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Financing Biomedical Innovation

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Abstract

We review the recent literature on financing biomedical innovation, with a specific focus on the drug development process and how it may be enhanced to improve outcomes. We begin by laying out stylized facts about the structure of the drug development process and its associated costs and risks, and we present evidence that the rate of discovery for life-saving treatments has declined over time while costs have increased. We make the argument that these structural features require drug development (i.e., biopharmaceutical) firms to rely on external financing and at the same time amplify market frictions that may hinder the ability of these firms to obtain financing, especially for treatments that may have large societal value relative to the benefits going to the firms and their investors. We then provide an overview of the evidence for various types of market frictions to which these drug development firms are exposed and discuss how these frictions affect their incentive to invest in the development of new drugs, leading to underinvestment in valuable treatments. In light of this evidence, numerous studies have proposed ways to overcome this funding gap, including the use of financial innovation. We discuss the potential of these approaches to improve outcomes.

1. INTRODUCTION

The healthcare system is essential to the global economy. As the recent COVID-19 pandemic has starkly demonstrated, the functioning of the economy is intimately tied to its ability to manage health, as efforts to contain the virus led to the partial shutdown of the global economy. Moreover, the healthcare system's effectiveness in meeting its challenges may be the bellwether of the future health of the global economy. Health care expenditures in the United States have steadily risen over the past few decades to more than 19% of GDP as of 2020 (CMS 2021).

The foundation of the healthcare system is the development of new therapeutics that provide societal value. However, the development and delivery of therapeutics require significant amounts of funding, which closely connects the expansion of healthcare to finance. A major challenge in the development of new treatments is that the required investments are large, the gestation lags are long, and the payoffs are highly uncertain, with daunting risks that include not only scientific risk but also the regulatory risks of drug approval and financing risks. This challenge has led to a funding gap between the aggregate amount of capital needed to invest in all welfare-enhancing therapeutic development projects and the amounts actually available. What gives rise to this funding gap? How can finance help to close it?

In this review, we consider the academic research surrounding these questions. We explain how firms that engage in the development of life-saving therapies may face market frictions related to their need to finance their investments. These frictions can potentially alter their investment decisions, resulting in fewer therapies that reach patients and profound implications for society.

We begin by describing the types of firms that engage in drug development[1]—biotechnology and pharmaceutical firms—collectively referred to as biopharmaceutical (biopharma) firms. We then describe the process that these firms must go through to obtain regulatory approval for a new drug. We lay out certain stylized facts about the costs and risks associated with the drug development process—specifically, that it is lengthy, risky, and expensive—and describe the evidence that these costs and risks have increased over time. In stark comparison, $1 billion of (real) investment was able to produce dozens of drugs in 1950 (Scannell et al. 2012), an amount that would be insufficient to successfully develop even a single drug on average from start to finish today.

We argue that the institutional features, costs, and risks associated with drug development lead to four important conclusions. First, the large costs of drug development faced by biopharma firms necessitate reliance on external financing. Second, this requirement creates a strong link between the prospects of biopharma firms and financial markets, exposing these firms to external financing frictions, capital market imperfections, and aggregate market risk (i.e., beta). Third, the institutional features of drug development that are relatively unique to biopharma end up amplifying these external financing frictions, leading to underinvestment in R&D and in therapies that are potentially valuable from a societal perspective. Fourth, financial innovations offer the promise of overcoming these impediments to enhance aggregate investment in drug development, making a case for more normative research in financial innovation for healthcare applications.

We then provide an overview of the body of evidence in support of these conclusions. We describe how biopharma firms use financing sources, and how frictions such as asymmetric information may alter the ability of these firms to access financing and make optimal investment decisions. We also delve into the use of equity markets by biopharma firms, the competitive structure of the industry, the effects of the regulatory environment, and the markets for technology and venture capital (VC)/private equity (PE). When put together, these observations provide strong

[1] For expositional simplicity, when we use the term "drug development," we are implicitly including the development of medical devices, diagnostics, and health-related technologies unless otherwise specified.

evidence that the investment incentives of drug development firms are influenced by the various frictions to which they are exposed and that these incentives impinge on their financing decisions.

Given the importance of developing new therapeutics and the documented difficulties faced by biopharma firms, several studies have proposed more sophisticated types of contracts and other financial engineering solutions to overcome these impediments. We survey these potential solutions, which include various types of financial innovation coupled with changes to the therapeutic development process.

Finally, we note that beyond the social value of improving outcomes in the biopharma industry, the R&D-intensive nature of biopharma means that studying this industry also offers more generalized insights into the R&D and innovation investment process as well as its associated corporate financial decisions and regulatory policy (e.g., Lakdawalla 2018).[2] A particular advantage of focusing on biopharma in this regard comes from data availability; detailed, granular data about clinical trials are freely available to researchers examining drug development. The innovation literature typically uses patents to measure innovation activity, but patents have a number of shortcomings as an innovation proxy (e.g., Williams 2017; Freilich 2019). By allowing researchers to view actual project-level decisions through the clinical trials process—for example, firms initiating clinical trials to treat rare diseases—drug development affords new measures of innovation that do not rely on patents.

Moreover, measures have been developed for estimating the novelty of new compounds in the drug development process (Krieger, Li & Papanikolaou 2022). From a broader corporate finance perspective, the ability to track individual project decisions for both public and private firms offers a view into corporate decision-making not usually available in other contexts. For example, much of the extant literature on mergers and acquisitions (M&A) focuses on acquisitions of entire firms; data on drug development allow researchers to examine both whole-firm acquisitions as well as acquisitions of individual projects.

In Section 2, we provide a brief overview of the drug development process, including the types of firms involved in drug development and the regulatory approval process for new drugs. In Section 3, we connect these institutional features to the financing of projects, and we explain why the prospects of biopharma firms are so strongly linked to financial markets and how this may lead to underinvestment in drug development. Section 4 contains a survey of the empirical evidence for the exposure of biopharma firms to market frictions, how they connect to financing, and their effect on investment incentives. We discuss potential solutions to the problem of underinvestment in drug development in Section 5, including financial innovation, and conclude in Section 6. For a more detailed discussion of these topics, please see Lo & Chaudhuri (2023).

2. THE DRUG DEVELOPMENT PROCESS

To understand how frictions in financing may affect investment incentives in drug development, it is important to understand the process that firms must undergo to bring a new therapeutic to market. In this section, we first describe the types of firms that undertake drug development and the growing role of academia in biomedicine. We then review the regulatory process for obtaining approval to market a new drug and provide stylized facts about the risk and cost of this process. This section lays the foundation for explaining why drug development firms are more exposed to financial markets.

[2] Empirical patterns that have been broadly documented for R&D and productivity may also be driven by the biopharma industry. For example, Benmelech et al. (2021) show that the stylized fact of increased investment in intangible capital but sluggish productivity growth since the 1990s can be attributed to pharmaceutical firms but that improvements in treatments may not be accurately reflected in aggregate productivity measures.

2.1. Types of Drug Development Firms

Firms that engage in drug development are often separated into two main categories: biotechnology (biotech) and pharmaceutical (pharma) companies. Biotech companies are distinguished from pharma companies through several features, none of them unique to either group, so the separation is not always clear-cut (e.g., Carlson 2016). Biotech companies tend to be smaller (as measured by people, revenues, number of products, age, and other metrics) and more numerous than pharma firms, due to the confluence of several trends: breakthroughs in our understanding of the biology of human diseases and how to intervene; technological improvements in chemical, biological, and drug manufacturing processes and bioinformatics; and the ease of entry in the development of biological drugs. They generally have no approved therapeutics (and, in many cases, nothing in clinical trials), are typically focused on biological processes and materials (often called large-molecule drugs) versus purely chemical compounds (known as small-molecule drugs), and are usually generating net losses because of their lack of revenues and intensive focus on R&D.

In contrast, pharma companies are typically much larger, with a portfolio of approved products and a pipeline of therapeutic candidates across multiple diseases (also known as indications) and in various phases of clinical trials. And although, historically, pharma has roots in the chemical industry—hence its early focus on small-molecule drugs—the many breakthroughs in the biotech industry have forced every pharma company to engage with large-molecule drugs in some manner (often through acquisitions of earlier-stage biotech companies). The typical pharma company's collection of approved products also means they are usually profitable, often with significant amounts of cash on their balance sheets and the ability to raise additional capital via debt financing.

These differences can greatly affect the conclusions of economic analyses that focus on these industries. For example, Thakor et al. (2017) show that the profitability of biotech firms tends to be significantly lower than that of pharma firms, in line with the tendency of pharma firms to have more approved drugs and therefore more positive cash flows. Thakor et al. (2017) also show that the assessment of the attractiveness of an investment in the pharma industry relative to the biotech industry is dependent on the classification method used, with some classification methods suggesting a heavy underperformance for biotech investments and others coming to a different conclusion. They make the broad point that both inclusion criteria and weighting schemes can affect these conclusions due to the differences between pharma and biotech firms. For example, in a sample that includes both pharma and biotech firms, one might conclude that investment performance in the biopharma industry is strong, when in fact the positive performance is largely due to a handful of pharma firms, which are more heavily weighted in the analysis because they are larger, while the majority of biotech firms tend to perform poorly from an earnings perspective.

However, it is important to understand that most biotech companies are not striving to generate cash flows but rather to reach scientific and medical milestones that confirm the therapeutic value of their drug candidates. In much the same way that online retail businesses focus more on gathering users and market share in the initial phases of their business—irrespective of the negative earnings they may be generating in the process—early stage biotech companies know that positive cash flows will come easily if and when they hit their clinical targets. The impact of this single-minded corporate focus on R&D versus short-term financials is illustrated in **Table 1**, which compares the 30 top-selling drugs based on worldwide sales in 2000 versus 2018, with drugs originating from academia or biotech highlighted in blue. In 2000, only 4 of the top 30 came from these two sources, but by 2018, 24 of the top 30 and 9 out of the top 10 had their roots in academia and biotech. This stark shift in the balance of economic power has led many biopharma experts to declare that the twentieth century was the Age of Chemistry, during which big pharma and small

molecules were dominant, whereas the twenty-first century is the Age of Biology, in which small biotechs and large molecules have taken the lead.

The differences between biotech and pharma highlighted above suggest that special attention should be paid to firm classifications when conducting research on the biopharma industry using financial databases such as Center for Research in Security Prices (CRSP) and Compustat. A researcher may be interested in analyzing the drug development industry as a whole or either the pharma or biotech sector individually. When analyzing the industry as a whole, a researcher often must query firm information using formalized industry classification codes [i.e., the Standard Industry Classification (SIC) and the North American Industry Classification System (NAICS)]. However, multiple industry codes correspond to pharma and biotech. For example, at least five 4-digit SIC codes and at least six 6-digit NAICS codes can be reasonably mapped to pharma or

Table 1 Comparison of top 30 drugs by worldwide sales in (*a*) 2000 and (*b*) 2018[a]

	Product	Marketer(s)	Sales ($M)	Organization responsible for discovery/development of product[b]
(*a*) Top 30 drugs in 2000				
1	Prilosec	AstraZeneca	$6,260	NA
2	Zocor	Merck	$5,280	NA
3	Lipitor	Pfizer	$5,030	NA
4	Norvasc	Pfizer	$3,361	NA
5	Prevacid	TAP Pharmaceuticals	$2,740	NA
6	Procrit	J&J	$2,709	Amgen → J&J
7	Celebrex	Pharmacia	$2,614	NA
8	Prozac	Eli Lilly	$2,585	NA
9	Zyprexa	Eli Lilly	$2,366	NA
10	Paxil	GSK	$2,349	NA
11	Claritin	Schering-Plough	$2,194	NA
12	Vioxx	Merck	$2,160	NA
13	Zoloft	Pfizer	$2,140	NA
14	Epogen	Amgen	$1,963	Amgen
15	Premarin	Wyeth	$1,870	NA
16	Augmentin IR	GSK	$1,847	NA
17	Vasotec	Merck	$1,790	NA
18	Pravachol	Bristol Myers	$1,766	NA
19	Glucophage IR	Bristol Myers	$1,718	NA
20	Cozaar	Merck	$1,715	NA
21	Tylenol	J&J	$1,680	NA
22	Insulin	Novo Nordisk	$1,671	NA
23	Cipro/Ciprobay	Bayer	$1,648	NA
24	Risperdal	J&J	$1,603	NA
25	Taxol	RTI → Bristol Myers	$1,561	NA
26	Zithromax	Pliva → Pfizer	$1,382	NA
27	Intron A	Schering-Plough	$1,360	NA
28	Viagra	Pfizer	$1,344	NA
29	Neurotonin	Pfizer	$1,334	NA
30	Flixotide/Flovent	GSK	$1,334	NA

(*Continued*)

Table 1 (*Continued*)

