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A PORTFOLIO APPROACH TO ACCELERATE THERAPEUTIC INNOVATION IN OVARIAN CANCER

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We consider a portfolio-based approach to financing ovarian cancer therapeutics in which multiple candidates are funded within a single structure. Twenty-five potential early-stage drug development projects were identified for inclusion in a hypothetical portfolio through interviews with gynecological oncologists and leading experts, a review of ovarian cancer-related trials registered in the ClinicalTrials.gov database, and an extensive literature review. The annualized returns of this portfolio were simulated under a purely private sector structure both with and without partial funding from philanthropic grants, and a public–private partnership that included government guarantees. We find that public–private structures of this type can increase expected returns and reduce tail risk, allowing greater amounts of private sector capital to fund early-stage research and development.

1 Introduction

Ovarian cancer is one of the most lethal gynecologic malignancies worldwide, with approximately 239,000 new cases and 152,000 deaths annually (Reid *et al.*, 2017). The current standard of care involves cytoreductive surgery (i.e., tumor removal) followed by chemotherapy. This can provide patients with months to years

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of progression-free survival. However, a majority of ovarian cancer patients relapse after this first-line treatment, resulting in a 5-year relative survival rate of less than 50% (Baldwin *et al.*, 2012). Despite this unmet medical need, there have been relatively few significant advances in ovarian cancer treatment in the past decade.

Several clinical and scientific factors have made therapeutic innovation in ovarian cancer challenging. An asymptomatic early-stage presentation makes screening for the disease difficult. As a result, 70% of patients are diagnosed with advanced stage disease (Cortez *et al.*, 2017). In addition, the heterogeneity of tumor subtypes in ovarian cancer poses a considerable scientific challenge to its treatment. The unique histopathology, morphology, and genomic alterations of each subtype may require the development of multiple treatments, each involving a distinct mechanism of action (Prat, 2012). For example, PARP inhibitors have recently been used in addition to chemotherapy to increase treatment effectiveness. However, PARP inhibitors are most effective for women who have the BRCA 1 or BRCA 2 mutation, which make up only 15% of ovarian cancer diagnoses (Pal *et al.*, 2005).

These technical challenges are compounded by the fact that ovarian cancer receives disproportionately less public funding relative to other diseases. For example, as measured by its National Cancer Institute funding-to-lethality score, ovarian cancer received an average of only $97,000 in funding per years of life lost per 100 new cases, one-nineteenth of the amount allocated to either prostate or breast cancer (Spencer, 2019). Moreover, private investors are not incentivized to bridge this funding gap because of the substantial costs, long time horizon, and low success rates associated with these projects. However, by investing in many programs simultaneously, a "multiple shots-on-goal" approach can reduce the risk of both scientific failure and financial loss (Fernandez *et al.*, 2012).

In this paper, we demonstrate that both the dearth of funding and the need for multiple therapies to treat this heterogeneous disease can be addressed by a public–private portfolio approach. Similar to Das *et al.*'s (2018) analysis of pediatric oncology therapeutics, we simulate the financial performance of a portfolio of ovarian cancer projects, and show that, in combination with public funding, this framework can mitigate the downside risk associated with early-stage projects, thus increasing their attractiveness to private capital. Moreover, this approach would enable development programs to be undertaken simultaneously instead of in sequence, ultimately accelerating the rate of therapeutic innovation.

2 Methods

Fernandez *et al.* (2012) illustrate the benefits of a portfolio approach applied to biomedical research and development. In their analysis, Monte Carlo simulation is used to assess the financial returns of a hypothetical portfolio of cancer therapeutics. In this article, we extend their analysis to model the returns of an ovarian-cancer-specific portfolio. These simulations are calibrated by specifying six key factors: the portfolio constituents, the clinical trial success probabilities and correlations, the trial costs and durations for each phase, and the profitability of a successful compound. Table 1 summarizes the baseline assumptions used in these simulations. Readers are encouraged to rerun our simulations with their own preferred set of inputs using our open-source simulation software, which is described in detail in, and can be accessed through, the online Appendix.

2.1 Portfolio constituents

A portfolio of ovarian cancer therapeutics should cover a variety of research programs to maximize

Table 1 Summary of simulation assumptions.

