

**SB**

**253**

No. 1

Bill Version: SB 253

(S) Publish Date: 3-14-96

# FISCAL NOTE

## STATE OF ALASKA 1996 LEGISLATIVE SESSION

Revision Date: \_\_\_\_\_ Department: Commerce and Economic Development  
 Title: Insurance for Prostate Cancor Testing BRU: Insurance  
 Component: Operations  
 Sponsor: Senator Duncan  
 Requestor: Labor & Commerce Committee COMPONENT SERIAL NO. #354

Expenditures/Revenues (Thousands of Dollars)

	FY 97	FY 98	FY 99	FY 00	FY 01	FY 02
<b>OPERATING EXPENDITURES</b>						
PERSONAL SERVICES						
TRAVEL						
CONTRACTUAL						
SUPPLIES						
EQUIPMENT						
LAND & STRUCTURES						
GRANTS, CLAIMS						
MISCELLANEOUS						
<b>TOTAL OPERATING</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>

<b>CAPITAL EXPENDITURES</b>						
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<b>CHANGE IN REVENUES</b>						
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FUND SOURCE (Thousands of Dollars)

	FY 97	FY 98	FY 99	FY 00	FY 01	FY 02
1002 Federal Receipts						
1003 GF Match						
1004 General Fund						
1005 GF/Program Receipts						
1006 GF/MHTIA						
Other						
<b>TOTAL</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>

Estimate of any current year (FY 96) cost: \$ 0.0

POSITIONS

	FY 97	FY 98	FY 99	FY 00	FY 01	FY 02
FULL-TIME	0	0	0	0	0	0
PART-TIME						
TEMPORARY						

ANALYSIS: (Attach a separate page if necessary)  
 No fiscal impact.

Prepared by: Joan Brown, Administrative Officer *[Signature]* Phone: 465-2597  
 Division: Insurance Date: 2/9/96  
 Approved by Commissioner: William L. Hensley *[Signature]* Date: 2-13-96  
 Agency: Commerce and Economic Development

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ZERO FISCAL - COMM. & ECON. DEV. - INSURANCE - OPERATIONS

# FISCAL NOTE

No. CS 88253(FIN)

STATE OF ALASKA  
996 LEGISLATIVE SESSION

Version: CS 88253(FIN)  
(S) Publish Date: 4-3-96

Revision Date: \_\_\_\_\_  
Title: An Act relating to insurance coverage for costs of prostate cancer detection.  
Sponsor: Duncan  
Requestor: (S) FEN

Department Affected: All Agencies  
BRU: All Agencies  
Component: All Agencies

COMPONENT SERIAL NO. 64

**Expenditures/Revenues:**

(Thousands of Dollars)

OPERATING EXPENDITURES	FY 97	FY 98	FY 99	FY 00	FY 01	FY 02
PERSONAL SERVICES	0.0	0.0	0.0	0.0	0.0	0.0
TRAVEL						
CONTRACTUAL						
SUPPLIES						
EQUIPMENT						
LAND & STRUCTURES						
GRANTS, CLAIMS						
MISCELLANEOUS						
<b>TOTAL OPERATING</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>

CAPITAL EXPENDITURES	0.0	0.0	0.0	0.0	0.0	0.0
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CHANGE IN REVENUES ( )	0.0	0.0	0.0	0.0	0.0	0.0
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**FUND SOURCE:**

(Thousands of Dollars)

1002 Federal Receipts	0.0	0.0	0.0	0.0	0.0	0.0
1003 GF Match						
1004 GF						
1005 GF/Program Receipts						
1037 GF/Mental Health						
OTHER						
<b>TOTAL</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>

Estimate of any current year (FY 96) cost: \$ zero

**POSITIONS:**

FULL-TIME	0	0	0	0	0	0
PART-TIME						
TEMPORARY						

**ANALYSIS:** (Attach a separate page if necessary.)

Currently the State's plan pays for the Prostate Specific Antigen (PSA) test only when there are clinical signs or symptoms of prostate disease. This bill would expand health coverage to include routine prostate cancer screening. The State's health insurance premiums are based on the experience of the plan. We anticipate an increase in health costs of approximately \$60,000 per year.

This bill also mandates the coverage of PAP tests. These tests are already covered under the State's plan; therefore, there will be no increased cost for that coverage.

Prepared by: Robert F. Stalnaker  
Division: Retirement & Benefits

Phone: 465-4470  
Date: \_\_\_\_\_

Approved by Commissioner: Mark Boyer  
Agency: Department of Administration

Date: 4/2/96

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HOUSE COMMITTEE REPORT

(7)

Date Referred to Committee: April 15, 1996

FURTHER REFERRALS: Labor and Commerce  
State Affairs

Date of Committee Action: 4/25/96

The HEALTH, EDUCATION AND SOCIAL SERVICES Committee considered:

CSSB 253(FIN)

CS FOR SENATE BILL NO. 253(FIN)

INS.FOR PROSTATE & CERVICAL CANCER TESTS

"An Act relating to insurance coverage for costs of prostate cancer or cervical cancer detection."

recommends it be replaced with the following committee substitute HCS CS SB 253 (HES)  the same title  a new title

additional referral to \_\_\_\_\_ Committee  
 attached amendment(s)

ADOPTS: \_\_\_\_\_ Letter of Intent

ATTACHES NEW FISCAL NOTE(S): (Dept) \_\_\_\_\_

APPROVES PREVIOUS: (Dept/Date) \_\_\_\_\_

fiscal note(s) \_\_\_\_\_

fiscal note(s) \_\_\_\_\_

zero fiscal note(s) \_\_\_\_\_

zero fiscal note(s) CED/3-14-96 (2)  
All Agencies/4-3-96

SIGNING WITH RECOMMENDATIONS	DP	DNP	NR	AM
<i>[Signature]</i>			<input checked="" type="checkbox"/>	
<i>[Signature]</i>	<input checked="" type="checkbox"/>			
<i>[Signature]</i>	<input checked="" type="checkbox"/>			
<i>[Signature]</i>			<input checked="" type="checkbox"/>	
<i>[Signature]</i>				<input checked="" type="checkbox"/>

CHAIR'S SIGNATURE *[Signature]*

HOUSE CS FOR CS FOR SENATE BILL NO. 253(HES)

IN THE LEGISLATURE OF THE STATE OF ALASKA

NINETEENTH LEGISLATURE - SECOND SESSION

BY THE HOUSE HEALTH, EDUCATION AND SOCIAL SERVICES COMMITTEE

Offered:  
Referred:

Sponsor(s): SENATORS DUNCAN, Ellis, Salo, Zharoff, Lincoln, Kelly

REPRESENTATIVES Robinson, Kubina, Navarre

A BILL

FOR AN ACT ENTITLED

1 "An Act relating to insurance coverage for costs of prostate cancer or cervical  
2 cancer detection."

3 BE IT ENACTED BY THE LEGISLATURE OF THE STATE OF ALASKA:

4 \* Section 1. AS 21.42 is amended by adding a new section to read:

5       Sec. 21.42.395. COVERAGE FOR PROSTATE AND CERVICAL CANCER  
6 DETECTION. (a) An insurer authorized under AS 21.09 to offer, issue for delivery,  
7 deliver, or renew an individual or group disability insurance policy for medical  
8 coverage on an expense incurred basis in the state, a hospital or medical service  
9 corporation authorized under AS 21.87 to offer or renew a subscriber's contract for  
10 medical coverage in the state, or a health maintenance organization authorized under  
11 AS 21.86 to offer an enrollee contract to provide health care services on a prepaid  
12 basis shall offer coverage for the costs of prostate cancer screening tests as required  
13 under the schedule described under (b) of this section, and shall offer coverage for the  
14 costs of cervical cancer screening tests as required under (c) of this section. The

1 coverage required to be offered by this section is subject to standard policy provisions  
2 applicable to other benefits including deductible or copayment provisions. If a  
3 physician recommends that an insured, subscriber, or enrollee undergo prostate cancer  
4 screening by taking a prostate antigen blood test, coverage may not be denied because  
5 the insured, subscriber, or enrollee has already had a digital rectal exam and the exam  
6 results were negative.

7 (b) The minimum coverage required to be offered under (a) of this section  
8 includes an annual prostate cancer screening test for a person who is

9 (1) at least 40 years of age but less than 50 years of age and the person  
10 is in a high risk group; in this paragraph, "high risk" means a person who is an  
11 African-American or who has a family history of prostate cancer; or

12 (2) 50 or more years of age.

13 (c) The minimum coverage required to be offered under (a) of this section for  
14 cervical cancer screening is an annual pap smear cancer screening test for a person  
15 who is 18 or more years of age.

16 (d) This section does not apply to a supplemental insurance contract covering  
17 a specified disease or offering limited benefits.

18 (e) In this section, "prostate cancer screening tests" includes a prostate antigen  
19 blood test or another test that is equivalent or better in cancer detection.

20 \* Sec. 2. This Act applies to a policy of insurance entered into or renewed or, or after the  
21 effective date of this Act.



**SENATOR JIM DUNCAN**  
*ALASKA STATE LEGISLATURE*

Alaska State Senate

State Capitol • Room 119 • Juneau, Alaska 99801-1182 • (907) 465-4766 • Fax 465-4748

*Memorandum*

**Date:** April 16, 1996

**To:** Representative Con Bunde, Co-Chair  
Representative Cynthia Toohey, Co-Chair  
House Health, Education & Social Services Committee

**From:** Senator Jim Duncan

**Subject:** SB 253, An Act relating to insurance coverage for costs of prostate cancer or cervical cancer detection.

I request that you schedule SB 253, relating to insurance coverage for costs of prostate cancer or cervical cancer detection, for a hearing in the House Health, Education & Social Services Committee as soon as possible.

Prostate cancer is a serious health concern to men over the age of fifty. Prostate Specific Antigen (PSA) blood tests can be done to detect the presence of cancer and alert men of potential health problems. Currently, insurance companies are not required by Alaska law to include this test in their coverage package. SB 253 will require that insurance companies cover the PSA on annual physical exams when appropriate.

The importance of screening for malignant cancer is well documented. Prostate cancer accounts for 36% of all male cancers and is the second leading cause of death in men after lung cancer as reported by the National Cancer Institute. Although often presumed to develop slowly, nearly two thirds of new cancer cases have spread beyond the prostate gland by the time of diagnosis.

In addition to coverage of the PSA, SB 253 would require coverage of cervical cancer screening. Early detection of cervical cancer involves the Pap Smear, a test that takes a small sample of cervical cells. The American Cancer Society recommends that all women who are sexually active or over the age

REQUEST FOR HEARING

of eighteen should have a Pap test each year. About 90% of cervical cancer cases can be detected early through the use of Pap smears. If discovered early, cervical cancer is almost 100% curable.

SB 253 makes health issues a priority. I would welcome your support in requiring that insurance companies cover the cost of prostate and cervical cancer screening and request that you schedule this bill for a hearing in the House Health, Education & Social Services Committee as soon as possible.

Attachments

## New Cancer Test For the Prostate Appears Promising

By RIM WINSZUK

Staff Reporter of THE WALL STREET JOURNAL

Medical researchers said a new version of a widely used screening test for prostate cancer appears to improve its accuracy in detecting the disease.

If the results are borne out in further studies, the test may yield fewer false positive readings for cancer and thus reduce by 31% to 76% the number of men who undergo unnecessary biopsies and other examinations to confirm whether they have cancer.

Use of the current test, known as PSA, for prostate-specific antigen, has increased among men over 50. But it also has provoked controversy in part because only one in three men who have positive readings turns out to have cancer. That means the tests cause two out of three to undergo unnecessary and sometimes painful biopsies and other tests.

The high rate of false positive results occurs because PSA is also elevated in older men with a common noncancerous condition called benign prostatic hyperplasia.

The new test measures two forms of PSA, one that binds to certain blood proteins and another that is free-floating in the blood stream. For reasons not understood, men with prostate cancer have significantly lower levels of free PSA than men with BPH, said William J. Catalona, chief of urologic surgery at Washington University School of Medicine, St. Louis, and lead author of the study. As a result, the study indicated, the new test can better distinguish between men with prostate cancer and those with BPH.

In the study, published in today's Journal of the American Medical Association, researchers used frozen blood samples taken from 113 men over 50 whose original readings were between four and 10. Among those, who had also undergone biopsies and rectal exams, 63 had been diagnosed with BPH and 50 had prostate cancer.

In general, researchers found that men whose free-floating PSA was significantly below 20% of their total PSA levels were more likely to have cancer than those with free PSA levels above 20%.

The study found that the free PSA test would have eliminated 76% of unnecessary biopsies among men who didn't have BPH and 38% of the biopsies among those with the benign condition. In a third group, who had BPH and no cancerous symptoms when doctors felt the prostate during a rectal exam, the free PSA test would have eliminated 31% of unnecessary biopsies.

Dr. Catalona said a new national trial to involve 12,000 patients at eight medical centers around the U.S. has been launched in an effort to verify the results.

— included in this  
packet of articles  
see JAMA. Oct. 18.

# Evaluation of Percentage of Free Serum Prostate-Specific Antigen to Improve Specificity of Prostate Cancer Screening

William J. Catalona, MD; Deborah S. Smith, PhD; Robert L. Wolfert, PhD; Tang J. Wang, PhD;  
Harry G. Rittenhouse, PhD; Timothy L. Ratliff, PhD; Robert B. Nadler, MD

**Objective.**—To evaluate measurement of percentage of free prostate-specific antigen (PSA) in serum to improve the specificity of prostate cancer screening in men with serum PSA levels between 4.1 and 10.0 ng/mL.

**Design.**—Retrospective, nonrandomized analysis using a research assay for measuring free PSA in frozen serum from men with a spectrum of prostate sizes and digital rectal examination results.

**Setting.**—General community outpatient prostate cancer screening program at a university center.

**Patients.**—One hundred thirteen men aged 50 years or older, 99% of whom were white, with serum PSA concentrations of 4.1 to 10.0 ng/mL, including 63 men with histologically confirmed benign prostatic hyperplasia, 30 with prostate cancer with an enlarged gland, and 20 with cancer with a normal-sized gland. All study volunteers had undergone prostatic ultrasonography and biopsy.

**Main Outcome Measures.**—Percentage of free PSA in serum and percentage of free PSA cutoff that maintained at least 90% sensitivity for prostate cancer detection.