Product		Marketer(s)	Sales ($M)	Organization responsible for discovery/development of product	
				University/hospital	Biotech company[b]
(*b*) Top 30 drugs in 2018					
1	Humira	AbbVie	$20,476	University of Cambridge; Scripps Research Institute	CAT → Knoll
2	Revlimid	Celgene	$9,816	Boston Children's Hospital	Celgene
3	Enbrel	Amgen (Immunex)/Pfizer	$8,538	Massachusetts General Hospital	Immunex
4	Rituxan	Roche (Genentech)	$7,547	NA	IDEC Pharmaceuticals → Genentech
5	Opdivo	Bristol Myers	$7,524	NA	Medarex
6	Keytruda	Merck	$7,198	LifeArc	NA
7	Eylea	Regeneron/Bayer	$7,164	NA	Regeneron
8	Herceptin	Roche (Genentech)	$7,140	University of California, Los Angeles	Genentech
9	Avastin	Roche (Genentech)	$7,004	NA	Genentech
10	Eliquis	Bristol Myers	$6,438	NA	Bristol Myers
11	Xarelto	Bayer	$6,166	NA	NA
12	Remicade	J&J (Centocor)/Merck	$6,002	New York University	Centocor
13	Prevnar 13	Pfizer	$5,901	NA	NA
14	Stelara	J&J	$5,293	NA	Centocor
15	Lyrica	Pfizer	$5,004	Northwestern University	NA
16	Genvoya	Gilead	$4,737	KU Leuven; Emory University	Triangle; Gilead
17	Neulasta	Amgen	$4,596	Memorial Sloan Kettering Cancer Center	Amgen
18	Imbruvica	AbbVie/J&J	$4,454	NA	Pharmacyclics
19	Tecfidera	Biogen	$4,274	NA	Fumapharm
20	Lantus	Sanofi	$4,211	NA	NA
21	Ibrance	Pfizer	$4,118	NA	Onyx
22	Januvia	Merck	$3,984	Demuth; Tufts University	Prosidion
23	Victoza	Novo Nordisk	$3,857	NA	NA
24	Lucentis	Roche/Novartis	$3,743	NA	Genentech
25	Botox	Allergan	$3,577	NA	NA
26	Soliris	Alexion	$3,563	Oklahoma Medical Research Foundation	Alexion
27	Triumeq	Pfizer/ViiV Healthcare/GSK	$3,535	NA	NA
28	Zytiga	J&J	$3,498	The Institute of Cancer Research	Cougar
29	Mavyret	AbbVie	$3,438	NA	NA
30	Gilenya	Novartis	$3,380	Kyoto University	Novartis

Table adapted with permission from Royalty Pharma.

Abbreviations: CAT, Cambridge Antibody Technology; GSK, GlaxoSmithKline; IR, immediate release; J&J, Johnson & Johnson; NA, not applicable; RTI, Research Triangle Institute.

[a]Drugs originating from academia or biotech companies are highlighted in blue.

[b]Arrows indicate rights licensed from one party to another for further development and commercialization.

biotech, and some biopharma firms are classified by codes that are shared by non-biopharma firms (e.g., Thakor et al. 2017). Therefore, the potential for erroneous inclusions and exclusions can be significant. When focusing on either pharma or biotech firms, standard classification systems like SIC and NAICS codes do not always offer a clean distinction between pharma and biotech companies, with one classification method designating a firm as pharma that another designates as biotech. Furthermore, a firm may start out as a small biotech firm but then grow over time into a pharma firm (e.g., Amgen, Biogen, and Gilead), and most traditional classification systems are not dynamic and cannot account for these transitions.

New alternative classification methods offer promising ways to identify pharma and biotech companies using various data sources. For example, Thakor et al. (2017) use machine-learning techniques with financial and accounting data to classify pharma and biotech companies on a rolling-window basis, thereby capturing the trajectory of biotech companies as they grow into pharma companies. Hoberg & Phillips (2010, 2016) use textual analysis methods and Form 10-K filings to classify firms in terms of their product similarity.

In the rest of this article, we refer to drug development firms generally as biopharma firms for convenience. However, we are careful to distinguish between pharma and biotech when needed.

2.2. The Growing Importance of Academia

Academic institutions are playing increasingly more significant and direct roles in the biopharma industry due to a phenomenon called convergence by Sharp, Jacks & Hockfield (2016)—the convergence of the life sciences, physical sciences, and various engineering disciplines. Many experts acknowledge that convergence has brought biomedicine to an inflection point in our ability to treat and, in a growing number of cases, completely cure a number of diseases. However, few data are yet available on the magnitude of this impact.

To address this gap, Huang et al. (2021) published the first systematic study of technology licensing in the life sciences by a major university, the Massachusetts Institute of Technology (MIT). In addition to tabulating the number of companies launched, jobs created, and funds raised by entities that have licensed MIT life sciences patents, they find that 4 approved small-molecule drugs cite MIT patents and another 31 US Food and Drug Administration (FDA)–approved drugs have some involvement of MIT licensees. Of the 31 approved drugs that involved an MIT licensee, 55% are a new molecular or biological entity, and 55% were granted priority review by the FDA, an indication that they address an unmet medical need. Such impact is especially impressive given the fact that MIT does not have a medical school or affiliated teaching hospital.

Another example of academic impact in biomedicine is seen in Vasileva et al.'s (2022) case study of the Breast Cancer Research Foundation (BCRF), a nonprofit organization established in 1993 that has raised more than half a billion dollars to support breast cancer research. Using survey data gathered from BCRF grantees, the authors documented significant impact in multiple dimensions: 19.5% of BCRF grantees filed patents, 35.9% had a project that reached clinical development, and 12 companies have or will be spun off from existing projects, thus creating 127 new jobs. Noncommercially, 441 graduate students have been trained by 116 grantees, 767 postdoctoral fellows have been trained by 137 grantees, 66% of grantees have used funding for faculty salaries, 93% have achieved collaboration with other researchers, and 42.7% have enacted process improvements in research methodology.

The outsized role of academia in biomedicine has also been highlighted in two case studies, one on the I-SPY adaptive platform trial (APT) cited in Section 5.1 (Das & Lo 2017) and another on the Stanford School of Medicine's SPARK program (Kim, Omura & Lo 2017). The latter program was created in 2006 to educate Stanford medical school students and faculty about

bringing academic research from bench to bedside by providing mentorship and funding for approximately a dozen SPARK scholars interested in developing therapeutics based on their academic research, with a particular focus on impacting patient lives, regardless of economic factors. These two case studies and the MIT patents study by Huang et al. (2021) underscore the critical role that academia and teaching hospitals play in the biomedical ecosystem. A natural application of financial innovation to this setting would be the creation of a multi-university consortium to raise a private-sector fund that invests in the combined intellectual property of the consortium, perhaps in coordination with government efforts such as the Small Business Innovation Research and Small Business Technology Transfer programs. Examples that hint of the possibility of such a multi-university megafund include the Tri-Institutional Therapeutics Discovery Institute (TDI)[3] and Deerfield Management's 16 academic partnerships. A fully articulated business model of such a multi-university consortium has yet to be developed and is a worthy topic for future research.

2.3. The FDA Drug Approval Process

The development of drugs in the United States and other countries is highly regulated, as governments require a demonstration of both the safety and efficacy of treatments before they are allowed to reach consumers. In the United States, the FDA is responsible for the regulation and oversight of any firm developing a drug.

The FDA approval process for a new drug is illustrated in **Figure 1**.[4] The beginning of the process is a more informal preclinical phase, which consists of the discovery or identification of new types of treatments, such as new molecular or biological compounds or new mechanisms of delivery of existing compounds to treat specific diseases. An important part of this phase is determining if a drug has the potential to cause harm before it is tested on humans; thus, the developing biopharma firm must conduct laboratory testing to determine the drug candidate's safety profile.

After preclinical testing comes the clinical trial testing of the drug compound, which consists of three phases, denoted phase 1, phase 2, and phase 3. These clinical trials involve administering the drug to human subjects, with the smallest number of subjects (20–100) in phase 1 trials and the largest number of subjects (hundreds or thousands) in phase 3 trials. Phase 1 trials typically focus only on determining safety and the maximum tolerable dose of a drug; hence, volunteers in this phase are typically healthy adults who do not suffer from the specific disease the drug is targeting.

If no severe safety concerns are identified in this phase, the drug passes and is allowed to continue to phase 2, in which the drug is tested on a larger group of volunteers who suffer from the target disease and are chosen carefully to be most likely to respond to the drug. If sufficient evidence is found that these patients do respond, then the drug passes phase 2 and is allowed to move into phase 3, which involves an even larger sample of patients more representative of the broader patient population, rather than the cherry-picked sample in phase 2.

If the drug demonstrates efficacy in this larger and more heterogenous sample, the sponsoring biopharma company is allowed to submit a new drug application (NDA) or biologic license application (BLA), depending on whether the compound is chemical or biological in nature.

[3] TDI is a collaboration between Memorial Sloan Kettering Cancer Center, Rockefeller University, and Weill Cornell Medicine focused on drug discovery and supported by Takeda Pharmaceuticals. For details, see **https://www.tritdi.org**.

[4] The approval process for medical devices is significantly shorter than that for drugs, but evidence shows that uncertainty and other institutional features of the device approval process affect the innovation incentives of device manufacturers. For example, see Stern (2017).

Figure 1

The US Food and Drug Administration (FDA) approval process, from preclinical discovery and screening through the clinical trials process when drug candidates are tested in humans (phases 1–3) to review of the new drug application (NDA) for drug candidates that show safety and efficacy and to post-marketing once a new drug is approved (phase 4). Figure reproduced from **https://www.fda.gov/drugs/information-consumers-and-patients-drugs/fda-drug-approval-process-infographic-horizontal**; PDF infographic was downloaded on July 25, 2022.

Upon a successful review of the phase 3 data as well as the quality of the sponsor's manufacturing facilities and delivery mechanism, the drug is approved for consumer use after the labeling and prescription information is determined. After approval, the FDA also conducts post-marketing drug safety monitoring to discover any potentially harmful effects of the drug that were not

detected during the approval process, and it may take measures to limit the use of the drug by consumers if new safety and/or efficacy concerns arise.

The rigorous requirements of the drug approval process help to protect the end users of a drug by ensuring that an approved product has the necessary levels of safety and efficacy. However, this rigor also creates challenges for the firms developing the drugs given that the resulting process is lengthy, expensive, and risky. We consider the first two issues here and turn to the issue of risk in Section 3.

For a typical drug candidate, the development process takes several years from start to finish. The FDA estimates the length of phase 1 trials as "several months," phase 2 trials as "several months to 2 years," and phase 3 trials as "1 to 4 years" (FDA 2018). These time spans are consistent with the evidence provided by DiMasi & Grabowski (2007), which shows that phase 1 trials take an average of 1.3 years to complete, phase 2 trials an average of 2.3 years, phase 3 an average of 2.8 years, and the NDA or BLA review process takes an average of 1.4 years. In total, the average development time of a drug from start to finish was 8.1 years for biotech firms and 7.5 years for pharma firms.[5]

The empirical evidence suggests that the cost of developing a drug is high and rising over time. Using a sample of 93 drugs from 12 pharmaceutical firms, DiMasi et al. (1991) estimated the average cost of developing a drug to be $523 million, including capitalized costs over the entire length of development. However, DiMasi, Hansen & Grabowski (2003) estimated this cost to be $1.2 billion, and the most recent estimate by DiMasi, Grabowski & Hansen (2016) is $2.851 billion (all figures converted to 2020 dollars). It should be noted that this number is an estimate of the cost of developing an approved drug from beginning to end, including the possibility of multiple failed attempts. The out-of-pocket expense of a single attempt from phase 1 through approval has been estimated at roughly $200 million, given survey evidence of an average cost of $35,000 per patient per clinical trial (although substantial heterogeneity is found in these costs, e.g., Fernandez, Stein & Lo 2012).

This trend of increasing development costs over time was laid out starkly by Scannell et al. (2012), who demonstrated the declining R&D efficiency of the industry by showing how $1 billion (inflation-adjusted) of R&D spending could produce dozens of drugs in the 1950s but by 2010 was not sufficient for even a single drug (see **Figure 2**). However, a follow-up study by Ringel et al. (2020) using more recent data shows that this trend may finally be reversing, although it is still too early to tell whether this is a random blip or a genuine change in trend.

2.4. Benefits of Regulatory Approval

What about the benefits to a firm that succeeds in developing an approved drug? Approval by the FDA allows the drug maker to enjoy a marketing exclusivity period for the drug. This period typically lasts from 3 to 7 years, depending on the type of drug and particular areas of development that regulators want to incentivize. For example, an approved orphan drug (targeting a rare disease) currently has an exclusivity period of 7 years, with the goal of improving the financial reward for firms to develop such drugs. Similarly, an initiative to develop new antibiotics allows

[5]This development time can be reduced in some special cases. First, a biopharma firm developing a generic drug—that is, an equivalent drug to a marketed drug that enters after the marketed drug's exclusivity period—can file an Abbreviated New Drug Application and bypass the majority of the drug development process, so long as the generic manufacturer can prove bioequivalence to the marketed drug. Second, recent FDA initiatives such as the Breakthrough Therapy, Fast Track, and Accelerated Approval designations seek to expedite the development and review process if a drug meets certain criteria (such as being the first available treatment or having a distinct advantage over existing treatments).

