

New Business Models to Accelerate Innovation in Pediatric Oncology Therapeutics

A Review

Sonya Das; Raphaël Rousseau, MD, PhD; Peter C. Adamson, MD; Andrew W. Lo, PhD

IMPORTANCE Few patient populations are as helpless and in need of advocacy as children with cancer. Pharmaceutical companies have historically faced significant financial disincentives to pursue pediatric oncology therapeutics, including low incidence, high costs of conducting pediatric trials, and a lack of funding for early-stage research.

OBSERVATIONS Review of published studies of pediatric oncology research and the cost of drug development, as well as clinical trials of pediatric oncology therapeutics at ClinicalTrials.gov, identified 77 potential drug development projects to be included in a hypothetical portfolio. The returns of this portfolio were simulated so as to compute the financial returns and risk. Simulated business strategies include combining projects at different clinical phases of development, obtaining partial funding from philanthropic grants, and obtaining government guarantees to reduce risk. The purely private-sector portfolio exhibited expected returns ranging from -24.2% to 10.2%, depending on the model variables assumed. This finding suggests significant financial disincentives for pursuing pediatric oncology therapeutics and implies that financial support from the public and philanthropic sectors is essential. Phase diversification increases the likelihood of a successful drug and yielded expected returns of -5.3% to 50.1%. Standard philanthropic grants had a marginal association with expected returns, and government guarantees had a greater association by reducing downside exposure. An assessment of a proposed venture philanthropy fund demonstrated stronger performance than the purely private-sector-funded portfolio or those with traditional amounts of philanthropic support.

CLINICAL RELEVANCE A combination of financial and business strategies has the potential to maximize expected return while eliminating some downside risk—in certain cases enabling expected returns as high as 50.1%—that can overcome current financial disincentives and accelerate the development of pediatric oncology therapeutics.

JAMA Oncol. doi:10.1001/jamaoncol.2018.1739
Published online June 2, 2018.

+ Supplemental content

Author Affiliations: MIT Laboratory for Financial Engineering, Sloan School of Management, Cambridge, Massachusetts (Das, Lo); MIT Department of Mathematics, Cambridge, Massachusetts (Das); MIT Department of Electrical Engineering and Computer Science, Cambridge, Massachusetts (Das, Lo); Gritstone Oncology, San Francisco, California (Rousseau); Cancer Center, Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia (Adamson); Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia (Adamson); MIT Computer Science and Artificial Intelligence Laboratory, Cambridge, Massachusetts (Lo); Santa Fe Institute, Santa Fe, New Mexico (Lo).

Corresponding Author: Andrew W. Lo, PhD, MIT Laboratory for Financial Engineering, Sloan School of Management, 100 Main St, E62-618, Cambridge, MA 02142 (alo-admin@mit.edu).

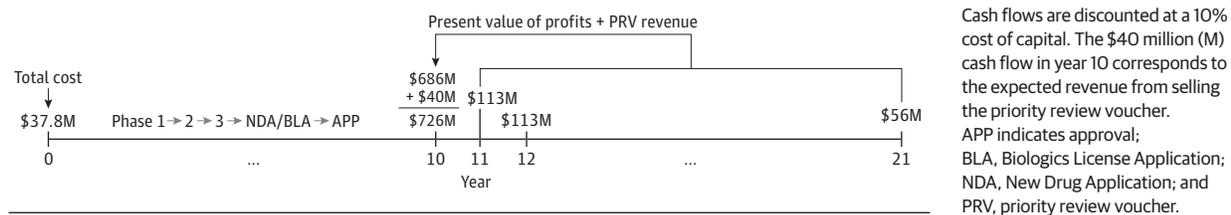
Cancer in children is one of the most challenging disease areas in drug development. Compared with adult cancers, pediatric cancers are a lower priority for many pharmaceutical companies because of scientific hurdles, additional regulatory burdens, and financial disincentives.¹ Accounting for 1% of all cancer cases in the United States, pediatric cancers are categorized as orphan diseases.² Owing to the rarity of these diseases, the clinical research necessary for a drug or biologic agent to reach US Food and Drug Administration (FDA) approval can be arduous and financially draining. The process of accruing a sufficient number of patients for clinical trials and taking a treatment from phase 1 through to an FDA New Drug Application or Biologics License Application submission can take more than a decade³ and cost more than \$100 million for a successful candidate.⁴ Moreover, the lack of “druggable targets” or mutations makes clinical trial outcomes difficult to estimate; only

12% of pediatric tumors are likely to possess currently known mutations.⁵

In the case of general orphan diseases, the small patient populations and recent scrutiny on drug pricing make these therapeutic efforts less attractive to for-profit entities. Furthermore, the lack of druggable targets creates an additional degree of uncertainty regarding the clinical viability of drug candidates.⁶ Given that 84% of orphan drugs are developed by small, emerging companies with limited capital,⁷ pediatric oncology faces even greater challenges than the usual funding gap in translational medicine known as the “valley of death.” Consequently, the number of drugs that have been developed and approved specifically for pediatric oncology purposes has been scant.

