Predictive Probability of Serum Prostate-Specific Antigen for Prostate Cancer

An Approach Using Bayes Rule

Robin T. Vollmer, MD

Key Words: Prostate cancer; Prostate-specific antigen; Age; Probability; Bayes theorem

DOI: 10.1309/R5H6VUQ32KGJW448

Downloaded from https://academic.oup.com/ajcp/article/125/3/336/1759688 by guest on 17 April 2024

Abstract

This article introduces the use of Bayes probability rule to calculate age and serum prostate-specific antigen (PSA)-specific positive predictive values (PPVs) for prostate cancer. The PPV is the conditional probability of having prostate cancer, given a value of PSA and a particular age group. The formulation uses values of sensitivity obtained from previously reported studies of more than 2,700 men with prostate cancer, and it uses values of specificity obtained from previously reported studies of more than 99,000 men without prostate cancer. The formulation also introduces the use of a population-based and age-specific probability of prostate cancer, and for this it relies on the National Cancer Institute–sponsored Surveillance, Epidemiology and End Results data. The Bayes PPV suggests that in younger men, cut points defining an elevated PSA level should be raised rather than lowered. The Bayes formulation also provides estimates of the PPV for narrow intervals of PSA, and these tabulated results may provide useful guidelines for the implications of serum PSA levels at specific age groups.

Prostate-specific antigen (PSA) was discovered during the late 1970s,[1] introduced as a serum test in 1980,[2] and as a serum test was demonstrated to be related positively to the presence of prostate cancer.[3-5] In 1986, the US Food and Drug Administration approved its use for monitoring men with prostate cancer. Subsequently, testing for serum PSA became common in screening for prostate cancer, and in 1992, the Food and Drug Administration approved its use for screening.

Now, serum PSA level combined with clinical symptoms, digital rectal examination (DRE), and, sometimes, ultrasound examination constitute the main ways to screen men for prostate cancer. For men with abnormal screening results, needle biopsy of the prostate is used to diagnose the tumor, and the serum PSA level is combined further with clinical staging and grade to decide overall stage and choice of treatment.[6] Thus, it is easy to understand how the serum PSA level could be described as the ideal serum tumor marker[7] and the major "cause" of the increasing incidence of prostate cancer in the 1990s.[8] However, some of the PSA-associated increase in diagnosis of prostate cancer is thought to be overdiagnosis of tumors that otherwise might go unnoticed during the men's lifetimes,[9-11] and the serum PSA level has been criticized as not specific.[12,13] In fact, it is likely that in men with localized cancer of the prostate, more of their serum PSA level is due to benign tissues than to tumor.[14,15] Finally, controversies continue regarding the ideal thresholds or cut points in serum PSA level for deciding when to biopsy the prostate.

In my opinion, the first step needed to address uncertainties regarding the use of the serum PSA level in screening is to form an accurate and logically correct model for the positive predictive value (PPV) of serum PSA, that is, the probability of a man having cancer, given a particular value, or

© American Society for Clinical Pathology

range of values, of serum PSA. In the past, the PPV was determined empirically from small to moderately sized data bases, some of which were from single institutions. In what follows, I consolidate the sensitivity and specificity data from large numbers of previous studies and use Bayes theorem to calculate the PPV. I also introduce the use of the underlying population-based probability of prostate cancer as a necessary part of estimating the PPV of the serum PSA level.

Materials and Methods

PPV and Bayes Rule

Although the sensitivity and specificity of the PSA level for prostate cancer are common topics of concern, the conditional probability of greatest interest to the patient and his physician is the PPV. The PPV is defined as the probability of disease, given that the laboratory test result is positive. For serum PSA, PPV is the conditional probability P(Ca | PSA > x), where x represents the cut point in serum PSA used to define a positive result. Bayes rule[16] tells us that PPV can be written as **Equation 1**:

$$P(Ca \mid PSA>x) = \frac{P(PSA > x \mid Ca) * P(Ca)}{P(PSA > x \mid Ca) * P(Ca) + P(PSA > x \mid B9) * P(B9)}$$

On the right side of Equation 1 are 4 probability terms: P(PSA > x | Ca) is the sensitivity of the serum PSA level; P(Ca), the prior or underlying probability of prostate cancer, that is, the probability without reference to serum PSA; P(PSA > x | B9), the false-positive probability (FP) of PSA (ie, FP or 1 – specificity); and P(B9), the prior or underlying probability of not having prostate cancer, which can be written as 1 – P(Ca).

