# Process-Based Drug Development, Drug Pricing, and the Incentives to Innovate

Marina Chiara Garassino
University of Chicago Comprehensive Cancer Center

Kunle Odunsi
University of Chicago Comprehensive Cancer Center

Marciano Siniscalchi
Northwestern University

Pietro Veronesi
University of Chicago, NBER, and CEPR

September 8, 2026

**Abstract**

Recent regulatory reforms introduced process-based approval pathways, which evaluate drug development processes rather than individual molecules. We formulate and calibrate a dynamic model of entry and R&D investment to quantify firms' incentives and drug pricing under process-based versus traditional regulatory regimes. For rare genetic alterations, empirical and model results show that traditional pathways lead to underinvestment, prohibitive pricing, constrained revenues, and low clinical trial enrollment. Transitioning to process-based discovery for personalized therapies improves efficiency: the model predicts lower equilibrium prices, elevated developer revenues, and robust R&D investment incentives.

Keywords: targeted therapies, precision medicine, genetic alterations.
JEL codes: I11, I18, O32, O38

---

* Veronesi acknowledges financial support from the Fama-Miller Center for Research in Finance. For useful comments, we thank workshop participants at the Chicago Fed, Bocconi University, University of Chicago, the 2025 Health Economics Conference at the Becker Friedman Institute, the 2025 WashU Conference on the Economics and Finance of Healthcare and Medicine. We thank Eric Budish, Alex Frankel, Lars Hansen, Andrew Lo, and Tong Liu (discussant) for insightful comments. We also thank Salem Soin-Voshel for excellent research assistance. Errors are our own. The views expressed in this paper are our own and do not necessarily reflect the views of our respective employers. Siniscalchi declares that he has no relevant or material financial interests that relate to the research described in this paper. Garassino, and Veronesi's spouse, declares that she serves as paid consultant of several pharmaceutical companies, and also serves on their steering committees for clinical trials. Odunsi is supported by P30CA014599 grant from the NIH and is a co-founder of Tactiva Therapeutics. Contact information: Marina Garassino: mgarassino@bsd.uchicago.edu; Kunle Odunsi: odunsia@bsd.uchicago.edu; Marciano Siniscalchi: marciano@northwestern.edu; Pietro Veronesi: pietro.veronesi@chicagobooth.edu. An earlier version of this paper circulated under the title "On the impossibility of personalized medicine, and a solution".

*"Bespoke, personalized therapies, which hold tremendous promise, challenge traditional models of drug and biologic development. The Food and Drug Administration (FDA) is committed to providing regulatory guidance and encouragement, outlining a path to market entry for products where a randomized trial is not feasible."* Vinay Prasad (Chief Medical and Scientific Officer, FDA) and Martin A. Makary (Commissioner, FDA), New England Journal of Medicine, Nov 12, 2025.

*"This month Britain's Medicines and Healthcare products Regulatory Agency (MHRA) approved a novel sort of clinical trial. Ten children, each suffering from an ultra-rare genetic neurodegenerative disease that threatens his or her life, will each receive a unique version of a known drug molecule. If the trial is successful, the MHRA will give the nod not to each custom drug one by one, but to the process of making them."* The Economist, Jan 22, 2026.

# 1. Introduction

The publication of the initial sequencing of the human genome (International Human Genome Sequencing Consortium, 2001) opened the road to modern personalized medicine: that is, the delivery of the right drug to the right patient based on their genomic profile. Technological advances over the last twenty-five years have enabled the development of effective treatments for diseases that affect increasingly smaller subgroups of patients. Promising advances in personalized medicine are occurring in lung cancer, ovarian cancer, hematological, cardio-vascular, immunological and neurodegenerative disorders, and rare genetic diseases. Such results warrant a degree of optimism that a new era of personalized medicine will bring about significant improvements for patients affected by devastating illnesses. However, the highly targeted nature of personalized medicine introduces new challenges. The very notion of personalized medicine implies that, theoretically, each patient can become a unique case. By contrast, the traditional regulatory infrastructure is founded on statistical testing for safety and effectiveness, and thus assumes the availability of sufficiently large subject pools.

As the quotes above show, regulatory agencies have recently put forward new approval pathways, which effectively shift the focus from the approval of individual drugs to the approval of *processes* for personalized drug development. For a recent example, consider the melanoma vaccine intismeran: "a sample of a person's tumor is sequenced to identify mutations that have developed in their cancer cells. These mutations mean that a cancer cell expresses abnormal proteins called neoantigens [...]. An mRNA vaccine is developed according to each person's cancer neoantigens, and once injected, it instructs the body to make the neoantigens — priming the body to recognize the threat." (Fieldhouse et al., 2026). The vaccine given to each individual with melanoma is different from the one given to other

patients because it is designed based on the genomic characteristic of that individual's specific tumor. To accommodate this development, regulatory agencies would not approve a specific vaccine, but rather the process of making the individualized vaccine through specialized technologies. Clinical trials would need to ensure that the process for making these targeted drugs produces treatments that are more effective than the standard of care, and safe for the patients.

This paper investigates whether recently proposed process-based drug approval regimes provide stronger incentives to develop new, personalized treatments compared to the traditional regime, which centers on approving individual therapies. Furthermore, we investigate differences in market pricing and the social costs of personalized medicine under process-based drug approval relative to the traditional regime. To this end, we introduce a model of firms' investment decisions, market entry, and bargaining between firms and health insurance companies. Within this common framework, we characterize and compare economic sustainability, R&D incentives, equilibrium drug prices, and social costs under both traditional and process-based approval pathways.

We focus on targeted therapies in lung cancer as a good "case study": research has already identified alterations that affect extremely small percentages and numbers of patients, but no approval of a process for developing targeted treatments exists as of yet. We can think of rare alterations as a proxy for fully personalized treatments. We can also view them as an intermediate step between broadly targeted and personalized therapies; this allows us to determine how rare alterations need to be for process-based approval pathways to become necessary. Importantly, unlike for other instances of personalized drug development processes, we are able to obtain data on targeted therapies, including individual clinical trials, costs, and drug prices. This enables us to calibrate our model, and thus obtain predicted drug prices under a hypothetical alternate process-based paradigm.

Traditionally, regulatory agencies such as the Food and Drug Administration (FDA) or the European Medicines Agency (EMA) require that new drugs be validated as more effective than previously available treatments through randomized controlled trials (RCT).[1] This process involves different phases (see Section 4), but the basic structure is as follows: patients are randomly assigned to a "treatment" group, which receives the new proposed (targeted) therapy, or a "control" group, which receives the best currently available therapy. Patients are then followed for years, and survival statistics are used to compare "success rates" in the two groups. The new treatment is approved if the difference in success rates is medically as well as statistically significant.

[1]Over the years, the regulatory agencies have relaxed some of the strict requirements and allowed for accelerated approvals for some specific cases. See https://www.fda.gov/drugs/development-approval-process-drugs for details about the FDA approval process and designations.

Given this structure, potential new firms must decide whether to enter the market to develop new drugs for alterations that affect small fractions of the population, anticipating that profits will depend on the pricing obtained through bargaining with health insurance companies, and that new competitors may enter the market in the future. We first show that rarer alterations elicit less or even no entry, and thus less or no new research; firms' break-even drug prices are higher for rarer alterations; and that there are fewer patients enrolled in clinical trials for rarer alterations. Our model's implications are consistent with the data from lung cancer research (see Section 3).

If private firms will not invest, it may in principle be feasible for governments to subsidize R&D. However, we show that the societal costs of government-sponsored research would become unsustainable as the number of new rare alterations keeps increasing. This is due to the exorbitant R&D costs that the government, too (the social planner) would need to bear in order to develop drugs for all rare alterations.

We then apply our model to study the incentives to innovate in the new framework in which regulatory agencies approve the *process* for drug discovery, rather than individual therapies. Specifically, we analyze a variant of our model in which firms research, develop, and seek approval for competing process-based drug development (PBDD for short) approaches, rather than individual targeted treatments. Under the same assumptions about investment, entry decision, and bargaining with insurance companies as in our first model, we show that the resulting PBDDs are economically sustainable. Moreover, drug prices under PBDD are lower than the average price under the traditional targeted therapies framework, and firms' profits increase as PBDDs become better in identifying new personalized drugs. The simple intuition is that each PBDD sidesteps the expensive RCTs for each individual ultra-rare alteration, but performs the RCT only once, to establish the ability of the process for drug discovery to deliver new personalized treatments.

Our calibration to lung cancer data in Section 6 also reveals some interesting predictions about investments in research and drug pricing within both the traditional approval regime and the new process-based drug development approval regime. Specifically, our calibration first shows that under the traditional approval regime, research will evaporate for alterations that affect approximately 0.06% of the lung cancer population. On the one hand this low cutoff is consistent with the explosion in targeted therapies in lung cancer research – some of which are as rare as affecting just 0.1% of the lung cancer patients – over the past two decades. However, we also report in the next section that scientific research has already uncovered a large number of genetic alterations that affect *less* than 0.06% of the lung cancer population, thereby showing we are reaching the breaking point of the traditional approval regime for targeted therapies. Because modern oncology increasingly treats lung cancer as

a collection of numerous rare alterations, the overall development of new therapies for lung cancer stands to stall under the traditional regulatory framework. In addition, without a change to a process-based approval regime, societal costs would run in the trillions of dollars per year, and indeed, the cost per patient per year to treat such rare alterations would vastly exceed the current estimates of value per statistical life year. Even from a societal perspective, it is not feasible to subsidize the research and development of targeted drugs.

Our calibrated model allows us to calculate drug pricing and the incentives to innovate under an alternative framework in which regulatory agencies approve the process for drug discovery, rather than individual therapies. We estimate the drug prices that would be charged by firms under the PBDD model. While the current targeted therapies range in price between \$250,000 for the treatment of EGFR mutation (14.5% of incidence) and \$525,000 for NTRK fusion (0.1% of incidence), we find that the PBDD drug price would be somewhere in the range between \$400,000 and \$280,000, depending on the ability of the PBDD to find new alterations and related new therapies, as well as the survival rates from such therapies. This price would apply to all patients *independently* of their specific alteration identified through the PBDD. Even setting aside expensive individual RCTs for rare alterations that push up prices, the process-based drug development approach would still yield relatively expensive treatments. However, we also find that social costs of personalized medicine are far lower with PBDDs than with the traditional approval process.

Finally, we find that the present value of future profits increases substantially as the PBDD becomes more effective in detecting new molecular alterations and increasing the survival rate of patients. The critical point is that the PBDD applies to all lung cancer patients rather than subgroups; therefore, drug prices decline and profits scale up with improvements in detection and survival probabilities. This in turn implies that firms retain the incentive to develop more effective PBDDs—which benefits both the companies themselves and their patients. The latter would receive highly personalized treatments that would increase their life expectancy at costs that are not as exorbitant as current ones.

Our paper is related to several strands of literature, both in the medical field and in the economics field. In the medical field, our work is related to both the literature documenting the progress in targeted therapies (see e.g. Hendriks et al., 2024 for a recent review), the costs of targeted therapies (see e.g. Leighl et al., 2021), and the recent work on the use of computers for protein projection and compound discovery (see e.g. Ren et al., 2023). However, none of this previous work appears to have tackled the profitability of drug discovery as the number of alterations increase. To the best of our knowledge, the personalized drug discovery process we analyze is also novel.

In economics, a relatively recent literature examines the problem of regulating the ap-

proval of new products such as drugs: e.g. Carpenter and Ting (2007), Henry and Ottaviani (2019), and Henry, Loseto, et al. (2022). This literature emphasizes that the regulator faces a trade-off between inducing an appropriate level of experimentation, which is socially beneficial, and preventing harmful products from reaching consumers. More broadly, this approach is related to the analysis of strategic experimentation (e.g. Guo, 2016; McClellan, 2022), (dynamic) persuasion (Kamenica et al., 2011; Honryo, 2018), and the positive relation between drug market and the intensity of R&D (Acemoglu and Linn, 2004). Our paper is also related to the recent literature on investments of firms in drug development. Frankel, Krieger, Li, and Papanikolaou (2024) compares novel or "breakthrough" drugs vs. incremental drugs, and finds that firms have stronger incentives to invest in the latter, despite the fact that the former yield greater knowledge spillovers.

While these contributions focus on different aspects and trade-offs related to experimentation and discovery of new, safe treatments, we take the discovery of new targetable alterations as the starting point, take the regulatory process as given, and study the resulting incentives for firms to enter the market over time. Furthermore, we compare the current regulatory regime with one that is tailored to personalized medicine.

Budish, Roin, and Williams (2015) shows that commercialization lags and patent terms distort firms' incentives in R&D relative to the social optimum; for cancer drugs, this leads, for instance, to limited investment in preventative treatments, and overinvestment in drugs for late-stage cancers. One of their proposed solutions involves targeting surrogate (non-survival) outcomes in the approval process, which in our model is comparable to an increase in the probability of approval. Our paper differs in that it focuses on the details of the approval process, in particular as it applies to personalized medicine. Furthermore, we analyze the entry of new firms in the market for (targeted) treatments.

## 2. Targeted Therapies in Lung Cancer

According to GLOBOCAN 2022, lung cancer is the most commonly diagnosed cancer, accounting for 12.1% of all cancers, and the leading cause of cancer-related deaths, responsible for 18.8% of all cancer-related fatalities, with an estimated 1.8 million deaths worldwide.[2]

Lung cancer is also one of the most aggressive tumors, with a very high mortality rate. Until the early 2000s, the only available medical treatment was chemotherapy. Over the past fifteen years, however, major advances in understanding the biology of tumors have led to the advent of targeted therapies and immunotherapy. These discoveries brought about a

[2]See https://gco.iarc.fr/today/en/dataviz/pie?mode=cancer&group_populations=1&populations=900&age_end=17&types=1 accessed on 1/20/2024.

major increase in patient survival expectancy. For instance, in metastatic patients, median survival went from months to years.

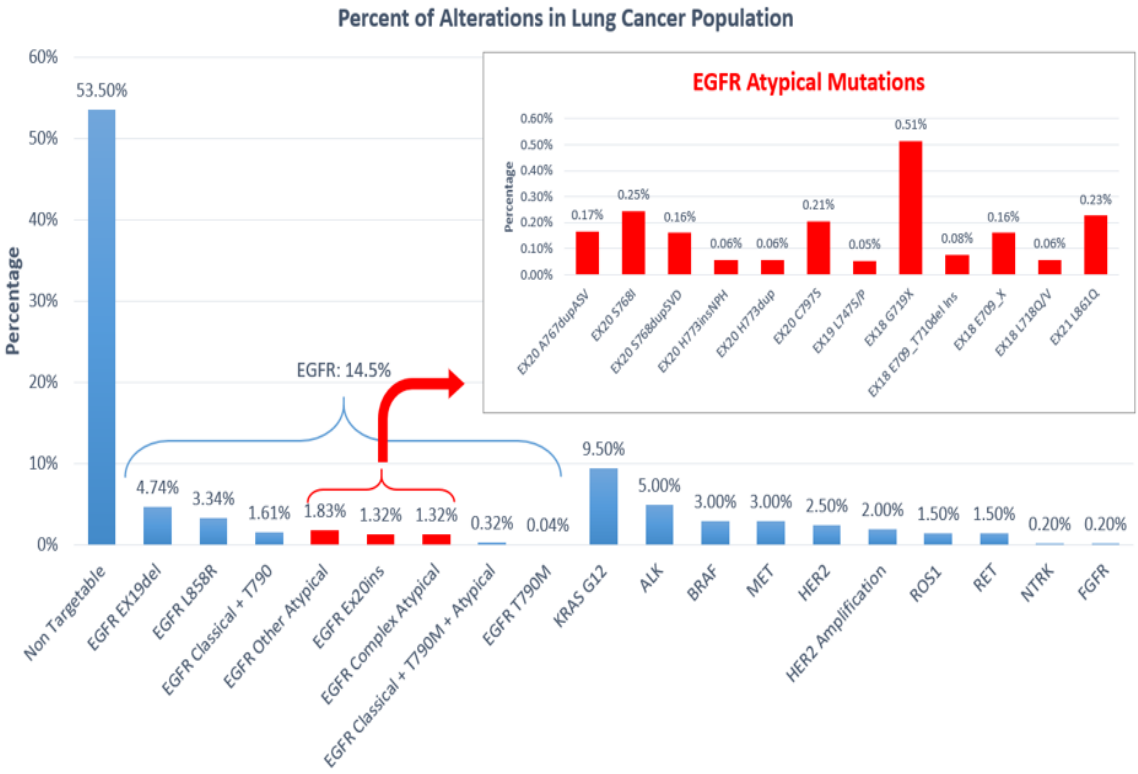
In 2004, for the first time, lung cancer researchers identified specific genomic mutations in a portion of a gene called EGFR in the patients' tumor. Patients harboring these alterations in the tumor were very sensitive to a particular class of agents, called EGFR tyrosine inhibitors. This discovery opened up the era of personalized medicine in lung cancer, as well as in many other tumors. Through randomized clinical trials, in the following few years, medical research demonstrated that these drugs were superior to the "one-size-fits-all approach" of chemotherapy. Many other targets were found in lung cancer and in other tumors. Conversely, those patients without these alterations were totally resistant to the new drugs. This finding created a paradigm shift: for each altered gene there was a corresponding tyrosine inhibitor. Such alterations are typically more prevalent in the population of patients who never smoked, which is about 15% of the overall lung cancer population in the U.S.

Following the discovery of EGFR mutations in 2004, several other targets were identified. ALK and ROS1 fusions were identified in 2007, followed by BRAF, RET, HER2, MET, NTRK, KRAS G12, EGFR Exon 20, and NRG1. Figure 1 indicates the frequency of alterations in lung cancer patients.[3] About 53.5% of patients with lung cancer do not have any specific alteration for which target treatment is available. Approximately 14.5% have the EGFR alteration, about 9.5% have the KRAS G12 mutation, and so on. A few of these alterations, such as ROS1 or RET, affect only 1% to 2% of the population; and others still, such as NTKR and FGFR, only affect less than 0.2% of the population.

Moreover, even within pre-defined groups of alterations, there is still some heterogeneity that can be responsible for a different prognosis and a different sensitivity to drugs. For instance, the red panel in Figure 1 shows the percentages of specific atypical EGFR alterations, which have different degrees of sensitivity to EGFR tyrosine kinase inhibitors, even within the same EGFR family. The frequencies of some of these atypical alterations are as low as 0.05%. Figure 2, taken from Figure 2 of Robichaux et al. (2021), shows the vast number of possible alterations even within the EGFR group, and the relative efficacy (or lack thereof) of known therapies across alterations. Similarly, Figure 11 in the appendix reports the large number of subtypes across alterations groups that have incidence below 0.1% of the lung cancer population, and for which no alteration-specific TKI exists. Indeed, Roskoski Jr (2024) reports that, as of 2024, there are only 80 FDA-approved drugs that target about two dozens of different protein kinases, which still represent "a small fraction of the 518-member

[3]These estimates are from Taha et al. (2021), who report ranges of frequencies. In particular, they report that between 39% and 68% of patients with lung cancer do not have any specific alteration; between 12% and 17% have a genetic alteration called EGFR, between 7% and 12% they have the alteration KRAS G12, and so on. The figure reports the midpoints of the respective ranges for simplicity.

Figure 1: **Percentage of Alterations in Lung Cancer Patients**



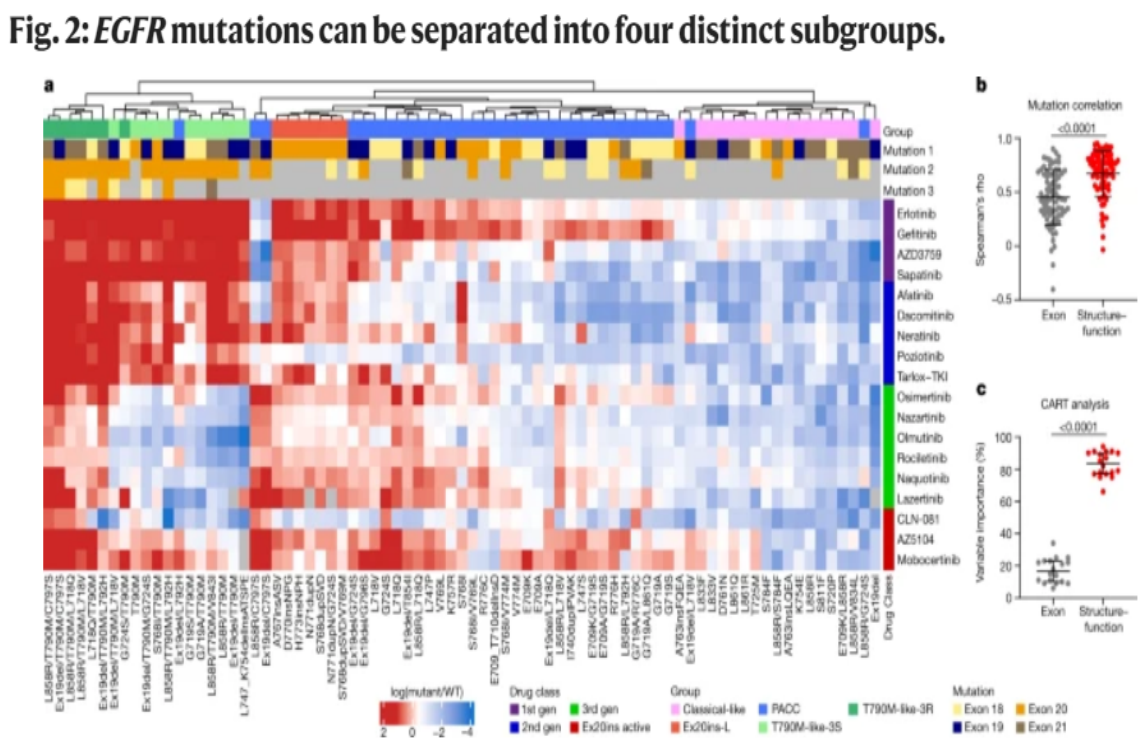

Source: Taha et al. (2021), Robichaux et al. (2021)

protein kinase enzyme superfamily." While there are currently 180 clinical trials worldwide studying orally effective protein kinase inhibitors, there are still a vast number of potential alterations that are not researched on, or grouped in a pre-defined category. A serious obstacle to further drug developments are the exorbitant R&D costs, which do not appear to have declined in the past several years (see Figure 10 in Appendix A).

Each of these alterations acts differently on the cellular system, and thus requires a specific targeted therapy that acts on each of the specific alterations. The number of new targeted therapies has exploded in recent years, as each different treatment targets the same alteration with different specific compounds (see Figure 3). The development of targeted drugs has not been confined to the treatment of lung cancer: it has extended to many other tumors, such as melanoma, thyroid cancer, gastric cancer, etc. In addition, over time, these tumors have become resistant to the first generation of drugs. Consequently, new generations of drugs have been developed to overcome the resistance to the previous inhibitors. Table 1 shows the list of FDA–approved treatments for various alterations. This table indicates an acceleration in the number of available treatments over the last decade.[4] Numerous

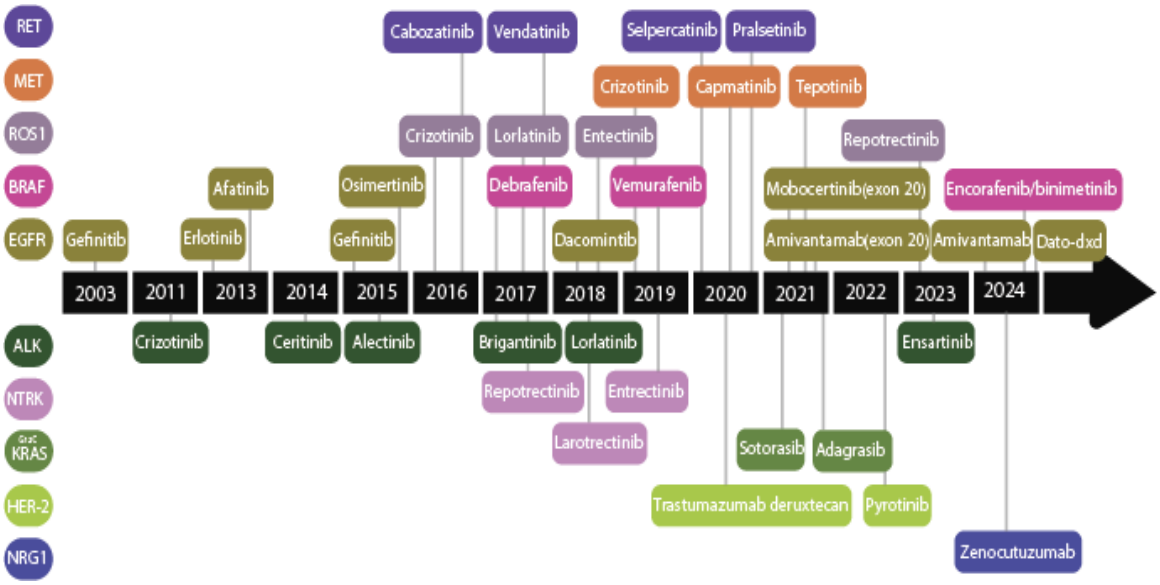
[4]The table reports the initial approval time, as some drugs first receive accelerated approval before final approval. Others gain approval for certain indications first, later expanding to additional uses, sometimes with other treatments.

Figure 2: **EGFR alterations**




(Source: Figure 2 in Robichaux et al. 2021)

Figure 3: **Drug Discovery Progression**




randomized control trials for new treatments are ongoing.

