

Are Pharmaceuticals Cost-Effective? A Review Of The Evidence

Do drug treatments give value for the money? Careful analysis can yield useful information, this study finds.

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PROLOGUE: A study of prescription drugs' cost-effectiveness might seem like an arcane research subject, but in fact it lies at the heart of the current debate over the growing use (and rising cost) of prescription drugs. Advocates argue that drugs offer value for the money, substituting for more costly and invasive treatments and hospitalizations. This study offers a cogent framework in which to determine prescription drugs' value in making treatment decisions. It is based on cost-utility analysis, which measures benefit in terms of quality-adjusted life years gained by drug therapies. Although, as the authors note, the approach has some limitations, such a measure enables comparisons across diverse conditions and allows the measure of benefit to take into account the value different people place on their treatment options.

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ABSTRACT: The argument that prescription drugs are cost-effective has been made both by the pharmaceutical industry to support rising drug prices and expenditures, and by advocates of expanded drug coverage for elderly and low-income persons. A new database of 228 published cost-utility analyses sheds light on the issue. According to published data, some drugs do save money or are cost-effective, but the issue depends critically on the context in which the drug is used and the intervention with which it is compared. Cost-utility analyses funded by the drug industry tend to report more favorable results than do those funded by nonindustry sources. Cost-effectiveness analysis can help policymakers to determine whether drugs and other interventions offer value for money.

THE NOTION THAT PHARMACEUTICALS are cost-effective plays an important role in the debate over a Medicare prescription drug benefit and the larger national discourse over appropriate coverage and reimbursement policies for prescription drugs. Representatives of the pharmaceutical industry have made the cost-effectiveness argument for years, maintaining that drugs provide good value—even saving money in the long run in many cases by averting other costly health care services—and thus warrant their prices.¹ Indeed, industry officials have argued that drug expenditures have risen faster than other types of health spending in recent years precisely because pharmaceuticals are cost-effective (and therefore their use has been encouraged more heavily by cost-conscious managed care plans).²

But arguments like the cost-effectiveness one have gained currency in other quarters as well. For example, the *New York Times* recently cited a Clinton administration internal document stating that for every dollar spent on drugs there would be \$3.50 in savings on hospital spending, a claim repeated elsewhere by analysts in the popular press.³ In addition, analysts arguing for expanded drug coverage for low-income Medicare beneficiaries have used a cost-effectiveness rationale, pointing to research showing that limits on the number of prescriptions that chronically ill elderly persons could fill actually increased total health costs.⁴

This paper considers the evidence on the cost-effectiveness of pharmaceuticals and its implications for a Medicare drug benefit. We start by defining terms used in economic evaluations. Next, we review the data, using a new database of cost-effectiveness analyses developed by researchers at the Harvard School of Public Health. In the final section we discuss policy implications.

■ **Data and methods.** The field of economic evaluation of health and medical interventions (including pharmaceuticals) has expanded rapidly in recent years.⁵ While the evaluations have taken on a number of forms, cost-effectiveness analysis (CEA) has emerged as

the recommended analytic technique for the field.⁶ The appeal of CEA is that it provides a convenient means of quantifying both economic and health benefits in a single ratio and—if the numerators and denominators of cost-effectiveness ratios are reported in standard terms and obtained using comparable methods—can inform decisions about how to allocate health resources efficiently.

Standards for the field have been reported in recent years by the U.S. Public Health Service Panel on Cost-Effectiveness in Health and Medicine.⁷ Notably, the panel recommended use of a “reference case,” or standard set of methodologic practices that an analyst would seek to follow in a CEA if results from different studies are to be compared. The panel recommended that reference case analyses use “cost-utility analysis,” in which cost-effectiveness ratios are presented in terms of costs per quality-adjusted life year (QALY) gained.⁸ QALYs are recommended because they capture gains from both prolongation and quality of life in a single health outcome, and because they incorporate the value people place on different outcomes.⁹ Although only a subset of economic evaluations use this methodology, cost-utility analysis is arguably the best approach for making comparisons across diverse conditions.

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To understand the evolution and current state of cost-utility analysis, and to help readers make sound comparisons across studies, we recently developed a database of published cost-utility analyses. A detailed description of our methods is provided elsewhere.¹⁰ Briefly, the database was constructed through an extensive search for original cost-utility analyses using publication databases such as MEDLINE, HealthSTAR, CancerLit, and others for the years 1975–1997. These databases were searched for medical subject headings (MeSH) or text keywords “quality-adjusted,” “QALY,” and “cost-utility analysis.” In addition, we screened the titles of more than 6,000 articles in two extensive bibliographies of the field.¹¹

Each article was scrutinized with the aid of a standard data auditing form to determine its transparency, completeness, and quality. For each study, detailed descriptive data were abstracted on the intervention under investigation; the methods used to estimate costs, effects, and preference weights; and the degree to which the article met recommended protocols for reporting and discussing findings. We also recorded a subjective overall quality score for each article on a Likert-type scale from 1 (low) to 7 (high). In total, information on sixty-nine items was collected for each study.