**Results.**—Median percentage of free PSA was 9.2% in men with cancer and a normal-sized gland, 15.9% in men with cancer and an enlarged gland, and 18.8% in men with benign prostatic hyperplasia ( $P<.001$ ). The percentage of free PSA cutoff was higher in men with an enlarged gland and in those with a palpably benign gland. In men with an enlarged, palpably benign gland, a free PSA cutoff of 23.4% or lower detected at least 90% of cancers and would have eliminated 31.3% of negative biopsies.

**Conclusions.**—Measurement of percentage of free serum PSA improves specificity of prostate cancer screening in selected men with elevated total serum PSA levels and can reduce unnecessary prostate biopsies with minimal effects on the cancer detection rate; however, further studies are needed to define optimal cutoffs. Final evaluation of PSA screening also must consider the ability of current treatments to improve the prognosis of screen-detected prostate cancer.

(*JAMA*. 1995;274:1214-1220)

From the Division of Urologic Surgery, Department of Surgery, Washington University School of Medicine, St. Louis, Mo (Drs Catalona, Smith, Ratliff, and Nadler), and Department of Research and Development, Myriadtech Incorporated, San Diego, Calif (Drs Wolfert, Wang, and Rittenhouse).

Reprint requests to Division of Urologic Surgery, 4960 Children's Pl, St. Louis, MO 63110 (Dr Catalona).

MEASUREMENT of serum prostate-specific antigen (PSA) concentrations is widely used as an aid in the early detection of prostate cancer.<sup>1</sup> Although concern has been expressed that screening with PSA may detect insignificant can-

cer, this has not been borne out. The large majority of cancers detected have the pathological features of progressive cancers.<sup>1,2</sup> Recent studies using frozen serum samples from more than a decade ago have shown that men who developed prostate cancer 5 to 10 years after their serum was drawn could have been identified with high accuracy based on their initial serum PSA levels.<sup>3,7</sup>

In screening studies, most men with elevated serum PSA concentrations have PSA levels in the 4.1 to 10.0 ng/mL range, and many have enlarged, palpably benign prostate glands on digital rectal examination. Overall, only one quarter of these men have cancer detected by an initial prostatic needle biopsy.<sup>1,2</sup> However, rebiopsy of these patients within 6 to 12 months shows that the initial biopsy missed cancers and that closer to one third of patients in this group actually had prostate cancer.<sup>8</sup> Most prostate cancer patients with slightly elevated PSA concentrations have early-stage disease, whereas more than half of patients with PSA concentrations higher than 10.0 ng/mL have advanced disease.<sup>1,2</sup> Thus, the detection of prostate cancer in its curable stages requires the use of relatively low PSA cutoffs (4.0 ng/mL) for screening. Unfortunately, the use of low PSA cutoffs produces high false-positive rates, leading to unnecessary biopsies (ie, negative for cancer). The most common causes of false-positive PSA elevations are benign prostatic hyperplasia and prostatitis.<sup>9</sup> One potential way of reducing false-positive results is measurement of the free and bound forms of PSA in serum.<sup>10-12</sup>

rostate-specific antigen in serum is found predominantly to the protease inhibitors  $\alpha_1$ -antichymotrypsin (PSA-T) and  $\alpha_2$ -macroglobulin (PSA-AMG); free PSA also binds in trace amounts to  $\alpha_1$ -antitrypsin and inter-alpha trypsin inhibitor.<sup>10-12</sup> Most complexed PSA is used in commercial immunoassays such as PSA-CT. Virtually all of the remaining PSA in serum is in the free form. Failure to detect PSA-AMG is due to the concealment of the relevant antigenic epitopes.<sup>11,13</sup>

Experimental immunoassays have been developed for separate measurement of free PSA and PSA-CT. Preliminary evidence in heterogeneous patient populations suggests that (for unknown reasons) the proportion of free PSA is lower with prostate cancer than in benign prostatic hyperplasia, and that measurements of PSA forms could help distinguish between hyperplasia and cancer.<sup>6,11-13</sup>

In the current study, we examined the usefulness of free PSA measurements in men with serum PSA concentrations of 4.1 to 10.0 ng/mL. We also evaluated the free PSA cutoffs needed to maintain at least 90% sensitivity in detecting cancer in subsets of men with different ultrasonographically measured prostate sizes and findings on digital rectal examination.

## METHODS

### Subjects and Procedures

From July 1989 through March 1995, we measured total serum PSA levels in 249 ambulatory men aged 50 years or older (range, 50 to 90 years; mean ( $\pm$ SD) age, 62.7 ( $\pm$ 6.9) years).<sup>2,14</sup> These men responded to a press release asking healthy men to participate in a study of PSA measurement as a screening test for prostate cancer. None had a history of prostate cancer, and those with a history of prostatitis were excluded. Men with symptoms of benign prostatic hyperplasia were not excluded. We did not perform a digital rectal examination at the time of the blood test.

We have previously described the study protocol, which was approved by the Human Studies Committee of Washington University.<sup>2,14</sup> We obtained informed consent from all study subjects. Men whose initial serum PSA levels were 4.0 ng/mL or lower, no further evaluation was performed. Rather, their PSA levels were measured again at month intervals for the duration of the study unless the PSA level increased higher than 4.0 ng/mL. If the value was higher than 4.0 ng/mL, another blood sample was collected within 1 to 2 weeks to verify the elevation. Men who had

two serum PSA concentrations higher than 4.0 ng/mL within the 1- to 2-week period underwent both digital rectal examination and prostatic ultrasonography. If either or both of these procedures revealed abnormal or suspicious findings, we performed a needle biopsy of the prostate under ultrasound guidance. If the PSA concentration was higher than 4.0 ng/mL but the rectal and ultrasound examinations yielded normal findings, no biopsy was performed. Men whose biopsy specimens did not show cancer had serum PSA measurements at 6-month intervals. Repeated rectal examination, ultrasonography, and biopsy, if indicated, were recommended for men whose PSA levels were again higher than 4.0 ng/mL at a later evaluation. Fewer than 1% of the screening volunteers were African American, Asian, or Hispanic.

We measured serum PSA concentrations using an immunoenzymetric assay (Tandem-E PSA, Hybritech Inc, San Diego, Calif). We used the normal range recommended by the manufacturer (0 to 4.0 ng/mL) and considered PSA values higher than 4.0 ng/mL grounds for suspecting prostate cancer. The performance characteristics of the assay have been reported.<sup>12,14</sup>

The following data were recorded: (1) findings on digital rectal examination, which were categorized as normal, abnormal but benign (including enlargement), or suspicious for cancer (including induration, asymmetry, and irregularity); (2) ultrasound findings, categorized as normal, abnormal but benign (including enlargement, asymmetry, calculi, and transition-zone hypoechoic areas), or suspicious for cancer (hypoechoic area in the posterior peripheral zone); (3) PSA level in serum drawn before each rectal examination, ultrasonographic examination, or biopsy; (4) results of biopsy; (5) clinical and pathological tumor stage; and (6) tumor grade.

**Monoclonal Antibody Immunoassay Specific for Free PSA.**—A sandwich immunoassay was developed using a monoclonal antibody highly specific to free PSA and a second monoclonal antibody recognizing free and bound PSA equally. In this format, less than 0.7% cross-reactivity to PSA-CT was demonstrated.

The solid-phase capture antibody was incubated with 200  $\mu$ L of sample for 2 hours at room temperature, washed, and then incubated for an additional 2 hours with the second monoclonal antibody conjugated to alkaline phosphatase. Beads were washed, incubated for 1 hour with the chemiluminescent substrate 4-methoxy-4-(3-phosphatophenyl)spiro [1,2-dioxetane-3,2'-adamantane] disodium salt (LumiPhos 480, Lumigen, Inc.

Southfield, Mich), and read in a luminometer (MGM Instruments, Inc, Hamden, Conn). The free PSA calibrators, with the range of 0 to 10.0 ng/mL, were value assigned by the Tandem-R PSA assay to obtain mass-weight values. The analytical detection limit of the free PSA immunoassay was 0.05 ng/mL. The intra-assay coefficient of variation was between 2.5% and 12.5% across the calibrator range. The interassay coefficient of variation was 6.3% at 0.77 ng/mL concentration and 4.8% at 3.98 ng/mL concentration.

**Measurement of Free PSA in Selected Subgroups.**—Serum samples had been routinely frozen at  $-80^{\circ}\text{C}$  and stored for all study volunteers enrolled from July 1989 through January 1991. We systematically selected a sample of study volunteers for whom frozen stored serum samples were available for measurement of free and total PSA concentrations. Because men with borderline PSA elevations (4.1 to 10.0 ng/mL) frequently pose a diagnostic dilemma, we first identified all men enrolled before January 1991 whose initial PSA screening measurements were in this range. Since the purpose of our study was to determine the percentage of free PSA in men with a spectrum of ultrasonographically measured prostate sizes with or without detectable prostate cancer, this sample was further subdivided according to estimated prostate volume and biopsy results. Prostate volume was calculated via the prolate spheroid formula<sup>15</sup> using the transrectal ultrasound scan from the first biopsy.

Using these additional parameters, we identified the following study groups: (1) 67 men with biopsy-verified benign prostatic hyperplasia as determined by three or more sets of prostatic biopsy specimens (four to six biopsy cores in each set) that were negative for prostate cancer (ultrasonographically estimated gland volume of  $\geq 40$  cm<sup>3</sup>); (2) 33 men with biopsy-verified prostate cancer and an enlarged prostate gland (ie, ultrasonographically estimated gland volume of  $\geq 40$  cm<sup>3</sup>) with prostate cancer detected within 24 months of the initial screening visit (to include the cancers that were missed on the initial biopsies); and (3) 21 men with prostate cancer and a relatively normal-sized gland (ie, ultrasonographically estimated gland volume  $< 40$  cm<sup>3</sup>) with prostate cancer detected within 24 months of the initial screening visit. In total, frozen serum samples from 121 men were selected for further study. All of the men with prostate cancer had clinically localized cancer, and all but one were treated with radical prostatectomy.

Using the Hybritech research assay

specific for free PSA and the Tandem-E PSA assay for measurement of total PSA, we measured free PSA and reassessed total PSA in the stored serum samples from the initial screening visit in the three study groups.

Since other researchers<sup>6</sup> have reported loss of detectable PSA immunoreactivity following long-term storage of serum samples, we evaluated the stability of total serum PSA as measured in fresh and frozen stored serum samples. The mean coefficient of variation ( $\pm$ SD) for total serum PSA concentration in all fresh and stored pairs was 9.2% ( $\pm$ 16.6%). Overall, total PSA as measured in stored serum decreased in 82.6% (100 of 121) of the samples and increased in the remainder. The mean ratio ( $\pm$ SD) of stored to fresh total PSA (ie, [total PSA measured in stored serum]/[total PSA measured in fresh serum]) was 0.88 ( $\pm$ 0.14) for the 100 cases in which the total PSA decreased and 1.05 ( $\pm$ 0.06) for the 21 cases in which the total PSA increased when reassessed in stored serum. For the cases in which PSA decreased, outliers that fell below 1 SD of the mean ratio of stored to fresh total PSA (ie, the stored total PSA was  $<$ 74% of total PSA as measured in fresh serum) were eliminated from further analyses ( $n=5$ ). Similarly, for cases in which total PSA increased, outliers that increased more than 1 SD above the mean ratio of stored to fresh total PSA (ie, the stored total PSA was  $>$ 111% of fresh total PSA) also were eliminated ( $n=3$ ). Overall, 6.6% of cases were eliminated from further analysis (final  $n=113$ ); elimination of cases was uniform across the three study groups described above (generalized Fisher's exact test,<sup>16</sup>  $P=.80$ ).

**Pathological Tumor Staging.**—Pathological staging was performed as previously described.<sup>8</sup> For this analysis, study volunteers whose cancer was confined to the prostate and had clear margins were categorized as having pathologically organ-confined cancer (stage pT1 or pT2). Those with microscopic periprostatic cancer extension and those whose resected prostate gland contained cancer at the margins (stage pT3a), those with cancer invading into the seminal vesicles (stage pT3b), and those with lymph node metastases (stage N1) were classified as having pathologically advanced cancer.

**Tumor Grading.**—Gleason score was recorded for the radical prostatectomy specimens (49 [98%] of 50 of the included cancer cases were treated with radical prostatectomy). In three cases (6%), the pathologist recorded only the tumor grade (ie, well, moderately, or poorly differentiated). To estimate Gleason score for these cases, we graded the remainder of the tumors as well (Gleason score of 2 to

4), moderately (Gleason score of 5 to 7), or poorly (Gleason score of 8 to 10) differentiated and calculated the median Gleason score for each grade. This value was substituted for Gleason grade when Gleason score was not recorded.

#### Statistical Analysis

We calculated one-way analysis of variance, Mann-Whitney  $U$  tests, and  $\chi^2$  tests to assess differences in the study groups with regard to clinical characteristics (ie, age at first screening visit, proportion with digital rectal examination results suspicious for prostate cancer at the most recent biopsy, and estimated prostate volume at first biopsy).

Since previous studies have suggested that the percentage of free PSA (vs the absolute free PSA value) best discriminates between prostate cancer and benign hyperplasia,<sup>13</sup> we calculated the percentage of free PSA as the ratio of free PSA to total PSA multiplied by 100. The total PSA concentration was that measured in the repeated assay performed on the stored serum samples. We compared total PSA and the percentage of free PSA across the three study groups via a Kruskal-Wallis test. We used Mann-Whitney  $U$  tests for post hoc pairwise comparisons. To reduce the likelihood of type I error, the significance level for the post hoc comparisons was corrected for the number of comparisons (ie, Bonferroni correction =  $\alpha$  divided by the number of comparisons).<sup>17</sup> Therefore, we considered a  $P$  value  $\leq .02$  (.05/3) significant for all post hoc pairwise comparisons.

Combining the two study groups of men with cancer, we used hierarchical logistic regression analysis to assess the importance of percentage of free PSA in predicting prostate cancer while controlling for age at first screening visit, presence of suspicious findings on rectal examination, and total serum PSA concentration (estimated prostate volume was not included in this model since by design our study groups differed in prostate volume). We report the Wald statistic and the adjusted odds ratio (OR) with 95% confidence interval (CI) for the percentage of free PSA.<sup>18</sup>

To determine whether the percentage of free PSA remained a significant predictor of prostate cancer in the subset of men with an enlarged prostate gland (ie, ultrasonographically estimated gland volume of  $\geq 40$  cm<sup>3</sup>), we computed a second logistic model excluding the study group of men with prostate cancer and a relatively normal-sized gland. Similar to the first logistic model, the significance of the percentage of free PSA in predicting prostate cancer was assessed after controlling for age at first screening visit, presence of suspicious

findings on rectal examination, and total serum PSA concentration. Since the estimated prostate volume differed between those with and without prostate cancer, estimated volume was included as an additional predictor.

