

An examination of the dynamic changes in prostate-specific antigen occurring in a population-based cohort of men over time

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OBJECTIVE

- To determine whether prostate-specific antigen velocity (PSA-V), PSA doubling time (PSA-DT), or PSA percentage change (PSA-PC) add incremental information to PSA alone for community-based men undergoing prostate cancer (PCa) screening.

PARTICIPANTS AND METHODS

- A population-based cohort of 11 872 men from Olmsted County, MN undergoing PSA screening for PCa from 1993 to 2005 was analysed for PSA, PSA-DT, PSA-PC and PSA-V and subsequent PCa.
- Receiver-operating characteristics curves and logistic regression were used to calculate the area under the curve (AUC) and Akaike's information criterion.
- Reclassification analysis was performed and the net reclassification improvement

What's known on the subject? and What does the study add?

A single serum PSA measurement is commonly used as a screening test to identify men with prostate cancer. A rise in PSA over time may identify men at increased risk of prostate cancer. Dynamic measures of PSA change (ex: PSA velocity, PSA doubling time) are frequently used to justify prostate biopsy in men.

We demonstrate that the current serum PSA is the best predictor of future prostate cancer risk among commonly available clinical variables. We show that dynamic measures of PSA change do not improve upon PSA's ability to predict future prostate cancer. Our study suggests that dynamic measures of PSA change may not be useful in screening for prostate cancer.

and integrated discrimination improvement were measured.

- The method of Begg and Greenes was used to adjust for verification bias.

RESULTS

- The single best predictor of future PCa was PSA (AUC = 0.773) with PSA-V (AUC = 0.729) and PSA-DT/PSA-PC (AUC = 0.689) performing worse.
- After age adjustment, combining PSA with PSA-V (AUC = 0.773) or PSA-DT/PSA-PC (AUC = 0.773) resulted in no better predictions than PSA alone.
- Reclassification analysis showed that adding PSA-V or PSA-DT/PSA-PC to PSA

did not result in a meaningful amount of reclassification.

CONCLUSIONS

- PSA is a better predictor of future PCa than PSA-V, PSA-DT, or PSA-PC.
- Adding PSA-V, PSA-DT, or PSA-PC to PSA does not result in clinically relevant improvements in the ability to predict future PCa.

KEYWORDS

prostate cancer, prostate-specific antigen, PSA doubling time, PSA velocity, PSA percentage change

INTRODUCTION

Prostate-specific antigen (PSA) screening has revolutionized the diagnosis and management of prostate cancer (PCa). Since the introduction of PSA screening, the overall incidence of clinically diagnosed PCa has increased, the incidence of locally advanced PCa has dropped, and PCa mortality rates have fallen [1–5]. These

findings suggest that PSA screening has improved the impact of PCa on the community at large.

Though PSA screening is an established practice in many western countries, much uncertainty exists as to what the optimal policy for PSA screening should be. For instance, the optimal age at which to start screening, the preferred screening interval,

and the PSA measure that should trigger prostate biopsy are not known with certainty. It is likely that currently recommended policies for PSA screening are suboptimal and could be improved.

Serum PSA level is a continuous variable and can be measured repeatedly in the same individual, so an opportunity exists to evaluate how its value changes over time

and to determine whether measures of this dynamic change improve its ability to identify patients with PCa. Various measures of PSA dynamics have been proposed including: PSA doubling time (PSA-DT) [6], PSA velocity (PSA-V) [7,8] and PSA percentage change (PSA-PC) [9]. Although there are several studies evaluating the usefulness of these dynamic measures in predicting outcomes after radical prostatectomy, only a small amount of literature has been published regarding their properties and the implications that these might have on their use as screening tests. In this manuscript, we use a large population-based dataset of men followed longitudinally over time to show some key characteristics of dynamic PSA measurements and what effect they might have on PCa screening decisions.

