BRIEF REPORT: Free Prostate-Specific Antigen Test Utilization

Consistency with Guidelines

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BACKGROUND: The American Cancer Society and American Urologic Association recommend prostate cancer screening for average-risk men between the ages of 50 and 75 years using digital rectal examination and prostate-specific antigen (PSA) testing. Measuring the percent free PSA may improve test specificity for detecting prostate cancer when the total PSA is between 2.5 and 10 ng/mL.

OBJECTIVE: To assess whether free PSA testing practices are consistent with published screening guidelines.

DESIGN: Retrospective analysis of free PSA testing performed by a national reference laboratory between October 1, 2003 and September 30, 2004.

MEASUREMENTS: Free PSA and total PSA results and the age of the patient at testing.

RESULTS: Over 24% of free PSA tests were performed on patients greater than 75 years of age, and 38% were performed on patients with a total PSA either less than 2.5 ng/mL or greater than 10.0 ng/mL.

CONCLUSIONS: A substantial proportion of free PSA tests performed in a national reference laboratory appeared to be inconsistent with existing screening guidelines. This raises concern that some of these patients may have received inappropriate diagnostic workup and/or therapy, resulting in excess medical costs and potential harms.

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Despite controversy about its benefits, prostate cancer screening is widely performed in the U.S.^{1,2} According to guidelines from both the American Cancer Society (ACS)³ and the American Urologic Association (AUA),⁴ screening should begin at age 50 for average risk men and stop when life expectancy is less than 10 years (age 75 by actuarial tables). Screening should include digital rectal examination (DRE) and measurement of total prostate-specific antigen (PSA). If the DRE is abnormal or the PSA result is greater than 10.0 ng/mL then the patient should be referred for a prostate biopsy; if the result is less than 4.0 ng/mL (or less than 2.5 ng/mL, depending on preference) and the DRE is normal then the patient can resume routine screening. However, for patients with total PSA results between 4.0 and 10.0 ng/mL (or between 2.5 and 10.0 ng/mL if the lower cutoff is chosen), free PSA measurements may be used to improve specificity,⁵ with biopsy restricted to patients whose percent free PSA is below some cutoff (20% in the case of the ACS guideline).

Previous studies based on both chart review^{6,7} and national surveys⁸ have demonstrated that the use of total PSA for prostate cancer screening often does not conform to estab-

lished guidelines. Despite the guidelines that recommend screening only those patients with at least a 10-year life expectancy, numerous studies have shown that a large proportion of the patients undergoing screening are older than 75 years.^{1,2,6–8}

Guidelines support free PSA testing to improve the specificity of intermediate-level total PSA results. However, little information is available about how clinicians actually utilize free PSA testing. The purpose of our study was to use data from a national reference laboratory to examine whether free PSA testing practices are consistent with published guidelines.

METHODS

Associated Regional and University Pathologists (ARUP) is a reference laboratory owned by the University of Utah that serves several hundred hospitals nationwide. Associated Regional and University Pathologists has access to a large volume of laboratory data but only limited demographic data—such as age at testing—and no clinical data. We studied free PSA as opposed to total PSA with ARUP data because free PSA measurements are intended specifically for screening settings, whereas total PSA is used for detecting recurrence and monitoring disease as well as in screening. We could thus make a reasonable assumption about the clinical indication for the free PSA tests even in the absence of linked clinical data.

We obtained the results of all free PSA tests performed at ARUP between October 1, 2003 and September 30, 2004. For each free PSA order, both a free PSA and a total PSA were performed in order to calculate the percent free PSA. Our laboratory offers the option of ordering free PSA as a “reflex” test whereby the total PSA is performed first, and if that result is in the appropriate range, a free PSA test is automatically performed. Reflex tests account for less than 1% of free PSA tests performed at our laboratory and were excluded from this analysis. We report the distribution of the associated total PSA results and patient age at testing for the free PSA tests. The study was performed on fully deidentified data and was approved by the University of Utah Institutional Review Board.