Before we calculated the logistic models, the assumption of a linear relationship with presence of prostate cancer was confirmed for each continuously scaled predictor. We determined quartiles for the distribution of each predictor (ie, age, total serum PSA concentration, estimated prostate volume, and percentage of free PSA) and calculated the ORs for the prediction of cancer based on the comparison of each quartile to the lowest quartile. We then plotted the log of the OR against the midpoint of each quartile to assess the shape of the relationship.<sup>18</sup> Visual inspection indicated that none of the continuously scaled predictors were associated with the presence of prostate cancer in a markedly nonlinear manner. Consequently, we modeled these predictors as simple linear effects in the logistic models.

To assess whether using the percentage of free PSA as a screening test for prostate cancer would increase the specificity of PSA-based screening, we preset sensitivity to at least 90% and determined the cutoffs for percentage of free PSA for the combined study groups of men with prostate cancer, for the study group with cancer and a gland 40 cm<sup>3</sup> or larger, and for the study group with cancer and a gland smaller than 40 cm<sup>3</sup> (here "sensitivity" is used in the context of specific subgroups and not the general screening population; that is, we do not include the full range of normal and elevated serum PSA concentrations). We then computed specificity (ie, the proportion of men without prostate cancer who would have been considered to have a negative screening test) using each percentage of free PSA cutoff. We repeated this analysis in the subsample of men without findings suspicious for prostate cancer on digital rectal examination (all had serum PSA concentrations between 4.1 and 10.0 ng/mL initially).

Finally, we calculated a point biserial  $r$  to assess the relationship between the presence of pathologically advanced cancer and the percentage of free PSA. A Pearson correlation coefficient was calculated to assess the relationship between Gleason score and the percentage of free PSA.

## RESULTS

### Comparison of Clinical Characteristics Across Study Groups

Table 1 summarizes the clinical characteristics (ie, age at first screening visit,

Table 1.—Clinical Characteristics of Study Groups

Characteristic	Benign Prostatic Hyperplasia (n=63)	Cancer With Gland $\geq 40$ cm <sup>3</sup> (n=30)	Cancer With Gland $< 40$ cm <sup>3</sup> (n=20)	P*
Age in years, mean ( $\pm$ SD)	66.3 ( $\pm$ 5.6)	68.5 ( $\pm$ 6.5)	66.2 ( $\pm$ 4.3)	.20
Rectal examination findings suspicious for prostate cancer, No. (%)†	14/62 (22.6)	4/30 (13.3)	10/20 (50.0)	.02
Median ( $\pm$ SIR‡) prostate volume	50.8 ( $\pm$ 11.0)	49.5 ( $\pm$ 7.2)	33.1 ( $\pm$ 3.9)	.005

\*P values for age and digital rectal examination results represent three-way comparisons via one-way analysis of variance and  $\chi^2$ , respectively. The P value for prostate volume represents a Mann-Whitney U test comparing men with benign prostatic hyperplasia and men with prostate cancer with an enlarged gland ( $\geq 40$  cm<sup>3</sup>).

†Findings from digital rectal examination were unavailable for one study volunteer.

‡SIR indicates semi-interquartile range ((75th percentile - 25th percentile)/2).

Table 2.—Median Total Serum PSA Concentration and Percentage of Free Serum PSA Concentration for Study Groups\*

Concentration	Benign Prostatic Hyperplasia (n=63)	Cancer With Gland $\geq 40$ cm <sup>3</sup> (n=30)	Cancer With Gland $< 40$ cm <sup>3</sup> (n=20)	P†
Median ( $\pm$ SIR) total PSA	6.0 ( $\pm$ 1.4)	6.6 ( $\pm$ 1.5)	5.3 ( $\pm$ 1.3)	.50
Median ( $\pm$ SIR) % free PSA	18.8 ( $\pm$ 6.8)	15.9 ( $\pm$ 3.9)	9.2 ( $\pm$ 3.3)	<.001

\*PSA indicates prostate-specific antigen; and SIR, semi-interquartile range ((75th percentile - 25th percentile)/2).

†P values represent three-way comparisons via Kruskal-Wallis tests. For the percentage of free PSA, all Mann-Whitney U pairwise comparisons between groups were significant at  $P < .002$ .

digital rectal examination results at the time of the most recent biopsy, and estimated prostate volume at first biopsy) for the three study groups. The study groups did not differ with regard to mean age ( $P = .20$ ). As expected, men with prostate cancer were significantly more likely to have digital rectal examination findings suspicious for prostate cancer ( $\chi^2[2] = 8.0$ ;  $P = .02$ ). As defined by our selection criteria, the study groups also differed significantly with regard to estimated prostate volume. A pairwise comparison indicated that the men with benign prostatic hyperplasia had significantly larger prostate glands than the men with prostate cancer and an enlarged prostate gland (Mann-Whitney  $U P = .005$ ).

#### Distribution of Total PSA and the Percentage of Free PSA in Stored Samples

As shown in Table 2, total PSA as measured in stored samples did not differ across study groups (Kruskal-Wallis  $P = .60$ ). In contrast, the percentage of free PSA differed significantly across groups (Kruskal-Wallis  $P < .001$ ). Men with prostate cancer (with a normal-sized or an enlarged prostate) had a significantly lower percentage of free PSA than men with benign prostatic hyperplasia only (all Mann-Whitney  $U P$  values  $< .002$ ). Additionally, men with prostate cancer and a normal-sized prostate had a significantly lower percentage of free PSA than men with prostate cancer and an enlarged prostate ( $P = .002$ ).

#### Use of Percentage of Free PSA for Differentiating Benign Prostatic Hyperplasia From Prostate Cancer

The results of the logistic regression model including both study groups of

men with prostate cancer (113 men) indicated that the percentage of free PSA added significantly to the prediction of cancer in men with elevated PSA levels, even after controlling for age, suspicious findings on rectal examination, and total serum PSA (Wald  $\chi^2[1] = 19.3$ ;  $P < .001$ ; adjusted OR, 0.4 [95% CI, 0.3 to 0.6] for each 5% increase in the percentage of free PSA).

Similar results were found for the logistic model that included only the 93 men with an enlarged prostate gland. Measurement of the percentage of free PSA added significantly to the prediction of prostate cancer, even after controlling for age, findings suspicious for cancer on rectal examination, total serum PSA, and estimated prostate volume (Wald  $\chi^2[1] = 4.6$ ;  $P = .03$ ; adjusted OR, 0.6 [95% CI, 0.4 to 0.9] for each 5% increase in the percentage of free PSA).

These results indicate that measurement of the percentage of free PSA gives predictive information about the presence or absence of prostate cancer above that provided by other clinical indexes such as age, total PSA level, suspicious results on rectal examination, and prostate size. Figure 1 illustrates for our combined study groups the systematic decrease in the simple proportion of men with prostate cancer with each 5% increase in the percentage of free PSA.

#### Percentage of Free PSA as a Screening Test for Prostate Cancer

To determine whether assessment of percentage of free PSA could increase the specificity of PSA-based prostate cancer screening in men with serum PSA levels of 4.1 to 10.0 ng/mL, we calculated percentage of free PSA cutoff points that would predict cancer with at

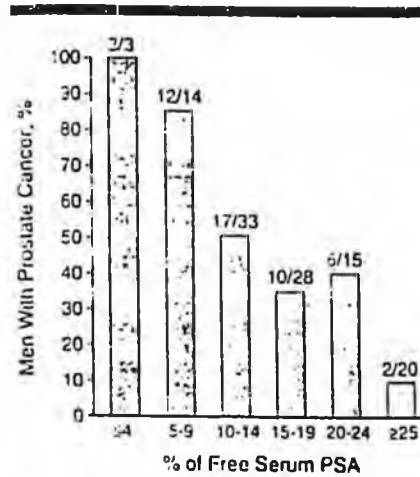


Figure 1.—Decreasing simple proportion of men in the combined study groups found to have prostate cancer on biopsy with each 5% increase in the percentage of free prostate-specific antigen (PSA) in serum (ratio of free PSA to total PSA multiplied by 100).

least 90% sensitivity. As shown in Table 3, we calculated a percentage of free PSA cutoff point combining both study groups of men with prostate cancer. Cutoff points for percentage of free PSA also were calculated separately for each study group. As expected, the percentage of free PSA cutoff point was lower in the men with prostate cancer and a normal-sized gland.

Setting sensitivity to at least 90% would have resulted in five missed cancers in the combined cancer study groups. All five men had clinically localized cancer and underwent radical prostatectomy; two were pathologically upstaged to grade pT3. Two of the men had well-differentiated tumors and three had moderately differentiated tumors.

The proportion of men in the benign prostatic hyperplasia study group that would exceed the percentage of free PSA cutoffs and therefore would be considered "true negatives" also is presented in Table 3. Using a free PSA cutoff of 20.3% or lower (which would result in 90% sensitivity if both prostate cancer study groups were combined) would have resulted in negative screens in 33.1% of the benign prostatic hyperplasia group. Consequently, if this cutoff had been used as a criterion for prostatic biopsy, 33.1% of the men with benign prostatic hyperplasia would have been spared biopsy (see Figure 2, patients with benign prostatic hyperplasia above the cutoff line).

Since current standard medical practice mandates the performance of prostatic biopsies in men with rectal examination findings suspicious for prostate cancer, we determined the percentage of free PSA cutoffs (and resultant specificity) for prediction of cancer in men with nonsus-

Table 3.—Percentage of Free PSA Cutoff Points and Resultant Specificity for Predicting Cancer With at Least 90% Sensitivity\*

Variable	No. With Cancer	No. Without Cancer	% Free PSA Cutoff	Specificity (95% CI)
In All the Men				
All cancers	50	63	≤20.3	38.1 (25.4-50.8)
Cancer with gland ≥40 cm <sup>3</sup>	30	63	≤20.5	38.1 (25.4-50.8)
Cancer with gland <40 cm <sup>3</sup>	20	53	≤13.7	76.2 (64.8-87.6)
In Men With Nonsuspicious Findings on Digital Rectal Examination				
All cancers	26	49	≤23.4	31.3 (17.2-45.4)
Cancer with gland ≥40 cm <sup>3</sup>	16	48	≤23.4	31.3 (17.2-45.4)
Cancer with gland <40 cm <sup>3</sup>	10	48	≤13.8	79.2 (66.8-91.6)

\*PSA indicates prostate-specific antigen; and CI, confidence interval.

†Proportion of biopsies with findings negative for prostate cancer that could be eliminated using the percentage of free PSA cutoff as a criterion for performing the biopsy.

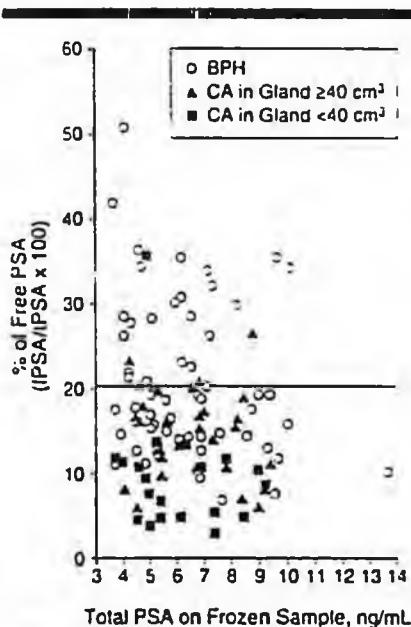


Figure 2.—Percentage of free prostate-specific antigen (PSA) and total PSA (IPSA) concentration in frozen serum from men with benign prostatic hyperplasia (BPH) and men with prostate cancer (CA), regardless of findings of rectal examination. Cutoff point of 20.3% for greater than 90% sensitivity eliminates 38.1% of biopsies in BPH group.

picious digital rectal examination results (Table 3). Overall, a free PSA cutoff point of 23.4% or lower would have eliminated 31.3% of the biopsies while maintaining 90% sensitivity (Figure 3).

#### Correlation of Percentage of Free PSA With Cancer Stage and Grade

Within the relatively narrow range of cancer stages represented in our study population, the percentage of free PSA was not associated with the presence of pathologically advanced cancer ( $r=0.10$ ;  $P=0.50$ ). Similarly, the percentage of free PSA was not correlated with Gleason score ( $r=-0.07$ ;  $P=0.60$ ). Pathological stage and tumor grade were missing for one man who did not undergo radical prostatectomy.

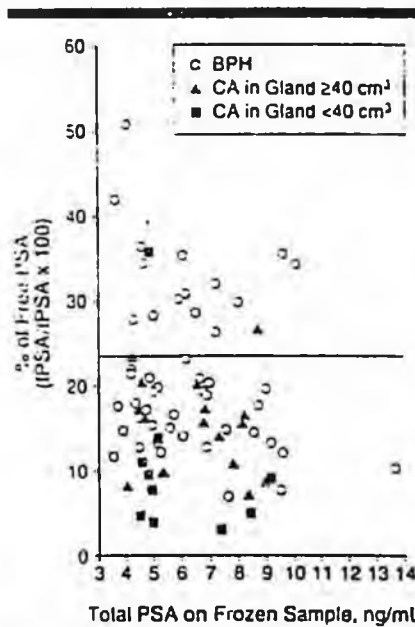


Figure 3.—Percentage of free prostate-specific antigen (PSA) and total PSA (IPSA) concentration in frozen serum from men with benign prostatic hyperplasia (BPH) and men with prostate cancer (CA). The group includes only men without suspicious findings on rectal examination. Cutoff point of 23.4% for greater than 90% sensitivity eliminates 31.3% of biopsies in BPH group.

#### COMMENT

Serum PSA testing for early prostate cancer detection is widely used. Recent studies have shown that measurements of PSA in frozen serum samples drawn more than a decade ago can identify accurately men who developed prostate cancer within 5 to 10 years after the blood samples were drawn.<sup>6,7</sup> These cancers had a high lethal potential, with those patients having high initial serum PSA levels being most likely to have incurable disease.

Prostate-specific antigen may prove to be a valid screening test for early prostate cancer, and a reduction in prostate cancer mortality rates may be achieved by detecting and treating early-

stage prostate cancer in men whose life expectancy exceeds 10 years. However, to prove the utility of screening, a reduction in mortality or increase in quality of life in screened patients would have to be demonstrated in prospective studies with length and quality of life as end points.

