Prostate-Specific Antigen Testing Practices and Outcomes

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OBJECTIVES: To characterize prostate-specific antigen (PSA) testing practices in a hospital-based primary care clinic, and to determine the outcomes of PSA testing, including urology referrals, biopsies, cancers detected, and cancer treatments.

DESIGN: Retrospective cohort study. Data were obtained from computerized Department of Veterans Affairs (VA) files and the statewide New Mexico Surveillance, Epidemiology, and End Results (SEER) tumor registry.

SETTING: Primary care clinics in a university-affiliated VA Medical Center.

PATIENTS: Subjects were 1,448 men without cancer undergoing PSA testing in 1993 with follow-up through 1994.

MAIN RESULTS: Twenty-one percent of clinic enrollees at least 40 years of age were tested with PSA, including 58 who were 75 years of age or older. By the end of 1994, 40.0% (95% confidence interval [CI] 37.2%, 42.8%) were retested; 25.6% (95% CI 21.7%, 29.5%) of initial retesting occurred within 6 months. Overall, 20.7% (95% CI 18.9%, 22.5%) of PSA tests in the cohort were for men aged 75 years or older and were repeated within 6 months. Among the 193 subjects with PSA values ≥ 4.0 ng/mL, 86.0% (95% CI 81.1%, 90.9%) were followed-up in urology clinic, and 46.1% (95% CI 39.1%, 53.1%) underwent biopsy. Only 11 of 51 men aged 75 years or older who were referred to urologists for an elevated PSA underwent biopsy. Forty cancers were diagnosed—a detection rate of 2.8% (95% CI 2.0%, 3.6%). Of these, 28 were organ-confined, 7 had regional invasion, and 3 had distant metastases.

CONCLUSIONS: Primary care providers frequently ordered PSA tests, but a substantial proportion of testing occurred outside recommended age ranges and screening intervals. Older patients with elevated PSA values often did not complete diagnostic workups. Better adherence to screening guidelines may limit the number of both PSA tests and urology referrals.

KEY WORDS: prostate cancer; prostate-specific antigen (PSA); outcomes.

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Screening with prostate-specific antigen (PSA) has become widely used in clinical practice, despite considerable controversy between professional organizations. The evidence-based U.S. Preventive Services Task Force,¹ the American College of Physicians,² the National Cancer Institute,³ and the Canadian Task Force on the Periodic Health Examination⁴ all oppose PSA screening because there is no evidence that screening reduces prostate cancer mortality. Nonetheless, both the American Cancer Society and the American Urological Association recommend annual screening with PSA and digital rectal examination beginning at age 40 years for men with risk factors (African Americans and men with first-degree family history) and at age 50 years for all other men.^{5,6} Although no upper age limit for screening is proposed, there is consensus that screening should not be offered to men with a life expectancy of less than 10 years.⁷ In the average man, this would imply PSA testing be discontinued by the mid to late 70s.⁸ Despite the abundance of epidemiologic data on prostate cancer, little information is available on actual testing practices and outcomes, especially in primary care settings.

We studied testing practices and outcomes for the Albuquerque VA Medical Center primary care continuity clinics, which are staffed by attending and resident physicians and physician assistants. In 1993, nearly 7,000 male patients older than 40 years were enrolled in these primary care clinics. All of the patients' laboratory and pathology results were entered into the VA Decentralized Hospital Computer Program (DHCP).

The objectives of the study were to characterize PSA testing practices in a hospital-based primary care clinic, and to determine the outcomes of PSA testing, including urology referrals, biopsies, cancers detected, and cancer treatments.

METHODS

PSA test results for calendar years 1993 and 1994 were obtained using the Laboratory Test Utilization program, a locally developed personal computer-based program package written in the MUMPS language. Each month, the custom utility program was used to download data on every test performed in the hospital laboratory. A PSA testing database was created that included the patient's name, social security number, age at testing, ordering provider, practice site, and the PSA value. The study cohort comprised only veterans who underwent PSA testing in the primary care clinics from January 1 through December 31, 1993. The DHCP database was then searched through December 31, 1994, to identify any follow-up PSA tests ordered on the study cohort and

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to determine whether the patient was still receiving care at the Albuquerque VA Medical Center. A pharmacy prescription database was used to identify subjects being treated with testosterone or finasteride because, in our hospital, these men routinely undergo PSA testing at 6-month intervals.

