

## Do Drug Formulary Policies Reflect Evidence of Value?

Peter J. Neumann, ScD; Pei-Jung Lin, MS; Dan Greenberg, PhD; Marc L. Berger, MD; Steven M. Teutsch, MD; Edward Mansley, PhD; Milton C. Weinstein, PhD; and Allison B. Rosen, MD, ScD

**Objective:** To investigate the extent to which preferred drug lists and tiered formularies reflect evidence of value, as measured in published cost-utility analyses (CUAs).

**Methods:** Using 1998-2001 data from a large registry of cost-effectiveness analyses, we examined the 2004 Florida Medicaid preferred drug list and the 2004 Harvard Pilgrim Pharmacy Program 3-tier formulary, and compared cost-utility ratios (standardized to 2002 US dollars) of drugs with preferred and nonpreferred status.

**Results:** Few drugs on the formularies had any cost-utility data available. Of those that did, median cost-utility ratios were somewhat higher (less favorable) for Florida's preferred drugs compared with the nonpreferred drugs (\$25 465 vs \$13 085;  $P = .09$ ). Ratios did not differ for drugs on tiers 1 and 2 of the Harvard Pilgrim formulary, although they were higher for tier 3 and for excluded drugs (\$18 309, \$18 846, \$52 119, and \$22 580, respectively;  $P = .01$ ). Among therapies reported to be cost-saving or to have cost-utility ratios below \$50 000, 77% had favored status in Florida Medicaid and 73% in Harvard Pilgrim. Among dominated drug interventions (reported to be more costly and less effective than alternatives), 95% had favored status in Florida Medicaid and 56% in Harvard Pilgrim.

**Conclusions:** This study underscores the paucity of published cost-utility data available to formulary committees. Some discrepancies prevail between the value of drugs, as reflected in published cost-utility ratios, and the formulary placement policies of 2 large health plans.

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Formularies with tiered copayment structures or preferred drug lists have become increasingly popular, as plans seek to provide financial inducements for enrollees to select the least expensive drugs while avoiding the restrictions of entirely closed formulary systems.<sup>1,2</sup>

Mounting evidence suggests that incentive-based formularies are associated with lower costs and smaller increases in drug utilization and expenditures compared with control groups.<sup>3-7</sup> But researchers also have found that they are associated with undesirable effects: patients suddenly faced with higher copayments are more likely to switch medications or to discontinue medications entirely.<sup>7-9</sup> Moreover, studies have found that cost sharing may be followed by reductions in the

use of "essential" drugs, higher rates of serious adverse events, and increased use of emergency department visits and hospital days.<sup>9,10</sup>

In theory, plan formulary placement decisions should be guided by information about a drug's overall value or cost effectiveness. Ideally, drugs with favorable cost effectiveness would receive preferential formulary status (ie, physicians would have incentives to prescribe these drugs rather than nonpreferred drugs). Instead, observers complain that plans often base patient contributions on drugs' acquisition costs and, in fact, do not consider value in formulary placement decisions.<sup>1,11</sup>

However, there has been little empirical evidence on whether formulary policies actually reflect evidence of value in terms of cost effectiveness. The objective of this study was to examine whether the formulary drug-placement decisions of 2 large healthcare providers reflect the findings of published cost-utility analyses (CUAs). We acknowledge at the outset that this is an exploratory exercise whose purposes are to investigate the type and quality of cost-utility data available to formulary decision makers, and to further discussions about the need to move the healthcare system toward value-based benefit design.

To measure a drug's value, we focused on CUA, a special type of cost-effectiveness analysis in which health effects are measured in terms of quality-adjusted life years (QALYs) gained. Leaders in the field have recommended this outcome as the standard for cost-effective-

From the Department of Health Policy and Management and Center for Risk Analysis, Harvard School of Public Health, Boston, Mass (PJN, PJJ, DG, MCW); the Department of Health Policy and Administration, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC (PJJ); the Department of Health Systems Management, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel (DG); Merck & Co, Inc, West Point, Pa (MB, ST, EM); and the Division of General Medicine, Department of Health Management and Policy, University of Michigan Schools of Medicine and Public Health, and Center for Practice Management and Outcomes Research, Ann Arbor Veterans Affairs Medical Center, Ann Arbor, Mich (ABR).

