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The Benefit and Cost of Prostate Cancer Early Detection

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Abstract

Cost-effectiveness calculations of prostate cancer early detection have not been possible due to the lack of any data demonstrating reduction in mortality from any test or procedure. Prior analyses focused only on cost assessments without consideration of any possible benefits. We used current data from three consecutive years of the American Cancer Society-National Prostate Cancer Detection Project to assess different economic perspectives of test performance, marginal costs, and benefit-cost analysis.

The marginal cost, or cost per cancer, of digital rectal examination (DRE) markedly increased by the third year relative to several proposed prostate-specific antigen (PSA) scenarios. Sensitivity analysis for average cost showed that at 4 ng/ml, pricing PSA below $30 would be the most potent factor in potentially lowering costs. Analysis of receiver operator characteristic curves suggested that optimal performance for PSA may be at 3 ng/ml when combined with DRE or between 2 to 3 ng/ml when used alone.

Benefit-cost calculations demonstrated that DRE when performed by highly skilled examiners had the lowest cost. However, DRE became one of the most costly detection scenarios when a minor decrease in performance was assumed. Sensitivity analysis demonstrated that the three most determinant parameters of net benefit, in decreasing order, are: specificity, benefits from earlier therapy, and prevalence. If a slightly more specific PSA assay is developed, the higher prevalence of clinically detectable prostate cancer could also make screening less costly than breast cancer screening. Under the assumptions of these analyses, the combination of PSA and DRE appears to represent an ethical and economical detection choice for individual patients in consultation with their physicians. Additional research is needed to quantify the significance of differences between different screening strategies.

Introduction

Prostate cancer is the second leading cancer killer in men and the most commonly diagnosed cancer in men.[1] For African-American men, the incidence rate is nearly twice that of the general population, and the death rate is up to three times greater.[2,3] Prostate cancer control represents a serious public health issue, which may only intensify due to

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the increasing age of the US population. While the disease has a high likelihood of cure when found at an early stage, a recent survey by the American College of Surgeons showed that 33 percent of patients still have advanced cancer at the time of diagnosis.[4] Nonetheless, compared with the results from earlier surveys,[5,6] this represents an improvement in the percentage of earlier-stage cancer diagnosed, an improvement that may be due in part to increasing public awareness and the application of early-detection techniques.

However, the effectiveness of prostate cancer early detection remains a dilemma, since no randomized, controlled study has ever demonstrated disease-specific mortality reduction from any test or procedure, including digital rectal examination (DRE).[7] Prior economic evaluations of prostate cancer screening, produced from extrapolation of autopsy prevalence, focused on the potential for exorbitant medical and human costs.[8] Within the medical community, this perspective has fortified a more nihilistic attitude toward early detection, yet the general public continues to demand improved diagnosis regardless of the absence of any conclusive medical benefits. Our analysis attempts to address the questions of whether any economic benefit exists for early detection and whether it is prudent to continue the current trend toward improved diagnosis of prostate cancer.

In 1987, the American Cancer Society-National Prostate Cancer Detection Project (ACS-NPCDP) was conceived and launched as a multidisciplinary, multicenter trial to assess the feasibility of early prostate cancer detection by DRE, transrectal ultrasound (TRUS), and prostate-specific antigen (PSA). In the hope of better understanding the role of early detection and its economic impact, yearly costs were assessed, and a framework was developed for a benefit-cost analysis.

Methods

The ACS-NPCDP reported on 2,425 men at the end of the first year, and diagnostic criteria were described.[9] As of January 1993, there was a complete data base of 1,449 patients with results from three consecutive years. Table 1 lists the total number of cancers detected per year and the breakdown by directed biopsy, interval cancers via transurethral resection, biopsies driven by PSA alone, and cancers with currently incomplete data sets. Test positivity and biopsy results for nine hypothetical detection scenarios are listed in Table 2. These nine approaches were chosen to reflect current discussion regarding the use of DRE, PSA, and TRUS, or their combination, using three different PSA decision levels.

The effectiveness of prostate cancer early detection remains a dilemma, since no randomized, controlled study has ever demonstrated disease-specific mortality reduction from any test or procedure.

All patients in the ACS-NPCDP received all three tests, and biopsy decisions were initially intended only to reflect DRE- or TRUS-positive cases such that PSA-driven biopsies represent a small fraction of cancer detection. In retrospect, the majority of cancers with PSA-driven biopsies had lesions visible by TRUS that had been disregarded or missed by initial TRUS.