METHODS

After approval from the Mayo Clinic Institutional Review Board, we obtained the results of all PSA tests performed in Olmsted County, MN from 1993 to 2005. A total of 11 872 men underwent PSA testing during this period with a total of 50 589 PSA test results. The medical records linkage system of the *Rochester Epidemiology Project* was then used to identify all patients that underwent a prostate biopsy or that had a pathological diagnosis of PCa during this same period of time [10]. All healthcare providers in Olmsted County participate in the records linkage system, and more than 95% of Olmsted County residents receive their medical care in Olmsted County, implying that missed prostate biopsies and PCa diagnoses are unlikely. We merged the PSA data with the clinical data to obtain a comprehensive longitudinal dataset of PSA screening occurring in a fixed geographic population of men not subject to major referral biases.

To characterize the changes in PSA that occurred over time we restricted our analysis to patients that had two or more PSA values obtained at least 6 months apart. The PSA-DT was calculated by taking the inverse of the slope of a regression line fitted to the \log_2 values of the PSA points and was reported as the number of years required for the serum PSA level to double. The PSA-V was calculated by using the slope of a regression line fitted to the PSA values

and represents the increase in PSA in ng/mL that occurs per year. The PSA-PC was defined as the percentage change after a year, which can be calculated by a one-to-one mapping from PSA-DT : PSA-PC = $2^{1/PSA-DT} - 1$, measured in %/year. Note that because of a one-to-one mathematical correspondence between PSA-DT and PSA-PC, these two dynamic measures have the same predictive values for PCa. However, PSA-DT is not continuous when the patient's PSA level is steady (e.g. steady PSA level can have very large negative, very large positive, or infinite PSA-DT). On the other hand, steady PSA corresponds to the neighbourhood of 0 in terms of PSA-PC. Therefore our analysis is performed based on PSA-PC in this paper. The results for PSA-PC are identical to those for PSA-DT.

We removed from our dataset all PSA values occurring after a diagnosis of PCa, because of our focus on PCa screening. When evaluating the predictive performance of PSA, the latest PSA value is used for each individual patient. The two measures of dynamic change that were assessed, PSA-V and PSA-PC, were calculated using regression over all the PSA test results for each patient. The total number of patients remaining in our dataset was 8563.

To evaluate the ability of age, current static PSA, and the dynamic measures of PSA (PSA-V and PSA-PC) to predict the presence of PCa we constructed receiver-operating characteristics (ROC) curves and calculated the area under the curve (AUC) as a measure of diagnostic discrimination. We also fitted logistic regression models for different variable combinations for our dataset to (i) investigate the best discriminator of the presence of PCa, (ii) investigate how PSA can be combined with dynamic measures of PSA to improve predictive performance, and (iii) measure the extent of predictive improvement. We performed reclassification analysis to determine whether adding dynamic measures of PSA change improved on the performance of PSA alone. To this end the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated [11]. As it is possible that some men with PCa were never subjected to biopsy and therefore never diagnosed, some verification bias exists in our dataset [12]. We used the method of Begg and Greenes to adjust for verification bias [13,14]. This method

TABLE 1 Clinical and demographic characteristics of the screened cohort

Variable	Value
Sample size, n (%)	
Overall	11 872 (100.0)
With one PSA test	3309 (27.9)
With more than one PSA test	8563 (72.1)
Age (years), mean (SD)	63.0 (12.7)
Race	
Caucasian	96
Other	4
PSA group, n (%)	
0–1 ng/mL	5428 (45.7)
1–2.5 ng/mL	3657 (30.8)
2.5–4 ng/mL	1230 (10.4)
4–7 ng/mL	868 (7.3)
7–10 ng/mL	302 (2.5)
>10 ng/mL	387 (3.3)
Prostate biopsy, n (%)	
Have at least one biopsy	908
Have exactly one biopsy	739
Outcomes, n	
Prostate cancer diagnosis	628

PSA, prostate-specific antigen.

assumes that patients who have positive biopsies are true 'cancer patients' and those who have negative biopsies are true 'no cancer patients'. We first separate the patients into different groups according to their PSA values (in ng/mL: 0–1, 1–2.5, 2.5–4, 4–7, 7–10 and ≥ 10) and ages (in years: 40–50, 50–60, 60–70, 70–80 and ≥ 80). Within each group, we assume patients without a confirmative test (biopsy) have the same probability of PCa as patients who have had a confirmative test. The probability of having PCa based on patients with confirmative tests is used to infer the cancer state of patients without confirmative tests. Statistical models were fitted using R statistical software version 2.13.0 with the PREDICTABEL package installed [15].

