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Financing Drug Discovery for Orphan Diseases*

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An orphan-disease "megafund" of less than a billion dollars can provide sufficient risk reduction to be financed by long-term bonds and still generate attractive investment returns with only 10 to 20 projects in the portfolio.

ABSTRACT

Recently proposed "megafund" financing methods for funding translational medicine and drug development require billions of dollars in capital per megafund to de-risk the drug discovery process enough to issue long-term bonds. Here we demonstrate that the same financing methods can be applied to orphan drug development, but because of the unique nature of orphan diseases and therapeutics—lower development costs, faster FDA approval times, lower failure rates, and lower correlation of failures among disease targets—the amount of capital needed to de-risk such portfolios is much lower. Numerical simulations suggest that an orphan-disease megafund of only $575 million may yield double-digit expected rates of return with only 10 to 20 projects in the portfolio.

Introduction

The drug development process has become expensive, lengthy, and risky. In response to these characteristics, and to the lackluster performance of investments in the biotech and pharma sectors over the past decade, traditional sources of financing for such endeavors—private and public equity—are waning as capital shifts to less risky investments. Fernandez *et al*. [1] have argued that this problem can be addressed by increasing the scale of investment and pooling a large number of drug development efforts into a single financial entity or "megafund". The benefits of diversification—lower aggregate risk with more "shots on goal"—yield a more attractive risk-adjusted return and a higher likelihood of success. This, in turn, allows the megafund to raise the required amount of capital to achieve sufficient diversification by issuing "research backed obligations" (RBOs), bonds

that are collateralized by the portfolio of potential drugs and their associated intellectual property. Because RBOs are structured as bonds, they can be designed to appeal to fixed-income investors, who collectively represent a much larger pool of capital than venture capitalists and who have traditionally not been able to participate in investments in early stage drug development. For example, the total size of the U.S. venture capital industry in 2012 was $199 billion whereas the comparable figure for the U.S. bond market was $38 trillion.

To illustrate the mechanics of megafund financing using RBO securities, Fernandez *et al.* [1] provide an analytic framework, simulation software, and empirical examples involving cancer drug-development programs. Their simulation results suggest that RBO structures are, in principle, able to generate reasonable returns for both debt and equity investors, while also providing a bridge for translational research in the drug approval process. In a follow-on study, Fagnan *et al.* [2] propose an analytic framework for evaluating the impact of third-party guarantees on RBO transactions, and find that such guarantees can improve the economics of RBO transactions at very low expected cost to the guarantor. However, the examples in Fernandez *et al.* [1] and Fagnan *et al.* [2] rely on very large portfolios of hundreds of candidate compounds, which raises a number of operational challenges in the practical implementation of such a megafund.

In this article, we explore the applicability of the RBO approach by extending the framework to accommodate drug discovery for orphan diseases. Because of the unique pathological characteristics of many orphan diseases, as well as the considerable support provided by the Orphan Drug Act of 1983 (ODA), orphan drug development projects frequently have higher success rates and shorter times to approval, but still generate potential lifetime revenues that are comparable to non-orphan drugs despite their much smaller target patient population. To capture a realistic representation of the RBOs, we use numerical simulation techniques to compute the investment returns of a hypothetical portfolio of orphan drug development projects. Given empirically plausible assumptions for revenues, costs, and probabilities of success for orphan diseases, we find that much smaller portfolios than those of Fernandez *et al.* [1]—containing only 10 to 20 compounds and less than $250 million in capital—are sufficiently diversified to yield reasonable investment returns for RBO investors. While the investment returns of RBOs are positively related to portfolio size due to the impact of financial leverage, for certain types of projects the required threshold of assets may be quite modest and it may be worthwhile to target these projects for an initial "proof-of-concept" of the megafund financing structure.

Orphan Diseases and the Orphan Drug Act

In the thirty years since the passage of the Orphan Drug Act (ODA), the orphan disease landscape has changed drastically. Orphan diseases, formally defined as those that affect fewer than 200,000 individuals in the United States [3], were once anathema to the pharmaceutical industry. Today, this once-ignored category of diseases commands a market worth nearly $90 billion annually [4] and is believed to serve more than twice the number of all U.S. cancer patients—at least 25 million Americans are afflicted with one of almost 7,000 recognized rare diseases [5]. Clearly, as a collective, rare diseases are not rare at all.

