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Despite High Costs, Specialty Drugs May Offer Value For Money Comparable To That Of Traditional Drugs

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ABSTRACT **Specialty drugs are often many times more expensive than traditional drugs, which raises questions of affordability and value. We compared the value of specialty and traditional drugs approved by the Food and Drug Administration (FDA) in the period 1999–2011. To do this, we identified published estimates of additional health gains (measured in quality-adjusted life-years, or QALYs) and increased costs of drug and health care resource use that were associated with fifty-eight specialty drugs and forty-four traditional drugs, compared to preexisting care. We found that specialty drugs offered greater QALY gains (0.183 versus 0.002 QALYs) but were associated with greater additional costs ($12,238 versus $784), compared to traditional drugs. The two types of drugs had comparable cost-effectiveness. However, the distributions across the two types differed, with 26 percent of specialty drugs—but only 9 percent of traditional drugs—associated with incremental cost-effectiveness ratios of greater than $150,000 per QALY. Our study suggests that although specialty drugs often have higher costs than traditional drugs, they also tend to confer greater benefits and hence may still offer reasonable value for money.**

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Despite substantial increases in drug companies' investment in research and development, the number of drugs approved each year by the Food and Drug Administration (FDA) has remained relatively constant.[1] What has changed is the nature of the drugs that are approved. Today the majority of approved drugs are specialty drugs, which are often referred to as "large molecule" products. They are produced using advanced biotechnology and require special administration, monitoring, and handling.[2] In the past, the majority of approved drugs were small-molecule products. They are manufactured using simpler processes, are typically self-administered, and are most often dispensed through high-street retail pharmacies.

Specialty drugs offer therapeutic advances for a range of conditions, including cancer, hepatitis C, rheumatoid arthritis, and multiple sclerosis. However, these medications have attracted attention from policy makers because of their high cost—which on average is ten times more than the cost of traditional drugs.[3,4]

Specialty drugs' high prices raise questions not only about their affordability, but also about whether their cost is worth the clinical benefits they provide.[5–8] The drugs accounted for less than 1 percent of US prescriptions in 2013 but for more than a quarter of prescription drug spending.[9] Payers typically group specialty drugs separately from traditional drugs to facilitate specific management strategies.

We evaluated incremental health improvements and incremental costs associated with

specialty drugs upon their introduction into the market, relative to prevailing treatment options—that is, existing drug or nondrug treatments. We then compared our findings with those obtained from equivalent analyses of traditional—that is, nonspecialty—drugs.

Incremental health improvements are reported as the additional quality-adjusted life-years (QALYs) offered by a new treatment, compared to previous treatment options. Incremental costs are reported as the additional costs associated with a new treatment compared to existing treatment options, with both drug costs and other related costs—such as those of hospitalizations and health care resource use—accounted for during the time period used in the studies we reviewed. To our knowledge, this study is the first to evaluate systematically the additional health gains and costs associated with FDA-approved specialty drugs. It thus provides a new perspective on the debate regarding the value of pharmaceuticals.

Study Data And Methods

We developed a data set of incremental QALY gains and incremental costs associated with specialty and traditional drugs. The QALY is a standard metric of health impact that accounts for both length and quality of life. A year of perfect health is equal to one QALY, and a year of less-than-perfect health is equal to less than one, depending on the level of impairment or disability. For example, two years of life lived at perfect health equal two QALYs. Five years of life experienced with a quality of life of 0.4 per year also equal two QALYs. The advantage of QALYs is that they combine in one number both morbidity and mortality effects. Thus, their use facilitates the comparisons of treatments across diseases.[10–12]

SEARCH STRATEGY AND DATA We used the FDA's website to identify all new molecular entities (NMEs)—that is, drugs that had not previously been approved by the FDA or marketed in the United States—that were approved in the period 1999–2011.[13] We classified each approved pharmaceutical as a specialty drug or a traditional drug, depending on its inclusion (or lack thereof) in the specialty drug lists of the two largest pharmacy benefit managers in the United States, CVS Caremark and Express Scripts.[14,15]

For each drug, we searched the PubMed database for cost-utility studies—that is, cost-effectiveness studies reporting a cost per QALY gained—and for comparative effectiveness studies that compared the risks and benefits of competing treatments in terms of QALYs. We searched using the drug's chemical and brand names and the search term *quality adjusted life year OR QALY*. We limited our search to studies that involved human participants and whose results were published in English-language journals.