RESULTS

Detailed demographic information is presented in Table 1. The age-related density of PSA screening and frequency of PSA screening episodes are shown in Figs 1 and 2. This shows that PSA screening intensity

FIG. 1. Histogram of prostate-specific antigen (PSA) screening intensity as a function of patient age.

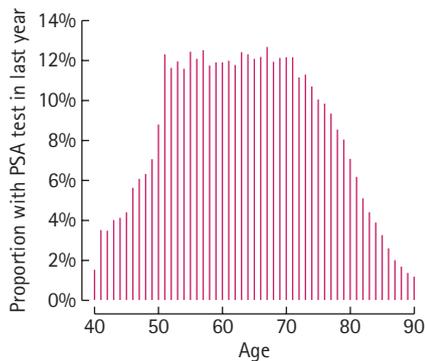


FIG. 2. Histograms of (a) the number of prostate-specific antigen (PSA) measurements per patient and (b) the time interval between consecutive PSA measurements.

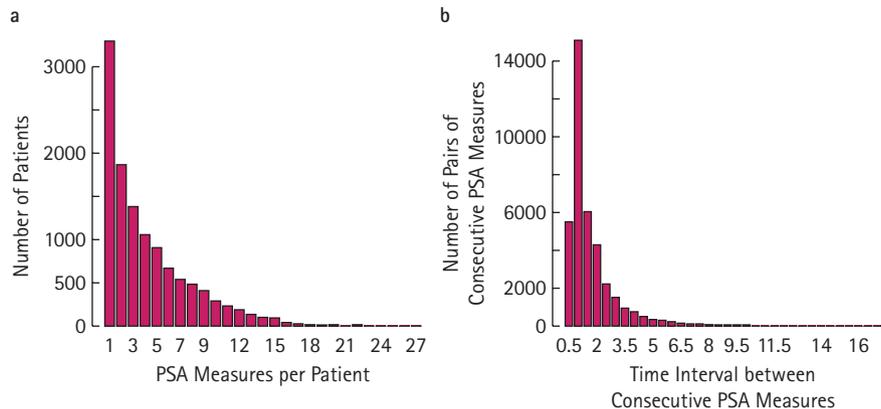
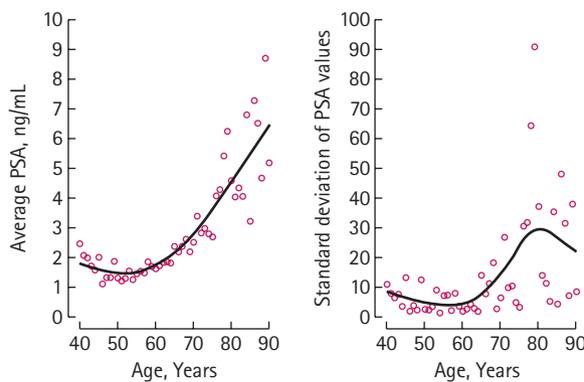


FIG. 3. (A) Mean prostate-specific antigen (PSA) values by age group. (B) Standard deviation of PSA values by age group. Lines represent smoothed means.



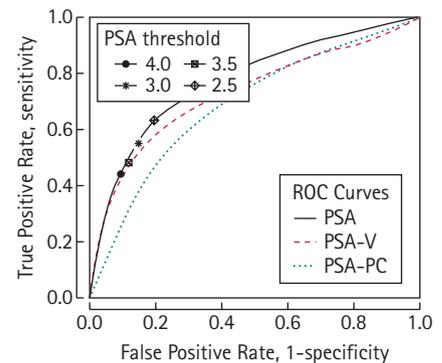
was not uniform across all age groups and that men between the ages of 50 and 70 years had the highest intensity of PSA screening, consistent with the screening guidelines of the AUA. Figure 3 shows the mean PSA value as a function of age as well as the variability in PSA values that was observed. The average PSA value increases as a function of patient age, presumably as the result of benign enlargement of the prostate gland. This plot also shows that the variability in PSA values also increases with age, implying that spurious changes in PSA (and consequently the dynamic measures of PSA change – PSA-V and PSA-PC) are more common as age increases.