Prior to 1983 and the ODA, orphan diseases posed too many challenges for industry to seriously confront the disease category. Approximately 80% of rare diseases are caused by underlying genetic defects, which can be hard to identify [6]. Still others are caused by exposures to rare and unusual toxins. Some orphan diseases are so uncommon that afflicted individuals may not be correctly diagnosed for many years, and there are instances of afflicted individuals never receiving a correct diagnosis [7]. Additionally, the rigorous standards of the Food and Drug Administration (FDA) for clinical trials often meant that assembling patient populations of sufficient size for testing was exceedingly difficult. The ODA has been broadly acclaimed for its effectiveness in diminishing these barriers to development.

The ODA and its subsequent revisions provided a number of important economic incentives to sponsors of orphan drugs. To jumpstart therapeutic development in the rare disease category, the ODA created research grants specifically for orphan drug research, implemented tax credits of up to 50% for clinical testing costs, authorized expedited regulatory review for orphan drugs and, most importantly, established a seven-year period of marketing exclusivity that precludes FDA approval of any same or generic drug for the same orphan indication [8]. The exclusivity provision is distinct from a patent and, in many cases, provides additional protection from competition by generics and other potential market entrants.

The combination of the ODA's incentive program and a number of significant scientific breakthroughs in molecular biology and genome sequencing has resulted in three decades of innovative and fruitful orphan drug discovery. Prior to the passage of the ODA, the FDA had approved fewer than 10 drugs for orphan diseases; today, that figure stands at more than 350 unique drugs (see: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/). Currently, orphan drugs are at the forefront of global pharmaceutical R&D trends. While the compound annual growth rate (CAGR) between 2001 and 2010 for new molecular entities as a whole was negative, the CAGR for orphan designations over the same period was robust at approximately 10% [9]. The overall drug market also reflects this trend. Orphan drugs currently comprise 22% of total drug sales with a CAGR of 25.8% over 2001–2010, compared to 20.1% for the non-orphan market [8]. Some industry developments suggest that these strong figures may continue to rise as the evolution toward more targeted therapies and stratified medicine progresses.

The Suitability of Orphan Drugs for RBO Financing

For a number of reasons, orphan drugs are particularly well suited to portfolio financing. Chief among these are the significantly higher rates of success that orphan drug development projects enjoy when compared to those of other disease groups such as oncology or neurodegenerative disorders. Orphan diseases are largely caused by a mutation in an individual's genetic code, most commonly manifested as a malfunction or absence of one or more key proteins. If the underlying genetic defect can be identified and characterized, it is often possible to create highly targeted and effective therapies to address the malfunction and its symptoms [9]. Similar targeting methodologies have been used to combat rare cancers, notably in drugs like Rituxan and Gleevec. Consequently, the odds of a new orphan drug receiving FDA approval are significantly higher than those of a

non-orphan counterpart. For orphan drugs that entered clinical testing between 1993 and 2004, we estimate the overall regulatory success rate to be approximately 22%, whereas the comparable figure for non-orphan drugs was approximately 11% [10], and the rate for cancer compounds was even lower at only 6 to 7% [10].

The success or failure of orphan drug development projects is also less likely to be correlated across diseases due to the large proportion of orphan diseases that display monogenic pathology or act through largely unrelated mechanisms [11]. This observation is particularly significant given the central role that correlation plays in determining the risk of a portfolio of candidate drug compounds. Although we are not aware of any longitudinal estimates of historical correlations among drug development projects, the scientific basis of orphan drugs suggest that correlations are likely to be quite small, especially when contrasted with other disease groups, such as oncology. Many types of cancer have similar pathologies, such as the deregulation of specific signaling pathways and mutations in critical oncogenes. As an example, consider the JAK/STAT and TGF-β pathways, each of which has been linked to dozens of oncologic diseases [12,13]. Of course, a number of orphan drugs are in oncology, but in contrast to larger classes of oncology drugs that share a common mechanism such as tyrosine kinase inhibition or anti-angiogenesis, orphan drugs (as a distinct category) act against a wider variety of targets.