A more sustainable financing model is needed to foster innovation in pediatric oncology therapeutics. Herein we examine “a mul-

Figure 1. Financial Timeline of an Investment in a Clinic-Ready Pediatric Oncology Drug Program, Assuming a Dose Price of \$250 000



tiple shots on goal" approach in which many programs are funded simultaneously to reduce the risk of failure.

Motivation

Fernandez et al⁸ originally proposed financing drug discovery via a "megafund"—a much larger pool of capital than the typical venture capital fund—and using both debt and equity rather than equity alone. In this structure, investors finance many diverse projects in parallel, raising the likelihood of finding a successful therapy, thereby reducing risk and improving financial returns. Development programs for drugs and biologic agents are undertaken simultaneously rather than serially (ie, as a portfolio) and are funded by issuing equity (eg, stock) and, if feasible, debt (eg, bonds or loans) and as claims on the portfolio.

Recent examples of the megafund model put into practice in health care include BridgeBio Pharma,^{9,10} Roivant Sciences, Ltd,¹¹ and UBS Oncology Impact Fund.¹² Outside of health care, the megafund model has been applied successfully with many types of assets, including mortgages, auto loans, student loans, music royalties, and even portfolios of Hollywood films.

Methods

To assess the financial returns of a hypothetical portfolio of pediatric cancer therapeutics, we used Monte Carlo simulation to randomly generate many realizations of the portfolio. These simulations are calibrated using key factors as described in this section. Our open-source simulation software can be accessed in the eAppendix in the [Supplement](#), and readers are invited to rerun our simulations with their own preferred set of variables.

Selection of Portfolio Constituents

A crucial component of the megafund is project selection. This is typically done by 1 or more portfolio managers—often venture capitalists or biopharmaceutical executives—exercising scientific and business judgment developed through years of experience investing in biotechnology. For our purposes, we identified promising pathways and molecular targets from a broad reading of the pediatric oncology literature, a review of pediatric oncology trials in the ClinicalTrials.gov database, and from informal discussions with experts in the field. This process yielded 77 hypothetical projects—by no means exhaustive—that are listed in the eAppendix in the [Supplement](#).

Profitability of a Successful Drug

To analyze the success of a pediatric oncology megafund, we first need to calculate the total economic value or net present value (NPV) of a successful drug. The NPV includes the present value of all fu-

ture revenues minus the present value of all future costs, as reduced by a constant discount rate to reflect the cost of capital. **Figure 1** illustrates the investment timeline in greater detail. Because pediatric oncology has had a limited number of recent drug approvals, there are few historical datapoints to estimate the profitability of an FDA-approved drug as Fernandez et al⁸ does for adult oncology assets. Our experimental design uses an approach similar to that of Lo et al,¹³ relying on a set of assumed variables to compute the NPV of an FDA-approved pediatric oncology drug ([Table](#)).

We also perform sensitivity analyses by recomputing our simulations under various sets of values for key variables. For example, future revenues are based on an average incidence rate of 1500 new patients per year¹⁵ while varying price per dose (where we assume for simplicity that only 1 dose is needed, hence our dose price is the amortized cost of the entire course of treatments needed for each patient). The NPV of a successful pediatric oncology drug will range from \$68 million (priced at \$10 000 per dose) to \$2.9 billion (priced at \$1 million per dose). Our simulation framework allows the calculation of the minimum dose price needed to achieve a positive expected return on investment, which serves as an indicator of the economic viability.

Probability of Clinical Success

Using the financial assumptions described above, we can calculate a best-case expected rate of return for a successful pediatric oncology drug. For example, an initial \$37.8 million investment producing a drug worth \$726 million after 10 years represents a compound annual rate of return of $(\$726 / \$37.8)^{1/10} - 1 = 34.4\%$ during the 10-year development period.

However, this rate of return is realized only if the drug is successful; the expected return is lower because it also reflects the prospect of failure. Thus, an accurate assessment requires an estimate of the probability of success for each of the 77 hypothetical projects in the portfolio. In addition, because the success or failure of 1 project is likely not mutually independent of that of another project, we also require the pairwise correlations between the 2926 ($77 \times 76 / 2$) unique pairs of projects in the portfolio. The methodology to determine the pairwise correlations between projects is discussed in the eAppendix in the [Supplement](#).