Marginal cost (ie, cost per cancer per year) was defined as the yearly in-

Table 1
Prostate Cancer Detection in 1,449 Men over Three Consecutive Years*

	Year 1	Year 2	Year 3	Total
Total Number Cancers	78	38	13	129
Cancer detection by:				
DRE and/or TRUS	61	29	9	99
TUR (interval)	6	1	0	7
PSA-driven biopsy	7	7	3	17
Missing PSA value	4	1	1	6
Total Detection (N = 2,425)	3.2%	1.6%	0.5%	5.3%
DRE/TRUS Detection (N = 2,425)	2.5%	1.2%	0.4%	4.1%

*Breakdown of cancer detection by year and mode of detection for men returning for three consecutive years in the American Cancer Society-National Prostate Cancer Detection Project. Comparison of cancer yield in these 1,449 men is compared with that in the total cohort (N = 2,425) for a more representative detection estimate.

DRE = digital rectal examination; TRUS = transrectal ultrasound; TUR = transurethral resection; PSA = protate-specific antigen

curred diagnostic costs, including biopsy, for each proposed detection scenario divided by each scenario's yearly cancer yield for directed biopsy. Average cost was defined as the sum of the three-year detection costs divided by the total three-year cancer yield. Marginal and average cost analyses were therefore done on the data set of 1,449 men using test positivity, biopsy, and cancer detection rates given in Table 2. This selected group overestimates the actual detection rate due to sampling bias of cancer cases within the reduced total-detection population. The overall prevalence was therefore adjusted to 5.3 percent (129/2,425) (Table 1) for subsequent benefit-cost analysis to account for the original cohort size. Sensitivity analysis of average cost was performed for each proposed detection scenario to assess any change when individual test costs were varied over the following ranges: DRE = $10 to $50; PSA = $10 to $50; TRUS = $50 to $250; and biopsy = $200 to $800. All data were recorded in a spreadsheet, which allowed multiple calculated cells to be varied independently, thereby assessing overall changes for sensitivity analyses. The performance of each scenario over the range of PSA values was demonstrated through receiver operator characteristic (ROC) curves.

Cost per cancer (or marginal cost) is a familiar concept, which can be compared with other prostate cancer detection efforts,[10,11] yet does little to address the economic utility of screening. Like-

Table 2
Test Positivity, Biopsy, and Cancer Detection Rates for Nine Proposed Scenarios*

	Percent Positive				Number of Biopsies/1000				Number of Cancers/1000			
	Year 1	Year 2	Year 3	Total	Year 1	Year 2	Year 3	Total	Year 1	Year 2	Year 3	Total
TRUS Alone	12.5	7.9	5.0	8.5	115.2	62.8	39.3	217.4	35.9	14.5	5.5	55.9
DRE Alone	7.0	3.8	2.2	4.3	57.2	31.8	13.8	102.8	26.9	12.4	2.1	41.4
DRE, TRUS, PSA	15.1	10.2	6.4	10.6	132.0	82.8	46.9	261.6	42.1	20.0	6.2	68.3
PSA2 + DRE	38.9	34.8	34.4	35.9	92.2	57.3	32.4	181.5	39.4	20.0	6.2	65.6
PSA3 + DRE	25.8	22.6	20.4	22.9	80.9	49.7	27.6	158.0	37.3	17.9	6.2	61.4
PSA4 + DRE	19.3	15.9	14.1	16.5	76.8	45.6	24.2	146.3	35.2	17.9	6.2	59.4
PSA2	36.4	33.5	33.1	34.3	75.0	46.2	23.5	144.2	38.0	18.6	5.5	62.1
PSA3	22.1	20.9	18.8	20.6	54.0	35.2	16.6	105.6	33.1	15.2	4.8	53.1
PSA4	14.8	13.6	12.3	13.6	43.0	26.2	12.4	81.4	26.9	13.8	4.8	45.6

* Projected results from nine detection scenarios based on the three-year data from the American Cancer Society-National Prostate Cancer Detection Project, which is best represented by the approach labeled "DRE, TRUS, PSA." Different decision levels of PSA from 2 to 4 ng/ml are listed for scenarios using their combination with DRE (ie, PSA2 + DRE, PSA3 + DRE, and PSA4 + DRE) and alone (ie, PSA2, PSA3, and PSA4). "Percent positive" refers to the percent of patients with a positive initial test result.

N = 1,449; total cancers = 99

TRUS = transrectal ultrasound; DRE = digital rectal examination; PSA = prostate-specific antigen

wise, a total-cost projection alone simply reiterates the huge potential drain on limited heath care funding. Breast cancer detection programs have used cost-efficacy analysis,[12-14] however, this requires an estimate of eventual mortality reduction from screening. Since there are no data demonstrating a reduction in mortality for any test for prostate cancer, a benefit-cost analysis was performed, including thorough assessments and conservative estimates of the benefits and costs of both detection and therapy. Subsequent sensitivity analysis of the defined parameters help address any skepticism or debate over individual procedure costs and test probabilities.

