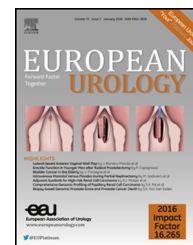


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Prostate Cancer

Refined Analysis of Prostate-specific Antigen Kinetics to Predict Prostate Cancer Active Surveillance Outcomes

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Abstract

Background: For men on active surveillance for prostate cancer, utility of prostate-specific antigen (PSA) kinetics (PSAk) in predicting pathologic reclassification remains controversial.

Objective: To develop prediction methods for utilizing serial PSA and evaluate frequency of collection. **Design, setting, and participants:** Data were collected from men enrolled in the multicenter Canary Prostate Active Surveillance Study, for whom PSA data were measured and biopsies performed on prespecified schedules. We developed a PSAk parameter based on a linear mixed-effect model (LMEM) that accounted for serial PSA levels.

Outcome measurements and statistical analysis: The association of diagnostic PSA and/or PSAk with time to reclassification (increase in cancer grade and/or volume) was evaluated using multivariable Cox proportional hazards models.

Results and limitations: A total of 851 men met the study criteria; 255 (30%) had a reclassification event within 5 yr. Median follow-up was 3.7 yr. After adjusting for prostate size, time since diagnosis, biopsy parameters, and diagnostic PSA, PSAk was a significant predictor of reclassification (hazard ratio for each 0.10 increase in PSAk = 1.6 [95% confidence interval 1.2–2.1, $p < 0.001$]). The PSAk model improved stratification of risk prediction for the top and bottom deciles of risk over a model without PSAk. Model performance was essentially identical using PSA data measured every 6 mo to those measured every 3 mo. The major limitation is the reliability of reclassification as an end point, although it drives most treatment decisions.

Conclusions: PSAk calculated using an LMEM statistically significantly predicts biopsy reclassification. Models that use repeat PSA measurements outperform a model incorporating only diagnostic PSA. Model performance is similar using PSA assessed every 3 or 6 mo. If validated, these results should inform optimal incorporation of PSA trends into active surveillance protocols and risk calculators.

Patient summary: In this report, we looked at whether repeat prostate-specific antigen (PSA) measurements, or PSA kinetics, improve prediction of biopsy outcomes in men using active surveillance to manage localized prostate cancer. We found that in a large multicenter active surveillance cohort, PSA kinetics improves the prediction of surveillance biopsy outcome.

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1. Introduction

Given the prolonged natural history and indolent behavior of most low-risk prostate cancers [1], active surveillance (AS) has been developed as an alternative to immediate treatment. Surveillance is now recognized as a preferred strategy for low-risk disease [2], and is offered to a large and growing proportion of men, both in the USA [3,4] and internationally [5]. While substantial variation persists in terms of eligibility criteria for surveillance, follow-up intervals, and triggers for intervention, all AS protocols are based principally on repeated prostate-specific antigen (PSA) measurements and periodic rebiopsy [2].

However, it remains unclear how to collect and interpret serial PSA data optimally in the AS setting. In most centers, PSA is collected quarterly, with the goal of identifying men with a rapid PSA rise, which may signify aggressive disease. However, studies to date have not shown analyses of PSA kinetics to be informative in most cases. In multiple cohorts, PSA kinetics consistently failed to predict reclassification based on biopsy parameters (ie, increase in biopsy Gleason grade and/or tumor volume) [6–8]. In the prospective, multicenter Canary Prostate Active Surveillance Study (PASS), PSA doubling time (PSADT) of <36 mo was originally a criterion for progression, but since consistently few men met this threshold it was dropped from the protocol [9].

Limiting factors in most AS cohorts reporting outcomes are the relatively short duration of follow-up and limited longitudinal PSA data. As the PASS cohort has matured with longer follow-up, additional PSA measurements, and more reclassification events, we have an opportunity to determine the extent to which PSA kinetics might facilitate improved decision making for men on surveillance for low-risk prostate cancer. We also aimed to determine whether quarterly PSA measurements are necessary for accurate assessment of PSA kinetics or whether semiannual measurement would be sufficient.