The auditing process for each article consisted of a systematic inspection by two trained readers using the data auditing form. The readers independently read and audited each article and then convened for a consensus audit to resolve discrepancies. The final data-

base contains 228 studies and more than 700 cost-utility ratios (the number of ratios exceeds the number of studies, because some articles contained more than one usable comparison).¹² All of the ratios were standardized to 1998 dollars.

In this paper we analyze only the articles in our database that focus on drug therapies. In particular, we examine the cost-effectiveness of drug compared with nondrug interventions. We also investigate a subset of drugs pertinent to the Medicare population. Finally, we analyze the impact of a study's funding source on the results of the analysis, because industry sponsorship has been implicated by some observers as an important influence on results in cost-effectiveness research.¹³

Study Results

The number of cost-utility analyses of drug and nondrug interventions has increased steadily over time. During the 1970s and 1980s only a few studies were being published each year. By 1997 the number had risen to thirty-three nondrug and seventeen drug interventions published. The studies have covered a range of interventions, with drugs, surgical procedures, and various diagnostic procedures as the top three categories (Exhibit 1). The studies also have covered a wide range of conditions, with particular emphasis on the circulatory system, cancer, and infectious diseases. Pharmaceuticals were the subject of a large percentage of cost-utility analyses in the areas of mental disorders, neoplasms, and the genitourinary system. Funding for studies came primarily from government organizations, foundations, and drug companies. In more than one-third of the studies, the funding source was not disclosed. Studies on drugs were funded mostly by drug companies.

The median cost-effectiveness ratios for the interventions have varied considerably (Exhibit 2). The median ratio for pharmaceutical interventions is \$11,000, which places it fourth in our categorization of intervention types, after immunizations, care delivery, and surgical interventions.¹⁴

Exhibit 3 shows a list of cost-utility ratios for selected drug therapies of potential relevance to the Medicare population. The results vary widely across strategies from cost savings (for example, treatment with acyclovir versus no treatment in patients with herpes zoster virus infection) to positive but relatively low (favorable) cost-effectiveness ratios (for example, captopril therapy versus no treatment in eighty-year-old patients surviving myocardial infarction with a ratio of \$4,300 per QALY) to relatively high (unfavorable) cost-effectiveness ratios (for example, antiemetic therapy with ondansetron versus antiemetic therapy with metoclopramide

EXHIBIT 1
Cost-Utility Analyses Of Pharmaceuticals Published, 1976-1997

Type of intervention	Number	Percent
Pharmaceutical	73	32.0%
Surgical	41	18.0
Diagnostic	26	11.4
Screening	24	10.5
Medical procedure	16	7.0
Care delivery	13	5.7
Health education	12	5.3
Immunization	9	3.9
Medical device	6	2.6
Other	2	0.9

Study characteristics	Total	Nondrug	Drug	Drug as percent of total
All studies	228	157	71	31.1%
Country of study				
United States	141	101	40	28.4
Other	87	56	31	35.6
Condition				
Circulatory system	55	39	16	29.1
Neoplasm	39	19	20	51.3
Infectious and parasitic	36	25	11	30.6
Genitourinary system	14	8	6	42.9
Digestive system	12	9	3	25.0
Musculoskeletal system	9	7	2	22.2
Endocrine, nutritional, and metabolic	10	10	0	0.0
Nervous system and sense organs	11	10	1	9.1
Mental disorders	11	5	6	54.5
Source of study funding ^a				
Government	107	83	24	22.4
Foundation	42	28	14	33.3
Pharmaceutical company	27	4	23	85.2
Medical device company	5	5	0	0.0
Health care organization	5	4	1	20.0
Other	3	3	0	0.0
Not disclosed	78	54	24	30.8

SOURCE: Authors' analysis.

^a Sponsorship as stated in article. Some studies had more than one sponsor.

in certain patients receiving cisplatin chemotherapy, with a ratio of \$460,000 per QALY).¹⁵ The median ratio for all drugs in our database that are currently paid for by Medicare (that is, drugs administered on an inpatient basis) is \$17,500 per QALY.

Exhibit 4 presents the cost-effectiveness ratios stratified by type of funding source. Studies funded by industry (including both the pharmaceutical and device industries) have lower (that is, better) median cost-effectiveness ratios (\$6,000), compared with those having nonindustry sponsorship (\$13,000) (Exhibit 4).¹⁶ More industry-sponsored studies show cost savings (21 percent) compared with non-industry-sponsored studies (9 percent), and fewer pre-

EXHIBIT 2

Median Cost-Effectiveness Ratios, By Type Of Intervention

Intervention type	Number of ratios	Median cost-effectiveness ^a
Immunization	38	\$2,000
Care delivery ^b	36	6,000
Surgical	128	10,000
Pharmaceutical	251	11,000
Screening	72	12,000
Other public health ^c	8	15,000
Health education/counseling	28	20,000
Diagnostic	83	20,000
Device	22	40,000
Various	3	68,000
Medical procedure ^d	42	140,000
All interventions	647	12,000

SOURCE: Authors' analysis.

NOTE: Excludes dominated interventions. The number of ratios exceeds the number of studies because some studies report more than one ratio.

^a Dollars per quality-adjusted life year (QALY) saved, in 1998 dollars.

^b Includes interventions defined by setting of care (for example, intensive care unit versus standard ward treatment).

^c Includes interventions not classified elsewhere (examples include fortification of cereal grain product with folic acid versus no program and the use of driver airbags versus no airbags in automobiles).