The general public continues to demand improved diagnosis regardless of the absence of any conclusive medical benefits.

Decision analysis can incorporate probabilities and costs, but if benefits are ignored,[8] appropriate choices may be summarily rejected. Decision analysis may also be effectively performed through an equation that encompasses the cost and probability of each procedure or decision. An economic framework for gonorrhea screening was developed in this manner, and the generalized nature of its aggregate-benefits equation[15] provided an excellent format to use the current ACS-NPCDP data. Table 3 describes this equation and defines each parameter. Detailed explanations have been reserved for brevity and will be given in a forthcoming article comparing benefit-cost analysis to cost-efficacy results. A wide variety of factors were considered while deriving parameters, such as medical savings from treating earlier disease, lost wages, differential age and wage at diagnosis,[16] cancer staging differences,[4,17] cost of TRUS and biopsy, and potential complications of biopsy and therapy. Consensus-development exercises were previously used to derive values for subjective parameters[15] but were eliminated for simplicity in our analysis in the belief that sensitivity analysis may compensate for broad assumptions. Due to the high costs of using all three screening tests simultaneously, or just TRUS alone, benefit-cost analysis was limited to DRE and PSA scenarios. The following limited descriptions are provided.

Dollar Value Parameters

The dollar value of benefits accrued due to earlier detection and treatment, **B**, requires more lengthy explanation but can be summarized:

B = (Future medical savings from treating earlier cancer + reduced suffering from prevention of advanced disease + lost wages) • percent increase in earlier-stage disease.

The cost of treating advanced disease has been estimated to be between $35,000 and $100,000, and an intermediate value of $70,000 was arbitrarily chosen. This broad range may be better defined when a projected Medicare data base from the Health Care Finance Administration allows better estimates of stage-specific treatment costs.[14] The prevention of pain and suffering primarily accounts for lifestyle disruptions to the patient (or immediate family) and was simply set at the conservative value derived from a prior consensus estimate of preventing gonorrhea from causing pelvic inflammatory disease: $15,000.[15] Lost wages will not be detailed here but amounted to only $5,495. The fraction of increased early-stage cancer was produced by subtracting the American College of Surgery estimate of 56 percent Stage A and B disease in 1986 (ie, prior to wider PSA and TRUS use) from our ACS-NPCDP value of 95 percent (95 − 56 = 39%). Therefore, we simply

Table 3
Benefit-Cost Equation with Definitions of Variables*

$$V = pnwB + (1-p)cR - S - [pn + (1-p)(1-c)]w(T + A) - (1-p)(1-c)F$$

Dollar Values	Where each variable is defined as:
V	Net benefit per individual screened
B	Value of benefits from early detection and treatment
R	Value of reassurance from a negative test
S	Cost of screening test, procedure, or scenario
T	Cost of staging and treatment received as a result of screening
A	Cost of adverse effects of screening tests and subsequent follow-up tests and morbidities of therapy
F	Potential psychic cost of false-positive test result
Probabilities	
p	Prevalence of prostate cancer (fraction of patients who demonstrate cancer during screening sequence, as well as from interval detection)
n	Sensitivity (probability of a positive result when clinically detectable cancer is present)
c	Specificity (probability of a negative result when no cancer is evident from the screening test or sequence)
w	Probability of a patient returning for therapy and/or having a cancer stage or medical condition appropriate for therapy

*Equation used to assess net benefits, V, to participants in a screening program.[15]

let **B** = [($70,000 − 15,000) + $15,000 + $5,495] • 0.39 = $29,443.

The value of reassurance from a negative test result, **R**, is also subjective and was simplified to equal the value of the detection test, **S**, regardless of the approach. The cost of detection tests, **S**, was taken from the median values in the average-cost analysis of $30 each for DRE and PSA, $150 for TRUS, and $500 for biopsy. The cost of TRUS and biopsy will be accounted for in **A**, the cost of adverse diagnosis and treatment, since it also considers the cost of false-positive tests and their associated probability.