2. Patients and methods

The Canary PASS is a multicenter, prospective cohort study enrolling men on AS at nine North American centers. Men eligible for AS provide informed consent under institutional review board supervision (clinicaltrials.gov NCT00756665). In PASS, PSA is measured every 3 mo, clinic visits occur every 6 mo, and ultrasound-guided biopsies are performed 6–12 mo after diagnosis, 24 mo after diagnosis, and then every 2 yr. Other tests, including magnetic resonance imaging, are performed at the clinicians' discretion; however, as enrollment started in 2008, the majority of men did not undergo these procedures. For the current study, participants were enrolled before February 2016 and had diagnostic Gleason grade $\leq 3+4$ and <34% of biopsy cores involved with cancer, no history of 5 α -reductase inhibitor (5ARI) use, and at least one PSA and one biopsy following diagnosis. The primary outcome was tumor reclassification, defined as an increase in primary or secondary Gleason grade, or an increase in tumor volume to $\geq 34\%$ of total biopsy cores involved. Tumor risk at diagnosis was summarized using the validated Cancer of the Prostate Risk Assessment (CAPRA) score [10].

2.1. Statistical analysis

PSA may be measured irregularly during AS and is characterized by within-individual random variation, which may attenuate associations between PSA kinetics and clinical outcomes. To study longitudinal PSA measurements as predictors of reclassification while accommodating these complicating factors, a two-stage procedure was used [11,12]. Through this process, we derived a novel PSA kinetic parameter (designated PSAk), which we treated like a biomarker, and our approach conformed to the REMARK criteria for novel biomarkers [13].

First, we calculated PSAk using a linear mixed-effect model (LMEM), in which the natural logarithm of PSA ($\ln[\text{PSA}]$) was modeled as a linear function of time since diagnosis, with a random intercept indicating the individual-specific $\ln(\text{PSA})$ at diagnosis and a random slope reflecting the individual-specific rate of change over time. PSAk for each participant based on all his PSA measurements from diagnosis to a specific observation time was derived using the best linear unbiased predictor (BLUP) estimator from the LMEM (see the Supplementary material, Methods). Intraclass correlation (ICC) was calculated to assess how much of the variability in PSA was explained by between-participant variance compared with total variance. A high ICC indicates strong correlations among PSA measurements from the same individual.

Two other approaches for calculating PSA kinetics were considered: a linear regression model using all the PSA measurements from diagnosis to an observation time (simple PSAk [PSAkS]), and a slope change using two PSA measurements closest to and including the observation time (restricted simple PSAk [PSAkRS]). Models were adjusted for prostate size.

Second, Cox proportional hazards (PH) models were used to determine the risk of future reclassification as a function of covariates at each observation time. The outcome was defined as time from each PSA measurement to reclassification or censoring. Participants were censored at treatment, last study contact, or 2 yr after biopsy; the latter criterion was included to control for patients who do not undergo ongoing serial biopsies, and therefore may accrue long-term follow-up but do not have the possibility of meeting the reclassification outcome. Individual-specific PSAk at each measurement time estimated from stage 1 was the key covariate. Other covariates considered were the following: age, $\ln(\text{prostate size})$, $\ln(\text{observation time since diagnosis})$, diagnostic Gleason (3 + 3 or 3 + 4), percent of positive biopsy cores, number of biopsies since diagnosis (0, 1, 2, 3, or 4+), negative biopsy since diagnosis, recent biopsy result (cancer vs no cancer), and $\ln(\text{diagnostic PSA})$. Tests for proportionality confirmed that the PH assumptions were valid.

Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated with robust variance estimates to account for correlations from multiple observations from the same individual. Model fit was compared using the Akaike information criterion (AIC); a smaller AIC indicated better goodness of fit. Nonsignificant variables were backward eliminated using a *p* value cutoff of 0.05.

To address whether our results were biased by an increase or a decrease in PSAk that influenced the decision to undergo or delay a biopsy, several steps were taken. Timing of each biopsy was defined as “on time,” “early,” or “late” based on the PASS protocol. Multinomial regression analyses were used to determine whether biopsy timing was associated with PSAk. Three different sensitivity analyses were performed: compliant participants only (all biopsies needed to be compliant to the protocol), compliant biopsies only (only data preceding on-time biopsies were included), and adjusted event or censor time (early and late biopsies were adjusted by a randomly selected time within the “on-time” window). Further details are provided in the Supplementary material.