^d Includes nondiagnostic, nonscreening, nonsurgical procedures (such as blood transfusions).

sent “dominated” interventions (that is, interventions that are more costly and less effective than the comparator). Studies sponsored by pharmaceutical companies alone had the lowest median cost-effectiveness ratios (\$5,000), followed by those in which the funding source was not disclosed (\$10,000), and sponsorship by government (\$16,000) and foundations (\$31,000).

Policy Implications

The data presented here underscore several important points about the cost-effectiveness of pharmaceuticals. First, unlike many unsupported assertions made over the years about the “cost-effectiveness” of drugs or other medical practices, these studies quantify costs and health effects using data and a standard, well-accepted methodological technique.¹⁷ Second, according to the peer-reviewed literature, many drugs are indeed cost-effective. Examples in our database of cost-utility analyses include warfarin therapy to prevent stroke in those with atrial fibrillation, immunosuppressive drugs for those with kidney transplants, and treatment with mood-altering drugs for those suffering from depression.¹⁸ These interventions provide good value in the sense that they produce health benefits for relatively little cost or may actually save money for the health care system. Note that there is no accepted standard for what constitutes “good value,” although the range from \$50,000 to \$100,000 per QALY has often been used as a rough benchmark for the United States.¹⁹

EXHIBIT 3
Selected Cost-Effectiveness Ratios For Pharmaceuticals, With A Focus On The Medicare Population

Reference	Intervention vs. base case in target population	Dollars per QALY gained ^a
Sarasin and Eckman (1993)	Long-term anticoagulant therapy versus observation in lung cancer patients with acute deep venous thrombosis	Cost-saving
Paul et al. (1995)	Treatment with acyclovir (Zovirax) versus no treatment in patients with herpes zoster virus infection	Cost-saving
Tsevat et al. (1995)	Captopril therapy versus no captopril in 80-year-old patients surviving myocardial infarction	\$4,000
Trallori et al. (1997)	Treatment with mesalazine versus no treatment to maintain remission in Crohn's disease	\$6,000
Geelhoed et al. (1994)	Estrogen therapy from age 50, lifetime versus no treatment with hormone replacement therapy in healthy caucasian women age 50	\$12,000
Rose et al. (1990)	One-year course of isoniazid (INH) chemoprophylaxis versus no INH chemoprophylaxis in 55-year-old white male tuberculin reactors with no other risk factors	\$18,000
Bennett et al. (1996)	Flutamide plus orchiectomy versus orchiectomy alone in 70-year-old men with newly diagnosed, untreated minimal metastatic prostate carcinoma with good performance status	\$21,000
Jonsson et al. (1996)	Treatment to reduce the incidence of osteoporotic hip fracture versus no treatment in 62-year-old woman with established osteoporosis	\$34,000
Oster et al. (1994)	Ticlopidine versus aspirin in 65-year-old with high risk of stroke	\$48,000
Desch et al. (1993)	Chemotherapy versus no chemotherapy in 75-year-old with breast cancer	\$58,000
Edelson et al. (1990)	Captopril versus propranolol in persons in the U.S. population ages 35–64 without the diagnosis of coronary heart disease but with essential hypertension	\$150,000
Zbrozek et al. (1994)	Antiemetic therapy with ondansetron versus antiemetic therapy with metoclopramide in 70-kg patient receiving cisplatin chemotherapy who had not been previously exposed to antineoplastic agents	\$460,000

SOURCE: For a complete bibliography, contact the authors at Harvard School of Public Health, 718 Huntington Avenue, Second Floor, Boston, Massachusetts 02115.

^a QALY is quality-adjusted life year; 1998 dollars.

Third, *cost-effectiveness* does not mean *cost savings*. These terms have often been confused. But as Peter Doubilet and colleagues have noted, restricting the term *cost-effective* to mean cost-saving interventions (where equal or better health outcomes are implied) would exclude many widely accepted interventions, which do not save money but are “cost-effective” in the sense that their additional benefits are worth their additional cost.²⁰ A more appropriate use of the term *cost-effective* would include situations in which one strategy is less costly than and at least as effective as another but also some that are more costly and more effective, as long as society is willing to pay for the QALYs gained or other health outcomes produced.²¹

A related point is that a critical aspect of any drug’s cost-

EXHIBIT 4
Cost-Effectiveness Ratios, By Type Of Funding Source

	Number of studies	Median ICER^a	Percent cost saving	Percent dominated
Sponsor of study				
All studies	647	\$12,000	11%	10%
Industry sponsored ^b	77	6,000	21	6
Nonindustry sponsored	570	13,000 ^c	9 ^d	10
Type of sponsor				
Pharmaceutical company	70	5,000	23	4
Government	353	16,000	7	12
Foundation	158	31,000	4	13
Device company	7	36,000	0	29
Health care organization ^e	27	56,000	7	7
Not disclosed	204	10,000	12	9

SOURCE: Authors' analysis.

^a ICER is incremental cost-effectiveness ratio; (n = 583) excludes dominated interventions.

^b Includes medical device company-sponsored articles.

^c p = .003, Mann-Whitney two-sample statistic for difference between medians.

^d p = .002, chi-square statistic.