The chance of achieving cure can be high only with the use of low total serum PSA cutoffs for screening, but low cutoffs (4.0 ng/mL) produce appreciable false-positive results (ie, the positive predictive value is only about 35%) caused by benign hyperplasia or prostatitis. This is particularly true with PSA levels of 4.1 to 10.0 ng/mL in men with findings of benign enlargement on digital rectal examination. Only about 20% of such men have cancer diagnosed by biopsy; however, some men also will have cancer detected by repeated biopsies.<sup>8</sup>

Alternative measures proposed to increase the specificity of serum PSA testing include measuring the rate of change of the serum PSA concentration, called PSA velocity<sup>19,20</sup>; assessing the ratio of blood PSA concentration to ultrasonographically measured gland volume, called PSA density<sup>21</sup>; and using age-specific PSA reference ranges.<sup>22,23</sup> Each of these measures has its own sensitivity-specificity trade-offs that result in either missing a substantial proportion of curable cancers or yielding a high false-positive rate.<sup>24,25</sup> Although it was beyond the scope of this study, we computed sensitivity and specificity in our study groups using published standards for PSA density (ie, 0.15)<sup>27</sup> and PSA age-specific reference ranges (ie, age 50 through 59 years, >3.5 ng/mL; age 60 through 69 years, >4.5 ng/mL; age ≥70 years, >6.5 ng/mL).<sup>22</sup> These calculations show low sensitivity for both measures (48% and 72%, respectively), high specificity for PSA density (87%), and low specificity for age-specific reference ranges (16%). However, these findings cannot be considered a direct comparison with the results reported for the percentage of free PSA because we pre-set sensitivity for this measure. In a separate logistic model, including age, total PSA, rectal examination results, PSA density, and percentage of free PSA (with both PSA density and percentage of free PSA entered as continuously scaled predictors), both PSA density and percentage of free PSA independently contributed significantly to the prediction of prostate cancer (data not shown). Prospective studies are needed to further compare these methods.

Previous studies have demonstrated that the percentage of serum PSA that exists in the free form is lower in patients with prostate cancer than in those

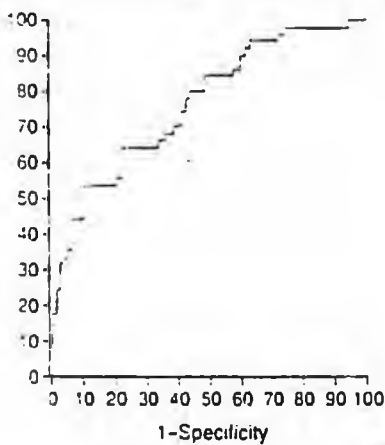


Figure 4.—Receiver operating characteristic curve of detection of prostate cancer based on the percentage of free prostate-specific antigen in frozen serum from men with benign prostatic hyperplasia and men with prostate cancer, regardless of findings on digital rectal examination.

with benign hyperplasia; this disparity can be exploited clinically to distinguish between cancer and hyperplasia.<sup>6,10-12</sup> Stenman et al<sup>11</sup> and Leinonen et al<sup>12</sup> reported that the use of the ratio of free PSA to total PSA could eliminate half of the false-positive results without appreciable loss of sensitivity in a study group of men whose total serum PSA concentrations ranged from 2.5 to 25.0 g/mL. Christensson et al<sup>13</sup> reported similar results in 66 men with untreated prostate cancer: specificity was increased using a cutoff level of less than 3% free PSA with only a 10% loss of sensitivity. However, these studies both included heterogeneous patient populations with a wide spectrum of total serum PSA concentrations, prostatic sizes, and digital rectal examination findings.

Currently there is little argument about the need for performing prostatic biopsies in men with very high serum PSA concentrations (>10 ng/mL) or those whose rectal examination findings are suspicious for cancer. For men with these findings, measurement of free PSA does not materially influence the decision-making process. However, it is important to examine the results of free serum PSA measurements in men with PSA concentrations of 4.1 to 10.0 ng/mL and benign findings on digital rectal examination for whom some physicians may not recommend biopsy. These men frequently present a diagnostic dilemma.

The results from our logistic regression models confirm the findings of previous studies, showing that within the range of PSA concentrations tested (4.1 to 10.0 ng/mL), the percentage of free PSA provides independent predictive information about the presence of prostate cancer. Our results extend these

observations, showing that the free PSA cutoff required to maintain at least 90% sensitivity of cancer detection was higher in men with an enlarged prostate gland and those with a benign-appearing gland. For example, in men whose prostate size was relatively normal (<40 cm<sup>3</sup>), a free PSA cutoff of 13.7% or less would have detected at least 90% of the cancers while eliminating 76.2% of the unnecessary biopsies; however, a cutoff of 30.5% or less was required to detect at least 90% of the cancers in men with a larger gland. This higher cutoff still would eliminate 38.1% of the unnecessary biopsies. For free PSA measurements to be helpful in men whose prostate gland was both enlarged and palpably benign (and whose PSA level was 4.1 to 10.0 ng/mL), the cutoff would have to be increased to 23.4% to detect at least 90% of the cancers. If this cutoff had been used, 31.3% of unnecessary biopsies could have been eliminated. However, under present practice, some physicians would not perform biopsies on older men or men with very large glands.

While avoiding unnecessary biopsies is desirable, missing 10% of the cancers is still of concern. Additionally, not pursuing the diagnosis in men with elevated PSA levels may be more psychologically problematic to some physicians and patients as compared with not pursuing diagnosis in men with normal PSA levels. It has been suggested that this loss of sensitivity may be acceptable because of the general slow development of prostate cancer<sup>6</sup>; however, not all cancers missed are low grade and indolent, and the consequences in terms of missing opportunities for cure also may be greater than for men with normal PSA levels.

We evaluated the reciprocal relationship between sensitivity and specificity by plotting true-positive (sensitivity) vs false-positive (1 - specificity) results in a receiver operating characteristic curve. As shown in Figure 4, sensitivity could have been increased in our sample (ie, >90%) with a modest loss in specificity.

In our study, measurements of the percentage of free PSA did not distinguish between early and advanced cancers, nor did they correlate with Gleason score; however, the range of cancer stages and grades represented in our study was narrow.

Our results should be interpreted with caution. Our study is not definitive in that our sample size is small, especially when cases with suspicious rectal examination findings and/or prostate cancer with a small gland are removed for subset analysis. Additionally, possible loss of detectable PSA immunoreactiv-

ity may have occurred from long-term storage of the serum samples. Stenman et al<sup>6</sup> compared the geometric mean of PSA concentrations in fresh control serum samples with those of comparable men whose serum samples had been stored at -20°C for 9 to 13 years (and thawed and refrozen once during that interval) and found a 38% lower mean PSA concentration in the frozen samples. Stenman et al concluded that measurable PSA was lost with prolonged freezing and that the PSA-ACT form was preferentially lost. In contrast, our samples were kept frozen at -80°C, were frozen for 3 to 5 years, and were not thawed and refrozen before testing. As a result, our repeated analyses of total PSA levels showed a much more modest loss in immunoreactivity.

Furthermore, preliminary studies performed in 11 serum samples (excluding one outlier) indicate that both the free PSA and total PSA immunoreactivity remained stable for at least 3 months when stored at -20°C or -70°C. The mean (±SD) free PSA immunoreactivity was 93.1% (±3.7%) of the initial baseline value when serum was stored at -20°C and 99.9% (±3.3%) of baseline when stored at -70°C. The mean (±SD) total PSA immunoreactivity was 97.7% (±2.8%) and 95.4% (±4.6%) of the baseline value when stored at -20°C and -70°C, respectively. The free-to-total ratio (96.4% [±5.5%] of the baseline value when stored at -20°C and 105.3% [±8.5%] when stored at -70°C) also remained stable. Serum specimens (n=4) subjected to five freeze-thaw cycles showed a mean recovery of 99.8% (±4.6%) of baseline values. However, serum samples stored at 2°C to 8°C lost approximately 30% of free PSA and about 15% of total PSA immunoreactivity after 15 days. Further studies of the stability of PSA forms are in progress. In addition, initial sample handling is important; samples frozen within 24 hours showed minimal loss of reactivity, whereas those stored at 4°C for longer periods showed considerable decay. In the current study, samples that showed the greatest divergence on repeated analysis (in either a positive or negative direction) were eliminated; however, our results should be verified using fresh serum samples.

Another caveat in interpreting the results of our study is that our volunteers were selected from a small geographic area and examined by selected clinicians. Since our study groups were neither a randomly selected nor a consecutive series, a selection bias also could have been introduced. For example, our volunteer sample may have been enriched for men with symptoms of benign hyperplasia.

is may have exaggerated the ability percentage of free PSA to distinguish between benign prostatic hyperplasia and prostate cancer in the 4.1 to 10.0 ng/mL range. Although we did not collect symptom information in the study population from which our samples were drawn, we can estimate likely symptom prevalence from a second PSA screening study currently ongoing at our institution.<sup>1</sup> In a population of community volunteers recruited in a similar fashion, approximately 50% of the men without prostate cancer and with PSA levels between 4.1 and 10.0 ng/mL reported

one or more symptoms at study entry. For these reasons, the extrapolation of our results to other patient populations is not established and should be confirmed in prospective studies of representative groups of men.

Our results suggest that the use of measurements of free PSA concentrations can reduce unnecessary biopsies in selected men with elevated total serum PSA levels who are undergoing evaluation for prostate cancer. Further studies are needed to define appropriate cutoffs for men with modest total serum PSA elevations and enlarged, palpably benign

findings on digital rectal examination, to evaluate the percentage of free PSA in fresh serum samples, and to examine cost-effectiveness of screening with the percentage of free PSA. Ultimately, final evaluation of PSA screening in general also must consider the ability of current treatments to improve the prognosis of men with screen-detected cancers.

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## CURRENT CONCEPTS

## SCREENING FOR PROSTATE CANCER WITH PROSTATE-SPECIFIC ANTIGEN

## An Examination of the Evidence

STEVEN H. WOOLF, M.D., M.P.H.

AFTER lung cancer, prostate cancer is the leading cause of deaths from cancer among men in the United States. It will claim 40,000 lives in 1995.<sup>1</sup> Studies in the early 1990s demonstrated that levels of prostate-specific antigen (PSA), a serine protease, are elevated in most men with clinically important prostate cancer and that measuring them is the best means for early detection of the disease.<sup>2-5</sup> In 1993, the American Cancer Society recommended that clinicians measure PSA in all men 50 years of age and older as part of an annual prostate examination and that PSA screening should begin at the age of 40 in men at high risk.<sup>6</sup> The American Urological Association issued similar recommendations. Support for PSA screening is not universal, however. Recommendations against PSA screening have been issued by the U.S. Preventive Services Task Force, the Canadian Task Force on the Periodic Health Examination, and the Canadian Urologic Association.<sup>7,8</sup> Recommendations by the American College of Physicians and the American Academy of Family Physicians are currently under review. Physicians in practice have opposing views about PSA screening.<sup>9</sup>

The debate about whether to perform PSA screening has important implications for both individual and public health, but the setting of appropriate policy has been hindered by inadequate data. Screening may reduce morbidity and mortality associated with prostate cancer, but this hypothesis is unproved. On the other hand, widespread testing may set off a cascade of diagnostic and treatment procedures with potentially serious complications, but the magnitude of these risks is uncertain. The overall balance of benefits and harms is therefore unclear. The economic implications of PSA screening are also unknown: testing all men over the age of 50 could cost the country billions of dollars, but the investment might be justified if suffering from prostate cancer could be reduced.

This article reviews the central scientific arguments in the controversy over PSA screening. The discussion is organized around the principal scientific questions that should be asked when one is evaluating any screening test: Is the target condition serious? Is the screening test accurate? Does early detection improve outcome?

Is screening or treatment harmful? Does screening do more good than harm?

## ANALYTIC ISSUES

## Is Prostate Cancer Serious?

There is little doubt about the seriousness of progressive prostate cancer (tumors that spread beyond the capsule or metastasize). Thousands of men suffer painful complications and die prematurely from such tumors. Ten-year survival rates are 75 percent when the cancer is confined to the prostate, 55 percent with regional extension, and 15 percent with distant metastases.<sup>10</sup> Age-adjusted mortality from prostate cancer has increased by 24 percent in recent years<sup>11</sup> and, largely because of increased screening, the incidence of new cases has risen by 40 percent.<sup>12</sup>

Not all prostate cancers are serious, however, because of the frequently indolent behavior of the disease. Autopsy studies report that about 30 percent of men over the age of 50 have histologic evidence of prostate cancer.<sup>13</sup> Extrapolation of these rates to U.S. census data suggests that as many as 9 million men could harbor latent prostate cancers (Table 1). Since there are about 40,000 deaths each year from the disease,<sup>1</sup> it seems likely that most prostate cancers in the population are not clinically important. Most men with latent prostate cancer die with, rather than from, the disease.

## Is PSA Screening Accurate?

Because it might be unethical for researchers to perform biopsies on men with normal PSA results, the true sensitivity and specificity of PSA screening are unknown. The test has a reported sensitivity of up to 80 percent in detecting prostate cancer in screened men,<sup>4</sup> but it lacks specificity. False positive results due to the presence of benign prostatic hypertrophy or prostatitis are common; 25 to 46 percent of men with benign prostatic hypertrophy have elevated PSA values.<sup>23,24</sup> PSA values may also fluctuate by as much as 30 percent for physiologic reasons.<sup>25</sup> The reported positive predictive value of PSA in screening studies is 28 to 35 percent, which means that one third of men with elevated PSA levels (>4 mg per milliliter) will be found to have prostate cancer on biopsy and two thirds will not (i.e., will have false positive results).<sup>1,2,4,5</sup> Participants in these studies were either patients seen at urology clinics or community volunteers, which has caused some to question whether the positive predictive value might be lower when screening occurs in primary care settings.