Using published estimates derived from historical data, our simulations assume the following probabilities of success: 62.8% for phase 1, 24.6% for phase 2, 40.1% for phase 3, and 82.4% for New Drug Application or Biologics License Application approval.¹⁶ These figures combine to an overall 5.1% probability of a clinic-ready drug achieving FDA approval. Given the high levels of risk in our simulated portfolios, issuing bonds with acceptable levels of risk and reward is infeasible; hence, we consider equity-only megafunds.

Table. Assumptions and Variable Values Used to Compute the Net Present Value of an FDA-Approved Drug Project

Variable	Assumed Value
Cost of drug development	\$37.8 Million per project, comprising the total cost of clinical discovery ⁴ ; given the potential of drug repurposing in the pediatric space, ¹⁴ the cost of preclinical research was excluded
Duration of clinical development	10 y ³
Duration of marketing exclusivity postapproval	10.5 y, Assuming a standard 20-y patent and a 6-mo patent extension owing to developing a pediatric drug under the Best Pharmaceuticals for Children Act ³¹
Market size	1500 New patients per year, the average incidence rate across broad pediatric cancer subtypes ¹⁵
Market penetration	30%, Estimated to account for competing formulations and ability to disseminate the drug
Dose price per patient	Ranges from \$10 000 to \$1 million
Additional revenues	\$40 Million in PRV proceeds at year 10; these vouchers are awarded to a company on achieving FDA approval for a pediatric drug, enabling the company to receive an expedited review on any of the other drugs in their pipeline; the PRV can be sold to other companies and has an estimated market value of \$50 million during the next few years; from communication with individuals involved in the process, ⁹ it is estimated that 4 of 5 of priority designation applications are accepted by the FDA, and so we assume that 80% of projects in the portfolio will be eligible for priority designation, making the expected value of the PRV \$40 million
Cost of capital	Constant rate of 10% to reflect the market rate of interest

Abbreviations: FDA, US Food and Drug Administration; PRV, priority review voucher.

⁹ Email correspondence between Laura Thrall, MS, and Gregory Reaman, MD, of the FDA Center for Drug Evaluation and Research; September 5, 2017.

New Business and Funding Models

We consider 3 business and funding models: 1 purely private-sector fund and 2 public-private partnerships, with 1 involving government and the other a philanthropic organization. The objective is to assess the economic viability of each of these models for supporting pediatric oncology therapeutic development.

Private Sector Investment

We first assess the viability of a megafund fully funded through the private sector. The estimated risks (proxied by return SD) and expected returns from megafunds during a 10-year development period are given in Figure 2 under various combinations of the variable values. All definitions and derivations of the statistics used in our simulations are available in the eAppendix in the Supplement. Specifically, we consider price points for the dose per patient ranging from \$10 000 to \$1 million and pairwise correlations from 0% to 80%.

The best private-sector scenario is when drug development programs in the portfolio are mutually uncorrelated and treatment price is \$1 million. In this extreme case, the fund yields a positive expected return of 25.9% and an SD of 18.1% (panel 1 of eTable 1 in the Supplement). Such a portfolio has an attractive risk-reward profile, but it is achieved only at a prohibitively expensive dose price and under the unrealistic assumption that there is no pairwise statistical correlation between the outcomes of any 2 assets in the portfolio. Assuming an uncorrelated portfolio, the \$100 000 dose price has the potential to break even and return investors' capital within the 10-year period (panel 1 of eTable 1 in the Supplement), which compares favorably with the quoted price of \$475 000 for the recently approved chimeric antigen receptor T-cell therapy, tisagenlecleucel (Kymriah; Novartis), for pediatric patients with acute lymphoblastic leukemia.¹⁷ However, the Novartis business model is slightly different from our setup; they elect not to charge patients who fail to respond to the treatment after 1 month.¹⁸ This performance guarantee has the potential to hinder Novartis' return on investment, which could explain the higher price. This example demonstrates that a more-sophisticated pricing model is likely necessary for private sector-only initiatives.

