Due to the increasing availability and costs of biopharmaceuticals, policymakers are questioning whether they provide good value relative to other health interventions and many are increasingly relying on cost-utility analyses (CUAs) to supplement decision-making. Analyzing data from the Tufts Medical Center Cost-Effectiveness Analysis Registry, this study critically reviewed the cost-utility literature for biopharmaceuticals and compared their value to other health interventions. Of 2,383 studies in the registry through 2009, biopharmaceutical CUAs comprised the sixth largest category of interventions at 11%. Characteristics of biopharmaceutical articles were similar to other CUAs; however, they displayed slightly better quality. The median cost-effectiveness ratio of biopharmaceuticals was less favorable (i.e., higher) than other interventions, though many seem to provide value for money. A logistic regression showed that among biopharmaceuticals the cost-effectiveness of industry-sponsored studies and products that treat infectious diseases were significantly more likely to be favorable (less than the overall median), while cancer and neurological treatments were significantly less likely.

Introduction

Over the last three decades, the market availability of biopharmaceutical products derived from recombinant DNA has grown rapidly. While just 29 such products were approved by the FDA in the 15 y prior to 1996, the number had more than doubled to 65 by 2007.1,2 Currently, biopharmaceuticals account for approximately one-third of all FDA approvals annually.3 The landscape of available biopharmaceuticals, which are a special subset of the broader category of biologics, encompass a range of therapeutic products including early products developed to treat ischemic heart disease and hepatitis to more recent innovative therapies with the ability to target a number of rare, life-threatening and chronic conditions at the molecular level.

Along with their growing role in patient care, biopharmaceuticals also pose substantial costs to individuals and society. Products often carry annual costs in excess of $50,000 per year, and several now rank among the list of 20 top selling drugs, each with global sales surpassing $4 billion annually.4 Moreover, spending on these products is growing at a rapid pace. In 2010, expenditures for biopharmaceuticals grew 6.6%, an amount nearly three times the percentage increase for all pharmaceuticals combined.5

As wider availability of biopharmaceuticals has contributed to an ever greater share of the increases in total health expenditures, the products have drawn increased scrutiny from policymakers struggling to strike a balance across fiscal sustainability, patient access and innovation.6,7 At issue is whether their exceptionally high prices are justified by the health benefits they afford patients. In other words, do biopharmaceuticals provide good “value for money”? Economic evaluations using cost-utility analyses (CUAs) have become an

Key words: biopharmaceuticals, cost-effectiveness, cost-utility analysis, value for money, quality adjusted life-year, economic analysis

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important tool in informing the coverage and reimbursement decisions of public and private payers in many countries. A subset of cost-effectiveness analysis, CUAs are a well-accepted method of evaluating and comparing the relative health outcomes and resource costs associated with different health interventions. CUAs present the incremental costs per quality-adjusted life year (QALY) associated with the use of an intervention compared with an alternative (e.g., standard of care). QALYs provide a way of encapsulating both improvements in quality and quantity of life in a single outcome metric.

When measured in this way, the value of two health interventions that differ widely in terms of clinical context (e.g., drug-eluting stents vs. smoking cessation programs) can be compared against a common benchmark. Numerous CUAs have been performed for many types of interventions spanning the entire spectrum of care. Selected examples of biopharmaceutical studies and their associated cost-effectiveness ratios are shown in Table 1.

If they are of high quality and conducted in accordance with recommended methodological standards, CUAs can help decision-makers better allocate scarce resources in ways that maximize health gains for a population most efficiently. While previous studies have systematically examined the cost-utility literature for a variety of health interventions, disease states and populations, none to our knowledge have specifically examined the subset of biopharmaceuticals. The purpose of this study was to: (1) assess the characteristics and methodological quality of the published CUA literature for biopharmaceuticals; (2) examine how the cost-effectiveness of biopharmaceuticals compare with other health interventions; and (3) understand which categories of biopharmaceuticals provide better value than others.