Dividing the numerator and denominator of the right side of Equation 1 by P(PSA > x | Ca) * P(Ca) and substituting sensitivity, FP, and 1 – P(Ca) where appropriate allows Equation 1 to be simplified to **Equation 2**:

$$P(Ca \mid PSA>x) = \frac{1}{1 + \frac{FP * (1 - P(Ca))}{Sensitivity * P(Ca)}}$$

Thus, if one can estimate FP, sensitivity, and P(Ca), then one can use Equation 1 to estimate the PPV.

To estimate sensitivity, I used previously published results of serum PSA levels from patients with prostate cancer. First, I consolidated the raw sensitivity data published in 4 large studies, each of which gave sufficient details by values of serum PSA from 0 to 20 ng/mL and patient age in 3 groups: 50 to 59, 60 to 69, and 70 to 79 years.[17-20] Then I summed the numerators and denominators of the raw counts of patients at each value of serum PSA, so that the final plots of sensitivity vs serum PSA were derived from more than 2,700 men with prostate cancer. To obtain a continuous expression of sensitivity as a function of serum PSA, I used a nonlinear least squares algorithm[21] to model the consolidated sensitivity data using the sum of a gamma distribution function and an exponential distribution function **Appendix 1**.

I modeled the FP from previously published data for serum PSA levels from patients without prostate cancer. Specifically, I consolidated the raw false-positive data from 10 previously published studies, each of which gave sufficient details to form distribution functions by values of serum PSA from 0 to 20 ng/mL and patient age for the 3 age groups: 50 to 59, 60 to 69, and 70 to 79 years.[17-20,22-27] When the published specificity data were limited to fewer values of serum PSA, I first verified that the published data for FP followed an exponential distribution and then used an exponential fit to extrapolate for the unpublished values of serum PSA. As before, I summed the resulting numerators and denominators of the counts of patients at each value of serum PSA, so that the final plots of FP vs serum PSA level were derived from more than 99,000 men without prostate cancer. To obtain a continuous expression of FP as a function of serum PSA, I used a nonlinear least squares algorithm[21] to model the consolidated false-positive data with an exponential function (Appendix 1).

Using Surveillance, Epidemiology, and End Results Data to Estimate P(Ca)

Although previous publications of PPV for serum PSA values have used values of P(Ca) obtained directly from their data, it is preferable to obtain P(Ca) from a broader population. Otherwise, the resulting PPV might not be generally applicable. The National Cancer Institute–sponsored Surveillance, Epidemiology, and End Results (SEER) data provide estimates of P(Ca) for a broad population, and from its Web site (http://canques.seer.cancer.gov/) devcan2001 program, I obtained estimates of the cumulative incidence of prostate cancer for men of ages 55, 65, and 75 years, respectively, as 0.959%, 5.015%, and 11.947%. Dividing these values by 100 converts these percentages to probabilities, that is, to values between 0 and 1.

PPV for a Range of Serum PSA Levels

Equations 1 and 2 are formulas for the PPV for prostate cancer, given that serum PSA level exceeds a certain threshold value, x. Consequently, these formulas can be used to evaluate cut points in serum PSA levels to be used for further clinical actions such as biopsy of the prostate. Of equal interest, however, to a patient with a particular level of serum PSA is the PPV for a more narrow range of serum PSA levels. Suppose, for example, we consider the interval of values in serum PSA between x1 and x2. We symbolize this interval as I, which is written as:

$I = x1 < PSA \leq x2$

Downloaded from https://academic.oup.com/ajcp/article/125/3/336/1759688 by guest on 17 April 2024

© American Society for Clinical Pathology

DOI: 10.1309/R5H6VUQ32KGJW448

Bayes rule tells us that the PPV of prostate cancer given that PSA falls in the interval I can be written analogous to Equation 1 as **Equation 3**:

$$P(Ca \mid PSA \text{ in } I) = \frac{P(PSA \text{ in } I \mid Ca) * P(Ca)}{P(PSA \text{ in } I \mid Ca) * P(Ca) + P(PSA \text{ in } I \mid B9) * P(B9)}$$

The rules of probability and simple algebra indicate that the PPV for an interval of PSA values can be simplified to **Equation 4**:

$$P(Ca \mid PSA \text{ in } I) = \frac{1}{1 + \frac{\{FP(x1) - FP(x2)\} * (1 - P(Ca))}{\{Sensitivity(x1) - Sensitivity(x2)\} * P(Ca)}}$$