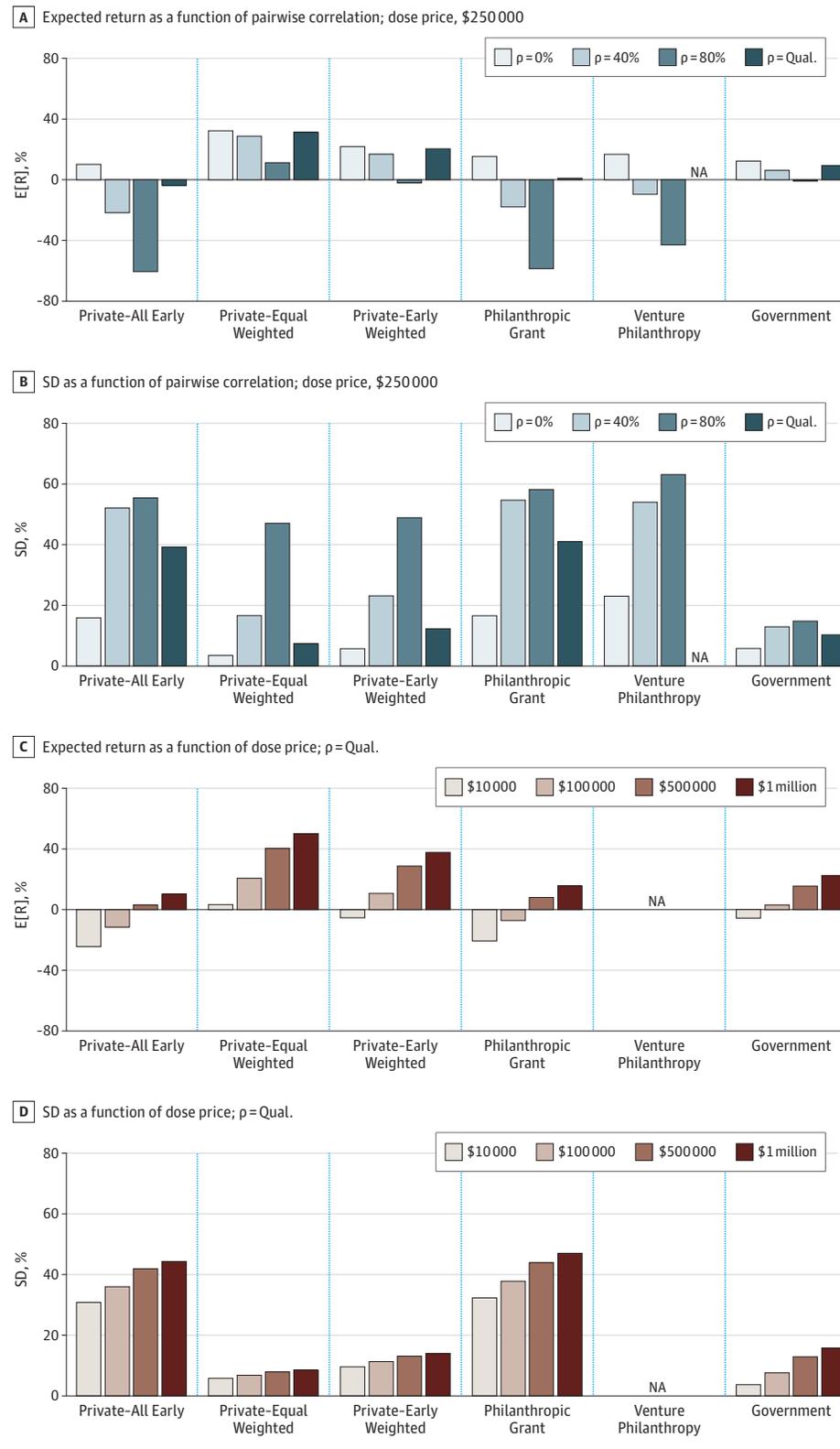
Furthermore, the best-case scenario must be weighed against the less-attractive results of the more-correlated cases. For example, the scenario in which all projects have an 80% pairwise correlation yields a -54.8% expected return and a 63.4% SD even at the highest price of \$1 million per dose (panel 1 of eTable 1 in the Supplement). The most realistic case (denoted *qualitative*), which uses qualitatively calibrated correlation values based on expert opinion and publications, yields mixed expected returns in plausible price ranges, with an expected return of -24.2% at a price of \$10 000 per dose, which many would argue is a reasonable price point for payers; the portfolio just about breaks even with an expected return of 3.0% and an SD of 41.9% at \$500 000 per dose (Figure 2C and D). The \$1 million price point yields an expected return of 10.2% and SD of 44.8% (Figure 2C and D).

These results suggest that a pediatric oncology megafund financed only by the private sector is unlikely to be economically viable unless drugs are priced at prohibitively high levels. Even in the case of ultrahigh prices, there exists substantial downside risk; hence, the risk-reward profile may not be sufficient to attract investor capital.

One reason for the unattractive risk-reward profile is the fact that the simulated portfolios considered so far consist entirely of assets ready for phase 1. With only a 5.1% probability of an oncology drug's approval from prephase 1 status,¹⁶ it is not surprising that the risk of a portfolio containing only phase 1 assets is high.