Parameter	Assumed value
Number of assets	25
Cost of drug development from P1 to APP	$296 million per project
Duration of clinical development	10.3 years
Economic value of an approved drug	$2.1 billion
Probability of success from P1 to APP	12.6%
Correlation between project outcomes	Pairwise correlations are assigned values of 10%, 25%, 75%, or 90%, as assessed by ovarian cancer scientists and physicians

Additional details are described in this section and the online Appendix. P1 indicates phase 1; APP indicates regulatory approval.

the benefits of diversification while maintaining an attractive expected return. Well-developed and promising avenues of research would be allocated relatively more funding in the portfolio, while more speculative hypotheses might only include one project until more evidence is proven. For example, research programs involving PARP inhibitors, anti-angiogenesis agents, immunotherapy, or molecular-targeted therapies involving P53 might consist of multiple projects within this portfolio.

In practice, these decisions would be made by a team of medical experts and portfolio managers exercising scientific and business judgment developed through years of domain-specific experience. For our purposes, we identified promising pathways based on interviews with gynecological oncologists and leading experts, a review of ovarian cancer-related trials registered in the ClinicalTrials.gov database, and an extensive literature review. Each pathway is based on an actual project investigating a target specific to ovarian cancer. This process yielded 25 hypothetical projects, which are listed in Table 2.

2.2 *Probability of success*

We used the clinical success rates reported by Wong *et al.* (2018) to estimate the probability of success for oncology-specific lead indications. These estimates were then adjusted downwards by 15% to account for the historical observation that ovarian cancer compounds tend to fail clinical trials at a higher rate relative to the average cancer compound (Thomas *et al.*, 2016). Our simulation assumes the following probabilities of success: 66.9% for phase 1, 45.8% for phase 2, 43.3% for phase 3, and 95.2% for New Drug Application (NDA) or Biologics License Application approval. These figures combine to give an overall 12.6% probability of success from phase 1 to FDA approval.

2.3 *Correlation*

The success or failure of a single project in the portfolio is likely correlated to that of another project in the portfolio. Therefore, to quantify the level of risk reduction achieved by diversification, we estimate the pairwise correlations between the 300 ($25 \times 24/2$) unique pairs of projects in the portfolio. These correlations were qualitatively assessed as low, low–medium, medium–high, or high by physicians, and these labels were assigned numerical values of 10%, 25%, 75%, 90%, respectively. Figure 1 shows a heat map of the correlations, which was then translated to the nearest positive definite matrix (Qi and Sun, 2006). For

Table 2 Twenty-five potential ovarian cancer therapeutic projects.

Category	Projects
PARP inhibitors	BRCA 1/2 mutations, treatments
	Non-BRCA 1/2 mutations, other HRD (homologous repair deficiencies) treatments
	Non-BRCA 1/2 mutations, non-HRD treatments
Angiogenesis inhibitors	VEGF inhibitors
	VEGF receptor inhibitors
	Angiopoietin inhibitors
Checkpoint inhibitors	PD-1/PD-L1 inhibitors
	CTLA-4 inhibitors
P53 targeting	Conversion of mutant P53 to wildtype P53
	Prevention of P53 degradation
	Gene therapy delivering wildtype P53
c-MYC targeting	c-MYC silencing in platinum-resistant ovarian cancer
Folate receptor α	Antibody to target Frα
	Antibody–drug conjugate to deliver drug
	Folate conjugates
Therapeutic vaccines	Dendritic cell vaccines
	Peptide/protein-based vaccines
	Genetic vaccines
	Epigenetic vaccines
Low-grade serous therapies	MEK inhibitors
	mTor pathway inhibitors
Other therapies	FAK inhibitors targeting cancer stem cells
	RNA polymerase II transcription inhibitor
	LncRNAs and MicroRNA
	CAR-T cell therapy

completeness, we also simulate the performance of our portfolio using an equicorrelation matrix. Implementation details are provided in the online Appendix.

2.4 Trial costs and duration

For compounds in clinical phases, Paul *et al.* (2010) provide estimates of the cost of development at each stage. We adjust these costs from 2008 dollars to 2018 dollars using the Biomedical Research and Development Price Index (BRDPI). Finally, the average duration for each phase transition was calibrated to match Fernandez *et al.* (2012). Development costs and durations are reported in Table 3.