Results

Bayes Estimate of PPV at PSA Cut Points

Figure 1 shows the calculated PPV from Equation 2 for various cut points in serum PSA levels and for the 3 age groups (50-59, 60-69, and 70-79 years). In general, and as expected, the curves demonstrate that when cut points in serum PSA are low, the PPV is low, and when cut points are high, the PPV is high. Furthermore, the 3 age group curves generally are close to one another and demonstrate several points of crossing. Nevertheless, the respective locations of the 3 curves provide details that are not intuitively obvious. At low cut points in serum PSA levels, the PPV is lowest for men ages 50 to 59 years and highest for men ages 70 to 79 years, and this difference reflects the effect of P(Ca), which is lowest for the 50- to 59-year age group. On the other hand, at higher PSA cut points, the calculated PPV is highest for men ages 50 to 59 years, and this reflects the combination of low false-positive rate for higher values of serum PSA in the 50- to 59-year age group and high false-positive rate in older men owing to their enlarged prostates. In this manner, the Bayes approach logically reflects age effects on benign prostate tissues combined with the age effects on the incidence of prostate cancer.

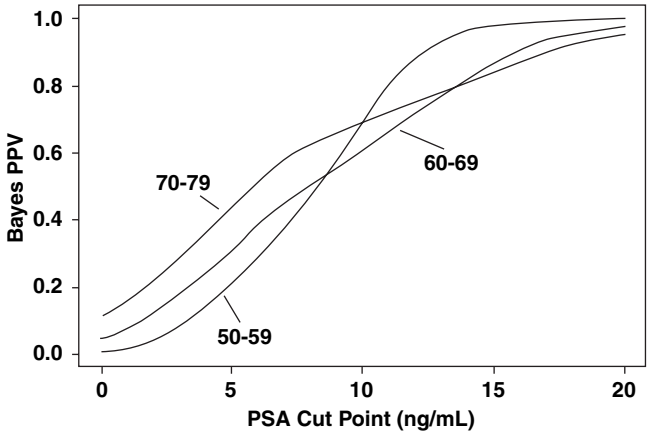


Figure 1 Plot of Bayes calculated positive predictive value (PPV) vs cut points in serum prostate-specific antigen (PSA) level (ng/mL). The 3 lines are for the 3 age groups (50-59, 60-69, and 70-79 years).

Further details of the calculated PPV are provided for several cut points in **Table 1**. For example, using a cut point for a serum PSA of 1 ng/mL in men ages 50 to 59 years implies that just 2% should have prostate cancer, whereas 98% should not. For men ages 70 to 79 years, the same cut point of 1 ng/mL implies that 16% should have prostate cancer, whereas 84% should not. Suppose further that one wanted a cut point in serum PSA that implies that at least 15% of men with a positive value would have prostate cancer and 85% or fewer would not. For men 50 to 59 years old, the cut point expected to meet this goal would be 5 ng/mL. On the other hand, for men age 70 to 79 years, a PSA cut point as low as 1 ng/mL would accomplish this goal. Thus, the Bayes algorithm using P(Ca) and the sensitivity and false-positive rates of serum PSA suggests higher, not lower, cut points for younger men.

Bayes Estimate of PPV for PSA Intervals

Table 2 shows calculated PPVs for various intervals in serum PSA using Equation 4. The results demonstrate that once again, the PPV rises with serum PSA levels for each age group. At the lowest values of PSA, the PPV is highest for men 70 years or older, reflecting once again the influence of higher P(Ca) in older men. On the other hand, at higher levels of serum PSA, the PPV becomes high regardless of age, reflecting the strong regression relationship between mass of tumor and serum PSA.[15] When the serum PSA level exceeds 4 ng/mL, the PPV for prostate cancer becomes relatively uniform among the 3 age groups.

To partially validate the Bayes approach, I compared the calculated Bayes PPV to the observed PPV reported by the Rotterdam section of the European Randomized Study of

Table 1
Bayes Positive Predictive Values for Several Cut Points in Serum PSA Values*

	Age (y)		
PSA Cut Point (ng/mL)	50-59	60-69	70-79
1	2	8	16
2	4	12	22
3	8	17	29
4	14	24	37
5	21	31	45
6	29	38	52
8	46	50	63

PSA, prostate-specific antigen.
* The entries are the probability of prostate cancer, given a serum PSA value that exceeds the listed cut point, and the values were calculated from Equation 2. The positive predictive values are given as percentages.