^e Includes hospitals, managed care plans, and other health care organizations.

effectiveness involves the manner in which the question is framed. A drug is not intrinsically cost-effective or cost-ineffective. It is only meaningful to say that a drug is cost-effective compared with something else. Similarly, claims of cost-effectiveness often depend on the population under investigation. For example, statin drugs used to lower blood cholesterol levels have been found to be relatively cost-effective as secondary prevention in persons with existing heart disease but much less cost-effective as primary prevention.²²

For similar reasons, one would not expect a Medicare drug benefit to save money, despite the fact that individual drugs may produce savings in certain situations and despite the fact that restrictive policies (for example, reimbursement caps) have been found to increase net health costs in certain cases.²³ Adding a drug benefit for elderly Americans without coverage will result in expanded use of cost-increasing drugs, including expensive breakthrough products.²⁴ Some of these drugs will be “cost-effective” in the sense that their health benefits will be worth their additional costs, but some will likely be used in situations where they greatly increase costs at little or no additional health benefit.²⁵

Note that many Medicare recipients already receive many outpatient drugs, which are paid for by private supplemental insurance or out of pocket.²⁶ From a societal perspective, the relevant incremental analysis concerns the prescriptions induced by the policy. If the most cost-effective drug indications are already being practiced, at the margin Medicare drug-coverage expansion would be less cost-effective.²⁷

■ **Influence of industry funding.** The vast majority of the stud-

ies we reviewed were funded by drug companies (although only about one-tenth of all studies in the database were funded by industry). The influence of such funding has been a heated topic in recent years, as the number of industry-sponsored studies in our database has risen (from no studies in 1976 to seventeen in 1997). The drug industry has argued that the studies respond to managed care plans' growing demand for demonstrated value for money.²⁸ But some have charged that industry-funded economic analyses reflect the hidden biases of their sponsors.²⁹

The *New England Journal of Medicine* has imposed strict guidelines for publishing effectiveness analyses, including a ban on industry-funded research in which authors receive a direct salary, have an equity interest in the company, or are members of an ongoing consultancy or board.³⁰ Other journals have required full disclosure of funding sources, called for authorial independence, improved the peer-review process, and published guidelines for the content of economic studies.³¹

How much influence does industry sponsorship actually have? Exhibit 4 indicates that cost-utility analyses funded by industry have somewhat better results than non-industry-sponsored research.³² One explanation is that this reflects a "publication bias," which may exist on several levels: Sponsors may only fund studies on products likely to show cost-effectiveness (or may restrict investigators from publishing "negative" results); investigators may submit only those analyses with favorable results for publication; or editors may selectively publish "positive" studies.³³ Another is that funders may influence the assumptions made in a particular analysis, which can in turn influence results.³⁴ Yet another is that the high cost of drug development leads industry to selectively bring to market drugs that provide good value.

It is difficult to gauge the magnitude of these potential biases in our data. Publication bias is a well-documented problem in the medical literature, where researchers have demonstrated that journals are more likely to publish analyses with interesting or contentious findings and less likely to publish negative or unfavorable results.³⁵ In terms of industry involvement, the medical field—like all areas of science—may be influenced in a variety of ways.³⁶ Researchers have found, for example, that industry-sponsored drug trials rarely report either that the drug under investigation is inferior to its comparator and that there is a strong relationship between expert authors' published positions on the safety of some drugs and their financial relationships with pharmaceutical manufacturers.³⁷ With respect to CEAs, there may be some specific concerns, including the fact that input data used in analyses (for exam-

ple, from clinical trials) may themselves be biased, and the fact that CEAs rely heavily on assumptions, which might be manipulated by analysts. Notably, another recent analysis of the same topic using different data and different methods came to the same conclusion: that drug company-sponsored studies were less likely than non-profit-sponsored studies were to report unfavorable results.³⁸

Government and nonprofit sponsors may, of course, have their own biases and may exert external influence. One of the notable findings in Exhibit 4 is that regardless of funding source, few investigators report very high (poor) cost-effectiveness ratios.³⁹ Furthermore, there is no evidence that the quality of analyses funded by industry differs from those funded by other sources. Exhibit 5 shows that industry-funded studies are no different than non-industry-funded studies in their adherence to certain recommended study protocols. In terms of the overall subjective quality score we assigned to each article, industry-funded studies actually fared slightly better than those funded by nonindustry sources, although the difference was not statistically significant. Investigators in industry-sponsored studies also were much more likely to disclose their source of funding (which could simply reflect journals' disclosure requirements regarding industry-funded studies).⁴⁰ It is important to stress that we did not test the quality of the actual clinical and economic assumptions made in analyses, only whether recommended protocols were followed.