The cost of treatment, **T**, was increased to $20,000 to also account for staging costs. This represents an estimated cost of therapy for early detection of prostate cancer, since 95 percent of the

Table 4
Marginal and Average Costs for Nine Detection Scenarios*

	Marginal Cost			Average Cost
	Year 1	Year 2	Year 3	
TRUS Alone	$5,783	$12,517	$30,731	$9,994
DRE Alone	$2,178	$3,693	$17,823	$3,415
DRE, TRUS, PSA	$6,556	$12,562	$37,588	$11,135
PSA2 + DRE	$4,174	$7,037	$20,579	$6,594
PSA3 + DRE	$3,731	$6,618	$16,809	$5,895
PSA4 + DRE	$3,618	$5,942	$15,010	$5,516
PSA2	$3,501	$6,087	$18,350	$5,592
PSA3	$2,924	$5,613	$14,929	$4,780
PSA4	$2,905	$4,897	$12,079	$4,482

* Marginal- and average-cost values based on the data given in Table 2.

TRUS = transrectal ultrasound; DRE = digital rectal examination; PSA = prostate-specific antigen; PSA2 = PSA at 2 ng/ml; PSA3 = PSA at 3 ng/ml; PSA4 = PSA at 4 ng/ml

ACS-NPCDP patients had Stage B or less disease[17] and theoretically could have received definitive therapy. The cost of staging was added according to Health Care Finance Administration and American College of Radiology reimbursable values: bone scan = $347, computed tomography scan = $642, and magnetic resonance imaging = $1,094. The total for T is **T** = ($15,000 • 0.95) + ($70,000 • 0.05) + 2,083 = $19,833.

The cost of adverse diagnosis and therapy, **A**, as described by Goddeeris and Bronken,[15] was modified for the current analysis to include adverse costs of false-positive detection tests, as well as potential adverse treatment reactions. The cost of **A** is different for each screening approach due to differences in false-positive, biopsy, and cancer-detection rates. Further details will be provided in our subsequent paper, and the following was used to calculate **A** for each approach:

A = (percent test positive)•(Cost of TRUS) + [(percent biopsied)(Cost of biopsy) + Cost of DRE* + Cost of biopsy complications + Cost of unnecessary therapy for overdiagnosis + Cost of therapy complications].

*Added cost of DRE applies only to screening approaches using PSA alone.

The psychic cost, or suffering induced, of a false-positive test result, **F**, was chosen to be the same as the estimated adverse cost, **A**, calculated for each detection scenario. This is in keeping with our prior pattern of setting the

value of reassurance, **R**, equal to test cost, **S**. Once again, sensitivity analysis may account for broad ranges.

Probability Parameters

The population "prevalence," **p**, in the original equation actually refers to the overall detection incidence in our study. Depending on whether we assume a yearly or cumulative detection rate, cancer detection rate by directed detection tests or total cancers (interval cancers, inclusive), and a denominator based on the total number of patients in the study cohort (Table 1) or the number of patients with results from three consecutive years, the "prevalence" can vary from 2.4 percent (58/2,425) to 8.9 percent (129/1,449). The most accurate representation is probably 5.3 percent (129/2,425) and approximates the five percent cancer-detection rate in a recent PSA-based study by Labrie et al.[18]

Sensitivity, **n**, and specificity, **c**, of each detection approach was based on the complete data set of 1,449 patients over three years using definitions previously described.[9,10] Sensitivity estimates included only the 99 cancers detected by directed biopsy, since these were the initial biopsy criteria of the ACS-NPCDP. This was also done to remain consistent with the marginal-cost analysis and produces little change in net benefit, **V**. Specificity values for this study are robust and change little with respect to alterations in both cancer detection and total cohort values. An additional scenario of DRE detection by more generalized detection performance (DRE^G) was added in the benefit-cost analysis to estimate an arbitrary reduction of 20 percent in both DRE sensitivity and specificity relative to highly skilled examiners or urologists(DRE^U). Again, sensitivity analysis accounted for greater variation in values.

The probability of returning for treatment, **w**, was estimated from the American College of Surgeons' 1990 survey, which showed that only 15 percent of Stage B or higher cancers were not treated.[4] Therefore, a value of 0.85 was chosen for **w**.

Results

Marginal-cost analysis helped quantify individual test performance and incremental impact over time. Table 4 gives the marginal and average costs for each detection approach. At the median dollar values chosen for each test, DRE has the lowest marginal cost in the first two years. However, marginal cost for DRE rapidly increased in year three such that any PSA-oriented approach using decision levels of 3 or 4 ng/ml became less costly. In year three, the marginal cost for DRE increased by more than eightfold while marginal costs for all other scenarios increased only about fivefold. These important trends are obscured in the three-year average cost column.

Due to the high costs of using all three screening tests simultaneously, or just TRUS alone, benefit-cost analysis was limited to DRE and PSA scenarios.

