The Relationship of the Intensity of Posttreatment Prostate-Specific Antigen Surveillance and Prostate Cancer Outcomes: Results From a Population-Based Cohort

Mohammed Nabhan, MD; Simon P. Kim, MD, MPH; Nilay D. Shah, PhD; Stephanie M. Bagniewski, BS; Qian Shi, PhD; R. Jeffrey Kames, MD; Christopher J. Weight, MD; Brian J. Davis, MD, PhD; Manish Kohli, MD; and Jon C. Tilburt, MD

Abstract

Objective: To determine whether higher intensity of prostate-specific antigen (PSA) surveillance was associated with earlier detection of biochemical recurrence (BCR) or survival.

Patients and Methods: We identified a population-based cohort of 832 men diagnosed with nonmetastatic prostate cancer between January 1, 1995, and July 31, 2006. These men were treated with radical prostatectomy (RP), brachytherapy or external beam radiation therapy (RT), or primary androgen deprivation therapy or chose watchful waiting. To test the associations of intensity in PSA surveillance with study outcomes, we used a 2-year landmark analysis to assess whether the number of PSA tests during the first 2 years after treatment was associated with earlier detection of BCR, prostate cancer–related mortality, and all-cause mortality. We used landmark analysis to assess the association of PSA intensity, adjusting for clinicopathologic covariate, with outcome.

Results: Median follow-up time for the entire cohort was 6.7 years. Higher Gleason score was the only clinicopathologic variable associated with higher PSA frequency in multivariable analysis for both the RP and RT groups (*P* value of .001 and .05, respectively). After adjustment for other covariates, the frequency of PSA tests during the first 2 years after RP did not increase the ability to detect BCR (hazard ratio, 1.00; 95% confidence interval, 0.84-1.19) or all-cause mortality (hazard ratio, 0.95; 95% confidence interval, 0.70-1.30) in the landmark analysis.

Conclusion: Higher intensity of PSA surveillance during the 2 years after RP or RT did not improve earlier detection of BCR or survival. Evidence-based guidelines for PSA surveillance after primary treatment are needed.

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From the Knowledge and Evaluation Research Unit (M.N., N.D.S., J.C.T.), Department of Urology (S.P.K., R.J.K., C.J.W.), Division of Health Care and Policy (N.D.S.), Department of Health Sciences Research (S.M.B., Q.S.), Department of Oncology (M.K.), Department of Radiation Oncology (B.J.D.), and Biomedical Ethics Research Unit (J.C.T.), Mayo Clinic, Rochester, MN.

Prostate cancer remains the noncutaneous malignancy with the highest annual incidence in the United States and ranks second in cancer-related deaths.¹ Although approximately 32,000 deaths are attributable to prostate cancer annually, there are an estimated 2 million prostate cancer survivors because of the protracted natural history of the disease.^{1,2} The risk of prostate cancer–related death remains low for individuals diagnosed with localized disease who undergo radical prostatectomy (RP), radiation therapy (RT), or androgen deprivation therapy (ADT) or elect watchful waiting (WW), and many will live with prostate cancer rather than die of it.³⁻⁷ Most prostate cancer survivors live for decades after their diagnosis concerned about the possibility of recurrence.⁸ Many survivors also experience adverse effects from initial treatments, the uncertainty of whether the disease will recur, and other important quality-of-life changes.⁹

Treatment decisions for men diagnosed with nonmetastatic prostate cancer focus on risk stratification according to the pathologic features at the time of diagnosis or surgery. Pathologic factors shown to predict biochemical recurrence (BCR) and prostate cancer–specific mortality (PCSM) reliably include baseline prostate-specific antigen (PSA) level and pretreatment PSA velocity, clinical tumor stage and Gleason score at the time of incident diagnosis, prostate cancer involvement of the seminal vesicles and pelvic lymph nodes, and margin status for RP, among others.¹⁰⁻¹³ Posttreatment PSA levels are used to define treatment outcome. Hence, it is intuitively appealing to hypothesize that a higher intensity of PSA surveillance after treatment may increase the ability to detect BCR, which has been shown to be associated with PCSM for RP, and improve survival.¹⁴⁻¹⁶ To date, however, few studies have explored whether intensive PSA monitoring after primary treatment improves outcomes with ear-

lier detection of BCR. A single-institution study recently reported an association between increased PSA monitoring and BCR detection among individuals with nonmetastatic prostate cancer who were treated with RP or RT with external beam radiation or brachytherapy.¹⁷ In another study, BCR was associated with a small but increased risk of prostate cancer mortality for patients treated with RP and RT, although the frequency of PSA monitoring was not assessed.¹⁸