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Address correspondence to: Peter J. Neumann, ScD, Harvard School of Public Health, 718 Huntington Ave, 2nd Floor, Boston, MA 02115. E-mail: pneumann@hsph.harvard.edu.

ness research.<sup>12</sup> Though not without limitations, CUAs are appealing as a measure of overall value for several reasons: they capture in a single measure gains from both prolongation and quality of life, they incorporate the value or preferences people place on different health outcomes, and they provide a common metric for comparing analyses of diverse interventions and conditions.<sup>13</sup>

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## DATA AND METHODS

### Cost-utility Analyses of Drug Therapies

*The Cost-Effectiveness Registry.* Data on the cost effectiveness or value of drugs were derived from the Harvard Center for Risk Analysis Cost-Effectiveness Registry, a database of 539 original CUAs published in the public health and medical literature from 1976 through 2001. Cost-utility analyses were included if they were published in a MEDLINE-referenced journal and provided an original cost-utility estimate. Review papers and methodological papers were excluded. More detail about the registry is provided elsewhere.<sup>14,15</sup>

Briefly, 2 readers independently collected data on each article and then convened for a consensus review to resolve discrepancies. Data were collected on a wide range of items related to the methods used to estimate and report costs, health effects, preference weights, modeling assumptions, and study limitations. We also included a subjective assessment of overall study quality on a Likert-type scale from 1 (low) to 7 (high), which reflects readers' evaluation of the rigor, reasonableness, and usefulness of each analysis. Data on the cost-utility ratios associated with each intervention also were collected and standardized to 2002 US dollars.<sup>15</sup>

*Drug Data in the Cost-utility Analysis Registry.* For this study we focused on CUAs in the registry pertaining to pharmaceutical interventions (378 CUAs reporting 898 cost-utility ratios). To exclude potentially outmoded analyses, we further restricted the sample to studies published from 1998 through 2001, leaving a final sample of 112 studies and 266 cost-utility ratios (the number of ratios exceeds the number of studies because some analyses contain more than 1 ratio). The complete list of references is available from the authors.

### Identifying Formulary Policies

We examined publicly available formularies of 2 healthcare providers, the Florida Medicaid preferred drug list and the Harvard Pilgrim Healthcare Pharmacy Program (HPHC) in Boston. These plans were chosen arbitrarily, based on the availability of formulary information, although we did set out to select plans

representing different geographic regions and types of payers.

The Florida Medicaid program lists prescription products on a preferred drug list selected by the pharmaceutical and therapeutics committee as "efficacious, safe, and cost effective choices when prescribing for Medicaid patients."<sup>16</sup> Our analysis used the March 22, 2004, updated list, which contained 1749 drugs.

The HPHC categorizes medications into 1 of 3 tiers. Patients make the lowest copayment for drugs on tier 1, which consists of generic drugs approved by the US Food and Drug Administration (FDA). Tier 2 drugs are brand-name drugs granted preferred status (and a moderate copayment) by HPHC based on reviews of their relative safety, effectiveness, and cost.<sup>17</sup> Tier 3 contains nonpreferred drugs for which patients make the highest copayment. The actual copayment amount varies, depending on which benefit design is selected by the beneficiaries' employer group. Some prescription medications are excluded from coverage, such as Avage (tazarotene) for skin conditions and the weight-loss treatments Meridia (sibutramine) and Xenical (orlistat).

### Data Analyses

We examined the relationship between the placement of drugs on formularies and evidence of value, as reflected in published cost-utility ratios. Specifically, we investigated whether the drugs on Florida Medicaid's preferred lists had lower (ie, more favorable) cost-utility ratios than those with nonpreferred status. Similarly, we investigated whether drugs on HPHC's lower tiers (reflecting lower copayments) had more favorable cost-utility ratios than those on higher tiers.

