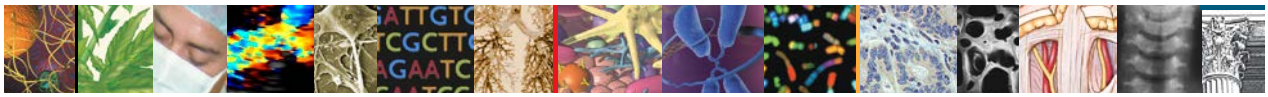

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Perspective

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The $2.6 Billion Pill — Methodologic and Policy Considerations

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The introduction of several new astonishingly expensive prescription drugs has rekindled debate over the origins of and justifications for those prices. At a press conference in Boston last November, the Tufts Center for the Study of Drug Development announced it had calculated that it costs pharmaceutical companies $2.6 billion to develop a new drug[1] — up from the $802 million the Center estimated in 2003. Because the new findings were presented at a media event that offered limited information regarding the methods used to arrive at this figure, it is difficult to know much about the solidity of the approach or the validity of the reported number. Before the findings could appear in the peer-reviewed literature, the figure was catapulted into the midst of the current hot debate about the pricing of many new drugs.[2]

Since the figure's release, it has been used to justify the cost of several expensive medications and to support longer periods of marketing exclusivity for new drug products. These arguments are based on the proposition that drug companies (which are major supporters of the Tufts center) must be helped to recoup the huge capital needs required to discover the cures of tomorrow.

The methods used to generate the $2.6 billion figure will require careful scrutiny once they are available for detailed review. The analysis was based on data that 10 unnamed drug makers provided on 106 unnamed investigational compounds that they had "self-originated." The raw numbers on which the analysis is based are not available for transparent review — and are likely never to be divulged. The study included both products that made it to market and a much larger number that did not — a fair approach, since a balanced assessment would have to take into account the costs of failures as well as successes. But because we cannot know which compounds were studied, it is hard to evaluate the key assumption that more than 80% of new compounds are abandoned at some point during their development — a key driver of the findings.

Notably, as in the Center's previous estimates, nearly half the cost of drug development was accounted for not by research expenditures but by the cost of capital. The analysts justified that assumption by noting that during the years a company spends develop-

ing a new product, it incurs opportunity costs by not using those dollars for other purposes. That argument is plausible, and such calculations can be an appropriate component of such analyses. However, nearly half the total cost of developing a new drug ($1.2 billion) was ascribed to this cost of capital, with only $1.4 billion attributed to funds actually spent on research. These capital costs were assessed at 10.6% per year, compounded — despite the fact that bonds issued by drug companies often pay only 1 to 5%. In terms of access to capital, it's interesting to note that large drug makers are among the U.S. firms with the highest amounts of profits held overseas. Two pharmaceutical companies are ranked third and fourth among all U.S. corporations in this regard: Pfizer ($69 billion) and Merck ($57 billion), respectively. Collectively, another eight drug companies reportedly have an additional $173 billion of capital that is retained overseas, untaxed by the United States.[3] Such funds could potentially help with the cash-flow problem that plays such a large role in these estimated costs of drug development.

The Tufts calculations also explicitly do not take into account the large public subsidies provided to pharmaceutical companies in the form of research-and-development tax credits or substantial payments received from the federal government for other research activities, such as testing their products in children. Perhaps most important, because the calculations are based only on products that the companies described as "self-originated," the $2.6 billion figure does not consider drug-development costs borne by the public for the large number of medications that are based on external research that elucidated the disease mechanisms they address. One recent analysis showed that more than half of the most transformative drugs developed in recent decades had their origins in publicly funded research at nonprofit, university-affiliated centers.[4]

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Without knowing which drugs were included in the Tufts analysis, there is no way to know how many of the "self-originated" products also built on underlying basic science research whose costs were borne by the public. In the debate over what it costs to bring a new drug to market and who should be compensated at what level to keep new-product pipelines full, this aspect of drug research and development must also be taken into account. The question of how best to fund such research is particularly relevant given that the current budget of the National Institutes of Health (NIH), in inflation-adjusted dollars, is at its lowest level in 15 years.[5]