Little is known about optimal biochemical monitoring or whether regular monitoring makes any difference in outcomes. The National Comprehensive Cancer Network guidelines for the management of localized prostate cancer recommend a broad range in the frequency of PSA surveillance after definitive therapy.¹⁹ In this context, we used a population-based cohort of men diagnosed with nonmetastatic prostate cancer from 1995 to 2006 to characterize the association of the intensity of post-treatment PSA monitoring with prostate cancer outcomes. Our objective was to describe the patterns of PSA utilization by treatment groups, identify clinical and demographic correlates of PSA utilization frequency, and determine whether the intensity of PSA utilization early in their initial posttreatment course was independently associated with BCR, PCSM, and all-cause mortality (ACM).

PATIENTS AND METHODS

Study Population

After obtaining approval from the Mayo Clinic Institutional Review Board, we conducted a retrospective cohort analysis of 832 men diagnosed with nonmetastatic prostate cancer from the Mayo Clinic Tumor Registry (Rochester, Minnesota) from January 1, 1995, to July 31, 2006. Men were eligible if they had been diagnosed with clinical stage I to III prostate cancer; did not have any prior diagnosis of cancer; resided in Olmsted County, Minnesota; and had at least one posttreatment PSA value. Furthermore, for men in the RP group, PSA had to be undetectable in the first year, and for men in the RT group, at least one PSA test was needed in the first year after treatment. During this study period, residents from Olmsted County generally sought care at 1 of 2 facilities: Mayo Clinic or Olmsted Medical Center.²⁰

Definition of PSA Use

From our population-based cohort of individuals, we identified all PSA tests performed on the study population documented in Mayo Clinic laboratory data between January 1, 1995, and July 31, 2009. We counted the number of PSA tests performed up to 2 years after treatment for RP and RT, after hor-

mone initiation for ADT, or after diagnosis for WW. The end of this 2-year time period was then used as the start of our follow-up time for landmark analysis, which assessed the association between short-term PSA surveillance and time-to-event clinical outcomes.

Covariates

The Mayo Clinic Tumor Registry and pathology and laboratory databases provided all demographic characteristics (age, sex, and marital status), along with the pathologic characteristics for each incident case of prostate cancer, such as baseline and all post-treatment PSA levels, clinical stage (I-III), and Gleason score. We stratified Gleason scores to 6 or less, 7, and 8 to 10, similar to the D'Amico classification system for risk stratification.²¹

To enumerate the treatments patients received and baseline comorbidities at the time of diagnosis, we used both the tumor registry and administrative data from Mayo Clinic. We defined treatment groups as follows: RP, RT, or primary ADT within 1 year of diagnosis. Radiation therapy was defined as brachytherapy or external beam radiation therapy. We defined the primary ADT group as patients receiving no other prostate cancer–related treatments except luteinizing hormone–releasing hormone agonists or antiandrogens in the first year after diagnosis. If a patient did not receive any of these interventions, he was then categorized in the WW group. The severity of comorbidities was stratified by the Elixhauser method.²²

Outcomes

The primary outcomes for the study were time to BCR, PCSM, and ACM. However, because of the limited number of cancer-related deaths, PCSM was not analyzed. According to current guidelines, we defined BCR events as having a PSA value of 0.2 ng/mL or more (to convert PSA value in ng/mL to $\mu\text{g/L}$, multiply by 1.0.) after RP, and we used the Phoenix definition of an increase in PSA value of 2.0 ng/mL or more above the nadir for RT.^{14,23} We used the lowest PSA value within the first year after treatment for the RT group as the nadir. The cause of death was verified by death certificate or the clinician. The last date used to inquire follow-up data in our data sources was July 31, 2009. Therefore, the time to PCSM and ACM was censored at this date for patients who were alive up to this date. In other words, we only have partial information about these patients' survival status up to July 31, 2009, and beyond this date the vital status of these patients is unknown.