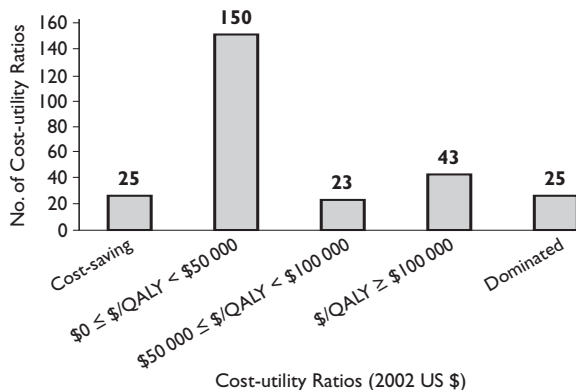
We compared the median cost-utility ratios between preferred and nonpreferred drugs in the Florida Medicaid program, and among drugs with different tier classifications on the HPHC formulary. We used the Wilcoxon rank sum and Kruskal-Wallis nonparametric tests because of heteroskedasticity and heavily skewed ratio distributions.<sup>18</sup> We also sought to find examples of drugs with good overall cost effectiveness or value that were *not* on preferred lists or favorable tiers, and conversely whether preferred lists or favorable tiers contained drugs with unfavorable cost effectiveness. These "discordant" pairs were then reviewed to explore possible reasons for discrepancies. Note that we excluded from our analysis combination therapies (drug A + drug B) for which the plan pays only partially (either drug A or B). For example, a CUA might analyze etoposide plus cisplatin versus gemcitabine in patients with metastatic non-small-cell lung cancer. In the Harvard Pilgrim Health Plan, etoposide is covered, while cisplatin is not.

**Table 1.** Characteristics of Cost-utility Ratios for Drug Interventions in the CEA Registry, 1998-2001\*

Characteristic	No. (%)
No. of cost-utility ratios	266
Disease category	
Infectious disease	81 (31)
Malignant neoplasms	45 (17)
Musculoskeletal and rheumatologic diseases	35 (13)
Cardiovascular diseases	34 (13)
Neuropsychiatric and neurologic conditions	29 (11)
Other	42 (16)
Treatment course	
Short term (<2 mo)	41 (15)
Intermediate (2-18 mo)	69 (26)
Long term (≥18 mo)	156 (59)
Sponsorship of study	
Could not be determined	91 (34)
Pharmaceutical/medical device company	87 (33)
Government	67 (25)
Foundation	12 (5)
Other	9 (3)

CEA indicates cost-effectiveness analysis.

\*The 266 cost-utility ratios come from 112 individual studies (some studies published more than 1 ratio) and represent 102 different drugs.

**Figure 1.** Distribution of Cost-utility Ratios of Pharmaceuticals

QALY indicates quality-adjusted life year.

## RESULTS

The 266 cost-utility ratios in our sample (representing 102 drugs) covered a wide range of disease categories, most commonly infectious diseases (31%),

malignancies (17%), musculoskeletal and rheumatologic diseases (13%), and cardiovascular disease (13%) (Table 1). The majority (59%) were drugs for chronic diseases (treatment course of 18 months or longer). In terms of sponsorship, 33% came from studies funded by the pharmaceutical industry and 25% from government-funded studies; in 34%, the funding source could not be determined from the article.

Of the 266 cost-utility ratios pertaining to these 102 drugs, 150 (56%) were in the 0–\$50 000 per QALY range (a range often cited as representing good value for money);<sup>19</sup> 43 (16%) were more than \$100 000 per QALY; and 25 (9%) each were cost saving or dominated (ie, meaning the cost of the drug in question was higher and its health effects lower than its comparator) (Figure 1).

Of 1749 drugs on the Florida Medicaid preferred list, 102 drugs (5.8%) had any recently published data from CUAs. Median cost-utility ratios for drugs on Florida Medicaid's preferred list (\$25 465) were higher than those on the nonpreferred list (\$13 085) ( $P = .09$ , Wilcoxon rank sum test) (Table 2). Median ratios for drugs on tiers 1, 2, and 3 of the HPHC plan were \$18 309, \$18 846, and \$52 119, respectively, and \$22 580 for excluded drugs ( $P = .01$  by the Kruskal-Wallis test, meaning that at least 1 tier had either a higher or a lower median cost-utility ratio than the other tiers).