2.5 Profitability of a successful compound

To analyze the performance of an ovarian cancer portfolio, we must estimate the total economic value of a single successful compound. Previous megafund simulations have estimated the net present value of all estimated future cash flows

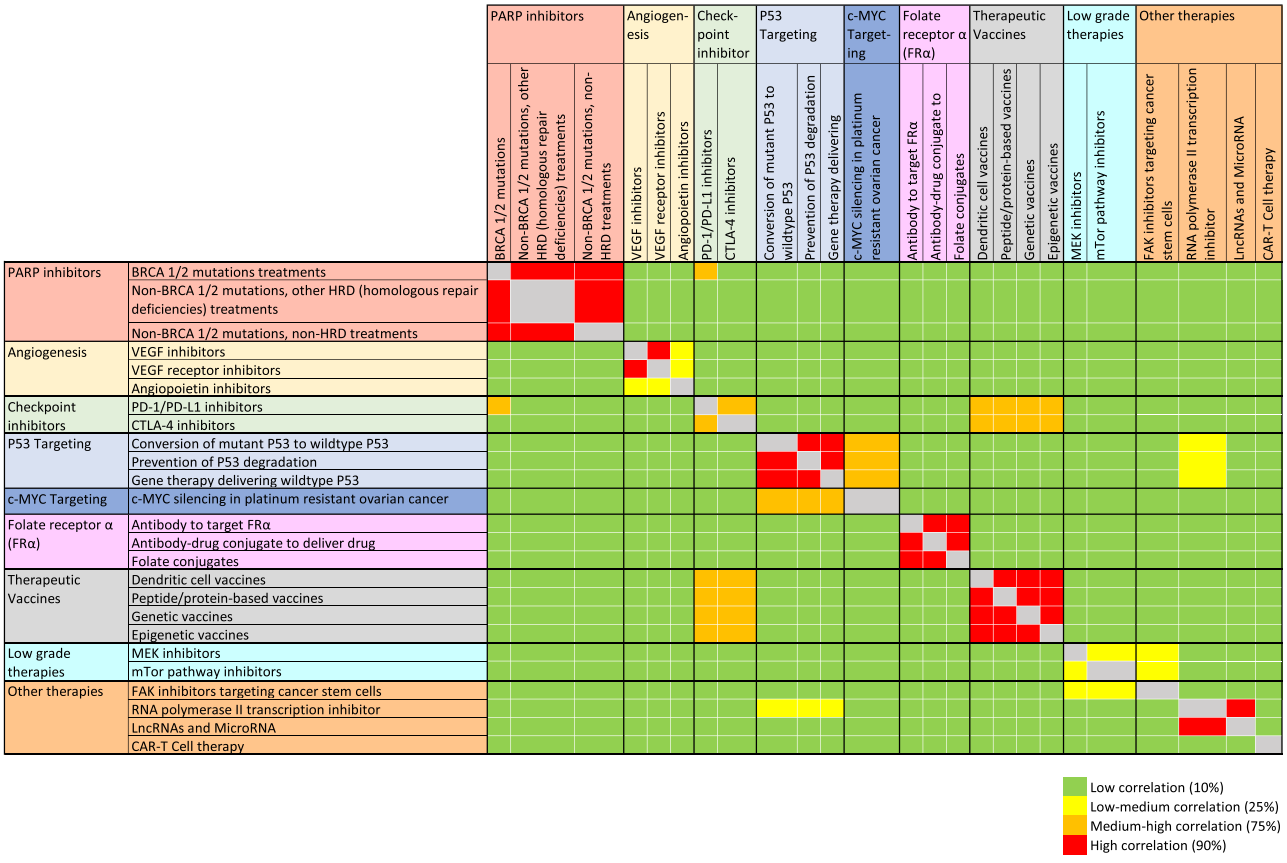

Figure 1 Correlation matrix of ovarian cancer projects. Heat map representation of pairwise correlation among 25 hypothetical ovarian cancer therapeutic projects (as assessed by gynecologists and ovarian cancer scientists). Red indicates high correlation (90%), orange indicates medium–high correlation (75%), yellow indicates low–medium correlation (25%), and green indicates low correlation (10%).