Statistical Analyses

Because of possible selection bias, we conducted statistical analyses within initial treatment groups only. We report descriptive statistics as means and percentages for clinical factors within each of the treatment groups and overall for the entire population. We performed univariate and multivariable analyses to evaluate factors associated with increased intensity in the frequency of PSA tests using ordinary least squares regression. We evaluated associations between the following factors and frequency of PSA tests: age at diagnosis, baseline PSA value, clinical stage, Gleason score, and Elixhauser comorbidities.

To control for the fact that our predictor, PSA surveillance, would otherwise be part of the definition of the outcome (BCR for RP and RT), a landmark method was chosen for our analysis to test the association of PSA frequency during the 2 years after treatment and outcomes (time to BCR, prostate cancer-specific survival, and all-cause survival).²⁴ This method has been used as a means of reducing an inherent bias of assessing survival as a function of response. Patients who had recurrence or died before the landmark point were excluded from analysis (22 RP, 17 RT, and 5 ADT patients and 1 WW patient). As a result, for the landmark analysis, we were able to include 438 RP, 226 RT, 45 ADT, and

78 WW patients for a total of 787 patients. For time to BCR using landmark analysis, we were able to include 599 patients who had not died, had recurrence, or had their last PSA value before 2 years (395 RP and 204 RT patients).

We adjusted for other covariates using Cox proportional hazards models. The multivariable analyses evaluating the association between number of PSA tests in the first 2 years and time to BCR and overall survival were adjusted for age at diagnosis, baseline PSA value, Gleason score, clinical stage of cancer, and number of Elixhauser comorbidities. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC), and *P* values less than .05 for 2-sided tests were considered statistically significant.

RESULTS

Table 1 presents the clinical and demographic characteristics of our population-based cohort. Overall, we identified 832 men in Olmsted County diagnosed with nonmetastatic prostate cancer from 1995 to 2006. Of the 832 men, 460 (55.3%) underwent RP, 243 (29.2%) received RT, 50 (6.0%) had primary ADT, and 79 (9.5%) chose WW. When compared with other treatment groups, patients who underwent RP were younger and had fewer

TABLE 1. Demographic and Pathologic Characteristics From the Population-Based Cohort of Prostate Cancer Survivors Diagnosed With Nonmetastatic Prostate Cancer in Olmsted County, MN (N=832)^{a,b}

Characteristic	RP (n=460)	RT (n=243)	ADT (n=50)	WW (n=79)	<i>P</i> value
Mean age, y (SD)	61.2 (7.3)	70.1 (6.2)	76.9 (8.0)	74.0 (6.8)	<.001
White	417 (90.7)	228 (93.8)	46 (92.0)	74 (93.7)	.47
Married	404 (87.8)	191 (78.6)	34 (68.0)	63 (79.7)	<.001
Clinical stage					<.001
I	14 (3.0)	18 (7.4)	8 (16.0)	27 (34.2)	
II	386 (84.0)	219 (90.1)	41 (82.0)	52 (65.8)	
III	60 (13.0)	6 (2.5)	1 (2.0)	0 (0)	
Baseline PSA level ng/mL, median (range) ^c	5.2 (0.1-37.3)	7.0 (0.9-163.0)	9.8 (0.6-219.0)	5.8 (0.1-47.4)	<.001
Gleason score					<.001
≤6	314 (68.3)	143 (66.2)	26 (54.2)	68 (88.3)	
7-10	146 (31.7)	73 (33.8)	22 (45.8)	9 (11.7)	
Elixhauser index					<.001
0	115 (25.0)	60 (24.7)	2 (4.0)	7 (8.9)	
1	178 (38.7)	57 (23.5)	11 (22.0)	23 (29.1)	
2	109 (23.7)	67 (27.6)	17 (34.0)	22 (27.8)	
≥3	58 (12.6)	59 (24.4)	20 (40.0)	27 (34.2)	

^a ADT = androgen-deprivation therapy; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiation therapy; WW = watchful waiting.

^b Values are presented as No. (percentage) of patients unless indicated otherwise.

^c To convert to mμg/L, multiply by 1.0.

