THE POTENTIAL IMPACT OF COMPARATIVE EFFECTIVENESS RESEARCH ON U.S. HEALTH CARE EXPENDITURES*

DANIELLA J. PERLROTH, DANA P. GOLDMAN, AND ALAN M. GARBER

Comparative effectiveness research (CER) has the potential to slow health care spending growth by focusing resources on health interventions that provide the most value. In this article, we discuss issues surrounding CER and its implementation and apply these methods to a salient clinical example: treatment of prostate cancer. Physicians have several options for treating patients recently diagnosed with localized disease, including removal of the prostate (radical prostatectomy), treatment with radioactive seeds (brachytherapy), radiation therapy (IMRT), or—if none of these are pursued—active surveillance. Using a commercial health insurance claims database and after adjustment for comorbid conditions, we estimate that the additional cost of treatment with radical prostatectomy is $7,300, while other alternatives are more expensive—$19,000 for brachytherapy and $46,900 for IMRT. However, a review of the clinical literature uncovers no evidence that justifies the use of these more expensive approaches. These results imply that if patient management strategies were shifted to those supported by CER-based criteria, an estimated $1.7 to $3.0 billion (2009 present value) could be saved each year.

The dissemination of new and expensive medical technologies has been blamed for much of the growth in U.S. health care spending in recent decades (Goldman et al. 2005; Newhouse 1992). Consequently, the high rate of technological innovation in medicine is both criticized and extolled: many new interventions confer large health benefits, but to the extent that it stimulates increases in medical expenditures, technological innovation contributes to the growth in the number of uninsured Americans and may ultimately threaten the economy (Cutler, Rosen, and Vijan 2006; Murphy and Topel 2006). Policymakers have responded by promoting methods to better understand the benefits of new technology and service delivery on cost and health outcomes. One promising research method to accomplish this task is comparative effectiveness research (CER). CER seeks to measure the relative benefits of alternative approaches to health care. It is distinguished from research on clinical efficacy by its focus on comparisons among clinically relevant alternatives rather than comparisons with placebo, and by its attention to real-world performance (effectiveness) rather than performance in the highly controlled, atypical circumstances of most experimental studies. CER, it is believed, can reduce expenditures by reducing the use of ineffective care and by identifying expensive forms of care that are no more effective than lower-cost alternatives.

CER has the potential to influence all aspects of health care, but its impact may be greatest when applied to the health care of the elderly. All elderly Americans receive health insurance through Medicare, a public program whose future liabilities are thought to represent the single greatest threat to the fiscal health of the U.S. economy in the coming

*Daniella J. Perlroth, Stanford Health Policy, Stanford University, 105 Encina Commons, Stanford, CA 94305-6019; e-mail: dperl@stanford.edu. Dana P. Goldman, University of Southern California, Los Angeles; and the RAND Corporation, Santa Monica, CA. Alan M. Garber, Stanford Health Policy, Stanford University; and Veterans Affairs Palo Alto Health Care System, Palo Alto, CA. This research was supported by UnitedHealthcare and the National Institute on Aging through its support of the Roybal Center for Health Policy Simulation (P30AG024968) and the Center on Demography and Economics of Health and Aging (P30 AG 17253). The authors are solely responsible for this research. The authors would also like to thank Mark Totten of the RAND Corporation for his contribution to the data acquisition and analysis.

decades. The Hospital Insurance Trust Fund, which receives Medicare payroll tax funds and is responsible for funding hospital care under Medicare Part A, will be depleted in 2017 (Geithner 2009). By 2050, at current rates of Medicare expenditure growth and with the continuation of current funding rules, the unfunded portion of Medicare (expenditures in excess of dedicated revenues, such as the Medicare payroll tax and premium payments) is projected to reach 6% of gross domestic product (GDP). The Congressional Budget Office (CBO) forecasted an even more dire rate of expenditure growth, particularly beyond two to three decades, with Medicare expenditures alone estimated to increase from 3% of GDP today to 17% by 2082 (CBO 2007a). Thus, the need to rationalize the use of health care resources among the elderly is a critical policy issue. In addition, because chronic disease is so common among the elderly, significant changes in medical care will be felt sooner and more extensively by Medicare beneficiaries.

Comparative effectiveness research can improve the quality of health care delivered to the elderly simply by identifying the most effective approaches to the management of conditions that are common at advanced ages. It can direct patients to more appropriate care by comparing the health benefits, risks, and long-term costs for specific clinical strategies and practices. CER might reveal that a strategy produces equal outcomes at lower comprehensive costs than one or more alternatives. It could also identify interventions whose long-term savings in averted disease exceed their costs (e.g., use of statins to lower cholesterol in patients at high risk for acute myocardial infarction; see Cutler and McClellan 2001). These types of interventions are often underused. Without extensive modeling, it has not been possible to produce precise estimates of the financial payoff of such research, but the Lewin Group estimated that application of such findings from CER could save $18 billion in the first year and $368 billion over 10 years (Schoen et al. 2007).

The June 2, 2009, report of the Council of Economic Advisors called for efforts to slow the annual growth rate of health care costs by 1.5 percentage points annually, and stated that systematic efforts to look "at what works and what doesn't in order to provide more high-value care" would be crucial to the success of such efforts (Executive Office of the President, Council of Economic Advisors 2009). This is precisely what CER attempts to do. However, the potential impact on health expenditures of implementing the findings from these studies is largely unknown (CBO 2007b). As the future of Medicare, and U.S. health care in general, is shadowed by increasingly dire financial forecasts, a better understanding of the effects of CER can inform debates about reform of the Medicare program and of the U.S. health care system more broadly.

We thus sought to estimate how the results of comparative effectiveness research, if fully or partially implemented, might affect U.S. health care expenditures in the area of localized prostate cancer. Prostate cancer is a high-priority area for CER because the condition is common, treatment is costly, and there is uncertainty about the relative effectiveness of different treatment approaches. Nearly a quarter of a million new cases of prostate cancer were diagnosed in 2009 (American Cancer Society 2009), approximately 80% of them localized (National Cancer Institute 2008a). Medicare spent an estimated $1.58 billion on initial prostate cancer treatment in 2002; total expenditures today are undoubtedly much greater (Warren et al. 2008). Recently, the Institute of Medicine's Committee on Comparative Effectiveness Research released priority research areas after receiving testimony and topic nominations from the public and a wide range of interested parties. They assigned treatment for prostate cancer to the top quartile of research priorities (Institute of Medicine 2009). Alternatively, this research method can help in bounding the potential economic benefit of further research to define effectiveness for the management of localized prostate cancer (e.g., conducting the definitive randomized controlled trial between treatment options for localized prostate cancer). The example of localized prostate cancer provides the simplest case for this type of research—when current evidence suggests that interventions vary in costs but do not offer definite differences in effectiveness.

METHODS

Characterizing Findings From CER

Comparative effectiveness research—although it is often viewed as a comparison of simply defined interventions, such as different drugs—has an important and substantively different goal than do clinical trials. It is intended to select among alternative management strategies. A therapeutic intervention may be an important or the most important part of a management strategy, but its use is often part of a well-specified algorithm, which may include decisions about dosage or mode of delivery (of a therapy), or approaches to deciding when and whether to stop its use, and so on. Thus, the first step in estimating the effects of comparative effectiveness research is to define the set of choices for a key management decision.

