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Conflict of Interest Disclosures: None reported.

1. Littmann L, Potter JK, Hoglund JR. Profound electrocardiogram changes in a patient with liver cirrhosis. *JAMA Intern Med*. 2018;178(2):286-288. doi:10.1001/jamainternmed.2017.7059

2. Cosardereliogluc C, Cosar AM, Gurakar M, et al. Portopulmonary hypertension and liver transplant: recent review of the literature. *Exp Clin Transplant*. 2016;14(2):113-120.

3. Colle IO, Moreau R, Godinho E, et al. Diagnosis of portopulmonary hypertension in candidates for liver transplantation: a prospective study. *Hepatology*. 2003;37(2):401-409.

Assessing Pharmaceutical Research and Development Costs

To the Editor The Original Investigation by Prasad and Mailankody[1] published in a recent issue of *JAMA Internal Medicine* and concerning cancer drug research and development (R&D) costs and revenues suffers from selection bias and other flaws that render their cost estimates substantially downwardly biased. The authors presume that they have adequately adjusted for risk because, aside from the single cancer drug each company had approved, the companies had a number of drugs in clinical development that have not been approved (they do not list these other drugs, specify whether they are cancer drugs, indicate whether they have failed, or what their development status is if they have not failed). Even if one assumes that all of the unapproved drugs fail, the data in the study by Prasad and Mailankody[1] suggest an overall clinical approval success rate for these companies of 23%. This is substantially more than recent rigorously developed estimates of clinical approval success rates for drugs as a whole.[2,3] One recent analysis[4] puts the clinical approval success rate for oncology indications at 5%. If some of the drugs in development at these companies are approved in the future, thereby increasing the implied success rates, it would mark these companies as even more atypical for the period analyzed. Only one company (Exelixis) in the sample has an implied success rate (9%) that is roughly similar to established industry success rate estimates. The out-of-pocket R&D cost for the approved cancer drug manufactured by Exelixis (cabozantinib) listed in the article is $2.0 billion, and when capitalized at the (too-low) cost of capital rate Prasad and Mailankody[1] used, the R&D cost estimate becomes $2.6 billion. Research and development costs associated with the purported failures are also likely underestimated since they could have incurred costs outside of the periods examined.

After consulting a subscription pipeline database (IQVIA)[5] for the development histories of the 10 sampled drugs, I found that 6 of them had R&D conducted prior to the R&D start dates in the article (2 at least 6 years earlier, 1 at least 10 years earlier, and another at least 12 years earlier). I write "at least" because the earliest date found in commercial pipeline databases is often the date when a patent was filed, which typically occurs some years after discovery, or the start of preclinical development, and is usually close to the start of clinical testing. It is not known how much these additional years would add to R&D costs.

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1. Prasad V, Mailankody S. Research and development spending to bring a single cancer drug to market and revenues after approval. *JAMA Intern Med*. 2017;177(11):1569-1575. doi:10.101001/jamainternational.20173601

2. Paul SM, Mytelka DS, Dunwiddie CT, et al. How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nat Rev Drug Discov*. 2010;9(3):203-214. doi:10.1038/nrd3078

3. DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: New estimates of R&D costs. *J Health Econ*. 2016;47:20-33. doi:10.1016/j.jhealeco.2016.01.012

4. BIO. Biomedtracker, Amplion. BIO Industry Analysis: Clinical Development Success Rates 2006-2015. https://www.bio.org/sites/default/files/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016.pdf. Accessed September 13, 2017.

5. IQVIA website. http://www.iqvia.com/contact. Accessed January 10, 2018.

To the Editor In their Original Investigation published in a recent issue of *JAMA Internal Medicine*, Prasad and Mailankody[1] examine the costs of bringing a single drug with an oncological indication to the market. They conclude that 10 selected companies had a median investment cost of $648 million for the development of their drug, whereas the median revenue in 4 years on average was $1658.4 million. This further reinforces the notion that there are large profits to be made with drug development, and that current pharmaceutical drug prices are unrelated to the actual costs for research and development.

There are, however, some caveats to the analysis by Prasad and Mailankody.[1] The authors only selected companies that had no other drugs on the market at the time of filing for US Food and Drug Administration approval, meaning only small companies. It is possible that small companies have a leaner organization and can work more efficiently than larger pharmaceutical companies can, so the generalized conclusion that it costs $648 million to bring a drug to market is, even if regarding only the market for oncology drugs, a potentially inaccurate extrapolation of their findings. The costs of bringing a drug to the market might be lower for a small company than for a larger company.