TABLE 2. Association Between Clinicopathologic Factors and Posttreatment PSA Testing Frequency From a Population-Based Cohort in Olmsted County, MN (N=832)

Factor	RP		RT		WW		ADT	
	Coefficient (SE)	P value	Coefficient (SE)	P value	Coefficient (SE)	P value	Coefficient (SE)	P value
Age at diagnosis	0.002 (0.01)	.83	0.02 (0.02)	.29	0.02 (0.04)	.54	−0.10 (0.05)	.04
Baseline PSA level	0.03 (0.02)	.06	0.02 (0.01)	.08	−0.004 (0.03)	.89	0.01 (0.01)	.52
Elixhauser index								
0	Referent		Referent		Referent		Referent	
1	−0.11 (0.18)	.53	0.03 (0.36)	.93	−0.29 (0.91)	.75	2.45 (2.57)	.35
2	0.27 (0.2)	.18	0.35 (0.35)	.32	−0.52 (0.9)	.56	−0.31 (2.56)	.91
≥3	0.10 (0.25)	.70	0.33 (0.36)	.37	−0.70 (0.89)	.44	−1.0 (2.56)	.70
Gleason score								
6	Referent		Referent		Referent		Referent	
7	0.28 (0.17)	.11	−0.10 (0.25)	.69	−0.73 (0.74)	.33	2.57 (1.02)	.02
≥8	1.02 (0.31)	.001	1.03 (0.51)	.05	−2.15 (2.06)	.30	0.86 (0.99)	.39
Clinical stage								
I	Referent		Referent		Referent		Referent	
II	0.08 (0.41)	.85	−1.08 (0.41)	.01	1.20 (0.46)	.01	1.41 (1.17)	.24
III	0.34 (0.46)	.46	−1.48 (0.76)	.05	N/A	N/A	−0.06 (2.92)	.98

ADT = androgen-deprivation therapy; N/A = not available; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiation therapy; WW = watchful waiting.

comorbidities. This group also had a lower baseline PSA value than the RT and ADT groups.

The median follow-up time for the entire cohort was 6.7 years, with 134 individuals (16.1%) experiencing BCR at a median follow-up time of 3.4 years. Overall, there were 146 deaths (17.5%), of which 14 were attributable to prostate cancer (1.7%). The total number of person-years of follow-up was 3384, 1458, 265, and 555 for the RP, RT, primary ADT, and WW groups, respectively.

PSA Surveillance Intensity Within Treatment Groups

From the 832 men in our cohort, we identified a total of 8582 PSA values after treatment for RP, RT, and ADT and after diagnosis for WW (4808 for RP, 2490 for RT, 557 for primary ADT, and 727 for WW). For the RP group (n=460), 79% of all PSA tests occurred in the time period between surgery and BCR or last PSA, and for the RT group (n=243), 86% occurred between treatment and BCR or last PSA. The median number of PSA tests performed from the 2-year landmark to the BCR or last follow-up was 4 (range, 1-33) for the RP group and 5 (range, 1-23) for the RT group.

BCR developed in 95 patients (20.7%) who received primary therapy with RP and 39 (16.1%) who received primary therapy with RT. The median times to BCR for RP and RT were 3.1 and 3.9 years,

respectively. Median PSA values at the time of BCR for RP and RT were 0.3 (range, 0.2-177.0) and 3.6 (range, 2.2-19.4), respectively.

Associations Between Posttreatment PSA Surveillance Intensity and Baseline Factors

To characterize the frequency of PSA testing from RP, univariate analysis demonstrated that higher baseline PSA and higher Gleason score (7 and 8-10) were associated with higher frequency of PSA testing ($P < .05$). After adjustment for clinicopathologic covariates, higher Gleason score remained the only variable that showed a statistically significant association with higher intensity of PSA monitoring in the RP and RT groups. Table 2 provides the multivariable analysis of the characteristics of covariates tested for PSA frequency for the 4 groups.

PSA Surveillance Intensity as a Predictor of BCR and Survival

Because few deaths were attributable to prostate cancer, we performed a 2-year landmark analysis for ACM only. Table 3 presents the multivariable analysis for ACM with clinicopathologic covariates and intensity of posttreatment PSA monitoring. For the RP treatment group, patient age was associated with a statistically significant risk of ACM (hazard ratio [HR], 1.08; $P = .02$). Elixhauser index of 3 or more was associated

TABLE 3. Multivariable Analysis for All-Cause Mortality With Clinicopathologic Covariates and Intensity of 2-Year Posttreatment PSA Monitoring (N=787)^{a,b}