To address this issue, we consider a mixed-phase portfolio in which later-stage candidates are also included. These assets have the potential to reduce the risk of the portfolio and boost expected returns by increasing the probability of developing at least 1 successful drug. The progression of phases is simulated using the phase transition probabilities discussed in the Methods section. We investigate 2 variations of this theme to illustrate a range of performance: 1 variation with a high skew toward early-stage candidates (a 70:20:10 ratio of phase 1, 2, and 3 assets, respectively, denoted *early-stage weighted*), and an equal-weighted portfolio of candidates (a 1:1:1 ratio of phase 1, 2, and 3 assets, denoted *equal weighted*). The results for these 2 solely private-sector funded, mixed-phase funds are reported in Figure 2.

Figure 2. Expected Returns and Risks of Simulated Hypothetical Pediatric Megafunds for 6 Different Business Models and Various Values of Pairwise Correlations (ρ) and Drug Prices



A and B, Performance statistics for the 6 models with respect to different ρ levels and a drug dose price of \$250 000. C and D, Performance statistics for the 6 models with respect to different drug prices and $\rho = \text{Qual.}$ E[R] indicates expected return, or mean, of the simulated portfolio; NA, not applicable; Private-All Early, all early-stage private-sector portfolio of 77 drug candidates in a 10-year horizon; Private-Early Weighted, a private-sector portfolio of 77 drug candidates with a 70:20:10 distribution of projects in phases 1, 2, and 3, respectively, in a 10-year horizon; Private-Equal Weighted, a private-sector portfolio of 77 drug candidates with an equal distribution of projects in phases 1, 2, and 3 during a 10-year horizon; Philanthropic Grant, the same fund as Private-All Early, but with the added feature of a \$5 million philanthropic grant per drug project; $\rho = \text{Qual.}$, qualitatively calibrated pairwise correlations based on the relevant literature; and Venture Philanthropy, a hypothetical \$100 million fund of 20 drug candidates in a 5-year horizon; and Government, the same fund as Private-All Early, but with the added feature of a \$250 million government guarantee.

Diversifying the megafund by phase increases performance considerably. For example, our qualitatively calibrated scenario with a \$250 000 per dose price for a mixed portfolio has an expected return of 20.4% and risk of 12.3% (early-stage weighted) or an even

more satisfactory expected return of 31.2% and risk of 7.4% (equal weighted), depending on the mix of phases (Figure 2A and B). These expected returns are high enough to be attractive to a broad range of investors, whereas the -3.7% expected return from the purely early-stage portfolio with the same correlation and pricing assumptions (Figure 2A) is unlikely to attract any private-sector capital. The 50.1% expected return and 8.5% risk from the equal-weighted portfolio, \$1 million dose price qualitatively correlated scenario exceeds the historical risk-reward profile of most US venture capital and hedge funds (Figure 2C and D).¹⁹ While some scenarios with higher correlations or lower price points still yield negative expected returns, such as the -5.3% return at the \$10 000 price in the qualitatively correlated scenario (Figure 2C and D), the mixed-phase portfolios offer higher expected returns and lower risks than the all-early-stage portfolio in all cases.

Although the mixed-phase approach is promising, the unique challenges of pediatric oncology make later-stage assets harder to obtain. Therefore, early-stage-weighted portfolios are more realistic. In such cases, the price needed to generate positive expected returns ranges from just under \$100 000 to more than \$250 000, depending on the pairwise correlation. However, for a portfolio of only phase 1 assets, this price can be substantially more than \$1 million. These results imply that prohibitive pricing may be necessary to justify private-sector investment; hence, we consider other strategies that can help to reduce prices in all-early-stage portfolios.

Public Sector Guarantees

One such strategy is the use of government-backed guarantees to lower the risk of early-stage research. In a guarantee structure, a third party—typically a government agency, but philanthropic organizations have also played this role—agrees to take the first losses on the portfolio for a predetermined amount, which we specify as \$250 million for our simulated megafund. In other words, in the event of a negative portfolio return, the government will cover up to \$250 million of the loss, cushioning the consequences for private-sector investors. The role of selecting portfolio constituents would remain a private-sector-led effort.

Various forms of guarantees have served as an effective strategy to attract private capital to neglected industries and initiatives. Development impact bonds have enabled organizations to secure low-cost and flexible funding from investors with the promise of a third-party outcome funder providing payouts to investors based on progress.²⁰ A successful example in health care is Global Alliance for Vaccines and Immunizations (GAVI) bonds to help disseminate vaccinations in developing nations. Since 2006, through \$6.5 billion in committed backing by several nations and philanthropic organizations, such as the Bill and Melinda Gates Foundation, the International Finance Facility for Immunization (GAVI's partner organization), has been able to raise more than \$5.7 billion in funding from capital market investors.^{21,22}

A notable feature of a guarantee is its low expected cost. In their proposed megafund, Fagnan et al²³ demonstrated that guarantees typically have a potential loss of 0.1% to 1.0% of their face value. For a \$250 million guarantee, this implies an expected cost of \$2.5 million, which is a small fraction of the current National Cancer Institute budget.²⁴ Because of its ability to minimize downside for investors at a low expected cost, this approach holds considerable promise.