To assess the performance of the multivariable model incorporating PSAk, the Cox PH model was used to calculate individual risk of having a

reclassification event at 4 yr from 1 yr after diagnosis for each participant, using PSA data from diagnosis to 1 yr. Time-dependent receiver operating characteristic (ROC) curves and areas under the curve (AUCs) were used to quantify the performance of models. Bootstrapping methods were used to obtain 95% CIs for AUCs. ROC curves and AUCs accounted for censoring prior to 4 yr, and compared model-based individual risk with each participant's event or censor outcome. To evaluate the usefulness of PSAk for risk stratification, we categorized the model-based risk as follows: lowest 10%, middle, and highest 10% risk. We compared reclassification-free probabilities among these risk groups using a Kaplan–Meier (KM) analysis. Risk groups were generated using models with and without PSAk.

We ran an additional analysis comparing modeling performance for PSA measured every 6 versus every 3 mo since diagnosis, and assessed whether semiannual and quarterly PSA measurement yielded similar predictions. As an additional sensitivity analysis, we also analyzed PSAk based on the end point of grade reclassification only. A two-sided p value of <0.05 was considered significant for analyses, which were performed using R version 3.3.0.

3. Results

Of 1278 men in PASS, 107 did not yet have a surveillance biopsy, 193 had a history of 5ARI use, 70 did not meet study risk criteria, and 57 had missing data. Thus, 851 (67%) men were included in this analysis. Median (interquartile range [IQR]) follow-up among censored participants was 3.7 (2.4–5.2) yr. Among all participants, 291 (34%) were reclassified by an increase in biopsy Gleason grade or tumor volume to $\geq 34\%$ of total biopsy cores with cancer, of whom 210 (25%) and 255 (30%) were reclassified within 3 and 5 yr of diagnosis, respectively. Of the 291 men, 247 (85%) were reclassified based on Gleason grade and only 44 by the extent of biopsy involvement only. Only 46 men (8%) were censored based on treatment in the absence of progression. The median participant age was 62 yr. Six percent were African Americans and 4% belonged to other non-Caucasian races. Eighty percent of biopsies were per protocol (on time), 10% early, and 9% late. Table 1 summarizes the clinical characteristics of the cohort. Reclassified participants had similar clinical risk to censored participants, as assessed by the CAPRA score ($p = 0.95$); however, compared with censored participants, reclassified participants had smaller prostates, a higher PSA density (PSAD), and a higher

proportion of diagnostic biopsy cores involved (all $p < 0.001$).

The annual percent change in PSA estimated by the LMEM was 4.3 (95% CI 3.4–5.2, $p < 0.001$). As determined by the ICC, 85% of the observed variation in PSAk was explained by between-participant variation and 15% by within-participant variation. By LMEM estimation, PSA increased 8.1% annually (95% CI 6.0–10.3, $p < 0.001$) for reclassified participants and 0.8% (95% CI –0.7 to 2.4, $p = 0.33$) for censored participants (Fig. 1).

The median PSAk at 1 yr from diagnosis was 0.04. In a Cox PH model including both $\ln(\text{diagnostic PSA})$ and PSAk, PSAk was independently associated with reclassification, with an HR of 1.5 (95% CI 1.1–1.9) for each 0.1 unit increase. The HR for $\ln(\text{diagnostic PSA})$ at diagnosis was 1.3 (95% CI 1.0–1.6). In a multivariable model adjusted for prostate size, time since diagnosis, percent of biopsy cores involved in the most recent biopsy, and any negative biopsy after diagnosis, the HRs for $\ln(\text{diagnostic PSA})$ and PSAk remained significant: 1.7 (95% CI 1.3–2.2) and 1.6 (95% CI 1.2–2.1), respectively.

In a secondary analysis modeling PSAk calculated using three different methods, a PSAkRS (see methods) was not associated with time to reclassification ($p = 0.10$). The association between PSAkS from linear regression and time to reclassification was less significant ($p = 0.002$, compared with $p = 0.0006$ for PSAk) and not as strong (HR = 1.02, 95% CI 1.01–1.03 for each IQR increase) as PSAk based on the BLUP estimator from the LMEM (HR = 1.25, 95% CI 1.10–1.42 for each IQR increase). The model with PSAk had the highest goodness of fit with respect to AIC. In a model that contained all three PSAk measurements, PSAk was statistically significant, while PSAkS and PSAkRS were not (Table 2). Thus, the simple methods of calculating PSAk were not considered further. No meaningful differences in parameter estimates or statistical significance were observed in sensitivity analyses that minimized potential ascertainment bias (see the Supplementary material for more details).

