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Accelerating glioblastoma therapeutics via venture philanthropy

Kien Wei Siah [a,b,1], Qingyang Xu [a,c,1], Kirk Tanner [d], Olga Futer [d], John J. Frishkopf [d], Andrew W. Lo [a,b,c,e,*]

[a] MIT Laboratory for Financial Engineering, Cambridge, MA, USA
[b] MIT Department of Electrical Engineering and Computer Science, Cambridge, MA, USA
[c] MIT Operations Research Center, Cambridge, MA, USA
[d] National Brain Tumor Society, Newton, MA, USA
[e] Sante Fe Institute, Santa Fe, NM, USA

Development of curative treatments for glioblastoma (GBM) has been stagnant in recent decades largely because of significant financial risks. A portfolio-based strategy for the parallel discovery of breakthrough therapies can effectively reduce the financial risks of potentially transformative clinical trials for GBM. Using estimates from domain experts at the National Brain Tumor Society (NBTS), we analyze the performance of a portfolio of 20 assets being developed for GBM, diversified across different development phases and therapeutic mechanisms. We find that the portfolio generates a 14.9% expected annualized rate of return. By incorporating the adaptive trial platform GBM AGILE in our simulations, we show that at least one drug candidate in the portfolio will receive US Food and Drug Administration (FDA) approval with a probability of 79.0% in the next decade.

Keywords: Glioblastoma; Biomedical megafund; Adaptive clinical trial platform; Parallel drug discovery

Introduction

GBM is the most common and most lethal malignant primary brain tumor in the USA. It has a poor prognosis because of an unclear pathogenesis and a lack of curative treatments. A 2017 study reported that GBM accounted for 47.1% of primary malignant brain tumor incidence in the USA, while its 5-year relative survival rate was only 5.5%, significantly worse than the survival rate for all malignant brain and central nervous system tumors combined (34.9%) [1]. Under the current standard of care, comprising maximal surgical resection followed by chemoradiation [2], ~70% of patients with GBM experience recurrence within 1 year of diagnosis, and the median survival time is merely 14.4 months [3].

Developing curative treatments for GBM is an urgent social imperative. Nevertheless, it is financially risky because of a long investment horizon and a low probability of success. The financial risks of GBM drug development could be mitigated via the 'multiple shots on goal' strategy of a 'megafund' vehicle [4]. Instead of placing its entire stake into a single asset, a megafund invests in a sizable portfolio of clinical assets diversified across development stages and therapeutic mechanisms. The risk–return performance of such a portfolio can be made attractive to many private-sector investors. Furthermore, the parallel discovery approach increases the chance of producing breakthrough therapies for presently incurable diseases.

The megafund vehicle was originally proposed to finance translational research in oncology [4], and it was subsequently adapted to specific disease areas, such as orphan diseases [5], Alzheimer's disease (AD) [6], and ovarian cancer [7]. It is currently under consideration as a financing vehicle by NBTS, the largest

* *Corresponding author at: MIT Sloan School of Management, 100 Main Street, E62-618, Cambridge, MA 02142, USA.* Lo, A.W. (alo-admin@mit.edu)
[1] Co-first authors.

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nonprofit organization dedicated to advancing innovative treatments of brain tumors in the USA.

In this study, we demonstrate the viability of applying the megafund vehicle to finance drug development programs for GBM. Using estimates from the NBTS network of GBM experts and an extensive literature review, we perform Monte Carlo simulations to analyze the performance of such a megafund. We find that diversifying the portfolio across different stages of development and therapeutic mechanisms makes the risk–return profile attractive to a large group of investors in the private sector. Furthermore, we demonstrate the synergy between the megafund and the Glioblastoma Adaptive Global Innovative Learning Environment (GBM AGILE) [8,9] platform clinical trial program in simultaneously reducing the scientific and financial risks of developing innovative GBM therapies.