Table 3 Average trial costs and duration by development phase.

	Phase 1 to 2	Phase 2 to 3	Phase 3 to NDA	NDA to approval
Cost ($MM)	23	61	212	–
Duration (months)	31.2	38.6	39.6	13.8

upon FDA approval (Lo *et al.*, 2014; Das *et al.*, 2018). However, in this analysis, we estimate the economic value of a successful compound as a multiple of its projected peak revenues. This technique is commonly used by industry professionals to analyze risky early-stage biotech assets where future cash flows are difficult to forecast precisely. To implement this approach, we analyzed the revenues from a set of 86 ovarian cancer-specific compounds in the Cortellis database. Using a 4-fold increase in value-to-peak sales, a ratio suggested by industry experts as a conservative valuation, we obtained an average valuation estimate of $2.1 billion. We perform sensitivity

analyses by recomputing our simulations using value-to-peak sales ratios between 2 and 6.

3 Results

Similar to the analysis in Das *et al.* (2018), we evaluate three types of funding structures: a purely private sector fund, a private sector fund supported by philanthropic grants, and a public–private partnership backed by government guarantees. We simulate these funding structures using early-stage phase 1 assets only and a 60:40 mix of phase 1 and phase 2 assets. Our goal is to determine the economic viability of these funds to support ovarian cancer therapeutic development.

3.1 Private sector investment

As a baseline, we first determine the economic viability of an early-stage asset portfolio funded entirely through the private sector. The estimated expected annualized returns[1] ($E[R_a]$), probability of loss (PoL), and expected shortfall at the 25% level ($ES_{25\%}$) — a measure of tail risk that measures the expected cumulative return on the portfolio in the worst 25% of cases — are reported in panel 1 of Table 4 for different assumptions of pairwise correlations and profitability. In particular, we consider equicorrelation matrix entries ranging from 0% to 80% and value-to-peak sales ratios between 2 and 6.

As expected, the top-performing portfolio occurs when the underlying projects are mutually uncorrelated and the value-to-peak sales multiplier is 6. In this best-case scenario, the fund yields a positive expected annualized return of 19.4% per annum and PoL of 6.6%. Such a fund achieves an attractive rate of return, but the result requires the unrealistic assumption of uncorrelated outcomes between any two projects in the portfolio and an optimistic valuation. This extreme scenario must be compared against the performance achieved under higher correlations and lower valuations. For example, in the most realistic case, using qualitatively calibrated correlations based on expert opinion and a value-to-peak sales multiplier of 4, the portfolio yields an expected annualized return of 8.5% per annum, a PoL of 31.4%, and $ES_{25\%}$ of –80.3%. This large tail risk suggests that an ovarian cancer fund financed using only private capital is unlikely to be attractive to investors. Even when the multiplier is increased to 6, the expected cumulative return on the portfolio in the worst 25% of cases is –70.5%.

One key factor that contributes to the unattractive risk–reward profile of this private sector fund is the fact that the portfolio consists only of early-stage phase 1 assets. Since the cumulative probability of an ovarian cancer therapy's approval from pre-phase 1 status is only 12.6%, it is not surprising that this fund has substantial downside risk. To mitigate this risk, we consider mixed-phase portfolios in which later-stage assets are included in the portfolio. These later-stage assets increase the probability of developing multiple successful candidates, and therefore increase expected returns and decrease risk.

We simulate an early-stage weighted portfolio which contains a 60:40 ratio of phase 1 and 2 assets, respectively. We also include acquisition costs for phase-2-ready assets of $23 million, which is estimated by weighting the average value of an approved compound by the phase transition probabilities, and discounting at a per annum rate of 10% for the NDA to Market phase, 12.5% for phase 3 to NDA, and 17.5% for earlier phases to reflect the higher risk of early-stage projects. The results for this purely private sector, mixed-phase fund are reported in panel 4 of Table 4.

Diversifying the portfolio by including assets ready for phase 2 increases the performance of the fund considerably. For example, in the qualitatively calibrated correlation scenario with a

Table 4 Performance statistics for each simulated portfolio with respect to different correlation (ρ) levels and value-to-peak sales valuations upon regulatory approval.