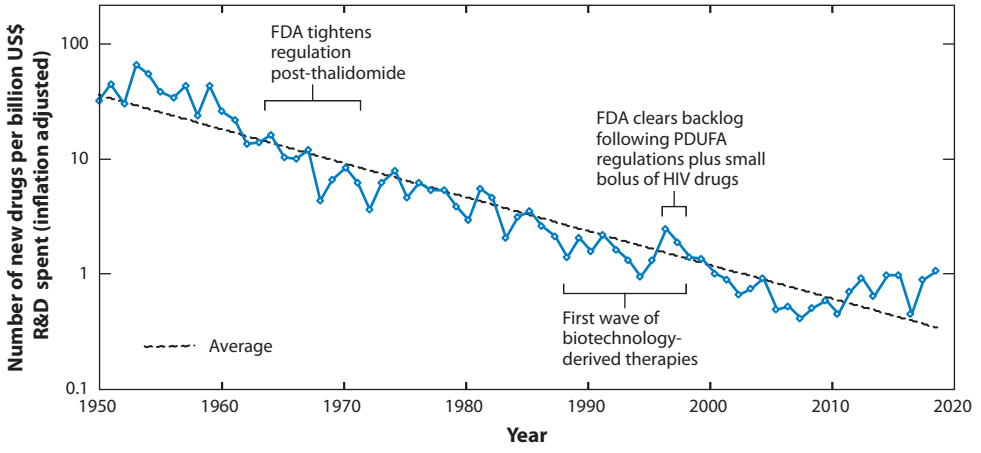

Figure 2

Declining R&D efficiency in biopharma. The number of drugs developed per billion US dollars spent on R&D has trended downward since the 1950s. Abbreviations: FDA, Food and Drug Administration; PDUFA, Prescription Drug User Fee Act. Figure adapted with permission from Scannell et al. (2012) and Lo & Chaudhuri (2023).

5 years to be added to the exclusivity period in certain circumstances. Thus, all else being equal, a firm that has a new product approved will enjoy monopoly profits on that drug for a significant amount of time, but afterward it faces potential competition. Marketing exclusivity is distinct from patent protection—patents for drugs are typically granted early on in the development process and focus on active ingredients, formulation, and methodology of delivery. In contrast, marketing exclusivity prevents the approval of any competing drug. As a result, marketing exclusivity typically offers stronger protection than patents—for example, once marketing exclusivity expires, generic drugs can potentially invalidate existing patents and enter the marketplace (e.g., Grabowski & Kyle 2007; Li, Lo & Thakor 2021; Gaessler & Wagner 2022).[6] Nonetheless, it has been shown that both patent protection and marketing exclusivity serve as important regulatory tools to enhance the profits of developing firms, with the goal of incentivizing further innovation (see, e.g., Eisenberg 2001; Grabowski 2002).[7]

However, although there are the positive regulatory-induced benefits that come with drug approval, Grabowski & Vernon (1990) show that firms with approved drugs face a skewed distribution of returns, with blockbuster drugs achieving much higher returns than other drugs. Thus, given the large investment costs of drug development, a very successful commercial result is often needed to justify the high up-front investment in the project. This observation is consistent with the evidence provided by Kyle (2018) that measures of market reward are often only weakly

[6]Consistent with this observation, Duggan, Garthwaite & Goyal (2016) find only small price impacts and little impact on quantities of drugs when patent protection on them was strengthened in India due to a 2005 legislative reform intended to comply with international Trade-Related Aspects of Intellectual Property Rights agreements.

[7]The use of patent protection, marketing exclusivity periods, and other regulatory features such as priority review for certain new drugs (such as orphan drugs) highlights a broader debate on the effectiveness of various push/pull incentives on innovation; for a review, see, e.g., Di Stefano, Gambardella & Verona (2012). For example, a proposed alternative way to incentivize innovation, which could be used alongside existing incentives, is the use of prizes for successful innovation (e.g., Kremer & Williams 2010).

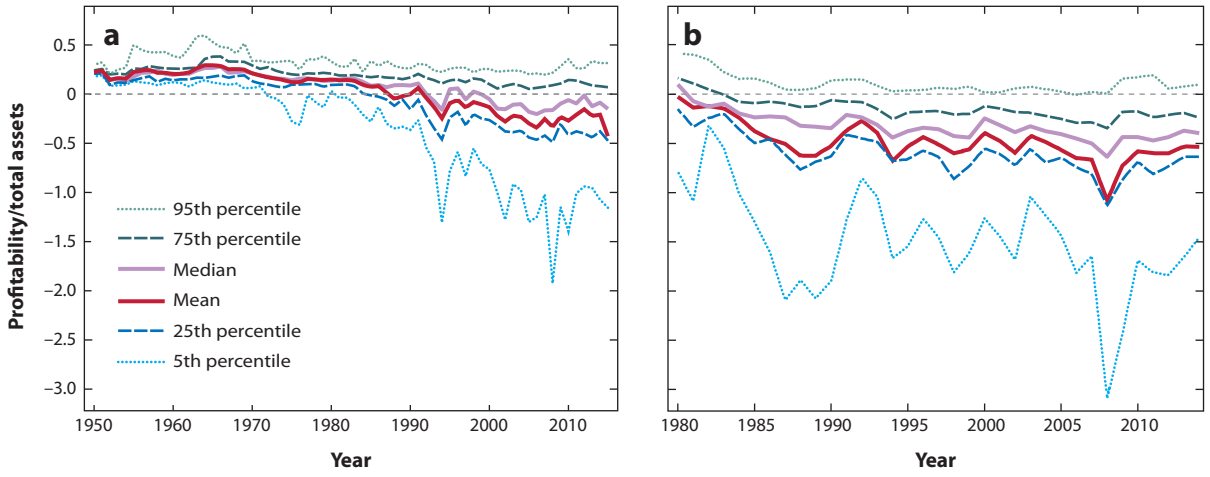

Figure 3

Declining profitability in biopharma. The profitability of the (*a*) pharmaceutical sector and (*b*) biotech sector, scaled by total assets to account for size differences across companies, where profitability is defined as earnings (revenues minus costs) before interest and taxes. After 1990, the median pharma company's profitability declined and, after 2000, turned consistently negative. Similarly, for biotech firms, profitability has been declining over time and is consistently negative, even for firms in the 75th percentile. Figure adapted with permission from Thakor et al. (2017).

related to measures of therapeutic value for new drugs, and it is also consistent with the empirical evidence that the majority of biopharma firms have negative profitability and that profitability in the industry has been consistently declining on average, as shown in **Figure 3** (from Thakor et al. 2017). However, as **Figure 3** shows, marked heterogeneity is still seen in the prospects of firms within the industry, with some earning substantially high profits.

Developing a drug also produces the benefit of knowledge capital, such as scientific expertise, understanding of research and production methods, connections with physicians, and so forth, that can potentially be deployed for subsequent drugs under development to improve their odds of success. For example, a biopharma firm that has spent the money to successfully develop a vaccine can apply that knowledge when developing subsequent vaccine candidates. However, one caveat is that this knowledge capital is not always suitable for redeployment across therapeutic areas. For example, knowledge capital built up in vaccine development may not be applicable to cancer therapeutics. Krieger, Li & Thakor (2022) develop a model that includes knowledge capital as a feature and provide evidence that it creates path dependencies in drug development, which can affect ex ante investment incentives.

3. DRUG DEVELOPMENT, FINANCING, AND INVESTMENT

When considered together, the institutional features of the drug development process lead to a number of important financial implications for biopharma firms. In this section, we discuss these features as well as the related risks and measures to better manage those risks.

3.1. The Outsized Cost of Drug Development

First, the large costs associated with drug development imply that drug development firms are forced to rely on external financing to fund their activities, given the inadequacy of internal funds in fully satisfying their operating costs. This is partly because many firms in the industry without

an approved product have few sources of revenue (Thakor et al. 2017). Biopharma firms tend to rely largely on equity financing, limiting the use of debt for the most part (Thakor et al. 2017; Giambona, Golec & Lopez-de-Silanes 2021; Thakor & Lo 2022). Biopharma firms in particular are able to tap public equity markets through initial public offerings (IPOs) even if they only have preclinical projects (Aghamolla & Thakor 2022a).

This reliance on equity financing is similar to that of many other R&D-intensive firms (Brown, Fazzari & Petersen 2009). The traditional explanation for why such firms do not utilize substantial amounts of debt is that they lack sufficient tangible assets to offer as collateral, their low profitability and uncertain cash flows amplifying the agency frictions that impede debt financing.[8] Myers & Howe (1997) create a model in which large pharma investment costs create R&D leverage—a commitment to continue spending funds so as to reach the later phases of drug development—which effectively increases financial leverage. However, recent evidence suggests that biopharma firms can use patents as collateral in lieu of traditional hard assets, enhancing their ability to take on more debt (Deshpande & Nagendra 2017; Mann 2018).

3.2. Biotech's Bigger Betas

Second, the reliance on external financing means that the prospects of biopharma firms will be strongly linked to the state of the market. During rising equity markets, external financing will generally be plentiful, but during market downturns, it will typically be harder for biopharma firms to finance their drug development programs. This suggests that the smaller cash-poor biotech companies are much more sensitive to financing risk and should therefore have higher stock market betas than their cash-rich and profitable big pharma counterparts, as Thakor et al. (2017) observe. This insight is also in line with earlier finance literature that has documented a significant link between the supply of equity financing and R&D more generally (e.g., Brown, Fazzari & Petersen 2009).

This intuition is confirmed in **Figure 4**, which contains the 250-day rolling-window daily beta estimates of the NYSE Arca Pharma and Biotech Indexes from November 30, 1995, to December 31, 2020. Over the entire sample period, the Biotech Index beta is almost always higher than the Pharma Index beta, and on average, the Biotech Index beta exceeds 1, the exceptions being periods when biotech VC funding is more plentiful, the IPO markets are more active, and, consequently, the biotech sector is less likely to run into funding shortages when capital is needed.

Table 2 presents the stock market betas of a selection of individual big pharma companies and biotech companies as of August 14, 2020, along with the implied capital asset pricing model (CAPM) costs of capital assuming a 4% risk-free rate and 6% risk premium. Except for Moderna, the higher betas of the biotechs imply costs of capital as high as 16%, whereas all the big pharma costs of capital are below 10%, and Eli Lilly's is 5.32%. Moderna is an outlier, not only due to its stock-price run-up from the success of its COVID-19 vaccine but also because it had raised significant amounts of capital even before the pandemic and is therefore insulated to a significant degree from the financing risk that affects most biotech companies.

3.3. Financial Frictions and R&D Underinvestment

Third, the institutional features of biopharma, including the regulatory approval process and the difficulty for investors to assess the financial ramifications of technical details involved in drug

[8]For theoretical models of these effects, see, e.g., Besanko & Thakor (1987a,b) and Rampini & Viswanathan (2013).

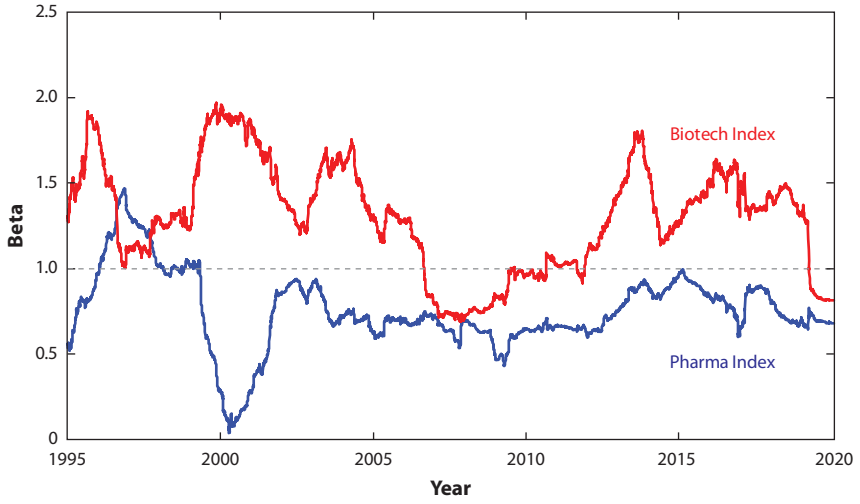

Figure 4

The 250-day rolling-window daily market beta estimates for the NYSE Arca Pharma Index (*blue*) and Biotech Index (*red*) from November 30, 1995, to December 31, 2020. The market proxy is the Center for Research in Security Prices (CRSP) value-weighted return including dividends.

development, mean that the frictions associated with the financing–investment link are amplified. This leads to underinvestment in R&D and therapies that are potentially valuable from a societal perspective. Put differently, the difficulties faced by biopharma firms in procuring financing for some projects may lead to an underprovision of therapies relative to the social optimum.[9]

Table 2 Stock market betas of a selection of big pharma and biotech companies on August 14, 2020, and implied CAPM cost of capital assuming a 4% risk-free rate and a 6% market risk premium

Big pharma			Biotech		
Company	**Beta**	**CAPM cost of capital**	**Company**	**Beta**	**CAPM cost of capital**
Eli Lilly	0.22	5.32%	Agios	2.03	16.18%
Gilead	0.66	7.96%	Alexion	1.39	12.34%
GSK	0.40	6.40%	Alnylam	1.80	14.80%
J&J	0.69	8.14%	BridgeBio*	1.14	10.84%
Merck	0.49	6.94%	Editas	1.98	15.88%
Novartis	0.41	6.46%	Moderna**	0.10	4.60%
Pfizer	0.73	8.38%	Sarepta	1.83	14.98%
Sanofi	0.47	6.82%	Solid	1.16	10.96%

Table adapted with permission from Lo & Chaudhuri (2023).
Abbreviations: CAPM, capital asset pricing model; GSK, GlaxoSmithKline; J&J, Johnson & Johnson.
Risk-free rate (R_f) = 4%.
Expected return of the market ($E[R_m]$) = 10%.
*Estimated, 6/28/19 to 8/14/20.
**Estimated, 12/10/18 to 8/14/20.