An assessment of PSA-V and PSA-PC with respect to the presence or absence of cancer is shown in Table 2. This table shows (i) that the dynamic values of PSA change are different for varying age strata (though tests for trend were insignificant), (ii) that the modifying effect of age on dynamic measures of PSA may be higher for PSA-V,

(iii) that the variability of dynamic PSA measures increases with age, (iv) that the presence of PCa is a much more important driver of changes in dynamic measures of PSA than age, and (v) that PSA-PC appears to distinguish patients with cancer from those without better than PSA-V within age strata.

The ROC curves adjusted for age illustrate the value of static PSA, PSA-V and PSA-PC for the detection of PCa (Fig. 4). The AUC was 0.773 for static PSA, 0.729 for PSA-V and 0.689 for PSA-PC. From Fig. 4 we can see that PSA is better than PSA-V and PSA-PC in discriminating the presence of PCa. The probability of having PCa was estimated using logistic regression. Sensitivity, specificity, and positive and negative predictive values for different commonly used PSA and PSA-V thresholds are illustrated in Table 3. Several models were considered, including age, static PSA and dynamic PSA measures. Table 4 shows the age-adjusted empirical probability of

FIG. 4. Age-adjusted receiver-operating characteristic (ROC) curves of static prostate-specific antigen (PSA; solid line), PSA velocity (PSA-V; dashed line), and PSA percentage change (PSA-PC; dotted line). PSA thresholds of 2.5, 3.0, 3.5 and 4.0 are shown.



PCa according to static and dynamic PSA measures. The data show that the probability of having PCa depends on both the static and dynamic PSA values. In general, the higher the baseline PSA and the faster the rate of PSA change, the higher the probability of PCa.

To estimate the probability of PCa more accurately, we modelled age, static PSA and dynamic PSA measures as continuous variables in logistic regression models. Static PSA values are log-transformed to \log_2 PSA in the logistic regression analysis because the distribution of PSA levels was skewed toward higher levels. Note that \log_2 PSA is a one-to-one monotonic mapping from PSA, which fits the logistic function much better than static PSA, and that PSA-DT and

TABLE 2 Average (SD) values of dynamic measures of prostate-specific antigen (PSA) change and their association with age

	40-49		50-54		55-59		60-64		65-69		70-74		75-79		80+	
Average (SD) values																
PSA-V (ng/mL/year)																
NC	-0.30 (8.24)	0.02 (2.07)	-0.04 (1.02)	-0.02 (1.12)	0.00 (1.49)	0.03 (0.95)	-0.27 (6.06)	0.10 (2.16)								
C	0.52 (1.39)	0.14 (1.09)	0.25 (1.31)	1.65 (16.09)	1.29 (14.03)	2.67 (31.58)	0.20 (9.15)	-0.73 (47.22)								
P value*	0.02	0.16	<0.01	0.10	0.10	0.14	0.26	0.60								
PSA-PC (%/year)																
NC	6.4 (133.8)	4.5 (49.9)	1.7 (28.9)	6.2 (120.7)	4.6 (81.8)	3.2 (36.7)	1.8 (19.3)	1.6 (16.2)								
C	33.3 (64.3)	11.3 (46.0)	11.4 (24.5)	118 (1073)	14.7 (52.2)	16.0 (80.6)	10.0 (18.9)	11.9 (30.6)								
P value*	0.01	0.07	<0.01	0.10	0.01	0.01	<0.01	<0.01								
Sample size in each group																
NC	214	663	939	924	1187	998	1041	1359								
C	38	114	160	156	200	168	174	228								

*Wald two-sample t test. NC, 'no cancer patients'; C, 'cancer patients'; PSA, prostate-specific antigen; PSA-V, PSA velocity; PSA-PC, PSA percentage change.