A final point concerns the curious finding that few managed care plans or other payers fund CEAs themselves, despite the fact that one would expect them to be the primary beneficiaries of such analyses. Moreover, payers have expressed skepticism about CEAs, precisely because they are sponsored by the drug industry.⁴¹ There are several possible explanations, including the fact that plans may believe that CEAs are not relevant to their own narrower "perspectives" and that from the plans' viewpoint using CEAs explicitly to

EXHIBIT 5
Quality Of Pharmaceutical Intervention Studies, By Funding Source

	Industry (n = 32)	Nonindustry (n = 118)	Sponsor not disclosed (n = 78)	Industry vs. nonindustry	Disclosed vs. not disclosed
Adequate description of alternatives	75.0%	73.0%	87.0%	0.30	0.26
Study perspective clearly stated	53.1	53.3	48.7	0.98	0.51
Discounted both costs and QALYs if needed	75.0	79.0	65.0	0.65	0.04
Incremental analyses performed correctly	50.0	47.0	44.0	0.73	0.59
Quality as judged by readers (scale of 1 to 7 with 7 being best)	4.38	4.19	3.88	0.49	0.06

SOURCE: Authors' analysis.

NOTE: QALY is quality-adjusted life year.

withhold an intervention risks negative publicity and even litigation.⁴² A third reason involves the public-good nature of the research; that is, no single plan has the incentive to sponsor research, because it is difficult to keep the information proprietary and to capture the full return on the investment.⁴³

■ **Limitations and strengths of cost-utility analyses.** In interpreting our data, we emphasize that cost-utility analyses represent only a subset of all economic evaluations. In one large international database of economic evaluations, for example, only about 8 percent are cost-utility analyses.⁴⁴ In contrast, many more take the form of cost-consequence studies, or CEAs that measure health effects in terms other than QALYs.⁴⁵ Many of these analyses also have found that pharmaceuticals can be cost-effective or cost-saving interventions, including drugs to treat stroke, migraine, and schizophrenia.⁴⁶

Moreover, the use of QALYs has been criticized on both theoretical and practical grounds, as has the use of cost-utility analysis for purposes of societal resource allocation decisions.⁴⁷ Representatives of managed care plans have sometimes criticized QALYs as being not easily understandable and cost-utility analysis for its focus on long-run societal consequences instead of narrower budgetary impacts. Other approaches, such as assessing a drug's cost impact for a patient population within a given health system, or simply comparing costs and clinical effects of competing products but not aggregating the information into a single metric, can also provide useful information, depending on the setting and purpose.⁴⁸

Despite these drawbacks, cost-utility analysis has the distinct advantage of incorporating a set of methodological standards and permitting meaningful comparisons across diverse interventions. Unlike other approaches, it conveys information about the relative health benefits produced per dollar spent for different interventions using similar terminology. Although debate continues over measurement and conceptual issues, consensus has emerged over the basic methodology, and the technique has been recommended by leaders in the field in the United States and abroad.⁴⁹

■ **Lessons for Medicare.** In adding a prescription drug benefit, Medicare would inevitably confront questions of cost-effectiveness and affordability. Like other payers, Medicare will need to decide—either explicitly or implicitly—whether the health outcomes associated with new drugs are worth their costs, as well as what price to pay for the benefits conferred. Medicare can learn from experiences of the growing number of payers that have developed policies to address the issue, and from its own clouded history with CEA.

For years Canada and Australia have maintained permanent pharmacoeconomic advisory boards to provide input to national

authorities on drug coverage and pricing decisions.⁵⁰ A number of other countries, including the United Kingdom, the Netherlands, and Finland, have commenced or are actively considering such steps.⁵¹ Government officials in these countries have argued that explicit consideration of the cost-effectiveness of new drugs has helped to better target subsidies, identify key uncertainties underlying analyses, and raise the standard for the field of economic evaluation.⁵² On the other hand, industry has opposed the policies as burdensome and harmful to innovation.⁵³

Attempts by U.S. public payers to use CEA in an explicit fashion have met with resistance. When the Health Care Financing Administration (HCFA) tried to add a formal cost-effectiveness criterion to its coverage process for new medical technologies, it encountered strong opposition from industry and consumer groups and ultimately abandoned the effort.⁵⁴ Similarly, the Oregon Medicaid program's attempt to use a cost-effectiveness-like paradigm to prioritize the services it would cover met similar resistance: The cost-effectiveness part of the plan was essentially dropped, and the approach has not been emulated by other states.⁵⁵

Cost-effectiveness information has at times played an important role in certain Medicare coverage decisions, particularly in preventive services such as colorectal cancer screening, osteoporosis screening, and immunization against influenza and pneumococcal disease.⁵⁶ However, experience in the United States shows that broad use of a cost-effectiveness criterion by a public payer is probably politically infeasible (and the Clinton administration's Medicare drug proposal does not include such a criterion).

Still, Medicare might consider several options. One is for HCFA to use CEA explicitly only in the context of prevention rather than treatment, thus avoiding the politically unpalatable position of withholding therapies on economic grounds to those already ill. A second involves using CEA to guide pricing and reimbursement decisions, rather than coverage decisions per se. A third involves disseminating the information to managed care plans and to the private-sector pharmacy benefit managers who would oversee the drug program and negotiate discounts under the Clinton proposal. Several U.S. managed care plans have already adopted or are considering formal pharmacoeconomic guidelines to help guide coverage and payment policies.⁵⁷ A fourth option involves more government funding of CEA, which could be conducted or funded by the National Institutes of Health, the Centers for Disease Control and Prevention, the Agency for Healthcare Research and Quality, and the Department of Veterans Affairs, as well as by HCFA itself. Finally, Medicare might convene an advisory group to learn from the

experience of other payers and chart a course for the future.