[9]A number of studies have provided evidence from a variety of perspectives that investment in societally beneficial treatments is lower than optimal. For example, Krieger, Li & Papanikolaou (2022) provide evidence that novel drugs have higher ex ante economic value but that firms underinvest in them. Kyle (2018) uses a French

Hall & Lerner (2010) refer to this problem as a funding gap for R&D investment by innovative firms (see also Kerr & Nanda 2015).

A variety of financial frictions may contribute to this funding gap. One classic financing friction is asymmetric information, which leads to adverse selection costs in raising financing (e.g., Myers & Majluf 1984). Thakor & Lo (2017) make the theoretical argument that low probabilities of success combined with the specialized expertise needed to assess project prospects—particularly in the case of biopharma investments—lead to adverse selection that distorts investment away from the first-best choice, because firms are unable to raise financing for those investments. In particular, there may be investments that are both positive net present value (NPV) for the firm and valuable for society but in which the firms are unable to invest. Thakor & Lo (2017) also observe that the technical nature of R&D and low probabilities of success make agency problems and moral hazard harder to detect, which further exacerbates the problem. This is because outsiders may lack the technical knowledge to distinguish between good and bad projects. Furthermore, it becomes difficult to ascertain ex post whether project failure is due to the inherent low chance of success or because it was a bad project from the beginning. Jørring et al. (2021) make similar points theoretically.

The underprovision of socially valuable treatments represents an inefficient equilibrium from a social welfare standpoint. In order to find potential solutions to this problem, it is essential to understand the particular frictions that cause it to arise. We turn to this issue in Sections 4 and 5.

3.4. Estimating Probabilities of Success

One of the biggest risks facing biopharma companies and their investors is the risk of scientific failure, i.e., the failure of a drug candidate to meet clinical standards of safety and efficacy. To underscore the role that this risk plays in biopharma decision-making processes, Lo & Chaudhuri (2023) provide a stylized summary of the value of a typical drug development project, which they dub the Fundamental Law of Healthcare Finance:

$$\mathrm{E[NPV]} = \mathrm{PV(Earnings)} \times \mathrm{PoS} - \mathrm{PV(Costs)}, \qquad 1.$$

where PoS is the probability of success of the project, PV(Earnings) is the present value of all future earnings of the drug if approved, and PV(Costs) is the present value of the drug's development costs. This simple relation highlights the binary nature of drug development and the importance of the PoS parameter in determining the financial viability of biomedical R&D. Therefore, a considerable amount of attention has been paid to estimating and forecasting PoS in the drug development literature.

The historical evidence on the successes and failures of drug development clearly shows a substantial scientific risk of failure. Using a sample of 1,316 drugs from 50 pharma companies, DiMasi et al. (2010) found an average clinical approval success rate from phase 1 to approval of 19%. Using detailed data from a much broader sample of clinical trial outcomes from 2003 to 2011, Hay et al. (2014) report an average probability of successful approval from phase 1 across all indications of 10.4%. Thomas et al. (2016) use a similarly broad sample from 2006 to 2015 and report an average probability of successful approval from phase 1 of 9.6%.[10]

government assessment of therapeutic value and finds evidence suggesting that countries are overinvesting in drugs with less therapeutic value.

[10]Assessing the risk of drug development has been made easier with the mandated reporting of clinical trial outcomes for many drugs, which was put into place following the FDA Amendments Act (FDAAA) of 2007. Trial information and summary results are required to be posted to the FDA's website, **https://clinicaltrials.gov**,

In the most comprehensive sample to date of more than 400,000 clinical trial registrations from 2000 to 2015, Wong, Siah & Lo (2019a) estimate an average probability of successful approval from phase 1 of 6.9% (see **Table 3**). However, Wong, Siah & Lo (2019a) argue that the traditional approach of estimating PoS using the historical relative frequencies of the number of clinical trials in each phase can yield significant biases due to missing data. In particular, a number of cases have occurred in which a drug successfully completes phase 1 and phase 3 trials for a specific indication but no record of a phase 2 trial exists.[11] Using phase-by-phase relative frequencies would underestimate the probability of transitioning from phase 1 to phase 2 because no phase 2 trial is recorded in this case—when, in fact, the drug was so successful that it proceeded directly to phase 3. Therefore, Wong, Siah & Lo (2019a) propose to impute such missing data, which is tantamount to taking a path-by-path approach to estimating PoS rather than the traditional phase-by-phase approach used by other studies. **Figure 5** contains a graphical illustration and simple numerical example of the two approaches and how they can lead to different numerical PoS estimates.

Using the path-by-path approach and a data set that is one to two orders of magnitude larger than those used by previous studies, Wong, Siah & Lo (2019a) compute the overall PoS to be 13.8%, double the phase-by-phase estimate of 6.9%. This difference is meaningful not only statistically but also economically when we consider that the expected revenue of an approved drug is often billions of dollars. Even a single percentage point difference in the PoS multiplier of the valuation in Equation 1 can have tremendous consequences for go/no-go decisions in the biopharma industry.

Wong, Siah & Lo (2019a) also provide more detailed PoS estimates by disease group and find considerable variability in success rates (see **Table 4**). For example, oncology has a PoS of only 3.4%—in sharp contrast to vaccines, which have a PoS of 33.4%. They also produce PoS estimates for several other stratifications, including rare/nonrare diseases, with/without biomarkers, industry-led/nonindustry-led trials, and rolling-window time series estimates, to capture time variation in PoS.

Given the importance of these estimates for biopharma decision-making and financial risk management, Wong and colleagues have produced a series of follow-on studies focused on cancer (Wong, Siah & Lo 2019b), vaccines (Lo, Siah & Wong 2020), and opioids and related pain management therapeutics (Maher et al. 2022). Quarterly updates of PoS estimates are also released into the public domain through MIT's Project ALPHA (Analytics for Life-sciences Professionals and Healthcare Advocates) at **https://projectalpha.mit.edu/pos/**.

3.5. Predicting Clinical Trial Outcomes

In addition to estimating historical success rates, researchers have applied a variety of statistical and artificial intelligence techniques to predicting clinical trial outcomes. For example, Goffin et al. (2005) study the tumor response rates of 58 cytotoxic agents in 100 phase 1 trials and 46 agents in 499 phase 2 trials; El-Maraghi & Eisenhauer (2008) look at the objective responses of 19 phase 2 anticancer drugs in 89 single-agent trials; Malik et al. (2014) examine the trial objective responses of 88 anticancer agents in phase 1; DiMasi et al. (2015) analyze 62 cancer drugs and propose an approved new drug index algorithm with four factors to predict approval for lead indications

within a certain time period after completion (see Hsu et al. 2019). This data availability has also enhanced the ability of researchers to view the actual project-level investment decisions of these companies, as we discuss in more detail later.

[11] This situation may be the result of a clerical error, but in a growing number of cases, it is because the drug demonstrated such efficacy in phase 1 that, for ethical reasons, regulators allowed the trial sponsor to skip phase 2 and proceed directly to a phase 3 trial so as to expedite the approval process.

Table 3 PoS estimates of clinical trials from 2000 to 2015 by Wong, Siah & Lo (2019a) and comparison to previous estimates obtained in other studies[a]

Method	Wong, Siah & Lo (2019a), all indications (industry)				Wong, Siah & Lo (2019a), lead indications (industry)		Thomas et al. (2016), all indications		Hay et al. (2014), all indications		Hay et al. (2014), lead indications		DiMasi et al. (2010), lead indications	
	Path-by-path		Phase-by-phase		Path-by-path		Phase-by-phase		Phase-by-phase		Phase-by-phase		Phase-by-phase	
	$PoS_{i,i+1}$	$PoS_{i,APP}$	$PoS_{i,i+1}$	$PoS_{i,APP}$	$PoS_{i,i+1}$	$PoS_{i,APP}$	$PoS_{i,i+1}$	$PoS_{i,APP}$	$PoS_{i,i+1}$	$PoS_{i,APP}$	$PoS_{i,i+1}$	$PoS_{i,APP}$	$PoS_{i,i+1}$	$PoS_{i,APP}$
Phase 1 to 2	66.4%	13.8%	38.8%	6.9%	75.8%	21.6%	63.2%	9.6%	64.5%	10.4%	66.5%	15.3%	71.0%	19.0%
Phase 2 to 3	48.6%	21.0%	38.2%	28.8%	55.6%	26.4%	30.7%	15.2%	32.4%	16.2%	39.5%	23.1%	45.0%	26.8%
Phase 3 to approval	59.0%	59.0%	59.0%	59.0%	67.7%	67.7%	49.6%	49.6%	50.0%	50.0%	58.4%	58.4%	60.0%	59.5%
Phase 1 to approval	NA	13.8%	NA	6.9%	NA	21.6%	NA	9.6%	NA	10.4%	NA	15.3%	NA	19.0%
Number of drugs	15,102						Unknown		5,820		4,736		1,316	
Years of source data (time span)	2000–2015 (16 years)						2006–2015 (10 years)		2003–2011 (9 years)				1993–2009 (17 years)	
Number of companies	5,764						1,103		835				50	

Table adapted from Wong, Siah & Lo (2019a, table 1).

Abbreviations: APP, approval; NA, not applicable; PoS, probability of success.

[a]$PoS_{i,i+1}$ indicates the probability of success of going from the current phase, i, to the next phase, $i+1$, while $PoS_{i,APP}$ indicates the probability of success of going from the current phase to approval.

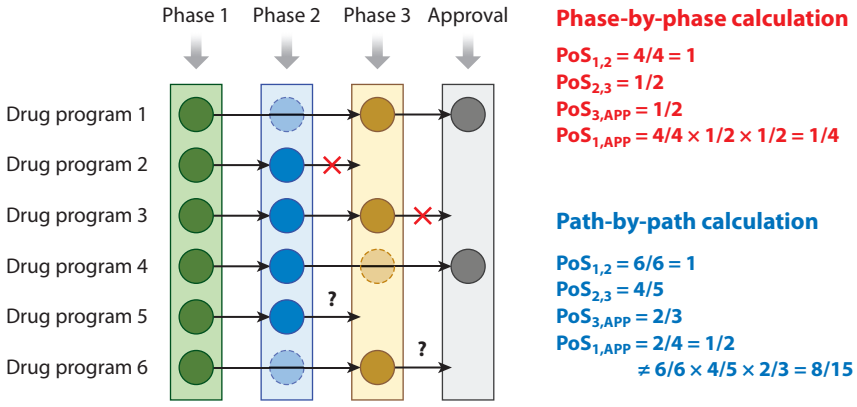

Figure 5

A visualization of the distinction between phase-by-phase and path-by-path calculations of probability of success (PoS) for drug development programs. Each row represents a drug development path, and each column refers to a phase in the clinical trial development process. A solid circle represents an observed trial for the drug development program. Dashed circles represent development stages where no trial in that phase is observed but we know that it must have occurred because a trial in the next phase took place. The arrows represent possible phase transitions. A red X on the arrows tells us that the drug development program failed to move to phase $i+1$ from phase i. A question mark above the arrows tells us that we do not know if the phase transition is a failure or a success because the trial is still in progress. Calculations in red represent phase-by-phase estimation in which missing data are ignored, and calculations in blue represent path-by-path estimation in which missing data are imputed.

Table 4 PoS estimates of clinical trial data from 2000 to 2015 by Wong, Siah & Lo (2019a) by disease group for all indications

	All indications (industry)							
	Phase 1 to phase 2		Phase 2 to phase 3			Phase 3 to approval		Overall
Therapeutic group	Total paths	$PoS_{1,2}$, % (SE, %)	Total paths	$PoS_{2,3}$, % (SE, %)	$PoS_{2,APP}$, % (SE, %)	Total paths	$PoS_{3,APP}$, % (SE, %)	PoS, % (SE, %)
Oncology	17,368	57.6 (0.4)	6,533	32.7 (0.6)	6.7 (0.3)	1,236	35.5 (1.4)	3.4 (0.2)
Metabolic/ endocrinology	3,589	76.2 (0.7)	2,357	59.7 (1.0)	24.1 (0.9)	1,101	51.6 (1.5)	19.6 (0.7)
Cardiovascular	2,810	73.3 (0.8)	1,858	65.7 (1.1)	32.3 (1.1)	964	62.2 (1.6)	25.5 (0.9)
CNS	4,924	73.2 (0.6)	3,037	51.9 (0.9)	19.5 (0.7)	1,156	51.1 (1.5)	15.0 (0.6)
Autoimmune/ inflammation	5,086	69.8 (0.6)	2,910	45.7 (0.9)	21.2 (0.8)	969	63.7 (1.5)	15.1 (0.6)
Genitourinary	757	68.7 (1.7)	475	57.1 (2.3)	29.7 (2.1)	212	66.5 (3.2)	21.6 (1.6)
Infectious disease	3,963	70.1 (0.7)	2,314	58.3 (1.0)	35.1 (1.0)	1,078	75.3 (1.3)	25.2 (0.8)
Ophthalmology	674	87.1 (1.3)	461	60.7 (2.3)	33.6 (2.2)	207	74.9 (3.0)	32.6 (2.2)
Vaccines (infectious disease)	1,869	76.8 (1.0)	1,235	58.2 (1.4)	42.1 (1.4)	609	85.4 (1.4)	33.4 (1.2)
Overall	41,040	66.4 (0.2)	21,180	48.6 (0.3)	21.0 (0.3)	7,532	59.0 (0.6)	13.8 (0.2)
All without oncology	23,672	73.0 (0.3)	14,647	55.7 (0.4)	27.3 (0.4)	6,296	63.6 (0.6)	20.9 (0.3)

Table adapted from Wong, Siah & Lo (2019a, table 2).
Abbreviations: CNS, central nervous system; PoS, probability of success; SE, standard error.

in oncology after phase 2 testing; Jardim et al. (2017) examine the response rates of 80 phase 3 oncology drugs to identify factors associated with failures; and Siah et al. (2019) apply machine-learning techniques to predict clinical trial outcomes for patients with advanced non-small cell lung cancer. However, one of the biggest challenges to all of these predictive models is missing data; not just missing clinical trial outcomes as discussed in Section 3.4 but also missing predictive features such as a drug's route of administration (oral tablet, intravenous infusion, etc.) or a trial sponsor's prior track record of other approvals. The naïve approach used by some researchers of simply omitting clinical trials containing missing data suffers from serious drawbacks, including survivorship bias and much larger estimation error due to an order of magnitude reduction in sample size.