Value to-sales	$\rho = 0\%$			$\rho = 40\%$			$\rho = 80\%$			$\rho =$ Qualitative		
	$E[R_a]$	PoL	$ES_{25\%}$	$E[R_a]$	PoL	$ES_{25\%}$	$E[R_a]$	PoL	$ES_{25\%}$	$E[R_a]$	PoL	$ES_{25\%}$
Panel 1: Purely private sector fund, *N=25* early-stage assets												
2x	0.0% p.a.	50.7%	−58.7%	−1.2% p.a.	60.9%	−99.8%	−3.0% p.a.	72.2%	−100.0%	−0.6% p.a.	56.4%	−90.2%
3x	4.8% p.a.	24.2%	−38.0%	3.1% p.a.	46.6%	−99.7%	0.4% p.a.	66.4%	−100.0%	3.9% p.a.	39.9%	−85.3%
4x	9.7% p.a.	15.2%	−17.4%	7.3% p.a.	38.7%	−99.6%	3.8% p.a.	63.4%	−100.0%	8.5% p.a.	31.4%	−80.3%
5x	14.5% p.a.	11.5%	3.3%	11.6% p.a.	33.2%	−99.5%	7.2% p.a.	60.0%	−100.0%	13.1% p.a.	25.8%	−75.4%
6x	19.4% p.a.	6.6%	23.9%	15.9% p.a.	29.9%	−99.4%	10.5% p.a.	58.7%	−100.0%	17.6% p.a.	22.1%	−70.5%
Panel 2: Philanthropic grants & private sector fund, *N=25* early-stage assets												
2x	0.8% p.a.	44.4%	−54.9%	−0.5% p.a.	57.3%	−99.8%	−2.4% p.a.	70.6%	−100.0%	0.2% p.a.	52.3%	−89.4%
3x	6.1% p.a.	20.5%	−32.3%	4.2% p.a.	43.8%	−99.7%	1.2% p.a.	65.4%	−100.0%	5.1% p.a.	36.9%	−84.1%
4x	11.3% p.a.	13.8%	−9.8%	8.8% p.a.	36.2%	−99.7%	4.9% p.a.	61.5%	−100.0%	10.1% p.a.	28.8%	−78.8%
5x	16.6% p.a.	9.0%	12.8%	13.5% p.a.	31.6%	−99.6%	8.5% p.a.	59.4%	−100.0%	15.0% p.a.	23.9%	−73.5%
6x	21.9% p.a.	5.2%	35.3%	18.1% p.a.	29.0%	−99.5%	12.1% p.a.	58.3%	−100.0%	20.0% p.a.	20.8%	−68.1%
Panel 3: Government-guaranteed private sector fund, *N=25* early-stage assets												
2x	1.2% p.a.	25.0%	−24.7%	1.0% p.a.	42.6%	−53.9%	0.6% p.a.	51.9%	−67.7%	1.2% p.a.	38.3%	−49.4%
3x	5.4% p.a.	12.0%	−13.4%	4.9% p.a.	32.6%	−50.3%	3.8% p.a.	46.9%	−67.0%	5.3% p.a.	27.3%	−43.5%
4x	10.0% p.a.	7.0%	−1.3%	8.9% p.a.	28.0%	−47.9%	7.1% p.a.	44.8%	−66.6%	9.6% p.a.	22.1%	−38.9%
5x	14.7% p.a.	4.1%	13.2%	13.1% p.a.	25.5%	−46.2%	10.4% p.a.	43.5%	−66.4%	14.0% p.a.	19.4%	−36.7%
6x	19.5% p.a.	3.5%	30.5%	17.3% p.a.	24.1%	−44.9%	13.8% p.a.	42.6%	−66.4%	18.5% p.a.	17.9%	−34.8%

$E[R_a]$ indicates the expected annualized return; PoL indicates the probability of loss; $ES_{25\%}$ indicates the expected shortfall at the 25% level (i.e., the expected cumulative return on the portfolio in the worst 25% of cases); p.a. indicates per annum; highlights indicate realistic, base-case assumptions.