Simulation methods

In this study, we quantitatively demonstrate the synergy between a GBM megafund portfolio and an adaptive clinical trial platform in expediting the drug development process of GBM while achieving a risk–reward profile attractive to a wide group of financial investors. To this end, we analyze a hypothetical portfolio of 20 real-world GBM clinical trials (Table 1), selected by the NBTS network of experts in GBM drug development. By combining their domain expertise with an extensive literature review, we estimate the probability of success of each drug candidate, the correlations between clinical trial outcomes, and the revenue of a transformative GBM therapy. We also include the adaptive clinical trial platform GBM AGILE in our simulations of clinical trial developments of the assets of the portfolio. A detailed description of our assumptions and methodology is provided in the supplemental information online, and we have made the simulation software freely available online for readers to experiment with their own calibrations (please see https://projectalpha.mit.edu/resources).

Simulation results

The performance statistics of GBM megafund simulations are summarized in Table 2. The mixed-stage portfolio (row 1 in Table 2) illustrates the performance of the fund under the baseline assumptions specified in the supplemental information online. We find that its expected annualized return of 14.9% outperforms similar megafund portfolios for AD [6] and ovarian cancer [7] and, thus, it might attract a wide group of private-sector investors. Its net present value (NPV) is US$82 million, indicating that the megafund is likely to generate financial value for investors.

By contrast, this portfolio has a high volatility and large probabilities of loss and wipeout, a limitation imposed by the scientific challenges of GBM therapeutic innovation. Nonetheless, our simulation shows that, on average, more than two therapies financed by the megafund will receive FDA approval. There is a 79.0% probability that at least one therapy in the portfolio will receive FDA approval, and the average duration from the initial acquisition of the assets until the first FDA approval is 8.3 years.

To analyze the robustness of the simulation results against each model assumption, we perform sensitivity analyses on the acquisition strategy, the correlation structure, and the added value of biomedical expertise, as well as the effect of inclusion of portfolio assets in the GBM AGILE platform trial.

TABLE 1

Hypothetical GBM megafund portfolio of brain cancer therapeutics.[a,b]

Therapeutic area	Project	Patient population	Phase	GA	ODS	PP	TT
IMM	T cell activation	Recurrent GBM	II	Yes	Yes	No	Yes
			II	Yes	No	No	Yes
			II	Yes	Yes	No	Yes
	Personalized dendritic cell vaccine	Newly diagnosed GBM and HGGs	I	Yes	Yes	Yes	Yes
	Retroviral replicating vectors	HGG	Preclinical	No	Yes	Yes	Yes
	Oncolytic virus	Recurrent GBM	Preclinical	Yes	Yes	No	Yes
	Autologous tumor cell vaccine	Newly diagnosed GBM	II	Yes	Yes	No	Yes
DDR	DNA-PK inhibitor	Newly diagnosed uMGMT GBM	II	Yes	Yes	No	Yes
	ATM inhibitor	Newly diagnosed uMGMT GBM	II	Yes	Yes	No	Yes
		Pediatric gliomas	Preclinical	No	Yes	Yes	Yes
	FGFR inhibitor	Recurrent GBM	II	Yes	Yes	No	Yes
	DNA repair inhibitors	Newly diagnosed uMGMT GBM	Preclinical	No	Yes	No	No
	ATR inhibitor	Newly diagnosed GBM	II	Yes	Yes	No	Yes
TM	LPCAT1 inhibitor	Newly diagnosed and recurrent GBM	Preclinical	No	Yes	No	No
PM	DRD2 receptor antagonist	Recurrent GBM with EGFR-low and DRD2-high tumor phenotype	II	Yes	Yes	Yes	Yes
	BBB-penetrant signaling inhibitor	Newly diagnosed GBM	Preclinical	Yes	Yes	No	No
	CRISPR-Cas9 gene editing	Newly diagnosed and recurrent GBM	Preclinical	Yes	Yes	No	Yes
	BBB-penetrant transcription factor inhibitor	Newly diagnosed GBM	Preclinical	Yes	Yes	No	No
		Brain metastases	Preclinical	Yes	Yes	No	No
DE	Fluorescence-guided surgery	Brain tumor	II	No	Yes	No	No

[a] We assume that projects targeting pediatric patients are eligible for priority review vouchers.