Furthermore, orphan drugs have been shown to have nearly equivalent lifetime revenue potential as non-orphan therapies. According to Thomson Reuters, an average orphan drug can be expected to attain sales of $100 to $500 million per year [14]. Small patient population sizes are often compensated for by high per-patient revenues. For example, Soliris, a drug to treat paroxysymal nocturnal hemoglobinuria (a rare blood disease affecting fewer than 6,000 individuals in the US), is priced at more than $400,000 per patient per year [9]. Consequently, the blockbuster drug model that is characteristic of many top-selling non-orphan drugs is equally applicable to the orphan market: compounds in the top 29% of orphan drugs are each expected to earn more than $1 billion in revenue per year over their lifetime [14]. As an extreme example of the potential profitability of orphan drugs, we consider again Rituxan, an orphan drug that is expected to attain discounted lifetime sales of over *$150 billion*, a figure surpassed only by Pfizer's non-orphan Lipitor [14].

Finally, the ODA's marketing exclusivity clause provides a key financial incentive for orphan drug development. One analysis of the seven-year exclusivity provision found that its impact extended the average combined patent/exclusivity period by nearly a year, resulting in an average competition-free marketing period of 11.7 years [15]. For therapies that receive approval later in their patent lifespans, the increase in the exclusivity period can be significantly longer. Assuming average annual sales of $200 million and a 10% cost of capital [16], we estimate that the average present value of an orphan drug's revenue over its competition-free lifespan is $1.36 billion. In addition, we assume that the profit margin, including cost of goods sold (COGS) and marketing costs, is 60%, resulting in a final average valuation of $818 million. To demonstrate the sensitivity of our simulation experiments to valuation assumptions, we also employ a less conservative estimation of annual revenues of $400 million [9], which results in a final average valuation of $1.63 billion.

In the next section, we use these values along with some additional parameters to conduct a series of simulation experiments demonstrating how an orphan drug portfolio might be used as collateral for an RBO structure.

Orphan Disease Megafund Simulation

The financial engineering technique of securitization involves creating a legal entity that issues debt and equity to investors and uses the proceeds to purchase a portfolio of assets. The debt and equity securities are said to be "backed" by the assets in the portfolio in the sense that the holders of such securities have certain ownership rights to those assets. In particular, the cash flows from the assets are used to repay the debt, and any residual value after the debt is fully repaid is paid to the equity holders. A primary motivation for securitization is to reduce the risk of the individual assets through diversification and to allow fixed-income investors to invest in asset classes that would otherwise be too risky or fragmented to be of interest to them. In a biomedical RBO, the assets are a diverse collection of biomedical projects that may span the entire range from preclinical research to new drug applications (NDAs) or focus on particular segments of the drug development process.

However, unlike existing drug royalty securitization transactions (e.g., Royalty Pharma, DRI), our proposal accommodates investment in early-stage projects that may be far from FDA approval hence they have no discernible royalty stream at the time of investment. As a result, the risk is much higher, creating the need for more sophisticated financial modeling of the economic value of the portfolio's assets as they progress from the preclinical stage into clinical trials.

Fernandez *et al.* [1] present a stylized mathematical example of securitization of experimental drug compounds and Fagnan *et al.* (see: http://ssrn.com/abstract=2203203) develop this example in more detail. While illustrative, this example oversimplifies the economics of the biopharma industry. The authors also provide results of a more detailed set of simulation experiments that incorporate more realistic features of the drug-development process including correlated assets, stochastic transitions between clinical trial phases, the need to manage cash to pay interest and principal, realistic valuations of compounds that are sold during intermediate stages of the clinical trials process, and the need to manage cash to fund new trials during the approval process. Fagnan *et al.* (see: http://ssrn.com/abstract=2203203) extends this work by analyzing the impact of third-party default guarantees for a subset of the RBO securities. They find that such guarantees can greatly increase the attractiveness of RBOs, enhancing their fundraising potential.

These simulation experiments extend the framework of the stylized example to a richer multi-state, multi-period setting that includes path-dependence and correlated asset valuations. The need to extend the single-period model arises due to the nature of the drug trial process. At each stage of this process, larger and larger cash inflows are required to fund additional testing. Importantly, new investment at each stage can only occur when there is sufficient capital available that is not required for other uses such as debt service or repayment.