### Results

A breakdown of articles by each intervention category is listed in Table 2. Overall, the CEA Registry contained a total of 2,383 CUAs published from 1976 through 2009. The 258 articles (10.8%) examining biopharmaceuticals represented the sixth largest category of interventions. It should be noted that categories in Table 2 are not mutually exclusive because each article could be assigned to more than one intervention category.

The number of published articles pertaining to biopharmaceuticals has increased over time, particularly since 2000 (Fig. 1). Whereas they accounted for just 3% of all CUAs published between 1976 and 1990, they doubled to 7% over the period 1991–2000. Between 2001 and 2009, the proportion increased to about 12%.

Infectious diseases (17.8%) and malignant neoplasms (16.7%) were the most common disease areas studied among biopharmaceutical CUAs. These were followed by rheumatologic diseases (13.6%), endocrine disorders (12.4%) and neurological conditions (7.4%). Among conventional pharmaceuticals, cardiovascular diseases accounted for 18.3% of studies followed by malignant neoplasms (15.3%), neurological conditions (14.2%) and infectious diseases (13.4%). For all interventions the top three disease areas studied were cardiovascular diseases (17.3%), malignant neoplasms (12.7%) and infectious diseases (11.4%).

The United States was the most frequent country of origin for biopharmaceutical CUAs (30.6%), however this proportion was lower than that for conventional pharmaceuticals (42.2%) and all studies (44.0%) (Table 3). Other countries of origin frequently represented in CUAs for conventional pharmaceutical and all interventions were also common among biopharmaceutical articles. Greater proportions of biopharmaceutical CUAs were funded by industry sponsors.
and focused on treatments at the tertiary level of prevention relative to other intervention groups. See Table 3 for additional results.

Biopharmaceutical CUAs displayed somewhat better adherence to recommended methods of cost-effectiveness analysis (Table 4). The percentage of biopharmaceutical CUAs was statistically greater for two of the five criteria (stated study perspective and correctly calculated ICER) compared with other health interventions. On average, studies for biopharmaceuticals also had a significantly higher average quality rating (4.55 vs. 4.33).

Distributions of weighted cost-utility ratios for each group of interventions are listed in Table 5. Given this study’s inclusion criteria, there were 4,608 ratios included in the Registry with a weighted median of $9,041 per QALY (in 2008 US$). Biopharmaceuticals had a median value of $15,412, which was less favorable than the overall median (higher numbers reflect less efficient ways to produce units of health (QALYs)). Compared with other categories of health interventions, they were the least favorable group (see Table 5). There was a smaller percentage of cost-saving biopharmaceutical ratios compared with the total proportion. The percentage of dominated ratios was also smaller.

The influence of sponsorship and type of disease studied on the favorability of cost-utility ratios for the subset of biopharmaceuticals are displayed in Table 6. Odds ratios represent how much each factor increases (if greater than 1) or decreases (if less than 1) the odds that the weighted ratio of a biopharmaceutical intervention is less, or more, favorable than the overall weighted median of all ratios ($9,041 per QALY) after controlling for all factors listed relative to the reference category. Thus, after adjustments, ratios for biopharmaceutical CUAs sponsored by industry sources were almost four times more likely to be favorable than CUAs that did not disclose the funding source. Similarly, controlling for type of sponsor revealed that biopharmaceuticals for infectious diseases were also significantly more likely to be favorable as compared with those for “other” diseases. Ratios for malignant neoplasms and neurological conditions were significantly likely to be unfavorable. Non-industry sponsorship indicated an association with favorability, though the result was not significant. Endocrine disorders and rheumatologic diseases had virtually no influence.

Discussion

The analysis indicates that therapeutic biopharmaceuticals occupy a small but growing share of the cost-utility literature, particularly over the last ten years. In 2009, the latest year available in the CEA Registry at the time of this study, articles focusing on biopharmaceuticals accounted for 12% of all studies, a 4-fold increase from the period prior to 1990. Given that biopharmaceuticals comprise approximately one-quarter of total prescription drug spending, which itself is just 10–20% of health spending in most developed countries, the focus being placed on biopharmaceuticals is somewhat greater than their current economic impact.5,14,27

As noted above and elsewhere, however, this is not altogether surprising. Many payers now require economic evidence as part of their coverage and reimbursement decision-making processes, at least for drugs and biologics.22 Given that the combination of growing demand and high per unit prices make biopharmaceuticals one of the fastest growing areas of health spending, it makes sense that policymakers are beginning to scrutinize these products more carefully than other categories of health expenditures.