The AUC for the full multivariable model including PSAk in predicting 4-yr reclassification outcomes from a measurement time of 1 yr after diagnosis was 0.80 (95% CI 0.75–0.85). As illustrated in Figure 2, when subgroups of low,

Table 1 – Participant characteristics

	All participants (n = 851)	Reclassified participants (n = 291)	Censored participants (n = 560)
Time to event/censor (yr), median (IQR)	3.0 (1.7–4.8)	2.0 (1.1–3.2)	3.7 (2.4–5.2)
No. of PSA values, median (IQR)	8 (4–13)	5 (3–9)	9 (5–14)
Dx PSA, median (IQR)	4.8 (3.6–6.3)	4.9 (3.9–6.3)	4.7 (3.5–6.3)
Prostate size, median (IQR)	40 (30–54)	35 (27–46)	44 (32–58)
Dx PSA density, median (IQR)	0.11 (0.08–0.16)	0.14 (0.10–0.18)	0.10 (0.07–0.14)
Dx core percentage, median (IQR) ^a	8 (8, 17)	17 (8, 17)	8 (8, 17)
Dx age, median (IQR)	62 (57–67)	63 (58–67)	62 (57–67)
Dx CAPRA score, n (%) ^a			
0	30 (4)	9 (3)	21 (4)
1	510 (64)	177 (64)	333 (64)
2	206 (26)	73 (26)	133 (25)
3+	56 (7)	19 (7)	37 (7)

CAPRA = Cancer of the Prostate Risk Assessment; Dx = at diagnosis; IQR = interquartile range; PSA = prostate-specific antigen.

^a Of the participants, 28 and 49 are missing cores percentage and CAPRA score at diagnosis, respectively.

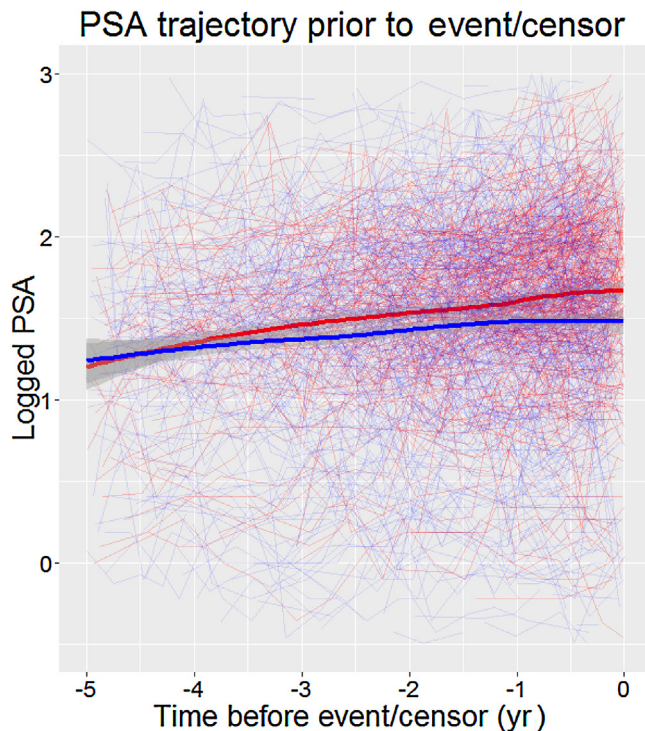


Fig. 1 – PSA trajectory prior to reclassification or censoring. In this spaghetti plot, individual $\ln(\text{PSA})$ trajectories are plotted in red for reclassified participants and in blue for censored participants, omitting PSA data within 2 yr prior to censor date to look at long-term nonevents. Smoothed trend lines were added using LOESS. A separate LMEM analysis found a slope of 8.1%/yr for reclassified participants and 0.8% for censored participants (for interaction between reclassification group and PSA change: $p < 0.001$). LMEM = linear mixed-effect model; PSA = prostate-specific antigen.

middle, and high risk for reclassification were identified based on models with and without PSAk, the inclusion of PSAk was better able to distinguish between extreme subgroups of individuals (10% of each cohort) with low and high event rates in the years after the prediction. The reclassification-free probability based on the KM estimator in the low-risk group at 4 yr after the 1-yr measurement

time was 1.00 (95% CI 1.00–1.00) with PSAk and 0.94 (95% CI 0.87–1.00) without PSAk in the model. In contrast, the reclassification-free probability in the high-risk group at 2 yr after the 1-yr measurement time was 0.34 (95% CI 0.22–0.53) with PSAk versus 0.41 (95% CI 0.28–0.60) without PSAk. The analysis based on grade reclassification only yielded very similar results (HR for each 0.1 unit increase in PSAk 1.62, 95% CI 1.22–2.17).