Table 4 (*Continued*)

Value to-sales	$\rho = 0\%$			$\rho = 40\%$			$\rho = 80\%$			$\rho =$ Qualitative		
	$E[R_a]$	PoL	$ES_{25\%}$	$E[R_a]$	PoL	$ES_{25\%}$	$E[R_a]$	PoL	$ES_{25\%}$	$E[R_a]$	PoL	$ES_{25\%}$
Panel 4: Purely private sector fund, mixed-phase portfolio, *N=25* assets												
2x	0.3% p.a.	47.7%	−51.6%	−0.6% p.a.	58.6%	−94.5%	−1.9% p.a.	68.6%	−100.0%	−0.2% p.a.	54.1%	−82.9%
3x	5.3% p.a.	21.2%	−27.4%	3.9% p.a.	44.1%	−91.8%	2.0% p.a.	62.2%	−100.0%	4.6% p.a.	36.4%	−74.3%
4x	10.4% p.a.	10.2%	−3.2%	8.5% p.a.	36.3%	−89.1%	5.9% p.a.	58.4%	−100.0%	9.4% p.a.	28.0%	−65.8%
5x	15.4% p.a.	8.4%	21.0%	13.0% p.a.	30.1%	−86.3%	9.8% p.a.	54.6%	−100.0%	14.2% p.a.	22.6%	−57.2%
6x	20.4% p.a.	6.2%	45.2%	17.6% p.a.	26.2%	−83.6%	13.7% p.a.	52.9%	−100.0%	19.0% p.a.	18.8%	−48.7%
Panel 5: Philanthropic grants & private sector fund, mixed-phase portfolio, *N=25* assets												
2x	0.7% p.a.	44.2%	−49.3%	−0.2% p.a.	56.7%	−94.2%	−1.6% p.a.	67.8%	−100.0%	0.2% p.a.	51.8%	−82.0%
3x	6.0% p.a.	19.2%	−23.9%	4.5% p.a.	42.6%	−91.3%	2.4% p.a.	61.5%	−100.0%	5.2% p.a.	34.9%	−73.0%
4x	11.2% p.a.	9.5%	1.4%	9.3% p.a.	34.7%	−88.5%	6.5% p.a.	57.8%	−100.0%	10.2% p.a.	26.7%	−64.0%
5x	16.5% p.a.	7.8%	26.8%	14.0% p.a.	28.8%	−85.6%	10.6% p.a.	54.0%	−100.0%	15.2% p.a.	21.5%	−55.0%
6x	21.7% p.a.	5.3%	52.2%	18.8% p.a.	25.3%	−82.7%	14.6% p.a.	52.5%	−100.0%	20.2% p.a.	17.9%	−46.0%
Panel 6: Government-guaranteed private sector fund, mixed-phase portfolio, *N=25* assets												
2x	1.3% p.a.	24.3%	−22.8%	1.1% p.a.	44.8%	−57.8%	0.7% p.a.	62.3%	−71.1%	1.3% p.a.	38.3%	−50.3%
3x	5.8% p.a.	9.9%	−10.0%	5.3% p.a.	32.9%	−54.5%	4.4% p.a.	56.3%	−70.3%	5.6% p.a.	25.5%	−41.5%
4x	10.6% p.a.	6.3%	7.1%	9.6% p.a.	27.3%	−51.6%	8.2% p.a.	53.8%	−69.9%	10.2% p.a.	19.5%	−35.1%
5x	15.6% p.a.	3.5%	28.4%	14.0% p.a.	24.1%	−49.0%	12.0% p.a.	52.0%	−69.7%	14.9% p.a.	16.1%	−31.6%
6x	20.5% p.a.	2.0%	49.5%	18.5% p.a.	22.3%	−47.3%	15.9% p.a.	50.9%	−69.7%	19.6% p.a.	14.1%	−26.6%

value-to-peak sales multiplier of 4, the expected annualized return increases from 8.5% per annum to 9.4% per annum, and the $ES_{25\%}$ decreases from –80.3% to –65.8%. In particular, as seen in the top panel of Figure 2, the probability of the worst-case scenario where all 25 projects fail, resulting in a –100% return, decreases from 17.0% to 11.9%. In fact, the mixed-phase portfolio offers higher expected returns and lower risk than the early-phase portfolio in all scenarios. While most of these expected returns remain lower than the cost of capital required by early-stage R&D, they are a substantial improvement over the purely early-stage asset portfolio under the same scenario assumptions. However, they also demonstrate that a purely private sector fund is unlikely to be economically feasible. Therefore, we consider philanthropic grants and public-sector partnerships to improve expected returns and mitigate risk.