Figure 2 show the distributions of cost-utility ratios according to preferred/nonpreferred status in the Florida Medicaid plan. The figure shows, for example, that for drugs on the preferred list, 29 cost-utility ratios (17% of the total number of cost-utility ratios for drugs on the preferred list) were more than \$100 000 and an additional 20 were dominated; in contrast, for nonpreferred drugs, 2 ratios were cost saving and 32 were between 0 and \$50 000. Figure 3 shows an analogous distribution for cost-utility ratios of drugs on the various HPHC tiers. In some instances, drugs reported to have good value received unfavorable tier placement (eg, for drugs on tier 3, 1 cost-utility result was cost saving and QALY improving, and 19 ratios were less than \$50 000), and drugs with poor value received favorable tier placement (5 ratios for tier 1 were more than \$100 000 per QALY and 7 ratios for tier 1 drugs reflected dominated interventions).

Where cost-utility ratios were available for Florida Medicaid, 64% of preferred drugs (111 of 173 ratios) and 72% (34 of 47) of nonpreferred drugs had ratios below \$50 000, whereas for HPHC, those percentages were 71% (115 of 163) and 58% (42 of 73), respectively (where *preferred* is defined as tier 1 or 2).

The quality of CUAs varied slightly across formulary placement categories. For example, the quality score was 4.3 for CUAs of drugs on the Florida Medicaid preferred drug list vs 4.5 for CUAs of drugs on the nonpreferred list ( $P = .049$ ). For the HPHC formulary, the quality score was 4.4 for CUAs of drugs on tiers 1 and 2 and 5.4 for CUAs of drugs on tier 3 ( $P = .002$ ) (data not shown).

Table 3 provides selected examples of drugs with favorable cost-utility ratios that did not receive preferential status, as well as drugs with unfavorable cost-utility ratios that did receive preferential status. For example, interferon beta for multiple sclerosis and riluzole for amyotrophic lateral sclerosis received favorable status on both plans, despite high (less favorable) reported cost-utility ratios. In contrast, donepezil for Alzheimer's disease did not receive favorable tier placement, despite a favorable cost-utility ratio.

DISCUSSION

To our knowledge, this is the first study to examine whether tiered formularies and preferred drug lists reflect evidence of value, as measured in published CUAs. Our findings underscore the challenges inherent in this exercise: only 6% of drugs on the Medicaid preferred drug list had corresponding data from recently published CUAs, for example.

Where CUA data were available, they suggested that formulary decisions frequently reflect published evidence of value in that drugs with favorable formulary placement reflect products with "reasonable" cost-utility ratios. (Note that if we had used \$100 000 per QALY as the measure of societal willingness to pay, the consistency between formulary placement and evidence of value would have been greater.)

The results also suggest some room for improvement. There were numerous examples of reportedly cost-effective drugs excluded from preferred lists or favorable formulary tiers, as well as examples of drugs with unfavorable cost-effectiveness profiles that were included on preferred drug lists and favored formulary tiers. The data hint that HPHC's formulary may be more in-line with value (as measured by CUA) than that of Florida Medicaid. Pressure to cover drugs in public programs also could help explain why median cost-utility

Table 2. Cost-Effectiveness of Drugs by Formulary Policies\*

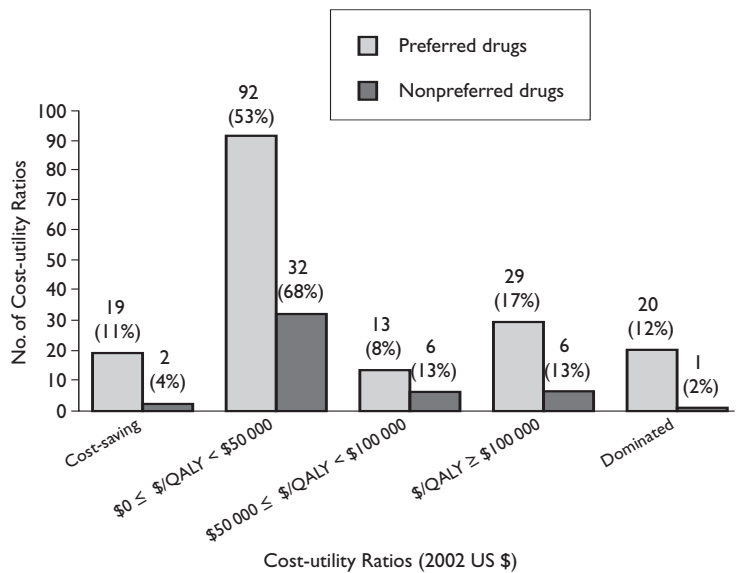
Formulary	Median Cost-utility Ratio (2002 US \$)	P
Florida Medicaid Program		
Preferred drugs (n = 173, 65%)	25 465	.09 <sup>†</sup>
Nonpreferred drugs (n = 47, 17.7%)	13 085	
Harvard Pilgrim Health Plan		
Drugs on tier 1 (n = 53, 19.9%)	18 309	.01 <sup>†</sup>
Drugs on tier 2 (n = 110, 41.4%)	18 846	
Drugs on tier 3 (n = 42, 15.8%)	52 119	
Excluded drugs (n = 31, 12.7%)	22 580	