Sensitivity analysis of average cost was performed for each proposed approach using the three-year summary data. The effect of variable test pricing on average cost for the three scenarios using PSA alone has similar patterns as when PSA was combined with DRE. The most dominant parameter of average cost was the price of TRUS when PSA was set at 2 ng/ml. For PSA at 3 ng/ml, PSA price became equivalent to TRUS price in affecting average cost. The cost

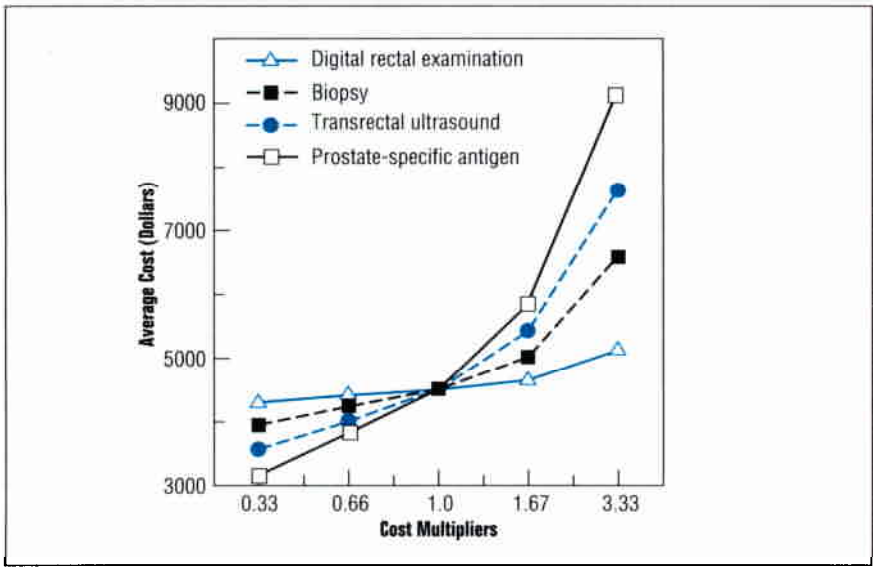

Fig. 1. Demonstration of sensitivity analysis for average cancer cost with prostate-specific antigen at 4 ng/ml. Median test costs (prostate-specific antigen = $30, digital rectal examination = $30, transrectal ultrasound = $150, biopsy = $500) were varied by factors ranging from 33 to 333 percent.

of PSA became the most dominant variable when its decision level was set at 4 ng/ml (Fig. 1). At 4 ng/ml, decreased sensitivity and fewer false positives produced an average cost that was more dependent on the cost of PSA than the primary follow-up procedure: TRUS. Despite having the highest test cost, variable biopsy pricing contributed only slightly more than DRE to average cost due to its relatively low probability of occurrence. However, if biopsy criteria of any proposed screening approach are altered to occur with each TRUS evaluation (eg, systematic biopsy of all patients with PSA over 4 ng/ml), it would make TRUS costs increase by over threefold ($500/$150).

Comparison of each scenario's detection performance was shown by ROC curves in Figure 2. The ROC curve graphically depicted the trade-offs of sensitivity and specificity for each scenario over the range of PSA decision levels.[18] Optimal test performance is suggested at the portion of the curve closest to 1.0, and the line of unity intersects the PSA-alone curve between 2 to 3 ng/ml but falls just above the 3 ng/ml point on the PSA + DRE curve due to the associated curve shift. The upward shift in the ROC curve produced by the addition of DRE to the PSA alone curve demonstrated the greater added benefit on sensitivity than specificity. This effect was most striking for PSA at 4 ng/ml. The DRE-alone curve did not fit into the usual ROC format because the second data point, DRE^G, assumed decreases in both sensitivity and specificity.

The benefit-cost analysis was able to account for several different variables not addressed by marginal-cost or ROC analysis. The values assigned to all parameters are listed in Table 5, along with the net benefit value for each detection