TABLE 3 Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for some commonly used static prostate-specific antigen (PSA) and PSA velocity (PSA-V) thresholds

	Sensitivity	Specificity	PPV	NPV
PSA				
2.5	0.63	0.81	0.36	0.93
3.0	0.55	0.86	0.39	0.92
3.5	0.48	0.88	0.41	0.91
4.0	0.44	0.91	0.45	0.91
PSA-V				
0.4	0.30	0.95	0.50	0.89
0.75	0.16	0.98	0.56	0.87
2	0.04	0.99	0.54	0.86

PSA-PC can be calculated directly from the log₂PSA slope. ROC curves were used to evaluate the efficiency of these logistic regression models to predict the presence of PCa and these are graphically illustrated in Fig. 5. The AUC was used to compare the discrimination of the models while the Akaike information criterion (AIC) was used to assess whether the added complexity of the multi-parameter models was worthwhile when compared with the simplest model containing just static PSA (Table 5). The preferred model is the one with the minimum AIC value and maximum AUC value. We found that static PSA is the best single indicator of the presence of PCa. Whereas PSA-V was also a good predictor, it was not better than PSA, and it was highly correlated with it. Dynamic measures become insignificant whenever static PSA is used. The logistic regression models confirmed that dynamic PSA values do not improve the predictive ability of static PSA to identify PCa patients. Reclassification analysis showed that adding PSA-V to PSA did not result in a meaningful amount of reclassification (NRI = 0.0009, 95% CI - 0.0025 to 0.0007; IDI = 0, 95% CI - 0.0003 to 0.0002). Similarly, adding PSA-PC to PSA did not result in meaningful reclassification (NRI = 0.0052, 95% CI - 0.0003 to 0.0101; IDI = 0.0005, 95% CI - 0.0003 to 0.0012). We then restricted the reclassification analysis to patients with PSA values in the 2.5-4.0 ng/mL range because these patients are subject to considerable diagnostic uncertainty. Adding PSA-V to PSA in this subgroup did not result in meaningful reclassification (NRI = 0, 95%

TABLE 4 Age-adjusted probability of prostate cancer (total number of people in each group) as a function of prostate-specific antigen (PSA) and dynamic measures of PSA change

PSA	PSA-V (ng/mL/year)							
	<0.0	0.0–0.1	0.1–0.2	0.2–0.3	0.3–0.5	0.5–1	1–2	>2
0–1	0.04 (2041)	0.05 (1449)	0.05 (92)	0.00 (20)	0.00 (11)	0.00 (5)	0.00 (3)	0.00 (1)
1–2.5	0.09 (720)	0.11 (1461)	0.11 (367)	0.06 (100)	0.09 (66)	0.05 (22)	0.10 (10)	0.33 (3)
2.5–4	0.19 (167)	0.12 (224)	0.26 (304)	0.30 (130)	0.39 (88)	0.41 (49)	0.60 (10)	0.25 (4)
4–7	0.18 (65)	0.29 (63)	0.28 (135)	0.39 (143)	0.48 (164)	0.56 (100)	0.50 (32)	0.60 (10)
7–10	0.14 (14)	0.43 (7)	0.43 (14)	0.33 (21)	0.52 (63)	0.55 (76)	0.82 (33)	0.67 (12)
>10	0.31 (16)	0.00 (1)	0.67 (3)	0.30 (10)	0.35 (17)	0.60 (65)	0.56 (73)	0.54 (79)

PSA	PSA-PC (%/year)							
	<0	0–5	5–10	10–20	20–50	50–100	100–200	>200
0–1	0.05 (2075)	0.06 (935)	0.04 (300)	0.03 (184)	0.07 (89)	0.04 (25)	0.00 (9)	0.00 (5)
1–2.5	0.09 (715)	0.11 (983)	0.13 (573)	0.10 (313)	0.07 (125)	0.04 (24)	0.00 (11)	0.40 (5)
2.5–4	0.18 (166)	0.14 (266)	0.26 (265)	0.32 (188)	0.41 (71)	0.50 (12)	0.50 (4)	0.50 (4)
4–7	0.20 (65)	0.26 (154)	0.39 (197)	0.49 (206)	0.56 (71)	0.56 (9)	0.57 (7)	0.67 (3)
7–10	0.07 (14)	0.44 (34)	0.45 (65)	0.62 (78)	0.76 (37)	0.56 (9)	0.50 (2)	1.00 (1)
>10	0.29 (17)	0.40 (20)	0.47 (47)	0.56 (75)	0.64 (72)	0.44 (16)	0.56 (9)	0.50 (8)

TABLE 5 Performance characteristics of various logistic regression models in predicting the presence of prostate cancer