Downloaded from https://academic.oup.com/ajcp/article/125/3/336/1759688 by guest on 17 April 2024

DOI: 10.1309/R5H6VUQ32KGJW448
© American Society for Clinical Pathology

Table 2
Bayes Positive Predictive Values for Serum PSA Falling Within Intervals*

	Age (y)		
PSA Interval (ng/mL)	**50-59**	**60-69**	**70-79**
1-2	0.06	0.3	1
2-3	0.4	1	2
3-4	2	4	3
4-5	6	9	8
5-6	13	16	17
6-7	20	25	29
7-8	26	32	42
8-9	32	39	51
9-10	36	44	58
10-20	56	54	65

PSA, prostate-specific antigen.
* The entries are the probability (%) of prostate cancer, given a serum PSA value that occurs within the listed interval, and the probabilities were calculated from Equation 4.

Screening for Prostate Cancer (ERSPC).[28,29] When the ERSPC study began, men were evaluated by serum PSA level and DRE, and by 2001, a total of 9,776 men had been screened. Because the median age of the men in this part of the ERSPC study was 63.2 years, I chose the SEER value of P(Ca) for men aged 65 years and sensitivity and FP for men in the age bracket 60 to 69 years. By using the same PSA intervals reported by Schröder et al[28] and Schröder and Kranse,[29] I compared the calculated PPVs with the reported PPVs for these 9,776 men, and **Figure 2** shows the results. In Figure 2, the calculated PPVs appear on the y-axis, the observed PPVs appear on the x-axis, and the points show how the PPVs compared with one another. The line shows where perfect agreement would occur, and it demonstrates that agreement between the Bayes PPV and the observed PPV was close. For example, linear regression analysis demonstrated a significant association between the Bayes PPV and the observed PPV ($t = 36$; $P \sim .000$) with more than 99.6% of the residual deviance explained.

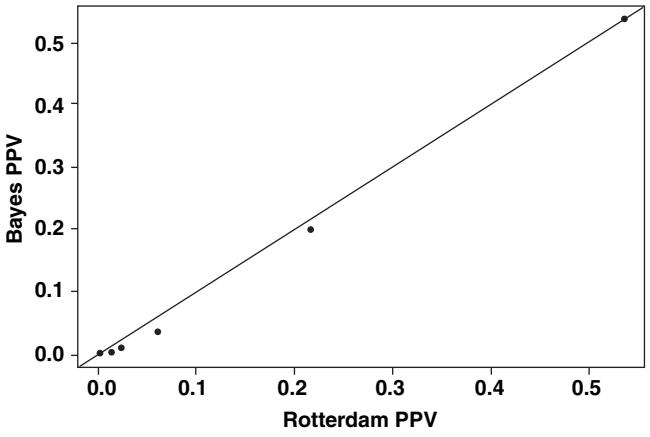


Figure 2 Plot of Bayes calculated positive predictive value (PPV) vs observed PPV (x-axis) obtained from the Rotterdam study (see text). The points are the results, and the line demonstrates where perfect agreement between the values of PPV would occur.

Discussion

The PPV is the conditional probability of prostate cancer, given that the serum PSA level falls within a critical range of values. Consequently, it must follow Bayes rule, because this is the nature of conditional probabilities. Nevertheless, the accuracy of the Bayes PPV depends on the accuracy of the 3 probabilities it uses: the false-positive rate of serum PSA, the sensitivity of serum PSA, and the underlying a priori probability of prostate cancer. For the false-positive rate to be accurate, it must be obtained from a broad population of men without prostate cancer. For the sensitivity to be accurate, it must be obtained from a broad population of men with prostate cancer. For P(Ca) to be accurate, it must be obtained in an unbiased manner from the population at large. Thus, estimates of each of these 3 values might involve some error. **Table 3** summarizes the nature of several potential errors and gives the correction required and the effect the correction would have on the calculated PPV.

Although the false-positive estimates used herein came from large studies of specificity of serum PSA levels in men thought not to have prostate cancer, few had prostate biopsies, and none had had their prostates removed. Thus, an unknown number of them could have had occult prostate cancer, which some have estimated to involve as many as 15% of men without an abnormal serum PSA or DRE result.[30,31] If autopsy results are used, the rate could be as high as 30%.[32] The effect of these undiagnosed cases on the false-positive rate is a matter for conjecture. For example, some men with very large prostates, high values of serum PSA, and low volumes of prostate cancer might have been included in specificity studies because biopsies missed their tumors. Such men constitute the first line of Table 3, and subtracting them from the specificity studies would lower the distribution of FP and raise the calculated PPV. Alternatively, some men with small prostates and small volumes of tumor may have had such low values of serum PSA and no abnormality found by DRE that they were included in specificity studies because they did not undergo biopsy. These constitute the second line in Table 3, and subtracting them from the specificity studies would raise the distribution of FP and lower the calculated PPV. This category of error has been termed *selection bias* or *verification bias*.[33,34]