Additionally, this analysis only considered companies that had been successful in pursuing market authorization for their product. Next to those, there were likely competitors with similar projects that did not yield a successful product. The costs of those unsuccessful investments should also be taken into account to make a fair estimation of the costs of development.

The study outcomes, however, are valuable and contribute to a larger movement we recently described in an article on drug pricing.[2] Prices of drugs are not related to their development costs but to what the market will pay for them. The double-digit profit margins commonly seen in the industry are a clear result of this. Without adequate regulation to control prices in the United States, drug prices can be expected to rise further. We agree with Prasad and Mailankody[1] that more transparency is needed to clarify the discrepancy between investments and prices in the pharmaceutical industry.

This analysis[1] highlights that society is overpaying for the products developed by drug companies. With more regulation on pricing, prices can be brought down significantly without discouraging innovation.

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1. Prasad V, Mailankody S. Research and development spending to bring a single cancer drug to market and revenues after approval. *JAMA Intern Med*. 2017;177(11):1569-1575. doi:10.1001/jamainternmed.2017.3601

2. Gronde TV, Uyl-de Groot CA, Pieters T. Addressing the challenge of high-priced prescription drugs in the era of precision medicine: a systematic review of drug life cycles, therapeutic drug markets and regulatory frameworks. *PLoS One*. 2017;12(8):e0182613. doi:10.1371/journal.pone.0182613

In Reply We thank DeMasi, as well as van de Gronde and Pieters, for their interest in our article[1] estimating the research and development (R&D) spending to bring a single cancer drug to the US market and its revenue postapproval.

First, both DeMasi and van de Gronde and Pieters raise the question of whether our analysis includes companies who were more successful than average, which would lead us to underestimate R&D spending.

The companies we examined reported a 23% chance of getting a drug that is in clinical trials approved by the US Food and Drug Administration (FDA).[1] This rate is nearly identical to a prior study paper by DeMasi and Grabowski[2] that shows the probability of FDA approval for oncology drugs in clinical trials is 26.1%.

In his letter, DeMasi highlights a 5.1% rate of clinical success for oncology drugs reported in a document by BIO Industry Analysis.[3] We acknowledge there are different estimates of clinical success rate of varying levels of transparency and peer review. Nevertheless, clinical success may truly vary by the size of a company, class of drug, or regulatory pathway of approval. Whether such differences are owing to biological challenges or the pursuit of an aggressive, high-risk clinical trials portfolio is unknown. For example, if the payoff for a single clinical trial with a *P* value less than .05 is billions of dollars, companies may move forward with drugs and indications for which clinical promise is low.[4,5] This appears to be the case for some cancer drugs.[6]

Van de Gronde and Pieters question why we do not include companies that did not bring any drugs to market in our costs. Notably, no published analysis—not by DeMasi and colleagues nor Public Citizen—includes companies that failed entirely, and such data are not available.

Second, van de Gronde and Pieters suggest that smaller companies may be more efficient. Indeed, we agree this may be true. Larger companies, by virtue of sustained profits, may have become inefficient in drug development or choose to move forward with more compounds of low promise, lowering success rates.

Third, DeMasi states that for 6 drugs we include, R&D began prior to the date stated in our analysis, and thus we omitted some R&D costs. One drug (eculizumab) had a typo in our table that was previously fixed, and all costs after 1992 were included, making the issue moot. Three drugs were acquired (irinotecan liposome, pralatrexate, vincristine liposome) through purchase, and we included costs of acquisition (upfront and milestone payments). Again, the point is moot. For the final 2 drugs, the preclinical data in the Insurance Management Services (IMS) filing and our start date are consistent, but IMS suggests that patents were filed earlier. In the case of brentuximab, this is 2 additional months, and in the case of ponatinib, this is 14 months. Including the cost of 12 additional months for brentuximab would add $4.9 million and for ponatinib would add $43.3 million. Thus, changing these 2 R&D start dates would not materially change our results. As the R&D start data are not publically available, we prespecified 2 years prior to the first mention of the compound in the biomedical literature as the start date, and adhered to that method.

These letters have confirmed the major virtue of our analysis.[1] Because our analysis is transparent, in contrast with some prior estimates, researchers can engage with our data and results. We have acknowledged the limitations of our estimate in the article, but we believe more transparency in data sets and further open investigations are needed in this space.

Finally, we note the one-sidedness of the objections. All objections concern reasons we may underestimate R&D, but there are important reasons why we overestimate it. Specifically, we do not include tax breaks, including those given for R&D and orphan indications that may lower the cost borne by companies substantially.[1]

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1. Prasad V, Mailankody S. Research and development spending to bring a single cancer drug to market and revenues after approval. *JAMA Intern Med*. 2017;177(11):1569-1575.

