cost generic drugs is associated with greater patient adherence, the use of REMS requirements to block the market entry of generic drugs could well lead to higher health care costs and adverse patient outcomes. This strategy for extending brand-name exclusivity also appears to violate congressional intent in the FDAAA, in which REMS requirements were presented as a means of preventing adverse effects, not preventing competition. Before the Actelion case was settled, the Federal Trade Commission filed an amicus brief arguing that the refusal of a pharmaceutical company to provide samples to its potential competitors may violate federal antitrust law. The FDA has promised to issue guidelines for generic drug companies seeking to obtain a ruling on the safety of their bioequivalency testing protocols, which would authorize brand-name drug manufacturers to supply drug samples without violating their REMS.

The issue of REMS patents is more complicated. The FDAAA's explicit language anticipating the existence of such patents stands in tension with the emphasis on shared REMS programs. Even if the FDA were to fulfill its promise to promulgate clearer guidelines for the development and implementation of shared REMS programs, the agency would still be powerless to prevent brand-name drug manufacturers from seeking to patent their REMS. Thus, it might be necessary for Congress to revisit the legislation and prohibit REMS patents, or at least restrict brand-name drug manufacturers from invoking REMS patents against potential generic competitors. Although it is understandable that drug companies would seek to protect their intellectual property and creativity in developing a REMS, permitting programs of education, monitoring, and controlled dispensing to be patented by a single company can undermine patient safety once a generic version of the drug is available.

We think that a single, shared REMS system for a given drug would be the best way of seamlessly and consistently providing guidance to prescribers, pharmacists, and patients; preventing adverse events; eliminating unnecessary confusion; and reducing administrative burdens on all participants. Manufacturers already receive substantial benefits from the REMS system because it facilitates FDA approval of drugs whose widespread availability might otherwise have been delayed pending further testing. The importance of protecting patients' health demands that an efficient and effective risk-management approach be available to both brand-name and generic drug companies.

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Comparative Effectiveness Questions in Oncology

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The high cost of cancer drugs has been criticized by leading academics[1] and lamented in the popular press.[2] The average price of 1 year of treatment with a new cancer drug now exceeds $100,000,[1] and the benefits of many of these therapies — often improvement in median survival on the order of weeks to months — do not appear commensurate with their prices.[2] Expensive cancer drugs cost society in two ways. First, high prices are borne by payers each time these drugs are prescribed. And second, high prices preclude independent comparative effectiveness trials that would seek to establish equally effective but cheaper alternatives — thereby protecting the market share of expensive drugs.

Consider abiraterone acetate, an inhibitor of the cytochrome P450 c17 (CYP17) class of enzymes, which are responsible for

Estimated Sample Sizes and Costs for Clinical Noninferiority Trials Comparing Biosimilar Cancer Drugs.*

Disease	"Next-Generation" Drug	"Parent" Drug	Size of Each Treatment Group	Estimated Drug Cost for the Trial in U.S. $
Metastatic pancreatic cancer	Nab-paclitaxel	Paclitaxel	925	37,715,000
Renal-cell carcinoma	Temsirolimus	Sirolimus	995	25,009,000
Metastatic breast cancer	Everolimus	Sirolimus	985	35,881,000
Metastatic prostate cancer	Abiraterone	Ketoconazole	1122	68,882,000
Metastatic colorectal cancer	Regorafenib	Sorafenib	872	28,764,000

* Sample-size calculations represent a one-sided (0.10) test of significance for the equivalence (noninferiority) of the parent agent as compared with the next-generation drug, with the assumptions of 80% power, 36 months of enrollment, no more than 48 months of follow-up, a 1:1 randomization ratio, no dropouts, and a 0.90 limit on the hazard ratio as the boundary of noninferiority. (Power calculations were performed by Dr. Seth M. Steinberg of the National Cancer Institute.) The average wholesale price for each next-generation drug was obtained from the most recent online version of the Red Book, and the drug cost for the trial was estimated as the product of the average wholesale price of the newer drug, the best estimate of the required duration of treatment, and the sample size of the study.

the extragonadal conversion of pregnenolone to testosterone, a key biochemical pathway exploited by castration-resistant prostate cancer. Abiraterone's mechanism of action is remarkably similar to that of an older drug, ketoconazole, which also inhibits CYP17. In fact, before the approval of abiraterone for castration-resistant prostate cancer, ketoconazole had been used off-label for this purpose, a practice supported by improved response rates in modestly powered clinical trials.[3] Although abiraterone is widely touted as having more specific 17-alpha-hydroxylase inhibitory activity, and thus fewer off-target effects on cortisol and aldosterone pathways, both drugs have enough off-target effects to necessitate steroid supplementation.

