the patient does or does not have prostate cancer, respectively. Consider the following probability

statement relative to this random variable, Y: $P(Y = 1|x_i, i = 1, \cdots, n) = p$ and $P(Y = 0|x_i, i = 1, \cdots, n) = 1 - p$. The expected value and variance of Y is p and $p(1 - p)$, respectively. Suppose the model for Y is as follows, where $\underline{x}$ is the vector notation for the variables x_i, $i = 1, \cdots, n$:

$$Y = f(\underline{x}) + \varepsilon. \tag{1}$$

Here, $f(\underline{x})$ is an unknown function of some or all of the following variables: patient's current age, current PSA, and the six patient-specific signature parameters, while ε is a random variable with mean zero and some unknown standard deviation, σ. For this model, σ^2 is equal to $p(1 - p)$, which not a constant, which violates the linear regression assumption. The logistic transformation in (2) which is the natural logarithm of the odds-ratio is one way to stabilize the variance of Y, defined as the probability that the patient has prostate cancer [23].

$$T(Y) = \ln[Y/(1 - Y)] = \ln\{f(\underline{x})/[1 - f(\underline{x})]\}. \tag{2}$$

The maximum likelihood estimators of the parameters in the model $f(\underline{x})$ can be computed with the software program, JMP8. In this program the probability generated is the probability of "Not 0", or the probability of not having cancer, which is $1 - f(\underline{x})$.

Using stepwise linear regression methods, both forward selection with review and backward elimination, subject to the principle of parsimony, as suggested by Neter, Wasserman, and Kutner in Chapter 12: "Building the Regression Model" [23], a model for $T(Y)$ was developed as shown in Table 1. Both forward selection with review and backward elimination resulted in essentially the same model. The stopping rule used with both stepwise procedures to generate the model requires that all terms in the model must have a p-value less than or equal to 0.05, and all terms not in the model must have p-values greater than 0.05. Based on this rule, the model shown in Table 1 did not include any terms related to PSAV. This does not imply that ln(PSAV) is irrelevant, but it does indicate that a better way to characterize the variation in PSA for a patient is to measure the patient's inherent baseline variation using $S_{\text{pcl-ln(PSA)}}$.

Table 1: MLE-PSA model coefficients/significance

Variable	**Coefficient**	**Chi-Square**	***p*-value**
intercept	4.79455682	77.74	< 0.0001
ln(PSA)	-2.3315404	211.93	< 0.0001
Years of Age	-0.0763164	91.44	< 0.0001
baseline median ln(PSA)	3.30859725	329.11	< 0.0001
$S_{\text{pcl-ln(PSA)}}$	-9.5079525	207.68	< 0.0001
ln(PSA) special cause	-2.2862254	158.62	< 0.0001

3. Results

3.1 Predictability of MLE Probability of Prostate Cancer Model

Using the MLE model, if a patient's predicted probability of prostate cancer is greater than or equal to 50%, the patient is predicted to have cancer and otherwise not to have cancer, which is an unbiased criterion. Using this criterion, the MLE-PSA model for Caucasians developed for $T(Y)$ has a sensitivity of 87% and specificity of 85%, PPV of 89%, and NPV of 82% as shown in Table 2.

Table 2: Performance of MLE-PSA model with a 50% critical probability

MLE-PSA Predictor	Cancer*	No Cancer*	
Predicted Cancer	1016	121	PPV = 89%
Predicted No Cancer	151	688	NPV = 82%
	Sensitivity = 87%	Specificity = 85%	

*Based on needle biopsy of 8 to 10 core samples.

But using a PSA threshold of 4.0 for a single PSA test to signal the likelihood of cancer within the same population of patients, the sensitivity is 59%, the specificity is 33%, the PPV is 56% and the NPV is 33% as shown in Table 3 ([7]). This comparison indicates the improvement that can be achieved using the proposed metrics and MLE model for predicting the probability of prostate cancer among Caucasians with a critical probability of 50%.