■ **Enhancing CEAs' usefulness.** For CEAs to be useful to policymakers, they should be framed as specifically as possible. Ideally, the comparison strategy should be a clinically plausible management option. The target population should include relevant candidates for treatment. Unfortunately, not all studies are clear about these issues, and in some cases, inappropriate reference groups are used.⁵⁸ In other cases, the comparator used in an analysis has become obsolete. One study in our database, for example, reported that a drug to help dissolve gallstones was cost-effective compared with an operation to remove the gallbladder.⁵⁹ However, the appropriate comparator today is laparoscopic surgery, which has much less morbidity than previous forms of surgery had and thus may alter the results of the analysis.

There also is a need for better studies. Numerous studies have shown that methods used to estimate cost-effectiveness can differ widely and that many are of poor quality, making comparisons among them difficult.⁶⁰ More consistency and transparency in methods and reporting would help. There also is a need for studies to be updated over time.

Finally, more independence of investigators is needed. Regardless of the funding source, investigators should retain independence on design, interpretation, and publication. In addition, manuscripts should disclose funding sources, and models and assumptions should be as straightforward and transparent as possible.

A GREAT DEAL OF INFORMATION about the cost-effectiveness of various pharmaceutical therapies has become available to policymakers in recent years. Our new database of cost-utility analyses underscores the mixed results: Some drugs reduce net health costs, while others increase them, but the issue depends critically on the context in which the drug is used and the intervention to which it is being compared. Comparisons across studies must be made with caution, because the methods used to construct cost-effectiveness ratios may vary. Also, CEAs funded by the drug industry tend to report more favorable results than those funded by nonindustry sources, which may reflect a selectivity with regard to which studies receive funding and are published.

Individual CEAs cannot be used to make estimates about the overall costs of adding a prescription drug benefit to the Medicare program, because the studies are always selective and provide only a snapshot of the field. However, the information can shed light on the likely impacts of such a policy. A Medicare drug benefit will add to overall health spending, because it will result in expanded use of

drugs that increase net health costs.

In adding a drug benefit, Medicare will inevitably face issues of cost-effectiveness. CEAs can help policymakers to determine which drugs offer value for money and in which contexts. But to improve the state of the field, there is a need for more precise use of terms, and for better and more transparent analyses.

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6. M.C. Weinstein et al. for the Panel on Cost-Effectiveness in Health and Medicine, “Recommendations of the Panel on Cost-Effectiveness in Health and Medicine,” *Journal of the American Medical Association* 276, no. 15 (1996): 1253–1258; and M.F. Drummond et al., *Methods for the Economic Evaluation of Health Care Programmes* (Oxford: Oxford University Press, 1997). Other analytic approaches are cost-consequence analysis (which involves estimating and listing separately the net costs and health consequences of competing interventions) and cost-benefit analysis (in which all costs and benefits are measured and compared in dollar terms). An appeal of CEA is that unlike cost-benefit analysis, it avoids the requirement for the monetary valuation of health benefits, which raises measurement difficulties and often political objections.
7. M.R. Gold et al., *Cost-Effectiveness in Health and Medicine* (Oxford: Oxford University Press, 1996).
8. Note that many cost-effectiveness analysts have expressed health benefits in terms of intermediate outcomes specific to the treatment and disease under

investigation or in terms of life-years gained. See T.O. Tengs et al., "Five-Hundred Life-Saving Interventions and Their Cost-Effectiveness," *Risk Analysis* 15, no. 3 (1995): 369–390. For example, a researcher studying alternative strategies to prevent cancer might evaluate and compare each strategy according to the costs incurred per cancer case prevented. The approach is advantageous in that it focuses narrowly on the clinical problem and is familiar to the clinicians who treat the disease, but it does not permit comparisons of treatments for cancer with interventions for other conditions.