Model	AIC	AUC
log ₂ PSA	6035	0.773
PSA-V	7072	0.729
PSA-PC	7056	0.689
log ₂ PSA + PSA-V*	6037	0.773
log ₂ PSA + PSA-PC*	6035	0.773
log ₂ PSA + PSA-V* + PSA-PC*	6036	0.773

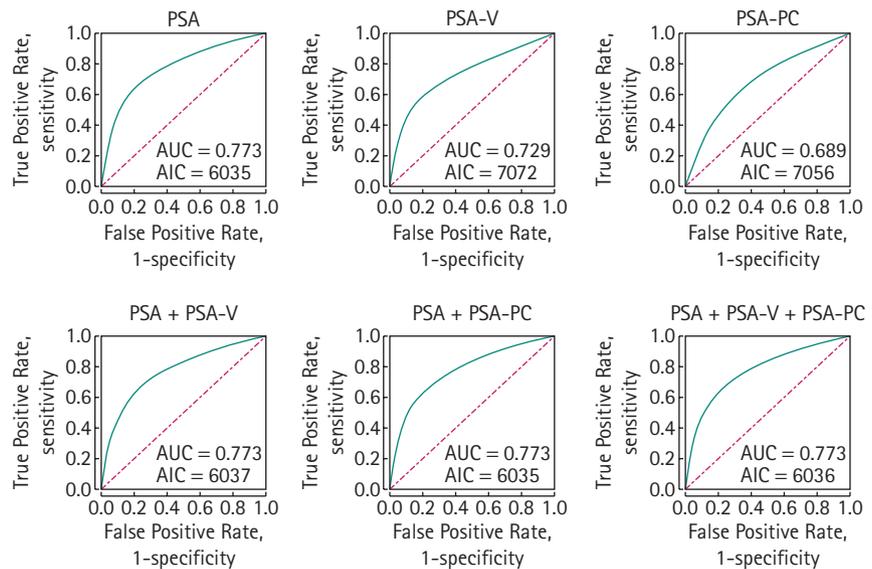
*Insignificant terms in the model. AIC, Aikake's information criterion; AUC, area under the receiver-operating characteristics curve; PSA, prostate-specific antigen; PSA-V, PSA velocity; PSA-PC, PSA percentage change.

CI 0–0; IDI = 0, 95% CI – 0.0001 to 0). However, adding PSA-PC to PSA did result in a minor but significant amount of reclassification in this patient subgroup (NRI = 0.0217, 95% CI 0.0059–0.0374; IDI = 0.0005, 95% CI 0.0001–0.0009) indicating that PSA-PC did add diagnostic information in this subgroup whereas PSA-V did not.

DISCUSSION

Previous studies assessing the value of dynamic PSA changes have often been

FIG. 5. Receiver-operating characteristic curves of the logistic regression models for predicting the presence of prostate cancer, corrected for verification bias.



limited to the assessment of their role in predicting post-treatment outcomes [16]. Although such studies are critically important, and have clarified how PSA can be used before and after PCa treatment to predict treatment outcomes, they do not assess the far more common situation of the patient that has never had a diagnosis of PCa but is being screened for it. In this screening population, it is unclear whether dynamic measures of PSA change improve

upon the static PSA level or whether one particular dynamic measure of PSA change is best. This lack of clarity is perhaps best reflected in PCa screening guidelines. The National Comprehensive Cancer Network, for example, recommends biopsy in men with a PSA-V >0.35 ng/mL/year whereas the AUA guidelines state that the PSA-V should be taken into account when making biopsy decisions [17,18]. In contrast, the European Association of Urology and the American

Cancer Society do not recommend using PSA-V for prostate biopsy decision making [19,20]. Given the divergence among guidelines and studies considering the role of dynamic PSA measures and PCa screening [16], there appears to be a clear need for further information on this topic.

In the current paper we describe the role of dynamic measures of PSA change in aiding the diagnosis of PCa in a longitudinally screened population of community-dwelling men. We show that there are several ways to measure PSA change over time and that each method has somewhat different properties. We also show that of the three dynamic PSA measurements that we assessed, PSA-V was the best predictor of a future diagnosis of PCa, though the static PSA value remained the single best predictor of PCa overall. Although PSA-DT and PSA-PC are one-to-one corresponded and should provide the same predictive values, PSA-PC is favourable in ROC and logistic regression analysis because of its mathematical continuity when PSA is steady. Last, we found that knowing the rate of change of PSA did not add incremental predictive information beyond the static PSA in the PCa screening setting.