Table 3: Performance of single PSA test with 4.0 ng/ml threshold

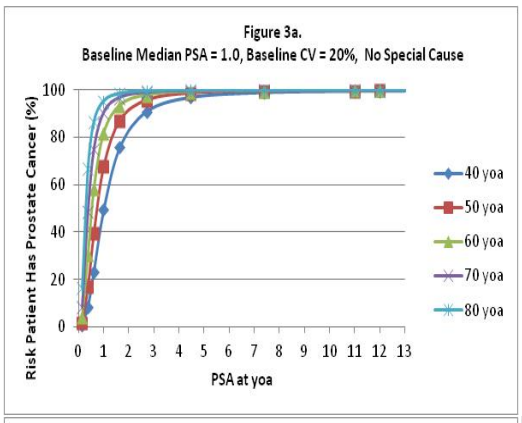
Single PSA with 4ng/ml Threshold	Cancer*	No Cancer*	
Predicted Cancer	689	542	PPV = 56%
Predicted No Cancer	478	267	NPV = 36%
	Sensitivity = 59%	Specificity = 33%	

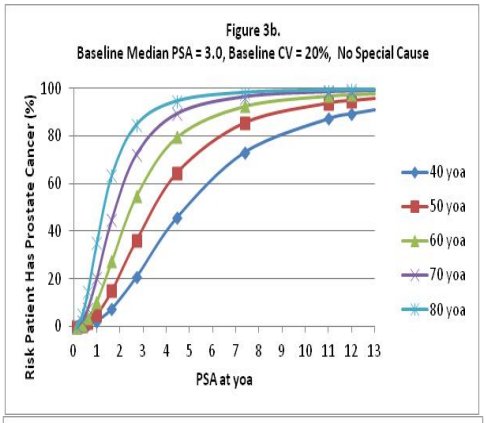
*Based on needle biopsy of 8 to 10 core samples.

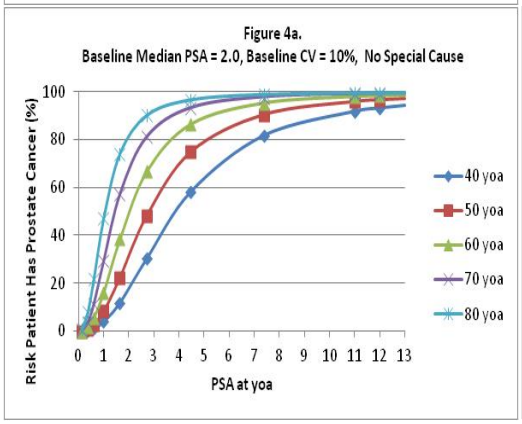
To better understand this model and to interpret the significance of the variables, Figures 3, 4, and 5 illustrate the effects of Median PSA, CV, and presence of special causes in the series of PVA results. The graphical representation of this logistic model is the function as shown below:

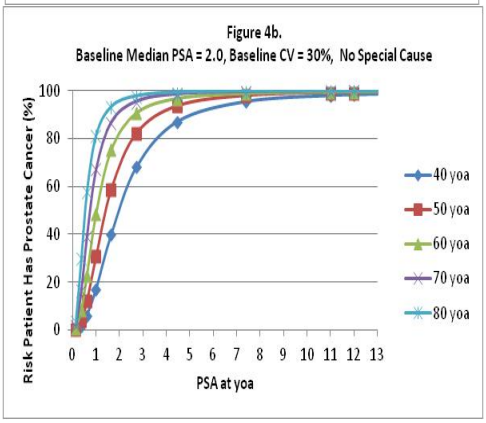
$$f(\underline{x})_{\text{predicted}} = 100 \exp[T(Y)]/\{1 + \exp[T(Y)]\}.$$

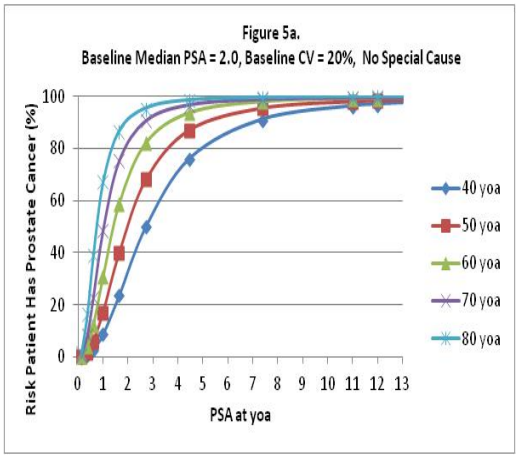
The predicted values for $f(\underline{x})$, denoted by $f(\underline{x})_{\text{predicted}}$ in the above equation, as illustrated in Figures 3a-b to 5a-b, indicate that as the ln(PSA) at a particular