\*Frequencies and percentages in parentheses indicate the distribution of cost-utility ratios (not drugs).

<sup>†</sup>Wilcoxon rank sum test.

\*Kruskal-Wallis test.

Figure 2. Distribution of Cost-utility Ratios by Preferred/Non-preferred Status, Florida Medicaid Program\*



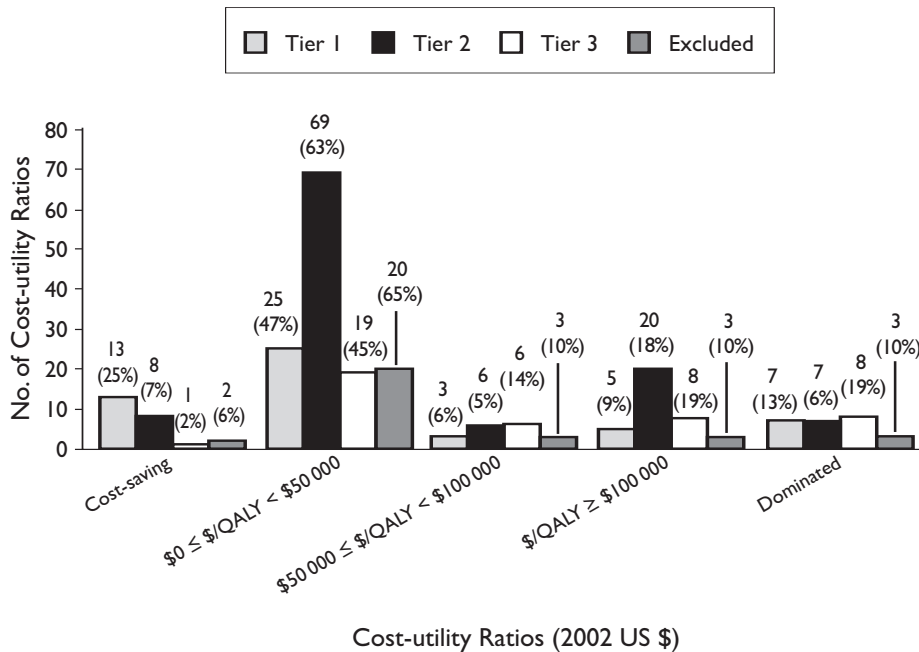
QALY indicates quality-adjusted life year.

\*Percentages refer to the proportion of cost-utility ratios within each formulary category (preferred or nonpreferred). For example, 11% (19/173) of cost-utility ratios corresponding to preferred drugs were cost saving.

ratios in our sample were higher for drugs on Florida's preferred list than for those on HPHC's, as well as the fact that Florida Medicaid covered expensive cancer therapies that were dominated by other treatments. We emphasize, however, that more work is needed on this question and that we have not provided new evidence that anyone is hurt by a specific formulary decision.