The names and social security numbers of the study cohort were linked with cancer cases from the New Mexico Tumor Registry (NMTR). The NMTR is a member of the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute.⁹ The NMTR has recorded population-based cancer incidence in New Mexico since 1969. Cancer cases are identified through active surveillance of hospital and outpatient clinic records, pathology and autopsy reports, and radiation therapy records. The registry staff also reviews state death certificates that mention cancer. The NMTR records cancer diagnoses only for New Mexico residents; the estimated completeness of case ascertainment is 97%.¹⁰ Less than 1% of the Albuquerque VA primary care patients were not residents of New Mexico. We used NMTR data to identify and exclude all cases of prostate cancer prevalent at the time of initial PSA testing in 1993.

We characterized testing practices according to patient age, whether repeated PSA testing occurred, the time to first repeated testing, and whether the provider ordering the test was a physician or a physician assistant. Because PSA values ≥ 4.0 ng/mL (Abbott AXSYM System) are considered abnormal in our laboratory, we assessed outcomes of patients with PSA values in this range. Follow-up data on urology referrals, biopsies, and pathology were obtained by searching the DHCP system. Data were available on the dates of any scheduled urology clinic appointments, including unkept appointments, and the dates and pathology results from prostate biopsies. The NMTR database was used to identify incident cases of prostate cancer detected through December 31, 1994, and to obtain information on tumor staging, treatment, and mortality. Chart reviews also were performed on all tested subjects younger than age 40 years and on a random 20% sample of subjects aged 40 to 49 years to assess indications for early testing.

Testing and referral practices and PSA diagnostic performance characteristics were analyzed with descrip-

tive statistics. Confidence intervals for binomial parameters were estimated using the normal theory method; the exact method was used for small sample sizes.¹¹ Associations between continuous variables and categorical variables were tested with analysis of variance (ANOVA) or Student's *t* test. Categorical data were compared with the χ^2 test. Linear regression analyses were used to test associations between continuous variables. The associations between age intervals and categorical follow-up outcomes were tested with χ^2 tests for slope and linearity.¹² A *p* value $< .05$ was considered statistically significant.

RESULTS

In 1993, 1,507 patients underwent PSA testing in primary care clinics; 59 were excluded from our analyses because of previously diagnosed prostate cancer—leaving 1,448 disease-free or undiagnosed subjects. Providers ordering PSA tests included 17 physician assistants, 14 attending physicians, and 70 medicine residents. According to DHCP enrollment data for the primary care clinics, approximately 21.0% (95% confidence interval [CI] 20.0%, 21.9%) of men older than 40 years were tested. Testing rates were highest for men in their 60s and 70s—28.4% (95% CI 26.4%, 30.3%) and 28.3% (95% CI 26.2%, 30.4%), respectively. Rates were 12.4% (95% CI 10.8%, 14.0%) for men in their 50s, but only 6.0% (95% CI 4.9%, 7.1%) for men younger than 50 years and 9.7% (95% CI 7.3%, 12.1%) for men 80 years or older. The median PSA value was 1.1 ng/mL, and values ranged from < 0.03 to 88.0 ng/mL. The mean age $\pm$ SD of tested subjects was 66 ± 9.3 years, ranging from 30 to 96 years. Age-specific median PSA values and testing frequencies are shown in Table 1; PSA values significantly increased with age, $p < .0001$. Based on chart review, none of the men younger than 40 years had any documented risk factors for prostate cancer. We randomly sampled 20 charts of men between 40 and 49 years. Only one man met criteria for early testing (family history); none were identified as African American.

The 1,448 subjects were tested 2,042 times during the study period, an average of 1.4 tests per person. By the end of the study period, 1,192 members of the cohort not diagnosed with cancer were still receiving care

Table 1. PSA Testing by Age

Age Range, Years	Patients, <i>n</i>	PSA Median (Range), ng/mL	Repeated Tests*		Repeated Tests < 6 Months*	
			<i>n</i>	% (95% CI)	<i>n</i>	% (95% CI)
< 40	5	1.0 (0.4, 1.4)	0	0 (0, 60.0)	0	0 (0, 60.0)
40–49	100	0.6 (0.06, 26.1)	31	40.8 (29.8, 51.8)	2	6.5 (0, 16.0)
50–59	201	0.6 (0.1, 48.2)	65	41.1 (33.4, 48.8)	13	20.0 (10.3, 29.7)
60–69	591	1.1 (0.05, 23.1)	210	42.1 (37.8, 46.4)	49	23.3 (17.3, 28.7)
70–79	496	1.6 (0.03, 37.0)	154	37.4 (32.7, 42.1)	49	31.8 (24.6, 39.4)
≥ 80	55	1.9 (0.2, 88.0)	17	38.6 (24.2, 53.0)	9	52.9 (29.3, 76.7)