This problem was solved by Lo, Siah & Wong (2019) by using statistical imputation techniques to estimate missing data and then applying machine learning to the augmented data. In the largest study of its kind to date, they use data from 2003 to 2015 on several thousand drug/indication pairs with more than 140 predictors across 15 disease groups and find significant predictive power ranging from 0.78 to 0.81 for the standard area under the curve (AUC) machine-learning metric.[12] Moreover, they conduct an out-of-sample test to compare predictions with realized clinical trial outcomes and show statistically significant predictive power.

A more recent out-of-sample study was performed by QLS Advisors, a healthcare analytics and investment advisory services company, using a commercial version of the Lo, Siah & Wong (2019) model in which the machine-learning forecasts were constructed using 80% of the data and tested on the remaining 20%.[13] The results—histograms of out-of-sample realized success rates for quintiles of forecasted rates—are reported by Thomas et al. (2021, figure 16) and reproduced in **Figure 6**, which clearly shows significant predictive power across all forecasted quintiles and clinical phases. Both Lo, Siah & Wong (2019) and Thomas et al. (2021) find that key factors for predicting success are trial outcomes, trial status, trial accrual rates, duration, prior approval for another indication, and sponsor track records, which provide insights into how the drug development process can be improved.

An interesting extension to the work by Lo, Siah & Wong (2019) involved a collaboration with the big pharma company Novartis and the MIT Laboratory for Financial Engineering to hold a company-wide data science and artificial intelligence challenge. Teams of Novartis data scientists and biomedical experts were invited to submit competing predictive algorithms in an attempt to beat the Lo, Siah & Wong (2019) model, using that model's source code as the starting point.[14] Two teams won the challenge, and their specific algorithms are published by Siah et al. (2021a). These collaborations can greatly increase the ability of all biomedical stakeholders to more accurately assess the risks and rewards of their portfolio of drug development programs, which in turn will lead to more efficient capital allocation decisions, a lower cost of capital, and more investment capital available.

4. EVIDENCE OF MARKET FRICTIONS AND INVESTMENT INCENTIVES

The main conclusion from the previous section is that the amplified frictions faced by biopharma firms can cause higher equity betas in early stage companies and underinvestment in valuable

[12]The AUC measure is similar to the traditional R^2 measure for linear regressions, except that an AUC of 0.5 indicates no predictive power and an AUC of 1.0 indicates perfect predictive power.

[13]In the interest of full disclosure, both authors are affiliated with QLS Advisors.

[14]That source code, along with source code for other MIT Laboratory for Financial Engineering–related publications, is publicly available at **https://projectalpha.mit.edu/resources/**.

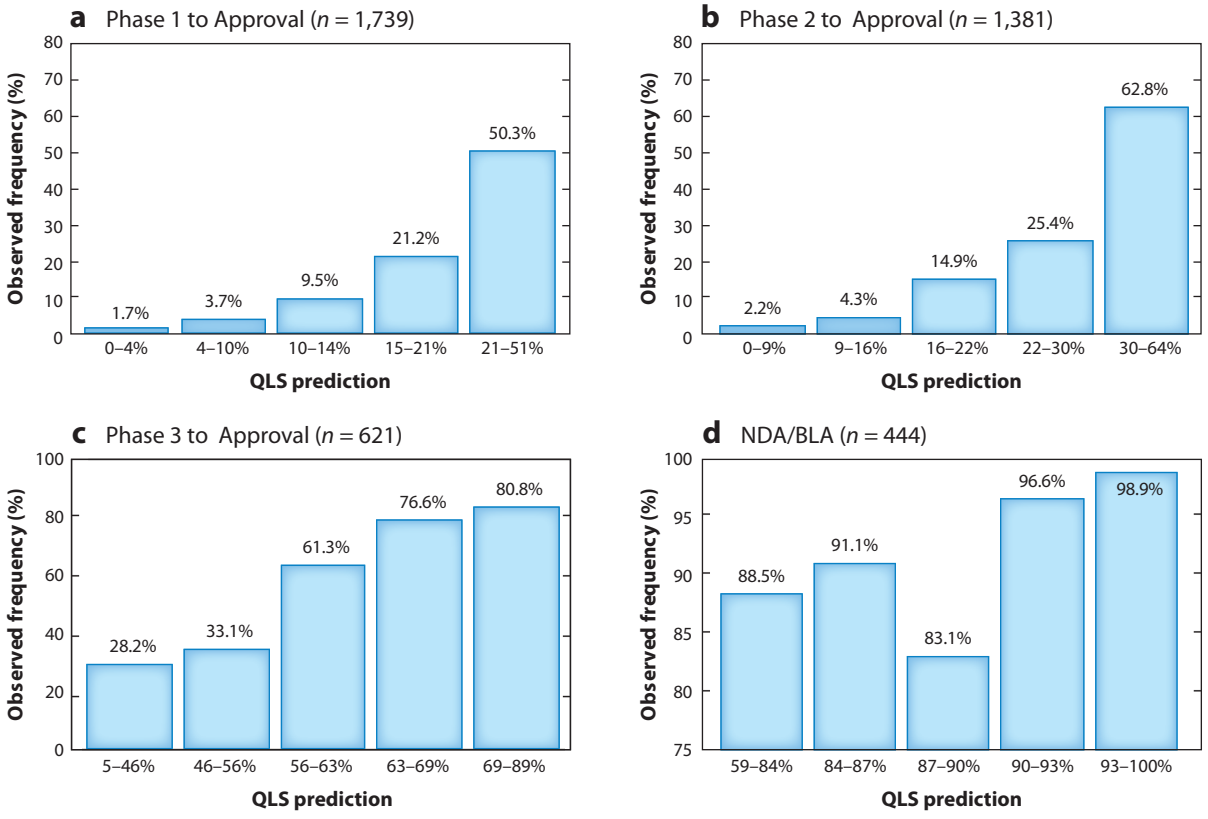

Figure 6

Histogram of machine-learning forecasts of drug development programs transitioning to approval using the most recent 20% of the data set. Higher forecasts are associated with higher rates of approval, which indicates positive forecast power. Estimates for each phase are grouped into quintiles. Abbreviations: BLA, biologics license application; NDA, new drug application; QLS, QLS Advisors. Figure adapted with permission from Thomas et al. (2021, figure 16).

R&D. In this section, we survey the empirical evidence on how market frictions affect biopharma investments and the role that financial markets play in this relationship.

4.1. Equity Markets and Investment

A body of empirical evidence has demonstrated a link between equity markets and biopharma investment.[15] Substantial evidence documents that biopharma firms have a high degree of market-related risk. Using data on publicly traded biopharma firms, Harrington (2012), Thakor et al. (2017), and Lo & Thakor (2019) all document positive and relatively high betas, often significantly

[15]There are also studies that have explored the link between equity markets and medical device companies. For example, using data on firms in the medical device industry, Phillips & Sertsios (2017) show that publicly traded firms have a higher external financing sensitivity than private firms when faced with shocks to investment opportunities (stemming from Medicare coverage decisions). The impact of public markets on medical device and drug companies may differ due to the different risk/reward profiles, institutional features, regulatory oversight, and reimbursement models for each type of company. For further discussion, see Lo & Chaudhuri (2023).

above 1.0, for biopharma firms. This high level of market risk is particularly salient since the scientific risk inherent in R&D is idiosyncratic, as Jørring et al. (2021) demonstrate using project-level data. A consequence of this high level of market risk is a high cost of capital for biopharma firms (e.g., Cockburn & Lerner 2006; Harrington 2012), which adds further challenges to the prospect of evaluating drug projects as positive NPV.

Studies using clinical trial data have shown how the link between biopharma firms and equity markets can cause suboptimal investment. Lerner, Shane & Tsai (2003) provide empirical evidence that due to their reliance on financing via stock issues, biotech firms are more likely to fund their R&D through inefficient (i.e., significantly less successful) alliances during periods of reduced public equity market financing.[16] Mace (2020) provides evidence that even short-term declines in equity markets can cause biopharma companies to abandon early stage drugs, which can be attributed to financing constraints and changes in discount rates. Krieger, Li & Papanikolaou (2022) use detailed clinical trial data and a new method for identifying novel drugs using chemical similarity to show that novel drugs have lower success rates but higher economic value ex ante. They provide evidence that firms underinvest in novel drugs, possibly due to external financing frictions: Firms experiencing a positive net-worth shock generated by an expansion of Medicare Part D developed more novel drugs in response.

Raising financing through equity markets may also cause firms to reduce their investment due to other frictions. For example, Ferreira, Manso & Silva (2014) and Boot & Vladimirov (2019) theoretically predict that private firms will innovate more than public firms, due to agency and informational frictions causing external shareholders to be less tolerant of failure than insiders. This finding is consistent with the empirical evidence by Bernstein (2015) that innovation (as measured by patents) declines when private firms go public. Aghamolla & Thakor (2022a) show that this is the case for biopharma firms as well; firms conduct fewer drug trials and focus on less risky indications (i.e., those with a higher success rate) when they go public.

While evidence has been found that innovative firms in general do employ some debt financing (for a review, see Kerr & Nanda 2015) and that biopharma firms are able to use limited amounts of debt, little empirical work has been done to examine whether debt hinders or enhances drug investment. Recent advances on this front suggest that, when faced with the need to increase investment, biopharma firms shy away from debt. Thakor & Lo (2022) provide evidence that biopharma firms reduce their debt when faced with increased competition that drives additional R&D investment. Giambona, Golec & Lopez-de-Silanes (2021) use the Biologics Price Competition and Innovation Act as a shock to investment opportunities and show that affected firms financed new assets primarily through equity and furthermore decreased their leverage and sought less-restrictive debt covenants. The use of debt financing in drug development represents an important and underexplored area that is ripe for future work and opens the possibility of a link between credit markets and the supply of new therapeutics.

4.2. The Competitive Structure of the Industry

A key feature that affects the innovation incentives of biopharma firms is the set of frictions related to competition in the industry that, as a number of studies have documented, has increased

[16] As evidence of suboptimal overinvestment, Guedj & Scharfstein (2004) use a sample of 235 cancer drug trials and show that younger, earlier-stage firms are more likely to advance unpromising drug candidates through clinical trials, in contrast to larger and more mature firms. The pattern is strongest for firms with larger cash reserves. The authors interpret the evidence as consistent with agency problems between managers and shareholders, in which managers are reluctant to drop poor projects when they have no other promising drugs in the pipeline and are able to use excess cash to continue them (e.g., Jensen 1986).

over time. A fuller understanding of the channels through which investment can be affected by competition opens up the possibility of spurring beneficial drug investment by changing the level of competition. For example, legislation has often aimed to increase competition in the industry with the dual goals of promoting additional innovation and offering more choices to consumers.[17] However, as noted in the innovation literature by Aghion et al. (2005), among others, the theoretical relationship between competition and innovation is not clear-cut. Increased competition may either encourage or dampen innovative incentives.

A salient source of competition in the industry comes from the regulatory environment in which drug development firms operate. Budish, Roin & Williams (2015) argue that the patent system enhances short-term incentives, pushing firms toward more late-stage research. Garfinkel & Hammoudeh (2022) show that regulatory breakthrough therapy designations for drugs, which allow the expedited development and review of drugs intended to treat serious conditions, can lead rivals to increase or decrease their development activities, depending on two perspectives on competition: the overall competitiveness of the disease treatment area, and the rival's competitive position within that area.[18]

The marketing exclusivity period awarded to approved drugs is a critical regulatory feature influencing competition between firms, since generic versions of an approved drug from other producers can enter the marketplace when the exclusivity period expires, with substantially lower prices than the existing brand-name drug (e.g., Danzon & Chao 2000). While it has been argued that the ability of generic drugs to enter the marketplace may enhance consumer welfare (e.g., Branstetter, Chatterjee & Higgins 2016), the effect of generic entry on the innovation incentives of incumbent firms has been the subject of numerous studies. Branstetter, Chatterjee & Higgins (2014) estimate a negative relationship between generic entry and early stage research in the affected therapeutic area. Thakor & Lo (2022) examine the economic effects of the implementation of the Hatch-Waxman Act of 1984, which eased the ability of generic drugs to enter into markets by allowing generic producers to bypass portions of the FDA approval process if bioequivalence has been established. They find that the increase in competition brought about by the Hatch-Waxman Act led to incumbent firms "focusing" their R&D effort—increasing their R&D investment but reducing the number of patents produced. Li, Lo & Thakor (2021) highlight the ability of the legal environment to affect investment incentives, showing that the negative relationship between innovation and generic entry can be reversed when incumbents are restricted in their ability to enter into contracts to delay generic entry.