In contrast with studies of specificity, studies of sensitivity undoubtedly comprise men with prostate cancer, that is, they are not contaminated by men who do not have tumor. The

Downloaded from https://academic.oup.com/ajcp/article/125/3/336/1759688 by guest on 17 April 2024

© American Society for Clinical Pathology

DOI: 10.1309/R5H6VUQ32KGJW448

Table 3
Errors in PPV

Study Type	Cause	Correction	PPV
Specificity	Undiagnosed cancer in men with high PSA level	Decrease FP	Increase
Specificity	Undiagnosed cancer in men with low PSA level	Increase FP	Decrease
Sensitivity	Undiagnosed cancer in men with low PSA level	Decrease sensitivity	Decrease
Sensitivity	Undiagnosed cancer in men with few core biopsy specimens	Unknown	Unknown
Population	Undiagnosed cancer	Increase P(Ca)	Increase

FP, false-positive probability; P(Ca), prior or underlying probability of prostate cancer; PPV, positive predictive value; PSA, prostate-specific antigen.

question to consider is how accurately their values of serum PSA represent all men with prostate cancer, especially because an elevated serum PSA level often was the reason for performing a biopsy. If studies of sensitivity of serum PSA excluded men with cancer and low serum PSA (third line of Table 3), then addition of these unrecognized cases to studies of sensitivity would lower the sensitivity and decrease the calculated PPV. If some cases were underdiagnosed because too few core biopsy specimens were obtained (fourth line of Table 3), then the corrective effect on the distribution of sensitivity could be increased, decreased, or remain the same depending on their values of serum PSA.

A method for correcting specificities and sensitivities of serum PSA levels for selection bias was introduced by Begg and Greenes[33] and applied to prostate cancer by Punglia et al,[34] but I did not use it here for several reasons. The method assumes that the decision to biopsy the prostate is conditionally independent from the presence of prostate cancer, an assumption that may not be justified. The method discards useful information by combining the distribution functions of serum PSA for control and patient populations. Although the method uses logistic regression to estimate PPV among the study patients who underwent biopsy, it does not use the a priori probability of prostate cancer in the population. Finally, the method assumes that the derived logistic model for PPV can be applied to men who did not undergo biopsy.

Regarding the last line of Table 3, epidemiologic studies of large populations such as the SEER study might have underdocumented the presence of prostate cancer, once again because of occult prostate cancer, so that a correction to increase P(Ca) would, in turn, increase PPV.

Thus, most of the errors that could affect the calculated PPV are due to undetected cases of cancer. The questions to ponder are just how important such missed cases are and how seriously the resulting errors affect the calculated PPV, especially if the involved tumors would not be diagnosed during the lifetime of the patient. Some suggest that even many conventionally diagnosed cases of cancer are overdiagnosed.[11] Thus, there is no easy answer to questions about which cases of prostate cancer need to be diagnosed and which do not. For the moment, the best way to view the collected studies of specificity and sensitivity used here is that they comprise, respectively, men without and with carcinoma of the prostate as diagnosed by conventional methods, that is, diagnosed via the combination of serum PSA, DRE, clinical symptoms, and routine biopsy procedures. In this way, the results of Equations 2 and 4 should be viewed as providing reasonable estimates of PPV for conventionally diagnosed prostate cancer.

Regardless of the aforementioned issues, I believe that the relative trends suggested in Tables 1 and 2 are not likely to be affected by errors in diagnosis. These trends do not favor the lowering of cut points in serum PSA for younger men as some have suggested.[34-37] Instead the results imply that lowering the PSA cut point will result in many biopsies of the prostate on men unlikely to have prostate cancer, and they validate the observations of Schröder et al[28] and Schröder and Kranse[29] that when the serum PSA level is between 1 and 1.9 ng/mL, 2,663 biopsies would be required to detect 96 patients with tumor.

In this study, I used Bayes rule and just 3 explanatory variables to calculate the PPV of prostate cancer. These 3 are the value of serum PSA, the patient's age group, and the underlying population-based probability of prostate cancer. However, the PPV undoubtedly depends on more than these 3 variables. For example, variables such as race, family history, prostate gland volume, results of DRE, percentage of free serum PSA, and previous biopsy findings also are important.[13,19,38-40] For a single additional factor such as race, all one need do is to repeat the process described in the methods separately for each race. In other words, one needs only to collect the data for sensitivity, FP, and P(Ca) in race- and age-specific groups and apply the methods described herein to achieve race- and age-specific versions of Equations 2 and 4.