CUAs for biopharmaceuticals displayed similar characteristics as compared with conventional pharmaceuticals and other interventions. Studies were conducted in a variety of countries and from a diverse set of perspectives. They were also published in many leading health economics, methods and medical journals, including Pharmacoeconomics, the International Journal of Health Technology Assessment in Health Care, Value in Health, Vaccine and the Annals of Internal Medicine. Biopharmaceutical CUAs focused more frequently on rheumatologic diseases and endocrine disorders.

Based on recommended methods for conducting and reporting health economic evaluations, the results showed better methodological quality for biopharmaceutical CUAs than those of other studies in the CEA Registry for two of the five criteria examined. Previous work has found a gradual improvement in the quality of the cost-utility literature over time, especially following publication of a number of methodological guidelines and recommendations in the mid–1990s.11,14 Given that the rise in published articles on biopharmaceuticals has largely coincided with this trend, it is perhaps to be expected that adherence to accepted standards was somewhat better. Still, the findings show room for improvement. For example, more than 16% of the articles on biopharmaceuticals failed to state the year of currency used and just over 14% incorrectly calculated the incremental cost-effectiveness ratio in terms of the incremental costs divided by the incremental QALYs.

While biopharmaceuticals were found to be less favorable than other health interventions, they remain well within the
Table 3. Characteristics of CUAs for biopharmaceuticals and conventional pharmaceuticals

| Characteristic                                      | Biopharmaceuticals n = 258 (%) | Conventional pharmaceuticals n = 845 (%) | All interventions |
|-----------------------------------------------------|---------------------------------|------------------------------------------|-------------------|
| **Country**                                         |                                 |                                          |                   |
| United States                                       | 79 (30.6)                       | 358 (42.4)                               | 1049 (44.0)       |
| United Kingdom                                      | 62 (24.0)                       | 155 (18.3)                               | 428 (18.0)        |
| Canada                                              | 19 (7.4)                        | 65 (7.7)                                 | 165 (6.9)         |
| Netherlands                                         | 6 (2.3)                         | 35 (4.1)                                 | 147 (6.2)         |
| Sweden                                              | 20 (7.8)                        | 42 (5.0)                                 | 97 (4.1)          |
| Other/Multinational                                 | 72 (27.9)                       | 190 (22.5)                               | 497 (20.9)        |
| **Sponsor**                                         |                                 |                                          |                   |
| Industry                                            | 133 (51.6)                      | 392 (46.4)                               | 679 (28.5)        |
| Non-industry                                        | 64 (24.8)                       | 294 (34.8)                               | 1146 (48.1)       |
| Non-disclosed                                       | 61 (23.6)                       | 159 (18.8)                               | 558 (23.4)        |
| **Prevention stage**                                |                                 |                                          |                   |
| Primary                                             | 2 (0.8)                         | 77 (9.1)                                 | 389 (16.3)        |
| Secondary                                           | 18 (7.0)                        | 176 (20.8)                               | 474 (19.9)        |
| Tertiary                                            | 238 (92.2)                      | 592 (70.8)                               | 1520 (63.8)       |
| **Study theme**                                     |                                 |                                          |                   |
| Public health                                       | 2 (0.8)                         | 50 (5.9)                                 | 350 (14.7)        |
| Men’s health                                        | 1 (0.4)                         | 30 (3.6)                                 | 62 (2.6)          |
| Women’s health                                      | 11 (4.3)                        | 108 (12.3)                               | 245 (10.3)        |
| Elderly                                             | 5 (1.9)                         | 28 (3.3)                                 | 99 (4.2)          |
| Children                                            | 15 (5.8)                        | 24 (2.8)                                 | 147 (6.2)         |
| None/NS*                                            | 224 (86.8)                      | 605 (71.6)                               | 1480 (62.1)       |
| **Top ten journals of publication (%)**             |                                 |                                          |                   |
| Pharmacoeconomics (7.4)                             | Value Health (6.2)              | Int J Technol Assess Health Care (2.9)   |
| Pharmacoeconomics (9.9)                             | Rheumatology (4.3)              | Curr Med Res Opin (4.7)                  |
| Pharmacoeconomics (4.6)                             | Curr Med Res Opin (3.9)         | Ann Intern Med (2.4)                     |
|                                             | Int J Technol Assess Health Care (3.5) | Osteoporos Int (2.4)                  |
|                                             | Aliment Pharmacol Ther (2.7)    | Clin Ther (2.0)                          |
|                                             | Ann Intern Med (2.7)            | Eur J Health Econ (1.7)                  |
|                                             | Clin Ther (2.3)                 | Med Decis Making (1.5)                   |
|                                             | J Clin Oncol (2.3)              | Breast Cancer Res Treat (1.4)            |
|                                             | Eur J Health Econ (1.9)          | Cancer (1.3)                             |
|                                             | Other (62.8)                    | Other (67.5)                             |