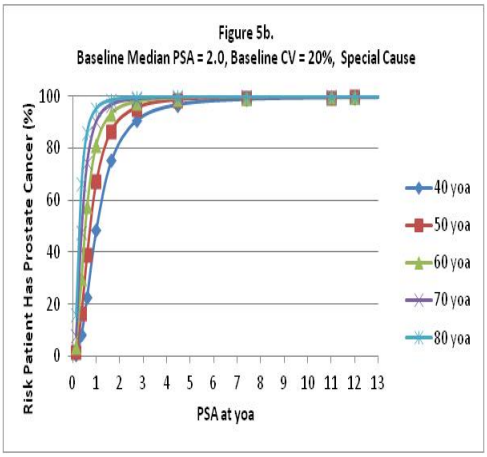












age increases, the risk of prostate cancer increases as expected. Also, the risk of prostate cancer increases with age. As the baseline median ln(PSA) increases, the risk of prostate cancer declines, which suggests that for the PSA test to be used for screening purposes, the data must be treated as patient-specific, rather than simply comparing a patient's PSA result to a threshold.

$S_{\text{pcl-ln(PSA)}}$ can be expressed as a coefficient of variation (CV) in percentage units as specified in the following equation:

$$\text{CV}(\%) = 100\{\exp(S_{\text{pcl-ln(PSA)}}) - 1\}.$$

Since there is a monotone relationship between $S_{\text{pcl-ln(PSA)}}$ and the CV(%), as the coefficient of variation increases, the risk of a patient having prostate cancer increases, which also emphasizes the importance of using patient-specific PSA test data, rather than a threshold to estimate the risk of prostate cancer. Finally; when a special cause is indicated in a patient's ln(PSA) profile, based on a 3-sigma quality control criterion, the risk of the patient having prostate cancer increases significantly.

The model developed for $f(\underline{x})$ along with patient-specific PSA data (current ln(PSA), patient's age, and median baseline ln(PSA), baseline $S_{\text{pcl-ln(PSA)}}$, and upper control limit for ln(PSA)) can be utilized by urologists to screen Caucasians for prostate cancer. The model may look complicated, but software is available that can be used with Excel® to compute the patient-specific baseline parameters and the probability or risk that a patient has prostate cancer, and therefore should have a biopsy of his prostate gland. A sample of the spreadsheet for these calculations is shown in Table 4.

Table 4: Sample spreadsheet for calculating the probability of cancer using MLE-PSA model

Patient M(edical)R(ecord)N(umber)					
Test #	**Age**	**PSA**	**ln(PSA)**	**MR-ln(PSA)**	
1	40	3.00	1.0986123		
2	42	3.20	1.1631508	0.064538521	
3	44	3.10	1.1314021	0.031748698	
4	46	3.00	1.0986123	0.032789823	
5	48	3.10	1.1314021	0.032789823	
6	50	3.00	1.0986123	0.032789823	
			Median Baseline ln(PSA)	**Baseline S-pcl**	**UCL-ln(PSA)**
Patient Name:			1.1150072	0.034370883	1.21811985
			***T*(*Y*)**	**Risk of Prostate Cancer**	**ln(PSA) Special Cause? 1 = yes 0 = no**
7	52	3.3	1.4047386	19.71	0
8					
9					

The MRN, Test#, Age, and PSA in this spreadsheet are to be filled in by the physician or by any nursing staff. A baseline of six PSA tests are needed to estimate the patient-specific baseline median ln(PSA), $S_{\text{pcl-ln(PSA)}}$, and upper control limit for ln(PSA). After the baseline has been established, subsequent age and PSA values can be entered into the rows opposite test 7, 8, etc. from which the program will compute the probability that the patient has prostate cancer. In Table 4, since the probability of cancer is less than 0.50 or 50%, it follows that no needle biopsy would be recommended because the probability is 80%, and that no cancerous cells would be detected by needle biopsy as will be shown in Section 3.2. Once this analysis is complete the physician and the patient can discuss options based on the risk calculation.