In this application, we begin with the decision faced by the patient who has a diagnosis of localized prostate cancer. (Strategies for detecting either asymptomatic prostate cancer through screening or symptomatic disease through diagnostic algorithms raise distinct issues that we do not consider here.) For a patient newly diagnosed with prostate cancer, the disease is most frequently confined to the prostate gland (localized), and several initial management strategies will be considered. This is likely to be the most important management decision in prostate cancer, not only because localized disease is so common and the costs of alternative treatments vary greatly, but also because it has a favorable prognosis overall (Figure 1).

For localized prostate cancer, the most common initial management approaches are (1) active surveillance (also known as watchful waiting), (2) radical prostatectomy (RP), (3) brachytherapy, (4) external beam radiation therapy (EBRT), and (5) intensity-modulated radiation therapy (IMRT). They are described in detail in Table 1.

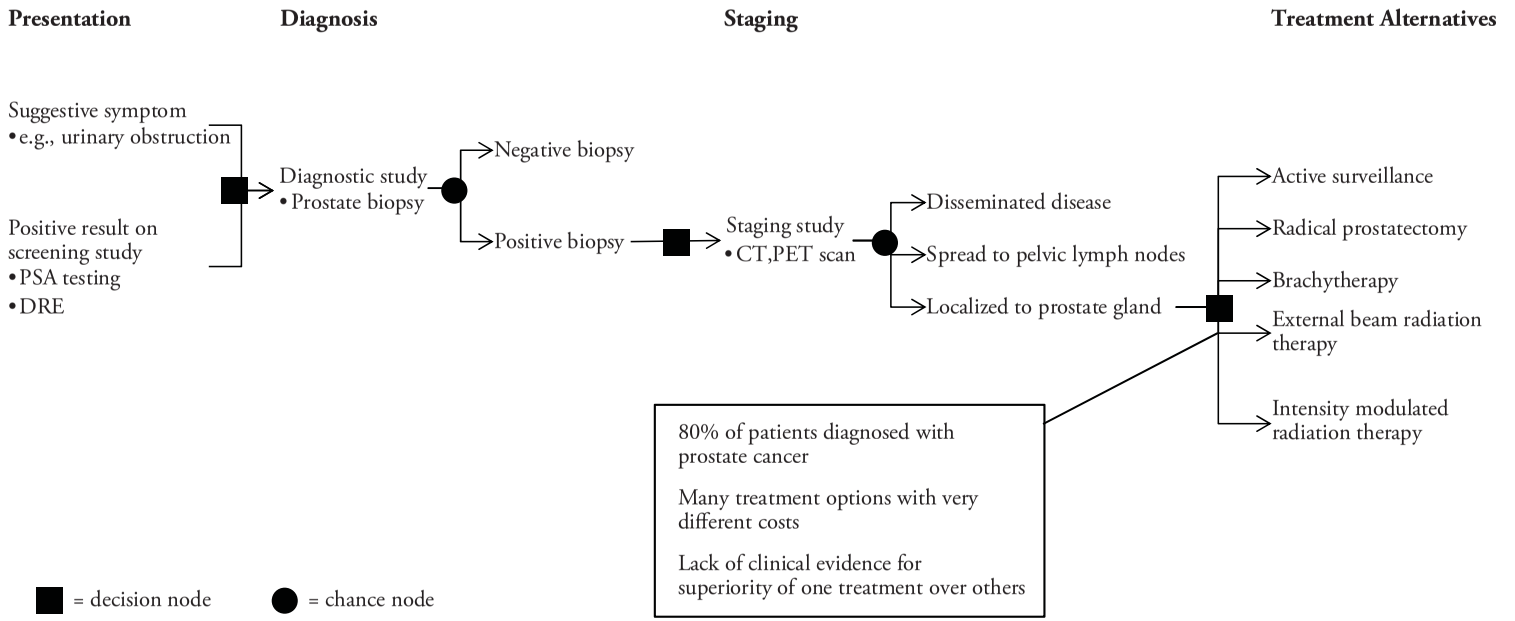
After defining alternative management strategies, we reviewed the clinical evidence to find high-quality synthesized data relevant to the treatment of localized prostate cancer. We reviewed the medical literature (PubMed from 1966 to 2009) for randomized trials, analyses of microlevel observational data, systematic reviews, and meta-analyses. We searched for evidence reports from the Agency for Healthcare Research and Quality (AHRQ) (Agency for Healthcare Research and Quality 2009), Cochrane Collaboration reports, and reviews from the (U.K.) National Institute of Health and Clinical Excellence.

Data Sources and Patient Selection

To estimate costs, we employed an extensive commercial database, obtained from Ingenix (Eden Prairie, MN), containing claims data for 42 large employers. These data have been used extensively to examine pharmacy and medical spending in previous research (Goldman et al. 2004; Goldman, Joyce, and Karaca-Mandic 2006; Joyce et al. 2002; Joyce et al. 2008; Joyce et al. 2007). The data capture all health care claims, including prescription drugs and inpatient, emergency, and ambulatory services. Information on members (employees and dependents) includes age, sex, plan type, zip code of residence, and relationship to employee. The claims data are linked with information about plan benefits, abstracted from photocopies of the summary of benefits provided by the companies to their employees. Forty-four percent of plans cover retiree benefits, so there is substantial representation of older Americans in the data. All insurance plans represented in the 2004 data set contributed data in 2005 and 2006.

Using these data, we identified patients with a new diagnosis of prostate cancer in 2004 or 2005—confirmed by a code for prior prostate biopsy—among those for whom we had one year of claims experience prior to diagnosis and at least two years following diagnosis. We excluded patients older than 75 years of age to increase the likelihood of selecting a group that has a life expectancy of at least 10 years and is fit for surgery or radiation therapy (important factors to consider when selecting initial treatment options for localized prostate cancer). We also excluded those with diagnostic codes for disseminated

Figure 1. Schematic Representation of Medical Decision Making in Patients With Prostate Cancer