*NS = Not specified.

range of generally acceptable levels of cost-effectiveness ($<$30,000–50,000 per QALY) and thus, on average, seem to offer good value for money. Nevertheless, there was substantial variation in the ratios, with the cost-effectiveness of many biopharmaceuticals being either highly favorable or highly unfavorable. To illustrate, treatment of chronic hepatitis B with pegylated interferon α-2a compared with conventional interferon α yielded a weighted cost-utility ratio of $308 per QALY, while the weighted ratio for use of cetuximab plus best supportive care compared with best supportive care only in patients with metastatic colorectal cancer was $144,713 per QALY.28,29 This variability was further observed in the results of the regression analysis. Specifically, ratios for malignant neoplasms were strongly associated with less favorable cost-effectiveness while...
versions of off-patent biopharmaceuticals. Available estimates expect the costs of these products to average about 15–30% less.36 Should biosimilars possess comparable safety and effectiveness profiles and be clinically interchangeable to the originator product, they will likely have more favorable cost per QALY ratios due to lower incremental costs. Because of the inherent technical and scientific challenges in developing a product that is truly comparable, however, the actual effect of biosimilars remains uncertain.37

Finally, the findings of a strong association between industry sponsorship and favorability of cost-effectiveness continue to raise questions about why the differences exist.14,26 One possibility is that drug and device manufacturers may only seek marketing approval for products that provide good value. It could also be that manufacturers only choose to fund studies that are likely to find a product to be cost-effective. Or, sponsors may have a direct influence on decisions made about

Table 4. Methodological quality of cost-utility literature

| Methodological criteria                  | Biopharmaceuticals n = 258 | Non-biopharmaceutical interventions n = 2125 | p value |
|-----------------------------------------|-----------------------------|---------------------------------------------|---------|
| Stated study perspective                | 88.0%                       | 81.9%                                       | 0.007   |
| Costs and QALYs discounted              | 86.4%                       | 84.7%                                       | 0.447   |
| Stated time horizon                     | 91.9%                       | 87.8%                                       | 0.057   |
| Stated year of currency                 | 83.5%                       | 83.1%                                       | 0.417   |
| Correctly calculated ICER              | 85.7%                       | 73.1%                                       | <0.001  |
| Average quality score                 | 4.55                        | 4.33                                        | <0.001  |

Note: *ICER = Incremental cost-effectiveness ratio ($/QALY); †Based on the subjective reviewer rating.