[b] Abbreviations: ATM, ataxia-telangiectasia mutated; ATR, ataxia telangiectasia and Rad3-related protein; BBB, blood–brain barrier; DDR, DNA damage repair; DE, devices; DNA-PK, DNA-dependent protein kinase; DRD2, dopamine receptor D2; EGFR, epidermal growth factor receptor.; FGFR, fibroblast growth factor receptor; GA, eligibility for GBM AGILE; HGG, high-grade gliomas; IMM, immunotherapy; LPCAT1, lysophosphatidylcholine acyltransferase 1; ODS, eligibility for orphan drug status; PM, precision medicine; PP, target pediatric patients; TM, tumor metabolism; TT, transformative treatment; uMGMT, unmethylated O6-methylguanine DNA methyltransferase.

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TABLE 2

Performance of GBM megafund portfolio.[a]

Portfolio	E[R_a]	SD[R_a]	E[NPV]	SD[NPV]	E[N_a]	SD[N_a]	E[T_a]	SD[T_a]	PoL	PoW
Baseline	14.9% p.a.	24.3%	82	776	2.2	2.0	8.3	1.7	25.7%	21.0%
Preclinical	11.5% p.a.	26.3%	−20	399	1.5	1.6	11.5	0.9	37.1%	33.7%
$\rho = 0\%$	17.4% p.a.	18.6%	82	576	2.2	1.4	8.2	1.6	14.3%	9.5%
$\rho = 10\%$	16.1% p.a.	21.4%	82	670	2.2	1.7	8.2	1.6	19.8%	14.8%
$\rho = 40\%$	12.1% p.a.	29.1%	82	955	2.2	2.5	8.2	1.6	35.1%	30.4%
$\rho = 80\%$	4.4% p.a.	42.7%	84	1416	2.2	3.8	8.1	1.5	56.6%	53.6%
$\alpha_{skill} = 1$	12.9% p.a.	25.0%	19	741	2.0	1.9	8.3	1.7	29.2%	24.8%
$\alpha_{trans} = 1$	8.7% p.a.	19.3%	–61	434	2.2	2.0	8.3	1.7	31.6%	21.0%
$r_{mkt} = 10\%$	6.4% p.a.	17.5%	−94	375	2.2	2.0	8.3	1.7	32.8%	21.0%
$r_{mkt} = 30\%$	18.1% p.a.	27.0%	168	1184	2.2	2.0	8.3	1.7	24.4%	21.0%

[a] E[R_a] denotes expected annualized return of the megafund portfolio and SD[R_a] its standard deviation; NPV denotes net present value, in millions of US$; N_a and T_a denote the number of approved assets and time until the first FDA approval, respectively; PoL indicates the probability of loss (negative return) and PoW the probability of wipeout (all projects fail). In equicorrelated portfolios, ρ denotes the correlation between each pair of therapies; p.a. indicates per annum. The baseline portfolio assumes skill and access factor $\alpha_{skill} = 1.25$, transformative factor $\alpha_{trans} = 2$, market penetration $r_{mkt} = 20\%$ and correlation derived from estimates by NBTS network of experts. Results are computed with 1 million Monte Carlo simulations.

Early-stage versus mixed-stage

The performance of the portfolio hinges on its diversification. To gauge the effect of diversifying the assets across different stages of development, we simulate a comparison portfolio (row 2 in Table 2) with the same drug development programs, but acquiring all its assets at their preclinical stage. Preclinical acquisition requires an average investment of only US$673 million, much lower than the US$1.037 billion of the mixed-stage portfolio, because market valuations are based on lower probabilities of success and longer investment horizons. However, a lack of diversification across different development stages significantly increases the risk that no therapy in the portfolio will receive FDA approval, leading to a 3.4 percentage point decrease in its expected annualized return, an 11.4 and 12.7 percentage point increase in its probabilities of loss and wipeout, respectively, and a negative NPV. It also delays the expected time until the first approved drug by 3.2 years. We conclude that, to ensure an attractive risk–return profile of the megafund, it is crucial to structure the portfolio with assets acquired in different stages of development.