A more insidious consequence of the loss of exclusivity and increased competition is the potential decline in supply of life-saving drugs because biopharma companies no longer have an incentive to supply them at their lower postexclusivity prices. According to Gogineni, Shuman & Emanuel (2013), at the same time that the prices of certain cancer drugs reached all-time highs, other kinds of cancer drugs experienced severe shortages, apparently because their prices were too low. In a survey of 214 oncologists from September 2012 through March 2013, they found that 83% were unable to prescribe the preferred chemotherapy agent because of shortages at least once during the previous 6 months. As a result, 78% of the oncologists surveyed switched chemotherapy regimens, 43% delayed treatment, 37% excluded some patients, 29% omitted doses, and 20% reduced doses.

[17] See Grabowski & Vernon (1986, 1990, 1992), Caves, Whinston & Hurwitz (1991), Grabowski & Kyle (2007), and Thakor & Lo (2022). Garthwaite (2018) provides an overview of the welfare implications of this tension.
[18] Ball, Shah & Wowak (2018) provide evidence that the level of competition in the pharmaceutical industry may affect the quality of products that firms produce.

In its analysis of this problem, the US Department of Health and Human Services determined that the issue largely revolved around sterile injectable drugs (Haninger, Jessup & Koehler 2011). It found that the drugs experiencing shortages also experienced price declines, and the ones not in shortage tended to have rising prices. Generic drug firms were choosing not to build excess capacity for drugs that had recently gone off patent, because they were unlikely to earn much market share. Broadly consistent with this, a strand of the literature has provided evidence that drug price controls result in a decline in investment by developing firms and also a reduction in entry (e.g., Vernon 2005; Kyle 2007). Apparently, in some cases, it is possible for drug prices to be too low from a societal perspective.[19]

The competitive environment that biopharma firms operate in, combined with their need for external financing, creates an interaction between competition, investment, and financing that recent studies have begun to explore. One of the key conceptual points is that high levels of competition combined with the knowledge-intensive nature of the industry mean that informational effects are particularly important. Competitors learn from the outcomes experienced by any firm. Recent studies have been able to use detailed clinical trial data to demonstrate the salience of these informational effects between competitors. Krieger (2021) and Krieger, Li & Thakor (2022) show how negative news about a firm (e.g., trial failures or safety warnings on marketed products) can alter the investments of a firm's competitors when they learn about the information. Hsu et al. (2019) examine an increase in disclosure requirements and show that peer firms learn from the disclosed information through increased trial suspensions.

Informational effects are strongly linked to external financing because firms need to disclose information to investors in order to secure financing in public markets, but this information may also fall into the hands of competitors. This has been referred to in the literature as the two-audience signaling problem (see Kamien & Schwartz 1978; Bhattacharya & Ritter 1983; Gertner, Gibbons & Scharfstein 1988; Bhattacharya & Chiesa 1995). Thus, a firm needing external financing faces a trade-off between the lower cost of external finance due to the information it discloses to investors (to lessen adverse selection costs) and the damage to real cash flows due to the inadvertent leakage of this information to competitors. This two-audience signaling problem can be particularly damaging given the winner-take-all feature of the patent and market exclusivity systems.

As evidence of this link between information and financing, Aghamolla & Thakor (2022a) examine how disclosure requirements affect the propensity of private firms to undertake an IPO and enter public equity markets. They use the FDA Amendments Act (FDAAA) of 2007 as an exogenous shock to disclosure requirements, following which all biopharma firms have been mandated to publicly post clinical trial registrations and summary results for phase 2 and above trials. Their results show that private biopharma firms were significantly more likely to tap into public equity markets following the increase in disclosure requirements, consistent with the declining marginal cost of disclosure through IPOs, since firms already had to disclose more information. Along similar lines, Dambra, Field & Gustafson (2015) and Lewis & White (2020) show that IPOs by

[19] A more complex example of how drug prices are connected to supply is the history of Acthar Gel, a biological compound produced from animal tissue that proxies for a particular human hormone. Despite its ability to treat life-threatening conditions like infantile spasms, it nearly disappeared from the market because its revenues did not cover the cost of manufacturing it. In 2001, the drug was acquired by Questcor, which was eventually forced to raise the price of Acthar Gel by several orders of magnitude to stay in business. Not surprisingly, these price hikes generated significant controversy, but the profits generated by the increased revenues allowed the firm to conduct additional clinical trials for new indications, yielding FDA approvals for 19 different diseases. For details, see Burnham, Huang & Lo (2017).

biotech firms increased substantially following a reduction in compliance costs brought about by the Jumpstart Our Business Startups (JOBS) Act of 2012.

The link between disclosure and financing represents an important channel through which biopharma firms may choose a financing source, thus becoming exposed to different financing risks since different securities involved in financing involve different information sensitivities. For example, Boot & Thakor (1993) and DeMarzo & Duffie (1999) argue on theoretical grounds that equity is more informationally sensitive than debt; Bhattacharya & Chiesa (1995) point out that the use of bank financing permits firms to avoid revealing their proprietary information to competitors, unlike external financing. Additional empirical work is needed to show how informational effects may affect the choice by biopharma firms of financing sources, such as equity, public debt, bank debt, and VC, and the subsequent impact of this choice on drug investment.

Apart from information disclosure, increased competition can move firms toward different sources of financing in and of itself because of the need to stay competitive with peers. Aghamolla & Thakor (2022b) exploit similarities across firms' development portfolios to demonstrate that there are peer effects in the propensity of private biopharma firms to tap public equity markets through an IPO. They provide evidence that firms are more likely to undertake an IPO following their peers due to competitive pressures; an IPO and the large influx of capital it brings provide a competitive advantage to a firm, causing its peers to follow suit to maintain a more level playing field. Aghamolla & Thakor (2022b) also show similar effects for other sources of funding, such as VC. Thakor & Lo (2022) show that an increase in competition induces biopharma firms to hold less debt. They argue that the need for firms to invest in new R&D rather than in existing assets to escape competitive pressures reduces the fixed asset base that can be used as collateral, while the potential for inefficient liquidation due to debt is more damaging with greater R&D investment. More research on competitive effects related to other sources of financing for biopharma firms is needed.

4.3. Markets for Technology

Markets for technology generally entail significant M&A and licensing activity (e.g., Gans & Stern 2003). These activities offer biopharma firms an important alternative means to develop drugs. Firms have the choice of developing new drugs in-house, entering into licensing agreements to codevelop with other firms, or acquiring projects (such as late-stage research) from other firms to develop them further toward commercialization. A small firm without access to enough capital to develop a drug through to FDA approval also may opt to sell the drug (e.g., patents, rights, equipment) to a capital-rich firm like a large pharma company. A stylized fact has emerged that many biotech firms engage in early stage research with the express intention of selling their research to larger pharma firms when it has progressed to a certain point of clinical development. Detailed project-level data from clinical trials allow researchers to closely track these sorts of agreements, which also allows broader insights into acquisition markets not offered in other contexts—for example, the ability to observe acquisitions of individual projects rather than acquisitions of entire firms.

The empirical evidence supports the notion of markets for technology being an important source to which biopharma firms can turn, particularly given the institutional details of the drug development process (see, e.g., Grabowski & Kyle 2012). Additionally, it supports the idea that these markets may help to guide drug projects to their first-best developers. Hermosilla & Wu (2018) show how cooperation via technology licensing can lead to improved outcomes because it pools the complementary capabilities of firms; these gains are especially salient in larger markets. Danzon, Epstein & Nicholson (2007) examine biopharma M&A activity from 1988 to 2001

and find that M&A are typically a response to financial trouble or gaps in a firm's pipeline. Along similar lines, Higgins & Rodriguez (2006) and Krieger, Li & Thakor (2022) show that biopharma firms with weaker internal pipelines are likely to engage in acquisitions in order to replenish their pipelines, rather than initiating new drug trials or continuing to develop their existing projects. Part of the reason for this strategy is that developing new products internally is too time-consuming and expensive for firms experiencing a negative shock or declining productivity, whereas acquiring projects offers a quick and efficient way to replace lagging products. Furthermore, firms with accumulated knowledge capital in a particular therapeutic area may reap the benefits of redeploying that capital on newly acquired projects, thus enabling an efficient reallocation of drug projects to their first-best users (e.g., Krieger, Li & Thakor 2022).[20]

However, frictions related to control rights have the potential to limit the effectiveness of markets for technology. Cunningham, Ederer & Ma (2021) provide evidence that incumbent pharma firms may use acquisitions as a means to consolidate their market power by shutting down competing projects. Hermosilla (2021) shows that firms rush to acquire replacement products after phase 3 failures, but these acquisitions subsequently underperform due to the contract negotiations in the acquisition process. The allocation of control rights between partners in pharmaceutical alliances can affect the efficiency of drug development conducted by those alliances (Lerner, Shane & Tsai 2003; Higgins 2007). More research is needed to understand whether the net effects reflect efficiencies or inefficiencies in the drug development process and the circumstances in which they arise. Furthermore, acquiring a project or company requires financing, and licensing requires a contribution of financial resources from participating firms; this financing connection and how it contributes to the efficiency of markets for technology is also an area that needs further exploration.

Related to this link, a recent development (particularly since 2020) is the growing popularity of acquisitions as an avenue for firms to go public and tap external equity markets. Special Purpose Acquisition Companies (SPACs) are financing "shell" companies that contain no assets but which go public through an IPO with the intention of later acquiring a firm. Once the acquisition is done, the SPAC itself dissolves, leaving the acquired company as a publicly traded entity. SPACs have been touted as an alternative to a traditional IPO, as a firm is able to become publicly traded without having to file a prospectus or go through the regulatory IPO process. Several biopharma companies have gone public via SPAC acquisitions. The consequences of SPACs for the drug development process are still unexplored and constitute a new area for research.

4.4. Venture Capital and Private Equity

VC and PE are other avenues of financing available to biopharma firms. The extant VC and PE finance literature has shown that these are important sources of funding that foster innovation (e.g., Kortum & Lerner 2000). VC and PE funding is particularly important for earlier-stage biotech firms that require start-up capital but lack the means to access broader public financing markets.

The nature of VC and PE investment creates a large degree of risk and uncertainty for drug development. VC investments are highly cyclical, which can cause difficulty for capital-intensive, high-risk, and long-duration projects—even the most successful biopharma firms are sometimes unable to secure capital when they need it. Furthermore, scale matters, since VC investment

[20]Henderson & Cockburn (1996) also argue that productivity increases with firm size in the pharmaceutical industry, due to economies of scope and scale, thus providing another potential incentive for pharma firms to engage in acquisitions.

rounds are typically smaller, with an average biopharma VC funding round of $8 million (Aghamolla & Thakor 2022b). With high and rising development costs for drug projects, venture capitalists now need a much larger fund and are less able to diversify. Over the course of the past few years, PE funds have become more involved in financing biopharma investments. Large PE firms have launched funds but have tended to focus on investments in later-stage assets rather than preclinical drugs.

The possibility of hold-up problems in VC and PE firm investment contracts has been shown to introduce inefficiencies in such arrangements (e.g., Kaplan & Strömberg 2004). Recent evidence suggests that these types of problems can affect investments by biopharma firms. Li, Liu & Taylor (2021) provide evidence that common ownership of drug projects across firms by venture capitalists can lead them to shut down some drug development projects to reduce competition across portfolios. The role of VC and PE firms in the drug development process remains an understudied area with important consequences.

5. SOLUTIONS TO UNDERINVESTMENT

The previous sections have laid out the case that the unique challenges of drug development cause many frictions for biopharma firms, leading to greater systematic risk and underinvestment in R&D. This may be particularly problematic for drugs that are valuable to society, given that the risks of development outweigh the potential economic benefits to firms. For example, cancer drugs tend to have the lowest probability of success (less than 5% on average), and thus firms and investors may shy away from developing potentially valuable cancer treatments. Researchers have offered a number of potential solutions to this problem. In this section, we survey these insights.

5.1. The Drug Development Process

A variety of solutions have been proposed on the regulatory front, from changes to patent policy and competition to public funding mandates. In some cases, initiatives have promoted further research into diseases by biopharma firms, but in other cases the efficacy of policy initiatives has been limited. For example, as discussed in the previous sections, policies such as enhanced patent protection may improve or hinder innovation incentives. Similarly, public funding allocations may be suboptimal.[21]

One potential policy solution that has been offered is to change the FDA approval process itself. Some recent initiatives by the FDA offer a faster review and approval process for certain qualifying drugs (such as the Breakthrough Therapy Designation), while the 21st Century Cures Act has allowed the introduction of real world evidence such as observational studies and patient input to complement the FDA review process in order to expedite approvals (Lo, Philipson & von Eschenbach 2016; Lo 2017).