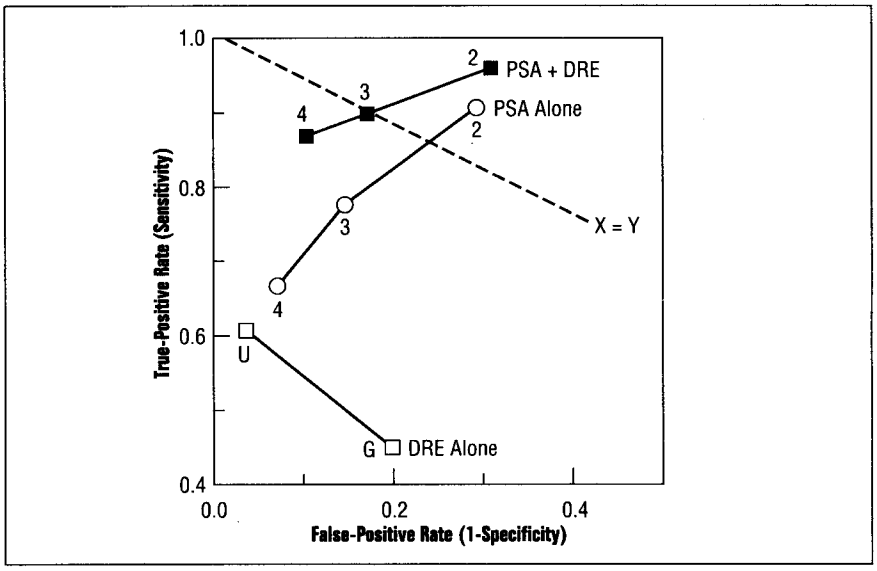

Fig. 2. Receiver operator characteristic (ROC) analysis of early detection: ROC curves demonstrate the balance of sensitivity and specificity, with optimal performance suggested near the line of unity, X=Y. This occurs for the "PSA Alone" curve between 2 and 3 ng/ml and at 3 ng/ml for the "PSA+DRE" curve due to the added sensitivity offered by DRE. (PSA = prostate-specific antigen; DRE = digital rectal examination; U = optimal DRE performance by highly skilled examiner; G = DRE performance generalized to large-scale detection)

approach. Net benefit, **V**, demonstrated negative values, or cost, for all scenarios. For any scenario, sensitivity analysis demonstrated the three most determinant parameters of net benefit, **V**, in decreasing order are: specificity, benefits from earlier therapy, and prevalence (ie, $\mathbf{c} > \mathbf{B} > \mathbf{p}$). Sensitivity analysis for the various scenarios (results detailed in a future paper) demonstrated the operator-dependent instability of DRE performance. Even if sensitivity were to remain unchanged, a 20 percent decrease in specificity is conceivable for the DRE when potential false positives due to gland alterations from benign prostatic hyperplasia are considered. Unfortunately, this would make DRE the second most costly detection approach.

Table 5 demonstrates that while DRE done by highly skilled examiners has the lowest cost, any approach using PSA at 3 or 4 ng/ml could be less costly than DRE alone if a modest decrease in sensitivity and specificity is assumed. Table 5 assumes a conservative benefit value, **B**, and tripled screening costs, **S**, to account for total (three-year) cancer "prevalence." Decreases in sensitivity produced by further inclusion of cancer detection by nondirected biopsy produced minimal decrease in net benefit.

An estimated benefit-cost calculation for breast cancer detection showed a cost similar to DRE^U and was relatively close to any PSA approach set at 4 ng/ml. An increase of four percent (0.927 to 0.965) in PSA4 specificity and 13 percent (0.853 to 0.960) in PSA3 specificity produced lower net costs than even DRE^U. The greater potential benefit, or lower cost, for prostate cancer versus breast

Table 5
Parameter Values for Benefit-Cost Analysis*

	B	R	S	T	A	F	p	n	c	w	V
DRE^U	$29,443	$90	$90	$20,000	$1,391	$1,391	0.053	0.606	0.963	0.85	-$ 474
DRE^G	$29,443	$90	$90	$20,000	$1,391	$1,391	0.053	0.484	0.770	0.85	-$4,112
DRE + PSA2	$29,443	$180	$180	$20,000	$1,470	$1,470	0.053	0.960	0.688	0.85	-$5,544
DRE + PSA3	$29,443	$180	$180	$20,000	$1,438	$1,438	0.053	0.899	0.827	0.85	-$2,936
DRE + PSA4	$29,443	$180	$180	$20,000	$1,421	$1,421	0.053	0.869	0.896	0.85	-$1,646
PSA2	$29,443	$90	$90	$20,000	$1,477	$1,477	0.053	0.909	0.705	0.85	-$5,216
PSA3	$29,443	$90	$90	$20,000	$1,436	$1,436	0.053	0.778	0.853	0.85	-$2,473
PSA4	$29,443	$90	$90	$20,000	$1,413	$1,413	0.053	0.667	0.927	0.85	-$1,126
Mammography	$29,443	$50	$50	$20,000	$1,450	$1,450	0.005	0.80	0.97	0.99	-$ 562

* Dollar values used for benefit-cost equation (Table 3) demonstrating net costs, or negative values, of V for all approaches. Depending on its performance, DRE alone could vary from the least costly to one of the most costly detection approaches, surpassed only by those using PSA at a level of 2 ng/ml. The assumed high specificity of mammography makes it comparable to prostate cancer detection despite its low prevalence.