Variable	RP		RT		WW		ADT	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
PSA tests in first 2 y after treatment	0.95 (0.70-1.30)	.75	1.01 (0.86-1.21)	.83	1.17 (0.94-1.47)	.17	1.08 (0.88-1.32)	.45
Age	1.08 (1.01-1.16)	.02	1.01 (0.96-1.05)	.87	1.07 (0.99-1.15)	.07	1.06 (0.98-1.15)	.18
Baseline PSA level	1.04 (0.97-1.12)	.24	1.01 (0.99-1.02)	.52	1.02 (0.95-1.10)	.61	1.01 (1.00-1.01)	.26
Elixhauser index								
0, 1	Referent		Referent		Referent		Referent	
2	0.65 (0.18-2.38)	.51	1.26 (0.56-2.86)	.58	1.03 (0.35-3.09)	.95	3.74 (0.89-15.73)	.07
≥3	4.02 (1.60-10.13)	.003	2.72 (1.34-5.55)	.006	1.79 (0.58-5.59)	.31	4.52 (1.03-19.77)	.045
Gleason score								
≤6	Referent		Referent		Referent		Referent	
7-10	0.47 (0.15-1.42)	.18	2.72 (1.43-5.18)	.002	1.52 (0.36-6.43)	.57	0.57 (0.22-1.48)	.25
Clinical stage								
I, II	Referent		Referent		Referent			
III	0.99 (0.29-3.39)	.99	2.09 (0.49-8.94)	.32	12.46 (0.81-191.2)	.07	NA	

^aADT = androgen-deprivation therapy; CI = confidence interval; HR = hazard ratio; NA = not available; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiation therapy; WW = watchful waiting.

^bHazard ratio is not available for the androgen-deprivation therapy group because there was no reported mortality in this group.

with higher ACM for patients treated with RP (HR, 4.02; $P=.003$), RT (HR, 2.72; $P=.006$), and ADT (HR, 4.52; $P=.045$). In the RT treatment group, increased risk of ACM was also associated with a Gleason score of 7 or more (HR, 2.72; 95% confidence interval, 1.43-5.18; $P=.002$). Baseline PSA level and clinical stage were not associated with ACM on multivariable analysis. Because there were no deaths in the WW group, the HR was not reportable. Interestingly, higher intensity of posttreatment PSA monitoring failed to provide any improved survival from ACM across all treatment groups.

In testing the association of the intensity of PSA monitoring from the 2-year landmark analysis with time to BCR, we observed no statistically significant effects in the association with higher intensity of PSA monitoring and BCR. Among men who underwent RP, higher risk of BCR was correlated with a Gleason score of 7 or more (HR, 2.53; $P<.001$) and clinical stage III (HR, 2.08; $P=.02$). None of the other clinicopathologic covariates was associated with risk of BCR for patients receiving RT on multivariable analysis. For both RP and RT treatment groups, higher intensity of PSA monitoring also failed to provide any improved outcomes with lower BCR on multivariable analysis (Table 4).

DISCUSSION

In this cohort of prostate cancer survivors whose disease was diagnosed from 1995 to 2006 in a geo-

graphically defined, free-living population from Olmsted County, we examined whether the intensity of PSA surveillance after definitive therapy, or for WW, for nonmetastatic prostate cancer varied according to different treatment groups and affected outcomes. In our study, very few patients diagnosed with and treated for prostate cancer had died of the disease after nearly 7 years of follow-up, and prostate cancer accounted for just 10% of ACM in this group of prostate cancer survivors. In both univariate and multivariable models in patients receiving RP or RT, the frequency of posttreatment PSA surveillance was not associated with differences of BCR, PCSM, and ACM. These data suggest that greater intensity of posttreatment PSA surveillance may not increase the ability to detect BCR or confer improved survival.

Our findings suggest that overtesting may not be causing overt harm in any measurable sense insofar as it does not seem to be causing overdiagnosis of BCR that may or may not ultimately influence prognosis. Higher intensity of PSA monitoring in prostate cancer survivors after primary therapy or in individuals who elect WW appears to have no demonstrable positive effect on their disease-specific or overall survival. In a recent study, patients diagnosed with low-risk prostate cancer and treated with RP had minimal risk for BCR, suggesting that lifelong PSA surveillance may be unnecessary.²⁵ Furthermore, greater frequency of testing may have

TABLE 4. Multivariable Analysis for Biochemical Recurrence With Clinicopathologic Covariates and Intensity of 2-Year Posttreatment PSA Monitoring (N=599)