Other proposals include the use of APTs to advance the clinical trial process. These trials are new designs of randomized controlled trials (RCTs) that are able to test multiple interventions for a disease or condition on an ongoing basis, with interventions entering and leaving the platform on the basis of a predefined algorithm (Angus et al. 2019). The most established APT is I-SPY 2, a phase 2 trial investigating neoadjuvant (preliminary) therapies for breast cancer in conjunction with standard chemotherapy compared to standard chemotherapy for women diagnosed with local metastatic breast cancer before surgical resection (Das & Lo 2017). A framework for modeling

[21] For a review and discussion of these initiatives, see Kyle (2020).

the accrual of information in an adaptive clinical trial as a sequence of real options is developed by Chaudhuri & Lo (2020), following the example of Royalty Pharma's financing of Sunesis Pharmaceuticals' phase 3 adaptive clinical trial of its leukemia drug, vosaroxin (Lo & Naraharisetti 2014). Berry et al. (2020) determine that an adaptive trial provides the maximal net benefit for trials of COVID-19 vaccine candidates in number of averted infections and deaths, short of the deliberate infection of volunteers in human challenge trials.

Another approach involves the use of Bayesian decision analysis (BDA) to improve the criteria used in determining efficacy from clinical trial data. The traditional hypothesis testing framework in an RCT begins by setting a statistical threshold of significance to minimize the chances of approving an ineffective therapy, a false positive, or Type I error. The standard approach is to choose an evidentiary threshold so that the Type I error is 5%, and the statistical significance of the clinical evidence is evaluated using this threshold. If results are inconsistent with the null hypothesis of no efficacy at a significance level, or p value, less than 5%, then the null hypothesis is rejected and, in our context, the therapy is approved.

The question raised and answered by BDA is "why 5%?" For fatal diseases with no existing treatments, patients may be willing to accept a much higher false positive rate, especially if it yields a lower false negative rate, or Type II error, as is often the case. For example, suppose the conventional Type I error of 5% is associated with a Type II error of 25%. A glioblastoma patient that has exhausted the standard of care may be comfortable with a Type I error of 20% if it is associated with a Type II error of 10%. Given that such patients have no other recourse for this terminal illness, the relative importance of false positives and negatives should reflect their circumstances. To do so, a new regulatory approval threshold can be computed by explicitly minimizing the expected loss to patients due to both Type I and II errors, where the expected loss is the weighted sum of the measured impact of false positives and false negatives, weighted by their probabilities. This minimization process yields optimal false positive and false negative rates that reflect the different costs and benefits of each type of error, yielding an outcome that offers the greatest good for the greatest number. A graphical illustration of this trade-off and the BDA optimal values is provided in **Figure 7**.

Montazerhodjat et al. (2017) find that the optimal alphas determined by BDA were often much larger than 2.5% for terminal cancers with short survival times and no effective therapies, such as glioblastoma (a 47.5% BDA optimal Type I error), and smaller than 2.5% for less serious cancers with long survival times and multiple effective therapies (e.g., a 0.9% BDA optimal Type I error for early stage prostate cancer). Isakov, Lo & Montazerhodjat (2019) provide corresponding results for the 25 most lethal diseases in the United States (see **Table 5**).

Chaudhuri et al. (2020) apply Bayesian patient-centered models to anti-infective therapeutics, incorporating epidemiological models to determine the optimal alpha during outbreaks of epidemic disease. Most recently, a survey of more than 2,700 Parkinson's disease (PD) patients by Hauber et al. (2021) finds that risk thresholds in a BDA framework for new neurostimulative devices in the treatment of PD increase markedly with the perceived benefit of the device to the patient (see also Chaudhuri et al. 2022). BDA has also been applied retrospectively to medical devices for treating obesity (Chaudhuri et al. 2018) and to APTs (Chaudhuri & Lo 2021a), and it is being considered as a prospective input to the trial design of devices to treat kidney disease (Chaudhuri & Lo 2021b).

BDA applications do require more information than the traditional approach—the losses under both types of errors must be specified, and in some cases these losses may be difficult to gauge. However, several metrics have been developed for this purpose in the health technology assessment literature, including quality adjusted life years to assess burden of disease, and sophisticated

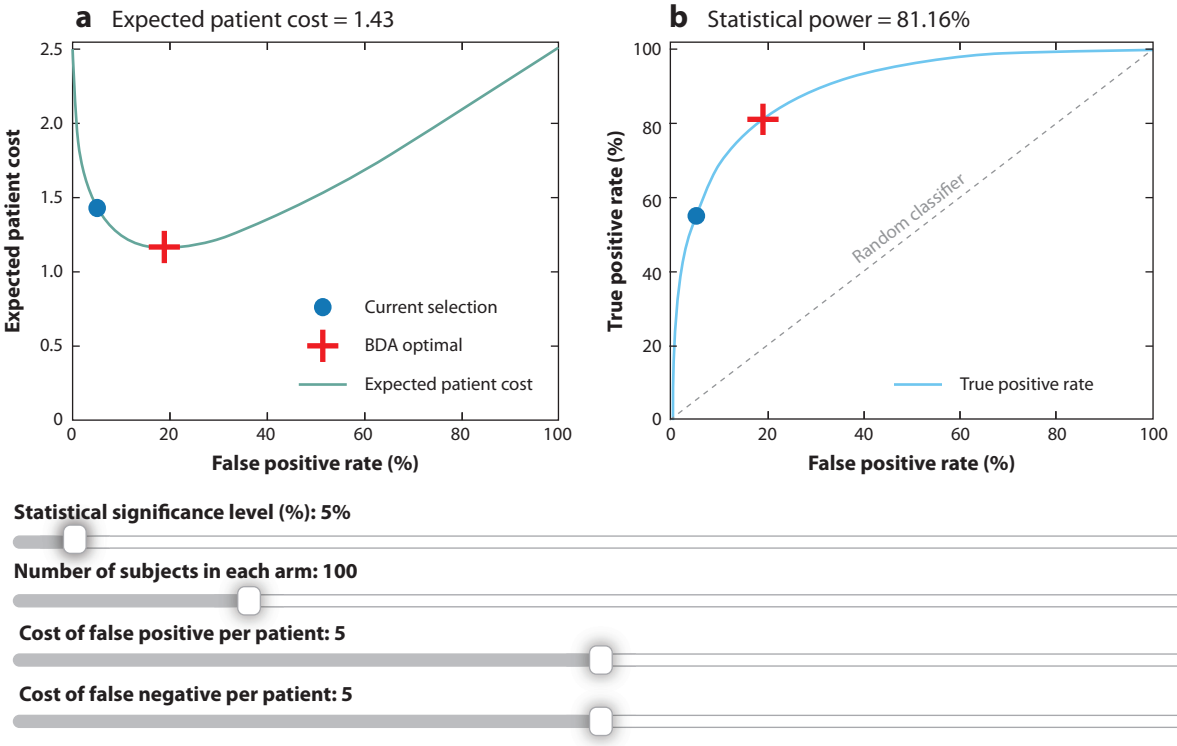

Figure 7

Bayesian decision analysis–optimized false positive rate (Type I error) and true positive rate (1 − Type II error) for a given clinical trial with costs of Type I and II errors. An interactive version is available online (**https://bit.ly/3POaKPy**; see Lo 2019), where the scales shown along the bottom can be adjusted to display (*a*) the expected cost to patients with a particular significance level and (*b*) the trade-off between the false positive rate and the true positive rate for the given clinical trial design.

econometric survey tools have been designed by patient advocacy groups to measure the preferences of their constituents.

The most challenging practical issue in implementing this framework is the consequences of a larger number of false positives. This can be addressed by creating a temporary license to market speculative therapies that expires after a short period (say, 2–3 years). During this period, the licensee is required to collect and share data on the performance of its therapy, and if the results are positive, the license converts to a standard approval; otherwise, the therapy is withdrawn upon expiration. Regulators should have the right to terminate the temporary license at any time in response to adverse events or significantly negative data. Such licenses would greatly accelerate the pace of therapeutic development for many underserved medical needs without limiting regulatory flexibility.

Flexibility is particularly important because any system can be gamed, leading to unintended outcomes; hence, no single interest group should be allowed to exercise undue influence in this process. Therefore, regulators must, and do, apply discretion, judgment, and a wealth of experience in their review process. Nevertheless, a systematic, rational, transparent, reproducible, and practical framework in which regulators' decisions can be clearly understood by and communicated to all stakeholders while explicitly incorporating their feedback may still have value.

Table 5 Optimal Type I error rates (α), power, and sample sizes of BDA fixed-sample hypothesis tests of clinical trial outcomes for 25 leading causes of premature mortality in the United States[a]

YLL rank	Disease name	Prevalence (thousands)	Severity	Sample size	Critical value	α (%)	Power (%)
1	Ischemic heart disease	8,895.61	0.12	806	1.853	3.2	74.4
2	Lung cancer	289.87	0.45	521	1.094	13.7	82.2
3a	Ischemic stroke	3,932.33	0.15	767	1.755	4.0	75.6
3b	Hemorrhagic/other non-ischemic stroke	949.33	0.16	751	1.723	4.2	75.8
4	Chronic obstructive pulmonary disease	32,372.11	0.06	940	2.182	1.5	70.1
7	Diabetes	23,694.90	0.05	958	2.226	1.3	69.5
8	Cirrhosis of the liver	78.37	0.49	491	1.024	15.3	82.5
9	Alzheimer's disease	5,145.03	0.18	727	1.652	4.9	76.8
10	Colorectal cancer	798.90	0.15	752	1.727	4.2	75.7
11a	Pneumococcal pneumonia	84.14	0.30	596	1.351	8.8	79.0
11b	Influenza	119.03	0.20	679	1.584	5.7	76.4
11c	*H. influenzae* type B pneumonia	21.15	0.26	545	1.378	8.4	75.4
11d	Respiratory syncytial virus pneumonia	14.90	0.07	–	–	–	–
13	Breast cancer	3,885.25	0.05	951	2.218	1.3	69.4
16	Chronic kidney disease	9,919.02	0.04	981	2.288	1.1	68.5
18	Pancreatic cancer	22.67	0.71	384	0.711	23.9	84.6
20	Cardiomyopathy	416.31	0.17	729	1.677	4.7	76.1
21	Hypertensive heart disease	185.26	0.27	633	1.429	7.6	78.7
22	Leukemia	139.75	0.21	671	1.551	6.0	77.0
23	HIV/AIDS	1,159.58	0.10	830	1.926	2.7	73.3
24	Kidney cancers	328.94	0.12	794	1.864	3.1	73.4
25	Non-Hodgkin lymphoma	282.94	0.13	766	1.792	3.7	74.4
27	Prostate cancer	3,709.70	0.05	967	2.259	1.2	68.8
28	Brain and nervous system cancers	59.76	0.30	585	1.339	9.0	78.8
30	Liver cancer	31.27	0.44	492	1.080	14.0	81.1

Table adapted from Isakov, Lo & Montazerhodjat (2019, table 3).

Abbreviations: BDA, Bayesian decision analysis; YLL, number of years of life lost due to premature mortality.

[a]The alternative hypothesis corresponds to a treatment effect $\delta = \sigma/8$.

5.2. Financial Innovation

To address the high-risk high-cost challenges of drug development, Fernandez, Stein & Lo (2012) propose the use of financial innovation, which can be used to transfer risks to market participants that are more willing to bear them. As a result, more funding can be channeled toward drug development, particularly in areas where there may be greater societal need but higher risks for firms. In particular, they propose the idea of a megafund that pools together a large number of different projects. The idea relies on basic financial portfolio theory and the notion of diversification, that some of the individual risks associated with drug projects will cancel each other out, reducing the overall risk of the fund.

With a well-diversified portfolio of projects, the megafund is then able to issue tranches of debt as well as equity because of its lower risk. This, in turn, provides a more attractive risk-return

profile to large investors, thus allowing additional funds to flow to these investments. However, the term megafund conveys the key challenge to creating such portfolios—they require an outsized amount of capital. In the work by Fernandez, Stein & Lo (2012), $5 to $15 billion is proposed, depending on the clinical phases of the programs in the portfolio. At the right scale, the risk-adjusted returns of the megafund become sufficiently appealing to attract the required amount of capital to achieve such returns.

This approach is generalizable to any large investment project with a low probability of success, a long gestation lag, large required up-front investment, and very large payoffs relative to the investment, provided that the basic assumptions of diversification hold for the individual projects within the portfolio. Hull, Lo & Stein (2019) call such investments long shots and show that securitization techniques can finance them in cases where more traditional funding sources such as VC and PE have been reluctant to do so.

Since the publication of Fernandez, Stein & Lo (2012), several other studies have validated and extended their simulations. Yang et al. (2016) demonstrate the importance of empirical validation in selecting projects for a cancer megafund, and Mishra et al. (2018) propose a novel cryptocurrency megafund structure to alleviate adverse selection and moral hazards from information asymmetry and misaligned utilities among biomedical stakeholders and investors. And Lo & Siah (2021) develop a more general megafund simulation framework that can accommodate correlated projects.

In addition to the original application to cancer, the megafund structure has also been proposed as a funding model for more targeted therapeutics, including pediatric cancer (Das et al. 2018), ovarian cancer (Chaudhuri et al. 2019), brain cancer (Siah et al. 2021b), and rare diseases (Fagnan et al. 2014, 2015), the latter of which is discussed in more detail in the next section. In each of these cases, the simulations show that at sufficient scale, the expected returns and risk of a megafund are comparable with or better than traditional financial investments such as stocks, mutual funds, exchange-traded funds, and other common risky assets.