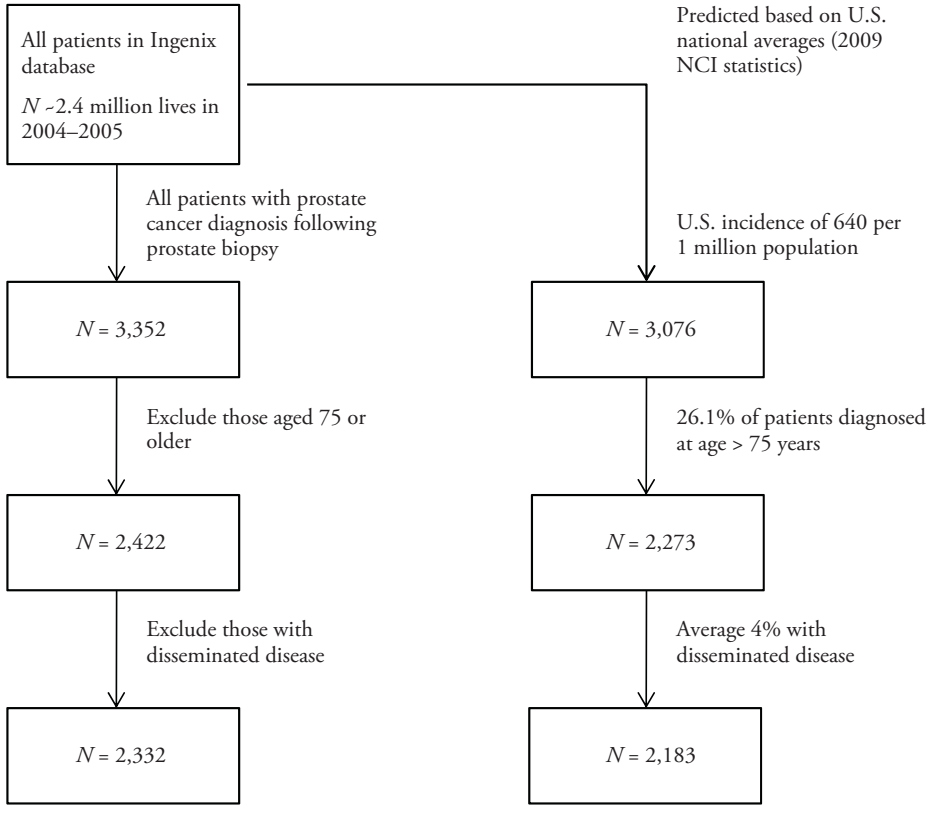


Notes: The presentation, diagnostic workup, and treatment options are illustrated for localized prostate cancer. Black squares (decision nodes) indicate a decision point in the process, and black circles (chance nodes) indicate a probability associated with certain outcomes. Decisions not to proceed with a diagnostic or staging study are not shown. PSA = prostate-specific antigen; DRE = digital rectal examination; CT = computed tomography; and PET = positron emission tomography.

Table 1. Standard Initial Management Options and Their Trade-offs for Localized Prostate Cancer

Treatment	Description	Pros	Cons
Active Surveillance (watchful waiting)	Active plan to postpone intervention for close monitoring with digital rectal exams, prostate-specific antigen testing, and early repeat prostate biopsies.	No treatment-related side effects.	For some individuals, may be anxiety-provoking not to treat cancer.
Radical Prostatectomy (RP)	Complete surgical removal of prostate gland; nerve-sparing techniques are latest advance.	One-time treatment. Lacks gastrointestinal side effects. Nerve-sparing techniques have likely decreased sexual and genitourinary side effects.	Surgical complications include 0.5% risk of death, 4%–10% risk of complications. Generally thought to have more initial side effects than radiation therapy on sexual function. Need to be healthy enough to tolerate surgery with general anesthesia.
Brachytherapy (seed implants)	Radioactive implants (I^{125}) placed as permanent, low-dose "seeds" in prostate gland.	One- or two-day treatment. May be superior to radiation therapy for large glands in terms of side-effect profile.	Must be able to tolerate spinal/general anesthesia. Must have no previous history of prostate procedures (e.g., TURP). Gland must be between 20–60 grams.
External Beam Radiation Therapy (EBRT)	Multiple doses of radiation from an external source applied over several weeks, two-dimensional beam and three-dimensional conformal.	Not used much anymore; largely replaced by IMRT as standard radiation option.	Most common side effects are inflammation of the colon, diarrhea, and pain or blood with urination. Requires 7–8 weeks of weekday therapy.
Intensity-Modulated Radiation Therapy (IMRT)	Next generation three-dimensional conformal radiotherapy that radiates tumor by controlling the radiation beam's intensity.	Assumed to have better side-effect profile than RP (may not be true of nerve-sparing techniques). Few exceptions to patient selection.	Requires 7–8 weeks of weekday therapy. Recurrence after radiation typically precludes surgical option (same for EBRT also).

Figure 2. Patient Selection and Exclusion Criteria



Notes: The flow diagram illustrates the initial pool of individual patient data narrowed down for specific selection and exclusion criteria. The overall numbers are compared with estimates based on national averages from the SEER database and reported by the National Cancer Institute (2008b).

disease, bone cancers, and pelvic or other lower extremity lymph node cancers if present in the data from one year prior to one year following prostate cancer diagnosis. These criteria were intended to more precisely select a population with localized disease. The process of winnowing the Ingenix data to the 2,332 patients included in this analysis is illustrated in Figure 2. These data were used to estimate the two-year total health expenditures following diagnosis, stratified by initial treatment. This cost information was then linked with representative data from the Surveillance, Epidemiology, and End Results (SEER) database (2001–2005) on the distribution of initial treatment strategies for patients younger than 75 years old at diagnosis.

Statistical Analysis

Our general method for estimating health expenditure savings is to (1) estimate average health expenditures per patient treated with each of the initial management strategies (obtained from the commercial database described above), (2) calculate estimated total U.S. expenditures on health care for treating localized prostate cancer based on current treatment

patterns (obtained from the SEER database), and (3) estimate savings to the health care system by changing initial management strategies from today's treatment mix to both fully and partially adopted least-cost alternative management strategies.

Estimating incremental expenditures. There are two principal methods for estimating costs of care associated with different treatments for localized prostate cancer. The first approach imputes an incremental cost to a management strategy at the individual patient level by performing a regression of expenditures (e.g., total expenditures over two years) on health and demographic characteristics, considering all medical expenditures regardless of whether they were incurred in the management of prostate cancer. The incremental cost is the estimated coefficient (suitably transformed) of the dummy variable for the treatment (initial management strategy) in question. The second approach identifies and calculates expenditures that are "related" to the medical condition of interest. This approach is one that investigators have frequently used in other settings, including randomized trials with embedded cost components, but it requires a sometimes arbitrary assignment of expenditures into related and unrelated categories. For example, assignment of care for prostate cancer treatment is relatively straightforward when the claims are for the treatment itself, but follow-on costs cannot be readily assigned because the relationship of a claim to the treatment can be unclear. Erectile dysfunction, urinary incontinence, and diarrhea are side effects of prostate cancer treatments but are also common among untreated prostate cancer patients and men of similar age. Thus, it is unclear whether to assign costs of care for such conditions to the prostate cancer treatment, since a portion of these costs would have been incurred anyway. We use both approaches (total costs and prostate cancer–related costs) to estimate health expenditures in our general methodology.

In any observational analysis of health outcomes, nonrandom treatment assignment might bias comparisons of treatment costs and outcomes. We controlled for known variables that influence treatment choice and outcomes in the regression analysis, as described below. Our examination of the data (including, for example, health care spending prior to prostate cancer diagnosis) suggests that such remaining bias is unlikely to have changed the qualitative findings of this study.

Using the claims data described previously, we divided patients into initial management strategies based on claims (or lack of them) for specific prostate cancer treatments within one year of the initial diagnosis. We considered five therapeutic management strategies individually, including the strategy of active surveillance, and a sixth group (i groups each with x total number of individuals) receiving combinations of individual strategies (henceforth also called "treatments" or "treatment groups"). The next step was to estimate the impact of initial treatment on spending. We calculated average total health expenditures (T_c) for medical care by treatment group by summing all prescription drug costs, physician costs, ancillary services (such as laboratory and diagnostic testing), and inpatient and outpatient hospitalization costs for the subsequent two years following diagnosis. Average total health expenditures (T_{c_i}) were thus calculated for each management strategy:

$$T_{c_i} = \frac{\sum_{0}^{24}(pharm_c + provider_c + ancillary_c + hosp_c)}{x} \quad (1)$$

We also calculated medians, quartiles, and 95% confidence intervals for total health expenditures by initial treatment strategy. Again, this was done for both total health expenditures and prostate cancer–related health expenditures. Costs were converted to 2004 U.S. dollars.