Table 1: **FDA Approved Drugs for Targeted Therapies**

| Agent | Control | Manufacturer | FDA Approval | Price per week | mPFS (months) | R&D Cost (millions) |
|---|---|---|---|---|---|---|
| **Panel A: First Line** | | | | | | |
| EGFR (12% - 17%) | | | | | | |
| Gefitinib | vs. chemo | AstraZeneca | 2003* | $1,942 | 10.8 vs 5.4 | |
| Erlotinib | vs. chemo | Roche | 2004* | $2,078 | 9.7 vs. 5.2 | $124 |
| Afatinib | vs. chemo | Boehringer | 2013 | $2,939 | 12.4 vs. 6.8 | |
| Dacomitinib | vs. Gefitinib | Pfizer | 2018 | $4,115 | 14.7 vs. 9.2 | |
| Osimertinib | vs. Gefitinib | AstraZeneca | 2018 | $4,394 | 18.9 vs. 10.2 | $594 |
| ALK (3% - 7%) | | | | | | |
| Crizotinib | vs. chemo | Pfizer | 2011 | $5,924 | 7.7 vs. 3.0 | |
| Ceritinib | vs. chemo | Novartis | 2014 | $3,681 | 16.6 vs. 8.1 | $1,095 |
| Alectinib | vs. Crizotinib | Roche | 2015 | $4,851 | 34.8 vs. 10.9 | $409 |
| Brigatinib | vs. Crizotinib | Ariad | 2020 | $5,181 | 24.0 vs. 11.1 | $491 |
| Lorlatinib | vs. Crizotinib | Pfizer | 2021 | $5,322 | NR vs. 9.1 | |
| Ensartinib | vs. Crizotinib | Xcovery | 2024 | $4,781 | 25.8 vs. 12.7 | |
| ROS1 (1% - 2%) | | | | | | |
| Crizotinib | vs. chemo | Pfizer | 2016 | $5,924 | 18.4 vs. 8.6 | |
| Entrectinib | SA | Roche | 2019 | $3,681 | 19.0 | $451 |
| Repotrectinib | SA | Brystol-Myers Squibb | 2023 | $7,667 | 35.7 | |
| RET (1% - 2%) | | | | | | |
| Selpercatinib | vs. chemo | Eli Lilly | 2022 | $5,914 | 24.8 vs. 11.2 | $511 |
| Pralsetinib | SA | Roche/Blueprint | 2023 | $5,556 | NR | $260 |
| BRAF (1% - 5%) | | | | | | |
| Dabrafenib Trametinib | SA | Novartis | 2017 | $6,217 | 14.4 | $1,239[1] |
| Encorafenib Binimetinib | SA | Pfizer | 2023 | $7,402 | 30.2 | |
| MET ex 14 (2% - 4%) | | | | | | |
| Capmatinib | SA | Novartis | 2020 | $6,232 | 12.4 | $561 |
| Tepotinib | SA | Merck | 2021 | $6,423 | 11.0 | |
| NTRK (<1%) | | | | | | |
| Larotrectinib | SA | Bayer | 2018 | $10,101 | 24.6 | $809 |
| Entrectinib | SA | Roche | 2019 | $5,244 | 11.2 | $451 |
| EGFR Exon 20 (1.3%) | | | | | | |
| Amivantamab - chemo | vs. chemo | J&J | 2021* | $7,709 | 11.4 vs. 6.7 | |
| **Panel B: Second Line** | | | | | | |
| EGFR (12% - 17%) | | | | | | |
| Osimertinib | vs. chemo | AstraZeneca | 2018 | $4,394 | 10.1 vs. 4.4 | $594 |
| Amivantamab/chemo | vs. chemo | J&J | 2021 | $7,709 | 8.2 vs. 4.2 | |
| KRAS G12C (7% - 12%) | | | | | | |
| Sotorasib | SA | Amgen | 2021 | $5,419 | 6.8 | |
| Adagrasib | SA | Mirati | 2022 | $5,629 | 6.5 | |
| HER2 (1% - 4%) | | | | | | |
| Trastuzumab Deruxtecan | SA | Roche | 2022 | $4,943 | 8.2 | |

Source: National Cancer Institute, FDA, Drugs.com, Taha et al. (2021). Prices are from drug.com, accessed on 5/28/2025. R&D costs are from Henderson et al. (2023), supplemental table S3. Footnotes: * denotes first FDA approval. [1] R&D cost for Trametinib itself, approved in 2013.

### 2.1. Patent Protection for Personalized Treatment

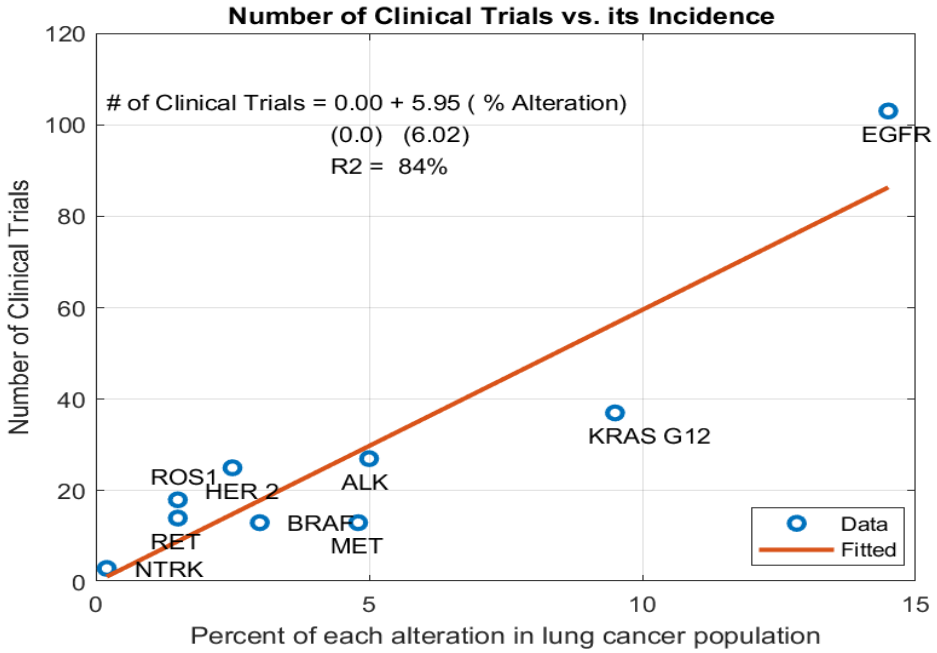
An additional issue with personalized medicine is the extent of patent protection of treatments. Because targeted therapies are based on very specialized molecules, and relatively small variations thereof may constitute new treatments without infringing on earlier patents, the effective protection for targeted treatments is far shorter than the usual 20 years. In fact, new treatments for the same alteration may occur within a span of just a few years.

To illustrate, consider again Table 1. The first treatment for EGFR was discovered in 2004, and almost 10 years passed before an alternative was developed. However, targeted treatments for e.g. ALK alterations have been approved at a much faster rate. Crizotinib (Pfizer) was approved in 2011. Then, two new drugs were approved in a span of just a few years: Ceritinib (Novartis) in 2014; Alectinib (Roche) in 2015. And then three more in the space of another 4 years: Brigatinib (Ariad) in 2020, Lorlatinib (Pfizer) in 2021, and Ensartinib (Ariad) in 2024. Given the large investments in R&D that firms have to bear (cf. the last column of Table 1), the short life span of these new treatments, and the increasingly smaller number of patients that they target, cast doubts on whether firms will continue to have incentives to innovate. This is not just a hypothetical scenario: in February 2023, Roche announced that it was going to end the collaboration with Blueprint to further develop Pralsetinib, a drug for RET alteration (1%-2% of the lung cancer population) which is competing with Selpercatinib, a contemporaneous drug developed by Eli Lilly to treat the same alteration.

## 3. Empirical evidence

In this section, we discuss evidence on research and drug pricing for rare alterations in lung cancer. We begin by documenting the strong negative relation between the incidence of an alteration in the lung cancer population and the intensity of scientific research for that alteration. A proxy for the amount of research undertaken on a particular alteration is the number of interventional clinical trials for that alteration over some specific time interval following its discovery. Figure 4 shows the relation between the total number of interventional clinical trials over a 10-year period since discovery of each alteration (EGFR, ALK, etc.) and the percentage of lung cancer population affected by each alteration. Even with few observations, a nearly linear relation emerges between the frequency of each alteration in the population and the number of clinical trials: Over the 10-year period following the discovery of the EGFR alteration, which affects about 14.5% of the lung cancer population, 103 clinical trials have been carried out. In contrast, during the 10-year period since the discovery of e.g. ALK, which affects about 5% of the population, only 29 clinical trials have been carried

Figure 4: **Cumulative Number of Clinical Trials vs. its Percentage in Population**



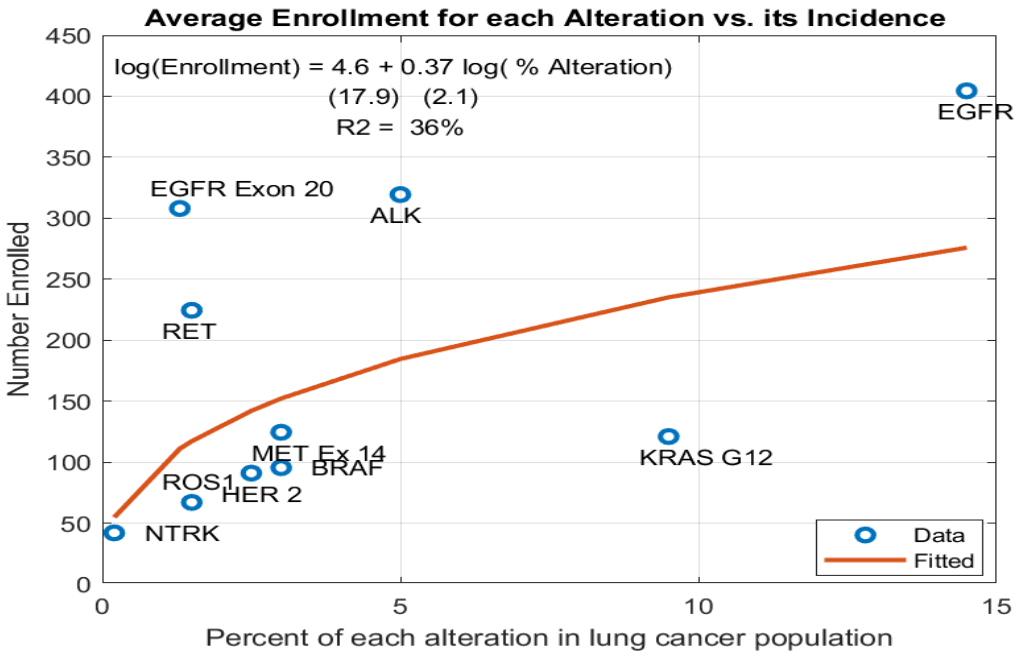

Notes: The figure plots the cumulative number of clinical trials over a 10-year period since discovery of each alteration versus its incidence in the lung cancer population. Data are from ClinicalTrials.gov, accessed on 1/18/2024. We only consider the subset of lung cancer clinical trials that are interventional and not retrospective, observational, or real-world data (RWD). For consistency across alterations, we define "discovery" of an alteration the year of its first clinical trial. The percentage of lung cancer patients affected by each alterations on the horizontal axis is from Figure 1. T-statistics are in parenthesis.

out. In an even sharper contrast, during the 10-year period since the discovery of the NTRK alteration, which affects 0.2% of the population, only 3 clinical trials have been carried out.[5] In sum, genetic alterations that are less common elicit less research.

As additional evidence on the difficulty of running clinical trials for small populations, we document the lower enrollment in clinical studies for rarer alterations, a feature that is consistent with our model below. Figure 5 shows the average enrollment of lung cancer patients that are reported in the published studies underlying the statistics in Table 1 for each alteration versus its incidence in the lung cancer population. Although data are more scattered in this case, we can find a non-linear positive relation between the two quantities. While the choice of sample size certainly depends on many factors, including the expected standardized improvement of each therapy over the standard of care, the positive relation also suggests more difficulty in securing large samples for more rare alterations.

[5]We also included time fixed-effects to ensure the result is not due to a timing effect, e.g. more biotech research in earlier than later periods, and the results are the same. Similar results obtain if we consider a shorter horizon than ten years.

Figure 5: **Average Patients' Enrollment of Approved Treatments for each Alteration vs. its Incidence**




Notes: Lung cancer enrollment data are from the published articles for each of the studies in Table 1. The percentage of lung cancer patients affected by each alterations on the horizontal axis is from Figure 1.

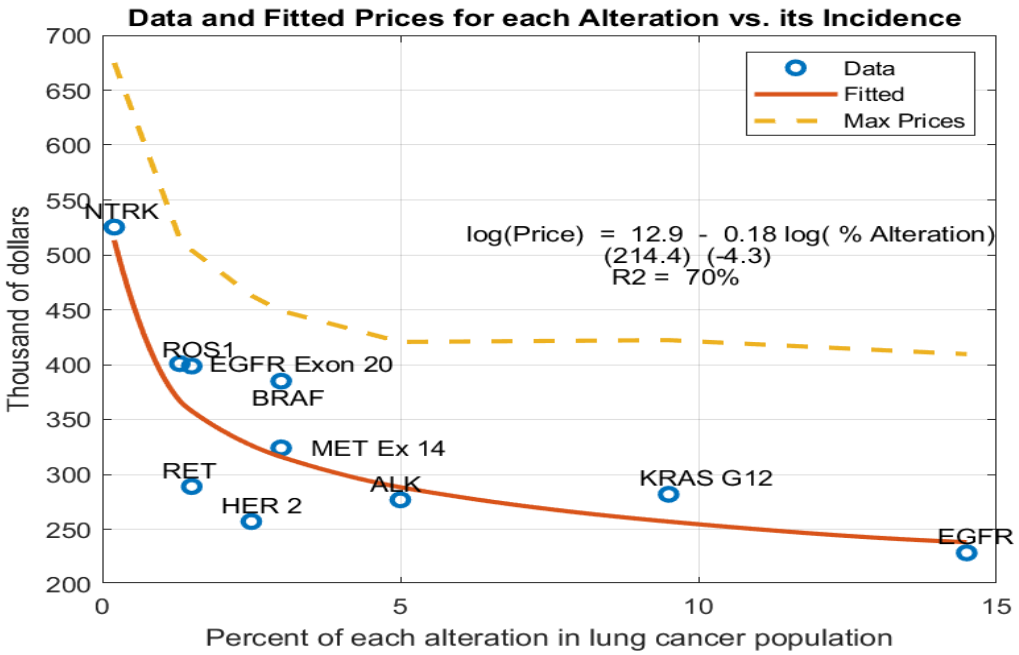
We now turn to drug prices and their relation with the incidence of each alteration. We first collect the price for the best available treatment for each alteration, according to the data in Table 1. Figure 6 shows the data and the fitted line from the simple regression

$$log(Price_i) = \alpha + \beta\, log(Incidence_i) + \epsilon_i$$

We find strongly significant coefficients with an $R^2 = 70\%$, showing that lower incidence correlates with higher prices, with an exponential pattern. We note that such pattern would not follow from a standard micro argument that relates marginal costs to marginal revenues, without an assumption that marginal costs are higher for rarer alterations. There does not seem to be any evidence of exponentially higher marginal costs for the production of drugs for rarer alterations. Our model in the next section instead delivers this pattern through a simple bargaining model between firms that develop the new drugs and health insurance companies.

What about revenues? Are they also increasing with prices? We now show that this is not the case. Even if prices are (much) higher for rarer alterations, the firms' revenues are *lower* for rarer alterations. Specifically, Figure 7 shows that the expected revenue per year, $P_i \times q_i$, where $q_i$ is the incidence of alteration $i$ in the lung cancer population, is linearly

Figure 6: **Prices per Year of Best Treatment for each Alteration versus its Incidence**




Notes: Price data are from Drugs.com and reported in Table 1 and they are for Osimertinib (EGFR), Lorlatinib (ALK), Repotrectinib (ROS1), Pralsetinib (RET), Encorafenib plus Binimetinib (BRAF), Capmatinib (MET Ex 14), Larotrectinib (NTRK), Amivantamab (EGFR Exon 20), Sotorasib (KRAS G12), and Trastuzumab Deruxtecan (HER 2). The percentage of lung cancer patients affected by each alterations on the horizontal axis is from Figure 1. The dashed line "Max Prices" reports the model-implied max prices the insurance company would be willing to pay for each drug while still breaking even.

related to its incidence, with $R^2 = 97\%$. That is, while prices are indeed higher for less common alterations, the total average revenue per alteration is lower for the same, given their lower incidence. This pattern is also consistent with our model.

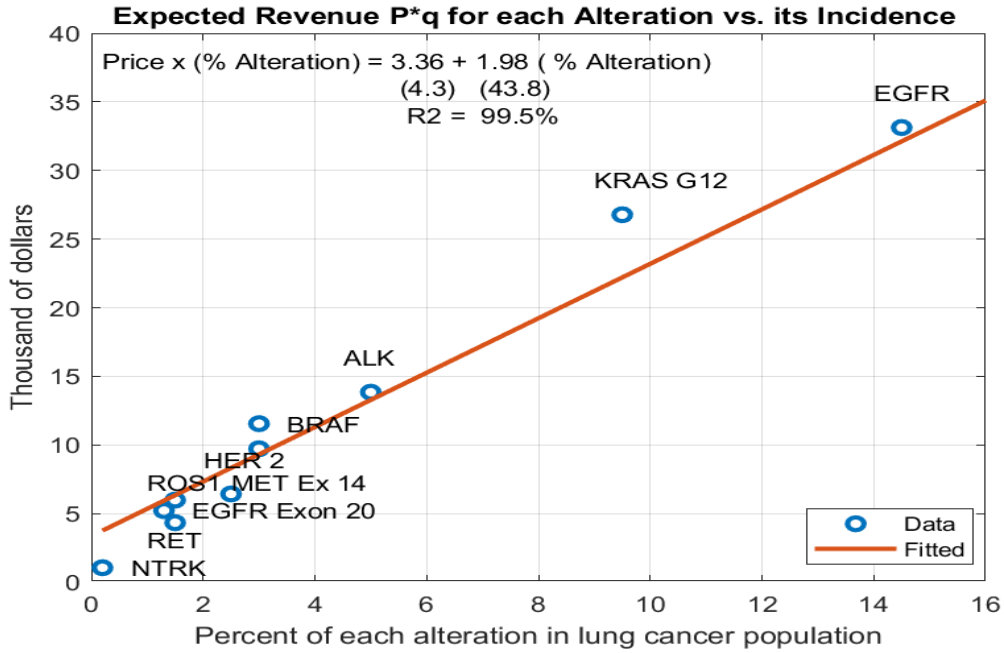
# 4. Model

In this section, we present a model that accounts for the empirical patterns discussed in the previous section. The model is sufficiently rich to be calibrated to the data, and thus bring additional insights about firms' investments decisions.

## 4.1. Overview

Our stylized market for treatments features four different types of participants: patients, firms, insurance companies, and the regulatory authority. Patients do not have an active

Figure 7: **Expected Revenues $Pq$ of Best Treatment vs. its Incidence**




Notes: Price data are from Drugs.com and reported in Table 1 and they are for Osimertinib (EGFR), Lorlatinib (ALK), Repotrectinib (ROS1), Pralsetinib (RET), Encorafenib plus Binimetinib (BRAF), Capmatinib (MET Ex 14), Larotrectinib (NTRK), Amivantamab (EGFR Exon 20), Sotorasib (KRAS G12), and Trastuzumab Deruxtecan (HER 2). The percentage of lung cancer patients affected by each alterations on the horizontal axis is from Figure 1.

role in our model. As far as the regulator is concerned, we do not take a mechanism-design perspective and instead study the implications of the current regulatory regime, as well as (in Section 5.1) of an alternative regime that seeks to approve drug development processes rather than individual drugs.

We analyze the steady-state equilibrium of a dynamic model of drug discovery, development, regulatory approval, and commercialization with entry; Section 4.2 outlines the overall timeline. At each time $t$, a new firm discovers a treatment for a targetable alteration. It then engages in price bargaining with a health insurance company; given the agreed-upon price, the firm begins the drug development and approval process.[6] If approval is granted, the firm sells the treatment to all patients with the given alteration (since the price is determined by bargaining, so long as it is above marginal cost and covers fixed costs, it is optimal for the firm to do so). However, at any time $t' > t$, a new treatment (discovered by a different firm ) may be approved with positive probability. We assume that, if this drug is approved

[6]In appendix B, we show a model with debt financing and bankruptcy costs that delivers the same results, but with bargaining occurring after the drug approval.

after the time-$t$ firm's drug has been approved, the time-$t$ firm exits the market;we motivate this assumption in Section 4.4. Finally, firms are heterogeneous in their R&D costs, which, for simplicity, are publicly observed at each time $t$; the entry decision is endogenously determined by whether or not their R&D cost is low enough to warrant developing, seeking approval for, and marketing the treatment, given the price agreed upon with the insurance firm. For simplicity, we assume that the costs of regulatory approval and production are the same for all firms.

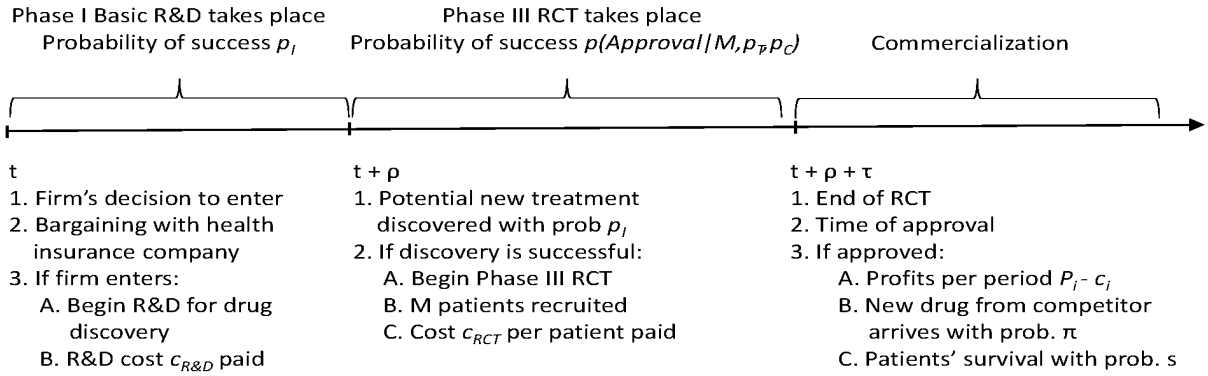
We solve the model backwards. As noted above, upon approval, the firm will sell its treatment to all patients exhibiting a given alteration, so long as the bargained price covers fixed and variable costs. Thus, working backwards, Sections 4.4–4.8 analyze the decisions faced by a firm in the course of the development and approval process, highlighting the (lack of) incentive to pursue approval for treatments targeting rare alterations or diseases. We then analyze bargaining between firms and insurers in Section 4.9. Finally, we analyze the entry decision, formalize our notion of steady-state equilibrium, and state our main existence result in Section 4.10; we also formally establish that there will be no entry of new firms for sufficiently rare alterations. From a welfare perspective, Section 4.11 shows that, under the assumed regulatory regime and market structure, if a social planner wanted to subsidize R&D for such rare alterations, the cost would be prohibitive—in fact, unbounded as the number of alterations grows.

We explicitly model the multi-sided nature of markets for drugs for two reasons. First, in most developed economies, targeted treatments are partially paid for by intermediaries (whether insurance companies or the national health service). Second, while stylized, our model is still rich enough to match many empirical facts on drug development and pricing for rare targets. The richness of the model allows us to calibrate the model and provide forecasts about pricing even in a new paradigm in which regulatory agencies approve the process, rather than individual therapies, as developed in Section 5

## 4.2. Drug development and approval

Let $N$ be the number of new patients diagnosed with a given illness per year. In every period $t$, a new firm enters the model and must decide whether to invest to start developing a new treatment for a given alteration. Developing a new drug, testing it for safety and effectiveness in small-scale studies, and eventually obtaining approval from the regulatory authority after large-scale studies is a multi-stage, multi-year process: a description of the steps required by the US Food and Drug Administration (FDA) can be found at https://www.fda.gov/drugs/development-approval-process-drugs. For simplicity, we split the entire process into two phases, which, in a rough parallel with the FDA's terminology,

Figure 8: Timeline of Drug Development




we call "Phase I" and "Phase III." The first comprises identifying a new compound, testing it for safety in animals first and human volunteers later, and finally gathering preliminary data on its effectiveness;[7] we assume this stage entails a cost $c_{R\&D}$, takes $\rho$ years to complete, and has success probability $p_I$.

The second phase comprises the large-scale randomized clinical trial (RCT) required to secure approval; we call this "Phase III," again in line with FDA's terminology. This is also a fairly complex process, which normally involves patient recruiting and coordination across multiple hospitals, complex protocols to adhere to, and so on. To capture the essence of the decision, however, we simplify the process as follows. Assume the firm has identified $M$ patients with the given alteration (we return to this point below). Conducting the RCT costs $c_{RCT}$ per patient, net of any credit or savings, such as those provided by the Orphan Drug Act. The $M$ patients are split into two groups of equal size, one treated with the new drug and the other with a control, which has a known success probability of $p_C$. (Success here can be measured in various ways, such as extending the survival probability by a given number of years; we provide further details in Section 6) As for the new treatment, in reality, the firm is uncertain about its success probability $p_T$; we take this into account in our calibrations of Section 6. For simplicity, in this section only, we assume that $p_T$ is known to the firm. Overall, the RCT lasts $\tau$ years. Following approval, the firm commercializes the drug and earns a (monopoly) profit per patient for every year the patient is alive, until a competitor enters the market with a new drug. As noted above, for simplicity, we assume that the new competitor completely displaces the firm's treatment. The overall timeline is depicted in Figure 8.

We first analyze the decision to carry out RCTs, conditional on having developed the

[7]This corresponds to the phases the FDA calls "animal testing," "IND Application," "Phase I," and "Phase II:" see https://www.fda.gov/drugs/information-consumers-and-patients-drugs/fdas-drug-review-process-ensuring-drugs-are-safe-and-effective.

drug, and having identified $M$ patients with the alteration of interest. Then, we tackle the key issue introduced by personalized medicine—the fact that, out of the total pool of subjects recruited by a firm, only a fraction will in fact exhibit the alteration being studied. Finally, we work backward and consider whether firms actually have incentives to invest in discovering a new treatment.