In a similar population-based screening study from Ireland, Connolly *et al.* [21] found that PSA-V had a high sensitivity and specificity for PCa detection (approximately 80% each at a threshold of 0.3 ng/mL/year) and that as the PSA-V increased so did the rate of high-grade tumours. Unfortunately, these authors did not compare the performance of PSA-V with that of static PSA nor did they examine other dynamic measures of PSA. Ulmert *et al.* [8] assessed the PSA in 4907 Swedish men that had stored blood for other purposes on two separate occasions roughly 6 years apart. These authors found, as we did, that static PSA was a better predictor of future PCa risk than PSA-V and like our study they did not find that PSA-V added major incremental information above PSA alone. Several differences exist between our studies, however. First, Ulmert *et al.* had only two PSA values to work with and, because of variability in PSA assessment [22], several authors have suggested that at least three PSA values are required for accurate assessment of PSA-V [7,23]. Second, because the median age at the second screening round was only 53 years and the

performance of PSA-V is probably age-dependent, and correlated with static PSA (which is low in 40-year-old men) [24–26], it is possible that the value of PSA-V was underestimated in their study. Loeb *et al.* [27] report data from the Baltimore Longitudinal Study of Aging that suggest that PSA-V may add information to static PSA, although their analysis does directly quantify the gain in model performance obtained by adding PSA-V. Additionally, recent results from randomized trials including the Prostate, Lung, Colon and Ovarian (PLCO) screening trial [28], the European Randomized Study of Screening for Prostate Cancer (ERSPC) [29–31], and the Prostate Cancer Prevention Trial (PCPT) [32] suggest that PSA-V does not add incremental information to PSA in the screening setting. Unfortunately, each of these clinical trials has significant pitfalls, such as limitations on the age of the screening cohort, restrictions on the minimum or maximum PSA value for inclusion, and a number of exclusion criteria for participation in the trial. Overall, it is not certain that these clinical trial results can be generalized to the broader population at risk of PCa [33].

The presence of verification bias is an important limitation of our dataset. Therefore, we used statistical methods [12,13] to attempt to correct for verification bias and found that this shrank our estimates of AUC towards the null but that our results remained qualitatively unchanged. Our study is also limited by the fact that we did not assess the ability of the various dynamic PSA measures to predict the presence of different prognostic groups of PCa (e.g. D'Amico low-risk vs high-risk). Additional limitations of our study are that our dataset did not allow for ascertainment of the presence of certain factors known to affect PSA levels (e.g. 5 α -reductase inhibitor use, the presence of urinary tract infection, or recent urological manipulation) and that the population was predominantly Caucasian and, consequently, validation in ethnically diverse populations is needed.

In conclusion, using a large population-based sample, we show that PSA is a better predictor of future PCa than PSA-V or PSA-DT/PSA-PC. Adding PSA-V or PSA-DT/PSA-PC to a model containing PSA does not result in clinically relevant improvements in the ability to predict future PCa. Measuring

changes in PSA does not appear useful in the setting of PCa screening.

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CONFLICT OF INTEREST

None declared.

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- Abbreviations:** PSA, prostate-specific antigen; Pca, prostate cancer; PSA-V, PSA velocity; PSA-DT, PSA doubling time; PSA-PC, PSA percentage change; ROC, receiver-operating characteristics; AUC, area under the curve; NRI, net reclassification improvement; IDI, integrated dissemination improvement; AIC, Akaike information criterion.

EDITORIAL COMMENT

AN EXAMINATION OF THE DYNAMIC CHANGES IN PROSTATE-SPECIFIC ANTIGEN OCCURRING IN A POPULATION-BASED COHORT OF MEN OVER TIME

Inman *et al.* should be congratulated on a thorough and well-written analysis of PSA kinetics in a large group of men from Olmsted County, MN. They found that, in general, higher baseline PSA and greater rate of change in PSA were associated with an increased probability of prostate cancer.