We considered cost-utility and comparative effectiveness studies that evaluated drugs in our sample for a labeled indication and also those that compared the drugs with alternative therapeutic approaches available at the time of FDA approval. When a study compared the drug of interest to multiple alternatives, we selected as the comparator the most effective available intervention at the time of FDA approval—that is, the comparable drug with the largest reported QALY gain.

For example, one article[16] compared the drug of interest—treprostinil, a specialty drug approved by the FDA in 2002 for the treatment of pulmonary arterial hypertension—to five FDA-approved alternatives: epoprostenol (approved in 1995), bosentan (2001), iloprost (2005), sildenafil (2005), and ambrisentan (2007). Of the drugs that were available before the FDA approved treprostinil, bosentan was estimated to be most effective: Its additional QALY gain was reported to be 0.06 QALYs, compared to treprostinil. We therefore included a QALY gain of −0.06 for treprostinil in our data set.

We considered the study investigators' reasoning for the choice of comparators—for example, it was consistent with treatment guidelines or represented prevailing practice. We excluded studies that evaluated the drug of interest for an off-label indication; compared the drug to treatments that were not available on the date of its FDA approval; or did not, in our judgment, compare the drug to an appropriate active treatment—that is, the drug was compared to a placebo or no treatment, despite the availability of an active comparator.

We also categorized each study according to its source of sponsorship: whether it was sponsored by the pharmaceutical industry, was sponsored by a nonindustry source, or was unfunded.

QALY GAINS AND ADDITIONAL COSTS We used the included studies to develop the data set mentioned above of incremental QALY gains and incremental costs associated with each specialty and traditional drug and the available comparator intervention. We relied on values reported in each study's base-case analysis, since we deemed them to be the most accurate estimates.

When multiple incremental QALY gains and incremental costs were reported in the base case—such as results pertaining to different patient populations or time horizons—we included each of them in our data set. For example, Maurizio Benucci and coauthors[17] compared adalimumab to alternatives for the treatment

Our study suggests that many new specialty and traditional drugs offer relatively modest benefits over preexisting care.

of rheumatoid arthritis using two time horizons—twelve months and twenty-four months—in base-case analyses; thus, we included both. In such instances, we took an average of the reported values to assign a single estimate of incremental QALY gain and incremental cost for each study.

When a drug was associated with multiple studies, we calculated an aggregate estimate of incremental QALY gain and incremental cost by applying an equal weight to each study. For example, if a drug was associated with four studies, we assigned a weight of one-quarter to each study estimate. In this way, we estimated a single incremental QALY gain and incremental cost for each drug.

When necessary, for the reported incremental costs, we converted foreign currency into US dollars using foreign exchange rates obtained from the US Federal Reserve website.[18] We inflated or deflated the results to 2013 values using the US Consumer Price Index.[19]

For each drug, we calculated an aggregate incremental cost-effectiveness ratio—that is, cost per QALY gained—by dividing the average incremental cost by the average incremental QALY gain.

ANALYSIS There is evidence that pharmaceutical industry funding may influence cost-utility study findings. Therefore, to be conservative, our analysis included only studies that were funded by nonindustry sources and those that were unfunded.[20,21] We compared incremental QALY gains and incremental costs for specialty versus traditional drugs using Mann-Whitney U tests (to compare median values of the different distributions) and Kolmogorov-Smirnov tests (to compare the shape of different distributions). We compared the aggregate cost-effectiveness of specialty and traditional drugs, also using Mann-Whitney U and Kolmogorov-Smirnov tests.[22] We used these nonparametric statistical tests because of the number of drugs with high QALY gains and high incremental costs that skewed the data set.

In sensitivity analyses, we compared specialty versus traditional drugs' incremental QALY gains and incremental costs, using the highest, and then the lowest, reported estimates of incremental QALY gains and costs for each drug. We also performed a sensitivity analysis to evaluate the effect of considering each drug only for its first FDA-approved indication. In other words, for drugs with estimates for multiple approved indications, in this sensitivity analysis we included only studies using the indications for which the drugs were first approved, and we excluded studies for indications that the FDA approved after the original approval.

LIMITATIONS This study has a number of limitations.