## 4.3. Approval probabilities for given subject pool

Let $x_T$ and $x_C$ be the number of individuals who are successfully treated in the treatment and control groups respectively. Conditional on $M$, the respective success rates are then $\widetilde{p}_T = \frac{x_T}{M/2}$ and $\widetilde{p}_C = \frac{x_C}{M/2}$. To bring about intuition, in this section we utilize a normal distribution approximation, as it is in fact regularly done in practice: e.g. Lo et al. (2022). Specifically, conditional on identifying $M$ patients with the given alteration,

$$\widetilde{p}_T \approx N\left(p_T, \frac{p_T(1-p_T)}{M/2}\right); \quad \widetilde{p}_C \approx N\left(p_C, \frac{p_C(1-p_C)}{M/2}\right)$$

The trial is deemed successful if it clears the usual statistical bar for type 1 error:[8]

$$\widetilde{z} = \frac{\widetilde{p}_T - \widetilde{p}_C}{\sqrt{\frac{\widetilde{p}_T(1-\widetilde{p}_T)}{M/2} + \frac{\widetilde{p}_C(1-\widetilde{p}_C)}{M/2}}} > z(\alpha) \tag{1}$$

where, denoting by $\Phi(.)$ the standard normal cumulative density, $z(\alpha) = \Phi^{-1}(1-\alpha)$ is the threshold for a one-sided $\alpha-$confidence test under the null hypothesis $H_0 : p_T \leq p_C$. Conditional on success probabilities $p_T$ and $p_C$, the probability of rejecting $H_0$ and thus accepting the new drug is

$$Pr(\text{Approval}_T | p_T, p_C, M) = 1 - \Phi\left(z(\alpha) - \kappa\sqrt{\frac{M}{2}}\right) \tag{2}$$

where $\Phi(.)$ is the cdf of the standard normal distribution, and

$$\kappa = \frac{p_T - p_C}{\sqrt{p_T(1-p_T) + p_C(1-p_C)}} \tag{3}$$

is the standardized improvement of the treatment $T$ against its control $C$.[9]

Clearly, ex-ante, as $M$ declines, the probability of accepting the new drug (when $p_T > p_C$) declines. On the other hand, for given $M$, the probability of accepting the drug increases with the effectiveness of the new therapy compared to the earlier one, that is, as $\kappa$ increases.

[8] Clinical trials target not only the size of the test ($\alpha$) but also its power ($\beta$). Sample sizes are normally chosen to match some values of both. For simplicity, we only consider the size of the test in this paper.

[9] The Bernoulli distribution of random variable $Y$ has mean $E[Y] = p$ and variance $\sigma(Y)^2 = p(1-p)$. Hence, $\kappa = E[Y_T - Y_C]/\sigma(Y_T - Y_C)$.

## 4.4. Pharma profits and discounting

Let $P$ denote the price of the new treatment agreed upon with the health insurer, and $c$ the marginal cost of producing it, once it has been approved. The profit to the firm per year and per individual is $(P-c)$ for as long as the firm remains a monopolist in the specific therapy. Recall that we assume that drug development takes $\rho$ years, and conducting an RCT takes $\tau$ years. Subject to approval, $j$ periods after time $\rho+\tau$ (i.e., at calendar time $t=\rho+\tau+j$), there are $N \times (1+s+s^2+..+s^j) = N \times \frac{1-s^j}{1-s}$ patients to treat, where $N$ is the number of new cases per year, and $s$ is the (expected) progression free survival rate—that is, the probability that a patient is still alive and has not progressed to a more severe stage of the disease.[10]

In every period, there is probability $\pi$ that a new entrant appears in the market with a new, approved drug; call this the **successful entry probability**. This is a crucial element of our analysis. Section 4.10 shows how this probability is determined endogenously in steady state; until then, we take it to be exogenous. We assume that, if an entrant appears *after* the (time-$t$) firm's treatment has been approved, the time-$t$ firm exits the market.[11] While stark, this simplifying assumption is consistent with observed behavior. Once the time-$t$ firm's drug is approved and becomes the "standard of care," any subsequent treatment is tested against it. For instance, Table 1 shows that, among drugs targeting EGFR, Dacomitinib and Osimertinib were tested against Gefitinib. By definition, if subsequent treatments are approved, they are found to be superior to that of the time-$t$ firm, and thus become the new standard of care. (For instance, Gefitinib is currently prescribed only in countries where Osimertinib is not available.) Our main objective is to capture a key, realistic aspect of competition among firms: the possibility of entry reduces the benefit to R&D. Our simplifying assumption achieves this objective. Moreover, while—as shown in Table 1—there are alterations for which multiple treatments are currently approved, these treatments have different side effects and tolerability. In effect, each such treatment targets a subset of the patients with the given alteration, and is the only one to do so.

To sum up, at each time $t=\rho+\tau+j$, the firm realizes a profit with "survival" probability $(1-\pi)^j$. We endogenize $\pi$ in Section 4.10. Finally, we let $t_c$ be the corporate tax rate.

Given these assumptions, the present value of future profits, conditional on the drug

[10] In the calibration of the next section, the survival rate is $s = s_T \times s_{other}$ where $s_T$ is the survival rate due to the treatment, while $s_{other}$ is the survival rate for other causes of death.

[11] If an entrant appears during the development and approval phase, we assume that the time-$t$ firm is unaffected. This is necessary to treat all firms symmetrically: the entrant is the firm who will face competition as soon as the time-$t$ firm's treatment is approved.

being approved, is given by $A_{III} \cdot (P - c) \cdot N$ where $A_{III}$ is the after-tax discount factor

$$A_{III} = (1 - t_c) \times \sum_{j=1}^{\infty} \frac{(1-\pi)^j}{(1+R)^{\tau+j}} \times \frac{1 - s^j}{1 - s} = \frac{(1 - t_c)(1 - \pi)}{(1 + R)^{\tau}(R + \pi)} \times \frac{1 + R}{1 + R - (1 - \pi)s} \tag{4}$$

and $R$ is the firm's discount rate. We discount profits realized at dates $\rho+\tau+1, \rho+\tau+2, \ldots$ back to time $t = \rho$ because that is the point in time when the firm must decide whether or not to undertake the RCT.

## 4.5. Personalized medicine: finding a large enough subject pool

Personalized medicine allows physicians to start from the population of $N$ patients with a given illness (e.g. cancer), perform additional tests (e.g. gene sequencing to detect alterations), and categorize patients into $n$ mutually exclusive subgroups to receive targeted therapies. These tests are normally not expensive and one recently discovered test, the NGS (Next Generation Sequencing) test, can determine the specific genomic alteration (Mirza et al., 2024). We set this cost to be zero, for simplicity.

The key implication for our analysis is that, when conducting an RCT to test the effectiveness of a new drug against a specific alteration, the number $M$ of patients with the given alteration is *not* a choice variable for the firm. To elaborate, let $i = 1, ..., n$ be an index denoting each subgroup. Let each subgroup $i$ have size $q_i \in (0, 1)$, with $\sum_{i=1}^{n} q_i = 1$ (see Figure 1). If the firm recruits a total of $K$ patients with the given illness to run a clinical trial for group $i$, the probability that $M$ out of those $K$ patients belong to group $i$ is then

$$\Pr(M|K, q_i) \quad = \quad \left( \begin{array}{c} K \\ M \end{array} \right) (q_i)^M (1 - q_i)^{K-M} \tag{5}$$

Hence, for alterations that affect a smaller size of the population with a given disease, the probability of securing a large enough sample $M$ of patients to conduct an RCT for a *specific* subgroup declines. Indeed, since $M$ follows a binomial distribution,

$$E[M|K, q_i] = Kq_i \tag{6}$$

As $q_i$ decreases, for a fixed total number $K$ of subjects recruited, the expected number of patients in subgroup $i$ declines. Thus, $K$ must increase in order to allow for a sufficient number of patients in each RCT for each targeted therapy $i$. Clearly, $K$ is bounded by $N$, the total number of patients with the given illness.

The choice variable for the firm is thus $K$. In addition, each new targeted therapy for group $i$ will only be beneficial to $Nq_i$ patients, rather than the full group of $N$ patients. To sum up, as the fraction $q_i$ decreases, it becomes harder to recruit a sufficient number of patients for each subgroup $i$, *and* the addressable market for each targeted therapy also shrinks.

## 4.6. Phase III for personalized medicine

From sections 4.4, the present value formula for each treatment $i$ with incidence $q_i$ is :

$$PV_{III,i}(K, q_i) = \{p_i(K, q_i)\, A_{III}\ (P_i - c_i)\ N\ - c_{RCT}\, K\}\ q_i \tag{7}$$

where $A_{III}$ is as in Eq. (4) and $p_i(K, q_i)$ is the probability of approval, given by

$$p_i(K, q_i) = \sum_{m=1}^{K/2} \Pr[2m \leq M \leq 2m+1 | K, q_i] \left[1 - \Phi\left(z(\alpha) - \kappa_i \sqrt{m}\right)\right]. \tag{8}$$

where $\kappa_i = \frac{p_i - p_C}{\sqrt{p_i(1-p_i)+p_C(1-p_C)}}$. To interpret, suppose zero or one out of $K$ recruited patients exhibits alteration $i$: then, the RCT cannot be run, and so the new treatment cannot be approved. If $2m \geq 2$ patients exhibit the alteration, then $m$ are assigned to the treatment group, and $m$ to the control group. The same occurs if $2m+1$ patients exhibit alteration $i$; the $(2m+1)$-st patient is not assigned to either group.

## 4.7. R&D disincentives for rarer targets

We now assume that $q_i$ is sufficiently small so that the binomial distribution (5) can be approximated by the Poisson distribution[12]:

**Assumption (Poisson Approximation)** In calculating $p(K, q_i)$, the firm adopts the approximation

$$\Pr(M = m) = e^{-Kq_i} \frac{(Kq_i)^m}{m!} \tag{9}$$

We then obtain:

**Proposition 1** *Let the Poisson Approximation Assumption hold. Then, everything else equal, for $\alpha \geq 2.3\%$, the present value $PV_{III,i}(K, q_i)$ decreases as $q_i$ decreases.*

The intuition of this result is that the probability of approval declines as $q_i$ declines (i.e. $\frac{\partial p_i(K,q_i)}{\partial q_i} > 0$), as it becomes increasingly difficult to secure large samples.

Clearly, a firm can take two actions as a consequence of proposition 1: Increase the number of patients $K$ and/or increase the price $P_i$. We study the latter strategy further below. As for the former strategy, from Equation (7), increasing $K$ only works if $\partial p(K, q_i)/\partial K$ is sufficiently large. Moreover, $K$ is bounded above by $N$ itself. The following proposition, which does not rely on the approximation assumption, makes the point that such strategy does not work for small $q_i$:

[12] A known upper bound on the total variation distance between the binomial distribution with parameters $K$ and $q_i$ and the Poisson distribution with parameter $\lambda = Kq_i$ is $\frac{1-\exp(Kq_i)}{Kq_i} \cdot Kq_i^2 = [1 - \exp(Kq_i)]q_i$: see e.g. Steele (1994), §5.

**Proposition 2** *For every value of $A_{III}, P_i, c_i$ and $N$, there is $\bar{q}_i$ such that $PV_{III}(K, q_i) < 0$ for all $q_i \leq \bar{q}_i$.*

Proposition 2 captures a straightforward, yet important insight: $q_i$ is small, then it will be virtually impossible for firms to conduct an RCT, simply because, for any alteration, there will not be sufficient patients in the treatment group. Under the traditional approval process in which regulatory agencies approve individual therapies, a truly personalized medicine is economically infeasible.

## 4.8. Phase I for personalized medicine

The firm will take into account the difficulties to secure a proper sample size earlier on in the development of the new drugs. Indeed, moving backward to time 0, as per Fig. 8, the first step in the drug development process is to identify a treatment for a specific alteration $i$, and then to carry out the initial testing. Let $c_{R\&D,i}$ denote the R&D cost incurred in this phase. Let $p_{I,i}$ be the probability of advancing to Phase III (i.e. to the randomized clinical trial), and denote by $A_I = (1+R)^{-\rho}$ the discount factor corresponding to Phase I, which takes into account the time $\rho$ between Phase I and Phase III. Then, the present value of carrying out the R&D for the new drug for alteration $i$, and subsequently conducting an RCT to secure approval for it, is

$$PV_I(q_i) = p_{I,i}\, A_I\, \{p(K^*, q_i)\, A_{III}\, (P_i - c_i)\, N - c_{RCT}\, K^*\}\, q_i - c_{R\&D,i} \tag{10}$$

where $K^*$ is the optimized number of patients performed in previous step (Phase III). Clearly, as $q_i$ decline, so does $PV_{I,i}$, which reaches zero for a higher value of $q_i$ than $PV_{III,i}$ because of the additional discount $p_{I,i}\, A_0$ and the additional R&D cost $c_{R\&D,i}$. A result similar to Proposition 2 clearly holds in this case as well.

## 4.9. Insurance market and bargaining

We now endogenize the drug price $P_i$ through a simple bargaining model between firms and health insurance companies. We only consider insurance for a single disease of interest (e.g. lung cancer) to maintain a sharp focus. Let the total insured population be $N_{pop}$, and let $q$ be the i.i.d. probability that any insured individual develops the disease. Each person pays a health insurance premium $C$; if the person is affected by the disease, the insurance company fully covers the treatment (so there are no copays or deductibles). The total profit for the insurance company is thus

$$\Pi = C\, N_{pop} - N_{pop}\, q \sum_{i=1}^{n} P_i\, q_i \tag{11}$$

where each $P_i$ is the *actual* price the insurance company and firm $i$ agree upon, as we describe momentarily. For each alteration $i$ the insurance company must conduct its bargaining with the specific firm $i$ that is developing the drug. To simplify the multi-lateral bargaining, we assume that the insurance company sets a maximum price $\overline{P}_i$ that is willing to pay for each drug $i$, such that, at these prices, the insurance company would break even in expectation:

$$\frac{C}{q} = \sum_{i=1}^{n} \overline{P}_i \, q_i \tag{12}$$

The profit for the insurance company can then be written as

$$\Pi = N \left( \sum_{i=1}^{n} (\overline{P}_i - P_i) \, q_i \right) \tag{13}$$

where $N = q \, N_{pop}$ is the number of patients per year with the diseases. Each maximum price $\overline{P}_i$ for therapy $i$ may depend on $i$, as well as on the fractions $q_1, \ldots, q_n$. While we do not micro-found the determination of such maximum prices, we estimate them below from observed prices. Allowing for different maximum prices $\bar{P}_i$ for different alterations accommodates (but does not require) cross-subsidization: in particular, the health insurer might entertain a higher maximum price for rarer alterations, provided it can secure a lower price for more prevalent alterations so that the overall budget constraint in Eq. (12) holds.

The actual price $P_i$ of each drug is set by bargaining between each insurance company and the firm. The firm will not enter the market and develop the new drug if the present value $PV_I$ in equation (10) is negative. Solving for the break-even price, the firm will not enter the market if

$$P_i < P_i^{BE} = c_i + \frac{p_I \, A_I \, c_{RCT} \, K^*_{BE} \, q_i + c_{R\&D}}{p_I \, A_I \, p(K^*_{BE}, q_i) \, A_{III} \, N \, q_i}. \tag{14}$$

In this equation, $K^*_{BE}$ is the optimal choice of sample size given price $P_i^{BE}$. In other words, $P_i^{BE}$ is such that, if the firm chooses $K$ optimally, profits upon approval are just enough, in expectation, to cover R&D costs $c_{R\&D}$. Hence, if the insurance company had all bargaining power, it would set $P_i = P_i^{BE}$.[13]

If the firm had full bargaining power, instead, then $P_i = \overline{P}_i$: that is, the drug price would exactly match the maximum price the insurance company is willing to pay, and the insurance company ends up with zero profits. We assume a simple $\gamma$-split in the bargaining power, so that the drug price $P_i$ is set according to

$$P_i = \gamma \, \overline{P}_i + (1 - \gamma) \, P_i^{BE} \tag{15}$$

under the condition $P_i \leq \overline{P}_i$.

[13]Here we assume that bargaining occurs before the firm decides to enter the market. The appendix shows that the same results obtain with bargaining after drug approval if the firm issues debt to finance the investments and the firm is subject to bankruptcy costs.

**Proposition 3** *For fixed $\pi$ and $c_{R\&D}$, the break-even price $P_i^{BE}$ increases as $q_i$ declines.*

Intuitively, there are two reasons why the break-even price $P_i^{BE}$ increases as $q_i$ declines, when $c_{R\&D} > 0$: In the denominator, both the incidence $q_i$ and the probability of approval $p(K, q_i)$ decline as the incidence $q_i$ declines. However, $q_i$ also appears in the numerator, and in addition, the optimal choice of $K_{BE}^*$ depends on $q_i$. The proof in the Appendix shows that, regardless, the net effect of a decline in $q_i$ is to increase the break-even price $P_i^{BE}$.

One caveat is that the above result does *not* take into account the equilibrium effects of changes in $q_i$ on the probability $\pi$ of successful entry. However, it highlights a key force shaping the decision faced by the firm and the interaction with the health insurer.

## 4.10. Endogenous entry and intensity of R&D

Finally, we close the model by analyzing the equilibrium entry decision of firms. This also allows us to analyze the incentives for drug development when other firms can enter the market. Specifically, we now endogenize the probability $\pi$ that a competitor enters the market with a superior treatment and steals the market from the incumbent. To simplify the analysis, we characterize the steady state of the model, and establish its existence.

We assume that firms have heterogeneous R&D costs $c_{R\&D}$, independently drawn from the uniform distribution on some interval $[c_L, c_H]$. Each firm knows its own R&D cost $c_{R\&D}$, but is uncertain about its standardized improvement coefficient $\kappa$; specifically, every firm knows that $\kappa$ is independently drawn according to the same density $f_\kappa(\cdot)$.

We analyze the market for each alteration $i$ separately. In every period, and for every $i$, a new firm draws the cost of R&D $c_{R\&D,i}$, decides whether to start the development and approval process, and if so, engages in bargaining with the insurance company. The firm's entry decision depends upon the present value formula in Eq. (10):

$$PV_{I,i} = p_{I,i}\, A_I\, \{p_i\, A_{III}\, (P_i - c_i)\, N - c_{RCT}\, K^*\}\, q_i - c_{R\&D,i} \tag{16}$$

where $P_i$ is the (anticipated) price determined by bargaining, as in the previous section, and the Phase-III approval probability $p_i = p_i(K^*, q_i)$ is as in (8), with $K^*$ being the optimal choice given the price $P_i$, except that the last term is $E_\kappa\left[\Phi\left(z(\alpha) - \kappa\sqrt{m}\right)\right]$ to reflect the fact that the firm does not know its own standardized incremental improvement.

It is important to note in Eq. (16) that the choice of $K^*$, and hence the probability $p_i$ of approval, as well as the discount factor $A_{III}$, depend upon the (steady-state) successful entry probability $\pi_i$. In turn, $\pi_i$ is determined by the firm's decision to start R&D. By inspecting Eq. (16), this decision has a simple cutoff structure: if the firm's R&D cost realization $c_{R\&D,i}$

is below the cutoff

$$\bar{c}_{R\&D,i} = p_I \, A_I \, \{p_i \, A_{III}(P_i - c_i) \, N - c_{RCT} \, K^*\} \, q_i. \tag{17}$$

the firm starts R&D; otherwise, it leaves the market. Therefore, the steady-state probability of successful entry must satisfy

$$\pi_i = p_{I,i} \, \frac{1}{c_H - c_L} \int_{c_L}^{\bar{c}_{R\&D,i}} p_i \, dc_{R\&D}. \tag{18}$$

That is, $\pi_i$ equals the probability of successfully completing Phase-I trials, multiplied by the expected probability of approval in Phase III, taken over firms with low enough R&D cost. In this equation, we recall that the probability $p_i$ depends upon the optimal choice of sample size $K^*$, which in turn depends upon the price $P_i$, which depends itself on the R&D costs $c_{R\&D}$ through the bargaining process. Firms with higher R&D costs have higher break-even prices and thus are able to get higher prices through bargaining (see Eqs. (15) and (14)).

**Proposition 4** *Fix an alteration $i$ with incidence $q_i$. If $c_L > 0$ is sufficiently low, for any $\bar{P}_1, \ldots, \bar{P}_n$ such that Eq. (12) holds, there exists a successful entry probability $\pi_i^*$, a cutoff $\bar{c}_{R\&D,i}^*$, and, for every $c_{R\&D} \in [c_L, \bar{c}_{R\&D,i}^*]$, approval probabilities $p(c_{R\&D})$, sample sizes $K^*(c_{R\&D})$ and prices $P_i(c_{R\&D})$ such that*

1. *for every $c_{R\&D} \in [c_L, \bar{c}_{R\&D,i}^*]$, the negotiated price $P_i(c_{R\&D})$ is determined as in Section 4.9, given R&D costs $c_{R\&D}$ and successful entry probability $\pi_i^*$;*
2. *for every $c_{R\&D} \in [c_L, \bar{c}_{R\&D,i}^*]$, $K^*(c_{R\&D})$ is the optimal sample size in Phase III given price $P_i(c_{R\&D})$ and successful entry probability $\pi_i^*$;*
3. *for every $c_{R\&D} \in [c_L, \bar{c}_{R\&D,i}^*]$, $p(c_{R\&D})$ is the probability of approval in Phase III given the optimal sample size $K^*(c_{R\&D})$;*
4. *$\pi_i^*$ is determined by Eq. (18) given the cutoff $\bar{c}_{R\&D,i}^*$ and the approval probabilities $p(c_{R\&D})$ for each $c_{R\&D} \in [c_L, \bar{c}_{R\&D,i}^*]$.*

The following result is immediate:

**Proposition 5** *If $c_L > 0$, then there is $q_i$ sufficiently low for which $\bar{c}_{R\&D,i}^* < c_L$ and thus $\pi_i^* = 0$ in steady state.*

The last two propositions show that there are two values of $q_i$ such that the probability of a potential entrant is larger for higher $q_i$. While a more general statement is harder to establish due to the non-linearity of $PV_{I,i}$, a continuity argument suggests a positive relation between $q_i$ and the endogenous probability of successful entry $\pi_i^*$ for some range of $q_i$. That is, alterations with higher incidence in the population attract more investments in drug discovery. We will find such relation in our calibrated simulations below.

## 4.11. The social costs of personalized medicine

The analysis above shows that even when science generates significant improvements in healthcare for a given disease via personalized treatments, it is effectively impossible for firms to be profitable. In turn, this will stall scientific research. In principle, the government could step in and sustain science development. However, we now show that the social costs for government intervention are unbounded as the number of new discoveries $n$ increases.

We now consider the case in which the entire population of patients with the disease (e.g. lung cancer) is distributed symmetrically in $n$ groups, each with incidence $q_i = 1/n$. Given the symmetry across alterations, we assume here that the price $P_i$ is the same for each alteration $i$, and denote this common price by $P(n)$ to emphasize the dependence on the number of alterations. Similarly, we assume that all firms have the same marginal cost $c_p$ and standardized improvement $\kappa$. The aggregate present value of developing treatments for all alterations depends on the specific R&D costs of the firms that are targeting each alteration $i = 1, .., n$. Recalling that such $c_{R\&D} \sim U[c_L, \bar{c}_{R\&D}]$, the aggregate expected present value at the industry level using the expected R&D cost:

$$E[PV_I(n)] \;=\; p_I A_I \left\{ p(K^*(n), n)\, A_{III}(n)\, \left[P(n) - c_p\right]\, N \, - c_{RCT}\, K^*(n) \right\} - 0.5(c_L + \bar{c}_{R\&D})\, n \tag{19}$$

where the acceptance probability $p(K^*(n), n)$ is as in Equation (8) with $q_i = 1/n$, and $K^*(n)$ reflects the optimized number of patients for each $n$.

Consider now a social planner who wishes to develop targeted treatments for all alterations, but must nevertheless conduct clinical trials as in the current approval process; this seems both realistic and necessary to ensure that patients and doctors trust the outcomes of scientific research. To keep the analysis consistent with the previous section, we calculate the breakeven price $P^{BE}$ that ensures that $E[PV_I] = 0$. This yields the minimum annual cost of treating each patient. We set the corporate tax $t_c$ and any tax credit incentives to zero: those represent transfers to and from the social planner, which can be omitted if the social planner herself sets prices. Under these assumptions, the break-even price is the same as in equation (14) with $q_i = 1/n$.

We then have:

**Proposition 6** *For every value of $c_p, c_{R\&D}$ and $N$, and for every $P^*$, there is $\overline{n}$ such that $P^{BE} > P^*$ for $n > \overline{n}$.*

Proposition 6 shows that the break-even price becomes unboundedly large as $n$ increases. This implies that societal costs for targeted therapies are unbounded.

Section 6 complements this qualitative result with a quantitative comparison with standard measures of value per statistical life year.

One caveat is that there may be spillover effects across groups, so that the cost $c_{R\&D}$ may be a function of $n$ itself. Indeed, we expect that $c_{R\&D}$ for targeted therapies will decline substantially in the future as $n$ increases. Still, unless $c_{R\&D}$ decreases faster than $\frac{1}{n}$, the overall effect of an increase in $n$ will still be to increase the break-even price.

# 5. Process-based drug development

In this section we consider a process-based approach to drug discovery. We imagine a situation in which biotechnology and AI allow for the determination of a genomic expression of each individual patient with a disease (say, lung cancer) and in which the technology allows for the determination of a specific, personalized drug (e.g. a cancer vaccine) for that specific individual, if possible. In the case of Moderna's cancer vaccine, for instance, AI technology is used to identify the patients' neoantigens that are most likely to trigger a strong immune response (see Fieldhouse et al. (2026)). Similarly, the appendix discusses a specific proposal put forward by Garassino et al. (2026) for the case of lung cancer. We consider however the possibility that the technology is not sufficient to determine the specific, personalized drug, in which case the patient must be treated according to the best existing standard of care.

For easier reference going forward, we call this process-based approach to drug development the "Process-based Drug Development", or PBDD for short.

## 5.1. Competition in PBDDs

We envision firms developing competing PBDDs which may differ from each other due to differences in technologies, algorithms, datasets, and computing power. For instance, in the cancer-vaccine area there are multiple firms developing vaccines, such as Moderna/Merck, BionTech, Roche/Genentech. One key aspect of our analysis is, again, entry: we want to ensure that, if PBDDs become the prevailing approach to developing drugs, firms have incentives to innovate (see Proposition 8 and our calibration results in the next section).