The Food and Drug Administration (FDA) approved abiraterone acetate in 2011 for patients with castration-resistant prostate cancer who had received previous chemotherapy, on the basis of a phase 3, randomized clinical trial comparing the drug in combination with prednisone to prednisone alone. In the study, which enrolled nearly 1200 patients, abiraterone increased median survival from 10.9 to 14.8 months.[4] Ketoconazole was not the comparator in this study, because its survival benefit had not been established. However, ketoconazole had never been put to a similarly rigorous test. The largest randomized trial included slightly more than 250 patients in aggregate[3] and showed improved response rates and a trend toward improved progression-free survival, but it was underpowered to assess differences in mortality.

Although the biologic difference between ketoconazole and abiraterone may be small, the difference in price is not. Ketoconazole is a widely available, generic medication and costs $500 to $700 per month. Abiraterone costs in excess of $7,000 per month — 10 times as much as ketoconazole, though the question remains whether it is any better.

Conducting a noninferiority, randomized, controlled trial comparing abiraterone with ketoconazole is one logical next step. Such a trial could adjudicate questions regarding efficacy as well as toxicity. If just half of the 32,000 patients who die of prostate cancer annually in the United States could be treated with ketoconazole instead of abiraterone, such a comparative effectiveness trial could save payers more than $1 billion per year. It would be unwise, however, for Johnson & Johnson, the manufacturer of abiraterone, to fund such a study, since its findings could only erode the company's market share. And it is equally unlikely that the company would facilitate such a trial conducted by someone else by providing abiraterone free of charge. Instead, to test the hypothesis, a third party would probably need to purchase both drugs in addition to incurring the fixed costs of running a trial.

Just how much would abiraterone cost for such a study? The surprising answer is nearly $70 million. The table shows the purchase price for the "next-generation" drug in five hypothetical comparative effectiveness trials of cancer drugs. Each of the examples shares the five key principles illustrated by abiraterone and ketoconazole: the newer drug

gained FDA approval in a comparison against placebo (or, in one case, interferon alfa); the benefit of the new agent was marginal (for these five drugs, the median improvement in overall survival was 2.0 months, and the median improvement in progression-free survival was 2.7 months); some preclinical or early-phase trial evidence supports a comparison with the less expensive "parent" compound, which has never been similarly tested; a demonstration of equivalent efficacy would mean substantial savings; and the purchase price of the newer drug makes the cost of a comparative effectiveness study prohibitive.

The sample sizes given in the table are designed to test a noninferiority margin of 0.90. The calculated costs are then a product of sample size, the best estimate of the required duration of treatment, and the average wholesale price of the newer drug. A more permissive noninferiority margin (e.g., 0.80) would reduce sample sizes and decrease costs but would lead to considerable ambiguity in trial interpretation. For instance, abiraterone improves survival by 3.9 months over placebo. Accepting a drug that is only 80% as good as abiraterone would leave doubt as to whether it provides any improvement over placebo.

Consider another case: the use of albumin-bound paclitaxel (nab-paclitaxel) in the treatment of pancreatic cancer. In 2013, nab-paclitaxel in combination with gemcitabine was shown to increase overall survival in pancreatic cancer from 6.7 to 8.5 months as compared with gemcitabine alone.[5] Nab-paclitaxel, an alternative formulation of paclitaxel, is more costly and of uncertain biologic superiority. For example, in advanced non–small-cell lung cancer and metastatic breast cancer, the drugs have resulted in similar overall survival in head-to-head studies, despite differences in dosing. Paclitaxel has never undergone testing in combination with gemcitabine in a similar-sized randomized trial involving patients with pancreatic cancer. Unfortunately, to test whether these two drugs are equivalent, nearly $38 million of nab-paclitaxel would need to be purchased.

The comparisons that we highlight suggest an underappreciated consequence of the prices themselves: high prices protect a drug's market share, precluding challenges from cheaper alternatives.

The high price of cancer drugs is unsustainable, and the need for less costly alternatives is greatest in cases where the benefit of new therapies is marginal (i.e., the cost-effectiveness ratio is mostly unfavorable). The five comparisons that we highlight suggest an underappreciated consequence of the prices themselves: high prices protect a drug's market share, precluding challenges from cheaper alternatives.

How then can we make progress toward conducting these potentially cost-saving cancer trials? First, despite the cost of these studies, there remain parties interested in the answers that such trials would provide. Collaborations among stakeholders such as the National Cancer Institute's Cancer Therapy Evaluation Program, the large oncologic cooperative groups, and large payers could generate the revenue needed for such trials. The argument that cooperative groups should strive solely to find "better" therapies and not less expensive alternatives is increasingly untenable in the United States. Second, companies could provide their drugs free of cost to investigators. If these drugs were true advances, companies could benefit from formal demonstration of that fact, which would appeal to oncologists' desires to use the best treatment. Finally, trialists could employ innovative study designs, whereby patients receiving the newer drug could use insurance as a payment mechanism (as they would if they were being treated off-protocol), and only the parent drug would need to be purchased. Although this design has been successfully employed, it remains the exception and not the rule.

The realization that prices threaten comparative effectiveness trials of cancer drugs provides yet another challenge to the research community — but one that we believe we must be ready to confront.

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