For more variables, the straightforward use of Bayes rule can become unwieldy unless the additional variables are statistically independent of one another—an unlikely event for variables significantly related to PPV. Perhaps the best way to deal with the overall multivariable problem is to use logistic regression to model the probability of prostate cancer directly as a function of serum PSA level, patient age, race, and other key explanatory variables in some study population.[38,39] The

Downloaded from https://academic.oup.com/ajcp/article/125/3/336/1759688 by guest on 17 April 2024

DOI: 10.1309/R5H6VUQ32KGJW448
© American Society for Clinical Pathology

underlying, population-based P(Ca) then also can be included as a potential explanatory variable.

Appendix 1

I modeled sensitivity as **Equation A1**:

$$\text{Sensitivity} = \gamma * (1 - \text{Fg}) + (1 - \gamma) * \exp(-\theta * \text{PSA})$$

Here, γ is a coefficient with a value between 0 and 1, and Fg is a gamma distribution function written mathematically as **Equation A2**:

$$\text{Fg} = \int \frac{(\lambda)^n}{\Gamma(n)} (\text{PSA})^n \exp(-\lambda * \text{PSA})\, d\text{PSA}$$

$\Gamma(n)$ is the gamma function, and γ and n are the parameters for the gamma distribution function Fg. In Equation A1, θ is a parameter that is always positive.

I modeled FP as **Equation A3**:

$$\text{FP} = \exp(-\alpha * \text{PSA})$$

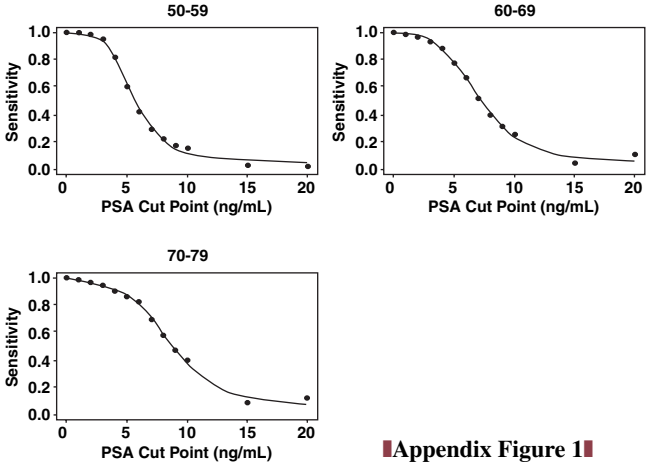
Here, α is always positive.

The least squares fitting algorithm resulted in the following estimates for the parameters of the preceding equations:

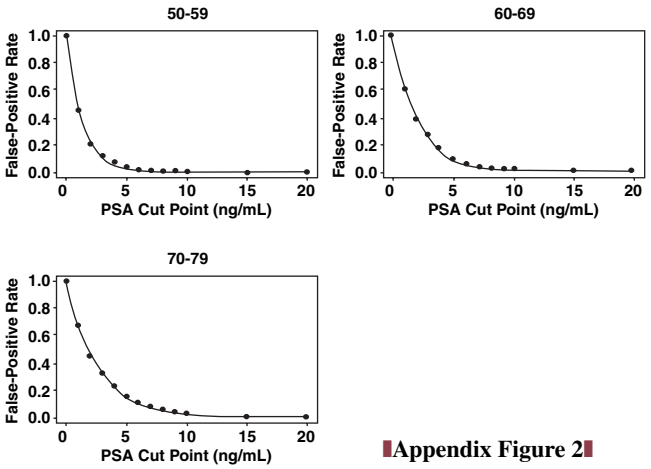
	Sensitivity*				False-Positive Probability†
Age Range (y)	γ	n	λ	θ	α
50-59	0.832	8.50	1.50	0.0618	0.762
60-69	0.793	7.01	0.966	0.0617	0.483
70-79	0.695	10.6	1.19	0.0656	0.382

* γ, n, λ, and θ are the parameters used in the Equation 1 model for a continuous function of sensitivity vs serum PSA cut point.
† α is the parameter used in the Equation 4 model for a continuous function of FP vs serum PSA cut point.

The following figures demonstrate how well the models fit, respectively, the consolidated sensitivity data and consolidated FP data for the 3 age groups (50-59, 60-69, and 70-79 years). In the figures, the points are the observed data, and the smooth lines are the fit provided by the models.