Regulatory authorities such as the FDA and EMA have now to approve PBDDs and therefore ask firms to run randomized clinical trials to ensure that (a) treatments produced via PBDDs are better than the standard of care; and (b) any new PBDD improves over the PBDD currently in place. Crucially, the RCT is run over the entire lung cancer population, irrespective of which targetable alteration, if any, any single recruited patient has. Thus, the economic viability of a PBDD is independent of the rarity of the various alterations.

More concretely, the randomized clinical trial is now set up in the same format as in Section 4. It is still convenient to divide a firm's decision to enter the PBDD's market in two phases, phase I and phase III. In phase I we assume the firm must acquire the necessary know-how—hire human capital, build or secure access to computing power, develop algorithms, and buy datasets, in addition of course to running the smaller trial on patients as in standard Phase I/II. Let $c_{tech}$ be the initial fixed costs of Phase I. Once the firm has acquired the necessary know-how and run Phase I/II, in phase III, it must run a RCT. As in Section 4, $M$ patients are divided into a test group $T$ and a control group $C$. The $C$ group will receive the best existing treatment, or the currently best PBDD; for short, we refer to this as the "standard of care." The $T$ group undergoes the new PBDD to determine the individualized treatment. The patients in the two groups are then followed for $\tau$ periods. Crucially, we do not differentiate across alterations. All patients with lung cancer are considered as just one group. All other steps in the RCT are otherwise the same, and after the observation period of $\tau$ periods the usual calculations are performed.

Let $Q_T$ be the probability that the new PBDD detects a new alteration and develops a treatment for it, or develops a new drug for a known alteration. $s_T^{new}$ denotes the survival probability of the new drug. As in previous sections, we define $\kappa$ as the standardized improvement of $T$ versus $C$, and we assume $\kappa \sim U[\kappa_L, \kappa_H]$ as in previous sections. In fact, we make the same distributional assumptions of $T$ versus $C$ to focus on the order of magnitudes of prices.

The present value of future profits at the beginning of phase III is then

$$PV_{III}^{PBDD} = p_{III}(M)\left(Q_T\, A_{III}\,(P^{PBDD} - c^{new}) - c_{PBDD}\right) N - c_{RCT}\, M \tag{20}$$

where $p_{III}(M)$ is the probability of approval of the PBDD, given a sample of size $M$; $A_{III}$ is the discount factor given by equation (4); and $c_{PBDD}$ is the (variable) cost of running the PBDD, once the fixed costs have all been paid up. We make the pessimistic assumption that the firm makes profits on a patient only if it detects a new alteration or develops a new drug (which occurs with probability $Q_T$): in case it does not, the patient receives the standard of care, which we assume is delivered by a different firm. This minimizes the possible profits of the firm, and hence reinforces our results on the viability of competition in PBDDs.

The decision to enter the market depends on the cost of acquiring the know-how, which we assume to be heterogeneous across firms. We then have

$$PV_I^{PBDD} = p_I A_I P_{III}^{PBDD} - c_{tech} \tag{21}$$

where $A_I = (1+R)^{-\rho}$ is the discount factor reflecting the time to acquire the necessary know-how and run Phase I/II. We assume that the firm can always procure the necessary

hardware and software, access datasets and so on: the only uncertainty is whether their new PBDD will be better than the standard of care in phase I/II. To keep symmetry with the case studied in previous section, we use the same probability $p_I$ as before. As in the case of targeted treatments, we assume that technology acquisition costs are heterogeneous: $c_{tech} \sim U[c^L_{tech}, c^H_{tech}]$.

## 5.2. The price of drugs under the PBDD

We continue to assume that the price of drugs from the PBDD, $P^{PBDD}$ above, is determined by bargaining between the firm and a health insurance company. As in section 4.9, the insurance company is not willing to pay more than $C/q = \sum_i^n q_i \overline{P}_i$ for the PBDD. Assuming again an $\gamma : (1-\gamma)$ split of the surplus between firm and health insurance company, the price of PBDD is given by

$$P^{PBDD} = \gamma \frac{C}{q} + (1-\gamma) P^{BE}_{PBDD} \tag{22}$$

where $P^{BE}_{PBDD}$ is the breakeven price from setting $PV_I^{PBDD} = 0$ in (21), explicitly given by

$$P^{BE}_{PBDD} = c^{new} + \frac{c_{tech} + p_I A_I c_{RCT} M^*}{p_I A_I p_{III}(M^*) Q_T A_{III} N} + \frac{c_{PBDD}}{Q_T A_{III}} \tag{23}$$

where $M^*$ is the optimal choice of sample size given the break-even price itself. The constraint for the pricing to be viable is that $P^{BE}_{PBDD} < C/q$, otherwise firms will not enter the market. Importantly, neither the present value $PV_I^{PBDD}$ equation (21) nor the break-even price $P^{BE}_{PBDD}$ in (23) depend on the number of alterations $n$ or the incidence $q_i$ of a given alteration. That is, as $n$ increases, or $q_i$ declines, nothing changes in these quantities.

On the other hand, Proposition 6 shows that, as $n$ grows large, the break-even price for a treatment targeting a single alteration is unbounded. In particular, there is $n$ large enough so that this price exceeds $P^{PBDD}$. Since, for firms to enter the market under the traditional approval regime, the price $P_i$ for each drug must at least break even, we have:

**Proposition 7** *Everything else equal, for a number of alterations $n$ large enough but still such that individual treatments are offered, the PBDD price is lower than the average price of targeted therapies:*

$$P^{PBDD} < \sum_{i=1}^{n} q_i P_i \tag{24}$$

This proposition shows that as the number of identified alterations $n$ increases, even if the present value for firms offering individual treatments is non-negative, the drug price per patient stemming from the PBDD is lower than the average price paid under the traditional

framework of approving individual targeted therapies. This implies that on average, approving the process for drug development instead of individual therapies brings about financial benefits for the patients.

## 5.3. Incentives to innovate

In section 4.10 we showed that under the traditional approval process the incentives to innovate evaporate for targeted therapies that affect an increasingly small number of patients $q_i$. We now show that the process-based approach to drug discovery provides the proper incentives to research:

**Proposition 8** *Everything else equal, the present value of future profits $PV_I^{PBDD}$ in equation (21) increases, and the break-even price $P_{PBDD}^{BE}$ in equation (23) declines, as the ability of PBDD of detecting a new alteration and find a new drug $Q_T$ increases.*

The increase in $PV_I^{PBDD}$ as $Q_T$ increases entails that firms have an incentive to keep exploring new systems to increase $Q_T$ over their competitors.

To close the model, as in Section 4.10, the probability of successful entry equals the average probability of approval, taken over firms whose Phase-I expected profits are non-negative:

$$\pi = \frac{1}{c^H - c^L} \int_{c^L}^{\bar{c}_{tech}} p_{III}\, dc_{tech}, \quad \text{where} \quad \bar{c}_{tech} = A_I PV_{III}^{PBDD}. \tag{25}$$

The following result characterizes the resulting equilibrium:

**Proposition 9** *If $c_{tech}^L > 0$ is sufficiently low, there exists a successful entry probability $\pi^*$, a cutoff $\bar{c}_{tech}^*$, and, for every $c_{tech} \in [c_L, \bar{c}_{tech}^*]$, approval probabilities $p(c_{tech})$, sample sizes $M^*(c_{tech})$ and prices $P^{PBDD}(c_{tech})$ such that*

1. *for every $c_{tech} \in [c_{tech}^L, \bar{c}_{tech}^*]$, the negotiated price $P^{PBDD}(c_{tech})$ is determined as in Eq. (22), given technology acquisition costs $c_{tech}$ and successful entry probability $\pi^*$;*

2. *for every $c_{tech} \in [c_{tech}^L, \bar{c}_{tech}^*]$, $M^*(c_{tech})$ is the optimal sample size in Phase III given price $P^{PBDD}(c_{tech})$ and successful entry probability $\pi^*$;*

3. *for every $c_{tech} \in [c_{tech}^L, \bar{c}_{tech}^*]$, $p(c_{tech})$ is the probability of approval in Phase III given the optimal sample size $M^*(c_{tech})$;*

4. *$\pi^*$ is determined by Eq. (25) given the cutoff $\bar{c}_{tech}^*$ and the approval probabilities $p(c_{tech})$ for each $c_{tech} \in [c_{tech}^L, \bar{c}_{tech}^*]$.*

Differently from the equilibrium under the traditional approval method, the incidence of individual alterations $q_i$ does not appear in this proposition, and thus there is no room for research to evaporate for low incidence.

### 5.4. The social cost of personalized medicine under PBDDs

We finish this section by showing that the social costs of personalized medicine are lower under PBDDs than under the traditional approval process. This result stems directly from Proposition 6. Since the breakeven price $P^{BE}_{PBDD}$ in Equation 23 is independent of the number of alterations $n$ identified by scientific research, we immediately have the following:

**Corollary 1** *For every value of $c_p, c_{R\&D}$ and $N$, and for every $P^*$, there is $\overline{n}$ such that $P^{BE} > P^{BE}_{PBDD}$ for $n > \overline{n}$.*

That is, the social planner break-even price under the traditional approval process is higher than the social planner break-even price under the process-based approval process once the number of alterations $n$ is large enough.

In the next section, we calibrate the model to provide insights about the magnitudes of all these theoretical findings.

## 6. Calibration to lung cancer research

The previous sections show that as researchers discover new alterations that affect an increasingly smaller fraction of the population, the approval probability drops and the financial incentives to undertake R&D investments evaporate. The question is for what fractions $q_i$ such profits vanish and what are the social costs of personalized medicine under the current approval framework. In this section we provide a calibration using parameters from lung cancer research to answer these questions. (Section G in the Appendix provides robustness checks of the calibration results below).

### 6.1. Parameters

Table 2 collects the parameters of the calibration. First, there are about 2.5 million new lung cancer cases per year in the world, including about 220,000 in the U.S.[14] However, about 50% of lung cancer patients are currently not tested at all (see e.g. Smeltzer et al., 2025) due to lack of awareness or technology in many hospitals. Thus, we set the number of new

[14]See e.g. https://www.cancer.org/cancer/types/lung-cancer/about/key-statistics.html.

Table 2: Parameters in Calibration

| Description | Parameter | value |
|---|---|---|
| New cases per year | $\overline{N}$ | 2,500,000 |
| Average Percent of Tested Patients | $adj$ | 0.5 |
| Actual new cases per year | $N$ | 1,250,000 |
| Eligibility for RCT | | 10% |
| Adjustment to $N$ for RoW | $x$ | 0.196 |
| Pharma's discount rate | $R$ | 10.5% |
| Length of clinical trial | $\tau$ | 4 years |
| Length of Phase I | $\rho$ | 6 years |
| Pharma bargaining power | $\gamma$ | 0.5 |
| Expected standardized improvement | $E[\kappa]$ | 0.35 |
| Probability $\kappa < 0$ | | 0.3 |
| Annual survival rate for T | $\overline{s}$ | 0.8 |
| Annual survival rate for other causes | $s_{other}$ | 0.95 |
| Corporate tax rate | $t_c$ | 21% |
| Orphan Drug tax credit | $tc_{OD}$ | 25% |
| Annual cost of RCT per patient | $c_{RCT}$ | $\$100,000$ |
| Success probability of Phase I | $p_0$ | 16.8% |

targetable cases per year at $N = 2.5$ million/2=1.25 million. The population that could be subject to clinical trials, however, is lower, due to eligibility criteria. We assume that only 10% of potential patients are eligible for clinical trials (see e.g. Unger et al., 2024).

The length of a randomized clinical trial is set at $\tau = 4$ years, while the pre-clinical, Phase I and Phase II are set to $\rho = 6$ years. As for the success rate of the new treatment, we choose parameters based on the Osimertinib against Gefitinib trial in EGFR. In this case, we have $\kappa = 0.344$. We assume that all entrant firms have an expected standardized improvement $E[\kappa] = 0.35$, but also a 30% probability that $\kappa < 0$—an optimistic number, since about 36% of clinical trials with biomarkers in oncology fail in Phase III (see Wong et al., 2019, Table 3). Under the uniform distribution assumption, $\kappa \sim U[a, b]$, $a = -.525$ and $b = 1.225$ yields the desired properties. We use Monte Carlo simulation together with small-sample statistics to ensure the proper calculation of rejections probability when sample sizes are small, since the normal distribution assumption discussed in Section 4 is only appropriate for large sample sizes. The appendix discusses the nature of the Monte Carlo simulations.

Similarly, Wong et al. (2019), Table 3, shows that the probability of reaching Phase III with biomarkers in oncology is just $p_0 = 0.168$; we adopt this number in our calibration. The discount factor $A_{III}(\pi)$ also depends on the survival probability $s$, which we set $s = \overline{s} \times s_{other}$ where $\overline{s} = 0.8$ is the survival probability due to the treatment (life expectancy of 5 years) and $s_{other} = 0.95$ is the survival rate for all other causes (life expectancy of 20 years for non-cancer

related causes). Finally, we set the R&D cost pre-Phase III to between $50 million and $1 billion, consistent with the costs calculated from Henderson et al. (2023, Supplemental Table S1) and reported in Table 1.

Turning to the discount rate $R$, based on DiMasi, Grabowski, and Hansen (2016), we set $R = 10.5\%$. We let the corporate tax rate be $t_c = 21\%$, and reduce the cost of running RCTs ($c_{RCT}$) by $tc_{OD} = 25\%$ tax credit as provided by the Orphan Drug Act in the US.[15]

We finally need a further adjustment. Drug prices outside the U.S. are lower than U.S. prices (see e.g. Goldstein et al. (2017)). Furthermore, targeted therapies are not as broadly available in many foreign countries as they are in the U.S., due to stricter regulatory requirements, and/or high costs. To jointly capture these price and market penetration differences, we leverage the fact that the U.S. accounts for about 45% of the total global spending in cancer drugs (see IQVIA, 2024, exhibit 53.) This implies that $45\% = \frac{P_i \times N^{US}}{P_i \times x \times N^W}$ where $N^{US}$ and $N^W$ are the U.S. and world population of lung cancer patients respectively, and $x$ is the adjustment factor capturing price and market penetration differences. Since the number of U.S. lung cancer patients $N^{US}$ is about 8.8% of all lung cancer patients worldwide ($N^{US} = 0.088 \cdot N^W$), we conclude that $x = .196$. We thus take into account the lower prices and lower penetration by defining an effective world population $N = 0.196 \times N^W$ when we calculate profits or break-even prices.[16]

## 6.2. Endogenous variables

For every alteration $i$, we must solve for the equilibrium quantities, namely the successful entry probability $\pi_i^*$, the cutoff R&D cost $\bar{c}_{R\&D,i}^*$, approval probabilities $p_i^*$, the optimal sample sizes $K_i^*$ and the prices $P_i$ (see Proposition 4). We exploit observed drug prices $\widehat{P}_i$, to obtain these endogenous quantities. To do so, we adopt a simplifying assumption. Recall that firms are heterogeneous in their cost of $R\&D$, $c_{R\&D,i}$. In Proposition 4, the price each firm secures through bargaining depends upon their realized R&D cost; hence, so does their chosen sample size $K_i^*$ and approval probability $p_i$. As we do not observe the R&D costs of the firms themselves, our simplifying assumption is that, instead, the observed price $\widehat{P}_i$ is determined by the average firm that seeks approval—that is, the firm with R&D costs $c_{R\&D,i} = E[c_{R\&D,i}] = 0.5(c_L + \bar{c}_{R\&D,i}^*)$. (This quantity is still endogenous, because it depends upon the cutoff cost $\bar{c}_{R\&D,i}^*$, which is itself endogenous.) Since, under this assumption, all

[15] We implicitly assume that the tax credit offsets the tax liability of firms from other business lines. The qualification as an Orphan Drug may also provide market exclusivity for seven years, but this benefit does not seem to accrue to targeted therapies due to the specifics of the molecular alterations.

[16] We could equivalently define an effective world price, but below we use the observed U.S. prices to estimate certain quantities, and such adjustments make the calculations non-transparent. An effective world population is easier to work with.

firms face the same price $\widehat{P}_i$, their optimal choice $K_i^*$ and approval probabilities $p_i$ are the same. (However, their *entry decisions* are still different, as they are determined by their cost of R&D.)

Summing up, the probability of successful entry in Eq. (18) becomes

$$\pi_i^* = p_{I,i}\ p_i(E[c_{R\&D,i}])\ \mu_i^* \tag{26}$$

where

$$\mu_i^* = \frac{\bar{c}_{R\&D,i}^* - c_L}{c_H - c_L} \tag{27}$$

is the equilibrium entry probability, that is, the probability that the firm has R&D costs below $\bar{c}_{R\&D,i}^*$ and thus seeks approval for its drug. (We call $\mu_i^*$ simply the *entry probability*, to distinguish it from the *successful entry* probability $\pi_i^*$—the probability that a firm seeks *and obtains* approval, and is thus able to sell its drug to patients.) The strategy to identify the fixed point is then as follows: We start with postulating a level of $\mu_i^*$ and use Eq. (26) to calculate the probability of successful entry $\pi_i^*$. Given $\pi_i^*$ and the implied discount $A_{III}(\pi_i^*)$, we then use the observed drug price $\widehat{P}_i$ as input in the maximization of $PV_{III,i}$ in equation (7), which then pins down $K_i^*$ and $\bar{c}_{R\&D,i}^*$ from equation (17). The latter quantity defines which firms seek approval, and hence the entry probability $\mu_i^*$ using Eq. (27). We iterate this procedure to determine the fixed point $\mu_i^*$. In the process, we also calculate the breakeven price $P_i^{BE}$ in equation (14), again for the "average firm" with R&D cost $c_{R\&D}$ given by its expected value: $E[c_{R\&D}] = 0.5(c_L + \bar{c}_{R\&D,i}^*)$. In the equation for $P_i^{BE}$, we set the marginal cost to $c_i = pc\, P_i$ with $pc = 10\%$: that is, marginal costs are 10% of the drug price (see Leighl et al. (2021)).

Finally, we use this break-even price together with the observed price $\widehat{P}_i$ to estimate the insurance company's maximum price $\bar{P}_i$ by inverting Eq. (15):

$$\overline{P}_i = \frac{1}{\gamma}\widehat{P}_i - \frac{1-\gamma}{\gamma}P_i^{BE} \tag{28}$$

We then estimate $C/q$ using the break-even relation (12):[17]

$$\frac{C}{q} = E\left[\overline{P}_i\right] = \sum_{i=1}^{n} q_i \overline{P}_i.$$

## 6.3. Calibration results under traditional approval process

The top-left panel of Figure 9 plots the present value of investing in the development of a treatment for a specific alteration, with R&D cost equal to the expectation $E[c_{R\&D}] =$

[17] The incidence parameters $q_i$ are from Figure 1, but they only sum up to 91%, including the 53.5% of non-targetable patients. We assume the latter are treated with immunotherapy, whose price is \$202,592/year. In addition, we conservatively assume that the remaining 9% incidence is made up by ten extremely rare diseases not captured in the figure and use extrapolated prices $\widehat{P}_i$ for those.

$0.5(c_L + \bar{c}_{R\&D})$. The horizontal axis reports the percentage of lung cancer patients with the given alteration, and the figure demonstrates that the present value converges to zero as the percentage of lung cancer patients affected by the alteration decreases. This result takes into account both the lower probability that potential competitors may arrive due to lower incidence, as well as the higher expected drug prices for the same as shown in Figure 6. As such, this result is consistent with the expected revenues dropping to zero as incidence declines, as shown in Figure 7. The calibration also reveals that the present value hits zero at 0.06% of incidence. That is, in our model, alterations that affect less than 0.06% of lung cancer populations are not financially viable. This also implies that alterations with incidence above 0.06% are financially viable, which explains the surge in research and commercialization of cancer drugs even for rare alterations, such as NTRK, which only affects about .1% of the population (see Figure 3).

The non-linearity that is evident in the top-left panel is due to the general equilibrium effect that rarer alterations imply a lower entry probability $\mu$ that a firm has low enough cost to seek approval for its treatment. The entry probability $\mu$ is shown in the top-right panel. This lower entry probability implies a lower probability $\pi$ that a new entrant will steal the market, as shown in the bottom-right panel. A lower probability of entry in turn yields an increase in the discount factors $A_{III}(\pi)$. The increase in discount factor increases the present value of future profits, everything else equal. Notwithstanding all these equilibrium counter effects, the present value of future profits declines to zero as the alteration becomes rarer, due to the lower number of patients available to sell the drug to, but also due to the lower probability of acceptance of the new drug, as shown in the bottom-left panel of the figure.

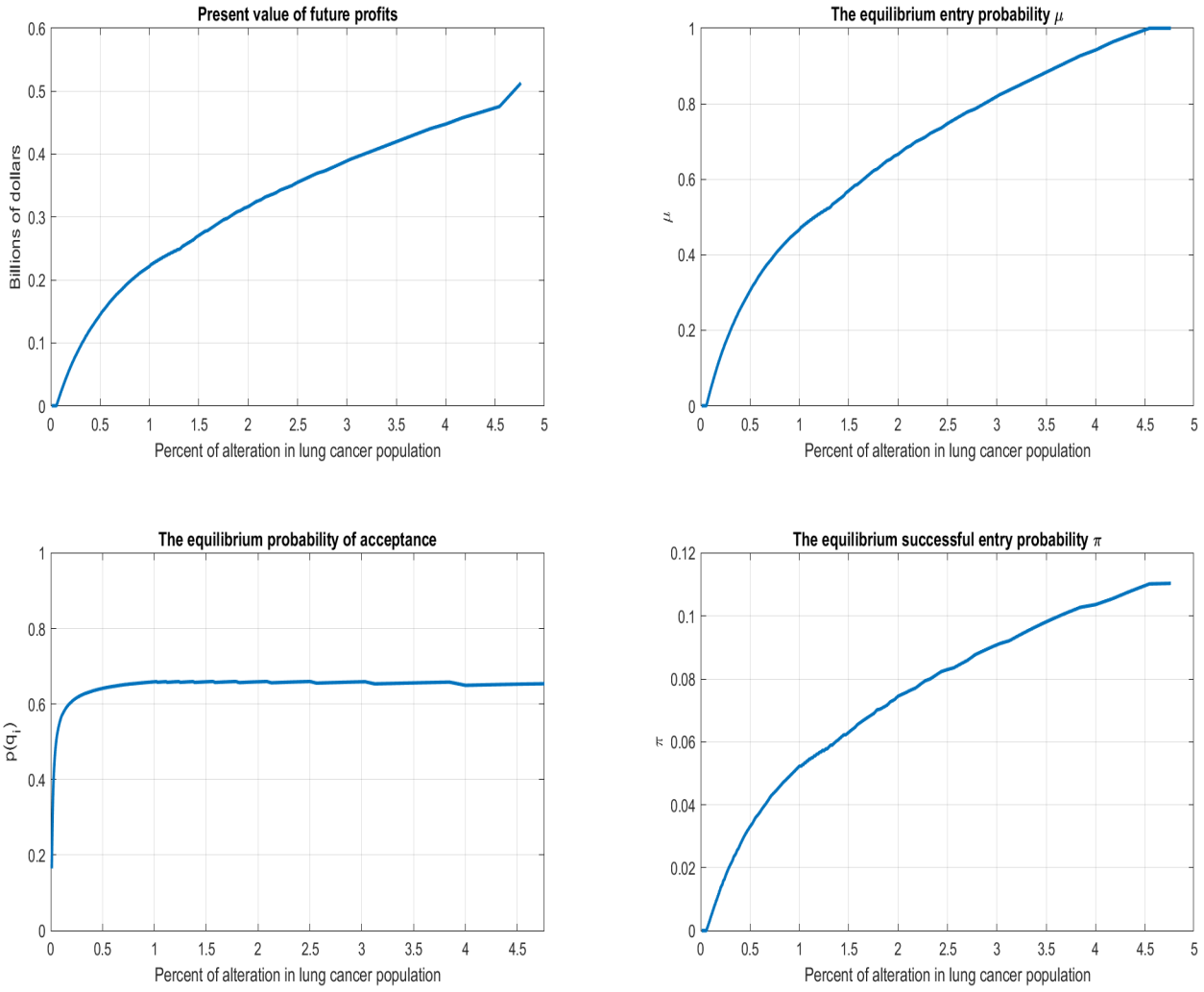
Cross-sectionally, these results also imply that we should observe more research intensity for alterations that affect a higher percent of the population. A higher $\mu$ for more common alterations implies that there are more firms doing experimentation for alterations that are more common. This is consistent with the data shown in Figure 4.

Finally, the bottom-left panel shows that the optimal sample size declines substantially as incidence declines. This is intuitive as the number of patients with a rare genetic alteration becomes so low that it makes it difficult to find patients to run the clinical trial. This is consistent with the results in Figure 5.

The calibrated model also provides evidence that insurance companies cross-subsidize across alterations. Figure 6 shows that the inferred max prices $\overline{P}_i$ increase as incidence $q_i$ declines. In the model, this implies that the insurance company is willing to subsidize the drugs for very rare alterations, such as NTRK, using the additional revenues it gets from overcharging for EGFR.

From the max prices $\overline{P}_i$ we obtain $C/q = 447,110.4$. Given the incidence of 2.5 million

Figure 9: **Equilibrium Present value of Future Profits**




new lung cancer cases per year over 8.3 billion world population, i.e. $q = 2.5/8300 = 0.03\%$, we obtain an insurance premium $C = \$134.67$, which does not appear unreasonable. Indeed, according to Yousefi et al. (2023) the cost of lung cancer ranges between 0.03% and 0.83% of total US health expenditures. The US spends about \$15,474 per person,[18] which therefore translates into a cost of lung cancer per person between \$4.6 and \$128.4, a range that is close to the premium $C$ derived above.

We finally calculate the social costs as in Section 4.11, assuming that the social planner aims to break even and cover the entire world population. Panels A and B of Table 3 show

[18]See CMS report at https://www.cms.gov/data-research/statistics-trends-and-reports/national-health-expenditure-data/nhe-fact-sheet.