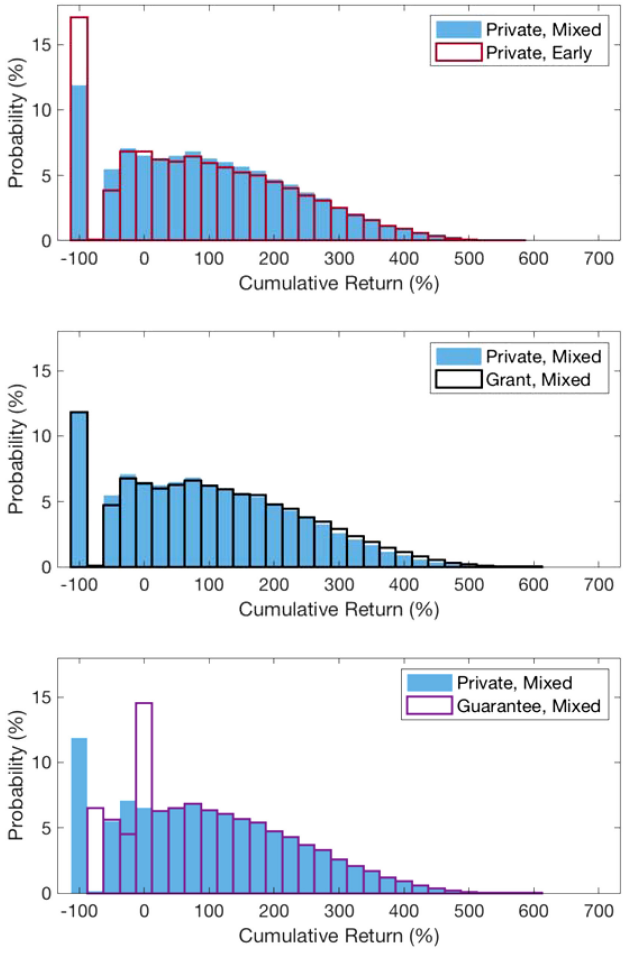

Figure 2 Histograms of Monte Carlo simulation cumulative returns for various ovarian cancer portfolio strategies. Distributions are shown for the base-case scenario with qualitative correlations and a value-to-peak sales ratio of 4.

3.2 Philanthropic grants

The most common form of funding from nonprofit organizations comes in the form of philanthropic grants. Many of these grants are designed to accelerate innovation in a particular therapeutic area by funding basic scientific or early-stage translational research. In our simulations, we model the effect of a $10 million grant for each project in early-stage phase 1 development. We find that, on their own, the effect of these grants on portfolio performance is marginal (see panel 5 in Table 4) and would do little to increase the attractiveness of these projects to private investors. For example, compared to the mixed-phase private sector portfolio, philanthropic grants increased the expected annualized return from 9.4% to 10.2% per annum, but only decreased the $ES_{25\%}$ from –65.8% to –64.0%. As illustrated in the middle panel of Figure 2, this minimal effect results from the fact that the grants do not affect the tail risk. In particular, the probability of the worst-case scenario, where all 25 projects fail and investors suffer a –100% return, remains the same.

In response, many philanthropic organizations have begun to explore different funding models in order to leverage their return on investment, a return which may be measured in terms of social, medical, and, in some cases, financial metrics. One such model, venture philanthropy, applies the principles of venture capital to invest directly in projects that promote the social good. Like

venture capital, venture philanthropy is characterized by a high degree of investor engagement. In addition to providing capital, venture philanthropists also offer operational and managerial advice. In contrast to venture capital, where success is measured by financial return, the success of venture philanthropy is measured by its social impact. However, the financial returns of such an investment may be sufficient to allow a philanthropic organization to further its mission without needing additional donor contributions.