However, there are limits to what this type of financial innovation can fund. In the case of Alzheimer's disease (AD), Lo et al. (2014) and Cummings et al. (2022) conclude that even a $38 billion megafund that funded 64 programs would not be sufficiently large to generate attractive returns (e.g., an expected return of −0.4% and a standard deviation of 38.5% in one particular simulation). The reasons have to do with the low probability of success of AD drug development projects—which reflects the nascent state of our scientific understanding of the basic biological mechanisms of the disease and how to intervene effectively—as well as the higher costs of AD clinical trials. Vu et al. (2022) reach a similar conclusion for vaccines using realistic assumptions about the costs and revenues of the vaccine business prior to the COVID-19 pandemic, with double-digit negative simulated expected returns and high volatility.

Business models such as the megafund are simply not attractive enough to be viable from a purely commercial perspective in these cases. However, from social impact and public health perspectives, investing in AD and infectious disease therapeutics is highly compelling, which suggests a role for the public sector. We consider this alternative in Section 5.3.[22]

Financial innovation has also been proposed as a means to manage the risk of therapeutic development. Jørring et al. (2021) explore the idea of FDA hedges, which are insurance contracts that offer payouts upon the failure of individual drug projects to gain FDA approval. In a

[22] Financial intermediaries also have the potential to play an important role in fostering this type of financial innovation and broadly helping to mitigate the underinvestment problem. These issues are discussed in depth by Lo & Thakor (2022).

theoretical model of these near-perfect analogs of Arrow–Debreu securities, Jørring et al. (2021) show how these contracts address informational frictions so as to reduce underinvestment in R&D and enhance welfare. They also provide evidence that these contracts have little systematic risk and are therefore ideal investments for institutional investors seeking new sources of diversification. Jørring et al. (2021) also provide a discussion of the practical aspects of launching a market for such contracts.

5.3. Rare Disease Megafunds

The degree of correlation of success or failure between portfolio development projects is critical to the success or failure of the megafund, with statistically independent projects favoring its success; however, the basic "vanilla" structure is able to maintain promising returns even with a moderate degree of correlation using the most recent drug development project data, according to the work by Lo & Siah (2021). However, the degree of leverage depends not only on the pairwise correlation of the assets but also on the amount of cash generated by those assets. For early stage drug discovery companies, the lack of cash flows eliminates the possibility of most forms of debt financing. But as assets progress through the clinical trials process and eventually begin generating cash flows, leverage becomes possible. Montazerhodjat, Frishkopf & Lo (2016) show that a dynamic leverage policy—in which a constant level of default risk is maintained as a megafund's capital structure shifts from all-equity to a mix of equity and an increasing amount of debt—can boost equity returns and create significant value for both investors and patients.

The issue of correlation is especially relevant for determining the risk of a megafund given that the number of covariances grows much faster than the number of variances as the number of assets in the portfolio increases. For this reason, Fagnan et al. (2014, 2015) focus on a megafund simulation consisting solely of rare disease therapeutics because the diverse and heterogeneous nature of these diseases generally implies low pairwise correlations between the successes or failures of these drug development programs. According to the Orphan Drug Act of 1983, an orphan disease is defined in the United States as any disease affecting fewer than 200,000 patients. Examples include hemophilia, cystic fibrosis, amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease), Duchenne muscular dystrophy, pediatric cancers, and many other genetic and inherited disorders. Although any single rare disease may affect only a relatively small number of patients, it is estimated that there are more than 7,000 rare diseases affecting as many as 30 million Americans in total—more than the estimated number of Americans with cancer. Therefore, from both patient and financial perspectives, a rare disease megafund is a compelling application of the portfolio approach.

Using data from the rare disease unit of the National Center for Advancing Translational Sciences to calibrate their simulations, Fagnan et al. (2015) show that a portfolio of only 16 programs and $420 million in capital is sufficient to achieve highly attractive returns for both equity and debt investors, with debt tranches yielding market rates and the equity tranche generating a simulated modified internal rate of return of more than 20%. These simulations motivated the establishment of BridgeBio Pharma, a biotechnology company specializing in treatments for genetic diseases, many of which are rare and ultra-rare.[23]

As additional evidence for the financial viability and attractiveness of rare disease assets, Lo & Thakor (2019) construct a stock market index of publicly traded rare disease companies, which they call ORF, using historical data from 2000 to 2015. ORF underperformed other biopharma

[23] For more information, readers are referred to **https://bridgebio.com**. In the interest of full disclosure, A.W. Lo is affiliated with BridgeBio Pharma.

companies and the overall stock market in the early 2000s; however, from 2010 to 2015, ORF returned 608%, far exceeding the returns of 317%, 320%, and 305% of the S&P, NASDAQ, and NYSE Arca Biotech indexes, respectively, and the 83% return of the S&P 500. ORF does have higher volatility than the other indexes but still outperforms even on a risk-adjusted basis, with a Sharpe ratio of 1.24 versus Sharpe ratios of 1.17, 1.14, and 1.05 for the other three biotech indexes, respectively, and 0.71 for the S&P 500. This discrete shift in performance may signal an inflection point in both scientific and commercial strategies for addressing this historically underserved patient population.

More direct evidence for the feasibility of unique financing strategies to facilitate rare disease therapeutics is provided by several case studies spanning multiple diseases and organizations: cystic fibrosis and the Cystic Fibrosis Foundation (CFF) (Kim & Lo 2019), Duchenne muscular dystrophy and Solid Biosciences (Kim & Lo 2016), AADC (aromatic L-amino acid decarboxylase) deficiency and Agilis Biotherapeutics (Das, Huang & Lo 2019), and glioblastoma and the National Brain Tumor Society (Siah et al. 2021b).

In some cases, the profitability of certain therapeutic areas is not enough to attract sufficient private capital, in which case a portfolio approach that includes some form of public–private partnership—including government guarantees—is needed. Examples include therapeutics for pediatric (Das et al. 2018) and ovarian (Chaudhuri et al. 2019) cancer, AD (Lo et al. 2014; Cummings et al. 2022), pain management and opioid use disorder (Siah, Maher & Lo 2022), and, prior to the COVID-19 pandemic, vaccines and antibiotics (Vu et al. 2022). Fagnan et al. (2013) show that even modest government guarantees are sufficient to greatly increase the attractiveness of megafund portfolios, thereby drawing substantial private capital into these therapeutic development programs. They also point out that government need not be the only provider of guarantees—impact investors such as patient advocacy groups can also provide guarantees via capital markets (e.g., total return and credit default swaps). We discuss this in more detail in Section 5.4 in the context of venture philanthropy.

5.4. Venture Philanthropy and Other Organizational Innovations

Philanthropic organizations have changed their stance on using their resources to further their goals, particularly through venture philanthropy (VP), a funding model in which nonprofit, mission-driven organizations fund initiatives to advance their objectives while achieving returns to be reinvested toward their goal. VP has been gaining popularity among patient advocacy groups since the notable financial success of the CFF in funding the development of Kalydeco, the first disease-modifying therapy approved to treat cystic fibrosis, and several other successful follow-on drugs. In Kim & Lo's (2019) case study, they discuss the $150 million investment the CFF made in Vertex Pharmaceuticals over a 12-year period, which yielded the CFF a payout of nearly $4 billion when the CFF sold their royalty interests in Vertex products, allowing the CFF to fund even more ambitious therapeutic programs to cure the disease via gene-based therapies.

However, the impact of the CFF goes far beyond cystic fibrosis—their example illustrates the surprising principle that social impact and financial gain need not be mutually exclusive. In fact, their example illustrates an even more important and counterintuitive principle: In some cases, mission-driving impact is a prerequisite for financial gain. This principle has been formally developed for general impact investments by Lo & Zhang (2021), who show in a theoretical framework that, contrary to popular belief, impact investing can outperform traditional investments under certain conditions, and the CFF's investment in Vertex is a prime example.

In particular, a major source of success of the CFF–Vertex partnership is the fact that the CFF provided critical funding that was solely focused on developing an approved drug rather than on generating shorter-term profits. In addition, philanthropic organizations can provide scientific

assistance—access to disease experts, patient registries, natural history studies, and other critical resources—to derisk the drug development process. Siah et al. (2021b) provide a current example with the National Brain Tumor Society and the resources they bring to their impact fund to treat glioblastoma. Alvarez & Lo (2022) provide a more general perspective on how VP can facilitate biomedical innovation and provide mini-case studies of three VP initiatives—the JDRF T1D Fund for type 1 diabetes research, the MPM Oncology Impact Fund, and the American Heart Association's Cardeation Capital™—as examples.

Other recent changes in organizational structure of the firm may also enhance biopharma funding. For example, Forman et al. (2015) argue that the business development company—a closed-end investment fund with relaxed requirements that allow it to raise money in the public equity and debt markets—can be used to fund multiple early stage ventures for long-term investors in biomedical innovation. Lo & Pisano (2016) observe that the outsourced and episodic nature of the Hollywood film industry—in which teams of experts (actors, set designers, special effects companies, etc.) collaborate to shoot a given movie and then disperse to other projects—can increase the efficiency of the biopharma industry through project-focused organizations. In fact, such gig economy collaborations are already happening organically, with specialized staff joining an early stage biotech company and then moving on shortly after an IPO or similar major milestone.

6. CONCLUSION

In this review, we have surveyed the literature on drug development financing, providing stylized facts showing that the drug development process is lengthy, risky, and expensive and that these costs and risks have increased over time. The institutional features and economic incentives associated with drug development result in biopharma firms relying more heavily on external financing to fund their investments, creating a strong link between drug development and financial markets. This link—when combined with the institutional features of drug development—creates challenges in funding certain potentially valuable R&D efforts, leading to an underprovision of social welfare–enhancing therapies.

We surveyed the body of empirical evidence that demonstrates how market frictions and financial markets interact with and affect the investment incentives of biopharma firms. We concluded by surveying research that proposes solutions to the underinvestment problem, including changes to the drug development process and financial innovation. Throughout, we have highlighted areas that are understudied, presenting fertile opportunities for potentially high-impact research.

In addition to its implications for improving the drug development process, financial research on the biopharma industry also offers valuable insights into the processes of R&D and innovation investment as well as general corporate financial decision-making. This setting offers granular data on clinical trials, providing researchers with multiple measures of innovation and the ability to track individual project decisions for both public and private firms. This opens up the possibility of garnering a variety of novel insights about firms outside the biopharma industry through extrapolation.

Our focus has been on financing drug development, but this is only one part of the broader healthcare system. After a new therapy has been approved, it must be delivered to patients, which raises a host of issues related to the healthcare payments system (for a review, see Gruber 2022), not the least of which is price. For example, recent breakthroughs in gene therapies—one-time cures that provide a lifetime of health—have commanded multi-million-dollar price tags. Wong et al. (2021) estimate that, between January 2020 and December 2034, total cumulative spending on these therapies could be as high as $306 billion. How will the healthcare system afford such costs? Once more, financial innovation provides a potential solution: drug mortgages, first proposed by

Montazerhodjat, Weinstock & Lo (2016), which are amortized payment plans allowing health insurers to spread payments over a period of years. These drug mortgages can then be pooled and securitized in much the same way that home mortgages are treated, bringing much larger amounts of capital into this sector to fund these life-saving therapies.

Another area at the intersection of finance and healthcare is the financing of hospitals, clinics, and nursing homes that are on the frontlines of delivering health care to patients. These entities have goals that both overlap with and differ from those of firms in other industries, which creates unique challenges for making financing and investment decisions in response to informational and other frictions. A nascent literature focusing on these issues is ripe for additional contributions.[24]

DISCLOSURE STATEMENT

A.W.L. reports personal investments in private biotechnology companies, biotechnology venture capital funds, and mutual funds. A.W.L. is a co-founder and principal of QLS Advisors LLC, a healthcare analytics and investment advisory services company; a director of AbCellera, Annual Reviews, Atomwise, BridgeBio Pharma, and Roivant Sciences; and an advisor to Apricity Health, Aracari Bio, BrightEdge Impact Fund, Enable Medicine, Financial Industry Regulatory Authority (FINRA), Lazard, National Center for Advancing Translational Sciences, Quantile Health, Roivant Social Ventures, SalioGen Therapeutics, Swiss Finance Institute, and Thalēs. During the most recent six-year period, he has received speaking/consulting fees from AbCellera, AlphaSimplex Group, Annual Reviews, Apricity Health, Aracari Bio, Atomwise, Bernstein Fabozzi Jacobs Levy Award, BridgeBio, Cambridge Associates, Chicago Mercantile Exchange, Enable Medicine, Financial Times Prize, Harvard Kennedy School, International Monetary Fund, *Journal of Investment Management*, Lazard, National Bank of Belgium, New Frontier Advisors/Markowitz Award, Oppenheimer, Princeton University Press, Q Group, QLS Advisors, Quantile Health, Research Affiliates, Roivant Sciences, SalioGen Therapeutics, Swiss Finance Institute, and WW Norton. R.T.T. is an advisor and consultant to QLS Advisors LLC, a healthcare analytics and investment advisory services firm based in Cambridge, Massachusetts.

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