Table 3: **Break-even Prices and Global Societal Costs of Targeted Therapies**

| Panel A: Breakeven Annual Cost per Patient | | | | |
|---|---|---|---|---|
| Number $n$ | Percent in | Cost of pre-Phase III R&D | | |
| of alterations | Population | 50 million | 100 million | 500 million |
| 10 | 10 | 31,330 | 35,580 | 69,560 |
| 20 | 5 | 39,000 | 45,950 | 101,560 |
| 50 | 2 | 53,230 | 67,490 | 181,570 |
| 100 | 1 | 71,490 | 96,690 | 298,270 |
| 200 | 0.5 | 97,920 | 143,440 | 507,590 |
| 500 | 0.2 | 158,620 | 261,330 | 1,083,070 |
| 1000 | 0.1 | 256,220 | 456,650 | 2,060,100 |
| 2000 | 0.05 | 493,010 | 929,820 | 4,424,360 |
| 5000 | 0.02 | 1,696,020 | 3,333,420 | 16,432,620 |
| 10000 | 0.01 | 6,619,730 | 13,173,540 | 65,604,070 |
| Panel B: Breakeven Societal Cost (million of USD) | | | | |
| Number $n$ | Percent in | Cost of pre-Phase III R&D | | |
| of alterations | Population | 50 million | 100 million | 500 million |
| 10 | 10 | 38,292 | 43,487 | 85,018 |
| 20 | 5 | 47,667 | 56,161 | 124,129 |
| 50 | 2 | 65,059 | 82,488 | 221,919 |
| 100 | 1 | 87,377 | 118,177 | 364,552 |
| 200 | 0.5 | 119,680 | 175,316 | 620,388 |
| 500 | 0.2 | 193,869 | 319,403 | 1,323,752 |
| 1000 | 0.1 | 313,158 | 558,128 | 2,517,900 |
| 2000 | 0.05 | 602,568 | 1,136,447 | 5,407,551 |
| 5000 | 0.02 | 2,072,913 | 4,074,180 | 20,084,313 |
| 10000 | 0.01 | 8,090,781 | 16,100,993 | 80,182,752 |

the break-even price per year per patient, and the societal costs, respectively. For these calculations, we set the corporate tax $t_c$ and the Orphan Drug tax credit to zero to estimate societal costs (see discussion after Proposition 6). We consider three different levels of $R\&D$ costs, spanning from \$50 million to \$500 million. The latter figure is in line with the current ex-post costs of R&D as per Table 1.

More specifically, Panel A of Table 3 shows that as the number of discovered alterations increases, with each affecting a smaller number of patients, the break-even prices increase substantially. For instance, for $n = 1000$, which implies that each alteration affects 0.1% of the lung cancer population, the minimum break-even price for R&D costs per drug of just $c_{R\&D} = \$50$ million is $P^{BE} = \$256,220$ per year, per patient. Assuming more realistic R&D costs of \$500 million per drug, the break-even price rises to $P^{BE} = \$2.1$ million per year, per patient. When $n = 2,000$, for an incidence of 0.05% in the lung cancer population, the break-even prices equal $P^{BE} = \$493,010$ and \$4.4 million per year, per patient, for $c_{R\&D} = \$50$ and $= \$500$ million, respectively.

At these break-even prices, societal costs are enormous. We collect them in Panel B. Consider the case with a number of alterations $n = 2,000$, which entails each alteration has

an incidence of 0.05%. Recall that this is realistic, in view of the data in Figure 1. In this case, societal costs would be $602 billion per year when $c_{R\&D} = \$50$ million, and $5.4 trillion per year when $c_{R\&D} = \$500$ million. And this only for lung cancer.

We can also assess the magnitude of societal costs by comparing our annual break-even costs of developing targeted therapies to the estimates of the Value of Statistical Life Year (VSLY) from the U.S. Department of Health and Human Services (HHS).[19] The Value of Statistical Life estimates the amount individuals are willing to pay to marginally increase life expectancy. VSLY is its annualization which takes individuals' life expectancy into account. HHS benchmark estimates of VSLY range between $231,000 and $754,000. A glance at Panel A of Table 3 reveals that annual break-even costs of developing targeted therapies are higher than these values once the number of alterations $n$ is over 2000, i.e. for an incidence of 0.05%.

## 6.4. Calibration results under process-based drug discovery

We now take the calibration parameters used in the previous section and apply them to the process-based drug discovery regime. The model in Section 5 involves several uncertain quantities, however, such as the probability of successfully identifying the personalized therapy, $Q_T$, and the surviving probability with the personalized therapy, $s_T^{new}$. The reason is that no firm has implemented the PBDD in its entirety yet for the case of targeted therapies. To address this issue, we calculate values for a range of parameter values for some of these key quantities. First, we allow $Q_T$ to range between .1 and .9. Second, we keep the quantities related to the phase–III RCT as in previous section: namely, $\tau = 4$ years, $c_{RCT} = \$100,000$ per patient, and the probability of approval is calculated assuming $\kappa$ has $E[\kappa] = 0.35$ and $pr(\kappa < 0) = 0.3$, as before. Although speculative, these values provide some baseline for the prices $P^{PBDD}$ we are looking for, and allow a comparison with prices under the traditional regulatory regime. We again assume it takes $\rho = 6$ years to acquire the know-how, hardware, software, data, and do the Phase I/II in our Phase I. Finally, we assume $c_{tech} \sim U[c_{tech}^L, c_{tech}^H]$ where $c_{tech}^L = \$500$ million and $c_{tech}^H = \$1.5$ billion, as in previous section, and the cost for each patient to go through the steps necessary to identify their genomic profile is $c_{PBDD} = \$1000$. To understand the latter numbers, for reference, the cost of the Aurora supercomputer at the Argonne National Laboratory was $500 million to build. The marginal cost $c^{new}$ is set conservatively equal to the one used for the rarest alteration in Section 6, namely $c^{new} = 10\% P^{NTRK}$, where the latter is the price for Larotrectinib for NTRK alteration.

[19] See e.g. https://aspe.hhs.gov/sites/default/files/documents/cd2a1348ea0777b1aa918089e4965b8c/standard-ria-values.pdf

Table 4: **Forecasted PBDD Prices and Present Value of Future Profits**

| Panel A: Drug Prices and Net Present Values | | | | | | |
|---|---|---|---|---|---|---|
| | PBDD Prices | | | PV of Future Profits (Billions of USD) | | |
| $Q_T$ | $s_{PBDD}$ =.7 | $s_{PBDD}$ =.8 | $s_{PBDD}$ =.9 | $s_{PBDD}$ =.7 | $s_{PBDD}$ =.8 | $s_{PBDD}$ =.9 |
| 0.1 | 398,644.8 | 395,885.6 | 392,412.5 | 0.1218 | 0.1359 | 0.1559 |
| 0.2 | 387,362.3 | 385,000.2 | 382,301.8 | 0.1924 | 0.2124 | 0.2388 |
| 0.3 | 381,739.3 | 364,919.0 | 343,808.5 | 0.2453 | 0.3564 | 0.5477 |
| 0.4 | 351,098.1 | 335,994.2 | 320,161.3 | 0.4730 | 0.6425 | 0.8975 |
| 0.5 | 330,722.4 | 318,639.3 | 305,973.0 | 0.7168 | 0.9285 | 1.2473 |
| 0.6 | 317,138.6 | 307,069.3 | 296,514.1 | 0.9605 | 1.2146 | 1.5970 |
| 0.7 | 307,435.9 | 298,805.1 | 289,757.7 | 1.2042 | 1.5007 | 1.9468 |
| 0.8 | 300,158.9 | 292,606.9 | 284,690.5 | 1.4480 | 1.7867 | 2.2966 |
| 0.9 | 294,499.0 | 287,786.1 | 280,749.3 | 1.6917 | 2.0728 | 2.6463 |
| Panel B: Entry probabilities | | | | | | |
| | Entry probability $\mu$ | | | Successful entry probability $\pi$ | | |
| $Q_T$ | $s_{PBDD}$ =.7 | $s_{PBDD}$ =.8 | $s_{PBDD}$ =.9 | $s_{PBDD}$ =.7 | $s_{PBDD}$ =.8 | $s_{PBDD}$ =.9 |
| 0.1 | 0.4873 | 0.5435 | 0.6237 | 0.1603 | 0.1489 | 0.1226 |
| 0.2 | 0.7696 | 0.8495 | 0.9551 | 0.1631 | 0.1404 | 0.1282 |
| 0.3 | 0.9810 | 1.0000 | 1.0000 | 0.1637 | 0.1500 | 0.1336 |
| 0.4 | 1.0000 | 1.0000 | 1.0000 | 0.1662 | 0.1500 | 0.1336 |
| 0.5 | 1.0000 | 1.0000 | 1.0000 | 0.1662 | 0.1500 | 0.1336 |
| 0.6 | 1.0000 | 1.0000 | 1.0000 | 0.1662 | 0.1500 | 0.1336 |
| 0.7 | 1.0000 | 1.0000 | 1.0000 | 0.1662 | 0.1500 | 0.1336 |
| 0.8 | 1.0000 | 1.0000 | 1.0000 | 0.1662 | 0.1500 | 0.1336 |
| 0.9 | 1.0000 | 1.0000 | 1.0000 | 0.1662 | 0.1500 | 0.1336 |

Panel A of Table 4 reports the prices $P^{PBDD}$ and the present value of future profits $PV_I^{PBDD}$ under three assumptions about the survival rate $s_{PBDD}$. First, we see that the PBDD prices range between \$271,947 and \$350,189 per year for $s_{PBDD} = 0.7$. Interestingly, this range of prices is higher than the average price across the alterations in Figure 6, which is given by $\frac{\sum_{i=1}^n q_i P_i}{\sum_{i=1}^n q_i} = \$280,980$, where we are dividing by $\sum_{i=1}^n q_i$ as we are only considering the targetable alterations in the figure (about 50% of all lung cancer). This result is seemingly in contrast with Proposition 7, which shows that, for large $n$, the price from the process-based drug discovery approach is lower than the average price from targeted therapies $P^{PBDD} < \sum_{i=1}^n q_i P_i$. The reason is indeed the "large $n$". For instance, in the calculation we considered EGFR as just one alteration affecting 14.5% of the population and with a relatively low price of \$228,000 per year. Now that science has identified subtypes of EGFR that affect tiny fractions of the population (see Figure 1), if for each we need to run a clinical trial, we would expect much higher drug prices. For instance, the price to treat EGFR Exon 20 – which affect only 1.3% of the lung cancer population – is already in the \$400,000 range per year, which is indeed higher than the range of PBDD prices in Table 4.

Importantly, for given survival probability $s_{PBDD}$, the equilibrium price is lower the higher the probability $Q_T$ of finding a new treatment. The reason is that a higher probability

Table 5: **Break-even Prices and Societal Costs of PBDDs**

| | Panel A: Breakeven Annual Cost per Patient | | | |
|---|---|---|---|---|
| $Q_T$ | Cost of pre-Phase III R&D | | | |
| | \$50 million | \$100 million | \$500 million | \$ 1 billion |
| 0.1 | 68,607.1 | 83,498.4 | 202,629.3 | 351,542.8 |
| 0.2 | 64,006.9 | 75,557.9 | 167,965.8 | 283,475.6 |
| 0.3 | 61,240.0 | 70,348.6 | 143,217.3 | 234,303.2 |
| 0.4 | 58,762.2 | 65,593.7 | 120,245.2 | 188,559.6 |
| 0.5 | 57,275.6 | 62,740.7 | 106,461.9 | 161,113.4 |
| 0.6 | 56,284.5 | 60,838.7 | 97,273.1 | 142,816.0 |
| 0.7 | 55,576.5 | 59,480.2 | 90,709.6 | 129,746.4 |
| 0.8 | 55,045.6 | 58,461.3 | 85,787.0 | 119,944.2 |
| 0.9 | 54,632.6 | 57,668.8 | 81,958.4 | 112,320.3 |
| | Panel B: Societal Costs (million of USD) | | | |
| $Q_T$ | Cost of pre-Phase III R&D | | | |
| 0.1 | 83,853 | 102,054 | 247,658 | 429,663 |
| 0.2 | 78,231 | 92,349 | 205,292 | 346,470 |
| 0.3 | 74,849 | 85,982 | 175,043 | 286,371 |
| 0.4 | 71,820 | 80,170 | 146,966 | 230,462 |
| 0.5 | 70,004 | 76,683 | 130,120 | 196,916 |
| 0.6 | 68,792 | 74,358 | 118,889 | 174,553 |
| 0.7 | 67,927 | 72,698 | 110,867 | 158,579 |
| 0.8 | 67,278 | 71,453 | 104,851 | 146,598 |
| 0.9 | 66,773 | 70,484 | 100,171 | 137,280 |

implies a lower break-even price for the firm, and thus less effective "bargaining power." Still, even with lower prices, the present value of future profits increases as $Q_T$ increases: In fact, for each $s_{PBDD}$, it increases tenfold from $Q_T = .1$ to $Q_T = .9$. For instance, for $s_{PBDD} = 0.8$, the present value of future profits increases from \$0.12 billion for $Q_T = 0.1$ to \$1.7 billion for $Q_T = 0.9$. This is in line with Proposition 8.

Similarly, as we move across survival rates $s_{PBDD}$ we see that PBDD prices are rather similar, but the present value of future profits increase substantially. For instance, for $Q_T = 0.5$, $PV_I^{PBDD}$ increases from \$0.7 billion to \$1.2 billion, a 45% increase.

These results show that it is in the interest of the new firms that compete on PBDD to find increasingly better systems that provide new personalized therapies and higher survival rates. Indeed, we see in Panel B, the equilibrium fraction of firms that decide to enter $\mu$ equals one for $Q_T \geq 0.4$. This is in stark contrast with the traditional approval regime, under which firms have the opposite incentive to lower the investments in rare alterations, including declining to enter the market altogether. Interestingly, the successful entry probability $\pi$ declines as the survival rate $s_{PBDD}$ increases.

We finally calculate the social costs of the process-based drug discovery in Table 5. As in Section 6.3, we consider a social planner who performs the PBDD (that is, fully subsidizes it) and we look at the break-even prices (Panel A), as well as the total societal costs (Panel

B). We consider four levels of pre-clinical R&D costs, now ranging from $50 million to $1 billion (as opposed to only $500 million). The reason is that the new technologies may require additional costs in terms of know-how, computing power, and so on, compared to the traditional methods. We do this exercise assuming the survival probability from the PBDD is $s_{PBDD} = 0.8$. Consider the column $500 million. The breakeven prices range between $200,692 for $Q_T = .1$ and $81,950 for $Q_T = 0.9$, which are far lower than the case for targeted therapies as $n$ was diverging to a large number. Moreover, they are far lower than the current prices for targeted therapies. Even for the case in which the R&D costs are $1 billion, breakeven prices drop quickly to below $200,000 for a $Q_T = 0.4$. All these values are below the estimates of the value of a statistical life year (VSLY), which range between $231,000 and $754,000.

Panel B reports the implied societal costs, which still run in the $100s of billions, but far below the trillion dollar numbers discussed in the previous section.

Note the difference in prices between the break-even social planner costs in Table 5 and the private market prices in Table 4. The reason for the large difference is the following: Recall that the price in the private market is set by bargaining between the insurance company and the firm. The insurance company is not willing to pay less than $C/q = \$447,110$ per treatment in PBDD, while the firm does not pay less than the break-even price. We take as a representative firm the one with average $c_{tech}$, which is endogenously determined, but turns out to equal $1 billion, i.e. similar to the last column in Panel A of Table 5 (there is a small difference as the firm also pays taxes and receives the orphan drug credit). The price $P_i$ in Table 4 is the 50-50 average between $C/q$ and the break-even price, which yields rather high values for the prices $P_i$.

# 7. Conclusions

Regulatory agencies' potential approval of the process to develop new drugs, as opposed to individual therapies, yields strong incentives for pharmaceutical firms to innovate, thanks to higher revenues for more effective processes, and yields lower drug prices than in the traditional regime of approving individual targeted therapies for rare genetic alterations.

We focused on the targeted therapies in lung cancer, an area in which scientific progress has identified a large number of genetic alterations, some of which have a tiny incidence in the population. We exploited the data from targeted therapies, such as drug prices, incidence, development costs and so on, to study the incentives of firms to further innovate under the traditional regime of approving individual therapies, and found that for genetic alterations affecting fewer than .06% of lung cancer patients, there are no economic benefits

to innovate. We extrapolated our calibration results to process-based drug development and found that drug prices under the new regime would still be relatively high – higher, indeed, than current average drug prices – due to high R&D costs. The benefit, however, is that we do not expect those prices to increase further as science identifies additional alterations for even rarer subpopulations.

Our theoretical results apply well beyond lung cancer treatments, however. Indeed, considerable progress in targeted therapies has been made for other types of cancer as well, including breast, colon, ovarian cancers, as well as hematological malignancies. Similar progress in personalized medicine has also been made in the last decade in other areas of medicine, including hematology, cardiology, neurology, and more. Recent research has pushed personalized medicine into the fight against antibiotic resistance, for instance.

The general point, however, is that personalized medicine is akin to turning all diseases into rare diseases, which discourages discovery under the traditional approval process. Yet, new technologies based on machine learning and artificial intelligence now allow for personalized drugs to be developed in silico. We show that regulatory agencies' approval of the *process* for drug discovery, as opposed to individual therapies, can avoid the difficulties and the large costs of undergoing the different phases of the traditional drug discovery process (Phase I, II, and III), thereby providing the proper incentives for researchers and firms to develop new personalized treatments.

# References


[1] Josh Abramson et al. "Accurate structure prediction of biomolecular interactions with AlphaFold 3". In: *Nature* (2024), pp. 1–3.

[2] Daron Acemoglu and Joshua Linn. "Market size in innovation: Theory and evidence from the pharmaceutical industry". In: *Quarterly Journal of Economics* 119.3 (2004), pp. 1049–1090.

[3] Eric Budish, Benjamin N Roin, and Heidi Williams. "Do firms underinvest in long-term research? Evidence from cancer clinical trials". In: *American Economic Review* 105.7 (2015), pp. 2044–2085.

[4] D Ross Camidge et al. "Brigatinib versus crizotinib in ALK inhibitor–naive advanced ALK-positive NSCLC: final results of phase 3 ALTA-1L trial". In: *Journal of Thoracic Oncology* 16.12 (2021), pp. 2091–2108.

[5] Daniel Carpenter and Michael M Ting. "Regulatory errors with endogenous agendas". In: *American Journal of Political Science* 51.4 (2007), pp. 835–852.

[6] Joseph A DiMasi, Henry G Grabowski, and Ronald W Hansen. "Innovation in the pharmaceutical industry: new estimates of R&D costs". In: *Journal of health economics* 47 (2016), pp. 20–33.

[7] Rachel Fieldhouse and Mohana Basu. "Moderna cancer vaccine stops melanoma returning: what's next for personalized treatments?" In: *Nature* (Aug. 2026). doi:https://doi.org/10.103
026-02612-3.

[8] Alexander P Frankel, Joshua L Krieger, Danielle Li, and Dimitris Papanikolaou. *Evaluation and Learning in R&D Investment*. Tech. rep. University of Chicago, 2024.

[9] Marina Chiara Garassino et al. *Reimagining a drug discovery and drug development process with Artificial Intelligence (AI): Overcoming Economic Barriers in Personalized Medicine*. Tech. rep. University of Chicago, 2026.

[10] Daniel A Goldstein et al. "A global comparison of the cost of patented cancer drugs in relation to global differences in wealth". In: *Oncotarget* 8.42 (2017), p. 71548.

[11] Yingni Guo. "Dynamic delegation of experimentation". In: *American Economic Review* 106.8 (2016), pp. 1969–2008.

[12] Raymond H Henderson et al. "Delivering the precision oncology paradigm: reduced R&D costs and greater return on investment through a companion diagnostic informed precision oncology medicines approach". In: *Journal of Pharmaceutical Policy and Practice* 16.1 (2023), p. 84.

[13] Lizza EL Hendriks et al. "Non-small-cell lung cancer". In: *Nature Reviews Disease Primers* 10.1 (2024), p. 71.

[14] Emeric Henry, Marco Loseto, and Marco Ottaviani. "Regulation with experimentation: Ex ante approval, ex post withdrawal, and liability". In: *Management Science* 68.7 (2022), pp. 5330–5347.

[15] Emeric Henry and Marco Ottaviani. "Research and the approval process: The organization of persuasion". In: *American Economic Review* 109.3 (2019), pp. 911–955.

[16] Takakazu Honryo. "Dynamic persuasion". In: *Journal of Economic Theory* 178 (2018), pp. 36–58.

[17] International Human Genome Sequencing Consortium. "Initial sequencing and analysis of the human genome". In: *nature* 409.6822 (2001), pp. 860–921.

[18] IQVIA. *Global Oncology Trends 2024: Outlook to 2028*. Tech. rep. IQVIA Institute, 2024. URL: https://www.iqvia.com/insights/the-iqvia-institute/reports-and-publications/reports/global-oncology-trends-2024.

[19] Emir Kamenica and Matthew Gentzkow. "Bayesian persuasion". In: *American Economic Review* 101.6 (2011), pp. 2590–2615.

[20] Christoph Kornauth et al. "Functional precision medicine provides clinical benefit in advanced aggressive hematologic cancers and identifies exceptional responders". In: *Cancer discovery* 12.2 (2022), pp. 372–387.

[21] Natasha B Leighl et al. "An arm and a leg: the rising cost of cancer drugs and impact on access." In: *American Society of Clinical Oncology Educational book. American Society of Clinical Oncology. Annual Meeting*. Vol. 41. 2021, pp. 1–12.

[22] Andrew W Lo and Shomesh E Chaudhuri. *Healthcare Finance: Modern Financial Analysis for Accelerating Biomedical Innovation*. Princeton University Press, 2022.

[23] Andrew McClellan. "Experimentation and approval mechanisms". In: *Econometrica* 90.5 (2022), pp. 2215–2247.

[24] Myriam Mirza et al. "Assessing the Cost-Effectiveness of Next-Generation Sequencing as a Biomarker Testing Approach in Oncology and Policy Implications: A Literature Review". In: *Value in Health* (2024).

[25] Tony Mok et al. "Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung cancer in the ALEX study". In: *Annals of oncology* 31.8 (2020), pp. 1056–1064.

[26] Chiara Pizzamiglio et al. "Designing clinical trials for rare diseases: unique challenges and opportunities". In: *Nature Reviews Methods Primers* (2022), pp. 1–2.

[27] Feng Ren et al. "AlphaFold accelerates artificial intelligence powered drug discovery: efficient discovery of a novel CDK20 small molecule inhibitor". In: *Chemical science* 14.6 (2023), pp. 1443–1452.

[28] Jacqulyne P Robichaux et al. "Structure-based classification predicts drug response in EGFR-mutant NSCLC". In: *Nature* 597.7878 (2021), pp. 732–737.

[29] Robert Roskoski Jr. "Properties of FDA-approved small molecule protein kinase inhibitors: A 2024 update". In: *Pharmacological research* (2024), p. 107059.

[30] Matthew P. Smeltzer, Jennifer C. King, Casey Connolly, et al. "The 2024 International Association for the Study of Lung Cancer Global Survey on Biomarker Testing". In: *The Journal of Thoracic Oncology* 20.12 (2025), pp. 1801–1813.

[31] Benjamin J Solomon et al. "Lorlatinib Versus Crizotinib in Patients With Advanced ALK-Positive Non–Small Cell Lung Cancer: 5-Year Outcomes From the Phase III CROWN Study". In: *Journal of Clinical Oncology* (2024), JCO–24.

[32] J Michael Steele. "Le Cam's inequality and Poisson approximations". In: *The American Mathematical Monthly* 101.1 (1994), pp. 48–54.

[33] Tarek Taha et al. "Treatment of rare mutations in patients with lung cancer". In: *Biomedicines* 9.5 (2021), p. 534.

[34] JM Unger et al. "National Estimates of the Participation of Patients With Cancer in clinical Research Studies Based on Commission on Cancer Accreditation Data." In: *J Clin Oncol.* 42.18 (2024), pp. 2139–2148.

[35] Chi Heem Wong, Kien Wei Siah, and Andrew W Lo. "Estimation of clinical trial success rates and related parameters". In: *Biostatistics* 20.2 (2019), pp. 273–286.

[36] Mahmood Yousefi et al. "Cost of lung cancer: A systematic review". In: *Value in Health Regional Issues* (2023), pp. 17–26.

[37] Kang Zhang et al. "Artificial intelligence in drug development". In: *Nature Medicine* (2025), pp. 1–15.