We calculated costs directly related to prostate cancer for each individual in the data diagnosed in 2004 by including direct treatment charges and major ancillary services charged on the same day of treatment, such as laboratory and diagnostic testing. For active surveillance, we calculated charges for follow-up prostate biopsies.

We first compared raw (unadjusted) health expenditures and used standard methods to estimate the sampling variability associated with each average total and direct health expenditure result by treatment group, including 95% confidence intervals. We then adjusted the raw outcome differences for age of the patient and comorbid health conditions, including angina, coronary artery disease, dementia, depression, anxiety, pain, COPD, lung cancer, colon cancer, skin cancers, rheumatoid and osteoarthritis, hip and knee replacements, and trauma based on the presence of ICD-9 diagnostic codes in the patient-level data. We adjusted for comorbid conditions using the Dartmouth-Manitoba inpatient adaptation (Ghali et al. 1996) of the Charlson comorbidity index (Charlson et al. 1987). Furthermore, we adjusted two-year health expenditures for the prior level of health spending (12 months preceding the initial cancer diagnosis) to determine whether selection bias might have influenced the results—that is, whether heavier utilizers of care were preferentially assigned to particular prostate cancer treatments.

Additionally, we estimated how often patients in the active surveillance group received one of the other treatments more than a year after diagnosis. We recorded which treatments were given in the second year and compared them with active treatments selected during the first year after diagnosis.

Estimating population level savings. We calculated the potential savings from adopting (or partially adopting) the lowest-cost treatment option(s) at the population level. This requires understanding currently prevalent management strategies. Sources containing data about current practice patterns include literature reviews; clinical studies; large databases, such as the Surveillance, Epidemiology, and End Results (SEER) database for management of cancer; and representative large claims data sets, such as Medicare claims files. Based on these types of sources, the change in multiyear health expenditures that would result if patients received the strategies supported by comparative effectiveness or cost-effectiveness analyses can be calculated.

For this analysis, we estimated the current treatment distributions for localized prostate cancer from the 2001–2005 SEER database. SEER represents a larger and likely more representative population than is contained in the Ingenix claims files. We calculated total estimated health expenditures (C_{today}) based on the average treatment costs for each management strategy (T_{c_i}), obtained from the preceding analysis, applied to current frequencies (f) of use of each of the six (including combined) treatment options (i).

$$C_{today} = \sum_{0}^{6} T_{c_i} \times f_i \tag{2}$$

We then estimated the change in health expenditures from migrating practice patterns to initial management strategies supported by the findings from CER ($C_{withCER}$)—those with the least cost but for which evidence does not suggest a difference in effectiveness. We did this by estimating the cost of care for localized prostate cancer with alternative frequencies for the use of each treatment alternative, as supported by CER. The health savings with CER is thus estimated by subtracting these equations: $C_{today} - C_{withCER}$ (i.e., Eq. (2) – Eq. (3)).

$$C_{withCER} = \sum_{0}^{6} T_{c_a} \times f_t \tag{3}$$

We inflated the base year for these costs to 2009 based on the estimated 2004–2009 GDP deflator (NASA n.d.).

Finally, we calculated partial adoption scenarios in which only a portion of the patients currently receiving higher-cost treatment alternatives migrate to the preferred management strategy(ies) as defined by CER.

RESULTS

Findings From CER on Localized Prostate Cancer

In addition to our own review of the literature on the efficacy of the various first-line treatments for localized prostate cancer, we were able to draw upon an extensive and recent systematic review of the efficacy of treatments for localized prostate cancer (Wilt et al. 2008). This review confirmed that the evidence base from which to choose initial therapy is limited. There are three published randomized trials comparing treatments for prostate cancer—two comparing radical prostatectomy (RP) with active surveillance and one comparing RP with external beam radiation therapy (EBRT). The most recent trial, and arguably the only one conducted in the modern treatment era, compared RP with watchful waiting for 695 Scandinavian men followed for an average of 8.2 years (Bill-Axelson et al. 2005). Although all patients in this trial had disease localized to the prostate gland, only 12% of the cases were detected by an elevated prostate-specific antigen (PSA) screening test. Today, PSA testing is the most common basis for detecting prostate cancer in the United States. Prostate cancer detected by other means tends to be "bulkier" disease (typically a larger tumor burden), as demonstrated by presentation with symptoms or detection on physical examination. Bill-Axelson and colleagues found that 30 of 347 men assigned to surgery (8.6%) and 50 of 348 men assigned to watchful waiting (14.4%) died from prostate cancer (risk reduction [RR] for death from prostate cancer of 0.56, with a 95% confidence interval of 0.36 to 0.88), and an absolute reduction of 5.0% in the risk of death (RR of 0.74, 95% confidence interval of 0.56 to 0.99). Subgroup analysis of this randomized trial showed that the survival benefit was limited to those younger than 65 years at diagnosis and that this benefit did not begin until year 5 of the trial analysis. Two other randomized trials (between RP and watchful waiting, and RP and EBRT) were conducted in the 1960s and 1970s, when treatment and disease detection were significantly different than they are today, and neither trial found that one treatment modality produced better overall outcomes than the other (Iversen, Madsen, and Corle 1995; Paulsen et al. 1982; Wilt et al. 2008). No randomized trial has evaluated and shown that one radiation therapy modality is superior to another, to active surveillance, or to radical prostatectomy.

Thus, no specific treatment for localized prostate cancer has been proven to be superior to another, particularly among patients 65 years old and older (Wilt et al. 2008). Furthermore, because most localized prostate cancer is detected today by a screening PSA level rather than by symptomatic presentation or physical examination, the patients included in earlier trials may have had more aggressive or advanced disease at the time of presentation, suggesting that the benefits of any active treatment might not be as great today. This does not mean that all treatment approaches are equally effective for every patient; clearly, better evidence of effectiveness would have the potential to improve decisions about initial management. But because existing evidence does not establish the superiority of a particular management strategy, the results of comparative effectiveness research suggest that unless there are reasons why an individual patient should not receive a particular treatment (e.g., prostatectomy is only an option for patients who can tolerate surgery), there is little justification for choosing a more expensive treatment.

Statistical Analysis

Most patients in the Ingenix claims database were managed with either active surveillance (41%) or radical prostatectomy (33%). IMRT was infrequently selected as initial treatment (5%), but its use grew rapidly over the period of analysis. Total health expenditures on IMRT per covered life (controlling for changes in the covered population) increased by an 80% compound annual growth rate between 2002 and 2006. The percentage of patients in the Ingenix database treated with IMRT increased from 1.5% to more than 6% during that period. Almost 5% of patients received more than one treatment modality within the first

Table 2. Summary Statistics by Initial Management Strategy for Localized Prostate Cancer

Treatment	Frequency (N = 2,337)	%	Health Expenditures[a] ($ 2004) Mean	Median	25th Percentile	75th Percentile
Active Surveillance	969	42	53,900	29,900	11,400	78,400
Radical Prostatectomy	765	33	49,800	34,000	22,300	58,200
Brachytherapy	358	15	67,700	57,500	35,500	86,400
EBRT	26	1	77,500	54,000	33,500	96,200
IMRT	118	5	96,300	84,200	50,500	133,900
Multiple Treatments	96	4	114,600	101,200	63,600	139,400

Note: EBRT = external beam radiation therapy; IRMT = intensity-modulated radiation therapy.

[a]Unadjusted two-year total health expenditures.