9. Drummond et al., *Methods for the Economic Evaluation*, 139–204.
10. P.J. Neumann et al., "A Formal Audit of 228 Published Cost-Utility Analyses" (Working paper, Harvard School of Public Health, 1999).
11. Elixhauser et al., "Health Care CBA/CEA"; and Elixhauser et al., "Health Care CBA and CEA from 1991 to 1996."
12. R.H. Chapman et al., "A Comprehensive League Table of Cost-Utility Ratios and a Sub-Table of 'Panel-Worthy' Ratios," *Medical Decision Making* 19, no. 4 (1999): 521 (abstract).
13. J. Kassirer and M. Angell, "The Journal's Policy on Cost-Effective Analyses," *New England Journal of Medicine* 331, no. 10 (1994): 669–670; R. Evans, "Manufacturing Consensus, Marketing Truth: Guidelines for Economic Evaluation," *Annals of Internal Medicine* 123, no. 1 (1995): 59–60; and M. Friedberg et al., "Evaluation of Conflict of Interest in Economic Analyses of New Drugs Used in Oncology," *Journal of the American Medical Association* 282, no. 15 (1999): 1453–1457.
14. The calculation of medians includes cost-saving interventions that also produce gains in QALYs.
15. J.E. Paul, J.A. Mauskopf, and L. Bell, "Cost-Consequence Models for Varicella-Zoster Virus Infections" (Part 2), *Pharmacotherapy* 15, no. 5 (1995): 49S–58S; J. Tsevat, D. Duke, and L. Goldman, "Cost-Effectiveness of Captopril Therapy after Myocardial Infarction," *Journal of the American College of Cardiology* 26, no. 4 (1995): 914–919; and A.S. Zbrozek, S.B. Cantor, and M.P. Cardenas, "Pharmacoeconomic Analysis of Ondansetron versus Metoclopramide for Cisplatin-Induced Nausea and Vomiting," *American Journal of Hospital Pharmacy* 51, no. 12 (1994): 1555–1563.
16. Of the subset of studies dealing with pharmaceutical interventions, the median cost-utility ratios were \$5,900 for industry-sponsored analyses and \$12,000 for non-industry-sponsored analyses ($p = .11$).
17. P. Doubilet, M.C. Weinstein, and B.J. McNeil, "Use and Misuse of the Term 'Cost-Effectiveness' in Medicine," *New England Journal of Medicine* 314, no. 4 (1986): 253–256.
18. B.F. Gage, A.B. Cardinalli, and G.W. Albers, "Cost-Effectiveness of Warfarin and Aspirin for Prophylaxis of Stroke in Patients with Non Valvular Atrial Fibrillation," *Journal of the American Medical Association* 274, no. 23 (1995): 1839–1845; T. Schneider, F. Fagnani, and J.L. Lanoe, "Economic Analysis of an Immunosuppressive Strategy in Renal Transplantation," *Health Policy* 9, no. 1 (1988): 75–89; and M.S. Kamlet, N. Paul, and J. Greenhouse, "Cost Utility Analysis of Maintenance Treatment for Recurrent Depression," *Controlled Clinical Trials* 16, no. 1 (1995): 17–40.
19. In our database, for example, seventy-eight (34 percent) of the 228 articles mention an explicit dollar threshold for this value, with a median amount of \$50,000. Note, though, that this threshold has no solid analytic foundation. So-called value-of-life studies in the United States have estimated revealed preferences on the order of \$100,000 to \$500,000 per life year saved, with no quality adjustment. See K.P. Viscusi, *Fatal Trade-offs* (New York: Oxford University Press, 1992).

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20. Doubilet et al., "Use and Misuse of the Term 'Cost-Effectiveness' in Medicine."
21. *Cost-effective* might also include situations in which a strategy is less costly and less effective, as long as society is willing to trade off the loss in health outcomes for dollar savings.
22. L. Goldman et al., "Cost-Effectiveness of HMG-CoA Reductase Inhibition for Primary and Secondary Prevention of Coronary Heart Disease," *Journal of the American Medical Association* 265, no. 9 (1991): 1145-1151.
23. Soumerai et al., "Effects of Medicaid Drug-Payment Limits."
24. Statement of Dan L. Crippen, director, Congressional Budget Office, on the president's proposal for Medicare reform, before the Senate Committee on Finance, 22 July 1999. In estimating the cost of the Clinton proposal, the CBO noted that projections for the rate of growth in drug use and prices is highly uncertain. On the one hand, new breakthrough drugs would tend to increase both the use and the average price of prescription drugs in the future. On the other hand, a number of heavily used brand-name drugs are about to lose their patent protection, which would allow entry of generic substitutes and drive prices down somewhat. The CBO also emphasizes that another area of uncertainty is the extent to which the new coverage would actually increase enrollees' use of drugs, given the fact that half of them already have drug coverage and that the proposed benefit has a cap.
25. P.J. Neumann and M.C. Weinstein, "Diffusion of New Technology: Costs and Benefits to Health Care," in *The Changing Economics of Technological Innovation in Medicine*, ed. A.C. Gelijns and E.A. Halm (Washington: National Academy Press, 1991), 21-34.
26. J.A. Poisal et al., "Prescription Drug Coverage and Spending for Medicare Beneficiaries," *Health Care Financing Review* (Spring 1999): 18-28.
27. Milton Weinstein, professor of health policy and management, Harvard School of Public Health, personal communication, September 1999.
28. P.J. Neumann, "Paying the Piper for Pharmacoeconomic Studies," *Medical Decision Making* (Supplement 1998): S23-S26.
29. Kassirer and Angell, "The Journal's Policy on Cost-Effective Analyses"; and R. Evans, "Manufacturing Consensus, Marketing Truth."
30. Kassirer and Angell, "The Journal's Policy on Cost-Effective Analyses." Note that the policy stipulates that the journal will publish industry-funded CEAs if the research is in the form of a grant to a not-for-profit entity.
31. M.F. Drummond et al, "Guidelines for Authors and Peer Reviewers of Economic Submissions to BMJ," *British Medical Journal* 313, 7052 (1996): 275-283; A. Elstein, "MDM Policy Regarding Financial Support of Authors," *Medical Decision Making* 17, no. 4 (1997): 497-498; and Neumann, "Paying the Piper."
32. Note that the difference in the means of the cost-effectiveness ratios funded by industry and nonindustry sources also is statistically significant and is heavily influenced by a few non-industry-funded studies with extremely high cost-effectiveness ratios (for example, exceeding \$50 million per QALY).
33. R. King, "Bitter Pill: How a Drug Company Paid for University Study, Then Undermined It," *Wall Street Journal*, 25 April 1996, 1; and D. Rennie, "Thyroid Storm" (Editorial), *Journal of the American Medical Association* 277, no. 15 (1997): 1238-1243.
34. M.L. Brown and L. Fintor, "Cost-Effectiveness of Breast Cancer Screening: Preliminary Results of a Systematic Review of the Literature," *Breast Cancer Research and Treatment* 25, no. 2 (1993): 113-118.
35. C.B. Begg, "Publication Bias," in *The Handbook of Research Synthesis*, ed. H. Cooper and L.V. Hedges (New York: Russell Sage Foundation, 1994); and N. Freemantle and J. Mason, "Publication Bias in Clinical Trials and Economic Analyses,"