Promising techniques to improve the accuracy of PSA screening include measuring PSA density<sup>26</sup> (the PSA concentration divided by the volume of the gland) or the rate of change in PSA over time.<sup>27</sup> A third approach is to use age-adjusted reference ranges,<sup>28</sup> since PSA values increase with age. Finally, some advocate measuring the ratio of free to complexed PSA.<sup>29</sup> PSA bound to alpha<sub>1</sub>-antichymotrypsin accounts for a larger proportion of total PSA in patients with prostate cancer than in those with benign prostatic hypertrophy. No single approach has yet been proved to be more accu-

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rate than another. For now, the best way to reduce the frequency of false positive results is to combine PSA screening with the digital rectal examination, which increases the positive predictive value from 32 to 49 percent if the results of both are abnormal.<sup>1</sup>

A more fundamental problem than false positive results, however, has been how to determine whether cancers detected through PSA screening (true positives) are clinically important. As has already been noted, autopsy studies suggest that 30 percent of men over the age of 50 have latent prostate cancers that are unlikely to produce symptoms or affect survival. It has long been feared that population screening would preferentially identify these latent cancers (rather than aggressive disease) and that thousands of men who are more likely to die of other causes (e.g., coronary artery disease) would be subjected to unnecessary testing and treatment for prostate cancer. Recent evidence suggests, however, that cancers detected through PSA screening may be more aggressive and clinically important than latent cancers found on autopsy. About 31 to 53 percent of cancers identified through PSA screening and radical prostatectomy have evidence of extracapsular extension, poorly differentiated cells, large volume, or metastases.<sup>2,30,31</sup> These features are associated with an increased risk of progression, although they are not pathognomonic of aggressive disease. Autopsy studies also report capsular penetration, local tissue invasion, and diffuse or poorly differentiated cells in 10 to 88 percent of men with no antemortem prostate history.<sup>10,19,42</sup> For now, neither PSA values nor histologic findings can predict with certainty whether a newly diagnosed prostate cancer will progress or remain latent.

#### Does Early Detection of Prostate Cancer Improve Outcomes?

Ultimately, accuracy is less important than clinical outcomes in judging the efficacy of screening. Debates about the relative superiority of density, rate-of-change, and other indexes in improving the accuracy of PSA screening are irrelevant unless early detection improves the patient's health. PSA screening is often defended incorrectly on the basis of what has been discussed thus

far, with the evidence that the test can detect organ-confined cancer cited as sufficient grounds for screening. Screening cannot be justified unless patients who are screened have better health outcomes than those who are not. The literature provides such evidence for breast, cervical, and colorectal cancer screening.<sup>7</sup>

There is little direct evidence, however, that screening for prostate cancer reduces morbidity or mortality. Indeed, few controlled studies have ever addressed this question. Observational studies of screening by digital rectal examination reported no benefit,<sup>43,44</sup> and no controlled study of health outcomes after PSA screening has yet been reported. Randomized, controlled trials addressing the health benefits of screening are under way in the United States and Europe, but the results will be unavailable for more than a decade.<sup>45</sup>

There is some indirect evidence that early detection may be beneficial. Men who undergo PSA screening are more likely to have early-stage disease at diagnosis (a phenomenon known as "stage shift") than unscreened men, and the proportion of cancers that are clinically or pathologically advanced appears to decrease with each successive year of testing.<sup>46</sup> Survival data suggest that men with localized tumors at diagnosis live longer than those with more advanced disease.<sup>1</sup> It is unclear, however, whether these findings reflect lead-time and length biases rather than an actual improvement in outcome. (Lead-time bias occurs when survival appears to be lengthened because the diagnosis was made earlier, rather than because death was delayed. Length bias refers to the tendency of screening to generate favorable outcomes by preferentially detecting slowly growing, indolent tumors, as opposed to aggressive tumors that are present in the population relatively briefly.)

One reason for questioning the effectiveness of early detection is the lack of direct evidence that treatment for prostate cancer improves outcomes. Arguments for the effectiveness of the principal treatments for prostate cancer — radical prostatectomy, radiation therapy, and hormonal treatment — are supported mainly by uncontrolled observational reports. The lack of controls and other design flaws limit the persuasiveness of this evidence. A randomized, controlled trial conducted in the 1970s reported that radical prostatectomy did not improve 15-year survival, but the trial suffered from numerous methodologic problems.<sup>47</sup> Well-designed randomized, controlled trials of treatment are now under way in the United States and Europe, but the results will be unavailable for more than a decade.<sup>22</sup>

Skepticism about the efficacy of treatment has been heightened in recent years by evidence that patients with early-stage prostate cancer have good outcomes even without treatment. Johansson<sup>48</sup> and colleagues followed a population-based cohort of 223 Swedish men with initially untreated prostate cancer. After 12.5 years, only 10 percent had died of prostate cancer and 56 percent had died of other causes; the 10-year disease-specific survival rate was 85 percent. Critics argued that survival may have been inflated by the inclusion of a large proportion of older men with small, well-differentiated tumors.<sup>49</sup> Moreover, of the patients

Table 1. Estimated Prevalence of Latent Prostate Cancer in the United States, According to Age.\*

AGE RANGE	U.S. POPULATION	REPORTED PREVALENCE OF LATENT PROSTATE CANCER (%)†	PREDICTED NO. OF U.S. MEN WITH LATENT PROSTATE CANCER
40-49	10,632,000	22.1	2,349,672
50-59	9,710,000	26.1	2,535,310
60-69	5,849,000	37.8	2,210,922
70-79	2,155,000	45.7	1,157,235
Total	—	—	8,253,139

\*Values are for men over the age of 40, the population for which screening is typically indicated. Autopsy studies indicate that the prevalence of latent carcinoma in men 40 to 49 years of age is about 1 percent, and the autopsy study of men 50 to 49 years of age reported a prevalence of 30 percent.<sup>10</sup> Thus, the total population of American men with latent prostate cancer may be larger.

†Data are from the U.S. Bureau of the Census.

‡Values are weighted, age-specific means for cases of latent carcinoma as reported in seven autopsy studies that used systematic step-section analysis of prostate gland specimens from a total of 915 patients.<sup>10</sup>

who were alive at 10 years, 45 percent had tumor growth or metastasis, prompting speculation that a survival disadvantage might have become apparent if the follow-up period had been longer.

More recent studies of conservative treatment have failed to resolve the issue. A review of all men with prostate cancer who died between 1988 and 1990 in Göteborg, Sweden, reported that men with conservatively treated localized tumors had mortality rates of 50 to 100 percent, but the retrospective and selective study design (which included, for example, only decedents, rather than all men with prostate cancer, in the denominator) limits the utility of the data. In the United States, an analysis of prostate cancer cases in Connecticut estimated that, after a mean follow-up of 16 years, life expectancy with conservative treatment of localized prostate cancer (either no treatment or hormonal therapy) was unchanged from that of the general population if the tumor was of low grade but was reduced by as much as 4 to 5 years or 6 to 8 years if the tumor was of moderate or high grade, respectively. These data derive from a retrospective chart review of cases diagnosed between 1971 and 1976, however, and include only patients 65 to 75 years of age.<sup>41</sup>

Researchers have pooled study data to model the natural history of untreated prostate cancer, but their findings have also been criticized. On the basis of data from 144 articles, Wasson et al.<sup>42</sup> estimated that the annual risks of metastasis and death from untreated prostate cancer were low (1.7 percent and 0.9 percent, respectively). This study was criticized for including a large proportion of patients with well-differentiated tumors and patients receiving androgen-deprivation therapy. On the basis of six major studies, Chodak et al.<sup>43</sup> reported that conservative management (delayed hormone therapy but no surgical or radiation therapy) was associated with a 10-year disease-specific survival rate of 87 percent for men with well-differentiated or moderately differentiated tumors and 34 percent for men with poorly differentiated tumors. For patients alive after 10 years, the probability of having metastatic disease was 19 percent, 42 percent, and 74 percent, respectively, for well-, moderately, and poorly differentiated cancers. Although critics disagree with the study's probability estimates,<sup>44</sup> the findings underscore the role of cell differentiation in predicting future tumor progression.

#### Is Screening or Treatment Harmful?

The potential benefits of any screening test must be weighed against the potential harm of testing and treatment. In the case of PSA screening, the physical effects of venipuncture are trivial, but the consequences of false positive (and false negative) results deserve consideration. If the reported positive predictive value of 23 to 35 percent is assumed to be correct, two out of three men with abnormal results on routine PSA screening will not have cancer. Before cancer can be ruled out, however, they must undergo the inconvenience and discomfort of follow-up testing (e.g., repeat PSA testing, ultrasonography, and biopsy) and the anx-

ety of waiting for results. Needle biopsy is performed in about 20 percent of screened men and is complicated by infection or bleeding in 0.1 to 4 percent of patients and by discomfort and anxiety in 58 to 68 percent of patients.<sup>23,49</sup>

A more serious source of concern than testing is the potential complications of treatment (e.g., impotence, incontinence, and death), the probabilities of which are summarized in Table 2. Although experts report anecdotally that their complication rates are lower than those in published reports, complication rates in the community are thought to be higher (Table 3). Reported mortality rates for radical prostatectomy are 0.2 to 2 percent, with lower rates reported by urologists at specialized centers and in studies involving patients under the age of 65.<sup>47,49-51</sup>

#### Does Screening Do More Good Than Harm?

Ultimately, the most important question about PSA screening is whether it improves the overall health and well-being of patients. As has already been noted, clinical trials that will provide this information are currently in progress. In the meantime, researchers have used decision analysis to try to estimate the net effect of benefits and risks on quality-adjusted survival, but both the methods and results of these analyses are controversial. Decision analyses of screening<sup>32,33</sup> have even suggested that quality-adjusted survival is reduced by screening, but the models' assumptions have been challenged.<sup>34</sup> Other decision analyses have focused on the effects of treatment. Fleming et al.<sup>35</sup> concluded that treatment, when compared with observation, increases quality-adjusted survival by less than one year and decreases survival in men over the age of 70 and those

Table 2. Reported Complication Rates for Radical Prostatectomy and External-Beam Radiation Therapy.\*

COMPLICATION	REPORTED INCIDENCE (%)
Radical prostatectomy	
Impotence	20-85
Incontinence	1-27
Urethral stricture	10-18
Thromboembolism	2-30
Permanent rectal injuries	1-3
Peroperative death	0.3-2
Radiation therapy	
Acute gastrointestinal or genitourinary complications	3-67
Chronic complications requiring surgery or prolonged hospitalization	1-2
Anorectal complications	2-23
Impotence	41-67
Urethral or bladder complications	1-17
Incontinence	1-3
Death	0.2-0.5

\*Data were collated from 23 studies, 11 of which were published between 1993 and 1995 (citations are available from the author on request). Reported rates vary partly because definitions of complications vary from study to study and because some symptoms (e.g., impotence) are common preexisting conditions in this age group. Experts report anecdotally that current complication rates are lower than in published reports. Surgical complications have been reduced to some extent by the use of bilateral nerve-sparing techniques and by limiting the operation to younger and healthier men. Improvements in radiation therapy (e.g., three-dimensional external radiotherapy) may also produce fewer side effects.

Table 3. Adverse Outcomes of Radical Prostatectomy Reported by a National Probability Sample of Medicare Patients.\*

CONDITION	% OF MEN REPORTING
Attributable 30-day postoperative mortality	11.6
Cardiopulmonary complications (congestive heart failure, myocardial infarction, pulmonary embolism, or respiratory failure)	4-5
Incontinence	
Wore pads or other devices for incontinence	31
Dropped more than a few drops daily	23
Underwent surgical treatment for incontinence	9
Had a catheter	7
Erectile impotence	
Was able to have erections before surgery	81
Had no full or partial erections since surgery	71
Had erections firm enough for intercourse in previous month	41
Underwent medical or surgical treatment for stricture, two to four years after surgery	29

\*Data are from Fowler et al.<sup>12</sup> as reproduced with additional material in a publication of the U.S. Office of Technology Assessment.<sup>14</sup>

with well-differentiated disease. Critics questioned the probability estimates and the inclusion of a relatively older population of men with small, well-differentiated tumors.<sup>36,37</sup>

In assessing whether PSA testing does more good than harm, one must consider the effect of screening on other health care services. Screening typically occurs in the primary care setting, where busy clinicians are concerned with other preventive services (e.g., breast-cancer screening, immunizations, and smoking cessation) and caring for sick patients. Time devoted to prostate screening may come at the expense of other conditions that pose a greater threat to individual and public health. A similar phenomenon can occur on a national level, where other health care services could be affected by the provision of prostate screening and follow-up to the 28 million American men over the age of 50 to whom the recommendations of the American Cancer Society apply. The first year of screening could cost an estimated \$12 billion to \$28 billion,<sup>38,39</sup> and subsequent screening might cost \$3 billion per year.<sup>39</sup> If screening can reduce the disease burden from prostate cancer, this large investment might be worthwhile,<sup>40</sup> but its ability to do so remains unproved.<sup>18</sup>

### IS THERE ENOUGH EVIDENCE?

Definitive evidence of whether prostate screening and treatment improve health will be unavailable until the turn of the century, when current clinical trials will be completed. For now, the debate centers on what the appropriate policy should be in the meantime, a period during which thousands of men will die of prostate cancer. Since screening has the potential to save lives (although its actually doing so is unproved), few would question the appropriateness of screening were it not for its potential harm. Proponents and critics of PSA screening differ in the ways they balance the benefits and risks.

Proponents believe that the benefits outweigh the risks; they argue that waiting for better evidence is unnecessary and that withholding screening while men die of prostate cancer is unethical. Critics of screening worry that the risks may outweigh the benefits. They

believe that current evidence does not ensure safety and that encouraging screening without this evidence is unethical (*primum non nocere*). Until better data become available, the true balance of benefits and risks remains a matter of opinion.

### HOW TO ADVISE THE PATIENT

These uncertainties must be acknowledged when physicians counsel patients. Physicians should neither recommend nor discourage PSA testing without, first, ensuring that patients have complete information about potential benefits and risks, and second, determining their personal preferences. Although it is advisable to obtain informed consent for any screening test, it is especially important for PSA screening, because the data are unclear and patients face potentially serious consequences to health and survival by either accepting or declining the test. Patient education is also important, because most men receive incomplete or inaccurate information about PSA from acquaintances, advertisements, and the lay media.

Therefore, the first step in counseling patients is to present the facts about the benefits and harm that can result from testing and treatment. Fact sheets<sup>41</sup> and videotapes<sup>42</sup> can help provide an unbiased summary of both sides. The second step is to assess the patient's preferences. This step is necessary because the fear of cancer, the potential impact of iatrogenic complications on the quality of life, and the absence of "proof" from controlled studies mean more to some men than others. Before deciding on testing, the patient should consider the procedures that would necessarily follow an abnormal screening result and whether he would want to be treated if cancer were diagnosed. In particular, men with a life expectancy of less than 10 years should be advised that screening and treatment are unlikely to be helpful and may worsen the quality of their lives.