Qualitative correlation versus equicorrelation

The volatility of the portfolio is largely determined by the correlation structure of the drug development programs in the portfolio. It is reasonable to expect that drugs with similar therapeutic mechanisms are highly correlated, leading to greater volatility. We simulate portfolios where the correlation, ρ, between any two distinct assets is the same, and set to 0, 10%, 40%, and 80%, respectively (rows 3 to 6 in Table 2). We find that the expected annual return decreases for higher correlation, whereas all risk measures (probability of loss and wipeout, volatility of annual return) increase.

The correlation structure of our mixed-stage portfolio is based on the qualitative assessment of program similarity by domain experts (see supplemental information 4 online). Although certain groups of drugs in the portfolio are highly correlated because of similar therapeutic mechanisms, diversification across different therapeutic mechanisms can lower the overall correlation to the equivalent of a uniform correlation between 10% and 40%.

Skill and access factor

There is an intrinsic limitation on GBM megafund performance because of scientific challenges of developing curative treatments for GBM. The financial viability of the GBM megafund relies on the assumption that biomedical experts are skilled at identifying promising drug candidates. This boost in probability of success is modeled by the skill and access factor, α_{skill}, which is set to 1.25. Reducing α_{skill} to 1 (implying no incremental improvement in the probability of success above the industry average), decreases the expected annualized return by 2.0 percentage points and increases the probabilities of loss and wipeout by 3.5 and 3.8 percentage points, respectively (row 7 in Table 2). The expected NPV also decreases to less than a quarter of its original value. The sensitivity of megafund performance to α_{skill} reveals the importance of biomedical expertise in active management of the portfolio.

Transformative factor

Our simulation also assumes that domain experts can identify potentially transformative therapies that, once approved, will become the standard of care for GBM, thus generating higher revenue than palliative therapies. This boost in future revenue for transformative therapies is modeled by the transformative factor, α_{trans}, which is set to 2. Reducing α_{trans} to 1 yields a 6.2 percentage point decrease in the expected annualized return, and a 5.9 percentage point increase in the probability of loss (row 8 in Table 2). Furthermore, the expected NPV becomes negative, which indicates that the ability to identify transformative therapies significantly impacts the market valuation of the portfolio.

Market penetration rate

A key factor in determining the revenue of the GBM megafund is the market penetration rate of an FDA-approved therapy (i.e., the proportion of the target patient population who will receive this therapy once it enters the market). Our baseline model assumes that the maximum market penetration rate of any approved asset, r_{mkt}, is 20%. This estimate is likely conservative, because no curative treatment for GBM is currently available. However, once a transformative therapy receives FDA approval, it is expected to become the new standard of care and might acquire a market share well above 20%.

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Boosting r_{mkt} to 30% increases the expected annualized return by 3.2 percentage points and doubles the expected NPV (row 9 in Table 2). However, reducing r_{mkt} to 10% decreases the expected annualized return by more than half, and the expected NPV becomes negative (row 10 in Table 2). The impact of the market penetration rate on the expected return illustrates the significant potential for the biopharma industry to develop high-risk yet truly transformative therapies for presently incurable diseases such as GBM.

Quantiles of annualized return and NPV

We report the 25%, 50%, and 75% quantiles of the annualized return and NPV in Table 3 to measure the volatility of the megafund portfolio. We note that, whereas the median of annualized return (column 4) closely tracks its mean value (column 1), the median NPV (column 9) is significantly lower than its mean value (column 6), and is negative for all simulated portfolios except for those with zero correlation (row 3), the portfolio with minimum volatility. The histogram of the NPV of the baseline portfolio (Fig. 1) reveals a bimodal distribution with a heavy right tail. The probability of a negative NPV is 54.9%, whereas the probabilities of an NPV above US$100 million and US$1 billion are 40.4% and 12.7%, respectively. The GBM megafund portfolio necessarily involves large volatility, reflecting not only the inherent scientific challenges to develop an effective therapy for GBM, but also the considerable revenue once an effective therapy is approved.