3.2 Conditional Probability of Cancer on Needle Biopsy

The probability of cancer on needle biopsy in what follows is conditioned on the probability being greater than 0.50 of prostate cancer from the MLE model. Let the event space, Ω, be the union of the disjoint events, prostate cancer based on needle biopsy, C_B, and its complement, C'_B. Applying Bayes' Theorem one can write the following conditional probability, where C_{PSA} is the event $\{\underline{x}\colon f(\underline{x})_{\text{predicted}} > 0.5\}$ and $f(\underline{x})_{\text{predicted}}$ is the estimated model for $f(\underline{x})$.

$$P\{C_B|C_{PSA}\} = P\{C_{PSA}|C_B\}P\{C_B|C\}/[P\{C_{PSA}|C_B\}P\{C_B|C\} + P\{C_{PSA}|C'_B\}P\{C'_B|C\}].$$

Based on the Aetna Clinical Policy Bulletin: Prostate Saturation Biopsy, #0698, the $P\{C_B|C\}$ is 0.62, thus $P\{C'_B|C\}$ is 0.38. From Table 2, $P\{C_{PSA}|C_B\}$ is 0.87 and $P\{C_{PSA}|C'_B\}$ is 0.15. Consequently $P\{C_B|C_{PSA}\}$ is 0.90 and $P\{C'_B|C_{PSA}\}$ is 0.10. Using similar logic it can be shown for the complement event to C_{PSA} that $P\{C'_B|C'_{PSA}\}$ is 0.80 and $P\{C_B|C'_{PSA}\}$ is 0.20. Consequently using the MLE-PSA model, the false positives are only 10% and the false negatives are only 20%. Comparing the MLE-PSA model to the use of a single PSA result with a 4.0 ng/ml threshold for predicting prostate cancer, this represents a 26% reduction in false positives and a 30% reduction in false negatives.

4. Discussion

Certain limitations of the methodology at hand are that the data is retrospective and are from a single-institution population assumed of having prostate cancer, and are undergoing biopsy. Without biopsy on all patients, there would be a verification bias that would underestimate the presence of cancer in patients that did not undergo biopsy. Furthermore, it is well recognized that biopsy will fail to detect several instances of prostate cancer, so up to 38% of men who had

a negative biopsy might have clinically undetected cancer. Notably, this further reinforces the robustness of the model because of its aptitude to discern patients with clinically detectable cancer; this may reduce the risk of the phenomenon described in the literature as "over-detection" or "over-diagnosis" [4]. This is consistent with the efforts to limit diagnosis of prostate cancer to those with clinically significant cancers that are likely to be detrimental to the patient.

Based on our research, we strongly recommend the annual practice-based PSA testing as a screening tool for prostate cancer for men with no previous diagnosis of prostate cancer over biopsy. Consistent with the guidelines of the American Urological Association, it is recommended that PSA testing begin for patients in their 40's, and that measurements be made at least every two years, in order to develop data that helps to characterize patient-specific PSA profile or signature by age 50. This to some extent coincides with the new guidelines from the American Cancer Society. Using our model, subsequent PSA test scores can be analyzed by the attending physician, to facilitate the clinician and the patient with a better risk assessment, with respect to prostate cancer.

Other potentially important factors should be considered to further enhance this research model by including other clinical parameters as well as emerging biomarkers. For men, especially those with moderate to severe BpH, a PSA test result may serve as a useful metric for prostate volume and be helpful in choosing treatment options, predicting future symptom severity or determining the likelihood of developing acute urinary retention or symptom progression requiring future surgery [25, 26, 27].