Calculating PSAk based on semiannual rather than quarterly PSA measurements yielded tightly correlated results: $r = 0.95$, $p < 0.001$ (Fig. 3). Recalculating the multivariable Cox PH model described above using only semiannual PSA measurements yielded substantially similar results, with the new HRs for $\ln(\text{PSA})$ and PSAk being 1.6 (95% CI 1.3–2.1) and 1.9 (95% CI 1.3–2.6), respectively. The AUCs for 3- and 6-mo models are similar (Supplementary Fig. 2).

4. Discussion

PSA kinetics have long been studied as an indicator of prostate cancer prognosis, at decision points ranging from whether a man should undergo initial prostate biopsy [14] to early identification of advanced disease progression [15]. The utility of PSA kinetics in the pretreatment setting has been difficult to establish for a number of reasons, including a close correlation with static PSA at diagnosis [16], relatively short follow-up and limited longitudinal data in most series, PSA “noise” from noncancer sources, and the myriad published definitions of PSA kinetics such as velocity, doubling time, and other measures of growth [17]. We found stronger strength of association and better prediction calibration when PSAk was calculated based on an LMEM that accounted for both the general trend of increasing PSA over time in the cohort and individual-specific trajectories, while discounting the random noise in the PSA measurements.

For men on AS for low-risk prostate cancer, a rapidly rising PSA would intuitively seem to predict aggressive disease and adverse outcomes. In fact, in the Toronto cohort,

Table 2 – Comparing simple PSAk (PSAkS), restricted simple PSAk (PSAkRS), and PSAk in Cox PH models ($n = 841$)^a

Variable	PSAkS model		PSAkRS model		PSAk model		Model containing all PSAk measurements	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Dx PSA	1.84 (1.41, 2.39)	<0.001	1.80 (1.39, 2.34)	<0.001	1.88 (1.43, 2.46)	<0.001	1.90 (1.44, 2.49)	<0.001
PSAkS (IQR increase)	1.02 (1.01, 1.03)	0.002					1.01 (1.00, 1.02)	0.12
PSAkRS (IQR increase)			1.01 (0.99, 1.02)	0.10			1.01 (0.99, 1.02)	0.3
PSAk (IQR increase)					1.25 (1.10, 1.42)	<0.001	1.24 (1.09, 1.41)	0.001
AIC	26 388		26 403		26 287		26 286	

AIC = Akaike information criterion; CI = confidence interval; Dx = at diagnosis; HR = hazard ratio; IQR = interquartile range; PH = proportional hazards; PSA = prostate-specific antigen; PSAk = prostate-specific antigen kinetics.

^a Participants were required to have nonmissing PSAkS, PSAkRS, and PSAk to be considered in the model comparison. All models were adjusted for prostate size. Note that IQR increase was equivalent to 0.23 for PSAkS, 0.94 for PSAkRS, and 0.05 for PSAk.