Variable	RP		RT	
	HR (95% CI)	P value	HR (95% CI)	P value
PSA tests in first 2 y after treatment	1.00 (0.84-1.19)	.98	0.93 (0.72-1.20)	.57
Age	1.01 (0.97-1.05)	.68	1.05 (0.96-1.14)	.27
Baseline PSA level	1.02 (0.98-1.06)	.29	0.99 (0.96-1.03)	.72
Elixhauser index				
0, 1	Referent		Referent	
2	0.89 (0.49-1.63)	.71	1.47 (0.56-3.90)	.44
≥3	1.38 (0.70-2.74)	.35	0.84 (0.24-2.95)	.79
Gleason score				
<6	Referent		Referent	
7-10	2.53 (1.44-4.46)	<.001	2.40 (0.94-6.17)	.07
Clinical stage				
I, II	Referent		Referent	
III	2.08 (1.12-3.88)	.02	2.03 (0.27-15.49)	.49

CI = confidence interval; HR = hazard ratio; PSA = prostate-specific antigen; RP = radical prostatectomy; RT = radiation therapy.

adverse effects on psychological parameters, such as worry and anxiety, which this analysis was unable to assess. Notably, Wallner et al²⁶ recently found that psychosocial variables, such as worry and marital status, were associated with PSA test frequency in the screening setting. An analogous phenomenon may be happening in this cancer survivor population. Although we did not specifically measure anxiety, we speculate that although survivors may insist on the importance of getting a regular PSA test and physicians may use the test to allay patient anxiety, overutilization of PSA surveillance in the asymptomatic early years after definitive treatment may fuel rather than allay anxieties. Another inference from our results here relates to the increased costs attributable to health care. More specifically, prostate cancer represents a significant annual expenditure for Medicare, estimated at \$7 billion.²⁷ Our results suggest that an evidence-based protocol for PSA monitoring after primary therapy may help lower health care costs related to prostate cancer, but further analyses would help establish those parameters with greater specificity. In the absence of evidence that more aggressive monitoring saves lives, these data offer little rationale for aggressive testing strategies in patients who have undergone definitive treatment for prostate cancer. Identifying an “optimal” PSA monitoring strategy for prostate cancer recurrence in the posttreatment period remains an important objective for future research.

Inferences from such analyses should be approached with caution. Failing to identify hypothe-

sized associations between PSA testing frequency and BCR, as well as mortality, does not establish a sound basis for changes to clinical practice or evidence-based guidelines. Further, this study had limited power to detect change in mortality due to prostate cancer. These data are not prospective, so our ability to make causal inferences is limited. Another possible limitation of our study is shorter duration of follow-up. There is also a concern for ascertainment bias in that increased intensity of PSA testing after treatment (or diagnosis for WW) may influence the detection of BCR. Also, it is plausible that a time frame greater than 2 years of posttreatment PSA testing may have altered the results of the study. However, we also extended the time interval for PSA surveillance to a 3-year landmark analysis, which did not change results showing that frequency of posttreatment PSA testing was not associated with BCR or ACM. To best answer this clinical question about posttreatment PSA surveillance intensity, a randomized controlled trial of varying intensity of PSA monitoring after treatment in prostate cancer patients would best define the optimal posttreatment surveillance guidelines.

CONCLUSION

Understanding how physicians use cancer tests and the relationship between variability in the use of those tests and clinically relevant outcomes is essential to the quality of care for cancer survivors. Moreover, primary care physicians have assumed an increasing role not only in routine health care, but also

with cancer surveillance for survivors. Better characterization of how PSA and other cancer biomarkers work in clinical practice may help shape cogent clinical practice improvements to optimize follow-up care for an important but unpredictable cancer.

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Abbreviations and Acronyms: **ACM** = all-cause mortality; **ADT** = androgen deprivation therapy; **BCR** = biochemical recurrence; **HR** = hazard ratio; **PCSM** = prostate cancer-specific mortality; **PSA** = prostatic-specific antigen; **RP** = radical prostatectomy; **RT** = radiation therapy; **WW** = watchful waiting

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Correspondence: Address to Jon C. Tilbert, MD, Biomedical Ethics Research Unit, Knowledge and Evaluation Unit, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (Tilbert.Jon@mayo.edu).

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