*Denominator excludes cancer patients and patients no longer followed in the clinic.

through the Albuquerque VA Medical Center. A second test was ordered for 477 of these patients (40.0%; (95% CI 37.2%, 42.8%); 95 (8.0%; 95% CI 6.5%, 9.5%) were tested a third time, 16 (1.1%; 95% CI 0.5%, 1.7%) were tested a fourth time, and 1 subject was tested five times. Overall, the same provider ordered the initial and first repeated test for 401 patients. Repeated testing was more frequent in men with PSA values ≥ 4.0 ng/mL (56.1% vs 37.7%, $p < .0001$).

The median time to the first repeated test within the study period (after excluding four men receiving testosterone) was 317 days, and 122 of these tests (25.6%; 95% CI 21.7%, 29.5%) were repeated within 6 months. Only 14 of these repeated tests were ordered by a different provider. The rate of repeated testing within 6 months increased with age, $p = .008$ (Table 1). Early repeated testing was more frequent in men with PSA values ≥ 4.0 ng/mL (54.2% vs 19.5%, $p < .0001$), although 80 men with normal PSA values and no biopsies were retested within 6 months. Among the 32 men 75 years or older who underwent early repeated testing, 20 either had initial PSA values < 4.0 ng/mL or had not undergone biopsy. Overall, 23.7% of all repeated tests (95% CI 20.3%, 27.1%) were ordered within 6 months of a previous test. There were no significant differences between provider levels in the rate of early repeated PSA testing.

Table 2 shows the outcomes for the 193 men with initial PSA values ≥ 4.0 ng/mL; their mean age was 71 ± 6.8 years (range 46–94 years). Urology appointments were made for 166 patients (86.0%; 95% CI 81.1%, 90.9%), and kept by 145 patients (87.3% of scheduled; 95% CI 82.2%, 92.4%). Eighty-nine of the men keeping appointments underwent biopsy (61.4%; 95% CI 53.5%, 69.3%). Thirty-six cancers were detected—18.7% (95% CI 13.2%, 24.2%) of all men with PSA ≥ 4.0 ng/mL and 40.4% (95% CI 30.2%, 50.6%) of those biopsied.

Data were further stratified by PSA values. There were 157 men with PSA values between 4.0 and 9.9 ng/mL with a mean age of 71 ± 6.3 years (range 55–88 years). Urology appointments were scheduled for 130 (82.8%; 95% CI 76.9%, 88.7%), and kept by 116 (89.2% of scheduled; 95% CI 83.9%, 94.5%). Sixty-nine men underwent biopsy (59.5%; 95% CI 50.6%, 68.4%), and 26 can-

cers were detected. Cancer was diagnosed in 16.6% (95% CI 10.8%, 22.4%) of men with PSA values between 4.0 and 9.9 ng/mL, and 37.7% (95% CI 26.3%, 49.1%) of those who underwent biopsy. Thirty-six patients had PSA values ≥ 10 ng/mL with a mean age of 72 ± 8.9 years (range 46–94 years). All men were scheduled for urology appointments, and 29 (80.6%; 95% CI 67.7%, 93.5%) kept the appointment. Twenty (69.0%; 95% CI 52.2%, 85.8%) underwent biopsy, and 10 cancers were detected. Cancer was diagnosed in 27.7% (95% CI 13.1%, 42.3%) of men with PSA values ≥ 10 and 50.0% (95% CI 28.1%, 71.9%) of those who underwent biopsy.

Among patients with a PSA value ≥ 4.0 ng/mL, increasing age intervals were inversely and linearly associated with the proportion of men keeping urology appointments and undergoing biopsy (Table 2). Older men were significantly less likely to undergo biopsy ($p < .001$), and there was a trend for missing appointments ($p = .09$). Only 11 of the 51 men aged 75 years or older who were referred to urologists for an elevated PSA level underwent biopsy. Age was not related to appointment scheduling or cancer diagnosis. PSA values and provider level were not significant predictors for keeping appointments or undergoing biopsy, although we had limited power to detect differences between provider levels.