The associations of a \$250 million government guarantee with our 77-drug, all-early-stage portfolio is presented in Figure 2. Compared with the private sector-funded all-early-stage fund, the guarantees improve the unattractive investment returns, particularly in the high-correlation scenarios. For example, consider the -54.8% expected return and 63.4% SD of the private-sector fund in the 80% correlation scenario at the highest price of \$1 million discussed earlier. This same scenario with the government guarantee yields an expected return of 4.8% and SD of 22.1%, implying a higher probability that investors will not lose money (panel 6 of eTable 1 in the Supplement). The difference between these 2 cases is striking—the guarantee transforms an uninvestable portfolio of drug candidates into one that could conceivably attract some capital. While some cases of negative expected returns in the higher correlated scenarios still exist, these can be addressed by adjusting the size of the guarantee.

In some cases, the portfolio appears to be attractive, such as a 22.5% expected return when the price is \$1 million and qualitative correlations are used (Figure 2C). However, the risk-reward profile is also feasible at more reasonable dose prices (eg, -0.6% to 12.2% at the \$250 000 price point) (Figure 2A).

Philanthropic Grants

Nonprofit organizations typically do not take an equity stake in the companies that they support. Rather, their grants are intended to achieve a positive outcome, typically by funding basic scientific or early preclinical research. We consider the consequence of a \$5 million grant for each project in the early-stage megafund portfolio and find that, by themselves, small grants improve performance only marginally. Compared with the all-early-stage private-sector portfolio, its philanthropic counterpart increased expected returns by 2% to 5% (Figure 2). These results help us to understand how, despite the estimated \$4.5 billion annually invested in medical and health research and development by US foundations,²⁵ these foundations rarely earn an attractive rate of return on their funding (nor do most of them seek to earn such return).

However, during the past decade, more philanthropic organizations outside of pediatric oncology have begun to explore new funding models in which some form of return is expected, where return is measured by several metrics, including monetary reward. The leading example of what is now called “venture philanthropy” is the Cystic Fibrosis Foundation, which invested \$150 million in Vertex Pharmaceuticals over 12 years to develop molecules for treating cystic fibrosis. Vertex brought ivacaftor (Kalydeco) to market in 2014, and through a transaction with Royalty Pharma, the Cystic Fibrosis Foundation received \$3.3 billion in exchange for its royalty interests in ivacaftor and related assets.²⁶ After this success, despite potential concerns raised with the venture philanthropy approach,²⁷ several other disease-specific nonprofits have followed suit.²⁸ In strategic models like this, the returns may be sufficient to allow the nonprofit organization to continue funding its mission without any additional donor contributions, yielding a sustainable business model.

To explore this approach, we consider a public-private venture philanthropy fund proposed by CureSearch for Children's Cancer, a US-based nonprofit organization. We simulate a portfolio using the following assumptions. The model requires raising \$100 million in philanthropic donations to develop a portfolio of 20 to 30 projects—at an average cost of up to \$5 million per project—to help fund phase 1 trials and an equity investment in the spinout company during a 5-year period. If phase 1 and 2 trials of a project are successful, it is likely that

the company will seek a sale, at which point there will be a return on investment. The goal will be to break even initially and then to build a sustainable revenue stream to fund additional projects.

In the case of a hypothetical 20-drug portfolio, its financial returns are driven by the sale of successful phase 2 projects to a pharmaceutical buyer and a 10% royalty on any profits from a priority review voucher, which is a transferable voucher issued by the FDA that gives the holder the right to receive faster review of a New Drug Application. For a successful phase 2 project, the drug is sold at a value that gives buyers a 15% expected return on their investment.

With only 20 drugs in 5 years and a fund size of \$100 million, the model demonstrates promising performance compared with our private-sector all-early-stage portfolio, which requires 10 years and more than \$858 million of capital to fund 77 projects. For example, in the uncorrelated case, the breakeven dose price is less than \$100 000 for the model (not shown in Figure 2), which is comparable to that of the uncorrelated scenario in the private-sector portfolio (panel 1 of eTable 1 in the [Supplement](#)). At the higher price points in the uncorrelated scenario, the venture philanthropy model can achieve substantial returns as high as 34.5% with an SD of 26.5% (not shown in Figure 2; see panel 5 of eTable 1 in the [Supplement](#)). While the break-even price in the highly correlated cases in the model is above \$1 million, the venture philanthropy model may be more viable than the private sector or standard philanthropic grant structures owing to its smaller size and funding needs.