Impact of GBM AGILE

The GBM megafund and GBM AGILE share the same 'multiple shots on goal' strategy and have complementary goals: the former facilitates the financing of drug development programs, whereas the latter expedites the clinical trial process. The simulated megafund portfolio includes 15 out of its 20 assets eligible for GBM AGILE. Through detailed modeling of the GBM AGILE platform, we find that the combination of these two novel models generates significant synergy, accelerating the development of innovative therapeutics for GBM. The impact of GBM AGILE on the megafund performance is summarized in Table 4.

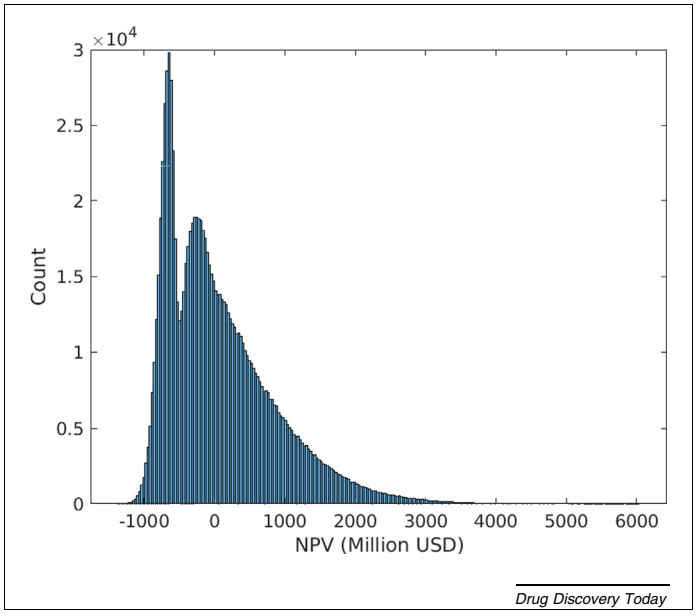

FIGURE 1

Histogram of net present value (NPV) of the baseline portfolio. The baseline portfolio (row 2 of Table 1 in the main text) has a bimodal distribution of NPV with a heavy right tail, which suggests that the megafund involves both significant risks of financial loss (left peak with negative NPV) and considerable financial returns once a drug candidate is approved (right tail with large positive NPV). Histogram is generated with 1 million Monte Carlo simulations. NPV is measured in units of million US$.

Probability of inclusion

Each eligible asset in the megafund portfolio, upon successful completion of its Phase I trial, has a probability p_{inc} to be included in stage 1 of GBM AGILE. The decision to include an asset is based on multiple factors, including its Phase I results, the current number of experimental arms in the platform, and the expertise of the NBTS network of experts in selecting drug candidates with promising enrichment biomarkers. Our baseline model assumes a $p_{inc} = 33\%$. Varying p_{inc} from 0 to 66% (rows 2 to 5 in Table 4), we find that the expected annualized return increases by 7.4 percentage points, the probability of loss and wipeout decrease by 5.6 and 3.8 percentage points, respectively, and the expected time until first approval shortens by 1 year. In

TABLE 3

Quantiles (25%, 50%, 75%) of annualized return (R_a) and net present value (NPV).[a]

Portfolio	E[R_a]	SD[R_a]	25% Qt.	50% Qt.	75% Qt.	E[NPV]	SD[NPV]	25% Qt.	50% Qt.	75% Qt.
Baseline	14.9% p.a.	24.3%	−0.7%	14.4%	30.7%	82	776	−551	−98	499
Preclinical	11.5% p.a.	26.3%	−14.2%	10.5%	28.9%	−20	399	−311	−128	179
$\rho = 0\%$	17.4% p.a.	18.6%	5.4%	17.1%	29.4%	82	576	−345	17	441
$\rho = 10\%$	16.1% p.a.	21.4%	3.0%	15.9%	30.0%	82	670	−424	−34	470
$\rho = 40\%$	12.1% p.a.	29.1%	−14.2%	10.2%	30.6%	82	955	−622	−214	492
$\rho = 80\%$	4.4% p.a.	42.7%	−26.6%	−14.2%	26.4%	84	1416	−677	−547	289
$\alpha_{skill} = 1$	12.9% p.a.	25.0%	−4.9%	12.4%	29.1%	19	741	−586	−158	407
$\alpha_{trans} = 1$	8.7% p.a.	19.3%	−3.1%	9.0%	21.5%	−61	434	−392	−147	180
$r_{mkt} = 10\%$	6.4% p.a.	17.5%	−4.0%	6.8%	17.7%	−94	375	−369	−170	106
$r_{mkt} = 30\%$	18.1% p.a.	27.0%	0.8%	16.9%	35.7%	168	1184	−806	−115	809