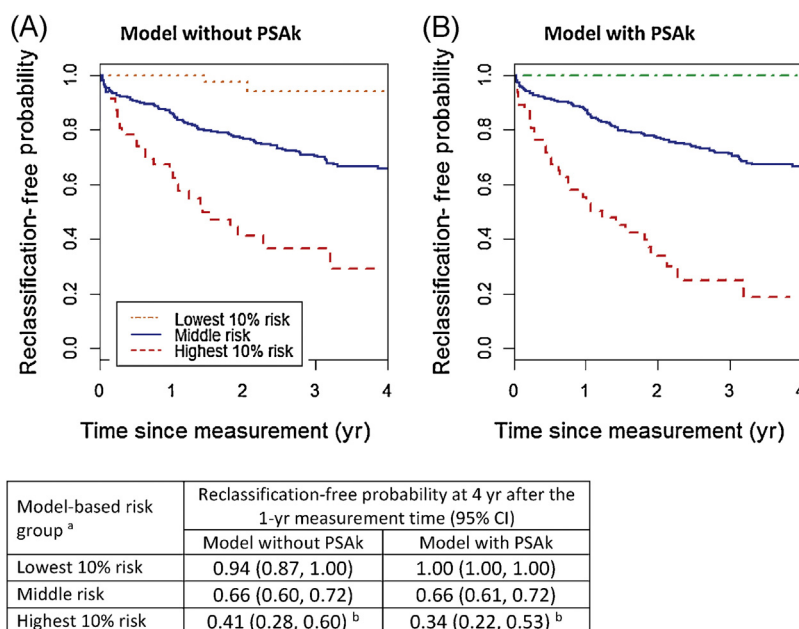


Fig. 2 – Predicting reclassification outcomes. Kaplan–Meier plots showing reclassification-free probabilities at 4 yr after the 1-yr measurement time, using data up to 1 yr after diagnosis. (A) Model-based risk categories from Cox PH model adjusted for PSA at diagnosis, prostate size, time since diagnosis, most recent percent of biopsy cores involved, and history of any negative biopsy—but not PSAk. (B) Similar analysis adjusted for the same variables in addition to PSAk. The PSAk model improved stratification of risk prediction for the top and bottom deciles of risk over a model without PSAk. CI = confidence interval; PH = proportional hazards; PSA = prostate-specific antigen; PSAk = prostate-specific antigen kinetics. ^a Model-based risk is calculated at a measurement time of 1 yr after diagnosis using all data available up to the measurement time. ^b Reclassification-free probability at 2 yr after the 1-yr measurement time due to small numbers.

one of the earliest AS cohorts in North America, PSADT of <2 yr was initially the primary trigger for intervention. This threshold was found to be inadequately sensitive and was extended to <3 yr. However, while the definition of rapid PSADT in this cohort predicts outcomes after definitive treatment for men initially on AS, PSADT alone was found to be nonspecific and is now considered in the context of other indicators, particularly grade reclassification [18]. In other

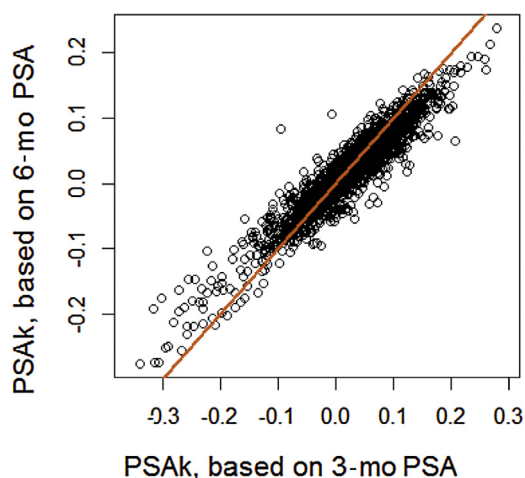


Fig. 3 – Quarterly versus semiannual PSA measurement. Correlation between PSAk calculations based on every 3- versus every 6-mo PSA measurements is illustrated. Pearson correlation (r) 0.95, $p < 0.001$. PSA = prostate-specific antigen; PSAk = prostate-specific antigen kinetics.

large cohort studies, PSA kinetics have not been proved useful with relatively short-term follow-up. In the international, multicenter Prostate Cancer Research International Active Surveillance study, PSA kinetics (PSADT <3 yr) was not predictive of pathologic reclassification [8]. In the University of California, San Francisco, cohort, PSADT of <3 yr was associated with an increased risk of reclassification—but only one man in the first 241 enrolled met this threshold [7]. In the Johns Hopkins cohort, both PSADT and PSA velocity, calculated as PSA multiplied by the slope of a linear regression of $\log(\text{PSA})$, were poor predictors of reclassification, with AUCs of 0.59 and 0.61, respectively [6]. In this cohort, however, enrollment criteria for AS are very restrictive, yielding a narrow dynamic range in terms of progression risk in which to evaluate PSA kinetics.