5. Strength and Limitations

Direct comparison of these results with other studies is complicated because of different methodologies and the diverse populations studied. However, the overall level of testing was broadly consistent with rates reported elsewhere in the US among Caucasian men without a prior diagnosis of prostate cancer. This being said, the overall strength of the MLE-PSA model is in the reduction in the false positives from 36% to 10% for Caucasians, which reduces the number of un-necessary needle biopsies, and the increase in correct negatives from 50% to 80%, when compared to the use of a single PSA test result using a 4.0 ng/ml threshold for signaling prostate cancer. Using the MLE-PSA model will in fact reduce the number of unnecessary needle biopsies and their associated costs and risks of infection due to the invasive nature of the procedure by 26%.

This study has a couple of limitations. First, though data were available for 368 African Americans, their PSA tests were not performed at an early enough age to obtain a suitable baseline of data from which to estimate the median ln(PSA) and $S_{\text{pcl-ln(PSA)}}$. Thus the results shown are only for Caucasians. Follow-

up research with African American males is strongly recommended based on the positive results obtained with Caucasians. The second constraint of this study is the retrospective nature of the data from a single-institution population suspected of having prostate cancer for which biopsies were performed. This was necessary because of the known underlying prevalence of clinically undetected prostate cancer in the population.

In conclusion, our study provides evidence that supports the necessity for the PSA testing in general practice for detection of localized prostate cancer in the US.

References

[1] Beck, M. The Man, the Gland, the Dilemmas. Wall Street Journal. http://online.wsj.com/article/SB123845699393571631.html (March 31, 2009).

[2] Brawer, M. K., Chetner, M. P., Beatie, J., Buchner, D. M., Vessella, R. L. and Lange, P. H. (1992). Screening for prostatic carcinoma with prostate specific antigen. *Journal of Urology* **147**, 841-845.

[3] Catalona, W. J., Smith, D. S., Ratliff, T. L., Dodds, K. M., Coplen, D. E., Yuan, J. J. J., Petros, J. A. and Andriole, G. L. (1991). Measurement of prostate-specific antigen in serum as a screening test for prostate cancer. *New England Journal of Medicine* **324**, 1156-1161.

[4] Cooner, W. H., Mosley, B. R., Rutherford, C. L. Jr., Beard, J. H., Pond, H. S., Terry, W. J., Igel, T. C. and Kidd, D. D. (1990). Prostate cancer detection in a clinical urological practice by ultrasonography, digital rectal examination, and prostate specific antigen (with discussion). *Journal of Urology* **143**, 1146-1154.

[5] Krumholtz, J. S., Carvalhal, G. F., Ramos, C. G., Smith, D. S., Thorson, P., Yan, Y., Humphrey, P. A., Roehl, K. A. and Catalona, W. J. (2002). Prostate-specific antigen cutoff of 2.6 ng/ml for prostate cancer screening is associated with favorable pathologic tumor features (with discussion). *Urology* **60**, 469-474.

[6] Labrie, F., Candas, B., Dupont, A., Cusan, L., Gomez, J. L., Suburu, R. E., Diamond, P., Lévesque, J. and Belanger, A. (1999). Screening decreases prostate cancer deaths: first analysis of the 1988 Quebec prospective randomized controlled trial. *Prostate* **38**, 83-91.

[7] Thompson, I. M., Pauler, D. K., Goodman, P. J., Tangen, C. M., Lucia, M. S., Parnes, H. L., Minasian, L. M., Ford, L. G., Lippman, S. M., Crawford, E. D., Crowley, J. J. and Coltman, C. A. Jr. (2004). Prevalence of

prostate cancer among men with a prostate-specific antigen level ≤ 4.0 ng per milliliter. *New England Journal of Medicine* **350**, 2239-2246.

[8] Wang, M. C., Valenzuela, L. A., Murphy, G. P. and Chu, T. M. (1979). Purification of a human prostate specific antigen. *Investigative Urology* **17**, 159-163.

[9] Townsend, A. Prostate cancer test needs improvement. Cleveland Plain Dealer. http://www.cleveland.com/medical/plaindealer/index.ssf?/base/news/1254213076184631.xml&coll=2 (September 29, 2009).

[10] Glass, L. and Kaplan, D. (1993). Time series analysis of complex dynamics in physiology and medicine. *Medical Progress Through Technology* **19**, 115-128.