Because estimates of incremental QALY gains and incremental costs were not available for all FDA-approved drugs, our sample was not entirely representative of the universe of such drugs. Moreover, because we included only drugs approved by the FDA in the period 1999–2011, our data set did not include all of the therapeutic options that are currently available for the diseases we studied. For instance, our data set included various drugs indicated for rheumatoid arthritis, including abatacept (Orencia), adalimumab (Humira), and anakinra (Kineret). However, it did not include important therapies approved outside the study period, such as etanercept (Enbrel), which was approved by the FDA in 1998. Therefore, this research is insufficient for people who use cost-effectiveness evidence to select the most appropriate therapeutic option from available treatment options.

Another limitation is that published studies vary with respect to country setting, methodology, perspective, and so forth.[23–25] In addition, our study averaged QALY gains across studies and did not account for how health gains were distributed among patients. Some patients may benefit much more than others, and costs can differ substantially across patients.

Incremental cost and cost-effectiveness findings should be interpreted with caution. We relied on the incremental costs reported in the cost-utility studies—that is, the aggregate additional cost associated with a treatment, including costs of drugs, hospitalizations, and the use of other health care resources. Thus, we were unable to make drug-specific cost adjustments. To facilitate comparisons, we inflated costs to a 2013 value using the Consumer Price Index. However, in doing so we did not account for how actual drug prices might have changed since

the time when the study was conducted.

Furthermore, cost-utility analyses typically incorporate a drug's list price, which rarely reflects the actual price paid by the health plan. And our conversion of costs in foreign currency to US dollars (explained above) did not account for variations in drug prices across countries.[26]

The aim of this study was to assess the impact of new drugs compared to that of preexisting treatment options. Thus, the choice of comparator was integral to our research. Because of our reliance on published estimates, on occasion the comparator varied across studies. However, for studies that reported results for multiple comparators, we mitigated this limitation by selecting the most effective comparator available at the time the drug was introduced.

We used the drug as the unit of analysis. We considered all FDA-approved indications concurrently, taking into account the average incremental QALY gains and incremental costs of the drug across all indications for which estimates were available. For instance, for adalimumab (Humira), a specialty drug approved for a variety of indications, we identified separate cost and QALY estimates for rheumatoid arthritis, psoriatic arthritis, and Crohn's disease. For pregabalin (Lyrica), we identified estimates for diabetic neuropathy and postherpetic neuralgia.

So that each drug would appear only once in the data set, we took the average of the reported incremental QALY gains and costs across indications. As noted above, we performed a sensitivity analysis when we included only estimates of QALY gains and costs for the first approved indication.

Study Results

The FDA approved 279 NMEs in the period 1999–2011, of which 154 (55.2 percent) were specialty drugs. We identified at least one relevant cost-utility or comparative effectiveness study (comparing the risks and benefits of competing treatments in terms of QALYs) for 102 (37 percent) of the NMEs, of which 58 were specialty drugs. Our data set included 244 cost-utility studies and 9 comparative effectiveness studies. Forty-six drugs were associated with a single study.

The median incremental QALY gain across all drugs was 0.031 QALYs, or roughly one and a half weeks of quality-adjusted survival gain (Exhibit 1). The mean QALY gain was 0.17 QALYs. Specialty drugs and traditional drugs had median QALY gains of 0.183 and 0.002, respectively (Mann-Whitney U test: $p < 0.01$; Kolmogorov-Smirnov test: $p < 0.01$), and mean QALY gains of 0.25 and 0.08, respectively.

Thirty-two drugs in our data set (31 percent) were estimated to be less effective or no more effective than existing care—that is, they had zero or negative incremental QALYs. This was the case for fifteen of the specialty drugs (26 percent) and seventeen of the traditional drugs (39 percent).

Payers have not yet found the formula for managing specialty drugs.

The median additional cost over preexisting care across all drugs was $2,950, and the mean difference was $42,561 (Exhibit 1). Specialty drugs and traditional drugs were associated with median additional costs of $12,238 and $784 (Mann-Whitney U test: $p < 0.01$; Kolmogorov-Smirnov test: $p < 0.01$), respectively, and mean incremental costs of $72,917 and $3,237, respectively.