In general, we emphasize that ours is a descriptive and exploratory exercise and that one should exercise caution

**Figure 3.** Distribution of Cost-utility Ratios by Tier Status, Harvard Pilgrim Pharmacy Program



\*Percentages refer to the proportion of cost-utility ratios within each formulary tier. For example, 25% (13/53) of cost-utility ratios corresponding to tier 1 drugs were cost saving.

about inferring causality between the cost-utility literature and formulary placement decisions. It is difficult to obtain a clear reading from publicly available CUAs about the actual choices facing the formulary managers, or about the trust they place in the data. Researchers have documented the fact that methods used for conducting and reporting cost-utility analyses are highly variable.<sup>14,20-22</sup> Moreover, the decisions of a pharmacy and therapeutics committee are complex and reflect a multitude of factors, including the size and makeup of the pharmacy and therapeutics committee and the incentives facing the director of the pharmacy.<sup>23</sup>

A key problem for our study is that published CUAs may not include an appropriate comparator therapy. The extent to which drugs have treatment alternatives is a key factor in determining actual formulary placement. Some products are expensive, but because there is little or no alternative they are likely to receive favorable formulary placement. On the other hand, some drugs have many treatment alternatives or close substitutes, and as a result are assigned to a higher tier or receive nonpreferred status. In the HPHC formulary, for example, all of the drugs assigned to tier 2 or 3 had treatment alternatives; in contrast, of the 21 unique drugs assigned to tier 1, 10 were generics and 9 of the remaining 11 were arguably the

drug of choice for at least 1 indication.

However, published CUAs may exclude the relevant comparator. They may compare a new drug with placebo or with an inferior alternative, rather than to the next-best intervention, thus exaggerating the value of the drug in question. Another problem is that study authors may fail to present results of CUAs in all relevant population subgroups. Drugs may be cost effective for some indications and not others, but CUAs are not always clear about distinctions.

A measure of the degree to which the comparator drug and target population differ can be seen in the case of inter-

feron  $\beta$ -1b for multiple sclerosis, where cost-utility ratios varied from \$44 000 per QALY for patients with secondary progressive multiple sclerosis (where the treatment comparator was no treatment) to \$1.9 million per QALY for interferon compared with “best practice” in ambulatory patients with secondary progressive multiple sclerosis.

There are other problems with trying to match published CUAs to formulary decisions. One is that cost-effectiveness studies often are not available at the time of FDA approval, and published CUAs of a drug tend to lag behind published clinical studies.<sup>24</sup> Another is that CUAs typically do not incorporate or anticipate generic drugs as comparator therapies, which can dramatically change cost-utility ratios. Some observers have noted that CUAs may better help with decisions about whether a new class of drugs are cost effective rather than which drugs within a class are appropriate.<sup>25</sup>

Furthermore, even if the ratios do reflect a reasonable measure of societal value, it is possible that they do not reflect value from the perspective of health plans. Importantly, we lack data on the actual drug prices paid by the plans, which could be considerably lower than the drug prices used in the CUAs, and hence improve the drug's cost effectiveness. Plans—and pharmacy benefits managers, who frequently negotiate sizable dis-

**Table 3.** Selected Drugs With Potentially Discordant Formulary Policies\*

Drug/Intervention	Cost-Utility Ratio (\$/QALY)	Coverage
Interferon $\beta$ -1b (compared with standard care without interferon) for relapsing remitting multiple sclerosis	415 000–1 480 000	Preferred (Florida Medicaid) Tier 2 (Harvard Pilgrim)
Second-line chemotherapy with paclitaxel vs combination therapy with vinorelbine plus mitomycin C in female patients (aged 18-70 years) histologically diagnosed with metastatic breast cancer and progressive disease after first-line chemotherapy	Dominated	Preferred (Florida Medicaid)
Second-line chemotherapy with docetaxel vs combination therapy with vinorelbine plus mitomycin C in female patients (aged 18-70 years) histologically diagnosed with metastatic breast cancer and progressive disease after first-line chemotherapy	Dominated	Preferred (Florida Medicaid)
Riluzole (compared with placebo) for patients with amyotrophic lateral sclerosis (Lou Gehrig's disease)	104 000	Preferred (Florida Medicaid) Tier 2 (Harvard Pilgrim)
Recombinant human erythropoietin (epoetin) (compared with blood transfusions) in anemic patients with cancer undergoing chemotherapy	124 000	Preferred (Florida Medicaid) Tier 2 (Harvard Pilgrim)
Donepezil (compared with no therapy) in community-dwelling individuals with mild Alzheimer's disease	10 000	Tier 3 (Harvard Pilgrim)
Entacapone (compared with Levodopa therapy with extra add-on medication) in patients with Parkinson's disease	Cost-saving	Tier 3 (Harvard Pilgrim)

QALY indicates quality-adjusted life year.