RESULTS

From October 1, 2003 to September 30, 2004, we performed 40,618 free PSA assays. The distribution of free PSA tests according to total PSA result and patient age at testing is shown in Table 1. Overall, 38% of tests were performed when the total PSA was outside the range of 2.5 to 10.0 ng/mL, and 19% were performed when the total PSA was outside the range of 1.0 to 15.0 ng/mL. The median age of tested subjects was 68 years, and 24% of tests were performed for patients older than 75 years.

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Table 1. Distribution of Specimens Submitted for Free PSA Testing According to Patient Age at Testing and Total PSA Result

Age at Testing (years)	Total PSA Levels (ng/mL)					All results (%)
	≤ 1.0 (%)	1.1 to 2.4 (%)	2.5 to 3.9 (%)	4.0 to 10.0 (%)	> 10 (%)	
≤ 50	3.1	1.2	0.6	0.7	0.2	5.7
51 to 60	4.4	3.5	4.0	7.5	0.9	20.3
61 to 65	2.0	2.1	3.0	7.4	1.1	15.7
66 to 70	2.0	2.1	3.4	9.0	1.5	18.0
71 to 75	1.7	1.8	2.8	8.3	1.7	16.3
76 to 80	1.5	1.3	2.2	6.6	1.4	12.9
> 80	1.6	1.2	1.5	5.1	1.9	11.2
All ages	16.2	13.2	17.3	44.6	8.7	100.0

PSA, prostate-specific antigen.

DISCUSSION

We found a substantial proportion of free PSA testing occurring outside of the indicated total PSA range and in patients older than 75 years. The rationale for including free PSA testing within prostate cancer screening algorithms is that both sensitivity and specificity of cutoffs based on total PSA alone are poor within the range of 2.5 to 10 µg/L, levels at which most treatable cancers are detected.^{5,9} Restricting biopsy in this setting to patients with a percent free PSA of less than 20% modestly improves specificity without greatly sacrificing sensitivity,⁵ and thus prevents unnecessary biopsies. Some investigators have advocated using free PSA in patients with total PSA as low as 2.0,^{10,11} but others have found that the discriminatory power of free PSA is extremely poor in patients with total PSA less than 4.0.⁹ The 16% of free PSA testing that occurred when total PSA was less than 1.0 ng/mL is clearly unsupported by the medical literature. For patients with total PSA greater than 10.0 ng/mL, free PSA is unnecessary because the positive predictive value is already quite high.¹² Nonetheless, nearly 9% of free PSA testing occurred when total PSA levels were above 10.0 ng/mL. Additionally, about 24% of free PSA testing occurred in men older than age 75, including 7% in men older than 80.

Because inappropriate laboratory tests do not inflict direct harm in the same fashion as inappropriate medications or surgical procedures, it is tempting to dismiss laboratory testing as a contributor to patient harm. However, doing so ignores the fact that laboratory testing is a major driver of clinical decisions regarding medications and procedures. Prostate cancer screening on men with less than 10 years of life expectancy may lead to unnecessary biopsies and treatment, with attendant morbidity⁸ and mortality. Free PSA results on patients with total PSA less than 2.5 ng/mL may in some cases influence physicians to perform unnecessary biopsies. Conversely, free PSA results on patients with total PSA greater than 10.0 ng/mL may in some cases influence physicians to inappropriately forego biopsy.

The cost implications of misuse are also substantial. Assuming that approximately 40% of free PSA tests are ordered unnecessarily, then this represents between \$500,000 and \$1 million in excess phlebotomy and testing costs just for tests performed at our laboratory. The non-laboratory cost implications are at least as great. If 10% of these inappropriate tests led to an unnecessary workup including biopsy, then that would add approximately \$1 million,¹³ not including the costs of treatment or complications of treatment. As our laboratory represents only a small fraction of all free PSA testing in the

United States, the national financial impact is many times larger.