The median and mean values differed because a number of drugs were associated with notably high QALY gains and additional costs (Exhibits 2 and 3). Thirteen of the top fifteen drugs in terms of QALY gains were specialty drugs (Exhibit 4), as were all of the top fifteen drugs in terms of largest additional costs (Exhibit 5).

Two specialty drugs and five traditional drugs were estimated to be dominant (more effective and less costly than the comparator); six specialty drugs and thirteen traditional drugs were estimated to be dominated (less effective and more costly than the comparator) (Exhibit 1). For the distribution of aggregate incremental cost-effectiveness ratios across specialty and traditional drugs, see online Appendix Exhibit 1.[27] Nine specialty drugs and four traditional drugs were estimated to be less effective and less costly than the comparator.

We found that the distributions of cost-effectiveness differed somewhat. There were sixty-two drugs with positive incremental cost-effectiveness ratios. Among the forty specialty drugs, fifteen (38 percent) were associated with ratios of at least $150,000 per QALY (Exhibit 1). The same was true of four of twenty-two (18 percent) of the traditional drugs). We found no significant difference between the cost-effectiveness of specialty and traditional drugs (Mann Whitney U test: $p = 0.88$; Kolmogorov-Smirnov test: $p = 0.35$).

The results of sensitivity analyses when we

EXHIBIT 1

Overview Of Study Findings: Comparison Of Specialty Drugs With Traditional Drugs In Terms Of Cost Utility And Value

	All drugs	Specialty drugs	Traditional drugs
Number	102	58	44
QALY gain compared to previous treatment options			
Median	0.031	0.183	0.002
Interquartile range	(0.31)	(0.48)	(0.06)
Mean	0.17	0.25	0.08
Standard deviation	(0.88)	(1.15)	(0.22)
Additional costs[a] ($)			
Median	2,950	12,238	784
Interquartile range	(19,732)	(35,248)	(3,572)
Mean	42,561	72,917	3,237
Standard deviation	(371,831)	(494,678)	(6,341)
Aggregate incremental cost-effectiveness ratios[b]			
Dominant (more effective and less costly)	7	2	5
Less than $25,000	13	8	5
$25,000 to <$50,000	12	5	7
$50,000 to <$100,000	10	6	4
$100,000 to <$150,000	8	6	2
$150,000 to <$200,000	5	4	1
$200,000 to <$250,000	1	1	0
$250,000 to <$300,000	3	3	0
$300,000 or more	10	7	3
Dominated (less effective and more costly)	19	6	13
Less costly and less effective	13	9	4
Disease category			
Cancer	25	22	3
Infectious disease	16	12	4
Circulatory disease	14	4	10
Endocrine disorders	11	2	9
Musculoskeletal and rheumatologic disease	11	8	3
Neuropsychiatric and neurological conditions	10	1	9
Eye conditions	3	3	0
Genito-urinary disease	3	1	2
Hematologic disease	2	2	0
Respiratory system disease	2	1	1
Multiple[c]	2	1	1
Digestive disease	1	1	0
Skin and subcutaneous tissue disease	1	0	1
Other	1	0	1

SOURCE Authors' analysis. [a]Over the time period used in the reviewed cost-utility study compared to previous treatment options. Both drug costs and other related costs, such as those of hospitalizations and health care resource use, were accounted for during the time period used in the studies that we reviewed. [b]Cost per quality-adjusted life-year (QALY) calculated from the average of incremental changes in QALYs and costs for each drug. [c]Two drugs, duloxetine hydrochloride (Cymbalta) and adalimumab (Humira), were associated with multiple disease categories. Duloxetine hydrochloride is approved by the FDA for use with neuropsychiatric and neurological conditions and endocrine disorders. Adalimumab is approved for use with musculoskeletal and rheumatologic diseases and digestive disease.