DRE = digital rectal examination
DRE^U = DRE alone done by a highly skilled examiner
DRE^G= DRE alone done by a more generalized detection effort
PSA = Prostate-specific antigen
PSA2 = PSA at 2 ng/ml
PSA3 = PSA at 3 ng/ml
PSA4 = PSA at 4 ng/ml

cancer early detection through improved PSA specificity also highlights the importance of prevalence. The prevalence of clinically detectable prostate cancer in our study may well be an order of magnitude greater than prior breast cancer detection trials.

Discussion

The cost effectiveness of prostate cancer early detection cannot be directly calculated without evidence to suggest decreased mortality from any screening approach. Decisions regarding early detection may remain an individual decision between patient and doctor, yet our current data suggest that early detection could become even more economical than other accepted screening programs. In addition, successful accrual to a randomized, long-term trial seems improbable in today's consumer-oriented society. The informed public may never agree to remain in a control group when readily available information suggests that they are not receiving currently available tests or treatment. This could produce significant contamination of established control groups or severely limit enrollment and follow-up of proposed trials.

Patterns of diagnosis and care suggest that many physicians are already using newly available technology for their patients, despite maintaining the belief that early detection is inappropriate on a large-scale level. This dichotomy of reasoning has significant potential for wasting limited resources through uninformed choices or inadequate sequencing of clinically appropriate tests. The American College of Radiology, the American Urological Association, and the American Cancer Society have made recommendations to limit TRUS to patients with abnormal DRE and/or PSA elevation. The results of our marginal-cost and benefit-cost analyses support these positions. Yet placing PSA at a diagnostic parallel with DRE may cause some consternation regarding its ability to detect earlier-stage prostate cancer,[19] as well as concern over the number of false positives associated with prostate enlargement.[20–22]

The justification of PSA as part of an emerging standard of care required an assessment of its economic prudence, as well as its clinical utility. The purpose of using current ACS-NPCDP data was to assess the impact of several potential detection scenarios and compare them with the current standard of DRE. However, DRE must also be acknowledged as an operator-dependent test with high variability between observers and with limited access to the expertise needed to reproduce documented test performance. In other words, there may not be sufficient numbers of available urologists, or skilled examiners, to duplicate the sensitivity and specificity parameters needed for large-scale screening efforts. Likewise, individual urologists may not reproduce the DRE results found in detection studies. No study to date has established the diagnostic performance of DRE by physicians or health care providers in general practice. We therefore emphasize that the performance of the DRE in the ACS-NPCDP should also be viewed as a best-case scenario. This is not unlike the operator-dependent nature of TRUS and its optimal performance by experienced sonographers in our study. Figure 2 and Table 5 show how a slight decrease in test performance by nonurologists could actually make DRE one of the most costly detection approaches.

Marginal cost analysis helped quantify individual test performance and incremental impact over time.

There are several important issues and caveats that should be kept in mind when interpreting the significance of the

results. Values used for calculating costs and benefits versus costs were imputed and are subject to debate. Using actual screening cost expenditure data may be preferable to our approach of compensating for error through sensitivity analysis. Our assumption of a 5.3 percent prevalence rate may be in error. The true prevalence of screen-detectable prostate cancer is unknown, and the experience with this subset of men in the ACS-NPCDP, although supported by other data, may not be generalizable to the general population. The confidence intervals around estimates made herein are not quantified, and the statistical significance of differences between different early detection strategies has not been determined. Finally, reporting a complete presentation of the methods and assumptions elsewhere places the sophisticated reader at a disadvantage that can be addressed only by combining this synopsis with the more extended exposition.

Our economic analysis produces new insight about several important aspects of detecting early prostate cancer. While it may appear repetitive or excessive, different analyses of the same data were used in order to highlight any potential differences in interpretation of the economic impact of prostate cancer detection. The performance of DRE, PSA, and TRUS over time was best illustrated by marginal-cost analysis. ROC curves allowed better depiction of PSA performance over a range of decision levels. Benefit-cost analysis included many variables that have been considered intangible, yet demonstrate relatively low economic costs for early detection, even with conservative estimates. The merits and insights of each analysis appear to complement one another.