The dominant source of cash flow for the megafund is from the sale of compounds out of the portfolio. Profits or losses accrue when the megafund purchases a compound in one phase and subsequently sells it at another phase. Analysis of the portfolio primarily

involves the specification of four quantities: the transition probabilities, the distribution of trial costs in each phase, the distribution of valuations for each compound that is sold in a specific phase, and some form of dependence amongst the compound valuations. See Fagnan *et al.* (see: http://ssrn.com/abstract=2203203) and the Supplemental Information section of [1] for details of the models and estimation. Pseudo-code for these simulations is given in [1], and the source code is available from the authors.

Following Fernandez *et al.* [1] and Fagnan *et al.* (see: http://ssrn.com/abstract=2203203), we consider an RBO transaction with a capital structure consisting of a senior tranche, mezzanine tranche, and equity tranche. Because of the complexities of the waterfall and the drug approval process, numerical simulations are used to evaluate the RBO securities. We focus only on early stage investment (preclinical and Phase 1), which represents the riskiest portion of the drug-development process and where funding is scarcest. We simulate acquiring an equal number of preclinical and Phase 1 compounds, with the goal of selling any drugs that successfully complete Phase 1 trials.

Our simulation relies on several key assumptions and parameters including clinical trial costs, valuations, and duration of each phase. We derive our preclinical estimates from [17], making the assumption that the preclinical phase is similar for orphan and non-orphan drugs. Kaitin and Dimasi [18], report that orphan-drug trials in recent years take approximately 5.9 years from Phase 1 to NDA with an additional 0.8 years required for the approval process. The time for each phase is calculated by scaling the relationships used in [1].

Clinical transition probabilities were estimated from [19] based on a large molecule dataset, which we have assumed to be a close approximation for orphan drugs due to the increased targeting specificity that characterizes biologics drug development. Furthermore, we believe the resulting success rate from preclinical to approval (21.8%) to be reasonable based on our analysis of recent orphan drugs developed by pharmaceutical companies. Valuations for each phase were obtained by discounting the estimate described above based on the probability of success and using discount rates of up to 30% per year. Upon acquisition of compounds, we follow [1] and assume that upfront and milestone payments are proportional to clinical costs. In addition, we increase our assumed upfront payment amounts. Lastly, we estimate clinical trial costs using conservative values for the number of patients per clinical trial [20] and cost per patient [21]. We assume a higher cost per patient in Phase 1 to account for expenses associated with locating suitable candidates for the trial, which is inherently more difficult for an orphan drug.

While we believe our parameter assumptions to be reasonable, to permit other researchers to experiment with different values, we have made all of our assumptions and the source code for our simulations available in open source format. (For further discussion of all parameters, see Supplemental Information and Parameters.)

Simulation Results

Table 1 compares the simulation performance (using 2,000,000 simulations) of an (approximately) optimized RBO structure to a traditional equity model, assuming a fixed correlation of 20%. For comparison, we include results for the equity-only structure using the *same equity amount* used in the RBO, as well as a second set of results for an equity structure, but using the *same total capital* of the RBO.

The simulation acquires 10 or 16 orphan drugs (depending on the capital), with an equal number of compounds in preclinical and Phase 1 using a total capital of $373.75 or $575 million, respectively, substantially less than in the case of candidate compounds in oncology as discussed in [1]. The simulation extends for a horizon of 6.5 years (in 6-month increments), with an additional year used for the selling of compounds upon liquidation of the remaining drugs in the portfolio. The simulation is targeted to sell compounds once they (successfully) complete Phase 2 trials, but compounds can be sold earlier in the process in anticipation of bond coupon or service payments. Readers are encouraged to download our simulation software and re-run simulations with their own parameters and assumptions. For example, purchasing drugs earlier in discovery or using an alternative target selling phase. (For sensitivity analysis of some of the parameters, see Supplemental Information and Parameters.)

Phase	Clinical Trial Cost ($MM)	Clinical Trial Success Rate	Clinical Trial Duration (years)	Valuation ($MM)
Preclinical	5	69%	1.00	7.1
Phase 1	5	84%	1.66	27.6
Phase 2	8	53%	2.09	75.6
Phase 3	43	74%	2.15	321.5
NDA	—	96%	0.80	701.9
APP	—	—	—	817.6

Table 1: RBO simulation parameters.