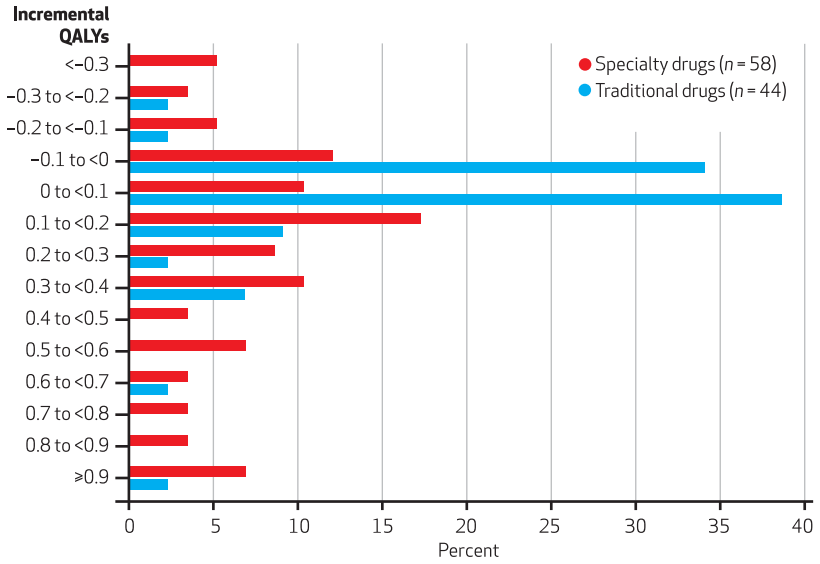
included the highest and lowest reported estimates of incremental QALY gains and incremental costs were qualitatively the same in terms of the significance, sign, and order of magnitude. As noted above, we also conducted a sensitivity analysis for drugs with multiple indications by including only studies of the indication for which the drug was first approved. The results were qualitatively the same as our primary findings.

Discussion

Our study suggests that many new specialty and traditional drugs offer relatively modest benefits over preexisting care. Thirty-two percent of the drugs in our data set (26 percent of the specialty drugs and 39 percent of the traditional drugs) offered no health benefit over preexisting treatments. Of the drugs that did offer health benefits, approximately one-third (data not shown) offered less than 0.1 incremental QALYs (specialty drugs, 14 percent; traditional drugs, 63 per-

EXHIBIT 2

Distribution Of Incremental Quality-Adjusted Life-Years (QALYs) Across Specialty And Traditional Drugs



SOURCE Authors' analysis.

cent; Exhibit 2), or roughly five weeks of perfect health. Two-thirds (data not shown) offered less than 0.3 incremental QALYs (specialty drugs, 49 percent; traditional drugs, 81 percent; Exhibit 2), or roughly fifteen weeks of perfect health. The magnitude of the health gain that we identified is largely consistent with other estimates of the health benefits of medical interventions.[28]

Encouragingly, we identified a number of drugs that offered substantial health gains. Fourteen of the specialty drugs (24.1 percent) and two traditional drugs (4.5 percent) offered more than half a QALY, or six months of quality-adjusted life expectancy (Exhibit 2). We found that specialty drugs tended to offer greater health improvements over preexisting care than did traditional drugs, and that thirteen of the fifteen drugs with the largest health gains were specialty drugs (Exhibit 4). We also found that specialty drugs tended to be associated with larger incremental costs than traditional drugs, and that all of the fifteen drugs with the largest additional costs were specialty drugs (Exhibit 5).

We used the aggregated incremental QALY and cost data to calculate cost-effectiveness ratios for each drug, and we found that the distributions of cost-effectiveness ratios differed somewhat. However, there was no significant difference in cost-effectiveness between specialty and traditional drugs. In other words, specialty drugs were associated with greater incremental costs, but they were also associated with larger QALY gains.

The fact that specialty drugs were associated with some of the largest health gains is not entirely surprising. Specialty products were often introduced for diseases with substantial unmet health needs, such as cancer or multiple sclerosis. In contrast, many of the traditional drugs in our sample were indicated for conditions—such as influenza, gastroesophageal reflux disease, type 2 diabetes, or chronic obstructive pulmonary disease—that have been fairly well managed by existing therapies, at least for many patients.