[a] E[R_a] denotes expected annualized return of the megafund portfolio and SD[R_a] its standard deviation; NPV denotes net present value, in millions of US$; Qt denotes quantile. The quantiles show large deviations in both annualized return and NPV from their mean values. In particular, the median (50% Qt.) NPV is negative for all megafund portfolios except the one with zero correlation (row 3). We also note that the significant risks of financial loss are compensated by the attractive annualized return and NPV values at the 75% Qt. Results are computed with 1 million Monte Carlo simulations.

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TABLE 4

Impact of GBM AGILE on megafund portfolio performance.[a]

Portfolio	E[R_a]	SD[R_a]	E[NPV]	SD[NPV]	E[N_a]	SD[N_a]	E[T_a]	SD[T_a]	PoL	PoW
Baseline	14.9% p.a.	24.3%	82	776	2.2	2.0	8.3	1.7	25.7%	21.0%
$p_{inc} = 0\%$	11.5% p.a.	22.3%	–40	712	2.2	2.0	8.9	1.3	28.6%	23.0%
$p_{inc} = 16\%$	13.1% p.a.	23.1%	20	743	2.2	2.0	8.6	1.5	27.1%	22.0%
$p_{inc} = 50\%$	16.9% p.a.	25.6%	147	809	2.2	2.0	8.1	1.7	24.2%	20.0%
$p_{inc} = 66\%$	18.9% p.a.	27.0%	205	835	2.3	2.0	7.9	1.7	23.0%	19.2%
$v_{mon} = 20$	14.5% p.a.	23.6%	31	713	2.2	2.0	8.9	1.4	25.5%	20.9%
$v_{mon} = 40$	15.1% p.a.	24.6%	114	817	2.2	2.0	8.0	1.9	25.6%	20.9%
$v_{mon} = 50$	15.3% p.a.	24.8%	134	843	2.2	2.0	7.8	2.1	25.5%	20.9%

[a] E[R_a] denotes expected annualized return of the megafund portfolio and SD[R_a] its standard deviation; NPV denotes net present value, in millions of US$; N_a and T_a denote the number of approved assets and time until the first FDA approval, respectively; PoL indicates the probability of loss (negative return) and PoW the probability of wipeout (all projects fail); p_{inc} denotes the probability that each eligible asset is included in GBM AGILE; v_{mon} denotes the monthly patient accrual rate into the GBM AGILE platform. The baseline portfolio assumes $p_{inc} = 33\%$ and $v_{mon} = 30$ patients per month. If assets in the megafund portfolio are more likely to be included in GBM AGILE (larger p_{inc}) or more patients are enrolled in the adaptive trial platform each month (larger v_{mon}), the GBM megafund achieves a higher annualized return and NPV and lower risks for financial loss and wipeout. Results are computed with 1 million Monte Carlo simulations.

the absence of GBM AGILE ($p_{inc} = 0$), the expected NPV of the portfolio becomes negative, indicating that the megafund will not generate financial value for the investors. Having more assets included in the GBM AGILE platform boosts the annualized return and NPV of the portfolio, reduces its risks, and accelerates the advent of transformative GBM therapies.

Monthly patient accrual

Another crucial factor of GBM AGILE is the monthly patient accrual rate into the platform. A lower accrual rate delays the completion of stage 1 and 2 investigations and lowers the NPV because of longer investment horizons. We assume an accrual rate $v_{mon} = 30$ patients per month in our baseline model. This is a relatively conservative estimate, because GBM AGILE might recruit patients in the USA, Canada, China, Europe, and Australia. Increasing v_{mon} to 40 and 50 patients per month (rows 7 to 8 in Table 4) increases the expected NPV of the megafund from US$82 million to US$114 million and US$134 million, respectively, and shortens the expected time until first approval from 8.3 years to 8.0 and 7.8 years, respectively. By contrast, reducing v_{mon} to 20 patients per month (rows 6 in Table 4) lowers the expected NPV to US$31 million, and extends the expected time until first approval from 8.3 to 8.9 years. The success of the GBM megafund hinges crucially on the steady accrual of new patients to support the speedy completion of stages 1 and 2 of GBM AGILE.