Appendix Figure 1



Appendix Figure 2

From the Departments of Laboratory Medicine, Veterans Affairs Medical Center and Duke University Medical Center, Durham, NC.

Address reprint requests to Dr Vollmer: Laboratory Medicine 113, VA Medical Center, 508 Fulton St, Durham, NC 27705.

References

1. Wang MC, Valenzuela LA, Murphy GP, et al. Purification of a human prostate specific antigen. *Invest Urol*. 1979;16:159-163.
2. Kuriyama M, Wang MC, Papsidero LD, et al. Quantitation of prostate-specific antigen in serum by a sensitive enzyme immunoassay. *Cancer Res*. 1980;40:4568-4662.
3. Killian CS, Yang N, Emrich LJ, et al. Prognostic importance of prostate-specific antigen for monitoring patients with stages B2 to D1 prostate cancer. *Cancer Res*. 1985;45:886-891.
4. Killian CS, Emrich LJ, Vargas RP, et al. Relative reliability of five serially measured markers for prognosis of progression in prostate cancer. *J Natl Cancer Inst*. 1986;76:179-185.
5. Stamey TA, Yang N, Hay AR, et al. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. *N Engl J Med*. 1987;317:909-916.
6. Partin AW, Kattan MW, Subong ENP, et al. Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer; a multi-institutional update. *JAMA*. 1997;277:1445-1451.
7. Andriole GL. Serum prostate specific antigen: the most useful tumor marker. *J Clin Oncol*. 1992;10:1205-1207.
8. Brawley OW, Knopf K, Merrill R. The epidemiology of prostate cancer, part I: descriptive epidemiology. *Semin Urol Oncol*. 1998;16:187-192.
9. Etzioni R, Penson DF, Legler JM, et al. Overdiagnosis due to prostate-specific antigen screening: lessons from the US prostate cancer incidence trends. *J Natl Cancer Inst*. 2002;94:981-990.
10. Yao S-L, Lu-Yao G. Understanding and appreciating the overdiagnosis in the PSA era. *J Natl Cancer Inst*. 2002;94:958-959.
11. Davidov O, Zelen M. Overdiagnosis in early detection programs. *Biostatistics*. 2004;5:603-613.

Downloaded from https://academic.oup.com/ajcp/article/125/3/336/1759688 by guest on 17 April 2024