Table 5. Distribution of weighted cost-utility ratios* by type of intervention

| No.          | Median       | Inter-quartile range | Cost-saving (%) | Dominated (%) |
|--------------|--------------|----------------------|-----------------|---------------|
| All ratios   | 4608         | $9,041               | $2,439–$26,478  | 16.9          | 8.5           |
| Biopharmaceuticals | 538         | $15,412              | $3,2845–$45,287 | 15.2          | 5.6           |
| Care delivery | 493         | $11,617              | $3,239–$37,385  | 17.6          | 6.3           |
| Conv. pharmaceuticals | 1863       | $7,094               | $1,813–$23,323  | 18.6          | 9.6           |
| Diagnostic   | 422          | $8,846               | $2,705–$29,775  | 13.7          | 19.0          |
| Health ed. or behavior                | 362          | $5,279               | $1,662–$17,988  | 21.0          | 3.0           |
| Immunizations                          | 366          | $8,852               | $2,697–$21,931  | 18.0          | 4.1           |
| Medical device                          | 366          | $14,236              | $4,778–$48,761  | 23.2          | 8.2           |
| Medical procedure                       | 429          | $13,877              | $4,307–$44,995  | 21.0          | 17.2          |
| Screening                               | 617          | $8,785               | $2,763–$20,893  | 11.0          | 9.9           |
| Surgical                               | 574          | $8,790               | $1,937–$25,492  | 15.3          | 10.8          |

*Presented as $US/QALY (in 2008 USD); †Interventions with improved health benefits and decreased costs; ‡Interventions with decreased health benefits and greater costs.

ratios for infectious diseases were much more likely to be favorable. These findings are suggestive of observations made elsewhere about the value of certain biopharmaceuticals. The value of new anti-cancer therapies has been increasingly questioned in recent years because many are perceived as providing few benefits despite their high costs.30,31 Moreover, the results of the regression appear to contradict assertions that use of the tumor necrosis factor-inhibitors may be cost-effective for rheumatological conditions, though the result was not significant.32,33

Even where biopharmaceuticals are inefficient, it is worth pointing out that some could still provide important benefits. Efficiency is but one criterion involved in health care decision-making and other attributes not well captured by CUAs, such as fairness and justice, are also crucial for determining how limits on access should be apportioned throughout a population.10 In Australia, for example, the Pharmaceutical Benefits Advisory Committee (PBAC), the government agency charged with issuing coverage recommendations for the national prescription drug benefit, considers a range of factors alongside a drug’s cost per QALY, including clinical need, disease severity and affordability.34 Because other criteria are involved as inputs into decision-making, data on cost-effectiveness may be weighted differently depending on the context. Indeed, the PBAC has refused to recommend coverage for certain drugs with relatively favorable cost per QALY ratios; it has also recommended coverage for certain drugs with relatively unfavorable ratios, albeit with strict limitations on patient access.5,35

In the medium- to long-run, the emergence of biosimilar products resulting from the development of a viable regulatory pathway for market authorization in the United States and Europe could gradually alter the value of some biopharmaceutical products. As their name suggests biosimilars are similar, but not identical, versions of off-patent biopharmaceuticals. Available estimates expect the costs of these products to average about 15–30% less.36 Should biosimilars possess comparable safety and effectiveness profiles and be clinically interchangeable to the originator product, they will likely have more favorable cost per QALY ratios due to lower incremental costs. Because of the inherent technical and scientific challenges in developing a product that is truly comparable, however, the actual effect of biosimilars remains uncertain.37
the study itself, either by influencing the assumptions made in the analysis or by denying publication of undesirable results. It could also reflect a publication bias on the part of journal editors, as they favor publication of more favorable results.

This study has several limitations. First, although the quality of CUAs was assessed in terms of adherence to accepted methodological criteria for conducting economic evaluations, they were not evaluated in terms of the validity of the clinical and modeling assumptions made. This includes differences in the methods used to derive QALYs, study perspective, comparator intervention and costs included in the analysis (e.g., direct vs. indirect). Such issues could impact the comparability of articles. Second, it is unknown how closely the data in the CEA Registry reflects the actual distribution of the full cost-effectiveness literature because it excludes non-English language articles, CUAs not published in MEDLINE or the peer-reviewed literature and evaluations measuring health outcomes in units other than QALYs. Lastly, readers who conduct evaluations for the Registry are not blinded to the journal of publication or authors of articles. Lack of blinding has the potential to introduce bias in the data, particularly for the subjective reviewer score.