[11] Carter, H. B., Pearson, J. D., Metter, E. J., Brant, L. J., Chan, D. W., Andres, R., Fozard, J. L. and Walsh, P. C. (1992). Longitudinal evaluation of prostate specific antigen levels in men with and without prostate disease. *Journal of the American Medical Association* **267**, 2215-2220.

[12] Jones, J. S. (2008). *The Role of Prostate-Specific Antigen Velocity in the Diagnosis and Management of Prostate Cancer.* Chapter 6, *Prostate Biopsy: Indications Techniques and Complications*, 61-70. Humana Press, Totowa, New Jersey.

[13] Schröder, F. H., Carter, H. B., Wolters, T., van den Bergh, R. C., Gosselaar, C., Bangma, C. H. and Roobol, M. J. (2008). Early detection of prostate cancer in 2007. Part 1: PSA and PSA kinetics. *European Urology* **53**, 468-477.

[14] Ross, A. E., Loeb, S., Landis, P., Partin, A. W., Epstein, J. I., Kettermann, A., Feng, Z., Carter, H. B. and Walsh, P. C. (2010). Prostate-specific antigen kinetics during follow-up are an unreliable trigger for intervention in a prostate cancer surveillance program. *Journal of Clinical Oncology* **28**, 2810-2816.

[15] Individual Risk Assessment of Prostate Cancer. http://www.uroweb.org/.

[16] Vickers, A. J., Savage, C., O'Brien, M. F. and Lilja, H. (2009). Systematic review of pretreatment prostate-specific antigen velocity and doubling time as predictors for prostate cancer. *Journal of Clinical Oncology* **27**, 398-403.

[17] Lilja, H., Savage, C., Gerdtsson, A., Bjork, T., Manjer, T., Nilsson, P., Dahlin, A., Bjartell, A., Scardino, P. T., Ulmert, D. and Vickers, A. J.

(2011). Toward a rational strategy for prostate cancer screening based on long-term risk of prostate cancer metastases and death: data from a large, unscreened, population-based cohort followed for up to 30 years. Memorial Sloan-Kettering Cancer Center, New York.

[18] New York Times. Questioning Prostate Cancer Tests. http://www.nytimes.com/2011/10/11/opinion/questioning-prostate-cancer-tests.html (October 10, 2011).

[19] USA Today. Panel advises against prostate cancer screening. Associated Press. http://usatoday30.usatoday.com/news/health/medical/health/medical/cancer/story/2011-10-07/Panel-advises-against-prostate-cancer-screening/50686266/1 (October 7, 2011).

[20] Lehman, E. L. (1983). *Theory of Point Estimation.* Wiley, New York.

[21] Wheeler, D. J. (1995). *Advanced Topics in Statistical Process Control*: *The Power of Shewhart's Charts.* SPC Press, Knoxville, Tennessee.

[22] Ott, E. R. (1975). *Process Quality Control*: *Troubleshooting and Interpretation of Data.* McGraw Hill, New York.

[23] Neter J., Kutner, M. H., Nachtsheim, C. J. and Wasserman, W. (1996). *Applied Regression Models*, 3rd edition. McGraw-Hill, Boston.

[24] Jones, J. S. (2008). Prostate cancer: are we over-diagnosing-or underthinking? *European Urology* **53**, 10-12.

[25] Williams, N., Hughes, L. J., Turner, E. L., Donovan, J. L., Hamdy, F. C., Neal, D. E., Martin, R. M. and Metcalfe, C. (2011). Prostate-specific antigen testing rates remain low in UK general practice: a cross-sectional study in six English cities. *BJU International* **108**, 1402-1408.

[26] Roehrborn, C. G., McConnell, J. D., Lieber, M., Kaplan, S., Geller, J., Malek, G. H., Castellanos, R., Coffield, S., Saltzman, B., Resnick, M., Cook, T. J. and Waldstreicher, J. (1999). Serum prostate-specific antigen concentration is a powerful predictor of acute urinary retention and need for surgery in men with clinical benign prostatic hyperplasia. PLESS Study Group. *Urology* **53**, 473-480

[27] Peakman, M. J., Kirby, R. S., Joyce, A., Abrams, P. and Pocock, R. (2004). Guideline for the primary care management of male lower urinary tract symptoms. *BJU International* **93**, 985-990.

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