2. DiMasi JA, Grabowski HG. Economics of new oncology drug development. *J Clin Oncol*. 2007;25(2):209-216.

3. Biomedtracker BIO. Amplion. BIO Industry Analysis: Clinical Development Success Rates 2006-2015. https://www.bio.org/sites/default/files/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016.pdf. Accessed September 13, 2017.

4. Fojo T, Mailankody S, Lo A. Unintended consequences of expensive cancer therapeutics—the pursuit of marginal indications and a me-too mentality that stifles innovation and creativity: the John Conley Lecture. *JAMA Otolaryngol Head Neck Surg*. 2014;140(12):1225-1236.

5. Gyawali B, Prasad V. Pemetrexed in nonsquamous non-small-cell lung cancer: the billion dollar subgroup analysis. *JAMA Oncol*. 2018;4(1):17-18.

6. Mattina J, Carlisle B, Hachem Y, Fergusson D, Kimmelman J. Inefficiencies and patient burdens in the development of the targeted cancer drug sorafenib: a systematic review. *PLoS Biol*. 2017;15(2):e2000487.

Methods Used to Assess Pharmaceutical Research and Development Costs

To the Editor This letter addresses the methods in an Original Investigation titled "Research and Development Spending to Bring a Single Cancer Drug to Market and Revenues After Approval" by Prasad and Mailankody[1] and published in a recent issue of *JAMA Internal Medicine*. Specifically, it calls attention to the fact that these methods do not appropriately apply accounting or finance standards, and, consequently, measure neither "spending" nor "revenues."

The method Prasad and Mailankody[1] use purports to extract spending and revenue data from the audited financial statements of biotechnology companies developing their first product. Financial statements follow a set of definitions and standards established by the Financial Accounting Standards Board (FASB). Just as the International Classification of Diseases provides a set of definitions designed to standardize communication among health professionals, FASB provides definitions to standardize financial communication. This Original Investigation, however, disregards these standards.

For example, the paper claims to assess research and development (R&D) "spending." While the method identifies certain R&D "expenses," it does not account for the fact that R&D spending can be considered either an expense or a capital investment, depending on the circumstances.[2-4] This is particularly true for acquisition of products initiated in other organizations and development that is outsourced to contract research organizations. This method also fails to identify spending by pharmaceutical partners, who contractually contributed up to 60% of the costs for some products in this study.[1] Thus, the method in this paper identifies only a fraction of actual spending on R&D.

Prasad and Mailankody[1] also claim to assess "revenues since approval." The term "revenue," however, is used interchangeably with "earnings" and "profit," and it is unclear which metric is intended. Revenue is a measure of proceeds from sales, while income, profit, and earnings include adjustments for cost of goods and specified business expenses. Moreover, the authors[1] add the market value of the company at acquisition to its revenues, which has no rational interpretation in accounting or finance. Thus, the method in this article[1] does not provide a meaningful measure of "revenues since approval."

The quality and integrity of research in accounting and finance, as in medicine, is grounded in the rigor of its methodology.[5] This work by Prasad and Mailankody[1] is dismissive of rudimentary standards of accounting or finance and, as a result, promulgates an unsubstantiated, erroneous picture of corporate finances associated with drug development.

Interdisciplinary work is inherently challenging, which contributes to the complexity of integrating best practices of medicine with those of business. Rather than advancing such an integration, this Original Investigation[1] is emblematic of the gap between these professional and academic disciplines that remains unbridged.

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1. Prasad V, Mailankody S. Research and development spending to bring a single cancer drug to market and revenues after approval. *JAMA Intern Med*. 2017;177(11):1569-1575.

2. Financial Accounting Standards Board. FASB Accounting Standards No. 2: Accounting for Research and Development Costs. 1974. http://www.fasb.org/resources/ccurl/286/565/fas2.pdf. Accessed January 31, 2018.

3. Financial Accounting Standards Board. Statement of Financial Accounting Standards No. 142: Goodwill and Other Intangible Assets. 2001. http://www.fcscfg.com/index.php/terminology/fasb-142-goodwill-and-other-intangibles-assets. Accessed January 31, 2018.

4. Healy PM, Myers SC, Howe CD. R&D accounting and the tradeoff between relevance and objectivity. *J Account Res*. 2002;40(3):677-710.

5. Ryan B, Scapens RW, Theobald M. *Research Method and Methodology in Finance and Accounting*: 2nd edition. Cengage Learning (EMEA) Limited; 2002.