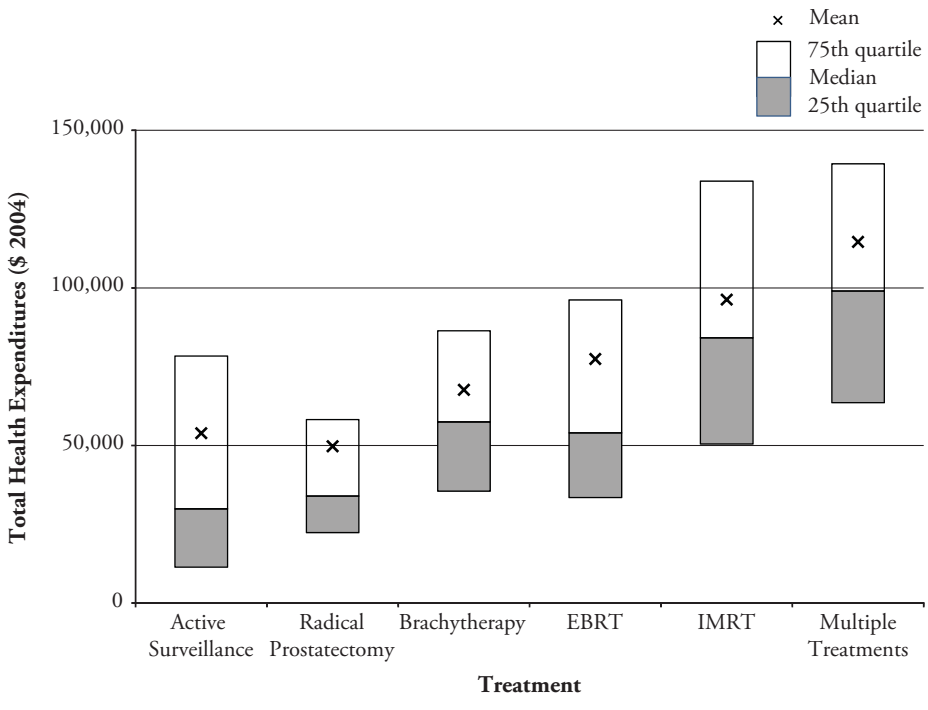
year of diagnosis. The most common combination of treatments (40%) consisted of both brachytherapy and IMRT (Table 2).

The two-year (unadjusted) mean medical expenditures following a diagnosis of localized prostate cancer ranged from $49,800 for radical prostatectomy and $53,900 for active surveillance to $96,300 for IMRT (Table 2). Median medical expenditures, which provide less weight to positively skewed outliers typical for health care data, were $29,900 for active surveillance, $34,000 for radical prostatectomy, $57,500 for brachytherapy, and $84,200 for IMRT. The frequencies, two-year mean, median, and 25th and 75th percentile results for unadjusted health expenditures by initial management strategy are further described in Table 2 and Figure 3.

Table 3 shows the results for the regression models adjusting for, in the first case, age and comorbid conditions, and, second, age, comorbid conditions, and preceding 12-month health expenditures. Adjusting for age and all comorbid conditions, the two-year mean total health expenditures for an otherwise healthy 65-year-old—that is, with no comorbid conditions but with prostate cancer—ranged from $21,400 for active surveillance to $68,300 for IMRT. As expected, total health costs increased across all treatment groups as age increased. The full model that considered all three sets of adjustments best explained the underlying data (R^2 of .29). For this model, treatment with radical prostatectomy, brachytherapy, or IMRT was associated with a statistically significant greater cost than treatment with active surveillance after adjusting for all explanatory variables. However, the additional cost of treatment with radical prostatectomy is $7,300, while other alternatives are considerably more expensive—$19,000 for brachytherapy and $46,900 for IMRT. The total two-year health expenditures for an otherwise healthy 65-year-old with newly diagnosed prostate cancer were $18,400 if treated with active surveillance, $37,500 if treated with brachytherapy, and $65,400 if treated with IMRT (Table 3). These costs significantly increase with the presence of additional comorbid conditions, such that a 65-year-old with diabetes and newly diagnosed prostate cancer will cost an average of $33,700 if managed with active surveillance, $41,000 with radical prostatectomy, $52,700 with brachytherapy, and $80,600 with IMRT. Figure 4 shows the additional estimated costs attributable to major comorbid conditions for an otherwise healthy 65-year-old with localized prostate cancer.

The estimated costs directly attributable to the management of localized prostate cancer, as opposed to all health-related expenditures, for two years following diagnosis are shown in Figure 5. These data represent the subset of patients in the analysis diagnosed with prostate cancer in 2004. Even though active surveillance required frequent monitoring

Figure 3. Unadjusted Total Health Expenditures by Initial Management Strategy



Notes: Mean, median, and 25th and 75th quartile total health expenditures are shown by initial treatment group. The black cross indicates the mean value, the middle horizontal line indicates the median value, the top horizontal line indicates the 75th quartile, and the lower horizontal line represents the 25th quartile of health expenditures. Costs are discounted to 2004 USD. EBRT = external beam radiation therapy; IMRT = intensity-modulated radiation therapy.

with blood tests and repeated prostate biopsies, it was associated with the lowest average treatment-related cost per patient of $1,350. IMRT was the most costly at an average of $50,700 per patient.

An additional 3.2% of patients who started in the active surveillance group were treated in the second year following initial diagnosis. Of those later receiving active treatment, 39% were treated with IMRT, 27% with brachytherapy, 22% with radical prostatectomy, and 12% with EBRT. This compares with 56% receiving radical prostatectomy, 26% brachytherapy, 2% EBRT, and 8.7% IMRT if actively treated during the first year.

To calculate the potential impact of a CER-supported strategy, we estimated the national expenditure reductions that would result from moving patients into the less-expensive initial management strategies. Using the SEER data, we identified 104,802 patients younger than 75 years with localized prostate cancer diagnosed between 2001 and 2005 and calculated the proportion receiving each treatment. We then calculated changes in health expenditures (for two years following diagnosis) that would result from shifting patients to various strategies, as supported by our previous cost analysis. Table 4 shows the results of a shift toward lower-cost treatment strategies. A move from IMRT to active surveillance would generate unadjusted savings of $1.25 billion over two years for a

Table 3. Incremental Expenditures[a] ($ 2004) Attributed to Initial Management Strategy of Localized Prostate Cancer Adjusted for Age and Common Comorbidities

		Initial Treatment Strategy[b]				
Models	Assumptions	AS	RP	EBRT	Brachy	IMRT
Age and Comorbid Conditions (R^2 = .27)						
Age adjusted, otherwise healthy	55 years old	17,000	22,800	22,000	35,800	63,900
	65 years old	21,400	27,200	26,500	40,200	68,300
	75 years old	53,700	58,000	47,200	61,000	89,000
Age (assumes 65 years) and comorbid conditions	Coronary artery disease	43,900	49,700	43,900	47,000	90,800
	Diabetes	38,700	44,500	43,700	57,400	85,600
	Peripheral vascular disease	53,900	59,700	59,000	72,700	100,800
Age, Comorbid Conditions, and Preceding 12-Month Health Expenditures (R^2 = .29)						
Age adjusted, otherwise healthy	55 years old	14,900	22,200	21,500	33,900	61,800
	65 years old	18,400	25,700	25,100	37,500	65,400
	75 years old	23,500	45,700	30,100	57,400	85,400
Age (assumes 65 years) and comorbid conditions	Coronary artery disease	33,000	40,300	39,700	52,000	79,900
	COPD	26,900	34,200	33,500	45,900	73,800
	Diabetes	33,700	41,000	40,400	52,700	80,600

[a]Regression-adjusted two-year total health expenditures.