Discussion

The development of transformative therapeutics for GBM has been largely unsuccessful not only because of the inherent scientific challenges of development, but also because of the significant financial risks of investing in early-stage clinical programs. The performance of a GBM megafund might attract a wide group of investors from both the public and private sectors, especially if it has a suitably diversified portfolio managed by domain experts.

In addition, the use of the novel GBM AGILE platform generates significant synergy with the megafund. Inclusion of portfolio assets in the platform boosts its annualized return and NPV, reduces its risks, and expedites the ultimate delivery of transformative GBM therapies, making it more attractive to private-sector investors. The GBM AGILE platform also provides a financially efficient means to collect valuable clinical data for a therapeutic asset to guide its subsequent development in clinical trials, even if the therapy does not meet the criteria to enter stage 2 of the platform.

In our simulations, we assume that enough capital exists to finance the entire portfolio through all stages of development. In practice, it might be difficult for nonprofit organizations, such as NBTS, to raise nearly US$1.5 billion at the outset. To address this issue, the fund could consider a mixture of equity and debt in its capital structure and adjust the leverage dynamically as the clinical trials progress into later stages [10]. Under a tight budget constraint, it might also be necessary to acquire drug development programs dynamically, liquidating some projects during intermediary development to fund more promising ones. Our simulation results can be regarded as an upper bound on the performance of a GBM megafund in practice.

Concluding remarks

Developing curative treatments for GBM is an urgent social imperative. However, the high development costs, long investment horizons, and significant risks of failure in the clinical trial process have prevented private-sector investors from investing in GBM drug development programs to treat this disease. Here, we demonstrate the potential viability of the megafund vehicle to finance a portfolio of 20 GBM drug development programs. Through the appropriate diversification of the portfolio across different stages of development and therapeutic mechanisms, while simultaneously leveraging the novel GBM AGILE platform to improve development outcomes, the risk–reward profile of such a megafund should interest many private-sector investors.

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salaried by their institutions during the period of writing, though no specific salary was set aside or given for the writing of this manuscript. 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 above.

Declaration of interests

J.F. is the treasurer and a board member of NBTS and also a board member of the Global Coalition for Adaptive Research, a non-profit organization that sponsors and manages GBM AGILE. He receives no compensation for either of these roles. J.F. is a partner of QLS Advisors, a healthcare analytics and consulting company. A.L. has advised NBTS on a pro bono basis on potential financing strategies, and has not received any form of financial compensation or support from NBTS or any other entity for this case study, nor does he have any financial interest in NBTS, its affiliates, or any of its current investments. A.L. reports personal investments in public and private biotech companies, biotech venture capital funds, and mutual funds. A.L. is a cofounder and partner of QLS Advisors, a healthcare analytics and consulting company; an advisor to BrightEdge Ventures; a director of BridgeBio Pharma, Roivant Sciences, Atomwise, and Annual Reviews; chairman emeritus and senior advisor to AlphaSimplex Group; and a member of the Board of Overseers at Beth Israel Deaconess Medical Center and the NIH's National Center for Advancing Translational Sciences Advisory Council and Cures Acceleration Network Review Board. During the most recent six-year period, A. L. has received speaking/consulting fees, honoraria, or other forms of compensation from: AIG, AlphaSimplex Group, BIS, BridgeBio Pharma, Citigroup, Chicago Mercantile Exchange, Financial Times, FONDS Professionell, Harvard University, IMF, National Bank of Belgium, Q Group, Roivant Sciences, Scotia Bank, State Street Bank, University of Chicago, and Yale University. Q.X. reports personal investments in publicly-traded pharmaceutical companies.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.drudis.2021.03.020.

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