3.3 Public sector guarantees

Another possible public–private partnership that can be used to reduce the risk of early-stage research is the use of government-backed guarantees. Various forms of guarantee structures such as development impact bonds have been used effectively to attract private capital to previously neglected initiatives (Oroxom *et al.*, 2018). In the structure we consider, a government agency (or, in certain instances, a mission-driven organization like the Gates Foundation) promises to absorb the initial losses on the portfolio to a predetermined amount, shielding private sector investors from substantial negative returns. Although the public sector is involved, the selection and management of the portfolio would remain led by the private sector.

In our simulation, in the event of a negative portfolio return, the government agrees to cover the first $1 billion of losses, reducing the downside risk experienced by private sector investors. The effect of a $1 billion cushion on our 25-project, mixed-phase fund is reported in panel 6 of Table 4. Relative to the purely private sector fund, the government-backed guarantee significantly improves the previously unattractive investment returns. For example, in the base-case scenario with qualitative correlations and a value-to-peak sales ratio of 4, the expected annualized return increases from 9.4% to 10.2% per annum, and the $ES_{25\%}$ decreases from –65.8% to –35.1%. The bottom panel of Figure 2 illustrates how the government guarantees partially protect investors from substantial downside risk by cutting off the left tail of the distribution where all 25 projects fail.

A notable feature of this guarantee is its low expected cost relative to the size of the guarantee. For the proposed 25-project, mixed-phase portfolio, the guarantee has an expected cost of $237 million or 23.7% of its face value. When amortized over the 10.3-year time horizon of the portfolio, this cost represents a small fraction of NIH's research portfolio which provided $151 million in funding for ovarian cancer in 2017 alone (NIH, 2018).

This result demonstrates that the guarantee structure has the potential to transform a financially unattractive portfolio of ovarian cancer therapeutic candidates with substantial tail risk into one that could realistically attract private sector capital. This structure could then be further reinforced with other revenue-boosting mechanisms such as advance market commitments and priority review vouchers. Because of its ability to minimize the downside risk for investors at low expected cost, this approach holds considerable promise.

4 Discussion

Ovarian cancer differs from many other oncological conditions. Its asymptomatic onset makes early detection difficult, while its heterogeneous nature may necessitate treatments that use multiple mechanisms of action. These scientific challenges are a significant impediment to the medical innovation required to cure a disease that affects hundreds of thousands of patients each year, as is the dearth of available funding for research and development. Moreover, these factors, along with the limited number of potential projects, help to

explain why the financial returns of a purely private sector fund in this area are not as attractive as those of a general oncology megafund (Fernandez *et al.*, 2012).

The strategic use of a public–private portfolio structure would be able to address some of these issues by leveraging multiple sources of funding, diversifying risk, and fostering critical partnerships between the public and private sectors. In order to make this proposition attractive to investors, however, a collaborative investment framework is required. Philanthropic funding and government guarantees are able to support private investment by mitigating the downside risk at a relatively low expected cost to taxpayers. In particular, financial guarantees that shield investors from the substantial downside risk of the worst-case scenario can significantly improve the risk–reward profile of these portfolios. Finally, a mixed-phase portfolio seems to be more attractive than an entirely phase-1-ready early-stage fund because the expected number of successful projects is increased.

5 Conclusion

The interests of multiple stakeholders, including patients, investors, and payers, need not be misaligned in the search for breakthrough treatments for ovarian cancer or attractive returns on investment. The appropriate business models and financing structures can greatly amplify the scale and scope of current research and development efforts, as shown by our simulations. Our simulation results are particularly relevant for the emerging practice of impact investing in which investors wish to effect change as well as earn an attractive return on investment. Both are simultaneously achievable, but active collaboration between the private and public sectors will be necessary to address the financial issues impeding the rate of medical innovation, and we hope this article will serve as a catalyst for such collaboration.

Note

[1] The annualized return, R_a, is calculated by dividing the cumulative return by the time horizon of the investment. This arithmetic average is used instead of the geometric average so that the order of annualization and expectation does not affect the expected annualized return.

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Competing interests

A.W.L. reports personal investments in private biotech companies, biotech venture capital funds, and mutual funds; 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.

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