\*A discordant formulary policy reflects favorable formulary placement despite unfavorable cost-utility ratios, or unfavorable placement despite favorable ratios.

counts—may indeed find it cost effective to give preferential status to discounted drugs, even if published CUAs suggest that, based on average wholesale prices, the drug in question is not cost effective.

Even if the prices used in the CUAs are accurate, strict rankings of cost-utility ratios may not reflect how plans wish to allocate resources. Results of CUAs, conducted from a societal perspective, may not be seen as relevant for health plan managers who worry about short-term financial shortfalls, total plan costs, and drug budget “silos.”<sup>26</sup> It is difficult to determine the impact of the CUA “perspective” in our sample, because many studies are not clear about their perspective. In addition, there is inconsistency in the manner in which analysts use the term *perspective*: some state a societal perspective, but only include direct healthcare costs and nominal nonhealth costs; others include productivity costs.

Empirical evidence suggests that public preferences for allocating society's resources may not be consistent with a goal of maximizing QALYs subject to a budget constraint. Instead people want to give hope to and avoid discrimination against patients with chronic illness or

disability even when treatments are not cost effective.<sup>27,28</sup> These inclinations may explain some of the discrepancies we found (eg, preferred formulary placement of drugs with high cost-utility ratios, such as drugs for multiple sclerosis and amyotrophic lateral sclerosis).

There may be pressure to cover certain therapies even if they have unfavorable cost-effectiveness ratios. This may be a particular concern for Medicaid programs, which may be more sensitive to public pressure than private plans.

Despite these concerns, we believe that our analyses provide important information and hope that they further policy discussions about the need to move the healthcare system toward value-based benefit design. Many reimbursement authorities abroad have used CUAs (and other forms of economic evaluation) to inform formulary decisions. In the United States, initiatives such as the US Preventive Services Task Force have begun to consider cost effectiveness in their deliberations. Moreover, although health plans may not adopt a societal perspective, they do compete for enrollees and it is not unreasonable to believe that CUAs approximate value in many and even most cases.

For these reasons, we believe more consideration of data from CUAs would represent a positive step forward for US formularies.

Despite limitations, CUA remains an important technique for measuring value. The number of CUAs has been growing and their quality may be improving.<sup>14</sup> Some payers have found that CUAs can be an important part of a sequenced assessment of value that begins with the application of evidence-based medicine. In this characterization, consideration of clinically important benefits and harms, as well as the subpopulations for which products have specific advantages, forms the basis for assessments of medication value. Cost-utility analyses can be a useful extension of that assessment when they focus on the specific clinical situations for which the medication is most appropriate.

Some formulary committees are beginning to incorporate evidence of value explicitly into their deliberations and in some cases are requesting or requiring that drug firms formally submit evidence of value to their formulary committees.<sup>29</sup> Our study suggests that these efforts should go further.

Our data suggest a need for formulary policies to offer more targeted guidance for drugs. Formularies tend to be blunt instruments, broadly covering the use of a drug. Yet whether a drug is cost effective depends on the specific characteristics of the recipients (eg, age, clinical condition). Ideally, formulary policy will be defined accordingly. For example, guidelines for lipid-lowering drugs reflect patient-specific characteristics such as prior infarction. In practice, however, it is a challenge to incorporate heterogeneity in potential benefit among patients.<sup>1</sup>

More and better data will be needed if we are to truly move toward value-based formulary decision making. Congress and other federal officials also might help by addressing gaps in the evidence base, for example, by funding more “pragmatic” clinical trials to aid decision makers,<sup>30-32</sup> and by funding cost-effectiveness analyses.<sup>33</sup>

In the future it will be important to update these analyses and expand them to include other health plans. As more studies provide information on drug value, our next challenge is to incorporate value into formularies to increase the use of effective and cost-effective medications.

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