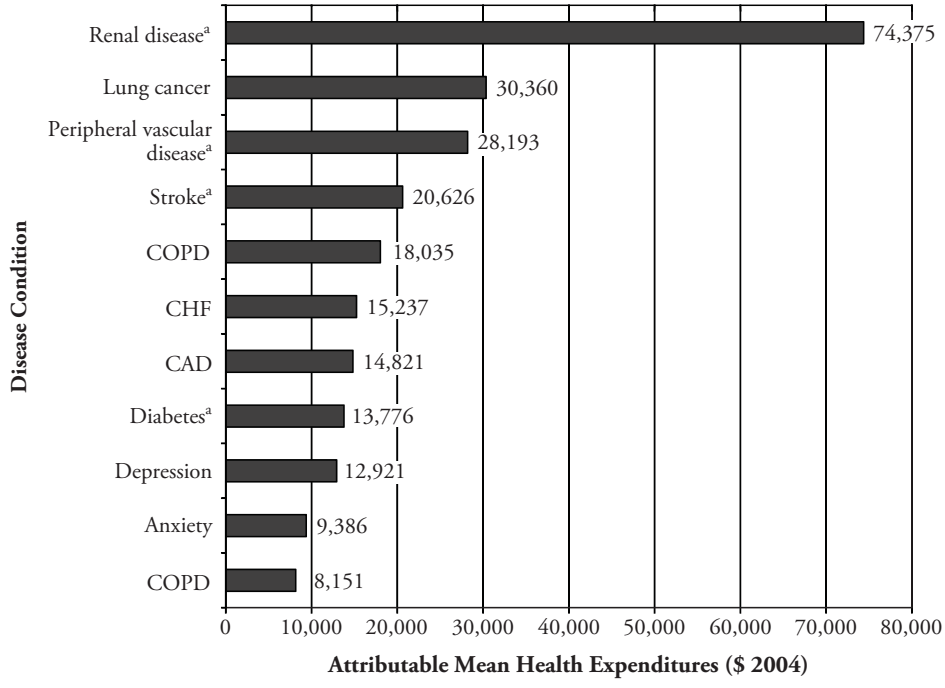
[b]AS = active surveillance; RP = radical prostatectomy; EBRT = electron beam radiation therapy; Brachy = brachytherapy; and IMRT = intensity-modulated radiation therapy.

population of men aged 65 and without comorbid conditions. Using the full specification (which includes preceding health expenditures as a control), the savings would be similar—$1.38 billion. A switch from brachytherapy to active surveillance would add another $320 to $440 million in estimated savings. Radical prostatectomy was the least costly of the active treatment strategies. Migrating patients receiving IMRT to radical prostatectomy and active surveillance in equal proportion would also save an estimated $1.27 to $1.50 billion in two-year health expenditures. Estimated savings based on shifting patients receiving multiple treatments to single-treatment strategies are between $570 million and $1.49 billion each year.

DISCUSSION

We estimate that a treatment strategy for prostate cancer based on comparative effectiveness research could reduce U.S. health expenditures by $1.7–$3.0 billion (2009 net present value) over a two-year period. The savings from this change in the treatment of localized prostate cancer alone could finance all the comparative effectiveness research funds ($1.1 billion) allocated in the American Recovery and Reinvestment Act. Extending these savings over a 10-year period and assuming an adoption rate equal to only 50%,

Figure 4. Estimated Cost Attributable to Major Comorbid Conditions for an Otherwise Healthy 65-Year-Old With Prostate Cancer



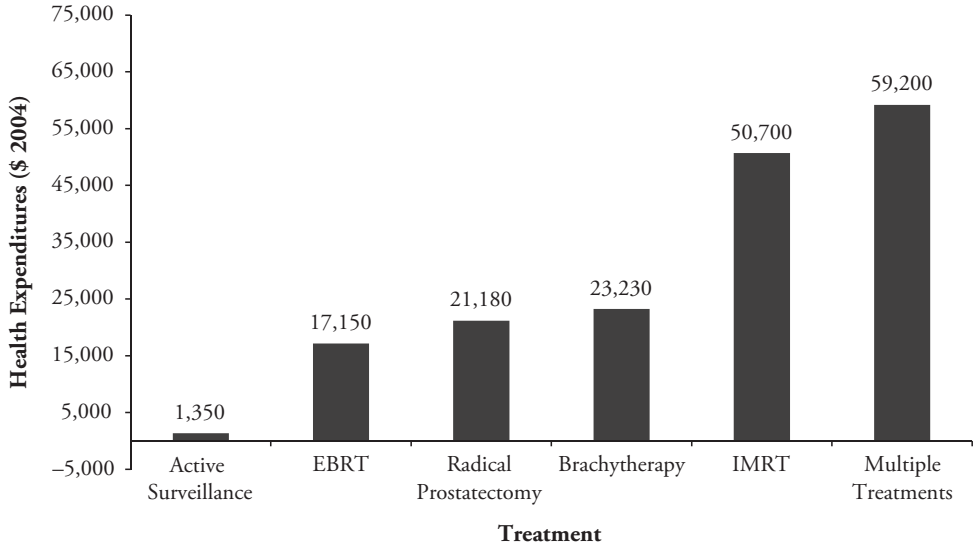
Notes: The estimated mean two-year cost attributable to a disease condition for a 65-year-old man with prostate cancer and no other comorbidities is shown. All comorbidities shown are statistically significant. Costs are discounted to 2004 USD.

[a]Adjustments are based on Charlson index; otherwise, adjustments are based on the presence of an ICD-9 code occurring within the two-year time frame of the analysis.

we estimate potential savings to U.S. health expenditures of $8.3–$14.5 billion (2009 net present value). Specifically, our analysis shows that this savings could be achieved by shifting patients currently receiving IMRT and brachytherapy to alternative strategies of active surveillance, or by dividing them equally between active surveillance and radical prostatectomy (the least costly active treatment alternative). Expenditures could also be sharply reduced by shifting patients currently receiving multiple treatments for localized prostate cancer (a practice that has not been shown to improve outcomes in randomized trials) to single therapeutic strategies. The great variation in costs observed in our study suggests that a definitive randomized trial of the treatment alternatives for localized prostate cancer could be worth billions of dollars over a 10-year period. The expected value of performing such a conclusive trial could be estimated based on the probabilities that different treatment strategies will prove superior. Such a calculation is beyond the scope of this analysis but would help elucidate the consequences of investment decisions in CER across disparate clinical areas.

These calculations may underestimate future savings. Increasingly, patients are receiving more expensive treatment options, despite the lack of evidence of superiority. This shift in treatment could be driven by several factors. Clinicians may be guiding

Figure 5. Health Expenditures Directly Related to Prostate Cancer, by Initial Management Strategy



Notes: Expenditures directly attributed to the treatment or surveillance of prostate cancer are shown by initial treatment group. Costs are discounted to 2004 USD. EBRT = external beam radiation therapy; IMRT = intensity-modulated radiation therapy.