**Supplemental Appendix to Accompany the Paper**

# On the Economic Infeasibility of Personalized Medicine, and a Solution

Marina Chiara Garassino
University of Chicago Comprehensive Cancer Center

Kunle Odunsi
University of Chicago Comprehensive Cancer Center

Marciano Siniscalchi
Northwestern University

Pietro Veronesi
University of Chicago, NBER, and CEPR

## A. Appendix: The R&D Costs of Personalized Medicine

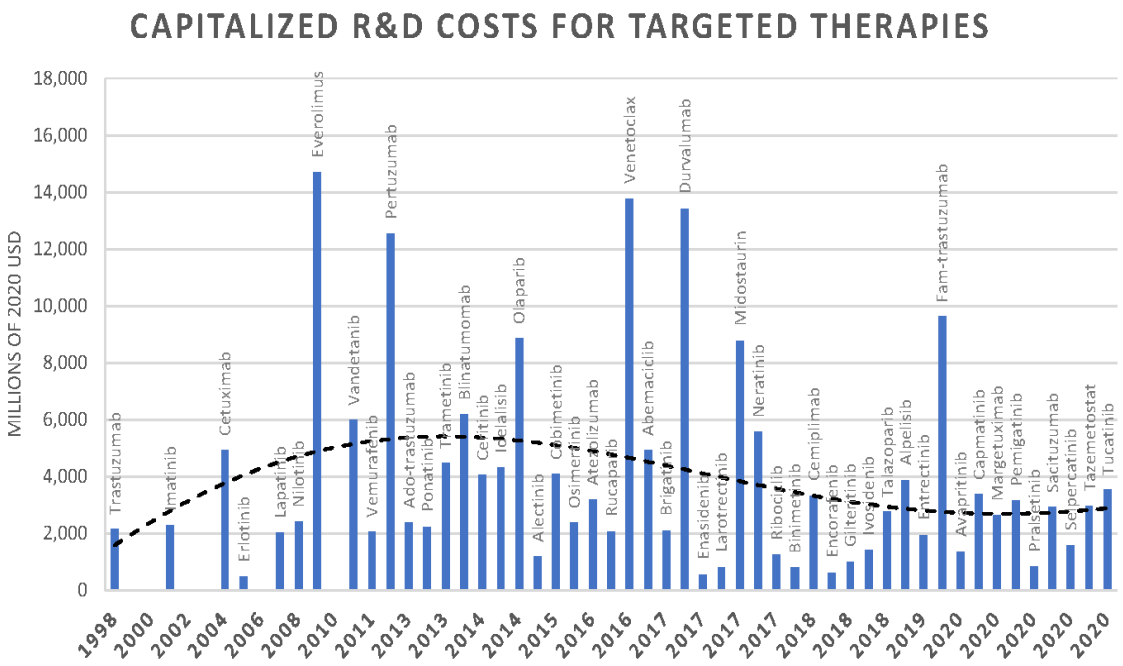
The revolution that took place in 2004 with the discovery of EGFR and targetable genetic mutations might lead one to conjecture that R&D costs may be declining due to researchers' learning about the alterations' biology, the workings of TKIs, and technological advances. We show here that it is unlikely to be the case. Figure 10 shows the capitalized average R&D cost per drug estimated by Henderson et al. (2023) for cancer drugs in precision medicine, plotted over time. We also show a time-trend line. We expand the calendar time on the horizontal axis to account for the volume of cancer drugs launched in the same year. As is apparent, the costs of discovery has not decreased over the years, as it has been running at around $2 billion per drug over the last several years.[20]

## B. Appendix: Ultra-rare subtypes of alterations

In this section, we document existing ultra-rare subtypes of alterations that have incidence lower than 0.1% of the lung cancer population. The on-line search, helped by the use Chat-GPT to identify studies, produced Figure 11 , whose frequencies have then been validated by a research assistant.

[20] In a nutshell, the capitalized average R&D cost per drug are calculated using out-of-pocket R&D expenses for each drug, dividing it by the probability of final approval to account for failures, and then taking a future value up to launch date. All values are then inflated to 2020 dollars.

Figure 10: **Capitalized Average R&D Costs per Drug**



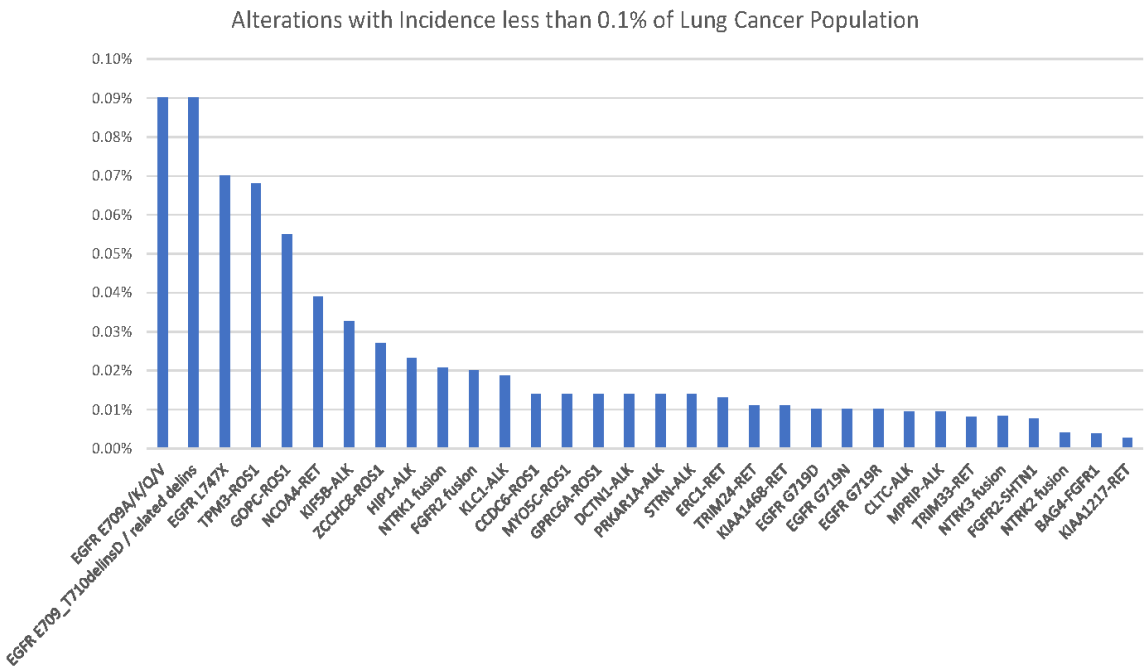

Notes: Capitalized average R&D costs are from Henderson et al. (2023) (supplemental tables), also plotted in their Figure 2, Panel A. The horizontal axis reports calendar time, but expanded on occasion to account for the volume of drugs launched in a given year.

# C. Appendix: An Equivalent Model with Financing and Bargaining at Commercialization

In the main body of the paper, we consider a simple setting of a fully financed firm that needs to decide ahead of time whether to enter the market or not, and whose decision depends on the outcome of bargaining with the health insurance company. For simplicity, we assumed that bargaining occurred at the time of the entry decision, so that the firm knows the price it will be able to charge if the drug is finally approved. In this appendix we show an equivalent model with debt financing that yields the same results. Indeed, debt financing in the form of convertible bonds is widespread in the biotech world, and so this assumption does not appear questionable. The model, however, becomes significantly more complicated. The main assumption throughout the model is that in case of default – due to scientific failure and inability to secure a sufficiently high drug price after approval – the value of the firm drops to zero. This high bankruptcy cost is the main departure from Modigliani-Miller framework and yields the equivalent result as in the main text.

We use Arabic numbers for phases here to differentiate variables from the main text. The timing is as follows:

Figure 11: **Ultra-rare Subtypes of Alterations**




Notes: This figure shows the incidence in the lung cancer population of ultrarare subtypes of known genetic alterations that we obtained through an on-line search of studies, helped by ChatGPT. The search has been done in August 2026. Data were validated by a human research assistant.

Phase 1 Biotech entrepreneurs (equity holders) issue debt $D_1$ with face value $F_1$ and maturity $\rho$ to raise funds to pay $c_{R\&D}$, the cost of initial research and development.

Phase 3 If Phase 1 is successful, equity holders rollover the time-1 debt and issue new debt $D_3$, with an aggregate face value $F_3$ and maturity $\tau$, to raise additional funds to pay for the Phase 3 clinical trial; recall that total RCT costs when recruiting $K$ subjects equal $c_{RCT}Kq_i$. If phase 3 is not successful (i.e, the treatment is not approved), the firm value is zero, and both equity and debt holders receive zero.

Phase 4 If the treatment is approved and the value of the firm is sufficiently high, equity holders repay the debt $F_3$, and receive profits $(P_i - c)Nq_i$ in every subsequent year, while taking into account the possibility of an entrant with probability $\pi$ and the surviving population $s_T$.

Moving backward, consider first the value of assets. We use risk-neutral pricing to ensure consistency in the valuation of the various securities (equity and debt).

Phase 4 The value of assets is

$$PV_4 = A_4(P_i - c)Nq_i \tag{29}$$

where $A_4 = \frac{(1-t_c)(1-\pi)}{R+\pi}\frac{1+R}{1+R-(1-\pi)s}$.

Phase 3 The value of assets at the beginning of Phase 3 after investments is

$$PV_3 = p_3^*(K, q_i)A_3^* PV_4 - c_{RCT}Kq_i \tag{30}$$

where $p_3^*(K, q_i)$ is the risk neutral probability of approval, and $A_3^* = (1 + r_f)^{-\tau}$ is the risk-free discount factor.

Phase 1 The value of assets at the beginning of Phase 1 after investments is

$$PV_1 = p_1^* A_1^* PV_3 - c_{R\&D} \tag{31}$$

where $p_1$ is the risk neutral probability of approval, and $A_1^* = (1+r_f)^{-\rho}$ is the risk-free discount factor.

We now consider the decisions of equity holders and the financing using debt.

Phase 1. Equity holders issue debt for the current value of $D_1 = c_{R\&D}$. In order to raise this amount, the face value $F_1$ must satisfy

$$D_1 = A_1^* p_1^* F_1 \tag{32}$$

That is,

$$F_1 = \frac{c_{R\&D}}{p_1^* A_1^*} \tag{33}$$

The value of equity after the investment is

$$E_1 = p_1^* A_1^* PV_3 - D_1 \tag{34}$$

where the first term is the value of assets after the investment takes place.

Phase 3 The firm rolls over the existing debt with face value $F_1$ at this time, and issues new debt to pay for $c_{RCT}Kq_i$. The face value $F_3$ must then satisfy

$$D_3 = F_1 + c_{RCT}Kq = p_3^*(K, q_i)A_3^* F_3 \tag{35}$$

or

$$F_3 = \frac{\frac{c_{R\&D}}{p_q^* A_1^*} + c_{RCT}Kq_i}{p_3^*(K, q_i)A_3^*} \tag{36}$$

The value of equity is then

$$E_3 = p_3^*(K, q_i)A_3^* PV_4 - D_3 \tag{37}$$

where again, the first term is the value of the firm after the investment took place. Equity holders choose the sample size $K$ to maximize equity value, while taking into account the equilibrium price to be bargained in Phase 4 (described below):

Phase 4 At this last point, assuming the drug is approved, the firm needs to pay back its debt with face value $F_3$. At this time the firm bargains with the insurance company. The value of equity at time 4 is

$$E_4 = A_4(P_i - c)Nq_i - F_3 \tag{38}$$

The brekeven price for the firm is then the one that gives $E_4 = 0$, which is given by:

$$P_i^{BE} = c + \frac{F_3}{A_4 N q_i} = c + \frac{c_{R\&D} + p_q^* A_1^* c_{RCT} K q_i}{p_q^* A_1^* p_3^*(K, q_i) A_3^* A_4 N q_i} \tag{39}$$

This is identical to the breakeven price in the text. Any price below this breakeven price would imply that the firm defaults. In case of default, we assume that the firm's value goes to zero, and that the drug is not produced. Thus, if the firm defaults, the insurance company also makes zero profits, as it can no longer buy (or produce) the drug. Therefore, for entry to be successful, we must have $P_i \geq P_i^{BE}$. We also know that $P_i \leq \overline{P}_i$ which is the max price the insurance company is willing to pay for alteration $i$. Assuming a $\gamma$ split as in the main text, the equilibrium price $P_i$ is given by

$$P_i = \gamma \overline{P} + (1 - \gamma) P_i^{BE} \tag{40}$$

Given this equilibrium price, we can also rewrite the value of equity at the beginning of Phase 3 as:

$$E_3 = \gamma \left[ p_3(K, q_i) A_3^* A_4 (\overline{P}_i - c) N q_i - \left( \frac{c_{R\&D}}{A_i^* p_i^*} + c_{RCT} K q_i \right) \right] \tag{41}$$

Finally, the value of equity at the beginning of Phase 1 is then

$$E_1 = p_1^* A_1^* \left[ p_3^*(K, q_i) A_3^* A_4 (P_i - c) N q_i - c_{RCT} K q_i \right] - c_{R\&D} \tag{42}$$

The decision of entry depends on $E_1 > 0$. From the definition of risk neutral probabilities in our context, we have

$$p_1^* = p_1 \frac{(1 + r_f)^\rho}{(1 + R)^\rho} = p_1 \frac{A_1}{A_1^*}; \quad p_3^*(K, q_i) = p_3(K, q_i) \frac{(1 + r_f)^\tau}{(1 + R)^\tau} = p_3(K, q_i) \frac{A_3}{A_3^*}; \tag{43}$$

which show that the expression for $E_1$ is the same as $PV_I$ in the text, and thus the decision to entry is the same.

# D. Appendix: Monte Carlo Simulations

In this appendix we describe the procedure to obtain the results in the calibration section. We perform all calculations using the statistics for small-sample distributions through Monte

Carlo simulations. In particular, for a given sample $M$ of patients, with $M/2$ in the treatment and control group, and with $x_T$ and $x_C$ as the number of successes for the treatment and control group, respectively, the distribution under the null hypothesis $p_T = p_C$ can be written as the hypergeometric function:

$$Prob\left(X_T = x_T | X_T + X_C = t, H_0\right) = \frac{\left(\begin{array}{c} M/2 \\ x_T \end{array}\right)\left(\begin{array}{c} M/2 \\ t - x_T \end{array}\right)}{\left(\begin{array}{c} M \\ t \end{array}\right)}. \tag{44}$$

The Exact Fisher Test rejects the null hypothesis $p_T = p_C$ whenever the number of successes in the treatment group $x_T$ is larger than a cutoff point $c(t)$, i.e. $x_T > c(t)$, which can be obtained by inverting the hypergeometric function in equation (44) at the desired level of confidence $1 - \alpha$.

For given $n$, we then proceed as follows:

- For each $M$ running from $M = 2$ to $M = N$ (only even numbers) we simulate $Sim = 100,000$ samples of $M$ uniformly distributed random variables. We also simulate $Sim = 100,000$ samples of random variable $\kappa \sim U[a, b]$ with $a$ and $b$ chosen to have $E[\kappa] = 0.35$ and $Pr(\kappa < 0) = 0.3$. We set $p_C = 0.35$ and then for each simulated $\tilde{\kappa}$ we invert the function $\tilde{\kappa} = (\tilde{p}_T - p_C)/\sqrt{p_C(1-p_C) + \tilde{p}_T(1-\tilde{p}_T)}$ to obtain simulated samples of $\tilde{p}_T$. Denote the realization of $\tilde{p}_T$ in sample $sim$ as $p_T^{sim}$.

- We divide each sample in two groups of size $M/2$, and simulate the number of successes (1's) and fails (0's) for each subgroup according to the probabilities $p_T^{sim}$ and $p_C$, where the former is itself simulated from the truncated normal distribution. Denote by $x_T^{sim}$ and $x_C^{sim}$ the number of successes for each group, respectively, in simulation $sim$.

- Determine $t^{sim} = x_T^{sim} + x_C^{sim}$ and compute the 95% cutoff $c(t^{sim})$ by inverting the hypergeometric cumulative distribution in equation (44).[21]

- If $x_T^{sim} > c(t^{sim})$ we reject the null hypothesis that $p_T = p_C$, and thus assume that FDA will accept the new treatment.

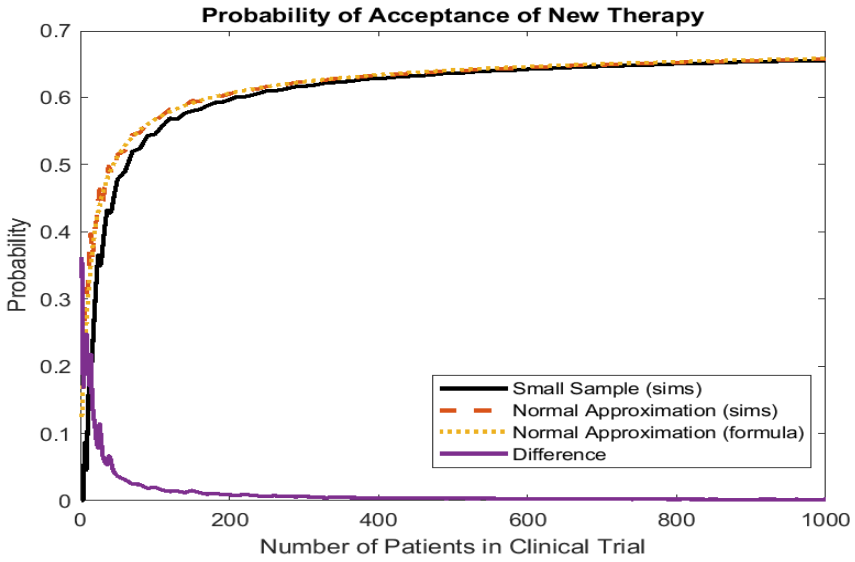
- The ex-ante probability of rejection can be computed as

$$Pr(Approval|M, n) = E\left[1_{x_T > c(t)}\right] = \frac{1}{Sim}\sum_{sim=1}^{Sim} 1_{x_T^{sim} > c(t^{sim})}$$

  where $1_{x_T > c}$ denotes the indicator function for $x_T > c$.

[21] The inverse of the hypergeometric cumulative distribution is available in standard statistical packages. We use Matlab with $c(t) = hygeinv(.95, M, M/2, t)$.

Figure 12: **Probability of Acceptance of New Treatment**




- Given the $Pr(Approval|M,n)$ for each $M$, we can now move to compute the $Pr(Approval|K,n)$ by using expression

$$\Pr\left(Approval|K,n\right) = 1 - \sum_{M=2}^{K} Pr(M|K)Pr(Approval|M,n) \tag{45}$$

  where recall that $Pr(M|K,n)$ is given by expression (5).

- We then repeat the whole procedure above for $n = 2$ to $n = 10000$.

To verify the simulation procedure and that the number of simulations $Sim = 100,000$ are sufficient, we perform the same calculations as above using the normal distribution approximation; the only difference is that the rejection of the null hypothesis $H_0$ is computed using the cutoff rule (1) for each simulated sample.

Figure 12 shows that indeed, the exact Fisher test is more likely to reject the new treatment for small number of patients compared to the normal distribution. However, the two distributions converge as the number $M$ of patients in clinical trial increases. The figure also shows that the number of simulations are sufficient to provide accurate statistics, as the case with simulated normal random variables overlays the one from the theoretical formula.

## D.1. Standardized Marginal Improvement and Success Uncertainty

As noted at the end of Section 4.7, the fact that new targeted treatments are compared to the best available treatment at the time of the trial implies that the standardized marginal

Table 6: ALK Alteration and Approval Probabilities

| | | | Standardized marginal improvement $\kappa$ for two $\Delta p = p_T - p_C$ | | Probability of approval with sample $M = 400$ and | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | no uncertainty | | uncertainty on $p_T$ | |
| | Date | 3-year PFS ($p_C$) | $\Delta p = 10\%$ | $\Delta p = 15\%$ | 10% | 15% | 10% | 15% |
| Chemo | – | 5.0 % | 0.24 | 0.33 | 92% | 100% | 72% | 81% |
| Crizotinib | 2013 | 20.2% | 0.16 | 0.24 | 64% | 93% | 55% | 65% |
| Brigatinib | 2018 | 43.0% | 0.14 | 0.21 | 52% | 86% | 51% | 61% |
| Alectinib | 2015 | 50.6% | 0.14 | 0.22 | 53% | 87% | 51% | 60% |
| Lorlatinib | 2021 | 65.0% | 0.16 | 0.24 | 59% | 93% | 53% | 57% |
| Hypothetical | | 75.0% | 0.18 | 0.28 | 71% | 98% | 52% | 51% |

improvement $\kappa$ may either decrease or increase as the number of alterations $n$ increases. We now illustrate this point using recent developments in treatments for ALK alterations as a concrete example.

Column 3 in Table 6 shows the progression of treatment of patients with this alteration (see T. Mok et al., 2020, D Ross Camidge et al., 2021 and Solomon et al., 2024). As it can be seen, since 2013, the 3-year progression free survival (PFS) has increased from 5% with chemotherapy, to 20% with the first targeted therapy in 2013 (Crizotinib), and all the way to 65% with Lorlatinib in 2021 (we inverted Brigatinib with Alectinib in the chronological order to rank the treatment by progression-free survival rate in column 3.) When the benchmark was chemotherapy with PFS = 5%, the standardized marginal improvement $\kappa$ could be rather large even for treatments with small improvements in PFS. Taking $p_C = PFS$ as our measure of success, Columns 4 and 5 of Table 6 show the standardized marginal improvement $\kappa$ for two assumptions about the marginal improvements of each new therapy: $\Delta p = p_T - p_C =$ 10% and 15%. When the benchmark is chemotherapy, $\kappa$ is 0.24 and 0.33, respectively, for the two scenarios. Consider now the benchmark as being Crizotinib, which yields a $PFS = p_C = 20.2\%$. Now, new treatments that improve over the new benchmark by the same margins (i.e. 10% and 15%) would have $\kappa$ equal 0.16, and 0.24, respectively, which are far lower than they would be if chemotherapy was the benchmark. Indeed, Alectinib became the benchmark in 2018; under this benchmark, the $\kappa$'s would decrease further for the same marginal improvement. A lower $\kappa$ implies a lower probability of acceptance, as shown in equation (2), and thus a higher required number of patients for the randomized clinical trial.

As the benchmark $p_C$ increases, a second issue comes to play: any uncertainty around the success of the new treatment $p_T$ further decreases the probability of acceptance for given

sample size, and thus the incentives to develop new drugs. To see this in a simple example, consider first the probability of acceptance using a sample size of $M = 400$ patients. With no uncertainty about $p_T$ and using formula (2), the probabilities of acceptance are as in columns 6 and 7 in Table 6. Notice that the probability of acceptance is monotonic in $\kappa$. In particular, for given $M$, the probability of acceptance follows a U-shape, with the minimum probability of acceptance being for intermediate values of $p_C$.

Assume now that $p_T$ is a truncated normal distribution with $\tilde{p}_T \sim TrN(p_T, \sigma^2_{p_T}, 0, 1)$. We set $\sigma_{P_T} = (p_T - p_C)/0.55$: that is, $Pr(p_T < p_C) = 30\%$ under the normal distribution. Columns 8 and 9 of Table 6 now show a nearly monotonically declining pattern of the probability of acceptance as the benchmark $p_C$ increases. As $p_C$ increases and $p_T = p_C + \Delta p$ increases, we are shifting some mass to the left of distribution. In essence, it becomes increasingly less likely to beat the benchmark. While this is just an example that depends on our parametric assumptions, the general point is that there need not be a tight relation between $\kappa$ and the probability of acceptance when there is uncertainty about $p_T$. In the limit, if the baseline PFS is $p_C = 90\%$, it becomes very unlikely to find a successful competing drug with $p_T > 90\%$.

# E. Appendix: Process-based Drug Development for Lung Cancer

In a companion paper focused on drug discovery, Garassino et al. (2026) put forward a process-based approach to drug discovery for lung cancer. This new approach is made possible by recent advances in biomedicine (specifically, genome sequencing), the availability of relatively inexpensive computational power, and developments in artificial intelligence. The next section briefly describes this process; we then turn to the main focus of our analysis in Sections 5.1 and 6.4, where we assess the economic viability of the PDDP, exploiting our calibrations from Section 6 in the specific case of lung cancer treatment.

## E.1. The Process-Based Drug Development Method

The new drug discovery process would comprise the following steps:

**A. Identification of driver alterations.** As described in Section 2, certain genetic alterations are critical to tumor growth. Through the sequencing of tumor DNA and RNA, it is now possible to identify the majority of these critical drivers.

**B. Rebuilding the altered protein.** Methodologies have recently been developed that are able to rebuild the altered protein: see the examples below. Evidence shows that such

methods are able to rebuild the altered proteins with high level of precision. This process, which can now be done quickly in silico, used to take years in the past through experiments at the bench in wet laboratories.

**C. Drug matching.** The structure of the altered protein "signals" (i.e., essentially, triggers) tumor growth, cancer cell survival, and metastasization. This step exploits supercomputers to screen billions of molecules and identify those (new or existing) that can "block" the altered protein from signalling tumor growth.

**D. Drug discovery.** Not all the potential molecules identified in the previous step may be active enough or viable safe solutions for actual use. The next task is thus to identify the ones that can be absorbed and tolerated by humans, leveraging the existing (and ever increasing) knowledge of the molecular structure of existing safe drugs, together with machine-learning methodologies. It is also possible that the an effective compound with the proper molecular structure may be found within the universe of existing drugs, and thus ensure its safe use.

**E. Drug production.** Once the new compound has been identified, the new personalized drug must be physically produced. New automated machines, aided by 3D printing technologies, are considered to be viable technologies to produce ad-hoc drugs for individuals.

As discussed in Garassino et al. (2026), teams around the world have already been implementing some of these steps. Ren et al. (2023) demonstrated for the first time that, by using Google Deepmind AlphaFold, steps (A) to (D) can be carried out to identify a new inhibitor within one month. They identified a novel hit molecule against a novel target for the treatment of hepatocellular carcinoma without any experimental structure within 30 days. Relatedly, Abramson et al. (2024) show that AlphaFold 3 is able to provide accurate structure prediction of biomolecular interactions. Finally, Kornauth et al. (2022) conducted a feasibility study and prospectively tested an image-based, single-cell functional approach to guide treatments in 143 patients with advanced aggressive hematologic cancers. 56 patients (39%) were treated according to functional results. In 54% of patients, there was a demonstrated clinical benefit over traditional therapies.

Beyond cancer treatment, Zhang et al. (2025) provides a general overview of advances in the drug development process that have been driven by AI. In particular, the authors highlight how AI is accelerating all stages of drug development, from target identification (our step A) to drug discovery (steps B through D). Moreover, recently the FDA issued a new draft guidance and call for comments on AI-driven drug development (see https://www.fda.gov/media/184830/download) as well as for the plausible mechanism approval of individualized drugs (see https://www.fda.gov/media/191247/download), which further validates the new methodologies. To sum up, from a science perspective, the personalized

drug development process we analyze aligns with broad trends in biomedicine; our objective in this section is to highlight its economic implications.

# F. Appendix. Existing solutions

The concern for the lack of R&D for the treatment of rare diseases is not new. (What is new is the realization that targeted therapies are progressively turning many diseases into collections of rare diseases.) For instance, Pizzamiglio et al. (2022) lists different trial designs that have been put forward to date for rare diseases. The designs considered therein include: (1) Cross-over, in which participants receive a random sequence of different treatments, each followed by a "wash-out" period, so that participants are effectively their own controls; (2) Delayed start, in which initially only a placebo-controlled phase is carried out, and treatment occurs during a second phase; (3) Randomized withdrawal, in which all participants first receive treatment, and then randomization is only carried out among those that initially respond; (4) Group sequential, in which the number of participants is not pre-set, but the RCT is monitored through pre-determined interim analysis which determines the possible need to terminate early; (5) Adaptive, in which the probability of randomization to one group shifts towards more promising treatments, based on partial results.