Overall, 40 cancers were diagnosed in the study subjects, a detection rate of 2.8% (95% CI 2.0%, 3.6%). Twenty-eight cancers were organ-confined, seven had regional invasion, and three had distant metastases. Data were unavailable for two cases. The four cancer cases with PSA values < 4.0 ng/mL all had abnormal digital rectal examinations and organ-confined cancers. Elevated PSA values did not discriminate organ-confined and extraprostatic cancers. Twenty-two of 28 patients with organ-confined cancers and 6 of 10 with extraprostatic cancers had PSA values < 10 ng/mL, $p = .23$. The mean PSA $\pm$ SD for organ-confined cancers was 9.7 ± 8.9 ng/mL, and for extraprostatic cancers, 11.7 ± 8.6 ng/mL, $p = .55$. Twelve men underwent radical prostatectomy, and 12 were treated with external beam radiation. By the end of 1995, there were five deaths, three from prostate cancer, including two men who had metastatic disease at the time of presentation.

Table 2. Outcomes for Patients with PSA ≥ 4 ng/mL

Age Range, Years	Patients, n	Urology Appointments Scheduled		Urology Appointments Kept		Biopsies		Cancers	
		n	% (95% CI)*	n	% (95% CI)*	n	% (95% CI)*	n	% (95% CI)*
<55	1	0	—	—	—	—	—	—	—
55–59	9	8	88.9 (51.8, 99.7)	8	100 (63.1, 100)	8	100 (63.1, 100)	1	12.5 (0.32, 48.3)
60–64	22	15	68.2 (45.1, 86.1)	15	100 (78.2, 100)	14	93.3 (68.1, 99.8)	4	28.6 (8.4, 58.1)
65–69	40	32	80.0 (64.4, 91.0)	31	96.9 (83.8, 99.2)	26	83.9 (66.3, 94.6)	9	34.6 (17.2, 55.7)
70–74	63	59	93.7 (84.5, 98.2)	50	84.8 (73.0, 92.8)	31	62.0 (47.2, 75.4)	17	54.8 (36.0, 72.7)
75–79	45	38	84.4 (70.5, 93.5)	31	81.6 (65.7, 92.3)	9	29.0 (14.2, 48.0)	4	44.4 (13.7, 78.8)
≥ 80	13	13	100 (75.3, 100)	10	76.9 (46.2, 95.0)	2	20 (2.5, 55.6)	1	50 (1.3, 98.7)

*Percentage based on previous column.

Even though our laboratory used a cutoff of 4.0 ng/mL to define abnormal results, we reanalyzed our data to determine whether providers were using age-specific PSA reference ranges to guide referrals and biopsies.¹³ None of the men aged 40 to 49 years with PSA values between 2.5 and 4.0 ng/mL ($n = 3$), nor any of the men aged 50 to 59 years with PSA values between 3.5 and 4.0 ng/mL ($n = 4$) were referred to the urology clinic. Men aged 60 to 69 years underwent biopsy at nearly identical rates whether their PSA was less than (88.9%) or greater than (86.1%) the recommended age-specific cutoff of 4.5 ng/mL, $p = .8$. Results were similar in men aged 70 years and older; biopsy rates were 37% for PSA values below the 6.5 ng/mL cutoff and 46.9% above the cutoff, $p = .7$.

DISCUSSION

Using a VA computerized database, we found that primary care practitioners frequently ordered PSA tests to detect prostate cancer, although testing rates were quite low for men in their 50s. Testing practices varied considerably from published guidelines. A substantial proportion of testing occurred outside recommended upper and lower age limits, and the recommendation for annual testing^{5,6} was not closely followed. Less than half of the men tested in 1993 were retested by the end of 1994, but 23.7% (95% CI 20.3%, 27.1%) of repeated tests occurred within 6 months of a previous test. Practitioners consistently referred patients with PSA values ≥ 4 ng/mL to urologists, although older men were less likely to complete workups. The overall cancer detection rate in our cohort was 2.8% (95% CI 2.0%, 3.6%), and 90% (95% CI 76.3%, 97.2%) of cancers were found in men with PSA values ≥ 4.0 ng/mL. Seventy percent (95% CI 53.5%, 83.4%) of the cancers were organ-confined, and most of these patients underwent curative treatment.