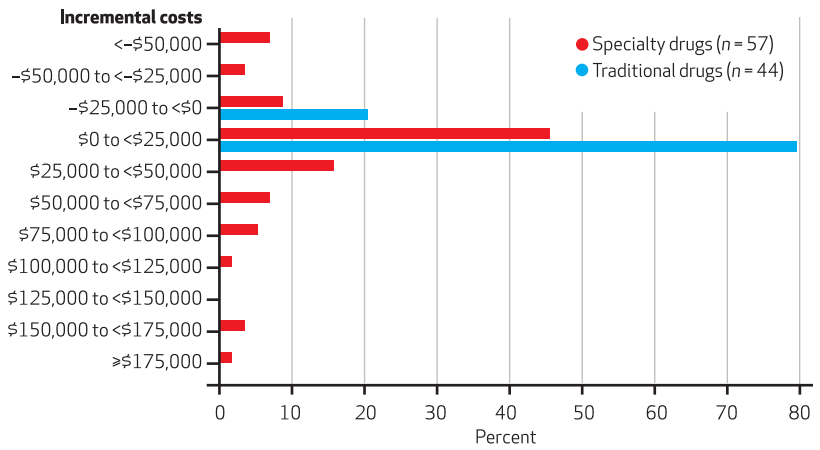
Furthermore, many of the specialty drugs in our data set were approved for use with diseases that had few preexisting treatment options. For example, imatinib (Gleevec) was approved for use with chronic myeloid leukemia, and ranibizumab (Lucentis) for age-related macular degeneration. This was less often the case with traditional drugs, many of which entered a crowded marketplace. For example, both rosuvastatin (Crestor) and ezetimibe (Zetia) were approved for use with hypercholesterolemia.

Our study suggests that specialty drugs often have higher costs than traditional drugs, but that they also tend to confer greater benefits and hence may still offer reasonable value for money. We found that five of the fifteen drugs with the largest additional costs were also among the fifteen drugs with the largest added benefits. For example, imatinib (Gleevec) was estimated to have the third-largest incremental cost ($151,746) and the second-largest incremental QALY gain (4.1 QALYs), with a corresponding incremental cost-effectiveness ratio of $36,921 per QALY (Exhibits 4 and 5).[29,30]

Of the fifteen drugs with the largest additional

EXHIBIT 3

Distribution Of Incremental Costs Across Specialty And Traditional Drugs



SOURCE Authors' analysis. **NOTE** Studies of one specialty drug, natalizumab (Tysabri), did not report incremental costs, so it is not included in this exhibit.

EXHIBIT 4

Fifteen Drugs With The Largest Incremental Quality-Adjusted Life-Year (QALY) Gains Over Preexisting Care

Chemical name (brand name)	Indication	Specialty status?	Year of FDA approval	Average incremental QALY gain	Average incremental cost over the time period used in the reviewed cost-utility study ($)	Aggregate ICER ($)[a]
Deferasirox (Exjade)[b]	Hemosiderosis caused by transfusion-dependent thalassemia	Yes	2005	4.2	168,469	40,144
Imatinib mesylate (Gleevec)[c]	Chronic myeloid leukemia	Yes	2001	4.1	151,746	36,921
Linezolid (Zyvox)[d]	Bacterial infections	No	2000	1.1	752	684
Ranibizumab (Lucentis)[e]	Neovascular age-related macular degeneration	Yes	2006	1.1	70,048	64,501
Bosentan (Tracleer)[f]	Pulmonary arterial hypertension	Yes	2001	1.0	−107,826	Dominant
Oxaliplatin (Eloxatin)[g]	Metastatic carcinoma of colon or rectum	Yes	2002	0.9	21,778	25,231
Dasatinib (Sprycel)[h]	Chronic myeloid leukemia	Yes	2006	0.8	97,987	118,952
Enfuvirtide (Fuzeon)[i]	HIV-1 infection	Yes	2003	0.8	72,215	91,227
Entecavir (Baraclude)[j]	Chronic hepatitis B	Yes	2005	0.8	3,178	4,119
Agalsidase beta (Fabrazyme)[k]	Fabry disease	Yes	2003	0.7	3,663,381	5,233,402
Adefovir dipivoxil (Hepsera)[l]	Chronic hepatitis B	Yes	2002	0.7	10,179	15,269
Lanthanum carbonate (Fosrenol)[m]	Hyperphosphatemia in end-stage renal disease (second-line therapy)	No	2004	0.6	23,561	37,280
Drotrecogin alfa (Xigris)[n]	Severe sepsis	Yes	2001	0.6	13,216	23,616
Epirubicin hydrochloride (Ellence)[o]	Adjuvant chemotherapy for breast cancer	Yes	1999	0.5	5,111	9,644
Peginterferon alfa-2b (Pegintron)[p]	Chronic hepatitis C	Yes	2001	0.5	7,514	14,197