Using an equity-only structure with capital of $135 million, Table 2 reports that the mean return on equity in our experiments was 10.7%, nearly 3% below the RBO, while the probability of loss of equity was also higher, resulting in 16.1% compared to 13.1% for the RBO. By increasing the capital used in the equity-only model to $575 million, the probability of loss to equity is reduced to 10.1%, with a smaller improvement to expected return on equity, which had a mean value of 11.8%. Using the higher level of capital, both the RBO and same-capital equity-only structures sell around 5 Phase 3 compounds on average, compared to about 3 for the smaller level of capital. Thus, the RBO achieves a higher return on equity, a modest increase in the probability of loss, but more than twice the probability of receiving a return on equity larger than 25%. This higher equity return is due to the increased use of leverage, which comes with more risk to equityholders, as can be seen from the much higher probability of all equity being lost in the RBO versus either of the equity-only cases (60 basis points (bp) versus less than 1bp).

The leverage is achieved in the RBO structure through the issuance of two tranches of structured bonds. The default rate on the senior tranche of the RBO is approximately 1 bp, which is comparable to the historical default rates for bonds rated at the highest levels by rating agencies. The default rate on the mezzanine tranche is 56 bp with an expected loss of 15bp. Such relatively low default rates would likely be attractive to fixed-income investors, given the assumed coupon rate on the debt (5% and 8%, respectively).

	All Equity (Same Equity)	RBO	All Equity (Same Capital)
Number of Compounds			
Preclinical	5	8	8
Phase 1	5	8	8
Research Impact			
Number sold in Phase 2	1.1	2.2	1.7
Number sold in Phase 3	3.1	4.7	5.0
Liabilities			
Capital ($ millions)	373.75	575	575
Senior tranche ($ millions)	—	86.25	—
Junior tranche ($millions)	—	115	—
Equity tranche ($millions)	373.75	373.75	575
Equity tranche performance			
Average annualized ROE	10.7	13.4	11.8
Prob. (equity wiped out)	0.2bp	60bp	<0.1bp
Prob. (return on equity < 0)	16.1	13.1%	10.1%
Prob. (return on equity > 10%)	54.7%	66.7%	59.77%
Prob. (return on equity > 25%)	7.8%	18.4%	6.27%
Debt tranches performance			
Senior tranche: default prob., expected loss (bp)	—	0.8, <0.1	—
Junior tranche: default prob., expected loss (bp)	—	56, 15	—

Table 2: RBO simulation results using a target selling phase of Phase 3.

To develop a sense of the range of investment returns that are possible, Table 3 reports the outcome of the same simulations but assuming annual revenues of $400 million instead of the original $200 million for the same capital structure used in the experiment of Table 2. As a result of these higher valuations, we see expected returns of 20% to 34% with a higher level of debt supported by the RBO.

Under this aggressive revenue assumption, there is little need for debt financing, given that a 19.6% rate of return is considerably higher than the average biotech VC firm over the past decade (but comparable with the returns of the most successful ones). However, at the same time, the impact to the fund's risk profile from acquiring significant debt is minimal. In particular, RBOs increase the probability of default over an all-equity model—with the same amount of equity—by only 79 bp.

The risk of extreme losses in this structure involves a trade-off between increasing diversification due to larger capital pool on the one hand, and increasing leverage due to debt issuance on the other. Specifically, although the average return on equity increases from 19.6% in the all-equity-financed case to 33.8% in the RBO-financed case, the probability of total loss for the equity holders also increases by a factor of 40. Even so, many investors might still prefer the leveraged financing structure to the all-equity version because of its boost to returns. However, it should be emphasized that the proper use of RBOs does rely more heavily on the accuracy of the assumed parameters, given that the default probabilities of the bonds and ROE may vary materially for different parameter assumptions.

	All Equity (Same Equity)	RBO	All Equity (Same Capital)
Number of Compounds			
Preclinical	3	8	8
Phase 1	3	8	8
Research Impact			
Number sold in Phase 2	0.7	2.3	1.7
Number sold in Phase 3	1.8	4.6	5.0
Liabilities			
Capital ($ millions)	230	575	575
Senior tranche ($ millions)	—	115	—
Junior tranche ($millions)	—	230	—
Equity tranche ($millions)	230	230	575
Equity tranche performance			
Average annualized ROE	19.6%	33.8%	23.2%
Prob. (equity wiped out)	2bp	81bp	<0.1 bp
Prob. (return on equity < 0)	10.4%	2.5%	14bp
Prob. (return on equity > 10%)	79.1%	95.4%	93.7%
Prob. (return on equity > 25%)	40.5%	82.9%	45.7%
Debt tranches performance			
Senior tranche: default prob., expected loss (bp)	—	1.2, <0.1	—
Junior tranche: default prob., expected loss (bp)	—	80, 27	—

Table 3: RBO simulation results using a target selling phase of Phase 3, a Phase 2 valuation of $174 million and a Phase 3 valuation of $643 million, corresponding to sales of $400MM per year [9].