The overall PSA testing rate of approximately 21% in the Albuquerque VA Medical Center primary care clinic was similar to the 18% rate for Medicare beneficiaries in four SEER sites,¹⁴ and the 25% rate reported for 58 community-based primary care practices in Virginia.¹⁵ A study from Olmsted County, Minnesota, however, reported substantially higher rates, ranging from 14% in men aged 50 to 54 years to 47% in men aged 80 to 84 years.¹⁶ These higher rates were attributed to the large proportion of the study population employed in health care. The actual testing rate among eligible VA subjects could be much higher because many veterans have serious comorbidity that precludes screening efforts.

Routine testing in men older than 75 years is not recommended by any guideline, although we found 214 tested patients in this age range, accounting for 16.0% (95% CI 14.4%, 17.6%) of all tests. Furthermore, testing between the ages of 40 and 49 is recommended only for African Americans or when a first-degree relative has prostate cancer.^{5,6} Chart reviews, however, indicated an appropriate indication for testing in only 5% of these

younger men. The high rate of retesting within 6 months is not supported by any practice guideline although some experts recommend early retesting following a negative biopsy if the PSA value is > 10.0 ng/mL.¹⁷ In our cohort, most of the patients being retested within 6 months had normal PSA values and no previous biopsy.

The failure of older men to undergo biopsy may reflect either patient reluctance or a conservative approach by the urologists. A recent national survey of 444 primary care physicians and 394 urologists favored the latter explanation.¹⁸ Barry et al. found that primary care physicians were more inclined than urologists to pursue screening diagnoses of prostate cancer in older men. Only 25% of urologists recommended performing PSA tests at least half of the time for men older than 79 years, while 73% of primary care physicians reported frequent testing in this age group. Most urologists were reluctant to biopsy men older than 74 years and felt that PSA tests were overused for older men.

The positive predictive value for PSA ≥ 4.0 ng/mL was 38% among those undergoing biopsy, comparable to values reported in the literature.¹⁹⁻²³ Catalona et al. reported a slightly higher cancer detection rate (3.1%) than we found, but that study enrolled volunteers who had a 95% biopsy rate.²⁴ Our cancer detection rate and positive predictive value for PSA probably would have been greater if the older patients, who were more likely to have cancer, underwent biopsy at a higher rate. Most cancers were organ-confined, but PSA values did not discriminate between organ-confined and extraprostatic cancers.

Our study results may have been biased by using only a VA database. Even though a patient was enrolled in a VA clinic, he may have undergone PSA testing or biopsy at another institution. This could lead to underestimating age-specific screening rates and appointment and biopsy rates for elevated PSA values. However, any patient diagnosed with cancer in the state of New Mexico would be identified as a case by the NMTR. We found that 34 of the 36 men with prostate cancer and a PSA ≥ 4.0 ng/mL had undergone their biopsy at the VA hospital. This suggests that men with elevated PSA values were not likely to go outside the VA system for further evaluation, and that appointment and biopsy rates were reasonably accurate. Another limitation of using the database was the lack of information on indications for PSA testing, including symptoms and digital rectal examination findings. Consequently, we were unable to determine the rate of testing in asymptomatic men (screening). We were also unable to determine the indications for urology referrals. However, none of the 49 unbiopsied men 70 years or older with PSA ≥ 4.0 ng/mL (42 underwent biopsy) were empirically treated for prostate cancer with gonadotropin-releasing hormone agonists, antiandrogens, or orchiectomy. Eighteen patients were medically treated with α blockers or finasteride or both, but none underwent transurethral resection of the prostate. This suggests that a third of these older patients were not referred for markedly abnormal

digital rectal examinations or symptoms, and that PSA testing was being used for screening. Finally, our results may not be generalizable to non-VA clinics, although PSA predictive values and cancer detection rates were consistent with results from community-based studies.¹⁹⁻²²

In summary, the testing practices of hospital-based primary care practitioners were frequently at odds with the guidelines supporting screening. The variations from the guidelines were generally unproductive for patients and for the health care system. Although testing older men often led to urology referrals, many of these appointments were missed. The financial costs of testing and referring patients are not inconsequential, and false-positive tests, which occur frequently in older men, can cause considerable anxiety and confusion. Repeated testing at short intervals and testing younger men without risk factors are inappropriate uses of resources. In our cohort, only 1 of the 201 patients younger than 55 even had a PSA > 4.0 ng/mL, and none were referred to urology. If primary care providers are going to test for prostate cancer, following published guidelines for PSA testing may lead to a more cost-effective approach to screening by limiting the number of PSA tests and subsequent urology referrals.

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