Discussion

Over the past 60 years, pediatric oncologists have optimized the treatment of many childhood cancers with drugs discovered in

the 1950s-1970s. However, the short- and long-term morbidity are substantial, with some subtypes of cancer producing more than 90% mortality.²⁹ Future progress requires the development of new targeted agents with a specifically pediatric focus. The strategic use of a megafund model could accelerate the development of new treatments for children with cancer by fostering critical partnerships between the public and private sectors.

Pediatric cancers differ from most orphan diseases because of the lack of known druggable targets and the small population of existing subtypes. These factors help to explain why the returns of a hypothetical private sector–funded megafund are significantly less attractive than those of the adult oncology megafund of Fernandez et al⁸ or the orphan disease megafund of Fagnan et al.³⁰

To make this challenging space attractive to both investors and the private sector, a strategic and collaborative investment framework will be required. A mixed-phase investment strategy seems to be more effective than an all-early-stage fund, but sourcing projects ready for phase 2 or 3 of drug development may be challenging in the near term. Philanthropic grants can help to relieve financial pressure in the early stages of development, but only marginally. Government guarantees, however, have the potential to cushion the downside of the investment at a relatively low expected cost to taxpayers.

Conclusions

Pharmaceutical innovation and financial profitability need not be mutually exclusive in pediatric oncology. Both are achievable—and at a reasonable price for payers and patients—if stakeholders collaborate within the appropriate business and financing model.

ARTICLE INFORMATION

Accepted for Publication: April 2, 2018.

Published Online: June 2, 2018.
doi:10.1001/jamaoncol.2018.1739

Conflict of Interest Disclosures: Dr Rousseau is an employee of Gritstone Oncology and is an unpaid advisor to CureSearch for Children's Cancer; Dr Adamson is chair of the Children's Oncology Group; Dr Lo has personal investments in private biotech companies and is an advisor to BridgeBio Pharma, a director of Roivant Sciences and the MIT Whitehead Institute for Biomedical Research, and an overseer of Beth Israel Deaconess Medical Center.

Meeting Presentation: This paper was presented at the 2018 Annual Meeting of the American Society of Clinical Oncology (ASCO); June 2, 2018; Chicago, Illinois.

Disclaimer: The views and opinions expressed in this article are those of the authors only and do not necessarily represent the views and opinions of any institution or agency, any of their affiliates or employees, or any of the individuals acknowledged below.

Additional Contributions: Smita Bhatia, MD (University of Alabama at Birmingham); Jayna Cummings, MBA (MIT Laboratory for Financial Engineering); Tess Mattingly, BA, and Laura Thrall, MS (formerly with CureSearch for Children's Cancer); the CureSearch team; and attendees of

the 2017 CureSearch Catapult Summit provided helpful comments and discussion. Jayna Cummings, MBA (MIT Laboratory for Financial Engineering) provided editorial assistance. There was no financial compensation. Research support from the MIT Laboratory for Financial Engineering is acknowledged.

REFERENCES

- Vanchieri C, Butler AS, Knutsen S. *Addressing the Barriers to Pediatric Drug Development: Workshop Summary*. Washington, DC: National Academies Press; 2008.
- More support for clinical trials in children. *Nature*. 2016;535(7613):465-466.
- US Food and Drug Administration. The Drug Development Process—Step 3: Clinical Research. <https://www.fda.gov/ForPatients/Approvals/Drugs/ucm405622.htm>. Updated January 4, 2018. Accessed December 27, 2017.
- Sertkaya A, Wong H-H, Jessup A, Beleche T. Key cost drivers of pharmaceutical clinical trials in the United States. *Clin Trials*. 2016;13(2):117-126.
- Shukla N, Ameur N, Yilmaz I, et al. Oncogene mutation profiling of pediatric solid tumors reveals significant subsets of embryonal rhabdomyosarcoma and neuroblastoma with mutated genes in growth signaling pathways. *Clin Cancer Res*. 2012;18(3):748-757.
- Smith MA, Reaman GH. Remaining challenges in childhood cancer and newer targeted therapeutics. *Pediatr Clin North Am*. 2015;62(1):301-312.
- Thomas D, Wessel C. Emerging Therapeutic Co Investment and Deal Trends. <https://www.bio.org/sites/default/files/BIO%20Emerging%20Therapeutic%20Company%20Report%202007-2016.pdf>. Published June 2017. Accessed December 27, 2017.
- Fernandez J-M, Stein RM, Lo AW. Commercializing biomedical research through securitization techniques. *Nat Biotechnol*. 2012;30(10):964-975.
- BridgeBio. Targeting Genetic Diseases at Their Source. Who we are. <https://bridgebio.com/#about>. Published 2018. Accessed March 23, 2018.
- Ramsey L. A biotech company focused on inherited diseases just raised \$135 million from a bunch of Wall Street firms. *Business Insider*. <http://www.businessinsider.com/bridgebio-pharma-raises-135-million-from-private-equity-2017-9>. Published September 13, 2017. Accessed March 23, 2018.
- Roivant Sciences raises \$1.1 billion in equity investment led by SoftBank Vision fund. *Roivant Sciences*. <http://roivant.com/roivant-sciences-raises-1-1-billion-equity-investment-led-softbank-vision-fund/>. Published August 9, 2017. Accessed March 24, 2018.