Our results have some potential limitations. We assumed that each free PSA order represented a follow-up to a recently performed total PSA test. Because of in vivo fluctuations in total PSA levels, it is possible that some patients may have had a total PSA between 2.5 and 10.0 ng/mL to trigger the free PSA test, yet had a total PSA outside this range upon retesting at ARUP. However, this likely represents a small proportion of the total orders. For a hypothetical population of patients with total PSA uniformly distributed over the range of 2.5 to 10.0 ng/mL, and assuming short-term variation in total PSA levels to be normally distributed with a 15% biologic coefficient of variation,¹⁴ then approximately 10% of these patients' subsequent total PSA results will be outside the range of 2.5 to 10.0 ng/mL, and less than 1% will be outside the range of 1.0 to 15.0 ng/mL. These theoretic proportions are much lower than the observed proportions of 38% and 19%, respectively.

Another limitation to this study is the inability to link results to other clinical data. For example, it is possible that some of the tests were erroneously ordered in place of total PSA for monitoring patients with known prostate cancer. Similarly, some may have been ordered as part of a diagnostic workup on a suspected cancer. Using this deidentified data set we are unable to determine the rate of repeat testing on a single patient, the time intervals between prior PSA tests and the free PSA test on each patient, or the type of provider (e.g., family practitioner, urologist, etc.) ordering the test. We also were unable to accurately determine the facility that ordered the test and cannot compare testing practices across different clinical settings.

Overall, our findings suggest that a substantial portion of prostate cancer screening in this country is at variance with the major published guidelines. Some patients may receive suboptimal care as a result. Health care organizations need better mechanisms to reinforce adherence to cancer screening guidelines, and such mechanisms need to go beyond simply monitoring the proportion of patients screened.

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REFERENCES

1. Sirovich BE, Schwartz LM, Woloshin S. Screening men for prostate and colorectal cancer in the United States: does practice reflect the evidence? *JAMA*. 2003;289:1414–20.

2. **Ross LE, Coates RJ, Breen N, Uhler RJ, Potosky AL, Blackman D.** Prostate-specific antigen test use reported in the 2000 National Health Interview Survey. *Prev Med.* 2004;38:732–44.
3. **Smith RA, von Eschenbach AC, Wender R, et al.** American Cancer Society guidelines for the early detection of cancer: update of early detection guidelines for prostate, colorectal, and endometrial cancers. *CA Cancer J Clin.* 2001;51:38–75.
4. **Carroll P, Coley C, McLeod D, et al.** Prostate-specific antigen best practice policy—part I: early detection and diagnosis of prostate cancer. *Urology.* 2001;57:217–24.
5. **Catalona WJ, Partin AW, Slawin KM, et al.** Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease. *JAMA.* 1998;279:1542–7.
6. **Hoffman RM, Blume P, Gilliland F.** Prostate-specific antigen testing practices and outcomes. *J Gen Intern Med.* 1998;13:106–10.
7. **Poteat HT, Chen P, Loughlin KR, et al.** Appropriateness of prostate-specific antigen testing. *Clin Chem.* 2000;113:421–8.
8. **Lu-Yao G, Stukel TA, Yao SL.** Prostate-specific antigen screening in elderly men. *J Natl Cancer Inst.* 2003;95:1792–7.
9. **Hoffman RM, Clanon DL, Littenberg B, Frank JJ, Peirce JC.** Using the free-to-total prostate-specific antigen ratio to detect prostate cancer in men with nonspecific elevations of prostate-specific antigen levels. *J Gen Intern Med.* 2000;15:739–48.
10. **Gann PH, Hennekens CH, Stampfer MJ.** A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. *JAMA.* 1995;273:289–94.
11. **Vashi AR, Oesterling JE.** Percent free prostate-specific antigen: entering a new era in the detection of prostate cancer. *Mayo Clin Proc.* 1997;72:337–44.
12. **Catalona WJ, Richie JP, Ahmann FR, et al.** Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. *J Urol.* 1994;151:1283–90.
13. **Coley CM, Barry MJ, Fleming C, Fahs MC, Mulley AG.** Early detection of prostate cancer. Part II: estimating the risks, benefits, and costs. *Ann Intern Med.* 1997;126:468–79.
14. **Ornstein DK, Smith DS, Rao GS, Basler JW, Watliff TL, Catalona WJ.** Biological variation of total, free and percent free serum prostate-specific antigen levels in screening volunteers. *J Urol.* 1997;157:2179–82.