The Tufts study did identify one aspect of drug development whose costs were actually lower than those in the Center's previous analysis: the time required for regulatory approval has been shortened somewhat. This finding is supported by extensive data showing that most regulatory bodies are impressively prompt in making approval decisions once the results of drug trials have been submitted by a manufacturer. The Food and Drug Administration is now particularly quick, reviewing drugs at least as rapidly as drug-regulatory bodies in many other countries and often more quickly. By contrast, the highest cost the Tufts researchers identified was that of the failure of compounds earlier in development because of unanticipated problems with safety, lack of efficacy, or both. This expensive weakest link points not to costly regulatory delay but to the limits of companies' ability to efficiently choose compounds for development and to identify adverse effects or limited efficacy earlier in the development process.

Of course, it is extremely expensive and risky to develop a new medication, and inevitably many promising new treatments will fail before they can be marketed. Pharmaceutical companies do invest heavily in the work needed to bring successful products to market and often in the underlying research on which those products are based. But as risky as drug development is, the pharmaceutical and biotech industries remain among the most profitable sectors of the U.S. economy and actually spend only a small fraction of their revenues on truly innovative research. Furthermore, some of the most important recent new medications

were not developed by large drug manufacturers but were acquired through purchase of the biotech firms that discovered them. These, in turn, are often spinoffs based on the discoveries of NIH-funded university research laboratories. For example, Gilead Sciences did not invent its blockbuster treatment for hepatitis C, sofosbuvir (Sovaldi), which it priced at $1,000 per pill. Rather, it acquired the product from a small company founded by the drug's inventor, a faculty member at Emory University, much of whose work on the usefulness of nucleoside viral inhibitors was federally funded. Gilead paid $11 billion in late 2011 for the rights to market Sovaldi, an amount it totally recouped in its first year of sales after approval of the drug in late 2013.

An audio interview with Dr. Avorn is available at NEJM.org

We need an accurate determination of all the costs that go into the creation of a new drug, to inform ongoing discussions about how best to foster such development and the most reasonable way of paying for truly innovative medications — especially given the proliferation of "specialty" drugs that can cost patients and payers as much as $300,000 per year. These analyses will in turn require a broad-based and transparent reckoning of the costs of all the research and development that lead up to the creation of a new drug. Such a comprehensive accounting could well lead to policy decisions focused less on the need to replenish the capital of pharmaceutical companies and more on preserving the taxpayer-supported scientific sources of new drug discovery on which so many therapeutic advances depend.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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Protection or Harm? Suppressing Substance-Use Data

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What if it were impossible to closely study a disease affecting 1 in 11 Americans over 11 years of age — a disease that's associated with more than 60,000 deaths in the United States each year, that tears families apart, and that costs society hundreds of billions of dollars?[1] What if the affected population included vulnerable and underserved patients and those more likely than most Americans to have costly and deadly communicable diseases, including HIV–AIDS? What if we could not thoroughly evaluate policies designed to reduce costs or improve care for such patients?

These questions are not rhetorical. In an unannounced break with long-standing practice, the Centers for Medicare and Medicaid Services (CMS) began in late 2013 to withhold from research data sets any Medicare or Medicaid claim with a substance-use–disorder diagnosis or related procedure code. This move — the result of privacy-protection concerns — affects about 4.5% of inpatient Medicare claims and about 8% of inpatient Medicaid claims from key research files (see table), impeding a wide range of research evaluating policies and practices intended to improve care for patients with substance-use disorders.

The timing could not be worse. Just as states and federal agencies are implementing policies to address epidemic opioid abuse and coincident with the arrival of new and costly drugs for hepatitis C — a disease that disproportionately affects drug users — we are flying blind.

The affected data sources include Medicare and Medicaid Research Identifiable Files, which