12. UBS raises record \$471 million for oncology impact fund. MPM Capital. <http://www.mpmcapital.com/press/ubs-raises-record-471-million-oncology-impact-fund/>. Published April 27, 2016. Accessed March 23, 2018.
13. Lo AW, Ho C, Cummings J, Kosik KS. Parallel discovery of Alzheimer's therapeutics. *Sci Transl Med*. 2014;6(241):241cm5.
14. Boguski MS, Mandl KD, Sukhatme VP. Drug discovery. Repurposing with a difference. *Science*. 2009;324(5933):1394-1395.
15. SEER Cancer Statistics Review (CSR) 1975-2014. National Cancer Institute. https://seer.cancer.gov/csr/1975_2014/. Updated April 2, 2018. Accessed December 27, 2017.
16. Thomas DW, Burns J, Audette J, Carroll A, Dow-Hygelund CHM. 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 December 27, 2017.
17. Miller J. Profit on \$475,000 Novartis cancer drug could be a while coming. <https://www.reuters.com/article/us-novartis-fda-price/profit-on-475000-novartis-cancer-drug-could-be-a-while-coming-idUSKCN1BB2EA>. Published 2017. Accessed December 28, 2017.
18. Sagonowsky E. At \$475,000, is Novartis' Kymriah a bargain—or another example of skyrocketing prices? FiercePharma. <https://www.fiercepharma.com/pharma/at-475-000-per-treatment-novartis-kymriah-a-bargain-or-just-another-example-skyrocketing>. Published August 31, 2017. Accessed December 20, 2017.
19. Kaplan SN, Schoar A. Private equity performance: returns, persistence, and capital flows. *J Finance*. 2005;60(4):1791-1823.
20. Oroxom R, Glassman A, McDonald L. Structuring and funding development impact bonds for health: nine lessons from Cameroon and beyond. Washington; 2018. <http://www.cgdev.org>. Accessed March 21, 2018.
21. International Finance Facility for Immunisation. Overview. <http://www.iffim.org/about/overview/>. Accessed March 22, 2018.
22. Bowden A. Development Impact Bonds are Making Money While Doing Good. Conscious Co Media. <https://consciouscompanymedia.com/the-new-economy/development-impact-bonds-are-making-money-while-doing-good/>. Published April 4, 2015. Accessed March 22, 2018.
23. Fagnan DE, Fernandez JM, Lo AW, Stein RM. Can financial engineering cure cancer? *Am Econ Rev*. 2013;103(3):406-411.
24. I Care I Cure Foundation. Childhood Cancer Facts. website. <http://www.icareicure.org/get-informed/childhood-cancer-facts/>. Accessed December 27, 2017.
25. Research!America. US Investments in Medical and Health Research and Development Report, 2013-2015. <http://www.researchamerica.org/blog/us-investments-medical-and-health-research-and-development-report-2013-2015>. Published September 26, 2016. Accessed December 27, 2017.
26. Higgins RF, LaMontagne S, Kazan B. Vertex Pharmaceuticals and the Cystic Fibrosis Foundation: venture philanthropy funding for biotech. <https://www.hbs.edu/faculty/Pages/item.aspx?num=35037>. Updated July 2013. Accessed December 27, 2017.
27. Hinkes-Jones L. Stop Subsidizing Big Pharma. The New York Times. January 5, 2015.
28. Jarvis LM. Advancing R&D by venture philanthropy. *Chem Eng News*. 2012;90(45):14-18. <https://cen.acs.org/articles/90/i45/Advancing-RD-Venture-Philanthropy.html>. Accessed December 27, 2017.
29. National Cancer Institute. Browse the SEER Cancer Statistics Review (CSR) 1975-2012. https://seer.cancer.gov/archive/csr/1975_2012/browse_csr.php. Accessed December 27, 2017.
30. Fagnan DE, Gromatzky AA, Stein RM, Fernandez J-M, Lo AW. Financing drug discovery for orphan diseases. *Drug Discov Today*. 2014;19(5):533-538.
31. National Institute of Child Health and Human Development. Best Pharmaceuticals for Children Act (BPCA). 2002. <https://bpca.nichd.nih.gov/Pages/default.aspx>. Accessed May 3, 2018.