Once fully informed about the consequences, some patients find it difficult to make this decision and prefer instead to seek the doctor's advice. Offering an opinion in response to this invitation is entirely appropriate, but physicians who uniformly encourage or discourage PSA testing without first reviewing the facts and exploring preferences are unfairly imposing their values on the patient. For this reason, adding a PSA measurement to a panel of other tests, as one would add a potassium or hemoglobin measurement, is inappropriate if it is not preceded by the kind of discussion described above. It is equally inappropriate for a physician opposed to PSA screening to avoid the topic when patients do not request the test. Patients who are unfamiliar with PSA testing have a right to know about the availability of the test and the recommendations of groups that encourage screening.

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1-800-ACS-2345

Document 10021

**CERVICAL CANCER**

**DEFINITION**

The cervix is the narrow opening of the uterus (womb) that leads into the vagina (female sex organ). The cells lining the interior of the cervix produce mucus (a body fluid) that keeps the vaginal area moist. In childbirth, the cervix dilates (opens) to allow passage of the infant through the birth canal.

Cervical cancer is cancer that begins in the cervix. It first appears as low-grade (slow-growing) squamous intraepithelial (lining cell) lesions (sometimes referred to as LGSIL) or dysplasia, a condition in which cervical cells go through subtle changes that are clearly abnormal but are not clearly cancerous. These changes can be observed in cell samples, examined under a microscope by a trained technologist.

Next, high-grade (fast-growing) squamous intraepithelial (lining cell) pre-cancerous lesions (sometimes called HGSIL) called carcinoma in situ develop. "In situ" means that the lesion--which is not yet viewed as a true cancer--has not spread beyond the site where it started. If detected at this stage, it can be cured. Left untreated, it can become a true cancer and metastasize (spread) to distant organs, posing a threat to life.

Since the cervix is located deep in the body, and this type of cancer usually doesn't cause any discomfort or symptoms during early development, the only way to detect cervical cancer early is to have a screening test, called the Pap smear, at regular intervals.

**EPIDEMIOLOGY**

Cervical cancer is a relatively common cancer, accounting for about 16% of all cancers in women. The American Cancer Society estimates that about 80,800 new cases of cervical cancer will be diagnosed in 1995. Of these, 15,800 will be invasive (spreading into other organs) and 65,000 will be in situ.

Over the past thirty years, as the number of women having the Pap test has gone up, the number of advanced cervical cancer cases has gone down; however, the number of cases in women over the age of 50 has increased. In populations where women do not have the Pap smear, including in some groups in the United States and in all developing countries, cervical cancer rates are high, cases are diagnosed at a late stage, and the rate of deaths is higher than in women who do

have the Pap smear. It is the second leading cancer in women worldwide.

### **SIGNS AND SYMPTOMS**

- Cervical cancer may develop and begin to spread without showing any symptoms.
- Unusual bleeding, spotting (blood spots or light bleeding), or other unusual discharge from the vagina, not from the normal monthly period, may be a sign of cervical cancer.
- Pain may develop in the uterus or in the tummy area, but pain does not usually occur in the early stages of the disease.

These symptoms can be caused by a number of conditions, including some sexually transmitted diseases. If you have these symptoms, don't try to guess, and don't wait for pain to develop. See your health provider promptly.

### **RISK FACTORS**

The following conditions or situations often, but not always, lead to dysplasia or cervical cancer.

- HPV (human papillomavirus or genital warts).** HPV is a sexually transmitted disease--that is, it is passed from one person to another during sex. While men have no cervix (and therefore cannot develop cervical cancer), men can get HPV and pass it on to female partners. If you are concerned that you may have been infected with HPV, but you have no symptoms, you should request an HPV test when you have your yearly Pap smear and pelvic examination. If you have genital warts or any other symptoms that cause concern, you should see your health provider promptly.
- Having a high number of male sexual partners, or having sex with high-risk men.** In terms of cervical cancer, "high-risk men" means men who have had many sexual partners. More than five is considered high. Having many sex partners greatly increases the likelihood of infection with HPV (and therefore, the likelihood of cervical cancer). It also increases the risk of AIDS. These conditions are so closely related that the U.S. Centers for Disease Control and Prevention now defines AIDS in women as: a positive blood test for HIV (infection with the virus that causes AIDS) plus cervical cancer.
- Having sexual intercourse at a young age (loss of virginity)**
- Smoking or other tobacco use.** Nicotine and other chemicals and byproducts of smoking affect more than the lungs. These harmful substances have been found in washings taken from the cervix of women who smoke. Researchers believe that these substances damage the genetic makeup of cells in the cervix, and this damage leads to cancer.
- A high number of pregnancies, even if the pregnancy was not carried to term (there was no birth)**
- Low income level**

## EARLY DETECTION OF CERVICAL CANCER: THE PAP SMEAR

In a Pap smear, a small sample of cervical cells and the mucus made by the cervix is lightly scraped onto a swab, spatula, or brush. The sample is then "smear" onto a glass slide. The slide is sent to a laboratory where a specially trained technologist examines it under a microscope.

The Pap test can be performed by a physician, nurse practitioner, physician's assistant, or nurse, in the office. It takes only a few moments and normally, is not painful, although some women experience very mild, momentary cramping when the smear is done. Usually, a pelvic examination is also done, immediately after the smear is taken.

The Pap test can find developing cancer cells before they have a chance to spread to other places in the body. About 90% of cervical cancer cases can be detected early through the use of Pap smears. If found early, cervical cancer is almost 100% curable. Also, the earlier the cancer is found, the less complicated its treatment will be.

## WHO SHOULD GET A PAP TEST

All women who are sexually active or over the age of 18 should have a Pap test each year. Even women who have had a hysterectomy (surgery to remove the uterus), should continue to have annual vaginal examinations and Pap smears because these can help to detect cancer of the vagina.

## WHAT THE PAP SMEAR RESULTS MEAN

An abnormal result of a Pap smear does not necessarily mean cancer. In addition to finding cancer cells, the Pap test can also show dysplasia, which means that there are abnormal, but not cancerous cells.

If your Pap smear shows abnormal (not normal, average, or typical) cells, you may need an additional test called a colposcopy. In colposcopy, an instrument with a magnifying lens is inserted into the vagina. The lens makes it possible to see the tissues of the vagina and cervix more closely. This examination has no side effects. If you are pregnant, your health care provider may choose to wait until after the delivery to do the colposcopy; however, it can be done safely during pregnancy.

Two types of cancer are found in the cervix:

- Squamous cell carcinoma comprises 90% of cervical cancers. Squamous cells are scale-like cells that make up passage membranes such as the cervix.
- The remaining 10% are adenocarcinomas, which begin in the cervical glands.

In examining the Pap smear, the technologist uses a classification system and terminology, called the Bethesda system, to answer the following questions:

- Is the sample adequate for evaluation? If not, it will be necessary to have the test again.
- Are the sample cells normal, going through benign (non-cancerous) changes, or abnormal?

- If the changes are benign; are they due to infection with yeast, fungus, bacteria, or virus? Or are the changes reactive--caused by routine cellular repair work, or aging, or an intrauterine contraception device (IUD)?
- If the changes are abnormal, do they indicate cancer development? If yes, is the cancer squamous cell or adenocarcinoma? Is the cancer high-grade (fast-growing) or low-grade (slow-growing)?
- If the cancer is adenocarcinoma (glandular), did it begin in the cervix, in the lining of the womb, or in the uterus?
- If a vaginal smear has been taken, is the hormonal pattern of the vaginal cells normal for the woman's age and history?

## STAGING

Once a diagnosis of cervical cancer is certain, the next step is to determine the stage (extent) of the cancer. Staging is a very important step, because selecting the most effective treatment depends on the stage of the cancer. If you have cervical cancer, ask your cancer care team to explain the stage of your disease. This way, you can participate in making informed decisions about treatment.

For staging, your cancer care team considers:

- The size of the lesion or tumor
- How deeply the tumor has invaded the tissues at the site of development
- The extent of any invasion into surrounding organs (the uterus, the pelvic wall, the vagina, the rectum, the bladder)
- The extent of invasion of distant organs

To obtain this information, you will need additional tests, which may include:

- Biopsy**, removal of a sample of the cancerous lesion, for examination under a microscope. Selection of areas to be biopsied may be based on the colposcopy results.
- Cone biopsy**, in which a cone-shaped portion of tissue is removed for examination under a microscope. This type of biopsy shows how deeply the tumor is invading underlying tissue.
- A complete physical examination**, with special attention to the lymph nodes (for evidence of metastasis), the bladder (for evidence of blockage or local extension of the tumor), and the cervical ligaments and rectum (for evidence of local extension). Based on the findings of the physical examination, **cystoscopy** (examination of the bladder) or **proctoscopy** (visual inspection of the rectum by way of a lighted tube) may be needed.
- A chest x-ray**, if the cancer is not in a very early stage (cervical cancer can spread to the lungs, but this is very rare)
- Computed tomography (CT) scans**, to check the urinary tract and the lymph nodes. In this imaging method, an x-ray beam rotates around the body, taking images at various angles. The images are then put together into 3-dimensional views by a computer. A contrast medium (special dye) may be injected, to highlight details. If the lymph nodes look suspicious, they may be biopsied, using the CT scan or ultrasound imaging as a guide.
- Examination of the cervix under anesthesia**, to determine the extent of

disease in the cervix, especially if radical hysterectomy (surgical removal of the uterus, tissues around the uterus, and a segment of the vagina) is under consideration. If surgery is performed, the retroperitoneal lymph nodes (those at the rear of the abdominal and pelvic wall) may be examined.

- Cystoscopy (examination of the bladder)
- Proctoscopy (examination of the rectum)

Invasive cervical cancer can spread through the bloodstream or the lymph nodes (a network of pea-sized glands that produce white blood cells and fight infection) into other parts of the body. Occasionally, cervical cancer behaves in an unpredictable manner, showing up as a small tumor, but with new tumors already establishing themselves at a distant site. Most cervical cancer takes ten to twelve years to develop to the point of invasive cervical cancer; however, in about 10% of women, invasive cervical cancer can develop in one year or less.

If you have cervical cancer, ask your cancer care team to explain the stage of your disease. This way, you can participate in making an informed decision about treatment.

#### **DESIGNING A TREATMENT STRATEGY**

After the diagnostic tests, when your disease stage is known, your cancer care team will recommend a treatment strategy. Consider the options without feeling rushed, and if there is anything you don't understand, ask to have it explained again. Your overall physical health, the nature of your disease, and your unique situation in life are all essential factors for determining a treatment plan. Together, you and the members of your cancer care team should develop a plan and a follow-up program that fits your particular needs.

Whatever your situation, you may want to seek a second opinion for personal or practical reasons. Personally, pursuing another medical perspective can deepen your understanding of your treatment options. A second opinion may reassure you in your decision to work with the first medical team you consulted, or you may find that the second treatment situation suits you better. On the practical side, some insurance companies require a second opinion before authorizing reimbursement (payment for your cancer care expenses).

#### **TREATMENT FOR SQUAMOUS INTRAEPITHELIAL LESIONS (LGSIL, HGSIL)**

Although squamous intraepithelial lesions are not cancer, it may need to be treated. Treatment choices are:

- Cryosurgery: Freezing and then removing abnormal cells.
- Laser surgery: A focused laser beam is used to burn off abnormal cells.
- Electrosurgical loop excision diathermy (LEEP): Use of a small looped wire with electric current to generate heat and burn off cancerous cells.
- Electrocautery: With electric current, burning off abnormal cells.
- Hysterectomy: Surgical removal of the uterus and cervix.

#### **IF YOU ARE PREGNANT**

Treatment for cervical cancer may differ significantly if you are pregnant. If you have cervical cancer and are pregnant, talk with your cancer care team about your options.

### **IF YOU ARE NOT PREGNANT**

The choice of treatment depends on your age, the stage of the cancer, and whether you wish to have children. Hysterectomy means that you can no longer bear children.

### **TREATMENT OF CERVICAL CANCER, ACCORDING TO STAGE**

The stage of cervical cancer is classified by the FIGO system. (FIGO stands for International Federation of Gynecologists and Obstetricians). In general, the higher the stage, the more difficult the cancer is to treat successfully. Metastasis means that the disease is spreading beyond the original tumor.

When radiation is used, it may be given as external beam radiation, which is like having an x-ray, but for a longer period of time and at a higher dose of x-rays, or as a radiation implant, which is inserted into the cervical area for a specified period of time.

**Stage 0** means the tumor is in situ (it has not begun to spread into adjacent or nearby tissues).

**Stage I** means that the tumor involves more tissue, but has not spread beyond the cervix. Treatment at these stages is usually highly successful. During pregnancy, no treatment is given for these stages. Otherwise, treatment options include:

- Electrosurgical loop excision diathermy (LEEP), as described above.
- Laser surgery, as described above.
- Conization: Removal of a cone-shaped section of tissue that includes the cancer. Cold-knife conization means that high-frequency current is used for the procedure.
- Cryotherapy, as described above.
- Radiation (without surgery): A radiation implant is applied to the affected area. This method is chosen only if other health conditions make it risky or impossible to perform a hysterectomy. Depending on the size of the lesion, external radiation may also be performed.
- Total hysterectomy (removal of the uterus and cervix): This may be done via an incision through the abdomen or through the vagina. This treatment is often recommended for women past the childbearing years, or when the cancer has begun to spread to areas surrounding the cervix. Depending on age and the circumstances, oophorectomy (removal of the ovaries) may also be done. If it appears that the tumor has begun to spread beyond the original site, it will be necessary to check the lymph nodes during surgery.
- Radical hysterectomy, with bilateral pelvic lymphadenectomy. More extensive (wider) surgery to remove the uterus and cervix, plus removal of the pelvic lymph nodes to check for spread of the disease. This is sometimes

followed by external beam radiation to the pelvic area (the area between the hips).

**Stage II:** The cancer has spread beyond the cervix, but not past the upper third of the vagina or into the uterus, or the tumor has spread to the uterus, but not beyond. The options are:

- Radiation: External beam or implant(s), with or without hydroxyurea (a cancer-fighting drug).
- Radical hysterectomy and pelvic lymphadenectomy, often followed by external beam radiation to the pelvic area: Removal of the uterus, cervix, and nearby lymph nodes.

**Stage III:** The cancer extends to the pelvic wall or the tumor involves the lower third of the vagina, or the cancer has spread to one or both kidneys, or is blocking the flow of urine to the bladder. Treatment options include:

- Radiation: External beam or implant(s), with or without hydroxyurea.