From the perspective of our model, these methodologies can help in that they decrease the total fixed R&D costs (e.g. through parallel testing), and the total number of patients $M$ needed per alteration. However, Table 3 suggests that, even for low costs of $R\&D$, as the number of alterations $n$ increases, the break-even price increases by several orders of magnitude. It seems highly unlikely that the savings resulting from the adoption of the methodologies just described would be able to offset this effect. Indeed, the quotations at the beginning of this article suggest that even regulatory agencies realize that these methodologies will not be sufficient for rare alterations. We need a new paradigm, discussed next.

# G. Appendix. Calibration Robustness

The calibration results depend on numerous parameter values. We now briefly discuss some important variations to some parameters.

First, we use the standard statistical percentile of 5% as FDA cutoff to approve or reject the results of clinical trials. It may be argued that the FDA may be willing to accept higher cutoffs for rarer alterations. For instance, Table 1 shows that some drugs have been approved even in single arm (SA) trials. Our results are not too sensitive to this cutoff. Even assuming

a statistical percentile of 30%, we obtain an incidence of 0.05% (instead of .06%) below which a firm would not enter the market. Moreover, break-even prices in the calculation of social costs are also similar: For instance, for an incidence of .05%, the break-even prices per patient per year range between $\$426,525$ and \$3.8 million, vs. between \$493,010 and \$4.4 million in our main calibration (see Table 3), for pre-phase III R&D costs ranging between \$50 million and \$ 500 million. These similarities stem from the fact that the main reason driving the rejection or approval of new drugs is not the percentile cutoff that the FDA uses (which mostly determines the optimal sample size), but rather the prior uncertainty about the standardized improvement $\kappa$, which we assume has a 30% probability of being negative (i.e., the firm assigns significant probability to the event that the new drug is no better than the current standard of care).

For this reason, as a second robustness check, we consider a smaller prior uncertainty over $\kappa$. We keep $E[\kappa] = 35\%$ but we put the prior probability of negative $\kappa$ at 0% instead of 30%. That is, the firm is confident that the new drug will work better than the previous standard of care. Even so, our calibration does not change very much. In this case, the incidence under which firms do not enter the market is still 0.06% , and the break-even prices per year per patient in the calculation of social costs for, e.g., an incidence of 0.05%, range between \$503,603 and \$4.5 million as R&D costs range between \$50 million and \$500 million.

Third, we consider the possibility of faster clinical trials, possibly due to learning about the science behind new alterations. We shorten the length of Phase I to $\rho = 4$ years (down from 6 years), and also shorten the duration of the clinical trial to $\tau = 2$ years (instead of 4 years). With scientific research taking half the time, we find that the minimum incidence for which firm would still enter the market is .04% (instead of .06%) and the break-even prices per year per patient in the calculation of social costs for, e.g., an incidence of 0.05%, range between \$350,577 and \$3.0 million as R&D costs range between \$50 million and \$500 million. Indeed, faster discovery helps increasing the discount factors and thus the present value of future profits.

Fourth, we consider an exclusivity period during which a firm is guaranteed not to have competitors coming to the market. We choose $\tau^* = 7$ years after $\tau$ during which the probability of new entrant is $\pi = 0$. In this case, we find the results are nearly identical as in the main case. The minimum incidence for which firms would still enter the market is unchanged at .06%, and the break-even prices per year per patient in the calculation of social costs for, e.g., an incidence of 0.05%, are also unchanged, as they range between \$493,006 and \$4.4 million as R&D costs range between \$50 million and \$500 million. The similarity of the results stems from the fact that at the threshold $q_i = 0.06\%$ at which point $PV_{I,i} = 0$ we have that the equilibrium $\pi = 0$ and so there is no difference between the general case and

this restricted case.

Fifth, we consider drastically lower RCT costs per-patient; specifically, we consider $c_{RCT} = \$50,000$ and even $c_{RCT} = \$10,000$, instead of $\$100,000$. Once again, results are very similar. The reason is that the total costs of RCT are bounded above by the maximum number of patients that can be enrolled in clinical trials (= 10% enrollment eligibility $\times 1.25$ million tested patients). This upper bound is small compared to the aggregate potential profits from the new drugs.

Finally, we consider a higher discount rate, as suggested in e.g. Lo et al., 2022 for biotech companies. We set the discount rate $R = 13\%$ instead of 10.5%. We find that the incidence of 0.09% (instead of .06%) below which a firm would not enter the market. The break-even prices in the calculation of social costs are higher. For instance, for an incidence of .05%, the break-even prices per patient per year range between $\$707,614$ and \$7.1 million, vs. between \$493,010 and \$4.4 million in our main calibration (see Table 3), for pre-phase III R&D costs ranging between \$50 million and \$ 500 million.

Overall, reasonable variations of parameters lead to results that are in the same order of magnitudes as the main results.

# H. Proofs

## H.1. Preliminaries: Comparative Statics of Approval

**Proposition 10** *Let the Poisson Approximation Assumption hold. Then, for $\alpha \geq 2.3\%$, the probability of approval $p_i(K, q_i)$ is increasing in $q_i$ and $K$:*

$$\frac{\partial p_i(K, q_i)}{\partial q_i} > 0; \qquad \frac{\partial p_i(K, q_i)}{\partial K} > 0 \tag{46}$$

Define the function $g : [0, \infty) \to \mathbb{R}$ as:

$$g(x) = \Phi\left(z - \theta\sqrt{x}\right) \tag{47}$$

where $z = z(\alpha)$ and $\theta > 0$. Note that $\alpha \geq 2.3\%$ (approximately) implies $z \leq 2$: this is used in the proof of Lemma 4.

Let $M$ be a discrete random variable following a Poisson distribution with parameter $\lambda > 0$, such that the probability mass function is $P(M = m) = e^{-\lambda}\frac{\lambda^m}{m!}$ for integers $m \geq 0$.

Define the expectation function $H : (0, \infty) \to \mathbb{R}$ as:

$$H(\lambda) = \mathbb{E}[g(M)] = \sum_{m=0}^{\infty} g(m)e^{-\lambda}\frac{\lambda^m}{m!} \tag{48}$$

We will prove that $H(\lambda)$ is strictly decreasing ($H'(\lambda) < 0$) and strictly convex ($H''(\lambda) > 0$) for all $\lambda > 0$. Since $\lambda = Kq$ in Proposition 10, the result follows.

**Lemma 1 (Derivatives of the Poisson Expectation)** *For any $\lambda > 0$,*

$$H'(\lambda) = \sum_{m=0}^{\infty} \Delta g(m) e^{-\lambda} \frac{\lambda^m}{m!}$$
$$H''(\lambda) = \sum_{m=0}^{\infty} \Delta^2 g(m) e^{-\lambda} \frac{\lambda^m}{m!}$$

*where $\Delta g(m) = g(m+1) - g(m)$ and $\Delta^2 g(m) = g(m+2) - 2g(m+1) + g(m)$.*

**Proof:** The series $H(\lambda) = e^{-\lambda} \sum_{m=0}^{\infty} g(m) \frac{\lambda^m}{m!}$ is the product of $e^{-\lambda}$ and a power series. Since $|g(m)| \in (0,1)$, the power series converges absolutely and uniformly on any bounded interval in $(0, \infty)$. Thus, we may differentiate term-by-term.

$$\begin{aligned} H'(\lambda) &= \sum_{m=0}^{\infty} g(m) \frac{d}{d\lambda} \left( e^{-\lambda} \frac{\lambda^m}{m!} \right) \\ &= \sum_{m=0}^{\infty} g(m) \left( -e^{-\lambda} \frac{\lambda^m}{m!} + e^{-\lambda} \frac{m\lambda^{m-1}}{m!} \right) \\ &= -H(\lambda) + \sum_{m=1}^{\infty} g(m) e^{-\lambda} \frac{\lambda^{m-1}}{(m-1)!} \end{aligned}$$

Shifting the index of the second summation by substituting $k = m - 1$:

$$H'(\lambda) = -\sum_{m=0}^{\infty} g(m) e^{-\lambda} \frac{\lambda^m}{m!} + \sum_{k=0}^{\infty} g(k+1) e^{-\lambda} \frac{\lambda^k}{k!} = \sum_{m=0}^{\infty} [g(m+1) - g(m)] e^{-\lambda} \frac{\lambda^m}{m!}$$

This establishes the first derivative as the expectation of $\Delta g(m)$. Applying the identical term-by-term differentiation operator to $H'(\lambda)$ yields:

$$H''(\lambda) = \sum_{m=0}^{\infty} \Big( [g(m+2) - g(m+1)] - [g(m+1) - g(m)] \Big) e^{-\lambda} \frac{\lambda^m}{m!}$$

which simplifies to the expectation of the second forward difference $\Delta^2 g(m)$. *Q.E.D.*

**Lemma 2** *For all $\lambda > 0$, $H'(\lambda) < 0$.*

**Proof:** We analyze the function $g(x)$ in Eq. (47) for $x \geq 0$. Let $u(x) = z - \theta\sqrt{x}$, so $g(x) = \Phi(u(x))$. For any real numbers $x_1, x_2$ such that $0 \leq x_1 < x_2$, $\sqrt{x_1} < \sqrt{x_2}$. Since $\theta > 0$, $\theta\sqrt{x_1} > z - \theta\sqrt{x_2}$. Thus, $u(x_1) > u(x_2)$. Hence $u(\cdot)$ is strictly decreasing on $[0, \infty)$.

The standard normal cdf $\Phi(u)$ is strictly increasing for all $u \in \mathbb{R}$. Hence $g$ is strictly increasing on $\mathbb{R}_+$. In particular, for any integer $m \geq 0$, $g(m) > g(m+1)$, which means the first forward difference is strictly negative:

$$\Delta g(m) = g(m+1) - g(m) < 0$$

By Lemma 1, $H'(\lambda)$ is an infinite series where every term is the product of a strictly negative number $\Delta g(m)$ and a strictly positive Poisson weight $e^{-\lambda}\frac{\lambda^m}{m!}$. Therefore, the entire sum converges to a strictly negative value, and $H'(\lambda) < 0$ for all $\lambda > 0$. *Q.E.D.*

**Lemma 3** *For any integer $m \geq 0$, there exists a real number $\xi_m \in (m, m+2)$ such that:*

$$\Delta^2 g(m) = g''(\xi_m)$$

**Proof:** The function $g(x) = \Phi(z - \theta\sqrt{x})$ is continuous on $[0, \infty)$ and twice differentiable on $(0, \infty)$. Define an auxiliary function $h : [0, 1] \to \mathbb{R}$ by:

$$h(t) = g(m + t + 1) - g(m + t)$$

Because $m \geq 0$, $(m+t), (m+t+1) \in [m, m+2] \subset [0, \infty)$ for all $t \in [0, 1]$. Therefore, $h(t)$ is continuous on $[0, 1]$. Furthermore, $m + t, m + t + 1 > 0$ for all $t \in (0, 1)$ and $m \geq 0$, so $h(t)$ is also differentiable on $(0, 1)$.

By the Mean Value Theorem (MVT), there is a constant $c \in (0, 1)$ such that

$$h(1) - h(0) = h'(c) \cdot (1 - 0)$$

Substituting the definition of $h(t)$ back into this equation gives:

$$[g(m+2) - g(m+1)] - [g(m+1) - g(m)] = g'(m + c + 1) - g'(m + c)$$

The left-hand side is exactly $\Delta^2 g(m)$. To evaluate the right-hand side, we apply the MVT a second time to the function $g'$ on the interval $[m + c, m + c + 1]$.

Because $c \in (0, 1)$ and $m \geq 0$, $m + c > 0$. Thus, $g'$ is continuous on $[m+c, m+c+1]$ and differentiable on $(m+c, m+c+1)$. By the MVT, there exists a constant $\xi_m \in (m+c, m+c+1)$ such that:

$$g'(m + c + 1) - g'(m + c) = g''(\xi_m) \cdot ((m + c + 1) - (m + c)) = g''(\xi_m)$$

Since $\xi_m \in (m + c, m + c + 1)$ and $c \in (0, 1)$, it follows that $\xi_m \in (m, m + 2)$. *Q.E.D.*

**Lemma 4** *For all $x > 0$, $g''(x) > 0$.*

**Proof:** Again, let $u(x) = z - \theta\sqrt{x}$. Then $g(x) = \Phi(u(x))$. We compute the derivatives:

$$u'(x) = -\frac{\theta}{2\sqrt{x}}$$
$$u''(x) = \frac{\theta}{4x^{3/2}}$$

Using the chain rule and the property of the standard normal density $\phi'(u) = -u\phi(u)$:

$$\begin{aligned} g'(x) &= \phi(u(x))u'(x) \\ g''(x) &= \phi'(u(x))[u'(x)]^2 + \phi(u(x))u''(x) \\ &= -u(x)\phi(u(x))[u'(x)]^2 + \phi(u(x))u''(x) \\ &= \phi(u(x))\Big[u''(x) - u(x)[u'(x)]^2\Big] \end{aligned}$$

Substituting the expressions for $u(x)$, $u'(x)$, and $u''(x)$ into the brackets:

$$\begin{aligned} u''(x) - u(x)[u'(x)]^2 &= \frac{\theta}{4x^{3/2}} - (z - \theta\sqrt{x})\left(-\frac{\theta}{2\sqrt{x}}\right)^2 \\ &= \frac{\theta}{4x^{3/2}} - (z - \theta\sqrt{x})\frac{\theta^2}{4x} \end{aligned}$$

Factoring out $\frac{\theta}{4x^{3/2}}$, we obtain:

$$g''(x) = \frac{\theta}{4x^{3/2}}\phi(z - \theta\sqrt{x})\Big[1 - z\theta\sqrt{x} + \theta^2 x\Big]$$

Because $\theta > 0$, $x > 0$, and $\phi(\cdot) > 0$, the sign of $g''(x)$ is determined by the quadratic in $\sqrt{x}$ inside the brackets. Let $y = \sqrt{x}$ and define the polynomial $Q(y) = \theta^2 y^2 - z\theta y + 1$.

Now $Q'(y) = 2\theta^2 y - z\theta$ and $Q''(y) = 2\theta^2 > 0$, so $Q$ is strictly convex and attains a minimum at $y = z/2\theta$. This minimum is $\theta^2 \cdot z^2/4\theta^2 - z\theta \cdot z/2\theta + 1 = z^2/4 - z^2/2 + 1 = 1 - z^2/4$ which is positive for $z \leq 2$. *Q.E.D.*

**Proposition 11 (Strict Monotonicity and Global Convexity)** *The expectation function $H(\lambda) = \mathbb{E}[g(M)]$ is both strictly decreasing and strictly convex for all $\lambda > 0$; that is, $H'(\lambda) < 0$ and $H''(\lambda) > 0$.*

**Proof:** The strict monotonicity is established directly by Lemma 2, which rigorously proves that the first derivative $H'(\lambda)$ is strictly negative for all $\lambda > 0$.

To prove strict convexity, we evaluate the second derivative. By Lemma 1, the second derivative is given by:

$$H''(\lambda) = \sum_{m=0}^{\infty} \Delta^2 g(m) e^{-\lambda}\frac{\lambda^m}{m!}$$

By Lemma 3, for every integer $m \geq 0$, there is $\xi_m \in (m, m+2)$ such that $\Delta^2 g(m) = g''(\xi_m)$. Because $m \geq 0$, $\xi_m > 0$. By Lemma 4, $g''(x) > 0$, for all $x > 0$, so in particular $g''(\xi_m) > 0$, and therefore $\Delta^2 g(m) > 0$ for all integers $m \geq 0$. Because the Poisson probability weights $e^{-\lambda}\frac{\lambda^m}{m!}$ are strictly positive for all $\lambda > 0$ and all $m \geq 0$, $H''(\lambda) > 0$ for all $\lambda > 0$. *Q.E.D.*

## H.2. Proof of Proposition 1

Let $q < q'$ and denote by $K$ and $K'$ the optimal choices of sizes for $q$ and $q'$, respectively. By Proposition 10,

$$PV_{III}(K, q) = p(K, q) \cdot C - K \cdot c_{RCT} < p(K, q') \cdot C - K \cdot c_{RCT} = PV_{III}(K, q');$$

furthermore, since $K'$ is optimal for $q$, $PV_{III}(K', q') \geq PV_{III}(K, q')$. Thus, as claimed, $PV_{III}(K, q) < PV_{III}(K', q')$. *Q.E.D.*

## H.3. Proof of Proposition 2

It is enough to show that $p(K, q) \to 0$ as $q \to 0$ (since there are finitely many possible values of $K$ for every fixed $N$, the convergence is uniform). From Eq. (8), since $1 - \Phi\left(z(\alpha) - \kappa_i\sqrt{m}\right) \in [0, 1]$

$$p_i(K, q) \leq \sum_{m=1}^{K/2} \Pr[2m \leq M \leq 2m+1 | K, q] = \Pr[M \geq 2 | K, q] \leq \frac{\mathrm{E}[M|K, q]}{2} = \frac{K}{2} q \to 0,$$

where the second inequality follows from Eq. (6) and Markov's inequality. *Q.E.D.*

## H.4. Proof of Propositions 3 and 4

We fix an alteration $i$ throughout. To both clarify and simplify notation, we omit $i$ throughout this section, but make the dependence on all endogenous variables explicit. We also emphasize the dependence on the exogenous parameter $q \equiv q_i$ in order to prove Proposition 3. Specifically, write the Phase III present value as follows:

$$PV_{III,q}(K, P, \pi) = p_q(K) \cdot A_{III}(\pi)(P - c)N - c_{RCT}K$$

Here, $p_q(K) = \mathrm{E}[1 - g(M)]$ is the approval probability under the Poisson approximation, which depends upon the choice of $K$ (endogenous) and the alteration share $q$ (exogenous). By Lemma 1 and Proposition 11, $p_q(\cdot)$ is twice continuously differentiable, strictly increasing, and strictly concave in $K$ for every $q > 0$, and in $q$ for every $K > 0$. Note for future reference

that $p_q(K)$ is bounded above by $\bar{p} \equiv p_1(N) < 1$; furthermore, the probability of successful entry, $\pi$, cannot be greater than this maximum probability of approval, $\bar{p}$ (we verify this in the construction of the equilibrium). Below, $p'_q$ and $p''_q$ mean $\partial p_q(K)/\partial K$ and $\partial^2 p_q(K)/\partial K^2$: we denote derivatives with respect to $q$ explicitly. Moreover, $A_{III}(\pi) > 0$ for $\pi < 1$, and $A_{III}(\cdot)$ is continuous (in fact, differentiable).

Consider the problem faced by the firm in Phase III:

$$\max_{K \in [0,N]} PV_{III,q}(K, P, \pi)$$

where we allow $K$ to be any real number between 0 and $N$.

**Lemma 5** *For $q > 0$, $P > c$ and $\pi < 1$, the optimal sample size $K_q^*(P, \pi)$ is given by*

$$K_q^*(P, \pi) = (p'_q)^{-1} \left( \frac{c_{RCT}}{A_{III}(\pi)(P - c)N} \right).$$

*For $P_{\min} > c$, the function $[P_{\min}, \infty) \times [0, \bar{p}] \mapsto K_q^*(P, \pi)$ is jointly continuous, Lipschitz continuous in $P$ with constant $L_q > 0$ uniformly over $\pi$, strictly increasing in $P$ for fixed $\pi$, and strictly decreasing in $\pi$ for fixed $P$.*

**Proof:** Because the objective is strictly concave in $K$, the FOC is necessary and sufficient:

$$p'_q(K) \cdot A_{III}(\pi)(P - c)N - c_{RCT} = 0$$

which yields the expression for $K_q^*$ in the statement. If $P$ increases, the argument of $(p'_q)^{-1}$ decreases, and since $p'_q$ (and hence its inverse) is decreasing, this means that $K_q^*$ increases. If $\pi$ increases, $A_{III}(\pi)$ decreases, so the argument of $(p'_q)^{-1}$ increases, so $K_q^*$ decreases. Furthermore, $K_q^*$ is jointly continuous (indeed, differentiable) in its arguments $P$ and $\pi$ for every $q > 0$, provided $P > c$, which is ensured by $P_{\min} > 0$ and $P \geq P_{\min}$.

To see that $K_q^*$ is Lipschitz in $P$ on $[P_{\min}, \infty)$ for fixed $p \in [0, \bar{p}]$, differentiate $K_q^*$ with respect to $P$ using the inverse function rule and chain rule:

$$\frac{\partial K_q^*}{\partial P} = \frac{-c_{RCT}}{p''_q(K^*)A_{III}(\pi)(P - c)^2 N}.$$

Since $p_q$ is twice continuously differentiable, in particular $p''_q$, and hence $|p''(K)_q|$, is continuous on $[0, N]$. Therefore, $|p''(K)_q|$ attains a strictly positive minimum $m_q > 0$. For $P \geq P_{\min} > c$, $(P - c)^2 \geq (P_{\min} - c)^2 > 0$. Furthermore, $A_{III}(\pi)$ attains a strictly positive minimum $A_{\min} > 0$ at $\pi = \bar{p}$. Thus, the absolute value of the derivative is bounded by:

$$\left| \frac{\partial K^*}{\partial P} \right| \leq \frac{c_{RCT}}{m_q \cdot A_{\min} \cdot (P_{\min} - c)^2 \cdot N} \equiv L_q.$$

Since $L_q$ does not depend on $\pi$ or $P$, $K^*$ is Lipschitz in $P$ with constant $L_q$. *Q.E.D.*

Now consider the Phase I present value:

$$PV_{I,q}(P, \pi, c_{RD}) = p_I \cdot A_I \cdot PV_{III,q}(K_q^*(P, \pi), P, \pi) \cdot q - c_{RD}.$$

We show that there exists a *break-even* price $P_{BE0}$ such that, if the firm collects $P_{BE}$ per patient after the drug is approved, and chooses $K$ optimally in Phase III given this price $P_{BE0}$, then expected revenues exactly cover its R&R costs $c_{RD}$. (However, this price may exceed the maximum price $\bar{P}$ that the insurance company is willing to pay; we will address this issue below.)

**Lemma 6 (Break-Even Price)** *For every $q > 0$, $\pi \leq \bar{p}$ and $c_{RD} \in [c_L, c_H]$, there exists a unique break-even price $P_{BE0,q}(\pi, c_{RD}) > c$ such that $PV_{I,q}(P_{BE0,q}(\pi, c_{RD}), \pi, c_{RD}) = 0$. For fixed $c_{RD}$, the function $\pi \mapsto P_{BE0,q}(\pi, c_{RD})$ is strictly decreasing and continuous. Hence, $\underline{P} = \min_{\pi \in [0,\bar{p}]} P_{BE0,q}(\pi, c_L)$ is well-defined and satisfies $\underline{P} > c$. Finally, for fixed $\pi \leq \bar{p}$, the function $c_{RD} \mapsto P_{BE0,q}(\pi, c_{RD})$ is strictly increasing and Lipschitz continuous, with constant $M_q > 0$ independent of $\pi$.*

**Proof:** Fix $q > 0$ throughout. For fixed $\pi \leq \bar{p} < 1$, $P \mapsto PV_{III,q}(K_q^*(P, \pi), P, \pi)$ is continuous and strictly increasing on $[c, \infty)$. Continuity follows from the fact that $K_q^*$ is continuous in $P$, $p_q$ is continuous in $K$, and so $PV_{III,q}$ is itself a continuous function of continuous functions of $P$. To see that it is strictly increasing, suppose $P' > P$. Then $PV_{III,q}(K_q^*(P, \pi), P', \pi) > PV_{III,q}(K_q^*(P, \pi), P, \pi)$, where the strict inequality holds because $\pi < 1$; and furthermore $PV_{III,q}(K_q^*(P', \pi), P', \pi) \geq PV_{III,q}(K_q^*(P, \pi), P', \pi)$.

It follows that, for fixed $\pi \leq \bar{p} < 1$ and $c_{RD} \in [c_L, c_H]$, $P \mapsto PV_{I,q}(P, \pi, c_{RD})$ also is continuous and strictly increasing. Therefore, there exists a unique price $P_{BE0,q}(\pi, c_{RD})$ such that $PV_{I,q}(P_{BE0,q}(\pi, c_{RD}), \pi, c_{RD}) = 0$. In addition, this price is strictly increasing in $c_{RD}$ for fixed $\pi \leq p < 1$.

For fixed $c_{RD}$, the function $\pi \mapsto P_{BE0,q}(\pi, c_{RD})$ is strictly increasing. This is because $PV_{III,q}(K, P, \pi)$ is strictly decreasing in $\pi$ for fixed $K$ and $P$, and $K_q^*(P, \pi)$ is strictly decreasing in $\pi$ for fixed $P$ by Lemma 5. Hence, if $\pi' > \pi$, $PV_{I,q}(P_{BE0,q}(\pi, c_{RD}), \pi', c_{RD}) < PV_{I,q}(P_{BE0,q}(\pi, c_{RD}), \pi, c_{RD}) = 0$; since $PV_{I,q}$ is strictly increasing in $P$, it must be that $PV_{I,q}(\pi', c_{RD}) > PV_{I,q}(\pi, c_{RD})$. Furthermore, $\pi \mapsto P_{BE0,q}(\pi, c_{RD})$ is continuous. To see this, fix a convergent sequence $(\pi^k)_{k \geq 1}$ in $[0, \bar{p}]$ and let $\pi^\infty \in [0, \bar{p}]$ be its limit. By definition, $PV_{I,q}(P_{BE0,q}(\pi^k, c_{RD}), \pi^k, c_{RD}) = 0$ for all $k$. By monotonicity of $P_{BE0,q}$ in $\pi$, $P_{BE0}(\pi^k, c_{RD}) \in [P_{BE0,q}(0, c_{RD}), P_{BE0,q}(\bar{p}, c_{RD})]$ for all $k = 1, 2, \ldots, \infty$. If $(\pi^{k(\ell)})_{\ell \geq 1}$ is any subsequence along which $\left(P_{BE0}(\pi^{k(\ell)}, c_{RD})\right)_\ell$ converges, let $P_\infty$ be the limit; by continuity of $PV_{I,q}$ in prices and $\pi$'s, $PV_{I,q}(P_\infty, \pi^\infty, c_{RD}) = 0$. Since $PV_{I,q}$ is strictly increasing in prices

for fixed $\pi$ and $c_{RD}$, $P_\infty$ must be the limit of any convergent subsequence $\left(P_{BE0}(\pi^{k(\ell)}, c_{RD})\right)_\ell$, so $P_{BE0}(\pi^k, c_{RD}) \to P_\infty$. Furthermore, $P_\infty = P_{BE0,q}(\pi^\infty, c_{RD})$. Hence, $P_{BE0,q}$ is continuous in $\pi$. The statements about $\bar{P}$ now follow; in particular, $P_{BE0,q}(\pi, c_L) > c$ for $\pi < 1$, because if the firm gets a price equal to $c$, $PV_{III,q} = 0$, whereas $c_L > 0$.