- Pharmacoeconomics* 12, no. 1 (1997): 10–16.
36. D. Blumenthal et al., “University-Industry Research Relationships in Biotechnology: Implications for the University,” *Science* 232, no. 4756 (1986): 1361–1366; R.P. Schwarz, “Maintaining Integrity and Credibility in Industry-Sponsored Research,” *Controlled Clinical Trials* 12, no. 6 (1991): 753–760; D.F. Thompson, “Understanding Financial Conflicts of Interest,” *New England Journal of Medicine* 329, no. 8 (1993): 573–576; T. Lemmens and P.A. Singer, “Bioethics for Clinicians: 17. Conflict of Interest in Research, Education, and Patient Care,” *Canadian Medical Association Journal* 159, no. 8 (1998): 960–965; and S. Krimsky and L.S. Rothenberg, “Financial Interest and Its Disclosure in Scientific Publications,” *Journal of the American Medical Association* 280, no. 3 (1998): 225–226.
 37. P.A. Rochon et al., “A Study of Manufacturer-Supported Trials of Nonsteroidal Anti-Inflammatory Drugs in the Treatment of Arthritis,” *Archives of Internal Medicine* 154, no. 2 (1994): 157–163; R. Koeppe and S.H. Miles, “Meta-Analysis of Tacrine for Alzheimer Disease: The Influence of Industry Sponsors,” *Journal of the American Medical Association* 281, no. 24 (1999): 2287–2288; and H.T. Stelfox et al., “Conflict of Interest in the Debate over Calcium-Channel Antagonists,” *New England Journal of Medicine* 338, no. 2 (1998): 101–106.
 38. Friedberg et al., “Evaluation of Conflict of Interest.”
 39. Only 23 percent of the ratios in our database were above \$50,000 per QALY, for example, and only 13 percent were over \$100,000 per QALY. But of the seventy-six ratios above \$100,000, only 4 percent were industry sponsored.
 40. A follow-up investigation of the articles that did not disclose the funding source revealed that few of these were funded by the pharmaceutical industry. Of the seventy-eight articles, twenty-four (31 percent) were self-financed, twelve (15 percent) were government funded, seven (9 percent) were funded by a foundation, and only three (4 percent) were funded by a pharmaceutical company. In thirty-six cases (46 percent), the authors did not respond to our inquiry. (Note that some articles have more than one source of funding.)
 41. See, for example, J. Lax and E. Moench, “Pharmacoeconomics and Managed Care: Understanding the Issues, Concerns, and the Environment”; W. Zellmer, “Comments of the American Society of Health-System Pharmacists” (Presentations at the Food and Drug Administration hearing, “Pharmaceutical Marketing and Information Exchange in Managed Care Environments,” Silver Spring, Maryland, 19 October 1995); and F.A. Sloan, K. Whetten-Goldstein, and A. Wilson, “Hospital Pharmacy Decisions, Cost-Containment, and the Use of Cost-Effectiveness Analysis,” *Social Science and Medicine* 45, no. 4 (1997): 525–533.
 42. Neumann, “Paying the Piper.”
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 45. *Ibid.* See also Elixhauser et al., “Health Care CBA/CEA”; and Elixhauser et al., “Health Care CBA and CEA from 1991 to 1996.”
 46. S.C. Fagan et al., “Cost-Effectiveness of Tissue Plasminogen Activator for Acute Ischemic Stroke,” *Neurology* 50, no. 4 (1998): 883–890; R.F. Legg et al., “Cost-Effectiveness of Sumatriptan in a Managed Care Population” *American Journal of Managed Care* 3, no. 1 (1997): 117–122; and R. Rosenheck et al., “A Comparison of Clozapine and Haloperidol in Hospitalized Patients with Refractory Schizophrenia,” *New England Journal of Medicine* 337, no. 12 (1997): 809–815.
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48. Langley, “Meeting the Information Needs of Drug Purchasers.”
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 51. M. Drummond et al., “Current Trends in the Use of Pharmacoeconomics and Outcomes Research in Europe,” *Value in Health* 2, no. 5 (1999): 323–332.
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 54. P.J. Neumann, “Government Uses of Cost-Effectiveness Information on Drugs,” in *Policy Issues in Pharmaceutical Cost-Effectiveness Research* (Presentation at the American Enterprise Institute, Washington, D.C., November 1996).
 55. Ibid.; and T.O. Tengs et al., “Oregon’s Medicaid Rankings and Cost-Effectiveness: Is There Any Relationship?” *Medical Decision Making* 16, no. 2 (1996): 99–107.
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