**Stage IV:** This means that the cancer has spread beyond the pelvis or into the bladder or rectum or both, or the kidneys, or to one or more distant organs. The preferred treatment is:

- Radiation: External beam or implant(s), with or without hydroxyurea.
- Chemotherapy: Treatment with powerful cancer-fighting drugs, especially cisplatin or ifosfamide, when distant organs are involved.

### **RECURRENT (RE-OCCURRING) CERVICAL CANCER**

If the recurrence is at a distant site, there is no standard treatment. If the recurrence is not distant, very extensive pelvic surgery to remove all of the affected tissue and organs may be used, often in addition to radiation or chemotherapy (or both), using fluorouracil, with or without mitomycin. To relieve painful symptoms of advanced disease, chemotherapy with cisplatin, ifosfamide, or a combination including ifosfamide or radiation therapy may be helpful.

### **SIDE EFFECTS OF TREATMENT**

Before you begin treatment, it's a good idea to ask your treatment team about the side effects you can expect. They should have a good idea about what side effects are usually experienced during therapy, how long they might last, and how serious they might be. This can help you to plan and manage your normal activities during the time you will be treated.

If you experience any symptoms related to your treatment, be sure to report them right away to your cancer care team, especially the nurse. There may be ways to relieve the symptoms. For example, new medications recently developed can be given before, after, or during chemotherapy to prevent or stop nausea and vomiting. Also, if you are having trouble staying on therapy, for any reason, don't quit. Talk with your cancer care team. It may be possible to adjust the dosage or the treatment schedule to make it easier for you to complete all the treatments you

need.

### **PROGNOSTIC (OUTCOME) FACTORS**

Early detection of cervical cancer saves lives. Ninety percent of women who have been diagnosed with in situ cervical tumors survive five years or more.

For those women who have invasive cervical cancer, the survival rate varies a great deal, depending on where the cancer has spread.

If you have questions about your personal chances of cure of cervical cancer, or how long you might survive such a cancer, talk with the people who know your unique circumstances best—your cancer care team.

### **ORGANIZATIONS AND RESOURCES**

For additional information on cervical cancer, contact the National Cancer Institute's Cancer Information Service at 1-800-4-CANCER. A list of clinical trials appropriate for your unique situation will be sent on request.

### **REFERENCES.**

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**SENATOR JIM DUNCAN**  
*ALASKA STATE LEGISLATURE*

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Alaska State Senate

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State Capitol • Room 119 • Juneau, Alaska 99801-1182 • (907) 465-4766 • Fax 465-4748

February 2, 1996

**SB 253**

**Mandating Insurance Coverage for Prostate Antigen Blood Tests**

Senator Jim Duncan today introduced legislation which will require that insurance companies doing business in Alaska include Prostate-Specific Antigen (PSA) screening as a covered benefit.

Many insurers do not cover this blood test which the American Cancer Society recommends be performed annually on all men 50 years of age and older as a part of an annual prostate examination. The American Cancer Society also recommends that PSA screening begin at the age of 40 for men at high risk.

"I believe providing coverage for this important test can save lives or improve the quality of life for many Alaskan males," Duncan, a Juneau Democrat, said. "In 1991, the Legislature mandated insurance coverage for mammograms, and SB 253 represents a similar step towards preventative health care for men."

According to the National Cancer Institute, prostate cancer is the most common malignant cancer in American men. Prostate cancer is now the second leading cause of death in men, the first being lung cancer. The PSA test clearly increases the detection rate of early stage cancers, thus resulting in better, less invasive medical treatment for the patient.

-30-

PRESS RELEASE

March 26, 1996



R. McCaughan, M.D.

Diplomate,  
American Board  
Of  
Urology

227 Glacier Highway  
Juneau, Alaska 99801

(907) 586-5656  
Fax (907) 588-0081

Senator James Duncan  
FAX 465-4748

Dear Senator Duncan:

Thank you for your request for testimony in regard to your wish to have Aetna cover the cost of prostate-specific antigen testing on a routine screening basis.

As you have undoubtedly learned, this is not currently covered as a screening test. To be fair, its reputation as a screening test is controversial. However, we all know of personal anecdotal incidences, and as a urologist I know of many situations whereby curable prostate cancer was diagnosed solely on the basis of the patient having had a PSA determination. Admittedly, it is falsely positive on numerous occasions. However, it is impossible to place a value on a life saved by early detection of prostate cancer.

As you likely know, the incidence of the diagnosis of prostate cancer, particularly in a curable stage, has dramatically increased over the past few years. While our ultimate ability to make the diagnosis depends on prostate ultrasound and ultrasonically-guided needle biopsy as well, the initial suspicion of the possibility of prostate cancer is almost always the result of an elevated PSA. The time-honored method of diagnosing prostate cancer has heretofore been the annual rectal examination. There are increasingly dismal statistics to back up the fact that while this exam certainly does pick up curable prostate cancer, it also simply points out the probability of prostate cancer, which in many cases is no longer curable.

To summarize, PSA determination is indeed an important, and perhaps the most important, first line test for the early diagnosis of curable prostate cancer. Like many medical tests, it certainly has a significant incidence of false positivity, however, the fact remains that it is essential as a part of our diagnostic armamentarium in regard to uncovering curable prostate cancer. The current recommendations, depending on various sources, would generally suggest that annual PSAs be done on the 50 to 60-year-old age group, and semiannual PSAs beginning at age 60. This should be done ten years earlier if there is a first degree relative with the diagnosis of prostate cancer or if one is an African American.

I regret that I could not attend your committee meeting to testify in person. My failure to do so does not indicate a lack of interest, but rather a schedule which could not be changed without inconveniencing multiple patients to do so.

If I may be of further help in achieving your goal of including PSA determination under Aetna coverage, please do not hesitate to call or write.

Sincerely,

Mark R. McCaughan, M.D.

MRM/blh

- LETTERS OF SUPPORT (3)

TO: JIM DUNCAN  
466-4748

FIXED: 10:05 a.m.  
3-7-96

FROM: JIM STUGHTON

March 5, 1996

Senator Jim Duncan  
Alaska State Capitol  
Room 117  
Juneau, AK 99801-1182

Dear Senator Duncan:

It's my understanding that you are introducing a bill for all insurance companies to pay for a prostate specific antigen or PSA testing for Prostate Cancer. I think this is wonderful and way past due for prevention and early detection of Prostate Cancer.

In addition, I recommend that you include coverage for a PAP test which is required if someone has an elevated PSA result. Also, please consider coverage for a penile implant. Many men lose the ability to obtain an erection after surgery due to nerve damage, including myself who underwent Prostate surgery at the age of 55.

I did not have any symptoms of Prostate Cancer, but it was discovered with the PSA screening done at an routine physical. Having had the surgery after a second opinion by a Urologist in Seattle, I have and will take for my lifetime a chemotherapy oral medication and a monthly injection. These two medications cost \$298.35 and \$523.25 per month.

The American Cancer Society promotes prevention and early detection. Having the insurance companies pay for the PSA screening which is approximately \$200.00 as likewise a PAP screening if required will save money and lives.

My coverage under the State of Alaska's Aetna plan will not cover a penile implant. Yet, the same plan will cover a breast reconstruction for a women that has had to undergo a mastectomy. The breast is a non operating organ. I do not resent this because there is also an psychological impact with either of these procedures for a cancer patient.

Please consider amending your bill to cover all of these procedures.

I would like to testify at the hearing, but unfortunately, I work for the Alaska Marine Highways and will be out on the ship. Please accept this letter as my testimony.

According to the American Cancer Society, Prostate Cancer incidence rates increased 50% between 1980 and 1990, largely due to improved detection. There was approximately 40,000

due to improved detection. There was approximately 40,000

deaths in 1995, the second leading cause of cancer death in men, with lung cancer being number one. The 5 year survival rate for patients with prostate cancer diagnosed while it is still localized is 94%.

Sincerely,

*Jim Stoughton*

Jim Stoughton  
4410 Riverside Dr.  
Juneau, Ak 99801

I am here to speak in support of SB 253, relating to insurance coverage for costs of prostate cancer detection. Presently, women live longer than men. This bill would increase men's odds of survival!

If you exclude skin cancer, prostate cancer is the leading cause of cancer in men. In the U.S., there were 200,000 new cases in 1994. It is the second leading cause of death from cancer in men, causing 38,000 deaths in the U.S. in 1994.

Certain factors place some men at greater risk for developing prostate cancer. These include: African-American background, increasing age, and perhaps a diet high in fat intake. The course of prostate cancer is extremely variable. Some tumor subsets are aggressive, grow rapidly, metastasize quickly and lead to a rapid death. Generally, they are slow growing, do not present symptoms, and are only found incidentally at autopsy.

PSA is an enzyme test that measures prostate specific antigen in the blood. This protein is specific to the prostate, but not to prostate cancer. So blood levels of the protein correlate to the amount of prostate tissue. This means that all kinds of prostate tissue, whether it is normal or malignant, may increase the PSA. Eighty percent of men with prostate cancer, will have an increase in PSA. A smaller increase is occasionally seen in older men with an enlarged prostate, which is a common condition in elderly males. If PSA results are low (< 4 ng/ml.), one feels reassured. If results are high (>10 ng/ml.) the client is referred to a urologist. Results between 4-10 are in "the gray zone". This is considered a minimal elevation. Twenty five % of these men (with results between 4-10) will have prostatic cancer, regardless of the finding on a digital rectal examination.

Most authorities who recommend the PSA test, advocate combining it with other modalities such as digital rectal examination or trans-urethral ultrasound. Although PSA misses about 20-30% and digital rectal exams miss about 50% (range, 14-64%) of prostate cancer, the two together detect an additional 15-20% or more over results from either one alone.

The treatment for prostate cancer is surgery and/or radiation. Urinary incontinence is a complication in 30% of cases.

1

Routine screening of men without symptoms of prostate cancer is controversial. Presently, no data links PSA screening with a decrease in deaths from prostate cancer. The FDA has not approved PSA as a screening test for early detection, although it is approved for monitoring patients who already have prostate cancer.

The American Cancer Society (ACS) and American Urological Assn. (AUA) recommend annual PSA testing for all men aged 50 and older. Both of these professional organizations recommend annual screening for men younger than age 50 who are in high-risk groups. This includes men 40 and over with a family history of prostate CA & men who have had their vasectomy at 40 or older.

The AUA recommends stopping annual testing at 70.

The ACS recommends screening be stopped when the patient's life expectancy is <10 years.

The American Academy of Family Physicians, Canadian Task Force on Periodic Health Examinations, National Cancer Institute, and US Preventive Services Task Force do not recommend routine screening in asymptomatic men

The negative side of this testing is that up to 70% of men with PSA levels b/w 4-10 will not have prostate cancer and may undergo the expense, discomfort and emotional stress of additional diagnostic studies for no benefit.

The possible benefits of PSA screening are:

- men are more willing to have a blood test than a physical exam.
- if it is combined with a digital rectal examination, there is a 2-3 time increase in prostatic cancer detection rate
- a decrease in death from prostate cancer that is discovered early. However, there is no current data available to demonstrate this. (This test has only been available since 1979, hence the reason for the lack of long-term data)
- PSA may improve the specificity of prostate cancer screening and reduce unnecessary biopsies.
- it is the most cost effective way of screening for prostatic CA. (The cost of a PSA at Corning Lab is \$43.30. A trans-urethral ultrasound in a urology office is \$325.00)

More specific screening tests are needed. As we speak are being developed. They include:

- adjusting for increasing age
- measure serial PSA's and calculate the rate of change
- calculate the ratio of PSA level to the volume of the prostate (PSA Density)

Although this is not a perfect test, it is the best that we have for now. The Alaska Nurse Practitioner Association recommends that this bill be passed with the goal of detecting prostatic cancer at a curable stage, thereby improving men's health.

*Mary Anne Wilson*

Testimony presented by  
Mary Anne Wilson, MS, RN, CS, ANP  
Alaska Nurse Practitioner Association  
Secretary and Legislative Representative

MR. EVANS replied it would be considered in the underwriting process. Any mandated benefit usually leads to some sort of an increase in premiums. He noted that he is covered by state health insurance through his wife, and they have always paid for PSA tests for him. So he does not know why they say some companies aren't covering it now.

CHAIRMAN KELLY asked if there is anyone who disagrees that the state health insurance policy pays mandated benefits.

Number 207

CAROL EDWARDS, RN and nationally certified oncology nurse, stated her husband was turned down for his PSA screening. She believes that men deserve the same rights in PSA testing that women receive in mammogram testing. Mandating insurance companies to pay for mammogram screening is now common throughout the United States. She believes that mandating payment by insurance companies for PSA screening will follow. Prostate cancer is the most commonly occurring cancer in men in the United States: 41% of all cancers in men are prostate cancers. A lot of men die with prostate cancer, and not of it. If a man lives to be 90 years old, he will probably have prostate cancer, although it will probably not be the cause of death.

Number 244

Ms. Edwards stated that the younger a man is, the more aggressive prostate cancer will be, and the more likely that it will be the cause of death. Early detection of prostate cancer is the best chance for a cure. Ms. Edwards stated that unfortunately, she mostly sees patients with cancer in more advanced stages. Ms. Edwards stated that Aetna refused to pay for a PSA test for her husband, even though his father died of prostate cancer. He has a State of Alaska health insurance policy, and he carries the rider for the annual physical. In a letter, Aetna stated they would not pay for the PSA test, even though he was considered high risk, because it was a questionable test. Ms. Edwards stated it is a debatable test.

CHAIRMAN KELLY asked if that test that will be mandated by SB 253.

MS. EDWARDS responded it is.

CHAIRMAN KELLY asked if the state will, at this time, pay for prostate examinations.

MS. EDWARDS replied they will pay for a digital rectal examination. They will pay for a cardiac risk profile: her husband has no risk of cardiac disease, but they will pay for that test. He does have a risk of prostate cancer, but they will not pay for a PSA test. They won't pay for this one particular test, which at Bartlett Memorial Hospital costs between \$60.00 - \$70.00. She stated that her family is personally willing to pay for that, because they are capable of doing so. But it is the individual who is less knowledgeable and would not know the value of the test who might not be so likely to pay out of pocket. Ms. Edwards stated that in the oncology world there is a phrase called "oncology family

syndrome". This phrase means that if there are three generations of cancer in your family, and it does not have to be the same type of cancer, then you are considered to be at high risk for having cancer.

CHAIRMAN KELLY asked how family is defined.