### Methods

This project analyzed data from the Cost-Effectiveness Analysis Registry (CEA Registry), which is maintained by the Center for the Evaluation of Value and Risk in Health at Tufts Medical Center in Boston, MA (www.cearegistry.org). The CEA Registry contains detailed descriptive and analytical information on over 2,300 original cost-utility analyses, including 6,200 cost-utility ratios, published in the peer-reviewed literature between 1976 and 2009 (and is updated regularly). Individual articles are identified through MEDLINE searches using the keywords “QALYs,” “quality-adjusted” and “cost-utility analysis.” Abstracts of articles are screened to determine if the paper contains an original cost-utility estimate. Review articles, editorials, methodological articles, cost-effectiveness analyses that do not use QALYs to quantify health benefits and non-English articles are excluded from the database.

Articles flagged for inclusion in the Registry are extracted and assessed for clarity, completeness and methodological quality by two independent readers with graduate-level training in decision analysis and cost-effectiveness analysis. To ensure that articles are interpreted uniformly, readers follow a detailed set of instructions and a standardized auditing form that is based on a variety of published methodological guidelines and recommendations for reporting cost-utility analyses, such as the Panel on Cost-Effectiveness in Health and Medicine.10,12

Data on over 40 variables are collected for each article, ranging from descriptive information to the methodology used to derive the cost-utility estimates. Basic descriptive characteristics include the bibliographic information (e.g., author, author affiliation, publication, year, etc.), as well as the type of health intervention, comparator, country of study, target population, primary disease treated and source of funding. Methodological variables include study time horizon (e.g., 5 y, 10 y, lifetime, etc.), study perspective (e.g., societal or health care payer) and discounting methods. Each unique cost-utility ratio is recorded as the incremental costs per QALY. Non-US currency ratios are converted into US dollars and all prices are adjusted to 2008 price levels. A score of each reader’s subjective assessment of the overall quality of the methods, assumptions and reporting contained in the article based on a scale from 1 (low) to 7 (high) is also included.

Although reviewers for the CEA Registry record separately whether the intervention is a pharmaceutical or immunization (among other categories), they do not identify biopharmaceutical products specifically. Therefore, all biopharmaceuticals were matched to the list of approved products contained in the Biotechnology Database maintained by the Center for the Study of Drug Development, which contains data on over 2,800 investigational and marketed biopharmaceutical products. While there is a general lack of consensus about what qualifies as a “biopharmaceutical,” for the purposes of this project they were defined as all protein-derived therapeutic products, including synthetic peptides.25

The analytic plan for this project closely followed the approach used in an earlier analysis of pharmaceutical CUAs by Neumann, et al.14 First, basic descriptive characteristics of all articles published between 1976 and 2009 were examined, including the proportion of articles in each intervention category and the number of biopharmaceutical, conventional pharmaceutical (i.e., chemical compounds) and non-pharmaceutical articles

### Table 6. Influence of factors on the favorability of biopharmaceutical cost-utility ratios

| Sponsorship          | Adjusted OR\(^a\) | 95% Confidence Interval | p value |
|----------------------|-------------------|-------------------------|---------|
| Industry             | 3.85              | 2.22–6.68               | <0.001  |
| Non-industry         | 1.58              | 0.89–2.18               | 0.118   |

Disease

| Disease                        | Adjusted OR\(^a\) | 95% Confidence Interval | p value |
|-------------------------------|-------------------|-------------------------|---------|
| Infectious disease            | 5.34              | 3.11–9.16               | <0.001  |
| Malignant neoplasms           | 0.50              | 0.26–0.96               | 0.037   |
| Rheumatologic diseases        | 0.93              | 0.53–1.65               | 0.813   |
| Endocrine disorders           | 1.07              | 0.56–2.04               | 0.832   |
| Neurological conditions       | 0.39              | 0.17–0.89               | 0.025   |