© American Society for Clinical Pathology

DOI: 10.1309/R5H6VUQ32KGJW448

12. Barry MJ. Prostate-specific-antigen testing for an early diagnosis of prostate cancer. *N Engl J Med*. 2001;344:1373-1377.
13. Schmid H-P, Riesen W, Prikler L. Update on screening for prostate cancer with prostate-specific antigen. *Crit Rev Oncol Hematol*. 2004;50:71-78.
14. Stamey TA, Johnstone IM, McNeal JE, et al. Preoperative serum prostate specific antigen levels between 2 and 22 ng/mL correlate poorly with post–radical prostatectomy cancer morphology: prostate specific antigen cure rates appear constant between 2 and 9 ng/mL. *J Urol*. 2002;167:103-111.
15. Vollmer RT. Race and the linkage between serum prostate-specific antigen and prostate cancer: a study of American veterans. *Am J Clin Pathol*. 2004;122:338-344.
16. Woodworth GC. *Biostatistics; A Bayesian introduction*. Hoboken, NJ: John Wiley & Sons; 2004:66.
17. Catalona WJ, Hudson MA, Scardino PT, et al. Selection of optimal prostate specific antigen cutoffs for early detection of prostate cancer: receiver operating characteristic curves. *J Urol*. 1994;152:2037-2042.
18. El-Galley RES, Petros JA, Sanders WH, et al. Normal range prostate-specific antigen versus age-specific prostate-specific antigen in screening prostate adenocarcinoma. *Urology*. 1995;46:200-204.
19. Morgan TO, Jacobsen SJ, McCarthy WF, et al. Age-specific reference ranges for serum prostate-specific antigen in black men. *N Engl J Med*. 1996;335:304-310.
20. Anderson JR, Strickland D, Corbin D, et al. Age-specific reference range for serum prostate-specific antigen. *Urology*. 1995;46:54-57.
21. Venables WN, Ripley BD. Non-linear models. In: *Modern Applied Statistics With S-PLUS*. 3rd ed. New York, NY: Springer-Verlag; 1999:241-280.
22. Jacobsen S, Bergstralh EJ, Guess HA, et al. Predictive properties of serum prostate-specific antigen testing in a community-based setting. *Arch Intern Med*. 1996;156:2462-2468.
23. DeAntoni EP, Crawford ED, Oesterling JE, et al. Age- and race-specific reference ranges for prostate-specific antigen from a large community-based study. *Urology*. 1996;48:234-239.
24. Sawyer R, Berman JJ, Borkowski A, et al. Elevated prostate-specific antigen levels in black and white men. *Mod Pathol*. 1996;9:1029-1032.
25. Weinrich S, Jacobsen SJ, Weinrich SP, et al. Reference ranges for serum prostate-specific antigen in black and white men without cancer. *Urology*. 1998;52:967-973.
26. Fowler JE, Bigler SA, Kilambi NK, et al. Relationships between prostate-specific antigen and prostate volume in black and white men with benign prostate biopsies. *Urology*. 1999;53:1175-1178.
27. Cooney KA, Strawderman MS, Wojno KJ, et al. Age-specific distribution of serum prostate-specific antigen in a community-based study of African-American men. *Urology*. 2001;57:91-96.
28. Schröder FH, Roobol-Bouts M, Vis AN, et al. Prostate-specific antigen–based early detection of prostate cancer: validation of screening without rectal examination. *Urology*. 2001;57:83-90.
29. Schröder FH, Kranse R. Verification bias and the prostate specific antigen test: is there a case for lower threshold for biopsy? *N Engl J Med*. 2003;349:393-395.
30. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. *N Engl J Med*. 2003;349:215-224.
31. Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level ≤4.0 ng per milliliter. *N Engl J Med*. 2004;350:2239-2246.
32. Godley PA, Schell MJ. Adjusted odds ratios under nondifferential misclassification: application to prostate cancer. *J Clin Epidemiol*. 1999;52:129-136.
33. Begg CB, Greenes RA. Assessment of diagnostic tests when disease verification is subject to selection bias. *Biometrics*. 1983;39:207-215.
34. Punglia RS, D'Amico AV, Catalona WJ, et al. Effect of verification bias on screening for prostate cancer by measurement of prostate-specific antigen. *N Engl J Med*. 2003;349:335-342.
35. Smith DS, Carvalhal GF, Mager DE, et al. Use of lower prostate specific antigen cutoffs for prostate cancer screening in black and white men. *J Urol*. 1998;160:1734-1738.
36. Lodding P, Aus G, Bergdahl S, et al. Characteristics of screening detected prostate cancer in men 50 to 66 years old with 3 to 4 ng/mL prostate specific antigen. *J Urol*. 1998;159:899-903.
37. Catalona WJ, Ramos CG, Carvalhal GF, et al. Lowering the PSA cutoffs to enhance detection of curable prostate cancer. *Urology*. 2000;55:791-795.
38. Grönberg H, Wiklund F, Damber J-E. Age specific risks of familial prostate carcinoma: a basis for screening recommendations in high risk populations. *Cancer*. 1999;86:477-483.
39. Kranse R, Beemsterboer P, Rietbergen, et al. Predictors for biopsy outcome in the European randomized study of screening for prostate cancer (Rotterdam region). *Prostate*. 1999;39:316-322.
40. Smith DS, Bullock AD, Catalona WJ, et al. Racial differences in a prostate cancer screening study. *J Urol*. 1996;156:1366-1369.

Downloaded from https://academic.oup.com/ajcp/article/125/3/336/1759688 by guest on 17 April 2024

DOI: 10.1309/R5H6VUQ32KGJW448
© American Society for Clinical Pathology

HOLOGIC®

First and Only FDA Cleared
Digital Cytology System

Genius™ Cervical AI

Genius™ Review Station

Genius™ Digital Imager

Empower Your Genius With Ours

Make a Greater Impact on Cervical Cancer
with the Advanced Technology of the
Genius™ Digital Diagnostics System

Click or Scan
to discover more

ADS-04159-001 Rev 001 © 2024 Hologic, Inc. All rights reserved. Hologic, Genius, and associated logos are trademarks and/or registered trademarks of Hologic, Inc. and/or its subsidiaries in the United States and/or other countries. This information is intended for medical professionals in the U.S. and other markets and is not intended as a product solicitation or promotion where such activities are prohibited. Because Hologic materials are distributed through websites, podcasts and tradeshows, it is not always possible to control where such materials appear. For specific information on what products are available for sale in a particular country, please contact your Hologic representative or write to **diagnostic.solutions@hologic.com**.

genius™
DIGITAL DIAGNOSTICS