MS. EDWARDS thinks it goes back through generations. She knows that mother, grandmother, and great-grandmother are considered to be in those studies.

CHAIRMAN KELLY asked Ms. Edwards what word is used to describe family relationship and degrees of family relationships.

MS. EDWARDS stated she would be willing to find that information for the committee.

CHAIRMAN KELLY stated the committee would appreciate that. He asked if there were any questions. Hearing none, he asked if anyone knew the word used to define that whole phrase.

MS. EDWARDS asked if the chairman was thinking of "immediate family".

CHAIRMAN KELLY responded that is not the word. He came across it when he was working for the Nevada Legislature. He called Mr. Chisholm to testify.

Number 299

BILL CHISHOLM stated he works in the claims field for the State of Alaska, and is covered by Aetna for almost everything. He stated he spends a great deal of time reviewing insurance provisions and supports SB 253. Mr. Chisholm stated that in 1991 during his annual physical, his physician recommended he take the exam. He did, and Aetna paid for it. Aetna also paid for the PSA exam for his 1992 physical. In 1993, Aetna would not pay for the test, and they have not paid for it since then. When he called Aetna to inquire why they did not pay for the test, he was told that the test was not an acceptable diagnostic tool. He believes that a test of this type is probably more accurate than the examination which involves a physician facing a somewhat squirming subject and trying to determine size and hardness or softness of a particular part of the body. In looking at the 1994 denial, it states that, "Services must be broadly accepted, professionally as effective, appropriate and essential treatment of disease or injury. Based on that, this is not covered." Mr. Chisholm pointed out that whether it's a PSA screening or a digital rectal exam, they are both for detection, not for treatment. He believes that men should be entitled to have the best screening possible for a potential disease of this type.

CHAIRMAN KELLY asked Dr. Palmer to testify.

Number 348

DR. PALMER, a Juneau physician, explained family genetic are such that certain problems can skip generations in people who are

SUNDAY

4/21/96

from the  
**SIDELINES**

# With Miller back, I feel lots better

By MIKE STEWART  
THE JUNEAU EMPIRE

**W**hat a joy it was to see Mike Miller at the Augustus Brown poolside in the Southeast Regional Championships over the weekend.

Here he was helping kids with their techniques, jotting notes, talking to parents and helping direct the meet, just as he's done for the past 14 years as the coach of the Glacier Swim Club.

The pool - indeed, the community - hasn't felt right in the past few months in his absence. Selfishly, it made me feel much better to see him in the role of a coach again, instead of wondering how he was doing far away in an Oregon hospital as a patient.

For those who aren't aware, Miller was diagnosed with prostate cancer on Jan. 17. That bad news quickly got worse when it was discovered it had spread to bone cancer. He now has a tumor on his spine at the base of his neck and three more on his skull.

"They have what's called a staging cell of A through D," Miller explained of cancer cell progression on Saturday in his office above the pool. On the deck below, some 250 kids from five Southeast communities battled for region honors. "I'm at a D-2 range, which is classified as incurable."

On a scale of 1-10, Miller was told his form cancer was a very aggressive, high-grade 9. The bat-

## Next stop: Olympics



BRIAN WALLACE / THE JUNEAU EMPIRE

Glacier Swim Club coach Mike Miller talks to Eric Moss, 8, on Saturday during the Southeast Regional Championship meet at the Augustus Brown pool. Miller was at poolside for the first time nearly three months since being diagnosed with prostate cancer. He's wearing sunglasses by

ressive, high-grade. The bottom line: he was given 17 to 35 months to live.

"You're scared, you just go numb," he said of his reaction upon learning his condition. "My immediate concern was for my wife (Judy) and my whole family."

The Millers thought they could handle anything. They've had good training for this sort of situation. It was only five years ago when their son, Todd, faced another life-threatening situation. He was hit by a truck while riding his bike. For a few agonizing days they didn't know if Todd would survive. Thankfully, he's since made a near-complete recovery.

"We'd been through this trauma once before," Miller recounted. "We felt like we'd have a better go-round because of our experience."

But they learned the pain, the fear, doesn't go away, no matter how many times a family is confronted with death.

"That hasn't been the case," Miller quietly agreed. "It's been difficult at times."

Despite having every reason to feel cheated and bitter for all of their recent hardships, the Miller family members have tried to remain positive throughout. And, Miller added, there is reason to be positive.

First, he said the love from his family and the overwhelming support he's received from the community are a springboard to health in even the most dire situations, regardless of how bleak the prognosis is.

"That's the bottom line," he said. "You have this awareness of how much love they have for you, and you for them. It makes all of us strong."

To the point of healing?

"I believe it can do that."

Further, Miller has undergone a radically new - and dangerous - treatment which has been remarkably successful. A normal prostate specific antigen count is around four or below. When Miller was first tested, his PSA count was a whopping 26.6.

What does this mean in medical terms?

"Basically, I was off the Richter scale," he chuckled.

But in the less than two months that he's received hormonal treatment in combination with the drug Suramin, his PSA level has dropped to a minuscule .05.

"That makes everyone at Oregon Science Health University kind of jazzed," Miller said, referring to the clinic where he receives treatment. "There's only 20 people in the country getting this same treatment, and I've had

Please see Sidelines, Page B3

nearly three months since being diagnosed with prostate cancer. He's wearing sunglasses because of the treatment he's receiving.

## Suddenly cool Mariners lead

THE ASSOCIATED PRESS

SEATTLE - Juan Guzman allowed five hits in eight innings, and Shawn Green homered and doubled in the go-ahead run Saturday night, leading the Toronto Blue Jays over the Seattle Mariners 3-1.

Ken Griffey Jr., batting just .217, accounted for Seattle's run with his sixth homer. The Mariners lost their second straight following an eight-game winning streak, which tied a team record.

Guzman (3-1) allowed five hits in eight innings, struck out seven and walked two. Mike Timlin pitched a perfect ninth for his third save.

After allowing Griffey's homer in the first, Guzman loaded the bases on walks to Edgar Martinez and Paul Sorrento and an error by centerfielder Otis Nixon on a drive by Jay Buhner.

Guzman retired Doug Strange on a liner to shortstop, ending the inning, and Seattle failed to get a runner past first base after that.

Paul Menhart (0-2), who has a

## Yanks 'Doc' not feeling well after getting sent to bullpen

THE ASSOCIATED PRESS

MINNEAPOLIS - Dwight Gooden, 0-3 with an 11.48 ERA in three starts for the New York Yankees, was demoted to the bullpen Saturday.

Gooden, back in the majors after a 1½-year suspension for violating his drug aftercare program, was dropped from the rotation a day after his worst outing of the season, a 7-1 loss to Minnesota.

"I have no problem with it," Gooden said. "That tells me a lot of work needs to be done."

Gooden gave up six runs, three hits and four walks in three innings Friday night. Manager Joe Torre informed Gooden of the decision when the pitcher arrived at the Metrodome for Saturday night's game.

"We have no choice at this point," Torre said.

Torre said he considered moving Gooden to the minors. He believes pitching coach Mel Stottlemyre is the best person to coach Gooden. Stottlemyre, Gooden's pitching coach with the Yankees, said:

Please see Gooden, Page B3

7.15 ERA, gave up all three runs and seven hits in six innings.

He opened the game with walks to Nixon and Domingo Cedeno, then allowed a two-out infield sin-

gle to Joe Carter that scored on.

Green led off the second with his first homer of the year, Toronto a 2-1 lead. Doubles

## Mets top Rockies, halt skid

■ Vizcaino's two-out, run-scoring hit in 10th inning decides it

THE ASSOCIATED PRESS

NEW YORK - Jose Vizcaino, back in the lineup after the birth of his son, singled home the winning run with two outs in the 10th inning Saturday and the New York Mets beat the Colorado Rockies 4-3, ending a three-game losing streak.

Andres Galarraga homered twice, doubled and drove in all three Rockies runs. He led off the ninth inning with a home run against John Franco (2-0), tying it at 3.

Rey Ordóñez opened the Mets' 10th with a bloop single off John Habyan (1-1) and moved to second on a two-strike sacrifice by pinch-hitter Brent Mayne. Vizcaino sin-

Please see NL Page B3



He's Met his match: Colorado's Walt Weiss, right, is about to hit Jose Vizcaino on Saturday at Shea Stadium as Weiss tries to turn a double play.



CHRIS WALLACE / THE JUNEAU EMPIRE  
Soccer player Heidi JunEAU on Saturday in a scrimmage. Kristi West moves in their regular season this

gled, and Ordonez slid home ahead of right fielder Dante Bichette's throw.

Viccaino left Friday night's game for a pinch-hitter when his wife, Jessica, went into labor with the couple's third child. Their son, Jonathan, was born later in the evening.

#### Giants 8, Cubs 4

Barry Bonds homered, doubled and drove in three runs Saturday and the San Francisco Giants ended Chicago's four-game winning streak.

The teams combined for five home runs, taking advantage of 21 mph winds. A day earlier, the clubs hit nine homers.

Bonds went 3-for-5. He led off the third inning with his sixth homer, towering shot onto Sheffield Avenue beyond the right-field bleachers, and had a two-run double in the fourth.

Steve Scarsone also homered for the Giants. Brian McRae homered to lead off the

was the loser.

#### Expos 11, Pirates 2

Darrin Fletcher hit his first grand slam and tied a career-high with five RBIs and Henry Rodriguez homered twice, leading Pedro Martinez and the Montreal Expos past Pittsburgh.

Martinez (1-1) pitched three-hit ball for eight innings, giving up home runs to Nelson Liriano and Jeff King.

Rodriguez, who also doubled and drove in four runs, and Moises Alou hit consecutive home runs in the first inning against John Ericks (0-3). Ericks has lost eight straight decisions since last Aug. 5.

Fletcher hit grand slam off reliever Lee Hancock during a six-run third inning and added an RBI single in the fifth.

#### Cardinals 1, Phillies 0

Brian Jordan singled home the winning run with two outs in the ninth, giving St. Louis its second straight 1-0 victory over Philadelphia.

Ricky Bottalico (1-1) walked Royce Clayton leading off the ninth, Pat Borders sacrificed and Willie McGee walked. Ron Gant struck out and

finished with a perfect ninth for his fifth save.

#### Braves 6, Padres 5

Ryan Klesko matched his career high with four hits, including a double and triple, and scored the go-ahead run.

With one out in the eighth and the score tied 5-all, Klesko tripled off Doug Bochtler (0-1). Javy Lopez walked and pinch-hitter Dwight Smith lifted a sacrifice fly to right, the first RBI this season by a Braves pinch-hitter.

Greg McMichael (1-0) pitched a perfect eighth, and Mark Wohlers got three outs for his fifth save. Atlanta has won five of its last six, including three straight over the Padres.

#### Marlins 7, Dodgers 4

Hideo Nomo, who struck out a career-high 17 against the Marlins in his previous outing, was knocked out in the fifth inning.

Joe Orsulak hit a two-run homer just inside the right-field foul pole, his first home run since last Aug. 17. Gary Sheffield hit a solo shot off the upper-deck facade, his seventh homer of the season, helping the Marlins win their third straight.

Casey will get only his fourth start since he was recalled from the International Hockey League on Feb. 21. He appeared in seven others as a backup. Casey, however, is not a playoffs rookie. In 1991, Casey led the underdog Minnesota North Stars to the Stanley Cup finals.

"Fortunately for us, he's an experienced goalie," general manager-coach Mike Keenan said. "He took a team to the Stanley Cup finals. He may rise to the occasion."

#### Detroit at Winnipeg

The Jets are hoping for a boost from a sell-out crowd of 15,000 at Winnipeg Arena, where the Jets were 22-16-3 during the regular season. Winnipeg, which was outshot 34-18 Friday night, also was 12-11-4 against Central Division opponents, including Detroit, this season.

#### Blackhawks at Flames

With Calgary blaming poor officiating in part for its deficit, Chicago center Jeremy Roenick is trying to guard against a Flames backlash.

"I'm sure they're an angry team, a team that's going to be motivated," Roenick said

## Sidelines...

Continued from Page B1  
the fastest drop."

However, there are potentially disastrous side effects to this treatment.

"It's highly toxic. If your body rejects it, you die," Miller said. "It was frightening, but I said, 'Sign me up.'"

Less frightening side effects exist, too. For instance, his testosterone level has been depleted significantly by the doctors, because it is a carrier of the cancer cells. The testosterone is replaced with estrogen, a female sex hormone.

This leads Miller to be more emotional than he'd like at times, and he also experiences uncomfortable hot flashes, much like a woman who is going through menopause.

Yet he says with a smile, "I have the best of both worlds, I'm

a guy on the outside and a woman on the inside."

The way he sees it, these are minor nuisances in the road to recovery.

While Miller certainly appreciates the help he's received from some of the finest medical help in the country, he said the flip side of all this has been that being away from home for such long periods of time has been agonizing. He's only been out of Portland for about a week since starting his treatment.

"You have your ups and downs. It was really bad around Easter; I was really homesick."

Miller believes recovery is possible, but he doesn't put up any kind of a false front. He isn't giddy with an artificial excitement, nor does he weave around the room throwing left jabs at an imaginary foe, promising to go the distance if that's what is required to beat this puzzling illness.

Instead, he emits a sort of comfortable reassurance.

"The whole key is just having a chance to prolong your life," Miller said. "I guess I can accept facing death a little better now. We're all going to die. How long do I have? I don't want to put a timeline on it. I just want to enjoy each day."

This appreciation, he said, is a silver lining in what has been a very cloudy past two months. Enjoying life isn't a convenient excuse to make the prospect of death easier to accept, he added. You can't ignore death, but if we incessantly worry when we might die, Miller said, we miss celebrating every moment of life.

"I've always been sort of emotional about things," Miller said. "But now I have an even more intense feeling; I'm much more sensitive. I look across the channel to the mountains and see the snow and trees and really enjoy it. You just have so much more of

an appreciation for life."

It was a very reassuring thing to see Miller again. He looked wonderful and healthy. Except for the dark glasses he had to wear - the treatment he's received makes his eyes sensitive to bright light - one wouldn't have noticed anything different about him at all.

Maybe that's because there is nothing different. He's the same caring, thoughtful person we all knew him to be three months ago when he left for treatment.

I confessed to Miller that I think his visit here helped me more than it helped him. He said that was normal, noting that he's learned it's important for those ailing not to hole up in a hospital or health-care facility.

"It's better for people to see me; it reassures them. You have cancer and they think automatically you're dying," he said.

Mike Miller's message is clear: I'm more alive than ever.