SOURCE Authors' analysis. **NOTES** Incremental costs and incremental cost-effectiveness ratios (ICERs) are reported in 2013 US dollars. Full citations of the items cited in the exhibit footnotes are provided in the online Appendix (see Note 27 in text). "Dominant" is defined in the text and Exhibit 1. FDA is Food and Drug Administration. [a]Aggregate ICERs are calculated from the average of incremental changes in QALYs and costs for each drug. [b]Ho et al., 2013; Keshtkaran et al., 2013; and Luangasanatip et al., 2011. [c]Chen et al., 2009 (Note 30 in text); and Dalziel et al., 2005 (Note 29 in text). [d]McComb et al., 2014. [e]Hernández-Pastor et al., 2010; Hernandez-Pastor et al., 2008; Hodge et al., 2010; Hurley et al., 2008; and Stein et al., 2013. [f]Chen et al., 2009; Garin et al., 2009 (Note 16 in text); and Highland et al., 2003. [g]Ayvaci et al., 2013; Eggington et al., 2006; Shiroiwa et al., 2012; and van Gils et al., 2013. [h]Hoyle et al., 2011; Loveman et al., 2012; Pavey et al., 2012; and Rochau et al., 2014. [i]Sax et al., 2005. [j]He et al.,2012; Toy et al., 2012; Wiens et al., 2013; Wu et al., 2010; and Wu et al., 2012. [k]Rombach et al., 2013. [l]Takeda et al., 2007; and Wiens et al., 2013. [m]Goto et al., 2011. [n]Green et al., 2006; and Hjelmgren et al., 2005. [o]Campbell et al., 2011. [p]Fonseca et al., 2009; Grieve et al., 2006; Hartwell et al., 2011; Salomon et al., 2003; Shepherd et al., 2004; and Shepherd et al., 2007.

costs, five were associated with ratios of less than $100,000 per QALY, and two with ratios of less than $50,000 per QALY (Exhibit 5), which are commonly recognized benchmarks of cost-effectiveness.[31,32] Six other drugs—all specialty products—were associated with ratios of greater than $250,000 per QALY.

Addressing The Cost Of Specialty Drugs

The high costs of specialty drugs are placing an increasing burden on payers, employers, and patients. Payers have responded in large part by shifting drug costs to patients. For example, some payers have added a specialty drug tier to their drug formularies, which requires patients to pay copayments of $500 per month or coinsurance of up to 50 percent of the drug's cost.[7,33] Given that some specialty drugs cost more than $100,000 per year, this practice has put many important drugs out of financial reach for some patients.[7,34,35]

Formulary exclusion lists that the largest pharmacy benefit managers have recently implemented include drugs that are more expensive

EXHIBIT 5

Fifteen Drugs With The Largest Additional Costs Over Preexisting Care

Chemical name (brand name)	Indication	Specialty status?	Year of FDA approval	Average incremental QALY gain	Average incremental cost over the time period used in the reviewed cost-utility study ($)	Aggregate ICER[a] ($)
Agalsidase beta (Fabrazyme)[b]	Fabry disease	Yes	2003	0.7	3,663,381	5,233,402
Deferasirox (Exjade)[c]	Hemosiderosis caused by transfusion-dependent thalassemia	Yes	2005	4.2	168,469	40,144
Imatinib mesylate (Gleevec)[d]	Chronic myeloid leukemia	Yes	2001	4.1	151,746	36,921
Omalizumab (Xolair)[e]	Moderate to severe asthma	Yes	2003	0.3	101,342	331,398
Dasatinib (Sprycel)[f]	Chronic myeloid leukemia	Yes	2006	0.8	97,987	118,952
Crizotinib (Xalkori)[g]	Metastatic non-small-cell lung cancer	Yes	2011	0.4	96,506	254,632
Cabazitaxel (Jevtana Kit)[h]	Hormone-refractory metastatic prostate cancer	Yes	2010	0.3	77,955	311,822
Enfuvirtide (Fuzeon)[i]	HIV-1 infection	Yes	2003	0.8	72,215	91,227
Ranibizumab (Lucentis)[j]	Neovascular age-related macular degeneration	Yes	2006	1.1	70,048	64,501
Fingolimod (Gilenya)[k]	Relapsing forms of multiple sclerosis	Yes	2010	0.2	62,516	315,736
Cetuximab (Erbitux)[l]	Metastatic colorectal carcinoma	Yes	2004	0.4	57,839	156,323
Abatacept (Orencia)[m]	Rheumatoid arthritis	Yes	2005	0.2	47,354	263,080
Temsirolimus (Torisel)[n]	Advanced renal cell carcinoma	Yes	2007	0.2	41,743	173,929
Cinacalcet hydrochloride (Sensipar)[o]	Secondary hyperparathyroidism in chronic kidney disease	Yes	2004	0.5	39,358	82,599
Ambrisentan (Letairis)[p]	Pulmonary artery hypertension	Yes	2007	0.0	36,440	Dominated