Note: Reference categories are non-disclosed sponsorship and “other” diseases. *Presented as $US/QALY (in 2008 USD); †Adjusted Odds Ratio: Indicates how much a factor increases or decreases the probability the ratio of a biopharmaceutical is favorable (i.e., below the weighted median of all ratios included in the analysis ($9,041 per QALY)) relative to the reference category. For example, ratios of biopharmaceuticals from CUAs sponsored by industry sources are 3.85 times more likely than CUAs that did not disclose the sponsorship to be below the overall weighted median.
published each year. The proportion of articles by country of study, sponsorship, study theme (e.g., public health, men’s health, women’s health, elderly and children), primary disease of study, prevention stage and the top ten journals of publication were also compared for biopharmaceuticals, conventional pharmaceuticals and all interventions. For sponsorship, articles naming any industry source (i.e., pharmaceutical or medical device company) as a study funder were counted as ‘industry-sponsored.’ Articles reporting funding from sources other than industry (i.e., government agencies, foundations, health care organizations and professional member organizations) were counted as ‘non-industry sponsored’. Where source of funding was not reported in a study, or if sponsorship could not be determined, the funding source was counted as ‘not disclosed’.

For biopharmaceutical and non-biopharmaceutical interventions, the proportion of articles adhering to recommended methodological criteria of health economic studies were compared using the chi-square test. Specific criteria assessed included: (1) whether the study perspective was clearly stated; (2) whether the costs and health gains were properly discounted when the time horizon exceeded one year; (3) whether the time horizon analyzed in the study was clearly stated; (4) whether the year of the currency the results were reported in was stated; and (5) whether the cost-effectiveness ratio was correctly calculated as the incremental costs divided by the incremental QALYs (or if the information needed to carry out the calculation was provided). A Student’s t-test with the Cochran Cox approximation was also used to compare the difference in the average subjective reviewer score.

The second set of analyses assessed the cost-effectiveness ratios of all articles included in the CEA Registry between 2000 and 2009. Ratios of articles published prior to 2000 were excluded to ensure better consistency in the methodological quality of articles and to remove potential comparisons that may be no longer relevant. Ratios in which the articles did not report the analytic time horizon or had a time horizon of greater than 5 y but did not properly discount future costs and benefits were further excluded. Because an average of five ratios were reported per article and ranged as high as 21, it was possible that articles with a high number of ratios could disproportionately skew the results. To account for any potential bias that could be introduced by a single article, each ratio was multiplied by a weight of 1/n, with n being the number of reported ratios in the article. Moreover, in the analysis of median ratios, cost-saving ratios (interventions that improve health outcomes and decrease costs) were valued at negative $1 per QALY, while dominant ratios (interventions that decrease health outcomes but increase costs) were valued at $1 trillion per QALY. This ensured that cost-saving interventions were correctly treated as more favorable (i.e., less) than interventions with the lowest ratios and dominant ratios were treated as less favorable (i.e., greater) than interventions with the highest ratios.

To compare the cost-effectiveness of biopharmaceuticals with other health interventions, the distribution of ratios were reported for each intervention category. Cost-saving and dominated interventions were excluded from these calculations and analyzed separately. For the subset of biopharmaceutical interventions, a logistic regression (PROC LOGISTIC, SAS, v9.1, Cary, IN) was used to evaluate how the primary disease studied and study sponsorship influence the probability that a ratio is more favorable than the median weighted ratio of all interventions included in the analysis. The model controlled for both factors, of which sponsorship has been found to be associated with the level of cost-effectiveness.14,26 Not disclosed sponsorship and the group of primary diseases not among the five most frequently studied within the group of biopharmaceutical articles served as reference categories.

**Conclusion**

It appears the increasingly important role biopharmaceuticals are playing in patient care is being matched by a growing presence in the cost-utility literature. This is not surprising given the rising costs of biopharmaceuticals as no health system can provide unchecked access to every new medical technology that comes to market. Instead, each must carefully decide how to allocate limited resources given the inevitable trade-offs that must be made. To do this effectively, coverage and reimbursement decisions should make full use of all available data, including evidence on the incremental costs and benefits of health interventions. On the surface, biopharmaceuticals broadly appear to be less favorable than other areas of health and medicine, though, in many cases, they do provide value for money. Going forward it appears the specific characteristics of biopharmaceuticals will continue to challenge policymakers as they struggle to balance efficient use of financial resources with patient access to new and innovative treatments.

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