It remains to be shown that $c_{RD} \mapsto P_{BE0,q}(\pi, c_{RD})$ is Lipschitz continuous. By the implicit function theorem and the envelope theorem,

$$\begin{aligned}\frac{\partial P_{BE0,q}(\pi, c_{RD})}{\partial c_{RD}} &= -\frac{\left.\frac{\partial PV_{I,q}(P,\pi,c_{RD})}{\partial c_{RD}}\right|_{P=P_{BE0,q}(\pi,c_{RD})}}{\left.\frac{\partial PV_{I,q}(P,\pi,c_{RD})}{\partial P}\right|_{P=P_{BE0,q}(\pi,c_{RD})}} = -\frac{\left.\frac{\partial PV_{I,q}(P,\pi,c_{RD})}{\partial c_{RD}}\right|_{P=P_{BE0,q}(\pi,c_{RD})}}{p_I A_I(\pi) \cdot \left.\frac{\partial PV_{III,q}(K,P,\pi)}{\partial P}\right|_{\substack{K=K_q^*(P_{BE0,q}(\pi,c_{RD}),\pi) \\ P=P_{BE0,q}(\pi,c_{RD})}} \cdot q} \\ &= \frac{1}{p_I A_I p_q(K_q^*(P_{BE0,q}(\pi, c_{RD}), \pi)) A_{III}(\pi) N q} \\ &\leq \frac{1}{p_I A_I(0) p_q(K_q^*(\underline{P}, \bar{p})) A_{III}(\bar{p}) N q} \equiv M_q.\end{aligned}$$

Thus, $P_{BE0,q}(\pi, c_{RD})$ is Lipschitz in $c_{RD}$ with constant $M_q$. *Q.E.D.*

As in the main text, denote by $\bar{P}$ the maximum price that the insurance company is willing to pay for the alteration under consideration. Assume that $\bar{P} > \underline{P}$, and define $P_{BE,q}(\pi, c_{RD}) = \min(P_{BE0,q}(\pi, c_{RD}), \bar{P})$, the "capped" break-even price. This function retains the Lipschitz constant $M_q$ for fixed $\pi \leq \bar{p} < 1$. In addition:

**Lemma 7** *The function $\pi \mapsto P_{BE,q}(\pi, c_{RD})$ is continuous in $\pi$ for fixed $c_{RD}$.*

**Proof:** Suppose $\pi_\ell \to \pi$ and let $P_\ell = P_{BE,q}(\pi_\ell, c_{RD})$. Let $P$ be the limit of a convergent subsequence of $(P_\ell)$, which exists because $P_\ell \in [\underline{P}, \bar{P}]$ for every $\ell$. To save notation, temporarily denote the subsequence by $(P_\ell)$ itself. We have $PV_{I,q}(P_\ell, \pi_\ell, c_{RD}) = 0$ for all $\ell$. Since $K_q^*$ is continuous, $K_q^*(P_\ell, \pi_\ell) \to K_q^*(P, \pi)$; hence also $PV_{III,q}(K_q^*(P_\ell, \pi_\ell), P_\ell, \pi_\ell) \to PV_{III,q}(K_q^*(P, \pi), P, \pi)$. This implies that $PV_{I,q}(P_\ell, \pi_\ell, c_{RD}) \to PV_{I,q}(P, \pi, c_{RD})$. Moreover, $PV_{I,q}(P_\ell, \pi_\ell, c_{RD}) = 0$ for all $\ell$. Therefore, $PV_{I,q}(P, \pi, c_{RD}) = 0$, so $P = P_{BE0,q}(\pi, c_{RD})$. In addition, $P_\ell \leq \bar{P}$ for each $\ell$, so $P \leq \bar{P}$ as well, and thus $P = P_{BE,q}(\pi, c_{RD})$. Finally, if $P$ and $P'$ are two limits of different convergent subsequences, then $P = P_{BE0,q}(\pi, c_{RD}) = P'$ because $P_{BE0,q}(\pi, c_{RD})$ is uniquely defined. Therefore, $P_{BE,q}$ is continuous in $\pi$ for fixed $c_{RD}$. *Q.E.D.*

**Proof of Proposition 3**: we first calculate $\partial P_{BE0,q}(\pi, c_{RD})/\partial q$. Again, we need to use

the implicit function theorem and the envelope theorem.

$$\frac{\partial P_{BE0,q}(\pi, c_{RD})}{\partial q} = -\frac{\left.\frac{\partial PV_{I,q}(P,\pi,c_{RD})}{\partial q}\right|_{P=P_{BE0,q}(\pi,c_{RD})}}{\left.\frac{\partial PV_{I,q}(P,\pi,c_{RD})}{\partial P}\right|_{P=P_{BE0,q}(\pi,c_{RD})}} =$$

$$= -\frac{p_I \cdot A_I(\pi) \cdot \left( PV_{III,q}(K_q^*(P_{BE0,q}(\pi, c_{RD}), \pi), P_{BE0,q}(\pi, c_{RD}), \pi) + \left.\frac{\partial PV_{III,q}(K,P,\pi)}{\partial q}\right|_{\substack{K=K_q^*(P_{BE0,q}(\pi,c_{RD}),\pi) \\ P=P_{BE0,q}(\pi,c_{RD})}} \cdot q \right)}{p_I A_I(\pi) \cdot \left.\frac{\partial PV_{III,q}(K,P,\pi)}{\partial P}\right|_{\substack{K=K_q^*(P_{BE0,q}(\pi,c_{RD}),\pi) \\ P=P_{BE0,q}(\pi,c_{RD})}} \cdot q}$$

$$= -\frac{PV_{III,q}(K_q^*(P_{BE0,q}(\pi, c_{RD}), \pi), P_{BE0,q}(\pi, c_{RD}), \pi) + \left.\frac{\partial p_q(K)}{\partial q}\right|_{K=K_q^*(P_{BE0,q}(\pi,c_{RD},\pi))} \cdot A_{III}(\pi)(P_{BE0,q}(\pi, c_{RD}) - c)N}{p_q(K_q^*(P_{BE0,q}(\pi, c_{RD}), \pi))A_{III}(\pi)Nq};$$

All the terms in the numerator and denominator of the fraction on the last line are positive: in particular, $p_q(K) = 1 - H(K \cdot q)$, where $H$ is as in Eq. (48), so $\partial p_q(K)/\partial q = -H'(K \cdot q) \cdot K > 0$ by Lemma 2, and $P_{BE0,q}(\pi, c_{RD}) > c$. Therefore, $\partial P_{BE0,q}(\pi, c_{RD})/\partial q < 0$, and so $q \mapsto P_{BE,q}(\pi, c_{RD})$ is weakly decreasing, and strictly so for $q$ such that $P_{BE,q}(\pi, c_{RD}) \leq \bar{P}$. *Q.E.D.*

Finally, define the actual bargained price $P_q(\pi, c_{RD}) = \gamma \bar{P} + (1 - \gamma) P_{BE,q}(\pi, c_{RD})$. By Lemma 6, this is continuous in $\pi$ and Lipschitz in $c_{RD}$ with constant $(1 - \gamma) M_q$. Note that $P_q(\pi, c_{RD})$ takes values in $[\underline{P}, \bar{P}]$, where $\underline{P}$ is as in Lemma 6 and satisfies $\underline{P} > c$.

To establish the existence of equilibrium, we define a mapping $\mathbf{T}$ from successful entry probabilities $\pi$, sample size choices per R&D cost $c_{RD} \mapsto K(c_{RD})$, and R&D cost cutoffs $\bar{c}_{RD}$ to itself, and show that this mapping admits a fixed point. (Proposition 4 defines two additional objects: the negotiated prices and probabilities of approval for each R&D cost; however, those can be derived from the equilibrium $\pi$ and $K_q(\cdot)$.) Again, this analysis holds the value of $q > 0$ fixed.

Formally, define $\mathbf{T} : [0, \bar{p}] \times \mathcal{C}[c_L, c_H] \times [c_L, c_H] \to [0, \bar{p}] \times \mathcal{C}[c_L, c_H] \times [c_L, c_H]$, where $\mathcal{C}[c_L, c_H]$ is the Banach space of continuous functions on $[c_L, c_H]$ equipped with the supremum norm, as $\mathbf{T}(\pi, K, \bar{c}) = (\pi^+, K^+, \bar{c}^+)$ where:

- $\pi^+ = \frac{p_I}{c_H - c_L} \int_{c_L}^{\bar{c}} p_q(K(c_{RD}))\, dc_{RD} \leq \bar{p}$.
- $K^+(c_{RD}) = K_q^*(P_q(\pi^+, c_{RD}), \pi^+)$ for all $c_{RD} \in [c_L, c_H]$.
- $\bar{c}^+ = \sup \left\{ c_{RD} \in [c_L, c_H] : P_{BE,q}(\pi^+, c_{RD}) < \bar{P} \right\}$.

A fixpoint of $\mathbf{T}$ characterizes an equilibrium in which the successful entry probability of competitors $\pi$ equals the probability that they successfully complete drug development and Phase I trials, and also obtain approval in Phase-III trials, taking into account the optimal

$K$ given their cost of R&D. Furthermore, the optimal $K$ per cost $c_{RD}$ of R&D is a function of the bargained price. Finally, the mass of firms with cost low enough to warrant entry is determined by the ability to break even given the maximum price the insurance company is willing to pay.

**Theorem 1 (Existence of Equilibrium)** *The mapping* $\mathbf{T}$ *admits a fixed point.*

**Proof:** Consider a sequence $(\pi_\ell, K_\ell, \bar{c}_\ell) \to (\pi, K, \bar{c})$.

First,

$$\pi_\ell^+ = \frac{p_I}{c_H - c_L} \int_{c_L}^{\bar{c}_\ell} p_q(K_\ell(c_{RD}))\, dc_{RD} = \frac{p_I}{c_H - c_L} \int_{c_L}^{c_H} p_q(K_\ell(c_{RD})) \mathbf{1}_{[c_L, \bar{c}_\ell)}(c_{RD})\, dc_{RD}$$
$$\to \frac{p_I}{c_H - c_L} \int_{c_L}^{c_H} p_q(K(c_{RD})) \mathbf{1}_{[c_L, \bar{c})}(c_{RD})\, dc_{RD} = \pi^+$$

where the limit follows from bounded convergence because $K_\ell \to K$ uniformly, hence pointwise, and $\mathbf{1}_{[c_L, \bar{c}_\ell)} \to \mathbf{1}_{[c_L, \bar{c})}$ pointwise.

Second, for every $c_{RD} \in [c_L, c_H]$,

$$K_\ell^+(c_{RD}) = K_q^*(P(\pi_\ell^+, c_{RD}), \pi_\ell^+) \to K_q^*(P(\pi^+, c_{RD}), \pi^+) = K^+(c_{RD})$$

because it was just shown that $\pi_\ell^+ \to \pi^+$, $P$ is continuous, and $K_q^*$ is continuous. Furthermore, as a composition of continuous functions, $K^+$ is itself continuous.

Third, by definition

$$\bar{c}^+ = \sup \left\{ c_{RD} \in [c_L, c_H] : P_{BE,q}(\pi^+, c_{RD}) < \bar{P} \right\}.$$

For every $\epsilon > 0$, $P_{BE,q}(\pi^+, \bar{c}^+ - \epsilon) < \bar{P}$; since $P_{BE,q}$ is continuous in $\pi$ for fixed $c_{RD}$, there is $L(\epsilon)$ such that $P_{BE,q}(\pi_\ell^+, \bar{c}^+ - \epsilon) < \bar{P}$ for all $\ell \geq L(\epsilon)$. Hence, by definition, $\bar{c}_\ell^+ \geq \bar{c}^+ - \epsilon$ for all $\ell \geq L(\epsilon)$. Therefore, along any convergent subsequence, $\lim_\ell \bar{c}_\ell^+ \geq \bar{c}^+ - \epsilon$ for every $\epsilon > 0$, which implies that $\lim_\ell \bar{c}_\ell^+ \geq \bar{c}^+$, again along any convergent subsequence. Suppose there is a convergent subsequence along which $\lim_\ell \bar{c}_\ell^+ > \bar{c}^+$. Then there is $L'$ and $\delta > 0$ such that for $\ell \geq L'$, $\bar{c}_\ell^+ \geq \bar{c}^+ + \delta$. This implies that, for all such $\ell$, $P_{BE,q}(\pi_\ell^+, \bar{c}^+ + \delta/2) < \bar{P}$. By continuity of $P_{BE,q}$ in $\pi$ for fixed $c_{RD}$, $P_{BE,q}(\pi^+, \bar{c}^+ + \delta/2) \leq \bar{P}$.

There are two cases. First, if $P_{BE,q}(\pi^+, \bar{c}^+ + \delta/2) = \bar{P}$, then $P_{BE0,q}(\pi^+, \bar{c}^+ + \delta/2) \geq P_{BE,q}(\pi^+, \bar{c}^+ + \delta/2) = \bar{P}$; since $\pi^+ \leq \bar{p} < 1$, $P_{BE0,q}$ is strictly increasing in its second argument, so $P_{BE0,q}(\pi^+, \bar{c}^+ + 2\delta/3) > \bar{P}$; therefore, for $\ell$ large, by continuity of $P_{BE0,q}$ in $\pi$ for fixed $c_{RD}$, also $P_{BE0,q}(\pi_\ell^+, \bar{c}^+ + 2\delta/3) > \bar{P}$, which implies that $P_{BE,q}(\pi_\ell^+, \bar{c}^+ + 2\delta/3) = \bar{P}$, which contradicts the fact that $\bar{c}_\ell^+ \geq \bar{c}^+ + \delta$. Second, if $P_{BE,q}(\pi^+, \bar{c}^+ + \delta/2) < \bar{P}$, since $\delta > 0$, this contradicts the definition of $\bar{c}^+$. Therefore, for every convergent subsequence of $(\bar{c}_\ell^+)$, the limit is exactly $\bar{c}^+$: hence, $\bar{c}_\ell^+ \to \bar{c}^+$.

To sum up, we have just shown that $\mathbf{T}$ is a continuous mapping. We now show that the image of $\mathbf{T}$ is contained in a compact subset. Specifically, we show that closure of its image is compact.

Because $K^*$ is Lipschitz in $P$ with constant $L$ (Lemma 5), and $P$ is Lipschitz in $c_{RD}$ with constant $(1-\gamma)M_q$ (Lemma 6), the function $K^+$ is Lipschitz continuous with constant $(1-\gamma)LM$, independent of arguments to $\mathbf{T}$.

Consider a sequence $(\pi_\ell^+, K_\ell^+, \bar{c}_\ell^+)$ in the image of $\mathbf{T}$. The sequence $(K_\ell^+)$ is uniformly bounded (by $N$) and uniformly equicontinuous (as all functions share the same Lipschitz constant). By the Arzela-Ascoli theorem, $(K_\ell^+)$ admits a convergent subsequence in $\mathcal{C}[c_L, c_H]$. Since $(\pi_\ell^+)$ and $(\bar{c}_\ell^+)$ are sequences in compact intervals, there is a further subsequence of $(\pi_\ell^+, K_\ell^+, \bar{c}_\ell^+)$ that converges in $[0, \bar{p}] \times \mathcal{C}[c_L, c_H] \times [c_L, c_H]$. Therefore, the closure of the image of $\mathbf{T}$ is compact in the Banach space $[0, \bar{p}] \times \mathcal{C}[c_L, c_H] \times [c_L, c_H]$.

Because $\mathbf{T}$ is a continuous mapping from a non-empty, closed, bounded, and convex subset of a Banach space into itself, and the image of $\mathbf{T}$ is contained in a compact subset of a Banach space, Schauder's Fixed Point Theorem guarantees the existence of a fixed point. *Q.E.D.*

## H.5. Proof of Proposition 5

The claim follows from the fact that for given set of parameters, there exists $q_i$ sufficiently small for which $PV_I(q_i) < 0$. From Proposition 4 the only fixed point must have $\mu(q_i) = 0$. Q.E.D.

## H.6. Proof of Proposition 6

Setting $E[PV_I] = 0$ we obtain

$$P^{BE} = c_p + \frac{p_I \, A_I(n) \, c_{RCT} \, K^*(n) + c_{R\&D} n}{p_I \, A_I(n) \, p(K^*(n), n) \, A_{III}(n) \, N}. \tag{49}$$

As $n$ increases, the equilibrium probability of a new successful entry declines and thus the discounts $A_I(n)$ and $A_{III}(n)$ increase. However, $A_I(n)$ and $A_{III}(n)$ are bounded (the upper bounds are given by the case of no (successful) entry, $\pi = 0$). Similarly, $K^*(n) \leq N$. Since $q \to 0$ implies $p(K^*(n), n) \to 0$, the claim follows from the expression of $P^{BE}$ in (49). Q.E.D.

## H.7. Proof of Proposition 8

Let $PV_{III}^{PDDP}(M, Q_T)$ denote the expression for Phase-III profits in Eq. (20). If $Q_T' > Q_T$ and $M$ maximizes $PV_{III}^{PDDP}(\cdot, Q_T)$, then $PV_{III}^{PDDP}(M, Q_T') > PV_{III}^{PDDP}(M, Q_T)$. Thus, the

maximized value of $PV_{III}^{PDDP}(\cdot, Q_T')$ is also strictly greater than that of $PV_{III}^{PDDP}(\cdot, Q_T)$. Hence, for fixed $c_{tech}$, $PV_I^{PDDP}$ is also increasing in $Q_T$.

Now observe that $\partial^2 PV_{III}^{PDDP}(M, Q_T)/\partial M \partial P > 0$. Hence, by standard arguments, an increase in $P$ yields an increase in the optimal choice of $M$. Increasing both $P$ and $M$ then increases the value of $PV_{III}^{PDDP}$, and hence the value of $PV_I^{PDDP}$.

Combining these results, for fixed $c_{tech}$, if $P_{BE}$ is the break-even price for given $Q_T$, and $Q_T' > Q_T$, the break-even price $P_{BE}'$ corresponding to $Q_T$ must be lower to ensure that $PV_I^{PDDP} = 0$. *Q.E.D.*

## H.8. Proof of Proposition 9

We mimic the proof of Proposition 4 and omit details that can be easily adapted from the latter. Write the Phase III present value as follows:

$$PV_{III}(M, P, \pi) = p(M) \cdot (Q_T A_{III}(\pi)(P - c) - C_{PDDP})\, N - c_{RCT} M$$

(cf. Eq. 20; we remove the "PDDP" and "New" superscripts when no confusion can arise. Here, $p(M) = 1 - g(M)$ is the approval probability, which is twice continuously differentiable and strictly increasing by inspection, and strictly concave by Lemma 4. It is bounded above by $\bar{p} \equiv p(N) < 1$. Moreover, $A_{III}(\pi) > 0$ for $\pi < 1$, and $A_{III}(\cdot)$ is continuous (in fact, differentiable).

Consider the problem faced by the firm in Phase III:

$$\max_{M \in [0,N]} PV_{III}(M, P, \pi)$$

where we allow $M$ to be any real number between 0 and $N$.

**Lemma 8** *For $P > c$ and $\pi < 1$, the optimal sample size $M^*(P, \pi)$ is given by*

$$M^*(P, \pi) = (p')^{-1}\left(\frac{c_{RCT}}{(Q_T A_{III}(\pi)(P - c) - C_{PDDP})\, N}\right).$$

*The function $M^*(P, \pi)$ is jointly continuous, Lipschitz continuous in $P$ with constant $L > 0$ uniformly over $\pi$, strictly increasing in $P$ for fixed $\pi < 1$, and strictly decreasing in $\pi$ for fixed $P > c + \frac{C_{PDDP}}{Q_T A_{III}(\pi)}$.*

**Proof:** adapted from the proof of Lemma 5. *Q.E.D.*

Now consider the Phase I present value (cf. Eq. 21):

$$PV_I(P, \pi, c_{RD}) = A_I \cdot PV_{III}(M^*(P, \pi), P, \pi) - c_{tech}.$$

We show that there exists a *break-even* price $P_{BE0}$ such that, if the firm collects $P_{BE}$ per patient after the drug is approved, and chooses $M$ optimally in Phase III given this price $P_{BE0}$, then expected revenues exactly cover its tech acquisition cost $c_{tech}$. (However, this price may exceed the maximum price $\bar{P}$ that the insurance company is willing to pay; we will address this issue below.)

**Lemma 9 (Break-Even Price)** *For every $\pi \leq \bar{p}$ and $c_{tech} \in [c^L, c^H]$, there exists a unique, continuous break-even price $P_{BE0}(\pi, c_{tech}) > c + \frac{C_{PDDP}}{Q_T A_{III}(\pi)}$ such that $PV_I(P_{BE0}(\pi, c_{tech}), \pi, c_{tech}) = 0$. For $\pi \leq \bar{p}$, the function $c_{tech} \mapsto P_{BE0}(\pi, c_{tech})$ is Lipschitz continuous in $c_{tech}$, with constant $M_{PDDP} > 0$. Hence, $\underline{P} = \min_{\pi \in [0,\bar{p}]} P_{BE0}(\pi, c_L)$ is well-defined and satisfies $\underline{P} > c + \frac{C_{PDDP}}{Q_T A_{III}(0)}$.*

**Proof:** adapted from the proof of Lemma 6, with the following additional argument to prove the lower bound on $\underline{P}$. For fixed $\pi \leq \bar{p} < 1$ and $c_{tech} \in [c^L, c^H]$, $P \mapsto PV_I(P, \pi, c_{tech})$ is continuous and strictly increasing. Therefore, there exists a unique price $P_{BE0}(\pi, c_{tech})$ such that $PV_I(P_{BE0}(\pi, c_{tech}), \pi, c_{tech}) = 0$. This price is strictly increasing in $\pi$ for fixed $c_{tech}$: the reason is that, by the envelope theorem and the fact that $A'_{III}(\pi) < 0$, an increase in $\pi$ decreases $PV_{III}(M^*(P, \pi), P, \pi)$ for fixed $P$; thus, $P$ must increase to ensure that the firm breaks even in Phase I. And finally, $P_{BE0}(\pi, c_L) > c + c_{PDDP}/(Q_T A_{III}(\pi))$ for $\pi \leq p < 1$, because if the firm gets a price equal to $c + c_{PDDP}/(Q_T A_{III}(\pi))$ or smaller, $PV_{III} = 0$, whereas $c^L > 0$. Summing up, $\underline{P} = \min_{\pi \in [0,\bar{p}]} P_{BE0,q}(\pi, c^L)$ is attained for $\pi = 0$, and as noted above, $P_{BE0,q}(0, c^L) > c + \frac{c_{PDDP}}{Q_T A_{III}(0)}$.

Now, given the maximum price $\bar{P}$ that the insurance company is willing to pay, define $P_{BE}(\pi, c_{tech}) = \max(P_{BE0}(\pi, c_{tech}), \bar{P})$, the "capped" break-even price. This function retains the Lipschitz constant $M_{PDDP}$ for fixed $\pi < 1$. In addition:

**Lemma 10** *The function $\pi \mapsto P_{BE}(\pi, c_{tech})$ is continuous in $\pi$ for fixed $c_{tech}$.*

**Proof:** adapted from the proof of Lemma 10. *Q.E.D.*

Finally, define the actual bargained price $P(\pi, c_{tech}) = \gamma \bar{P} + (1 - \gamma) P_{BE}(\pi, c_{tech})$. By Lemma 9, this is continuous in $\pi$ and Lipschitz in $c_{tech}$ with constant $(1 - \gamma) M_{PDDP}$. Note that $P(\pi, c_{tech})$ takes values in $[\underline{P}, \bar{P}]$, where $\underline{P}$ is as in Lemma 9 and satisfies $\underline{P} > c + \frac{c_{PDDP}}{Q_T A_{III}(0)}$.

To establish the existence of equilibrium, we define a mapping $\mathbf{T}$ from successful entry probabilities $\pi$, sample size choices per tech acquisition cost $c_{tech} \mapsto M(c_{tech})$, and tech acquisition cost cutoffs $\bar{c}_{tech}$ to itself, and show that this mapping admits a fixed point.

Formally, define $\mathbf{T} : [0, \bar{p}] \times \mathcal{C}[c_L, c_H] \times [c_L, c_H] \to [0, \bar{p}] \times \mathcal{C}[c_L, c_H] \times [c_L, c_H]$, where $\mathcal{C}[c_L, c_H]$ is the Banach space of continuous functions on $[c^L, c^H]$ equipped with the supremum norm, as $\mathbf{T}(\pi, M, \bar{c}) = (\pi^+, M^+, \bar{c}^+)$ where:

- $\pi^+ = \frac{1}{c_H - c_L} \int_{c_L}^{\bar{c}} p(M(c_{tech}))\, dc_{tech} \leq \bar{p}$.
- $M^+(c_{tech}) = M^*(P(\pi^+, c_{tech}), \pi^+)$ for all $c_{tech} \in [c_L, c_H]$.
- $\bar{c}^+ = \sup\left\{c_{tech} \in [c_L, c_H] : P_{BE}(\pi^+, c_{tech}) < \bar{P}\right\}$.

**Theorem 2 (Existence of Equilibrium)** *The mapping* $\mathbf{T}$ *admits a fixed point.*

**Proof:** adapted from the proof of Theorem 1. *Q.E.D.*