In this study, we analyzed PSA kinetics in a multicenter cohort with PSA data collected at protocol-mandated intervals, relatively long follow-up, and centralized analysis. We employed an analytic strategy that allowed the models to account for prior PSA history at each individual PSA measurement in an individual participant's trajectory, while borrowing information from the general trend across all participants and accommodating for random variability in PSA. In a plot of individual PSA trajectories, a higher overall slope was found for those who were reclassified versus those who were not (Fig. 1). Moreover, the addition of PSAk to a rich multivariable model improved the performance of the model, suggesting that PSAk may be considered an additional biomarker for outcomes on AS and is predictive independent of the absolute PSA level. In general, this

finding suggests that collecting PSA measurements over time to provide an updated outcome is clinically useful, and our approach of calculating PSAk provides a summary that effectively reflects the changes of PSA over time. On the contrary, given essentially identical results analyzing every 3- versus every 6-mo PSA data, we suggest that in most cases PSA may not need to be measured any more often than semiannually, with the important qualification that this finding remains to be validated in other cohorts.

The imaging and molecular tests available to supplement standard clinical data to guide decision making for men with low-risk disease are proliferating rapidly, and the potential clinical utility of PSAk should be considered in this context. We have adhered to the REMARK criteria for biomarker reporting [13] to as great an extent as possible. In particular, we stress that all PSA and outcome data have been collected and reported prospectively throughout the duration of PASS, and all analyses conducted centrally. Although several biomarkers, as well as multiparametric magnetic resonance imaging, are currently marketed for decision making with respect to AS [19], so far none has been validated in a prospective AS cohort. Moreover, PSAk has the advantage of requiring neither any additional biomaterial nor any incremental cost.

A few caveats should be noted. PSA levels are reported directly from the Canary PASS clinical sites, and reflect different laboratories. We, therefore, cannot control for interassay variability in PSA levels. However, men are instructed to use the same laboratory consistently for their PSA measurements, and we expect that assay variability would introduce a bias toward a null result rather than a false-positive result. We examined the performance of PSAk above and below the PSAD threshold of 0.15 to better understand the performance of PSAk relative to PSAD. Our finding of differential performance at high and low PSAD is intriguing—perhaps reflecting better information from PSA trends in the absence of substantial benign prostatic hyperplasia—and merits further examination. As changes in PSA may affect decisions regarding biopsy performance (and therefore the opportunity to identify reclassification), a risk of ascertainment bias exists. However, compliance with biopsy schedules in PASS is generally excellent (80% of biopsies on time), and the sensitivity analysis excluding men with noncompliant biopsies did not change the results. The BLUP methodology does not lend itself to simple calculation at the point of care and requires a robust background of PSA data. We plan to incorporate PSAk, together with other parameters predictive of AS outcomes, in a web-based, multivariable risk calculator that will be presented in a future publication.

Perhaps the most important limitation is the reliability of our end point. The principal question was the ability of PSAk to predict biopsy reclassification. We acknowledge that reclassification itself is an imperfect end point, as it may reflect initial undersampling [20], variation in the interpretation of different pathologists [21], and/or minimal changes in the tumor, which have little clinical importance. However, our reclassification definition is consistent with those used by most other AS cohorts, and

these changes frequently drive treatment decision making in contemporary practice. Therefore, while perhaps not biologically optimal, we believe that our findings are quite relevant for current clinical management and can in fact improve AS care.

5. Conclusions

We found that a sophisticated mathematical approach to measuring PSAk, as reflected in the novel PSAk parameter, can improve prediction of outcomes for men on surveillance for prostate cancer and that PSA may need to be measured no more often than semiannually. Obviously, PSA should never be interpreted in a vacuum, and we did not identify a PSAk threshold that should always indicate treatment. These results, which must be validated in other surveillance cohorts, suggest that PSAk or similar assessments of kinetics should be considered in future multivariable models of AS outcomes.

Author contributions: Matthew R. Cooperberg had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Cooperberg, Brooks, Lin, Zheng.

Acquisition of data: Newcomb, Carroll, Dash, Fabrizio, Gleave, Thompson, Wagner, Lin.

Analysis and interpretation of data: Faino, Zheng, Cooperberg, Brooks, Lin, Newcomb, Kearns.

Drafting of the manuscript: Cooperberg, Brooks, Lin, Zheng, Newcomb, Faino.

Critical revision of the manuscript for important intellectual content: Cooperberg, Brooks, Faino, Newcomb, Kearns, Carroll, Dash, Etzioni, Fabrizio, Gleave, Nelson, Thompson, Wagner, Lin, Zheng.

Statistical analysis: Faino, Zheng.

Obtaining funding: Cooperberg, Lin, Nelson.

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Appendix A. Supplementary data

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