Table 4. Health Expenditure Savings[a] Estimates ($ millions 2009) for Adopting Initial Management Strategies Supported by CER for Localized Prostate Cancer

Strategy[b]	Unadjusted	Adjusted for Age 65 and Preceding Health Expenditures
Shifting all patients to AS	2,536	3,574
Shifting patients receiving IMRT to AS	1,250	1,380
Shifting patients receiving IMRT to RP/AS	1,520	1,270
Shifting patients receiving brachy to AS	320	440
Shifting patients receiving brachy to RP/AS	370	390
Shifting patients receiving multiple treatments to single treatments (baseline proportional)	930	1,490
Shifting patients receiving multiple treatments to single EBRT/IMRT/brachy treatments (baseline proportional)	570	1,180

[a]Two-year health expenditure savings.

[b]AS = active surveillance; IMRT = intensity-modulated radiation therapy; RP = radical prostatectomy; EBRT = electron beam radiation therapy; and brachy = brachytherapy.

patients toward strategies that they believe are associated with better health outcomes, whether a result of greater efficacy or fewer adverse effects of treatment. There are trade-offs involved in treatment-associated side effects for the management of localized prostate cancer. For example, the largest observational study of treatment-associated side effects reported that urinary leakage was more common with radical prostatectomy (35%) than

with radiation therapy (12%), but that bowel urgency occurred more commonly with radiation (3%) than with radical prostatectomy (1%), and that erectile dysfunction was highly prevalent after all treatments (Hoffman et al. 2003). It is difficult to weigh the preferences for disparate side effects such as these. Is the potential reduction in urinary leakage from radiation treatment worth the small increase in bowel urgency? From a social perspective, side effects raise issues of the value of the quality—rather than the quantity—of life. For example, is it worth an additional $40,000 to treat patients with IMRT and reduce the risk of a bothersome, but not life-threatening, side effect such as urinary leakage? In addition, reimbursement likely plays a prominent role in the increasing use of more expensive treatments. IMRT, for example, is much more lucrative to the physician and facility than active surveillance, and this reinforces aggressive treatment decisions.

We chose to study localized prostate cancer because the justification for more intensive treatment is limited in this context. There are many other clinical areas in which CER could point to opportunities to substitute less costly but equally effective clinical strategies for commonly used approaches to patient care. A key challenge will therefore be the identification of the highest payoff areas for such research (Garber and Meltzer 2009). They can be identified by considering (1) the potential for growth and adoption of a clinical strategy, (2) the degree to which clinical practice is known to vary from the evidence-based (based on literature review) approach or, where definitive studies are unavailable, among providers (e.g., across geographies or race/ethnic groups), (3) the ability to segment the population into target groups that greatly differ in their responses to the clinical strategy, and (4) the practical consideration that administrative data can address the research question on a given medical topic (Garber and Meltzer 2009).

Research on comparative effectiveness can, as in this case, reveal that the evidence does not support superiority of one diagnostic or therapeutic option over others. This might occur either because there is ample evidence suggesting that there are no significant differences ("evidence of absence" of differences) or because the evidence base is insufficient to demonstrate that there are differences in effectiveness ("absence of evidence"). Lack of evidence is likely to be more common, often resulting in calls for collection of more data, in the form of either randomized trials or prospective observational analyses. In either case, when existing evidence does not demonstrate superiority of one approach, we propose modeling the migration of current medical practice patterns to the lowest-cost alternative, providing results for full (maximum potential cost savings) and partial adoption (e.g., 40% of patients with localized prostate cancer receiving IMRT shifted to active surveillance or radical prostatectomy).

Not all patients within a population may respond exactly the same way to a treatment. Often, patients vary in the severity of their disease, preferences toward alternative outcomes, or in other ways. Such sources of heterogeneity need to be recognized. For example, patients with localized prostate cancer who are 75 or older may not benefit as much from radical prostatectomy, perhaps because the risks associated with surgery rise with age. Treatment decisions should consider whether individuals or groups of patients are likely to respond differently to a treatment than the groups studied in formal trials. For example, for this research we excluded this patient population because of a high likelihood of expected differences in response to treatment as opposed to a younger population at diagnosis. The results of studies such as these should be interpreted with any potential for patient heterogeneity in mind.

Our results are most limited by the inclusion of only two years of follow-up expenditure data after initial diagnosis. In order to include newer technologies such as brachytherapy and IMRT, we had to use only recent data for this analysis. Limiting the consideration of total health expenditures to two years following diagnosis potentially biases the results toward active surveillance by not including later costs that would be attributed to the progression of some patients to active treatment. A recent long-term

prospective cohort study reported that the average time to treatment for patients initially managed with active surveillance (N = 3,331) was 3.9 years, and that by 8 years of follow-up, 49% of patients had received active treatment (Shappley et al. 2009). Even under this scenario, in which only half of the initial savings from active surveillance would eventually be realized, the health expenditure savings would still approach $1.5 billion for the initial two years and $7 billion (2009 net present value) for a 10-year period after initiating strategies supported by CER.

Our method is subject to the usual limitations of observational analyses. With nonrandom assignment to treatment, selection effects can bias cost estimates, just as they bias survival estimates. For example, only healthy men may be offered radical prostatectomy as a treatment, so greater health expenditures among men treated with other means might merely reflect their greater burden of underlying illnesses. If such effects are important, the estimated savings from implementation of comparative effectiveness research could be overstated. To overcome potential bias related to the use of observational data, we adjusted for observed characteristics that might have influenced treatment choice and outcomes, such as comorbidities and prior health expenditures. In other contexts, it might be possible to apply methods to adjust for selection effects, such as propensity scores (Rosenbaum and Rubin 1984) and instrumental variables (IV) estimators. Propensity score and instrumental variables methods both deal with the endogeneity of the treatment by developing predictive equations for treatment choice. Propensity score methods, strictly speaking, require that no variables omitted from the treatment choice equation be correlated with the outcome. Identification of an instrumental variables model requires one or more variables that predict treatment choice but that are not associated with the outcome; one such variable might be the distance to a hospital that offers specialized services (McClellan, McNeil, and Newhouse 1994). In our example, the local availability of specialist physicians (e.g., radiation oncologists) and various hospital facilities (e.g., facilities capable of offering IMRT or EBRT) could induce supply-side variability that will affect treatment decisions.

Lastly, our research does not address how findings from CER, such as the substitution of active surveillance or radical prostatectomy for more expensive treatment alternatives, might be practically implemented. Further research efforts investigating the most effective methods to influence health care decisions, such as the use of payment reform or expert recommendations and guideline committees, are needed. Another application of such results is the design of payment policies to better match reimbursement to value as supported by CER across alternative management strategies. For example, Medicare could set reimbursement rates for providers for the most expensive treatment choices to rates similar to the least expensive, yet equally effective, alternative management strategies. Creative payment policies by large purchasers, such as Medicare, that more closely match value for the health care dollars spent may be facilitated by these research methods. Because of implementation uncertainties like these, our estimates thus represent *potential* cost savings. The actual savings will depend on the ways that the information is incorporated into clinical practice or payment systems.

REFERENCES

Agency for Healthcare Research and Quality. 2009. “EPC Evidence Reports.” U.S. Department of Health and Human Services, Washington, DC.

American Cancer Society. 2009. “Cancer Facts & Figures 2009.” Atlanta, GA: American Cancer Society.

Bill-Axelson, A., L. Holmberg, M. Ruutu, M. Haggman, S.O. Andersson, S. Bratell, A. Spangberg, C. Busch, S. Nordling, H. Garmo, J. Palmgren, H.O. Adami, B.J. Norlen, and J.E. Johansson. 2005. “Radical Prostatectomy Versus Watchful Waiting in Early Prostate Cancer.” *New England Journal of Medicine* 352:1977–84.