SOURCE Authors' analysis. **NOTES** Incremental cost-effectiveness ratios (ICERs) are reported in 2013 US dollars. "Dominated" is explained in the text and Exhibit 1. FDA is Food and Drug Administration. QALY is quality-adjusted life-year. Full citations of the items cited in the exhibit footnotes are provided in the online Appendix (see Note 27 in text). [a]Aggregate ICERs are calculated from the average of incremental changes in QALYs and costs for each drug. [b]Rombach et al., 2013. [c]Ho et al., 2013; Keshtkaran et al., 2013; and Luangasanatip et al., 2011. [d]Chen et al., 2009 (Note 30 in text); and Dalziel et al., 2005 (Note 29 in text). [e]Norman et al., 2013; and Wu et al., 2007. [f]Hoyle et al., 2011; Loveman et al., 2012; Pavey et al., 2012; and Rochau et al., 2014. [g]Djalalov et al., 2014. [h]Zhong et al., 2013. [i]Sax et al., 2005. [j]Hernández-Pastor et al., 2010; Hernandez-Pastor et al., 2008; Hodge et al., 2010; Hurley et al., 2008; and Stein et al., 2013. [k]Campbell et al., 2013; and Lee et al., 2012. [l]Hoyle et al., 2013; and Mittmann et al., 2009. [m]Malottki et al., 2011. [n]Hoyle et al., 2010; and Thompson Coon et al., 2010. [o]Garside et al., 2007; and Komaba et al., 2012. [p]Garin et al., 2009.

than alternatives and that offer only questionable health benefits. This suggests that simply shifting costs to patients is no longer tenable.[36] Ideally, payers will find alternative strategies to address the challenge of ensuring that patients have access to specialty drugs while reining in drug spending.

For instance, in an attempt to make the management of specialty drugs more efficient, various health plans have contracted with specialty pharmacies to deliver specialty drugs to patients and monitor the drugs' use.[37] Others are integrating specialty drugs—most of which, because they are administered by physicians, are covered through a plan's medical benefit—into their pharmacy benefits to better monitor the drugs' use by patients and identify areas for efficiency gains.[38,39] Payers are also increasingly adopting value-based insurance designs—which align patient cost sharing with treatment cost-effectiveness—in an attempt to improve drug adherence and health outcomes and to contain costs by encouraging the use of high-value care.[33,40,41]

Commonly applied by Medicare, but less so by private payers, are policies that provide coverage with evidence development—that is, they cover

promising treatments on the condition that additional effectiveness data are collected. These policies thus permit the earlier adoption of promising treatments and the better evaluation of their benefits.[42] Performance-based risk-sharing agreements, sometimes called just risk-sharing agreements, expand upon coverage with evidence development policies and tie reimbursement to patient outcomes by limiting reimbursement to treatments that prove effective.[43] This approach is promising. However, experience has shown that difficulties in establishing suitable data infrastructures, measurement challenges, and implementation costs limit its use in practice.[44]

Payers have not yet found the formula for managing specialty drugs. Insurers should continue to experiment with a combination of existing formulary management tools and novel strategies to maximize patient access to specialty drugs while minimizing their cost.

Conclusion

The health care system faces the challenge of paying for effective specialty drugs while ensuring that patients have access to them and that the system is receiving good value for money it spends.[35] Our research shows that, compared to traditional drugs, specialty drugs often offer substantially increased health benefits over preexisting care. We also found that in the period 1999–2011, many of the drugs that have offered the largest clinical advancements have been specialty drugs. However, the incremental costs for specialty drugs have exceeded the incremental costs of more conventional novel treatments. Nevertheless, specialty drugs can offer good value for various complex and burdensome diseases. ■

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