Cost per cancer over time has also been called marginal-cost assessment,[23] and our article attempts to reintroduce this terminology. In the cost analysis of colorectal cancer screening using stool guaiac tests, marginal cost of screening was defined as the incremental increase in cost divided by the incremental gain in cancer detection. This is similar to the prostate cancer cost values given in Table 4 for each of the three years of screening. As with each repeated stool guaiac test, all proposed prostate cancer detection scenarios demonstrated a continued increase in marginal cost over time. Each scenario showed a stable fivefold increase in marginal cost from the first to the third year, except for DRE. It developed an eightfold increase in marginal cost, making DRE more costly than any PSA scenario using a decision level of 3 or 4 ng/ml by the third year.

While DRE done by highly skilled examiners has the lowest cost, any approach using PSA at 3 or 4 ng/ml could be less costly than DRE alone if a modest decrease in sensitivity and specificity is assumed.

The identification of a breakpoint in DRE cancer detection relative to the other proposed approaches suggests a limited clinical utility in recommending annual use of DRE after year three. This is especially true when we consider DRE reproducibility among different examiners (Table 5). Further data from the remaining two years of the ACS-NPCDP may confirm this trend such that yearly recommendations for DRE may be limited. However, we must be careful not ignore its additional diagnostic benefit for colorectal disorders.

Sensitivity analysis of average cost

demonstrated that PSA and TRUS are the most dominant costs, while PSA becomes the prime cost determinant when set at 4 ng/ml (Fig. 1). Cost containment for PSA thus becomes crucial, since 4 ng/ml is the currently accepted definition of upper normal limits, and the American Cancer Society has added PSA at this level to the routine screening guidelines for the cancer-related checkup.[24] The advent of automated PSA assays, higher volume, and more centralized laboratories has allowed PSA costs to gradually decrease. PSA can now be obtained for less than $15 in Michigan, for example.[25] This would place the average detection cost on the lower part of the PSA curve in Figure 1, which could produce marked average-cost reductions.

If PSA decision levels are reduced below 4 ng/ml, cost containment of TRUS pricing may need more focus on preventing cost increases rather than expecting similar decreases as noted for PSA. The effect of performing systematic biopsy on all patients with PSA levels above 4 ng/ml would drive overall TRUS prices to the high-cost end of the curves seen in Figure 1. A recent study suggested that systematic biopsies do not produce overdetection of very low volume, clinically irrelevant prostate cancers.[26] However, the long natural history for early disease also makes the need for immediate biopsy questionable. Further work is needed on the marginal cost of increased cancer detection provided by systematic biopsies of TRUS-benign areas, particularly in patients with normal PSA-to-gland-volume relationships (ie, serum PSA below the predicted).[27-30]

Detection approaches using PSA alone at either 3 or 4 ng/ml, or their combination with DRE, all suggested a lower cost of early detection than do more generalized DRE detection efforts, DRE^G. Optimal DRE performance, DRE^U, remained the lowest detection cost. Sensitivity analysis of each parameter also produced clinically important observations. Using autopsy prevalence to estimate the national impact of early prostate cancer detection is inherently flawed,[8] since it includes disease that will not affect survival and exaggerates human suffering caused by overdiagnosis and treatment. Increasing the estimated disease prevalence should actually lower screening costs (ie, increase benefits), assuming that the detected disease actually requires therapy.

The primary drawback of our analysis may thus be the assumption that any benefit can be derived from treatment of early prostate cancer.[31] Patients with early prostate cancer may have a good 10-year survival without therapy, but this should primarily argue for a limitation of the upper age of screening rather than for not screening at all. In younger patients, greater disease progression is anticipated, and the natural history of clinically significant cancer can also be estimated from ^{125}I-radiation-therapy trials, which have led to insufficient treatment of the primary cancer.[32] DRE by highly skilled examiners has nearly the same sensitivity as PSA used alone at 4 ng/ml (Table 5), but DRE alone has been considered too insensitive to potentially alter mortality.[7] The combination of DRE and PSA at 4 ng/ml markedly improves sensitivity and currently represents the least costly detection approach to potentially decrease the mortality from prostate cancer.[24]

There may not be sufficient numbers of available skilled examiners to duplicate the sensitivity and specificity parameters needed for large-scale DRE screening efforts.

For the future, one of the more en-

lightening results of our analysis suggests that the development of a more specific PSA assay needs to be highly encouraged. More sensitive PSA decision levels could then be easily justified, since a more cancer-specific assay would also be the most potent factor in lowering net detection costs. Recent studies suggest that PSA elevations produced by benign prostatic hyperplasia may be fractionated and differentiated from elevations produced by cancer. Assays are also being developed for other cancer-related proteins, and continued research in this area now has an economic basis to focus on improving the specificity over PSA. For now, the combination of DRE and PSA at 4 ng/ml may be the most prudent approach, combining improved sensitivity with sufficient specificity to produce low-cost early detection of prostate cancer. CA

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