Conclusion

A confluence of factors is responsible for the lower number of new drugs approved over the past decade, causing some authors to suggest that the current business model for life sciences research and development is flawed [22,23,24]. The productivity of large pharmaceutical companies—as measured by the number of new molecular entity and biologic license applications per dollar of R&D investment—has declined in recent years (see: http://ssrn.com/abstract=2203203), and their stock-price performance over the last decade—an annualized return of 1.2% for the New York Stock Exchange Arca Pharmaceutical Index during the period from January 2, 2002 to July 1, 2013—has been equally disappointing. Despite the near doubling of the aggregate R&D budget of the pharmaceutical industry from $68 billion in 2002 to $127 billion in 2010, there has been little appreciable impact on the number of new drugs approved (see: http://www.evaluatepharma.com/EvaluatePharma_World_Preview_2016.aspx).

Fernandez *et al.* [1] introduced the concept of RBOs as a means of channeling funds from global capital markets to early stage drug development. A complication regarding the original RBO model was that constructing portfolios of the size described in the methodology was untested and introduced a number of potential operational challenges. In this article, we have tried to address this by reporting the results of a series of experiments that suggest that smaller portfolios—on the order of as few as 10 compounds and $135 million of capital—can still be used as collateral for RBO transactions and deliver reasonable investment returns.

The three biggest drivers of this result are the assumptions of a higher probability of success, uncorrelated failures, and a much lower cost of conducting clinical trials for orphan drug development programs. Although the recent scientific literature and biopharma experience in orphan diseases seem to be consistent with these assumptions, this is still a relatively young field with new findings published almost daily, some of which could change the simulation parameters and its result. Therefore, our simulation results are, at best, suggestive and not conclusive. Readers are invited to download our simulation software and re-run the simulations with their own combination of preferred parameter values. Nevertheless, we believe that across a reasonable range of simulation parameters, certain biomedical challenges can be met with megafunds of much smaller scale than that proposed by Fernandez *et al.* [1].

Another implication of our analysis is that asset selection—based on a deep understanding of both the scientific and financial aspects of the projects being considered—is central to successful portfolio construction, and that there are at least two paths to achieve such success. In cases where success rates are unavoidably low and failure is positively correlated between projects, a large number of projects and vast amounts of capital may be needed to achieve sufficient diversification and an acceptable risk/reward profile. However, when success rates are higher and projects are less correlated, fewer projects and less capital may be required.

This trade-off suggests that more efficient business models for drug discovery can be developed by allowing the scientific and engineering challenges of translational medicine to determine the financing structure used to support them, and not vice versa. Relying on existing financing methods such as venture capital and public equity may be inadequate to address the rapidly shifting economic incentives arising from scientific breakthroughs such as big data, biomarkers, the "omics" revolution and precision medicine, and political and regulatory changes.

These changes may not bode well for the profitability of orphan drugs. Indeed, there is a growing concern that the rising cost of drugs like Soliris is unsustainable; hence our simulation results should be re-generated and re-evaluated as the economic landscape changes. But one of the primary drivers of the megafund concept is the financial efficiency gains from pooling a large number of diverse investments into a single portfolio. Such efficiency gains may, in fact, contribute to a lowering of the cost of developing drugs for rare diseases and accelerate the industry toward a more sustainable business model.

Finally, our orphan drug development simulations hint at an intriguing potential future for the biopharma industry. As diagnostic techniques and our understanding of the molecular basis of disease become more and more precise, it is conceivable that most diseases could eventually be "orphanized." By stratifying patient populations sufficiently finely to increase the efficacy of a candidate drug—thereby increasing the probability of approval and decreasing the correlation of failure among projects—we reduce both the amount of capital and the number of shots on goal needed to achieve an attractive risk/reward profile. The financial economics of orphan drug development show that, in addition to scientific and ethical motivations for developing targeted therapies, there are important financial incentives as well.

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