Charlson, M.E., P. Pompei, K.L. Ales, and C.R. MacKenzie. 1987. "A New Method of Classifying Prognostic Comorbidity in Longitudinal Studies: Development and Validation." *Journal of Chronic Diseases* 40:373–83.

Congressional Budget Office (CBO). 2007a. "The Long-Term Outlook for Health Care Spending." Publication No. 3085. CBO, Washington, DC.

———. 2007b. "Research on the Comparative Effectiveness of Medical Treatments: Issues and Options for an Expanded Federal Role." Publication No. 2975. CBO, Washington, DC.

Cutler, D.M. and M. McClellan. 2001. "Is Technological Change in Medicine Worth It?" *Health Affairs* 20(5):11–29.

Cutler, D.M., A.B. Rosen, and S. Vijan. 2006. "The Value of Medical Spending in the United States, 1960–2000." *New England Journal of Medicine* 355:920–27.

Executive Office of the President, Council of Economic Advisors. 2009. "The Economic Case for Health Care Reform." June 2009. Available online at http://www.whitehouse.gov/assets/documents/CEA_Health_Care_Report.pdf.

Garber, A.M. and D.O. Meltzer. 2009. "Setting Priorities for Comparative Effectiveness Research." Pp. 15–33 in *Implementing Comparative Effectiveness Research: Priorities, Methods, and Impact*. Washington, DC: Brookings Institution.

Geithner, T.F. 2009. "2009 Annual Report of the Boards of Trustees of the Federal Hospital Insurance Trust Fund and the Federal Supplementary Medical Insurance Trust Fund." Available online at http://www1.cms.gov/ReportsTrustFunds/downloads/tr2009.pdf.

Ghali, W.A., R.E. Hall, A.K. Rosen, A.S. Ash, and M.A. Moskowitz. 1996. "Searching for an Improved Clinical Comorbidity Index for Use With ICD-9-CM Administrative Data." *Journal of Clinical Epidemiology* 49:273–78.

Goldman, D.P., G.F. Joyce, J.J. Escarce, J.E. Pace, M.D. Solomon, M. Laouri, P.B. Landsman, and S.M. Teutsch. 2004. "Pharmacy Benefits and the Use of Drugs by the Chronically Ill." *Journal of the American Medical Association* 291:2344–50.

Goldman, D.P., G.F. Joyce, and P. Karaca-Mandic. 2006. "Varying Pharmacy Benefits With Clinical Status: The Case of Cholesterol-Lowering Therapy." *American Journal of Managed Care* 12(1):21–28.

Goldman, D.P., B. Shang, J. Bhattacharya, A.M. Garber, M. Hurd, G.F. Joyce, D.N. Lakdawalla, C. Panis, and P.G. Shekelle. 2005. "Consequences of Health Trends and Medical Innovation for the Future Elderly." *Health Affairs* 24(Suppl. 2):W5R5-17.

Hoffman, R.M., W.C. Hunt, F.D. Gilliland, R.A. Stephenson, and A.L. Potosky. 2003. "Patient Satisfaction With Treatment Decisions for Clinically Localized Prostate Carcinoma. Results From the Prostate Cancer Outcomes Study." *Cancer* 97:1653–62.

Institute of Medicine. 2009. "Initial National Priorities for Comparative Effectiveness Research." Washington, DC: The National Academies Press.

Iversen, P., P.O. Madsen, and D.K. Corle. 1995. "Radical Prostatectomy Versus Expectant Treatment for Early Carcinoma of the Prostate. Twenty-three year follow-up of a prospective randomized study." *Scandinavian Journal of Urology and Nephrology Supplement* 128:502–504.

Joyce, G.F., J.J. Escarce, M.D. Solomon, and D.P. Goldman. 2002. "Employer Drug Benefit Plans and Spending on Prescription Drugs." *Journal of the American Medical Association* 288: 1733–39.

Joyce, G.F., D.P. Goldman, P. Karaca-Mandic, and G.D. Lawless. 2008. "Impact of Specialty Drugs on the Use of Other Medical Services." *American Journal of Managed Care* 14:821–28.

Joyce, G.F., D.P. Goldman, P. Karaca-Mandic, and Y. Zheng. 2007. "Pharmacy Benefit Caps and the Chronically Ill." *Health Affairs* 26:1333–44.

McClellan, M., B.J. McNeil, and J.P. Newhouse. 1994. "Does More Intensive Treatment of Acute Myocardial Infarction in the Elderly Reduce Mortality? Analysis Using Instrumental Variables." *Journal of the American Medical Association* 272:859–66.

Murphy, K.M. and R.H. Topel. 2006. "The Value of Health and Longevity." *Journal of Political Economy* 114:871–904.

National Aeronautics and Space Administration (NASA). n.d. "Gross Domestic Product: Deflator Inflation Calculator." Washington, DC: NASA.

National Cancer Institute. 2008a. "Surveillance and Epidemiology End Results Stat Fact Sheets." U.S. National Institutes of Health, Bethesda, MD.

———. 2008b. "Surveillance, Epidemiology, and End Results (SEER) Program SEER*Stat Database: Incidence—SEER 17 Regs Limited-Use + Hurricane Katrina Impacted Louisiana Cases, Nov 2007 Sub (1973–2005 varying)—Linked To County Attributes—Total U.S., 1969-2005." Division of Cancer Control and Population Sciences, Surveillance Research Program, Cancer Statistics Branch, Bethesda, MD.

Newhouse, J.P. 1992. "Medical Care Costs: How Much Welfare Loss?" *Journal of Economic Perspectives* 6(3):3–21.

Paulson, D.F., G.H. Lin, W. Hinshaw, and S. Stephani. 1982. "Radical Surgery Versus Radiotherapy for Adenocarcinoma of the Prostate." *Journal of Urology* 128:502–504.

Rosenbaum, P.R. and D.B. Rubin. 1984. "Reducing Bias in Observational Studies Using Subclassification on the Propensity Score." *Journal of the American Statistical Association* 79:516–24.

Schoen, C., S. Guterman, A. Shih, J. Lau, S. Kasimow, A. Gauthier, and K. Davis. 2007. "Bending the Curve: Options for Achieving Savings and Improving Value in U.S. Health Spending." Report. The Commonwealth Fund, New York.

Shappley, W.V., III, S.A. Kenfield, J.L. Kasperzyk, W. Qiu, M.J. Stampfer, M.G. Sanda, and J.M. Chan. 2009. "Prospective Study of Determinants and Outcomes of Deferred Treatment or Watchful Waiting Among Men With Prostate Cancer in a Nationwide Cohort." *Journal of Clinical Oncology* 27:4980–85.

Warren, J.L., K.R. Yabroff, A. Meekins, M. Topor, E.B. Lamont, and M.L. Brown. 2008. "Evaluation of Trends in the Cost of Initial Cancer Treatment." *Journal of the National Cancer Institute* 100:888–97.

Wilt, T.J., R. MacDonald, I. Rutks, T.A. Shamliyan, B.C. Taylor, and R.L. Kane. 2008. "Systematic Review: Comparative Effectiveness and Harms of Treatments for Clinically Localized Prostate Cancer." *Annals of Internal Medicine* 148:435–48.