# Serial Percent Free Prostate Specific Antigen in Combination with Prostate Specific Antigen for Population Based Early Detection of Prostate Cancer

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**Purpose:** We characterized the diagnostic properties of serial percent free prostate specific antigen in relation to prostate specific antigen in a multiethnic, multiracial cohort of healthy men.

**Materials and Methods:** A total of 6,982 percent free prostate specific antigen and prostate specific antigen measurements were obtained from participants in a greater than 12-year Texas screening study comprising 1,625 men who never underwent biopsy, 497 who underwent 1 or more biopsies negative for prostate cancer and 61 diagnosed with prostate cancer. We evaluated the ROC AUC of percent free prostate specific antigen and the proportion of patients with fluctuating values across multiple visits determined according to 2 thresholds (less than 15% vs 25%). The proportion of cancer cases in which percent free prostate specific antigen indicated a positive test before prostate specific antigen greater than 4 ng/ml did and the number of negative biopsies that would have been spared by negative percent free prostate specific antigen test results were calculated.

**Results:** Percent free prostate specific antigen fluctuated around its threshold of less than 25% (less than 15%) in 38.3% (78.1%), 42.2% (20.9%), and 11.4% (25.7%) of patients never biopsied, and with negative and positive biopsies, respectively. At the same thresholds, percent free prostate specific antigen tested positive earlier than prostate specific antigen in 71.4% and 34.2% of cancer cases, respectively. Among men with multiple negative biopsies and PSA greater than 4 ng/ml, percent free PSA would have tested negative in 31.6% and 65.8%, respectively.

**Conclusions:** Percent free prostate specific antigen should accompany prostate specific antigen testing to potentially spare unnecessary biopsies or detect cancer earlier. When near the threshold, both tests should be repeated due to commonly observed fluctuation.

**Key Words:** prostatic neoplasms, prostate-specific antigen, mass screening, diagnosis, biopsy

**Abbreviations and Acronyms**

CV = coefficient of variation

DRE = digital rectal examination

PSA = prostate specific antigen

SABOR = San Antonio Biomarkers of Risk of Prostate Cancer Study

Accepted for publication March 6, 2016.

No direct or indirect commercial incentive associated with publishing this article.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

Supported by Grants U01 CA086402, P30 CA054174 and R01 CA183570.

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PROSTATE cancer causes almost 30,000 deaths annually in the United States but PSA screening programs include too many unnecessary tests and biopsies, inflating costs and increasing patient burden. In 2012 USPSTF (United States Preventive Services Task Force) recommended

0022-5347/16/1962-0355/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2016.03.011
Vol. 196, 355-360, August 2016
Printed in U.S.A.

against annual serum PSA testing for most men, instead suggesting alternative public health approaches for reducing mortality from the disease.[1] This guidance prompted recommendations for alternative screening strategies, ranging from a single PSA measurement at an early age and selective repeat PSA testing following an abnormal test to identify spurious elevated PSA levels as well as incorporation of additional markers or subsequent reflex tests.[2–7]

Percent free PSA is a biomarker that has shown promise as an adjunct test to PSA for prostate cancer detection. Percent free PSA has proved to be as or more accurate than PSA for the early detection of prostate cancer with a threshold of less than 25% as suggestive of cancer that could be used concurrent with PSA testing or selectively for equivocal PSA values between 2 and 10 ng/ml.[6–10] Confirmation of the independent predictive value of percent free PSA to PSA as well as to established risk factors for prostate cancer, including DRE, race, age, family and prior biopsy history, has led to its inclusion in prostate cancer risk prediction tools, including PCPTRC (Prostate Cancer Prevention Trial Risk Calculator).[11]

An Achilles' heel of cancer biomarkers can be test variability with time. Studies investigating annual PSA measurements have observed a remarkable pattern of reversion of abnormal tests at 1 year to normal test values a year later. In 1 retrospective analysis of serum PSA levels taken annually during a 4-year period among men participating in the Polyp Prevention Trial, of 154 with an abnormal PSA test greater than 4 ng/ml 44% had a normal PSA finding 1 or more years later.[4] This led the investigators to conclude that an isolated elevated PSA level should be subsequently confirmed before proceeding with further diagnostic workup, sparing unnecessary biopsies. Significant annual PSA fluctuation was confirmed in a larger cohort of 2,578 participants in a San Antonio prostate cancer screening study with 23% of abnormal PSA tests returning to normal 1 year later. For comparison, 70% of abnormal DRE tests reverted to normal examinations 1 year later in the same study.[5]

Because the SABOR cohort provides more than 10 years of annual followup with serum screens and PSA prompted biopsies, it permits separate analysis of fluctuation depending on the long-term outcome of men on study. The majority concerns men in whom biopsy was never clinically indicated. Men such as these could be spared relief from the anxiety surrounding a single elevated level. Another group comprises men who had undergone 1 or more negative biopsies in the long term and who likely have benign disease. Such men could be spared the morbidity and anxiety of unnecessary procedures. Finally, among men ultimately diagnosed with cancer on biopsy constancy of elevated prediagnostic measures permits potential earlier confirmative diagnosis and moving forward to treatment.

Motivated by these aims for the different patient populations, percent free PSA testing was initiated in the San Antonio cohort so that its cross-sectional and serial operating characteristics could be prospectively evaluated.

## MATERIALS AND METHODS

SABOR was initiated in 2000 as a NCI (National Cancer Institute) sponsored clinical validation center recruiting San Antonio and South Texas area men without a prior diagnosis of prostate cancer. It now comprises more than 4,000 participants. The study was approved by the internal review board at University of Texas Health Science Center at San Antonio and all men provided written informed consent upon study entry, whereupon extensive demographic and medical data were documented. From 2000 to 2010 participants were seen annually for PSA and DRE, which was thereafter reduced to biannually in men with lower risk based on PSA levels. Prostate biopsy was recommended for men with PSA greater than 2.5 ng/ml or an abnormal DRE during the annual visits up through 2010. Beginning in 2007 percent free PSA was included in annual testing.

Participants with at least 1 paired percent free PSA and PSA value collected at the same clinical visit while the patient was on study (and before biopsy if one was performed) were included in this analysis. These participants were stratified into 1 of 3 groups, including 1) those who never underwent biopsy, 2) those who had 1 or more negative biopsies and 3) those diagnosed with prostate cancer on biopsy. Baseline characteristics of the 3 groups were compared using the chi-square and Kruskal-Wallis tests for categorical and continuous measures, respectively. The CV was calculated as the percent ratio of the SD to the mean.

A variety of thresholds for a biomarker can be used to indicate a positive abnormal test with the operating characteristics, in particular the tradeoff between sensitivity and specificity, strongly linked to the choice. We were concerned with evaluation of the thresholds currently used in practice and so chose less than 25% as an indicator of an abnormal percent free PSA and greater than 4 ng/ml as an abnormal PSA test as reported by Eastham et al.[4] However, since clinical experience with percent free PSA is much less than that with PSA and we observed high false-positive rates with the less than 25% threshold, we additionally considered a more conservative threshold of 15% for comparison.

We tested whether the degree of fluctuation was greater for percent free PSA than for PSA using the McNemar test for correlated categorical measures. In the group of men with 1 or more negative biopsies during the course of study, using the last observations of percent free PSA and PSA we calculated the number in which percent free PSA would have spared a biopsy by testing negative in the presence of a positive PSA test. We also calculated